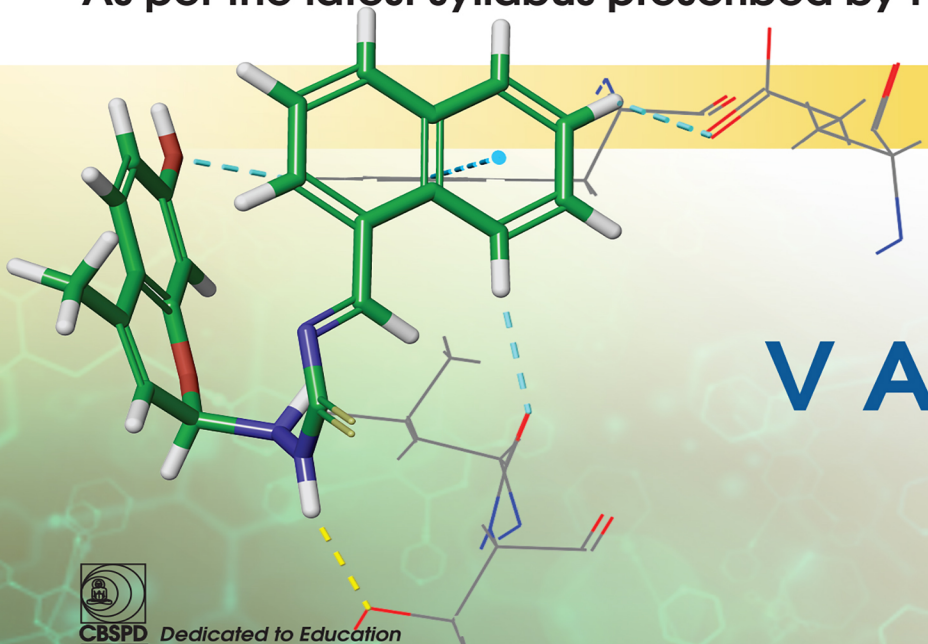
Volume 1

Textbook of Medicinal Chemistry

As per the latest syllabus prescribed by Pharmacy Council of India



Fourth Edition

V Alagarsamy

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Preface to the Fourth Edition

The subject of medicinal chemistry has grown so fast and we find developments in many areas of this subject. Even though, it is a difficult task for the author to match the pace of developments of the subject, it is a great pleasure for the author and the publisher to present this revised and updated fourth edition of the *Textbook of Medicinal Chemistry*.

The enthusiastic comments received from faculty members and student community across India, as mentioned below, have inspired me to present this fourth and updated edition of the *Textbook of Medicinal Chemistry*.

- A unique book containing updated information about medicinal chemistry by complying the revised syllabus of Pharmacy Council of India (PCI).
- This book is comprehensive with all the aspects of medicinal chemistry discussed at one place.
- It is a good companion for GPAT aspirants.
- It is a favourite book for students willing to learn medicinal chemistry.
- It is presented in an attractive and easy-to-read manner.
- It is presented in student-friendly style and approach.
- It is presented in a down-to-earth fashion avoiding unnecessary complicated details.
- This is a perfect textbook.
- It helps faculty members a lot while teaching students.
- Elegant presentation of chemical structures helping students to remember and reproduce well in examinations.

Since its first edition, in 2009, *Textbook of Medicinal Chemistry*, serves as an authentic and reliable source for the medicinal chemistry aspects of the drugs. The overwhelming response to the first edition was immediate throughout the country due to its comprehensive content (especially, the classification, synthesis and drug profile and SAR). As the number of drugs available for therapeutic use is increasing day-by-day, all the chapters have been updated with newer drugs.

New to this Edition

The major goal of the author is to provide the students of pharmacy and allied health professions with a book that not only describes the chemical aspects of drugs but also reflects pharmacological aspects that are important in the field of medicine. Following are some features of the fourth edition:

- **Updated information provided** and complied with the revised PCI syllabus.
- **Attractive layout and design.**
- **Physicochemical parameters** have been explained with further information and two new chapters—Protein Binding of Drugs and Biotransformation or Metabolism of Drugs—are added under the section Physicochemical Factors in Relation to Biological Activity of Drugs.

- **New topics** like Pharmacophore Modelling, Docking and Antisense Technology are added under the section Drug Design.
- **Based on PCI syllabus, new topics** like Drugs Used in Congestive Cardiac Failure, Thyroid and Antithyroid Drugs, Antiscabies and Antipedicular Agents, Preservatives and Diagnostic Agents are introduced.
- **Several newer drugs** are incorporated in different chapters.
- **PCI syllabus-based classification of drugs** is provided for easy to study and write in examination.

I hope this new edition of the *Textbook of Medicinal Chemistry* will be welcomed by the teachers and students of pharmacy, pharmaceutical chemistry, chemistry and the related fields. You are most welcome with your valuable feedback to *authoralagarsamy@gmail.com.*

V Alagarsamy

Preface to the First Edition

Medicinal chemistry emerged as a specialized area due to the development in chemistry and biology, hence it is considered as a highly interdisciplinary science combining a wide variety of subjects such as organic chemistry, pharmacology, biochemistry, toxicology, pharmacognosy, molecular biology, genomics, proteomics, computational chemistry, physical chemistry and statistics. Now, the growth of medicinal chemistry has reached a stage where the activity-guided synthesis of compounds is possible rather than screening of synthesized compounds for different biological activities. This field also penetrates into the areas of gene therapy and biochemistry-based virtual drug receptors with the help of computer-aided molecular modelling techniques.

This book is an upshot of my vision to discover the best book on medicinal chemistry, which deals about the concise description of diseases, clear classification of drugs with their chemical structures, synthesis of each drug with different routes, mode of action, metabolism, physical and pharmacological properties along with their therapeutic uses, assay technique, dose, official dosage forms and summary of structure–activity relationship (SAR) studies. Swathing the entire features of medicinal chemistry, first of its kind, is the unique feature of this book. It facilitates the students to understand the subject more easily and interestingly.

While writing this book, I felt that the book will bring about a re-orientation in the teaching and learning process of medicinal chemistry. Academic community in India is faced with scarcity of books to cater to their needs. Numerous foreign writers' books deal well about basics and pharmacological aspects related to medicinal chemistry, but lack two major requirements, i.e. synthesis and clear classification of drugs used. Some Indian authors filled this lacuna to a certain extent by including the synthesis, but failed to give a clear classification of drugs with their chemical structure. For this, the content of this book has been carefully tailored to cater to the needs of the academicians belonging to all Indian universities, pharmacologists, clinical and industrial pharmacists by incorporating the missing links between general synthetic organic chemistry and medicinal chemistry.

This *Textbook of Medicinal Chemistry* is presented in two volumes. Volume I consists of six sections. The first section is devoted to the physicochemical properties and their relation to biological activities and the second section provides the framework of drug design, which together form the basic aspects of medicinal chemistry. The remaining sections, III to VI, deal with chemical, pharmacological, biochemical and toxicological aspects of organic medicinal compounds used in various diseases associated with different systems of the human body such as CNS, ANS, CVS and urinary system.

We hope that this special volume will be a good source of information and reference for not only graduate and postgraduate students but also basic and applied researchers in this field. Moreover, it will also be of interest to a wide range of scientists, including organic chemists, biochemists, pharmacologists and clinicians, who are interested in drug research. I welcome suggestions and constructive criticism from all corners of scientific community.

V Alagarsamy

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I wish to place on record my heartfelt thanks to everyone who have made this book possible, especially my beloved teachers from first standard to doctoral programme, guides, Dr Rajani Giridhar and Dr M R Yadav.

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I express my sincere appreciation to my students, Dr V Raja Solomon (postdoctoral researcher, Canada), Dr J C Hanish Singh, Dr P Parthiban, Mr S Thiru Senthil Murugan and Ms J Rajeshwari, for helping me author this book. I also thank my colleagues, especially, Dr S Satheesh Kumar, Dr B Subba Rao, Dr K Dhanabal, Mr M Murugan, Dr M T Sulthana, Dr B Narendhar and Dr K Lahari, for their untiring support in making this book.

The friendly interaction I had experienced with the Elsevier team—Mr Subodh K Chauhan, Mr Nitin Valecha and Mr Ankush—and Televijay Technologies, Project Manager Ms Usha K Nair, offered a plenty of energy to eliminate the fatigue during the preparation of this book. If the author gets such a cooperative and energetic publication team, publishing any number of books will not be a difficult task. I thank them wholeheartedly for helping me reach this target and am requesting them to continue their service to the author community in the same intensity.

I also acknowledge the support extended by the CBS Publishing team Mr Y N Arjuna (Senior Vice-President, Publishing, Editorial and Publicity) and his entire team comprising Ms Ritu Chawla (AGM Production), Ms Baljeet (graphic artist), Ms Hemlata (DTP operator), and Mr Neeraj Kumar Sharma (editor) in this revised edition.

I am also grateful to the faculty members of Faculty of Technology, Osmania University, Hyderabad, for their academic support and encouragement.

The stimulation I got from my father, mother, sister, brothers and wife to reach this target is more than analeptics, and the patience and cooperation extended by my children, Aishwarya (B Pharm) and Abhinaya, made me think of the goal without any diversion. To express my thankfulness, I pray The Almighty to bless my children with teachers like those I got in my life so that they too are inspired by their teachers and dedicate to the field of medicinal chemistry and, in turn, serve for the suffering humanity.

V Alagarsamy

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Introduction to Medicinal Chemistry

Medicinal chemistry is a discipline at the intersection of chemistry and pharmacology that involves the identification, synthesis, and development of new chemical entities that are suitable for medical or pharmaceutical use. Medicinal chemistry is an interdisciplinary science combining variety of subjects such as organic chemistry, phytochemistry, pharmacology, toxicology, molecular biology, biochemistry, computational chemistry, physical chemistry, and statistics. It also includes the study of existing drugs, their pharmacological properties, toxic effects, and their quantitative structure–activity relationships (QSARs).

Majority of the medicinal compounds, which are used as medicines are natural products and synthetic organic compounds. However, metal-containing compounds are also found to be useful as drugs. For example, cisplatin series of platinum-containing complexes are used as anticancer agents. These compounds are known as *metal-based drugs*.

PROCESSES OF DRUG DISCOVERY

Discovery

The initial step of drug discovery involves the identification of new active compounds, often called *hits or leads*, which are found by screening many compounds of synthetic or natural sources, such as plants, animals, or microorganisms for their targeted biological properties. More often, the hits use to come from synthetic sources, such as historical compound collections and combinatorial chemistry.

Optimization

The second step in drug discovery involves further chemical alterations on structure–activity relationship (SAR) basis to enhance the biological and physicochemical properties of a given candidate compound library. The chemical modifications can improve the binding property and interaction (pharmacophores) of the drug candidate compounds, their affinities, and pharmacokinetics, or indeed, their reactivity and stability during their metabolic degradation. Among the methods that have contributed to the quantitative metabolic prediction, a recent example is substrate product occurrence ratio calculator (SPORCalc). The identified pharmacophores play an important role in finding the lead compounds, which exhibit the most potency, the best pharmacokinetics, and the least toxicity. The QSAR molecular modelling tools, such as comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA), which leads to tabulated data and first- and

second-order equations. Among the theories related to these, the most relevant being Hansch's analysis that involves Hammett electronic parameters, steric parameters, and Log P (lipophilicity) parameters.

Development

The final step involves rendering the lead compounds that are suitable for use in the clinical trials after their successful pharmacodynamic optimization in clinical trials, the optimization of the synthetic route for bulk production, and the preparation of a suitable drug formulation.

HISTORY AND DEVELOPMENT OF MEDICINAL CHEMISTRY

Although medicinal plants and minerals were used as a remedy since the ancient civilisation, the field of medicinal chemistry has been developed due to the great efforts made by the scientists who are working in drug design mechanism one side and the chemists who are working seriously in order to modify the chemical substance into a useful drug on the other side.

Many years ago, peoples used a wide range of natural products for medicinal purpose. These products obtained from animals, vegetables and mineral sources were sometimes very effective. But, many of the products were found to be toxic and it is interesting to note that the Greeks used the same word 'pharmakon' for both poisons and medicinal products. Literatures about the ancient remedies were not readily available for use until the invention of the printing press in the 15th century.

In the 19th century, extraction procedures and pure isolated entities (i.e. pure form of substances, such as alkaloids, carbohydrates, etc.) were reported to be in existence. Some of the isolated compounds were proved to be satisfactory as therapeutic agents. The majority of the plant or natural products were believed to be too toxic, such as morphine and cocaine, which was extensively prescribed by physicians.

In 19th century, the great development in knowledge of chemistry was very much used in the herbal pharmacopoeia. Further the active ingredients responsible for pharmacological activity were isolated during this period. Some of the isolated active ingredients are listed in the Table 1.1.

Table 1.1: Isolated active pharmaceutical ingredients from plants

S. No.	*Active ingredient isolated*	*Source*	*Year*	*Scientist*
1.	Morphine	Opium	1804	Friedrich Sertürner
2.	Emetine	*Ipecacuanha*	1816	Pierre-Joseph Pelletier
3.	Digitoxin	*Digitalis*	1841	E. Humolle and T. Quevenne
4.	Cocaine	Coca	1860	Albert Niemann
5.	Physostigmine	Calabar bean	1864	Albert Niemann

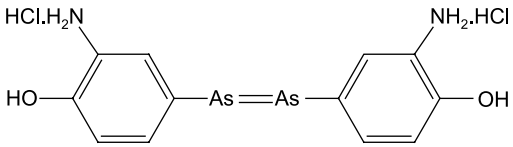
As a result of isolation of these active ingredients and the development in synthetic organic chemistry, organic compounds like acetic acid were synthesized by the chemists in the laboratory and the pharmaceutical industries established in late 19th century.

In the search of finding less toxic medicines than these, on the basis of natural sources, resulted in the introduction of synthetic substances such as drugs in the late 19th century. These improvements were based on the structures of the known biologically active compounds, now referred to as 'leads'. By adopting this approach, structurally related compounds were developed for the targeted activity. These lead-related compounds are referred to as analogues.

In 1910, Paul Ehrlich and Sahachirō Hata synthesized the first synthetic drug, Arsphenamine, by combining synthesis with reliable biological screening and evaluation procedures. At the beginning of 19th century, Ehrlich recognized the fact that expected biological and toxic properties of drugs were important in their screening. He demonstrated that the more effective drugs showed a greater selectivity for target microorganism than its host. Consequently, to compare the effectiveness of different compounds, he expressed drug selectivity by a term known as chemotherapeutic index, which he defined as follows:

Chemotherapeutic index = Minimum effective dose/maximum tolerable dose

On the basis of this concept, over 600 structurally related arsenic compounds were tested and catalogued in terms of the therapeutic index by Paul and Hata. This has led to the discovery of Arsphenamine (Salvarsan, Hoechst, German) in 1909, that could cure mice infected with syphilis. This drug was found to be effective in humans, but it must be used with extreme care, as it is very toxic. However, it was replaced by penicillin in mid-1940s.



Arsphenamine (salvarsan)

Ehrlich's method of approach is still one of the basic techniques used to design and evaluate new drugs in medicinal chemistry. Recently, chemotherapeutic index has been updated to take into account the variability of individuals, and is now defined as its reciprocal, therapeutic index or ratio.

$$\text{Therapeutic index} = LD_{50}/ED_{50}$$

where LD_{50} is the lethal dose that is required to kill 50% of the test animals or microorganisms, and ED_{50} is the effective dose that is required to produce a therapeutic response in 50% of the test animals or microorganisms. However, the therapeutic index values can only be used as a limited guide of relative usefulness for the different compounds.

The discovery of prontosil and penicillin enhanced the ability of human beings to fight against the deadly bacterial infections. Followed by this many of the drugs acting on various systems of human body were discovered and developed as potent drugs with limited toxicity, resulted in increase in life expectancy.

Apart from this, serendipity has played a large part in the discovery of drugs. For example, the development of penicillin by Florey and Chain was possible only because of Alexander Fleming, who noted the inhibition of *Staphylococcus* by *Penicillium notatum.* Despite our increased knowledge base, it is still necessary to pick a correct starting point for an investigation, if a successful outcome is to be achieved.

Recent Developments in Medicinal Chemistry

It is well known that genetics plays an important role in individual's normal physiological functions. Based on this, **imatinib** was discovered for the treatment of chronic myeloid leukemia, by using the knowledge of high-throughput screening (HTS) and medicinal chemistry. Thus, in this century medicinal chemistry is developed in such a way that the drugs are guaranteed to reach the specific targets in the body by using the knowledge of pharmacogenetics.

The modern techniques such as computerised molecular modelling, HTS and combinatorial chemistry were developed by the pharmacology and biotechnology departments became the time and cost-effective approach, which overcome the problems associated in drugs developed by random screening through which medicinal chemistry developed the drugs for many decades which was not cost-effective and time consuming process with many of the failures.

MODERN DRUG DISCOVERY

A new approach to drug discovery is to understand how the diseases and infections are controlled at the molecular and physiological level and to target specific entities based on this knowledge. This process of drug discovery involves the identification of the candidates, synthesis, characterization, screening, and assays for its therapeutic efficacy. Once a compound has proved its value in these tests, the process of drug development starts prior to the clinical trials.

Despite the advances in technology and understanding of the biological systems, drug discovery is still a long process with a low rate of new therapeutic discoveries. Information on the human genome, its sequence, and what it encodes has been hailed as a potential windfall for drug discovery, promising to virtually eliminate the bottlenecks in therapeutic targets that have been one of the limiting factors on the rate of therapeutic discovery.

Targets: New and Established

Those targets for which there is good scientific understanding, supported by lengthy publication history of both as to how the target functions in normal physiology and how it is involved in human pathology are called 'established targets'. It is directed to the extent of background information available on a target, in particular, functional information and does not imply that the mechanism of the action of drugs that are thought to act through particular established targets is fully understood. Less investment is, generally, required to develop a therapeutic agent directed against the target for which more such information is available, The process of gathering such functional information is called 'target validation' in pharmaceutical industry parlance. Established targets provide information on the chemical feasibility of developing a small molecular therapeutic against the target, and can provide licensing opportunities and freedom to operate indicators with respect to small molecule therapeutic candidates.

In general, 'new targets' are those targets that are not 'established targets', but which have been or are the subject of drug discovery campaigns. These typically include newly discovered proteins or proteins whose functions have now become clear as a result of basic scientific research. The majority of the targets currently selected for drug discovery efforts are proteins. Two classes of proteins predominate: G-protein-coupled receptors (GPCRs) and protein kinases.

SCREENING AND DESIGNING

The process of finding a new drug against a desired target for a particular disease usually involves high-throughput screening (HTS), wherein large libraries of compounds are tested for their ability to modify the target. For example, if the target is a novel GPCR, compounds will be screened for their ability to inhibit or stimulate that receptor. If the target is a protein kinase, the chemicals will be tested for their ability to inhibit that kinase.

Another important function of HTS is to show the selectivity of compounds for the desired target. The idea is to find a molecule that will interfere with only the chosen target, but not the other related targets. For this, other screening runs will be performed to see whether the 'hits' against the chosen target will interfere with other related targets. This process is called cross-screening. More unrelated targets a compound hits, the more likely it is that off-target toxicity will occur with that compound, hence cross-screening is important.

Although HTS is a commonly used method for novel drug discovery. It is often possible to start from a molecule, which already has some of the desired properties. Such a molecule might be extracted from a natural product or even be a drug on the market, which could be improved upon (called 'me too' drugs). Other methods, such as virtual HTS, where screening is done using the computer-generated models and attempting to 'dock' virtual libraries to a target, are also often used.

Another important method for drug discovery is drug designing, whereby the biological and physical properties of the target are studied, and a prediction is made about the sort of chemicals that might fit into an active site. From these exercises, novel pharmacophores can emerge very rapidly.

Once a lead-compound series has been established with sufficient target potency, selectivity, and favourable drug-like properties one or two compounds will then be proposed for drug development. The best of these is generally called the lead compound, while the other will be designated as the 'backup'.

NATURE AS A SOURCE OF DRUG COMPOUNDS

Despite the rise of combinatorial chemistry as an integral part of lead-discovery process, the natural products still play a major role as starting materials for drug discovery. A recent study suggested that about 1000-small-molecule new chemical entities were developed in the past 25 years; among these, 50% were natural, derived, or semisynthetic derivatives of natural products. For certain therapy areas, such as antimicrobials, antineoplastics, antihypertensive, and anti-inflammatory drugs, natural products may be useful as a source of novel chemical structures for modern techniques of development.

Plant-derived Bioactive Materials

Before Paracelsus, vast majority of the traditionally used crude drugs in Western medicine were plant-derived extracts. This has resulted in an inherited pool of information of the healing potential of plant species, thus making them an important source of starting materials for drug discovery. A different set of metabolites is sometimes produced in the different anatomical parts of the plant (i.e. roots, leaves, and flowers), and botanical knowledge is crucial also for the correct identification of bioactive plant materials.

Microbial Species with Bioactive Metabolites

Microbes have to compete for living space and nutrients. To survive in these conditions, many microbes have developed abilities to prevent the competing species from proliferation. This phenomenon has led to the microbes being the main source of antimicrobial drugs. *Streptomyces* species have been a source of antibiotics. The classical example of an antibiotic discovered as a defence mechanism against another microbe is the discovery of penicillin in bacterial cultures contaminated by Penicillium fungi in 1928.

Marine Invertebrates as a Source of Bioactive Compounds

Marine environments are potential sources of new bioactive agents. Arabinose nucleosides discovered from marine invertebrates in 1950s, demonstrated that sugar moieties other than ribose and deoxyribose can yield bioactive nucleoside structures. However, it was in 2004, when the first marine-derived drug was approved. The cone snail toxin, ziconotide, also known as Prialt, was approved by Food and Drug Administration (FDA, USA) to treat severe neuropathic pain. Several other marine-derived agents are now in clinical trials for indications, such as cancer, inflammation, and pain. One class of these agents are bryostatin-like compounds, under investigation as anticancer agent.

Chemical Diversity of Natural Products

As mentioned earlier, combinatorial chemistry was a key technology enabling the efficient generation of large screening libraries for the needs of HTS. It has been pointed out that, despite the increased efficiency in chemical synthesis, no increase in lead or drug candidates have been reached even after

two decades of combinatorial chemistry. This has led to an analysis of the chemical characteristics of combinatorial chemistry products, as compared to the existing drugs and the natural products. The chemoinformatics is a concept of chemical diversity depicted as the distribution of compounds in the chemical space on the basis of their physicochemical characteristics, and is often used to describe the difference between combinatorial chemistry libraries and natural products. The synthetic, combinatorial library compounds seem to cover only a limited and quite uniform chemical space, whereas existing drugs, particularly, natural products exhibit much greater chemical diversity, distributing more evenly to the chemical space. The most prominent differences between natural products and compounds in combinatorial chemistry libraries are the number of chiral centres (much higher in natural compounds), structure rigidity (higher in natural compounds), and number of aromatic moieties (higher in combinatorial chemistry libraries). Other chemical differences between these two groups include the nature of heteroatoms (O and N enriched in natural products; S and halogen atoms more often present in synthetic compounds), as well as level of non-aromatic unsaturation (higher in natural products). As both structure rigidity and chirality are well-established factors in medicinal chemistry and are known to enhance compounds specificity and efficacy as a drug, it has been suggested that natural products compare favourably to today's combinatorial chemistry libraries as potential lead molecules.

Methodologies in Natural Product Drug Discovery

Identification of Biologically Active Material

Random collection or screening of material, or exploitation of ethnopharmacological knowledge in the selection are the main approaches exist for the finding of new bioactive chemical entities from natural sources. The former approach is based on the fact that only a small part of earth's biodiversity has ever been tested for biological activity, and organisms living in a species-rich environment need to evolve defence and competition mechanism to survive. A collection of plant, animal, and microbial samples from rich ecosystems might give rise to novel biological activities. One example of a successful use of this strategy is the screening for antitumour agents, by the National Cancer Institute in USA, started in 1960s. Paclitaxel was identified from Pacific yew tree *Taxus brevifolia.* Paclitaxel showed antitumour activity through a previously undescribed mechanism (stabilization of microtubules), and is now approved for clinical use for the treatment of lung, breast, and ovary cancer, as well as for Kaposi's sarcoma.

The selection of the starting materials may be done by collecting knowledge about the use of plants and the other natural products as herbal medicines, and thereby getting an idea of their potential biological activities. Ethnobotany, the study of the use of plants in the society, and particularly, ethnopharmacology, an area inside ethnobotany, focused on medicinal use of plants. Artemisinin, an antimalarial agent, from sweetworm tree, *Artemisia annua,* used in Chinese medicine since 200 BC, is one of the drugs used as a part of combination therapy for multiresistant, *Plasmodium falciparum.*

Structural Elucidation

The elucidation of the chemical structure is critical to avoid double hits (i.e. the identification of a chemical agents that are already known for its structure and chemical activity), and for a long time remained as the most time-consuming step in the natural product drug discovery process. Mass spectrometry (MS) is a method in which individual compounds are identified based on their mass/charge ratio, after ionization and it has contributed to the enhanced ease of structure determination. Chemical compounds exist in nature as mixtures, therefore, the combination of liquid chromatography and mass spectrometry (LC-MS) is often used to separate the individual chemicals. Mass spectral databases for known compounds are available. Apart from MS, nuclear magnetic resonance (NMR)

spectroscopy is another important technique for determining chemical structures of natural products. NMR yields information about individual hydrogen and carbon atoms in the structure, allowing detailed reconstruction of the molecule's architecture.

DRUG DESIGNING

It is an approach of finding drugs by designing, based on their biological targets. Typically, a drug target is a key molecule that is involved in a particular metabolic or signalling pathway that is specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen. Some approaches attempt to inhibit the functioning of the pathway in the diseased state by causing a key molecule to stop functioning. Drugs may be so designed that they bind to the active region and inhibit this key molecule. However, these drugs would also have to be designed in such a way as not to affect any other important molecules that may be similar in appearance to the key molecules. Sequence homologies are often used to identify such risks. Other approaches may be to enhance the normal pathway by promoting specific molecules, which are affected in the diseased state.

Using computational tools the structure of the drug molecule that can specifically interacted with the biomolecules can be modelled. These tools can allow a drug molecule to be constructed within the bio-molecule, using the knowledge of its structure and the nature of its active site. Depending on whether the core or the R-groups are chosen first, construction of the drug molecule can be made inside or outside. However, many of these approaches are plagued by the practical problems of chemical synthesis. Newer approaches have also suggested the use of drug molecules that are large and proteinaceous in nature, rather than small molecules. There have also been suggestions to make these using messenger ribonucleic acid (mRNA). Gene silencing may also have therapeutical applications.

Rational Drug Design

Rational drug design begins with a knowledge of the specific chemical responses in the body or the target organism, and tailoring the combinations to fit a treatment profile in contrast to the historical method of drug discovery, by trial-and-error testing of chemical substances on cultured cells or animals and matching the apparent effects to treatments, In drug metabolism, knowledge of the stability and the reactivity of libraries of potential drug compounds, the predicted metabolic and toxicological outcomes, and rational redesign of possible drug candidates is essential. Due to the complexity of the drug design process, two terms of interest are still serendipity and bounded rationality. These challenges are caused by the large chemical space describing potential new drugs without side effects.

Typical example of rational drug design involves the use of three-dimensional information about biomolecules obtained from such techniques as X-ray crystallography and NMR spectroscopy. This approach to drug discovery is called structure-based drug design. The first example of the application of structure-based drug design leading to an approved drug is the carbonic anhydrase inhibitor dorzolamide, which was approved in 1995.

Another important candidate discovered in rational drug design is a tyrosine kinase inhibitor imatinib, designed specifically for the BCR-ABL fusion protein that is characteristic for Philadelphia chromosome-positive leukaemias (chronic myelogenous leukaemia and, occasionally, acute lymphocytic leukaemia). Imatinib is substantially different from the earlier drugs for cancer, as most of the agents of chemotherapy simply target on the rapidly dividing cells not differentiating between cancer cells and other tissues.

The activity of a drug at its binding site is only one part of its design. Another part to be taken into account is the molecule's drug likeness, which summarizes the necessary physical properties for effective absorption. One way of estimating drug likeness is by Lipinski's rule of five.

Computer-assisted Drug Design

Computational chemistry is used to discover, enhance, and study drugs and related biologically active molecules in computer-assisted drug design. Methods used typically include molecular modelling and simple methods from machine learning and statistics. In QSAR of candidate drugs regression is heavily used. Molecular mechanics, molecular dynamics, semiempirical quantum chemistry methods, ab initio quantum chemistry methods, and density functional theory are also used. The purpose is to reduce the cost and time necessary for the development of a new drug.

SECTION I

Physicochemical Factors in Relation to Biological Activity of Drugs

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CHAPTER 1

Physicochemical Properties

INTRODUCTION

The biological activity of a targeted drug molecule is solely dependent on its physicochemical characteristics, essentially the nature and type of functional moieties, and the spatial arrangement of such groups in the molecule. Modulating the structure of a drug implies introduction, elimination, or substitution of certain groups in the drug. This may lead to the development of a parallel drug with the characteristics similar to the lead compound. Hence, the activity is maintained, although the structure is changed. This can be expressed by an idea of bioisosteric groups that generally have similar biological activity. Physicochemical properties play an important role in modifying the biological activities of many compounds. Thus, pharmacological or therapeutic effects of a drug also relate to its biodistribution or physicochemical parameters of a drug such as:

- Hydrogen bonding
- Chelation
- Oxidation–reduction potential
- Dissociation constant
- Bioisosterism
- Surface activity

The physicochemical parameters that affect the biological activity can be divided into three main groups, as listed below.

1. Parameters that are an expression of the hydrophobic aggregation forces at the site of action. These parameters contribute relatively large to binding energy. Examples for these parameters are listed below.
   - Partition coefficient
   - Rf value
   - Surface activity
   - Partial vapour pressure of a solution
2. Parameters that are an expression of the charge distribution in the molecule and the electrostatic forces at the site of action. They are relatively large or contribute more to drug–receptor interaction. The examples for these parameters are enumerated below.
   - Acid–base dissociation constant (pK_a)
   - Dipole moment

- Redox potential
- Electronic potential
- Resonance effect for conjugated system
- Hydrogen bonding

3. Parameters that are an expression of spatial arrangement of the molecule, which includes the ones listed below.
   - Spatial arrangement of various groups in molecule
   - Steric hindrance

Medicinal chemistry undoubtedly rests its main focus on the broad-based variations embracing the influence of numerous possible manipulations with regard to the chemical structure on the biological activity. In light of the above statement of facts supported by copious volumes of scientific evidence reported in many of the literatures, it is important and necessary for the medicinal chemist to decipher and logically understand not only the 'mechanism of drug action' *in vivo* by which a drug substance exerts its effect, but also the overall physicochemical properties of the molecule. In a rather most recent conceptualized theoretical basis, the terminology *physicochemical characteristics* invariably refers to the cognizable influence of the plethora of organic functional moieties strategically positioned within a drug substance. It is, however, pertinent to mention here that most of the aforesaid properties covertly and overtly exert a significant influence on the various biological phenomena *in vivo*, such as absorption, distribution, metabolism, and excretion of newer targeted drug molecules.

Therefore, a creative medicinal chemist should ponder over the intricacies, complexities, and legitimate presence of each functional moiety to the overall physical and chemical properties of the targeted drug molecule with a view to arrive at or design safer, better, and efficacious medicinal agents. Nevertheless, such critical studies have to be carried out in a rather methodical and systematic manner vis-à-vis their effects on biological activities.

CHAPTER 2

Ferguson Principle

INTRODUCTION

The observation that many compounds containing diverse chemical groups exhibit narcotic or anaesthetic action is indicative of the fact that mainly physical rather than chemical properties are involved. The fact that narcotic action is attained rapidly and remains at the same level as long as reservoir or critical concentration of the drug is maintained but quickly disappears when the supply of drug is removed suggests that equilibrium exists between the external phase and the biophase.

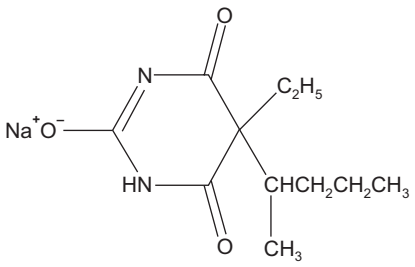
According to Ferguson, it is unnecessary neither to define the nature of the biophase or the receptor nor to measure the concentration of the drug at this site. If equilibrium conditions exist between the drug in molecular biophase and in extracellular fluids, the tendency to escape from each phase is the same, even though the concentrations in the two phases are different. This tendency is called *thermodynamic activity*. It is approximately equivalent to the degree of saturation of each phase. Since the thermodynamic activity is the same in both the biophase and the extracellular phase, measurements made in the extracellular phase, which is measurable, may be directly equated with biophase, which is not possible to be measured.

Pharmacologically active drugs are classified into two main categories (Table 2.1):

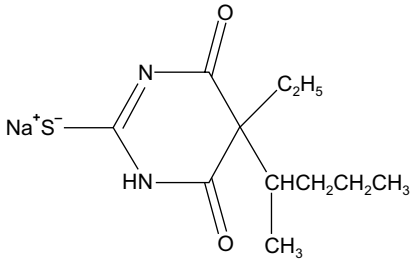
1. Structurally specific drugs
2. Structurally non-specific drugs

Structurally specific drugs: These drugs produce their effect by binding with specific receptors. The physical property of the drug plays an important role on its biological activity, yet the chemical properties do exert their influence on the activity.

Example 1: Pentobarbitone sodium (short-acting hypnotic drug; duration of action less than 3 hrs)



Example 2: Thiopental sodium (ultra short-acting hypnotic drug; duration of action 15 min)



Structurally non-specific drugs: They do not interact with receptors but penetrate to the cell or accumulate in cell membranes where they interfere, e.g. hypnotics, volatile insecticides, bactericidal agents, etc.

The thermodynamic activity of non-volatile drugs may be calculated from the expression S/S_o, where S = molar concentration of the drug and S_o = solubility of the drug.

In the case of volatile drugs, their thermodynamic activity is calculated by using the formula p_t/p_s, where p_t = Partial pressure of the substance in solution.

$p_t = 760 \times (C/100)$

p_s = Saturated vapour pressure

C = Concentration

For example,

Saturated vapour pressure of $CHCl_3$ (p_s) = 324

Narcotic concentration, $C = 0.5$

Partial pressure of $CHCl_3$ (p_t) $= 760 \times (C/100)$

$= 760 \times (0.5/100)$

$= 760 \times 0.005$

$= 3.8 \approx 4$

Approximate thermodynamic activity $= p_t/p_s$

$= 4/324$

$= 0.01$

Table 2.1: Differences between structurally non-specific drugs and structurally specific drugs

S. No.	*Structurally non-specific drugs*	*Structurally specific drugs*
1.	Their biological action is directly related to the thermodynamic activity	Their biological action does not depend on the thermodynamic activity
2.	Thermodynamic activity value varies from 0.01 to 1	Thermodynamic activity value is below 0.01
3.	High doses are needed for biological activities	They are effective in low concentrations
4.	Chemical structures are different, but they produce similar biological responses	They have some structural characteristics in common to produce the biological responses
5.	Slight modifications in their chemical structure do not result in pronounced changes in biological action	Slight modifications in their chemical structures may result in substantial changes in biological activity

The isoanaesthetic concentrations of gases and vapours are given in Table 2.2.

Table 2.2: Isoanaesthetic concentrations of gases and vapours in man at 37°C

Substance	*Vapour pressure, P (mm Hg)*	*Anaesthetic concentration (C)*	*Partial pressure at anaesthetic concentration, p_t 760 × (C/100)*	*Approximate thermodynamic activity (p_t/ p)*
Nitrous oxide	59,300	100	760	0.01
Ethylene	49,500	80	610	0.01
Acetylene	51,700	65	495	0.01
Ethyl chloride	1780	5	38	0.02
Ethyl ether	830	5	38	0.05
Vinyl ether	760	4	30	0.04
Ethyl bromide	725	1.9	14	0.02
1,2-Dichloroethylene	450	0.95	7	0.02
Chloroform	324	0.5	4	0.01

These findings coined the Ferguson's principle, which states that 'substances that are present at the same proportional saturation in a given medium have the same degree of biological action'.

CHAPTER 3

Hydrogen Bonding

INTRODUCTION

Hydrogen bond (H-bond) is a bond in which a hydrogen atom serves to hold two other atoms together. The H-bond usually is formed only between hydrogen and electronegative atoms. In addition, the atoms capable of forming H-bonds have at least one unshared pair of electrons.The most common atoms capable of forming H-bonds are F, O, and N, and to a lesser extent Cl and S.

The compounds that are capable of forming H-bonds are only soluble in water. Proteins are held in a specific configuration by H-bonds, and denaturations of proteins involve the treating of some bonds.

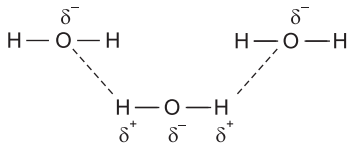
CLASSIFICATION

Generally, hydrogen bonding is classified into two types:

1. Intermolecular hydrogen bonding
2. Intramolecular hydrogen bonding

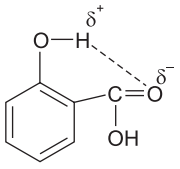
Intermolecular Hydrogen Bonding

Hydrogen bonding occurs between two or more molecules.

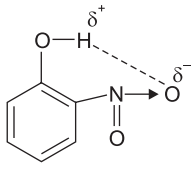


Intramolecular Hydrogen Bonding

Hydrogen bonding occurs within the molecules.



Salicylic acid



o-Nitrophenol

Table 3.1: H-bond and its bond strength

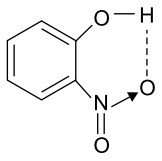
H-bond	*Bond strength (kcal/mol)*
F–H.....F	7
O–H.....O	4.5–7.6
O–H.....N	4–7
C–H.....pi electrons	2–4
C–H.....O	2–3
N–H.....O	2–3
N–H.....N	1.3

There is also some evidence that the hydrogen attached to a triple-bonded carbon (e.g. HCN and $CHCl_3$) forms a H-bond. The strength of H-bonds ranges from 1 to 10 kcal/mol, and usually is about 5 kcal/mol. The distance between the electronegative elements in a H-bond is usually in the range of 2.5–2.7 Å. At distance greater than 3 Å, there is very little interaction (Table 3.1). The stability of H-bonds falls roughly in the order: OHO > OHN >NHN.

H-bonds may occur between molecules (intermolecular H-bond), within one molecule (intramolecular H-bond), or as a combination of these two. Intermolecular bonds are frequently much weaker than the intramolecular bonds. Multiple hydrogen bonding groups in any drug molecule would greatly increase its potential for aqueous solubility. Minimal aqueous solubility is essential for all the drug molecules to transport to the site of action on a receptor.

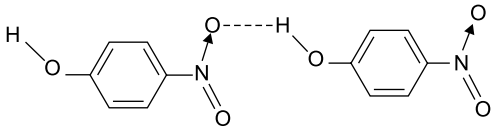
Generally, the more H-bonds that are possible, the greater the water solubility of the molecule. The strength of the H-bond depends on the solvent as well as on the physical state. For example, the H-bond strength of O–H ····· O for CH_3COOH dimer in vapour state is 7.64 kcal/mol, but CH_3COOH dimer in benzene is 4.85 kcal/mol. In water, the H-bond strength is 4.5 kcal/mol; in ice, the bond strength is 6 kcal/mol.

Intramolecular hydrogen bonding



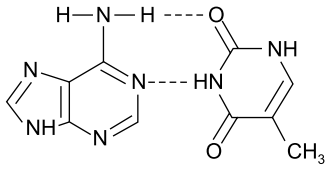
o-Nitrophenol

Intermolecular hydrogen bonding

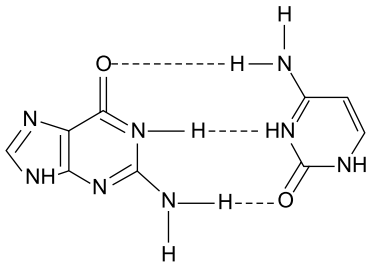


p-Nitrophenol

The description of the drug receptor interaction based on hydrogen bonds is closely related to the importance of these bonds in maintaining the integrity of biological systems and in determining the physicochemical properties of drug molecules. The physical states of substances, such as water, DNA, protein, and various drug molecules, are maintained by hydrogen bonding. The most frequently observed H-bonds in biological systems are between the hydroxyl (OH) and amino (NH) groups. In the DNA helix, hydrogen bonding links the complementary base pairs of adenine–thymine and guanine–cytosine.



Adenine-thymine



Guanine-cytosine

Since the physical and chemical properties of a compound may be greatly altered by hydrogen bonding, it is reasonable to expect that it may also have a significant effect and some correlation with biological properties. In a number of cases, such a correlation is present (Tables 3.2 and 3.3).

Table 3.2: Differences between 1-phenyl-3-methyl-5-pyrazolone and 1-phenyl-2,3-dimethyl-5-pyrazolone (antipyrine)

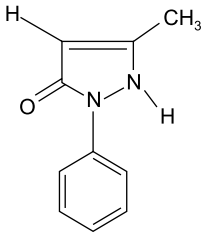
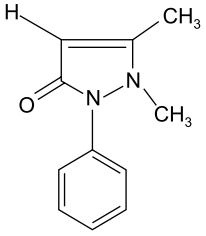
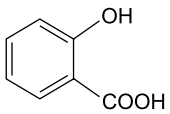
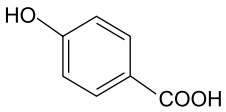
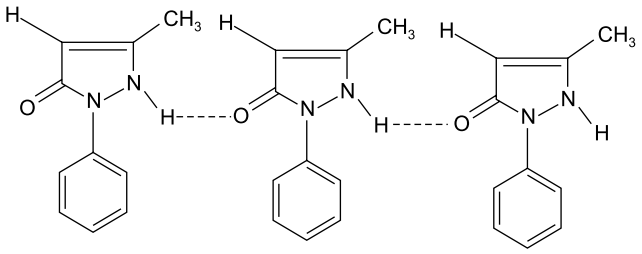
1-Phenyl-3-methyl-5-pyrazolone	***1-Phenyl-2,3-dimethyl-5-pyrazolone (antipyrine)***
	
No analgesic property Melting point 127°C, Insoluble in water Slightly soluble in ether Forms intermolecular hydrogen bonding	Good analgesic agent Melting point 112°C Soluble in water Moderately soluble in ether Does not form intermolecular hydrogen bonding

Table 3.3: Differences between *o*-hydroxybenzoic acid and *p*-hydroxybenzoic acid

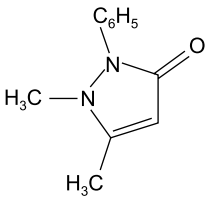
o-Hydroxybenzoic acid (salicylic acid)	***p-Hydroxybenzoic acid***
	
pK_a 3.0 Less soluble in water Low-melting point Good antibacterial action Forms intramolecular hydrogen bonding	pK_a 4.5 More soluble in water High melting point Low antibacterial action Forms intermolecular hydrogen bonding

1-Phenyl-3-methyl-5-pyrazolone forms intermolecular hydrogen bonding.

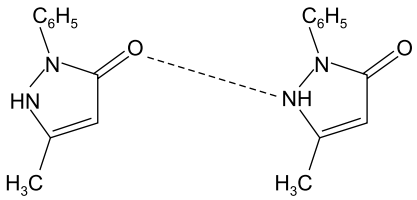


The alkylating agents (nitrogen mustards) are thought to act by replacing the weak and reversible H-bonds between adjacent nucleic acid strands with strong and relatively irreversible covalent bonds. In this way, nucleic acid regeneration and cell division in the rapidly proliferating cancer cells may be inhibited.

Antipyrine, 1-phenyl-2,3-dimethyl-5-pyrazolone has analgesic activity, but 1-phenyl-3-methyl-5-pyrazolone is inactive. This is due to the formation of hydrogen bonding in the 1-phenyl-3-methyl-5-pyrazolone and gives rise to a linear polymer, which cannot pass through biomembranes.



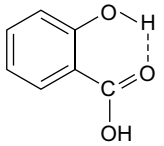
Antipyrine



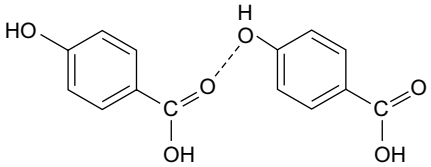
1-Phenyl-3-methyl-5-pyrazolone

Salicylic acid (*o*-hydroxy benzoic acid) has antibacterial activity, but not the *p*-isomer and *m*-isomer; that is, *p*- and *m*-hydroxy benzoic acids are inactive. This is because salicylic acid forms intramolecular hydrogen bonding; therefore, it is less water-soluble and its partition coefficient is also greater.

The *m*- and *p*-isomers can form intermolecular H-bonds, result in dimer, and do not easily pass through the biomembranes. Their partition coefficient is also less, and hence, low antibacterial action.



Salicylic acid
(intramolecular hydrogen bonding)



Dimer of *p*-hydroxy benzoic acid
(intermolecular hydrogen bonding)

CHAPTER 4

Ionization and pK_a Value

INTRODUCTION

If the biological activity of a drug results from ions, the activity intensifies with increase in the degree of ionization. However, if the activity results from undissociated molecules, increase in the degree of ionization of active compounds causes a decrease in activity.

Increase in ionization intensifies a drug's water solubility and decreases its liposolubility or lipophilicity. In general, drugs cross cellular membranes in undissociated forms, as intact molecules, and act in dissociated forms, as ions. This happens because the passage of ions across the cellular membrane is prevented by two factors.

1. The cellular membrane is made up of layers of electrically charged macromolecules (lipids, proteins, and mucopolysaccharides) that attract or repel ions.
2. Hydration of ions increases their volumes rendering their diffusion through pores difficult.

Weakly acidic drugs are predominantly of the unionized form at lower pH of the gastric fluid, and absorbed from the stomach as well as intestine. Some very weak acidic drugs, such as phenytoin and many barbiturates, whose p$K_a$values are greater than 7, are essentially unionized at all pH values. Therefore, for these weak acidic drugs transport is more rapid and independent of pH.

Most weak bases are poorly absorbed in the stomach since they are present largely in the ionized form at low pH. Strong bases, those with pK_a values between 5 and 11, show pH-dependent absorption. Stronger bases, such as guanithidine (pK_a >11), are ionized throughout the gastrointestinal tract and tend to be poorly absorbed.

The compounding or the formulation, pharmacist can adjust the pH to ensure water solubility or maximum solubility in non-polar media. So the understanding of acid–base chemistry becomes important.

Note the following reactions:

HA	+	H_2O	↔	H_3O^+	+	A^- (ionized)
Acid (unionized)		Base	↔	Conjugated acid		Conjugated base
BH^+	+	H_2O	↔	H_3O^+	+	B (unionized)
Acid (ionized)		Base	↔	Conjugated acid		Conjugated base

Acids can be divided into two types: HA and BH^+. HA acids go from unionized (non-polar) acids to ionized conjugated bases, while BH^+ acids go from ionized (polar) acids to unionized (non-polar) conjugated bases.

Pharmaceutically, important HA acids are listed below:

- Inorganic acids: HCl, H_2SO_4
- Carboxylic acids: Salicylic acid, arylanthranilic acid of low molecular weight
- Amides: Sulfonamides
- Imides: Saccharin
- Enols: Hydantoins, barbiturates

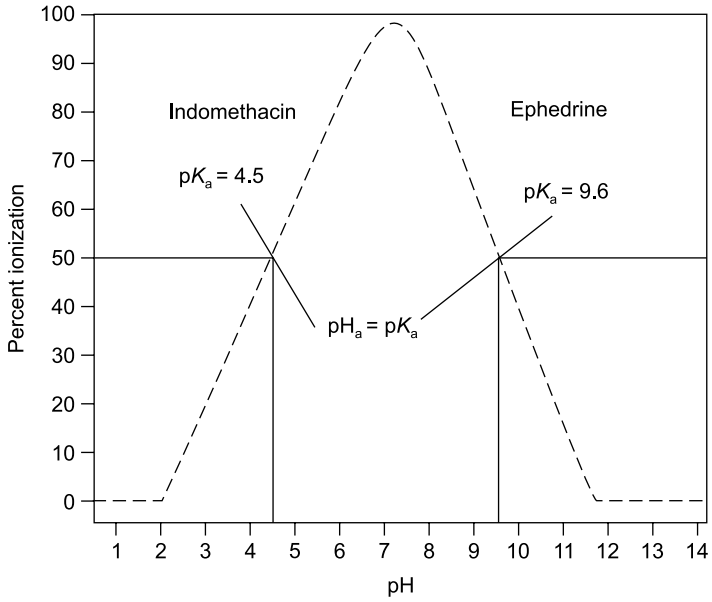


Figure 4.1: Percent ionized versus pH for indomethacin (pK_a 4.5) and ephedrine (pK_a 9.6).

Relationship between Percent Ionization and pH

A plot of percent ionization versus pH shows how the degree of ionization can be influenced by small changes in the pH. For example, the curves for an HA acid (indomethacin) and BH^+ (protonated ephedrine) are shown in Figure 4.1.

When the pK_a= pH, the molar concentration of the acid equals the molar concentration of its conjugated base.

In Henderson–Hasselbalch equation,

$$pK_a = pH\ [(\text{Conc. base})/(\text{Conc. acid})] = 1$$

An increase in 1.0 pH value causes a 90.9 percent ionization of indomethacin, but in ephedrine (HCl) the percent ionization is only about 9.1 percent.

A pH increase of 2 units shifts the HA indomethacin to 99 percent ionization (complete), but BH^+ acid (ephedrine) to non-conjugated form (0.99%).

Therefore, whenever the non-polar form of an acid or a base is used, the rate of percent ionization will be maintained. This ratio depends on the pK_a and pH of the medium.

pK_a VALUE

The partially lipidic nature of cellular membranes, such as the ones that enwrap the stomach, small intestine, mucosa, and nervous tissue, facilitate the passage of drugs with high liposolubiltiy across them. The liposolubility is affected by pH of the environmental medium and by the degree of dissociation pK_a. Usually, drugs are weak acids or weak bases. The degree of dissociation, pK_a, is calculated from the following Henderson–Hasselbalch equation.

In the case of acid,

$$pH = pK_a + \log \frac{\text{Ionized drug concentration}}{\text{Unionized drug concentration}}$$

$$\text{Percentrage of drug ionized} = \frac{10^{pH - pK_a}}{1+10^{pH - pK_a}} \times 100$$

In the case of unionized acid,

$$pH = pK_a + \log \frac{\text{Unionized drug concentration}}{\text{Ionized drug concentration}}$$

$$\text{Percentrage of drug ionized} = \frac{10^{pK_a - pH}}{1+10^{pK_a - pH}} \times 100$$

The biological activity of certain acids and bases is directly related to their degree of ionization. While some (e.g. phenols, carboxylic acids) act in the molecular form, others (quaternary ammonium salts) act in an ionized form. In these cases, the pH plays an important role. For example, acids are more active at lower pH and bases are more active at higher pH.

- Strong acid has low pK_a value.
- Weak acid has high pK_a value.
- Strong base has high pK_a value.
- Weak base has low pK_a value.

Drug Exerting Action as Undissociated Molecules

In a large number of potent medical compounds, the dissociation plays a vital role for their respective biological characteristics. The unusual structural grouping in the tetracycline results in three distinct acidity constants in aqueous solutions of the acid salts. The particular functional groups responsible for each of the thermodynamic pK_avalue have been determined by Lessen *et al.*, as described in Figure 4.2.

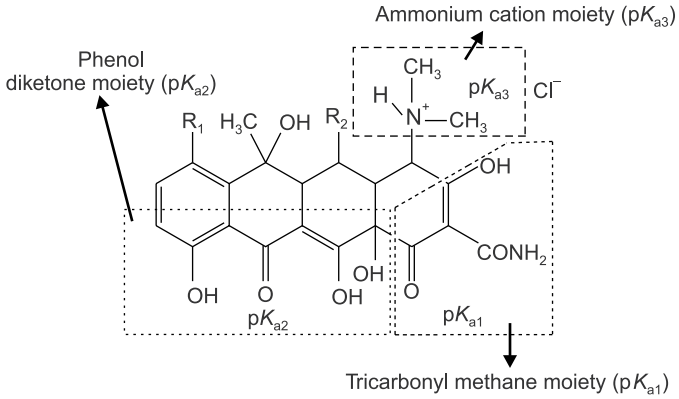


Figure 4.2: Functional groups responsible for each of the thermodynamic pK_a value.

Table 4.1: pK_a values of tetracyclines

S. No.	Name	pK_{a1}	pK_{a2}	pK_{a3}
1.	Tetracycline	3.3	7.7	9.5
2.	Chlorotetracycline	3.3	7.4	9.3
3.	Demeclocycline	3.3	7.2	9.3
4.	Oxytetracycline	3.3	7.3	9.1

The approximate pK_a values for each of these groups in the four commonly used tetracyclines are shown in Table 4.1.

Besides the activities of several local anaesthetics, *d*-tubocurarine and phenol have also been proved to be related to their degree of ionization.

Drug Exerting Action as Ionized Molecules

A plethora of medicinal compounds exerts their pharmacodynamic action exclusively as the ionized molecules, namely acetylcholine, quaternary salts as ganglionic blocking agents, muscle relaxants, and antiseptics.

CHAPTER 5

Redox Potential

INTRODUCTION

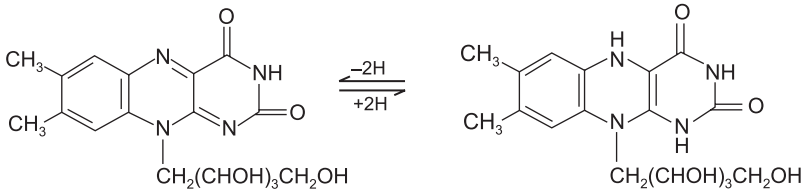
Redox potential may be defined as a quantitative expression of the tendency of a compound that has to give or receive electrons. It may be compared with an acid–base reaction. In the case of acid–base reaction, there is transfer of a proton from an atom in one molecule to the atom in another molecule, while in the case of oxidation–reduction reaction, there is an electron transfer. Since living organisms function at an optimum redox potential range, which varies with the organism, it might be assumed that the redox potential of the compounds of a certain type would correlate with the observed biological effect. This correlation is applicable for all compounds of similar structure and physical properties.

The redox potential of a system may be calculated from the following equation: $E_h = E_1^0 - 0.06/n$ (concentration of reductant/concentration of oxidant), where

E_h = Redox potential of the system being studied
E_1^0 = Standard potential at given pH
n = Number of electrons transferred

However, there are a number of reasons why only a few satisfactory correlations have been observed:

- The redox potential applies to a single reversible ionic equilibrium, which does not exist in a living system.
- A living cell carries on many reactions simultaneously involving oxidation of ionic and non-ionic character, some of which are reversible and others are irreversible.
- The access of a drug to the sites of oxidation–reduction reactions in the intact animal is hindered by the complex competing events occur during absorption, distribution, metabolism, and excretion.

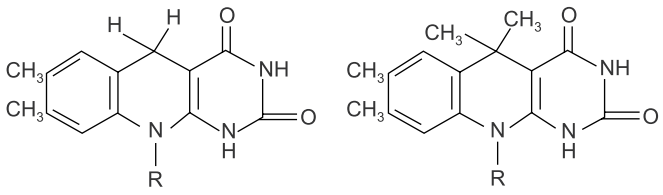


Riboflavin (**I**) Dihydroriboflavin (**II**)

- Therefore, it is to be expected that correlations between redox potential and biological activity, generally, hold only for compounds of very similar structure and physical properties. In such series, variations in the route of distribution and in steric factors, which might modify the redox system interaction, would be minimized.

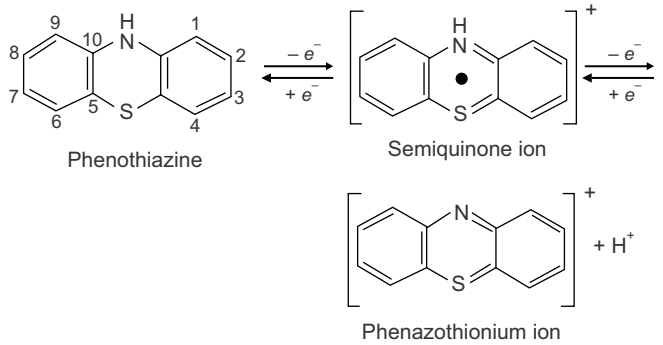
When riboflavin (I) accepts electrons, it is converted into its dihydro (II) form. This reaction has a redox potential E_0 = –0.185 volt. Kuhn (1943) prepared the analogue in which the two methyl groups of riboflavin were replaced by chlorine. The resulting compound had a potential of E_0 = –0.095 volt, and its antagonistic properties were suggested as being due to the dichloro-dihydro form being a weaker reducing agent than the dihydro form of riboflavin. It may be absorbed at the specific receptor site, but may not have a negative potential to carry out the biological reductions of riboflavin.

Reist *et al.* (1960) prepared the non-redox analogues of riboflavin as potential anticancer agents. Replacement of the N_5-nitrogen of dihydroriboflavin (1,5-dihydro-7,8-dimethyl-10-ribitylisoalloxazine) by a methylene group (III) would be expected to have a profound effect on the redox potential as compared to riboflavin. Similarly, replacement of the N_5-nitrogen of dihydroriboflavin by an isopropylidene group (IV) fixes the molecule in the dihydro form, thus eliminating the redox system completely.



Although compound IV is derived from dihydroriboflavin (II) rather than from riboflavin, the redox enzyme system employing riboflavin coenzymes utilizes both the oxidized and reduced forms; thus, analogues of either I or II should be effective antagonists.

Craig *et al.* (1960) studied a series of substituted phenothiazine with regard to potentiometric titration, electrode potentials, and their correlation with anthelmintic activity. They measured them in the biological assay using mixed infestation of *Syphacia obvelata* and *Aspicularis tetraptera* in mice. From these studies, it appeared that two factors were necessary for their activity, namely, the ability to form a high proportion of a stable semiquinone radical (as measured by the index potential in aqueous CH_3COOH) and the presence of free 3 or 7 position.



In addition to the two factors mentioned above, Craig *et al.* (1960) also noted that only these compounds with electrode potential in the range of 550–850 mV in aqueous CH_3COOH had significant activity. If the toxic or paralyzing effect of the phenothiazines was due to an inhibition by the semiquinone of the oxidation–reduction system in the parasite, it would seem reasonable that active phenothiazines would

have reduction potentials corresponding to those of oxidation–reduction enzyme system or the system which they inhibit. At similar potentials, the semiquinone concentration would be maximal, and thus facilitates or competes with the electron transfers in the enzyme system involved.

For example, it has been suggested that the semiquinone of chlorpromazine is responsible for the inhibition of certain oxidoreductase *in vitro* and some of the biological activities of phenothiazines correlate with the formation of their semiquinones *in vivo*.

CHAPTER 6

Surface Tension

INTRODUCTION

A surfactant is defined as a material that can reduce the surface tension of water at lower concentrations. This molecule is made up of water-soluble and water-insoluble components. Surface agent may enhance or retard the drug absorption, which depends upon the chemical nature of surfactant, its concentration, its effect on biological membrane, and micelle formation.

At lower concentrations, the surfactant enhances the absorption rate; the same in higher concentrations reduces the absorption rate. In lower concentrations, they reduce the surface tension and bring about better absorption through better contact of the molecules with absorbing membrane, but when the concentration crosses the critical micelle concentration, the surfactant aligns them at the surface so that the hydrophilic end is towards the water and hydrophobic end is squeezed away from the water. These molecular aggregates are called *micelle*, which entrap the drug molecule in their hydrophobic core, and result in the retardation of the rate of absorption (Figure 6.1).

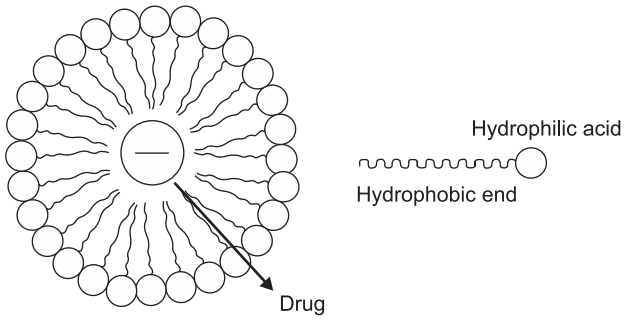


Figure 6.1: Micelle formation

The orientation of surface-active molecules at the surface of water or at the interface of polar and non-polar liquids takes place with the non-polar (hydrocarbon) portion of the molecule oriented towards the non-polar liquid or vapour phase and polar groups (e.g. –COOH, –OH, $–NH_2$, $–NO_2$, etc.) towards the polar liquid. Three forces are involved in the orientations of this type, namely, Van der Waals forces, hydrogen bonds, and ion dipoles.

A surfactant molecule exhibits two distinct regions of lipophilic and hydrophilic character, and such compounds are commonly categorized as *amphiphilic* or as *amphiphils*. Molecules of this type may

vary markedly from predominantly hydrophilic to predominantly lipophilic, depending on the relative ratio of polar to non-polar groups present.

CLASSIFICATION

Surface-active agents are classified as follows:

- Anionic surfactants: Ordinary soaps, salts of bile acids, salts of the sulphate or phosphate esters of alcohols, salts of sulphonic acids
- Cationic surfactants: High molecular weight aliphatic amines, quaternary ammonium derivatives
- Non-ionic surfactants: Polyethylene ethers, glycol esters of fatty acids
- Amphoteric surfactants

Applications

The bactericidal activity of cationic quaternary ammonium compounds, such as benzalkonium chloride, cetrimide, cetyl pyridinium chloride, etc., is explained through their surface-active property. Many compounds such as detergents, disinfectants, and antibiotics act through the surface phenomenon.

The anthelmintic activity of hexylresorcinols is reported to be increased by low concentrations of soap and decreased by high concentrations of soap. If the soap concentration is kept below critical micelle concentration (CMC), a 1:1 association of phenol and soap occurs, which facilitate the penetration of phenol through the surface of the worm. If the CMC is exceeded, the micelle competes favourably with the worms for phenol, and there is decreased activity.

Compounds showing pronounced surface activity usually are unsuited for use in the animal body. Such compounds are lost through their adsorption by proteins, and they also have an undesirable feature of disorganizing the cell membrane and producing haemolysis of red blood cells. In general, highly surface-active agents are not used internally, but only topically, as skin disinfectants or sterilizers for sterilization of instruments. This is the case for ionic surfactants. Non-ionic surfactants are largely employed in pharmaceutical preparations for oral (sometimes even parenteral) use as solubilizing agents of water-insoluble or slightly soluble drugs.

Surface-active agents can be expected to have a pronounced effect on the permeability of a cell. Mildly surface-active agents may be adsorbed by cell membranes, and thereby interfere with the absorption of other compounds through this membrane or may alter membrane structure and function. Many central nervous system depressant drugs, such as sedative–hypnotic, anticonvulsant, and central relaxant agents possess the general structure of non-ionic surface-active compounds.

The most commonly used surfactants are anionic and non-ionic surfactants. Since the process of solubilization occurs due to the presence of micelles, generally, high concentrations of surfactants are needed to improve drug solubility significantly. One example of a surfactant-based solution is Taxol (paclitaxel, Sigma- Aldrich, USA), an anticancer drug that is solubilized in 50% solution of Cremophor. Other examples include Valrubicin in 50% Cremophor and Cyclosporin in 65% Cremophor.

Surfactant preparations are used as replacement therapy for the treatment of premature infants suffering from neonatal respiratory distress syndrome (also known as hyaline membrane disease). A substantial deficiency in the endogenous lung surfactant is the principal factor contributing to the pathology of respiratory distress syndrome. The lung surfactant preparations are used in combination with supplemental oxygen and mechanical ventilation to facilitate gas exchange. The exogenous surfactants are either derived from animals or synthesized, for example Beractant (modified bovine extract), Calfactant (extracted from the lungs of calves), and Poractant alfa (extract of porcine lung).

CHAPTER 7

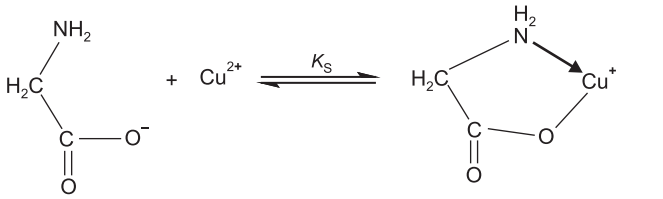
Complexation

INTRODUCTION

Complexes or coordination results from a donor–acceptor mechanism (donating/accepting electron or rather an electron pair) or Lewis acid–base reaction (donating accepting protons). Since complex drugs cannot cross the natural membranous barriers, they reduce the rate of absorption of the drug. The compounds that are obtained by donating electrons to metal ions with the formation of ring structures are called chelates. The compounds that are capable of forming a ring structure with metal atoms are termed as ligands.

Both biological molecules and medicinal agents may develop chelate structures by forming a ring structure with a metal through coordinate bonds (i.e. bonds in which electron pairs are from the same atom).

Example: Glycine forms complex with Cu^{2+}.



Glycine anion Copper Glycine–copper complex

The stability constant (K_S) reflects the strength of the interaction, and larger the constant the greater the stability.

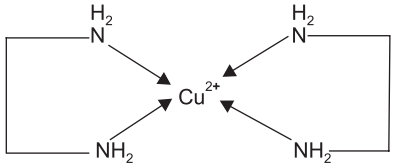
$$K_s = \frac{[\text{Complex}]}{[\text{Glycine}]\,[Cu^{2+}]}$$

Two coordinate covalent bonds are formed between glycine and copper in the complex. The nitrogen and oxygen atoms of glycine serve as the electron-donating groups, each supplying an electron pair, whereas the cupric ion is the electron acceptor.

Electron-donating groups are almost always limited to O, N, and S atoms; electron acceptors include various bivalent and trivalent metals, particularly those of the transition group. Stability of the metal ions in the complex:

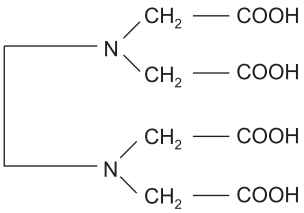
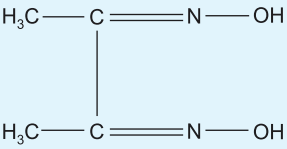
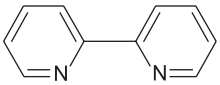
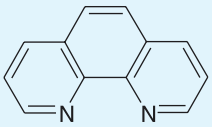
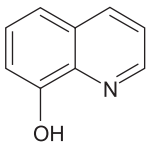
$Fe^{3+}, Hg^{2+} > Cu^{2+}, Al^{3+} > Ni^{2+}, Pb^{2+} > Co^{2+}, Zn^{2+} > Fe^{2+}, Cd^{2+} > Mn^{2+} > Mg^{2+} > Ca^{2+}$

A ligand, such as ammonia, that has a single basic group capable of bonding to the metal ion is a unidentate ligand. A ligand having more than one accessible basic binding site is multidentate, for example ethylenediamine, $NH_2CH_2CH_2NH_2$, is a bidentate ligand form and chelates with Cu(II).



Some important multidentates are listed in Table 7.1.

Table 7.1: Multidentates

Ethylenediamine	$NH_2\ CH_2\ CH_2\ NH_2$
Ethylenediamine tetra acetic acid	
Dimethylglyoxime	
2,2-Bipyridine	
1,10-Phenanthroline	
8-Hydroxyquinoline	

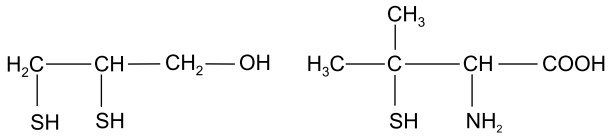
The number of rings formed in the chelate depends on the electron-donating groups. S can form the stable four-member rings, O and N can form five- and six-member rings, but five-member rings are generally more stable. Heavy metals are required for the following enzymes and biomacromolecular components (Table 7.2).

Important metal-binding hormones are thyroxine, insulin, histamine, epinephrine, and norepinephrine. In clinical practice, chelating agents have been used primarily as antidotes in heavy metal poisoning. In principle, any chelating agent with a sufficiently high K_S value *in vitro* could be used as an antidote, but some limitations are there. For example, ethylene diamine tetra acetic acid (EDTA) because of its powerful chelating effect can displace toxic heavy metals, such as lead and mercury from cellular layer, but EDTA is not highly selective in its action; it tightly binds some essential metals, including calcium.

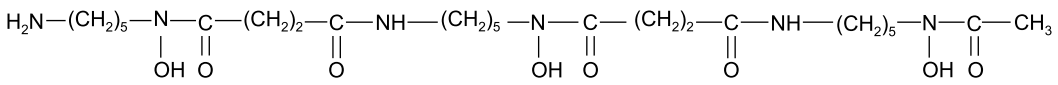
Table 7.2: Metals required for enzymes and biomacromolecular components

S. No.	Metal	Cellular components
1.	Cobalt	Vitamin B_{12}, carboxypeptidase
2.	Copper	Oxidase enzymes
3.	Iron	Porphyrin enzymes, haemoglobulin,iron-storage molecules (ferritin, haemosiderin)
4.	Magnesium	Chlorophyll
5.	Manganese	Chloroplasts
6.	Molybdenum	Xanthine oxidase, aldehyde oxidase
7.	Nickel	Urease
8.	Zinc	Carbonic oxidase, alcohol dehydrogenase

To prevent excessive loss of calcium from the body during EDTA therapy, it is necessary to administer this antidote as disodium calcium salt. Iron deficiency anaemia may be treated using the iron complex of EDTA in place of ferrous sulphate or ferrous gluconate. Pernicious anaemia is treated effectively using Vitamin B_{12}, a naturally occurring cobalt complex. Deferoxamine is a highly selective antidote, which strongly chelates iron in iron poisoning. Dimercaprol (BAL) is used in the treatment of lead poisoning. L-Penicillamine is used in the treatment of copper and Wilson's disease.



Dimercaprol L-Penicillamine



Deferoxamine

Numerous antimicrobial and antineoplastic agents are believed to exert their action by means of complex formations with DNA base pairs. These drug molecules are large planar aromatic compounds, and they can be inserted between the planar base pair assemblies on the DNA double helix. This type of inserted molecular interaction is called *intercalation*. Intercalating drugs include ethidium, quinacrine, proflavin, daunorubicin, adriamycin, and actinomycin D.

Undesirable side effects are caused by drugs that chelate with metals. A side effect of hydralazine, an antihypertensive agent, is the formation of anaemia, and this is due to chelation of the drug with iron. 8-Hydroxy quinoline and its analogues act as antibacterial and antifungal agents by complexing with iron or copper.

CHAPTER 8

Solubility

Solubility is the ability of a substance to dissolve in a solvent. Solubility of a substance in a solvent depends on the nature of the solute and solvent, and the interactions involved. It is expressed by molarity, molality and percentage. In general, polar solvents dissolve polar solutes and non-polar solvents dissolve non-polar solutes, and semipolar solvents act as intermediate. Electrolytes have appreciable solubility and their solubility depends largely on the electrostatic forces of attraction and repulsion.

All biochemical reactions are based on the solubility of a particular drug molecule in an aqueous phase or on macromolecules, in this phase usually body. A highly important physical property of all physiologically and pharmacologically important drug molecules is their solubility in body's aqueous and non-aqueous environment, because the solution form of the drug can interact with cellular and subcellular structures that carry drug receptors, triggering pharmacological reactions. The degree of solubility differs in each compartment.

The proportion of concentrations at equilibrium is called *partition coefficient*. Most of the drugs exhibit solubility to some extent in both water and lipid environments.

Solubility is a function of many molecular parameters, as mentioned below:

- Ionization
- Size and molecular structure
- Stereochemistry
- Electronic structure

All the above parameters are involved in the interaction between the solvent and the solute. For example, H_2O forms hydrogen bonds with ions or non-polar compounds through –OH, –SH, –NH and –C=O groups or with lone pair of electrons of O and N atoms.

The interaction of non-polar drugs with lipids is based on hydrophobic interaction, e.g. the solubility with pharmacological activity.

1. Local anaesthetic activity of *para*-amino benzoic acid (PABA) esters partially depends on their lipid solubility.
2. In the homogeneous series beginning with *n*-butanol and ending with *n*-octanol, the bactericidal activity changes with molecular weight. *n*-Butanol and *n*-pentanol are active against *Staphylococcus aureus*. Higher members of this series fail to kill the bacteria since the necessary concentration cannot be reached due to the lack of solubility in water.

Solubility of Weak Electrolytes

Most of the drugs are either weak acids or weak bases, which are less soluble in water. Their solubility depends on the pH. They are reacted with acids or bases to produce respective salts to make it water soluble. Here, we consider the two factors:

1. Increase the solubility of the weak electrolyte by adjusting the polarity of the solvent.
2. Decrease the dissociation of weak electrolyte (pK_a increases) to decrease the solubility.

The solubility of weakly acidic and basic drugs may be enhanced by micellar solubilization.

The solubility of weakly acidic or weakly basic drugs depends on the pH.

Consider the following equation:

$$NaD \longrightarrow Na^+ + D^-$$

(Salt of weakly acidic drug)

$$D^- + H_2O \rightleftharpoons HD + OH^-$$

NaD is dissolved in water. HD = Conjugate acid

Then,

$$pH_{(p)} = pK_a + \log (C_s - S_o/S_o)$$

where, $pH_{(P)}$ = pH below which precipitation occurs

K_a = Ionization constant for conjugate acid (HD)

C_s = The total amount of drug in solution (ionized + unionized)

S_o = Aqueous solubility of unionized drug (HD)

For weak base

$$pH_{(p)} = pK_a + \log (S_o/C_s - S_o)$$

where pK_a = Ionization constant for conjugate acid

According to *Indian Pharmacopoeia* (IP), the solubility is indicated by the following table:

Descriptive term	***Parts of solvent required for part of solute***
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Insoluble	More than 10,000

Factors Affecting Solubility of Drugs

The factors affecting solubility of drugs are classified as follows:

1. *Solute related (nature of solute)*: Size, shape, melting point, pK_a, etc.
2. *Solvent related (nature of solvent)*: Polarity, pH, etc.
3. *Environmental related*: Temperature and pressure
4. *Formulation related*: Surfactants, common ion effect and other electrolytes effect

Applications of Solubility

1. The solubility of drug in gastrointestinal fluids (dissolution) is important for better absorption of drugs. If the aqueous solubility of drug is more than 1 percent, good absorption of drug will take place.
2. The action of drug also depends on the poor aqueous solubility.
3. The release and absorption of drug from an ointment or intramuscular injection depends on the degree of saturation of the drug in the particular solvent.
4. Solubility of the drug provides information about intermolecular forces of interaction, which is useful for finding out the drug–receptor interaction.
5. Solubility is used for purification purpose of drugs, e.g. extraction and recrystallization.

Drug Solubility and Absorption

An important prerequisite for the absorption of drug by all mechanisms (except endocytosis) is that the drug must be present in aqueous solution.

After oral administration, absorption of the particular drug depends mainly on two factors (Figure 8.1):

1. Drug solubility and rate of dissolution
2. Permeation rate of the drug through membrane

The desired solubility of a particular drug for good oral absorption depends on permeability of the drug, and the required doses are mentioned in Table 8.1.

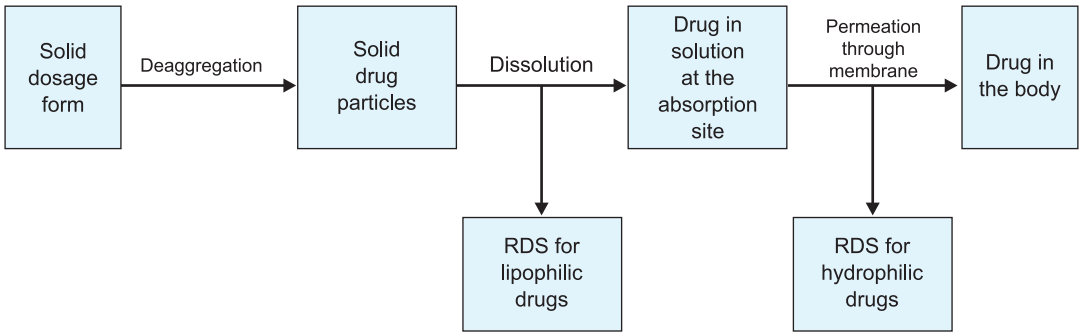


Figure 8.1: Two rate-determining steps (RDSs) in the absorption of drugs from oral administration.

Table 8.1: Desired solubility related to therapeutic doses

Dose (mg/kg)	*Desired solubility values (mg/ml) for drug with*		
	High permeability	*Medium permeability*	*Low permeability*
0.1	1	5	21
1	10	52	207
10	100	520	2100

The maximum absorbable dose (MAD) of a particular drug also depends on its solubility.

$$MAD = K_a S_{GI} V_{GI} t_r$$

where,

K_a = Intrinsic absorption rate constant
S_{GI} = The solubility of the drug in GIT fluid
V_{GI} = The volume of GIT fluid
t_r = Residence time of drug in GIT

From the above equation, the two drugs have same K_a value, but one with greater or higher solubility will have a high MAD value.

Based on the solubility and permeability of drugs, Amidon *et al.* developed biopharmaceutics classification system of drugs, which is shown in Table 8.2.

Table 8.2: Biopharmaceutics classification system for drugs

Class	*Solubility*	*Permeability*	*Absorption*	*Example*	*RDS in absorption*
I	High	High	Well absorbed	Diltiazem	Gastric emptying
II	Low	High	Variable	Nifedipine	Dissolution
III	High	Low	Variable	Insulin	Permeability
IV	Low	Low	Poor absorption	Taxol	Variable by each one (case by case)

Drug Design Related to Solubility and Membrane Permeability

We shall now look how drug design principle can be used to solve some pharmacokinetic problems faced by drugs. In this aspect, first of all we consider about how the solubility and membrane permeation of a drug can be improved. In this respect, the ionization and drug's polarity are two important considerable factors.

Drugs with high polarity do not cross cell membranes and are easily excreted, whereas non-polar drugs are poorly soluble in hydrophilic (aqueous) solution and absorbed by fatty tissues. In common, the polarity and ionization of compounds can be altered by changing the substituents. The following approaches are adopted to perform this operation:

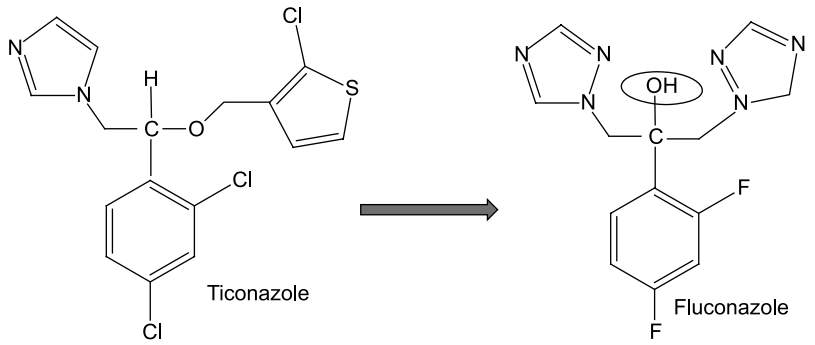
1. Varying polar functional group to alter polarity
2. Variation of N-alkyl substituents to vary pK_a
3. Variation of aromatic substituents to vary pK_a
4. Variation of acyl or alkyl substituents to alter polarity

Let us discuss each of them one by one.

1. Varying polar functional groups to alter polarity

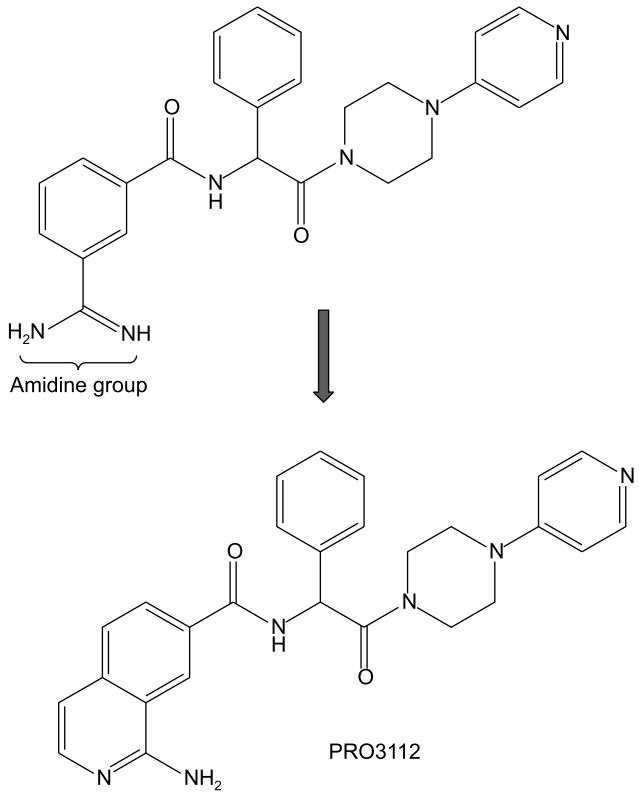
A polar functional group is added to a drug to increase its polarity, e.g. the antifungal agent ticonazole. Ticonazole is used only for skin infection because of its poor solubility in blood and non-polar nature.

The oral activity of the compound is increased by adding one polar hydroxyl group, and polar heterocyclic ring leads to the formation of an antifungal agent, fluconazole, with high solubility and enhanced (improved) activity against systemic infection.



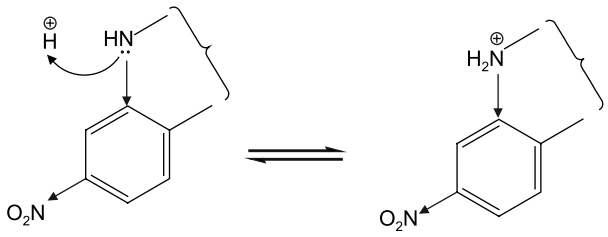
2. Variation of N-alkyl substituents to vary pK_a

Drugs having pK_a more than 6–8 are easily ionized and poorly absorbed through the membranes. However, the pK_a can be altered within the preferred range. For example, the benzamidine structure of the following antithrombic drug is too basic due to the presence of amidine group. The incorporation of isoquinoline ring reduces basicity and increases permeability.



3. Variation of aromatic substituents to vary pK_a

The pK_a value of a carboxylic acid or amine can be altered by adding electron-withdrawing or electron-donating group. For example, the antischistosomiasis drug oxaminaquine pK_a is increased by high electronegative substituent NO_2 group because a strongly electron-deficient aromatic ring pulls the lone pair of electrons present in the nitrogen atom into the ring that reduces its basicity. This, in turn, increases the pK_a, ionization and solubility of the drug totally, which increases the permeation of the drug.

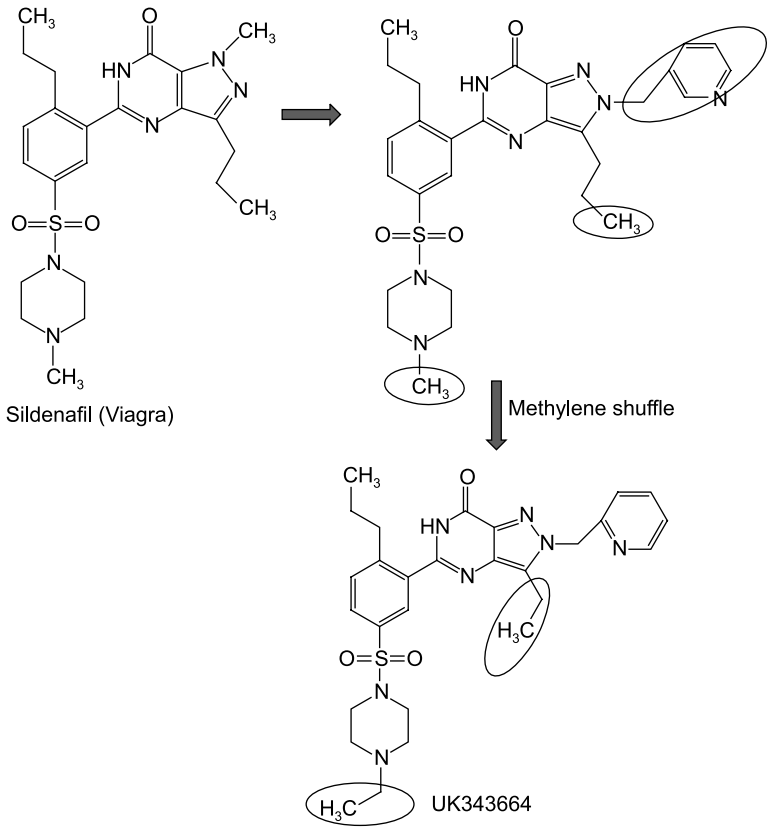


4. Variation of acyl or alkyl substituents to alter polarity

Molecules with high polarity can be converted into those with low polarity using the following ways:

- Protecting or masking a polar functional group with acyl or alkyl group
- Adding an extra large hydrophobic group

Molecules with low polarity can be converted into those with high polarity by using the opposite strategy, i.e. entirely removing the alkyl group or replacing the bulky alkyl group with smaller alkyl groups or increasing the size of another one. This strategy is known as *methylene shuffle*, which is used to increase the hydrophobicity of a compound, e.g. antiimpotence drug sildenafil (Viagra).



In the above compound, methylene shuffle is carried out in a propyl, and a methyl group results in two ethyl groups, which reduces its lipid solubility and increases the *in vivo* activity.

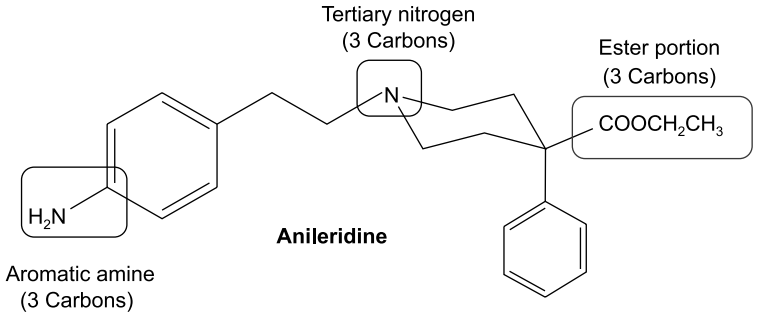
Predicting Water Solubility by Empirical Approach

The water solubility of molecules is based on carbon-solubilizing potential of the organic functional groups (Table 8.3). If the solubilizing potential of the drug or functional group exceeds the total number of carbon atoms present, then the drug is considered water soluble.

Table 8.3: Water solubilizing potential of organic functional groups

Functional group	*Monofunctional molecule*	*Polyfunctional molecule*
Alcohol	5–6 carbons	3–4 carbons
Phenol	6–7 carbons	3–4 carbons
Ether	4–5 carbons	2 carbons
Aldehyde	4–5 carbons	2 carbons
Ketone	5–6 carbons	2 carbons
Amine	6–7 carbons	3 carbons
Carboxylic acid	5–6 carbons	3 carbons
Ester	6 carbons	3 carbons
Amides	6 carbons	2–3 carbons
Urea, carbonate, carbamate		2 carbons

Let us discuss here an example of anileridine, a narcotic analgesic that contains three organic functional groups, which determine water solubility.



The three organic functional groups are (1) an aromatic amine (very weak base), (2) a tertiary alkylamine (weak base) and (3) an ester (neutral).

The compound contains 21 carbon atoms with a solubilizing potential of 9 carbon atoms. Since the solubilizing potential is less than that of the total number of carbon atoms present, the prediction would be that the drug is insoluble in water, but according to the *United States Pharmacopeia* (USP), it is soluble in water (1/10000 ml), which indicates that not only the three functional groups and solubilizing potential of 9 carbon atoms, but it also depends upon the positive charge of alkyl ammonium group.

The charge of the solubilizing potential for this group (anileridine HCl) is 29–39 carbons, which is more than that of the total number of carbon present. Hence, this compound is soluble in water.

CHAPTER 9

Partition Coefficient

The hydrophobicity of a drug can be determined experimentally by the relative distribution of the drug in an octanol–water mixture. Hydrophobic molecules prefer to dissolve in the octanol layer of this two-phase system. Hydrophilic molecules prefer the water layer. The relative distribution of drug between the two-phase systems is called *partition coefficient* (*P*).

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in water}}$$

Hydrophobic compounds will have a high *P* value and hydrophilic compounds will have a low *P* value.

Partition coefficient is difficult to measure *in vivo*. They are usually determined *in vitro* only by using n-octanol as a lipid phase and water or aqueous phosphate buffer (pH 7.4) as an aqueous phase. This gives the standardized measurement of *P*, since it is the ratio. *P* is an additive property and is dimensionless, so it is used to determine the polarity, and hydrophilic and lipophilic characters of the molecule.

Partition Coefficient Versus Biological Activity

Partition coefficient fully influences the drug transport characteristics during pharmacokinetic phase.

It affects the way a drug reaches the site of action. Extremely water-soluble drugs cannot penetrate the lipid barriers (blood–brain barriers), and hence cannot exhibit the CNS activity. The biological activity of anticonvulsants and general anaesthetics depend on the partition coefficients of these drugs only.

Lead compounds with different substituents yield a series of analogues of varying hydrophobicities and different *P* values. Any relationship between partition coefficient and biological activity of these drugs is determined by plotting these *P* values against the biological activity.

The biological activity is expressed as $1/C$.

Here, *C* is concentration of drug needed to produce a defined level of biological (pharmacological) activity.

Generally, the reciprocal of concentration ($1/C$) is used, since more active drugs will produce particular biological activity at low concentration.

The graph is drawn by plotting $1/C$ versus log *P*.

For the log *P* values between 1 and 4, a straight line graph is obtained (Figure 9.1).

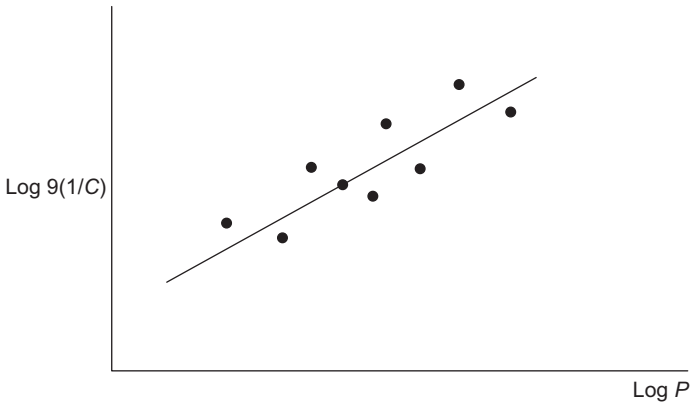


Figure 9.1: Biological activity versus partition coefficient.

It indicates the relationship between hydrophobicity and biological activity, e.g. binding of serum albumin.

The binding of serum albumin is determined by their hydrophobicity. A study of 40 compounds results in the following equation:

$$\text{Log } (1/C) = 0.75 \log P + 2.30$$

The above equation indicates that increase of log *P* increases serum albumin-binding capacity.

Compounds containing the log *P* values from 0.78 to 3.82 have restricted serum albumin binding.

When we plot the values, a parabolic graph is obtained (Figure 9.2). In the graph shown below, the biological activity increases as log *P* increases until a maximum value is obtained.

In the graph shown below, log P° = Optimum partition coefficient for biological activity. Beyond this point, an increase in log *P* results in decrease in biological activity.

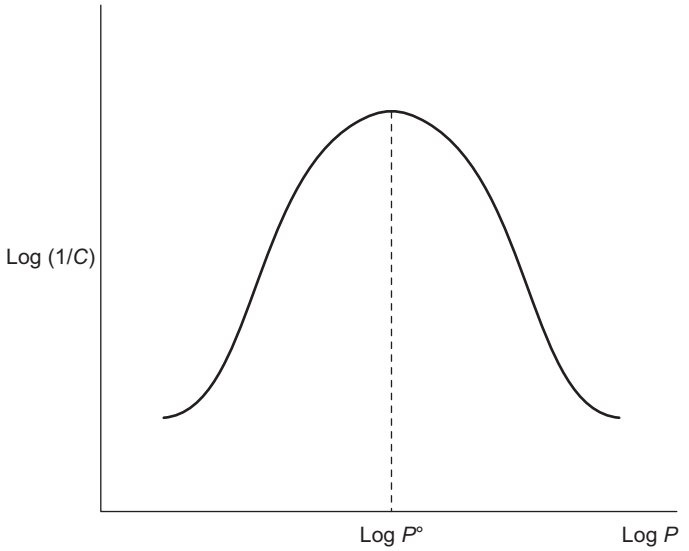
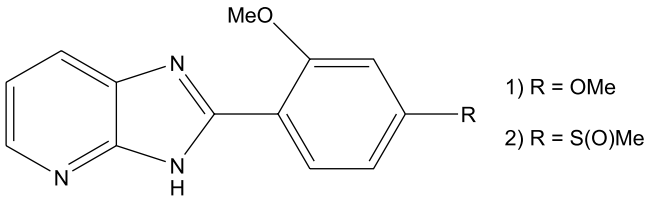


Figure 9.2: Parabolic log (1/C) versus log *P*.

Examples for Drugs in which Biological Activity is Related to the Log *P* Factor Alone

1. **General anaesthetics:** The main mechanism of general anaesthetics is entering the CNS and dissolving into cell membranes where it affects membrane structure and nerve function. In this condition, the action of drug is purely controlled by its hydrophobicity. From the series of QSAR studies, the optimum hydrophobicity (log P°) value for anaesthetic activity is found to be around 2.3.
2. Compounds having a log *P* value close to 2 should be capable of entering into CNS efficiently. For example, the log *P* value of potent barbiturates for sedative and hypnotic activity is close to 2.

The cardiotonic agent sulmazole, which enters the CNS due to log *P* value of 2.59, was found to produce 'bright visions' in some patients.



Sulmazole [R = S(O)Me]

To prevent the entry of drug into CNS, the 4-methoxy group was replaced by 4-S(O)Me group with a low log *P* value of 1.17. Now, the drug is too hydrophilic, hence unable to enter the CNS and was free of CNS side effects.

From the above examples, we conclude that the partition coefficient is a measure of the drug's overall hydrophobicity, and it is an important measure of how efficiently a drug is transported to its target's site.

Determination of Partition Coefficient

The determination of partition coefficient is a time-consuming procedure and depends on the stability and purity of the particular drug. One of the most popular method or approach has been HPLC or TLC.

In this case, the mobile phase usually contains some water-miscible organic solvent. The stationary phase is non-polar by using octadecylsilane, mineral oils or coating of octanol.

Determination of Partition Coefficient through Regression Analysis by Using the Following Equation

Log $P = a$ (log retention) + C

a = Regression coefficient or slope of the straight line

C = The intercept terms on the y-axis (physical and chemical properties equal to 0.)

This method or model has the following two limitations:

1. Partition coefficient of related compounds is same.
2. The retention in chromatographical system.

Determination of Partition Coefficient on the Basis of Atomic Components of the Molecule

According to this model, each atom type is assumed to contribute a fixed amount to the chemical partition coefficients, e.g. cyclohexane. The major disadvantage of this model is that it needs several of correction factors.

There are several methods or commercial drug design software packages that contain modules determining chemical partition coefficient.

CHAPTER 10

Steric Features of Drugs

INTRODUCTION

The potential biological activity of a targeted drug molecule solely depends on its physicochemical characteristics and essentially comprises the nature and type of functional moieties and also the spatial arrangement of such groups in the molecules. Interestingly, the human body itself represents an asymmetric environment, wherein drug molecules interact with proteins and biological macromolecules (receptors). Hence, it is virtually important and necessary that the decisive functional moieties must be strategically located with respect to exact spatial region circling the targeted drug molecule, so as to enable the crucial and productive bonding interactions, particularly with the receptor, thereby potentially accomplishing the desired pharmacological effect. It is, however, pertinent to state here that the right fitment of correct 3D-orientation of the functional moieties in a drug substance may ultimately result in the formation of an extremely viable and reasonably strong interaction with its receptor.

Steric factors determined by the stereochemistry of the receptor site surface and that of the drug molecules are, therefore, of primary importance in determining the nature and the efficiency of the drug–receptor interaction. The drug must approach and fit closely into the receptor surface to evoke the pharmacological action. Hence, the drug must possess a high degree of structural specificity or stereoselectivity. Many drugs show stereoselectivity because mostly receptor binds are optically active biological macromolecules, such as proteins, polynucleotides, or glycolipids.

GEOMETRICAL ISOMERISM

Isomerism caused by the difference in spatial arrangement of groups about the double bonded carbon atoms is known as geometrical isomerism. Due to the hindered rotation, the positions of different groups attached to the two carbon atoms are fixed in space. Two different compounds are distinguished by the terms *cis* and *trans*.

Cis Isomer

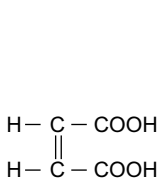
In this isomer, similar groups lie on the same side and it is known as *cis* isomer (in Latin term *cis* means—same side).

Trans Isomer

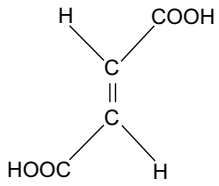
In this isomer, similar groups lie on opposite side and is known as *trans* isomer (in Latin term *trans* means—across).

Due to *cis* and *trans* isomers, geometrical isomerism is otherwise known as *cis-trans* isomerism.

Example: Maleic acid and fumaric acid possess same molecular formula of $C_4H_4O_4$, but they differ each other in most of their physical properties and some of their chemical properties.



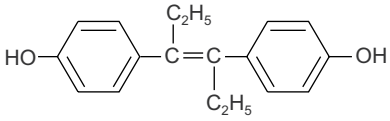
Cis form (maleic acid)



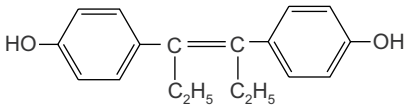
Trans form (fumaric acid)

The two isomers exhibit different pharmacological response due to their orientation in the body enzymes or receptors. Some of the examples are described below.

Diethylstilbestrol exists in two fixed stereoisomeric forms—*trans*-diethylstilbestrol is oestrogenic, whereas *cis* isomer is only 7% active. In *trans*-diethylstilbestrol, resonance interaction and minimal stearic interference tend to hold the two aromatic rings and connecting ethylene carbon atom in the same plane.



Trans-diethylstilbestrol

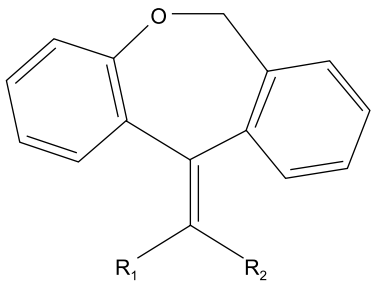


Cis-diethylstilbestrol

In geometric isomers, *cis* and *trans* isomers differ in their physical and chemical properties. Therefore, distribution in the biological medium is different.

The geometric isomers (E–Z forms) of some drugs are found to be pharmacologically active and are approved for various therapeutic uses as shown below.

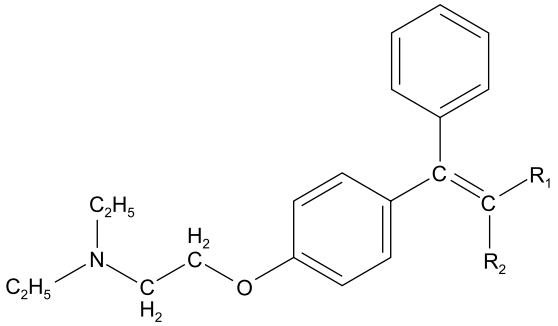
Doxepin



Z-Doxepin: $R_1 = CH_2CH_2N(CH_3)_2$, R_2 = H; ***E*-Doxepin:** R_1 = H, $R_2 = CH_2CH_2N(CH_3)_2$

Used as a mixture of E–Z isomers in the ratio of 85:15 (approximately) for treatment of insomnia.

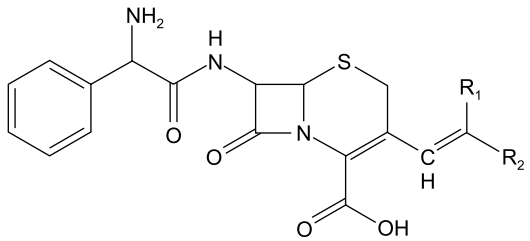
Clomiphene



***Z*-Clomiphene:** R_1= C_6H_5, R_2 = Cl; ***E*-Clomiphene:** R_1 = Cl, R_2 = C_6H_5

It contains the mixture of E–Z isomers and used as an orally active non-steroidal agent.

Cefprozil



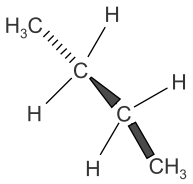
***Z*-Cefprozil:** R_1= H, R_2 = CH_3; ***E*-Cefprozil:** R_1 = CH_3, R_2 = H

It is a cephalosporin antibiotic exhibits E–Z isomerism, used to treat bronchitis, skin and ENT infections.

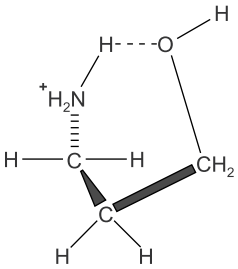
Conformational Isomers

Different arrangements in the space for atoms or groups in single bonds are called *conformations*. Rotations about the bonds allow interconversion of conformers (conformational isomers). The energy barrier between isomers is often high enough for their independent existence and reaction. Differences in the reactivity of functional groups or interaction with biological receptors may be due to differences in steric requirements of the receptors.

Open chains of atoms form an important part of many drug molecules. Energy barrier to the free rotations of the chains is present because of the interactions of non-bonded atoms; for example, the atoms tend to position themselves in space so that they occupy staggered positions with no two atoms directly facing each other (eclipsed). Non-bonded interactions in polymethylene chains tend to favour the most extended anticonformations, although some partially extended gauche conformations also exist. The conformational isomers show significant differences in biological activities.

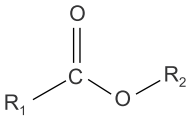


n-Butane anticonformation

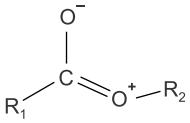


3-Amino-*n*-propanol eclipsed conformation

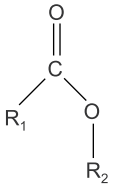
Stabilized planar structure of esters



Antistablized

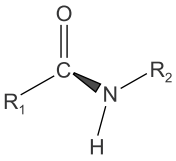


Resonance stabilized

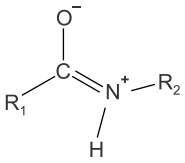


Gauche

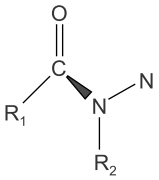
Stabilized planar structure of amides



Antistabilized

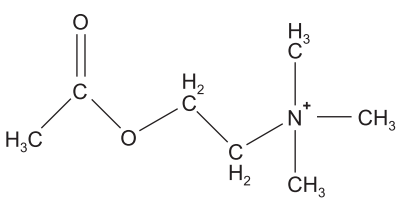


Resonance stabilized

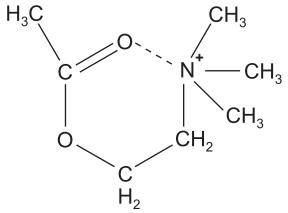


Gauche

The potential interaction energy of trimethyl ammonium ion and acetoxy group is lowest in the staggered (also called, though erroneously, *trans* or *transoid*) conformation, and highest when the two groups are eclipsed (*cis* or *cisoid* conformation). It has been suggested that acetylcholine interacts with the muscarinic receptor in fully extended staggered conformation and interacts with nicotinic receptor in folded (gauche) conformation. To study the relationship between the possible conformations of rigid analogues of acetylcholine and their biological effects conformationally rigid analogues of acetylcholine have been used. The *cis* and *trans* isomers of 2-acetoxy cyclopropyl trimethyl ammonium iodide are two such compounds. The (+) – *trans* isomer in which the quaternary nitrogen atom and acetoxy groups are held apart in a shape approximating that of extended conformation of acetylcholine was found to be almost equipped with acetylcholine at the muscarnic receptor, but shows little nicotinic activity. It is easily hydrolyzed by acetyl cholinesterase. In contrast (+) – *cis* isomer showed practically no activity at the nicotinic or muscarinic receptor. The results indicate that acetylcholine assumes staggered conformation at the muscarinic receptors.

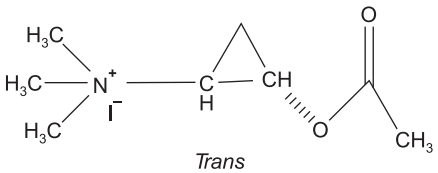


Extended

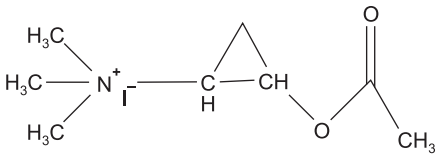


Quasi-ring

Acetylcholine



Trans



Cis

2-Acetoxy cyclopropyl trimethylammonium iodide

Acetylcholine conformation

OPTICAL ISOMERISM

When a plane polarized light passes through a solution of chiral compound, plane of polarization changes because the molecules are asymmetric. Hence, a chiral compound rotates plane polarized light either clockwise or anticlockwise direction. A compound which rotates a plane polarized light is said to be optically active. In other words chiral compounds are optically active and achiral compounds are optically inactive.

Dextrorotatory: If an optically active compound or chiral compound rotates the plane polarized light in a clockwise direction, it is known as dextrorotatory and indicated by the symbol (+).

Levorotatory: If an optically active compound or chiral compound rotates the plane polarized light in anticlockwise direction, it is known as levorotatory and indicated by the symbol (–). 'Dextro and levo' are Latin prefixes for 'to the right' and 'to the left', respectively.

While naming stereochemical compounds, the D, L, R, S indicates stereochemical relation (structural features) and the (+) or (–) indicates actual direction of rotation of plane polarized light.

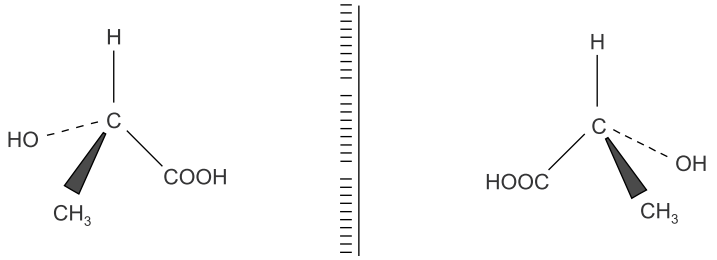
Note: Do not get confuse (+) and (–) with R and S or D and L. The (+) or (–) symbol indicates the direction in which a chiral compound rotates a plane polarized light. But R and S or D and L indicate the arrangement of the groups around a chiral centre.

Enantiomers

If four different atoms or groups are attached at the four corners of a regular tetrahedron, then the molecule is asymmetric and can exist in two forms. The three-dimensional structures cannot be superimposed on each other, and hence, are different, even though they represent the same structural arrangement of

atoms. They bear a relationship to each other corresponding to what exists between an object and its mirror image. Mirror image molecules are not superimposable and are called *enantiomers*.

A tetrahedral carbon atom carrying four groups that are all different, therefore, must invariably constitute a centre of asymmetry and permits two arrangements of the groups in space. This asymmetry calls for the existence of two isomers identical in all respects except optical properties, for example lactic acid and 2-hydroxy propanoic acid.



(+)-Lactic acid Mirror (–)-Lactic acid

A chiral compound containing one asymmetric centre has two enantiomers. Although each enantiomer has identical chemical and physical properties, they may have different physiological activities such as the interaction with receptor, metabolism, and protein binding.

Examples of enantiomers possessing varying biological activity are the following:



(S)(+)-Naproxen sodium
Active as analgesic, antipyretic and anti-inflammatory

(R)(–)-Naproxen sodium
(inactive)

Many optical isomers exhibit variation in the intensity of their biological properties. For example,

(–)-Hyoscyamine is 15–20 times more active as a mydriatic than (+)-hyoscyamine.

(–)-Hyoscine is 16–18 times as active as (+)-hyoscine.

(–)-Epinephrine is 12–15 times more active as vasoconstrictor than (+)-epinephrine.

(–)-Isoprenaline is 800 times more active bronchodilator than (+)-isoprenaline.

(+)-Nor homoepinephrine is 160 times more active as a pressor than (–)-nor homoepinephrine.

(+)-Amino acids are sweet, whereas (–)-amino acids are either sweetless or bitter.

(+)-Ascorbic acid has good antiscorbutic properties, whereas (–)-ascorbic acid has none.

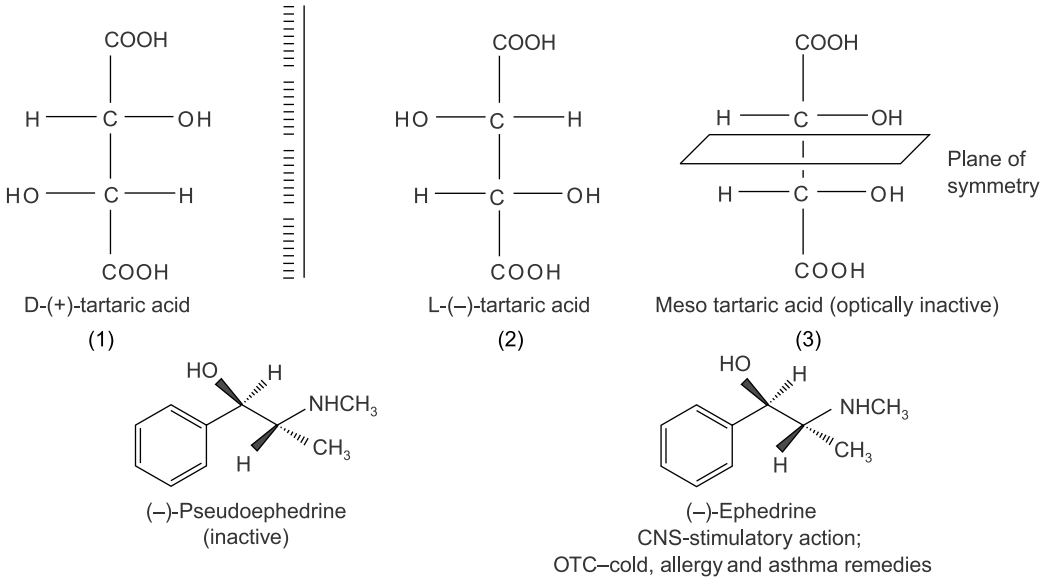
(S)-Thalidomide is more teratogenic than (R)-thalidomide.

Diastereomers

Tartaric acid is an example of a compound having two similar asymmetric carbon atoms since each carbon atom has attached hydrogen atom, a hydroxyl group, a carboxyl group (CH OH COOH group).

If we represent the configurations of two mirror images about each asymmetric carbon atom, then the structures are represented as enantiomers of D- and L-tartaric acid.

A third structure is possible, which possesses a plane of symmetry (achiral) and is, therefore, optically inactive. Such molecules are designated as *mesoforms*. Stereoisomers (1) and (2) are enantiomers, but (1) and (3) are not enantiomers, they are called *diastereomers*. These stereoisomers are not mirror images, unlike enantiomers, but diastereomers possess different physical and chemical properties. Examples of diastereomers possessing varying activity are the following.



Reasons Behind Varying Activity of Optical Isomers

The difference is due to the interaction of asymmetric carbon atom of the molecule with stereospecific receptors. According to Easson-Stedman hypothesis, if binding ions are specific for one enantiomer, then a three-point attachment must occur between the enantiomer and the asymmetric surface of the receptor, since only one of the entantiomers will fit, and the other one is only capable of a two-point attachment, as shown in Figure 10.1.

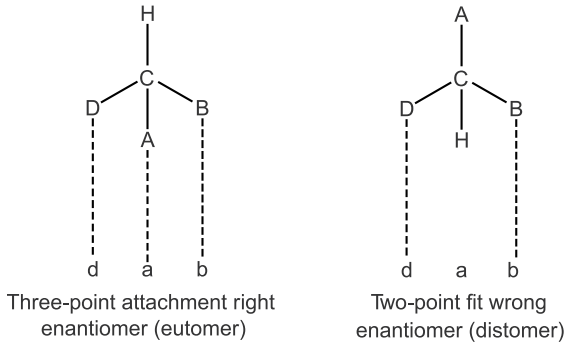


Figure 10.1: Varying activity of optical isomers.

Binding of Enantiomers to Receptors

The enantiomer (Figure 10.2) that has a high affinity for receptor is called *eutomer*, whereas the one with a lower affinity is called *distomer*. The ratio of activity of the eutomer and distomer is called *eudismic ratio*.

Examples of Easson-Stedman principle: For epinephrine, the benzene ring, benzylic hydroxyl, and protonated amine bind with the hydrophobic or aromatic region, anionic site, and hydrogen bonding at the centre of the receptor.

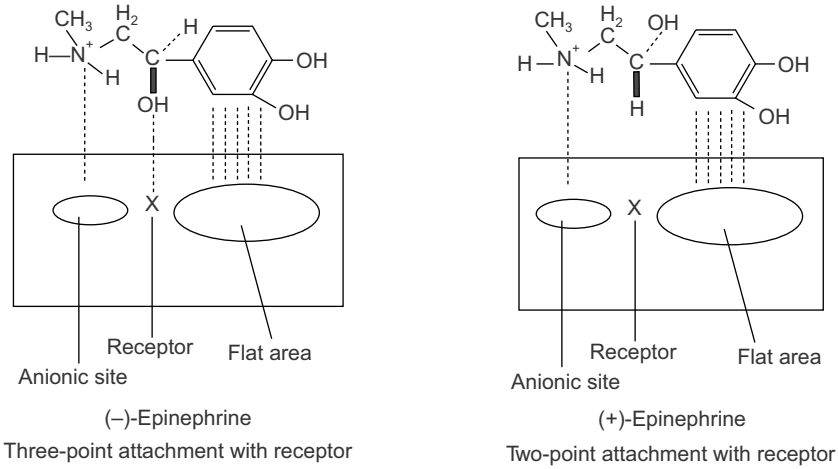


Figure 10.2: Binding of epinephrine with receptor.

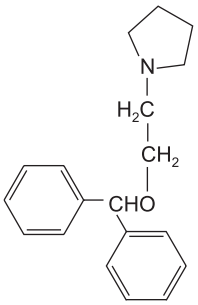
CHAPTER 11

Bioisosterism

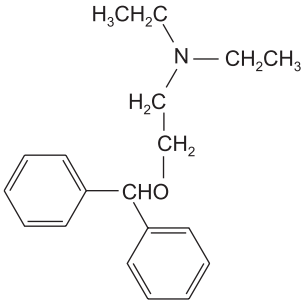
INTRODUCTION

Isosterism is of vital importance to the medicinal chemists because the biological characteristics of isosteres appear to be similar, more frequently than physical or chemical characteristics. Keeping in view the numerous advantageous application of isosterism in resolving biological problems effectively, Friedman proposed the following definition of bioisosterism—the phenomenon by which compounds usually fit the broadest definition of isosteres and possess the same type of biological activity.

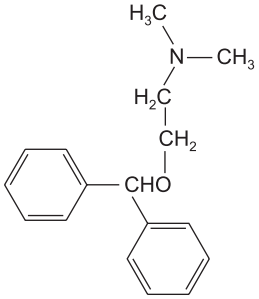
For instance, among antihistamines it is always preferable to have small compact substituents on the terminal nitrogen.



(a) Pyrrolidone analogue



(b) Diethyl analogue



(c) Dimethyl analogue

In the above-mentioned three-structural analogues, it has been observed that 'A' possesses twice the activity of 'C', whereas it showed an activity that is many times greater than that of the open-chain diethylamino analogue.

It has been duly observed that it is more or less difficult to correlate the biological properties vis-a-vis physicochemical properties inherited by specific individual atoms, functional groups, or entire molecule by virtue of the glaring and established fact that a host of physical and chemical parameters are involved simultaneously, and therefore, it is extremely difficult to quantify them justifiably.

Besides simpler relationships, for example, isosterism invariably does not delay across the several varieties of biological systems that are often encountered with medicinal agents. In other words, a specific isosteric replacement in one particular biological system may either work or fail in response to the other. Thus, bioisosteres were further explained as follows: Bioisosteres are (functional) groups or molecules that have chemical and physical similarities producing broadly similar biological properties.

CLASSIFICATION

Bioisosteres are classified into the following two types:

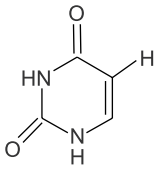
1. Classical bioisosteres
2. Non-classical bioisosteres

Classical Bioisosteres

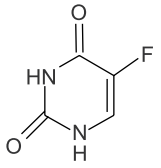
Classical bioisosteres have similarities in shape and electronic configuration of atoms, groups, and molecules, that they replace. Actual applications of bioisosteres in the successful design of a specific given molecule interacting with particular receptor is one glaring example, and very often either fails or negates the biological characteristics in another environment. Therefore, it is pertinent to state at this juncture that the logical use of biological replacement (classical or non-classical) in the design of a new target drug molecule is solely and significantly depend on the specific biological system under critical investigation. Hence, there are no predetermined, well-established, predictable hard and fast guidelines, or laid generalized rules that may be useful to a medicinal chemist to affect biosteric replacement gainfully towards improved biological activity. Various classical bioisosteres with their appropriate examples are listed as follows:

1. Monovalent atoms and groups

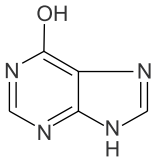
- F, H
- OH, NH
- F, OH, NH, or CH_3 for H
- SH, OH
- Cl, Br, and CF_3



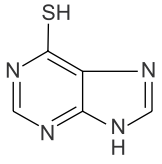
Uracil



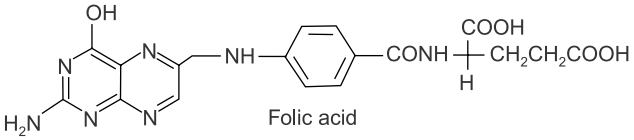
5-Fluorouracil



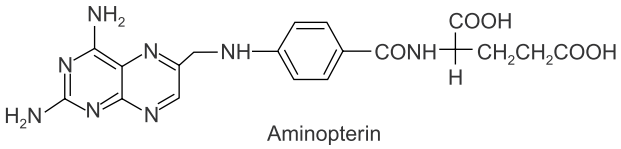
Hypoxanthine



6-Mercaptopurine



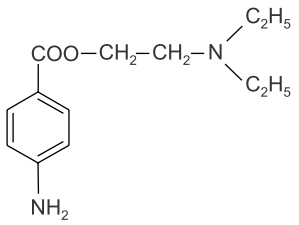
Folic acid



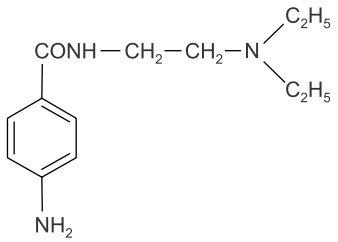
Aminopterin

2. Divalent atoms and groups

–C=S, –C=O, –C=NH, –C=C–



Procaine



Procainamide

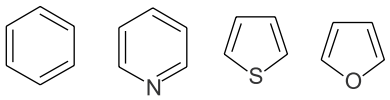
3. Trivalent atoms and groups

–CH=, –N=, –P=, –As=

4. Tetravalent atoms and groups

$=N^{+}=$, =C=, $=P^{+}=$, $=As^{+}=$

5. Ring equivalents

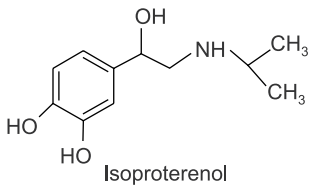


Non-classical Bioisosteres

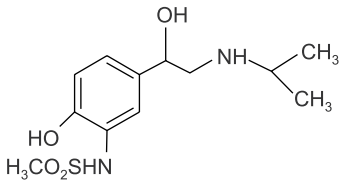
They do not obey the steric and electronic definition of classical isosteres. Also, they do not have the same number of atoms as replacement. Although, many of these functional moieties practically just behave as one, they have one of the following characteristic features, such as

- Electronic properties
- Physicochemical properties
- Spatial arrangements
- Functional moiety critical for biological activity

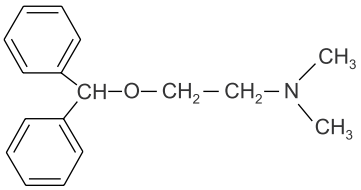
1. Exchangeable groups



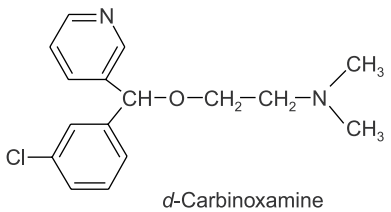
Isoproterenol



Soterenol

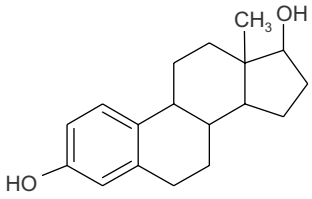


Diphenhydramine

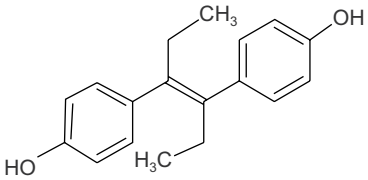


d-Carbinoxamine

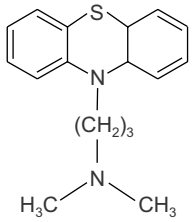
2. Cyclic versus non-cyclic structure



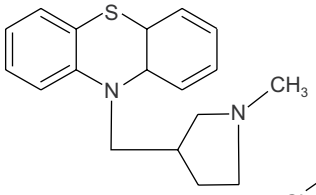
Estradiol



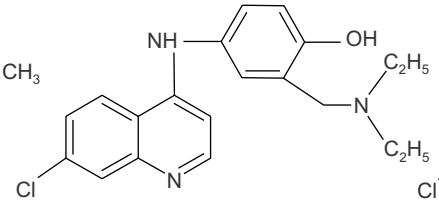
Diethylstilbestrol (*trans*)



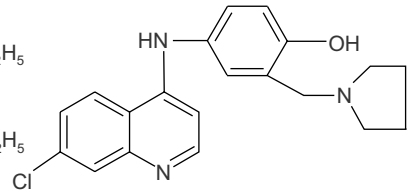
Promazine



Methdilazine



Amodiaquine



Amopyroquine

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CHAPTER 12

Protein Binding of Drugs

Once the drug enters into the systemic circulation, it undergoes various binding events. It may be present in solution, but majority of drugs bind with various proteins such as albumin, etc. The drug can interact with various tissue components such as blood and extravascular tissues. The interacting molecules are DNA or adipose tissues.

"The phenomenon or process of formation of complex with proteins is known as protein binding of drugs."

CLASSIFICATION OF PROTEIN BINDING

1. Intracellular binding
2. Extracellular binding

Intracellular Binding: In this process, the drug is bound to the cell proteins such as drug receptors which produces the pharmacological response. This kind of receptors are called primary receptors.

Extracellular Binding: In this process, the drug is bound to the extracellular proteins but does not elicit any pharmacological response. This kind of receptors are called secondary receptors or silent receptors. The secondary receptors are plasma proteins.

MECHANISM OF PROTEIN–DRUG BINDING

Binding of drugs to the proteins is a reversible reaction and involves weak chemical bonding. The different types of bond occur between the drugs and the proteins are as follows.

1. Hydrogen bonds
2. Hydrophobic bonds
3. Ionic bonds
4. Van der Waals forces

Irreversible binding of drugs leads to the carcinogenicity or tissue toxicity. For example, irreversible covalent binding of drug paracetamol to the liver tissue leads to hepatotoxicity.

Binding of drugs is categorized into two classes:

I. Binding of drugs into blood components such as
   i. Plasma proteins
   ii. Blood cells
II. Binding of drugs into extravascular tissues.

Let us discuss in detail.

I. Binding of Drugs into Blood Compartments

Once the drug reaches the systemic circulation, first it can interact with plasma proteins, blood cells and haemoglobin. Due to the abundant or huge amount of plasma proteins, the drug mainly interacts with these proteins. The process of drug binding to the plasma proteins is reversible one. The order of binding of drug to the plasma proteins is as follows:

Albumin > α_1-Acid glycoprotein > Lipoproteins > Globulins

The process of protein binding involves the following steps:

1. Binding of drugs to human serum albumin (HSA)
2. Binding of drugs to α_1-acid glycoprotein (AAG)/binding of drugs to orosomucoid
3. Binding of drugs to lipoproteins
4. Binding of drugs to globulins
5. Binding of drugs to blood cells

1. Binding of Drugs to HSA

It has the largest amount of plasma proteins and has the capacity to bind with maximum number of drugs. Most of the drugs as well as the endogenous substances such as tryptophan, bilirubin, etc. can also bind with HSA. HSA contains four different drug-binding sites as mentioned below.

- **Site-I or Warfarin and azapropazone binding site:** In this site, large number of drugs interact and bound. Example for drugs binding to these sites are various kind of NSAIDs (indomethacin, naproxen, etc.) sulphonamides, phenytoin and bilirubin.
- **Site-II or Diazepam binding site:** Example for drugs binding to this region are ibuprofen, probenecid, cloxacillin, benzodiazepines, etc.
- **Site-III or Digitoxin binding site and site -IV or tamoxifen binding site:** Site-I and II are the most important drug binding sites for maximum number of drugs. Very few number of drugs are binding to the site-III and IV. If the drug is bound to more than one site, then majority binding site of the drug is called primary binding site or the other site is known as secondary binding site.

2. Binding of Drugs to α_1-Acid Glycoprotein (AAG)/Binding of Drugs to Orosomucoid

The plasma concentration range of this protein is 0.04 to 0.1g. The examples for drug binding to this protein are imipramine, propranolol, lidocaine (basic drugs), etc.

3. Binding of Drugs to Lipoproteins

Lipoproteins are classified into four types according to their density. They are:

1. Chylomicrons (least dense and largest in size)
2. Very low-density lipoproteins (VLDL)
3. Low-density lipoproteins (LDL) (mostly present in humans)
4. High-density lipoproteins (HDL) (denser and smallest in size)

The molecular weight of lipoproteins ranges from 2 lakhs to 34 lakhs depending upon their chemical compositions. The main role of lipoproteins is the transport of lipids from the circulation to the tissues. They also transport or circulate the drugs to the tissues. Binding of drugs to the lipoproteins is a non-competitive process, i.e. there is no specific or absence of specific binding site. Binding of drugs do not depend upon the concentration. Examples of drug bound to the lipoproteins are acidic drug—diclofenac, basic drug—chlorpromazine and the neutral drug such as cyclosporine A.

4. Binding of Drugs to Globulins

The various types of globulins are α_1, α_2, β_1, β_2, and γ-globulins.

1. **α_1-globulins or transcortin or corticosteroid binding globulin:** Steroidal drugs like cortisone, prednisone and thyroxin, cyanocobalamine are the examples of the drugs which bind to the globulins.
2. **α_2-globulin or ceruloplasmin:** Fat soluble vitamins A, D, E, K and cupric ions bind to this site.
3. **β_1-globulin or transferring:** Ferrous ions bind to this site.
4. **β_2-globulins:** Carotenoids bind to this site.
5. **γ-globulins:** Antigens bind to this site.

5. Binding of Drugs to Blood Cells

The major cellular component in the blood is RBC cell. Hence, the drugs majorly bind with RBC cells only. The three major components of RBC cells to which drugs bind are:

1. **Haemoglobin:** Drugs like phenytoin, phenobarbital and phenothiazine bind to this.
2. **Carbonic anhydrase:** Carbonic anhydrase inhibitors such as acetazolamide and chlorthalidone are drugs which bind to this.
3. **RBC cell membrane:** Drugs like chlorpromazine and imipramine bind to the RBC cell membrane.



Note: Highly lipophilic drugs bind to RBCs than hydrophilic drugs such as ampicillin, etc.

II. Binding of Drugs to Extravascular Tissues

Some kind of drugs possess special affinity towards certain tissue components. Hence, it increases the duration of action of the drug and decreases the elimination of drug.

Importance of Tissue–Drug Binding

1. It increases the apparent volume of distribution of drugs.
2. It leads to the localization and accumulation of drug into specific site of the body.

Factors Influencing the Tissue–Drug Binding

1. Structural features of the drug
2. Lipophilicity or hydrophobicity of the drug
3. pH difference
4. Perfusion rate

The extensive binding of drugs to the tissues leads to storage of that drugs in that site.

The order of binding of drugs into tissue is as follows.

Liver > kidney > lungs > muscles

Some examples of drugs which bind to the various tissues are as follows (Table 12.1).

Table 12.1: Drugs which bind to the various tissues

S. No.	*Tissues in which drugs to be bind*	*Drugs*	*Responses*
1.	Liver	Paracetamol, halogenated hydrocarbons	Covalent binding leads to hepatotoxicity
2.	Lungs	Antihistamines, imipramine and chlorpromazine	—
3.	Kidney	Lead, mercury and cadmium bind with the metallothionin	Toxicity
4.	Skin	Phenothiazine and chloroquine bind with the tissue by interaction with melanin	—
5.	Eyes	Phenothiazine and chloroquine bind with the tissue by interaction with melanin	Retinopathy
6.	Hairs	Arsenicals, chloroquine	—
7.	Bones	Tetracyclines	Discoloration of teeth
8.	Fats	Thiopental and DDT	—
9.	Nucleic acids	Chloroquine and quinacrine	Distortion of double helical structure

Factors Influencing Drug–Protein Binding

Various factors affect the binding of drugs to the proteins. They are described as follows:

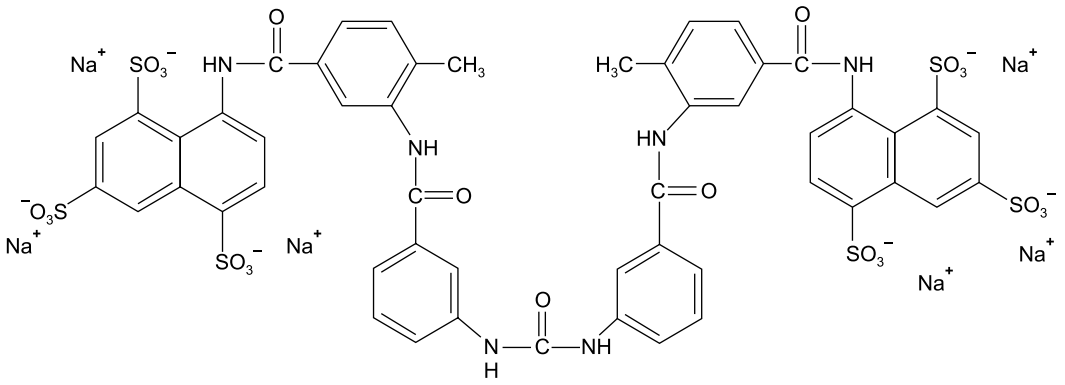
1. **Drug-related factors**
   i. Physicochemical properties of the drug
   ii. Drug concentration
   iii. Drug affinity to the particular binding site
2. **Protein- or tissue-related factors**
   i. Physicochemical properties of the protein
   ii. Protein or drug binding component concentration
   iii. Number of binding sites on the protein or binding agent
3. **Patient-related factors**
   i. Age
   ii. Disease condition
   iii. Intersubject variations
4. **Drug interactions**
   i. Competition between drugs for the binding sites or proteins
   ii. Competition between drugs and the normal body constituents
   iii. Allosteric variations or changes in the binding proteins

Applications of Protein Binding

1. The albumin–drug complex acts as a reservoir to provide the required concentration of drug to elicit pharmacological response.

2. It may also limit the access to body compartments. The placenta prevents the entry of drugs from maternal to fetal circulation. Protein binding prevents the normal passage through placental barrier and produce toxicity to that area in the maternal circulation and bound to the mother's serum protein.
3. The protein binding of drugs prolongs or increases the duration of action of drugs. The drug–protein complex is too long and big, large to pass via the renal globular membranes that prevents the rapid excretion of drugs.
4. It also prevents the metabolism of drugs and the interaction of drugs with receptor site.

   For example, the drug suramin is used to treat sleeping sickness remains in the body in the form of protein bound as long as 3 months. The maintenance dose of the drug is administered once in a week. It produces advantages to the patient and at the same time leads to several side effects.



Suramin sodium

5. The protein binding of drugs phenomenon leads to some clinically important drug–drug interactions. Hence, one drug displaces another one from its binding site on albumin. For example, anticoagulant drug warfarin is displaced from its binding site albumin by various kind of drugs. This increases the concentration of warfarin at receptors, leading to increase in prothrombin time and severe haemorrhage.

CHAPTER 13

Biotransformation or Metabolism of Drugs

INTRODUCTION

The biochemical process of conversion of drugs or xenobiotics in the body is called biotransformation or metabolism. During this process, the drugs are converted into water soluble conjugates and eliminated through kidney. Body treats drugs as a xenobiotics. Hence, metabolism plays a peculiar role in the elimination of drugs and xenobiotics. A well-known understanding of metabolic pathway of drugs is an important tool for the pharmacist in selection and monitoring appropriate drugs in the treatment for their patients.

Importance of Metabolism

Most of the organic drugs are highly lipophilic in nature, when they are administered via oral route, they cross the lipoprotein membranes of GIT and reach the bloodstream. Once the drugs enter into various target organs, elicit their pharmacological response. Due to reabsorption in the renal tubule, the lipophilic drugs are not excreted from the body via urine. Hence, they undergo various changes by metabolic enzymes and render them to be more water soluble one, and then eliminated.

If the lipophilic xenobiotic is not metabolised to polar, readily excreted hydrophilic products, then they would remain in the body which leads to the development of toxic effects. It indicates that the conversion of lipid soluble xenobiotics into highly hydrophilic compounds not only increases the drug metabolism but it also leads to the compounds that are pharmacologically inactive metabolites and non-toxic compounds. Hence, the drug metabolism is also known as **detoxification.**

During the metabolism not all drugs are converted into the inactive form. The consequences of drug metabolism are as enumerated below.

1. Conversion of drugs into pharmacologically active metabolites, e.g. morphine to codeine
2. Conversion of inactive xenobiotics into active metabolite (prodrug), e.g. levodopa, bacampicillin, prednisone, etc.
3. Conversion of active drug into inactive metabolite, e.g. ibuprofen, lignocaine, etc.
4. Conversion of active drug into toxic metabolites, e.g. paracetamol, cyclophosphamide, etc.

General Pathways of Drug Metabolism

Drug metabolism reactions are broadly classified into two types:

1. Phase-I reactions or functionalisation reactions
2. Phase-II reactions or conjugation reactions

Phase-I or Functionalisation Reactions

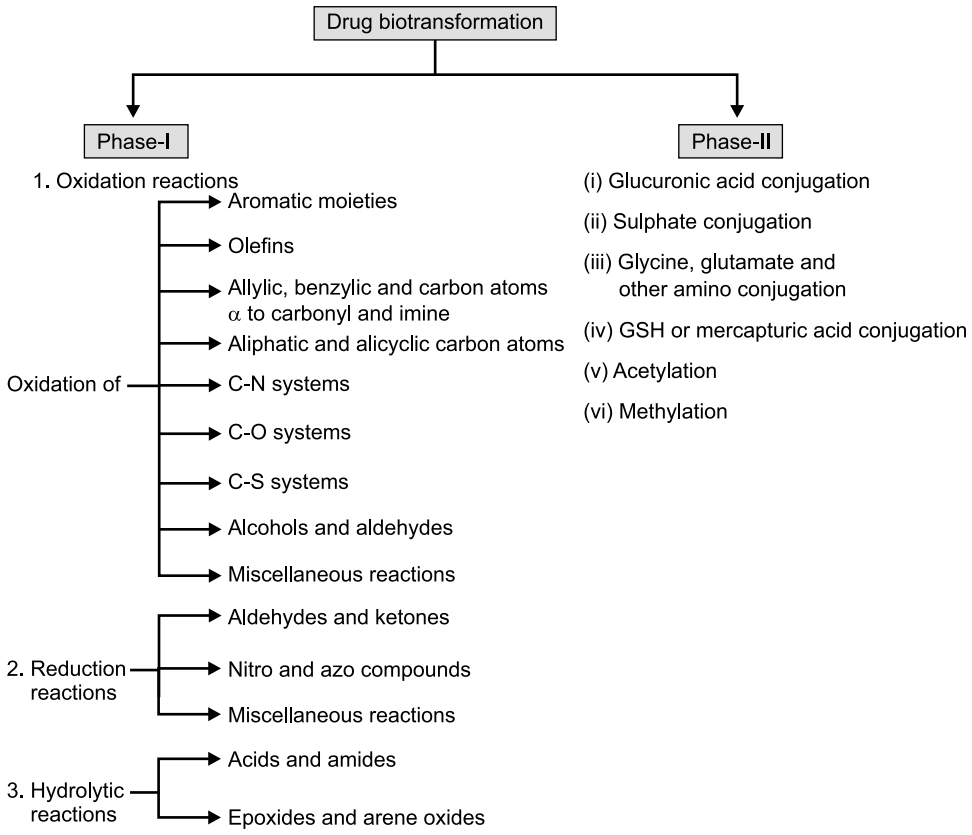
The main principle of this reaction is to introduce or attach polar functional groups such as –OH, –COOH, $–NH_2$ to the xenobiotic and convert them into a highly water-soluble compounds. This can be performed or achieved by two ways:

1. Direct introduction of the functional group by aromatic or aliphatic hydroxylation.
2. Modifying or masking the already existing functional groups by the reactions like oxidation of alcohols to acids, hydrolysis of ester and amides, reduction of aldehydes and ketones to alcohols, etc.

The phase-I reactions involve hydroxylation, oxidation, reduction and hydrolytic transformation reactions.

Phase-II Reactions or Conjugation Reactions

These reactions help to attach a small, polar and easily ionizable endogenous substances such as glucuronic acid, sulphates, glycine and other amino acids into the functional group of phase-I metabolites or parent compounds that already possess suitable functional moieties to form highly water-soluble conjugate products. These conjugates generally does not possess any pharmacological activity and are non-toxic to human being. These are readily excreted by urine. The other phase-II reactions involve acetylation and methylation which does not increases the water solubility but attenuate or terminate the pharmacological activity, whereas glutathione conjugation protects the body from the effect of chemical reactive conjugates or metabolites.



Phase-I and phase-II reactions are competent to one another, by this way detoxifying and facilitating the elimination of drugs and xenobiotics from the body take places.

Sites of Drug Metabolism

Drug metabolism occurs in various tissues of our body. Liver is a major organ for the biotransformation of major number of drugs, i.e. endogenous or exogenous compounds. The second organ or site especially for the metabolism of orally administered drugs is intestinal mucosa. The intestinal mucosa contains the enzyme cytochrome P-450 and P-glycoprotein that can capture the drugs and secrete it back into the intestinal tract. But the liver secretion contains lot of drug metabolising enzymes.

Once the drug is administered via oral route, it gets absorbed by bloodstream and enter into the liver before distributing into the various compartments of body. Hence, they easily undergo hepatic metabolism called first pass effect, before entering into the systemic circulation, hence oral availability of the drug gets reduced. For example, nitroglycerine, pentazocine, propranolol, lidocaine, etc.

Many of the aromatic nitro drugs and azo drugs are metabolised in the bacterial flora present in the colon. The intestinal β-glucuronide conjugate takes place and it is excreted in the bile, thereby producing the free drug or its metabolite for reabsorption known as enterohepatic cycle.

The other organs involved in biotransformation are lungs, kidney, placenta, brain, adrenal glands and skin.

Cytochrome P-450 or Monooxygenase Enzymes and their Role in Oxidative Biotransformations

Among the various phase-I reactions, the oxidative biotransformation processes are the most common and most important one in drug biotransformation process. The general oxidation reactions of many xenobiotics substrates (RH) into their respective oxidized metabolites (ROH) involve the following chemical equation:

$$R\text{–}H + NADPH^{+} + O_2 \longrightarrow ROH + NADP^{+} + H_2O$$

Enzymes which participate or carry out these reactions are collectively called monooxygenases or mixed function oxidases.

Nomenclature of CYP-450 Enzymes

In the nomenclature, the CYP refers cytochrome system. This is followed by the Arabic numbers specifies the cytochrome family (CYP1, CYP2). Next the capital letter indicates the subfamily (CYP1A, CYP1B etc). Finally, the last Arabic number next to the capital letter indicates the specific enzyme involved in the particular reaction (CYP1A2, CYP12C9).

Reaction Process

1. The reaction needs both molecular oxygen and the reduced form of NADPH.
2. During this reaction, one oxygen atom is added into the substrate RH to give ROH and the other oxygen atom is attached into the water.
3. The CYP-450 enzyme is responsible for the transfer of oxygen atom to the substrate molecule.
4. The other two enzymes NADPH-dependent cytochrome P-450 reductase and NADPH-linked cytochrome b_5 which is responsible for the supply of reducing electrons needed for the overall reactions. The overall reaction is depicted as follows.

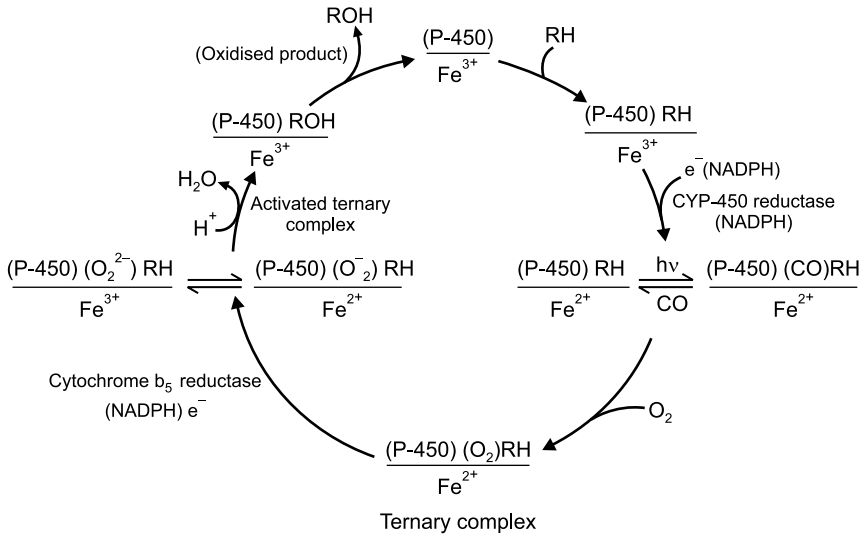


Figure 13.1: Catalytic reaction cycle involving cytochrome P-450.

The reaction sequence is as follows:

1. The first step of the reaction involves the attachment of the substrate to the (oxidised form of Fe^{3+}) resting state of CYP-450 to yield a P-450 (Fe^{3+}) substrate complex.
2. The second step is the transfer of one electron from the NADPH dependent CYP P-450 reductase to the CYP-450 (Fe^{3+}) substrate complex, that leads to the formation of P-450 (Fe^{2+})(RH). During this reaction, the oxidised form of Fe^{3+} is reduced to the Fe^{2+} which is capable of binding with molecular oxygen.
3. The complex obtained from the above step further reduced to yield a peroxide dianions P-450 (Fe^{3+})–substrate complex.
4. Water is eliminated from the intermediate to yield activated oxygen–P-450 substrate complex.
5. The activated oxygen $(FeO)^{3+}$ in this complex is highly electron deficient and a potent oxidising agent.
6. The activated O_2 is transferred to the substrate (RH) and the oxidised product (ROH) is released from the complex to regenerate the oxidised form of cytochrome P-450.

PHASE-I REACTIONS OR ASYNTHETIC REACTIONS OR FUNCTIONALIZATION REACTIONS

Characteristic Properties of Phase-I Reactions

1. **Improves the hydrophilicity:** In phase-I reactions, polar functional groups like –OH, $–NH_2$, –COOH, etc. are introduced into the lipid soluble substrate or unmasked the protecting groups which are already existing in the substrate. These are also called asynthetic reactions which are opposite to the phase-II reactions.
2. **Facilitation or improving conjugation:** During phase-I reactions, the substrate is made susceptible to phase-II reactions which convert the non-polar substrate into highly polar compounds which are easily excreted through urine.

3. **Reduction in stability:** These phase-I reactions reduce the stability of drug and enable the drugs to react with cellular components.

Phase-I Reactions

These are classified into three types.

1. Oxidative reactions
2. Reductive reactions
3. Hydrolytic reactions.

OXIDATIVE REACTIONS

These are the most common and most important metabolic reactions. Maximum all type of drugs or xenobiotics undergo these reactions.

Objectives

1. Oxidative reactions increase the water solubility of the compounds by introducing polar functional groups. Hence, these compounds easily undergo phase-II reactions and excreted through kidney.
2. Oxidation of xenobiotics is catalyzed by various kind of enzymes present in microsomes which needs molecular oxygen and reducing agent NADPH which affects the reaction. These enzymes are called mixed function oxidases.

Steps involved in oxidation reactions

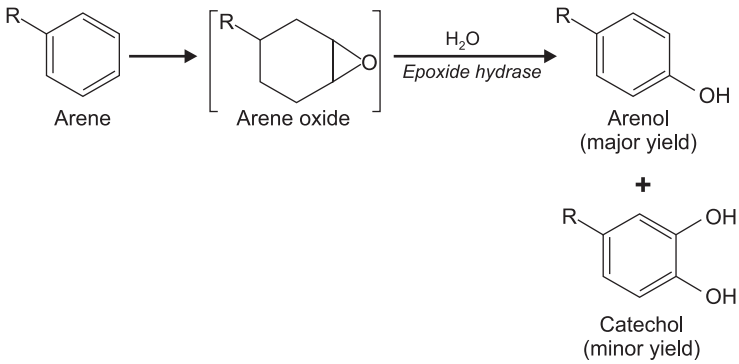
1. Reaction or binding of the xenobiotics or substrates or drugs (RH) to the oxidized cytochrome P-450 reductase, leads to the formation of complex.
2. Transfer of one electron from NADPH to the complex by the enzyme cytochrome P-450 reductase, leads to the formation of Fe^{2+}–P-450-substrate complex (reduced form of substrate enzyme complex).
3. Combination of molecular oxygen with the reduced form of substrate–enzyme complex to yield ternary complex.
4. The second electron transfer from NADPH to ternary complex in the presence of the enzyme cytochrome b_5 reductase to form a ternary activated oxygen–P-450–substrate complex.
5. The final step of the reaction is combination of one oxygen atom from the activated oxygen complex to the substrate to give the oxidized form of the product. The other atoms react together to form water.
6. Now, the free form of cytochrome P-450 is readily available to attach another molecule of xenobiotics.

Reactions

The various oxidation reactions of phase-I reactions can be explained as follows.

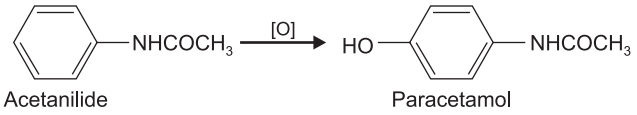
1. **Oxidation of aromatic carbons or aromatic hydroxylation:**

   The basic principle of the reaction involves the formation of highly effective arene oxide or epoxide of the substrate or drugs which undergo rearrangement to yield arenols.



Note: Monosubstituted arenes are oxidized at *ortho*, *para* or *meta* positions but *para* product is formed normally.

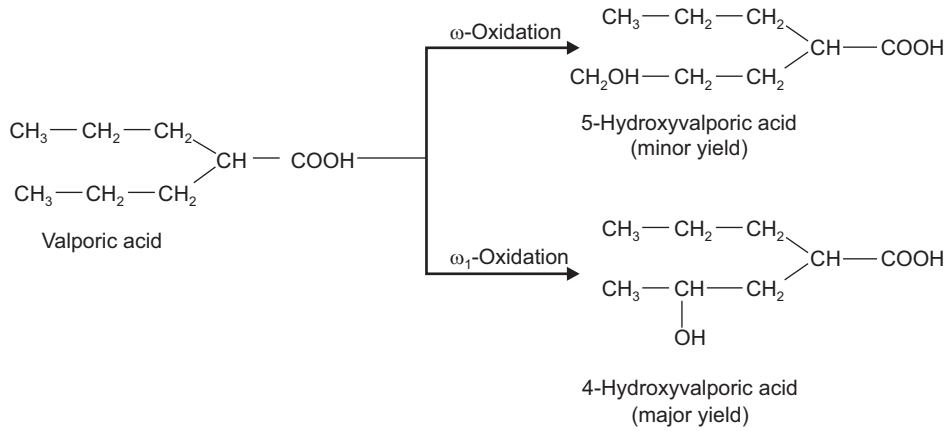
Example: Oxidation of acetanilide to paracetamol.



2. Oxidation of aliphatic carbons or aliphatic hydroxylation

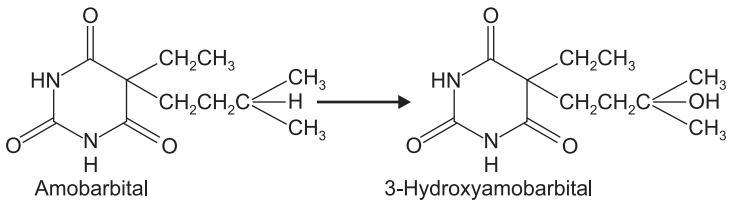
The aliphatic or alkyl carbon atoms are oxidized at two positions such as terminal methyl group (ω-oxidation) and the penultimate atom (ω_1-oxidation), but the later one predominates.

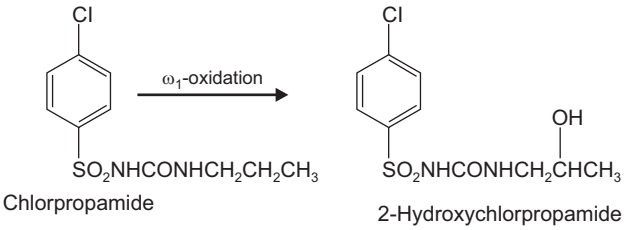
Example 1: Oxidation of the NSAIDs drug valproic acid.



This type of oxidation is called mixed function oxidation.

Example 2: Maximum number of barbiturates and some oral hypoglycemic sulphonylureas are metabolized by ω- and ω_1-oxidation method.



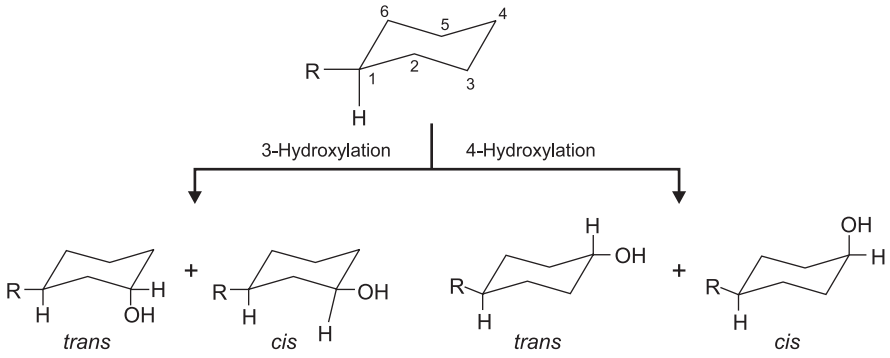


The other examples of drugs which undergo aliphatic hydroxylation are phenylbutazone, glutethimide, meprobamate etc.

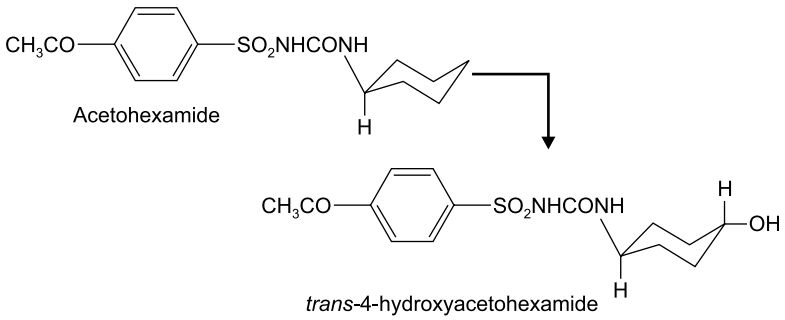
Note: The initial products obtained undergo oxidation to give aldehydes, ketones or carboxylic acids. These may also undergo glucuronide conjugation. This type ω- and ω_1-oxidation commonly occurs in drugs containing straight or branched chains.

3. Oxidation of alicyclic carbons or alicyclic hydroxylation

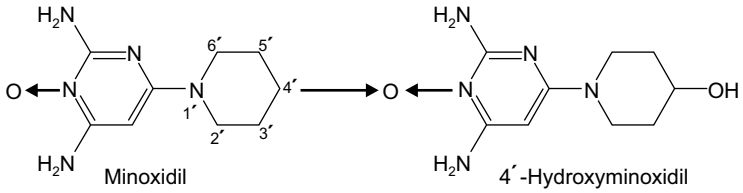
The cyclohexyl group present in many of the drugs undergoes mixed-function oxidation. The metabolism of these drugs mainly takes place in C-3 or C-4 position and gives *cis* and *trans* isomers. In human beings, the *trans* isomers are obtained as the major metabolite.



Example 1:



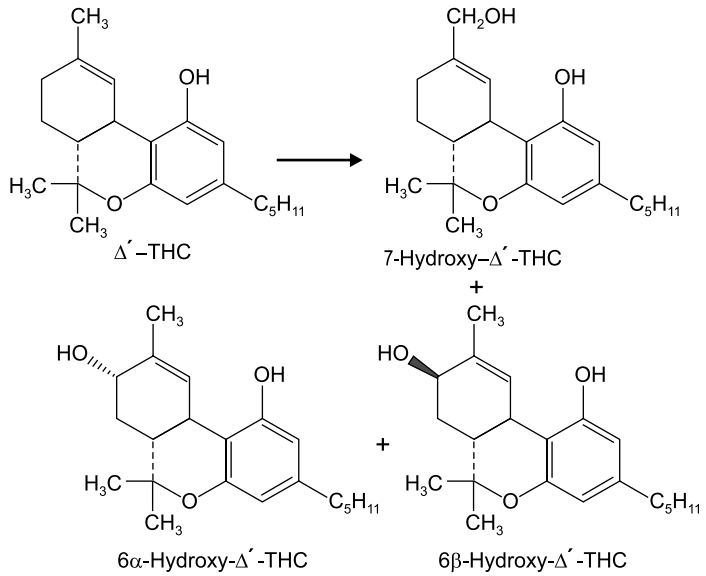
Example 2: Metabolism of alicyclic six-membered piperidyl moiety in minoxidil also follow the above hydroxylation.



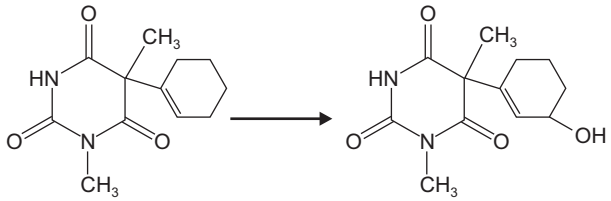
4. Oxidation of allylic carbon atoms:

Allylic carbon atoms also metabolized by hydroxylation.

Example: Metabolism of psychoactive drug Δ′-tetra hydrocannabinol-(Δ′-THC). This drug contains 3-allylic carbon centres, i.e. C-3, C-6 and C-3′. But the allylic hydroxylation chiefly takes place in C-7 carbon centre. The 7-hydroxy metabolite obtained is pharmacologically more active than the parent drug.



The S (+)-isomer of hexobarbital is easily metabolized by hydroxylation than *R* (–)-isomer.

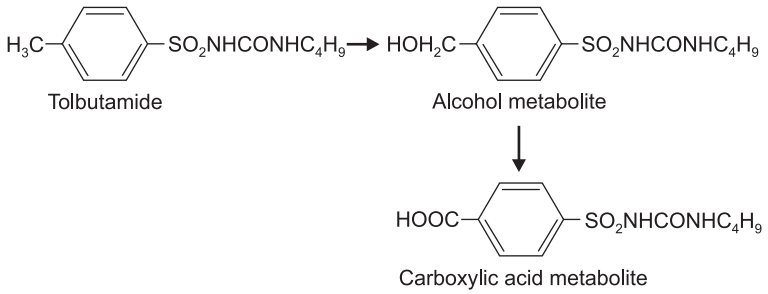


Note: Generally, allylic hydroxylation does not form any reactive intermediates.

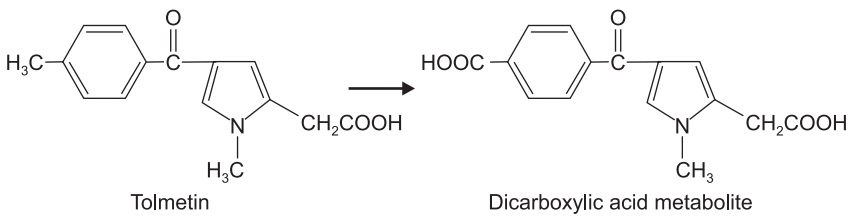
5. Oxidation of benzylic carbons or benzylic hydroxylation

Carbon atoms attached to the aromatic ring undergo oxidation and form respective carbinol or alcohol. The primary alcoholic metabolites obtained are further oxidized to yield aldehydes and carboxylic acids and the 2° alcoholic metabolites are converted into ketones with the aid of soluble alcohol and aldehyde dehydrogenase enzymes. Sometimes, the alcohol may be conjugated with glucuronic acid directly.

Example 1:



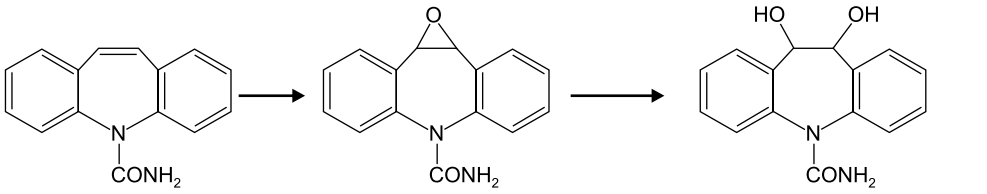
Example 2:

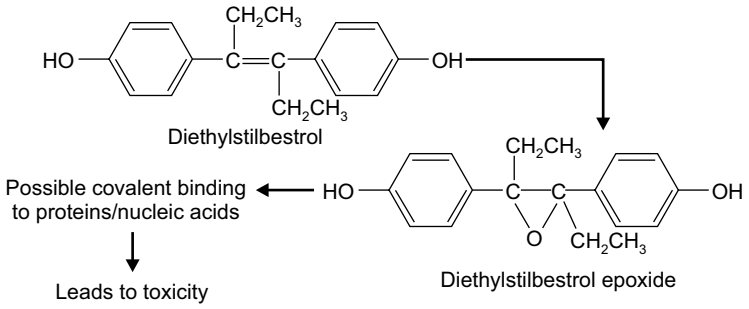


6. Oxidation of olefins

Olefins undergo metabolism and lead to the formation of corresponding epoxides or oxiranes which are stable than arene oxides. The epoxide metabolites further undergo enzymatic hydration by epoxide hydrase to form *trans*-1,2-dihydrodiols or 1,2-diols or 1,2-dihydroxy compounds.

Example:

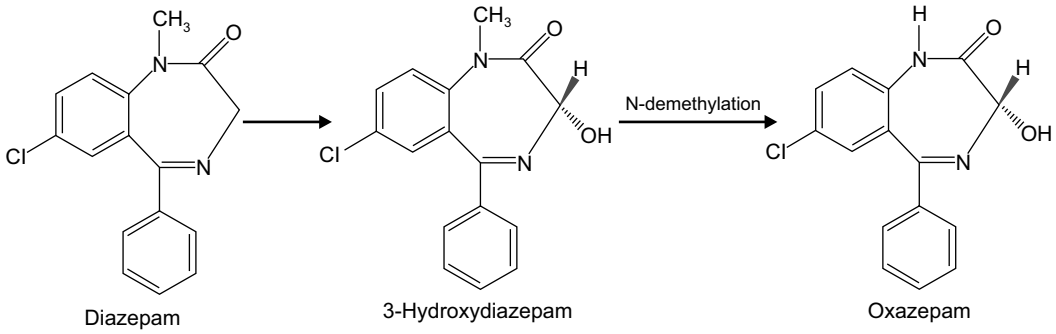




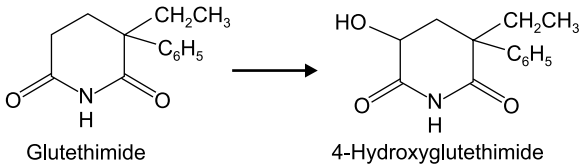
7. Oxidation of carbon atoms α to carbonyls and imines

The mixed functional oxidase also metabolizes the carbon atoms adjacent to carbonyl and imino groups.

Example 1:



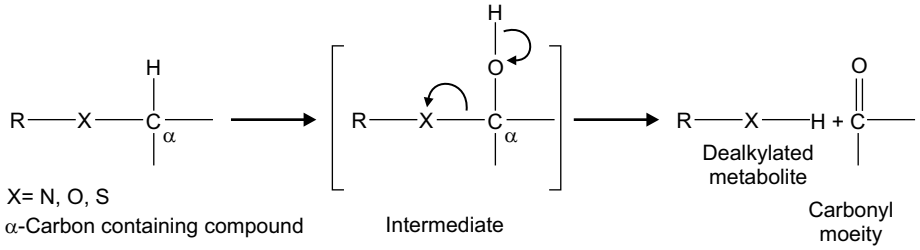
Example 2:



8. Oxidation involving carbon-heteroatom

Maximum number of drugs contains nitrogen and oxygen atoms. Sulphur atom is present occasionally. Metabolic oxidation of C-N, C-O, C-S involves two basic types.

1. Hydroxylation of the α-carbon which is directly attached to the N (nitrogen), O (oxygen) and S (sulphur). The intermediate obtained is unstable and decomposes with the cleavage of C-hetero-atom bond.



The reactions of oxidative N-dealkylation, O-dealkylation and S-dealkylation belong to this category.

2. Hydroxylation or oxidation of the heteroatoms (N, S-only undergoes this type of reaction), depending upon various factors one of the above pathways is preferred among this.

a. Oxidation involving Carbon–Nitrogen Systems

Biotransformation of nitrogen containing compounds are important one because of their occurrence in many natural products and in vast number of important drugs such as alkaloids, antihistamines, benzodiazepines, etc.

Nitrogen containing compounds are classified as follows:

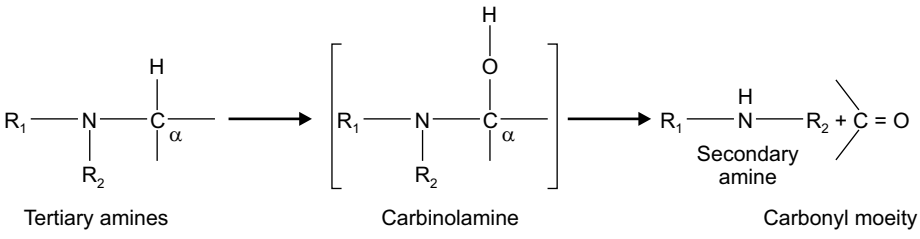
1. Aliphatic (1°, 2°, 3°) and alicyclic (2°, 3°) amines
2. Aromatic amines
3. Amides

The main enzymes responsible for these reactions are cytochrome P-450 mixed function oxidases and amine oxidases or N-oxidases. The activation of later one needs NADPH and molecular oxygen. Biotransformation of C-N system takes places by following reactions.

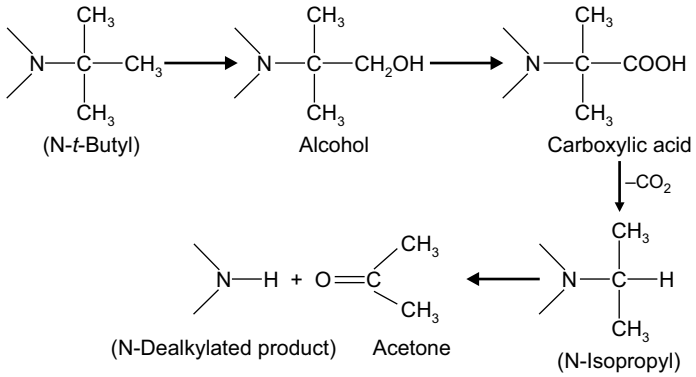
i. N-Dealkylation
ii. Oxidative deamination
iii. N-oxide formation
iv. N-Hydroxylation.

i. N-Dealkylation

3° aliphatic and alicyclic amines: The oxidative removal of alkyl groups from 3° aliphatic and alicyclic amines is called oxidative N-dealkylation. These reactions are carried out by cytochrome P-450 mixed function oxidase enzyme. This reaction takes place via the formation of unstable carbinolamine intermediate which upon the hydrolytic cleavage of C–N gives the 2° amines and carbonyl moiety (aldehyde or ketones).

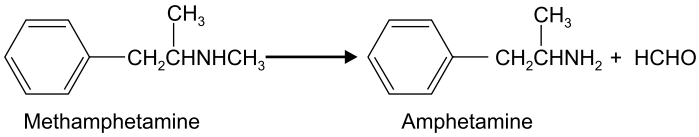


When compared with 2° nitrogen, 3° nitrogen easily undergoes dealkylation because of its higher solubility. Thus, the first alkyl group is removed fast and the second one is removed slowly. N-dealkylation of 3° butyl group is not possible because the α-carbon cannot be hydroxylated.

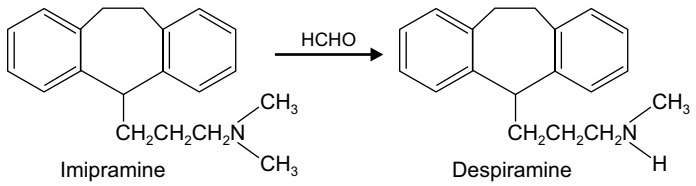


If the tertiary nitrogen atom is attached to different alkyl groups, then the smaller sized alkyl group is dealkylated first.

Secondary aliphatic amines:

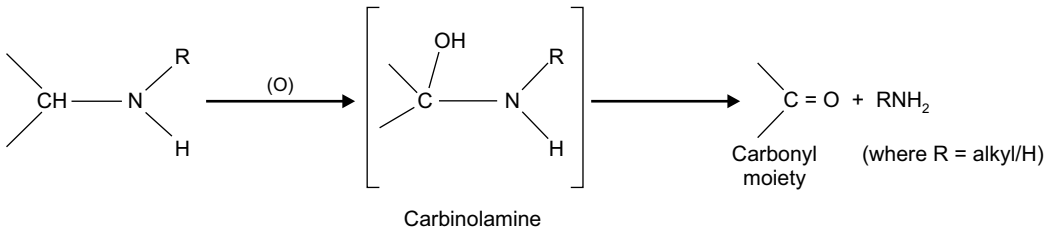


Tertiary aliphatic amines:

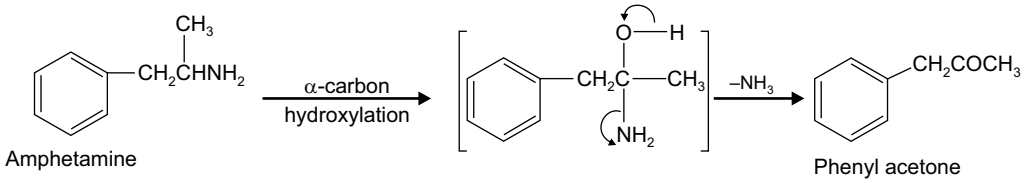


ii. Oxidative deamination:

This reaction also takes place via the formation of carbinolamine intermediate. Here, the C-N bond breaking takes place where the bond links the amino group to the larger portion of the molecule gets cleaved.



The oxidative deamination is carried out by the enzyme mixed-function oxidases. Endogenous neurotransmitters are metabolized by a specialized family of enzymes, known as monoamine oxidases (MAOs).

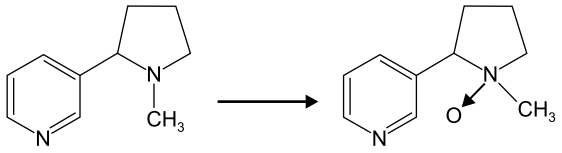


Amphetamine Phenyl acetone

iii. N-Oxide formation:

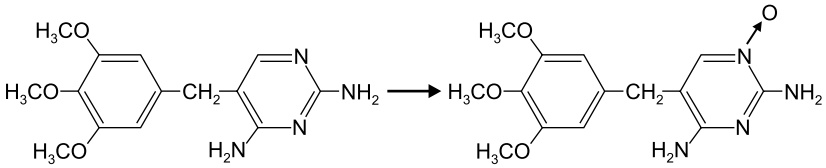
Tertiary amines with basic properties undergo N-oxide formation. The various types of tertiary amines are:

1. Aliphatic amines
2. Alicyclic amines



Nicotine Nicotine-N-oxide

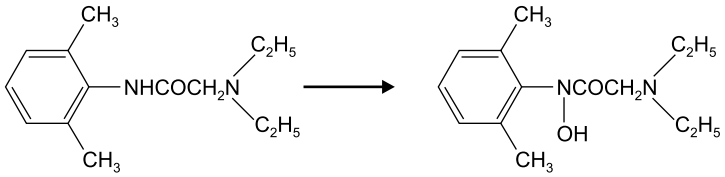
3. Aromatic heterocycles containing nitrogen



Trimethoprim Trimethoprim-N-oxide

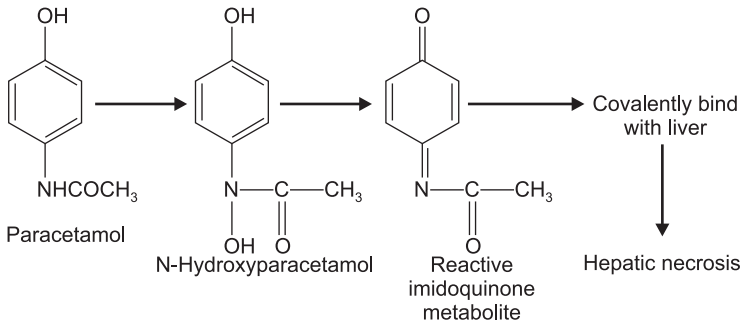
iv. N-Hydroxylation:

i. *Amide nitrogen containing compounds*

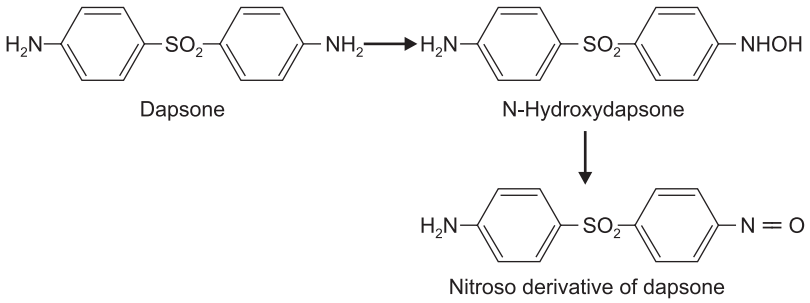


Lidocaine N-Hydoxylidocaine

N-hydroxylation of amide sometimes gives chemically reactive intermediate which covalently binds with the receptors. The best example for this reaction is paracetamol Therapeutic doses of paracetamol are safe because it produces the active metabolite of paracetamol imidoquinone and it is neutralized by glutathione. But in higher doses, the paracetamol metabolite covalently binds with liver tissue and produces hepatic necrosis.

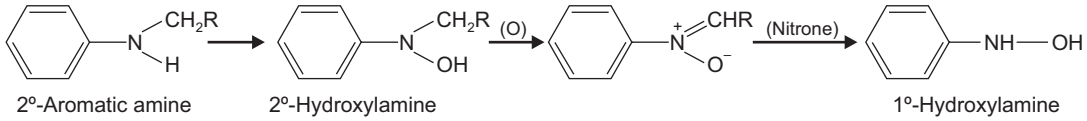


ii. *N-Hydroxylation of 1° amines:* Primary amines are hydroxylated and give nitroso derivatives.

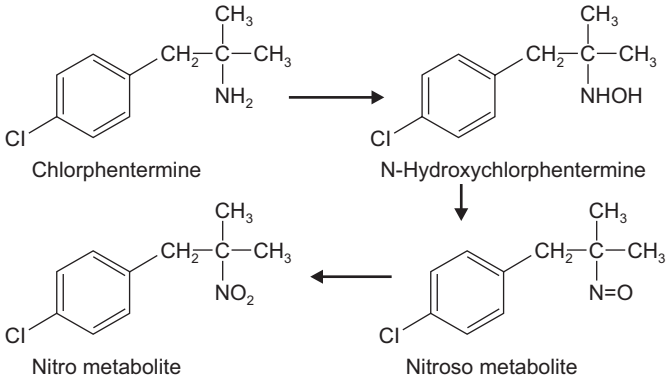


Note: N-Hydroxydapsone oxidizes the ferrous form of hemoglobin into ferric form which leads to the toxicity of methemoglobinemia.

iii. *N-hydroxylation of 2º-amines:* 2º-aromatic amines undergo N-hydroxylation to yield 2º-hydroxylamine which upon oxidation leads to nitrone. Hydration of later provides 1º-hydroxylamine.

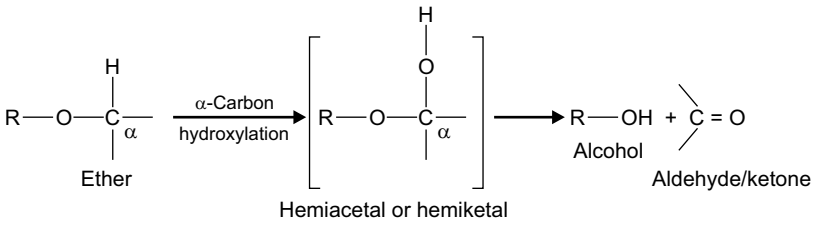


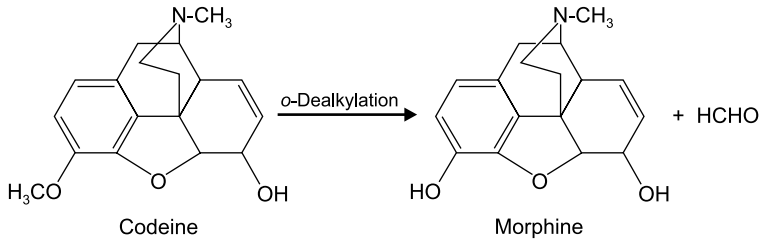
iv. *N-hydroxylation of α-substituted 1° amines:*

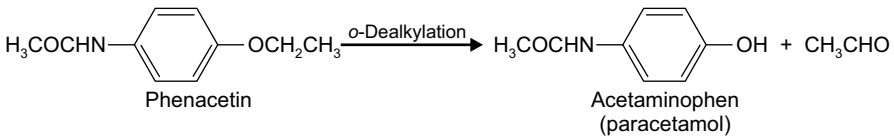


b. Oxidation of Carbon–Oxygen Systems

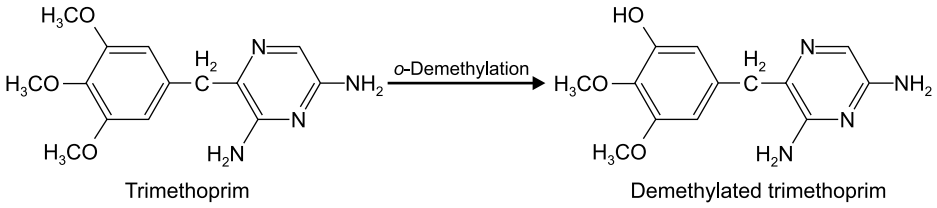
The metabolism of C–O system involves the formation of hemiacetal and hemiketal by the hydroxylation of α-carbon which further undergoes spontaneous C–O bond cleavage to yield phenol or alcohol and aldehyde or ketone. Small alkyl groups like methyl, ethyl, propyl, etc. attached to the oxygen atoms gets dealkylated rapidly.







The other drugs which follow this reaction are indomethacin, metoprolol, etc. some of the drugs contains non-equivalent $-OCH_3$ groups, in that case one particular methoxy group preferentially undergoes *o*-demethylation as shown in the following example:



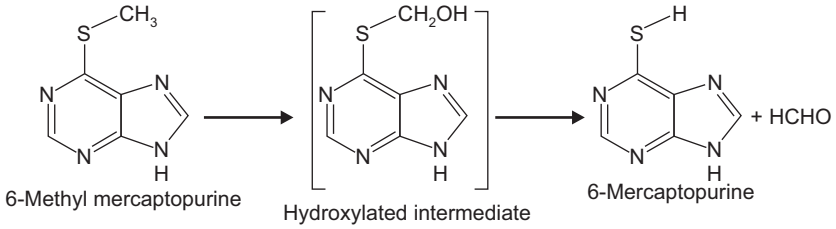
Oxidation of Carbon–Sulphur Systems

Oxidation of carbon–sulphur systems involves the following reactions.

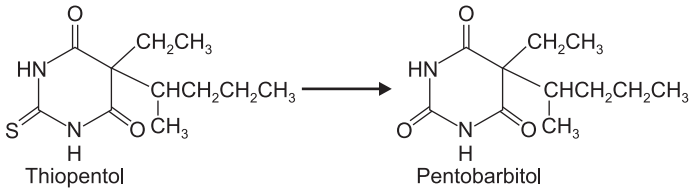
1. S-dealkylation
2. S-oxidation
3. Desulphuration

The S-dealkylation and desulphuration needed oxidative C-S bond cleavage.

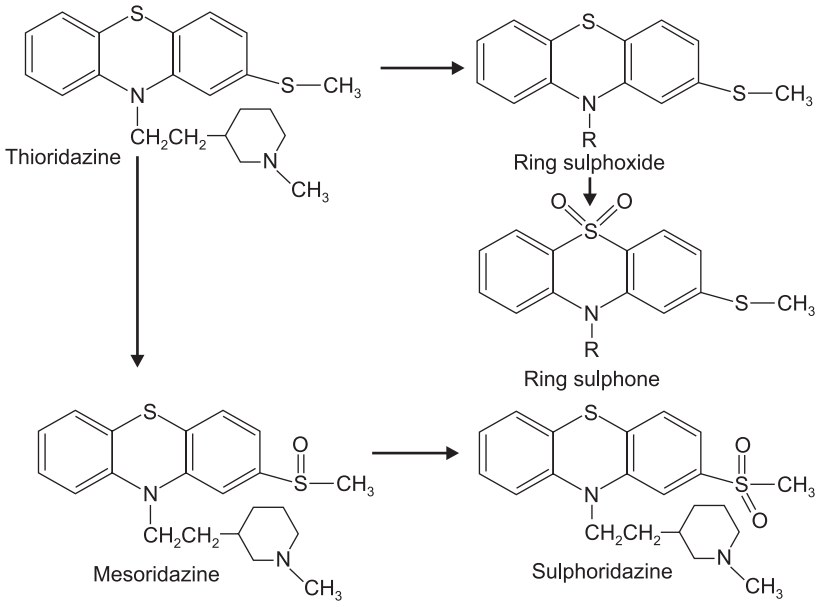
1. **S-dealkylation:** The metabolism by S-dealkylation in human is less.



2. **Desulphuration:** Oxidative conversion of carbon–sulphur double bond into carbon–oxygen double bond is called desulphuration.



3. **S-oxidation:** Many phenothiazine derivatives and organosulphur containing xenobiotics are metabolized by S-oxidation.

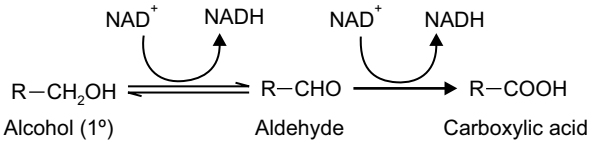


Note:

1. S-oxidation is an important way of metabolism of H_2-antihistamines like cimetidine.
2. Sulphoxide drugs and metabolites further undergo oxidation leads to sulphones.

9. Oxidation of alcohols and aldehydes

Many oxidation reactions leads to the formation of alcohols, as these reactions lead to the formation of alcohols as reactive intermediates. If they do not undergo phase-II reactions, they are further oxidized and converted into aldehydes and ketones. The aldehyde metabolic product is also obtained from oxidative deamination of 1° aliphatic amines which are further oxidized to carboxylic acids and its derivatives.



The bioconversion of alcohols to aldehydes and ketones is catalyzed by the enzyme soluble *alcohol dehydrogenase* present in liver and other tissues. NAD^+ and $NADP^+$ are needed as coenzyme. The further conversion of aldehydes to their respective carboxylic acids is effected by *aldehyde oxidase* and *xanthine oxidase*.

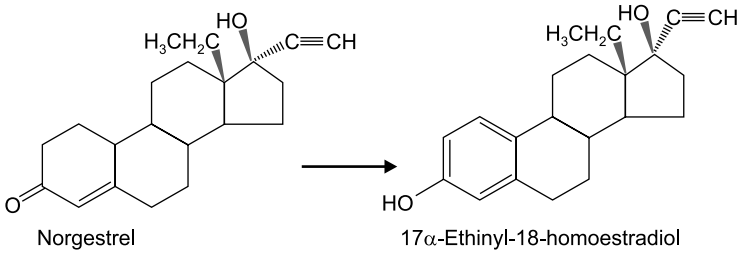
10. Miscellaneous oxidation reactions

It includes the following two reactions.

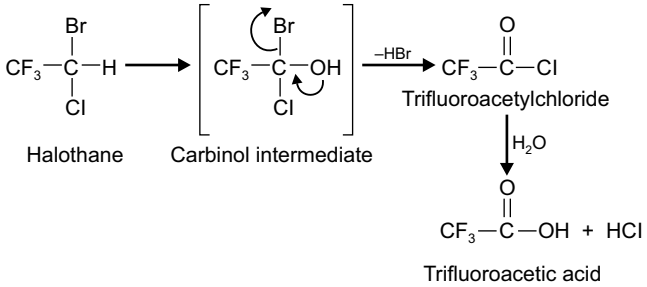
a. Oxidative aromatization/dehydrogenation
b. Oxidative dehalogenations

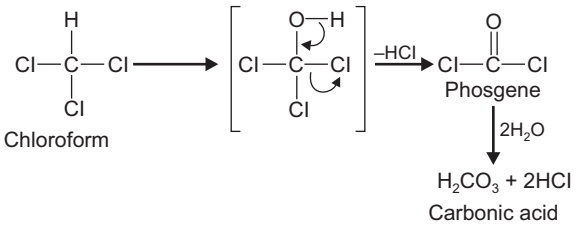
Let us discuss these reactions.

a. Oxidative aromatization results in the formation of aromatic ring as shown in norgestrel steroidal drug.



b. Oxidative dehalogenation: Many of the halogen containing compounds are metabolized by oxidative dehalogenation. For example, halothane and chloroform.





Note: Oxidative dehalogenation leads to the formation of toxic acylhalide intermediates.

REDUCTIVE REACTIONS

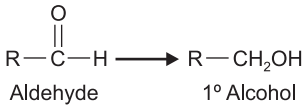
Reductive reactions are important one for compounds containing carbonyl, nitro and azo groups. The bioreduction of carbonyl compounds yields alcohol derivatives whereas the nitro and azo compounds give amino derivatives.

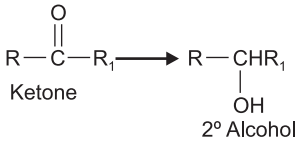
1. Reduction of Aldehydes and Ketones

According to the reactivity towards bioreduction carbonyl compounds are classified into three categories:

1. Aliphatic aldehydes and ketones
2. Aromatic aldehyde and ketones
3. Ester, acids and amides.

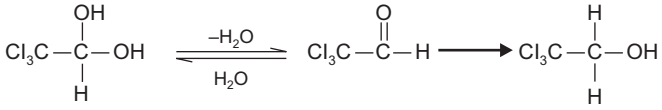
Majority of the drugs have ketone groups. The aldehyde group present in the substrate is reduced to primary alcohols whereas the ketones are reduced to 2° alcohols. The metabolites formed in this further undergoes conjugation with glucuronides.



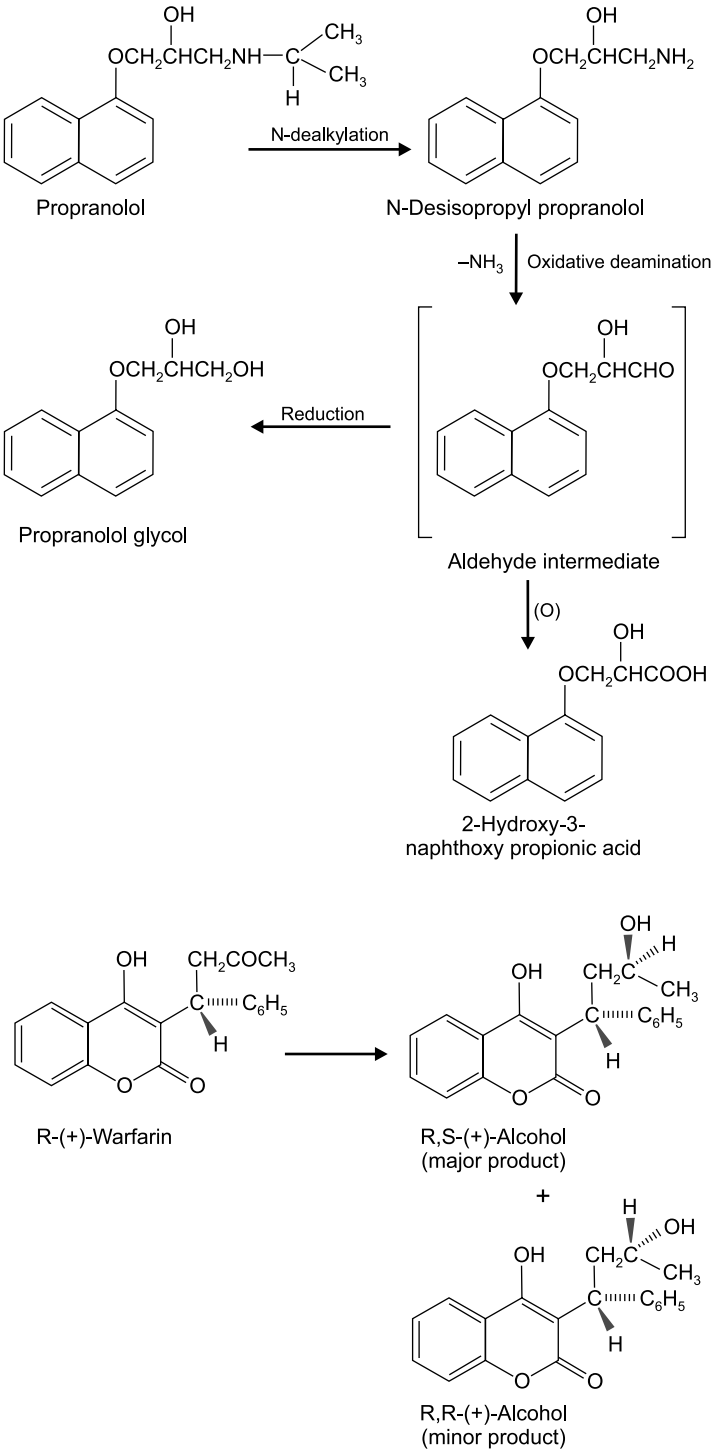


The enzyme aldo-keto reductase is responsible for this reaction. Sometimes, other *oxidoreductase* enzymes are also involved in these reactions. Various examples for this reaction are as follows.

a. Aliphatic aldehydes

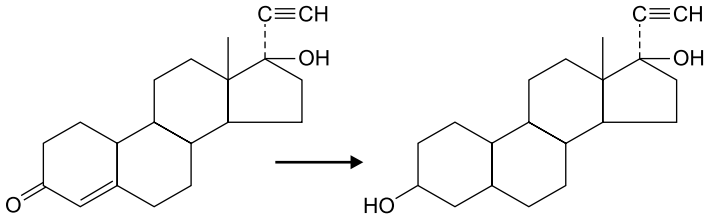


Sometimes, the metabolites obtained from oxidative deamination also undergo reduction to a minor extent.


OH
OCH2CHCH2NH—C
CH3
CH3
H
N-dealkylation
OH
OCH2CHCH2NH2
Propranolol
N-Desisopropyl propranolol
–NH3
Oxidative deamination
OH
OCH2CHCHO
OH
OCH2CHCH2OH
Reduction
Propranolol glycol
Aldehyde intermediate
(O)
OH
OCH2CHCOOH
2-Hydroxy-3-
naphthoxy propionic acid
OH
CH2COCH3
C6H5
H
O
O
R-(+)-Warfarin
OH
H
CH2C
CH3
C6H5
R,S-(+)-Alcohol
(major product)
+
R,R-(+)-Alcohol
(minor product)

2. Reduction of α,β-unsaturated Ketones

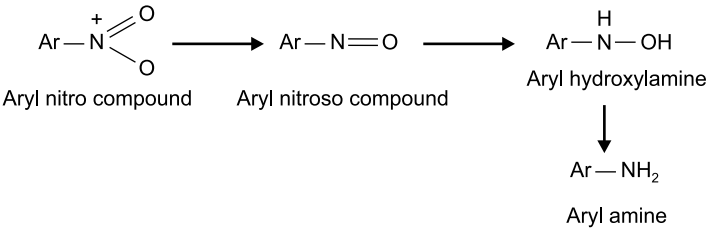
These compounds are not only reduced at ketone group but also reduced at carbon-carbon double bond.



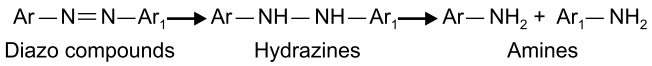
Norethindrone 3β,5β-Tetrahydronorethindrone

3. Reduction of Nitro and Azo Compounds

The reduction of nitro and azo compounds leads to the formation of aromatic primary amine metabolites, the sequence of reductions is as follows.

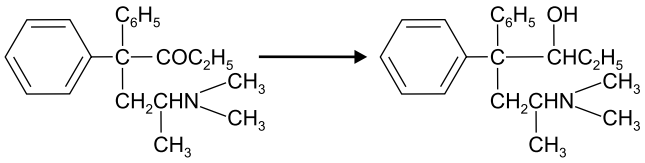


Aryl nitro compound → Aryl nitroso compound → Aryl hydroxylamine → Aryl amine



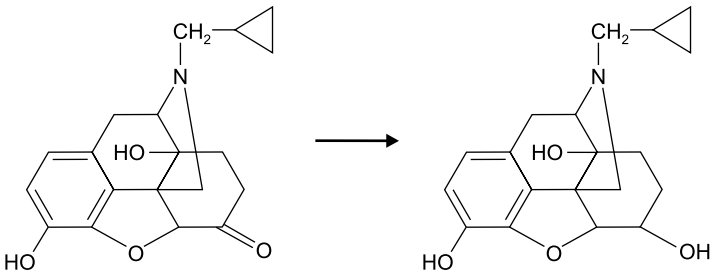
Diazo compounds → Hydrazines → Amines

Aliphatic ketones



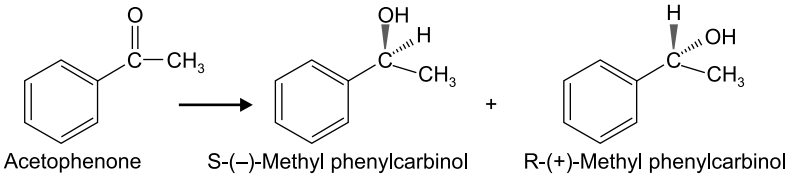
Methadone Methadol

Alicyclic ketones



Naltrexone Naltrexol

Aromatic ketones

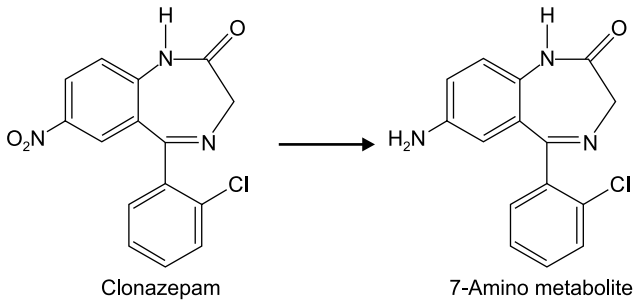


Acetophenone S-(–)-Methyl phenylcarbinol R-(+)-Methyl phenylcarbinol

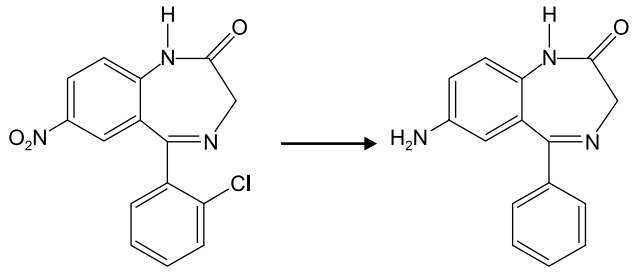
Ketones with chiral carbons also reduced to two epimeric or diastereomeric alcohols. For example, warfarin is reduced to R, S-(+)-alcohol and R, R-(+)-alcohol.

Bioreduction of nitro compounds is carried out by NADPH-dependent nitro reductase enzymes. The reduction of azo compounds is carried out by the enzyme bacterial hepatic microsomal reductase. The enzyme bacterial hepatic microsomal reductase also reduces nitro and azo compounds.

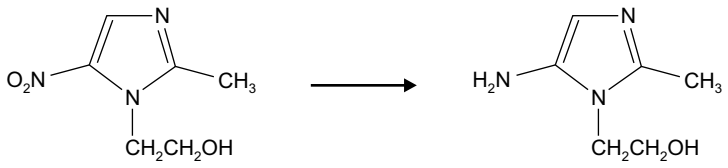
Example:



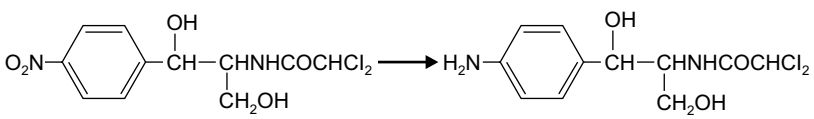
Clonazepam 7-Amino metabolite



Nitrazepam Amino metabolite

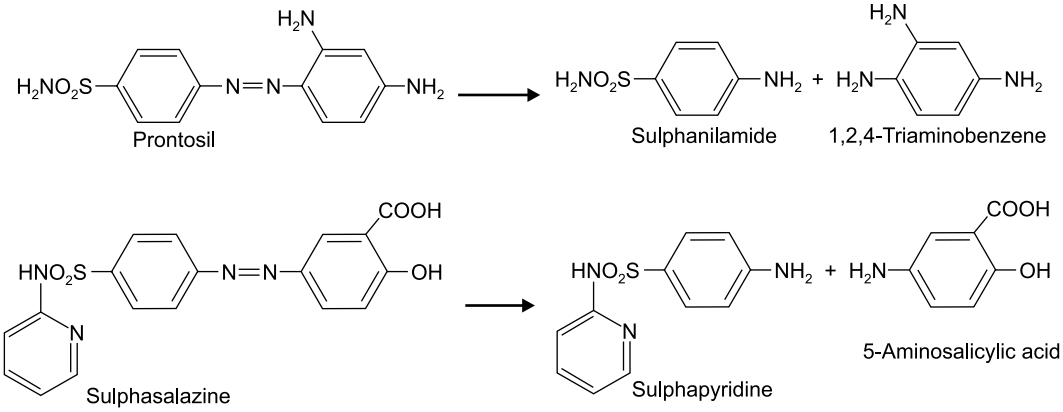


Metronidazole Amino metabolite



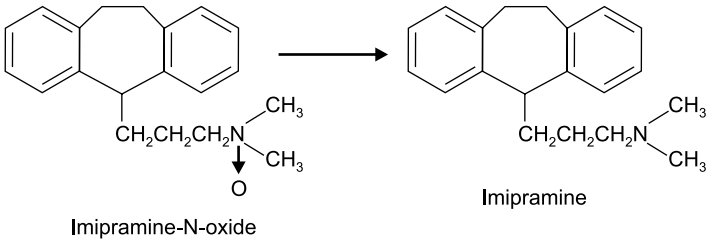
Chloramphenicol Amino metabolite

Reduction of azo compounds is an historical example for the discovery of sulphanilamide antibiotic from prontosil. Bacterial reductase in the intestine is responsible for the reduction of azo compounds.

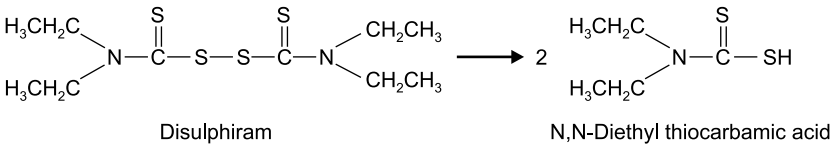


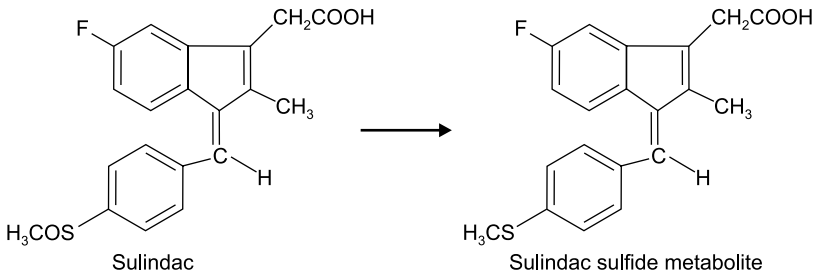
4. Miscellaneous Reductions

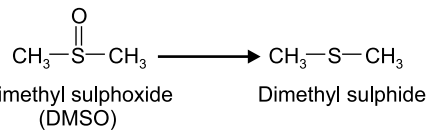
1. **Reduction of N-oxides:** N-oxides are reduced to respective tertiary amines.



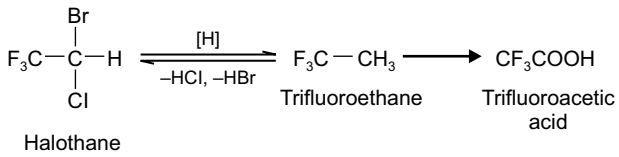
2. **Reduction of sulphur containing compounds:** It is a minor pathway of metabolic reductions.







3. **Reductive dehalogenation:** This reaction follows the displacement or removal of halogen atom from the attached carbon atom.

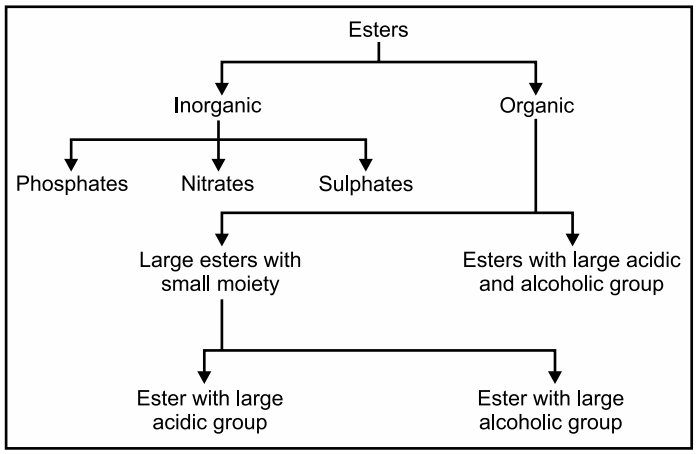


HYDROLYTIC REACTIONS

Hydrolysis plays an important role in the metabolism of amide linkage and ester linkage containing drugs. In most of the drugs, it is catalyzed by the hydrolytic enzymes. The metabolic products obtained are polar compounds and are excreted easily from body.

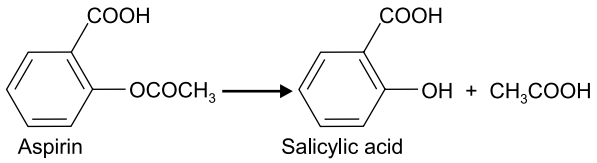
Hydrolysis of Esters

CLASSIFICATION OF ESTERS

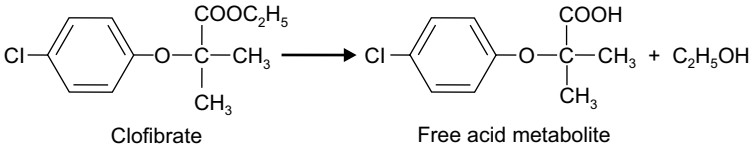


Organic acid esters

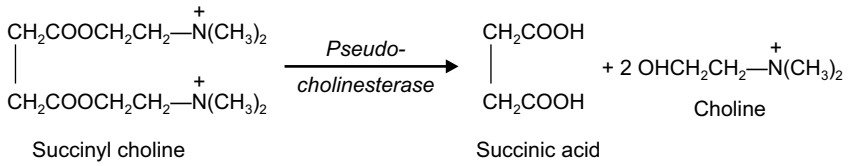
1. **Esters with large alcoholic group**



2. **Esters with large acidic group and small alcoholic group**



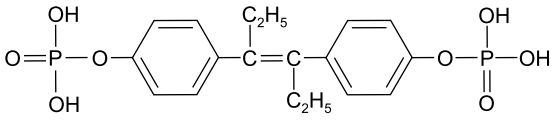
3. **Esters with large acidic and alcoholic group**



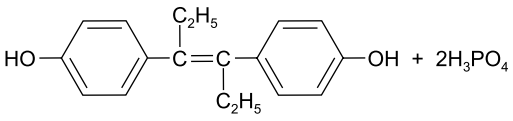
Succinyl choline → Succinic acid

Inorganic Acid Esters

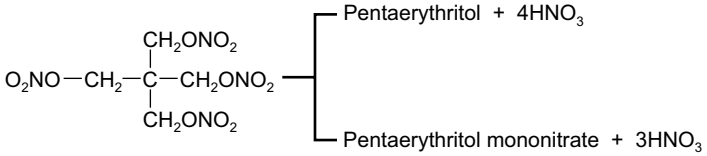
Example: Sulphate esters



Stilbestrol diphosphate



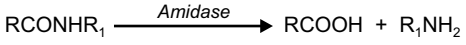
Stilbestrol



Pentaerythritol tetranitrate

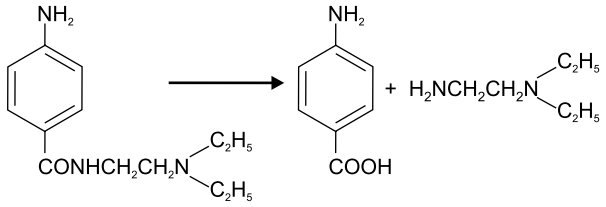
Hydrolysis of Amides

The rate of hydrolysis of amides is lower than esters. Amides are hydrolyzed by the enzyme amidase which involves the cleavage of C-N linkage to yield corresponding carboxylic acids.



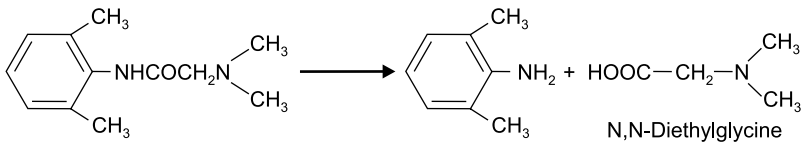
Amide → Acid + Amine

1. **Secondary amides with aliphatic substitution at N-atom**



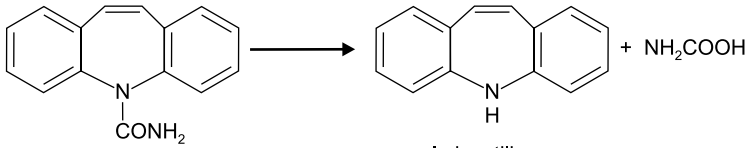
Procainamide → *Para* amino benzoic acid

2. **Secondary amides with aromatic substitutes at N-atom**



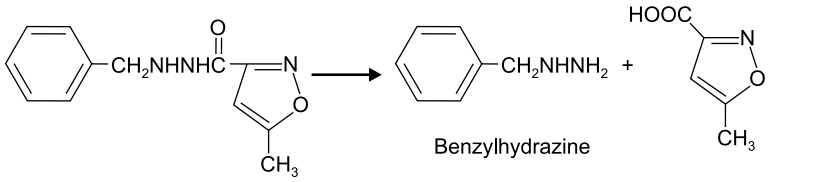
Lidocaine — 2,6-Xylidine — N,N-Diethylglycine

3. **Tertiary amides**



Carbamazepine — Iminostilbene

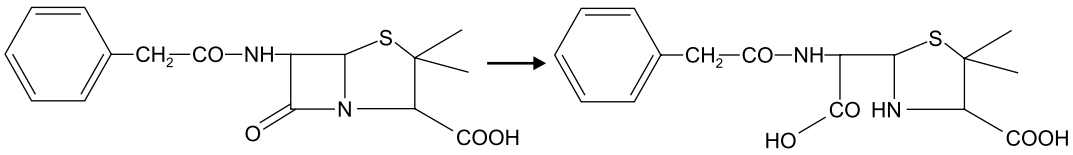
4. **Hydrazides**



Isocarboxazide — Benzylhydrazine — 5-Methylisoxazole-3-carboxylic acid

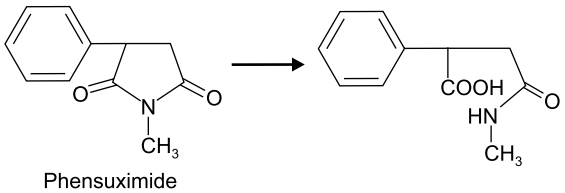
Hydrolysis of Non-aromatic Heterocycles

1. **Four-membered lactam rings**



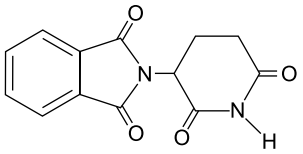
Benzyl pencillin — Pencillonic acid

2. **Five-membered lactam rings**



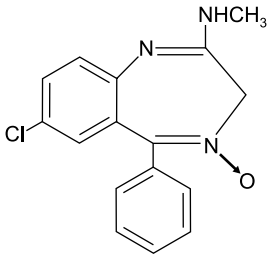
Phensuximide

3. **Six-membered lactam rings**



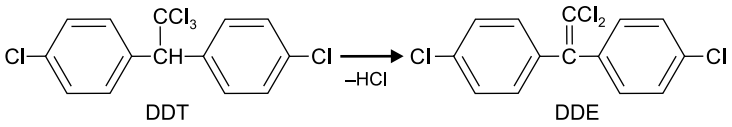
Phthalidomide

4. **Seven-membered lactam rings:**



Chlordiazepoxide

5. **Hydrolytic dehalogenation:** Example for this reaction is the pesticide DDT.



DDT DDE

Miscellaneous Hydrolytic Reactions

Recombinant human peptide drugs and hormones at the N- or C- terminal amino acids undergo phase-I metabolism by carboxy and amino peptidases. Example for this category is growth hormone, human insulin, parathyroid hormone, etc.

PHASE-II REACTIONS OR TRUE DRUG DETOXIFICATION PROCESS OR CONJUGATION REACTIONS

The phase-I reactions do not yield fully hydrophilic or pharmacologically inactive metabolites. But the phase-II reactions convert the metabolites formed from the phase-I reactions into highly polar and water-soluble products. The phase-II conjugation reactions required many number of conjugative enzymes. The main role of this enzyme is attaching a small, polar and ionizable endogenous molecules such as, glucuronic acid, glycine sulphate and glutamine to the phase-I metabolites or products or parent xenobiotics. The resulting conjugates formed are relatively water soluble and excreted rapidly from the body. The conjugates formed are non-toxic and pharmacologically inactive in nature. The other phase-II reactions such as acetylation and methylation do not increase the hydrophilicity of the drugs but attenuate or terminate the pharmacological activity of the drug molecules. The role of glutathione (GSH) is to combine with chemically reactive compounds to inhibit damage to the important biomacromolecules such as DNA, RNA and proteins. Hence, the phase-II reactions are called true detoxification process or reaction pathways in drug biotransformation.

Distinguishing Features of Phase-II Reactions

1. Glucuronic acid, sulphate, acetyl and methyl conjugation takes place and the conjugative groups are initially activated in the form of a co-enzyme before attaching to accepting substrate in the presence of corresponding transferase enzyme.
2. In glycine and glutamine conjugation, the substrate is activated initially.
3. Apart from this, many endogenous compounds such as catecholamines, steroids, bilirubin and histamine also undergo conjugation by using the same coenzymes or specific transferase enzymes.
4. Other than the above said conjugation reactions, conjugation with glycosides, phosphate and other amino acids, cyanide to thiocyanate also involved, but they do not play a role in drug metabolism.

Glucuronic Acid Conjugation/Glucuronidation

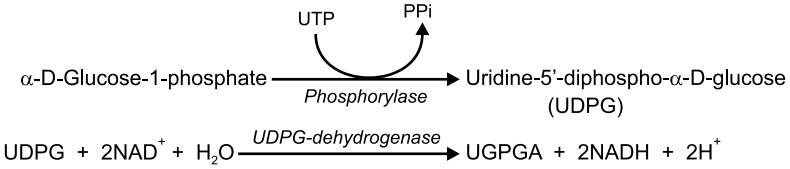
It is the most common pathway in phase-II drug metabolism. The various reasons behind this reaction are as follows:

a. The D-glucuronic acid required for this reaction is easily derived from D-glucose.
b. Large number of functional groups are easily attached to the glucuronic acid.
c. Combination of glucuronic acid with various functional groups increases the hydrophilicity of parent xenobiotics or conjugated products.

Formulation of β-glucuronide conjugates: It involves two steps:

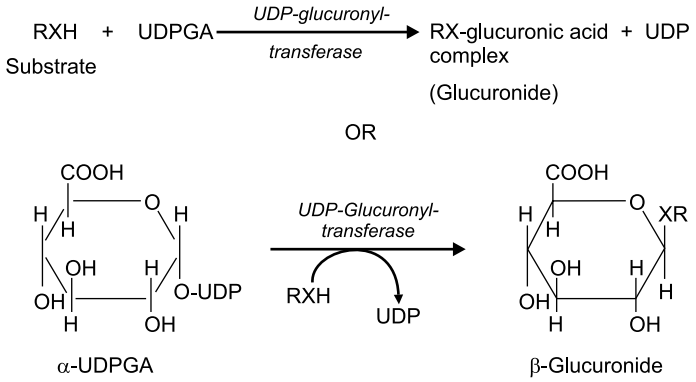
Step 1 [Synthesis of UDPGA (uridine-5'-diphospho-α-D-glucuronic acid), an active co-enzyme]:

The active co-enzyme UDPGA is synthesized from UDP-glucose (UDPG). Here, the co-enzyme UDPGA acts as a donor of glucuronic acid. The UDPG needed for this reaction is synthesized by the reaction between α-D-glucose-1-phosphate and UTP (uridine triphosphate).



Step 2: Transfer of glucuronyl moiety from UDPGA to the substrate or the product of phase-I metabolism:

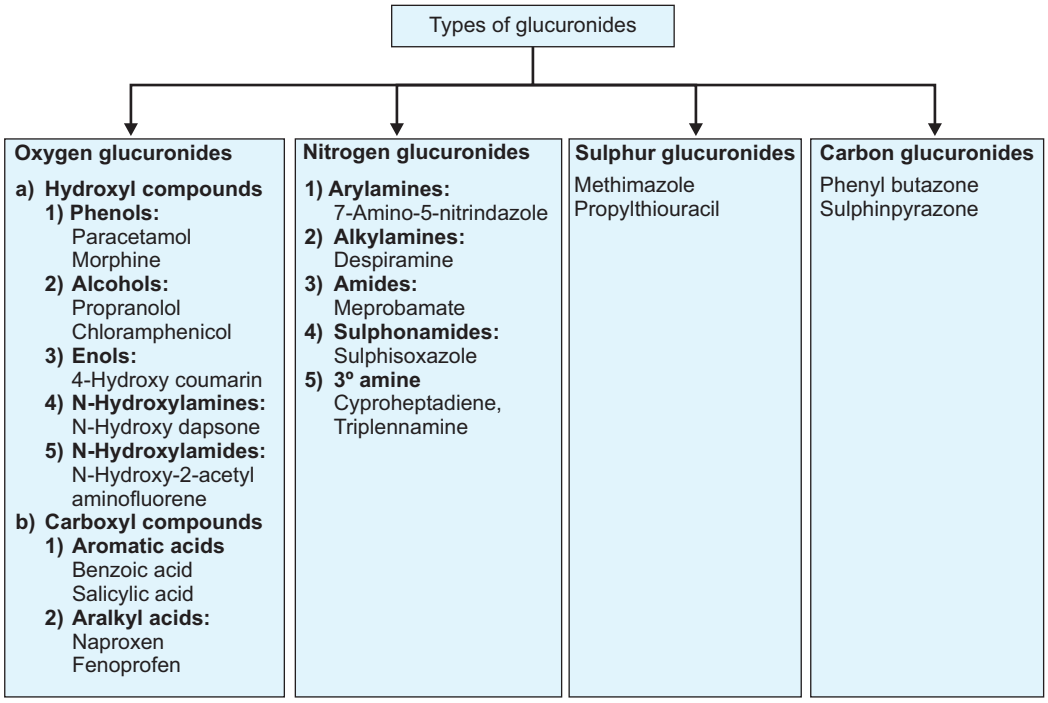
The glucuronyl moiety present in the UDPGA is transferred into the substrate by UDP-glucuronyl transferase to give the substrate glucuronic acid conjugate. The glucuronyl transferase enzyme is mainly present in the liver.



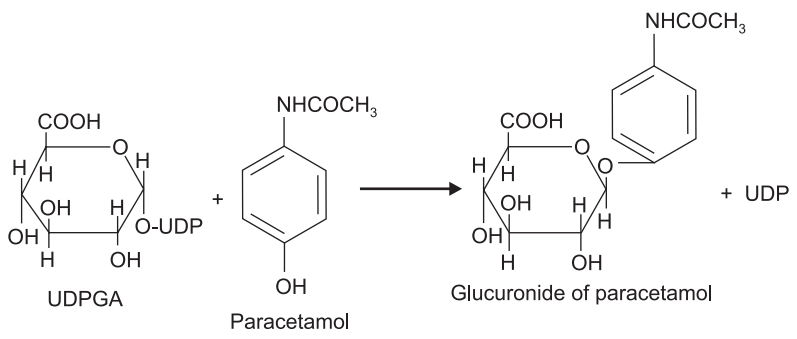
Note:

1. All the glucuronide conjugates possess β-linkage or β-configuration at C-1, but the co-enzyme UDPGA has α-linkage.
2. In the enzymatic transfer, replacement of α-linked UDP-moiety from UDPGA to the substrate molecule RXH takes place via the complete inversion of configuration, at C-1 position to yield β-glucuronide.
3. Glucuronidation of one functional group is an effective way of elimination of metabolites.

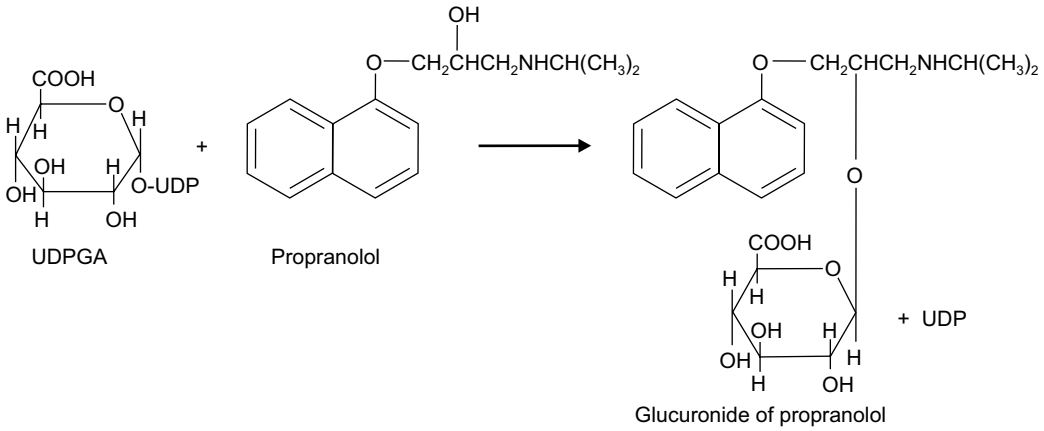
The metabolic products obtained are classified as oxygen, sulphur, nitrogen or carbon-glucuronides depending upon the type of heteroatom attached to the C-1 atom of glucuronyl moiety.



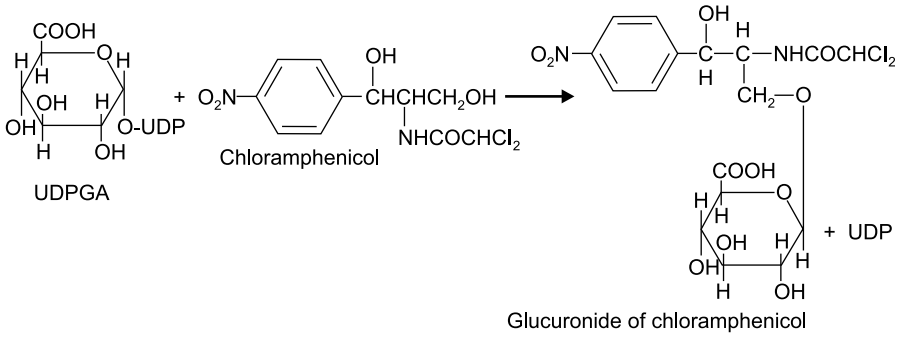
- **Oxygen glucuronides:** Phase-I products or xenobiotics containing hydroxyl (–OH) and carboxyl (–COOH) group easily undergo O-glucuronidation. In that, phenol and hydroxyl groups are the important functional groups which easily get glucuronised. For example:
  a. *Phenol derivatives:* Phase-II reaction of paracetamol.



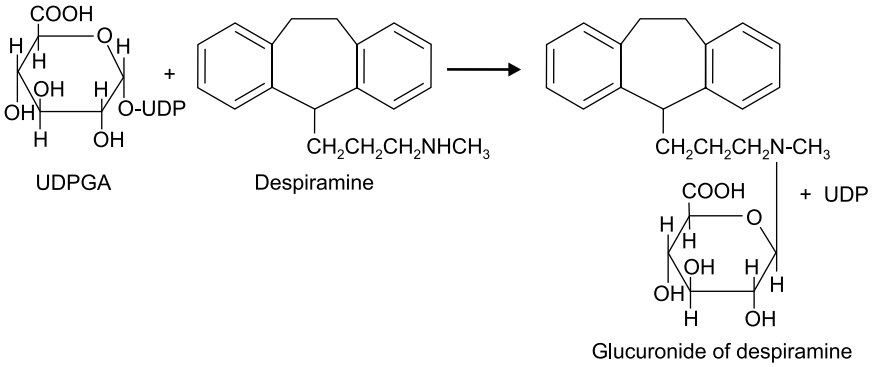
b. *Alcohols:* Phase-II reaction of the antihypertensive drug propranolol.



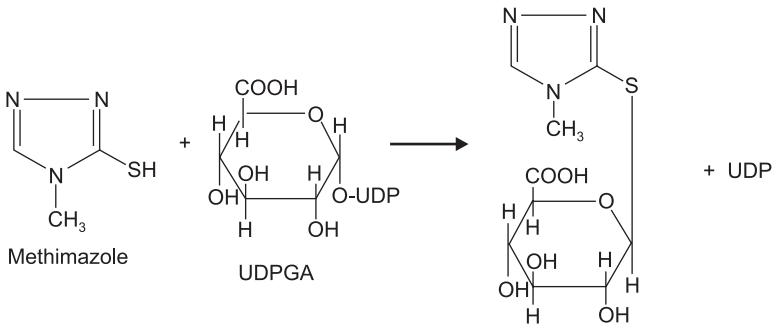
c. *Hydroxyl compounds:* Phase-II reaction of chloramphenicol.

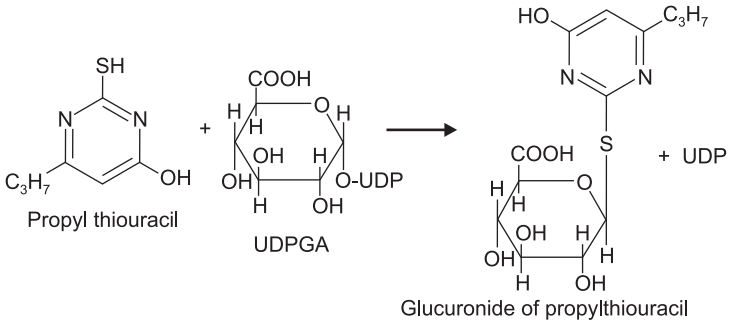


d. *Nitrogen glucuronides:* N-Glucuronides are also obtained with aliphatic amines, arylamines, amides, sulphonamides, etc. It is a minor pathway when compared with N-acetylation and oxidative deamination. Example for this reaction is the metabolism of desipramine mentioned below.

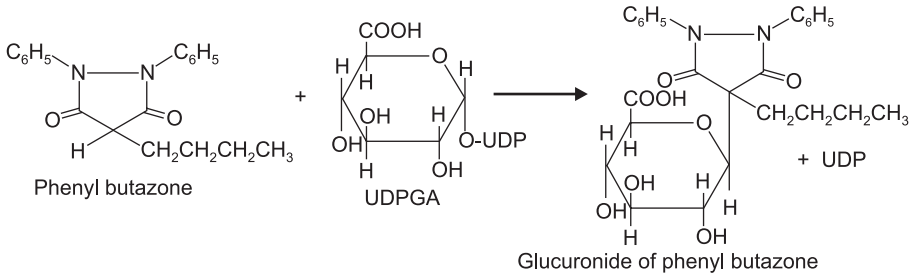


- **Sulphur glucuronides:** Only few numbers of drugs undergo this reaction due to the minimal usage of sulphur containing drugs. Some of the examples are mentioned below.





- **Carbon glucuronides or C-glucuronides:** The formation of C-glucuronides is an important pathway in drug metabolism as shown below.



Note:

1. Apart from the above mentioned heteroatoms, some of the xenobiotics also undergo glucuronidation such as steroids and bilirubin, these conjugates are primarily excreted from urine easily.
2. If the molecular weight of the glucuronides is more than 300 Dalton, then they are chiefly excreted from bile, which may undergo hydrolysis by β-glucuronidase present in the intestine and get reabsorbed, thus lead to enterohepatic recycling. In neonates and children the glucuronidation process is not completely developed, hence the drugs and hormones are accumulated and lead to severe toxicity. For example, the inability of neonates and infants to conjugate bilirubin and chloramphenicol that leads to neonatal hyperbilirubinemia and Grey baby syndrome, respectively.

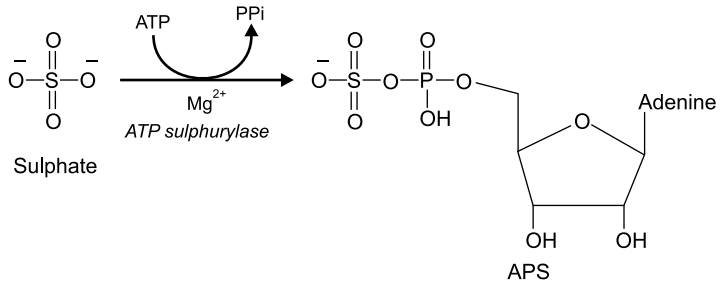
SULPHATE CONJUGATION

Conjugation of xenobiotics or substrate with sulphate primarily takes place with phenols and occasionally occurs in alcohols, aromatic amines, etc. The limited amount of sulphate moiety is available in our body; hence it utilizes significant amount of sulphate pool to make conjugate with numerous endogenous substances such as steroids, catecholamines, heparin, thyroxin, etc.

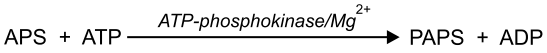
Principle: The main principle involved in this reaction is the synthesis of activated co-enzyme 3′-phosphoadenosine-5′-phosphosulphate which takes place in two steps.

Step 1:

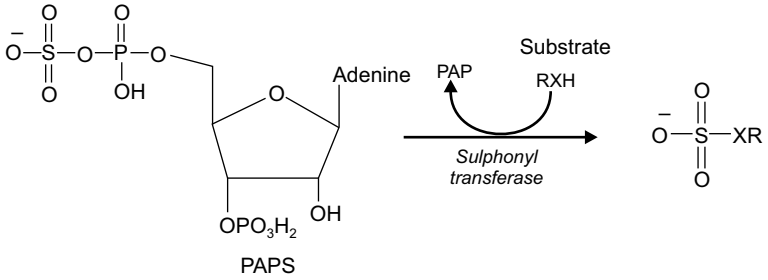
a. **Synthesis of adenosine-5′-phosphosulphate (APS):** It is prepared by the reaction between sulphate and ATP in the presence of ATP sulphurylase to yield APS.



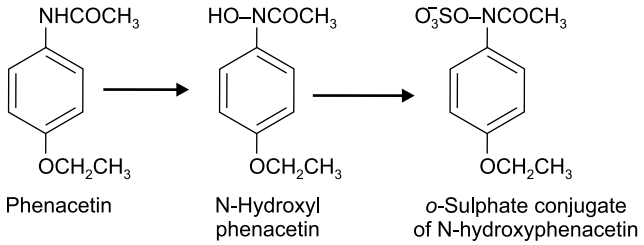
b. **Activation of APS to PAPS (3-phosphoadenosine-5-phosphate):**



Step 2: Transfer of sulphate group from PAPS to the substrate RXH in the presence of soluble sulphotransferase enzyme or sulphokinase, followed by the liberation of PAP (phosphoadenosine phosphate).



Phenolic compounds are the important group of compounds which undergo sulphate conjugation. But in phenolic compounds, glucuronidation predominates. Alcohols and aromatic amines also undergo sulphate conjugation but have minor metabolic pathways. For example, the sulphate conjugation reaction of phenacetin is as follows:

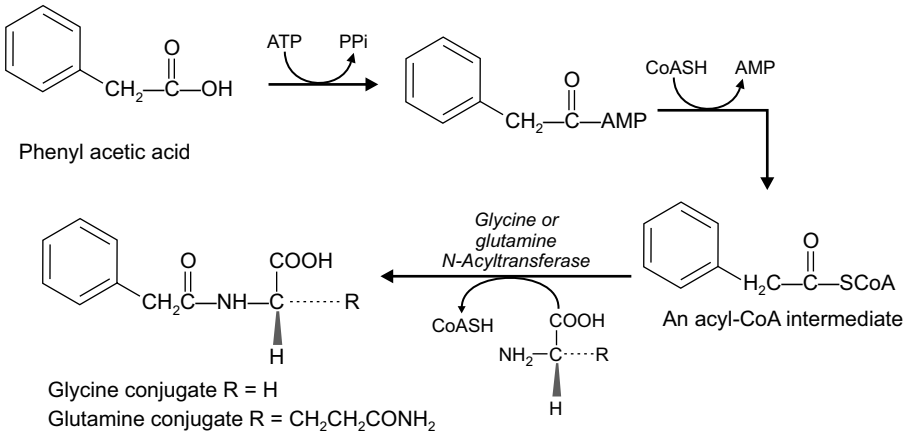


Conjugation with Glycine, Glutamine and Other Amino Acids

Carboxylic acids especially aromatic acids and aryl alkyl acids utilize this type of metabolism. Glycine conjugation is common to most mammals, whereas glutamine conjugation is common to mammals and other primates. The extent of amino acid conjugation formed by xenobiotics is less because of the limited availability of amino acids in the body. The main difference between the glucuronic acid, sulphate and the glycine, glutamine is the later one is not converted into activated co-enzymes.

The important conjugation reaction occurs in this reaction is as follows:

1. Activation of carboxylic acid drug substrate with ATP and the co-enzyme A (CoA) gives an acyl-CoA complex.
2. The intermediate obtained in the above step, acetylase glutamine or glycine catalyzed by the enzyme glutamine or glycine N-acyl transferase enzymes.
3. The activation and acylation steps occur in the mitochondria and kidney. The sequence of the reactions are explained as follows.

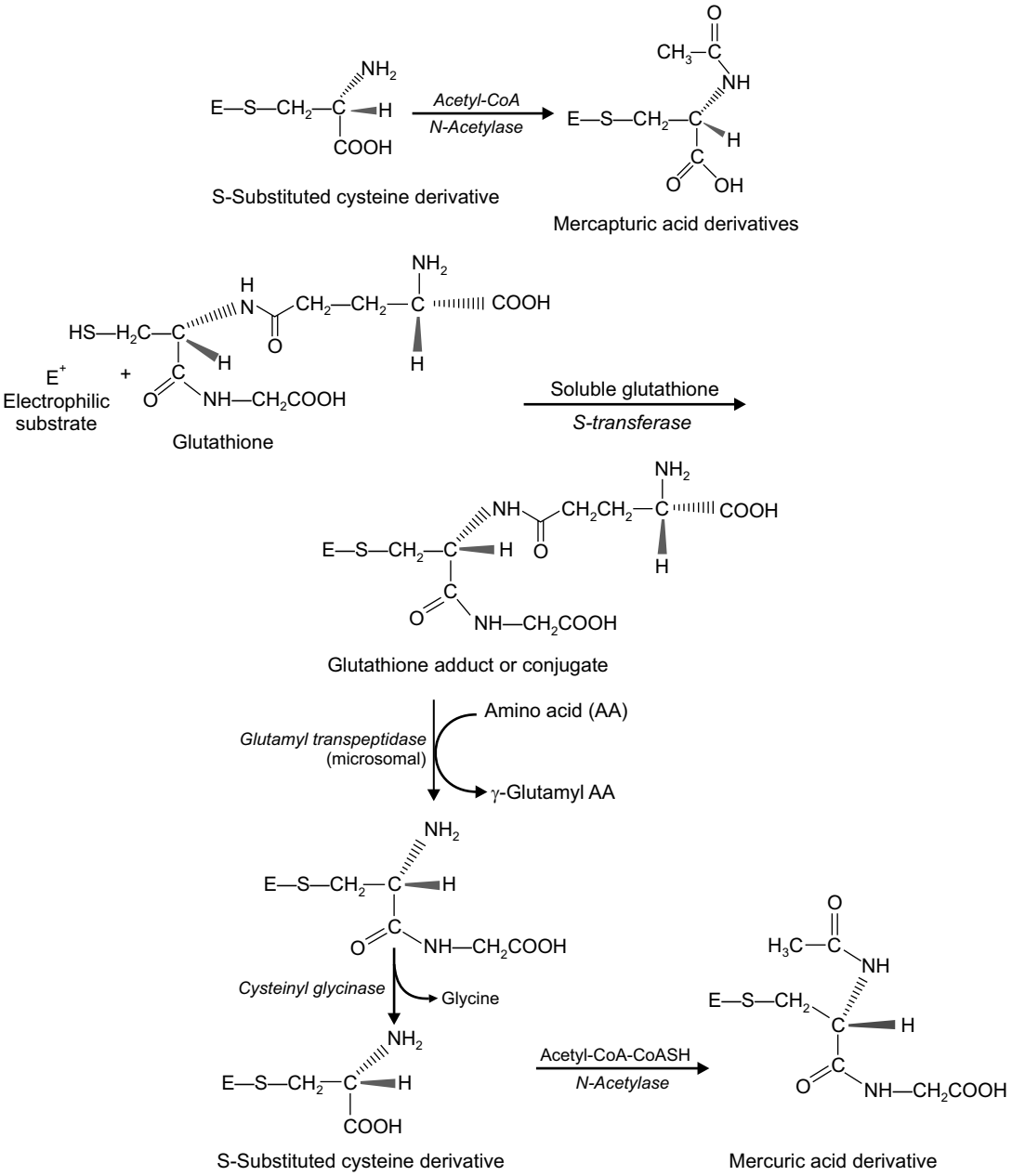


Other examples of drugs or compounds metabolized by this pathway are benzoic acid and salicylic acid. Aromatic acids and aralkyl acids are the major kind of substrate undergo glycine conjugation. Glutamine conjugation mainly takes place in aryl acetic acid such as phenylacetic acid and 3-indolyl acetic acid. Some other types of amino acids also involve in biotransformation such as aspartic acid and serine (in rats), ornithine (in birds), alanine (in mouse and hamster), etc.

Conjugation with GSH or Mercapturic Acid Conjugates

1. It is an important pathway of metabolism for detoxifying chemically reactive electrophilic compounds. Many serious kinds of toxicities are produced by the covalent binding of these reactive electrophilic compounds to the cellular nucleophiles of nucleic acids and vital cellular proteins.
2. GSH protects the nucleic acid and vital cellular proteins due to its nucleophilic sulfhydryl (SH) group.

3. The –SH group reacts with electron deficient compounds to form S-substituted GSH adducts. The reaction process is explained as follows.

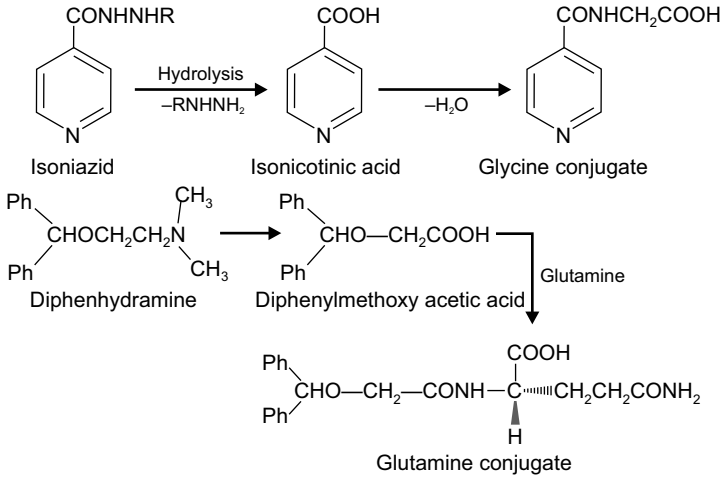


4. Actually, GSH is a tripeptide present in most tissues. Xenobiotics conjugated with GSH usually not excreted as such, but undergo further metabolism to yield S-substituted N-acetyl cysteine products known as mercapturic acids by the enzymatic cleavage of two amino acids from the initially formed GSH adduct and subsequent acetylation of the remaining S-substituted cysteine residue. This reaction is carried out by a family of cytoplasmic enzymes called glutathione-S-transferases. This GSH conjugation do not require the initial formation of an activated substrate

or co-enzyme. The energy needed for the reaction is provided by the reactivity of the nucleophilic GSH towards an electrophilic substrate. The main mechanism of the reaction is as follows.

a. Nucleophilic displacement at an electron deficient carbon or heteroatom.
b. Nucleophilic addition to an electron deficient double bond.

Examples of compounds undergoing mercapturic acid conjugation:



Many of alkyl, aryl, benzylic, allylic substrate, arene oxides, oxiranes also undergo GSH conjugates metabolism.

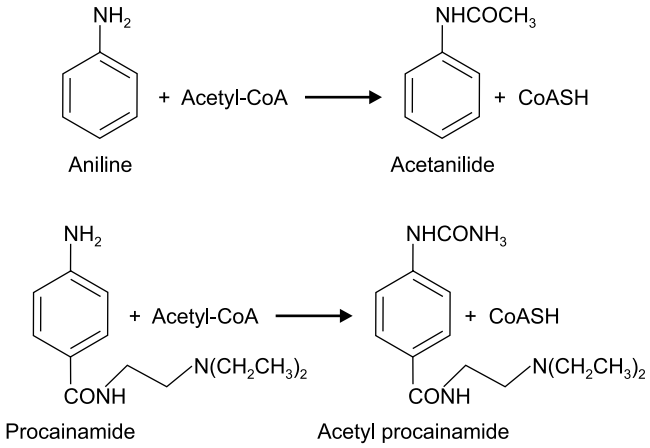
ACETYLATION

The drugs containing primary amino group easily get acetylated and hence it is the major metabolic route for them. During this reaction, the amine group is converted into amide functionalities and are inactive and non-toxic and the water solubility of the metabolites are not increased. Examples of amines undergoing this reaction are $ArNH_2$, $–CONHNH_2$, RNH_2 and sulphonamides.

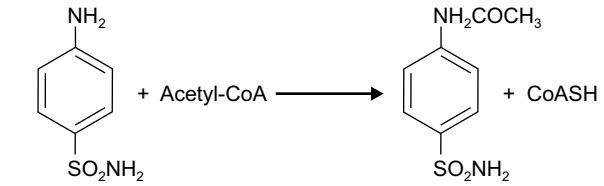
The acetyl group needed for this reaction is obtained from acetyl-CoA. The transfer of acetyl group to the xenobiotics is catalyzed by the enzyme N-acetyl transferase.

Example:

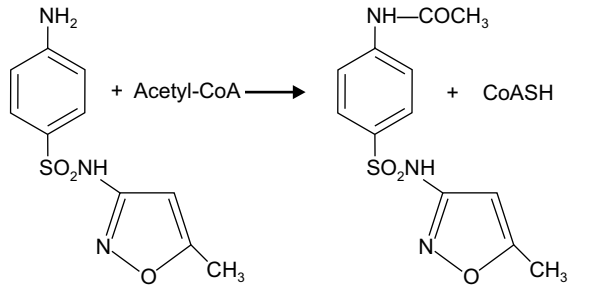
1. Aromatic amines



2. Sulphonamides

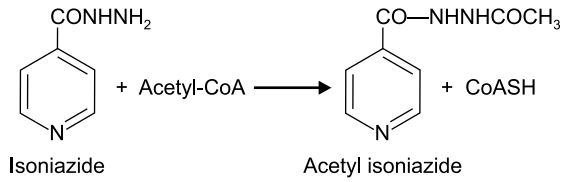


Sulphanilamide Acetyl sulphanilamide



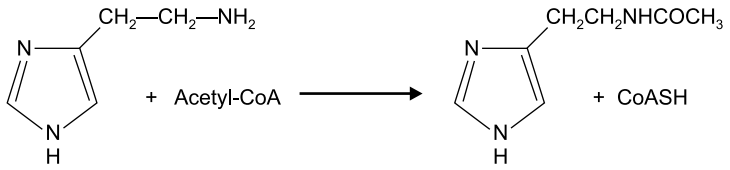
Sulphamethoxazole Acetyl sulphamethoxazole

3. Hydrazines



Isoniazide Acetyl isoniazide

4. Aliphatic amines



Histamine Acetyl histamine

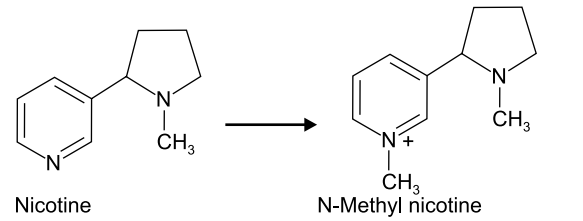
METHYLATION

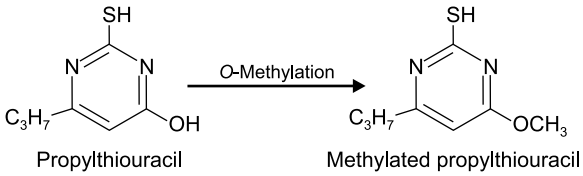
It is a minor pathway of metabolism of drugs. It plays a role for the synthesis of many endogenous compounds and inactivation of various biogenic amines. Methylation of xenobiotics leading to the formation of quaternary ammonium compounds that is in contrast to the reactions.

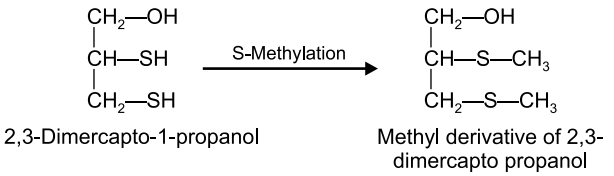
The co-enzyme required to carry out this reaction is S-adenosyl methionine (SAM). The transfer of methyl group from the SAM to the substrate or xenobiotic is catalyzed by different kind of cytoplasmic and microsomal methyltransferases, which mainly includes COMT (catechol-*O*-methyltransferase), phenol-*o*-methyltransferase, S-methyltransferase and N-methyltransferases. Out of these COMT is important one because it catalyses the *O*-methylation of important biotransmitters such as dopamine and norepinephrine. Transferases which are used to methylate histamine, epinephrine and serotonine does not participate in the metabolism of other xenobiotics.

Phenols, catechols, amines, thiols and N-heterocyclic compounds undergo methylation. Catechol and catecholamines are metabolized by methylation and converted into inactive monomethylated catechol products by COMT.

Examples:







Factors Affecting Biotransformation or Metabolism of Drugs

All the drugs and xenobiotics are metabolised by various kind of phase-I and phase-II reactions by various enzymes which form different metabolic products. Depending upon the concentration and activity of the metabolic enzymes, the relative amount of any kind of metabolites is determined. The rate of drug metabolism is important one for the pharmaceutical activity as well as the toxicity of the drugs. For example, when the metabolic rate of the drug increases the intensity and duration of biological action is decreased and if the metabolic rate of drug is decreased, the intensity and duration of action increases and toxicity of the drug also increases. The rate of metabolism is affected by various factors and are listed below.

1. Physicochemical factors/properties of the drugs
2. Chemical factors
    i. Enzyme induction
    ii. Enzyme inhibition
    iii. Environmental chemicals
3. Biological factors
    i. Age
    ii. Sex
    iii. Species variances
    iv. Strain variances
    v. Diet

vi. Stereochemical factors
vii. Altered physiological factors
  a. Disease conditions
  b. Hormonal imbalance/imbalanced hormone conditions
  c. Pregnancy
viii. Temporal factors
  a. Circannual rhythm
  b. Circadian rhythm

1. Physicochemical Properties of the Drug

Generally, absorption and distribution of any kind of drug is majorly depend upon the various types of physicochemical properties of that drug. Similarly, the drug metabolism also affected by the some factors such as molecular weight, size, shape, pK_a, acidity, basicity, solubility, steric and electronic characteristics. All the factors influence the interaction of the drug with its particular enzyme interaction sites and metabolism. But the mechanism of this phenomenon is not yet clearly explained.

2. Chemical Factors

i. Enzyme Induction

The exposure of various drugs, pesticides, environmental xenobiotics, etc. alters the cytochrome P-450 mixed function oxidase system. The process by which the activities of the drug metabolism increased is called enzyme induction. The activity is due to the increased amount of newly synthesized enzymes. Enzyme induction increases the drug metabolism rate and decreases the duration of action. Generally, enzyme inducers increase the rate of their own metabolism as well as those of other related/unrelated drugs or other xenobiotics. Hence, the concomitant administration of two or more drugs may have serious effect or severe drug interaction due to enzyme induction. For example:

a. **Phenobarbital and warfarin:** Phenobarbital is an enzyme inducer, hence, the effect of enzyme induction by phenobarbital increases the metabolism of warfarin and reduces the anticoagulant activity of warfarin. Hence, for the patients receiving anticoagulant therapy careful attention is required to administer phenobarbital by phenobarbital dose adjustment.
b. **Oral contraceptives and phenobarbital or rifampicin:** Concurrent administration of oral contraceptives and phenobarbital/rifampicin to the therapy of oral contraceptives receiving patients leads to decreased pharmacological activity of oral contraceptives due to the enzyme induction activity of the phenobarbital (increased the metabolism of 17-α-ethinyl estradiol) or induced metabolism by rifampicin.

Sometimes, the factors or the microsomal inducers also increases the metabolism of endogenous substances. For example, phenobarbital enhances the metabolism of vitamin D_3, bilirubin, cortisol, etc. in human beings. The increased metabolism of vitamin D_3 by phenobarbital leads to the development of osteomalacia in long-term therapy.

Enzyme induction by chemicals

Along with drugs, sometimes the other chemicals like polycyclic aromatic hydrocompounds and pesticides may also induce some kind of oxidative metabolic reactions.

Cigarette smoking contains minute quantity of polycyclic aromatic hydrocarbons, i.e. benzo[α] pyrene, which is a potent microsomal enzyme inducer. For example, theophylline gets metabolized faster in smokers than in non-smokers. The other drugs like pentazocine, propoxyphene also undergo more rapid metabolism in smokers.

The accidental and occasional exposure of chlorinated insecticides also increases the metabolic rate of particular drugs such as antipyrine, etc.

Some of the drugs like rifampicin, carbamazepine, meprobamate, etc. themselves increase their own metabolism rate, known as self-induction or autoinduction.

The enzyme induction effect leads to stimulation of toxic metabolites in the body.

Table 13.1: Enzyme inducers and their effect on drug metabolism

Enzyme	*Drugs*	*Inducers*
CYP1A2	Imipramine Haloperidol Cloimipramine	Cigarette smokers Ritanovir Ciprofloxacin
CYP2C19	Phenytoin Thioridazine	Carbamazepine Phenytoin
CYP3A4	Alprazolam Atorvastatin	Efavirenz Garlic supplements

ii. Enzyme Inhibition

The activity of metabolic enzymes is sometimes inhibited by drugs or other xenobiotics. A decrease in the metabolic activity of mixed function oxidase enzymes or metabolizing enzymes is called enzyme inhibition. When the metabolism of drugs are decreased means, the concentration or accumulation of drug in the body is increased, which leads to toxicity. There are two types of enzyme inhibition as mentioned below.

1. Direct inhibition
2. Indirect inhibition

1. **Direct inhibition:** It is due to the direct interaction of drugs or xenobiotics at the enzyme site which leads to alteration in the activity of enzyme. It is divided into three types:
   a. Competitive inhibition
   b. Non-competitive inhibition
   c. Product inhibition

   a. **Competitive inhibition:** It takes place due to the binding competition of structurally related analogues to the same active site of enzyme. This is reversible one and easily tackled by the addition of high concentration of any one of the substrates. Metabolism of acetylcholine is inhibited by methacholine by competing for choline esterase.

   b. **Non-competitive inhibition:** It is resulted due to the structurally unrelated agents interacting with the active site of the enzyme and inhibiting the metabolism. This type of interaction is irreversible one. Example, phenytoin metabolism is inhibited by INH.

   c. **Product inhibition:** It is resulted due to the competition between the metabolic products and substrate for the same enzyme. It is otherwise called autoinhibition.

2. **Indirect inhibition:** It takes place by two mechanisms:
   a. Repression
   b. Altered physiology

   a. **Repression or decrease in enzyme content:** In this process, the amount of metabolising enzymes is decreased due to the decreased rate of enzyme synthesis or increased rate of enzyme degradation.

Drugs like actinomycin D, methionine decreases the synthesis of enzymes. Similarly, drugs like disulphiram, carbontetrachloride, etc. increase the degradation of enzymes.

b. Altered physiology: The enzyme inhibition is also affected by hormonal imbalance or nutritional deficiency in the body.

The main example for enzyme inhibition is the effect of phenyl butazone on warfarin plasma concentration. The S-isomer of warfarin is five times more active than R-isomer. Stereoselective inhibition of the metabolism of S-isomer increases the anticoagulant property which leads to haemorrhage. Concomitant administration of isoniazid and phenytoin leads to the prevention of metabolism of phenytoin by former produces toxicity mainly in slow acetylators. Sometimes, the enzyme inhibition also occurs by grape juice. Grape fruit juice is an enzyme inhibitor of CYP_3A_4, if the drugs are administered with grape fruit juice, it alters the metabolic rate of the drug by enzyme inhibition. Some of the examples are given below.

Amiodarone + Grape juice ⟶ Increased bioavailability

Carbamazepine + Grape juice ⟶ Increased plasma level

Diazepam + Grape juice ⟶ Increased bioavailability

Biological Factors

Species Difference

The metabolism of many drugs and foreign substances is species dependent. Same drug or xenobiotic is metabolised in different pathway in different kind of animal species. This type of reactions creates problem in new drug development.

Example 1: Metabolism of phenytoin takes place in human beings by aromatic oxidation leads to (S) (–)-*p*-hydroxyphenytoin. But in dog, the main metabolite formed by oxidation is (R)-(+)-*m*-hydroxy-phenytoin.

Example 2: Metabolism of amphetamine occurs by two ways. They are aromatic hydroxylation and oxidative deamination. Oxidative deamination is predominant in rabbits, humans and guinea pigs, but in rats, amphetamine is predominantly metabolised by aromatic hydroxylation.

Species difference is also present in conjugation reactions, this occurs due to the presence or absence of transferase enzyme involved in the conjugation reaction. For example, in cats, phenolic xenobiotics are metabolised by sulphonation due to the absence of glucuronyltransferase but in case of pigs the phenolic xenobiotics are metabolised by glucuronidation.

The conjugation of aromatic acids with amino acids such as glutamine and glycine depends upon animal species as well as on substrate. For example, in many animals benzoic acid is metabolised by glycine conjugation but in certain birds such as ghoose, turkey and duck, benzoic acid is metabolised by ornithine conjugation.

Strain differences/pharmacogenetics

The altered mechanism of drug also seen in various strain differences especially in rabbits and mice. This is mainly due to the genetic variations in the amount of metabolising enzymes found among the different strains.

For example, the *in vitro* metabolic studies show that the cottontail rabbit metabolises hexobarbital about 10 times faster than New Zealand rabbits. Interindividual differences in metabolism also shown

by human beings. The influence of metabolic enzymes in substrate is under genetic control. Hence, the different metabolic ability is present in the different strains of same species.

Pharmacogenetics: The study of intersubject difference in drug response is known as pharmacogenetics. It is either monogenetically or polygenetically controlled. In identical twins, there is no difference in the metabolism of phenylbutazone, but the same process in non-identical twins showed peculiar differences.

Ethnic variations: Differences occur in the drugs among different races are called ethnic variations. This is may be monomorphic or polymorphic. The appearance of unimodal frequency of distribution present in total population is called monomorphic. For example, the small extent of metabolism of PABA and PAS in total human beings by acetylation. But the metabolism of INH is different in slow acetylator and fast acetylator. In slow acetylator (Japanese and Eskimose) the INH is metabolized slow and in fast acetylators (white and black populations) INH is metabolized fast. Hence, dose adjustment of INH is needed for slow acetylators, otherwise it leads to peripheral neuritis. The other examples of drugs shown strain differences are dapsone, phenytoin, sulphadimidine, etc.

Sex differences: The rate of metabolism of drugs also observed in different sex of population due to the variation in secretion of sexual hormones during puberty. For example, benzodiazepines are metabolized slowly in women than in men.

Age differences: The variations in the metabolic rate of drugs are observed in different age group such as variations in the enzyme secretion, amount of enzyme and haemodynamics. These are explained as follows.

Neonates: In neonates the microsomal enzymes are not fully developed, hence the metabolism occurs in slower rate. For example, absence of glucuronide enzyme in neonates leads to slow metabolism of chloramphenicol and produces Grey baby syndrome. Similarly, paracetamol and sulphonamides lead to hepatotoxicity and nephrotoxicity, respectively.

Infants: Infants also shows similar activity like neonates.

Children: In children and older infants the rapid metabolic rate is observed than adults. Hence, they need large dose than adults. For example, $t_{1/2}$ of theophylline in children is two-thirds of adults.

Elder patients: The decrease in rate of metabolism is observed in elder patients due to decreased hepatic flow and reduced cardiac output.

Diet: The dietary components also alters the metabolism of drugs and xenobiotics.

a. Low protein diet decreases and high protein diet increases the drug metabolism.
b. The high protein–carbohydrate ratio increases the CYP-450 mixed function oxidase activity.
c. Fat free diet decreases the metabolism.
d. Vitamin A, B_2, B_3, C and E deficiency and minerals like Ca, Mg, Cu, etc. retarded the metabolism.
e. Grape juice inhibits the metabolism of various drugs.
f. Malnutrition in females increases the metabolism of sex hormones.
g. Alcohol intake also alters the metabolism of drugs.

Stereochemical Factors

In market, many drugs are available in the form of racemic mixtures and they are also administered in the same form to the humans. The two enantiomers present in the racemic mixtures may differ in their

pharmacological activity. Normally, one enantiomer is more active than another. For example, the (S)-(–) isomer of warfarin is five times more potent than (R)-(+) isomer. In some case, the two enantiomers show totally different pharmacological activities. For example (+)-α-propoxyphene is an analgesic, whereas (–)-α-propoxyphene is an antitussive.

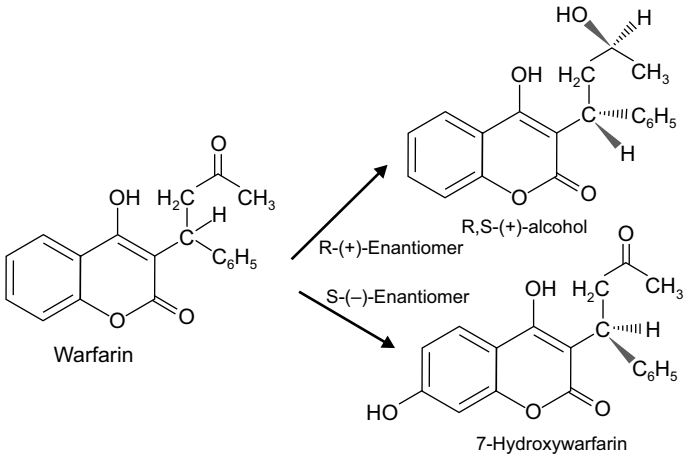
Alterations or differences in metabolism is observed among enantiomers, i.e. one isomer gets metabolized faster than another enantiomer. For example, the less active (+)-enantiomer of propranolol is more rapidly metabolised than corresponding (–) isomer. Another example is allylic hydroxylation of hexobarbital. The (R)-isomer is metabolized faster in humans than (S)-isomer.

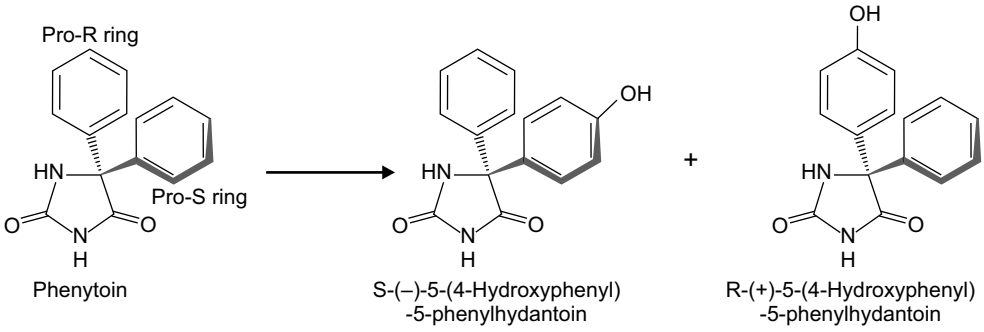
Sometimes, the individual enantiomers of racemic mixtures also metabolised by different pathways. This is called substrate stereoselectivity or enantioselectivity in drug biotransformation.

The more active (S)-(–) isomer of warfarin is metabolized by 7-hydroxylation. But in the less active (R,S) warfarin, alcohol is the major metabolic product.

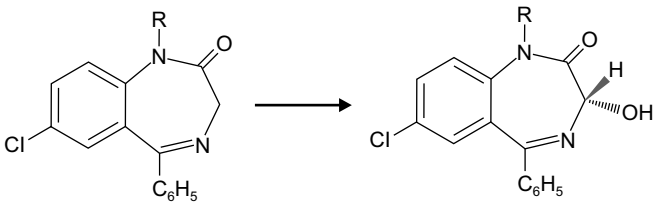
Drug metabolism also leads to the formation of new asymmetric centre in the metabolites or metabolic products. They are known as stereoisomeric or enantiomeric formation of products and are called product stereoselectivity.

Example 1: In humans, the metabolism of phenytoin occurs by aromatic hydroxylation. In which *p*-hydroxylation occurs preferentially (90%) at the pro-(S)-phenyl ring to yield (S)-(–)-5(4-hydroxy-phenyl)-5-phenyl hydantoin. But the hydroxylation of another phenyl ring occurs only in 10%.





Example 2: Microsomal hydroxylation of diazepam yields optically active metabolites. Both of the metabolites are active and one is marketed as a drug in the name of oxazepam.



Diazepam, R = CH_3
Desmethyldiazepam, R = H

(3S)-N-Methyloxazepam, R = CH_3
S-(+)-Oxazepam, R = H

Example 3: Pentazocine, the analgesic agent is metabolized by allylic hydroxylation or by the N-acetylation at the N-butyl side chain to yield *cis–trans* alcohols. In humans, monkey and mouse the *trans*-alcohol is the major metabolic product, whereas in rats *cis*-alcohol is major metabolic product.

Regioselectivity in drug metabolism also observed in some type of drug molecules.

In some drugs, the metabolic studies that denotes the selective metabolism of two or more similar functional groups such as –OH, $–NO_2$, etc. or two or more similar atoms that are positioned in different regions of molecule. For example, the four methoxy groups ($–OCH_3$) present in papavarine, are regioselectively *o*-demethylated in rats, dogs, rabbits, etc. Similarly, two sp^2-hybridised nitrogen atoms are present in trimethoprim (N_1 and N_3). In dogs, the regioselective oxidation of N_3 of trimethoprim yields respective 3-N-oxide.

Altered Physiological Factors

Pregnancy: The metabolic rate of many drugs is reduced during lateral stage of pregnancy, due to the huge amount of steroidal hormones secreted into circulation. For example, the anticonvulsant drugs are metabolized rapidly during pregnancy due to the induction of metabolic enzymes by the circulating progesterone.

Hormonal imbalance: Higher levels of one hormone may interfere the activity of an enzyme and may interfere the activity of another metabolic enzyme. Thyroidectomy and alloxan-induced diabetes in animals showed altered metabolic enzyme activity which leads to decreased metabolism of drugs. Stress-related changes in ACTH levels also effect the drug biotransformation.

Disease state: Liver is the major organ for drug metabolism. Any diseased condition of liver alters the secretion of microsomal enzymes as well as alters the biotransformation of drugs. For example, hepatic carcinoma, obstructive jaundice, etc. of liver reduces the rate of biotransformation. Any impairment of kidney or renal parts alters the biotransformation of salicylates, procaine, etc. In the diabetic patients, glucuronidation rate is decreased due to the decreased availability of UDPGA.

Temporal Factors

Circadian rhythms: Variations in the microsomal enzyme activity with light cycle is known as circadian rhythm in drug metabolism process. The enzyme activity is maximum during early morning (6 am to 9 am) and minimum in late afternoon (2 pm to 5 pm) which is related to the high and low serum levels of corticosterone (because the level of corticosterone depends upon the light–dark sequence in the day).

Chronopharmacology: The study of differences in drug response is influenced by time. The time-dependent change in kinetics is known as chronokinetics. For example, the $t½$ of metyrapone is 2.5 times longer during the night time than in the day in rats.

PROBABLE QUESTIONS

1. Describe the importance of physicochemical properties on biological activity of drug molecules.
2. Enumerate the different physicochemical properties of a drug molecule that influences the biological activity, and describe in detail about the (a) hydrogen bonding and (b) ionization.
3. Write in brief about the following physicochemical properties and their influence on biological activity of drugs (a) redox potential and (b) surface activity.
4. What is bioisosterism? Write its applications in the design of a new and potent drug molecule.
5. Write a brief note on the steric features of drugs and their effects on the biological activity.
6. Describe in detail about the effect of following physicochemical properties on biological activity:
   (a) Solubility
   (b) Partition coefficient
7. Describe in detail about the various methods of determination of partition coefficient.
8. Write a brief note on complexation and its importance on biological activity.
9. Write a note on role of steric features of drugs with suitable examples.
10. Define the following terms with suitable example of drugs.
    (a) Diastereomers (b) Enantiomers (c) conformational isomers
11. What is bio-isosterism and write the significance on biological activity of drugs?
12. Write in detail about classical bioisoteres with examples.
13. Write a short note on non-classical bioisoteres with examples.
14. Describe the importance of protein binding of drugs.
15. Write a note on mechanism of protein drug binding.
16. What is meant by metabolism or biotransformation of drugs and classify with examples.
17. Describe in detail about phase-I reactions.
18. What is meant by phase-II metabolic reactions and explain it with appropriate examples.
19. Enumerate the various factors influencing metabolism.
20. Explain in detail about the oxidation reactions of phase-I metabolism.

SECTION II

Drug Design

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CHAPTER 14

Concepts of Drug Design

INTRODUCTION

The drug discovery or design of new drugs requires a designing process along with the synthetic techniques, methods of administration, development of tests, and further procedures to establish pharmacodynamics and their toxicological assessment. The diversity in synthetic chemistry is ever increasing as a result of increase in the number of chemical compounds, which requires a sequence of screening modules with appropriate time consumption and affidavit, showing little success. These consequences made it necessary to find out the possibilities for the development of new, logical, and scientific approaches in the discovery of new molecules or drugs and came to be known as *drug designing*.

Drug design is an integrated advancing discipline, in which a biologically active molecule is produced by chemical synthesis followed by an evaluation of its activity and toxicological studies with the limitation of trial-and-error screening. In the broader sense, it implies the random evaluation of congeners produced from the lead molecule either by implementing tailor-made techniques or by applying the basic concepts of physicochemical properties to produce an able drug or medicine for human use.

DESIGN OF ANALOGUES AND PRODRUGS

Drug design involves the development of analogues by some chemical modifications from the lead molecule or from a parent compound by modifying the carbon skeletal transformation or by the synthesis of compounds of the same nucleus with various substitutions. Analogues can also be synthesized by changing the position of substitution group. For example, synthesis of *trans*-diethylstilbestrol by the modification of oestradiol produced better oestrogenic activity than the latter one.

The term *prodrug* means that pharmacologically active substance is administered in an inactive (or significantly less active) form. It will undergo the metabolism *in vivo* as an active metabolite. The prodrugs are discovered by the screening of active metabolites after *in vivo* biotransformation that is formed from parent compounds. For example, phenylbutazone is transformed into oxyphenbutazone by hydroxylation reaction mediated by phase I (nonsynthetic) metabolic reaction.

DESIGN OF LEAD AND LEAD DISCOVERY

The concept of lead discovery envisages two investigational processes:

1. **Exploration of leads:** Search of new molecules.
2. **Exploitation of leads:** Assessment, chemical modelling, and extension of leads.

Drug discoveries without a lead are quiet few in number. The most prominent examples are penicillium and librium. Librium is the first benzodiazepine tranquillizer. Prof. Leo Sternbach synthesized a series of quinazoline-3-oxides in a new tranquillizer development programme. None of the molecules produced reliable pharmacological activity. One of the molecules that had been missed and identified while a laboratory clean-up was happening was found to possess probable activity. Chemically, it was benzodiazepine-4-oxide. It was synthesized by reaction of chloromethyl quinazoline-3-oxide with methylamine. This lead identification was further exploited to develop potent analogues such as diazepam, which was found to be 10 times more potent than the lead.

Approaches to Lead Discovery

The lead identifications require a series of biological evaluations of the lead molecules. Once, after the identification, it can be structurally modified, the potency and the activity can be improved.

Random screening: The entire synthesized compounds or any chemical constituents obtained from natural products are evaluated in a series for their biologically active components. Thus, random screening may produce unexpected active medicines. Antibiotics such as streptomycin and tetracycline, and fungal metabolites such as lovastatin and cyclosporine were found through this method. This approach needs more manpower, and it is expensive and time-consuming and the success rate is considerably low.

Non-random screening: In this method, only compounds that possess similar structural skeletons were evaluated from their particular properties.

Pharmacokinetic studies: Biotransformation occurs as the fate by metabolizing enzymes. In order to develop new leads, the metabolites or biotransformed compounds are studied for their properties, and such studies are expected to assess the activity from a comparison with the parent molecule. For example, the discovery of sulphanilamide is reported through the metabolic studies of prontosil.

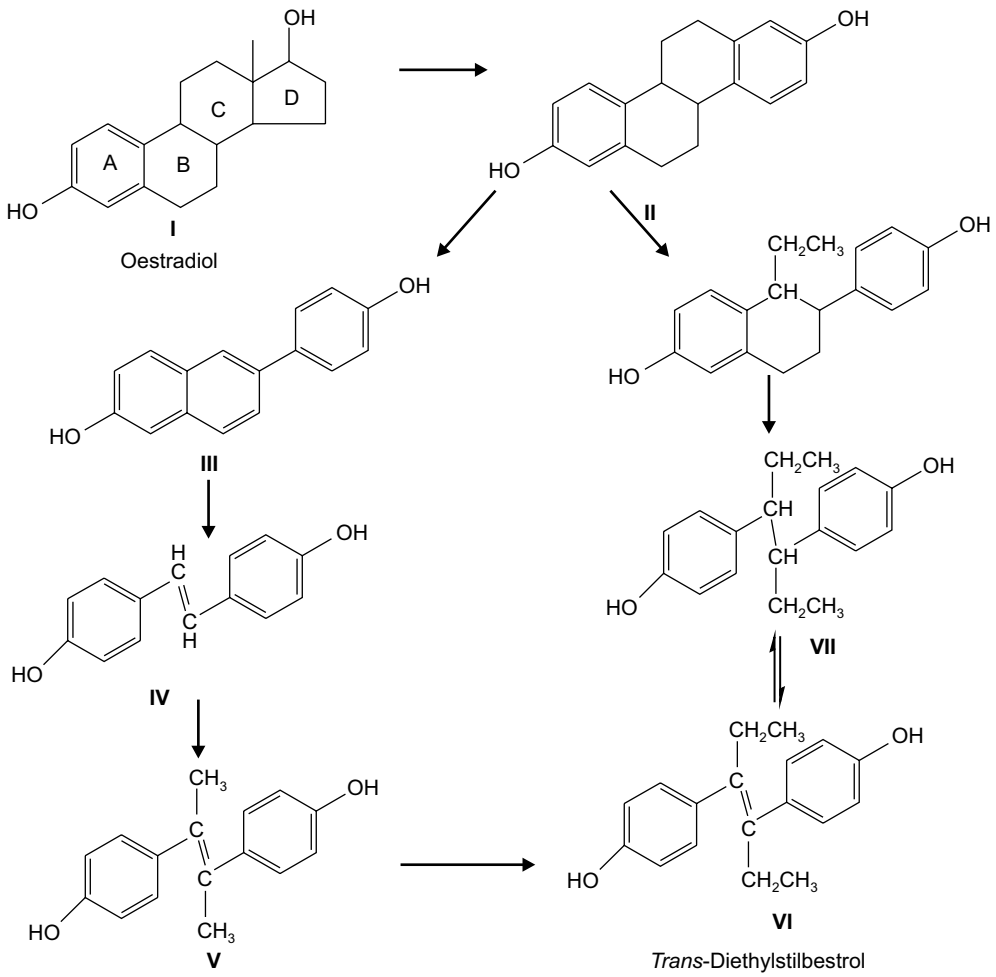
Pharmacodynamic studies: The effects apart from the therapeutic actions, that is, side effects may lead to the finding out of a new molecule with some appreciable structural modification. For example, sulphonamide used specifically for the treatment of typhoid lowered the blood sugar levels drastically. This exerted action led to the finding of aryl sulphonyl thiourea moiety responsible for the lowering of blood glucose level. Amino alkyl derivatives of iminodibenzyl were synthesized as analgesic, sedative, and antihistamines that were found to possess antidepressive action. This led to the synthesis of many tricyclic antidepressants.

Drug Design Through Disjunction

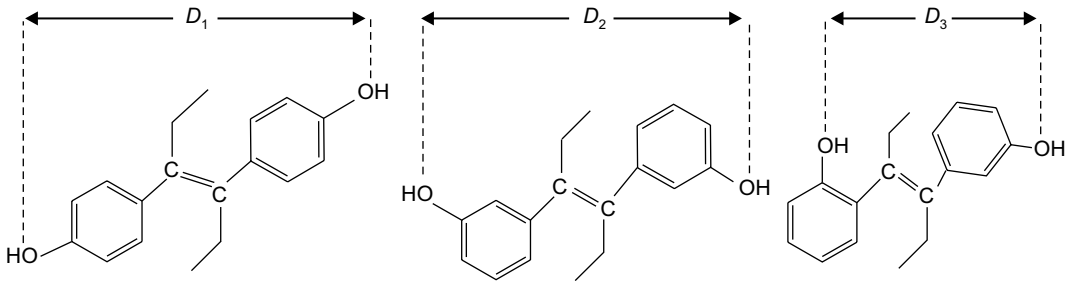
Disjunction comes into the systemic formulation of analogues of a prototype agent, generally towards structurally simpler products, which may be carried as quasireplicas or partials of the prototype agent. This is employed by various methods, as listed ahead.

- Unjoining of certain bonds
- Substitution of aromatic cyclic system for saturated bonds
- Elimination of the size of hydrocarbon portion of the parent molecule
- Decyclization of any ring system
- Cyclization of hydrocarbon chains

For example, oestrogenic study of oestradiol through drug design by disjunction produced successful molecules of *trans*-diethylstilbestrol.



The disjunction of various steps in the design from II to III and to IV has not successively produced a reliable molecule, but it has succeeded in the total elimination of ring B and C in oestradiol (I). By plotting the response curve, the maximal activity in the series was attributed to *trans*-diethylstilbestrol (*D*), and the possibility of reductions in activity depends on the distance between two hydroxyl groups.



$D_1 > D_2 > D_3$ [D_1 = 14.5 Å]

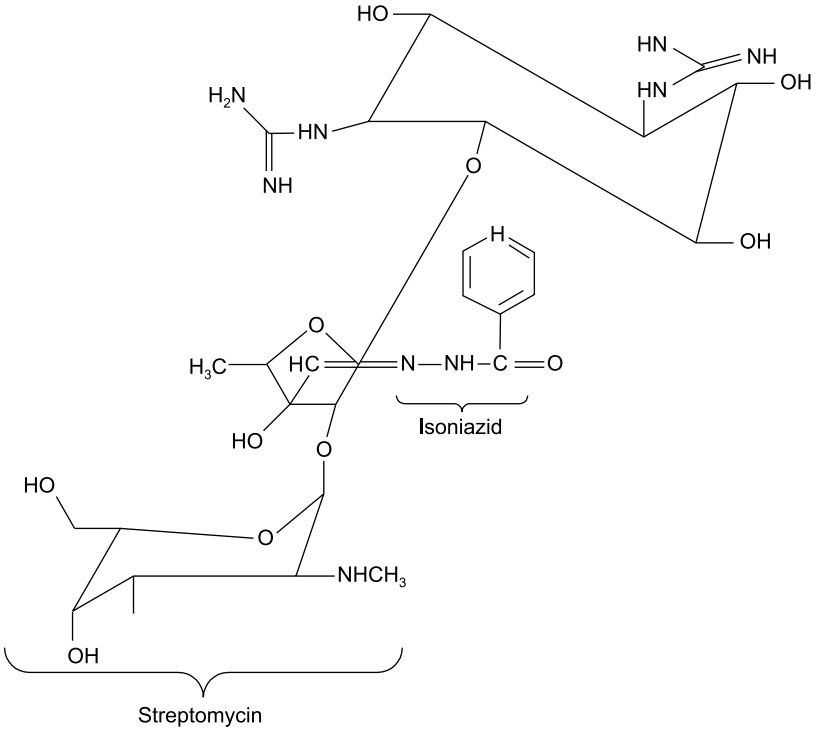
Drug Design Through Conjunction

In this method, a systemic formulation of analogues of a prototype agent is employed. In general, principally mixed moieties are derived by conjunction of two pharmacophoric molecules. An example for this is ganglionic blocking agents, and its development is based on the principle of mixed moieties. Acetylcholine is a neurotransmitter, which acts as a parasympathetic muscarinic stimulant and produces appreciable changes in ganglionic functions, whereas hexamethonium is a ganglionic blocker that possesses only a slight action at postganglionic parasympathetic endings and produces a high degree of ganglionic blockade. The evaluation of muscarinic moiety on being studied in relation with a particular bisquaternary type of structure, i.e. hexamethonium, promptly suggests the following proposed design, thus, embodying the ganglionic moiety and muscarinic moiety into a single molecule. It is, however, pertinent to mention here that the internitrogen distance essentially constitute an important factor in many of the series of *bis*-quaternary salts possessing ganglionic blocking activity. It is worthwhile when the distance is more or less the same as that in hexamethonium. However, the actual synthesis and pharmacological evaluation of conjunctioned hexamethyl analogue reveals the presence of both a weak muscarinic stimulant and possessing of a good ganglionic blocking action.

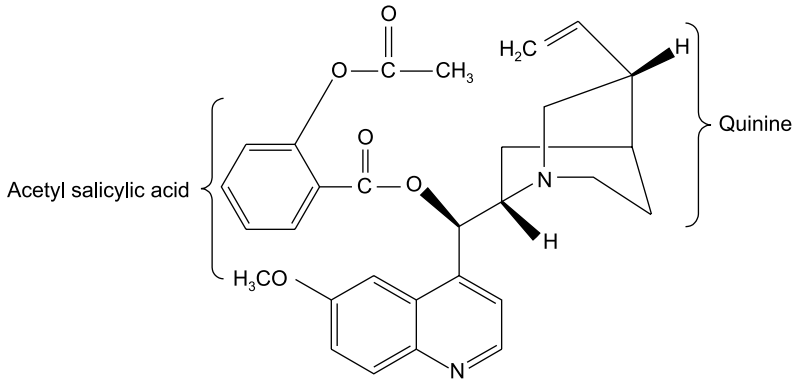
Molecular Hybridization in Drug Design

Molecular hybridization essentially embodies the synthesis of strategically designed new breeds of bioactive agents from two or more compounds having different characteristic features with the aid of covalent bond synthesis. In 1886, Necki exploited the beneficial properties of phenols and carboxylic acids possessing potent antibacterial characteristic feature into the design of newer drug molecules with better and improved pharmacological activities by simple esterification.

Example 1: A molecule of streptomycin and a molecule of isoniazid by means of a strong double bond between 'C' and 'N' forms a hybridized molecule through the elimination of a molecule of water. This hybridized molecule exhibits significant potentiated antibacterial and tuberculostatic activity.



Example 2: Hybridization of acetyl salicylic acid (antipyretic) and quinine (antimalarial) to lose a molecule of water to form a hybridized molecule for a potent antimalarial drug with substantial antipyretic and analgesic activity.



RATIONAL APPROACH TO DRUG DESIGN

There are many approaches to drug designing in relation with physiochemical parameters and electronic features taken into consideration for designing a drug. These are as follows:

1. **Approach with quantum mechanics:** This, also known as *wave mechanics*, comprises the fundamental physical properties of a molecule. These include the properties of protons, neutrons, and electrons, which are explained by quantum mechanics. The basis of drug molecule nature is altered by chemical alterations of the electronic features.
2. **Approach with molecular orbital theory:** This approach depicts the change in properties that shall be made by the alteration of orbits. Based on this, the electrons present in the molecules are linked with orbitals to change the electronic feature. The molecular orbital approach is the change on electronic charges, evidenced from the investigation of three volatile inhalation anaesthetics, and also on molecular conformation, as studied with respect to acetylcholine, in regard to bond lengths and angles including torsional angles. These interpretations are carried out by computational methods with respect to structure–activity relationship.
3. **Approach with molecular connectivity:** This is based on the structural features of a molecule. All steric and electronic parameters vary according to their configuration. These include cyclization, unsaturation, presence of heteroatom, skeletal branching, and position in molecules with the aid of numerical indices and the series of functional attachments.
4. **Approach of linear free energy:** Linear free energy approach was based on the selection of physiochemical parameters of a molecule with a specific biological activity. But the biological activity may vary in relation to the physiochemical properties of the drug or molecule and does not provide a prompt success, but it may reveal some beneficial features regarding the molecule.

MODERN STATE OF THE ART

In recent years, drug discovery transform based on the modern techniques to design, screen, modify, and optimize potential drug entities. The complete analysis of the human genome, molecular biology, robotics, and microelectronics will make everlasting impact on human diseases. The identification of novel therapeutic targets and drug development combined with latest technologies in bioinformatics and genetic diagnostics will allow pharmacological information to be analysed and managed on a very large scale in an extremely short time.

The speedy evolution of high-throughput techniques and microarray technologies are important for genome-wide mapping for assigning disease gene loci and monitoring kinetic expression of disease genes. The computer algorithms and neuronal networks are designed to rapidly analyse the wealth of data being generated by the millions of compounds produced by combinatorial and parallel synthetic techniques assisting in the intellectual guide for future directions of drug design.

CHAPTER 15

Receptors

INTRODUCTION

One of the basic tenets of pharmacology is that drug molecules exert some chemical influence on one or more constituents of the cells to produce a pharmacological response. Of course, the molecules in an organism are vastly outnumbered, but the drug molecules should be merely distributed at random to get a chance to interact with any particular class of proteins. The biological activity is studied by understanding the nature of binding sites and the mechanism by which the association of drug molecules takes place. There are four primary target regulator proteins that are commonly involved in the drug interactions to produce pharmacological actions. They are enzymes, carrier molecules, ion channels, and receptors.

The term *receptor* or *receptive substance* was used to denote a small region of macromolecule, which may be an isolable enzyme, a structural and functional compound of a cell membrane, or a specific intracellular substance, such as a protein or a nucleic acid. Occupation of a receptor by a drug molecule may or may not result in the activation of the receptor. Activation results in tissue responses. Binding and activation represent the two steps in the generation of receptor-mediated response by an agonist. If a drug binds to a receptor causing activation, and thereby prevents the agonist from binding, it is termed as a *receptor antagonist*, whereas the tendency for it once bound to activate the receptor is denoted by efficacy. Drugs with intermediate levels of efficacy produce submaximal response even at 100% receptor occupation, and are known as *partial agonist*. Those which produce maximum response after 100% receptor occupation are called *full agonists*.

TYPES OF RECEPTORS

Receptors elicit different types of cellular effect. Some of them are very rapid, e.g. those involved in synaptic transmission, operating within milliseconds, and other receptors for hormones that operate after hours and days. There are four types of receptors.

i. **Type 1:** Ligand-gated ion channels
ii. **Type 2:** G-protein-coupled receptors
iii. **Type 3:** Kinase-linked receptors
iv. **Type 4:** Nuclear receptors

i. **Ligand-gated ion channels:** The ligand-gated ion channels are also known as *ionotropic receptors*. These are membrane proteins with a similar structure to other ion channels, but incorporating a ligand-binding site (receptor), usually in an extracellular domain. Typically, these are the receptors on which neurotransmitters act fast.

Examples: Nicotinic acetylcholine receptor, GABA receptor, and glutamate receptor of N-methyl-D-aspartic acid (NMDA).

ii. **G-protein-coupled receptors:** These are also called *metabotropic receptors* or *seven-trans membrane spanning receptors* that act through a second messenger, which elicits an action. Second messengers are usually *cyclic* adenosine monophosphate (cAMP) and inositol trisphosphate (IP).

Examples: Muscarnic receptors, beta-adrenergic receptors, serotonin receptors and opioid receptors.

iii. **Kinase-linked or enzyme-linked receptors:** These constitute extracellular ligand-binding domain that is linked to an intracellular domain by a single transmembrane helix. In many cases, the intracellular domain is enzymatic in nature. Sometimes, the receptor subunit may bind to an enzyme called *Janus-Kinase*. Type 3 receptors include those for insulin and various cytokines.

iv. **Nuclear receptors:** The nuclear receptors regulate the gene transcriptions, are located in the cytosol, and migrate to the nuclear compartment when a ligand is present. The receptor protein is inherently capable of binding to specific genes. These include the receptors of glucocorticoids and thyroid hormone.

THEORIES OF RECEPTORS

Occupation Theory

Proposed by Gaddum and Clark, the theory states that the intensity of pharmacological effect is directly proportional to the number of receptors occupied by the drug. The pharmacological response of a drug molecule depends on the amount of dose, the total number of receptors available, and its intrinsic activity that can be expressed as $K\,[R] \times [A]$,

where K = Association constant

R = Concentration of the receptors not occupied by drugs

A = Concentration of drug molecules or dose

Similarly, the rate of dissociation of the drug receptor complex is given by the expression $K[RA]$.

K_2 = Dissociation constant

$[RA]$ = Concentration of receptors occupied by the drug

At equilibrium, $K_1[R] \times [A] = K_2[RA]$

$[R] + [RA]$ is equal to $[r]$ = Total concentration of the receptors

Thus, $K_1[A]\,[r] - [RA] = K_2[RA]$ (1)

or

$$[RA]/[r] = K_1[A]/K\,[A] + K_2 = 1/1 + K_2/K_1[A] \quad (2)$$

K_2/K_1 can be replaced by KA = Equilibrium constant

It is the reciprocal of the drug's affinity for the receptors.

The term $[RA]/[r]$ represents the fraction of the total number of receptors occupied by the drug.

When $[RA] = [r]$, that is, all receptors are occupied and the response is thus, proportional to its intrinsic activity X_n.

Relative response $= [RA]X/[r] = X/1 + KA/[A]$ (3)

This theory does not rationalize partial antagonists.

Rate Theory

The rate theory explains that the pharmacological activity is a function of the rate of association and dissociation of a drug with the receptor and is not the function of the number of occupied receptors.

At equilibrium, the rates of combination and dissociation of drug–receptor reactions are same and Eq. (1) can be written as

$$K_1[A]\,([r] - [RA])/[r] = K_2[RA]/[r] \quad (4)$$

or

$$\text{Rate of receptor occupation} = K_2/1 + RA/[A] \quad (5)$$

When the response is proportional to the number of receptors occupied, Eq. (3) is important and when the response is proportional to the rate of receptors, Eq. (5) is important.

Induced Fit Theory

It is proposed by Koshland to give explanation for the action of enzymes and substrates. It explains that the receptor (enzyme) need not necessarily exist in the same conformation that is required to bind the drug (substrate). As the drug approaches the receptor, a conformational change is induced for binding, which initiates the pharmacological activity.

Example: Acetylcholine interacts with the regulating protein and alters the normal forces that stabilize the structure of the protein, thereby producing a transient rearrangement in membrane structure and a consequent change in its ion-regulating property. These receptors are suggested to be elastic and returns to the original conformation after the drug releases.

According to this theory, an agonist will bind by conformational change with intrinsic activity and elicit a response, but an antagonist will bind by conformational change without intrinsic activity.

Macromolecular Perturbation Theory

According to this theory, the drug interaction with a receptor leads either to specific conformational perturbations (SCPs) or to non-specific conformational perturbations (NSCPs). An SCP will produce a specific response from an agonist in which the drug possesses intrinsic activity. In NSCP, no stimulant action, but may be antagonistic or blocking action, will be produced. If a drug possesses SCP and NSCP features, an equilibrium mixture of two complexes may result and leads to partial agonistic action. Example: Alkyl trimethyl ammonium ions.

C_1 to C_6: Alters receptor structure and produces muscarnic agonistic action

C_8 to C_{12}: Antagonistic action

Heptyl and octyl derivatives: Partial agonists (intermediate derivatives)

Activation–Aggregation Theory

According to this theory, even in the absence of drugs, a receptor is in a state of dynamic equilibrium between an activated form (R), which is responsible for biological responses and an inactive form (T_0). Agonists shift the equilibrium to activated form and antagonists shift the equilibrium to inactivated form. Partial agonists bind to both conformations during partial antagonistic action. The agonist-binding site and antagonist-binding site conformation may be different.

FORCES INVOLVED IN DRUG–RECEPTOR INTERACTION

Covalent Bonding

Covalent bonds are the ones that are produced by a strong energy. These are produced only when an irreversible antagonist inactivates the receptors. If a weak bond forms the drug–receptor complex, the complex formed will be a reversible type.

Example: Acetylcholinesterase is irreversibly inactivated by a number of phosphate esters (organophosphorus compounds includes pesticides). The nitrogen mustards are irreversible inhibitors of certain receptors.

Dipole–Dipole and Ion–Dipole Interactions

It is associated with electrostatic bonding. Molecules in which there is a partial charge separation between adjacent atoms or functional groups can interact either with each other or with NR3 ions. The carbon-X bonds in drugs and receptors (where X is an electronegative atom) will have asymmetric distribution of electrons. This produces electronic dipoles. The dipoles in a drug molecule can be attracted by ions (ion–dipole interaction) or by other dipole–dipole interaction (Figure 15.1). Ion–dipole interactions are more powerful and have high energy.

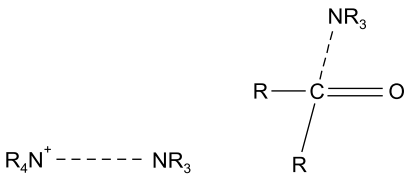


Figure 15.1: Ion–dipole and dipole–dipole interactions

Hydrogen Bonding

It forms a weak (energy from 7 to 40 kJ/mol) and easily breaking bond. Since drugs contain hydroxyl, amino, carboxyl, and carbonyl groups, it can form H-bonds with the receptors. H-bonding is a type of dipole–dipole interaction formed between the proton of a group X-H (X is an electronegative atom) and other electronegative atoms (Y) containing pairs of non-bonded electrons. X removes electron density from hydrogen. Therefore, it has a partial positive charge, which is strongly attached to non-bonded electrons of Y. H-bonding usually stabilizes the structures by intramolecular bond formation. Such bond formation occurs in protein alpha-helix and in base pair of DNA.

Electrostatic Bonding

The opposite-charged compound will interact with the opposite-charged part of the receptor. The positively charged quaternary N-acetylcholine may be attracted to the negative charge of an ionized carboxyl group in the receptor.

Charge Transfer Complex

A dipole–dipole interaction is produced and a charge transfer complex is formed when any molecule with electron-donating property comes near the electron-accepting group. Donor molecules are electrons rich in heterocycles, e.g. furan, thiophene, and aromatics with electron-donating substituents, or compounds with free non-bonding electron pair. Acceptor molecules are electron deficient systems such as purines and pyrimidines or aromatics with electron-withdrawing substituents. Examples of charge transfer complex in drug–receptor interaction are antimalarials with their receptors and antibiotics intercalating the DNA. The energy is not more than 30 kJ/mol.

Hydrophobic Forces

In the presence of non-polar molecules, the surrounding water molecules orient themselves, and therefore, are in a high-energy state, when two non-polar receptor groups (one from the drug and another from the receptor) approach disorder-ordered H_2O molecules in an attempt to associate with each other by increasing the enthalpy and decreasing the free energy to stabilize drug–receptor complex.

Van der Waals or London Dispersion Forces

Atoms in non-polar molecular structure have a temporary non-symmetrical distribution of electron density, which results in the generation of a temporary dipole that creates an intermolecule attraction called *Van der Waals force*. However, this is a weak bond.

FACTORS AFFECTING THE DRUG–RECEPTOR INTERACTION

Isosterism: Groups of atoms that possess similar physical or chemical properties of a molecule due to similarity in size, electronegativity, or stereochemistry are referred to as *isosteres*. The existence of such groups in molecules is termed *isosterism*. For example, N and CO both have 14 total electrons and no charges, and show same physical properties. In sulphonamides, the replacement of atoms or groups with various isosters, other analogues is developed. Potency of these agents varies according to their interaction with the target.

Steric features of a drug: The drug must possess stereoselective property to initiate a response at a particular receptor. For example, *trans*-diethylstilbestrol is oestrogenic while *cis*-isomer is almost inactive.

Optical isomerism: Enantiomers, asymmetry, and chirality are important concepts to give better receptor interaction with drugs. Although each enantiomer has some physical and chemical properties, they may act in different ways and in different sites to produce variable pharmacological action.

CHAPTER 16

Computer-aided Drug Design

INTRODUCTION

Computer-aided Drug Design (CADD) involves all the computer-assisted techniques that are used to discover, design, and optimize biologically active compounds with putative use as a drug having the desired structure and properties. It is an integrated discipline and works with the intersection of structural biology, biochemistry, medicinal chemistry, toxicology, pharmacology, biophysical chemistry and information technology.

The process of drug discovery and development is a long, tedious, and difficult one with the high demand for drugs on one side and the complexity of various biological systems on the other. Occasionally, new drugs are discovered by accident; more frequently, they are developed as a part of an organized effort to discover new ways to treat specific diseases. The trial-and-error method usually employed for new drug development is highly uneconomical, as it requires various predictions, such as pharmacokinetic, pharmacodynamic, and toxic properties before the synthesis of a chemical compound. Finally, after this, it is observed that out of the several thousand compounds synthesized and tested, hardly one, two, or even none clicks. Today, the emphasis is not just on finding new ways to treat human disease, but also on improving the quality of life in general. Computer-based drug design techniques have the ability to accomplish both these goals and improve the efficiency of the process as well. Commonly a therapeutic agent to reach patients, it takes more than 10 years and requires billions of dollars investment for the drug development process. In the recent advanced technology, some specifically automated platforms, computational chemistry and CADD are currently contributing good practices for the limiting factors of therapeutic discovery. CADD offers speedy and low-cost drug candidates by in silico alternative methods for medicinal chemistry techniques and has become an indispensable programme of major pharmaceutical companies.

The drug discovery and lead optimization process is currently dominated by developments in two fields: A rational design based on structural information and sophisticated computational methods to elucidate the structural prerequisites that are important for binding to a particular target. In this technique new mathematic algorithm is responsible for the prediction of desired properties and applies to current algorithms on molecular target, such as simulating protein–ligand or protein–protein interactions for biomolecular interactions. The rational drug design processes have changed the way in which potential new drugs are discovered. The rational drug design process starts with an understanding of the fundamental physiological and biochemical aspects of the disease or target, rather than random screening process. One method to bring about cost-effectiveness in drug design process is by applying both the knowledge of mechanistic basis of a target disease and molecular characteristics of the

compounds to have an effect on disease's state. This approach to therapeutic development is called *rational drug design approach*.

Generally speaking, CADD is a specialized branch that covers computational methods of calculation, and graphic techniques gives information about drug–receptor interactions. CADD methods are closely linked to bioinformatics application and databases (Figure 16.1).

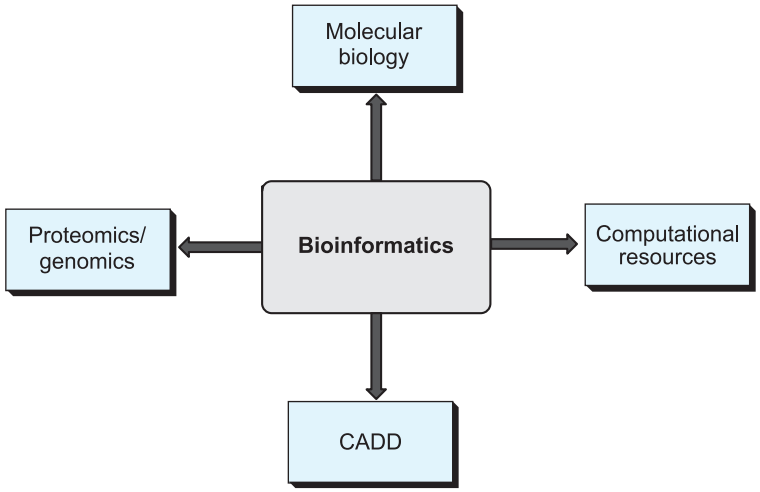


Figure 16.1: Role of bioinformatics in computer-aided drug design.

BIOINFORMATICS HUB

Bioinformatics can be thought of as a central hub that unites several disciplines and methodologies.

On the support side of the hub, computational resources and other software technologies like information technology, information management, and databases provide the infrastructure for bioinformatics.

On the scientific side of the hub, bioinformatics methods are used extensively in molecular biology, genomics, proteomics, and in CADD research.

Bioinformatics supports CADD research in the following aspects:

- **Virtual high-throughput screening:** High-throughput screening (HTS) is a conventional experimental method that was continued to quickly identify the drug leads. By performing individual biochemical evaluation, HTS assesses the fit molecules from millions of compounds. However, with the help of computational methodology called *vHTS*, the time required for screening was reduced to a margin with cost effect and in which screening method involves the application of *in silico* collection of compound libraries to check the binding affinity of the target receptor. In this method the complimentary target receptor for the lead molecule is identified by scoring function. HTS and vHTS are corresponding methods, and vHTS shows least false positives in HTS.
- **Sequence analysis:** The term *sequence analysis* indicates the subjection of DNA, RNA or peptide sequence for analytical methods, for determining physicochemical features, function, configuration, or evolution. These methodologies step forward with sequence alignment and biological database searching. The major parameter involved in the sequence analysis is determination of intrinsic features of the sequence like active sites, post-translational modification sites, regulatory elements, single nucleotide polymorphism, and finally, identification of molecular structure from the sequence.
- **Homology modelling:** One of the easiest methods in drug development was homology modelling. Two major observations are considered for this technique. The protein structure is uniquely

determined by its amino acid sequence to predict the suitable structure of lead molecule. For further evolution, the structure is highly stable and transforms very slowly. When the length of sequences and the probable percentage of similar residues fall in the province marked as 'safe', the sequences are practically suitable to target a similar structure. Homology modelling is a multistep development that can be reviewed in seven steps: (1) Template recognition and initial alignment, (2) alignment correction, (3) backbone generation, (4) loop modelling, (5) side-chain modelling, (6) model optimization and (7) model validation.

- **Similarity searches:** Many computational tools are available for this task. Of this, basic local alignment search tool (BLAST) is the most commonly preferred one. BLAST has two main advantages: The statistical representation for computing the significance of local sequence similarities and its speed. The maximal exact matches (MEMs) or the maximum unique matches (MUMs), or gapped seeds and alignment of homologous protein sequences are identified.
- **Drug lead optimization:** Lead optimization from a knock in discovery will be initiated by selecting the particular leads from secondary selection with proven specificity and highest binding affinities to the target of interest. The range of binding affinities begins from 1 to 10 μM and requires increase in potency up to five orders for consideration as drug candidate. On considering the potency, the selectivity, bioavailability, and toxicity should be accounted for the drug candidate.
- **Physicochemical modelling:** Physicochemical modelling was executed by the determination of different groups in terms of physical and chemical properties by considering the three-dimensional position and conformational analysis. In this, all the pharmacokinetic and dynamic properties are predicted by QSAR, e.g. prediction of solubility, oral absorption, intestinal permeability, blood–brain barrier permeability, hepatic metabolism and tissue distribution.
- **Drug bioavailability and bioactivity:** The structural information from ligand-target X-ray crystallization data generated during secondary screening will include IC_{50}/K information and the chemical structures. This will be useful for the elucidation of bioavailability and pharmacokinetics and required structural modification. However, the drug target ability with effective modifications like pH and other physiochemical properties determines the bioavailability.

PHASES OF CADD

Basic Functional Classification of CADD Methods

1. Structure-based drug design
2. Ligand-based drug design

1. Structure-based Drug Design

It is also known as *target drug design*, in this the receptor structure and the mechanism is known, but the ligand and the biological activity is not known. The construction of lead molecule was designed according to the receptor-binding cavity on a target site of receptor in terms with the biophysical interactions. This can be done by building, docking and linking of different groups for creating a ligand lead molecule and includes the following steps:

a. **Protein structure determination:** For structure-based drug design, the main concern before evaluating the receptor-ligand correlation was to attain the target structure. Two different major methods for protein structure determination are by physical measures: X-ray diffraction and NMR. In the Protein Data Bank library, the identified protein structures can be readily found. Further modelling approach can be used for the unsolved protein or a protein that is difficult to isolate.

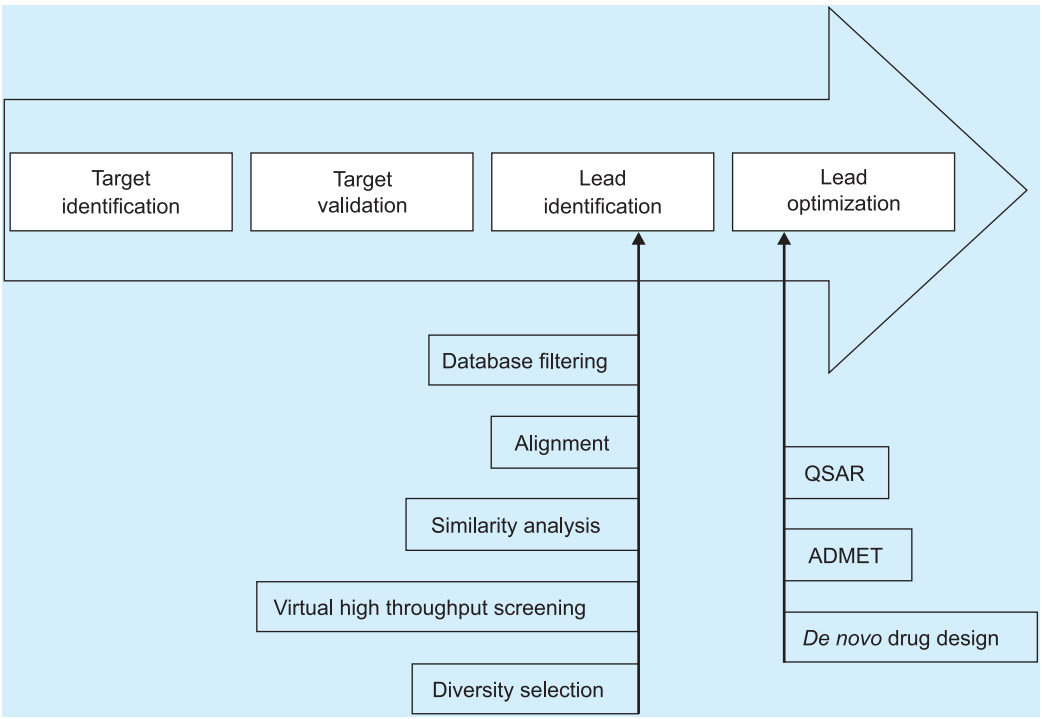


Figure 16.2: Phases of CADD indicating the integrative functional sequences of evaluations saving 12–15 years for drug development.

The fast method to predict the protein structures is homology modelling. The structural information of an unknown protein can be designed if it resembles over 30 percent of its known homologous templates.

For example, studies on H1N1 influenza virus evaluations have used homology modelling approach to construct hemagglutinin and neuraminidase structures from newly identified viral protein sequences and solved protein structures. The structures modelled can be modified further in model refinement to be constant with experiment statistics in geometry, covalent bonds, and energy configuration. Force fields, such as CHARMM, AMBER, CVFF, CFF91, and GROMOS are applied to molecules to calculate energy minimization.

$$E_{\text{total}} + E_{\text{stretching}} + E_{\text{bending}} + E_{\text{dihedral}} + E_{\text{out of plane}} + E_{\text{cross terms}} + E_{\text{VdW}} + E_{\text{Coulombic}}$$

b. **Folding recognition:** This process is also known as 'threading'. Folding recognition describes the background of residue interactions. The calculations involved in folding recognitions are the probabilities of the 3D structures form by a given protein sequence. The environment of residue interactions and the protein plane surface area were measured in threading protocol. The structure with highest likelihood is opted for the construction of protein model.

c. **Ab initio protein modelling:** This method is based on the physical principles, residue interaction centre and lattice illustration of a protein to construct the target. This technique is exceptionally practical when the other procedures fail to calculate an unidentified protein structure. However, the distinctiveness and precision excreted by ab initio replica could be inferior to other approaches.

Protein folding involves many biochemical actions and physical actions that originate from inherent residue interaction. Based on this perception, ab initio technique puts forward that during protein folding it would have a propensity to attain the most energetically favourable state.

d. **Hot spot prediction:** Another important parameter to consider in structure-based drug design is the determination of the ligand-active site. The active site is determined through ligand position in the crystal lattice surface by X-ray crystallography, and is impossible for the proteins that cannot be crystallized. Various binding site evaluation methods are invented to address the issue, and it can be done by FTMAP. This employs tiny molecular fragments as probe for exploring the protein surface. From this the druggable sites are determined in which the molecular fragments are clustered. The bond interactions such as hydrogen bonds and non-bound interactions are also forecasted for the drug target site.

Pharmacophore modelling

Pharmacophore modelling is a very efficient and successful field of CADD. The various concepts of this is used for designing novel drugs.

Pharmacophore: The functional groups or chemical moieties in a molecule which are responsible for the biological activity are called pharmacophore. According to IUPAC system pharmacophore is defined as "the collective of steric and electronic features that is necessary to ensure the optimal supramolecular interaction with a specific biological target and trigger or blocks its biological response".

Various concepts of pharmacophore in CADD: It is an important tool in CADD because each and every type of groups in a molecule elicits some type of properties related to molecular recognition and that can be converted to pharmacophore. These properties may be hydrogen bond donor and acceptor, aliphatic, aromatic, cation, anion, hydrophilic and hydrophobic character, etc. Various kind of molecules can be compared with their pharmacophore level and this process is called pharmacophore fingerprint. In 3D model, very smaller number of pharmacophore features are considered and known as pharmacophore query.

Pharmacophore fingerprint: It is a representation of a small molecule ligand explains annotated with molecular interaction features. All possible three-point or two-point interactions are enumerated for each ligand. The different distances between the features are calculated as number of bond lengths or calculated through space and frequency of occurring is stored in each string.

Applications of pharmacophore fingerprint:

1. It is used to identify and analyze the similarity between molecules or their library.
2. It is also used to analyze the common group or element responsible for biological activity.

Pharmacophore query: It consists of various features that indicate hydrogen bond donor, acceptor, hydrophilic, cationic and anionic character, etc. and organized in a particular 3D pattern. Each feature is indicated as a sphere with a radius determining the tolerance on the deviation from the exact position. These features are used as queries for determining the activity of small molecule libraries. In the library, all molecules are having low energy conformations. Each of these conformations are fitted to the pharmacophore query by aligning the pharmacophore features of the molecule and the query is composed. The molecule exactly fitted inside the sphere is considered as a hit molecule and the pharmacophore query is too complex from of a given molecular library, partial matching can be considered.

Pharmacophore modeling in the area of Virtual screening: Pharmacophore modelling is mainly applied in virtual screening to identify molecules producing biological activity. For this process, a pharmacophore model is created which most likely resembles as the correct 3D organization of the needed interaction protein.

Different options are available to construct such kind of query.

1. Absence of information about both ligand and protein structure.
2. Known about the ligand but the structure is unknown (Ligand-based virtual screening).

1. **Protein and ligand structure are not known:** In this case, pharmacophore modelling is impossible. The main or only option to apply the pharmacophore model is to design a diverse library of compounds.
2. **Unknown protein structure, but active ligand structures are known:** In this case, if the structure of receptor is unknown but the structure of single active molecule or ligand is known. In this condition, identifying the key contributing pharmacophore is impossible and the only option is utilising similarity searches.
3. **Both protein and ligand structures are known:** In this case, the structure information about both protein and ligands are known. In this condition the protein and ligand interactions can be mapped on to the bioactive conformation of the ligand. Generally, the model structure can be obtained from NMR or crystallographic data. Instead of this homology model, structural data details also can be used. This method is used to identify the multiple interaction about the ligands. LigandScout, is a first software used to automatically construct a query from one or more PDB files based on protein–ligand interactions. This structure-based pharmacophore queries involves multiple uses such as ligand binding pose prediction, virtual screening and binding site comparison.
4. **Only known protein structure is available:** In this case, the structural information about the protein is known, but there are no active ligands known. Here, a putative pharmacophore model can be constructed by analyzing the chemical properties of binding sites into queries. The DeNovo tool LUDI can be applied to create a pharmacophore query. Sometimes, the GRID package also used to identify the key interactions. By using the molecular interaction fields, the most favourable positions of atomic probes in the binding sites can be identified and converted into pharmacophore features.

Pharmacophore methods in docking studies: Molecular docking studies are computational methods which can be used to predict the binding mode of a ligand for a given receptor as well as the interaction quality and to find out the free energy binding or to predict the affinity by using a scoring function.

Various options are available to combine the docking based virtual screening with pharmacophore-based virtual screening. They are:

1. The ligands database can be prefiltered by using pharmacophore query, before evaluation by docking simulations.
2. This docking simulation can be post-filtered by using pharmacophore query in order to remove any compounds that failed to bind according or with respect to the pharmacophore query.
3. The pharmacophore alignment is used to guide the placement during the docking simulations.

Role of pharmacophores in ADME- toxicity: Poor ADME-toxicity is one of the major and important contributing factors for the failure of the drugs during clinical trials and drug development. Hence, the optimization of ADME-tox properties should be needed. In this area, the pharmacophore models can be used to identify the possible interactions between the drugs and drug metabolizing enzymes by matching the equivalent chemical groups of test molecules to those of drug molecules with a well-known ADME-tox profile.

Pharmacophore-based drug target identification: The main aim of CADD is to identify and optimize drug like molecules for a given target and vice versa. The pharmacophore model plays important role to find out the active ligand. The molecule or the given compound or ligand itself considered as a pharmacophore query. The main aim is to identify the most likely pharmacophore model that fits

the molecule. These collections of pharmacophore models are constructed manually or automatically obtained or generated from the PDB databases. This approach is also used to find out a target for a given ligand with a unknown activity.

Limitations:

1. Absence of good scoring metrics in virtual screening.
2. Pharmacophore model dependency on a precomputed conformation database.
3. Absence of clear-cut way to construct a pharmacophore query.
4. Plenty of experience and a certain dose of serendipity may be required for successful results.

Docking

Docking is a well-established computational technique which predicts the interaction energy between two molecules. This technique mainly uses the various algorithms like molecular dynamics, Monte Carlo simulation, fragment-based search methods.

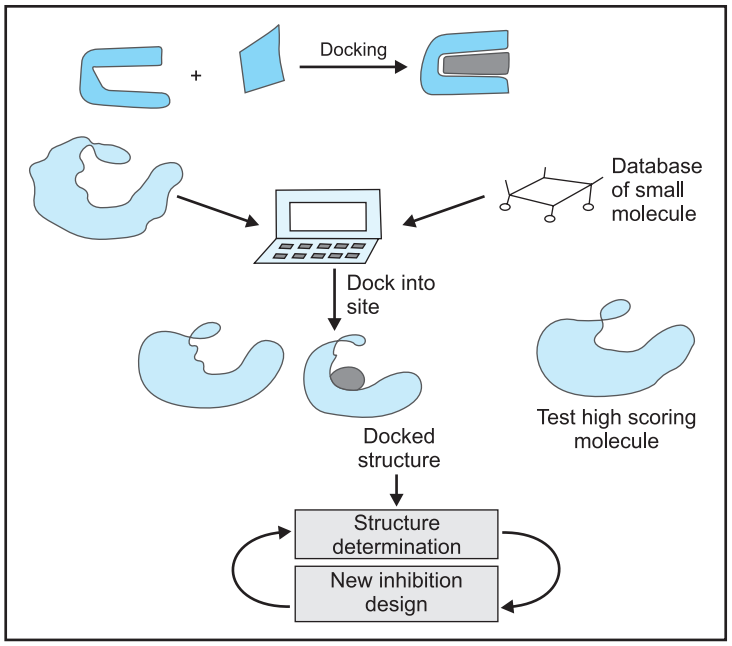


Figure 16.3: Principle of Docking.

Molecular docking studies are used to determine the interaction of two molecules and to find out the best orientation of ligand which would form a complex with overall minimum energy. The small molecule called ligand fits within protein cavity which is predicted by the search algorithm. These protein cavities become active when they come in contact with any external compounds and are called active sites.

Docking is frequently used to predict the binding orientation of small molecule drug candidates to predict protein targets in order to predict the affinity and activity of small molecules. Hence, docking plays an important role in the rational drug design.

The results obtained are analyzed by statistical scoring function which converts interacting energy into numerical values called docking scores and the interaction energy also calculated. The 3D pose of

the bound ligand can be visualized using different visualizing tool like PyMOL, RasMol which is in interference of the best fit of the ligand. Predicting the mode of the reaction, i.e. interaction can assume the active site of the protein molecules and also used in protein annotation. It is also the major useful tool in drug design and discovery.

Types of interactions:

1. **Electrostatic interactions:** Forces with electrostatic origin due to the changes between the molecules contained by the particular moiety or matters. Example: Charge–charge interactions, charge–dipole and dipole–dipole interaction.
2. **Electrodynamic interactions:** The mostly known interaction is Van der Waals interaction.
3. **Steric factors/steric forces:** Steric factors are generated when atoms in different molecules come into very close contact with another and start affecting the reactivity of each other. The resulting forces affect the chemical reactions and the free energy of a system.
4. **Solvent-related forces:** These are the forces generated due to the chemical reaction between the solvent and the protein or ligand. Example, hydrogen bonding and hydrophobic interactions.
5. **Other physical factors:** Conformational changes of either ligand or the protein is important for successful docking.

Molecular docking studies are divided into two separate sections.

1. Searching algorithm
2. Scoring function

Searching algorithm: It determines all possible optional conformations for a given complex (protein–protein, protein–ligand) in an environment, i.e. the position and orientation of both molecules relative to each other. They can also use the energy of the resulting complex and individual interactions.

Types of algorithms used in docking:

1. Molecular dynamics
2. Monte Carlo methods
3. Genetic algorithms
4. Fragment-based methods
5. Point complementary methods
6. Distance geometry methods
7. Systematic searches

Scoring function: These are mathematical functions used to predict the strength of the non-covalent interactions, known as binding energy of the two molecules after they have docked. Scoring function can also be developed to predict the strength of the other types of intermolecular interactions. For example, between two proteins or between protein and DNA or protein and drug. All these configurations are evaluated using scoring function to distinguish the experimental binding modes from all other modes explored through the scoring function.

For example: Empirical scoring function of any docking program is calculated as follows.

$$\text{Fitness} = Vd_w + H_{bond} + \text{Elec}$$

where,

Vd_w = Van der Waals forces

H_{bond} = Hydrogen bonding

Elec = Electrical forces

Binding energy, $\Delta G_{bind} = \Delta G_{Vdw} + \Delta G_{Hbond} + \Delta G_{elec} + \Delta G_{confrom} + \Delta G_{tor} + \Delta G_{solv}$

◆ *Types of Docking*

There are two types of docking:

1. Lock and Key or Rigid Docking
2. Induced Fit or Flexible Docking

Lock and Key or Rigid Docking: In this docking, both the internal geometry of receptor and ligand is kept fixed during docking.

◆ *Various Applications of Docking*

1. **Hit identification:** Docking combined with a scoring function can be used to quickly screen large databases of potential drugs insilico to identify molecules that are likely to be bind with the targets of interest.
2. **Lead optimization:** Docking can be used to predict the relative orientation of a ligand that binds to a protein which may be in turn used to design more potent and selective analogs.
3. **Bioremediation:** It is also used to predict pollutants which can be degraded by enzymes.

◆ *Docking Softwares Used in Study*

1. **Cambridge Crystallographic Data Centre (CCDC) GOLD:**
   - **Genetic Optimization for Ligand Docking (GOLD):** It is a genetic algorithm for flexible ligand docking into protein sites. GOLD is supplied as a part of the GOLD suite which includes two additional softwares such as Hermes and Goldmine.
   - **Hermes Visualizer:** It can be used to assist the preparation of input files for docking with GOLD, visualization of docking results and calculation of descriptors. It is also used to define the binding site and setting of constraints. GOLD offers a choice of scoring functions. The GOLD score, Chemscore, AsP which allow the user to modify an existing function or implement their own scoring function. The overall output of all of the above are same only.
2. **Schrödinger Glide:** Glide docks flexible ligands into a rigid/flexible receptor by rapid samplings of the conformational, orientational and positional degree of freedom of ligands. There are 3 modes of running glide which are differ in their ligand degrees of freedom are sampled and scoring function employed. All the three modes produce an exhaustive set of conformers for a ligand and employ a series of hierarchical filters to enable rapid evaluation of ligand degrees of freedom.
   - **SP Glide score:** Here scoring function is used to rank the compounds docked by SP or HTVS Glide.
   - **XP Guide:** It begins with SP Glide docking and then refines the predicted docking modes using an anchor and grow algorithm which is used more thoroughly to sample ligands of freedom. The main recognition of XP mode is to identify and reward structural motifs important to binding.
   - **AutoDock Vina:** AutoDock Vina is a comparatively new open source program for drug discovery, molecular docking and virtual screening. It provides multicore capability, high performance, enhanced accuracy and ease of use.

   It has been designed and implemented by Dr. OlegTroTt (2010) in the molecular graphics lab at the Scripps Research Institute. This AutoDock automatically calculates the map and clusters the results in a way transparent to the user.

Example for Docking

- Ligand protein docking

Step 1: Preparation of input

Step 2: Grid preparation

Preparation of input files

- **Ligand preparation**

1. Assign charges
2. Define rotatable bonds
3. Rename aromatic carbons
4. Merge non-polar hydrogens
5. Write—Pdbqt ligand file
6. Ligands can be obtained from various databases like PubChem/ZINC, etc.
7. Apply Lipinski's rule of five

- **Protein preparation:**

1. Add essential hydrogen bonds
2. Load charges
3. Merge lone pairs
4. Add solvation parameters
5. Write—Pdbqt protein file
6. PDB structures often contain H_2O molecules
7. Remove all H_2O molecules except the important one which coordinate with ligands.

3. Docking preparation—Grid

1. The ligand–protein interaction energies are pre-calculated.
2. Construction of Grid maps depends upon the atoms of interest in ligand.

   Then the ligands—protein energies are fixed, the best lead is identified.

   Binding free energy: The binding free energy is calculated by

   Energy of binding = Energy of complex – Energy of ligand – Energy of receptor

4. Flexibility of protein–ligand complex: Flexibility of ligand–protein complex can be calculated. It is calculated by

Flexibility = Score of ligand fit – Score of flexible docking

The results obtained from the molecular simulation is related to flexibility and a positive relationship can be obtained in flexibility *vs* molecular dynamics.

5. *De novo* Evolution: The modification ligands after docking can be obtained by two ways.

a. By using the original ligand scaffolds to develop derivatives which are complement to receptors.

b. Depending upon the active site identify the functional groups which produce interactions with the receptor, after that functional groups can be attached.

Docking—AutoDock: AutoDock is a software programme for docking tiny flexible ligands onto the rigid 3D structure of protein. A set of network is used to explain the 3D structure, based on the AMBER force field, and produced with AutoGrid for calculating the Coulombic and Van der Waals forces. In this the best binding models are also identified by the genetic algorithm and simulated annealing. In the contemporary versions, the linear regression analysis is also used to calculate the free-energy scoring function.

Flexible docking: This involves the method of receptor flexibility during the docking of flexible ligands. The objective receptor side chain conformations are considered in the preliminary step and are

spawned by ChiFlex algorithm. The ChiFlex algorithm generates a variety of protein conformations with diverse side chain orientations. The secondary step is providing stumpy energy conformations of ligands to the docking process. The binding sites where ligand polar and non-polar groups may be bound to the favourable positions of protein are determined by the LibDock programme. In the further step, the similar ligand poses are removed. Then by using ChiRotor algorithm and by CDOCKER for structure simulated annealing and energy minimization of each ligand pose, refinement was performed. Finally, flexible docking can optimize the flexibility of the side chains.

Ligand fit: It is a grid-based method for scheming receptor–ligand interaction energies, which plays an important role in initial ligand profile match to the receptor-binding site. This method processes through (1) definition of the active site, (2) ligand conformations analysis, (3) ligand docking to a preferred site and (4) scoring of the predicted poses. During the first step, if there are no active sites in 3D structure, the possible cavity region on the protein site can be determined by flood-filling algorithm. In the second step, the ligand conformations are generated by Monte Carlo (MC) method and after the conformation is generated, it will be engaged to dock towards the receptor. In the third step after docking to a preferred site, scoring is done by grid-based energy calculation, which is exerted by the interaction between ligand and the receptor.

2. Ligand-based Drug Design

When the target protein molecular structure is unknown or unpredicted by molecular modelling performance, the ligand-based drug design is followed. This method uses arithmetical approach to associate ligand movement to structural information, which is mentioned below.

a. **Quantitative structure–activity relationship (QSAR):** QSAR is a widely used technique in drug-designing process. It employs information and logical tools to explore the association between the structures of ligands and their corresponding effects. Hence, geometrical models are built based on structural consideration. 2D-QSAR was extensively used to link structural activities such as hydrophobicity, steric, electrostatic and geometric effects, which are responsible for the molecular biological activity. Mostly Hansch analysis was used. 2D-QSAR cannot accurately illustrate the relationship between the 3D spatial arrangement of the physiochemical properties and the biological activities, so 3D-QSAR approaches are adopted.

b. **CoMFA:** Comparative molecular field analysis is recognized on the concept that the biological activity of a fragment is reliant on the neighbouring molecular fields, such as steric and electrostatic fields. These are calculated by CoMFA using Lennard–Jones potential and Coulombic potential. Both potential occupation changes considerably near the Van der Waals surface of the molecule and, thus, cut-off values are often required.

c. **CoMSIA:** This is an advanced method of CoMFA. It includes more supplementary field properties. These are steric, electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor properties. CoMSIA is insensible to the orientation of aligned molecules and correlates to the grid by Gaussian function. Moreover, the improved function algorithm was very slightly influenced by the comparative distance to the Van der Waals surface and this model offers more precise structure–activity relationship than CoMFA.

d. **Comparative molecular moment analysis (COMMA):** It won't provide more information because it provides 3D descriptors that are independent of the orientation of the molecules in space, hence not used.

e. **GRID:** It is a good method which provides good description about hydrogen bonding. It also simultaneously evaluates or displays the energy counter surfaces and the macromolecular structures on the probable interaction sites between various functional groups on the ligand and enzyme surface.

f. **Hydrophobic interactions (HINT):** It provides potential hydrophobic and hydrophilic interactions between a molecule and a receptor.

g. **Hypothetic active site lattice (HASL):** This method creates a QSAR model from a composite lattice from each molecule. It utilizes the Van der Waals' radii of molecule and the biological activity value is averaged.

h. **Molecular dynamics simulations:** Molecular systems usually enclose a huge quantity of particles and analysing the complex system is highly complicated, so the utility of molecular dynamics (MD) simulation has received a great attention as one of the important tools for theoretical study of biological molecule. In this, the molecule is allowed to get simulation, for the interaction of atoms and molecules for a period of time and the motion for every atom is considered to determine the overall behaviour. The algorithms for an MD simulation include the following:

1. The prediction of the initial positions and velocities of every atom
2. The calculation of interatomic potentials
3. The progression of atomic positions and velocities through a short time period

Advantages of CADD

CADD methods and bioinformatics tools offer significant benefits for drug discovery programmes.

Cost saving: The cost of drug discovery and development has reached $800 million for a single drug to be successfully brought into the market. Recently, many pharmaceutical industries are focussing on the CADD to reduce this cost burden.

Time-to-market: The predictive power of CADD can reduce the time period for drug development and optimization and avoids potential 'dead-end' compound on final stage. It can get drugs to the market more quickly and cost-effectively.

Insight: The molecular graphics technique of CADD gives information about drug–receptor interaction and atomic scale binding properties to particular ligand or protein. It may give new ideas for researcher to modify the drug compounds for improved fit. Therefore, CADD and bioinformatics together are a powerful combination in drug research and development.

CHAPTER 17

Structure–Activity Relationship and Quantitative Structure–Activity Relationship

INTRODUCTION

Structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR) study, collectively referred to as *(Q)SAR*, are theoretical models that can be used to predict the physicochemical, biological, and environmental fate properties of molecules.

The aim of QSAR techniques is to develop correlations between biological or pharmacological activity, and physicochemical properties of a set of molecules, in particular, substituent properties. In general, QSAR has been adapted to cover correlations independent of actual physicochemical properties. In earlier days, QSAR started with similar correlations between chemical reactivity and structure. Ideally, the activities and properties are connected by some known mathematical function, F:

Biological or pharmacological activity = F (physicochemical properties)

It can be any measure of, such as C, K_i, IC_{50}, ED_{50}, and K_m.

The enormous range of physicochemical properties can be broadly classified into three general types such as electronic, steric, and hydrophobic property of biologically active molecules. The relationship or function is usually (but not always) a mathematical expression derived by statistical and related techniques, for example, multiple linear regression (MLR). The parameters describing physicochemical properties are used as independent variables, and the biological activities are dependent variables. Usage of such data may be possible with neural networks to deduce essential data for biological activities and then using them for prediction. For testing a model for validity, some data are used to generate a relationship (the training set), while another set of data is reserved as a test set on which predictions using the rule are made. The entire technique used to derive functional relationships between the data is collectively known as *chemometrics*.

HISTORICAL DEVELOPMENT OF QSAR

In early 1868, Crum-Brown and Fraser published an equation, which is considered to be the first general equation of QSAR. Richet discovered that the toxicity of organic compounds (aldehyde, alcohol, ethers, ketone, etc.) inversely follows their water solubility. Later, Meyer and Overton worked independently and observed the linear relationships between lipophilicity (oil–water partition coefficients) and narcotic activities. Further, Fuhner has given the first evidence of additivity of groups contributing to biological activity values in a homologous series of compounds for their narcotic activity. Ferguson postulated that the thermodynamic principles could be related to drug activities.

After 1950, QSAR methodology has progressed remarkably. During this year, Bruice, Kharasch, and Winzler reported group contributions to biological activity values in a series of thyroid hormone

analogues; this may be considered as a first Free-Wilson-type analysis. Zahradnik has tried to apply the concept of the Hammett equation. However, significant progress has occurred in the field of QSAR in 1960s through the research work of Bocek and Kopecky, Hansch, and Free-Wilson and Fujita. Among these, only Bocek-Kopecky method has become unsuccessful due to the involvement of a number of parameters. Among the different methods, Hansch, Free-Wilson, and modified Free-Wilson approaches are the widely practised ones for modelling the biological response. Also, QSAR is one of the approaches attracting increasing levels of interest in the pharmaceutical industry as a productive and cost-effective technology in the search for novel lead compounds.

Reasons for Carrying Out SAR

1. To synthesize a new compound with more specific activity.
2. To improve the biological activity of the lead compound.
3. To improve the potency and therapeutic index of the new compound as well as the lead compound.
4. To reduce the adverse reaction, toxicity, and other disadvantages associated with the lead compound as well as the new compound.
5. To find any new possible biological activity for the lead compound.

Methods for Performing SAR

1. Systemic modification
   (a) Homologation and chain branching
   (b) Ring chain transformation
   (c) Introduction of C=C and C≡C
2. Topological analogues
3. Synthesis of structural analogues of synthetic chemicals with interesting biological activity
4. Synthesis of novel compounds based on the known structures of naturally occurring biologically active substances of plant and animal origin
5. Specific design of a drug to interact with receptor site

Parameters Governing QSAR

The most commonly used parameters are electronic, steric, and parameters related to solubility.

I. Electronic parameters:

a. Hammett constant
b. Taft's substituent constant
c. Inductive substituent constant

II. Steric parameters:

a. Taft's steric substituent constant
b. Molecular connectivity
c. Van der Waals dimension
d. Parachor
e. Minimal steric difference
f. Sterimol parameters

III. Partition coefficients:

a. Hansch substituent constant
b. Fragmentation constant
c. Chromatographic R_m value

IV. Biological relationships:

a. Hansch analysis
b. Ferguson effect
c. Free-Wilson analysis

I. Electronic Parameters

a. Hammett constants: Extensive studies of electronic parameters indicated that electronic properties of molecules are intensively related to their chemical and biological activities of molecules. The introduction of substituent groups and the alteration of reaction rate is used to find out the total mechanism or overall mechanism of a reaction. Hammett equation is the measure of the size of electronic effect of a given substituent and indicates a measure of electronic charge distribution in the benzene nucleus. The Hammett equation is

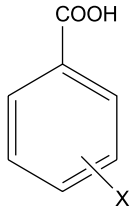
$$\sigma_x = \log K_x - \log K_H$$

or

$$\log (K_X/K_H) = -pK_X + pK_H$$

Electron withdrawing substituents are indicated by positive values, whereas electronic donating groups are indicated by negative values.

In 1940, Hammett introduced substituent constant that predicted equilibrium and rate constants for chemical reactions. According to which if an electron withdrawing group is attached to the aromatic ring of benzoic acid, it would increase the acid strength.



Hammett substituent constant is expressed as follows:

$$\sigma_x = \log (K_x/K_o)$$

where

σ_x = Hammett constant

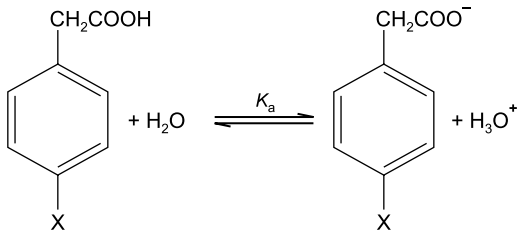
K_x = Benzoic acid substituted by the group 'x'

K_o = Dissociation constant of benzoic acid

The σ can be expressed by the following equation:

$$\sigma_x = pK_a^o - pK_a^x$$

In the extension of this work, the range of ionization of substituted phenyl acetic acid was determined.



The effect of 4-Cl substituent on the ionization of 4-chlorophenyl acetic acid was found to be proportional to its effect on the ionization of 4-Cl benzoic acid.

$$\log\left(K'_{Cl}(PA)/K'_{H}(PA)\right)\alpha \log K_{Cl}\left((BA)/K_{H}(PA)\right)$$

$$\text{Hence, } \log K_{Cl}(BA)/K_{H}(BA) = \sigma$$

$$\log K'_{Cl}/K'_{H} = \rho\sigma$$

where,

ρ-rho, proportionality constant which is a measure of the susceptibility of a reaction to substituent effects.

A 'positive' *p* value: Indicates the reaction is aided by the electron withdrawing substituents.

A 'negative' *p* value: Indicates the reaction is aided by the electron donating substituents.

Hammett also depicted that a plot of log k_A for benzoic acid versus log K for ester hydrolysis of a series of molecules is linear, which indicates that substituents produce a similar effect in dissimilar reactions.

The above details indicated that changes in structure leads to the proportional changes in the activation energy (ΔG) of such reactions, hence Hammett equation is popularly known as linear free energy relationship (LFER).

Limitations of Hammett Equation:

1. Primary σ values are obtained from the thermodynamic ionizations of benzoic acid at 25°C. But the secondary σ values are obtained by comparison with another series of compounds, hence may leads to error.
2. The lack of additivity is observed in multisubstituted compounds. Sigma values for smaller substituents are likely to be additive.
3. Any changes or deviation in mechanism or transition state leads to discontinuities in Hammett plots. Sometimes, non-linear plots are obtained for the reactions proceed by two concurrent ways.
4. Changes in solvent (polar to non-polar or non-polar to polar) may produce dissimilarities in reaction mechanisms.
5. The positions of the substituents also affect the sigma value. Substituents *ortho* to the reaction centre are difficult to describe.
6. Resonance or direct conjugation effects also produce breakdown in the Hammett equation. When the coupling or interaction takes place between the substituent and the reaction centre via л-electron system, reactivity is increased or decreased or mitigated by separation.
7. Most of the Hammett-type constants are related to aromatic systems.

The pK_a value of benzoic acid is 4.19 and *p*-toluic acid is 4.36 (x = p–CH_3). The change in acid strength brought about by the –CH_3 group is equal to 4.19 – 4.36 = –0.17. The limitation of this

constant can only be used for nuclear aromatic substituents and their effects on side chain groups in '*m*' or '*p*' position.

b. Taft's substituent constants: Taft equation is linear free energy relationship (LFER) and used in QSAR studies.

It was developed by Robert W. Taft in 1952.

The equation is

$$\rho^* \sigma^* + \delta Es = \log \frac{K_s}{KCH_3}$$

where, K_s/KCH_3 = Ratio of the rate of the substitution reaction compared to the reference.

Es = Steric substituent effects

ρ^* = Sensitivity factor for the reaction to polar effects

δ = Sensitivity factor for the reaction to the stearic effects

σ^* = Polar substituent constant

Taft plot: It is used to find out the biological activity and polar effects in the study of aminolysis of β-lactam antibiotics.

It is used to measure the polar effects of substituents in aliphatic compounds when the group does not form a part of a conjugated system. It is defined by the following equation:

$$\sigma^* = (1/2.48)\,[\log (K/K_o)_B - \log (K/K_o)_A]$$

where

σ^* = Taft's substituent constant

K = Rate constants for the hydrolysis of the substituted compound

K_o = Rate constants for the hydrolysis of the methyl derivative A = Acid hydrolysis

B = Base hydrolysis

c. Inductive substituent constants: Hammett substituent constants are used for the measure of both inductive and mesomeric effects. The *p*-substituent constant (σ_p) has more resonance component than *m*-substituent constant (σ_m). It can be used in aliphatic compounds in which the influencing and influenced groups does not form part of conjugated system. It can be expressed as follows:

$$\sigma_I = ½\,(3\sigma_p - \sigma_m)$$

where

σ_I = Inductive substituent constant

σ_p = *p*-substituent constant

σ_m = *m*-substituent constant

II. Steric Parameters

a. Taft's steric substituent constant: This constant is used to determine the acid hydrolysis, and it is defined by the following equation.

$$E_s = \log (K/K_o)_A$$

where

E_s = Taft's steric substituent constant

K = Rate constants for the hydrolysis of the substituted compound

K_o = Rate constants for the hydrolysis of the methyl derivative

A = Acid hydrolysis

E_s values are used to determine the effects of substituents 'x' on the antihistaminic activities of some analogues.

b. Molecular connectivities: It is one of the steric parameter and denoted by $^{m}\chi$, where the superscript 'm' denotes the order of the parameter. Zero-order connectivity ($^{o}\chi$) is the simplest, and it is defined by the following equation.

$$^{o}\chi = \sum(\delta_i)^{-1/2}$$

where

$^{o}\chi$ = Zero-order connectivity

δ_i = Number assigned to each non-hydrogen atom, which reflects the number of non-hydrogen atoms bonded to it

c. Van der Waals dimensions: Van der Waals volume (V_w) and Van der Waals radius (r_v) explain the actual dimensions of the group. Since chemical groups are rarely symmetrical, the r_v depends on the axis along which it is measured.

There are three types of radius, namely minimum radius $r_{v\,(min)}$, similar radius $r_v \parallel$, and maximum radius $r_{v\,(max)}$.

Van der Waals radius is defined as the distance of the group protrudes from the bulk of the parent molecule. It can be correlated with biological results in the same ways as Taft's steric substituent constant.

d. Parachor: It is molar volume 'V', which has been correlated for forces of intermolecular interaction and calculated by multiplying by the fourth root of surface tension γ. It is mathematically expressed by

$$[P] = V\gamma^{1/4}$$
$$= M\gamma^{1/4}/D$$

where

[P] = Parachor

V = Molar volume

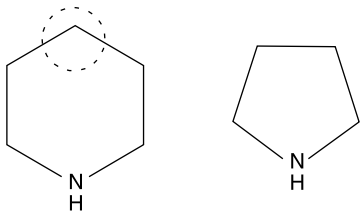
M = Molecular weight

D = Density

$\gamma^{1/4}$ = Fourth root of surface tension

e. Minimal steric difference (MSD): MSD assesses the difference between the molecules in terms of the parts that do not overlap when one chemical formula is placed on top of the other.

For example, when piperidine is compared with pyrrolidine, the $-CH_2$ group surrounded by the dotted circle will determine the MSD, since this is the only portion that does not overlap.



Piperidine Pyrrolidine

f. Sterimol parameters: Steric parameters explained above represent only one aspect of the shape of the group. For example, parachor represents the total volume of the group and r_v the width along one plane. These parameters were developed to overcome this weakness. Each chemical group

represents five sterimol parameters, i.e. L, which is the distance the group protrudes from the parent molecule; and B_1 to B_4, which give the widths of the group in four directions, 90° to each other and perpendicular to the 'L' axis.

III. Partition Coefficients

a. Hansch substituent constants: Hansch proposed a model for the first step in drug action that is solubility of the compound in 1-octanol which simulates a lipid membrane relative to that in water. For the calculation of lipid solubility. Hansch proposed the partition coefficient (*P*).

P = Measure of the solubility in 1-octanol *vs* water. It was determined by using the following equation,

$$P = \frac{[\text{Compound}]_{oct}}{[\text{Compound}]_{aq}(1-\alpha)} \longrightarrow (1)$$

α = Degree of dissociation of the compound in water, calculated from ionization constants.

Collander, the later scientist proposed that the rate of movement of variety of organic compounds through their cellular material was approximately proportional to the logarithm of their partition co-efficient between organic solvent and water.

So, the standard parabolic expression for lipophilicity is expressed by Hansch

$$\log 1/C = -K(\log P)^2 + K^1(\log P) + K^{11}$$

log 1/*C* = Relative potency of the drug.

According to the equation 1, if a compound is more soluble in water than in 1-octanol $P<1$, hence log P = negative.

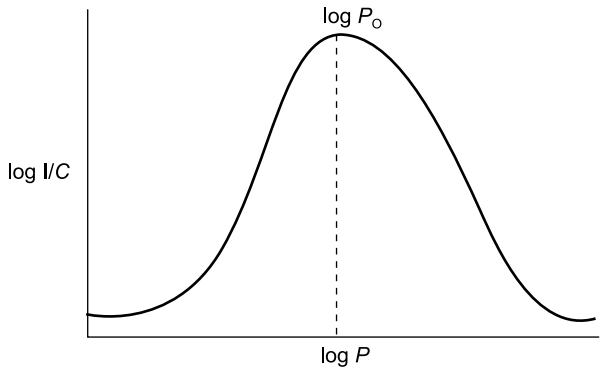
But if a molecule is more soluble in 1-octanol, the $P>1$, hence log *P* = positive.

Hence, the more positive the log *P*, the drug is more lipophilic. The larger the *P* value, there will be an interaction with the lipid phase. When P approaches infinity, micelles will form, leads to drug interaction will become great and the drug should not cross or reaches to the aqueous phase. When P reaches zero, the drug will be so water soluble it will not be capable of crossing the lipid phase and will be present in the aqueous phase.

Somewhere between $P = 0$ and $P = \alpha$, there will be a '*P*' value such that drugs having this value will be least hindered in their journey through lipid membrane. This value is called P_o.

P_o = Optimum partition coefficient for biological activity.

The graph is developed between log 1/*C* *vs* log *P* which forms parabolic relationship.



It indicates that, when the length of alkyl side chain increases, the '*P*' value increases and lipophilicity increases.

Example: The log P_o value normally ranges between 5–9 carbons. The log *P* value of '2' for non-specific set of hypnotics is needed for penetration into the CNS.

Most of the work in QSAR is based on 1-octanol-water system. Based on this system, Hansch substituent constants have been explained. It is defined by the following equation.

$$\pi = \log (P_x/P_H)$$

where

π = Hansch substituent constant

P_x = Partition coefficient of substituted group 'x'

P_H = Partition coefficient of unsubstituted compound

'x' values can be used to calculate 1-octanol-water partition coefficients. The relation between the partition coefficient in one solvent system (P_1) and those in another solvent system (P_2) is shown by the following equation.

$$\log P_1 = K_1 \log P_2 + K_2$$

where

K_1 and K_2 = Constants

$\log P_1 = K_1 \log P_2 + K P_1$ and P_2 = Partition coefficients in two different solvent systems

Determination of Log P Value:

1. **Shake-Flask method:** Transfer a compound into a separating funnel with different volumes of 1-octanol and water. After effective shaking, the concentration of the drug in each layer was calculated, by simple titration/HPLC/GC.
2. **Computerization methods:** Bodor *et. al.*, developed non-liner regression model for the estimation of partition coefficients such as molecular surface, volume, weight and charge densities.

Software packages used to determine log *P* values:

1. Daylight
2. ACD/logP DB
3. CTIS (Autolog)
4. Scilogp
5. Bio Rad.

b. Fragmentation constants: Hansch substituent constant can only be used in certain circumstances. For example, the values for methyl and methylenic groups are the same in the Hansch scheme. For this condition, the fragmentation constants are used as an alternative method for calculating 1-octanol-water partition coefficients. It is defined by the following equation.

$$\log P = \sum af$$

where

P = Partition coefficient

a = Number of times the group occurs

f = Hydrophobic fragmentation constants of various groups in the molecule

c. Chromatographic R_m values: R_m values have been used as a substitute for partition coefficients in QSAR investigations, when the solubility of a solute is greater in one phase than in the other. In this

case, the partition coefficients become difficult to determine experimentally. For this condition, chromatographic R_m values are used. The equation is given below:

$$R_m = \log [1/R_f + 1]$$

The relationship between R_m value and partition coefficient is shown by the following equation:

$$\log P = R_m + \text{Constant}$$

IV. Biological Relationships

a. Hansch analysis: The systems with which Ferguson's approach was successful (e.g. general anaesthetics) were those in which equilibrium was quickly established.

A linear multiple regression analysis.

The biological activity of the drug depends upon two factors. One is lipophilicity and second one is electronic factor. Hansch and co-workers developed one equation known as Hansch equation.

According to Hansch analysis, two stages were postulated in drug action.

Stage 1: A *random walk* from the point of drug administration into the site of action. This will involve passage over a series of membranes, and it is therefore related to partition coefficient. It is expressed as f(P), a function of partition coefficient.

Stage 2: Attachment to the receptor site and it is expressed mathematically as K_x, which depends on the shape of the molecule and electron density on the attachment groups.

Biological activity (R_b) will be dependent on concentration 'C' and the relationship between those as follows:

$$R_b = f(P)\, K_x\, C$$

where

R_b = Biological activity
$f(P)$ = Function of the partition coefficient
K_x = Attachment to the receptor site
C = Concentration

The Hammett relationship utilizes electronic properties as the descriptors of their chemical structure. Sometimes, difficulties were encountered when investigators attempted to apply Hammett-type relationships to biological systems. To overcome this problem, Hansch *et al.* entered the scenario with the numerical information on lipophilicity, electronic, and steric effect on the model development. The general form of Hansch equation is as follows:

$$\log BA = a \log p + b\, \sigma + c\, Es + \text{Constant (linear)}$$

$$\log BA = a \log p + b\, (\log p)^2 + c\, \sigma + d\, Es + \text{Constant (nonlinear)}$$

Hansch model correlates biological activity with physicochemical properties. The coefficients (a, b, c, d, and constant) are determined by multiple regression analysis.

Advantages:

1. Conformational changes in, receptors can be ignored, metabolism do not interfere.
2. The relationship between potency-lipophilicity is linear or parabolic.
3. Collection of various descriptors from single organic model to be used for complex system.
4. Predictions are quantitative with statistical confidence limits.
5. Inexpensive method.

Disadvantages:

1. Parameter values must be needed for the substituents in the data set.
2. A large number of compounds should be included.
3. Expertise and computer use is essential.
4. Small molecule models are imperfect.
5. *In vitro* interactions are sometimes differ from *in vivo*.
6. Organic reactions used to determine the descriptors usually are studied under acidic or basic conditions, when all analogs are fully protonated or in biological system partial protonation is possible.
7. It is only applied for lead optimization and not suitable for lead discovery.
8. Extrapolation leads to wrong discovery.

b. Ferguson effect: Ferguson, who connected the free energy with biological activity, took an example of homologous series of normal aliphatic alcohols and proved that the logarithm of toxic concentration of aliphatic alcohols varied with the carbon number and the properties that were linearly related to the free energy. According to Ferguson effect, the biological activity of a drug is controlled by the concentration of the content within the receptor cell and not by body fluids. If the cell contents are in equilibrium with the surrounding body fluid, the partial free energies in the two phases will be equal.

The above activities are expressed as C_e/C_s for solutions, where C_e = effective concentration and C_s = solubility.

Also gas concentrations are measured in terms of their partial pressure, the activities for gases and vapours are given by P_e/P_s, where P_e = effective vapour pressure and P_s = saturated vapour pressure.

c. Free-Wilson analysis: It is also known as the *additivity model* or *de novo* approach. This method is based on the assumption that the introduction of a particular substituent at a particular molecular position always contributes in the same way to the biological potency of the whole molecule, as expressed by the equation:

$$\log BA = \text{Contribution of unsubstituted parent compound} + \text{Contribution of corresponding substituents}$$

$$\log BA = \mu + \sum a_i a_j$$

where

a_i = Number of positions at which substitution occurs

a_j = Number of substituents at that position

μ = Overall average

The equation is solved by MLR using the presence (1) or absence (0) of the different substituents as independent parameters, while the measured activity serves as dependent variable.

Mixed Approach

Kubinyi has presented the combination of Hansch and Free-Wilson approach as mixed approach.

$$\log BA = k_1\pi + k_2\sigma + k_3 Es + k \text{ (Hansch analysis)}$$

$$\log BA = \mu + \sum a_i a_j \text{ (Free-Wilson approach)}$$

So, the mixed approach can be written as

$$\log BA = \sum a_i a_j + \sum k_i \phi_j + k$$

where

$\sum(a_i a_j)$ = Free-Wilson part for the substituents

ϕ_j = σ, π, and Es contribution of the parent skeleton

Among the above-mentioned approaches, Hansch approach became the most popular approach in QSAR. The high-dimensional QSAR analyses (3D, 4D, and 5D) are developed to avoid pitfalls of classical method and to create the hypothetical drug–receptor model.

Advantages of QSAR

- It quantifies the relationship between structure and activity with their physiochemical property basis.
- It is possible to make predictions of designed compounds before the chemical synthesis of novel analogues.
- It may help to understand the interactions between functional group of designed molecules and their activity of target enzyme or protein.

Disadvantages of QSAR

- Due to biological data experimental error, it may give false correlations.
- If training set of molecule is less, the data may not reflect the complete property and it cannot be used to predict the most active compounds.
- In some 3D QSAR study, ligands binding receptor or protein may not be available; in that case the common approach result may not represent the reality.
- It cannot be expected that the QSAR works all the time and gives successful applications.

A model perfectly predicts that the training data may not be good or even useless for prediction. The problem of QSAR is to find coefficients C_0, C_1, ... , C_n such that

Biological activity = $C_0 + (C_1 \times P_1) + ... + (C_n \times P_n)$

and the prediction error is minimized for a list of given compounds.

Partial least squares (PLSs) is a technique used for computation of the coefficients of structural descriptors.

BASIC REQUIREMENTS FOR QSAR ANALYSIS

Some basic requirements are very essential for the best model development. They are as follows:

- All analogues belong to a congeneric series (classical QSAR studies) exerting the same mechanism of action. This is a series of compounds with a similar basic structure, but with varying substituents. Non-congeneric series are widely used for higher dimensional (3D and 4D) studies.
- Also, the set of compounds with same mechanism of action is essential.
- Biological response should be distributed over a wide range.
- Observed biological activity should be in specific units (concentration in molar units or IC_{50} or percentage inhibition).
- A simple rule is that the total number of compounds in the training set divided by the number of variables in the final model should be greater than approximately five or six.

This will assure that a data set will not be *over predicted* and that the model will have a better chance to retain the predictive value.

Steps Involved in QSAR Studies

The QSAR methodology enables the development of mathematical models, which can be used to predict the biological activity of newly designed compounds. There are three steps involved in this

procedure: The first step is the creation of a database in which calculation of various physicochemical and structural parameters of a congeneric series takes place; the second step is regression analyses leading to model development between biological activities versus derived physiochemical descriptors. The third step involves the validation of the models and prediction of the biological activity of the designed compounds.

Statistical Methods Used in QSAR Analysis

Statistical methods are an essential component of QSAR work. They help to build models, estimate a model's predictive abilities, validate an already existing model, and find the relationships and co-relationship among the variables and the activities. Data analysis methods are used to recombine data into forms and groups and observations into hierarchies.

Regression Methods

It is a mathematical procedure, which correlates dependent (X) variable with the independent (Y) variables. There can be different forms of regression analysis:

- **Simple linear regression analysis:** An independent variable is correlated with a dependent variable and produces a linear one-term equation. It is useful for discovering some of the most important descriptors.
- **MLR analysis:** More than one independent variable is correlated with a dependent variable and a single multiterm equation is formed. The number of variables should be one-fifth of the molecules in a series, that is, for each five molecules in the series one can have one variable.
- **Stepwise linear regression analysis:** This is useful when the number of independent variables is very high and is thus correlated in a stepwise manner with the dependent variable producing a multiterm linear equation.

Partial Least Square (PLS)

Hundreds or even thousands of independent variables (X-block) can be correlated with one or several dependent variables (Y-block). PLS is used when X data contain colinearities or when N is less than $5M$, where N is the number of compounds and M is the number of independent variables. Often perfect correlations are obtained in PLS analysis because of the usually large number of X variables. Cross-validation procedure must be used to select the model that is having the highest predictive values. Several PLSs are performed in which one or several objects are eliminated from the data set. It is the method of choice in 3D QSAR method.

Genetic Function Approximation (GFA)

It provides multiple models that are created by evolving random initial models using a genetic algorithm. Models are improved by performing a crossover operation to recombine better sorting models. This method is used when dealing with a large numbers of descriptors.

Genetic Partial Least Squares (GPLSs)

This method combines the best of GFA and PLS. Each generation has a PLS applied to it instead of MLR and so each model can have more terms in it without fear of overfilling. GPLS retains the ease of interpretations of GFA by back transforming the PLS component to the original variable.

Principal Component Analysis (PCA)

PCA is a data reduction method using mathematical techniques to identify the pattern in a data matrix. The main element of this approach consists of the construction of a small set of new orthogonal, that is, uncorrelated variables derived from a linear combination of the original variables.

Statistical Measures Commonly Used in Regression Analysis

Correlation coefficient (r)/Square of the correlation coefficient (r^2): The correlation coefficient 'r' and square of the correlation coefficient (r^2) are measures of the quality of the fit of the model. It is computed using the following equation:

$$r = \sqrt{1 - \sum\Delta^2/\text{SSY}}$$

$$r^2 = 1 - \sum\Delta^2/\text{SSY}$$

where,

$$\text{SSY} = \sum(Y_{obs} - Y_{mean})$$

$$\sum\Delta^2 = \sum(Y_{obs} - Y_{cal})^2$$

Here,

SSY is the overall variance, that is, $S = \sum(Y_{obs} - Y_{mean})$

Y_{obs} is the observed biological activity.

Y_{mean} is the mean of biological activities value.

Y_{cal} is the calculated biological activity used in the equation.

A high value of correlation coefficient (r) indicates the statistical significance of the regression equation and thereby the participating substituent constants. The squared correlation r^2 is a measure of the explained variance, most often presented as a percentage value, for example, if $r = 0.8$, then $r^2 = 0.664$ or 66.4% as the variance accounted by regression parameters.

Standard error of the estimate (S): This is a measure of how well the function derived by the QSAR analysis predicts the observed biological activity. Its value considers the number of objects n and the number of variables k. Therefore, S depends not only on the quality of fit, but also on the number of degrees of freedom. The smaller the value of S, the better is the QSAR.

$$\text{DF} = n - k - 1$$

$$S = \sqrt{\Sigma\,(Y_{obs} - Y_{cal})^2/n - k - 1}$$

***F*-value:** It is a measure of the statistical significance of the regression model, the influence of the number of variables included in the model is even larger than the standard deviation.

$$F\text{-value} = r^2\,(n - k - 1)/k(1 - r^2)$$

Predicted sum of squares (PRESS): The sum of the overall compounds of the square difference between the actual and predicted value of dependent variables.

$$P = (Y_{obs} - Y_{pred})^2$$

Cross-validation $r^2(q^2)$: Cross-validation is an approach for assessing the predictive value of a model. The cross-validation $r^2(q^2)$ is generated during a validation procedure. It is calculated using the formula,

$$q^2 = 1.0 - \Sigma\,(Y_{pred} - Y_{obs})^2/\Sigma(Y_{obs} - Y_{mean})^2$$

where Y_{pred} is a predicted value; Y_{obs} is an actual value or experimental value; and Y_{mean} is the best estimate of the mean of all values that might be predicted.

A cross-validated r^2 is usually smaller than the overall r^2 for a QSAR equation. It is used as a diagnostic tool to evaluate the predictive power of an equation. Cross-validation proceeds by omitting one or more rows of input data, rederiving the model, and predicting the target property values of the omitted rows. The rederivation and predicting cycle continues until all the target property values have been predicted at least once. The root mean square error of all the target predictions and the PRESS are the basis for evaluating the model.

Outliers: An outlier is defined as a structure with a residual greater than two times the standard deviation.

Bootstrapping: Bootstrapping is another technique for final component model validation. This technique simulating a large number of data sets sampled from the original data set that are of the same size as the original. The same data can be sampled more than once. The statistical analysis is performed on each of the simulating data sets.

MODEL DEVELOPMENT PROCEDURES

Classical or 2D QSAR Analysis

The 2D descriptors are usually developed by using the atoms and connective information of the molecule, but 3D coordinates and individual conformations are not considered. In 2D QSAR, physicochemical parameters such as hydrophobic (π), steric (molar refractivity or MR), hydrogen acceptor (HA), hydrogen donor (HD), and electronic (field effect or F, resonance or R, Hammett's constant or σ) are normally used. In addition to these parameters, *de novo* constants or indicator variables with 0 or 1 values denoting the absence or presence of certain features *(cis/trans* ring atom and bridge atom or chain, different test model, etc.) are also used to adequately parameterize the compounds. In all this, many topological indices are also considered as parameters for analysis.

Drug distribution and binding processes are equilibrium processes governed by the corresponding free energy differences, $K = e^{-\Delta G/RT} = e^{-(\Delta H - T\Delta S)/RT}$, such relationships should use logarithmic scale. For these the biological inhibitory values, that is, IC_{50} or ED_{50} or LD_{50} or K_i must be converted into logarithmic form, such as log $(1/IC_{50})$ or log $(1/ED_{50})$ or log $(1/LD_{50})$ or log $(1/K_i)$ values to obtain appropriate activity parameters for the QSAR study. The logarithmic scales also ensure a normal distribution for the experimental error of biological tests, a requirement for regression-type statistical analyses. In some cases, the activity percentage (%) values (A) are converted to log $[A/(100 - A)]$ as a binding equilibrium constant, which physicochemically is more meaningful than A alone for QSAR analysis.

3D QSAR Analysis

3D QSARs are quantitative models that relate the biological activity of small molecules with their properties calculated in 3D space (Figure 17.1). Hence, 3D properties of a molecule are considered rather than that of the individual substituents. The 3D structures are usually generated from 2D or 2D with configurational information or 3D-structure database or X-ray crystallographic analysis or 2D NMR study. This structure is optimized to refine the geometry based on the size of the molecule such as molecular mechanics (large systems; thousands of atoms) or semiempirical (medium size systems; hundreds of atoms) or ab initio (small systems; tens of atoms), in order to obtain one lowest energy structure per molecule. There are many 3D QSAR techniques used for various purposes. A few of them are listed below:

- Comparative molecular field analysis (CoMFA)
- Comparative molecular similarity indices analysis (CoMSIA)

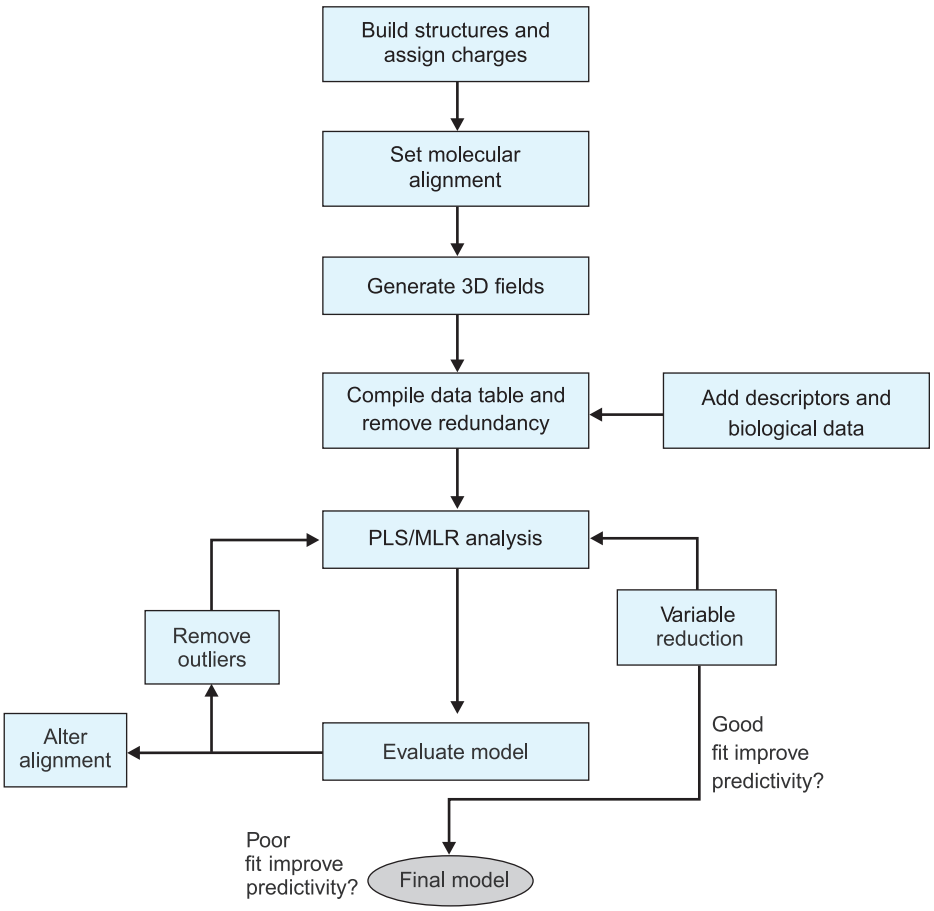


Figure 17.1: Systematic methodology for 3D QSAR analysis.

- Molecular shape analysis (MSA)
- The distance geometry approach
- The binding site model approach
- COMPASS, the hypothetical active lattice method
- The molecular similarity approach
- Genetically evolved receptor models

Among all the 3D QSAR techniques, CoMFA is the most widely used technique and has shown unprecedented accuracy in prediction. Some of these approaches to QSAR are based on the statistical analysis of the 3D interaction fields. These are generated by measuring over a regular 3D grid the interaction energy between a small probe atom or a group and the ligands. Initially, the 3D structures of the training set of compounds are aligned based on common molecular features, so as to occupy the same volume of space. The interaction energy of the small probe, usually, a methyl group and a proton, is measured with each of the training set compounds at each grid coordinates in space. The interaction energy at each grid point in space becomes a descriptor in a QSAR analysis. It results in a data table containing several hundreds or even thousands of descriptors for the analysis.

Comparative Molecular Field Analysis (CoMFA)

CoMFA is a 3D QSAR technique employing both interactive graphics and statistical techniques for correlating the shapes and the biological properties of the molecules. It was proposed and developed by R. D. Crame in 1988. The principle underlying CoMFA is that differences in a target property are related to differences in the shapes of the non-covalent fields of tested molecules. The molecular shape of the tested molecule into a QSAR table and the magnitude of steric (Lennard-Jones) and electrostatic (Coulombic) fields are sampled at regular intervals throughout a defined region of rigid box.

To do so, bioactive conformation of each compound is chosen and they are superimposed in a manner defined by the supposed mode of interaction with the target receptor. Further, CoMFA compares the steric and electrostatic fields calculated around the molecules with various probe groups in three dimensions and extract the important features related to the biological activity. With this information, CoMFA tries to identify the quantitative influence of the specific chemical features of the molecules on their potencies. In 3D space, the contour plots result shows that for biological activity, the important regions of designed or active molecules. Advantages of CoMFA technique include the prediction of activity of new compounds and representation of QSAR models in the form of contour maps.

There are many important aspects that need to be considered for developing a good CoMFA model. Following are the steps involved in developing a good model:

Step 1: Selection of series of compounds for the design.

Step 2: Generation of 3D structure of each selected molecule.

Step 3: Conformational analysis of each molecule.

Step 4: Establishment of bioactive conformation of each molecule, binding mode, and superimposition of the molecules.

Step 5: Position of lattice points, choice of force fields, and calculation of interaction energies.

Step 6: Statistical analysis of the data and selection of the 3D QSAR model.

Step 7: Display of results in contour plots and their interpretation, and design and forecasting the activity of unknown compounds.

Comparative Molecular Similarity Indices Analysis (CoMSIA)

The general methodology and crucial variables for CoMSIA are same as for CoMFA. The primary difference between them is that in case of CoMFA, the contribution due to dispersion forces between molecules are described by Lennard-Jones potential and electrostatic properties are characterized by Coulomb-type potential, whereas in CoMSIA a special Gaussian function is considered for the calculation of interaction energies.

CHAPTER 18

Combinatorial Chemistry

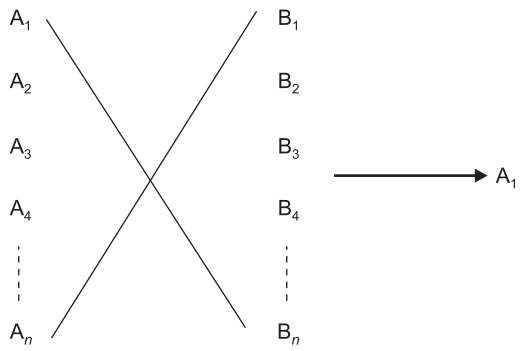
INTRODUCTION

Combinatorial chemistry is a technique through which large numbers of structurally distinct molecules may be synthesized at a time and submitted for high throughput screening (HTS) assay. Combinatorial chemistry is one of the recent methodologies to reduce the time and costs associated with producing successful and competitive new drugs. This method has profound effect on all the branches of chemistry, especially on drug discovery. With the rapidly evolving technology of combinatorial chemistry, it is now possible to produce HTS of compound libraries to screen for novel bioactivities from natural product libraries. With the help of this novel technology pharmaceutical companies are able to find novel drug candidates quickly, and save money in preclinical development costs.

The aim of this chapter is to provide a basic introduction to the field of combinatorial chemistry describing the development of major techniques and applications.

PRINCIPLES OF COMBINATORIAL CHEMISTRY

The key of combinatorial chemistry is that a large range of analogues are synthesized using the same reaction conditions and the same reaction vessels. In this way, the organic chemist can synthesize hundreds or thousands of compounds at one time instead of preparing only a few by a traditional methodology. For example, compound A would have been reacted with compound B to give product AB, which would have been isolated after reaction, work up, and purification. The size of the combinatorial libraries depends on the number of building blocks used per reaction and the number of reaction steps, in which a new building block is introduced, typical library consists of 10^2–10^5 compounds.



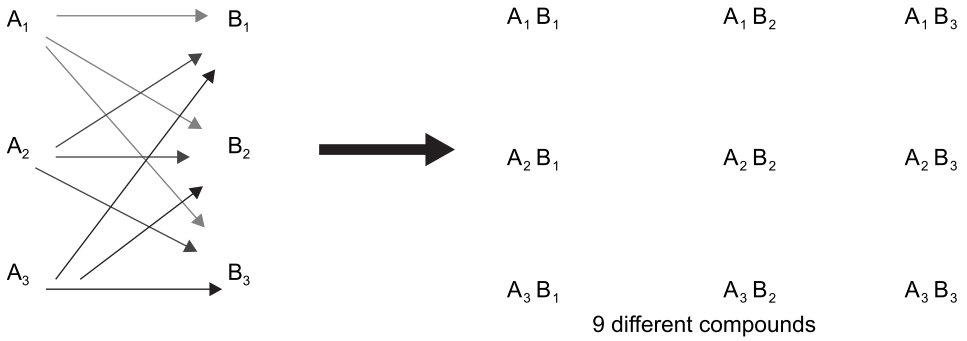
Combinatorial synthesis

$$A + B \longrightarrow AB$$

Orthodox synthesis

Conventional reaction: $A + B \longrightarrow A - B$

Combinatorial chemistry: $A(1-n) + B(1-n) \longrightarrow A(1-n) - B(1-n)$



In comparison to this approach, combinatorial chemistry offers to make every combination of a compound A_1–A_n with compound B_1–B_2.

The combinatorial solution or solid phase techniques are highly diverse, and these products could be made individually in a parallel or in mixtures. Whatever be the technique used, the common denominator is that productivity has been amplified beyond the level.

COMBINATORIAL COMPOUND LIBRARIES

In solid supports for peptide synthesis, by coupling the growing peptide to a solid support, such as a polystyrene bead, it is possible to use excess reagents and so ensure that the reaction proceeds to completion. Any excess reagent is simply washed away by filtration. The origin of combinatorial chemistry lies in the use of solid supports for peptide synthesis. This methodology could be used to generate large number of molecules using a scheme known as *split-mix technique*. This methodology starts with a set of reagents (which are referred to as monomers), each of which is coupled to the solid support. These are then mixed together and divided into equal-sized aliquots for reaction with the second reagent. The products from this reaction are reacted with the third reagent, and so on. If the number of reagents at each step is n_1, n_2, n_3, etc. then the total number of molecules produced is the product is n_1, n_2, n_3. The size of the library, thus, increases exponentially with the number of reagents—hence the use of the term *combinatorial*. The split–mix method is capable of producing extremely large libraries. The particular limitation is that the identity of the product on each bead is unknown (except for the final reagent) because of the various mixing stages. It is important to note that each bead contains just one discrete chemical entity.

Combinatorial Synthesis on Solid Phase

In 1963, Merrifield pioneered the solid phase synthesis (SPS) work, which earned him a Nobel Prize. He first reported examples of SPS of peptides using chloromethylated-polystyrene containing immobilized N-protected amino acids building blocks. This chemistry developed over the ensuing decade and became the basis for much of the progress in peptide chemistry. Merrifield's SPS concept was first applied for a developed biopolymer (proteins); recently it has spread in every field where organic synthesis is involved.

Nowadays, many academic laboratories and pharmaceutical companies focused on the development of the technologies and chemistry suitable for SPS. This resulted in the impressive outbreak of combinatorial chemistry, which profoundly changed the approach to new drugs, new catalyst, or new natural discovery.

The utilization of solid support for the organic synthesis relies on three interconnected requirements.

These are as follows:

1. A cross-linked, insoluble polymeric material should be inert to the condition of synthesis.
2. The linking substrate (linker) to the solid phase that permits selective cleavage of some or all the products from the solid support during synthesis for analysis of the extent of reaction(s) and ultimately gives the final product of interest.
3. The chemical protection strategy must allow selective protection and deprotection of reactive groups.

Advantages and Disadvantages of Solid Support Reagents

Advantages

- It is easily removed from reactions by filtration.
- Excess reagents can be used to drive reactions to completion.
- It is economical, environmentally sound, and efficient.
- Easy to handle (especially when dealing with costly or time-intensive catalysts, which can be included into flow reactors and automated processes).
- Safe to handle
- Very good selectivity

Disadvantages

- Some reagents may not interact well with solid support.
- The ability of recycled reagents is not assured on solid support.
- Due to diffusional constraints reactions may run more slowly.
- Can be very expensive to prepare specific polymeric support materials.
- Under harsh reaction conditions stability of the support material can be poor.
- Sometimes, side reactions with the polymer support.

Methodology of SPS

The SPS protocol synthesizes compounds on an inert polymeric resin bead, forces a reaction to complete by the addition of excess reagents and monomers, followed by removal of the unwanted material by simple filtration and wash.

Requirements for SPS

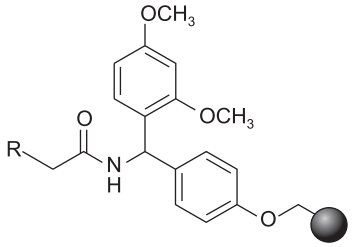
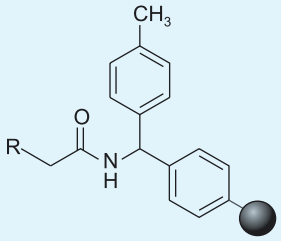
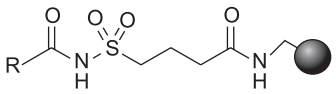
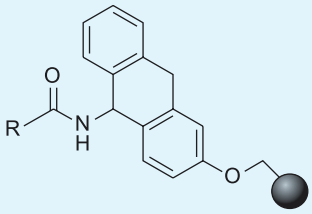
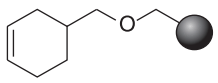
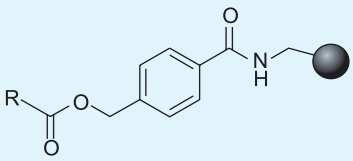
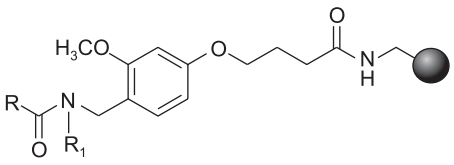
- A cross-linked, insoluble polymeric material that is inert to the reaction condition.
- A chemical protection strategy to allow selective orthogonal protection and deprotection of reactive groups in the monomers.
- Methods of linking the substrate to the solid phase that permits the cleavage of some or the entire product from the solid support during synthesis for analysis of the extent of reaction.
- Final cleavage from resin to give the final product of interest devoid of the polymer.

Resins for SPS

In SPS, resin supports for SPS include spherical beads of lightly cross-linked gel-type polystyrene (GPS) (1–2% divinylbenzene) and poly(styrene-oxyethylene) graft copolymers, which are functionalized to allow attachment of linkers and substrate molecules. Each of these materials has advantages and

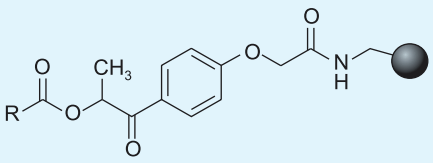
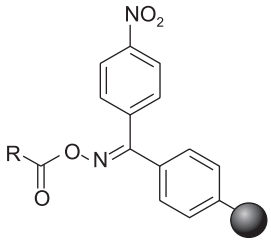
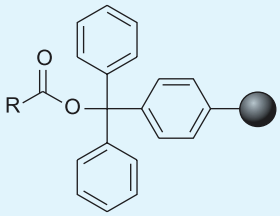
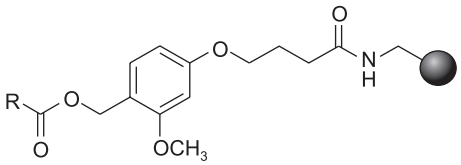
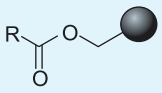
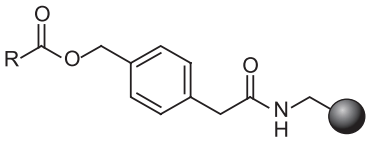
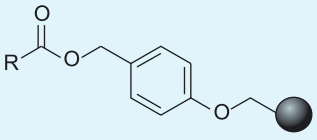
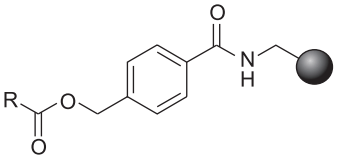
disadvantages, depending on the particular application. There are several types of resins available for different types of reactions, which have been mentioned in Table 18.1.

Table 18.1: Types of resins and reactions

Type of resin	*Chemical structure of resin*	*Protecting group*	*Deprotecting reagent*
Rink amide resin		Fmoc	95% TFA
MBHA resin		Boc	HF, TFMSA
4-Sulfamylbutyryl AM resin		Fmoc	1. TMS-CHN_2 2. RSH/NaSPHcat
Sieber amide resin		Fmoc	95% TFA
DHP HM resin		Fmoc	95% TFA
HMBA-AM resin		Fmoc	$NaBH_4$/EtOH
4-(4-Formyl-3-methoxyphenoxy) butyryl AM resin		Fmoc	95% TFA

Contd.

Table 18.1: Types of resins and reactions *(Contd.)*

Type of resin	*Chemical structure of resin*	*Protecting group*	*Deprotecting reagent*
Brominated PPOA resin		Boc	NaOH/Dioxane
Oxime resin		Boc	NaOH/Dioxane
2-Chlorotrityl chloride resin		Fmoc	1% TFA in DCM, AcOH/DCM/TFE
HMPB-AM resin		Fmoc	1% TFA in DCM
Merrifield resin		Boc	HF/TFMSA
PAM resins		Boc	HF/TFMSA
Wang resin		Fmoc	95% TFA
HMBA-AM resin		Fmoc	ROH/DIPEA/DMF

Methods of Combinatorial Chemistry

Split–Pool Synthesis

In the split–pool method, the starting compounds are attached to polymer beads. Then polymer beads are split into 50 groups and reacted with the second set of reagents. At the end of this reaction, all the beads are pooled, mixed together, and again split into 50 groups. Mixing should be efficient, each group contains approximately equal numbers of beads representing each of the 1000 first-generation products. The groups of beads are then reacted with the next set of reagents. After a split–pool synthesis, just one single compound is bound to each resin bead; this methodology of split–pool procedure requires a solid support.

A typical protocol involves the splitting of the resin, coupling with building blocks A_1–A_3 followed by pooling, washing, and deprotection. Further splitting and coupling with B_1–B_3 of the resin beds result in the first step followed by second pooling, washing, and deprotection leading to second generation, which is further split and coupled with C_1–C_3.

Parallel Synthesis

All the different chemical structure combinations are prepared separately, in parallel, using thousands of reaction vessels and a robot is programmed to add the appropriate reagents to each of the reaction vessels. This method is suitable for the creation of smaller and more specialized libraries based on a particular skeleton, which leads to each vessel containing one compound. Advantage of this approach includes each compound is substantially *pure* in its location vessel; this defined location provides the structure of a certain compound and its easier biological evaluation. It can be applicable for medium-sized libraries.

SOLUTION PHASE COMBINATORIAL CHEMISTRY

Introduction

At the emergence of combinatorial chemistry, the initial focus was on the solid phase synthesis only due to the availability of many advantages. Solution phase combinatorial chemistry is not suitable as a best method because of tedious isolation and purification. The main problem is to obtain a pure product which varies with the purpose for which a combinatorial chemistry is produced.

The solution phase synthesis which involves conducting the chemical reaction simultaneously in well-ordered arrays of reaction vessels in a solution. The solution phase work is free from some kind of constraints compared to solid phase synthesis but the major problem associated with the former one is the method used for purification of the products. Solution phase was first used for the synthesis of amides, urea, sulphonamides and heterocycles.

Advantages

1. Reactions carried out in solution phase require less time.
2. Synthesis is carried out in one or two steps only.
3. Many reactions can be optimised in solution phase.
4. Reactions that contain insoluble components are limited in solution phase synthesis.
5. There is no limitation of the thermal and chemical stability of the resin.

6. Monitoring the reaction by simple methods such as TLC, UV and NMR.
7. All reactive groups of the starting materials are available for structural modifications.

Disadvantages

1. The main disadvantage of this reaction is isolation and purification of the products obtained.
2. Multiple reagents are taken together in a solution which leads to serve side reactions may lead to polymerization and form tarry mass.

In a solution phase synthesis, soluble polymers are used as a support for the product. Polyethylene glycol (PEG) is used as a common vehicle for this process. PEG can be solid or liquid in RT, but it shows different degrees of solubility in an aqueous and organic solvents. The conversion of one –OH group of PEG into methyl ether, i.e. MeO-PEG-OH, a carboxylic acid group is attached to the free –OH group of PEG and further used in solution phase synthesis.

The other common support used in solution phase synthesis is Teflon liquid which consists of long chain $–CF_2$ group, attached to a silicon atom. The above said phases are used as a support for the isolation and purification of the product is an easier one in any type of organic solvent.

Solution Phase Synthesis of Pool of Compounds

Here, a mixture of reactions in a solution phase is used and the products obtained need either an effective decoding strategy or a particular purification process to allow the identification of products of interest.

Example 1: Synthesis of small drug-like molecule by Smith *et al.*

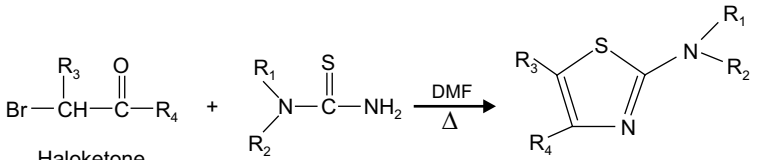
The reaction of 40 individual acid chlorides with equimolar quantity of 40 nucleophiles such as alcohols and amines and of the individual nucleophiles with an equimolar mixture of an acid chlorides leads to the formation of 1600 esters and amides as pools of 40 compounds. This orthogonal strategy indicated that each possible product should obtain as a unique pair of sample which permits the fast identification of lead compounds after screening.

Example 2: Synthesis of indexed libraries of carbamates.

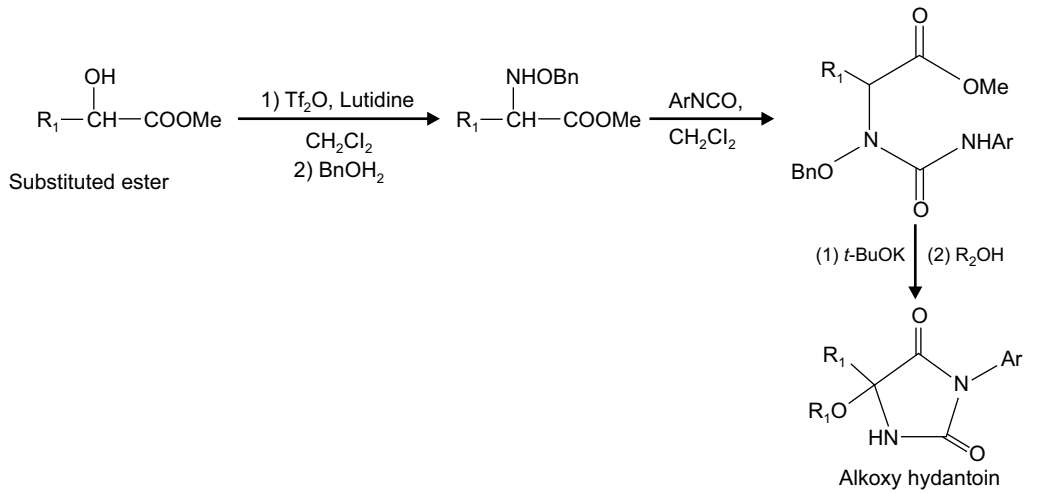
In this method, 54 carbamates are prepared by using nine alcohols and nine isocyanates. The combinatorial library was synthesized as 15 sub-libraries in which each of the alcohols and isocyanates react with equimolar mixture of other reagents and the products obtained were tested for their acetyl cholinesterase activity.

Solution-Phase Synthesis of Discrete Compounds

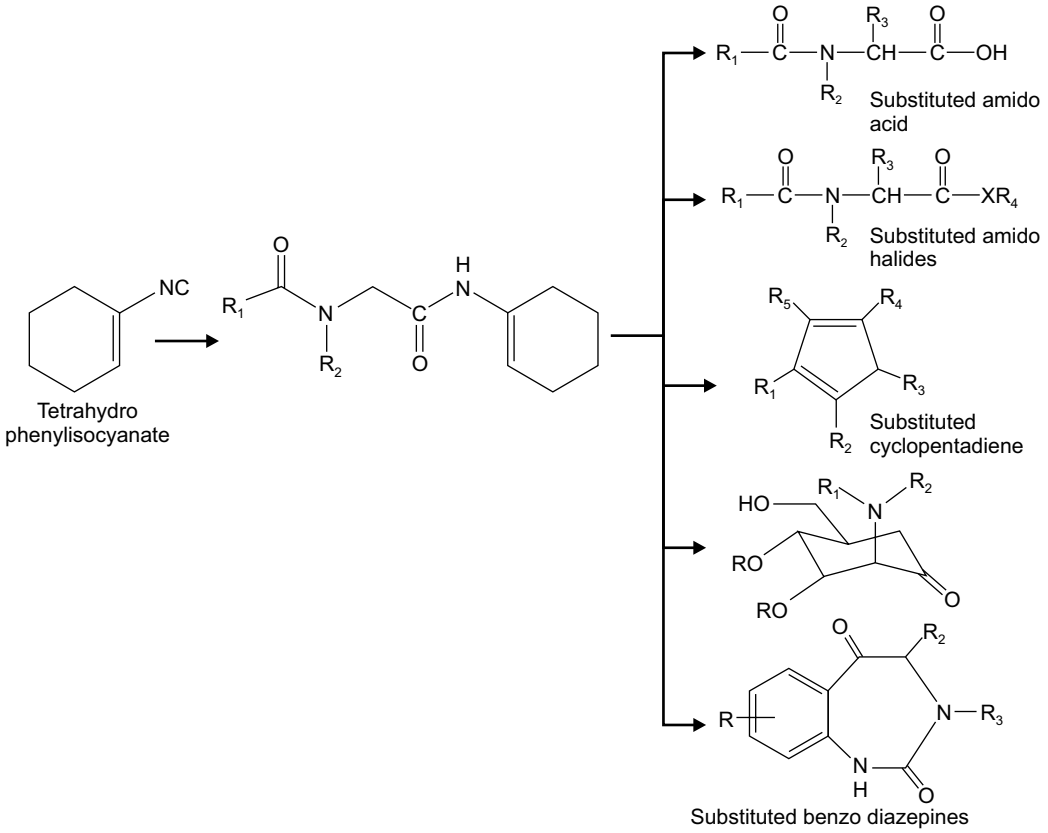
Example 1: Synthesis of 2-aminothiazole from halo ketones and thiourea.



Example 2: Synthesis of 25 derivatives of alkoxy hydantoins by solution phase and solid support.



Another popular example for solution-phase synthesis is a solution-phase Ugi four component reaction. This reaction was developed by Keating and Armstrong. In this, the α-acylamino amides are converted into new carboxylic acids, esters or thioesters, pyrroles and 1,4-benzodiazepines (this methodology allows the formation of products offering a wide range of diversity rather than impose the functionality derived from the commercially available monomers). The above work also introduced/ utilized an important concept of resin capture. In this method, the product formed is isolated by attachment to the resin via suitable functional handle.



CHAPTER 19

High-throughput Screening

It is the process of testing a large number of diverse chemical structures against disease targets to identify HITS with the use of robotics, automation and miniaturization. It helps to screen 50,000–1,00,000 compounds in a short span of time against validated biological target. It involves an automated operation system, a highly sensitive testing system, specific screening *in vitro* models, an abundant components library and a data acquisition and processing system. Characteristics of HTS are that it is simple and rapid, and detects ligand target interactions.

Activities of HTS: The activities of HTS are as mentioned below:

1. Identification of target (genomic, molecular biology groups)
2. Reagent preparation (protein expression purification)
3. Compound management
4. Assay development (biologist and pharmacologist)
5. High throughput library screening

The standard layout of HTS is as follows:

1. 96 microtitre plate (12 × 8)
2. Denser plates means 1536 wells/plates

IDENTIFICATION OR SELECTION OF TARGET

More than 500 targets are used by drug companies. It includes the following:

1. G-protein-coupled receptors (45%)
2. Enzymes (28%)
3. Hormones (11%)
4. Unknown (7%)
5. Ion channels (5%)
6. Nuclear receptors (2%)
7. DNA (2%)

HTS assays are divided into two main types:

1. Protein-based biochemical assays
2. Cell-based assays

1. **Protein-based biochemical assays:** These methods employ the utility of purified proteins, substrates and miniature compound inhibitors in different biological solutions to generate an optical (fluorescent, luminescent, etc.) readout, which could monitor enzymatic or binding activity with the aid of high-throughput plate readers. Small compound inhibitors are ranked on their ability to reduce the protein function, and by extension the optical signal, in this type of screen.
2. **Cell-based assays:** These assays can be RNAi or tiny compound assays that utilize cells plated in 96- or 384-well plates to generate a visual phenotypic alteration in the cells that can be measured. There are three major types of measurement (although others exist) of a cell-based assay, as follows:
   (1) *Uniform well readouts:* These include cell viability assays in microtitre well plate.
   (2) *High-content imaging (HCI) assays:* These include tiny compound as well as RNAi assays and are intended to determine the changes during a cellular phenotype (e.g. cellular morphology, localization of proteins, etc.). HCI assays employ specialized high-content images to produce high-content pictures, which can be used to measure phenotypic changes. These assays are content rich and can provide in-depth analysis of cell images. In addition, they can also be 'multiplexed' with multiple probes and DAPI (4',6-diamidino-2-phenylindole is a fluorescent stain) for DNA staining to endow with information on serial pathways to a cell's phenotype simultaneously and also it provides the cell cycle information.
   (3) *Reporter gene systems:* These are mostly high-throughput fluorescence-activated cell sorting (FACS) based assays and employ high-throughput FACS to produce readouts of green fluorescent protein (GFP).

SCREENING OF HTS LIBRARY

It involves screening compounds that are a part of corporate store house of compounds that are already synthesized or a combinatorial library. This library contains frozen or dried samples of compound in microgram/well. The size of libraries ranges from few 1000 compounds to nearly million. The compound that is screened must completely dissolve in the assay medium. For aiding solvation, 1% DMSO is added to the assay medium (10 μM). High concentration leads to false-positive results.

Ultrasound HTS (uHTS): This technique is used to screen 10,000–1,00,000 compounds within 24 hours.

TERMS USED IN HTS

HIT: A molecule with confirmed activity from primary HTS assay with a good profile in secondary assay with confirm structure.

Lead: A hit series exhibiting the SAR and demonstrating activities both *in vivo* and *in vitro*.

Types of HTS Detection

There are two types of HTS detections available, i.e. radiometric and non-radiometric.

1. **Radiometric methods:** These assays use radioactive isotopes, which include the following methods:
   a. Filtration assay
   b. Scintillation proximity assay
   a. **Filtration assay:** A radioactive substance bound to a capture group forms complex and is cleaved by its enzyme to remove the radioactive group from the capture group. The mixture is

then filtered through the special type of filter paper in which the capture group sticks to, but every other thing passes through the filter. Then the scintillation is added and the radioactivity of filtrate is measured. The degree of radioactivity is equal to the strength of inhibition.

b. **Scintillation proximity assay (SPA):** In this method, the radioactive substrate, enzyme and potential drugs are added. Then is added a special resin bead coated with a scintillant. The cleaved and uncleaved portions are bound to the bead. The bead will fluoresce where the radioactive part of substance is attached. The production of fluorescence implies that the test compound inhibited the enzyme. This method is used for the discovery of inositol phosphate inhibitors.

2. **Non-radiometric methods:** It includes the following:
   a. Fluorescence-based assays
   b. Luminescence spectroscopys
   c. Bead-based assays
   d. Absorbance-based assays

In this, the fluorescence- or luminescence-based assays are used to analyse the interactions between ligand and biological compartment.

a. Fluorescence-based Assays

Fluorescence-based assays are used to elucidate the molecular mechanism of receptor function and signal transduction. Various types of the fluorescence techniques are available, as discussed below.

Fluorescence anisotropy (FA): This technique is also called *fluorescence polarization* (FP). This technique involves the use of plane polarized light to excite fluorescent probe and the emitted fluorescence is recorded perpendicular and parallel to the plane of polarization.

Principle: When the ligand is free in solution low polarization is observed, but if the ligand is in binding, high polarization is observed. These results are used to find out the conformational changes in the receptors.

Fluorescence correlation spectroscopy (FCS): The molecular interactions produce measurable fluctuations in the fluorescence intensity. These fluctuations are observed and analysed by FCS. Advantage of this method is that the detection is done at nano scale level. It is used to find out the protein ligand interaction on membrane bound receptors in living cells.

Principle: The narrow laser beam is used, which is used to excite the fluorescence probe. Every single molecule diffusing through the illuminated area produces fluorescent light due to Brownian movement. Using software integration, it gives the concentration, diffusion time and intensity of all individual molecules. These parameters depend on the size and shape of the molecules.

Fluorescence resonance energy transfer (FRET): This method is based on dipole–dipole interaction between donor and acceptor chromophores. This method is used to determine the interactions between monoclonal antibodies and interlukin receptor-1 type.

Time resolve fluorescence resonance energy transfer (TR-FRET): This method is used to carry out the assay of *kinase autophosphorylation* and also for SAR studies.

Fluorescence lifetime imaging microscopy (FLIM): The sample to be analysed is illuminated with a modulated continuous light (laser), and the lifetime of fluorescent probe is determined. It is used to determine the molecular interactions on cell surfaces.

Fluorescent imaging plate reader (FLIPR): This technology is used for the detection of intracellular calcium homeostasis. It provides readouts for high-throughput, cell-based assays that characterize the different informations that are rich in kinetic data by 96- or 384-well format. Briefly, the target cells are loaded with a fluorescent indicator (e.g. Fluo-4 AM for calcium), which shows an absorption maxima with excitation at 488 nm with an argon ion laser source, leading to maximum emission at 516 nm with the presence of calcium. Fluorescence emission is provoked concurrently in all wells of a 96- or 384-well plate and the kinetics of intracellular calcium release, triggered because of exposure to responsible ligand, can be monitored at a maximum of 60 sequential measurements per minute. The FLIPR system rapidly distinguishes between full agonists, partial agonists and antagonists to accelerate primary and secondary screening.

FLIPR technology and ion channel assays: The identification of compounds, which modulates the ion channel activity, can be determined by this method. This is based on detection of the fluorescence-based assays of membrane potential changes using a potentiometric fluorescent probe, bis-(1,3-dibutylbarbituric acid) trimethine oxonol [DiBAC4(3)], that partitions involving the intracellular and extracellular compartments depending on electric potential across the membrane. During cell depolarization, the dye moves into the cell, binds to intracellular hydrophobic targets and results in an increase in fluorescence intensity. In opposition, hyperpolarization elicits dye extrusion from the cells and consequently reduces the fluorescence and based on the intensity of fluorescence the ion channel activity is measured.

Enzyme fragment complementation (EFC) technology: The EFC technology is based on genetically produced enzymes containing two fragments: Enzyme acceptor (EA) and enzyme donor (ED). The alienated fragments are stationary and only during spontaneous configuration of heterodimers will lead to an enzymatically active form. The HitHunter technology is based on a modified version of the β-galactosidase enzyme forming an EA/ED pair. The technology was carried for use in many different assays including kinase, progesterone receptor, oestrogen receptor and *c*AMP assays.

b. Luminescence-based Assays

The principle in this is that the reactive intermediates are produced from stable precursors at the surface of an electrode that reacts under various conditions to produce excited states that emits light. Chemiluminescence generates electromagnetic radiation as light due to the discharge of energy from a chemical reaction. The emitted light can be in the ultraviolet, visible or infrared region. Commonly visible light emitters are found.

Chemiluminescent reactions are of three types:

1. Chemical reactions using synthetic compounds and usually involving a highly oxidized species such as peroxide are commonly termed *chemiluminescent reactions*.
2. Bioluminescence resonance energy transfer (BRET): It is used to determine the protein–protein interactions. It is mainly used in case of cells or natural products. Bioluminescent reactions are those in which light-emitting reactions arise from a living organism, such as the firefly or jellyfish.
3. Light-emitting reactions that take place by the use of electrical current are designated *electrochemiluminescent reactions*. It is also used for the determination of activation-state insulin–receptor interaction and detection of G-protein-coupled receptor interactions due to the action potential evoked upon ligand binding.

Let us discuss electrochemiluminescence assay in detail.

Electrochemiluminescence assay: Common uses for chemiluminescence assays are as follows:

- Cytochrome inhibition and induction studies
- Hepatoxicity studies
- Determination of rat insulin

Other assays are discussed below.

1. **Flash plate technology:** These (flash plates) are white polystyrene microplates with inside coating of polystyrene (hydrophobic surface). This surface is used for the absorption of proteins (receptor-2 antibodies). The binder is coated with flash plate. The reaction of unlabelled ligand and radiolabelled tracer with the binder molecule leads to the detection of bounded radioactivity, which is done by scintillation counter. This method is used for the assay of PARP-1 inhibitors.
2. **Molecular beacon**

   Principle: It is based on the interaction between fluoro probe and quencher group. It contains a single-stranded DNA molecule composed of hairpin-shaped oligonucleotides that contains both fluoro probe and quencher group.

   Molecular beacons act like a switch. When the quencher and fluorophore are together, fluorescence is OFF. Any conformational changes open the hairpin, the fluorophore and quencher group are separated and the fluorescence is turned ON.

   Dual FRET method is used for mRNA detection in living cells. It is also used for the studies with proteins, unseparated target species.
3. **Surface plasmon resonance:** It is an optical technique based on the determination of change in refractive index. The binding between an analyte solution and the immobilized ligand on the sensor surface leads to the change in RI from that rate of association and dissociation and the amount of drug bound ligand can be measured. This method is used to detect the interaction between drug molecules and macromolecular targets, and is also used for the identification of binding partners.

CHAPTER 20

Prodrugs

INTRODUCTION

A prodrug is a chemically modified inert precursor of the drug that on biotransformation liberates the pharmacologically active parent compound. A prodrug is also called *proagent*, *bioreversible derivative*, or *latentiated drug*. The design of prodrug approach is also called *drug latentiation*.

Ideal Properties

The ideal properties of a prodrug are as follows:

- Drug and the carrier linkage must be cleared *in vivo*.
- It should not have intrinsic pharmacologic activity.
- It should rapidly transform, chemically or enzymatically, into the active form where desired.
- The metabolic fragments, apart from the active drug, should be non-toxic.

CLASSIFICATION OF PRODRUGS

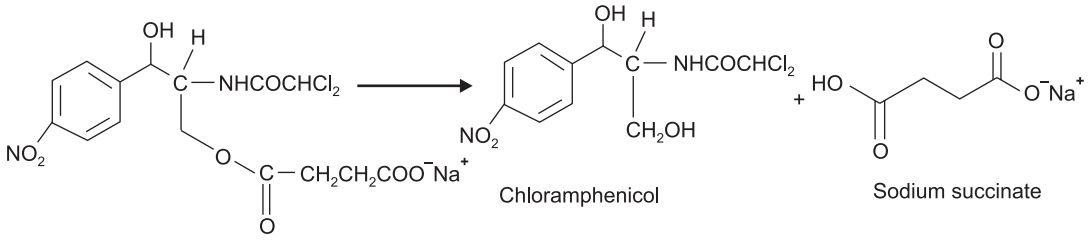
Depending on the constitution, lipophilicity, and method of bioactivation, prodrugs are classified into two categories.

1. Carrier-linked prodrugs
2. Bioprecursors

Carrier-linked Prodrugs or Simple Prodrugs

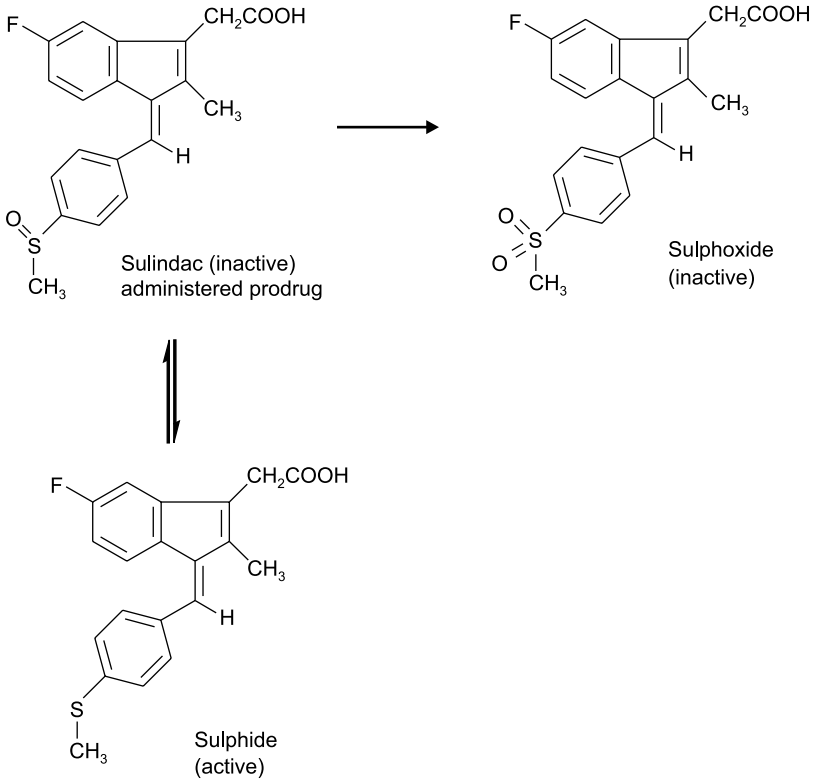
They are generally esters or amides. Carrier-linked prodrugs are the ones where the active drug is covalently linked to an inert carrier or transport moiety. Such prodrugs modify the lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage, either chemically or enzymatically.

Examples:



Bioprecursors

They are inert molecules obtained by a chemical modification of the active drugs, but do not contain a carrier. For example, non-steroidal antiinflammatory drug, sulindac, is inactive as sulphoxide and must be reduced metabolically to active sulphide.

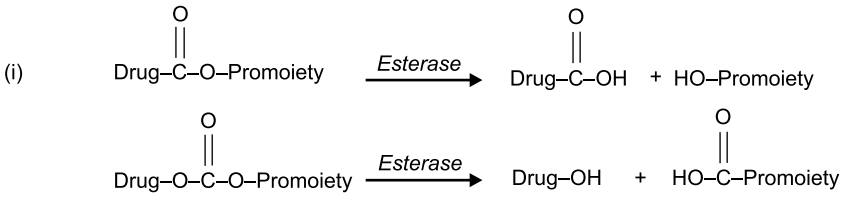


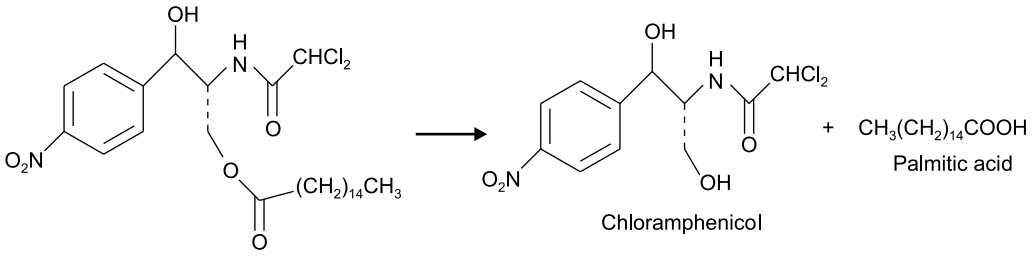
Prodrugs are also classified according to the functional group, as follows:

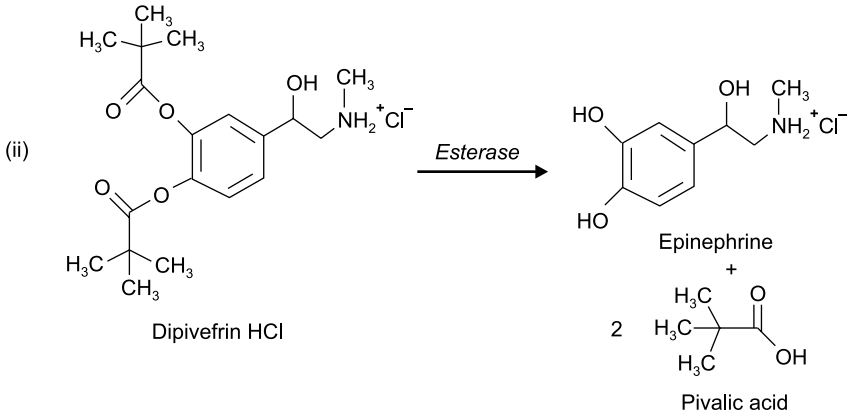
- Carboxylic acids and alcohols
- Amines
- Azo linkages
- Carbonyl compounds

Carboxylic acid and alcohols: Prodrugs of carboxylic acid and alcohol functionalities can be prepared by conversion to esters. The esters can be easily hydrolyzed by *esterase* enzymes (e.g. lipase, ester hydrolase, cholesterol esterase, acetyl cholinesterase, and carboxy peptidase) present in plasma and other tissues to give active drug.

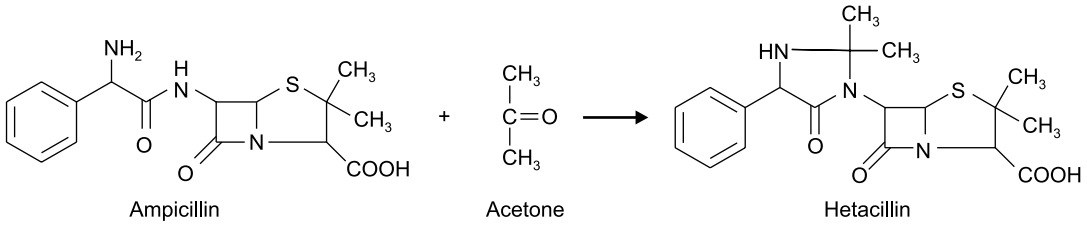
Example:



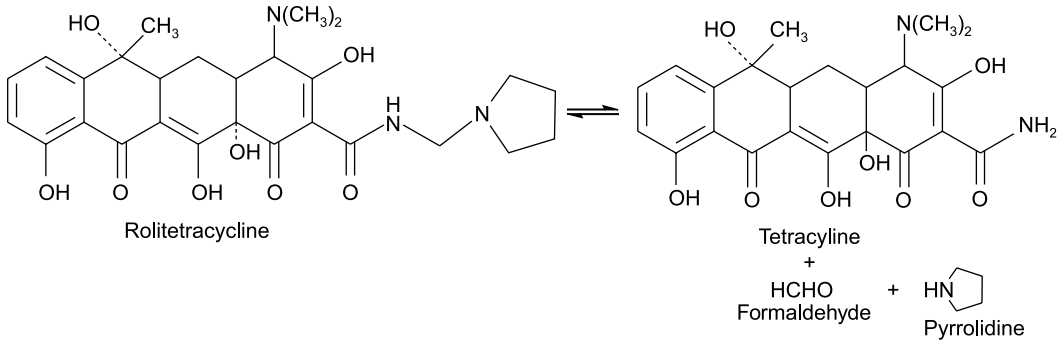




Amines: Due to the high stablility and lack of *amidase* enzyme necessary for hydrolysis, the conversion of amine to amide as a prodrug is not been used for most of the drugs. A more common approach adopted is to use Mannich bases as prodrug form of amines.



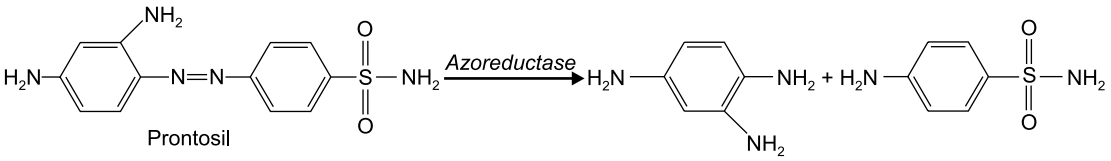
Hetacillin is a prodrug form of ampicillin in which amide nitrogen and α amino functionalities have been allowed to react with acetone to give a Mannich base (imidazolidine ring system). This leads to decrease in the basicity and increase in the lipophilicity and absorption.



In another example, the basic pyrrolidine nitrogen increases water solubility of the parent drug rolitetracycline. The Mannich base hydrolyzes completely and rapidly in aqueous media to give the active tetracycline.

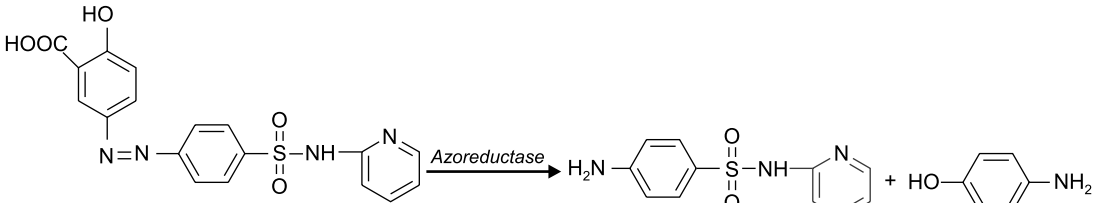
Azo linkage: Prodrugs of amines are occasionally prepared by incorporating them in to an azo linkage. By the action of *azo reductase* the amino compounds are released *in vivo*.

- Prontosil drug is inactive *in vitro*, but it is active *in vivo* since it is converted to sulphanilamide by *azo reductase* enzymes.



Prontosil — 1,2,4-Triamino benzene — Sulfanilamide (active drug)

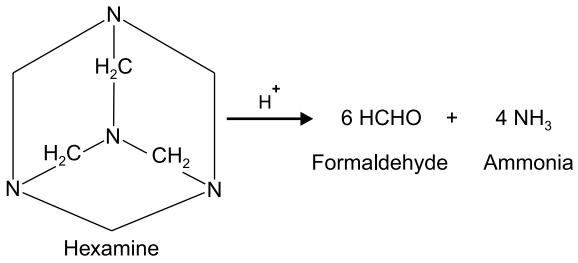
- Sulphasalazine by the action of *azo reductase* releases the amino salicylic acid and sulphapyridine. The generation of antiinflammatory salicyclic acid prior to absorption prevents the systemic absorption of the agents and enhances the concentration of it in active site.



Sulphasalazine — Sulphapyridine — Aminosalicylic acid

Carbonyl moiety: Conversion of carbonyl functionalities, such as aldehyde and ketone, to prodrug have not been found wide clinical use. They are converted into derivatives in which the sp^2 carbonyl carbon is converted as sp^3 hybridized carbon attached to heteroatoms. These prodrugs are re-converted to carbonyl compound by hydrolysis.

For example, hexamine releases formaldehyde in the urine (acidic pH), which acts as an antibacterial agent.



Hexamine — Formaldehyde — Ammonia

The differences between bioprecursors and carrier prodrugs are given in Table 20.1.

Table 20.1: Differences between bioprecursors and carrier prodrugs

Characteristic	*Carrier prodrugs*	*Bioprecursors*
Constitution	Active principles 1 Carrier group	No carrier group
Bioactivation	Hydrolytic	Oxidative or reductive
Catalysis	Chemical or enzymic	Only enzymatic
Lipophilicity	Strongly modified	Slightly modified

APPLICATIONS OF PRODRUG

The aim of prodrug development is, in most cases, to solve specific formulation or pharmacological and pharmacokinetic problems. The main objectives of prodrug development are as follows:

- Improvement of taste
- Improvement of odour
- Enhancement of bioavailability (lipophilicity)
- Improvement of stability and solubility properties
- Decreased toxicity and adverse reactions
- Increased site specificity
- Increased duration of pharmacological actions

Improvement of Taste

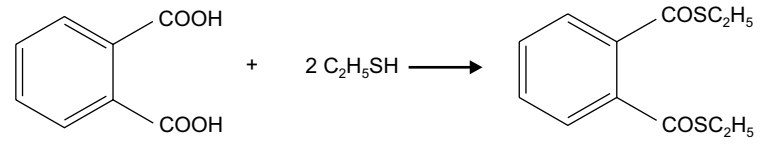
One of the reasons for poor patient compliance, particularly in case of children, is the bitterness, acidity, or causticity of the drug. Two approaches are adopted to overcome the bad taste of drug. The first is reduction of drug solubility in saliva and the other is to lower the affinity of drug towards taste receptors, thus, masking the bitterness. Some examples of drugs with improved taste are given in Table 20.2.

Table 20.2: Drugs with improved taste

Parent drug	*Prodrug with improved taste*
Chloramphenicol	Palmitate ester
Clindamycin	Palmitate ester
Sulfisoxazole	Acetyl ester
Erythromycin	Estolate

Improvement of Odour

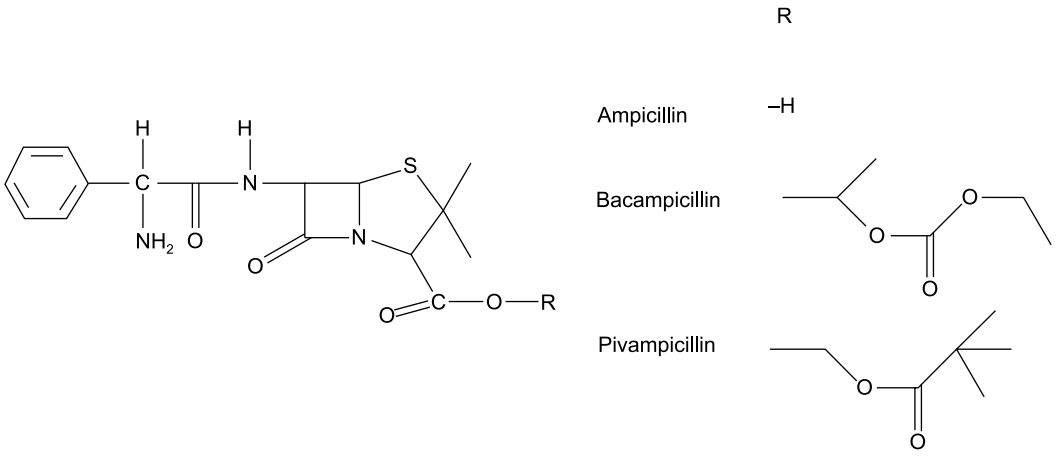
The odour of a compound depends on its vapour pressure; a liquid with high vapour will have a strong odour. For example, ethyl mercaptan is a foul smelling liquid used in the treatment of leprosy. This is converted to phthalate ester, a diethyl dithiophthalate that has higher boiling point and is odourless.



Phthalic acid — Ethyl mercaptan — Phthalate ester

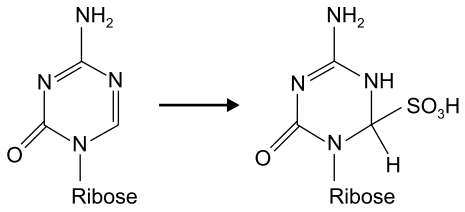
Enhancement of Bioavailability (Lipophilicity)

Due to the presence of an amino group in the side chain, ampicillin possesses low lipophilicity and is only 30–40% absorbed when taken by oral route. Altering the polarity of this antibiotic, by esterifying the free carboxyl group results in compounds that are completely absorbed, that is, with greater bioavailability than the parent ampicillin.



Improvement of Stability and Solubility Properties

Stability: To improve their stability, prodrug approach is a good technique. Several drugs may decompose in their shelf life or in the gastrointestinal tract (GIT) when used orally. An antineoplastic drug, azacytidine, hydrolyse readily in acidic pH, but the bisulphite prodrug of it is more stable.

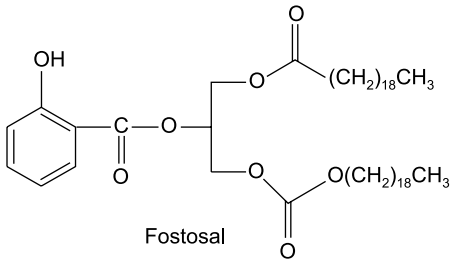


Solubility: Hydrophilic or water-soluble drugs are needed when parenteral or ophthalmic formulation of such agents is desired. Drugs with hydroxyl functional group can be converted to their hydrophilic form through the use of half ester such as hemiglutarate hemiphthalates, the other half of this acid carries sodium, potassium, or amine salts, and renders the moiety more soluble.

Parent drug	*Prodrug with enchanced hydrophilicity*
Tocopherols	Sodium succinate ester
Metronidazole	Amino acid esters

Decreased Toxicity and Adverse Reactions

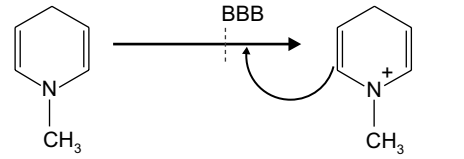
Carboxylic acids and phenols are sometimes too toxic to be employed as such in clinical practice. Ester prodrugs of the acidic non-steroidal anti-inflammatory drugs are devoid of gastric ulcerogenic activity and is considered as one of the responsible factors for the adverse reaction of these drugs.



Fostosal

Increased Site-Specificity

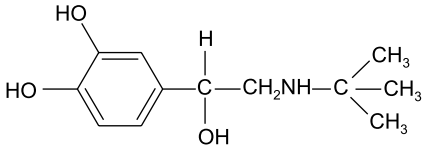
Many prodrugs could be so prepared that they will be delivered to a specific site, thus reducing the toxicity to other organs. The dihydropyridine/pyridinium redox chemical delivery system is very useful for the brain.



Dihydropyridine (lipophilic) Pyridinum system (hydrophilic)

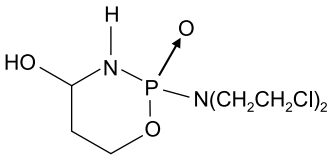
Increased Duration of Pharmacological Actions

The prodrug di-*p*-toluate ester of N-′butyl noradrenaline provides a longer duration of bronchodilator activity than the parent drug. The prodrug is preferentially distributed into the lung tissues rather than into the plasma or the heart, so that the bronchodilator effect is exerted.



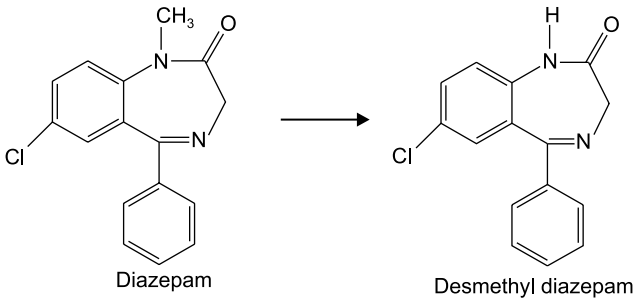
Bioprecursor Prodrug

Bioprecursor prodrug does not contain a carrier or a promoiety, but rather contains a latent functionality that is metabolically or chemically transformed into active drug molecule. The types of activation involves phase I, such as oxidation, reduction, phosphorylation, or chemical activation.

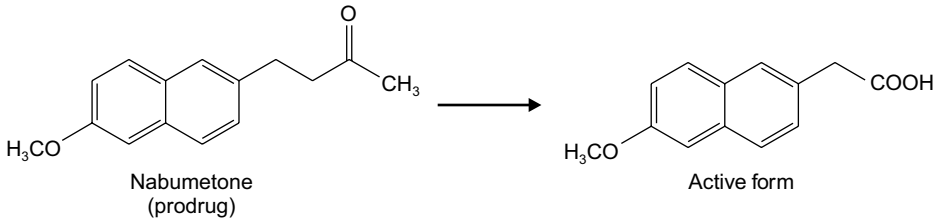


Bioactivation: Hydroxylation of cyclophosphamide followed by the metabolite decomposition converts the prodrug into the cytotoxic phosphoxamide mustard.

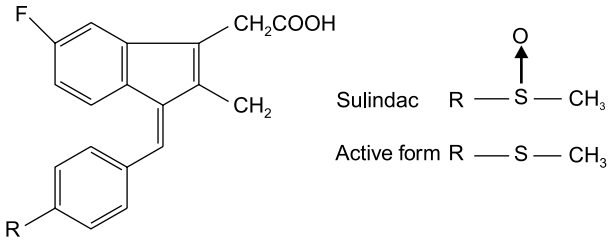
N-dealkylation: Many drugs are transformed into their active metabolite form by N-dealkylation.



Oxidation: The prodrug nabumetone in which the formyl group formed is oxidized into a carboxylate group and generating the active drug.



Reduction: The non-steroidal antiinflammatory drug sulindac is reduced *in vivo* to the active form.



CHAPTER 21

Antisense Technology

INTRODUCTION

"Diseases are often connected to the insufficient or excess production of certain proteins". If the production of these proteins is disrupted, many diseases can be treated or cured. Antisense technology is a method that can disturb protein production. It may be used to design new therapeutics for diseases in which the pathology of production of a specific protein plays crucial role.

Antisense technology is a tool used for the inhibition of gene expression. The principle behind is that "an antisense nucleic acid sequence base pairs with its complementary sense RNA strand and prevent it from being translated into a protein".

The complimentary nucleic acid sequence can be either a synthetic oligonucleotide, often oligodeoxy ribonucleotides of less than 30 nucleotides or longer antisense RNA (aRNA) sequences. An example of antisense RNA is given below.

$5^{1}ACGU3^{1}$ - - - - - - - - - mRNA

$3^{1}UGCA5^{1}$ - - - - - - - - - Antisense RNA

In antisense technology, synthetically produced complementary molecules seek out and bind to mRNA, blocking the final step of protein production. mRNA is the nucleic acid molecule that carries genetic information from the DNA to the other cellular machinery involved in the protein production. By binding to mRNA, the antisense drugs interrupt and inhibit the production of specific disease related proteins.

'Sense' refers to the original sequence of the DNA or RNA molecule. "Antisense refers to the complementary sequence of the DNA or RNA molecules."

The basic idea is that if an oligonucleotide RNA or DNA molecule complementary to a mRNA produced by a gene can be introduced into a cell, it will specifically bind to its target mRNA through the exquisite specificity of complementary base pairing, the same mechanism which guarantees the fidelity of DNA replication and of RNA transcription from the gene. This binding forms an RNA dimmer in the cytoplasm and halts protein synthesis. This occurs because the mRNA no longer has access to the ribosome and cytoplasm by ribonucleotide. Therefore, the introduction of short chains of DNA complementary to mRNA will lead to a specific deamination or blockage of protein. In short, gene will be turned off.

Antisense technology is a therapeutic intervention by inhibition of a gene at transcription or translation level and is more efficient than inhibition of the gene product. Antisense therapies focus on preventing

the production of disease causing proteins. Inhibition of gene expression should be more efficient than inhibitors of gene product. Antisense drugs are based on synthetic constraints of small DNA or RNA-oligonucleotides to bind to protein coding strand of genetic message (mRNA), blocking the translation of disease causing protein. By binding to mRNA, antisense drug (mRNA-antisense complex) prevents the genetic code from being read by the ribosome which is responsible for translating and production of proteins. When an antisense strand binds to the mRNA sense strand, the cell will recognize it as foreign to the cells into which they are introduced, prone to degradation by intracellular nucleases.

PRINCIPLE

Antisense therapeutic agents are based on a simple concept. As genes are expressed to produce specific proteins, the two complementary strands of DNA begin uncoiling within the nucleus. The 'sense' strand carries nucleic acid bases in an order that specifies which amino acids should be assembled to produce the protein. The complementary or 'antisense' strand is used as a template for assembling a complementary strand of mRNA in the process called transcription.

The mRNA will have the same sequences as the strand of DNA but is made up of ribose sugars instead of deoxyribose sugars in the nucleotide backbone. Antisense drugs are short stretches of deoxynucleotide analogues that bind to specific complementary areas of the mRNA (which have a sense sequence by Watson-Crick base pairing). In doing so, they can induce a nuclease (RNase H) that cleaves the mRNA at the site of the binding or other steps in mRNA processing and transport, thus stopping protein synthesis.

Antisense drugs therefore work at an early stage in the production of a disease causing protein and theoretically can be applied to a number of diseases for which the basic pathophysiology involves an overexpression or aberrant expression of given protein molecule.

Viral diseases, cancers and inflammatory diseases are all examples of such diseases that potentially can be treated by antisense mechanism. Another use of antisense oligonucleotide is to modify mRNA splicing.To get wide variety of proteins that humans produce, the pre-mRNA produced from these genes are spliced in a variety of ways to produce several different proteins from each gene. It is estimated that up to 60% of human genes are alternatively spliced at the pre-mRNA stage.

Aberrant splicing is because of genetic mutations and are estimated to cause approximately 50% of genetic disorders and lead to disease such as beta-thalassemia, cystic fibrosis and a variety of cancers. Antisense oligonucleotides can be used to inhibit aberrant splicing, thus correcting the genetic defect.

The oligonucleotides used for this purpose must not active RNase H, which would destroy the pre-mRNA target before it could be correctly spliced, and must be able to effectively compete with splicing factors to gain access to the target pre-mRNA.

Recently a new approach to antisense therapeutics has emerged with the discovery that the small interfering RNAs (siRNAs) can be used therapeutically. Naturally occurring siRNAs have been known as part of the defense by eukaryotic cells against invasion by double stranded RNA viruses.

Most recently the general principle has been applied to the design externally administered siRNA therapeutic agents that can be used to target and silence specific target mRNA sequences involved in the disease.

Double stranded RNA molecules enter the cell are cleaved by an enzyme called Dicer to generate 21 to 23 nucleotide fragments that contain two nucleotide 3' overhang and 5' phosphate groups.

Then, an ATP dependent helicase recognizes these short duplexes and resolves siRNA into two single strand RNAs. One strand is incorporated into a high molecular weight protein complex termed 'RNA-induced silencing complex' (RISC), where it serves to guide the RISC complex to the homologous target mRNA sequence where cleavage occurs.

Once one molecule of the mRNA is destroyed the RISC complex moves on to other molecule of the same mRNA and is recycled to perform multiple rounds of catalysis. This property of RISC accounts for the potent nature of the silencing effect.

The siRNA therapeutic agents are the most potent antisense agents available. In less than 5 years since the discovery of the silencing effect of double stranded RNA molecules, the first potential agents are showing positive results in clinical trials for macular degeneration and other diseases.

DESIGN AND DEVELOPMENT OF ANTISENSE OLIGONUCLEOTIDES (AS-ODNS) AS THERAPEUTICS

These can be designed on the basis of nucleotide sequence of the targeted gene. The prerequisites for the AS-ODNS's design includes knowledge about gene function, identification of the highly specific targets on the sequence, evaluation of the functional relevance of the selected targets and evaluation of the metabolic fate, toxicity, including side effects of the AS-ODNS.

The design of AS-ODNS should be given considerations for the length, chemistry, conformation and ability to hybridize with the target mRNA.The specificity and stability depend on its length.

Chemical modifications are introduced to the ODN backbone to improve the stability, better pharmacokinetics and pharmacodynamic activity. Protective modification could be introduced at three possible sites on the nucleotides sites, analogs with unnatural bases modified sugars and altered sugar phosphate backbone. These can be employed for *in vivo* antisense applications due to their enhanced stability and nuclease resistance.

Antisense drugs have the potential to provide a greater therapeutic advantages that is potential for specificity, effectiveness (bind to mRNA targets at a single receptor sites), less complexity, etc.

DRUG THERAPY

The first antisense therapeutic agent to reach the market is **Fomivirsen**.

It is a 21-merphosphothioate oligodeoxy nucleotide (Figure 21.1). It inhibits human cytomegalovirus, which is the most common cause of viral retinitis in immune compromised patients especially those with HIV infection. Fomivirsen inhibits cytomegalovirus by at least two mechanisms.

The first is a sequence-specific antisense binding to inhibit expression of immediate early genes, thus preventing viral replication. The second is sequence-independent and involves inhibition of adsorption of cytomegalovirus to the host cells probably by direct binding to viral coat proteins. The reduction of immediate early protein synthesis occurs in a dose-dependent manner.

Although, it inhibits viral replication, fomivirsen does not eradicate the virus whose DNA is integrated into the human genome. Therefore, treatment have to be continued for the lifelong of the patient.

The US Food and Drug administration approved fomivirsen as second-line treatment of cytomegalovirus retinitis in patients with AIDS who are intolerant or non-responsive to previous treatment for the disease.

DRUGS IN CLINICAL TRAILS

The following are some of the drugs in clinical trails:

Alicaforsen: It is a phosphorothioate oligonucleotide having 20 bases in length with a sequence complementary to the 3' untranslated region of human mRNA, used to inhibit expression of certain proteins in response to inflammatory stimuli.

Aprinocarsen: It is a phosphorothioate antisense agent targeted against protein kinase, a protein that is implicated in malignant transformation and proliferation.

Oblimersen: It is a phosphorothioate antisense drug which is complementary to first six codons of the open reading frame of the human bcl-2-mRNA sequence. Oblimersen turns off production of the apoptosis inhibitor Bcl_2 in tumour cells. This appears to increase a tumour cells sensitivity to a variety of other anticancer therapies and ultimately, may lead to cell death.

Monarsen: An antisense oligonucleotide targeted to acetyl cholinesterase gene, is delivered orally to treat patients with myasthenia gravis and exhibits efficacy in early trials.

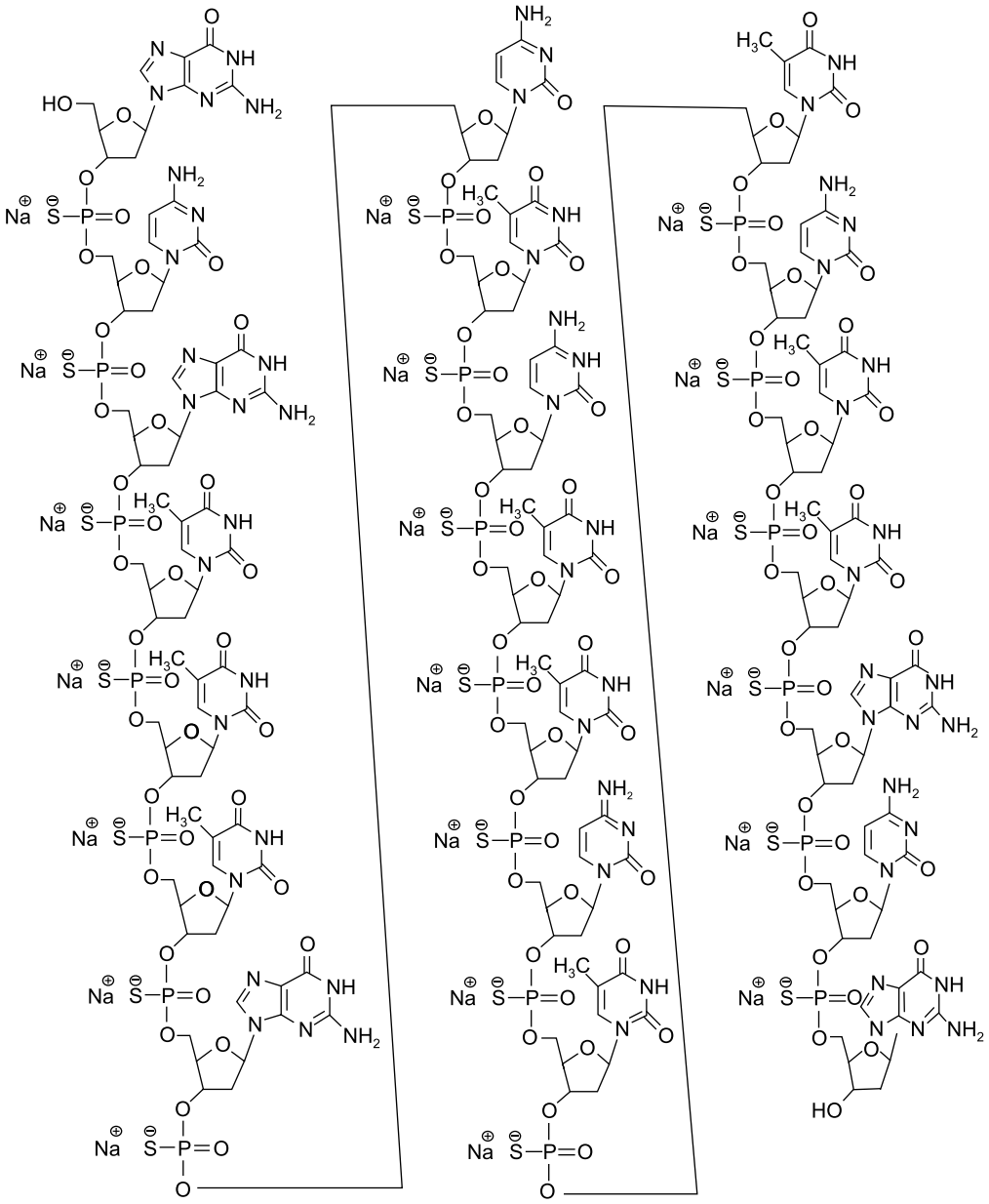


Figure 21.1: Structure of fomivirsen, the first marketed antisense therapeutic agent

PROBABLE QUESTIONS

1. Describe the various approaches of lead discovery.
2. What are the different types of receptors existing? Describe them with suitable examples.
3. What are the different forces involved in drug receptors interaction? Explain any two of them.
4. Explain the various factors affecting the drug-receptor interaction.
5. Write in detail about computer aided drug design (CADD).
6. Define QSAR and explain about Hansch analysis and Free-Wilson analsysis.
7. Write in detail about the steps involved in the QSAR studies.
8. Write a note on the following.
   (a) Comparative molecular field analysis (CoMFA)
   (b) Comparative molecular similarity indices analysis (CoMSIA)
9. What is combinatorial chemistry? Write its application in the drug discovery.
10. Write a note on combinatorial synthesis on solid phase.
11. What is prodrug? Write their classification based on the functional group.
12. What are the advantages of prodrugs? Explain with suitable examples.
13. Write a note on bioprecursor prodrug.
14. Write in detail about the types of high throughput screening methods.
15. Write in detail about antisense technology.

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SECTION III

Drugs Acting on Central Nervous System

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CHAPTER 22

Central Nervous System

INTRODUCTION

The drugs that act on the central nervous system (CNS) influence the lives of everyone at all times. These drugs can selectively relieve pain, reduce fever, suppress disordered movement, induce sleep or arousal, and reduce the desire to eat or ally the tendency to vomit. Selectively, acting drugs can be used to treat anxiety, mania, depression, or schizophrenia and do so without altering consciousness.

Monoamines were the first identified central nervous system transmitters. The pathways of noradrenergic, dopaminergic, and serotonergic neurons in laboratory animals were produced and the same basic features have been confirmed in human brain. Neurotransmitters are categorized according to their chemical nature, that is, amino acids, amines, monopeptide, and purines.

The electrophysiological signs of action in the CNS falls into two categories (1) excitatory (produce depolarization) and (2) inhibitory (produces hyperpolarization) in the neurons. Some of these that modulate the CNS are called neuromodulators. The excitatory action is produced by glutamate, aspartate, and other biogenic catecholamines. Inhibitory action is produced by GABA and glycine. The neuromodulators are circulating steroid hormones, locally released adenosine, and other purines. The neurotransmitters are discussed in the section on 'Functional Aspects'.

Amino Acids

There is a wide spread of GABA, glycine, and glutamate regulation seen in CNS. GABA releases correlate with the frequency of the nerve stimulation, which produce increased Cl^- ion conductance to produce inhibition through hyper-polarization and mediates presynaptic inhibition. GABA ergic system present in the cerebral cortex, olfactory bulb, hippocampus, and lateral septal muscles. GABA receptors exist in A and B types. Glycine is another inhibitory amino acid, prominent in the brain stem and the spinal cord. Glutamate and aspartate are found abundantly in the brain, and they are extremely powerful excitatory neurotransmitter acts through N-methyl D-aspartate (NMDA) receptor. Activation of NMDA receptors produces long-term potentiating in hippocampus and at high concentration, glutamate produces excitotoxicity leading to neurotoxic signs.

Adrenergic Pathway in CNS

The cell bodies of noradrenergic neurons occur in small clusters in pons and medulla and send extensively branched axons to many prominent clusters in locus cerulus. There is a close relationship

between moods and states of arousal; depressed individuals are usually lethargic and unresponsive to external stimuli. The catecholamine hypothesis of affective disorders suggested that depression results from a functional deficiency of noradrenaline in certain parts of the brain, while mania results from an excess, and the blood pressure regulation in CNS mediated through α_2-autoreceptors.

Functional Aspects of Dopamine

Dopamine is a neurotransmitter as well as a leading precursor of noradrenaline. It is degraded in a similar fashion to noradrenaline. They are connected with nigrostriatal pathway, which is important in motor control, mesolimbic pathways running from groups of cells in the midbrain to parts of the limbic system. Parkinson's disease is associated with a deficiency of nigrostriatal dopaminergic neurons. Behavioural effects of an excess dopamine activity constitute stereotyped behaviour patterns and can be produced by dopamine releasing agents.

Functional Aspects of 5-HT

The precise localization of the 5-HT neurons in the brain stem and throughout the brain parts regulates the hallucinations, behavioural changes, sleep, wakefulness, mood, feeding behaviour, and control of sensory transmission. The 5-HT receptors are concentrated in the midline raphe nuclei in the pons and medulla projecting diffusely to cortex, limbic system, hypothalamus, and spinal cord similar to noradrenergic neuron. They exert inhibitory or excitatory effects on individual neurons, acting either presynaptically or postsynaptically.

Cholinergic Transmission in CNS

Acetylcholine is widely distributed in the basal forebrain nuclei, septohippocampal projections; short interneuron in striatum and nucleus accumbans. Both nicotinic and muscarinic acetylcholine receptors are found predominantly in the CNS. The former mediate the central effects of nicotine through nicotinic receptors mainly located in presynapse. Muscarnic receptors appear to mediate main behavioural effects associated with acetylcholine such as arousal, learning, and memory. Certain neurodegenerative diseases, that is, dementia and Parkinson's disease are associated with abnormalities of cholinergic pathways.

Other Neurotransmitters and Functions in CNS

Histamine is another neurotransmitter, histaminergic neurons originate in a small area of hypothalamus and have a wide distribution. Histamine is active on waking hours and histaminic receptor antagonists are strongly sedative and antiemetic.

In purines, adenosine triphosphate (ATP) and adenosine are present. ATP is converted into adenosine diphosphate (ADP) and adenosine monophosphate (AMP). Adenosine mainly exerts inhibitory effects through A_1 and A_2 receptors resulting in sedative, anticonvulsant, and neuro-protective effect; it also acts as a safety mechanism.

These neurotransmitters and the functional aspects are necessary to maintain the homeostasis in the brain and many drugs act on these functions to alter the CNS activity and produce sedative, hypnosis, antianxiety, depression, antiepileptic, and anaesthetic actions.

CHAPTER 23

Sedatives and Hypnotics

INTRODUCTION

Sedatives are central nervous system (CNS) depressant drugs that reduce excitement, tension, and produce relaxation. Hypnotics are drugs that depress the CNS and produce sleep similar to that of natural sleep. Both sedative and hypnotic action may reside in the same drug. At lower dose, the drug may act as sedative, while at a higher dose the same drug may act as hypnotic.

Agents used as sedatives and hypnotics include a large number of compounds of diverse chemical structure given in classification and pharmacological properties, which have the common ability to induce a non-selective, reversible depression of the CNS.

Sedative and hypnotic drugs are frequently used in preanaesthetic medication and as an adjunctive therapy in psychiatry. A large number of sedative and hypnotic drugs cross the placental barrier, consequently their chronic use during pregnancy may cause withdrawal effect in the newborn infant. Many of these substances are excreted into the breast milk, and hence, their chronic use during breast-feeding may cause sedation to the infant.

Sedatives and hypnotics are also used as the following:

- Antianxiety agents
- Anticonvulsants
- Muscle relaxants
- General anaesthetics
- Preanaesthetic medication
- Antipsychiatrics to potentiate analgesic drugs
- Adjuvants to anaesthesia
- Co-drugs in the treatment of hypertension

The clinical pharmacology of the sedatives and hypnotics include the following.

Treatment of Anxiety States

The psychological behaviour and physiological responses that characterizes anxiety may be in many forms. Typically, the psychic awareness of anxiety is accompanied by an enhanced motor tension and autonomic hyperactivity. The benzodiazepines continue to be widely used for the management of anxiety states. Since anxiety symptoms may be relieved by many benzodiazepines, it is not easy to demonstrate the superiority of one individual drug over another.

Treatment of Sleep Problems

Non-pharmacological therapies are sometimes useful for sleep problems including proper diet and exercise, avoiding stimulants before retiring and ensuring a comfortable sleeping environment. In some cases, the patient will need and should be given a sedative and hypnotic. Benzodiazepines can cause a dose-dependent decrease in both rapid eyeball movement and non-rapid eyeball movement and slowly cause sleep, although to a lesser extent than barbiturates. Zolpidem and zaleplon are less likely to change sleep pattern than the benzodiazepines.

Other Therapeutic Uses

Long-acting drugs such as chlordiazepoxide, diazepam, and to a lesser extent phenobarbital are administered in progressively decreasing doses to patients during withdrawal from psychological dependence on ethanol or other sedative hypnotics. Meprobamate and other benzodiazepines are frequently used as skeletal muscle relaxants.

MOLECULAR BASIS OF INHIBITORY NEUROTRANSMITTERS

Gamma-aminobutyric acid (GABA) is the main inhibitory transmitter in the brain. GABA is formed from glutamate by the action of glutamic acid decarboxylase. Its action is terminated by reuptake, but also by deamination catalyzed by GABA transaminase. There are two types of GABA receptors, that is, $GABA_A$ and $GABA_B$. $GABA_A$ receptors, which occur mainly postsynaptically, are directly coupled to chloride channels, opening of which reduces membrane excitability. Other drugs that interact with GABA receptors and channels include benzodiazepines, neurosteroids, including endogenous progesterone metabolites and other CNS depressants, such as barbiturates, which facilitate the action of GABA. GABA receptors are G protein-coupled receptors linked to the inhibition of cAMP formation. They cause pre and postsynaptic inhibition by inhibiting Ca^{2+} channel openings and increasing K^+ conductance. Baclofen is a $GABA_B$ receptor agonist used to treat spasticity. Glycine is another inhibitory transmitter functionally similar to GABA action.

CLASSIFICATION

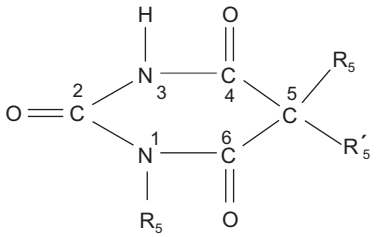
Sedatives and hypnotics are classified on the basis of their chemical structure, as follows:

1. Barbiturates
2. Benzodiazepines
3. Acyclic hypnotics containing nitrogen
4. Cyclic hypnotics containing nitrogen
5. Alcohols and aldehydes
6. Acetylene derivatives
7. Miscellaneous
    a. Inorganic salts
    b. Acids and esters
    c. Antihistaminic and anticholinergic agents
    d. Suphones
    e. Plant extracts
    f. Endogenous substances

g. Other opioids: Morphine, pethidine
h. Neuroleptics: Chlorpromazine, triflupromazine

8. Newer agents

1. Barbiturates

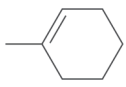


Barbiturates are further classified on the basis of duration of their action.

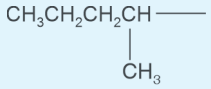
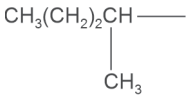
a. Long-acting barbiturates (6 h or more than 6 h)

Name	R_1	R_5	R_5'
Barbital	–H	$-C_2H_5$	$-C_2H_5$
Phenobarbital	–H	$-C_2H_5$	$-C_6H_5$
Mephobarbital	$-CH_3$	$-C_2H_5$	$-C_6H_5$
Metharbital	$-CH_3$	$-C_2H_5$	$-C_2H_5$

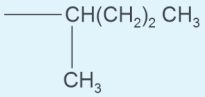
b. Intermediate-acting barbiturates (3–6 h)

Name	R_1	R_5	R_5'
Amobarbital	–H	$-C_2H_5$	$-CH_2CH_2CH(CH_3)(CH_3)$
Butabarbital	–H	$-C_2H_5$	$-CH(CH_3)-CH_2-CH_3$
Aprobarbital	–H	$CH_2=CH-CH_2-$	$(CH_3)_2CH-$
Talbutal	–H	$CH_2=CH-CH_2-$	$CH_3CH_2CH(CH_3)-$
Butalbital	–H	$CH_2=CH-CH_2-$	$(CH_3)_2CHCH_2-$
Hexobarbital	$-CH_3$	$-CH_3$	

c. Short-acting barbiturates (less than 3 h)

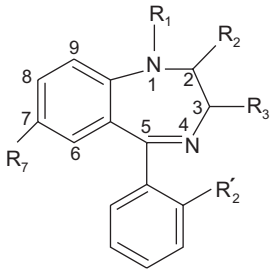
Name	R_1	R_5	R_5'
Pentobarbital	–H	$-C_2H_5$	
Secobarbital	–H	$CH_2 = CH - CH_2-$	
Cyclobarbital	–H	$-C_2H_5$	
Heptabarbital	–H	$-C_2H_5$	

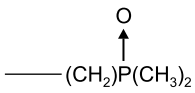
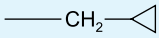
d. Ultrashort-acting barbiturates (15 min)

Name	R_1	R_5	R_5'
Thiopentone	–H	$-C_2H_5$	

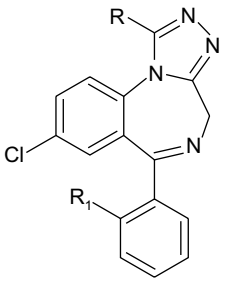
(At C – 2 = S instead of O)

2. Benzodiazepines

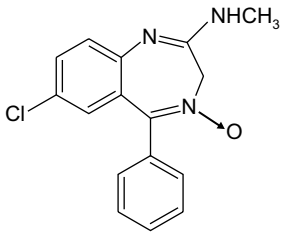


Name	R_1	R_2	R_3	R_7	R'_2
Diazepam	$-CH_3$	= O	–H	–Cl	–H
Oxazepam	–H	= O	–OH	–Cl	–H
Chlordesmethyl diazepam	–H	= O	–H	–Cl	–Cl
Fosazepam		= O	–H	–Cl	–H
Prazepam		= O	–H	–Cl	–H
Nitrazepam	–H	= O	–H	$-NO_2$	–H
Nordiazepam	–H	= O	–H	–Cl	–H
Nimetazepam	$-CH_3$	= O	–H	$-NO_2$	–H
Flunitrazepam	$-CH_3$	= O	–H	$-NO_2$	–F
Flurazepam	$-(CH_2)_2N(C_2H_5)_2$	= O	–H	–Cl	–F
Quazepam	$-CH_2CF_3$	= S	–H	–Cl	–F
Halozepam	$-CH_2CF_3$	= O	–H	–Cl	–H
Temazepam	$-CH_3$	= O	–OH	–Cl	–H
Lorazepam	–H	= O	–OH	–Cl	–Cl
Clonazepam	–H	= O	–H	$-NO_2$	–Cl
Doxefazepam	$-CH_2OH$	= O	–OH	–Cl	–F

Triazolo benzodiazepines



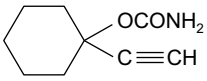
Name	R	R_1
Alprazolam	$-CH_3$	–H
Triazolam	$-CH_3$	–Cl
Estazolam	–H	–H



Chlordiazepoxide

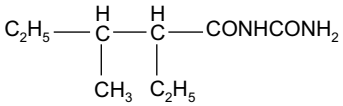
3. Acyclic Hypnotics Containing Nitrogen (Acyclic Ureides)

a. Urethanes

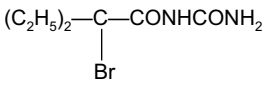


Ethinamate

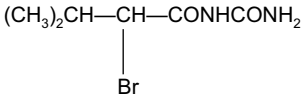
b. Ureides



Capuride

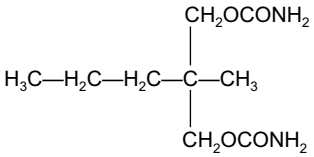


Carbromal



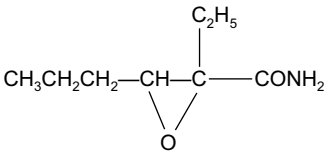
Bromovalurea

c. Carbamates

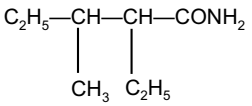


Meprobamate

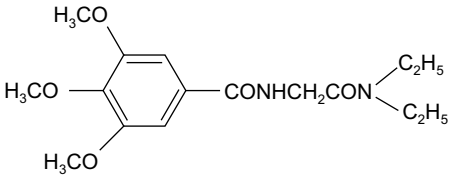
d. Amides



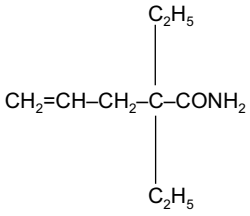
Oxanamide



Valnoctamide



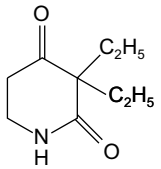
Trimethoxy benzglycine

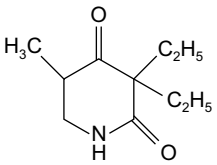


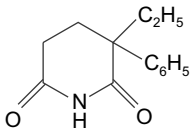
Diethyl allyl acetamide

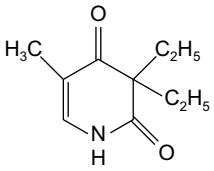
4. Cyclic Hypnotics Containing Nitrogen

a. Piperidinediones

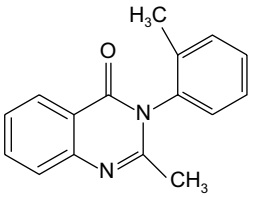

Dihydroprylone

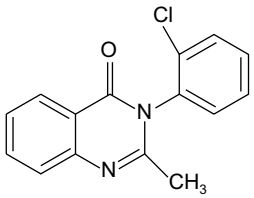

Methyprylone

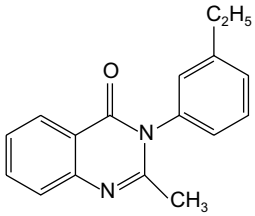

Glutethimide


Ethypicone

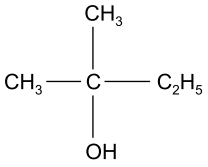
b. Quinazolinones

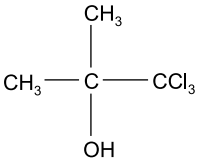

Methaqualone

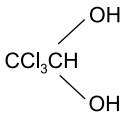

Mecloqualone

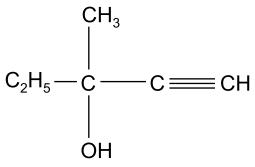

Ethinazone

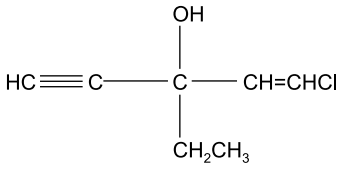
5. Alcohols and Aldehydes

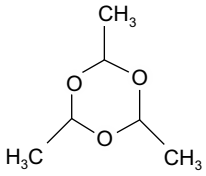

Amylene hydrate

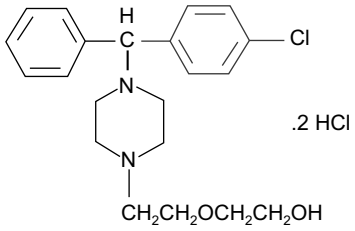

Chlorbutanol


Chloral hydrate

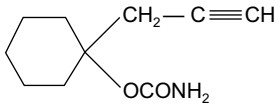

Methyl pentynol


Ethchlorvynol

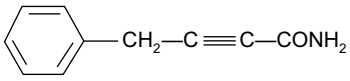

Paraldehyde


Hydroxyzine HCl

6. Actylene Derivatives



Hexapropymate



Carfimate

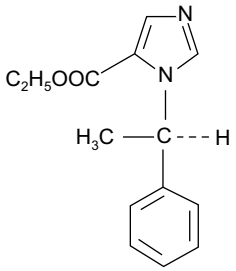
7. Miscellaneous

a. Inorganic salts: KBr, magnesium sulphate

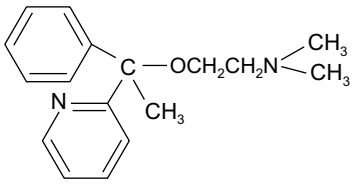
b. Acids and esters

Tryptophan, 5-hydroxy tryptophan

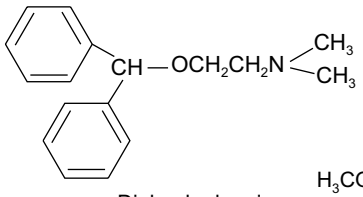
Etomidate



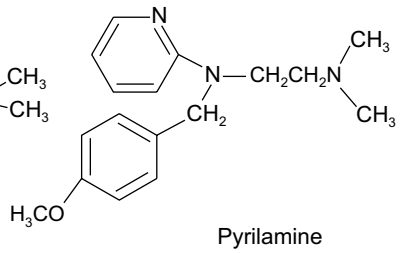
c. Antihistamines and anticholinergics



Doxylamine



Diphenhydramine



Pyrilamine

d. Sulphones

Toxic—not used.

e. Plant extracts

Radix valerianae

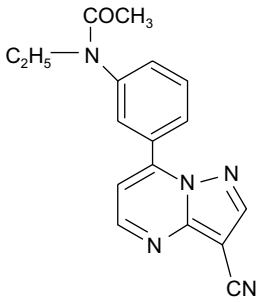
Rauwolfia serpentina

Avana sativa

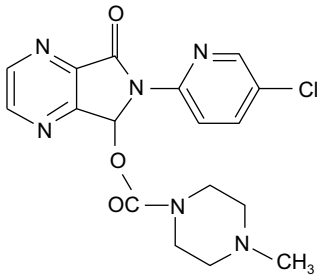
Glandula lupuli

f. Endogenous substances: Peptides

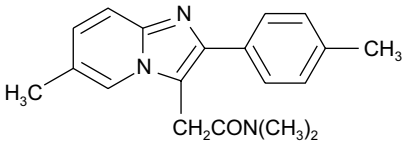
8. Newer Agents



Zaleplon



Zolpiclone



Zolpidem

SYNTHESIS AND DRUG PROFILE

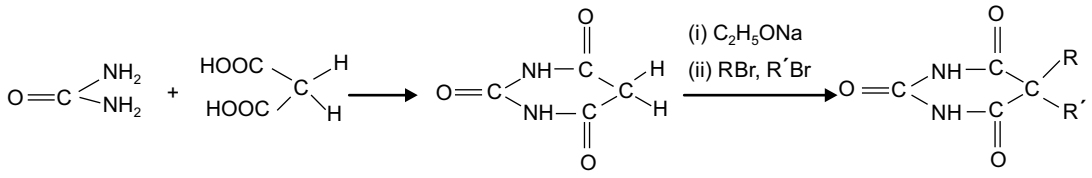
I. Barbiturates

Barbiturates are derivatives of barbituric acid. Their hypnotic activity is conferred by the replacement of H-atom attached to the C-5 position by aryl or alkyl radicals. They are generally synthesized by adopting the following route of synthesis.

Mode of action: Barbiturates primarily act on GABA-benzodiazepine receptor Cl^- channel complex and potentiate GABA ergic inhibitory action by increasing the lifetime of Cl^- channel opening induced by GABA. Barbiturates do not bind to benzodiazepine receptor promptly, but it binds to another site on the same macromolecular complex to exert the GABA ergic facilitator actions. The barbiturate site appears to be located on α and β subunit. At high concentrations, barbiturates directly increases Cl^- conductance and inhibit Ca^{2+} dependent release of neurotransmitters and they also depress glutamate-induced neuronal depolarization.

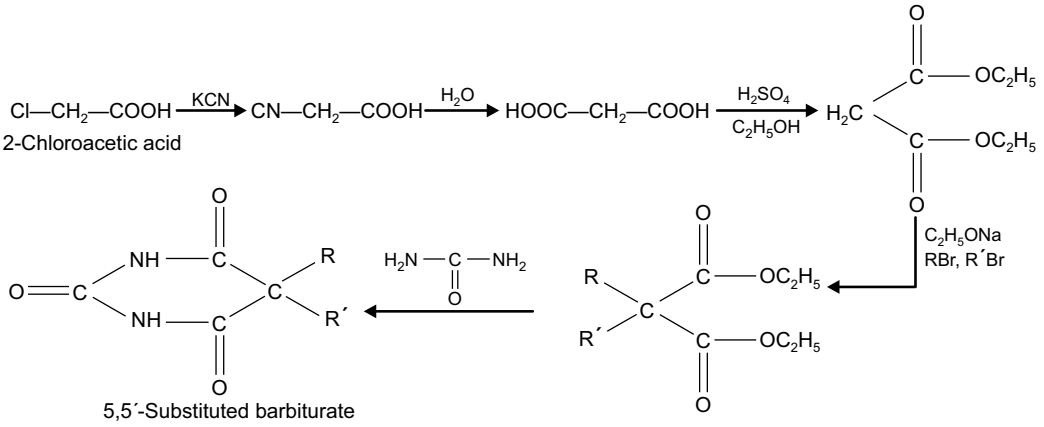
Synthesis

Route I: From urea and malonic acid



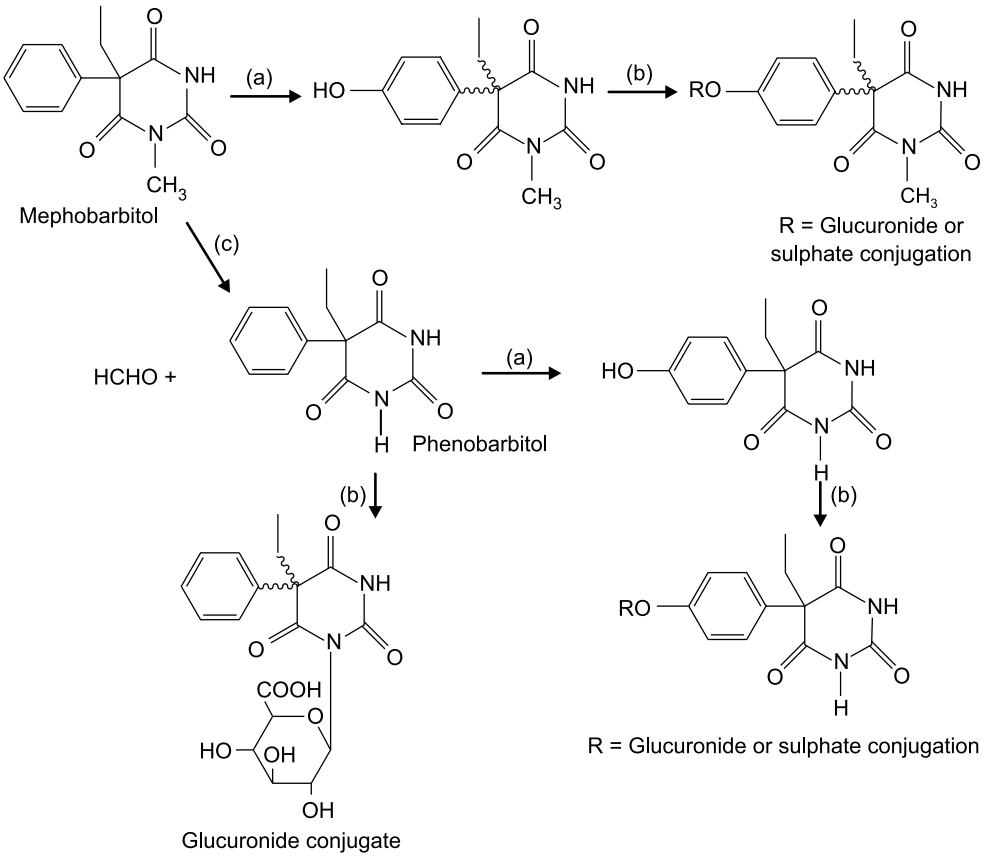
Urea Malonic acid Barbituric acid 5,5´-Substituted barbiturate

Route II: From chloroacetic acid



Metabolism of barbiturates: These drugs are metabolized in the liver and form less lipophilic compounds. These are mediated through glucuronide or sulphate conjugation.

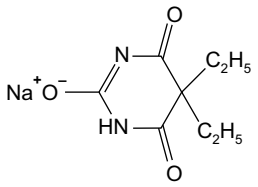
a. Oxidation of a substituent at C-5 forms alcohols or phenols, and these undergo further oxidation to form ketones or carboxylic acids. The barbiturates containing a propene at the fifth position inactivates CYP-450 by alkylation of the porphyrin ring of CYP-450.
b. The conjugation of heterocyclic nitrogen with glucuronic acid is due to the oxidative metabolism in the biotransformation of 5,5-disubstituted barbiturates (phenobarbital and amobarbital).



c. It undergoes oxidative *N*-dealkylation at nitrogen.
d. Oxidative desulphation of 2-thiobarbiturates yields more hydrophilic barbiturates, which is excreted through urine.

Uses: They are used as sedative, hypnotic and anticonvulsant. They are administered through the intravenous (IV) route for inducing anaesthesia.

1. Barbitone sodium (Barbital sodium)

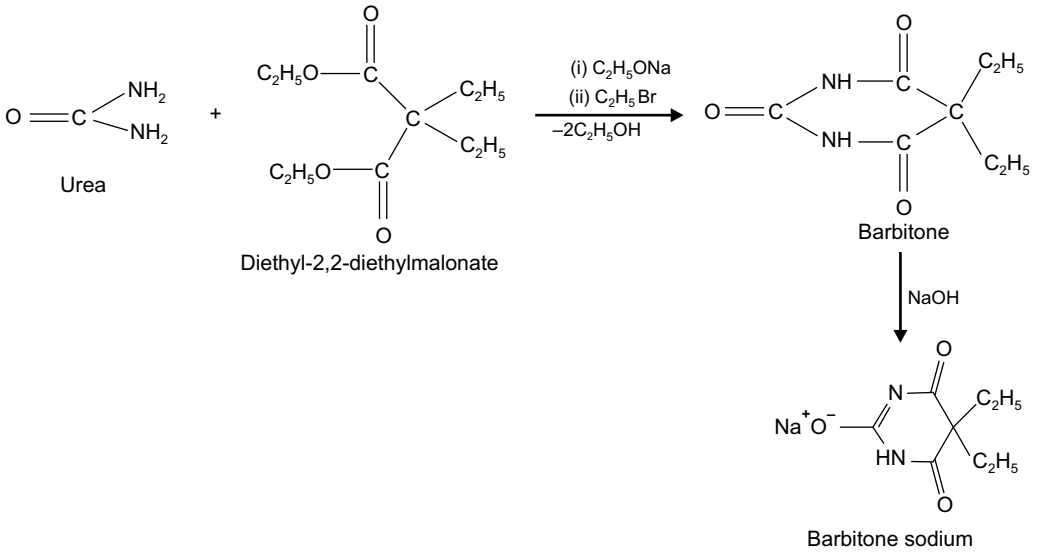


Sodium-5,5′-diethylbarbiturate

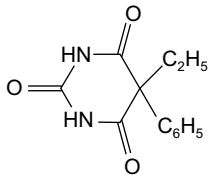
Properties and uses: Barbitone sodium exists as white, crystalline powder or colourless crystals that is soluble in boiling water and in alcohol, but only slightly soluble in water. It forms water-soluble salts with sodium hydroxide. It is a powerful hypnotic drug and generally used in the treatment of epileptic seizures.

Assay: Dissolve the substance in pyridine and to this add thymolphthalein solution and silver nitrate solution in pyridine and titrate the solution with 0.1 methanolic sodium hydroxide. End point is the appearance of blue colour.

Synthesis



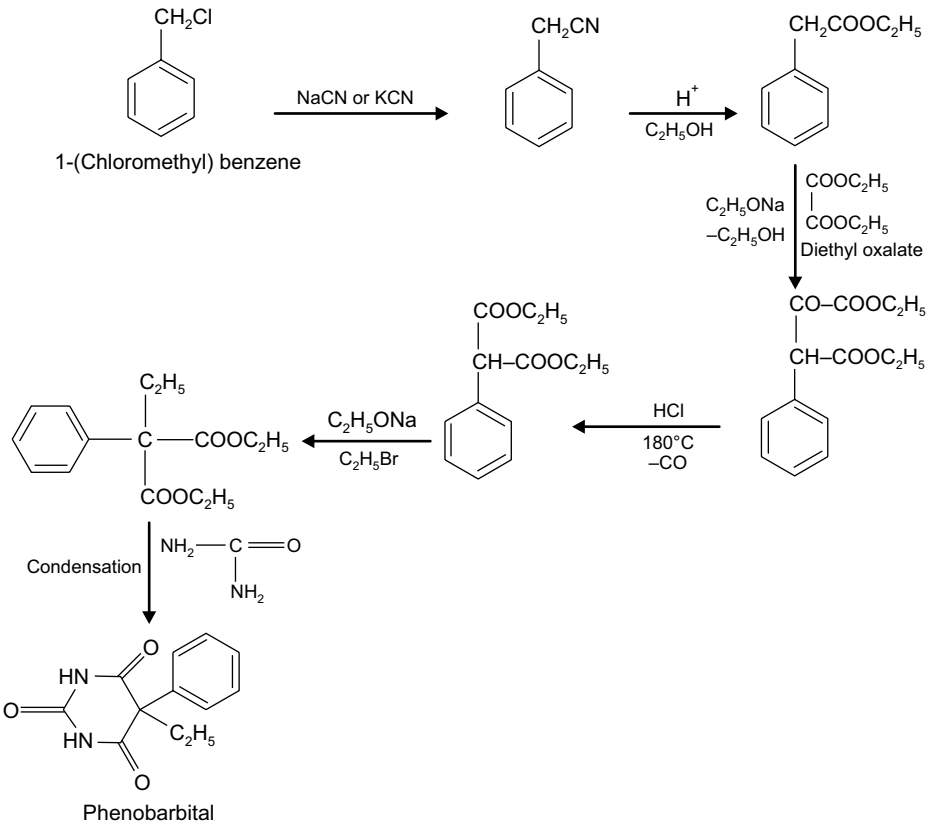
2. Phenobarbitone (Phenobarbital, Luminal)



5-Ethyl-5-phenyl barbituric acid

Properties and uses: Phenobarbital sodium is a hygroscopic substance. It is a white, crystalline powder, freely soluble in water and also soluble in alcohol. It is used as sedative, hypnotic and antiepileptic (drug of choice in the treatment of grandmal and petitmal epilepsy). It is useful in nervous and related tension states. An overdose of it can result in coma, severe respiratory depression, hypotension leading to cardiovascular collapse, and renal failure.

Synthesis



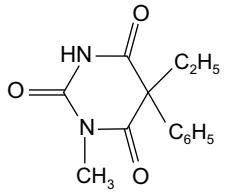
Assay: Dissolve the sample in water and add 0.05 M sulphuric acid. Heat the mixture to boiling point and then cool it. Add methanol and shake until dissolution is complete. Perform a potentiometric titration using 0.1 M sodium hydroxide. After the first point of inflexion, interrupt the addition of sodium hydroxide, add 10 ml of pyridine, mix, and continue the titration. Read the volume added between the two points of inflexion.

Storage: It should be stored in well closed airtight container.

Dose: For sedation: Adult: 30–120 mg/day in 2–3 divided doses. Children: 6 mg/kg/day. For hypnotic: Adult: 100–320 mg at bedtime. Do not administer for more than 2 weeks for the treatment of insomnia. Through IV route for preoperative sedation: Child: 1–3 mg/kg 1–1.5 h before procedure.

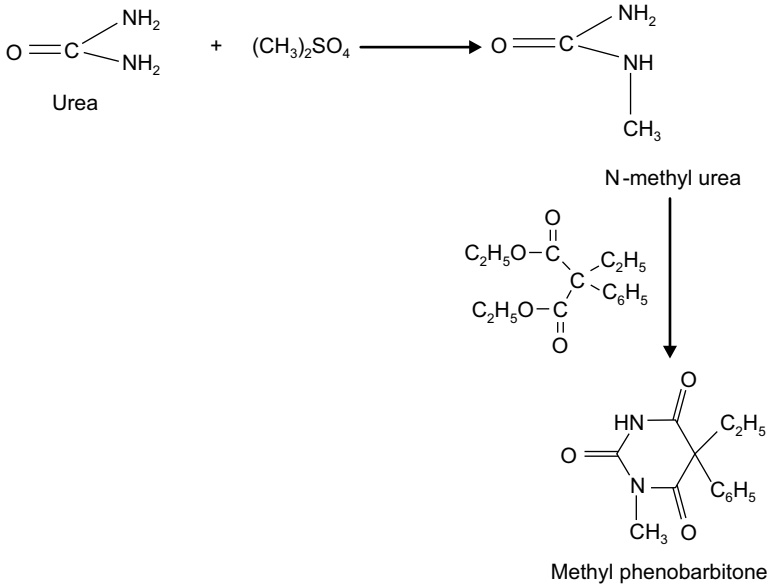
Dosage forms: Phenobarbital sodium tablets IP, BP, phenobarbital sodium injection IP, phenobarbitone tablets IP, phenobarbital injection BP, paediatric phenobarbital oral solution BP.

3. Methyl phenobarbitone (Mephobarbital)



5-Ethyl-1-methyl-5-phenyl barbituric acid

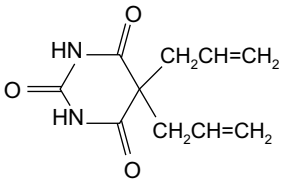
Synthesis



Properties and uses: It is a white, crystalline powder, odourless, with a bitter taste, and a saturated solution is acidic to litmus. Soluble in water, alcohol, chloroform, and in solutions of alkali hydroxides or carbonates. Mephobarbitone is a strong sedative with anticonvulsant action, but a relatively mild hypnotic. Hence, it is used for the relief of anxiety, tension, and apprehension, and is an antiepileptic in the management of generalized tonic-clonic and absence seizures.

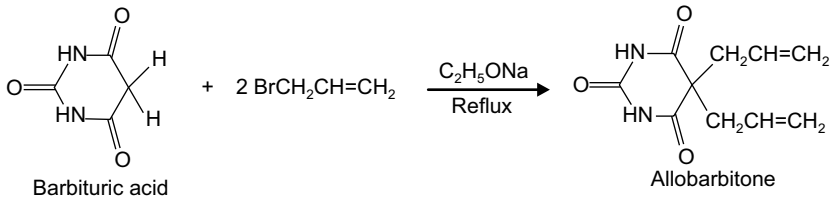
Dose: As a sedative 30–100 mg 3–4 times/day; as an anticonvulsant 400–600 mg daily.

4. Allobarbitone



5-5′-Diallyl barbituric acid

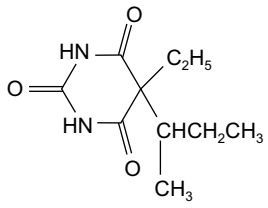
Synthesis



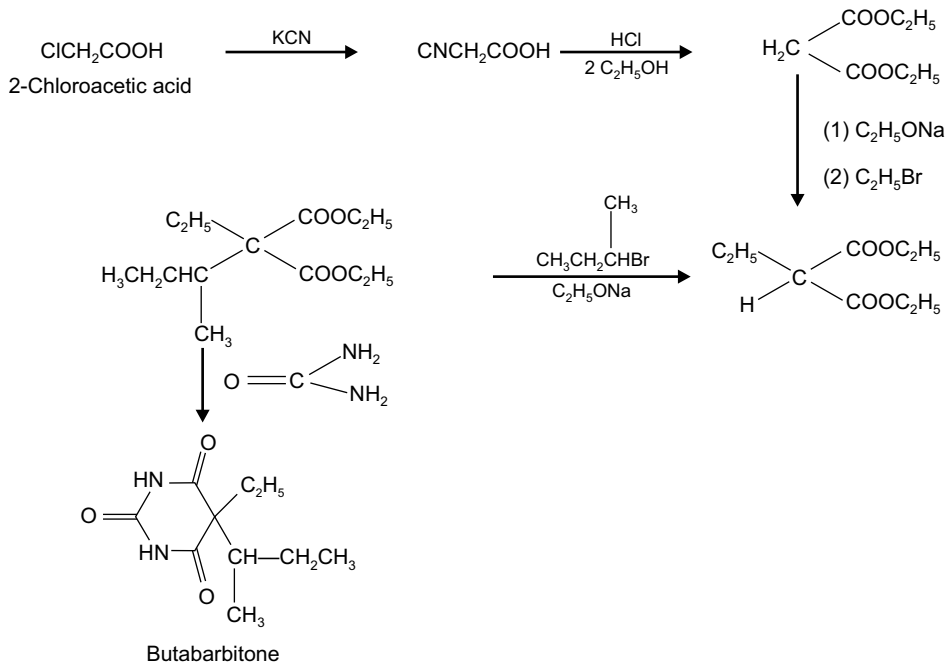
Uses: It can be used both as sedative and hypnotic at different dose intervals.

Dose: As a sedative 30 mg 3–4 times a day; as a hypnotic 100–200 mg at night.

5. Butabarbitone (Neonal)



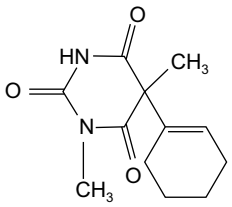
Synthesis



Properties and uses: It is used as a sedative and hypnotic, especially used for the short-term treatment of insomnia. Because of tolerance, barbiturates lose efficacy after 2 weeks of use.

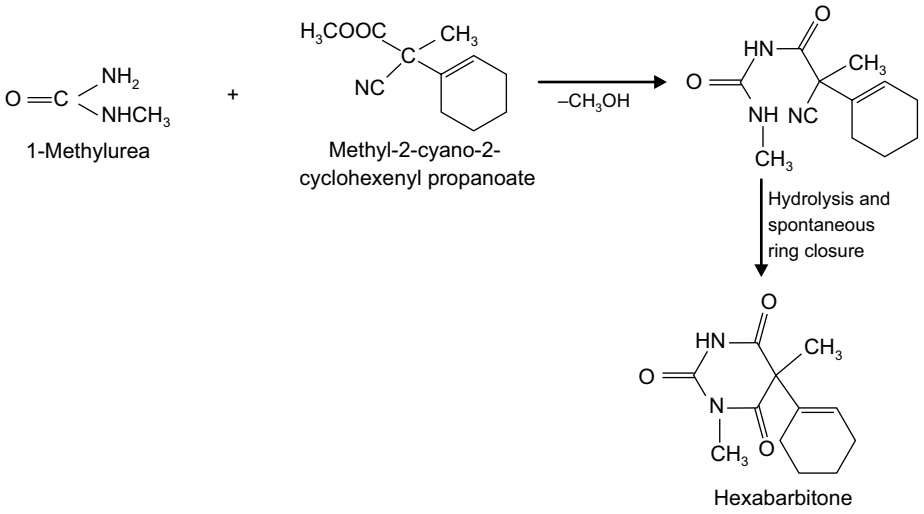
Dose: 30 mg as a sedative and 100–200 mg at night as a hypnotic.

6. Hexabarbitone (Hexobarbital, Evipal, Sombulex)



5-Cyclohexenyl-1,5-dimethylpyrimidin-2,4,6-trione

Synthesis

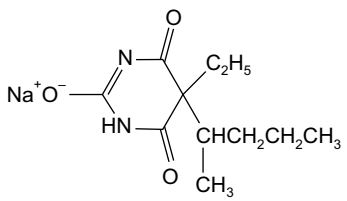


Properties and uses: It is a white, crystalline powder, very slightly soluble in water, sparingly soluble in alcohol. It forms sodium salt with sodium hydroxide, which is soluble in water. It is used as hypnotic.

Assay: Dissolve the sample in ethanol; to this add thymolphthalein solution and silver nitrate solution in pyridine. Titrate with 0.1 M ethanolic sodium hydroxide. End point is the appearance of blue colour.

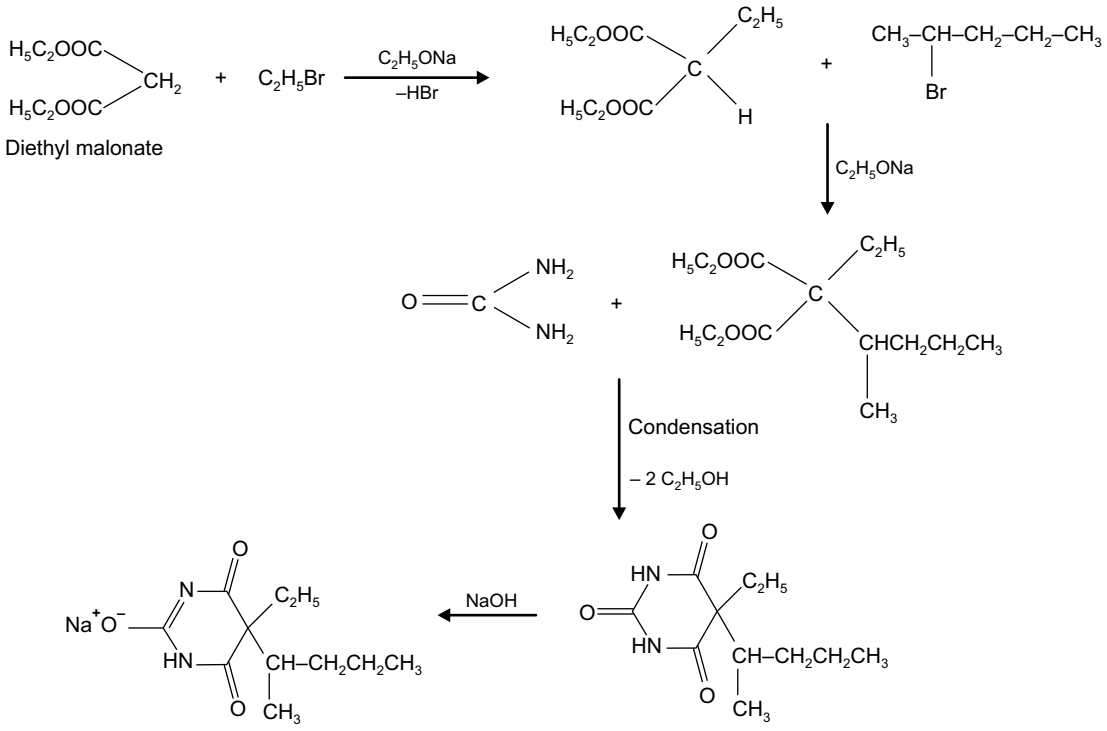
Dose: The usual dose for adult, oral hypnotic is 250–500 mg.

7. Pentobarbitone sodium (Pentobarbital sodium, Palapent, Sodital)



Sodium-5-ethyl-5-1-(1-methylbutyl) barbiturate

Synthesis



Properties and uses: It is hygroscopic in nature and a white crystalline powder, very soluble in water. It is used as a sedative or hypnotic for the short-term management of insomnia and is a preanaesthetic medication, used in the treatment of strychnine poisoning. It is also indicated in the anaesthetic doses and administered intravenously, for the control of certain convulsive syndromes. This barbiturate is thought to reduce cerebral blood flow and, thereby, decrease oedema and intracranial pressure.

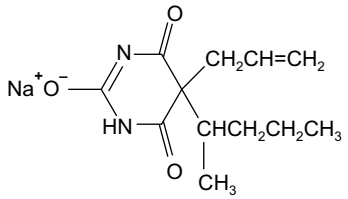
Assay: Dissolve the sample in silver nitrate solution in pyridine and titrate with 0.1 M ethanolic sodium hydroxide until a pure blue colour is obtained, using 0.5 ml of thymolphthalein solution as indicator.

Storage: It should be stored in well-closed airtight containers.

Dose: The usual oral sedative dose for adult is 30 mg 2–4 times daily. Through IM route, for preoperative, sedative, 150–200 mg. Through IV route, anticonvulsant, 100 mg initially up to 400 mg.

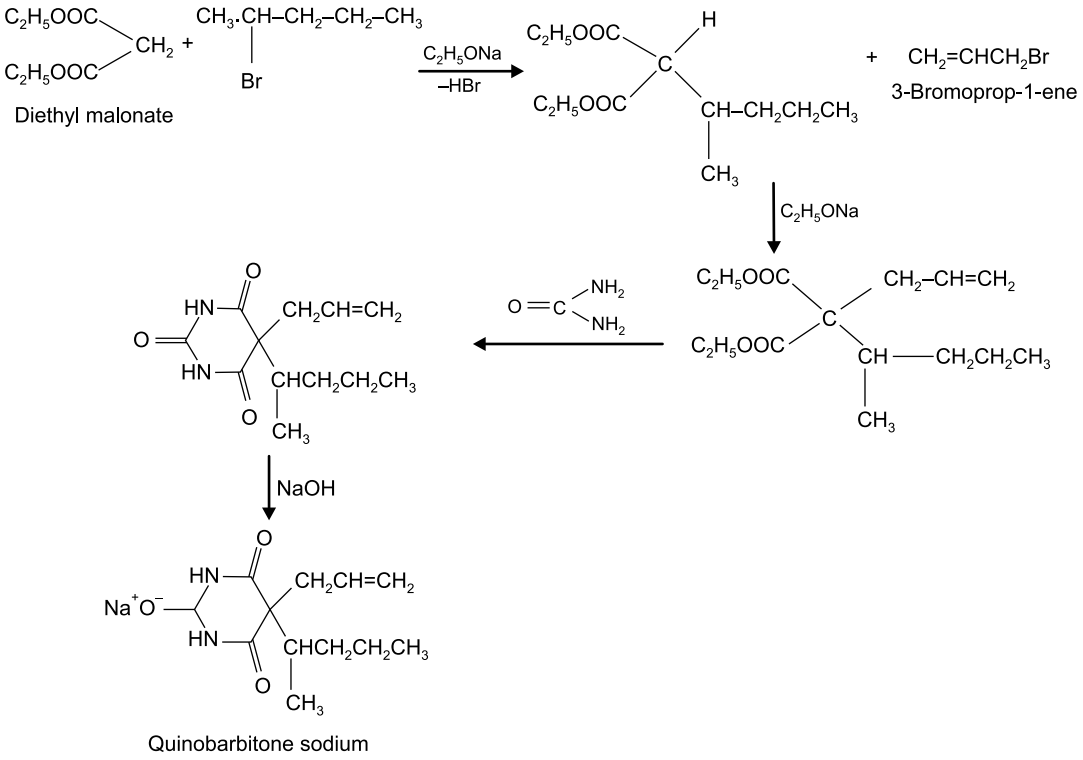
Dosage forms: Pentobarbital tablets IP, BP.

8. Quinobarbitone sodium (Secobarbital sodium)



Sodium-5-allyl-5-(1-methylbutyl) barbiturate

Synthesis



Properties and uses: It is a white, hygroscopic powder having a bitter taste, with pH between 9.7 and 10.5, soluble in water and alcohol. It is used in status epilepticus and in toxic reactions to strychnine and as local anaesthetic.

Dose: The usual adult dose is 50–200 mg.

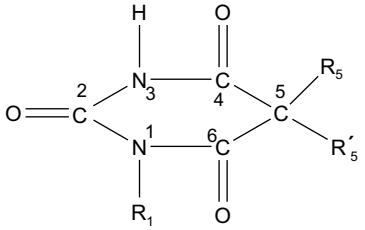
SAR of Barbiturates

A good hypnotic barbituric acid derivative must have the following properties:

1. The acidity value within certain limits to give proper ratio of ionized (dissociated) and unionized forms, which is important to cross blood–brain barrier (BBB). It takes approximately 40–60% dissociation to enable a barbiturate to cross BBB and exert effects on CNS. Determination of the pK_a can thus be predictive of the CNS activity.
2. Lipid water solubility (partition coefficient) should be in certain limits.

1. Acidity

On the basis of acidity values, barbiturates are divided into two classes:



Active class

i. 5,5′-disubstituted barbituric acids
ii. 5,5′-disubstituted thiobarbituric acids
iii. 1,5,5′-trisubstituted barbituric acids

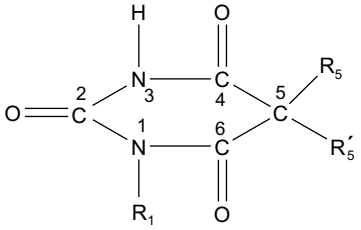
Inactive class

i. 1-substituted barbituric acids
ii. 5-substituted barbituric acids
iii. 1,3-disubstituted barbituric acids
iv. 1,5-disubstituted barbituric acids
v. 1,3,5,5′-tetrasubstituted barbituric acids

They are inactive since they are not acidic. These classes of agents depend on metabolism to produce 1,5,5′-trisubstituted barbituric acids, which are acidic. Attachment of alkyl substituent to both N^1 and N^3 renders the drug non-acidic, making them inactive.

2. Lipid–water solubility

Once the acidity value criteria is satisfied, the lipid–water solubility or partition co-efficient is calculated to find out whether the compound is active or not. The following structural skeleton is essential for hypnotic activity:

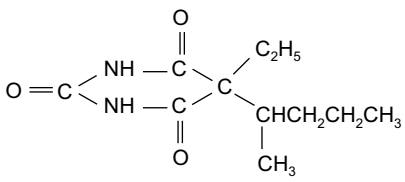


- The sum of the carbon atoms of both the substituents at C-5 should be between 6 and 10, in order to attain optimal hypnotic activity. This sum is also an index of the duration of action.

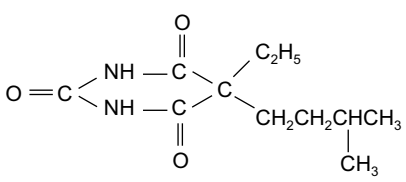
Sum of value	*Duration of action*
7–9	Rapid onset and shortest duration
5–7	Intermediate duration of action
4	Slowest onset and longest duration (two ethyl group or ethyl and phenyl)

- Within the same series, the branched chain has greatest lipid solubility and hypnotic activity, but has shorter duration of action.
- Branched cyclic or unsaturated chains at C-5 position, generally, reduce the duration of action, due to increased ease of metabolic conversion to more polar inactive metabolite.
- The greater the branching, more potent will be the drug.

  Example: Pentobarbital is more potent than amobarbital.



Pentobarbital



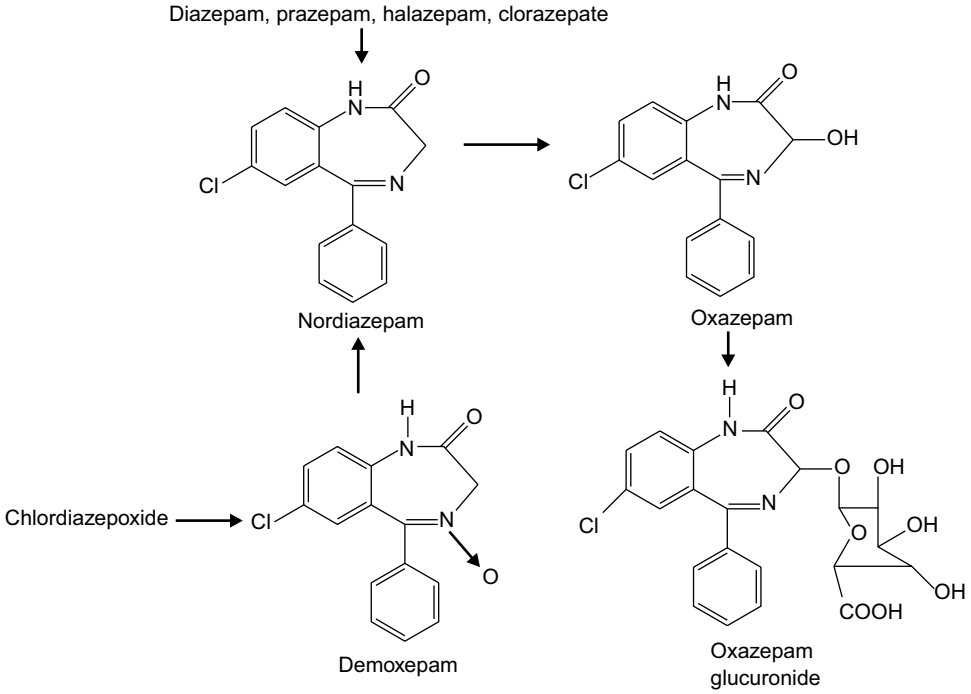
Amobarbitol

- However, the stereoisomers posses approximately the same potencies.
- Within the series, the unsaturated analogues (i.e. alkyl, alkenyl, and cycloalkenyl) may result in greater potency than the saturated analogues, with the same number of carbon atoms.
- Alicyclic or aromatic substituted analogues are more potent than analogues of aliphatic substitutions with the same number of carbon atoms.
- Introduction of a halogen atom into the C-5 substituents increase potency.
- Introduction of a polar substituents (OH, NH_2, COOH, CO, RNH, and SO_3H) into the aromatic group at C-5 results in decreased lipid solubility and potency.
- Alkylation at 1 or 3 position may result in compounds having shorter onset and duration of action since *N*-methyl group reduces acidity value.
- Replacement of oxygen by sulphur atoms at C-4 and C-6 position reduces the hypnotic activity.
- Replacement of oxygen by sulphur atom at C-2 position leads to rapid onset and shorter duration of action.

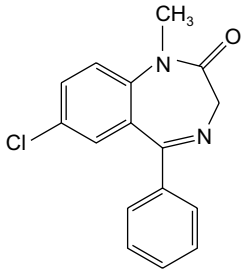
II. Benzodiazepines

Mode of action: Benzodiazepine receptors are present in the brain and they form a part of $GABA_A$ receptor's chloride ion channel macromolecular complex. Binding of benzodiazepines to these receptors produces activation of $GABA_A$ receptor and increases chloride conductance by increasing the frequency of opening chloride ion channel. These in turn inhibit neuronal activity by hyperpolarization and depolarization block.

Metabolism of benzodiazepines: Compounds without the hydroxyl group are non-polar, and undergoes hepatic oxidation. Compounds with hydroxyl groups have more polarity and are readily converted into the glucuronide conjugates and excreted easily. These compounds are also metabolized by 3-hydroxylation of benzodiazepine ring.

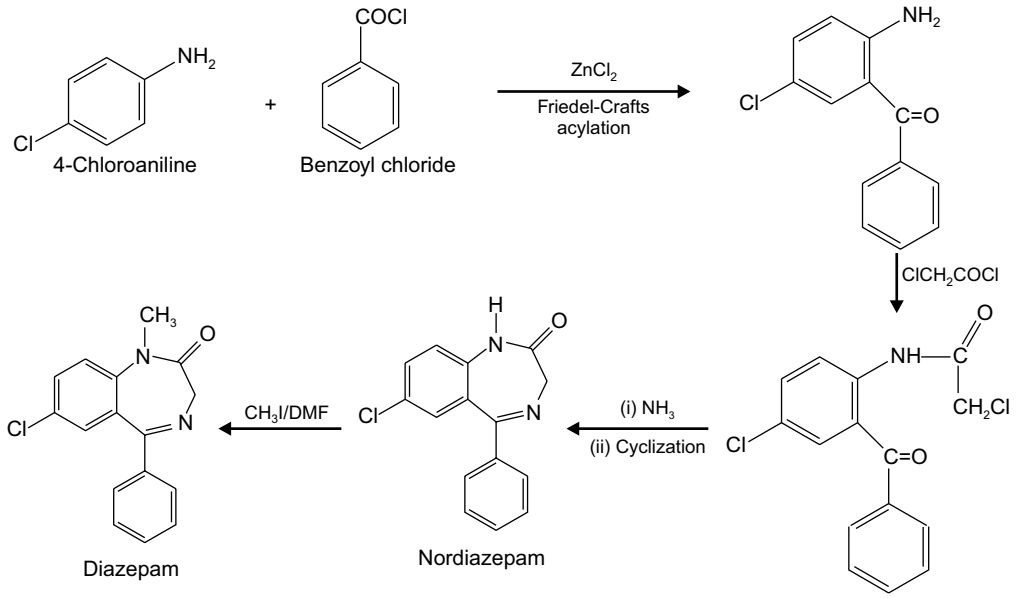


1. Diazepam (Calmpose, Valium, Diazep)



7-Chloro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one

Synthesis



Properties and uses: It is a white or almost white crystalline powder soluble in ethanol and very slightly soluble in water. It is used as a skeletal muscle relaxant, anticonvulsant and antianxiety agent. It may take a long time to achieve sedative and antianxiety effects, during which time the patient can usually be maintained by giving the drug once or twice a day. Patients on the drug should be cautioned not to drive an automobile or to operate dangerous machinery until a few days after the drug has been discontinued.

Assay: Dissolve the sample in acetic anhydride and titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

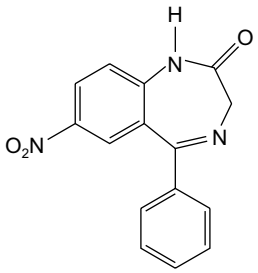
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For short-term management of anxiety: Adult—2 mg three times a day. Maximum: 30 mg daily. For insomnia associated with anxiety: Adult—5–15 mg at bedtime. Sleepwalking; night terrors: Children and adolescents (up to 18 years)—1–5 mg at bedtime. Anaesthetic premedication: Adult—5–15 mg given before general anaesthesia. Child: 1–12 month—250 µg/kg; 1–5 year—2.5 mg; 5–12 year—5 mg. For adjunct in the management of seizures: Adult—2–60 mg daily in divided doses. For muscle

spasms: Adult—2–15 mg daily in divided doses, increased up to 60 mg daily in severe spastic disorders. Maximum: 60 mg/day. Child: 1–12 month, 250 µg/kg; 1–5 years—2.5 mg; 5–12 years—5 mg; 12–18 year—10 mg. Maximum: 40 mg/day. Elderly: Dose reduction may be required.

Dosage forms: Diazepam tablets IP, BP, diazepam injection IP, BP, diazepam capsules IP, diazepam oral solution BP, diazepam rectal solution BP.

2. Nitrazepam (Dormin, Nipam, Nitorsun)



7-Nitro-5-phenyl-1,4-benzodiazepin-2-one

Properties and uses: It is a yellow crystalline powder slightly soluble in alcohol and insoluble in water. It is used as sedatives and hypnotics, and in the management of myoclonic seizures.

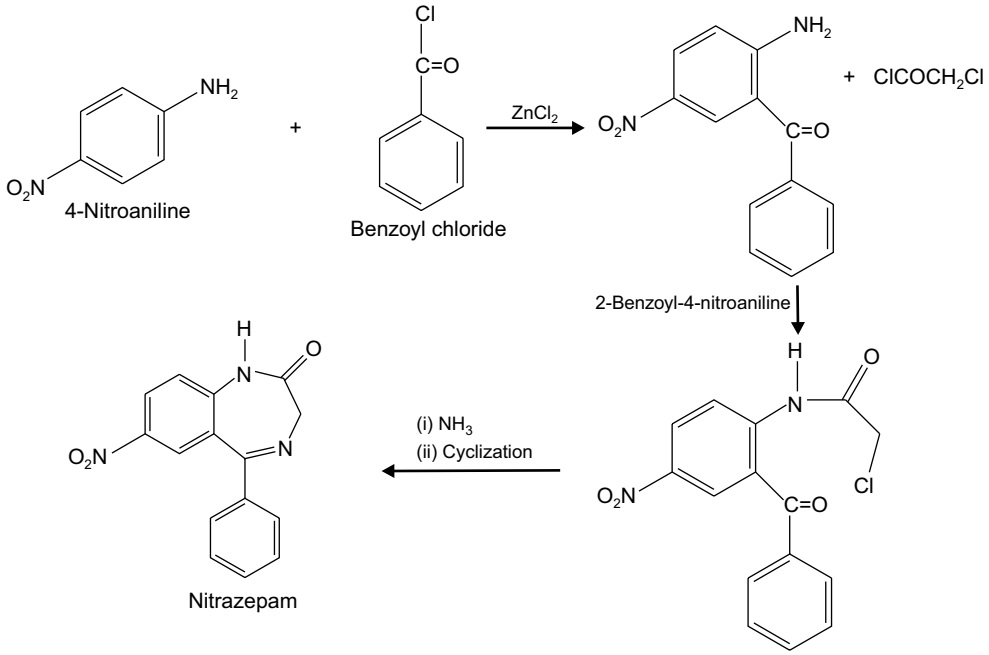
Assay: Dissolve the sample in acetic anhydride. Titrate the solution with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

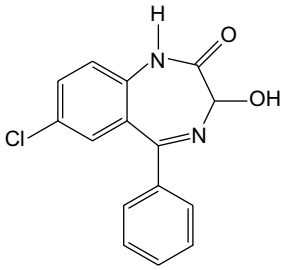
Dose: For short-term management of insomnia: Adult—5 mg at night; can increase to 10 mg, if necessary. Elderly and debilitated patients: Less than the normal adult dose. For infantile spasms: Child and infant, 125 µg/kg two times a day; gradually increase to 250–500 µg/kg two times a day.

Dosage forms: Nitrazepam tablets IP, BP, nitrazepam oral suspension BP.

Synthesis



3. Oxazepam (Serepax)



7-Chloro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one

Properties and uses: It is a white or almost white crystalline powder slightly soluble in ethanol and insoluble in water. It is useful for the control of acute tremulousness, inebriation, or anxiety associated with alcohol withdrawal. Side effects that have been observed include rashes, nausea, lethargy, oedema, slurred speech, tremor, and altered libido. More severe reactions include leucopenia and jaundice.

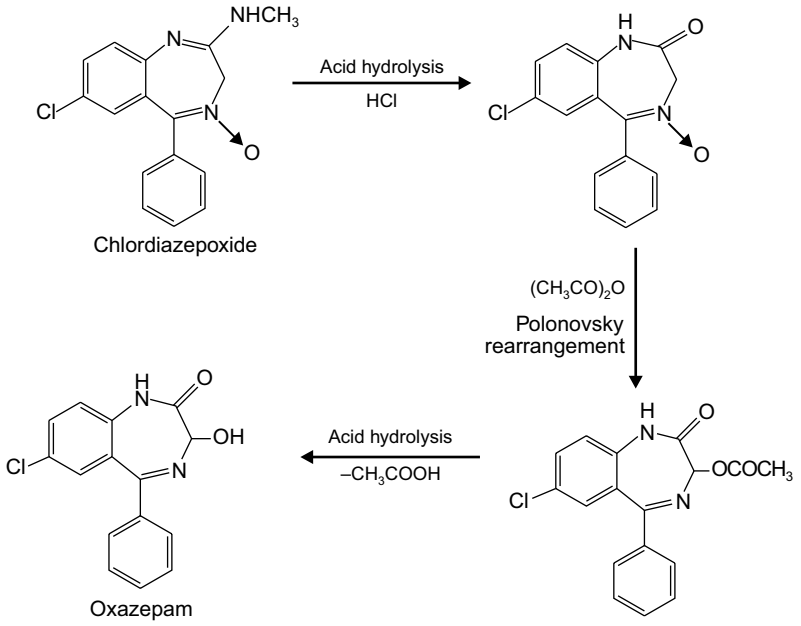
Assay: Dissolve the sample in anhydrous acetic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

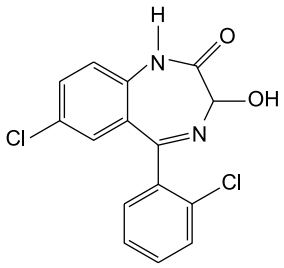
Dose: For anxiety, alcohol withdrawal syndrome: Adult—15–30 mg three or four times/day. Elderly or debilitated patients: Initially, 10 mg thrice/day; increase up to 10–20 mg three or four times/day, if necessary. For insomnia associated with anxiety: Adult—15–25 mg given 1 h before bedtime. Up to 50 mg may be occasionally required.

Dosage forms: Oxazepam tablets BP.

Synthesis

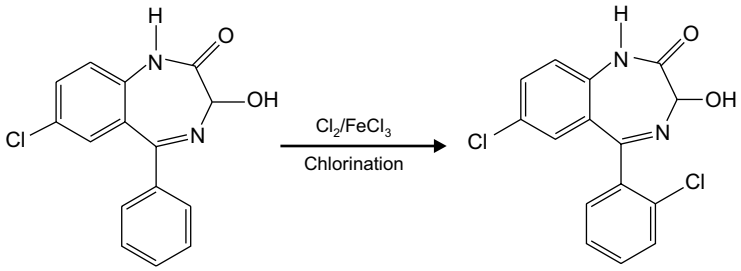


4. Lorazepam (Larposa, Lorvan)



7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,4-benzodiazepin-2-one

Synthesis



Oxazepam Lorazepam

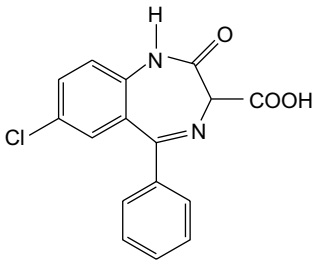
Properties and uses: It is a white or almost white crystalline powder, which is insoluble in water, sparingly soluble in ethanol, and sparingly soluble in methylene chloride. It shows polymorphism. It is used as sedative and hypnotic. It has much more polarity than diazepam, for example, metabolism is relatively uncomplicated, and the duration of action is short.

Assay: Dissolve the sample in dimethylformamide. Titrate with 0.1 M tetrabutylammonium hydroxide and determine the end point potentiometrically.

Dose: For anxiety: Adult—usual dose 1–6 mg daily in 2 or 3 divided doses. Largest dose taken at night. Up to 10 mg daily has been used. Elderly: Initial dose of 1–2 mg daily in 2 or 3 divided doses. Adjust as necessary. For insomnia associated with anxiety; adult—1–4 mg as a single dose given at bedtime. Elderly: 1–2 mg initially, adjust as needed.

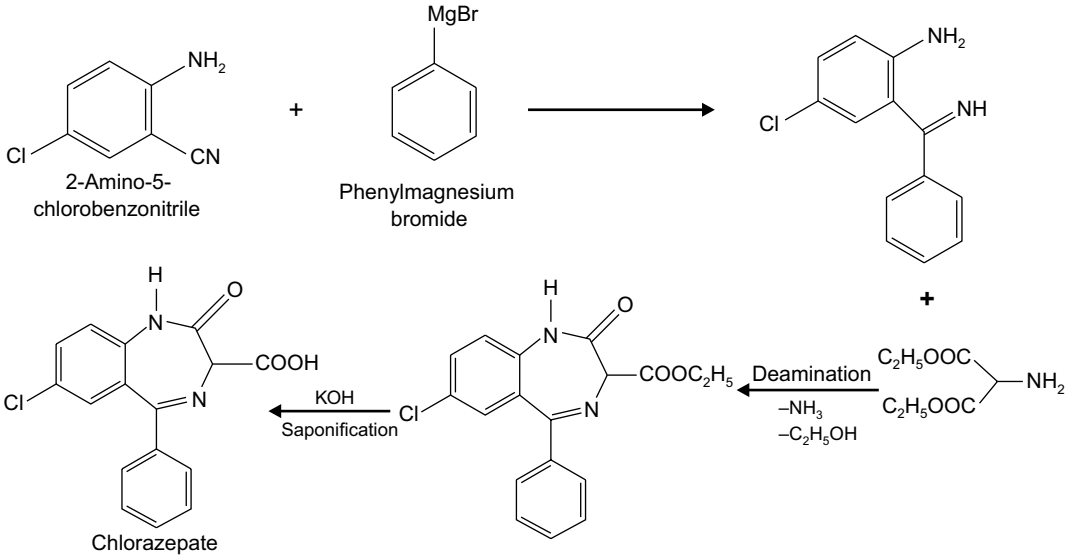
Dosage forms: Lorazepam injection BP, lorazepam tablets BP.

5. Chlorazepate



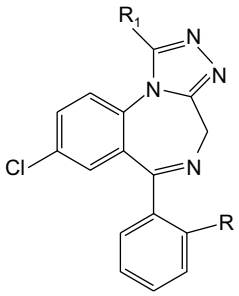
7-Chloro-2-oxo-5-phenyl-1,4-benzodiazepin-3-carboxylic acid

Synthesis



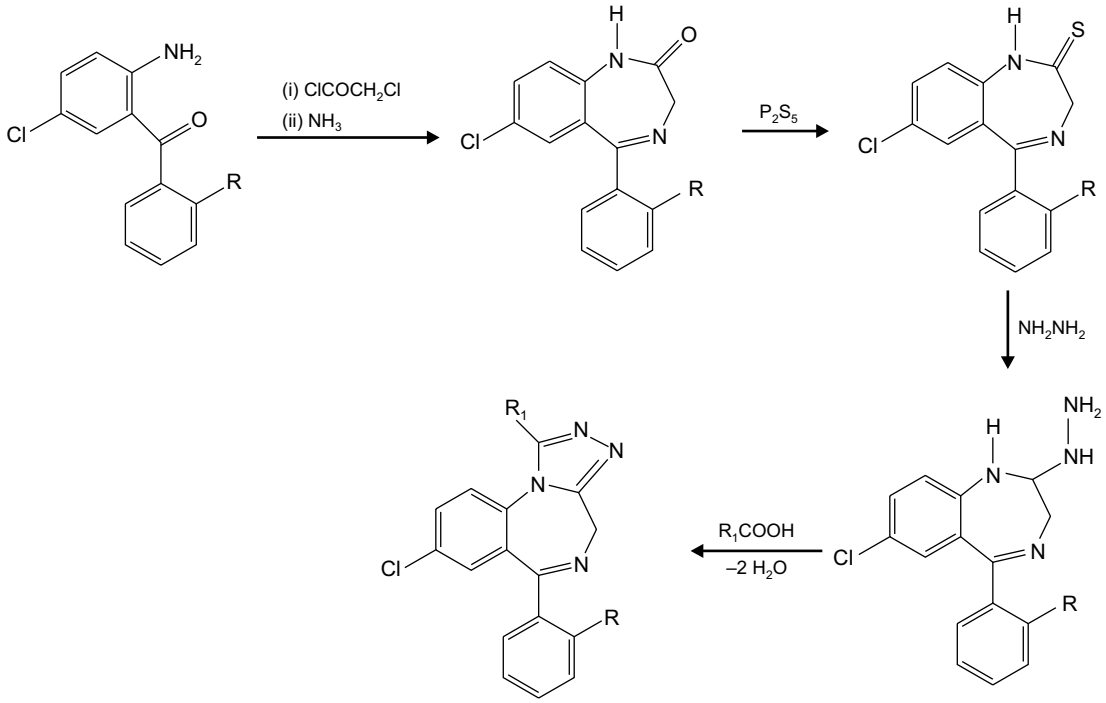
Uses: It is used as a sedative and hypnotic.

6. Triazolobenzodiazepines



- The structural modification of benzodiazepines with triazole or imidazole leads to the generation of triazolobenzodiazepines.
- Triazolam and alprazolam are belonging to the category of ultrashort-acting benzodiazepines (duration of action less than 6 hours).
- Alprazolam acts as a high potent anxiolytic agent at milligram dose level.
- Triazolam and estazolam possess high receptor binding capacity as well as rapid metabolism and elimination rate and hence the daytime sedation or hangover effects produced by other benzodiazepines are eliminated
- Triazolam and estazolam are mainly used as sleep inducers in elderly patients.

Synthesis (Estazolam, Triazolam, Alprazolam)



Estazolam	R = H, R_1 = H
Triazolam	R = Cl, R_1 = CH_3
Alprazolam	R = H, R_1 = CH_3

Metabolism of alprazolam: The methyl group of this drug is metabolized by oxidation reaction to methyl alcohol and conjugation reaction takes place.

Properties and uses

Estazolam: A triazolobenzodiazepine derivative that structurally resembles alprazolam and triazolam. It is useful in the management of insomnia. It has an intermediate half-life and the peak plasma concentration reaches 1.5 to 2 h after oral administration. It undergoes hepatic microsomal oxidation and has an elimination half-life 2 to 15 h. It causes more serious toxicity and withdrawal reactions than other benzodiazepines.

Dose: The usual required dose is 2 mg.

Triazolam (Halcion)**:** It is freely soluble in water and the metabolites, has little hypnotic action and is useful in the management of insomnia. The common adverse effects include drowsiness, dizziness, and headache.

Dose: The usual oral dose for an adult is 0.25–0.5 mg at bedtime.

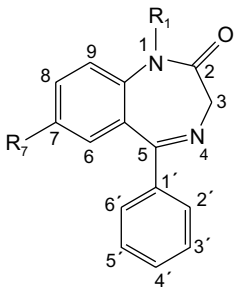
Alprazolam: It is a white crystalline powder, practically insoluble in water, freely soluble in methylene chloride sparingly soluble in acetone and in alcohol. It shows polymorphism. It is useful in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings,

and early morning awakenings. The duration of action is short and the drug is a highly potent anxiolytic in doses of milligram.

Assay of alprazolam: Dissolve the sample in a mixture of 3 volumes of anhydrous acetic acid and 2 volumes of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically. Titrate to the second point of inflexion.

Storage: It should be stored in well-closed airtight containers and protected from light.

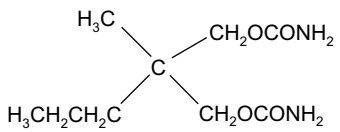
SAR of Benzodiazepines



- The presence of electron attracting substituents (Cl, F, Br, NO_2) at position C-7 is required for the activity, and of more electron attracting substituents leads to potent activity.
- Position 6, 8, and 9 should be unsubstituted for the activity.
- Phenyl or pyridyl at the C-5 position promotes activity. If the phenyl ring substituted with electron attracting groups at 2′ or 2′,6′ position, then the activity is increased.
- On the other hand, substituents at 3′, 4′, and 5′ positions decreases activity greatly.
- Saturation of 4, 5 double bond or shift of it to the 3, 4 position decreases the activity.
- Alkyl substitution at position 3 decreases the activity, but the presence or absence of hydroxyl group is essential. Compounds without 3-hydroxyl group are non-polar and usually have long half-life. Compounds with the 3-hydroxyl group have short half-life because of rapid conjugation with glucuronic acid.
- Substitution at N^1 by alkyl, halo alkyl, and amino alkyl group increases the activity.
- Reduction of carbonyl function at C-2 position to CH_2 yields less potent compound.
- Triazolobenzodiazepine (alprazolam) is found to be more potent, they do not require any substitution at 7th position.

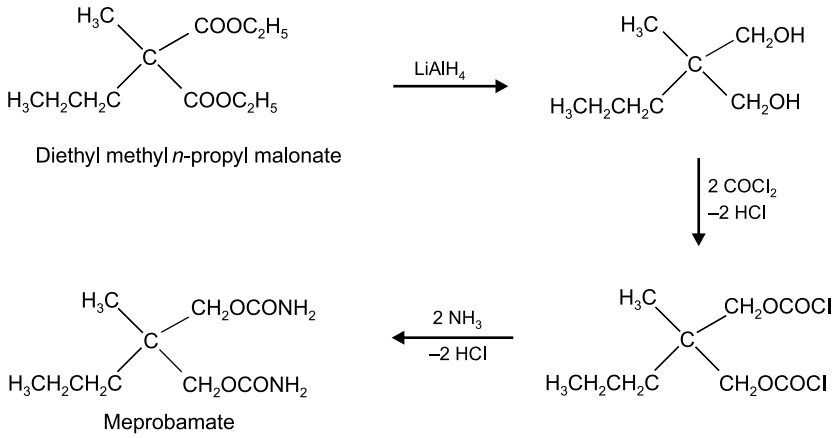
III. Acyclic Hypnotics Containing Nitrogen

1. Meprobamate (Miltown, Equanil)



2-Methyl-2-propyl-1,3-propanediol dicarbamate

Synthesis



Diethyl methyl *n*-propyl malonate

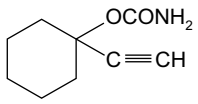
Meprobamate

Properties and uses: It is a white or almost white amorphous or crystalline powder slightly soluble in water and freely soluble in alcohol. It is used in the treatment of anxiety disorders. It is also a centrally acting skeletal muscle relaxant. The agents in this group find use in a number of conditions, such as strains and sprains that may produce acute muscle spasm.

Assay: Dissolve the sample in 25% V/V solution of sulphuric acid and boil under a reflux condenser for 3 h. Cool and dissolve by cautiously adding 30 ml of water, cool again and place in a steam-distillation apparatus. Add 40 ml of strong sodium hydroxide solution and distil immediately by passing steam through the mixture. Collect the distillate into 40 ml of a 40 g/L solution of boric acid R until the total volume in the receiver reaches about 200 ml. Add 0.25 ml of methyl red mixed solution. Titrate with 0.1 M hydrochloric acid until the colour changes from green to violet.

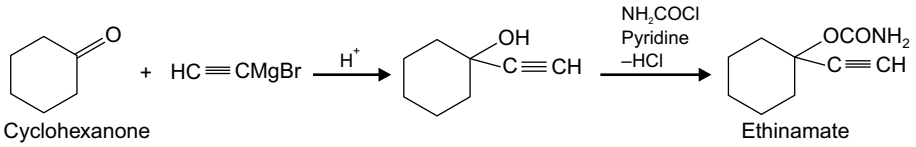
Dose: The usual oral dose for an adult is 400 mg.

2. Ethinamate



1-Ethynyl-cyclohexyl carbamate

Synthesis



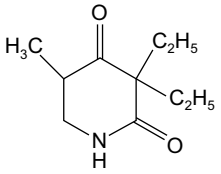
Cyclohexanone

Ethinamate

IV. Cyclic Hypnotics Containing Nitrogen

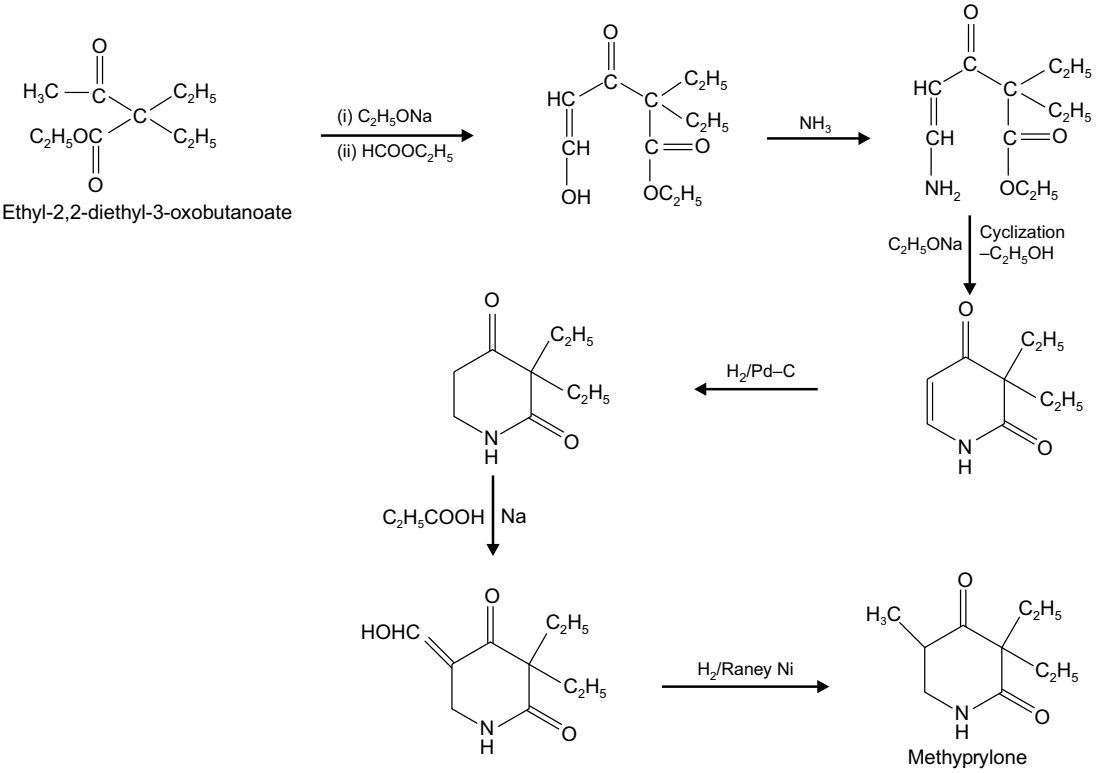
1. Piperidinedione derivatives

a. Methyprylone (Noludar)



3,3-Diethyl-5-methylpiperidine-2,4-dione

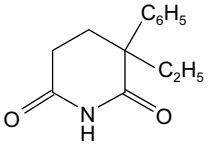
Synthesis



Properties and uses: Methyprylone exists as white crystalline powder and soluble in water. Used as a hypnotic agent, useful in the management of insomnia of varied etiology.

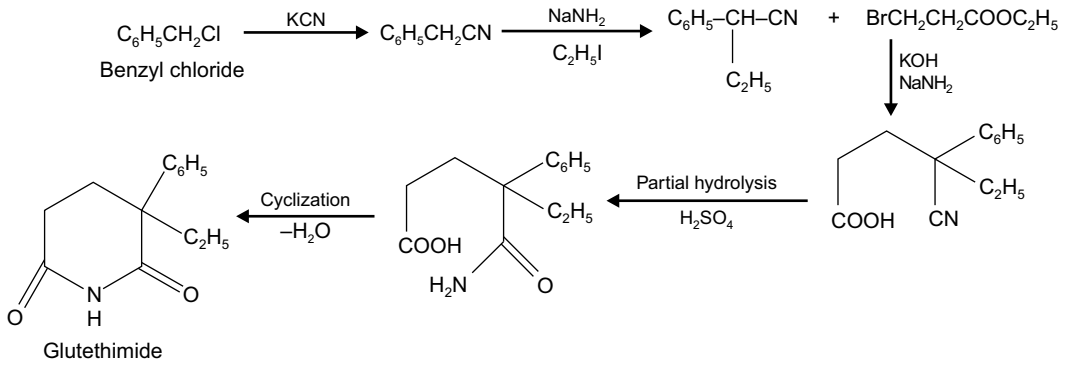
Dose: The usual adult dose is 200–600 mg for hypnotic; 50–100 mg for sedative.

b. Glutethimide



3-Ethyl-3-phenyl piperidine-2,6-dione

Synthesis

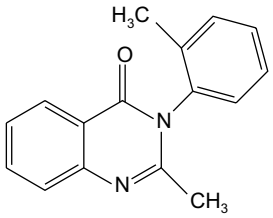


Properties and uses: It is used as a hypnotic drug to induce sleep without depressing respiration. Overdosage is less likely to depress respiration, but more likely to cause hypotension than most other barbiturates. Adverse reactions include a generalized rash, occasionally a purpuric or urticarial rash; exfoliative dermatitis has also been observed, rarely nausea, hangover, paradoxical excitation, and blurred vision have occurred. Some of these side effects may be due to the anticholinergic activity of this drug.

Dose: The usual adult dose is 250–500 mg.

2. Quinazolinone derivatives

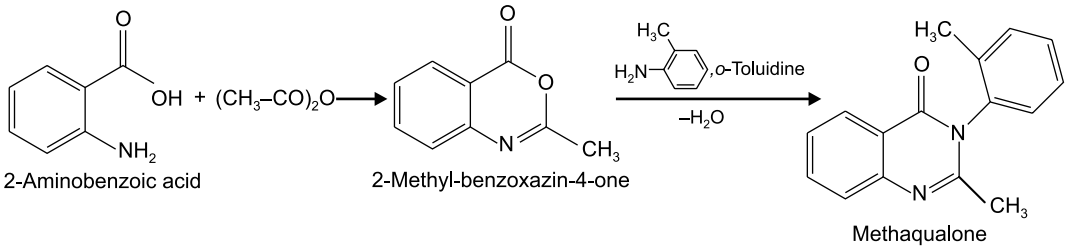
a. **Methaqualone** (Mequin)



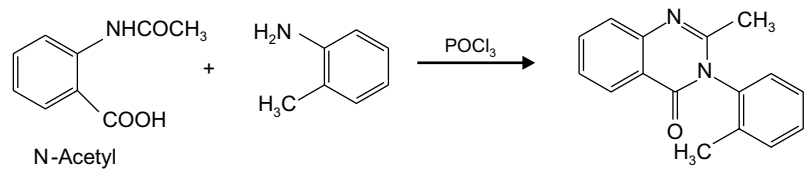
2-Methyl-3-*o*-tolylquinazolin-4-(3H)-one

Synthesis

Route I. From: Anthranilic acid



Route II. From: N-Acetyl anthranilic acid



N-Acetyl anthranilic acid | *o*-Toluidine | Methaqualone

Properties and uses: It is a white or almost white crystalline powder. It dissolves in dilute sulphuric acid and very slightly soluble in water and also soluble in alcohol. It is used as a hypnotic drug to induce sleep and as a daytime sedative. It may be administered along with an antihistaminic agent such as diphenhydramine.

Assay: Dissolve the sample in anhydrous acetic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

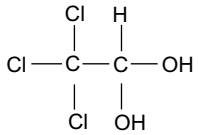
Dose: The usual adult dose is 50–150 mg.

V. Alcohols and Aldehydes

Mode of action: These drugs elicit the action and is similar to the mechanism of barbiturates. These are general CNS depressants, which produce profound hypnosis.

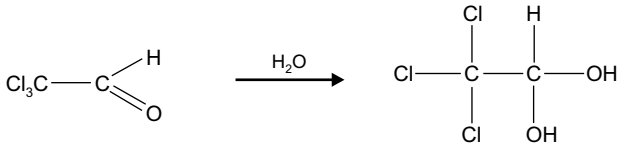
Metabolism: These are metabolized by alcohol dehydrogenase enzyme. Chloralhydrate undergoes oxidation to chloral and then to an inactive metabolite, trichloroacetic acid, via aldehyde dehydrogenase, which also is extensively metabolized to aryl glucuronides via conjugation with glucuronic acid and then excreted in urine.

1. **Chloral hydrate** (Noctec)



2,2,2-Trichloro-1,1-ethanediol

Synthesis



Chloral | Chloral hydrate

Properties and uses: Colourless, transparent crystals, very soluble in water and freely soluble in alcohol. Used principally for the short-term treatment of insomnia, it is used pre-operatively to allay anxiety and to induce sedation/sleep. It is used post-operatively as an adjuvant to opiates and other

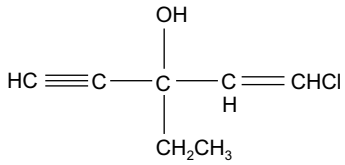
analgesics to control pain. It has also been used to produce sleep prior to electroencephalogram (EEG) evaluations. It is also effective in reducing anxiety associated with withdrawal of alcohol and other drugs, such as opiates and barbiturates.

Assay: Dissolve the sample in water and add 1 M sodium hydroxide solution. Allow to stand for exactly 2 min and titrate with 0.5 M sulphuric acid, using phenolphthalein solution as indicator. Titrate the neutralized solution with 0.1 M silver nitrate, using potassium chromate solution as an indicator.

Storage: It should be stored in well-closed airtight container.

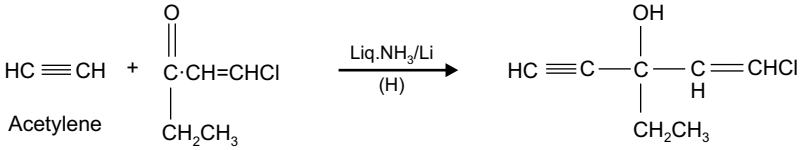
Dose: The usual adult dose is 500–1000 mg for hypnotic and 250 mg for sedative.

2. Ethchlorvynol (Placidyl)



1-Chloro-3-ethyl-1-penten-4-yn-3-ol

Synthesis



Acetylene

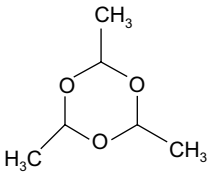
1-Chloro-3-oxo-1-pentene

Ethchlorvynol

Properties and uses: It also possesses muscle relaxant and anticonvulsant properties apart from CNS depressant action. Adverse effects include suppression of REM sleep, ataxia, and hypotension.

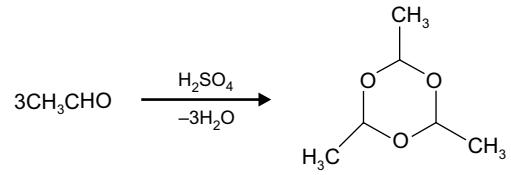
Dose: The usual adult dose is 500–1000 mg hypnotic and 100–200 mg sedative.

3. Paraldehyde



2,4,6-Trimethyl-1,3,5-trioxane

Synthesis



Acetaldehyde

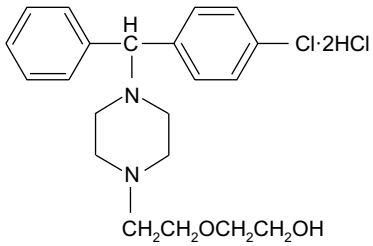
Paraldehyde

Properties and uses: It is a colourless or slightly yellow transparent liquid. It solidifies on cooling to form a crystalline mass. Miscible with alcohol and with essential oils, soluble in water, but less soluble in boiling water, it is exclusively used in the management of hospitalized patients undergoing alcohol withdrawal. Its CNS depressant activity resembles that of alcohol and chloral hydrates.

Storage: It should be stored in well-closed airtight containers and protected from light. If the substance has solidified, the whole contents of the container must be liquefied before use.

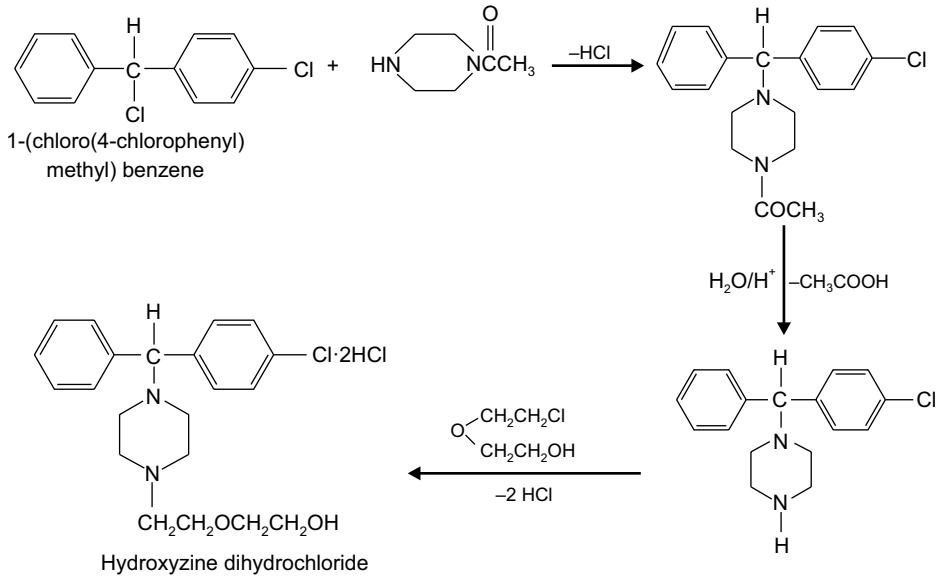
Dosage forms: Paraldehyde injection BP.

4. Hydroxyzine hydrochloride



2-(2-(4-[(4-Chloro phenyl) phenyl methyl)-1-Piperazinyl]-ethoxy) ethanol-dihydrochloride

Synthesis



Properties and uses: It is a hygroscopic crystalline powder, white or almost white in colour, freely soluble in water and in alcohol, very slightly soluble in acetone. It is useful in psychosomatic disturbances, nervous tension, and anxiety.

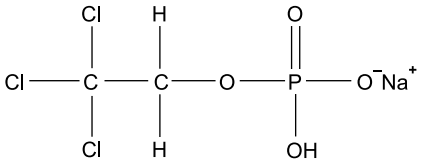
Assay: Dissolve the sample in 10 ml of anhydrous acetic acid and 40 ml of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Adult—IM injection as the hydrochloride in doses of 25–100 mg every 4–6 h; children—1 mg per kg body weight IM for pre and postoperative sedation.

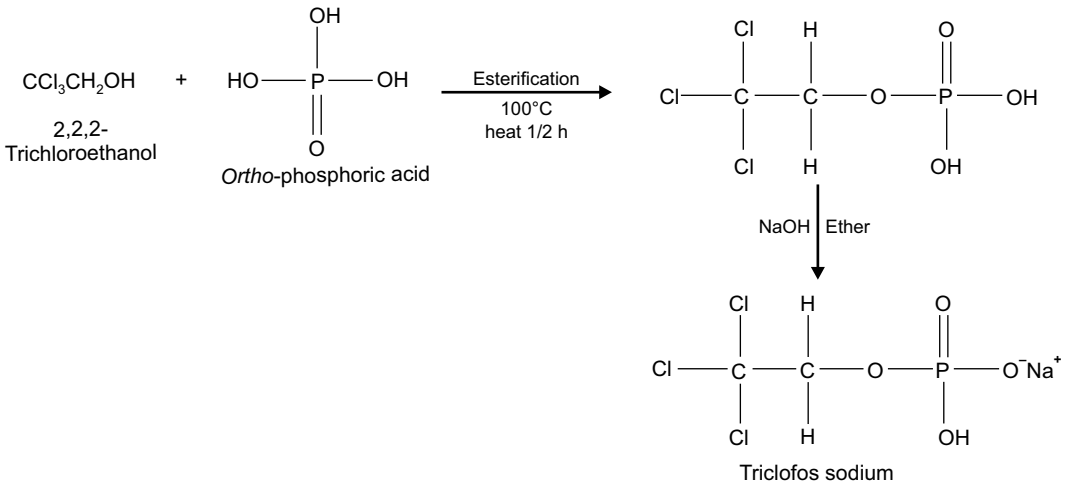
VI. Miscellaneous

1. Triclofos sodium



2,2,2-Trichloroethanol dihydrogen phosphate monosodium

Synthesis



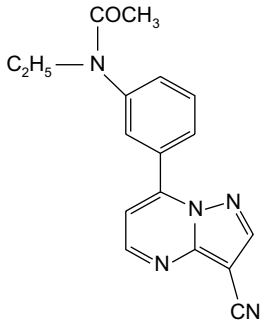
Triclofos sodium

Properties and uses: It is a white or almost white powder, hygroscopic in nature. Freely soluble in water, slightly soluble in ethanol, practically insoluble in ether. Used as hypnotic.

Preparation: Triclofos oral solution BP.

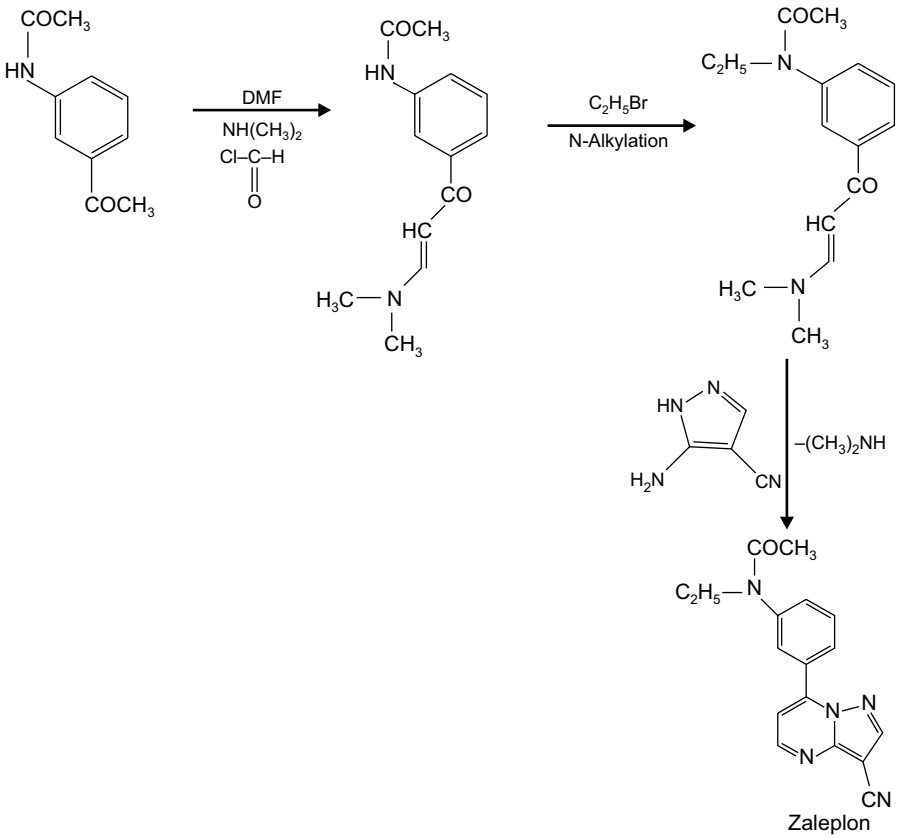
VII. Newer Agents

1. **Zaleplon** (Zaplon, Zaso)



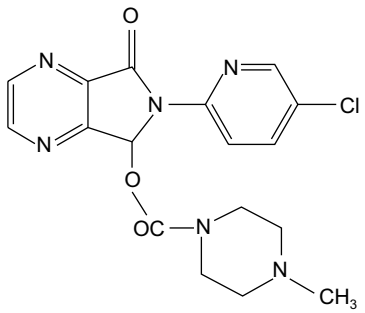
Properties and uses: Zaleplon is a non-benzodiazepine pyrazolopyrimidine derivative of a short-acting sedative and hypnotic. It acts as a selective agonist at the benzodiazepine α-receptor subunit on the GABA receptor complex in the brain. Subunit modulation of the GABA-BZD receptor is hypothesized to be responsible for its hypnotic properties.

Synthesis

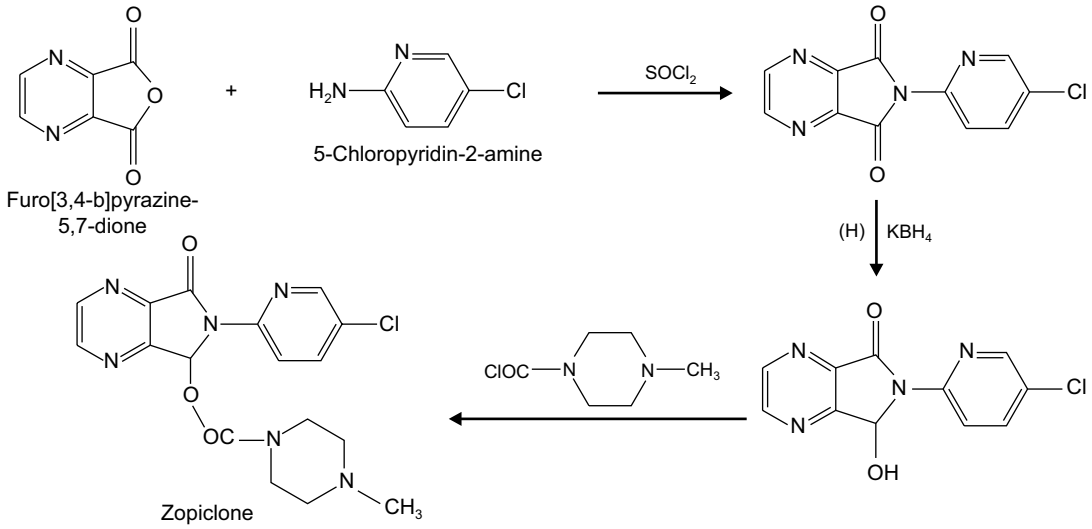


Dose: For insomnia: Adult—10 mg before bedtime. Maximum: 20 mg daily. Elder less than 65 year—5 mg before bedtime. Maximum 10 mg daily.

2. **Zopiclone** (Ziclone, Zopicon, Zonap)



Synthesis



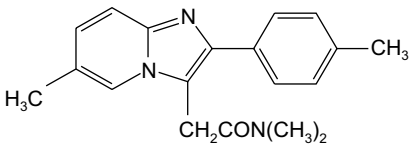
Properties and uses: It is a white or slightly yellowish powder, insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and insoluble in alcohol. It dissolves in dilute mineral acids. It is a new hypnotic agent structurally unrelated to barbiturates and benzodiazepines. It binds to the $GABA_A$ benzodiazepine receptor complex.

Assay: Dissolve the sample in a mixture of 10 ml of anhydrous acetic acid and 40 ml of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

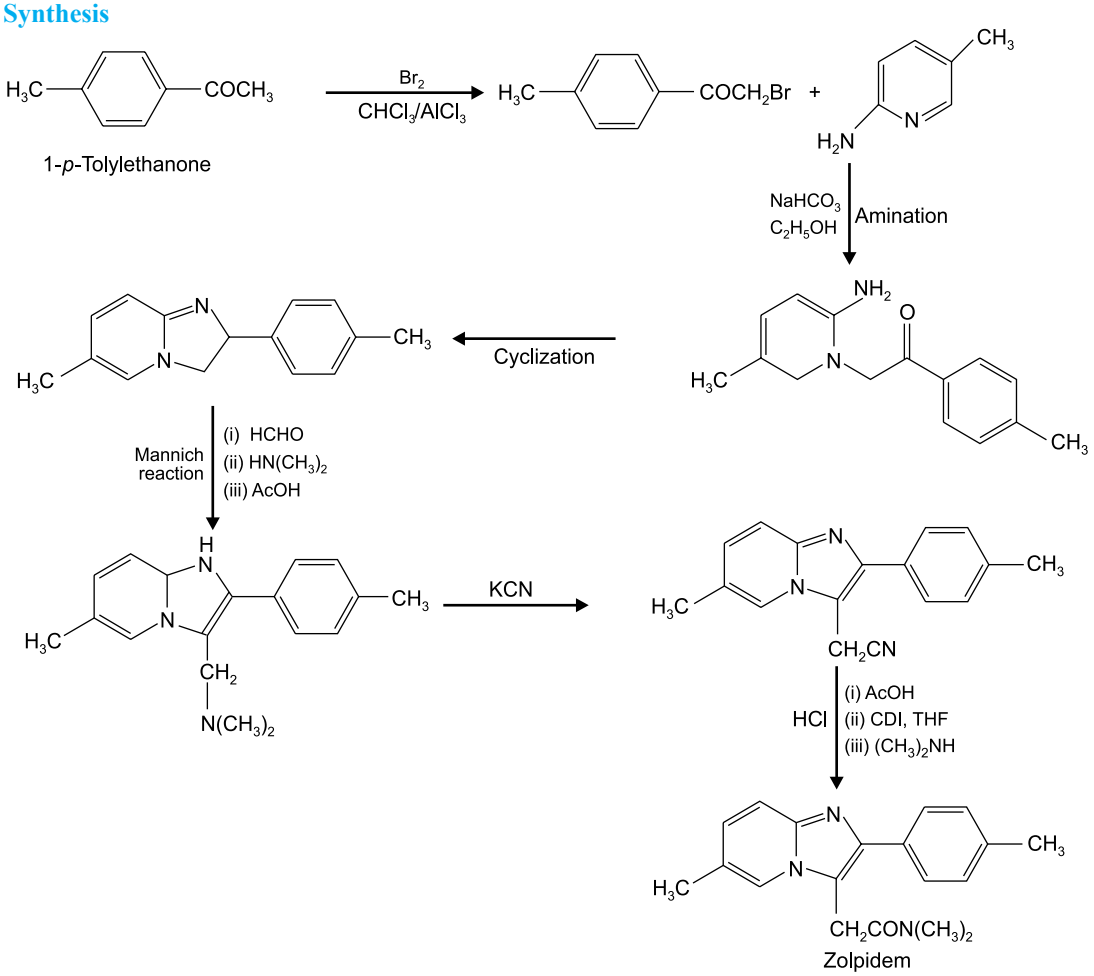
Dose: For short-term management of insomnia: Adult—7.5 mg at bedtime. Elderly—initially, 3.75 mg at bedtime.

3. Zolpidem



Properties and uses: It is a white or almost white crystalline powder, hygroscopic in nature, slightly soluble in water, sparingly soluble in methanol, and insoluble in methylene chloride. It is an imidazopyridine agent and is an agonist at the benzodiazepine α_1-receptor subunit of the $GABA_A$ receptor, used for the management of insomnia. The selective binding at α_1-receptors subunits of $GABA_A$ may explain the relative absence of myorelaxant and anticonvulsant effects as well as the preservation of deep sleep in human.

Synthesis

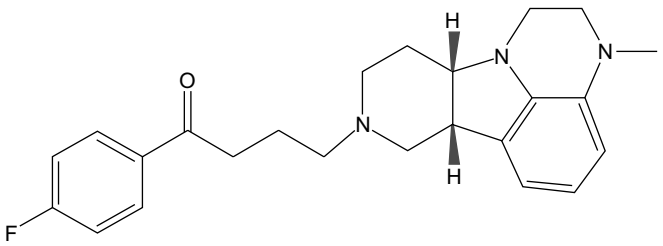


Assay: Dissolve the sample in a mixture of 20 ml of anhydrous acetic acid and 20 ml of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

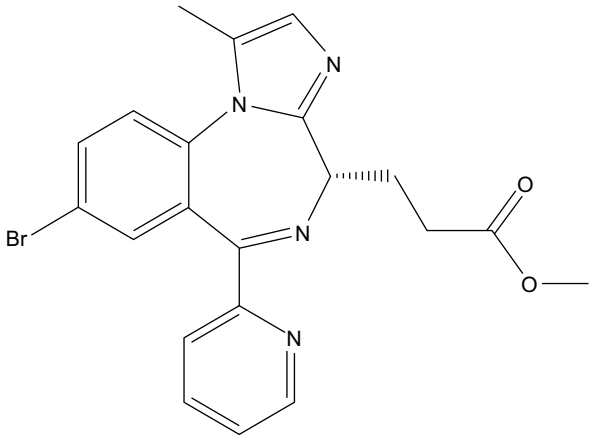
Newer Drugs

Lumateperone



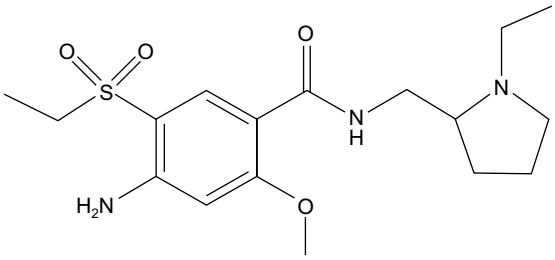
Uses: It is used as an antipsychotic drug.

Remimazolam



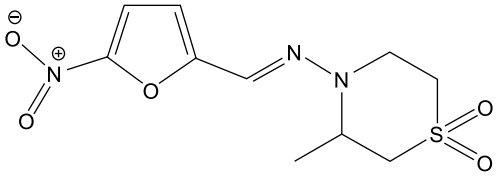
Uses: It is used as a sedative and hypnotic.

Amisulpride



Uses: It is used as an antiemetic and antipsychotic agent.

Nifurtimox

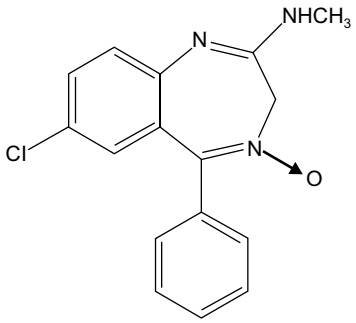


Uses: It is used to treat Chagas disease and sleeping sickness.

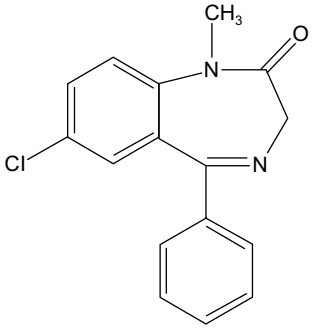
CLASSIFICATION BASED ON PCI SYLLABUS

Benzodiazepines

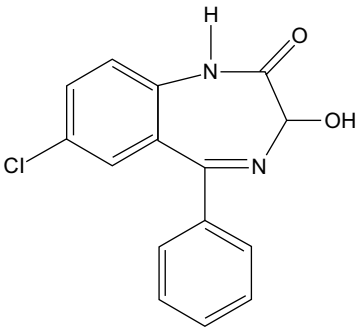
Chlordiazepoxide



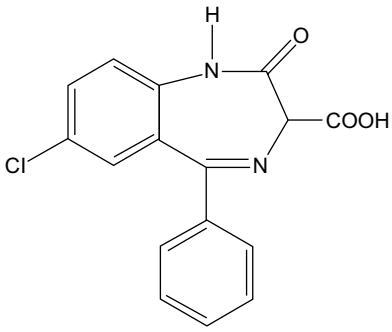
Diazepam



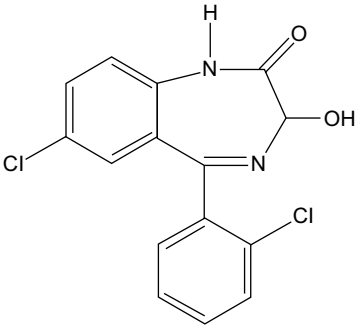
Oxazepam



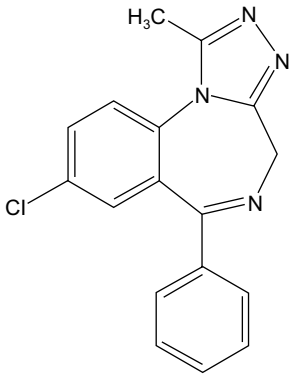
Chlorazepate



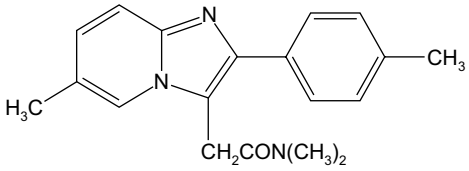
Lorazepam



Alprazolam

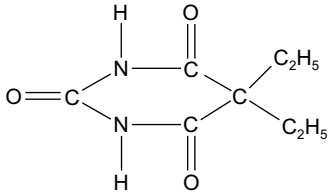


Zolpidem

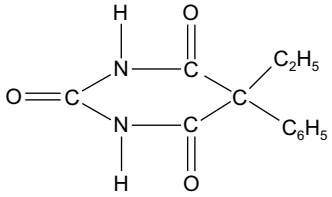


Barbiturates

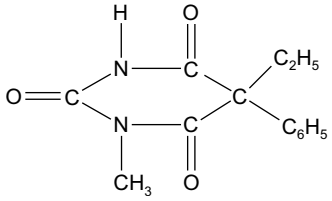
Barbital



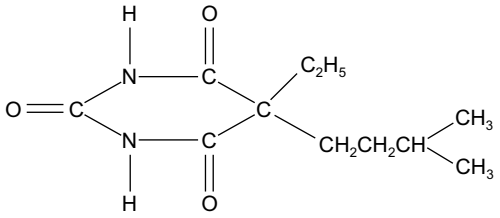
Phenobarbital



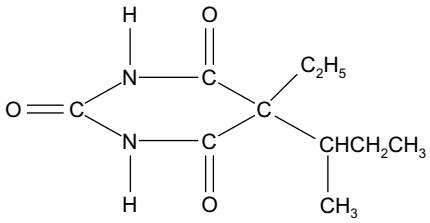
Mephobarbital



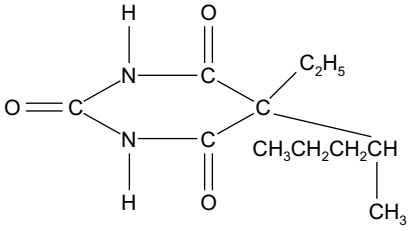
Amobarbital



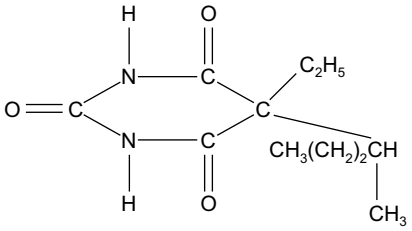
Butabarbital



Pentobarbital

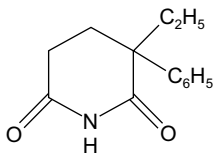


Secobarbital

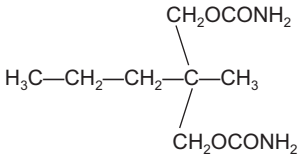


Miscellaneous

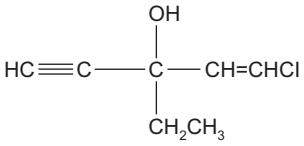
Glutethmide



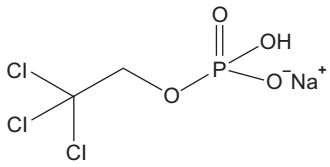
Meprobamate



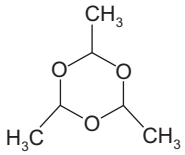
Ethchlorvynol



Triclofos sodium



Paraldehyde



Triclofas sodium

Properties and uses: It is a prodrug and metabolized in the liver and converted into trichloroethanol which is the active metabolite. Long-term usage of the drug is limited because it leads to liver damage.

PROBABLE QUESTIONS

1. Define and classify sedatives and hypnotics. Explain how the cyclic ureide barbituric acid may be prepared from (a) urea and malonyl dichloride and (b) urea and diethyl malonate.
2. Why the thiobarbiturates get metabolized *in vivo* faster than the barbiturates? Explain.
3. Explain the SAR of benzodiazepines.
4. How can the long-acting barbiturate phenobarbitone sodium be synthesized?
5. Name the barbiturate having allyl group at C-5 in the barbituric acid. Write its synthesis and uses.
6. Mention a drug having pyrimidine nucleus used as sedative and hypnotic. Write its structure, chemical name, synthesis, and uses.
7. A class of barbiturates find their use in the treatment of insomnia and preoperative medication. Name two potent drugs and discuss the synthesis of any one of them.

8. Write a note on triazolobenzodiazepines used as sedative and hypnotic.
9. Based on quinazolinone nucleus, a potent hypnotic drug was introduced. Name the compound and write its structure, synthesis, and uses.
10. Outline the metabolic pathway and mode of action of benzodiazepines and barbiturates.
11. Outline the synthesis of meprobamate and nitrazepam.
12. Write the structure, chemical name, and uses of a potent hypnotic drug having a benzodiazepine nucleus. Outline its synthesis and metabolic pathway.
13. Explain the following with suitable examples: (a) mode of action of barbiturates and (b) SAR of barbiturates.
14. A brand of barbiturates are usually employed to cause general anaesthesia and control convulsions. Name any one potent member and write its synthesis and metabolism *in vivo*.
15. Write a note on long-acting barbiturates.

SUGGESTED READINGS

1. Abraham DJ (ed). *Burger's Medicinal Chemistry and Drug Discovery* (6th edn). New Jersey: John Wiley, 2007.
2. Berger FM. 'Spinal cord depressant drugs'. *Pharmacol Rev* 1: 243–78, 1949.
3. *British Pharmacopoeia*. Medicines and Healthcare Products Regulatory Agency. London, 2008.
4. Bruntan LL, Lazo JS, and Parker KL. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics* (11th edn). New York: McGraw Hill, 2006.
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CHAPTER 24

General Anaesthetics

INTRODUCTION

General anaesthetics are group of drugs that produces loss of consciousness, and therefore, loss of all sensations. The absolute loss of sensation is termed as anaesthesia. General anaesthetics bring about descending depression of the central nervous system (CNS), starting with the cerebral cortex, the basal ganglia, the cerebellum, and finally the spinal cord. These drugs are used in surgical operations to induce unconsciousness and, therefore, abolish the sensation of pain.

Horace Wills, a dentist, in 1844 successfully used N_2O as an anaesthetic for tooth extraction. Mortan, a dentist, demonstrated ether as an anaesthetic agent and it became popular. In 1847, chloroform was used by Simpson in Britain for obstetrical purposes. The first intravenous anaesthetic, thiopentone, was introduced in 1935. In 1901, Mayer and Overton pointed out a direct parallelism between lipid/water partition coefficient of general anaesthetics and their anaesthetic property known as minimal alveolar concentration (MAC).

MAC is the lowest concentration of an anaesthetic in pulmonary alveoli that is needed to produce immobility in response to a painful stimulus in 50% of the individuals. MAC of a number of general anaesthetics shows excellent correlation with their oil/gas partition coefficients. However, this only reflects the capacity of anaesthetics to enter into the CNS and attain sufficient concentration in the neuronal membrane.

The basic molecular targets show that the ligand-gated ion channels are the major target of anaesthetic action. Many inhalation anaesthetics, such as barbiturates, benzodiazepines, and propofol potentiate the action of inhibitory transmitter GABA to open chloride channels. The action of glycine transmitter, which also activates chloride channels in the spinal cord and medulla, is augmented by barbiturates, propofol, and many other inhalation anaesthetics. N_2O and ketamine do not act on GABA or glycine, but they selectively inhibit the excitatory N-methyl D-aspartate (NMDA) type of glutamate receptor.

TYPES OF GENERAL ANAESTHETICS

General anaesthetics are usually given through inhalation or by intravenous injection.

Inhalation anaesthetics: Nitrous oxide, a gas at ambient temperature and pressure, continues to be an important compound of many anaesthesia regimens. Halothane, enflurane, isoflurane, desflurane, sevaflurane, and methoxyflurane are volatile liquids.

Intravenous anaesthetics: Several drugs are used intravenously, alone, or in combination with other

drugs to achieve an anaesthetic state for minute surgery of the patients in the intensive care unit. These drugs include the following:

1. Barbiturates (thiopental, methohexital)
2. Benzodiazepines (midazolam, diazepam)
3. Opioid analgesics (morphine, fentanyl, sulfentanyl, afentanil, remifentanil)
4. Propofol
5. Ketamine
6. Miscellaneous (droperidol, etomidate, dexmedetomide)

Mode of action: General anaesthetics target the ligand-gated ion channels and produce the anaesthetic action. The GABA receptor-gated chloride channels are the most important sites and open to perform the inhibitory action. N_2O and ketamine do not affect the GABA or glycine-gated Cl-channel, but they selectively inhibit the excitatory NMDA type of glutamate receptor, which belongs to calcium-gated channels in the neurons and leads to neuronal hyperpolarization.

STAGES OF ANAESTHESIA

Stage I (analgesia): The patient is conscious and experiences sensations of warmth, remoteness, drifting, falling, and giddiness. There is a marked reduction in the perception of painful stimuli. This stage is often used in minor surgery.

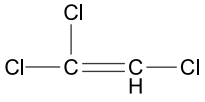
Stage II (delirium): This stage begins with the loss of consciousness. Depression of higher centres produces variety of effects including excitement, involuntary activity, and increased skeletal muscle tone, and the respiration is typically irregular.

Stage III (surgical anaesthesia): This is the stage of unconsciousness and paralysis of reflexes, respiration is regular and blood pressure is maintained. All surgical procedures are carried out in this stage.

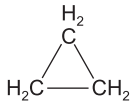
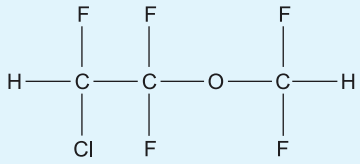
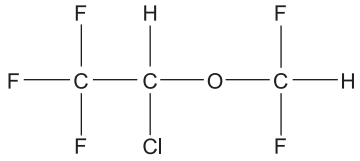
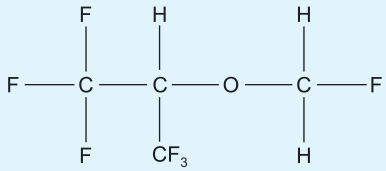
Stage IV (medullary paralysis): Respiratory and circulatory failures take place as a result of the depression of the vital centres of the medulla, and brain stem occurs.

CLASSIFICATION

I. Volatile/Inhalation Anaesthetics

S. No.	*Name*	*Formula/Structure*
1.	Chloroform	$CHCl_3$
2.	Diethyl ether	$C_2H_5OC_2H_5$
3.	Divinyl ether	$H_2C=CHOCH=CH_2$
4.	Trichloroethylene	

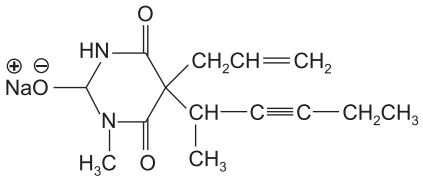
Contd.

S. No.	Name	Formula/Structure
5.	Ethyl chloride	CH_3CH_2Cl
6.	Cyclopropane	
7.	Halothane	$CF_3CHClBr$
8.	Tribromoethanol	Br_3CCH_2OH
9.	Fluroxene	$CF_3CH_2OCH=CH_2$
10.	Methoxyflurane	$CHCl_2CF_2OCH_3$
11.	Enflurane	
12.	Isoflurane	
13.	Sevoflurane	

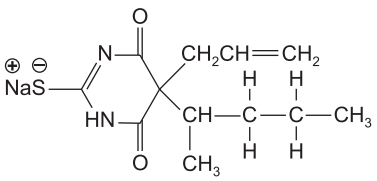
II. Non-volatile or Intravenous Anaesthetics

a. Ultrashort-acting barbiturates

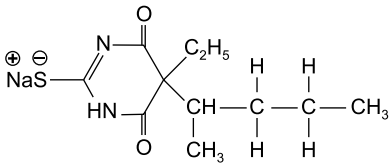
Methohexital sodium



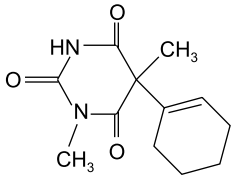
Thiomylal sodium



Thiopental sodium

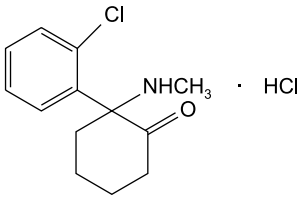


Hexobarbital



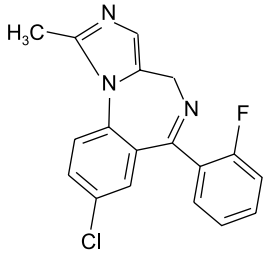
b. Aryl cyclohexylamines

Ketamine



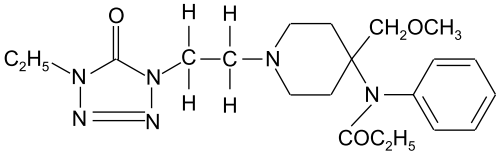
c. Benzodiazepines

Midazolam

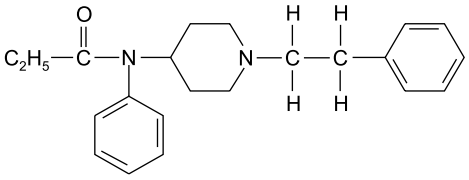


d. Narcotic analgesics

Alfentanyl

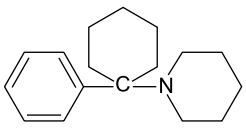


Fentanyl

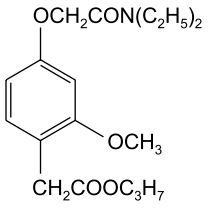


e. Miscellaneous

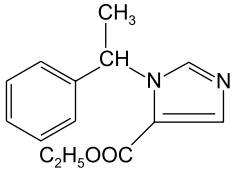
Phencyclidine



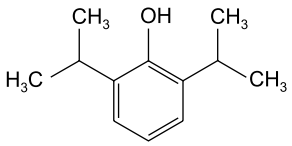
Propanidid



Etomidate



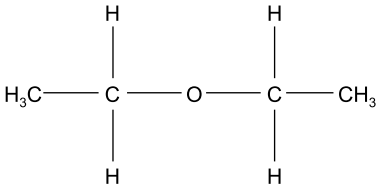
Propofol



SYNTHESIS AND DRUG PROFILE

I. Volatile/Inhalation Anaesthetics

1. Ether (Diethyl ether)



1,1-Oxybisethane

Synthesis

(i) $C_2H_5OH + H_2SO_4 \xrightarrow{130–137°C} C_2H_5HSO_4 + H_2O$

$C_2H_5HSO_4 + C_2H_5OH \longrightarrow C_2H_5—O—C_2H_5 + H_2SO_4$

Diethyl ether

(ii) Williamson's ether synthesis

$C_2H_5ONa + C_2H_5Br \longrightarrow C_2H_5OC_2H_5 + NaBr$

Sodium ethoxide — Bromoethane — Ethoxyethane

(iii) $H_2C{=}CH_2 + H_2SO_4 \longrightarrow C_2H_5HSO_4$

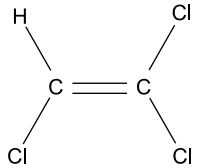
$C_2H_5HSO_4 \xrightarrow{C_2H_5OH} C_2H_5—O—C_2H_5 + H_2SO_4$

Diethyl ether

Properties and uses: It is a clear, colourless liquid, volatile, highly flammable, soluble in water, miscible with alcohol, methylene chloride, and with fatty oils. Low molecular weight ethers display anaesthetic activity that increases along with toxicity as the chain length increases. Introduction of unsaturation into the aliphatic ether increases potency and also shortens induction and emergence. Ether is an absolute anaesthetic with pungent, irritant odour. It is flammable and explosive at concentrations necessary for anaesthesia.

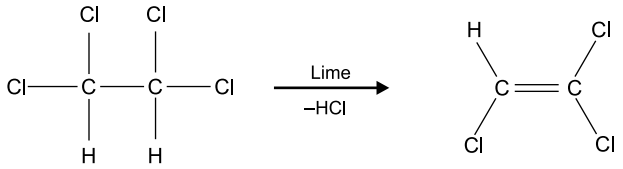
Storage: It should be stored in well-closed airtight containers and protected from light, stored at a temperature in between 8–15°C.

2. Trichloroethylene



1,1,2-Trichloroethene

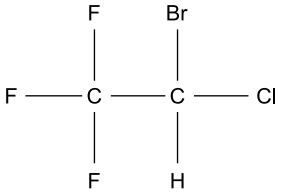
Synthesis



Tetrachloroethane — Trichloroethylene

Properties and uses: It may be used sporadically as a weak volatile anaesthetic, administered through inhalation. It possess an excellent analgesic property. It is frequently employed in short surgical operations, where a mild anaesthesia having potent analgesia is desired.

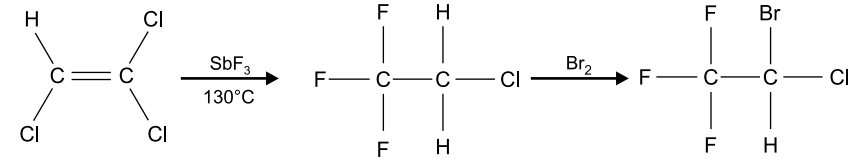
3. Halothane



2-Bromo-2-chloro-1,1,1-trifluoroethane

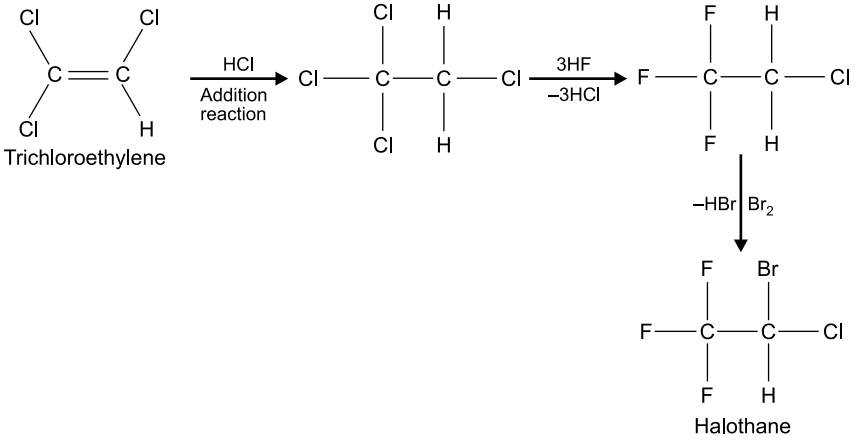
Synthesis

Route I. From: Trichloroethylene



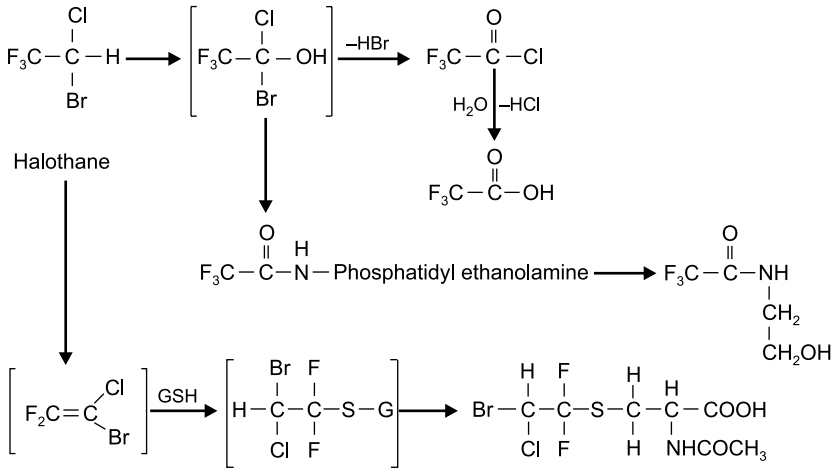
Trichloroethylene — Halothane

Route II. From: Trichloroethylene



Trichloroethylene — Halothane

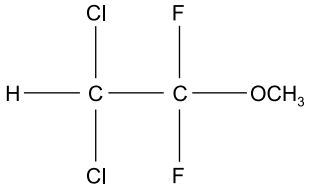
Metabolism: It is metabolized to three major metabolic products, trifluoroacetic acid, N-trifluoroacetyl ethanolamine, and N-acetyl-S-(2-bromo,2 chloro-1,1-difluoroethyl)-L-cysteine.



Properties and uses: It is a clear, colourless, heavy, non-flammable liquid, slightly soluble in water, miscible with ethanol, and with trichloroethylene. Halothane lacks flammability. It may produce any depth of anaesthesia without causing hypoxia. Being a non-irritant, its inherent hypotensive effect retards capillary bleeding and renders a comparatively bloodless field. It is a potent, relatively safe general inhalation anaesthetic used in conjunction with N_2O. For skeletal muscle relaxation, it is used with succinyl choline or tubocurarine.

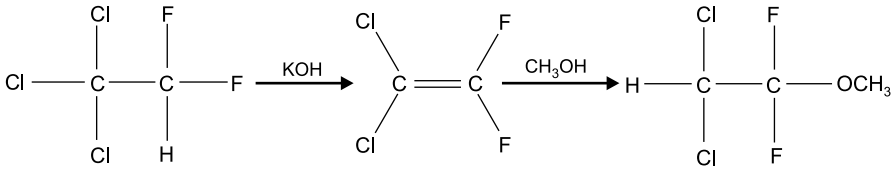
Storage: It should be stored in well-closed, airtight containers, protected from light, at a temperature not exceeding 25°C in a non-reactive metal container.

4. Methoxy flurane



(2,2-Dichloro-1,1-difluoroethyl) (methyl) ether

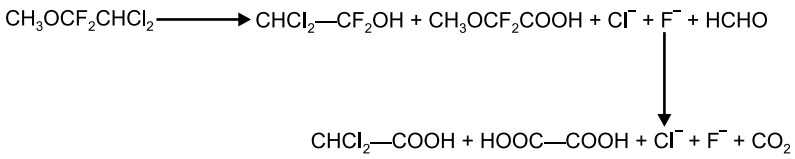
Synthesis



1,1-Difluoro-2,2,2-trichloro ethane

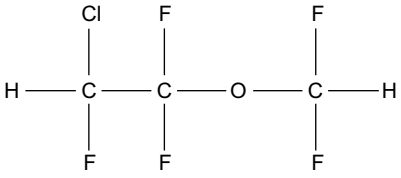
Methyl flurane

Metabolism: It is metabolized in the liver to produce fluoride ions, oxalic acid, difluoro methoxyacetic acid, and dichloroacetic acid. The high concentration of fluoride ions causes renal damage.



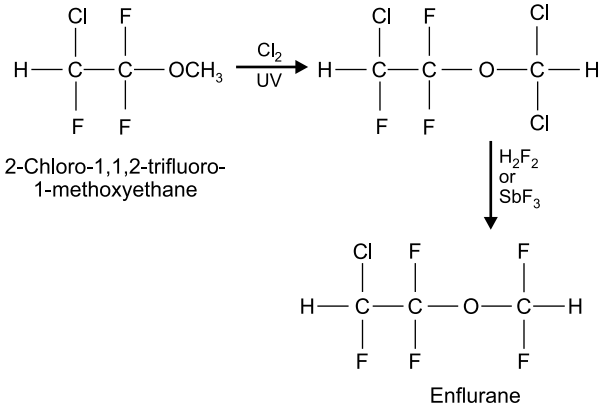
Properties and uses: It is a clear, colourless liquid, non-inflammable and non-explosive in air or oxygen in anaesthetic concentrations. It is the most potent of the inhalational agents. It is employed to cause light anaesthesia with deep analgesic and muscle relaxation feature, which makes it convenient for surgical operations.

5. Enflurane



(2-Chloro-1,1,2-trifluoroethyl) (difluoromethyl) ether

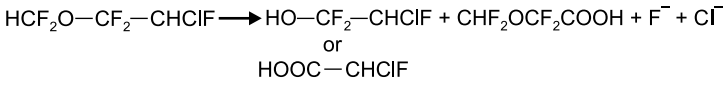
Synthesis



2-Chloro-1,1,2-trifluoro-1-methoxyethane

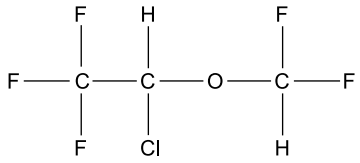
Enflurane

Metabolism: The principal metabolites are difluoromethoxy difluoroacetic acid and fluoride ion.



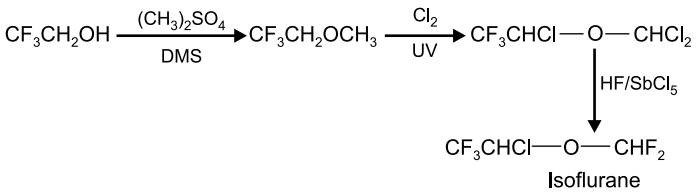
Properties and uses: It is a clear, colourless, volatile liquid with pleasant hydrocarbon-like odour. Soluble in water, miscible with organic solvents, chemically it is extremely stable. The induction of an emergence from anaesthesia and adjustment of anaesthetic depth during maintenance is smooth and moderately rapid. It is a non-inflammable halogenated ether anaesthetic and provides rapid induction with no excitement.

6. Isoflurane

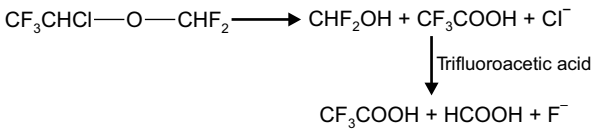


(1-Chloro-2,2,2-trifluoroethyl)(difluoromethyl) ether

Synthesis



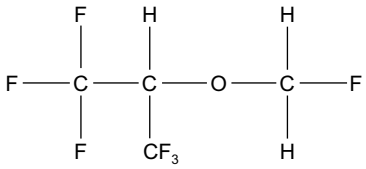
Metabolism: It is metabolized to trifluoroacetic acid and fluoride ion.



Properties and uses: It is a clear, colourless, heavy liquid, insoluble in water, miscible with ethanol, and trichloroethylene. It resembles its isomer enflurane in its properties. It is not flammable in air or oxygen. The depth of anaesthesia can be rapidly adjusted with it. Used for induction and maintenance of general anaesthesia.

Storage: It should be stored in well-closed airtight containers and protected from light.

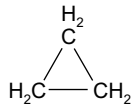
7. Sevoflurane



1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane

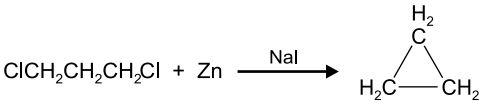
Properties and uses: Low boiling liquid with a slight odour; miscible with most organic solvents including fats or oils; practically insoluble in water. It is a non-flammable, non-irritating agent. The physical properties of this compound result in a more rapid induction and termination of anaesthetic when observed with the currently used agents.

8. Cyclopropane (Trimethylene)



Cyclopropane

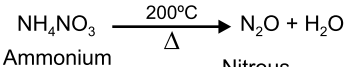
Synthesis



1,3-Dichloro propane — Cyclopropane

Properties and uses: It is non-irritant in nature and ensures rapid recovery from anaesthesia. The adverse effects are depressant effects on respiration, tendency to induce cardiac arrhythmias, and enhanced haemorrhage. Cyclopropane is an anaesthetic gas with a rapid onset of action. It may be used for analgesia, induction, or maintenance of anaesthesia.

9. Nitrous oxide (N_2O)



Ammonium nitrate — Nitrous oxide

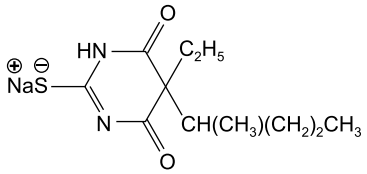
Properties and uses: It is a colourless gas, without appreciable odour to taste, soluble in water, freely soluble in alcohol, soluble in ether, or oils. This is the least toxic and least potent anaesthetic. It is a non-inflammable, non-irritating, and a powerful analgesic agent. Nitrous oxide is a weak anaesthetic with good analgesic properties, and relatively no skeletal muscle relaxant properties. It is an inhalation anaesthetic of choice in dental surgery.

II. Non-volatile or Intravenous Anaesthetics

a. Ultrashort-acting barbiturates

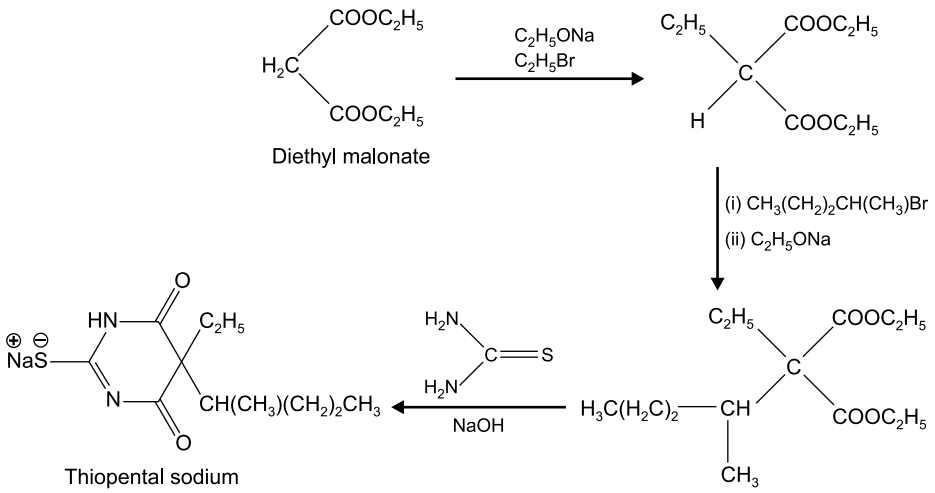
Metabolism of barbiturates: This is discussed in Chapter 23 'Sedatives and Hypnotics'.

1. Thiopentone sodium (Thiopental)



Sodium salt of 5-ethyl-5-(1-methyl butyl)-2-thiobarbiturate

Synthesis



Diethyl malonate

Thiopental sodium

Properties and uses: A yellowish-white powder, hygroscopic, freely soluble in water, and partly soluble in ethanol. These are usually administered intravenously for the production of complete anaesthesia of a short duration. It belongs to the category of ultrashort-acting barbiturates. Onset is rapid (about 30 sec) and duration is brief (10–30 min). By rectal route it is administered as a solution, suspension, or suppositories as basal anaesthetic. It is also used as a sedative, hypnotic, and anticonvulsant.

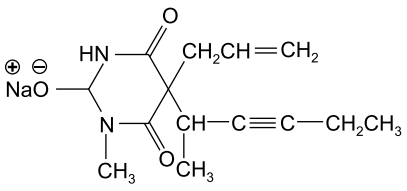
Assay for sodium: Dissolve the sample in water, add 0.1 ml of methyl red solution, and titrate with 0.1 M hydrochloric acid until a red colour is obtained. Boil the mixture gently for 2 min, cool it, and, if necessary, continue the titration with 0.1 M hydrochloric acid until the red colour is again obtained.

Assay for thiopental: Dissolve the sample in water, add 2 ml of dilute sulphuric acid, and shake with chloroform. Filter and evaporate the filtrate to dryness on a water-bath. Dissolve the residue in 30 ml of previously neutralized dimethylformamide and add thymol blue in methanol. Titrate immediately with 0.1 M lithium methoxide until a blue colour is obtained.

Storage: It should be stored in well-closed airtight containers and protected from light.

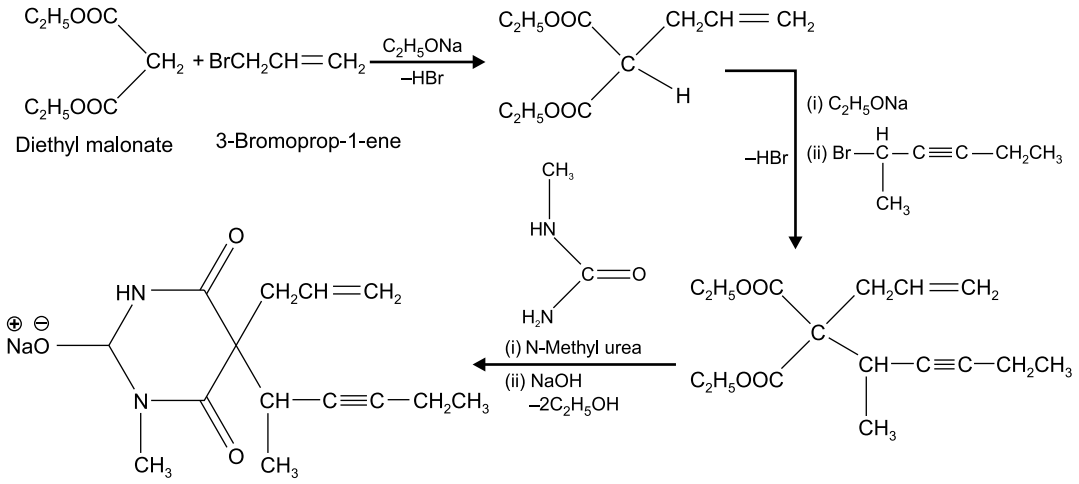
Dosage forms: Thiopental injection BP.

2. Methohexital sodium



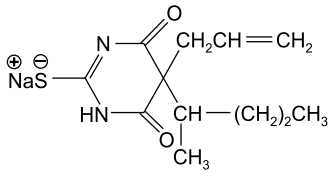
Sodium salt of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl) barbiturate

Synthesis



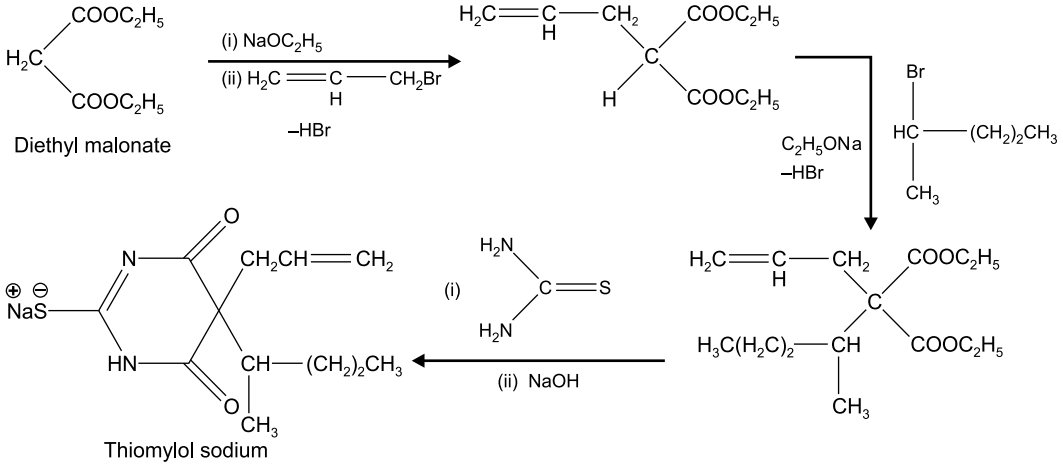
Properties and uses: White to off-white hygroscopic powder, essentially odourless, and the solution is alkaline to litmus, soluble in water. Methohexital produces more rapid recovery from unconsciousness than thiopental. It is more potent and has shorter duration of action. It is used for the induction of anaesthesia through the intravenous administration. It has two advantages over thiopental sodium. First, being it has less affinity towards fatty tissues and second, it has a greater potency. Its onset of action is quite speedy comparable to thiopental sodium while its recovery is more rapid. For these reasons, this intravenous anaesthetic is specifically useful for short surgical operations, such as oral surgery, gynaecological investigation, genitourinary procedures, and electroconvulsive therapy.

3. Thiomylal sodium



Sodium salt of 5-allyl-5-(1-methyl butyl)-2-thiobarbiturate

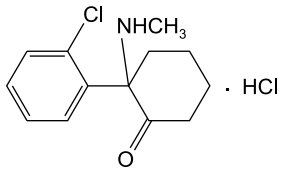
Synthesis



Properties and uses: Thiomylal is a highly hydrophobic thiobarbiturate having its structural features very much related to thiopental. Its biological activities are almost identical to thiopental. Used as intravenous anaesthetic.

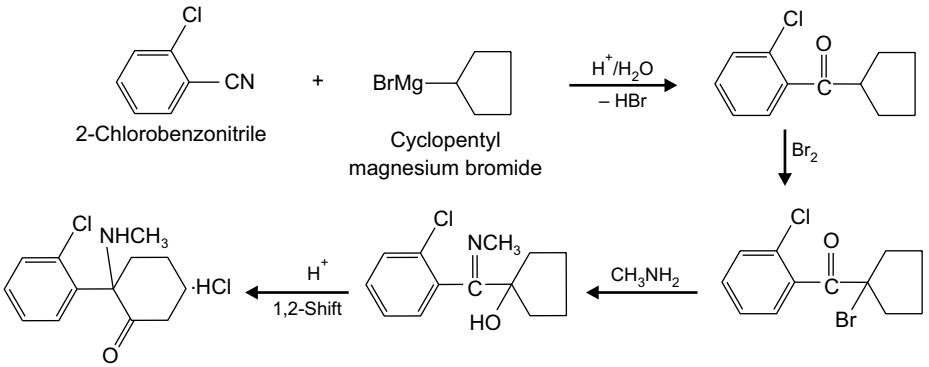
b. Arylcyclohexylamines

1. Ketamine HCl



2-(2-Chloro phenyl)-2-(methylamino) cyclohexanone

Synthesis



Ketamine hydrochloride

Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, methanol, and ethanol. Its another name is 'dissociative anaesthetic' because it produces unpleasant hallucinations and strong feelings of dissociation from the environment. It is a rapidly acting non-barbiturate general anaesthetic that produces anaesthesia and is characterized by profound analgesia.

Assay: Dissolve the substance in methanol and add 1.0 ml of 0.1 M hydrochloric acid, and perform potentiometric titration, using 0.1 M sodium hydroxide.

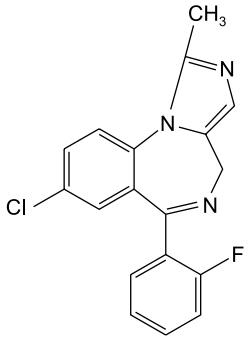
Storage: It should be stored in well-closed airtight containers, protected from light.

Dosage forms: Ketamine HCl injection IP, BP.

c. Benzodiazepines

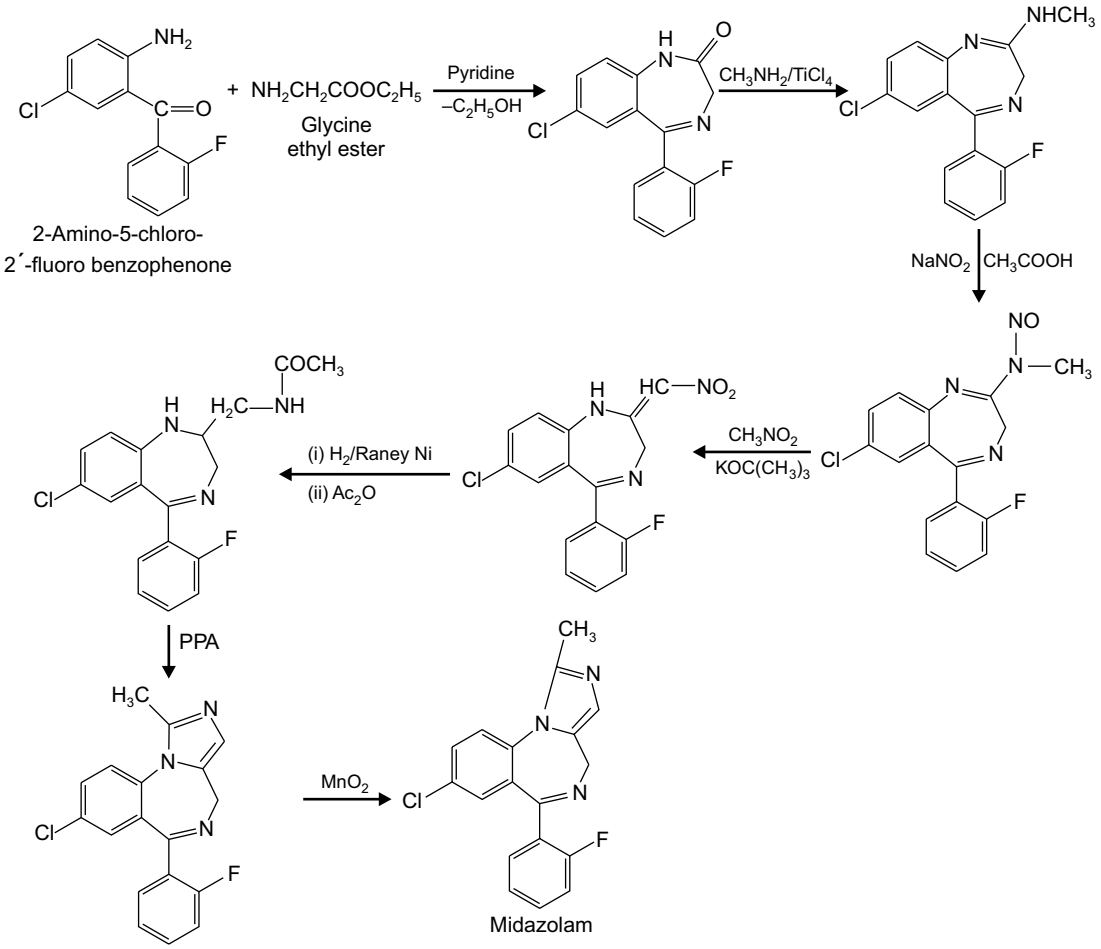
Metabolism: This is discussed in Chapter 23, 'Sedatives and Hypnotics'.

1. Midazolam



8-Chloro-6-(2-fluorophenyl)-1-methyl-imidazo[1,4]benzodiazepine

Synthesis



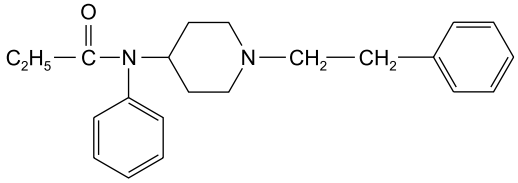
Properties and uses: It is a white or yellowish, crystalline powder, soluble in acetone, ethanol, and methanol, but insoluble in water. Midazolam has been used adjunctively with gaseous anaesthetics. The onset of CNS effect is slower than that of thiopental and it has a longer duration of action.

Assay: Dissolve the sample in anhydrous acetic acid and add aceticanhydride, titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Dosage forms: Midazolam injection BP.

d. Narcotic analgesics

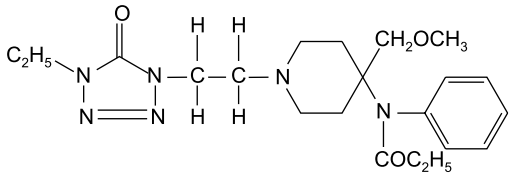
1. Fentanyl



N-(1-phenyl ethyl-4-piperidinyl) propionanilide

Synthesis and drug profile is discussed in Chapter 29 'Narcotic Analgesics'.

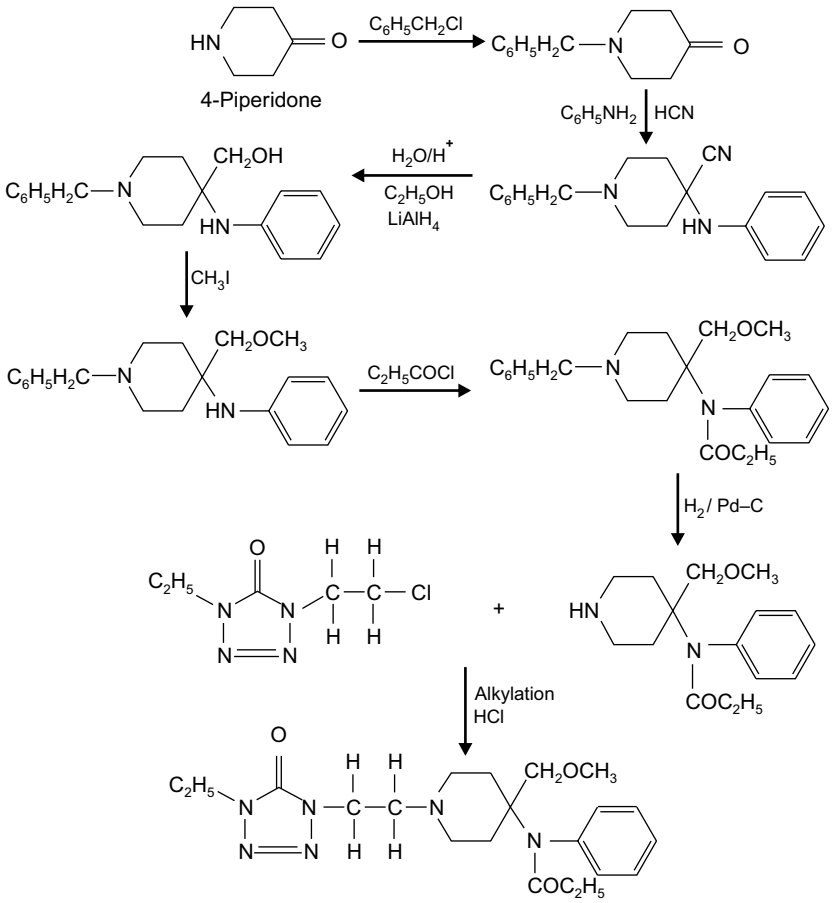
2. Alfentanil



N-[1-[2-(4,5-dihydro-5-oxo-tetrazol-1-yl)ethyl]-4-(methoxy methyl)-4-piperidinyl]-N-phenyl propionamide

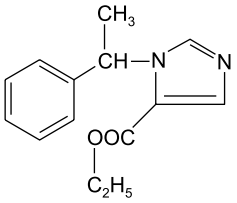
Properties and uses: It is closely related to fentanyl. It is a potent analgesic used as a primary anaesthetic or as an adjunct in the maintenance of anaesthesia. It has the same properties and side effects as fentanyl. It relieves moderate to severe break through pain.

Synthesis



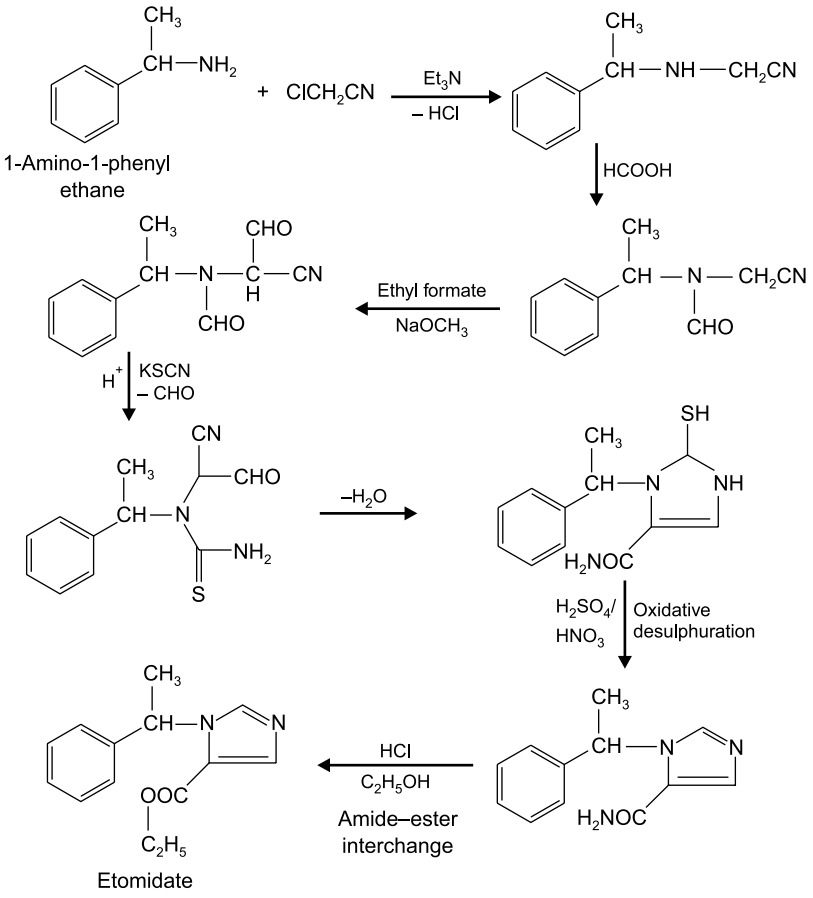
e. Miscellaneous

1. Etomidate



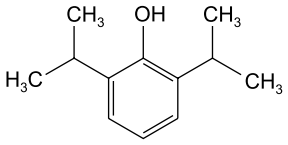
Ethyl-1-(1-methyl benzyl) imidazol-5-carboxylate

Synthesis



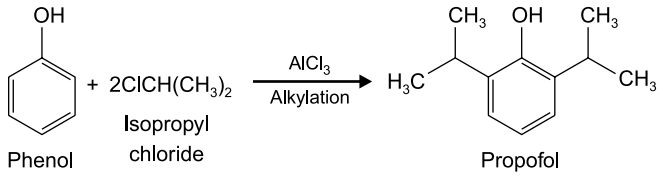
Properties and uses: It contains a 4-carboxylic acid ester-substituted imidazole moiety, which is also present in a number of compounds that are structural variants of the triazolo and imidazolo benzodiazepines. It is a positive allosteric modulator of GABA receptors.

2. Propofol



2,6-Diisopropyl phenol

Synthesis



Properties and uses: It is colourless or is a very light yellow in colour, clear liquid, very slightly soluble in water, miscible with hexane and with methanol. Propofol is useful for induction and maintenance of anaesthesia.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light under an inert gas.

Dosage forms: Propofol injection BP.

CLASSIFICATION BASED ON PCI SYLLABUS

Inhalation Anaesthetics

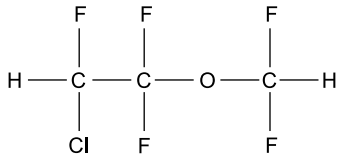
Halothane

$CF_3CHClBr$

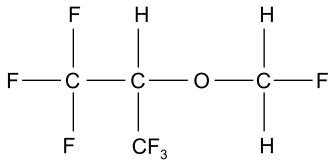
Methoxyflurane

$CHCl_2CF_2OCH_3$

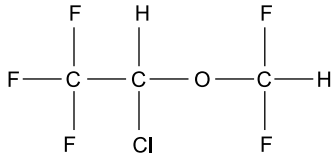
Enflurane



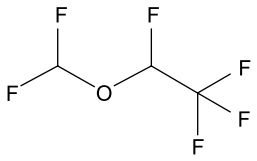
Sevoflurane



Isoflurane

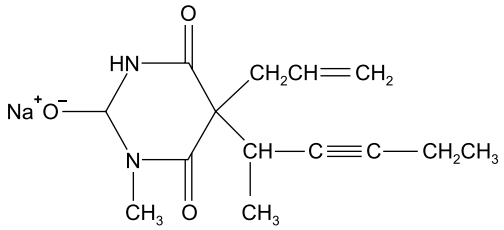


Desflurane

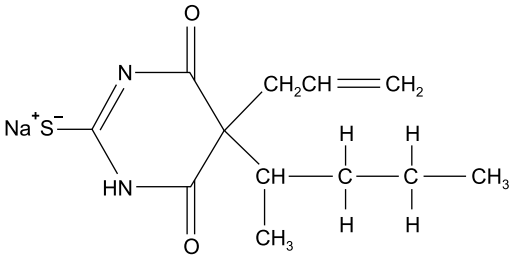


Ultrashort-acting Barbitutrates

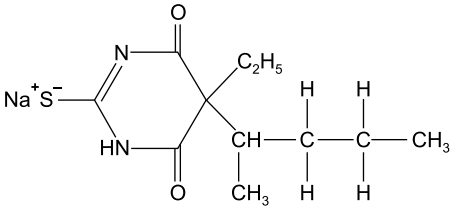
Methohexital sodium



Thiomylal sodium

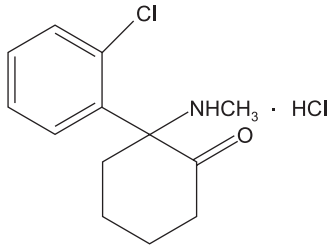


Thiopental sodium



Dissociative Anaesthetics

Ketamine hydrochloride



Methoxyflurane:

Properties and uses: It is administered by inhalation route. It is used to relief pain in trauma.

PROBABLE QUESTIONS

1. Define and classify general anaesthetics. Outline the synthesis of any two drugs synthesis that belongs to intravenous anaesthetics.
2. Write the different stages of anaesthesia and explain the mode of action of general anaesthetics.
3. How will you classify general anaesthetics? Write the structure, chemical name, and uses of two drugs from each class.
4. Write the synthesis of general anaesthetic having pyrimidine nucleus.
5. Name the three derivatives of barbiturates that are used abundantly as intravenous anaesthetics. Write their structure, chemical name, and uses.
6. Mention a benzodiazepine derivative used as a general anaesthetic. Write its chemical name and synthesis.
7. Write a note on fluorinated compounds employed as inhalation anaesthetics.
8. Outline the synthesis and assay of the following general anaesthetics: (a) Sevoflurane and (b) halothane.
9. What are intravenous anaesthetics? Outline the synthesis of the following: (a) Thiopental sodium, (b) ketamine hydrochloride, and (c) methohexital sodium.

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CHAPTER 25

Local Anaesthetics

INTRODUCTION

Local anaesthetics are drugs that when applied directly to the peripheral nervous tissue blocks nerve conduction and abolish all the sensations in that part supplied by the nerve. They are generally applied to the somatic nerves and are capable of cutting on axons, cell body, dendrites, and synapses.

These are used in dentistry, in ophthalmology, in minor surgical operations, including endoscopy, and for relieving pain in certain medical conditions such as tumours growing in the spine. Local anaesthetics are also used topically for the temporary relief of pain from insect bites, burns, and other surface wounds.

Most local anaesthetic agents are weak bases, consisting of lipophilic groups connected by an intermediate chain to the tertiary amino groups. For therapeutic application, they are usually made available as salts to increase the solubility and the stability in the body. They exist either as the unchanged base or as a cation.

The clinically used local anaesthetics have minimal local irritant action and block sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse, and receptors that function through increased net (nerve) permeability. They also reduce the release of acetylcholine from motor nerve endings. Sensory and motor fibres are inherently and equally sensitive. The sensitivity is determined by the diameter of the fibres as well as by the fibre type. Diameters remaining the same, myelinated neurons are blocked earlier than non-myelinated neurons. Autonomic fibres are generally more susceptible than somatic fibres. Among the somatic afferent order of blockade is pain, temperature, sense, touch and deep pressure sense, since pain is generally carried out by smaller diameter fibres than those carrying other sensations or motor impulses.

In clinical practice, a solution of local anaesthetic (except cocaine) often contains a vasoconstrictor (epinephrine, norepinephrine or phenylephrine). The vasoconstrictor serves dual purpose by decreasing the rate of absorption. It not only localizes the anaesthetic at the desired site, but also limits the rate at which it is absorbed into the circulation. The vasoconstrictor prolongs the action and lowers the systemic toxicity of local anaesthetics.

Mode of action: Local anaesthetics block both the generation and the conduction of the nerve impulse. The blockade probably results from the biochemical changes caused by the drug. Immediately after the nerve impulse had passed, the pores again become smaller. Sodium ions are pumped out of the fibre, at the same time potassium ions are transported into the fibre. Local anaesthetic decreases the permeability of cell membrane to sodium, thus preventing sodium depolarization.

Metabolism of local anaesthetics: Clinically available local anaesthetics are broadly divided into esters (e.g. procaine) and non-esters (e.g. lignocaine). The esters are hydrolyzed by esterases enzyme into *p*-amino benzoic acid and corresponding alcohols. The non-ester types are primarily metabolized in the liver by CYP450, for example, lidocaine is converted primarily into 3-hydroxy lidocaine to form 3-hydroxy monoethyl glycine-xylidine. Both may be excreted in their conjugated form. Lidocaine also metabolized into 4-hydroxy-2,6-dimethylanilide and 2-amino-3-methyl benzoic acid from the precursor metabolite 2,6-xylidine. The 2,6-xylidine is also directly excreted in its conjugated form, and it is formed from monoethyl glycine-xylidine, which is an immediate metabolite of lidocaine.

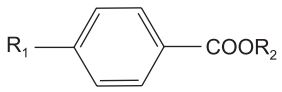
CLASSIFICATION

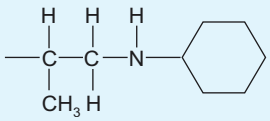
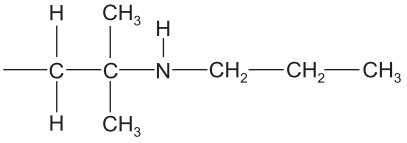
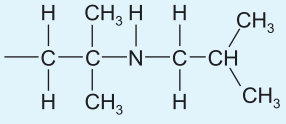
Local anaesthetics are generally classified into the following groups:

1. Natural agents: Cocaine
2. Synthetic nitrogenous compounds
   a. Derivatives of benzoic acid
   b. Derivatives of *p*-amino benzoic acid
      i. Freely soluble: Procaine, amethocaine.
      ii. Poorly soluble: Benzocaine, orthocaine
   c. Derivatives of acetanilide: Lignocaine, mepivacaine, bupivacaine, prilocaine, etidocaine.
   d. Derivatives of quinoline: Cinchocaine, dimethisoquin
3. Synthetic non-nitrogenous agents: Benzyl alcohol, propanediol
4. Miscellaneous drugs with local action: Clove oil, phenol, chlorpromazine and certain antihistamines, for example, diphenhydramine

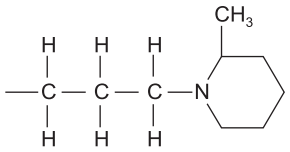
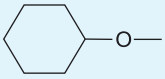
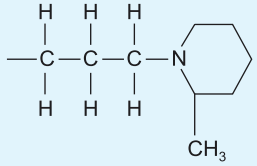
On the basis of chemical structure, local anaesthetics are classified as follows:

I. Benzoic acid derivatives

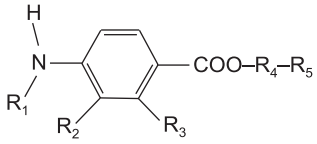


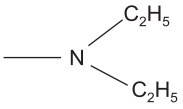
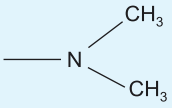
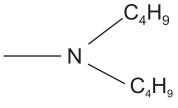
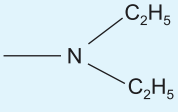
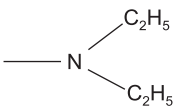
Name	R_1	R_2
Hexylcaine	–H	
Meprylcaine	–H	
Isobucaine	H	

Contd.

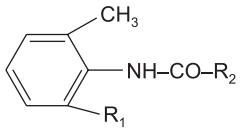
Name	R_1	R_2
Piperocaine	–H	
Cyclomethycaine		

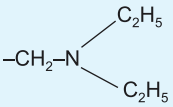
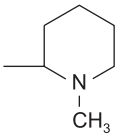
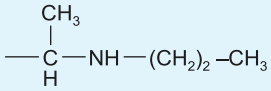
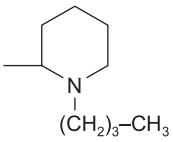
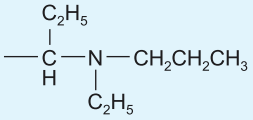
II. *p*-Amino benzoic acid derivatives



Name	R_1	R_2	R_3	R_4	R_5
Benzocaine	–H	–H	–H	$-CH_2-CH_3$	—
Butamben	–H	–H	–H	$-(CH_2)_3\ CH_3$	—
Procaine	–H	–H	–H	$-CH_2-CH_2-$	
Chlorprocaine	–H	–H	–Cl	$-CH_2-CH_2-$	
Tetracaine	–n-Butyl	–H	–H	$-CH_2-CH_2-$	
Butacaine	–H	–H	–H	$-CH_2-CH_2-CH_2$	
Binoxinate	–H	n-Butoxy	–H	$-CH_2-CH_2-$	
Propoxycaine	–H	–H	n-Propoxy	$-CH_2-CH_2-$	

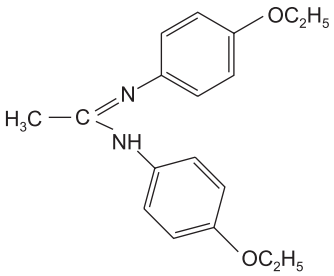
III. Anilide derivatives (2,6-Xylidines)



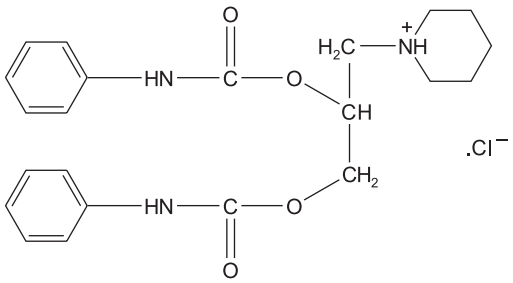
Name	R_1	R_2
Lidocaine/Lignocaine	$-CH_3$	
Mepivacaine	$-CH_3$	
Prilocaine	–H	
Bupivacaine	$-CH_3$	
Etidocaine	$-CH_3$	

IV. Miscellaneous

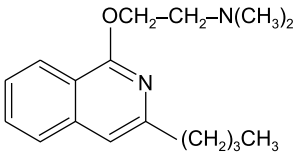
a. Phenacaine



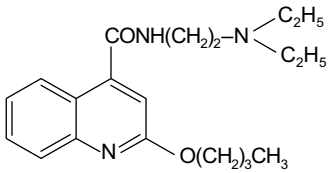
b. Diperodon HCl



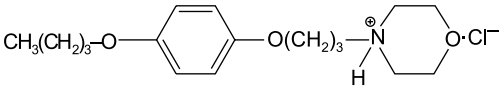
c. Dimethizoquine



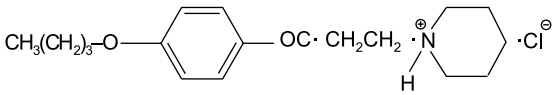
d. Dibucaine



e. Pramoxine HCl



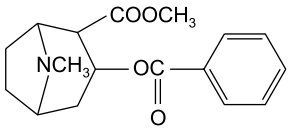
f. Dyclonine HCl



SYNTHESIS AND DRUG PROFILE

I. Benzoic Acid Derivatives

a. Cocaine

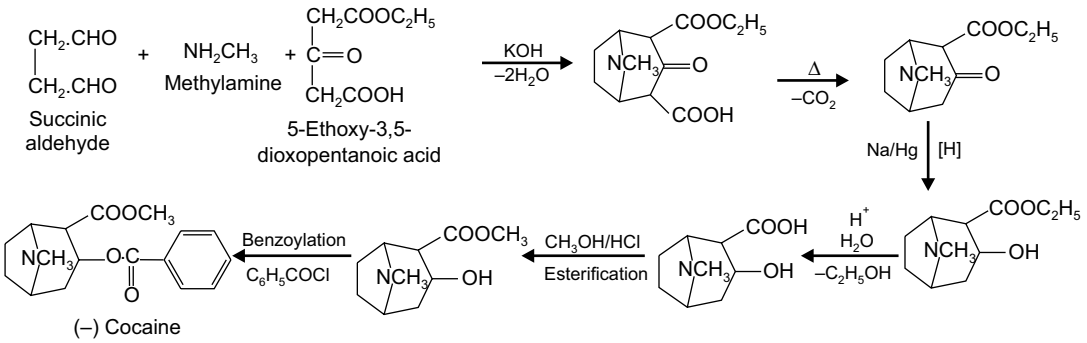


Properties and uses: Cocaine is the first local anaesthetic discovered; it is an alkaloid obtained from the leaves of *Erythroxylon cocca.* It is a white crystalline powder (or colourless crystals), very soluble in water, freely soluble in alcohol, and slightly soluble in methylene chloride. Though it is considered too toxic for any anaesthetic procedure requiring injection, it is still employed topically as a 1% or 2% solution for the anaesthesia of the ear, nose, throat, rectum, and vagina because of its intense vasoconstrictive action.

Assay: Dissolve the substance in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

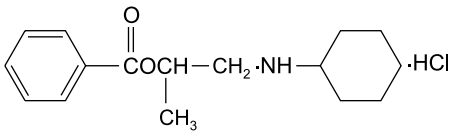
Synthesis



Dose: Employed topically in a 1% or 2% solution for anaesthesia of the ear, nose, throat, rectum, and vagina.

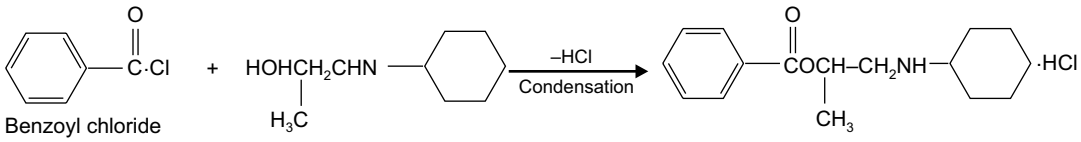
Dosage forms: Cocaine eyedrops BP.

b. Hexylcaine hydrochloride (Synonym: Cyanine)



1-(Cyclohexylamino)-2-propanol benzoate hydrochloride

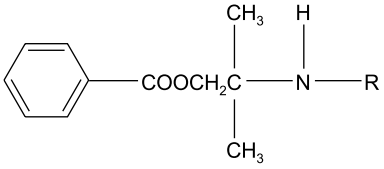
Synthesis



Properties and uses: It is a white powder, soluble in water, and chloroform. It is regarded as an all-purpose soluble local anaesthetic agent. The onset and duration of action is almost similar to that of lignocaine. It is mainly used as surface anaesthetic.

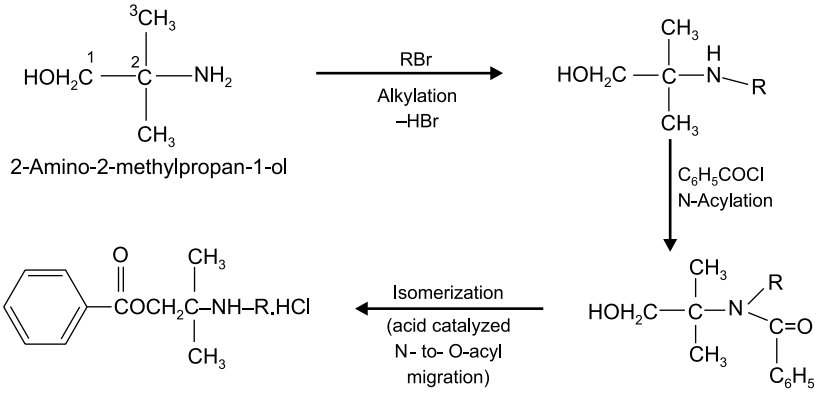
Dose: For infiltration anaesthesia, 1%; for nerve block anaesthesia, 1% and 2% solution; and for topical application to skin and mucous membrane, 1 to 5%.

c. Meprylcaine and isobucaine HCl

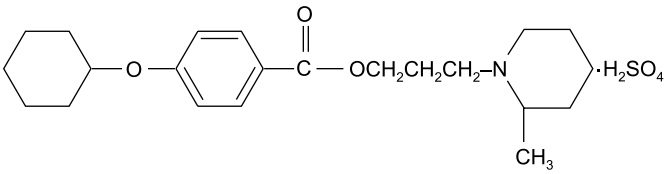


Meprylcaine
R = $–(CH_2)_2–CH_3$
Isobucaine
R = $–CH_2CH(CH_3)_2$

Synthesis



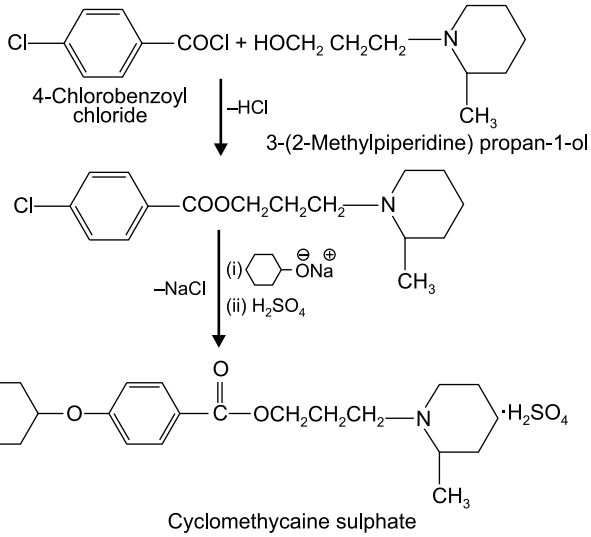
d. Cyclomethycaine sulphate



3-(2-Methyl piperidino)propyl-*p*-(cycloheyloxy)benzoate sulphate

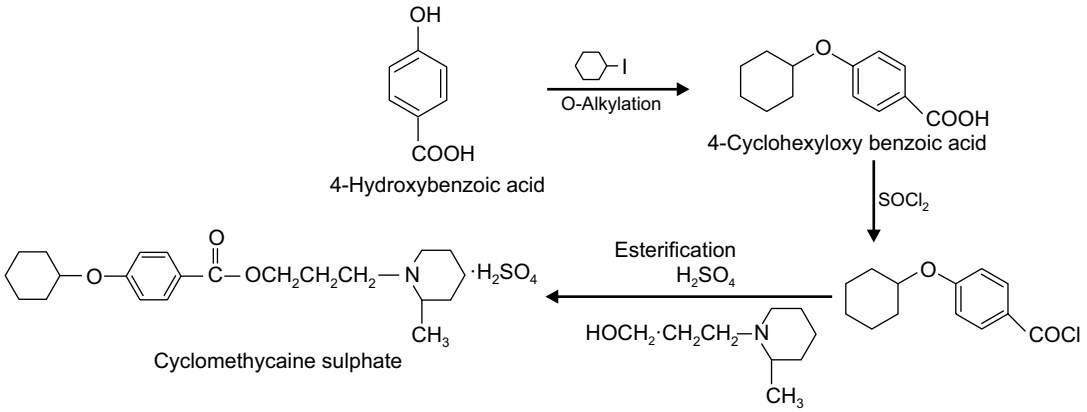
Synthesis

Route I. From: *p*-Chlorobenzoyl chloride



Cyclomethycaine sulphate

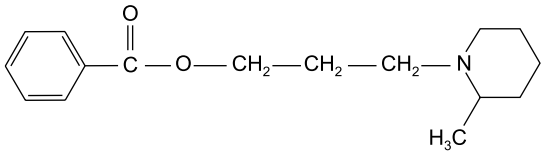
Route II. From: *p*-Hydroxy benzoic acid



Properties and uses: It is a white crystalline powder, soluble in water, and chloroform. Used to releive pain from damaged skin, mucous membrane of rectum, vagina, and urinary bladder.

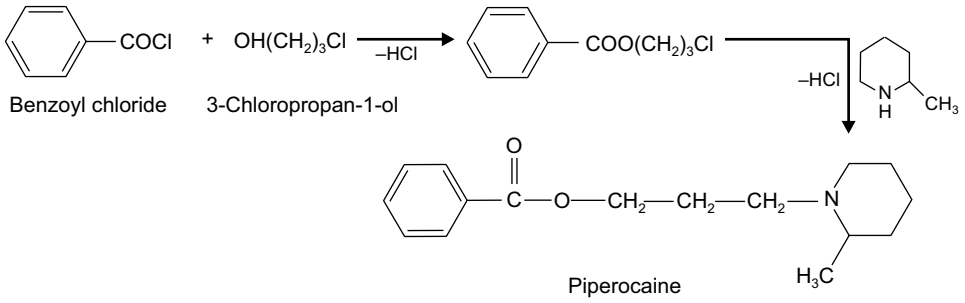
Dose: The usual dose for topical purpose is 0.25 to 1% in suitable form.

e. Piperocaine (Synonym: Metycaine)



3-(α-Methyl piperidino) propyl benzoate

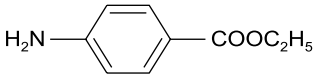
Synthesis



Properties and uses: Piperocaine is small, white, crystalline powder, soluble in water and chloroform. It is used as surface anasthesia for eyes, throat and caudal analgesia.

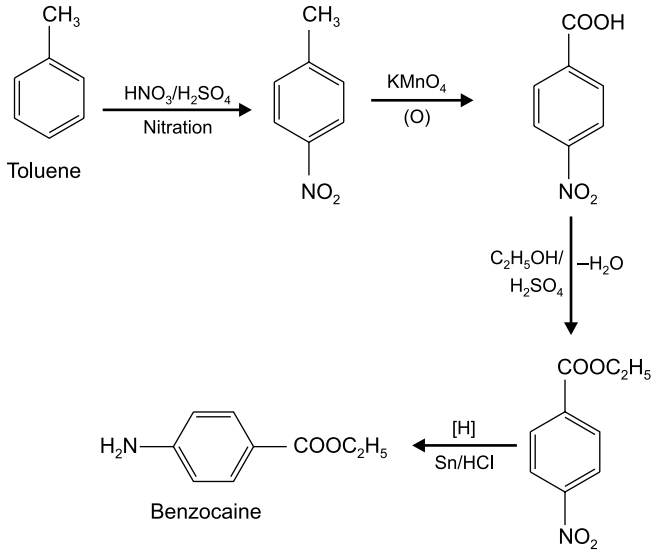
II. *Para*-aminobenzoic Acid Derivatives

a. Benzocaine (Americaine)



Ethyl-*p*-aminobenzoate

Synthesis



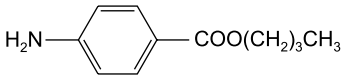
Properties and uses: It is a white crystalline powder or colourless crystals, freely soluble in alcohol, slightly soluble in water. Structurally, it lacks the terminal diethylamino group usually present in most of the anaesthetics, such as procaine. It is used to get rid of the pain caused by wounds, ulcers, and in mucous surface. It is non-irritant and non-toxic.

Assay: Dissolve the substance in a mixture of hydrochloric acid and water, and perform the determination of primary aromatic amino-nitrogen (diazotization method).

Storage: It should be stored in well-closed airtight container and protected from light.

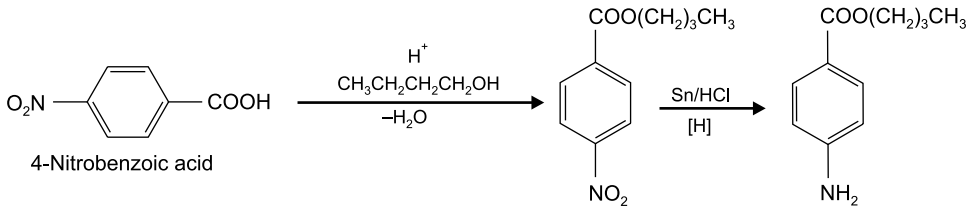
Dose: Topical, 1 to 20% in ointment, cream, and aerosol for skin.

b. Butamben (Butesin)



Butyl-*p*-aminobenzoate

Synthesis

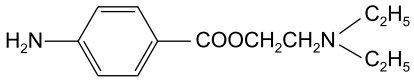


4-Nitrobenzoic acid — Butamben

Properties and uses: It is a local anaesthetic of relatively low solubility and used in a similar manner to benzocaine. It is more efficacious than its corresponding ethyl ester when applied to intact mucous membranes.

Dose: Topical, 1 to 2% in conjunction with other local anaesthetics in creams, ointments, sprays, and suppositories.

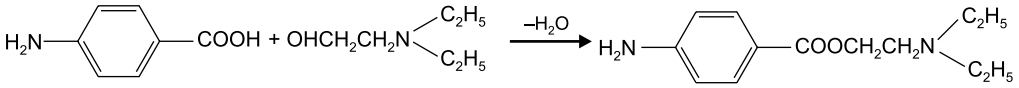
c. Procaine hydrochloride (Novocaine)



2-(Diethylamino)ethyl-*p*-aminobenzoate

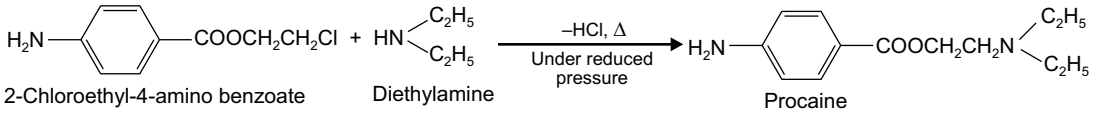
Synthesis

Route I. From: *p*-Aminobenzoic acid



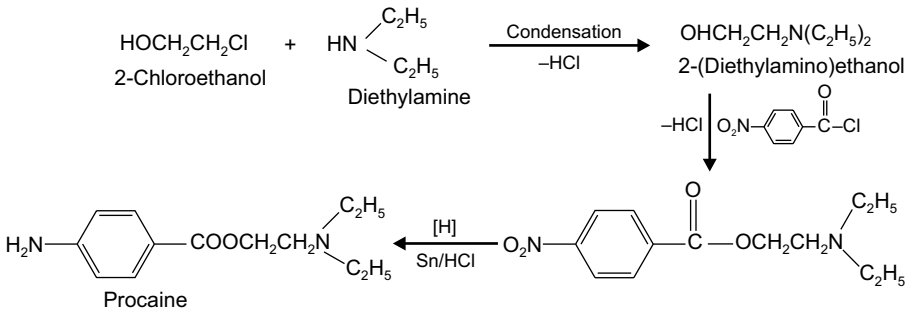
4-Aminobenzoic acid — 2-(N,N-diethylamino) ethanol — Procaine

Route II. From: 2-Chloroethyl-4-amino benzoate



2-Chloroethyl-4-amino benzoate — Diethylamine — Procaine

Route III. From: 2-Chloroethanol



Procaine

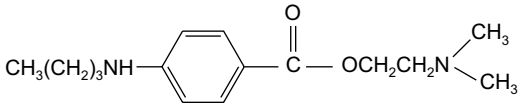
Properties and uses: It is a white crystalline powder or colourless crystals, soluble in water and alcohol. It has the advantage of lacking of local irritation, minimal systemic toxicity, longer duration of action, and low cost. It can be effectively used for causing anaesthesia by infiltration, nerve block, epidural block, or spinal anaesthesia.

Assay: Dissolve the substance in dilute hydrochloric acid and perform the determination of primary aromatic amino nitrogen (diazotization method).

Storage: It should be stored in well-closed airtight container, protected from light.

Dose: Usual infiltration, 50 ml of a 0.5% solution; usual peripheral nerve block, 25 ml of a 1% or 2% solution; usual epidural, 25 ml of a 1.5% solution.

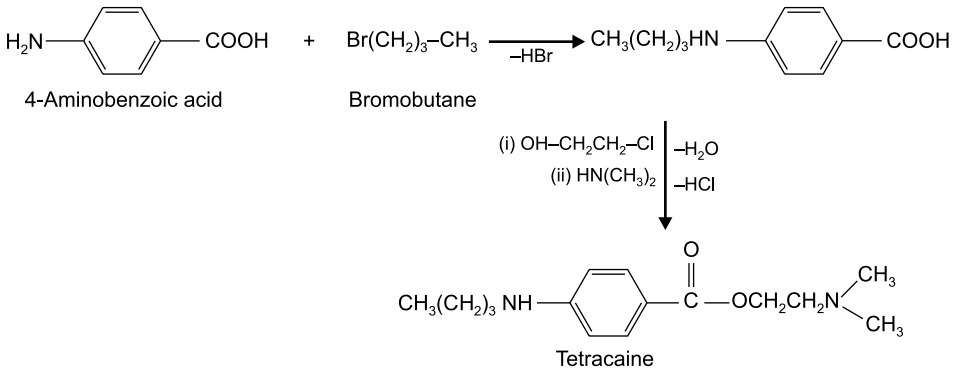
d. Tetracaine (Amethaine, Pontocaino hydrochloride)



2-(Dimethyl amino) ethyl-*p*-(butyl amino) benzoate

Synthesis

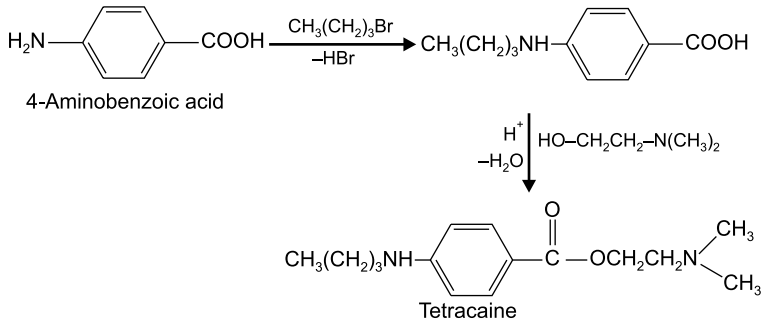
Route I. From: 4-Aminobenzoic acid



4-Aminobenzoic acid — Bromobutane

Tetracaine

Route II. From: 4-Aminobenzoic acid



Properties and uses: It is a white crystalline powder, slightly hygroscopic in nature, soluble in alcohol, and freely soluble in water. It is an all-purpose local anaesthetic drug used frequently in surface, infiltration block, caudal, and spinal anaesthesia. It is reported to be 10 times more toxic and potent than procaine. Its duration of action is twice than that of procaine.

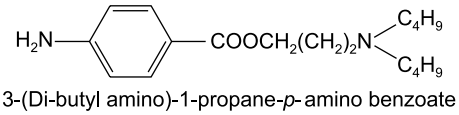
Assay: Dissolve the substance in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight container and protected from light.

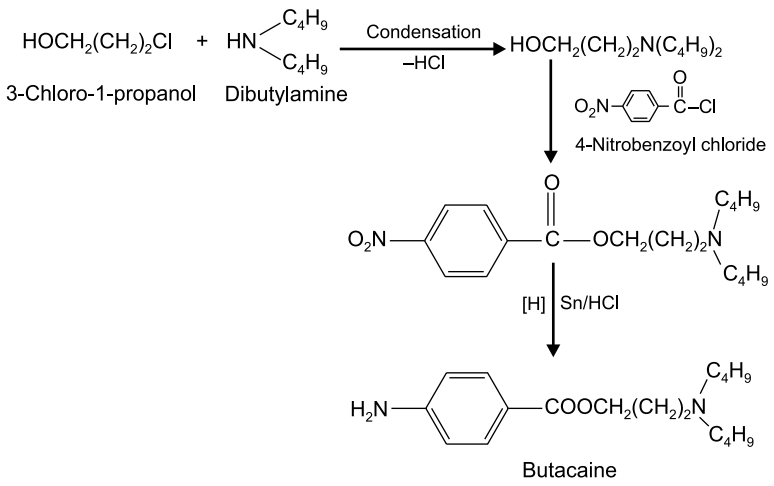
Dose: Usually, subarachnoid 0.5 to 2 ml as a 0.5% solution; topically, 0.1 ml of a 0.5% solution to the conjunctiva.

Dosage forms: Tetracaine eyedrops BP.

e. Butacaine (Butyn sulphate)

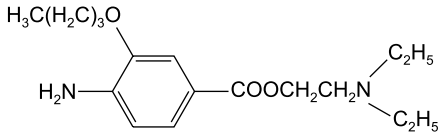


Synthesis



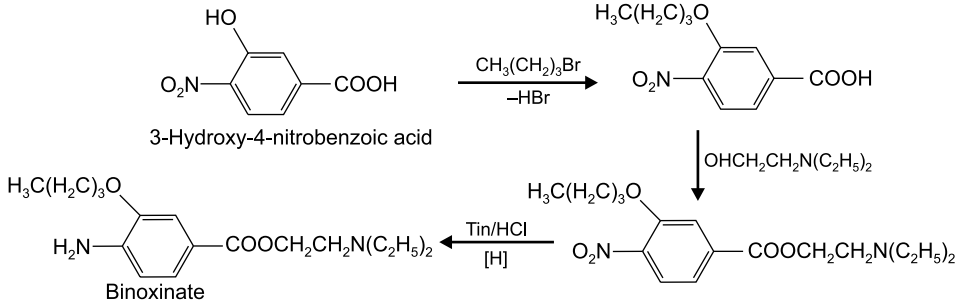
Dose: Several instillations of a 2% solution about 3 min apart allows most surgical procedures.

f. Binoxinate

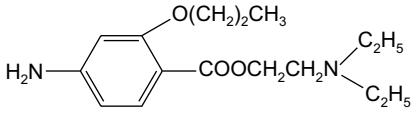


2-(Diethyl amino) ethyl-4-amino-3-butyloxy benzoate

Synthesis

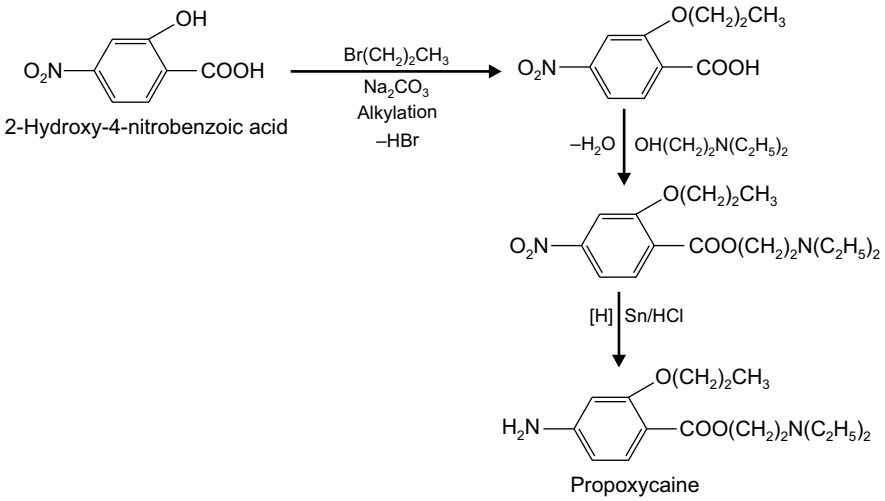


g. Propoxycaine (Blockhain)



2-(Diethyl amino) ethyl-4-amino-2-propoxy benzoate

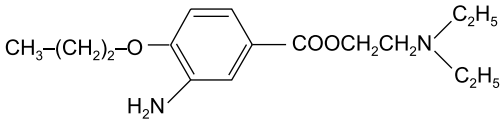
Synthesis



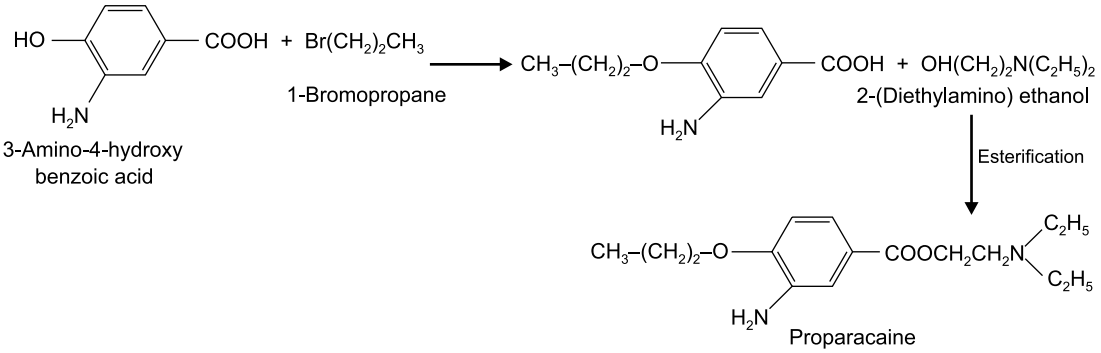
Properties and uses: Its local anaesthetic potency is reported to be seven or eight times more than that of procaine. It is a structural isomer of proparacaine, and is less toxic with slightly lower potency than proparacaine. It is mainly used for infiltration and nerve block anaesthesia.

Dose: Usually, 2 to 5 ml of 0.5% solution.

h. Proparacaine



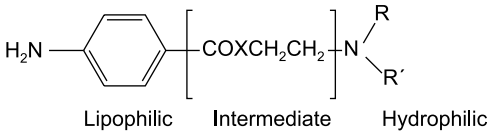
Synthesis



Properties and uses: An effective ester-type surface anaesthetic with potency about equal to that of tetracaine. It is a useful anaesthetic in ophthalmology and induces little or no initial irritation. It is useful for most occular procedures that require topical anaesthesia such as cataract extraction, tonometry, removal of foreign bodies and sutures, gonioscopy, conjunctival scraping for diagnosis and short-operative procedures involving the cornea and conjunctiva.

SAR of Benzoic Acid Derivatives

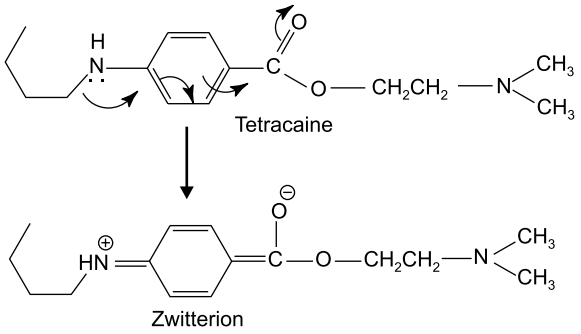
Most of these local anaesthetics are tertiary amines available as HCl salts with pK_a in the range of 7.5–9.0. Any structural modification of the local anaesthetic that causes change in pK_a will have pronounced effect to reach hypothetical receptor or the binding sites.



1. Lipophilic

- The clinically useful local anaesthetics of this class possess an aryl radical that is attached directly to the carbonyl group and are highly liphophilic. They appear to play an important role in the binding of local anaesthetics to the channel receptor protein.
- Placement of aryl group with substituents that increases the electron density of the carbonyl oxygen enhances the activity.

- Structural modification leads to change in physical and chemical properties. Electron withdrawing substituents in *ortho* or *para* or at both the positions leads to an increase of its local anaesthetic property.
- Amino (procaine, butacaine) alkyl amino (tetracaine) alkoxyl (cyclomethycaine) group can contribute to electron density in the aromatic ring by both resonance and inductive effects. Hence, the increase in local anaesthetic property.
- Any substitution that enhances Zwitterion formation will be more potent. Hence, *m*-position substitution decreases the activity.



- Tetracaine is more potent than procaine (40–50 times). Although the butyl group present in it increases lipid solubility, the potentiation is partly due to electron releasing property of the *n*-butyl group via inductive effect, which intends to increase the formation of the Zwitterion.
- Presence of electron withdrawing group such as C1– *ortho* to carbonyl pulls electron density away from carbonyl group, thus, making it more susceptible for nucleophilic attack by the esterase.

2. Intermediate

- In procaine series, anaesthetic potency decreases in the following order: Sulphur, oxygen, carbon, and nitrogen.
- Modifications also affect the duration of action and toxicity. In general, amides (X=N) are more resistant to metabolic hydrolysis than esters (X=O). Thioesters (X=S) may cause dermatitis.
- Placement of small alkyl groups (branching) around ester group (hexylcaine/meprylcaine) or the amide function also hinder hydrolysis, and hence, increase in duration of action.

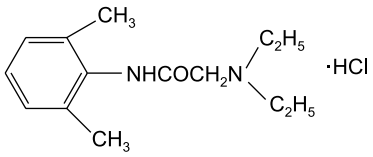
3. Hydrophilic portion

- The amino alkyl group is not necessary for local anaesthetic activity, but it is used to form water soluble salts such as HCl salts.
- Tertiary amines are more useful agents. The secondary amines appear to have a longer duration of action, but they are more irritating. Primary amines are not active/cause irritation.
- The tertiary amino group may be diethyl amino, piperidine, or pyrolidino, leading to a product that exhibits same degree of activity, essentially.
- The more hydrophilic morpholino group usually leads to diminished potency.
- In general, the local anaesthetic drug should have increased lipid solubility and lower pK_a values that lead to rapid onset and lower toxicity.

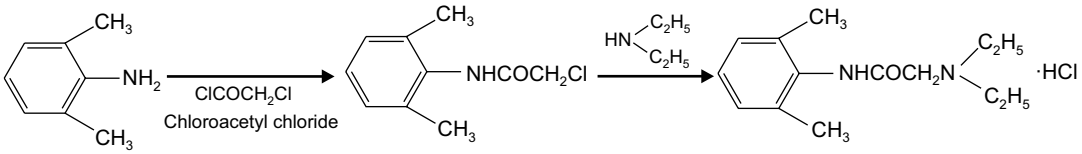
III. Anilides

Agents of this class are more stable to hydrolysis. They are more potent, have lower frequency of side effects, and induce less irritation than benzoic acid derivatives.

a. Lidocaine HCl (Synonym: Lignocaine, Xylocaine)



Synthesis



2,6-Xylidine

Lidocaine HCl

Metabolism: Undergoes N-de-ethylation to yield monoethyl glycinexylide followed by amidase action to N-ethyl glycine and 2,6-dimethylaniline.

Properties and uses: It is a white crystalline powder, very soluble in water, freely soluble in alcohol. It is a potent local anaesthetic. It is reported to be twice as active as procaine hydrochloride in the same concentrations. It has local vasodilating action, but usually used with vasoconstrictor adrenaline to prolong the local anaesthetic activity. It is also used as class I antiarrhythmic agent.

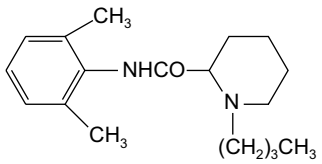
Assay: Dissolve the substance in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Infiltration or epidural up to 60 ml (or 100 ml with epinephrine) as 0.5% solution.

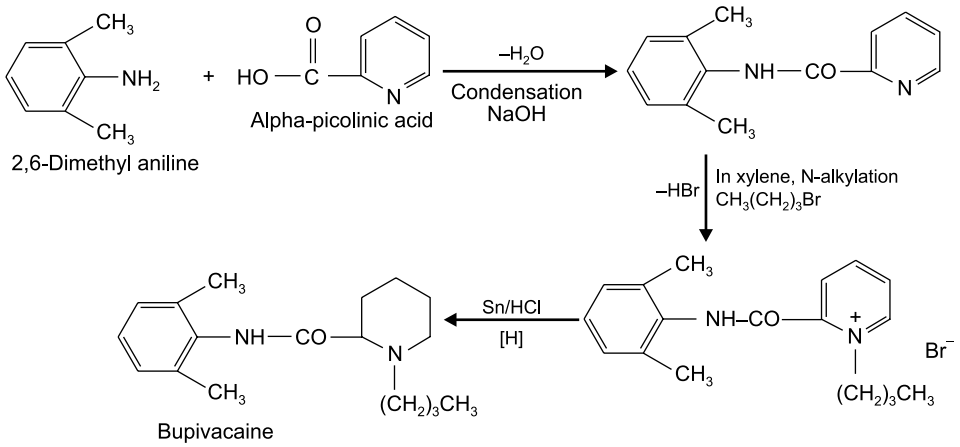
Dosage forms: Lidocaine gel BP, lidocaine and chlorhexidine gel BP, lidocaine injection BP, lidocaine and adrenaline injection/lidocaine and epinephrine injection BP, sterile lidocaine solution BP.

b. Bupivacaine (Marcaine)



1-Butyl-N-(2,6-dimethyl phenyl)-2-piperidin carboxamide

Synthesis



Properties and uses: It is a white crystalline powder or colourless crystals, soluble in water, freely soluble in alcohol. It is a long-acting local anaesthetic of the amide type, similar to mepivacaine and lidocaine, but about four times more potent. The effect of bupivacaine lasts longer than lidocaine hydrochloride. It is long-acting local anaesthetic mainly employed for regional nerve block.

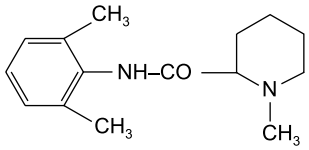
Assay: Dissolve the sample in a mixture of water and alcohol, to this add 0.01 M hydrochloric acid and carry out a potentiometric titration using 0.1 M ethanolic sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Regional nerve block, 0.25 to 0.5% solutions; lumbar epidural block, 15 to 20 ml of 0.25 to 0.5% solution; caudal block, 15 to 40 ml of 0.2% solution.

Dosage forms: Bupivacaine HCl injection IP, bupivacaine injection BP, bupivacaine and adrenaline injection/bupivacaine and epinephrine injection BP.

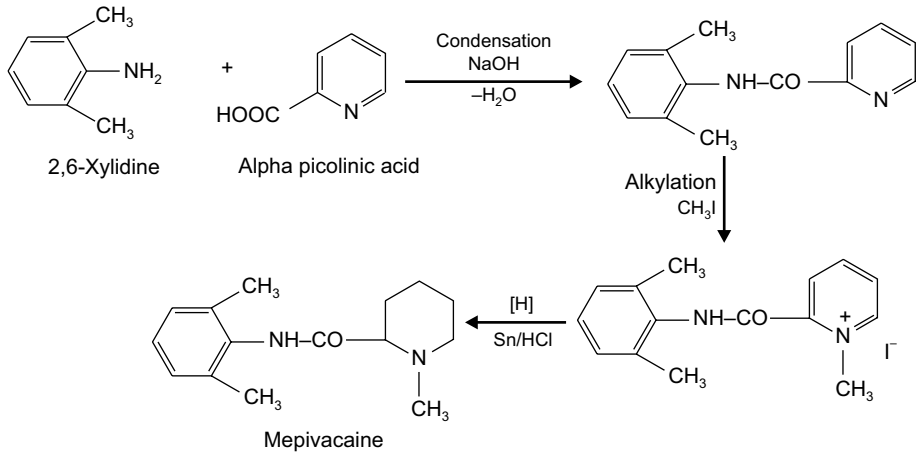
c. Mepivacaine (Carbocaine hydrochloride, Polocaine)



N-(2,6-dimethyl phenyl)-1-methyl-2-piperidin carboxamide

Properties and uses: It is a white crystalline powder, freely soluble in water and in alcohol, very slightly soluble in methylene chloride. The duration of action is significantly longer than that of lidocaine, even without adrenaline. It is of particular importance in subjects showing contraindication to adrenaline. It is a local anaesthetic used for infiltration, peridural nerve block, and caudal anaesthesia.

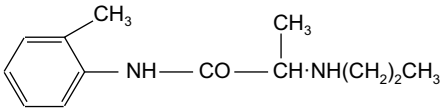
Synthesis



Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Dose: Infiltration and nerve block, 20 ml of 1% or 2% solution in sterile saline; caudal and peridural, 15–30 ml of 1%; 10–25 ml of 1.5% or 10–20 ml of a 2% solution in modified Ringer's solution.

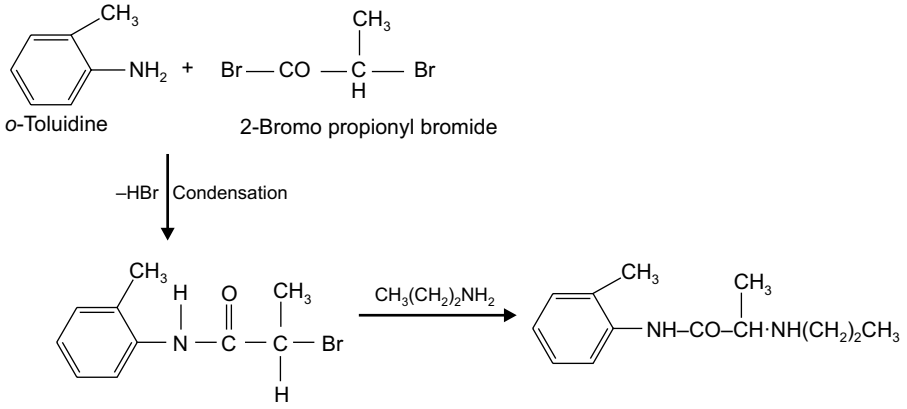
d. Prilocaine (Citanest hydrochloride)



2-(Propylamino)-*o*-propionotoluidine

Properties and uses: It is a white crystalline powder or colourless crystals, very slightly soluble in acetone, freely soluble in water and alcohol. It is a local anaesthetic of the amide type, which is employed for surface infiltration and nerve block anaesthesia. Its duration of action is in between the shorter-acting lidocaine and longer-acting mepivacaine. The solution of prilocaine HCl is specifically used for such patients who cannot tolerate vasopressor agents, patients having cardiovascular disorders, diabetes, hypertension, and thyrotoxicosis.

Synthesis

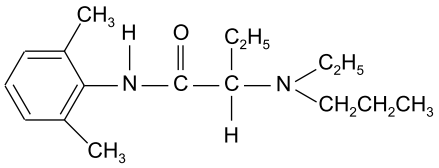


Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol and perform potentiometric titration, using 0.1 M sodium hydroxide.

Dose: Usually, therapeutic nerve block, 3 to 5 ml of a 1% or 2% solution; infiltration, 20 to 30 ml of a 1% or 2% solution; peridural, caudal, regional, 15 to 20 ml of a 3% solution; infiltration and nerve block, 0.5 to 5 ml of a 4% solution.

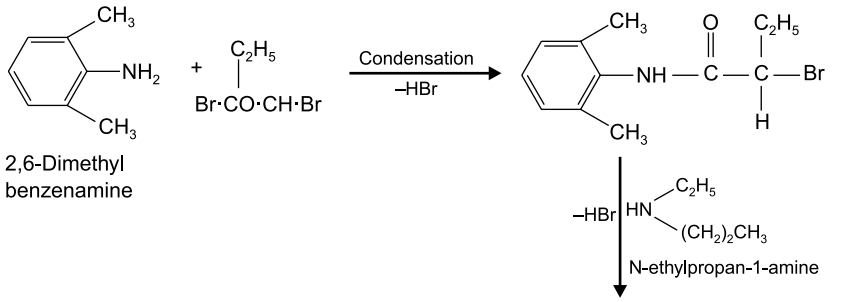
Dosage forms: Prilocaine injection BP.

e. Etidocaine (Duranest)



2-(Ethyl propyl amino)-2′,6′-butyroxylide

Synthesis

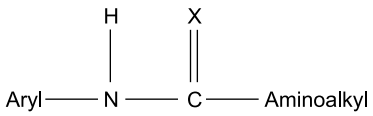


Properties and uses: It is a white crystalline powder, soluble in water, freely soluble in alcohol. It is used clinically in epidural, infiltrative, and regional anaesthesia. It has greater potency and longer duration of action than lidocaine.

Dose: Solution for injection: 1% without epinephrine and 1.5% with epinephrine.

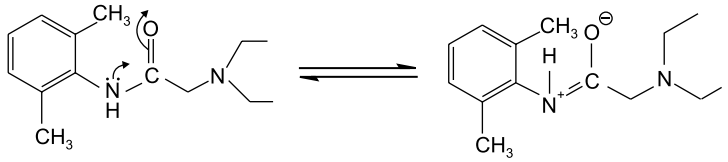
SAR of Anilides

General structure of anilides is represented as follows:



a. Aryl group

- The clinically useful local anaesthetics of this type possess a phenyl group attached to the sp^2- carbon atom through a nitrogen bridge.
- Placement of substituents on the phenyl ring with a methyl group in the 2 or 2 and 6-position enhances the activity. In addition, the methyl substituent provides steric hindrance to hydrolysis of the amide bond and enhances the coefficient of distribution.
- Any substitution on the aryl ring that enhances Zwitterion formation will be more potent.



Lidocaine Zwitterion

b. Substituent X

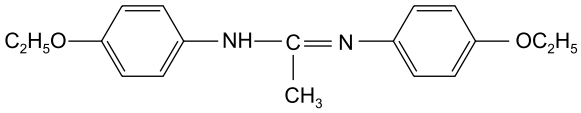
- 'X' may be carbon, oxygen, or nitrogen among them lidocaine series (X=O) has provided more useful products.

c. Amino alkyl group

- The amino function has the capacity for salt formation and is considered as the hydrophilic portion of the molecule.
- Tertiary amines (diethyl amine, piperidine) are more useful because the primary and secondary amines are more irritating to tissues.

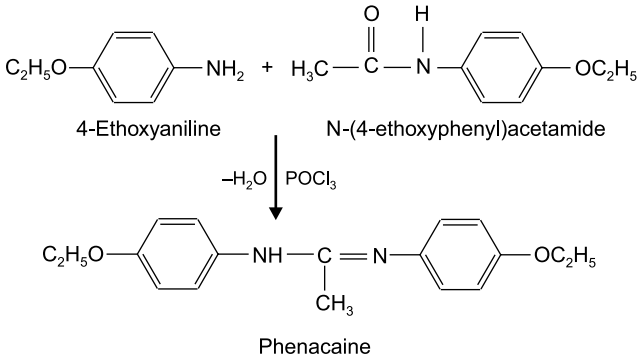
IV. Miscellaneous class

a. Phenacaine (Holocaine hydrochloride)



N,N′-*bis*(4-Ethoxyphenyl ethanimidamide)

Synthesis



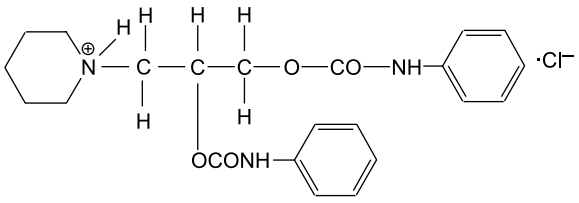
4-Ethoxyaniline N-(4-ethoxyphenyl)acetamide

Phenacaine

Properties and uses: It exists as small white odourless and crystalline powder. Structurally, it is related to anilides in that the aromatic ring is attached to a sp^2-carbon through a nitrogen bridge. It is one of the oldest synthetic local anaesthetic. It is used mainly for producing local anaesthesia of the eye.

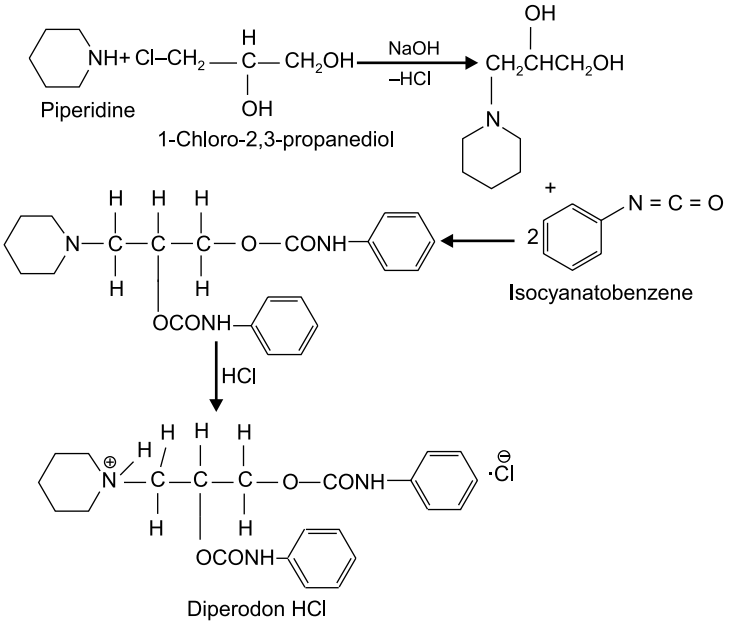
Dose: To the conjunctiva as 1–2% ointment or as a 1% solution.

b. Diperodon HCl (Diothane)



3-(1-Piperidinyl)-bis-(phenylcarbamate)-1,2-propandiol

Synthesis

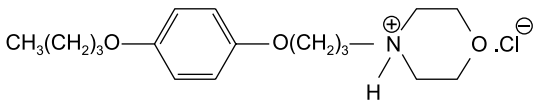


Diperodon HCl

Properties and uses: It exists as white crystals, soluble in water, and potent surface anaesthetic; used primarily for anus. Very toxic in nature.

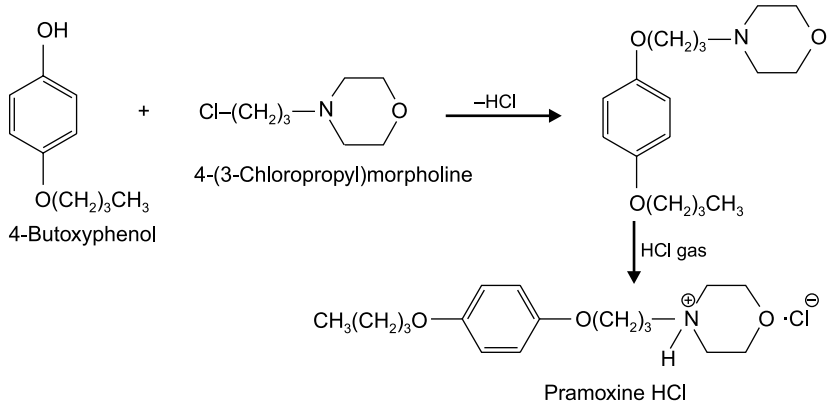
Dose: Topically, 0.5 to 1% solution, to the mucous membranes.

c. Pramoxine HCl (Traonaolene)



4-(-3(4-Butoxy phenoxy)propyl)morpholine.HCl

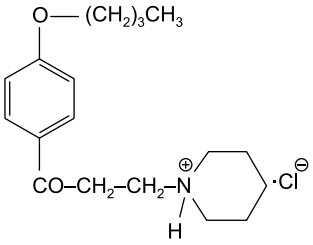
Synthesis



Properties and uses: White crystals or white crystalline powder, numbing taste, may have a slight aromatic odour. Soluble in chloroform, freely soluble in alcohol and water, very slightly soluble in ether. It is a surface anaesthetic, which possesses very low degree of toxicity and sensitization. It is applied locally as 1% solution in rectal surgery, itching, and minor burns. Structurally, it is unrelated to any of the amide type agents, simple ether linkage fulfils this function, and thus, exhibits the local anaesthetic activity.

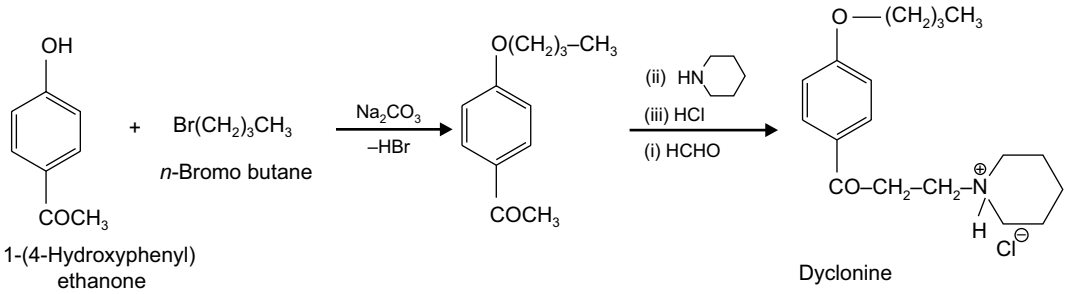
Dose: It is applied locally as 1% solution in rectal surgery, itching, and minor burns.

d. Dyclonine hydrochloride (Dyclone)



1-(4-Butoxy phenyl)-3-(1-piperidinyl)-1-propanone.HCl

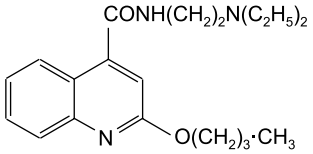
Synthesis



Properties and uses: Exists as white crystals or white crystalline powder and may have a slight odour. Soluble in water, alcohol, and chloroform, insoluble in ether and hexane. Dyclonine containing lozenges are used to relieve minor sore throat and mouth discomfort. It is used to anesthetize mucous membranes of mouth, trachea, and urethra prior to various endoscopic procedures.

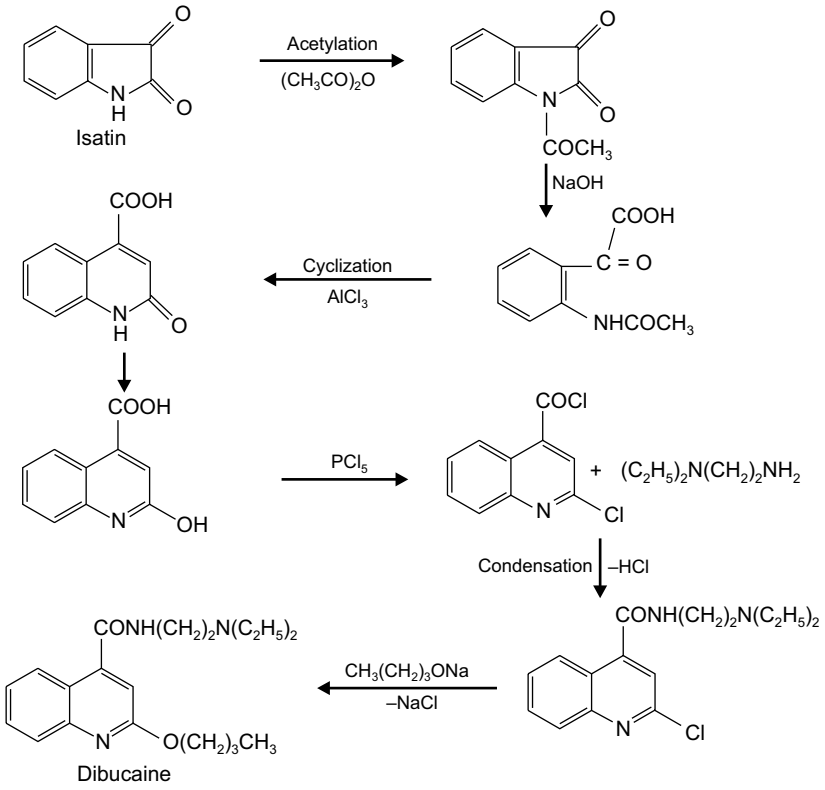
Dose: A 5% solution is used to relieve pain associated with oral or anogenital lesion.

e. Dibucaine (Nupercaine)



2-Butoxy-N-(2-(diethylamino)ethyl)-4-quinoline carboxamide

Synthesis

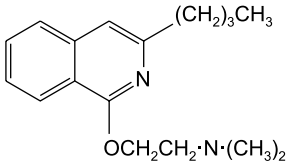


Properties and uses: Exists as white powder with slightly characteristic odour, somewhat hygroscopic, and darkens on exposure to light. Soluble in water, alcohol, chloroform, and in ether. Its anaesthetic

activity is similar to those of procaine or cocaine when injected. It is several times more potent than procaine when injected subcutaneously and five times more toxic than cocaine, when injected intravenously. It is the most potent toxic and long-acting local anaesthetics used as infiltration, surface and spinal anaesthesia.

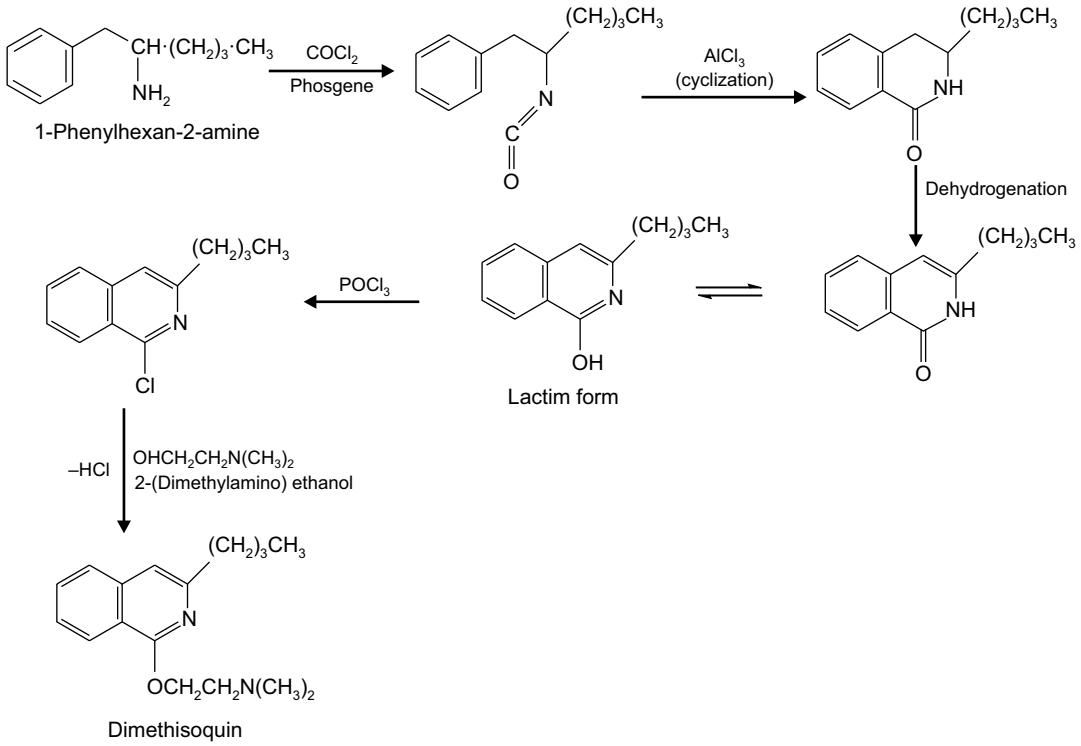
Dose: Subarachnoid, 0.5 to 2 ml of 0.5% solution; usually, 1.5 ml of a 0.5% solution.

f. Dimethisoquin (Synonym: Quinisocaine, Quotane)



3-Butyl-1-(2-(dimethylamino)ethoxy isoquinoline

Synthesis



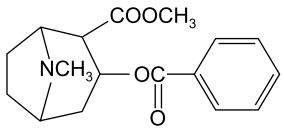
Uses: It is a surface anaesthetic used as an ointment or lotion for relief from irritation, itching, pain, or burning.

Dose: Topically, to the skin as a 0.5% ointment or lotion two to four times/day.

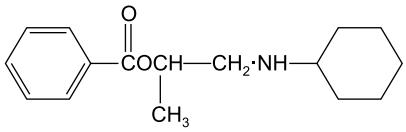
CLASSIFICATION BASED ON PCI SYLLABUS

Benzoic Acid Derivatives

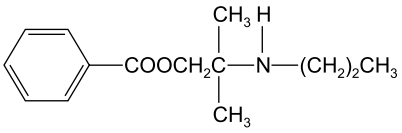
Cocaine



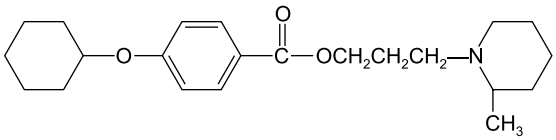
Hexylcaine



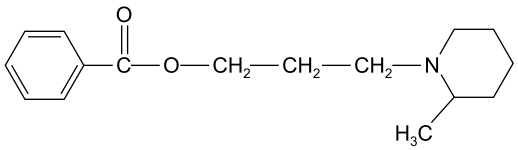
Meprylcaine



Cyclomethycaine

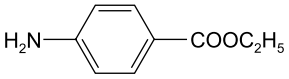


Piperocaine

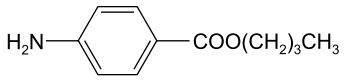


Aminobenzoic Acid Derivatives

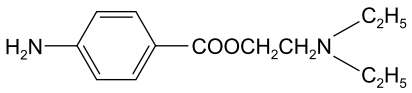
Benzocaine



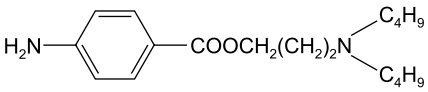
Butamben



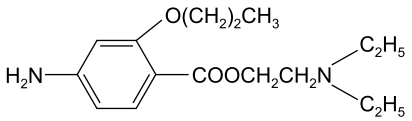
Procaine



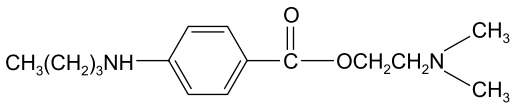
Butacaine



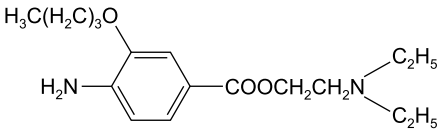
Propoxycaine



Tetracaine

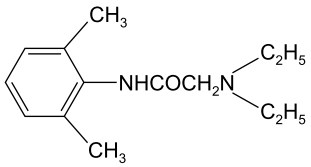


Benoxinate

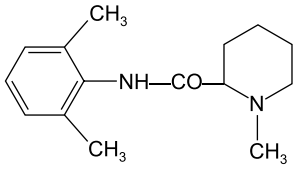


Lidocaine/Anilide Derivatives

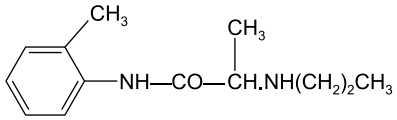
Lignocaine



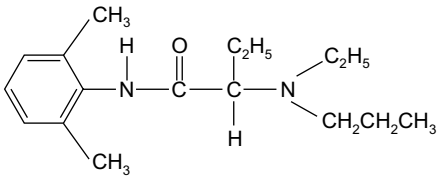
Mepivacaine



Prilocaine

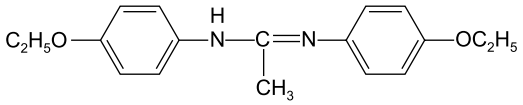


Etidocaine

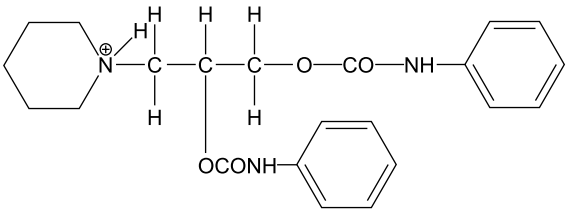


Miscellaneous

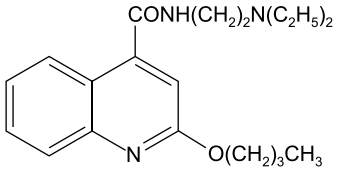
Phenacaine



Diperodon



Dibucaine



PROBABLE QUESTIONS

1. Define and classify local anaesthetics with suitable examples. Outline the synthesis of any two drugs from different class.
2. Differentiate between the local anaesthetics and the general anaesthetics. Is it necessary to include local anaesthetics as adjuncts in antiseptic creams used in severe burns and painful skin abrasions? Explain with typical examples.
3. Write the synthesis of local anaesthetics having the following functional group: (a) Ether, (b) amide (c) morpholine.
4. Outline the synthetic route leads to procaine using the following starting material:
   (a) 2-Chloroethyl-*p*-amino benzoate
   (b) 4-Aminobenzoic acid
   (c) 4-Nitrobenzoic acid
5. Justify why propoxycaine hydrochloride is more potent than procaine hydrochloride.
6. Mention a tropane derivative used as potent surface anaesthetic agent. Outline its synthesis starting from succinic aldehyde.
7. Write in detail about the SAR of benzoic acid derivatives used as local anaesthetics.
8. Amides and esters constitute an important category of local anaesthetics. Mention the examples with their chemical structure; outline the synthesis of any one drug from each category.
9. Describe the synthesis of a quinoline analogue used as a local anaesthetic starting from isatin.
10. Write the mode of action and general metabolic pathway of local anaesthetics.
11. Write in brief about anilides used as local anaesthetics.
12. Describe the synthesis of an isoquinoline analogue used as a local anaesthetic.

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CHAPTER 26

Tranquillizers

INTRODUCTION

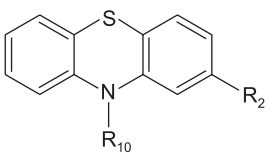
Tranquillizers are used primarily for the treatment of symptoms of mental diseases. They cause sedation without inducing sleep. They are essentially used in the symptomatic treatment of psychosis, such as schizophrenia and organic psychosis. The symptoms of schizophrenia can be divided into two types, positive and negative. Positive symptoms are those that are not normally found in healthy individuals, including hallucinations, delusions, and thought disorder. Negative symptoms represent the loss of qualities normally present in healthy individuals, including impoverishment of thought, blunted emotion, attention deficit, and lack of motivation or initiative. In addition, many of these drugs also act as skeletal muscle relaxants, antihypertensives, antiemetics, and antiepileptics.

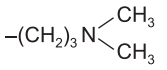
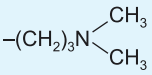
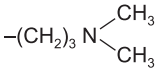
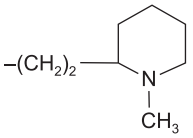
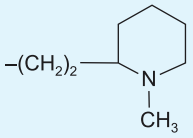
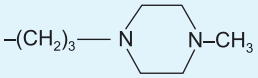
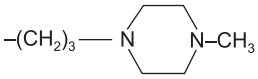
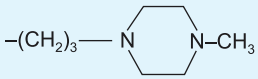
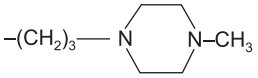
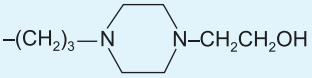
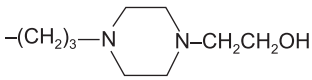
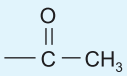
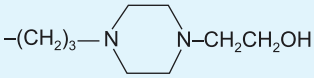
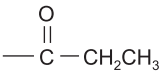
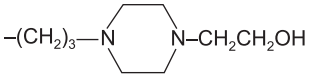
GENERAL MODE OF ACTION

All antipsychotics except clozapine have potent dopamine (D_2) receptor blocking action. Phenothiazines and thioxanthanes also block D_1, D_3 and D_4 receptors and have correlation with antipsychotic or tranquillizing property. Blockade of the dopaminergic projections to the temporal and the prefrontal area constitutes the limbic system, and in the mesocortical area, it is probably responsible for antipsychotic action. As an adaptive change, to blockades of D_2 receptor, the firing of DA neurons and DA turnover increases initially. However, over a period of time, this subsides and gives away diminished activity, especially in the basal to ganglia corresponding to the emergency of Parkinson's disease. Clozapine and other atypical antipsychotics have significant 5-HT_2 and α_1-blocking action and are relatively selective for D_4 receptor. Thus, antipsychotic property depends on a specific profile of action of the drugs on several neurotransmitter receptors.

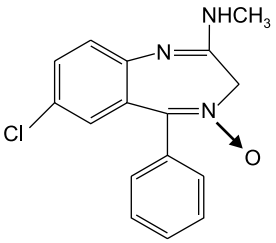
CLASSIFICATION

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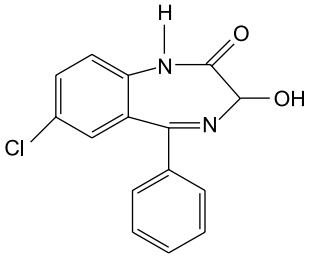


Name	R_2	R_{10}
Propyl dialkylamino side chain		
Promazine	–H	
Chlorpromazine	–Cl	
Triflupromazine	$-CF_3$	
Ethyl piperidyl side chain		
Thioridazine	$-SCH_3$	
Mesoridazine	$O\leftarrow SCH_3$	
Propyl piperazine side chain		
Prochlorperazine	–Cl	
Trifluperazine	$-CF_3$	
Thioethylperazine	$-SCH_2CH_3$	
Butaperazine	$-(CH_2)_3-CH_3$	
Perphenazine	–Cl	
Fluphenazine	$-CF_3$	
Acetophenazine		
Carphenazine		

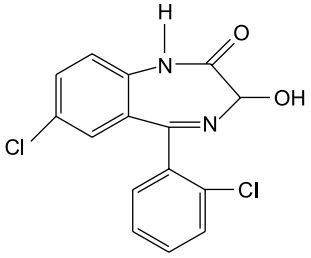
2. Benzodiazepines



Chlordiazepoxide



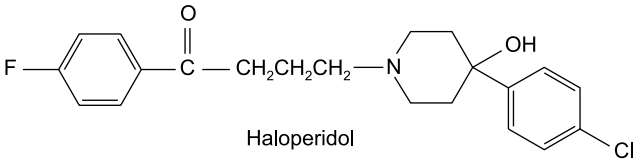
Oxazepam



Lorazepam

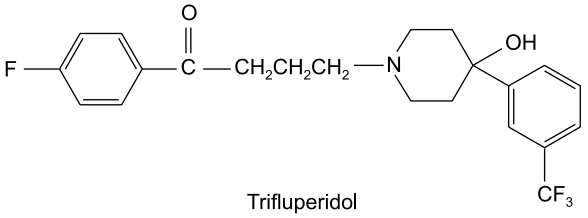
3. Fluorobutyrophenones

i.



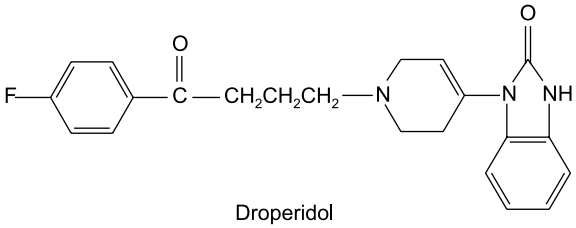
Haloperidol

ii.



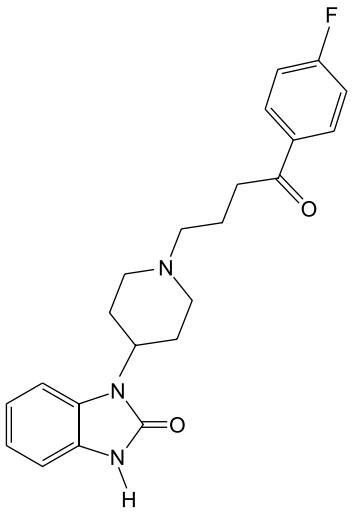
Trifluperidol

iii.



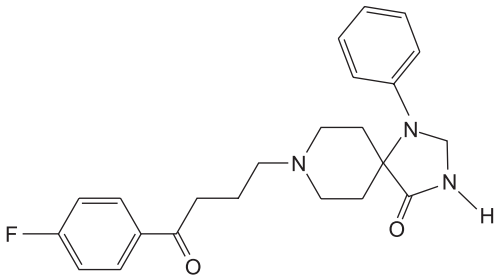
Droperidol

iv.



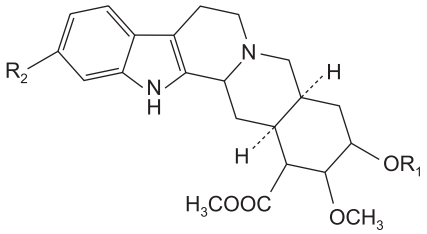
Benperidol

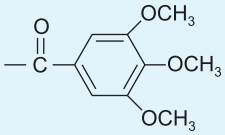
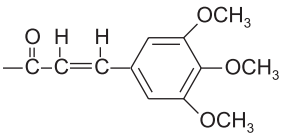
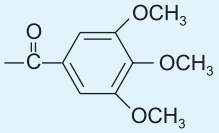
v.



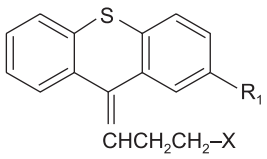
Spiroperidol

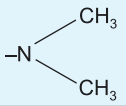
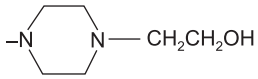
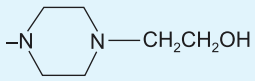
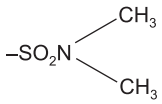
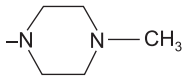
4. Rauwolfia alkaloids



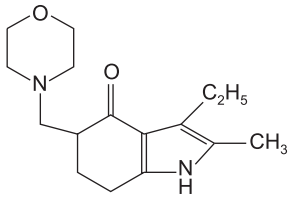
Name	R_1	R_2
Reserpine		$-OCH_3$
Rescinnamine		$-OCH_3$
Reserpidine		–H

5. Thioxanthines



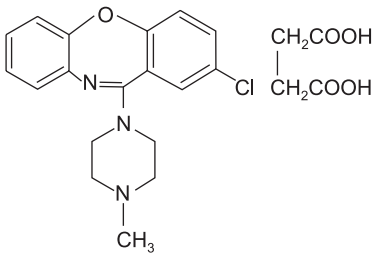
Name	R_1	R_2
Chlorprothixene	–Cl	
Clopenthixol	–Cl	
Flupenthixol	$-CF_3$	
Thiothixene		

6. Dihydroindolones



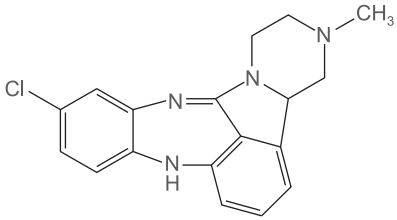
Molindone

7. Dibenzoxazepines



Loxapine succinate

8. Dibenzodiazepines



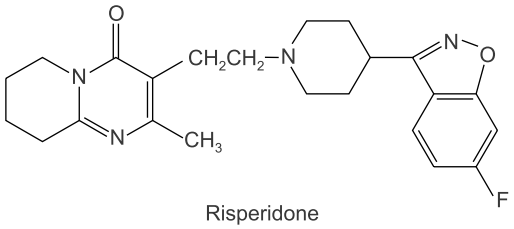
Clozapine

9. Diphenyl butyl piperidines

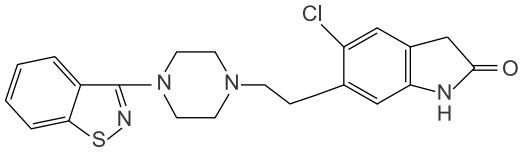
a. Pimozide

b. Penfluridat

10. Benzisoxazoles and benzisothiazoles



Risperidone



Ziprasidone

11. Thienbenzodiazepines

Olanzapine

12. Propanediol carbamates

Meprobamate

13. Miscellaneous

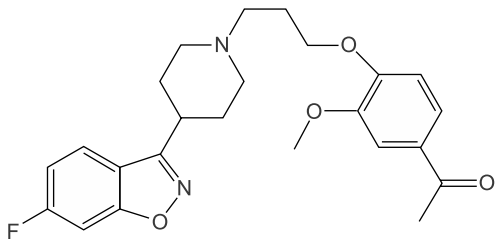
a. Oxypertine

b. Quetiapine

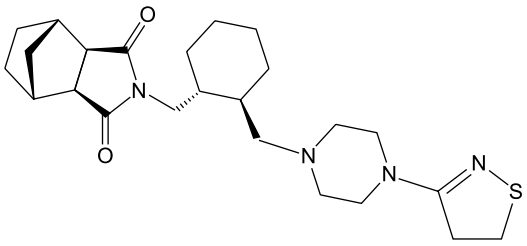
c. Seretindole

Newer Drugs

Iloperidone



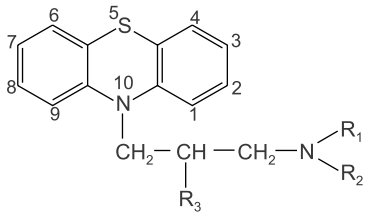
Lurasidone



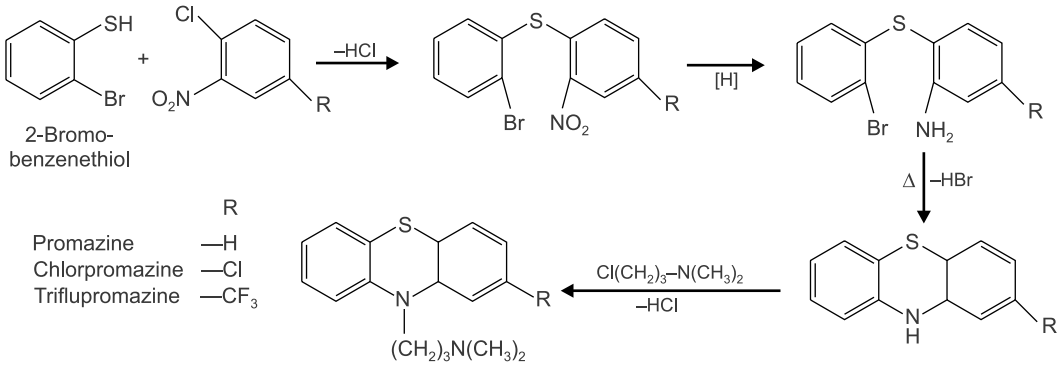
SYNTHESIS AND DRUG PROFILE

I. Phenothiazines

i. General synthesis of propyl dialkylamino side chain derivatives



Synthesis



Promazine

Properties and uses: It is a white or almost white crystalline powder, slightly hygroscopic in nature. It is well soluble in water, alcohol, and methylene chloride. It has low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action. It is used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and 50 ml of alcohol. Perform the potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight container and protected from light.

Dosage forms: Promazine injection BP, promazine oral suspension BP, promazine tablets BP.

Chlorpromazine (Cain, Megatil)

Metabolism: It is demethylated, sulphoxidized, hydroxylated, and glucuronidated to yield 7-*o*-glu-nor chlorpromazine.

Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and well soluble in water. The drug has significant sedative and hypotensive properties, possibly reflecting central and peripheral α_1-noradrenergic blocking activity and also effects the peripheral anticholinergic activity, used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the sample in a mixture of 0.1 M hydrochloric acid and ethanol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It decomposes on exposure to air and light, hence, it should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 75–80 mg daily in divided doses for psychiatric patients. As an antiemetic, it is 25–50 mg.

Dosage forms: Chlorpromazine HCl injection IP, chlorpromazine tablets IP, BP, chlorpromazine injection BP, chlorpromazine oral solution BP.

Triflupromazine

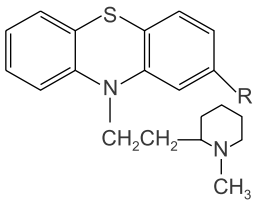
Properties and uses: It is a white to pale yellow, crystalline powder, hygroscopic in nature, soluble in alcohol and freely soluble in water. It has lower sedative and hypotensive effects than chlorpromazine, and greater milligram potency as an antipsychotic, used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the sample in alcohol, to this add 0.01 M hydrochloric acid and perform potentiometric titration, using 0.1 M sodium hydroxide.

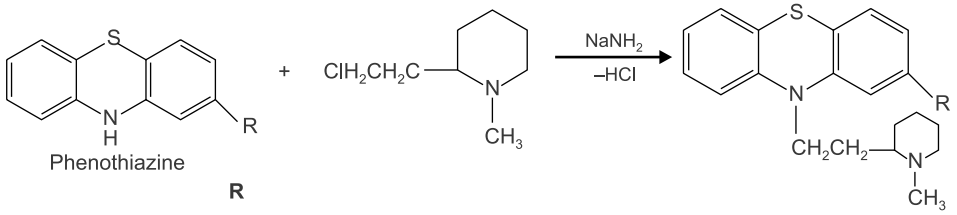
Storage: It should be stored in well-closed airtight container and protected from light.

Dosage forms: Triflupromazine HCl injection IP, triflupromazine HCl tablets IP, triflupromazine tablets BP.

ii. General synthesis of ethyl piperidyl side chain derivatives



Synthesis



R	
Thioridazine	—SCH_3
Mesoridazine	—$SOCH_3$

Uses: It is effective in the management and manifestations of psychotic disorders with minimal antiemetic action.

Thioridazine (Melozine, Ridazin, Melleril)

Properties and uses: It is a white or almost white crystalline powder, soluble in ethanol, freely soluble in water and in methanol. The drug exerts minimum antiemetic activity and thereby gives rise to

minimal extrapyramidal stimulation. The drug has sedative and hypotensive activity in common with chlorpromazine. It is effective in the management and manifestations of psychotic disorders, used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the substance in a mixture of anhydrous acetic acid and acetic anhydride and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

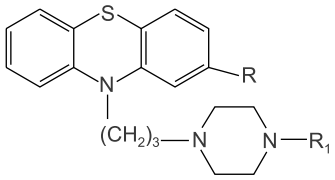
Dose: For schizophrenia: Adult—initially, 50–100 mg, three times/day and slowly titrated upwards at not more than 100 mg/week. Maximum of 800 mg daily in 2–4 divided doses. Child, 2–12 year: Initially, 0.5 mg/kg daily in divided doses, increased gradually until optimum effect is obtained. Maximum 3 mg/kg daily.

For depression: Adult—initially, 25 mg thrice/day, titrated to 20–200 mg daily.

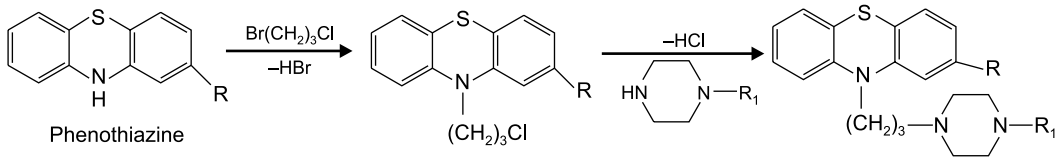
Mesoridazine

Properties and uses: It shares many properties with thioridazine, but no pigmentary retinopathy has been reported.

iii. General synthesis of propyl piperazine side chain derivatives



Synthesis



Name	*R*	R_1
Prochlorperazine	–Cl	$-CH_3$
Trifluperazine	$-CF_3$	$-CH_3$
Perphenazine	–Cl	$-CH_2CH_2OH$
Fluphenazine	$-CF_3$	$-CH_2CH_2OH$
Acetophenazine	$-COCH_3$	$-CH_2CH_2OH$
Carphenazine	$-COC_2H_2$	$-CH_2CH_2OH$

Perphenazine

Properties and uses: It is a white or yellowish-white crystalline powder soluble in dilute solutions of hydrochloric acid, soluble in alcohol, freely soluble in methylene chloride, and insoluble in water. It is used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid, and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight container and protected from light.

Dosage forms: Perphenazine tablets BP.

Prochlorperazine (Vometil, Stemetil, Emidoxyn)

Properties and uses: It is a white or pale yellow crystalline powder, well soluble in water and alcohol. It is more potent on a milligram basis than its alkylamino counterpart, chlorpromazine because of the high prevalence of extra-pyramidal symptom (EPS). It is mainly used for antiemetic effect, not for its antipsychotic effect, used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the sample in anhydrous acetic acid by warming on a water-bath and allow it to cool to room temperature. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight container and protected from light.

Dose: For nausea and vomiting: Adult—as mesylate—12.5 mg by deep IM. If required, may give further doses via oral route. For psychosis: Adult—as mesylate—12.5–25 mg by deep IM injection twice/day or thrice/day.

Dosage forms: Prochlorperazine maleate tablets IP, prochlorperazine mesylate injection IP, prochlorperazine tablets BP, prochlorperazine buccal tablets BP.

Fluphenacine (Anatensol, Decanoate, Fpz, Prolinate)

Properties and uses: It is a white or almost white crystalline powder, slightly soluble in ethanol and in methylene chloride, but freely soluble in water, used as dopamine receptor antagonist and neuroleptic.

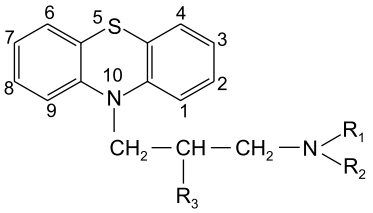
Assay: Dissolve the sample in a mixture of anhydrous formic acid and acetic anhydride and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight container and protected from light.

Dose: The usual dose is 1–2 mg daily for anxiety; up to 15 mg daily for schizophrenia.

Dosage form: Fluphenazine tablets BP.

SAR of Phenothiazines



It is presumed that phenothiazines (neuroleptic) mediate their pharmacological effect mainly through interaction with D_2 type dopamine receptors. Examination of X-ray structures of dopamine and chlorpromazine substituted with chlorine shows that these two structures can be partly superimposed. Chlorpromazine base could be superimposed on aromatic ring of dopamine base with sulphur atom aligned with *p*-hydroxy of dopamine. These substances are chemically constituted by lipophilic linearly fused tricyclic system having hydrophilic basic amino alkyl side chain.

Activity of phenothazines is determined by the following:

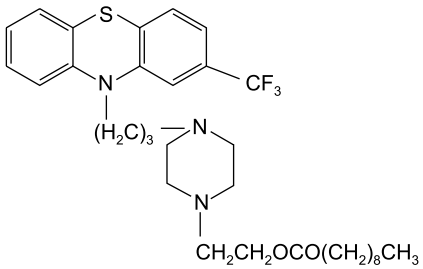
1. Nature of alkyl side chain at 10th position.
2. Amino group of side chain.
3. Substituents on aromatic ring.

1. Modification of alkyl side chain

- Potency is maximum when there are three carbons between two 'N' atoms (ring and side chain N).
- Introduction of methyl group at C-1 decreases antipsychotic activity and produces imipramine-like activity.
- If C-1 is incorporated into cyclopropane ring imipramine-like activity is obtained.
- When oxygen is introduced into C-1 results in potent antidepressant effect. Example: Chloracizine.
- Addition of $-CH_3$ at C-2 or C-3 has very little effect on activity.
- Bridging of position 3 of side chain to position 1 of phenothiazine nucleus decreases neuroleptic activity.

2. Amino group modification

- 3° nitrogen shows maximum potency and 2° or 1° nitrogen shows reduced or abolished activity. N-alkylation with more than one carbon decreases activity.
- Activity is decreased when dimethylamino group is replaced by pyrolidinyl, morpholinyl, or thiomorpholinyl groups. However, piperidine or piperazine is more potent than dimethylamino group.
- Bridged piperidine derivates retain high degree of activity although bulky.
- Introduction of OH, CH_3, CH_3CH_2 OH at C-4 of piperazine results in increased activity.



Fluphenazine deconoate

- Piperazine and phenothiazines may be esterified with long-chain fatty acids to produce slowly absorbed long-acting lipophilic prodrugs. Due to the slow release from oily deposition, significant activity is retained.
- When N-4 piperazine substituents are as large as phenyl, ethyl, or *p*-amino phenyl ethyl (e.g. azaspirane, chlorspirane) are active.

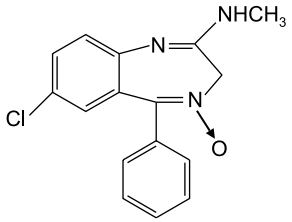
3. Phenothiazine ring

- Substitution at C-2 position is optimal for neuroleptic activity. In general, potency at different positions increases in the following order: 1 < 4 < 3 < 2. Potency of the various groups increases in the following order: OH < H< CN < CH_3 < Cl < CF_3.
- Disubstitution or trisubstitution of the C-2 substituted drugs results in harmful potency.
- CF_3 is more potent than Cl, but EPS appears, hence, chlorpromazine is much used, rather than triflupromazine.
- The electronegative chlorine atom at C-2 is responsible for imparting asymmetry to this molecule and the attraction of the amine side chain towards the ring containing the chlorine atom indicate an important structural feature of such molecules.
- Oxidation of the sulphur at 5th position of antipsychotic phenothiazine decreases activity.

II. Benzodiazepines

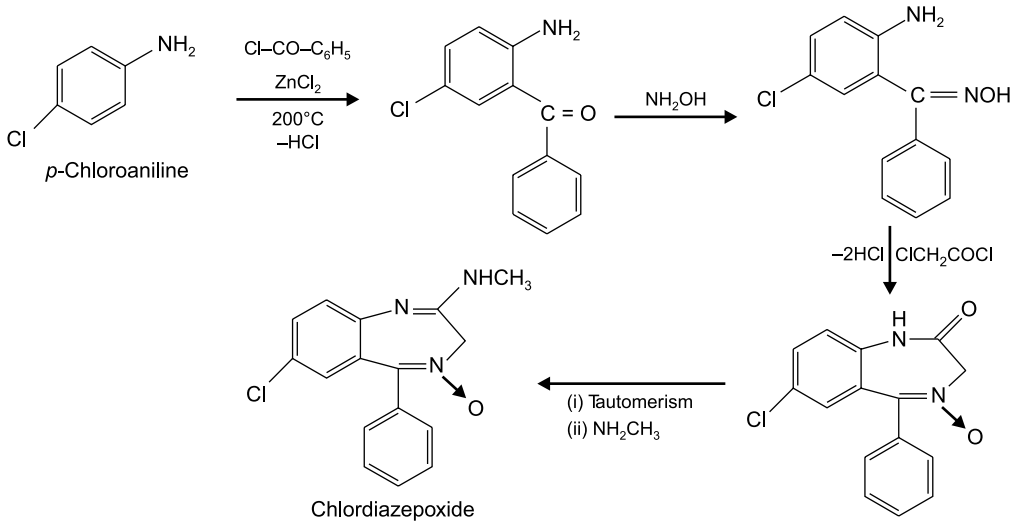
Metabolism is discussed under 'Sedatives and Hypnotics' in Chapter 23.

a. Chlordiazepoxide (Cebrum, Cloxide, Librium)



7-Chloro-5-phenyl-2-methylamino-1,4-benzodiazepine-4-oxide

Synthesis



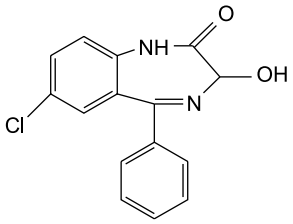
Properties and uses: It is a white or slightly yellow crystalline powder, sparingly soluble in ethanol and soluble in water. Chlordiazepoxide is also available commercially in anxiolytic products combined with anticholinergic and antidepressant agents. The therapeutic value of these fixed combinations has not been established. Adverse reactions include drowsiness, ataxia, confusion, skin eruptions, oedema, menstrual irregularities, nausea and constipation, EPS and decreased libido. In some patients; blood dyscrasias (agranulocytosis), jaundice, and hepatic dysfunction have occasionally been reported. Used for the relief of anxiety and tension, withdrawal symptoms of acute alcoholism, and also used as sedative as well as muscle relaxant.

Assay: Dissolve the sample in water and titrate with 0.1 M silver nitrate. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight container and protected from light.

Dose: For anxiety: Adult—30 mg daily in divided doses, up to 100 mg daily in severe conditions. Elderly and debilitated patients: Dose reduction may be needed. For muscle spasms: Adult—10–30 mg daily in divided doses. Elderly and debilitated patients: Dose reduction may be needed.

b. Oxazepam

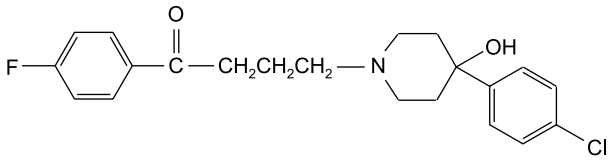


7-Chloro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one

Synthesis and drug profile are discussed under 'Sedatives and Hypnotics' in Chapter 23.

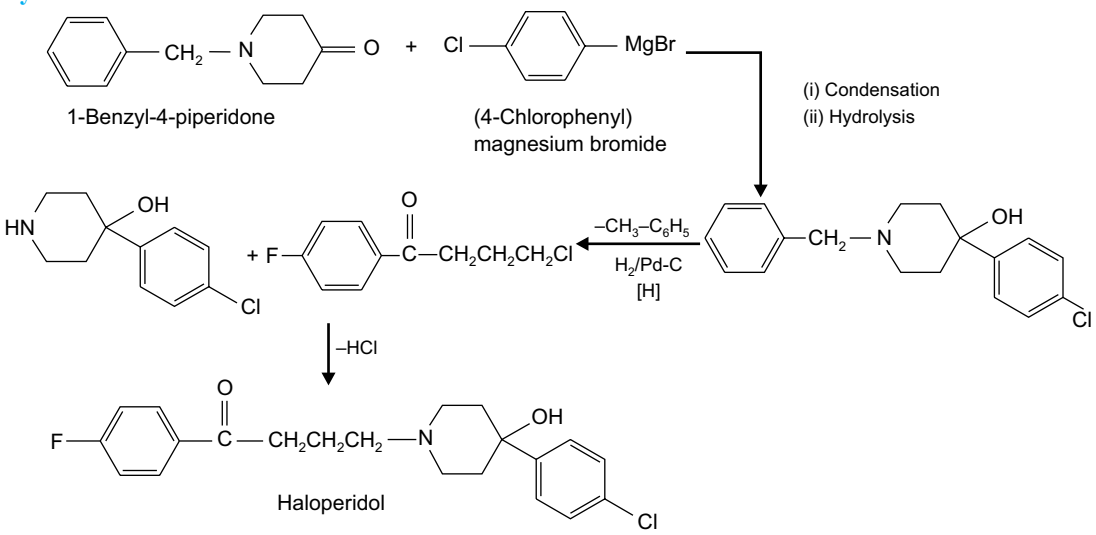
III. Fluorobutyrophenones

a. Haloperidol (Halidol, Hexidol, Cizoren)



4-[4-(*p*-Chlorophenyl)-4-hydroxypiperidinyl]-
1-(4-fluorophenyl)-1-butanone

Synthesis

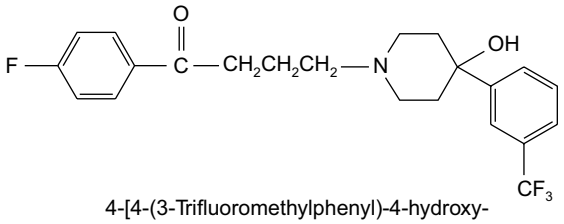


Metabolism: It is metabolized by oxidative N-dealkylation. The principal metabolites are oxidative products, such as 4-fluorobenzoyl propionic acid and 4-fluorophenylaceturic acid.

Properties and uses: It is useful in the management of psychotic reactions, hostility, and hyperactivity. It is a drug of choice for Tourett's syndrome. Haloperidol is an effective neuroleptic and also possesses antiemetic properties.

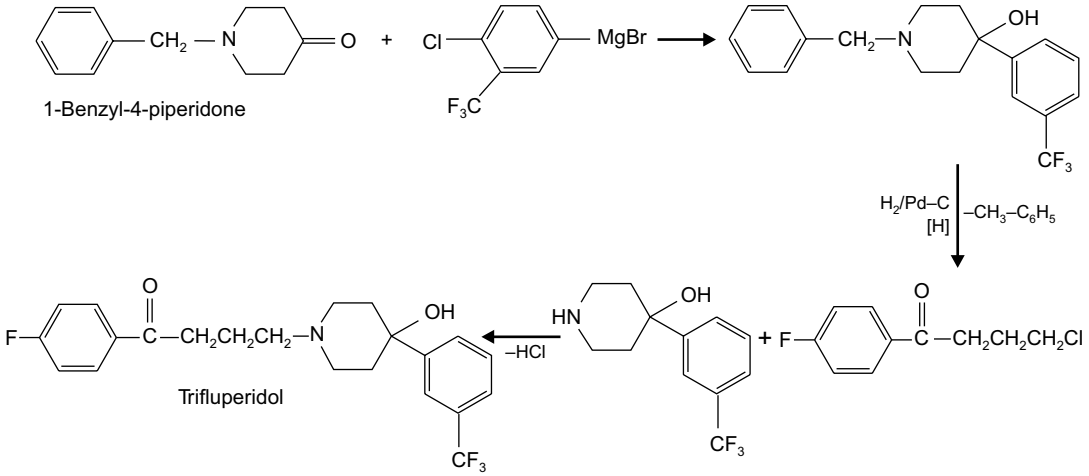
Dose: For restlessness and confusion: Adult—1–3 mg every 8 h. For psychoses: Adult—0.5–5 mg twice or thrice/day, may increase up to 100 mg daily in severe or resistant cases. Usual maintenance: 3–10 mg daily. Child: >3 years: Initially, 25–50 µg/kg daily in two divided doses, increased gradually if necessary. Maximum: 10 mg/day.

b. Trifluperidol



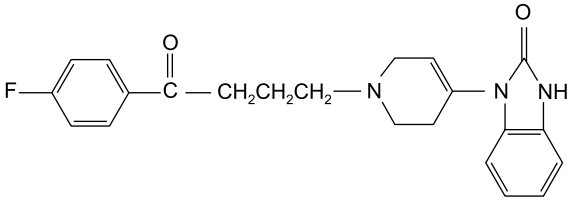
4-[4-(3-Trifluoromethylphenyl)-4-hydroxy-
1-piperidinyl]-1-(4-fluorophenyl)-1-butanone

Synthesis



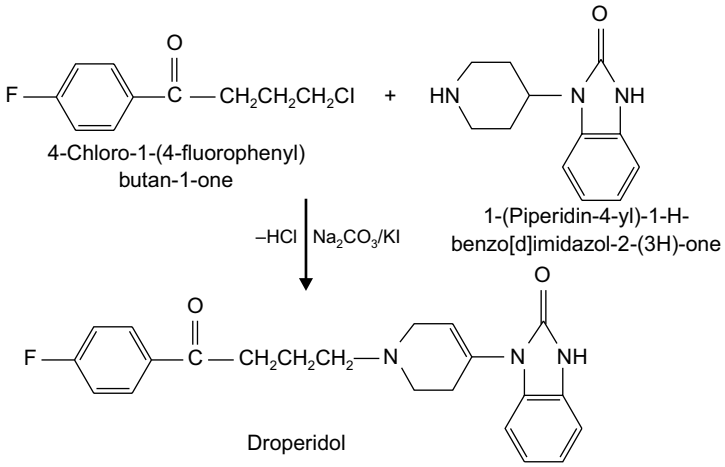
Uses: It is used for the treatment of schizophrenia and other psychosis, mania, and short-term adjunctive management of psychomotor agitation and excitement.

c. Droperidol



1-(1-(3-(p-Fluorobenzoyl)propyl)-1,2,3,6-tetrahydro
-4-pyridyl)- 2-benzimidazolinone

Synthesis



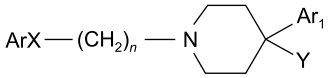
Properties and uses: It is a white or almost white powder insoluble in water, sparingly soluble in alcohol, freely soluble in dimethylformamide and in methylene chloride. The drug exhibits relatively low therapeutic potency, medium extrapyramidal toxicity, high sedative effect, and above all high hypotensive action. It is frequently used in combination with the nacrotic agents pre-anaesthetically. It is a neuroleptic used as an adjunct to anaesthesia to produce sedation and reduce incidence of nausea and vomiting. Also used as β-adrenoceptor agonist and α-adrenoceptor agonist.

Assay: Dissolve the sample in a mixture of 1 volume of anhydrous acetic acid and 7 volumes of methyl ethyl ketone. Titrate with 0.1 M perchloric acid, using naphthol benzene solution, and end point is the colour change from orange-yellow to green.

Storage: It should be stored in well-closed airtight container and protected from light.

Dosage forms: Droperidol injection BP, droperidol tablets BP.

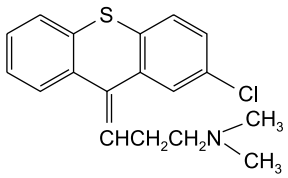
SAR of Butyrophenones



- Antipsychotic activity is seen when Ar group is an aromatic system in which fluoro-substituents at *para*-position enhances the activity.
- When X = carbonyl (C = O) optimal activity is seen, although other groups C(H)OH, C(H) aryl (pimozide) also afford good activity.
- When $n = 3$, activity is optimal, longer, or shorter chains decrease the activity.
- Aliphatic amino nitrogen is required and highest activity is seen when it is incorporated into a cyclic form.
- Ar_1 group should be an aromatic and is needed; it should be attached directly to the fourth position or occasionally separated from it by one intervening atom.
- The Y group can vary and assist the activity.
- The empirical SARs could be constructed to suggest that the 4-aryl piperidino moiety is super imposable on the 2-phenyl ethyl amino moiety of dopamine and accordingly could promote affinity for D_2 and D_3 receptors.
- The long N-alkyl substituent could help to promote receptor affinity and produce receptor antagonism activity or inverse agonism.

V. Thioxanthines

a. Chlorprothixene



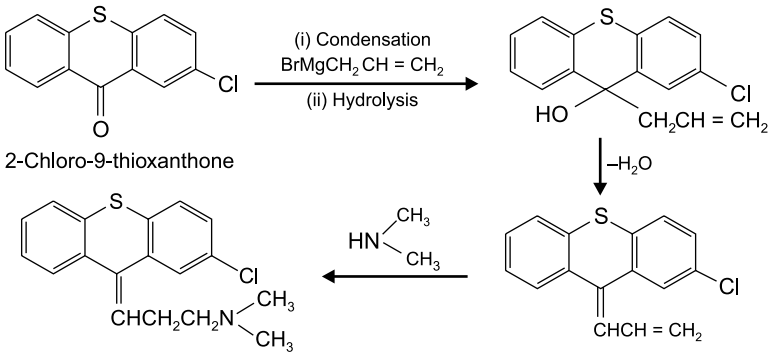
2-Chloro-9-(3,3-dimethylaminopropylidene)thioxanthene

Properties and uses: It is a white or almost white crystalline powder, slightly soluble in methylene chloride, and soluble in water and alcohol. It is used in the treatment of acute and chronic schizophrenia, psychotic and other conditions in which anxiety, agitation, and tension predominate.

Metabolism: Thioxanthines are closely related to the phenothiazine in their pharmacologic effects and there seems to be at least one major difference in metabolism, most of the thioxanthine do not form ring hydroxylated derivatives.

Assay: Dissolve the substance in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration, using 0.1 M sodium hydroxide.

Synthesis

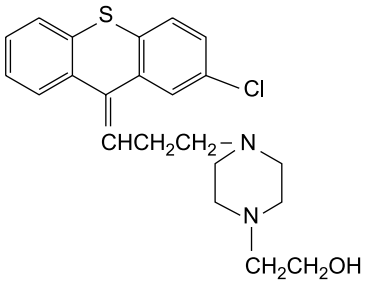


2-Chloro-9-thioxanthone

Chlorprothixene

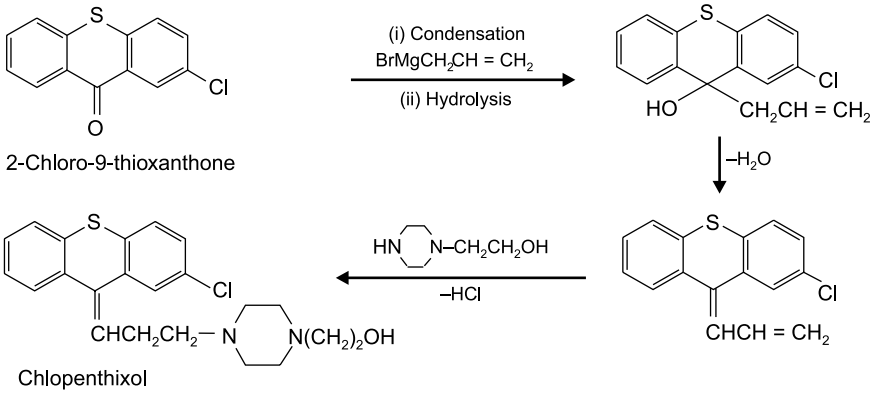
Storage: It should be stored in well-closed airtight container and protected from light.

b. Clopenthixol



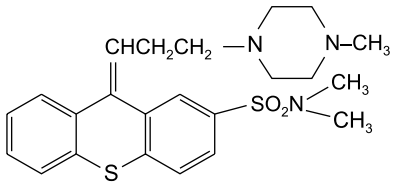
4-[3-(2-Chloro-thioxanthen-9-yliden) propenyl]-1-piperazin ethanol

Synthesis

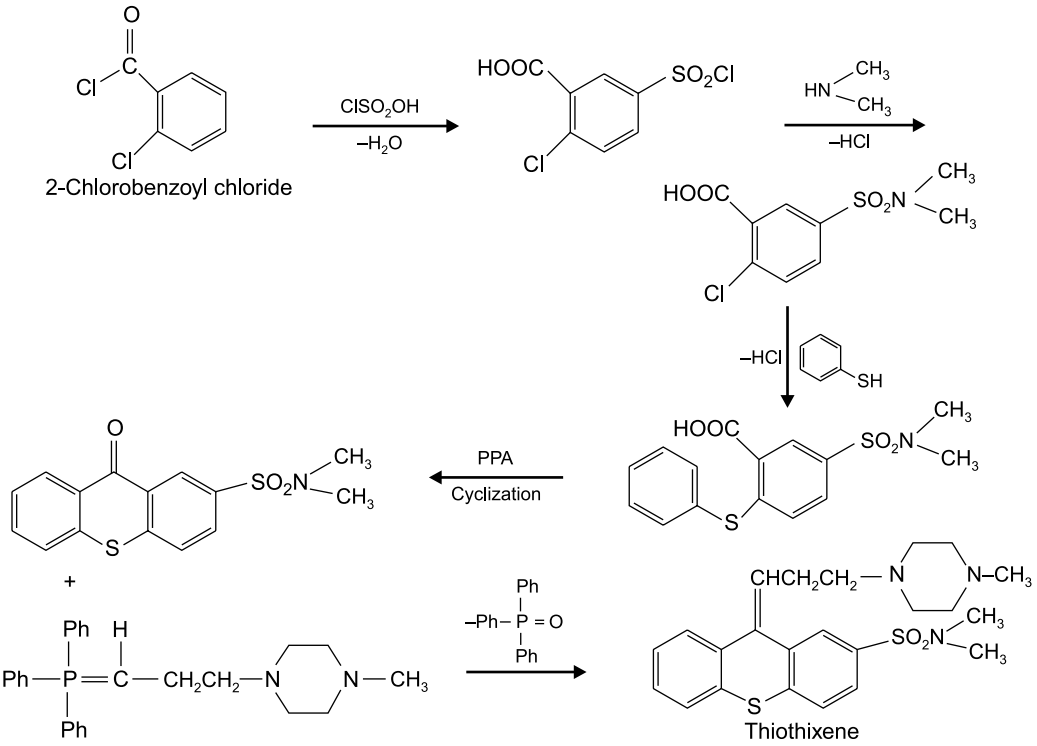


Uses: It is used in the treatment of schizophrenia and other psychotic states.

c. Thiothixene



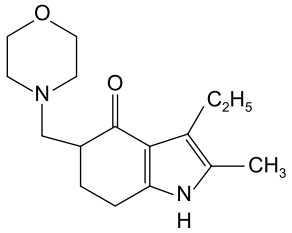
Synthesis



Properties and uses: White, or nearly white crystalline powder with slight odour, and affected by light, soluble in water, anhydrous alcohol, or chloroform, practically insoluble in benzene, acetone, or ether. The substituent in the second position produces Z and E isomers. The Z isomers are the more active antipsychotic isomers. It was introduced as an antipsychotic agent useful in the management of schizophrenia and other psychotic states. It is also helpful in the management of secondary symptoms of schizophrenia, such as hallucinations, tension, and suspiciousness. It also shows antidepressant property.

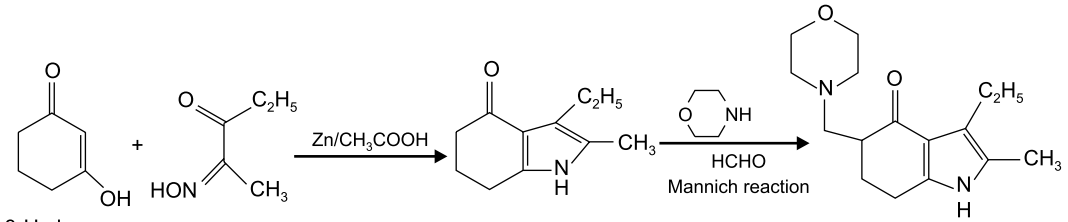
VI. Dihydroindolones

a. Molindone (Liclone, Moban)



3-Ethyl-2-methyl-5-(morpholinomethyl)-6,7-dihydro-indol-4-one

Synthesis



3-Hydroxy-cyclohex-2-enone

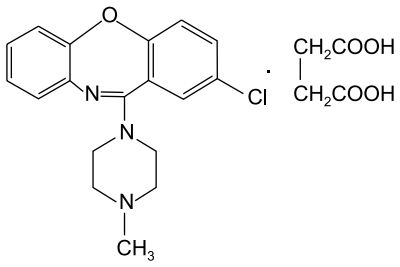
Molindone

Properties and uses: Exists as white crystals, freely soluble in water or alcohol, it is a potent antipsychotic as trifluoperazine and all the side effects resemble those of the phenothiazines. It is used in the treatment of schizophrenia and other psychosis.

Dose: The usual dose is 15–25 mg/day.

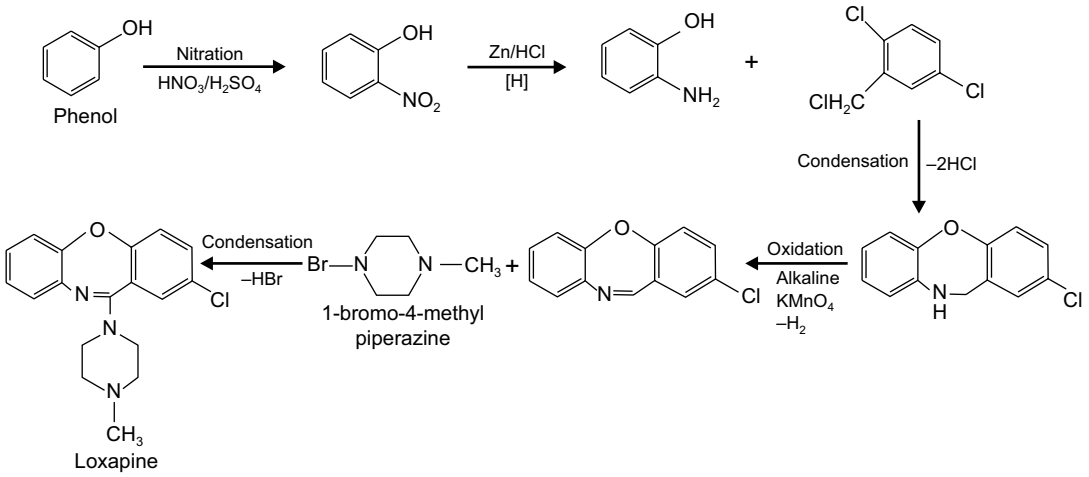
VII. Dibenzoxazepinones

a. Loxapine succinate (Loxapac)



2-Chloro-11-(4-methyl-1-piperazinyl)dibenz(1,4)oxazepine succinate

Synthesis

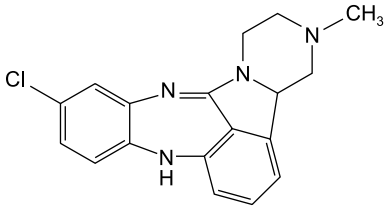


Properties and uses: Exist as white to off-white crystalline powder, slightly soluble in water or alcohol. It may give rise to possible anticholinergic and antiadrenergic activity. It must be employed with great caution in such patients who have either a history of glaucoma or urinary retention problems. It has resulted from the expansion of the six-membered central ring of phenothiazine followed by isosteric replacement of one or more atoms with oxygen. Because of its seven-membered central ring, the conformation of loxapine is more twisted than that of the phenothiazine rings. It is used for symptomatic control of schizophrenia.

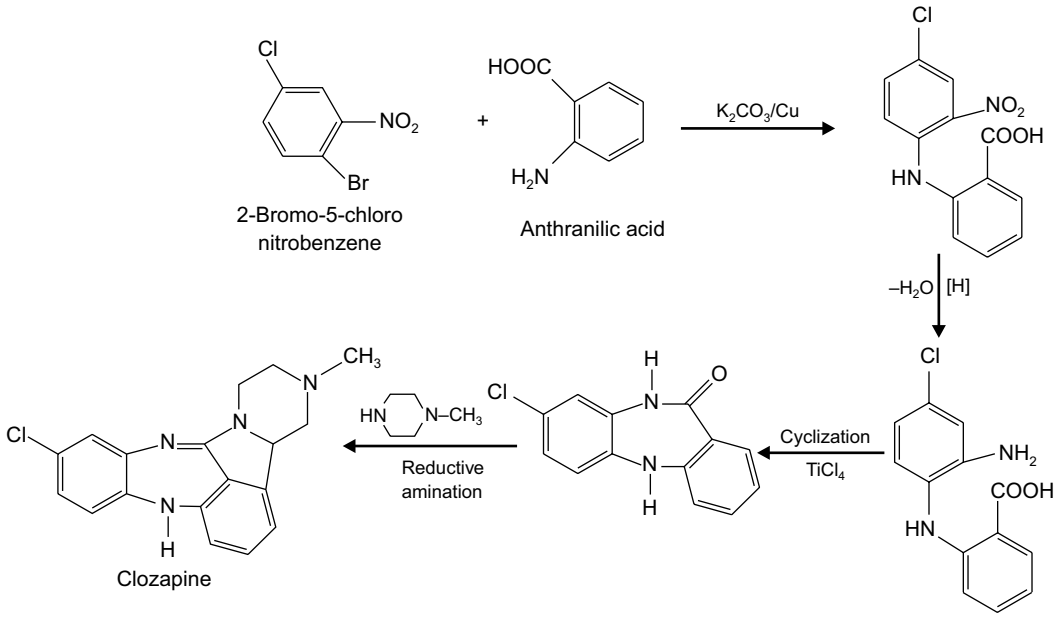
Dose: The usual dose is 20–250 mg/day.

VIII. Dibenzodiazepines

a. Clozapine (Lozapin, Sizopin, Clopaz)



Synthesis



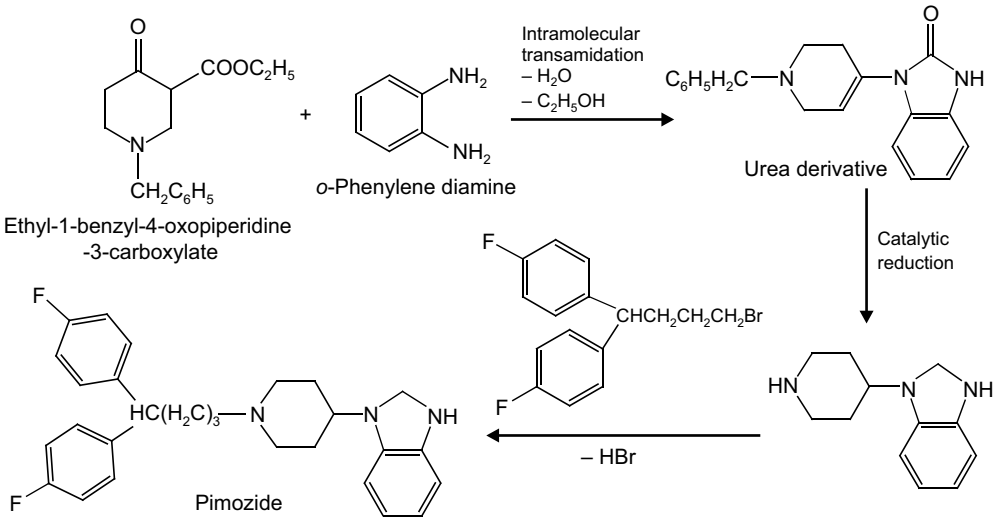
Properties and uses: It is a yellow crystalline powder, dissolves in dilute acetic acid, insoluble in water, freely soluble in methylene chloride, and soluble in alcohol. It has more affinity for D_1 and less for D_2 dopamine receptors. It may have its unique profile due to the blockade of D_1 receptors and M_1 muscarinic activity. It has high potentially fatal agranulocytosis. Other adverse side effects include drowsiness, dizziness, and dose-related seizures. It is effective in individuals suffering from disorganization. For example, loose associations, inappropriate effect, incoherence, and reduction in rational thought processes.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: For schizophrenia: Adult—12.5 mg 1–2 times on day 1 followed by 25 mg 1–2 times on day 2 increased gradually in increments of 25–50 mg up to a daily dose of 300 mg with 14–21 days. Subsequent increments of 50–100 mg may be made 1–2 times weekly. Usual dose is 200–450 mg/day. Maximum: 900 mg/day. Elderly: Initially, 12.5 mg on day 1 increased subsequently by increments of 25 mg. For psychosis in Parkinsonism: Adult—initially, 12.5 mg once daily at night, increased in steps of 12.5 mg up to two times each week, not >50 mg/day at the end of the second week. Usual dose: 25–37.5 mg daily. Maximum of 100 mg daily.

IX. Diphenyl Butyl Piperidine Analogues

a. Pimozide

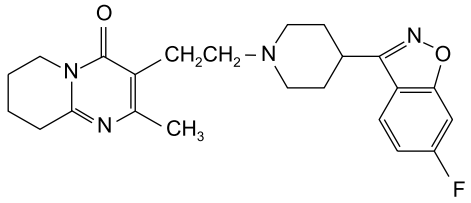


Properties and uses: It is a white or almost white powder, practically insoluble in water sparingly soluble in methanol and slightly soluble in alcohol. Used as a tranquillizing agent.

Assay: Dissolve the sample in 50 ml mixture of one volume of anhydrous acetic acid and seven volumes of methyl ethyl ketone and titrated with 0.1 M perchloric acid, using naphtholbenzein solution as an indicator.

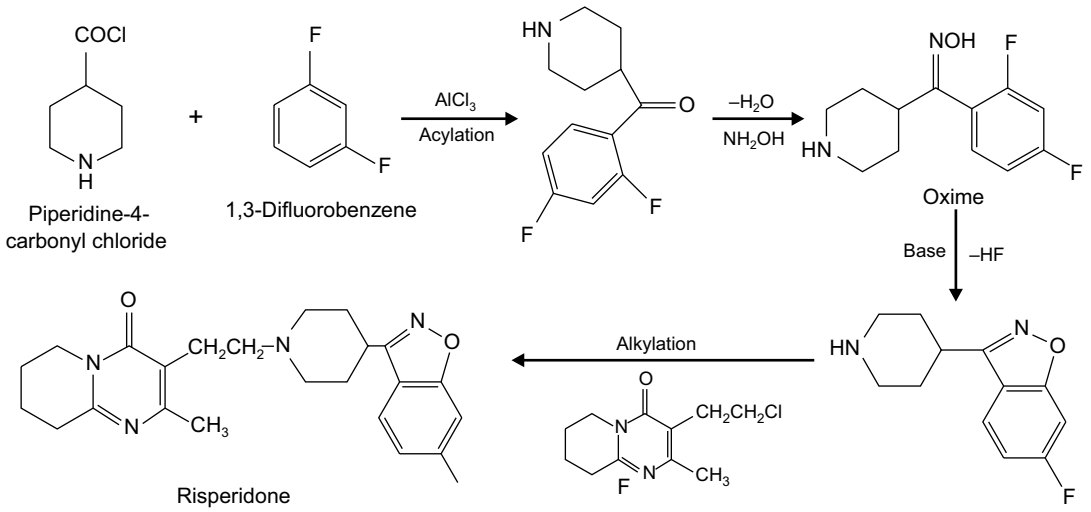
X. Benzisoxazoles

a. Risperidone (Respidon, Sizodon, Rispid)



3-[2-[4-(6-Fluoro-1,2-banzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido(1,2-a)pyrimidin-4-one

Synthesis



Properties and uses: It is a white or almost white powder, dissolves in dilute acid solutions, insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol. It is a typical antipsychotic and neuroleptic. Its adverse effects include nasal congestion, orthostastic hypotension, insomnia, and possible EPS. Causes more EPS than other atypical agents. May cause weight gain and an increased tendency for glucose intolerance. Risperidone has structural features of hybrid molecules between butyrophenone and trazodone. It is a typical antipsychotic, effective against the negative symptoms of schizophrenia.

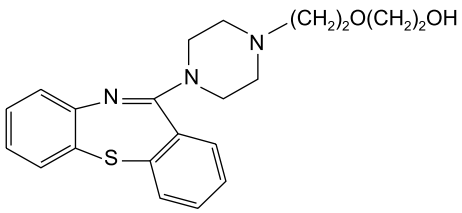
Assay: Dissolve the sample in 70 ml of a mixture of 1 volume of anhydrous acetic acid and 7 volumes of methyl ethyl ketone and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

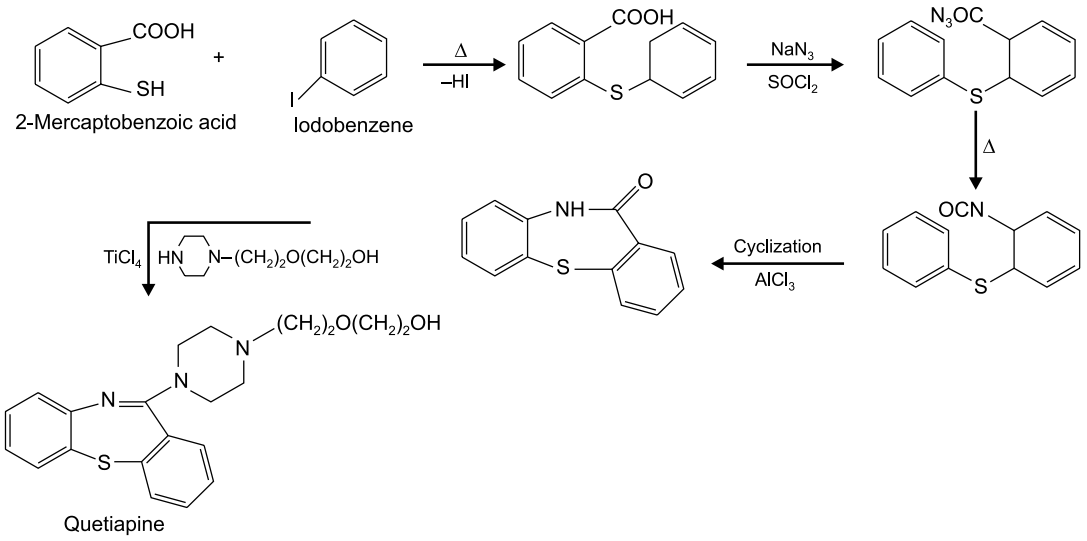
Dose: For schizophrenia: Adult—initially, 2 mg daily, may increase to 4 mg daily on the second day, adjusted further in increments or decrements of 1–2 mg daily at weekly intervals. Doses may be given in 1–2 divided doses. Maintenance: 4–6 mg daily. Maximum: 16 mg/day. For elderly: Initially, 0.5 mg two times a day gradually increased in increments of 0.5 mg twice a day. Maintenance: 1–2 mg twice a day.

XIII. Miscellaneous

Quetiapine (Placidin, Q-Pin, Pincalm)



Synthesis

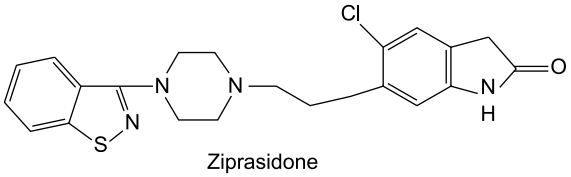


Quetiapine

Properties and uses: It exists as white crystals. Quetiapine is used orally to treat psychotic disorders and symptoms, such as hallucinations, delusions, and hostility.

Dose: For schizophrenia: Adult—initially, 25 mg twice a day on day 1 increased to 50 mg twice a day on day 2, 100 mg twice a day on day 3, and 150 mg twice a day on day 4. Usual dose range: 300–450 mg daily. Maximum: 750 mg/day. For elderly: Initially, 25 mg daily, increased in steps of 25–50 mg daily according to response.

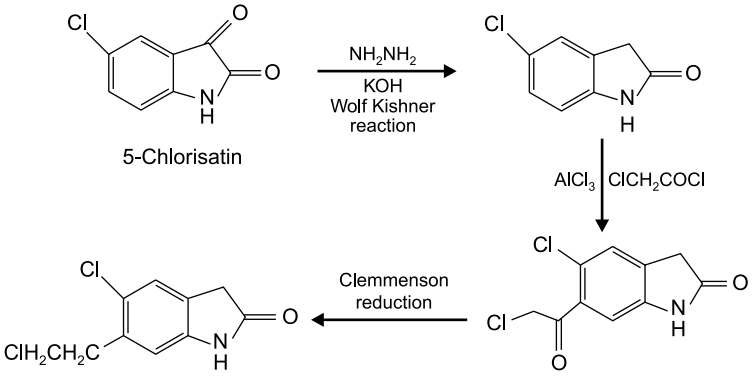
b. Ziprasidone (Azona, Zipsydon)



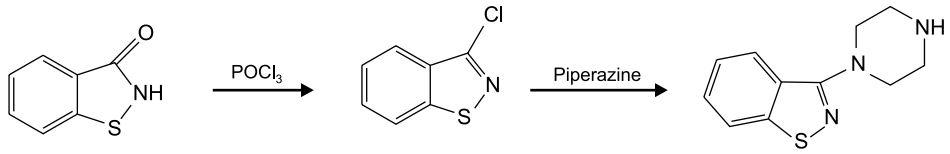
Ziprasidone

Synthesis

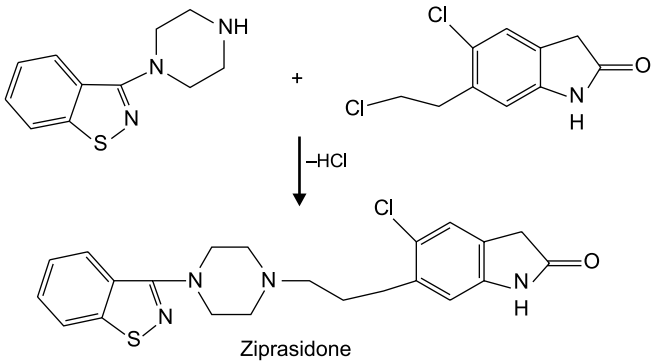
Step I



Step II



Condensation of products of *Step II* and *Step I*

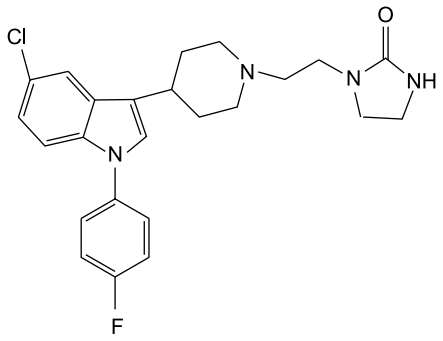


Ziprasidone

Properties and uses: It exists as a white to faint pink powder, hemihydrate. An atypical antipsychotic, this agent must be given with food twice daily for maximum effect. Adverse effects include somnolence and minor QTC prolongation. Currently, this is the only atypical antipsychotic available in a parenteral (IM) formulation.

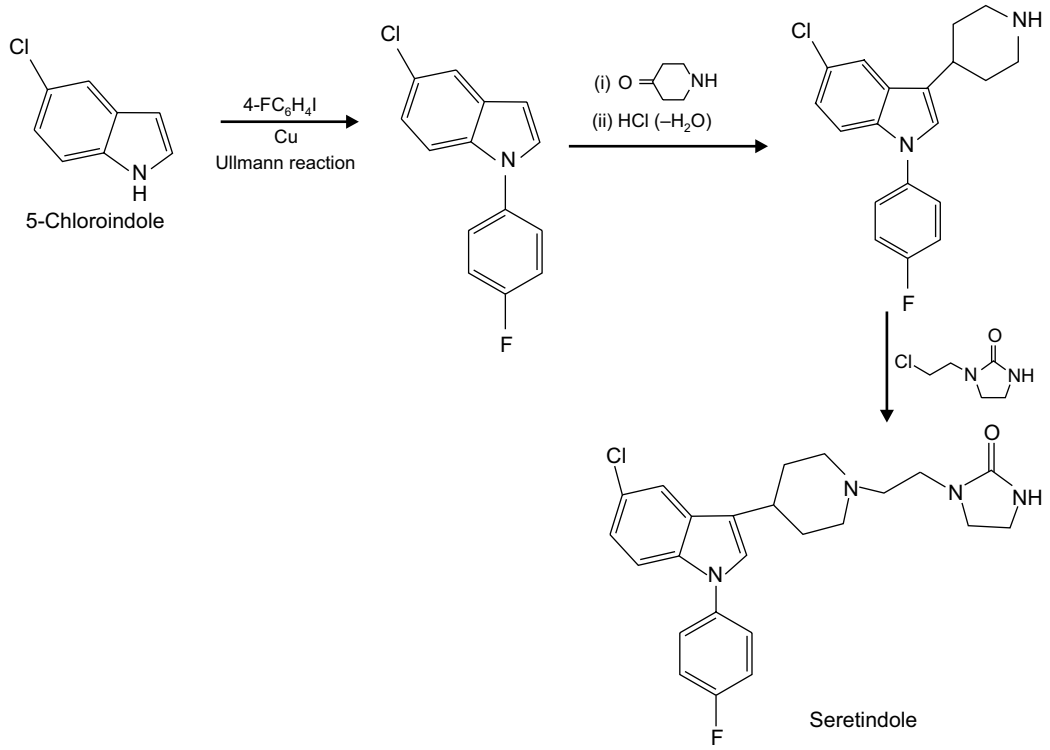
Dose: For schizophrenia: Adult—as hydrochloride—≥18 years—initially 20 mg twice a day, increase if necessary at intervals of not less than 2 days, up to 80 mg twice a day. Maintenance: 20 mg twice a day. Elderly: Lower initial dose with slow titration and close monitoring.

c. Seretindole

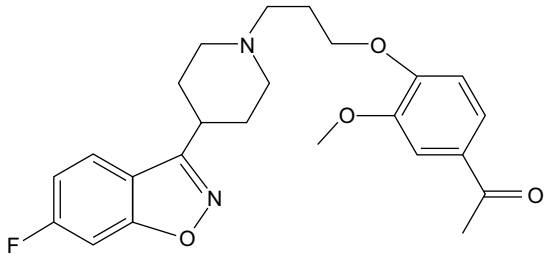


1-(2-(4-(5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl)piperidin-1-yl)ethyl)imidazolidin-2-one

Synthesis



d. Iloperidone (Fanapt)



Mode of action: The mechanism of action of iloperidone is unknown. However, it is proposed that the efficacy of iloperidone is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 ($5\text{-}HT_2$) antagonisms.

Properties and uses: Iloperidone is a psychotropic agent belonging to the chemical class of piperidinyl-benzisoxazole derivatives. It is specifically used for the acute treatment of adults with schizophrenia. Iloperidone is supplied as a tablet designed for oral administration. Iloperidone must be titrated slowly from a low starting dose to avoid orthostatic hypotension. Adverse events associated with the use of this drug include, dizziness, somnolence, dry mouth, nausea, tachycardia, diarrhea, orthostatic hypotension, weight gain.

Dose: The recommended starting dose for iloperidone tablets is 1 mg twice daily. Increases to reach the target dose range of 6–12 mg twice daily may be made with daily dosage adjustments to 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. The maximum recommended dose is 12 mg twice daily (24 mg/day).

e. Lurasidone (Latuda)

Mode of action: The mechanism of action of lurasidone is unknown, however has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine type 2 (D) and serotonin type 2 ($5HT_2A$) receptor antagonism.

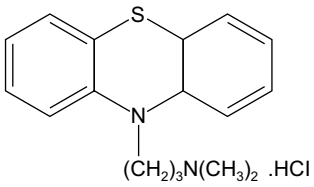
Properties and uses: Lurasidone is a psychotropic agent belonging to the chemical class of benzoisothiazol derivatives. It is used for the treatment of patients with schizophrenia. Adverse events associated with the use of lurasidone may include somnolence, akathisia, nausea, Parkinsonism, agitation.

Dose: The recommended starting dose is 40 mg once daily and the maximum recommended dose is 80 mg/day. Lurasidone should be taken with food (at least 350 calories). Dose adjustments are recommended for the following: Patients with moderate and severe renal impairment, patients with moderate and severe hepatic impairment, patients taking concomitant potential CYP3A4 inhibitors and patients taking concomitant potential CYP3A4 inducers.

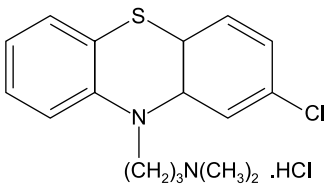
CLASSIFICATION BASED ON PCI SYLLABUS

Phenothiazines

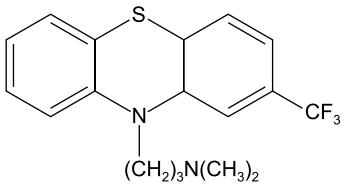
Promazine hydrochloride



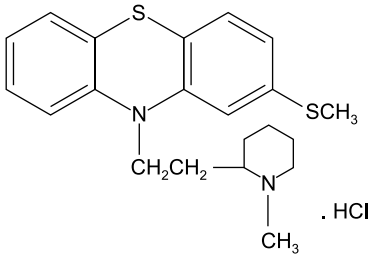
Chlorpromazine hydrochloride



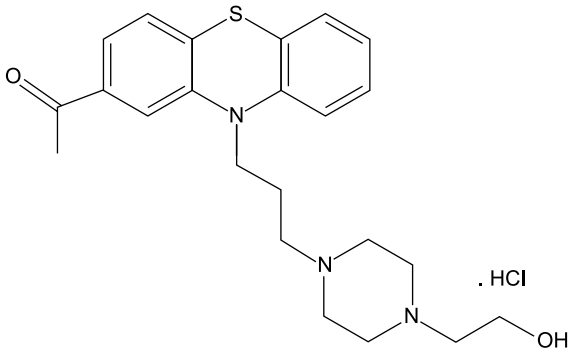
Triflupromazine



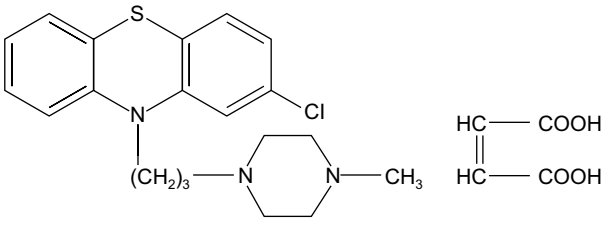
Thioridazine hydrochloride



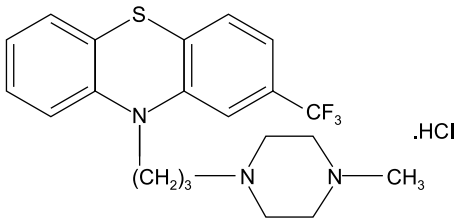
Piperacetazine hydrochloride



Prochlorperazine maleate

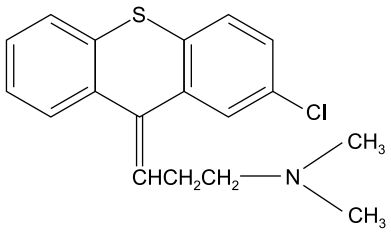


Trifluoperazine hydrochloride

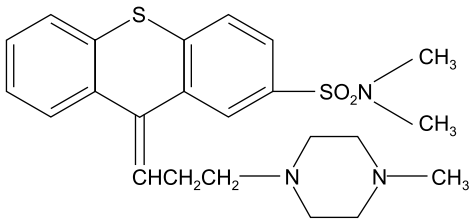


Ring Analogues of Phenothiazeines

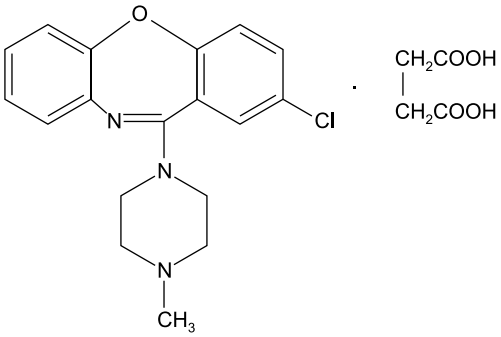
Chlorprothixene



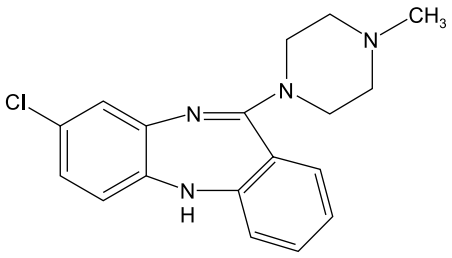
Thiothixene



Loxapine succinate

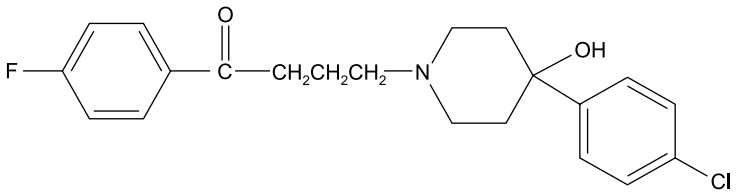


Clozapine

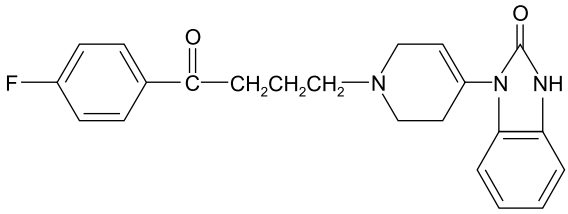


Fluorobutyrophenones

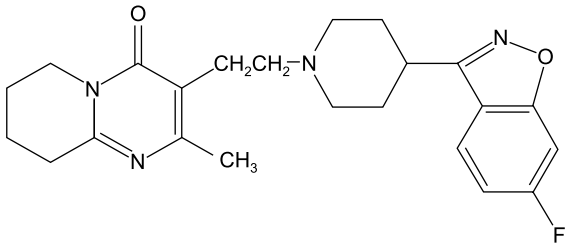
Haloperidol



Droperidol

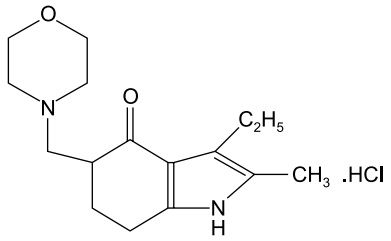


Risperidone



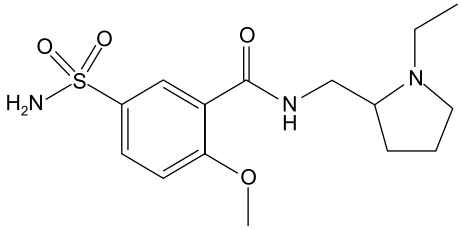
Beta Amino Ketones

Molindone hydrochloride



Benzamides

Sulpieride



PROBABLE QUESTIONS

1. What are tranquillizers? Write the mode of action and synthesis of any one benzodiazepine derivative.
2. Write note on fluorobutyrophenones used as tranquillizers.
3. Classify the phenothiazines used as tranquillizers, based on their substituents. Write the mode of action, synthesis, and uses of butaperazine.
4. Name some thioxanthines used as tranquillizers and write the synthesis and uses of chlorprothixene.
5. Write the synthesis and drug profile of chlorpromazine and chlordiazepoxide.
6. Write the SAR of phenothiazines used as tranquillizers.
7. Write the synthesis and uses of droperidol and clozapine.

CHAPTER 27

Antidepressants

INTRODUCTION

Antidepressants are drugs which enhance alertness and may result in an increased output of behaviour. They are used for the relief of symptoms of moderate and severe depressive disorder.

Depression is characterized by feelings of intense sadness or worry, agitation, self-depression, physical changes, such as insomnia, anorexia, loss of enthusiasm, and mental slowing. Major depression is one of the most common psychotic disorders. At any given moment, about 5–6% of the population is depressed and estimated 10% of the people may become depressed during their lives. Depression is a heterogeneous disorder that has been characterized and classified into a variety of types.

1. Reactive or secondary depression (occurs in response to illness and it is most common).
2. Endogenous depression (a genetically determined biochemical disorder).
3. Depression associated with bipolar effect (manic depression).

Endogenous depression occurs due to low concentration of various biogenic amines and other modulators of nervous transmission at neuronal level. Antidepressants are typically taken for at least 4–6 months.

Uses

Therapeutic uses of antidepressants are as follows:

- Moderate-to-severe depressive illness.
- Severe anxiety and panic attacks.
- Obsessive compulsive disorders.
- Chronic pain.
- Eating disorder.
- Post-traumatic stress disorder.

Antidepressants increase the availability of catecholamines at the appropriate receptor sites of the brain. Most of the antidepressants exerts important actions on the metabolism of monoamine neurotransmitters and their receptors particularly norepinephrine (NE) and serotonin. Their therapeutic activeness and actions together with strong evidence from genetic predisposition have lead to the speculation that the biological basis of major mood disorders may include abnormal function of monoamine neurotransmission disorders, including panic-agoraphobia, social and other phobias generalized anxiety and obsessive compulsive disorders that appear to be responsive with selective serotonin reuptake inhibitor. Mania and their association with bipolar disorders are less common

than major depression. Mania and its milder form is treated with antipsychotics, anticonvulsants, or lithium salts, sometimes supplemented with a potent sedative in short term and lithium salts or any anticonvulsants with mood stabilizing property. Imipramine, amitryptaline, and their N-demethyl derivatives are widely used for major depression. The ability of monoamine oxidase (MAO) inhibitors were noted in 1950, and they are also used in therapy for major depressions, but has limitations due to the toxicities. Presently, selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine are used.

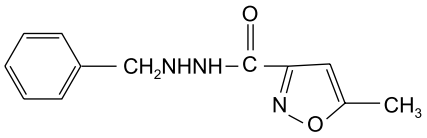
CLASSIFICATION

These drugs vary significantly in their chemical and pharmacological properties. One convenient way is to combine both aspects and classify accordingly.

I. Monoamine oxidase inhibitors (MAOIs)

1. Hydrazines

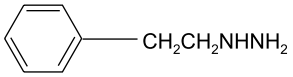
a. Isocarboxazide



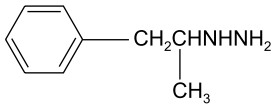
b. Iproniazid



c. Phenelzine

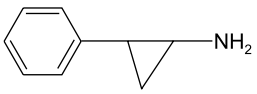


d. Pheniprazine

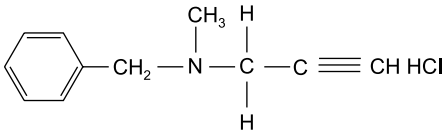


2. Non-hydrazines

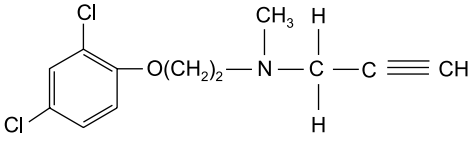
a. Tranylcypromine



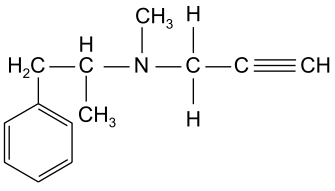
b. Pargyline HCl



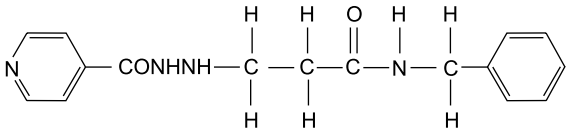
c. Clorgyline



d. Deprenyl

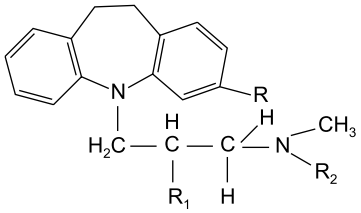


e. Nialamide



II. Tricyclic antidepressants (TCAs)

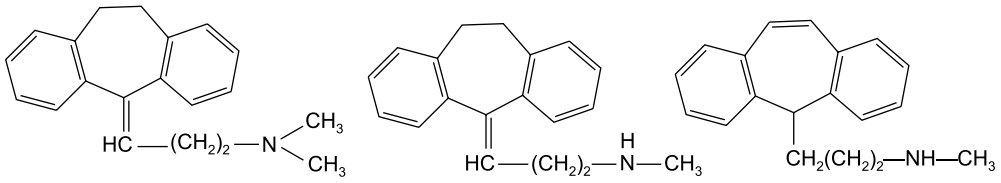
1. Dibenzazepines



S. No.	Drugs	R	R_1	R_2
1.	Imipramine	–H	–H	$-CH_3$
2.	Desipramine	–H	–H	–H
3.	Trimipramine	–H	$-CH_3$	$-CH_3$
4.	Chlorimipramine	–Cl	–H	$-CH_3$

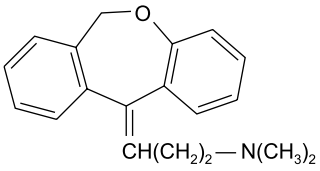
2. Dibenzocycloheptane derivatives

a. Amitryptyline **b. Nortryptyline** **c. Protriptyline**

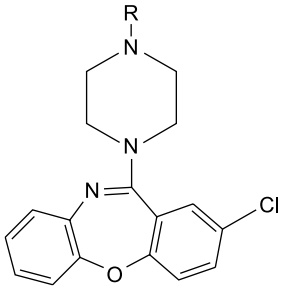


3. Dibenzoxepine derivatives

⋆ Doxepin



4. Dibenzoxazepine derivatives



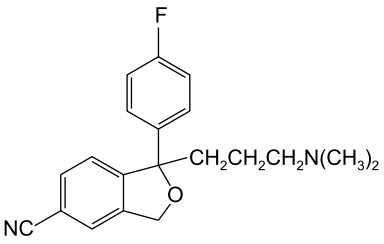
a. Amoxapine R = H
b. Loxapine R = $-CH_3$

III. Second-generation antidepressants

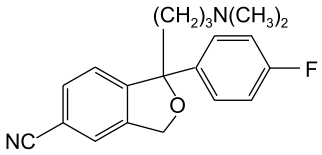
a. **Bicyclic:** Viloxamine, zimeldine
b. **Tricyclic:** Dibenzepine, amoxapine, imprindole
c. **Tetracyclic:** Mamprotiline, mianserin

IV. Selective serotonin reuptake inhibitors (SSRIs)

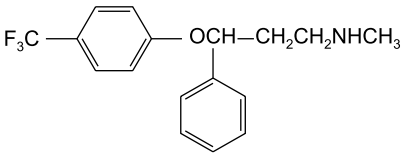
a. **Citalopram** (±) isomer



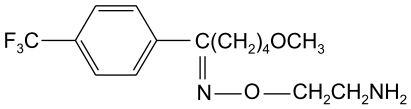
b. **Escitalopram** (+) isomer



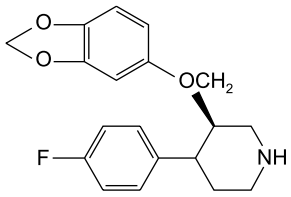
c. **Fluoxetin**



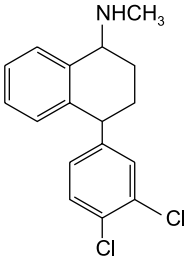
d. **Fluvoxamine**



e. **Paroxetine**

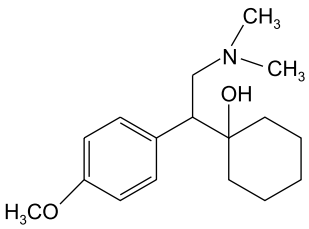


f. **Sertraline**

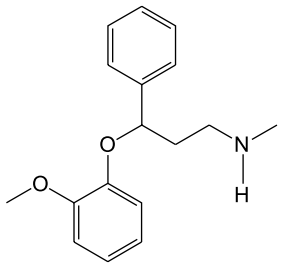


V. Selective NE reuptake inhibitors

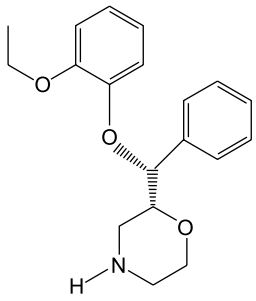
a. **Venlafaxine**



b. Nisoxetin



c. Roboxetine



VI. Benzodiazepines

For structure refer Chapter 23 'Sedatives and Hypnotics'.

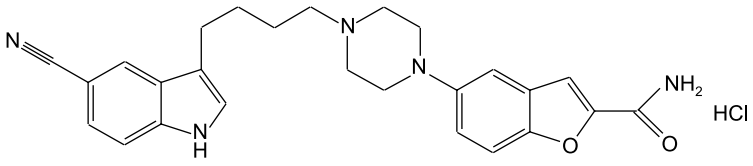
VII. Electroconvulsive therapy

VIII. Miscellaneous

a. β-Adrenoreceptor agonists: Salbutamol, clenbutral
b. Thyrotropine releasing hormone (TSH)
c. Others: Trazadone, nomifenzine, bupropion, fluvoxamine

Newer Drugs

Vilazodone hydrochloride (Viibryd)

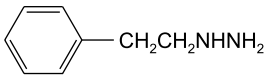


SYNTHESIS AND DRUG PROFILE

I. Monoamine oxidase inhibitors (MAOIs)

Mode of action: MAO is a family of enzymes located in the outer membrane of mitochondria. MAO inhibitors block the intracellular metabolism of biogenic amines, these results in increased amines concentration in the nerve terminals, whereas tricyclic antidepressants and others inhibit the reuptake of NE and serotonin by nerve terminals, this inturn facilitates adrenergic neurotransmission and produces an antidepressant action.

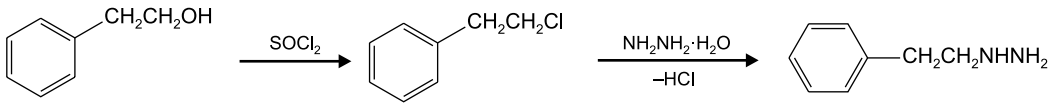
a. Phenelzine (Catron)



2-Phenyl ethyl hydrazine

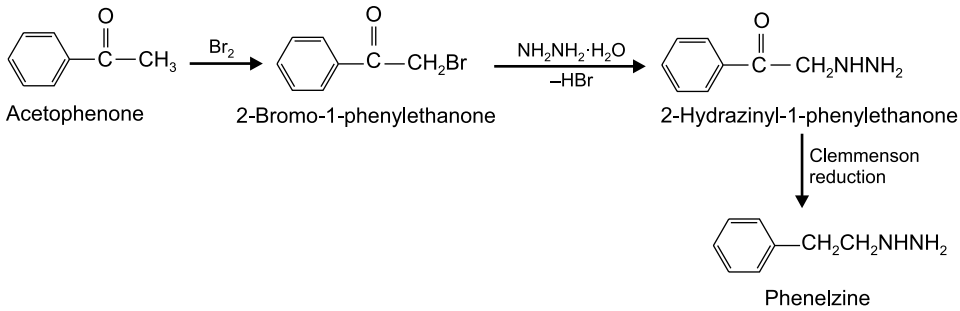
Synthesis

Route I. From: 2-Phenyl ethyl alcohol



2-Phenyl ethyl alcohol — Phenyl ethyl chloride — Phenelzine

Route II. From: Acetophenone



Acetophenone — 2-Bromo-1-phenylethanone — 2-Hydrazinyl-1-phenylethanone

Phenelzine

Properties and uses: It is a white powder or pearly platelets, insoluble in ethanol and in ether, but freely soluble in water. It is a MAOI with low sedative and antimuscarnic effects, causing weight gain. It is used primarily in the treatment of depression and certain phobic-anxiety states effective in neurotic or typical depressed patients.

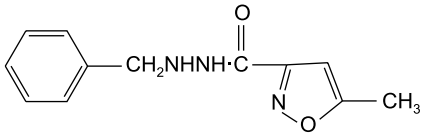
Assay: Dissolve the substance in water, add sodium hydrogen carbonate, and 0.05 M iodine VS, close the flask and allow to stand for 90 min. To this add 20 ml of 2 M hydrochloric acid and titrate with 0.1 M sodium thiosulphate, using starch mucilage as an indicator.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 15–30 mg/day, orally three times a day.

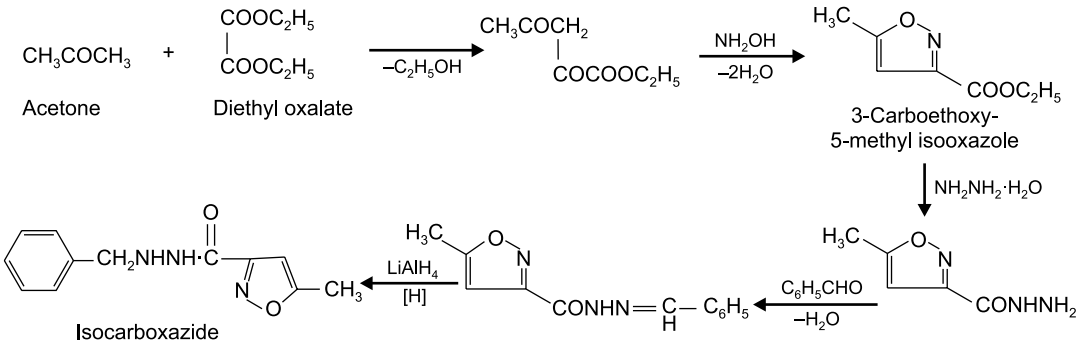
Dosage forms: Phenelzine tablets BP.

b. Isocarboxazide

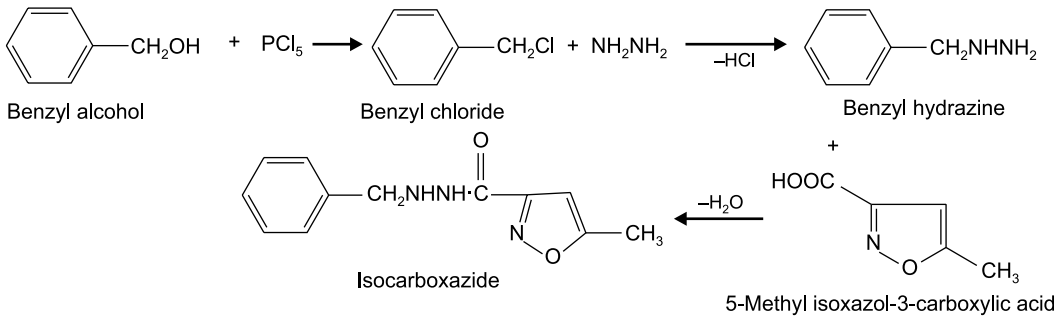


Synthesis

Route I. From: Acetone and diethyl oxalate

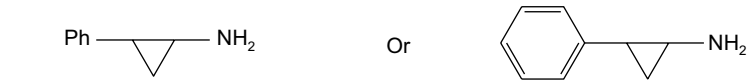


Route II. From: Benzyl alcohol



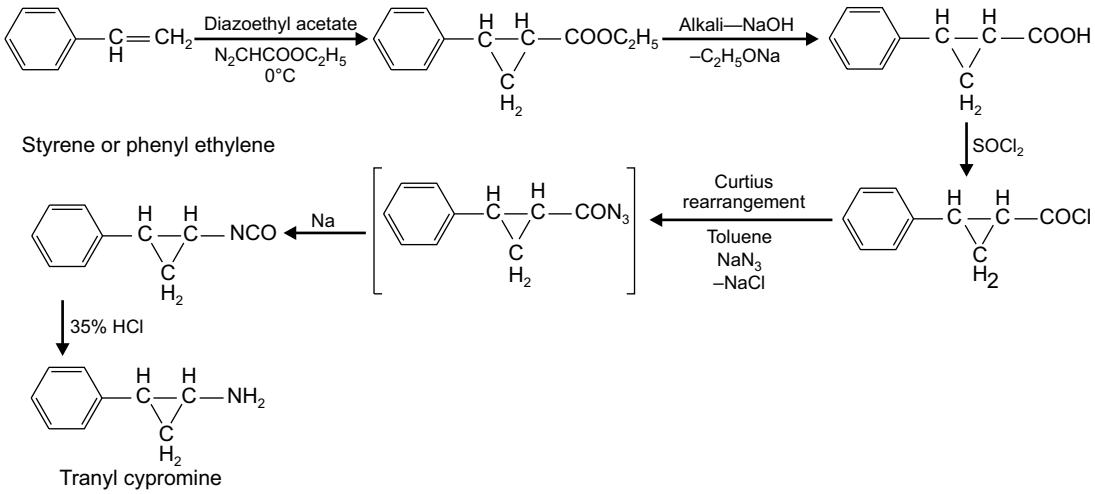
Properties and uses: It exists as white to off-white crystalline powder with slight characteristic odour, stable in dry air. Sparingly soluble in water, well soluble in ethanol, glycerol, or propylene glycol. An MAOI with low sedative and antimuscarnic effects causing weight gain, used in severe depressive state to whom tricyclic antidepressants (TCA) are contraindicated.

c. Tranyl cypromine (Synonym: Parnale)



(±)*trans*-2-phenylcyclopropyl amine

Synthesis (From: Styrene)



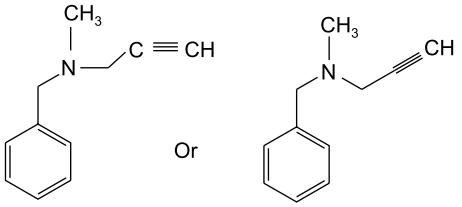
Properties and uses: It is a white or almost white crystalline powder, slightly soluble in ethanol and in ether, but soluble in water. It can be regarded as a ring-closed derivative of amphetamine. It will produce severe hypertensive crisis if taken together with cheese. It is not to be used in cardiovascular disease. It has amphetamine-like action and releases NE centrally. This perhaps accounts for the relative rapidity of action with this drug (in 48 h) in contrast to other MAO inhibitors, which have taken 2–3 weeks. It is used for hospitalized patients with endogenous depression, and who have not responded to other antidepressants. Can be indicated in elderly patients.

Assay: Assayed by non-aqueous titration and the end point determined potentiometrically.

Dose: Usual dose is 20–30 mg/day, orally in the morning and afternoon for 2 weeks.

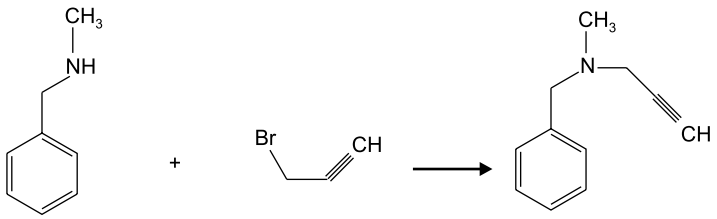
Dosage forms: Tranyl cypromine tablets BP.

d. Pargyline



N-Methyl-N-propynyl benzyl amine

Synthesis



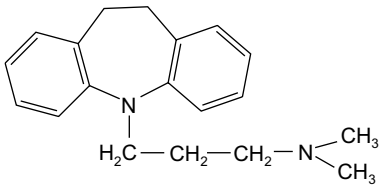
N-Methyl benzylamine + 2-Propynyl bromide → Pargyline

Properties and uses: It possesses hypotensive and stimulant properties. It is recommended for the treatment of hypertension rather than for use in depressed states. It may act through a negative feedback on NE synthesis, and has a long duration of action. Patient receiving pargyline should not receive sympathomimetic amines.

II. 1. Dibenzazepines

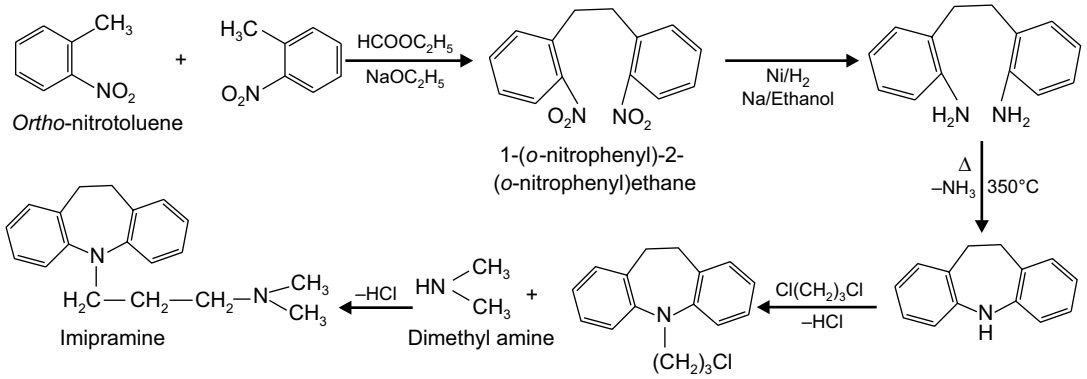
Mode of action: Tricyclic antidepressants inhibit the active reuptake of biogenic amines, that is, NE and 5-HT into their respective neurons, and thus, potentiate them. Following the release of NE by depolarization in the presence of Ca^{2+}, NE interacts with postsynaptic α- and β-adrenergic receptors as well as presynaptic α_2-autoreceptors. Inactivation of *trans*-synaptic communication occurs primarily by active transport (inhibited by tricyclics); secondary deamination by mitochondrial MAO blockade and inactivation of NE by tricyclics, initially, leads to α_2-receptor-mediated inhibition of the firing of neurons, and gradually on long-term administration of TCA, desensitize the α_2-autoreceptors and sensitizes the pre and postsynaptic NA/5-HT receptors and produces enhanced adrenergic and seretonergic transmission.

a. Imipramine (Synonym: Tofromil, Imavate, Microdep, Antidep, Depsol)



5-[3-(Dimethylamino)propyl]-10,11-dihydro-dibenzazepine

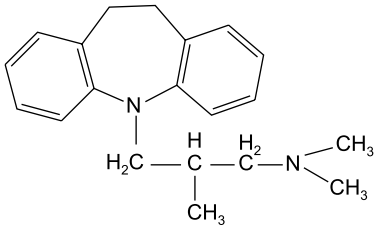
Synthesis



Properties and uses: Imipramine HCl is the lead compound of the TCAs. It is also closely related to the antipsychotic phenothiazines compounds. The compound has a tendency towards a high 5-HT/NE uptake block ratio. It is useful in treating endogenous depression particularly manic-depressive and involutional psychosis. It is also used routinely to treat nocturnal enuresis (bed wetting) in children aged 6 years and above.

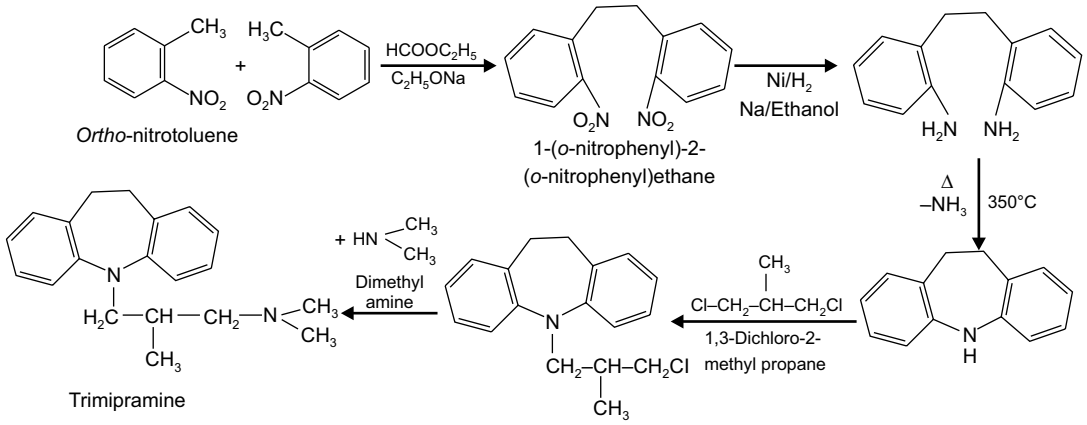
Dose: Usual dose is 50–150 mg daily in divided doses.

b. Trimipramine (Surmontil)



5-[3-(Dimethylamino)-2-methyl propyl]-10,11-dihydro-dibenzazepine

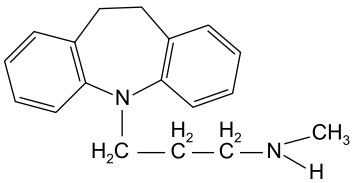
Synthesis



Properties and uses: It exists as white crystals, has bitter taste and slightly soluble in water or in alcohol, but freely soluble in chloroform. Replacement of hydrogen with an α-methyl substituent produces a chiral carbon. It is used as a racemic mixture. Biological properties reportedly resemble those of imipramine.

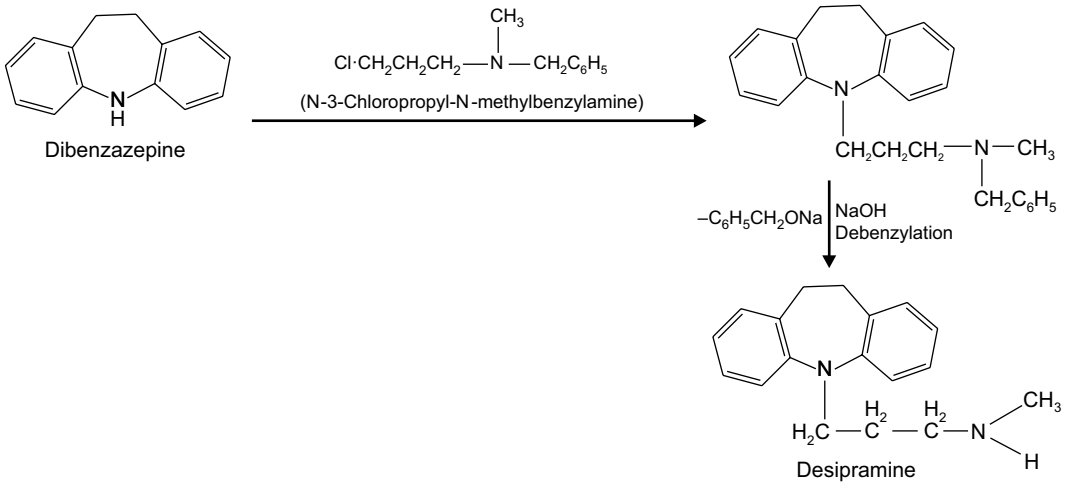
Dose: For depression: Adult—initially 50–75 mg daily, increased gradually as necessary to 150–300 mg daily. It may be given in divided doses during day or as a single dose at night. For elderly: Initially 50–75 mg daily, increased gradually if necessary. Maximum: 100 mg daily.

c. Desipramine



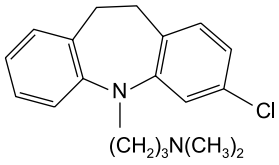
5-[3-(Methylamino)propyl]-10,11-dihydro-dibenzazepine

Synthesis



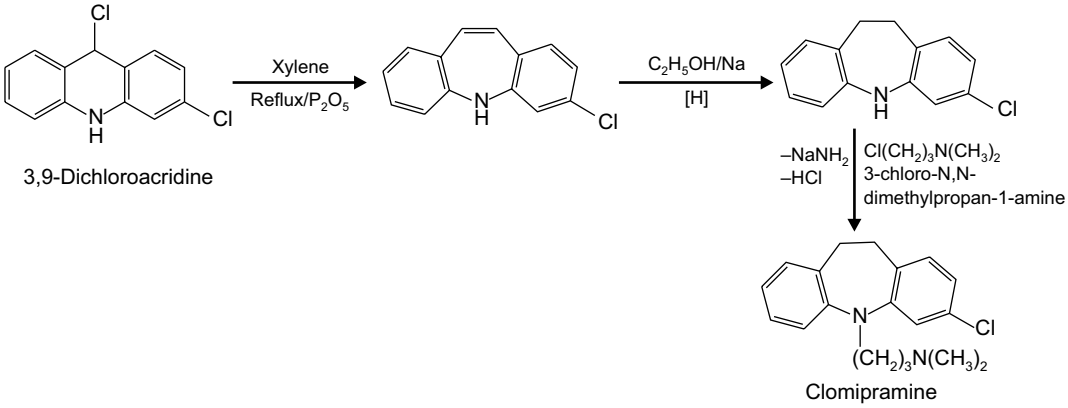
Properties and uses: It exists as white to off-white crystalline powder, odourless, with bitter taste, unstable after long exposure to light, heat, and air, soluble in water, alcohol, chloroform, or ether. It has few anticholinergic effects or (a low level of sedation). Used as an antidepressant with less antianxiety and sedative properties.

d. Clomipramine (Anafranil)



3-Chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-dibenzazepine

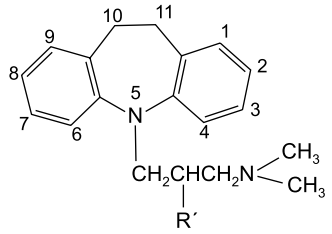
Synthesis



Properties and uses: It is a TCA with high sedative and intense antimuscarnic effects, causing hypotension and weight gain. Initially, indicated only for obsessive-compulsive disorder.

Dose: Usual dose is 25 mg twice or thrice/day.

SAR of Dibenzazepines



Variation in the side chain

- Maximum potency occurs when the basic nitrogen is separated from tricyclic nucleus by a propylene bridge.
- Ethylene in between ring and side chain 'N' atom gives significant activity.
- Increase in the 'C' length from propylene leads to it becoming ineffective or produce toxic effects.
- Branching does not affect the activity. For example, imipramine and trimipramine have same activity.
- A carbonyl functionality in position 1 of the propyl side chain of imipramine have antidepressant like activity.
- Side chain with quinuclidine, morpholine nuclei claimed to be potent.
- The tertiary amine and secondary amine in the side chain are important because they significantly affect both the monoamine reuptake activity as well as interaction with other receptors. For example, tertiary amines are more potent inhibitors of 5-HT reuptake, while secondary amines are more potent in their inhibition of NE reuptake. Tertiary amines also have more potent activity to α_1-adrenergic, muscarnic, and histaminic receptors.

Variation in the ring substituents

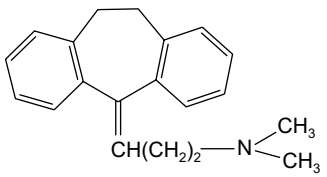
- Presence of chloro-substituent at C-3 is less active than imipramine.
- Presence of dimethyl or keto at C-10 leads to the compounds becoming ineffective.
- Placement of methyl group at 2,8 position or chloro group at 3,7 resulted in compounds becoming ineffective.

Variation in the ring system

- Iminostilbenes are equally active.
- Piperazinyl derivatives are ineffective.

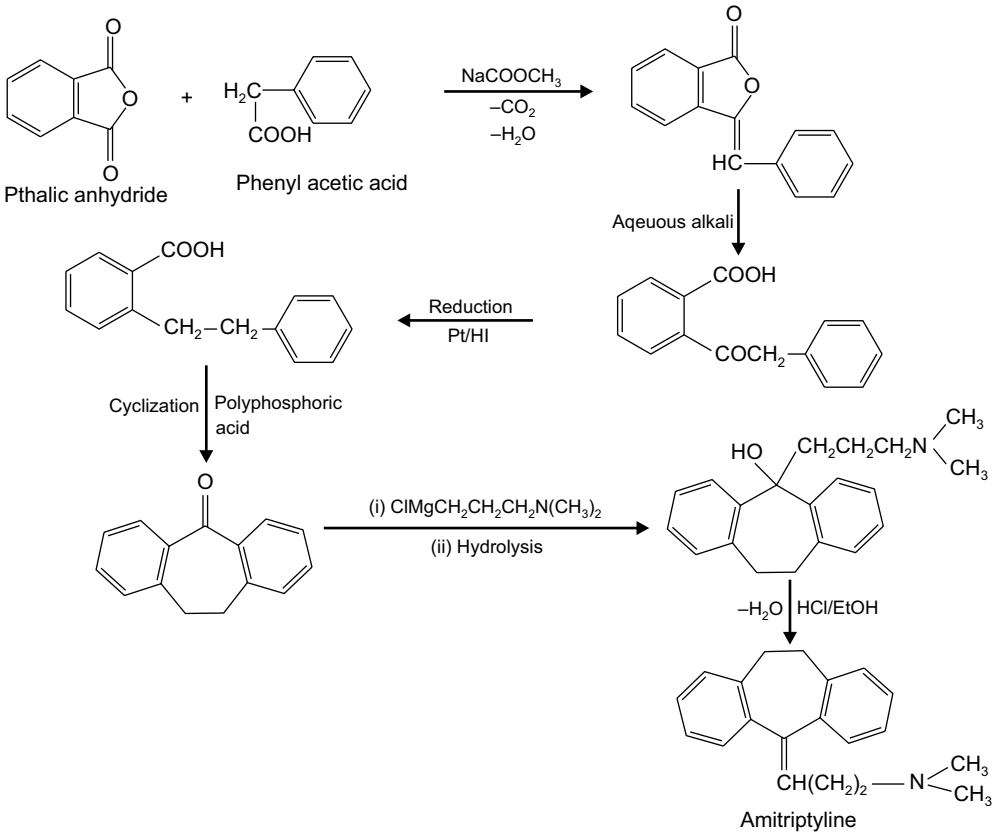
II. 2. Dibenzocycloheptane derivatives

a. Amitriptyline (Synonym: Envil, Amitril, Tryptomer, Amitone, Trilin)



5-(3-Dimethylaminopropyliden)-10,11-dihydro-dibenzocycloheptene

Synthesis



Properties and uses: It is a white or almost white powder or colourless crystals. Soluble in water, in alcohol, and in methylene chloride. It is one of the most anticholinergic and sedative of the TCAs, because it lacks the ring electron-enriching nitrogen atom of imipramine. Used for the treatment of depression associated with anxiety. It is also useful in the management of enuresis in children and adolescents.

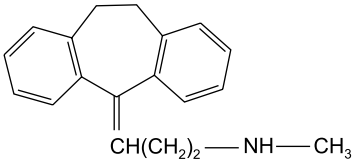
Assay: Dissolve the sample in alcohol. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Usual dose is 50–75 mg daily on divided doses or at single dose at night.

Dosage forms: Amitriptyline HCl tablets IP, amitriptyline tablets BP.

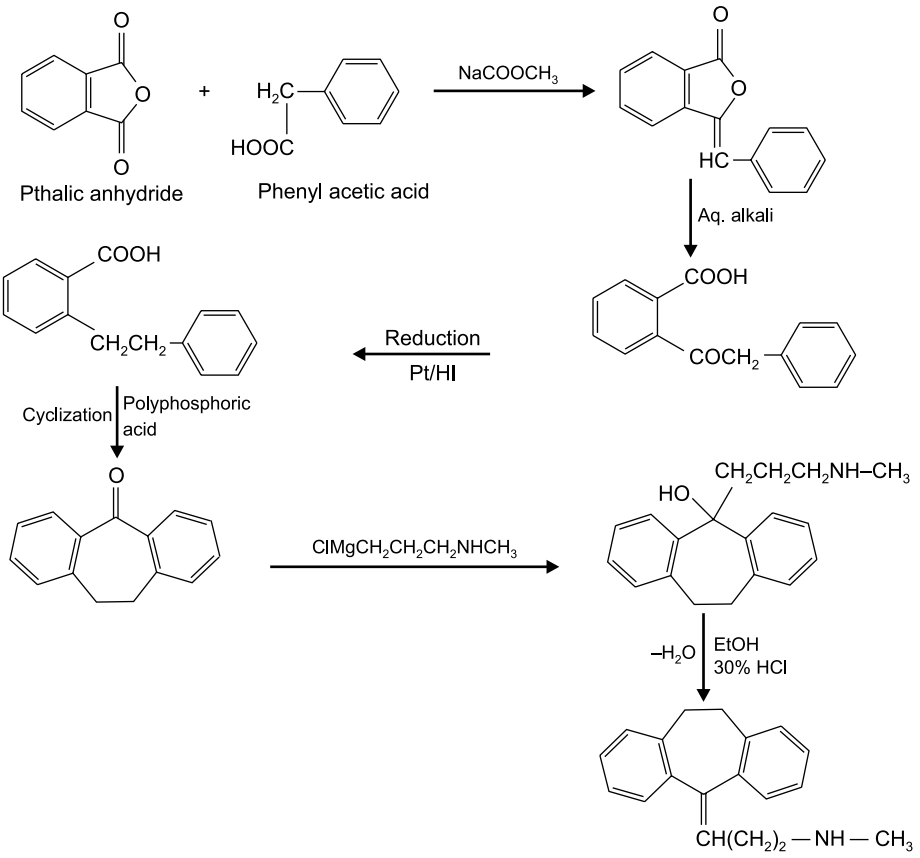
b. Nortriptyline (Synonym: Damelor, Aventyl HCl, Nordep, Nortin, Depival)



5-(3-Methyl amino propyliden)-10,11-dihydro-dibenzocycloheptene

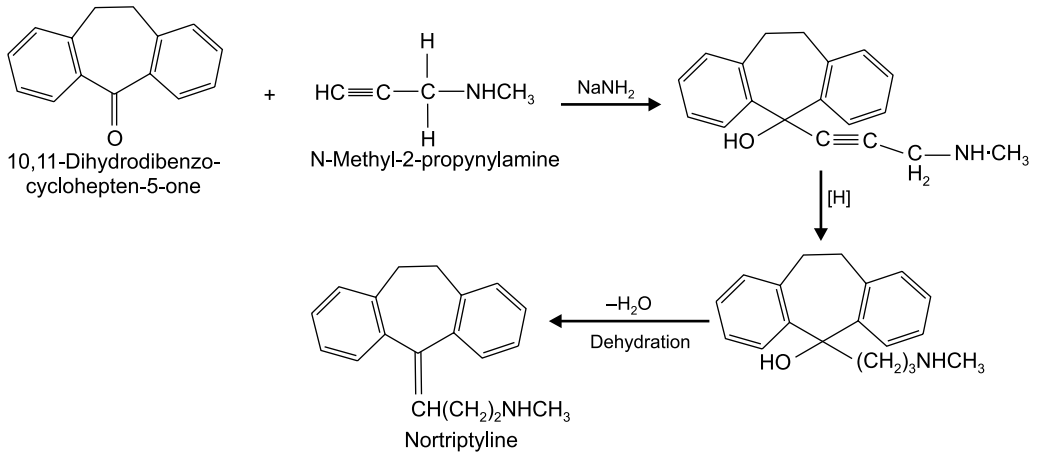
Synthesis

Route I. From: Phthalic anhydride



Nortriptyline

Route II. From 10,11-dihydrodibenzocyclohepten-5-one



Properties and uses: It is a white or almost white powder, soluble in ethanol and in methylene chloride, but sparingly soluble in water. A tricyclic, with moderate sedative and moderate antimuscarnic effects. It posseses antidepressant and tranquillizing properties, similar to those of the parent drug amitriptyline. It produces less anticholinergic, less sedative, and more stimulant action than amitriptyline.

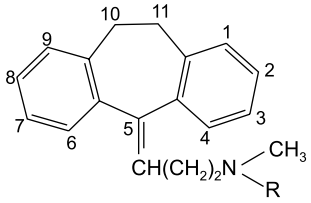
Assay: Dissolve the sample in ethanol, add 0.1 M hydrochloric acid and perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

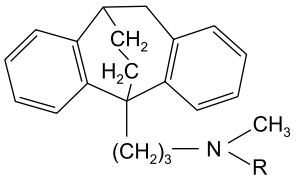
Dose: For depression: Adult—75–100 mg daily in 3–4 divided doses, increase gradually up to 150 mg daily in severe depression. Child: Adolescent—30–50 mg daily in divided doses. Elderly: 30–50 mg daily in divided doses.

Dosage forms: Nortriptyline HCl tablets IP, nortriptyline capsules BP, nortriptyline tablets BP.

SAR of Dibenzo Cycloheptane Derivatives



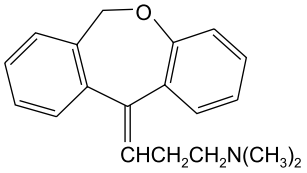
- Placement of –Cl at C-3 shows increase in activity, whereas, CH_3 at C-3 decreases CNS depression.
- Removal of N-methyl group of amitriptyline yielded nortriptyline, which is 2–5 times more potent than amitriptyline.
- Presence of double bond between 10th and 11th positions increases the activity.
- Unsaturation at C-5 enhances activity.
- When central ring size increases from 7 to 8 members (cyclo-octane), it is more effective.
- Several amitriptyline analogues in which replacement of C-11 with O, S, SO, SO_2, and NH are clinically effective antidepressants.
- Nortriptyline with exocyclic double bond and protriptyline with endocyclic double bond differ in their metabolism patterns. Protriptyline is less metabolized *in vitro* leading to a prolonged half-life and lower dose requirement.
- Novel bridged derivatives are very powerful, for example, maprotiline is a potent antidepressant, and the time to steady-state concentration is up to 7 days.



Maprotiline

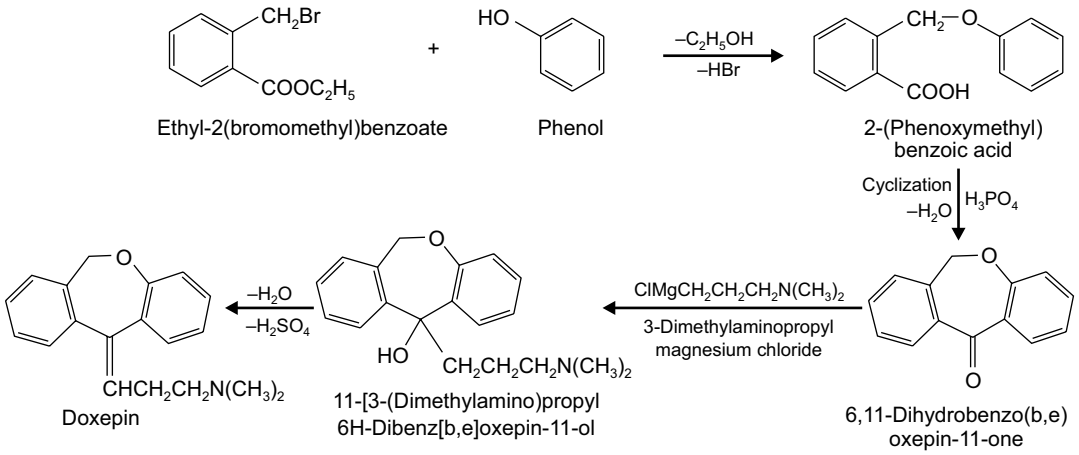
II. 3. Dibenzoxepine derivatives

1. Doxepin (Doxedep, Doxetar, Doxtin)



n-Dimethyl-3-[dibenzoxepin-11-ylidene]propylamine

Synthesis



Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, in alcohol, and in methylene chloride. One of the two carbon atoms of the ethylene bridge of the antidepressant may be replaced by oxygen. The side chain of amitriptyline can be attached resulting in the formation of doxepin. Used for the treatment of mild-to-moderate endogeneous depression, Doxepin is a mixture of *cis* and *trans* isomers with *cis* isomer being more active. The drug is a NE and 5-HT uptake blocker, used as monoamine reuptake inhibitor and as tricyclic antidepressant.

Assay: Dissolve the substance in a mixture of anhydrous acetic acid and acetic anhydride and titrate with 0.1 M perchloric acid until the colour changes from blue to green by using crystal violet as an indicator.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 75–150 mg/day by oral or oral liquid.

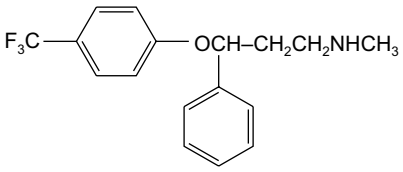
Dosage forms: Doxepin HCl capsules IP, Doxepin capsules BP.

IV. Selective serotonin reuptake inhibitors (SSRIs)

Mode of Action: SSRIs have analogues action to TCAs at serotonin containing neurons. Selective serotonin reuptake inhibitors inhibit reuptake of serotonin. After serotonin is released from neuron, it is removed from the extracellular space by transporters or reuptake sites, located on the cell membrane, SSRIs blocks serotonin reuptake to remain active in the synaptic binding site for longer time. Following the release of serotonin in nerve terminals, it interacts with postsynaptic 5-HT_{1-7} receptors and exerts their effects through a variety of phospholipase and cyclase-mediated mechanisms. Inhibitory autoreceptors include 5-HT_{1A} and perhaps 5-HT_7 subtypes at serotonin cell bodies as well as 5-HT_{1D} receptors in the nerve terminals, and dendrites become desensitized following prolonged treatment with SSRIs and enhances the excitatory function.

Structurally, the SSRIs differ from the tricyclic in that the center ring of tricyclic has been taken apart. The net effect is that the aryl amine similar to the grouping is present as in the tricyclics and the compound can compete for the substrate binding site of the serotonin transporter protein. As in the tricyclics the extra acyl group can add extra affinity and give favourable competition with the substrate serotonin.

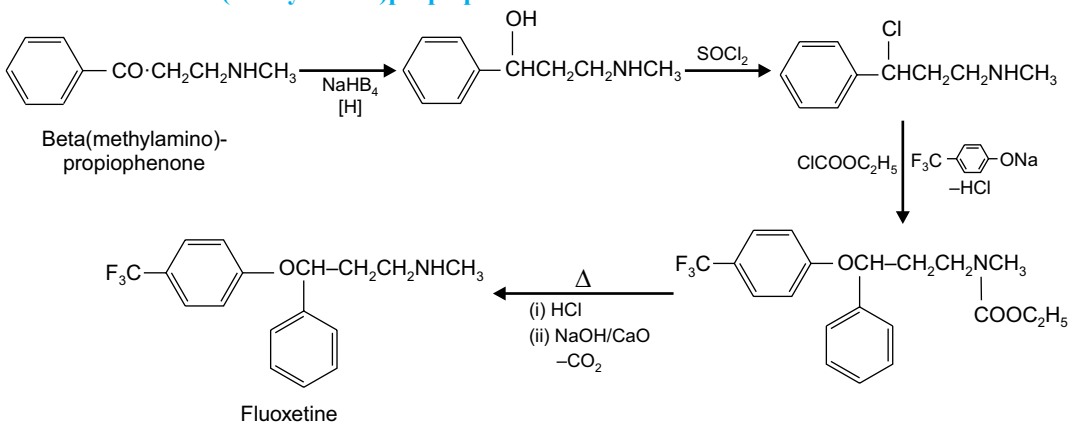
a. Fluoxetine (Fludac, Platin, Prodep)



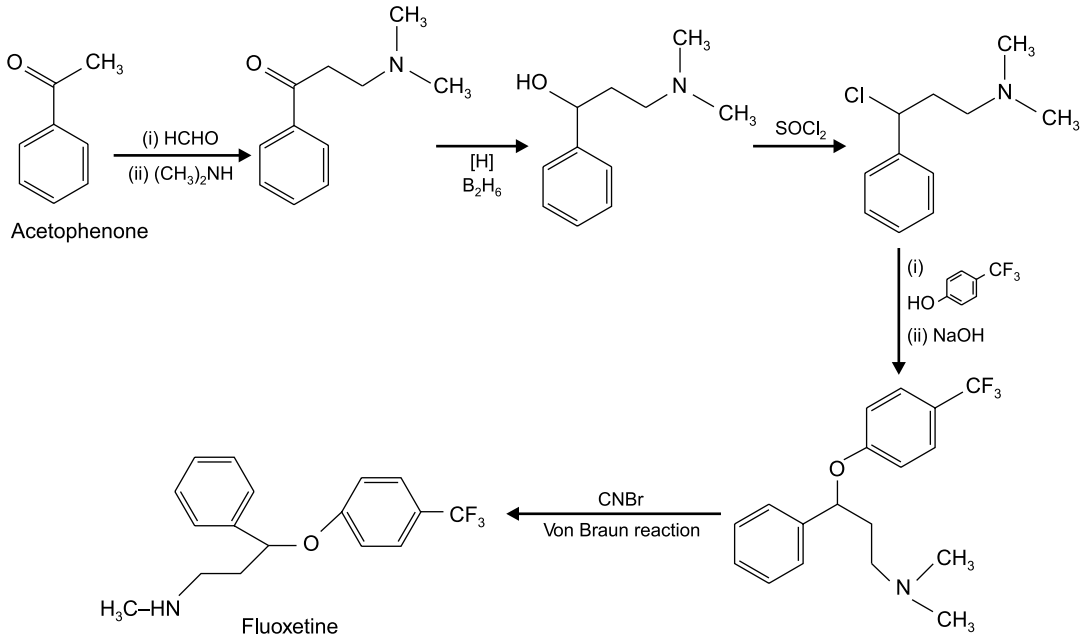
(±)-3-(*p*-Trifluoromethylphenoxy)-N-methyl-3-phenyl-propylamine

Synthesis

Route I. From: Beta(methylamino)propiophenone



Route II. From: Acetophenone



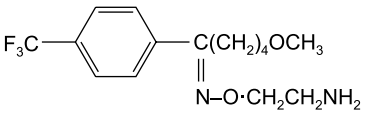
Properties and uses: It is a white or almost white crystalline powder, soluble in methanol, sparingly soluble in water, and in methylene chloride. It is a selective serotonin reuptake inhibitor and antidepressant. It is used for the treatment of endogeneous depression. It may be useful in treating obsessive-compulsive disorder, obesity, and alcoholism. It is a selective inhibitor of serotonin uptake in the CNS and has little effect on the control of NE or dopamine function.

Assay: Assayed by liquid chromatography method.

Dose: The usual dose is 20–80 mg/day.

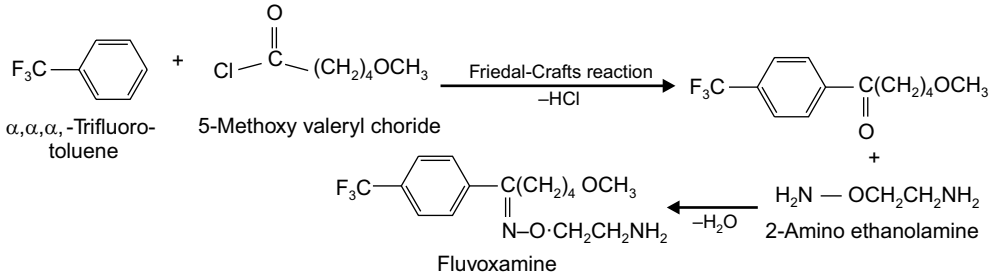
Dosage forms: Fluoxetine capsules BP, fluoxetine oral solution BP.

b. Fluvoxamine



E-5-Methoxy-1[4-(trifluoromethyl)phenyl]-*o*-(2-aminoethyl)oxim-1-pentanone

Synthesis



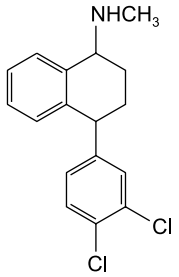
Properties and uses: It is a white to almost white crystalline powder, sparingly soluble in water, freely soluble in ethanol, and in methanol. It is a selective serotonin reuptake inhibitor, antidepressant, and effective in treating depressive disorders. It may be relatively safe to use in depressed individuals with cardiaovascular diseases. The most common adverse effects are nausea, headache, dry mouth, and insomnia.

Assay: It is assayed by titrating with 0.1 M perchloric acid (nonaqueous titration) and the end point is determined potentiometrically.

Storage: It should be stored in well-closed airtight containers.

Dosage forms: Fluvoxamine tablets BP.

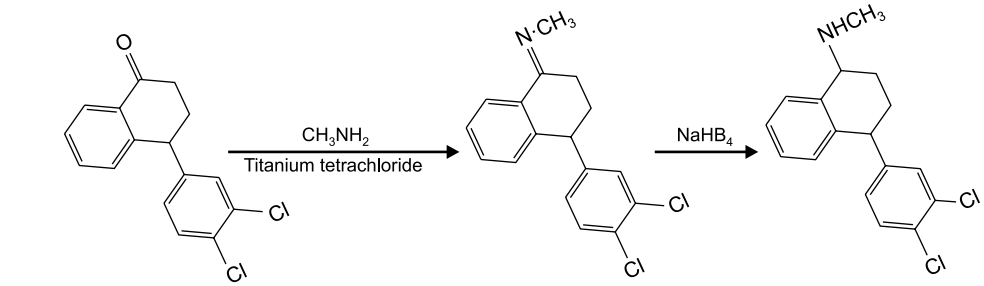
1. Sertraline



4-[3,4-Dichloro phenyl]-1,2,3,4-tetrahydro-N-methylnaphthalamine

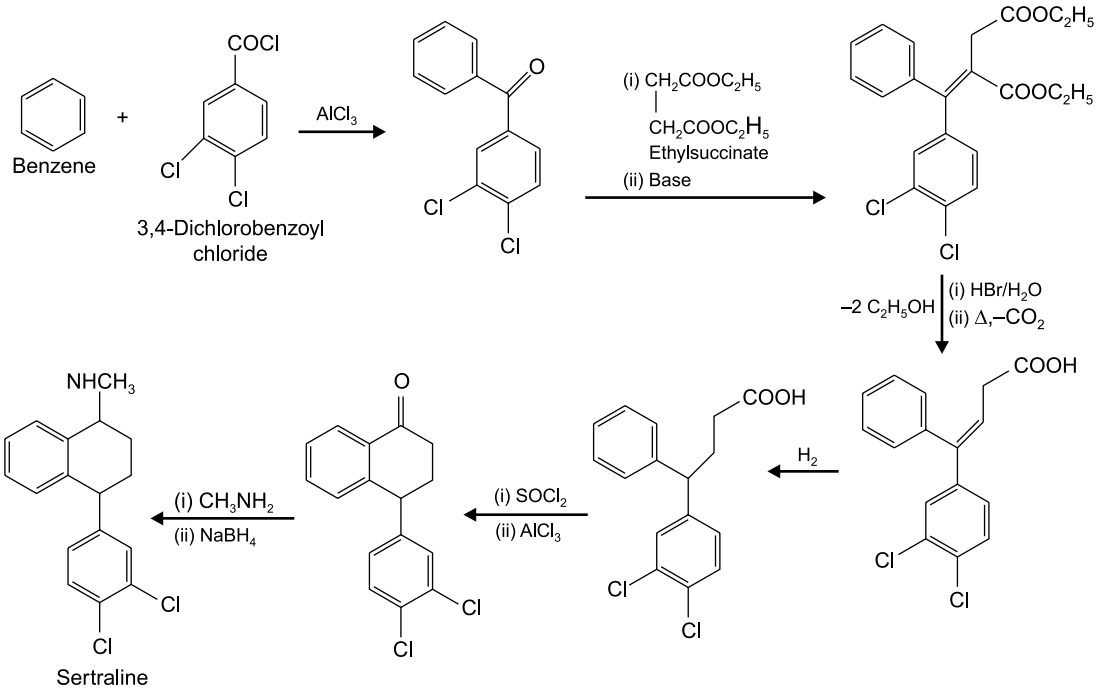
Synthesis

Route I. From: 4-(3,4-Dichlorophenyl)-3,4-dihydro-1-naphthalenone



4-(3,4-Dichlorophenyl)-3,4-dihydro-1-naphthalenone — Schiff's base — Sertraline

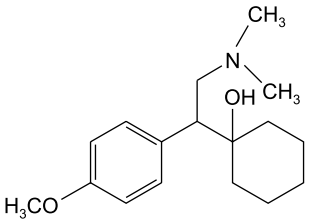
Route II. From: Benzene and 3,4-dichlorobenzoyl chloride



Properties and uses: Sertraline works by blocking presynaptic reuptake of serotonin and is considerably more potent in this effect than any antidepressant of this class. It is twice as potent in its inhibition of serotonin reuptake activity than in its inhibition of NE or dopamine uptake inhibiton. Used as selective serotonin reuptake inhibitor with low sedative and antimuscarnic activity, also used for panic disorder and premenstrual dysphonic disorder.

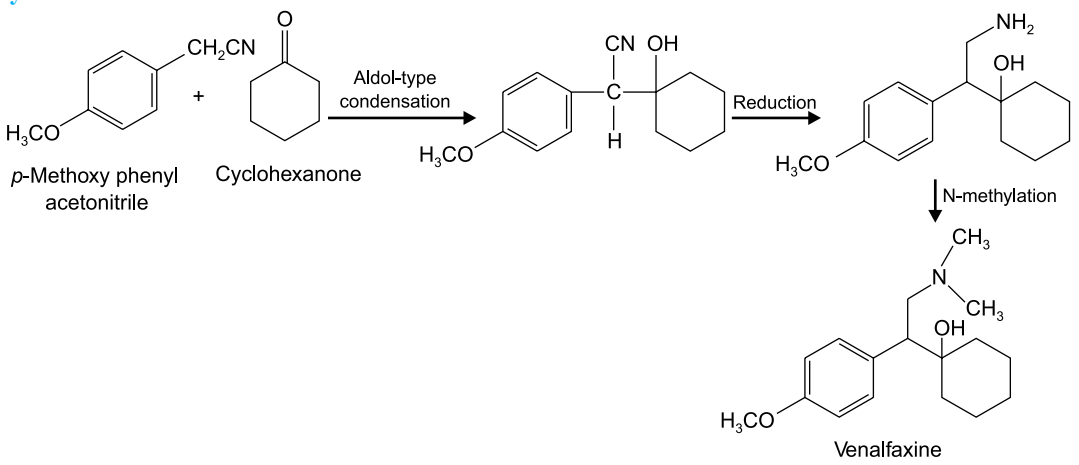
V. Selective norepinephrine reuptake inhibitors (SNERIs)

a. Venlafaxine



4-[3,4-Dichlorophenyl]-1,2,3,4-tetrahydro-N-methylnaphthalamine

Synthesis



Properties and uses: It is a white or almost white powder and exhibits the property of polymorphism. Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble, or practically insoluble in acetone. It is a phenylethylamine bicyclic compound with antidepressant effect similar to TCAs, but with fewer side effects. It is a selective inhibitor of 5-HT and NE reuptake. It also inhibits reuptake of dopamine, but to lesser extent.

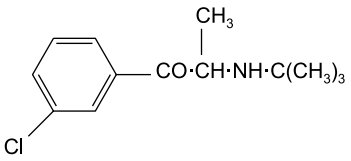
Assay: Dissolve the substance in a mixture of 0.01 M hydrochloric acid and ethanol. Perform potentiometric titration with 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers.

VII. Miscellaneous

a. Bupropion (Zyban)

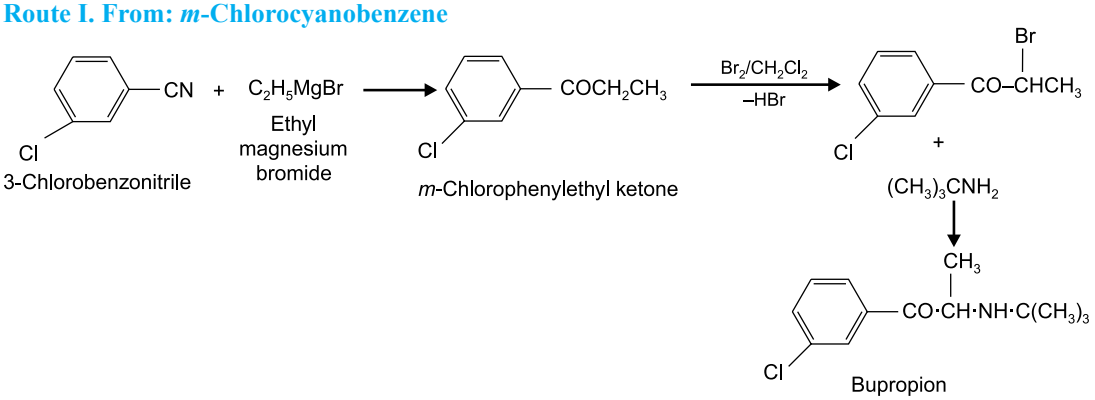
Bupropion is a novel, non-tricyclic antidepressant with a primary pharmacological action of monoamine uptake inhibition.



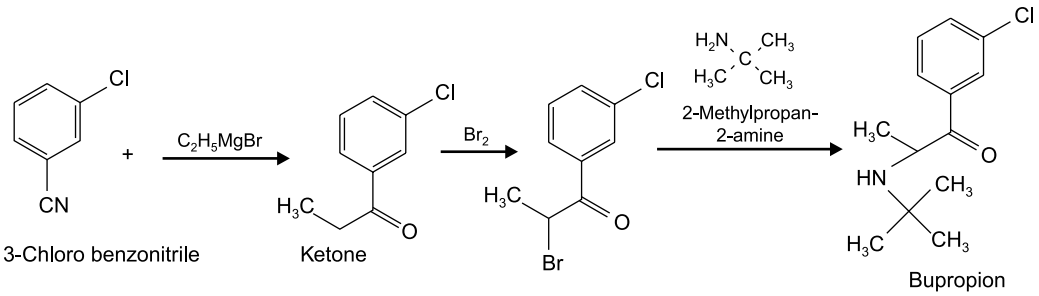
(±)-1-[(2-Dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol

Synthesis

Route I. From: *m*-Chlorocyanobenzene



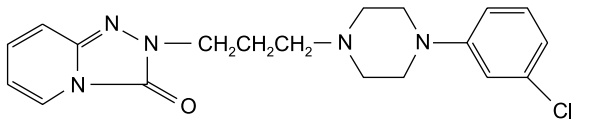
Route II. From: 3-Chloro benzonitrile



Properties and uses: It exists as a white solid, soluble in water or ethanol. A semisynthetic centrally acting opioid analgesic derived from thebaine, it is used for the relief of moderate-to-severe pain particularly associated with postoperative discomfort. It is approximately 30 times as potent as morphine and exerts its analgesic effect by binding to CNS opioid receptors. Bupropion is used to treat major depression, refractory depression, and seasonal effective disorder. It is also used to help people to stop smoking and to treat bipolar depression and attention defect disorder. It does not cause sedation and has minimal cardiovascular side effects. The most frequent side effect is agitation.

Dose: Initial dosing is 75–100 mg twice or thrice a day.

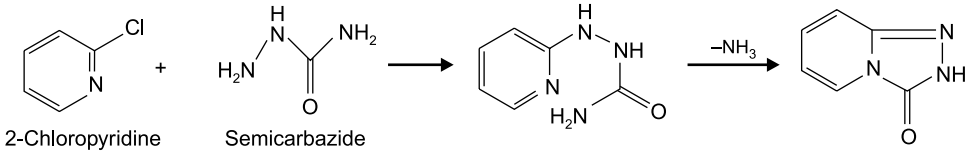
b. Trazodone (Tazodac, Trazalon, Trazonil)



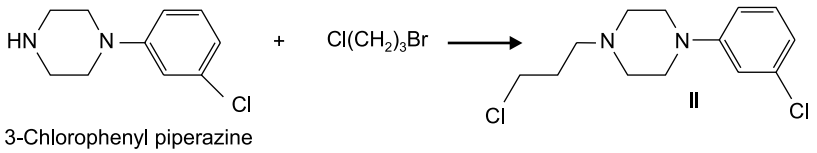
2-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}1,2,4-triazolopyridin-3-one

Synthesis

Step I. Preparation of 1,2,4-triazolopyridin-3-one

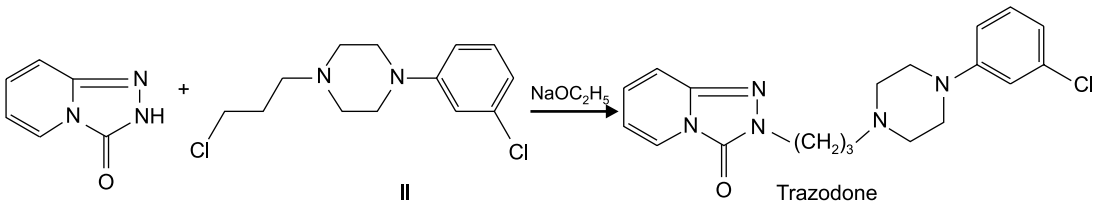


Step II. Preparation of 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine



3-Chlorophenyl piperazine

Condensation of *Step I* and *Step II* products

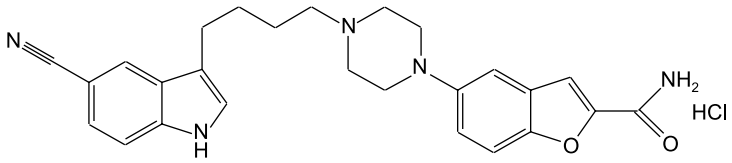


Properties and uses: It exists as white crystals, sparingly soluble in water or alcohol, soluble in chloroform. It is a heterocyclic compound with high sedative and no antimuscarnic effect. Antidepressant activity of trazodone is believed to be produced by blocking the reuptake of serotonin at the presynaptic neuronal memberane. Trazodone has no influence on the reuptake of NE or dopamine with the CNS. It has a sedative effect, which is believed to be produced by the alpha-adrenergic blocking action and modest histamine blockade.

Dose: The usual dose is 150–400 mg/day oral.

Newer Drugs

Vilazodone hydrochloride (Viibryd)



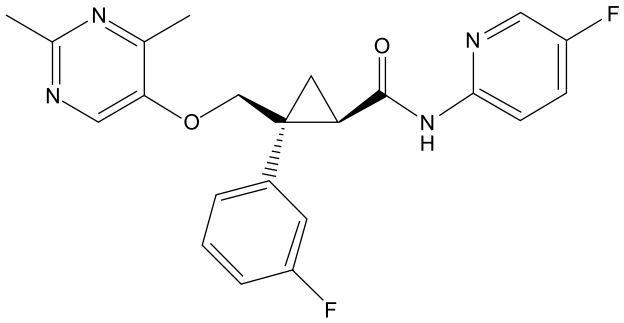
Mode of action: The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic 5-HT_{1A} receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

Properties and uses: Vilazodone hydrochloride is a selective serotonin reuptake inhibitor and a 5-HT receptor partial agonist. It is specifically used for the treatment of major depressive disorder. Adverse events associated with the use of vilazodone hydrochloride are diarrhea, nausea, vomiting and insomnia.

Dose: The suggested initial dose is 40 mg once daily. Treatment should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for additional 7 days, and then an increase to 40 mg once daily.

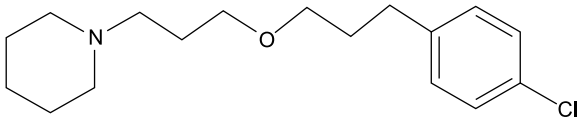
Newer Agents

Lembrorexant



Uses: It is used for the treatment of insomnia.

Pitolisant



Uses: It is a histamine 3 (H_3) receptor antagonist and for the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy.

PROBABLE QUESTIONS

1. Define and classify antidepressants and write the synthesis of any two of them. Mention their uses and metabolism.
2. Write the mode of action of MAO inhibitors, enumerate the various agents and write the synthesis and uses of isocarboxazid.
3. Write in detail about tricyclic antidepressants.
4. Write the synthesis, mode of action, and metabolic pathway of amitryptyline and imipramine.
5. Write a note on seletive serotonin reuptake inhibitors used as antidepressants.
6. Name some condensed seven-membered ring containing antidepressants and write the synthesis and uses of doxepin.

SUGGESTED READINGS

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CHAPTER 28

CNS Stimulants

INTRODUCTION

Central nervous system (CNS) stimulants are drugs that stimulate the CNS. They fall into the following three broad categories:

1. Convulsants and respiratory stimulants.
2. Psychomotor stimulants.
3. Psychomimetic drugs or hallucinogenic drugs.

Convulsants or respiratory stimulants (analeptics): They have little effect on the mental function and appear to act mainly on the brain stem and spinal cord, producing reflex excitability, as increase in the activity of the respiratory and vasomotor center and with higher doses it produce convulsions.

Psychomotor stimulants: They have a marked effect on mental function and behaviour, producing excitement, cessation of fatigue, and increase in motor activity. Examples: Amphetamine, caffeine, and cocaine.

Psychomimetic drugs: They mainly affect through pattern, perception, and mood producing effects that superficially resemble the changes seen in schizophrenia.

Analeptics: Analeptics (Greek—restorative) also called respiratory stimulants are general CNS stimulants. Analeptics are drugs that when administered stimulate all the parts of CNS, especially the brain medulla, thereby counteracting the depressant activity due to the administration of excess CNS depressants. Some of the CNS stimulants are mainly used as analeptics. Analeptics is a Greek word that can be translated as having the meaning 'picking up' those who have been cast down. Analeptics stimulate the CNS system and in large doses, they cause generalized convulsions.

CLASSIFICATION

1. **Those drugs acting directly on the CNS:**
   a. **Cortical stimulants:** Xanthine alkaloids, amphetamine, methyl amphetamine, methyl phenidate, and pipradiol.
   b. **Medullary stimulants:** Picrotoxin, nikethamide, amiphenazole, camphor, and carbon dioxide.
   c. **Spinal stimulants:** Strychnine

2. Those that stimulate the CNS reflexly:

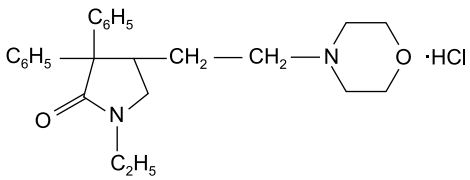
Lobeline, ammonia, veratrum, and nicotine.

According to the mode of action, analeptics may be divided into four groups. They are as follows:

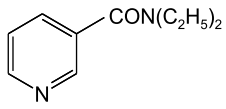
A. Respiratory stimulants
B. Psychomotor stimulants
C. Convulsants and stimulants
D. Psychomimetic drugs (Hallucinogenic drugs)

A. Respiratory stimulants

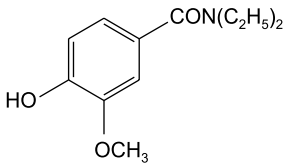
a. Doxapram HCl



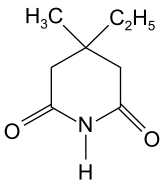
b. Nikethamide



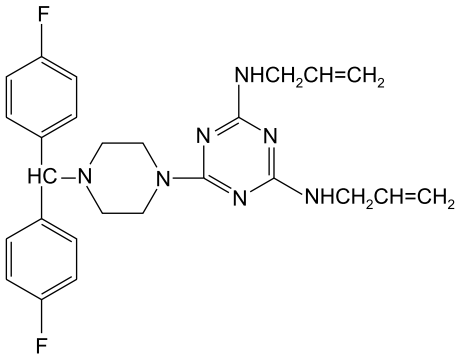
c. Ethamivan



d. Bemigride

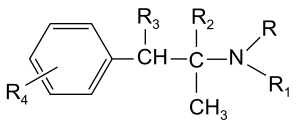


e. Almitrine dimesylate



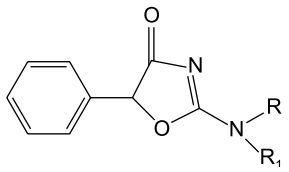
B. Psychomotor stimulants or central stimulants (Sympathomimetics)

a. β-Phenylethylamine derivatives (Amphetamine and related drugs)



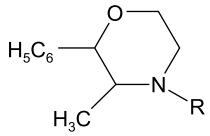
Name	R	R_1	R_2	R_3	R_4
Amphetamine (±)	–H	–H	–H	–H	–H
Dextroamphetamine(+)	–H	–H	–H	–H	–H
Methamphetamine(+)	$–CH_3$	–H	–H	–H	–H
Phenetermine	–H	–H	$–CH_3$	–H	–H
Benzphetamine	$–CH_3$	$–CH_2C_6H_5$	–H	–H	–H
Chlorophenetermine	–H	–H	$–CH_3$	–H	4–Cl
Phenyl propanolamine	–H	–H	–H	–OH	–H
Fenfluramine	–H	$–C_2H_5$	–H	–H	*m*-CF_3
Cloretermine	–H	–H	$–CH_3$	–H	*o*-Cl

b. Oxazolidinone derivatives



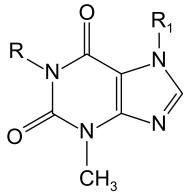
Name	R	R_1
Pemoline	–H	–H
Tozalinone	$–CH_3$	$–CH_3$
Fenozolone	–H	$–C_2H_5$

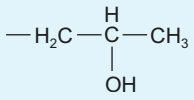
c. Morpholinones



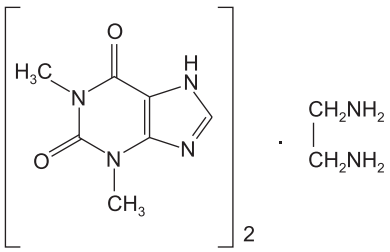
Name	R
Phenmetrazine	–H
Phendimetrazine	$–CH_3$

d. Methylxanthines

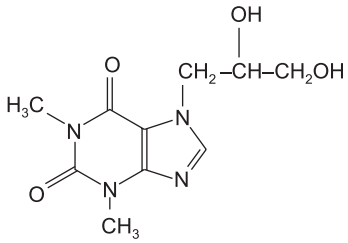


Name	R	R_1
Caffeine	$-CH_3$	$-CH_3$
Theophylline	$-CH_3$	$-H$
Theobromine	$-H$	$-CH_3$
Etophylline	$-CH_3$	$-CH_2CH_2OH$
Proxyphylline	$-CH_3$	
Pentoxyphylline	$-C_4H_8-CO-CH_3$	$-CH_3$

e. Aminophylline

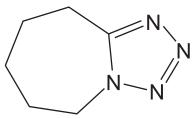


f. Dyphylline

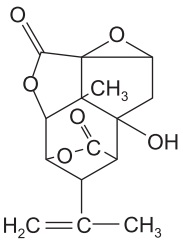


C. Convulsants and stimulants

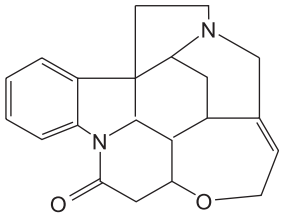
a. Pentylene tetrazole



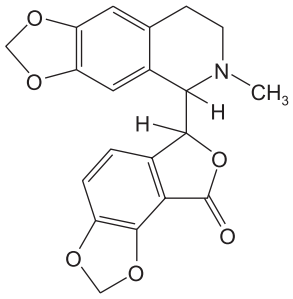
b. Picrotoxin



c. Strychnine



d. Bisucuilline

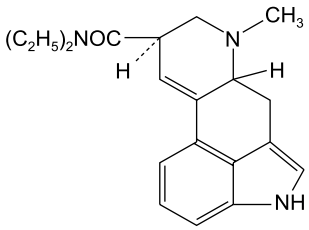


e. Fluoroethyl

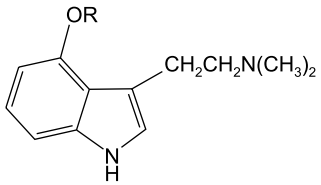
$CF_3CH_2-O-CH_2CF_3$

D. Psychomimetic drugs (Hallucinogenic drugs)

a. (+) Lysergic acid diethylamide

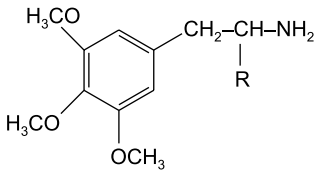


b. Indole derivatives



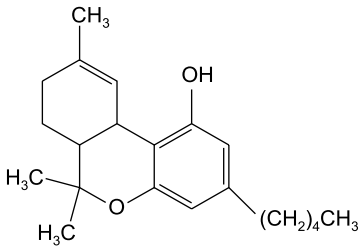
Name	*R*
Psilocyn	–H
Psilocybin	$-PO(OH)_2$

c. Phenylethylamine derivatives

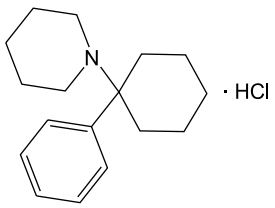


Name	*R*
Mescaline	–H
3,4,5-Trimethoxy amphetamine (TMA)	$-CH_3$

d. Cannabis



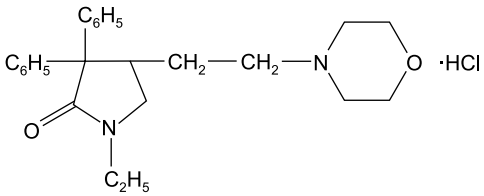
e. Dissociate agents: Phencyclidine HCl



SYNTHESIS AND DRUG PROFILE

A. Respiratory Stimulants

a. Doxapram (Carbopram)

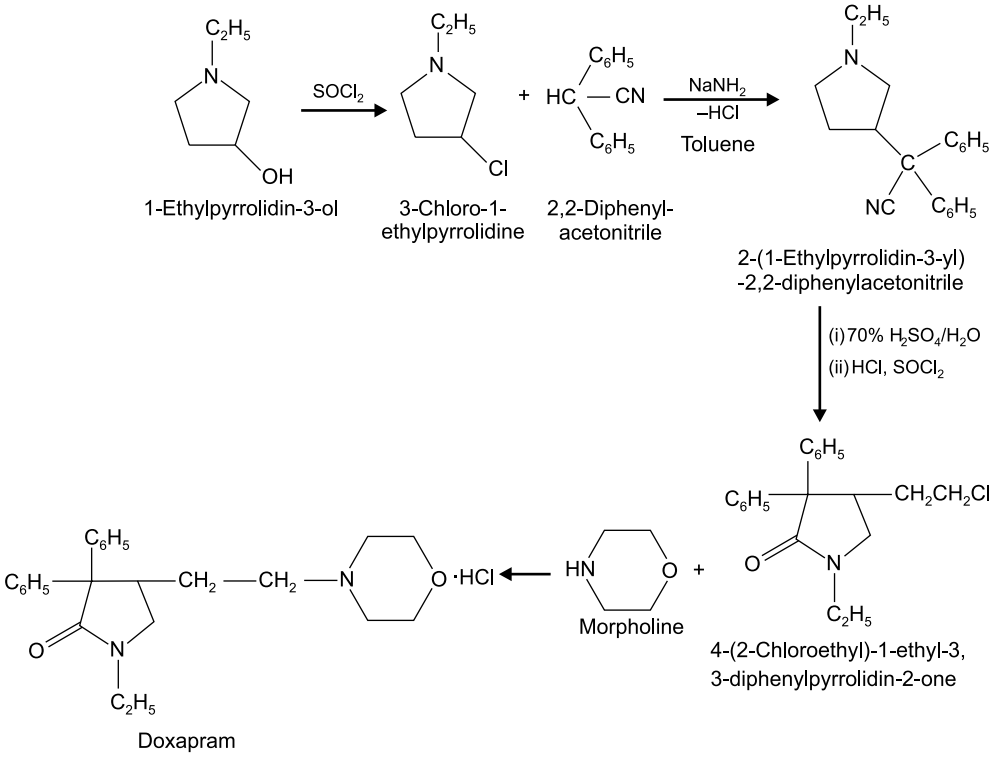


1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenylpyrrolidin-2-onehydrochloride

Properties and uses: It exists as white or almost white crystalline powder, soluble in water, in alcohol, and in methylene chloride. It is a respiratory stimulant possessing slight vasopressor characteristics. It stimulates the peripheral carotid chemoreceptor.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

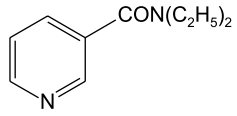
Synthesis



Dose: Usual dose for postanaesthetic: IV 0.5–1.0 mg/kg.

Dosage forms: Doxapram injection BP.

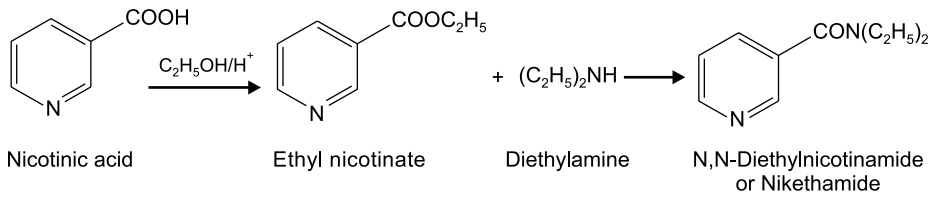
b. Nikethamide (Coramine)



Properties and uses: It is an oily liquid or a crystalline mass, colourless, or slightly yellowish, miscible with water and with alcohol. It is a weak analeptic employed as respiratory stimulant.

Assay: Dissolve the sample in a mixture of acetic anhydride and anhydrous acetic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Synthesis

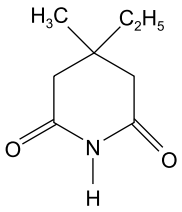


Nicotinic acid — Ethyl nicotinate — Diethylamine — N,N-Diethylnicotinamide or Nikethamide

Dose: 1 to 15 ml of 25% parenteral solution.

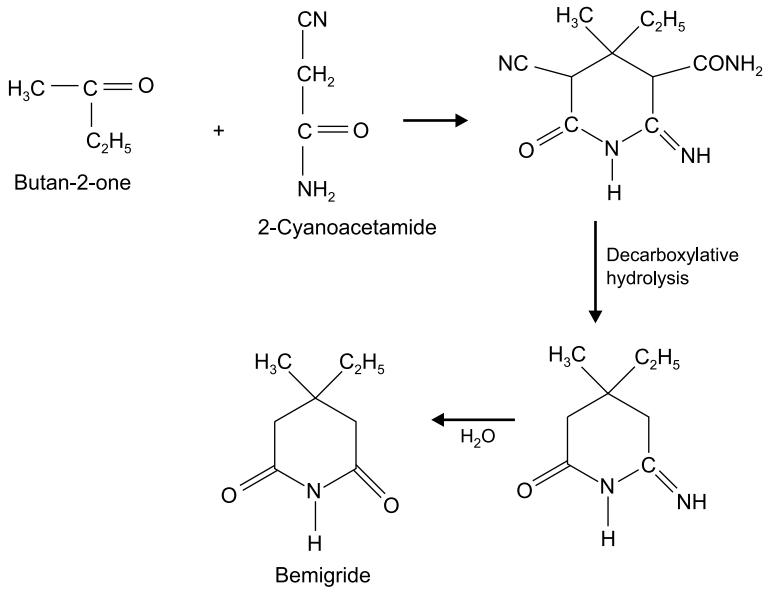
Dosage forms: Nikethamide injection BP.

c. Bemigride



4-Ethyl-4-methylpiperidine-2,6-dione

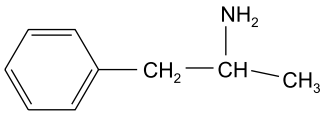
Synthesis



Uses: This agent is used in the treatment of barbiturate intoxication. It causes a rapid stimulation of the CNS.

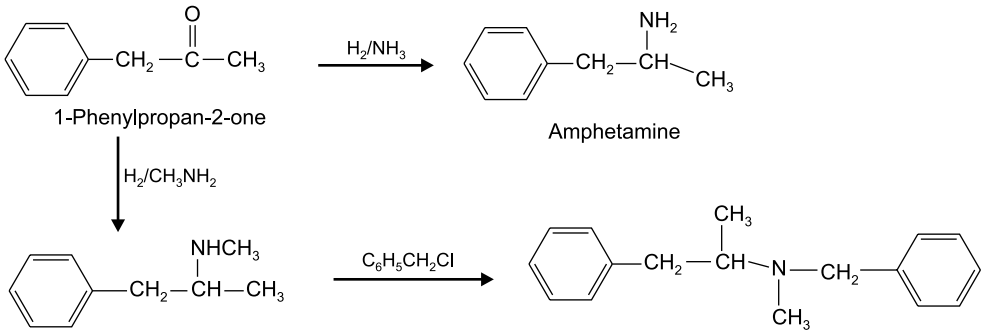
B. Psychomotor Stimulants

a. Amphetamine



1-Phenylpropan-2-amine

Synthesis

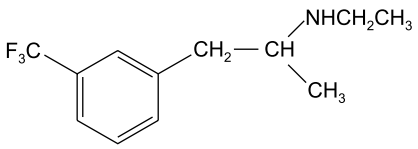


Mode of action: Amphetamine increases synaptic dopamine and noradrenaline primarily by stimulating presynaptic release rather than by blockade of the reuptake as in the case of cocaine.

Uses: It is an anorectic and has been used in the weight control of obese individuals. It has potential for abuse and cardiovascular effects.

Dose: For narcolepsy, 10 mg/day, for obesity, 5–10 mg/day, 30–60 min before meals.

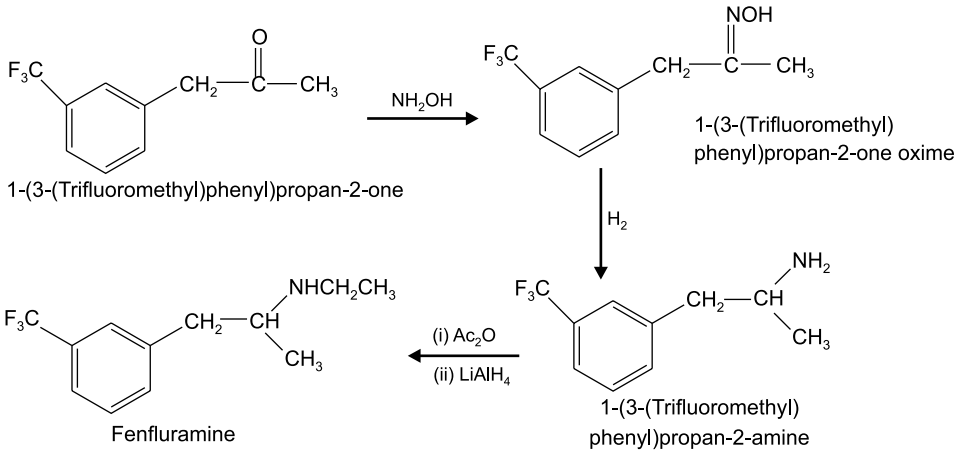
b. Fenfluramine (Pondialon)



Properties and uses: It is a white amophous powder, sparingly soluble in water, used as respiratory stimulant.

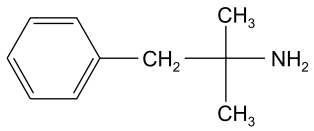
Assay: Dissolve the sample in chloroform and acetone. Add mercuric acetate solution and titrate with 0.1 N perchloric acid.

Synthesis

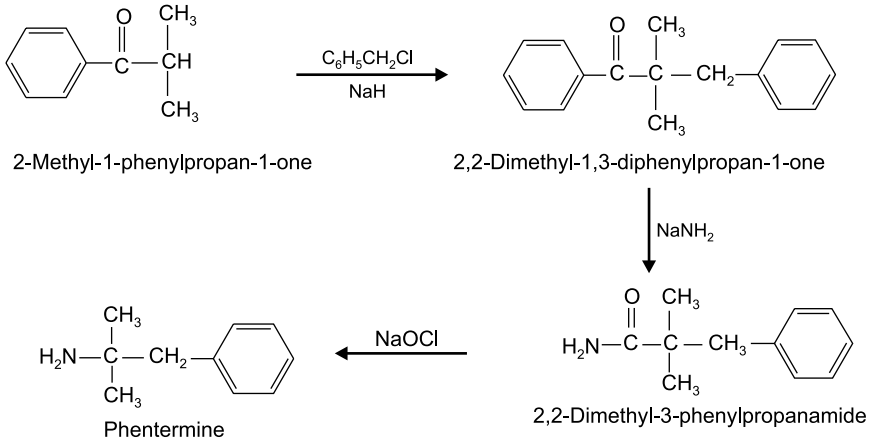


Dose: By oral route for adults: 20 mg thrice a day, 30 min to 1 h before each meal.

c. Phentermine



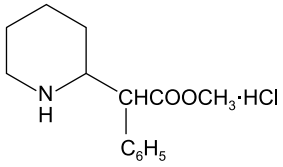
Synthesis



Use: It is used as an appetite suppressant.

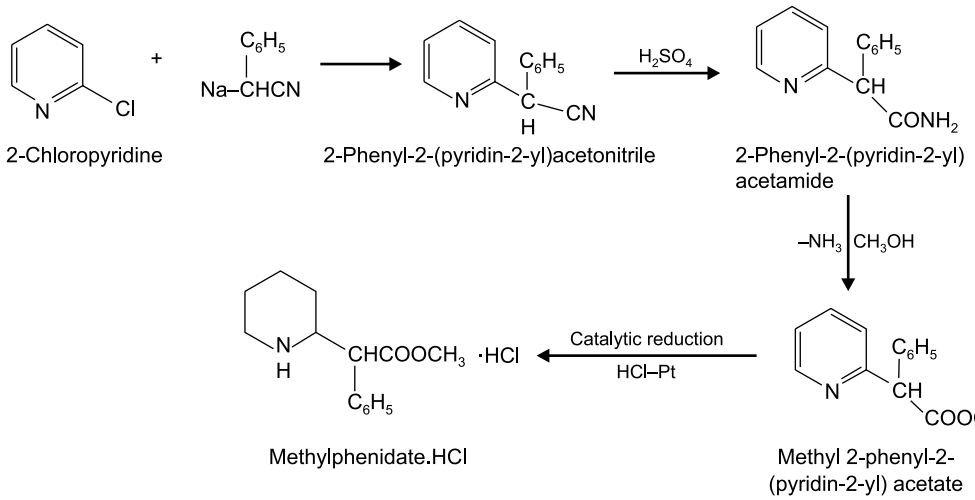
Dose: The usual dose is 15–30 mg at breakfast.

d. Methylphenidate HCl (Ritalin)



Methyl-2-phenyl-2-(piperidin-2-yl)acetatehydrochloride

Synthesis



2-Chloropyridine

2-Phenyl-2-(pyridin-2-yl)acetonitrile

2-Phenyl-2-(pyridin-2-yl) acetamide

Methyl 2-phenyl-2-(pyridin-2-yl) acetate

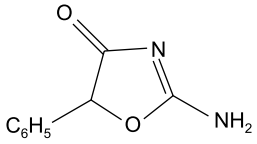
Methylphenidate.HCl

Mode of action: It is similar to amphetamine, but superior in its pharmacological action. It increases the release of dopamine and noradrenaline, and it is useful in hyperkinetic children.

Properties and uses: It is a white fine crystalline powder, soluble in water, and sparingly soluble in chloroform and acetone. It is used as a potent CNS stimulant.

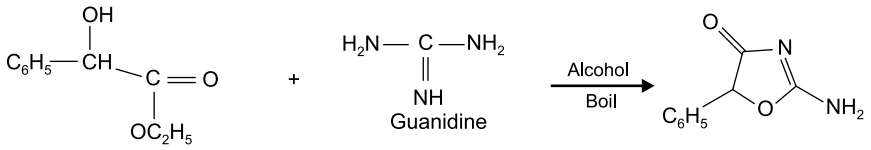
Dose: The usual dose by oral or parenteral is 10–60 mg/day.

f. Pemoline



2-Amino-5-phenyloxazol-4(5H)-one

Synthesis



Ethyl 2-hydroxy-2-phenylacetate — Pemoline

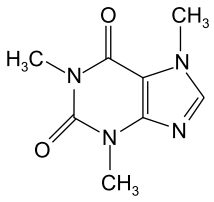
Properties and uses: It is a white crystalline powder, slightly soluble in alcohol. It is used in the treatment of narcolepsy fatigue, mental depression, chronic schizophrenia, and as a mild stimulant in geriatric patients.

Xanthine Derivatives

The naturally occurring xanthine derivatives are caffeine, theophylline, and theobromine. These agents generally cause mild CNS stimulation, and relax-smooth muscles, so it is used in the treatment of asthma. All xanthine derivatives produce diuresis by increasing glomerular filtration and blocking tubular reabsorption of sodium ions. It stimulates the medullary centre and overcomes fatigue.

Mode of action: These agents have mild stimulant action and increase the epinephrine secretion and enhance the neural activity in several areas of the brain. These agents act by producing antagonism of adenosine receptor. Adenosine is a neuromodulator, which influences numerous functions in the CNS and the blocking is responsible for stimulation.

a. Caffeine



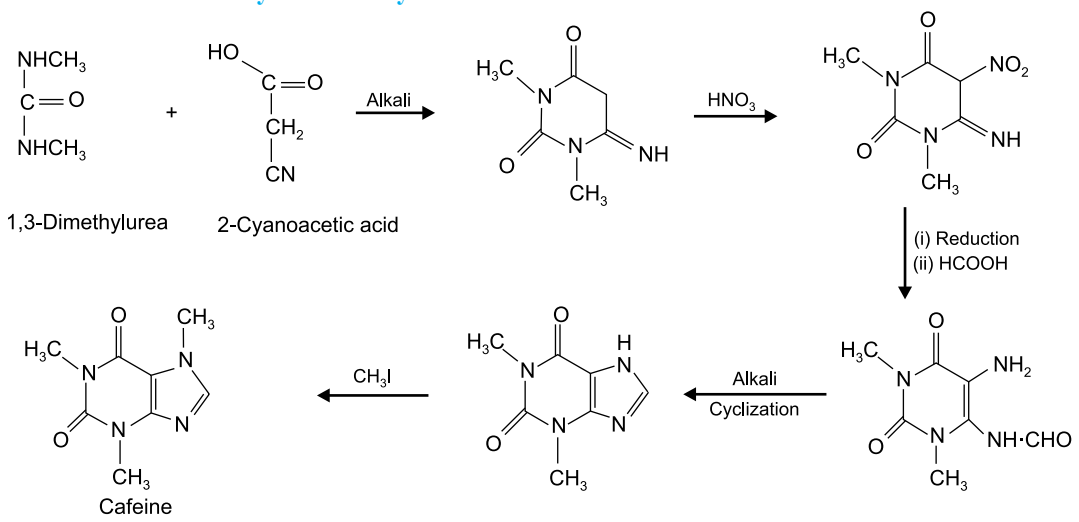
1,3,7-Trimethyl-1H-purine-2,6(3H,7H)-dione

Properties and uses: It exists as a white crystalline powder or silky white crystals, sublimes readily, sparingly soluble in water, freely soluble in boiling water, and slightly soluble in ethanol. It dissolves in the concentrated solutions of alkali benzoates or salicylates. Caffeine acts on the higher centres of the CNS and produces a condition of wakefulness. It stimulates the respiratory centre, increases rate and depth of respiration. The diuretic action of caffeine is weaker than theophylline. Caffeine is used along with ergotamine in the treatment of migraine.

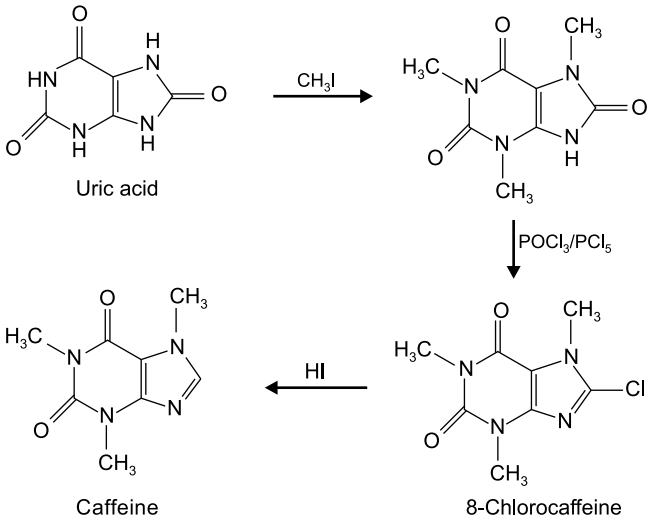
Assay: Dissolve the sample by heating in anhydrous acetic acid. Allow to cool, add acetic anhydride, and 20 ml of toluene. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Synthesis

Route I. From: Dimethylurea and cyanoacetic acid



Route II. From: Uric acid



Dosage forms: Aspirin and caffeine tablets BP, caffeine citrate injection BP, caffeine citrate oral solution BP.

b. Theophylline and Theobromine (Theobid, Theopa, Broncordil)



Synthesis: They can be synthesized by adopting the above route described for caffeine with the suitable reagents.

i. Theophylline hydrate

Properties and uses: It exits as white, crystalline powder, slightly soluble in water and sparingly soluble in ethanol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids. Used as non-selective phosphodiesterase inhibitor (xanthine) and in the treatment of reversible airways obstruction.

Assay: Dissolve the sample in water, add 0.1 M silver nitrate, and shake. Add bromothymol blue solution as indicator and titrate with 0.1 M sodium hydroxide.

Dose: For acute bronchospasm: Adult—as conventional tablet—5 mg/kg every 6–8 h. Child: As conventional tablet—5 mg/kg every 4–6 h. For chronic bronchospasm: Adult—as conventional dosage form 300–1000 mg in divided doses, every 6–8 h daily. As modified-release preparations: 175–500 mg every 12 h.

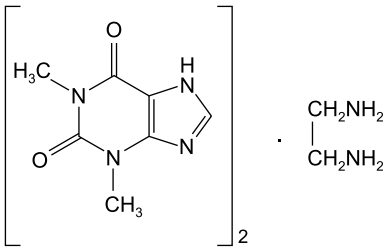
Dosage forms: Aminophylline injection BP, prolonged-release theophylline tablets BP.

ii. Theobromine

Properties and use: It is a white powder, very slightly soluble in water and in ethanol, slightly soluble in ammonia. It dissolves in dilute solutions of alkali hydroxides and in mineral acids. Theobromine is used as diuretic and used in the treatment of angina pectoris and hypertension. It is a non-selective phosphodiesterase inhibitor (xanthine) and used in the treatment of reversible airways obstruction.

Assay: Dissolve the sample in boiling water, cool to 50–60°C and add 0.1 M silver nitrate and titrate with 0.1 M sodium hydroxide using phenolphthalein solution as indicator, until a pink colour is obtained.

c. Aminophylline (Aminophyline, Minophyl)



Properties and uses: A white or slightly yellowish powder, sometimes granular, freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide), and practically insoluble in ethanol. It is used in the treatment of bronchial asthma, acts as a non-selective phosphodiesterase inhibitor and in the treatment of reversible airways obstruction.

Assay for Ethylenediamine

Dissolve the sample in water, to this add bromocresol green solution as indicator. Titrate with 0.1 M hydrochloric acid until a green colour is obtained.

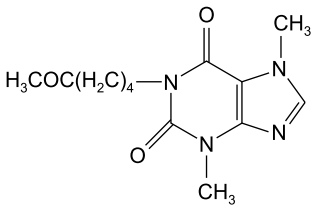
Assay for Theophylline

Heat the weighed quantity of the sample to constant mass in an oven at 135°C. Dissolve the residue by heating in water; allow to cool, adding 0.1 M silver nitrate and shake. Add bromothymol blue solution as indicator and titrate with 0.1 M sodium hydroxide.

Dose: The usual dose is oral 300–600 mg/day.

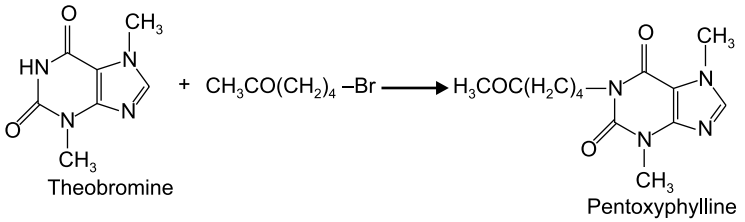
Dosage forms: Aminophylline injection BP.

d. Pentoxyphylline (Flexital, Pentovas, Trental)



3,7-Dimethyl-1-(5-oxohexyl)-1H-purine-2,6(3H,7H)-dione

Synthesis

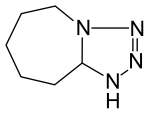


Uses: It is used in the relief of bronchospasm in asthma.

Dose: The usual dose is 400 mg, thrice daily with meals.

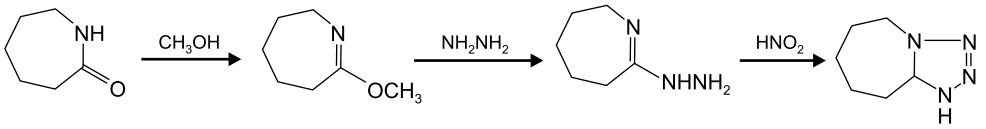
C. Convulsant Stimulants

a. Pentylene Tetrazole



5,6,7,8,9,9a-Hexahydro-1H-tetrazolo[1,5-a]azepine

Synthesis



Mode of action: It is a powerful CNS stimulant, believed to be acting by direct depolarization of the central neurons. However, it has also inhibited action on GABA channel openings. Low doses cause excitation, high doses cause convulsion.

Uses: It is used to induce convulsion in animals to locate epileptic foci in conjugation with the electro-encephalograph.

b. Strychinine

Mode of action: It stimulates the entire cerebrospinal neuroaxis and produces convulsion. It produces reflex tonic-clonic and symmetrical convulsions. Strychinine acts by blocking postsynaptic inhibition produced by inhibitory transmitter glycine. One of the site is Renshaw cell-motor neurojunction in the spinal cord through which inhibition of antagonistic muscle is achieved. Due to the synaptic inhibition, all the nerve impulses become generalized resulting in apparent excitation and convulsions.

c. Picrotoxin

Mode of action: It is a potent convulsant, produces clonic spontaneous and asymmetrical convulsions. The convulsions are accompanied by vomiting, respiratory and vasomotor stimulation. It acts by blocking presynaptic inhibition mediated by GABA. However, it is not a competitive antagonist, it acts on the distinct site of GABA receptors and prevents the chloride channel opening. Thus, produces depolarization of neurons and excite the central nervous system.

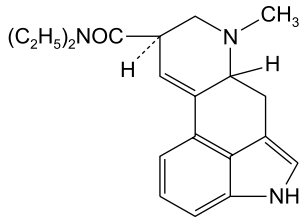
D. Psychomimetic Drugs

These are characterized by the fact that they affect thought perception and mood, without causing marked psychomotor stimulation or depression.

These drugs fall broadly into two groups.

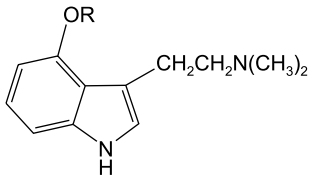
- **Those with a chemical resemblance to known neurotransmitter catecholamine:** These include LSD and psilocybin, which are related to 5-HT and mescaline that is similar in structure to amphetamine.
- **Drugs unrelated to monoamine neurotransmitter:** Cannabis and phencyclidine.

a. Lysergic acid diethylamide (LSD)



The chemical precursor lysergic acid occurs naturally in ergot, a microbial growth formed from the fungus *Claviceps prupurea,* which develops on various plants of the gramine, for example, rye LSD is a chiral molecule and the physiologically active isomer is (+). The 9,10 double bond is essential for activity. LSD is a potent psychomimetic drug.

b. Psilocyabin

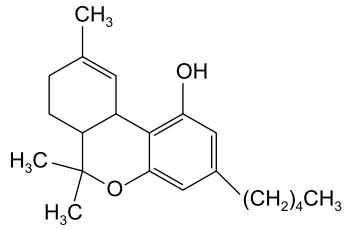


Psilocybin, R = H

Psilocybin R, –PO $(OH)_2$

It occurs in a mushroom, *Psilocybe maxicena*. It is converted to psilocin *in vivo*, both have activity similar to LSD, but are much less potent.

c. Cannabis



Δ^1-Tetrahydrocannabinol (THC) or Δ^9-THC

The dried flowering tops of the pistillate plants of *Cannabis sativa* (moraceac) contain THC. The drug is used as a depressant with stimulant sensation. The phenolic OH is required for activity. It produces giddiness and increased hunger. Several other medicinal effects of marijuana include antinausea effect (for anticancer therapy), anticonvulsant, muscle-relaxing, and treatment of glaucoma.

PROBABLE QUESTIONS

1. Name any five potent CNS stimulants. Write their structures, chemical name, and uses.
2. Classify the CNS stimulants and write the synthesis of one potent compound from each category.
3. Write a note on respiratory stimulants.
4. Write the structure of propoxyphylline and aminophylline. Explain why the former has better tolerance orally and intravenously than the latter.
5. Xanthines represent an important class of CNS stimulants. Write the structure, chemical name, and uses of any three potent drugs from this category and discuss the synthesis of any one of them.
6. Write the synthesis of the following drugs:
   (a) Doxapram
   (b) Nikethamide
7. Describe the synthesis of the following CNS stimulants:
   (i) Phentermine
   (ii) Bemegride
   (iii) Methylphenidate hydrochloride
8. Describe a comprehensive account on the various CNS stimulants used.
9. Write a note on naturally obtained CNS stimulants.

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CHAPTER 29

Narcotic Analgesics

INTRODUCTION

Analgesics are agents that relieve pain by acting centrally to elevate pain threshold without disturbing consciousness or altering other sensory modalities. Certain analgesics like aminopyrine and phenylbutazone also possess antiinflammatory properties. Such substances and the gold compounds are used in the treatment of arthritis.

Many drugs that are used to relieve pain are not analgesics; the general anaesthetics relieve pain by producing unconsciousness, local anaesthetics prevent pain by blocking peripheral nerve fibres, antispasmodics relieve pain by relaxing smooth muscles and the adrenal corticoids relieve pain associated with rheumatoid arthritis by antiinflammatory action.

Analgesics are classified into two major categories:

1. Opioid analgesics or narcotic analgesics (centrally acting).
2. Non-opioid analgesics (peripherally acting).

Opioid Analgesics

Opioid analgesics are drugs that denote all naturally occurring, semisynthetic and synthetic drugs, which have a morphine-like action, namely, relief from pain and depression of CNS associated with the drug dependence.

Opium is a dark brown resinous material obtained from the poppy (*Papaver somniferum*) capsule. It has two types of alkaloids: Phenanthrene derivatives and benzoisoquinoline derivatives. Opium has been known from 1500 BC. Serturner, a pharmacist isolated the active principle of opium in 1804 and named it morphine.

Narcotic analgesic agents cause sleep in conjunction with their analgesic effect. If a narcotic is used for a long time, it may become habit-forming (causing mental or psychological dependence) and physical dependence may lead to withdrawal side effects.

Opioid drugs are not only used as analgesics, but also possess numerous other useful properties. For example, morphine is used to induce sleep in the presence of pain, diarrhoea, suppress cough, and facilitate anaesthesia.

The term *opioid* is used generally to designate collectively the drugs, which bind specifically to any of the subspecies of the receptors of morphine and produce morphine like actions. They tend to produce euphoria, which is an important factor in their addictive property that limits their use.

Other limitations include, respiratory depression, decreased gastrointestinal motility leading to constipation, increased biliary tract pressure, and pruritis due to histamine release.

General Mode of Action

Three classical opoid receptors μ, κ, and δ (mu, kappa, and delta) have been extensively studied. Recently, N/OFQ (nociceptin/orphan) receptor, a fourth class has been identified. In addition, many subtypes have been identified in different species.

All these opoid receptors μ, κ, and δ are G protein-coupled receptors situated on prejunctional neurons. They exert inhibitory modulations by decreasing the release of junctional transmitter (i.e. noradrenaline, dopamine, 5HT), and glutamate. Opoid receptors activation reduce intracellular cAMP formation and open K^+ channels or suppress voltage-gated N type Ca^{2+} channels. These result in hyperpolarization in synaptic junctions and decrease the neurotransmitter release.

1. Mu (μ)-receptors are responsible for supraspinal analgesia mediated by μ_1 and spinal mediated by μ_2. Respiratory depression and gastric motility reduction is mediated by μ_2-subtypes. μ-receptor produces euphoria, physical dependence, and miosis.
2. Kappa-receptors appear to mediate spinal analgesia through κ_1-subtypes and supraspinal analgesia through κ_3-subtype. It produces respiratory depression, dysphoria, hallucination, miosis, sedation, and nicotinic effects.
3. Activation of δ-receptors produces spinal analgesia, respiratory depression, affective behaviour, reinforcing actions, and reduced GI motility.

The σ (sigma)-receptors are least considered because it is neither activated by morphine nor blocked by naloxone. However, certain narcotic analgesic drugs like pentazocine, butorphanol bind and produce dysphoria, psychotomimetic actions, tachycardia, and hallucinogenic effect (Figure 29.1).

Therapeutic Uses

- Management of acute, chronic, and severe pain of acute myocardial infarction, obstetric analgesia.
- Cough suppression (codeine and dextromethorphan).
- Treatment of diarrhoea (diphenoxylate and loperamide).

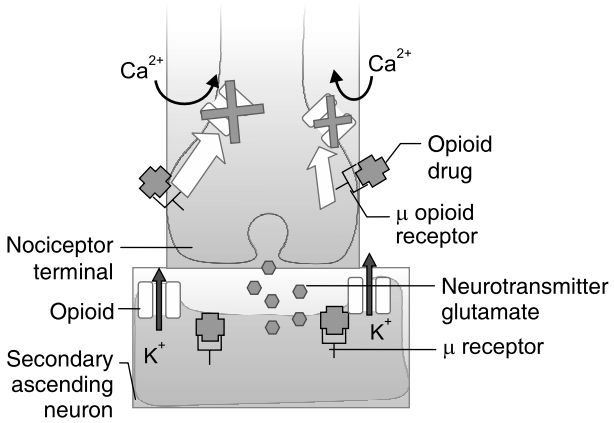
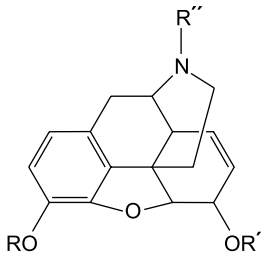


Figure 29.1: Opioid binding to ion channel associated μ receptors inhibit the influx of calcium ions into the presynaptic terminal and increase the outflow of K^+ ions from the postsynaptic membrane. This has the effect of reducing the release of the neurotransmitter glutamate and hyperpolarizing the postsynaptic membrane. Synaptic transmission is inhibited.

- Management of acute pulmonary oedema.
- Preoperative medication and intraoperative adjunctive agent in anaesthesia (fentanyl, alfentanyl, and sufentanyl).
- Maintenance programmes for addicts (methadone).

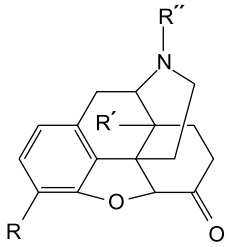
CLASSIFICATION

I. Morphine and its analogues



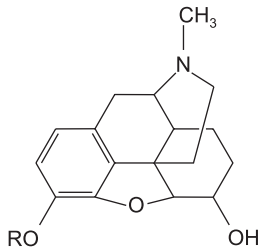
S. No.	Name	R	R′	R″
1.	Morphine	–H	–H	$-CH_3$
2.	Ethyl morphine	$-C_2H_5$	–H	$-CH_3$
3.	Codeine	$-CH_3$	–H	$-CH_3$
4.	Heroin	$-COCH_3$	$-COCH_3$	$-CH_3$
5.	Nalorphine	–H	–H	$-CH_2-CH=CH_2$

a. Hydromorphone derivatives



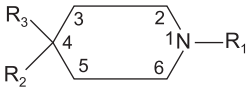
S. No.	Name	R	R′	R″
1.	Hydromorphone	–OH	–H	$-CH_3$
2.	Oxymorphone	–H	–OH	$-CH_3$
3.	Hydrocodone	$-OCH_3$	–H	$-CH_3$
4.	Oxycodone	$-OCH_3$	–OH	$-CH_3$

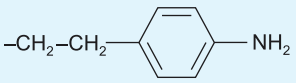
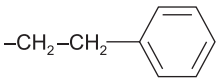
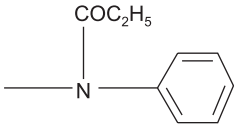
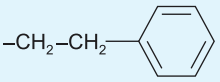
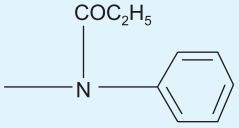
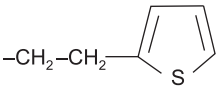
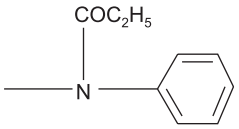
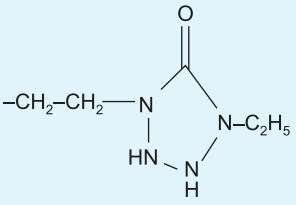
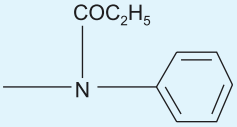
b. Dihydromorphine derivatives



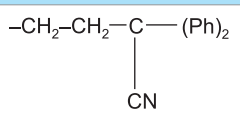
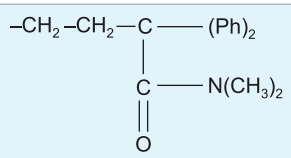
Name	R
Dihydromorphine	–H
Dihydrocodeine	$–CH_3$

II. Meperidine analogues

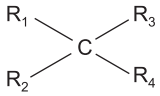


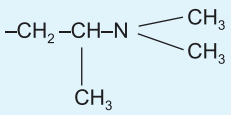
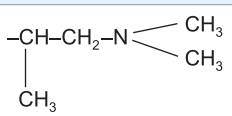
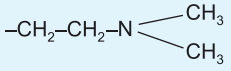
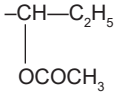
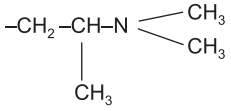
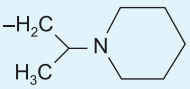
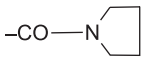
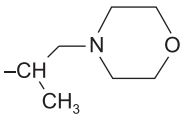
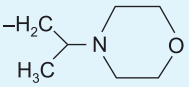
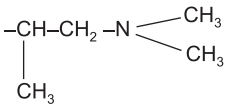
S. No.	Name	R_1	R_2	R_3
1.	Meperidine	$–CH_3$	$–C_6H_5$	$–COOC_2H_5$
2.	Bemidone	$–CH_3$	$–C_6H_4OH$	$–COOC_2H_5$
3.	Properidone	$–CH_3$	$–C_6H_5$	$–COCH(CH_3)_2$
4.	Ketobemidone	$–CH_3$	$–C_6H_4OH$	$–COC_2H_5$
5.	Anileridine		$–C_6H_5$	$–COC_2H_5$
6.	Fentanyl		–H	
7.	Lofentanil		$–COOCH_3$	
8.	Sufentanil		$–CH_2OCH_3$	
9.	Alfentanil		$–CH_2OCH_3$	

Contd.

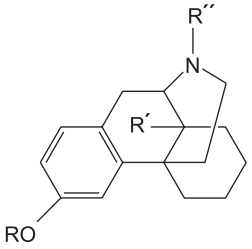
S. No.	Name	R_1	R_2	R_3
10.	Diphenoxylate		$-C_6H_5$	$-COOC_2H_5$
11.	Lopramide		$-C_6H_4Cl$	–OH

III. Methadone analogues



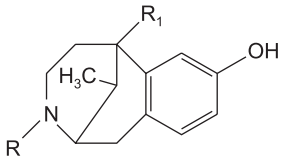
S. No.	Name	R_1	R_2	R_3	R_4
1.	Methadone	–Ph	–Ph	$-COC_2H_5$	
2.	Isomethadone	–Ph	–Ph	$-COC_2H_5$	
3.	Normethadone	–Ph	–Ph	$-COC_2H_5$	
4.	Alpha acetyl methadone	–Ph	–Ph		
5.	Dipanone	–Ph	–Ph	$-COC_2H_5$	
6.	Dextromoramide	–Ph	–Ph		
7.	Phenadoxone	–Ph	–Ph	$-COC_2H_5$	
8.	Propoxyphen	–Ph	$-CH_2-C_6H_5$	$-COC_2H_5$	

IV. Morphinan analogues



S. No.	Name	R	R′	R″
1.	Levorphanol tartrate	–H	–H	$-CH_3$
2.	Butorphanol tartrate	–H	–OH	$-H_2C-$ 
3.	Dextromethorphan	$-CH_3$	–H	$-CH_3$

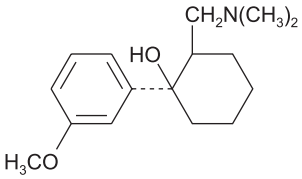
V. Morphan analogues or benzazocin derivatives



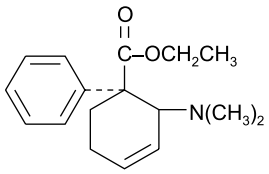
S. No.	Name	R	R_1
1.	Pentazocine	$-CH_2-CH=C(CH_3)_2$	$-CH_3$
2.	Phenazocine	$-CH_2-CH_2-C_6H_5$	$-CH_3$
3.	Cyclazocine	$-CH_2-$ 	$-CH_3$
4.	Ketazocine	$-CH_2-$ 	$=O$
5.	Metazocine	$-CH_3$	$-CH_3$

VI. Miscellaneous

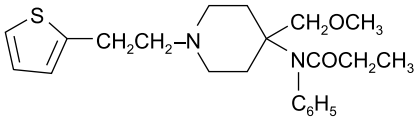
a. Tramadol



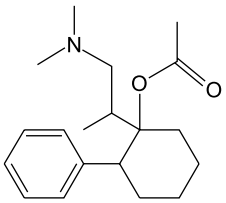
b. Tilidine



c. Sufentanil



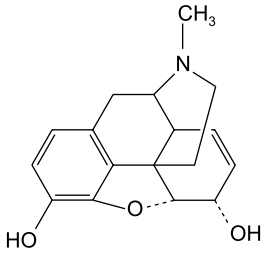
d. Nexeridine



SYNTHESIS AND DRUG PROFILE

I. Morphine analogues

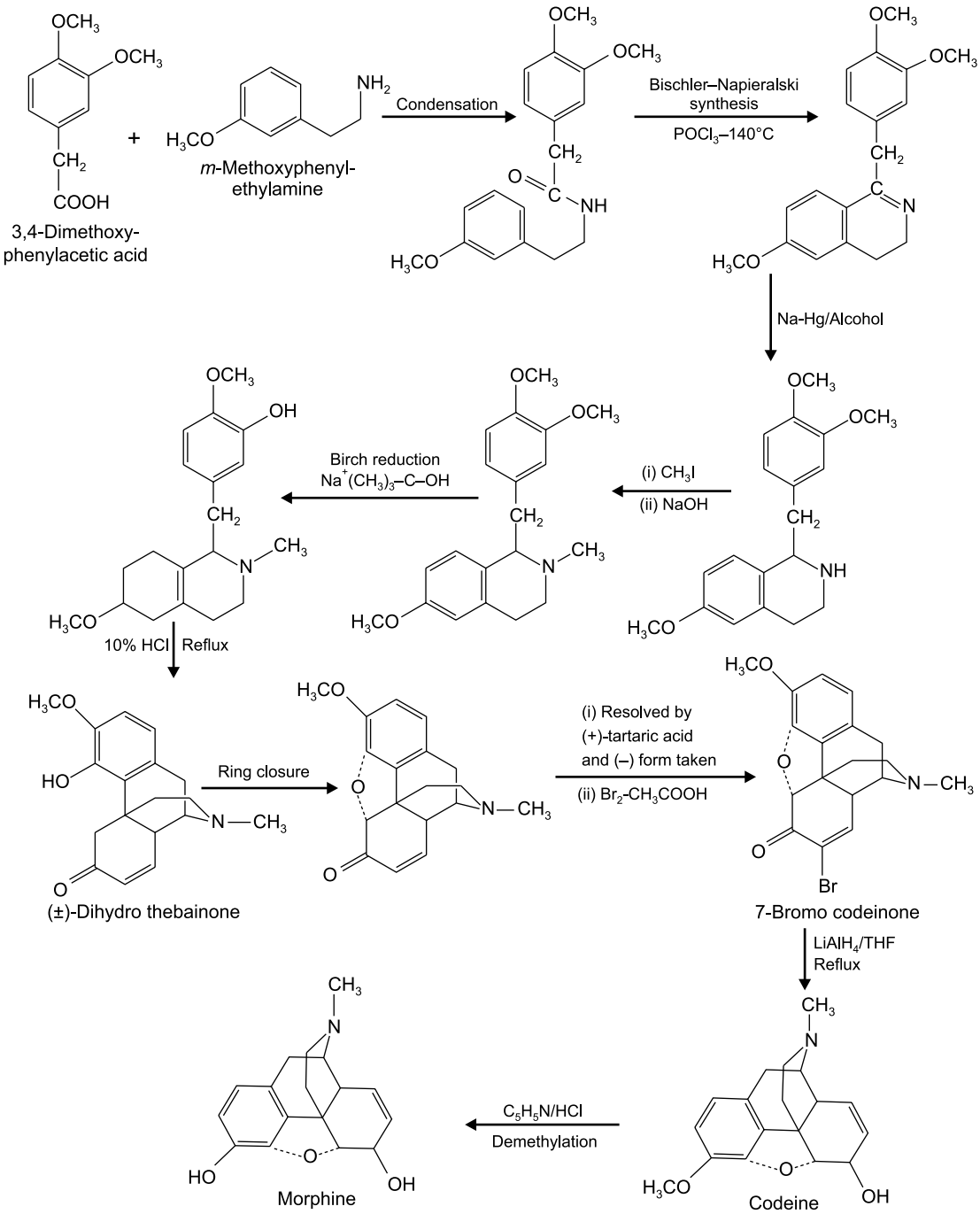
a. Morphine (Duraphine)



Metabolism of morphine: Morphine is conjugated by hepatic enzyme at phenolic (3-OH) position to from 3-glucuronide metabolite. Glucuronidation of morphine also leads to N-demethylation to normorphine, which has decreased opioid activity and it undergoes N and O conjugation and excreted. Compounds with N-alkyl groups larger than methyl get N-dealkylated as a major route of inactivation.

Properties and uses: It exists as a white or almost white crystalline powder or colourless, silky needles or cubical masses, efflorescent in a dry atmosphere. Soluble in water, slightly soluble in ethanol, and insoluble in toluene. It used as an opioid receptor agonist and analgesic.

Synthesis



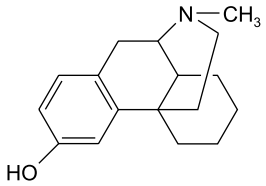
Assay: Dissolve the sample in a mixture of 0.01M hydrochloric acid and ethanol. Perform potentiometric titration, using 0.1M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

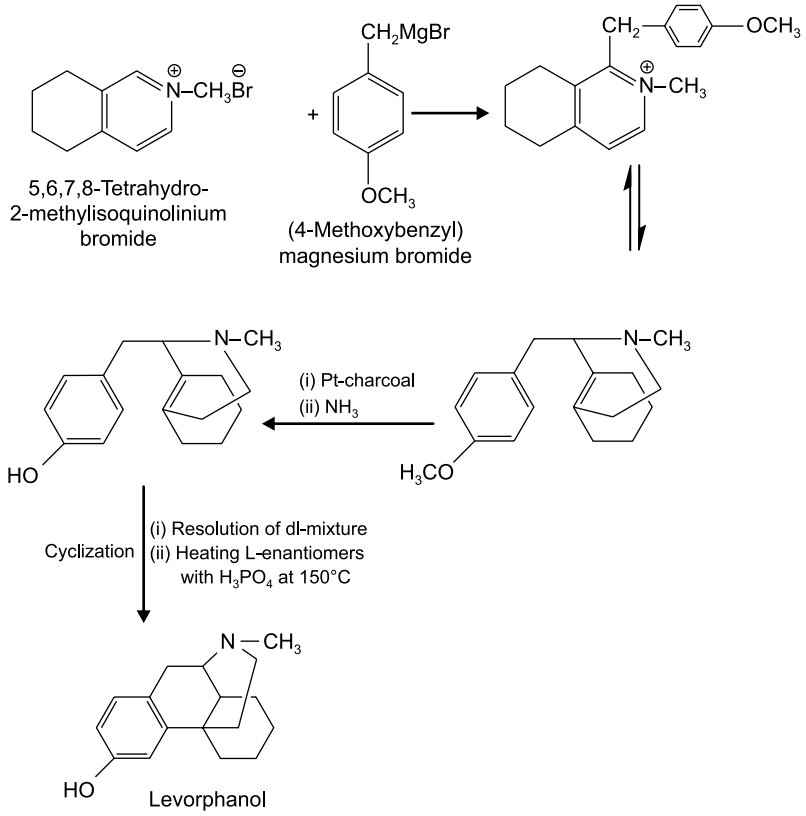
Dose: The usual, adult, oral dose is 10 to 30 mg six times/day.

Dosage forms: Chloroform and morphine tincture IP, BP, morphine suppositories IP, BP, morphine sulphate injection IP.

b. Levorphanol (Levo-Dromoran)



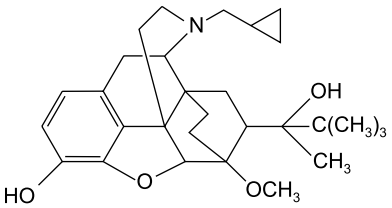
Synthesis



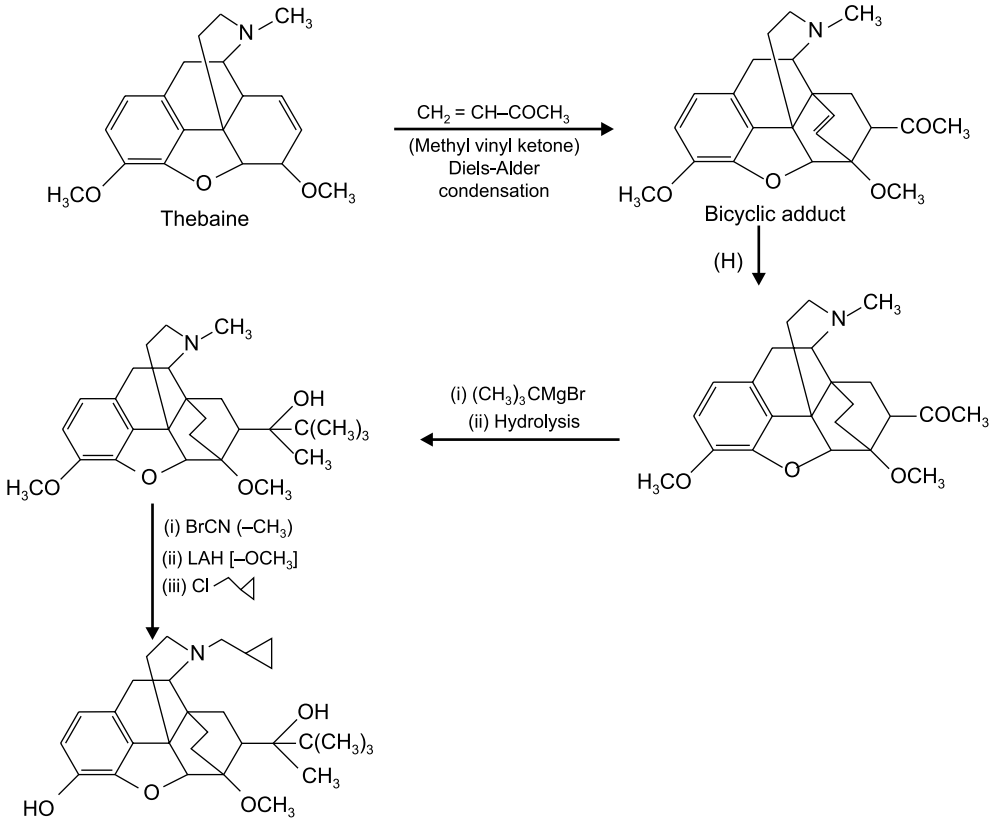
Properties and uses: It exists as white, odourless, crystalline powder, soluble in water and alcohol, insoluble in chloroform and ether. It is a potent narcotic analgesic having actions and structure similar to that of morphine. It is used effectively for the management of both moderate and severe pain. The *d*-isomer shows antitussive property .

Dose: By oral for severe pain, 1.5 to 4.5 mg, one or two times daily; by SC, IM, usual single dose is 2 to 4 mg.

c. Buprenorphine (Tidigesic, Norphin, Buprinor)



Synthesis



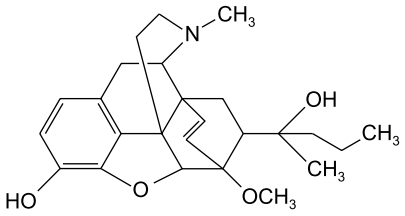
Properties and uses: It exists as a white or almost white crystalline powder. Insoluble in cyclohexane, sparingly soluble in water, freely soluble in methanol, and alcohol. Buprenorphine is a more complex molecule than morphine, which would interact with the opioid receptor (analgesic) and because of its complex structure it would not interact with other receptors that produce side effects. It is used as potent analgesic.

Assay: Dissolve the substance in anhydrous acetic acid and add acetic anhydride to this. Titrate against 0.1 M perchloric acid and determine the end point potentiometrically.

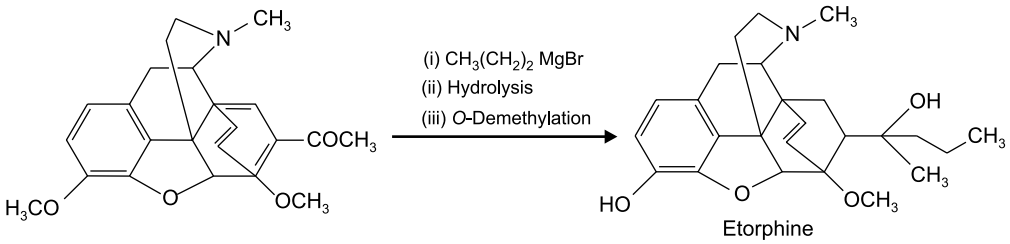
Storage: It should be stored in a well-closed airtight container and protected from light.

Dose: The usual dose is 0.3 mg IM every 6 hrs.

d. Etorphine



Synthesis



Properties and uses: It is a white or almost white microcrystalline powder, very slightly soluble in chloroform, insoluble in ether, sparingly soluble in water and in ethanol. Etorphine is thousand times more potent than morphine, which could be interpreted as having a better or a tighter fit to receptors. It is used primarily in veterinary medicine to immobilize large animals.

Preparations: Etorphine and acepromazine injection BP, etorphine and levomepromazine injection BP.

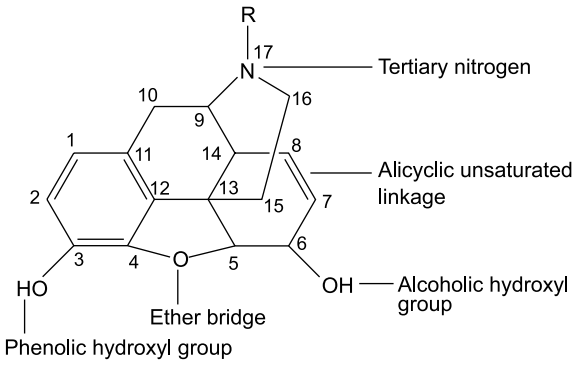
Assay: Assayed by non-aqueous titration, to a solution of a sample, add mercury(II) acetate solution and titrate against 0.1M perchloric acid, using crystal violet solution as indicator.

Storage: It should be stored in well-closed airtight containers and protected from light.

SAR of Morphine

SAR of morphine was studied by

1. Modification of alicyclic ring
2. Modification of aromatic ring
3. Modification of 3° nitrogen



1. Modification on alicyclic ring

- The alcoholic hydroxyl group at C-6 when methylated, esterified, oxidized, removed, or replaced by halogen analgesic activity as well as toxicity of the compound increased.
- The reduction of C-6 keto group to C-6 β-hydroxyl in oxymorphone gives nalbupine, it shows antagonistic action of μ-receptors.
- The saturation of the double bond at C-7 position gives more potent compound. Examples, dihydro morphine and dihydrocodeine.
- The 14 β-hydroxyl group generally enhances μ-agonistic properties and decreases antitussive activity.
- However, activity varies with the overall substitution on the structure.
- Bridging of C-6 and C-14 through ethylene linkage gives potent derivatives.
- Reaction of thebaine with dienophile (i.e. Diels-Alder reaction) results in 6,14-endoetheno-tetrahydro thebaine derivatives, which are commonly called *oripavines*. Some oripavines are extremely potent μ-agonist, for example, etorphine and buprenorphine are the best known. These derivatives are about thousand times more potent than morphine as μ-agonist.

2. Modification on phenyl ring

- An aromatic phenyl ring is essential for activity.
- Modification on phenolic hydroxyl group decreases the activity.
- Any other substitution on phenyl ring diminishes activity.

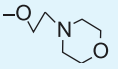
3. Modification of 3° nitrogen

- A tertiary amine is usually necessary for good opioid activity.
- The size of the N-substitution can dictate the compounds potency and its agonists and its reverse antagonistic property.
- The N-methyl substitution is having good agonistic property, when increased the size of the substitution by 3–5 carbons results in antagonistic activity. Still larger substitutent on N returns agonistic property of opioids, for example, N-phenyl ethyl substitution is ten times more potent than N-methyl groups.
- N-allyl and N-cylo alkyl group leads to narcotic antagonistic property.

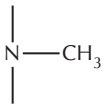
4. Epoxide bridge

- Removal of 3,4-epoxide bridge in morphine structure results in the compound that is referred to as morphinans.
- The morphinans are prepared synthetically. As the synthetic procedure yielded compound is a racemic mixture, only levo-isomer possesses opioid activity while the dextro-isomer has useful antitussive activity, for example, levorphanol and butorphanol.
- Levorphanol is a more potent analgesic than morphine.

Summarized SAR of morphine analogues is given below:

Functional group	*Modification*	*Observed effects*
Phenolic hydroxyl –OH	(i) –OH–H	Less analgesic effect
	(ii) –OH to $-COCH_3$	Less analgesic effect
	(iii) –OH to OCH_3	Less analgesic effect
	(iv) OH to OC_2H_5	Less analgesic effect
	(v) OH to 	Less analgesic effect

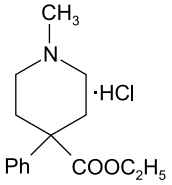
Contd.

Functional group	*Modification*	*Observed effects*
Alcoholic hydroxyl –OH	(i) OH to OCH_3 (ii) OH to OC_2H_5 (iii) OH to $OCOCH_3$ (iv) OH to = O (v) OH to H	More active than morphine More active than morphine More active than morphine Less active than morphine More active than morphine
Alicyclic unsaturated linkage –CH = CH–	–CH = CH to – CH_2–CH_2	More active than morphine
Tertiary nitrogen 	(i) N–CH_3 to NH (ii) N–CH_3 to N–CH_2–CH_2–Ph (iii) N–CH_3 to N-allyl, propyl	Less active than morphine More active than morphine Morphine antagonist

II. Meperidine analogues

Metabolism: Meperidine (pethidine) analogues results in rapid metabolism. Esterase cleaves the ester bond to leave the inactive 4-carboxylate derivatives. They also undergo N-demethylation to give normeperidine.

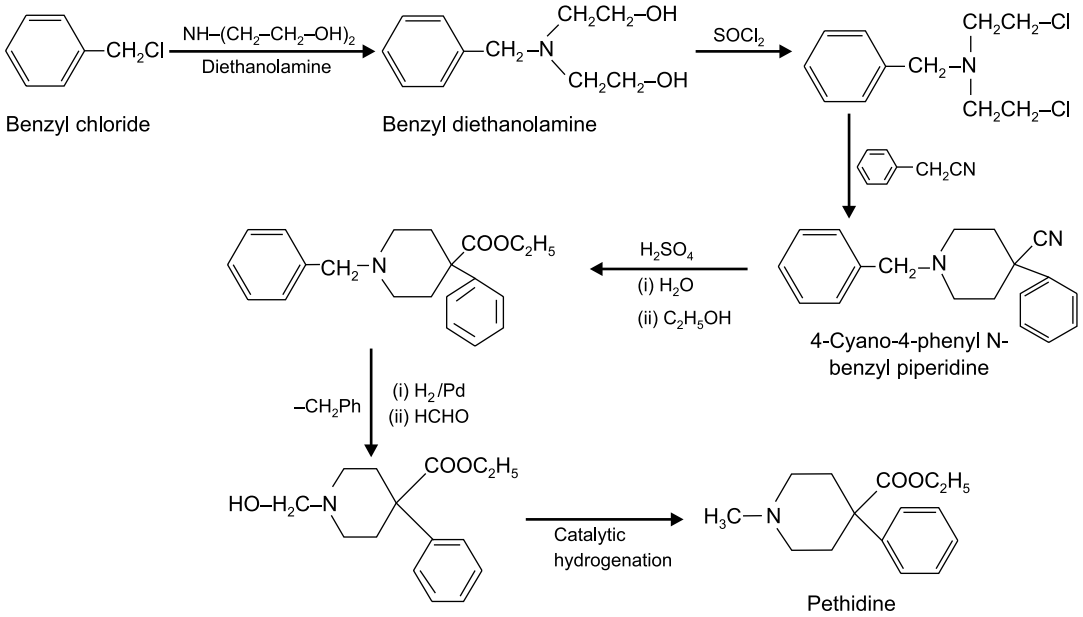
a. Pethidine hydrochloride (Meperidine HCl, Denerol, Mepadin)



4-Ethoxycarbonyl-1-methyl-4-phenylpiperidine

Synthesis

Route I. From: Benzyl chloride



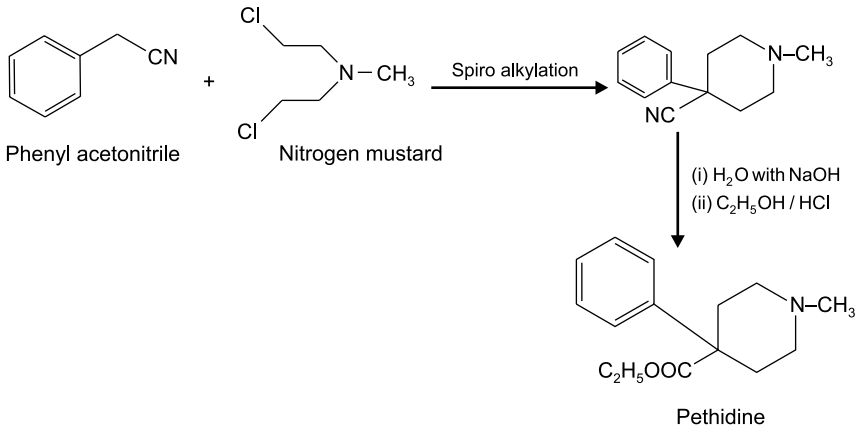
Benzyl chloride

Benzyl diethanolamine

4-Cyano-4-phenyl N-benzyl piperidine

Pethidine

Route II. From: Phenyl acetonitrile



Phenyl acetonitrile + Nitrogen mustard → Pethidine

Properties and uses: It is a white crystalline powder, soluble in water, and freely soluble in alcohol. It may be used for the relief of a variety of moderate-to-severe pain, including the pain of labour and postoperative pain. Pethidine has atropine-like action on smooth muscle. It is normally used to induce both sedation and analgesia simultaneously.

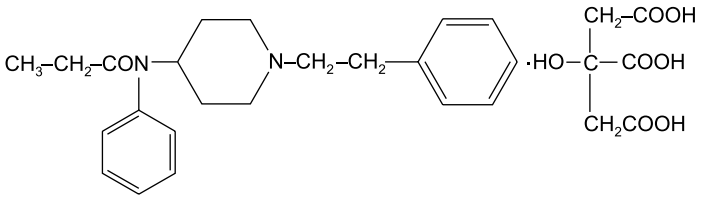
Assay: Dissolve the substance in alcohol and add 0.01 M hydrochloric acid. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Usual dose is 50 to 100 mg IM. Occassionally given orally.

Dosage forms: Pethidine HCl injection IP, pethidine HCl tablets IP, pethidine injection BP, pethidine tablets BP.

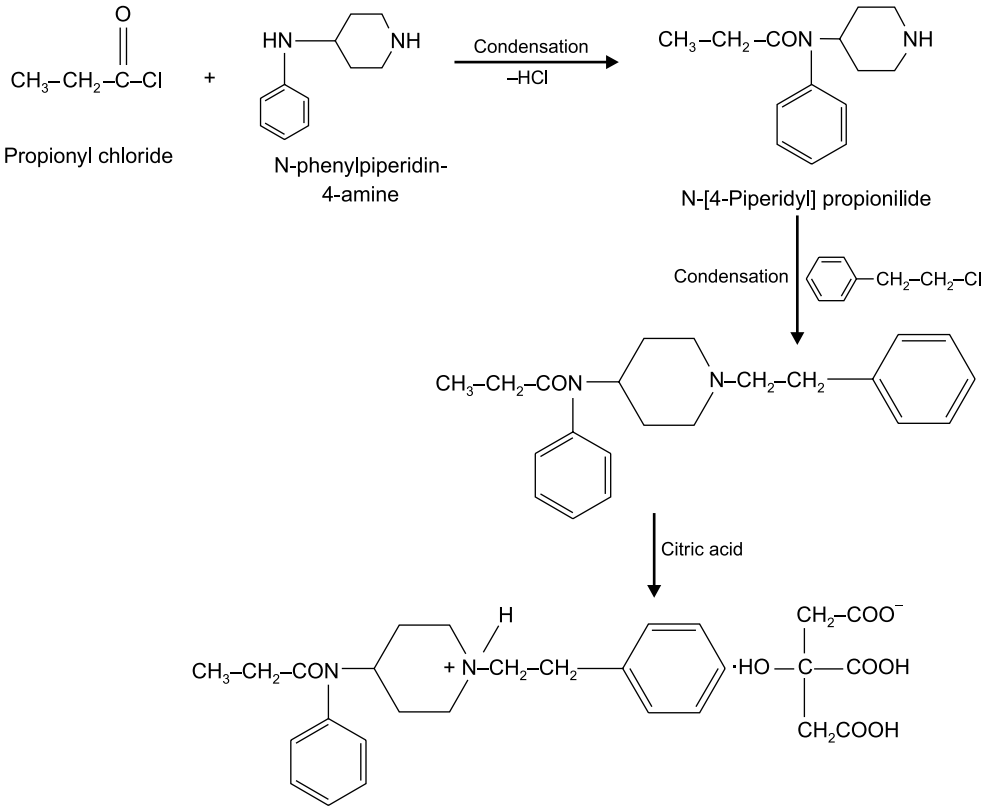
b. Fentanyl citrate (Durogesic)



N-Phenyl-N-[1-(2-phenyl ethyl)-4 piperidinyl] propanamide

Properties and uses: It is a white or almost white powder soluble in water, freely soluble in methanol, and sparingly soluble in alcohol. Fentanyl is related to pethidine and also to basic anilides with analgesic properties, and is characterized by high potency, rapid onset, and short duration of action. It is a potent narcotic analgesic employed for the arrest of pain and it may also be employed as an adjuvant for all such drugs mostly used for regional and general anaesthesia.

Synthesis



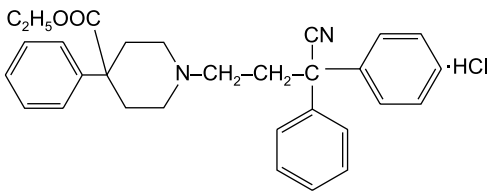
Assay: Dissolve the substance in a mixture of 1 volume of anhydrous acetic acid and 7 volumes of methyl ethyl ketone. Titrate with 0.1 M perchloric acid using naphtholbenzein solution as indicator.

Storage: It should be stored in well-closed airtight container and protected from light.

Dose: By IM in preoperative medication 0.05 to 0.1 mg, 30 to 60 min before surgical treatment, for rapid analgesic action, 0.05 to 0.1 mg by IV.

Dosage forms: Fentanyl injection BP.

c. Diphenoxylate hydrochloride



1-(3-Cyano-3,3-diphenyl propyl)-4-phenyl-4-piperidin-ethyl carboxylate

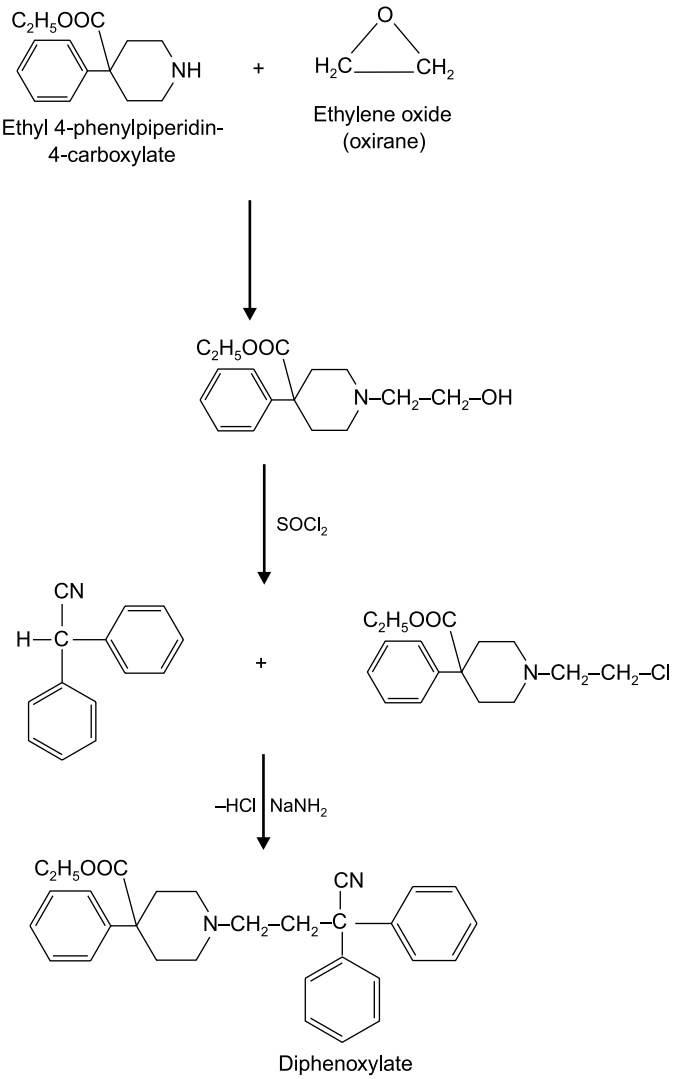
Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in alcohol, very slightly soluble in water, freely soluble in methylene chloride. It is a synthetic analogue of pethidine with some analgesic activity, but is mostly used in the treatment of diarrhoea associated with gastroenteritis, irritable bowel, acute infections, hypermotility, ulcerative colitis, and sometimes even in food poisoning.

Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration, using 0.1 M ethanolic sodium hydroxide.

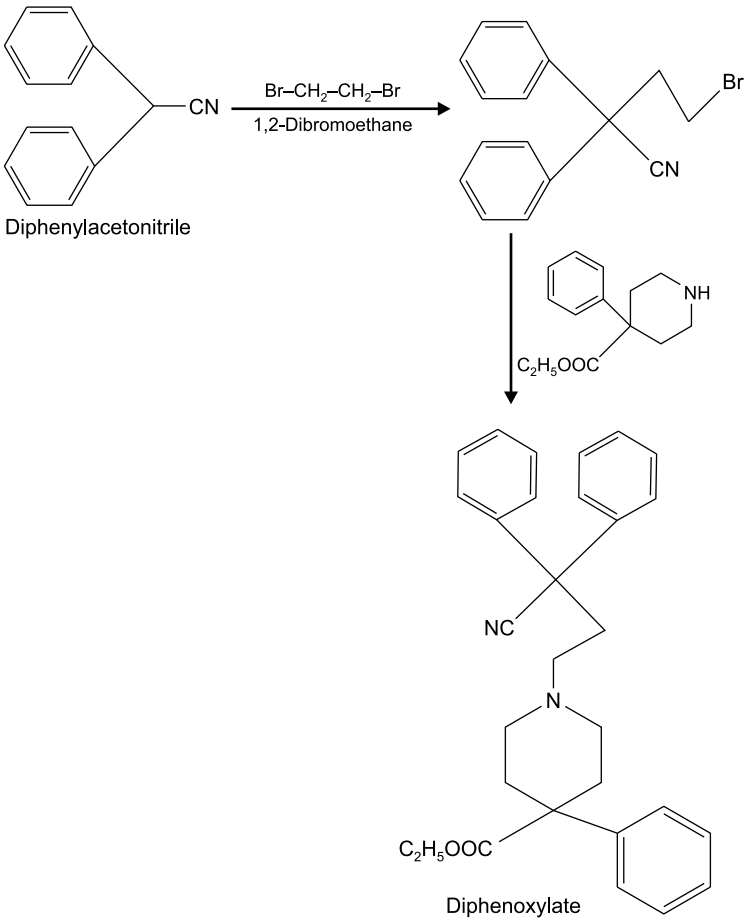
Storage: It should be stored in well-closed airtight containers and protected from light.

Synthesis

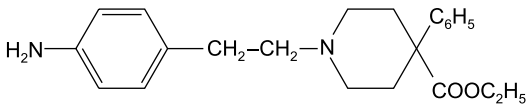
Route I. From: Ethyl-4-phenyl piperidine-4-carboxylate



Route II. From: Diphenylacetonitrile



d. Anileridine



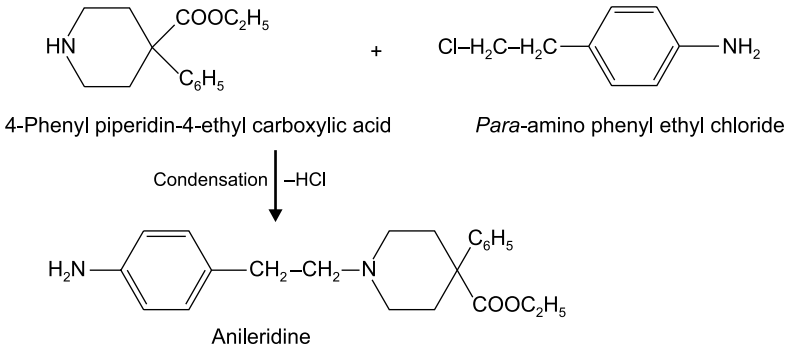
1-[2-(4-Amino phenyl) ethyl]-4-Phenyl-4-piperidin carboxylic acid ethyl ester

Properties and uses: It is a narcotic analgesic, having related chemical structure to that of pethidine. Anileridine is more active than merperidine and has the same uses and limitations.

Dose: The usual oral dose is 25 mg every 6 h.

Synthesis

Route I. From: 4-Phenyl piperidin-4-ethyl carboxylate

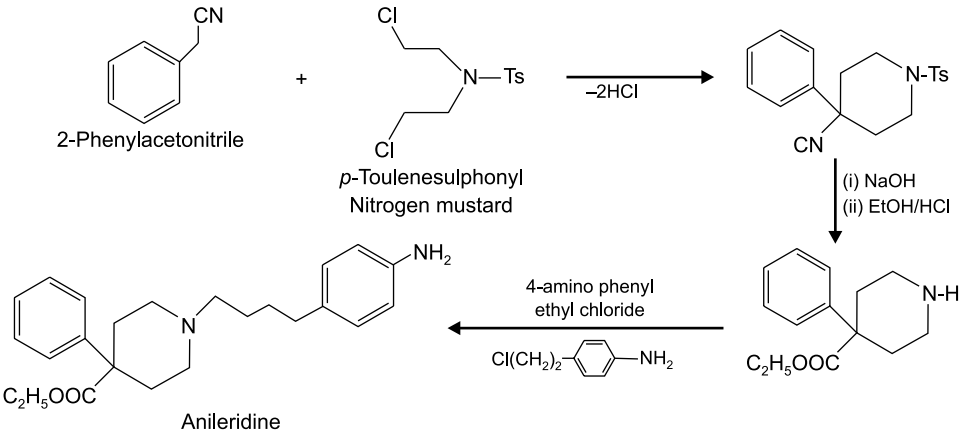


4-Phenyl piperidin-4-ethyl carboxylic acid

Para-amino phenyl ethyl chloride

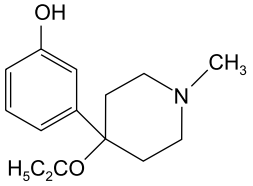
Anileridine

Route II. From: Benzyl cyanide or 2-phenylacetonitrile



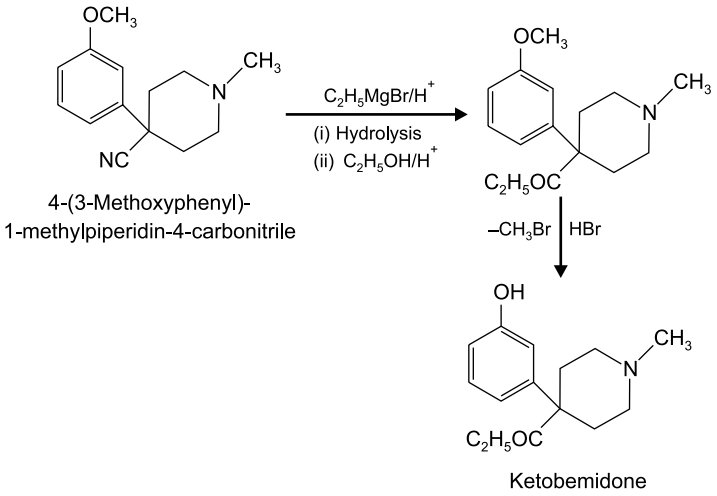
Anileridine

e. Ketobemidone



1-(4-(3-Hydroxyphenyl)-1-methylpiperidin-4-yl)propan-1-one

Synthesis



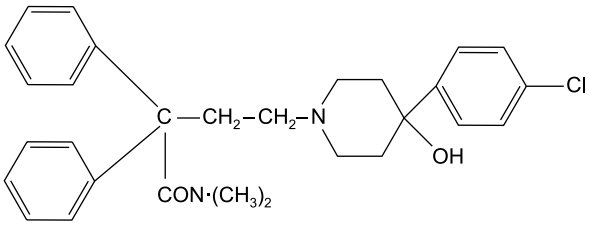
4-(3-Methoxyphenyl)-1-methylpiperidin-4-carbonitrile

Ketobemidone

Properties and uses: It is a white or almost white crystalline powder, soluble in alcohol, slightly soluble in methylene chloride, and freely soluble in water. Used as an opioid receptor agonist and analgesic.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and 50 ml of alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

f. Loperamide



4-((4-Chlorophenyl) hydroxy)-1-((3-N,N-dimethylamino carbonyl)1,1-diphenyl) propyl piperidine

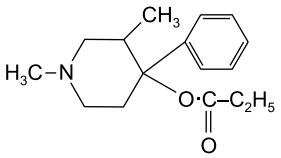
Properties and uses: It is a white or almost white powder, slightly soluble in water, freely soluble in alcohol and methanol. It is used as a safe and effective opioid derivative with pheripheral μ opioid and weak anticholinergic property.

Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid, perform potentiometric titration, using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Loperamide capsules BP.

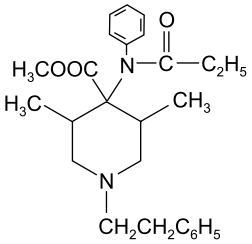
g. Alphaprodine



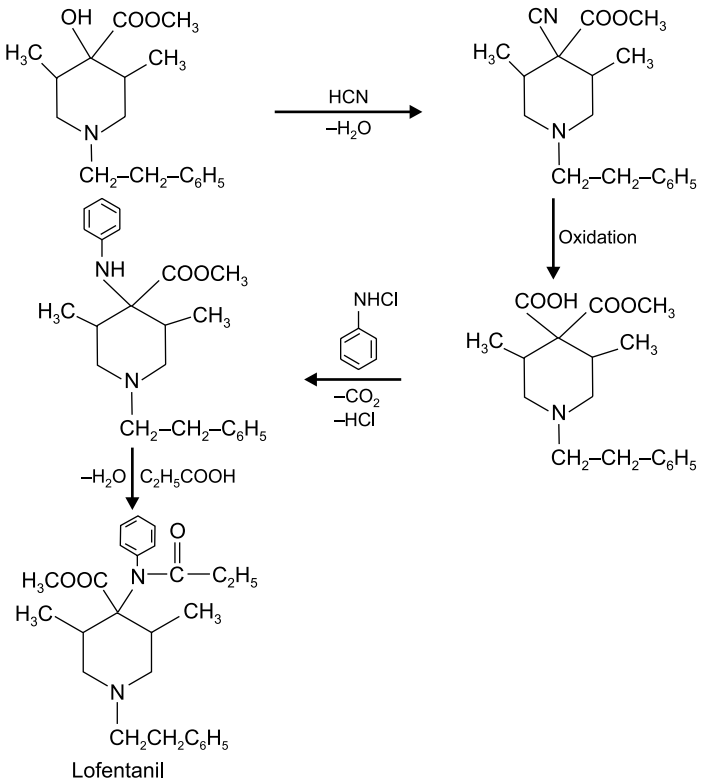
1,3-Dimethyl-4-phenyl-4-(piperidine)propanoate

Uses: It is an effective analgesic similar to meperidine.

h. Lofentanil

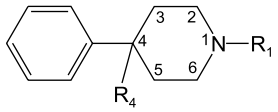


Synthesis



Lofentanil

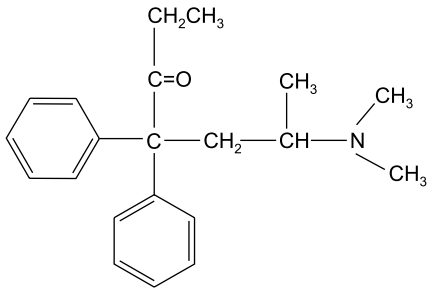
SAR of Meperidine Analogues



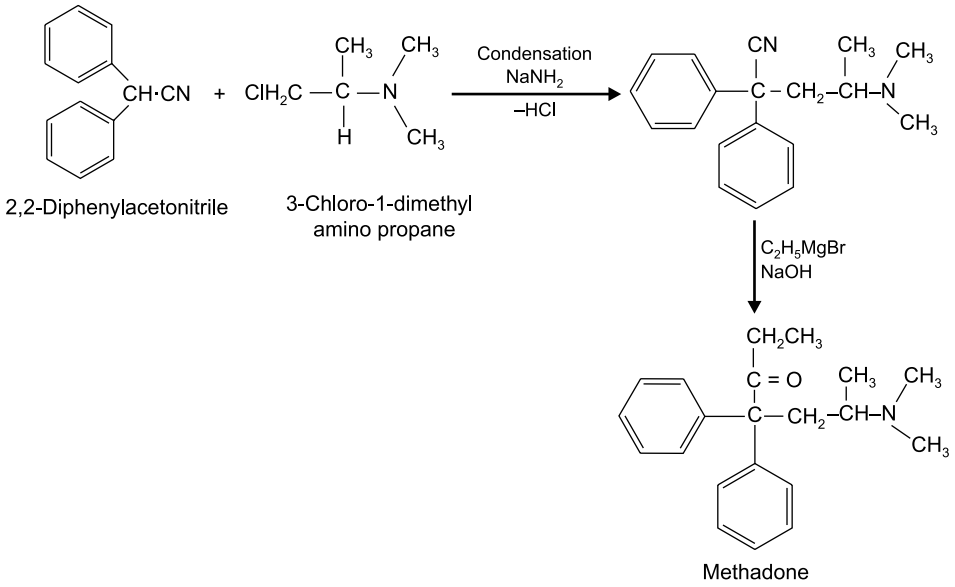
- Placement of *m*-hydroxyl group on the phenyl ring increases activity. The effect is more significant on the keto compound than on the pyridine.
- Substitution of carbethoxy group in meperidine by acyloxy group provides better analgesic as well as spasmolytic activity (alpha-prodine).
- The presence of phenyl and ester group at 4th position of 1-methylpiperdine results in optimum activity.
- The replacement of C-4 phenyl group of meperidine by hydrogen, alkyl, other aryl, aralkyl, and heterocyclic groups reduces analgesic activity.
- Replacement of phenyl group by phenyl ethyl derivatives is seen to be about three times as active as the meperidine. The amino analogue, anileridine is about four, times more active.
- Contraction of piperidiene ring to the pyrrolidine gives a more active compound, but causes abuse liability. For example, alpha-prodine and procilidine.
- Enlargement of piperidine ring to a 7-membered hexahydroazepine yield active compounds with low incidence of side effects. For example, proheptazine.
- The C-3 methyl analogue with an ester group at the C-4 position like lofentanil is 8400 times more potent than meperidine as an analgesic.
- In fentanyl, the phenyl and acyl groups are separated by nitrogen. It is 50 times stronger than morphine with minimal side effects. Its short duration of action makes it well suited for use in anaesthesia.
- The *p*-chloro analogue (loperamide) has been shown to bind to opiate receptors in the brain, but it cannot penetrate the blood–brain barrier sufficiently to produce analgesia.
- Diphenoxylate, a structural hybrid of meperidine and methadone type, devoid of analgesic activites. It is effective as an intestinal spasmolytic and is used in the treatment of diarrhoea.

III. Methadone analogues

a. Methadone



Synthesis



2,2-Diphenylacetonitrile

3-Chloro-1-dimethyl amino propane

Methadone

Metabolism: Methadone metabolizes to form an active α-dinormethadol and dinor-L-α-acetylmethadol (LAAM), then it undergoes N-demethylation to form inactive pyrrolidines and pyrrolines which are excreted in urine.

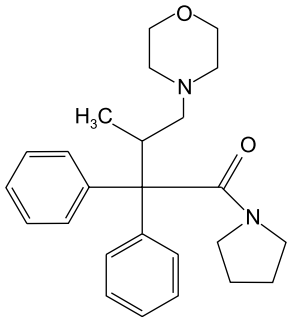
Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and soluble in water. Even methadone, which looks structurally different from other opioid agonists, has steric forces that produce a configuration that closely resembles the opioid agonists. Methadone is more active and more toxic than morphine. It can be used for the relief of many types of pain. In addition, it is used as narcotic substitute treatment because it prevents morphine abstinence syndrome. The toxicity of methadone is three to ten times that of morphine, but its analgesic effect is twice that of morphine and ten times that of meperidine.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and anhydrous ethanol by using 0.1 M sodium hydroxide to perform potentiometric titration.

Storage: It should be stored in well-closed airtight containers and protected from light.

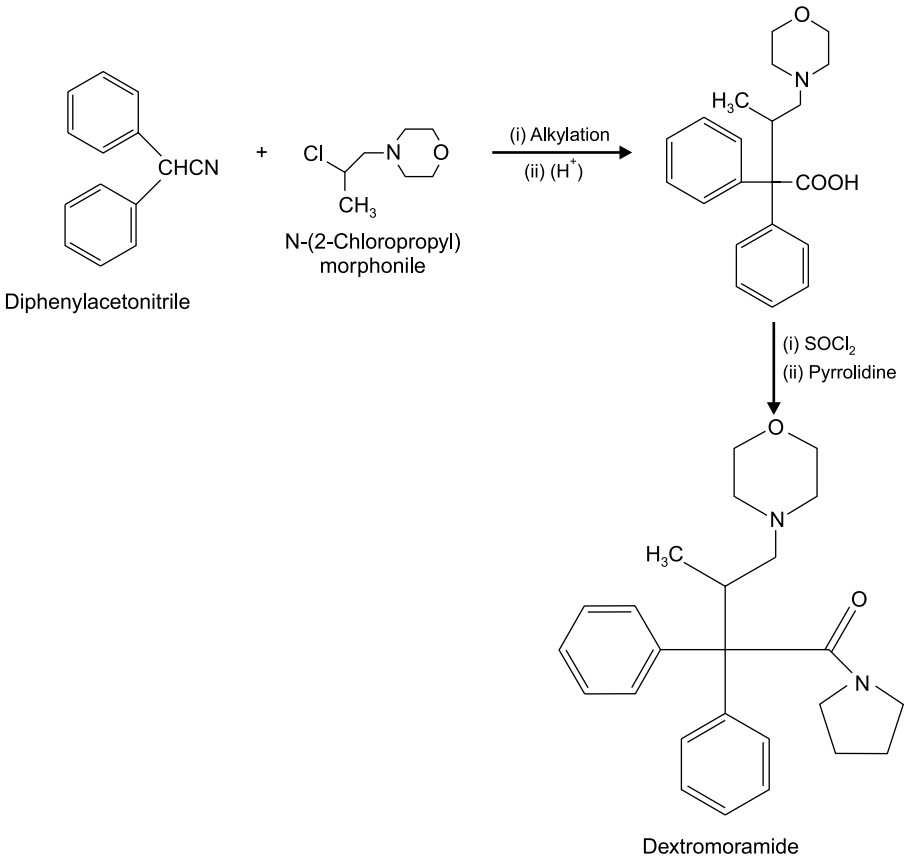
Dosage forms: Methadone HCl injection IP, methadone HCl tablets IP, methadone injection BP, methadone linctus BP, methadone oral solution (1 mg/ml) BP, methadone tablets BP.

b. Dextromoramide



3-Methyl-4-morpholino-2,2-diphenyl-1-(pyrrolidin-1-yl)butan-1-one

Synthesis

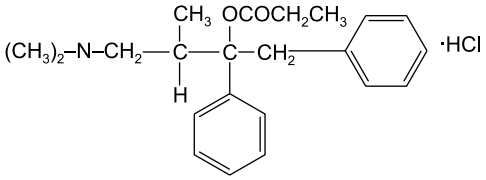


Properties and uses: It is a white amorphous or crystalline powder, soluble in water and sparingly soluble in alcohol. Used as an opioid receptor agonist, and thus, acts as an analgesic.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.05 M perchloric acid using naphtholbenzein solution as indicator.

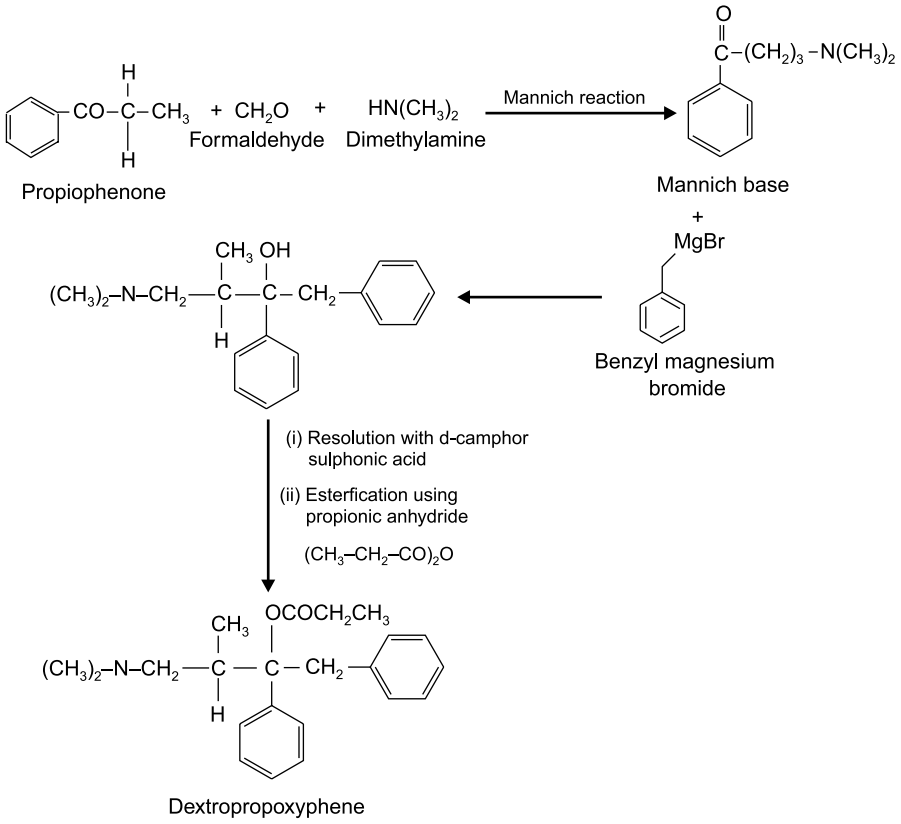
Dosage forms: Dextromoramide tablets BP

c. Dextropropoxyphene (Propoxyphene hydrochloride, Neurovon, Proxytab, Spasma Neurovon)



4-(Dimethyl amino)-3-methyl-1,2-diphenyl-2-butanolpropionate ester hydrochloride

Synthesis



Properties and uses: It is a white or almost white crystalline powder, very soluble in water and freely soluble in alcohol. It has no antiinflammatory or antipyretic action and has little antitussive activity despite the fact that its levo-isomer is used for this purpose. It is used to control mild-to-moderate pain and used along with other analgesics having antiinflammatory and antipyretic properties, such as paracetamol and aspirin.

Assay: Dissolve the sample in acetic anhydride and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual does is 65 mg, three or four times/day.

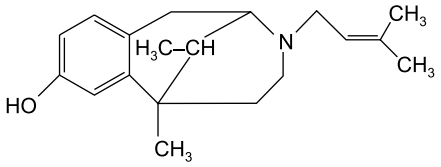
Dosage forms: Co-proxamol tablets BP.

SAR of Diphenyl Heptanone (Methadone Series)

- The reduction of keto and acetylation of resulting hydroxyl group gives the acetyl methadol, the useful antidiarrhoeal opioids, for example, diphenoxylate and loperamide.
- Removal of any of the phenyl group sharply decreases the activity.
- Placement of *m*-hydroxy group in the phenyl ring decreases analgesic activity.
- The levo-isomer of methadone and isomethadone are twice as effective as their racemic mixture.
- Substitution of terminal dimethylamino group by piperidine group decreases activity.
- Substitution of propionyl group by hydrogen, hydroxyl or acetoxyl decreases the activity, whereas amide analogue, pyrrolidinoyl and terminal morpholino moiety enhance the activity by several time.

IV. Morphan derivatives

a. Pentazocine (Fortstar, Fortwin, Zocin)



Properties and uses: It is a white or almost white powder sparingly soluble in water, soluble in ethanol, and sparingly soluble in methylene chloride. A synthetic analgesic agent, when administered orally in a 50 mg dose, it appears to be equivalent in analgesic effectiveness to 60 mg of codeine. Pentazocine in a parenteral dose of 30 mg or an oral dose of 50 mg is about as effective as 10 mg of morphine in most patients. There is some evidence that the analgesic action resides principally in the (–) isomer, and a dose of 25 mg is approximately equivalent to 10 mg of morphine sulphate.

Assay: Dissolve the sample in ethanol and add 0.01 M hydrochloric acid. Titrate against 0.1 M sodium hydroxide and determine the end point potentiometrically.

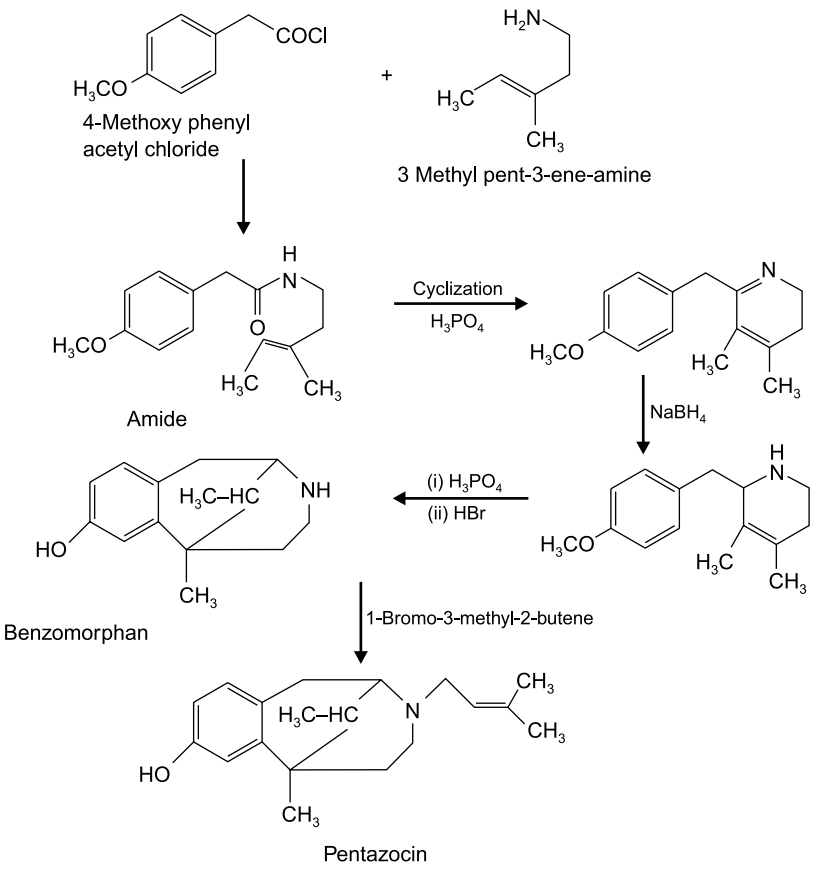
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: By parenteral, 20 to 60 mg (as lactate); usually 30 mg six to eight times/day; daily dose must not exceed 360 mg.

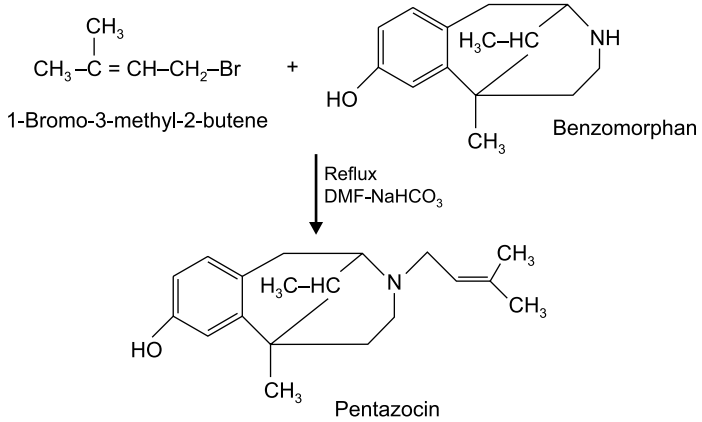
Dosage forms: Pentazocaine injection IP, pentazocaine HCl tablets IP, pentazocine capsules BP, pentazocine tablets BP.

Synthesis

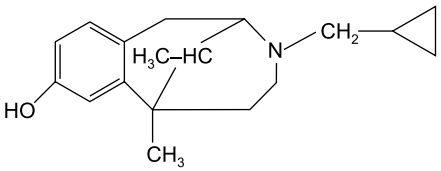
Route I. From: 4-Methoxy phenyl acetyl chloride



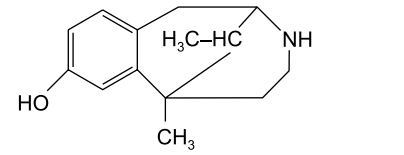
Route II. From: 1-Bromo-3-methyl-2-butene



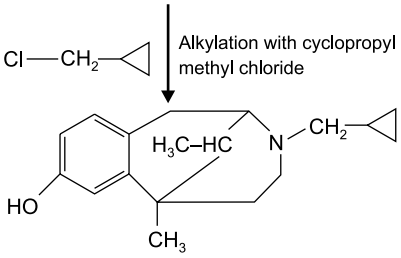
b. Cyclazocin



Synthesis



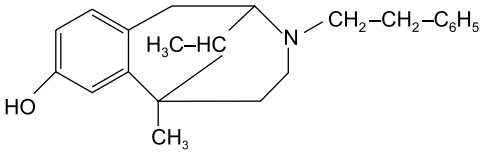
Benzomorphan



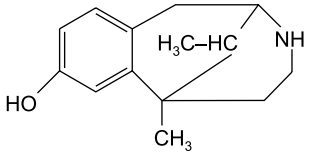
Cyclazocin

Uses: It is a potent narcotic antagonist that has shown analgesic activity in humans at 1 mg doses.

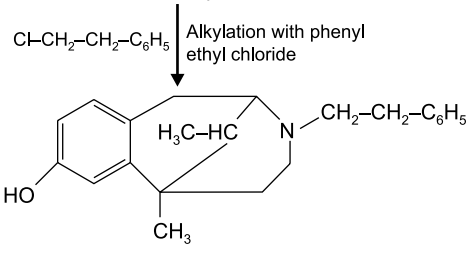
c. Phenazocine



Synthesis

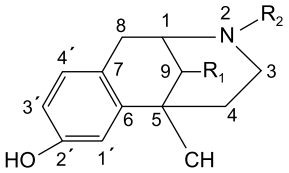


Benzomorphan



Phenazocin

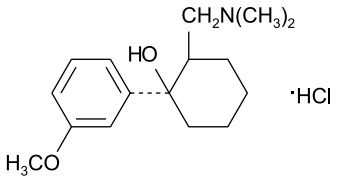
SAR of Benzomorphan Derivatives (Benzazocines)



- Pentazocine produces analgesia because of its agonistic action on kappa opioid receptors. Pentazocine is a week antagonistic at μ-receptors.
- The trimethyl compound ($R_1 = R_2 = CH_3$) is more active than dimethyl ($R_1 = H$, $R_2 = CH_3$) compound.
- Placement of N-phenyl ethyl results in more activity than N-methyl compound.
- Placement of methyl group in 9th position increases the activity. However, –OH group decreases the activity.
- N-allyl or N-cycloproyl methyl group confers antagonistic activity. For example, levallorphanol, naloxone, and naltreoxane.

VI. Miscellaneous

a. Tramadol hydrochloride (Domadol, Stemadol, Tramazac)



2-((dimethylamino)methyl)-1-
(3-methoxyphenyl)cyclohexanolhydrochloride

Properties and uses: It is a white crystalline powder, freely soluble in water and in methanol, very slightly soluble in acetone. The drug possesses opioid activity, but has other analgesic activity that is not reserved by naloxone. It is also used as noradrenaline reuptake inhibitor.

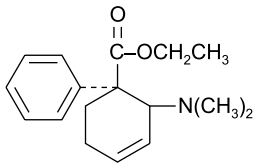
Assay: Dissolve the sample in a mixture of anhydrous acetic acid and add acetic anhydride. Titrate with 0.1 M perchloric acid, and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: IM or IV injection 50 to 100 mg; as suppository 100 mg.

Dosage forms: Tramadol capsules BP.

b. Tilidine HCl (Valoron, Tilidine)



2-(Dimethylamino)-1-phenyl-
3-cyclohexen-1-carboxylic acid ethyl ester

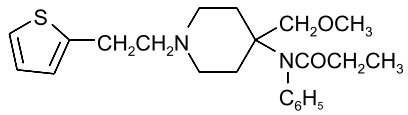
Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, methylene chloride, and alcohol. It is a narcotic analgesic employed in the treatment of moderate to severe pain.

Assay: Dissolve the substance in a mixture of anhydrous acetic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 50 to 100 mg four times/day.

c. Sufentanil



N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenyl propanamide

Properties and uses: It is a white or almost white powder soluble in water and in alcohol, freely soluble in methanol. It is a structural analogue of fentanyl, used in anaesthesia and as a narcotic analgesic.

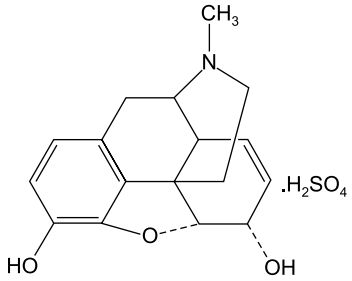
Assay: Dissolve the sample in a mixture of 1 volume of anhydrous acetic acid and 7 volumes of methyl ethyl ketone and titrate with 0.1M perchloric acid, using naphtholbenzein solution as indicator.

Storage: It should be stored in well-closed airtight containers and protected from light.

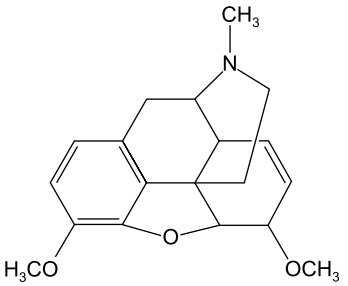
CLASSIFICATION BASED ON PCI SYLLABUS

Morphine and Related Drugs

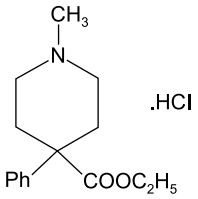
Morphine sulphate



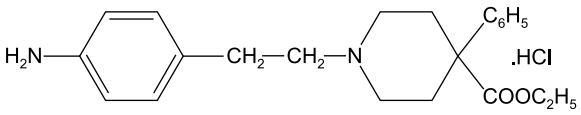
Codeine



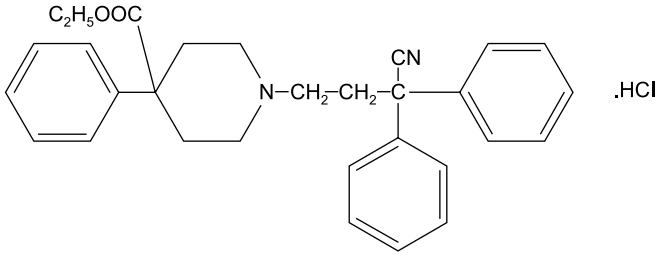
Meperidine hydrochloride



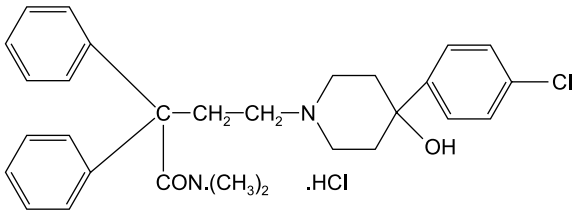
Anilerdine hydrochloride



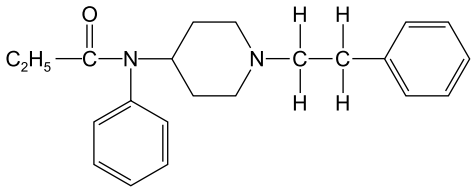
Diphenoxylate hydrochloride



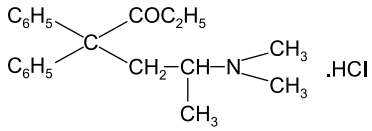
Loperamide hydrochloride



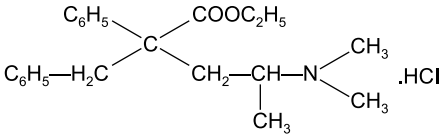
Fentanyl citrate



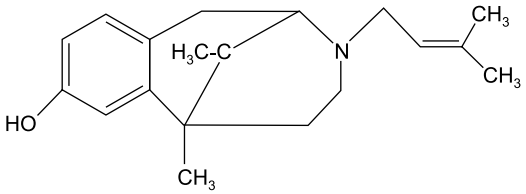
Methadone hydrochloride



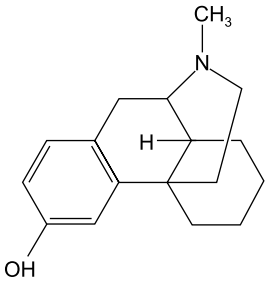
Propoxyphene hydrochloride



Pentazocine

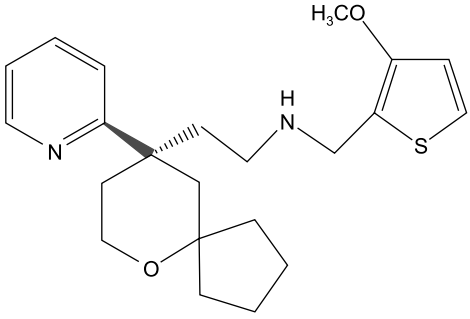


Levorphanol tartrate



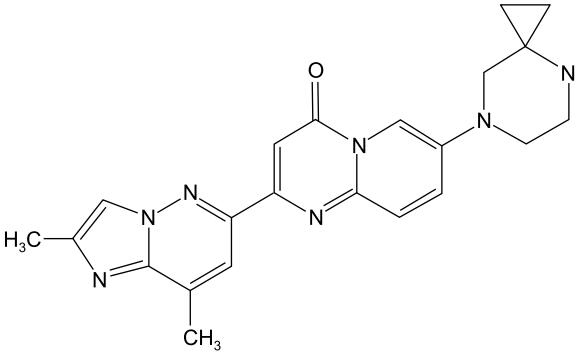
Newer Agents

Oliceridine



Uses: It is an opioid drug that is used for the treatment of moderate-to-severe acute pain in adults.

Risdiplam



Uses: It is a first oral route medication used to treat spinal muscular atrophy (SMA).

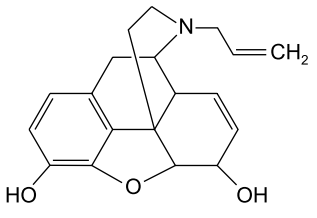
NARCOTIC ANTAGONISTS

The euphoria accompanying with use of heroin and other narcotics reinforces repeated drug-seeking behaviour as psychological dependence develops. Once tolerance develops, the opiate-dependent individual avoids painful withdrawal symptoms by continuously increasing the amounts of opiate consumed.

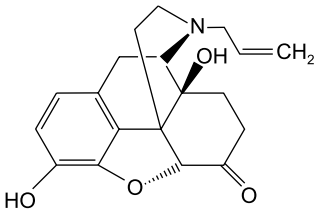
Narcotic antagonists: Prevents or abolishes excessive respiratory depression caused by the administration of morphine or related compounds. They act by competing for the same analgesic receptor sites. They are structurally related to morphine with the exception of the group attached to nitrogen.

CLASSIFICATION

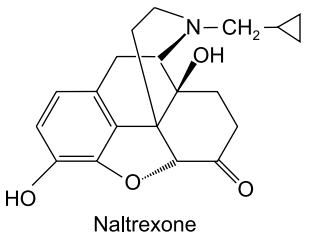
1. Pure antagonists (e.g. naloxone, naltrexone).
2. Partial agonists of nalorphine type (e.g. nalorphine, levallorphan, and cyclazocine).
3. Partial agonists of morphine type (e.g. propiram, profadol).



Nalorphine



Naloxone

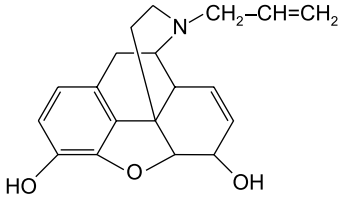


Naltrexone

Nalorphine precipitates withdrawal symptoms and produces behavioural disturbances in addition to the antagonism action. Naloxone is a pure antagonist with no morphine-like effect. It blocks the euphoric effect of heroin when given before it.

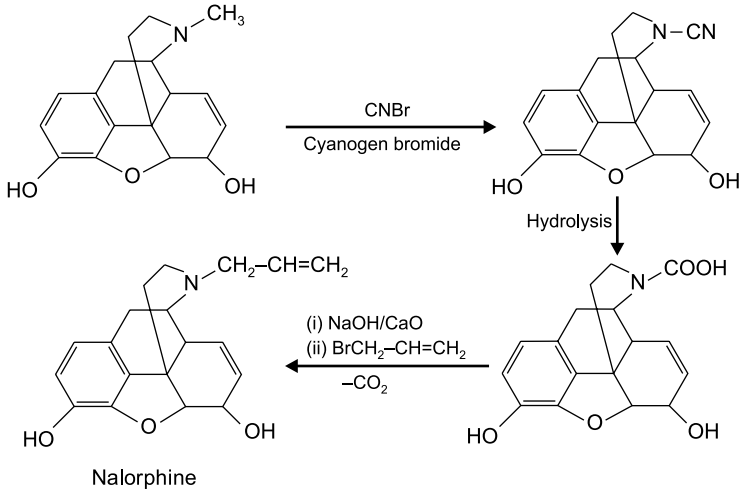
Naltrexone became clinically available in 1985 as a new narcortic antagonist. Its action resembles those of naloxone, but naltrexone is well absorbed orally, and is long acting. Necessitating only a dose of 50–100 mg, therefore, it is useful in narcotic treatment programmes, where it is desired to maintain an individual on chronic therapy with a narcotic antagonist. In an individual taking naltrexone, subsequent injection of an opiate will produce little or no effect. Naltrexone appears to be particularly effective for the treatment of narcotic dependence in addicts who have more to gain by being drug free rather than drug-dependent. Naltrexone is at least 17 times more potent than nalorphine in morphine-dependent humans and twice as potent as naloxone in precipitating withdrawal symptoms.

a. Nalorphine (Nalline)



Synthesis

From: Morphine

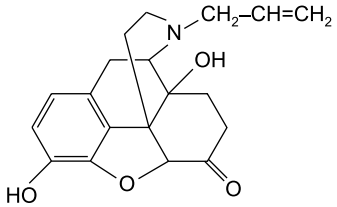


Nalorphine

Properties and uses: Nalorphine has a direct antagonistic effect against morphine, meperidine, methadone, and levorphanol. It has little antagonist effect towards barbiturate or general anaesthetic depression. However, it has strong analgesic properties, but it is not acceptable for such use owing to the high incidence of undesirable psychotic effects.

Dose: By IV 2 to 10 mg per dose; usually, 5 mg repeated twice at 3 min intervals, if required.

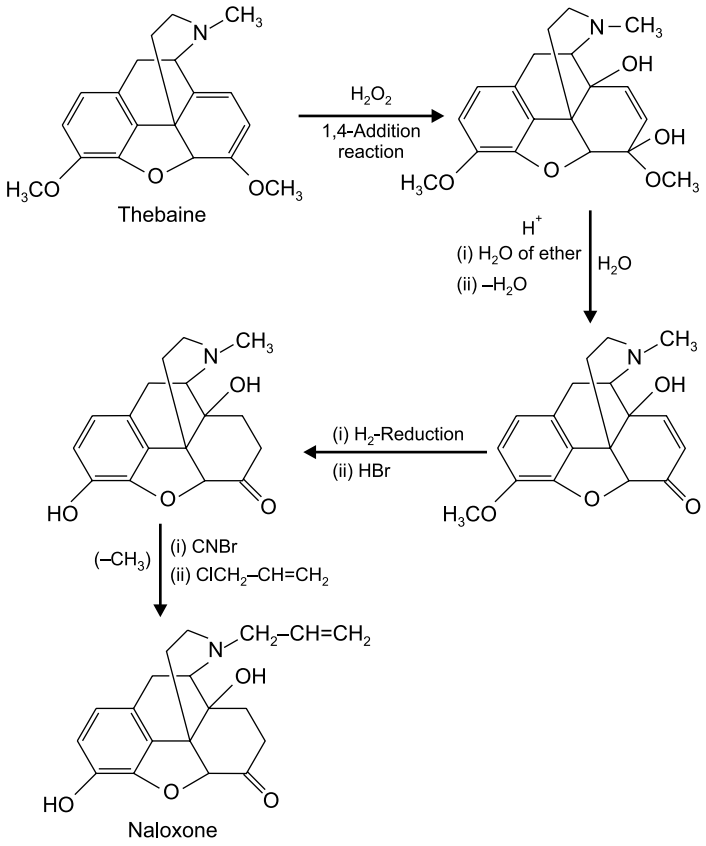
b. Naloxone (Narcotan, Nex)



Naloxone

Synthesis

From: Thebaine



Naloxone

Properties and uses: It is white or almost white hygroscopic crystalline powder, soluble in water, soluble in ethanol, and insoluble in toluene. It is almost seven times more active than nalorphine in antagonizing the effects of morphine. It shows no withdrawal effects after long-term administration. It lacks not only the analgesic activity shown by other antagonists, but also all of the other agonist effects. At higher doses, naloxone may be useful in the treatment of shock and spinal cord injury.

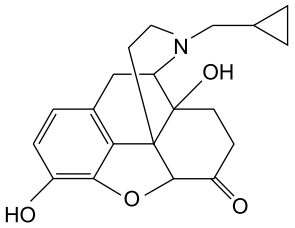
Assay: Dissolve the sample in ethanol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M ethanolic sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

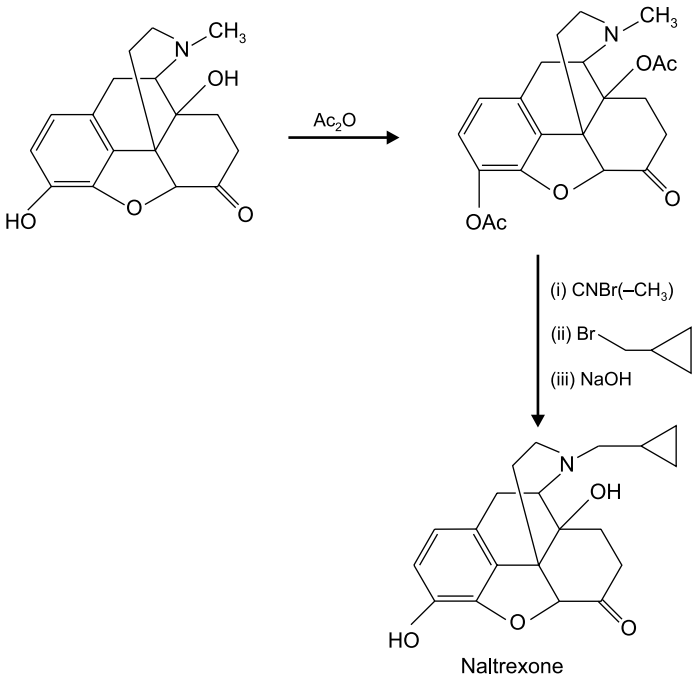
Dose: Usual dose by parenterally 0.4 mg (1 ml)/day.

Dosage forms: Naloxone injection BP, neonatal naloxone injection BP.

c. Naltrexone (Naltima)



Synthesis



Naltrexone

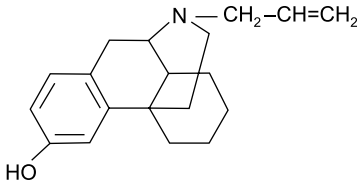
Properties and uses: It is a white or almost white powder, hygroscopic, insoluble in methylene chloride, freely soluble in water, and slightly soluble in ethanol. Its opioid antagonist activity is reported to be two to nine times that of naloxone and 17 times that of nalorphine.

Assay: Dissolve the sample in ethanol, add 0.1 M hydrochloric acid. Perform potentiometric titration, using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For opioid dependence: Adult—as hydrochloride—initially, 25 mg; increase to 50 mg daily, if no withdrawal signs occur. Maintenance: 350 mg weekly given as 50 mg daily or divided in 3 doses (given for 3 days in a week) for improved compliance. As an adjunct in the management of alcohol dependence: Adult—as hydrochloride—50 mg daily.

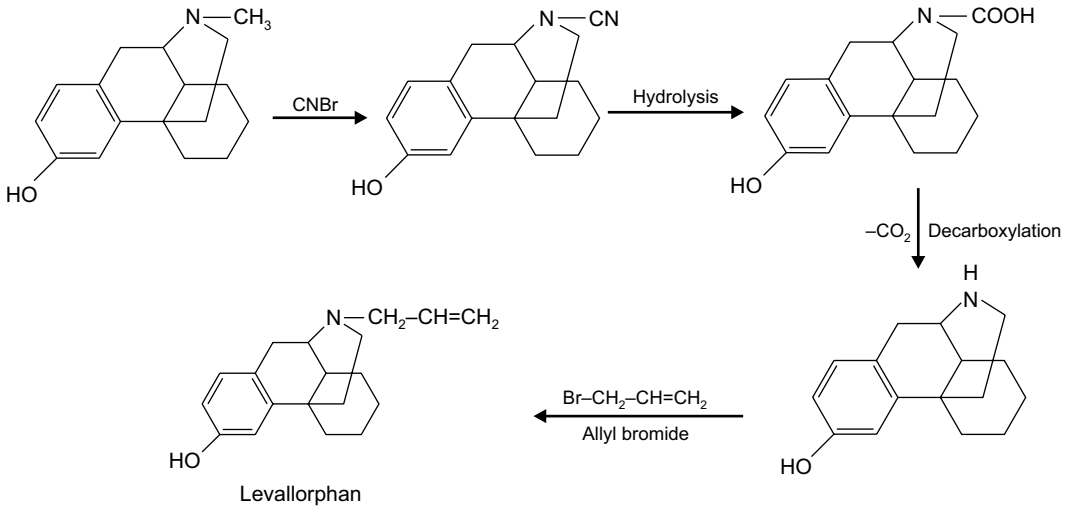
d. Levallorphan



Properties and uses: Levallorphan resembles nalorphine in its pharmacological action and is about five times more effective as a narcotic antagonist. It is useful in combination with analgesics, such as meperidine, alpha-prodine, and levorphanol to prevent the respiratory depression usually associated with these drugs.

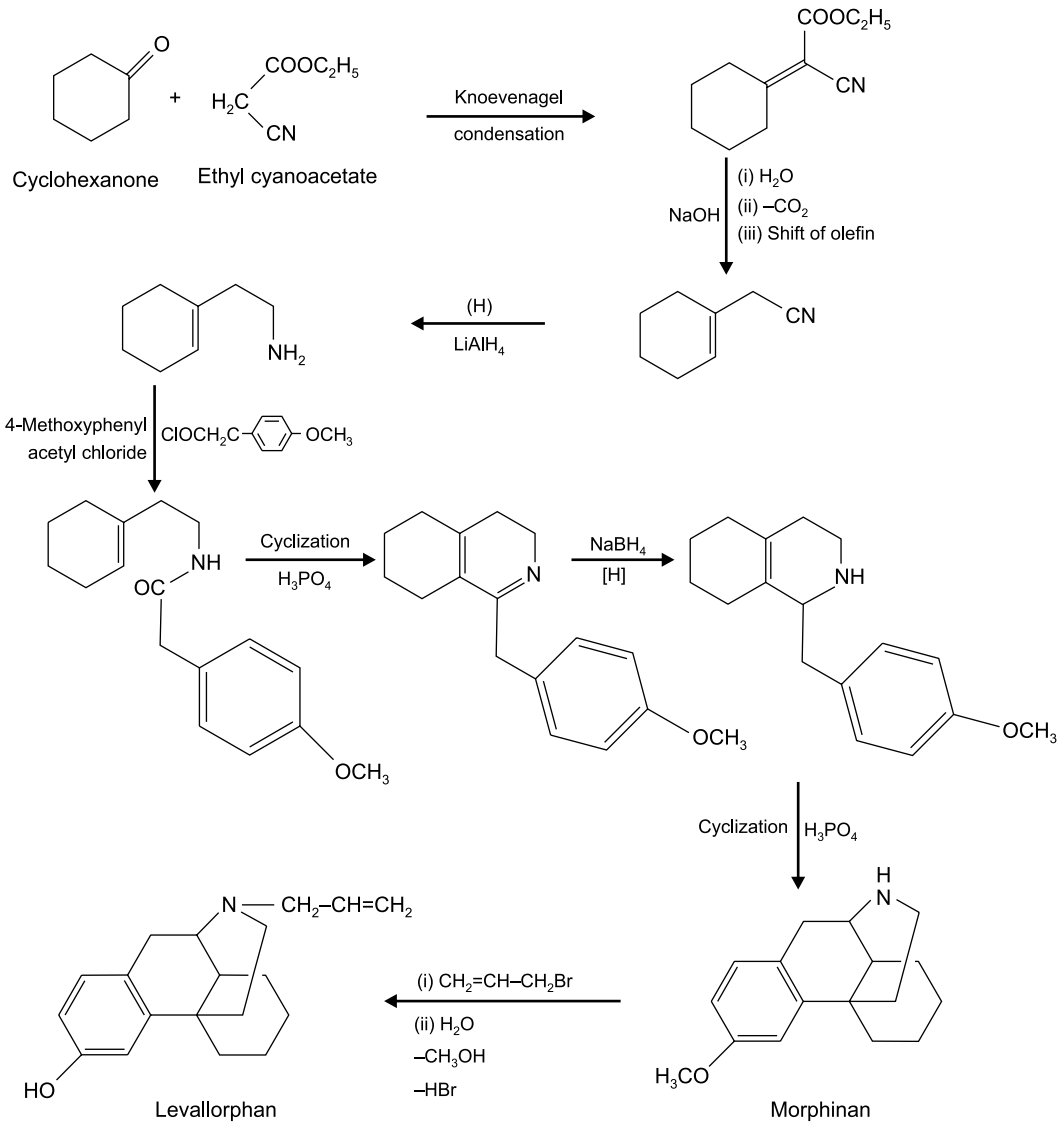
Synthesis

Route I. From: Morphinan



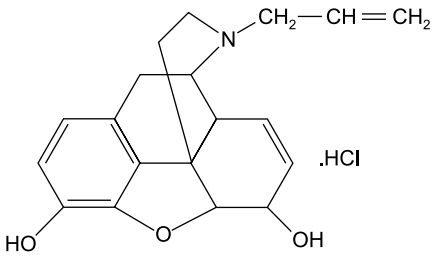
Levallorphan

Route II. From: Cyclohexanone

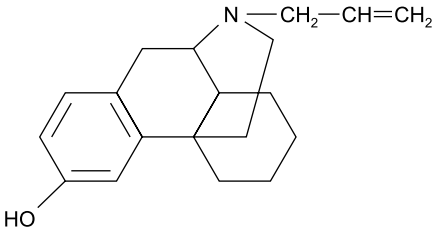


CLASSIFICATION BASED ON PCI SYLLABUS

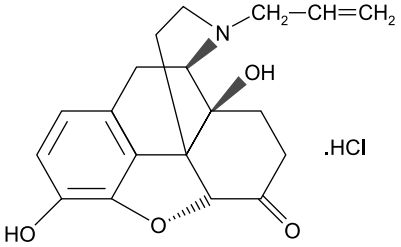
Nalorphine hydrochloride



Levallorphan tartrate



Naloxone hydrochloride



PROBABLE QUESTIONS

1. What are the three important alkaloids isolated from *Papaver somniferum*? Write the structure, chemical name, and uses of morphine.
2. What are narcotic analgesics? Classify with suitable examples and explain the general mode of action.
3. Classify narcotic analgesics by giving at least two typical examples in each class with its structure, chemical name, and uses. Write any two drugs synthesis from different class.
4. Discuss the morphine analogues and give the synthesis of any one of them.
5. Write the structure, chemical name, and uses of any two important members of morphinan analogues. Outline the synthesis of one of them.
6. Based on the morphan nucleus, i.e. a bridged perhyrazocine, three drugs have been synthesized, namely, metazocine, cyclazocine, and pentazocine. Write their structure, chemical name, and uses.

7. How will you synthesize pentazocine?
8. The 4-phenylpiperidine analogue led to the synthesis of much simpler compounds having potent analgesic properties. Discuss the synthesis of any one compound stated below:
   (a) Meperidine hydrochloride
   (b) Fentanyl citrate
9. Write the names of any two important drugs based on phenylpropylamine analogues and describe the synthesis of one of them.
10. Write a brief note on narcotic antagonists. Outline the synthesis of nalorphine hydrochloride.
11. Write the SAR of morphine and meperidine derivatives.
12. Write a note on methadone analogues.

SUGGESTED READINGS

1. Abraham DJ (ed). *Burger's Medicinal Chemistry and Drug Discovery* (6th edn). New Jersey: John Wiley, 2007.
2. *British Pharmacopoeia*. Medicines and Healthcare Products Regulatory Agency. London, 2008.
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CHAPTER 30

Anticonvulsants

INTRODUCTION

Anticonvulsants are drugs that are used to arrest convulsions or seizures caused in epilepsy. The term *epilepsy*, based on the Greek word *epilambian* (meaning to seize), has been first mentioned by Hippocrates. Epilepsy is a disease that occurs due to central nervous system (CNS) disorder, which is characterized by seizures and convulsions or abnormal body movements with the loss of consciousness.

Approximately, 1% of world's population has epilepsy, the second most common neurological disorder after stroke. Up to 1990, approximately 16 antiseizure drugs were available and 13 of them can be classified into five similar chemical groups, that is, barbiturates, hydantoins, oxazolidinediones, succinamides, and acetyl ureas. These groups have a common and similar heterocyclic ring structure with a variety of substituents for the drugs with this basic structure; the substituents on this heterocyclic ring determine the pharmacological class, either antimaximal electro shock or antipentylenetetrazole. The remaining drugs, carbamazepine, valproic acid, and benzodiazepines, are structurally dissimilar and the newer drugs used are felbamate, gabapentin, lamotrigine, oxcarbazepine, tigabatrine, topiramate, vigabatrin, and levetiracetam. The anticonvulsant therapy mediated by these drugs is through different aspects of neurotransmission inhibition in the brain:

- By inhibiting sodium channels (phenytoin).
- By inhibiting gamma amino butyric acid (GABA) transaminase enzyme (vigabatrin).
- By inhibition of T-type calcium currents (ethosuximide, valproate).
- By GABA agonistic activity (benzodiazepine).

Three principle types of epilepsy are found. They are as follows:

Grandmal: In which the seizures last from 2 to 5 min, being characterized by a sudden loss of consciousness, tonic and clonic convulsions of all muscles associated with urinary incontinence.

Petitmal: The seizures last from 5 to 30 sec, being characterized by brief attacks of unconsciousness, usually occur in children at the age of 4 to 8 years.

Psychomotor seizures: Characterized by attacks without convulsions and lasts from 2 to 3 min.

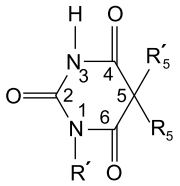
The ideal antiepileptic drug should completely suppress seizures in doses that do not cause sedation or other undecided CNS toxicity. It should be well tolerated and highly effective against various types of seizures and devoid of undesirable side effects on vital organs and functions.

CLASSIFICATION

I. Barbiturates
II. Hydantoins
III. Oxazolidinedione derivatives
IV. Succinimides
V. Phenyl acetyl ureas
VI. Benzodiazepines
VII. Carbonic anhydrase inhibitors
VIII. GABA analogues
IX. Iminostilbenes
X. Miscellaneous
XI. Newer anticonvulsants

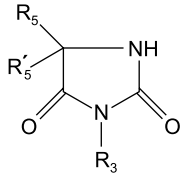
I. Barbiturates

Most of the barbiturates are sedatives and hypnotics. Only a few of them show anticonvulsant characters. Three important barbiturates that show anticonvulsant properties are the following:



Name	*R′*	*R5*	*R′5*
Phenobarbitone	—H	—Ph	—Et
Mephobarbiton	—CH_3	—Ph	—Et
Metharbital	—CH_3	—Et	—Et

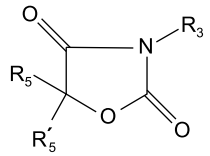
II. Hydantoins



The hydantoins are close structural relatives of barbituric acid, differing due to the lack of C-6 oxo group. The lack of this carbonyl group decreases the acidity. So, it is a weaker acid than that of barbiturates.

Name	*R3*	*R5*	*R′5*
Phenytoin	—H	—C_6H_5	—C_6H_5
Phenyl ethyl hydantoin	—H	—C_2H_5	—C_6H_5
Mephenytoin	—CH_3	—C_2H_5	—C_6H_5
Ethotoin	—C_2H_5	—H	—C_6H_5

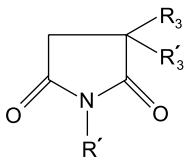
III. Oxazolidinediones



Replacement of the –NH group at position 1 of the hydantoin systems with oxygen atom yields the oxazolidine-2,4-dione system, trimethadione is only clinically used.

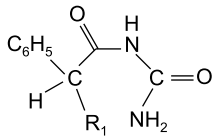
Name	R_3	R_5	R'_5
Trimethadione or troxidone	$-CH_3$	$-CH_3$	$-CH_3$
Paramethadione	$-CH_3$	$-CH_3$	$-C_2H_5$
Malidione	$-CH_2-CH=CH_2$	$-CH_3$	—H
Dimidone	$-C_2H_5$	$-CH_3$	$-CH_3$

IV. Succinimides



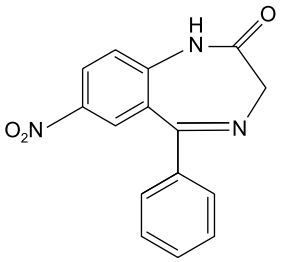
Name	R_1	R_3	R'_3
Phensuximide	$-CH_3$	—H	$-C_6H_5$
Methsuximide	$-CH_3$	$-CH_3$	$-C_6H_5$
Ethosuximide	—H	$-CH_3$	$-C_2H_5$

V. Acetyl urea derivatives or phenyl acetyl ureas

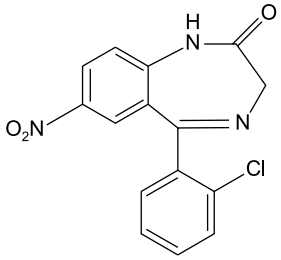


Name	R_1
Phenacemide	–H
Phenyl ethyl acetyl urea	$-C_2H_5$

VI. Benzodiazepines

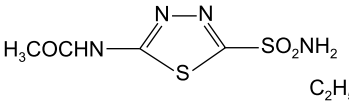


Nitrazepam

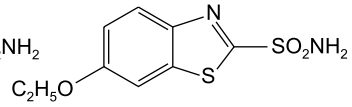


Clonazepam

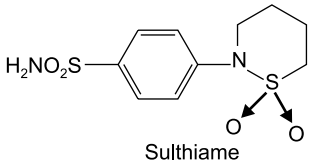
VII. Carbonic anhydrase inhibitors



Acetazolamide

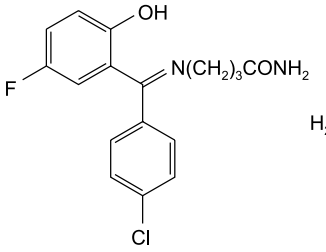


Ethoxazolamide

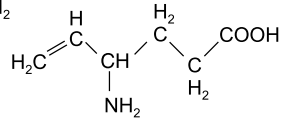


Sulthiame

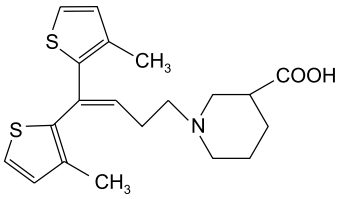
VIII. GABA analogues



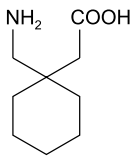
Progabide



Vigabatrin

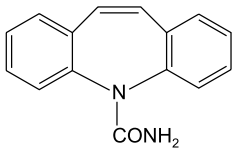


Tiagabin



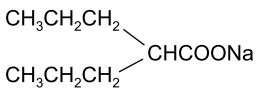
Gabapentin

IX. Iminostilbenes

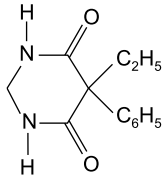


Carbamazepine

X. Miscellaneous

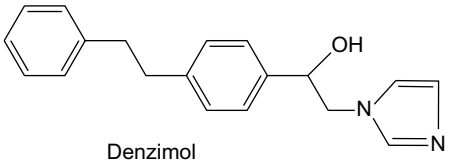


Sodium valproate

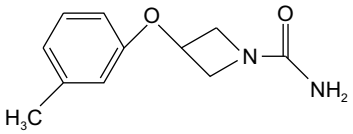


Primidone

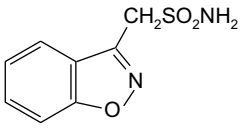
XI. Newer anticonvulsants



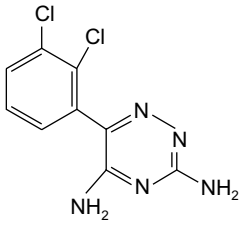
Denzimol



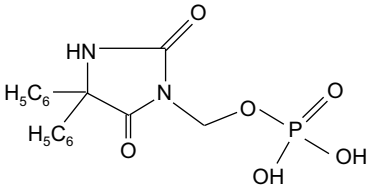
Denzinamide



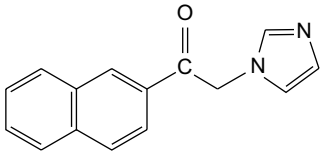
Zonisamide



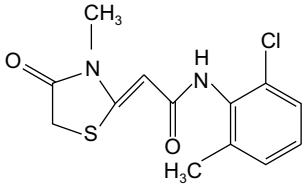
Lamotrigine



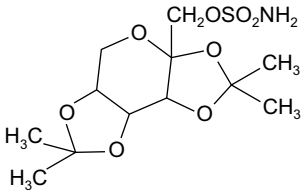
Fosphenytoin



Nafimidone



Ralitoline



Topiramate

Drugs used for treating epileptic disorders are listed in Table 30.1.

Pharmacological Classification

Based on the pharmacological action, anticonvulsant drugs can be classified as follows:

- Centrally acting: General anaesthetics, paraldehyde, barbiturates, and diazepam.
- Acting mainly on the spinal cord: Mephenesin.
- Peripheral skeletal muscle relaxants: *d*-Tubocurarine and succinyl choline.

Table 30.1: Drugs used for treating epileptic disorders

Disorder	*Primary drugs*	*Adjunctive drugs*
Partial seizures: Simple, complex, partial with secondarily generalized	Carbamazepine, phenytoin, phenobarbital, primidone, valproate	Lamotrigine, gabapentin, tiagabine, topiramide
Generalized seizures: Absence seizures	Ethosuximide,valproate, clonazepam	Lamotrigine
Myoclonic seizures	Valproate, clonazepam	
Atonic seizures	Valproate	Lamotrigine
Tonic-clonic seizures (Not preceded by partial seizures)	Carbamazepine, phenytoin, gabapentin, phenobarbital, primidone, valproate	Gabapentin, lamotrigine
Status epileptics	Diazepam, lorazepam, followed by phenytoin, fosphenytoin	

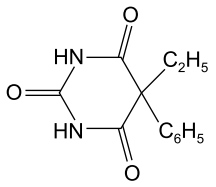
SYNTHESIS AND DRUG PROFILE

I. Barbiturates

Mode of action: The mechanism is facilitated by GABA receptor-mediated synaptic inhibition, opens the chloride channels, and inhibits the calcium dependent release of neurotransmitters. In addition, at very high concentrations, barbiturates depress sodium and potassium channels and reduce the abnormal discharge of electrical impulse.

Metabolism of barbiturates is discussed in Chapter 23: Sedatives and Hypnotics.

a. Phenobarbitol (Gardenal, Phenetone, Phenorbarb)

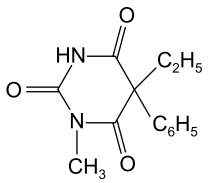


5-Ethyl-5-phenyl barbituric acid

Dose: The usual dose is 1 to 5 mg/kg daily.

Synthesis and drug profile is discussed in Chapter 23: Sedatives and Hypnotics.

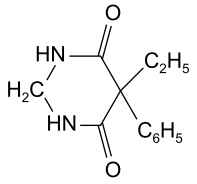
b. Mephobarbitone or Methyl phenobarbital



5-Ethyl-1-methyl-5-phenylbarbituric acid

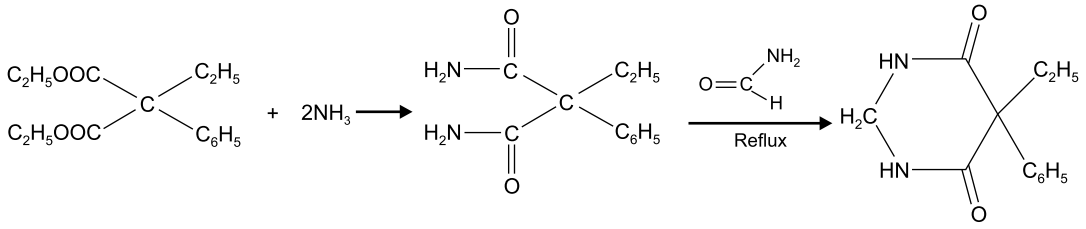
Synthesis and drug profile is discussed in Chapter 23: Sedatives and Hypnotics.

c. Primidone (Mysoline)



5-Ethyl-2-hydro-5-phenyl-4,6-pyrimidine-dione

Synthesis



Diethyl-2-ethyl-2-phenyl malonate 2-Ethyl-2-phenylmalonamide Primidone

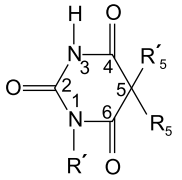
Properties and uses: It is a white or almost white crystalline powder. It dissolves in alkaline solutions, slightly soluble in water and ethanol. It is an active antiepileptic but is less potent and less toxic than phenobarbital. The most frequent side effects include ataxia and vertigo; these tend to disappear with continued or reduced therapy. It is an effective agent for treatment of all types of epilepsy except absence seizures. It is used in combination with phenytoin or carbamazepine.

Assay: Dissolve the sample in ethanol, cool, and dilute with the same solvent. Prepare a reference solution in the same manner using 60.0 mg of primidone. Measure the absorbance of the 2 solutions at the absorption maximum of 257 nm. Calculate the content of primidone from the absorbances measured and the concentrations of the solutions.

Dose: The usual dose is 500 mg/day, gradually increasing to a maximum of 2 g daily.

Dosage forms: Primidone oral suspension BP, primidone tablets BP.

SAR of Barbiturates

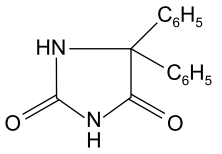


1. Optimum activity is observed when the substitution at C-5 is phenyl.
2. The 5,5'-diphenyl derivative has less activity than phenobarbitone.
3. N_1 and N_3 substituents in some cases resulted in an increase in activity.

II. Hydantoins

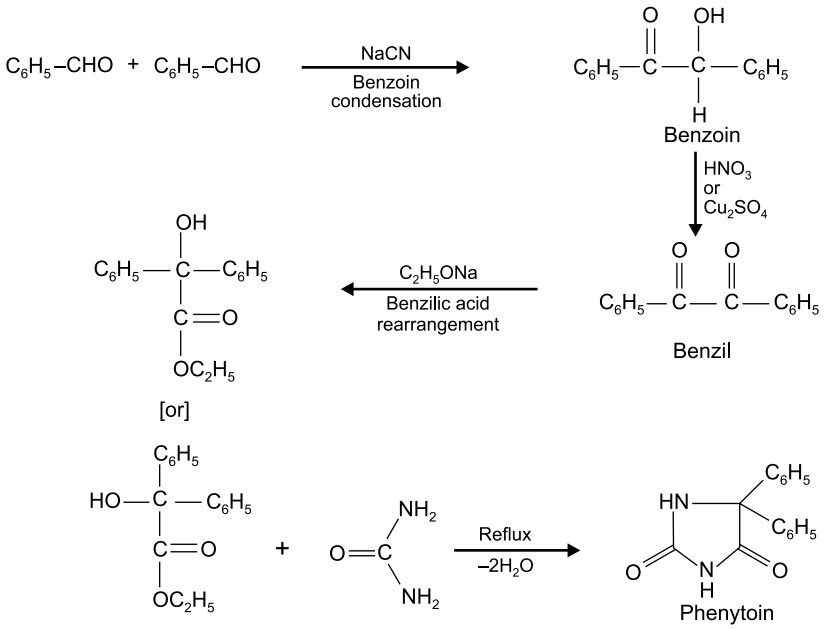
Mode of action: Hydantoins prevent repetitive detonation of normal brain cells during depolarization shift. This is achieved by prolonging the inactivated state of voltage gate sensitive sodium channels and governs the refractory period of specific neurons, moreover, reduces the calcium influx and inhibits the glutamate activity. Intracellular storation of Na^+ leads to the prevention of repetitive firing.

a. Phenytoin (Dilantin, Epsolin, Eptoin)



5,5-Diphenylimidazolidine-2,4-dione

Synthesis



Metabolism: Phenytoin is metabolized by CYPC9 into a primary metabolite 5-(hydroxyl phenyl)-5-phenyl hydantoin (HPPH).

Properties and uses: It is a white crystalline powder, slightly hygroscopic, insoluble in methylene chloride, soluble in water and alcohol. Phenytoin is the first anticonvulsant in which it was clearly demonstrated that anticonvulsant activity could definitely be separated from sedative-hypnotic activity. A common side effect is gingival hyperplasia, a reaction that seldom occurs with mephenytoin, and apparently, never with cardiac arrhythmias. It is one of the most widely used antiepileptic agents and it is effective in most forms of epilepsy, except absence seizures. Some cases of trigeminal and neuralgias respond well to phenytoin. It is also used in the treatment of cardiac arrhythmias.

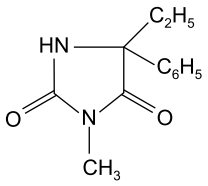
Assay: Suspend the sample in water, add 0.05 M sulphuric acid and heat gently for 1 min, to this add methanol and cool. Perform the potentiometric titration, using 0.1 M sodium hydroxide. After reaching the first point of inflexion, interrupt the addition of 0.1 M sodium hydroxide, add 5 ml of silver nitrate solution in pyridine, mix, and continue the titration. Read the volume of 0.1 M sodium hydroxide added between the two points of inflexion.

Storage: It should be stored in well-closed airtight containers.

Dose: The usual dose is 50 to 100 mg.

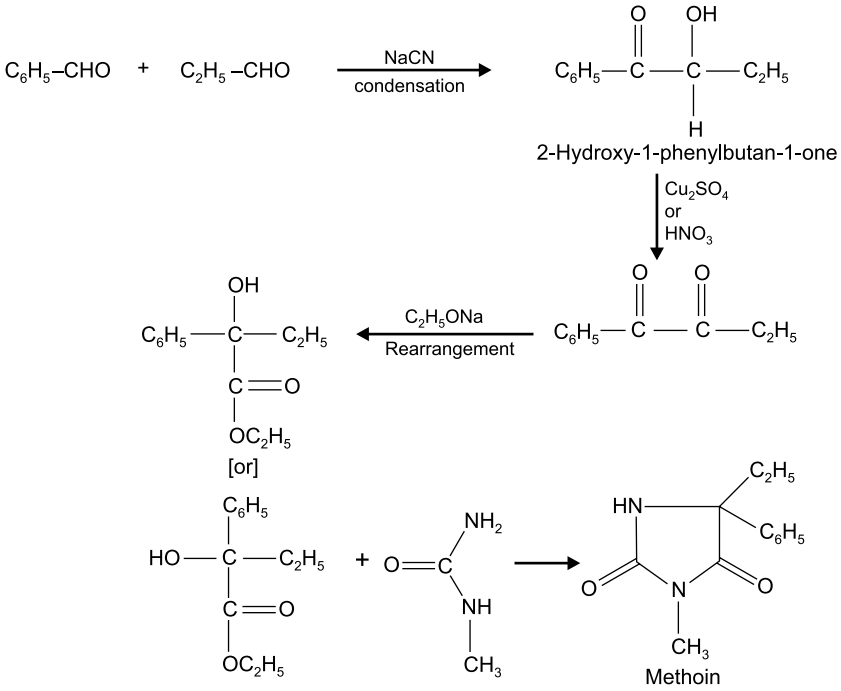
Dosage forms: Phenytoin capsules BP, phenytoin injection BP, phenytoin tablets BP.

b. Methoin or mephenytoin



5-Ethyl-3-methyl-5-phenylimidazolidine-2,4-dione

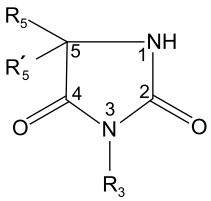
Synthesis



Metabolism: It is converted into N-demethyl metabolite 5-phenyl-5-ethyl hydantoin.

Properties and uses: It is one of the first hydantoin introduced into therapy. It was introduced as a sedative-hypnotic and anticonvulsant under the name Nirvanol, but it was withdrawn because of toxicity.

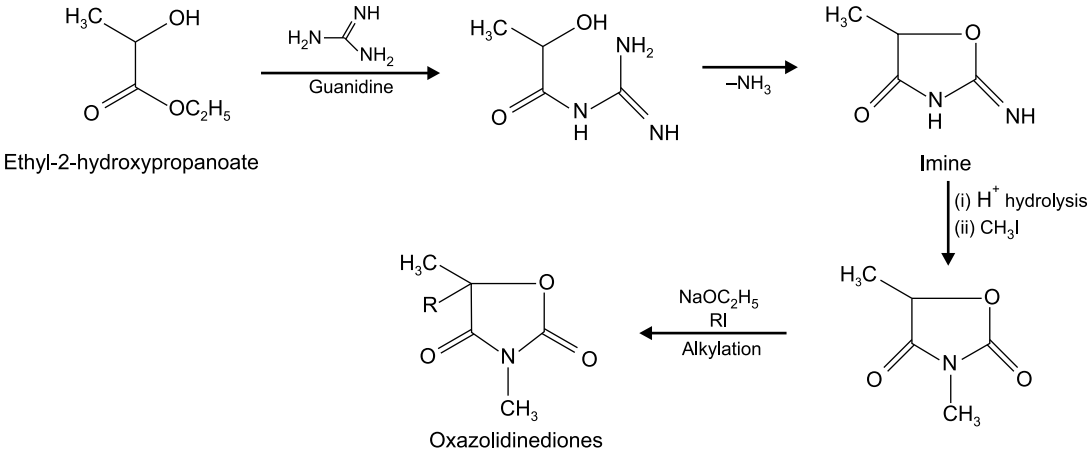
SAR of Hydantoins



- 5-phenyl or other aromatic substitution is essential for activity.
- Alkyl substituent at position 5 may contribute to sedation, a property absent in phenytoin.
- Among other hypnotics 1,3-disubstituted hydantoins, exhibit activity against chemically induced convulsion, while it remains ineffective against electric shock induced convulsion.

III. Oxazolidinediones

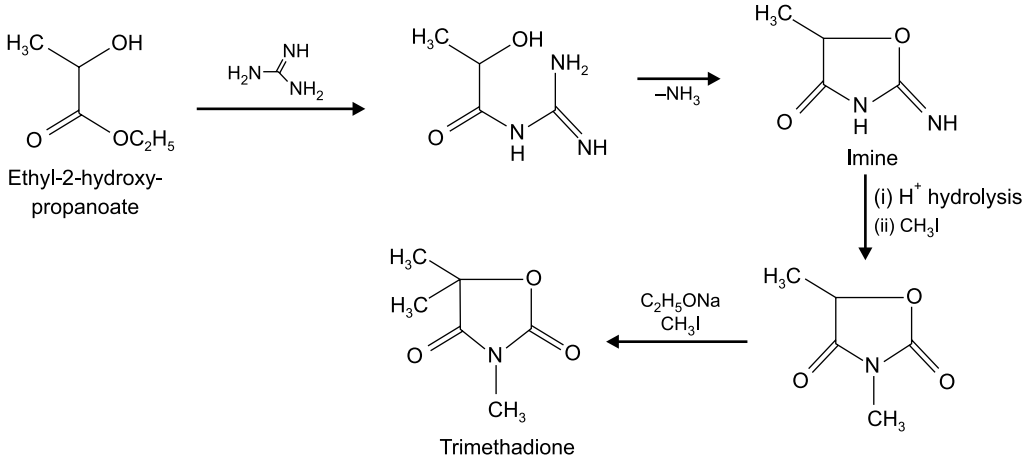
General method for synthesis of oxazolidinedione derivatives:



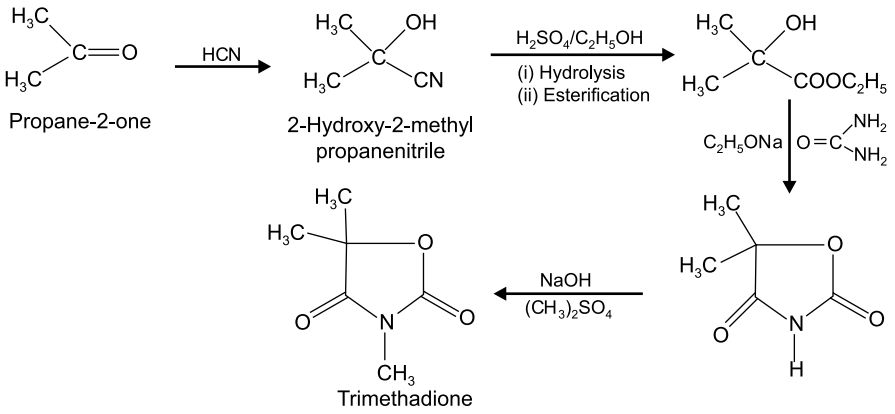
a. Trimethadione (Tridione)

Synthesis

Route I. From Ethyl-2-hydroxy propanoate



Route II. From: Propane-2-one



Metabolism: It is metabolized by N-demethylation to putative active metabolite dimethadone and it is further excreted unchanged.

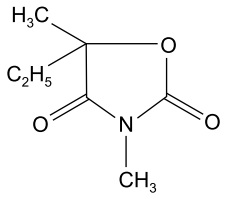
Properties and uses: It is a colourless or almost colourless crystals, soluble in water and alcohol. It is first drug introduced specifically for treating absence seizures. It is important as a prototype structure for antiabsence seizure compounds. It is used as an antipetitmal agent. It causes nephrosis, aplastic anaemia and bone marrow depression.

Assay: Assayed by adopting gas chromatography technique.

Storage: It should be stored in well-closed airtight containers.

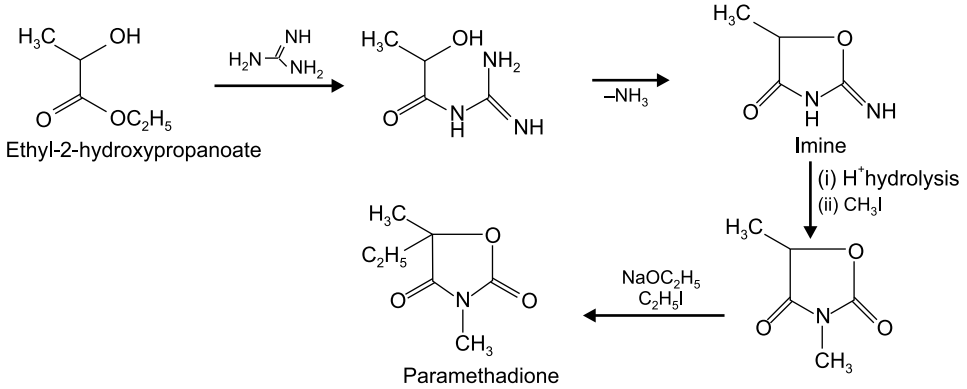
Dose: The usual dose is 900 mg to 2.4 g per day; usually 300 to 600 mg two to four times daily.

b. Paramethadione (Paradione)



5-Ethyl-3,5-dimethyl oxazolidine-2,4-dione

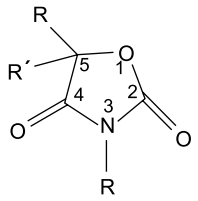
Synthesis



Properties and uses: It is an oily liquid, slightly soluble in water and freely soluble in ethanol. It is used as an anticonvulsant.

Dose: The usual dose is 300 mg to 2.4 g daily.

SAR of Oxazolidinediones

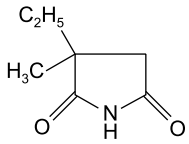


- Replacement of the –NH group at position 1 of the hydantoin system with an oxygen atom yields the oxazolidine-2,4-dione system.
- 3,5,5-Trimethadione (tridione) was the first drug introduced specifically for treating absence seizures. It is also important as a prototype structure.
- The nature of the substituent on C-5 is important, e.g. lower alkyl substituents towards antipetitmal activity while acyl substituents towards antigrandmal activity.
- The N-alkyl substituent does not alter or afford the activity since all the clinically used agents from this class undergo N-dealkylation in metabolism.

IV. Succinimides

Mode of action: Succinimides selectively acts on the transient current in calcium channels for the influx of calcium ions and inhibits the amplification of spikes.

a. Ethosuximide (Zarontin)



3-Ethyl-3-methyl-2,5-pyrrolidinedione

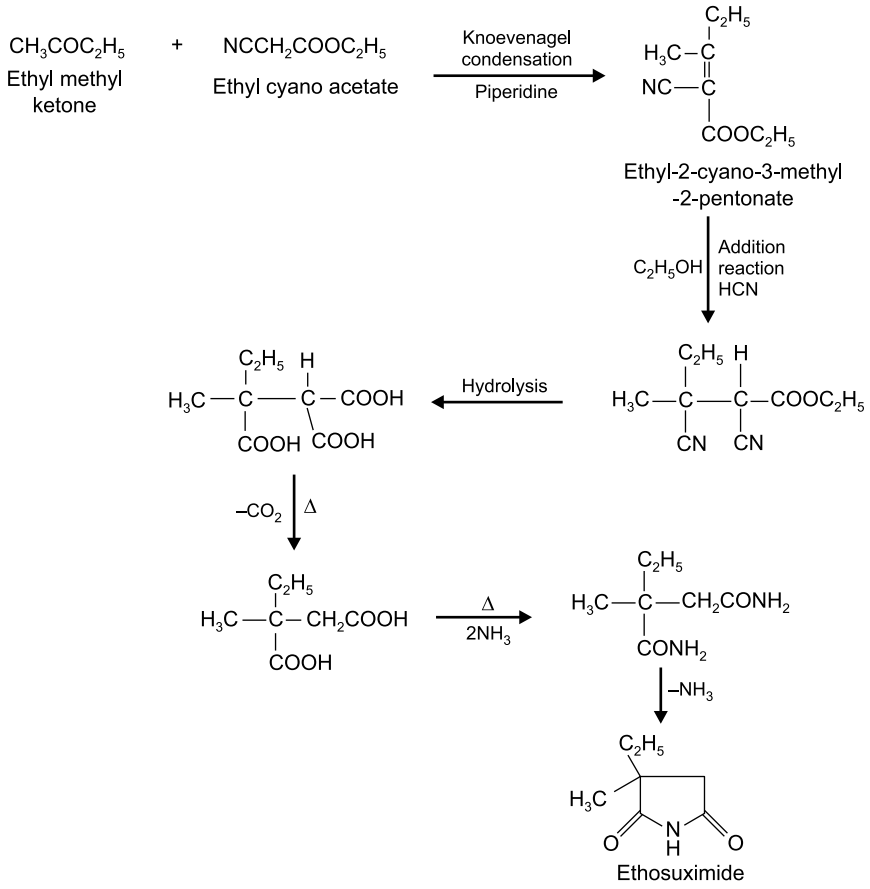
Metabolism: It is metabolized into 3-(1-hydroxyethyl) compound.

Properties and uses: It is a white or an almost white powder or waxy solid. Freely soluble in water, ethanol, and methylene chloride. It conforms very well to the general structural pattern for antiabsence activity. The drug is more active and less toxic than trimethadione. It is a calcium-T channel blocking drug, effective in the cure of petitmal epilepsy.

Assay: Dissolve the sample in dimethylformamide and titrate with 0.1 M tetrabutylammonium hydroxide. Determine the end point by potentiometric titration.

Storage: It should be stored in well-closed airtight containers.

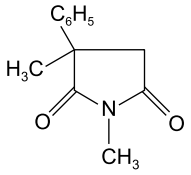
Synthesis



Dose: The usual dose is 500 mg/day, in divided doses.

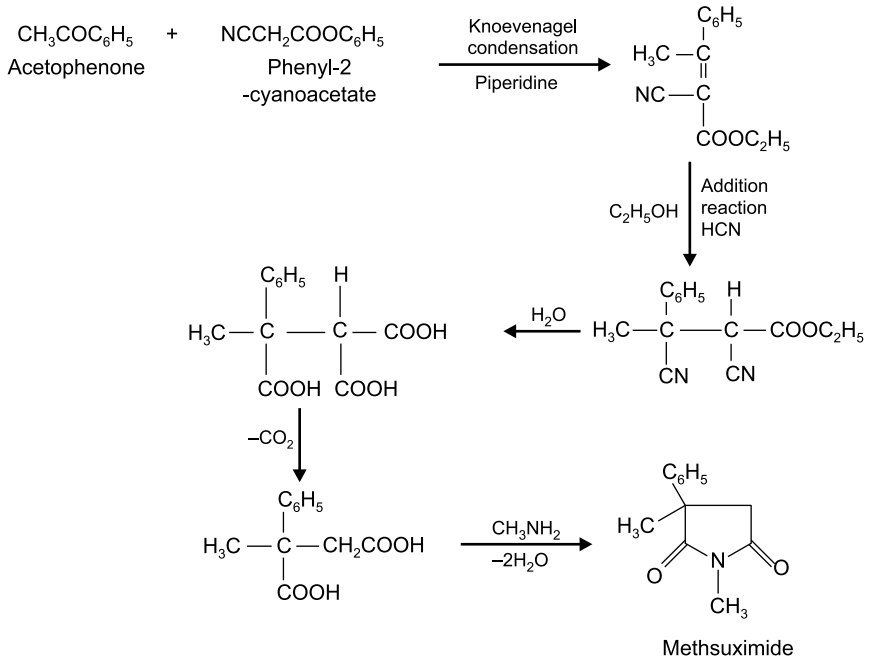
Dosage forms: Ethosuximide syrup IP, ethosuximide capsules IP, BP, ethosuximide oral solution BP.

b. Methsuximide (Celontin)



1,3-Dimethyl-3-phenyl-2,5-pyrrolidinedione

Synthesis



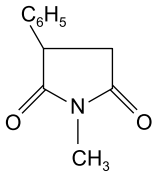
Methsuximide

Metabolism: It is metabolized into N-demethylsuximide and the metabolite is also an active compound.

Properties and uses: It is more active than phensuximide, and used in the treatment of petitmal epilepsy.

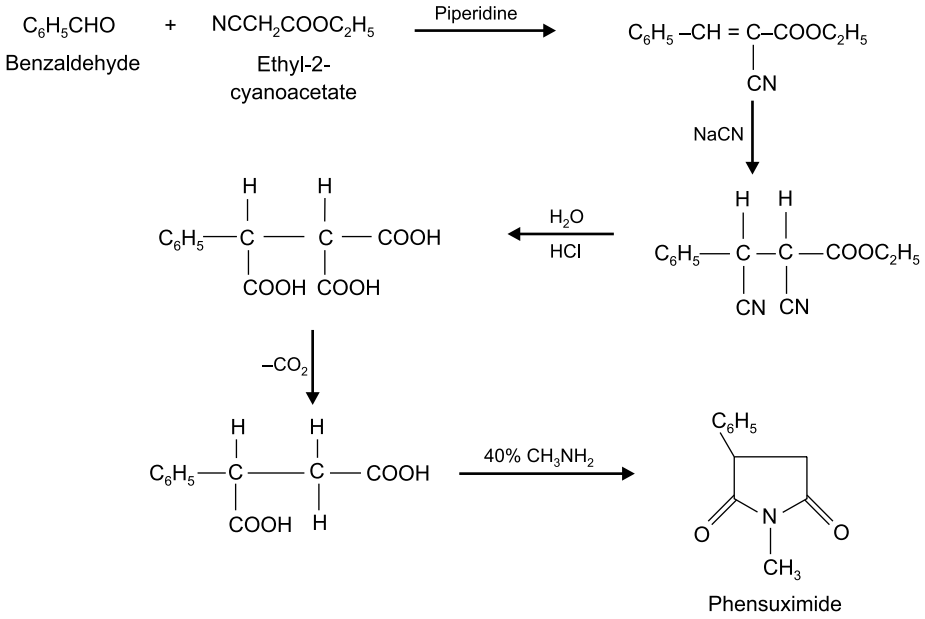
Dose: The usual dose is 300 mg/day; maintenance 0.3 to 1.2 g daily.

c. Phensuximide (Milontin)



1-Methyl-3-phenyl-2,5-pyrrolidinedione

Synthesis

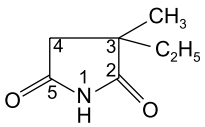


Metabolism: N-demethylation occurs to yield active metabolite, both phensuximide and N-demethyl metabolites are inactived by *para*-hydroxylation and conjugation.

Properties and uses: It is a crystalline solid, soluble in water and freely soluble in ethanol. It has low potency and is therefore related to secondary status. The phenyl substituent confers some activity against generalized tonic-clonic and partial seizures. It is used in the treatment of petitmal epilepsy.

Dose: The usual dose is 500 mg to 1 g two to three times/day.

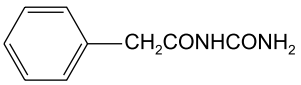
SAR of Succinimides



- The activity of antiepileptic agents, such as the oxazolidine 2,4-dione with substituted succinamides (CH_2 replace O) was logical choice for synthesis and evaluation.
- N-demethylation occurs to yield the putative active metabolite. Both phensuximide and the N-demethyl metabolite are inactivated by *p*-hydroxylation and conjugation.

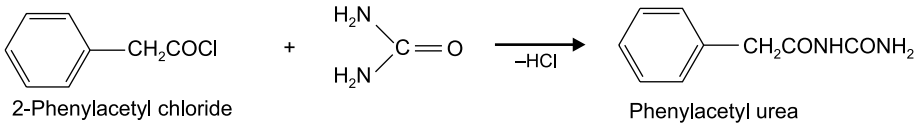
V. Phenyl acetyl urea derivatives

a. Phenacemide (Phenurone)



Phenylacetyl urea

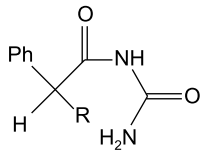
Synthesis



Uses: Used mainly in psychomotor epilepsy.

Dose: The usual dose is 0.5 g, orally, three times/day with meals.

SAR of Phenacemide



Name	*R*
Phenacemide	–H
Phenyl ethyl acetyl urea	$-C_2H_5$

Various substituents that are tested on the phenyl acetyl urea and their SAR is discussed as given:

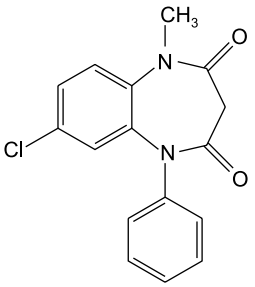
1. Among aliphatic acetyl ureas the highest anticonvulsant activity is found in those derived from the branched chain acids of about 7-carbon atoms.
2. With a further increase in molecular weight the anticonvulsant activity gradually terminates and hypnotic effect predominates.
3. Phenacemide is the most active agent among the aromatic acetyl ureas.
4. Any substitution in nitrogen of phenacemide does not increase further the anticonvulsant activity.
5. The activity decreases with aromatic substituents of phenacemide with a gradual increase in hypnotic activity.

VI. Benzodiazepines

Mode of action: Benzodiazepines act by enhancing pre and postsynaptic inhibition through benzodiazepine receptor, which is an integral part of $GABA_A$ receptor Cl channel. It opens the Cl^- channel through GABA facilitatory action. These drugs also induce hyperpolarization and decrease firing rate of neurons.

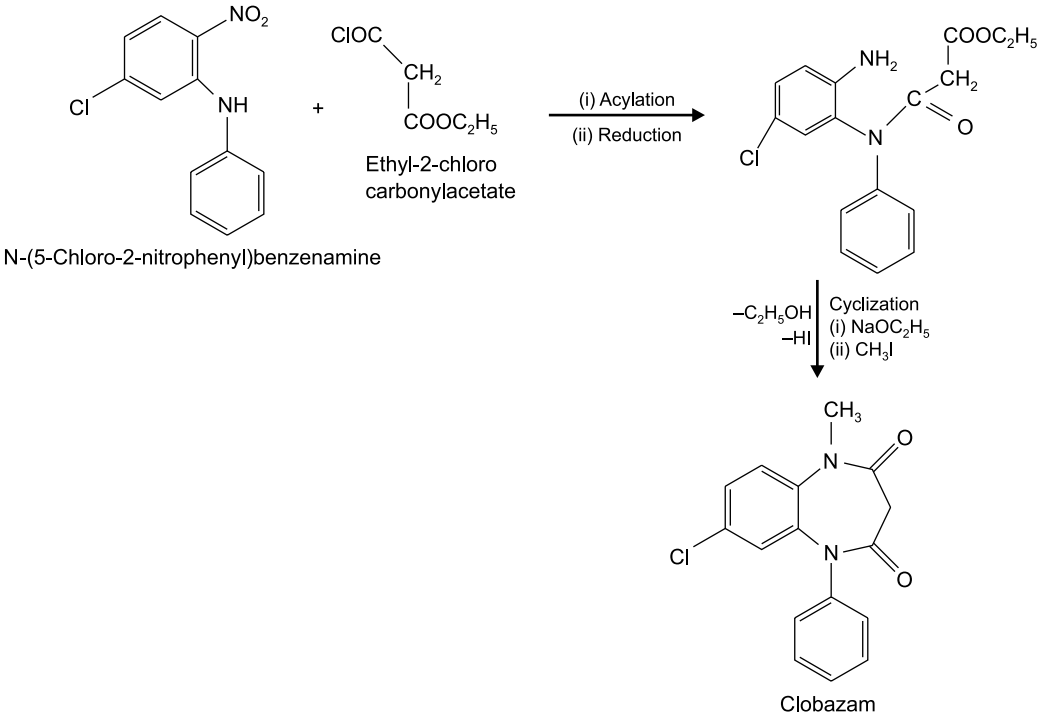
Metabolism of benzodiazepines is discussed in Chapter 23: Sedatives and Hypnotics.

⋆ **Clobazam** (Frisium, Lobazam, Cloba)



7-Chloro-1-methyl-5-phenyl-1,4-benzodiazepine-2,4-dione

Synthesis



N-(5-Chloro-2-nitrophenyl)benzenamine

Clobazam

Uses: It is used in the treatment of partial and generalized epilepsy.

Dose: The usual dose for adult is 20 to 30 mg daily.

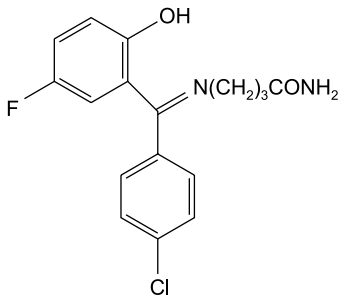
VII. Carbonic anhydrase inhibitors

Discussed in Section VI, Chapter 46: Diuretics.

VIII. GABA analogues

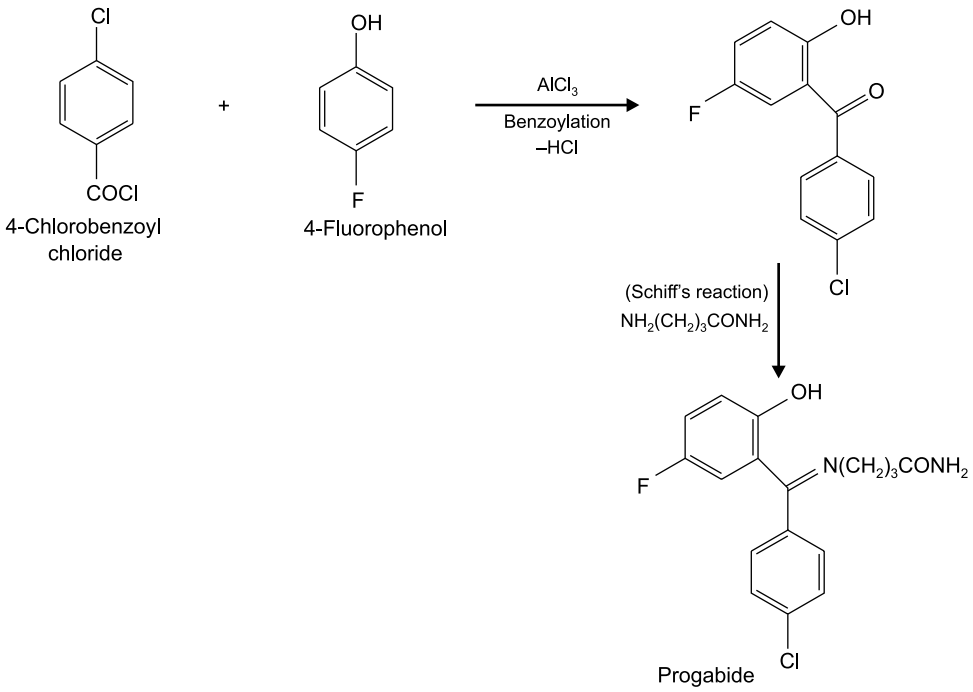
GABA is an inhibitory neurotransmitter. It cannot cross the blood–brain barrier (BBB). This problem is overcome by enhancing the lipid solubility by the formation of Schiff's base of gabamide.

a. Progabide



4-[(4-Chlorophenyl) (5-fluoro-2-hydroxy phenyl)methylene]aminobutanamide

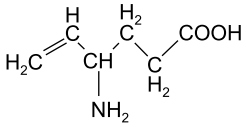
Synthesis



Mode of action: Progabide crosses the BBB readily and is biotransformed into its active acid metabolite. It acts as agonists for $GABA_A$ and $GABA_B$ receptors.

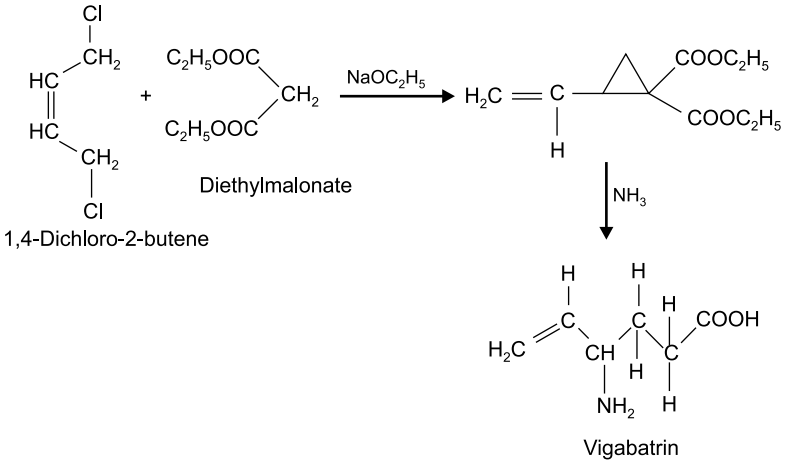
Properties and uses: It is a non-hygroscopic, microcrystalline, yellow powder, sparingly soluble in water. Used in simple and complex partial seizures, generalized tonic-clonic seizures, and myoclonic seizures.

b. Vigabatrin



4-Amino-5-hexenoic acid or γ-vinyl GABA

Synthesis

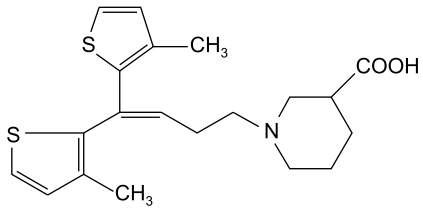


Vigabatrin

Mode of action: Vigabatrin readily crosses the BBB and raises brain GABA levels by virtual of GABA transaminase enzyme inhibiton. GABA-T is responsible for the metabolism of GABA.

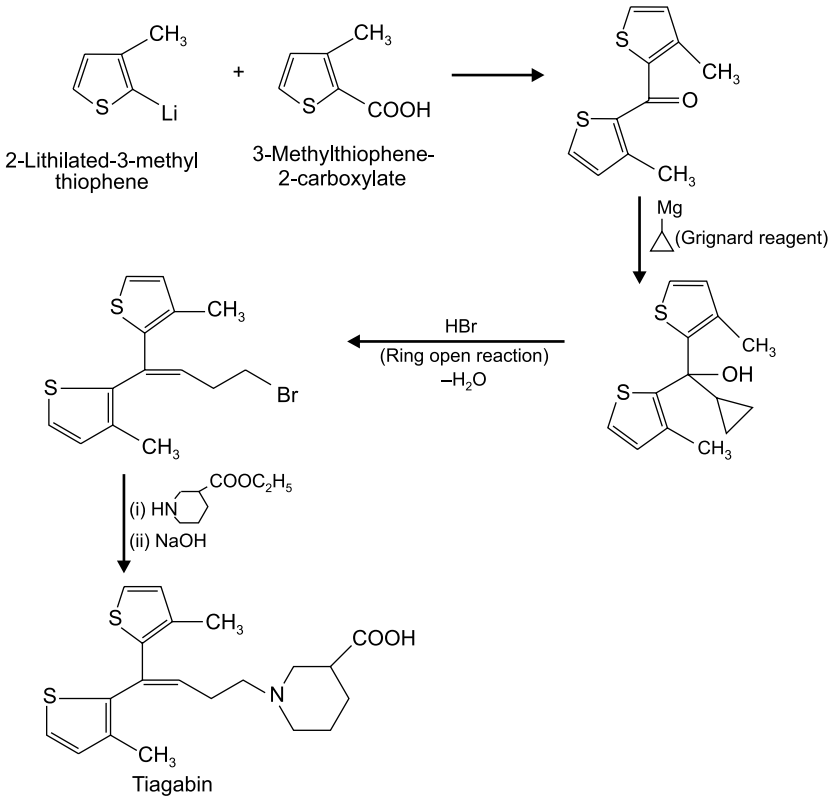
Properties and uses: The S (+)-enantiomer potently inhibits GABA-transaminase compared to the R-enantiomer, which is almost inactive in this respect.

c. Tiagabin (Gabitril)



1-[4,4-*Bis*(3-Methyl-2-thienyl)-3-butenyl]nipecotic acid

Synthesis

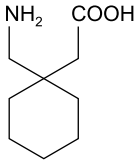


Mode of action: Tiagabin is a GABA reuptake inhibitor, which increases extracellular concentration of GABA, which in turn opens the chloride ion channels. These in turn inhibit neuronal activity by hyperpolarization and depolarization block.

Properties and uses: It exists as white crystalline powder, soluble in water and insoluble in hydrocarbons. It is proven to reduce partial seizures when given as adjunctive therapy. The most common adverse effects are dizziness, light headedness, asthma, and lack of energy.

Dose: The usual dose initially is 4 mg once daily.

d. Gabapentin (Gabantin, Gaba, Rejuron)



2-(1-(Aminomethyl)cyclohexyl) acetic acid

Mode of action: It is a lipid soluble GABA analogue. It does not bind with $GABA_A$ receptor, causes no inhibition on GABA reuptake and is not a $GABA^-_T$ (GABA amino transferase enzyme that metabolizes GABA to succinic semialdehyde) inhibitor, thus, the mechanism of action is unknown.

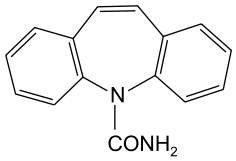
Properties and uses: It is a colourless, crystalline substance, soluble in water. It has been endorsed as an effective drug for the management of neuropathic pain.

Dose: For epilepsy (partial seizures with or without secondary generalization): Adult—initially, 300 mg on the first day; 300 mg twice/day on the second day; and 300 mg thrice/day on the third day. Thereafter, the dose may increase until effective antiepileptic control is achieved. Usual maintenance range: 0.9–3.6 g daily, daily dose to be taken in three equally divided doses and maximum dosing interval of 12 h. Maximum: 4.8 g daily.

IX. Iminostilbenes

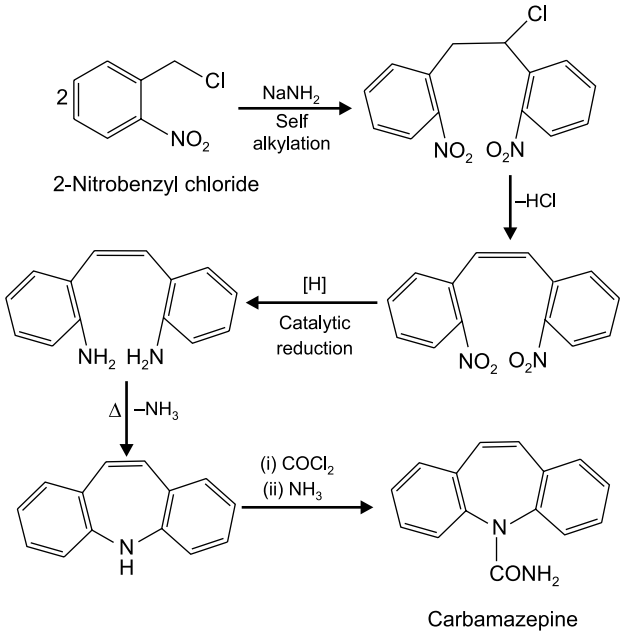
Mode of action: Similar to phenytoin, iminostilbenes limit the repetitive firing of action potential and appears to reduce the rate of recovery of voltage-gated sodium channel from inactivation.

- **Carbamazepine** (Tegretol, Zen, Zeptol)



Dibenzazepine-5-carboxamide

Synthesis



Carbamazepine

Metabolism: Metabolism proceeds largely through the epoxide form at the *cis*-stilbene double bond. The epoxide is further converted to 10s and 11s-*trans*-diol.

Properties and uses: It is a white or almost white crystalline powder and it shows polymorphism, slightly soluble in water, freely soluble in methylene chloride, but sparingly soluble in acetone and ethanol. Carbamazepine inhibits voltage-dependent sodium channels. Carbamazepine, a urea derivative, is a broad spectrum antiseizure agent, but is toxic, used to treat partial seizures and grandmal seizures. It is also useful in the treatment of pain associated with trigeminal neuralgia.

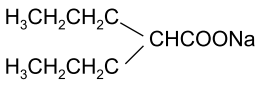
Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers.

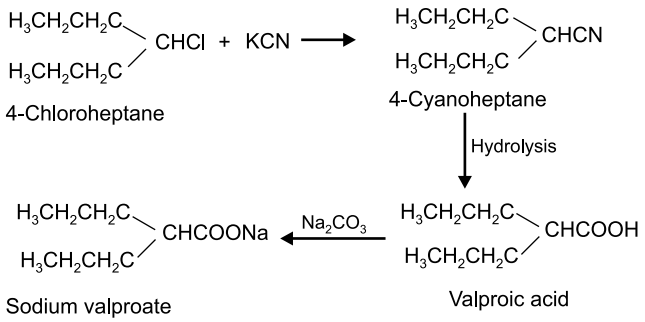
Dosage forms: Carbamazepine tablets BP.

X. Miscellaneous

- **Sodium Valproate** (Epilex, Epival, Valparin)



Synthesis



Mode of action: Valproate produces reduction in calcium channel influx and it also prolongs the transient activation time of inactivated sodium channels. Another potential mechanism contributed is to involve in the metabolism of GABA, which is an inhibitory neurotransmitter, by stimulating the GABA synthetic enzyme glutamic acid decarboxylase and inhibits the GABA degradative enzyme GABA transaminase.

Metabolism of valporic acid: It is metabolized by a conjugation of carboxylic acid group and oxidation on one of the hydrocarbon chains.

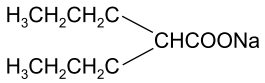
Properties and uses: It is a white or almost white crystalline powder, hygroscopic, very soluble in water, slightly to freely soluble in alcohol. It has been reported that there is a strong correlation between the anticonvulsant potency of valproate and other branched-chain fatty acids and their ability to reduce the concentration of cerebral aspartate. It has been effective in partial, generalized, and absence seizures.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers.

Dosage forms: Sodium valproate oral solution IP, BP, sodium valproate tablets IP, BP, gastroresistant sodium valproate tablets BP.

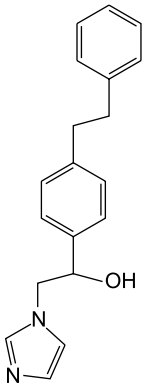
SAR of Sodium Valproate



- The anticonvulsant activity increases with increased chain length.
- Introduction of a double bond decreases the activity.
- Introduction of a 2° or 3° alcohol group or replacement of carbonyl or hydroxyl have no effect.

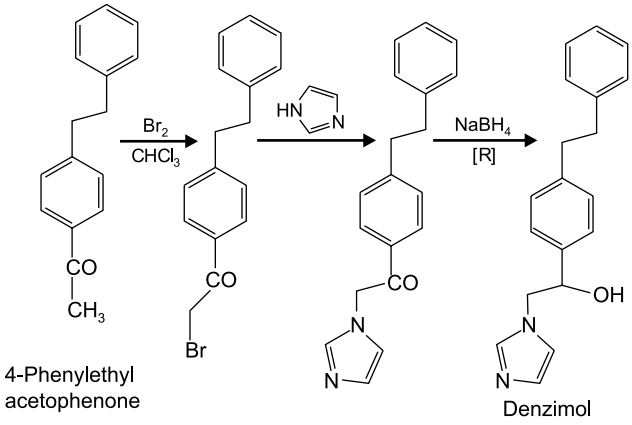
XI. Newer anticonvulsants

a. Denzimol



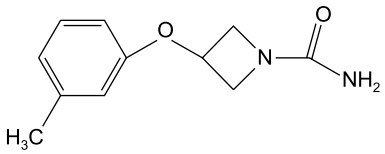
N-[β-[4-(-phenylethyl)phenyl]-β-hydroxyethyl]imidazole

Synthesis



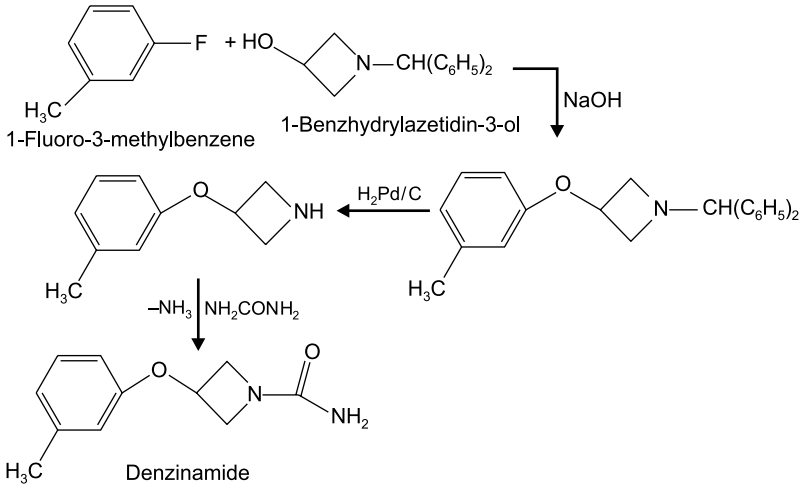
Properties and uses: It is a racemic mixture, white, odourless, and crystalline powder, soluble in water and alcohol, used in complex partial seizures.

b. Denzinamide



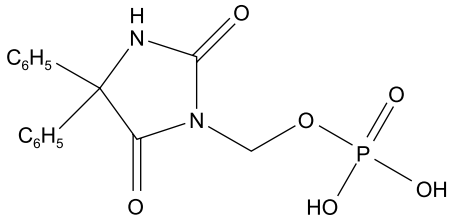
3-(*m*-Toluoxy) azetidine-1-carboxamide

Synthesis

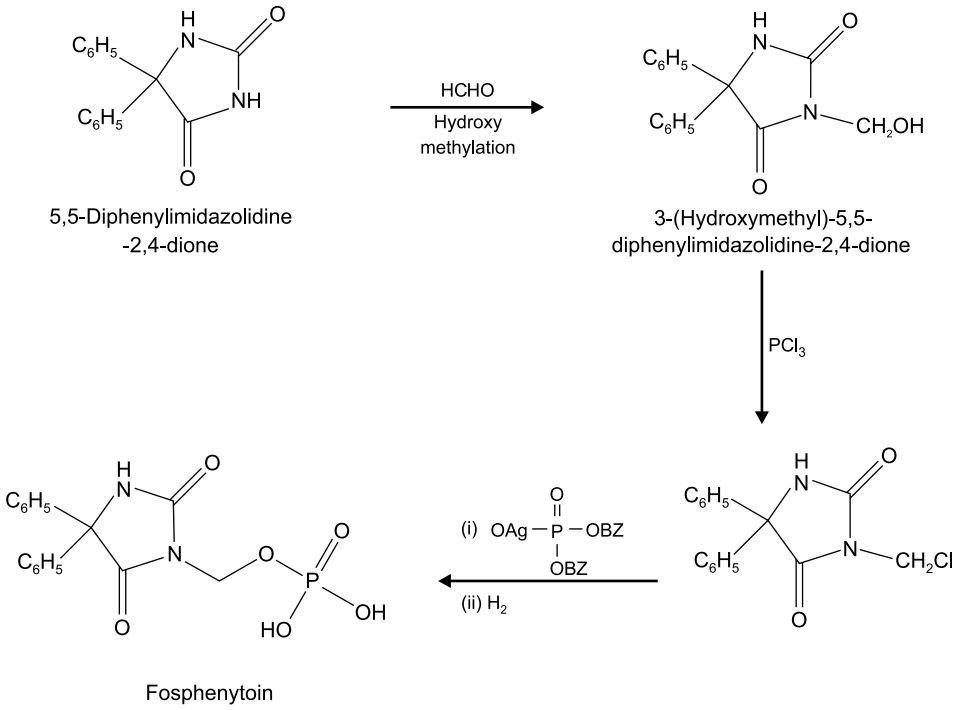


Uses: Used in partial and petitmal seizures.

c. Fosphenytoin (Fosolin, Fosphen)



Synthesis



5,5-Diphenylimidazolidine -2,4-dione

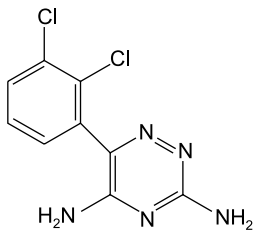
3-(Hydroxymethyl)-5,5-diphenylimidazolidine-2,4-dione

Fosphenytoin

Properties and uses: It is a prodrug form of phenytoin, and is rapidly cleared by phosphatases *in vivo* to form phenytoin.

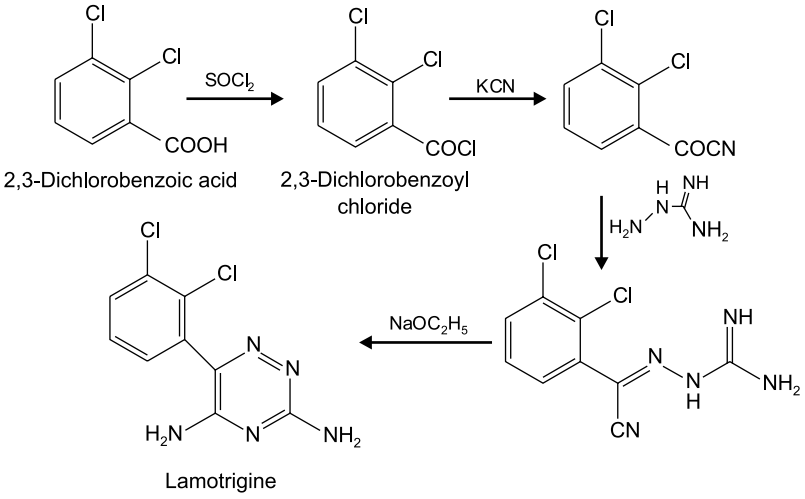
Dose: For tonic-clonic status epilipticus: Adult—as phenytoin Na equivalents (PSE). Loading dose: 15 mg/kg given, via IV infusion at a rate of 100–150 mg/min. Maintenance: Initially, 4–5 mg kg/day by IM injection or IV infusion at a rate of 50–100 mg/min; subsequent doses depend on patient's response and plasma phenytoin levels.

d. Lamotrigine (Lamogine, Lamitor, Lamorig)



3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

Synthesis



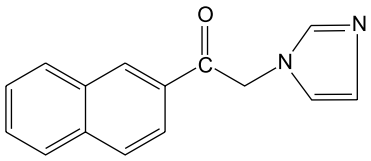
2,3-Dichlorobenzoic acid — 2,3-Dichlorobenzoyl chloride — Lamotrigine

Metabolism: It is metabolized by N-glucuronidation and subsequent urinary elimination of its major metabolite quarternary 2-N-glucuronide and minor 5-amino-N-glucuronide.

Properties and uses: It is one of the most potent and long acting anticonvulsant, with potency similar to or greater than that of phenytoin. It may prove to be of therapeutic value in several CNS-degenerative disorders, such as brain ischaemia, stroke and senile dementia. No toxic side effects have been noted. It is used as an add-on therapy for the treatment of generalized seizures not satisfactorily controlled by other antiepileptics. It acts as sodium channel blocker used for the management of generalized tonic-clonic, petitmal, myoclonic seizures, and myoclonic jerks in children.

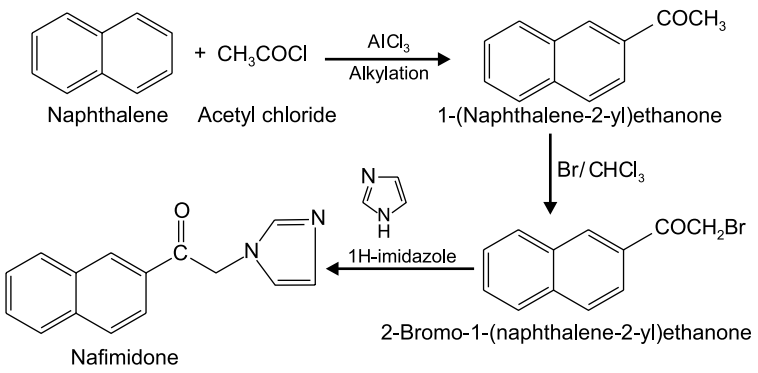
Dose: For monotherapy in epilepsy: Adult—initially, 25 mg once daily for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter, increase the dose by a maximum of 50–100 mg every 1–2 week to usual maintenance dose of 100–200 mg daily, as a single dose or in two divided doses. Some patients may require up to 500 mg daily.

e. Nafimidone



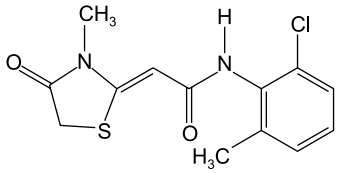
1-(2-Naphthoyl methyl) imidazole

Synthesis



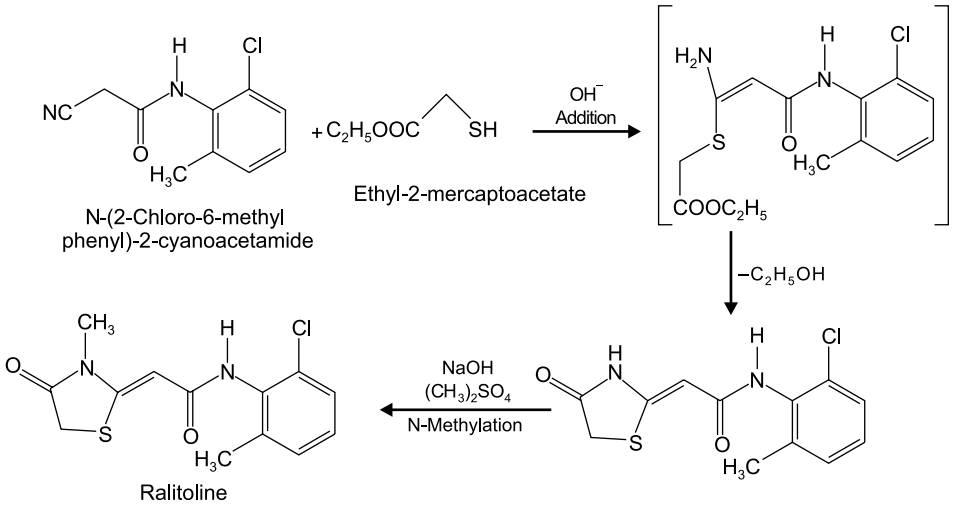
Properties and uses: Its pharmacological effect includes protection against both tonic-clonic and partial seizures in rodents with an ED_{50} comparable to those of phenytoin and phenobarbital. It is used in tonic-clonic and partial seizures.

f. Ralitoline



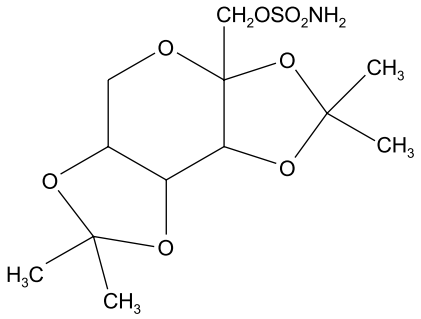
N-(2-Chloro-6-methyl phenyl)-3-(3-methyl-4-oxothiazolidin-2-ylidine) acetamide

Synthesis



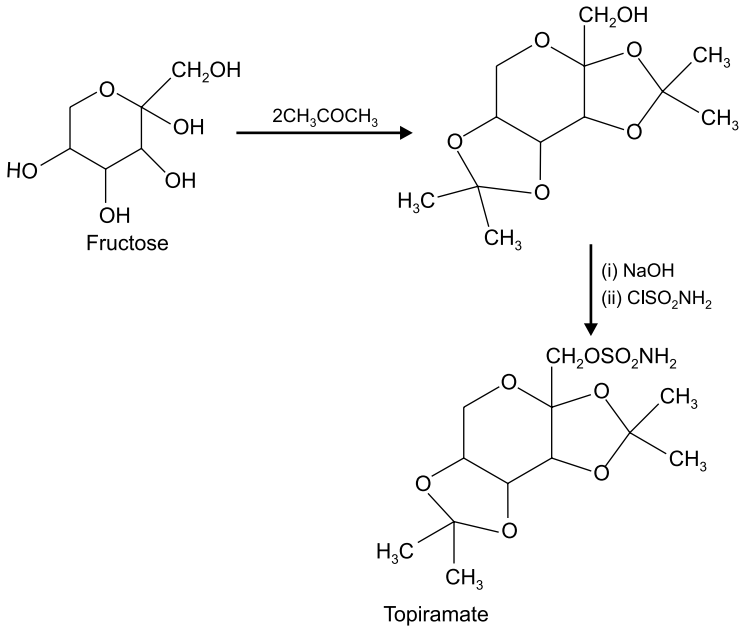
Properties and uses: It is a sodium channel blocker used for the management of generalized seizures.

g. Topiramate (Epitop, Topamac, Topamate)



2,3:4,5-*bis*-*o*-(1-methyl ethylidine)-β-D-fructopyranose sulphamate

Synthesis

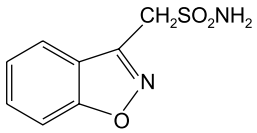


Topiramate

Properties and uses: It exists as white crystalline powder, includes efficacy against generalized seizures, absence, and myoclinic seizures.

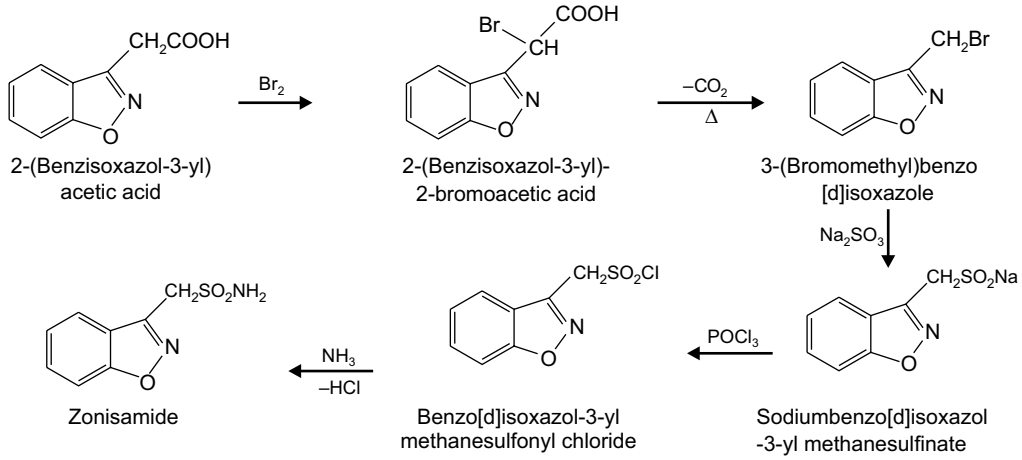
Dose: The usual dose 40 mg/day in two divided dose.

h. Zonisamide



1,2-Benzisoxazole-3-methane sulphonamide

Synthesis



Properties and uses: It exists as white needles, soluble in water, chloroform, hexane, methanol, ethanol, ethyl acetate and acetic acid. It also has weak carbonic anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide. Used as sodium channel blocker prevents tonic seizures.

Ezogabine (Potiga)

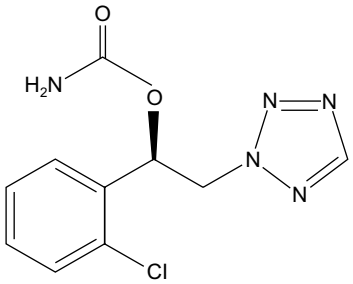
Mode of action: *In vitro* studies indicate that ezogabine enhances transmembrane potassium currents mediated by the KCNQ family of ion channels. By activating KCNQ channels, ezogabine is thought to stabilize the resting membrane potential and reduce brain excitability. *In vitro* studies suggest that ezogabine may also exert therapeutic effects through augmentation of GABA-mediated currents. GABA is an inhibitory neurotransmitter that may help suppress seizure activity.

Properties and uses: It is a potassium channel agent. The mechanism by which ezogabine exerts its therapeutic effects is not been fully established. It is specifically used as an adjunctive treatment of partial-onset seizures in adults. Adverse effects are, dizziness, somnolence, fatigue, confusional state, vertigo, tremor, abnormal coordination, diplopia, disturbance in attention, memory impairment, blurred vision.

Dose: The recommended initial dose is 100 mg three times daily. The dose should be increased gradually at weekly intervals by not more than 50 mg three times daily (increase in the daily dose of no more than 150 mg per day) up to a maintenance dosage of 200 to 400 mg three times daily (600 to 1200 mg per day), based on individual response and tolerability.

Newer Agents

Cenobamate

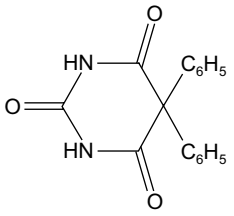


Uses: It is used for the treatment of partial onset seizures.

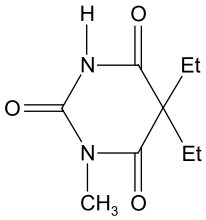
CLASSIFICATION BASED ON PCI SYLLABUS

Barbiturates

Phenobarbitone

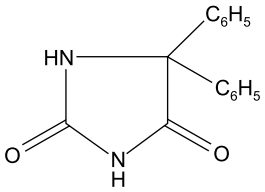


Methabarbital

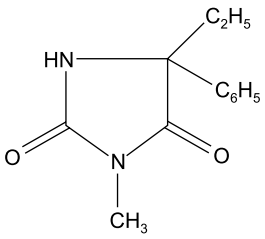


Hydantoins

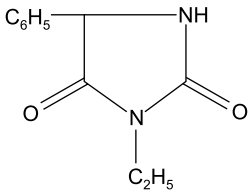
Phenytoin



Mephenytoin

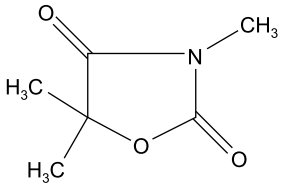


Ethotoin

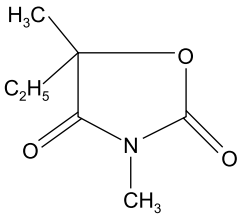


Oxazolidinediones

Trimethadione

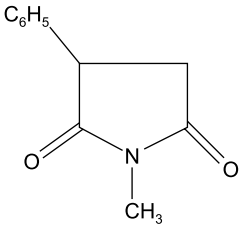


Paramethadione

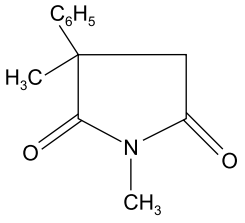


Succinimides

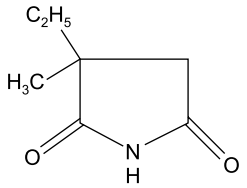
Phensuximide



Methsuximide

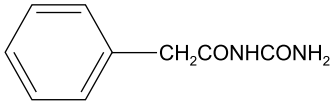


Ethosuximide

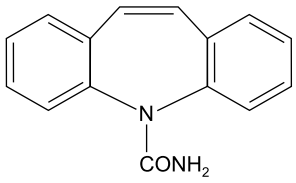


Urea and Monoacylureas

Phenacemide

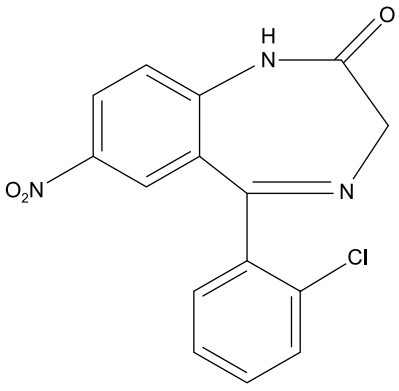


Carbamazepine



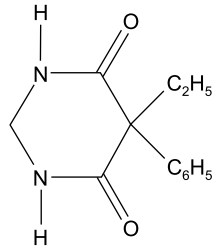
Benzodiazepines

Clonazepam

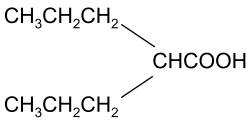


Miscellaneous

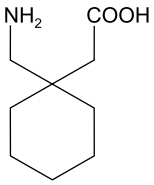
Primidone



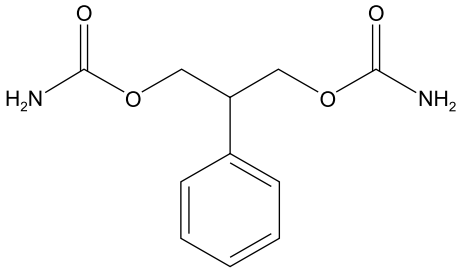
Valproic acid



Gabapentin



Felbamate



PROBABLE QUESTIONS

1. Define and classify the drugs used for convulsive seizures. Write the structure, chemical name, and uses of one important compound from each class.
2. Write a note on the uses of barbiturates in convulsion therapy.
3. Explain hydantoins as a potent anticonvulsant. Describe the synthesis and uses of phenytoin.
4. Write a note on phenyl acetyl urea derived anticonvulsants.
5. Discuss paramethadione as a therapeutic agent used in petitmal epilepsy.

6. Name few newer anticonvulsants and describe the synthesis of any one of them.
7. Succinimides afford better tolerated and less toxic anticonvulsants. Justify the statement with the help of a detailed account of one of the potent compounds belonging to this category.
8. Name the anticonvulsant drug obtained by replacing 'O' at C-2 of phenobarbital with 2H atom. Outline its synthesis and uses.
9. Describe an account of anticonvulsants having a dibenzodiazepine ring system with a carbamoyl moiety hooked on to the N-atom.
10. Describe the relative structural differences occurring amongst phensuximide, methsuximide, and ethosuximide. Give their chemical names, uses, and advantages of one over the other.
11. Describe the mode of action of hydantoins and primidone in the body.
12. How do the mode of action of oxazolidinediones and succinimides differ from hydantoins?
13. Describe in detail about benzodiazepines-derived anticonvulsants which possesses a broad-spectrum activity.

SUGGESTED READINGS

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CHAPTER 31

Antiparkinsonism Agents

INTRODUCTION

Parkinsonism, as a clinical entity, was first described by James Parkinson in 1817. It is a syndrome having the features of akinesia, muscular rigidity, tremor, excessive salivation, seborrhoea, mood changes (especially depression), and liver damage that may be present in certain patients.

The pathophysiologic basis of this idiopathic disorder may relate to exposure of some unrecognized neurotoxin or any generation of free radicals. Normally, the high concentrations of dopamine in basal ganglia of the brain is reduced in the case of Parkinson's disease and pharmacological attempts to restore dopaminergic activity with levadopa and dopamine agonist that have been successful in alternating many of the clinical features of this disorder. An alternative or complementary approach has been to restore the normal balance of cholinergic and dopaminergic influences on basal ganglia with antimuscarinic drugs.

The functional circuits between the cortex, basal ganglia, thalamus, and the neurotransmitters are indicated further. In Parkinson's disease, there is a degeneration of neurons in pars compacta of the substantia nigra, leading to hyperactivity in indirect pathways and increased glutamatergic activity by subthalamic nucleus (Figure 31.1).

General mode of action: Parkinson's disease is a progressive neurodegenerative disorder with motor defects due to the imbalance between the dopaminergic (inhibitory-D_2 and exitatory-D_1) receptors. These are amplified by K^+ channels and Ca^{2+} channels, respectively. Parkinson's disease is characterized by dopamine deficiency. Levodopa is considered to act through D_1 and D_2 receptors present in the striatum and it regulates the activity of the two pathways having opposite effects on thalamic input to the motor cortex to produce the smooth kinetic movements.

Other categories of antiparkinsonian drugs influence the metabolism of dopamine and levodopa. In peripheral system, levodopa is converted into 3-*ortho*-methyldopa in the presence of *catechol-O-methyl transferase (COMT)* and to dopamine in the presence of dopa decarboxylase. These metabolic pathways are inhibited by tolcapone, entacapone, and carbidopa, benserazide, respectively.

In brain, dopamine is converted into homovanillic acid catalyzed by *monoamine oxidase B (MAO-B)*. This is inhibited by MAO-B inhibitors selegiline and the dopamine is protected to remain in the neurons to regulate the inhibitory and excitatory balance.

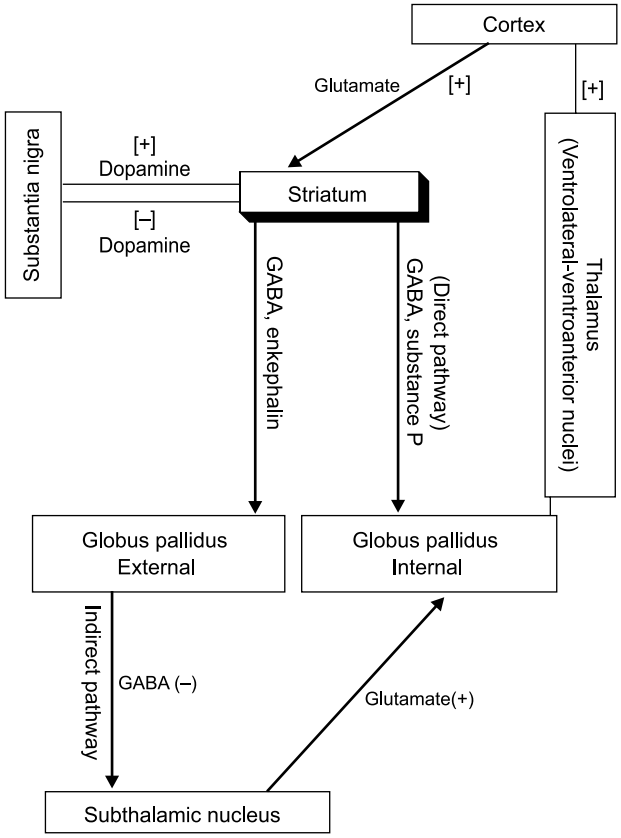


Figure 31.1: Functional circuits

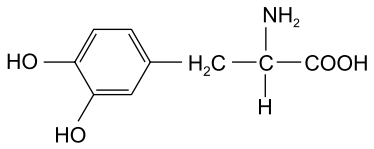
CLASSIFICATION

The drugs used in the treatment of parkinsonism can be classified as follows:

I. Drugs affecting brain dopamine

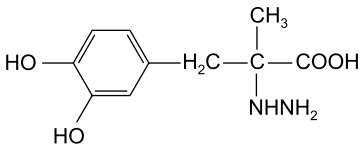
i. Drugs that increase brain levels of dopamine

- **Levodopa**

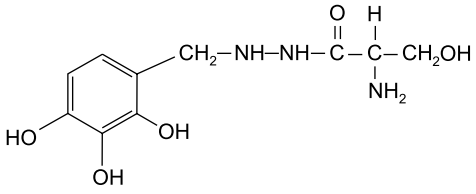


ii. Drugs that decrease dopamine metabolism

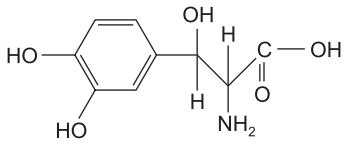
a. Carbidopa



b. Benserazide

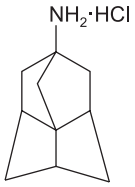


c. Droxidopa

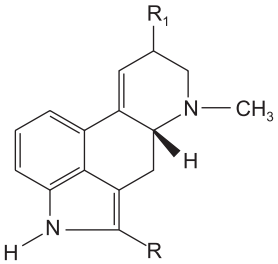


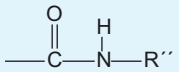
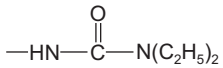
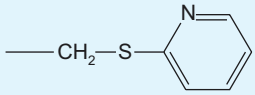
iii. Dopamine releasers

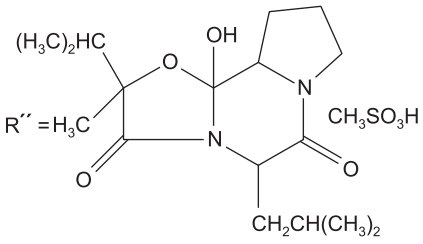
⋆ Amantadine HCl

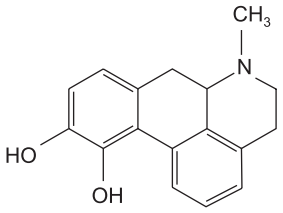


iv. Dopamine receptor stimulation: Dopaminergic agonists



Name	*R*	R_1
Bromocriptine	–Br	
Lisuride	–H	
Ergoline	–H	

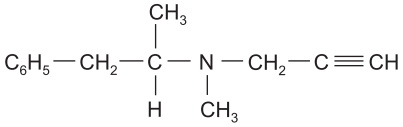




Apomorphine

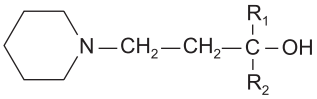
v. Dopamine conservation, MAO-B inhibitor

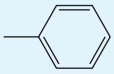
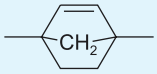
⋆ Selegiline HCl



II. Anticholinergic agents

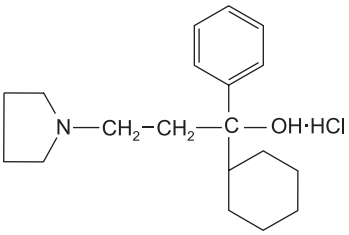
i. Piperidine analogues



S.No.	Name	R_1	R_2
1.	Biperiden		
2.	Cycri		
3.	Trihexyphenidyl hydrochloride		

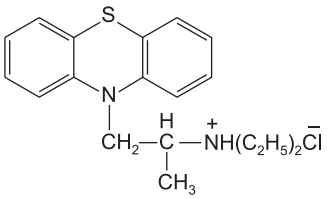
ii. Pyrrolidine analogues

⋆ Procyclidine HCl



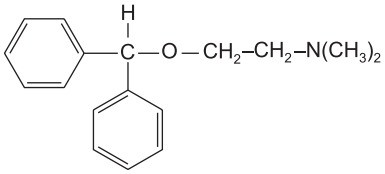
iii. Phenothiazine analogues

a. Ethopropazine HCl



Antihistamines with central anticholinergic activity.

b. Diphenhydramine



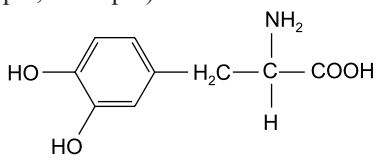
III. Miscellaneous drugs

- Antidepressants: Amitriptyline, trazadone
- α-tocopherol (vitamin E)
- Glutamate release inhibitor: Lamotrigine
- Glutamate receptor antagonist: Remacemide
- Glial-derived neurotrophic factor: GDNF
- Benztropine
- Orphenadrine citrate
- Chlorphenoxamine HCl

SYNTHESIS AND DRUG PROFILE

I. Drugs affecting brain dopamine

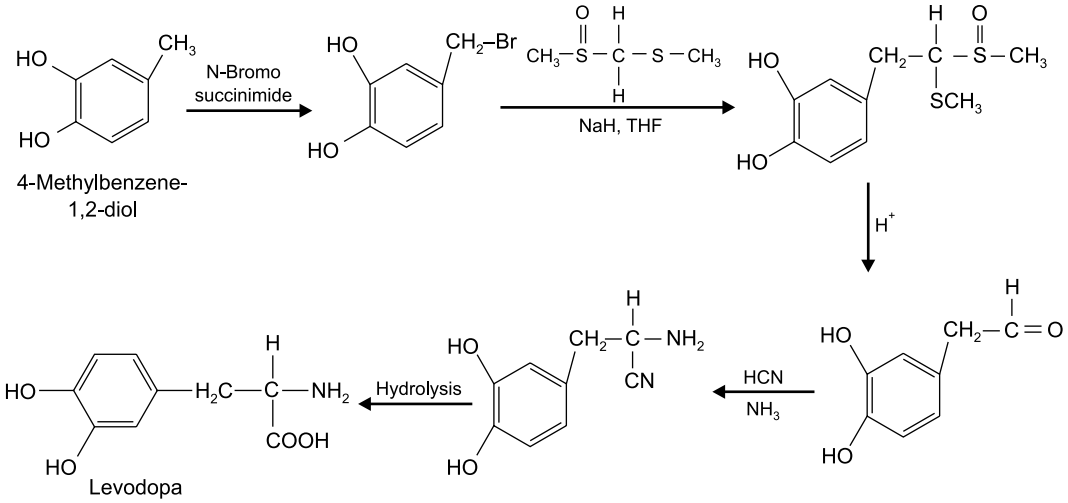
a. Levodopa (Bidopal, Benspar, Madopar)



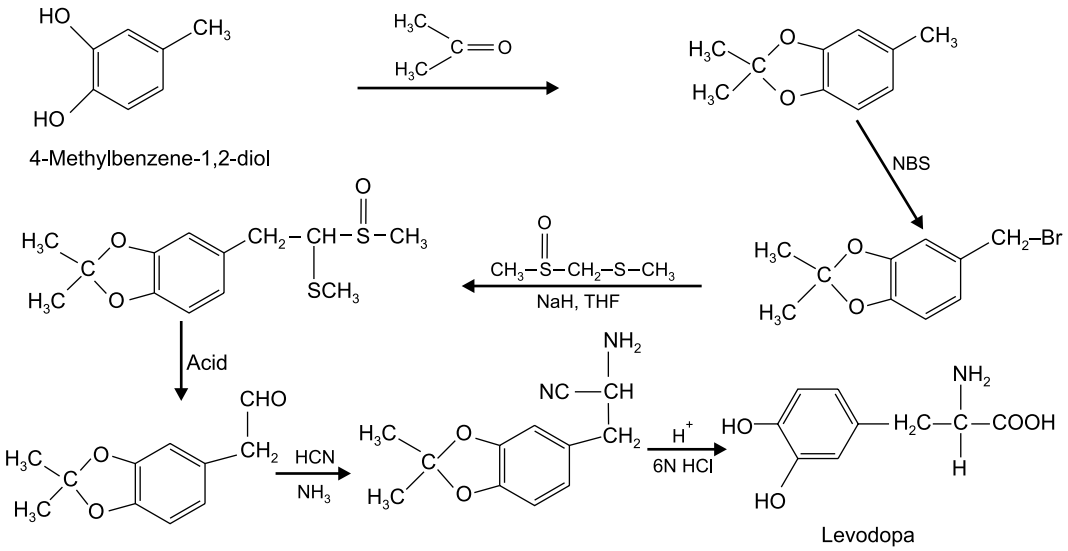
2-Amino-3-(3,4-dihydroxyphenyl) propanoic acid

Synthesis

Route I. From: 4-Methylbenzene-1,2-diol



Route II. From: 4-Methylbenzene-1,2-diol



Metabolism: Levodopa is rapidly absorbed by active transport in gastrointestinal (GI) tract and once absorbed, 95% is decarboxylated in the periphery to the dopamine, which is further metabolized to dihydrophenylacetic acid and homovanillic acid, which are excreted through urine.

Properties and uses: It is a white or almost white crystalline powder, freely soluble in 1 M hydrochloric acid, slightly soluble in water and insoluble in ethanol. Used as dopamine precursor and in the treatment of Parkinson's disease. It is also used to treat the parkinsonism-like neurological syndrome of manganese intoxication, in which there is also a deficiency of dopamine in the basal ganglia. Levodopa is a precursor of melanin and may activate latent malignant melanoma. The effects of levodopa on bradykinesia and rigidity are more rapid and complete than the effects on tremor.

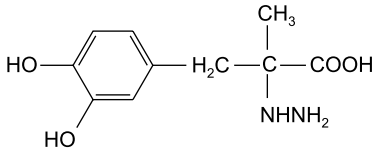
Assay: Dissolve the sample in anhydrous formic acid by heating, if necessary. To this add anhydrous acetic acid, dioxan, and crystal violet and titrate with 0.1 M perchloric acid. End point is the appearance of green colour.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The initial oral dose is 100 mg to 1 g/day in divided doses with meals; maintenance dose is 2.5 to 6 g daily and must not exceed 8 g.

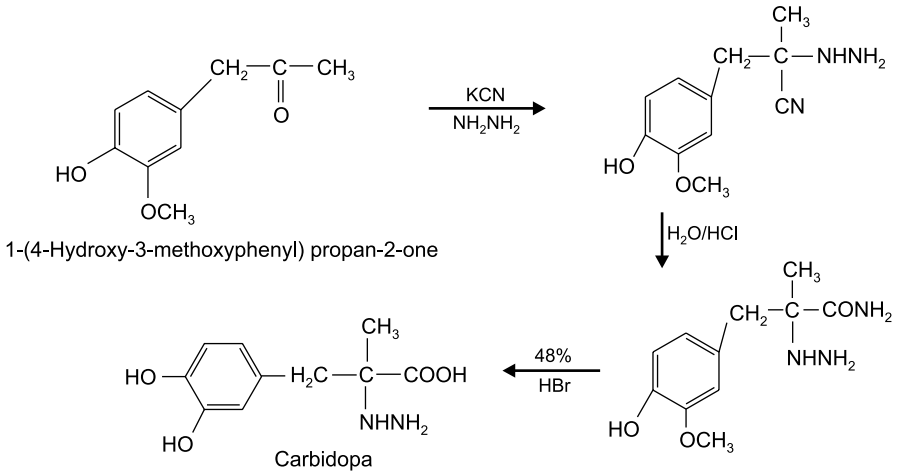
Dosage forms: Levodopa capsules IP, BP, levodopa tablets IP, BP, co-beneldopa capsules BP, dispersible co-beneldopa tablets BP, co-careldopa tablets BP.

b. Carbidopa (Lodosyn)



3-(3,4-Di-hydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid

Synthesis



1-(4-Hydroxy-3-methoxyphenyl) propan-2-one

Carbidopa

Metabolism of carbidopa: It is a synthetic amino acid precursor of (–) norepinephrine, which is absorbed from the gut and metabolized to norepinephrine. It is further metabolized by COMT and MAO to form metanephrine and normetanephrine. Further they undergo for the metabolism by MAO to 3-methoxy-4- hydroxy mandilic acid.

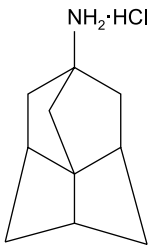
Properties and uses: It is a white or yellowish-white powder, dissolves in dilute mineral acids, slightly soluble in water, sparingly soluble in alcohol, insoluble in methylene chloride. It has no direct therapeutic actions on its own, but rather is used only to protect levodopa and L-5-hydroxytryptophan. Both of which are decarboxylated by aromatic amino acid decarboxylase. When it is given concomitantly with levodopa, only about 25% as much levodopa is needed. The onset of response is more rapid.

Assay: Dissolve the substance in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Co-carbidopa tablets IP, BP.

c. Amantadine HCl (Symmetrel)



Mode of action: Amantadine appears to act by promoting presynaptic synthesis and release of dopamine in the brain. It acts on glutamate receptors through which dopaminergic system exerts the possible influence on regulating the D_1 and D_2 receptors.

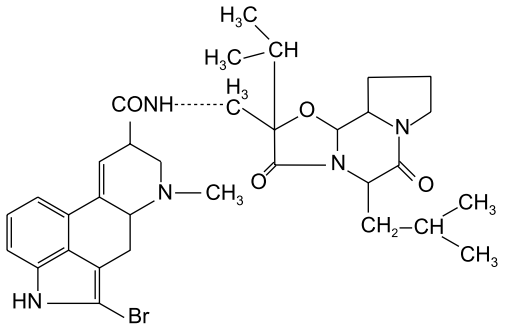
Properties and uses: It is a white or almost white crystalline powder, and it sublimes when heated. Freely soluble in water and in alcohol. Amantadine an organic cage amine, is an antiviral agent useful in preventing and treating influenza A_2. It possesses both antiparkinsonism and antiviral activity.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid. Perform potentiometric titration, using 0.1 M sodium hydroxide.

Dose: In the treatment of parkinsonism initial dose is 100 mg/day, increased to 100 mg twice daily, after one week.

Dosage forms: Amantadine HCl capsules IP, amantadine capsules BP, amantadine oral solution BP.

d. Bromocryptine mesylate (Parlodel, Proctinal, Sicriptin)



Properties and uses: It is a white or slightly coloured fine crystalline powder, insoluble in water, soluble in methanol and ethanol, sparingly soluble in methylene chloride. It is an ergot derivative. Bromocriptine mimics the action of dopamine. Addition of a bromine atom renders the alkaloid criptine a potent dopaminergic agonist at D_2 receptor and an antagonist at D_1 sites. It is used as an adjunct to levodopa.

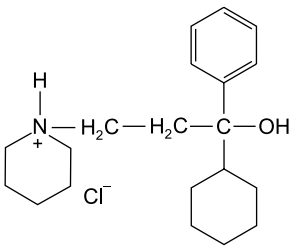
Assay: Dissolve the sample in a mixture of 10 volumes of anhydrous acetic acid and 70 volumes of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: Bromocriptine is very sensitive to light, and hence, it should be stored in well-closed airtight container and protected from light.

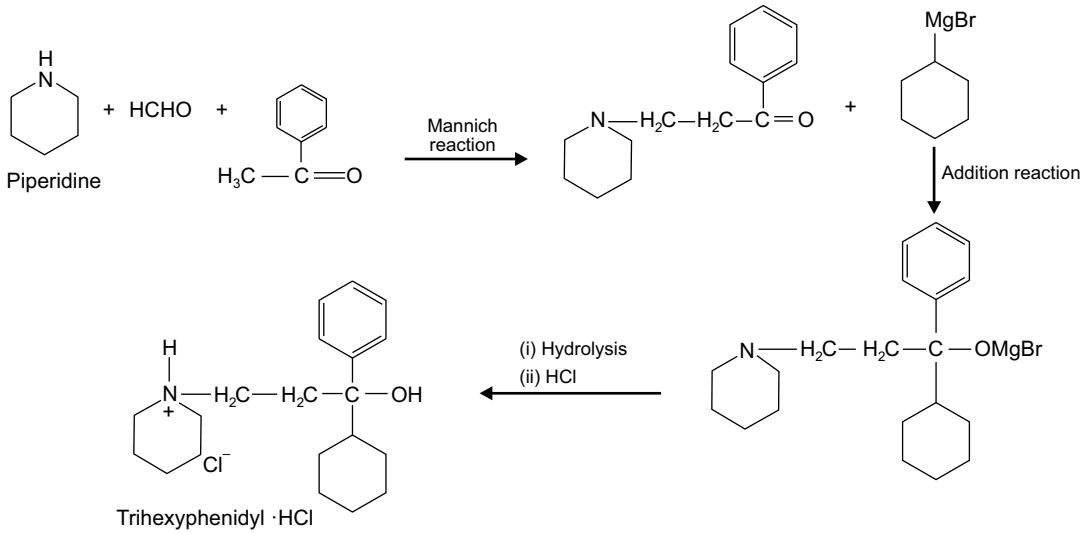
Dosage forms: Bromocriptine mesylate tablets IP, bromocriptine mesylate capsules IP, bromocriptine capsules BP, bromocriptine tablets BP.

II. Anticholinergic agents

a. Trihexyphenidyl HCl (Triphen, Parkin, Pacitane)



Synthesis



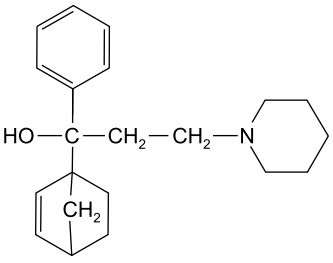
Properties and uses: It is a white crystalline powder, slightly soluble in water, sparingly soluble in alcohol, and methylene chloride. This drug introduced in 1958, has ganglion-blocking activity, its peripheral atropine-like activity predominates. Its therapeutic activity is based on the later activity. It is more effective than levodopa against Parkinson's tremor.

Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

Dose: The initial oral dose is 1 mg on first day, followed by 2 mg daily after 3 to 5 days; maintenance dose is 6 to 10 mg/day in 3 to 4 divided doses but not exceeding 20 mg/day.

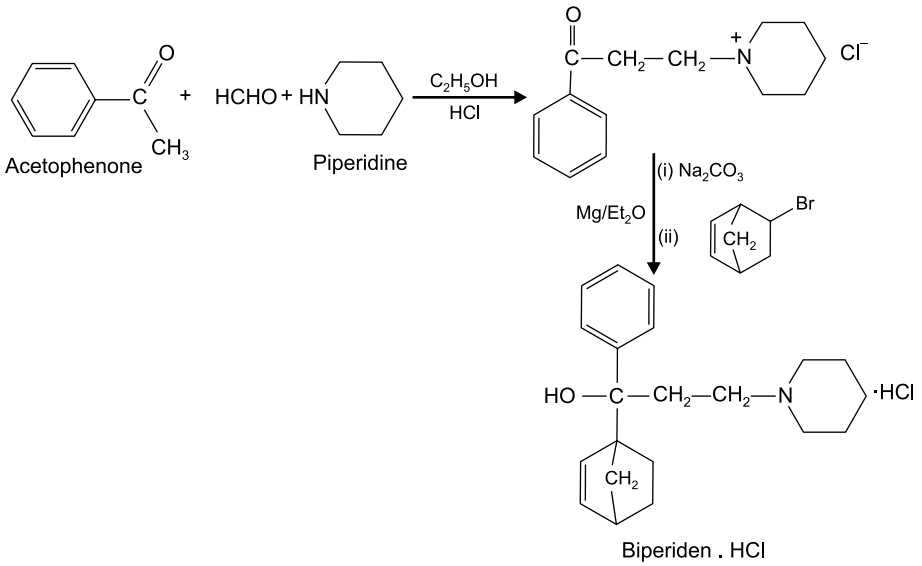
Dosage forms: Trihexyphenidyl tablets BP.

b. Biperiden HCl (Akineton hydrochloride)



1-(Bicyclohept-2-en-1-yl)-1-phenyl-3-(piperidin-1-yl)propan-1-ol

Synthesis



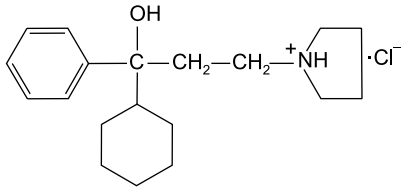
Properties and uses: It is a white crystalline powder, very slightly soluble in methylene chloride, slightly soluble in water, and in alcohol. It reduces tremor, akinesia, and muscle rigidity, drooling and sweating.

Dose: In the treatment of parkinsonism, 2 mg for three or four times/day.

Assay: Dissolve the sample in alcohol and titrate with 0.1 M alcoholic potassium hydroxide. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

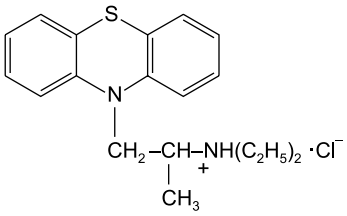
c. Procyclidine HCl (Kemadrin, Picidin, Prodine)



Dose: The initial oral dose is 7.5 mg/day in 3 or 4 divided doses after meals; maintenance dose is usually 20 to 30 mg/day.

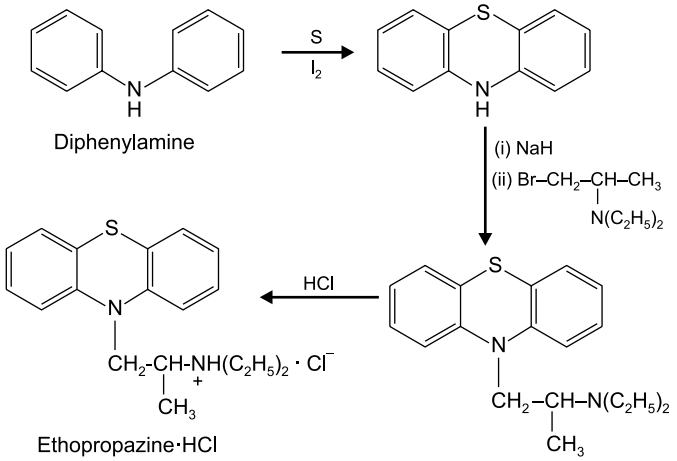
Synthesis and drug profile is discussed in Chapter 38: Anticholinergic Drugs.

d. Ethopropazine HCl (Parsidol)



10-[2-(Diethylamino)propyl]phenothiazine hydrochloride

Synthesis



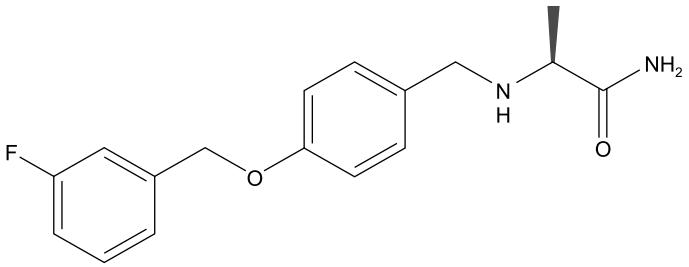
Mode of action: These drugs act by reducing the unbalanced cholinergic activity in the striatum of parkinsonian patients.

Properties and uses: Drowsiness is common and the drug can cause muscle cramps and hypertension. Used especially for control of rigidity. It is a useful adjunct to antiparkinson's agents.

Dose: The usual oral dose is initially 50 mg/day, slowly increased to 500 mg/day in divided doses.

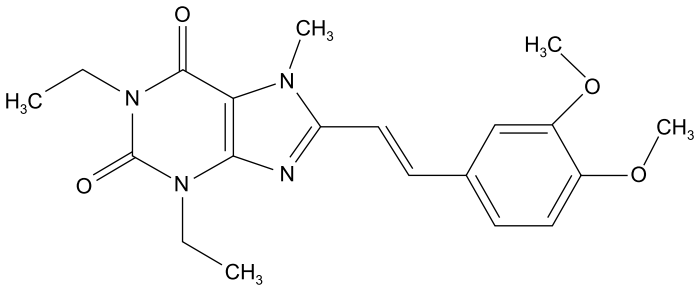
NEWER AGENTS

Safinamide



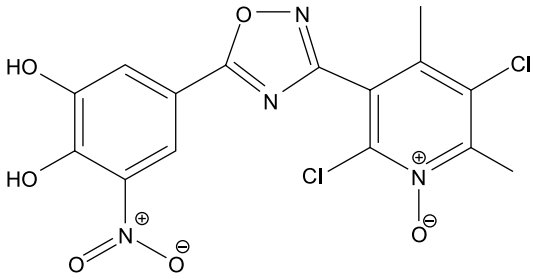
Uses: It is a monoamine oxidase B inhibitor and used as an add-on treatment for Parkinson's disease.

Stradefylline



Uses: It is used along with levodopa or carbidopa for the treatment of Parkinson's disease.

Opicapone



Uses: It is coadministered with levodopa in people with Parkinson's disease.

PROBABLE QUESTIONS

1. Define and classify antiparkinsonism agents. Describe the synthesis and uses of any two.
2. Write the general mode of action of antiparkinsonism agents and the synthesis of dopamine.
3. Outline the synthesis of ethopropazine and biperiden.

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CHAPTER 32

Skeletal Muscle Relaxants

INTRODUCTION

Skeletal muscle relaxants are drugs that are able to reduce unwanted spasm or spasticity without interfering with consciousness and normal voluntary movements. These drugs may find an important application in various neurological or muscular skeletal disorders.

Drugs that cause depression of the motor functions leading to a relaxation of voluntary muscles are known as muscle relaxants. Drugs that act on the skeletal muscles fall into two major therapeutic groups, those used during surgical procedures and in intensive care units to cause paralysis (i.e. neuromuscular blockers) and those used to reduce spasticity in a variety of neurological conditions (i.e. spasmolytic). Neuromuscular blockers inhibit the transmission at the neuromuscular end plate and blocks central nervous system control. These components are used primarily as adjuvant to general anaesthesia.

In the 16th century, European explorers found that the natives of Amazon Basin of South America were using an arrow poison (curare) that produced death by skeletal muscle paralysis. The active compound from curare, *d*-tubocurarine, and its synthetic derivatives had an enormous influence on the practice of anaesthesia and surgery.

In practice, the blockade of end plate function is accomplished by two basic mechanisms. Pharmacological blockade of physiological agonist acetylcholine is characteristic of the neuromuscular blocking drugs. These drugs prevent access of transmitters to the receptor and prevent depolarization. The prototype of this non-depolarizing subgroup is *d*-tubocurarine. Blocking of transmission can also be produced by an excess of depolarizing agonist, namely, acetylcholine and the depolarizing blocking drug, succinylcholine.

Skeletal muscle contractions occur when there is a release of acetylcholine from presynaptic vesicles, and acts on the postjunctional acetylcholinergic receptors in the motor end plate. An autoimmune disease, myasthenia gravis, associated with skeletal muscle relaxation is produced due to the loss of acetylcholinergic receptors in the neuromuscular junction. In normal physiological conditions, relaxation can be produced by the skeletal muscle relaxant, which binds to antagonize the action of acetylcholine on neuromuscular junction's acetylcholine receptors.

CLASSIFICATION

I. Neuromuscular blocking drugs

a. Non-depolarizing muscle relaxants

- Tubocurarine chloride

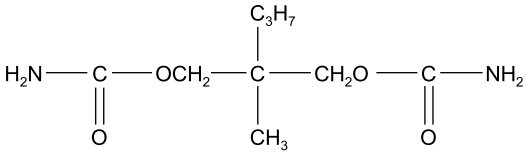
- Metocurine iodide
- Gallamine triethiodide
- Pancuronium bromide
- Hexafluoronium bromide
- Fazadinium bromide
- Alcuronium chloride
- Paucronium bromide
- Stercuronium iodide

b. Depolarizing neuromuscular blocking drugs

- Suxamethonium chloride or succinyl choline chloride
- Suxethonium chloride
- Decamethonium bromide

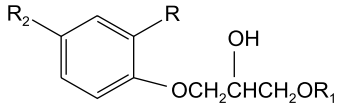
II. Centrally acting muscle relaxants

a. Carbamate



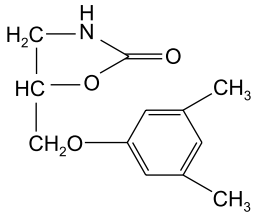
Meprobamate

b. Glycerol monoethers and analogues

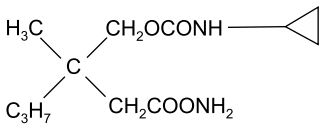


Name	*R*	*R_1*	*R_2*
Mephenesin	$-CH_3$	–H	–H
Mephenesin carbamate	$-CH_3$	$-CONH_2$	–H
Guaifenesin	$-OCH_3$	–H	–H
Methocarbamol	$-OCH_3$	$-CONH_2$	–H
Chlorphenesin carbamate	–H	$-CONH_2$	–Cl

c. Substituted alkanediols

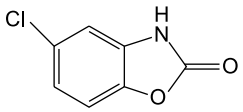


Metaxalone



Lorbamate or carisoprodal

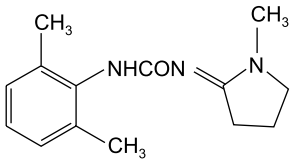
d. Benzoxazole analogues



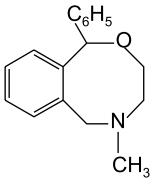
Chlorzoxazone

e. Heterocyclic bases

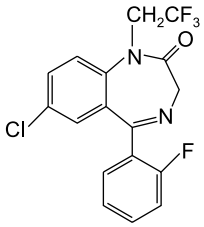
i. Xilobam



ii. Benzodiazepines

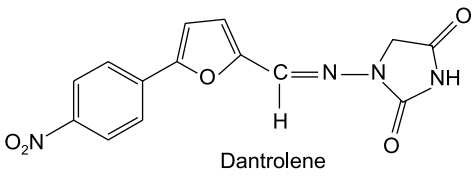


Nefopam



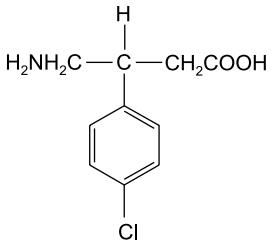
Fletazepam

f. Imidazole analogue

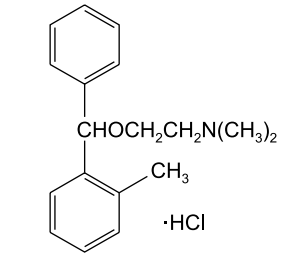


Dantrolene

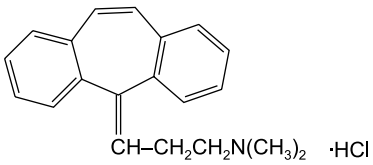
g. Miscellaneous drugs



Baclofen



Orphenadrine



Cyclobenzaprine

SYNTHESIS AND DRUG PROFILE

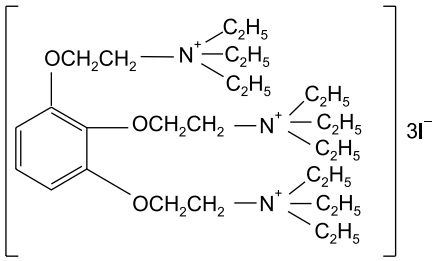
I. Neuromuscular blocking agents

a. Non-depolarizing blockers

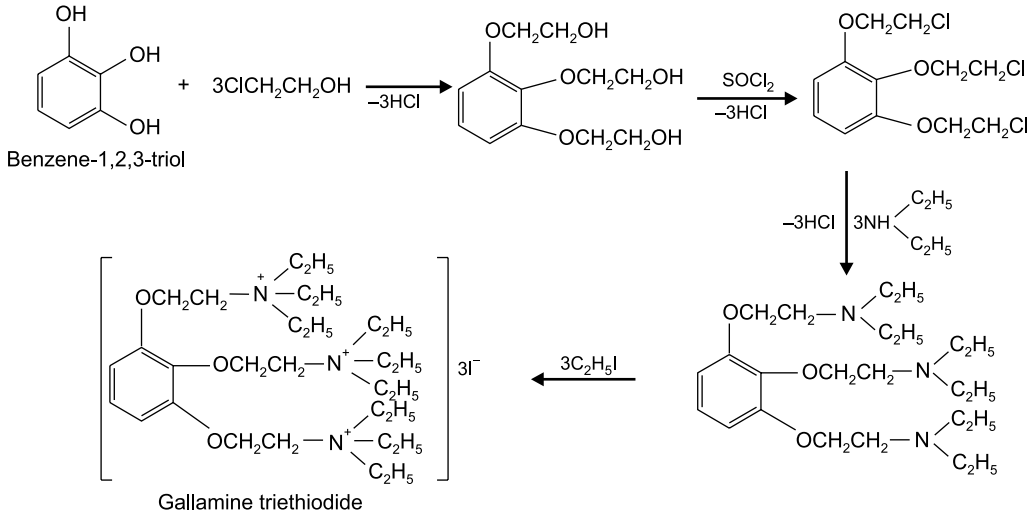
Mode of action: Non-depolarizing blockers have affinity for the cholinergic receptors at the muscle end plate. The receptor is a protein with five subunits arranged similar to a rosette, surrounding the sodium channel. The two subunits carry two acetylcholine binding sites; they have negatively charged groups, which combine with the cationic head of acetylcholine leads to the opening of sodium channel. Most of the non-depolarizing blockers have two or more quaternary nitrogen atoms, which provide the

necessary attraction to the same site for binding, so acetylcholine released from the nerve ending cannot bind to generate action potential and produces muscle relaxant property.

i. Gallamine triethiodide (Flaxedil)



Synthesis



Properties and uses: It is a white or almost white powder hygroscopic in nature. Insoluble in methylene chloride, soluble in water, and slightly soluble in alcohol. It is a non-depolarizing neuromuscular blocker used as adjuvant to anaesthesia, so as to achieve depot muscular relaxation.

Assay: Dissolve the sample in a mixture of anhydrous formic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For the treatment of limb muscle paralysis, initial dose by IV or IM 1 mg/kg of body weight; for abdominal surgery, 1.5 mg/kg of body weight; maintenance dose is 500 µg to 1 mg every 30 to 60 minutes, intervals, if required. The dose must be reduced when used along with anaesthetics like ether, cyclopropane, etc.

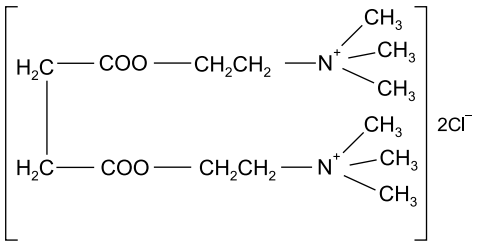
Dosage forms: Gallamine triethiodide injection IP, gallamine injection BP.

b. Depolarizing neuromuscular blockers

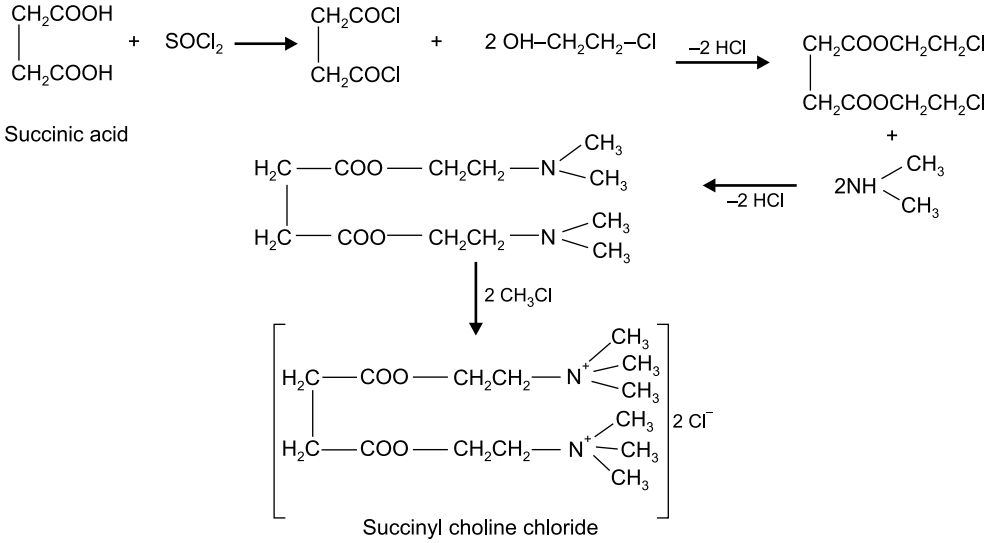
Mode of action: These drugs depolarize the muscle end plate potential by opening of Na^+ channels as acetylcholine initially produces twitching and fasciculation. They do not dissociate rapidly from the

receptors, and produce prolonged partial depolarization of muscles and plates leading to inactivation of sodium channels due to the dropping of membrane potential.

ii. Succinyl choline chloride



Synthesis



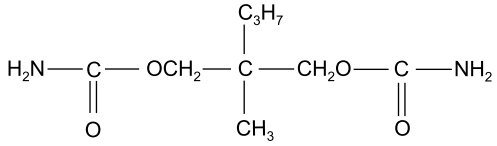
Uses: It is used to relax the skeletal muscle for orthopaedic manipulation of endotracheal intubation.

II. Centrally acting muscle relaxants

General mode of action: These selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex.

a. Carbamates

- **Meprobamate**

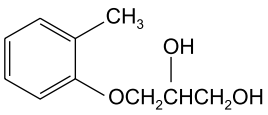


Synthesis and drug profile is discussed in Chapter 23: Sedatives and Hypnotics.

b. Glycerol monoethers and analogues

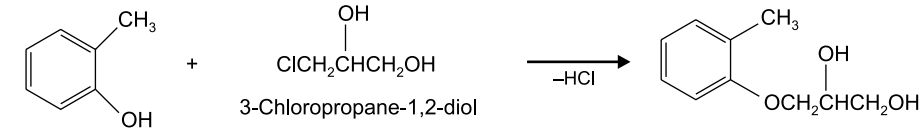
Synthesis of mephenesin (tolserol) and guaifenesin

i. Mephenesin



Mephenesin

Synthesis



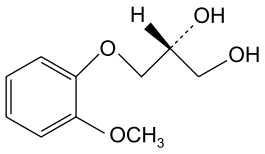
2-Methyl phenol

3-Chloropropane-1,2-diol

Metabolism of mephenesin derivatives: The major metabolic product of mephenesin is β-(*o*-toloxy)-lactic acid, which is inactive. Because of easy metabolism (oxidation) of mephenesin to the corresponding lactic acid, its carbamate or succinate derivatives show longer duration, although less active than the parent drug.

Dose: Mephenesin: Usual oral dose is 0.5 or 1g for one to six times per day as per requirement.

ii. Guaifenesin

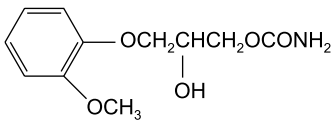


3-(2-Methoxyphenoxy)propane-1,2-diol

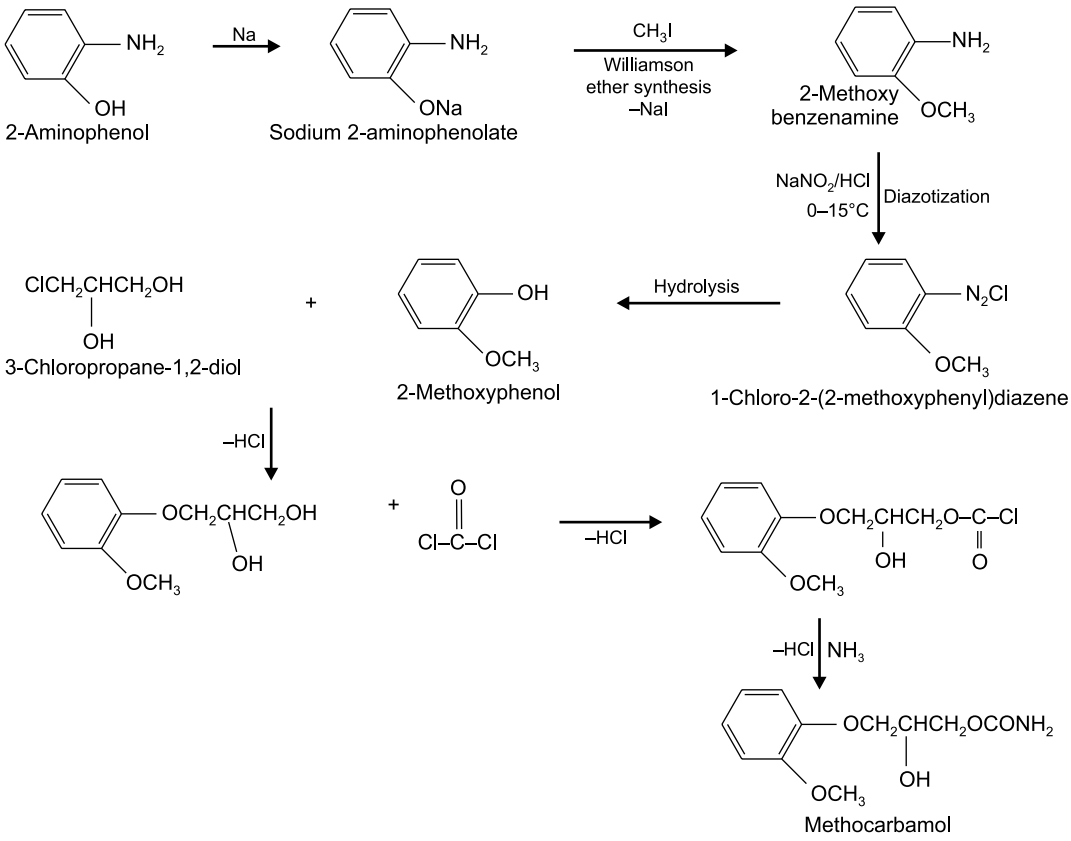
Properties and uses: It is a white or almost white crystalline powder, soluble in alcohol, sparingly soluble in water and used as an expectorant.

Assay: The substance is dissolved in freshly prepared mixture of 1 volume of acetic anhydride and 7 volumes of pyridine, boil under a reflux condenser and then cooled. To this add water and titrate with 1 M sodium hydroxide using phenolphthalein as indicator. End point is the appearance of pink colour.

iii. Methocarbamol (Robinax)



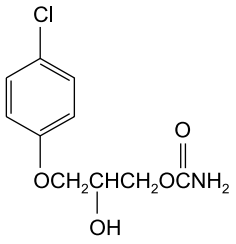
Synthesis



Uses: Used in parkinsonism and also in cerebrovascular mishaps.

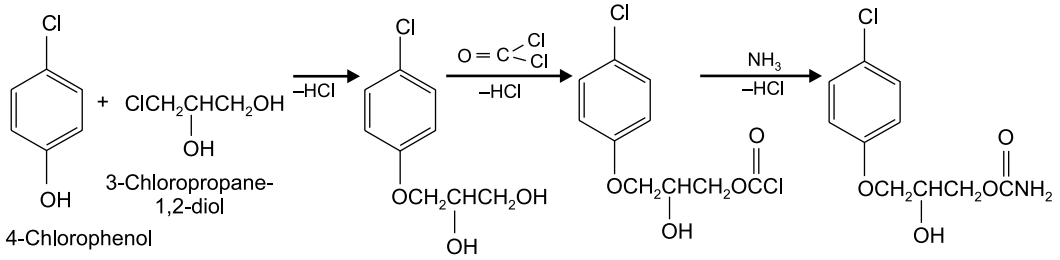
Dose: Initial oral dose is 1.5 to 2 g, four times daily for the first 2 or 3 days followed by 2.25 to 4.5 g per day in 2 or 4 divided doses; IV, 1 to 3 g per day administered at a rate not exceeding 0.3 g/min; by IM, 1 g every 8 h.

iv. Chlorphenesin carbamate (Maolate)



3-(*p*-Chlorophenoxy)-1,2-propanediol-1-carbamate

Synthesis

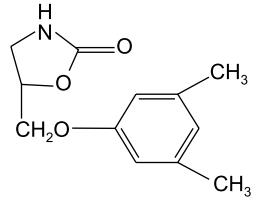


Uses: It is used to diminish skeletal muscle spasms resulting from osteoarthritis and vertebral disk syndrome.

Dose: The initial usual dose is 800 mg thrice/day and reduced to 400 mg four times/day, or less as required.

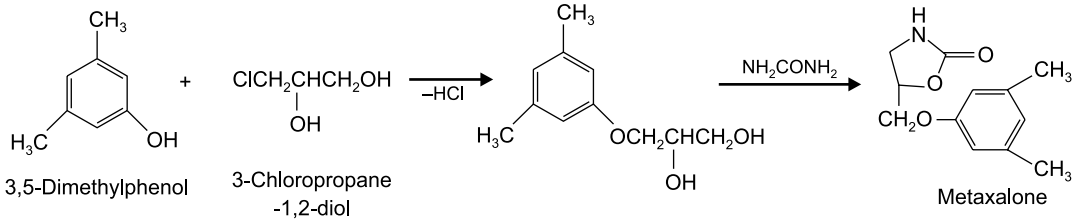
c. Substituted alkanediols

i. Metaxalone (Skelaxin)



5-[(3,5-Xylox)methyl]-2-oxazolidone

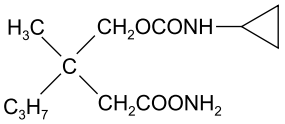
Synthesis



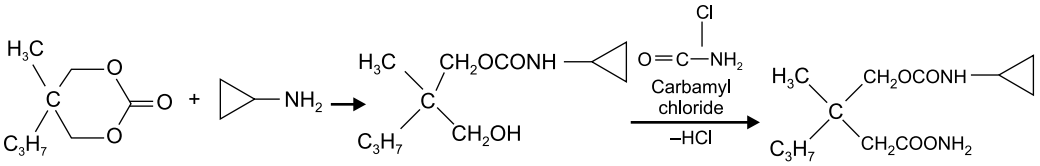
Uses: It is used for local skeletal muscle spasms.

Dose: The usual dose is 800 mg three or four times/day.

ii. Lorbamate



Synthesis

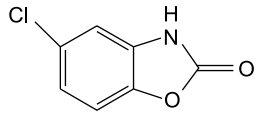


5-Methyl-5-propyl-1, 3-benzdioxan-2-one — Cyclopropanamine — Lorbamate

Uses: Used as a muscle relaxant.

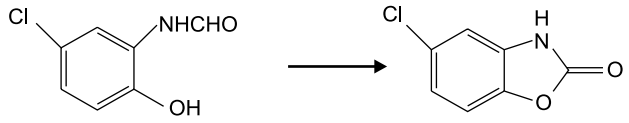
d. Benzoxazole analogues

- **Chlorzoxazone** (New Panazox, Ontacplus)



5-Chlorobenzo-oxazol-2-one

Synthesis



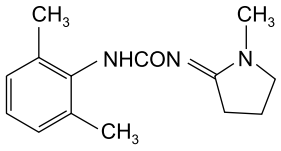
N-(5-Chloro-2-hydroxyphenyl) formamide — Chlorzoxazone

Uses: It is obtained by cyclization of the *o*-hydroxyl benzformamide. Used as skeletal muscle relaxant for the reduction of painful muscle spasm, such as mycositis sprains and acute or chronic back pain.

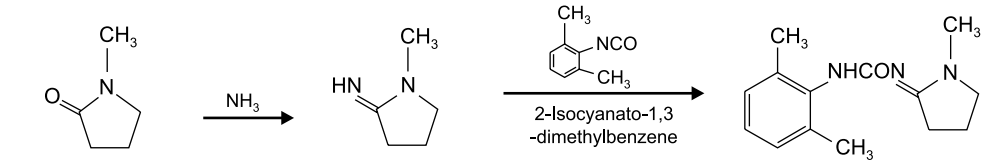
Dose: The usual initial dose is 500 mg three or four times/day, maintenance dose is 250 mg.

e. Heterocyclic bases

i. Xilobam



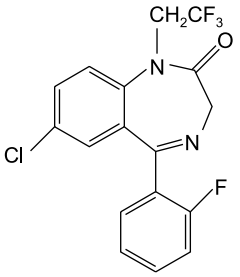
Synthesis



1-Methylpyrrolidin-2-one — Xilobam

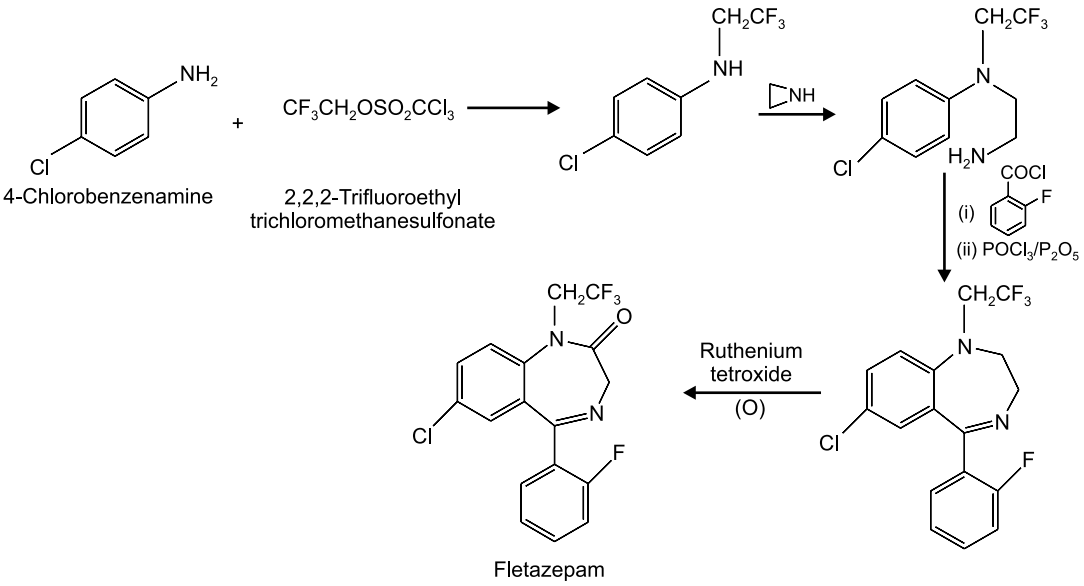
Mode of action of benzodiazepines: These drugs produce centrally mediated skeletal muscle relaxation by acting on the benzodiazepine receptors in midbrain reticular formation and on the limbic system. It acts on the benzodiazepine receptors, increases the chloride influx, and produces hyperpolarization and decreases the firing rate of neurons and inhibits the calcium dependent release of neurotransmitters.

ii. Fletazepam



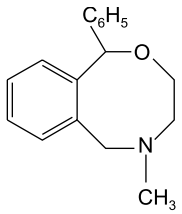
(E)-7-Chloro-5-(2-fluorophenyl)-1-
(2,2,2-trifluoroethyl)-benzo[1,4]diazepin-2-one

Synthesis



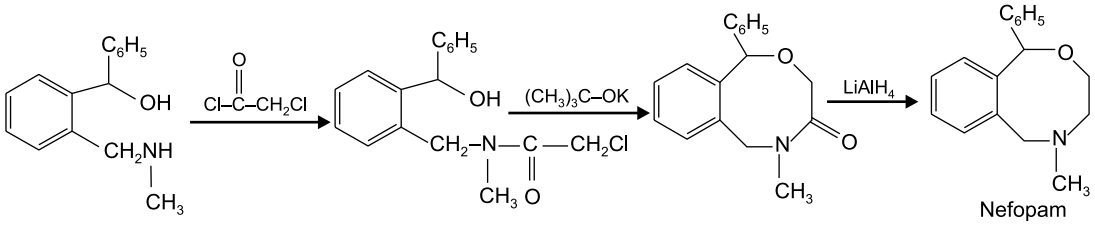
Fletazepam

iii. Nefopam



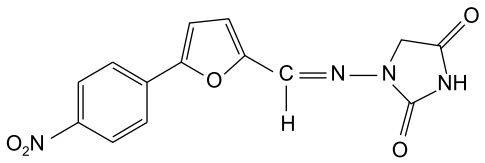
5-Methyl-1-phenyl-3,4,5,6-tetrahydro-
1H-benzo[f][1,4]oxazocine

Synthesis



f. Imidazole analogues

- **Dantrolene** (Dantrium)



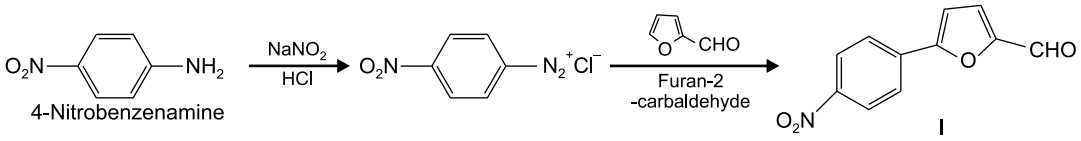
1-((5-(4-Nitrophenyl)furan-2-yl) methyleneamino)imidazolidine-2,4-dione

Mode of action: This does not affect the neuromuscular transmission of membrane action potential, but uncouples contraction from depolarization of muscle membrane. Depolarization triggered release of calcium from sarcoplasmic reticulum is reduced and the contraction of muscle is abolished.

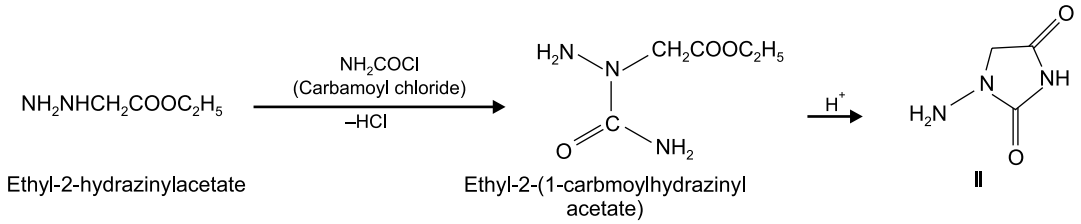
Dose: The initial dose by oral route is 25 mg/day, slowly increased over a period of 7 weeks to 100 mg, three to four times/day.

Synthesis

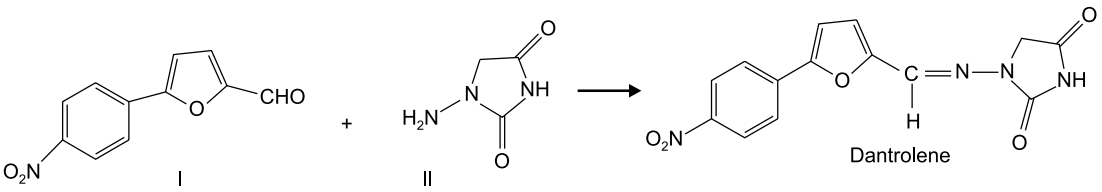
Step I. Synthesis of 5-(4-nitrophenyl)-2-furanal



Step II. Synthesis of 4-aminoimidazolidin-2,4-dione



Step III. Condensation of products of *Steps I* and *II*

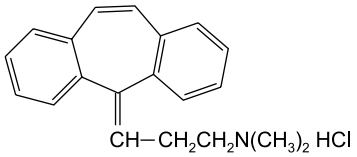


Metabolism: It is slowly metabolized to give 5-hydroxy and acetamide metabolites.

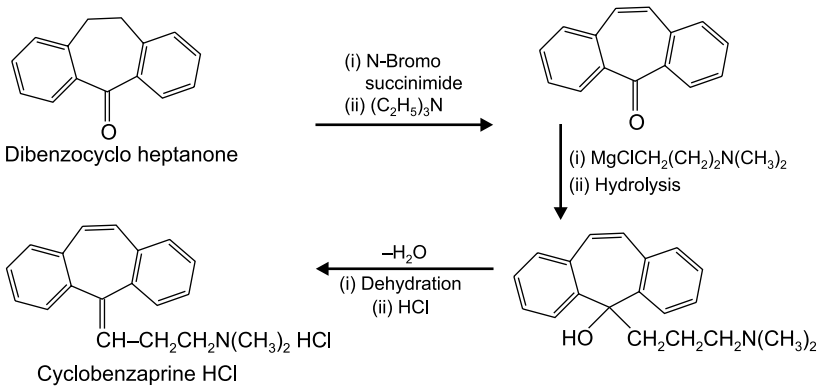
Uses: Used for the control of the spasticity, resulting from spinal cord injury, stroke, and multiple sclerosis.

g. Miscellaneous

i. Cyclobenzaprine HCl

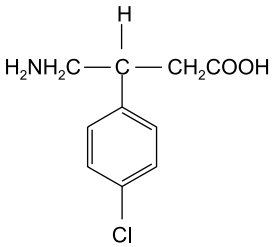


Synthesis



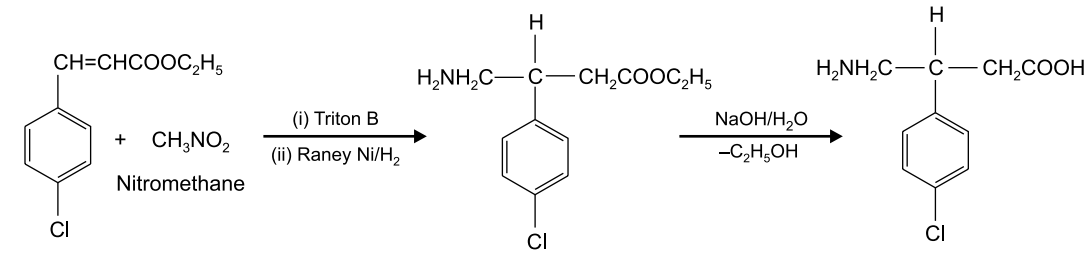
Uses: It is a centrally acting skeletal muscle relaxant that relieves acute and painful muscle spasm.

ii. Baclofen (Liofen, Lioresal)



4-Amino-3-(4-chlorophenyl)butanoic acid

Synthesis



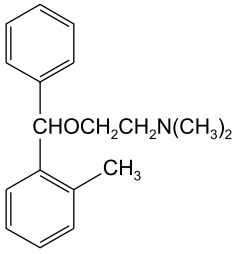
Ethyl-3-(4-Chlorophenyl) acrylate

Baclofen

Uses: Useful in treating spasticity associated with spinal cord tensions, as in multiple sclerosis.

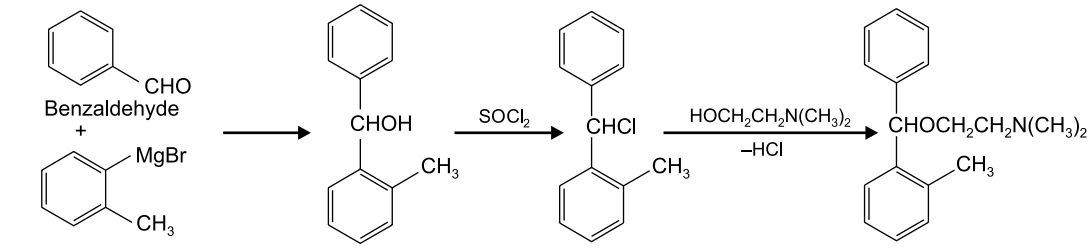
Dose: The initial dose is 5 mg thrice/day increased by 15 mg/day every fourth day to 20 mg thrice/day.

iii. Orphenadrine hydrochloride



N,N-Dimethyl-2-(phenyl(*o*-tolyl)methoxy)ethanamine

Synthesis



o-Tolylmagnesium bromide

Phenyl(*o*-tolyl) methanol

Orphenadrine

Uses: Used in the control of the symptoms of Parkinson's disease.

PROBABLE QUESTIONS

1. How will you classify the neuromuscular blocking drugs? Write the structure, chemical name and uses of any one agent from each category.
2. Explain the following: (a) mode of action of non-depolarizing blockers and (b) depolarizing blockers.
3. Classify the centrally-acting muscle relaxants and give the structure, chemical name, and uses of one important member of each class.

4. Discuss the synthesis of a potent glycerol mono-ether analogue.
5. How will you synthesize meprobamate? Discuss the various steps sequentially.
6. Name an important member of benzoxazole analogue employed as muscle relaxant. Outline its synthesis.
7. Write the structure, chemical name, and uses of dantrolene sodium.
8. Discuss the synthesis of the following important muscule relaxants (a) chlorophenesin carbomate (b) methocarbamol.
9. Describe the mode of action of various types of muscle relaxants by giving specific examples.

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CHAPTER 33

Alzheimer's Disease

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder primarily manifesting as a loss of memory, senile dementia, intraneuronal neurofibrillary tangle formation, and cerebral parenchyma deposition of the β-amyloid protein in the form of amyolid plaques and these constitute the most stereotypic cognitive defects and neuropathological hallmarks of AD. The earliest striking symptom is loss of short-term memory (amnesia). Behavioural disturbances include agitation, aggression, and depressive mood; sleep disorder and anxiety. AD was the 7th leading cause of death in 2004 with 65,829 number of deaths. There are an estimated 24 million people with dementia worldwide.

PATHOGENESIS

It has referred that 11 amino acid sequence of β-amyloid protein is neurotoxic for primary neurons. The cognitive deficits of patients with AD are closely associated with dysfunction of central cholinergic neurotransmission. There is a selective neuronal loss especially on the basal forebrain, which project to hippocampus and neocortex. It is generally believed that there are reductions of muscarinic (mAChR) and nicotinic (nAChR) acetylcholine receptors, which are located on presynaptic cholinergic terminals. Acetylcholinesterase (AChE) has been shown to be promoting the assembly of β-amyloid plaques into fibrils and is suggested to play a pathogenic role in AD by forming a complex, which has higher toxic effect than β-amyloid protein. The oxidative deamination of amines generates neurotoxic agents, that is, NH_3 and H_2O_2. Oxidative stress signalling is speculated in the pathology of AD and other neurodegenerative disorders. The free radicals produced during oxidative stress causes the DNA and RNA oxidation indicated by increased levels of 8-hydroxy-2-deoxyguanosine and 8-hydroxy guanosine, elevated level of protein carbonyl residue and the lipid peroxidation, which are marked by higher levels of thiobarbituric acid reacting substance (TBARS), malondialdehyde (MDA), 4-hydroxy transneoneal (HNE), and isoprostrane. It is hypothesized that β-amyloid protein accumulation and diffuse plaque formation is associated with local microglial activation, cytokine release, reactive astrocytosis, and a multiprotein inflammatory response. There is considerable evidence that the effects of β-amyloid initiated inflammatory and neurotoxic processes, including excessive generation of free radicals and peroxidative injury to proteins and other macromolecules in neurons.

Of all persons with AD, up to 25% of cases are thought to be part of a familial-based inheritance pattern, and therefore, are only determined based on family history or genetic test results. In general, these forms of AD are inherited as an autosomal dominant disorder. There are indications that loss of glutaminergic neurons and glutamate activity in AD patients correlates with the severity of dementia,

and glutaminergic disruption may be involved in the cognitive symptoms of this disorder. There is increasing speculation that AD may be linked aetiologically to the accumulation of aluminium in the brain. AD patients have inconsistently shown low concentration of norepinephrine, dopamine, and dopamine β-hydroxylase. These are often considered to improve the fluency and creativity. Interactions between the serotonergic and cholinergic systems are deregulated and are believed to play a role in the mechanism underlying both major depression and AD.

TREATMENT

There is currently no cure for AD. Currently available medications offer relatively small symptomatic benefit for some patients, but do not slowdown disease progression.

Acetylcholinesterase Inhibitors

Acetylcholinesterase (AChE) inhibition was thought to be important because there is a reduction in the activity of the cholinergic neurons. AChE-inhibitors reduce the rate at which acetylcholine (ACh) is broken down, and hence, increase in the concentration of ACh in the brain (combating the loss of ACh caused by the death of the cholinergic neurons). Tacrine—no longer clinically used; Donepezil—marketed as Aricept; Galantamine—marketed as Razadyne, Reminyl, or Nivalin; Rivastigmine—marketed as Exelon.

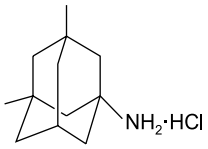
NMDA Antagonists

Recent evidence of the involvement of glutaminergic neuronal excitotoxicity in the aetiology of AD led to the development and introduction of memantine. Memantine is a novel NMDA receptor antagonist, and has been shown to be moderately clinically efficacious.

Tacrine

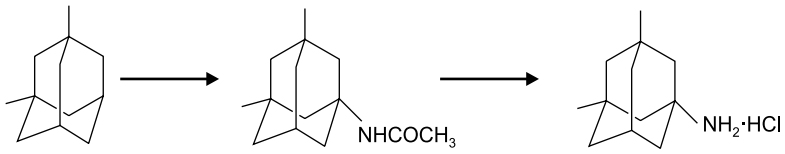
Properties and its uses: It is a parasympathomimetic and a centrally acting cholinesterase inhibitor (anticholinesterase). It was the first centrally acting cholinesterase inhibitor approved for the treatment of AD, and was marketed under the trade name Cognex.

a. Memantine



1-Amino-3,5-dimethyl-adamantane

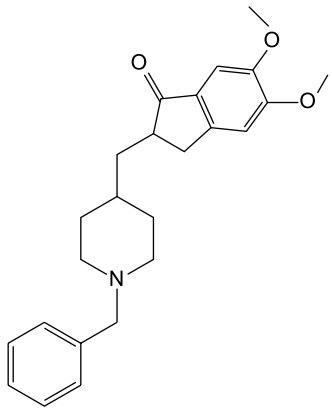
Synthesis



Memantine hydrochloride

Properties and uses: It is the first in a novel class of AD medications acting on the glutaminergic system by blocking NMDA glutamate receptors.

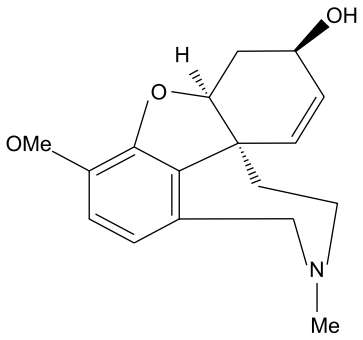
b. Donepezil



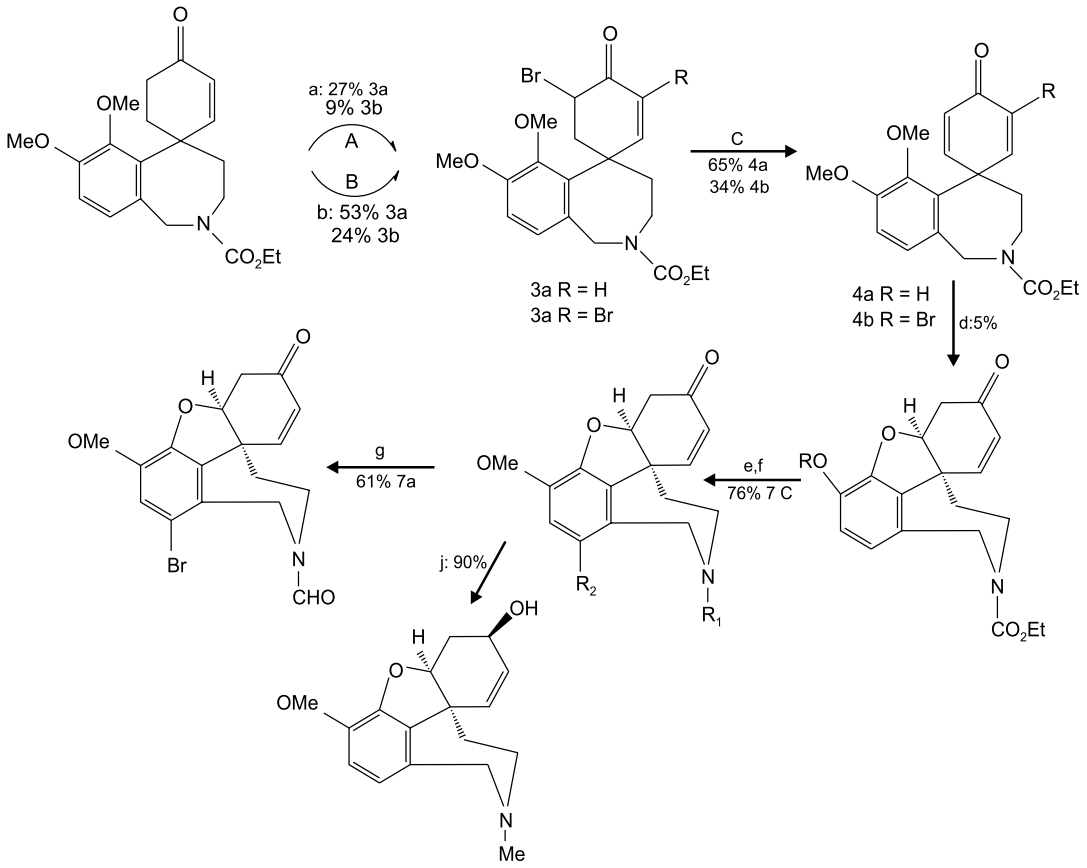
2-((1-Benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one

Properties and uses: It is marketed under the trade name, Aricept, and is a centrally acting reversible acetylcholinesterase inhibitor. Its main therapeutic use is in the treatment of AD where it is used to increase cortical acetylcholine.

c. Galantamine or galanthamine

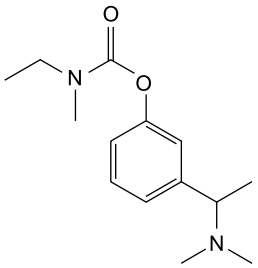


Synthesis



Properties and uses: It is an alkaloid obtained from the bulbs and flowers of the *Caucasian snowdrop* (Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae), and related genera such as *Narcissus* (daffodil), *Leucojum* (snowflake), and *Lycoris,* including *Lycoris radiata* (red spider lily). It is also synthetically prepared. The active ingredient that was isolated from a species traditonally used as a popular medicine in Eastern Europe. It has been used for decades in Eastern Europe especially in the symptomatic treatment of polio (poliomyelitis) and was later developed by Janssen Pharmaceuticals into the Alzheimer medication.

d. Rivastigmine

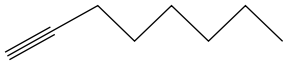


3-(1-(Dimethylamino)ethyl)phenyl ethyl(methyl)carbamate

Properties and uses: It is (sold under the trade name Exelon) is a parasympathomimetic or cholinergic agent for the treatment of mild-to-moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease.

Newer Drugs

Caprylidene (axona) (1-Octyne)



Mode of action: Brain-imaging scans of older adults and those with Alzheimer's disease reveal a dramatically decreased uptake of glucose, the brain's preferred source of energy. It is being developed to replace these depleted glucose levels to treat age-associated memory impairment (AAMI) and Alzheimer's disease. Caprylic triglyceride is converted by the liver into ketone bodies, which provide an alternative fuel for brain cells. Ketone bodies are naturally occurring compounds that are produced mainly by the liver from fatty acids during periods of extended fasting. The formed ketone bodies have the property to protect neuron cells.

Properties and uses: Caprylidene is a medical food that is metabolized into ketone bodies, which the brain can use for energy even when its ability to process glucose is impaired. Caprylidene is used for the clinical dietary management of the metabolic processes associated with mild-to-moderate Alzheimer's disease. Adverse events associated with the use of caprylidene include, diarrhea, flatulence, dyspepsia, dizziness, headache.

Dose: Caprylidene is supplied as a powder for oral formulation. Caprylidene should be administered once daily at breakfast. The recommended dosage is 40 grams (one packet of Axona powder, containing 20 grams MCTs) per day. The contents of each packet of Axona should be added to 4 to 8 ounces (118 to 236 milliliters) of water, as preferred, shaken until fully blended, and consumed immediately.

PROBABLE QUESTIONS

1. What is Alzheimer's disease? Enumerate the various agents used in the treatment of Alzheimer's disease and write the synthesis of any one among them.
2. Write briefly about acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease.
3. Write note on NMDA antagonists used in Alzheimer's disease.

SECTION IV

Drugs Acting on Autonomic Nervous System

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37. Adrenergic Blockers 499
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CHAPTER 34

Autonomic Nervous System

INTRODUCTION

Autonomic nervous system (ANS) represents the unconscious regulation and controls the visceral function. It consists of afferent central connections, and autonomic efferents. The afferent nerves are the first link in the reflex of ANS, which carries non-myelinated fibres from visceral parts to the cerebrospinal axis. Central connections refer to the integration of autonomic reflexes through hypothalamus and the nucleus solitary tract. Autonomic efferents are the principal peripheral connections that are divided into sympathetic and parasympathetic outflow. Neurotransmitter in all the pre- and parasympathetic postganglion fibres is acetylcholine and in sympathetic postganglionic release is norepinephrine. ANS is composed of (1) sympathetic system and (2) parasympathetic system.

SYMPATHETIC SYSTEM

Preganglionic nerves of the sympathetic system arise from the lateral gray horn of 12th thoracic segment and the first two lumbar segments of the spinal cord (thoracolumbar division). They form ganglia in the vertebral chain called paravertebral chain ganglion and supply the postganglionic fibres to effector organs. The principal neurotransmitter is adrenaline, so it is called *adrenergic system*.

Neurotransmission

In adrenergic neurons (sympathetic postganglion), the neurotransmitter released is norepinephrine, which is also called noradrenaline. There are closely related catecholamines (CAs), that is, adrenaline and dopamine that have minor effects secreted by adrenal medulla and in limbic system basal ganglia, respectively.

CAs are synthesized from amino acid phenylalanine. Tyrosine hydroxylase is the rate-limiting enzyme and its inhibition by α-methyl-*p*-tyrosine leads the CAs to dissipate. Other endogenous transmitter, that is, 5-HT produced by aromatic L-amino acid decarboxylase converts DOPAinto dopamine and methyl dopamine, and then, it is converted by dopamine β-hydroxylase to α-methyl norepinephrine. The steps involved in the synthesis of epinephrine and norepinephrine is depicted in Figure 34.1.

Regulation of Catecholamines

Noradrenaline is stored in the synaptic vesicles on the adrenergic nerve endings and released by exocytosis along with the storedadrenaline, ATP and dopamine β-hydroxylase. The CAs are metabolized

by monoamine oxidase (MAO) and catechol-*O*-methyl transferase (COMT) in the liver and other tissues into vanillyl mandelic acid (VMA) and 3-methoxy-4-hydroxy phenyl ethylene glycol with metanephrine and normetanephrine (Figure 34.2).

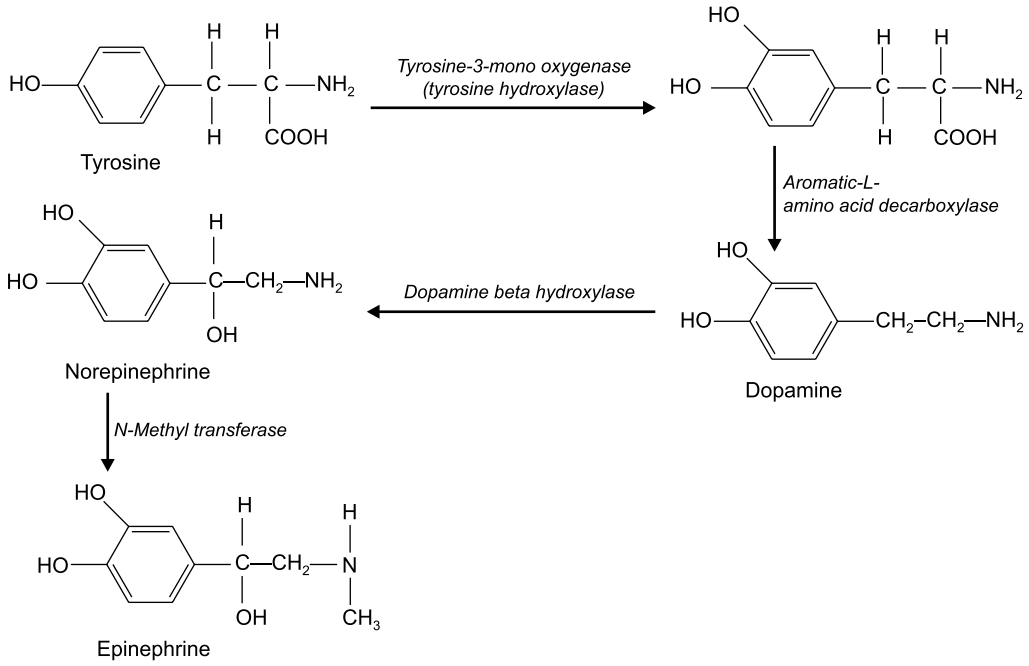


Figure 34.1: Biosynthesis of epinephrine and norepinephrine.

Adrenergic Receptors

They are membrane bound G-protein coupled receptors and classified as α (alpha) and β (beta) adrenoceptors (Table 34.1).

α-Receptors

They are further classified into α_1 and α_2. The selective agonist for α_1 is phenylephrine and antagonist is prazosin. α_2-receptors are stimulated by clonidine selectively and antagonized by yohimbine. Elicitation of α_1-receptors increases phospholipase C, D, A_2, and inositol-triposphate/diacylglycerol IP_3/DAG which contracts smooth muscles, genitourinary tracts, and increase the secretions of glands and in the heart, it increases the force of contraction. α_2-receptor stimulation causes decrease in cyclic AMP, Ca^{2+} L-type channels, and increases the IP_3/DAG. It decreases the insulin secretion, produces platelet aggregation, decreases the release of NE as it has autoregulation mechanism, and causes the vascular smooth muscle contraction.

β-Receptors

The β-receptors are further subdivided into three subtypes and distributed in the body, that is, β_1 (heart), β_2 (bronchi, smooth muscles), and β_3 (adipose tissue). Each has a selective agonist and antagonist. For β_1-receptors, the agonist is dobutamine and antagonists are atenolol and metaprolol. Agonists for β_2 are salbutamol and terbutaline and antagonist is propranolol.

The pharmacology of β-receptors indicate the biochemical increase of adenylcyclase, L-type calcium channels increment through β_1 causes increase in the force and rate of contraction of AV nodal conduction velocity. β_2-receptor stimulates bronchodilation through elicitation of adenylcyclase. β_3-stimulation increases adenylcyclase and causes lipolysis.

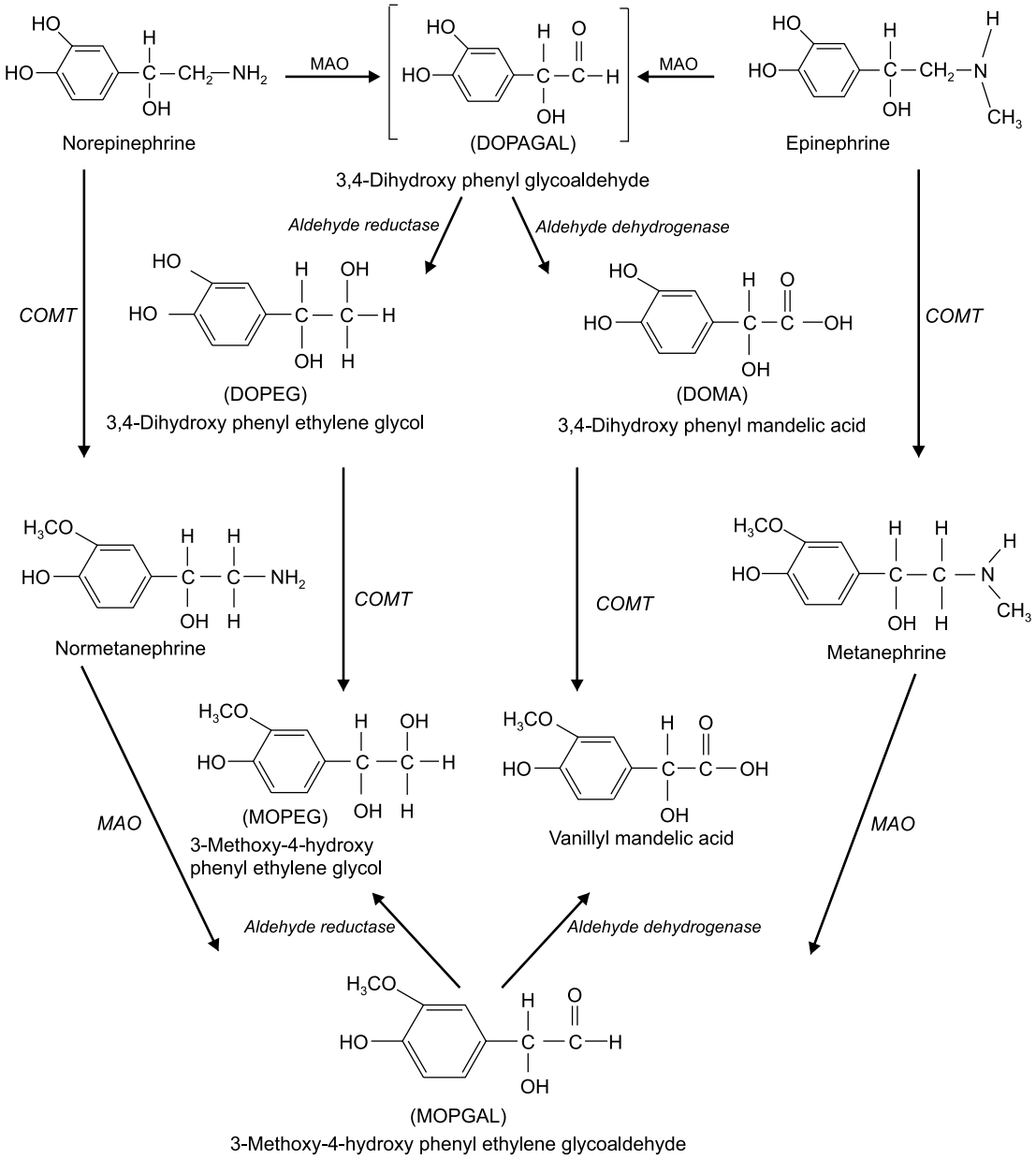


Figure 34.2: Metabolism of catecholamines.

Table 34.1: Distribution of adrenergic receptors and their biological functions

Receptor	*Location*	*Biological function*	*Selective agonist*	*Selective antagonist*
α_1	Postjunctional on effector organs	• GI smooth muscle—contraction • Gland—secretion • Heart—arrythmia	Phenylephrine Methoxamine	Prazosin
α_2	Prejunctional on nerve ending, post-junctional in brain, pancreatic β cells, extra-junctional in certain blood vessels and platelets	• Vasoconstriction, decreased insulin release, platelet aggregation	Clonidine	Yohimbine Rauwolscine
β_1	Heart, juxtaglomerular cells in kidney	Heart—increases rate and force of contraction	Dobutamine	Metoprolol Atenolol
β_2	Bronchi, blood vessels, uterus, liver, GIT, eye	Increases heart rate, blood vessels—dilation, ciliary muscle—dilates	Salbutamol Terbutaline	Butoxamine
β_3	Adipose tissue, detrusor muscle of urinary bladder	Skeletal muscle—thermogenesis Fat—lipolysis, thermogenesis	BRL37344	CGP20712A ICI118551

Parasympathetic System

Preganglionic neurons of parasympathetic system arise from III, VII, IX, and X cranial nerves and 2nd, 3rd, and 4th sacral portion of the vertebra, respectively, so it is named as craniosacral outflow. Acetylcholine (ACh) is the principal neurotransmitter and also called cholinergic neurons.

Neurotransmission

ACh is released into the synaptic vesicles of effectors junction by an impulse across the neuroeffector junction. This leads to the action potential that is due to the difference in the ionic gradients of Na^+ and K^+ equilibrium, and in other tissues, it is mediated along with calcium ion. ACh is synthesized locally in the cholinergic nerve ending by adenosine-triphosphate (ATP) dependent system (Figure 34.3). Choline is actively taken by the axonal membrane and acetylated with the help of ATP and coenzyme-A by the choline acetylase.

Regulation of ACh

ACh is stored in the synaptic vesicles and is extruded by miniature end plate potentials (MEPPs) of action potential. They are metabolized by enzymes acetyl cholinesterase and butyrocholinesterase. These convert the ACh into choline and acetate. ACh esterase comprises of an anionic site that posseses a glutamate residue and an esteric site in which histidine imidazole ring and a serine –OH group are present.

Hydrolysis of ACh involves electrostatic attraction of positively charged N^+ of ACh to aromatic pocket of ACh esterase and neucleophilic attack by serine –OH and activation. Hydrolysis, transfers acetyl group to serine –OH group, leaving acetylated enzyme molecule and free choline.

Cholinergic Receptors

These receptors comprise of G-protein coupled with muscarinic and ligand gated channelled nicotinic receptors.

Muscarinic Receptors

These are selectively stimulated by muscarine. The action of muscarinic receptors may be excitatory or inhibitory. They are primarily located in the heart, blood vessels, smooth muscles, and gastrointestinal tract (GIT), sweat glands and urinary tract. There are five subtypes, that is, M_1, M_2, M_3, M_4, and M_5. M_1 present in the autonomic ganglia causes depolarization and also histamine release and secretes acid from gastric glands. These functions are mediated through IP_3/DAG and increase in cytostolic Ca^{2+}. Specific antagonist is oxotremorine and agonists are pirenzepine and telenzepine. M_2 is found in the sinoatrial (SA) and atrioventricular (AV) node of the heart, which decreases the rate of impulse generation and velocity of conduction, respectively. In addition, it decreases the contractility. These functions mediated through K^+ channel opening decreased cAMP.

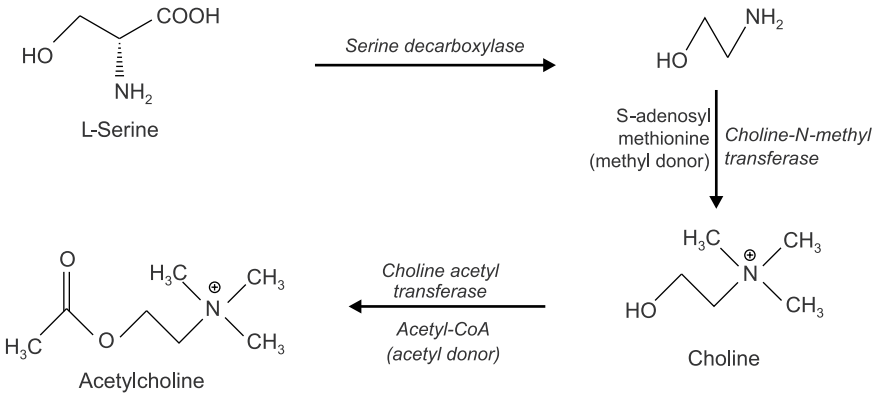


Figure 34.3: Biosynthesis of acetylcholine.

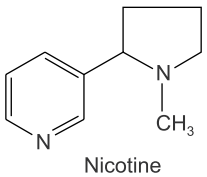
M_3 found in the visceral smooth muscle causes contraction, exocrine glands cause secretion, vascula endothelial release of nitiric oxide (NO) causes vasodilatation. The mechanism of the receptor is IP_3/DAG elicitation and increase in Ca^{2+}. The antagonist is hexahydrosiladifenidol and the agonist is bethanecol. M_4 is similar to M_2 and M_5. M_1 is similar to M_1 present in CNS.

Nicotinic Receptors

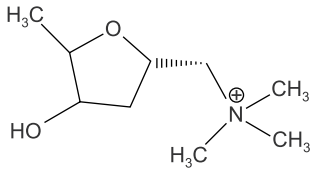
These receptors are selectively agonized by nicotine and blocked by D-tubocurarine or hexamethonium. The receptors are pentameric structured and further divided into N_M and N_N.

N_M present in neuromuscular junctions cause depolarization of muscle end plate leading to contraction of skeletal muscles. The transduction mechanism is through the opening of Na^+ and K^+ channels.

N_N is present in autonomic ganglia, in adrenal medulla, and in CNS. In the ganglia level, it causes depolarization and mediates the postganglionic impulse. In adrenal medulla, it stimulates the CA release through the opening of Na^+ and Ca^{2+} channels.



Nicotine



Muscarine

CHAPTER 35

Adrenergic Drugs

INTRODUCTION

Sympathetic nervous system is an important regulator of the activities of the vital organs, such as heart and peripheral vasculature, especially in response to stress. The effect of sympathetic stimulation is mediated by the release of norepinephrine from the nerve terminals that serve to activate the adrenoreceptors on postsynaptic sites. Also, in response to a variety of stimuli, such as stress, the adrenal medulla releases epinephrine, and it is transported in the blood to the target tissues. Drugs that mimic the action of sympathetic system are called sympathomimetic drugs. Like cholinomimetic drugs, the sympathomimetics can be grouped by their mode of action and by the spectrum of receptors. Some of the drugs (e.g. epinephrine, norepinephrine) act by a direct mode, that is, they interact with and activate adrenoceptor. Others act indirectly; their actions are dependent on the release of endogenous catecholamine. These indirect agents may have either of the different mechanisms:

1. Displacement of stored catecholamine from adrenergic nerve ending (e.g. amphetamine and tyramine).
2. By inhibition of reuptake of catecholamine already released (e.g. cocaine and tricyclic antidepressants).
3. Some drugs have both direct and indirect action.

PHYSIOLOGICAL BASIS OF ADRENERGIC RECEPTOR FUNCTION

The important factors in this function are the response of any cell or organ to the sympathomimetic amines due to the density and proportion of α- and β-adrenergic receptors, including their subtypes (discussed in section IV, Chapter 34, 'Autonomic Nervous System'). For example, norepinephrine has relatively little capacity to increase the bronchial airflow, the receptors in the bronchial smooth muscle are largely of β-subtype. In contrast, isoproterenolol and epinephrine are potent bronchodilators. Cutaneous blood vessels physiologically express almost exclusively α-receptors; thus, norepinephrine and epinephrine cause constriction of such vessels, whereas isoproterenolol has little effect. Most of the actions of sympathomimetics are broadly classified into seven types:

1. Peripheral excitatory action on certain types of smooth muscles (i.e. blood vessels supplying skin, kidney, mucous membrane, and glands).
2. A peripheral inhibitory action on certain other types of smooth muscles (i.e. gut, bronchial tree, and blood vessels supplying skeletal muscle).
3. Cardiac excitation leads to increase in the heart rate.

4. Metabolic action (i.e. glycogenolysis in tissues and muscle, liberation of fatty acids).
5. Endocrine actions (i.e. increase in release of hormones).
6. CNS stimulation (i.e. psychomotor stimulation, wakefulness, and respiratory stimulation).
7. A presynaptic action that results in either inhibition or excitation, physiologically the inhibitory action is more than excitatory motion.

Therapeutically, these agents are classified into the following:

- *Pressor agents*: Noradrenaline, ephedrine and dopamine
- *Cardiac stimulants*: Adrenaline, dobutamine and isoprenaline
- *Bronchodilators*: Isoprenaline, salbutamol, terbutaline, formeterol
- *Nasal decongesents*: Phenylephrine, naphazoline, pseudoephedrine
- *CNS stimulants*: Amphetamine, methamphetamine, dexamphetamine

Mechanism of Action of Sympathomimetics

β_1-Adrenergic Receptor Action

The β-adrenergic actions are mediated through cyclic AMP (cAMP). Adrenaline activates membrane bound enzyme adenylcyclase through regulatory protein Gs. Adenosine triphosphate (ATP) is broken into cAMP at the inner face. In the heart, proteins such as troponin and phospholamban, are phosphorylated and results in increased interaction with calcium at myofilaments, leading to increased force of contraction.

β_2-Adrenergic Receptor Action

β_2-receptors are predominantly found in the respiratory system. The β_2-receptor agonist produces bronchodilation by binding with the β_2-receptors.

α_1-Adrenergic Receptor Action

Stimulation of α_1-adrenergic receptors elicits a primary mode of signal transduction that involves the mobilization of intracellular Ca^{2+} from endoplasmic stores. This increase in intracellular Ca^{2+} is thought to result from the activation of phospholipase C_β isoforms through G_q family of G protein. The hydrolysis of membrane bound polyphosphoinositides through phospholipase *C* results in generation of diacylglycerol (DAG) and inositol-1,4,5-triposphate (IP_3). IP_3 stimulates the release of Ca^{2+} from intracellular stores. In smooth muscles, increased intracellular Ca^{2+} causes contraction, mediated by Ca^{2+} sensitive protein kinases, that is, calmodulin-dependent myosin light chain kinase.

α_2-Adrenergic Receptor Action

α_2-adrenergic receptors activate G protein gated K^+ channels resulting in hyperpolarization. These α_2-receptors are also capable of inhibiting voltage gated Ca^{2+} channels mediated by G protein and also activates the mitogen activated protein kinase (MAPK). These lead to activation of a variety of tyrosine kinase mediated downstream events, and these inhibit the release of norepinephrine from nerve endings and suppress the sympathetic outflow to the brain.

GENERAL CLASSIFICATION OF ADRENERGIC AGONISTS

Adrenergic agents are divided into three classes:

I. Direct-acting adrenergic agonists

They bind to and activate α_1-, α_2-, β_1-, and β_2-receptors. Naturally occurring molecules, which bind to these receptors include NE (a neurotransmitter which binds to α_1-, α_2-, and β_1-receptors), epinephrine (a hormone produced in and secreted from the adrenal medulla, which binds to α_1-, α_2-, β_1-, and β_2-receptors; it is a non-selective adrenergic agonist), and dopamine (also a neurotransmitter, which binds to α_1-, α_2-, and β_1-receptors).

Examples of drugs: Xylometazoline, phenylephrine, methoxamine.

II. Indirect-acting adrenergic agonists

They produce NE-like actions by stimulating NE release and preventing its reuptake and produces activation.

Example: Tyramine.

III. Dual-acting adrenergic agonists

These agents act as direct and indirect adrenergic agonists (hence, dual-acting). They bind to adrenergic receptors and stimulate NE release.

Examples: Ephedrine, amphetamine, mephenteramine.

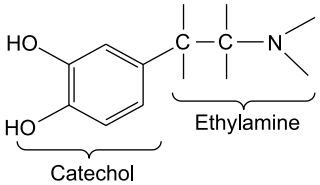
Classifications Based on Therapeutic Uses

- Adrenergic drugs used for raising blood pressure (vasoconstrictors): Noradrenaline, metaraminol
- Drugs used for their ionotropic action on the heart: Dopamine, dobutamine, xamoterol, amrinone
- Drugs used as central stimulants: Amphetamine (benzedrine)
- Drugs used as smooth muscle relaxants: Adrenaline (epinephrine), isoprenaline, isoxsuprine
- Selective β-stimulant: Salbutamol
- Drugs used in allergic reactions: Adrenaline, ephedrine
- Drugs used as local vasoconstrictors: Adrenaline, phenylephrine, naphazoline
- Drugs used for suppressing the appetite: Fenfluramine, phenteramine, amphetamine

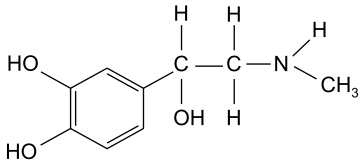
Classification Based on Chemical Structures

I. Catecholamines

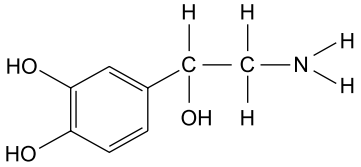
Compounds with hydroxyl (–OH) substitution in the third and fourth position of the benzene ring are termed as catecholamines.



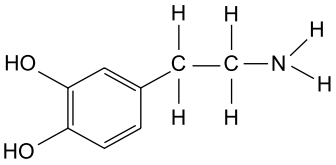
a. Adrenaline



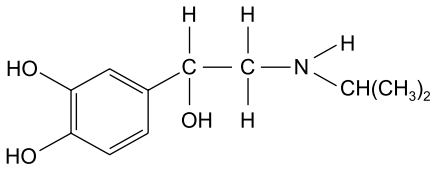
b. Noradrenaline



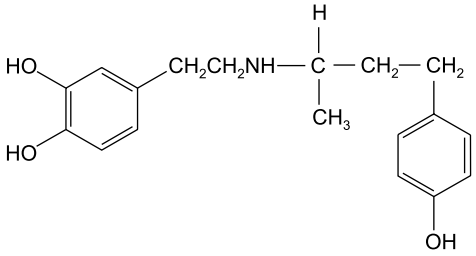
c. Dopamine



d. Isoprenaline



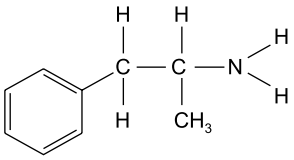
e. Dobutamine



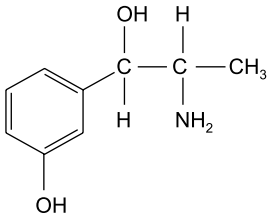
II. Non-catecholamines

Those compounds that lack the hydroxyl at third and fourth position of the benzene ring are non-catecholamines. They release noradrenaline or dopamine from the sympathetic neurons. This indirect action produces effects mainly resembling those of externally administered noradrenaline.

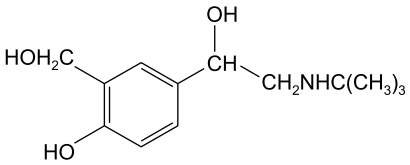
a. Amphetamine



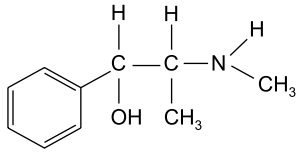
b. Metaraminol



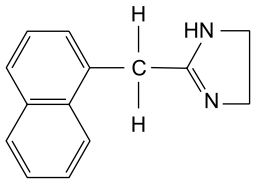
c. Salbutamol



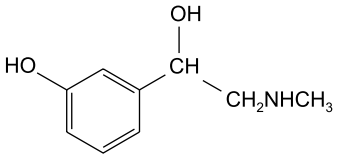
d. Ephedrine



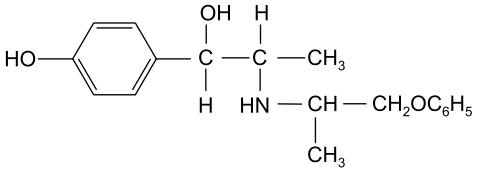
e. Naphazoline



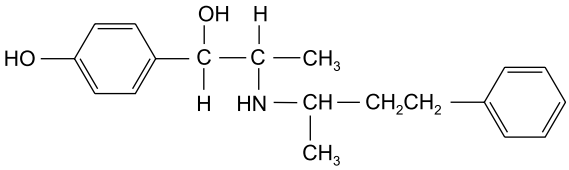
f. Phenylephrine



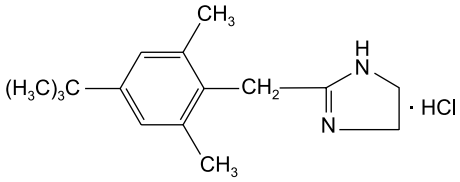
g. Isosupurine



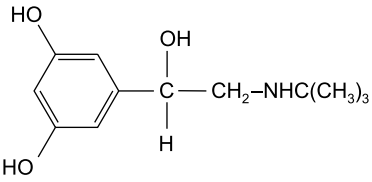
h. Nylidrine



i. Xylometazoline



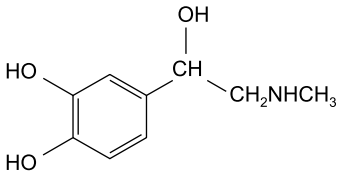
j. Terbutalin



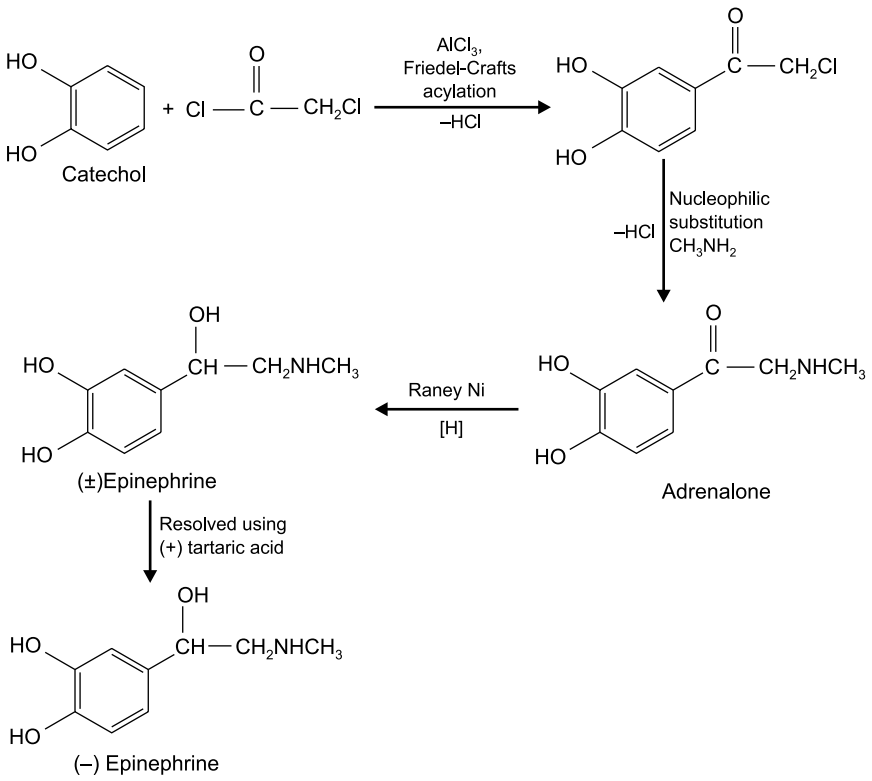
SYNTHESIS AND DRUG PROFILE

I. Catecholamines

a. Adrenaline (Synonym: Epinephrine)



Synthesis



Metabolism of adrenaline and noradrenaline (catecholamines): Endogenous and exogenous catecholamines are metabolized by two enzymes monoamino oxidase (MAO) and catechol-*O*-methyl transferase (COMT). MAO converts catecholamines to their corresponding aldehydes, and in the periphery, the aldehydes are rapidly metabolized by aldehyde dehydrogenase to the corresponding carboxylic acid. In case of noradrenaline, this yields dihydroxy mandelic acid (DOMA). The second major pathway for catecholamine metabolism involves the methylation on one of the catechol –OH groups to give methoxy derivatives. *O*-Methylation of noradrenaline gives rise to a metabolite normetanephrine. Normetanephrine undergoes metabolism by MAO and 3-methoxy-4-hydroxy mandelic acid [vanillyl mandelic acid (VMA)] is formed, which is the main final metabolite of adrenaline and non-adrenaline.

Properties and uses: Adrenaline is a catecholamine and belongs to the family of biogenic amines. It is a white or creamy white, sphaerocrystalline powder. It dissolves in solutions of mineral acids, potassium hydroxide, and of sodium hydroxide, but sparingly soluble in water, insoluble in ethanol and ether. It is used as a sympathomimetic, broncholytic, and antiasthmatic. It is used to prevent bleeding during surgery or in case of inner organ bleeding. Because adrenaline leads to constriction of blood vessel, it is administered in combination with local anaesthetics. In this combination, anaesthetics have long-lasting effect and can be administered in smaller doses. It is used in the treatment of heart block or circulatory collapse and open-angle glaucoma. It is usually the drug of choice in acute allergic disorders and histamine reactions.

(R)-Epinephrine is 12 times more active than S form. It has a potent stimulatory effect on both α- and β-adrenergic receptors and is light sensitive and easily oxidized on exposure.

Adrenaline is a potent stimulant for both α- and β-receptors, predominately on the β_1-receptor of myocardium and pacemaker. The mechanism of rise in blood pressure is by

- direct myocardial stimulant (positive ionotropic action),
- increase in heart rate (positive chronotropic action), and
- vasoconstrictor in the vascular beds.

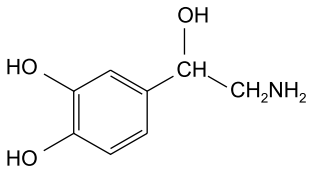
Assay: It is assayed by non-aqueous titration, the solution of the substance is titrated with 0.1 M perchloric acid, using crystal violet indicator.

Storage: Epinephrine is light sensitive and easily oxidized on exposure to air because of the catechol ring system. The development of a pink to brown colour indicates oxidative breakdown. To minimize oxidation, solutions of the drug are stabilized by the addition of a reducing agent, such as sodium bisulphite. Adrenaline should be stored in well-closed airtight containers, which is preferably filled with nitrogen, and protected from light.

Dose: By subcutaneous, 0.2 to 0.5 mg in 0.1% solution; intramuscularly 1 to 3 mg in a 0.2% oil suspension, repeated as required.

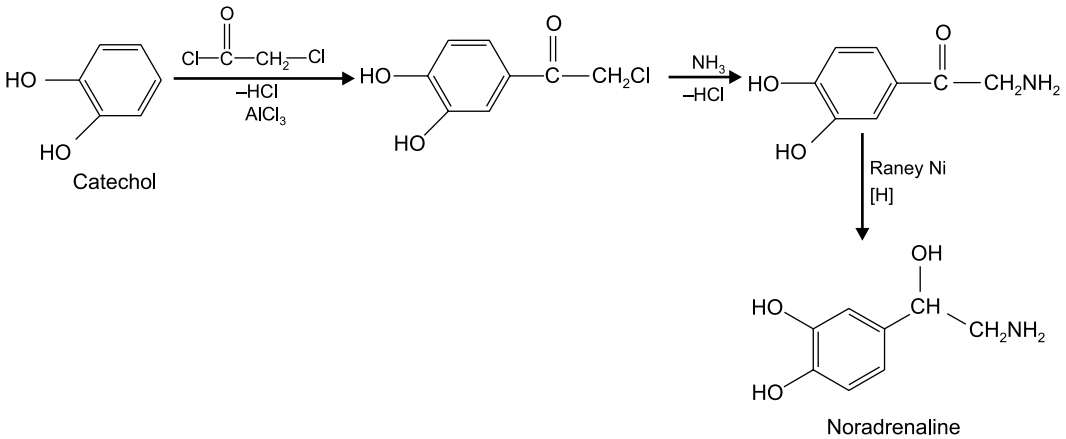
Dosage forms: Adrenaline injection IP, adrenaline eyedrops/epinephrine eyedrops BP, dilute adrenaline injection (1 in 10,000)/dilute epinephrine injection (1 in 10,000) BP.

b. Noradrenaline (Synonym: Norepinephrine, Nephridine)



L-1-(3,4-Dihydroxy phenyl)-2-amino ethanol

Synthesis



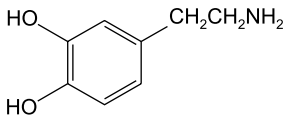
Noradrenaline

Properties and uses: It is a white or brownish-white, crystalline powder, slightly soluble in ethanol and soluble in water. It differs from adrenaline only by lacking the methyl substitution on the amino ethanol. L-Isomer is pharmacologically active. Noradrenaline is a potent agonist for α_1-receptors and has relative actions on β_2-receptors. By acting on these receptors, the systolic and diastolic pressures, and usually, pulse pressure are increased. It increases the peripheral vascular resistance. Its principle use is to support blood pressure in various acute hypotensive states, especially in myocardial shock. It is used as a vasoconstrictor in some local anaesthetic solutions for dental use.

Assay: Dissolve the sample in acetic anhydride and add anhydrous formic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It becomes coloured on exposure to air and light. It should be stored in well-closed airtight containers, preferably in a sealed tube under vacuum or under an inert gas and protected from light.

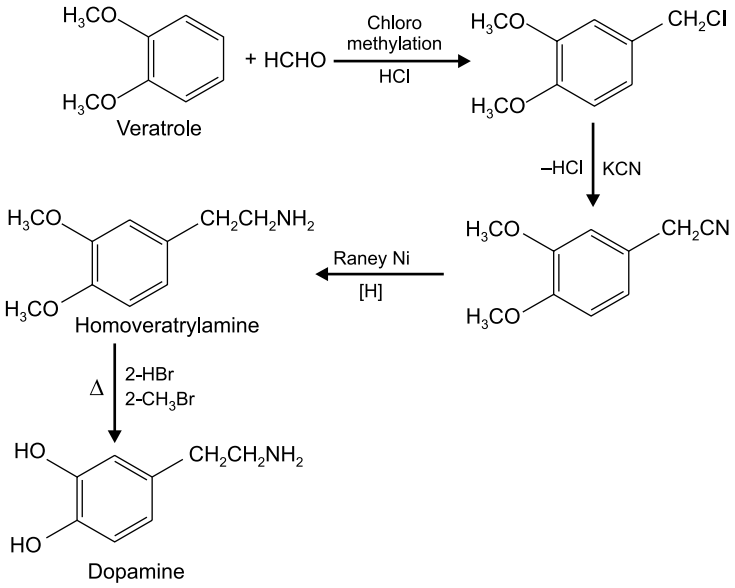
c. Dopamine (Domin, Dopacard)



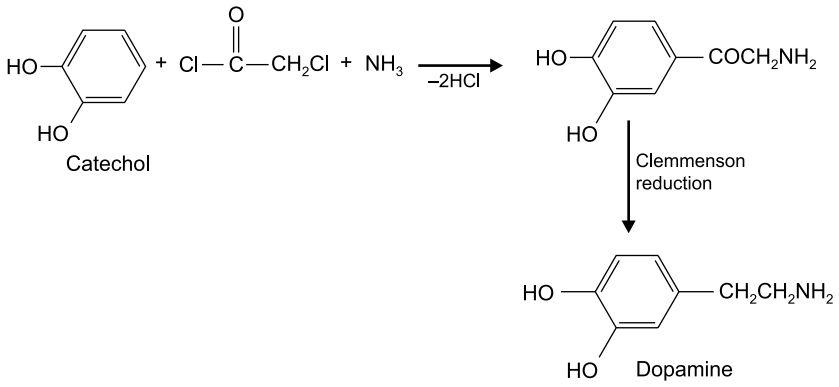
2-(3,4-Dihydroxy phenyl)-1-amino ethane

Synthesis

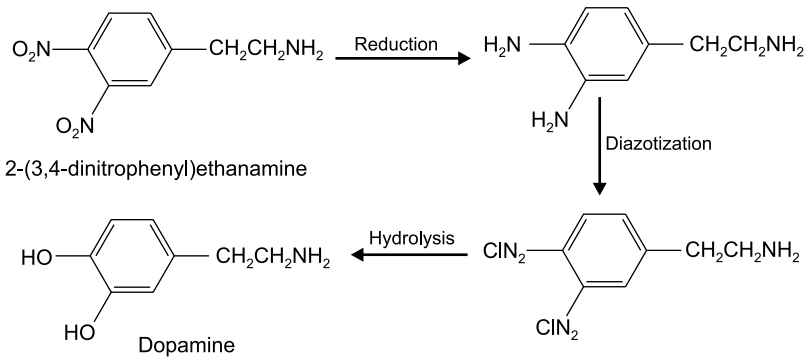
Route I. From: Veratrole



Route II. From: Catechol



Route III. From: 2-(3,4-dinitrophenyl) ethanamine



Properties and uses: It is a white or almost white crystalline powder, soluble in alcohol, sparingly soluble in acetone and methylene chloride, but freely soluble in water. It is used in the treatment of shock. It is ineffective orally in large parts because it is a substrate for both MAO and COMT. Dopamine exerts the CVS effects by interacting with D_1-dopaminergic receptors especially in the renal, mesenteric, and coronary beds. At high concentrations, dopamine acts on β_1-adrenergic receptors and causes positive ionotropic effects and also dopamine causes the release of norepinephrine.

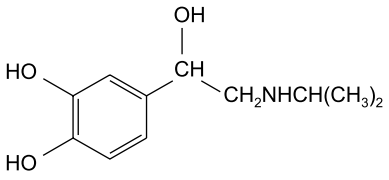
Assay: Dissolve the sample in anhydrous formic acid and add acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: Acute heart failure: Adult—initially, 1–5 µg/kg/min increased gradually by up to 5–10 µg/kg/min according to the patient's BP, cardiac output, and urine output. Up to 20–50 µg/kg/min may be required in seriously ill patients.

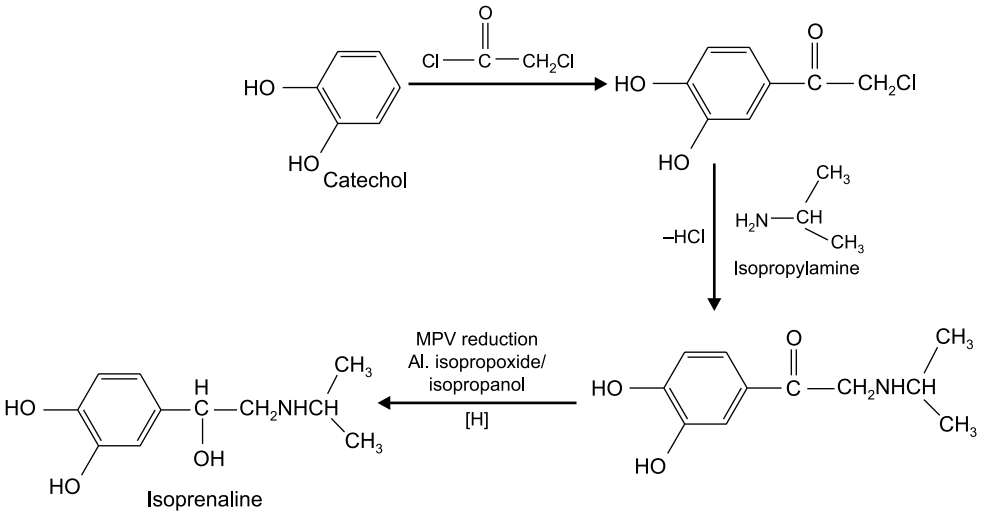
Dosage forms: Dopamine intravenous infusion BP.

d. Isoprenaline (Synonym: Isoproterenol, Isoprim, Isosol, Neo-Epinin)



1-(3,4-Dihydroxy phenyl)-2-isopropylamino ethanol

Synthesis



Metabolism: It is metabolized in the liver and other tissues by catechol-*O*-methyl transferase, which transfers the $–CH_3$ group to the –OH group. It acts as poor substrate for MAO, and it undergoes sulphate conjugation.

Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, sparingly soluble in alcohol, practically insoluble in methylene chloride. It is a synthetic isopropyl analogue of adrenaline, acting almost exclusively at β-receptor. It stimulates the action of adrenaline and has the advantage of being effective when given orally. It is a non-selective β-agonist and has strong β_1- and β_2-agonist activity. Its primary use is in the treatment of bronchial asthma. It is used as an antiarrhythmic agent and in the treatment of shock to increase heart rate.

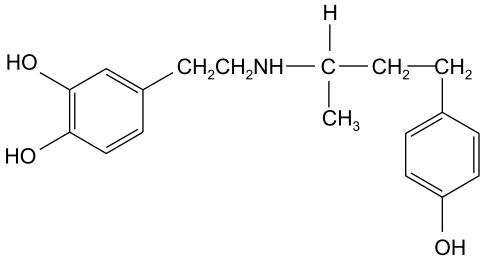
Assay: Dissolve the sample in anhydrous formic acid and add acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: Sublingual, 10 to 15 mg three to four times/day; IM or SC 0.01 to 0.2 mg; repeated as necessary; infusion, 1 to 2 mg per 500 ml of 5% dextrose infusion at such a rate so as to maintain blood pressure.

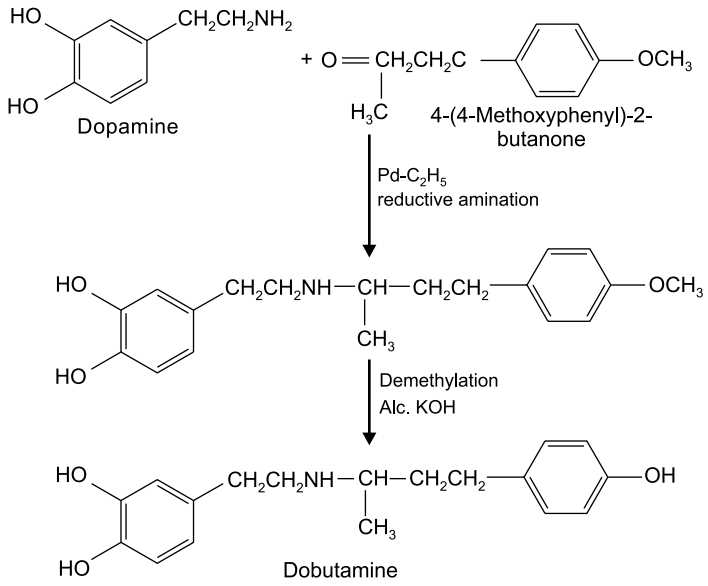
Dosage forms: Isoprenaline HCl injection IP, isoprenaline sulphate tablets IP, isoprenaline injection BP.

e. Dobutamine (Cardiject, Dotamin, Kardia)



N-[1-Methyl-3-(4-hydroxy phenyl)propyl]3,4-dihydroxy phenyl ethylamine

Synthesis



Metabolism: It is metabolized by COMT and conjugation, but not by MAO.

Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water and alcohol, and soluble in methanol. It resembles dopamine chemically, but possesses a bulky aromatic residue on the amino group despite the absence of a β-OH group. This substitution gives a compound that possesses an asymmetric carbon atom. Thus, dobutamine exists as a pair of enantiomers possessing a distinct pharmacology. The (+) enantiomer is a potent agonist at both β_1- and β_2-receptors. The (–) enantiomer is 10 times less potent at β_1- and β_2-receptors. The (–) enantiomer is a potent agonist at α_1-receptors. It acts by directly interacting with α- and β-adrenergic receptors. Racemic dobutamine increases the inotropic action due to α_1-receptor when compared to chronotropic actions, and the effects are mediated by β-receptors. It enhances the automaticity of SA node.

Storage: It should be stored in well-closed airtight containers and protected from light.

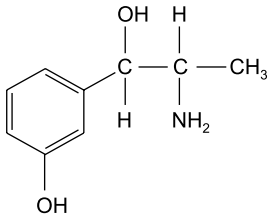
Assay: Dissolve the sample in anhydrous formic acid and add acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Dose: For acute heart failure: For adult—2.5–10 µg/kg, up to 0.5–40 µg/kg according to patient's heart rate, cardiac output, BP, and urine output. For cardiac stress test: Adult—5 µg/kg/min for 8 min using 1 mg/ml solution, dose is then increased at 5 µg/kg/min until 20 µg/kg/min, with each dose being infused for 8 min before the next increase.

Dosage forms: Dobutamine intravenous infusion BP.

II. Non-catecholamines

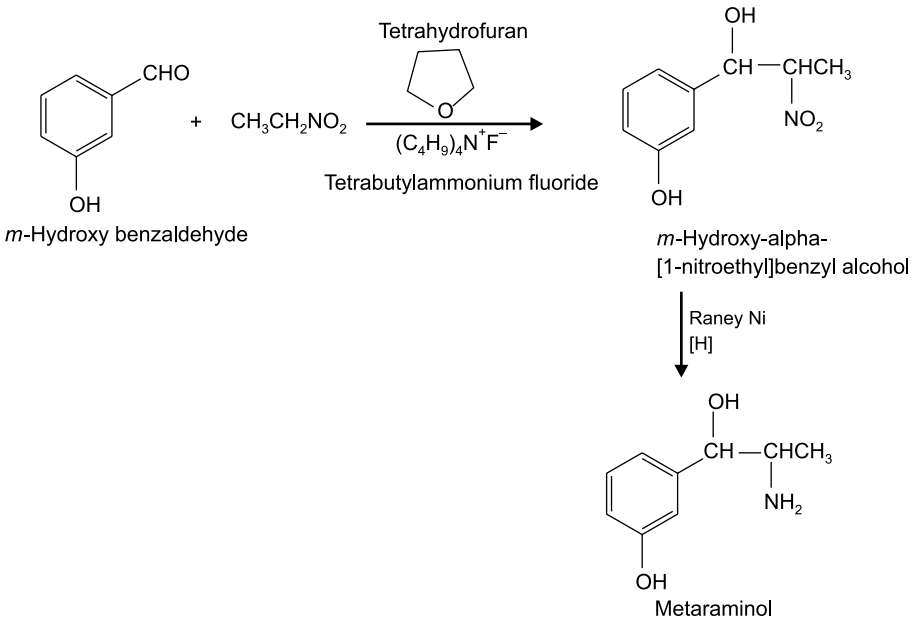
a. Metaraminol (Aramine)



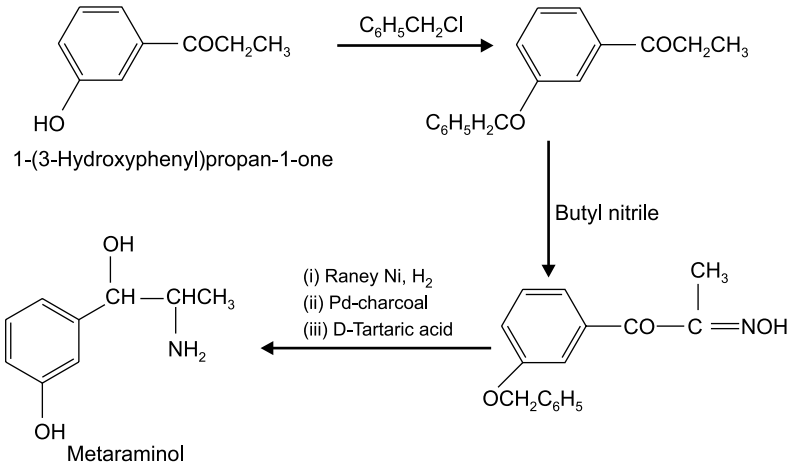
2-Amino-1-(3′-hydroxy phenyl)propanol

Synthesis

Route I. From: *m*-Hydroxy benzaldehyde



Route II. From: 1-(3-hydroxyphenyl)propane-1-one



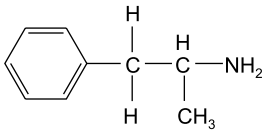
Properties and uses: It is a white crystalline powder, insoluble in ether, slightly soluble in ethanol, and freely soluble in water. It is structurally similar to phenylephrine. It enhances cardiac output, peripheral resistance, and blood pressure. It helps to increase the coronary blood flow thereby decreasing the heart rate. The drug is employed frequently in acute hypotensive states, such as anaphylactic shock or shock secondary to myocardial infarction and trauma.

Assay: It is assayed by non-aqueous titration—the solution of the substance is titrated with 0.1 M perchloric acid using crystal violet indicator.

Dose: By IV 0.5 to 5 mg in an emergency; by infusion, 15 to 100 mg/500 ml of dextrose injection or sodium chloride injection; by IM 2 to 12 mg.

Dosage forms: Metaraminol injection BP.

b. Amphetamine (Synonym: Benzedrine)



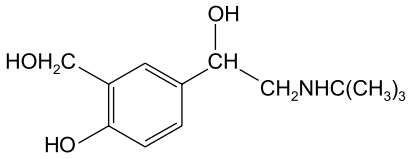
(+)-1-Phenyl-2-amino propane

Synthesis

It is synthesized by reductive amination by phenyl acetone.

Properties and uses: The racemic mixture has a higher proportion of cardiovascular effects than the dextro isomer. For most medical uses, the dextrorotatory isomer is preferred. It is one of the most important sympathomimetic agents. CNS stimulant effect is due to stimulation of the cortex. The D-isomer is three to four times more potent than the L-isomer. It also has an anorexic action and can be used in the treatment of obesity.

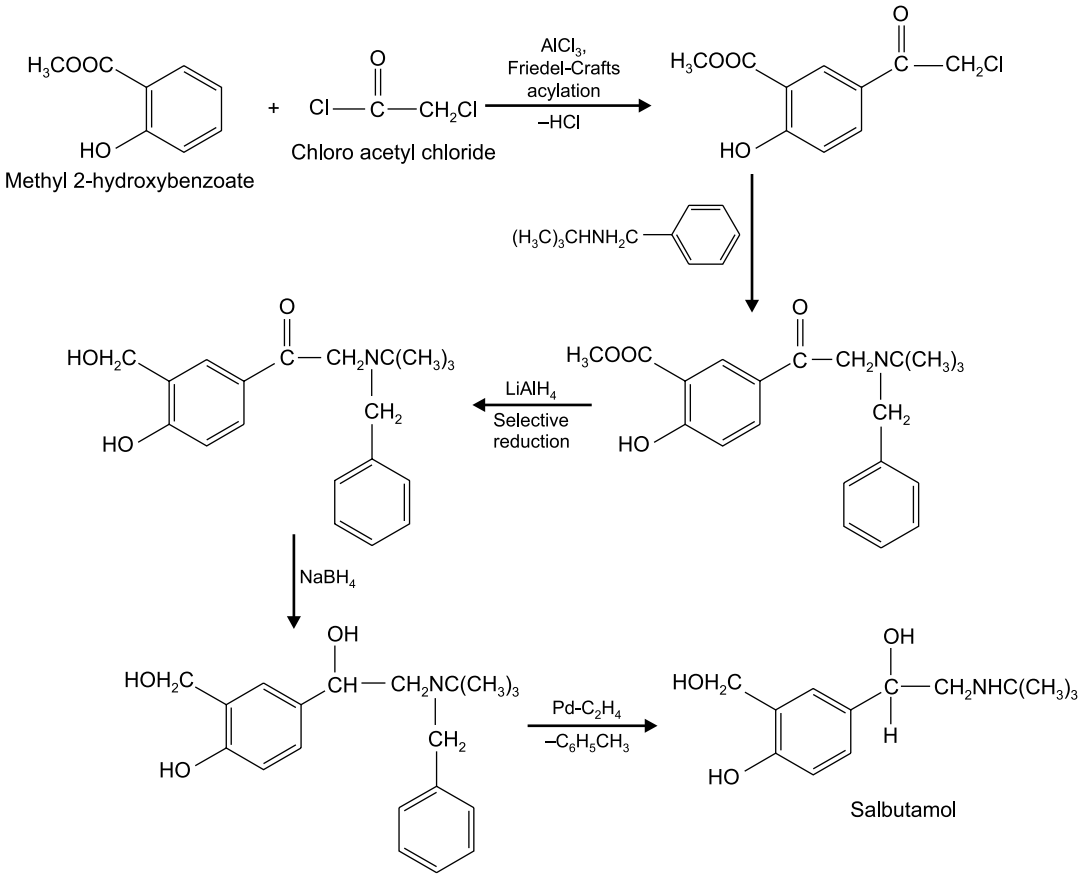
c. Salbutamol (Synonym: Albuterol, Asthalin, Salbid)



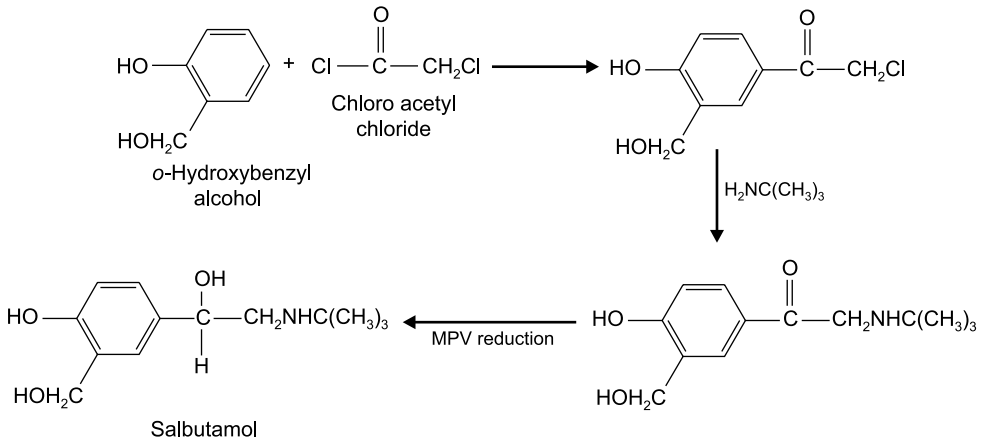
4-Hydroxy-3-hydroxy methyl-alpha-[(*tert*.-butylamino)methyl]benzyl alcohol

Synthesis

Route I. From: Methyl-2-hydroxybenzoate



Route II. From: *o*-Hydroxybenzyl alcohol



Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water, but freely soluble in ethanol. It has strong β_2-adrenergic activity. It is useful in the treatment of acute myocardial infarction, severe left ventricular failure. It has been used to arrest premature labour and is effective in ocular hypotension by topical application. It is used only as a bronchodilator and is the drug of choice in the treatment of bronchial asthma.

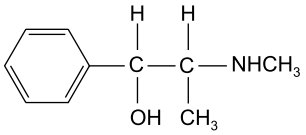
Assay: Dissolve the substance in alcohol, to this add 0.1 M hydrochloric acid, titrate with 0.1 M sodium hydroxide using methyl red as indicator. End point is the appearance of yellow colour.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: By oral inhalation, the adult dose is 100 microgram, followed by a second dose after 5 min, if required.

Dosage forms: Salbutamol tablets and inhaler IP, salbutamol pressurized inhalation BP.

d. Ephedrine (Epipres)

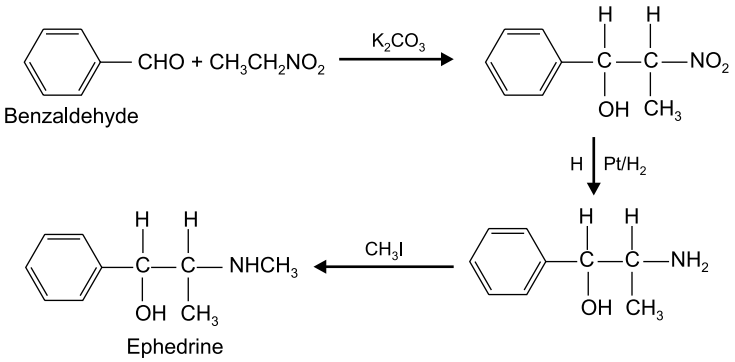


2-Methylamino-1-phenyl propan-1-ol

Metabolism: It is metabolized by COMT.

Properties and uses: Occurs as a waxy solid and as crystals, and has a characteristic pronounced odour. It is soluble in alcohol, water, and organic solvent. Ephedrine has two assymetric carbon atom and four optical isomers. The erythroracemate is called ephedrine. It has both α- and β-adrenergic agonistic effect. It is used in a variety of conditions, such as allergic disorder, colds, hypotension conditions, and narcolepsy. Also, occasionally, used to treat enuresis to dilate the pupil.

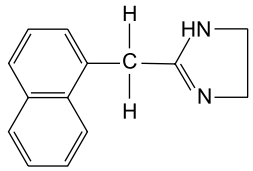
Synthesis



Assay: A sample is dissolved in alcohol and to this add 0.1 N HCl. The solution is titrated with 0.1 N NaOH, using methyl red as indicator.

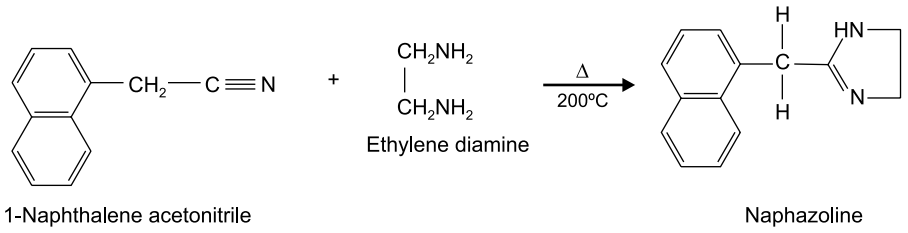
Dose: The usual dose is 10 to 25 mg every 3 to 4 h.

e. Naphazoline (Ocucel Eyedrops)



2-(1-Naphthyl methyl)-2-imidazoline

Synthesis



1-Naphthalene acetonitrile — Naphazoline

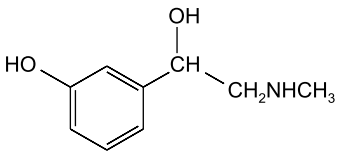
Properties and uses: It is a white crystalline, odourless, and bitter compound. The salt is soluble in water and in alcohol. They essentially exist in an ionized form at physiological pH because of the very basic nature of the imidazoline ring (pK_a 9 to 10). It is a directly acting sympathomimetic drug, which is mostly used as a local vaso-constrictor for the relief of nasal congestion due to allergic or infarction manifestations. It is also employed as an ophthalmic solution for the relief of ocular congestion and blepharospasm.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol. Titrate with 0.1 M sodium hydroxide and determine the end point by potentiometric titration.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For nasal mucosa, 2 drops of 0.05% solution; for conjunctivity, 1 to 2 drops of a 0.1% solution after every 3 to 4 hours.

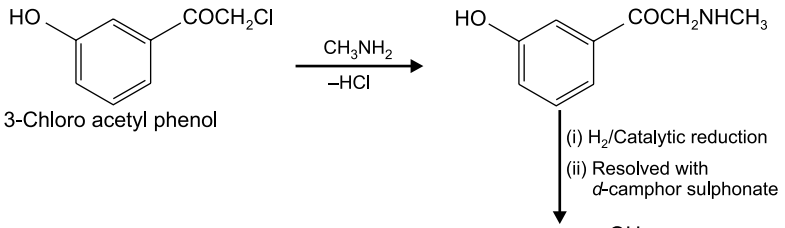
f. Phenylephrine



1-(3-Hydroxy phenyl)-2-methylamino ethanol

Synthesis

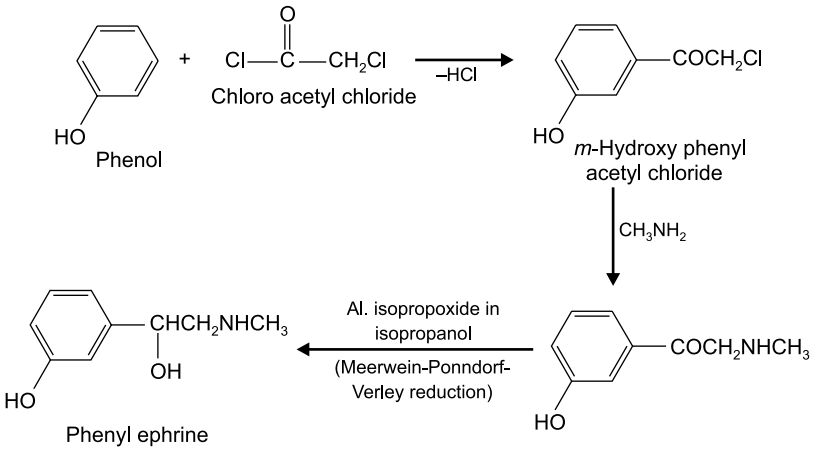
Route I. From: 3-Chloro acetyl phenol



3-Chloro acetyl phenol

(–)Phenylephrine

Route II. From: Phenol



Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and water. Phenylephrine differs from adrenaline only by lacking the 4th OH group on the benzene ring, and subsequently, resistant to COMT and has predominantly α_1-agonist effect. The L-isomer, causes

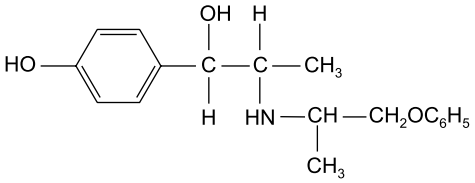
marked arterial vasoconstriction and is active when given orally. It finds its main use in the relief of nasal congestion and as a mydriatic. It is also used to prolong the action of local anaesthetics.

Assay: Dissolve the sample in a mixture of 0.1 M hydrochloric acid and ethanol. Titrate with 0.1 M ethanolic sodium hydroxide and determine the end point by potentiometric titration.

Dose: By topical, intranasal, adults dose is 2 to 3 drops or 1 or 2 sprays of 0.2 to 0.5% solution; intramuscular, adults, for mild-to-moderate hypotension: 2 to 5 mg repeated every 10 to 15 min.

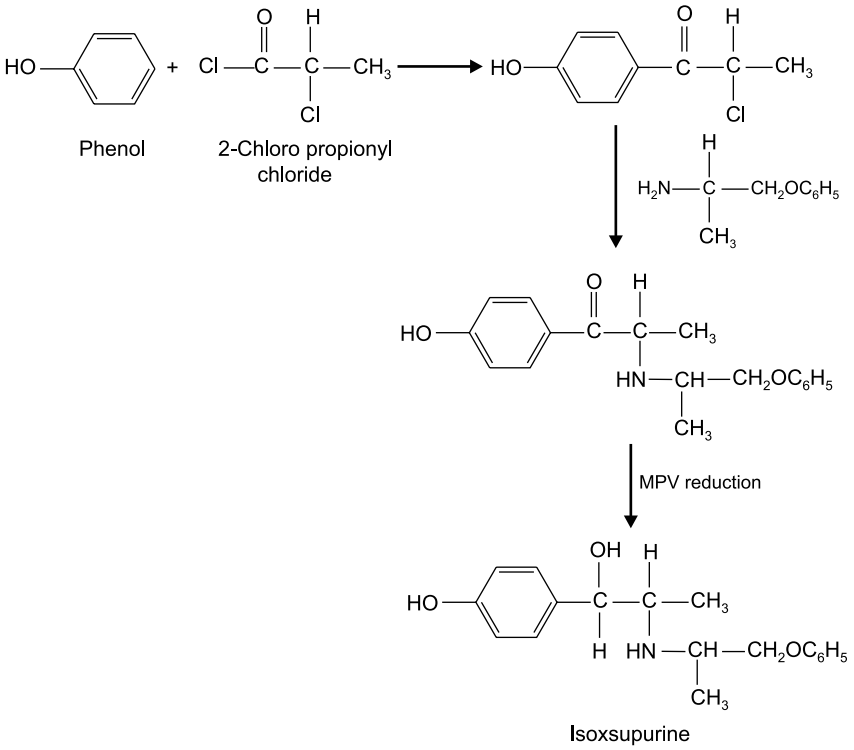
Dosage forms: Phenylephrine eyedrops BP, phenylephrine injection BP.

g. Isoxsupurine (Duvadilam, Suprox, Tidilan)



4-(1-Hydroxy-2-(1-phenoxypropan-2-yl-amino)propyl) phenol

Synthesis



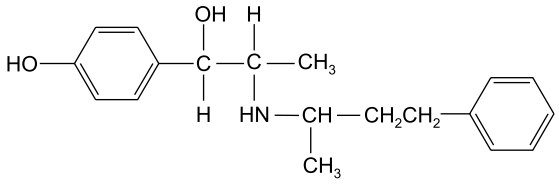
Properties and uses: It is a white or almost white crystalline powder, insoluble in methylene chloride, sparingly soluble in water and alcohol. It is used in the treatment of cerebral and peripheral vascular disease. It has also been employed in the treatment of Ménière's disease and similar disorders of the internal ear.

Assay: Dissolve the sample in alcohol and add 0.1 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

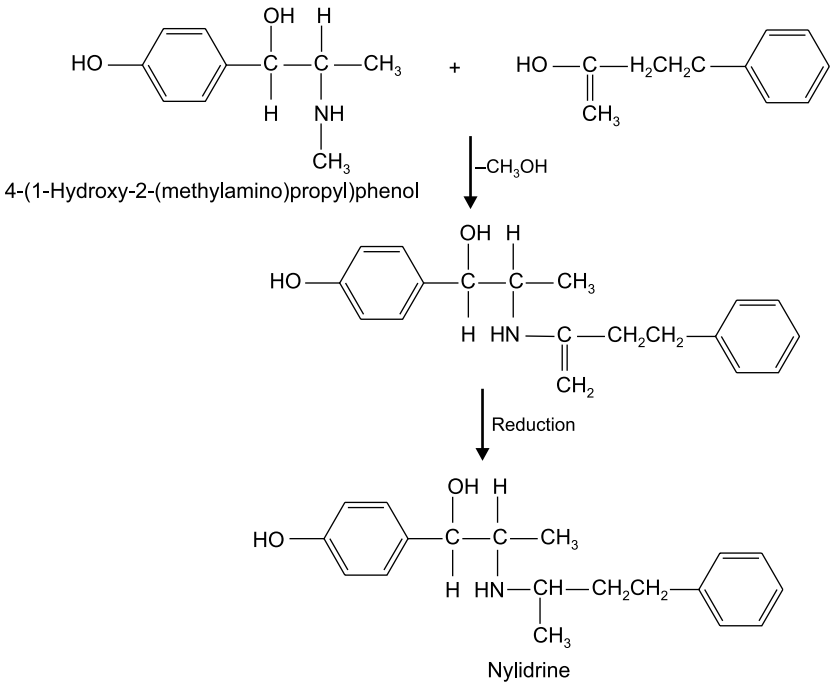
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Orally 20 mg four times/day; IV infusion as a solution containing 100 mg in 500 ml of sodium chloride solution.

h. Nylidrine HCl (Synonym: Arlidin)



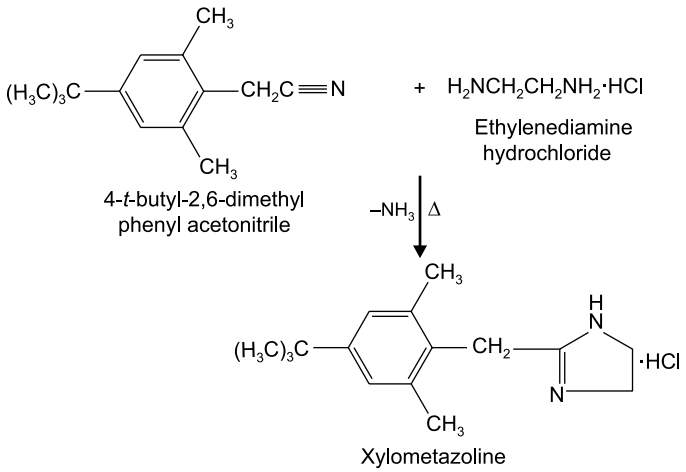
Synthesis



Dose: The usual dose initially by oral route 6 mg three times/day, which may be enhanced to 36 or 48 mg/day in divided doses.

i. Xylometazoline (Synonym: Otrivin, Otrinoz, Decon)

Synthesis

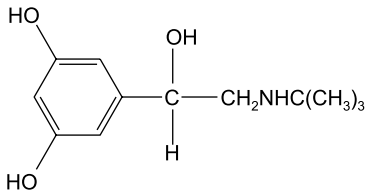


Xylometazoline

Properties and uses: It is a potent sympathomimetic agent, having marked and pronounced α-adrenergic pharmacologic profile. It is found to act as a vasoconstrictor, when applied topically to mucous membranes particularly. It is frequently employed as a local vasoconstrictor for nasal congestion caused by sinusitis or rhinitis.

Dose: By intranasal, 1 drop of a 0.1% solution in adult; or a spray of 0.05% solution.

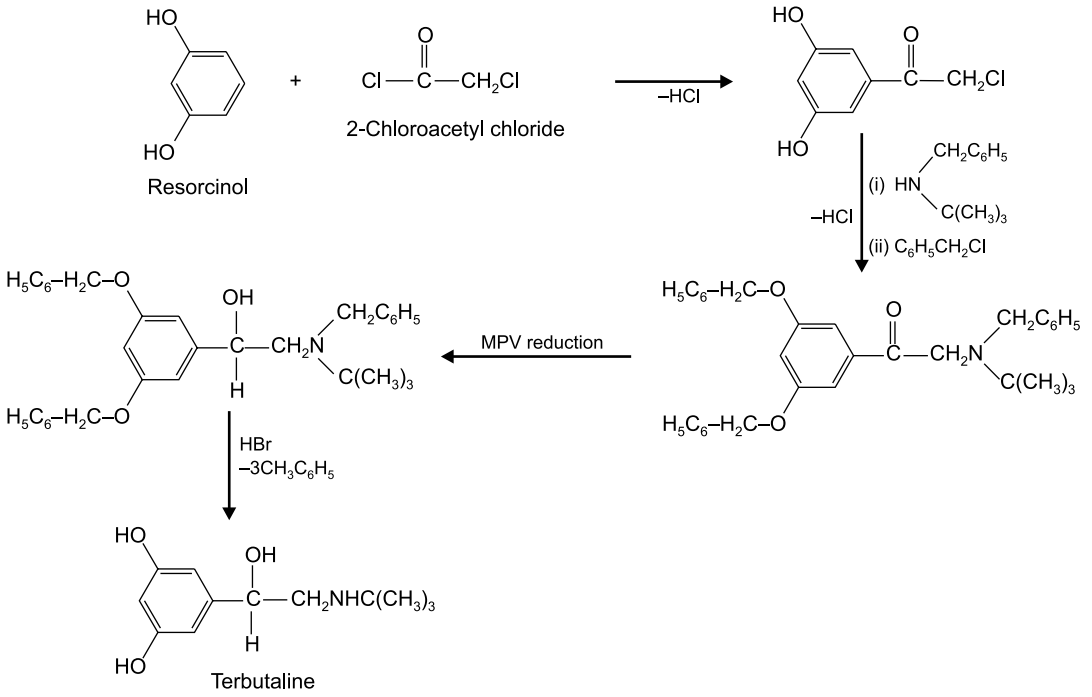
j. Terbutaline (Synonym: Bricanyl, Brethine, Asmaril)



5-(2-(*tert.*-butylamino)-1-hydroxyethyl)benzene-1,3-diol

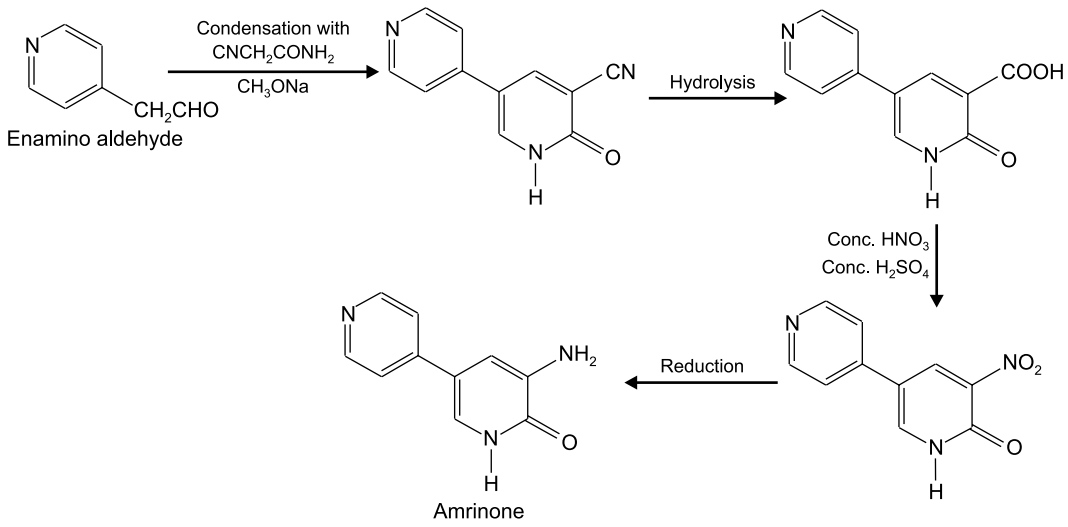
Properties and uses: It exists as a gray-white crystalline powder, odourless and with a bitter taste, soluble in water and alcohol. The drug exhibits the properties of a direct-acting sympathomimetic agent, having predominantly β-adrenergic activity, and has a selective action on the β_2-receptors (i.e. β_2-agonist). It is used only as a bronchodilator and in the treatment of asthma. It possesses strong β-agonistic activity.

Synthesis



Dose: Uncomplicated premature labour: Adult 5 mg/min for 20 min, increased every 20 min, steps of 2.5 µg/min until contractions have ceased (usually 10 µg/min sufficient), continue for 1 h, then decrease every 20 min in steps of 2.5 µg/min to lowest dose that maintains suppression, continue at this level for 12 h. Maximum dose is 20 µg/min. Switch to oral at 2.5–10 mg every 4–6 h, if indicated and tolerated. Continue as long as needed to prolong pregnancy.

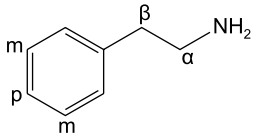
k. Amrinone (Inamrinone):



Properties and uses: It is a white powder, soluble in water and sodium hydroxide. It should be protected from light and to be preserved in well closed containers. Used as a cardiotonic agent.

STRUCTURE–ACTIVITY RELATIONSHIP

Many of the sympathomimetic drugs contain β-phenyl ethylamine as parent structure.



β–Phenyl ethylamine

I. Phenyl ring substitution

- Substitution on the *meta* and *para* positions of the aromatic ring and on the amino, α-, and β-positions of the ethylamine side chain influences the mechanism of sympathomimetic action and the receptor selectivity of the drug.
- Maximal activity is seen in β-phenyl ethylamine derivatives, containing hydroxyl groups in the *meta* and *para* positions of the aromatic ring (catechol) and a β-hydroxyl group of the correct stereochemical configuration on the ethylamine portion of the molecule.
- Although the catechol moiety is an important structural feature to obtain maximal agonistic activity at adrenergic receptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonism.
- For example, replacement of the catechol function of isoproterenol with the resorcinol structure gives the drug metaproterenol, which is a selective β_2-receptor agonist.
- In an other approach, replacement of the *meta*-hydroxyl of the catechol structure with a hydroxymethyl group afforded salbutamol, which shows selectivity to the β_2-receptor.
- The naturally occurring noradrenaline has 3,4-dihydroxy benzene ring (catechol) active at both α- and β-receptors. However, it has poor oral activity because it is rapidly metabolized by COMT, the change in substitution pattern 3,5-dihydroxy as in metaproterenol gives good oral activity. This is due to its resistance to metabolism by COMT. It also provides selectivity for β_2-receptors.

II. Substitution at nitrogen

- Amino group in phenylethylamines is important for direct agonistic activity.
- The amino group should be separated from the aromatic ring by two carbon atoms found among the potent direct-acting agonists.
- As the bulk of the nitrogen substituent increases, α-receptor agonistic activity decreases and β-receptor activity increases. Thus, NE that is an effective β_1-receptor agonist is also a potent α-agonist, while epinephrine is a potent agonist at α-, β_1- and β_2-receptors. N-tertiary butyl group enhances β_2-selectivity. As the size increases from hydrogen in noradrenaline to methyl in adrenaline, isopropyl in isoproterenol, the activity of α-receptor decreases and β-receptor increases.
- Primary and secondary amines are more potent direct-acting agonists than 3° or 4° amines.

III. Substitution on the carbon side chain

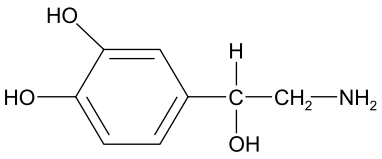
- Methyl or ethyl substitution on the α-carbon of the ethylamine side chain reduces direct receptor agonist activity at both α- and β-receptors.

- Importantly, an α-alkyl group increases the duration of action of the phenylethylamine agonist by making the compound resistant to metabolic deamination by MAO.
- α-substitution also significantly affects receptor selectivity.
- Another effect of α-substitution is the introduction of a chiral centre, which has pronounced effects on the stereochemical requirements for activity.

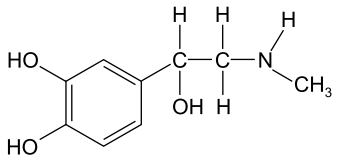
CLASSIFICATION BASED ON PCI SYLLABUS

Direct-acting Agents

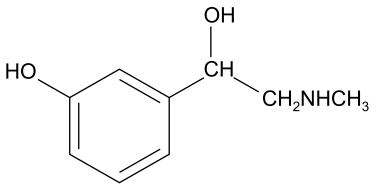
Norepinephrine (Noradrenaline)



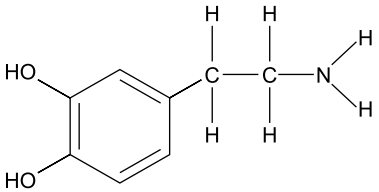
Epinephrine (Adrenaline)



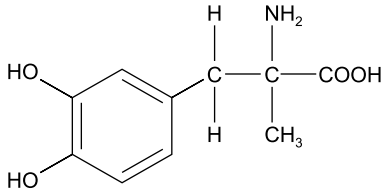
Phenylephrine



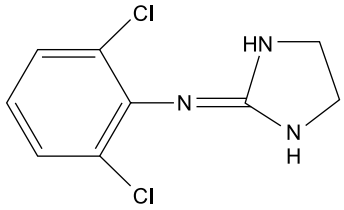
Dopamine



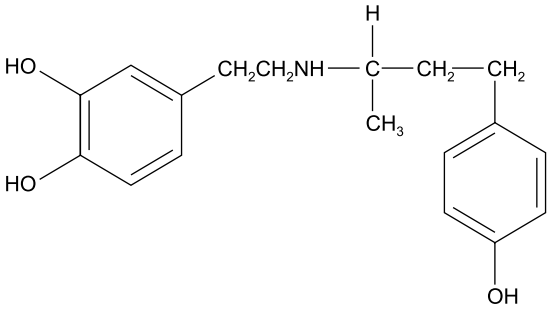
Methyldopa



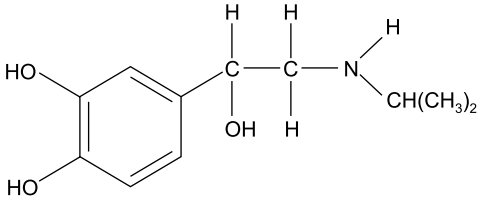
Clonidine



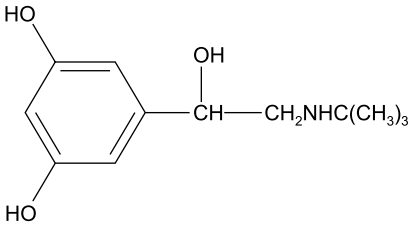
Dobutamine



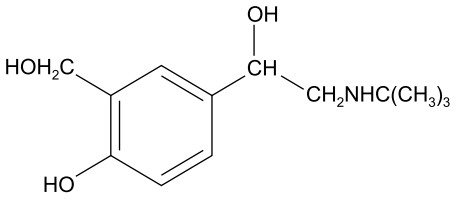
Isoproterenol



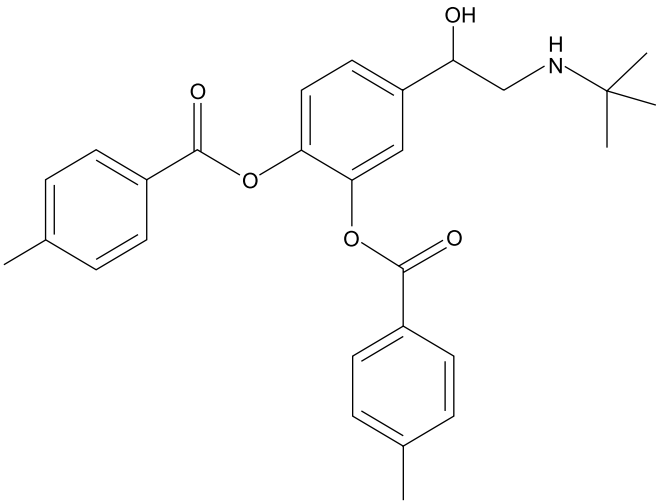
Terbutaline



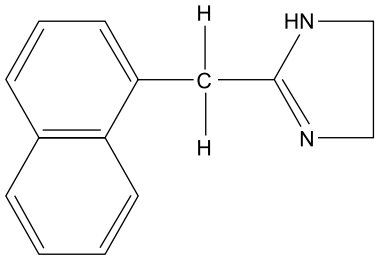
Salbutamol



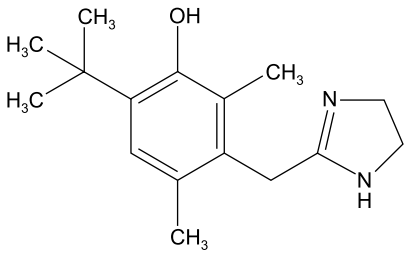
Bitolterol



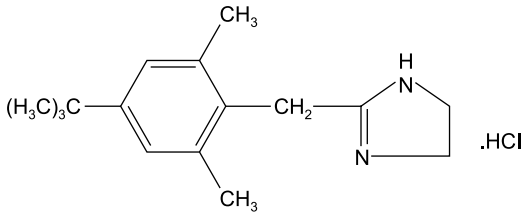
Naphazoline



Oxymetazoline

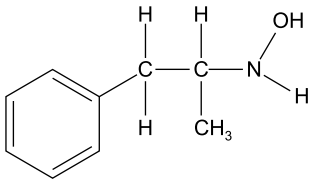


Xylometazoline

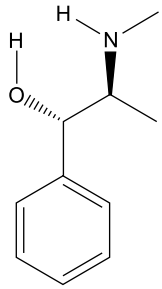


Indirect-acting Agents

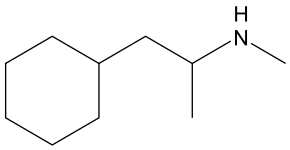
Hydroxyamphetamine



Pseudoephedrine

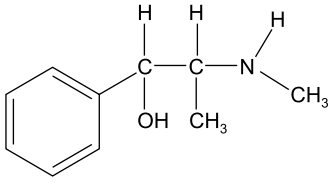


Propylhexedrine

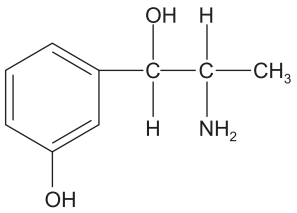


Agents with Mixed Mechanism

Ephedrine



Metaraminol



Bitolterol

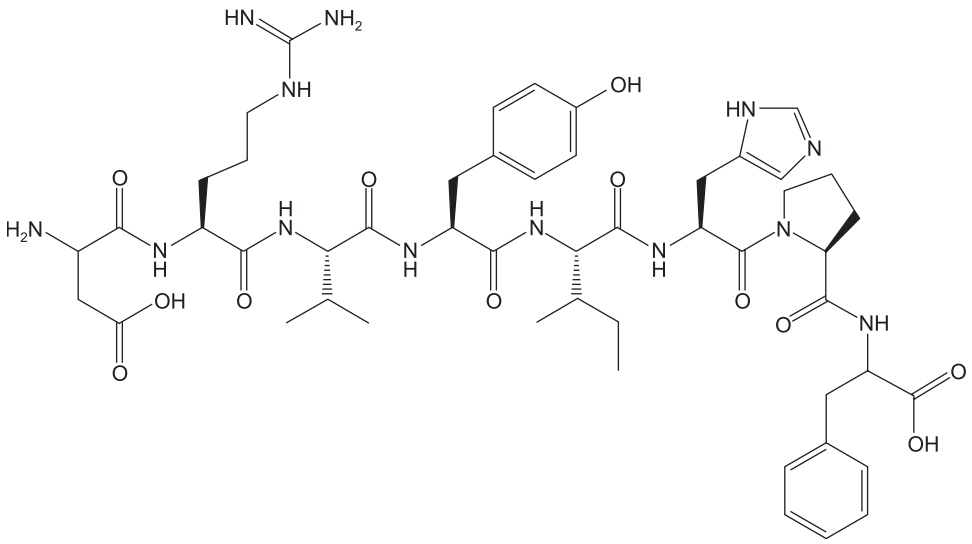
Properties and uses: It is a prodrug of colterol. It is used for the relief of bronchospasm in asthma, emphysema and chronic bronchitis.

Propyl hexedrine

Properties and uses: It is similar to methamphetamine structure and differs the later by the presence of cyclohexane ring. It is used as a psychostimulant, nasal congestant and appetite suppressant.

Newer Agents

Giapreza



Uses: It is a vasoconstrictor to increase the BP in adults with septic or other distributive shock.

CHAPTER 36

Cholinergic Drugs

INTRODUCTION

Acetylcholine receptor stimulants and cholinesterase inhibitors together comprise a large group of drugs, called cholinergic drugs that mimic the actions of acetylcholine. Cholinoceptor stimulants are classified pharmacologically by the spectrum of action depending on the type of receptor, muscarinic or nicotinic.

SPECTRUM OF CHOLINOMIMETIC DRUGS

Early studies of parasympathetic nervous system showed that the alkaloid muscarine mimicked the effects of parasympathetic nerve discharge, that is, the effects were parasympathomimetic. Application of muscarine to ganglion and to autonomic effector tissue (smooth muscle, heart, exocrine glands) showed that parasympathomimetic action of the alkaloid occurred through an action on receptors at effector cells, which are not in those of ganglia. Low concentrations of alkaloid nicotine stimulates autonomic ganglia and skeletal neuromuscular junction, but not autonomic effector cells. The ganglion and skeletal muscle receptors were, therefore, labelled nicotinic. Cholinoceptor are protein-linked (muscarinic) or ion-channel (nicotinic) families, which functions on the basis of their transmembrane signalling mechanism (Figure 36.1).

Direct-acting Cholinoceptor Stimulants

The direct-acting cholinomimetic drugs can be divided on the basis of their chemical structure into esters of choline (including acetylcholine) and alkaloids (muscarine and nicotine). A few drugs are highly selective for specific muscarinic and nicotinic receptor. Many have effects on both receptors, for example, acetylcholine.

Mechanism of Action of Directly-acting Cholinergic Drugs

These drugs mediate the actions through muscarinic and nicotinic receptor subtypes. Stimulation of M_1 or M_3 receptors causes hydrolysis of polyphosphoinositides and mobilization of intracellular Ca^{2+}, as a consequence of interaction with a G protein and phospholipase C is activated, which phosphorylates the target protein. In contrast, M_2 and M_4 inhibit adenylcyclase and regulate specific ion channels, that is, enhancement of K^+ conductance in cardiac arterial tissue. Cholinergic stimulation affects cardiac function directly by inhibiting the effects of adrenergic activation. As a part, it decreases the cAMP

formation and reduction on L-type Ca^{2+} channel activity. In arterial muscles, acetylcholine decreases the strength of contraction. This effect is due to M_2-receptor mediated action of G protein regulated K^+ channels. Increased K^+ permeability leads to hyperpolarization and shortens the duration of action potentials.

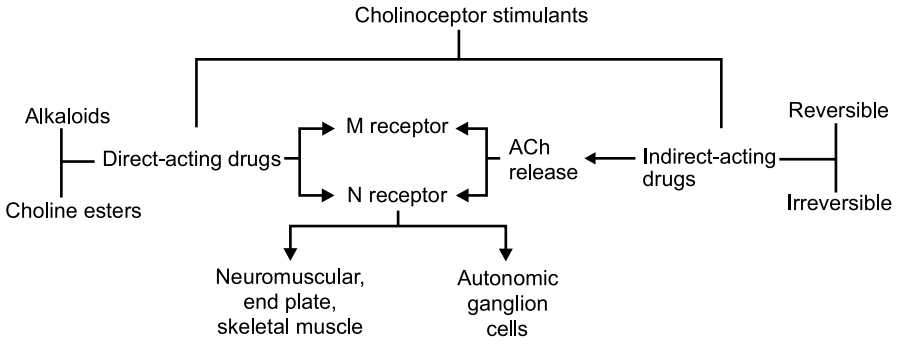


Figure 36.1: Major groups of cholinoreceptors-activating drugs, and target tissue.

Indirect-acting Cholinomimetic Drugs

The actions of acetylcholine released from autonomic and somatic motor nerves are terminated by enzymatic destruction of the molecule. Hydrolysis is accomplished by acetylcholinesterase. The indirect-acting drugs have primary effect on the active site of this enzyme, although some also have direct actions at nicotinic receptors. The common differences between members of the group are chemical and pharmacokinetic, but their pharmacodynamic properties are identical.

Mechanism of Action of Indirectly-acting Cholinergic Drugs (Anticholinesterase Agents)

Acetylcholinesterase (AChE) is a serine dependent isoenzyme capable of hydrolyzing ACh to choline and acetic acid. The active site of AChE comprises two distinct regions, an anionic site that possess a glutamate residue and an esteratic site in which histidine imidazole ring and serine –OH group are present. Catalytic hydrolysis occurs, thereby the acetyl group is transferred to the serine –OH group, leaving an acetylated enzyme molecule and a molecule of free choline. Spontaneous hydrolysis of the serine acetyl group occurs rapidly.

There are two main categories of AChE inhibitors:

1. The amine or ammonium AChE inhibitors react reversibly with enzymes, these compounds reversibly acylate the esteratic serine hydroxyl, their duration of action are few minutes to few hours.
2. The organophosphate type AChE inhibitors form an irreversible firm bond with the enzymes (esteratic site) and their duration of action are few weeks to months.

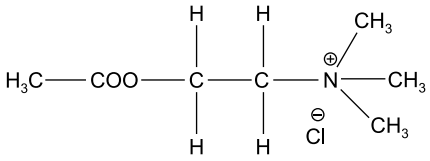
CLASSIFICATION

These agents mimic the actions of acetylcholine at parasympathetic system and based on their mechanism of action, they are classified as follows:

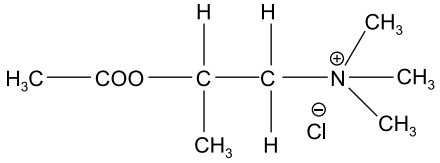
I. Directly-acting cholinergic drugs

A. Choline esters

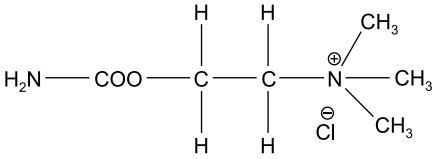
i. Acetylcholine



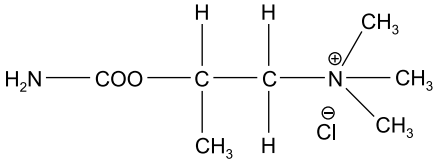
ii. Methacholine



iii. Carbachol

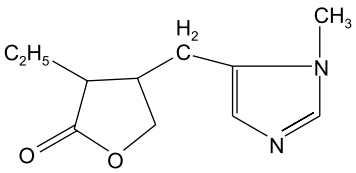


iv. Bethanechol

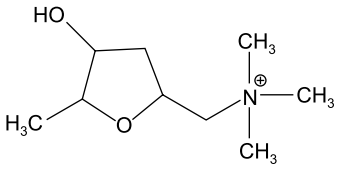


B. Cholinomimetic alkaloids

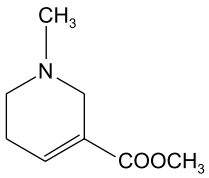
i. Pilocarpine



ii. Muscarine



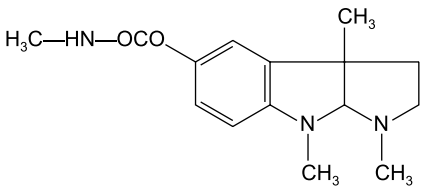
iii. Arecholine



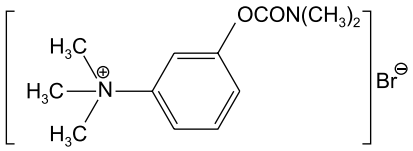
II. Indirectly-acting cholinergic drugs

A. Reversible cholinesterase inhibitors

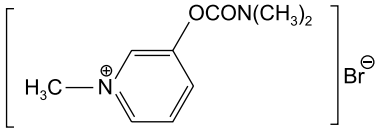
i. Physostigmine (Eserine)



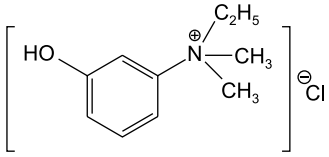
ii. Neostigmine bromide (Pristigmine)



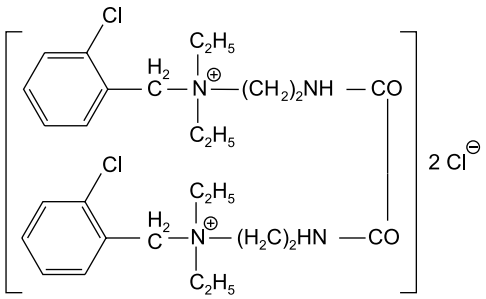
iii. Pyridostigmine bromide (Mestinon)



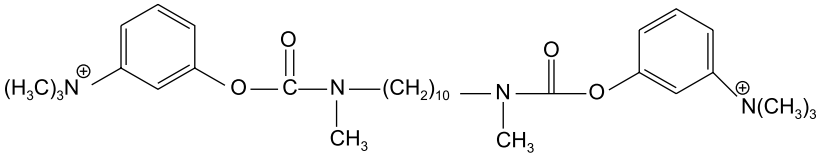
iv. Edrophonium chloride



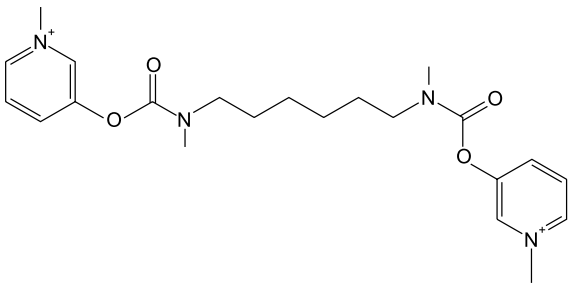
v. Ambenonium chloride (Mytelase)



vi. Demecarium (Humorsol)

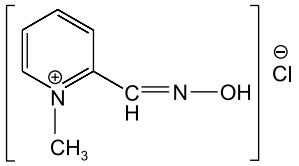


vii. Distigmine (Ubretid)

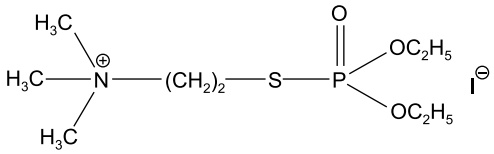


B. Irreversible cholinesterase inhibitors

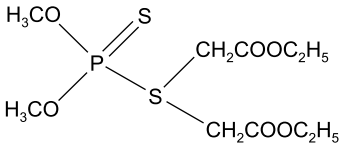
a. Pralidoxime chloride



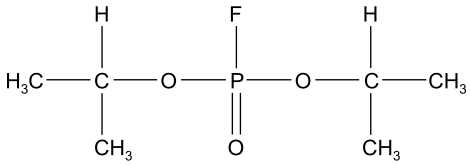
b. Echothiopate iodide



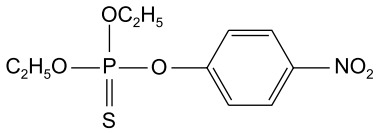
c. Malathion



d. Isofluorphate



e. Parathion



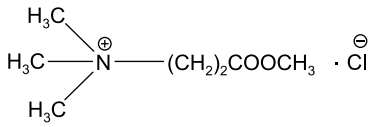
SYNTHESIS AND DRUG PROFILE

I. Direct-acting cholinergic drugs

The direct-acting agents exert their effects by stimulating muscarinic/nicotinic receptors.

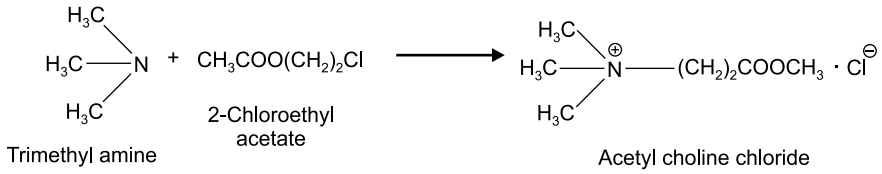
A. Choline esters

i. **Acetylcholine chloride** (Miochol)



(2-Acetoxyl ethyl)-trimethyl ammonium chloride

Synthesis



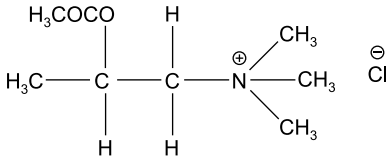
Properties and uses: It is a white or almost white crystalline powder or colourless crystals, very hygroscopic in nature, slightly soluble in methylene chloride, soluble in water and alcohol. It is a topical ophthalmic drug to induce miosis, during certain intraocular surgical procedures, such as cataract surgery, ridectomy, penetrating keratoplasty, and other anterior-segment surgery. Systemically administered ACh is rapidly hydrolyzed by acetylcholinesterase, hence, it has no clinical use. It is a cardiac depressant and effective vasodilator.

Assay: Dissolve the sample in water and neutralize with 0.01 M sodium hydroxide using phenolphthalein solution as indicator. Add 0.1 M sodium hydroxide solution, allow it to stand for 30 min and titrate with 0.1 M hydrochloric acid.

Storage: It should be stored in well-closed ampoules and protected from light.

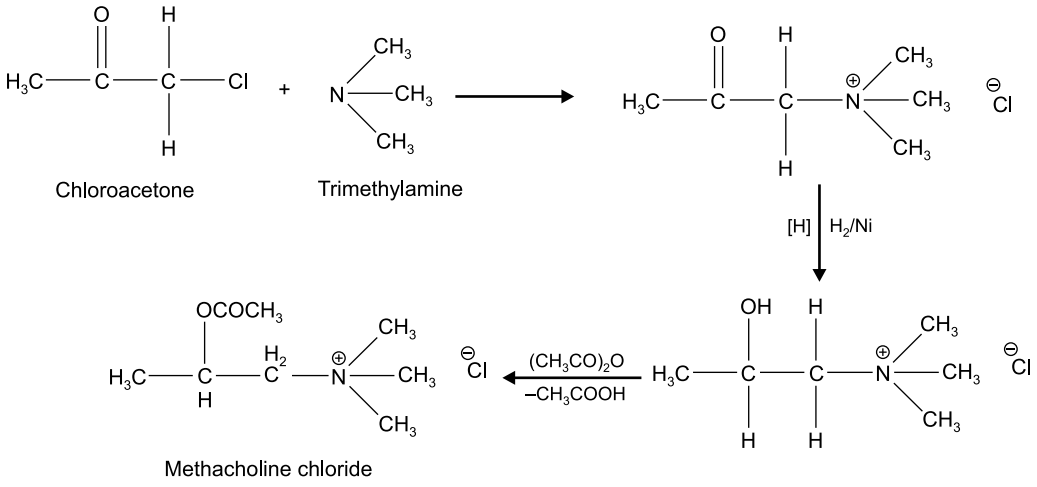
Dose: Topically as a 1% solution.

ii. Methacholine chloride (Provocholine)



(2-Acetoxy) trimethyl propanaminium chloride

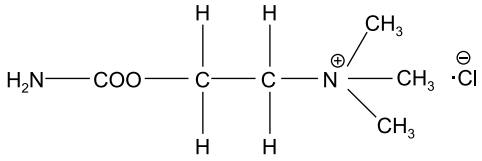
Synthesis



Properties and uses: It is highly deliquescent, has faint fishy odour, and aqueous solutions are neutral, soluble in water, alcohol, and $CHCl_3$. It is used to treat Reynaud's syndrome and glaucoma.

Dose: For usual paroxysmal tachycardia, 10 to 25 mg; by SC for peripheral vascular disease 10 to 25 mg.

iii. Carbachol (Synonym: Carcholin, Moistat)



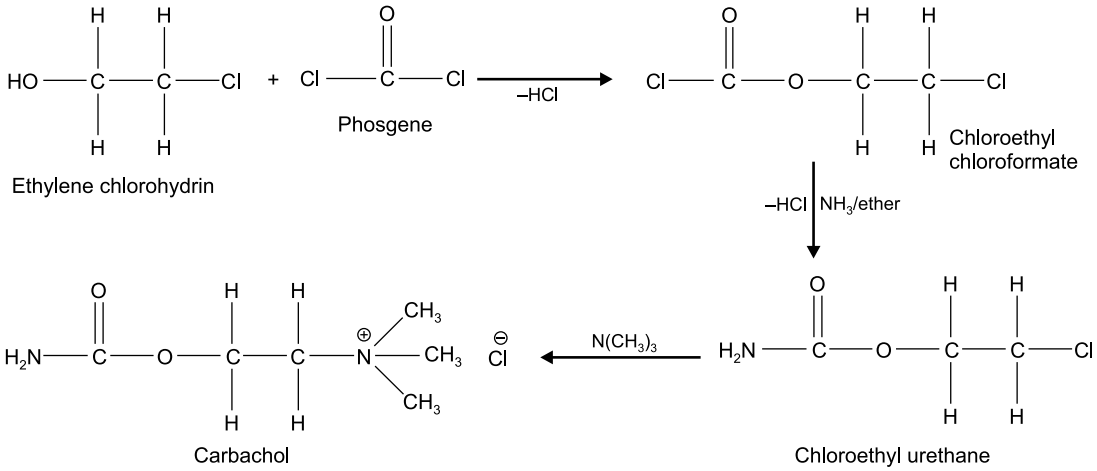
2-[(Amino carbonyl)oxy]-N,N,N-trimethylethan ammonium chloride

Properties and uses: It is a white crystalline, hygroscopic powder, soluble in water, sparingly soluble in alcohol, insoluble in acetone. It is an ester of carbamic acid, the terminal methyl group of ACh is replaced by amino group. It possesses both muscarinic and nicotinic properties by cholinergic receptor stimulation. It is more slowly hydrolyzed by acetylcholinesterase. It is used for its miotic actions in the treatment of glaucoma to reduce intraocular pressure.

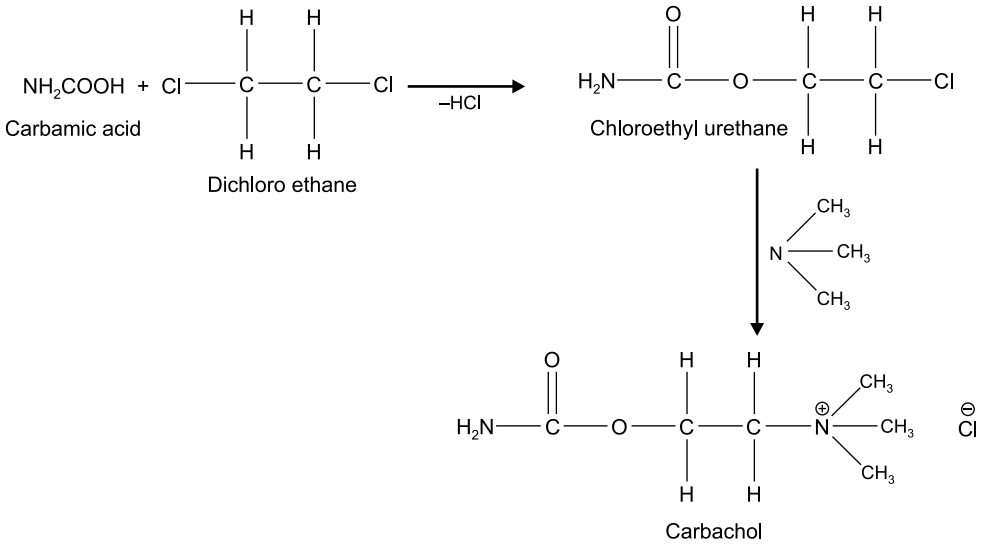
Assay: Dissolve the sample in a mixture of anhydrous acetic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Synthesis

Route I. From: Ethylene chlorohydrin



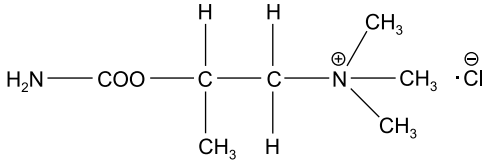
Route II. From: Carbamic acid



Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Topically 0.1 ml of 0.75 to 3% solution.

iv. Bethanechol chloride (Synonym: Urecholine, Myotonachol, Bethacol, Urotonin)

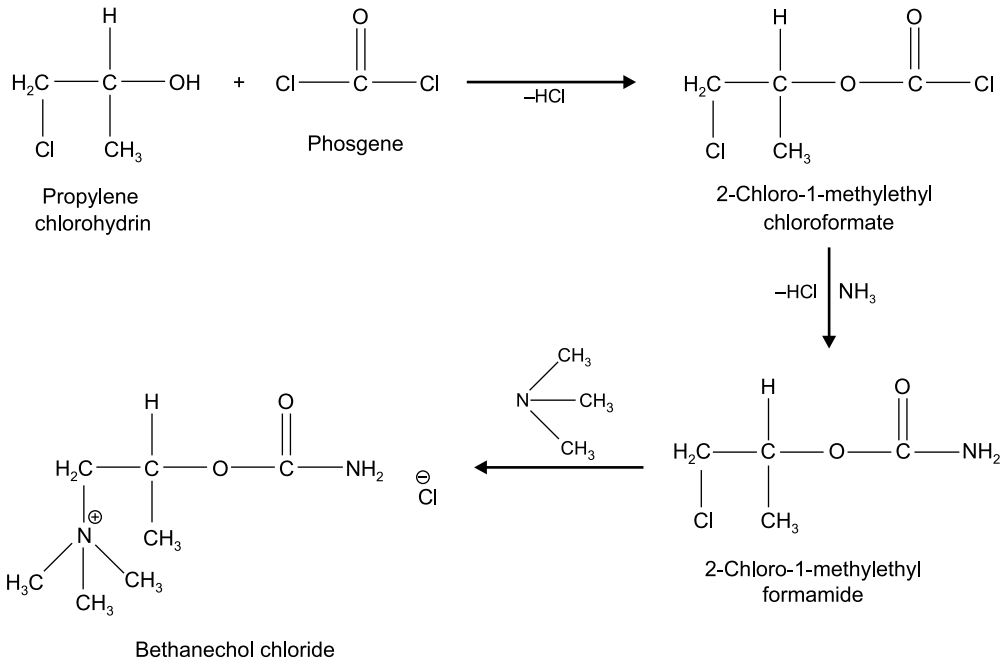


2-[(Amino carbonyl)oxy]-N,N,N-trimethylpropan ammonium chloride

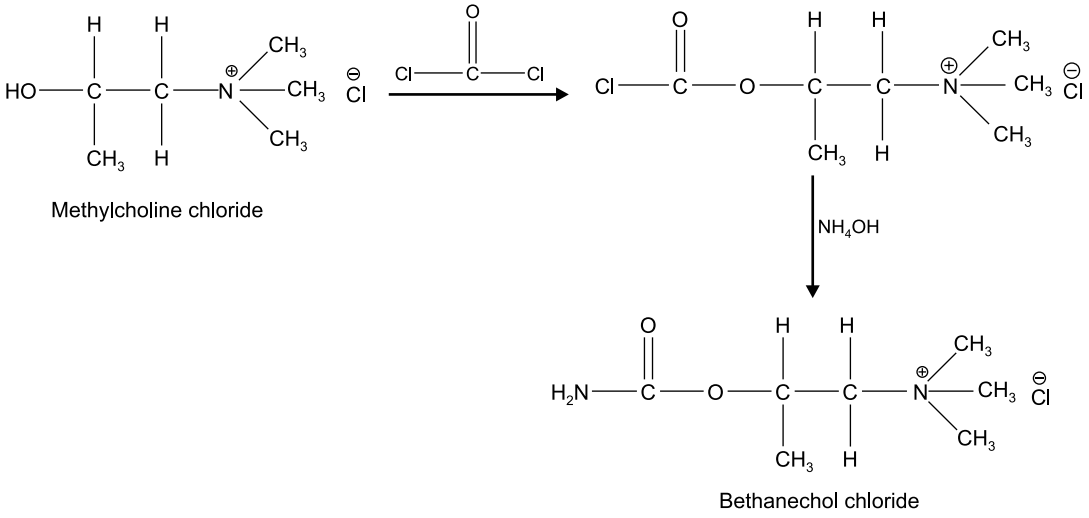
Properties and uses: It is a white crystalline hygroscopic powder, and it exhibits polymorphism, soluble in water and alcohol. It has pharmacological properties similar to those of methacholine. The presence of $-CH_3$ gives prolonged activity due to steric hindrance. It produces smooth muscle contractions. It is not well absorbed from the gastrointestinal tract. It can be given subcutaneously, but not by intramuscular (IM) or intravenous (IV) because of its severe side effects. It is used to relieve urinary retention and abdominal distention after surgery. This is one of the postvagotomy gastric drug.

Synthesis

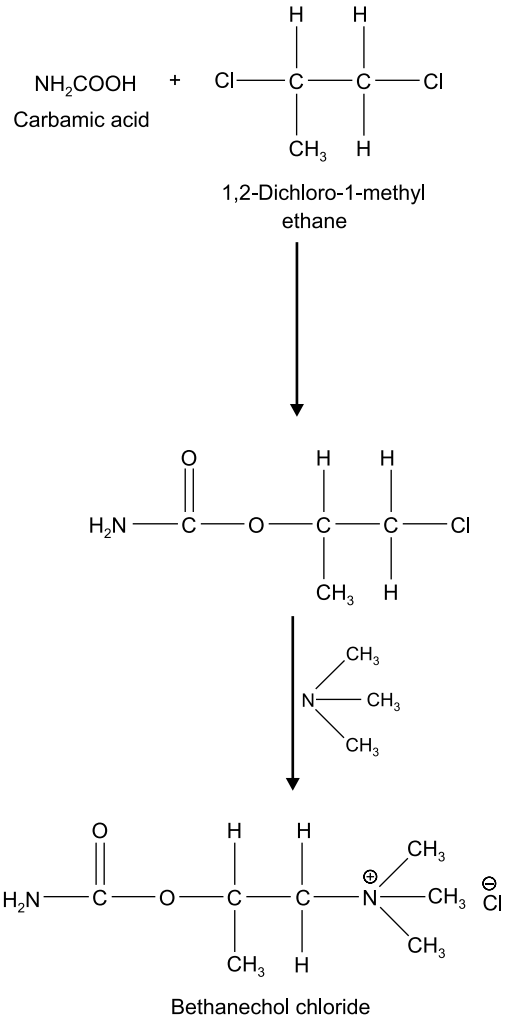
Route I. From: Propylene chlorhydrin



Route II. From: Methylcholine chloride



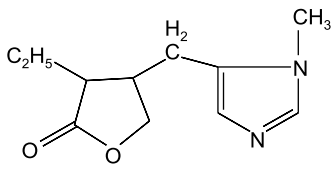
Route III. From: Carbamic acid



Dose: By oral 5 to 30 mg three or four times/day; By SC 2.5 to 10 mg three or four times/day.

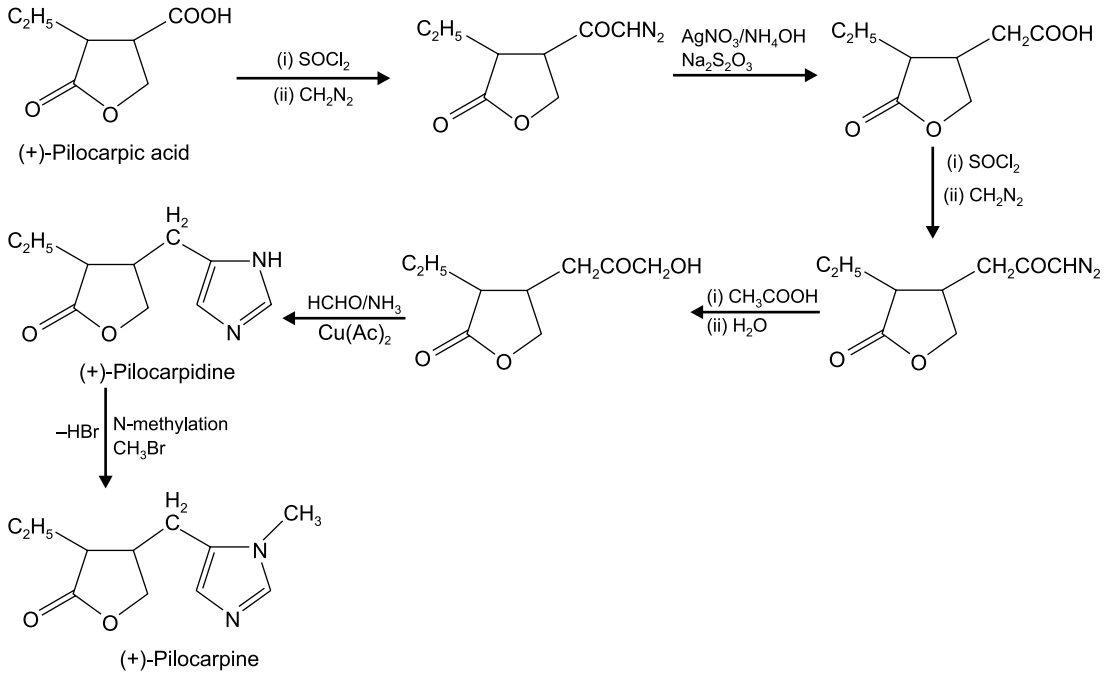
B. Cholinomimetic alkaloids

i. Pilocarpine (Pilicar, Carpine, Locarp)



3-Ethyl-4-[(1-methyl-imidazole-5-yl)methyl] tetrahydro-2-furanone

Synthesis



Properties and uses: It is a white or almost white crystalline powder or colourless crystals, hygroscopic, very soluble in water and in alcohol. Pilocarpine is an alkaloid obtained from the dried leaflets of *Pilocarpus jaborandi* and *Pilocarpus microphyllus* in which it occurs to the extent of about 0.5% together with other alkaloids. Pilocarpine is a non-selective agonist on the muscarinic receptors. It acts on M_3 receptors in smooth muscles and causes contractions in the gut, trachea, and eyes. It is used for the treatment of symptoms of dry mouth caused by radiotherapy for cancer of head and neck and the symptoms associated with Sjogren's syndrome.

Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers, and protected from light.

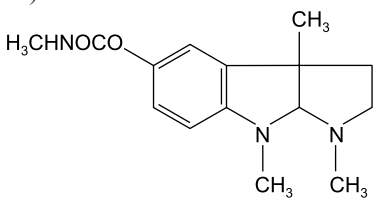
Dose: Topically 0.1 ml of 0.5–6% solution into the conjunctival sac 1–5 times/day.

Dosage forms: Pilocarpine hydrochloride eyedrops BP.

II. Indirectly-acting cholinergic drugs

A. Reversible blockers

i. Physostigmine (Isopto-Eserine)

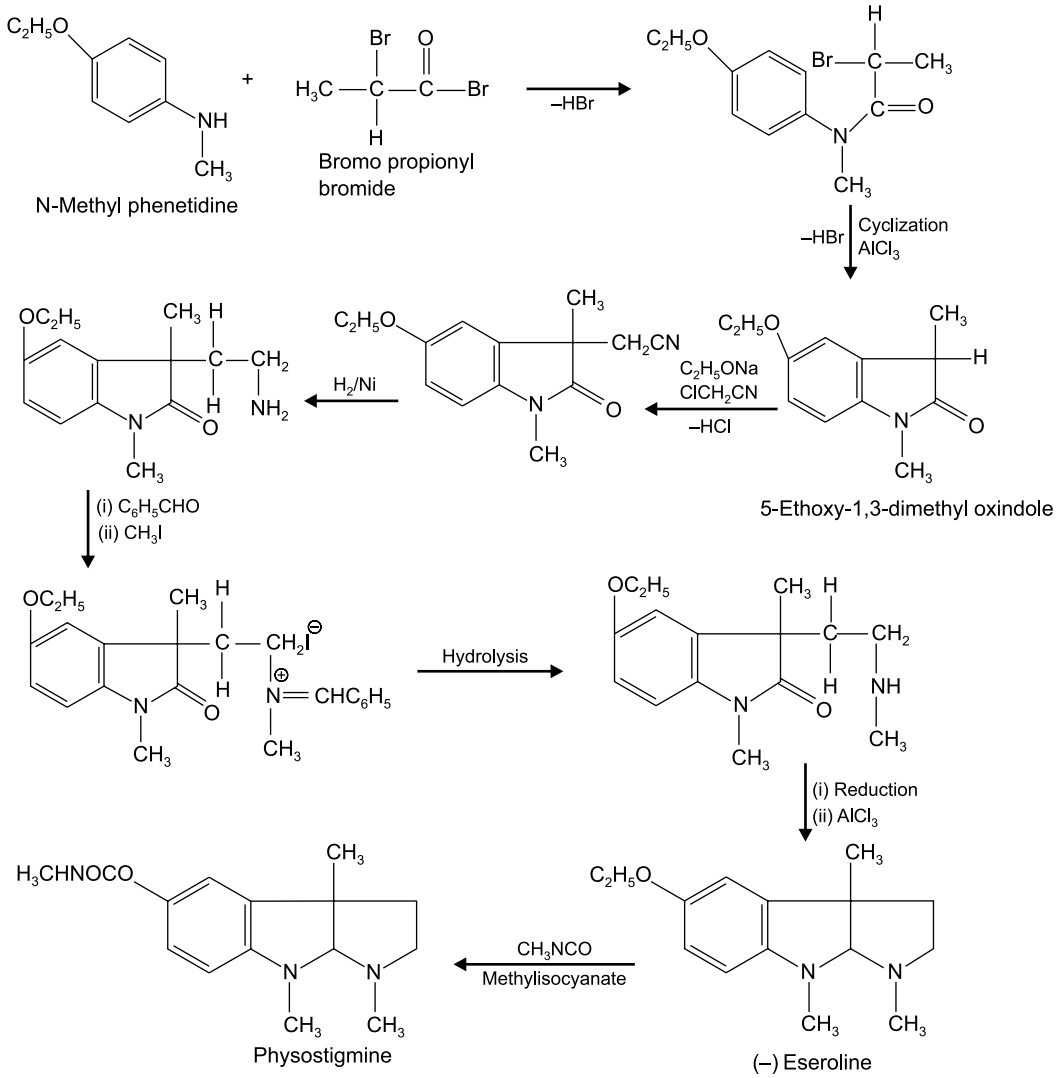


Properties and uses: It exists as a white or almost white crystalline powder, hygroscopic, very soluble in water, and freely soluble in alcohol. It gradually becomes red when exposed to air and light; the colour develops more quickly when the substance is also exposed to moisture. Aqueous solutions are unstable. It melts at about 145°C with decomposition. It is an alkaloid obtained from the dried ripe seeds of *Physostigma venenosum*. It occurs as a white, odourless, microcrystalline powder, slightly soluble in H_2O, freely soluble in alcohol, $CHCl_3$ and fixed oils. Physostigmine is an oldest anticholinesterase agent. It is used in the treatment of glaucoma. It can penetrate the blood–brain barrier and is employed to antagonize the toxic CNS effects of antimuscarinic drugs, tricyclic depressants, H_1 antihistamines, and benzodiazepines. It is also used in the treatment of Alzheimer's disease.

Assay: Dissolve the sample in a mixture of anhydrous acetic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

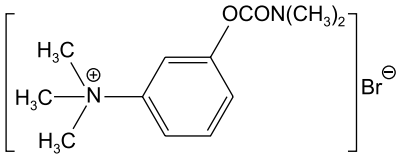
Storage: It should be stored in well-closed airtight glass container and protected from light.

Synthesis



Dose: Topically for open-angle glaucoma, 0.1 ml of 0.25–5% solution instilled into the conjunctival sac two or four times/day.

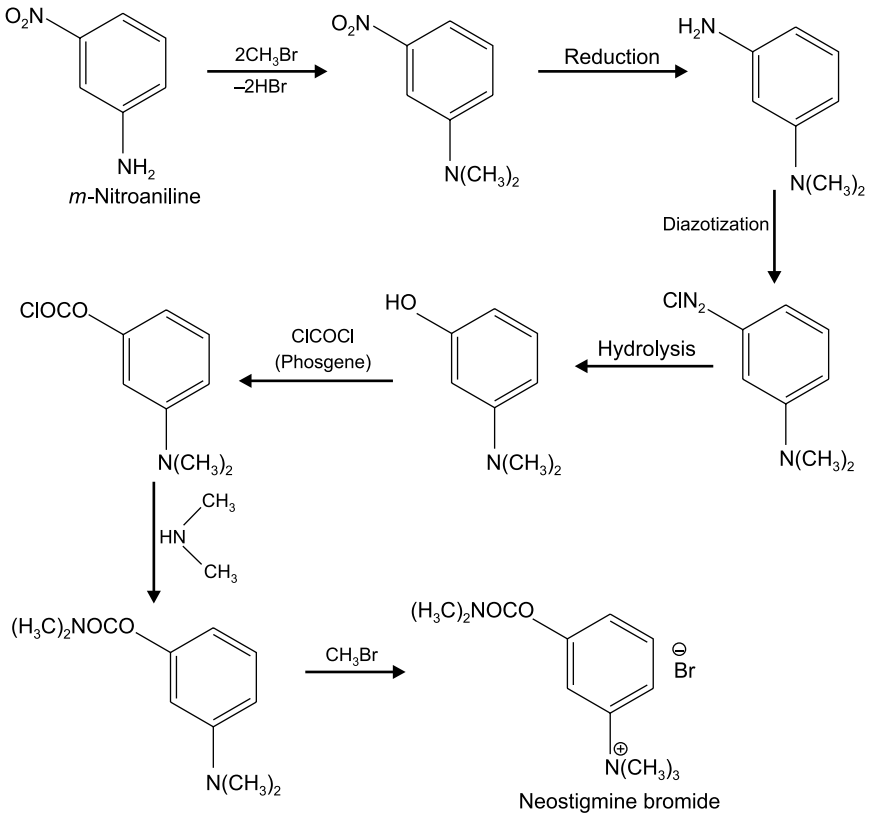
ii. Neostigmine bromide (Synonym: Prostigmine, Myostigmin, Tilstigmin)



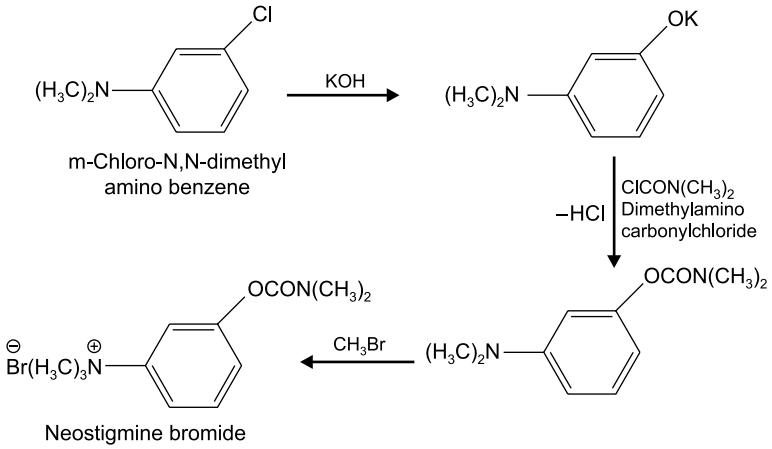
3-{[(Dimethyl amino) carbonyl]oxy}-N,N,N-trimethyl benzene ammonium bromide

Synthesis

Route I. From: *Meta*-nitroaniline



Route II. From: *m*-Chloro-N,N-dimethyl amino benzene



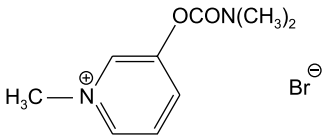
Properties and uses: It exists as white, odourless, crystalline powder with a bitter taste, freely soluble in water, alcohol, and insoluble in ether. Its solutions are neutral to litmus. It acts as a cholinesterase inhibitor.

Assay: Dissolve the sample in anhydrous formic acid, and then add acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight container and protected from light.

Dosage forms: Neostigmine bromide tablets IP, neostigmine methyl sulphate injection IP, neostigmine tablets BP.

iii. Pyridostigmine bromide (Synonym: Mestion, Pyrido, Trostigmin)



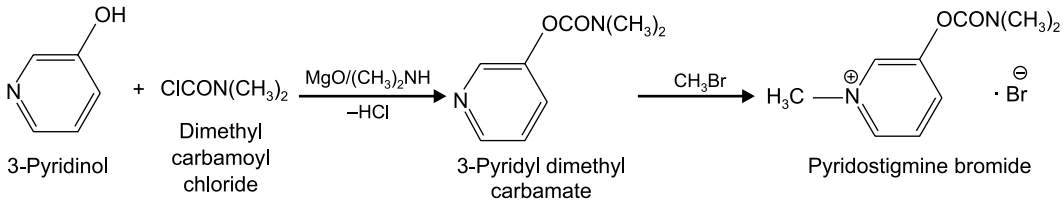
3-{[(Dimethyl amino) carbonyl]oxy}-N,N,N-trimethyl benzene ammonium bromide

Properties and uses: It exists as white, crystalline powder with a characteristic odour and bitter taste, soluble in water, alcohol, chloroform, slightly soluble in hexane, and insoluble in ether. It is hygroscopic in nature. It is used in the treatment of myasthenia gravis and it antagonizes the effects of neuromuscular blocking (NMB) agents.

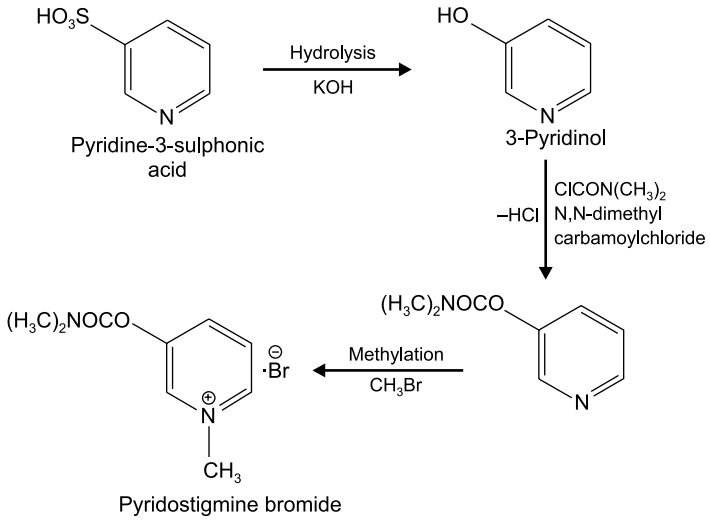
Assay: Dissolve the sample in anhydrous acetic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Synthesis

Route I. From: 3-Pyridinol



Route II. From: Pyridine-3-sulphonic acid

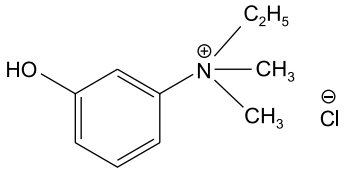


Storage: It should be stored in well-closed airtight container, protected from light. The sterile substance should be stored in airtight, tamper-proof containers, and protected from light.

Dose: Initially, 60 mg every 4 to 8 h, but 120 to 300 mg six times/day is the usual dose.

Dosage forms: Pyridostigmine tablets BP.

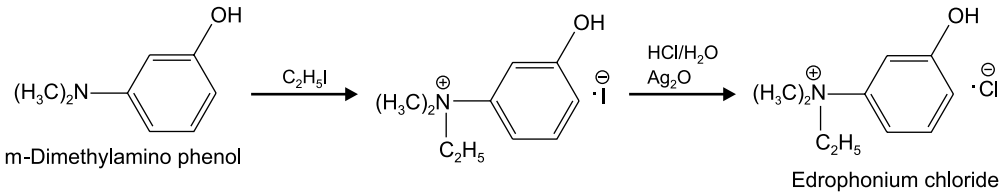
iv. Edrophonium chloride (Tensilon)



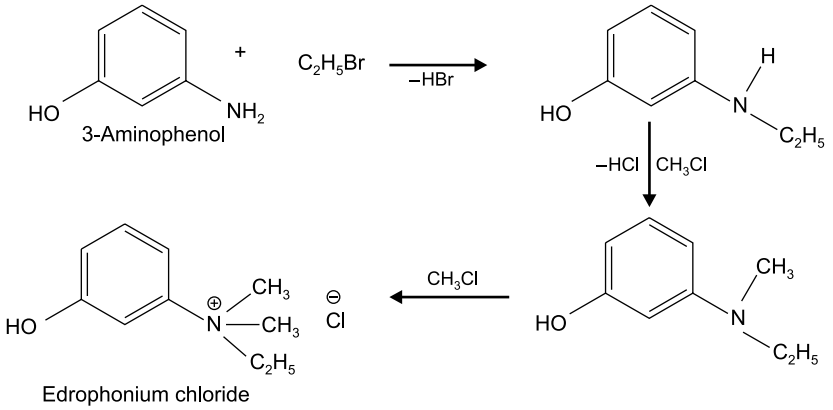
Ethyl (*m*-hydroxy phenyl) dimethyl ammonium chloride

Synthesis

Route I. From: *Meta*-dimethylamino phenol



Route II. From: 3-Aminophenol



Properties and uses: It exists as a white crystalline powder, soluble in water and alcohol, insoluble in methylene chloride. On parenteral administration, edrophonium has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium. It is used as an antiarrhythmic drug in paroxysmal atrial tachycardia. It is also used in the diagnosis of myasthenia gravis.

Assay: Dissolve the sample in a mixture of equal volumes of acetic anhydride and anhydrous acetic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

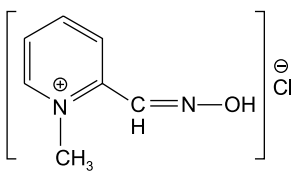
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: By IV. 2 to 10 mg; usually 2 mg is injected initially and if no adverse reaction takes place within 30 sec, the remaining 8 mg may be injected.

Dosage form: Edrophonium injection BP.

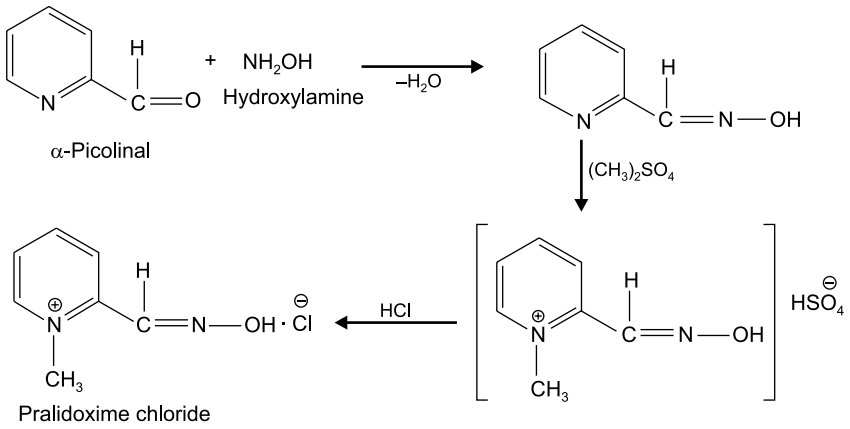
B. Irreversible blockers

i. Pralidoxime chloride



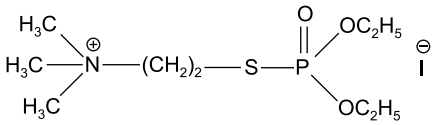
2-Formyl-1-methyl pyridinium chloride oxime

Synthesis



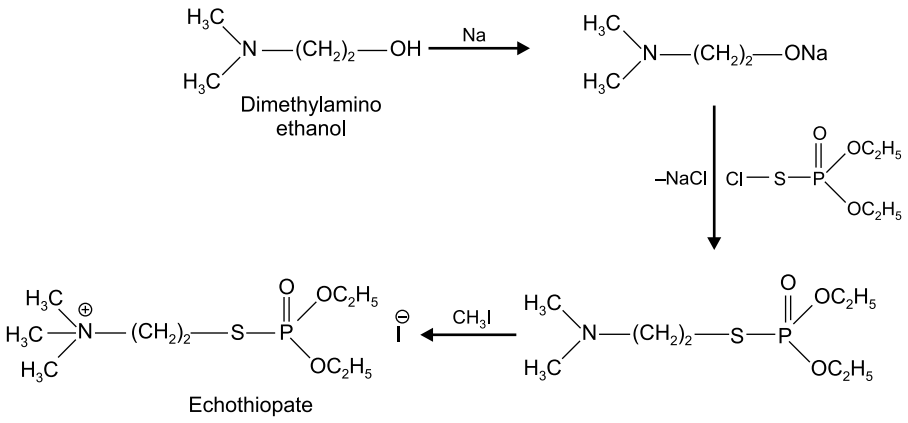
Properties and uses: It exists as a white to pale yellow crystalline powder, odourless, soluble in water. Used as an antidote for parathion and related pesticides poison.

ii. Echothiophate



2-[(Diethoxyphosphonyl)thio]-N,N,N-trimethylethan ammoniumiodide

Synthesis

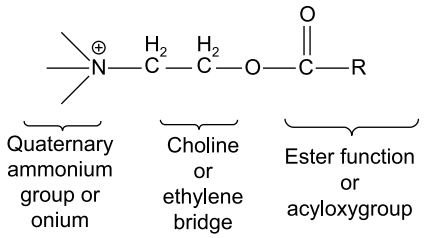


Properties and uses: It exists as white crystalline hygroscopic solid with slight mercaptane-like odour, soluble in water, methanol, or dehydrated alcohol, but insoluble in organic solvents. It is a long-acting irreversible antiAChE drug, used in the treatment of glaucoma.

Dose: Topically for adult in the treatment of glaucoma, 1 drop of 0.03% to 0.25% solution.

STRUCTURE–ACTIVITY RELATIONSHIP

- Acetylcholine can exist in a number of conformations. Four of these conformations are synplanar, synclinal, anticlinal, and antiplanar.
- The most active isomer is the (+) *trans* enantiomer, and it is identical to synclinal conformation of acetylcholine.
- The muscarinic receptors and acetylcholinesterase display stereoselectivity, the (S)-enantiomer of methacholine is equipotent with acetylcholine, while the R-(–)-enantiomer is about 20-fold less potent.



I. Modification of quaternary ammonium group

- The quaternary ammonium group is essential for intrinsic activity, and contributes to the affinity of the molecule for the receptors, partially through the binding energy and partially because of its action as a detecting group.
- The trimethyl ammonium group is the optimal functional moiety for the activity, although some exceptions are known (e.g. pilocarpine, nicotine, and oxotremorine), and it shows maximal muscarinic activity.
- Placement of primary, secondary, or tertiary amines leads to decrease in activity.

II. Modification of acyloxy group

- The ester group of ACh contributes to the binding of the compound to the muscarinic receptor.
- Replacement of methyl group by ethyl or large alkyl groups produces inactive compounds.
- Esters of aromatic or higher molecular weight acids possess cholinergic antagonist activity.

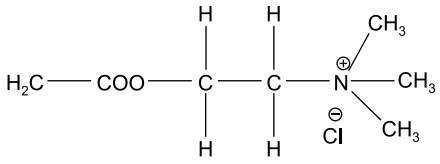
III. Modification of ethylene bridge

- The methyl ester is rapidly hydrolyzed by cholinesterase to choline and acetic acid. To reduce susceptibility to hydrolysis, carbamate esters of choline (carbachol) were synthesized and were found to be more stable than carboxylate esters.
- Placement of α-substitution in choline moiety results in a reduction of both nicotinic and muscarinic activity, but muscarinic activity to a greater extent.
- Incorporation of β-substitution leads to reduction of nicotinic activity to greater extent.
- Replacement of ester group with ether or ketone produces chemically stable and potent compounds.

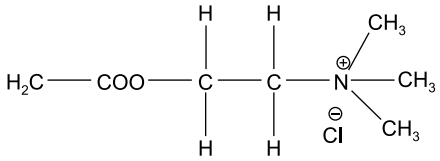
CLASSIFICATION BASED ON PCI SYLLABUS

Direct-acting Agents

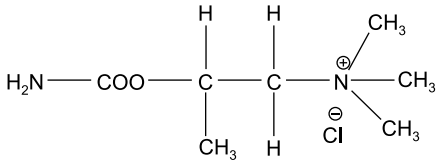
Acetylcholine



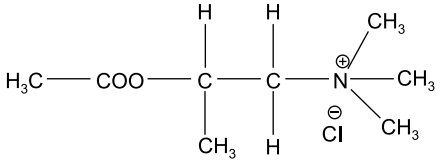
Carbachol



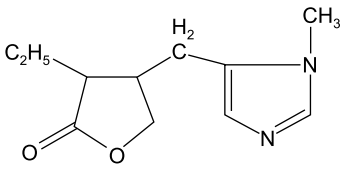
Bethanechol



Methacholine

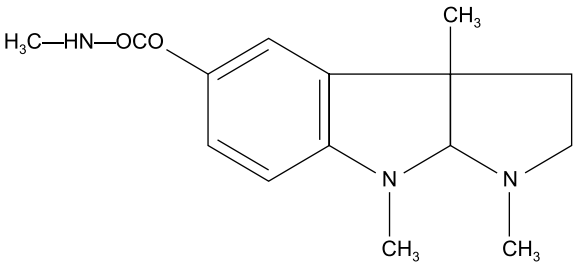


Pilocarpine

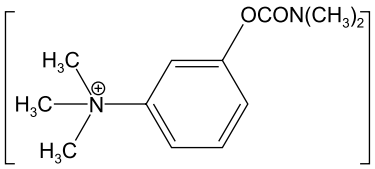


Indirect-acting/Cholinesterase Inhibitors (Reversible and Irreversible)

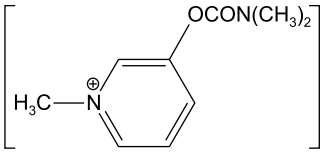
Physostigmine



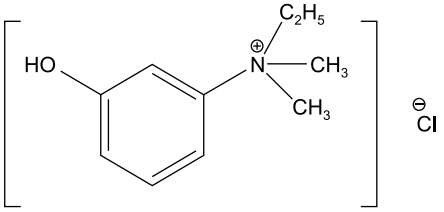
Neostigmine



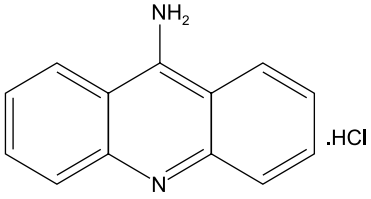
Pyridostigmine



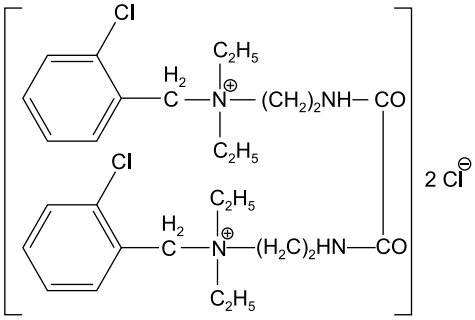
Edrophonium chloride



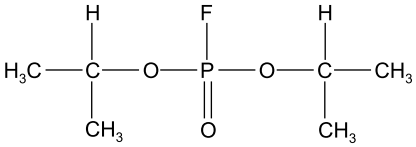
Tacrine hydrochloride



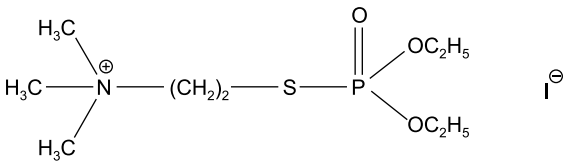
Ambenonium chloride



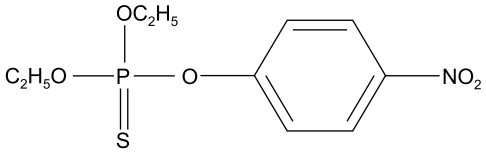
Isofluorphate



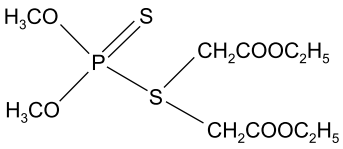
Echothiophate iodide



Parathione

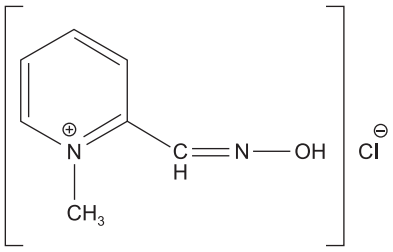


Malathion



Cholinesterase Reactivator

Pralidoxime chloride



Tacrine hydrochloride

Properties and uses: It is a centrally acting acetylcholinesterase inhibitor and indirect parasympathomimetic agent. It is used to treat Alzheimer's disease.

CHAPTER 37

Adrenergic Blockers

INTRODUCTION

Adrenergic blockers are also called antiadrenergic drugs or sympatholytics. Adrenergic blocking agents prevent the response of effector organs to endogenous as well as exogenous adrenaline and noradrenaline. These drugs block the actions of adrenergic drugs at alpha (α) or beta (β) adrenergic receptors.

Many types of adrenergic antagonists are used and several of these are clinically useful in medicine, particularly in the treatment of cardiovascular diseases. Drugs that decrease the amount of norepinephrine released as a consequence of sympathetic nerve stimulation as well as drugs that inhibit sympathetic nervous activity by suppressing sympathetic outflow is also widely used in medications. Almost all of these agents are competitive antagonists in their interactions with either α- or β-adrenergic receptors, and one exception is phenoxybenzamine, an irreversible antagonist that binds covalently to α-adrenergic receptors. These are due to important structural differences among the various types of adrenergic receptors. Selective β_1-antagonist drugs are used to act on the heart and selective β_2-antagonist drugs are used to act on the respiratory system.

PHYSIOLOGICAL BASIS OF ADRENERGIC RECEPTOR ANTAGONISTS

Blockade of vasoconstrictor α_1-receptors reduces peripheral resistance and causes reduced cardiac output leads to decreased blood pressure. The α-blockers abolish the pressor action of adrenaline, which then produces fall in the blood pressure due to β_2-mediated vasodilatation called *Dale's vasomotor reversal*. Pressor action of selective α-agonists is suppressed. Reflex tachycardia occurs due to the presynaptic α_2-receptors. Nasal stuffness and miosis result due to the blockade of α_2-receptors. The therapeutic application of drugs coming under the adrenergic antagonists are receptor oriented, especially β-blockers are used as antihypertensive, α-adrenergic antagonists are used to control the peripheral vascular resistance.

Mechanism of Action of α-adrenergic Blockers

α-Adrenergic receptor response in clinical relevance include α_1-receptor-mediated contraction of arterial and venous smooth muscle. α-adrenergic receptors are involved in suppressing sympathetic output, increasing vagal tone, facilitating platelet aggregation, inhibiting the release of norepinephrine, and acetylcholine from nerve endings. Blockade of α_1-receptors inhibits vasoconstriction induced by endogenous catecholamines. Vasodilatation may occur in both arteriolar resistance vessels and veins.

α_2-receptor regulates both central and peripheral sympathetic neurons. Acceleration of presynaptic α_2-receptors inhibits the norepinephrine release. In some vascular beds, these drugs promote vasodilatation through the release of nitric oxide (endothelial relaxing factor). Phenoxybenzamine inhibits the uptake of catecholamine from the nerve terminals. Phentolamine and tolazoline are competitive α-adrenergic antagonists and block the receptor for 5-HT and it causes the release of histamine from the mast cells, which is a potent vasodilator.

Mechanism of Action of β-adrenergic Receptor Blockers

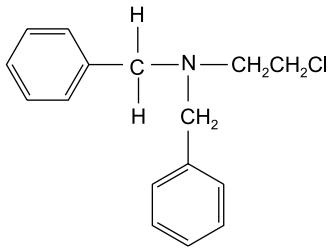
β-adrenergic receptor antagonists slow the heart rate and decrease the myocardial contractility, these prolongs the systolic conduction and disturbs the ventricular fibres. Dimensions of the ventricle is decreased, oxygen consumption is decreased, and thereby decreases the heart rate and aortic pressure. In blood vessels, these drugs reduce the noradrenaline release from the sympathetic terminals and decrease the renin from kidney due to the blockade of β-receptors.

CLASSIFICATION

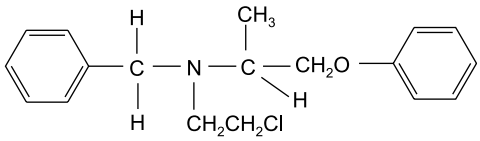
I. Alpha-receptor blocking agents

a. Beta-halo alkyl amines

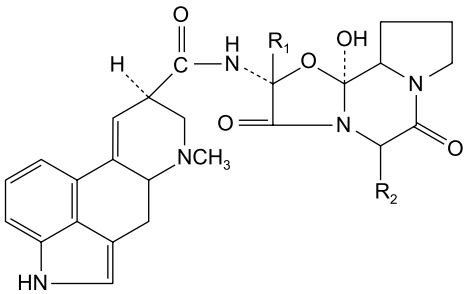
i. Dibenamine



ii. Phenoxy benzamine



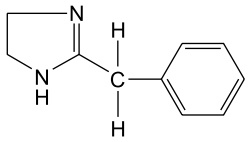
b. Natural and dehydrogenated ergot alkaloids



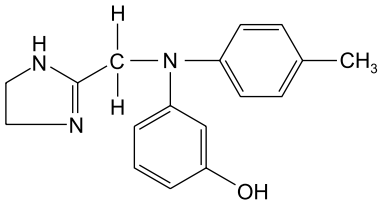
S. No.	Name	R_1	R_2
1.	Ergotamine	$-CH_3$	$-CH_2C_6H_5$
2.	Ergocristine	$-CH(CH_3)_2$	$-CH_2C_6H_5$
3.	Ergocriptine	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
4.	Ergocornine	$-CH(CH_3)_2$	$-CH(CH_3)_2$

c. Imidazole derivatives

i. Tolazoline

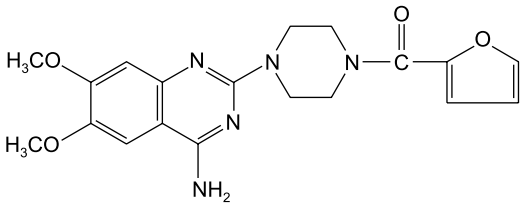


ii. Phentolamine

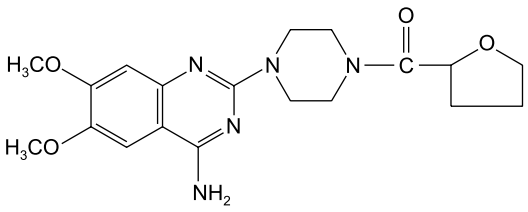


d. Quinazolines

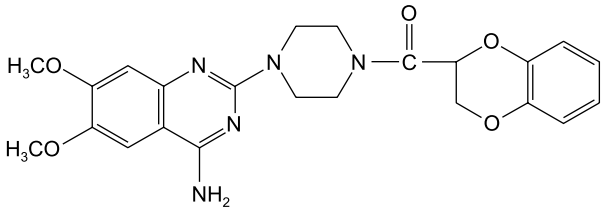
i. Prazosin



ii. Terazosin

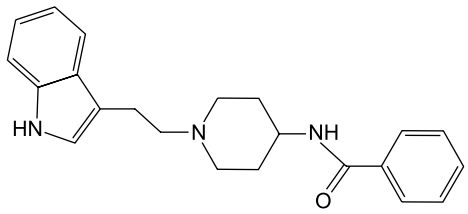


iii. Doxazosin

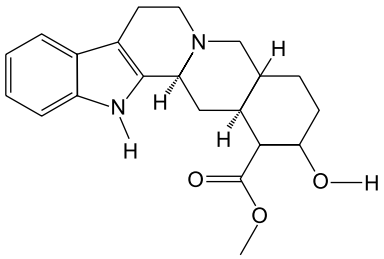


e. Miscellaneous

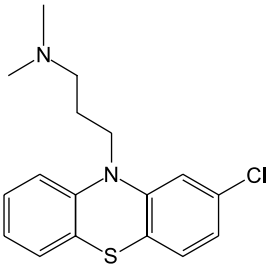
i. Indoramine



ii. Yohimbine



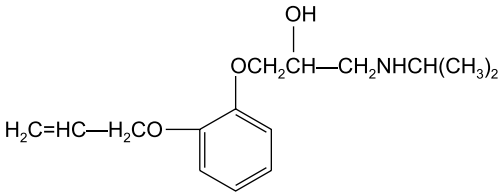
iii. Chlorpromazine



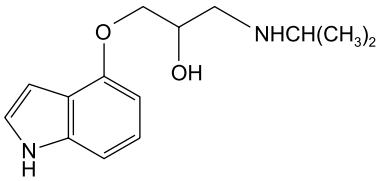
II. Beta-receptor blocking agents

a. β-Blockers with membrane stabilizing activity and intrinsic sympathomimetic property

i. Oxprenalol

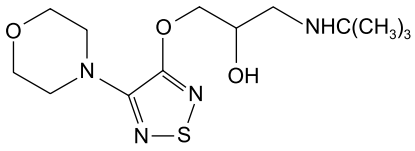


ii. Pindalol

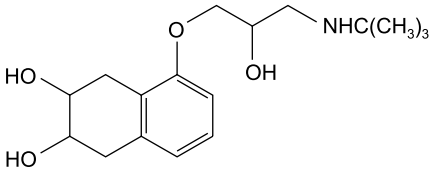


b. Specific β-blockers

i. Timolol

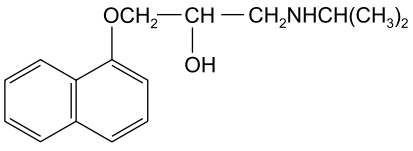


ii. Nodalol



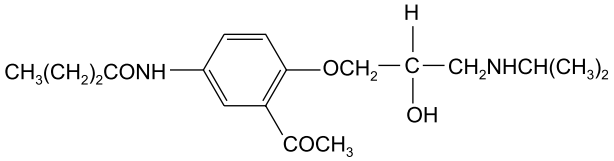
c. β-Blockers with membrane stabilizing activity

i. Propranolol

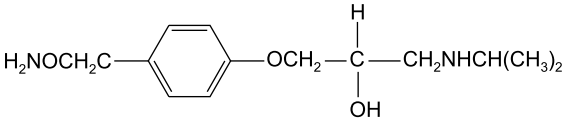


d. β-Blockers with cardioselective action

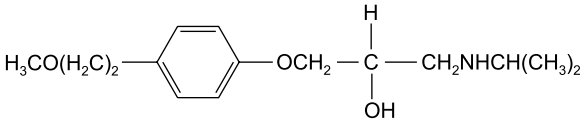
i. Acebutolol



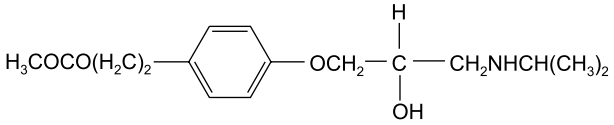
ii. Atenolol



iii. Metaprolol

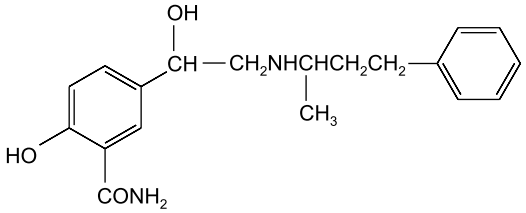


iv. Esmolol

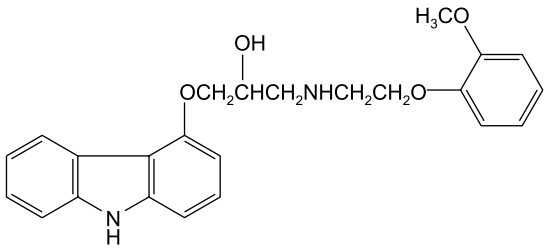


e. β-Blockers with α-blocking property

i. Labetolol



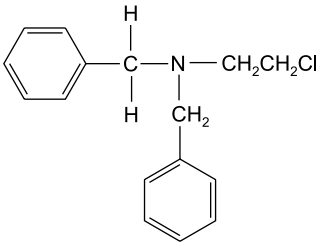
ii. Carvediol



SYNTHESIS AND DRUG PROFILE

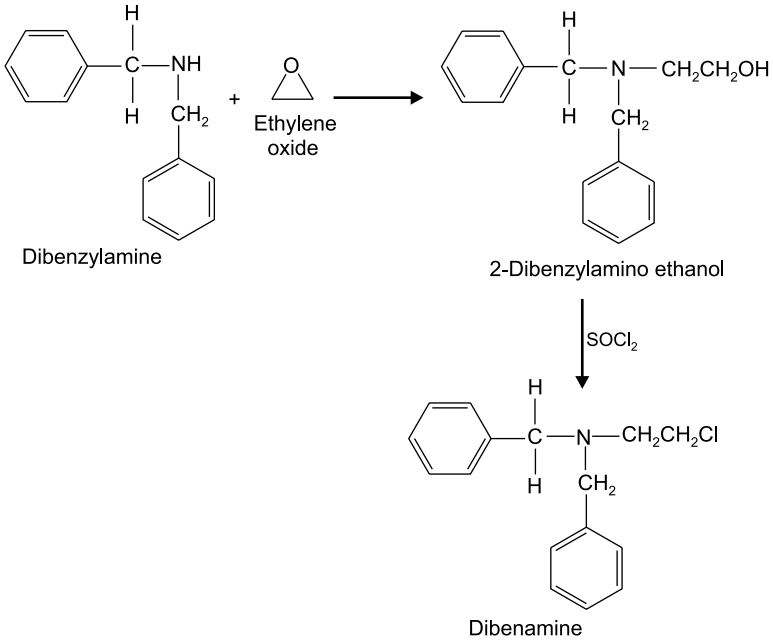
I. Alpha-receptor blocking agents

i. Dibenamine



N-(2-Chloro ethyl)-N-dibenzylamine

Synthesis



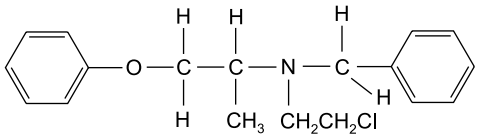
Dibenzylamine

2-Dibenzylamino ethanol

Dibenamine

Uses: Used as an antihypertensive agent.

ii. Phenoxybenzamine (Dibenzyline)



N-Benzyl-N-(2-chloroethyl)-1-phenoxypropan-2-amine

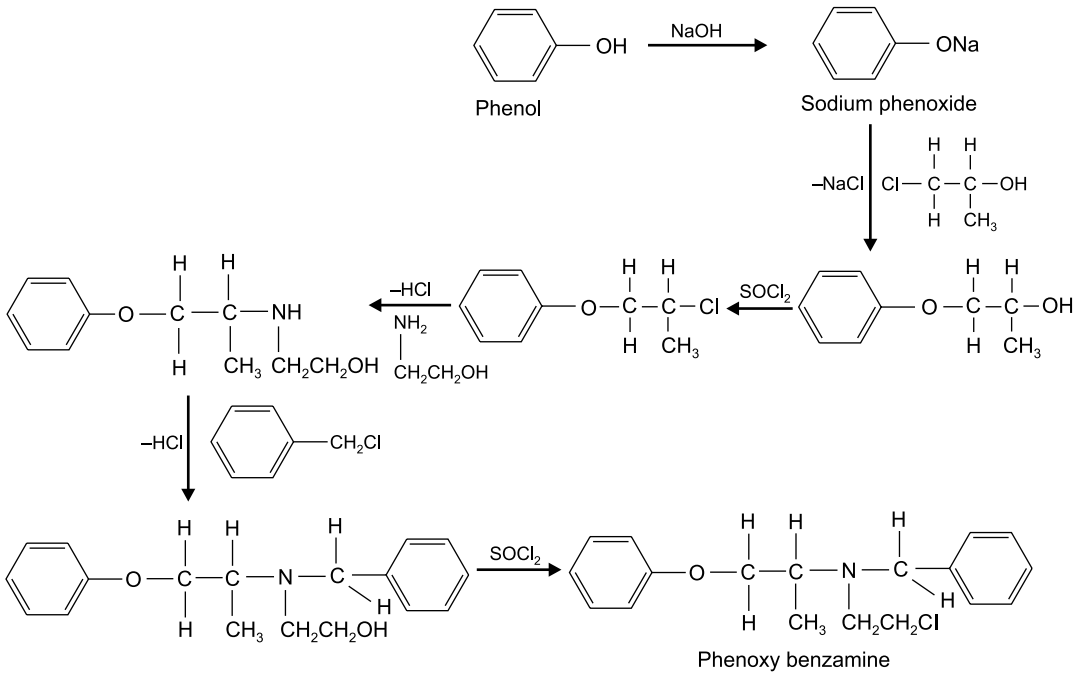
Properties and uses: Colourless, crystalline compound soluble in alcohol, water, and chloroform. Irreversible antagonist with non-selective actions, a major use of phenoxybezamine is in the treatment of pheochromocytoma (tumours of the adrenal medulla). It is used to treat peripheral vascular diseases, such as Raynaud's syndrome. It has also been used in the case of shock and frostbite to improve blood flow to peripheral tissues. Used in the treatment of shock and in the treatment of pulmonary oedema.

Assay: It is assayed by non-aqueous titration—the solution of the sample is titrated with 0.1 M perchloric acid using oracet blue B as indicator.

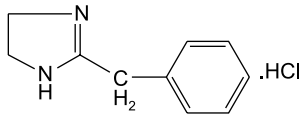
Dose: The usual dose initially 10 mg/day, increased gradually to 60 mg/day in divided doses.

Dosage forms: Phenoxybenzamine capsules BP.

Synthesis



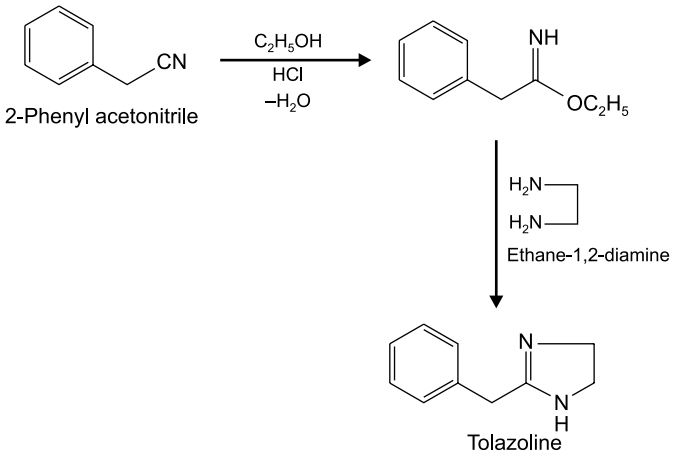
iii. Tolazoline (Synonym: Priscoline)



2-Benzyl imidazoline hydrochloride

Synthesis

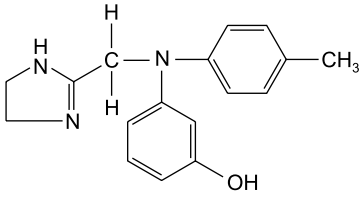
Route I. From: Phenyl acetonitrile



Properties and uses: It is a white, bitter taste, crystalline compound with a slight aromatic odour, soluble in water, alcohol, and chloroform, but sparingly soluble in ether. It is an imidazolidine derivative. It is a competitive alpha-adrenergic antagonist and possesses similar affinity for α_1- and α_2-receptors. It is a vasodilator and has a sympathomimetic effect to stimulate the heart and causes mydriasis. It is of some use in the treatment of Raynaud's disease, cerebral vascular accidents. It has been used in the treatment of persistent pulmonary hypertension of the newborn.

Dose: By IM, IV, SC, for adults—25 mg slowly, then increased up to 50 to 75 mg twice/day to two or three times/week.

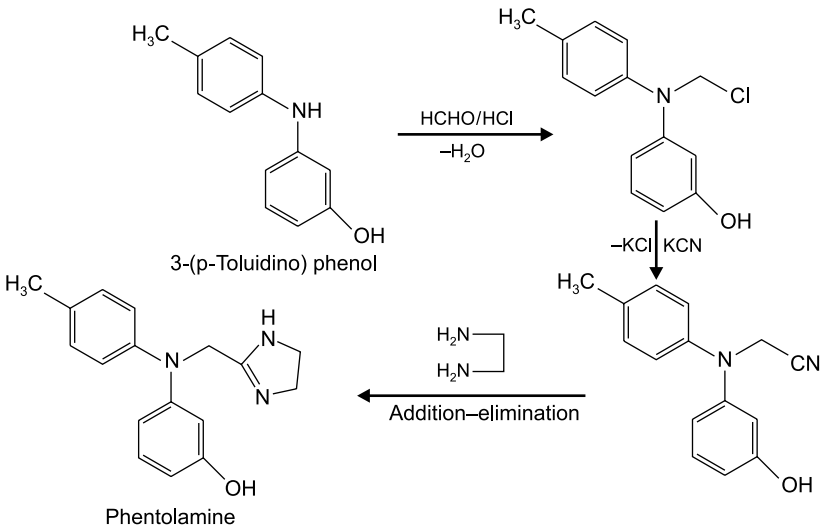
iv. Phentolamine mesylate



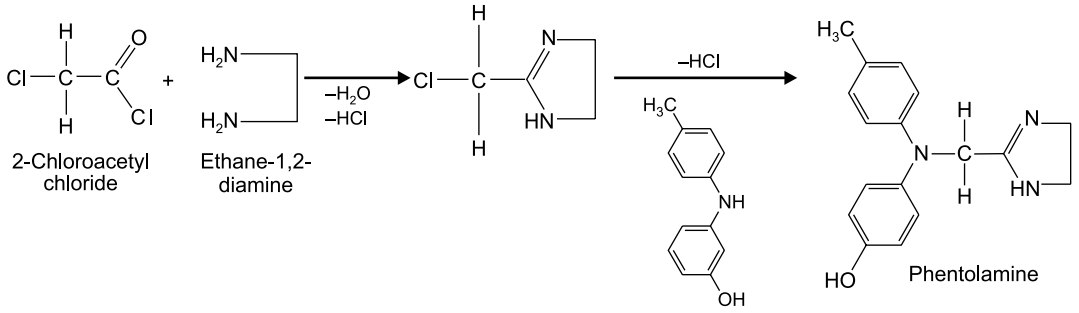
3[(4,5-Dihydro-1-imidazole-2yl)methyl](4-methyl-phenyl)amino phenol

Synthesis

Route I. From: 3-(*p*-Toluidino) phenol



Route II. From: 2-chloroacetyl chloride



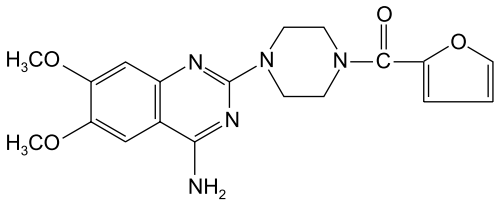
Properties and uses: It is a white, odourless, bitter powder, soluble in water and alcohol. Phentolamine is a non-selective α-adrenoreceptor antagonist with an immediate onset and short duration of action. In addition to α-blocking activity, it has weak muscarnic activity in the gastrointestinal tract and weak to mild histaminergic activity in the stomach. It is an α-adrenergic blocker used in urgent heart failure.

Assay: Dissolve the sample in 2-propanol and titrate under a current of nitrogen with 0.1 M tetrabutylammonium hydroxide in 2-propanol. Determine the end point potentiometrically, using a glass electrode as an indicator electrode and a calomel electrode containing a saturated solution of tetramethylammonium chloride in 2-propanol as the comparison electrode.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Phentolamine mesylate injection IP, phentolamine injection BP.

v. Prazosin (Minipress, Prazopress)



1-(4-Amino-6-7-dimethoxy-2-quinazolinyl)-
4-(2-furanyl carbonyl)-piperazine

Properties and uses: It is a white crystalline powder, soluble in water and alcohol. A selective α-antagonist, prazosin, reduces peripheral vascular resistance and lowers arterial blood pressure in both supine and erect patients. Dizziness, headache, and palpitations can occur. Used to treat hypertension of any degree. It has been used in decreasing cardiac overload.

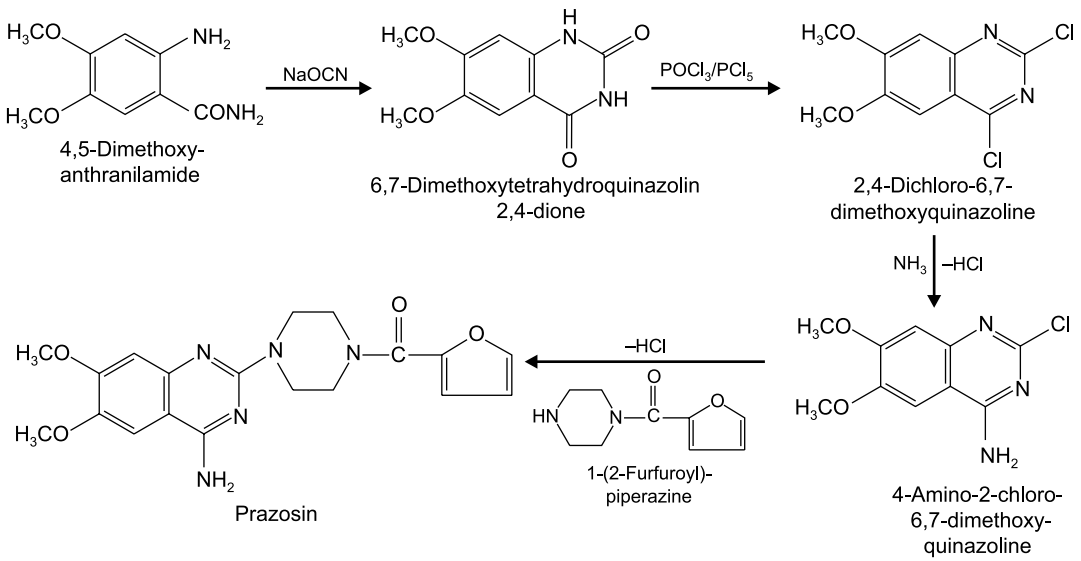
Assay: Dissolve the sample in acetic anhydride and add anhydrous formic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

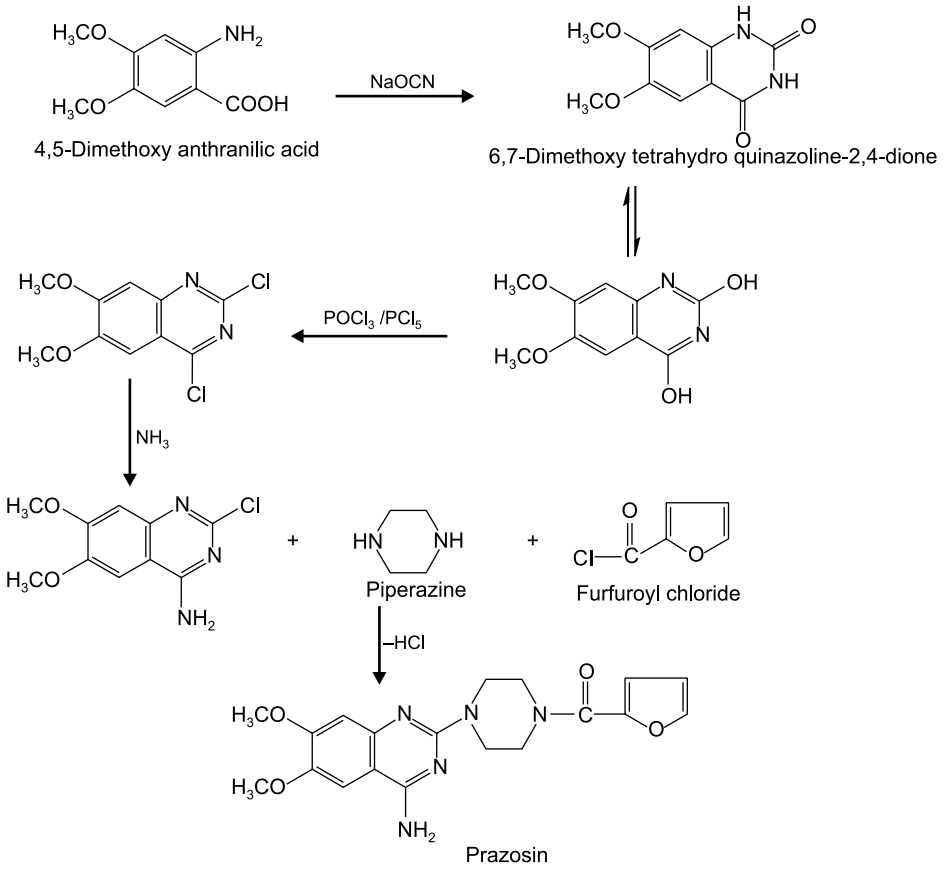
Dose: For hypertension—the adult dose as hydrochloride—initially, 500 µg twice to thrice/day for 3–7 days, increased to 1 mg two to three times for the next 3–7 days if tolerated and gradually increased thereafter according to the patient's response. Maximum dose is 20 mg/day.

Synthesis

Route I. From: 4,5-Dimethoxy anthranilamide



Route II. From: 4,5-Dimethoxy anthranilic acid

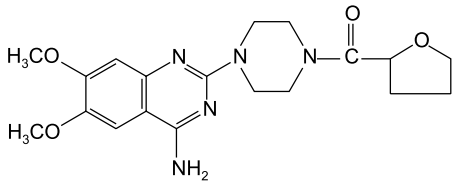


For heart failure: The adult dose as hydrochloride is initially, 500 µg twice to thrice/day, gradually increased according to response, maintenance dose is 4–20 mg day.

For Raynaud's syndrome: Benign prostatic hyperplasia (BPH): The adult dose initially is 500 µg twice/day, increased to a maintenance dose of <2 mg twice/day.

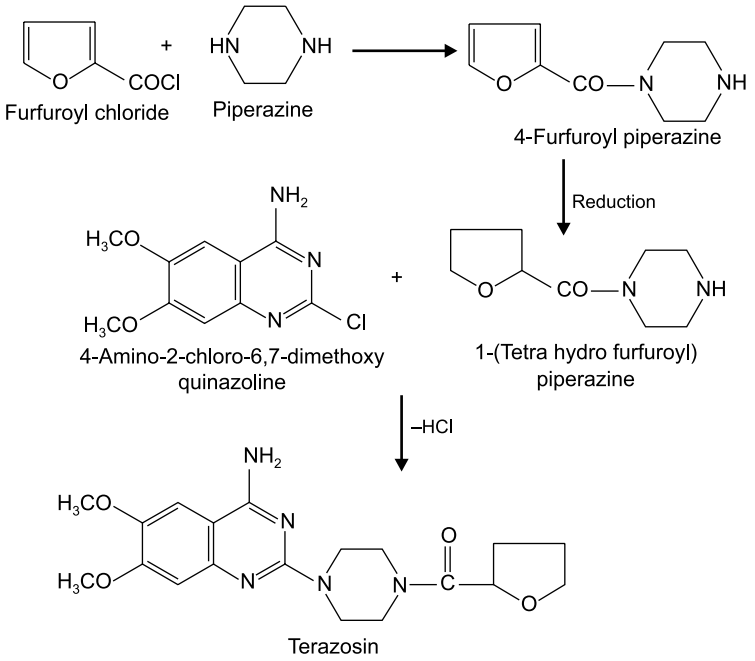
Dosage forms: Prazosin tablets IP, BP.

vi. Terazosin (Olyster, Teralfa, Terapress)



2{[4-(Tetrahydro-2-furanyl)-carbonyl]-1-piperazinyl}-6,7-dimethoxy-4-quinazolinamine

Synthesis



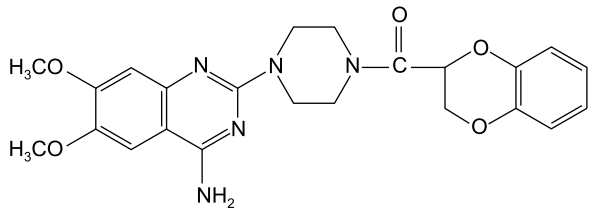
Properties and uses: It is a white or slightly yellow crystalline powder, insoluble in acetone, sparingly soluble in water, slightly soluble in methanol and ethanol. This α-adrenergic receptor blocker has a longer half-life (12 h) and longer duration of action (24 h) than prazosin, but is otherwise, similar to prazosin. Because the α_1-selective drugs have little action on presynaptic receptors, they do not increase norepinephrine concentrations and reflex sympathetic activity (tachycardia) is less likely to occur.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and methanol. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

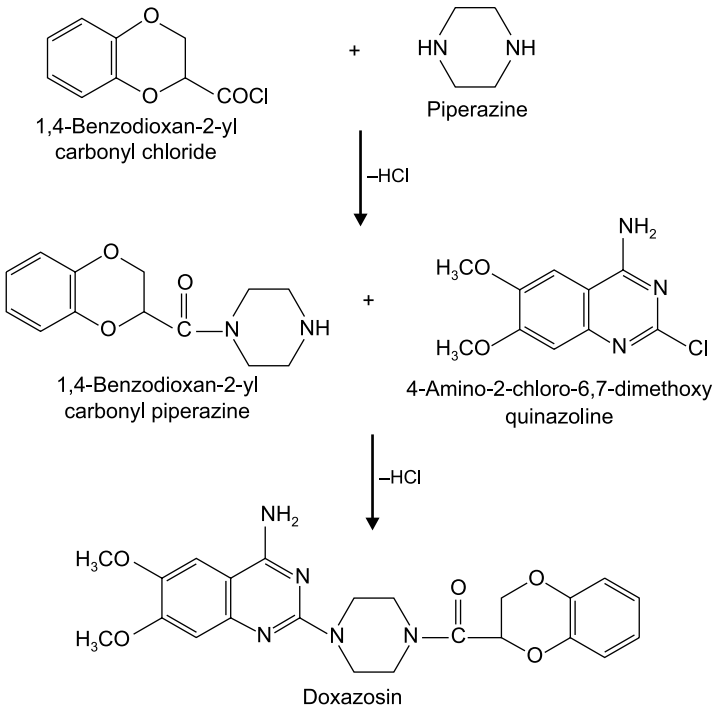
Dose: For hypertension—the initial dose for adult is 1 mg at bedtime, gradually increased two to three times a day according to the patient's response. Maintenance dose is 2–10 mg once daily. Maximum effect observed with 20 mg/day in 1 or 2 divided doses.

vii. Doxazosin (Alfazosin, Doxacard, Duracard)



1-(4-Amino-6,7-dimethoxy-2-quinozolinyl)-4-(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl piperazine

Synthesis



Properties and uses: It is a water soluble analogue of prazosin and terazosin. It is a white or almost white crystalline powder. It shows polymorphism and some forms may be hygroscopic. Slightly soluble in water, methanol, insoluble in acetone, but soluble in a mixture of water and tetrahydrofuran. It is a new selective α_1-adrenergic receptor antagonist similar to prazosin. Doxazosin, possibly, may prevent influx of extracellular calcium and cause relaxation of vascular smooth muscle. Headache and dizziness are the two most prevalent adverse effects.

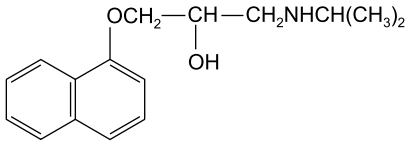
Assay: It is assayed by using liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For hypertension—for adult as mesylate, initial dose is 1 mg at bedtime increase after 1–2 week according to response. Maintenance dose is 4 mg once daily, maximum dose is 16 mg/ day.

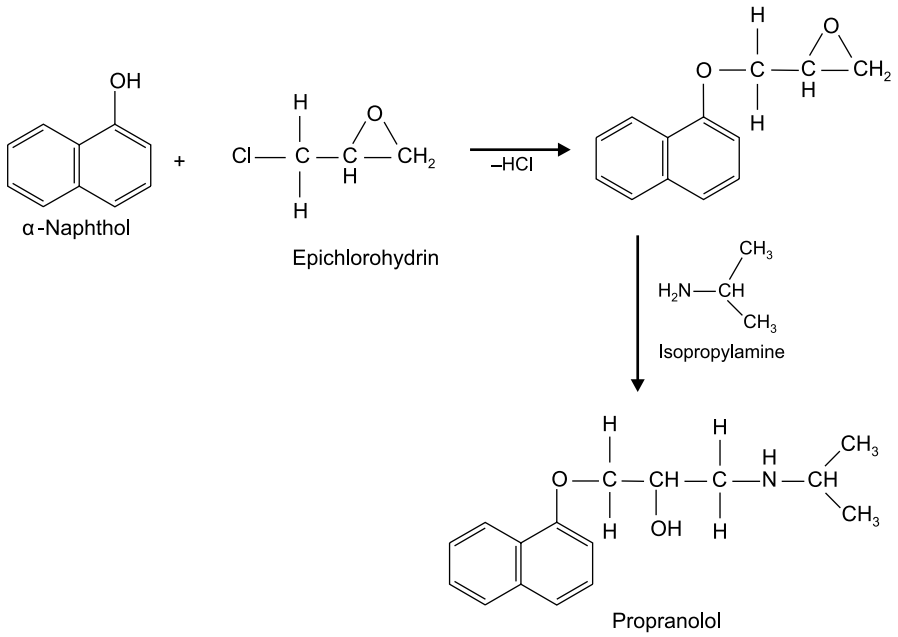
II. Beta-receptor blocking agents

i. Propranolol (Synonym: Inderal, Ipran, Manopralol, Beetacap)



1-(Isopropyl amino)-3-(1-napthyloxy)-2-propanol

Synthesis



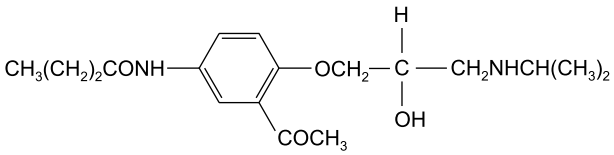
Properties and uses: It is a white or almost white powder, soluble in water and in ethanol. Currently, it is approved for hypertension associated cardiac arrhythmia, angina pectoris, due to coronary atherosclerosis and prophylaxis of migraine headache. It is a non-selective β-adrenergic antagonist and it has equal affinity for β_1- and β_2-receptors.

Assay: Dissolve the sample in ethanol and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: The oral adult dose for arrhythmias is 10 to 30 mg three to four times/day.

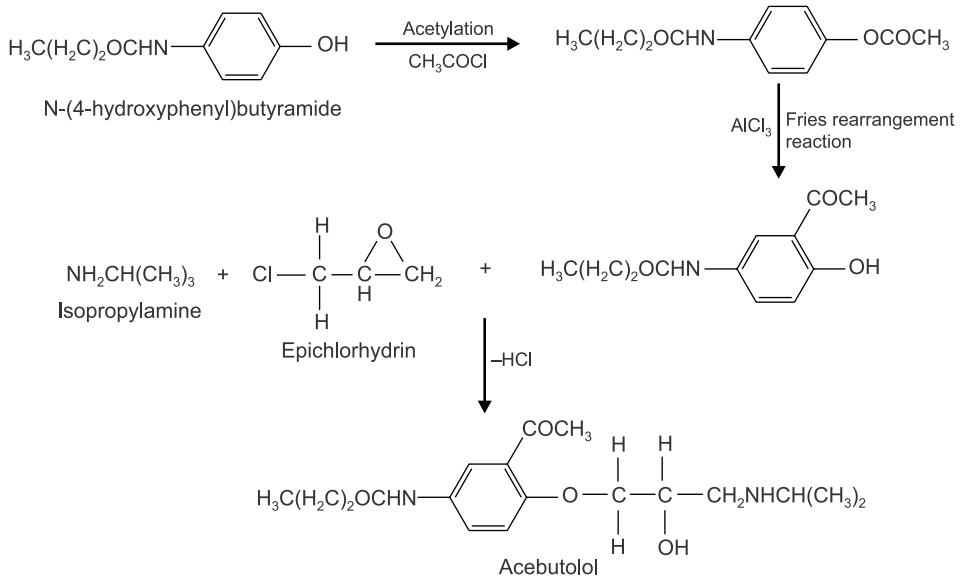
Dosage forms: Prolonged-release propranolol capsules BP, propranolol injection BP, propranolol tablets BP.

ii. Acebutolol (Sectral)



N-3-Acetyl-4-[2-hydroxy-3-(isopropyl)-amino propoxy]phenyl butyramide

Synthesis



Properties and uses: It is a white or almost white crystalline powder, slightly soluble in acetone and methylene chloride, but freely soluble in water and ethanol. It is one of the very few β-blockers with mild ISA and does not cause bradycardia as propranolol does. Acebutalol and betaxolol possess membrane stabilizing activity, but the activity is much weaker than that seen with propranolol.

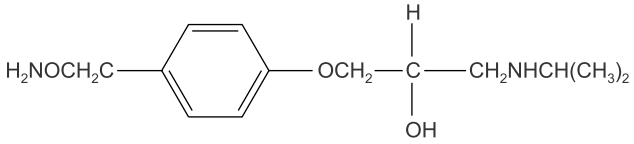
Assay: Dissolve the sample in ethanol and add 0.1 M hydrochloric acid. Perform potentiometric titration by titrating with 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: A dose of 400 mg/day given once daily.

Dosage forms: Acebutolol HCl tablets IP, acebutolol capsules BP, acebutolol tablets BP.

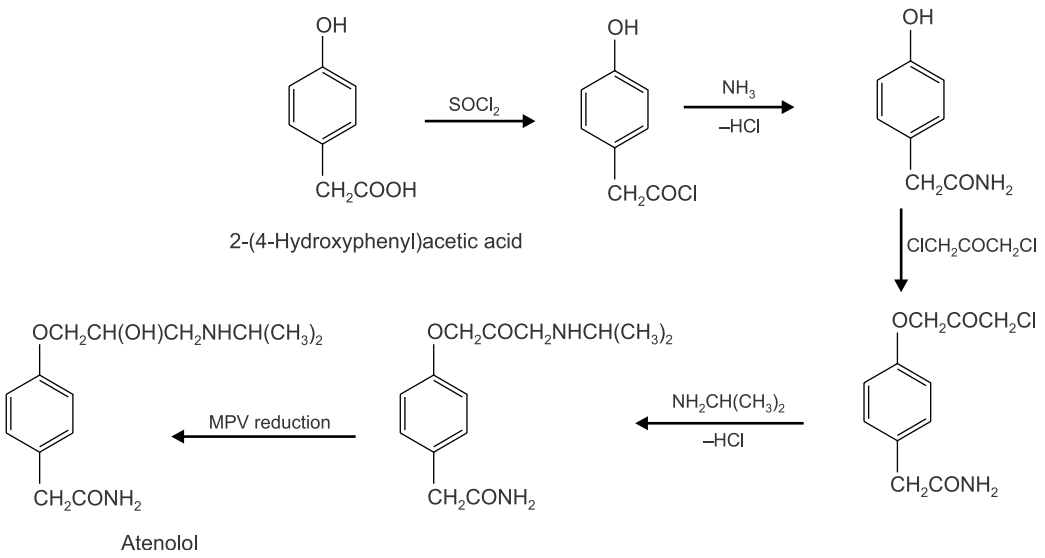
iii. Atenolol (Atenex, Aten, Betacard)



4-{2-Hydroxy-3-[(1-isopropyl) amino]propoxy}benzeneacetamide

Synthesis

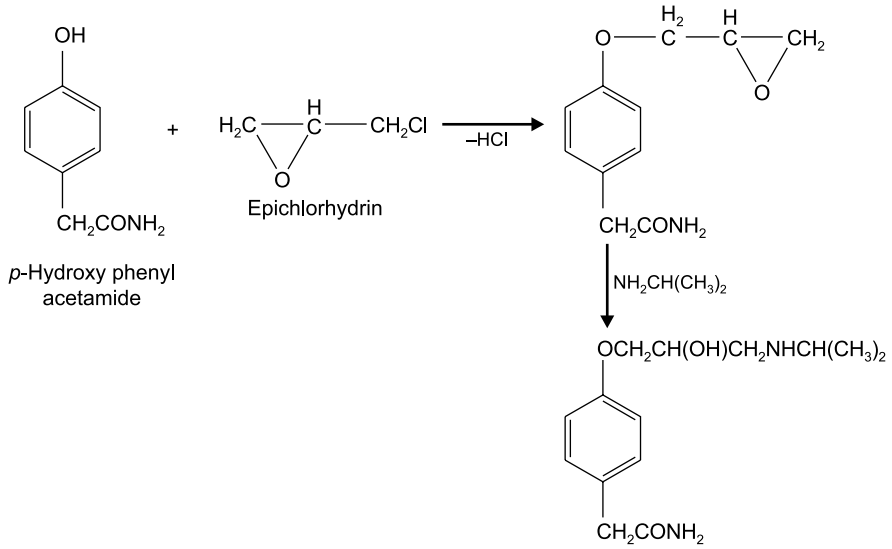
Route I. From: 2-(4-Hydroxyphenyl) acetic acid



2-(4-Hydroxyphenyl)acetic acid

Atenolol

Route II. From: *p*-Hydroxy phenyl acetamide



p-Hydroxy phenyl acetamide

Epichlorhydrin

Atenolol

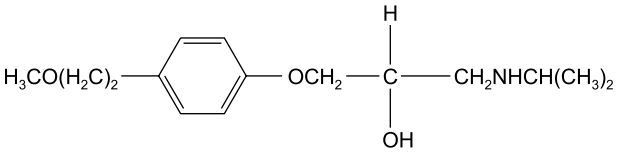
Properties and uses: It is a white or almost white powder, sparingly soluble in water, but soluble in ethanol. It is a β_1-selective drug with low lipid solubility. Mainly used in the treatment of essential hypertension.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The usual dose is 50 mg/day once daily.

Dosage forms: Atenolol tablets IP, BP, atenolol injection BP, atenolol oral solution BP, co-tenidone tablets BP.

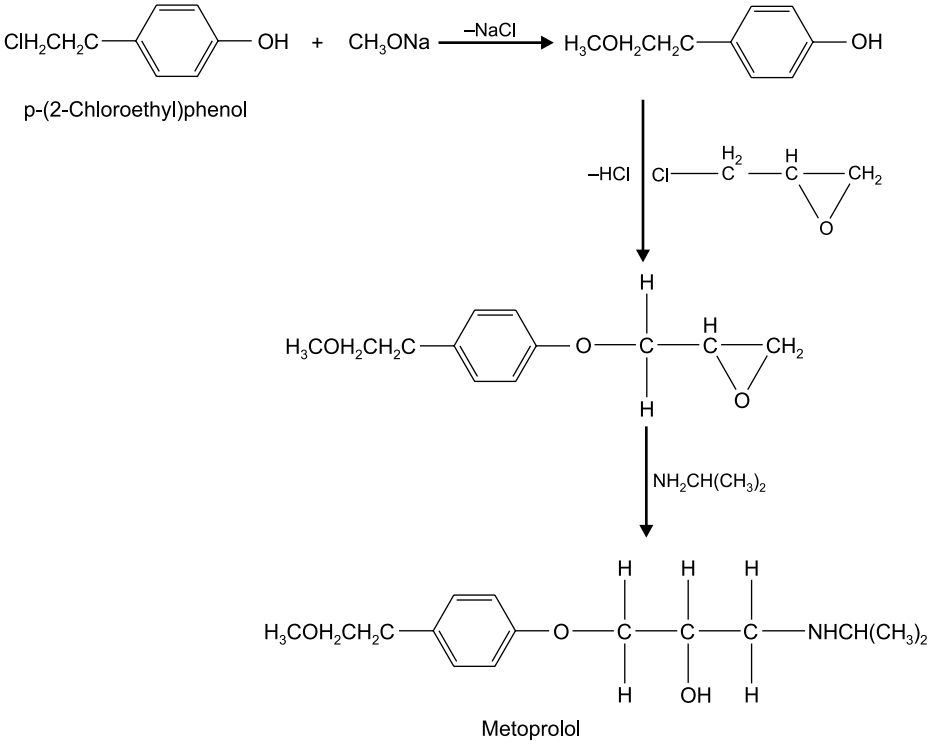
iv. Metoprolol (Betaloc, Lopresor, Metolar)



1-[4-(2-methoxy ethyl)phenoxy]-3-(isopropylamino)-2-propanol

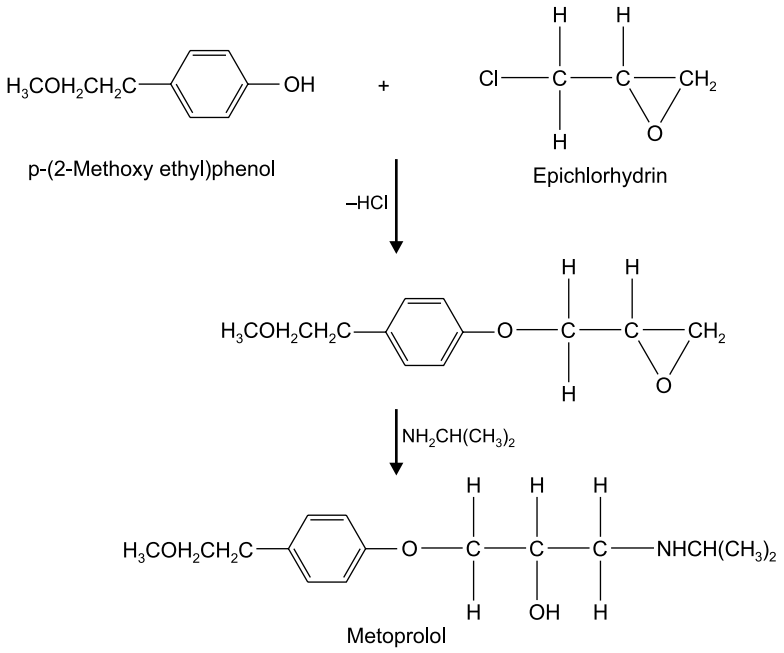
Synthesis

Route I. From: *p*-(2-Chloroethyl) phenol



Metoprolol

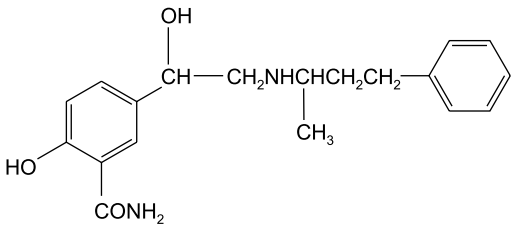
Route II. From: *p*-(2-Methoxy ethyl) phenol



Properties and uses: It is white, odourless powder, bitter in taste, soluble in water, alcohol, and chloroform, but insoluble in acetone and ether. It is a β_1-selective antagonist used in the treatment of hypertension.

Dose: The usual initial oral dose is 100 mg given preferably once daily.

v. Labetalol (Labesol, Normadate)



5-{1-hydroxy-2-[(1-methyl-3-phenyl propyl)amino]ethyl}salicylamide

Properties and uses: It is a white or almost white powder, sparingly soluble in water and alcohol, but insoluble in methylene chloride. Labetolol is a phenyl ethanol amine derivative that is a competitive inhibitor at both β_1- and β_2-adrenergic receptors and at the α_1-adrenergic receptor. It is more potent β-antagonist than α-antagonist, since it has two asymmetric carbon atoms (1 and 1'), it exists as a mixture of four isomers. It is the mixture that is used clinically in treating hypertension. The different isomers, however, posses different α- and β-antagonistic activities.

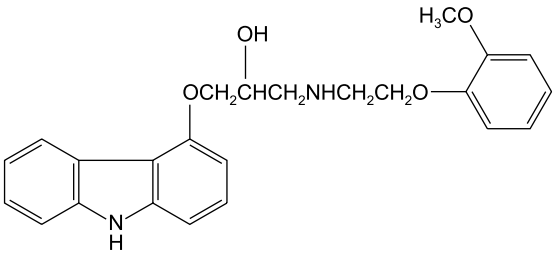
Assay: Dissolve the sample in a mixture of anhydrous formic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Dose: The usual initial dose is 100 or 200 mg twice/day with food.

Dosage forms: Labetalol injection BP, labetalol tablets BP.

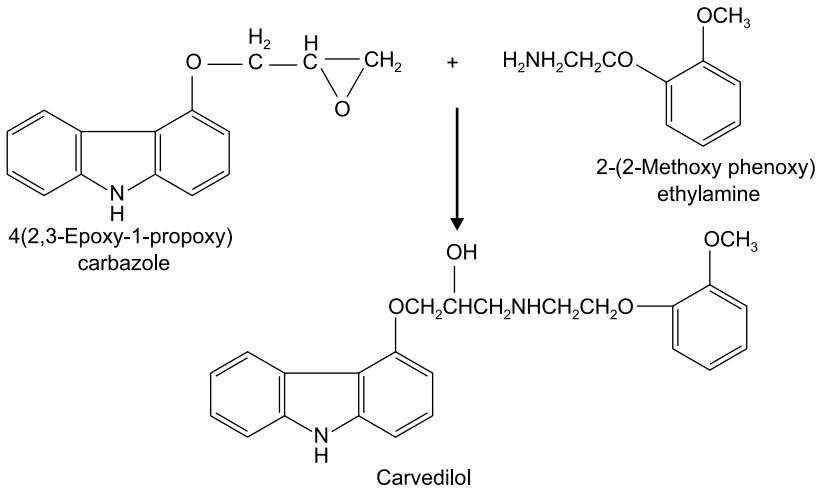
vi. Carvedilol (Cardivas, Carvedil, Carvipress)

It acts on both β- and α-adrenergic receptors. Only d-isomer is β-blocking, and both enantiomers have α-blocking activity.



1-(Carbazol-4-yloxy)-3-[2-(2-methoxyl phenoxy)ethyl amino]-2-propanol

Synthesis



Properties and uses: It is a white or almost white crystalline powder, insoluble in water and dilute acids, but soluble in alcohol. It shows polymorphism. Used in treating hypertension and congestive heart failure.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: For hypertension: Adult—initially, 12.5 mg once daily increased to 25 mg once daily after 2 days. Alternatively, initial dose of 6.25 mg twice/day increased to 12.5 mg twice/day after 1–2 week, increased further if necessary to 50 mg once daily or in divided doses. For elderly: 12.5 mg once daily.

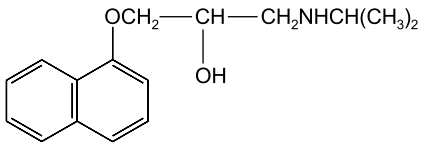
For angina pectoris: Adult—initially, 12.5 mg twice/day increased to 25 mg twice/day after 2 days.

For heart failure: Adult—initially, 3.125 mg twice/day, doubled to 6.25 mg twice/day after 2 weeks, if tolerated.

For left ventricular dysfunction: After myocardial infarction: adult—initially: 6.25 mg twice/day, if tolerated, after 3–10 days, increase to 12.5 mg twice/day and then to a target dose of 25 mg twice/day.

STRUCTURE–ACTIVITY RELATIONSHIP

Propranolol has become one of the most thoroughly studied and widely used drug in the therapeutic armamentarium; it is the standard against which all other β-antagonists are compared.



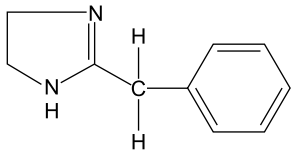
Propranolol

- The aromatic ring and its substituent are the primary determinant of β_1-antagonistic activity. The aryl group also affects the absorption, excretion, and metabolism of the β-blockers.
- β-blockers are structurally similar to β-agonist. The catechol ring can be replaced by a variety of ring system without loss of antagonistic activity.
- Replacement of catechol hydroxyl group with chlorine of phenyl ring system retains β blocking activity. Example—pronethalol, dichloroisoproterenol.
- N,N–disubstitution decreases the β-blocking activity, and the activity is maintained when the phenyl ethyl, hydroxy phenyl ethyl, or methoxy phenyl ethyl groups are added to amine as a part of the molecule.
- The two carbon chains are essential for activity.
- The introduction of -OCH_2 group into the molecule between the aromatic ring and the ethyl amine side chain provides β-blocking agents, for example, propranolol.
- As in the sympathomimetics, bulky aliphatic groups, such as the *tert.*-butyl and isopropyl groups are normally found on the amino function of the aryloxypropanolamine β-receptor antagonists. It must be a secondary amine for optimal activity.
- As with the sympathomimetic agents, the configuration of the hydroxyl bearing carbon of the aryloxy-propanolamine side chain play a critical role in the interaction of β-antagonist drugs with β-receptor. The carbon must possess the (S)-configuration for optimal affinity to the β-receptor. The enantiomer with the (R)-configuration is typically 100 times less potent.

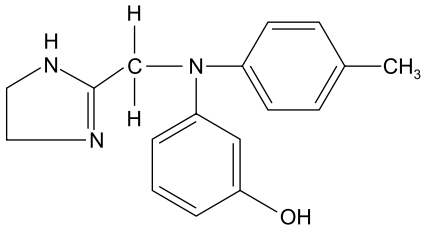
CLASSIFICATION BASED ON PCI SYLLABUS

Alpha-adrenergic Blockers

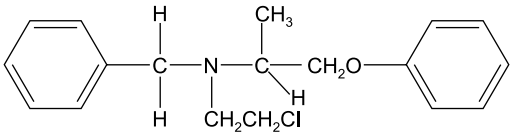
Tolazoline



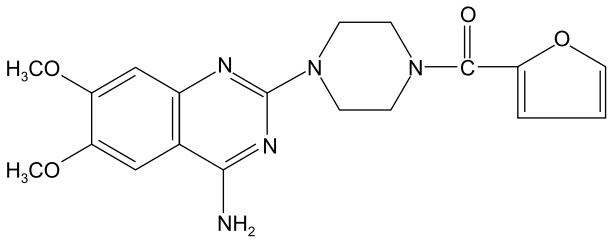
Phentolamine



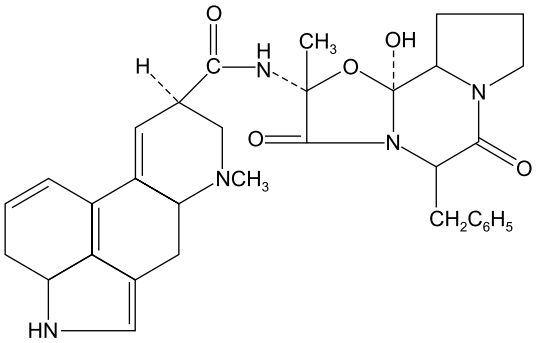
Phenoxy benzamine



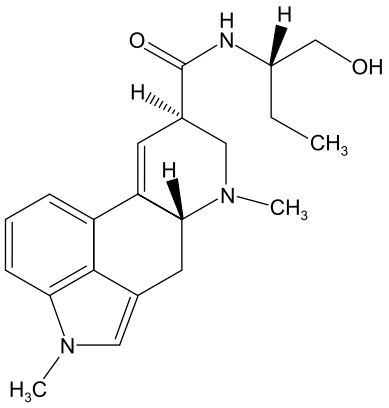
Prazosin



Dihydroergotamine

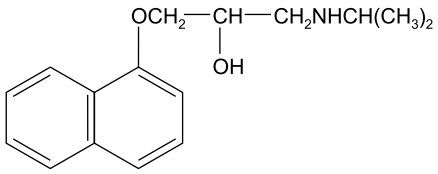


Methysergide

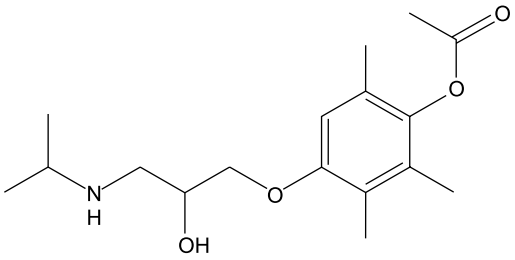


Beta-adrenergic Blockers

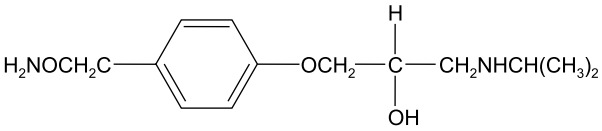
Propranolol



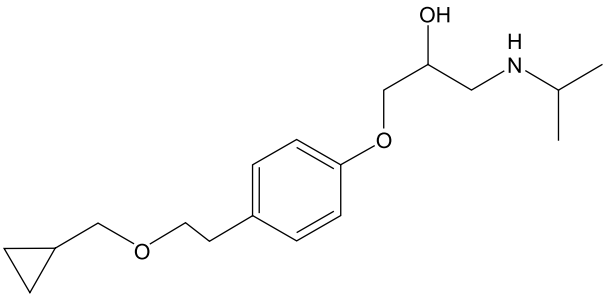
Metipranolol



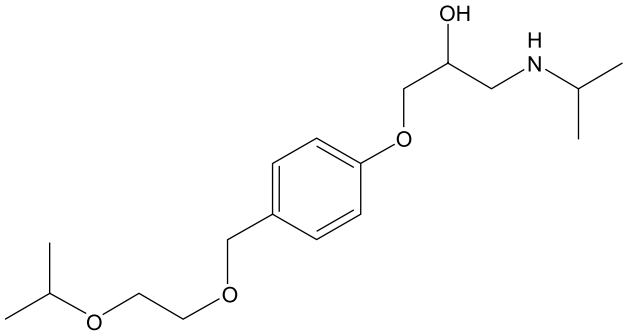
Atenolol



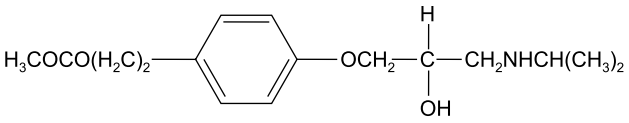
Betazolol



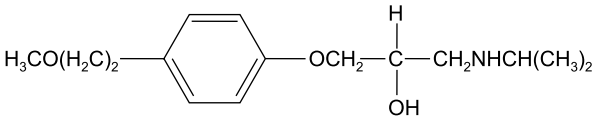
Bisoprolol



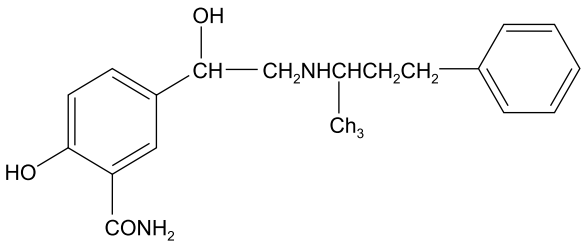
Esmolol



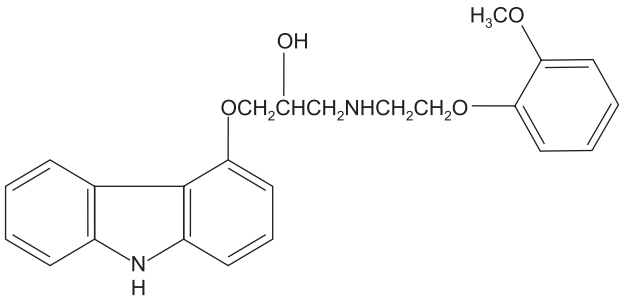
Metaprolol



Labetolol



Carvediol



Metipranolol

Properties and uses: It is a non-selective beta-blocker used to treat glaucoma. It is used in eyedrops.

Bisoprolol

Properties and uses: It is a beta-blocker used to treat high BP and chest pain due to less supply of blood to the heart.

CHAPTER 38

Anticholinergic Drugs

INTRODUCTION

The parasympatholytics or cholinergic blocking agents include atropine and related alkaloids obtained from plants, such as *Atropa belladona, A. accuminata, Hyosyamus niger, Scoplola carniolica*, *Datura strammonium,* and synthetic or semisynthetic atropine substitutes. These drugs in the therapeutic doses predominantly block the muscarinic actions of acetylcholine, but the ganglionic and skeletal neuromuscular actions of acetylcholine are not affected.

Cholinergic receptor blocking drugs or antagonists are divided into muscarinic and nicotinic subgroups on the basis of their specific receptor affinities. The antinicotinic drugs consist of ganglion blockers and neuromuscular junction blockers. The ganglion-blocking drugs have little clinical use. Muscarinic antagonists are often called parasympatholytics. There are naturally occurring compounds with antimuscarinic effects that have been known and used in medicines and cosmetics as well as in poisons. Atropine is a prototype of these drugs. Many similar plant alkaloids are known and hundreds of synthetic antimuscarinic compounds have been prepared.

Muscarinic receptor antagonists prevent the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscles, cardiac muscles and gland cells; in peripheral ganglia; and in the central nervous system. In general, M receptor antagonists cause little effect on the N receptor sites. However, quaternary ammonium analogues of atropine and related drugs, generally, exhibit a greater degree of nicotinic blocking activity, and consequently, are more likely to interfere with the ganglions on neuromuscular transmission. In the central nervous system (CNS) both muscarinic and nicotinic receptors are distributed at the spinal, subcortical, and cortical levels in the brain. At a high dose or a toxic dose, the actions in the CNS of the atropine and related drugs, generally, produce stimulation followed by depression.

Parasympathetic neuroeffector junctions in the different organs are not equally sensitive to even the non-selective muscarinic receptor antagonists. A small dose of atropine depresses salivary and bronchial secretion and sweating. With large doses, the pupil dilates, accommodation of lenses to near vision is inhibited. The heart rate is increased due to the vagal block. The actions of many of the clinically available muscarinic receptor antagonists differ only quantitatively from those of atropine considered as the prototype. The currently available classes of drugs include the following:

1. Naturally occurring alkaloid-atropine and scopolamine (atropine from a plant *A. belladona*).
2. Semisynthetic derivatives such as homatropine, atropine methonitrate, ipratropium bromide, and tiotropium bromide.
3. Synthetic congeners (show some selectivity for nicotinic and muscarinic receptors).

Out of these synthetic compounds, according to their various therapeutic uses, they have been segregated into mydriatics (cyclopentolate), antisecretory, and antispasmodics (propantheline, oxyphenonium, dicyclomine, and pirenzepine) and also antiparkinson's drugs (trihexyphenidyl, procyclidine, and biperiden). The cholinergic blocking agents can be grouped pharmacologically according to their location and type of cholinergic receptors into the following:

1. Parasympathetic postganglionic blocking agents or antimuscarinic agents. Example: Atropine, scopolamine.
2. Ganglionic blocking agents. Example: Hexamethonium, curare alkaloids, pancuronium bromide.
3. Neuromuscular blocking agents. Example: Tubocurarine, metocurine.

DIFFERENCE BETWEEN THE QUATERNARY AND THE TERTIARY ANTIMUSCARINICS

Quaternary Amines

- These drugs do not pass through the blood–brain barrier, and hence, lack CNS actions.
- Penetrate poorly into the eye from the bloodstream or cornea.
- The quaternary compounds have greater affinity for nicotinic receptors, so that a great degree of ganglionic blockade may result.
- These are mostly excreted unchanged into the urine.

Tertiary Amines

- These drugs can penetrate the cell membranes in the non-ionized form, and hence, can pass through the blood–brain barrier. In the brain, they can exert both therapeutic and toxic actions.
- These drugs penetrate through the cornea and cause mydriasis and cycloplegia.
- They do not have nicotinic receptor affinity.
- These drugs are biotransformed in the liver.

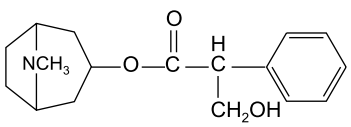
Therapeutic Uses

1. Used topically to dilate the pupil and paralyze accommodation.
2. Used as a preanaesthetic medication, to inhibit excessive salivary, bronchial secretions, and to prevent bronchospasm and laryngospasm.
3. The antisecretory effects are also sought in the treatment of acute coryza, hay fever, and rhinitis.
4. Used in the treatment of bronchial asthma and peptic ulcer.
5. Used in the treatment of Parkinson's disease.

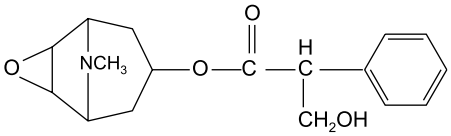
CLASSIFICATION

I. Solanaceous alkaloids and analogues

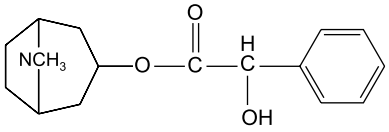
i. Atropine



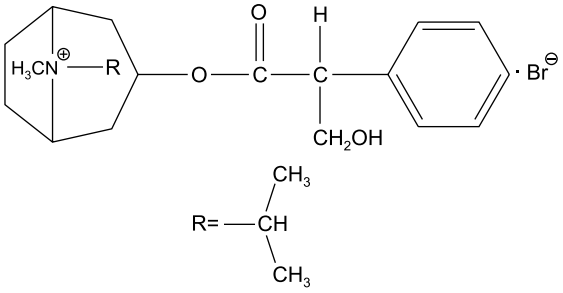
ii. Scopolamine (Hyoscine)



iii. Homatropine

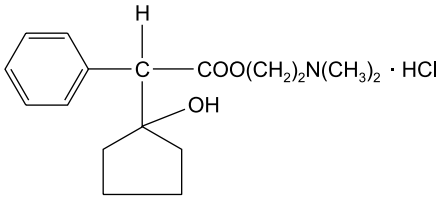


iv. Ipratropium bromide

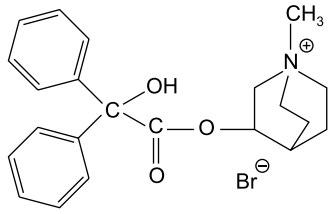


II. Amino alcohol esters

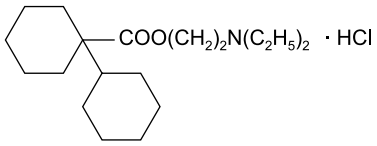
i. Cyclopentolate



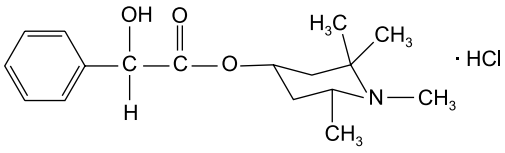
ii. Clidinium



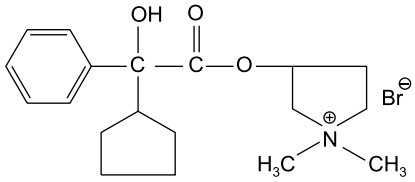
iii. Dicyclomine



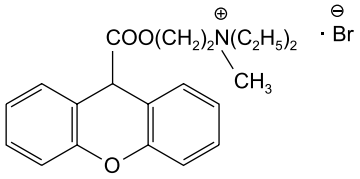
iv. Eucatropine HCl



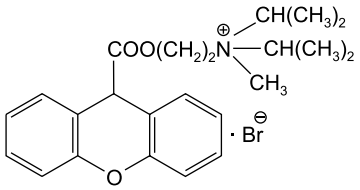
v. Glycopyrronium bromide



vi. Methantheline bromide

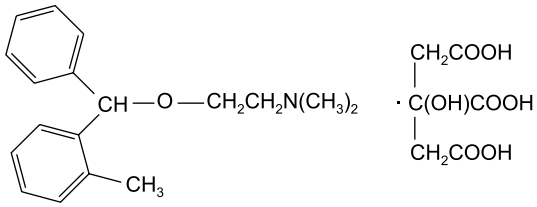


vii. Propantheline bromide

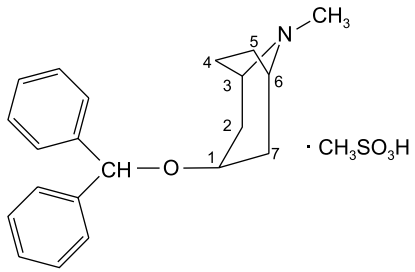


III. Amino ethers

i. Orphenadrine citrate

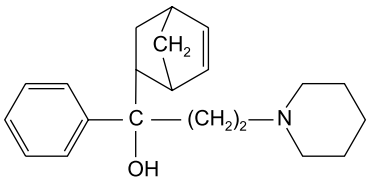


ii. Benztropine mesylate

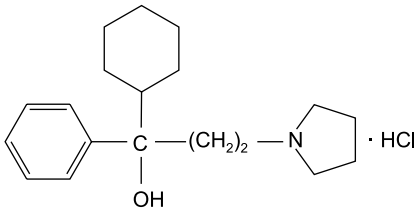


IV. Amino alcohols

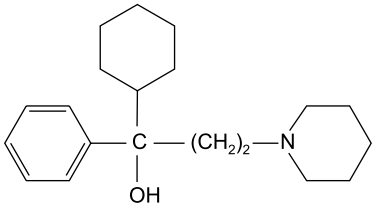
i. Biperiden



ii. Procyclidine HCl

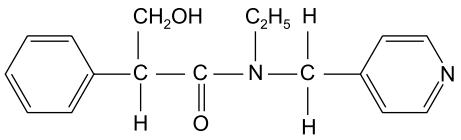


iii. Trihexyl phenidyl

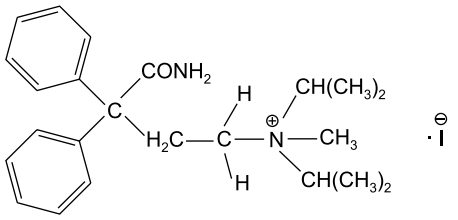


V. Amino amides

i. Tropicamide

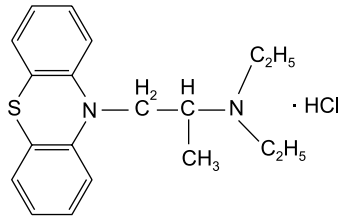


ii. Isopropamide iodide

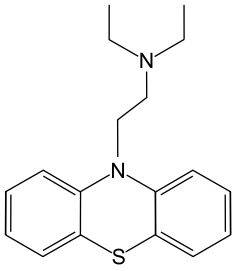


VI. Diamides

i. Ethopropazine HCl

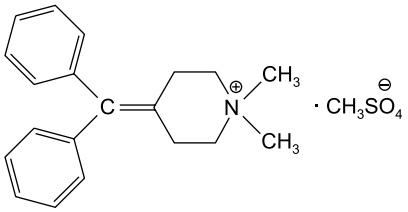


ii. Diethazine

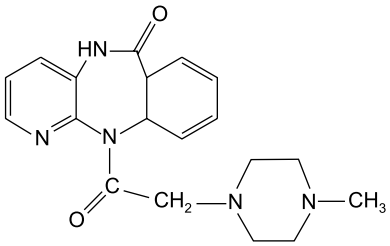


VII. Miscellaneous amines

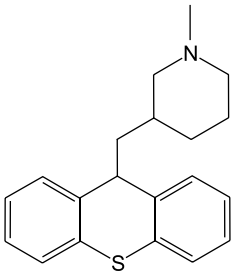
i. Diphenmail methyl sulphate



ii. Pirenzepine



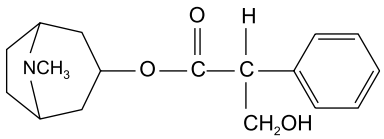
iii. Methixene



SYNTHESIS AND DRUG PROFILE

I. Solanaceous alkaloids and analogues

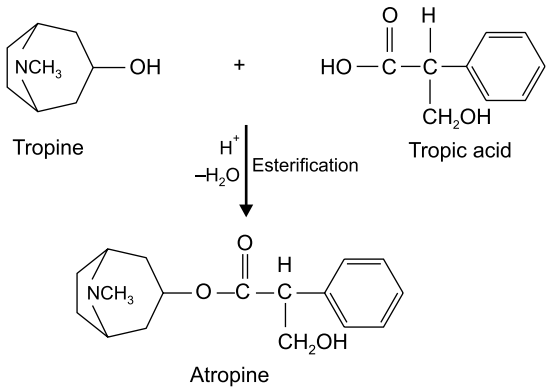
i. Atropine (Atp, Tropine)



8-Methyl-8-aza-bicyclo[3,2,1]octan-3-yl-3-hydroxy-2-phenylpropanoate

Properties and uses: It is a white crystalline powder or colourless crystals, freely soluble in alcohol, and well soluble in water. It is the tropine ester of racemic tropic acid and is optically inactive. The greater molar potency of atropine helps it to block several moles of acetylcholine. The umbrella-like atropine molecule may mechanically or electrostatically inactivate adjacent receptors on the cell surface so that these receptors are also unavailable for acetylcholine or other parasympathomimetic stimulants. Atropine has all the actions and uses of antimuscarinic drugs.

Synthesis



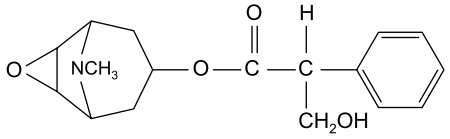
Assay: Dissolve the sample in anhydrous acetic acid and warm it, if necessary. Cool the solution and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

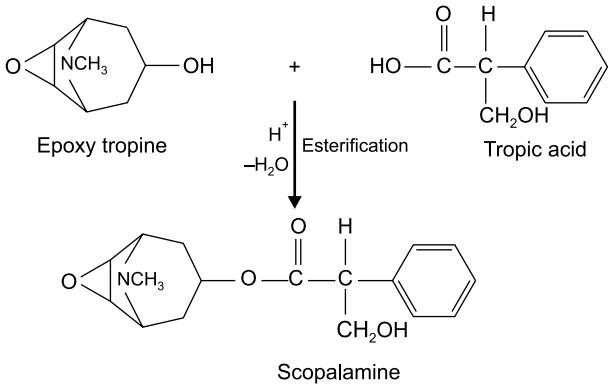
Dose: In bradycardia: Adult—500 µg every 3–5 min totally 3 mg.

Dosage forms: Atropine methonitrate injection IP, atropine sulphate injection IP, atropine sulphate tablets IP, atropine sulphate ointment IP, atropine eyedrops BP, atropine eye ointment BP, atropine injection BP, atropine tablets BP, morphine and atropine injection BP.

ii. Scopolamine

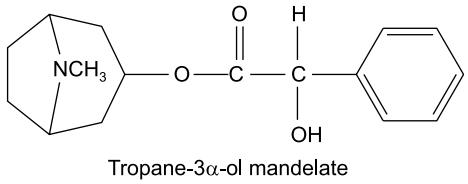


Synthesis



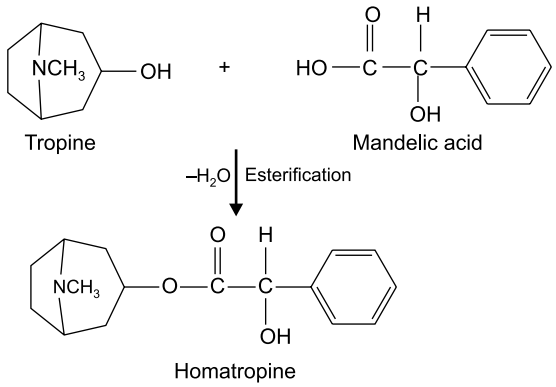
Properties and uses: It exists as colourless or white crystals or white granular powder, odourless, slightly efflorescent in dry air, and is an anhydrous salt, soluble in water or alcohol and in chloroform, insoluble in ether. Scopolamine is the levo component of the racemic mixture that is known as hyoscine. It is effective in the prevention of motion sickness. It is a competitive blocking agent of the parasympathetic nervous system like atropine, but it differs markedly from atropine in its action on the higher nerve centres.

iii. Homatropine (Isopto)



Tropane-3α-ol mandelate

Synthesis



Properties and uses: It is a white crystalline powder or colourless crystals, sparingly soluble in alcohol, but freely soluble in water. It is used topically on the ciliary structure of the eye to affect mydriasis.

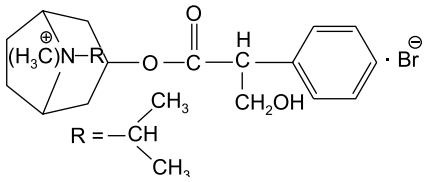
Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: Topically for adult, to the conjunctiva, 1 drop of a 2–5% solution given three times at 10 min intervals.

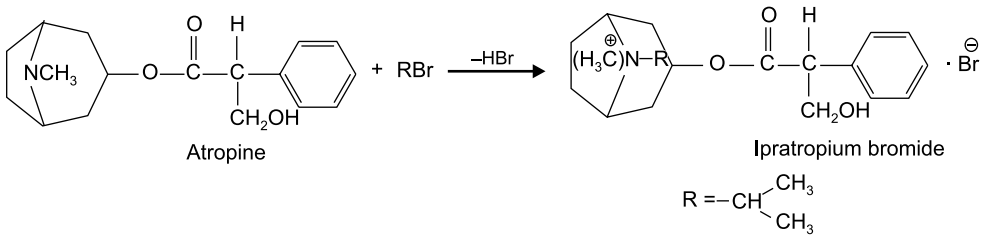
Dosage forms: Homatropine eyedrops BP.

iv. Ipratropium bromide (Ipneb, Ipranaseaq, Ipratop)



(±)-Endo-3-(3-hydro-1-oxo-2-phenyl propyl)-8-methyl-8-(1-methyl ethyl)-8-azoniabicyclo octane bromide

Synthesis



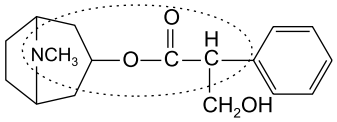
Properties and uses: It is a white or almost white crystalline powder, freely soluble in methanol, soluble in water, but slightly soluble in ethanol. It is used in the inhalation therapy to produce dilation of bronchial smooth muscle for acute asthmatic attacks. It produces bronchodilation by competitive inhibition of cholinergic receptors bound to the smooth muscles of the bronchioles.

Assay: Dissolve the sample in water and add 3 ml of dilute nitric acid. Titrate with 0.1 M silver nitrate and determine the end point potentiometrically.

Dose: For inhalation reversible airways obstruction and COPD, maximum dose is 320 µg daily as nebulized solution.

Dosage forms: Ipratropium nebuliser solution BP, ipratropium powder for inhalation BP, ipratropium pressurized inhalation BP.

SAR of Solanaceous Alkaloids (Atropine Analogues)

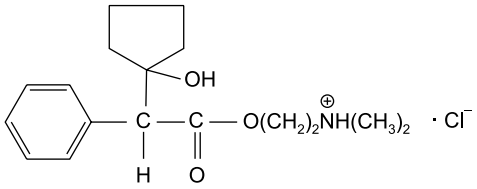


- The greater molar potency of atropine helps to block several moles of acetylcholine.

- The umbrella-like atropine molecule may mechanically or electrostatically inactivate adjacent receptors on the cell surface so that these receptors are also unavailable for acetylcholine or other parasympathomimetic stimulants.
- The circled portion of the atropine molecule depicts the segment resembling acetylcholine.
- The amine functional group is separated from the ester oxygen by more than two carbons, the conformation assumed by tropanol ring orients these two atoms such that the intervening distance is similar to that of acetylcholine. On the basis of the assumption that the size was a major factor in the blocking action, many substituted acetic acid ester of amino alcohol were prepared and evaluated for biological activity.
- The most potent compounds were those that possessed two lipophilic ring substituents on the carbon alpha to carbonyl of ester moiety for antimuscarinic activity.

II. Amino alcohol esters

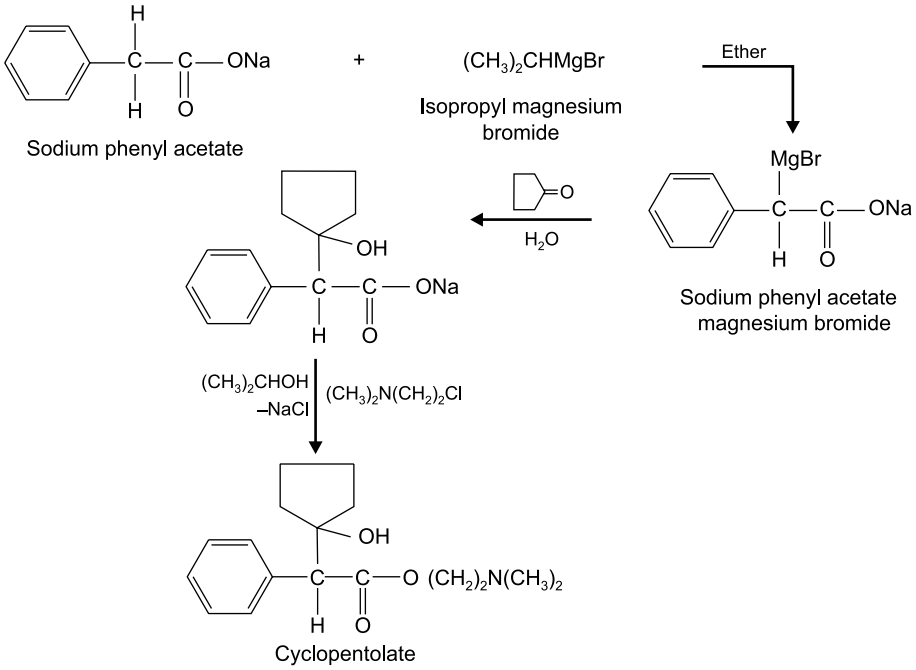
i. Cyclopentolate HCl (Cyclopent, Cyclate, Dilate)



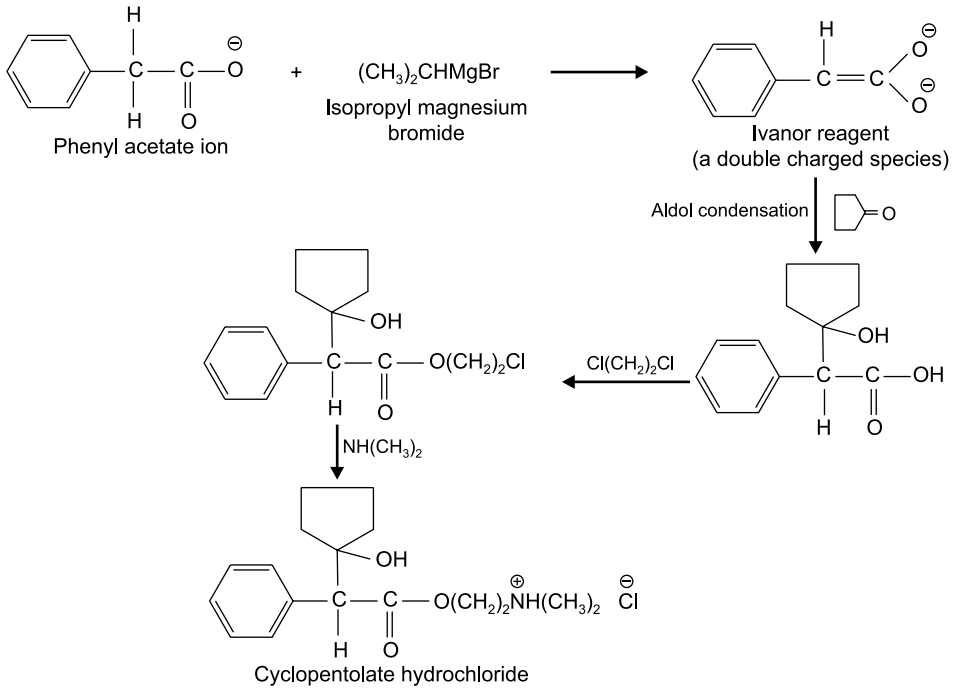
2-(Dimethylamino) ethyl-1-hydroxyl-phenyl cyclopentane acetate hydrochloride

Synthesis

Route I. From: Sodium phenyl acetate



Route II. From: Phenyl acetate ion



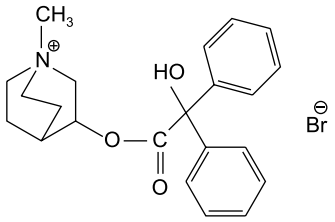
Properties and uses: It exists as white crystalline powder, soluble in water, methanol, and ethanol, but insoluble in toluene. Cyclopentolate is usually employed as eyedrops to cause cycloplegia and mydriasis. It acts much faster than atropine and possesses a relatively shorter duration of action.

Assay: Dissolve the sample in a mixture of 0.1 M hydrochloric acid and alcohol. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Dose: Topically for adult, 1 drop of 1% or 2% solution to the conjunctiva; for refraction 1 drop of a 0.5% solution repeated after 5 to 15 min.

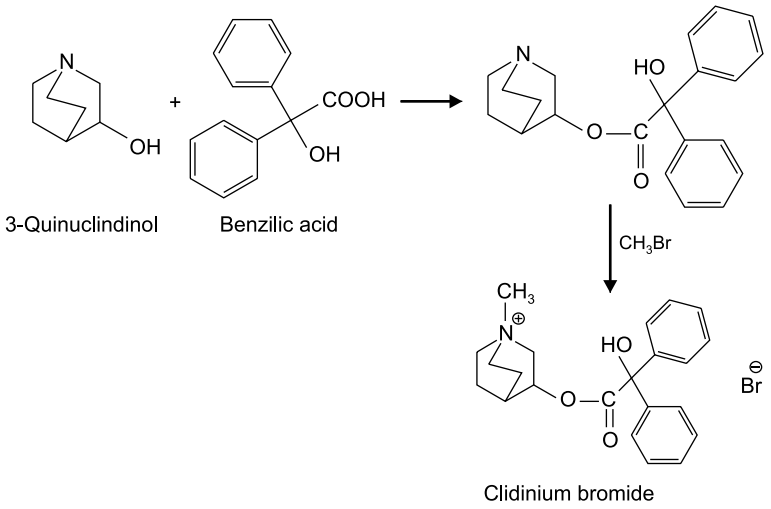
Dosage forms: Cyclopentolate eyedrops BP.

ii. Clidinium bromide



3-Hydroxy-1-methyl quinuclidium bromide benzilate

Synthesis

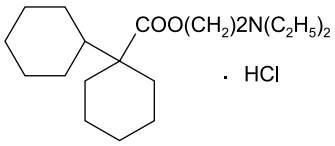


3-Quinuclindinol Benzilic acid

Clidinium bromide

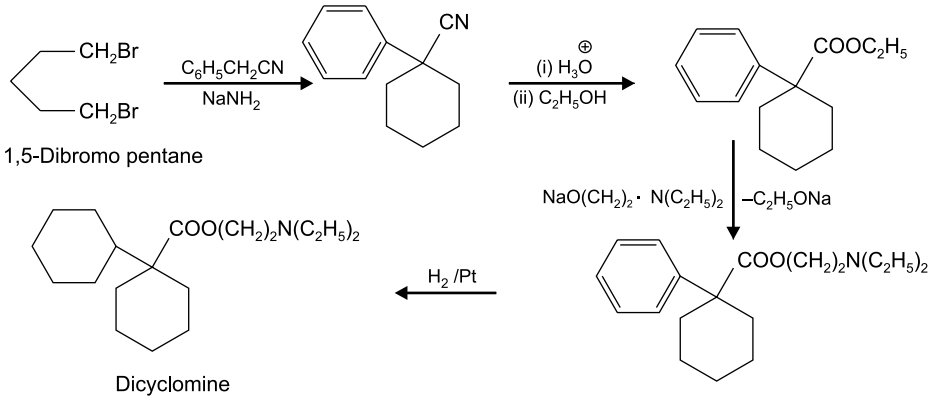
Uses: Used as a bronchodilator in asthmatic conditions. It has a longer lasting effect as compared to β-agonists.

iii. Dicyclomine HCl (Bentyl, Mesbentyl)



2-(Diethylamino) ethyl bicyclohexyl-1-carboxylate HCl

Synthesis



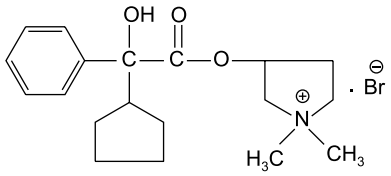
1,5-Dibromo pentane

Dicyclomine

Properties and uses: It exists as a white, crystalline powder with a bitter taste, soluble in water and chloroform. Dicyclomine HCl behaves both as an antimuscarinic and a non-specific antispasmodic agent. It was first introduced in 1950 and had minimized the adverse effects associated with the atropine type of compounds. Dicyclomine has spasmolytic effect on various smooth muscle spasms particularly those associated with the gastrointestinal (GI) tract. It is also used in dysmenorrhoea, pylorospasm, and biliary dysfunction.

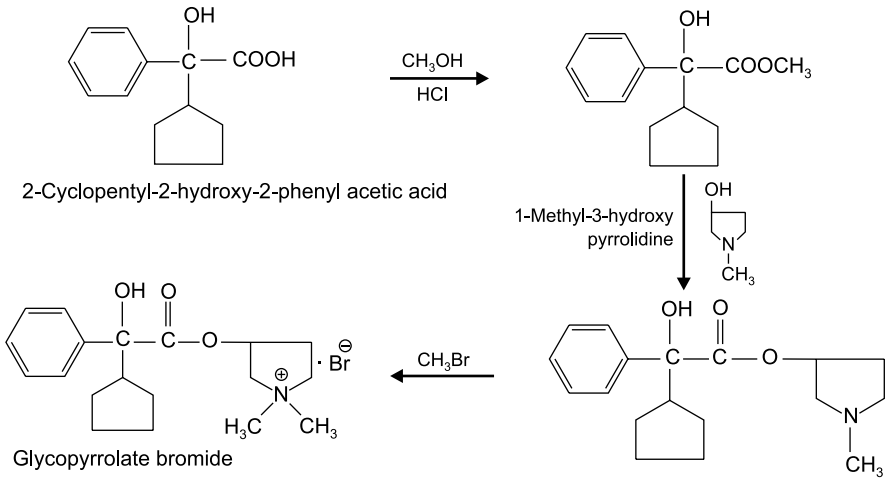
Dose: By oral or IM 10 to 20 mg per day in four divided dose.

iv. Glycopyrrolate bromide



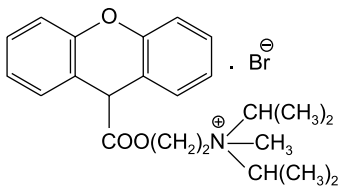
N,N-Dimethyl pyrrolidinium bromide-3-cyclopentyl mandelate

Synthesis



Properties and uses: It exists as a white, crystalline powder with a bitter taste, soluble in water and alcohol. It is used for suppressing gastric secretion and in the treatment of peptic ulcer and gastrointestinal disorder associated with spasm.

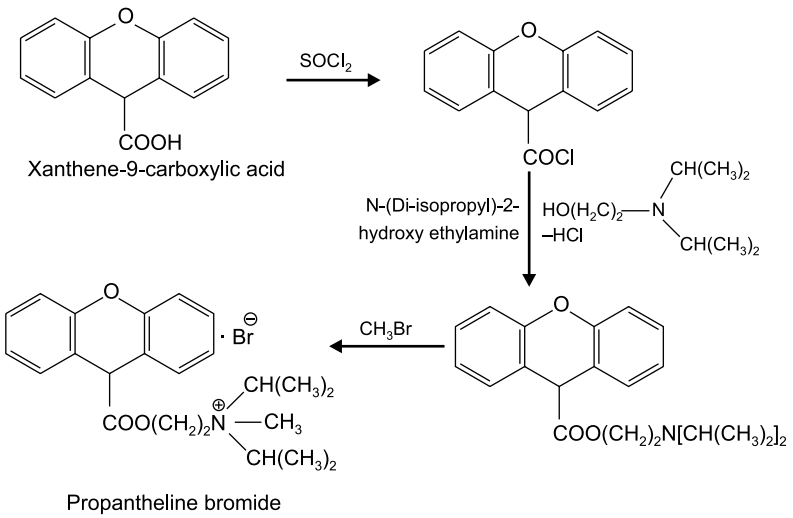
v. Propanthelin bromide (Probanthine, Spastheline)



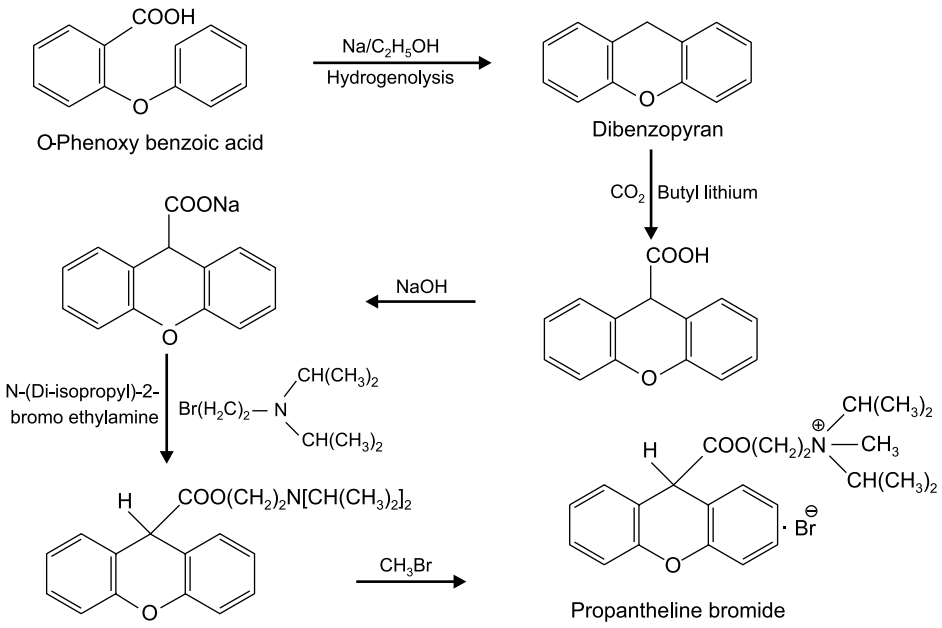
(Ethyl)-di-isopropyl methyl ammonium bromide xanthene-9-carboxylate

Synthesis

Route I. From: Xanthene-9-carboxylate



Route II. From: *o*-Phenoxy benzoic acid



Properties and uses: It is a white or yellowish-white powder, slightly hygroscopic, soluble in water, in alcohol, and in methylene chloride. It is beneficial for the treatment of peptic ulcer, due to the decreased gastric motility by this drug, and it may relieve the pain in this condition.

Assay: Dissolve the sample in acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

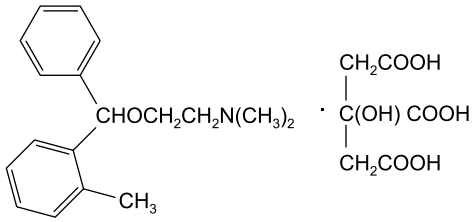
Storage: It should be stored in well-closed airtight container, and protected from light.

Dose: The usual initial dose is 15 mg thrice/day before meals; and 30 mg at bedtime.

Dosage forms: Propantheline bromide tablets IP, propantheline tablets BP.

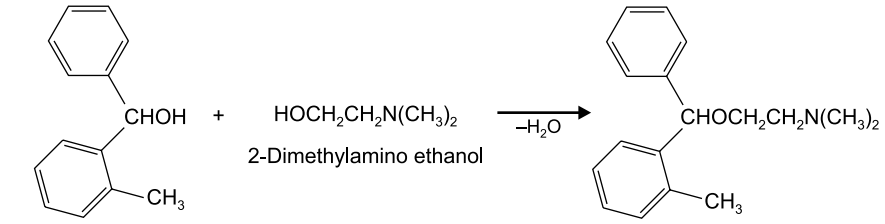
III. Amino ethers

i. Orphenadrine citrate (Orphipal)



N,N-Dimethyl-2-(*o*-methyl-α-phenyl benzyloxy) ethylamine citrate

Synthesis



2-Methyl benzhydrol Orphenadrine

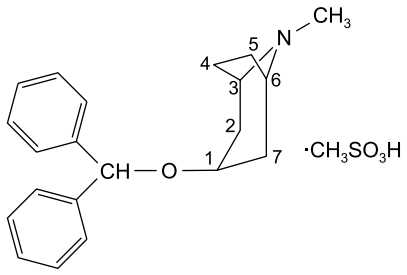
Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water, slightly soluble in alcohol. It is used for the symptomatic treatment of Parkinson's disease. It is also used as a skeletal muscle relaxant.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed containers. If the substance is sterile, it should be stored in a sterile, airtight, tamper-proof container, and protected from light.

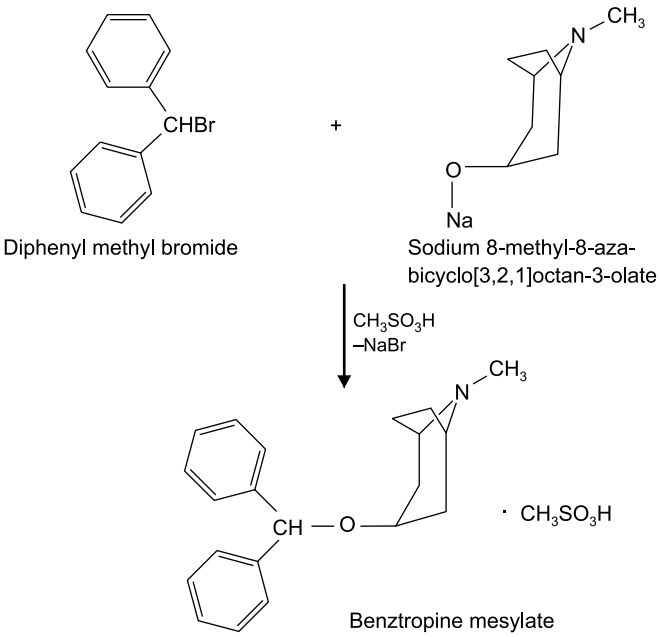
Dose: The initial oral dose is 100 mg twice/day; IM or IV 60 mg every 12 hrs.

ii. Benztropine mesylate



3α-(Diphenyl methoxy)-1αH,5αH-tropine methan sulphonate

Synthesis



Diphenyl methyl bromide

Sodium 8-methyl-8-aza-bicyclo[3,2,1]octan-3-olate

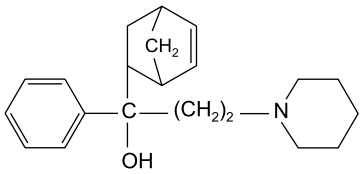
Benztropine mesylate

Properties and uses: It is a white crystalline powder, insoluble in ether, but soluble in water and ethanol. It has anticholinergic, antihistaminic, and local anaesthetic activities. It is used in the treatment of Parkinson's disease.

Dosage forms: Benztropine injection BP, benztropine tablets BP.

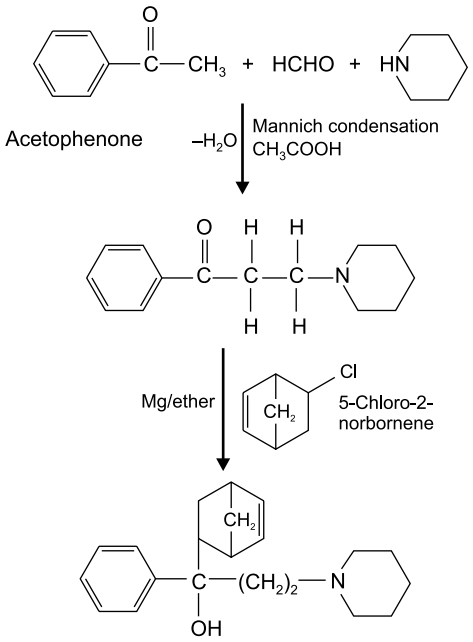
IV. Amino alcohols

i. Biperiden (Akineton Hydrochloride)



α-5-Norbornen-2-yl-α-phenyl-3-(piperidine-1-yl) propanol

Synthesis



Biperiden

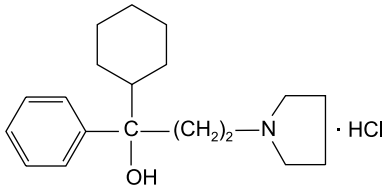
Properties and uses: It is a white crystalline powder, slightly soluble in methylene chloride, in water, and in alcohol. It has a relatively strong musculotropic action, which is about equal to that of papaverine, in comparison with most synthetic anticholinergic drugs. It is used in all types of Parkinson's disease.

Assay: Dissolve the sample in alcohol and titrate with 0.1 M alcoholic potassium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

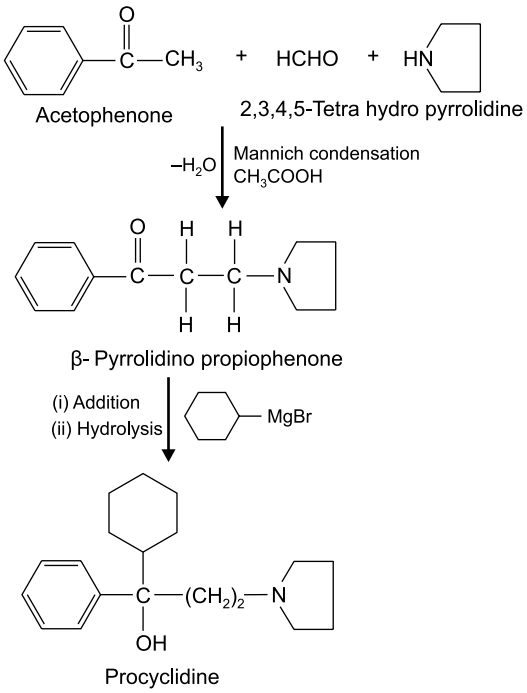
Dose: For parkinsonism, 2 mg three or four times/day.

ii. Procyclidine HCl (Kemadrin, Picidin, Prodine)



1-Cyclohexyl-1-phenyl-3-pyrrolidin-1-yl-1-propanol HCl

Synthesis



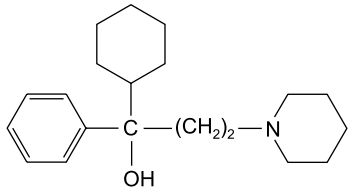
Properties and uses: It exists as white crystalline powder, and it has been used for peripheral effects that are similar to methantheline. Its clinical usefulness lies in its ability to relieve voluntary muscle spasticity through its central action. Procyclidine is used in the treatment of Parkinson's disease.

Assay: It is assayed by non-aqueous titration. The solution of the sample is titrated with 0.1 M perchloric acid using crystal violet as an indicator.

Dose: The initial oral dose is 7.5 mg/day in 3 or 4 divided doses after meals; maintenance dose is usually 20 to 30 mg per day.

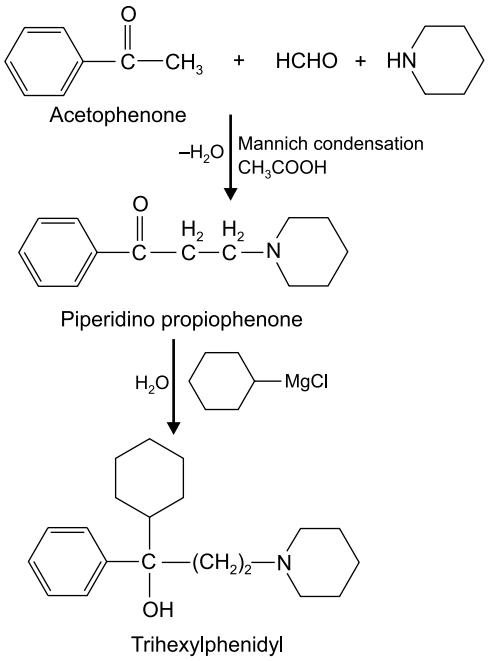
Dosage forms: Procyclidine injection BP, procyclidine tablets BP.

iii. Trihexylphenidyl (Pacitane, Parkin, Triphen)



α-Cyclohexyl-α-phenyl-1-piperidine propanol

Synthesis



Properties and uses: It is a white crystalline powder, slightly soluble in water, sparingly soluble in alcohol and in methylene chloride. It is used as antispasmodic and antiparkinsonian agent. Trihexylphenidyl is more effective than levodopa against Parkinson's tremor.

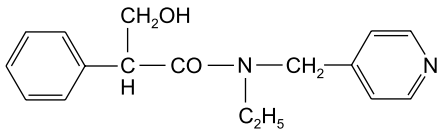
Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

Dose: Initial oral dose is 1 mg on first day, followed by 2 mg daily after 3 to 5 days; maintenance dose, 6 to 10 mg/day in 3 to 4 divided doses but not exceeding 20 mg/day.

Dosage forms: Trihexylphenidyl tablets BP.

V. Amino amides

- **Tropicamide** (Tropicamet, Tmide Ed, Optimide)



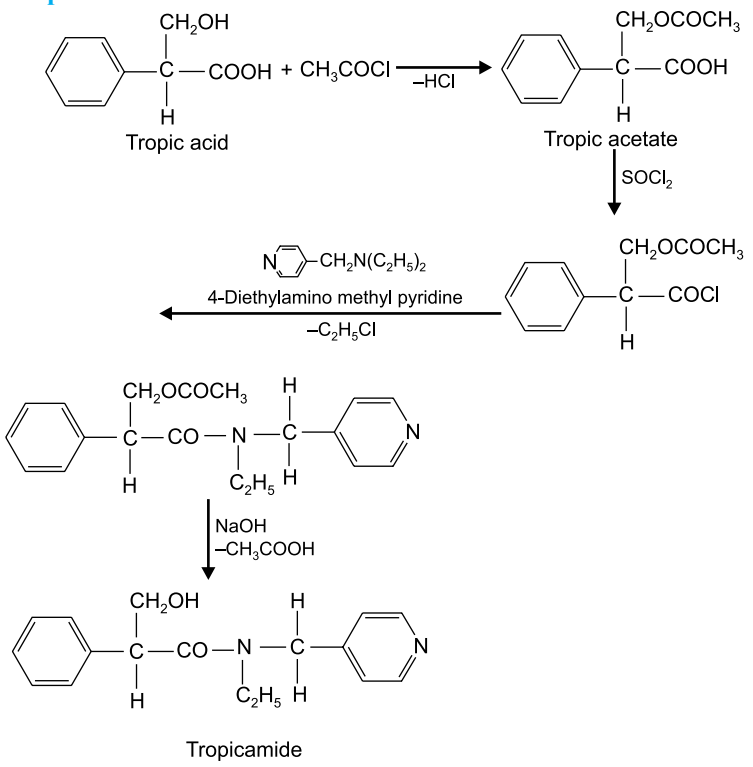
N-Ethyl-2-phenyl-N-(4-pyridylmethyl)-3-hydroxy-propionamide

Properties and uses: It is a white or almost white crystalline powder, soluble in alcohol and methylene chloride, but slightly soluble in water. Used to induce mydriasis and cycloplegia in ophthamologic practice and it has short duration of action.

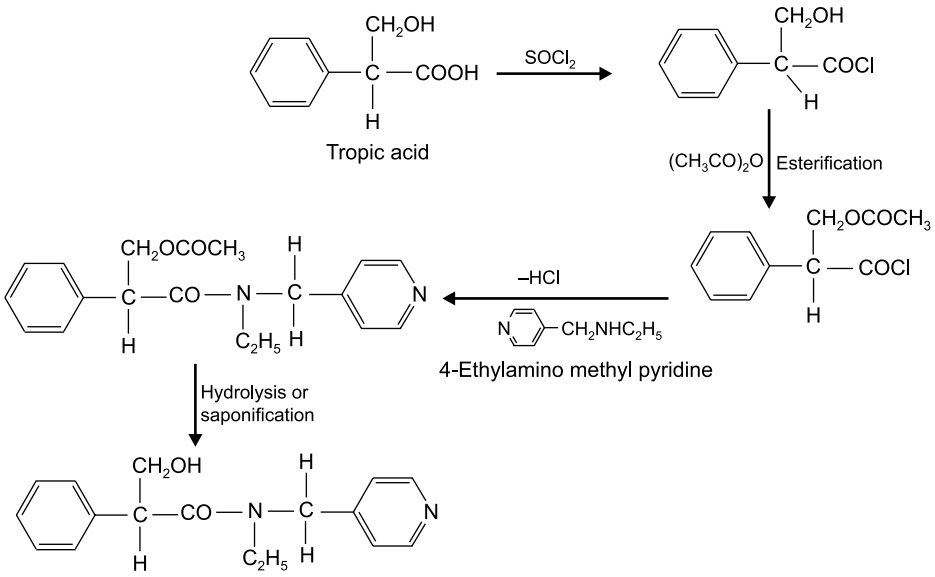
Assay: Dissolve the sample in anhydrous acetic acid, to this add naphtholbenzein solution, and titrate with 0.1 M perchloric acid. End point is the change of colour from orange to green.

Synthesis

Route I. From: Tropic acid



Route II. From: Tropic acid

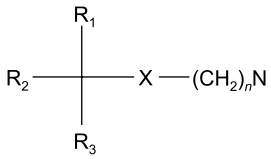


Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual adult topical dose is 1 to 2 drops of a 0.5% or 1% solution to the conjunctiva; for mydriasis 0.5% solution is employed, and for cycloplegia 1% solution.

Dosage forms: Tropicamide eyedrops IP, BP.

SAR of Muscarinic Antagonists

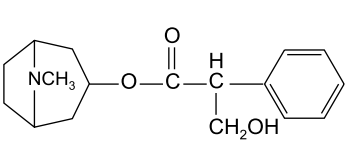


- For the potent cholinergic antagonist, the groups R_1 and R_2 must be hydrophobic in nature (usually, phenyl, cyclohexyl, or cyclopentyl).
- In the above general structure for amino alcohol, the substituents R_1 and R_2 should be a carbocyclic or a heterocyclic ring for maximal antagonistic potency.
- The ring may be identical, but the more potent compounds have different rings. The one ring is aromatic and other may be saturated or possessing only one olefine bond. Example: Propantheline.
- Their ability to do these effectively is because of the large group of R_1 and R_2 that enhance the binding to receptors since the antagonistics are larger than agonists.
- The R_3 substituent may be a hydrogen atom, hydroxyl group, hydroxy methyl group or a carboxy amide, or it may be a component of R_1 and R_2 ring system. When the substituent is a hydroxyl group or hydroxy methyl group the antagonist is usually more potent. Due to the hydroxyl group presumably there might be an increase in the binding strength by participating in a hydrogen bond interaction at the receptor.
- The X substituent in the most potent anticholinergic agent is an ester, but an ester functional group is not absolute necessary for muscarinic antagonistic activity.
- The N substituent is a quaternary ammonium salt in the most potent anticholinergic agents. Tertiary amine also possesses antagonist activity presumably by binding to the receptors in the cationic form. The alkyl substitution is usually methyl group, ethyl group, propyl, or isopropyl group.
- The distance between ring substituted carbon and amine nitrogen is apparently not critical, as much as the length of alkyl chain connecting this, may be from two to four carbons. The most potent anticholinergic agent has two methylene units in this chain.

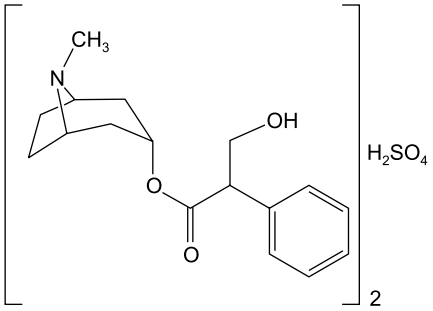
CLASSIFICATION BASED ON PCI SYLLABUS

Solanaceous Alkaloids and Analogues

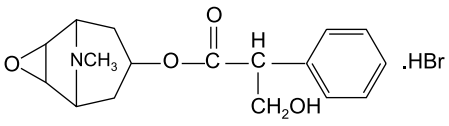
Atropine sulphate



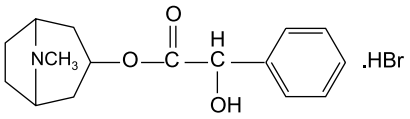
Hyoscyamine sulphate



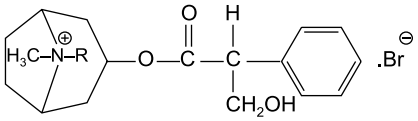
Scopolamine hydrobromide



Homatropine hydrobromide

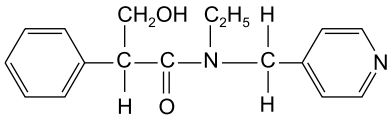


Ipratropium bromide

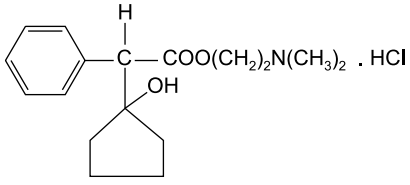


Synthetic Cholinergic Blocking Agents

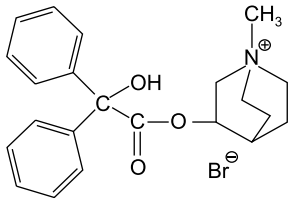
Tropicamide



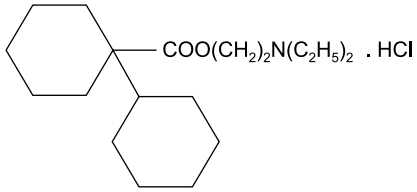
Cyclopentolate hydrochloride



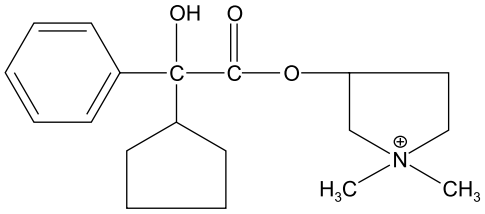
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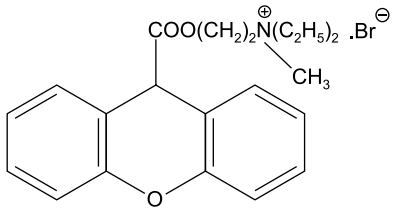
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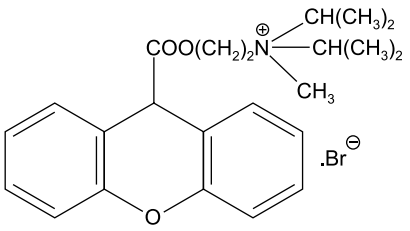
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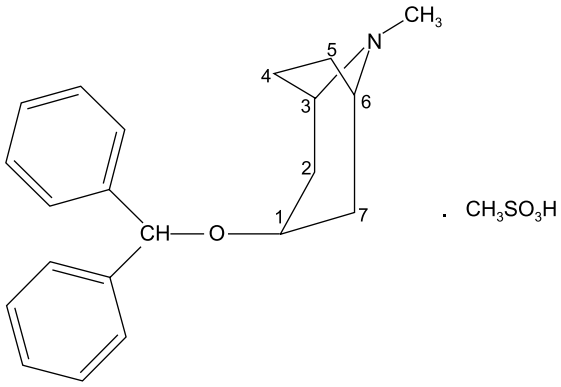
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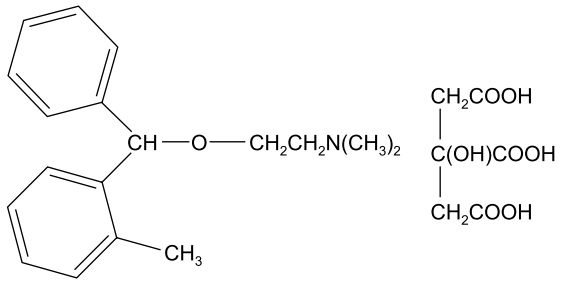
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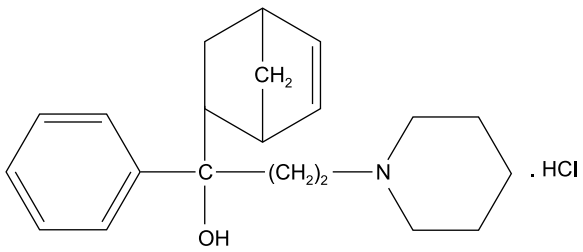
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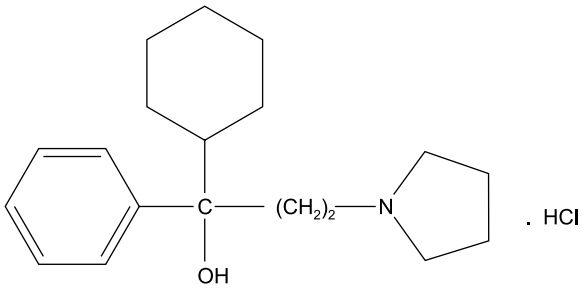
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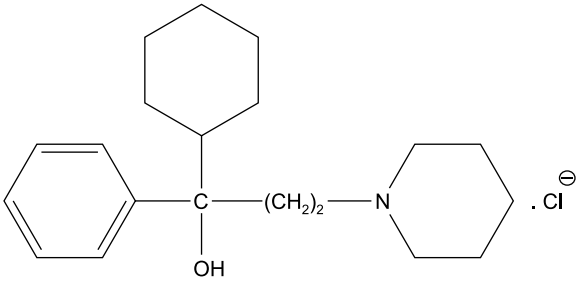
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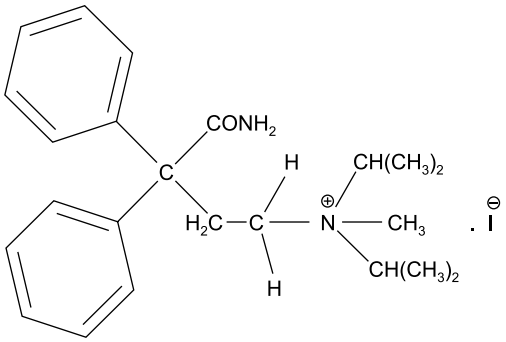
Procyclidine hydrochloride



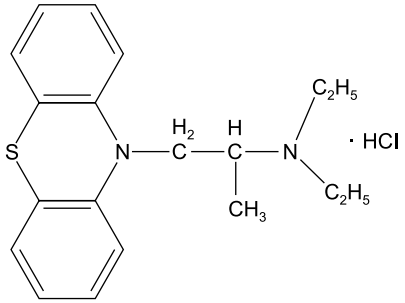
Tridihexethyl chloride



Isopropamide iodide



Ethopropazine hydrochloride



PROBABLE QUESTIONS

1. Classify the various receptors involved in ANS. Write the structure, chemical name, and uses of one potent drug acting in each receptor.
2. How will you classify the sympathomimetic agents on the basis of chemical structure? Outline the synthesis of one catecholamine and one non-catecholamine used in the treatment of bronchial asthma.
3. Write the structure, chemical name, and uses of any three important sympathomimetic drugs and discuss the synthesis of one such a compound selected by you.

4. Describe the synthesis and metabolic pathway of a sympathomimetic drug used in the treatment of hypotensive shock.
5. What are sympathomimetic agents? Classify them and write the synthesis of any three drugs from different class.
6. What is epinephrine and norepinephrine? Outline their biosynthetic pathway and metabolism in the body.
7. Write in detail about the SAR of sympathomimetics.
8. Write the mode of action of sympathomimetics on alpha- and beta-receptors.
9. Write note on drugs used for their ionotropic action on the heart.
10. Define and classify adrenergic blockers. Outline the synthesis and uses of any two of them from different class.
11. Outline the synthesis, mode of action, and uses of one important medicinal compound used as an autonomic drug belonging to the following categories:
    (a) Alpha-adrenoreceptor blocking agent
    (b) Beta-adrenoreceptor blocking agent
12. Name one compound belonging to the category of chlinomimetic drugs that are either directly acting or indirectly acting. Describe their synthesis and uses.
13. Write a comprehensive account of antimuscarinic agents by giving the structure, chemical name, and uses of one important representative from each category.
14. Write the mode of action of direct-acting cholinergic agents and indirect-acting cholinergic agents.
15. Define and classify cholinergic agents and write in detail about reversible cholinesterase inhibitors.
16. Write a brief note on cholinomimetic alkaloids.
17. Enumerate the importance of ganglionic blocking agents as autonomic drugs. Describe the synthesis of mecamylamine hydrochloride.
18. Write in brief about solanaceous alkaloids and its analogues.
19. Write the synthesis and uses of propanthelin bromide and trihexyphenidyl.
20. Write the SAR of muscarinic antagonists.
21. Write the structure, synthesis, chemical name, and uses of the following autonomic drugs:
    (a) Carbachol
    (b) Neostigmine
    (c) Pralidoxime
22. Describe the mode of action of the following:
    (a) Ganglionic blocking agents
    (b) Antimuscarinic agents
23. Write a comprehensive account of the adrenergic neurone blocking agents with specific reference to:
    (a) Bethanidine sulphate
    (b) Guanethidine monosulphate

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17. Salem MR. 'Therapeutic uses of ganglionic blocking drugs'. *Int Annesthesiol Clin* 16: 171, 1978.

SECTION V

Drugs Acting on Cardiovascular System

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CHAPTER 39

Cardiovascular System

INTRODUCTION

Arterial pressure is the product of cardiac output (CO) and peripheral vascular resistance. Hypertension is the most common cardiovascular disease. The pressure elevated from the normal arterial pressure induced pathological changes in the vasculature that produces hypertrophy of left ventricle, which principally causes stroke, myocardial infarction, cardiac arrest, renal insufficiency, and dissecting aneurysm of the aorta. It is important to note that the risk of both fatal and non-fatal cardiovascular disease in adults is lowest with systolic BP 120 mm Hg and diastolic 80 mm Hg. In severe levels of hypertension (systolic ≥210 and/or diastolic ≥120), some patients develop arteriolopathy characterized by endothelial injury and marked proliferation of cells in intima, leading to intimal thickening and causes occlusion. This may also lead to severe microangiopathic haemolytic anaemia. Effective antihypertensive therapy will almost completely prevent haemorrhagic stroke, cardiac failure, and renal insufficiency. The usual approach to a patient with diastolic BP in the range of 85–94 mm Hg is to use non-pharmacological therapy as the initial strategy, which includes the lifestyle strategy. As the arterial pressure is the product of peripheral vascular resistance (PVR) and cardiac output, it can be lowered by the action of drugs either on the peripheral vascular resistance or CO or both.

AETIOLOGY OF HYPERTENSION

It is important to consider specific causes in each of the case, however, because some of them are amenable to definite surgical treatment, renal artery constriction, and contraction of aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism. The patients in whom no specific cause of hypertension can be found are said to have essential hypertension. Elevated BP underlies epidemiological evidence that points to genetic inheritance, psychological stress, environmental, and dietary factors (increased salt and decreased potassium or calcium intake).

The hereditability of essential hypertension is estimated to be about 30%. Mutations in several genes have been linked to various rare causes of hypertension. Functional variations of genes for angiotensinogen, angiotensin-converting enzyme, and β_2 adrenoceptor appear to contribute to some cases of essential hypertension.

NORMAL REGULATION OF BLOOD PRESSURE

According to hydraulic equation, arterial blood pressure is directly proportional to CO and PVR.

$$BP = CO \times PVR$$

BP is maintained by moment-to-moment regulation of CO and PVR, exerted at three anatomical sites, that is, arterioles, postcapillary venules, and heart.

The fourth anatomical control site, the kidney contributes to the maintenance of blood pressure regulating fluid in the body. Baroreceptor reflexes mediated by ANS are in combination with humoral mechanisms, including the renin-angiotensin-aldosterone system to coordinate function at these four control sites and to maintain normal BP regulation. All antihypertensive drugs act by interfering with the above-specified mechanism. They are as follows:

1. Diuretics
    a. Thiazides and related agents
    b. Loop diuretics
    c. Potassium sparing diuretics
2. Sympatholytic drugs
    a. Centrally acting agent
    b. Adrenergic neuron blocking agent
    c. β-adrenergic antagonist
    d. α-adrenergic antagonist
    e. Mixed α- and β-adrenergic antagonist
3. Vasodilators
    a. Arterial vasodilators
    b. Arterial and venous vasodilators
4. Angiotensin converting enzyme inhibitors

CHAPTER 40

Antihypertensive Drugs

INTRODUCTION

Antihypertensive drugs are defined as the drugs which are used to decrease the elevated blood pressure (hypertension).

Hypertension

It is one of the common cardiovascular disorders and it is a state of the body in which the systolic blood pressure (BP) is 150 mm Hg or more and diastolic BP is 95 mm Hg or more. Hypertension may be classified into primary and secondary:

Primary Hypertension

It is otherwise known as essential hypertension. It is characterized by the following:

- Elevation of diastolic BP.
- Normal cardiac output.
- An increase in peripheral resistance.

Secondary Hypertension

Factors causing secondary hypertension are as follows:

- Acute or chronic renal disease.
- Hyperaldosteronism.
- Cushing's syndrome.
- Acromegaly.
- Pheochromocytoma.
- Oral contraceptives, steroids, estrogen, and sympathomimetics.

Antihypertensive drug therapy has improved remarkably in the last 50 years. Before 1950, less effective and less tolerated antihypertensive drugs were available. Veratrum and sodium thiocyanate could lower BP, but were toxic and difficult to use. The ganglion blockers that were developed in the 1950s were effective, but inconvenient. Reserpine was a breakthrough, but produced mental depression. The therapeutic potential of hydralazine was not tapped fully because of the marked side effects when

it was used alone. Guanethidine introduced in 1961 was an improvement on the ganglion blockers. The antihypertensives of 1960–70s were methyldopa, β-blockers, thiazides, high-ceiling diuretics, and clonidine. The antihypertensives of 1980–90s are angiotensin II converting enzyme inhibitors and calcium channel blockers. Angiotensin receptor blockers (losartan) are the latest antihypertensives. Diuretics and related drugs are the choice in uncomplicated hypertension. These drugs reduce plasma and extracellular fluid volume by 5–15% that decrease cardiac output. The reduction in total peripheral resistance is most probably an indirect consequence of small persisting Na^+ and volume defect. Decreased intracellular Na^+ concentration in the vascular smooth muscle may decrease stiffness of vessels wall, increase compliance, and dampen responsiveness to constrictor stimuli of noradrenaline and angiotensin II.

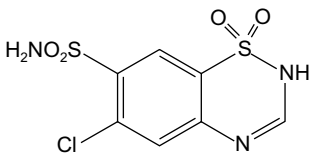
Angiotensin-converting enzyme (ACE) inhibitors are one of the first choice drugs in all the grades of essential as well as renovascular hypertension. When it is used alone, 50% of the patients are benefited and the addition of a diuretic/β blocker extends the efficacy to 90%. Angiotensin receptor blockers give peak action at 2–4 weeks. Calcium channel blockers such as dihydropyridines, phenylalkylamine, and benzothiazepine are equally effective antihypertensives. Beta adrenergic blockers give 30–40% efficacy in mild-to-moderate cases.

CLASSIFICATION

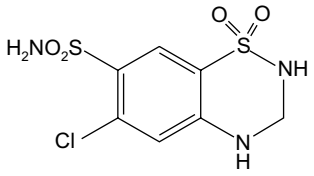
I. Diuretics

a. Thiazides

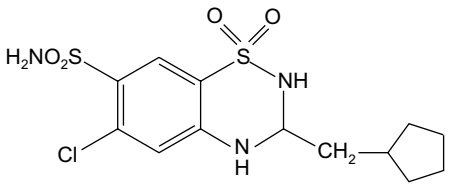
i. Chlorthiazide



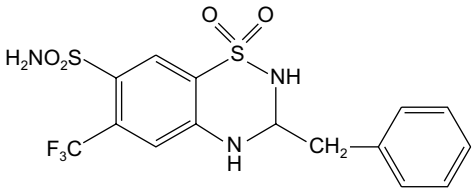
ii. Hydrochlorthiazide



iii. Cyclopenthiazide

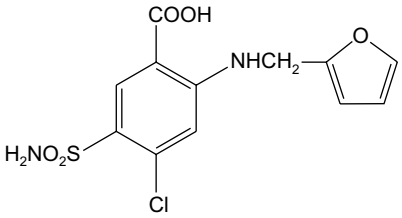


iv. Bendroflumethiazide

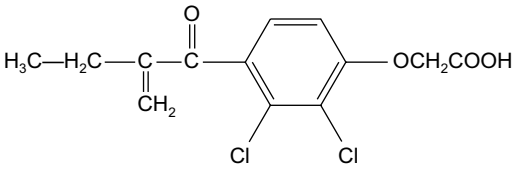


b. Loop diuretics

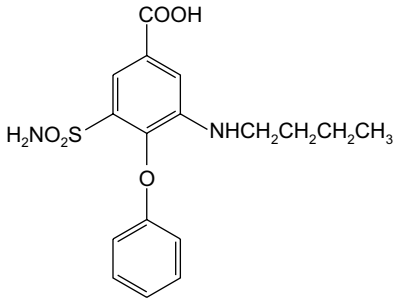
i. Frusemide or furosemide



ii. Ethacrynic acid

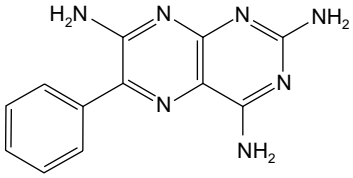


iii. Bumetanide

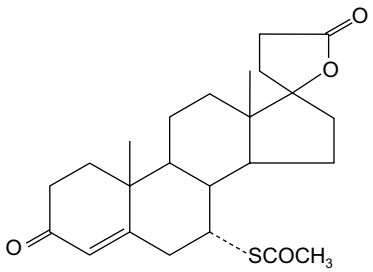


c. Potassium-sparing diuretics

i. Triamterene



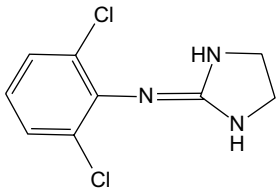
ii. Spiranolactone (Aldosterone antagonists)



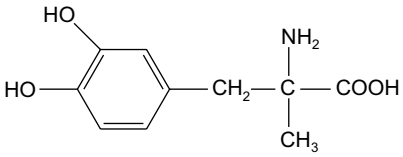
II. Drugs acting on sympathetic system

a. Centrally-acting drugs

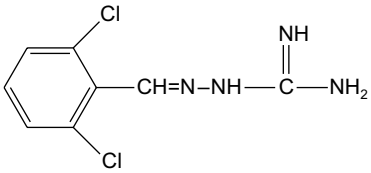
i. Clonidine



ii. α-Methyl dopa

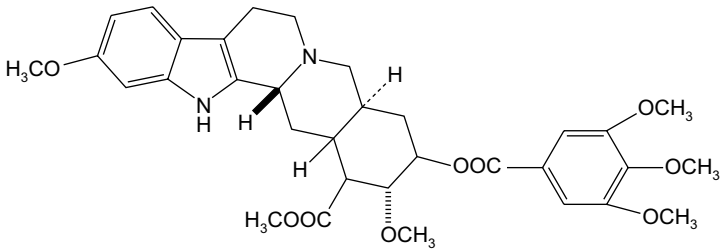


iii. Guanabenz



b. Catacholamine depletors

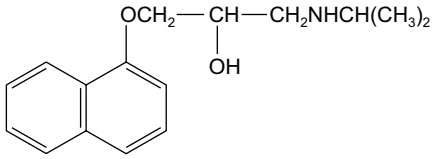
- **Reserpine**



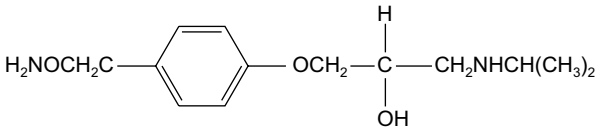
c. Adrenergic blockers

i. β-adrenergic blockers

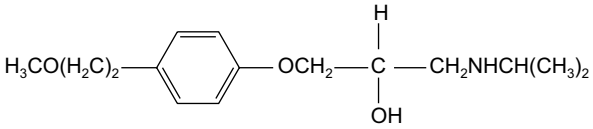
1. Propronolol



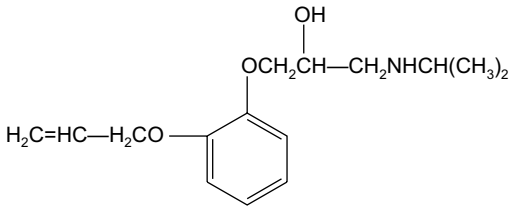
2. Atenolol



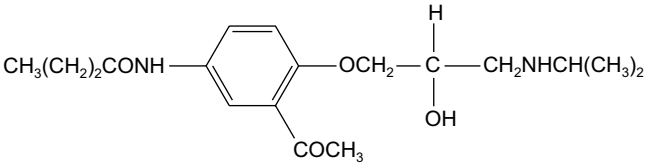
3. Metoprolol



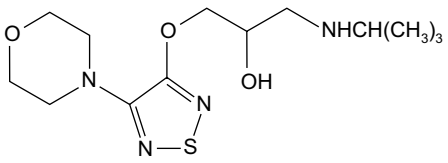
4. Oxprenolol



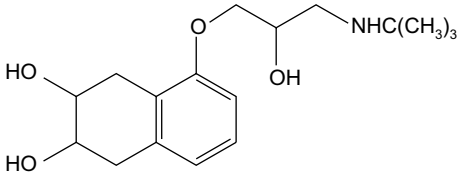
5. Acebutalol



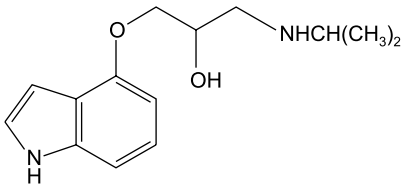
6. Timolol



7. Nadolol

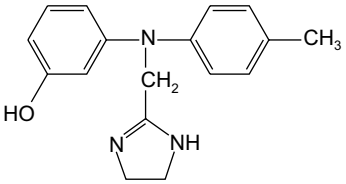


8. Pindolol

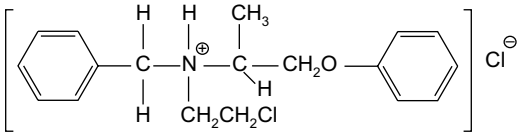


ii. α-Adrenergic blockers

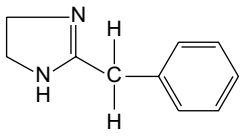
1. Phentolamine



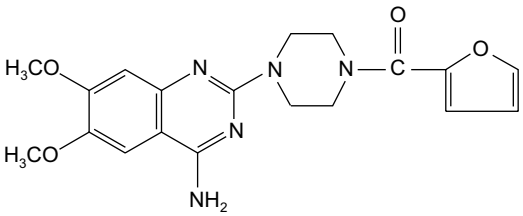
2. Phenoxy benzamine hydrochloride



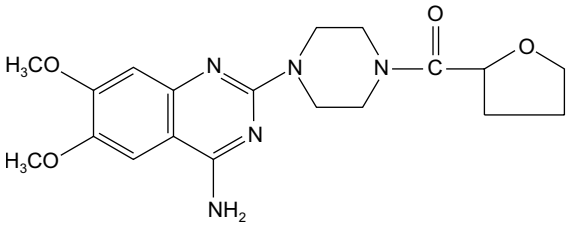
3. Tolazoline



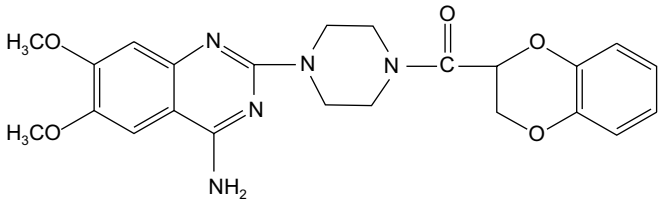
4. Prazosin



5. Terazosin

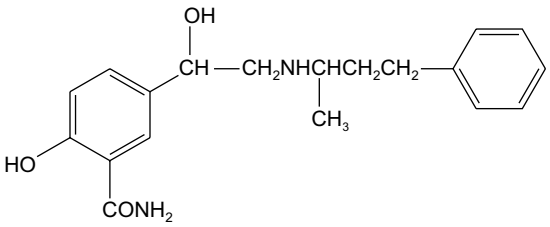


6. Doxazosin

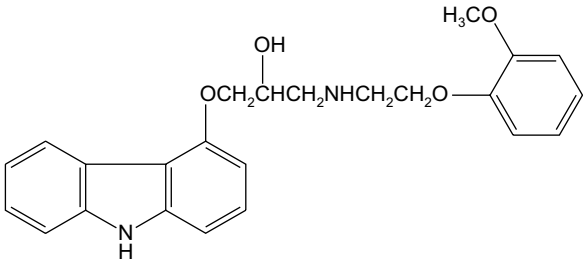


iii. Mixed α- and β-blockers (Non-selective)

1. Labetalol

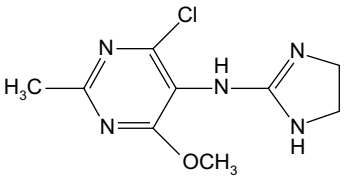


2. Carvedilol

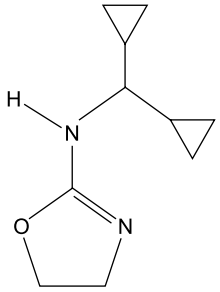


iv. Imidazoline receptor agonist

1. Moxonidine

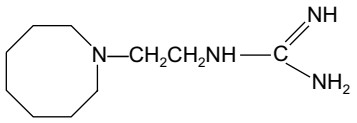


2. Rilmenidine

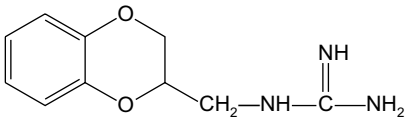


d. Adrenergic neuron blockers

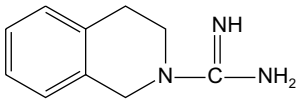
i. Guanethidine



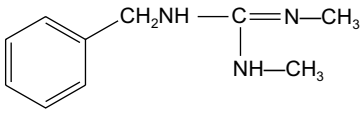
ii. Guanoxan



iii. Debrisoquine



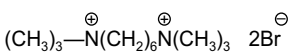
iv. Bethanidine



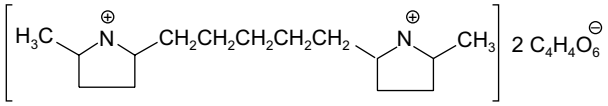
e. Ganglion blockers

i. Quaternary ammonium compounds

1. Hexamethonium bromide

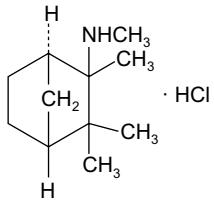


2. Pentolinium tartrate



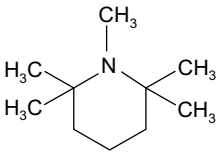
ii. Secondary amines

1. Mecamylamine HCl

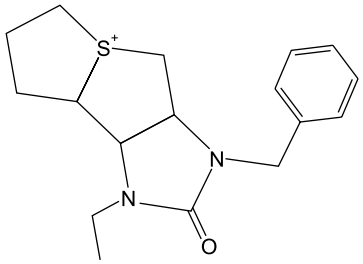


iii. Tertiary amines

1. Pempidine

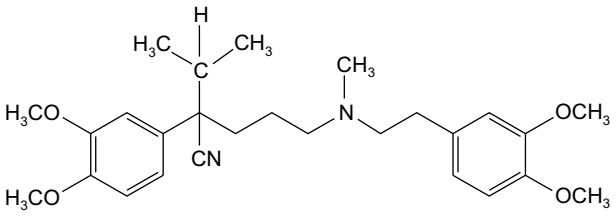


2. Trimethaphan

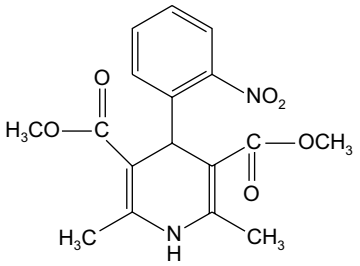


III. Calcium channel blockers

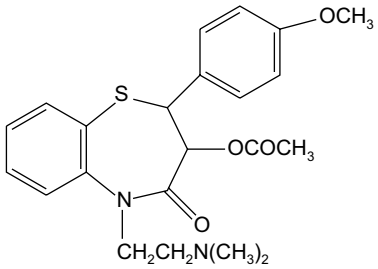
i. Verapamil



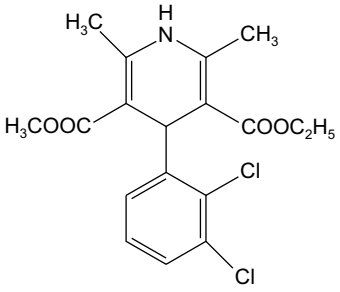
ii. Nifedipine



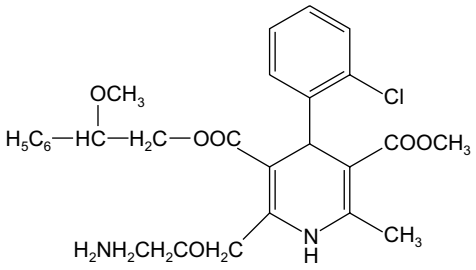
iii. Diltiazem



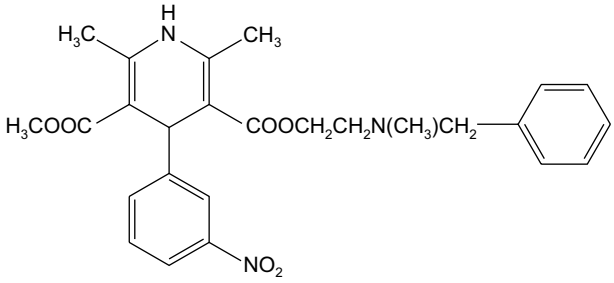
iv. Felodipine



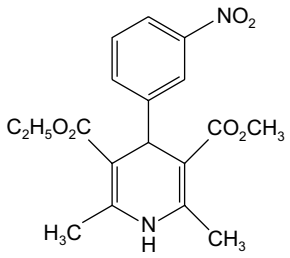
v. Amlodipine



vi. Nicardipine



vii. Nitrendipine



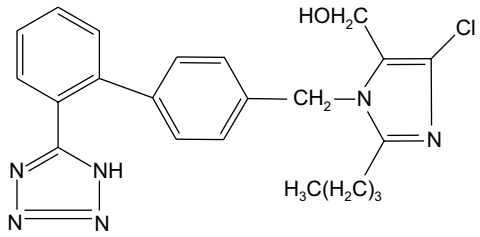
IV. Drugs acting on renin-angiotensin system

a. Drugs that block renin release: Propranolol.

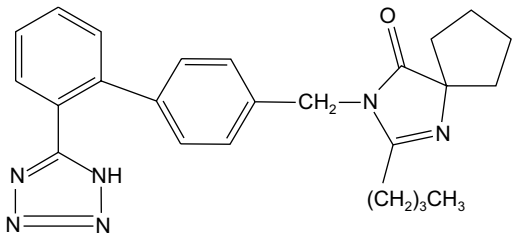
b. Drugs that inhibit angiotensin II: Saralasin.

c. Drugs that inhibit angiotensin II receptors.

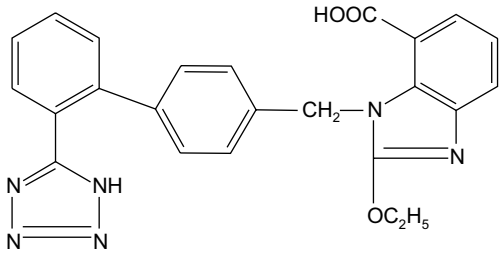
i. Losartan



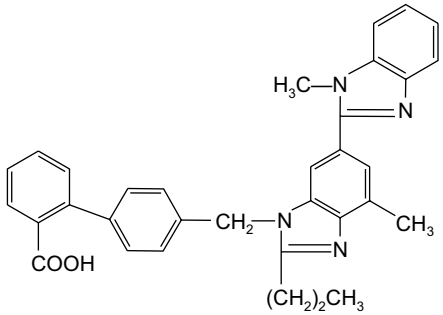
ii. Irbesartan



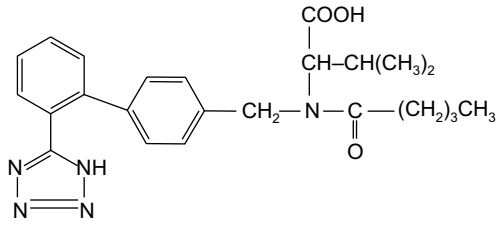
iii. Candesartan



iv. Telmiesartan



v. Valsartan

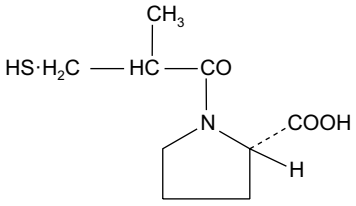


d. Drugs that inhibit aldosterone: Spironolactone

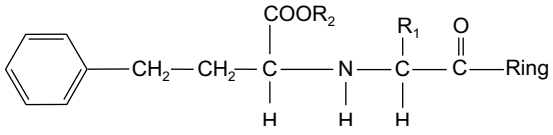
e. ACE inhibitors

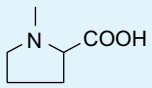
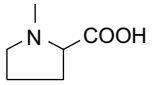
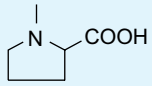
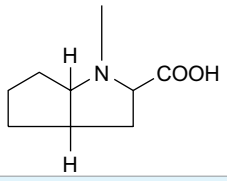
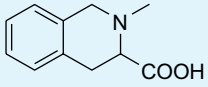
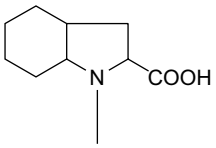
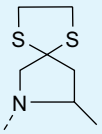
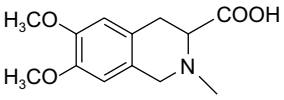
i. Sulfhydryl containing ACE inhibitors

Captopril



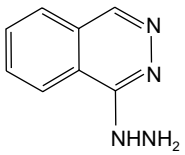
ii. Dicarboxylate containing ACE inhibitors



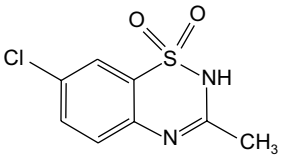
S. No.	Name	R_1	R_2	Ring
1.	Enalapril	$-CH_3$	$-C_2H_5$	
2.	Enalaprilat	$-CH_3$	$-H$	
3.	Lisinopril	$-(CH_2)_4NH_2$	$-H$	
4.	Ramipril	$-CH_3$	$-C_2H_5$	
5.	Quinapril	$-CH_3$	$-C_2H_5$	
6.	Trandolapril	$-CH_3$	$-C_2H_5$	
7.	Spirapril	$-CH_3$	$-C_2H_5$	
8.	Moexipril	$-CH_3$	$-C_2H_5$	

V. Vasodilators

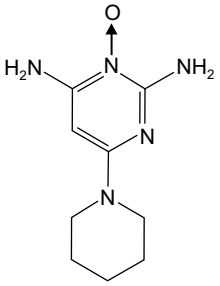
i. Hydralazine



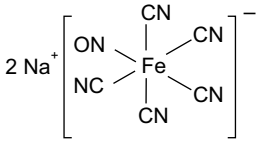
ii. Diazoxide



iii. Minoxidil



iv. Sodium nitroprusside

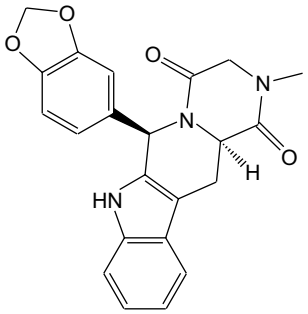


VI. Miscellaneous

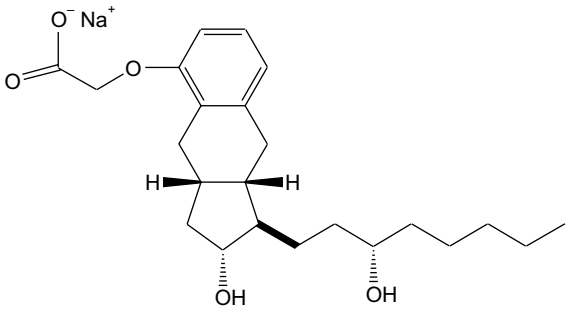
MAO inhibitors: Pargyline, metyrosine, pinacidil

Newer Drugs

Tadalafil



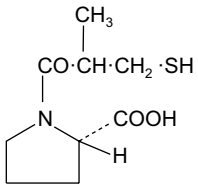
Treprostinil



SYNTHESIS AND DRUG PROFILE

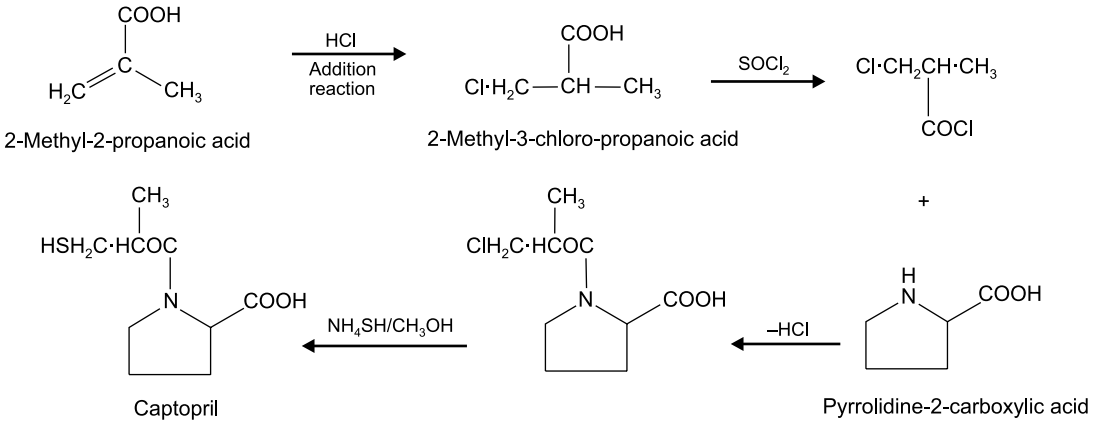
Drugs Acting on Renin–angiotensin System

i. Captopril (Aceten, Capotril)



1-[(2S)-3-Mercapto-2-methyl-1-oxopropionyl] pyrrolidine-2-carboxylic acid

Synthesis



Properties and uses: It is a white or almost white crystalline powder and it dissolves in dilute sodium hydroxide and potassium hydroxide solution. It is also soluble in water, methylene chloride, and methanol. The first orally effective ACE inhibitor to have been marketed, it is approved for use in the treatment of hypertension, heart failure, left ventricular dysfunction, and postmyocardial infarction.

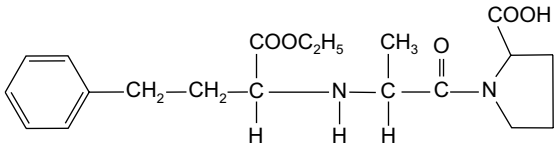
Assay: Dissolve the sample in water and titrate with 0.05 M iodine. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers, and protected from light.

Dose: The usual dose is 12.5 or 25 mg twice daily.

Dosage forms: Captopril tablets BP.

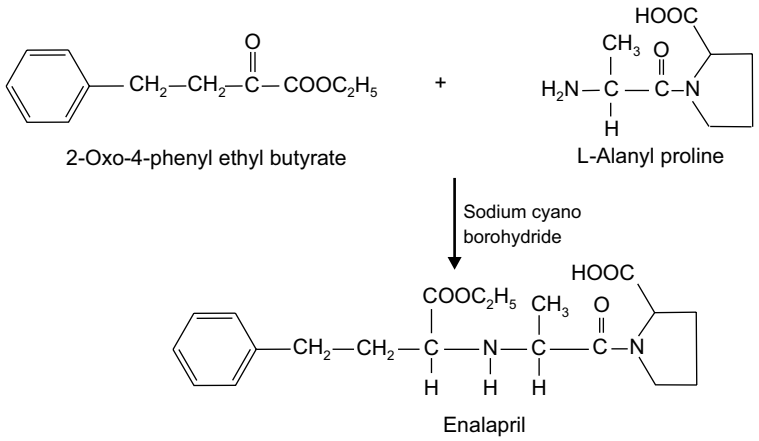
ii. Enalapril (Envas, Enace, Enam, Enapril)



1-[N(S)-1-Carboxy-3-phenyl propyl]-[alanyl]-l-proline-1′-ethyl ester

Properties and uses: It is a white or almost white, crystalline powder, and it dissolves in dilute solutions of alkali hydroxides, sparingly soluble in water, freely soluble in methanol, but insoluble in methylene chloride. A prodrug is converted to the active ACE inhibitor, enalaprilat. It is indicated for use in the treatment of hypertension, heart failure, and asymptomatic left ventricular dysfunction. It produces well to excellent responses in patients with essential hypertension.

Synthesis

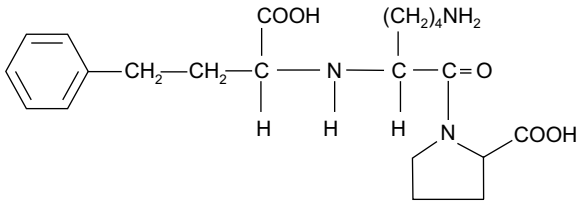


Assay: Dissolve the sample in water and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 10–40 mg in one or two divided doses by oral route.

iii. Lisinopril (Hipril, Lipril, Linvas)



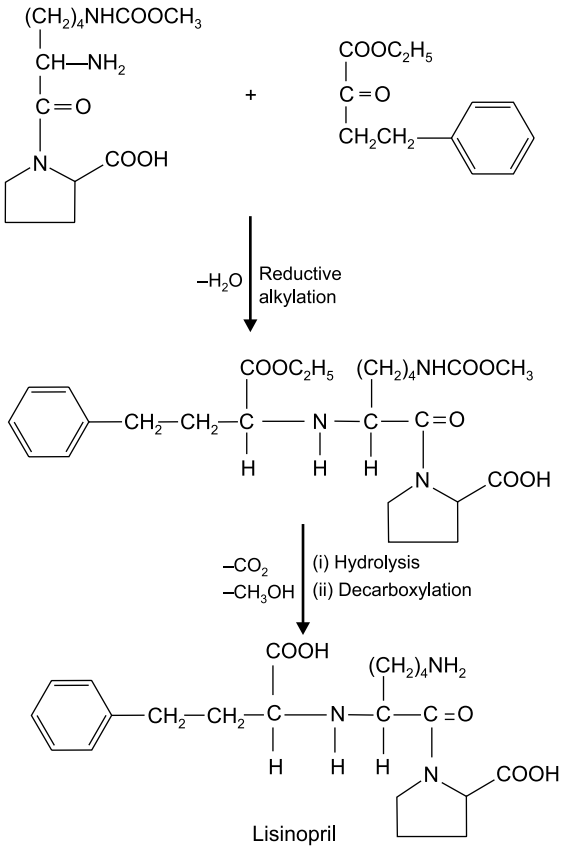
Properties and uses: It is a white or almost white crystalline powder, and is insoluble in acetone and in ethanol, soluble in water, but sparingly soluble in methanol. It is used in the treatment of renovascular hypertension, essential, malignant hypertension, and also for ventricular congestive heart failure.

Assay: Dissolve the sample in water and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: The usual dose is 10 mg/day.

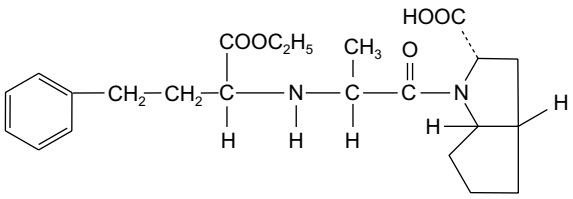
Dosage forms: Lisinopril tablets BP.

Synthesis



Lisinopril

iv. Ramipril (Hopace, Cardace, Race)

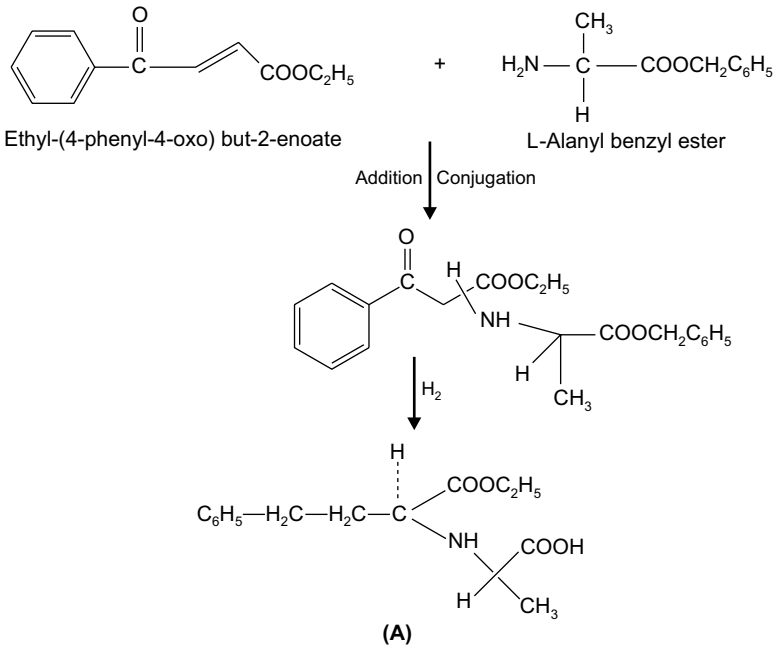


Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water, but freely soluble in methanol. It is used as an antihypertensive agent, and is also used in the treatment of nephropathy.

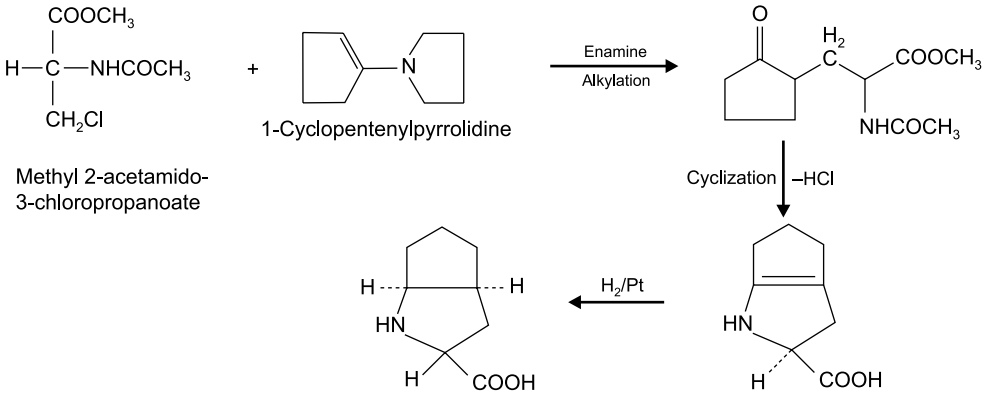
Assay: Dissolve the sample in methanol and add water. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Step I: Synthesis of compound A

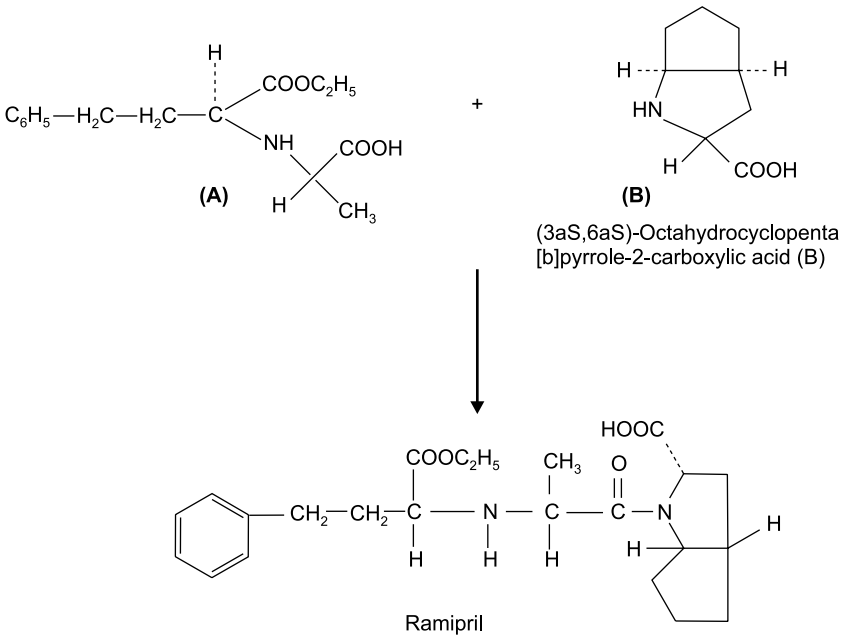


Step II: Synthesis of compound (3aS,6aS)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid (B)



(B) (3aS,6aS)-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

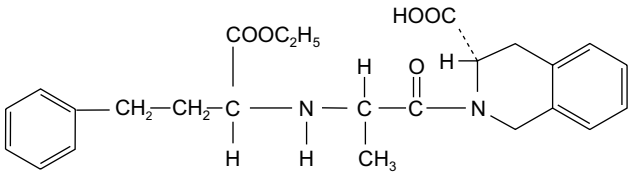
Step III: Condensation of products of *Step I* (A) and *Step II* (3aS,6aS)-octahydrocyclopenta [b]pyrrole-2-carboxylic acid



Dose: For hypertension: Adult—initial, dose is 1.25 mg once daily given at bedtime. Maintenance: 2.5–5 mg daily as a single dose, up to 10 mg daily as needed.

Dosage forms: Ramipril capsules BP, ramipril tablets BP.

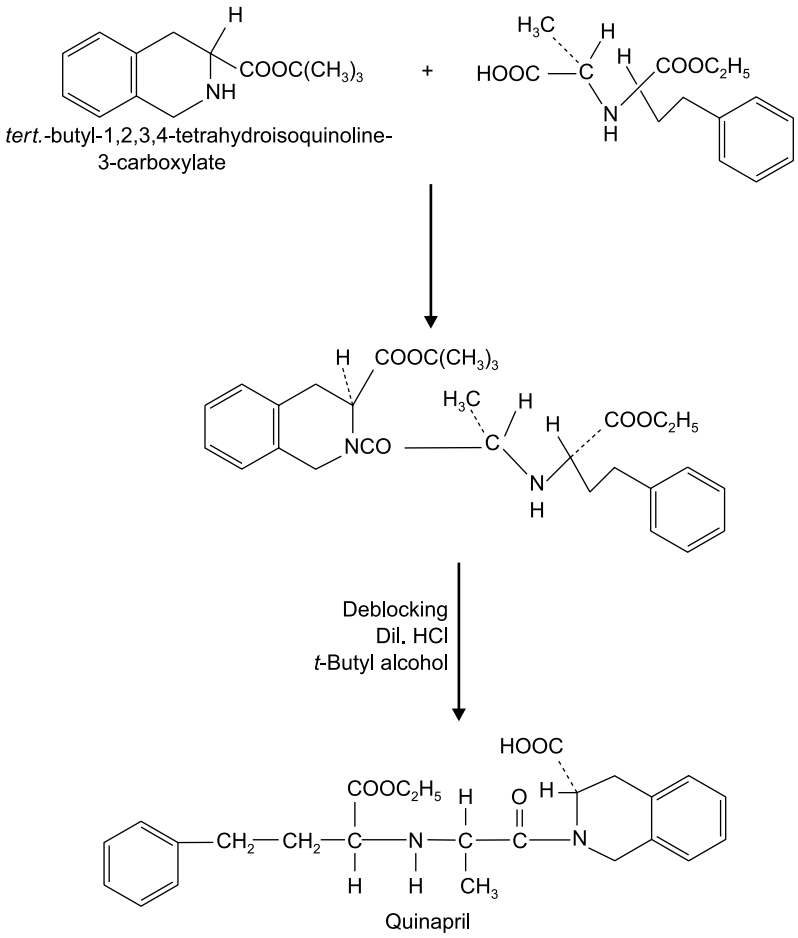
v. Quinapril



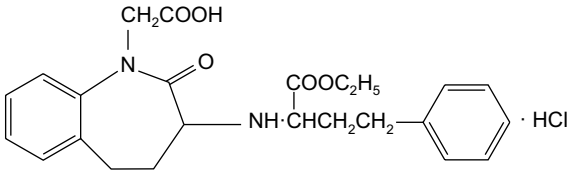
Properties and uses: It exists as white crystals. It is used as an antihypertensive agent and is also used in the treatment of congestive heart failure.

Dose: The initial oral dose is 10 mg once daily.

Synthesis



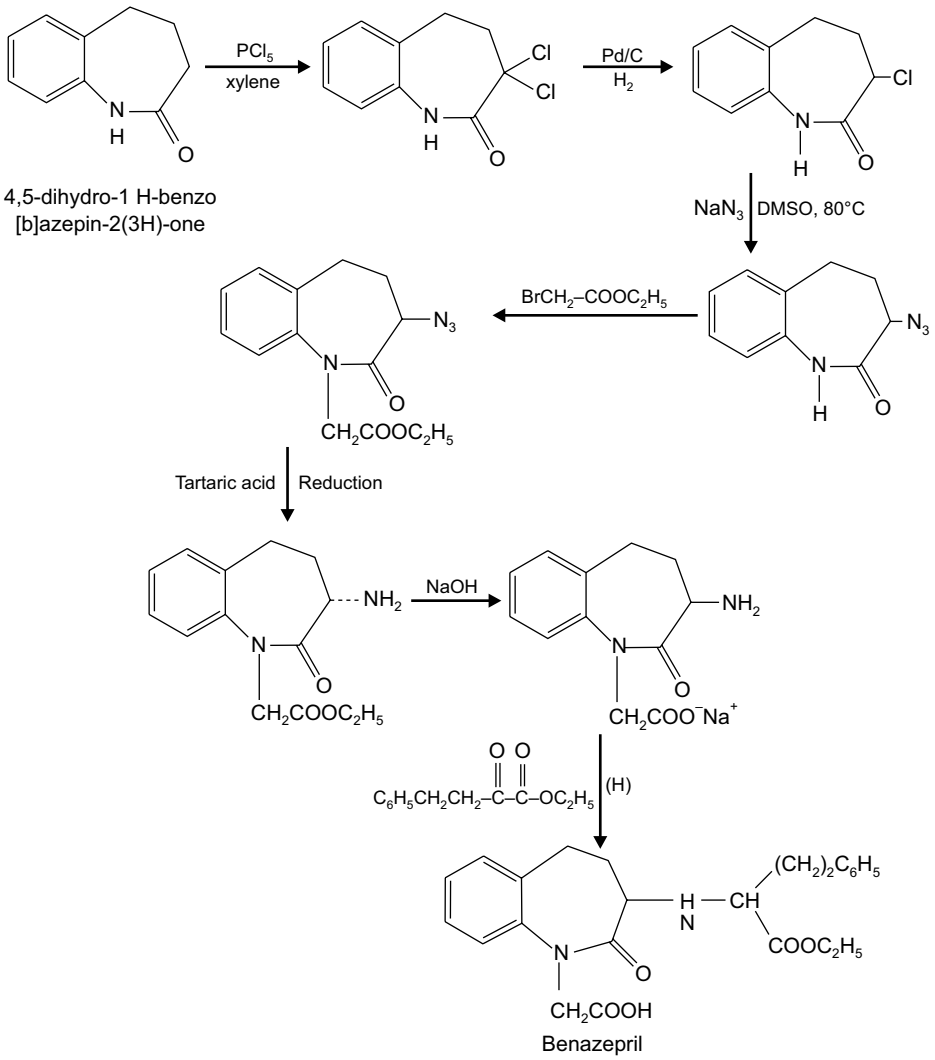
vi. Benazepril (Benace)



Properties and uses: It exists as a white crystalline powder that is soluble in water, ethanol, or methanol. It is beneficial for patients with congestive heart failure.

Dose: The benazepril, administered at 10 mg/day is as efficacious as captopril at 50 mg/day, enalapril at 20 mg/day.

Synthesis



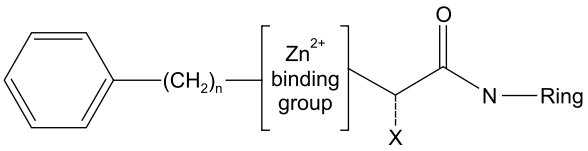
Adverse Effects of ACE Inhibitors

1. Dry cough due to increase bradykinin levels.
2. Angioedema, proteinuria, taste alteration, neutropenia, teratogenic effect (so contraindicated in pregnancy).
3. Severe hypotension may occur 1–2 h after taking the first dose. Hence, ACE inhibitors should be started with a small dose and then gradually increased.
4. Rashes, itching, loss of appetite, nausea, vomiting and diarrhoea.
5. Hyperkalemia may be seen in patients with renal insufficiency and when combined with K^+ sparing diuretics.

Adverse Effects of Angiotensin-II Receptor Blockers

They are well tolerated. They can cause hypotension and hyperkalemia like ACE inhibitors. They are contraindicated in pregnancy because of their teratogenic potential.

SAR of ACE Inhibitors



Zn^{2+} binding groups – a) $HS\text{-}CH_2\text{–}$ = Sulfhydryl

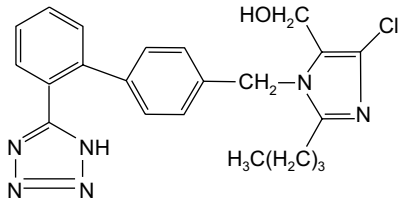
b) –CH–NH– = Carboxylic acid
COOH

OH
c) – P– = Phosphinic acid
O

1. The N- ring must contain a carboxylic acid to mimic the C-terminal carboxylate of ACE substrates.
2. Large hydrophobic heterocyclic rings (*i.e.* N-ring) increase potency and alter pharmacokinetic parameters.
3. The zinc binding groups can be either sulfhydryl (A), a carboxylic acid (B) or phosphinic acid (C).
4. The sulfhydral group shows superior binding to zinc (the side chain mimicking the carboxylate and phosphinic acid compounds partially compensates for the lack of a sulfhydral group).
5. Sulfhydral containing compounds produce high incidence of skin rash and taste disturbances.
6. Sulfhydral containing compounds can form dimers and disulfide, which may shorten the duration of action.
7. Compounds that bind to zinc through either a carbohydrate or phosphonate mimic the peptide hydrolysis transition state and enhance binding.
8. Esterification of the carbohydrate or phosphonate produces an orally bioavailable prodrug.
9. 'X' is usually methyl to mimic the side chain of alanine. Within the dicarboxylate series, when X equal n-butylamine (lysine side chain), this produces a compound that does not require prodrug for oral activity.
10. Optimum activity occurs when stereochemistry of inhibitor is consistent with L-amino acid stereo-chemistry present in normal substrates.

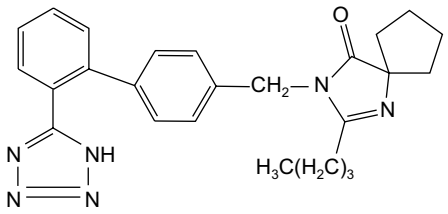
Angiotensin II Antagonist

i. Losartan



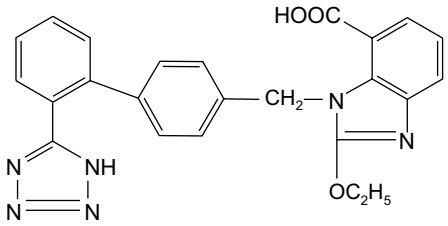
Properties and uses: It exists as white crystalline powder that is soluble in water, alcohol, acetonitrile, or 2-butanone. It is used as an antihypertensive agent and also in the treatment of heart failure.

ii. Irbesartan



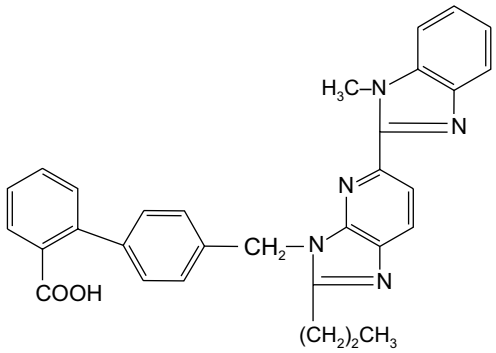
Properties and uses: It exists as white crystals that are soluble in ethanol or methylene chloride. It is an angiotensin II receptor antagonist.

iii. Candesartan



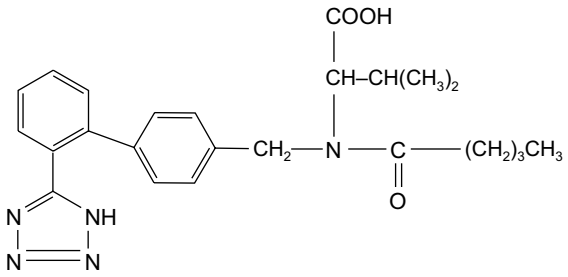
Properties and uses: It exists as colourless crystals and is used as an angiotensin II receptor antagonist.

iv. Telmisartan



Properties and uses: It exists as a white solid, insoluble in water or in aqueous solutions. It is used as an antihypertensive agent.

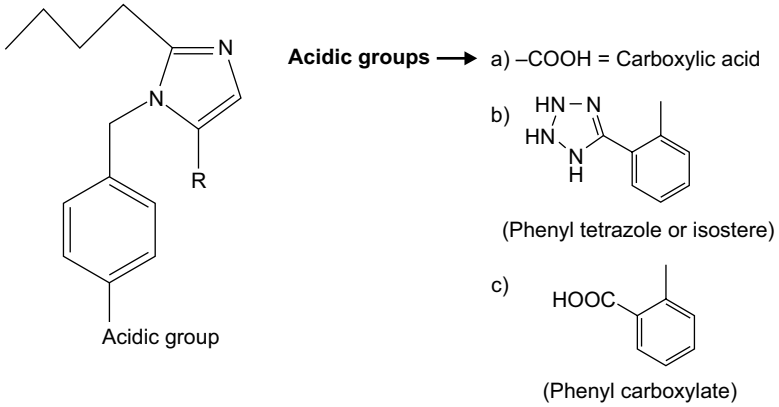
v. Valsartan



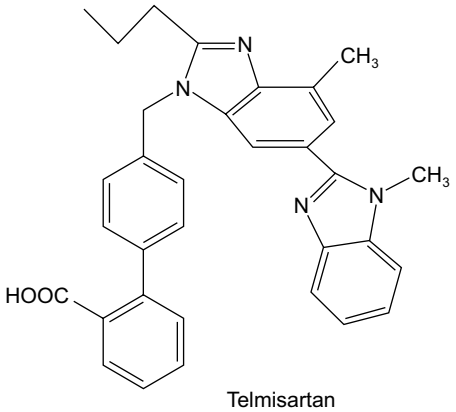
Properties and uses: It exists as white crystals and it is a non-peptide angiotensin II receptor antagonist.

SAR of Angiotensin Receptor Blockers (ARB)

All commercially available ARBs are analogues of the following general structure.



1. The acidic group is thought to mimic either through Tyr4 phenol or Asp1 carboxylate of angiotensin II capable of such a role include the A, B and C.
2. In the biphenyl series, the tetrazole and carboxylate groups must be in the *ortho* position for optimal activity (the triazole group is superior in terms of metabolic stability, lipophilicity and oral bioavailability.
3. The n-butyl group of the model compounds provides hydrophobic binding and must likely, mimics the side chains Ile5 of angiotensin II. This n-butyl group can be replaced with either an ethyl or n-propyl group, example telmisartan.

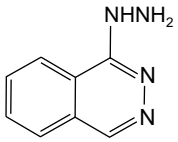


Telmisartan

4. The imidazole ring or an isosteric equivalent is required to mimic the His6 side chain of angiotensin II.
5. Substitution can vary at the R-position, A variety of R-groups, including a carboxylic acid, a hydroxyl methyl group, a ketone or a benzimidazole ring, are present in currently available ARBs and are thought to interact with AT receptor through either ionic, ion dipole or dipole-dipole bonds.

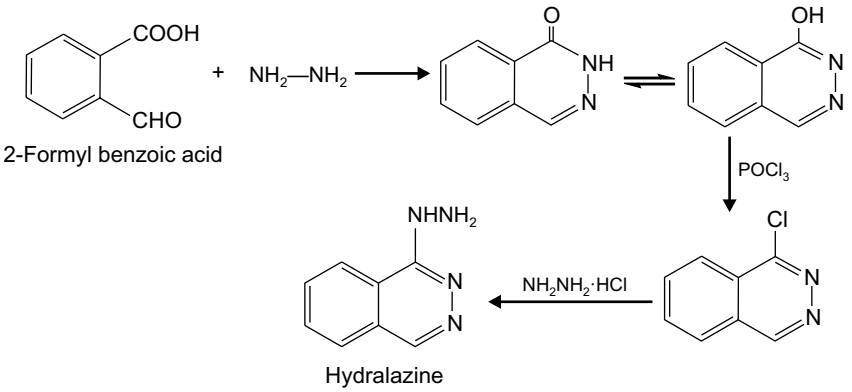
Vasodilators

i. Hydralazine (Apresoline)



1-(Phthalazin-1-yl)hydrazine

Synthesis



2-Formyl benzoic acid

Hydralazine

Properties and uses: It is a white or almost white crystalline powder, which is slightly soluble in methylene chloride, but soluble in water and slightly soluble in alcohol. It is one of the few drugs that cause substantial vasodilation in the kidney and it increases renal plasma flow even when the blood pressure drops considerably. The side effects of tachycardia and palpitations may precipitate attacks of angina pectoris. It is used in the treatment of moderate-to-severe hypertension.

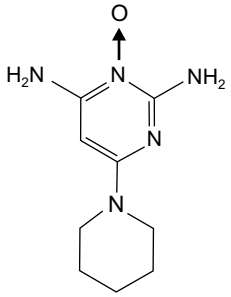
Assay: Dissolve the substance in water and add 35 ml of hydrochloric acid. Titrate with 0.05 M potassium iodate and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 25 to 100 mg oral twice daily; 20 to 40 mg IV in emergency.

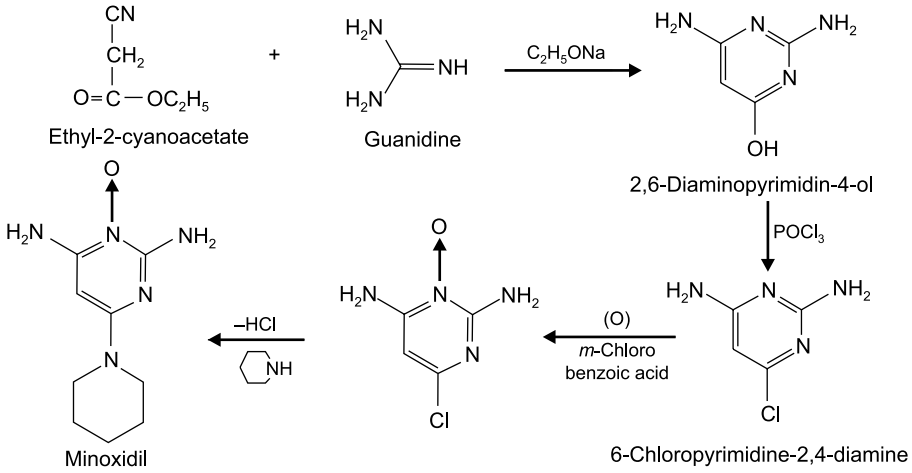
Dosage forms: Hydralazine HCl injection IP, hydralazine injection BP, hydralazine tablets BP.

ii. Minoxidil (Mintop, Coverit, Multigain)



2,4-Diamino-6-piperidino pyrimidine-3-oxide

Synthesis



Properties and uses: It is a white or almost white crystalline powder, which is slightly soluble in water, soluble in methanol and in propylene glycol. Minoxidil, which is a piperidino pyrimidine derivative directly relaxes arteriolar smooth muscle, and is indicated for patients with severe hypertension, who do not respond to other drugs. It is used as the last line of therapy to treat moderate-to-severe essential hypertension. It often is effective in hypertension refractory as compared to all other therapies. A side effect is excessive hair growth. Consequently, the drug is used topically to restore hair growth in androgenic alopecia and alopecia areata.

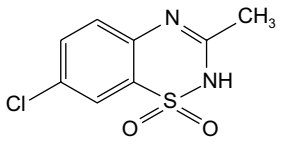
Assay: Dissolve in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is initially 5 mg; can be increased to 40 mg/day.

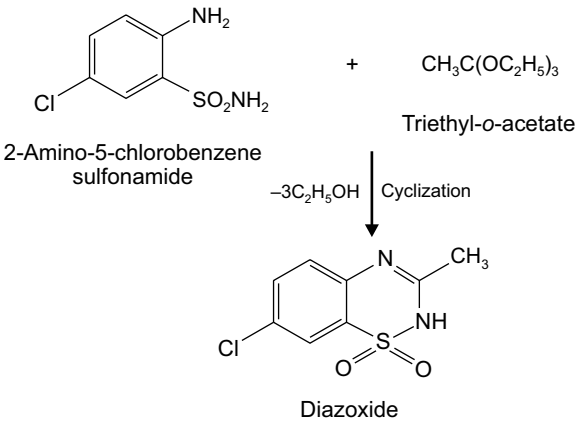
Dosage forms: Minoxidil scalp application BP.

iii. Diazoxide (Hyperstat)



7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide

Synthesis



Properties and uses: It is a white or almost white and fine crystalline powder that is soluble in dilute solutions of alkali hydroxides, in dimethylformamide, slightly soluble in alcohol, but insoluble in water. A potent vasodilator, especially in the intravenous route, it can be used intravenously as a hypotensive drug in acute hypertensive crisis. Vasodilation is primarily the result of arteriolar dilation, so that orthostatic hypotension is usually minimal. It is also used as antihyperglycemic agent.

Assay: Dissolve it by gentle heating in a mixture of water and dimethylformamide. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

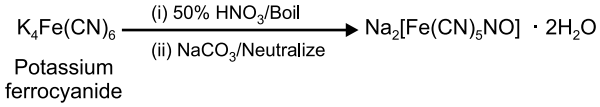
Dose: The usual dose is 1 mg/kg every 10 min.

Dosage forms: Diazoxide injection BP, diazoxide tablets BP.

iv. Sodium Nitroprusside (Nipride)

$Na_2[Fe(CN)_5NO].\ 2H_2O$

Synthesis



Properties and uses: It is a reddish-brown powder or crystals, which are freely soluble in water, but slightly soluble in alcohol. A potent directly acting peripheral vasodilator, this drug has an immediate onset of effect and short duration of action, therefore, it is effective in treating hypertensive emergencies, but must be given by continuous intravenous infusion. Side effects of this drug include significant hypotension and cyanide or thiocyanate toxicity.

Assay: Dissolve the substance in water and add dilute sulphuric acid. Titrate with 0.1 M silver nitrate and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 1 mg/kg/min by IV infusion.

Dosage forms: Sodium nitroprusside intravenous infusion BP.

Adverse Drug Reactions and Contraindications of β-blockers

Congestive cardiac failure: β-blockers prevent an increase in the heart rate and cardiac output. These effects may be dangerous in patients with CCF. They should be used cautiously and only in selected patients with CCF.

Bradycardia: They should be avoided in patients with bradycardia.

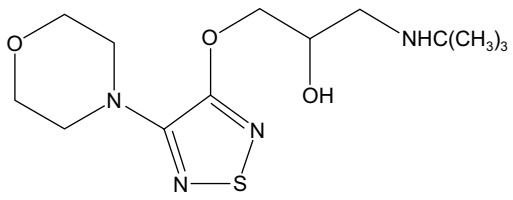
- β-blockers are contraindicated in patients with heart block because they depress AV conduction.
- They are to be avoided in patients with bronchial asthma and COPD. If needed, a cardioselective β-blockers may be used with caution.
- They should be avoided in diabetes because they mask the initial symptoms of hypoglycaemia.
- Sudden stoppage of β-blockers, after prolonged therapy, can produce withdrawal syndrome due to sympathetic overactivity.

Adverse effects

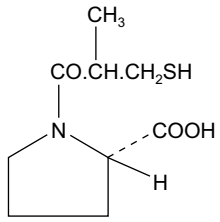
Common side effects of β-blockers are postural hypotension, palpitation, nasal stiffness, miosis, impaired ejaculation and impotency.

CLASSIFICATION BASED ON PCI SYLLABUS

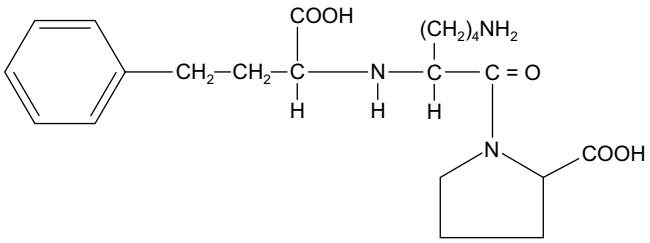
Timolol



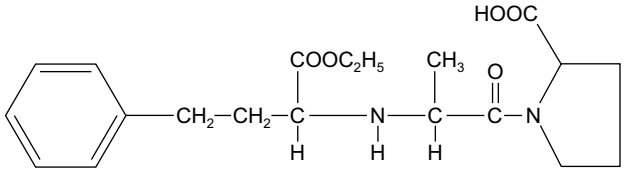
Captopril



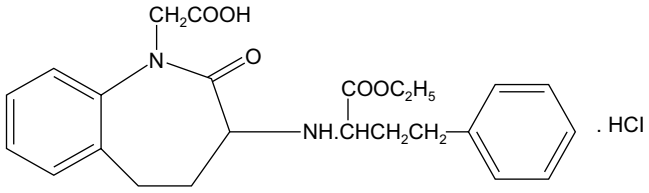
Lisinopril



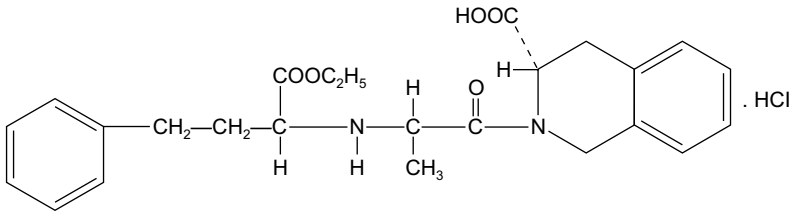
Enalapril



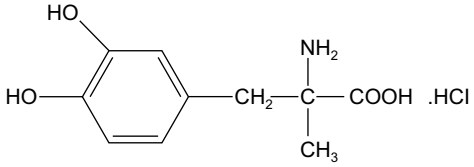
Benazepril hydrochloride



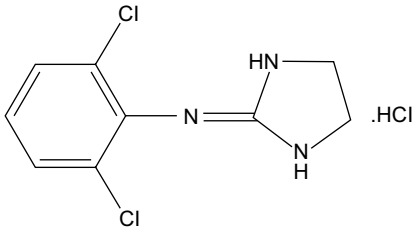
Quinapril hydrochloride



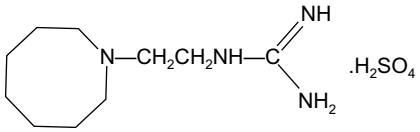
Methyldopate hydrochloride



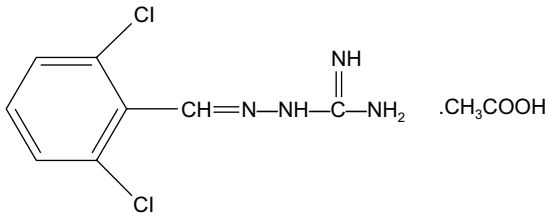
Clonidine hydrochloride



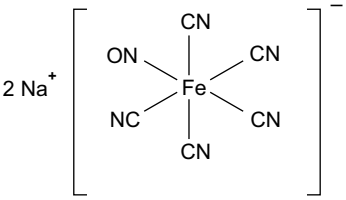
Guanethidine monosulphate



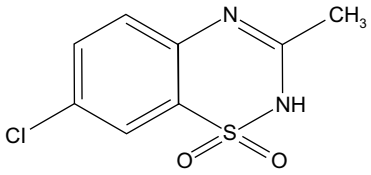
Guanabenz acetate



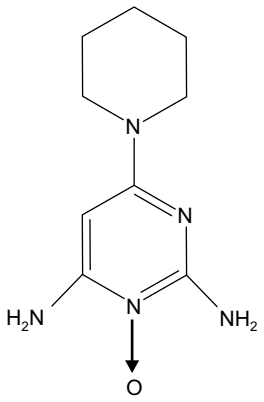
Sodium nitroprusside



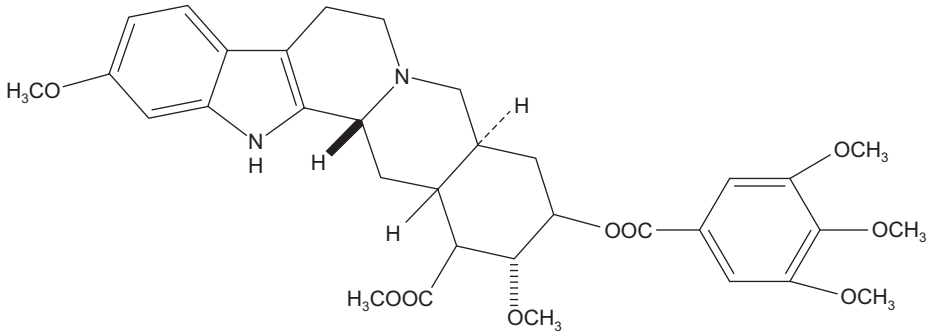
Diazoxide



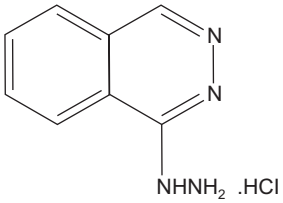
Minoxidil



Reserpine



Hydralazine hydrochloride

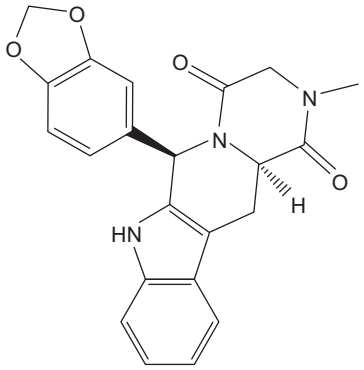


Benazepril hydrochloride

Properties and uses: It is used to treat high BP, heart failure and diabetic kidney failure. It is administered by oral route. It is combined and used along with hydrochlorothiazide or amlodipine.

Newer Drugs

Tadalafil (Adcirca)

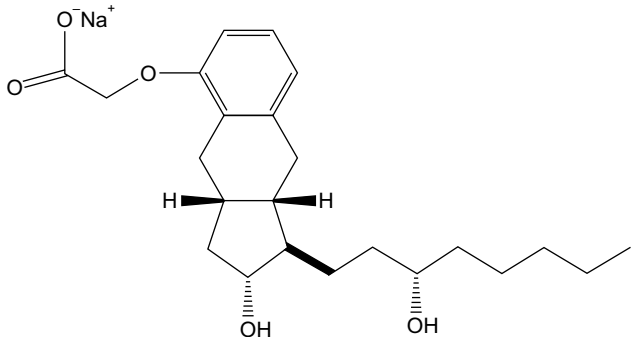


Mode of action: Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Properties and uses: It is an oral inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Tadalafil is specifically used for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. Adverse events associated with the use of tadalafil may include, headache, dyspepsia, myalgia, nausea, back pain, nasopharyngitis, flushing, respiratory tract infection, pain in extremity.

Dose: The recommended initial dose of the drug is 40 mg (two 20 mg tablets) taken once daily with or without food. Dividing the dose (40 mg) over the course of the day is not recommended.

Treprostinil (Tyvaso)



Mode of action: Treprostinil directs vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. It reduces the recruitment of fibrocytes to sites of vascular remodelling in hypoxic pulmonary hypertension and inhibits the adhesion and differentiation of fibrocytes by limiting the activity of (extracellular regulated kinase) ERK via the cAMP-Rap axis.

Properties and uses: Treprostinil is a prostacyclin analogue. It is used to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms. Adverse events associated with the use of treprostinil are cough, headache, throat irritation, nausea, flushing, syncope.

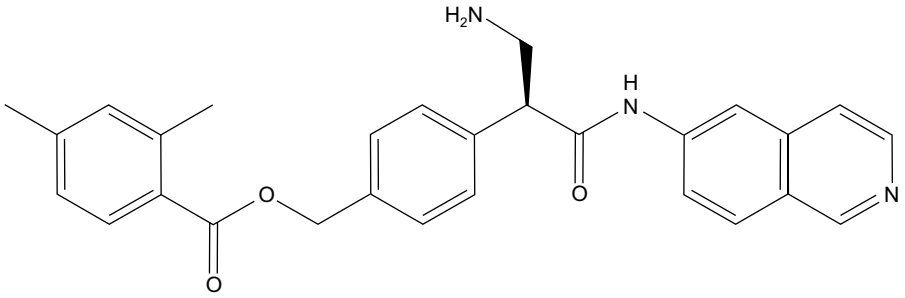
Dose: Treprostinil is supplied as a solution designed for oral inhalation. Treprostinil should be dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart.

Initial dose: Therapy should begin with 3 breaths of tyvaso (18 mcg of treprostinil), per treatment session, four times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance dose: Dosage should be increased by an additional 3 breaths at approximately 1–2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, four times daily. If adverse effects preclude titration to target dose, tyvaso should be continued at the highest tolerated dose. The maximum recommended dosage is 9 breaths per treatment session, four times daily.

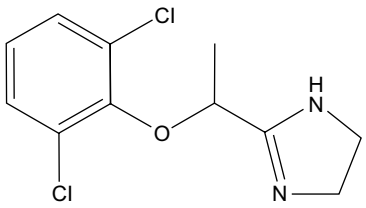
NEWER AGENTS

Rhopressa



Uses: It is a Rho kinase inhibitor used for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Lofexidine



Uses: It is used as an antihypertensive drug and also used for the patients with physical symptoms of opioid withdrawal.

CHAPTER 41

Antiarrhythmic Drugs

INTRODUCTION

Antiarrhythmic agents correct the arrhythmia of the heart. Cardiac arrhythmias are frequent problems in clinical practice, occurring in up to 25% of the patients treated with digitalis, 50% of the anaesthetized patients, and over 8% of the patients with acute myocardial infarction. Many factors can precipitate or exacerbate arrhythmias, ischaemia, hypoxia, acidosis, alkalosis, electrolyte abnormalities, excessive catecholamine exposure, autonomic influences, drug toxicity, overstretching of cardiac fibres, and the presence of any diseased tissue. However, all the arrhythmias results from the following:

1. Disturbances in impulse formation
2. Disturbances in impulse conduction
3. Or both

The different types of cardiac arrhythmias are the following:

1. **Extra systole:** Premature beats due to abnormal automaticity or after depolarization, arising from atrioventricular (AV) node, atrium, or ventricle.
2. **Paroxysmal supraventricular tachycardia:** Sudden onset of atrial tachycardia mostly due to circus re-entry type within or around the AV node.
3. **Atrial flutter:** Higher impulse and the arterial beat up to 200–350/min.
4. **Atrial fibrillation:** Arterial fibres are activated asynchronously at the rate of 300–550/min.
5. **Ventricular tachycardia:** It is a run of four consecutive ventricular extra systoles. It may be sustained or unsustained arrhythmia due to discharge from ectopic focus.
6. **Torsades de pointes:** Twisting of valves leads to polymorphic ventricular charge and produces asynchronous complexes.
7. **Ventricular fibrillation:** Fractional activation of ventricles resulting in coordinated concentration of fibres with loss of pumping function.
8. **Atrioventricular block:** It is due to depression of the impulse conduction through AV node and bundle of His due to vagal influence and ischaemias.

CLASSIFICATION

Antiarrhythmic drugs are classified into four types, according to their electrophysiological properties. The drugs that are used for arrhythmias are sodium, potassium, and calcium channel blockers. Some have additional or even primary autonomic effects.

Class 1: These have primary action on Na^+ and K^+ across the cell membrane.

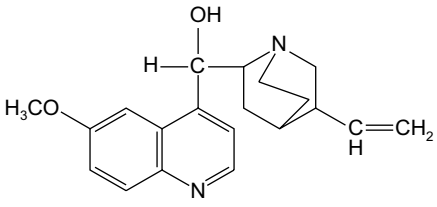
Class 2: These have primary action to suppress adrenergically-mediated ectopic activity.

Class 3: These are the drugs that prolong the repolarization. Action potential is widened and effective refractory period is increased.

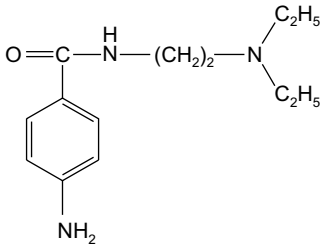
Class 4: Their primary action is to inhibit Ca^{2+}-mediated currents.

Class I: Blockade of fast sodium ion channel by depressing phase of the action potential

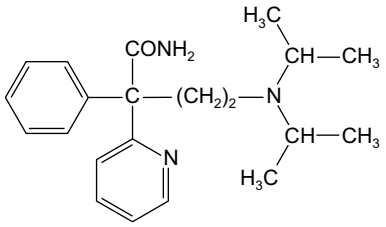
a. Moderate to marked sodium channel blockade agents



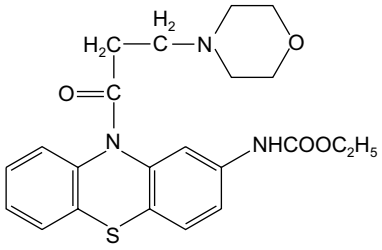
Quinidine



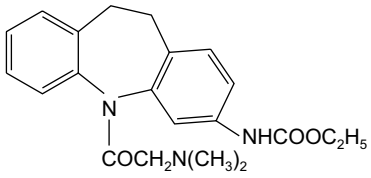
Procainamide



Disopyramide

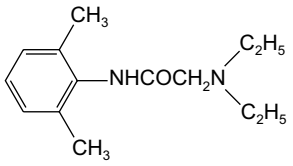


Moricizine

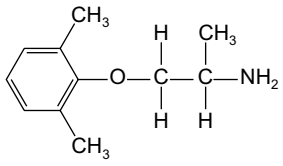


Tiracizine

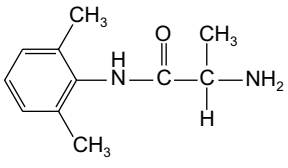
b. Mild-to-moderate sodium channel blockade agents



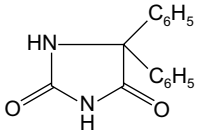
Lidocaine



Mexiletine

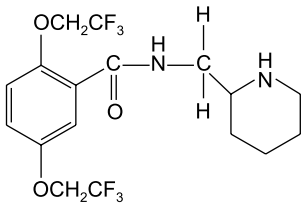


Tocainide

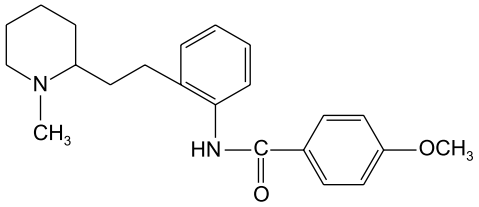


Phenytoin

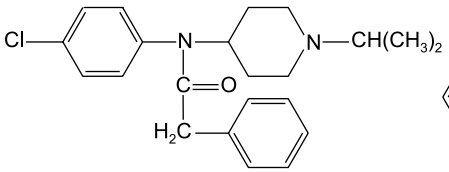
c. Marked sodium channel blockade agents



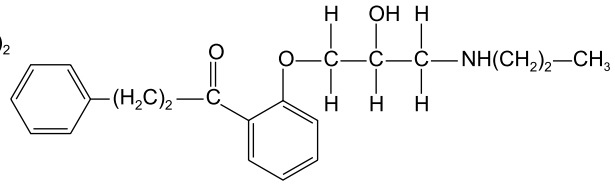
Flecainide



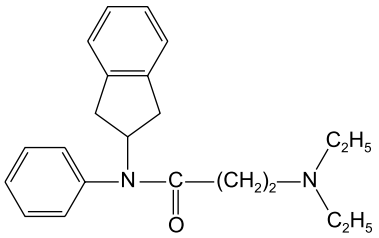
Encainide



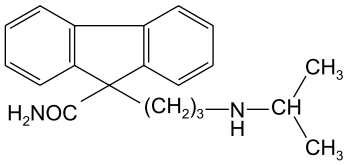
Lorcainide



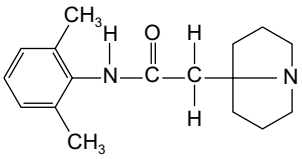
Propafenone



Aprindine

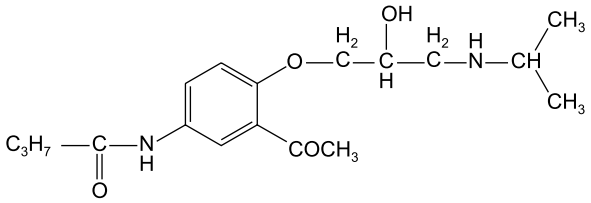


Indecainide

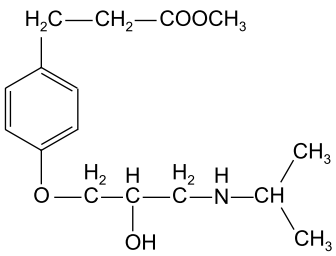


Pilsicainide

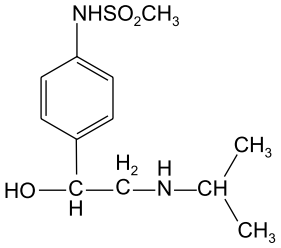
Class II: Beta-adrenergic Antagonists



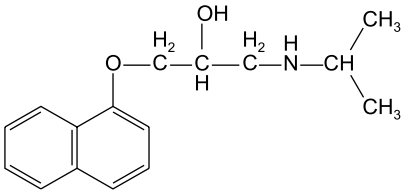
Acebutalol



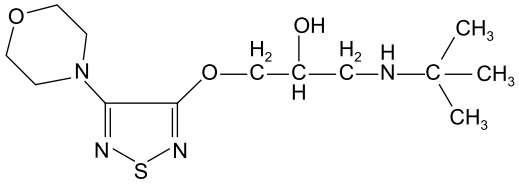
Esmolol



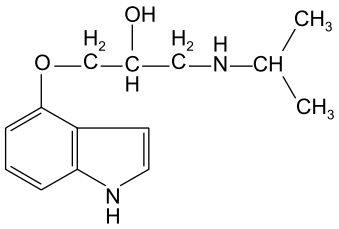
Sotalol



Propranolol

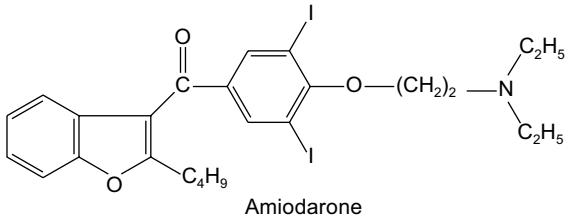


Timolol

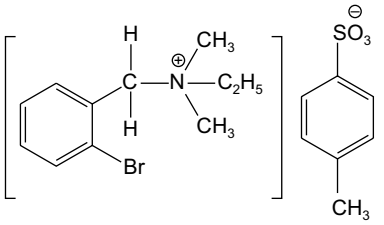


Pindolol

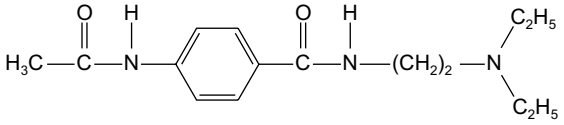
Class III: Repolarization prolongators



Amiodarone

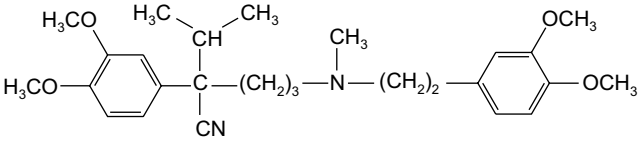


Bretylium tosylate

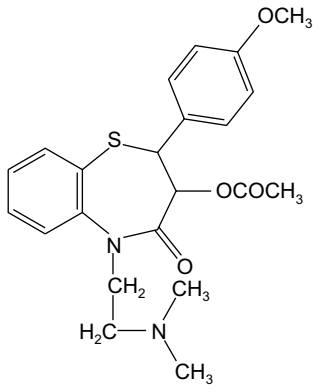


Acecainide

Class IV: Calcium channel blockers



Verapamil



Diltiazem

SYNTHESIS AND DRUG PROFILE

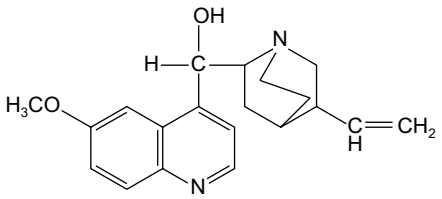
Class I: Blockade of fast sodium ion channel by depressing phase of the action potential

Mode of action: These agents block the specific channels and decrease the threshold for excitability. It decreases the conduction velocity in fast response tissues and increases QRS duration. These drugs also inhibit the triggered activity arising from delayed after depolarization (DAD) or early after

depolarization (EAD) and shifts the voltage dependence of recovery from inactivation to more negative potentials, thereby tending to increase the refractioners.

a. Moderate to marked sodium channel blockade agents

i. Quinidine sulphate



(6-Methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methanol

Metabolism: Once absorbed, quinidine is subjected to hepatic first-pass metabolism and is approximately 85% plasma protein bound, with an elimination half-life of approximately 6 h. It is metabolized mainly in the liver, and the renal excretion of unchanged drug also is significant (10–50%). The metabolites are hydroxylated derivatives at either the quinoline ring through first-pass *O*-demethylation or at the quinuclidine ring through oxidation of the vinyl group. These metabolites possess only about one-third of the activity of quinidine.

Properties and uses: It exists as a white or almost white crystalline powder or silky colourless needles. It is insoluble in acetone and slightly soluble in water, but soluble in boiling water and alcohol. Quinidine is an alkaloid isolated from cinchona bark. It is dextrorotatory diastereoisomer of quinine. Quinidine is very useful for long-term treatment of ventricular premature depolarization or to prevent recurrences of ventricular tachycardia after cardioversion of this arrhythmia. Quinidine should not be used without prior digitalization. It can cause cinchonism, characterized by hearing loss, vomiting, and diarrhoea.

Assay: Dissolve the sample in acetic anhydride and titrate with 0.1 M perchloric acid, using naphtholbenzein as an indicator.

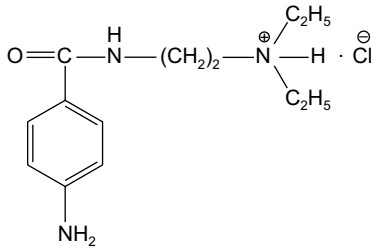
Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Quinidine sulphate tablets IP, BP, quinidine HCl tablets IP, quinidine dihydrochloride IP, quinidine bisulphate tablet IP.

Adverse drug reactions: Common side effects of quinidine are:

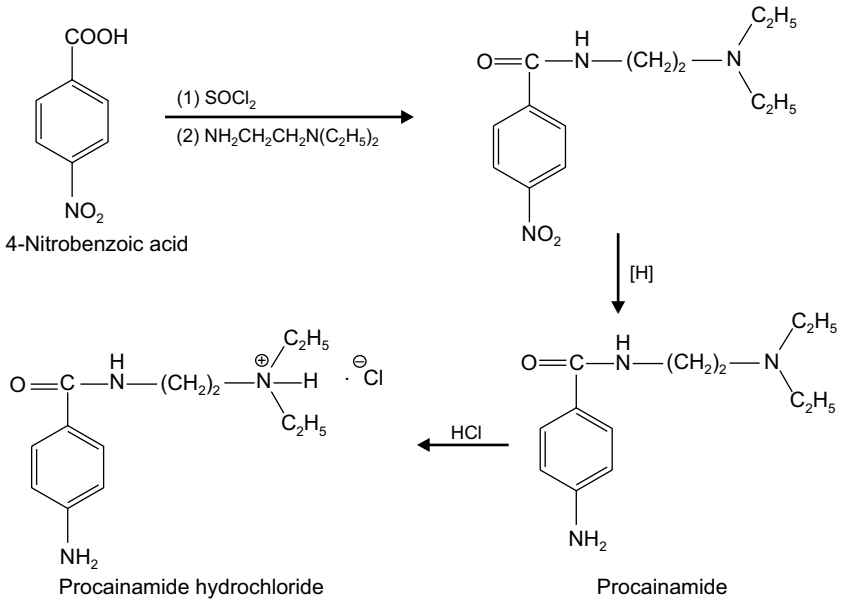
1. **Cardiac effects:** They are mainly due to extension of pharmacological actions of quinidine, due to cardiac depressant effect it shows
   i. Decrease in heart rate resulted in bradycardia.
   ii. Decrease in contractility results in congestive heart failure.
   iii. Decrease in conduction results in heart block.
   - Quinidine can cause ventricular tachycardia due to vagolytic effect.
   - Postural hypotension, torsades de pointes can also occur (torsades de points is a form of ventricular tachycardia associated with long QT interval).
2. **GIT:** Nausea, vomiting and diarrhoea.
3. **Hypersensitivity:** Fever, hepatitis and rarely asthmatic attack may be precipitated.
4. Large doses of quinidine may produce a syndrome ‘Cinchonas’.

ii. Procainamide HCl (Pronestyl)



p-Amino-N-(2-diethylaminoethyl) benzamide

Synthesis



Metabolism: Metabolites of procainamide include *p*-amino benzoic acid and N-acetyl procainamide. The acetylated metabolite also active antiarrhythmic agent. Metabolism is catalyzed by N-acetyl transferase.

Properties and uses: It is a white crystalline powder, odourless, and soluble in water, alcohol, slightly soluble in chloroform, very slightly soluble in ether. It was developed in the course of research for compounds structurally similar to procaine. It is also more stable in water than procaine. It is useful in suppressing arrhythmias of ventricular origin. It is also effective against premature artrial contractions and artrial fibrillations. It is used in the management of myotonia. It is also used in the treatment of arrhythmias in alcohol withdrawal.

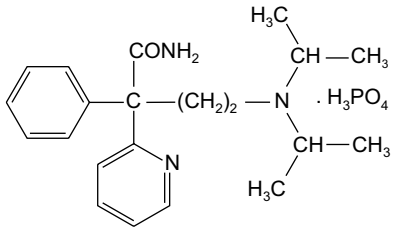
Assay: Dissolve the sample in dilute hydrochloric acid and perform the determination of primary aromatic amino-nitrogen (diazotization method).

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 3 to 6 g orally at intervals of 6 to 8 hrs.

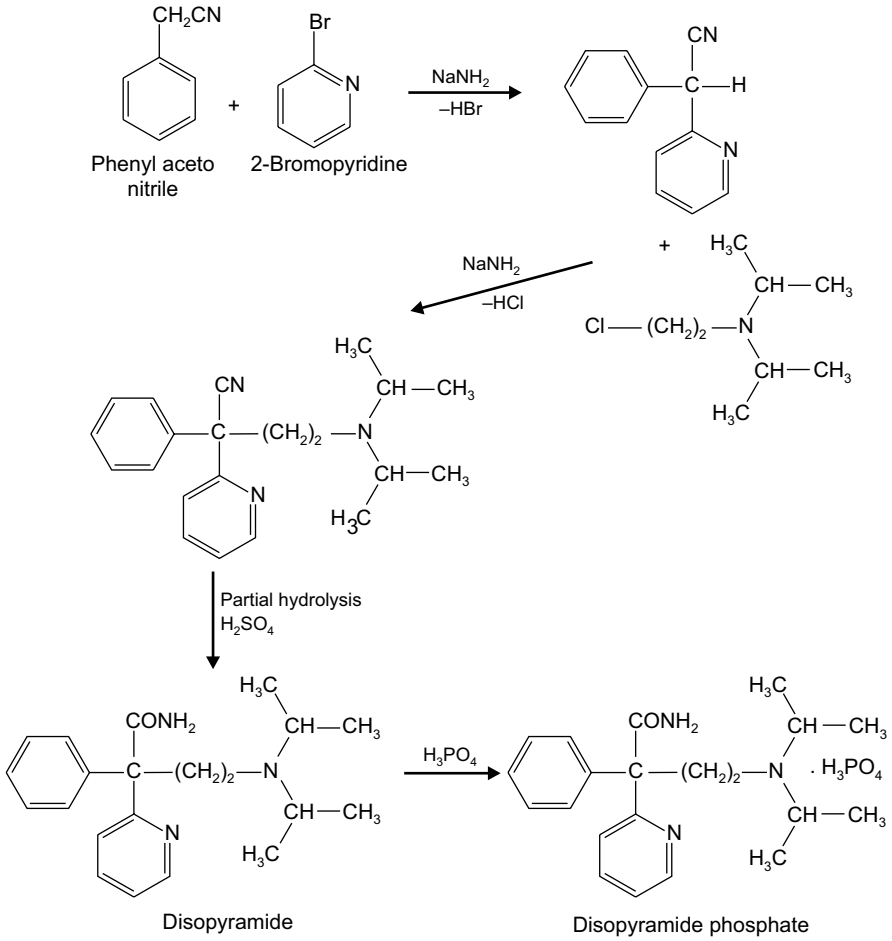
Dosage forms: Procainamide injection BP, procainamide tablets BP, procainamide HCl injection IP, procainamide HCl tablets IP.

iii. Disopyramide phosphate (Norpace, Regubeat)



α-[2-(Diisopropylamino)ethyl]-α-phenyl-2-pyridineacetamide

Synthesis



Metabolism: Half of the drug is excreted unchanged, rest of the amount undergoes hepatic metabolism to form N-dealkylated compound.

Properties and uses: It is a white or almost white powder, which is soluble in water, sparingly soluble in alcohol, and insoluble in methylene chloride. Used as an antiarrhythmic agent.

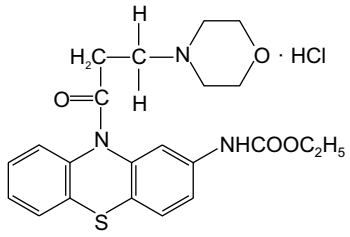
Assay: Dissolve the sample in anhydrous acetic acid and add naphtholbenzein indicator. Titrate with 0.1 M perchloric acid until the colour changes from yellow to green.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Total daily dose is 400–500 mg; 100–150 mg four times/day.

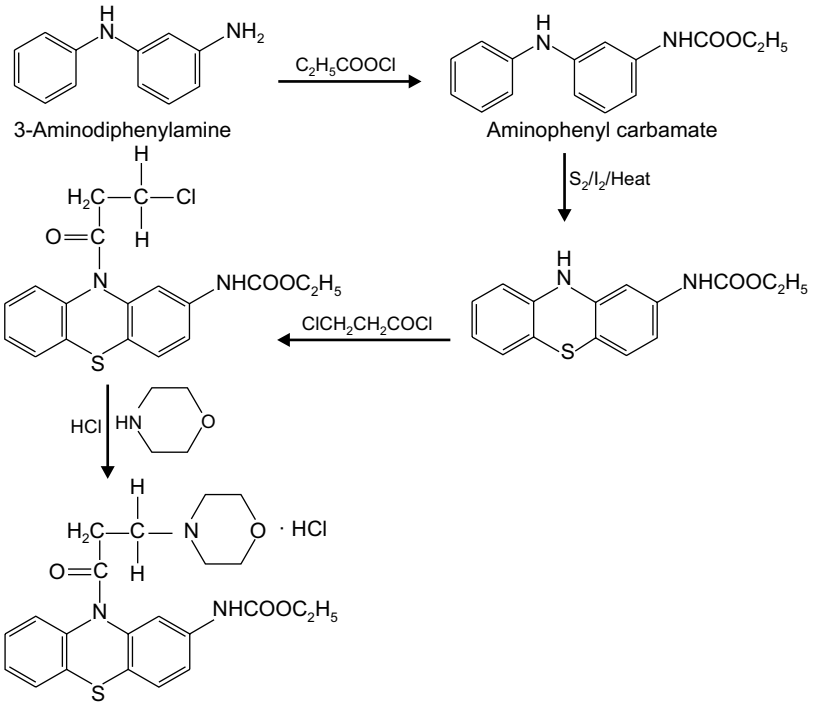
Dosage forms: Disopyramide phosphate capsules BP.

iv. Moricizine HCl (Ethmozine)



Ethyl-10-(3-morpholinopropanoyl)-phenothiazin-2-yl-carbamate hydrochloride

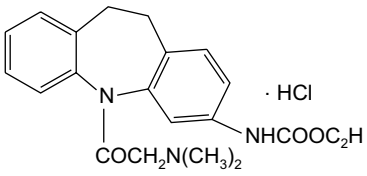
Synthesis



Properties and uses: These are white crystals, which are soluble in water or alcohol. It is used in the treatment of cardiac arrhythmia.

Dose: The usual dose is 600 mg/day in three divided doses. It infrequently causes gastrointestinal and CNS effects.

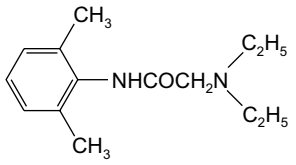
v. Tiracizine HCl



Properties and uses: Tiracizine hydrocholoride is an antiarrhythmic drug reported to reduce excitability of cardiac cells through blockade of fast sodium channels.

b. Mild-to-moderate sodium channel blockers

i. Lidocaine

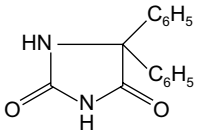


Adverse drug reactions: Common side effects of lignocaine are:

- Mainly related to CNS—headache, drowsiness, nystagmus, blurred vision. Confusion, muscle twitching and convulsions.
- In high doses it may cause hypotension due to myocardial depression.
- Side effects are potentiated in renal and hepatic failure.

Synthesis and drug profile are discussed in Chapter 25, 'Local Anaesthetics'.

ii. Phenytoin (Dilantin, Eptoin)



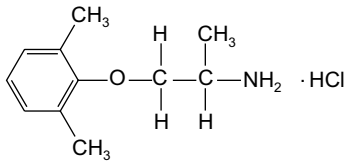
5,5-Diphenylimidazolidine-2,4-dione

Synthesis

Synthesis and drug profile are discussed in Chapter 30 'Anticonvulsants'.

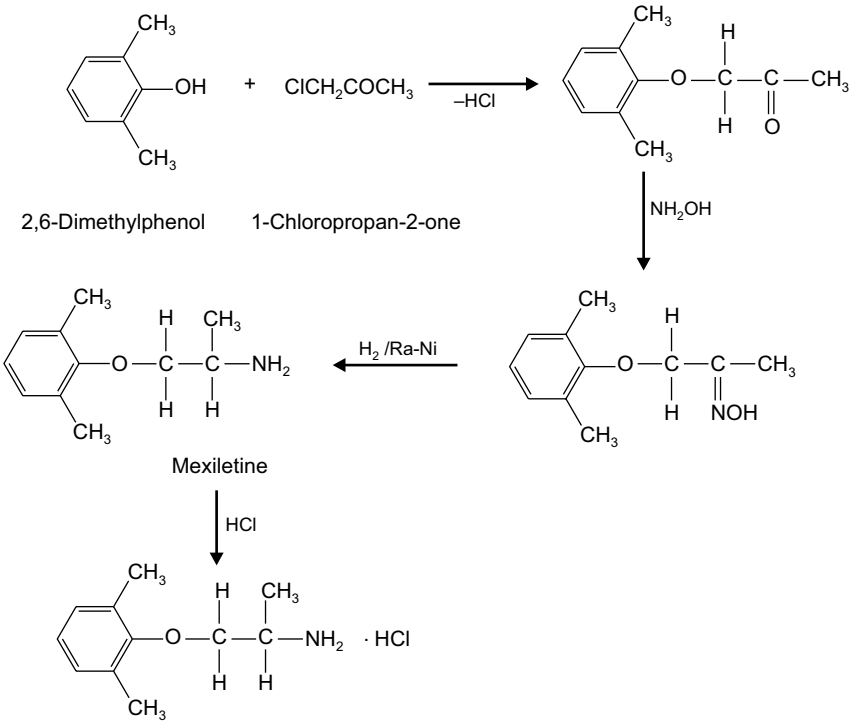
Dose: Orally 15 mg/kg first day; 7.5 mg/kg on the second day, followed by 300 to 400 mg per day.

iii. Mexiletine HCl



1-(2,6-Dimethylphenoxy)propan-2-amine hydrochloride

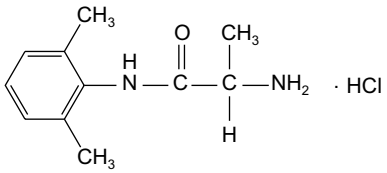
Synthesis



Mexiletine hydrochloride

Properties and uses: It exists as white crystals, which are soluble in water and alcohol. It resembles lidocaine as it possesses a xylyl moiety, but is otherwise different chemically. Mexiletine is most useful in suppressing symptomatic ventricular arrhythmias.

iv. Tocainide HCl (Tonocard)

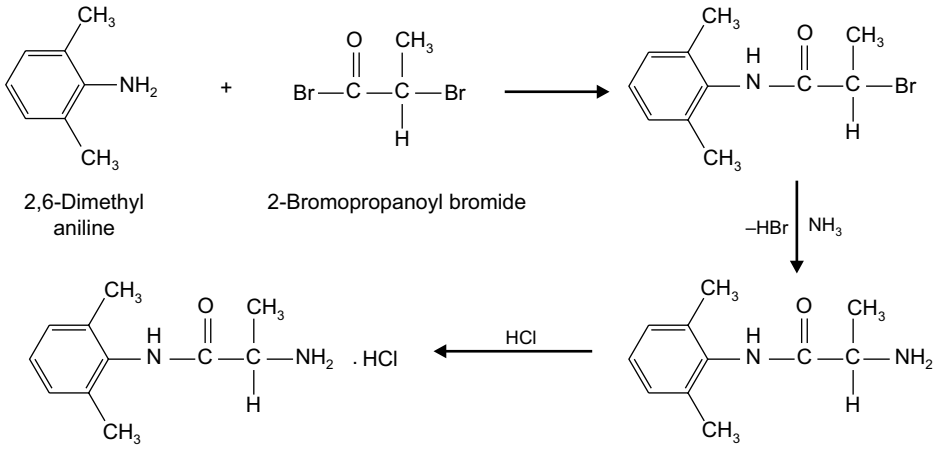


2-Amino-N-(2,6-dimethylphenyl) propanamide hydrochloride

Properties and uses: It exists as a white crystalline powder with bitter taste and soluble in water or in alcohol. Tocainide is another lidocaine congener and is similar to mexiletine in its electrophysiologic properties and antiarrhythmic action.

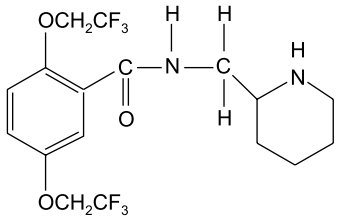
Dose: The usual dose is orally 400–1200 mg in two or three divided doses.

Synthesis



c. Marked sodium channel blockers

i. Flecainide (Tambocar)



2,5-*Bis*(2,2,2-trifluoroethoxy)-N-{(4-[2,2,2-trifluoroethoxy]piperidin-2-yl)methyl}benzamide

Properties and uses: It is a white or almost white crystalline powder, very hygroscopic, soluble in water and in ethanol, insoluble in dilute hydrochloric acid and soluble in dilute acetic acid. Flecainide represents the first fluorine containing newer group of antiarrhythmic drugs. It is indicated for use in patients with life-threatening arrhythmias, such as sustained ventricular tachycardia.

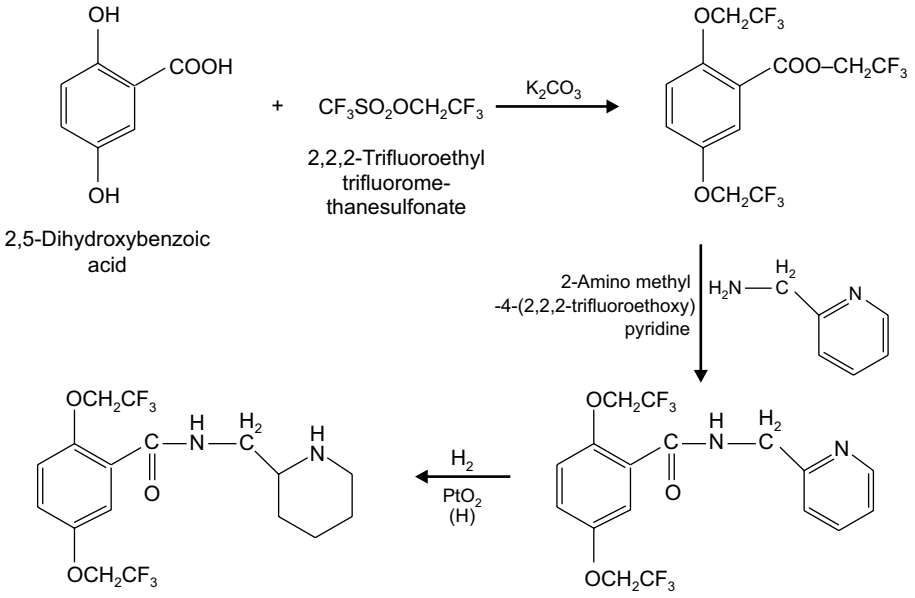
Assay: Dissolve the sample in anhydrous acetic acid. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

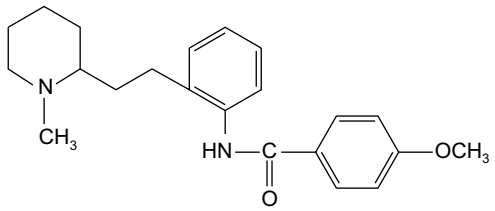
Dose: The usual dose is orally, 100 mg twice daily with an average daily maintenance doses from 200 to 600 mg.

Dosage forms: Flecainide injection BP, flecainide tablets BP.

Synthesis



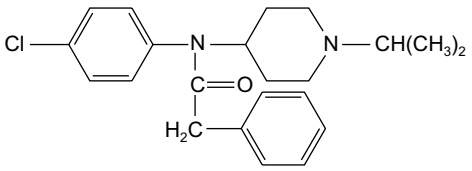
ii. Encainide HCl



4-Methoxy-N-(2-(2-(1-methylpiperidin-2-yl)ethyl)phenyl)benzamide

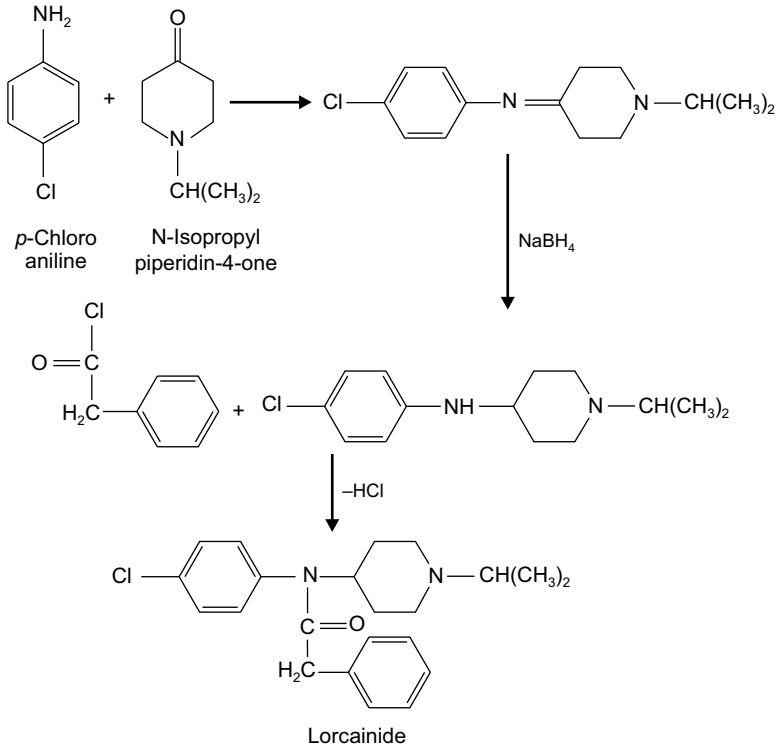
Uses: It is used in the treatment of cardiac dysfunction.

iii. Lorcainide HCl



N-(4-Chlorophenyl)-N-(1-isopropylpiperidin-4-yl)-2-phenylacetamide

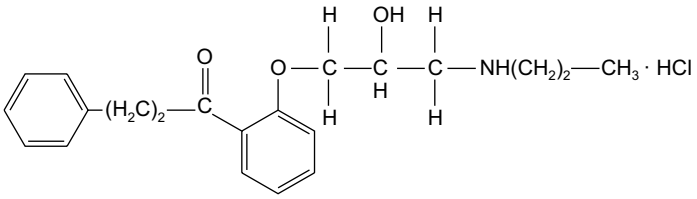
Synthesis



Properties and uses: Lorcainide proved to be effective in reducing ventricular arrhythmias and tachycardias.

Dose: The usual dose is 100 mg, two or three times/day.

iv. Propafenone HCl (Rhythmonorm)

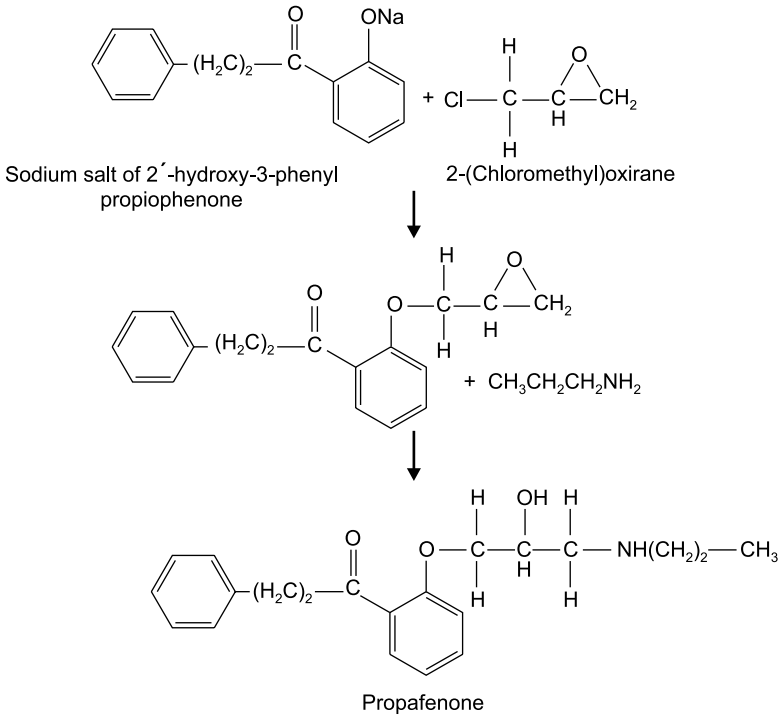


(±)2-(2-Hydroxy-3-propylamino propoxy)-3-phenyl propiophenone hydrochloride

Properties and uses: It exists as white crystals, which are soluble in hot water and in alcohol. It is slightly soluble in cold water. It is a class I-c antiarrhythmic drug and contains a chiral centre, and is marketed as the racemic mixture. The racemic mixture of propafenone produces effects that can be attributed to both (S) and (R) enantiomers. The (R) and (S) enantiomers exert similar Na^+ channel-blocking effects, the (S) enantiome also produces a β-adrenergic blockade. As a result, the (S) enantiomer is reported to be 40-fold more potent than the (R) enantiomers as an antiarrhythmic agent. The enantiomers also display stereoselective disposition characteristics. The (R) enantiomer is cleared

more quickly. It is useful in supraventricular and ventricular tachycardias and tachyarrhythmias. It resembles the β-adrenoceptor blockers of aryloxy propanol amines.

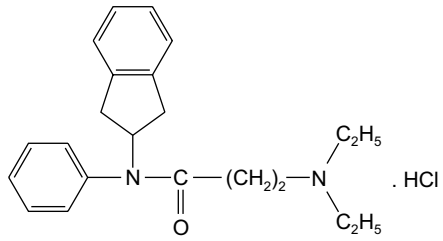
Synthesis



Assay: Dissolve the sample in anhydrous formic acid and add acetic anhydride. Titrate with 0.1 M perchloric acid, determine the end point potentiometrically.

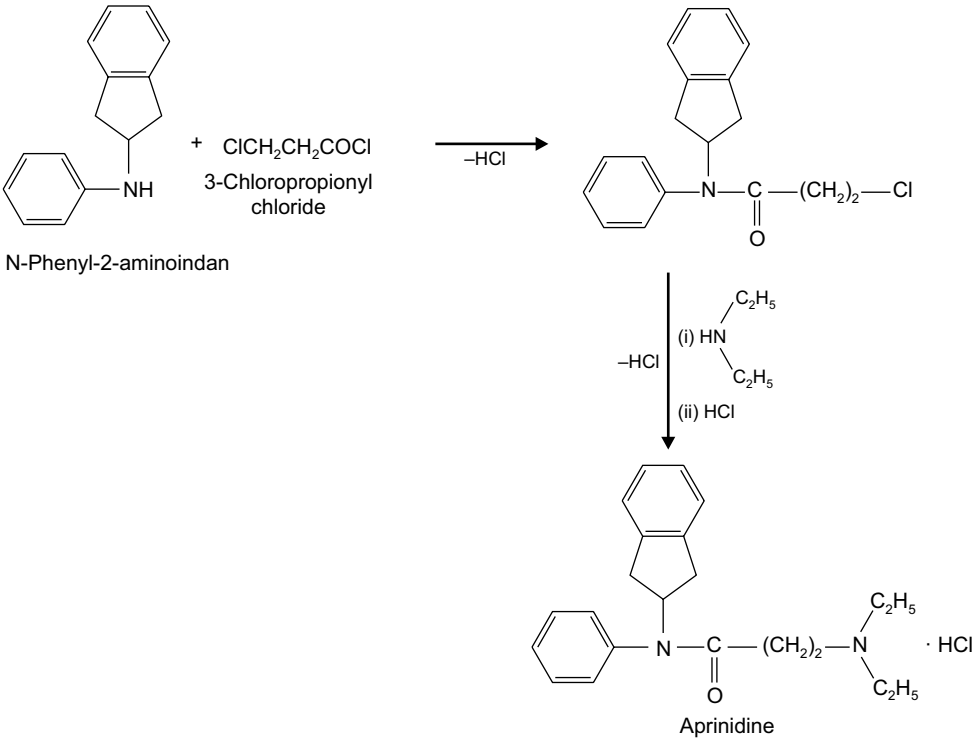
Dose: Initially 150 mg thrice/day which can be gradually increased to twice the initial dose.

v. Aprindine HCl



N-(3-Diethylamino propionyl)-N-phenyl-2-indanamide dihydrochloride

Synthesis

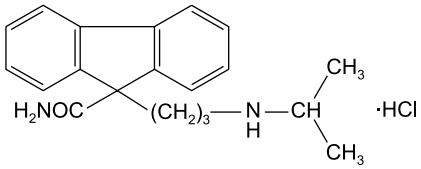


N-Phenyl-2-aminoindan

Aprinidine

Properties and uses: Aprindine is a powerful antiarrhythmic drug that may reverse both supraventricular and ventricular arrhythmias.

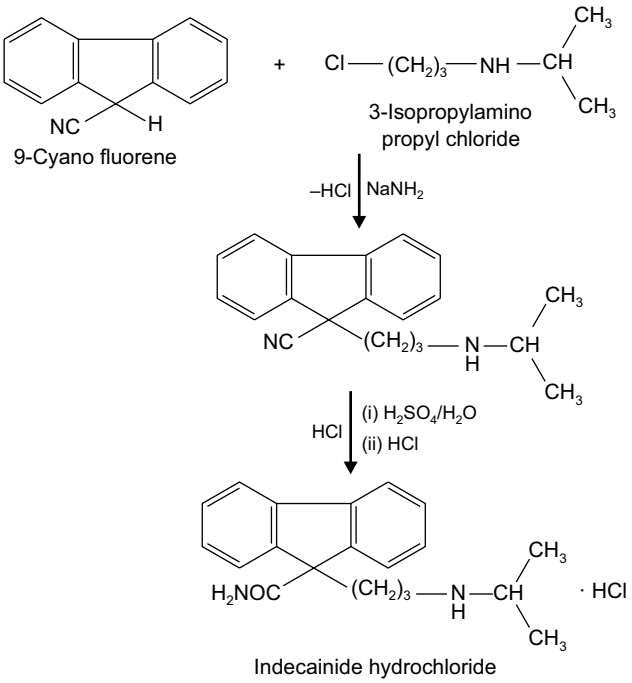
vi. Indecainide HCl



9-[3-(Isopropylamino-propyl)]-fluorene-9-carboxamide hydrochloride

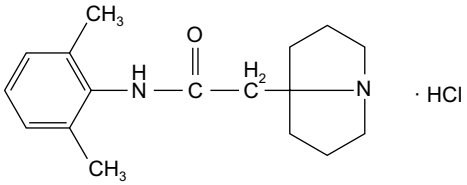
Properties and uses: It has shown itself to be a highly efficacious and well-treated antiarrhythmic drug for the suppression of ventricular tachycardias.

Synthesis



Indecainide hydrochloride

vii. Pilsicainide HCl



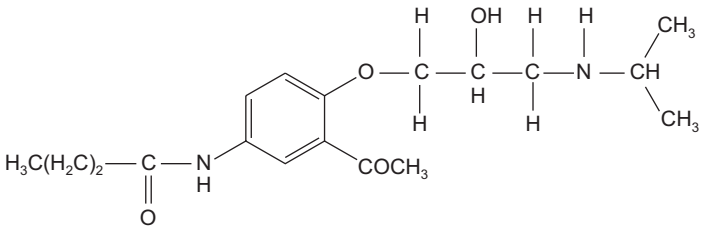
N-(2,6-Dimethylphenyl)-2-(hexahydro-1H-pyrrolizin-7a-yl)acetamide

Properties and uses: Pilsicainide hydrochloride is a new pyrrolizidine lidocaine derivative with antiarrhythmic activity. It is effective in the treatment of premature ventricular contraction.

II. β-Adrenergic receptor blockers

Mode of action: These are the drugs that mediate the actions through β-receptors. β-adrenergic receptor antagonists slow the heart rate and decrease the myocardial contractility; these also prolong the systolic conduction and disturb the ventricular fibres. Dimensions of the ventricle and oxygen consumption are decreased, and thereby decreases the heart rate and aortic pressure. In blood vessels, these drugs reduce the noradrenaline release from the sympathetic terminals and decrease the renin from the kidney due to the blockade of β-receptors.

i. Acebutolol

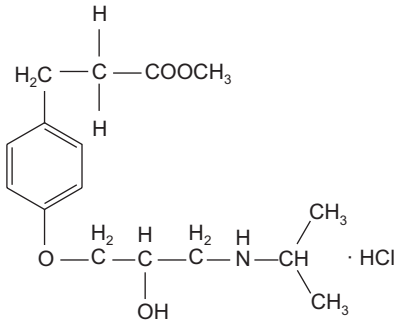


N-(3-Acetyl-4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)butyramide

Synthesis and drug profile are discussed in Chapter 37, 'Adrenergic Blockers'.

Properties and uses: It is a white to off-white powder that is soluble in water and alcohol. It is a β-selective adrenergic receptor blocker and is used for controlling ventricular pressure beats.

ii. Esmolol HCl (Cardesmo, Neotach)



Methyl 3-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)propanoate hydrochloride

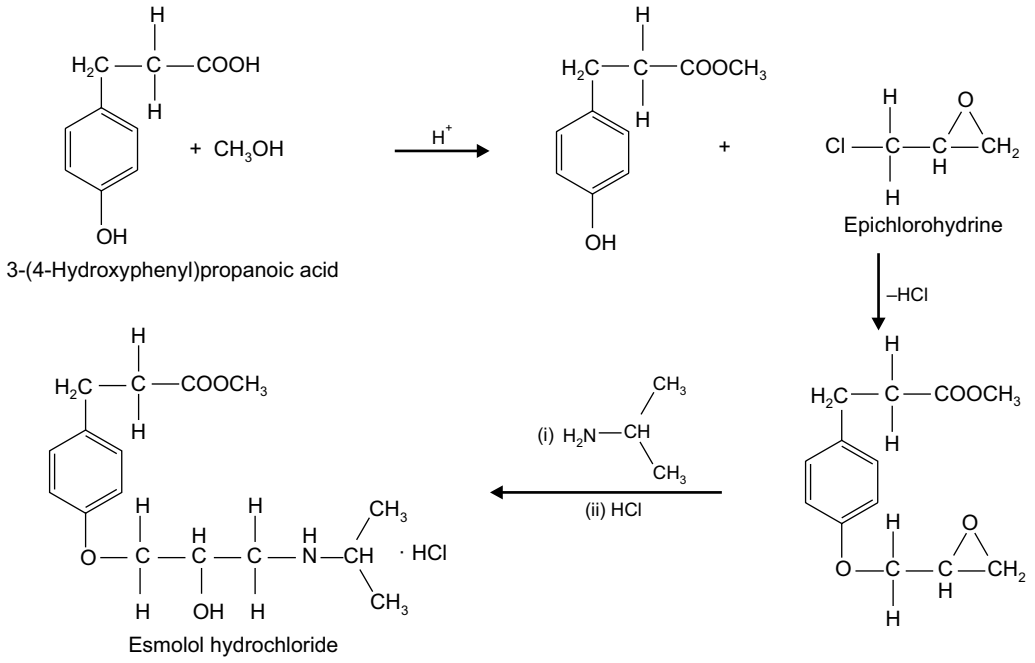
Properties and uses: It is available as white crystals and it is used in the treatment of supraventricular tachycardia.

Dose: A loading dose of 500 µg/kg/min is infused over 1 min followed by a maintenance dose of 50 µg/kg/min.

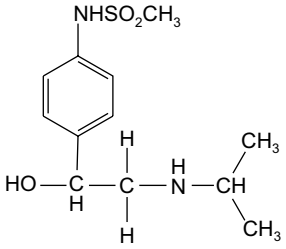
Cardioselective β1-Blockers

- These agents possess higher affinity to β1-receptors of the heart rather than the β2-receptors of other tissues.
- Due to this selectivity to the receptors, these are showing two important advantages. The first advantage is the absence of β2-antagonistic activity. Hence, these β1-blockers are safer drugs for patients with bronchial asthma. The second advantage is the absence of blockade of the vascular β2-receptors which mediate vasodilatation.
- Acebutolol and esmolol are used to treat certain kind of cardiac arrhythmias.
- Esmolol has rapid onset and short duration of action and hence it is useful for emergency situation for the shot-term control of heart rate.
- Betaxolol is the only β1-blocker used to treat glaucoma.
- The commonly used β1-blockers are atenolol, propranalol, metopropol while esmolol is used in emergency conditions and administered by intravenous infusions.

Synthesis



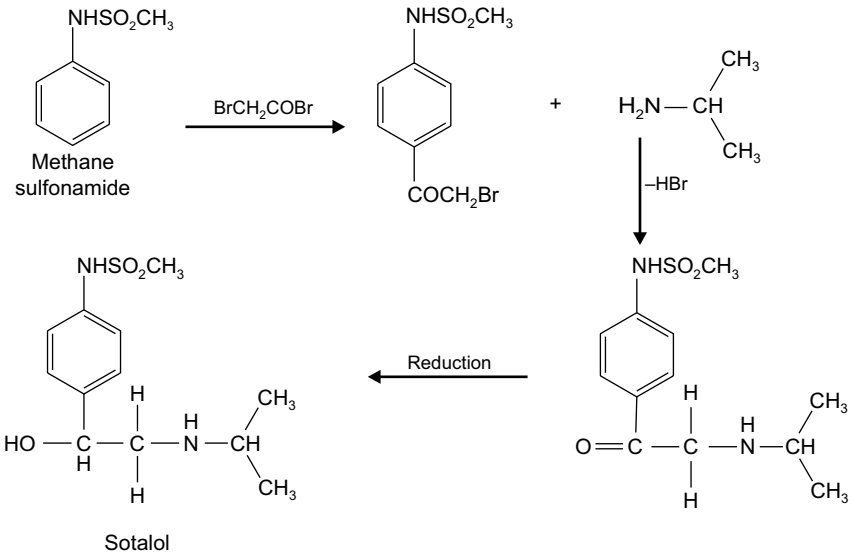
iii. Sotalol (Sotagrad)



N-(4-(1-Hydroxy-2-(isopropylamino)ethyl)phenyl)methane sulfonamide

Properties and uses: It is a white or almost white powder that is insoluble in methylene chloride, but freely soluble in water and in alcohol. It contains a chiral centre and is marketed as a racemic mixture. Because of its enantiomers, its mechanism of action spans two of the antiarrhytmic drugs classes. The L-(–)-enantiomer has both β-blocking agent (class II) and potassium channel-blocking (class III) activity. The D-(+)-enantiomer has class III properties similar to those of the (–)-isomer, but its affinity for the β-adrenergic receptors is 30–60 times lower. The sotalol enantiomers produce different effects on the heart. Class III action of D-sotalol in the sinus node is associated with slowing of the sinus heart rate, whereas β-adrenergic blockade contributes to the decrease in the heart rate observed with l or D-sotalol. It is effective against both supraventricular and ventricular arrhythmias.

Synthesis



Assay: Dissolve the sample in anhydrous formic acid and add acetic anhydride. Titrate with 0.1 M perchloric acid, determine the end point potentiometrically.

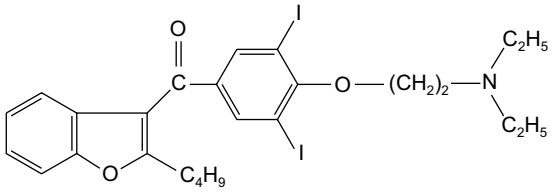
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual dose is 80 to 320 mg twice a day oral.

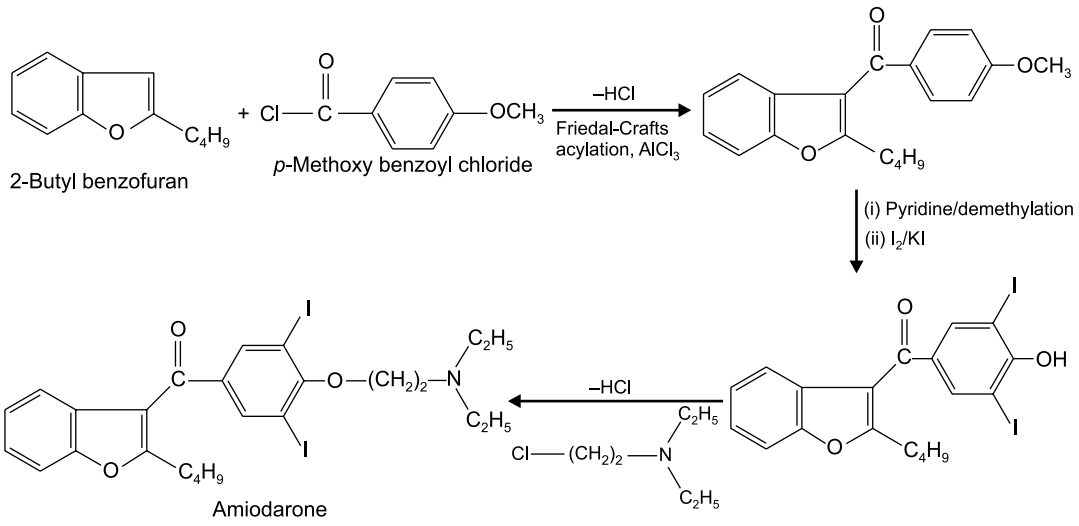
III. Repolarization prolongators

Mode of Action: The prolongation effect is mostly due to the blockade of K^+ channels, although enhanced inward Na^+ current also prolongs the action potentials, increased inward current produces the QT prolongation. The cardiac block of K^+ channels increases action potential duration and reduces normal automaticity.

i. Amiodarone (Cardarone, Aldarone, Amiodar)



Synthesis



Properties and uses: It is a white to cream-coloured crystalline powder, which is sparingly soluble in water, soluble in alcohol and chloroform. It is an iodinated benzofuran derivative, which is effective in maintaining rhythms in patients who has direct current shock for atrial fibrillation. It is also used as an antianginal agent.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and ethanol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light at a temperature not exceeding 30°C.

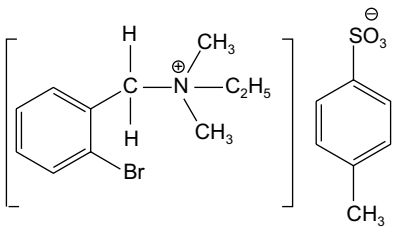
Dose: The usual dose is 400 mg alternating with 600 mg daily for 1–3 weeks orally.

Dosage forms: Amiodarone intravenous infusion BP, amiodarone tablets BP.

Adverse drug reactions: Common side effects of amiodarone are:

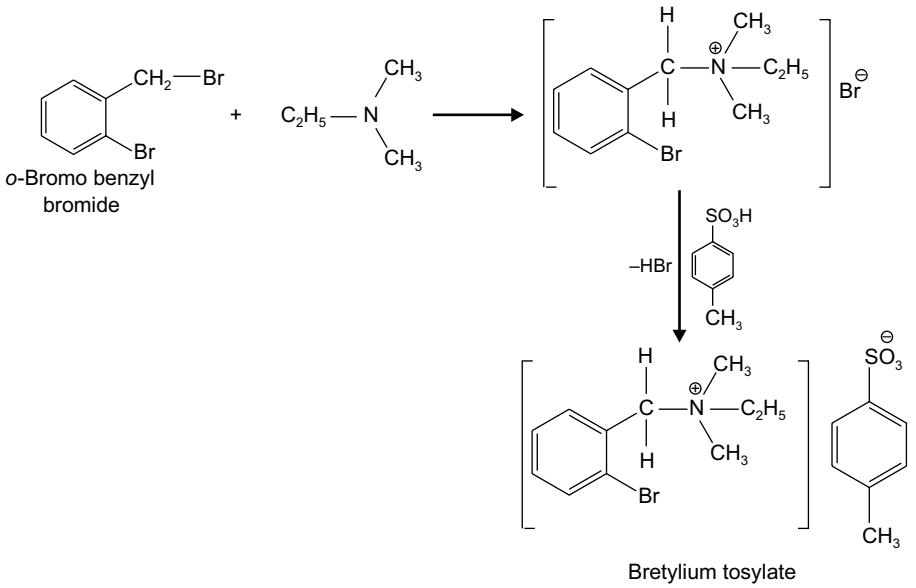
- Hypotension, CHF, peripheral neuropathy, pulmonary fibrosis, anorexia, nausea, vomiting and discoloration of skin, hypothyroidism and hyperthyroidism (T3 and T4) levels should be monitored during long-term therapy with amiodarone).
- Amiodarone inhibits the renal clearance of digoxin, thereby increases serum digoxin levels. It also increases concentration of quinidine and procainamide. Amiodarone potentiates the anticoagulant effect of warfarin.

ii. Bretylium tosylate



2-Bromo-1-(N-ethyl-N,N'-dimethylamino methyl) benzene salt with 4-methyl benzene sulphonic acid

Synthesis



Properties and uses: It is a white crystalline powder and exhibits polymorphism. Freely soluble in water, in ethanol, and in methanol. It is used as antiadrenergic, antiarrythmic, and antihypertensive agent.

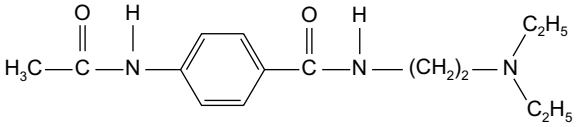
Assay: Dissolve the sample in 1,4-dioxan and titrate with 0.025 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

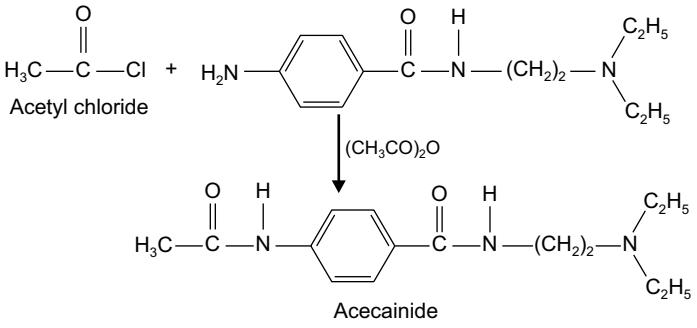
Dose: Administered by IM or by slow IV infusion of 5 to 10 mg/kg over 10 to 30 min.

Dosage forms: Bretylium injection BP.

iii. Acecainide



Synthesis



Uses: It is effective in suppressing a variety of ventricular arrhythmias.

IV. Calcium Channel Blockers

This is discussed in detail in Chapter 43: Antianginals.

i. Verapamil (Calaptin, Vasopten)

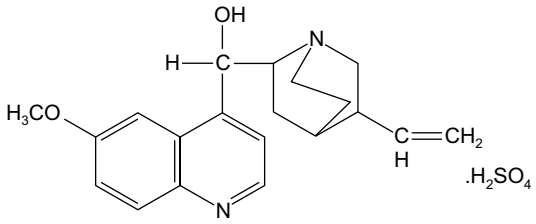
Dose: Daily oral dose is 180 to 480 mg in acute cases, 5 to 10 mg slow IV over 2 min.

ii. Diltiazem (Dilzem, Angizem, Cardisec)

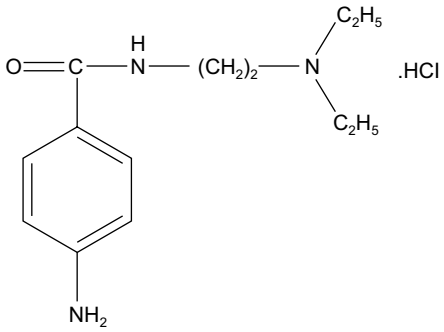
Dose: The usual dose is 60–90 mg of diltiazem, which can be given every 6 hrs for prophylactic control against paroxysmal supraventricular tachycardia.

CLASSIFICATION BASED ON PCI SYLLABUS

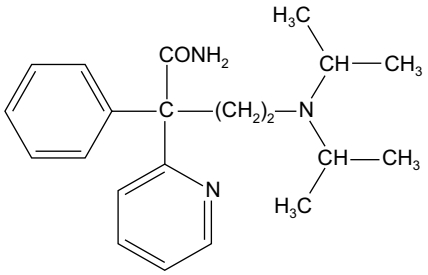
Quinidine sulphate



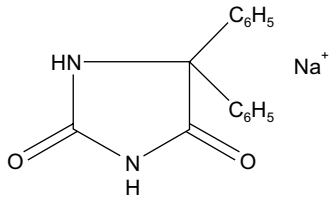
Procainamide hydrochloride



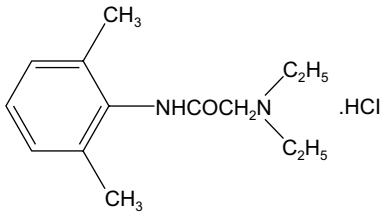
Disopyramide phosphate



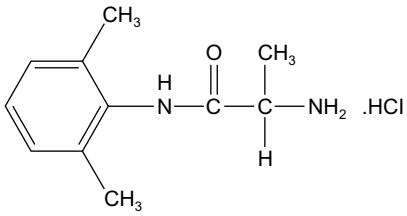
Phenytoin sodium



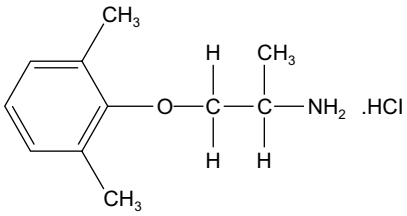
Lidocaine hydrochloride



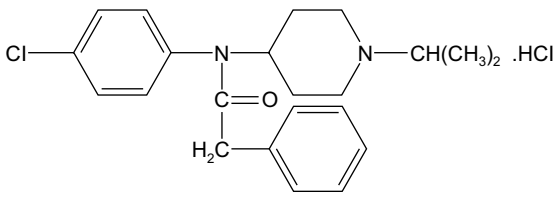
Tocainide hydrochloride



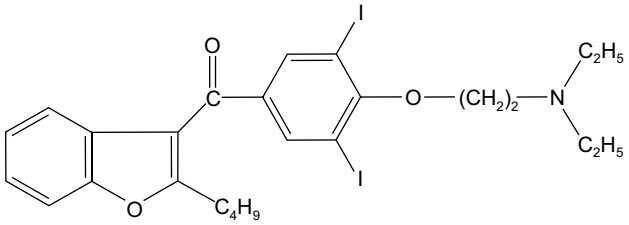
Mexiletine hydrochloride



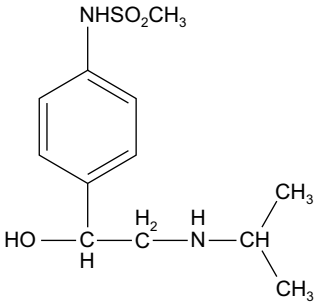
Lorcainide hydrochloride



Amiodarone



Sotalol



CHAPTER 42

Antihyperlipidaemic Agents

INTRODUCTION

The lipids of human plasma are transported into the macromolecular complex and termed as lipoproteins. A number of metabolic disorders that involve the elevation of any lipoprotein series are termed as hyperlipoproteinaemias or hyperlipidaemias. The two major clinical sequelae of the hyperlipoproteinaemia are the acute pancreatitis and atherosclerosis. Lipoproteins contain alipoprotein (*apo*). Blood conveys lipids into the artery wall that have low-density lipoprotein.

The pharmacological agents that reduce the concentration of plasma lipids are called hypocholestrolaemic agents. An increase in the plasma lipids, particularly cholesterol is a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischaemic heart diseases, myocardial infarction, and cerebrovascular accidents.

Lipids are insoluble in water, and they are transported into the plasma as lipoproteins, an increase in the plasma concentration of these substances is called hyperlipidaemia or hyperlipoproteinaemia. Lipoproteins consist of central core of hydrophobic lipids (triglycerides or cholesterylesters) encased in a more hydrophilic coat of polar substances—phospholipids, free cholesterol, and associated proteins, that is, apoproteins.

Lipoproteins are classified into four types—high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and chylomicrons.

Hyperlipoproteinaemias can be the following:

Primary

1. **Due to a single gene defect:** It is familial and called monogenic or genetic.
2. **Multiple gene:** Dietary and physical activity-related causes 'polygene' or multifactorial.

Secondary

These are associated with diabetes, myxoedema, nephritic syndrome, chronic alcoholism, and drugs (corticosteroids, oral contraceptives, β-blockers), etc. Globally, in blood, the primary carrier of plasma is cholesterol esters and very low-density lipoproteins. The current pharmacotherapy includes the following:

1. HMG-CoA reductase (or 3-hydroxy-3-methyl-glutaryl-CoA reductase or HMGR) inhibitors (statins).
2. Bile acid sequestrants (resins).

3. Drugs that activate lipoprotein lipase (fibric acid derivatives).
4. Drugs that inhibit lipolysis and triglyceride synthesis (nicotinic acid).

Combined therapeutic regimen is useful in the following cases:

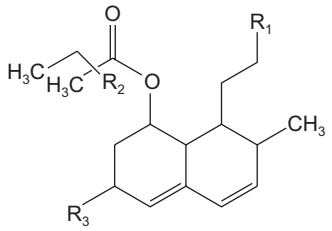
- When LDL levels are insignificantly increased during treatment of hypercholesterolaemia with a resin.
- When LDL and VLDL levels are both elevated initially.
- When LDL and VLDL levels are normalized with a single agent.
- When elevated level of lipoprotein or HDL deficiency coexist with other hyperlipidaemias.

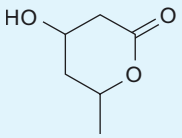
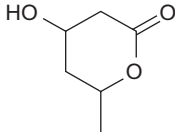
Fibric acid and bile acid sequestrants are useful in the treatment of familial hyperlipidaemia of which some are intolerant of niacin. HMG-CoA reductase inhibitors and bile acid sequestrants synergistically control the familial hypercholesterolaemia, but they may not control the levels of VLDL in some patients with familial combined hyperlipoproteinaemia. Niacin and bile acid sequestrants effectively control LDL levels during resin therapy of familial combined hyperlipoproteinaemia or other disorders involving both increased VLDL and LDL levels. Reductase inhibitors and ezetimibe are used in treating primary hypercholesterolaemia and has some use in the treatment of homozygous familial hypercholesterolaemia.

CLASSIFICATION

Antihypercholesterolemic agents act either by reducing the production of lipoproteins or by their removal from blood.

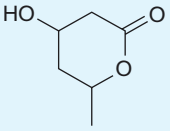
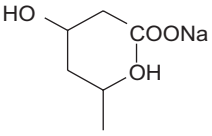
I. HMG-CoA reductase inhibitors



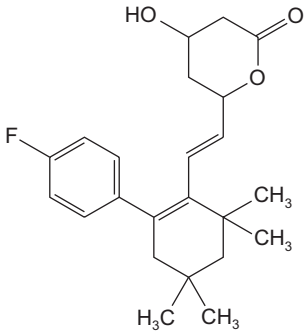
S.No.	Drug	R_1	R_2	R_3
1.	Metastatin		–H	–H
2.	Lovastatin		–H	$-CH_3$

Contd.

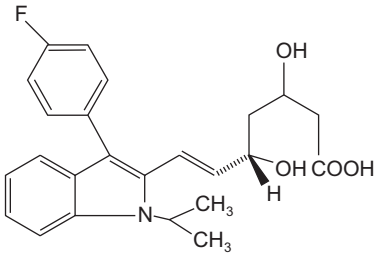
Contd.

S.No.	Drug	R_1	R_2	R_3
3.	Simvastatin		$-CH_3$	$-CH_3$
4.	Pravastatin		–H	–OH

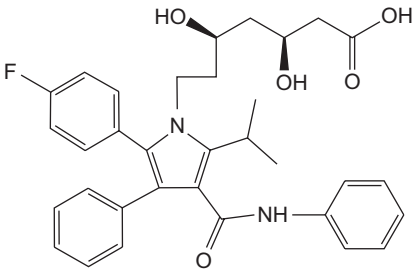
i. Dalvastatin



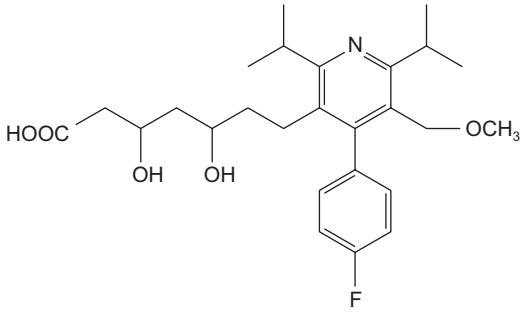
ii. Fluvastatin



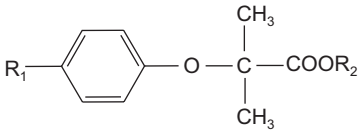
iii. Atorvastatin

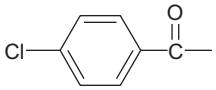
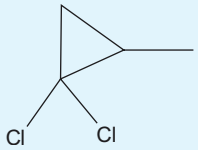
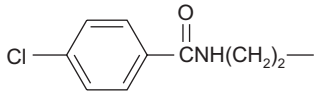


iv. Cerivastatin

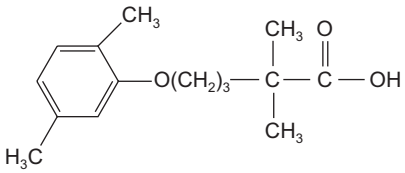


II. Fibric acid derivatives



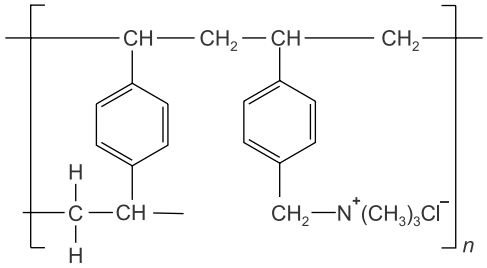
S.No.	Drug	R_1	R_2
1.	Clofibrate	–Cl	$-C_2H_5$
2.	Fenofibrate		$-CH(CH_3)_2$
3.	Ciprofibrate		–H
4.	Benzafibrate		–H

v. Gemfibrozil

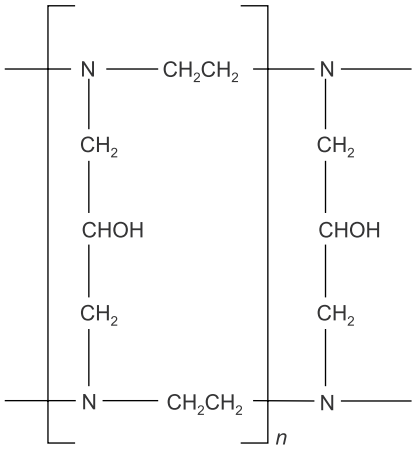


III. Bile acid sequestrants

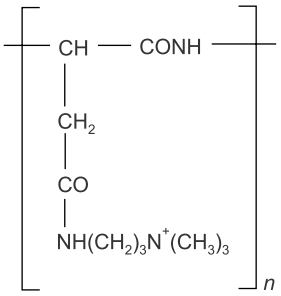
i. Cholestyramine



ii. Colestipol

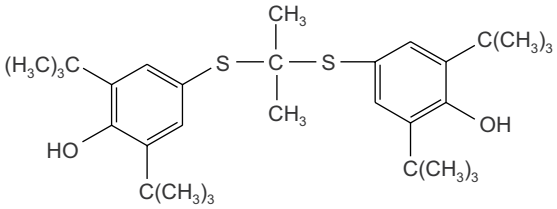


iii. Berlex



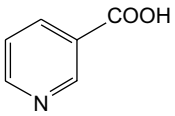
IV. Inhibition of LDL oxidation

i. Probucol



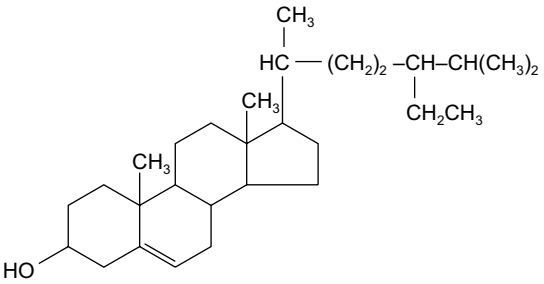
V. Pyridine derivative

i. Nicotinic acid (Niacin)

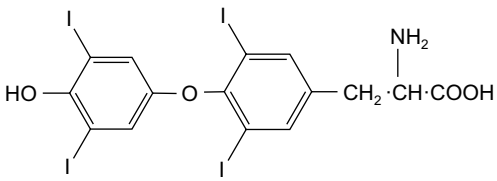


VI. Miscellaneous

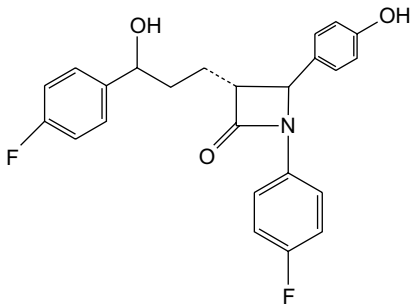
i. β-Sitosterol



ii. Dextrothyroxine

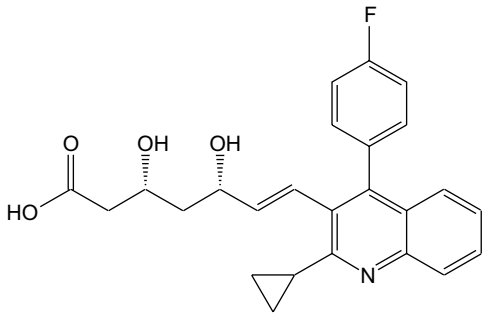


iii. Ezetimibe



Newer Drugs

Pitavastatin

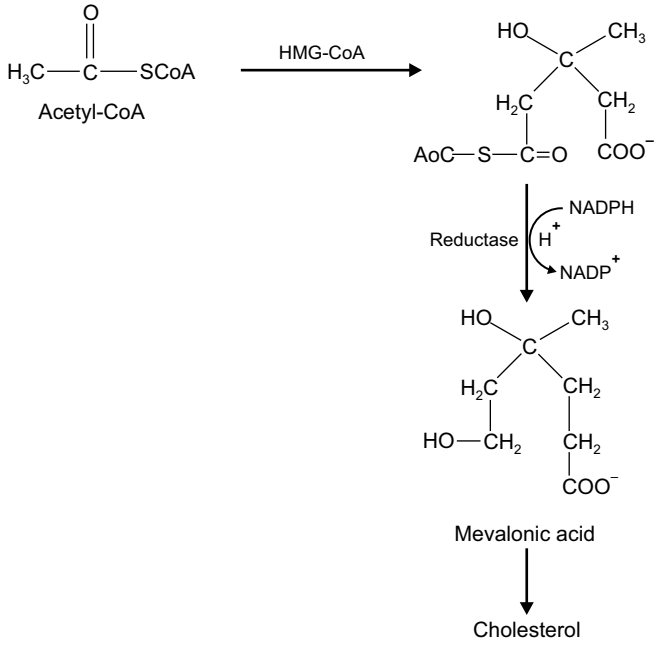


SYNTHESIS AND DRUG PROFILE

I. HMG-CoA reductase inhibitors

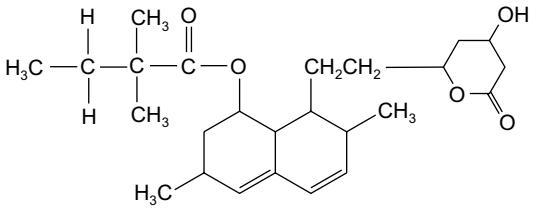
Mode of action: These kinds of drugs competitively inhibit the conversion of 3-hyroxy-3-methyl glutaryl coenzyme (HMG-CoA) to mevalonate, which is the rate-limiting step in cholesterol synthesis and results in receptor mediated uptake and catabolism of intermediate density lipoprotein and very low-density lipoprotein.

Synthesis of Cholesterol



Metabolism of HMG-CoA reductase inhibitors: Lovastatin and simvastain are inactive prodrugs that must undergo *in vivo* hydrolysis to produce their effects. The active forms of these two compounds as well as most HMGRIs undergo extensive first pass metabolism. The CYP3A4 isoenzyme is responsible for the oxidative metabolism of atrovastatin, lovastatin, and simvastatin. In the case of atrovastatin, the *ortho*- and *para*-hydroxylated metabolites are equiactive with the parent compound and contribute significantly to the overall activity of drugs.

i. Simvastatin (Simvas, Zosta, Siravotin)



Properties and uses: It is a white or almost white crystalline powder, insoluble in water, well soluble in methylene chloride and in alcohol. It is used as an antihyperlipidaemic agent.

Assay: It is assayed by adopting liquid chromatography technique.

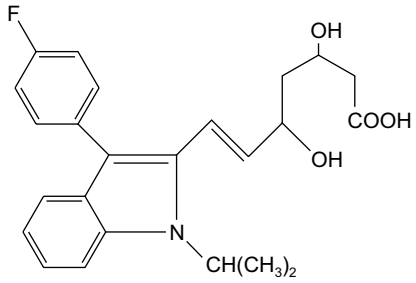
Storage: It should be stored in well-closed airtight containers under nitrogen and protected from light.

Dose: For hyperlipidaemias: Prevention of cardiovascular events—adult—initially, 10–20 mg/day, to be taken in the evening. May start with 40 mg once daily in patients with high cardiovascular risk. For patients with moderate cardiovascular risk, initiate with 10 mg once daily, may adjust dose at 4-weekly intervals. Maximum of 80 mg/day.

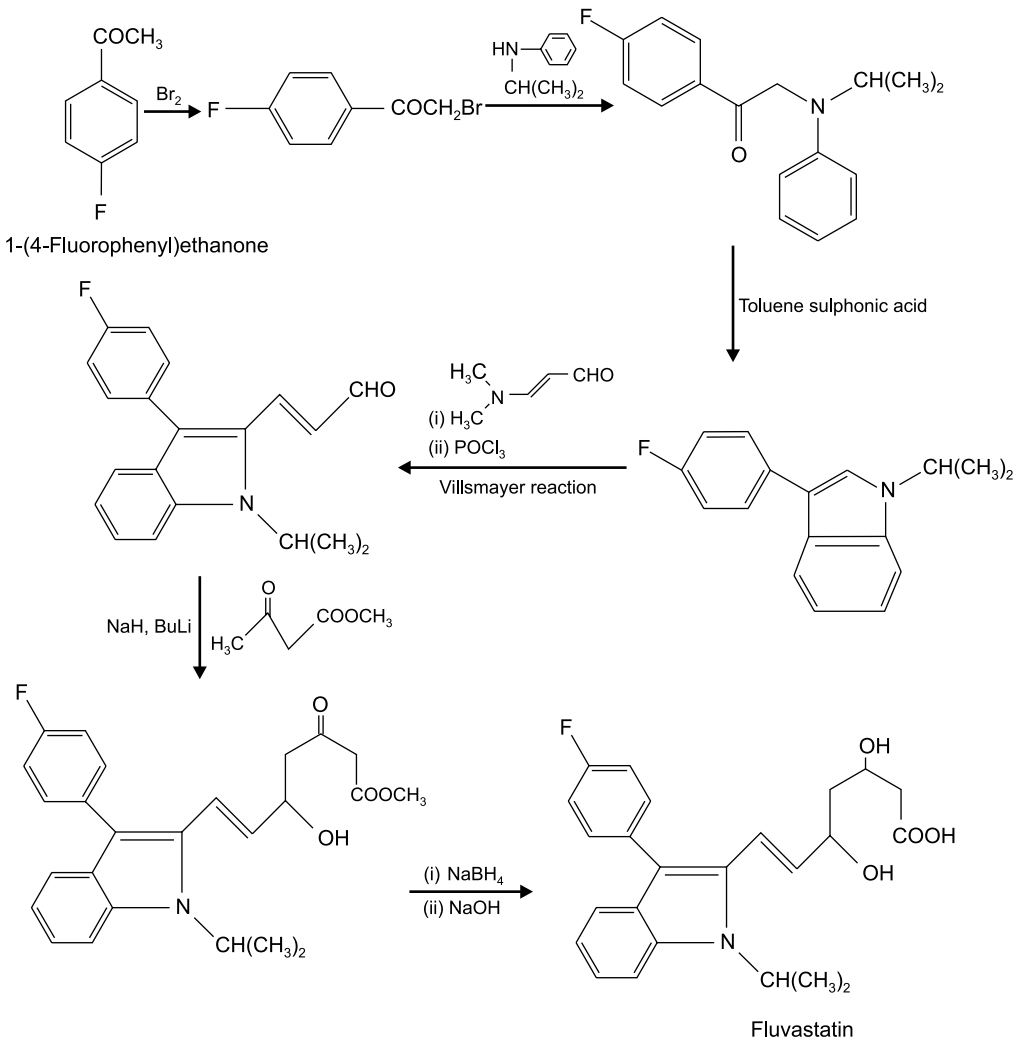
For homozygous familial hypercholesterolaemia—adult—intially, 40 mg once daily. May increase dose to 80 mg daily, given in three divided doses. Child: 10–17 years—initially, 10 mg daily. May increase to 40 mg daily according to response.

Dosage forms: Simvastatin tablets BP.

ii. Fluvastatin



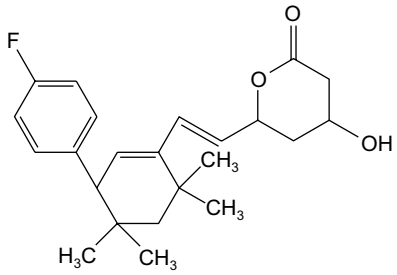
Synthesis



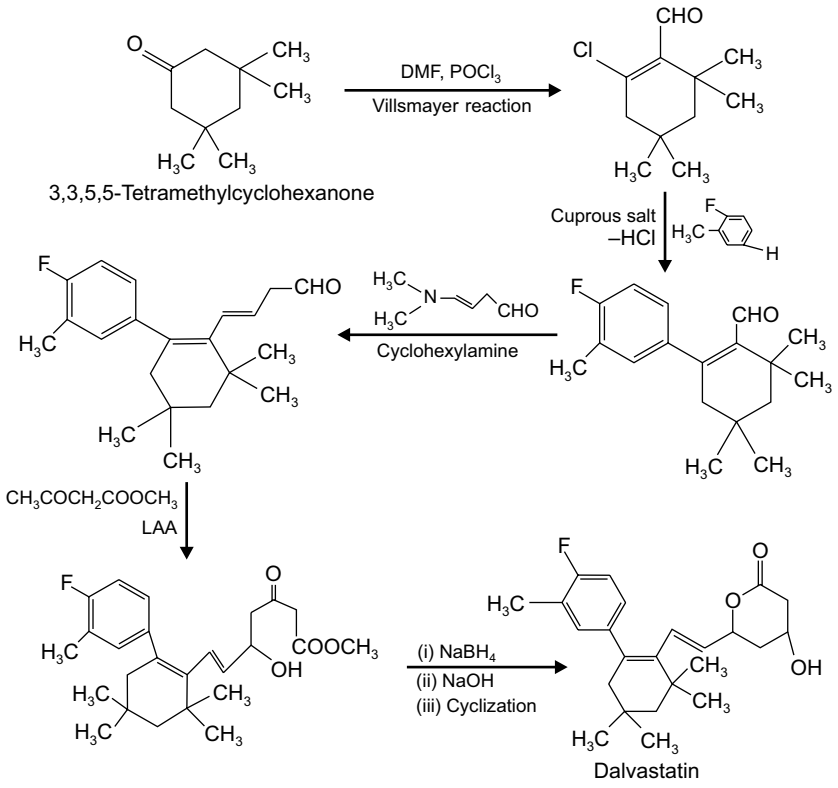
Metabolism: It is metabolized by the CYPC9 and CYP3A4 isoenzymes to active hydroxylated metabolites, however, these metabolites do not circulate systematically and do not contribute to the overall activity.

Properties and uses: It exists as a white to pale yellow hygroscopic powder, soluble in methanol and water or ethanol. It is used as an antihyperlipidaemic agent.

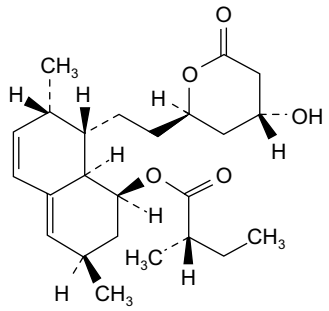
iii. Dalvastatin



Synthesis



iv. Lovastatin



Properties and uses: It is a white or almost white crystalline powder, insoluble in water, soluble in acetone, and sparingly soluble in ethanol. Used as HMG-CoA reductase inhibitor and lipid-regulating drug.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers under nitrogen at a temperature of 2°C to 8°C.

Adverse drug reactions: Common side effects of HMG-CoA reductase inhibitors are:

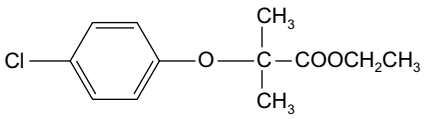
1. Hepatotoxicity with increase in serum transaminase levels.
2. Headache and sleep disturbances.
3. Myopathy—muscle pain and weakness with raised plasma creatinine kinase activity.
4. Gastrointestinal—anorexia, nausea, vomiting and diarrhea.
5. Statins are contraindicated in pregnancy because of teratogenic effect.

II. Fibric acid derivatives

Mode of action: These drugs activate receptors called α-peroxisome proliferator-activated receptors, which enhance the synthesis of lipoprotein lipase and increase the degradation of very low-density lipoprotein. This also enhances the fatty acid oxidation.

Metabolism of fibrates: The prodrug fenofibrate undergoes rapid hydrolysis to produce fenofibric acid. This active metabolite can then be further metabolized by oxidative or conjugate pathways.

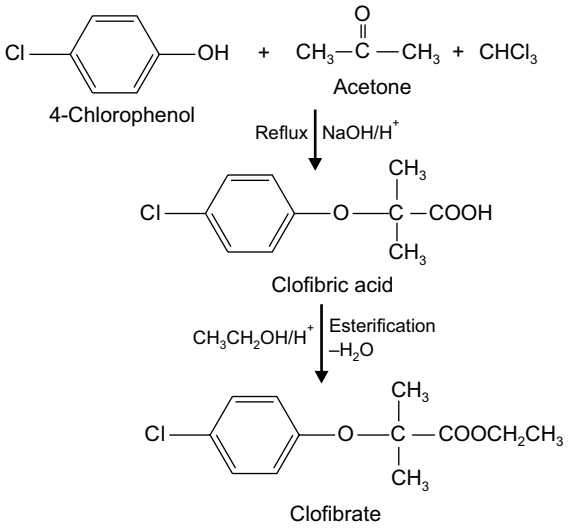
v. Clofibrate



Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate

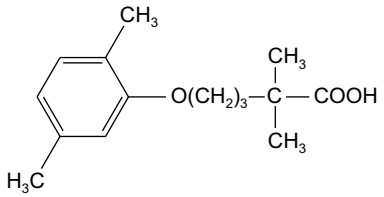
Properties and uses: It is a colourless to pale yellow liquid with acid taste, insoluble in water. It is a drug of choice in the treatment of type III, IV, and V hyperlipoproteinaemias.

Synthesis



Dosage forms: Clofibrate capsules BP.

vi. Gemfibrosil (Gempar, Lopid, Normolip)



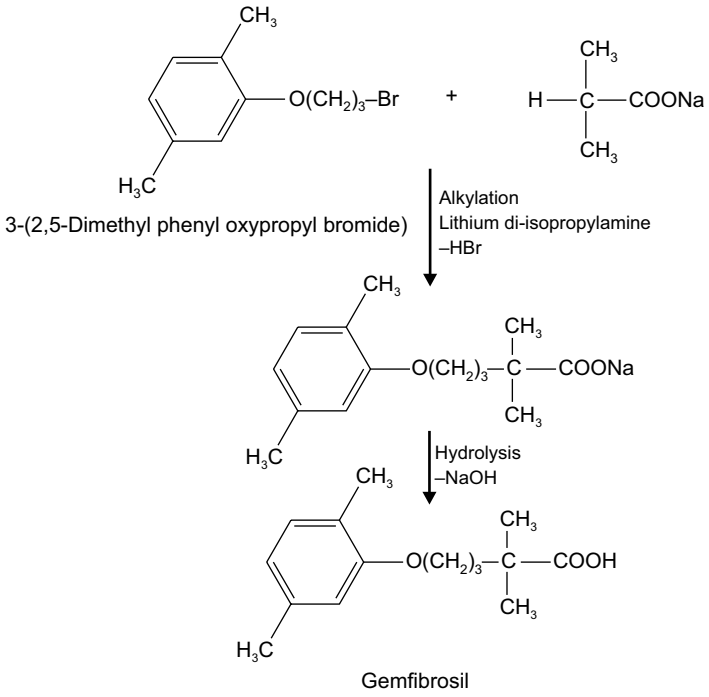
5-(2,5-Dimethylphenoxy)-2,2-dimethyl pentanoic acid

Metabolism: It is similar to fenofibric acid. It may undergo oxidation or conjugation. Oxidation of aromatic methyl group produces inactive hydroxymethyl and carboxylic acid analogues. As a drug class, fibrate and their oxidized analogues are primarily excreted as glucuronide conjugate in urine. Oxidation requires the CYP3A4 isoenzymes. However, because of the ability of these compounds to be conjugated and eliminated either with or without oxidation, drug interaction with other compounds affecting the CYP3A4 system are less important here than other drug classes.

Properties and uses: It is a white or almost white waxy and crystalline powder, insoluble in water, soluble in methylene chloride, in ethanol, and in methanol. It was used first in the treatment of hyperlipoproteinemia in the mid-1970s. Its mechanism of action and use are similar to those of clofibrate. It is used in the treatment of hyperlipidaemia. It is also useful in type V hyperlipoproteinaemia.

Assay: Dissolve the sample in methanol, to this add water and 0.1 M hydrochloric acid, and perform potentiometric titration, using 0.1 M sodium hydroxide.

Synthesis



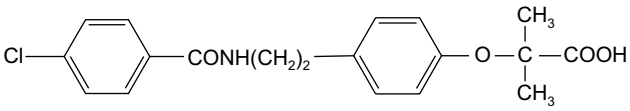
Gemfibrosil

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: (Adults only) 600 mg twice daily, taken 30 min before morning and evening meals.

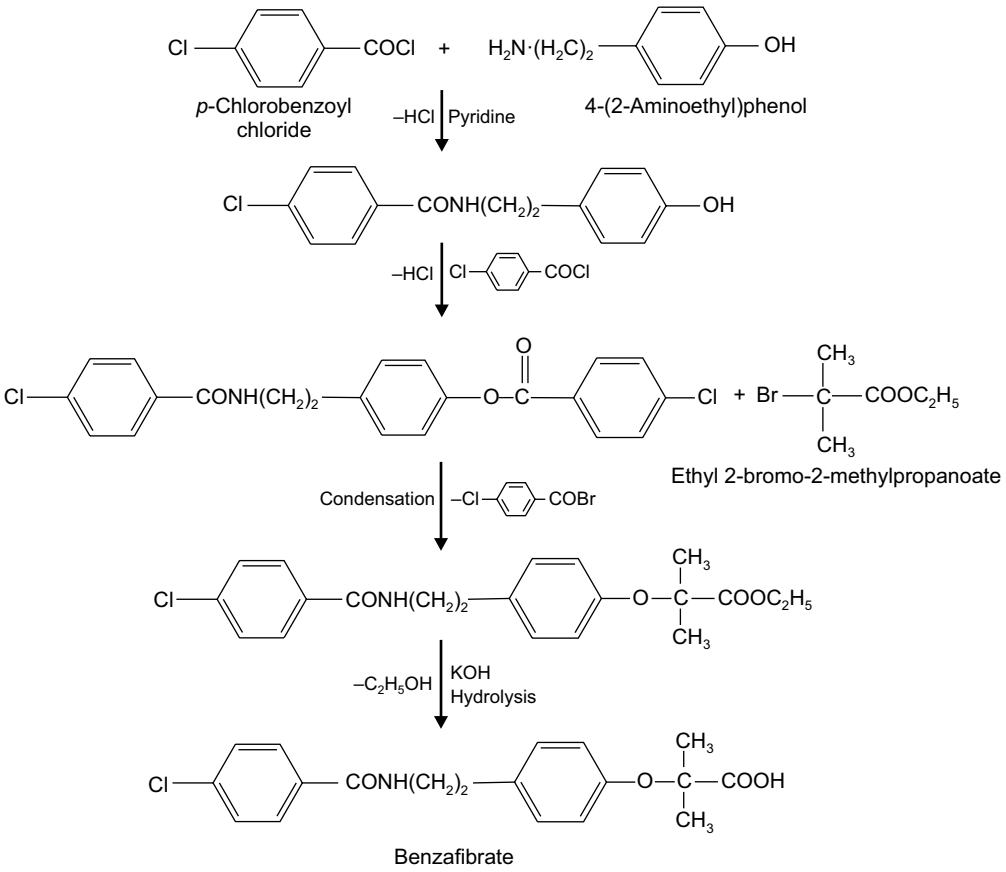
Dosage forms: Gemfibrozil capsules BP, gemfibrozil tablets BP.

vii. Benzafibrate (Beza-Xl, Bezalip)



Properties and uses: Benzafibrate is more potent than clofibrate and reduces HDL and LDL to a greater extent. It is a highly potent antihyperlipidaemic agent.

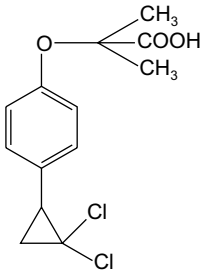
Synthesis



Benzafibrate

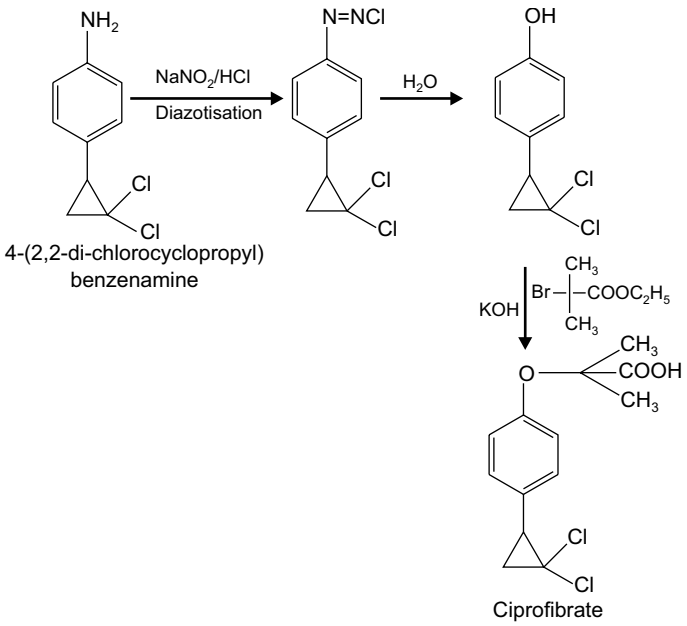
Dose: For hyperlipidaemias: Adult—200 mg thrice a day, may increase dose gradually over 5–7 days. Maintenance: 200 mg twice a day. As modified-release preparation: 400 mg daily.

viii. Ciprofibrate



2-(4-(2,2-Dichlorocyclopropyl)phenoxy)-2-methylpropanoic acid

Synthesis

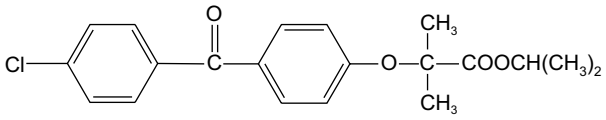


Properties and uses: It is a white or slightly yellow crystalline powder, insoluble in water, soluble in anhydrous ethanol, and in toluene. It is a more potent lipid-lowering agent than clofibrate, used in the treatment of hyperlipidaemic conditions.

Assay: Dissolve the sample in a mixture of water and anhydrous ethanol. Titrate with 0.1 M sodium hydroxide and determining the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

ix. Fenofibrate (Lipicard, Stanlip, Fibral)



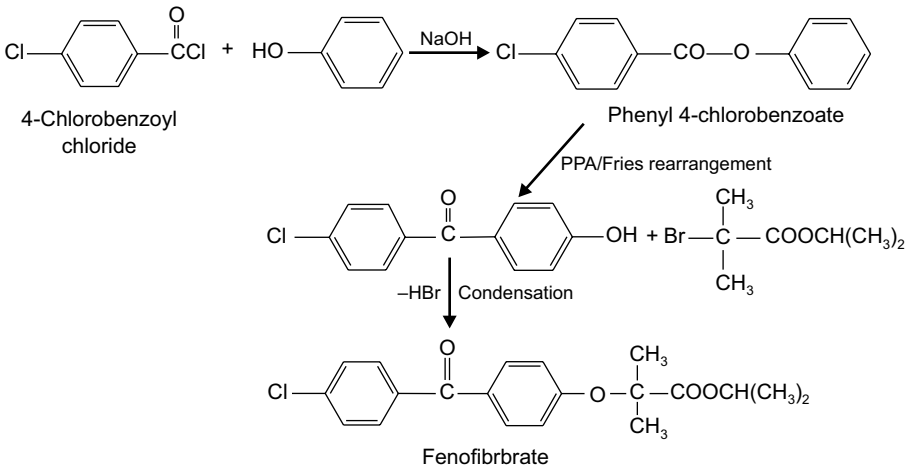
2-(4-(4-Chlorobenzoyl)phenoxy)-2-methylpropanoic acid-1-methyl ethyl ester

Properties and uses: It is a white or almost white crystalline powder, slightly soluble in ethanol, insoluble in water, and soluble in methylene chloride. Fenofibrate is a more potent hypocholesterolemic and triglycerides lowering agent.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light.

Synthesis



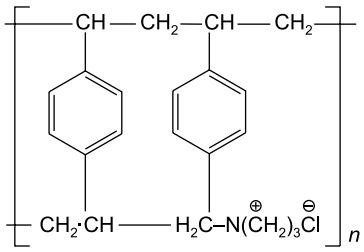
Dose: For hyperlipidaemias: Adult—dose depends on the formulation used. For standard micronized formulations: Initially, 67 mg thrice a day or 200 mg once daily. For non-micronized formulations: Initially, 200–300 mg daily in divided doses. Usual range: 200–400 mg daily. For formulations with improved bioavailability, doses between 40 and 160 mg daily may be used. Child: 5 mg/kg daily.

Adverse drug reactions: Fibrates are usually very well tolerated. Common side effects offibric acid derivatives are:

- Dyspepsia, nausea, vomiting, diarrhea and flu-like syndrome with muscle pain and headache.
- There is an increased incidence of gallstones with clofibrate.
- Fibrates can potentiate the effect of warfarin and oral hypoglycemic drugs.

III. Bile acid sequestrants

i. Cholestyramine resin



Mode of action: It is a styrene copolymer with divinyl benzene and quaternary ammonium functional group. The resin is insoluble in water, remains unchanged in the intestinal tract, unaffected by digestive enzymes, and is not absorbed. These are basic ion exchange resins, which binds with bile acids, interferes in the enterohepatic circulation, and leads to the excretion of cholesterol in faeces. This also indirectly leads to the enhanced hepatic metabolism of cholesterol to bile acids, so more LDL receptors are exposed on liver cells and the plasma intermediate density and very low-density lipoprotein clearance is more.

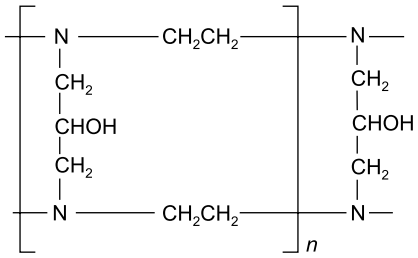
Properties and uses: It is a white or almost white fine powder, and is hygroscopic, insoluble in water, in methylene chloride and in ethanol, used as lipid-regulating drug.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Cholestyramine oral powder BP.

ii. Colestipol



Properties and uses: It exists as yellow to orange beads, hygroscopic in nature. It swells, but does not dissolve in water and dilute aqueous solutions of acids and alkali, insoluble in ethanol and in dichloromethane. It is an insoluble copolymer of diethylene triamine and epichlorhydrin, containing secondary and tertiary amine functionalities. It is potent in reducing cholesterol levels. It is effective in the treatment of type II hyperlipoproteinaemias.

Storage: Colestipol hydrochloride should be stored in airtight containers.

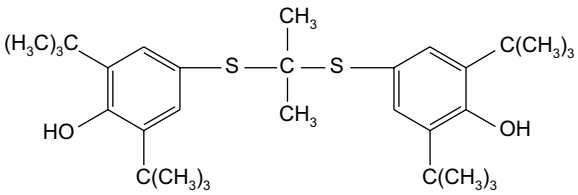
Adverse drug reactions: Since resins are not absorbed through the gut, systemic adverse effects are not seen.

- The common adverse effects are unpalatability, nausea, flatulence and constipation.
- They also bind to many other drugs like thiazides, digitalis, anticoagulants, propranolol, thyroxine, fat soluble vitamins, etc. in the gut and reduce their absorption.

Dosage forms: Colestipol granules BP.

IV. LDL oxidation inhibitors

i. Probucol (Lorelco)

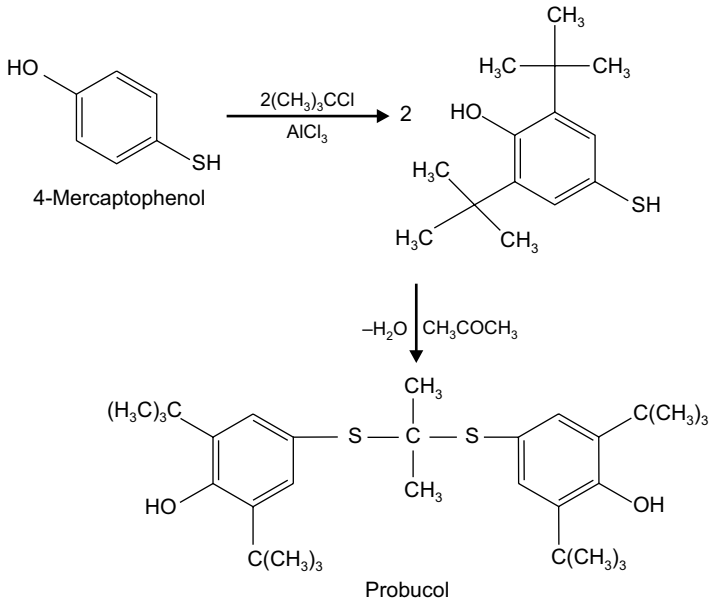


4,4'-[Methyl ethylidene]-bis(thio)bis[2,6-bis(1,1-dimethylethyl)]phenol

Properties and uses: It is a chemical agent that was developed for the plastic and rubber industry in 1960s. Probucol is a more potent cholesterol-lowering agent of a series of alkylidene dithiobisphenols. It is used as an antihyperlipoproteinaemic agent.

Dose: Adults only: 250–500 mg twice daily taken with morning and evening meals.

Synthesis

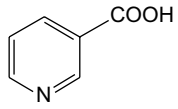


4-Mercaptophenol

Probucol

V. Pyridine derivatives

i. Nicotinic acid



Pyridine-3-carboxylic acid

Mode of action: Nicotinic acid inhibits the lipolysis of triglycerides by hormone sensitive lipase, which reduces transport of the free fatty acids to liver and decreases hepatic triglycerides synthesis. Reduction of triglycerides synthesis decreases the production of hepatic VLDL.

Metabolism: Nicotinic acid is a B-complex vitamin that is converted to nicotinamide, NAD^+, and $NADP^+$. The latter two compounds are coenzymes, and required for the oxidation/reduction reaction in a variety of biochemical pathways. Nicotinic acid is metabolized to a number of inactive compounds, including nicotinuric acid and N-methylated derivatives.

Properties and uses: It is a white, crystalline powder and it dissolves in dilute solutions of the alkali hydroxides and carbonates, soluble in boiling water and in boiling alcohol, sparingly soluble in water. It is used as an antihyperlipidaemic agent.

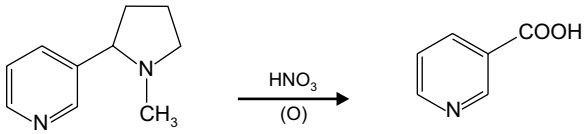
Synthesis

Method I: From 3-Methyl pyridine



3-Methylpyridine Nicotinic acid

Method II: From Nicotine



Nicotine → Nicotinic acid

Assay: Dissolve the sample in water and titrate with 0.1 M sodium hydroxide, using phenolphthalein solution as indicator. End point is the appearance of a pink colour.

Storage: It should be stored in well-closed airtight containers and protected from light.

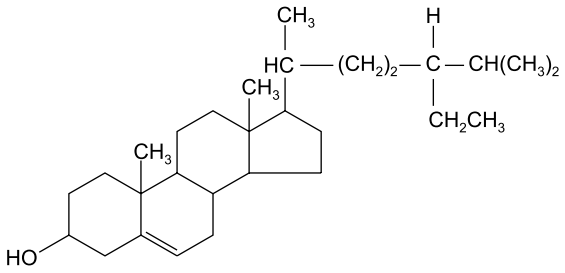
Dosage forms: Nicotinic acid tablets IP, BP.

Adverse drug reactions: Common side effects of nicotinic acid are:

- Mainly flushing (can be reduced by combining with aspirin) and dyspepsia.
- Other side effects include itching, headache, hyperpigmentation, peptic ulcer, hyperuricaemia, hepatotoxicity and hyperglycemia.
- Niacin may potentiate the effects of warfarin.
- Contraindicated in pregnancy.

VI. Miscellaneous Agents

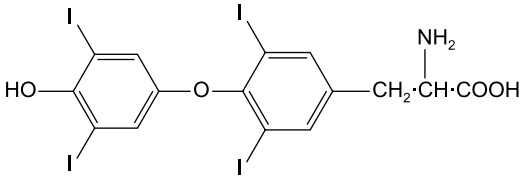
i. β-Sitosterol



3-β-Stigmast-5-en-3-ol

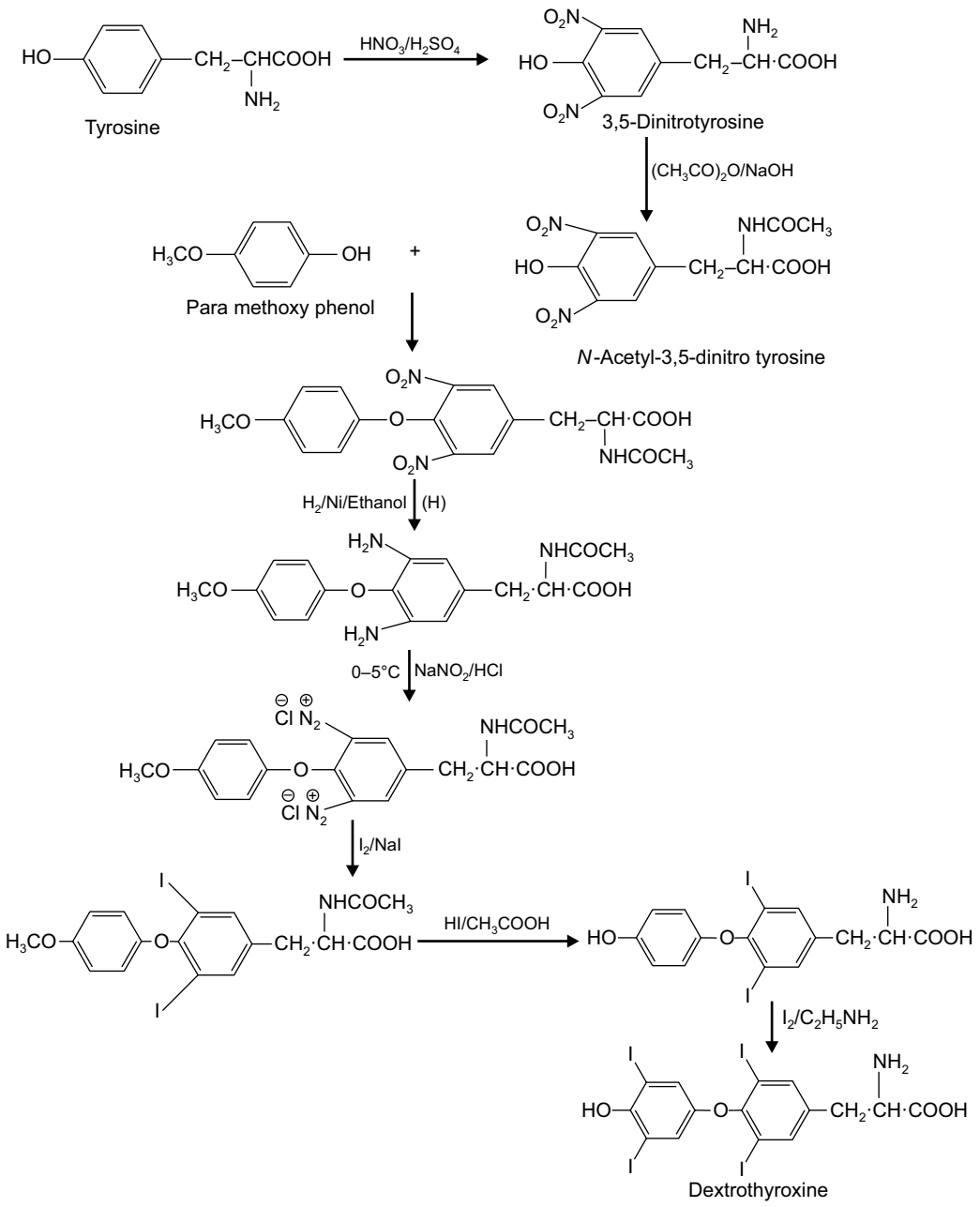
Properties and uses: β-sitosterol lowers plasma concentrations of LDL, and has no effect on VLDL. The sitosterol is believed to lower plasma levels of cholesterol by interfering with its absorption. It is used as an anticholesteremic agent and also used in the treatment of prostatic adenoma.

ii. Dextrothyroxine



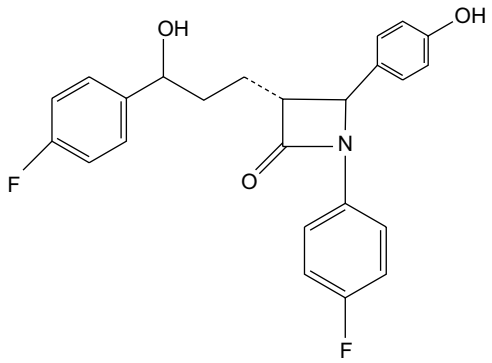
o-(4-Hydroxy-3,5-di-iodophenyl)-3,5-di-iodo-D-tyrosine

Synthesis



Uses: Used as antihyperlipidaemic agent.

iii. Ezetimibe



Metabolism of ezetimibe: It is metabolized rapidly and extensively in the intestinal wall and the liver to its active metabolite, a corresponding phenol glucuronide. This glucuronide is re-excreted in the bile back to its active site. A small amount of ezetimibe undergoes oxidation to convert the benzylic hydroxyl group to a ketone. Ezetimibe does not appear to exert any significant effect on the activity of CYP450 enzyme.

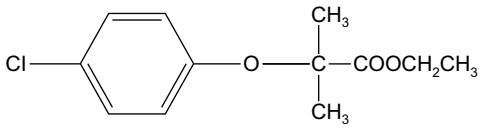
Uses: Used as an antihyperlipidaemic agent.

Adverse drug reactions: Common side effects of ezetimibe are:

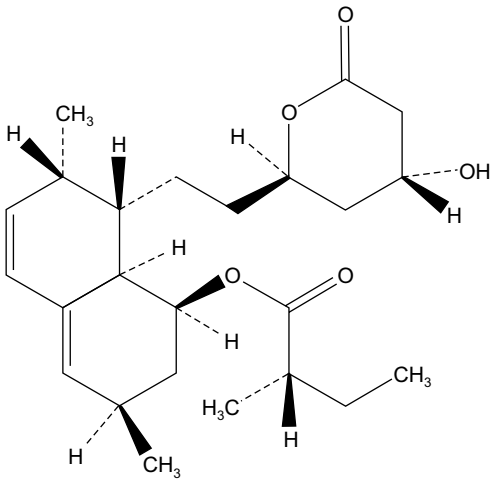
- Hepatotoxicity and elevated transaminases especially when combined with statins.

CLASSIFICATION BASED ON PCI SYLLABUS

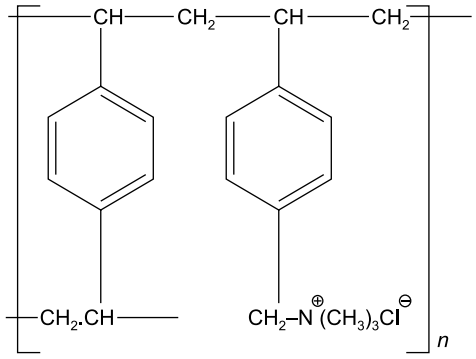
Clofibrate



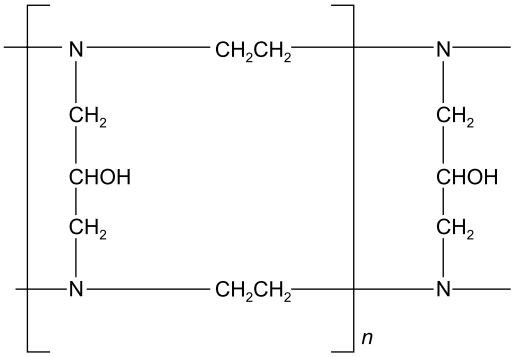
Lovastatin



Cholesteramine

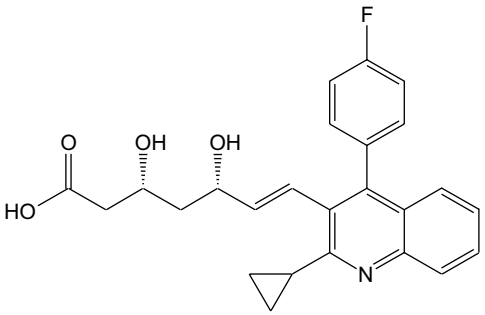


Cholestipol



Newer Drugs

Pitavastatin (Livalo)



Mode of action: The cyclopropyl group present in pitavastatin contributes to a more effective inhibition of the HMG-CoA reductase enzyme to inhibit cholesterol production, and potentially affords greater low-density lipoprotein cholesterol (LDL-C) clearance and reduction of plasma cholesterol. The expression LDL receptor, followed by the reuptake of LDL from the blood to liver is accelerated and decreases the plasma triglycerides. Moreover, pitavastatin binds on ATP binding cassette A-1 mediated efflux of lipid from macrophage and regulates the circulating levels and improves the aortic stiffness.

Properties and uses: Pitavastatin is a HMG-CoA reductase inhibitor. It differs from other statins in that it has a unique cyclopropyl group on the base structure. Pitavastatin is used as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidaemia. Adverse events associated with the use of pitavastatin may include back pain, constipation, diarrhea, myalgia, pain in extremity.

Dose: Pitavastatin is supplied as a tablet (1, 2, and 4 mg) for oral administration. The recommended initial dose of the drug is 2 mg and the maximum dose is 4 mg. After initiation or upon titration of pitavastatin, lipid levels should be analyzed after 4 weeks and the dosage adjusted accordingly.

CHAPTER 43

Antianginals

INTRODUCTION

Angina is caused by an accumulation of metabolites in the striated muscles and is associated with severe chest pain that occurs when the coronary flow is inadequate to supply oxygen required for the heart. Angina pectoris is the most common condition affecting significant number of population, involving tissue ischaemia in which vasodilators are used. Ischaemic heart disease is the most common serious health problem today. By far, the most frequent cause of angina is atheromatus obstruction of large coronary vessels (atherosclerotic angina and classic angina). However, in the transient spasm, localized portions of these vessels can also cause myocardial ischaemia and pain (spastic angina or variant angina). In theory, the imbalance between oxygen delivery and myocardial oxygen demand can be corrected by decreasing oxygen demand or by increasing delivery (by increasing coronary flow). Oxygen demand can be reduced by decreasing the cardiac work or according to recent studies, by shifting myocardial metabolism to substrates that require less oxygen per unit of adenosine triphosphate (ATP) production. In variant angina, spasm of coronary vessels can be reversed by nitrates or calcium channel blockers. It should be emphasized that all the vasodilators are effective in angina and, conversely, that some agents useful in angina (e.g. propranolol) are not vasodilators. Unstable angina, an acute coronary syndrome, is said to be present when there are episodes of angina at rest and when there is a change in character, frequency, and duration of chest pain as well as precipitating factors in patients with previously stable angina. In most cases, formation of non-occlusive thrombi at the site of a fissured or ulcerated plague is the mechanism.

PRINCIPLES OF THERAPY FOR ANGINA

Pharmacological therapy to prevent myocardial infarction and death is with antiplatelet agents (aspirin, clopidogrel) and lipid lowering agents. Recently, angiotensin-converting enzyme (ACE) inhibitors have also reported to reduce the risk from coronary artery disease. In unstable angina and nonST segment elevation myocardial infarction, and in coronary stenting, antilipid drugs, heparin, and antiplatelet agents are recommended.

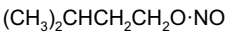
Angina of effort: For therapy of chronic stable angina, long-acting nitrates, calcium channel blockers, or β-blockers are chosen. The combination therapy has shown to be more effective than individual drugs used alone.

Vasospastic angina: Nitrites and calcium channel blockers are effective drugs for reducing and preventing ischaemic episodes in patients with variant angina. In approximately 70% of the patients treated with nitrites or calcium channel blockers, angina attacks are completely abolished.

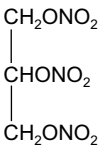
Unstable and acute coronary syndromes: In patients with unstable angina with recurrent ischaemic episodes at rest, recurrent thrombotic occlusions of the offending coronary artery occur as the result of fissuring of atherosclerotic plagues and platelet aggregation. Anticoagulant and antiplatelet drugs play an important role in these cases.

CLASSIFICATION

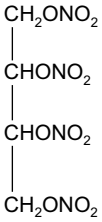
I. Nitrites and nitrates



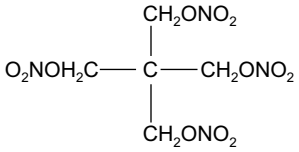
Amyl nitrite



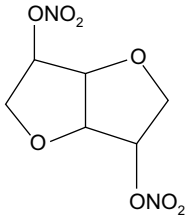
Nitroglycerine



Erythrityl tetranitrate

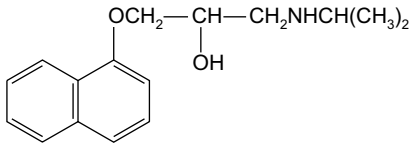


Pentaerythritol tetranitrate



Isosorbide dinitrate

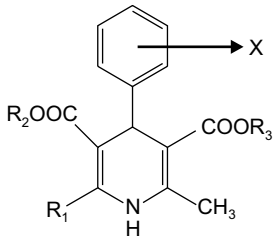
II. β-Adrenergic blocking agents



Propranolol

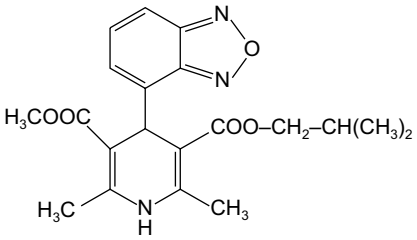
III. Calcium channel blockers

a. 1,4-Dihydro pyridines

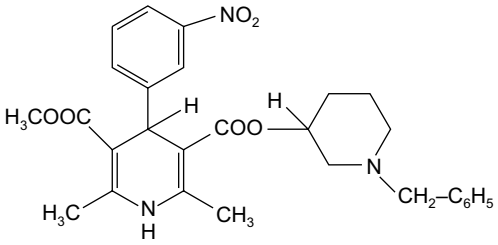


S. No.	Compound	R_1	R_2	R_3	X
1.	Amlodipine	$-CH_2O(CH_2)_2NH_2$	$-C_2H_5$	$-CH_3$	2–Cl
2.	Felodipine	$-CH_3$	$-C_2H_5$	$-CH_3$	2,3–Cl
3.	Nifedipine	$-CH_3$	$-CH_3$	$-CH_3$	2–NO_2
4.	Nitrendipine	$-CH_3$	$-CH_3$	$-C_2H_5$	3–NO_2
5.	Nimodipine	$-CH_3$	$-CH_2CH_2OCH_3$	$-CH(CH_3)_2$	3–NO_2
6.	Nisoldipine	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_3$	2–NO_2

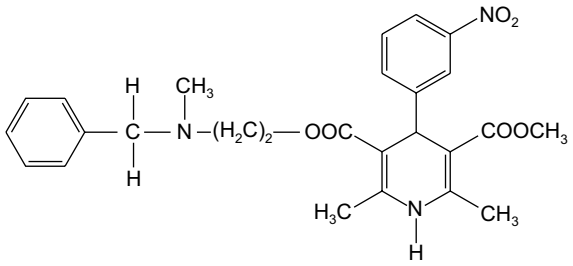
i. Isradipine



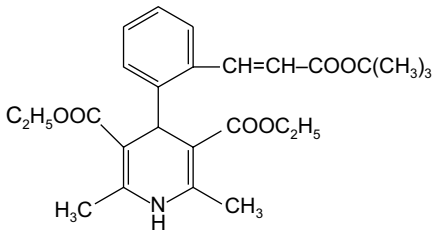
ii. Benidipine



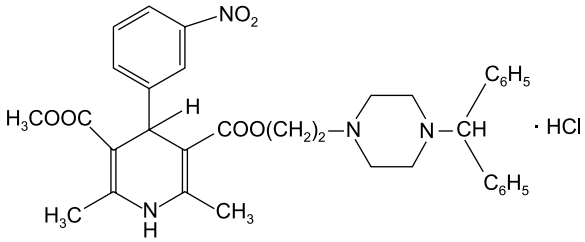
iii. Nicardipine



iv. Lacidipine

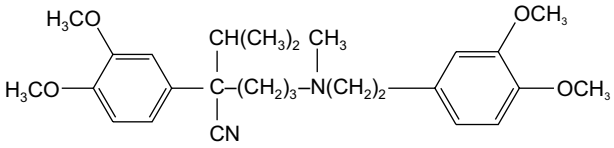


v. Manidipine HCl



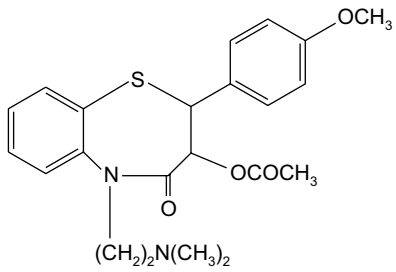
b. Diphenyl alkylamines

⋆ Verapamil



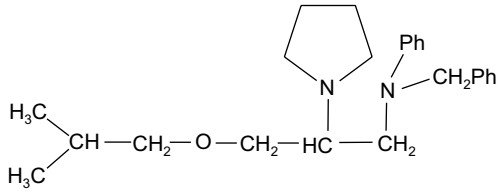
c. Benzothiazepine derivatives

⋆ Diltiazem

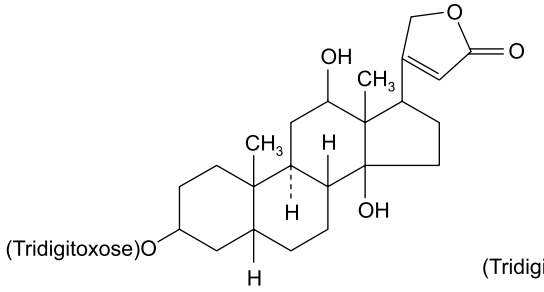


d. Diamino propanol ethers

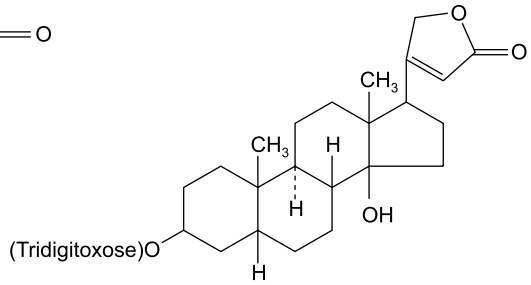
- **Bepridil**



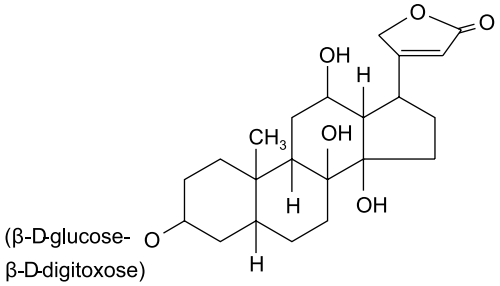
IV. Cardiovascular glycosides



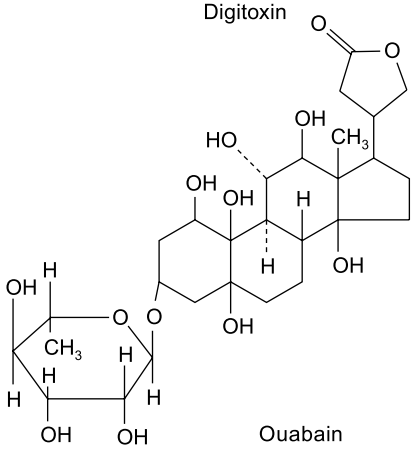
Digoxin



Digitoxin



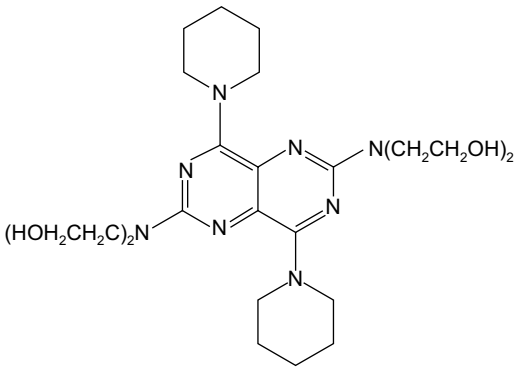
Deslanoside



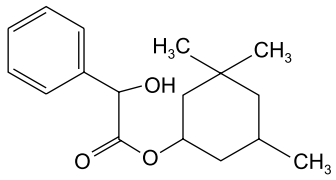
Ouabain

V. Miscellaneous

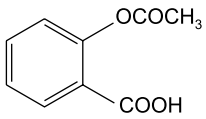
i. Dipyridamole



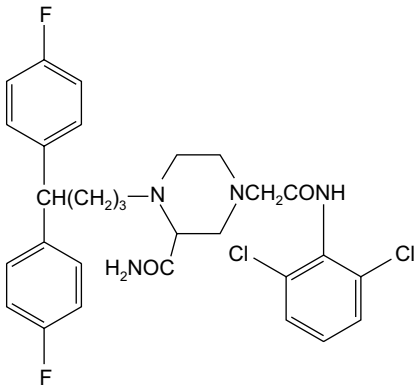
ii. Cyclandelate



iii. Aspirin



iv. Mioflazine



SYNTHESIS AND DRUG PROFILE

I. Nitrites and nitrates

Mode of action: These types of drugs are rapidly denitrated enzymatically in the smooth cells to release the reactive free radical nitric oxide (NO), which activates cytostolic guanyl cyclase and increases the cyclic guanosine monophosphate (cGMP) that causes dephosphorylation of myosin light chain kinase (MLCK) through cGMP dependent protein kinase. The reduction in phosphorylated MLCK interferes with myosin and fails to cause contraction. Relaxation also occurs due to reduced Ca^{2+} entry.

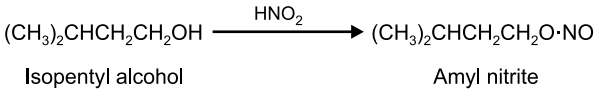
Metabolism: All organic nitrates are subjected to first-pass metabolism, not only by the action of glutathione nitrate reductase in the liver, but also in the extrahepatic tissues. Some metabolites of long-acting nitrates are active as vasodilators. An example of this is isosorbate dinitrate, which is metabolized primarily in the liver by glutathione nitrate recductase, which also participates in the metabolism of other organic nitrates, catalyzing the denitration of the parent drugs to yield two metabolites, 2- and 5-isosorbate mononitrate.

i. Amylnitrite (Vaporole)

$(CH_3)_2CHCH_2CH_2O.NO$

Dose: The usual dose of amyl nitrite 0.18 or 0.3 ml.

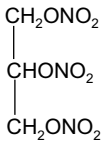
Synthesis



Properties and uses: It is a clear yellowish liquid with an ethereal, fruity odour, and pungent, aromatic taste. It is insoluble in water, but miscible with alcohol, chloroform, or ether. It is a mixture of isomeric amyl nitrites, but is principally isoamyl nitrite. It is mainly used to treat angina pectoris. It is also effective in the emergency management of cyanide poisoning by causing the oxidation of haemoglobin to the compound methemoglobin.

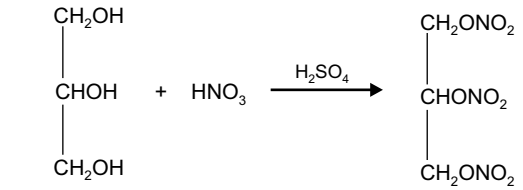
Dose: The usual dose of amyl nitrite is 0.18 or 0.3 ml.

ii. Nitroglycerine



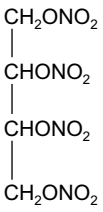
1,2,3-Propanetriol trinitrate

Synthesis



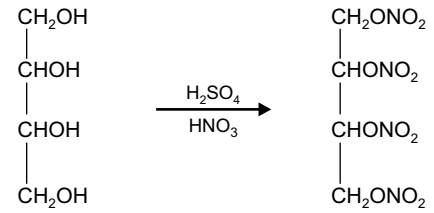
Properties and uses: It is a colourless, odourless liquid with a sweet taste. Glyceryl trinitrate is the trinitrate ester of glycerol. Nitroglycerine is used in angina pectoris and extensively as an explosive in dynamite. A solution of the ester, if spilled or allowed to evaporate, will leave a residue of nitroglycerine. To prevent an explosion of the residue, the ester must be decomposed by addition of alkali. Even then the material dispensed is so dilute that the risk of explosions does not exist.

iii. Erythrityl tetranitrate (Cardilate)



1,2,3,4-Butane tetrol tetranitrate

Synthesis

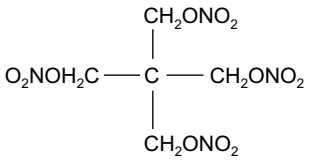


Erythritol — Erythrityl tetranitrate

Properties and uses: Erythrityl tetranitrate is a white powder with a slight odour of nitric oxide and bitter taste. It is soluble in acetone and alcohol, but insoluble in water. It is used in the treatment of angina pectoris and to reduce blood pressure in arterial hypertonia.

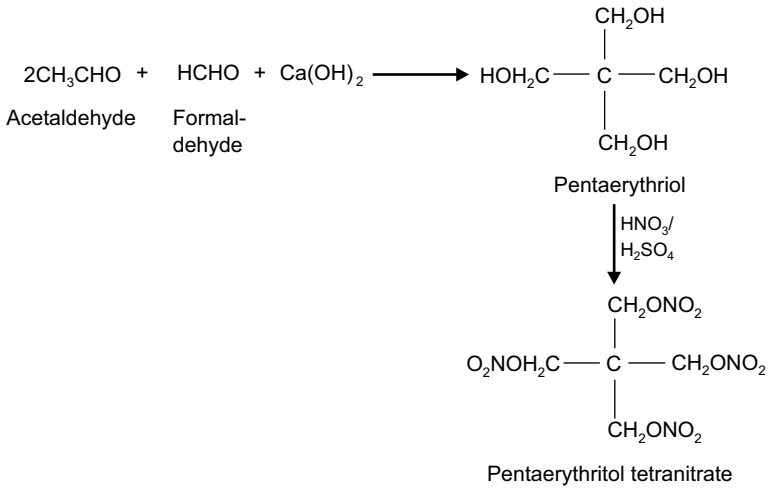
Dose: 10 mg thrice/day by oral tablet.

iv. Pentaerythritol tetranitrate



2,2-bis(hydroxy methyl)-1,3-propane diol tetranitrate

Synthesis



Pentaerythritol tetranitrate

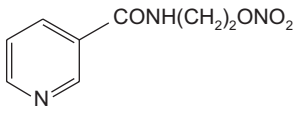
Properties and uses: It is a white or slightly yellowish powder that is practically insoluble in water, soluble in acetone, and slightly soluble in alcohol. It is used in the treatment of angina pectoris. It relaxes the smooth muscle of smaller vessels in the coronary vascular tree.

Assay: It is assayed by adopting liquid chromatography technique.

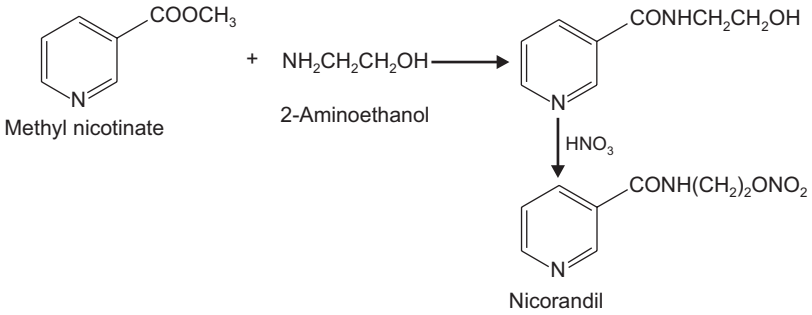
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: 40–80 mg every 4–6 hrs, orally.

v. Nicorandil (Nicoram, Corflo, Zynicor)



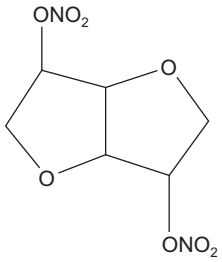
Synthesis



Properties and uses: The cardiac unloading effect of this drug contributes to its antianginal action.

Dose: Orally for angina pectoris: Adult—10 mg twice/day, increase if necessary. Usual dose: 10–20 mg twice/day. May use 5 mg twice/day for patients prone to headache. Maximum dose is 30 mg twice/day.

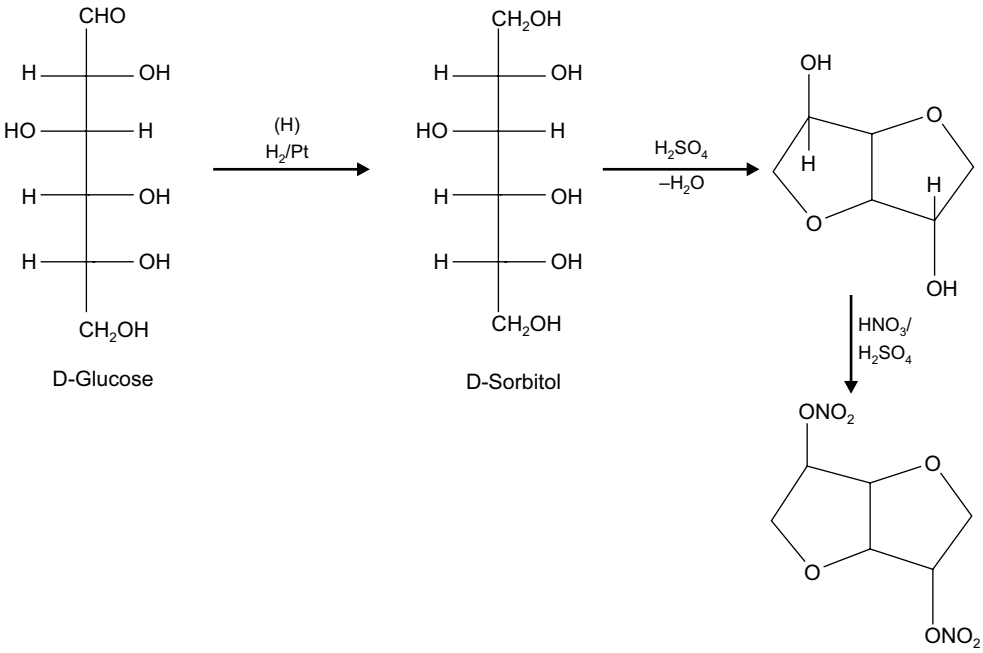
vi. Isosorbide dinitrate (Isordil, Orbitrate)



Nitrates and Nitrites (Vasodilators)

- The primary use of organic nitrates and nitrites and the inorganic nitrites is prophylaxis and in the treatment of angina pectoris.
- The greater potency of the drugs is mainly depending upon oil/water partition coefficient.
- The orientation of the groups within the molecule also affects the potency of the drug.
- Among all nitrates, nitroglycerin is an effective antianginal drug because it produces the redistribution of coronary blood flow to the ischemic regions of the heart and decreases myocardial oxygen demand which leads to the vasodilatation and pooling of blood in the peripheral veins and reduces the ventricular volume and cardiac output.
- Nitrates are only used in exceptional and unstable angina.
- The quick action of nitro vasodilators is the formation of short-lived nitric oxide (NO) frees radicals and diffuses into the smooth muscle where it activates guanyl cyclase leads to muscle relaxation.

Synthesis



Properties and uses: It is a fine white crystalline powder, slightly soluble in water, well soluble in acetone, but sparingly soluble in alcohol. It is effective in the treatment of acute angina attack.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Sublingual: 5–10 mg every 2–3 hrs; oral: 5–60 mg every 4–6 hrs; chewable tablet: 5–10 mg every 2–4 hrs.

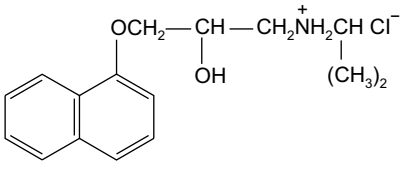
Dosage forms: Isosorbide dinitrate tablet BP.

Adverse drug reactions: Common side effects of nitrates and nitrites are:

1. Adverse drug reactions occur due to extensive vasodilation.
2. They are headache, postural hypotension, tachycardia, palpitation, weakness, flushing and rarely syncope.
3. To avoid these symptoms, the tablet may be spit out as soon as the pain is relieved.

II. β-Adrenergic blocking agents

i. Propranolol HCl



Synthesis and drug profile are given under section IV, Antiadrenergic agents.

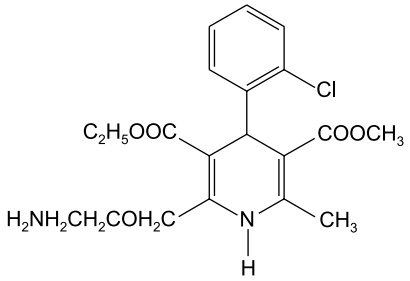
III. Calcium channel blockers

Mode of action: Calcium channel blockers act on the Ca^{2+} channel receptors, block the release of calcium, and, therefore, the calcium interaction with a protein calmodulin to form calcium calmodulin complex is decreased. This leads to the decreased activation of myosin light chain phosphorylation, which promotes muscle contraction by interacting between actin and myosin.

Metabolism: Prehepatic first-pass metabolism by CYP3A4 enzyme occurs with some orally administered calcium channel blockers, especially verapamil, with its low bioavailability of 20–35%. The bioavailability of dilitiazem is 40–67%, nicardipine is 35%, nifedipine is 45–70%, and amlodipine is 64–90%. Verapamil is metabolized by CYP3A4 N-demethylation to its principal metabolite, norverapamil, which retains approximately 20% of the activity of verapamil, and by *O*-demethylation (CYP2D6) into inactive metabolities. Dilitazem is metabolized by enzyme hydrolysis of its primary metabolite, diacetyl derivative, which retains approximately 25–50% of the activity of diltiazem.

Diltiazem undergoes N-demethylation by CYP3A4 and *O*-demethylation by CYP2D6. The N-demethylated metabolic pathways result in a mechanism-based inhibition of CYP3A4. The major metabolites are detected after oral and continuous intravenous administration, but not following rapid intravenous administration.

i. Amlodipine (Amlodac, Stamlo, Amlong)



3-Ethyl-5-methyl-2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

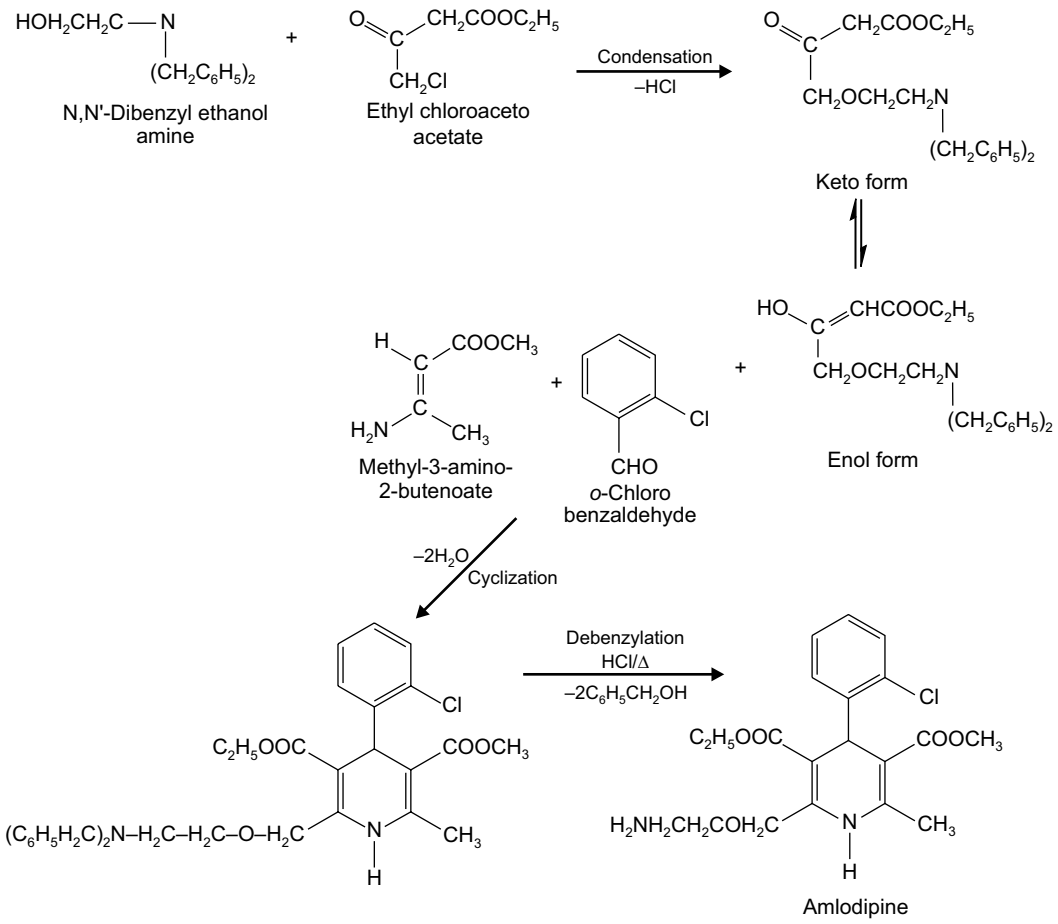
Properties and uses: It is a white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and 2-propanol. Used as an antianginal and antihypertensive agent.

Assay: It is assayed by adopting liquid chromatography technique.

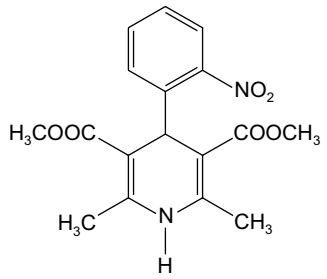
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: 2.5 to 10 mg/day amlodipine was equal to or superior to 160–320 mg/day verapamil, 50 to 100 mg/day captopril.

Synthesis



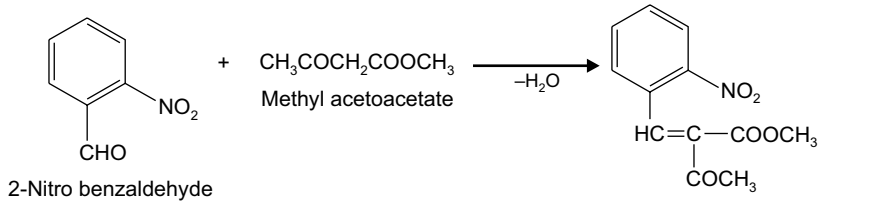
ii. Nifedipine (Caclcigard, Nicardia Retard, Depin)



3,5-Dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3,5-dicarboxylate

Synthesis (Hantzsch synthesis)

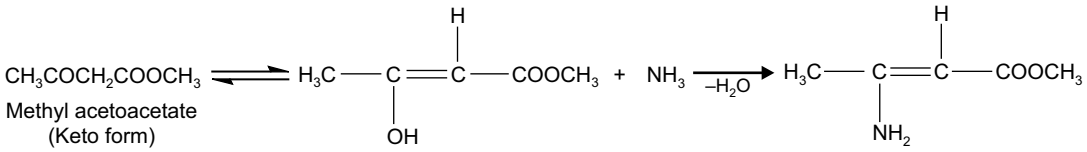
Step I. **Preparation of methyl-[2-acetyl-3-(2-nitrophenyl)]-2-propenoate**



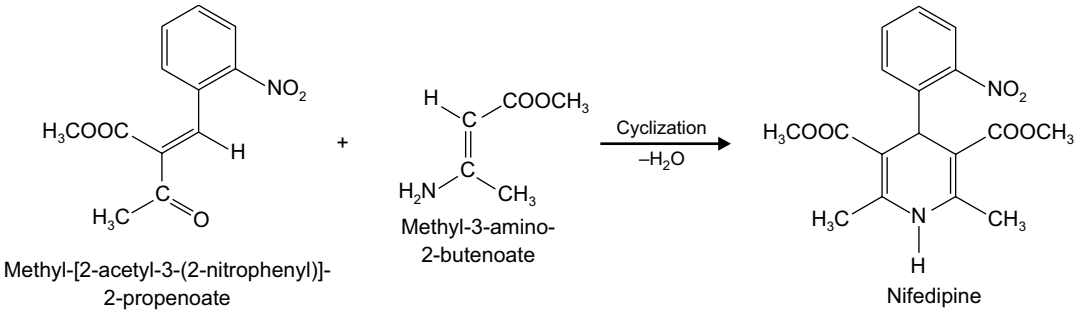
2-Nitro benzaldehyde

Methyl-[2-acetyl-3-(2-nitrophenyl)] -2-propenoate

Step II. **Preparation of methyl-3-amino-2-butenone**



Step III. **Condensation of products of *Steps I* and *II.***



Properties and uses: It is a yellow crystalline powder, sparingly soluble in ethanol, insoluble in water, but freely soluble in acetone. It is used in the treatment of vasospastic angina and hypertension.

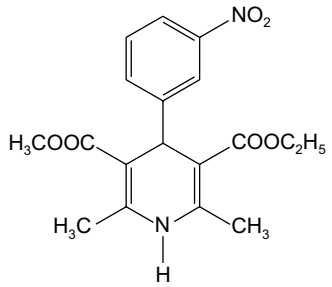
Assay: Dissolve the sample in a mixture of 2-methyl-2-propanol and perchloric acid solution. Titrate with 0.1 M cerium sulphate using ferroin as indicator. End point is the disappearance of pink colour.

Storage: When exposed to daylight and artificial light of certain wavelengths, it readily converts into a nitrosophenylpyridine derivative. Exposure to ultraviolet light leads to the formation of a nitrophenyl-pyridine derivative. Hence, it should be stored in well-closed airtight containers and protected from light.

Dose: For angina pectors: Adult—long-acting preparation—10–40 mg twice/day or 30–90 mg once daily.

Dosage forms: Nifedipine capsules IP, BP, nifedipine tablets IP.

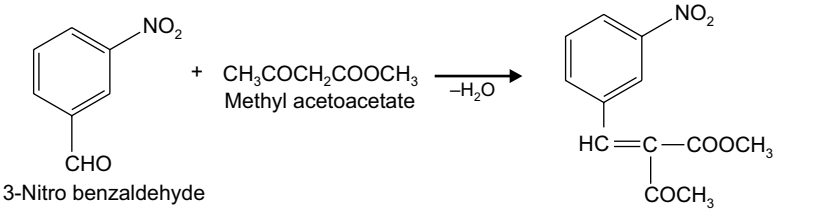
iii. Nitrendipine



3-Ethyl-5-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

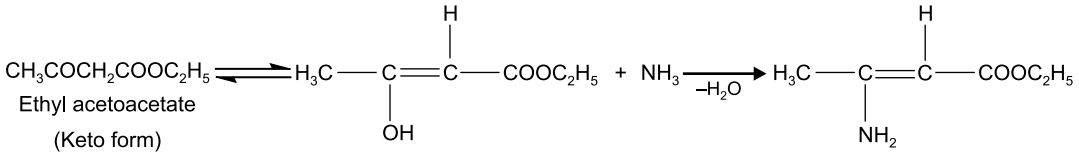
Synthesis

Step I. **Preparation of methyl-[2-acetyl-3-(nitrophenyl)]-2-propenoate**

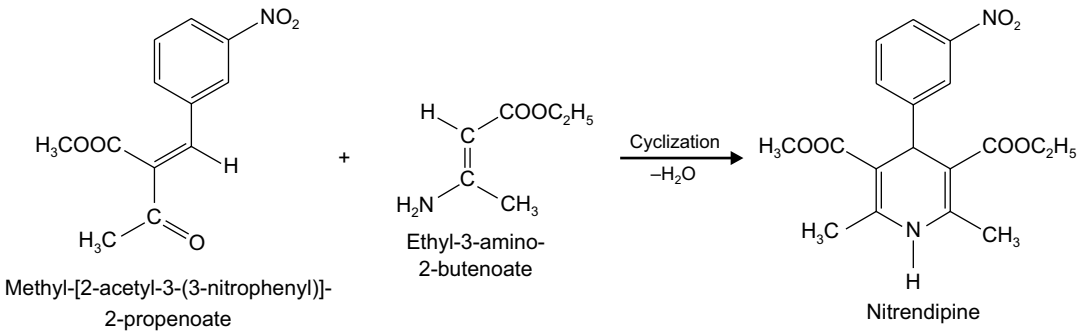


Methyl-[2-acetyl-3-(3-nitrophenyl)]
-2-propenoate

Step II. **Preparation of ethyl-3-amino-2-butenone**



Step III. **Condensation of products of *Steps I* and *II*.**

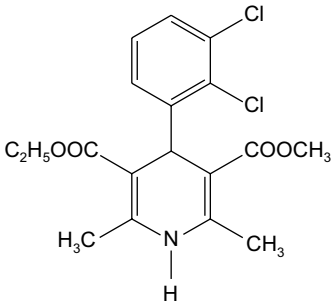


Properties and uses: It is a yellow crystalline powder exhibiting polymorphism, sparingly soluble in ethanol and methanol, insoluble in water, but freely soluble in ethyl acetate. It is used as a vasodilator and also used in the treatment of mild-to-moderate essential hypertension.

Assay: Dissolve the sample with gentle heating if necessary in a mixture of 2-methyl-2-propanol and perchloric acid solution. Titrate with 0.1 M cerium sulphate, using 0.1 ml of ferroin as indicator.

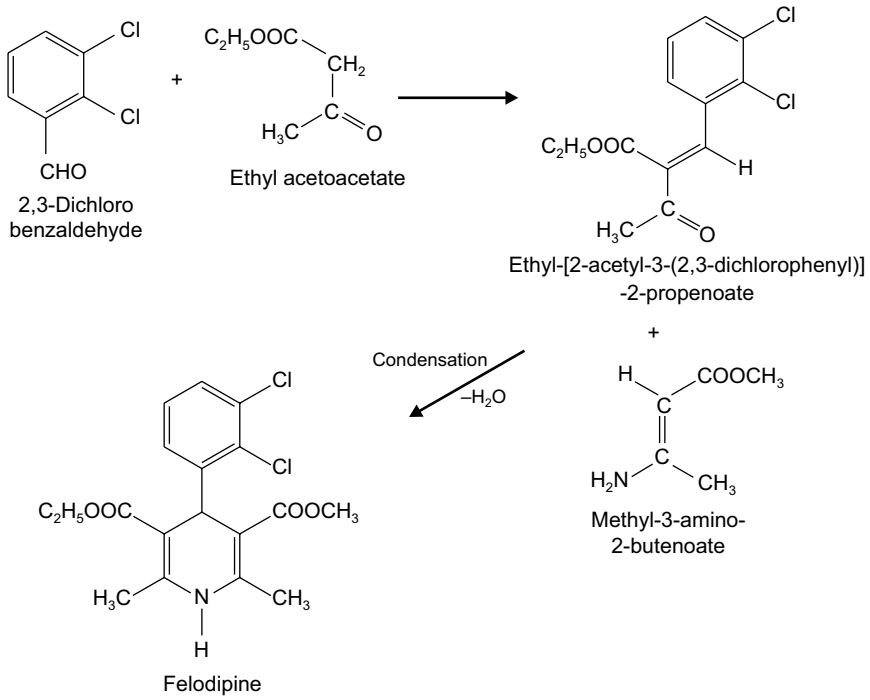
Storage: Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative. Hence, it should be stored in well-closed airtight containers and protected from light.

iv. Felodipine (Felogard, Plendil, Renedil)



3-Ethyl-5-methyl-4-(2,3-dichlorophenyl)-2,
6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Synthesis



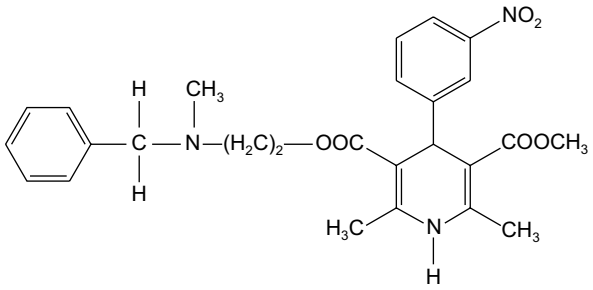
Properties and uses: It is a white or light yellow, crystalline powder, practically insoluble in water, freely soluble in acetone, ethanol, methanol, and methylene chloride. It is used in the treatment of angina and essential hypertension.

Assay: Dissolve the sample in a mixture of 2-methyl-2-propanol and perchloric acid solution. Add ferroin as an indicator and titrate with 0.1 M cerium sulphate until the pink colour disappears.

Dose: 2.5 to 20 mg alone or in combination with beta-blocker or 5 to 10 mg given once daily.

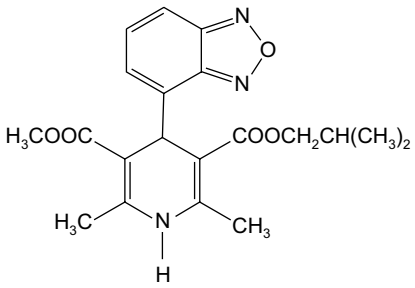
Storage: It should be stored in well-closed airtight containers and protected from light.

v. Nicardipine



Properties and uses: It exists as white crystals and is used in the treatment of angina and essential hypertension.

vi. Isradipine



3-Isobutyl-5-methyl-4-(benzo[1,2,5]oxadiazol-4-yl)
-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

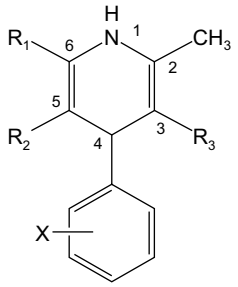
Properties and uses: It is a yellow crystalline powder, practically insoluble in water, freely soluble in acetone and soluble in methanol. It is used in the treatment of angina.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light.

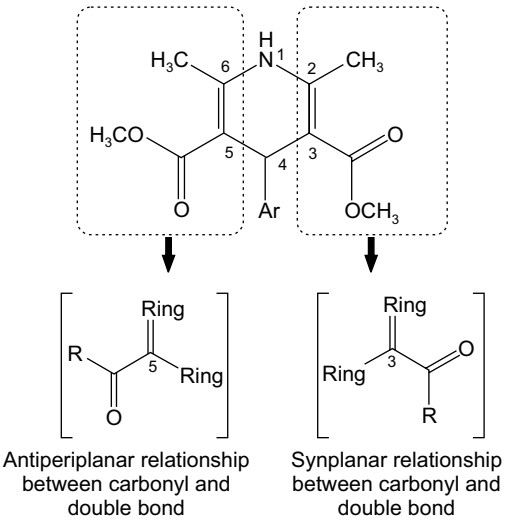
Dosage forms: Isradipine tablets BP.

SAR of Calcium Channel Blockers or SAR of 1,2-Dihydropyridines



General structure of 1,4-dihydropyridines

1. A substituted phenyl ring at the C-4 position optimizes activity. (Heteroaromatic rings such as pyridine, produce similar therapeutic effects but are not used because of observed animal toxicity.) C-4 substitution with a small non-planar alkyl or cyclo alkyl group increases activity.
2. Phenyl ring substitution X is important for size and position rather than for electronic nature.
3. Compounds with *ortho/meta* substitutions possesses optimal activity, whereas those that of unsubstituted or that contains a *p*-substitution shows a significant increase in the activity, despite the fact that all commercially available 1,4-DHPs have electron withdrawing *ortho/meta* substituents. This is not an absolute requirement, compounds with electron donating groups at the same positions also have demonstrated good activity, the importance of *ortho* and *meta* substituents is to provide sufficient bulk to lock the conformation of 1,4-DHP such that the C-4 aromatic ring is perpendicular to the 1,4 DHP ring, this perpendicular conformation has been proposed to be essential for the activity of 1,4-DHPs.
4. The 1,4-DHP ring is essential for the activity, substitution at the N-1 position or the use of oxidized or reduced piperidine ring systems greatly decreases or abolishes activity.
5. Ester groups at C-3, C-4, C-5 positions optimize activity, other electron withdrawing groups show increased antagonistic activity and may even show agonistic activity.
6. When the esters at C-3 and C-5 are non-identical, the C-4 carbon becomes chiral and stereo-selectivity between the enantiomers is observed; additionally, evidence suggest that C-3 and C-5 positions of dihydropyridine ring are not equivalent positions. Crystal sites of nifidipine, a symmetrical 1,4-DHP have shown that C-5 carbonyl synplanar to C_2–C_3 bond but C-5 carbonyl is antiperiplanar to the C5–C6 bond. Symmetrical compounds have shown enhanced selectivity for specific blood vessels and are preferentially developed. Nifidipine the first 1,4-DHP marketed is the only symmetrical compound in this chemical class.

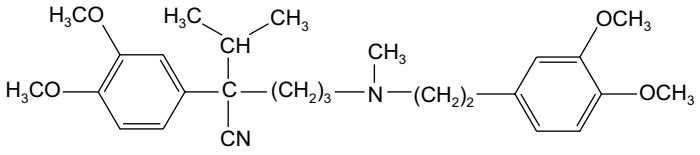


Antiperiplanar relationship between carbonyl and double bond

Synplanar relationship between carbonyl and double bond

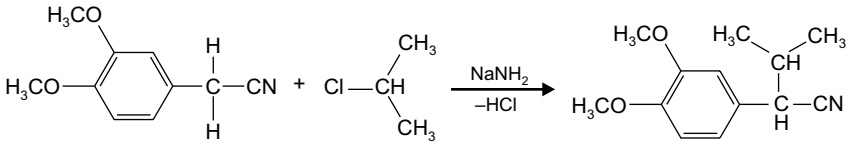
7. With the exception of amlodipine all 1,4-DHPs have C-2 and C-6 methyl groups. The enhanced potency of amlodipine (vs. nifidipine) suggests that the 1,4-DHP receptor can tolerate larger substituents at this position which enhances the activity.

i. Verapamil



Synthesis

Step I. **Synthesis of 3,4-dimethoxy-2-isopropyl valeronitrile.**

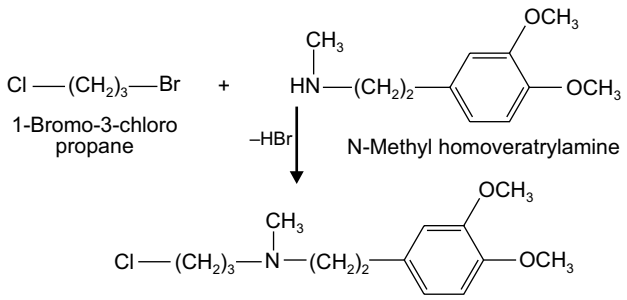


2-(3,4-Dimethoxyphenyl) acetonitrile

2-Chloropropane

3,4-Dimethoxy-2-isopropyl valeronitrile

Step II. **Preparation of 3,4-dimethoxy phenyl ethyl N-methyl-3-chloro propylamine.**

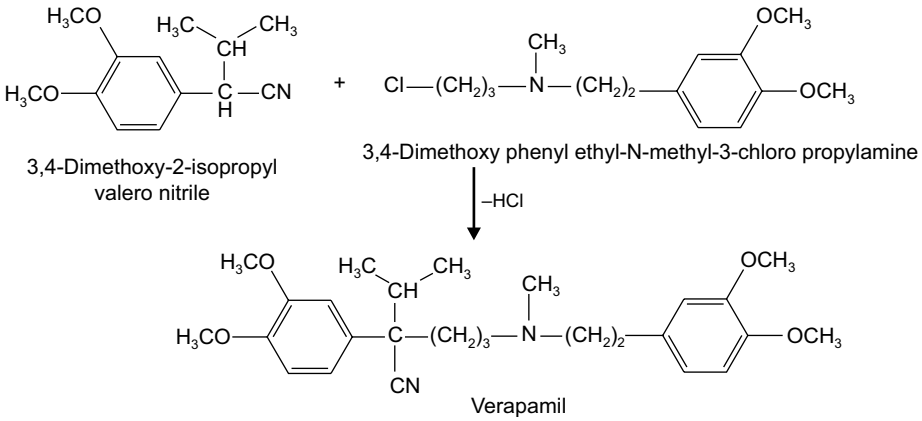


1-Bromo-3-chloro propane

N-Methyl homoveratrylamine

3,4-Dimethoxy phenyl ethyl-N-methyl-3-chloro propylamine

Step III. **Condensation of products of** *Steps I* **and** *II.*



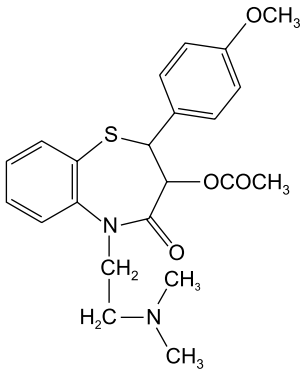
Properties and uses: It is a white crystalline powder, soluble in water, freely soluble in methanol, and sparingly soluble in alcohol. It is used in the treatment of angina pectoris, arrhythmias from ischaemic myocardial syndromes, and supraventricular arrhythmias.

Assay: Dissolve the sample in ethanol and add 0.01 M hydrochloric acid. Titrate with 0.1 M sodium hydroxide and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

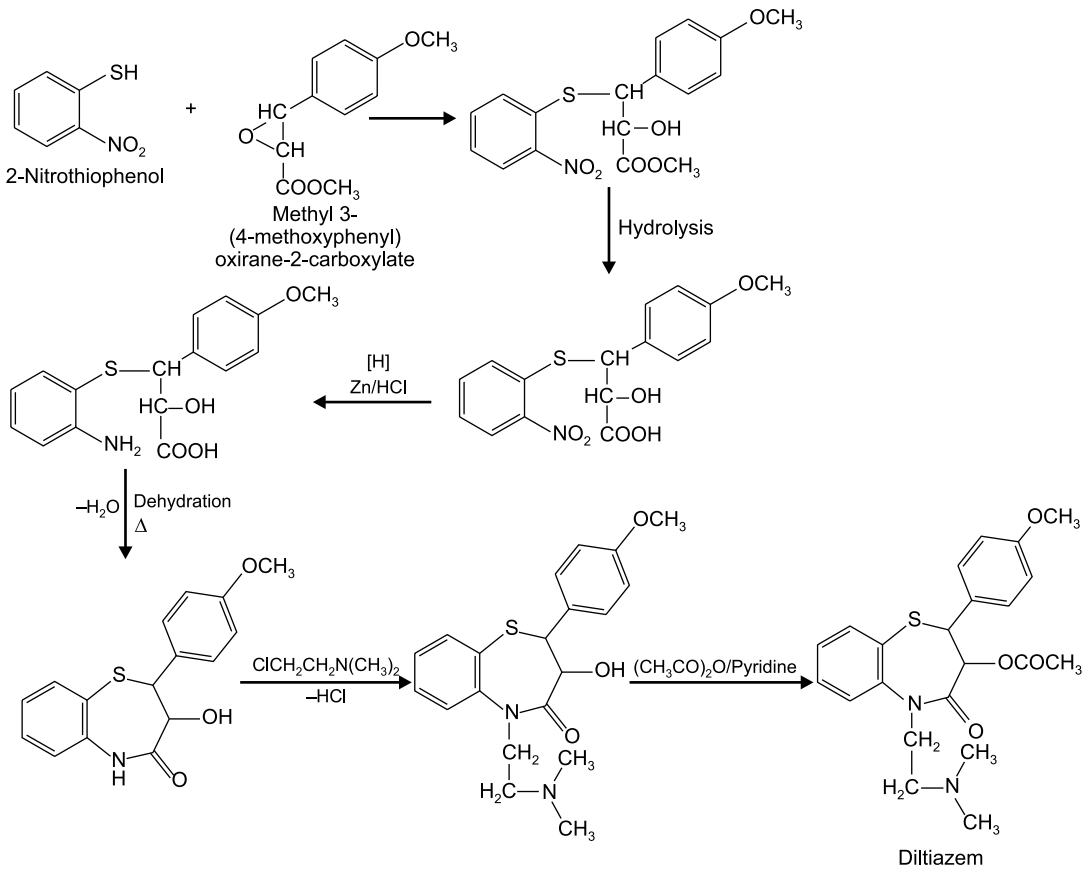
Dosage forms: Verapamil HCl injection IP, verapamil HCl tablets IP, verapamil injection BP, verapamil tablets BP, prolonged-release verapamil tablets BP.

ii. Diltiazem



5-(2-(Dimethylamino)ethyl)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,5]thiazepin-3-yl acetate

Synthesis



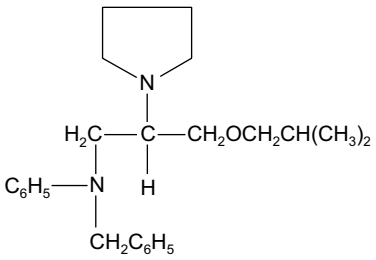
Properties and uses: It is a white crystalline powder, freely soluble in water, in methanol, and in methylene chloride, slightly soluble in ethanol. Diltiazem has two chiral centres (C_2 and C_3), the levorotatory *cis* antipode is more active form. It is used in the treatment of angina pectoris and also used as antiarrhythmic agent.

Assay: Dissolve the sample in a mixture of anhydrous formic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

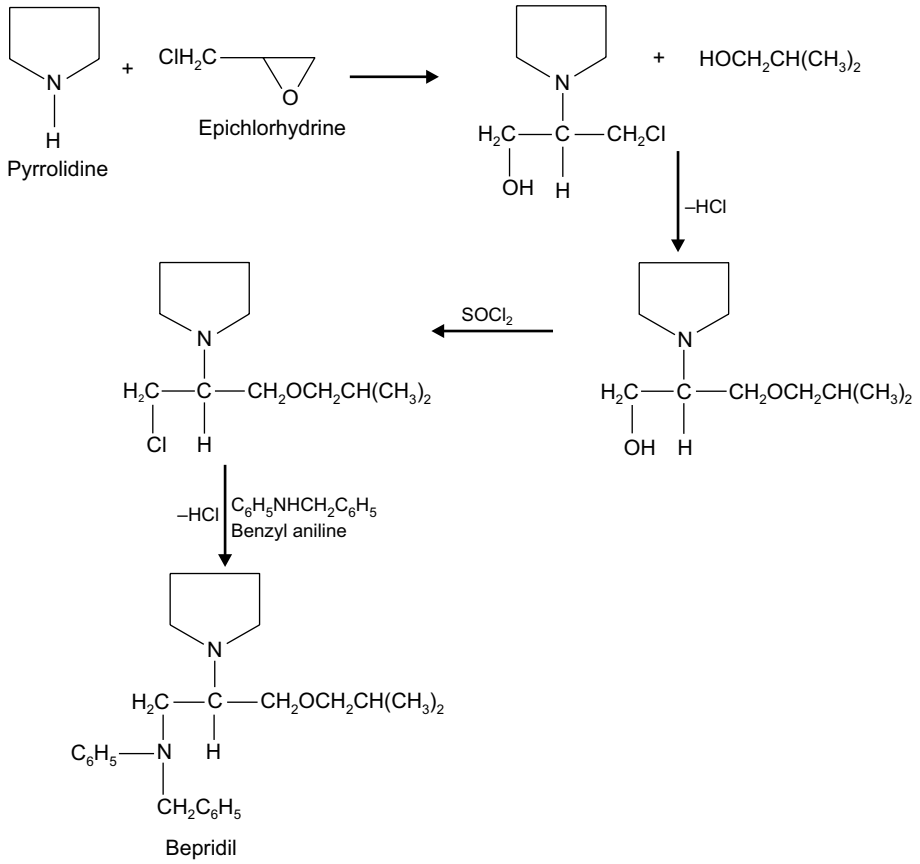
Second-generation Alkyl Amine Type Calcium Channel Blockers

i. Bepridil



N-benzyl-N-(3-isobutoxy-2-(pyrrolidin-1-yl)propyl)benzenamine

Synthesis



Properties and uses: Bepridil exists as white crystals and is used as a vasodilator and antianginal agent.

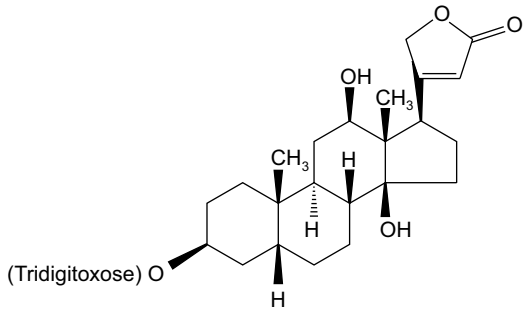
Dose: The usual dose is 5 mg/kg.

IV. Cardiovascular glycosides

Cardiovascular agents have their major pharmacological action in the ability to alter the cardiovascular function, cardiac glycosides, and certain other agents have positive inotropic effects. They are useful in the treatment of congestive heart failure. Several cardiac glycosides have been studied, which include glycosides of digitalis, squill, and strophanthus. Among all of them, the most predominant one is digitalis. *Digitalis lanata* and *D. purpurea* are the richest sources of cardiac glycoside. On hydrolysis (acid or alkali or enzymatic), they yield the corresponding steroidal aglycone and glycone (sugar). The cardiac activity resides in the aglycone portion, but the sugar moiety provides favourable solubility and distribution characteristics.

Uses: Cardiac glycosides are used to slow down the heart in the artrial arrhythmias, particularly artrial fibrillation. These drugs are also given in the case of congestive heart failure.

i. Digoxin



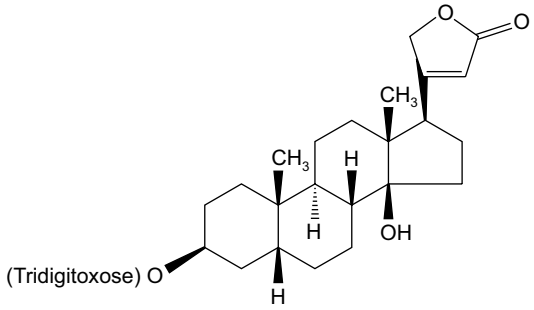
Properties and uses: It is a white or almost white powder or colourless crystals. It is freely soluble in a mixture of methanol and methylene chloride, slightly soluble in ethanol, but insoluble in water. It is used in the treatment of congestive heart failure with artrial fibrillation.

Assay: It is assayed by adopting liquid chromatography technique.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Paediatric digoxin oral solution IP, BP, digoxin tablets IP, BP, digoxin injection IP, BP, paediatric digoxin injection BP

ii. Digitoxin



Metabolism: Digitoxin is not extensively metabolized. It is transported from the intestinal enterocyte along with epithelium into the intestinal lumen by *p*-glycoprotein, which is also expressed in the kidney and liver.

Digitoxin is essentially metabolized by the liver to form a variety of metabolites, including 2-digitoxigenin (digitoxose), and 1-digitoxigenin (digitoxose).

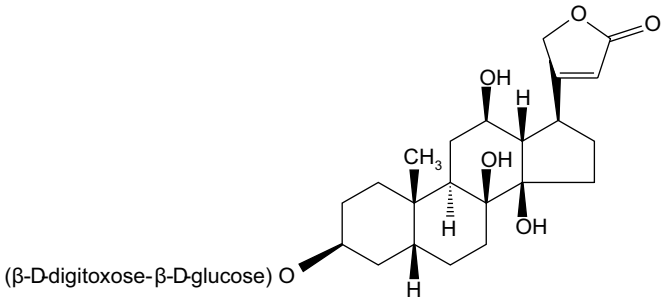
Properties and uses: It is a white or almost white powder, which is freely soluble in a mixture of methanol and methylene chloride, slightly soluble in alcohol and methanol, but insoluble in water. Digitoxin has action and uses similar to those of digoxin.

Assay: Dissolve the sample in alcohol. Dilute with alcohol and prepare a reference solution in the same manner, using digitoxin. To 5.0 ml of each solution add alkaline sodium picrate solution, allow to remain protected from bright light for 30 min and measure the absorbance of each solution at the maximum of 495 nm, using as the compensation liquid a mixture of 5.0 ml of alcohol and 3.0 ml of alkaline sodium picrate solution prepared at the same time. Calculate the content of digitoxin from the absorbances measured and the concentrations of the solutions.

Storage: It should be stored in well-closed airtight container and protected from light.

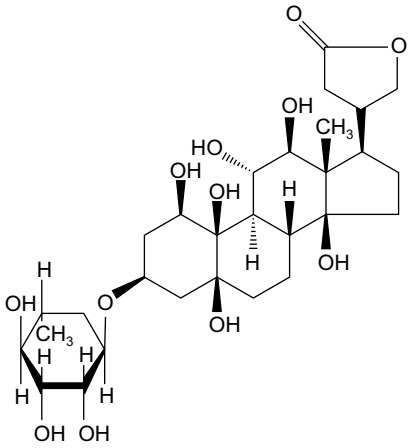
Dosage forms: Digitoxin tablets BP.

iii. Deslanoside



Properties and uses: It is a derivative of lanatoside-C. It has action and uses similar to those of digoxin.

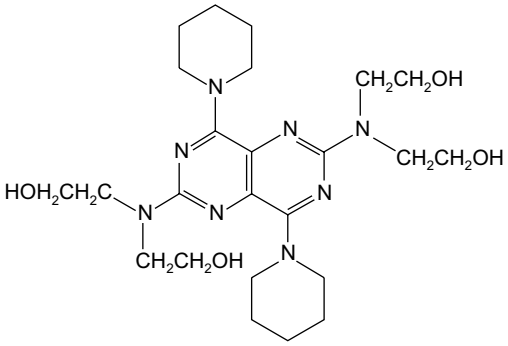
iv. Ouabain



Uses: It has action and uses similar to those of digoxin.

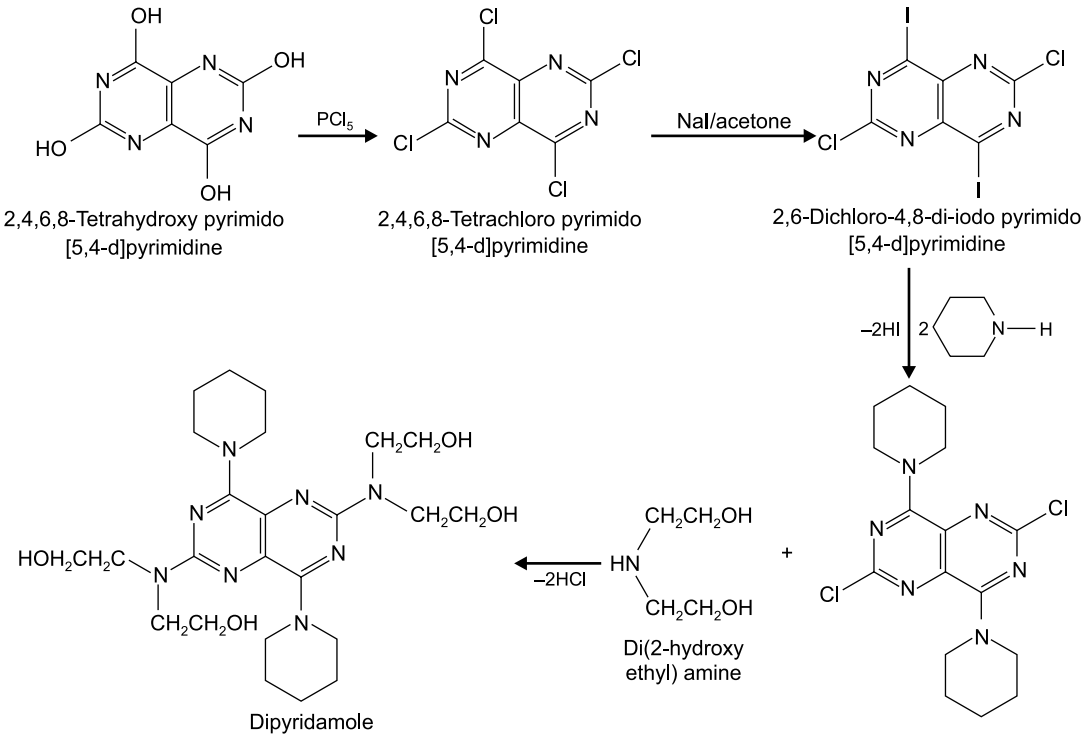
V. Miscellaneous

i. Dipyridamole



2,2-*bis*-[diethanol amino]-4,8-dipiperidine pyrimido-[5,4-d]-pyrimidine

Synthesis



Properties and uses: It is a bright yellow crystalline powder, which dissolves in dilute solutions of mineral acids, but insoluble in water, soluble in acetone and ethanol. The drug inhibits adenosine deaminase in erythrocytes and interacts with the uptake of vasodilator adenosine by erythrocytes. These actions potentiate the effect of prostacyclin, which acts as an inhibitor to platelet aggregation. It is a long-acting vasodilator. Its vasodilating effect is selective for the coronary system. It is also used to treat angina pectoris.

Assay: Dissolve the sample in methanol and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Dipyridamole tablets BP.

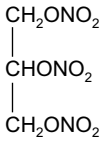
Classification Based on PCI Syllabus

Vasodilators

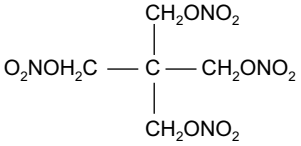
Amyl nitrite

$(CH_3)_2CHCH_2CH_2O.NO$

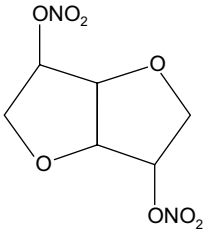
Nitroglycerin



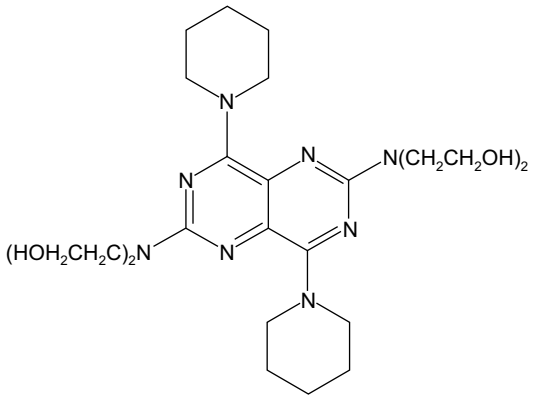
Pentaerythritol tetranitrate



Isosorbide dinitrite

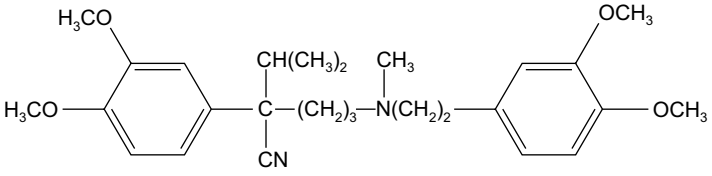


Dipyridamole

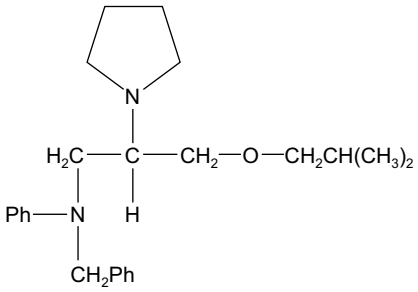


Calcium Channel Blockers

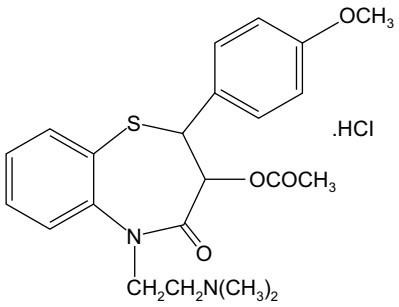
Verapamil



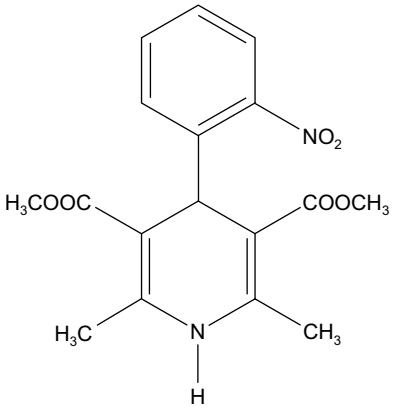
Bepridil hydrochloride



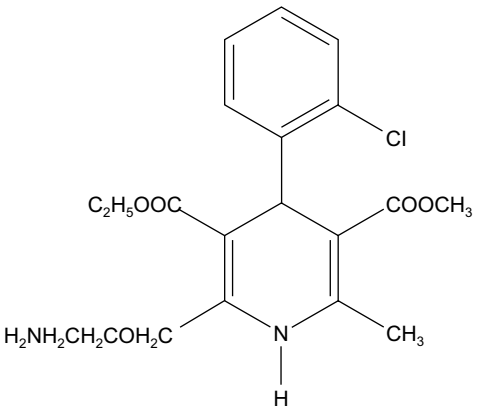
Diltiazem hydrochloride



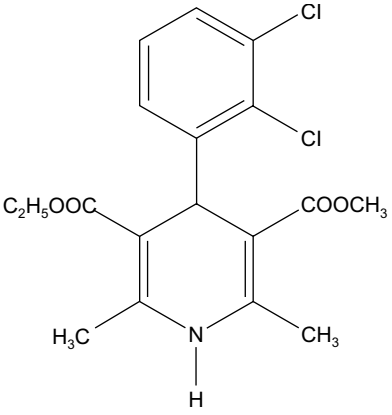
Nifedipine



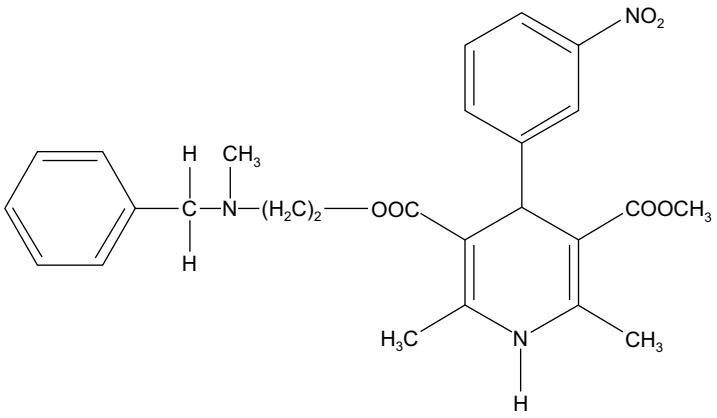
Amlodipine



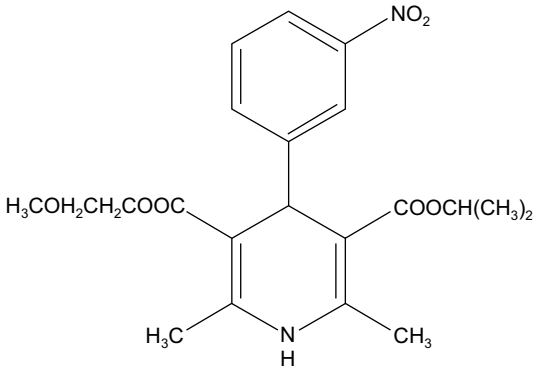
Felodipine



Nicardipine



Nimodipine



CHAPTER 44

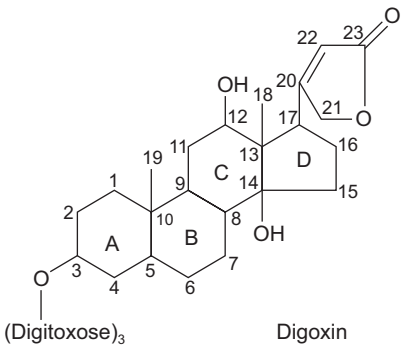
Drugs Used in Congestive Cardiac Failure (CCF) or Congestive Heart Failure (CHF)

When the pumping ability of heart is decreased and the cardiac output decreased, this condition is called congestive cardiac failure (CCF). During this condition, ventricles are not completely cleared or emptied leading to increased venous pressure in the pulmonary and systematic circulation. The ejection fraction of left ventricles is reduced to less than 40%.

DRUGS USED IN CCF

The main aim of the treatment of CCF is to reduce the morbidity and mortality by re-establishing the cardiac output and relieving congestion. Steroidal glycosides are used as heart stimulants (cardiotonics) since ancient times, as they exert action on failing heart and produce slowing and strengthening effect. At lower doses, they slowdown and strengthen the heartbeat but in excessive doses they may cause the cardiac arrest. The pharmacological effect of the cardiac glycosides (e.g. digoxin) depends on both the aglycones and the sugars attached. The inherent activity resides in aglycon only, but the sugars are responsible for solubility and fixation of the glycoside to the heart muscle. Cardiac glycosides are obtained from the plant of foxglove family. Digitoxin and digoxin are mainly obtained from the leaves of *Digitalis purpurea* and *Digitalis lanata.* But digitalis is widely used due to favourable pharmacokinetic properties.

Chemistry

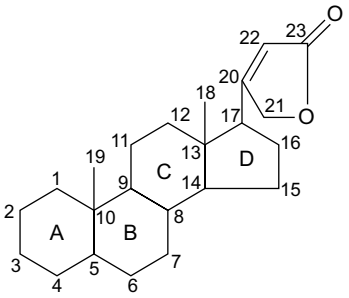


Digoxin

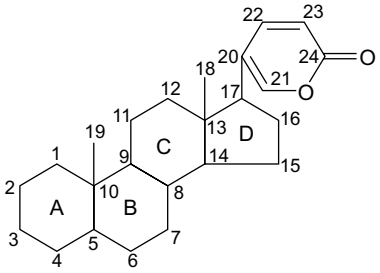
The sugar units, attached to the aglycone by a C-3 β-linkage are comprised of four sugar units which includes glucose or rhamnose together with other deoxy-sugars units (Table 44.1). Examples of deoxy-

sugars are 2,6-dideoxyhexoses (e.g. digitoxose) or their 3-O-methyl ethers (e.g. cymarose). The sugars are obtained by hydrolysis of cardiac glycosides are unique and not found elsewhere in nature.

Aglycones present in cardiac steroids may be distinguished based on the presence of five- or six-membered lactone ring. These types are known as cardenolides (e.g. digitoxigenin) and bufanolides or bufadienolides (example, scillarenin), respectively and the following formulae indicates their structure and ring numbering.

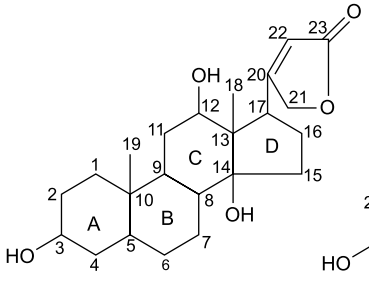


Cardenolide

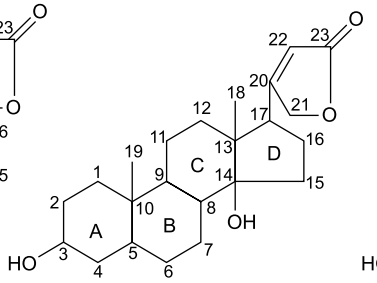


Bufadienolide

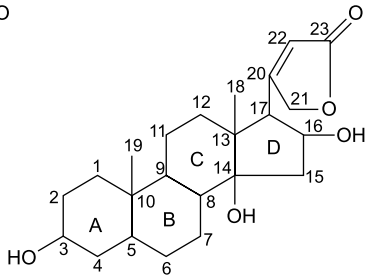
Cardenolide: It is a commonly found type and contains an α,β-unsaturated γ-lactone ring **(five-membered)**. They occur mostly in plants, certain genera of *Digitalis* particularly *D. Purpurea* is the main source for most of the drugs with therapeutic value. Chemical structure of some typical genins of cardenolides along with their substitutions are shown below.



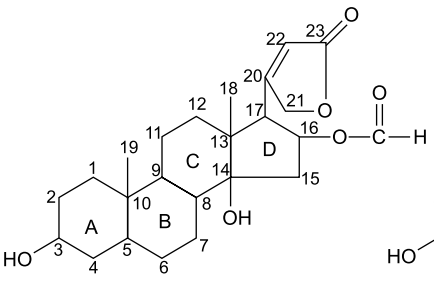
Digoxigenin



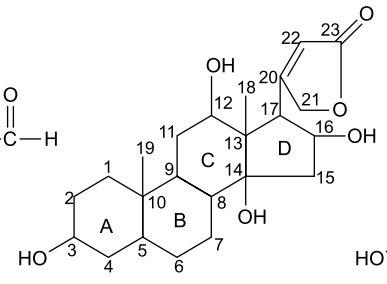
Digitoxigenin



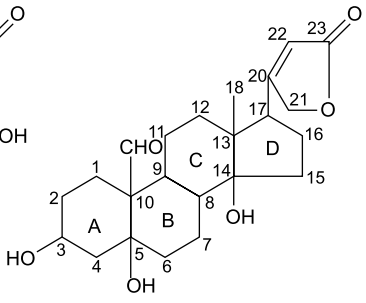
Gitoxigenin



Gitaloxigenin

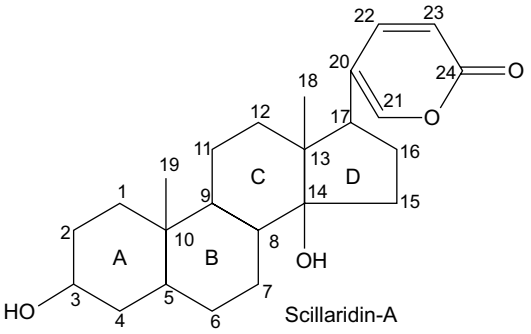


Diginatigenin

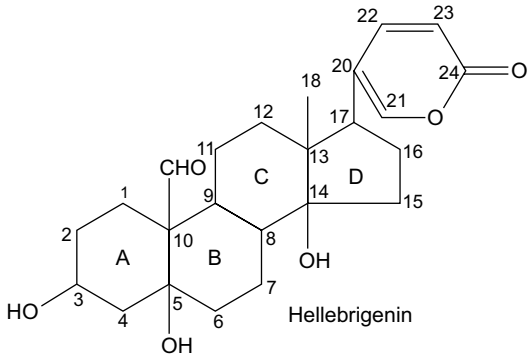


Strophanthidin

Bufadienolides or Scilladienolides: They contain a **δ-lactone ring (six-memebered)**, which has conjugated diene system. In plants they occur in squill family. Chemical structures of some typical genins of bufadienolides along with their substitutions are shown below.



Scillaridin-A



Hellebrigenin

Table 44.1: Glycone and aglycone portion of some important cardiac glycosides

Glycoside	*Aglycone*	*Sugar moieties*
Digoxin	Digoxigenin	$(Digitoxose)_3$
Digitoxin	Digitoxigenin	$(Digitoxose)_3$-
Acetyldigitoxin	Digitoxigenin	Acetyldigitoxose-$(digitoxose)_2$-
Lanatoside A	Digitoxigenin	Glucose-acetyldigitoxose-$(digitoxose)_2$-
Lanatoside B	Gitoxigenin	Glucose-acetyldigitoxose-$(digitoxose)_2$-
Lanatoside C	Digoxigenin	Glucose-acetyldigitoxose-$(digitoxose)_2$-
Acetyldigoxin	Digoxigenin	Acetyldigitoxose-$(digitoxose)_2$-
Deacetyl-lanatoside C	Digoxigenin	Glucose-$(digitoxose)_3$-
Lanatoside D	Diginatigenin	Glucose-acetyldigitoxose-$(digitoxose)_2$-
Lanatoside E	Gitaloxigenin	Glucose-acetyldigitoxose-$(digitoxose)_2$-

Mechanism of action:

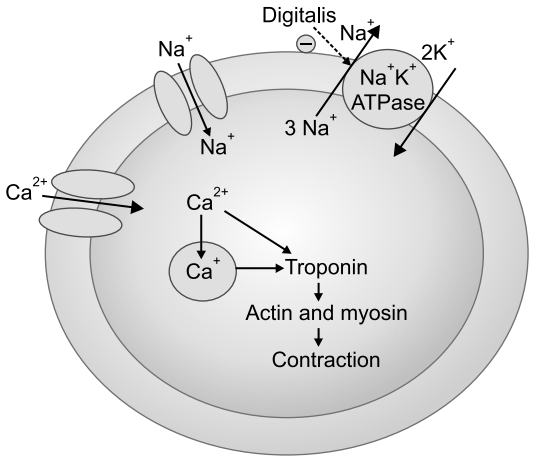


Fig. 44.1: Mechanism of action of cardiac glycosides.

The cardiac glycosides produce their effect by inhibiting the Na^+/K^+-ATPase pump which increases the intracellular sodium concentration, and prevents the efflux of Ca^{2+} ions. Hence, the intracellular concentration of Ca^{2+} increases which is readily available to activate the contractile proteins action and myosin which increases the force of contraction. Cardiac glycosides also exerts other compensatory mechanisms which includes baroreceptor sensitivity.

Tesosantan

Properties and uses: It is a non-selective ET_A and ET_B antagonist. It acts as a vasodialator and used to treat acute heart failure.

Bosentan

Properties and uses: It is an endothelin receptor antagonist. It is used to treat pulmonary arterial hypertension and decreases the digitalis-induced ulcers.

Nesiritide

Properties and uses: It is a recombinant form of a drug containing human β-type natriuretic peptide. It counter regulates renin-angiotensin-aldosterone system which stimulates cyclic guanosine monophosphate leads to smooth muscle cell relaxation. It is used to treat decompensated congestive cardiac failure.

Adverse drug reactions: Common side effects of digitalis are:

- Digoxin has a narrow margin of safety monitoring of serum digoxin, electrolyte levels and electrocardiogram (ECG) are important during digitalis therapy.

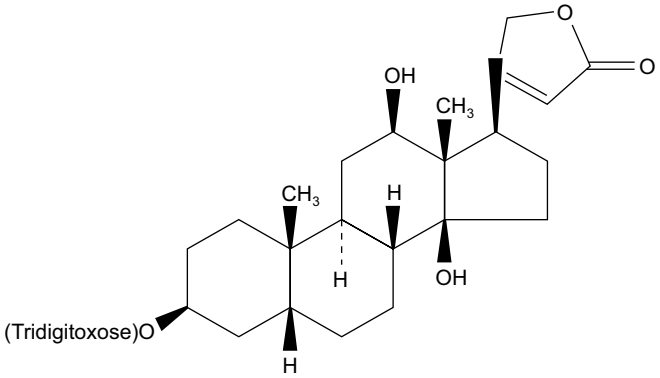
1. Extra cardiac toxicity:
   i. GIT—early symptoms of toxicity are anorexia, nausea and vomiting, which are due to GI irritation and CTZ stimulation.
   ii. CNS—headache, confusion, restlessness, disorientation, weakness, visual disturbances, altered mood and hallucinations.
   iii. Skin rashes and gynecomastia can occur occasionally.
2. Cardiac toxicity:
   - Digitalis can cause any type of arrhythmias.
   - Most common are ventricular premature beats and ventricular tachycardia.
   - It can also cause A-V block, atrial tachycardia, atrial fibrillation, atrial flutter and even severe bradycardia.

Cardiac Glycosides (Treatment for Digitalis Toxicity)

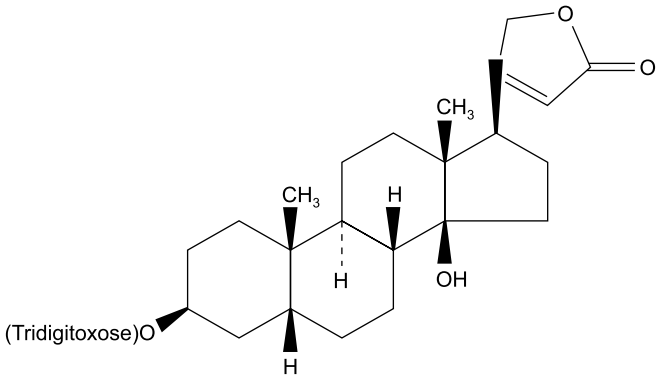
- First of all, stop the administration of digitalis.
- Start oral or parental K^+ supplements but careful monitoring of ECG is required for patients with AV block or hyperkalaemia.
- IV phenytoin/lignocaine is used to treat ventricular arrhythmias. Supraventricular arrhythmiasis is treated with propranalol.
- Bradycardia is treated with atropine.
- Antidigoxin immunotherapy is also used to treat digitalis toxicity.
- Diuretics, calcium, quinidine and methyldopa, etc. increases dioxin toxicity, while rifampicin, antacids and neomycin decrease digoxin levels by enzyme induction.

Drugs Used in Congestive Heart Failure

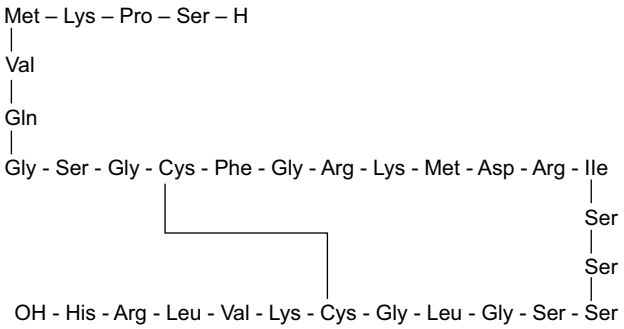
Digoxin



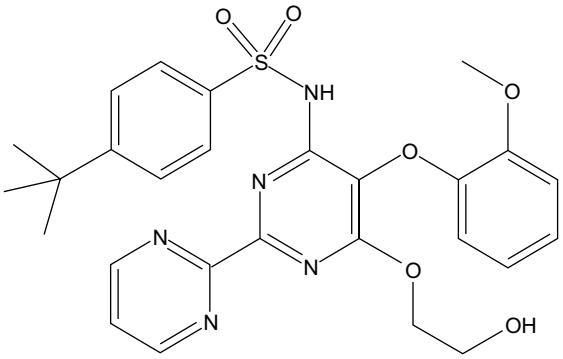
Digitoxin



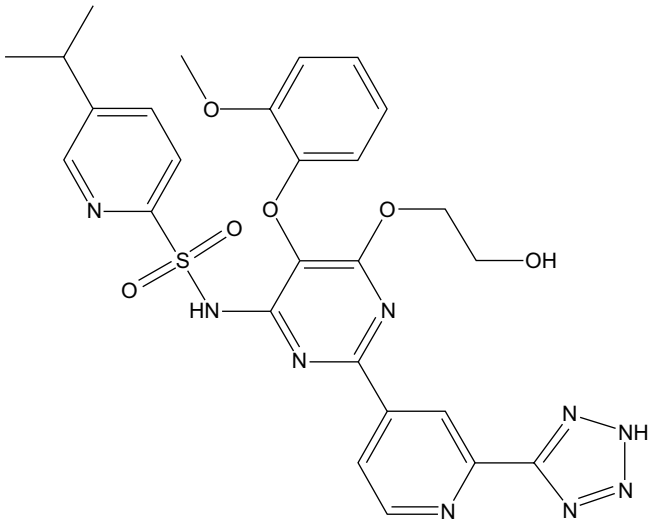
Nesiritide



Bosentan



Tezosentan



PROBABLE QUESTIONS

1. Write a note on diuretics used in the treatment of hypertension.
2. What is angiotensin? Write some examples used as ACE inhibitors. Outline the synthesis and metabolism of any two of them.
3. Leaves of *Digitalis lanata* gave two important cardiac glycosides. Write their structure, chemical name, and uses.
4. How will you classify the antihypertensive drugs? Support your answer by giving the structure, chemical name and uses of two potent compounds from each category.
5. Clonidine, hydralazine, methyldopa, and diazoxide are potent antihypertensive drugs. Write the structure, synthesis, and uses of any two compounds.
6. Describe the mode of action of some potent antihypertensive drugs being employed. Write their structures and chemical names.
7. Write in brief about beta-blockers used in bronchial asthma.

8. Write a note on vasodilators used in the treatment of hypertension.
9. Write in detail about antiarrythmic agents used as cardiovascular drugs. Support your answer with suitable examples.
10. Describe the mode and action of the different antiarrthmic agents used in the treatment of hypertension.
11. Describe the synthesis of any one of the calcium channel blockers.
12. Write the synthesis, mode of action, and uses of the following:
    (a) Disopyramide phosphate
    (b) Procainamide hydrochloride
13. Describe the synthesis, drug metabolism, and uses of propranolol hydrochloride.
14. Outline the synthesis of verapamil hydrochloride and describe its mode of action.
15. Write in brief about the organic nitrites and nitrates used in the treatment of angina pectoris.
16. Write the mode of action and synthesis of isosorbide dinitrate and diltiazem.
17. Define and classify antihyperlipidaemics with suitable examples. Write the synthesis and uses of any two of them.
18. Write the mode of action and metabolism of HMG-COA reductase inhibitors. Mention few drugs and outline the synthesis of any one of them.
19. Write note on fibric acid derivatives.
20. Classify antiarrhythmics and write in brief about the beta-adrenergic blockers used in cardiac arrhythmia.
21. Write the synthesis and uses of the following:
    (a) Flecainide
    (b) Bretylium tosylate

SUGGESTED READINGS

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SECTION VI

Drugs Acting on Urinary System

45. Urinary System 673

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CHAPTER 45

Urinary System

INTRODUCTION

The kidneys do the major work of urinary system. The structural and functional units of kidneys are nephron. The clinical importance of urinary system includes hypertension, heart failure, renal failure, nephritic syndrome, and cirrhosis. The haemodynamics of renal system has a capability to alter the aforesaid pathological conditions.

FUNCTIONS OF RENAL SYSTEM

The functions of renal system are as follows:

Regulation of blood ionic compounds: The kidneys help to regulate the blood ions, i.e. sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), chloride (Cl^-), and phosphate ions (HPO_4^{2-}).

Regulation of blood pH: The kidneys excrete a variable amount of hydrogen ions (H^+) into the urine and conserve bicarbonate (HCO_3^-) ions, which regulate pH of blood.

Regulation of fluid volume: The kidneys adjust blood volume by eliminating water in urine.

Regulation of blood pressure (BP): BP is regulated by the kidneys through an enzyme called renin secreted by juxtaglomerular cells, which activates the renin-angiotensin-aldosterone (RAA) pathway. Increased renin causes increase in BP.

Maintenance of blood osmolarity: The kidneys produce two hormones, calcitrol and erythropoietin. Calcitrol, the active form of vitamin D helps to regulate calcitrol homeostasis and erythropoietin stimulates the production of red blood cells (RBCs).

Regulation of blood glucose level: The kidneys can use the amino acid of glutamine in gluconeogenesis and release blood to maintain sugar level.

Excretion of metabolite waste products and foreign substances: Metabolic products like ammonia, urea, bilirubin, creatinine, uric acid, and other substances, i.e., toxins of exogenous compounds and drug metabolites, etc., are excreted through urine.

Renal haemodynamics is altered by diuretics in clinical medicine. The therapeutic applications of diuretics are mainly concerned with hypertension and heart failure.

The normal renal physiological process includes glomerular filtration and tubular reabsorption.

Principle of Glomerular Filtration

In glomerular capillaries, a portion of plasma water is formed through a filter, which functions due to the fenestrated capillary epithelial cells and the filtration diaphram formed by epithelial cells; solutes of small size flow with filtered water into the urinary space whereas formed elements and macromolecules are retained by the filtration barrier. The glomerular filtration depends on the hydrostatic pressure in Bowman's capsule space. Glomerular filtration rate (GFR) averages 125 ml/min in males and 105 ml/min in females. The mechanism regulates GFR in two ways—(i) by adjusting blood flow into and out of glomerulus and (ii) by altering glomerular capillary surface area available for filtration.

Principle of Tubular Reabsorption and Secretion

The volume of fluid entering the proximal convoluted tubules in half an hour is more than the total blood plasma volume—normally about 99% of filtered water is reabsorbed. Solutes that are reabsorbed by both active and passive process include glucose, amino acids, urea, and ions, i.e. Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^- (bicarbonates), and HPO_4^{2-} (phosphates). Once the fluid passes through the proximal convoluted tubule, the cells that are located more distally, tune the reabsorption processes to maintain homeostatic balance of water and selected ions. Most of the small proteins and peptides that pass through the filter is also reabsorbed by pinocytosis. In tubular secretion, the transfer materials from the blood and tubule cells enter into tubular fluid include hydrogen ions (H^+), potassium (K^+), ammonium (NH_4^+), creatinine, and certain drugs like penicillin. The general membrane transports are Na^+-ATPase pump, in basolateral membrane, which hydrolyzes ATP resulting in transport of Na^+ into intracellular and interstitial spaces. Na^+ may diffuse across the luminal membrane through sodium channels into epithelial cell down through the electrochemical gradient, which is established by basolateral Na^+-K^+-ATPases. In addition, free enzyme available in electrochemical gradient for Na^+ is trapped by integral protein of luminal membrane resulting in co-transporters of various solutes against their electrochemical gradient by symports (e.g. Na^+-glucose, Na^+-H_2PO_4, and Na^+-amino acid). Na^+ exits basolateral membrane into intercellular and interstitial spaces through Na^+ pump; their accumulation creates small osmotic pressure difference across the epithelial cell. In water-permeable epithelium, water moves into the intracellular spaces driven by osmotic pressure difference. Movement of water into intracellular space concentrates other solutes in the tubular fluid, resulting in an electrochemical gradient for these substances across the epithelium. Membrane permeable solutes then move down their electrochemical gradients into the intracellular spaces through both transcellular (e.g. simple diffusion, symporters, antiporters, uniporters, and channels) and paracellular pathways. Membrane impermeable solutes that remain in the tubular lumen are excreted in the urine with an obligatory amount of water. As water and solutes accumulate in intracellular space the hydrostatic pressure increases, providing a driving force for bulk water flow.

There are other mechanisms that secrete organic acid and organic base secretions. Nine different organic acids and five different organic base transporters exist. Other regulations include cation and anion by Ca^{2+}-ATPase, Na^+-Pi (sodium inorganic phosphate) symport, Na^+-Mg^{2+} antiport, and Mg^{2+}-ATPase.

The rate of urinary excretion can be expressed by the following equation:

Urinary output = Glomerular filtration + Tubular secretion – Tubular reabsorption

CHAPTER 46

Diuretics

INTRODUCTION

Diuretics increase the rate of urine flow and sodium excretion, and are used to adjust the volume or composition of body fluids in a variety of clinical situations, including hypertension, heart failure, renal failure, nephritic syndrome, and cirrhosis. The normal fluid filtration in human body is 180 litres, and about 1.5 litres of urine is formed in 24 hrs.

The diuretics act primarily by inhibiting tubular reabsorption; just 1% decrease in tubular reabsorption would produce more than double urine output. The action depends upon the drug by acting on various symport and antiport present in the nephron. All the transports depend on the basolateral membrane porters, especially in tubular reabsorption, which is divided into four sites:

1. Proximal tubule (PT)
2. Ascending limb of loop of Henle (AscLH)
3. Cortical diluting segment of loop of Henle
4. Distal tubule (DT)
5. Collecting duct

Proximal tubule: Transport of Na^+ and K^+ coupled with active reabsorption of glucose, amino acids, other organic anions, and PO_4^{3-} are transported through specific symporters. The exchange with H^+ happens in the PT cells, which secrete H^+ with the help of carbonic anhydrase (*CAse*). H^+ ion exchanges with Na^+-H^+ antiporter located in the luminal membrane and forms H_2CO_3 by combining with HCO_3^-. This H_2CO_3 is broken into H_2O + CO_2 by brush border *CAse*; both H_2O and CO_2 diffuse inside the cell and recombine to form H_2CO_3 with H^+. The dissociated HCO_3^- in the cell is transported to cortical extracellular fluid (ECF) by basolateral membrane, Na^+- HCO_3– symporter resulting in the net reabsorption of $NaHCO_3$. The HCO_3^- acetate, PO_4^- amino acid, and other anion reabsorption produces a passive driving force for Cl^- to diffuse through the para-cellular pathway.

Ascending limb of loop of Henle: In the medullary portion, a distinct terminal membrane carrier transports ions in the stoichiometric ratio of Na^+-K^+-$2Cl^-$ and is non-electrogenic. The Na^+ that enters the cell is pumped to the ECF by Na^+-K^+ ATPase at the basolateral membrane. In addition, a Na^+-Cl^- symporter moves Cl^- down its electrochemical gradient in the ECF and moves Na^+ along.

Cortical diluting segment of loop of Henle: Absorbs salt through Na^+-Cl^- symport.

Distal tubule and collecting duct: In DT and collecting duct Na^+ is again actively reabsorbed; the cation–anion balance being maintained partly by passive Cl^- diffusion and partly by secretion of K^+

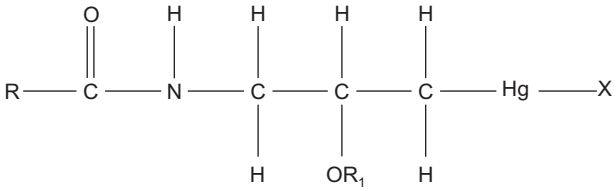
and H^+. Absorption of Na^+ at this site occurs through a specific amiloride sensitive Na^+ channel, and is controlled to a large extent by aldosterone. The luminal membrane provides an active secretory pump for H^+, which is again governed by the movement of Na^+ in reverse diffusion.

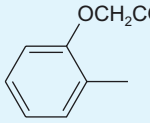
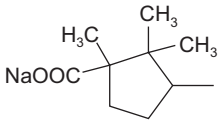
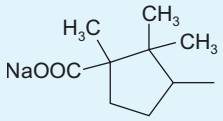
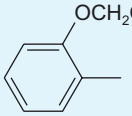
These are the processes of renal physiology for the reabsorption of water and minerals into the body. Blocking of the symporters and antiports with various drugs provides the diuretic effect according to the site of action.

CLASSIFICATION

Diuretics may be classified under the following two categories:

I. Mercurial diuretics

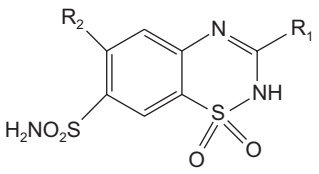


Name	*R*	*R_1*	*X*
Mersalyl		$-CH_3$	Theophylline
Mercurophyllin		$-CH_3$	Theophylline
Mercaptomerin		$-CH_3$	$-SCH_2COOH$
Chloromerodrin	$-NH_2$	$-CH_3$	$-Cl$
Merethoxyline		$-CH_2CH_2OCH_3$	$-OH$
Meralluride	$NaOOCCH_2CH_2CONH-$	$-CH_3$	$-OH$

II. Non-mercurial diuretics

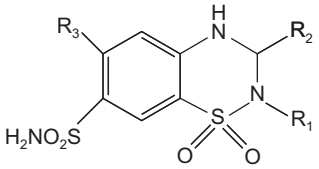
The non-mercurial diuretics may be classified on the basis of their chemical structure as follows:

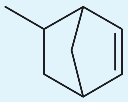
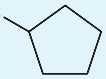
a. Thiazide derivatives



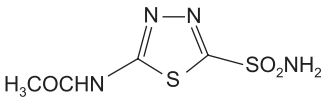
Name	R_1	R_2
Chlorthiazide	–H	–Cl
Benzthiazide	$–CH_2–S–CH_2–C_6H_5$	–Cl
Flumethiazide	–H	$–CF_3$

b. Hydrothiazides

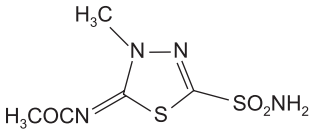


Name	R_1	R_2	R_3
Hydrochlorothiazide	–H	–H	–Cl
Bendroflumethiazide	–H	$–CH_2C_6H_5$	$–CF_3$
Cyclothiazide	–H		–Cl
Hydroflumethiazide	–H	–H	$–CF_3$
Cyclopenthiazide	–H		–Cl
Trichloromethiazide	–H	$–CHCl_2$	–Cl
Buthiazide	–H	$–CH_2CH(CH_3)_2$	–Cl
Methyclothiazide	$–CH_3$	$–CH_2Cl$	–Cl
Polythiazide	$–CH_3$	$–CH_2–S–CH_2–CF_3$	–Cl

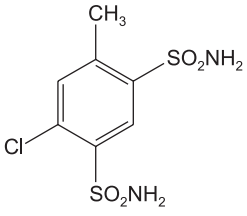
c. Carbonic anhydrase (CAse) inhibitors



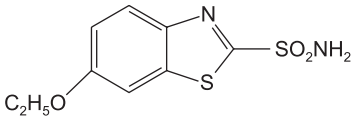
Acetazolamide



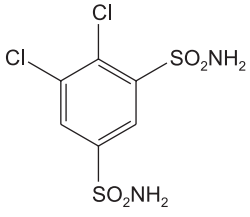
Methazolamide



Disulphamide

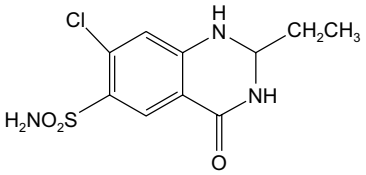


Ethoxazolamide

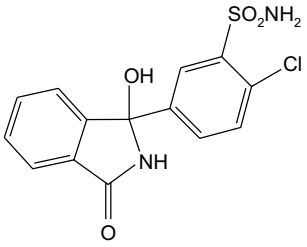


Dichlorophenamide

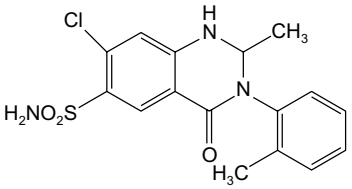
d. Sulphonamide diuretics



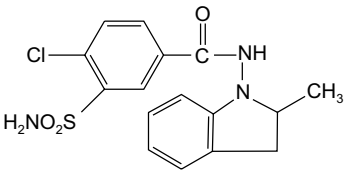
Quinethazone (quinazolinones)



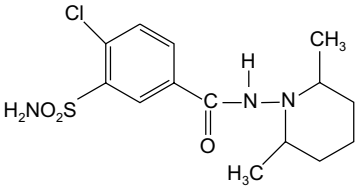
Chlorothalidone



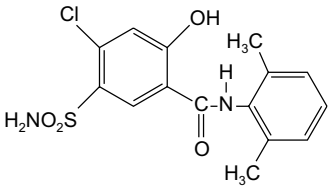
Metolazone



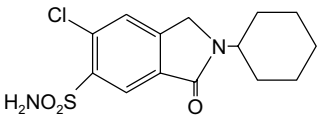
Indapamide (benzhydrazide)



Clopamide (benzhydrazide)

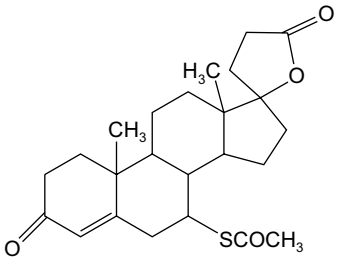


Xipamide (salicylanilide)

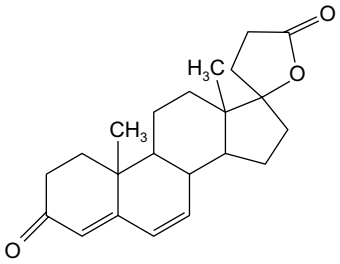


Clorexolone (oxoisoindoles)

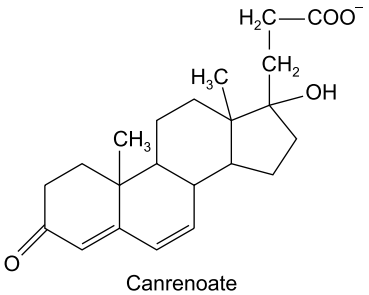
e. Aldosterone inhibitors



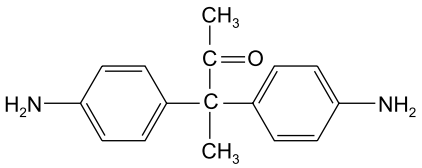
Spironolactone



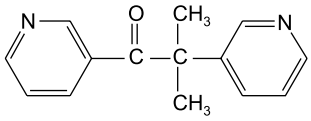
Canrenone



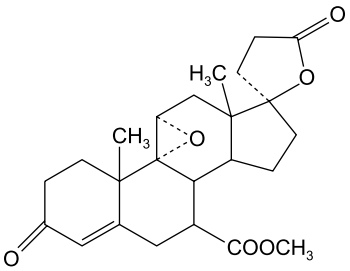
Canrenoate



Amphenone B

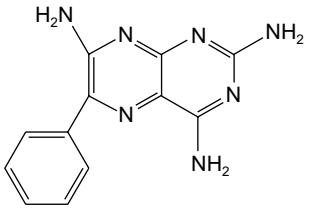


Metyrapone

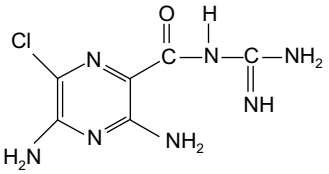


Eplerenone

f. Pteridine derivatives and related compounds

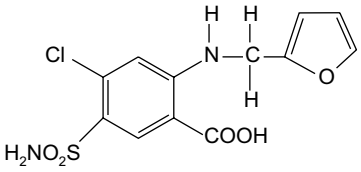


Triamterene

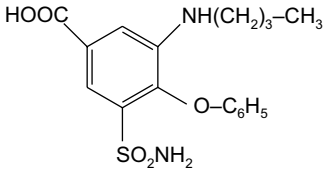


Amiloride

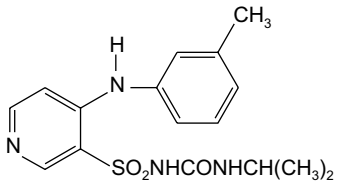
g. Sulphomoyl benzoic acid derivatives



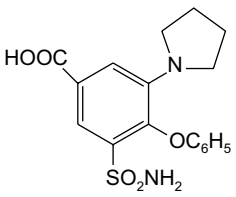
Furosemide



Bumetanide

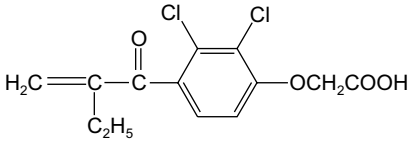


Toresemide

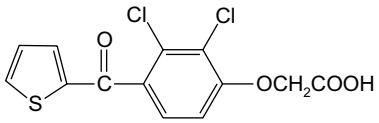


Piretanide

h. Phenoxyacetic acid derivatives

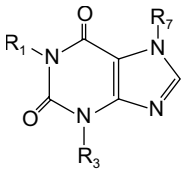


Ethacrynic acid



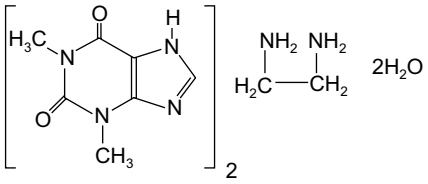
Ticrynafen

i. Purine or xanthine derivatives

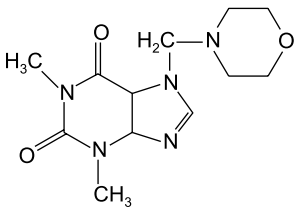


Name	R_1	R_3	R_7
Caffeine	$-CH_3$	$-CH_3$	$-CH_3$
Theophylline	$-CH_3$	$-CH_3$	–H
Theobromine	–H	$-CH_3$	$-CH_3$

Aminophylline

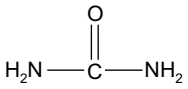


Xanturil

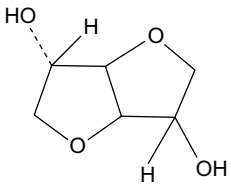


j. Osmotic diuretics

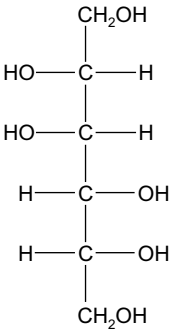
Sodium and potassium salt, urea, sucrose, mannitol, trometamol, sodium acid phosphate, potassium acetate, and glycerine are the osmotic diuretics.



Urea



Isosorbide



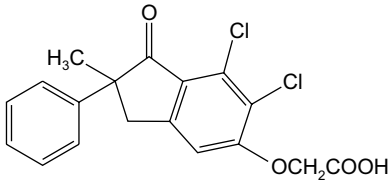
Mannitol

k. Acidic diuretics

Ammonium chloride is a acidic diuretic.

l. Uricosuric diuretics

i. Indacrinone



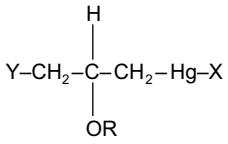
m. Miscellaneous

Example: Muzolimine

SYNTHESIS AND DRUG PROFILE

I. Mercurial diuretics

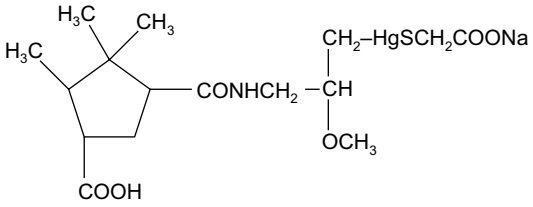
Calomel was used by Paracelsus in the 16th century as a diuretic. Most mercurial diuretics have the same general structure, which is a chain of at least three carbon atoms with one atom of mercury at one end of the chain. The group R is hydrophilic in nature, which determines the distribution and late excretion of the compound. The nature of α-substituent affects the toxicity of the compound, irritation at the site of injection, and rate of absorption.



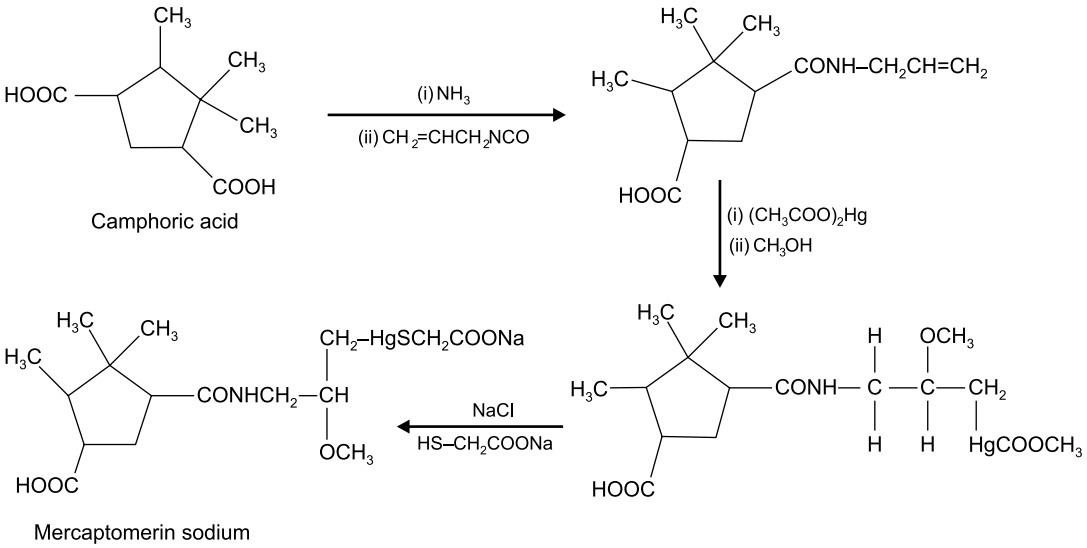
X—OH, halide or heterocyclic moiety
Y—Substituted side chain or aromatic function
R—Methyl group

Mode of action: These drugs primarily inhibit Na^+- K^+-2Cl *co-transporter* in the ascending limb of Henle's loop and produce acidic urine. It involves in the interactions with sulfhydryl enzymes in kidney tubules.

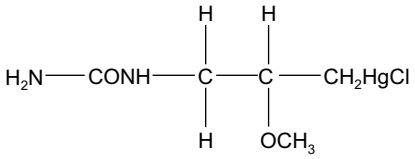
i. Mercaptomerin sodium



Synthesis

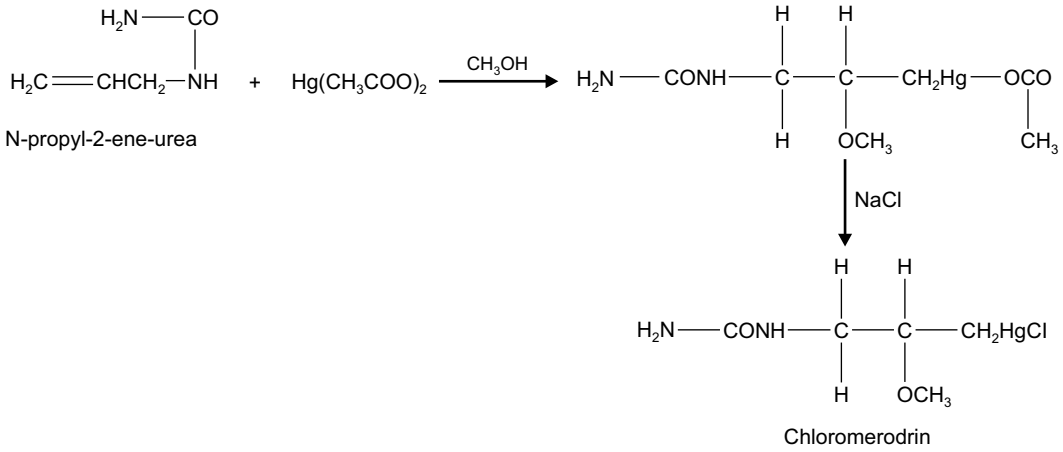


ii. Chloromerodrin



Chloro-(2-methoxy-3-uriedopropy1)-mercury

Synthesis



Uses: It is used in the treatment of congestive heart failure due to oedema, chronic nephritis, ascites of liver diseases, and nephrotic oedema.

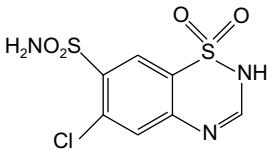
Dose: The usual oral dose is 18.3 to 73.2 mg per day (= 10 to 40 mg of mercury per day).

II. Non-mercurial diuretics

a. Thiazides

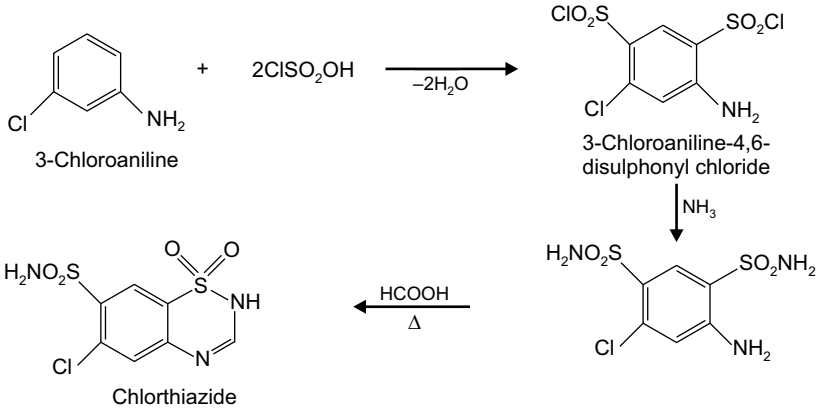
Mode of action of thiazides and hydrothiazides: The sites of action for these drugs are cortical diluting segment or DT. Here they inhibit Na^+-Cl^- symport at the luminal membrane.

i. Chlorthiazide



6-Chloro-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

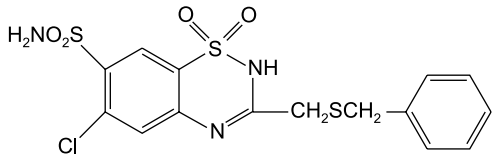
Synthesis



Properties and uses: Chlorthiazide is a white crystalline powder, soluble in dilute solutions of alkali hydroxides, slightly soluble in water and in alcohol and sparingly soluble in acetone. It is a prototype benzothiadiazine derivative, used in the treatment of oedema associated with congestive heart failure, renal, and hepatic disorders.

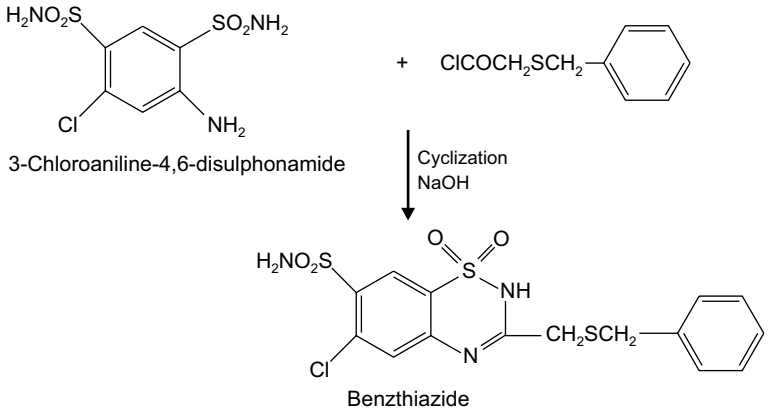
Assay: Dissolve the sample in dimethylformamide and titrate against 0.1 M tetrabutylammonium hydroxide in 2-propanol. Determine the end point potentiometrically.

ii. Benzthiazide (Exna, Aquataq)



3-[(Benzylthio)methyl]-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis

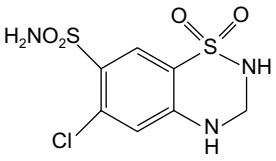


Properties and uses: It is a white crystalline powder with a characteristic odour and taste. Benzthiazide is soluble in water, alcohol, chloroform or ether, and in alkaline solutions. It is used in the treatment of oedema associated with congestive heart failure, renal, and hepatic disorders.

Dose: Usually as diuretic initial dose is 50 to 200 mg per day; maintenance, 50 to 150 mg per day; usual, antihypertensive, initial, 50 mg twice/day; maintenance, maximal dose of 50 mg thrice daily.

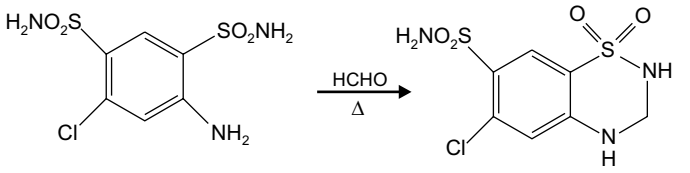
b. Hydrothiazides

i. Hydrochlorthiazide (Hydride, Aquazide, Bpzide)



6-Chloro-3,4-dihydro-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis



3-Chloroaniline-4,6 -disulphonamide

Hydrochlorthiazide

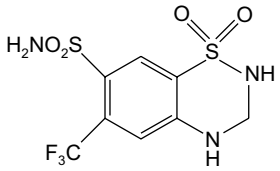
Properties and uses: Hydrochlorthiazide is a white crystalline powder, which is soluble in acetone and dilute alkali hydroxide solutions, but sparingly soluble in alcohol. It is similar to chlorothiazide, but it is ten times more potent. Used in the treatment of oedema associated with congestive heart failure, renal, and hepatic disorders.

Assay: Dissolve the sample in dimethyl sulphoxide and titrate against 0.1 M tetrabutylammonium hydroxide in 2-propanol. Determinine the end point potentiometrically.

Dose: 25 to 200 mg per day; usually 50 mg once or twice daily.

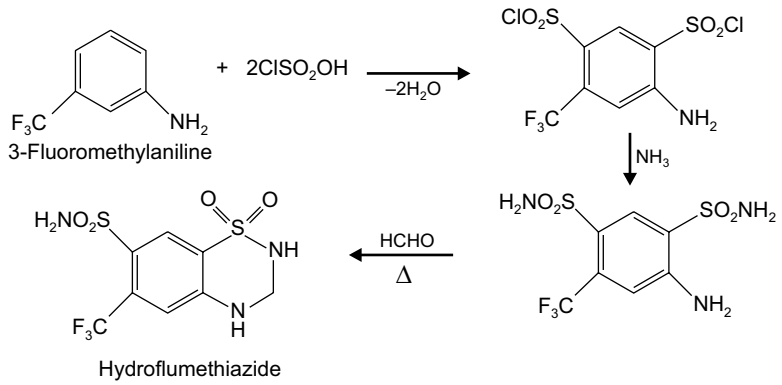
Dosage forms: Hydrochlorthiazide tablets IP, BP, co-amilozide oral solution BP, co-amilozide tablets BP, co-triamterzide tablets BP.

ii. Hydroflumethiazide (Naturetin, Neonaclex)



3,4-Dihydro-6(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis



3-Fluoromethylaniline

Hydroflumethiazide

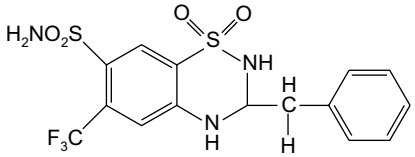
Properties and uses: Hydroflumethiazide is a white crystalline powder, practically insoluble in water and ether, soluble in ethanol. It is a potent oral thiazide diuretic, used in the management of oedema associated with cardiac failure, premenstrual tension, and hepatic cirrhosis.

Assay: Dissolve the sample in anhydrous pyridine and titrate against 0.1 M tetrabutylammonium hydroxide. Determine the end point potentiometrically.

Dose: 25 to 200 mg, usually 50 to 100 mg daily.

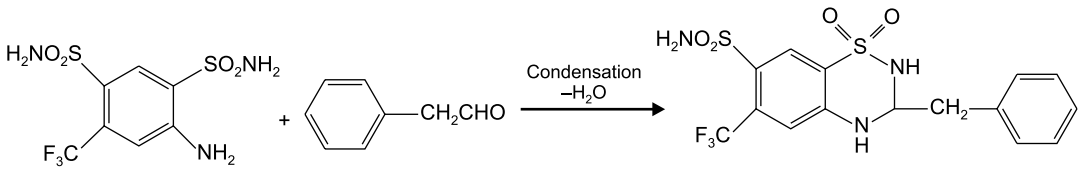
Dosage forms: Hydroflumethiazide tablets BP.

iii. Bendroflumethiazide (Diucardin, Saluron)



3-Benzyl-3,4-dihydro-6(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis



3-Amino-trifluoromethylcoo benzene-4,6-disulphonamide + Phenyl acetaldehyde → Bendroflumethiazide

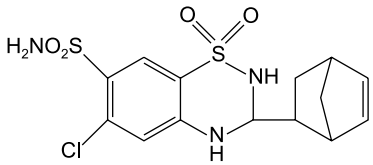
Properties and uses: Bendroflumethiazide is a white crystalline powder, practically insoluble in water, soluble in acetone and ethanol. A potent orally effective thiazide diuretic possesses both diuretic and antihypertensive actions.

Assay: Dissolve the sample in dimethyl sulphoxide and titrate against 0.1 M tetrabutylammonium hydroxide in 2-propanol. Determine the end point potentiometrically.

Dose: Initial, diuretic 5 to 20 mg per day; maintenance, 2.5 to 5 mg daily; as antihypertensive, initially 5 to 20 mg per day, maintenance, 2.5 to 15 mg per day.

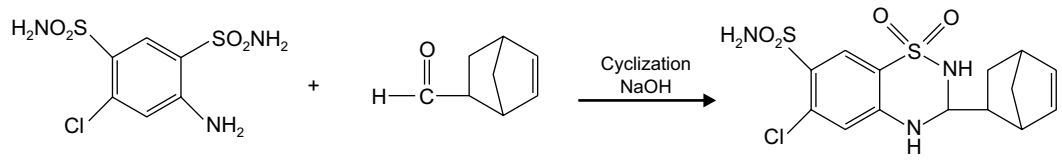
Dosage forms: Bendroflumethiazide tablets BP.

iv. Cyclothiazide (Anhydron, Fludil)



6-Chloro-3,4-dihydro-3-(5-nor-bornen-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis

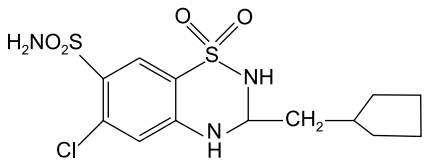


3-Chloroaniline-4,6-disulphonamide 5-Nor-born-2-carbonaldehyde Cyclothiazide

Properties and uses: It exists as white, odourless powder, soluble in alcohol or methanol but insoluble in water, chloroform, or ether. Used as both diuretic and antihypertensive.

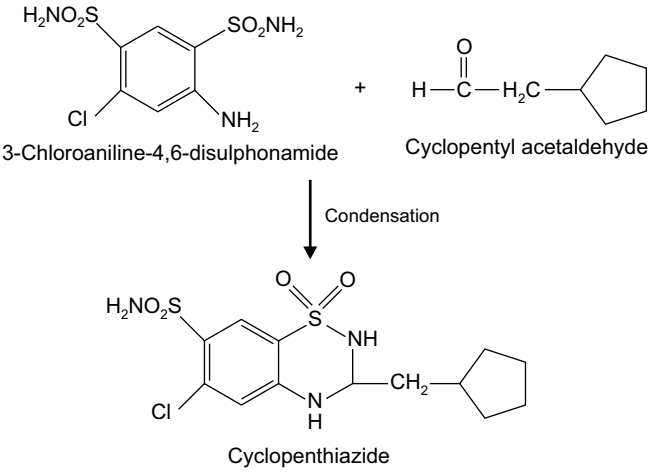
Dose: Usual initial dose as diuretic, 1 to 2 mg/day; maintenance, 1 to 2 mg on alternate days, or two or three times/week; as antihypertensive, 2 mg one to three times daily.

v. Cyclopenthiazide (Navidrex)



6-Chloro-3-(cyclopentylmethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis



3-Chloroaniline-4,6-disulphonamide Cyclopentyl acetaldehyde

Cyclopenthiazide

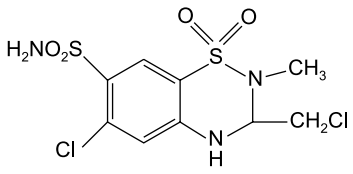
Properties and uses: Cyclopenthiazide is a white powder, practically insoluble in water, soluble in acetone and ethanol, very slightly soluble in ether. It is used in the treatment of oedema associated with congestive heart failure and renal and hepatic disorders.

Assay: Dissolve the sample in butylamine and titrate against 0.1 M tetrabutylammonium hydroxide using magneson solution as indicator.

Dose: For oedema, usual, initial dose is 0.5 to 1 mg per day, reduced to 250 to 500 µg/day or 500 µg on alternate days; for hypertension, usually 250 to 500 µg/day either alone, or in conjunction with other antihypertensive agents.

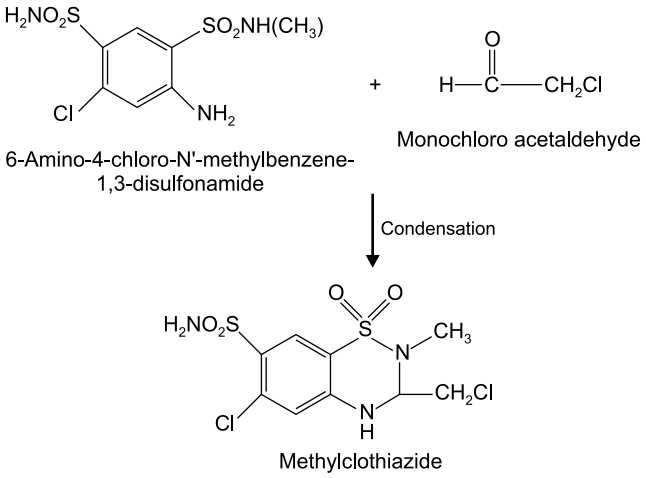
Dosage forms: Cyclopenthiazide tablets BP.

vi. Methylclothiazide (Enduron)



6-Chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

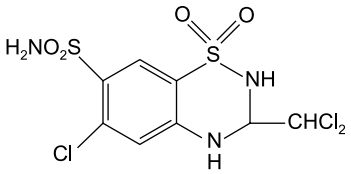
Synthesis



Properties and uses: It is a white crystalline powder, odourless, tasteless, soluble in water, alcohol, chloroform or ether, and acetone. It is effective as a diuretic and antihypertensive agent. It is about 100 times more potent than chlorothiazide.

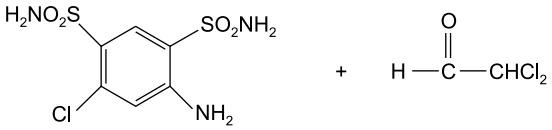
Dose: Usual dose maintenance, as diuretic and antihypertensive is 2.5 to 10 mg once per day.

vii. Trichlormethiazide (Metahydrin, Naqua)



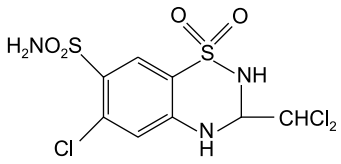
6-Chloro-3-(dichloromethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Synthesis



3-Chloroaniline-4,6-disulphonamide

Condensation

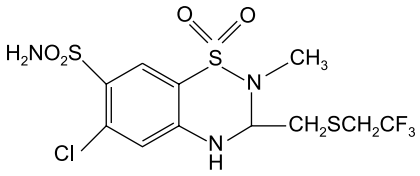


Trichlormethiazide

Properties and uses: It is a white crystalline powder, odourless, sometimes with a characteristic odour, soluble in water, alcohol, chloroform, or ether. It is used as an antihypertensive agent.

Dose: The usual dose is 2 to 4 mg twice daily; maintenance 2 to 4 mg once/day.

viii. Polythiazide (Renese)



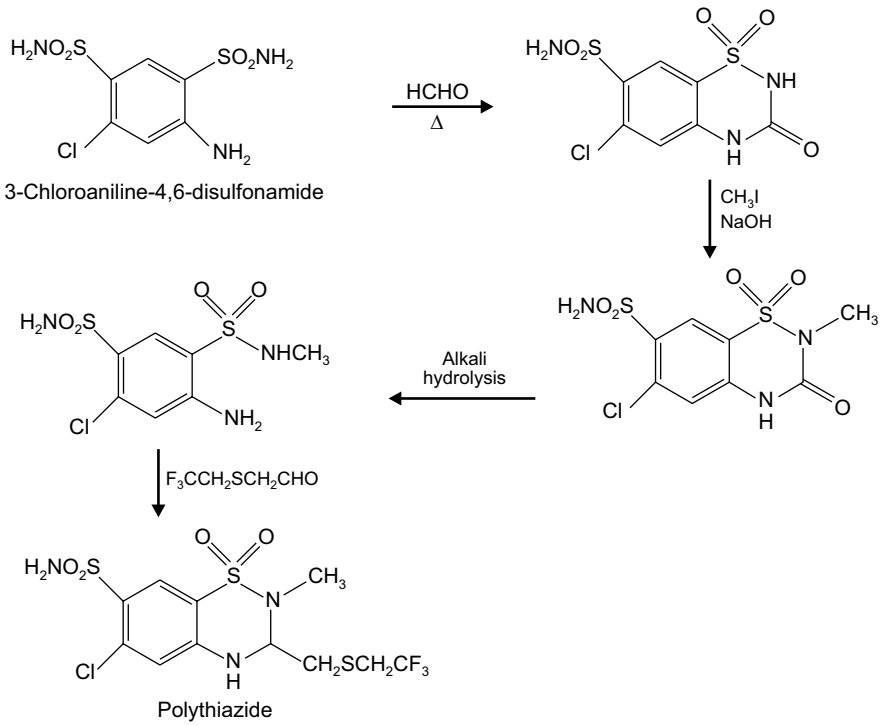
6-Chloro-3,4-dihydro-2-methyl-3-[2,2,2-trifluoroethyl thiomethyl]-2*H*-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide

Properties and uses: It is a white crystalline powder with characteristic odour, soluble in water, alcohol, chloroform, or ether, acetone and aqueous alkali carbonates or hydroxides. Used as potent diuretic and antihypertensive agent.

Assay: Dissolve the sample in methanol and measure the absorbance after suitable dilutions at the maxima of 268 nm using ultraviolet spectrophotometer.

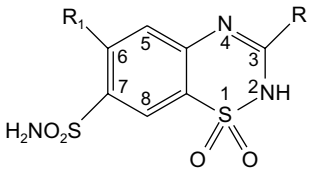
Dose: As diuretic, usually 1 to 4 mg/day; as antihypertensive, 2 to 4 mg as required.

Synthesis



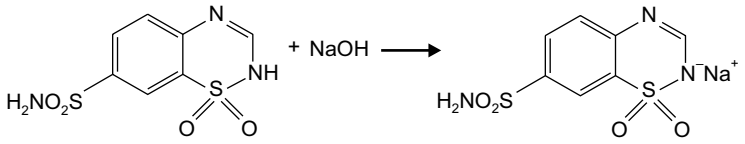
Dosage forms: Polythiazide tablets BP.

SAR of Thiazide Diuretics



- The 2nd position can tolerate the presence of small alkyl groups such as CH_3.
- Substituents with hydrophobic character in the 3rd position increases saluretic activity 1000 times. Substituents include $–CH_2Cl$, $–CHCl_2$, $–CH_2C_6H_5$, $–CH_2S$, $–CH_2$ $–C_6H_5$. The increase in saluretic activity correlates with the lipid solubility.
- Saturation of double bond between the 3rd and 4th position of nucleus increases the diuretic activity approximately 3-fold to 10-fold. Example, hydrochlorthiazide.
- Hydrogen atom at the 2nd position is more acidic due to the presence of neighbouring electron withdrawing the sulphone group.
- A free sulphamoyl or potentially free sulphamoyl group at 7th position is essential for activity. N^7-caproyl chlorthiazide is excreted as chorothiazide, the loss of sulphamoyl group eliminates the diuretic effect, but not the antihypertensive action. Example, diazoxide.
- Direct substitution of the 4th, 5th, or 8th position with an ethyl group usually results in diminished diuretic activity.

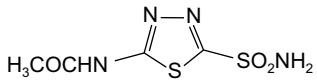
- Substitution of the 6th position with an activating group is essential for diuretic activity. The substituents include Cl, Br, and CF_3 groups.
- The acidic protons make positive the formation of water-soluble sodium salt that can be used for intravenous administration of the diuretics.



c. Carbonic Anhydrase (CAse) inhibitors

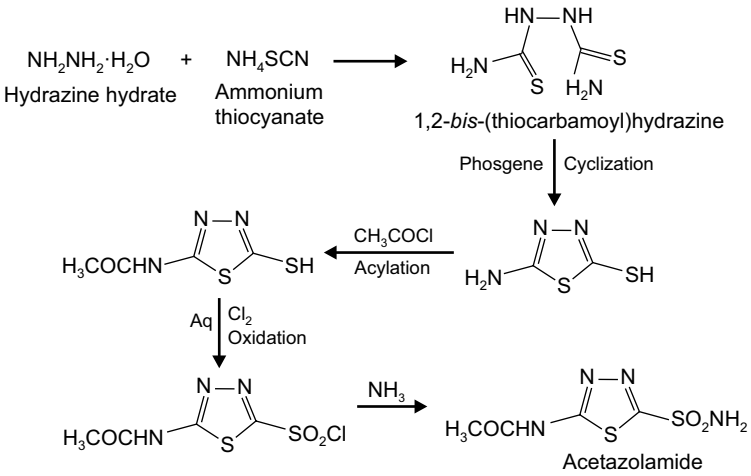
Mode of action: *CAse* is an enzyme that is present in the PT that catalyses the reversible reaction, $H_2O + CO_2 \leftrightarrow H_2CO_3$, carbonic acid spontaneously ionizes as $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$. *CAse* inhibitors reversibly inhibits *CAse* resulting in the slowing of hydration of CO_2 and decrease the availability of H^+ to exchange with luminal Na^+ through Na^+- H^+ antiporter.

i. Acetazolamide (Acetamide, Diamox, Ana)



N-(Sulphonamido-1,3,4-thiadiazol-2-yl)acetamide

Synthesis



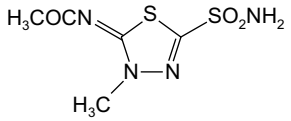
Properties and uses: Acetazolamide is a white crystalline powder, soluble in dilute alkali hydroxide solutions, slightly soluble in water and in alcohol. It is a *CAse* inhibitor effective for the adjunctive treatment of oedema due to congestive heart failure, drug-induced oedema, absence and other centrencephalic epilepsies, chronic simple (open angled) glaucoma, secondary glaucoma when it is desired to lower intraocular pressure prior to surgery. Acetazolamide is employed in the treatment of drug-induced oedema, oedema caused by congestive heart failure, and petitmal epilepsy.

Assay: Dissolve the sample in dimethylformamide and titrate against 0.1 M ethanolic sodium hydroxide. Determine the end point potentiometrically.

Dose: Usual dose is 250 mg two to four times/day.

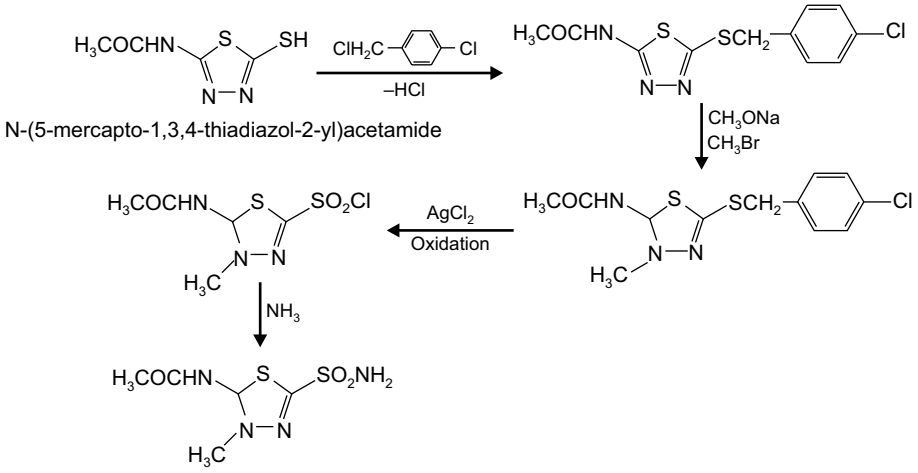
Dosage forms: Acetazolamide tablets IP, BP.

ii. Methazolamide (Neptazane)



N-(4-methyl-2-sulphonamido-1,3,4-thiadiazolin-5-ylidene)acetamide

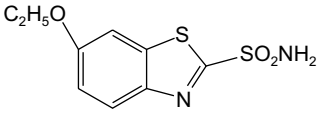
Synthesis



Properties and uses: Methazolamide is available as white or yellow crystalline powder with a slight odour, which is soluble in water, in alcohol or in acetone and dimethyl formamide. It is a more potent CA inhibitor than the prototypic acetazolamide and it is seldom used as a diuretic. Methazolamide displays improved penetration into the eye, a property that contributes to its usefulness in the treatment of glaucoma. It is employed in the treatment of drug-induced oedema, oedema caused by congestive heart failure and petitmal epilepsy.

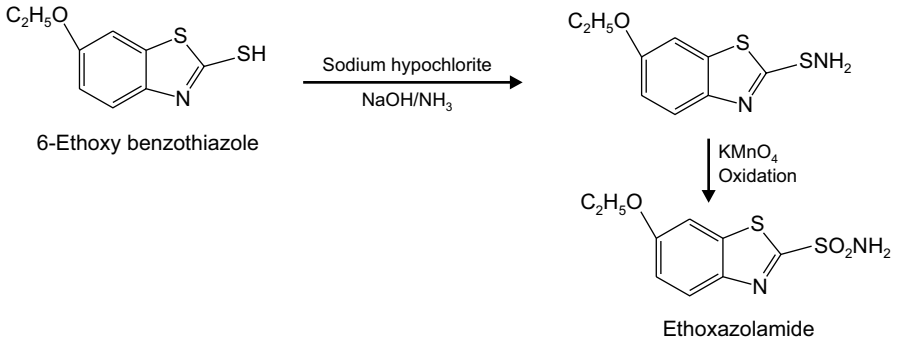
Dose: 100 to 600 mg per day; usually 50 to 100 mg two to three times/day.

iii. Ethoxazolamide (Cardrase)



6-Ethoxy-2-benzothiazole sulphonamide

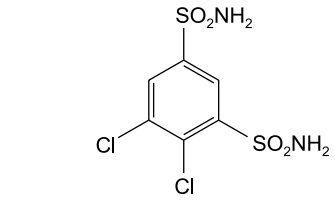
Synthesis



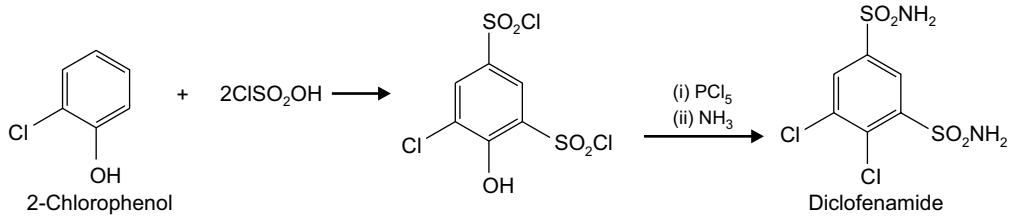
Uses: It is mainly used in acute angle-closure glaucoma, chronic simole glaucoma, and secondary glaucoma.

Dose: Usually 125 mg two to four times per day.

iv. Diclofenamide (Daranide, Oratrol)



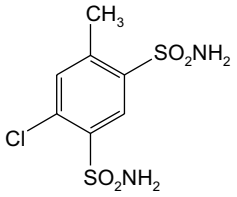
Synthesis



Properties and uses: It exists as white crystalline powder with a characteristic odour, soluble in water, sodium hydroxide, alcohol, and ether. Used as a diuretic and for the treatment of primary and the acute phase of secondary glaucoma. It produces less acidotic refractoriness to diuretic action than acetazolamide. It is used for the treatment of both primary and secondary glaucoma.

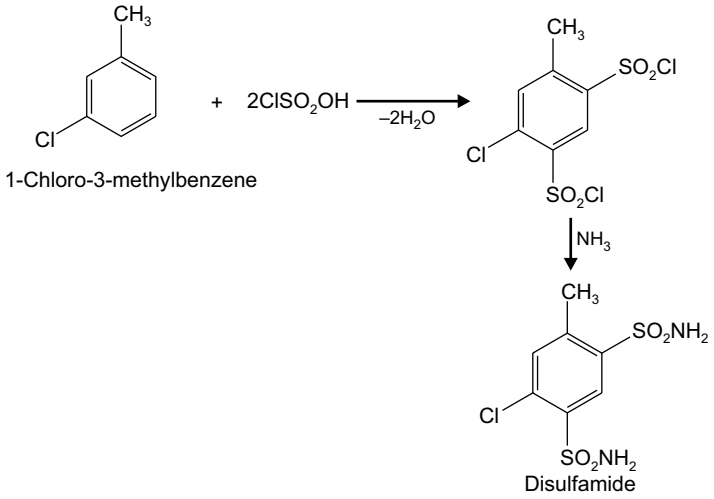
Dose: 50 to 300 mg per day; usually 25 to 50 mg one to three times daily.

v. Disulfamide (Diluen)



5-Chlorotoluene-2,4-disulphonamide

Synthesis



1-Chloro-3-methylbenzene

Disulfamide

Uses: It is used in the treatment of oedema.

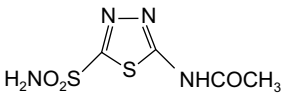
Dose: For oedema, usual, initial dose is 200 mg per day for 5 days a week or on alternate days, reduced to 100 mg per day.

SAR of CAse Inhibitiors

Two groups of *CAse* inhibitors are as follows:

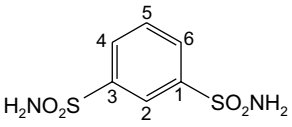
1. Heterocylic sulphonamides
2. *Meta*-disulphamoyl benzene derivatives

1. Heterocylic sulphonamides



- The C-2 sulphamoyl group is important for activity.
- The free sulphamoyl moiety is necessary to bind with Zn^{2+} in the enzyme; hence, substitution of sulphamoyl group gives inactive compound.
- The moiety to which the sulphamoyl group is attached must be aromatic in character.
- The heterocyclic sulphonamides with higher partition coefficient and lowest pK_a value have greatest *CAse* inhibitory and diuretic activites. Example, acetazolamide, methazolamide.
- *N*-alkylation with methyl group on ring N- of acetazolamide yields active compound (methazolamide).

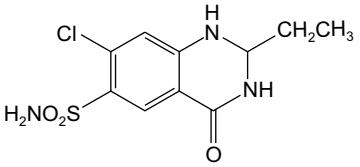
2. *m*-Disulphamoyl benzene derivatives



- *m*-Disulphamoyl benzene do not have diuretic activity.
- Substituted *m*-sulphamoyl benzene exhibits diuretic activity.
- The unsubstituted sulphamoyl moiety is essential for the activity; any substitution leads to affect the potency of the compound.
- The sulphamoyl moiety can be replaced with similar electrophilic groups (e.g. carboxyl, carbamoyl) that may increase the potency of the compound.
- Maximum diuretic activity is obtained when 4th is substituted by Cl, Br, CF_3, or NO_2 group.
- Substitution of amino group at 6th position increases aleuronic activity, but decreases *CAse* inhibitor activity.

d. Sulphonamide derivatives

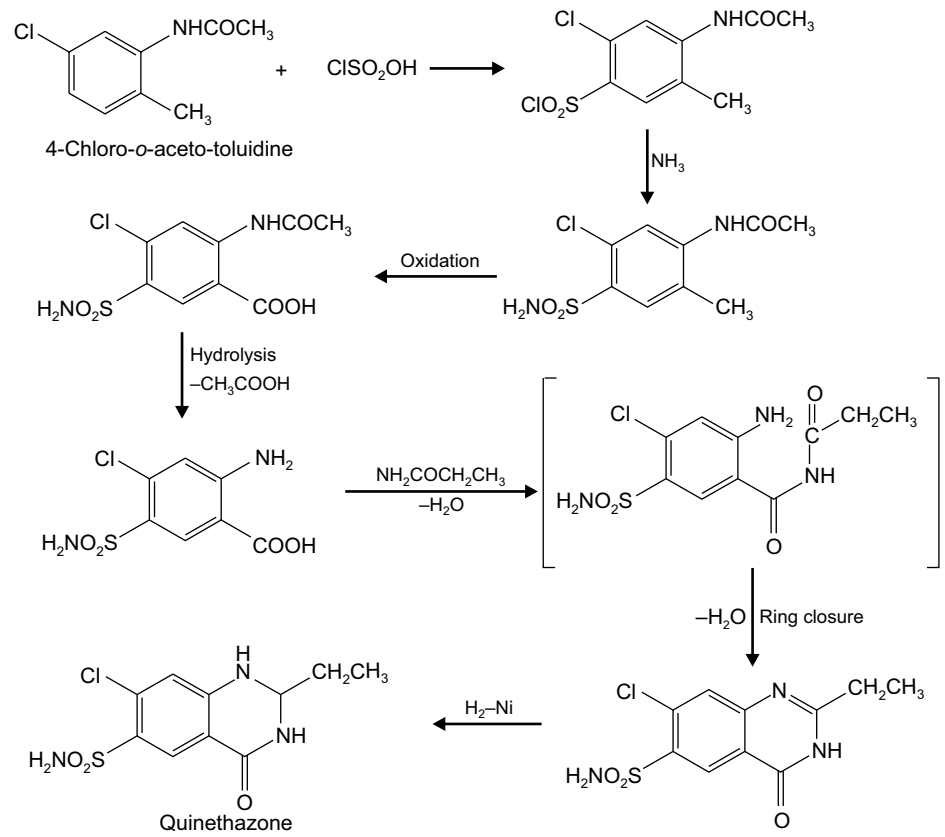
i. Quinethazone (Hydromox)



7-Chloro-2-ethyl-1,2,3,4-tetrahydro-
4-oxo-6-quinazoline sulphonamide

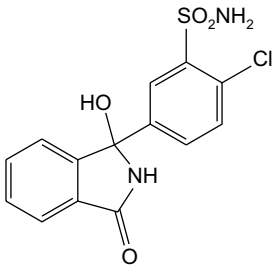
Properties and uses: Quinethazone is a quinazoline derivative with the effect similar to 6-thiazide. It is a yellowish white, odourless, crystalline powder, soluble in water and alcohol and freely soluble in solutions of alkali hydroxides and carbonates. Replacement of the ring sulphone group in thiazide by carbonyl yields quinazolones. These compounds have same diuretic response as the thiazides. The most potent compound of the series, quinethazone have high Na^+/K^+ excretion ratio. Used as both diuretics and antihypertensive.

Synthesis



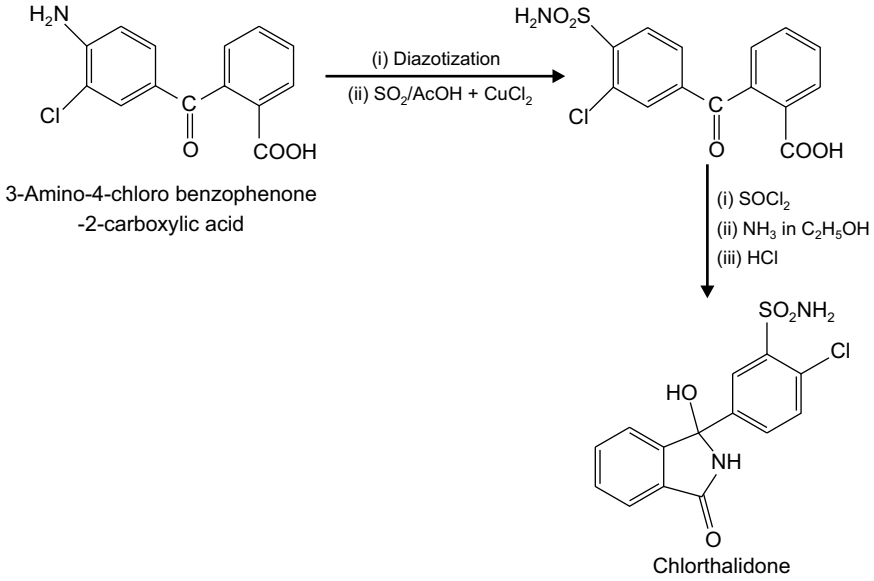
Dose: 50 to 200 mg/day; usually 50 to 100 mg once daily.

ii. Chlorthalidone (Hygroton)



2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulphonamide

Synthesis



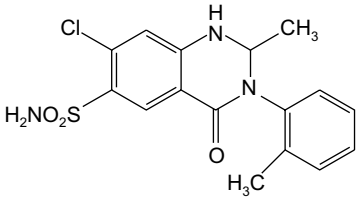
3-Amino-4-chloro benzophenone -2-carboxylic acid

Chlorthalidone

Properties and uses: Chlorthalidone is an orally effective non-thiazide diuretic. It is an adjunct in oedema associated with congestive heart failure and is used in the treatment of oedema associated with obesity, pregnancy, renal disease, hepatic cirrhosis, premenstrual syndrome, and in congestive heart failure.

Dose: As diuretic, 50 to 200 mg per day or alternate day; usually 100 mg once daily, as antihypertensive, 100 mg alternate day or 50 mg every day.

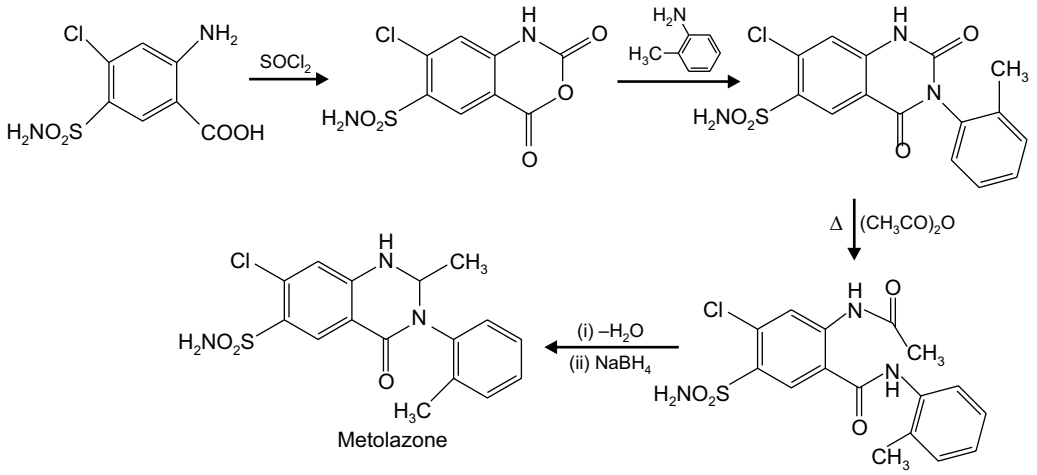
iii. Metolazone (Diulo, Zaroxolyn)



7-Chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazoline sulphonamide

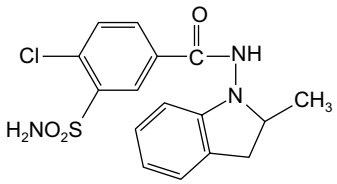
Properties and uses: Metolazone is a colourless, odourless, tasteless, crystalline powder, sparingly soluble in water or alcohol, but soluble in organic solvents. It is a quinazoline-derived non-thiazide diuretic, exerts its diuretic effect in the PT and in the cortical segment of the ascending limb of Henle or distal convoluted tubule. Patients with non-oedematous, stable chronic renal failure, and high dosage of metazoline increases urine flow significantly. It is used for hypertension and oedema accompanying congestive heart failure.

Synthesis



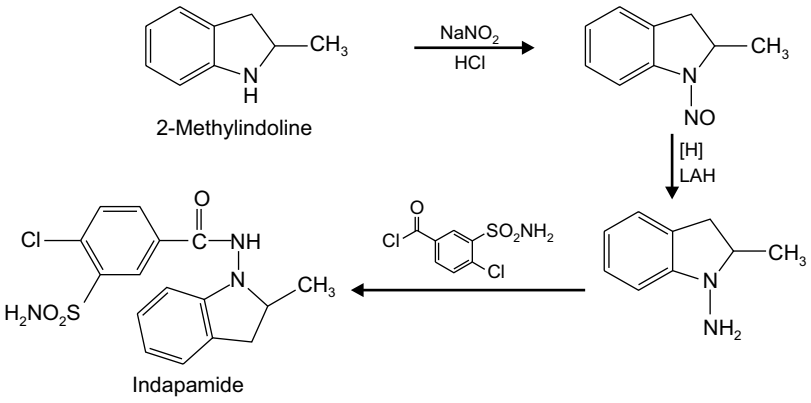
Dose: Usual, adult oral dose for oedema of cardiac failure is 5 to 10 mg once daily; oedema of renal disease, 5 to 20 mg once daily; mild essential hypertension, 2.5 to 5 mg once daily.

iv. Indapamide



3-(Aminosulphonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)-benzamide

Synthesis

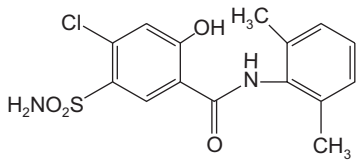


Properties and uses: Indapamide is a white powder, practically insoluble in water, and soluble in ethanol. It is an oral diuretic and antihypertensive related to the indolines. Used in oedema associated with congestive heart failure and hypertension.

Assay: It is assayed by adopting liquid chromatography technique.

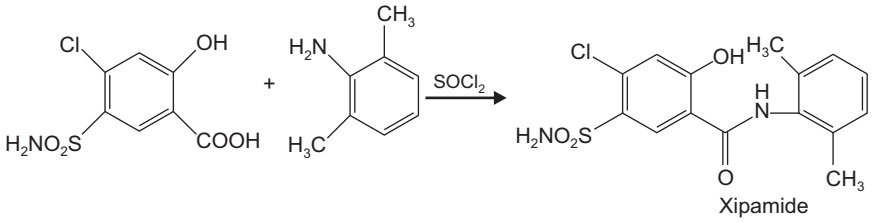
Dosage forms: Indapamide tablets BP.

v. Xipamide



4-Chloro-5-sulphamoyl-2′,6′-salicyloxylidide

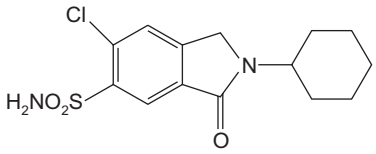
Synthesis



Xipamide

Properties and uses: Used in the treatment of hypertension and oedema.

vi. Clorexolone



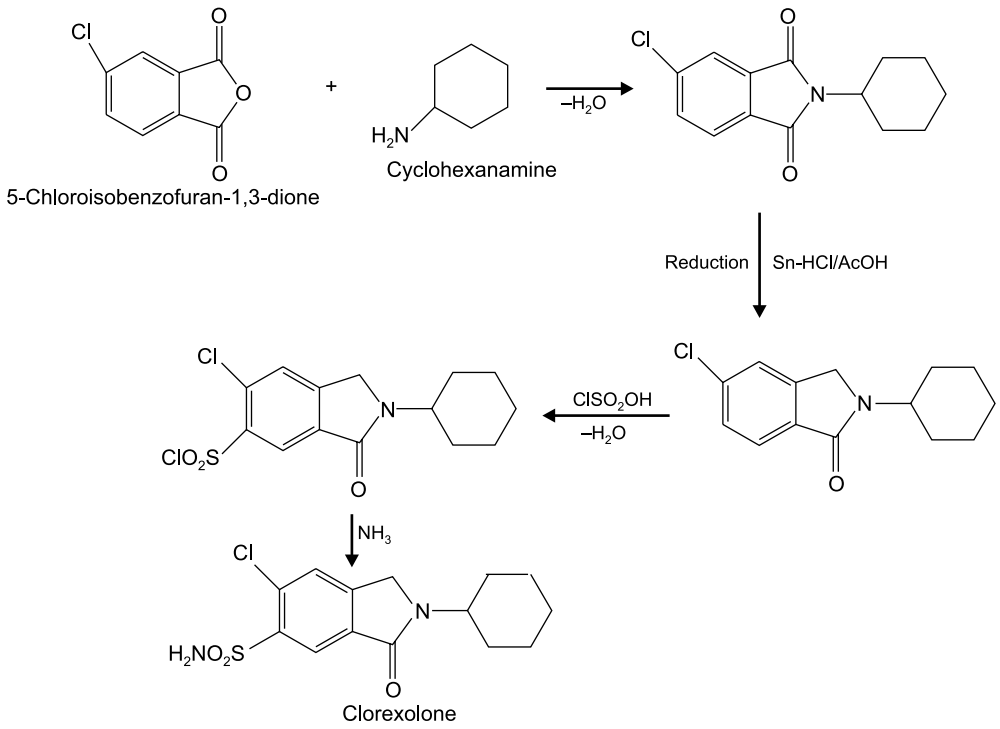
Uses: It is effective in the treatment of congestive heart failure and cirrhosis of the liver.

Sulphonamides

- In pharmaceutical industry, sulphonamide is a magic entity introduced as a main core for various kind of biological activities. Based upon the nature of substitutes, sulphonamides are classified in two major categories such as antibacterial sulphonamides and non-antibacterial sulphonamides.
- All of the antibacterial sulphonamides contain an aromatic amine which is attached to SO_2NHR group.
- The non-antibacterial sulphonamides include antihyperglycemic agents, diuretics, anti-inflammatory and antiseizure agents, HIV-protease inhibitors (amprenavir and fosamprenavir), antiarrhythmic agent (ibutilide), etc.

- The antihyperglycemic sulphonamides are mainly used to treat type 2 diabetes. These sulphonyl urea derivatives are derived from sulphonamides. Examples for antihyperglycemic sulphonamides are chlorpropamide, gliclazide, glibenclamide, glimipride, etc.
- Sulphonamide derived diuretics acts as carbonic anhydrase inhibitors and loop diuretics.

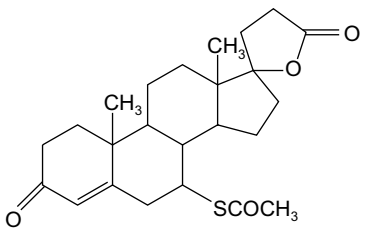
Synthesis



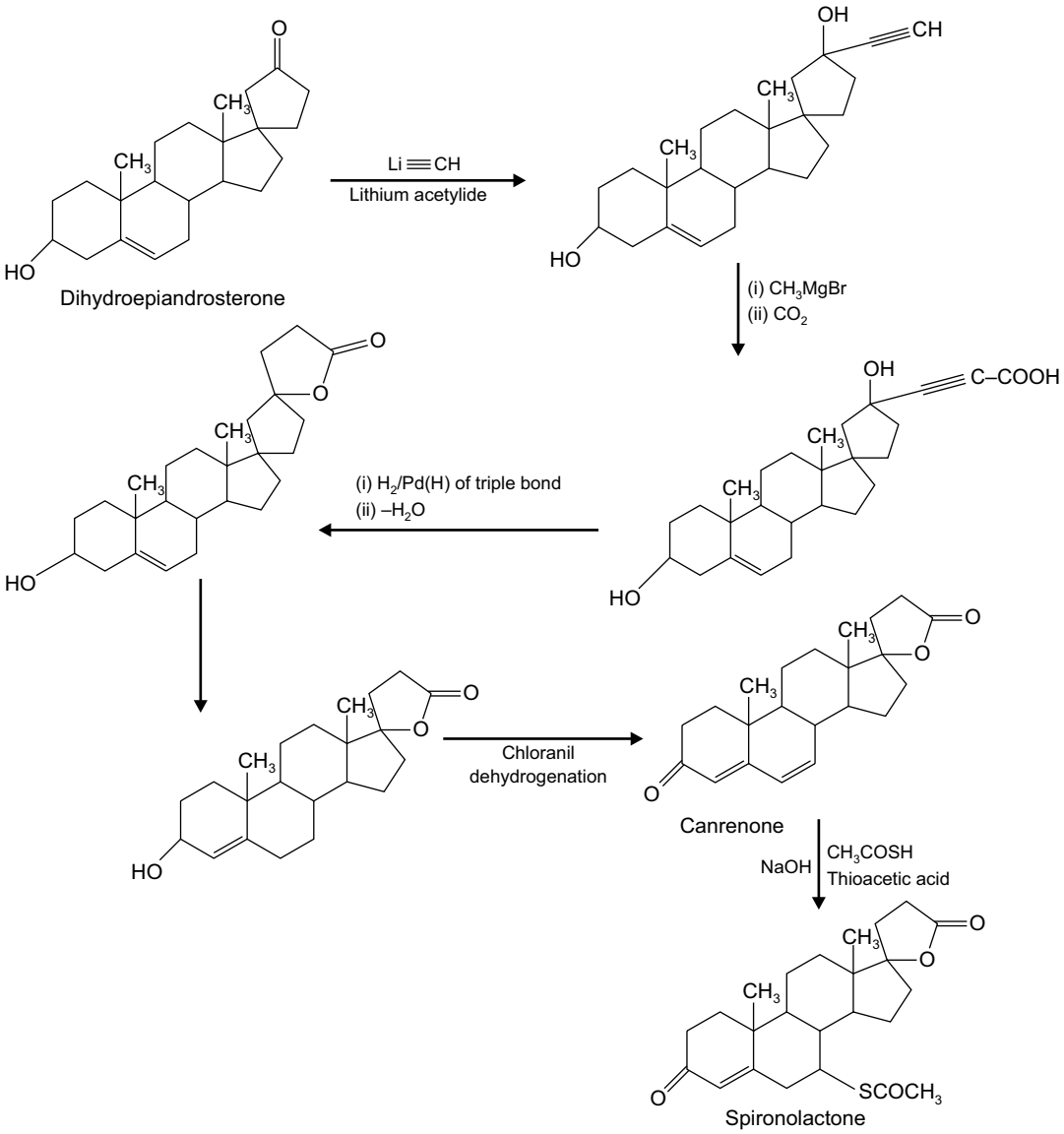
e. Aldosterone antagonists

Mode of action: Aldosterone inhibitors inhibit the aldosterone action on mineralocorticoid receptor, where aldosterone generates aldosterone-induced proteins along with Na^+-K^+-ATPase and amiloride sensitive Na^+ channels that lead to the reabsorption of Na^+. Aldosterone inhibitors limit the reabsorption by binding with mineralocorticoid receptor. Spironolactone is the only available aldosterone antagonist; a metabolite of spironolactone, canrenone is also active.

i. Spironolactone (Aldactone)



Synthesis



Properties and uses: Spironolactone is a white or yellowish-white powder, practically insoluble in water and soluble in alcohol. It is a synthetic steroid that acts as a competitive antagonist of the potent, endogenous mineralocorticosteroid, aldosterone. It has a slower onset of action than triamterene or amiloride, but its natriuretic effect is slightly greater during long-term therapy. It is indicated in the treatment of essential hypertension, oedema associated with congestive heart failure, hepatic cirrhosis with ascites, the nephritic syndrome and hypokalemia, and in the diagnosis of primary aldosteronism. It is useful in the treatment of cirrhosis of liver, aldosterone-secreting tumours, and high-renin hypertension.

Assay: Dissolve the sample in methanol and measure the absorbance of the solution after suitable dilution at the maxima of 238 nm using ultraviolet-spectrophotometer.

Diuretic-induced hypokalemia: Adult—25–100 mg daily. Child: Neonates—1–2 mg/kg daily; 1 month to 12 years; 1–3 mg/kg daily: 12–18 years: 50–100 mg daily. To be given in 1–2 divided dose. Elderly: Dosing adjustment may be required.

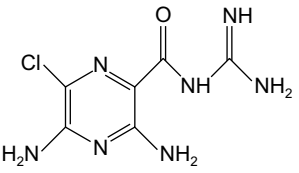
Hirsutism in women: Adult—50–200 mg daily. Elderly: Dosing adjustment may be required.

Dosage forms: Spironolactone tablets IP, BP.

f. Potassium sparing diuretics (Pteridine derivatives and related compounds)

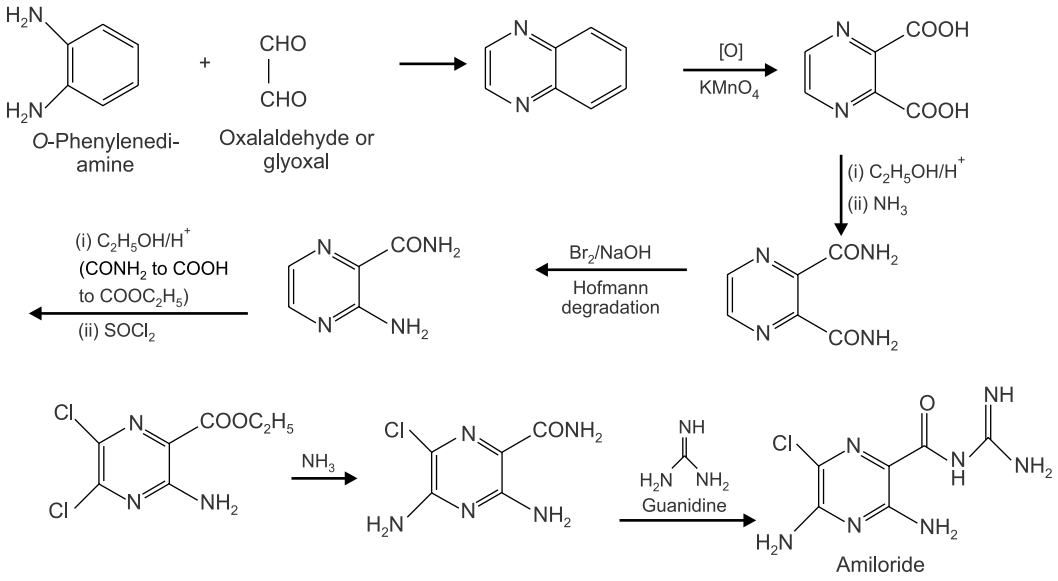
Mode of Action: These drugs act on Na^+ channel from the luminal side and block the actions. Thus, it reduces the lumen negative transepithelial potential difference, which governs K^+ and H^+ secretion.

i. Amiloride



3,5-Diamino-N-(aminoiminomethyl)-6-chlorpyrazine carboxamide

Synthesis

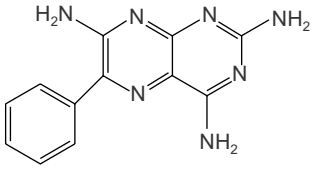


Properties and uses: Amiloride hydrochloride is a pale-yellow to greenish-yellow powder, slightly soluble in water and in anhydrous ethanol. It is a potassium-conserving drug with natriuretic, diuretic and antihypertensive activity. It is an aminopyrazine, considered an open chain analogue of triamterene. It blocks the reabsorption of sodium ion and the secretion of potassium ion. Amiloride is more potent than triamterene.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and ethanol and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

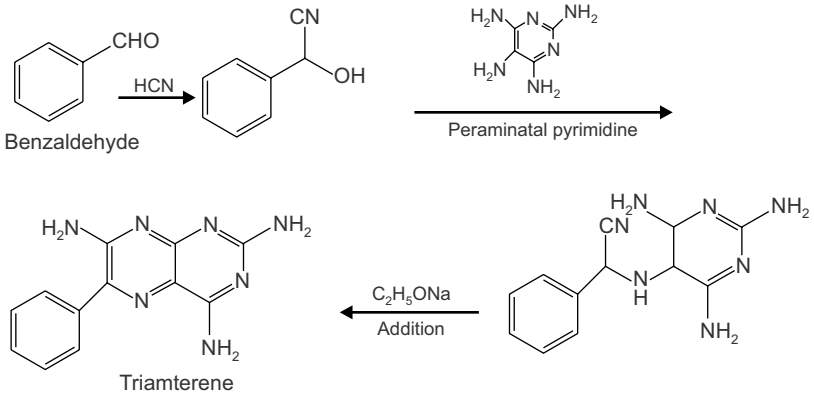
Dosage forms: Amiloride tablets IP, BP, co-amilofruse tablets BP, co-amilozide oral solution BP, co-amilozide tablets BP.

ii. Triamterene (Ditide)



2,4,7-Triamino-6-phenylpteridine

Synthesis



Properties and uses: Triamterene is a yellow crystalline powder, very slightly soluble in water and alcohol. It is a pteridine with structural resemblance to folic acid. Replacement of phenyl group with small basic heterocyclic nucleus such as thiazole and pyridine produces highly active compounds. 2 and 7 phenyl isomers of triamterene were very potent K^+ blockers. Triamterene may be used alone in the treatment of mild oedema associated with congestive heart failure or cirrhosis of the liver with ascites. It is used in the treatment of oedema associated with nephritic syndrome, cirrhosis of liver and congestive heart failure.

Assay: Dissolve the sample in anhydrous formic acid, add anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

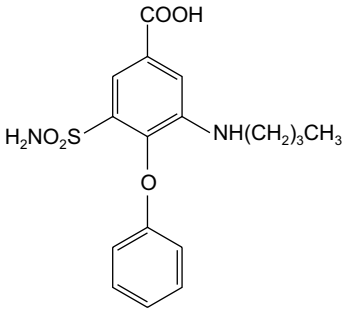
Dose: 100 mg every alternate day to 300 mg per day; usually 100 mg once daily.

Dosage forms: Triamterene capsules IP, BP, co-triamterzide tablets BP.

g. Sulphomoyl benzoic acid derivatives/High ceiling or loop diuretics

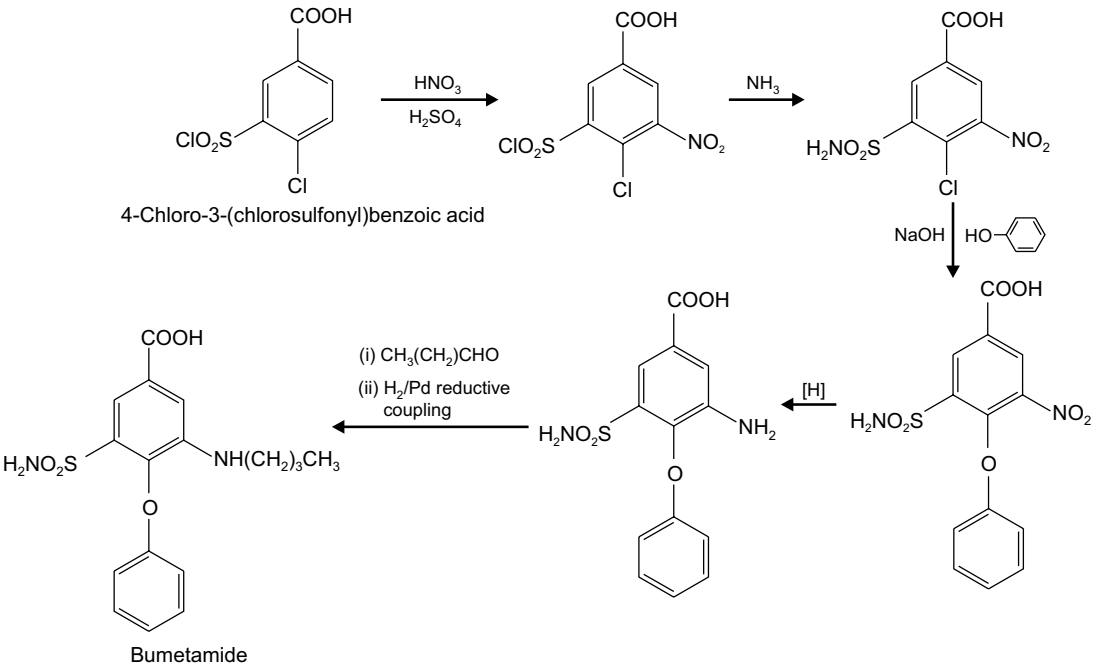
Mode of action: A glycoprotein with 12 membrane-spanning domains has found its function as Na^+-K^+-$2Cl^-$ *co-transporters*. Many epithelia in the loop of Henle performing secretory/absorbing functions, loop diuretics attach to the chloride-binding site of these proteins to inhibit transport functions.

i. Bumetanide (Bumex)



3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid

Synthesis



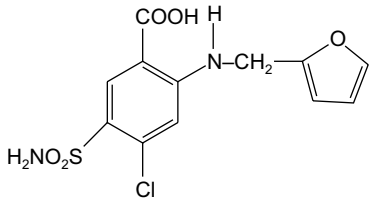
Properties and uses: Bumetanide is a white crystalline powder, practically insoluble in water, soluble in acetone, alcohol, and dilute solutions of alkali hydroxides, slightly soluble in methylene chloride. It is a 3-aminobenzoic acid, metanilamide derivative that is a potent loop diuretic with efficacy and biochemical effects similar to those of furosemide. Used in chronic congestive heart failure, chronic renal failure, chronic hepatic disease, and in the nephritic syndrome. It is used in the treatment of renal insufficiency and for the control and management of acute drug poisoning.

Assay: Dissolve the sample in alcohol and titrate against 0.1 M sodium hydroxide using phenol red solution as indicator until a violet-red colour is obtained. Perform a blank titration.

Dose: By oral 0.5 to 2.0 mg once daily. Parenteral: 0.5 to 1.0 mg intravenously. An equivalent dose of bumetanide is only one-fortieth that of furosemide, and its bioavailability is about twice.

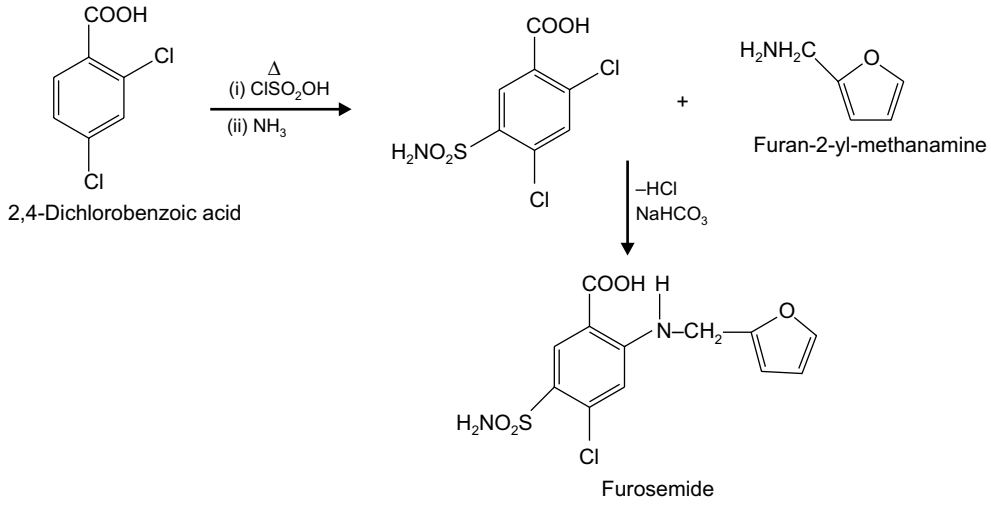
Dosage forms: Bumetanide injection BP, bumetanide oral solution BP, bumetanide tablets BP, Bumetanide and slow potassium tablets BP.

ii. Furosemide



4-Chloro-N-furfuryl-5-sulfamoylanthranilic acid

Synthesis



Properties and uses: Furosemide is a white crystalline powder, practically insoluble in water and in methylene chloride, soluble in acetone and in dilute solutions of alkali hydroxides, sparingly soluble in ethanol. A diuretic chemically related to the sulphonamide diuretics. It is slightly more potent than the organomercurial agents, is orally effective, and its diuretic action is independent of alterations in body acid–base balance. It is used for the treatment of oedema associated with renal disease, nephritic syndrome, cirrhosis of the liver, and congestive heart failure.

Assay: Dissolve the sample in dimethylformamide and titrate against 0.1 M sodium hydroxide using bromothymol blue solution as indicator.

Dosage forms: Furosemide tablets IP, BP, co-amilofruse tablets BP, furosemide injection BP.

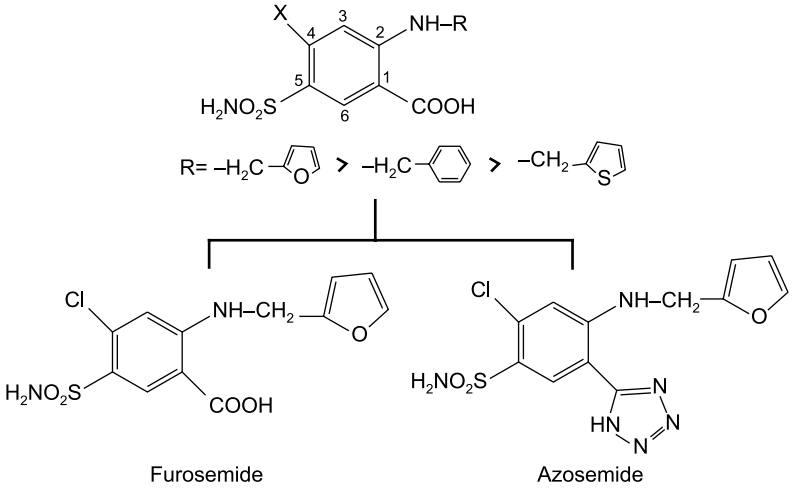
SAR of Loop Diuretics

They are either 5-sulphamoyl-2-amino benzoic acid or 5-sulphamoyl-3-amino benzoic acid derivatives.

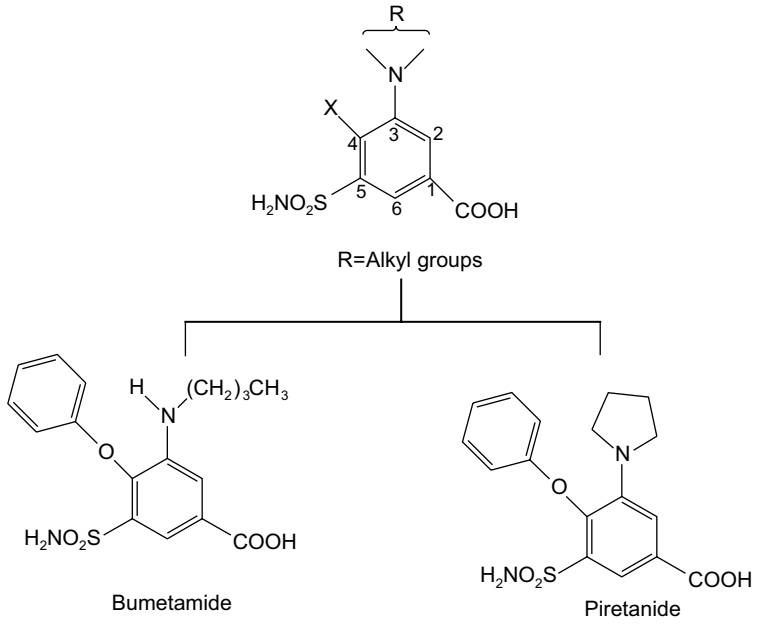
1. The carbonyl group at C-1 provides optimal diuretic activity.
2. The substitution of activating group (X) in the position 4 by Cl, alkoxy, aniline, benzyl, or benzoyl group at 4th position increases the diuretic activity.
3. The presence of sulphamoyl group in the 5th position is essential for activity.

4. The two series of 5-sulphamoyl benzoic acid differ in the nature of the functional group that substituted in 2nd and 3rd position.
5. The presence of furfuryl, phenyl, and thienyl methyl group at 2nd amino group of 5-sulphomoyl 2-amino benzoic acid gives maximum diuretic activity.
6. The wide range of alkyl group can be substituted at 3rd amino group of 5-sulfamoyl-3-amino benzoic acid without modifying the optimal diuretic activity.
7. A molecule with a weakly acidic group to direct the drug to the kidney and an alkylating moiety to react with sulfhydryl groups and lipophilic groups seemed to provide the best combination of a diuretic in the class.

i. 5-Sulphamoyl-2-amino benzoic acid derivatives

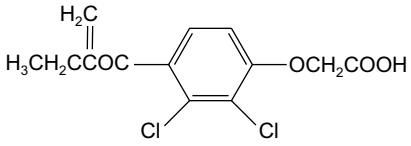


ii. 5-Sulphamoyl-3-amino benzoic acid derivatives



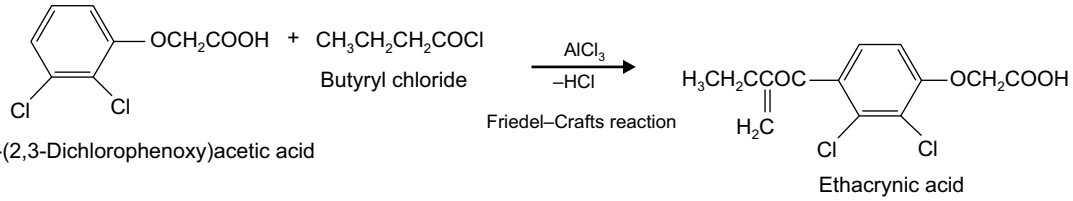
h. Phenoxyacetic acid derivatives

i. Ethacrynic acid



2,3-Dichloro-4-(2-methylene butyryl)phenoxy acetic acid

Synthesis



2-(2,3-Dichlorophenoxy)acetic acid

Ethacrynic acid

Properties and uses: It exists as a white crystalline powder that is odourless, soluble in alcohol, ether, or chloroform and in water, an aryloxyacetic acid derivative that is a potent, short-acting diuretic. It is used in the treatment of oedema caused by congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

i. Purine or Xanthine diuretics

Synthesis and drug profile of caffeine, theophylline, and theobromine are discussed in Chapter 28: CNS Stimulants.

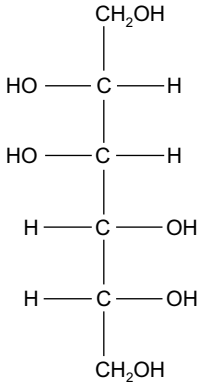
Properties

- The xanthines (caffeine, theophylline, and theobromine) have a weak diuretic activity.
- They have been known for their diuretic action, but currently it is rarely used.
- Aminophylline (theophylline ethylene diamine) is the most used member.
- Theophylline exerts its diuretic action by inhibition of Na^+ reabsorption in the proximal convoluted tubule.
- These drugs increase renal plasma flow, promoting a higher glomerular filtration rate.
- Adverse effects are central nervous system (CNS) stimulation and vomiting.

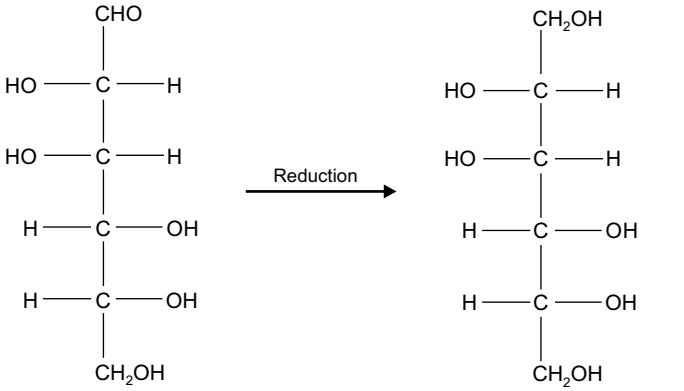
j. Osmotic diuretics

Osmotic diuretics are non-electrolytes, which are freely filtered at the glomerulus and are not significantly reabsorbed from the tubules, and presence of these agents in the urine causes an increase in the electrolytes and volume flow. Mannitol, urea, glycerol, and isosorbide are the four osmotic diuretics, which are freely filtered through the glomerulus and are insignificantly reabsorbed from the tubules; they mainly induce diuresis by inhibiting sodium and water reabsorption in the PTs and the Henle's loop.

i. Mannitol



Synthesis



2,3,4,5,6-Pentahydroxyhexanal — Hexane-1,2,3,4,5,6-hexaol

Properties and uses: Mannitol is a white crystalline powder or granules, soluble in water, very slightly soluble in ethanol. It is most widely used for acute renal failure, cardiovascular operation, and severe traumatic injury with nephrotoxic anticancer agents.

Assay: It is assayed by adopting the liquid chromatography technique

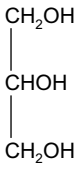
Dosage forms: Mannitol injection IP, mannitol intravenous infusion BP.

ii. Urea

$$NH_2CONH_2$$

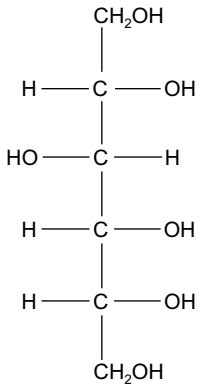
Properties and uses: It is a colourless white, prismatic crystals or a white crystalline powder, odourless with a saline taste, soluble in water, alcohol, methanol, or glycerol, but insoluble in chloroform or ether. It is administered intravenously in a solution containing 30% urea and 5 to 10% dextrose).

iii. Glycerine

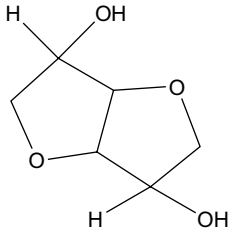


Properties and uses: It is used prior to ophthalmological procedures. Glycerine is an orally active diuretic and obtained from the production of soaps and fatty acids through hydrolysis or by hydration of propylene.

iv. Isosorbide



Sorbitol

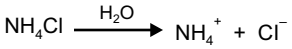


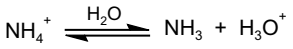
Isosorbide

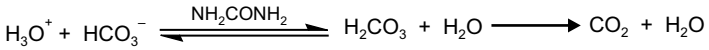
Properties and uses: Isosorbide is given orally to cause a reduction in intraocular pressure. Isosorbide is prepared by acid dehydration of sorbitol.

k. Acidic diuretics

Some inorganic cations produce weak acidiotic diuresis, such as ammonium chloride, ammonium nitrate, and calcium chloride. The mechanism of acidification is represented by the following equations.







Ammonium chloride is metabolized to urea in the liver with the formation of H^+. The excess acid (H^+) is buffered by HCO^-_3 to form carbon dioxide. This leads to an acidification of the urine. An excess Cl^- also occurs in the tubular lumen and takes Na^+ along with it to maintain electrical neutrality.

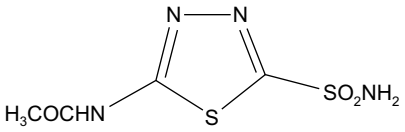
Adverse Effects

Common side effects of diuretics are hypokalemia, hyperglycaemia, hyperuricemia, hyperlipidaemia and hypercalcaemia.

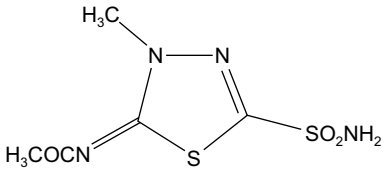
CLASSIFICATION BASED ON PCI SYLLABUS

Carbonic Anhydrase Inhibitors

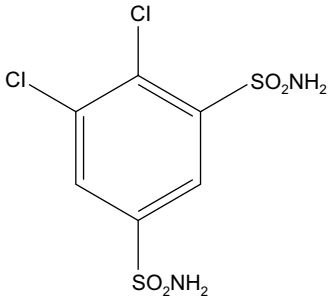
Acetazolamide



Methazolamide

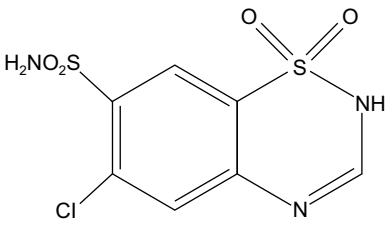


Dichlorphenamide

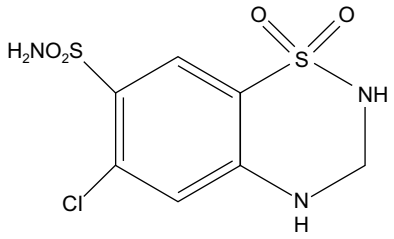


Thiazides

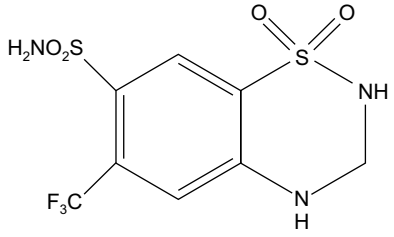
Chlorthiazide



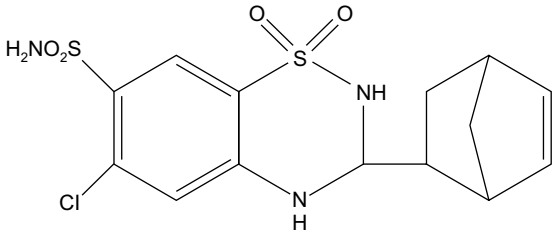
Hydrochlorothiazide



Hydroflumethiazide

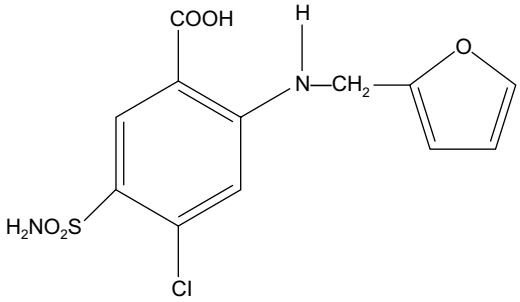


Cyclothiazide

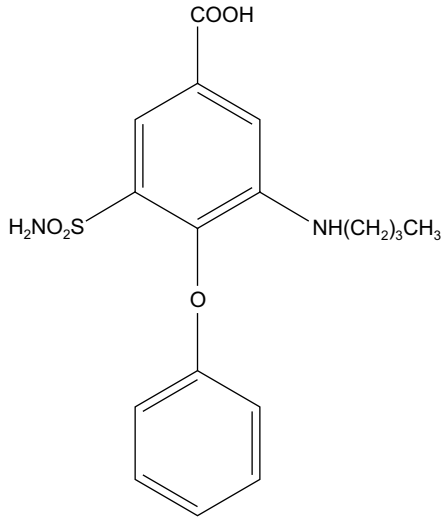


Loop Diuretics

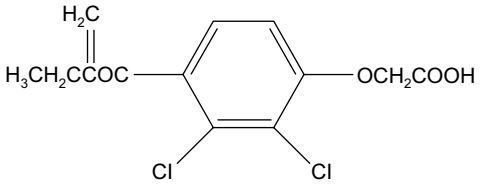
Furosemide



Bumetanide

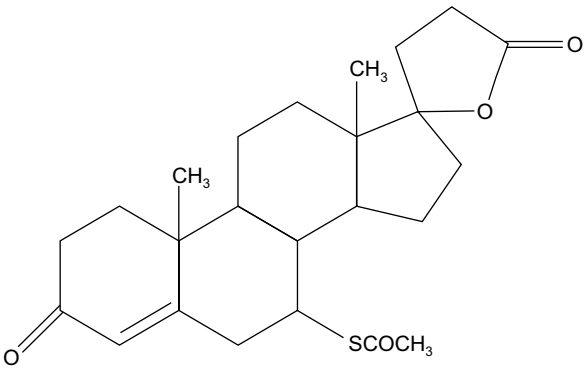


Ethacrynic acid

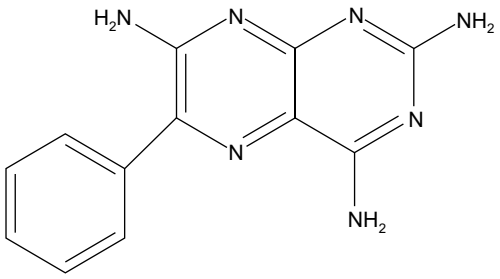


Potassium-sparing Diuretics

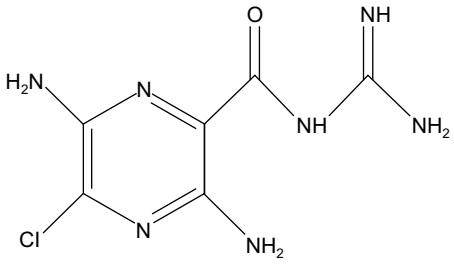
Spironolactone



Triamterene

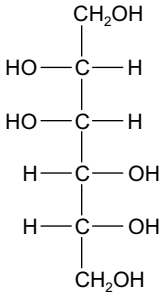


Amiloride



Osmotic Diuretics

Mannitol



PROBABLE QUESTIONS

1. Describe benzothiadiazines (thiazides) as an important class of diuretics. Write the structure, chemical name, and uses of any four official compounds.
2. Define and classify diuretics and write in detail about potassium-sparing diuretics.
3. What are diuretics? Classify diuretics by citing the structure, chemical name, and uses of at least two compounds from each category.
4. Write in detail about carbonic anhydrase inhibitors and aldosterone antagonists.
5. Why do the non-mercurical diuretics have an edge over the mercurial diuretics?

6. Acetazolamide, methazolamide, diclofenamide, and disulfamide are potent carbonic anhydrase inhibitors employed as diuretics. Discuss the structural difference amongst these drugs and give the synthesis of any two compounds.
7. How will you synthesize chlorthalidone, a sulphonamide diuretic.
8. High-ceiling diuretics exert an intense diuresis of relatively short duration (4–6 h) with a rapid onset (30 min). Justify the statement with the help of at least two important members of this class of drugs.
9. Write the SAR of carbonic anhydrase inhibiotors.
10. Write a brief note on the following:
    (a) Aminopteredines, (b) sapironolactone, and (c) phenoxyacetic acid derivatives.
11. How will you synthesize: (a) Furosemide, (b) Disulphamide, and (c) Chloromeridine.
12. With the help of some specific examples describe in detail about the following: (a) Osmotic diuretics and (b) loop diuretics.
13. Describe the mode of action of the following class of diuretics and mention few examples with their structure:
    (a) Thiazides, (b) carbonic anhydrase inhibitors, and (c) mercurial diuretics.

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