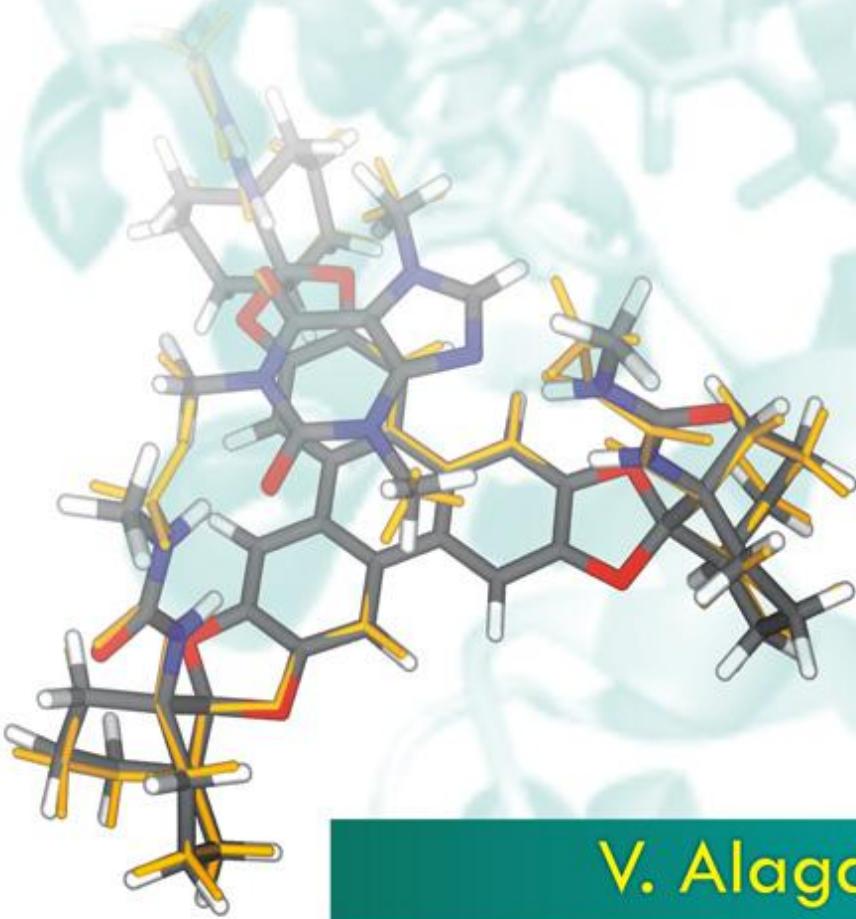




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TEXTBOOK OF

MEDICINAL CHEMISTRY



V. Alagarsamy

TEXTBOOK OF MEDICINAL CHEMISTRY

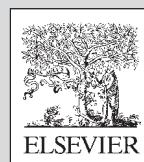
Volume II

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TEXTBOOK OF MEDICINAL CHEMISTRY

Volume II

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Professor and Principal
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Textbook of Medicinal Chemistry, Volume II

Alagarsamy

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Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The authors, editors, contributors and the publisher have, as far as it is possible, taken care to ensure that the information given in this text is accurate and up-to-date. However, readers are strongly advised to confirm that the information, especially with regard to drug dose/usage, complies with current legislation and standards of practice. ***Please consult full prescribing information before issuing prescriptions for any product mentioned in the publication.***

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Preface

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 modeling 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 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 II consists of six sections. The first section is devoted to drugs acting on inflammation and allergy. Sections II to V deal about the drugs acting on different systems of human body such as respiratory system, digestive system, blood and endocrines. Section VI is dedicated to chemotherapy, where detailed discussion from the history of development of antibiotics to the recent drugs approved for HIV infection is provided. In all these sections, chemical, pharmacological, biochemical and toxicological aspects of organic medicinal compounds are described elaborately.

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

Acknowledgements

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.

I am immensely grateful to Dr B. Suresh and Dr R.K. Goyal for inspiring and initiating me to write the book.

I am grateful to Shri M.N. Raju, Chairman, and Mr Ravi Varma, Director, MNR Educational Trust, Hyderabad, for providing constant encouragement and moral support to achieve this goal.

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

The friendly interaction I had experienced with the Elsevier team, Ms Ritu Sharma, Ms Nimisha Goswami, Mr Subodh K. Chauhan, 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.

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, Aish and Abhi, 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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SECTION I

DRUGS ACTING ON INFLAMMATION/ALLERGY

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| 2 | Prostaglandins | 46 |
| 3 | Analgesics Antipyretics and NSAIDs | 56 |

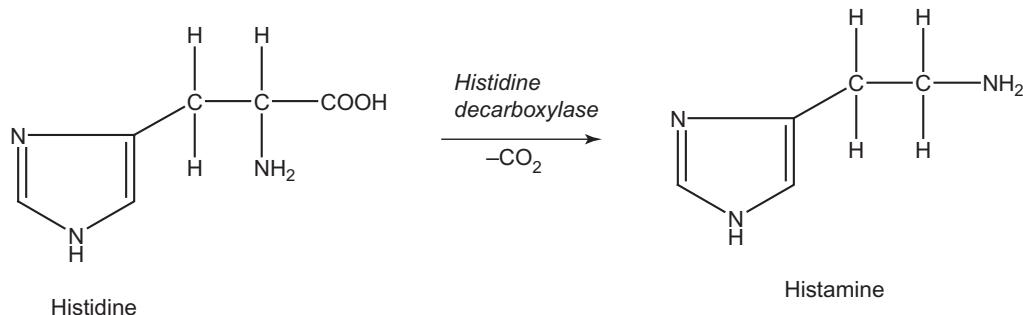
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Chapter 1

Antihistamines

INTRODUCTION

Histamine, [2-(imidazol-4-yl) ethylamine], which is biosynthesized by decarboxylation of the basic amino acid histidine, is found in all organs and tissues of the human body.



The histamine is stored in the secretory granules of mast cells (pH 5.5) as positively charged and ionically complexed with negatively charged acidic group on other seceretary granules, which constitutes heparin. The principal target cells of immediate hypersensitivity reactions are mast cells and basophils to generate IgE antibodies that binds to FC ϵ receptor on the granule surface. This leads to transmembrane activation of tyrosine protein kinase, which phosphorylates and activates the phospholipase. The phosphatidyl inositol biphosphate is converted into inositol triphosphate, which triggers the intracellular release of calcium ion. The calcium ion causes exocytic release of histamine with the transfer of Na⁺ ion from extracellular space. The released histamine targets the histaminergic receptors (H₁, H₂, and H₃) to elicit the actions.

Histamine is an important chemical messenger, communicating information from one cell to another, and is involved in a variety of complex biological actions. It is mainly stored in an inactive bound form, from which it is released as a result of an antigen–antibody reaction, initiated by different stimuli, such as venoms, toxins, proteolytic enzyme, detergents, food materials, and numerous chemicals. Systemically, histamine contracts smooth muscles of the lungs and the gastrointestinal system and cause vasodilation, low blood pressure, and increases the heart rate. It also causes symptoms such as itching, sneezing, watery eye, and running nose.

4 Drugs Acting on Inflammation/Allergy

Histamine exerts its biological function by interacting with at least three distinctly specific receptors H₁, H₂, and H₃. Historically, the term antihistamine has been used to describe a drug that acts on H₁ and H₂ receptors. An antihistaminic agent should ideally prevent the production or release of these autocoids by inhibiting the response of sensitized mast cells and basophils to specific antigens.

1. Antihistamines are drugs that competitively blocks the H₁ receptors.
2. Antihistamines antagonize the stimulant action of histamine on the smooth muscles of gastro intestinal tract (GIT), uterus, and blood vessels, and inhibit histamine augmented salivary secretion.
3. H₁-receptor antagonists have been used clinically to treat various allergic disorders, such as seasonal or perennial allergic rhinitis and chronic urticaria.

Release and Function of Endogenous Histamine

Histamine is released because of the interaction of an antigen with IgE antibodies on the mast cell surface and plays a central role in immediate hypersensitive reactions (Fig. 1.1).

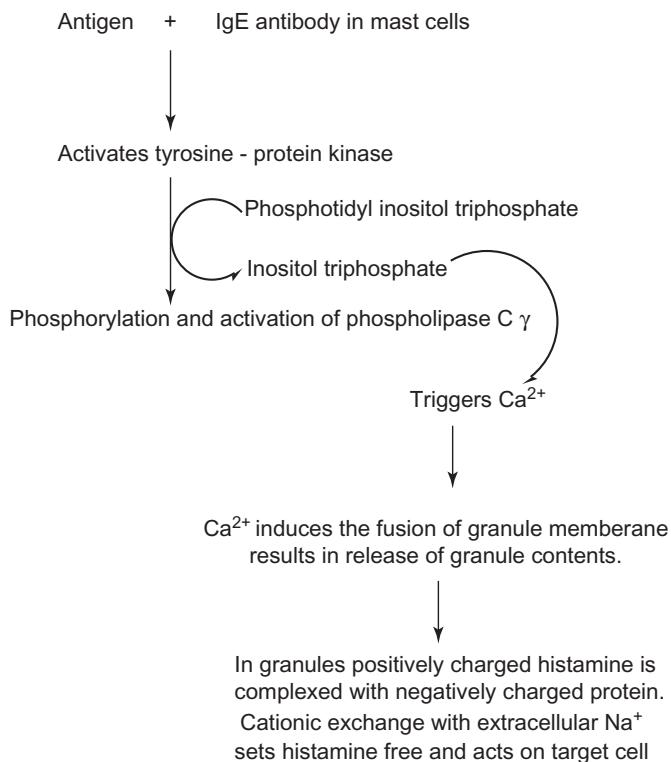


Figure 1.1 Steps involved in the release of histamine.

The release of histamine, in addition to the stimulation of IgE receptors, also activates the phospholipase A₂, leading to the production of host mediators, including platelet activating factors and metabolites of arachidonic acid. Leukotriene D₄ is also generated, which is a potent constrictor of smooth muscles. This mediates the constriction of bronchi.

Histamine and Gastric Acid Secretion

Histamine is a powerful gastric acid secretagogue and evokes a copious secretion of acid from the parietal cells by acting on the H_2 receptors. The output of pepsin and intrinsic factors are also increased. However, the secretion of acid is evoked by the stimulation of vagus nerve and by the enteric hormone gastrin. The mechanism operating at the gastric parietal cells is through $H^+ K^+$ ATPase (proton pump), which secretes H^+ ions in the apical canaliculi of parietal cells and also which can be activated by histamine (Fig. 1.2).

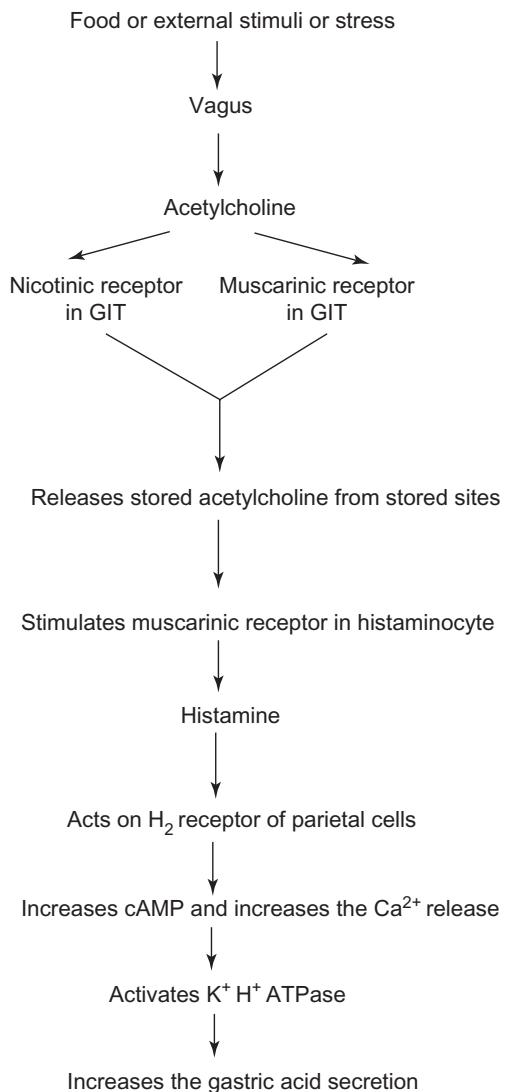


Figure 1.2 Histamine induced gastric acid secretion.

The therapeutically available antagonists of histamine receptors are used as antiallergic drugs by targeting H_1 receptors and as antiulcers by targeting H_2 receptors.

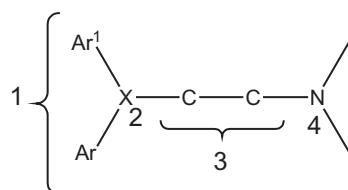
Mode of Action of Antihistamines

After the release of histamine by the mast cells, it binds with histaminergic receptors (H_1 , H_2 , and H_3) to elicit a series of events that mediates the characteristic responses through second messenger systems. The histaminergic receptors are G-protein coupled type. H_1 receptors are coupled to phospholipase-C and their activation leads to the formation of inositol phosphate (IP_3) and diacylglycerol (DAG), respectively, from phospholipids in cell membrane. IP_3 causes rapid release of Ca^{2+} from endoplasmic reticulum. DAG activates the protein kinase C. Altogether the turnover of Ca^{2+} and protein kinase-C activates Ca^{2+} /calmodulin dependent protein kinase and phospholipase A₂. The antihistaminergic (H_1 -antagonist) binds to the H_1 receptors and decreases the production of phospholipase-C and their activation to form IP_3 and DAG thereby blocks the characteristic response of histamine.

Histamine on H_2 receptors produces cAMP-dependent protein kinase (Cyclic adenosine monophosphate (cAMP), also known as cyclic AMP or 3'-5'-cyclic adenosine monophosphate) to elicit a response in the GIT. The H_2 antagonist reversibly binds the H_2 receptors and reduces the cAMP formation, which is responsible for the activation of proton pump and, subsequently, reduces the gastric acid formation in the GIT.

H_3 receptors are also G-protein coupled receptors, unlike H_1 and H_2 , and they produce a decreased Ca^{2+} influx. H_3 receptors function as feedback inhibitors for histamine and other neurotransmitters by decreasing the calcium influx into the cells in the central nervous system (CNS), and in the GIT, they reduce the secretion of gastrin and down-regulates histamine through auto-regulatory effects. Blocking H_3 receptors antagonize these effects, but the clinical extendibility is narrow for H_3 .

STRUCTURE ACTIVITY RELATIONSHIP— H_1 RECEPTOR ANTAGONISTS



1. Aryl groups

The diaryl substitution is essential for significant H_1 affinity. It is present both in first generation and second generation antihistamines. The optimal antihistaminic activity depends on the co-planarity of two aryl substitutions.

Active aryl substitutions are as follows:

Ar is phenyl and hetero aryl group like 2-pyridyl

Ar¹-Aryl or aryl methyl group

2. Nature of X

Antihistamines with X = carbon (pheniramine series) represents the stereo selective receptor binding to the receptors due to its chirality.

The active substitutions of X are as follows:

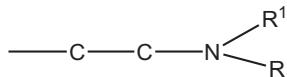
Where X = oxygen (amino alkyl ether analogue)

X = nitrogen (ethylene-diamine derivative)

X = carbon (mono amino propyl analogue)

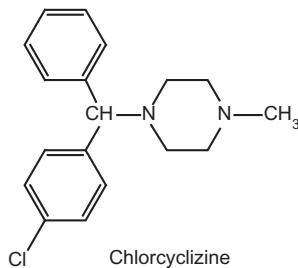
2. The Alkyl Chain

Most of the antihistamines have ethylene chain, and branching of this chain results in a less active compound.



All antihistamines contain this general chain.

3. Terminal nitrogen atom: The terminal N-atom should be a 3° amine for maximum activity. The terminal nitrogen may be a part of heterocyclic ring. For example, antazoline and chlorcyclizine, retains high antihistaminic activity. The amino moiety deserves the protonation on interaction with H₁ receptor due to the basicity with pKa 8.5-10.



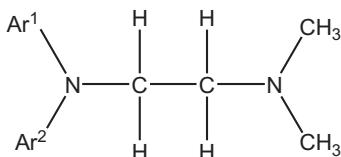
CLASSIFICATION

I. H₁-Antagonists with classical structures

According to the chemical features, they are further classified as follows:

- Ethylene diamine derivatives
- Amino alkyl ether analogues
- Cyclic basic chain analogues
- Mono amino propyl analogues
- Tricyclic ring system or Phenothiazine derivatives
- Dibenzocyclo heptenes
- Miscellaneous agents
- Newer agents

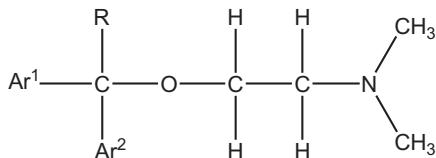
a. Ethylene diamine derivatives



8 Drugs Acting on Inflammation/Allergy

| Name | Ar ¹ | Ar ² |
|-----------------|-----------------|-----------------|
| Tripeleannamine | | |
| Pyrilamine | | |
| Methapyrilene | | |
| Thonzylamine | | |
| Zolamine | | |

b. Amino alkyl ethers



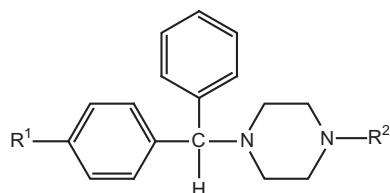
| Name | Ar ¹ | Ar ² | R |
|----------------------|-------------------------|-------------------------|----------------|
| Diphenhydramine | $-\text{C}_6\text{H}_5$ | $-\text{C}_6\text{H}_5$ | $-\text{H}$ |
| Bromodiphenhydramine | $-\text{C}_6\text{H}_5$ | | $-\text{H}$ |
| Doxylamine | $-\text{C}_6\text{H}_5$ | | $-\text{CH}_3$ |

(Continued)

(Continued)

| Name | Ar ¹ | Ar ² | R |
|------------------|-----------------|-----------------|----|
| Carboxamine | | | -H |
| Medrylamine | | | -H |
| Clemastine | | | |
| Diphenylpyraline | | | |

c. Cyclic basic chain analogues or piperazine derivatives

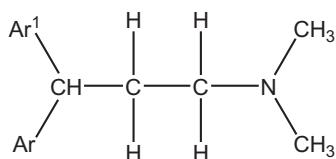


| Name | R ¹ | R ² |
|----------------|----------------|------------------|
| Cyclizine | -H | -CH ₃ |
| Chlorcyclizine | -Cl | -CH ₃ |

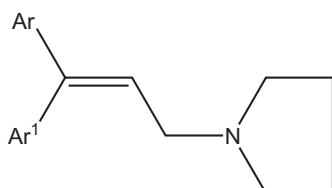
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| Name | R ¹ | R ² |
|-----------|----------------|----------------|
| Meclizine | -Cl | |
| Buclizine | -Cl | |

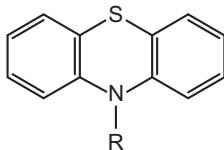
d. Mono amino propyl analogues**i. Saturated analogues**

| Name | Ar | Ar ¹ |
|------------------|----|-----------------|
| Pheniramine | | |
| Chlorpheniramine | | |
| Bromopheniramine | | |

ii. Unsaturated analogues

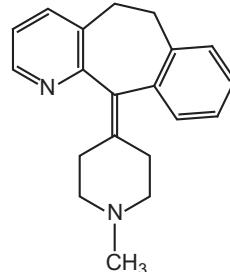
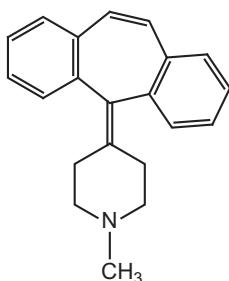
| Name | Ar | Ar ¹ |
|---------------|----|-----------------|
| Pyrrobutamine | | |
| Triprolidine | | |

e. Tricyclic ring systems or phenothiazine derivatives

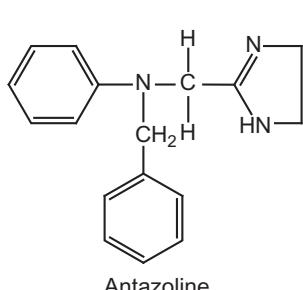


| Name | R |
|----------------------------|---|
| Promethazine hydrochloride | |
| Trimeprazine | |
| Methdilazine | |

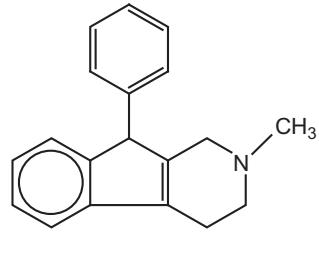
f. Dibenzocyclo heptenes



g. Miscellaneous

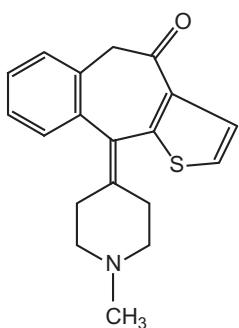


Antazoline

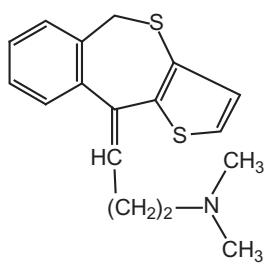


Phenindamine

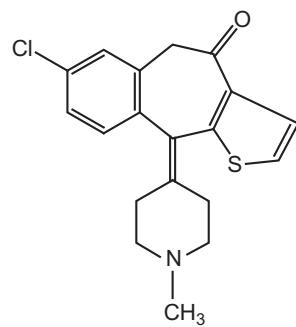
h. Newer agents



Ketotifene



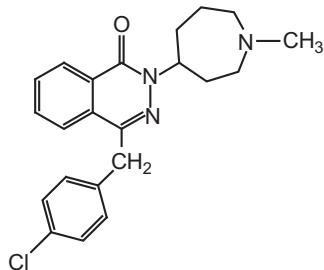
Dithiadene

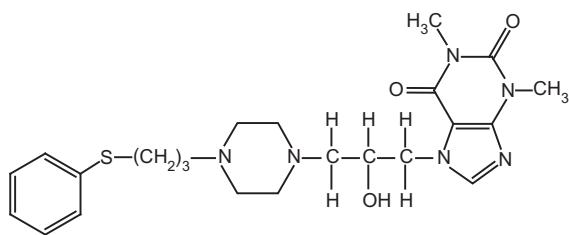
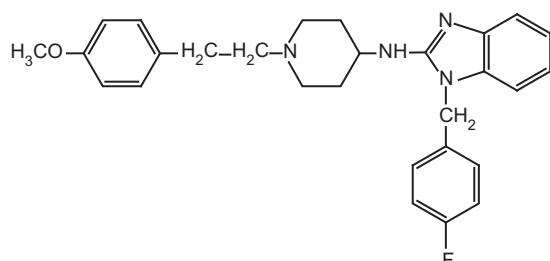


7-Chloro ketotifene

II. H₁-Antagonists with nonclassical structures

i. Azelastine

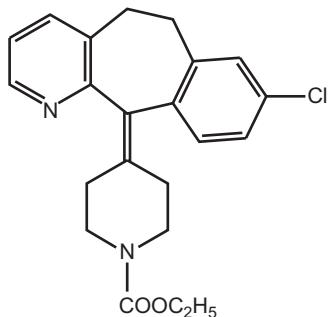
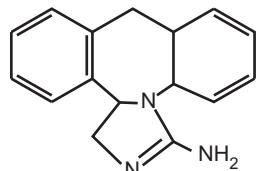
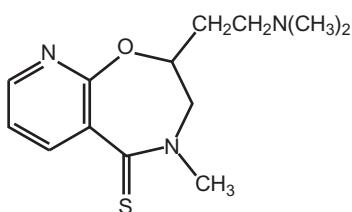
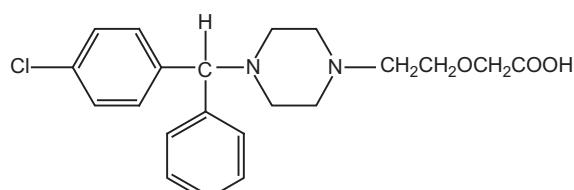


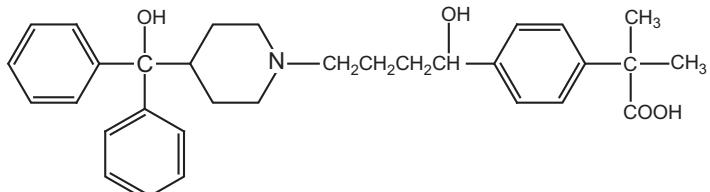
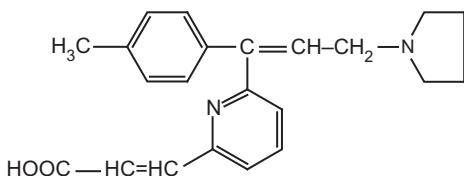
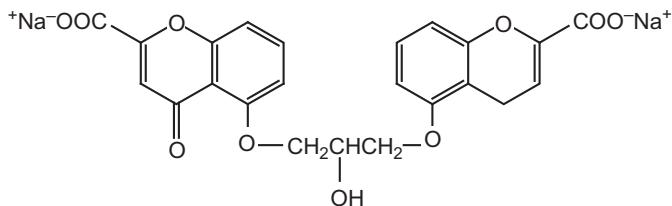
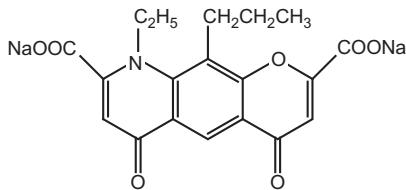
ii. Tazifylline**iii. Astemizole****III. Nonsedative H₁-antihistamines**

Nonsedative antihistamines bind only to peripheral H₁-receptors and produce with little or no sedation because of poor CNS penetration and lower affinity for central histaminic activity.

These are divided into two main classes:

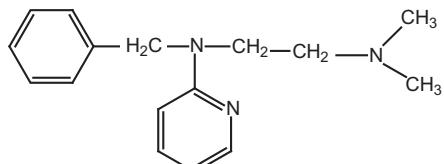
1. Piperazine derivatives—Cetirizine
2. Pyridine and piperidine derivatives—Loratadine, Fexofenadine, Terfenadine, Astemizole, Acrivastine

i. Loratadine**ii. Epinastine****iii. Rocastine****iv. Cetirizine**

v. Fexofenadine**vi. Acrivastine****IV. Inhibition of histamine release (mast cells stabilizers)****i. Cromolyn sodium****ii. Nedocromil sodium****SYNTHESIS AND DRUG PROFILE****I. H₁-antagonists with classical structure****a. Ethylene diamine derivatives**

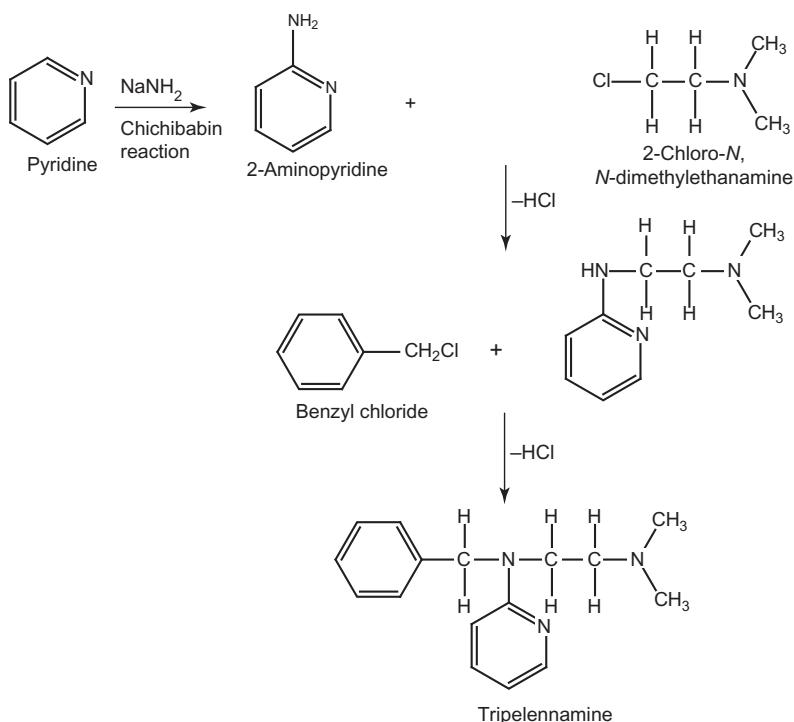
Metabolism of ethylene diamine derivatives: These antihistaminic drugs undergo *N*-demethylation and subsequent deamination. In addition, some compounds produce quaternary *N*-glucuronide as urinary metabolites, a process that occurs to some extent in many relatively unhindered tertiary aliphatic amines among the antihistamines and also in other lipophilic tertiary aliphatic amine drugs.

i. Tripelennamine (Pyribenzamine HCl)



2-(Benzyl[2-(dimethylamino)ethyl]amino)pyridine

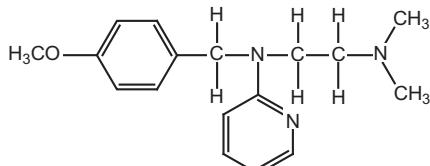
Synthesis



Properties and uses: It is a white, crystalline powder, soluble in water, freely soluble in alcohol and ether, but insoluble in chloroform or benzene. Tripelennamine is the first ethylenediamine developed in the American laboratories; it appears to be effective as diphenhydramine and may have the advantage of fewer and less severe side reactions. Drowsiness may occur and may impair the ability to perform tasks requiring alertness. The concurrent use of alcoholic beverage should be avoided. It is used in the treatment of allergic rhinitis, allergic conjunctivitis, angioedema, dermagraphism, and anaphylactic reactions.

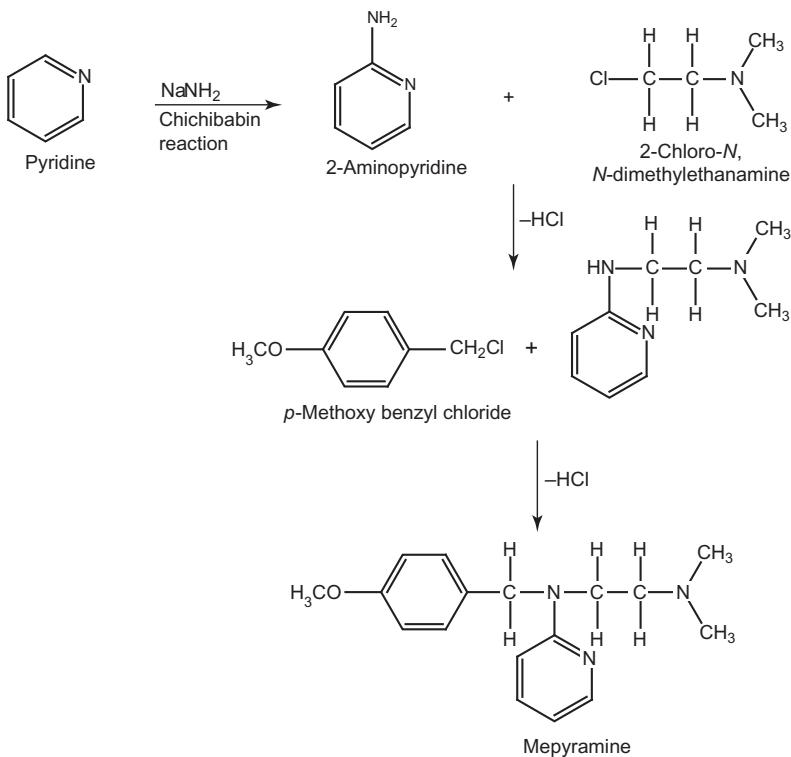
Dose: Usual dose is 25–50 mg for adults consumed orally four to six times a day.

ii. Pyrilamine (Mepyramine, Anthisan)



N-(4-Methoxybenzyl)-*N*-(2-(dimethylamino)ethyl)pyridin-2-amine

Synthesis



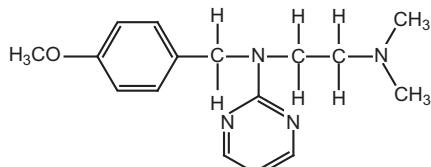
Properties and uses: Mepyramine maleate is a white or slightly yellowish crystalline powder, soluble in water and in ethanol. Pyrilamine differs structurally from tripelennamine having a methoxy group in the para position of the benzyl radical. It differs from its more toxic and less potent precursor phenbenzamine (antergan) having a 2-pyridyl group on the nitrogen atom in the place of a phenyl group. Clinically, pyrilamine and tripelennamine are considered to be among the less potent antihistamines. It is used as an antihistaminic agent with a low incidence of sedative effects; it is also used as an antiemetic.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: Usual dose is 25–50 mg for adults taken orally three to four times per day.

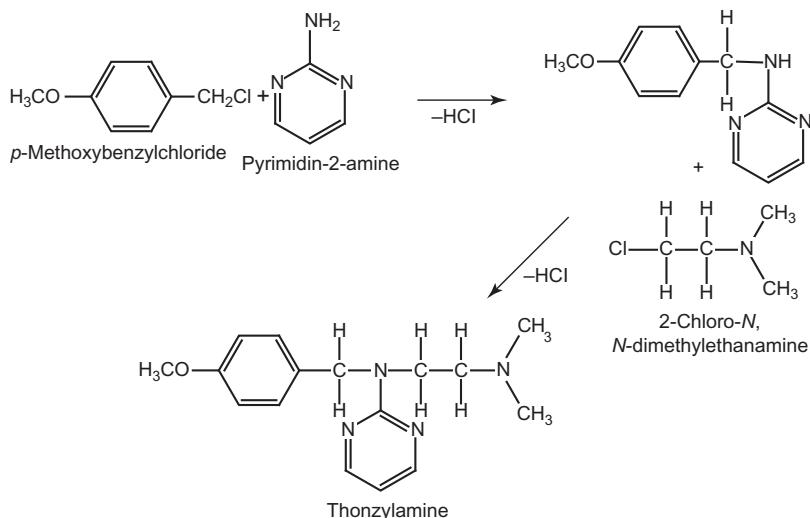
Dosage forms: Mepyramine tablets B.P.

iii. Thonzylamine (Resistab)



N-(4-Methoxybenzyl)-*N*-(2-(dimethylamino)ethyl)pyrimidin-2-amine

Synthesis

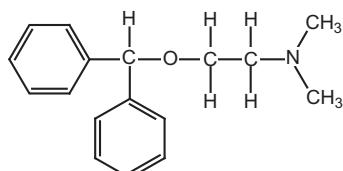


Properties and uses: It is recommended for use with streptomycin in exudative human tuberculosis. It is used in treating the symptoms of diseases, such as hay fever, urticaria, and other mild allergic conditions.

Dose: Usual dose is 50 mg for adults consumed orally up to four times a day.

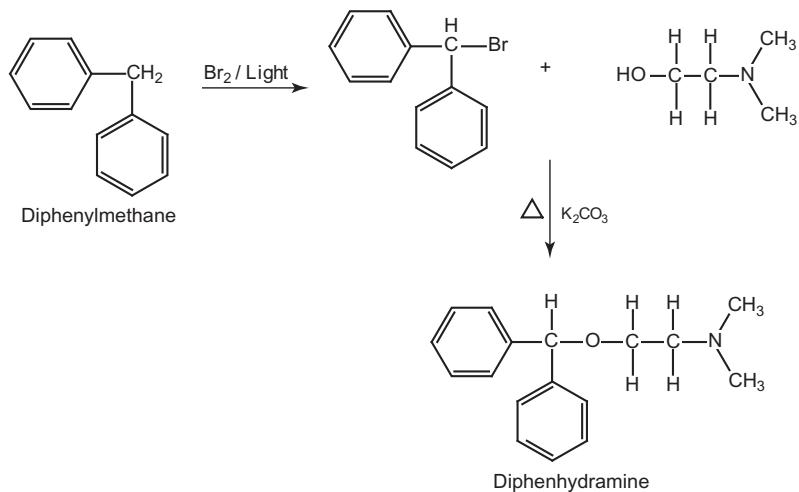
I. b. Amino alkyl ether analogues

i. Diphenhydramine (Benadryl, Bendylate)



2-(Benzhydryloxy)-*N,N*-dimethylethanamine

Synthesis



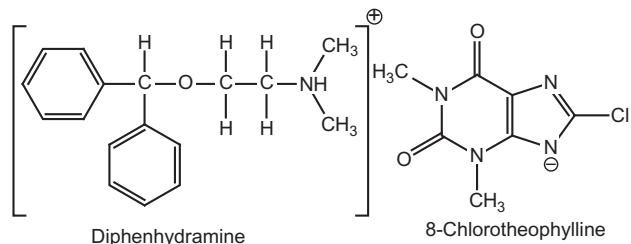
Properties and uses: Diphenhydramine hydrochloride is a white crystalline powder, soluble in water and in alcohol. In addition, to antihistaminic activity, diphenhydramine exhibits antiemetic, antitussive, and sedative properties.

Assay: Dissolve the sample in alcohol and add 0.01 M hydrochloric acid and titrate against 0.1 M sodium hydroxide. Determine end point potentiometrically.

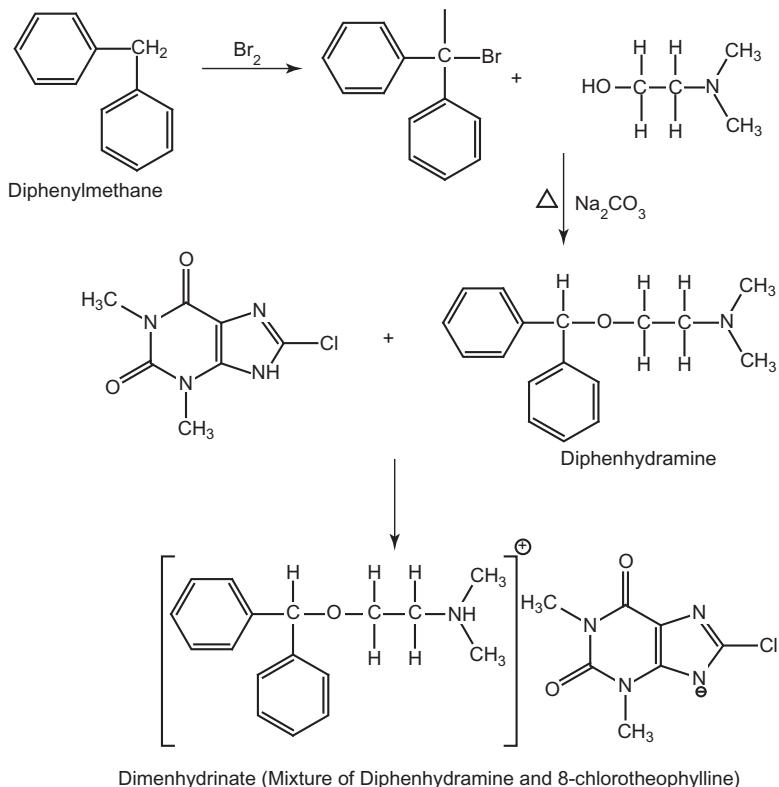
Dose: Usual dose is 25–50 mg for adult taken orally three to four times per day with maximum of 400 mg per day; for skin: used topically 2% of the cream three or four times per day.

Dosage forms: Diphenhydramine oral solution B.P.

ii. Dimenhydrinate (Dramamine)



Synthesis



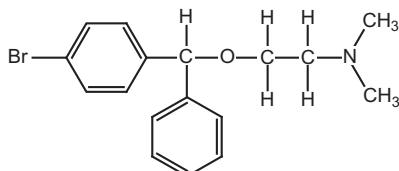
Properties and uses: Dimenhydrinate is a white crystalline powder or colourless crystals, slightly soluble in water and in alcohol. Used as histamine H₁-receptor antagonist, antinauseant, in motion sickness, radiation sickness, and also in the case of nausea during pregnancy.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: Usual dose is taken orally as 50 mg thrice/day.

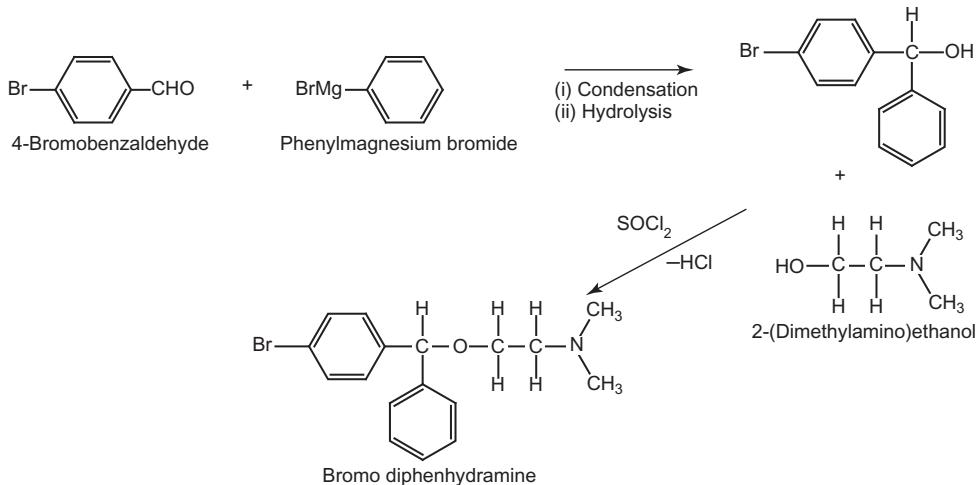
Dosage forms: Dimenhydrinate tablets B.P.

iii. Bromodiphenhydramine (Ambodryl hydrochloride)



2-[4-(4-Bromophenyl)(phenyl)methoxy]-N,N-dimethylethanamine

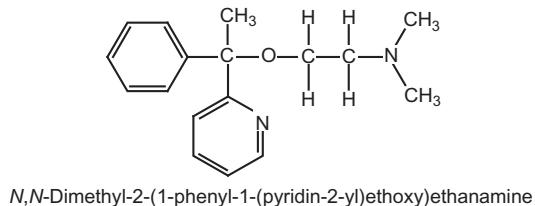
Synthesis



Properties and uses: It is effective for mild, local allergic reactions, physical allergy, and for minor drug reactions, characterized by pruritis.

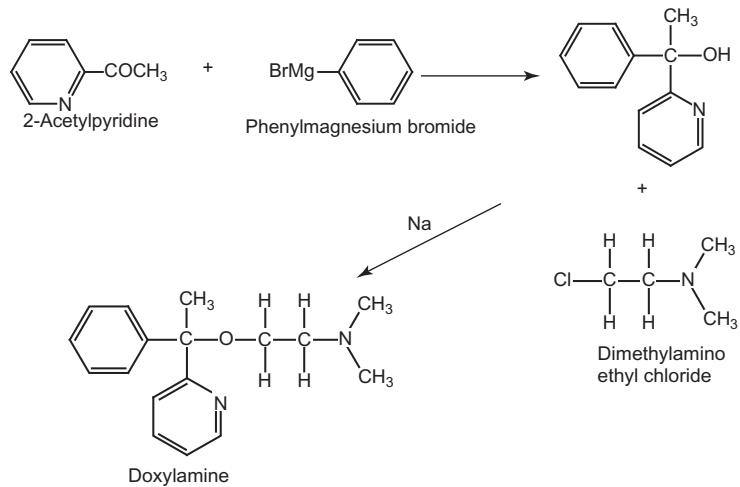
Dose: Usual dose is 25 mg three or four times per day.

iii. Doxylamine (Decapryn Succinate)



N,N-Dimethyl-2-(1-phenyl-1-(pyridin-2-yl)ethoxy)ethanamine

Synthesis

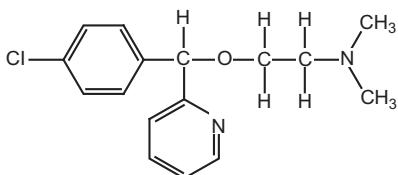


Properties and uses: Doxylamine succinate is a white powder, highly soluble in water and in alcohol. It is a relatively selective histamine H₁-receptor antagonist. In vivo studies have shown that concentrations dependent upon the inhibition of histamine stimulated vascular permeability in the conjunctiva following topical ocular administration. It appears to be devoid of effects on adrenergic, dopaminergic, and serotonin receptors. It is used with antitussives and decongestants for the relief of cough and cold.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

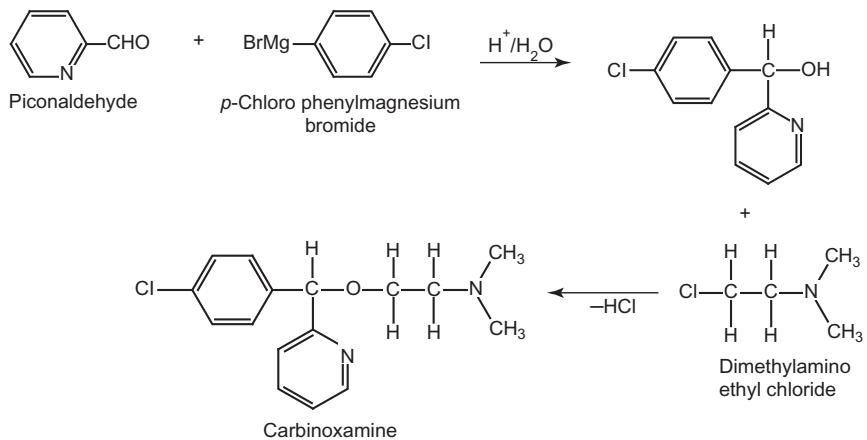
Dose: Usual dose is 12.5 to 25 mg for adult taken orally four to six times per day.

iv. Carboxamine

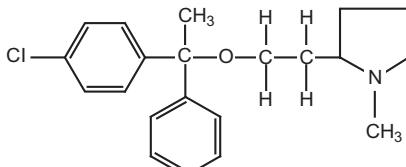


2-((4-Chlorophenyl)(pyridin-2-yl)methoxy)-N,N-dimethylethanamine

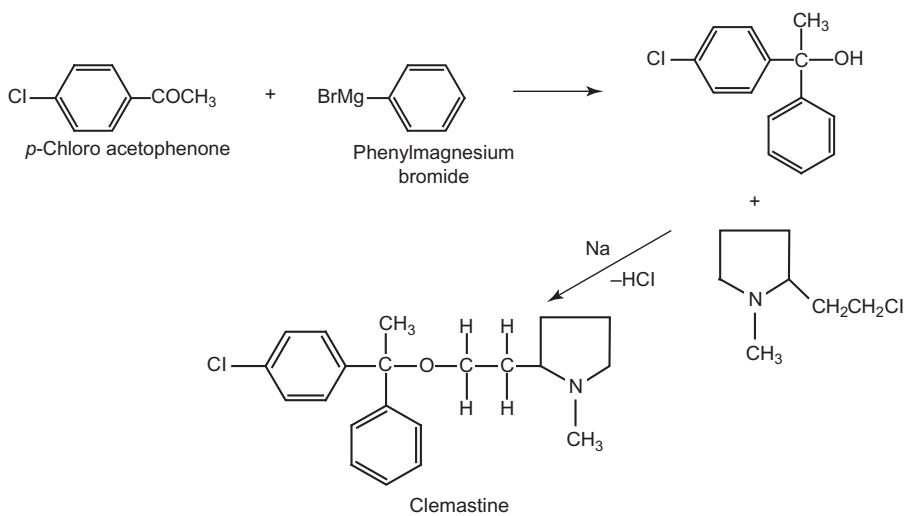
Synthesis



Properties and uses: Carboxamine is available as white, crystalline powder with no odour, soluble in water, alcohol, chloroform, or ether. It is a potent antihistaminic and is available as the racemic mixture. It differs structurally from chlorpheniramine only in having an oxygen atom separate from the asymmetric carbon atom in the aminoethyl side chain. The levo isomer of carboxamine is more active than dextro isomer (s-configuration) of chlorpheniramine.

v. Clemastine

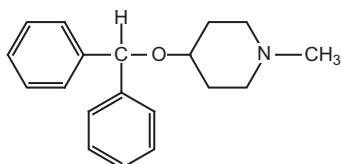
2-(2-1-(4-Chlorophenyl)-1-(phenylethoxy)ethyl)-1-methylpyrrolidine

Synthesis

Properties and uses: Clemastine fumarate is a white crystalline powder, very slightly soluble in water, slightly soluble in alcohol and methanol. It has two chiral centres, each of which is (R) absolute configuration. A comparison of the activities of the antipodes indicates that the asymmetric centre close to the side chain of nitrogen is of lesser importance to antihistaminic activity. It is a long-acting ethanolamine antihistamine with sedative and anticholinergic side effects.

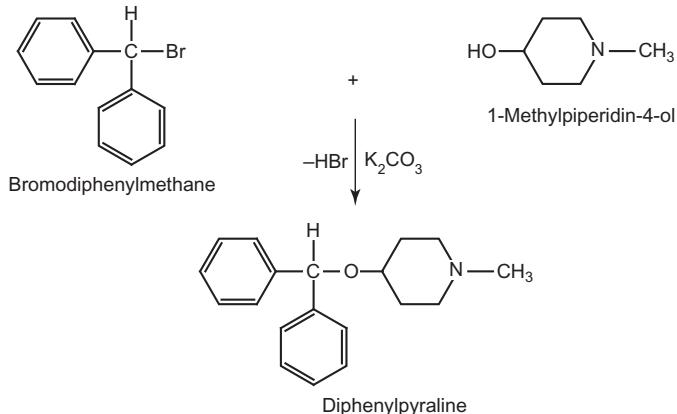
Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dosage forms: Clemastine oral solution B.P., Clemastine tablets B.P.

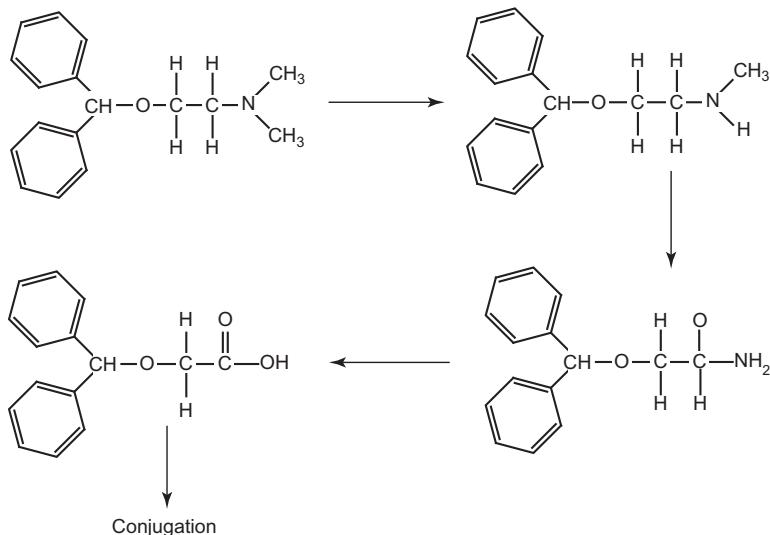
vi. Diphenylpyraline (Diaben)

4-(Diphenylmethoxy)-1-methylpiperidine

Synthesis



Metabolism: This type of drugs undergoes *N*-demethylation (formation of corresponding secondary amine) and subsequent deamination (formation of carboxylic acid metabolites) is the major pathway for diphenylpyraline and some of its analogues. Minor metabolites that are conjugates of the ether cleavage products have been found in some animal species.



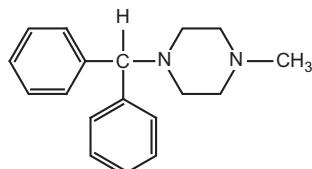
Properties and uses: Diphenylpyraline hydrochloride is a white powder, soluble in water and ethanol, practically insoluble in ether. It is structurally related to diphenhydramine with the aminoalkyl side chain incorporated in a piperidine ring. It is a potent antihistaminic agent.

Assay: Dissolve the sample in anhydrous acetic acid and add mercury (II) acetate solution and titrate against 0.1 M perchloric acid using oracet blue B solution as indicator.

Dose: Usual dose for adults taken orally is 5 mg two times per day.

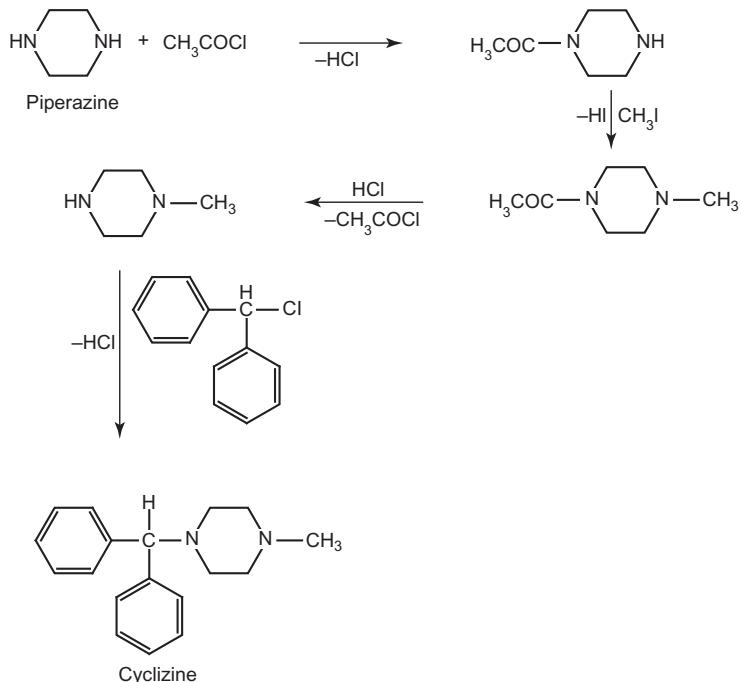
I.c. Piperazines derivatives

i. Cyclizine (Marezine)



1-Benzhydryl-4-methylpiperazine

Synthesis



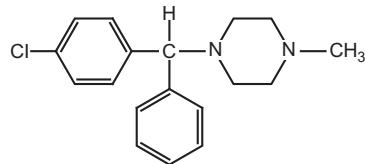
Properties and uses: Cyclizine hydrochloride is a white crystalline powder, slightly soluble in water and in alcohol. It is mostly employed as a prophylaxis and for the treatment of motion sickness.

Assay: Dissolve the sample in anhydrous formic acid, add acetic anhydride and titrates against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: Usual dose is 25–100 mg per day.

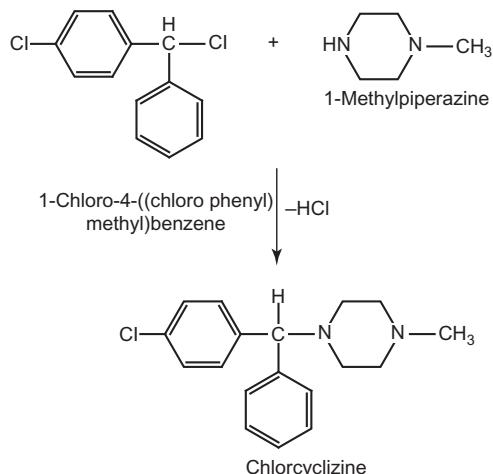
Dosage forms: Cyclizine HCl tablets I.P., Cyclizine injection B.P., Cyclizine tablets B.P., Dipipanone and cyclizine tablets B.P.

ii. Chlorcyclizine (Diparalene)



1-((4-Chlorophenyl)(phenyl)methyl)-4-methylpiperazine

Synthesis

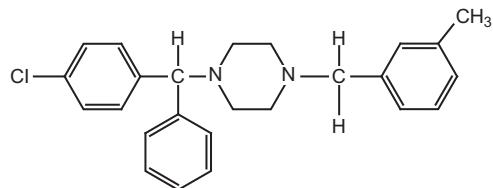


Properties and uses: Chlorcyclizine hydrochloride is a white crystalline powder, soluble in water, methylene chloride and in alcohol. Substitution of halogen in the 2nd or 3rd position of either of the benzhydryl rings results in a much less potent activity. Chlorcyclizine is indicated in the symptomatic relief of urticaria, hay fever, and certain other allergic conditions.

Assay: Dissolve the sample in a mixture of 0.1 M hydrochloric acid and methanol and titrate against 0.1 M sodium hydroxide. Determine end point potentiometrically.

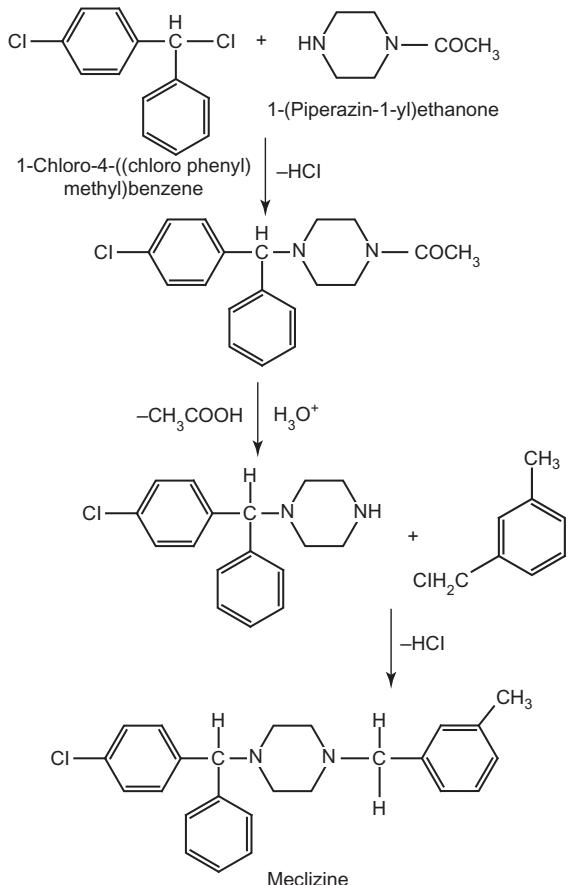
Dose: Usual dose is 50–200 mg per day.

iii. Meclizine (Antivert, Bonine)



1-(*p*-Chlorophenyl benzyl)-4-(3-methylbenzyl) piperazine

Synthesis



Properties and uses: It is a white or slightly yellowish, crystalline powder with no characteristic odour and taste. It is insoluble in water and in ether, but soluble in chloroform and alcohol. It is a moderately potent antihistaminic agent. It is used primarily as an antinauseant in the prevention and treatment of motion sickness; in the treatment of nausea and vomiting associated with vertigo and radiation sickness.

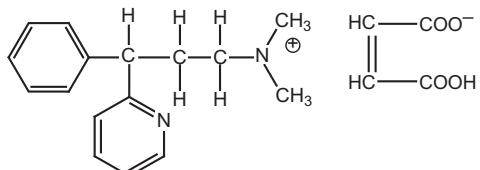
Assay: Dissolve the sample in alcohol and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: Usual dose is 25–50 mg per day.

I. d. Monoamino propylamine derivatives

i. Saturated analogues

1. Pheniramine Maleate (Avil, Polarmine)



N,N-Dimethyl-3-phenyl-3-(pyridin-2-yl)propan-1-amine

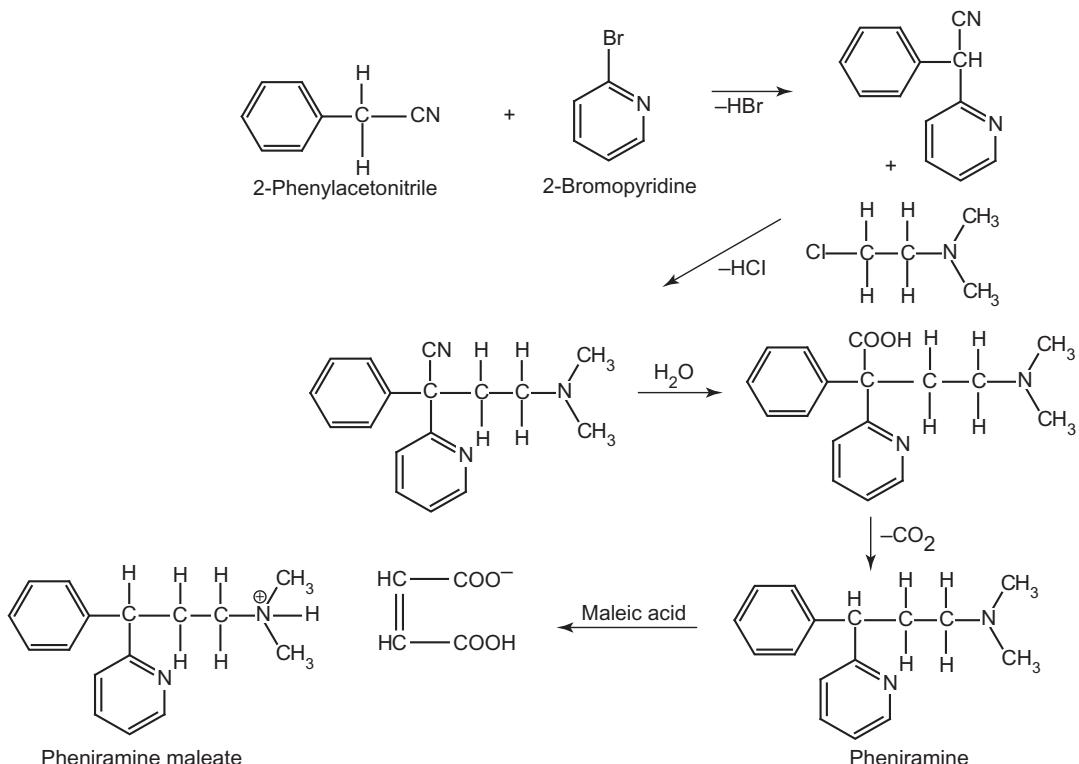
Properties and uses: Pheniramine maleate is a white crystalline powder, freely soluble in water, alcohol, methanol, and methylene chloride. This drug is the least potent member of the series and is marketed as the racemate.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

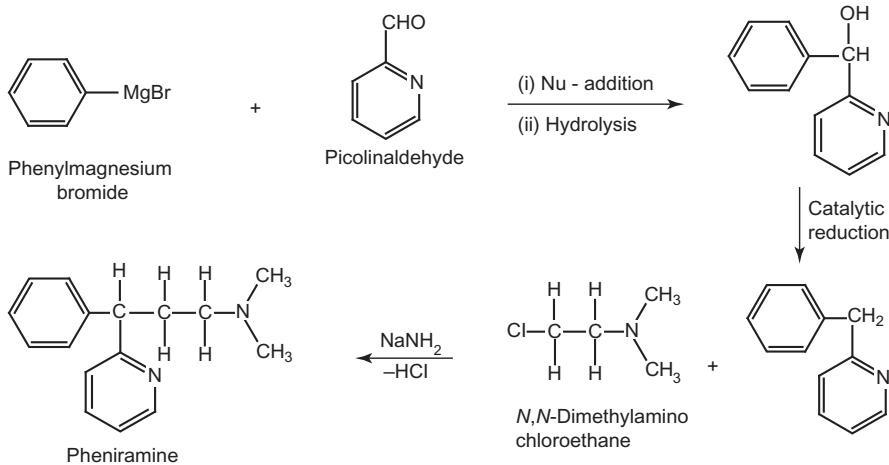
Dose: Usual dose is 25–30 mg per day in divided doses.

Synthesis

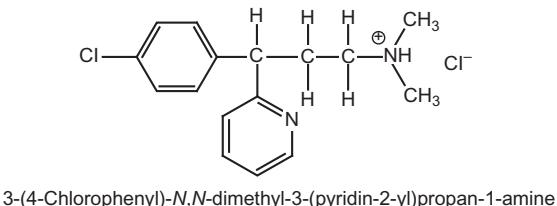
Route I. From: 2-Phenylacetonitrile



Route II. From: Picolinaldehyde

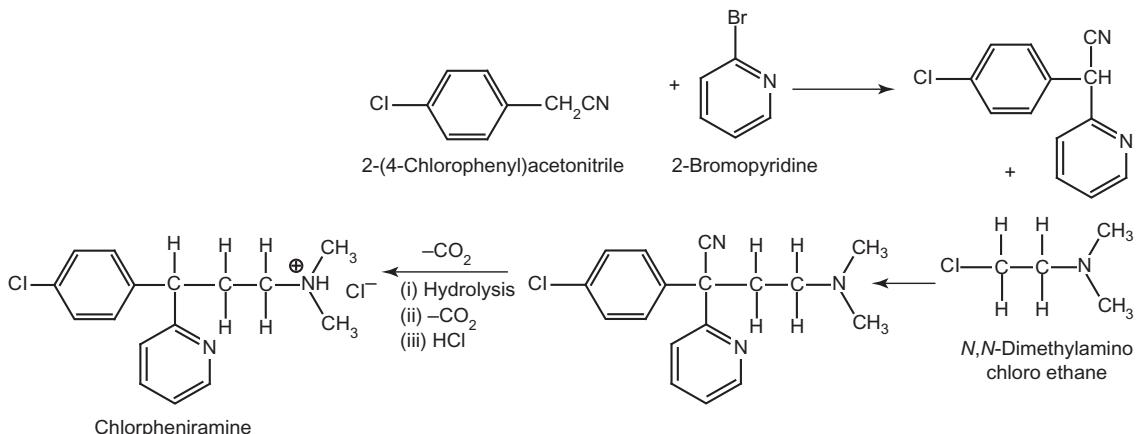


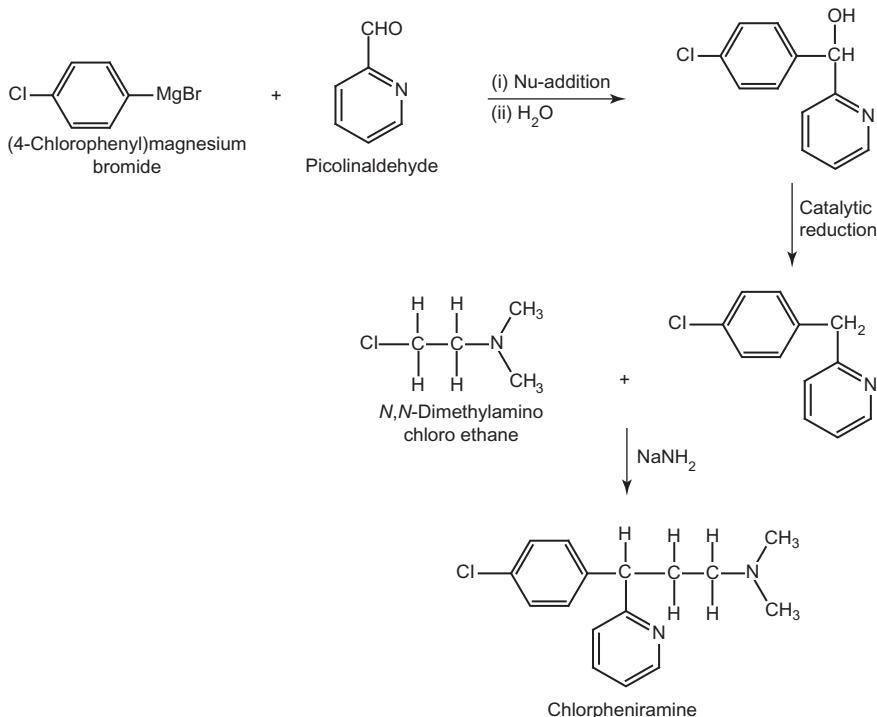
2. Chlorpheniramine HCl (Piriton, Alermine)



Synthesis

Route-I. From: 2-(4-Chlorophenyl)acetonitrile



Route-II. From: Picolinaldehyde


Properties and uses: Chlorpheniramine HCl is a white crystalline powder, soluble in water and in ethanol. Chlorination of pheniramine in the para position of the phenyl ring increases potency by almost 10-fold, with no appreciable change in toxicity. Most of the antihistaminic activity resides with the dextro isomer.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

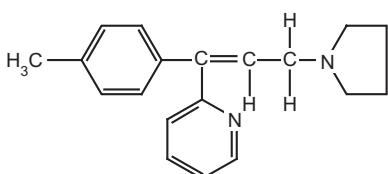
Dose: Usual oral dose is 5 mg three or four times per day.

Dosage forms: Chlorpheniramine maleate injection I.P., B.P., Chlorpheniramine maleate tablets I.P., B.P., Chlorpheniramine oral solution B.P.

I. d. Monoaminopropyl analogues

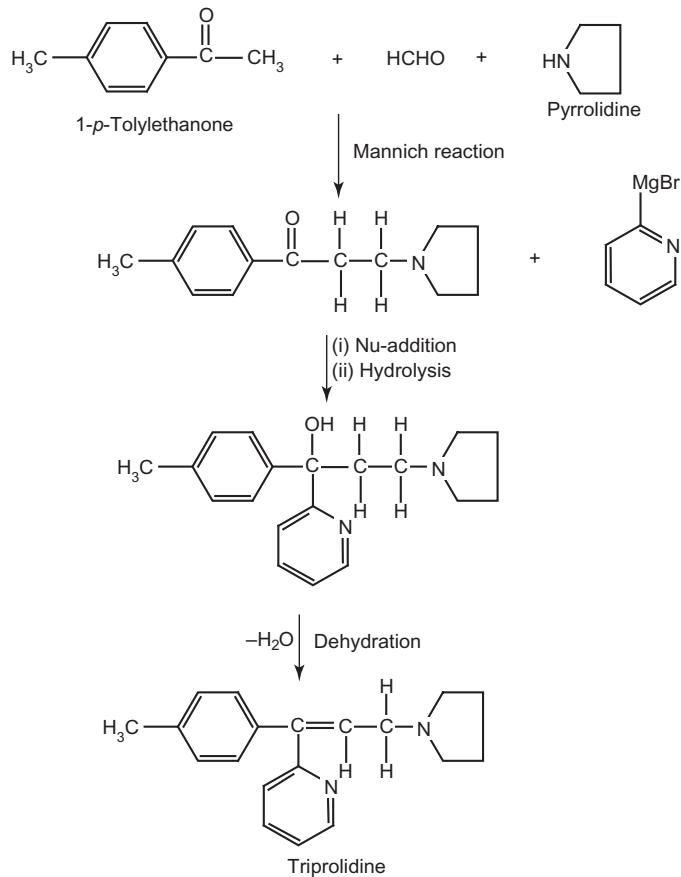
ii. Unsaturated analogues

1. Triprolidine (Actidil)



2-(3-(Pyrrolidin-1-yl)-1-p-tolylprop-1-enyl)pyridine

Synthesis



Properties and uses: Triprolidine hydrochloride is a white crystalline powder, practically insoluble in ether, soluble in water and in ethanol. The activity is mainly confined to the geometric isomer in which the pyrrolidino-methyl group is *trans* to the 2-pyridyl group. Pharmacological studies confirm the high activity of triprolidine and the superiority of (E) over corresponding (Z) isomers as H₁-antagonists. In guinea pig ileum sites, the affinity of triprolidine (E) for H₁-receptors was more than 1000 times the affinity of its (Z) partner.

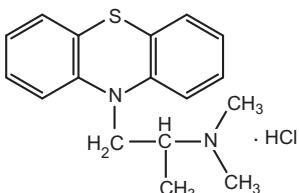
Assay: Dissolve the sample in a mixture of anhydrous acetic acid and acetic anhydride and titrate against 0.1 M perchloric acid using crystal violet solution as indicator.

Dose: Usual dose is 5–7.5 mg per day.

Dosage forms: Triprolidine HCl tablets I.P., Triprolidine tablets B.P.

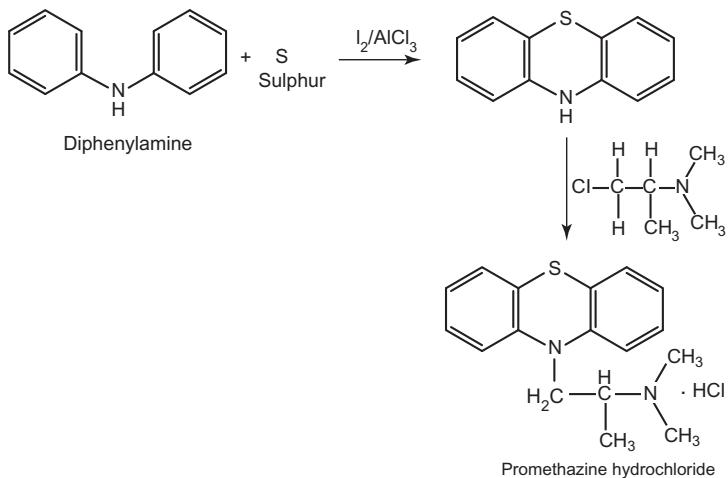
I. e. Tricyclic ring system or phenothiazines

1. Promethazine HCl (Phenargen)



N,N-Dimethyl-1-(phenothiazin-10-yl)propan-2-amine hydrochloride

Synthesis



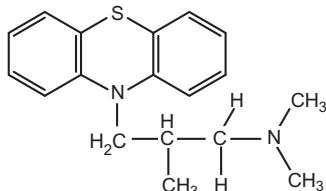
Properties and uses: Promethazine hydrochloride is a white or faintly yellowish crystalline powder, highly soluble in water, soluble in alcohol and in methylene chloride. It may be used effectively in perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods, and certain milder type of skin manifestations of urticaria. It also possesses some anticholinergic, antiserotonergic, and marked local anaesthetic properties.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol and titrate against 0.1 M sodium hydroxide. Determine end point potentiometrically.

Dose: Usual dose is 20–50 mg per day.

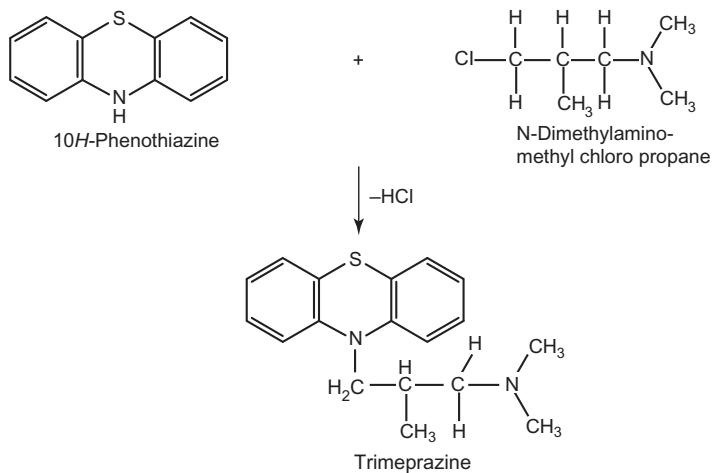
Dosage forms: Promethazine hydrochloride injection I.P., Promethazine hydrochloride tablets I.P., B.P., Promethazine hydrochloride syrup I.P., Promethazine injection B.P., promethazine oral solution B.P.

2. Trimeprazine (Temaril)



N,N,2-Trimethyl-3-(phenothiazin-10-yl)propan-1-amine

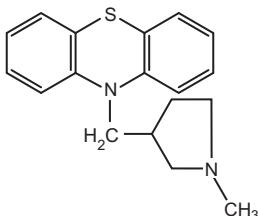
Synthesis



Properties and uses: It is a white crystalline powder, soluble in water. It is used as histamine H₁-receptor antagonist.

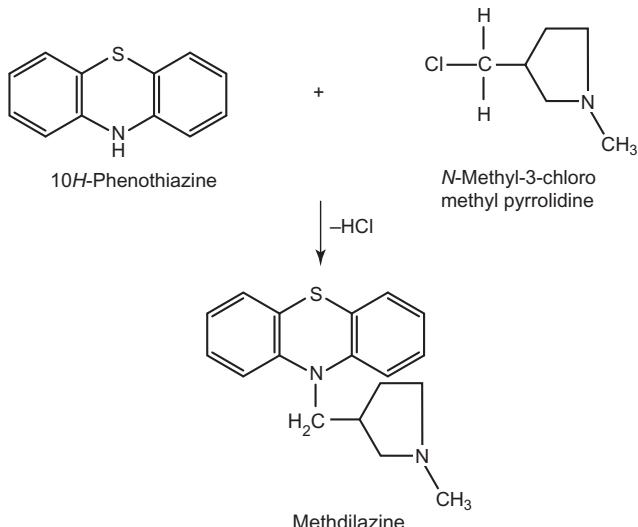
Dose: Usual dose for adults is 10–40 mg per day orally.

3. Methdilazine (Tacaryl HCl)



10-((1-Methylpyrrolidin-3-yl)methyl) phenothiazine

Synthesis

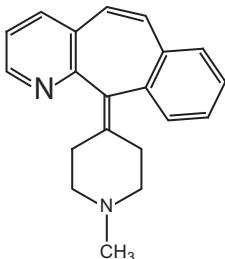


Properties and uses: It may be used for the symptomatic relief of urticaria. It has also been used successfully for the treatment of migraine headache.

Dose: Usual dose for adults is 8 mg taken orally two to four times a day.

I. f. Dibenzocyclo heptene derivatives

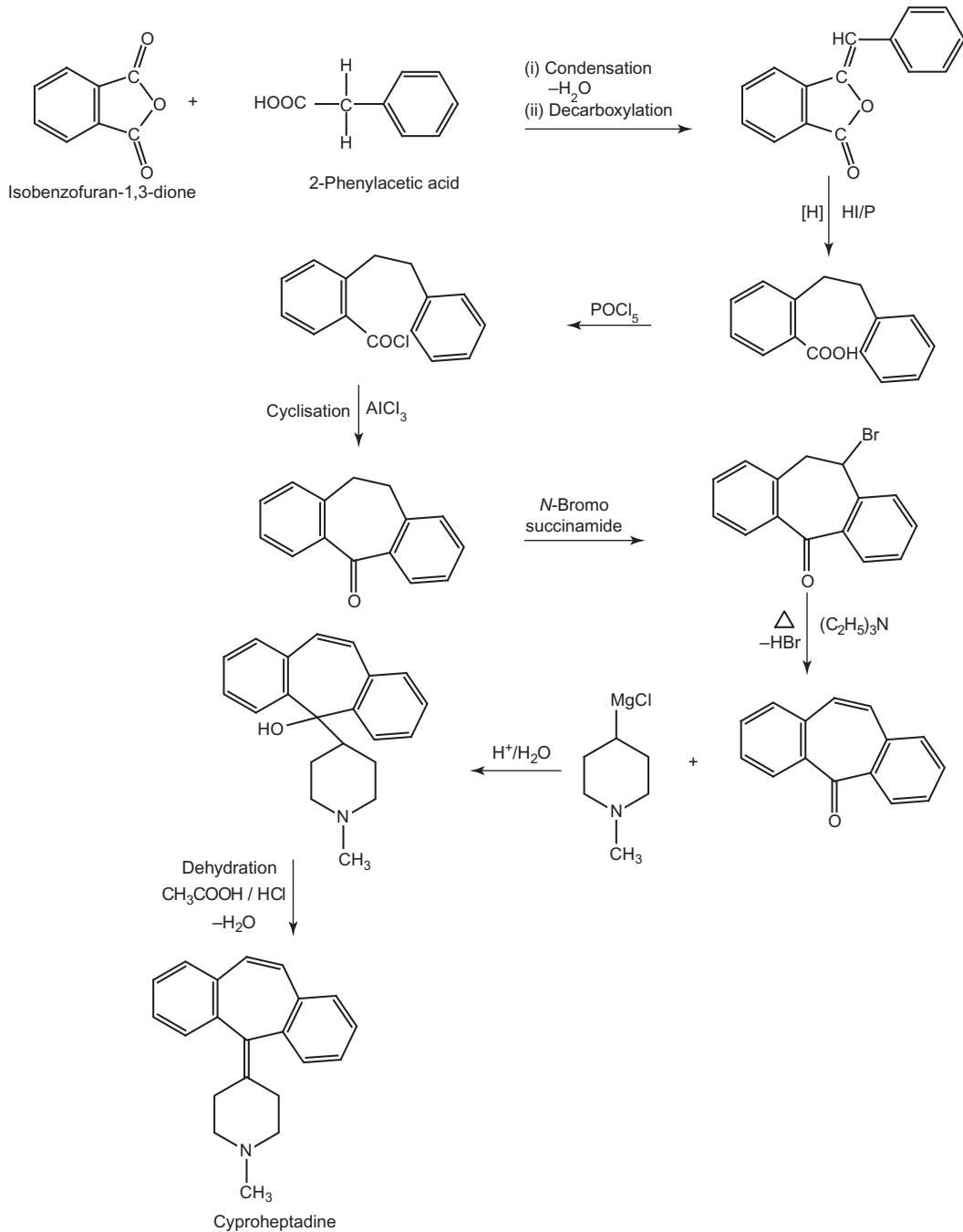
1. Cyproheptadine (Periacetin)



4-Dibanzo(a,d) cyclohepten-5-ylidene)-1-methyl piperidine

Properties and uses: Cyproheptadine hydrochloride is a white or slightly yellow crystalline powder, slightly soluble in water and methanol, sparingly soluble in alcohol. This dibenzocycloheptene may be regarded as a phenothiazine analogue in which the sulphur atom has been replaced by an isosteric vinyl group and the ring nitrogen replaced by a sp^2 carbon atom. It also possesses antiserotonin activity and is used as an anti-pruritic agent associated with skin disorders (urticaria, allergic dermatitis, neurodermatitis). It is used to stimulate the appetite in under-weight patients and those suffering from anorexia nervosa.

Synthesis

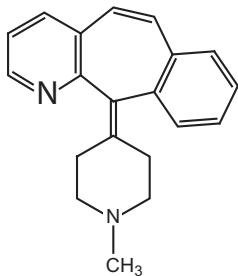


Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol and titrate against 0.1 M sodium hydroxide. Determine end point potentiometrically.

Dose: Usually, the dose is 4 mg taken orally three times a day.

Dosage forms: Cyproheptadine HCl syrup I.P., Cyproheptadine HCl tablets I.P., Cyproheptadine tablets B.P.

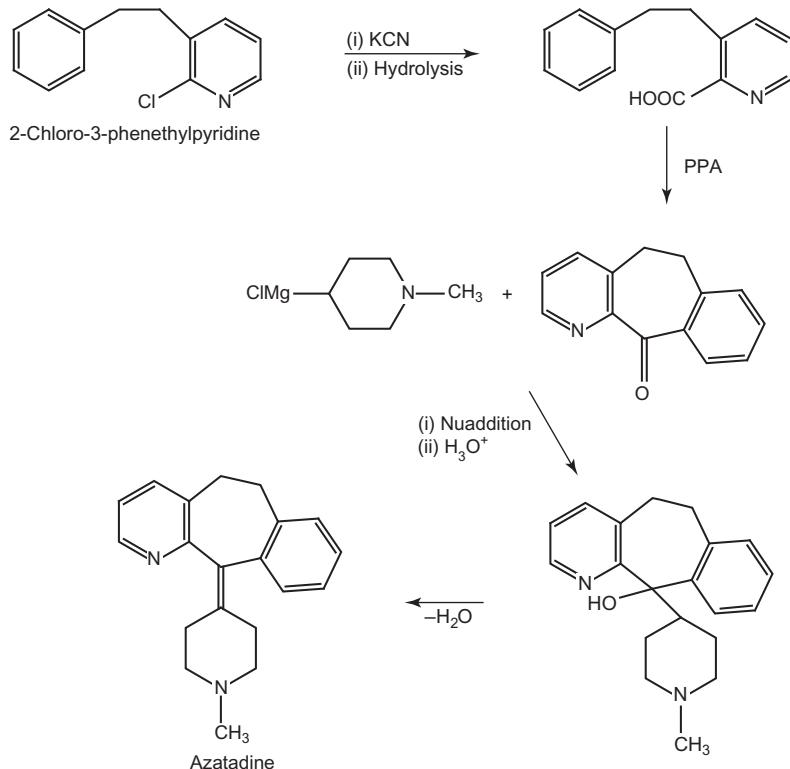
2. Azatadine



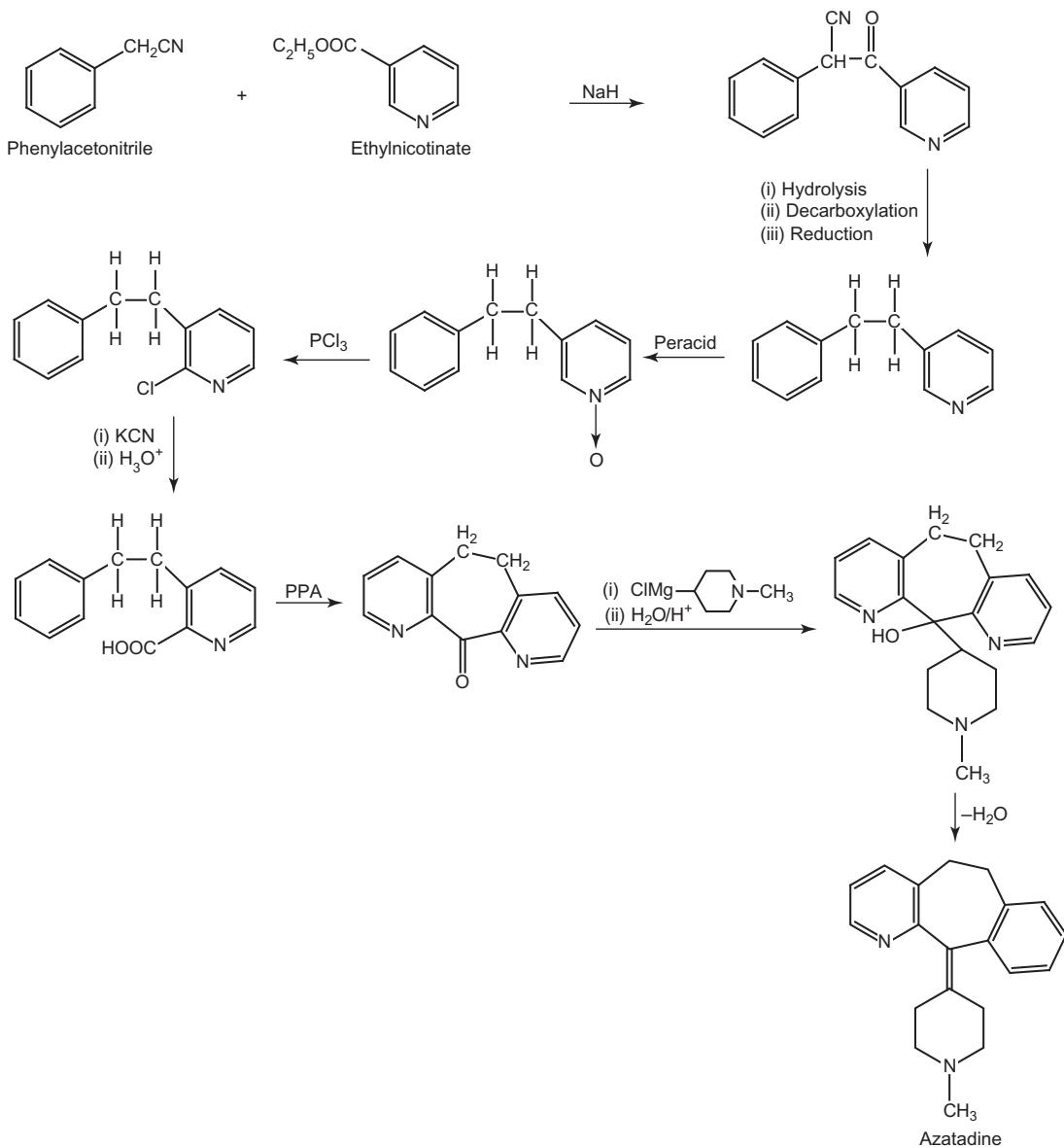
6,11-Dihydro-11-(1-methyl-4-piperidyllidene)-5H-benzo-[5,6]-cyclohepta-9-[1,2-6] pyridine

Synthesis

Route I. From: 2-Chloro-3-phenethylpyridine



Route II. From: Phenylacetonitrile

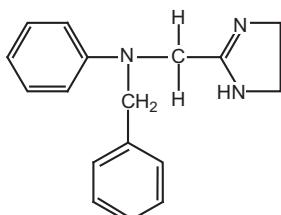


Properties and uses: Azatadine is a potent, long-acting antihistaminic with antiserotonin activity. In early testing, azatadine exhibited more than three times the potency of chlorpheniramine in the isolated guinea pig ileum screening and more than seven times the oral potency of chlorpheniramine in the protection of guinea pig against a double lethal dose of intravenously administered histamine.

Azatadine is an aza isostere of cyproheptadine in which the 10, 11-double bond is reduced. It has low sedative effect.

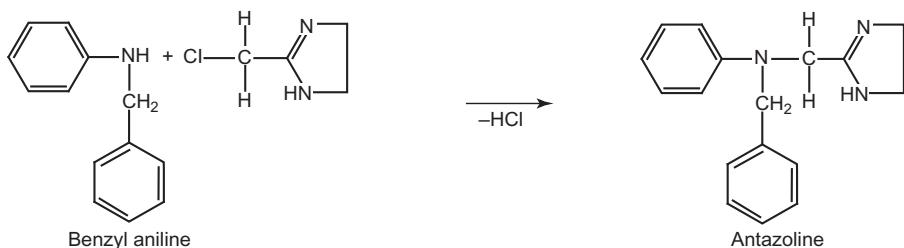
I. g. Miscellaneous

1. Antazoline (Antistine)



N-Benzyl-*N*-((4,5-dihydro-1*H*-imidazol-2-yl)methyl)benzenamine

Synthesis



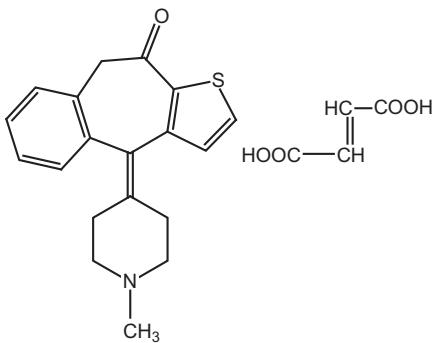
Properties and uses: Antazoline hydrochloride is a white crystalline powder, sparingly soluble in water, soluble in alcohol, and slightly soluble in methylene chloride. The phosphate salt is soluble in water, bitter taste. It is used for the treatment of rhinitis and conjunctivitis.

Assay: Dissolve the sample in alcohol and titrate against 0.1 M alcoholic potassium hydroxide using phenolphthalein as indicator.

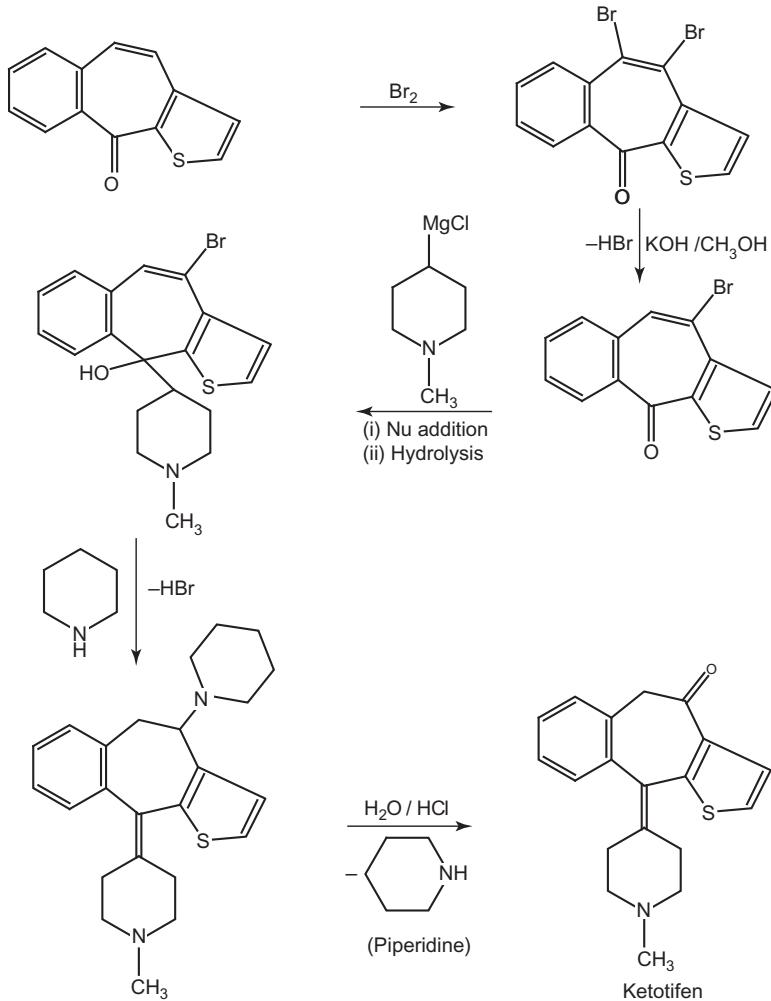
Dose: Usual dose is 50–100 mg per day.

I. h. Newer agents

1. Ketotifen Fumarate (Zaditen)



4-(1-Methyl-4-piperidylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10(9*H*)

Synthesis

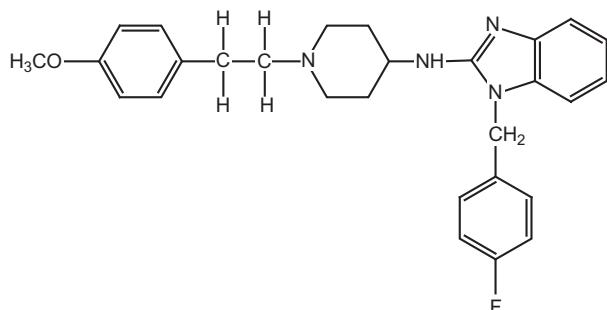
Properties and uses: Ketotifen fumarate is a white to brownish-yellow crystalline powder, sparingly soluble in water, slightly soluble in methanol and in acetonitrile. The recommended dose of ketotifen solution is one drop instilled into each affected eye every 8–12 hr. Most frequently used for conjunctival infection, and rhinitis. Ketotifen solution should be used with caution during pregnancy or during nursing. This is an analogue of the tricyclic H_1 -receptor antagonist and serotonin receptor antagonist. It has only minor anticholinergic and antiserotonergic activity. It has been used in the prophylactic treatment of asthma.

Assay: Dissolve the sample in a mixture of anhydrous acetic acid and acetic anhydride and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: Usually, the dose is 1 mg orally two times a day.

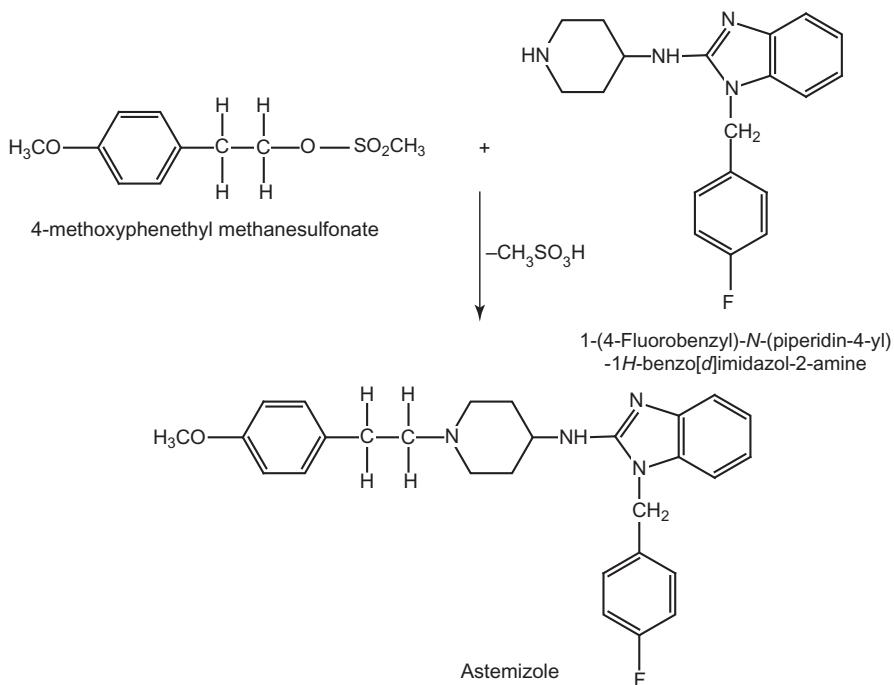
II. H₁-Antagonists with nonclassical structure

1. Astemizole (Histalong)



1-(4-Fluorobenzyl)-N-(1-(4-methoxyphenethyl)piperidin-4-yl)-1*H*-benzo[d]imidazol-2-amine

Synthesis

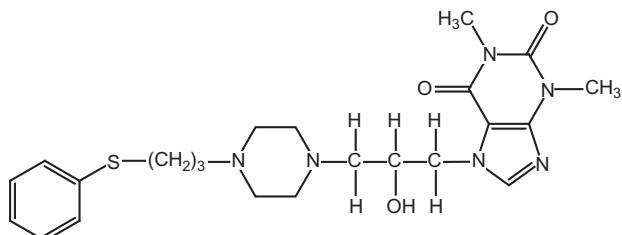


Properties and uses: Astemizole is a white powder, practically insoluble in water, soluble in methylene chloride, methanol, and in alcohol. The drug is found to be more potent and possesses longer duration of action than the terfenadine. It has a slow onset, is long acting, and nonsedating piperidine antihistaminic having practically little anticholinergic activity. It is indicated for seasonal allergic rhinitis and chronic urticaria. It is an effective antiallergic agent giving protection against asthma, hay fever, and chronic urticaria. It does not exhibit any noticeable CNS activity.

Assay: Dissolve the sample in a mixture of anhydrous acetic acid and methyl ethyl ketone, and titrate against 0.1 M perchloric acid using naphtholbenzein solution as an indicator.

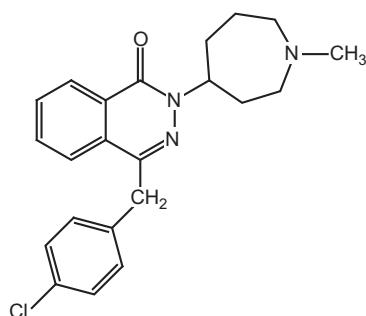
Dose: Usual dose is 10 mg (oral) increased, if required, to 30 mg per day for upto 7 days 1 h before meals. It is not recommended for children below 6 years.

2. Tazifylline



Properties and uses: Tazifylline is proved for its successful antiallergic activity, with no significant occurrence of side effects (dryness of mouth and sedation) and long duration of action.

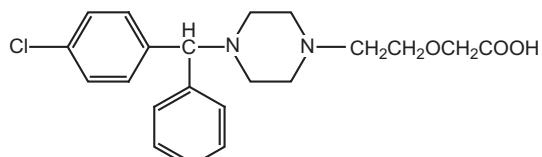
3. Azelastine



Properties and uses: It is a racemic mixture of white crystals, soluble in water, methanol or propylene glycol, but only slightly soluble in ethanol, octanol, or glycerine. It combines potent H₁-receptor antagonism with a negligible anticholinergic and moderate serotonergic activity. It is used in the treatment of itching of the eyes associated with allergic conditions.

III Nonsedative H₁-antihistamines (H₁-antagonists)

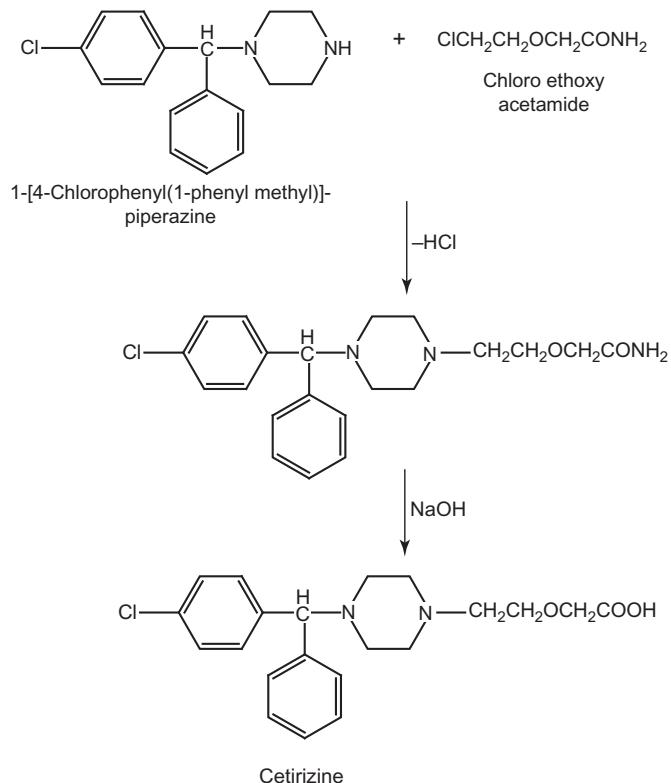
1. Cetirizine (Zirtin, Cetin, Cetzine)



2-(2-((4-Chlorophenyl)methyl)piperazin-1-yl)ethoxyacetic acid

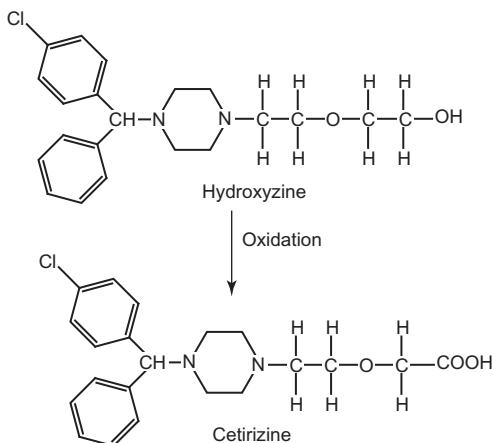
Synthesis

Route I. From: 1-[4-Chlorophenyl (1-phenylmethyl)]-piperazine



Route II. From: hydroxyzine

Cetirizine is an acid metabolite formed by the oxidation of primary alcohol of antihistamine hydroxyzine.

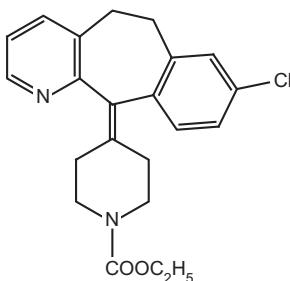


Properties and uses: Cetirizine hydrochloride is a white powder, soluble in water, practically insoluble in acetone and methylene chloride. This is the principal metabolic product of hydroxyzine, the polar acid group prevents its penetration into the CNS. It is used as an antihistamine to treat various allergic conditions. Cetirizine is one of the most widely prescribed H₁-antihistamines. It is highly selective in its interaction with various hormonal binding sites and highly potent as well. Other effects of this drug include fatigue, dry mouth, pharyngitis, and dizziness.

Assay: Dissolve the sample in a mixture of water and acetone (1:7) and titrate against 0.1 M sodium hydroxide to the second point of inflection and determine the end point potentiometrically.

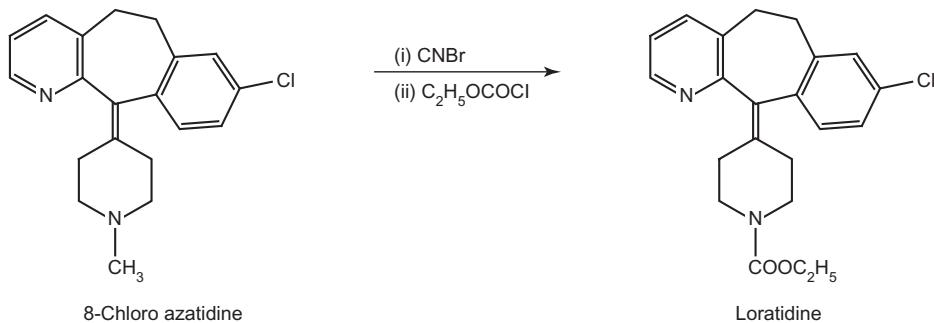
Dose: Usual dose is 5–10 mg thrice/day.

2. Loratadine (Alaspan, Lorfast)

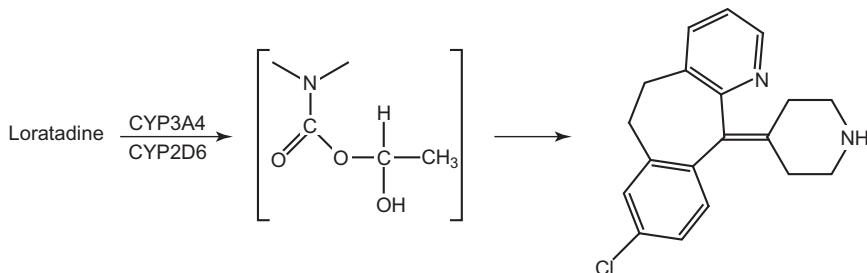


4-(8-Chloro-5,6-dihydro-benzocyclohepta pyridine-11-ylidene)-1-piperidine carboxylic acid ethylester

Synthesis



Metabolism: It is a nonsedative antihistaminic drug. The metabolite is desloratadine (descarboethoxy loratadine) is associated with potentially cardiotoxic effect.

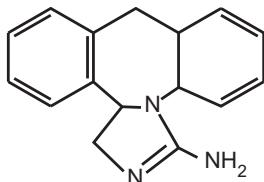


The metabolic conversion of loratadine to descarboethoxy loratadine occurs via oxidative process and not via hydrolysis, and both CYP2D6 and CYP3A4 are to be the isoenzyme catalyzing this oxidative metabolism.

Properties and uses: Loratadine is a white crystalline powder, practically insoluble in water, soluble in acetone and methanol. Loratadine is an azo isomer of cyproheptadine. The replacement of methyl group of azatadine (piperidine nitrogen) by corresponding carbamate and introduction of 8-chloro substitution preserve the antihistaminic action and reduces the CNS effect. The potency of loratadine is comparable with that of astemizole and greater than of terfenadine.

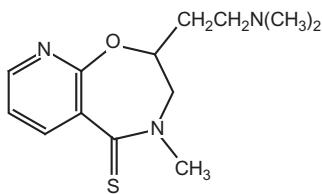
Assay: Dissolve the sample in glacial acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

3. Epinastine



Properties and uses: This is structurally related to the antidepressant and nonsedative H₁-receptor antagonist mianserin. Introduction of an amidine moiety preserve the antihistamine action and reduce the CNS effect (sedation).

4. Rocastine

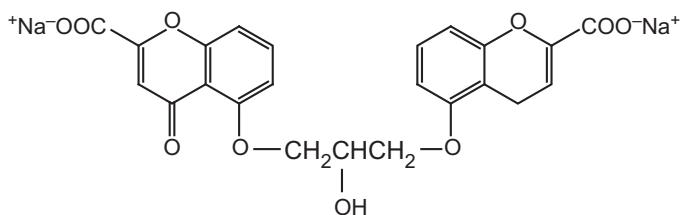


2-(2-(Dimethylamino)ethyl)-4-methyl-3,4-dihydro pyrido[3,2-f][1,4]oxazepine-5(2H)-thione

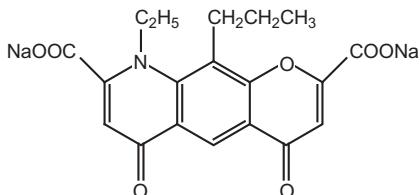
Properties and uses: It is a rapid acting, nonsedating H₁-antagonist. The R-enantiomer was at least 300 times more potent than S-enantiomer.

IV. Inhibition of histamine release (mast cell stabilizer)

i. Cromolyn sodium



ii. Nedocromil sodium



PROBABLE QUESTIONS

- What is histamine? What are its biological effects? Mention the different histamine receptors.
- What are allergens? What is the importance of antihistamines in combating various types of allergic conditions? Mention suitable examples to support your answer.
- Classify the histamine H₁-receptor antagonists. Write the structure, chemical name, and uses of one drug from each category.
- What are the side effects of classical antihistamines?
- Outline the synthesis of the following: Diphenhydramine, Chlorpheniramine maleate and Triprolidine.
- Name any three ethylenediamines being used as antihistamines. Outline the synthesis of any one of them.
- Write the chemical structure, chemical name, and uses of the following and describe the synthesis of any one drug.
 - Mepyramine maleate
 - Tripterygium hydrochloride
- Outline the synthesis of the following drugs and mention their uses.
 - Promethazine hydrochloride
 - Antazoline
 - Methdilazine hydrochloride
- Phenindamine tartarate and chlorpheniramine maleate are two important antihistamines. Describe the synthesis of any one drug in detail.
- Write a brief account of the following:
 - Drugs used in the prevention of histamine release
 - Newer antihistamines
- Write a comprehensive account of the following:
 - SAR of H₁-receptor blockers
 - Mode of action of antihistamines
- What are nonsedative antihistamines? Enumerate them with the chemical structure and write the synthesis of any one of them.

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Chapter 2

Prostaglandins

INTRODUCTION

Prostaglandins (PGs) occur virtually in all mammalian tissues and possess numerous and diverse pharmacological actions. They are comprised of a large number of unsaturated hydroxy, lipids like acids containing 20 carbon atoms. Since they were extracted from prostate gland and seminal vesicles of several animal species, including that of human semen, the term prostaglandin was used for them. It is isolated and purified as hydroxy fatty acid fraction from lipid extracts of seminal vesicles and from it the two biologically active substances, that is, PG E and F, were isolated. Some active compounds were derived from oxygenation of arachidonic acid, a precursor released from membrane phospholipids. The anti-inflammatory and analgesic effects of aspirin and the related nonsteroidal anti-inflammatory drugs (NSAIDs) are due to their inhibitory effects on PG formation.

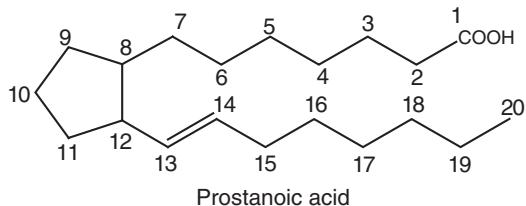
They are also reported to be present in significant quantities in the reproductive tissues, developing foetus and deciduals, umbilical cord, amniotic fluid, endometrium, menstrual fluid, epidermis, thymus, thyroid, and nerves. Further, in most of the organs, except for genital tissue, the PG is present as prostaglandin E (PGE) and prostaglandin F₂ (PGF₂). Therapeutic potential of PGs are in the treatment of blood pressure, bronchial functions, atherosclerosis, heart attack, inhibition of blood clot formation, childbirth, abortions, stomach ulcers, and other related syndromes.

FUNCTIONS OF PGs

There are varieties of physiological effects including the following:

1. Blood clots are formed when a blood vessel is damaged. A type of PGs called thromboxane (TxA₂) stimulates constriction and clotting of platelets. Conversely, PGI₂ have the opposite effect on the walls of blood vessels.
2. Certain PGs are involved in the induction of labour and other reproductive processes. PGE₂ causes uterine contractions and has been used to induce labour.

Nomenclature



PGs are considered as analogues of poly unsaturated fatty acids. It is a 20 carbon carboxylic acid containing a five-member ring. The PGs (Table 2.1) are classified according to the nature of:

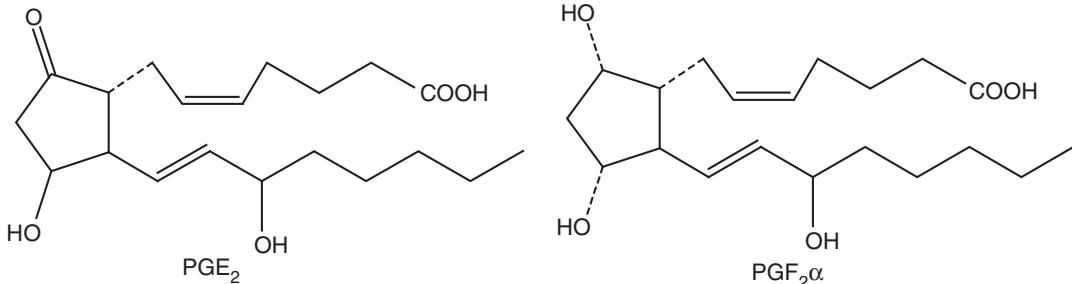
- Cyclopentane ring.
- Two side chain.
- Configuration of newly introduced functional group.

Table 2.1 Various types of PGs.

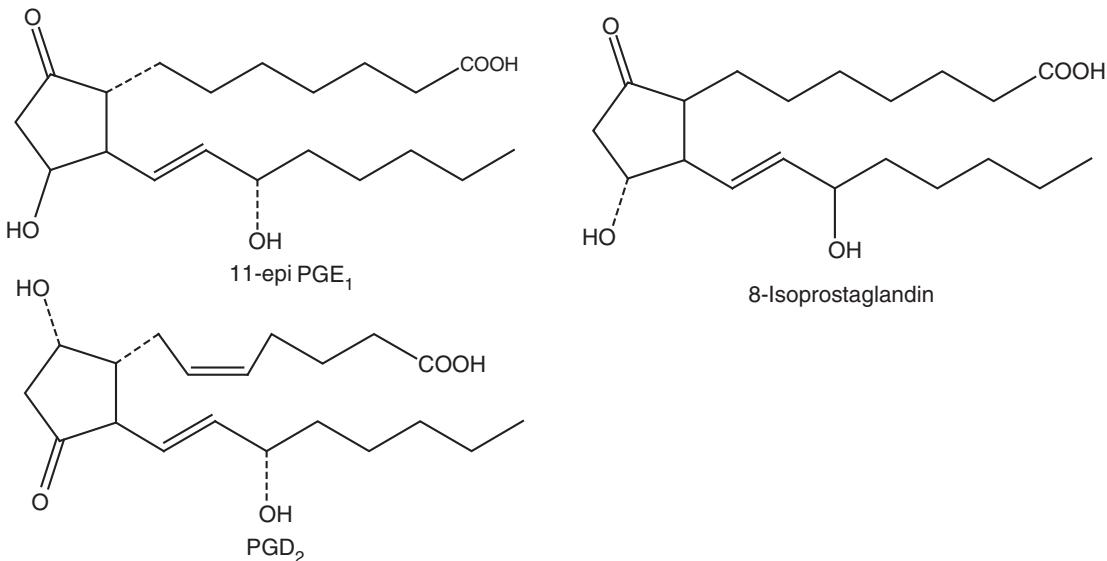
| | | |
|-------------|--|---|
| A- type PGA | | 10, 11-Uncsaturated-9-Keto function |
| B- type PGB | | 8, 12-Uncsaturated-9-Keto function |
| C- type PGC | | 11, 12-Uncsaturated-9-Keto function |
| D- type PGD | | 11-Keto-9-hydroxy function |
| E- type PGE | | β -hydroxyl ketone with keto moiety at C-9 and α -OH at C-11 |
| F- type PGF | | 1,3-Diols |

The main classes are further subdivided according to the number of double bonds in the side chain. This is indicated by the subscripts 1, 2, or 3 and refers to the fatty acid precursor in most instances.

Examples: PGE₂ and PGF₂ α .



Two side chains are attached to the cyclopentane ring at C-8 and C-12. The upper chain, having a carboxylic acid group at the terminal, is α -side chain and the lower chain, having OH group at C-15 position, is a β side chain. The α and β chains are in *trans* configuration in the prostanoic acid. The chiral centre C-15 is a δ nature (PGE). The OH group at C-11 in the E series has the α configuration, however, in unnatural configurations the 11-OH is called 11-epi PGs, having arms fused C to each other and are named as iso prostaglandins.



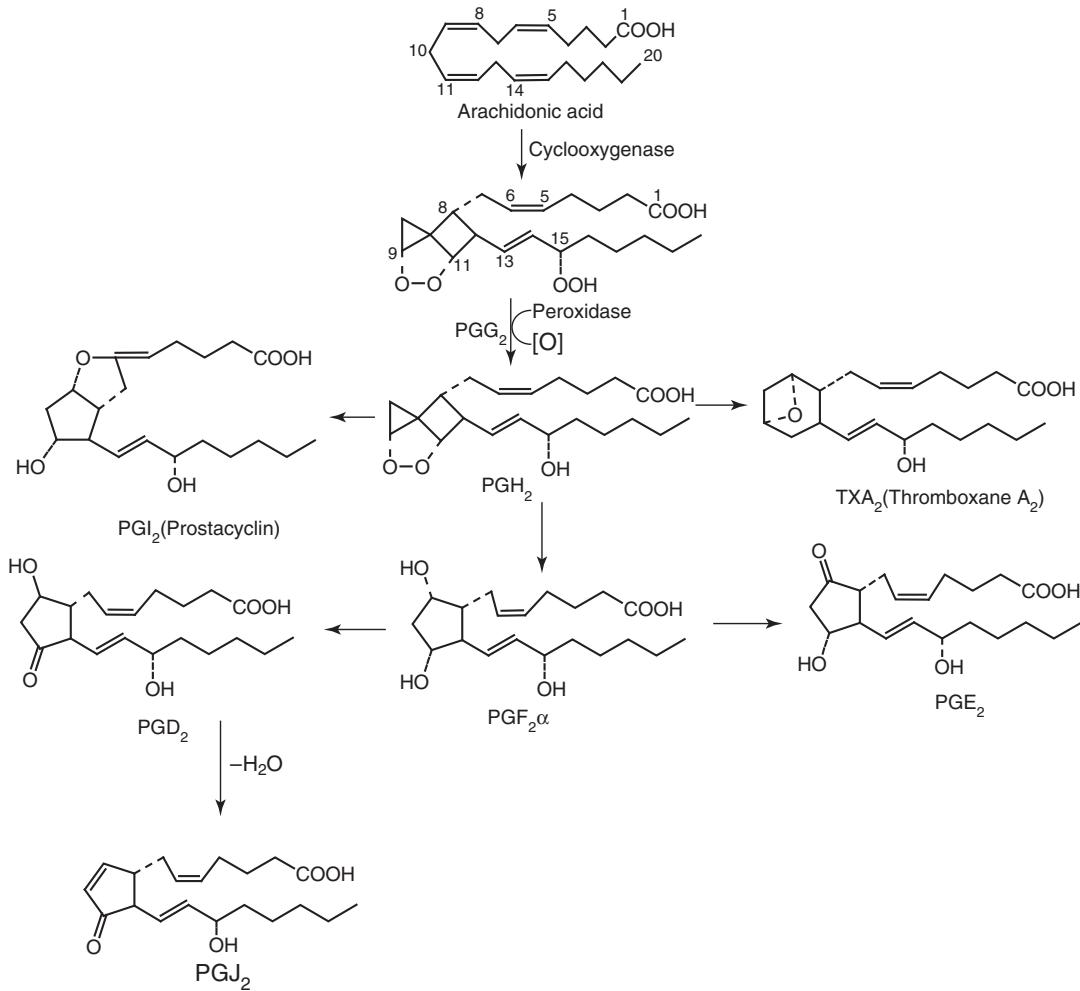
BIOSYNTHESIS

PGs are found in virtually all the tissues and organs. They are autocrine and paracrine lipid mediators that act on platelet endothelium, uterine tissues, and mast cells among others. The biosynthesis of PGE and PGF

has been thoroughly established and both of them are derived from arachidonic acid. Two types of pathways have been proposed and are designated as follows:

1. Cyclooxygenase pathway
2. Lipoxygenase pathway

CYCLOOXYGENASE PATHWAY

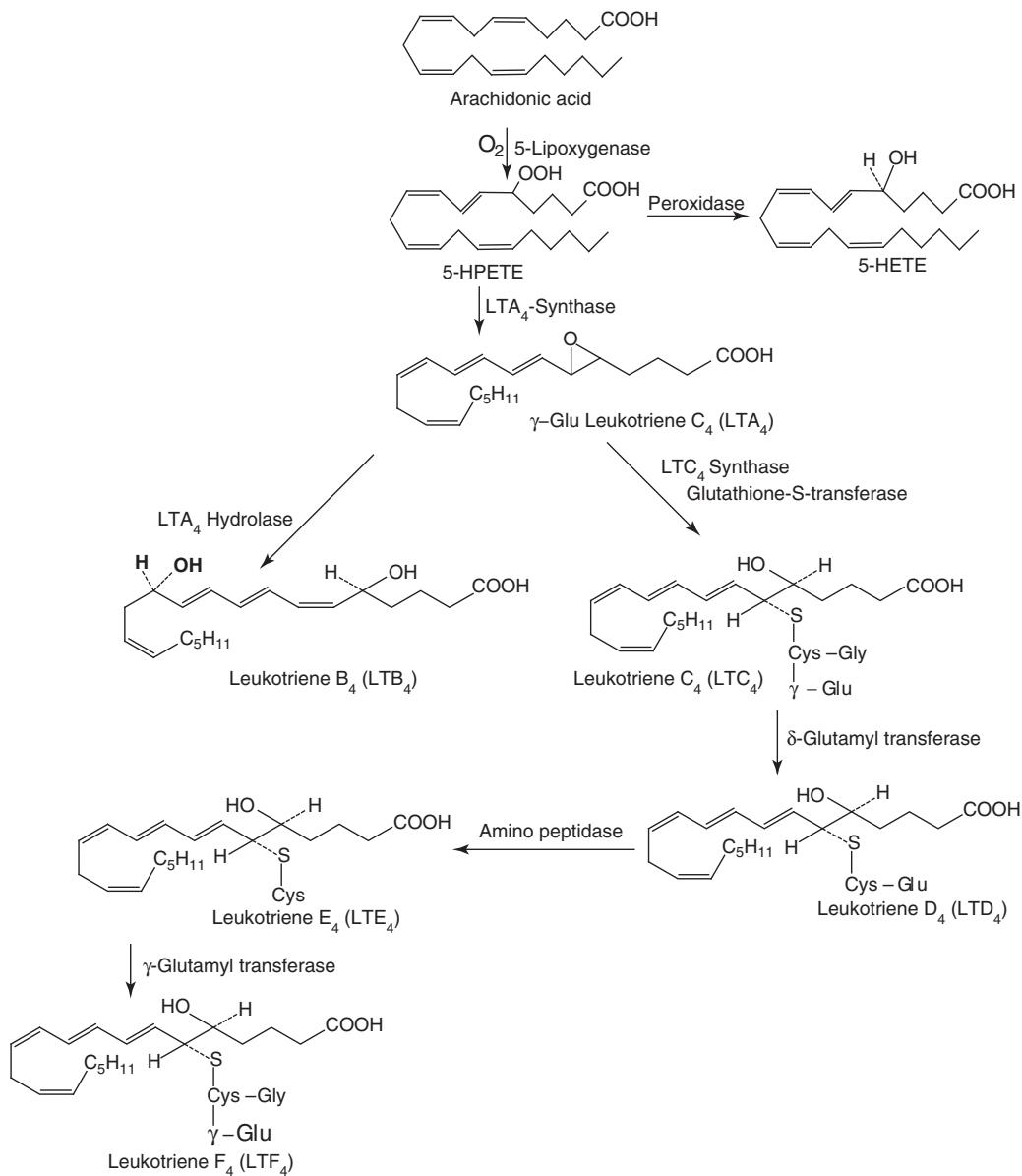


Arachidonic acid is derived from dietary linoleic acid. It is present as a conjugated component of the phospholipid matrix of the most cellular membrane. Release of free arachidonic acid is due to the stimulation of phospholipase enzyme in response to some traumatic events (tissues damage, toxin, exposure, and hormonal stimulation). The first step in this pathway is the interaction of arachidonic acid with PGH synthase, a haemoprotein, that catalyses both the addition of oxygen and subsequent reduction (peroxide activity) of the 15th position of hydroperoxide to 15(s) configuration alcohol prostaglandin H₂.

(PGH_2). PGH synthase is also called as cyclooxygenase I (COX-1) or cyclooxygenase II (COX-2). NSAIDs inhibit PGs synthesis; leading to relief of the pain, fever, and inflammation.

PGH_2 serves as a substrate for specific enzymes, leading to the production of various PGs, TXA_2 , and PGI_2 . While PGE_2 is formed by the action of endoperoxide isomerase on PGH_2 and PGD_2 by the action of isomerase or glutathione-s-transferase on PGH_2 , PGF_2 is formed from PGH_2 via endoperoxidase reductase. Thromboxane synthetase acts on PGH_2 to produce thromboxane A_2 .

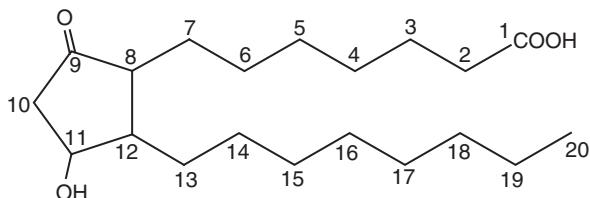
LIPOXIDASE PATHWAY



Lipoxygenase are a group of enzymes that oxidize polyunsaturated fatty acid possessing two *cis* double bond separated by a methylene group to produce lipid peroxides. Arachidonic acid is metabolized to form a number of hydroperoxy eicosatetraenoic acid (HPETE) derivatives. These enzymes differ in the position at which they peroxidize arachidonic acid and in the tissues specificity. For example, platelets possess only 12-lipoxygenase, whereas leukocytes possess both 12-lipoxygenase and 5-lipoxygenase. Leukotriens are products of the 5-lipoxygenase pathways and are divided into major classes.

Hydroxylate eicosatetraenoic acid (LTs) is represented by lymphotoxin β_4 (LTB_4) and peptido leukotrienes (PLTs), such as leukotriene C4 (LTC_4), leukotriene D4 (LTD_4), and LTE_4 . Lipoxygenase produces leukotrienase from 5-HPETE. Lysine epsilon-aminotransferase (LAT) synthetase converts 5-HPETE to unstable epoxide termed leukotriene A4 (LTA_4) that may be converted by the enzymes into the leukotriene, LTB_4 or by LTC_4 to other leukotrienes (e.g. LTD_4 , LTE_4 , and LTF_4), and reconjugation with glycine and glutamic acid, respectively.

SAR of PGs



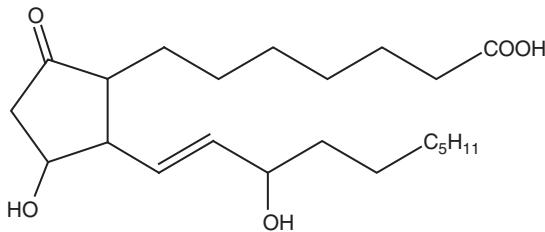
In the upper chain: Methyl esters (misoprostol), sulphonamide (sulprostone), and hydroxyl group (rioprost) possess greater activity than natural PGs.

In the cyclopentane ring: Variation in the cyclopentane ring results in a reduction in the PG activity. Enlargement of the ring or reduction of the ring leads to inactive compounds. Replacement of the carbon atom of cyclopentane ring by O, S, and N also leads to inactive compounds. Replacement of 9-keto group with =CH₂ group gives active (metenprost) PG.

In the lower chain: C-15 hydroxyl group is protected (from metabolism) by the introduction of methyl group at C-15 and gem dimethyl group at C-16. The shifting of C-15 hydroxyl to C-16 position increases the metabolic stability of alkoxy, phenoxy (enprostil, sulprostone) analogues, and they are more active than natural PGs. Introduction of acetylinic group at C-13 and C-14 increase the leuteolytic activity.

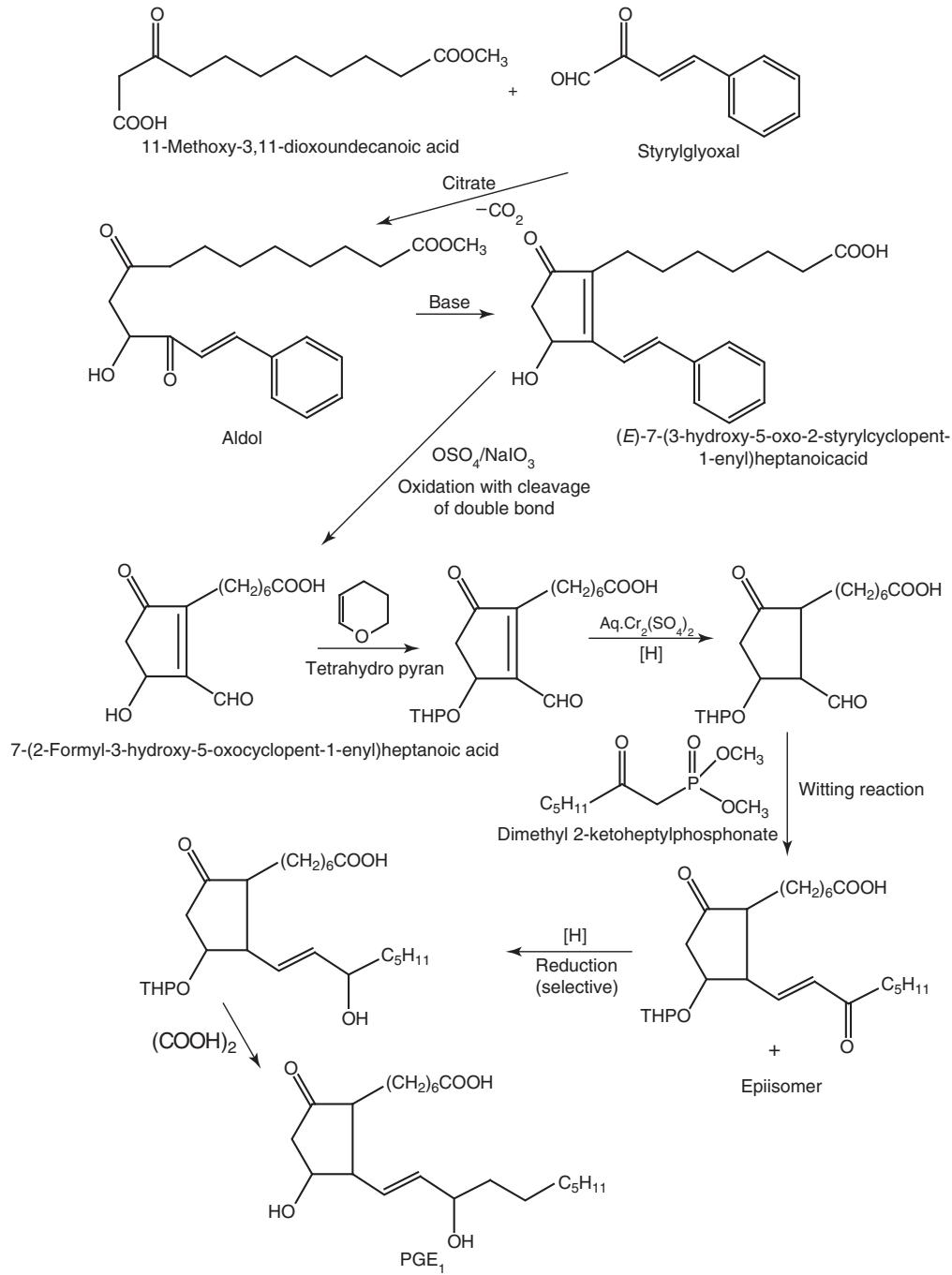
SYNTHESIS AND DRUG PROFILE

i. Prostaglandin E₁ (PGE₁)



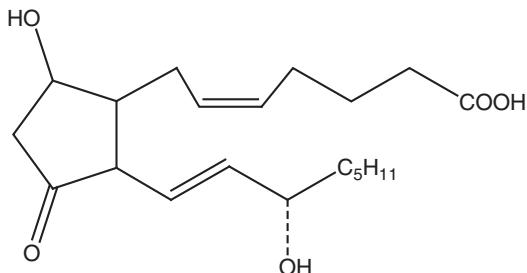
(E)-7-(3-hydroxy-2-(3-hydroxydec-1-enyl)-5-oxocyclopentyl)heptanoic acid

Synthesis



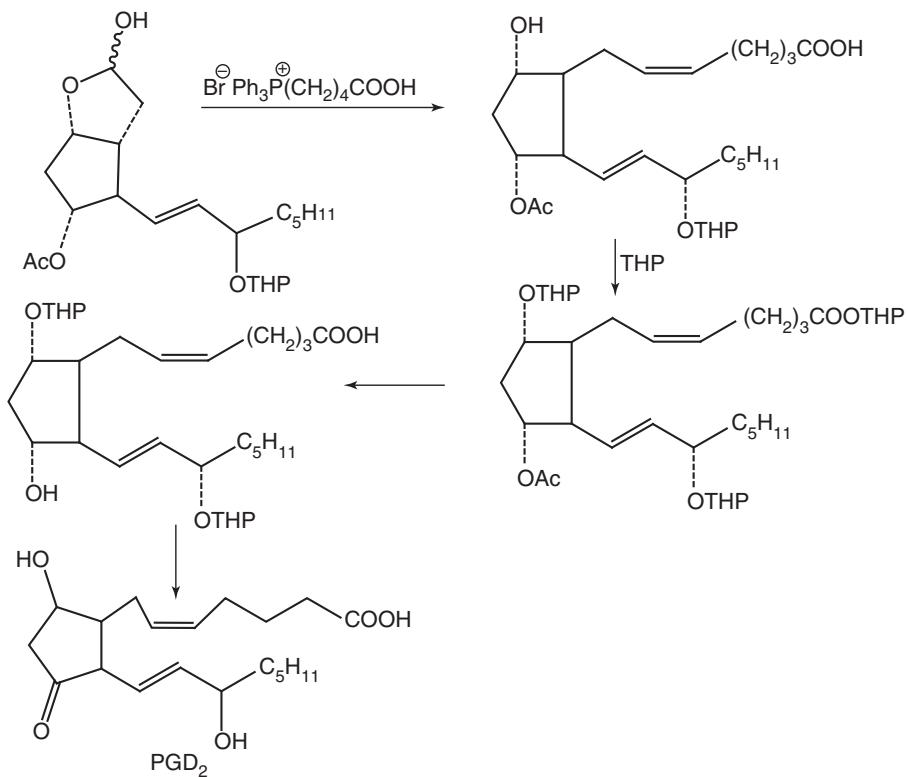
Dose: A dose of misoprostol, 200 µg three times a day for acute duodenal ulcer and comparable with cimetidine.

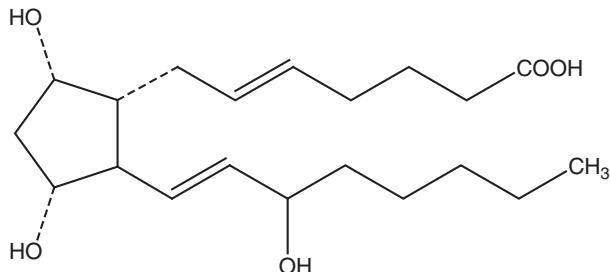
ii. Prostaglandin D₂ [PGD₂]



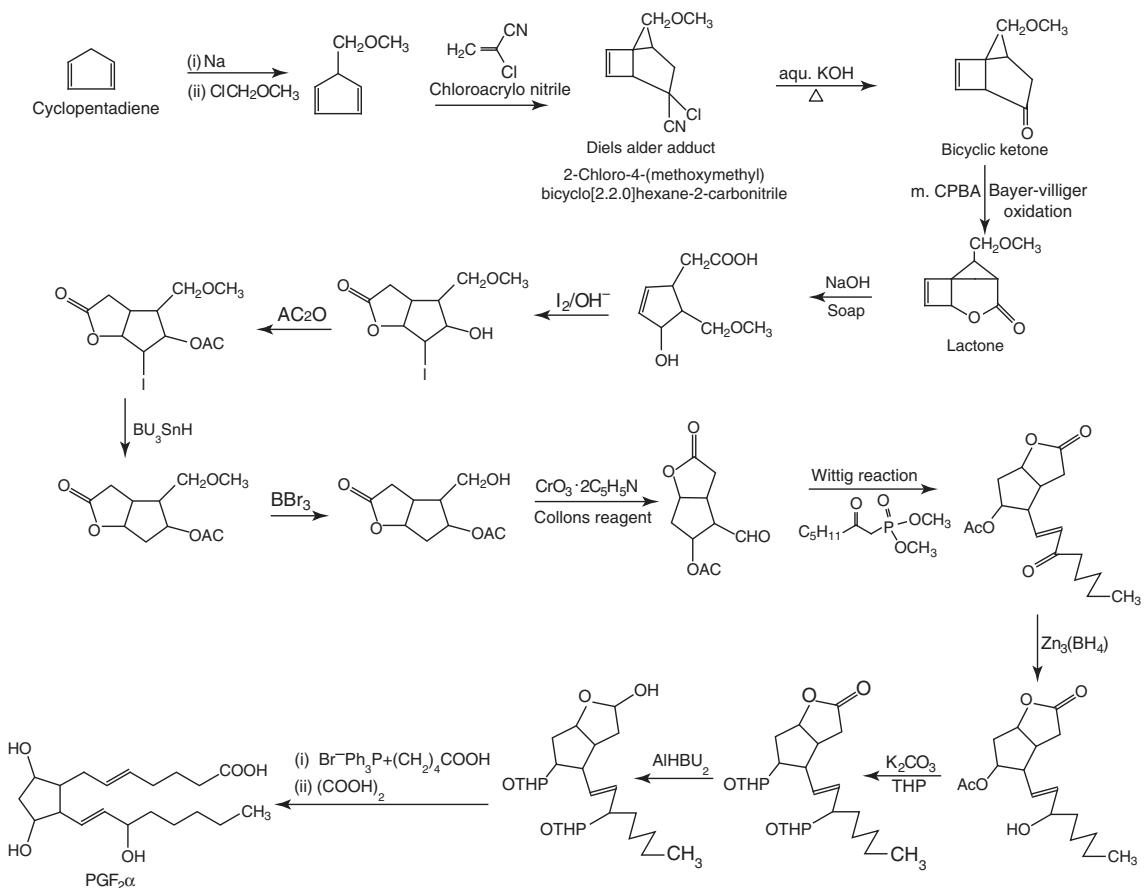
(Z)-7-(5-Hydroxy-2-((S,E)-3-hydroxyoct-1-enyl)-3-oxocyclopentyl)hept-5-enoic acid

Synthesis



PGF₂α

`(E)-7-((1R,3R,5S)-3,5-dihydroxy-2-((E)-3-hydroxyoct-1-enyl)cyclopentyl)hept-5-enoic acid

Synthesis

Metabolism: PGs are rapidly metabolized and inactivated by various oxidative and reductive pathways. The initial step involves rapid oxidation of the 15 α -OH group to the corresponding ketone by the PG-specific enzyme called PG 15 α -OH dehydrogenase. This is followed by a reduction of the C-13 and C-14 double bond by PG Δ^{13} -reductase to the corresponding dihydroketone, which represent the major metabolite in plasma. Subsequently, enzymes normally involved in 13 and ω oxidation of fatty acids more slowly cleave the α -chain and oxidize the C-20 terminal methyl group to the carboxylic acid derivative, respectively.

PROBABLE QUESTIONS

1. What are PGs? Classify them with their chemical structure.
2. Write the SAR of PGs.
3. Write the nomenclature of different types of PGs.
4. Write the structure, chemical name, synthesis, and uses of the following compounds.
(a) PGE₁ (b) PGD₂
5. Explain the role of PGs and eicosanoids to combat the following diseases:
(a) Gastric ulceration (b) Management of congenital heart disease

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Chapter 3

Analgesics, Antipyretics, and NSAIDs

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used primarily to treat inflammation, mild-to-moderate pain, and fever. Specific uses include the treatment of headache, arthritis, sports injuries, and menstrual cramps. Aspirin is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk. NSAIDs are also included in many cold and allergic preparations.

NSAIDs are associated with a number of side effects. The frequency of side effects varies according to the drugs; the most common side effects are gastro intestinal tract (GIT) disturbances, such as nausea, diarrhoea, constipation, vomiting, decreased appetite, and peptic ulcer. NSAIDs may also cause fluid retention, leading to oedema; the most serious side effects are kidney failure, liver failure, ulcers, and prolonged bleeding after an injury or surgery. Some individuals are allergic to NSAIDs and may develop shortness of breath when NSAIDs are administered. People with asthma are at a higher risk for experiencing serious allergic reaction to NSAIDs. Use of aspirin in children and teenagers with chicken pox or influenza has been associated with the development of Reye's syndrome. Therefore, aspirin and salicylate should not be used in children and teenagers with suspected or confirmed chicken pox or influenza.

Antipyretics are the drugs that reduce the elevated body temperature. Anti-inflammatory agents are used to cure or prevent inflammation caused by prostaglandin (PGE_2). These drugs are widely utilized for the alleviation of minor aches, pains, fever, and symptomatic treatment of rheumatic fever, rheumatoid arthritis, and osteoarthritis. The biosynthetic pathway of prostaglandins (PGs) is depicted in Figure 3.1

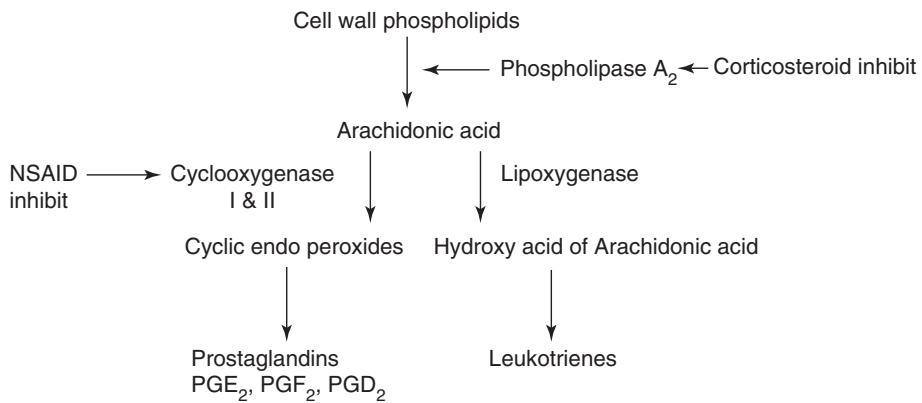
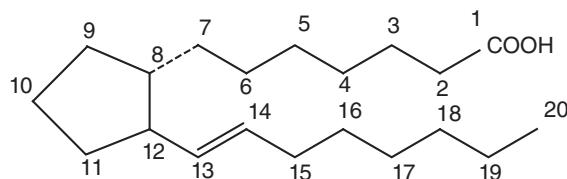


Figure 3.1 Biosynthetic pathway of PGs.

General Structure of PG

PG is a naturally occurring 20-carbon cyclopentano fatty acid derivative, derived from arachidonic acid.



Mode of action: NSAIDs inhibit cyclooxygenase (COX), the enzyme that catalyses the synthesis of cyclic endoperoxides, from the arachidonic acid to form PGs. The two COX isoenzymes are COX-1 and COX-2. The function of COX-1 is to produce PGs that are involved in normal cellular activity, (protection of gastric mucosa, maintenance of kidney function). While, COX-2 is responsible for the production of PGs at the inflammation sites. Most NSAIDs inhibit both COX-1 and COX-2 with varying degree of selectivity. Selective COX-2 inhibitor may eliminate the side effects associated with NSAIDs due to COX-1 inhibition, such as gastric and renal effect.

SIDE EFFECTS

In stomach: Biosynthesis of PGs, especially PGE₂ and PGI₂, serves as cytoprotective agents in gastric mucosa; these PGs inhibit acid secretion by the stomach, enhance mucosal blood flow, and promote the secretion of cytoprotective mucus in the GIT. Inhibition of the PGs synthesis may make the stomach more susceptible to damage and lead to gastric ulcer.

In platelets: Platelet's function get disturbed because NSAIDs prevent the formation of Thromboxane A₂ (TXA₂) in platelets, as TXA₂ is a potent platelet-aggregating agent. This accounts for the tendency of these drugs to increase the bleeding time and this side effect has been exploited in the prophylactic treatment of thromboembolic disorder.

In uterus: NSAIDs prolong gestation because of the inhibition of PGF₂ in uterus. PGF₂ is a potent uterotrophic agent and their biosynthesis by uterus increase dramatically in the hours before parturition. Accordingly, some anti-inflammatory drugs have been used as a colytic agent to inhibit preterm labour.

In kidney: NSAIDs decrease renal blood flow and the rate of glomerular filtration in patients with congestive heart failure, hepatic cirrhosis, and with chronic renal disease, in addition, they prolong the retention of salt and water, this may cause oedema in some patients.

CLASSIFICATION

- I. Salicylic acid derivatives: Aspirin, Diflunisal, Salsalate, Sulphasalazine.
- II. *p*-Amino phenol derivatives: Paracetamol, Phenacetin.
- III. Pyrazolidine dione derivatives: Phenyl butazone, Oxyphenbutazone, Sulphin-pyrazone.
- IV. Anthranilic acid derivatives: Mefenamic acid, Flufenamic acid, Meclofenamate.
- V. Aryl alkanoic acid derivative.
 - a. Indole acetic acid: Indomethacin.
 - b. Indene acetic acid: Sulindac.
 - c. Pyrrole acetic acid: Tolmetin, Zormipirac.
 - d. Phenyl acetic (propionic) acid: Ibuprofen, Diclofenac, Naproxen, Caprofen, Fenoprofen, Keto-profen, Flurbiprofen, Kеторолак, Etodaolac.
- VI. Oxicams: Piroxicam, Meloxicam, Tenoxicam.
- VII. Selective COX-2 inhibitors: Celecoxib, Rofecoxib, Valdecoxib.
- VIII. Gold compounds: Auronofin, Aurothioglucose, Aurothioglucamide, Aurothiomalate sodium.
- IX. Miscellaneous: Nabumetone, Nimesulide, Analgin.
- X. Drug used in gout: Allopurinol, Probenecid, sulphapyrazone.

I. Salicylates

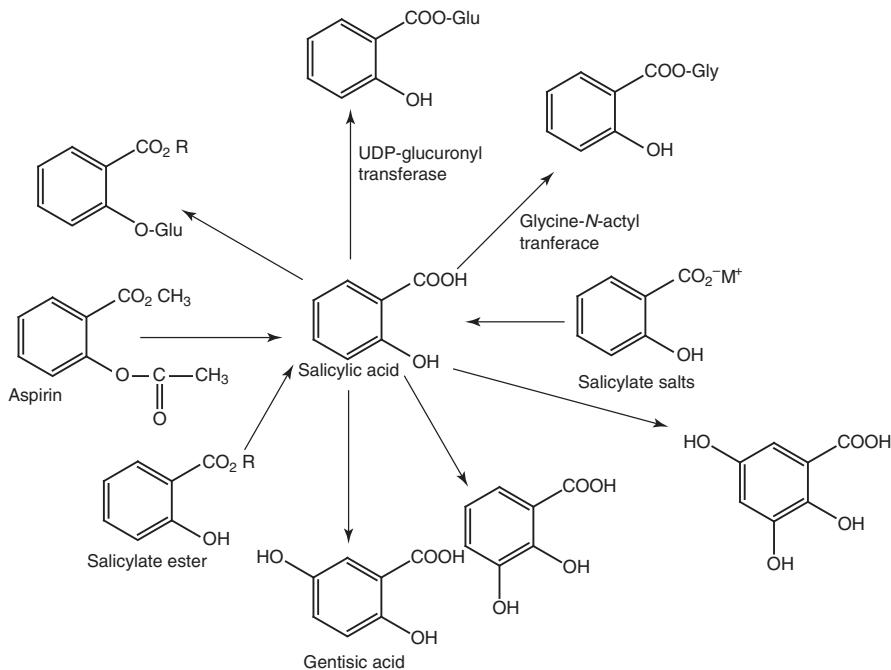
Salicylates not only possess antipyretic, analgesic, and anti-inflammatory properties, but also other actions that have been proven to be therapeutically beneficial because salicylates promote the excretion of uric acid and they are useful in the treatment of gouty arthritis. More attention has been given to the ability of salicylates (aspirin) to inhibit platelet aggregation, which may contribute to heart attack and strokes, and hence, aspirin reduces the risk of myocardial infarction. In addition, a recent study suggested that aspirin and other NSAIDs might be protective against colon cancer.

Structural Activity Relationship (SAR) of Salicylates

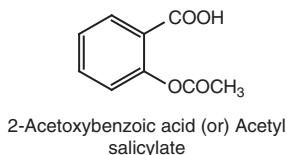
- The active moiety of salicylates is salicylate anion, side effects of aspirin, particularly GIT effects appear to be associated with the carboxylic acid functional group.
- Reducing the acidity of the carboxy group results in a change in the potency of activity. Example—the corresponding amide (salicylamide) retains the analgesic action of salicylic acid, but is devoid of anti-inflammatory properties.
- Substitution on either the carboxyl or phenolic hydroxyl group may affect the potency and toxicity. Benzoic acid itself has only weak activity.
- Placement of the phenolic hydroxyl group at meta or para to the carboxyl group abolishes the activity.

- Substitution of halogen atom on the aromatic ring enhances potency and toxicity.
- Substitution of aromatic ring at the 5th position of salicylic acid increase anti-inflammatory activity (diflunisal).

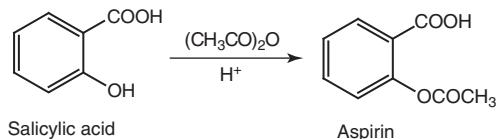
Metabolism of salicylic acid derivatives: The initial route of metabolism of these derivatives is their conversion to salicylic acid, which is excreted in urine as free acid (10%) or undergoes conjugation with either glycine to produce the major metabolites of salicylic acid (75%) or with glucuronic acid to form glucuronide (15%). In addition, small amount of metabolites resulting from microsomal aromatic hydroxylation leads to gentisic acid.



i. Aspirin (Emipirin, Bufferin)



Synthesis



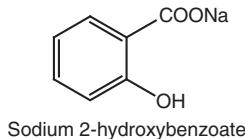
Properties and uses: Aspirin is a white crystalline powder, slightly soluble in water and soluble in alcohol, indicated for the relief of minor aches and mild-to-moderate pain in the conditions such as arthritis and related arthritic condition. Also used in myocardial infarction prophylaxis.

Assay: Dissolve the sample in alcohol and add 0.5 M sodium hydroxide. Allow to stand and titrate against 0.5 M hydrochloric acid using phenolphthalein as an indicator. Perform a blank titration.

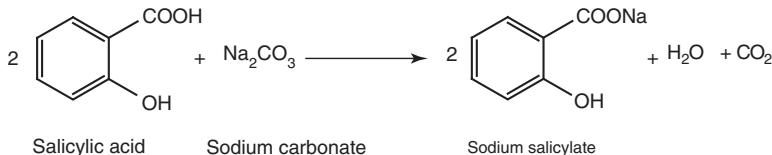
Dose: Usual adult dose: 300 to 650 mg every 3 or 4 h orally or 650 mg to 1.3 g as the sustained-release tablet every 8 h; rectal, 200 mg to 1.3 g three or four times a day.

Dosage forms: Aspirin tablets I.P., B.P., Dispersible aspirin tablets B.P., Effervescent soluble aspirin tablets B.P., Gastro-resistant aspirin tablets B.P., Aspirin and Caffeine tablets B.P., Co-codaprin tablets B.P., Dispersible co-codaprin tablets B.P.

ii. Sodium salicylate



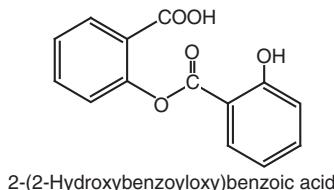
Synthesis



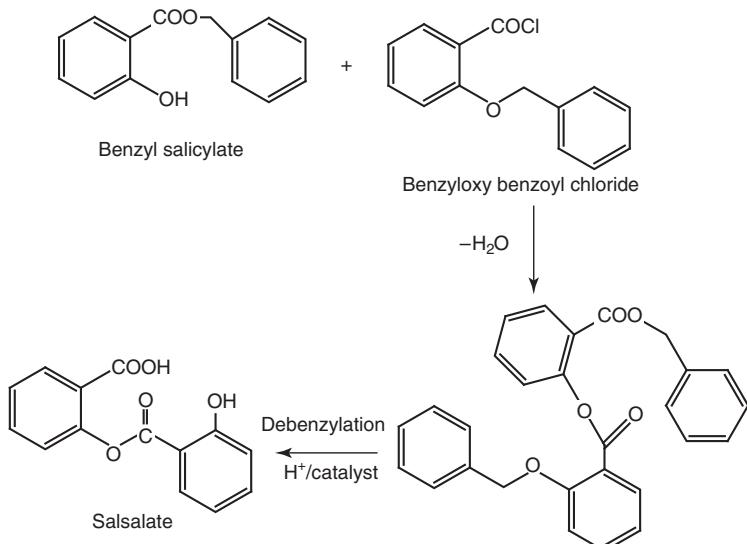
Properties and uses: Sodium salicylate is a white crystalline powder, soluble in water, sparingly soluble in alcohol. It is used for fever and for the relief of pain. It also possesses anti-inflammatory actions similar to aspirin and symptomatic therapy of gout.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end-point potentiometrically.

iii. Salsalate (Disalacid, Saloxium)



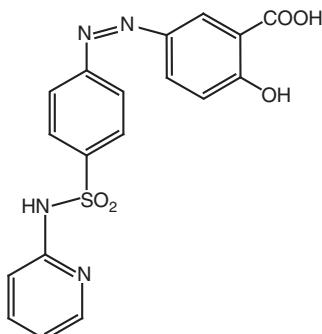
Synthesis



Properties and uses: Salsalate or salicylsalicylic acid is a dimer of salicylic acid. It is insoluble in gastric juice, but is soluble in the small intestine where it is partially hydrolyzed into two molecules of salicylic acid and absorbed. It does not cause GI blood loss. It has antipyretic, analgesic, and anti-inflammatory properties similar to those of aspirin. It is employed in the treatment of rheumatoid arthritis and other rheumatic disorders.

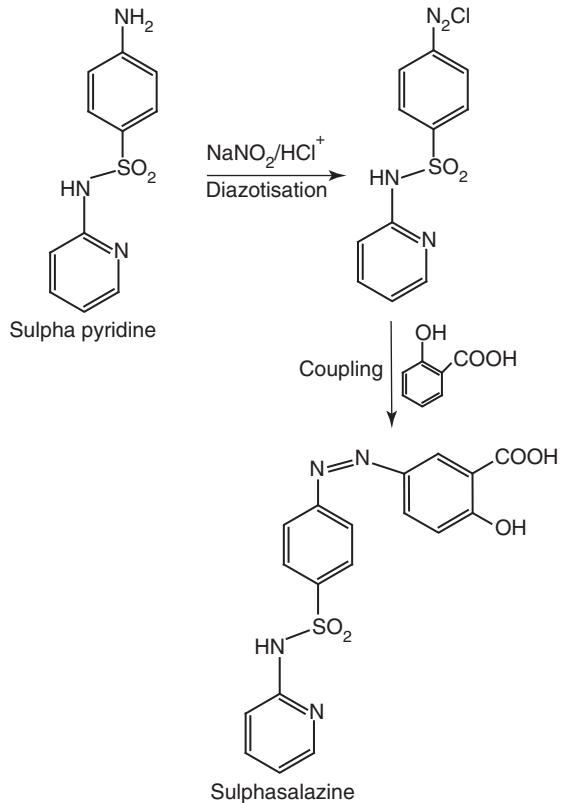
Dose: Usual adult dose is 325–1000 mg 2–3 times a day, orally.

iv. Sulphasalazine (Azultidine, Azaline)



Properties and uses: Sulphasalazine is a bright yellow or brownish-yellow fine powder, practically insoluble in water and methylene chloride, very slightly soluble in alcohol, soluble in dilute solutions of alkali hydroxides. Sulphasalazine is a mutual prodrug. In large intestine, it is activated to liberate 5-amino salicylic acid, which in turn inhibits PG synthesis and the sulphapyridine is useful for the treatment of infection. Hence, sulphasalazine is used in the treatment of ulcerative colitis.

Synthesis

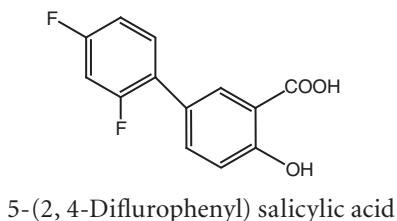


Assay: Dissolve and dilute the sample in 0.1 M sodium hydroxide and add 0.1 M acetic acid and measure the absorbance at the maxima of 359 nm using ultraviolet spectrophotometer. Prepare a standard solution at the same time and in the same manner, using sulphasalazine reference standard.

Dose: Dose orally is initially 3–4 g daily, followed by 500 mg four times a day for maintenance.

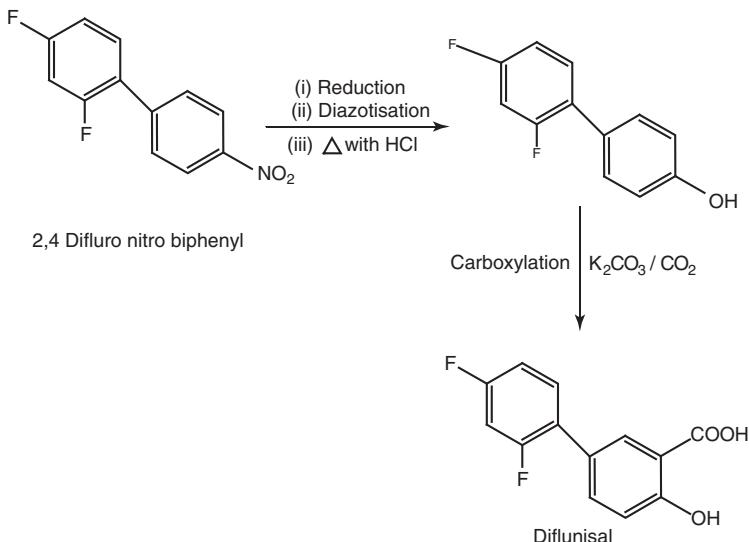
Dosage forms: Sulphasalazine tablets B.P.

v. Diflunisal



5-(2,4-Difluorophenyl) salicylic acid

Synthesis



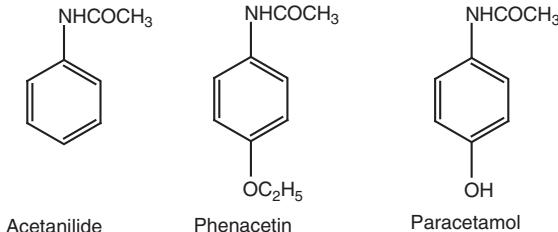
Properties and uses: Diflunisal is a white crystalline powder, practically insoluble in water, soluble in alcohol, and dilute solutions of alkali hydroxides. It is more potent than aspirin, but produces fewer side effects, and has a biological half-life 3–4 times greater than that of aspirin. It is a nonselective cyclooxygenase inhibitor used as antipyretic, analgesic, and anti-inflammatory.

Assay: Dissolve the sample in methanol, add water, and titrate against 0.1 M sodium hydroxide using phenol red as indicator, until the colour changes from yellow to reddish-violet.

II. *p*-Amino phenol derivatives

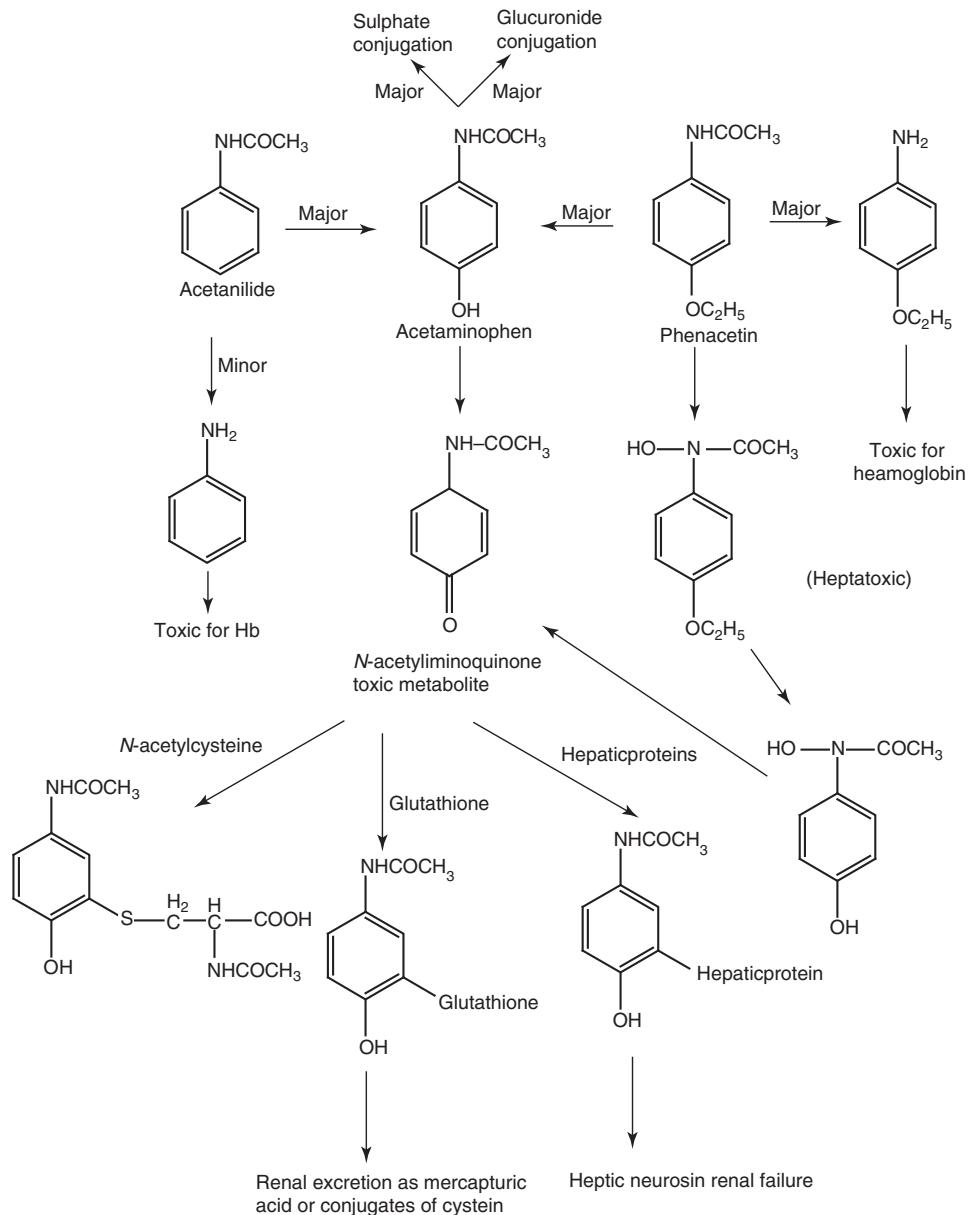
These derivatives possess analgesic and antipyretic action, but lack anti-inflammatory effects. Acetanilide was introduced into the therapy in 1886 as an antipyretic-analgesic agent. However, it was subsequently found to be too toxic, having been associated with methemoglobinemia and jaundice.

Phenacetin was introduced in the following year and was widely used but was withdrawn recently because of its nephrotoxicity. Acetaminophen (paracetamol) was introduced in 1893 and it remains the only useful agent of this group used as an antipyretic and an analgesic agent.



Metabolism of para aminophenol derivatives: These drugs undergo hydrolysis to yield aniline derivatives that produce directly or through their conversion to hydroxylamine derivatives, such as Acetaminophen

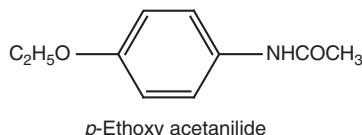
that undergoes rapid first pass metabolism in the GIT to *o*-sulphate conjugate. The *N*-hydroxylamine is then converted into a reactive toxic metabolite, acetiminoquinone, which produce toxicity to the kidney and liver in conjugation with hepatic glutathione to form mercapturic acid or cysteine conjugates.



SAR of *p*-amino Phenol Derivatives

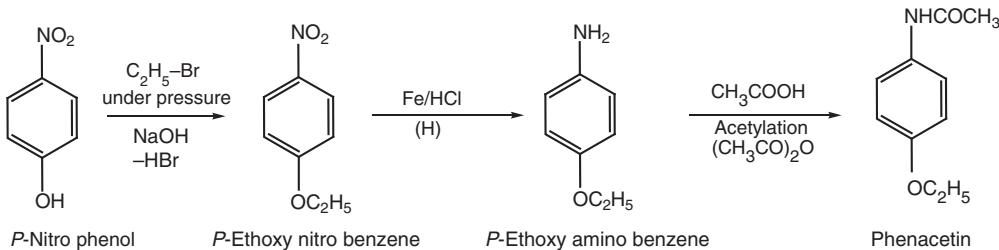
- Etherification of the phenolic function with methyl or propyl groups produces derivatives with greater side effects than ethyl derivatives.
- Substituents of the nitrogen atom, which reduce the basicity, also reduce activity unless the substituent is metabolically labile. Example—acetyl groups.
- Amides derived from aromatic acid. Example—*N*-phenyl benzamides that are less active or inactive.

i. Phenacetin (Acetophenetidin)

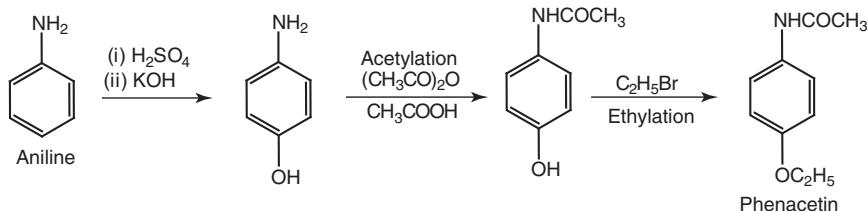


Synthesis

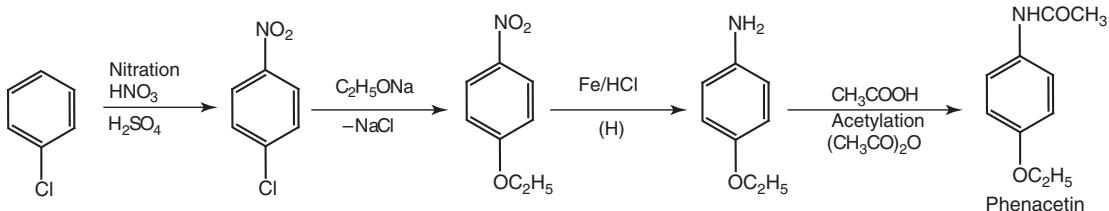
Route I. From: *p*-nitro phenol



Route II. From: aniline



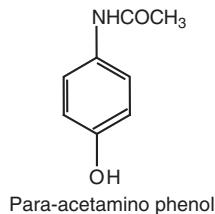
Route III. From: chlorobenzene



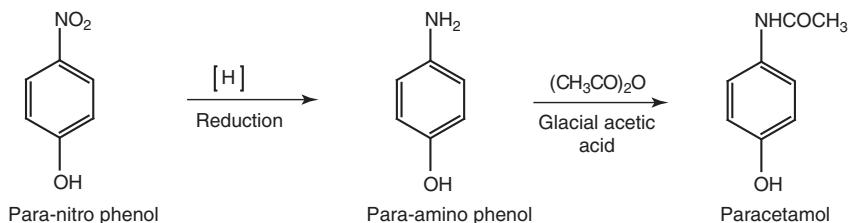
Properties and uses: It exists as a white glistening powder with a bitter taste, sparingly soluble in water and soluble in chloroform. It is an analgesic and an antipyretic with similar effectiveness as an aspirin. It has a greater potential for toxicity (hemolytic anaemia and methemoglobinemia) than paracetamol.

Dose: Usual dose as oral for adults is 300 mg to 2 g per day.

ii. Paracetamol (Metacin, Tylenol, Tapar, Calpol)



Synthesis



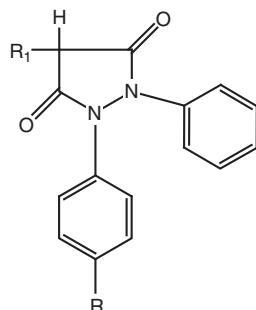
Properties and uses: Paracetamols exist as white crystalline powder, sparingly soluble in water, soluble in alcohol, and very slightly soluble in methylene chloride. Paracetamols produce antipyresis by acting on the hypothalamic heat-regulating centre and analgesia by elevating the pain threshold. Hepatic necrosis and death have been observed following over dosage; hepatic damage is likely in an adult who takes more than 10 g in a single dose or if a 2-year old child takes more than 3 g.

Assay: Dissolve the sample in a mixture of water and dilute sulphuric acid (1:3), reflux, cool, and dilute with water. Add dilute hydrochloric acid and titrate against 0.1 M cerium sulphate using ferroin as an indicator until a greenish-yellow colour is obtained. Perform a blank titration.

Dose: Usual oral adult dose is 500 mg to 1 g for three or four times a day.

Dosage forms: Paracetamol tablets I.P, B.P., Paracetamol syrup I.P., Co-codamol tablets B.P., Effervescent Co-codamol tablets B.P., Co-dydramol tablets B.P., Co-proxamol tablets B.P., Paracetamol capsules B.P., Paediatric paracetamol oral solution B.P., Paracetamol oral suspension B.P., Paracetamol suppositories B.P., Dispersible paracetamol tablets B.P., soluble paracetamol tablets B.P.

III. 3, 5-Pyrazolidinediones

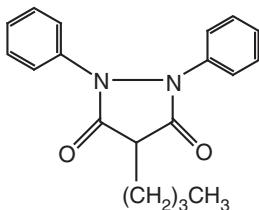


| Name | R | R ₁ |
|------------------|-----|--|
| Phenyl butazone | -H | -C ₄ H ₉ |
| Oxyphenbutazone | -OH | -C ₄ H ₉ |
| Sulphin pyrazone | -H | -(CH ₂) ₂ SOC ₆ H ₅ |

SAR of 3, 5-Pyrazolidinediones

- Replacement of one of the nitrogen atom in the pyrazolidinediones with an oxygen atom yields isoxazole analogues, which are as active as pyrazolidinediones derivatives.
- In 3, 5-pyrazolidinedione derivatives, pharmacological activities are closely related to their acidity, the dicarbonyl function at the 3rd and 5th positions enhance the acidity of hydrogen atom at the 4th position.
- Presence of a keto group in the γ -position of the butyl side chain produces the active compound.
- Decreasing or eliminating acidity by removing the acidic proton at 4th position (e.g. 4, 4-dialkyl derivatives) abolishes anti-inflammatory activity. Thus, if the hydrogen atom at the 4th position of phenyl butazone is replaced by substituents, such as a methyl group, antiinflammation activity is abolished.
- If acidity is enhanced too much, anti-inflammatory and sodium-retaining activities decrease while other properties, such as the uricosuric effect increases.
- Introduction of polar function in these alkyl groups give mixed results. The γ -hydroxy-*n*-butyl derivative posseses pronounced uricosuric activity, but give fewer anti-inflammatory effects.
- Substitution of 2-phenyl thio ethyl group at the 4th position produces antigout activity (sulphinpyrazone).
- Presence of both the phenyl groups is essential for neither anti-inflammatory nor analgesic activity.
- m*-Substitution of aryl rings of the phenyl butazone gives uniformly inactive compounds. *p*-Substitution, such as methyl, chloro, nitro, or OH of one or both rings retains activity.

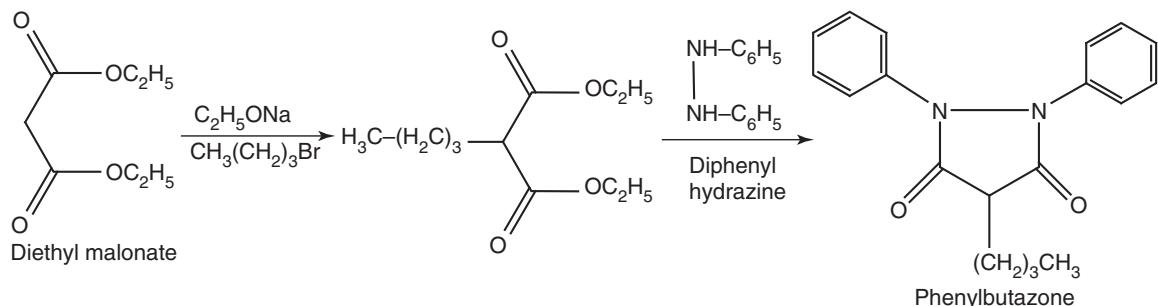
i. Phenylbutazone (Butazolidin, Busone)



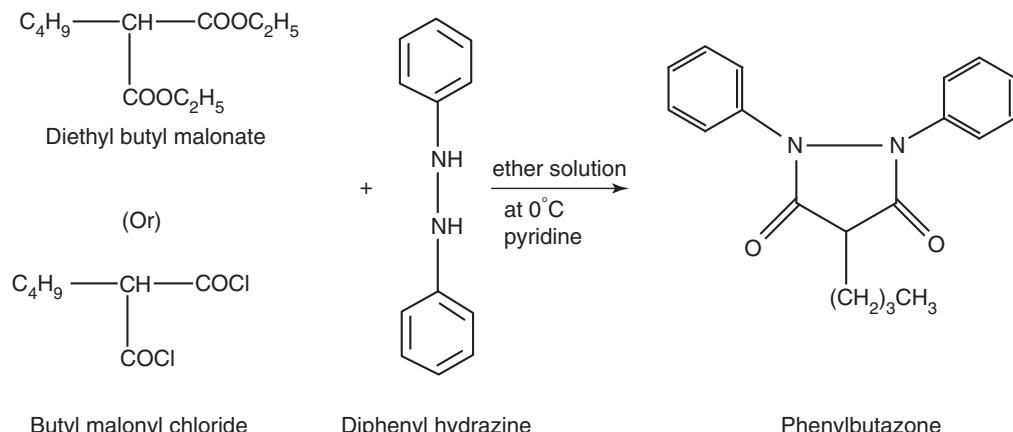
4-*n*-Butyl-1,2 biphenyl-3,5 pyrazolidinedione

Synthesis

Route I. From: Diethylmalonate



Route II. From: Diethyl-butyl malonate or butyl malonylchloride



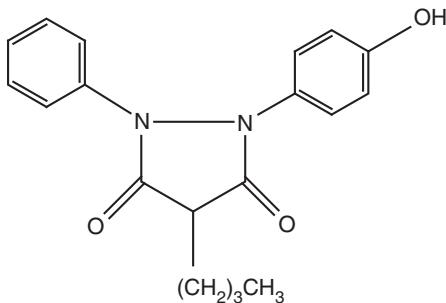
Properties and uses: Phenylbutazone is a white crystalline powder, practically insoluble in water, sparingly soluble in alcohol, and soluble in alkaline solutions. It is a pyrazole derivative that has antipyretic,

analgesic, and anti-inflammatory actions, because of its toxicity it is not used as a general antipyretic or analgesic. It is a usual practice reserved for use in the treatment of osteoarthritis, ankylosing spondylitis, arthritis, acute superficial thrombophlebitis, painful shoulder, and Reiter's disease, where less toxic drugs have failed.

Assay: Dissolve the sample in acetone and titrate against 0.1 M sodium hydroxide using bromothymol blue as indicator until a blue colour is obtained, which persists for few seconds. Perform a blank titration.

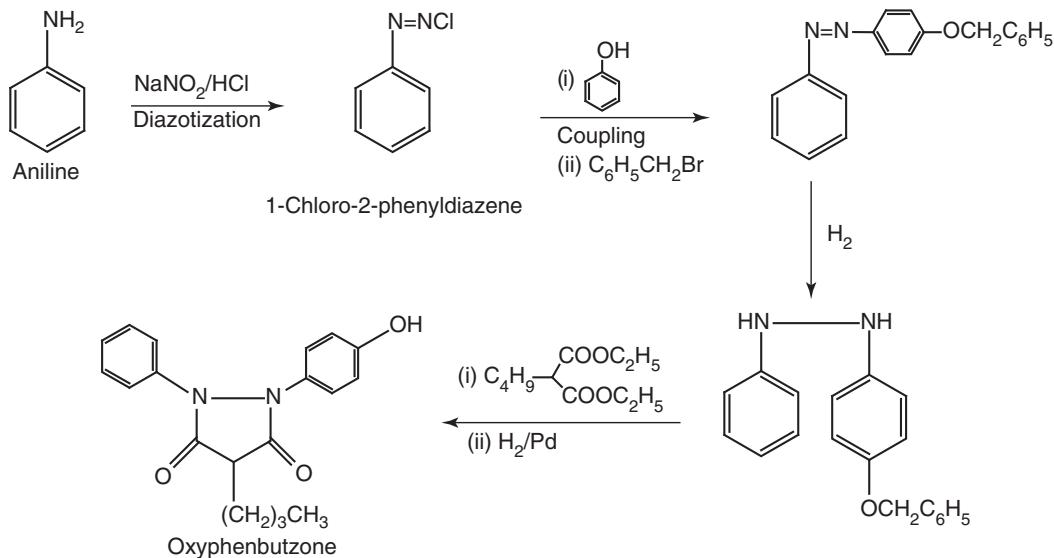
Dose: The usual dose is 100–600 mg per day.

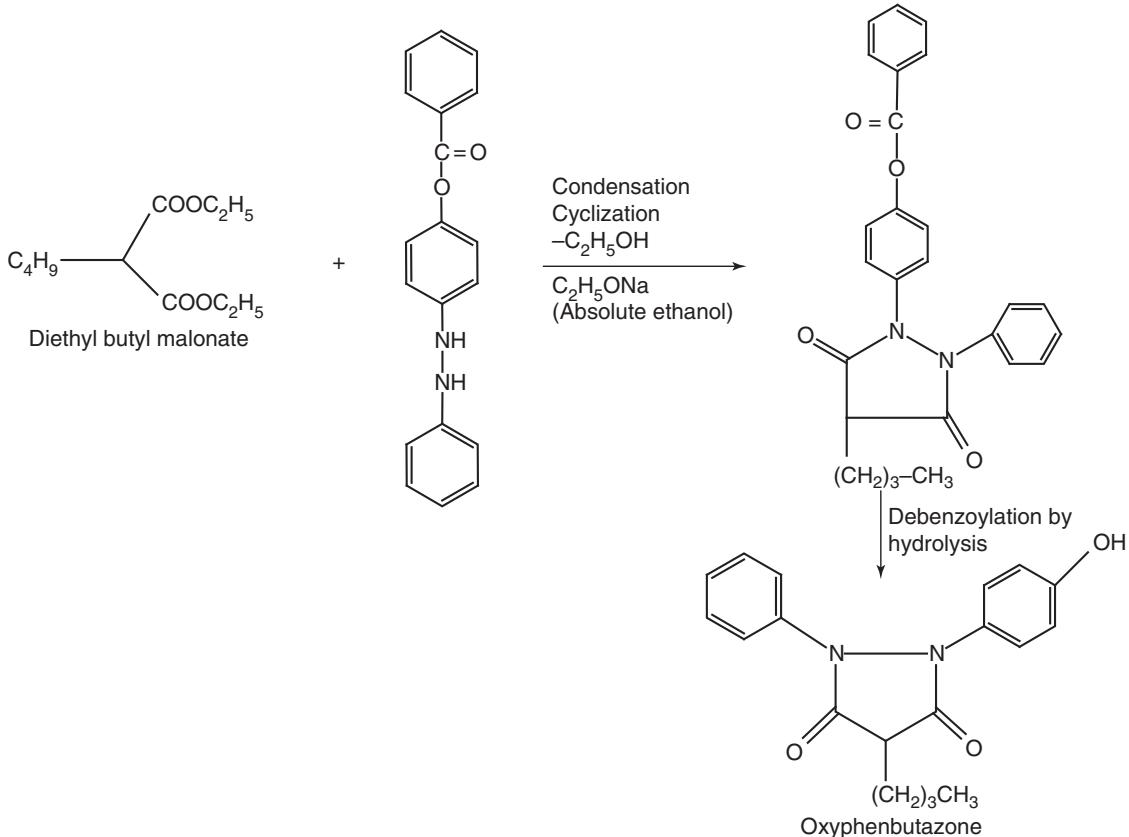
ii. Oxyphenbutazone (Tandearil, Oxaril)



Synthesis

Route I. From aniline



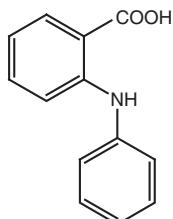
Route II. From: Diethyl butyl malonate

Properties and uses: It exists as a white to yellowish white, odourless, crystalline powder, soluble in water, alcohol, chloroform, and ether. Used as an analgesic and in arthritis.

Dose: Usual oral adult dose for antirheumatic is 100 or 200 mg three times daily; for maintenance the dose is 100 mg one to four times a day; for the treatment of gout 400 mg initially as a loading dose, then 100 mg every 4 h.

IV. Anthranilic acid derivatives (Fenamates)

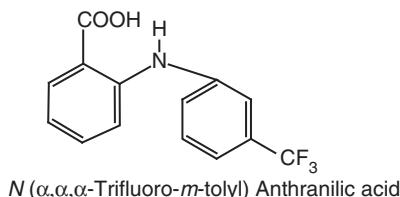
The anthranilic acid class NSAIDs result from the application of classic medicinal chemistry bioisosteric drug design concepts as these derivatives are nitrogen isoteres of salicylic acid.



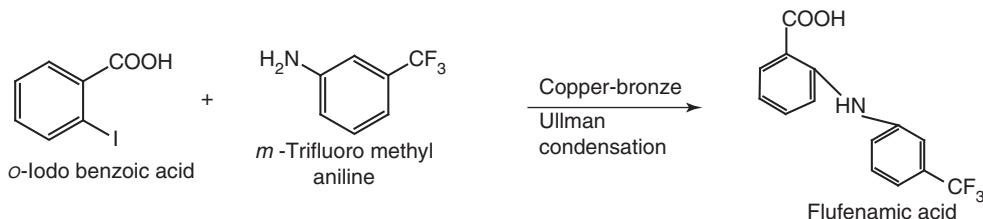
SAR of Anthranilic Acid Derivatives (Fenamates)

- The position of the carboxyl function is important for the activity of anthranilic acid derivatives that are active, whereas the 3 and 4 amino benzoic acid analogues are not active.
- Replacement of carboxylic acid function with the isosteric tetrazole results in the retention of anti-inflammatory activity.
- Placement of substitution on the anthranilic acid ring generally reduces the activity.
- Substitution on the *N*-aryl ring can lead to conflicting results. In the ultraviolet erythema assay for anti-inflammatory activity, the order of activity was generally $3' > 2' > 4'$ for mono substitution with CF_3 group (flufenamic acid) being particularly potent. The opposite order of activity was observed in rat paw oedema assay, the $2'-\text{Cl}$ derivatives being more potent than $3'-\text{Cl}$ analogues.
- In disubstituted derivatives, where the nature of the two substitutes is the same $2', 3'$ -disubstitution appears to be the most effective (mefenamic acid).
- The NH moiety of anthranilic acid is essential for the activity as the replacement of NH function with O, CH_2 , S, SO_2 , $\text{N}-\text{CH}_3$, or NCOCH_3 functionalities significantly reduced the activity.

i. Flufenamic Acid (Arlef, Tarlef)



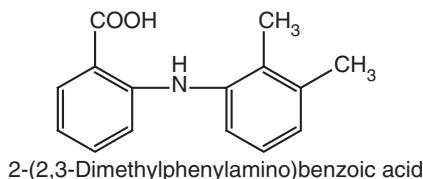
Synthesis



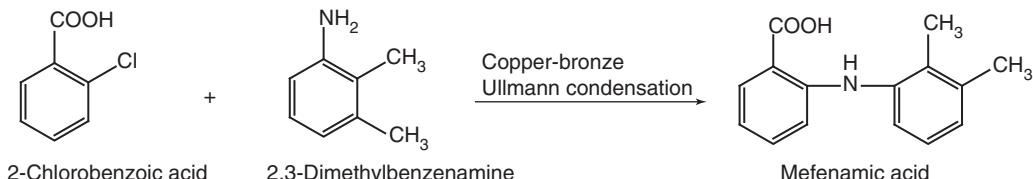
Properties and uses: Flufenamic acid is a pale yellow crystalline powder or needles. It has analgesic, anti-inflammatory, and antipyretic actions; it is employed in the treatment of rheumatic disorder and dysmenorrhoea.

Dose: 400–600 mg per day in divided doses.

ii. Mefenamic acid



Synthesis

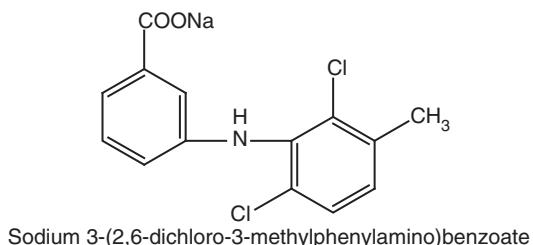


An analogous approach by reaction of *o*-chloro benzoic acid with 2,3-dimethyl aniline.

Metabolism: Its metabolism occurs through regioselective oxidation of 3-methyl group and glucuronidation of mefenamic acid. Majority of the 3-hydroxy methyl metabolite and dicarboxylic acid products are excreted.

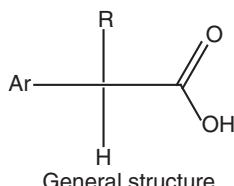
Uses: Used as an analgesic and anti-inflammatory agent.

iii. Meclofenamate Sodium



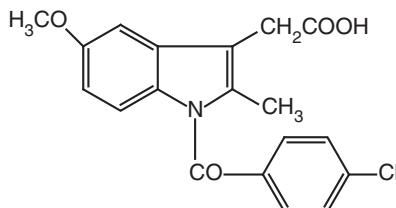
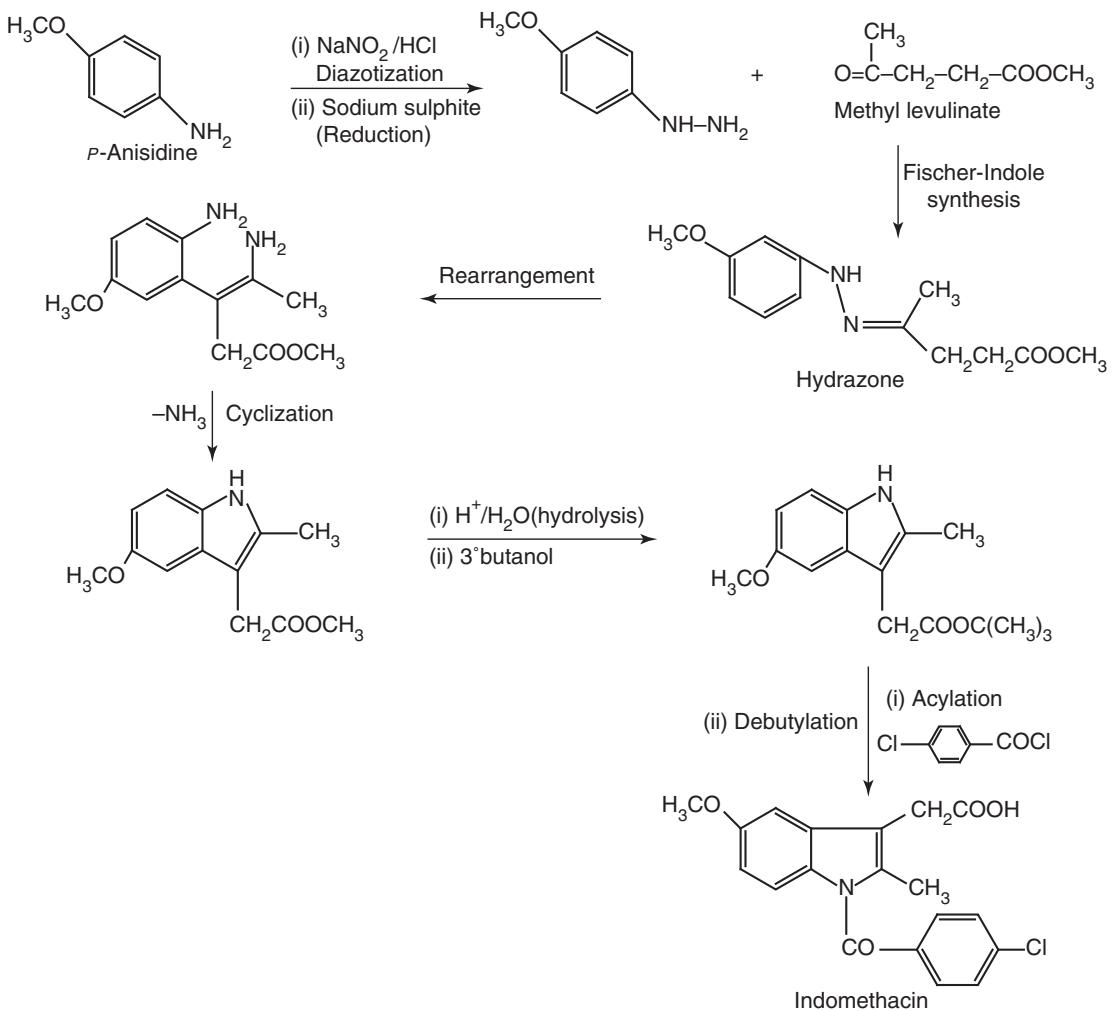
Synthesis: It is obtained by Ullman condensation employing 2,6 dichloro 3-methyl aniline.

V. Arylalkanoic acids

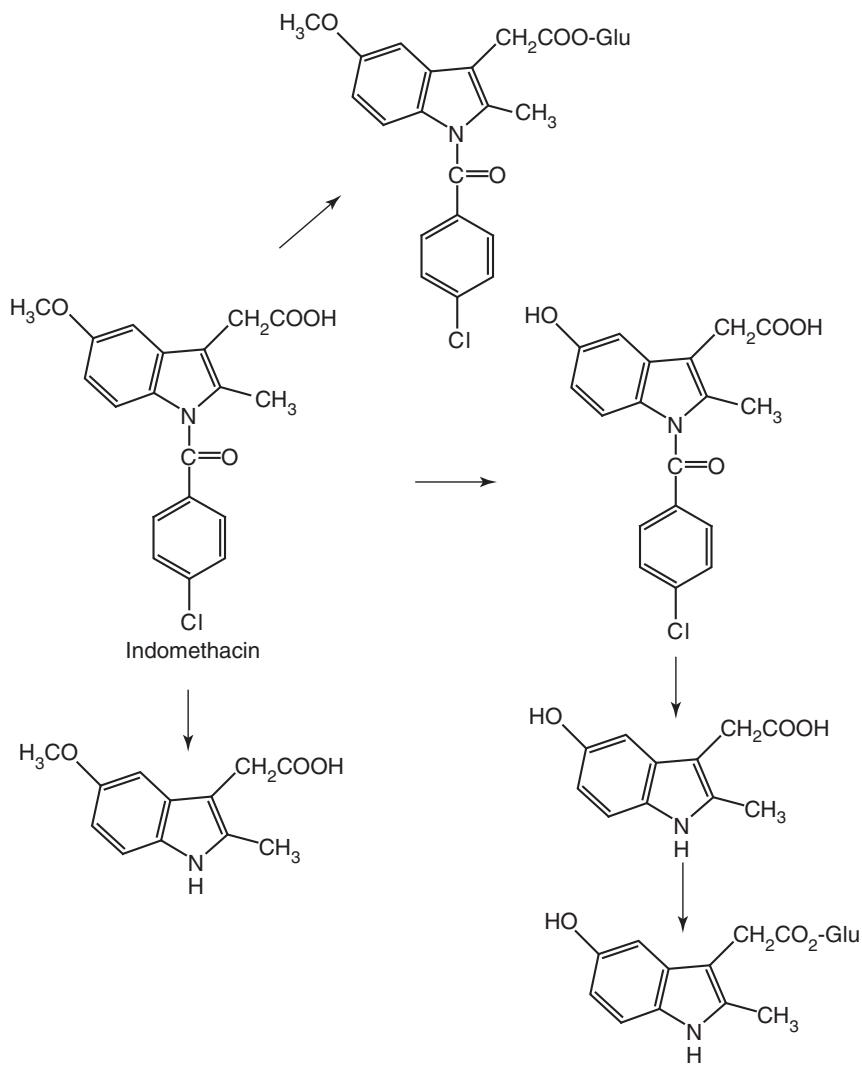


SAR of Arylalkanoic Acids

1. The centre of acidity is usually located one carbon atom adjacent to a flat surface represented by an aromatic or hetero aromatic ring.
2. The distance between these centres is critical because increasing this distance to two or three carbons generally decreases activity.
3. All agents possess a centre of acidity, which can be represented by a carboxylic acid and hydroxamic acid, a sulphonamide or a terazole.
4. Substitution of a methyl group on the carbon atom separating the aromatic ring leads to enhancement of anti-inflammatory activity.

a. Indole acetic acid derivatives**i. Indomethacin (Indocin, Indocid)**1-(*p*-Chloro benzoyl)-5-methoxy-2 methyl indole-3-acetic acid.**Synthesis**

Metabolism: It is converted into inactive metabolites, that is, 50% of single dose is 5-O-demethylated and 10% conjugated with glucuronic acid. Nonhepatic enzymes hydrolyze indomethacin to *N*-deacetylated metabolite.



Properties and uses: It is a white or yellow crystalline powder, insoluble in water and sparingly soluble in alcohol. Indomethacin is more effective than aspirin. The most frequent side effects are gastric distress and headache. It also has been associated with peptic ulceration, blood disorders, and possible death (these side effects appear to be closely related and sometimes can be minimized by reducing the dose). It is not recommended for use in children because of possible interference with the resistance to infection. Used as anti-inflammatory and analgesic in rheumatic arthritis, spondylitis, and to lesser extent in gout.

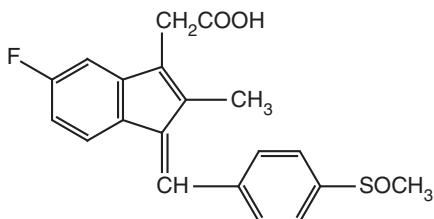
Assay: Dissolve the sample in acetone and pass nitrogen for 15 min and titrate with 0.1 M sodium hydroxide using phenolphthalein as indicator.

Dose: In gout, usual adult dose orally is 100 mg initially, followed by 50 mg three times a day until pain is relieved. As an antirheumatic by oral route, the dose is 50 mg two or three times a day. And as an antipyretic, the dose is orally 25–50 mg three times a day.

Dosage forms: Indometacin capsules I.P., B.P., Indometacin Suppositories I.P., B.P.

V. b. Indeneacetic acid derivatives

i. Sulindac (Clinoril)



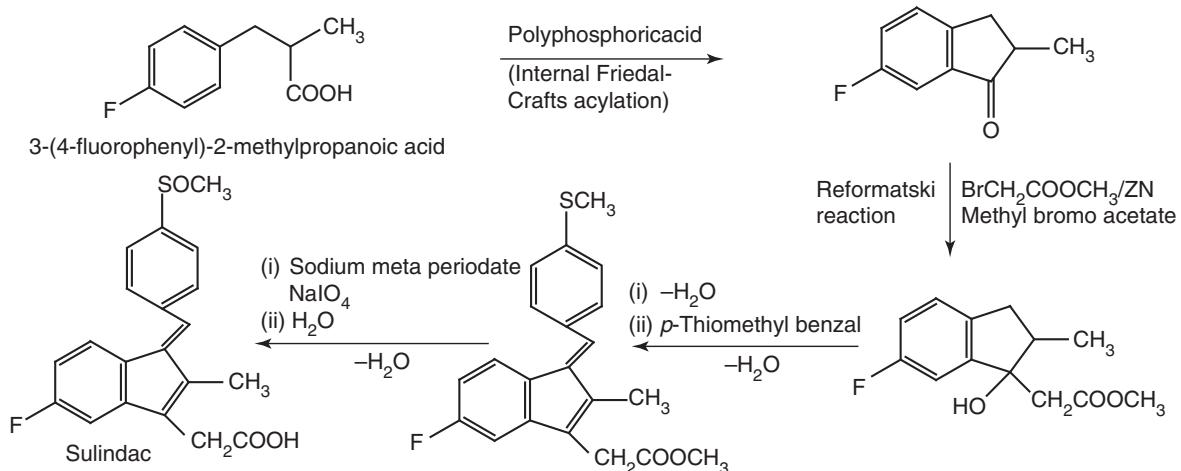
5 Fluoro-2-methyl-1[(4 methyl sulphinyl) phenyl methylene] Indene-3-acetic acid

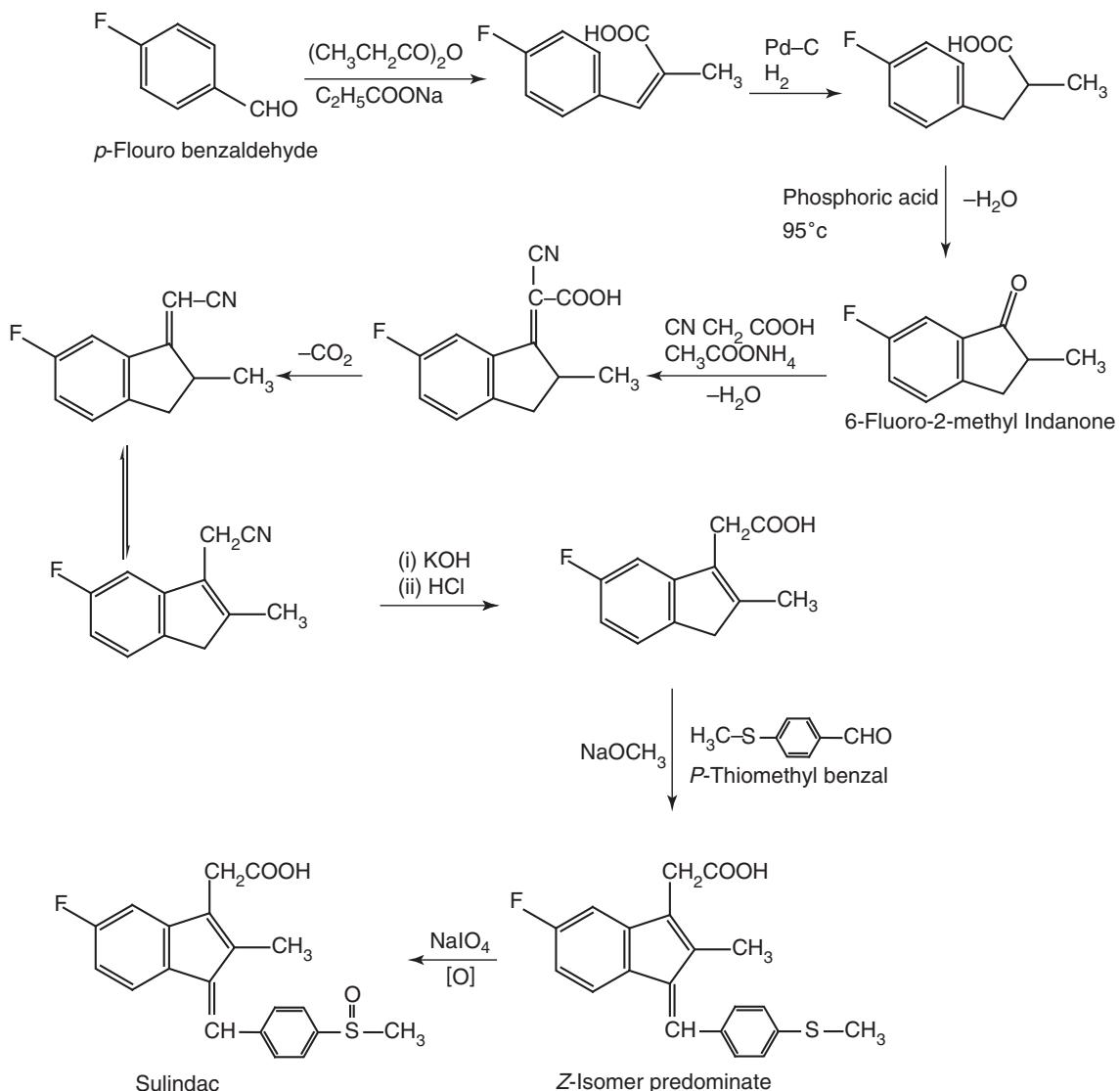
Metabolism: It is a prodrug to form active metabolites of sulphite. In addition to it, sulindac is oxidized to corresponding sulphone and other sulphone-glucuronide conjugates.

Properties and uses: Sulindac is a yellow crystalline powder, very slightly soluble in water, soluble in methylene chloride, and dilute solutions of alkali hydroxides, sparingly soluble in alcohol. The (Z) isomer of sulindac showed much more potent anti-inflammatory activity than the corresponding (E)-isomer. The more polar and inactive sulfoxide is virtually the only form excreted. It has analgesic, antipyretic, and anti-inflammatory properties. It is usually employed in the treatment of rheumatic and muscular skeletal disorders, acute gouty arthritis, and osteoarthritis.

Synthesis

Route I. From: 3-(4-fluorophenyl)-2-methyl propanoic acid

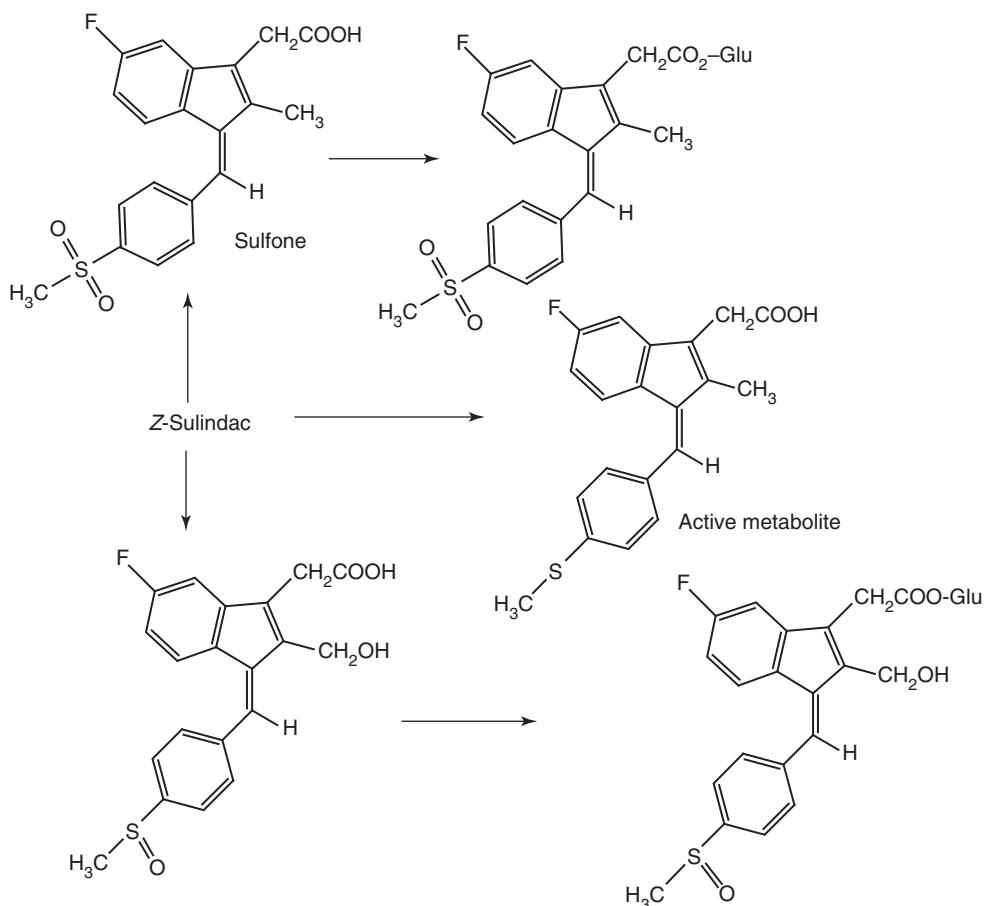


Synthesis**Route II. From *p*-Fluoro benzaldehyde**

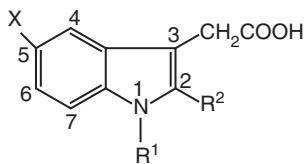
Assay: Dissolve the sample in methanol and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: Usual adult oral dose is 150 mg twice a day with food.

Dosage forms: Sulindac tablets B.P.



SAR of Indole Acetic Acid Derivatives



- Placement of other acidic functionalities instead of the carboxyl group decreases activity and the amide derivatives are inactive.
- Substituents of R^1 useful for increasing anti-inflammatory activity are ranked as $\text{C}_6\text{H}_4\text{CH}_2 > \text{alkyl} > \text{H}$.
- Acylation of the indole nitrogen with aryl/alkyl carboxylic acids results in the decrease of activity.

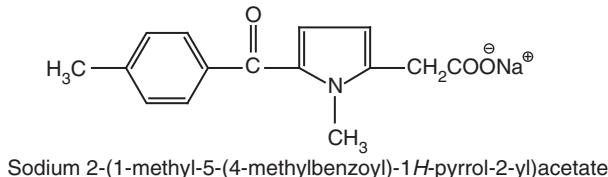
4. Presence of substituents on the *N*-benzoyl derivatives in the *p*-position with F, Cl, CF₃, or S-CH₃ groups provide greatest activity.
5. X substituents activity are ranked as 5-OCH₃ > N(CH₃)₂ > CH₃ > H.
6. The presence of indole ring nitrogen is not essential for activity because the corresponding 1-benzylidenylindene analogue (sulindac) is also active.
7. Alkyl groups especially methyl group at 2nd position is much active than aryl substituted analogues.
8. Substitution of a methyl group at the α position of the acetic acid side chain leads to equiactive analogues.
9. Anti-inflammatory activity was displayed only by the dextrorotatory enantiomer with similar absolute configuration; it has 25 times the activity of phenylbutazone.

SAR of Pyrrole Acetic Acid Derivative

V. c. Pyrrole acetic acid derivative

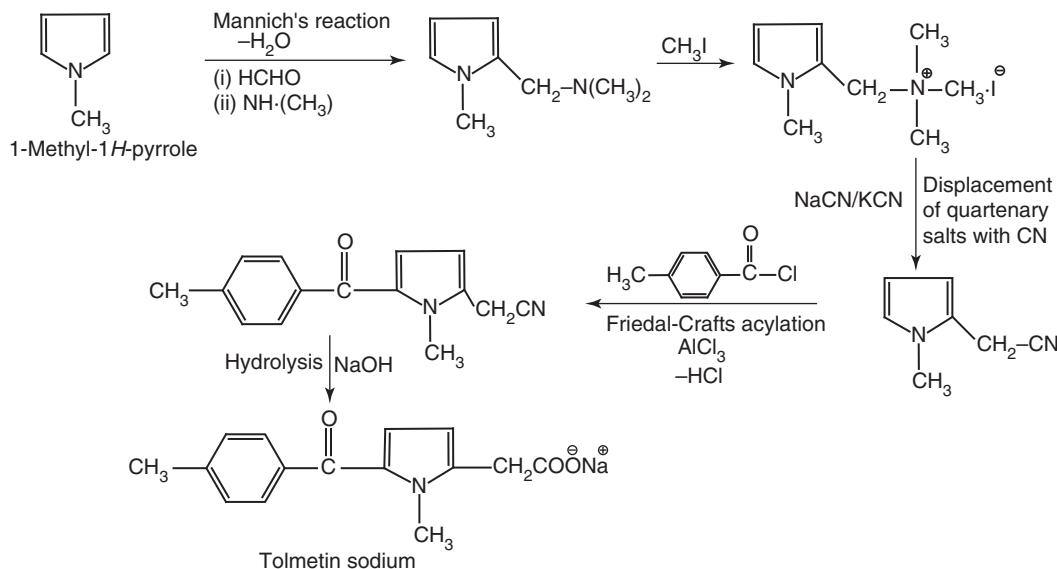
Replacement of the *p*-tolyl group with a *p*-chloro benzoyl moiety produced little effect on activity, whereas introduction of a methyl group in the 4th position and 5-*p*-chloro benzoyl analogues (zomepirac) proved to be four times potent as tolmetin.

i. Tolmetin Sodium (Tolectin)



Synthesis

From: 1-Methyl pyrrole

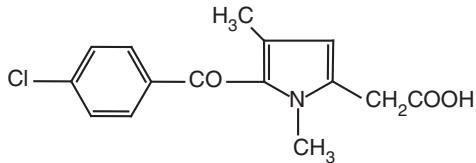


Metabolism: It is metabolized extensively first pass, involving hydroxylation of *p*-methyl group to primary alcohol, which is subsequently oxidized to dicarboxylic acid.

Properties and uses: It is a light yellow, crystalline powder, soluble in water, slightly soluble in alcohol. It has antipyretic, analgesic, and anti-inflammatory actions. It is employed in the treatment of rheumatic and musculoskeletal disorders. The drug is, however, comparable to indomethacin and aspirin in the control and management of disease activity.

Dose: Adult oral dose initially is 400 mg three times a day, subsequently adjusted as per patient's response.

ii. Zomepirac (Zomax)



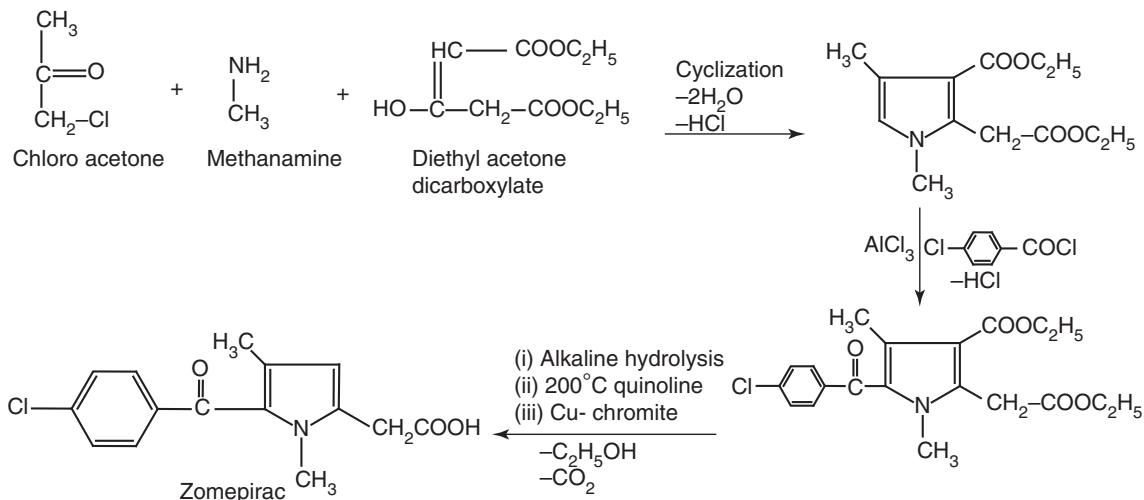
1, 4. Dimethyl-5-(*p*-chloro benzoyl) pyrrole-2-acetic acid

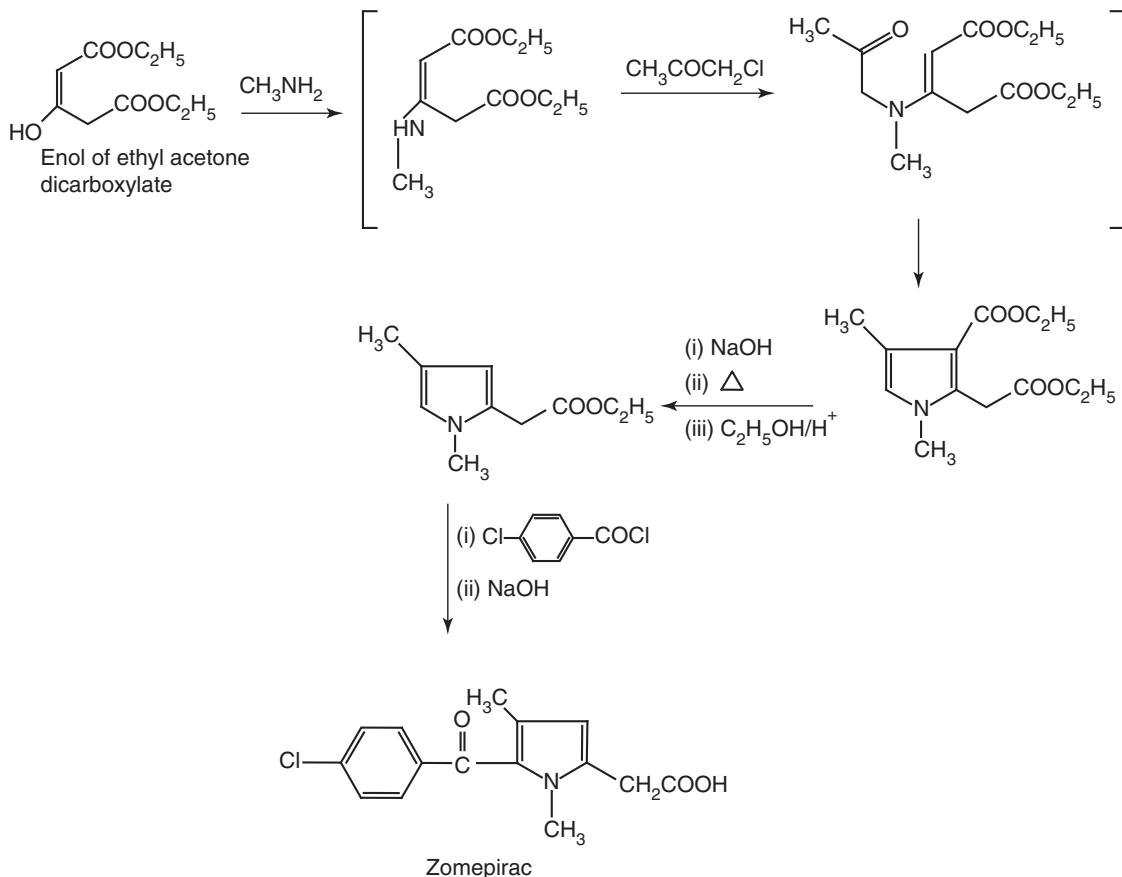
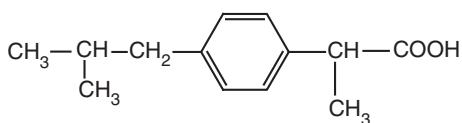
Properties and uses: A greater degree of analgesia for severe pain is claimed for Zomepirac. It is used as an analgesic and an anti-inflammatory drug. It is four times as potent as tolmetin.

Dose: Dose is 400 to 600 mg of zomepirac daily (zomepirac sodium 1.2 g is approximately equivalent to 1 g of zomepirac).

Synthesis

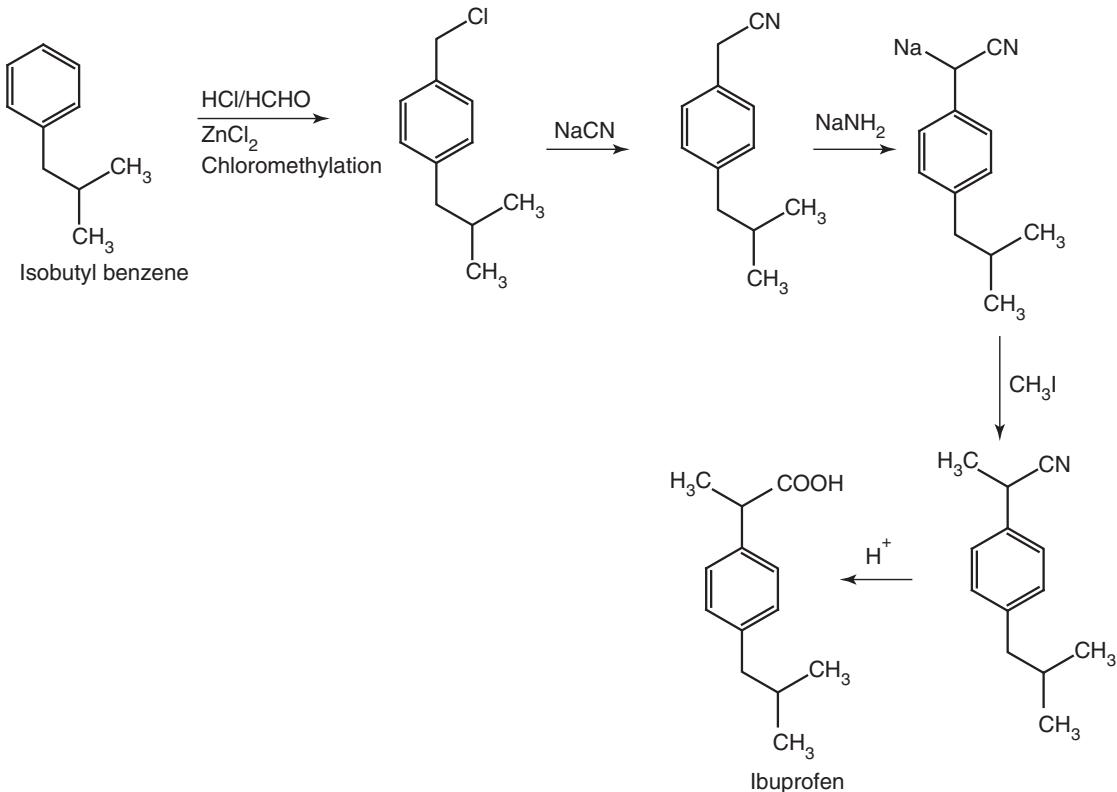
Route I. From Chloro acetone



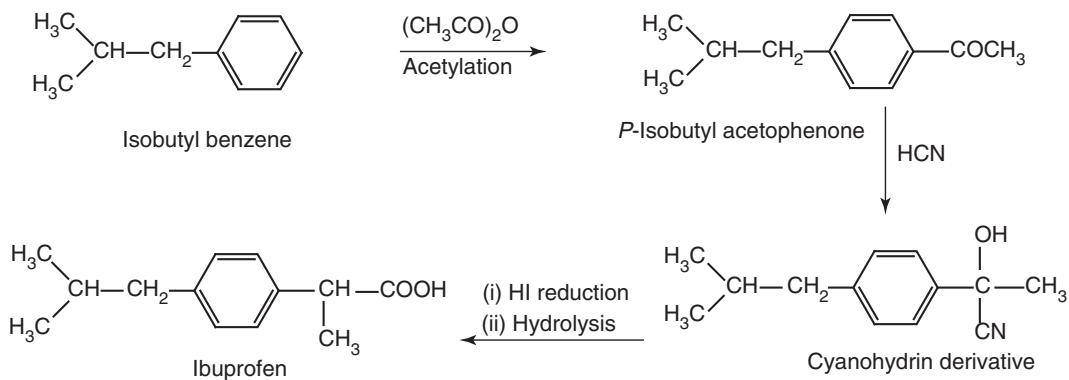
Route II. From: Enol of ethyl acetone dicarboxylate**V. d. Aryl and heteroaryl acetic/propionic acid derivatives****i. Ibuprofen (Brufen, Motrin)**2 (*p*-Iso butyl-phenyl) propionic acid

Synthesis

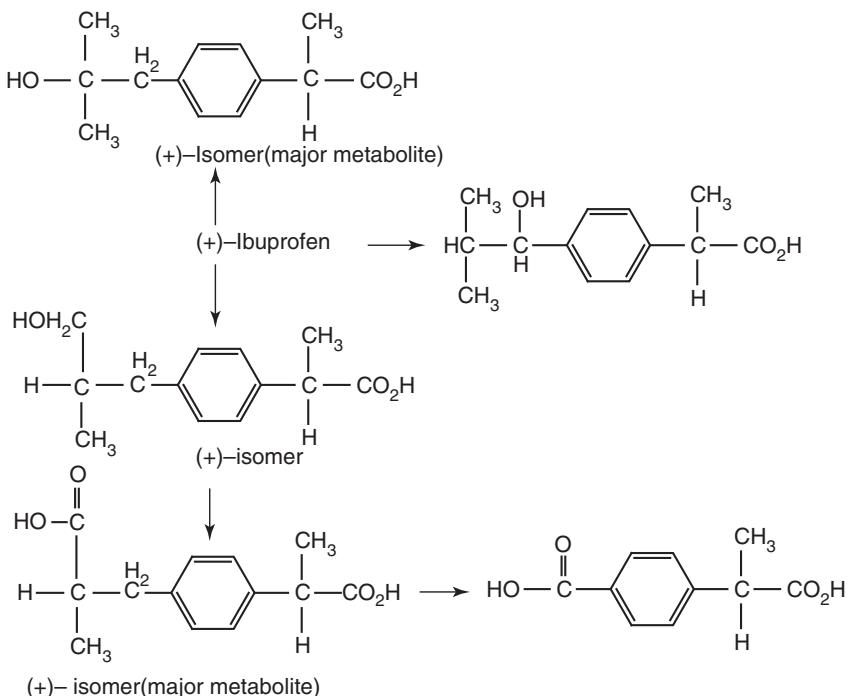
Route I. From Isobutyl benzene



Route II. From: Isobutyl benzene



Metabolism: Oxidative metabolite of ibuprofen and unchanged drugs are excreted in urine. Oxidation involves ω , ω_1 , and ω_2 oxidation of the para isobutyl side chain, followed by alcohol oxidation, resulting from ω oxidation to corresponding carboxylic acid.



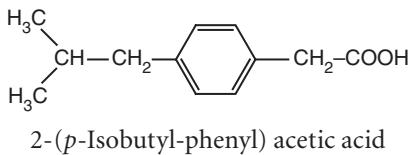
Properties and uses: Ibuprofen is a white crystalline powder or colourless crystals, practically insoluble in water, soluble in acetone, methanol, methylene chloride, and dilute solutions of alkali hydroxides and carbonates. The precursor Ibufenac, which was abandoned owing to hepatotoxicity, was less potent. Moreover, the activity resides in the (s)-(+) isomer, not only in Ibuprofen but also throughout the arylacetic acid series. Furthermore, these isomers are the more potent inhibitors of PG synthetase. It is an anti-inflammatory drug that possesses antipyretic and analgesic action and is used for the treatment of rheumatoid arthritis and osteoarthritis.

Assay: Dissolve the sample in methanol and titrate against 0.1 M sodium hydroxide using phenolphthalein as indicator, until red colour is obtained. Perform a blank titration

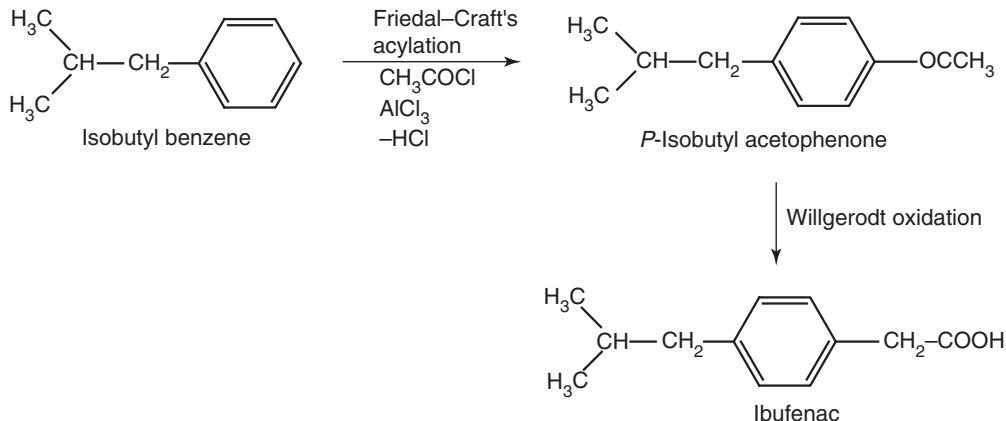
Dose: Usual oral adult dose as an analgesic (dysmenorrhoea) is 200–400 mg four to six times a day; in rheumatoid arthritis and osteoarthritis. The dose is 300–400 mg three or four times a day.

Dosage forms: Ibuprofen tablets I.P., B.P, Ibuprofen cream B.P., Ibuprofen gel B.P., Ibuprofen oral suspension B.P.

ii. Ibufenac

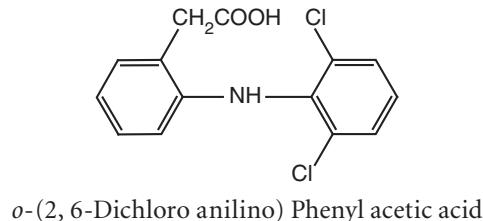


Synthesis



Properties and uses: It was formerly employed in the rheumatic conditions, but was found to cause hepatotoxicity. It has analgesic, antipyretic, and anti-inflammatory actions.

iii. Diclofenac (Voltaren, Voveran)



Metabolism: There are four major metabolites that are produced by aromatic hydroxylation, that is, 4-hydroxy derivative, 5-hydroxy, 3-hydroxyl, and 4,5-dihydroxy metabolites. Remaining metabolites are excreted as sulphate conjugates.

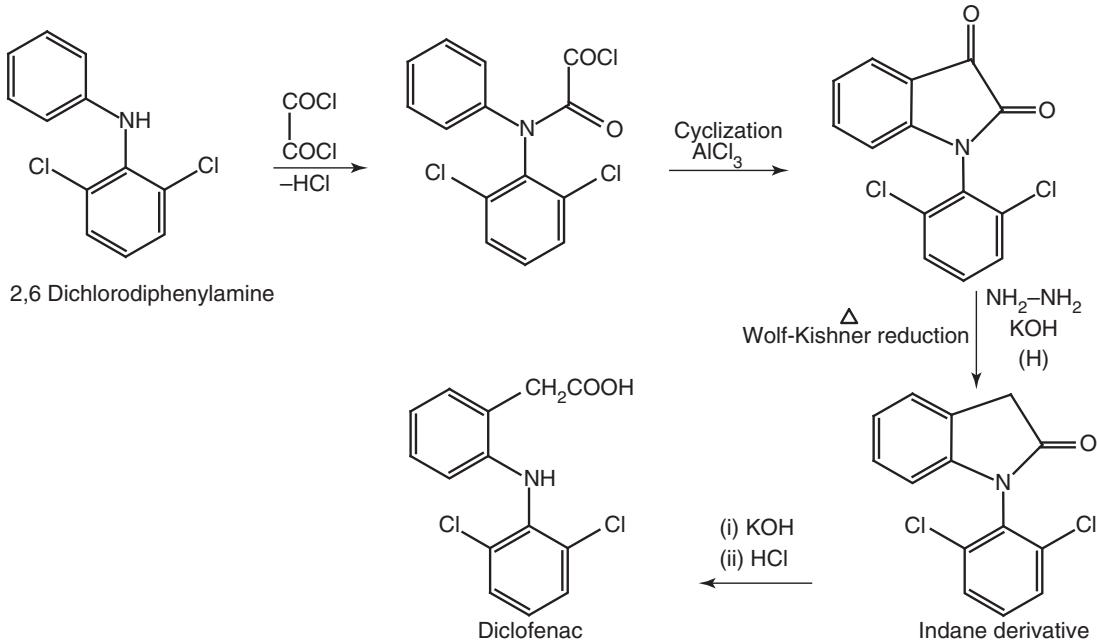
Properties and uses: Diclofenac sodium is a white or slightly yellowish crystalline slightly hygroscopic powder, sparingly soluble in water, soluble in methanol and alcohol, slightly soluble in acetone. Used in the treatment of rheumatic arthritis.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

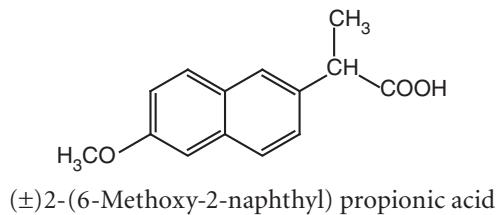
Dose: The usual dose is 20–50 mg three times a day. It can also be given as a suppository.

Dosage forms: Diclofenac tablets I.P., Diclofenac injection I.P., Prolonged-release diclofenac tablets B.P., Gastro-resistant diclofenac tablets B.P., Prolonged-release diclofenac injection B.P., Prolonged-release diclofenac capsules B.P.

Synthesis



iv. Naproxen (Naprosyn)



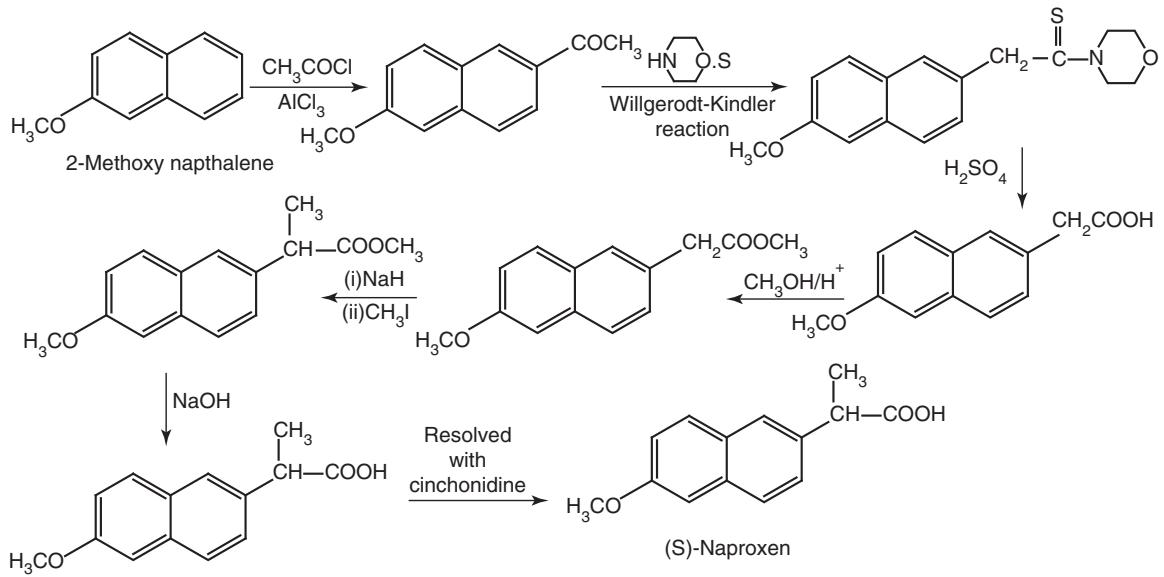
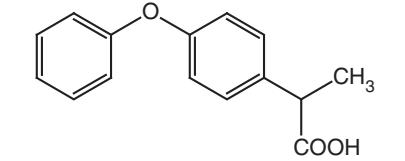
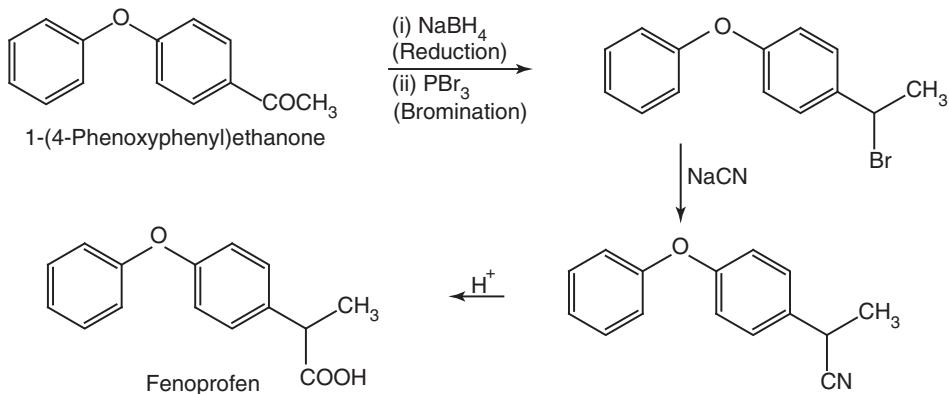
Metabolism: It is converted to 6-O-desmethyl metabolite and then to glucuronide conjugate.

Properties and uses: Naproxen is a white crystalline powder, practically insoluble in water, soluble in ethanol and in methanol. The drug is fairly comparable to aspirin both in the management and control of disease symptoms. Nevertheless, it has relatively lesser frequency and severity of nervous system together with milder GI-effects. It possesses analgesic, anti-inflammatory, and antipyretic actions, and it is used in the treatment of rheumatic arthritis, dysmenorrhea, and acute gout.

Assay: Dissolve the sample in a mixture of water and methanol (1:3) and titrate against 0.1 M sodium hydroxide, using 1 ml of phenolphthalein solution as indicator.

Dose: For adult in rheumatoid arthritis, 250–375 mg as initial dose two times a day; in acute gout, 750 mg as loading dose followed by 250 mg three times a day until relieved.

Dosage forms: Naproxen oral suspension B.P., Naproxen suppositories B.P., Naproxen tablets B.P., Gastro-resistant naproxen tablets B.P.

Synthesis**v. Fenoprofen (Nalton)****Synthesis**

Metabolism: It is metabolized through glucuronide conjugation with a parent drug and CYP2C9 to 4-hydroxy metabolites.

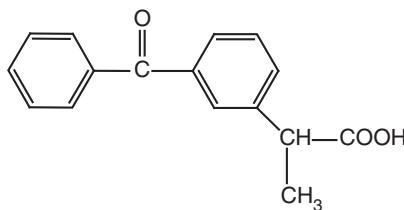
Properties and uses: Fenoprofen calcium is a white crystalline powder, slightly soluble in water and soluble in ethanol. Fenoprofen calcium has anti-inflammatory (antiarthritic) and analgesic properties. It has been shown to inhibit PG synthetase. It is known to reduce joint-swelling, decrease the duration of morning stiffness, and relieve pain. It is also indicated for acute flares and exacerbations and in the long-term management of osteoarthritis and rheumatoid arthritis.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically. Perform a blank titration.

Dose: Dose is 50–100 mg twice daily with food.

Dosage forms: Fenoprofen tablets B.P.

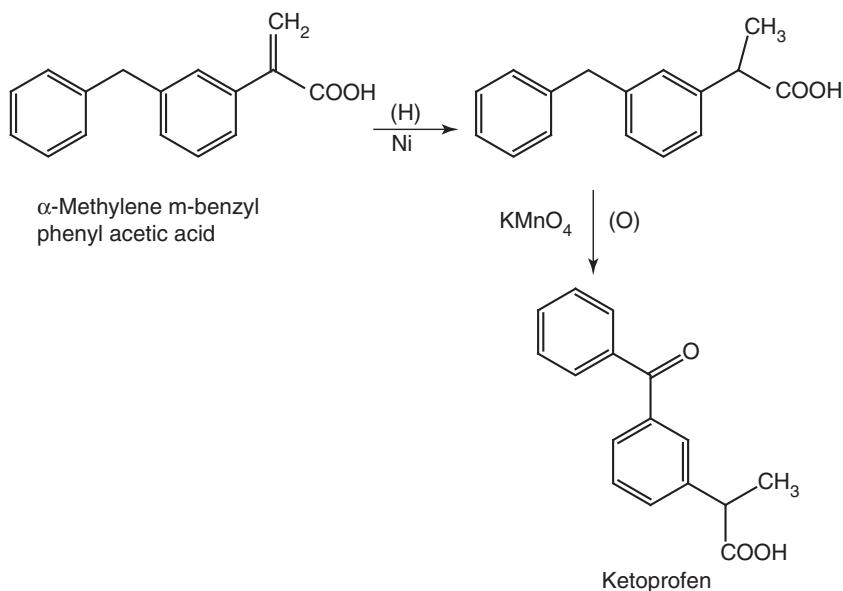
vi. Ketoprofen (Orudis)

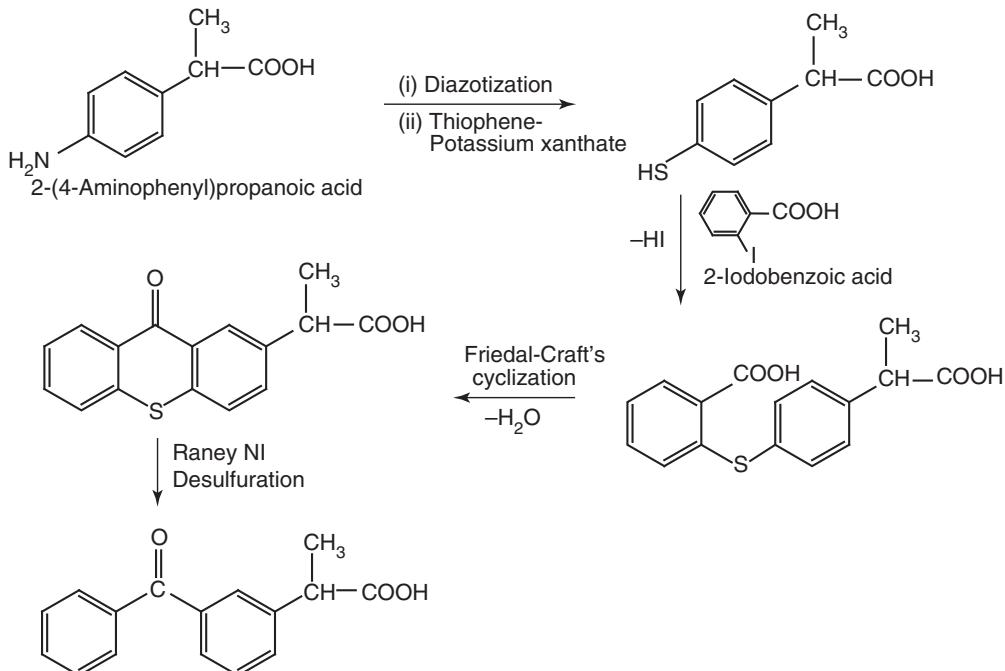


2-(3-Benzoyl phenyl) propionic acid

Synthesis

Route I. From: α -Methylene substituted *m*-benzyl phenyl acetic acid



Route II. From: 2-(4-Aminophenyl) propanoic acid

vii. Ketoprofen

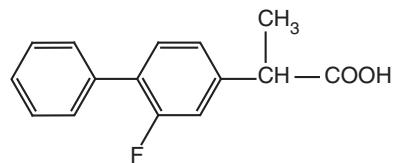
Metabolism: It is metabolized by glucuronidation of carboxylic acid, CYP3A4, and CYP2C9 hydroxylation of benzoyl ring and reduction of keto function.

Properties and uses: Ketoprofen is a white crystalline powder, practically insoluble in water, soluble in acetone, in ethanol, and in methylene chloride. It is closely related to fenoprofen in structure, properties, and indications and has a low incidence of side effects and has been approved for counter sale. It is used in the treatment of rheumatoid arthritis and osteoarthritis

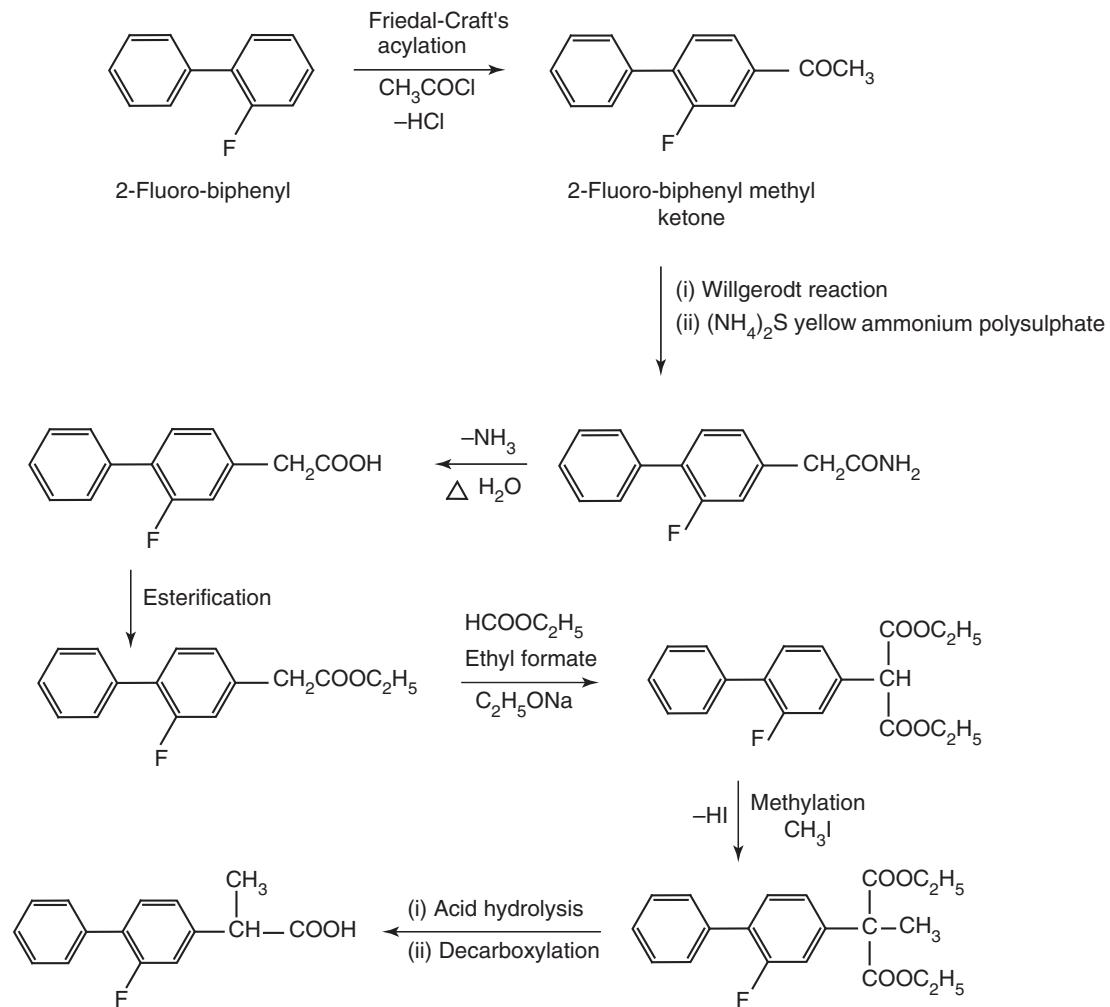
Assay: Dissolve the sample in ethanol and dilute with water and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: Usual adult oral dose for rheumatoid arthritis is 600 mg four times daily; for osteoarthritis the dose is 300–600 mg four times a day.

Dosage forms: Ketoprofen capsules I.P., B.P., Ketoprofen gel B.P.

viii. Flurbiprofen (Ansaid)


(±) -2-(2-Fluoro-4-biphenyl)-propionic acid

Synthesis

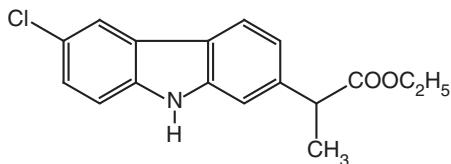
Properties and uses: Flurbiprofen is a white crystalline powder, practically insoluble in water, soluble in alcohol, in methylene chloride, and aqueous solutions of alkali hydroxides and carbonates. The drug is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen. Another hydroscopic acid analogue that is used in the acute or long-term management of rheumatoid arthritis and osteoarthritis, it possesses analgesic, anti-inflammatory, and antipyretic activities.

Assay: Dissolve the sample in alcohol and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: Usual adult dose is 150–200 mg a day in three to four divided doses.

Dosage forms: Flurbiprofen tablets I.P., B.P., Flurbiprofen suppositories B.P.

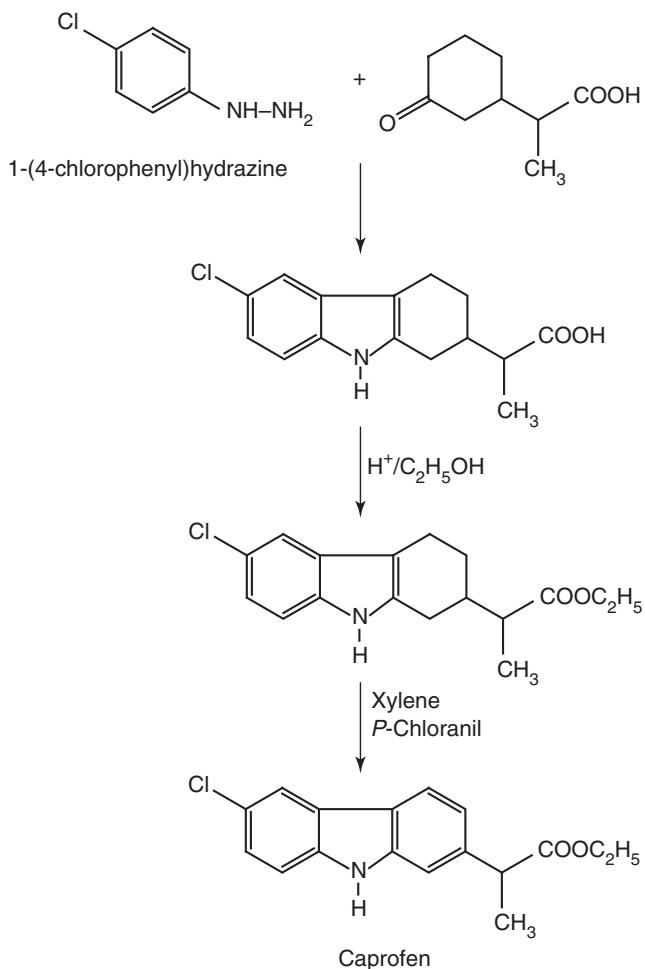
viii. Caprofen



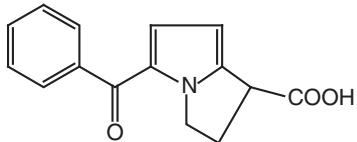
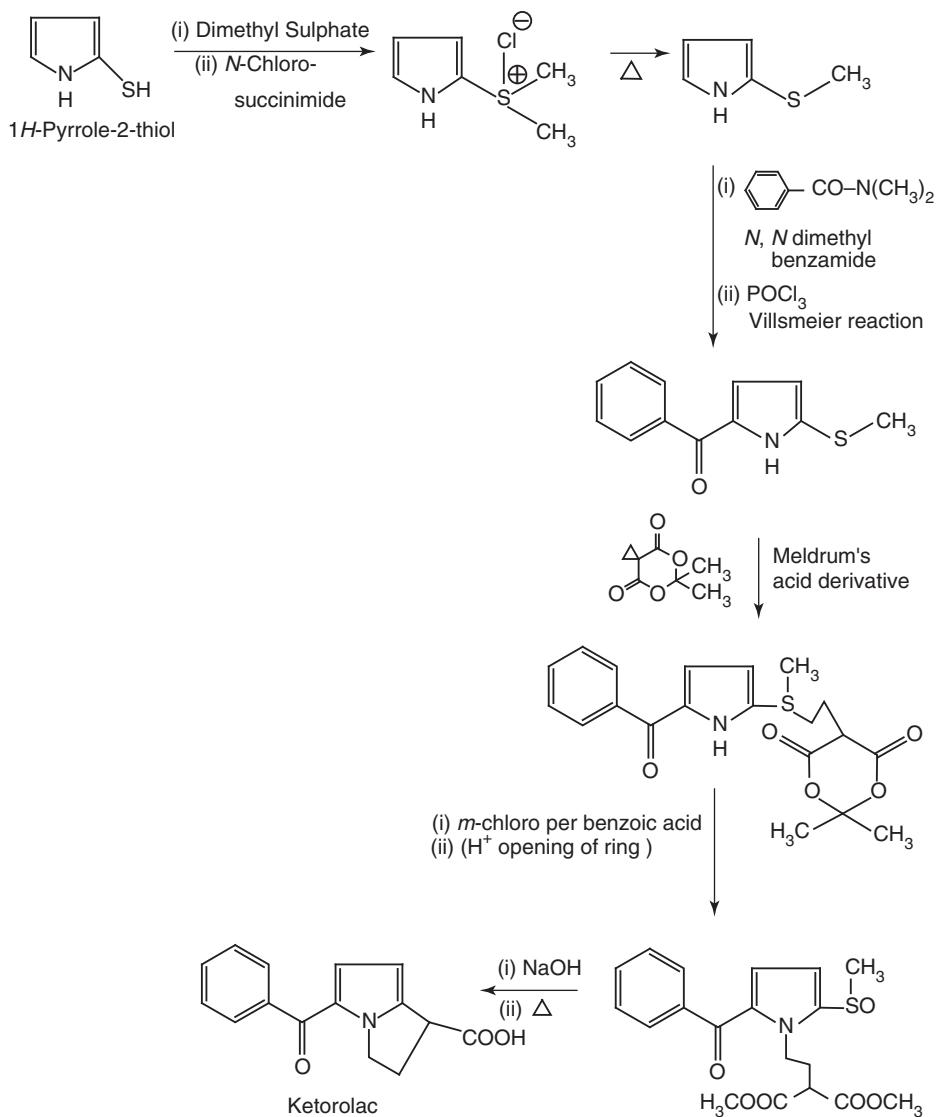
6-Chloro- α -methylcarbazole-2-acetic acid ethyl ester

Synthesis

From: 1-(4-chlorophenyl) hydrazine



Uses: Used as an analgesic and anti-inflammatory agent.

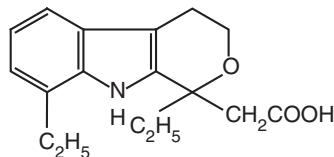
ix. Ketorolac (Acular, Ketodrops, Ketlur)5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid**Synthesis**

Properties and uses: Ketorolac is a white crystalline powder, soluble in water and in methanol, slightly soluble in ethanol, practically insoluble in methylene chloride. Ketorolac is a potent analgesic indicated for the treatment of moderately severe and acute pain.

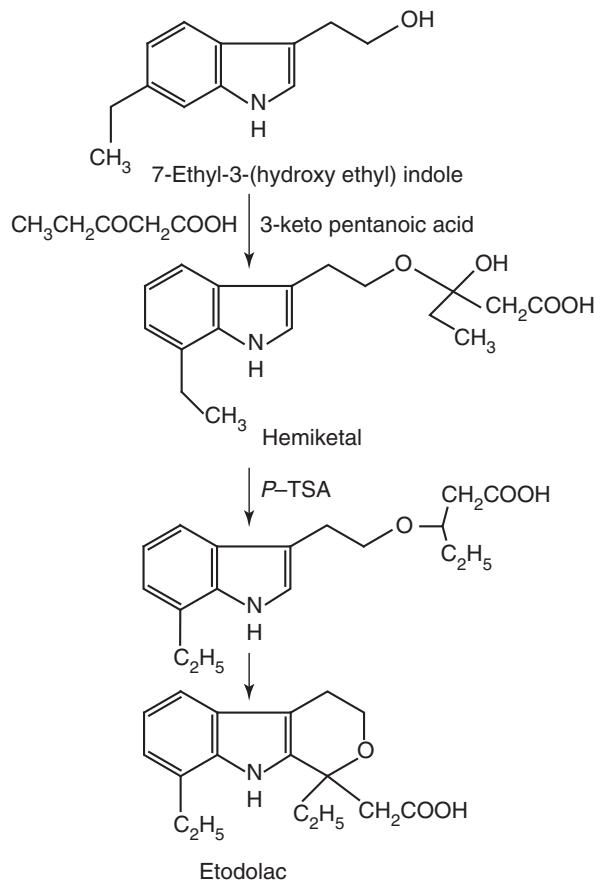
Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The dose for ocular itching, which is associated with seasonal allergic conjunctivitis, for reduction of ocular pain, and for photophobia in patients undergoing incisional refractive surgery, instil one drop of a 0.5% solution into the affected eyes four times daily.

x. Etodolac



Synthesis



Metabolism: It is metabolized to 3-hydroxylated metabolite and to glucuronide conjugates.

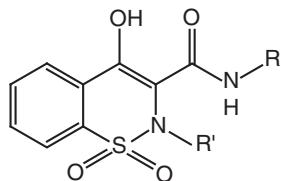
Properties and uses: Etodolac is a white crystalline powder, practically insoluble in water, soluble in acetone and in ethanol. It has anti-inflammatory activity and inhibits cyclooxygenase. It is used in the treatment of osteoarthritis and rheumatoid arthritis. Gastrointestinal irritation and ulceration is less with this drug than with other drugs.

Assay: Dissolve the sample in methanol and titrate against 0.1 M tetrabutylammonium hydroxide. Determine the end point potentiometrically. Perform a blank titration.

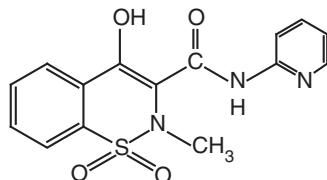
Dosage forms: Etodolac capsules B.P., Etodolac tablets B.P.

VI. Oxicams

The term oxicam described the relatively new enolic acid class of 4-hydroxyl -1,2 benzothiazine carboxamide with anti-inflammatory and analgesic properties.



i. Piroxicam



4-Hydroxy-2-methyl-N-(2-pyridinyl)-1,2-benzothiazine-3-carboxamide-1,1-dioxide

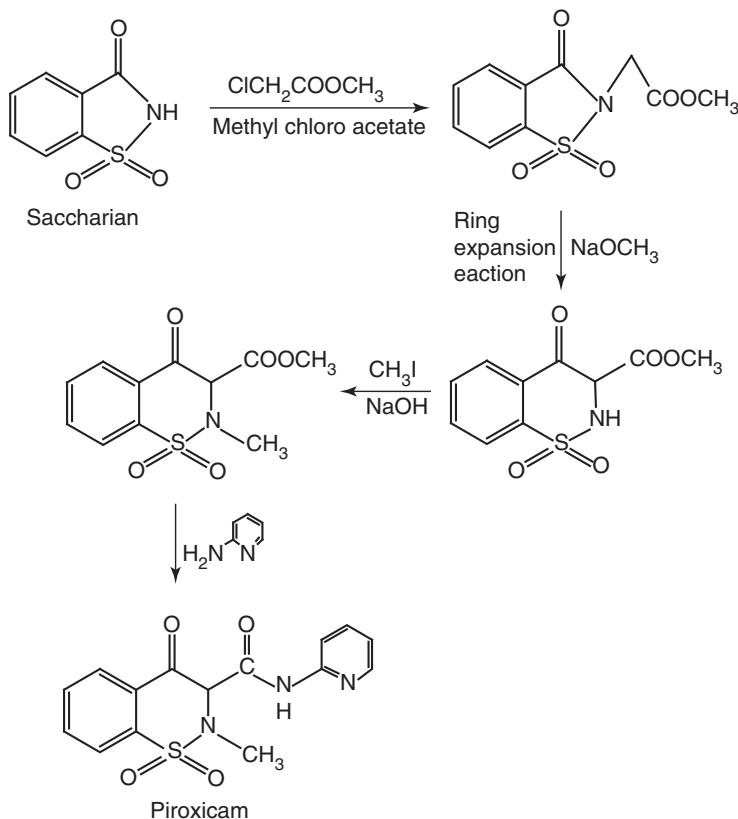
Properties and uses: Piroxicam is a white or slightly yellow crystalline powder, practically insoluble in water, soluble in methylene chloride, and slightly soluble in ethanol. It is employed for acute and long-term therapy for the relief of symptoms of osteoarthritis and rheumatoid arthritis. It also possesses uricosuric action and has been used in the treatment of acute gout.

Assay: Dissolve the sample in a mixture of equal volumes of acetic anhydride and anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end-point potentiometrically.

Dose: Usual adult oral dose is 20 mg per day.

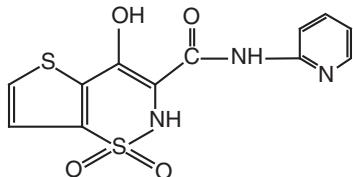
Dosage forms: Piroxicam capsules I.P., B.P., Piroxicam tablets I.P., Piroxicam gel B.P.

Synthesis



The two more closely related analogues are obtained by varying the heterocyclic amine used in the last step. 2-Amino thiazole thus leads to sudoxicam, while 3-amino-5-methylisoxazole affords isoxicam.

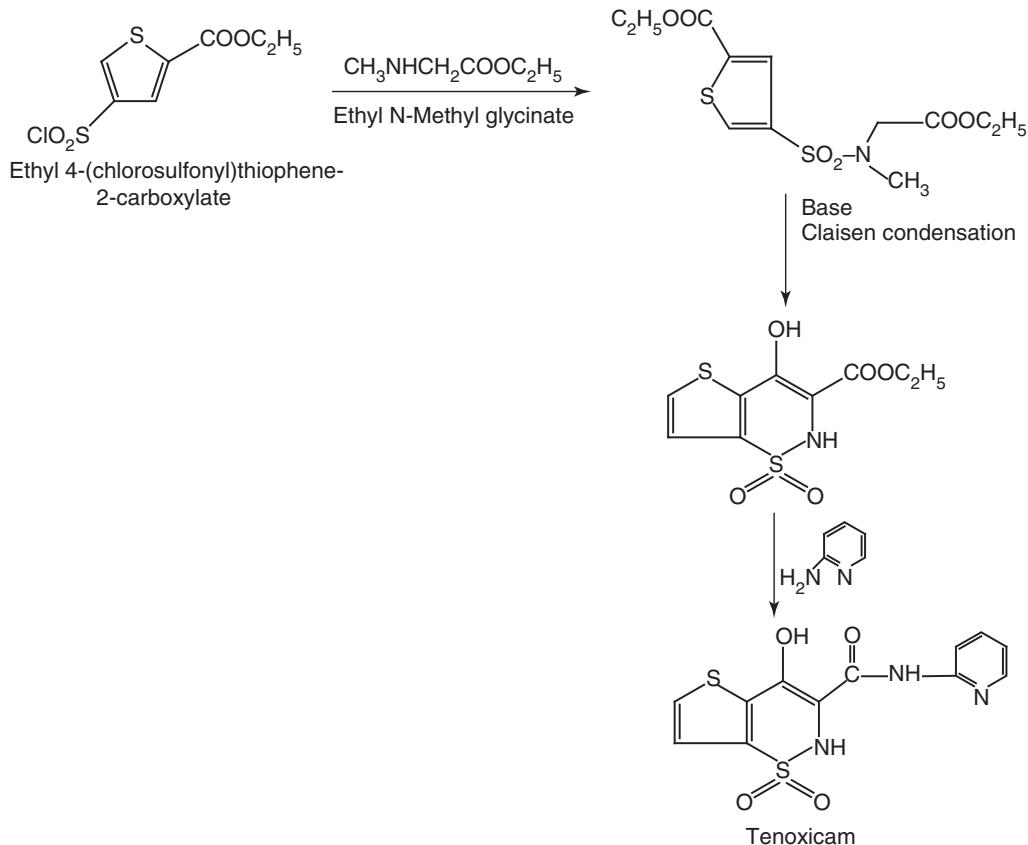
ii. Tenoxicam (Tobitil)



Properties and uses: Tenoxicam is a yellow crystalline powder, practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in ethanol, and soluble in solutions of acids and alkalis. Used as cyclooxygenase inhibitor, analgesic, and anti-inflammatory agent.

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.

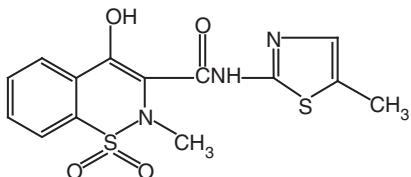
Synthesis



Dose: Dose in the case of musculoskeletal and joint disorders—such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis—and short-term management of soft tissue injury for adult is 20 mg as a single daily dose given for 7 days in acute cases. For musculoskeletal disorders and other related illnesses, the dose is a maximum of 4 mg a day up to 14 days in severe cases (short-term use).

Dosage forms: Tenoxicam injection B.P., Tenoxicam tablets B.P.

iii. Meloxicam



4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

Metabolism: This category of drugs undergoes aromatic hydroxylation at several positions of aromatic benzothiazine ring. Sudoxicam undergoes primary hydroxylation of thiazole ring, followed by ring opening, whereas isoxicam undergoes primary cleavage reaction of benzothiazine ring.

Properties and uses: Meloxicam is a pale yellow powder, practically insoluble in water, slightly soluble in acetone, soluble in dimethylformamide, very slightly soluble in ethanol and in methanol. Used as cyclooxygenase inhibitor, analgesic, and anti-inflammatory.

Assay: Dissolve the sample in a mixture of anhydrous acetic acid and anhydrous formic acid (10:1) and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dosage forms: Meloxicam tablets B.P.

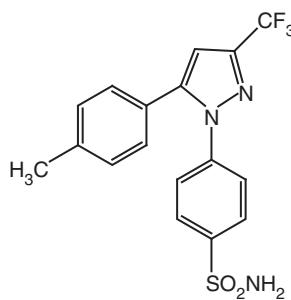
SAR of Oxicams

- The most active analogues have substituents CH_3 on the nitrogen and electron withdrawing substituents on the anilide phenyl groups, such as Cl and CF_3 .
- The introduction of heterocyclic ring in the amide chain significantly increases the anti-inflammatory activity. Example—2-thiazolyl derivative sudoxicam is more potent than indomethacin.
- The most active benzothiazine have acidities in the pKa range of 6–8.

VII. Selective COX-2 inhibitor

The PG that mediates inflammation, fever, and pain are produced solely via COX-2 (highly inducible by inflammatory response), and the PGs that are important in GIT, platelets, uterus, and adrenal function are produced solely via COX-1 (constitutively expressed). Selective COX-2 inhibitors (Celecoxib, Rofecoxib, and Valdecoxib) are devoid of side effects, such as gastric ulcer. It does not affect the normal functioning of platelets, uterus, and renal system.

i. Celecoxib (Celact, Cobix, Revibra)

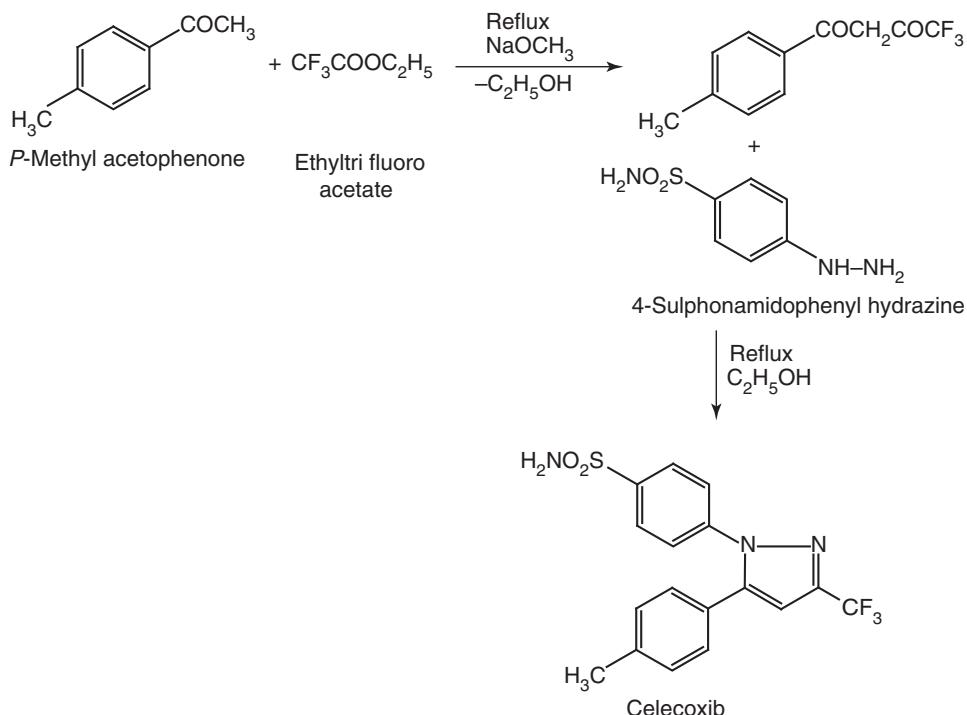


4-[5-(4-Methyl phenyl)-3-(trifluoro)-1H-pyrazo-lyl]-benzene sulphonamide.

Metabolism: Metabolism of celecoxib occurs in the liver, involves hydroxylation of 4-methyl group to primary alcohol, which is subsequently oxidized to its corresponding carboxylic acid.

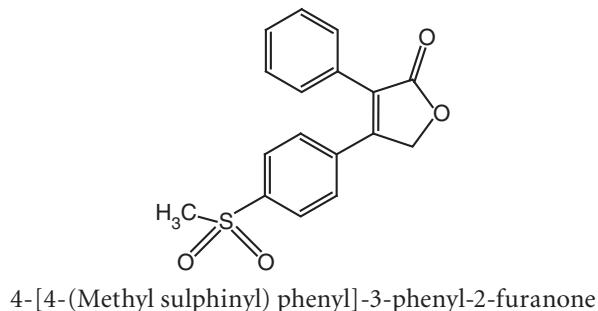
Properties and uses: It exists as pale yellow crystals, sparingly soluble in water. Celecoxib is used to treat arthritis, pain, menstrual cramps, and colonic polyps, and also for the relief of pain, fever, swelling, and tenderness caused by osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Synthesis

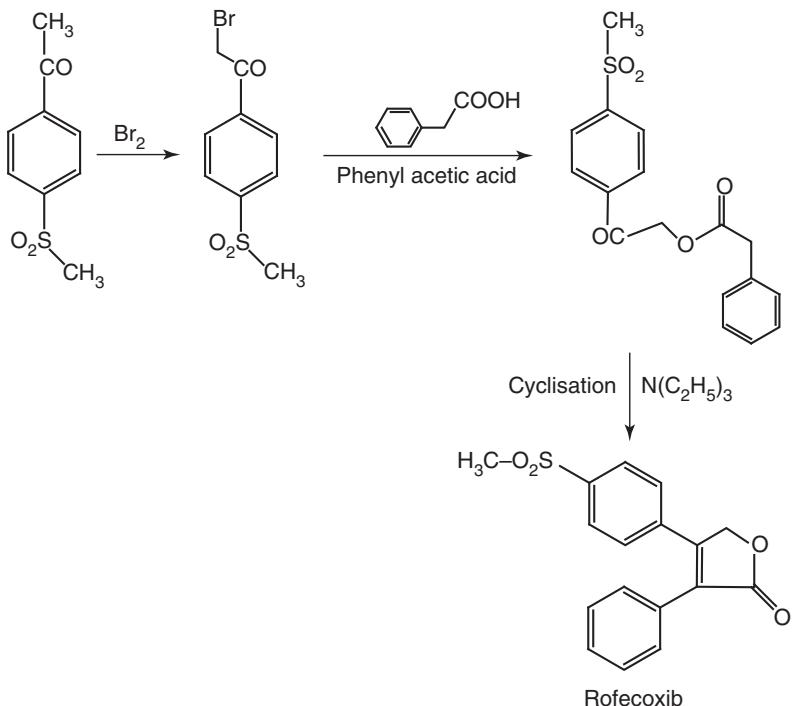


Dose: For osteoarthritis, the adult dose is 200 mg as a single dose or in two divided doses that may be increased to 200 mg two times a day, if necessary. For rheumatoid arthritis, the adult dose is 100–200 mg two times a day. For elderly people the dose is 100 mg two times a day. For dysmenorrhoea, initially the dose is 400 mg by 200 mg, if necessary, on the 1st day and maintenance dosage is 200 mg two times a day.

ii. Rofecoxib



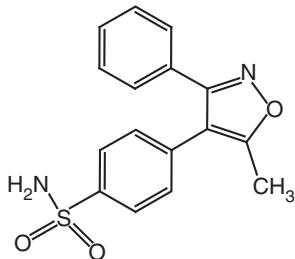
Synthesis



Metabolism: The metabolic route of Rofecoxib appears to follow the reduction of dihydrofuranone ring system by cytosolic enzyme to *cis* and *trans* hydroxy derivatives.

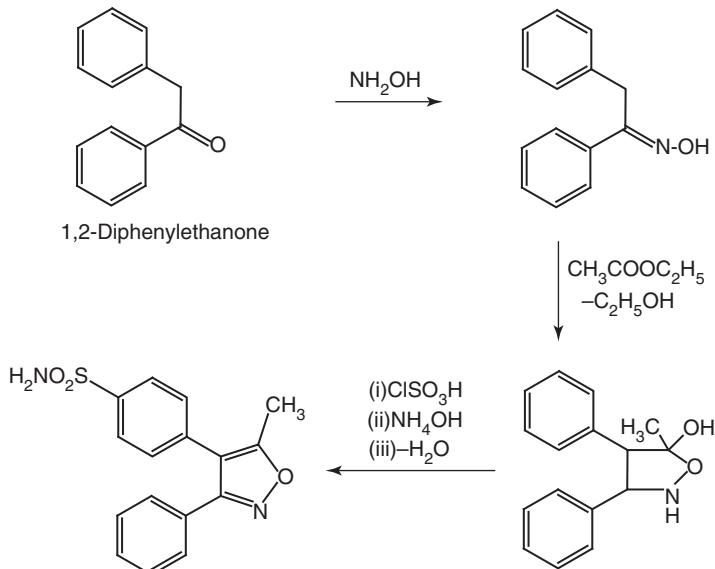
Properties and uses: It exists as white to light yellow powder, sparingly soluble in acetone, methanol, very slightly soluble in 1-octanol. It is a COX-2 inhibitor with greater potency and a longer half-life than celecoxib. Rofecoxib is used to relieve the pain, tenderness, inflammation (swelling), and stiffness caused by arthritis, and to treat painful menstrual periods and pain from other causes.

iii. Valdecoxib



4-[5-Methyl-3-phenyl isoxazol-4-yl]-benzene sulphonamide

Synthesis



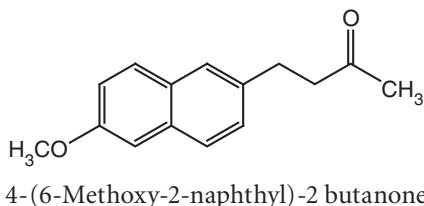
Metabolism: It is metabolized by hydroxylation of 5-methyl group and it is further metabolized to inactive carboxylate and *N*-Hydroxylation at the sulphonamide function, leading to the formation of corresponding sulphonic acid and sulphamic metabolites.

Properties and uses: It is soluble in most organic solvents, insoluble in water. It is a NSAID drug that exhibits anti-inflammatory, analgesic, and antipyretic activities.

Dose: For dysmenorrhoea the dose is 20 mg twice a day. For osteoarthritis and rheumatoid arthritis the dose is 10 mg once daily.

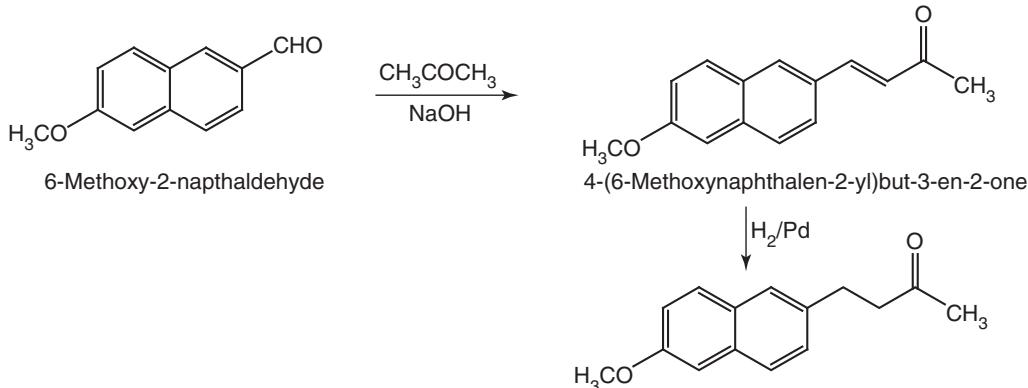
IX. Miscellaneous

i. Nabumetone (Nabuflam, Niltis)



Properties and uses: Nabumetone is a white crystalline powder, practically insoluble in water, freely soluble in acetone, and slightly soluble in methanol. It is a nonacidic compound and because of this nature, it produces minimum gastrointestinal side effect. It is indicated in the treatment of acute and chronic treatment of osteoarthritis and rheumatoid arthritis.

Synthesis

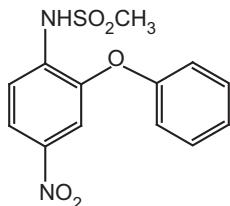


Dose: For pain and inflammation associated with osteoarthritis and rheumatoid arthritis adult dose is 1 g as a single dose in the evening followed by 0.5–1 g in the morning.

Dosage forms: Nabumetone oral suspension B.P., Nabumetone tablets B.P.

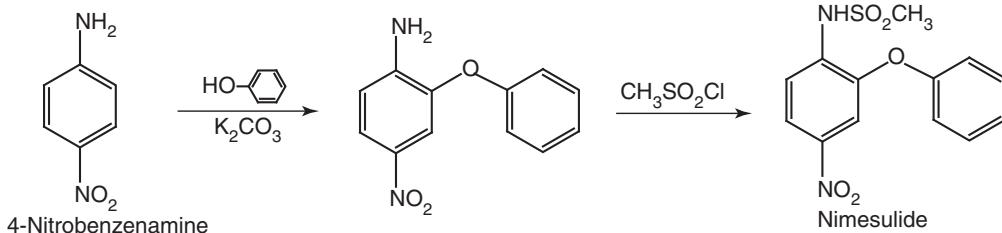
Assay: It is assayed by adopting liquid chromatography technique.

ii. Nimesulide



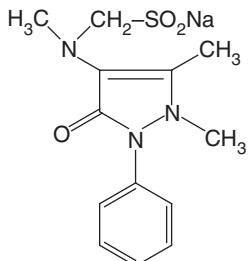
4-Nitro-2-phenoxy methane sulphonamide

Synthesis



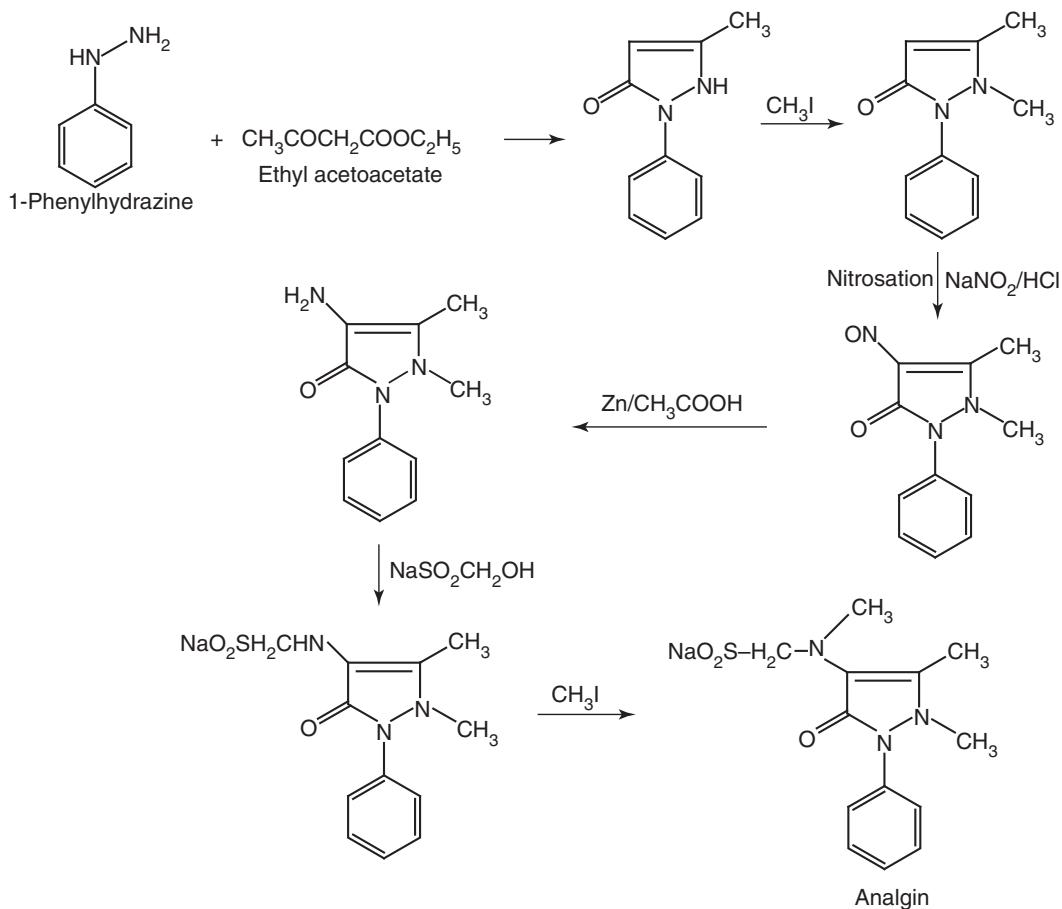
Properties and uses: Nimesulide is a yellowish crystalline powder, practically insoluble in water, soluble in acetone, and slightly soluble in anhydrous ethanol. It contains a sulphonamide moiety as an acidic group rather than a carbonic acid. It shows moderate incidence of gastric side effects because it exhibits significant selectivity towards COX-2, used as analgesic and anti-inflammatory agent.

iii. Analgin



Sodium *N*-(2, 3-dihydro-1, 5 dimethyl-3-oxo-2 phenyl-pyrazol-4-yl)-*N*-methyl amino methane sulphonate

Synthesis



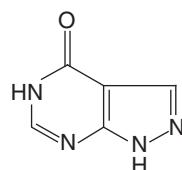
Uses: Used as an analgesic and anti-inflammatory agent.

X. Drugs used in the treatment of gout

An acute attack of gout occurs as a result of anti-inflammatory reaction to crystals of sodium ureate (the end product of purine metabolism in human beings) that is deposited in the joint tissues. Drugs used to treat gout may act in the following ways:

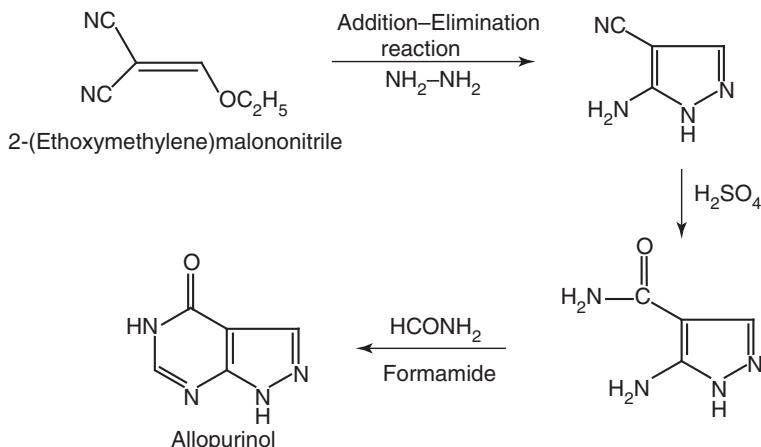
- By inhibiting uric acid synthesis: Allopurinol.
- By increasing uric acid excretion: Probenecid, Sulphinpyrazone.
- Miscellaneous: Colchicines (alkaloid obtained from *Colchicum autumnale*).

i. Allopurinol (Zyloprim)

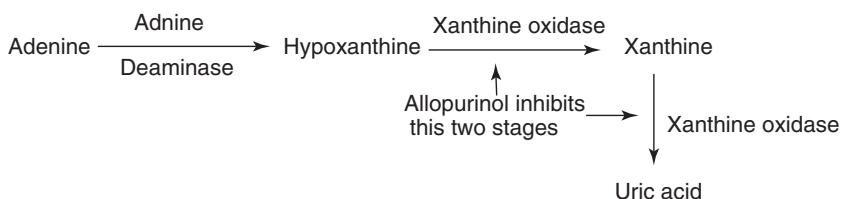


Pyrazolo pyrimidine-4-one

Synthesis



Mode of action: In human beings, uric acid is formed primarily by the xanthine oxidase-catalyzed oxidation of hypoxanthine and xanthine. At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme at high concentrations; it is a noncompetitive inhibitor.



Metabolism: It is rapidly metabolized via oxidation and numerous ribonucleoside derivatives are formed. The major metabolites are alloxanthine or oxypurinol.

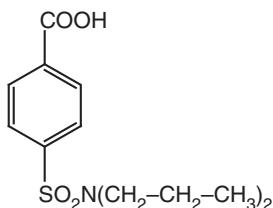
Properties and uses: Allopurinol is a white powder, very slightly soluble in water, in alcohol and in dilute solutions of alkali hydroxides. It is used in the treatment of gout and prevention of urate deposition in patients with leukaemia receiving anticancer drugs, which cause increasing serum uric acid levels.

Assay: It is assayed by adopting liquid chromatography technique.

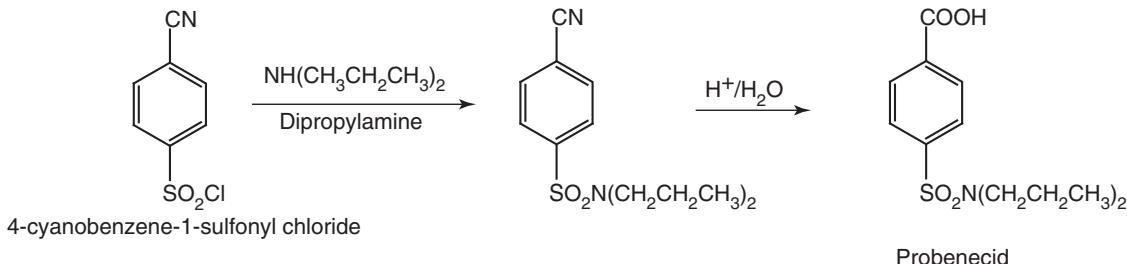
Dose: Usual adult oral dose for gout is 100–200 mg two or three times a day.

Dosage forms: Allopurinol tablets I.P., B.P.

ii. Probenecid (Benemid)



Synthesis



Metabolism: The metabolite is glucuronide conjugates of carboxylic acid, ω oxidation of *N*-propyl side chain, and subsequent oxidation, resulting in alcohol to carboxylic acid derivative. ω Oxidation of *N*-propyl side chain and *N*-dealkylation are the process steps in the metabolism of probenecid.

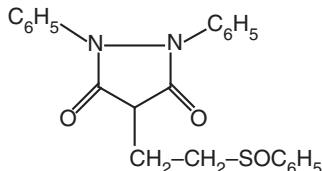
Properties and uses: Probenecid exists as white crystalline powder or small crystals, practically insoluble in water, soluble in acetone, and sparingly soluble in ethanol. Probenecid is uricosuric agent that increases the rate of excretion of uric acid and used in the treatment of chronic gout. The oral administration of probenecid in conjugation with penicillin G results in higher and prolonged concentration of the antibiotic in the plasma than when penicillin is given alone.

Assay: Dissolve the sample in alcohol, shaking and heating slightly, if necessary, and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

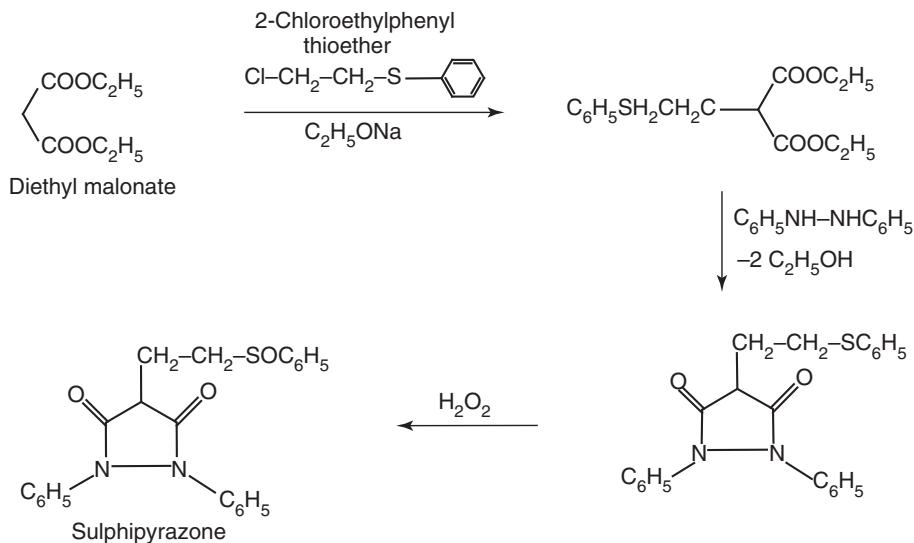
Dose: Adult oral dose is 500 mg–2 g per day; usually 250 mg two times a day for one week, then 500 mg twice a day thereafter.

Dosage forms: Probenecid tablets I.P., B.P.

iii. Sulphinpyrazone (Anuturane)



Synthesis



Metabolism: The metabolic product results from sulphoxide reduction, sulphur, and aromatic oxidation and C-glucuronidation of heterocyclic ring. The metabolite resulting from para hydroxylation of phenyl ring possesses uricosuric effect.

Properties and uses: Sulphinpyrazone is a white powder, very slightly soluble in water, sparingly soluble in alcohol, soluble in dilute solutions of alkali hydroxides and used as uricosuric agent.

Assay: Dissolve the sample in acetone and titrate against 0.1 M sodium hydroxide using bromothymol blue as an indicator, until the colour changes from yellow to blue.

Dose: Initial oral dose is 100–200 mg per day, taken with meals or milk.

Dosage forms: Sulphinpyrazone tablets B.P.

PROBABLE QUESTIONS

1. Explain schematically, the biosynthetic pathway of PGs and describe how does the NSAIDs act as antipyretics and analgesics?
2. Outline the synthesis of the following NSAIDs: Paracetamol, Phenylbutazone, and Indomethacin.
3. Classify the NSAIDs and write the structure, chemical name, and uses of at least one compound from each category.
4. Write the names of three drugs belonging to the category of aniline and para aminophenol analogues. Outline the synthesis of one of them.
5. What is cyclooxygenase II? Name the drugs that selectively inhibit the cyclooxygenase II along with the synthesis of any one of them.
6. Explain how the salicylic acid analogues act as potent antipyretics and analgesics. Mention suitable examples to support your answer.
7. Write the metabolism of para amino phenol derivatives with their chemical structure and indicate the metabolic product responsible for hepatotoxic.
8. The metabolite of phenylbutazone is a more effective drug. Outline its synthesis and the important uses.
9. Name a sulphur containing pyrazolidine drug used as an antipyretic and analgesic, and write its synthesis.
10. Structural analogues of *N*-aryl anthranilic acid yielded some potent antipyretics, analgesics, and anti-inflammatory compounds. Justify the statement with two examples and write their synthesis.
11. Outline the synthesis of the following NSAIDs: Ibuprofen, Diclofenac, and Nabumetone.
12. Explain the mode of action of antipyretics and analgesics by citing the examples of some typical drugs, which you have studied.
13. Write in detail about antipyretics and analgesics.
14. What are salicylates? Enumerate the derivatives of salicylic acid used as NSAIDs with their chemical structure. Describe the SAR and metabolism of salicylates.
15. Outline the synthesis and uses of the following NSAIDs: Piroxicam, Sulindac, and Zomepirac sodium.
16. Write a brief note on arylactic acid derived from NSAIDs.
17. What are the major side effects of NSAIDs? Explain how the GIT disturbances can be corrected.
18. Explain the mode of action of antigout drugs and outline the synthesis, metabolism, and uses of any two of them.

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DRUGS ACTING ON RESPIRATORY SYSTEM

1

Expectorants and Antitussives

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Chapter 1

Expectorants and Antitussives

INTRODUCTION OF RESPIRATORY SYSTEM

There are many drugs acting on respiratory system, that is, antitussives, antiasthmatics, expectorants, and mucolytics. There are some drugs that act centrally for suppression of cough through the inhibition of mechano or chemoreceptors. Normally, cough is beneficial for expelling all the dust particles that enter into the respiratory tract. However, when the cough becomes severe due to any inflammation in the respiratory tract or in the lungs, it is necessary to treat with some drugs, such as mucolytics, antiasthmatics, or any expectorants.

The drugs that are used for bronchial asthma are β_2 adrenergic agonists because it is caused due to the irregulation of autonomic control towards these receptors in the lungs and respiratory tract, which produces constriction. Therefore, the difficulty in breathing persists and can be treated, especially, with β_2 adrenergic agonists. For example, salmeterol, terbutaline, formeterol, and some methyl xanthines (caffeine, theophylline) as well as anticholinergics (ipratropium bromide, tiotropium bromide). The inflammation persisting may be treated better with corticosteroids. Bronchial asthma may also be due to the hypersensitive reactions, due to the release of histamine and acetylcholine in the tracheo-bronchial regions. These can be treated by using some mast cell stabilizers called sodium chromglycate and leukotriene antagonists, that is, montelukast and zafirlukast.

Antitussives are the drugs that act in the central nervous system (CNS) to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussual impulse, example, opioids and non-opioids.

Mucolytics are the drugs that depolymerize the mucopolysaccharides and they break the network of tenacious sputum. These events mark the expulsion of sputum with the help of ciliary movement. Examples: bromhexine, adothoda vasaka.

Expectorants are the drugs that increase the bronchial secretion and reduce the viscosity of sputum for removal by coughing. Sodium and potassium citrate and ammonium chloride are used as expectorants.

EXPECTORANTS AND ANTITUSSIVES

Antitussives are drugs that reduce coughing. Coughing may be diminished by reducing respiratory secretion, eliminating a source of irritation, or decreasing the sensitivity of irritant receptors within the respiratory tract. Antitussives can act either by raising the threshold of the cough centre or by reducing the number of impulses transmitted to the centre from the peripheral receptors. The antitussives are divided into two main classes:

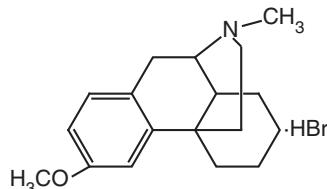
1. Centrally active antitussives that affect the cough centre in the medulla.
2. Peripherally active antitussives that act at the receptor level in the respiratory tract.

Pharyngeal demulcents soothe the throat and reduce the afferent impulse from the inflamed/irritated mucosa. Expectorants are drugs that increase the secretion of bronchus and reduce the viscosity, thereby removing cough and sputum. The drugs usually used as expectorants are salts of sodium, potassium, and ammonium compounds. Guaiphenesin, vasaka, and balsam of tolu are plant products. These also enhance the mucociliary movement. Ammonium salts are nauseating and reflexly increase the respiratory secretion. Antitussives act centrally and relieve the cough. They act on the cough centre in the medulla oblongata and increase the threshold to cough. These drugs control the cough rather than eliminate it. The drugs that are used as antitussives are codeine, an opium alkaloid, and selective drugs are also there for the action on the cough centre, but it may produce respiratory depression at higher dosage. In non-opioids, noscapine and dextromethorphan are usually used. Noscapine is an opium alkaloid of benzoisoquinoline series. It depresses cough, but has no narcotic, analgesic, or dependence effects. Dextromethorphan is a synthetic compound and it is a d-isomer and used as antitussives.

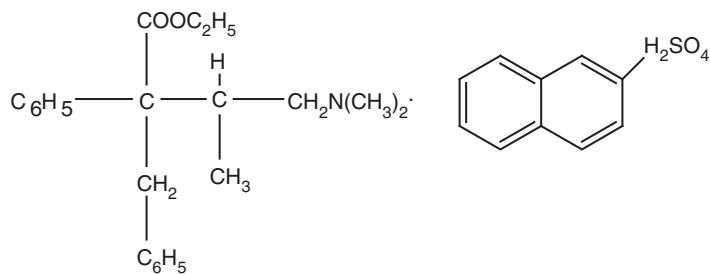
CLASSIFICATION

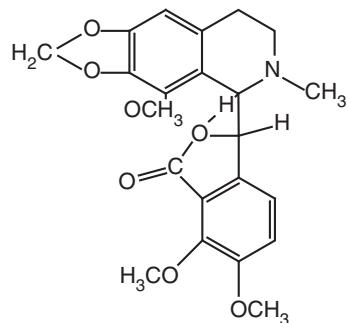
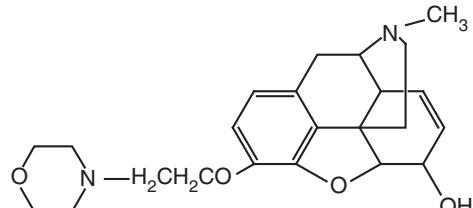
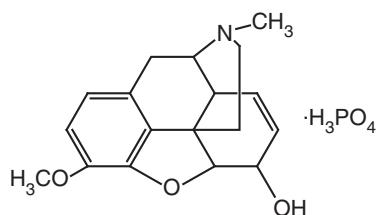
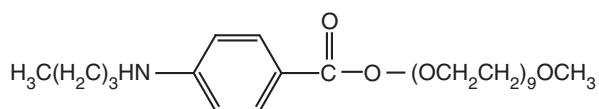
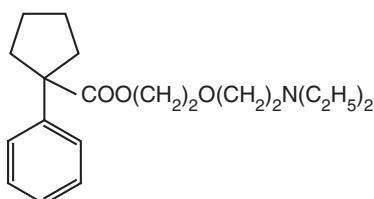
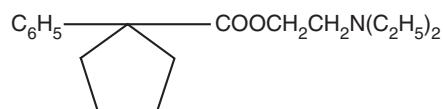
I. Centrally active antitussive agents

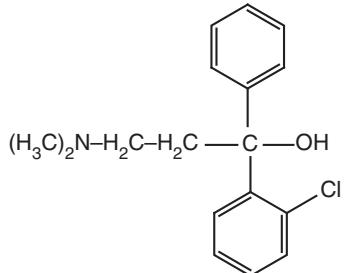
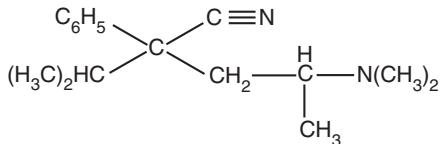
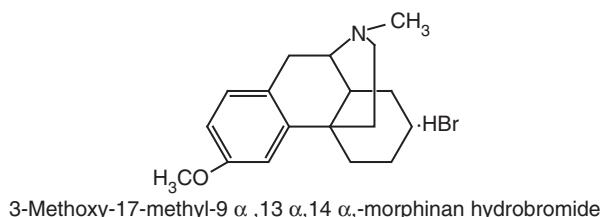
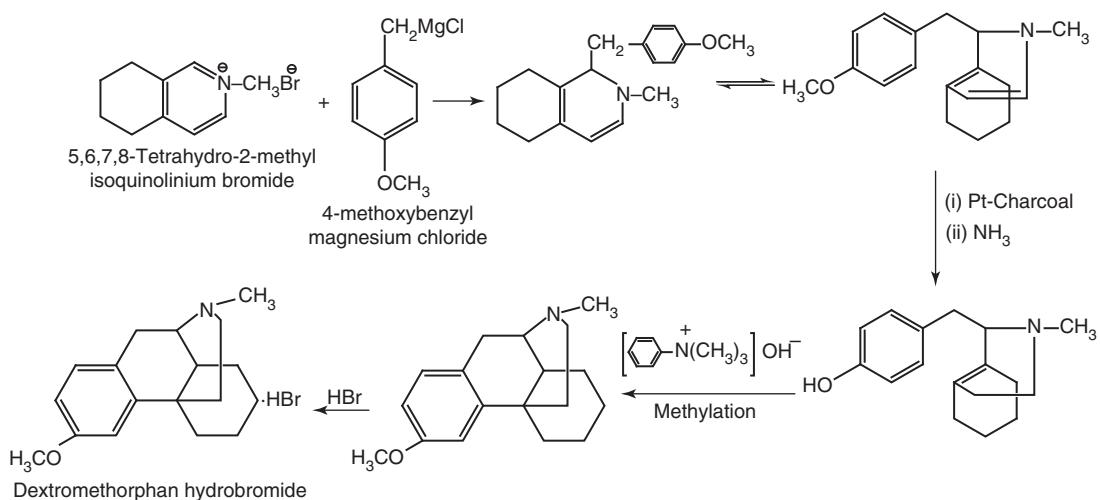
i. Dextromethorphan HBr



ii. Levopropoxyphene napsylate



iii. Noscapine**iv. Pholcodine****v. Codeine Phosphate****II. Peripherally acting antitussives****i. Benzonatate****ii. Carbetapentane****iii. Caramiphen**

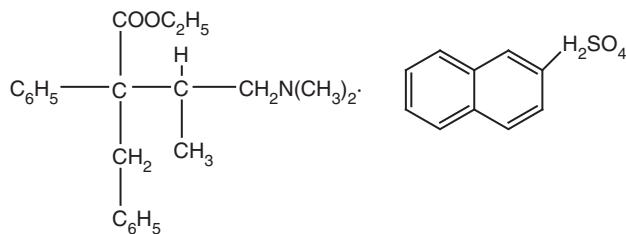
iv. Chlophedianol hydrochloride**v. Isoaminile****SYNTHESIS AND DRUG PROFILE****I. Centrally acting antitussive agents****i. Dextromethorphan HBr****Synthesis**

Properties and uses: Dextromethorphan hydrobromide (HBr) is a white crystalline powder, sparingly soluble in water, and soluble in alcohol. It is a substituted dextro isomer of the opioid levomethorphan.

It is not an analgesic or an addictive. Dextromethorphan HBr should not be given to patients who are on monoamine oxidase inhibitors therapy. It is an opioid receptor agonist used as a cough suppressant.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol (1:4) and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically. Read the volume added between the two points of inflection.

ii. Levoproxyphene napsylate (Novrad)

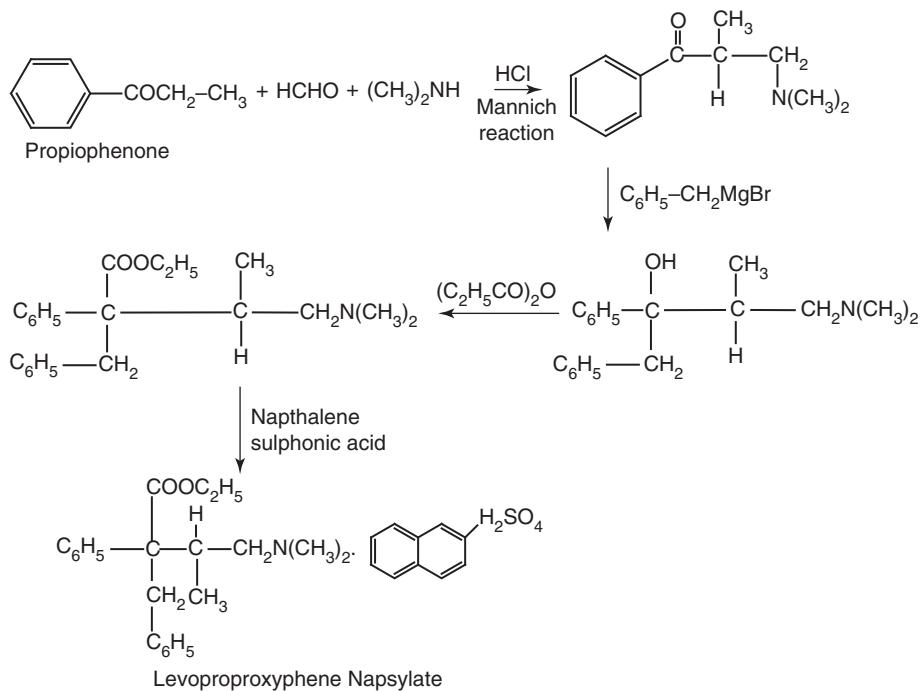


(-) α [(2-Dimethylamino)-1-methyl ethyl]- α -phenyl phenylethyl propionate(1:1)monohydrate-2-naphthalene.sulphonic acid salt

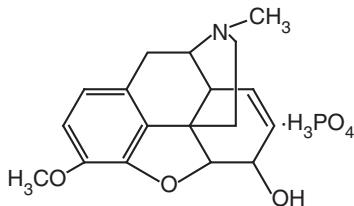
Properties and uses: It is a white, bitter, crystalline powder, odourless, soluble in water, alcohol, or chloroform. It has little or no analgesic activity. It has been found to be relatively less potent than codeine in the treatment of cough reflexes. The (-)-isomer of the drug showed greater antitussive activity in comparison to either the (+)-isomer or the racemic mixture.

Dose: Usually 50–100 mg after every 4 h.

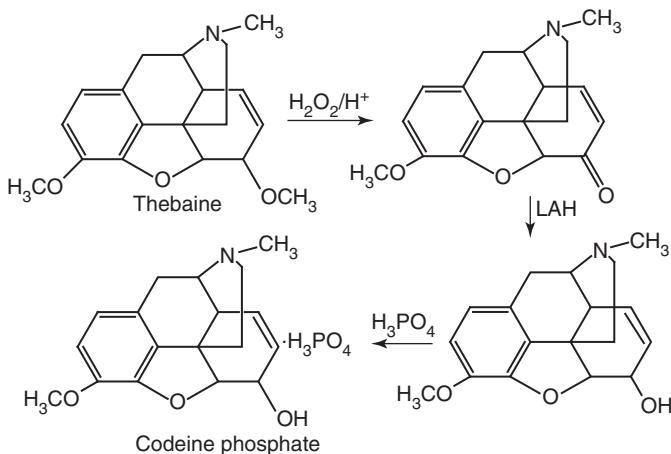
Synthesis



iii. Codeine phosphate (Zenodyl)



Synthesis



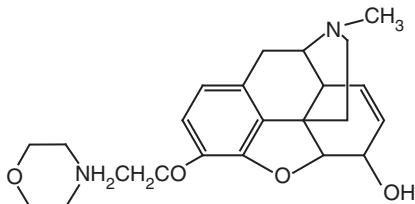
Properties and uses: Codeine phosphate is a white crystalline powder, soluble in water, and slightly soluble in ethanol. This drug acts by suppression of the cough centre in the brain stem.

Assay: Dissolve the sample in a mixture of anhydrous acetic acid and dioxan (1:2) and titrate against 0.1 M perchloric acid using crystal violet as indicator.

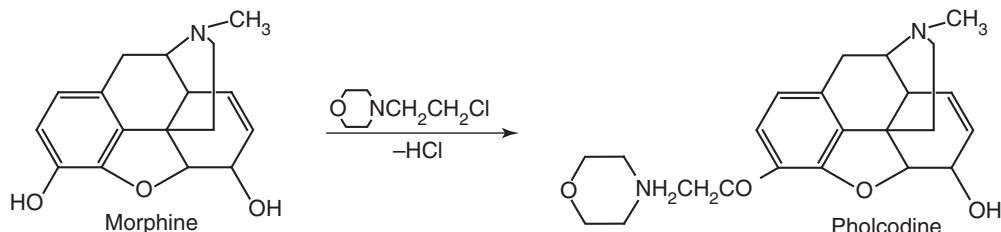
Dose: 10–20 mg every 4 to 6 h.

Dosage forms: Co-codamol tablets B.P., Effervescent co-codamol tablets B.P., Co-codaprin tablets B.P., Dispersible co-codaprin tablets B.P., Codeine linctus, paediatric Codeine linctus B.P., Codeine phosphate injection B.P., Codeine phosphate oral solution B.P., Codeine phosphate tablets B.P.

iv. Pholcodine (Ethnine, Simplex)



Synthesis



Properties and uses: Pholcodine is a white crystalline powder, sparingly soluble in water, soluble in acetone, alcohol, and dilute mineral acid. It is as effective as codeine. It is a cough suppressant with mild sedative, but practically negligible analgesic action. It is employed for the relief of unproductive cough.

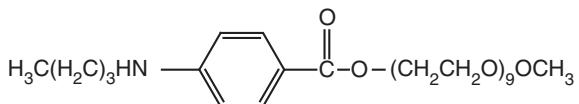
Assay: Dissolve the sample in anhydrous acetic acid, warm gently and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically at the second point of inflexion.

Dose: The dose for adults is 5–15 mg, for children over 2 years 5 mg, for children below 2 years 2.5 mg.

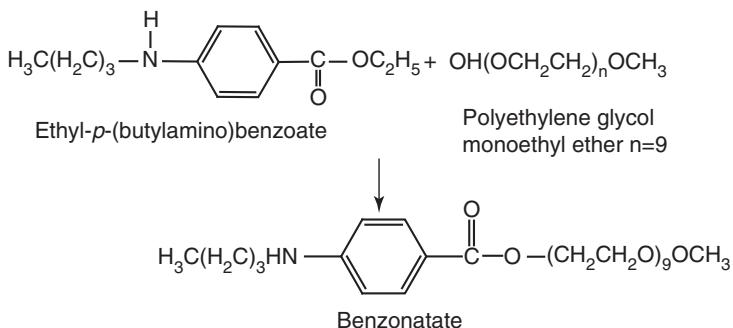
Dosage forms: Pholcodine linctus B.P., Strong pholcodine linctus B.P.

II. Peripherally acting antitussives

i. Benzonatate (Tessalon)



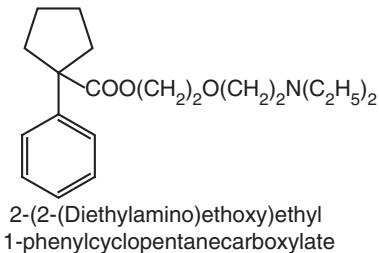
Synthesis



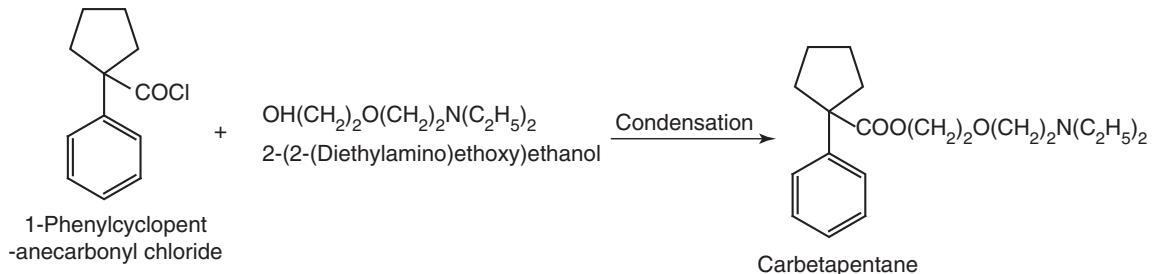
Properties and uses: It is a long-chain polyglycol derivative chemically related to tetracaine and benzocaine. It is a potent antitussive agent. It usually acts by inhibiting the transmission of impulses of the cough reflex in the vagal nuclei of the medulla and predominately depresses polysynaptic spinal reflexes. It is regarded as a cough suppressant acting both centrally and peripherally.

Dose: The usual dose is 100 mg three times daily.

ii. Carbetapentane (Tocla)



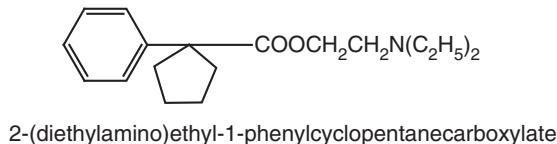
Synthesis



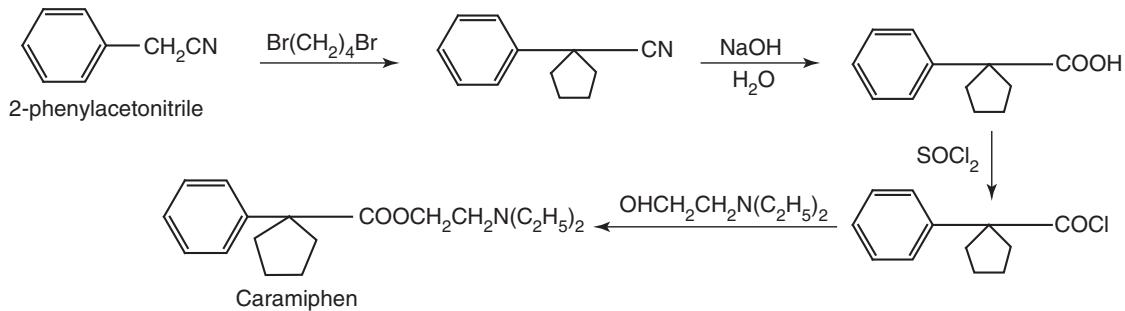
Properties and uses: It is a cough suppressant and is reported to reduce bronchial secretions. It is found to be effective in acute coughs associated with common upper respiratory infections.

Dose: The usual dose is 25–150 mg per day in divided doses.

iii. Caramiphen

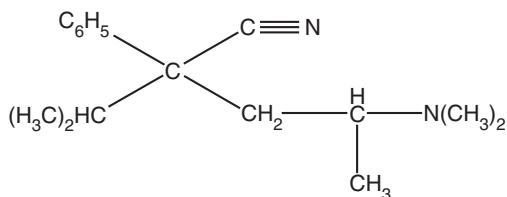


Synthesis



Uses: It is a cough suppressant, less active than codeine, but with longer duration of action. It has little effect on respiration and no tolerance or dependence develops.

iv. Isoaminile



Uses: Used for control and management of cough, it is also a bronchodilator.

PROBABLE QUESTIONS

- Define and classify the expectorants and antitussive agents. Support your answer with the help of two examples from each category along with the chemical structure.
- Write a brief account of the stimulant expectorants. Outline the synthesis of guaiphenesin.
- Outline the synthesis of the following drugs: (a) Benzonatate (b) Carbetapentane citrate
- Name two drugs that act as centrally acting antitussive agents and are analogues of morphine. Outline the synthesis of one such compound.
- Mannich reaction of propiophenone yields levopropoxphene napsylate. Describe the synthetic route to yield the final product.
- Write the structure and chemical name of the five important drugs that are used abundantly in suppressing cough.
- What are sedative expectorants? Classify them and give the structure, chemical names and uses of one compound from each group.
- Centrally acting antitussive agents act by depressing medullary cough centre in the CNS to suppress cough reflexes. Justify the statement by citing at least three potent drugs.

SUGGESTED READINGS

- Abraham DJ (ed). *Burger's Medicinal Chemistry and Drug Discovery* (6th edn). New Jersey: John Wiley, 2007.
- Boyd EM. 'Expectorants and respiratory tract fluids'. *Pharmacol Rev* 6(4): 521–42, 1954.
- 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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- Lednicer D and Mitscher LA. *The Organic Chemistry of Drug Synthesis*. New York: John Wiley, 1995.
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SECTION III

DRUGS ACTING ON DIGESTIVE SYSTEM

1

Antiulcer Agents

121

2

Antidiarrhoeals

137

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Chapter 1

Antiulcer Agents

INTRODUCTION

Antiulcer agents are drugs that are used in the treatment of peptic and gastric ulcers. These are classified on the basis of mechanism of action.

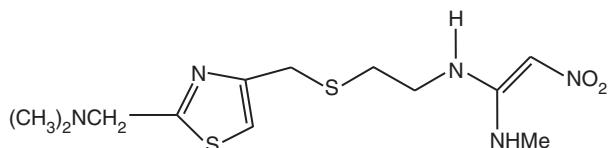
CLASSIFICATION

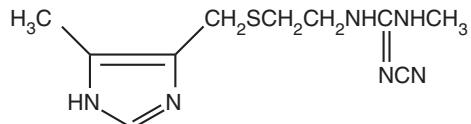
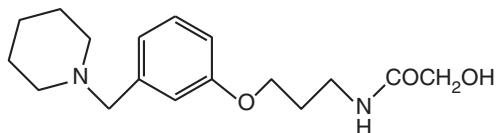
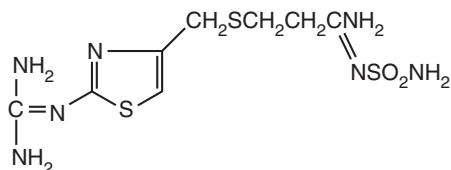
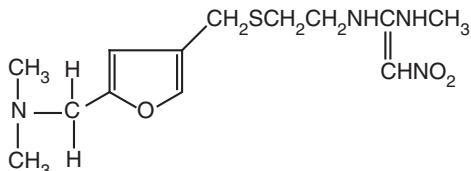
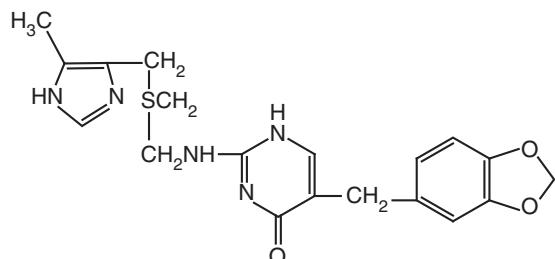
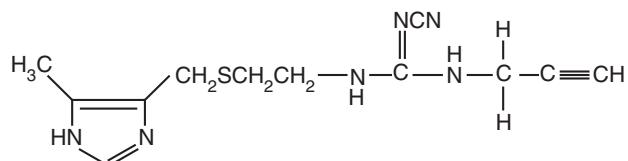
- I. Reduction of gastric acid secretion.
 - a. H₂-antihistamines: Cimetidine, Ranitidine, and Famotidine.
 - b. Proton pump inhibitors: Omeprazole, Lansoprazole, and Pantoprazole.
 - c. Anticholinergics: Pirenzepine, Propantheline, and Oxyphenonium.
 - d. Prostaglandin analogues: Misoprostol.
- II. Neutralization of gastric acid (Antacids).
 - a. Systemic: NaHCO₃ and Sodium citrate.
 - b. Nonsystemic: Mg(OH)₂, CaCO₃, Aluminium hydroxide gel and Magnesium trisilicate.
- III. Ulcer protectives: Sucralfate, Colloidal Bismuthsubcitrate (CBS).
- IV. Anti-*Helicobacter pylori* drugs: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, and Tetracycline.

CHEMICAL STRUCTURES OF GASTRIC ACID SECRETION INHIBITORS

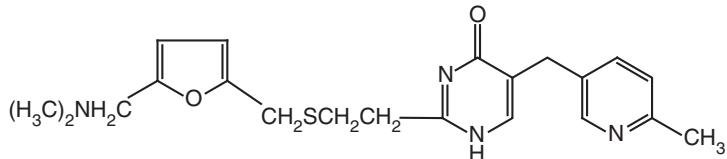
Ia. H₂-antihistamines

i. Nizatidine

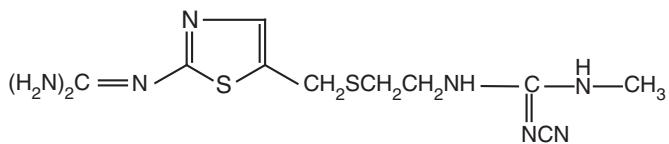


ii. Cimetidine**iii. Roxatidine****iv. Famotidine****v. Ranitidine****vi. Oxmetidine****vii. Etintidine**

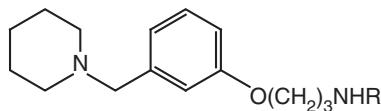
viii. Lupitidine



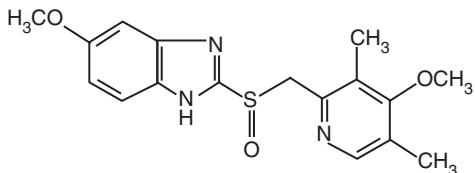
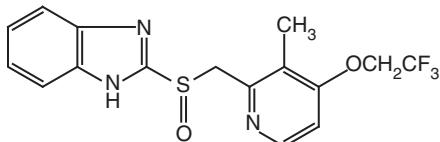
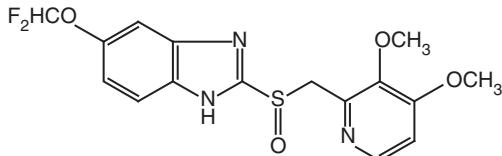
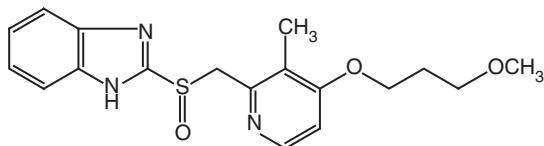
ix. Tiotidine



Lamitidine analogues

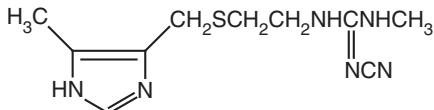


| Name | R |
|------------|---|
| Lamitidine | |
| Pifatidine | |
| Loxtidine | |

I b. Proton pump inhibitors**i. Omeprazole****ii. Lansoprazole****iii. Pantoprazole****iv. Rabeprazole****SYNTHESIS AND DRUG PROFILE****Ia. H₂-receptor antagonists**

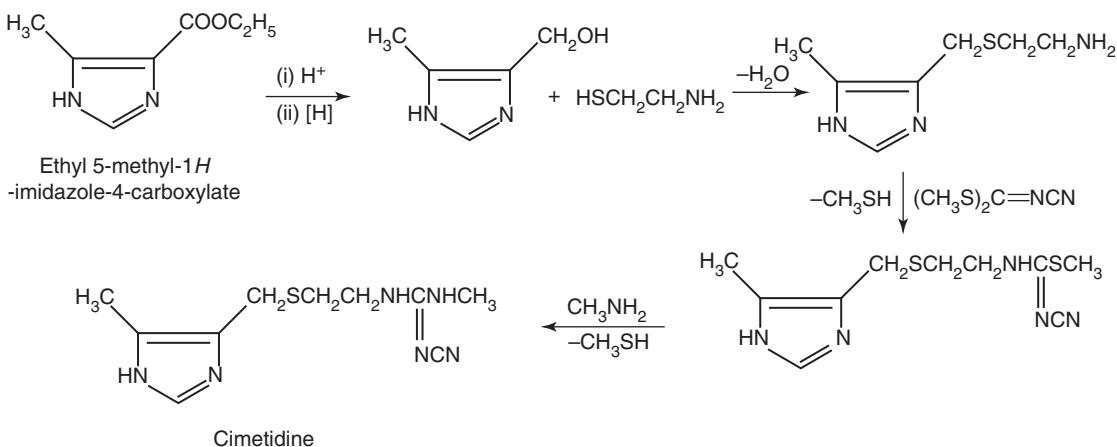
Mode of action: These drugs inhibit the acid production by reversibly competing with histamine for the binding with H₂-receptor on the basolateral membrane of parietal cells. The most predominant effect of H₂-receptor antagonist is on basal acid secretion. Histamine on H₂-receptors produces cAMP-dependent protein kinase to elicit the response in the gastrointestinal tract (GIT). The H₂-antagonists reversibly bind the H₂-receptors and reduce the cAMP formation, which is responsible for the activation of proton pump and subsequently reduces the gastric acid formation in the GIT.

i. Cimetidine (Tagamet)

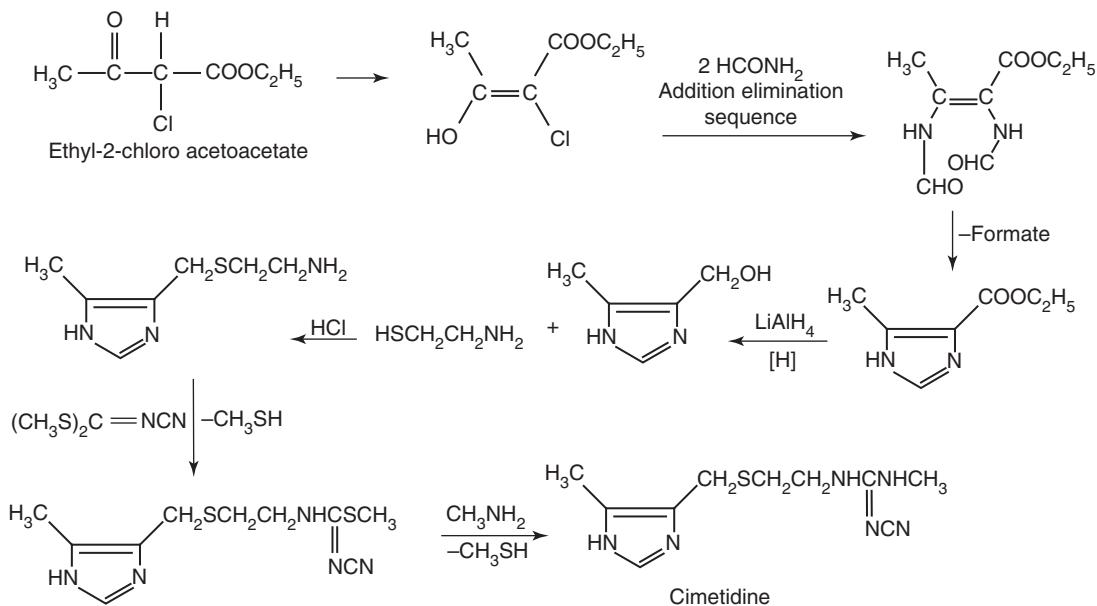


Synthesis

Route I. From: Ethyl 5-methyl-imidazole-4-carboxylate



Route II: From: Ethyl-2-chloro acetoacetate

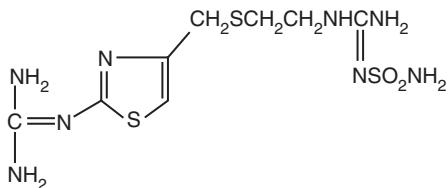


Properties and uses: Cimetidine hydrochloride is a white crystalline powder, soluble in water, and sparingly soluble in ethanol. It is a H_2 -receptor antagonist that not only inhibits gastric acid secretion, but also prevents other actions of histamine mediated by H_2 -receptors. It is used in the treatment of peptic ulceration. Cimetidine has a weak antiandrogenic effect. Gynaecomastia may occur in patients treated for a month or more.

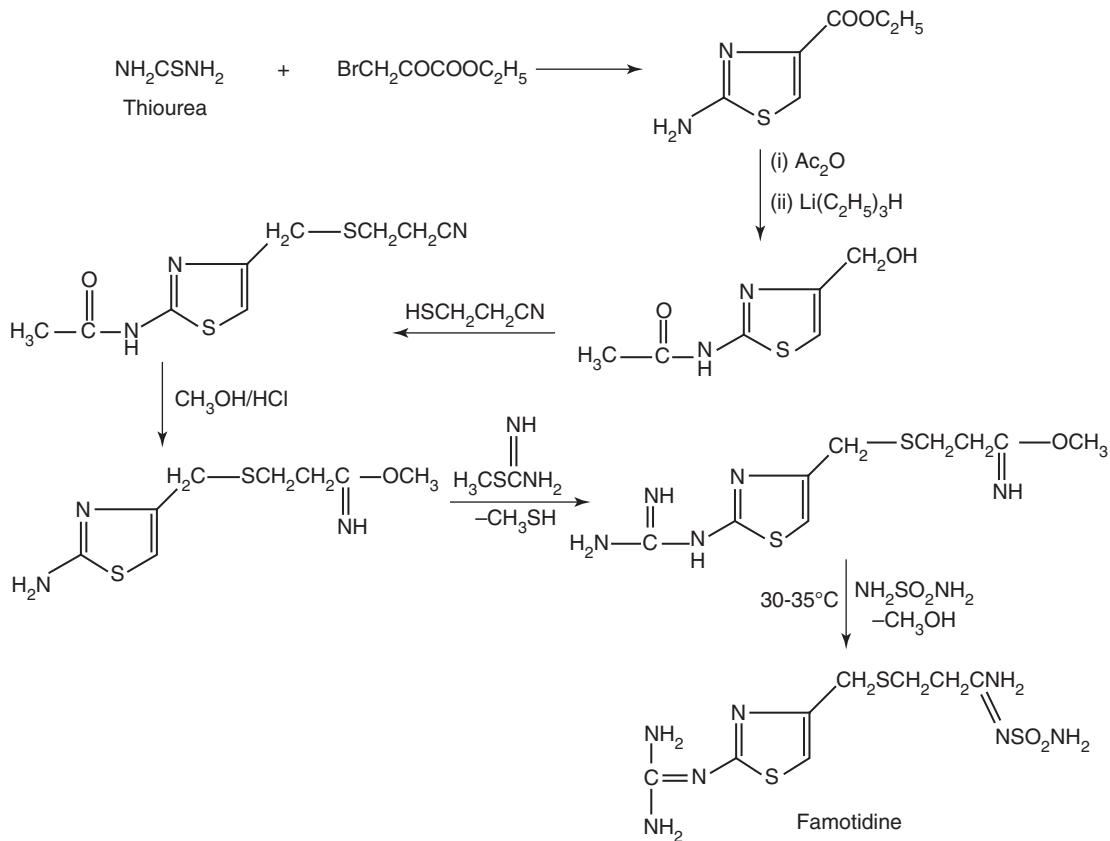
Assay: Dissolve the substance in a mixture of 0.01 M HCl and alcohol (1:10) and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: Oral dose is 200 mg thrice a day with meals and 400 mg at night.

ii. Famotidine (Famocid, Famtac)



Synthesis



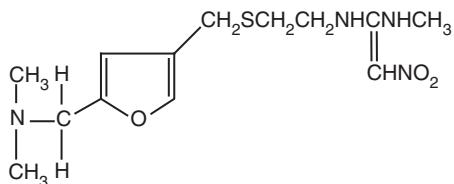
Properties and uses: Famotidine is a white or yellowish-white crystalline powder or crystals, very slightly soluble in water, soluble in anhydrous ethanol and glacial acetic acid, but practically insoluble in ethyl acetate. It acts as a competitive, reversible H₂-antagonist with a slow onset of equilibrium. This type of blockade is called nonequilibrium antagonism. It is used in the treatment of duodenal and gastric ulcers, Zollinger-Ellison syndrome, and heart burn.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end-point potentiometrically.

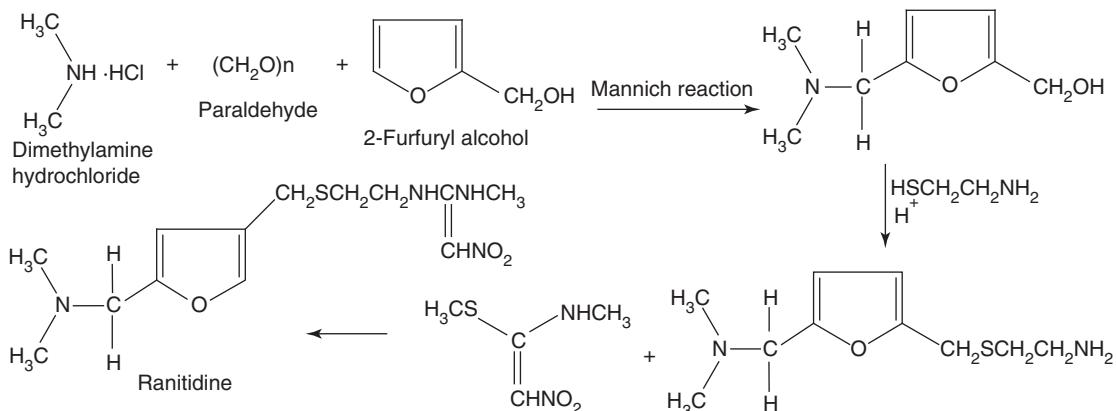
Dose: The dose for gastric or duodenal ulcer is 40 mg at night for 4–8 weeks. The dose for prophylaxis or relapse is 20 mg at night. Not recommended for usage in children.

Dosage forms: Famotidine tablets B.P.

iii. Ranitidine (Zantac)



Synthesis



Metabolism of cimetidine, ranitidine, and famotidine: Hydroxylation of the imidazole C-4 methyl group of cimetidine occurs. Ranitidine is excreted largely unchanged, but minor metabolic pathways include N-demethylation as well as N- and S-oxidation. The metabolites are thought not as contributing to the therapeutic properties of parent drugs, with the exception of nizanidine, from which the N-demethyl metabolites retains H₂-antihistamine activity.

Properties and uses: Ranitidine hydrochloride is a white or pale yellow crystalline powder, soluble in water, slightly soluble in anhydrous ethanol and methylene chloride. In Ranitidine, the imidazole ring of cimetidine was replaced by furan in conjugation with some rearrangement of the terminal functionality; the

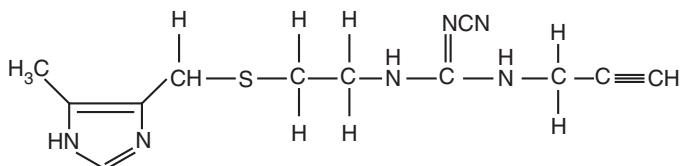
substituted guanidine group has been isosterically modified by utilizing a nitromethenyl moiety to basicity. It is used in the treatment of duodenal ulcer, gastric ulcer, and pathological hypersecretory conditions.

Assay: Dissolve the sample in water and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

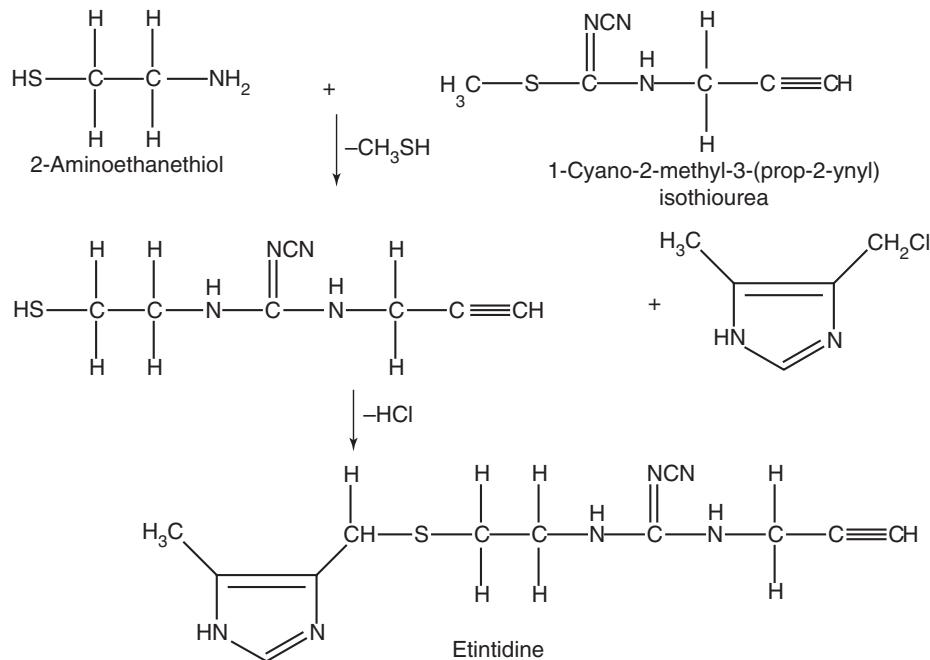
Dose: The dose is 150 mg (as the hydrochloride) two times a day.

Dosage forms: Ranitidine HCl injection I.P., Ranitidine HCl tablets I.P., Ranitidine injection B.P., Ranitidine oral solution B.P., Ranitidine tablets B.P.

iv. Entintidine

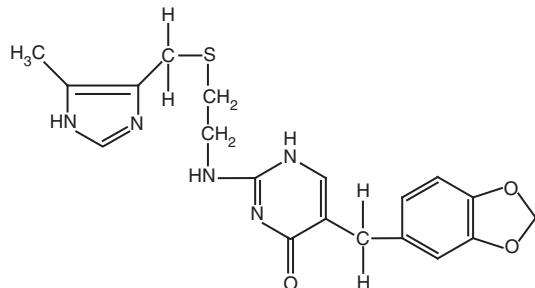


Synthesis



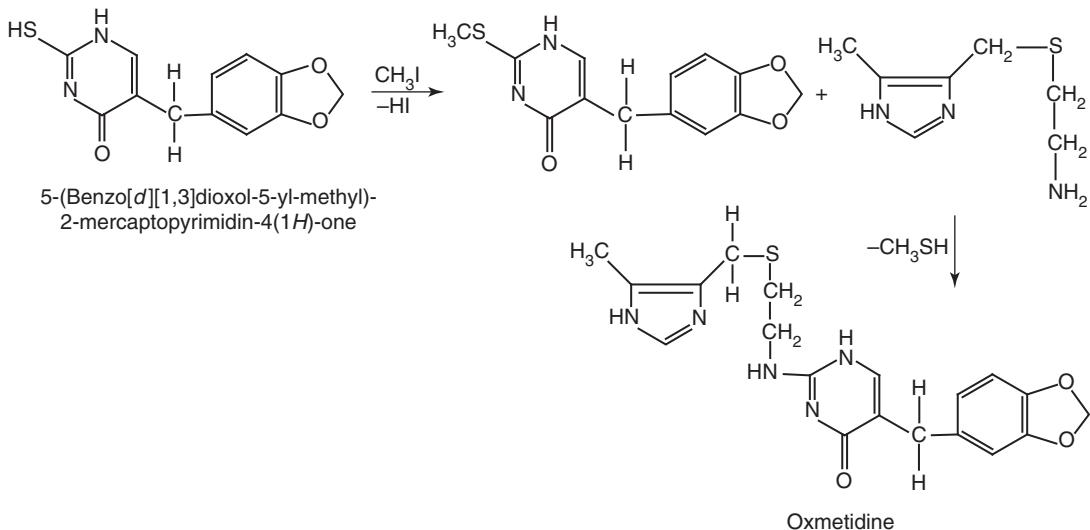
Uses: Used as antiulcer and it is twice as active as cimetidine.

v. Oxmetidine



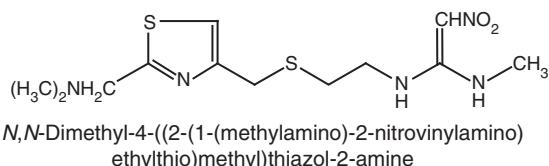
5-(Benzo[d][1,3]dioxol-5-yl methyl)-2-(2-((5-methyl-1*H*-imidazol-4-yl)methylthio)ethylamino)pyrimidin-4(1*H*)-one

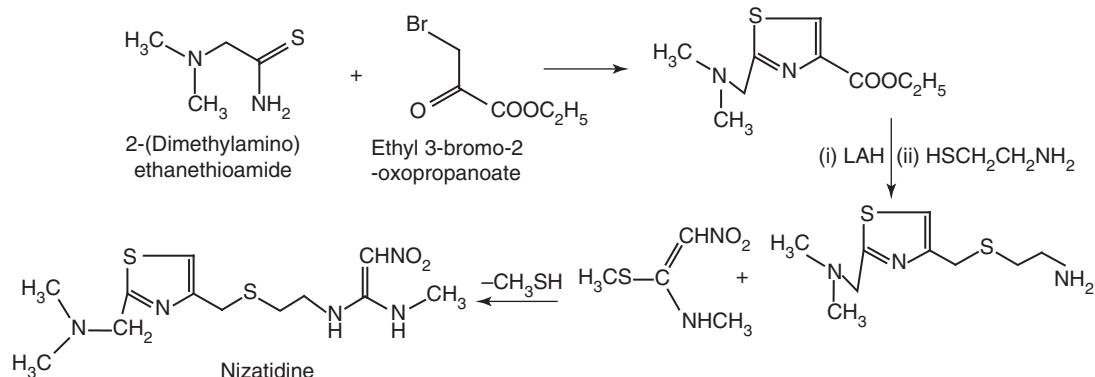
Synthesis



Properties and uses: It shows a time dependent and slow onset of action, which differentiates it from ranitidine. It is reported to have histamine H_2 -receptor blocking activity.

vi. Nizatidine

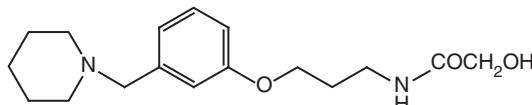
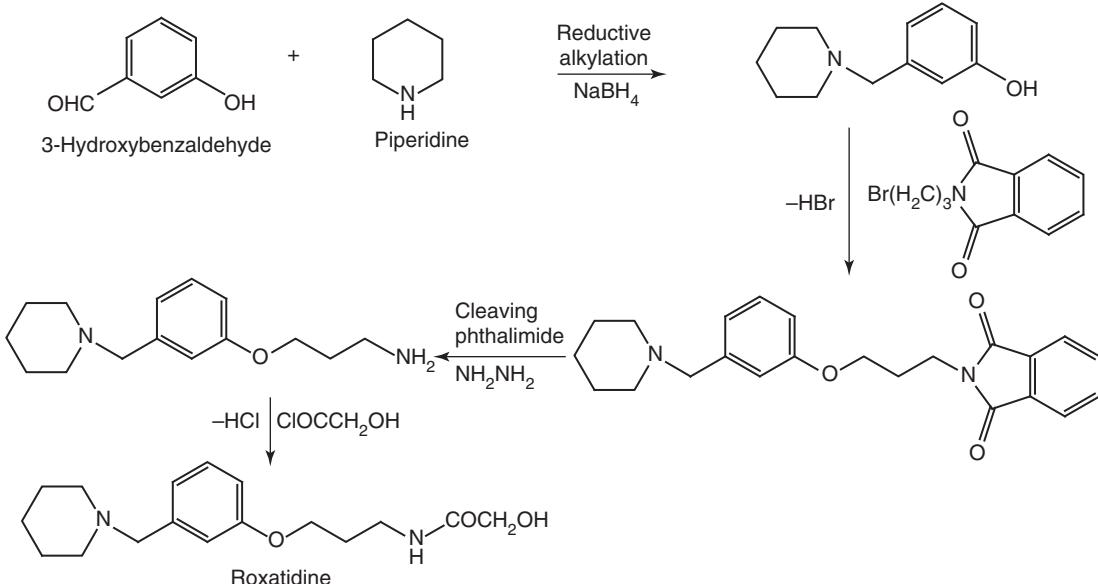


Synthesis

Properties and uses: Nizatidine is a white or slightly brownish crystalline powder, sparingly soluble in water, and soluble in methanol. It is used as histamine H₂-receptor antagonist in the treatment of peptic ulcer.

Assay: It is assayed by adopting liquid chromatography techniques.

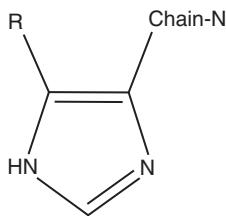
Dosage forms: Nizatidine intravenous infusion B.P.

vii. Roxatidine (Rotane, Zorpex)**Synthesis**

Dose and uses: Oral dose for peptic ulcer for adults is 150 mg at bedtime or 75 mg twice a day for 4–6 weeks; maintenance dose is 75 mg at bedtime. Dose for gastroesophageal reflux disease/oesophagitis, including erosions and ulcerations for adults is 75 mg twice a day or 150 mg at bedtime for 6–8 weeks. The dose for gastritis for adults is 75 mg once daily in the evening. For Zollinger–Ellison syndrome, the dose for adult is 75 mg twice a day. In anaesthetic premedication for adults, the dose is 75 mg in the evening on the day before surgery and repeated every 2 h before induction of anaesthesia, alternatively, 150 mg once on the night before surgery.

SAR of H₂-receptor Antagonists

The H₂-receptor antagonists were the result of the international modification of the histamine structure and deliberate search for a chemically related substance that would act as competitive inhibitor of the H₂-receptors.

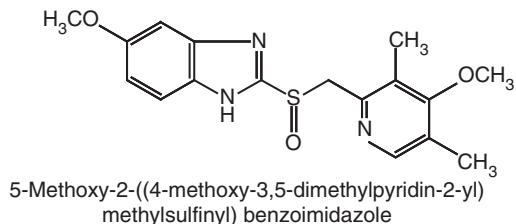


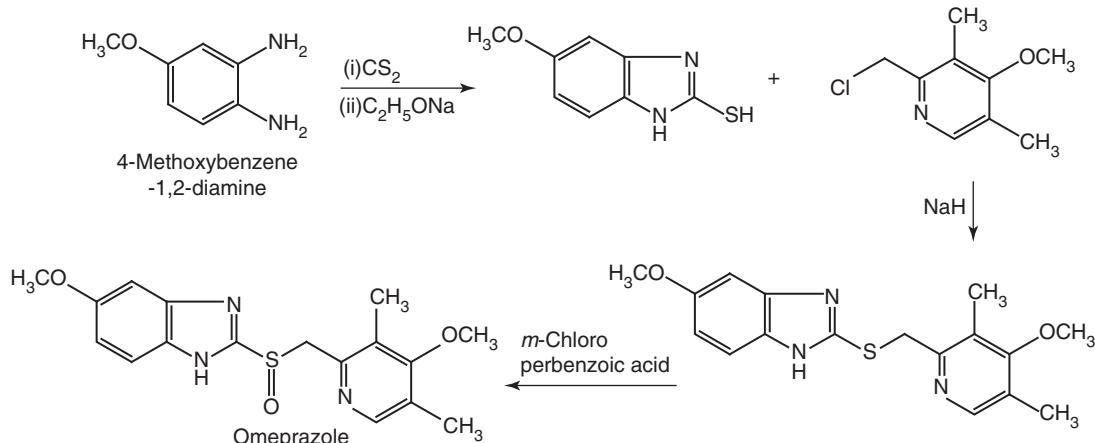
- Imidazole ring is not the only required ring for competitive antagonism of histamine H₂-receptors. Other heterocyclic rings (furan, thiophene, thiazole, etc) that enhance the potency and selectivity of H₂-receptor antagonism can be used.
- The ring and terminal nitrogen should be separated by four carbon atoms for optimum antagonistic activity. The isosteric thioether link is also present in certain drugs.
- The terminal nitrogen group should be polar, nonbasic substituents for maximal antagonist activity. In general, antagonistic activity varies inversely with the hydrophilic character of the nitrogen group (exception ranitidine and nizatidine)

I. b. Proton pump inhibitors

Mode of action: These drugs suppress gastric acid secretion through H⁺ K⁺ ATPase pump, the two major signalling pathways that are present with the parietal cells, that is, cAMP dependent and Ca²⁺. The respective receptors for the actions are M₃ and H₂. These receptors are modulated through the respective ionic mechanism and elicited by the acetylcholine from M₃ and histamine from H₂ receptor for release of the gastric acid mediated through H⁺ K⁺ ATPase pump. The proton pump inhibitors act on these receptors and inhibit H⁺ K⁺ ATPase, and reduce the activation of parietal cells to release the gastric acid.

i. Omeprazole (Ocid, Omez, Omicap)



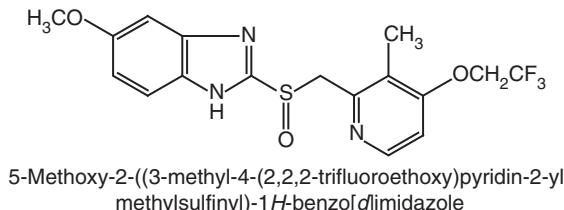
Synthesis

Properties and uses: Omeprazole sodium is a white hygroscopic powder, soluble in water, alcohol, and propylene glycol, very slightly soluble in methylene chloride. It is used in the treatment of duodenal ulcer, gastric ulcer, and pathological hypersecretory conditions.

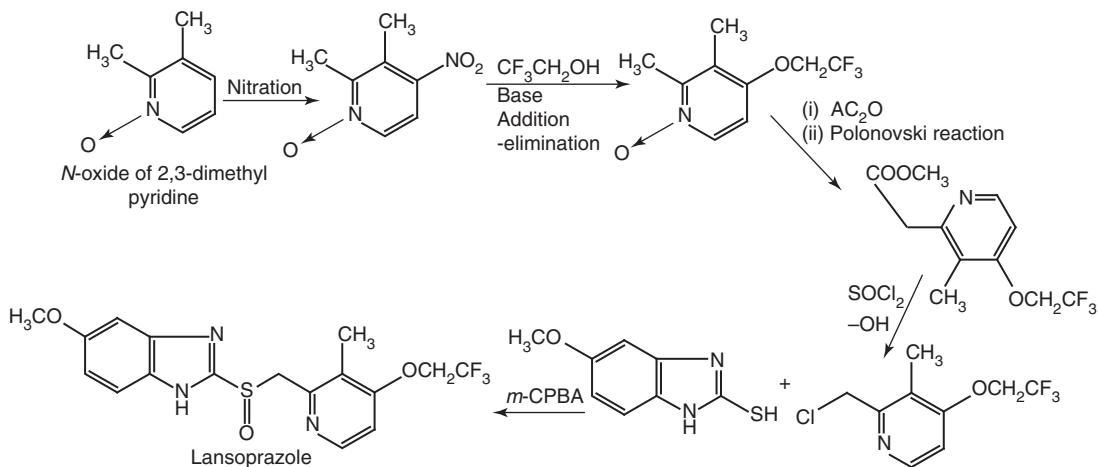
Assay: Dissolve the sample in water and titrate against 0.1 M HCl. Determine the end-point potentiometrically.

Dose: The oral dose for NSAID-associated duodenal or gastric ulcer, gastroduodenal erosions, and prophylaxis in patients with history of gastroduodenal lesions for adult is 20 mg daily. For prophylaxis of acid aspiration during anaesthesia, the dose for adults, initially, is 40 mg given in the evening before surgery and another dose is 40 mg 2–6 h before the procedure. For acid-related dyspepsia, the dose for adults is 10 or 20 mg daily for 2–4 weeks. For peptic ulcer, the dose for adult is 20 mg daily as a single dose or 40 mg daily in severe cases. Duration of treatment for duodenal ulcers is 4 weeks; gastric ulcers is 8 weeks. Maintenance dose is 10–20 mg once daily. Capsule/tablet should be swallowed whole, do not crush or chew. Eradication of *H. pylori* infection: Dose for this treatment for adults varies with regimen, that is, 20 mg once daily or 40 mg a day as single or in two divided doses, and requires combination therapy with antibiotics.

ii. Lansoprazole (Lanicid, Lancus, Lansec)



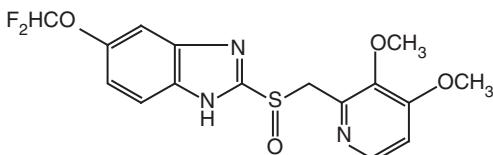
Synthesis



Properties and uses: This drug is used to protect the acidic environment in the stomach. It is used in the treatment and prevention of NSAIDs-induced gastric ulcers as well as Zollinger–Ellison syndrome.

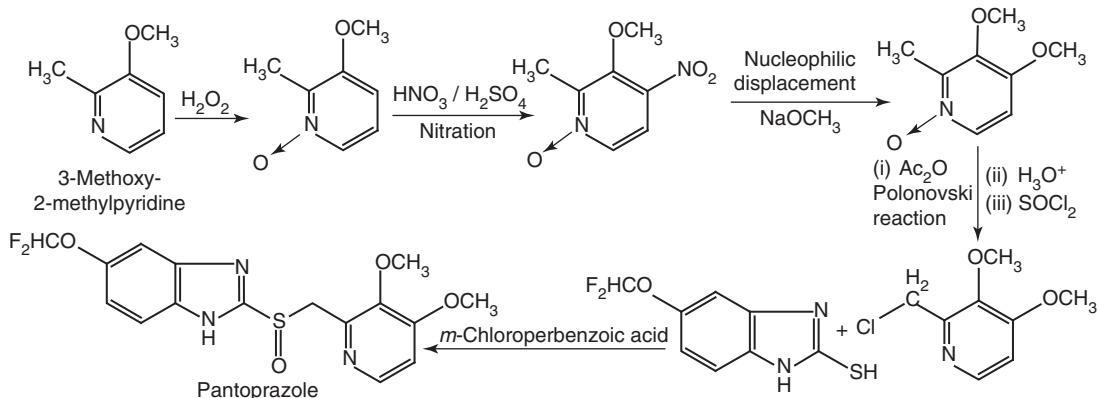
Dose: The oral dose for pathological hypersecretory conditions, example, Zollinger–Ellison syndrome, for adults initially is 60 mg daily and adjusted as required, daily doses greater than 120 mg should be given in two divided doses. For acid-related dyspepsia for adults, the dose is 15–30 mg once daily in the morning for 2–4 weeks. For peptic ulcer, the dose for adults is 30 mg once daily in the morning, given for 4 weeks (duodenal ulcer) or for 8 weeks (gastric ulcer). For NSAID-associated ulceration and prevention of NSAID-induced ulcers, the dose for adults is 15–30 mg daily for 4–8 weeks. For the eradication of *H. pylori* infection the dose for adults is 1-week triple therapy, that is, 30 mg two times a day combined with clarithromycin 500 mg two times a day and either amoxicillin 1 g two times a day or metronidazole 400 mg two times a day.

iii. Pantoprazole (Pantop, Pantodac, Pantocid)



5-(Difluoromethoxy)-2-((3,4-dimethoxypyridin-2-yl)methylsulfinyl)-1*H*-benzo[d]imidazole

Synthesis

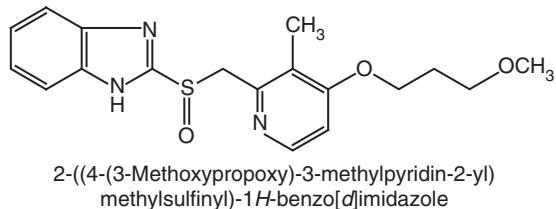


Properties and uses: It is used in the treatment of pathological hypersecretory conditions associated with Zollinger–Ellison syndrome. There is no evidence that any of the pantoprazole metabolites have significant pharmacological activity.

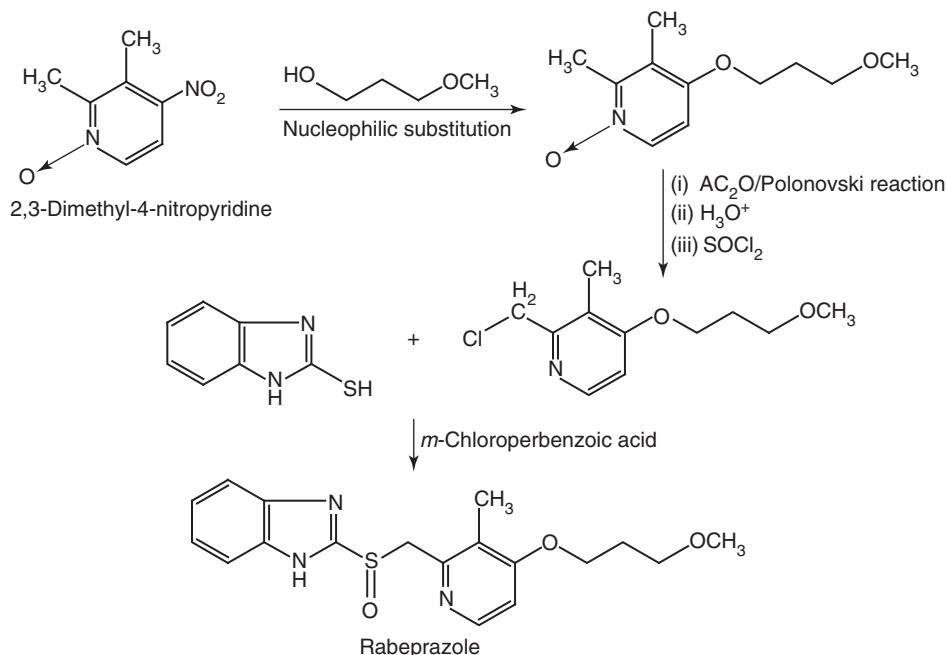
Dose: The oral dose for gastroesophageal reflux disease and oesophagitis, including erosions and ulcerations, for adults is 20–40 mg once daily in the morning for 4 weeks, increased to 8 weeks, if necessary. The maintenance dose is 20–40 mg daily increased to 40 mg each morning, if symptoms return. The dose for peptic ulcer for adults is 40 mg once daily in the morning for 2–4 weeks for duodenal ulceration or 4–8 weeks for benign gastric ulceration. The dose for the eradication of *H. Pylori* infection for adults for triple therapy is 40 mg twice a day combined with clarithromycin 500 mg two times a day and either amoxicillin 1 g twice a day or metronidazole 400 mg twice a day. The dose for prophylaxis of NSAIDs-associated peptic ulcer for adults is 20 mg daily. For Zollinger–Ellison syndrome and other hypersecretory states, the adult dose initially is 80 mg daily, adjusted to individual requirements. Maximum daily dose is 240 mg daily. Daily doses greater than 80 mg should be given in two divided doses.

Intravenous: The intravenous dose for Zollinger–Ellison syndromes and other hypersecretory states for adults is 80 mg (as the Na salt) daily over 2–15 min. Maximum doses are 240 mg daily in divided doses, if rapid control is required. In the cases of peptic ulcer, gastroesophageal reflux disease, oesophagitis, including erosions and ulcerations the adult dose is 40 mg (as the Na salt) daily (over 2–15 min) until the patient can be resumed.

iv. Rabeprozole (Rabeloc, Rabifast, Rabitop)



Synthesis

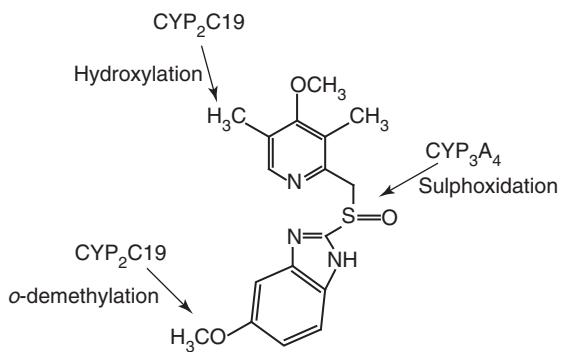


Uses: It is used in gastric hypersecretory disorders.

Dose: The dose for pathological hypersecretory conditions, example, Zollinger–Ellison syndrome, for adults initially is 60 mg daily, adjusted according to response. Maximum dose is 120 mg daily. For active peptic ulcer diseases for adults is 20 mg daily given for 4–8 weeks for duodenal ulcer and 6–12 weeks for gastric ulcer. In the case of eradication of *H. Pylori* infection the dose for adults as a combination with antibacterials is 20 mg twice a day combined with clarithromycin 500 mg twice a day and either amoxicillin 1 g twice a day or metronidazole 400 mg twice a day to be taken for a week.

Metabolism of proton pump inhibitors: Metabolism of omeprazole and other proton pump inhibitors occurs primarily in the liver. The sulphonated, hydroxylated, and O-demethylated metabolites have been reported as products. The oxidative metabolism of omeprazole is catalyzed principally by CYP2C19 (primarily 5'-hydroxylation and to a lesser extent, benzimidazole O-demethylation).

Different proton pump inhibitors depend differently on CYP2C19 for the oxidative metabolism, and the enantiomer show variation of independence on CYP2C19 and other pathways. Pantaprazole and lansoprazole show greater metabolism via CYP2C19. The enantiomer being affected differently than Rabeprazole, which is metabolized only to a small extent by oxidative CYP450 enzyme.



PROBABLE QUESTIONS

1. Define and classify antiulcer agents with one example in each category and write the synthesis and uses of one of them.
2. Write the mode of action of proton pump inhibitors. Outline the synthesis and uses of lansoprazole.
3. What are H₂-receptor antagonists? How does it act as antiulcer agents ? Describe the synthesis, metabolism, and uses of ranitidine.
4. Write a short note on anti-*H. pylori* drugs.
5. Name the thiazole and imidazole containing H₂ blockers and write the synthesis, metabolism, and uses of one of them.

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Chapter 2

Antidiarrhoeals

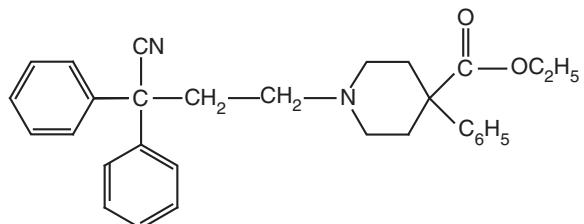
INTRODUCTION

Diarrhoea means loose bowel movements resulting into the frequent passage of watery, unformed stools with or without mucous and blood. This condition may arise due to the change in the nature of the diet and routine or sometimes due to bacterial infection. The former type of diarrhoea is the mild form while the infective diarrhoea is more powerful and persistent. Organism escapes from gastric acid and other digestive processes reaches the bowel. Their metabolic products irritate the nerve ending of intestinal wall leading to severe diarrhoea. In this condition, to compensate the loss of body fluids, a mixture of salt (sodium chloride or sodium bicarbonate) and water is to be given frequently. The simple type of diarrhoea may be controlled just by using intestinal adsorbents while infected diarrhoea needs the use of intestinal antiseptics.

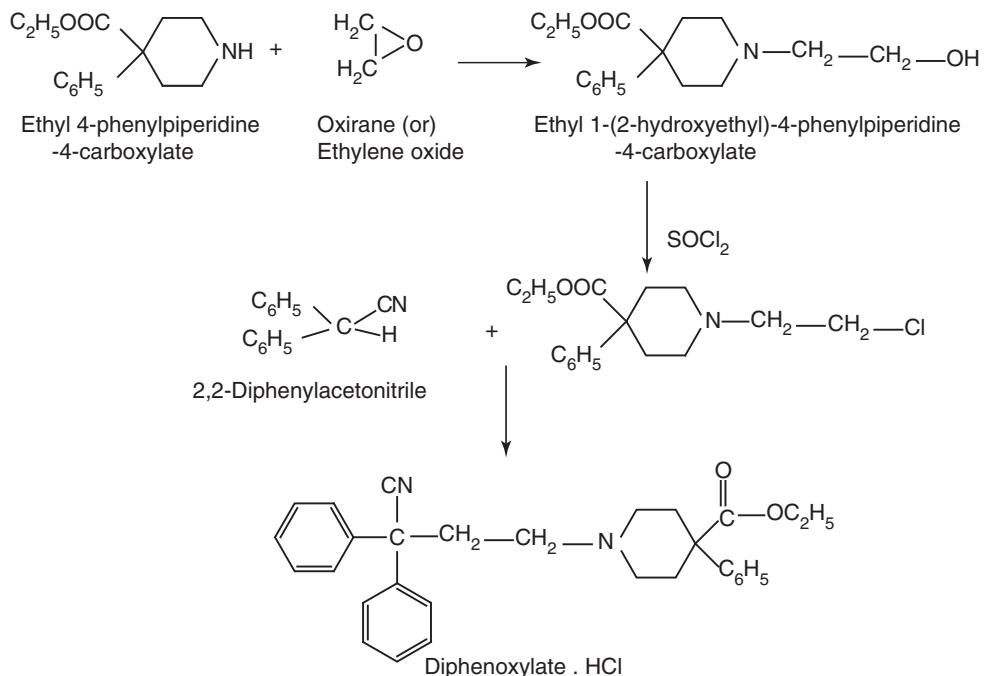
Adsorbents

These substances have the power of adsorbing gases, bacteria, and toxins without undergoing any chemical reaction. They also posses the protective property apart from their adsorbent action. They form a coating over the intestinal mucosa to reduce its irritation, example of this category are kaolin, calcium carbonate, magnesium trisilicate, and aluminium hydroxide, pectin, bismuth subsalicylate and polycarbophil and various psyllium seed derivatives.

1. Diphenoxylate HCl (Lemotil)



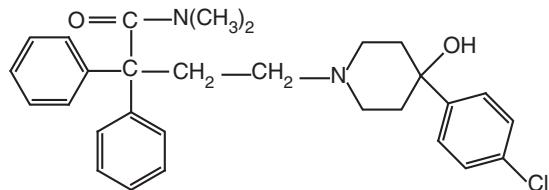
Synthesis



Properties and uses: It is a weak meperidine congener lacking analgesic activity. It is used for the symptomatic activity of diarrhoea in patients with mild chronic inflammatory bowel disease and for infectious gastroenteritis.

Dose: The usual adult dose orally is 5 mg four times a day.

2. Loperamide



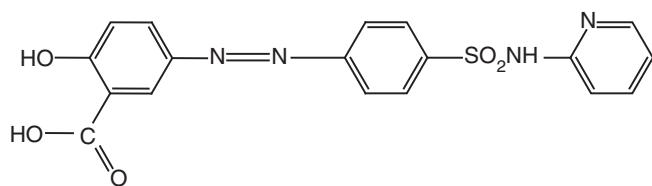
Properties and uses: It is a synthetic meperidine congener devoid of sedative or respiratory depressant actions. It is orally used as an antidiarrhoeal agent. Loperamide exerts spasmolytic effect on the gastrointestinal tract (GIT) muscle by depressing slow cholinergic phase and rapid prostaglandin mediated phase of smooth muscle contraction. It may act on the intestinal nerve endings or on the ganglia.

Intestinal Antiseptics

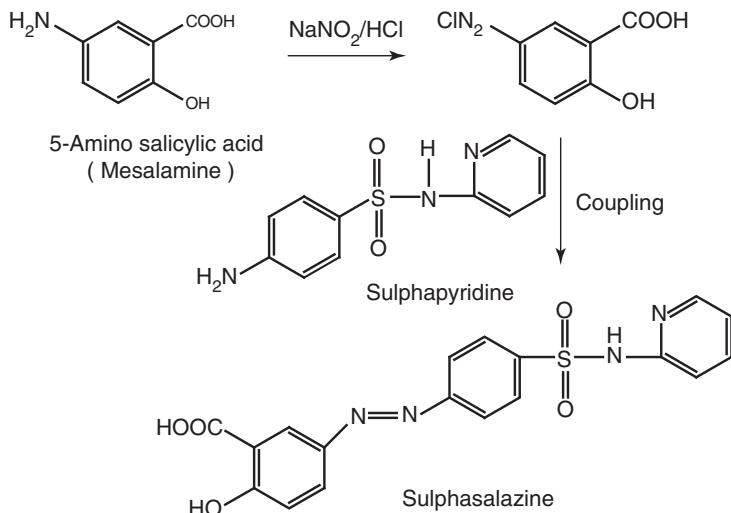
These agents are used to treat severe diarrhoeal forms, which are due to microbial infection. They mainly comprise of certain members of the sulphonamides and antibiotics that are poorly absorbable in the GIT, and thus, reach in high concentrations to the small and large bowels. Examples are sulphasalazine, sulphaguanidine, phthalyl sulphathiazole, succinyl sulphathiazole. Various combinations of sulphonamides and antibiotics along with kaolin are available either in the form of cream or suspension. Streptomycin, neomycin, chloramphenicol, tetracyclines and nystatin are the examples of such antibiotics used for this purpose.

1. Antisecretory drugs

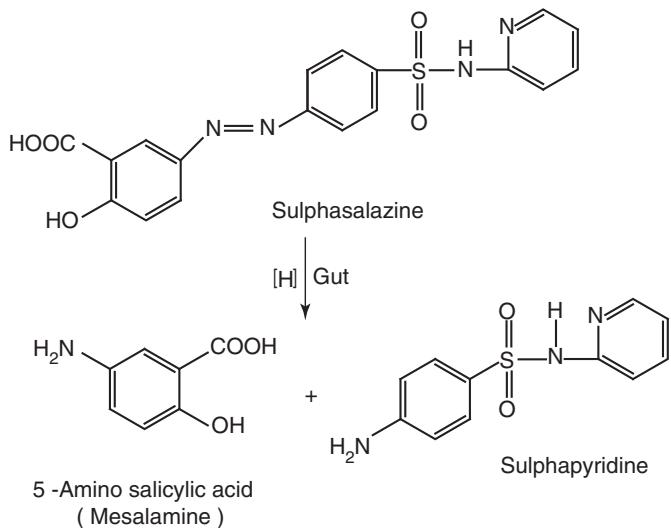
i. Sulphasalazine (salicylazosulphapyridine)



Synthesis



Metabolism: It undergoes reductive metabolism by gut bacteria, converting the drug into sulphapyridine and 5-amino salicylic acid, which are the active components.



Properties and uses: Sulphasalazine is a bright yellow or brownish-yellow fine powder, practically insoluble in water and methylene chloride and sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and used in the treatment of inflammatory bowel diseases such as ulcerative colitis.

Assay: Dissolve and dilute the sample in 0.1 M sodium hydroxide and add 0.1 M acetic acid and measure the absorbance at the maxima of 359 nm using ultraviolet spectrophotometer.

Dosage forms: Sulphasalazine tablets B.P.

ii. Bismuth subsalicylate

It acts by decreasing prostaglandin synthesis in the intestinal mucosa, thereby reducing Cl^- secretion. It has some prophylactic value in traveller's diarrhoea (probably due to weak antibacterial action also), but it is rather inconvenient to carry and take.

iii. Atropine: Atropinic drugs can reduce bowel motility and secretion, but have poor efficacy in secretory diarrhoeas. They may benefit nervous/drug (neostigmine, metaclopramide, reserpine) induced diarrhoeas and provide some symptomatic relief in dysenteries diverticulitis.

iv. Octreotide: This somatostatin analogue has a long plasma as well as potent antisecretory/antimotility action on the gut. It has been used to control diarrhoea in carcinoid and vasoactive intestinal peptide secreting tumours and for refractory diarrhoea in AIDS patients, but needs to be given by subcutaneous injections.

v. Racecadotril: This recently introduced prodrug is rapidly converted to thiopronin, an enkephalinase inhibitor. It prevents the degradation of endogenous enkephalins, which are mainly δ opioid receptor agonists. Racecadotril decreases intestinal hypersecretion, without affecting motility by lowering mucosal cAMP due to enhanced enkephalins action. It is indicated in the short-term treatment of acute secretory diarrhoeas.

PROBABLE QUESTIONS

1. Define and classify antidiarrhoeal agents with suitable examples. Write the synthesis and uses of any two of them.
2. Write short notes on antisecretory drugs used in diarrhoea.
3. Write the synthesis of loperamide and diphenoxylate.

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SECTION IV

DRUGS ACTING ON BLOOD AND BLOOD FORMING ORGANS

1

Coagulants

145

2

Plasma Expanders

160

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Chapter 1

Coagulants

INTRODUCTION

Homeostasis is the cessation of blood loss from damaged vessels. Platelets first adhere to macromolecules in the subendothelial regions of injured blood vessels; they aggregate to form the primary haemostatic plug. Platelets stimulate the local activation of plasma coagulation factors, leading to generation of a fibrin clot that reinforces the platelet aggregate. Later, as wound healing occurs, the platelet aggregates and fibrin clots are degraded. Thrombosis is a pathological process in which a platelet aggregates and a fibrin clot occludes blood vessels. Arterial thrombosis may result in ischaemic necrosis of tissues supplied by the artery (e.g. myocardial infarction due to thrombosis of coronary artery). Venous thrombosis may cause tissue drain by the vein to become edematous and inflamed.

Coagulation of blood comprises the formation of fibrin by a series of interactions among a large number of protein factors and other substances. Blood coagulation process requires coagulation factors, calcium, and phospholipids.

- The coagulation factors (proteins) are manufactured by the liver.
- Ionized calcium (Ca^{++}) is available in the blood and from intracellular sources.
- Phospholipids are prominent components of the cellular and platelet membranes. They provide a surface on which the chemical reactions of coagulation can take place. The coagulation factors are numbered in the order of their discovery.

Factor I—Fibrinogen

Factor II—Prothrombin

Factor III—Tissue thromboplastin (tissue factor)

Factor IV—Ionized calcium (Ca^{++})

Factor V—Labile factor or proaccelerin

Factor VI—Unassigned

Factor VII—Stable factor or proconvertin

Factor VIII—Antihæmophilic factor

Factor IX—Plasma thromboplastin component, Christmas factor

Factor X—Stuart–Prower factor

Factor XI—Plasma thromboplastin antecedent

Factor XII—Hageman factor

Factor XIII—Fibrin stabilizing factor

Mechanism of Blood Clotting

Coagulation can be initiated by either of the two distinct pathways (Fig. 1.1):

1. The intrinsic pathway can be initiated by events that take place within the lumen of blood vessels. This requires only elements (clotting factors, Ca^{++} platelet surface, etc) found within or intrinsic to the vascular system.
2. The extrinsic pathway is the other route to coagulation. It requires tissue factor (tissue thromboplastin), a substance that is extrinsic to or not normally cumulating in the vessel. Tissue factor is released when the vessel wall is ruptured.

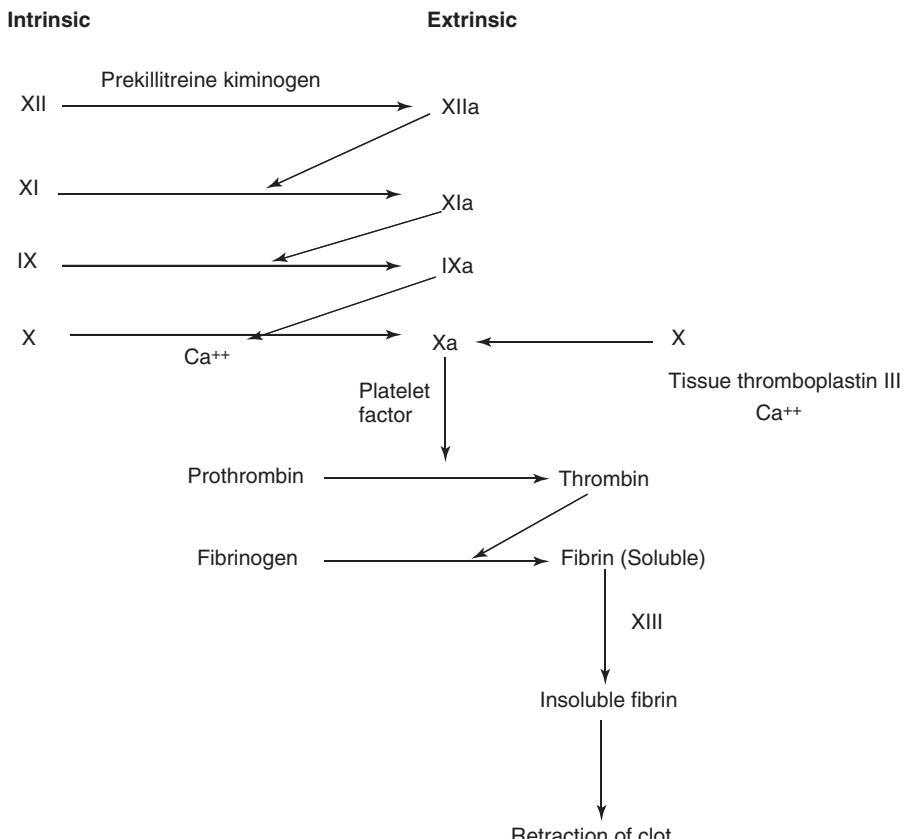
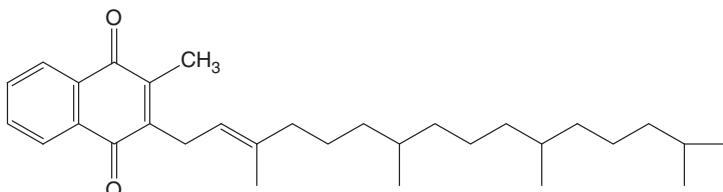


Figure 1.1 Mechanism of blood clotting.

1. Calcium salts: Calcium salts, especially Ca^{++} intravenous injections, are very popular, but it does not help much unless there is deficiency of Ca^{++} in the blood.

2. Vitamin K (Synonym: Vitamin K₁-Phytomenadione)

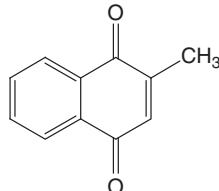


Properties and uses: Phytomenadione is a clear intense yellow viscous oily liquid, practically insoluble in water, sparingly soluble in ethanol, and miscible with fatty oils. Vitamin K is essential to keep up the prothrombin level in blood by forming prothrombin in the liver. Hence, it is used orally and intramuscular (IM), now water-soluble vitamin K is available for intravenous (IV) administration. This is called methyl naphthaquinone and is very useful in emergency.

Assay: It is assayed by adopting liquid chromatography technique.

Dosage forms: Phytomenadione injection B.P., Phytomenadione tablets B.P.

3. Vitamin K₃ (Menadione)



Properties and uses: Menadione is a pale-yellow crystalline powder, practically insoluble in water, soluble in toluene, sparingly soluble in alcohol and methanol. Used as source of vitamin K and has prothrombotic property.

Assay: Dissolve the sample in glacial acetic acid and add dilute hydrochloric acid and zinc powder. Allow the mixture to stand and titrate against 0.1 M ammonium ceric nitrate using ferroin as indicator.

Anticoagulants

Anticoagulants are drugs that prevent the clotting of blood. Heparin is a glucosaminoglycan found in the secretory granules of mast cells. It is synthesized from uridine diphosphate sugar precursor as a polymer of alternating D-gluconic acid and N-acetyl-D-glucosamine residue. About 10–15 glucosaminoglycan chains, each containing 200–300 monosaccharide units, are attached to a core protein and yield a proteoglycan with a molecular mass of 750,000–1,000,000 daltons. The glucosaminoglycan then undergoes a series modification, which includes *n*-acetylation and *n*-sulphonation of glucosamine, epimerization of D-gluconic acid to L-iduronic acid, O-sulphation of iduronic and glucoronic acid residues at the C₂ position, and O-sulphation of glucosamine residue at C₃ and C₆ position. Each of these modification reactions is incomplete, yielding variety of oligosaccharide structures. After the heparin proteoglycan has been transported to the mast cell

granule, an endo- β -D-glucuronidase degrades the glycosamionoglycan chains to 5000–30,000 dalton fragments over a period of hours.

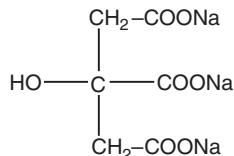
CLASSIFICATION

Anticoagulants are classified as follows:

- I. In vitro anticoagulants: Heparin, Sodium oxalate, and Sodium citrate.
- II. In vivo anticoagulants.
 - 1. Heparin: injectable
 - 2. Oral
 - a. Coumarin derivatives: Warfarin, Bishydroxycoumarin.
 - b. Indandiones: Phenindione, Diphenadion.

I. In vitro anticoagulants

Heparin, Sodium citrate, Sodium oxalate



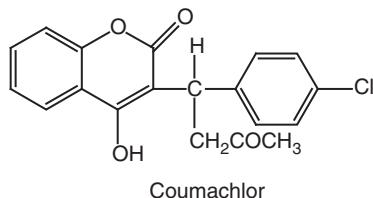
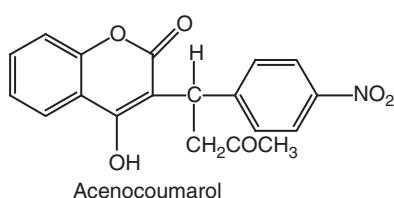
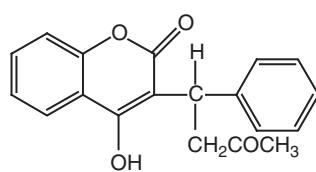
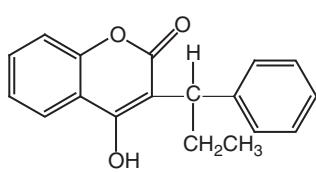
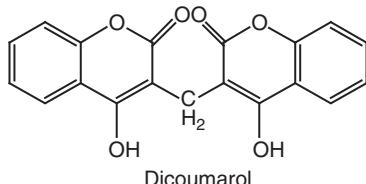
Sodium citrate

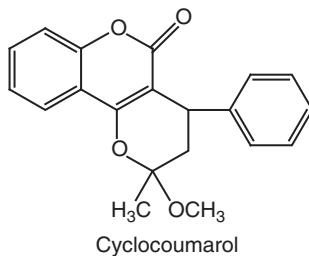


Sodium oxalate

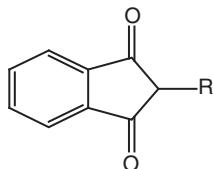
II. In vivo anticoagulants

a. Coumarin derivatives





b. Indandione derivatives

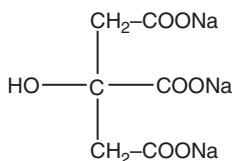


| Name | R ₁ |
|--------------|--|
| Phenindione | -C ₆ H ₅ |
| Anisindione | H ₃ CO-phenyl |
| Bromindione | Br-phenyl |
| Diphenadione | -COCH(C ₆ H ₅) ₂ |

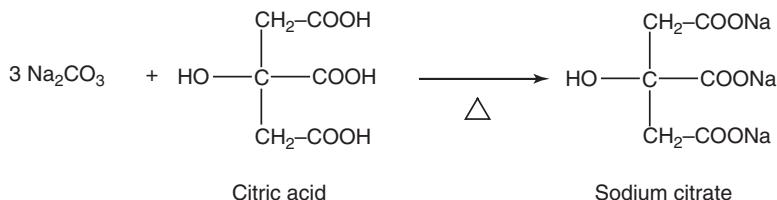
SYNTHESIS AND DRUG PROFILE

I. In vitro anticoagulants

i. Sodium citrate



Synthesis



Properties and uses: Sodium citrate exists as white crystalline powder or granular crystals, soluble in water, but insoluble in alcohol and used as systemic alkalinizing substance.

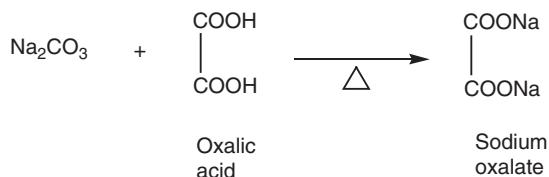
Assay: Dissolve the sample in anhydrous acetic acid. Heat it, allow to cool and titrate against 0.1 M perchloric acid using naphtholbenzein as indicator until a green colour is obtained.

Dosage forms: Sodium citrate eye drops B.P., Sodium citrate irrigation solution B.P.

ii. Sodium oxalate

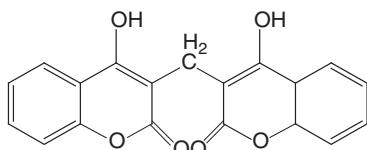


Synthesis



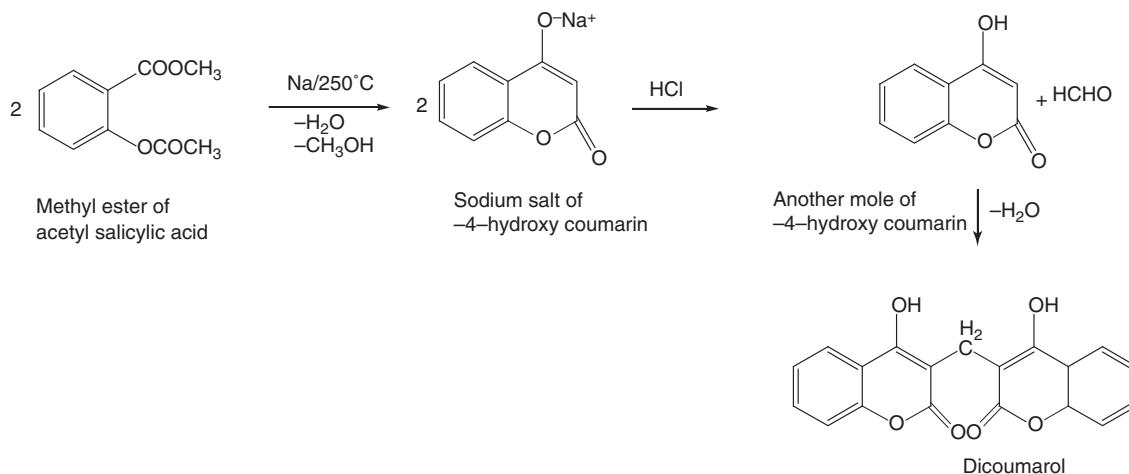
II. In vivo anticoagulants or coumarin derivatives

i. Bishydroxycoumarin (Dicoumarol)



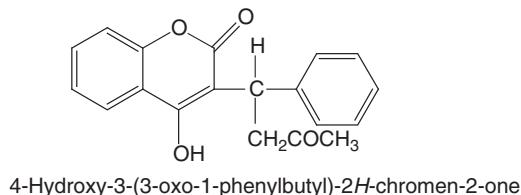
4-Hydroxy-3-((4-hydroxy-2-oxochroman-3-yl)methyl)-2H-chromen-2-one

Synthesis

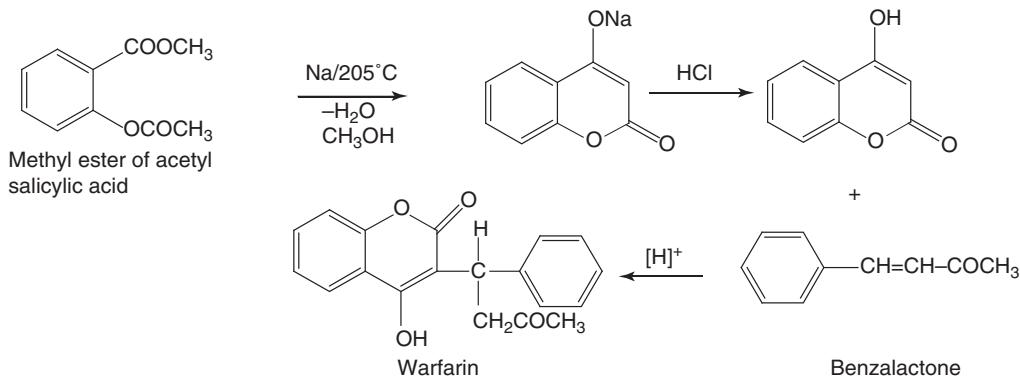


Properties and uses: It is used in postoperative thrombophlebitis, pulmonary embolus, acute embolic, and thrombotic occlusion of peripheral arteries.

ii. Warfarin (Coumarin, Coumadia)



Synthesis



Properties and uses: Warfarin sodium is a white hygroscopic powder, soluble in water, alcohol, and acetone, very slightly soluble in methylene chloride. The (-) (S) isomer of warfarin has shown itself to be five to eight times more potent than (+) (R) enantiomer. Warfarin is a synthetic anticoagulant used in patients undergoing orthopaedic surgery.

Assay: Dissolve the sample in 0.01 M sodium hydroxide and measure the absorbance after dilution at the maxima of 308 nm using ultraviolet spectrophotometer.

Dose: The dose for adults is 10–15 mg per day for 2 to 4 days.

Dosage forms: Warfarin tablets I.P., B.P.

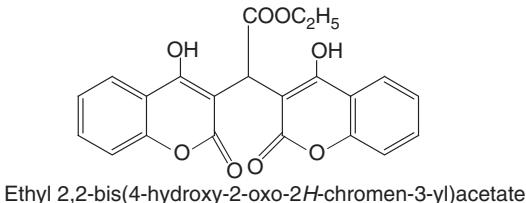
ii. Heparin

Properties and uses: Heparin sodium is a white hygroscopic powder, soluble in water and used as an anticoagulant.

Assay: It is assayed by adopting spectrophotometric method.

Dosage forms: Heparin injection B.P.

iii. Ethyl biscoumacetate



iv. Acenocoumarol

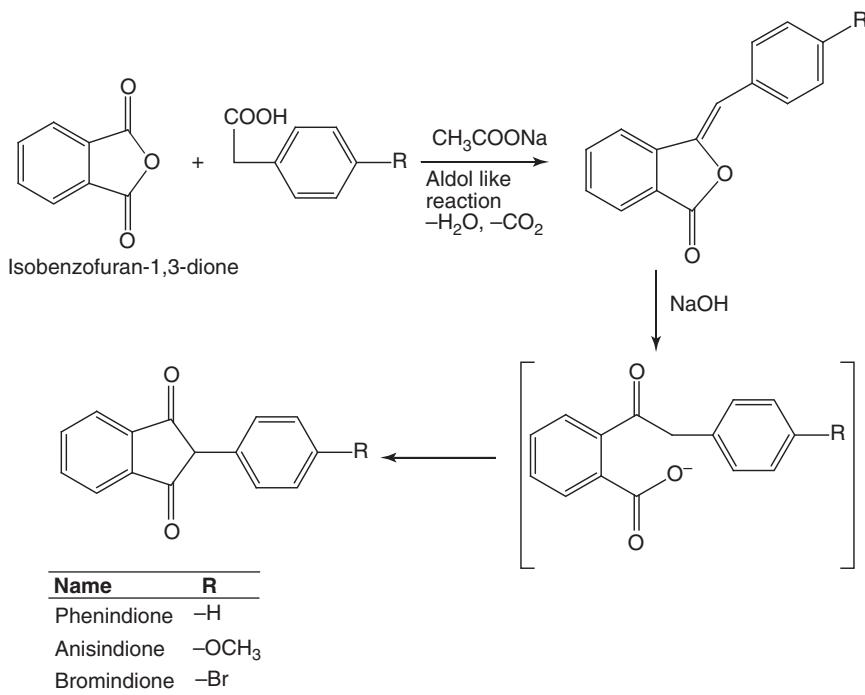
Properties and uses: Acenocoumarol is a white to buff-coloured powder, practically insoluble in water and ether, slightly soluble in ethanol. It dissolves in aqueous solutions of the alkali hydroxides. Used as vitamin K epoxide reductase inhibitor and as oral anticoagulant.

Assay: Dissolve the sample in acetone and titrate against 0.1 M sodium hydroxide using bromothymol blue as indicator.

Dosage forms: Acenocoumarol tablets B.P.

II. b. Indandione derivatives—General method of preparation

Synthesis of Phenindione, Anisindione, and Bromindione



These 1,3-indandiones have been recognized for their anticoagulant activity.

i. Phenindione

Properties and uses: Phenindione exists as white crystalline powder, very slightly soluble in water, slightly soluble in ethanol and ether. Used as oral anticoagulant.

Assay: To the sample, add ethanol and warm it, cool to room temperature, add 10% v/v solution of bromine in ethanol, and allow standing with occasional shaking. Add 2-naphthol and shake until the colour of the bromine is discharged. Add water, and dilute potassium iodide solution and titrate the liberated iodine against 0.1 M sodium thiosulphate using starch mucilage as indicator.

Dosage forms: Phenindione tablets I.P., B.P.

ii. Thrombolytics (Fibrinolytics)

Fibrinolytics are drugs used to lyse thrombi and to recanalize occluded blood vessels mainly coronary artery. Anticoagulants are designed to prevent thrombus formation. A proteolytic enzyme, known as plasmin, which is released by its precursor protein plasminogen causes the destruction or dissolution of a thrombus. Plasminogen activators (e.g. streptokinase, urokinase) bring about this conversion (Fig. 1.2).

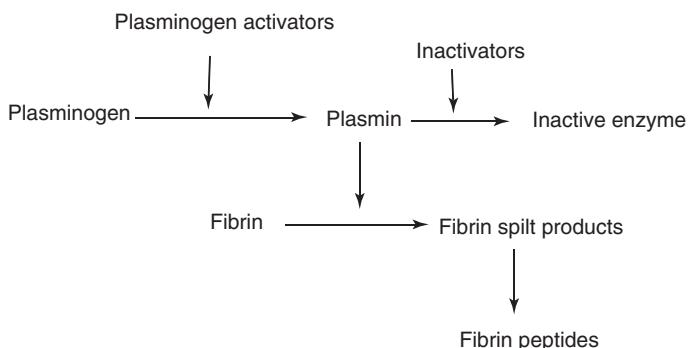


Figure 1.2 Dissolution of thrombus.

Certain other compounds have been found to promote the synthesis of various plasminogen activators. For example, anabolic steroids, act indirectly as fibrinolytic agents. All these agents are useful in the treatment of pulmonary embolic and acute coronary thrombosis. Streptokinase and urokinase are commonly used fibrinolytic agents in the treatment of acute thromboembolic diseases.

a. Streptokinase

Streptokinase is obtained from group-C beta haemolytic *Streptococci*. It is inactive; therefore, to be active it must be converted to plasminogen, which causes proteolysis of plasmin. It is typically used in myocardial infarctions and arterial thrombosis.

b. Urokinase

It is isolated from the human urine, now prepared from the cultures of human renal cells. It is nonantigenic and is a glycosylate serine protease containing 41 amino acid residues. It is a substrate for plasminogen, which is activated to plasmin.

c. Anistrepulse

It is a streptokinase–plasminogen complex in which plasminogen is isolated and acts as a slow released form of plasminogen activator. Coupling of the streptokinase–plasminogen complex to *p*-amidinophenyl-*p*-anisate blocks the catalytic centre of the complex, but allows it to bind to fibrin. As the anisoyl group is slowly hydrolyzed in vivo, the complex is allowed to bind to fibrin prior to activation. It is used in the management of acute myocardial infarction.

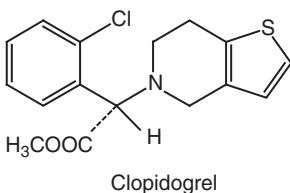
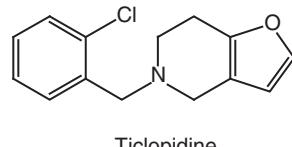
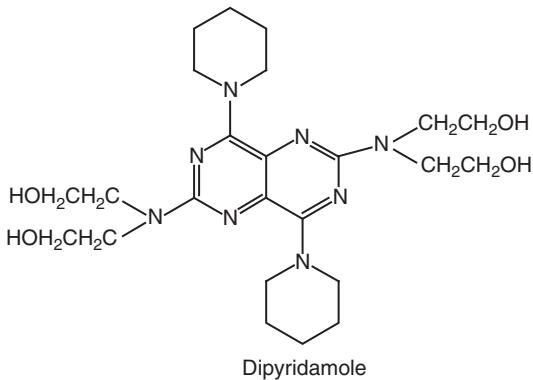
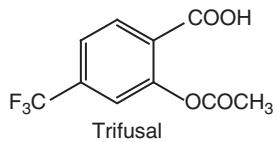
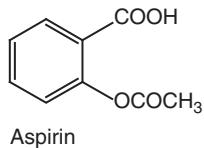
d. Aspirin

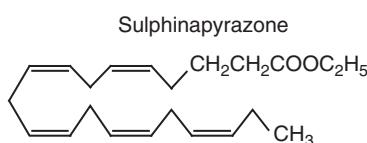
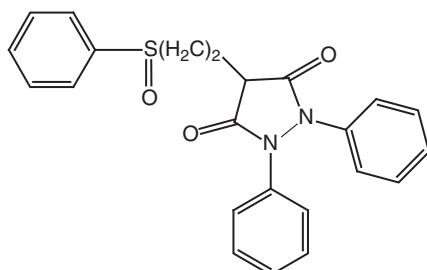
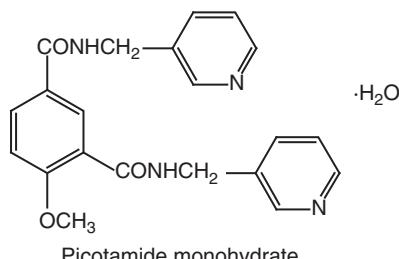
Synthesis and drug profile is discussed in sec I, NSAIDs.

Antiplatelet drugs (Antithrombocytic drugs)

Platelets provide the initial haemostatic plug at the sites of vascular injury. Platelet aggregation is implicated in thrombus formation in arterial systems and pathogenesis of atherosclerosis. Thus, agents that inhibit platelet aggregation should be able to modify or prevent atherosclerotic disease and thrombosis.

Drugs interfering with platelet functions are as follows:





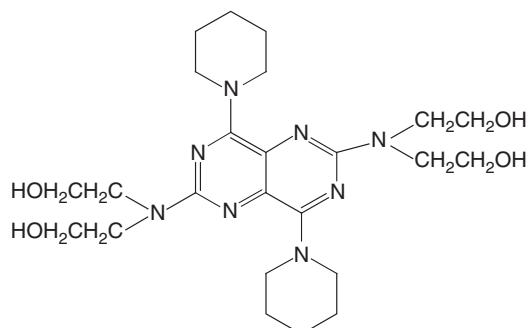
SYNTHESIS AND DRUG PROFILE

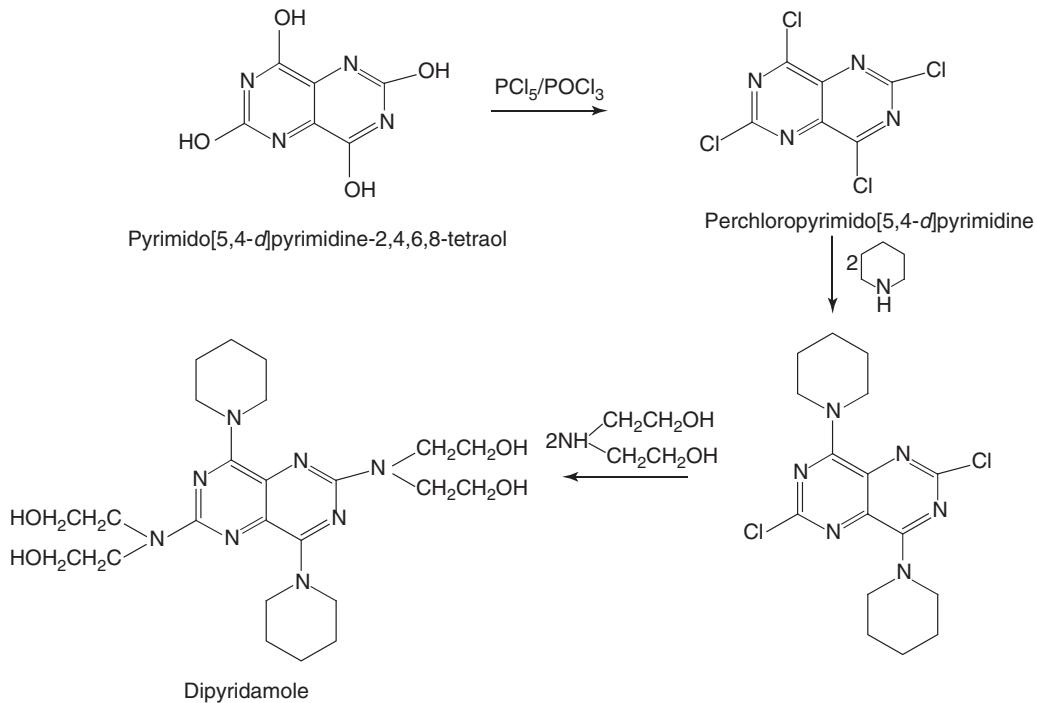
i. Aspirin

Mode of action: Aspirin inhibits the enzyme cyclooxygenase and thromboxane synthetase (TXA_2) by binding irreversibly and interfering with the platelet aggregation.

Synthesis and drug profile of Aspirin is discussed in under sec I, Chapter NSAIDs.

ii. Dipyridamole (Persantine, Cardiwell)



Synthesis

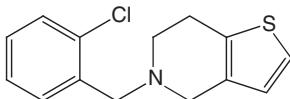
Properties and uses: Dipyridamole is a bright yellow crystalline powder, practically insoluble in water, soluble in acetone, ethanol, and dilute solutions of mineral acids. It is an adenosine reuptake inhibitor, inhibitor of platelet aggregation, and useful in transient ischaemic attacks and secondary prevention of myocardial infarction.

Assay: Dissolve the sample in methanol and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: 50–75 mg 8 hrly in combination with aspirin.

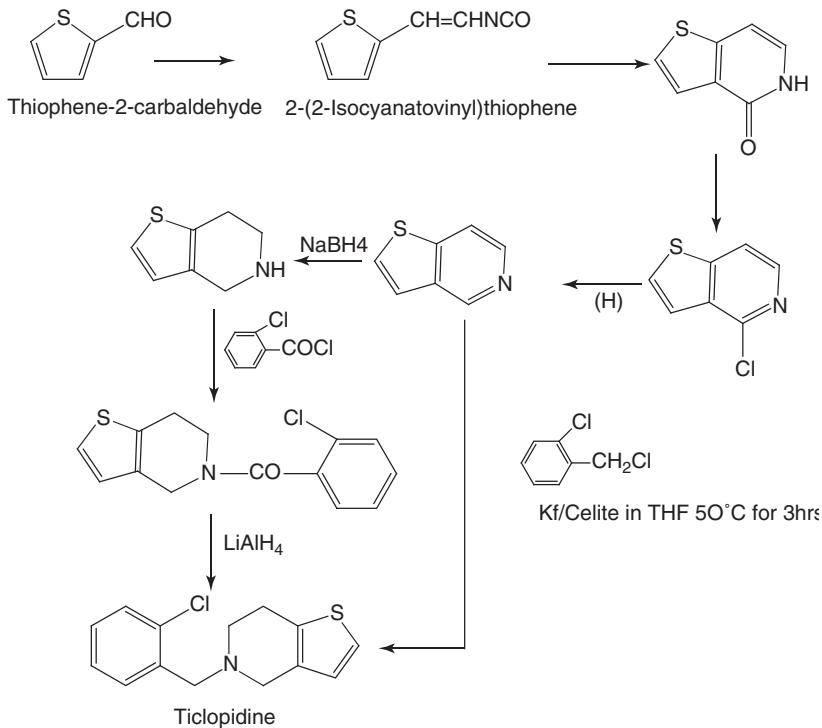
Dosage forms: Dipyridamole tablets B.P.

iii. Ticlopidine HCl (Tyklid, Ticlid)



Properties and uses: Ticlopidine hydrochloride is a white crystalline powder, sparingly soluble in water and ethanol, and very slightly soluble in ethyl acetate. Ticlopidine is a thieno pyridines used for thrombosis prevention in patients with atherosclerotic disease. It acts as an inhibitor of adenosine diphosphate (ADP)-mediated platelet aggregation, and hence, used as an antiplatelet drug.

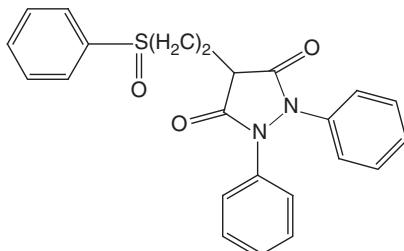
Synthesis



Dosage: The oral dose is 250 mg twice a day.

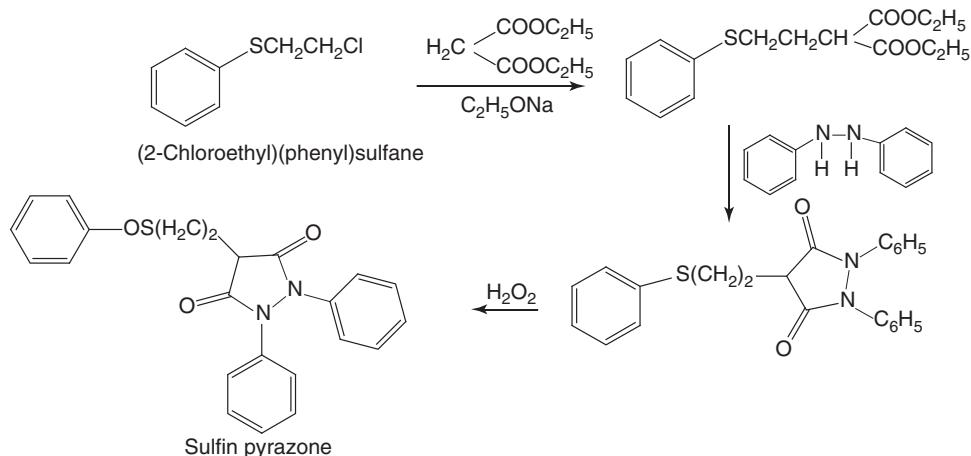
Assay: Dissolve the sample in anhydrous acetic acid and add acetic anhydride. Titrate against 0.1 M perchloric acid and determine the end point potentiometrically.

iv. Sulphinpyrazone (Anturane)



Properties and uses: Sulphinpyrazone is a white powder, very slightly soluble in water, sparingly soluble in alcohol, but soluble in dilute solutions of alkali hydroxides. It has antiplatelet and potent uricosuric effects, and hence, used in the treatment of gout.

Synthesis



Assay: Dissolve the sample in acetone and titrate against 0.1 M sodium hydroxide using bromothymol blue as indicator until the colour changes from yellow to blue.

Dose: The dose is 300 mg four times a day.

Dosage forms: Sulphinpyrazone tablets B.P.

v. Picotamide Monohydrate

Properties and uses: Picotamide monohydrate is a white crystalline powder, slightly soluble in water, soluble in ethanol, methylene chloride, and dilute mineral acids. It acts as thromboxane synthetase inhibitor and thromboxane receptor antagonist; used as antiplatelet agent.

Assay: Dissolve the sample in a mixture of anhydrous acetic acid and acetic anhydride (1:1) and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

PROBABLE QUESTIONS

1. Classify anticoagulants with suitable examples and write the synthesis of any two of them.
2. Enumerate the coumarin derived anticoagulants and write the synthesis of one of them.
3. Write a short note on *in vivo* anticoagulants.
4. Write a note on indanedione derivatives.
5. Describe in detail about antithrombocytic and fibrinolytic agents.

SUGGESTED READINGS

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Chapter 2

Plasma Expanders

INTRODUCTION

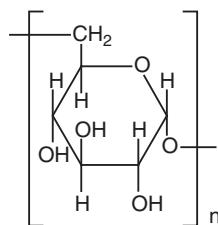
A haemorrhagic shock may result from the loss of blood during burns, wounds, or surgery. Mild shock results when there is a loss of 15% to 20% in the total blood volume. Further loss of blood, up to 40% of total blood volume may lead to severe shock during which the cardiovascular functioning is severely affected. To restore this functioning, saline should be administered as an initial emergency measure. Plasma expanders can also be used to overcome the initial losses.

There are of two types of plasma expanders: (i) Natural products and (ii) Synthetic products

Natural products: These include transfusion of whole blood or the preparations of plasma proteins. Blood products containing plasma proteins are human albumin (albumisol) and plasma protein fraction (PPF). Both of these preparations are usually given by intravenous infusion.

Synthetic products: Dextran, hetastarch, perfluorochemicals, polyvinylpyrrolidone, and gelatin are some of the synthetic plasma expanders, out of which dextran has been used extensively.

i. Dextran



Dextran could be considered as being almost close to ideal plasma expanders. Dextrans are colloidal glucose polymers that are obtained from sucrose by the action of bacteria, *Leuconostoc mesenteroides*. The dextran molecule consists mainly of 1:6 glucoside linkages with relatively few 1:4 linkages and has an average molecular weight of 40 millions. This form is not clinically suitable. Hence, it is partially hydrolyzed in vitro to give dextran with average molecular weight of 40,000, 70,000, 11,000, and 15,000 daltons. They

are known as dextran-40, dextran-70, dextran-110, and dextran-150, respectively. Of these, dextran-40 and dextran-70 are of clinical importance. Solutions of dextran in isotonic sodium chloride is used to increase the circulating blood volume and to maintain the venous pressure, right arterial pressure, stroke volume, and cardiac output. Only dextran solutions are used in the treatment of hypoproteinaemia, nephrosis, and toxæmia of late pregnancy. Dextran does not possess oxygen-carrying capacity.

The dextran solution is pharmacologically inactive and has been reported as having no significant deleterious effect on renal, hepatic, or any other vital functions. Occasionally, sensitization reaction may occur in some patients. The bleeding time, fibrin polymerization on platelet function may be impaired in vivo. Dextrans are contraindicated in patients with anaemia, severe thrombocytopenia, and low plasma fibrinogen level.

ii. Human albumin

It is obtained from pooled human plasma; 100 ml of 20% human albumin solution is the osmotic equivalent of about 400 ml of fresh frozen plasma or 800 ml of whole blood. It can be used without regard to the patient's blood group and does not interfere with coagulation. Unlike whole blood or plasma, it is free of risk of transmitting serum hepatitis because the preparation is heat-treated. There is also no risk of sensitization with repeated infusions. It has been used in acute hypoproteinaemia, acute liver failure, and dialysis.

iii. Degraded gelatin polymer (polygeline)

It is a polypeptide with an average MW 30,000, which exerts osmotic pressure similar to albumin, and is not antigenic and hypersensitivity reactions are rare. It does not interfere with the grouping and cross matching of blood and remains stable for 3 years. It can be used for the priming of heart-lung dialysis machines.

iv. Hydroxyethyl starch (HES, hetastarch)

It is a complex mixture of ethoxylated amylopectin of various molecular sizes, average MW 4.5 lakh (range 10,000–1 million). The colloidal properties of 6% HES approximate those of human albumin. Plasma volume expands slightly in excess of the volume infused. It has been used to improve harvesting of granulocytes because it accelerates erythrocyte sedimentation. Adverse effects are vomiting, mild fever, itching, chills, flu-like symptoms, swelling of salivary glands, urticaria, periorbital oedema, and bronchospasm are the anaphylactoid reactions.

v. Polyvinylpyrrolidone (PVP)

It is a synthetic polymer (average MW 40,000) used as a 3.5% solution. It interferes with the blood grouping and cross matching. It has been found to bind penicillin and insulin in circulation, so that the same is not available for action. It is not frequently used as a plasma expander.

PROBABLE QUESTIONS

1. What are plasma expanders? Write their uses and describe briefly about any two of the products used as plasma expanders.
2. Write a brief note on dextran.

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SECTION V

DRUGS ACTING ON ENDOCRINE SYSTEM

| | | |
|---|--------------------------|-----|
| 1 | Oral Hypoglycaemic Drugs | 165 |
| 2 | Steroids | 192 |
| 3 | Antithyroid Drugs | 215 |

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Chapter 1

Oral Hypoglycaemic Drugs

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidemia, negative nitrogen balance, and ketonaemia. Most patients can be classified, clinically, as having either type I diabetes mellitus (insulin dependent diabetes mellitus (IDDM) or type II noninsulin dependent diabetes mellitus (NIDDM). The incidence of each type of diabetes varies widely throughout the world. In the United States, about 5% to 10% of the diabetic patients have type I diabetes mellitus, with an incidence of 17 per 100,000 found in United Kingdom. The vast majority of diabetic patients have type II diabetes mellitus.

Type I diabetes is also called juvenile onset diabetes mellitus. There is β -cell destruction in the pancreatic islets of langerhans. Majority of the cases are due to autoimmune (type I A) antibodies that destroy β cells, are detectable in blood, but some are idiopathic (type I B) no β (beta) cell antibody is found. In all type I cases, circulating insulin levels are low or very low and ketosis may occur. Genetic predisposition is also a cause for this condition.

Type II diabetes is also called maturity onset diabetes mellitus. There is no loss or moderate reduction in the β cell mass, insulin in circulation levels is low and generally has a late onset of disease after middle age. This may be due to an abnormality in the glucoreceptors of β cells, therefore, they respond at higher glucose concentrations or at relative β cell deficiency. The reduced sensitivity of peripheral tissues to insulin and reduction in the number of insulin receptors are a consequence for producing diabetes. When glucagons exceed a normal amount, it produces hypoglycaemia. The insulin is secreted by the β cells of langerhans, synthesized by a single chain precursor of 110 amino acid preproinsulin. After translocation through the membrane of rough endoplasmic reticulum, the 24 amino acid N-terminal peptide of preproinsulin is rapidly cleared off to form proinsulin. Here, the molecules folds and the disulphide bonds are formed. In the conversion of proinsulin to insulin in the Golgi complex, four basic amino acids and the remaining connector or C peptide are removed by proteolysis. This gives rise to two peptide chains (A and B) of insulin molecules, which contains one intrasubunit and two intersubunits disulphide bonds. The A chain consists of 21 amino acids and B with 30 amino acids and molecular mass is about 5734 daltons.

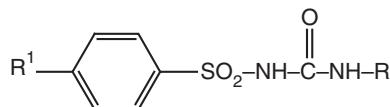
The regulatory factors of insulin secretion are chemical, hormonal, and neural. Chemical regulation depends upon the glucose entry in to the β cells by glucose transport. Once, after the entry of glucose and its phosphorylation by glucokinase, glucoreceptor activation indirectly inhibits the adenosine triphosphate (ATP) sensitive potassium channels and increases intracellular calcium, which triggers the exocytic release of insulin. Hormonal change in corticosteroids modify the release of insulin. Insulin inhibits glucagon secretion and glucagons increase the insulin secretion.

The neural control is mediated by α_2 and β_2 receptors. Stimulation of α_2 receptor decreases the insulin release and stimulation of β_2 receptors increases insulin release. Cholinergic stimulation increases the insulin secretion.

Hypoglycaemic drugs are agents, which decrease the blood sugar level. Oral hypoglycaemic agents must be distinguished from more hypoglycaemic drugs, such as salicylates, which are too toxic for clinical use in doses that effectively lower the blood sugar. An ideal antidiabetic drug should be nontoxic and correct the basic metabolic defects in diabetics, in addition to lowering the blood sugar.

CLASSIFICATION

I. Sulphonylureas



a. First-generation drugs

| Name | R | R¹ |
|-----------------|--------|--------|
| Carbutamide | -nC₄H₉ | -NH₂ |
| Tolbutamide | -nC₄H₉ | -CH₃ |
| Chloropropamide | -nC₃H₇ | -Cl |
| Tolazamide | | -CH₃ |
| Acetohexamide | | -COCH₃ |

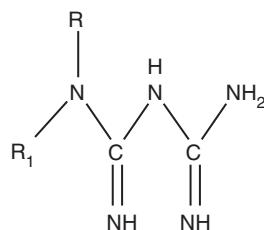
b. Second-generation drugs

| Name | R | R |
|---------------------------|---|---|
| Glibenclamide (Glyburide) | | |
| Glipizide | | |

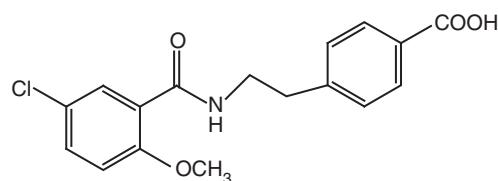
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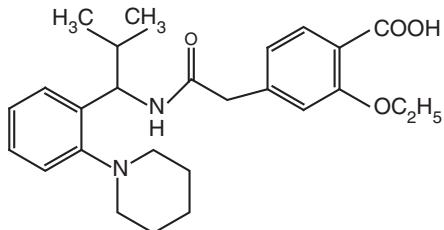
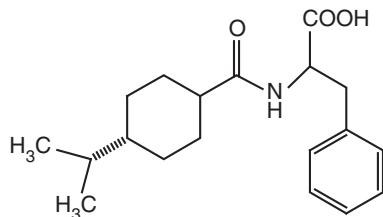
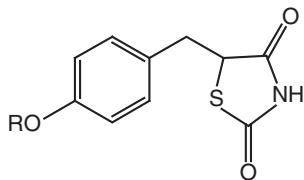
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| Name | R | R |
|--------------|---|------------------|
| Gliclazide | | -CH ₃ |
| Glibornuride | | -CH ₃ |

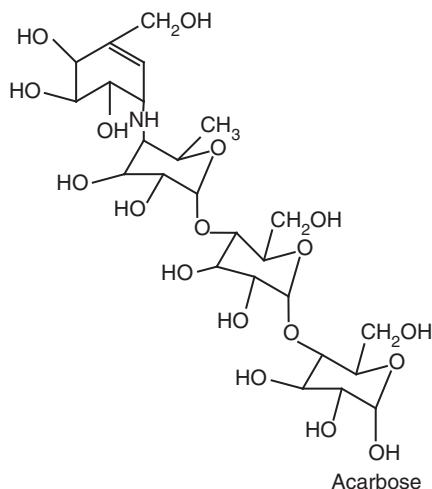
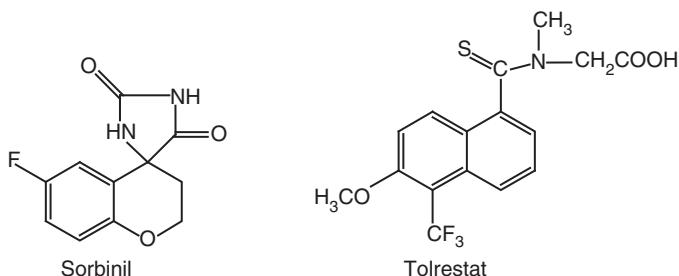
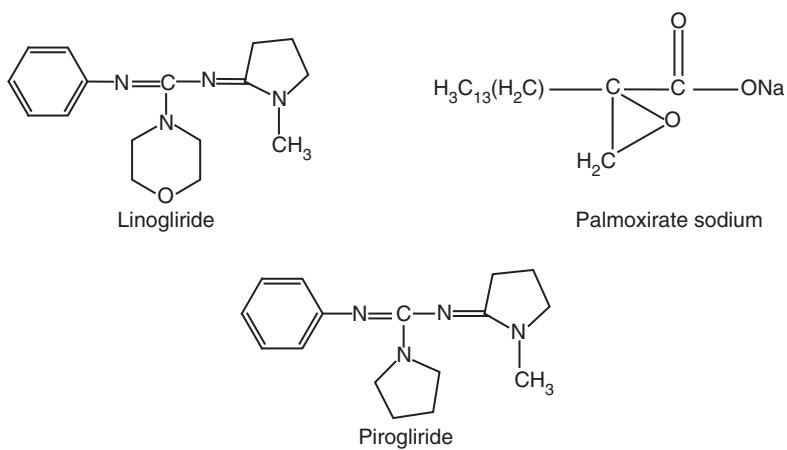
II. Biguanides

| Name | R | R ₁ |
|------------|--|------------------|
| Phenformin | | -H |
| Metformin | -CH ₃ | -CH ₃ |
| Buformin | -CH ₂ CH ₂ CH ₂ CH ₃ | -H |

III. Substituted benzoic acid derivatives (Meglitinides)**i. Meglitinide**

ii. Repaglinide**iii. Nateglinide****IV. Thiazolidinediones (Glitazones)**

| Name | R |
|---------------|---|
| Pioglitazone | |
| Ciglitazone | |
| Rosiglitazone | |

V. α -Glucosidase inhibitors**VI. Aldose reductase inhibitors****VII. Miscellaneous**

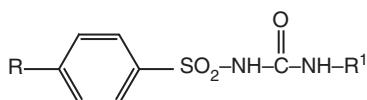
SYNTHESIS AND DRUG PROFILE

I. Sulphonylurea derivatives

a. First-generation drugs

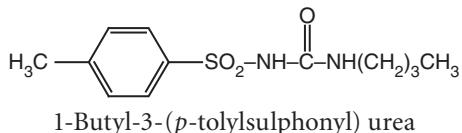
Mode of action: They target on the specific receptors in the β cells of islets of Langerhans called sulphonylurea receptors, and cause depolarization by reducing the conductance of ATP sensitive K^+ channels. This enhances the Ca^{2+} influx and produces degranulation, leading to the secretion of insulin.

The sulphonylureas may be represented by the following general structure



All members of this group are urea derivatives with an aryl sulphonyl group in the 1st position and an aliphatic group at the 3rd position. The R group on the aromatic ring primarily influences the duration of action of the compound.

i. Tolbutamide (Orinase)

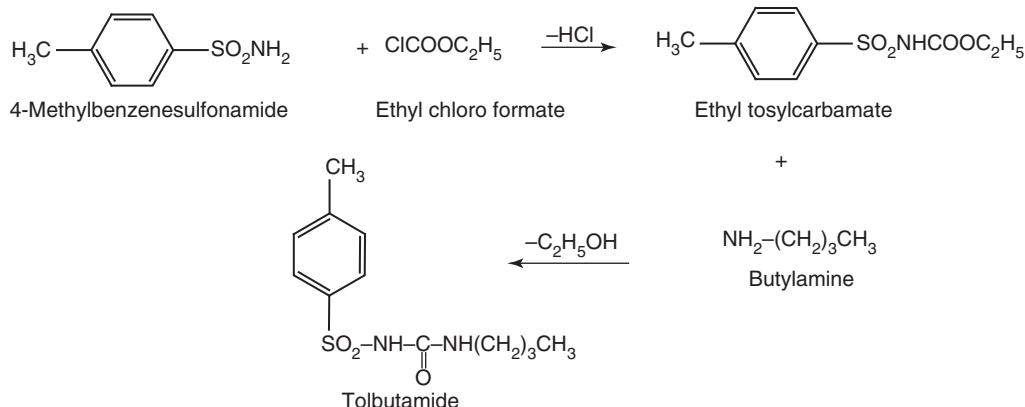


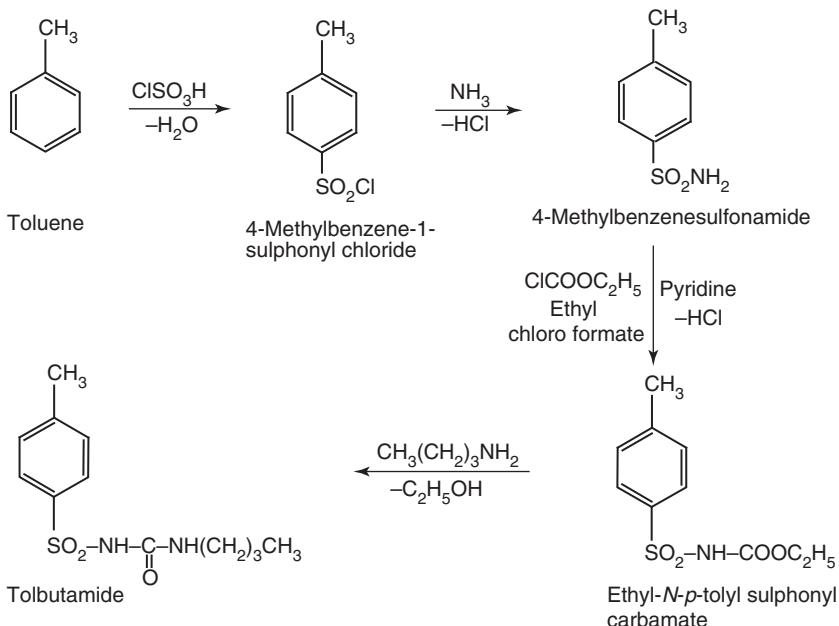
Properties and uses: Tolbutamide is a white crystalline powder, practically insoluble in water, soluble in acetone, alcohol, and dilute solutions of alkali hydroxides. It is useful in the treatment of selected cases of diabetes mellitus, namely, mild and uncomplicated, stable diabetes of adult.

Assay: Dissolve the sample in a mixture of water and alcohol (1:2) and titrate against 0.1 M sodium hydroxide using phenolphthalein as indicator.

Synthesis

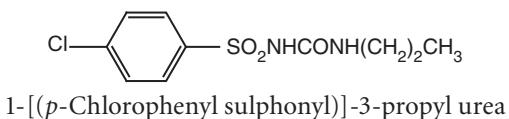
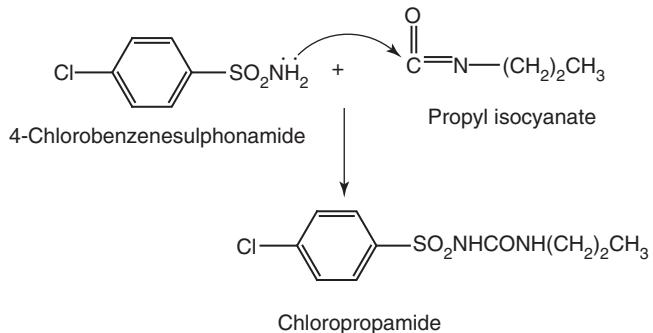
Route I. From: 4-Methylbenzene sulphonamide



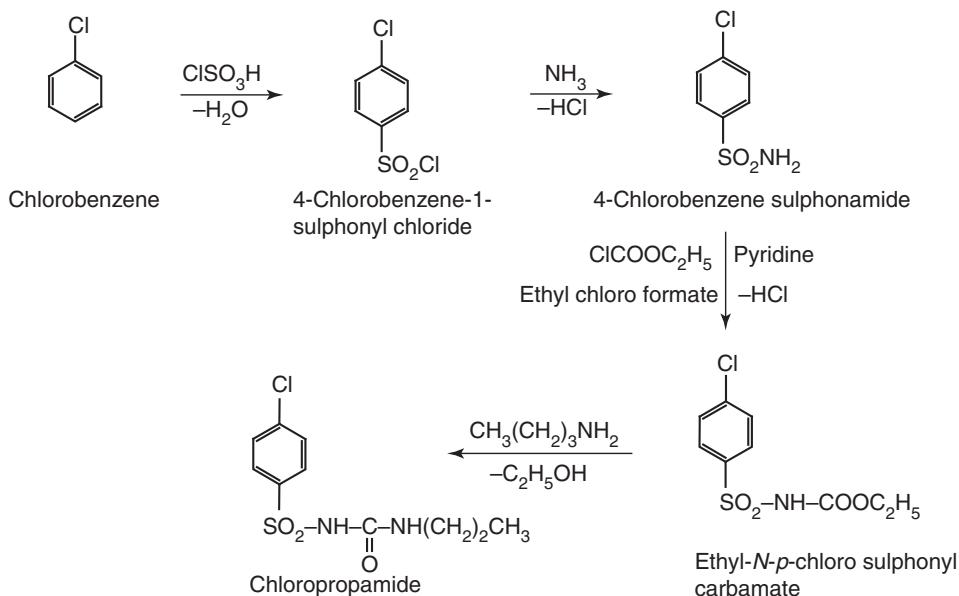
Route II. From: Toluene

Dose: The usual dosage is 250 and 500 mg with an initial dose of 500 mg.

Dosage forms: Tolbutamide tablets B.P.

ii. Chloropropamide (Diabenese)**Synthesis****Route I. From: 4-Chlorobenzenesulphonamide**

Ruote II. From: Chlorobenzene



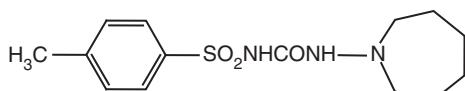
Metabolism: It is metabolized by ω or ω -1 hydroxylation of the propyl group. This reaction is slow and significant amount of the drug is excreted unchanged in urine.

Properties and uses: Chloropropamide is a white crystalline powder, practically insoluble in water, soluble in acetone, methylene chloride, alcohol, and dilute solutions of alkali hydroxides. Used in the treatment of diabetes mellitus.

Assay: Dissolve the sample in alcohol and add water. Titrate against 0.1 M sodium hydroxide using phenolphthalein as indicator until a pink colour is obtained.

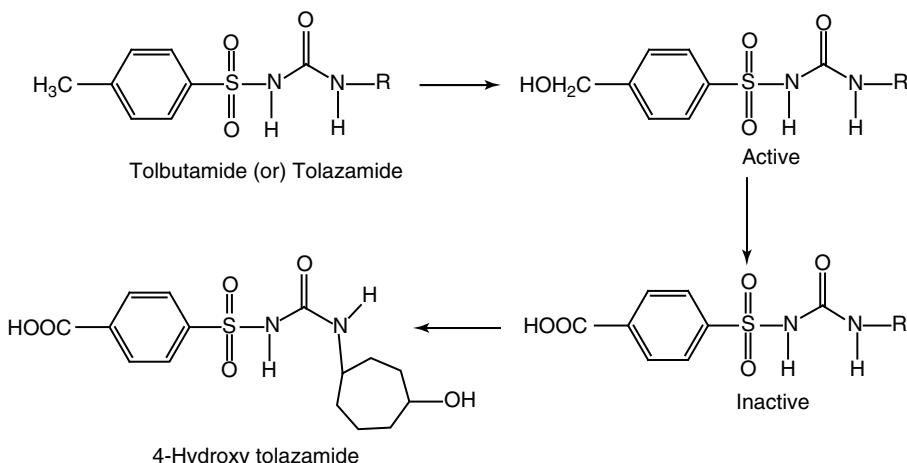
Dose: The usual dose is 100–250 mg per day.

iii. Tolazamide (Tolamide, Tolinase)

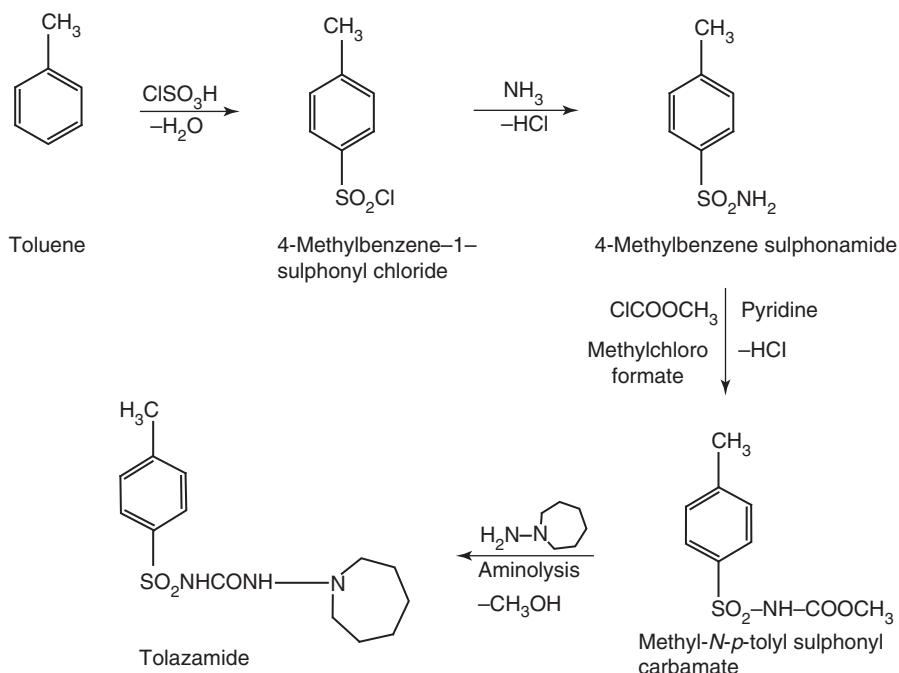


1-(Hexahydro-azepine-1-yl)-3-(*p*-tolylsulphonyl)urea

Metabolism of tolbutamide and tolazamide: They undergo a more rapid benzylic oxidation, leading to an inactive benzoic acid derivative. An alternative hydroxylation of the aliphatic ring of tolazamide becomes active and results in a metabolite of prolonged duration of action.



Synthesis



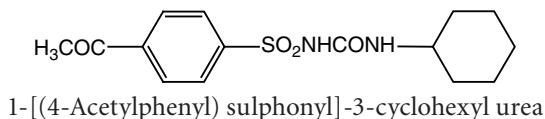
Properties and uses: Tolazamide is a white crystalline powder, very slightly soluble in water, soluble in chloroform and acetone, slightly soluble in ethanol. Used as an oral hypoglycaemic agent with action and uses similar to Tolbutamide.

Assay: Dissolve the sample in butan-2-one with the aid of gentle heat. Allow to cool, add 30 ml of ethanol and titrate with 0.1 M sodium hydroxide using phenolphthalein as indicator.

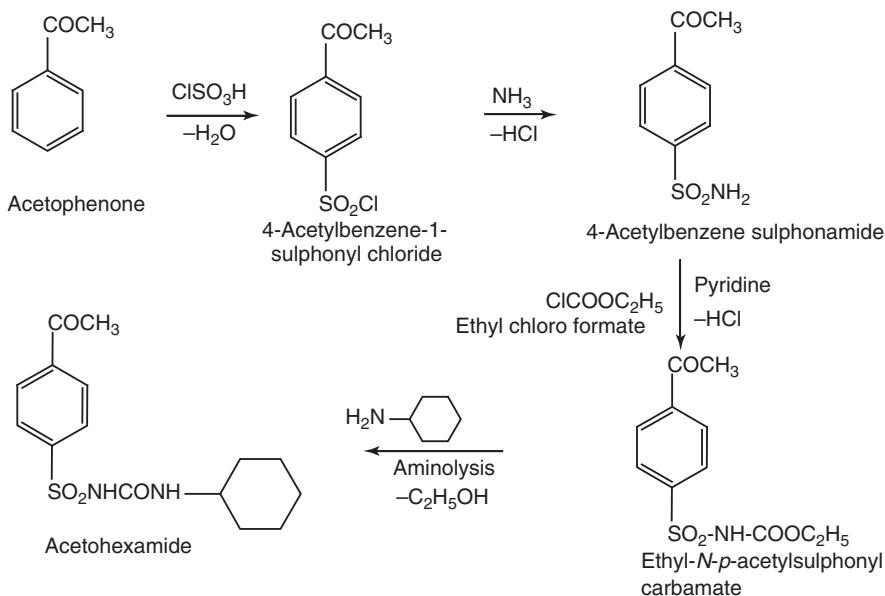
Dose: The dose is 100–250 mg daily.

Dosage forms: Tolazamide tablets B.P.

iv. Acetohexamide



Synthesis

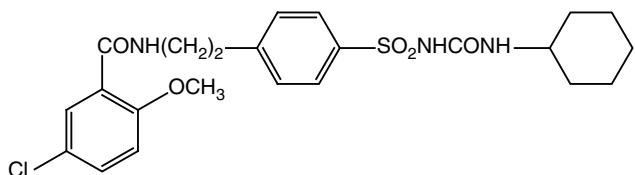


Metabolism: The major metabolite of acetohexamide is a reduced product of the keto group, forming an alcohol. The hydroxy metabolite exhibits 2.5 times the hypoglycaemic activity of the parent molecule.

Properties and uses: It is a white, odourless crystalline powder, soluble in alcohol and chloroform, but insoluble in water or ether. It is an orally active hypoglycaemic drug.

b. Second-generation drugs

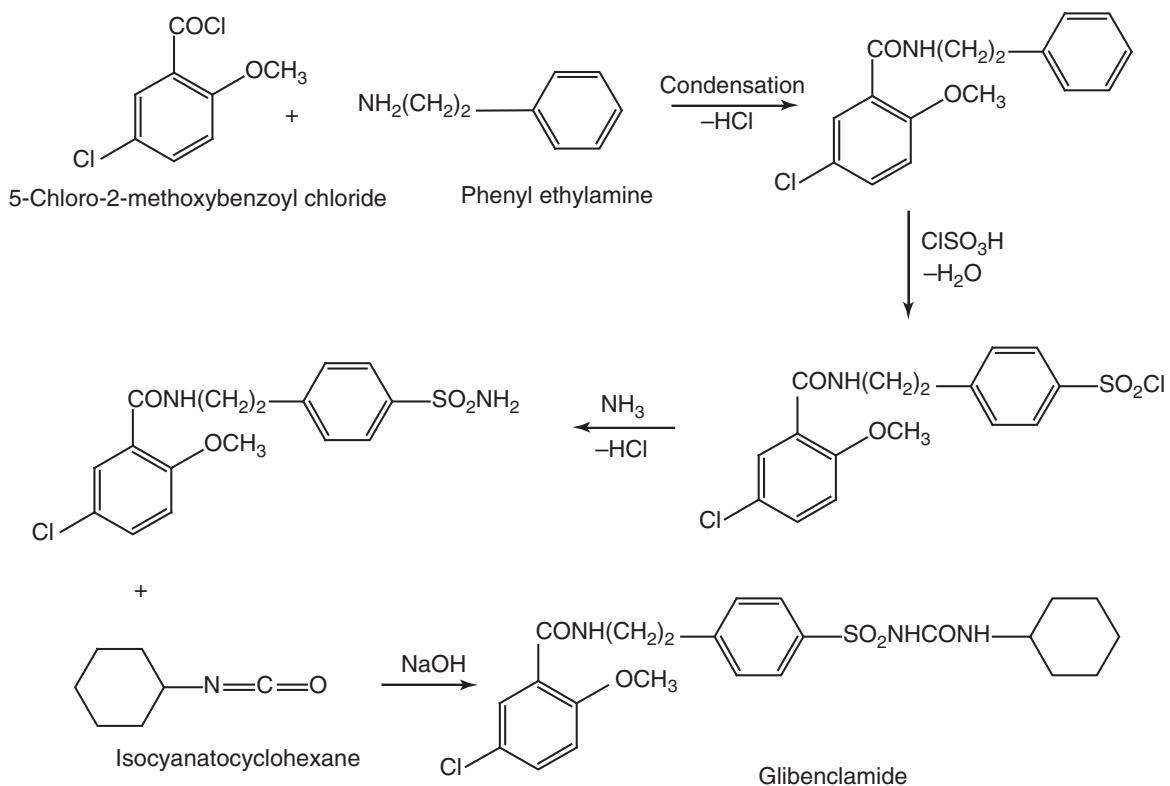
i. Glibenclamide (Glyburide)



5-Chloro-N-[2-4[[[(cyclohexylamino) carbonylamino] sulphonyl] phenyl] ethyl]-2-methoxy benzamide

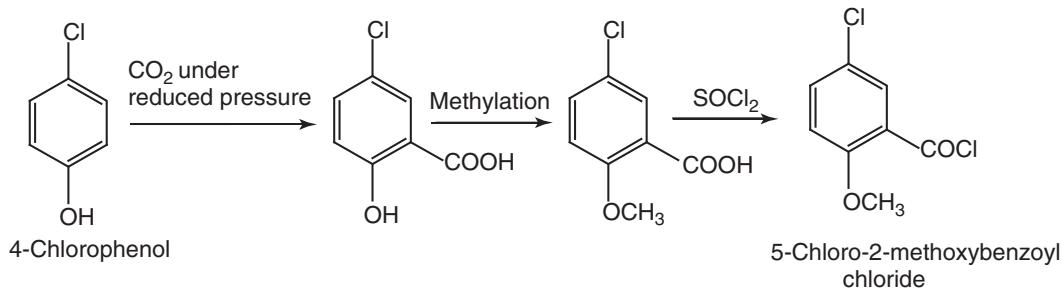
Synthesis

Route I. From: 5-Chloro-2-methoxybenzoylchloride

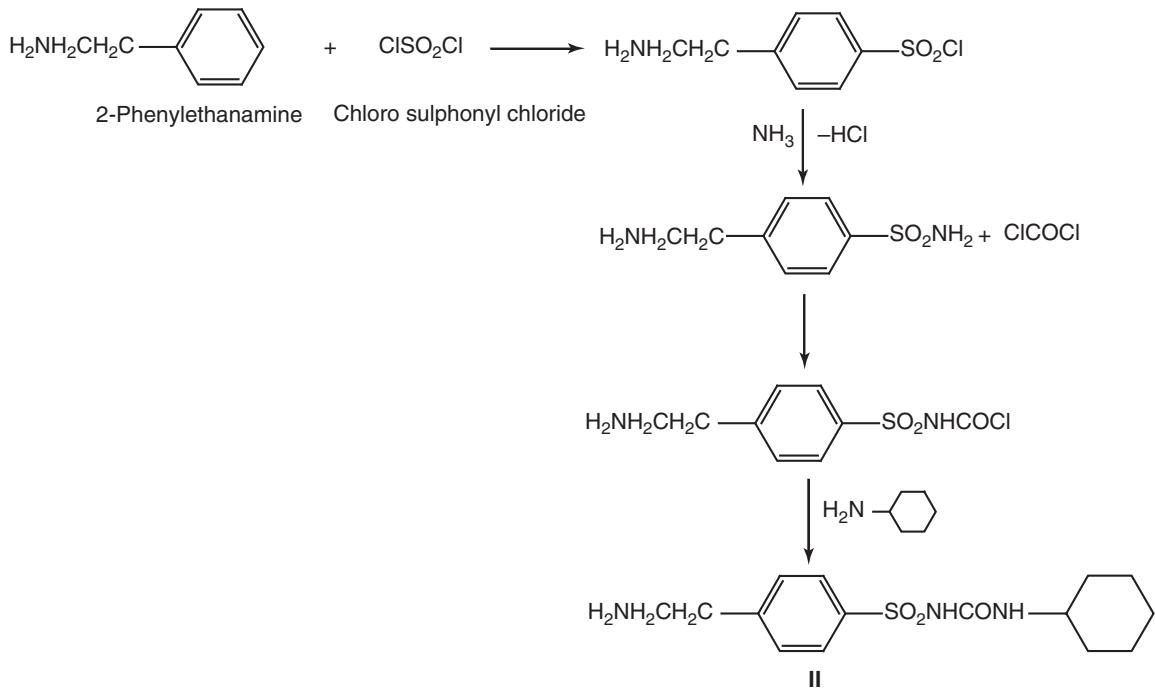


Route II.

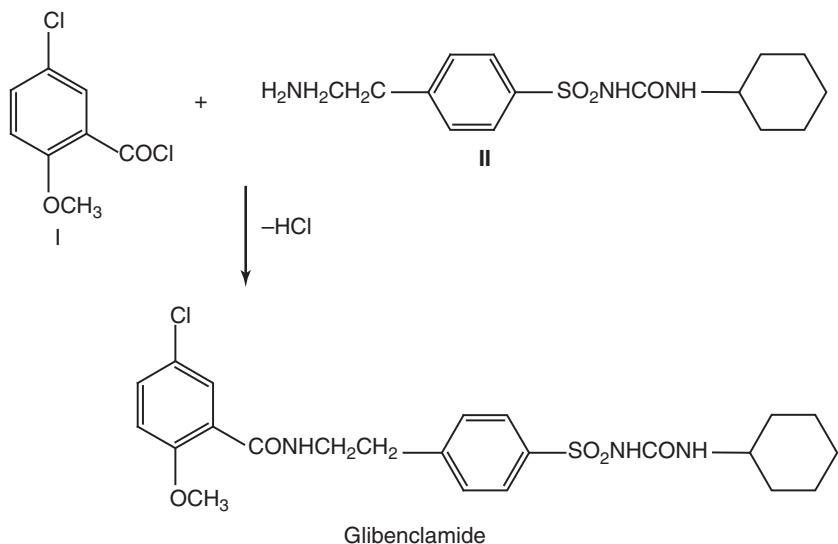
Step I: Synthesis of 5-chloro-2-methoxybenzoyl chloride



Step II: Synthesis of 4-(Aminoethyl)-1-cyclohexylamino carbonyl benzene sulphonamide



Step III: Condensation of product of *Step I* and *Step II*



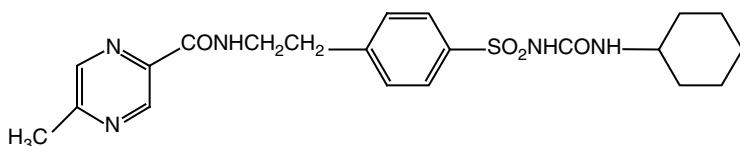
Properties and uses: Glibenclamide is a white crystalline powder, practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol and methanol. Used in the treatment of mild uncomplicated NIDDM unresponsive to diet alone.

Assay: Dissolve the sample in alcohol by heating and titrate against 0.1 M sodium hydroxide, using phenolphthalein as indicator, until a pink colour is obtained.

Dose: The dose is 2.5–5 mg per day to be taken with breakfast.

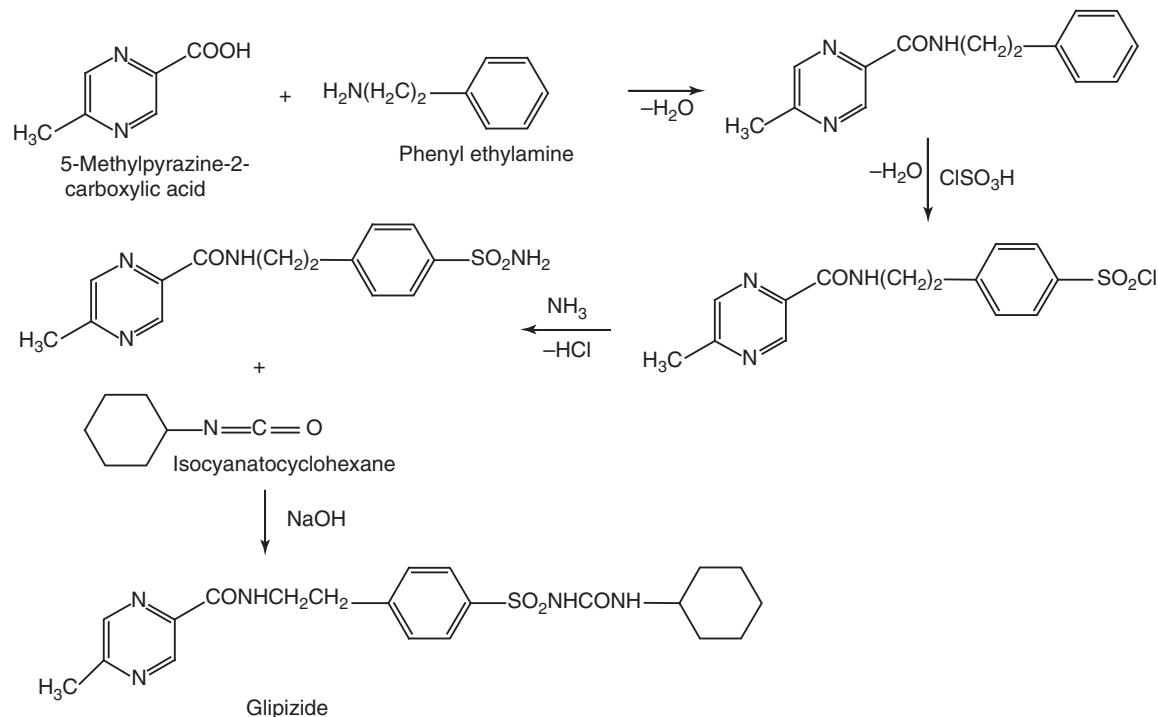
Dosage forms: Glibenclamide tablets B.P.

ii. Glipizide (Dibizide, Glucolip, Glynase)

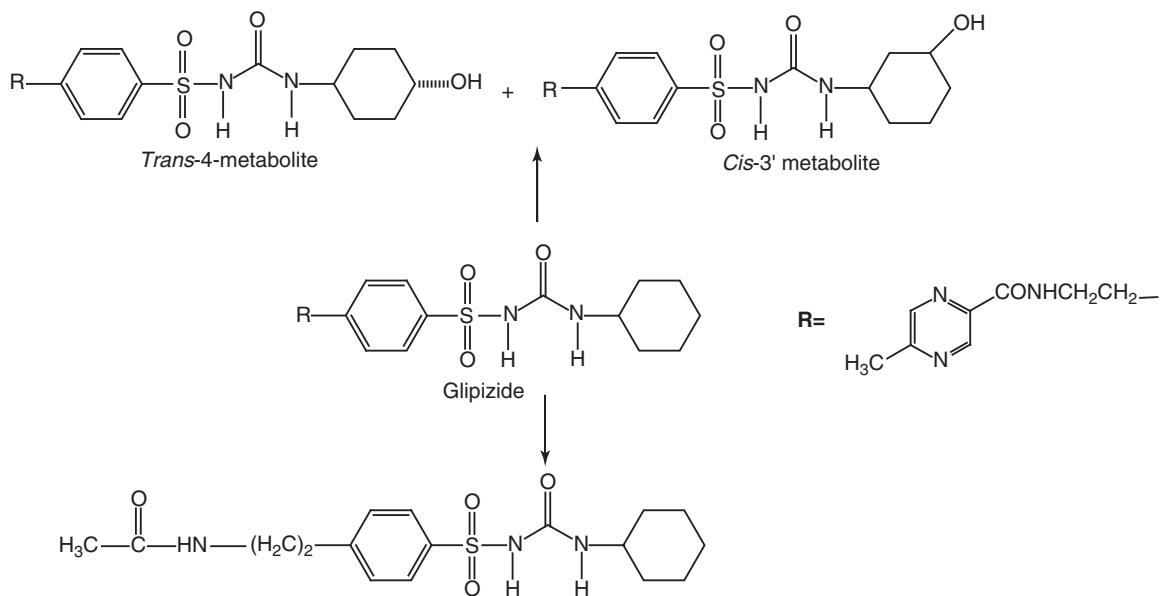


1-Cyclohexyl-3-[[*p*-[2-(5-methylpyrazine carboxamide) ethyl] phenyl] sulphonyl] urea

Synthesis



Metabolism: It is extensively metabolized to less active or inactive metabolites. Its metabolites are excreted primarily in the urine.



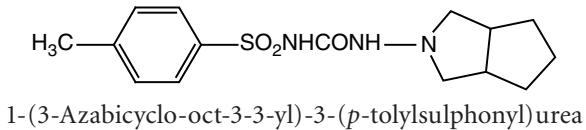
Properties and uses: Glipizide is a white crystalline powder, practically insoluble in water and ethanol, very slightly soluble in methylene chloride and acetone, soluble in dilute solutions of alkali hydroxides. It is an orally active hypoglycaemic drug.

Assay: Dissolve the sample in dimethylformamide and titrate against 0.1 M lithium methoxide add quinaldine red as indicator, until the colour changes from red to colourless.

Dose: The dosage is 25–50 mg once a day or in divided doses.

Dosage forms: Glipizide tablets B.P.

iii. Gliclazide

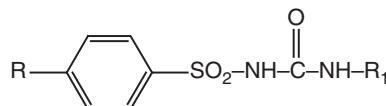


Properties and uses: Gliclazide is a white powder, practically insoluble in water, soluble in methylene chloride, sparingly soluble in acetone, and slightly soluble in alcohol. It is an orally active hypoglycaemic drug.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dosage forms: Gliclazide tablets B.P.

SAR of Sulphonylureas

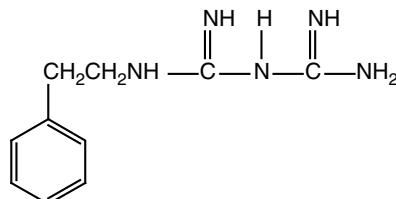


1. The benzene ring should contain a substituent preferably in the para position. The substituents, such as methyl, acetyl, amino, chloro, bromo, trifluoro methyl, and dithiomethyl were found to enhance the antihyperglycaemic activity.
2. When the para position of benzene is substituted with aryl carboxamidoalkyl group (second-generation sulphonylureas, such as glibenclamide) the activity was found to be enhanced further.
3. The size of the group attached to the terminal nitrogen is crucial for activity. The group should also impart lipophilicity to the compound *N*-methyl and ethyl substituents that show no activity, whereas *N*-propyl and higher homologues were found to be active and the activity is lost when the *N*-substituent contains 12 or more carbons.

II. Biguanides

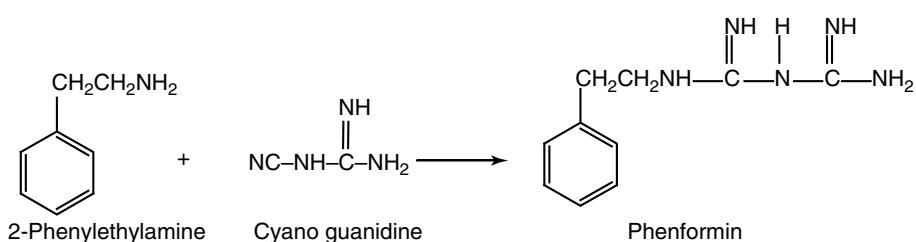
Mode of action: Biguanides do not have direct action on increasing or decreasing the glucose level. This reduces glucose levels primarily by decreasing hepatic gluconeogenesis by increasing the insulin action on muscles and fat. It also reduces the absorption of glucose from intestine.

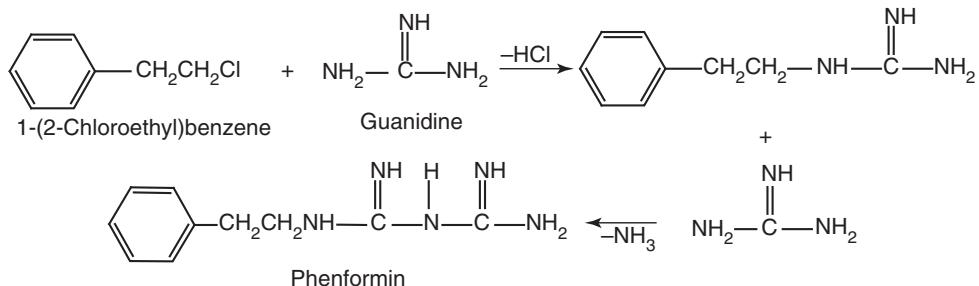
i. Phenformin



Synthesis

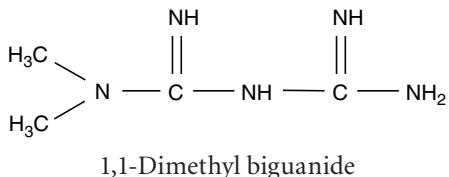
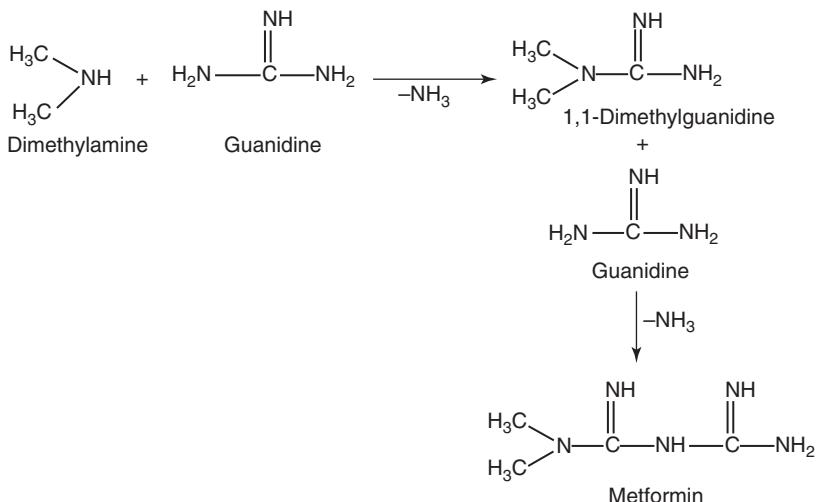
Route-I. From: 2-Phenylethylamine



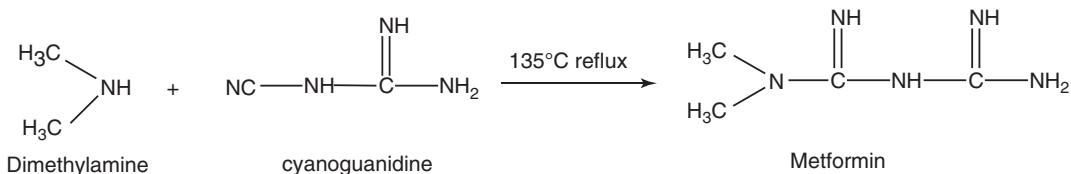
Route-II. From: 1-(2-Chloroethyl) benzene

Properties and uses: Used only in stable type II diabetics, it may be used alone or in conjunction with another oral hypoglycaemic agents, such as sulphonylureas or with insulin.

Dose: The normal dose is 25 mg tablets 1–4 times a day, usually 50–150 mg daily with breakfast.

ii. Metformin (Diamet, Diaphage Glyciphage, Glycomet)**Synthesis****Route I. From: Dimethylamine**

Route II. From: Dimethylamine



Properties and uses: Metformin hydrochloride exists as white crystals, freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and methylene chloride. It is usually given along with sulphonylureas.

Assay: Dissolve the sample in anhydrous formic acid, add acetonitrile, and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: Initial dose is 500 mg thrice daily or 850 mg twice daily with meals.

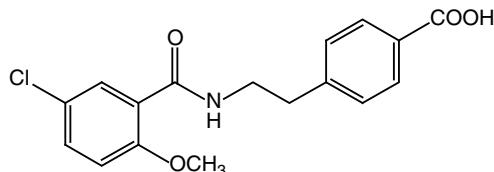
Dosage forms: Metformin tablets B.P.

III. Meglitinides (Benzoic acid derivatives)

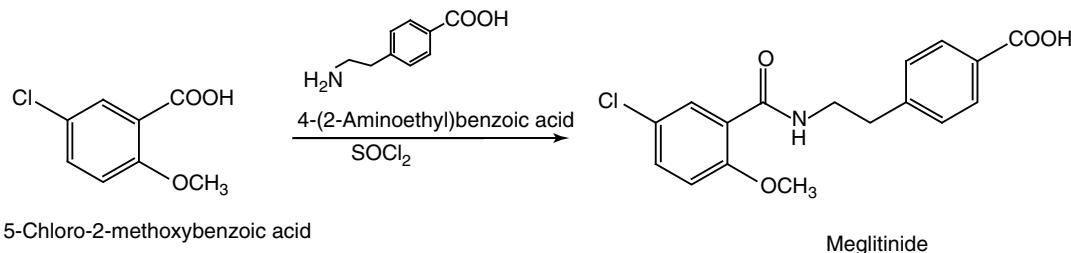
The meglitinides are similar in structure to sulphonylureas. The sulphonylurea and meglitinide classes of oral hypoglycaemic drugs are referred to as endogenous insulin secretagogues because they induce the pancreatic release of endogenous insulin.

Mode of action: Even though, these are not sulphonylureas they act on sulphonylurea receptors as well as the other variant receptors and closes the ATP dependent K^+ channels, leading to insulin secretion by depolarization.

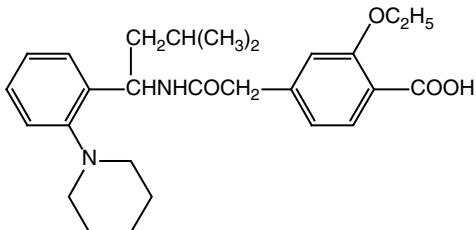
i. Meglitinide



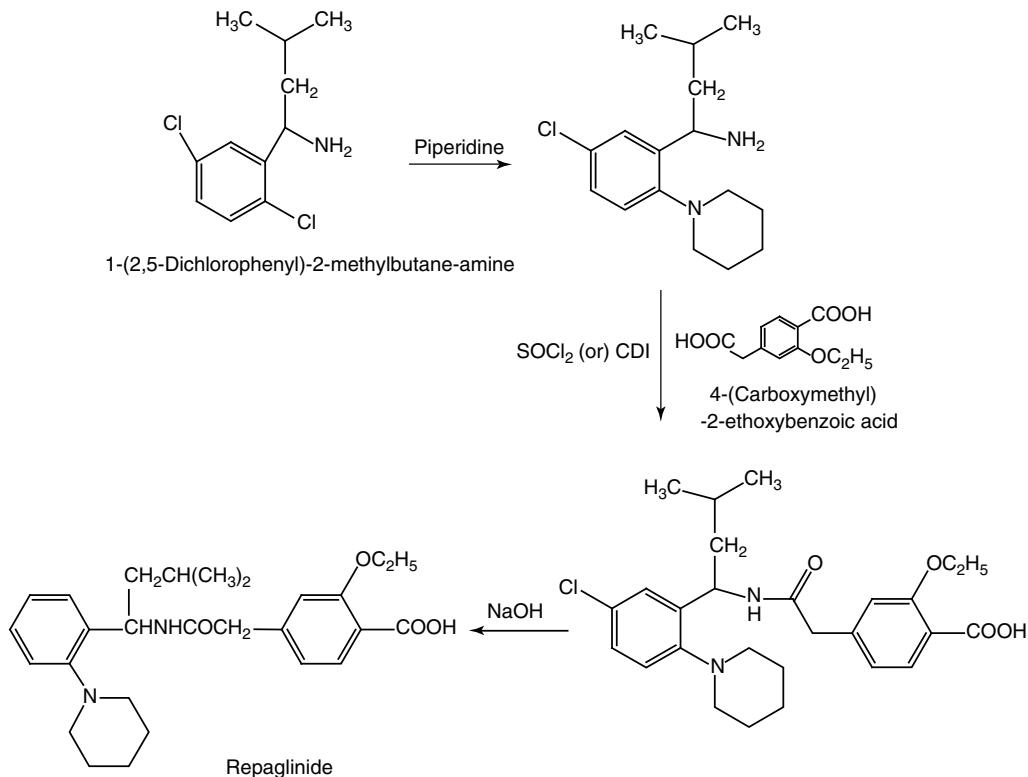
Synthesis



ii. Repaglinide (Repide, Repa, Eurepa)



Synthesis

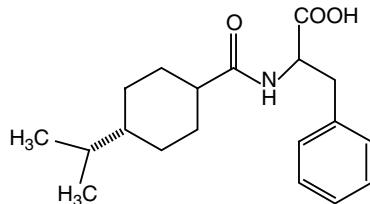


Properties and uses: Repaglinide is a white powder, practically insoluble in water, soluble in methanol, and methylene chloride. It stimulates insulin release and is used in the treatment of diabetes mellitus.

Assay: Dissolve the sample in methanol and add anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically

Dose: The usual initial dose for adults is 0.5 mg, taken within 30 min of main meals. Initial doses of 1 or 2 mg may be used in patients who have had previous hypoglycaemic treatment. Dose may be adjusted at intervals of 1–2 week up to 4 mg before meals; maximum dose is 16 mg daily.

iii. Nateglinide



Metabolism: It is metabolized in the liver and 16% is excreted in the urine unchanged. The major metabolites are hydroxyl derivative (CYP2C9 70%, CYP3A4 30%) that are further conjugated to the glucuronide derivative (Fig 1.1).

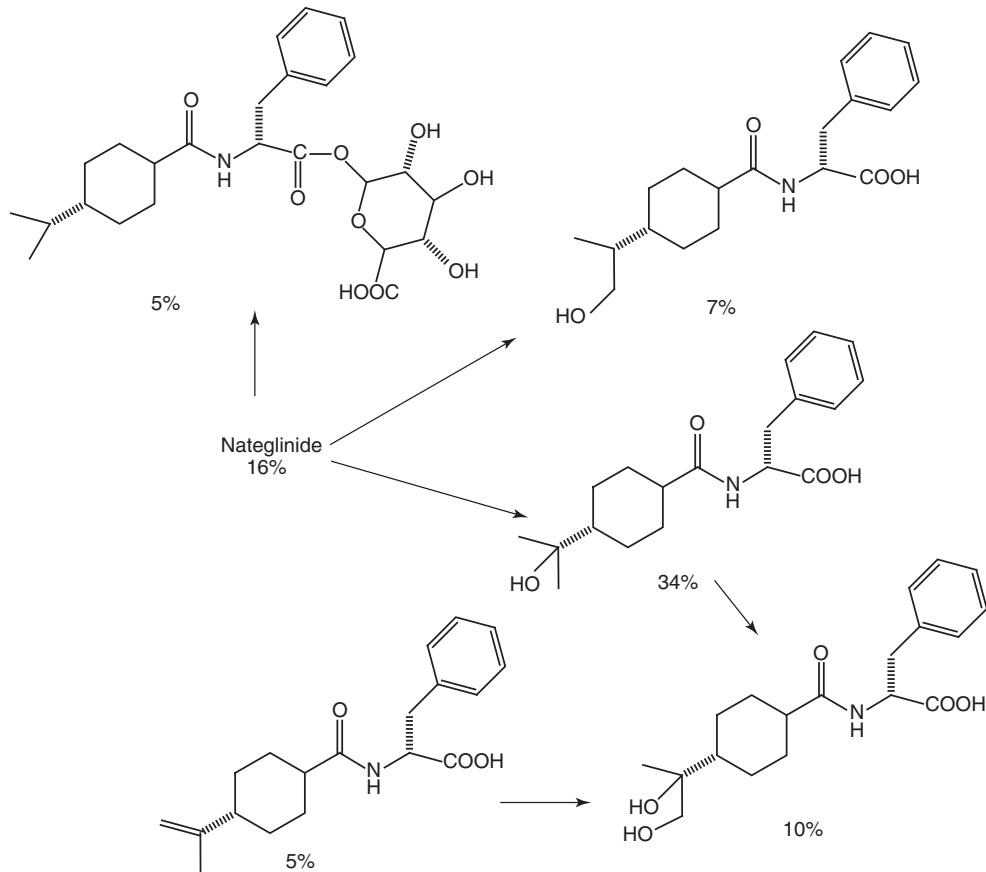


Figure 1.1 Metabolic pathway of nateglinide.

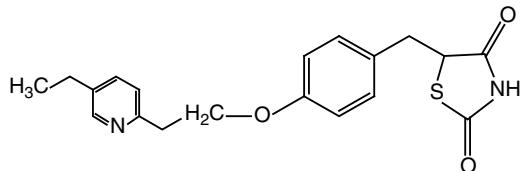
Uses: It is used as an oral hypoglycaemic agent in type II diabetic mellitus.

IV. Thiazolidinediones

Thiazolidinediones are a new class of oral antidiabetic agents (commercially known as glitazones) that enhance insulin sensitivity in peripheral tissues. It is relatively safe in patients with impaired renal function because they are highly metabolized by the liver and excreted in the faeces.

Mode of action: These drugs produce gene-mediated transcription for the release of insulin by forming new proteins. They act on the nuclear peroxisome proliferator activated receptor γ (*ppar* γ) and elicit the genes. It also inhibits the resistance to insulin by activating glucose transporters (Glut and Glut 1) in the plasma membrane.

i. Pioglitazone



Metabolism: It is metabolized and gives eight metabolic products. These products result from oxidation at either carbon adjacent to the pyridine ring. They are found as various conjugates in the urine and bile. Three metabolites appear to contribute to the biological activity of pioglitazone (Fig 1.2).

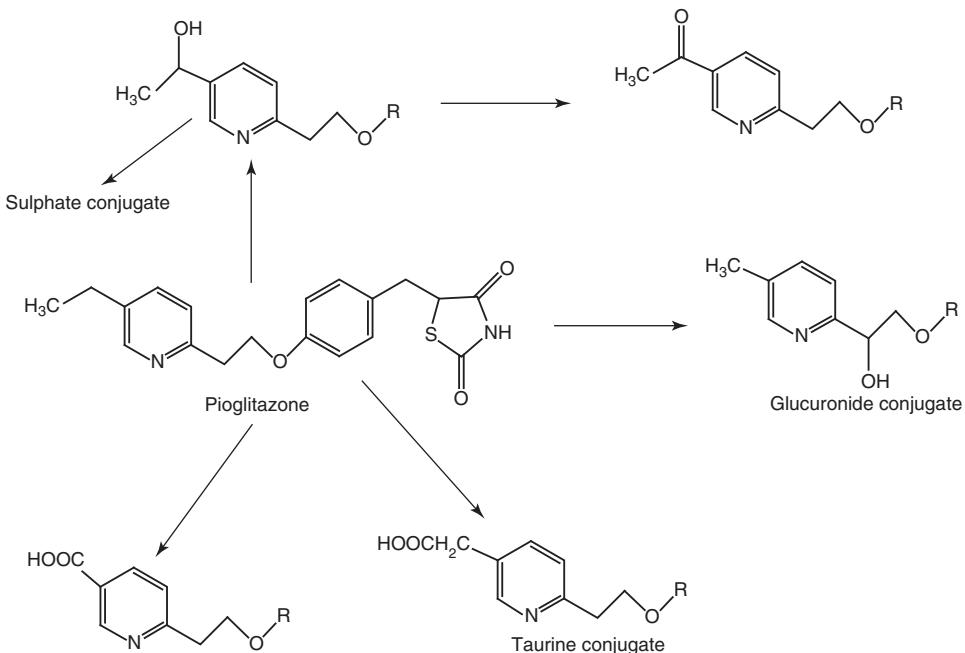
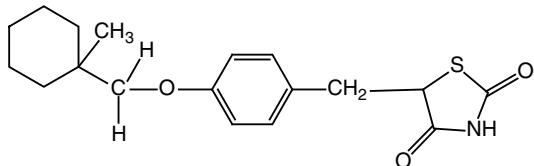
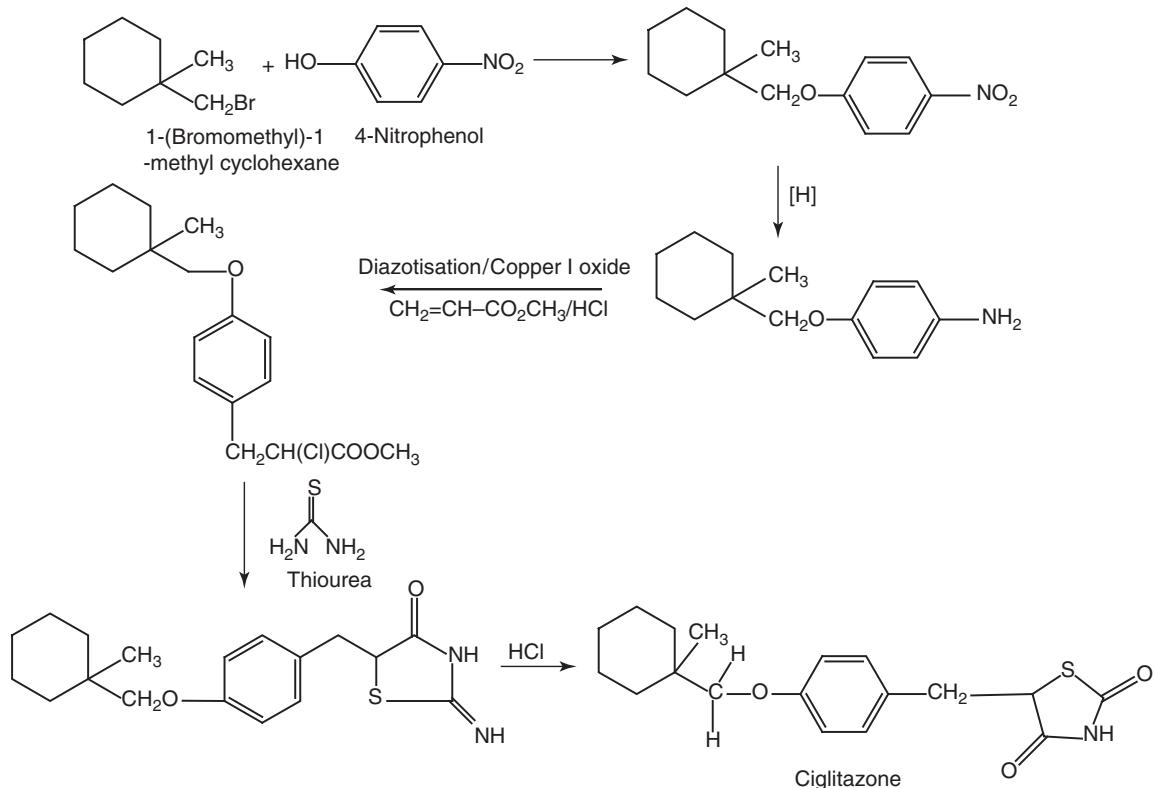


Figure 1.2 Metabolic pathway of pioglitazone.

ii. Ciglitazone

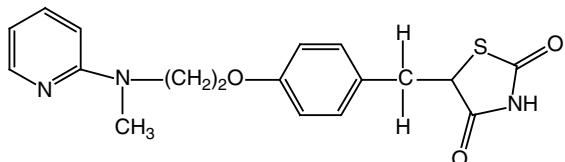


Synthesis

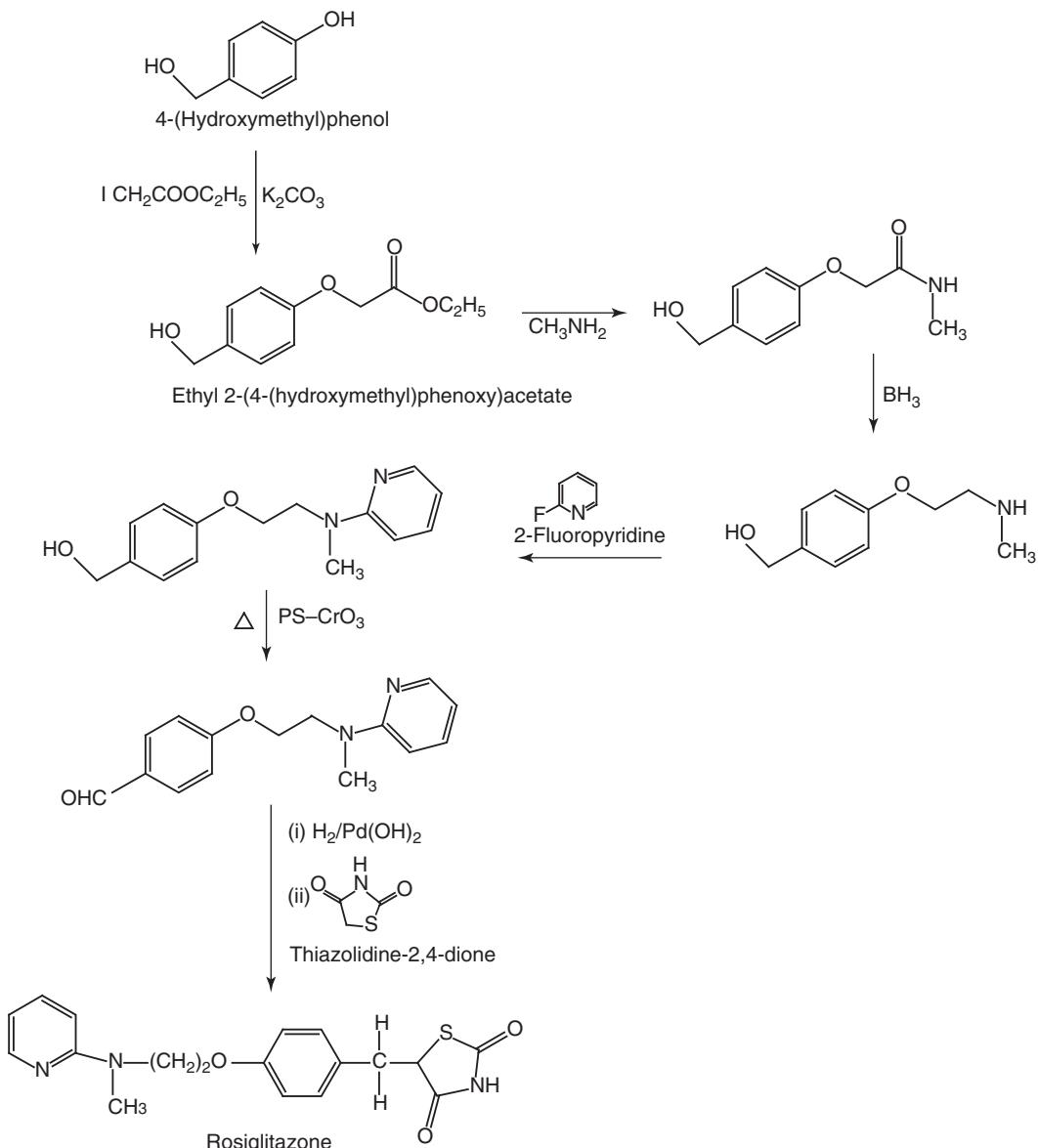


Use: It is used in the treatment of NIDDM.

iii. Rosiglitazone (Rosicon, Reglit, Rosinorm)



(±)-5-[[4-[2-Methyl-2-pyridinylamino]ethoxy]phenyl methyl]-2,4- thiazolidinedione

Synthesis

Metabolism: The primary metabolites consist of sulphate and glucuronic acid conjugates of hydroxylation and *N*-demethylation product. These metabolites contribute to the biological activity of rosiglitazone (Fig 1.3).

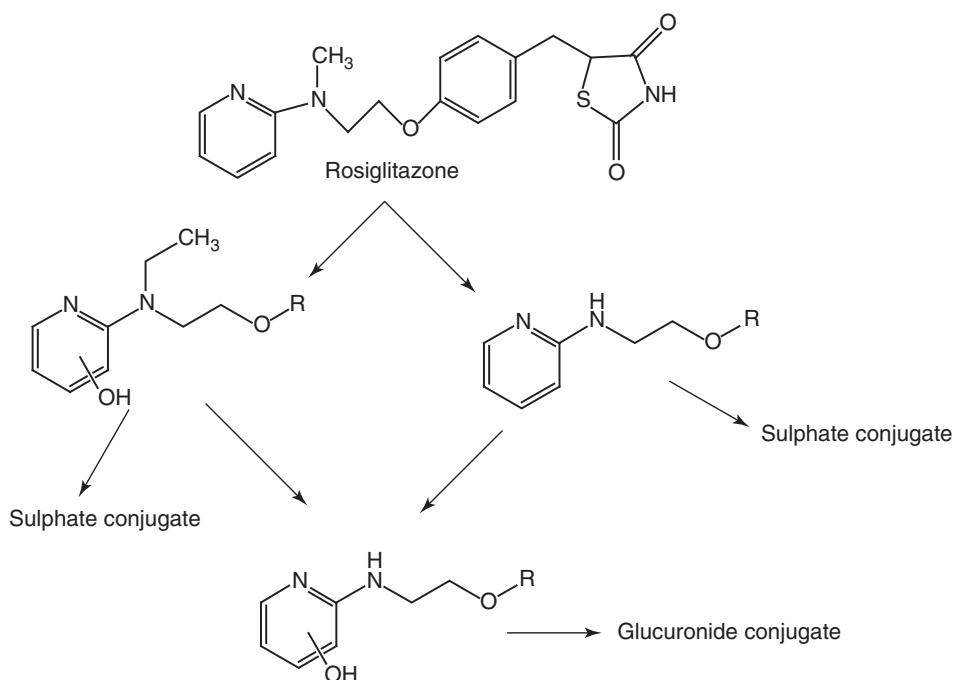


Figure 1.3 Metabolic pathway of rosiglitazone.

Uses: It is used in the treatment of NIDDM.

Dose: The dosage for type 2 diabetes mellitus for adult is 4 mg daily, which may be increased after 8–12 week of therapy, according to response and the maximum dosage is 8 mg daily.

iv. α -Glucosidase inhibitors

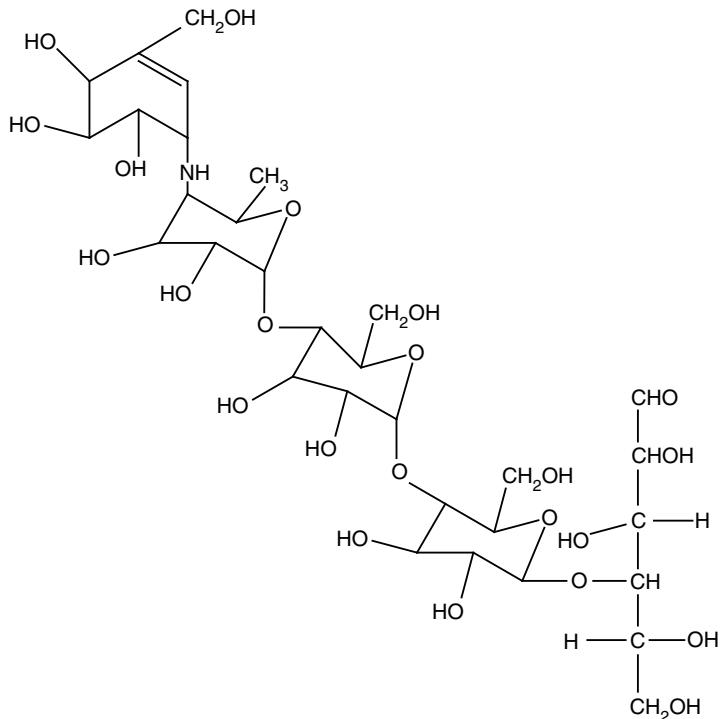
α -Glucosidase enzyme is responsible for breaking down the complex polysaccharides and sucrose to monosaccharides, which are then absorbed; α -glucosidase inhibitors decrease the rate of breakdown. They are also called starch blockers.

Mode of action: These acts on the final enzymes in the digestion of carbohydrates present in the brush border of small intestine and transport of polysaccharides and sucrose.

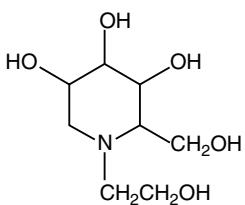
Properties and uses: Acarbose is a white or yellowish amorphous hygroscopic powder, very soluble in water, soluble in methanol, and practically insoluble in methylene chloride. It is an alpha-glucosidase inhibitor and used in the treatment of diabetes mellitus.

Assay: It is assayed by adopting liquid chromatography technique.

i. Acarbose



ii. Miglitol



Properties and uses: It is a crystalline substance, soluble in water. It is a α -glucosidase inhibitor and used as an antidiabetic agent.

V. Aldose reductase inhibitors

In diabetic complications, high concentrations of glucose is converted into sorbitol by aldose reductase by the polyol pathway (Fig. 1.4). Sorbitol is converted into fructose and these products accumulate in the nerves, kidneys, and retina, etc. Galactone is converted to galactitol, which is not metabolized and causes osmotic swelling. Aldose reductase inhibitors interfere in the polyol pathway of sorbitol and fructose and thereby cause hypoglycaemic effects.

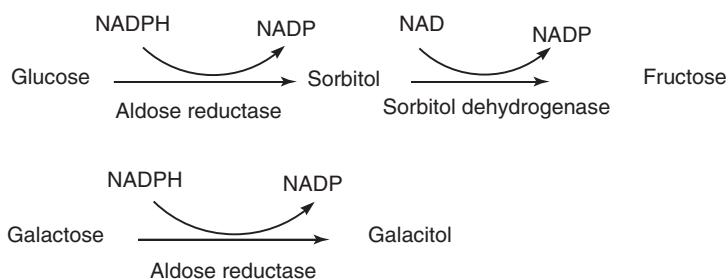
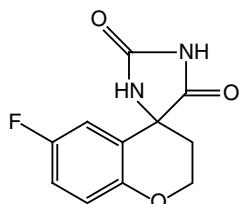


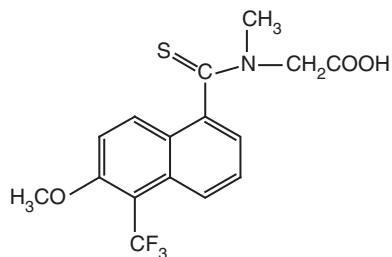
Figure 1.4 Polyol pathway.

i. Sorbinil



Uses: It is used in the treatment of diabetic neuropathy.

ii. Tolrestat

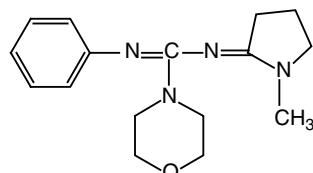


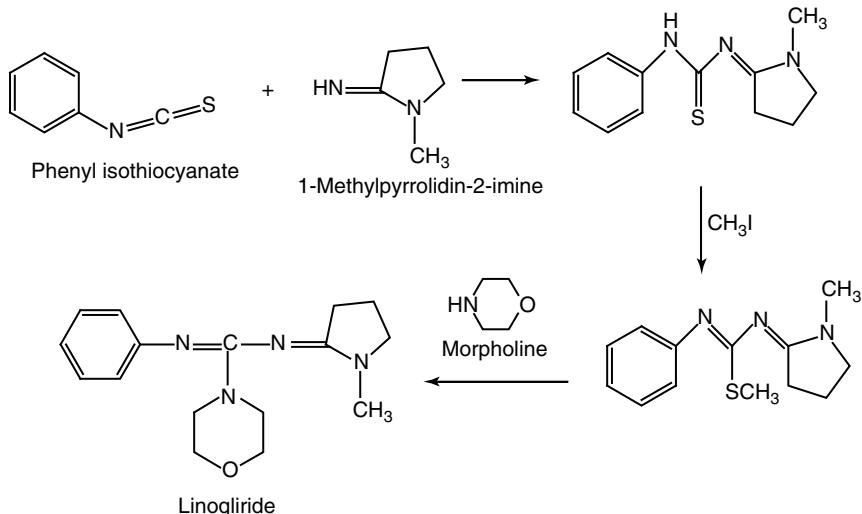
N-[6-Methoxy-5-trifluoromethyl-1-naphthyl(thiocarbonyl)]-*N*-methylglycine

Uses: It is useful in the prophylaxis of diabetic neuropathy and cataracts.

VI. Miscellaneous

Linogliride



Synthesis

Uses: Used in the treatment of diabetes mellitus.

PROBABLE QUESTIONS

1. Explain type I and type II diabetes with some typical examples.
2. How do you classify the oral hypoglycaemic agents? Write the structure, chemical names, and uses of at least two compounds.
3. Write the mode of action of Tolbutamide and Phenformin.
4. Write in detail about Thiazolidindiones with specific reference to the following drugs Rosiglitazone Troglitazone.
5. Write a short note on the following oral hypoglycaemic agents:
(a) Biguanides (b) α -Glucosidase inhibitors.
6. Write a brief account of the following with a few examples:
(a) First-generation sulphonylureas (b) Second-generation sulphonylureas
7. How will you synthesize the following drugs?
(a) Chloropropamide (b) Tolbutamide (c) Glipizide
8. Explain about the meglitinides' specific mechanism of actions. Write the structure, synthesis, metabolism, and uses of any one of them.

SUGGESTED READINGS

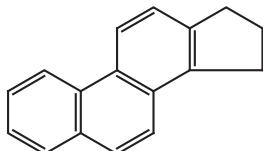
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2. *British Pharmacopoeia*. Medicines and Healthcare Products Regulatory Agency. London, 2008.
3. Brunton LL, Lazo JS, and Parker KL. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics* (11th edn). New York: McGraw Hill, 2006.
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15. Srivastava V and Pandeya SN. 'Recent trends in hypoglycemic research'. *J Sci Industr Res* 47: 706–21, 1988.

Chapter 2

Steroids

INTRODUCTION

The steroids form a group of structurally related compounds, which are widely distributed in animals and plants. The structures of steroids are based on the 1, 2-cyclopentanophenanthrene skeleton.



1,2-Cyclopentanophenanthrene

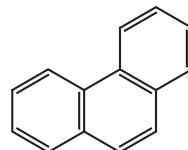
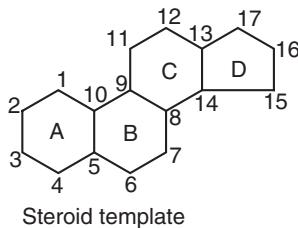
Steroids consist of four rings. Perhydrophenanthrene (rings A, B, and C) is a completely saturated derivative of phenanthrene, while D is a five-membered cyclopentane ring.

The major therapeutic classes of steroids are the following:

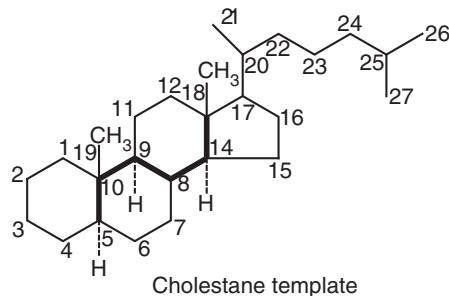
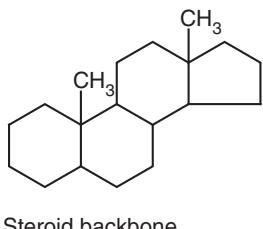
- Anti-inflammatory agents: Cortisone
- Sex hormones: Estrogen, progesterone, and testosterone
- Oral contraceptives: Norethisterone
- Cardiac steroids: Digitoxigenin
- Diuretics: Spironolactone
- Antibiotics: Fusidic acid
- Neuromuscular blockers: Pancuronium chloride
- Vitamin D precursor: Ergosterol

STEROID NOMENCLATURE AND STRUCTURE

Steroids consist of four fused rings (A, B, C, and D). Chemically, these hydrocarbons are cyclopentano per hydro phenanthrenes. They contain a five-membered cyclopentane (D) ring and the three rings of phenanthrene. A perhydro phenanthrene (ring A, B, and C) is the saturated derivative of phenanthrene.

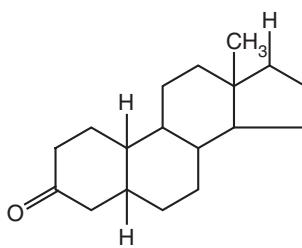


Phenanthrene

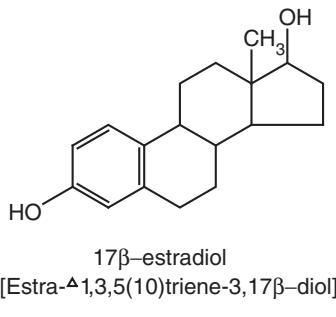


The polycyclic hydrocarbon, known as 5α -cholestane, is used to illustrate the numbering system for a steroid.

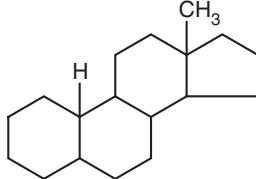
- The ring juncture or backbone carbons are shown in the structure of 5α -cholestane with a heavy dark line.
- Solid lines denote groups above the plane of the nucleus (β -configuration) and dotted or broken lines denote groups below the plane (α -configuration). If the configuration of substituent is unknown, its bond to the nucleus is drawn as a wavy line.
- The configuration of the H at C-5 is always indicated in the name.
- Circles were sometimes used to indicate α -hydrogens and dark dots to indicate β -hydrogens.
- Compounds with 5α -cholestane belong to allo-series, while compounds derived from 5β -cholestane belong to the normal series.
- If the double bond is not between sequentially numbered carbons, in such cases, both carbons are indicated in the same.
- When a methyl group is missing from the side chain, this is indicated by the prefix 'nor' with the number of carbon atom, which has disappeared.

 $5\beta,19$ -norandrost-3-one

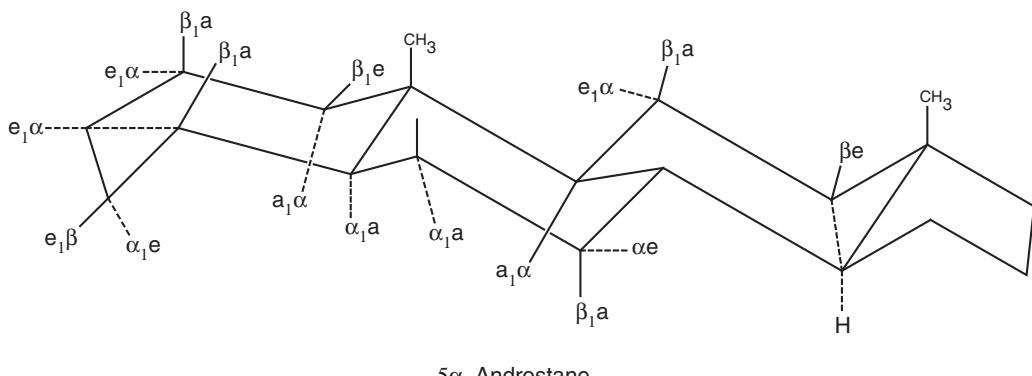
The symbol Δ is often used to designate a C = C bond in a steroid. If C = C is in between carbons 5 and 4, the compound is referred to as a Δ^4 steroid, and if the C = C bond is between positions 5 and 10, the compound is designated as $\Delta^{5(10)}$ steroid. Example, Estra-1,3,5(10) triene-3,17 β -diol.



Since 17 β -estradiol contains 18 carbon atoms, it is considered as a derivative of estrane, a basic nucleus.



Stereochemistry: The absolute stereochemistry of the molecule and any substituent is shown with solid (β) and dashed (α) bonds; a (axial) bond is perpendicular to the plane of the molecule while equatorial bond (e) is horizontal to the plane of the molecule.



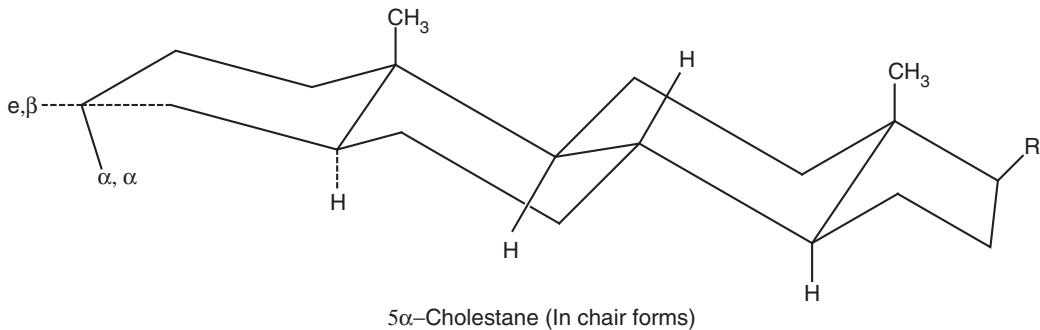
5 α -Androstane

The aliphatic side chain at position is always assumed to be of β -configuration.

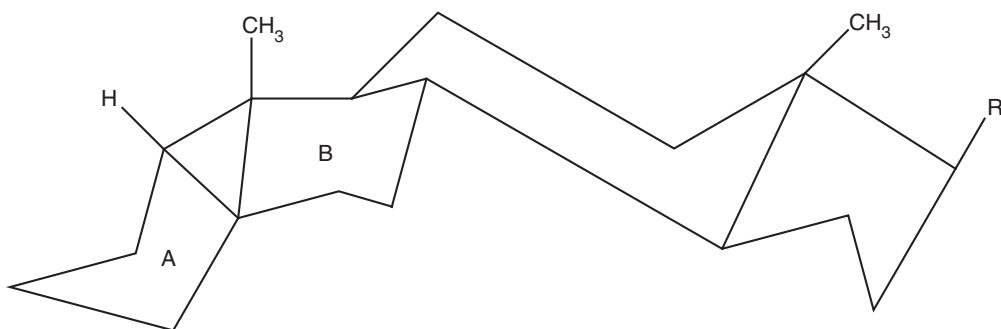
The term *cis* and *trans* are used occasionally to indicate the backbone stereochemistry between rings. For example, 5 α -steroids are A/B *trans* and 5 β -steroids are A/B *cis*. The terms syn and anti are used analogously to *trans* and *cis*.

Conformations: There are six asymmetric carbon atoms in the nucleus 5, 8, 9, 10, 13, and 14. Therefore, there are $2^6 = 64$ optically active forms possible. Cholestan, androstane, and pregnane can exist in two conformations, that is, chair form and boat form.

Cholestone A,B-*trans* form



Coprostane A,B-*cis* form



Chair confirmation is more stable than boat confirmation due to less angle strain, and hence, all cyclohexane rings in the steroid nucleus exist in the chair confirmation.

Classification

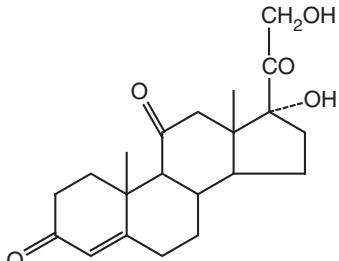
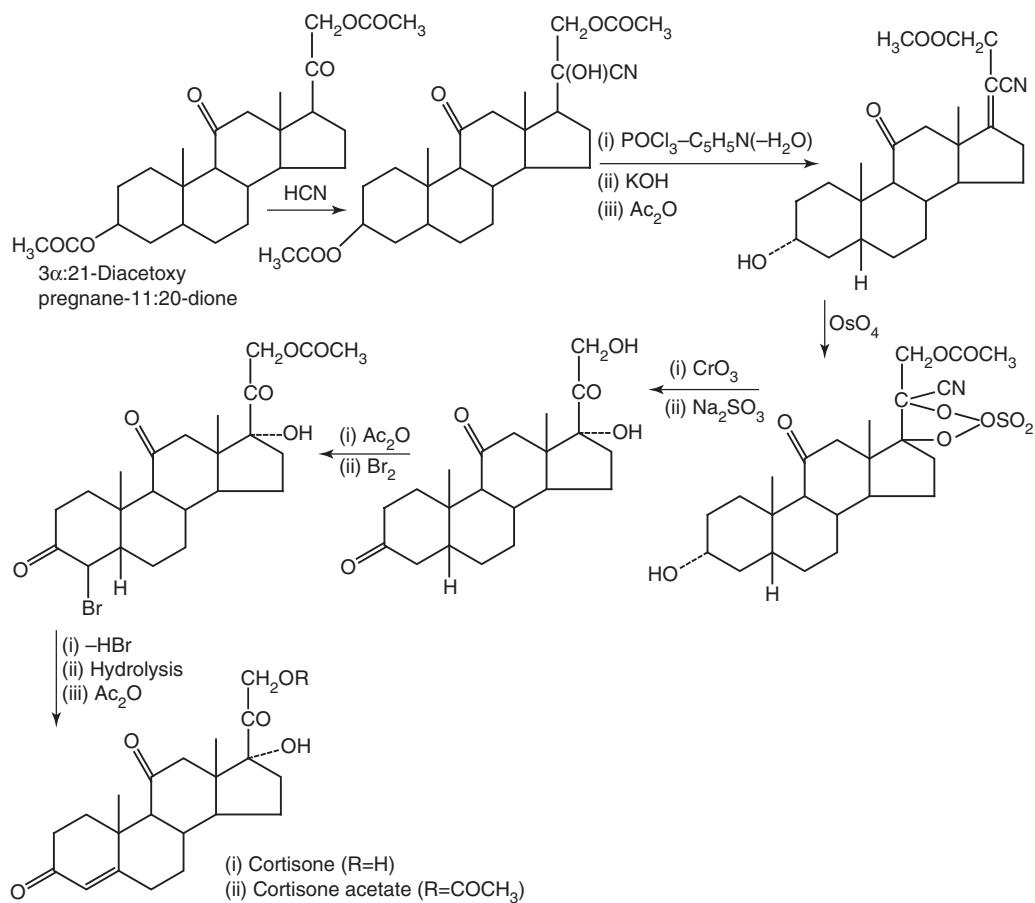
The adrenal cortex synthesizes two classes of steroids. They are as follows:

Glucocorticoids: These steroids regulate the carbohydrates, proteins, and the fat metabolism and are intimately involved in the operation of the processes that enable the body to resist infections and stress.

Example—hydrocortisone and cortisone.

Mineralocorticoids: These steroids mainly influence salt and water balance (and hence, the control of blood volume and blood pressure) by maintaining proper electrolyte balance.

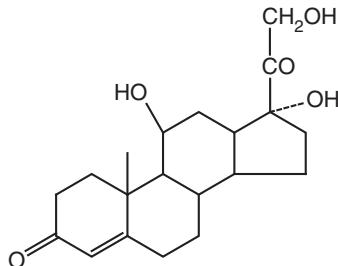
Example—aldosterone, 11-deoxycorticosterone.

i. Cortisone (Cortogen, Cortone)**Synthesis**

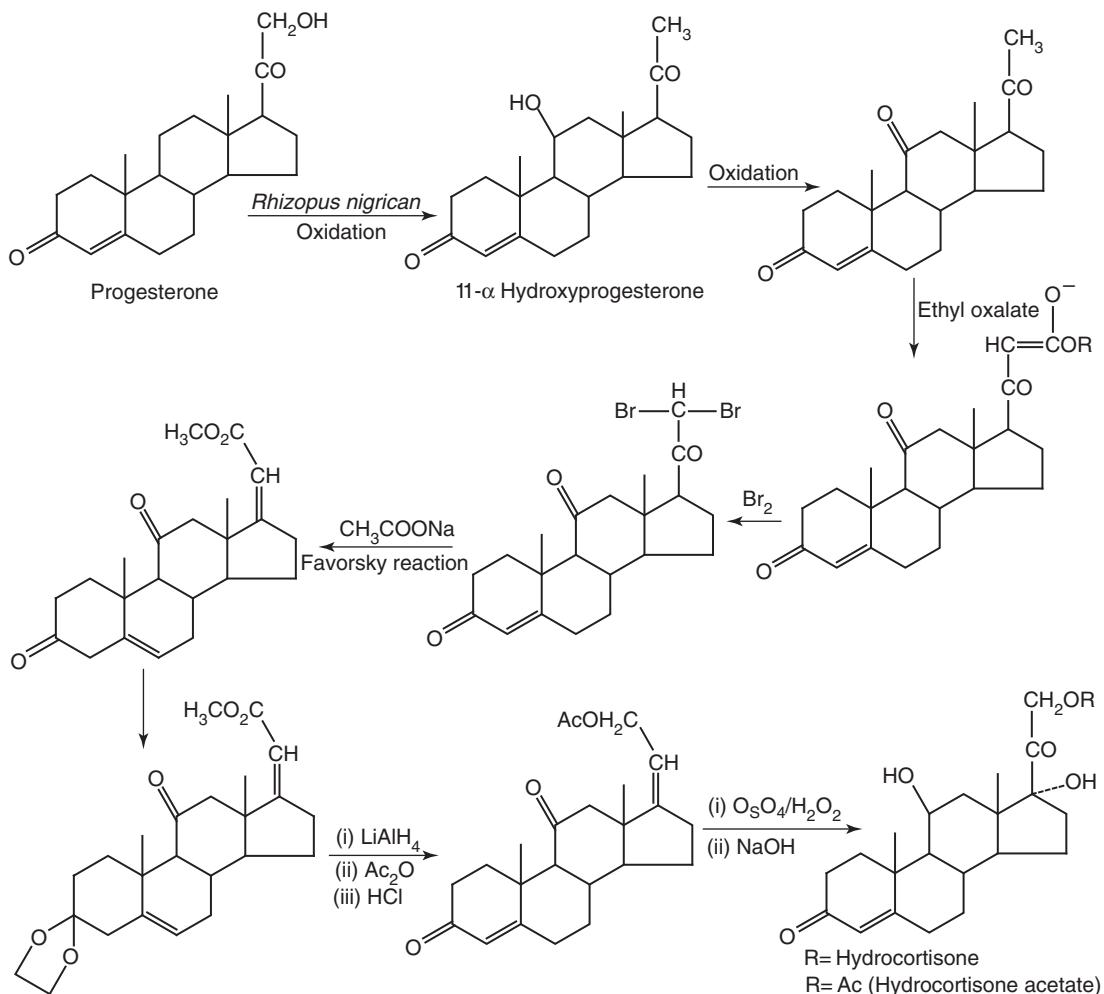
Properties and uses: It is a white, crystalline powder, insoluble in water, and soluble in alcohol. It is used in rheumatoid arthritis, severe shock, allergic conditions, and chronic lymphatic leukaemia.

Dose: The dosage for adults is 20–100 mg per day by oral or IM.

ii. Hydrocortisone (Hydrocortone, Lortef)



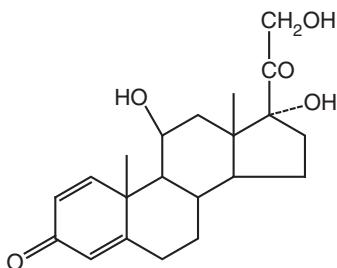
Synthesis



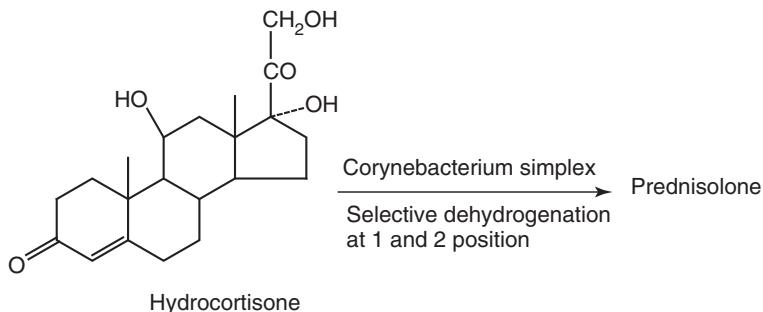
Properties and uses: It exists as white crystalline powder, soluble in water and in alcohol. It is used as an anti-inflammatory agent.

Dose: The dose as injection is 100 mg intramuscular (IM) and as topical cream 1%–2.5% for skin, ear, and eye.

iii. Prednisolone (Prelone, Emsolone)



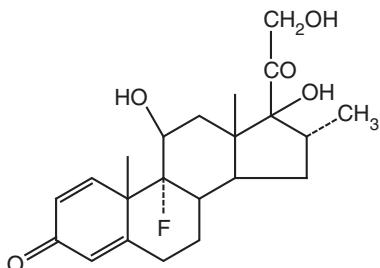
Synthesis



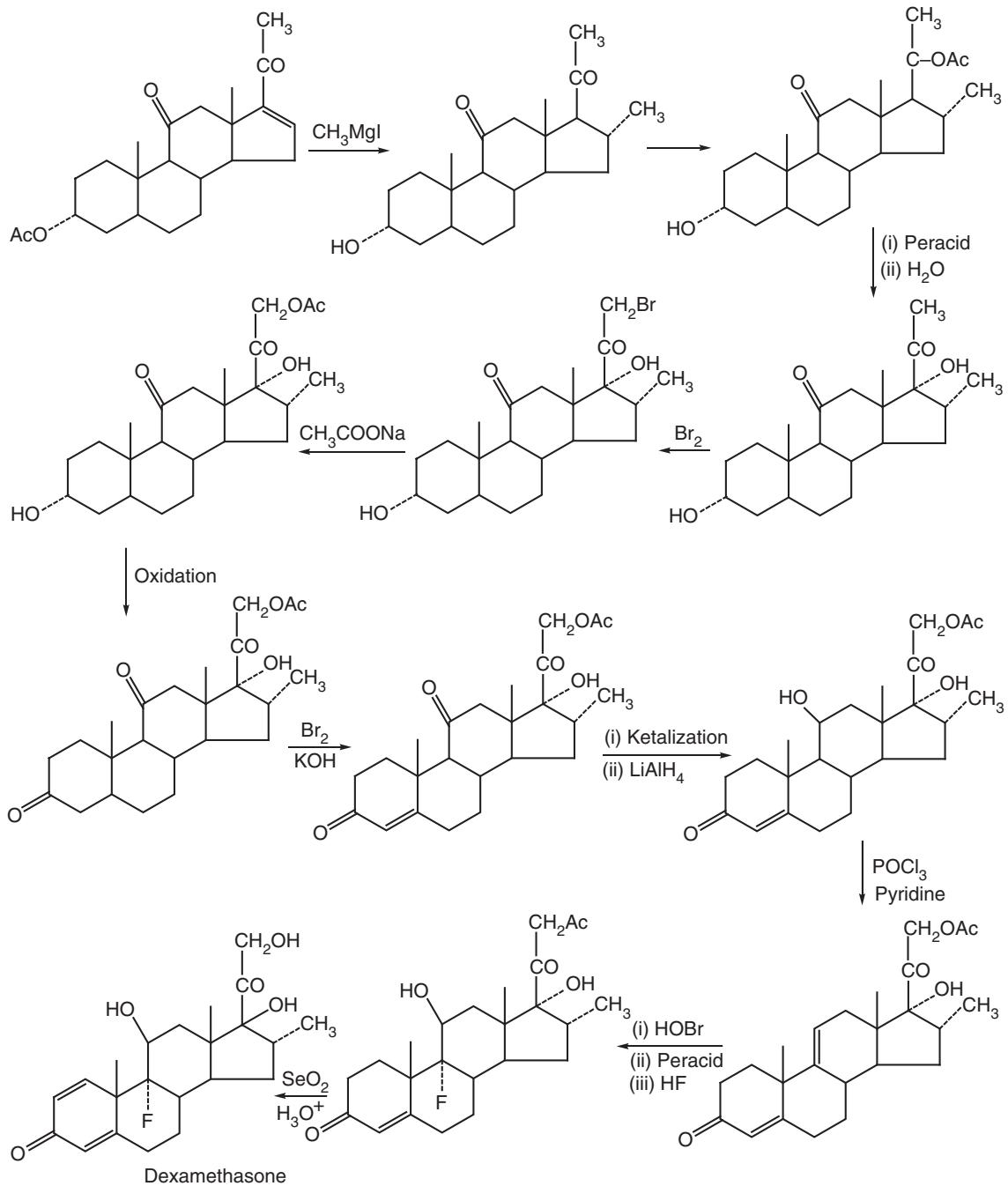
Properties and uses: It is a white crystalline powder, sparingly soluble in alcohol. It is four times as potent as hydrocortisone.

Dose: The oral dose for adult is 5–60 mg per day. As IM, IV, and intra-articular (IA) injection, the dose is 10–40 mg, and for topical use (skin and eyes), the dose is 0.25%.

iv. Dexamethazone (Dalamone)



Synthesis



Properties and use: It exists as white crystalline powder, soluble in alcohol and insoluble in water. Used as an anti-inflammatory and antiallergic drug.

Dose: Oral adult dose is 500 µg to 9 mg daily. The topical dose for conjunctiva is 1 drop of 0.1% suspension.

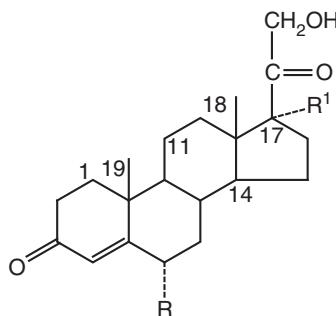
PROGESTOGENS

The natural progestational hormone or progestogen is progesterone, which is secreted mainly by the corpus luteum in the second part of the menstrual cycle. Small amounts are also secreted by the testis in the male and the adrenal cortex in both sexes, and large amounts are secreted by the placenta.

Classification

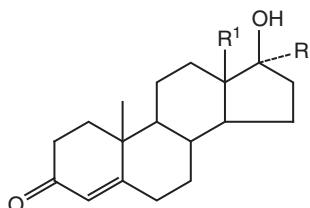
Progestogens could be broadly classified into two major classes:

1. Progesterone derivatives

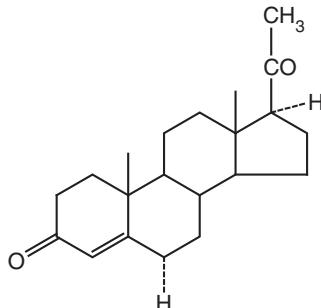
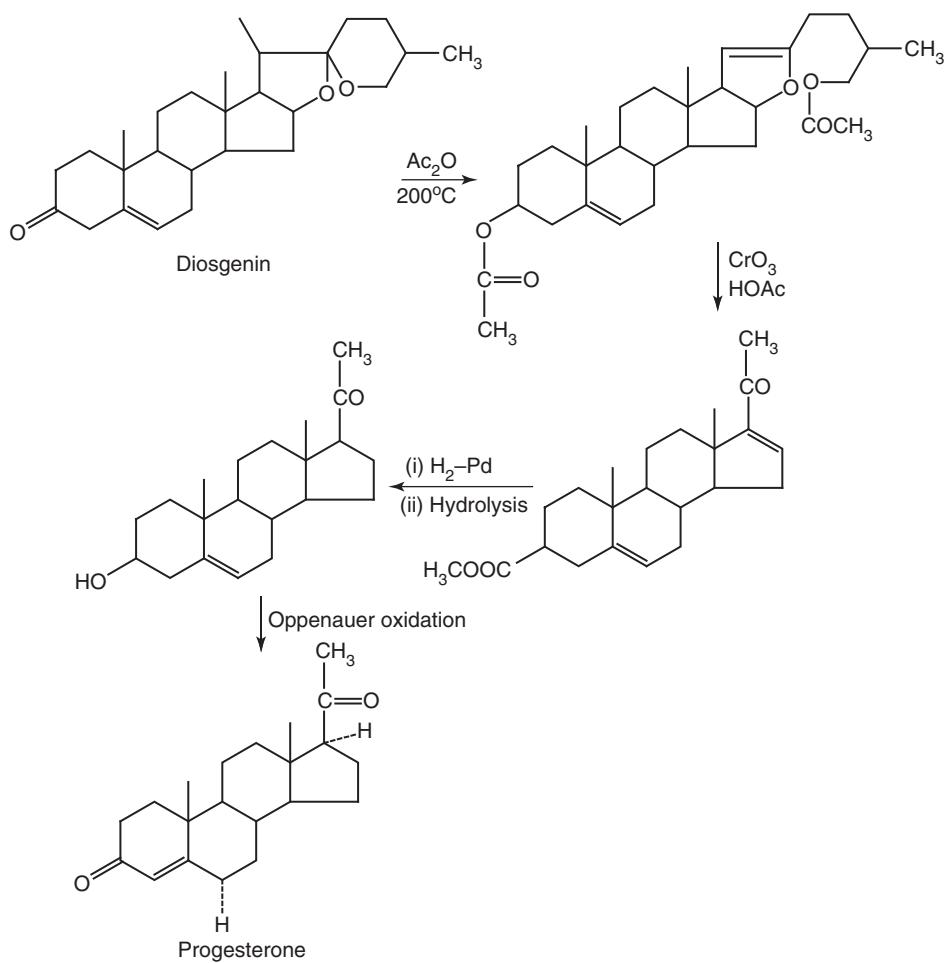


| Name | R | R ¹ |
|-------------------------------|------------------|---|
| Progesterone | -H | -H |
| Hydroxy progesterone caproate | -H | -OCO(CH ₂) ₄ CH ₃ |
| Methoxy progesterone acetate | -CH ₃ | -OCOCH ₃ |

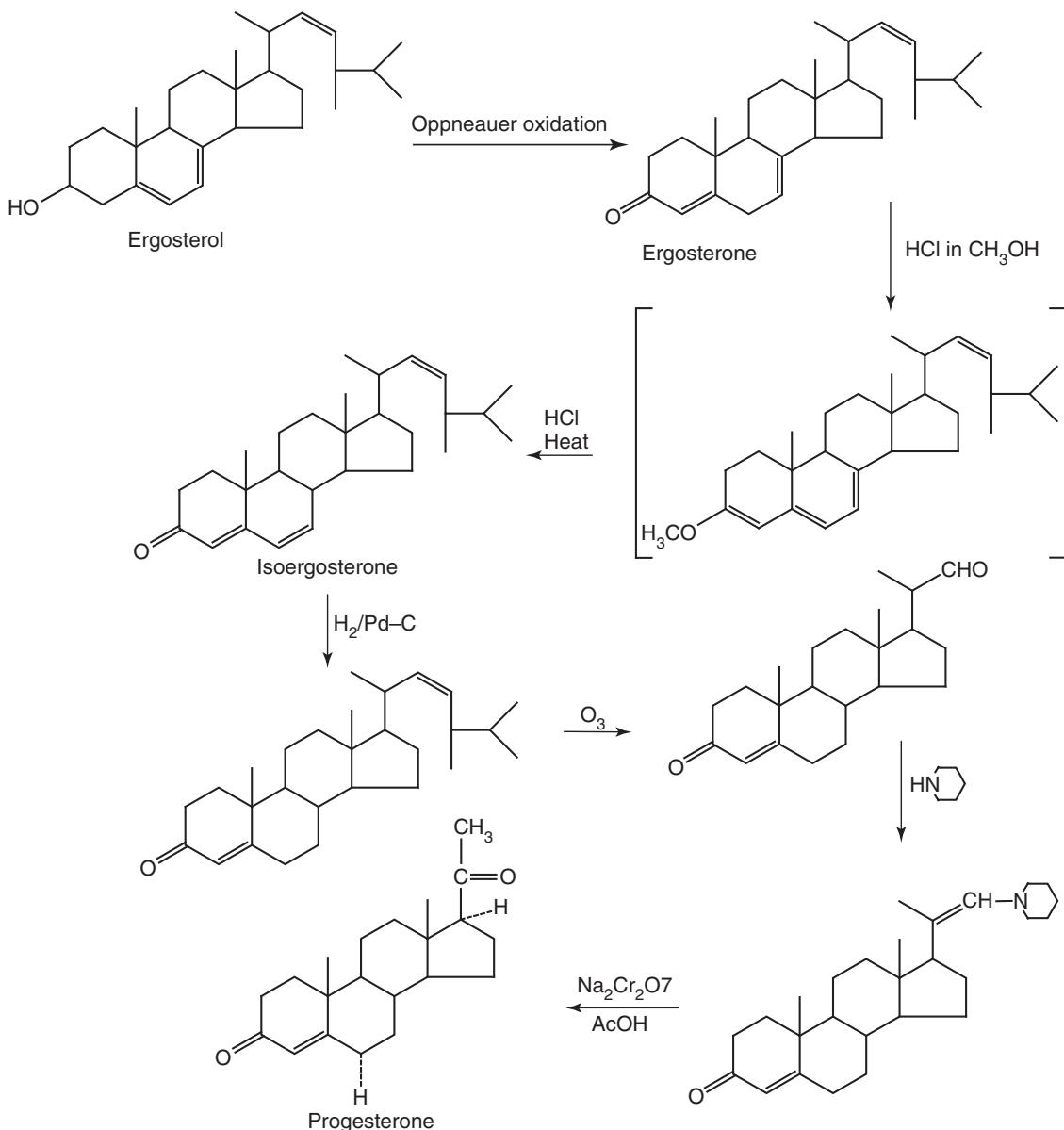
2. 19-Nor testosterone derivatives



| Name | R | R ¹ |
|-------------------------------|-------|--------------------------------|
| Norethisterone, Norethindrone | -C≡CH | -CH ₃ |
| Norgestrel | -C≡CH | -C ₂ H ₅ |
| 19-Nortestosterone | -H | -CH ₃ |

i. Progesterone (Alza)**Synthesis****Method-I From: Diosgenin**

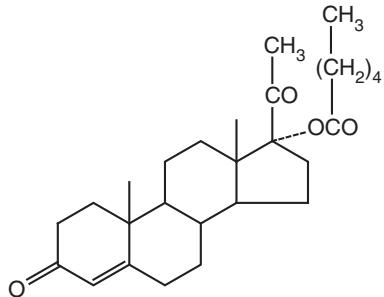
Method-II From: Ergosterol



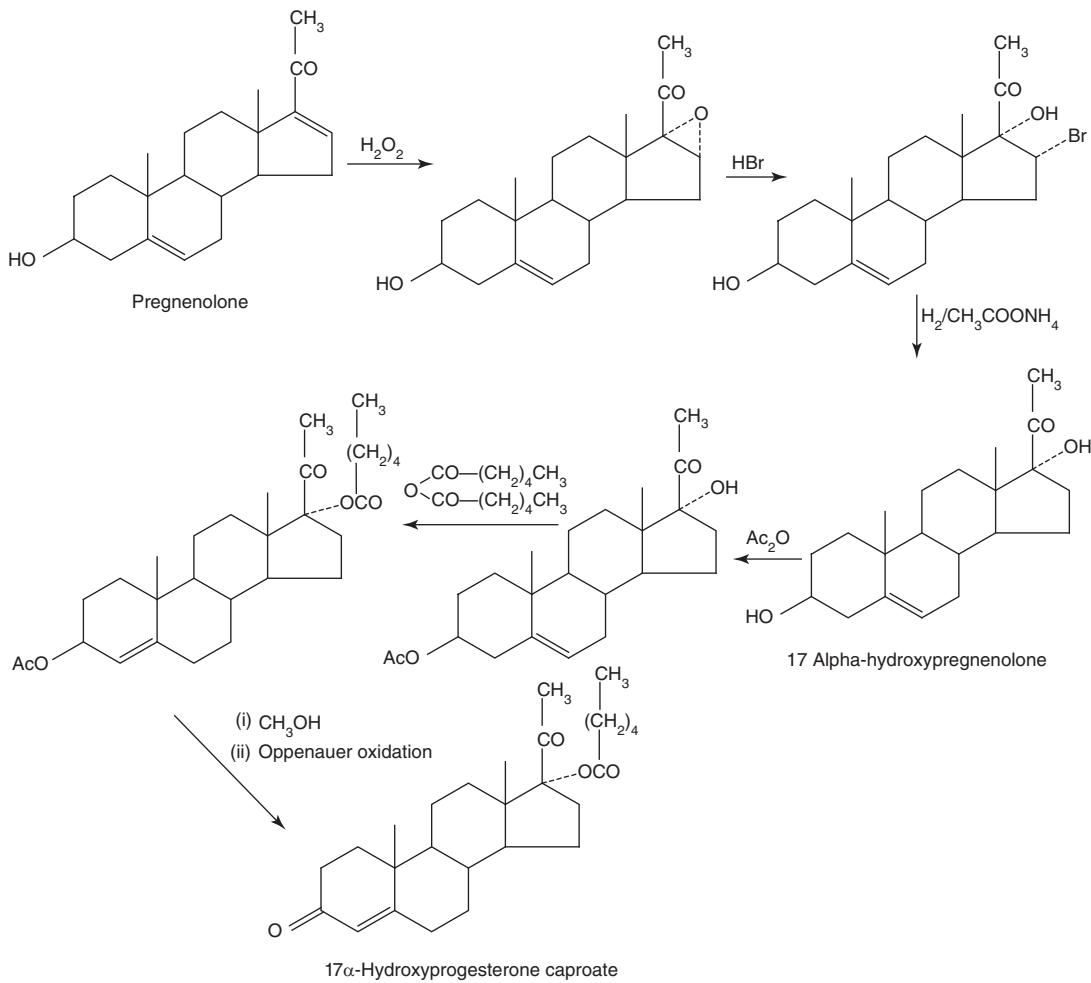
Properties: It exists as white crystalline powder, insoluble in water and in alcohol.

Dose: The dose for uterine bleeding is 5–10 mg injected per day up to 5–10 days. For habitual abortion, the dosage is 5–20 mg twice or thrice a week by IM injection.

ii. Hydroxyprogesterone caproate

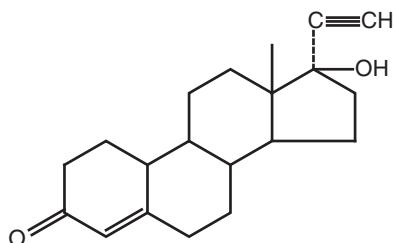


Synthesis

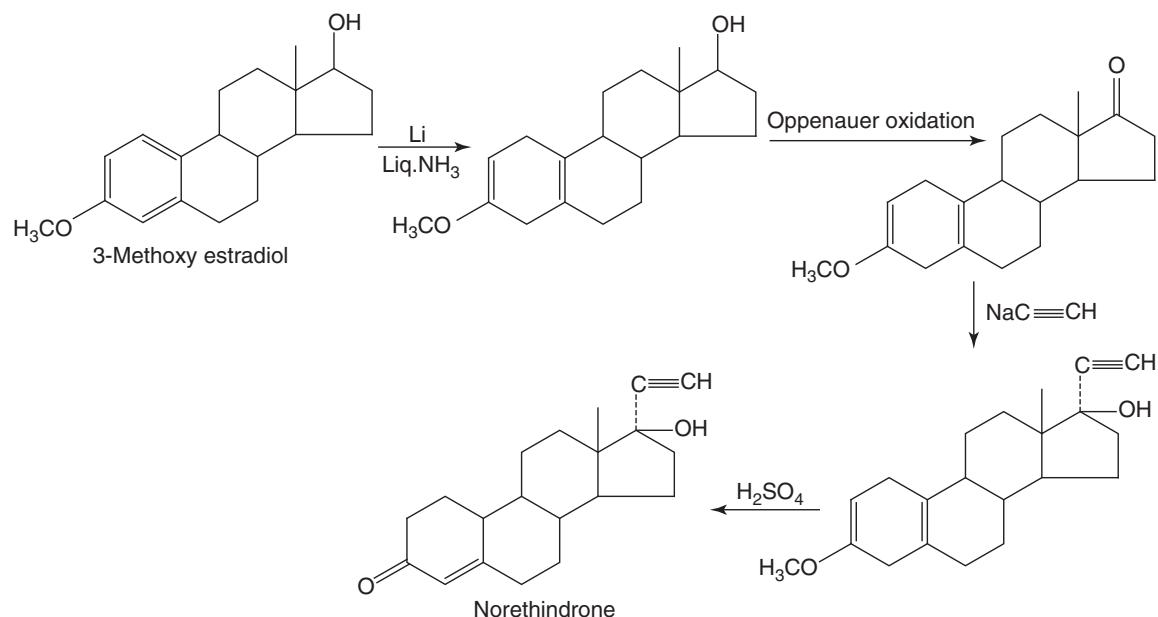


Properties and uses: It exists as white crystalline powder, insoluble in water, it is more potent than progesterone, and has longer duration with short onset of action.

iii. Norethindrone (Norethisterone, Micronor)



Synthesis

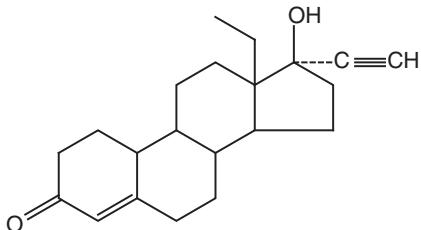


Properties and uses: It exists as white crystalline powder, insoluble in water. It is an important oral contraceptive and has the ability to postpone menstruation and prevent ovulation by suppressing pituitary gonadotropin. It is used in combination with mestranol and ethinestradiol.

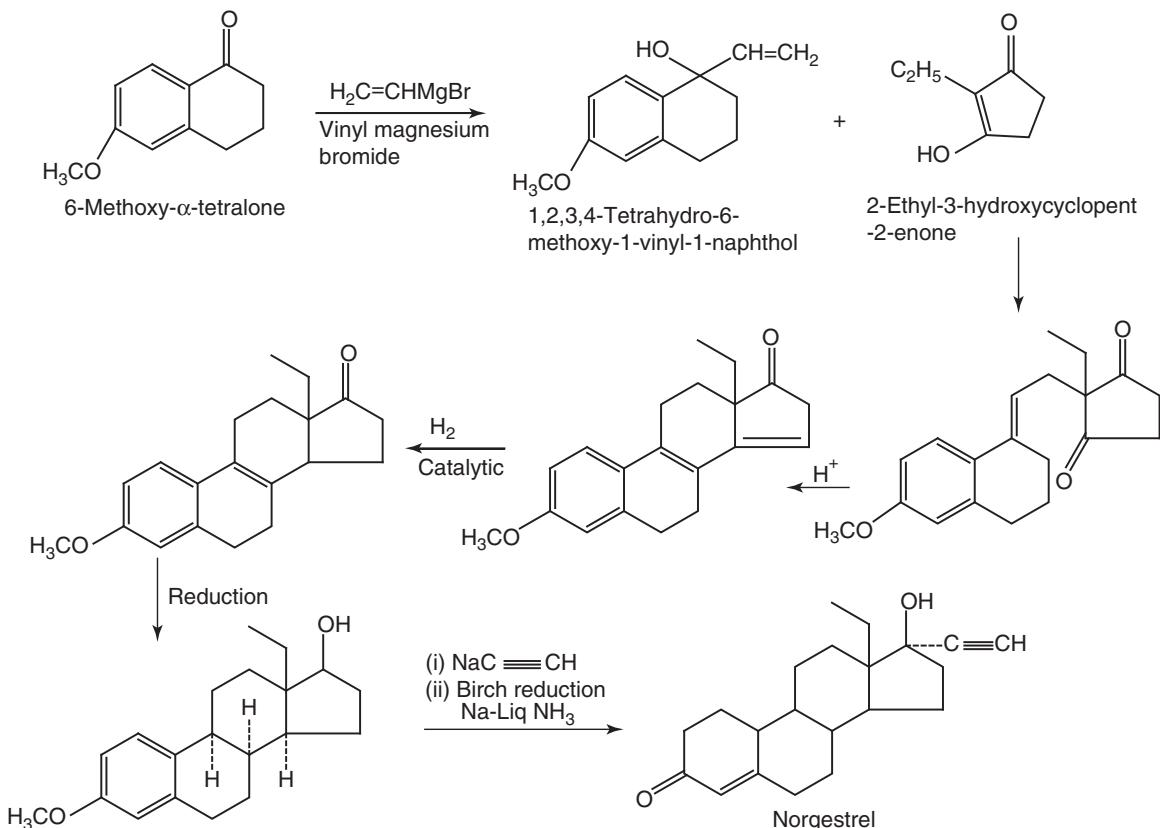
Assay: Dissolve the sample in tetrahydrofuran, add silver nitrate, and titrate the solution with 0.1 N NaOH. Determine the end point potentiometrically.

Dose: The oral dose for contraception is 2.5–10 mg daily for 21 days.

iv. Norgestrel (Ovrette, Ovval)



Synthesis



Properties and uses: It exists as white crystalline powder, insoluble in water, slightly soluble in alcohol. Used as an oral contraceptive.

Dose: The oral dose as a single agent is 75 μ g per day.

OESTROGENS

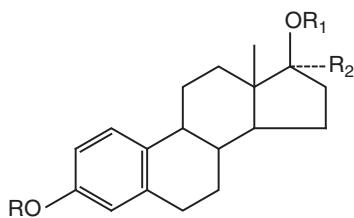
The mammalian ovary is a source of steroid hormones that maintain reproductive functions and oestrogen secretion in females.

Classification

Oestrogens could be classified as follows:

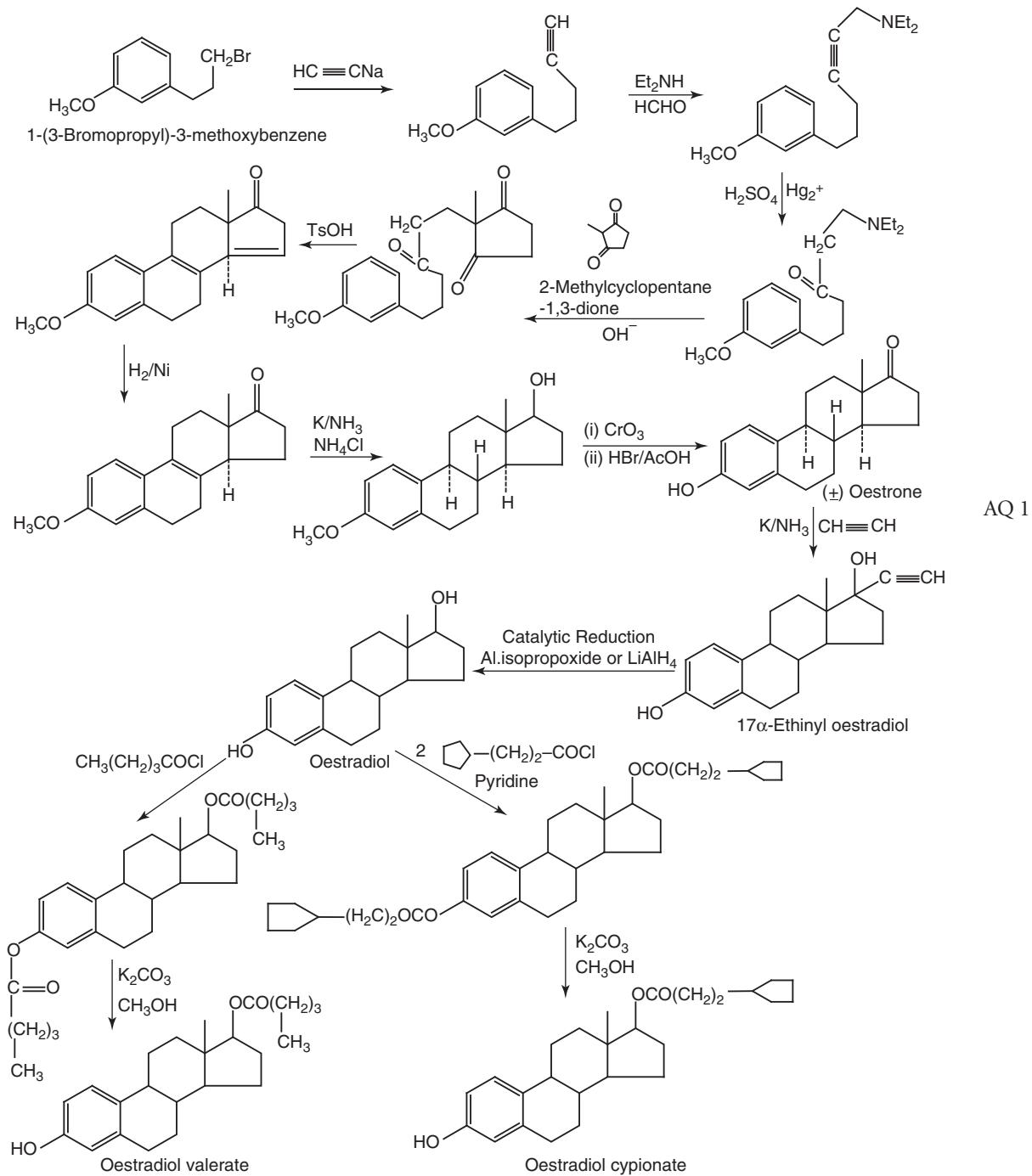
- i. **Natural steroidal:** Oestradiol, Oesterone
- ii. **Synthetic steroidal:** Ethynodiol diacetate, Mestranol
- iii. **Nonsteroidal synthetic:** Stilbestrol

i. Oestradiol derivatives



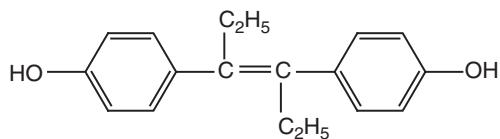
| Name | R | R ₁ | R ₂ |
|-------------------------|-----------------------------------|--|----------------|
| Oestradiol | -H | -H | -H |
| Oestradiol valerate | -H | -CO(CH ₂) ₃ CH ₃ | -H |
| Oestradiol cypionate | -H | -CO(CH ₂) ₂ — | -H |
| Oestradiol dipropionate | -COC ₂ H ₅ | -COC ₂ H ₅ | -H |
| Oestradiol benzoate | C ₆ H ₅ CO- | -H | -H |
| Ethinodiol diacetate | -H | -H | -C≡CH |
| Mestranol | CH ₃ | -H | -C≡CH |
| Quinestrol | | -H | -C≡CH |

Oestradiol Derivatives



Properties: It exists as a creamy white crystalline powder hygroscopic, insoluble in water and soluble in alcohol.

ii. Diethylstilbestrol (Stilbetin, Stilphstrol)

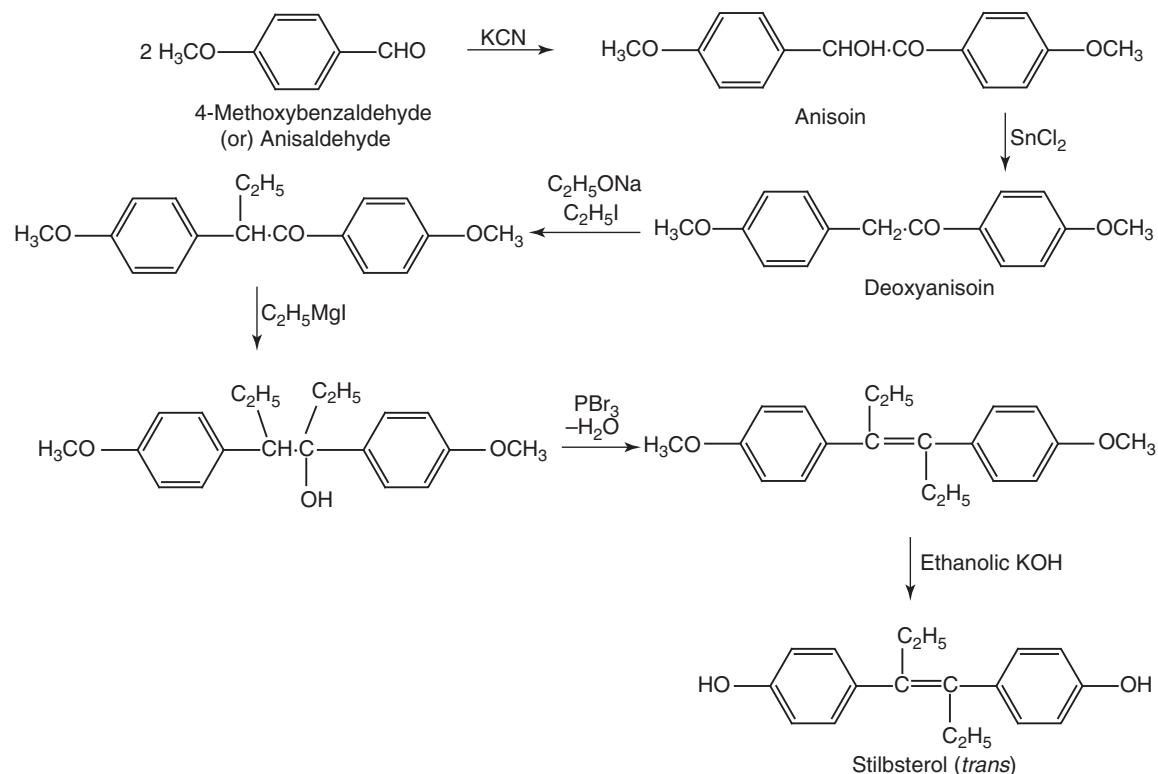


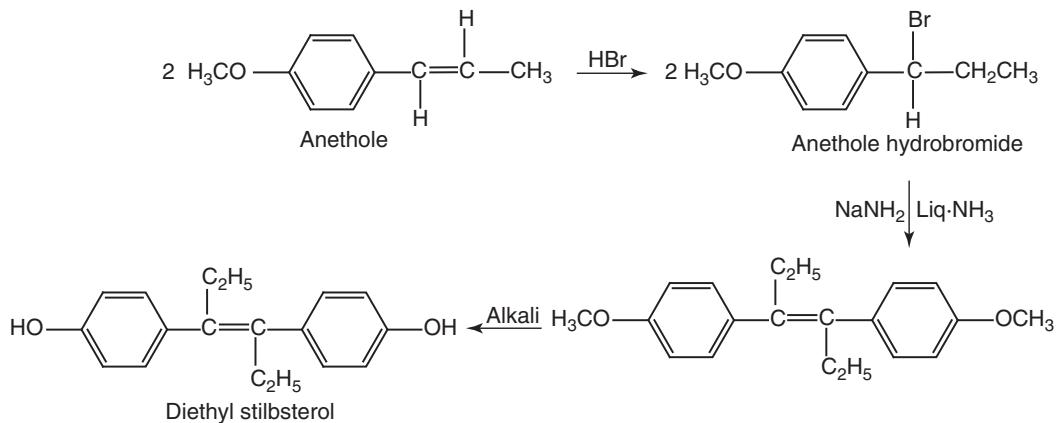
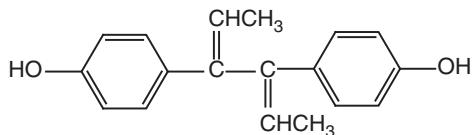
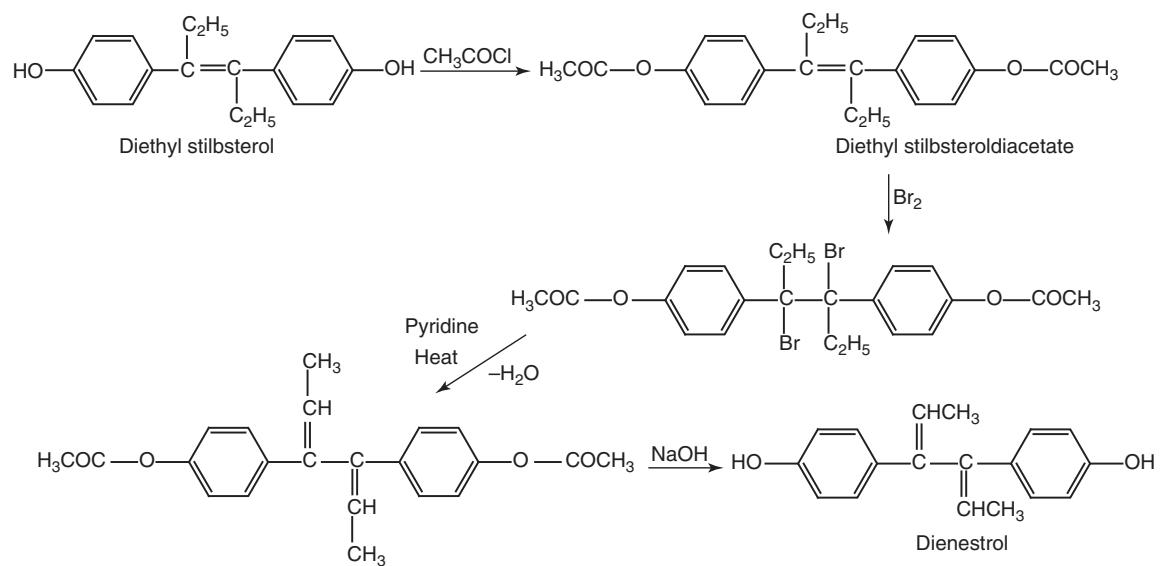
Properties: It is a white crystalline powder, insoluble in water and soluble in alcohol.

Dose: The dose for menopausal symptoms orally is 0.1–2 mg. For secondary amenorrhoea, the dose is 0.2–0.5 mg and for carcinoma, of the prostate the intake is 3 mg per day.

Synthesis

Method-I From: Anisaldehyde (Dodds method)



Method-II From: Anethole**iii. Dienestrol (Estragard)****Synthesis**

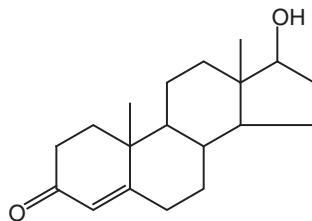
ANDROGENS AND ANABOLIC AGENTS

Androgens or male sex hormones are synthesized from cholesterol in the testes and adrenal cortex. In the liver, androgens are formed from C-21 steroids. The ovary also secretes small amounts of androgens.

Classification

- Androgenic or male sex characteristics promoting activity:** Compounds with androgenic activity are called androgens. It includes normal development, functioning, and maintenance of the male sex organs and sexual characteristics.
- Anabolic or muscle building activity:** Compounds with anabolic activity are called anabolic agents. It causes nitrogen retention by increasing the rate of protein synthesis, decreasing the rate of protein catabolism, and thus, promotes laying down of new tissues. It also stimulates the thickness rise and linear growth of the bones to some extent. The distinction of anabolic therapy of such wasting conditions such as cancer, trauma, osteoporosis, and also effects of immobilizations are also treated by the anabolic agents.

i. Testosterone (Nuvir, Andriol, Testoviron)

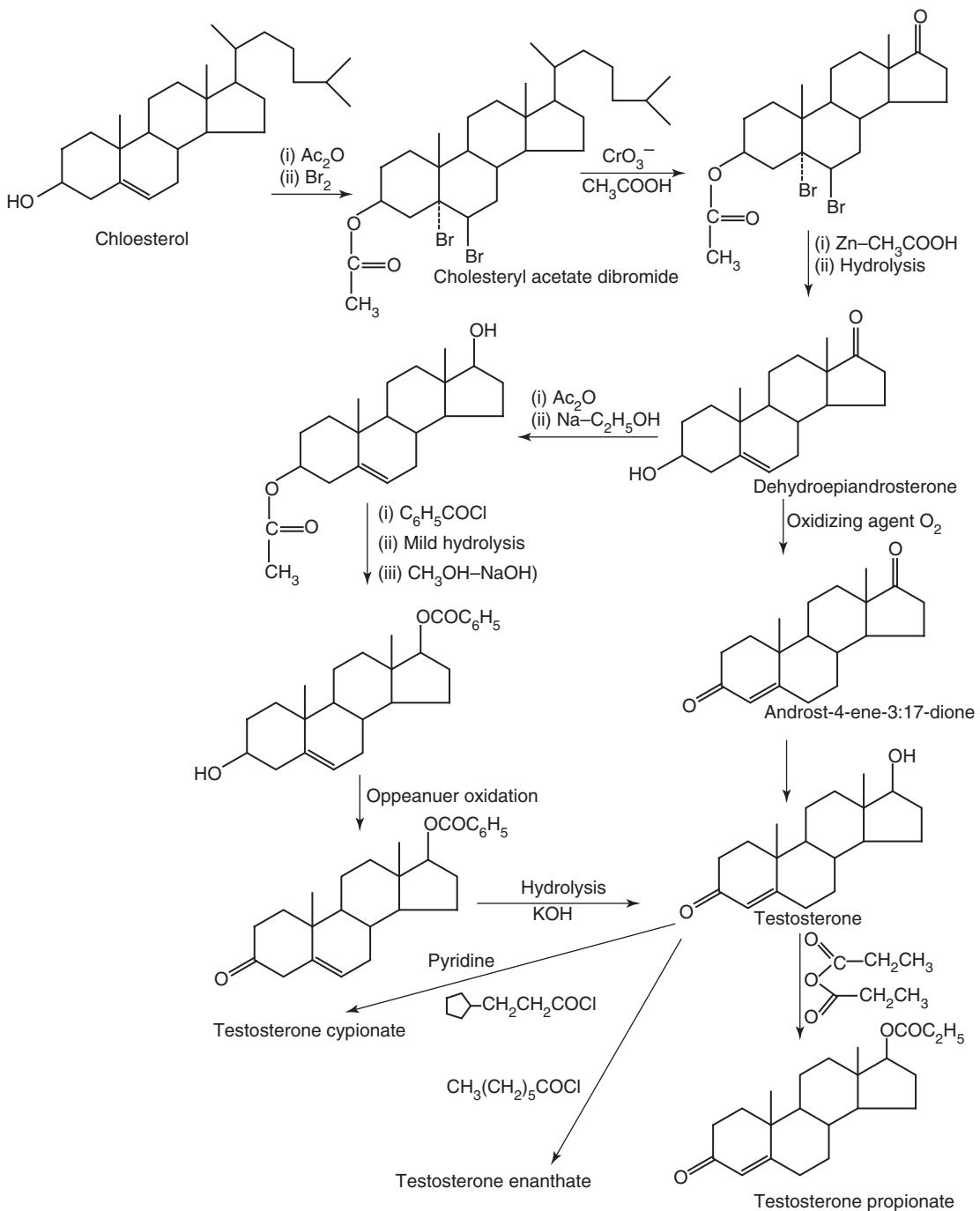


Properties and uses: It is a creamy white crystalline powder, insoluble in water, and soluble in alcohol. It may be used for palliative treatment of breast carcinoma in postmenopausal women.

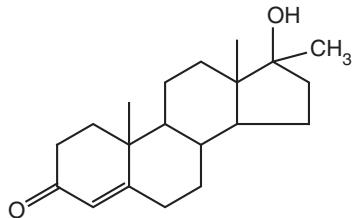
Assay: Dilute the sample in alcohol to 50 ml with ethyl alcohol. Measure the absorption at 241 nm.

Dose: The dose for prolonged treatment subcutaneously is 600 mg. For breast cancer, the dose is up to 1.5 g; alternatively, 10 to 30 mg per day through buccal administration.

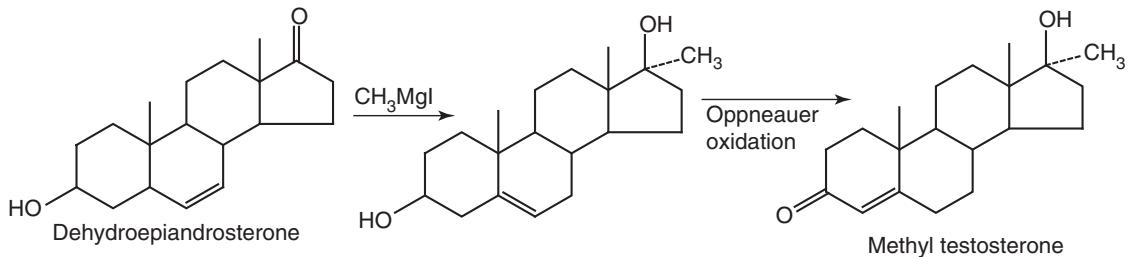
Synthesis



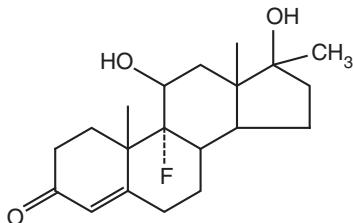
ii. Methyl testosterone



Synthesis



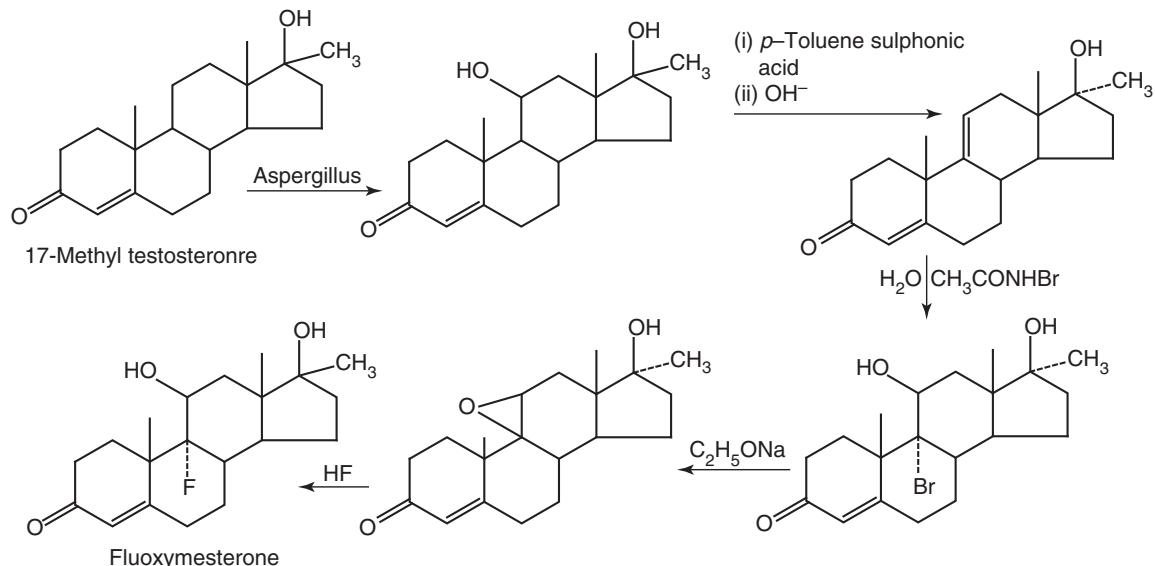
iii. Fluoxymesterone (Halotestin)



Properties: It exists as a white crystalline powder and insoluble in water. It is used in the treatment of postmenopausal osteoporosis in combination with an estrogen.

Dose: The dose orally for adults in the replacement therapy is 1–3 mg twice a day.

Synthesis



PROBABLE QUESTIONS

- What are steroids? Provide the nomenclature and stereochemistry of steroids.
- Classify steroids with suitable examples and mention their therapeutic uses.
- Write a brief account of the androgens. How will you synthesize testosterone from the following:
(a) Cholesterol (b) Dehydroepiandrosterone
- Describe the synthesis of cortisone and hydrocortisone
- Name the steroids used as contraceptives, draw their chemical structure, and write the synthesis of anyone of them.
- Write a brief note on progesterone derivatives
- Give the names and official status of at least five derivatives of the following, which are used in medicine.
(a) Testosterone (b) Estradiol

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Chapter 3

Antithyroid Drugs

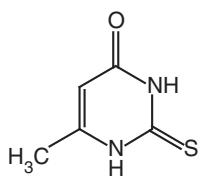
INTRODUCTION

Antithyroid drugs are compounds that act within the thyroid gland to inhibit the biosynthesis of the thyroid hormones. Excessive amount of thyroid hormones in the circulation are associated with a number of diseased states, including Grave's disease, toxic adenoma, goitre, and thyroiditis among others.

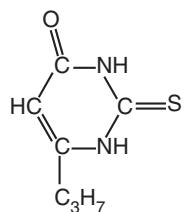
CLASSIFICATION

Antithyroid drugs are classified as follows:

- I. Thioureylenes
- i. Thiouracil derivatives

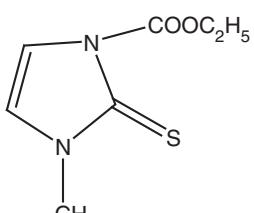


Methylthiouracil

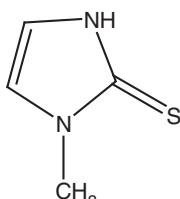


Propylthiouracil

- ii. Imidazoles

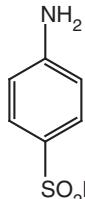


Carbimazole

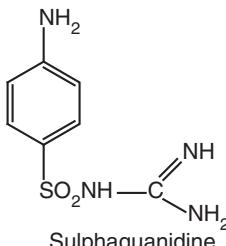


Methimazole

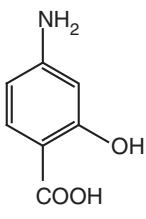
iii. Aniline derivatives



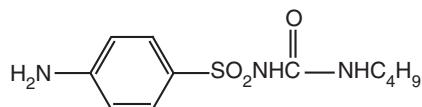
Sulphanilamide



Sulphaguanidine



p-Aminosalicylic acid

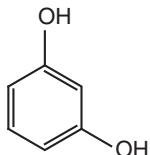


Carbutamide

Mode of action: These agents interfere with some of the process catalyzed by thyroid peroxidase, such as iodide oxidation, organification, and coupling of iodotyrosines.

II. Polyhydric phenols

i. Resorcinol



Mode of action: The only clinical agent from this category is resorcinol. It possesses same mechanism of action similar to that of thioamides.

III. Ionic inhibitors

- (a) Potassium perchlorate
- (b) Thiocyanate

Mode of action: These anions resemble iodide ions and affect the power of thyroid gland to accumulate iodine.

IV. Miscellaneous agents

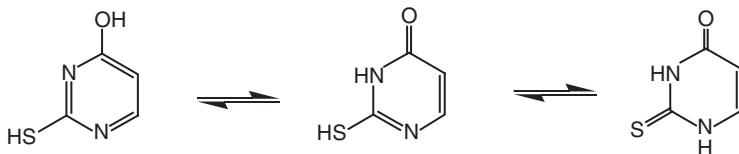
- (a) Lithium carbonate and
- (b) Adrenergic blockers

SYNTHESIS AND DRUG PROFILE

I. Thioureylenes

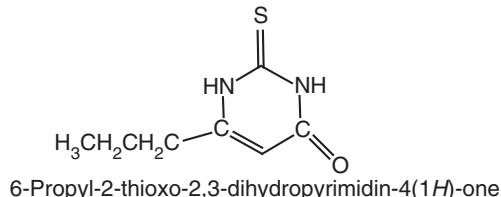
Mode of action: Thiourea and thiouracil derivatives are among the primary drugs to treat thyroid hyperactivity. Methyl and propylthiouracil derivatives are effective drugs in the treatment of thyroid-related problems. They prevent iodine incorporation into the organic form perhaps by antagonizing the iodide oxidation by peroxidase. They are also found to prevent coupling of iodotyrosines to form iodothyronines.

The 2-thiouracil derivatives, that is, 4-keto-2-thio pyrimidines, are undoubtedly tautomeric compounds and can be represented as follows:

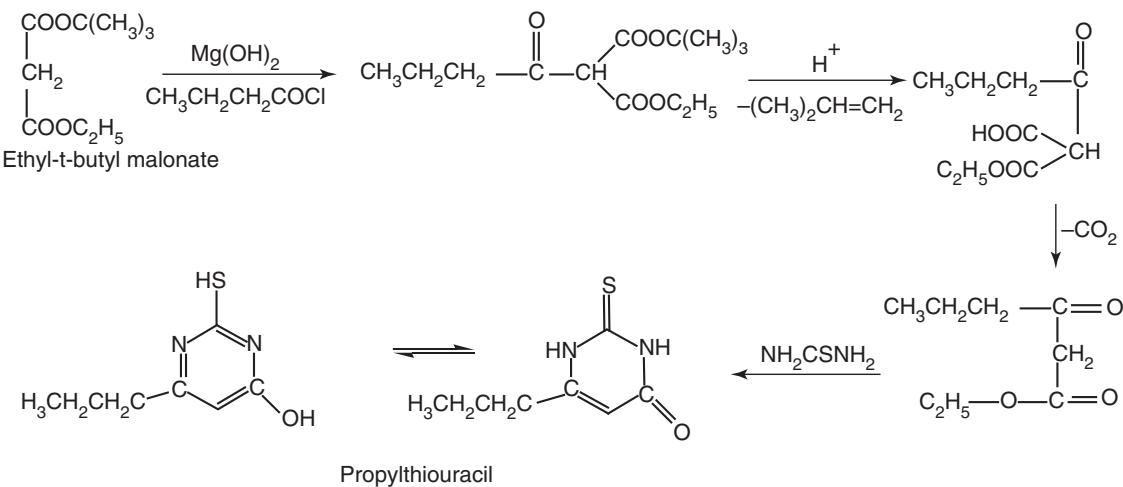


Some 300-related structures have been evaluated for antithyroid activity, but, of these, only the 6-allyl-2-thio uracil and closely related structure possess useful clinical activity. The most serious adverse effect of thiouracil therapy is agranulocytosis.

i. Propylthiouracil (Tietil)



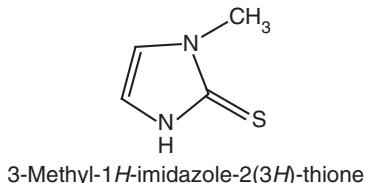
Synthesis



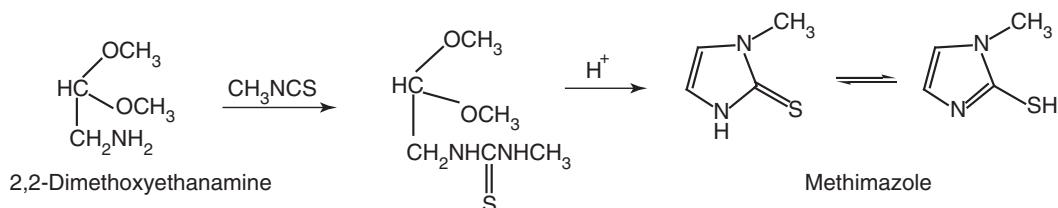
Properties and uses: It is a white powdery crystalline substance with bitter taste, soluble in water, alcohol, chloroform, and ether. Used in the management of hyperthyroidism.

Dose: For hyperthyroidism, the dose for adults initially is 200–300 mg per day in divided doses. When the patient attains normal basal metabolic rate (euthyroidism), the dose is usually reduced to a maintenance dose of 50–75 mg per day in two to three divided doses. In children, over 10 years old, initial dose is 150–300 mg per day in four divided doses until the child becomes euthyroid, then, usually, 100 mg daily is given in two divided doses, for maintenance.

ii. Methimazole (Tapazole)



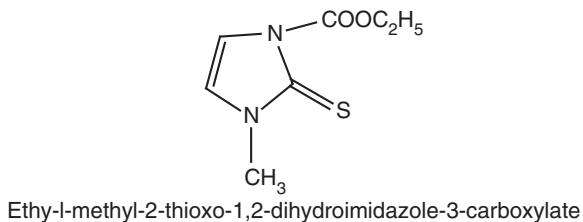
Synthesis



Properties and uses: It exists as white to pale-buff colour solid with characteristic odour and soluble in water. The drug is more potent, more prompt, and has more prolonged action than propylthiouracil. It is indicated in the treatment of hyperthyroidism.

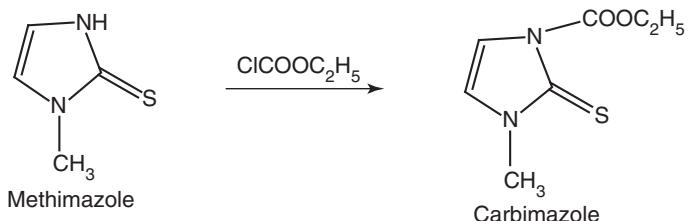
Dose: Usual initial dose is 5–20 mg every 8 h. When condition is stabilized (1–2 months), the dose is reduced to a maintenance dose of 5–15 mg per day. For children, the initial dose is 400 µg/kg body weight per day in divided doses.

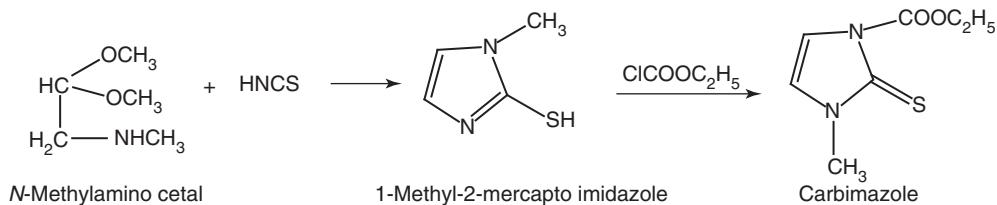
iii. Carbimazole



Synthesis

Route I: From: Methimazole



Route II. From: *N*-methylamino acetal**PROBABLE QUESTIONS**

1. Define and classify antithyroid agents and write the synthesis and uses of any two of them.
2. Write the synthesis and uses of methylthiouracil and propylthiouracil.

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SECTION VI

CHEMOTHERAPY

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Chapter 1

History and Development of Chemotherapy

INTRODUCTION

Chemotherapy is the treatment of systemic disease or infection with appropriate drugs, which are capable to produce retardation in multiplication of microorganism or to suppress their growth without affecting the host system. The word chemotherapy is applicable for the treatment of infection due to viral, bacterial, fungal, and protozoal infections. Antibiotics are substances produced by microorganisms, which selectively suppress the growth and proliferation or kill other microorganisms at very low concentration. As the analogues of the antibiotic products are produced semisynthetically they are also called as chemotherapeutic agents.

HISTORICAL BACKGROUND

There are three phases to explain the history of chemotherapy, such as empirical period, Ehrlich's phase, and the modern phase. In early empirical period of 16th century, Paracelsus used mercury for the treatment of syphilis and during 17th century cinchona bark was used for pyrexia. In 500 to 600 BC, molded curd of soybean was used in Chinese folk medicine for infection and wounds. In early period, during these phases, Hindus used chaulmoogra oil for the treatment of leprosy. In Ehrlich's phase, it was revealed that certain dyes produced toxicity and killed some microorganisms. So neoarsphenamine was developed by Ehrlich for the treatment of syphilis. The word antibiosis was coined after the killing of anthrax bacilli when grown in culture media with other bacteria during the 18th century. The modern phases demonstrated the therapeutic effect of prontosil (a sulphonamide) in pyrogenic infections in 19th century.

In 1929, Sir Alexander Fleming accidentally discovered the antibacterial properties of penicillin by destroying the *staphylococcus* in culture plate; this is broadly cited in modern antibiotic era. Chain and Florey followed up this observation in 1939 and later penicillin was clinically used during 1941. In 1942, Waksman proposed the search of *actinomycetes* and discovered streptomycin in 1944. Later, the advance in medicinal chemistry produced synthetic and semisynthetic agents.

SPECTRUM OF ACTIVITY OF CHEMOTHERAPEUTIC AGENTS

The ability of drug with all ranges (gram positive and gram negative) of antibiotic action, chloramphenicol, and tetracycline, to antagonize numerous pathogens have resulted mention as broad-spectrum antibiotics. Many of the broad-spectrum antibiotics are active only at high concentration. Some drugs are primarily static and they may exert cidal action at high concentration (e.g. sulphonamides, erythromycin, nitrofurantoin, etc). The bacteriostatic agents are those that interfere with the growth or replication of microorganisms, but does not kill it. The bactericidal drugs are those that kills the microorganisms. Concentration of drugs at the site of infection is an important factor for the therapeutic effect in case of antimicrobials. The classes of antibiotics and their spectrum of activity is detailed in Table 1.1.

Table 1.1 Classes of antibiotics and their spectrum of activity.

| Class of Antibiotics | Name of the Drug | Susceptible Organism |
|---------------------------|--------------------|--|
| Natural penicillins | Penicillin G and V | Gram positive bacteria— <i>streptococci</i> except <i>viridians</i> . Gram positive <i>Bacilli</i> , i.e. <i>B. anthracis</i> , <i>Corynebacterium diphtheriae</i> , and all <i>Clostridia</i> |
| Semisynthetic penicillins | Oxacillin | Penicillinase-resistant |
| | Ampicillin | Broad spectrum. It is active against all organisms, which are sensitive to penicillin G and many gram-negative organisms, i.e. <i>Haemophilus influenzae</i> , <i>Escherichia coli</i> , <i>Proteus</i> , <i>Salmonella</i> , and <i>Shigella</i> |
| | Amoxycillin | Broad spectrum antibacterial action with penicillinase inhibitor. It is less active against <i>Shigella</i> and <i>H. influenzae</i> |
| | Aztreonam | <i>Pseudomonas</i> and gram-negative organism |
| Cephalosporins | Cefazolin | It is active against all organisms and sensitive to penicillin, i.e. <i>Streptococci</i> , <i>Gonococci</i> , <i>Meningococci</i> , <i>C. diphtheriae</i> , <i>H. influenzae</i> , <i>Clostridia</i> , and <i>Actinomycetes</i> . Highly active against <i>Klebsiella</i> and <i>E. coli</i> |
| | Cephalothin | Similar in spectrum to Cefazolin, but less active against penicillinase producing <i>Staphylococci</i> and <i>H. influenzae</i> . Parenteral administration produces broad spectrum action |

(Continued)

Table 1.1 (Continued)

| Class of Antibiotics | Name of the Drug | Susceptible Organism |
|---------------------------------|---|--|
| Glycopeptide antibiotics | Cefotaxime | Potent action against aerobic gram negative and some gram positive, not active against anaerobes; <i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i> |
| | Bacitracin | Gram-positive organisms of both <i>cocci</i> and <i>bacilli</i> |
| | Vancomycin | Gram-positive bacteria. It is useful in case of methicillin resistant <i>Staphylococcus aureus</i> , <i>Streptococcus viridans</i> , and <i>Enterococcus</i> |
| Antimycobacterial antibiotics | Polymyxin | Gram negative, including <i>Pseudomonas</i> species |
| | Isoniazid, Ethambutol | <i>Mycobacterium</i> species |
| Inhibitors of protein synthesis | Chloramphenicol | Broad spectrum |
| Aminoglycosides | Streptomycin | Broad spectrum, including <i>Mycobacterium</i> species. Primarily active against aerobic gram-negative bacilli. |
| | Neomycin | Broad spectrum activity |
| | Gentamycin | Broad spectrum, including <i>Pseudomonas</i> species. Ineffective against <i>Mycobacterium tuberculosis</i> , <i>Streptococcus pyogens</i> , and <i>Pneumoniae</i> |
| Tetracyclines | Tetracycline, oxytetracycline, doxycycline, minocycline, and clortetracycline | All types of pathogens except virus and fungi. Broad spectrum including chlamydia, spirochetes, and rickettsia. <i>Mycoplasma</i> and <i>Actinomyces</i> are moderately sensitive. |
| Macrolides | Erythromycin | Gram-positive bacteria, highly active against <i>Str. pyogens</i> , <i>Neisseria gonorrhoeae</i> , <i>Clostridia</i> , <i>C. diphtheriae</i> , and <i>Listeria</i> |

(Continued)

Table 1.1 (Continued)

| Class of Antibiotics | Name of the Drug | Susceptible Organism |
|--|---|--|
| | Clarithromycin | Similar to erythromycin, in addition <i>M. avium</i> complex. More active against gram-positive cocci, <i>Moraxella</i> , <i>Legionella</i> , <i>Mycoplasma pneumoniae</i> , and <i>H. pylori</i> |
| | Azithromycin | Less effective in gram-positive cocci. Highly active against respiratory pathogens, i.e. <i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Moraxella</i> , <i>Pneumoniae</i> , and <i>Legionella</i> |
| Streptogramins | Quinupristin and dalfopristin | Vancomycin resistant, methicillin resistant gram-positive bacteria |
| Oxazolidindione | Linezolid | It is active against methicillin resistant <i>Staphylococcus aureus</i> . Cidal to <i>Streptococci</i> , <i>Pneumococci</i> , and <i>Bacteroides fragilis</i> |
| Quinolones and fluoroquinolones | Nalidixic acid, gatifloxacin, pefloxacin, norfloxacin, ciprofloxacin, etc | Most susceptible are gram negative <i>bacilli</i> . At high concentration gram positive bacteria highly susceptible bacteria are <i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter</i> , <i>Salmonella typhi</i> , <i>Shigella proteus</i> , <i>Campylobacter jejuni</i> , <i>Vibrio cholerae</i> , <i>Pseudomonas aeruginosa</i> , <i>Brucella</i> , <i>Listeria</i> , and <i>B. anthracis</i> are little susceptible |
| Sulphonamides | Cotrimoxazole and other sulpha drugs | Broad spectrum. Primarily bacteriostatic |
| Nucleoside and nonnucleoside analogues | Acyclovir, Ganciclovir, ribavirin, lamivudine | Herpes virus |
| | Cidofovir | Cytomegalovirus |
| Tricyclic amines | Amantidine, Rimantidine | Influenza virus |
| 8-Hydroxy quinolones | Quinidochlor | Malarial parasites |

(Continued)

Table 1.1 (Continued)

| Class of Antibiotics | Susceptible Organism | Susceptible Organism |
|-------------------------|--|--|
| Nitrimidazoles | Metronidazole and tinidazole | Broad spectrum action against protozoa, trichomoniasis, and Giardiasis infections |
| Benzimidazole | Albendazole, mebendazole | <i>Enterobias, Trichuris</i> infestations |
| Polyenes | Amphotericin B | Systemic fungal infection, active against wide range of yeasts and fungi, i.e. <i>Candida albicans, Histoplasma capsulatum, Blastomyces dermatitidis, Cryptococcus neoformans, Aspergillus, sporothrix, and Torulopsis</i> |
| Azole derivatives | Ketaconazole, clotrimaxazole, miconazole | Systemic fungal infection, Topical infection. Imidazole and triazole has broad spectrum antifungal action covering dermatophytes, <i>Candida, nocardia</i> , some gram positive and anaerobic bacteria, i.e. <i>Staphylococcus aureus, Bacillus fragilis, and leishmania</i> |
| Allylamines | Terbinafine, Naftidine | Resistant organisms for azoles |
| Heterocyclic benzofuran | Griseofulvin | Most dermatophytes of skin fungal infection but not against <i>Candida</i> |

Bacterial Resistance to Antimicrobial Agents

The bacterial resistance development depends on three factors. They are as follows:

- The necessary dose or concentration not reached to target.
- The chemotherapeutic agent is not active.
- The target is altered.

The outer membrane of the gram-negative bacteria is a permeability barrier that excludes large polar molecules, including antibiotic, through a protein called porins. Loss of porin channel may prevent the entry of antibiotics and reduces the concentration in target site. If there is an active transport mechanism for the entry of drug into the cell, mutational changes will occur in the transport to produce resistant. For example, passage of gentamycin across the microbial cell membrane by concentration gradient by involving the respiratory electron transport and oxidative phosphorylation. Mutation in this enzyme pathway decreases the concentration to the target.

Inactivation of drugs are seen in case of aminoglycoside and β -lactums. In aminoglycosides, the acquisition of cell membrane bound inactivating enzymes which phosphorylates/adenylates or acetylates the drug molecule and produces conjugated aminoglycosides. These conjugated amino glycosides do not bind to target ribosome and so are incapable of enhancing active transport. Nosocomial microbes have rich plasmids producing multidrug resistance and cross resistance.

In fluroquinolone, the resistance is occurred by alteration of target. The resistance is noted due to chromosomal mutations producing a DNA gyrase or topoisomerase IV with reduced affinity to the fluroquinolone or due to reduced permeability of the drug.

Selection of Antimicrobial Agents

The selection is based on thorough knowledge of pharmacological and microbiological factors. Antibiotics are used in three general ways such as empirical therapy, definitive therapy, and prophylactic therapy. When used in empirical, the drug intended should cover all the microorganisms, if the pathogen is exactly not known. In the *combination therapy*, treatment with a broad spectrum antibiotic is necessary. After the identification of infecting microorganism, selective drug can be used.

COMBINATION THERAPY

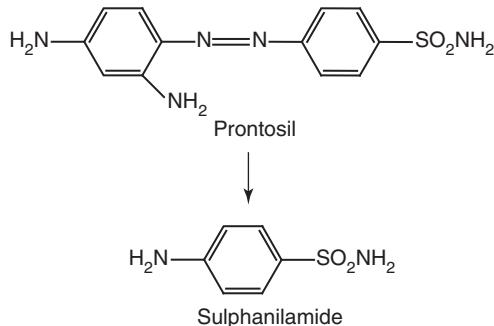
It is the combined use of drugs intended to achieve better action; in chemotherapy it is used for the synergistic action (e.g. a sulphonamide used with trimethoprim to produce additive action). Other examples are in the combination of β -lactamase inhibition by clavulanic acid or sulbactum with amoxycillin or ampicillin for β -lacamase producing *H. influenza*, *Neisseria gonorrhoeae*, and other organisms.. Combination of bactericidal with a bacteriostatic drug produces synergistic action. The combination therapy of antimicrobials are also used in the treatment of mixed infection and initial treatment of severe infections.

Chapter 2

Antibacterial Sulphonamides

INTRODUCTION

The term sulphonamides are employed as a generic name for the derivatives of para amino benzene sulphonamide (sulphanilamide). The sulphonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and treatment of bacterial infections in humans. The sulphonamides are bacteriostatic antibiotics with a wide spectrum action against most gram-positive bacteria and many gram-negative organisms. Actually it was found to be the metabolic product of Prontosil, which is responsible for antibacterial activity, and this has given the initiation to develop sulphonamides as anti-bacterial agents.



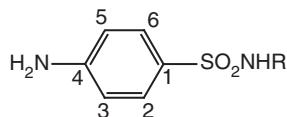
Sulphonamides are total synthetic substances that are produced by relatively simple chemical synthesis. The advent of penicillin and, subsequently of other antibiotics has diminished the usefulness of sulphonamides. Antimicrobial compounds contain sulphonamide (SO_2NH_2) group. This group (SO_2NH_2) is also present in other compounds, such as antidiabetic agents (e.g. Tolbutamide), diuretics (e.g. chlorthiazide and its congeners, furosemide, and acetazolamide), and anticonvulsants such as sulthiame. The sulphonamides exists as white powder, mildly acidic in character, and they form water-soluble salts with bases. The pH of sodium salts with some exception, for example, sodium sulphacetamide, is very high when given intramuscular (IM), the marked alkalinity causes damage to the tissues.

Microorganisms that may be susceptible *in vitro* to sulphonamides include *Streptococcus pyogens*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *H. ducreyi*, *Nocardia*, *Actinomyces*, *Calymmatobacterium*

granulomatis, and *Chlamydia trachomatis*. The minimal inhibitory concentration ranges from 0.1 µg/ml for *C. trachomatis* to 4–64 µg/ml for *E. coli*. Sulphonamides are selective drugs used to treat urinary tract infections, bacterial respiratory infections, and gastrointestinal (GI) infections.

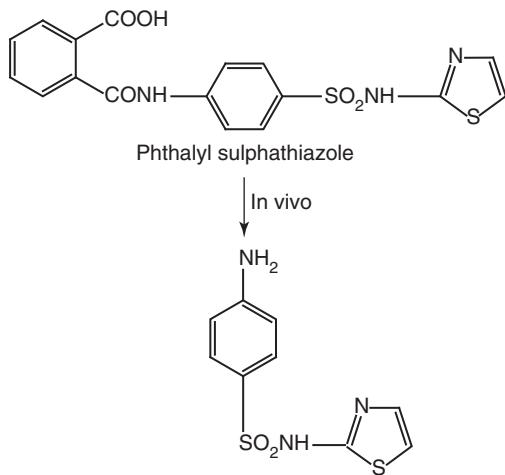
Mode of action: Sulphonamides are structure analogues and competitive antagonists of para-amino benzoic acid (PABA). They inhibit dihydropteroate synthetase, the bacterial enzyme responsible for the incorporation of PABA into dihydropteroic acid, and it is the intermediate precursor of folic acid. Synergistic effect is obtained by a combination of trimethoprim. The compound trimethoprim is a potent and selective inhibitor of microbial dihydrofolate reductase, the enzyme that reduces dihydrofolate to tetrahydrofolate. The simultaneous administration of sulphonamide and trimethoprim blocks the pathway of cell-wall synthesis sequentially.

SAR of Sulphonamides



The major features of SAR of sulphonamides include the following:

- Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity.
- The amino- and sulphonyl-groups on the benzene ring are essential and should be in 1 and 4 position.
- The N-4 amino group could be modified to be prodrugs, which are converted to free amino function in vivo.



- Sulphur atom should be directly linked to the benzene ring.
- Replacement of benzene ring by other ring systems or the introduction of additional substituents on it decreases or abolishes its activity.
- Exchange of the -SO2NH group by -CONH reduces the activity.

- On N-1-substituted sulphonamides, activity varies with the nature of the substituent at the amino group. With substituents imparting electron-rich characters to SO_2 group, bacteriostatic activity increases.
- Heterocyclic substituents lead to highly potent derivatives, while sulphonamides, which contain a single benzene ring at N-1 position, are considerably more toxic than heterocyclic ring analogues.
- The free aromatic amino groups should reside *para* to the sulphonamide group. Its replacement at *ortho* or *meta* position results in compounds devoid of antibacterial activity.
- The active form of sulphonamide is the ionized, maximum activity that is observed between the pKa values 6.6–7.4.
- Substitutions in the benzene ring of sulphonamides produced inactive compounds.
- Substitution of free sulphonic acid ($-\text{SO}_3\text{H}$) group for sulphonamido function destroys the activity, but replacement by a sulphinic acid group ($-\text{SO}_2\text{H}$) and acetylation of N-4 position retains back the activity.
- *m.* Sulphonamides bind to the basic centres of arginine, histidine, and lysine sites of proteins. The binding groups are alkyl, alkoxy, and halides. The binding affects the activity of sulphonamides; protein binding appears to modulate the availability of the drug and its half-life.
- The lipid solubility influences the pharmacokinetic and antibacterial activity, and so increases the half-life and antibacterial activity *in vitro*.

CLASSIFICATION

Sulphonamides can be classified in various ways:

On the basis of the site of action

- Sulphonamides for general infection: Sulphanilamide, Sulphapyridine, Sulphadiazine, Sulphamethoxacine, Sulphamethoxazole.
- Sulphonamides for urinary tract infections: Sulphaisoxazole, Sulphathiazole.
- Sulphonamides for intestinal infections: Phthalylsulphathiazole, Succinyl sulphathiazole, Sulphasalazine.
- Sulphonamides for local infections: Sulpahacetamide, Mafenamide, Silver sulphadiazine.
- Sulphonamides for dermatitis: Dapsone, Solapsone.
- Sulphonamides in combination: Trimethoprim with Sulphamethoxazole.

On the basis of the pharmacokinetic properties

- Poorly absorbed sulphonamides (locally acting sulphonamides)—Sulphasalazine, Phthalylsulphathiazole, Sulphaguanidine, Salicylazo sulphapyridine, Succinyl sulpha thiazole.
- Rapidly absorbed and rapidly excreted (systemic sulphanamides): Sulphamethoxazole, Sulphaisoxazole, Sulphadiazine, Sulphadimidine, Sulphafurazole, Sulphasomidine, Sulphamethiazole, Sulphacetamide Sulphachlorpyridazine.
- Topically used sulphonamides: Sulphacetamide, Mafenide, Sulphathiazole, Silver sulphadiazine.

On the basis of the pharmacological activity

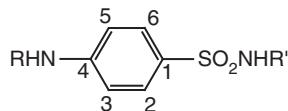
- Antibacterial agents: Sulphadiazine, Sulfisoxazole.
- Drugs used in dermatitis: Dapsone.

On the basis of the duration of action

- Extra long-acting sulphonamides (half-life greater than 50 h): Sulphasalazine, Sulphaclomide, Sulphalene.
- Long-acting sulphonamides (half-life greater than 24 h): Sulphadoxine, Sulphadimethoxine, Sulphamethoxy pyridazine, Sulphamethoxydiazine, Sulphaphenazole, Sulphamethoxine.
- Intermediate-acting sulphonamides (half-life between 10–24 h): Sulphasomizole, Sulphamethoxazole.
- Short-acting sulphonamides (half-life less than 20 h): Sulphamethiazole, sulphaisoxazole.
- Injectables (soluble sulpha drugs): Sulphafurazole, Sulphadiazine, Sulphamethoxine.

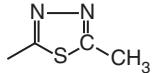
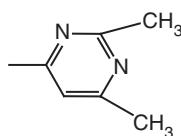
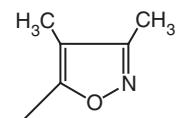
On the basis of the chemical structure

- N-substituted sulphonamide: Sulphadiazine, Sulphacetamide, Sulphadimidine.
- N-4 substituted sulphonamides (prodrugs): Prontosil.
- Both N-1 and N-4 substituted sulphonamides: Succinyl sulphathiazole, Phthalylsulphathiazole.
- Miscellaneous: Mefenide sodium.

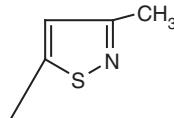
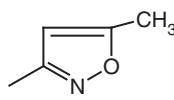
**I. N-1 Substituted sulphonamides**

| Name | R | R ¹ |
|----------------|----|--------------------|
| Sulphanilamide | -H | -H |
| Sulphapyridine | -H | |
| Sulphathiazole | -H | |
| Sulphacetamide | -H | -COCH ₃ |
| Sulphadiazine | -H | |
| Sulphadimidine | -H | |

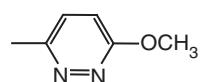
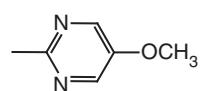
a. Short-acting sulpha drugs

| Name | R | R ¹ |
|-----------------|----|--|
| Sulphamethizole | -H |  |
| Sulphasomidine | -H |  |
| Sulphaisoxazole | -H |  |

b. Intermediate-acting sulphonamides

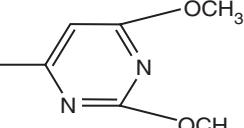
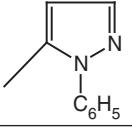
| Name | R | R ¹ |
|-------------------|----|--|
| Sulphasomizole | -H |  |
| Sulphamethoxazole | -H |  |

c. Long-acting sulphonamides

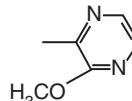
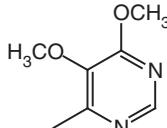
| Name | R | R ¹ |
|--------------------------|----|--|
| Sulphamethoxy pyridazine | -H |  |
| Sulphamethoxy diazine | -H |  |

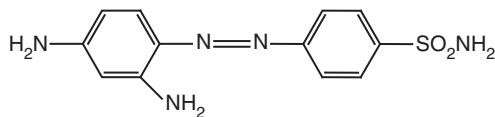
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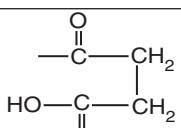
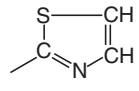
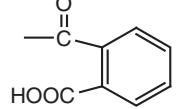
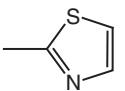
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| Name | R | R ₁ |
|--------------------|----|--|
| Sulpha dimethoxine | -H |  |
| Sulphaphenazole | -H |  |

d. Extra long-acting sulphonamides

| Name | R | R ₁ |
|------------------|----|---|
| Sulphalene | -H |  |
| Sulphormethoxine | -H |  |

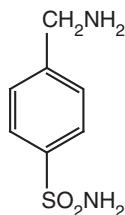
II. N-4 substituted sulphonamides**Prontosil****III. Both N-1 and N-4 substituted sulphonamides**

| Name | R | R ₁ |
|-------------------------|---|--|
| Succinyl sulphathiazole |  |  |
| Phthalysulphathiazole |  |  |

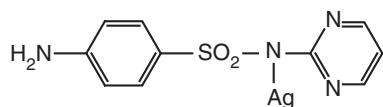
IV. Miscellaneous

a. Topically used sulphonamides

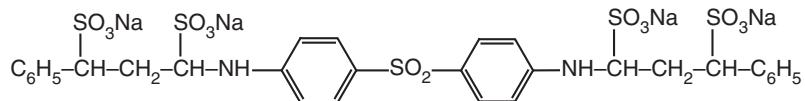
Mafenide



Silver sulphadiazine

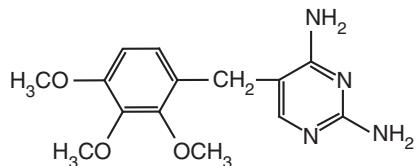


Solapsone



b. Drugs used in combination with sulphonamides

Trimethoprim



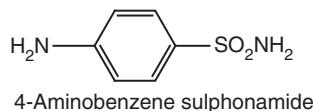
Pyrimethamine



SYNTHESIS AND DRUG PROFILE

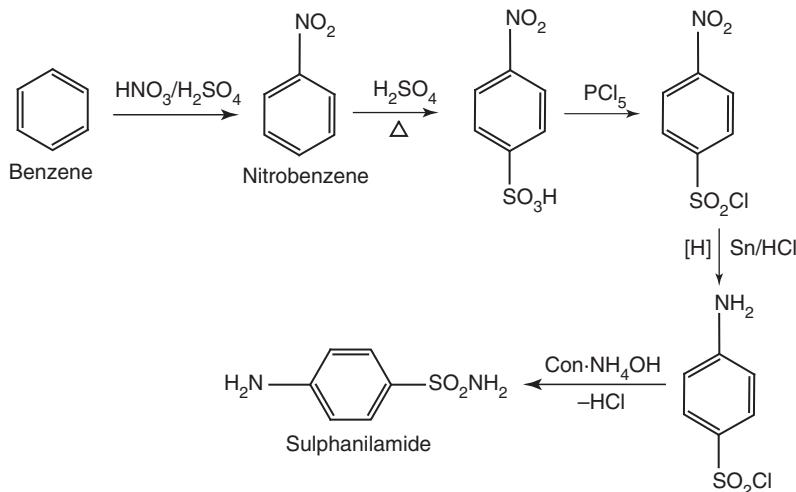
I. N-1 Substituted sulphonamides

i. Sulphanilamide

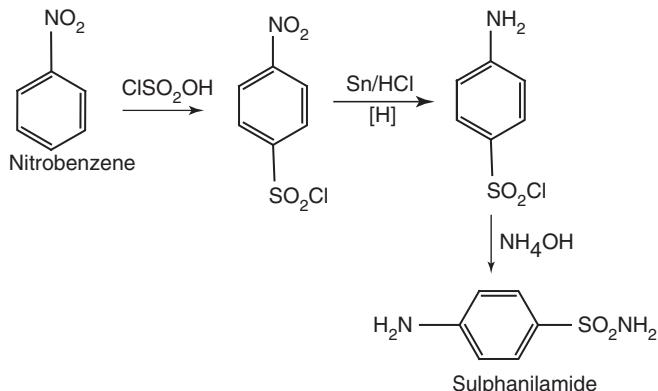


Synthesis

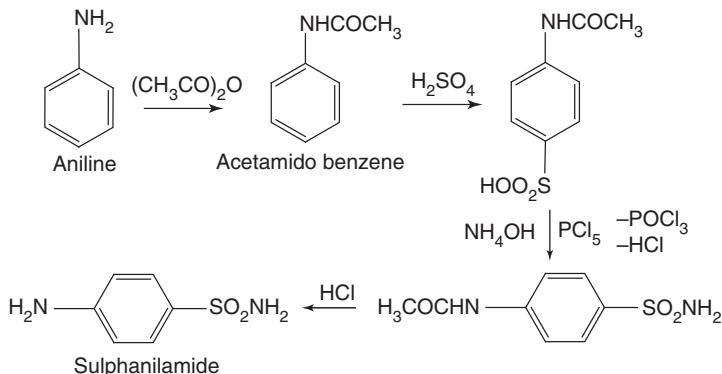
Route-I. From: Benzene



Route-II. From: Nitrobenzene

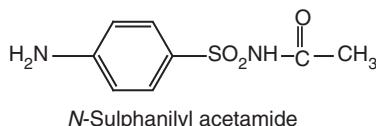


Route-III. From: Aniline

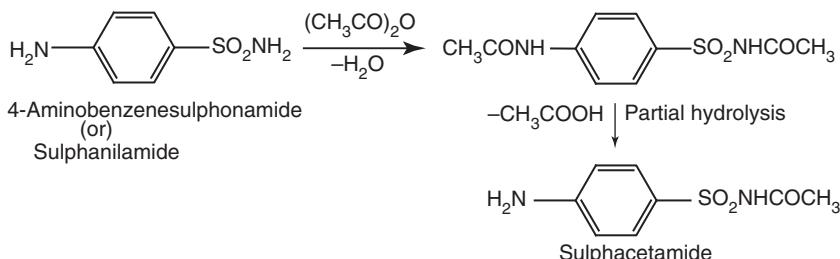


Uses: It is used in veterinary medicine as an antibacterial agent.

ii. Sulphacetamide (Albucid)



Synthesis

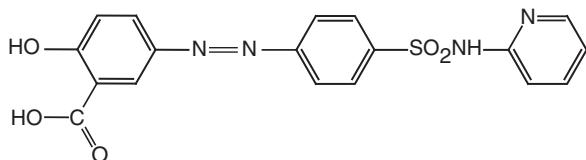


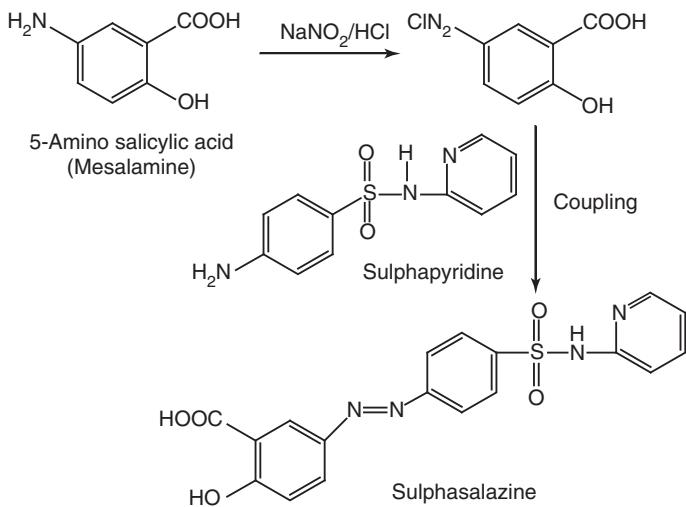
Properties and uses: It exists as white crystalline powder, bitter in taste. Used in the treatment of bacterial infections of urinary tract.

Assay: Dissolve the sample in water and hydrochloric acid. Titrate with sodium nitrite and determine the end point potentiometrically.

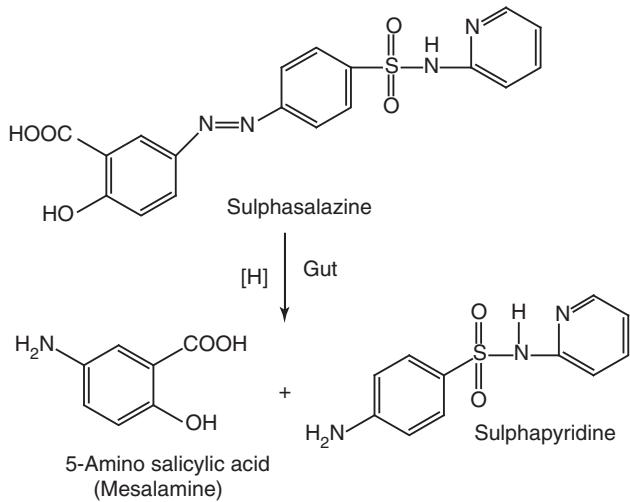
Dose: Dose for eyes, as drops 10%, 15%, 20%, and 30%; in ointments 2.5% and 6% of Sulphacetamide.

iii. Sulphasalazine



Synthesis

Metabolism: It undergoes reductive metabolism by gut bacteria, converting the drug into sulfapyridine and 5-amino salicylic acid, which are active components.

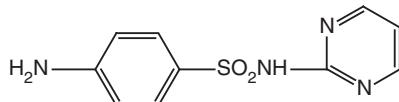


Properties and uses: Sulphasalazine is a bright yellow or brownish-yellow fine powder, very slightly soluble in alcohol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides. It is used in the treatment of ulcerative colitis.

Assay: Dissolve and dilute the sample in 0.1 M sodium hydroxide and add 0.1 M acetic acid and measure the absorbance at the maxima of 359 nm using ultraviolet spectrophotometer.

Dosage forms: Sulphasalazine tablets B.P.

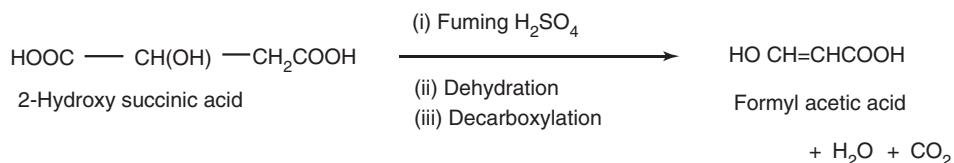
iv. Sulphadiazine



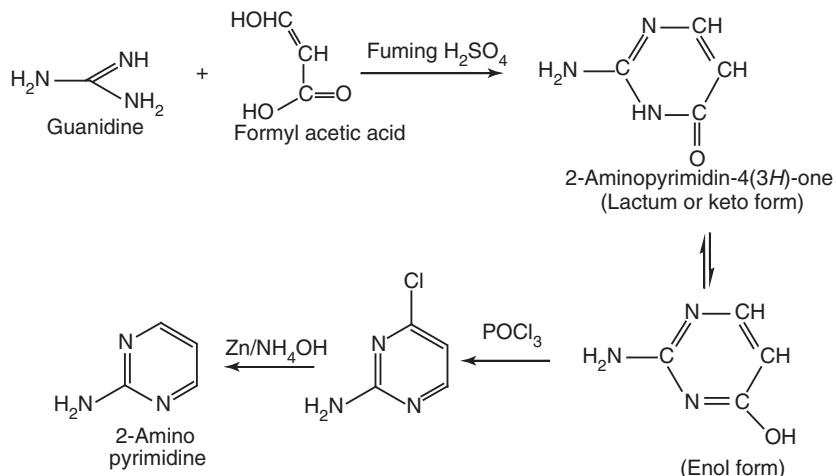
N'-2 Pyrimidinyl sulphanilamide

Synthesis

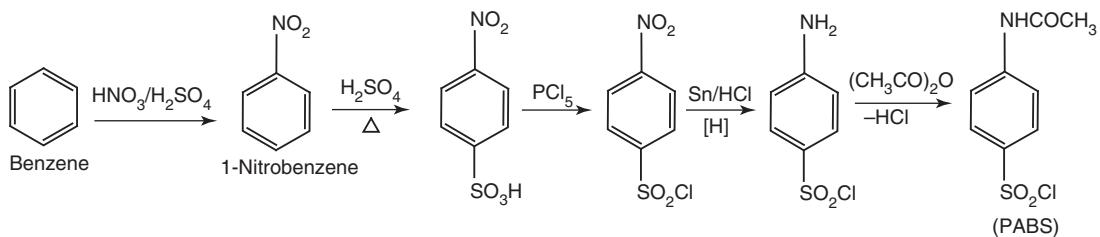
Step-I. Preparation of formyl acetic acid



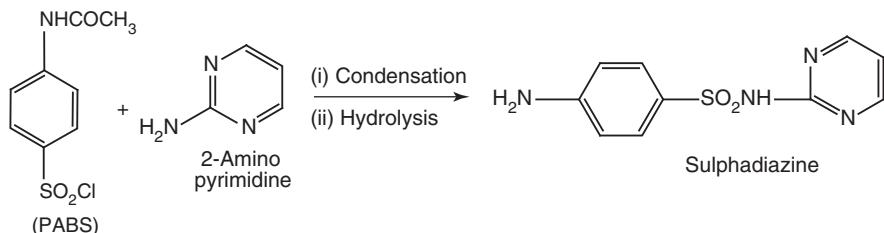
Step II. Synthesis of 2-Aminopyrimidine



Step III. Synthesis of p-acetamido benzene sulphonyl chloride (PABS)



Step IV. Condensation of *p*-acetamido benzene sulphonyl chloride with 2-amino pyrimidine



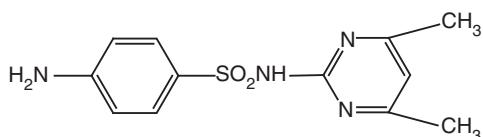
Properties and uses: Sulphadiazine is a white or yellowish-white or pinkish-white crystalline powder or crystals, insoluble in water, slightly soluble in acetone, very slightly soluble in alcohol, and soluble in solutions of alkali hydroxides and in dilute mineral acids. It is used in the treatment of cancerous and rheumatic fever.

Assay: Dissolve the sample in water and hydrochloric acid. Titrate the mixture with sodium nitrite and determine the end point potentiometrically.

Dose: Usual dose is 2–8 g per day

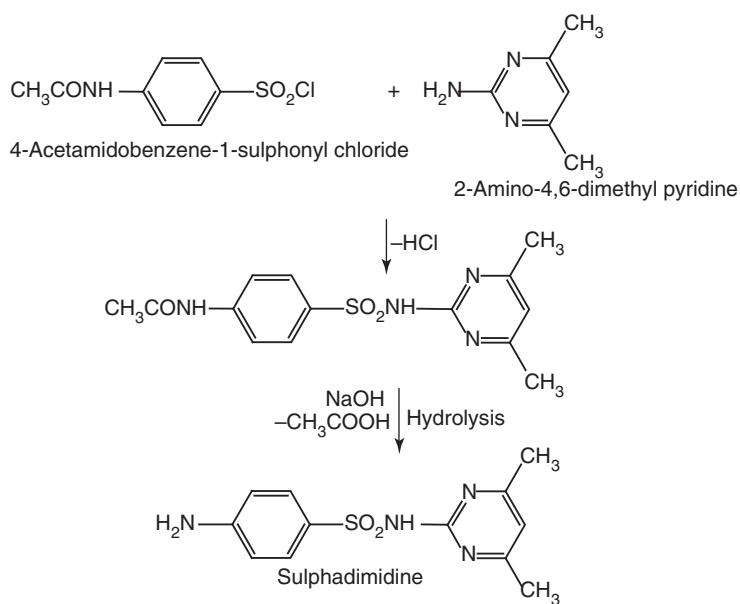
Dosage forms: Sulphadiazine tablets I.P., Sulphadiazine injection B.P.

v. Sulphadimidine



N' (4, 6-Dimethyl-2-pyrimidinyl) Sulphanilamide

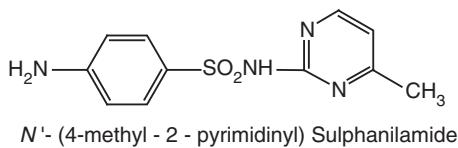
Synthesis



Properties and uses: It exists as white crystalline powder with a bitter taste, insoluble in water, and sparingly soluble in alcohol. It is less effective in meningeal infection because of its poor penetration into the cerebrospinal fluid.

Dose: Dose is 3 g initially and subsequent doses up to 6 g per day in divided doses.

vi. Sulphamerazine (Solumedine)

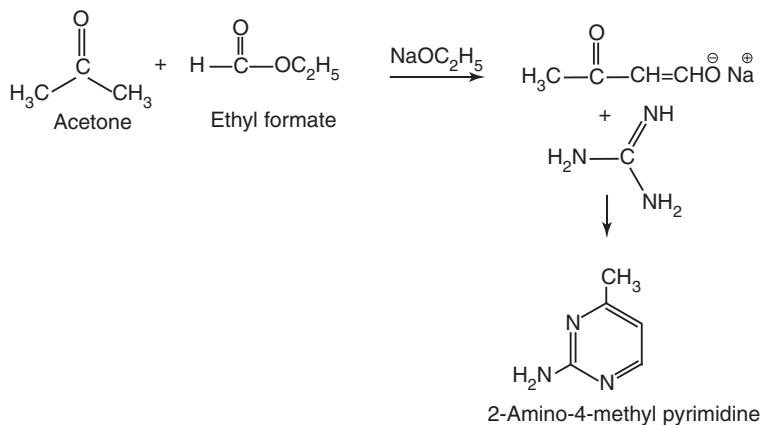


Synthesis

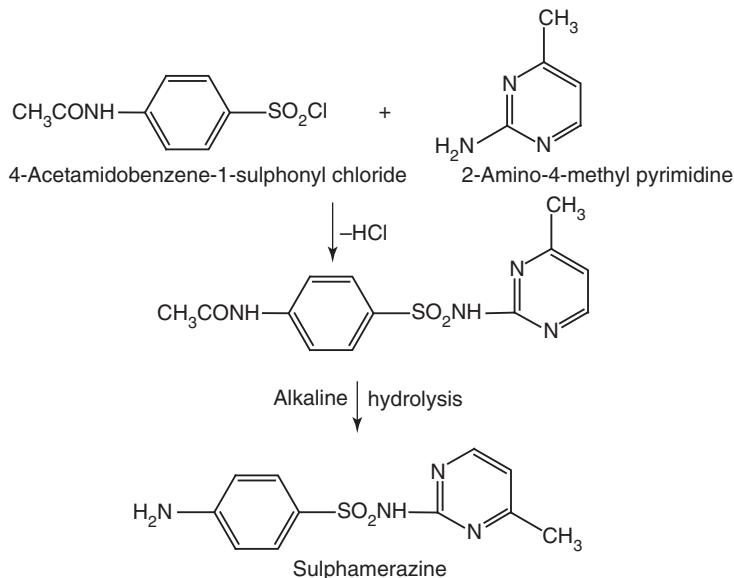
Step I. Preparation of PABS

Synthesized as mentioned under Sulphadiazine

Step II. Preparation of 2-amino-4-methyl pyrimidine



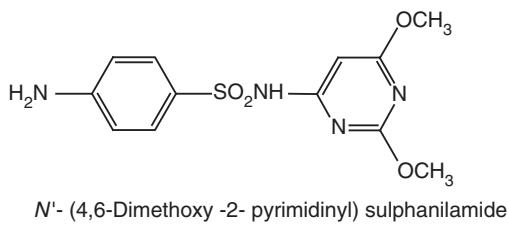
Step III. Condensation of products of *Step I* and *II*



Uses: Used as an antibacterial agent.

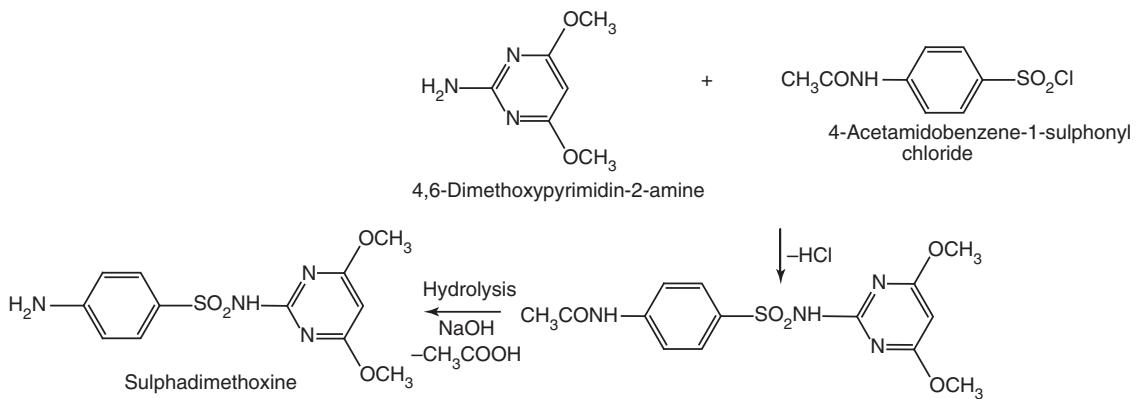
Dose: Dose is 4 g initially, and subsequent dose is 1 g every 6 h

vii. Sulphadimethoxine

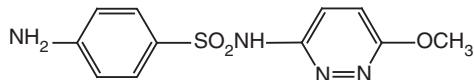


N'-(4,6-Dimethoxy-2-pyrimidinyl) sulphanilamide

Synthesis

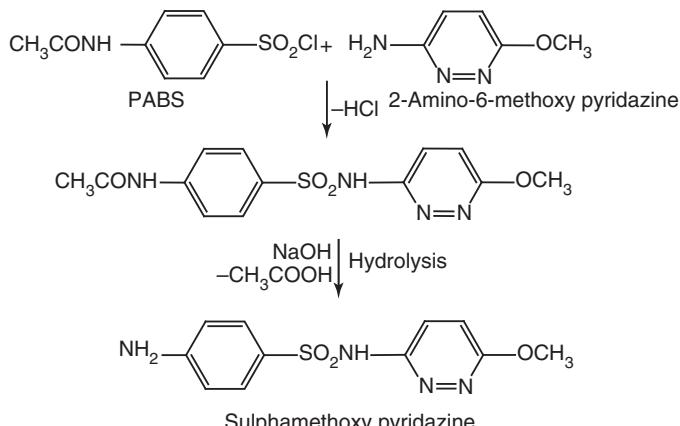


viii. Sulpha methoxy pyridazine

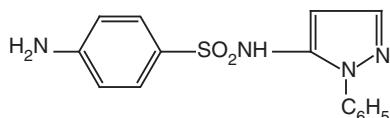


3-(4-Amino benzene sulphonamido)-6-methoxy pyridazine

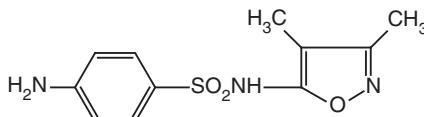
Synthesis



ix. Sulfaphenazole

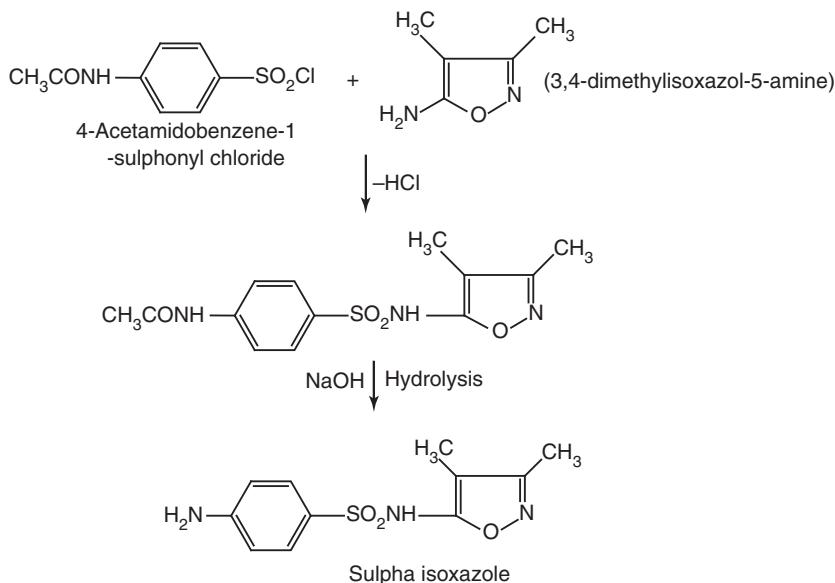


x. Sulpha Isoxazole (Lipo Gantrisin, Gantrisin)



5-(4-Aminobenzene sulphonamido)-3,4-dimethyl isoxazole

Synthesis

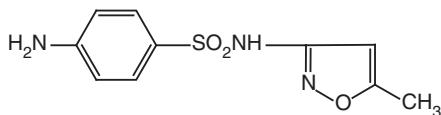


Properties and uses: It exists as white to slightly yellowish crystalline powder and is odourless, soluble in water and in dilute hydrochloric acid. Used in the treatment of urinary tract infections.

Assay: Dissolve the sample in water and hydrochloric acid. Titrate the mixture with sodium nitrite and determine the end point potentiometrically.

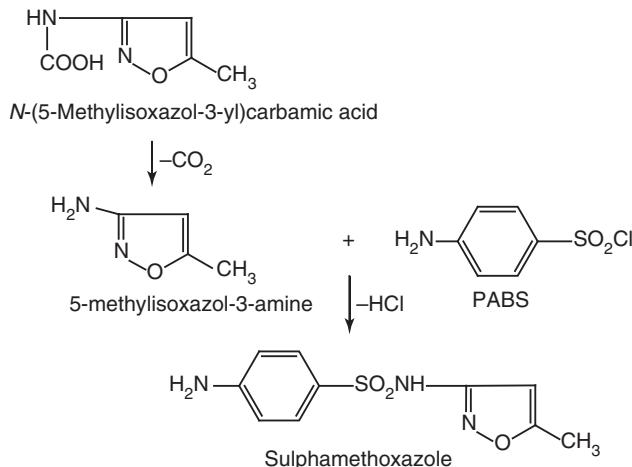
Dose: Initial dose is 2–4 g orally for adults and maintenance dose is 4–8 g per day in divided doses.

xi. Sulphamethoxazole (Gantanol)



3-(4-Amino benzene sulphonamido)-5-methyl isoxazole

Synthesis



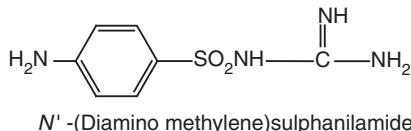
Properties and uses: Sulphamethoxazole is a white or almost white crystalline powder, practically insoluble in water, soluble in acetone, sparingly soluble in ethanol, dissolves in dilute solutions of sodium hydroxide and in dilute acids. Used in the treatment of bacterial infections.

Assay: Dissolve the sample in dilute hydrochloric acid and add potassium bromide. Cool in ice and titrate against 0.1N Sodium nitrate. Determine the end point electrometrically.

Dose: Orally 2 g followed by 1 g every 8 h.

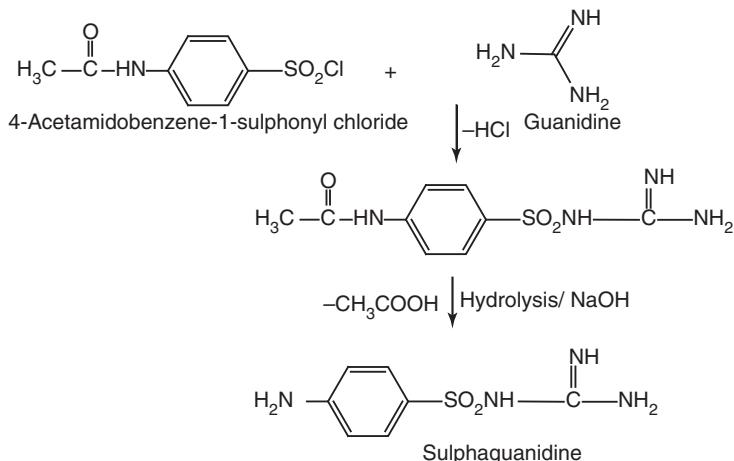
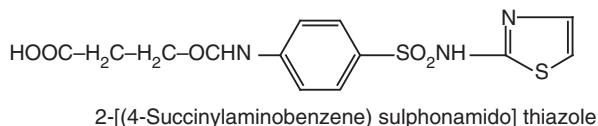
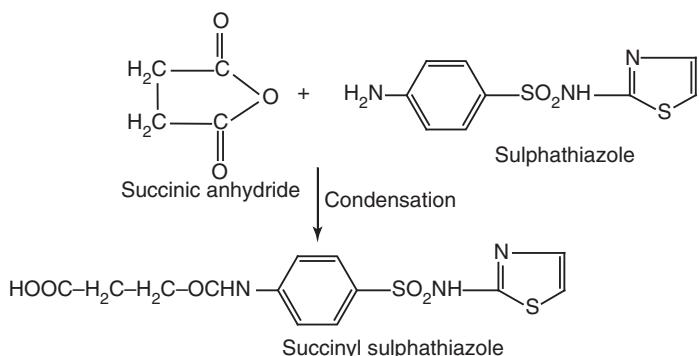
Dosage forms: Co-trimoxazole intravenous infusion B.P., Co-trimoxazole oral suspension B.P., Paediatric co-trimoxazole oral suspension B.P., Co-trimoxazole tablets B.P., Dispersible co-trimoxazole tablets B.P., Paediatric co-trimoxazole tablets B.P.

xii. Sulphaguanidine



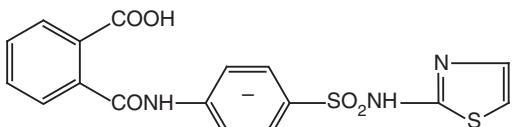
Properties and uses: Sulphaguanidine is a white, fine crystalline powder, soluble in dilute mineral acids, very slightly soluble in water and ethanol, slightly soluble in acetone, but insoluble in methylene chloride. Used in the treatment of local intestinal infections, specifically, bacillary dysentery.

Assay: Dissolve the sample in dilute hydrochloric acid and add potassium bromide. Cool in ice and titrate against 0.1N sodium nitrate. Determine the end point electrometrically.

Synthesis**III. Both N-1 and N-4 substituted sulphonamides****i. Succinyl sulphathiazole****Synthesis**

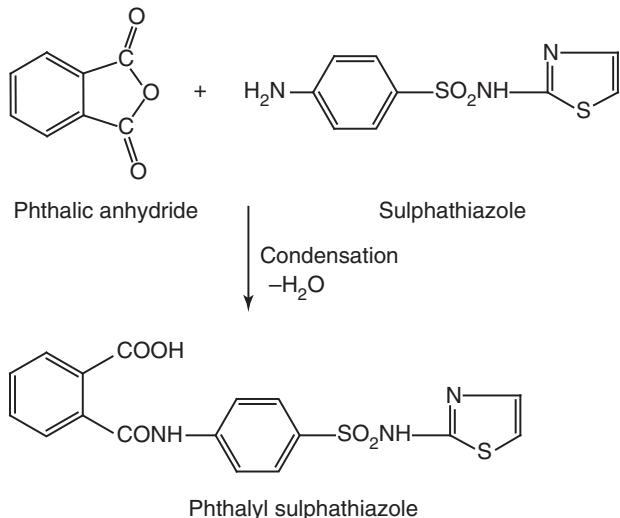
Uses: Used in bacillary dysentery and cholera.

Dose: Dose is 10–20 g per day in divided doses.

ii. Phthalyl Sulphathiazole (Thalazole)

4'-(2-Thiazolyl sulphonamoyl) phthalylamino benzene

Synthesis



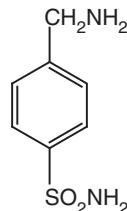
Properties and uses: Slightly soluble in alcohol and ether, but insoluble in water. It is used in the treatment of acute bacillary dysentery, bowel irregularities, and ulcerative colitis.

Dose: Dose is 5–10 g per day in divided doses.

IV. Miscellaneous

a. Topically used sulphonamides

i. Mafenide (Sulfamylon)

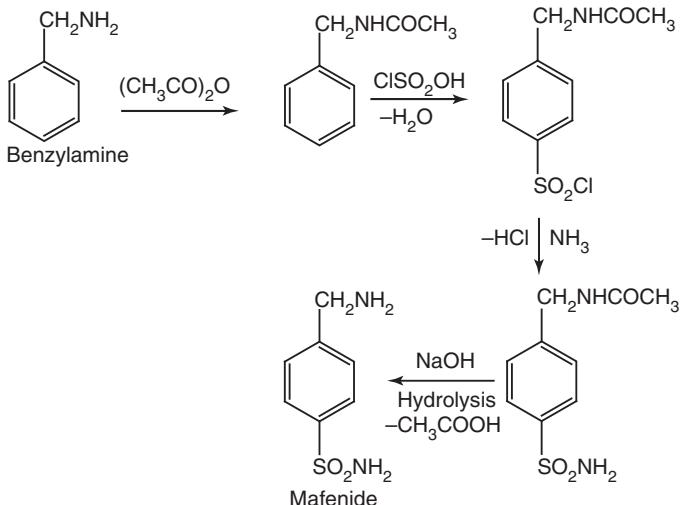


4-(Aminomethyl)benzene sulphonamide

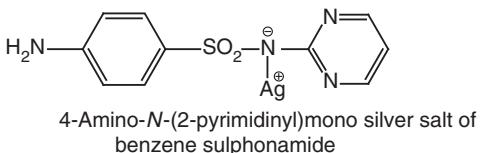
Uses: It is used in the treatment and cure of gas gangrene. It is also effective against *Clostridium welchii* on topical application.

Dose: Dose is 5% solution of mafenide hydrochloride or mafenide propionate for topical use.

Synthesis

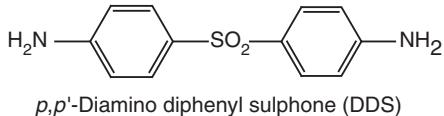


ii. Silver Sulphadiazine



Uses: It is an effective topical antimicrobial agent, especially, against *Pseudomonas* species; it finds extensive use in burn therapy.

iii. Dapsone (Avcosulfon)



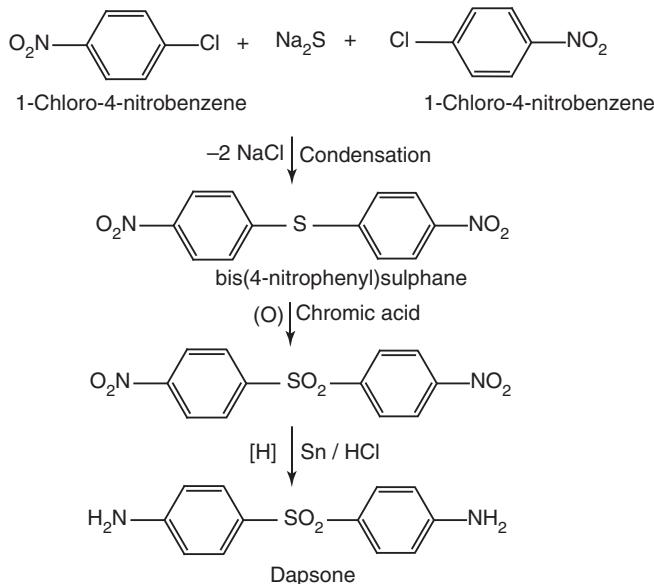
Action and use: Dapsone is a white or slightly yellowish-white crystalline powder, very slightly soluble in water, soluble in acetone and dilute mineral acids, sparingly soluble in alcohol. Used as folic acid synthesis inhibitor in the treatment of leprosy and nocardiosis.

Assay: Dissolve the sample in dilute hydrochloric acid, add potassium bromide, cool in ice, and titrate against 0.1N sodium nitrate. Determine the end point electrometrically.

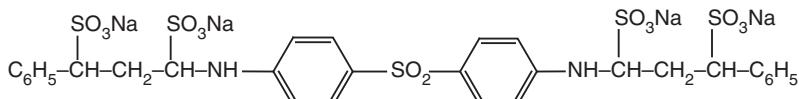
Dose: The dose as a leprostatic is 25 mg twice a week initially for 1 month followed by 25 mg per day each month. As suppressant for dermatitis herpetiformis the dose is 100–200 mg per day.

Dosage forms: Dapsone tablets B.P.

Synthesis

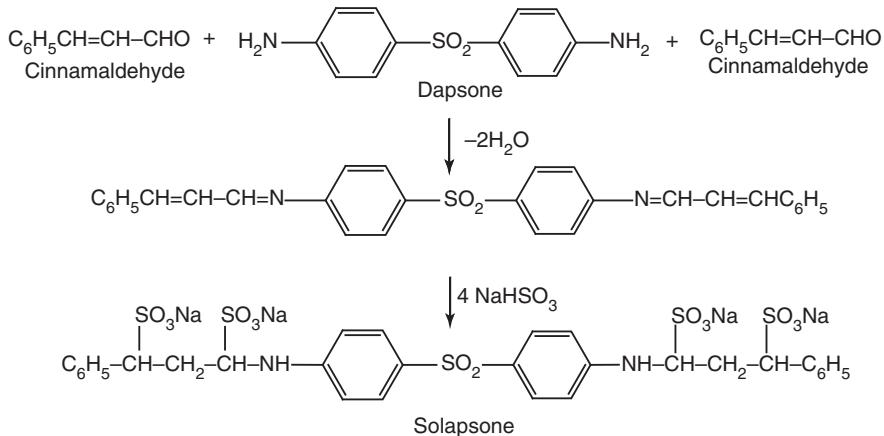


iv. Solapsone



1,1'-(Sulphonyl bis (4,4'-phenyleneimino)) bis [3-phenyl-1,3-propane disulphonic acid] tetra sodium.

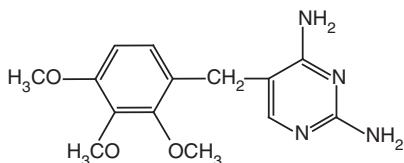
Synthesis



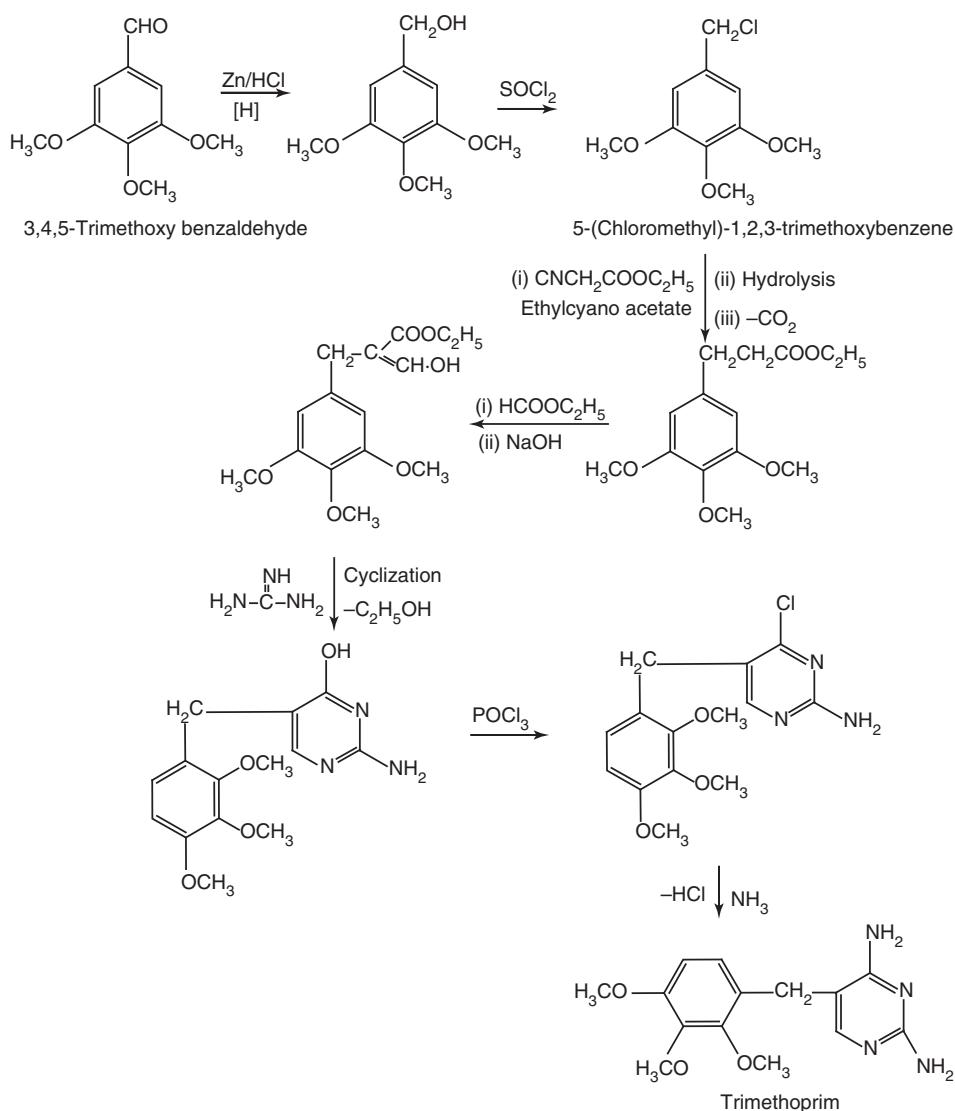
Uses: It is used in the treatment of leprosy.

V. Drugs used in combination with sulphonamides

i. Trimethoprim



Synthesis

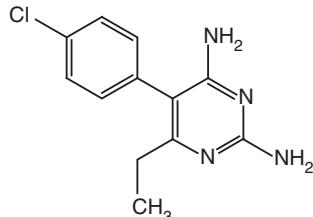


Properties and uses: Trimethoprim is a white or yellowish-white powder, very slightly soluble in water and slightly soluble in ethanol. It is used as dihydrofolate reductase inhibitor, effective against chloroquine and pyrimethamine resistant strains of *Plasmodium falciparum*.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end-point potentiometrically.

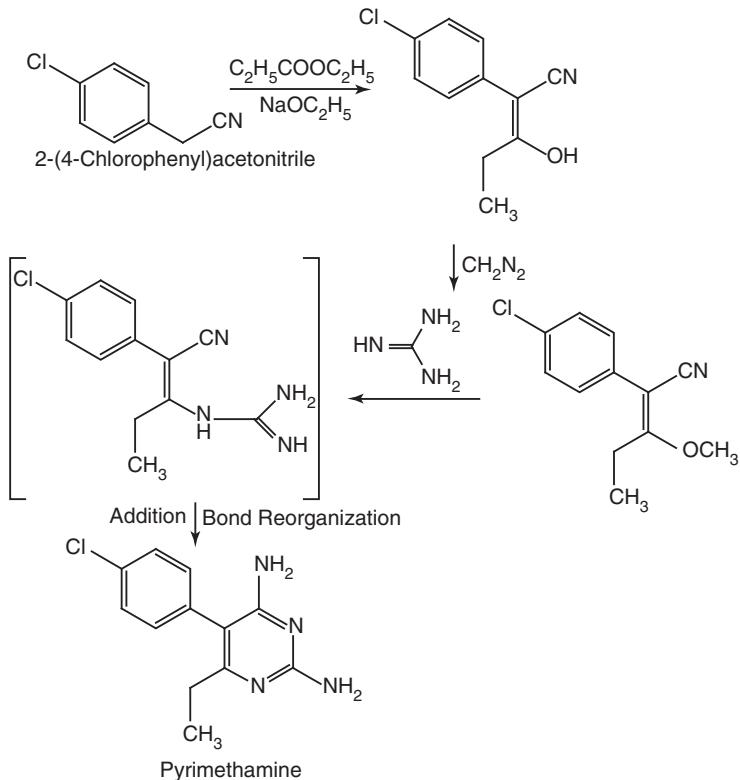
Dosage forms: Co-trimoxazole intravenous infusion B.P., Co-trimoxazole oral suspension B.P., Paediatric co-trimoxazole oral suspension B.P., Co-trimoxazole tablets B.P., Dispersible co-trimoxazole tablets B.P., Paediatric co-trimoxazole B.P., Tablets trimethoprim oral suspension B.P., Trimethoprim tablets B.P.

ii. Pyrimethamine



5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diamine

Synthesis



Properties and uses: Pyrimethamine is a white crystalline powder or colourless crystals, practically insoluble in water, and slightly soluble in alcohol. It is used in combination with sulphadoxine for the treatment of malaria.

Assay: Dissolve the sample in anhydrous acetic acid by heating gently. Cool and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dosage forms: Pyrimethamine tablets I.P., pyrime thamine tablets B.P.

PROBABLE QUESTIONS

1. What are sulphonamides? Write its mode of action and SAR.
2. Explain how an 'azo-dye' breaks down in vivo to yield sulphanilamide? N1-Substitution in sulphanilamide is more effective and useful than N4-substitution. Explain.
3. What are the different ways to classify sulphonamides and explain with suitable examples about the chemical classification.
4. Write the synthesis, metabolism, and uses of sulphasalazine and sulphaguanidine.
5. Name the sulphonamides used topically, write the synthesis, and uses of sulphacetamide.
6. How will you synthesize sulphanilamide from the following:
 - (a) Nitrobenzene
 - (b) Benzene
 - (c) Aniline
7. Write the structure, synthesis, brand name, assay, dosage forms, and uses of the following:
 - (a) Phthalyl sulphathiazole
 - (b) Sulphadiazine
 - (c) Sulphamethoxazole
8. Name the poorly absorbed sulphonamides and write the synthesis and uses of any one of them.
9. How will you synthesize the following drugs, employed for urinary tract infections:
 - a. Sulphacetamide from sulphanilamide
 - b. Sulphafurazole from *p*-acetamidobenzene sulphonyl chloride
10. Write the structure, chemical name, synthesis, dose, dosage forms, and uses of the following sulphonamides:
 - (a) Sulphaisoxazole
 - (b) Sulphaphenazole
11. Mention the sulphonamides used in the following and write the synthesis of any one among them
 - (a) Intestinal infections
 - (b) Second-and third-degree burns.

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1. Abraham DJ (ed). *Burger's Medicinal Chemistry and Drug Discovery* (6th edn). New Jersey: John Wiley, 2007.
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3. Brantun 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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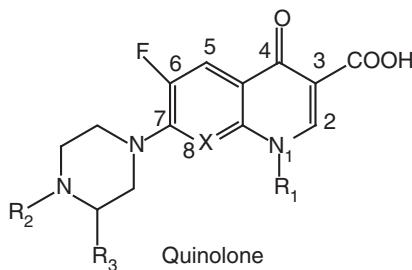
5. Goldstein A. 'Antibacterial chemotherapy'. *New England J Med.* 240: 258–61, 1949.
6. Hawking F and Lawrence JS. *The Sulfonamides*. New York: Grune and Stratton, 1961.
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9. Lednicer D and Mitscher LA. *The Organic Chemistry of Drug Synthesis*. New York: Wiley, 1995.
10. Northey EN. 'The sulfonamides and allied compounds'. In *American Chemical Society Monograph Series*, WA Hamor (ed), pp. 46–47. New York: Reinhold Publishing, 1948.
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14. Schuler FW (ed). *Molecular Modification in Drug Design: Advances in Chemistry Series No. 45*, Washington, DC: American Chemical Society, 1964.

Chapter 3

Quinolone Antibacterials

INTRODUCTION

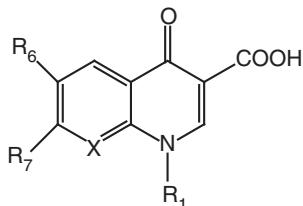
Quinolones constitute a large class of synthetic antimicrobial agents that are highly effective in the treatment of many types of infectious diseases, particularly those caused by bacteria. Quinolones are potent, broad-spectrum antibacterial agents. The early congeners (nonfluorinated at C-6 position, such as nalidixic acid) were limited to certain gram-negative infections, such as urinary tract infections. However, the modern generation of fluoroquinolones, containing C-6 fluoro substituent and a cyclic basic amine moiety at C-7 position, surpass their predecessors in terms of spectrum of activity and potency. This has allowed for their use against a variety of gram-negative as well as some gram-positive pathogens.



Many analogues have piperazine groups on C-7 because of which they broaden the spectrum, especially to gram-negative organisms, such as *Pseudomonas aeruginosa*, however, they also increase the affinity of the compound for the gamma-aminobutyric acid (GABA) receptor, which contributes to central nervous system (CNS) side effects. Quinolones are easily prepared and administered via parenteral and oral routes, and are well tolerated.

Mode of action: Quinolones inhibit the action of bacterial DNA gyrase enzyme. This enzyme is responsible for supercoiling and compacting bacterial DNA molecules into the bacterial cell during replication. This action is accomplished by modifying the topology of DNA via supercoiling and twisting of these macromolecules to permit DNA replication or transcription.

EFFECTIVE ANTIBACTERIAL QUINOLONE DERIVATIVES



| Name | X | R ₆ | R ₁ | R ₇ |
|----------------|-----|----------------|----------------------------------|--|
| Nalidixic acid | -N | -H | -CH ₂ CH ₃ | -CH ₃ |
| Enoxacin | -N | -F | -CH ₂ CH ₃ | H-N Cyclohexyl ring |
| Pipemidic acid | -N | -H | -CH ₂ CH ₃ | H-N Cyclohexyl ring |
| Norfloxacin | -CH | -F | -CH ₂ CH ₃ | H-N Cyclohexyl ring |
| Pefloxacin | -CH | -F | -CH ₂ CH ₃ | H ₃ C-N Cyclohexyl ring |
| Ciprofloxacin | -CH | -F | — | H-N Cyclohexyl ring |
| Amifloxacin | -CH | -F | -NHCH ₃ | H ₃ C-N Cyclohexyl ring |
| Sparfloxacin | -CF | -F | — | —N CH ₃ Cyclohexyl ring CH ₃ |
| Lomefloxacin | -CF | -F | -C ₂ H ₅ | —N CH ₃ Cyclohexyl ring CH ₃ |

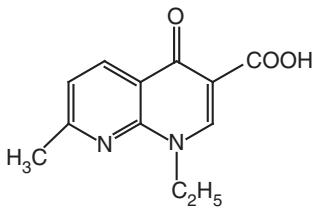
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(Continued)

| Name | X | R_6 | R_1 | R_7 |
|---------------|--------------------|-------|------------------------------------|-------|
| Fleroxacin | -CF | -F | -CH ₂ CH ₂ F | |
| Tefloxacin | -CH | -F | | |
| Gatifloxacin | -COCH ₃ | -F | | |
| Clinafloxacin | -CCl | -F | | |
| Sitaflloxacin | -CCl | -F | | |

SYNTHESIS AND DRUG PROFILE

i. Nalidixic acid



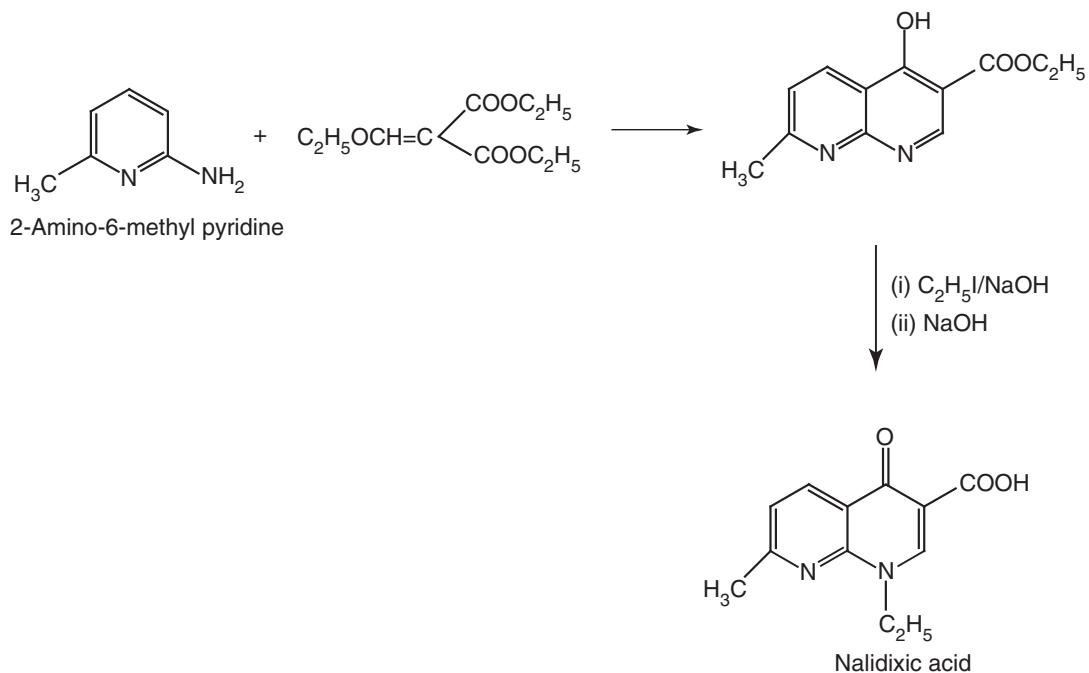
1-Ethyl-1,4-dihydro-7-methyl-4-oxo 1,8-naphthyridine-3-carboxylic acid

Properties and uses: Nalidixic acid is a white or pale yellow crystalline powder, practically insoluble in water, soluble in methylene chloride, slightly soluble in acetone, alcohol, and dilute solutions of alkali hydroxides. It is particularly effective against gram-negative bacteria that cause urinary tract infection. Nalidixic acid is biotransformed into hydroxy methyl derivative at the 7-methyl group, which is also active. A low incidence of adverse effects observed includes gastrointestinal (GI) disturbances, rashes, drowsiness, headache, and visual disturbances.

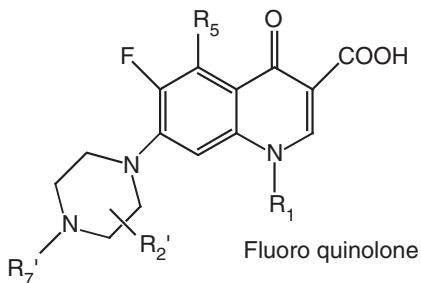
Assay: Dissolve the sample in methylene chloride and add 2-propanol and carbon dioxide-free water and pass nitrogen through the solution throughout the titration by maintaining a temperature between 15°C and 20°C and titrate against 0.1 M ethanolic sodium hydroxide. Determine the end point potentiometrically.

Dosage forms: Nalidixic acid oral suspension B.P., Nalidixic acid tablets B.P.

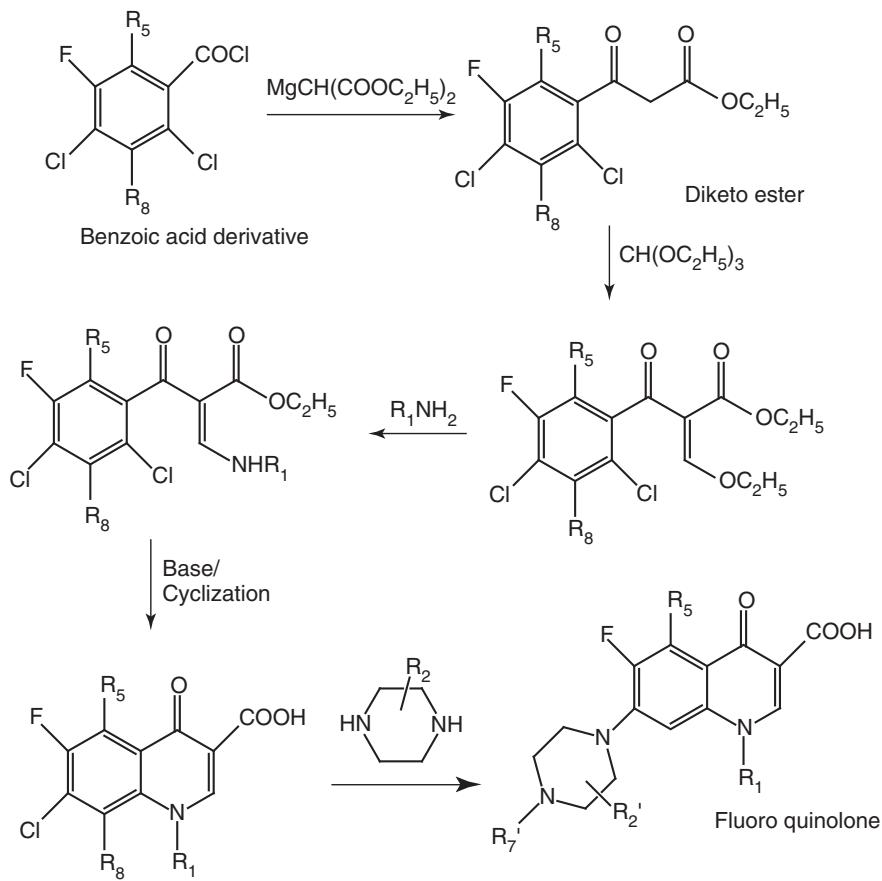
Synthesis



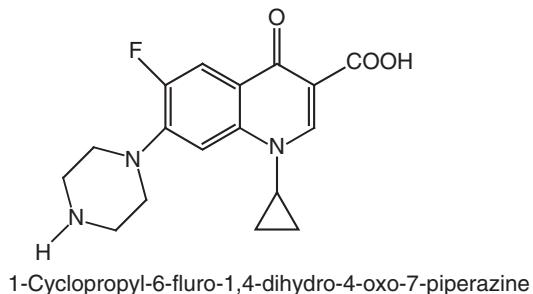
ii. Fluoroquinolones



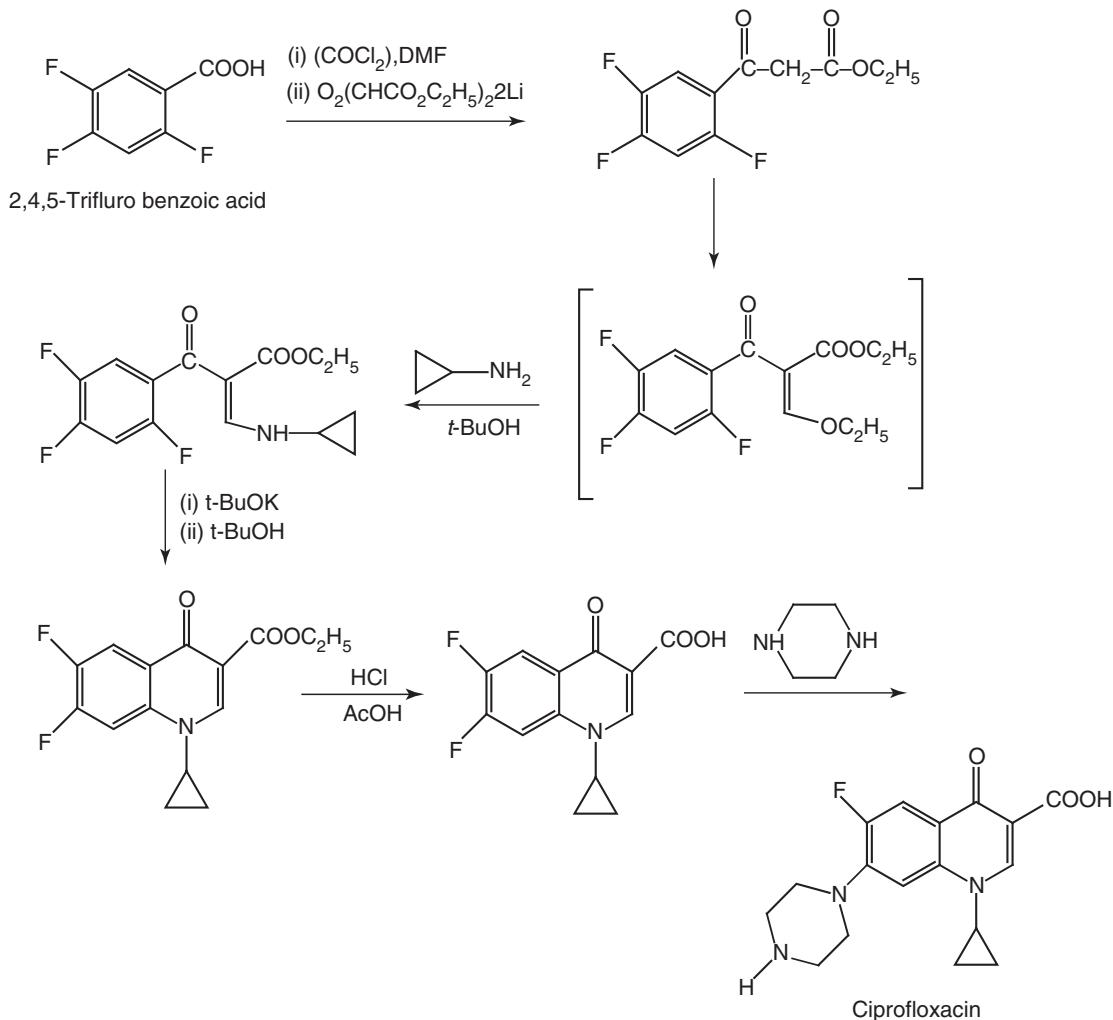
Synthesis



iii. Ciprofloxacin



Synthesis

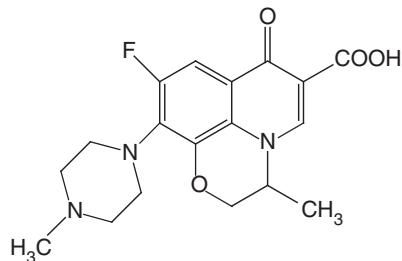


Properties and uses: Ciprofloxacin hydrochloride is pale yellow, crystalline in nature, slightly hygroscopic powder, soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, but insoluble in acetone, ethyl acetate, and methylene chloride. It is very effective for the treatment of urinary tract infection, prostatitis, and for acute diarrhoeal disease caused by *Escherichia coli*, *Shigella*, *Salmonella*, and *Campylobacter*.

Assay: It is assayed by adopting liquid chromatography technique.

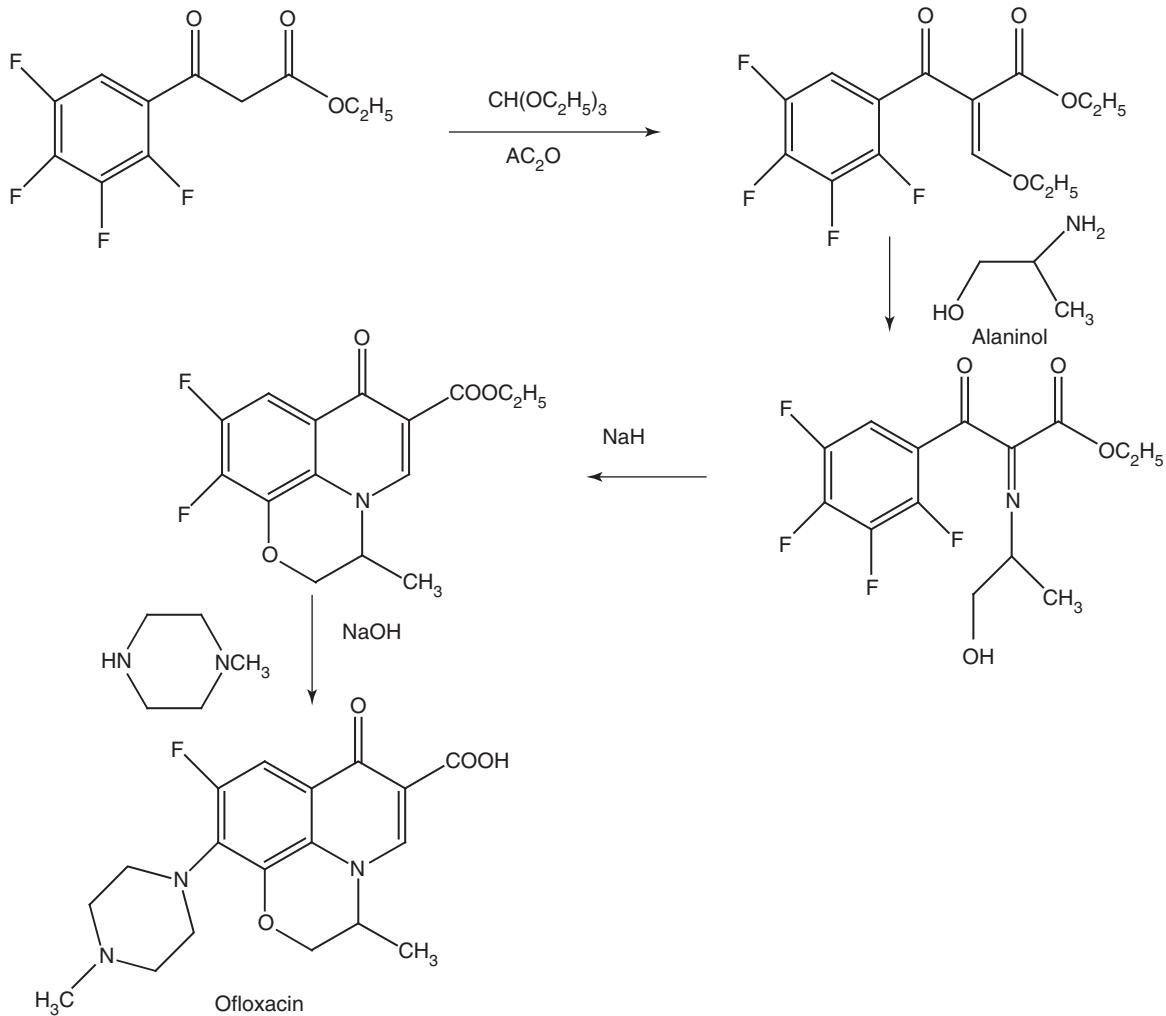
Dosage forms: Ciprofloxacin tablets B.P.

iv. Ofloxacin



9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo
-3,7-dihydro-2*H*-[1,4]oxazino[2,3-*i*]quinoline-6-carboxylic acid

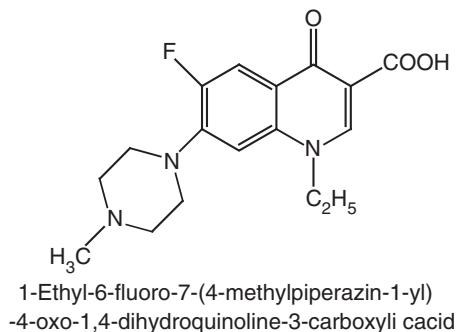
Synthesis



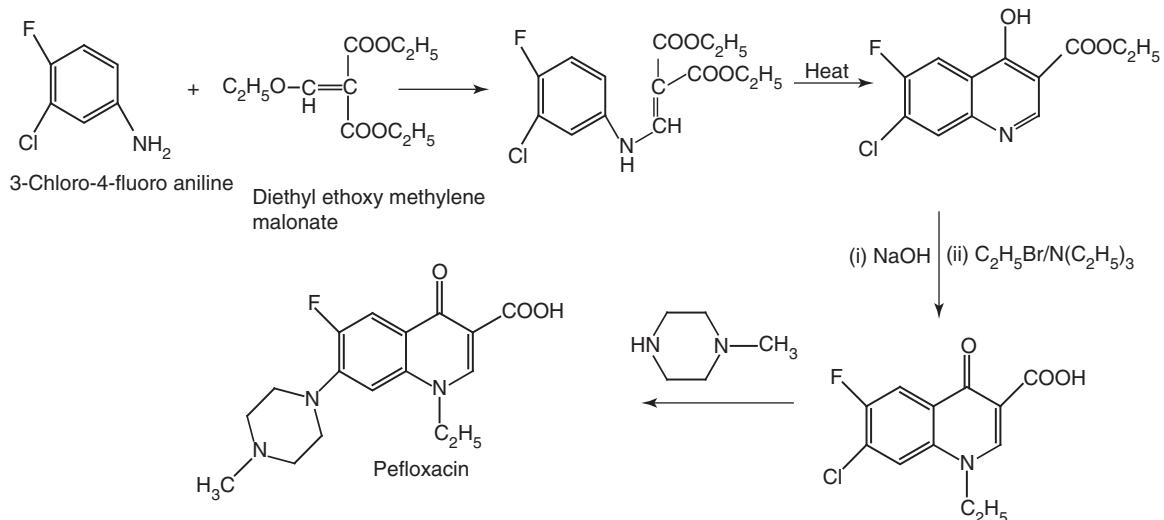
Properties and uses: Ofloxacin is a pale yellow or bright yellow crystalline powder, slightly soluble in water and methanol, and soluble in glacial acetic acid and methylene chloride. It is one of the most promising newer members of the fluoroquinolone family. In this product, *N*-ethyl moiety has been made rigid by incorporation into a heterocyclic ring. It is useful in the treatment of genitourinary, respiratory, gastrointestinal, skin, soft tissue infections, peritonitis, and gonorrhoea.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

v. Pefloxacin



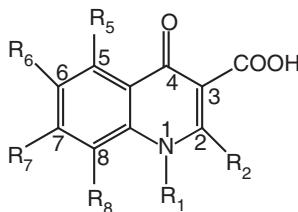
Synthesis



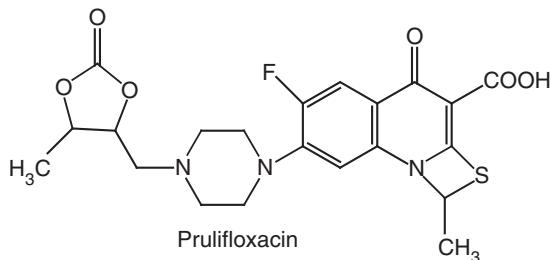
Properties and uses: Pefloxacin mesilate is a white powder, soluble in water, slightly soluble in alcohol, and very slightly soluble in methylene chloride, used as an antibacterial agent.

Assay: Dissolve the sample in anhydrous acetic acid, add acetic anhydride, and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

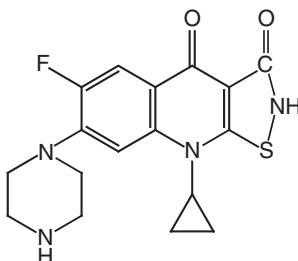
SAR of Quinolones



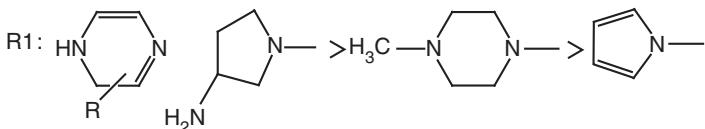
- Substituent at N-1 position:** The optimum substituents at position 1 appear to be ethyl, butyl, cyclopropyl, and difluorophenyl, and these substituents have resulted in potent compounds. Addition of a fluorine atom into the N-1 cyclopropyl group or the 1-butyl substituent resulted in compounds with overall improved activity against gram-positive bacteria.
- The simple replacement of C-2 hydrogen has been generally disadvantageous (e.g. C-2 methyl or hydroxy groups); however, some derivatives containing a suitable C-1, C-2 ring have shown to possess notable activity.



- The carboxy functions at position:** Modification of C-3 carboxylic acid group leads to decrease in antibacterial activity. However, replacement of C-3 carboxylic group with isothiazolo group afforded most active isothiazolo quinolone, which has been 4–10 times greater in *in vitro* antibacterial activity than ciprofloxacin. The isothiazolo system possesses aromatic character and the nitrogen proton is very acidic and can be considered as an carboxylic acid mimic, whereas other groups, such as sulphonate acid, phosphonic acid, tetrazole as well as derivatization, as an ester lead to loss of antibacterial activity.



4. The C-4-oxo group of the quinolone nucleus appears to be essential for antibacterial activity. Replacement with 4-thioxo or sulphonyl group leads to a loss of activity.
5. The incorporation of a group at the C-5 position has proven beneficial in terms of antibacterial activity. The order of activity is NH₂: CH₃>F, H>OH, or SH, SR.
6. The incorporation of a fluorine atom at the C-6 position of the quinolone is monumental. The order of activity is F>Cl, Br, CH₃>CN.
7. The introduction of a piperazine moiety at the C-7 position is essential. Other aminopyrrolidines also are compatible for activity.



8. In general, a C-8 fluoro substituent offers good potency against gram-negative pathogens, while a C-8 methoxy moiety is active against gram-positive bacteria. The order of activity is F, Cl, OCH₃>H, CF₃>methyl, vinyl, propargyl.
9. A halogen (F or Cl) at the C-8 position improves oral absorption.
10. Linking of N-1 group to the C-8 position with oxazine ring leads to active ofloxacin.

Uses: Fluoroquinolones are used to treat upper and lower respiratory infections, gonorrhoea, bacterial gastroenteritis, skin soft tissue infections, urinary tract infections, bone and joint infections, and against tuberculosis.

ADVERSE EFFECTS

The most common adverse reactions are nausea, headache, and dizziness. Some CNS problems, such as hallucination, insomnia, and visual disturbances can occur. Some side effects of the quinolones are class effects and cannot be modulated by molecular variation. Most of the fluoroquinolones produce photosensitivity reactions and cause convulsions particularly in concurrent administration of NSAID fenoprofen. Increasing steric bulk through alkylation ameliorates these effects. Phototoxicity is determined by the nature of the 8-position substituent with halogen causing the greatest photoreaction while hydrogen and methoxy show little light produced toxicity. These drugs are not recommended for use in pretubertal children or pregnant women.

PROBABLE QUESTIONS

1. Draw the structure and number the quinolone nucleus. Mention the position of substituents introduced in quinolone antibacterials. Write the SAR of quinolone antibacterials.
2. Enumerate the quinolone antibacterials with their chemical structures and write the synthesis and uses of ciprofloxacin.

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Chapter 4

Antibiotics

INTRODUCTION

The term antibiotic has its origin in the word antibiosis (i.e. against life). Antibiotics are chemical substances obtained from various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms and eventually may destroy them. The probable points of difference amongst the antibiotics may be physical, chemical, pharmacological properties, antibacterial spectra, and mechanism of action. They have made it possible to cure diseases caused by bacteria, such as pneumonia, tuberculosis, and meningitis, and they save the lives of millions of people around the world.

CLASSIFICATION

Antibiotics are classified on the basis of their mechanism of action and by its chemical nature.

Classification Based on Mechanism of Action

1. *Agents that inhibit the synthesis of bacterial cell wall:* These include the penicillins and cephalosporins that are structurally similar and dissimilar agents, such as cycloserine, vancomycin, bacitracin and the imidazole antifungal agents.
2. *Agents that act directly on the cell membrane of the microorganisms, affecting permeability, and leading to leakage of intracellular compounds:* These include polymyxin, polyene antifungal agents, nystatin, and amphotericin B that bind to cell wall sterols.
3. *Agents that affect the function of 30s and 50s ribosomal subunits to cause reversible inhibition of protein synthesis:* These include tetracyclines, erythromycins, chloramphenicol, and clindamycin.
4. *Agents that bind to the 30s ribosomal subunit and alter protein synthesis:* These include aminoglycosides that leads to cell deaths eventually.
5. *Agents that affect nucleic acid metabolism:* Such as rifamycins, which inhibit DNA dependent RNA polymerase.

Classification Based on Chemical Structure

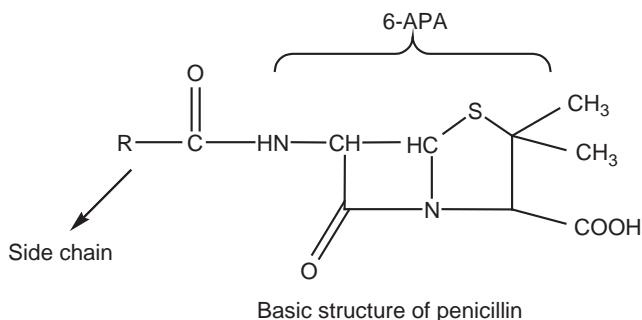
1. β -lactam antibiotics
2. Aminoglycoside antibiotics
3. Tetracycline antibiotics
4. Polypeptide antibiotics
5. Macrolide antibiotics
6. Lincomycins
7. Other antibiotics

1. β -lactam antibiotics

These consists of two major class of agents, that is penicillins and cephalosporins.

a. Penicillins

Penicillin, the most important antibiotic, was first extracted from the mould *Penicillium notatum*. Subsequently, a mutant of a related mould, *P. chrysogenum*, was found to give the highest yield of penicillin and is employed for the commercial production of this antibiotic. Penicillin belongs to a group of antibiotics called β -lactam antibiotics . The basic structure of the penicillins consists of a thiazolidine ring fused with a β -lactam ring, which is essential for antibacterial activity. These two rings constitute the fundamental nucleus of all the penicillins, namely, 6-amino penicillanic-acid (6-APA) A variety of semisynthetic penicillins are produced by altering the composition of the side chain attached to 6-APA nucleus. Both the 6-APA nucleus and side chain are essential for the antibacterial activity.



Nomenclature

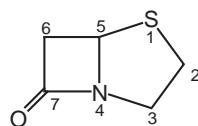
Penicillins are named in the following ways:

a. Chemical abstract

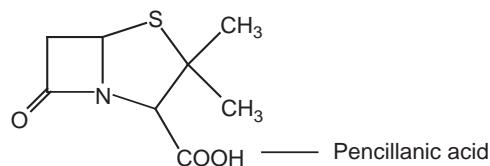
1. The penicillins are described as 4-thia-1-azabicyclo (3.2.0) heptanes.
2. Benzylpenicillin is 6-(2-phenylacetamido)-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid.

b. Penam

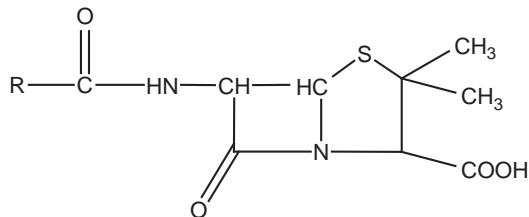
In order to simplify the unsubstituted bicyclic ring system of penicillin, it is given the name penam. Accordingly, the penicillins are 6-acylamino-2, 2-dimethyl penam-3-carboxylates.



c. Pencillanic acid derivatives



CLASSIFICATION



| Name | Nature of Substituent (R) |
|---|---------------------------|
| Penicillin G (Benzyl penicillin) | |
| Penicillin V (Phenoxy methyl penicillin) | |
| Phenethicillin | |

I. Penicillinase-susceptible penicillins

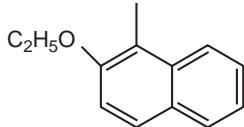
The general impact on antibacterial activity is as follows:

- Good gram-positive potency against susceptible *Staphylococci* and *Streptococci*
- Useful against some gram-positive *cocci*
- Not effective against gram-negative bacilli

| Name | R |
|--|---|
| (i) Methicillin | |
| (ii) Oxacillin ($R_1=R_2=H$) | |
| (iii) Cloxacillin ($R_1=H$, $R_2=Cl$) | |
| (iv) Dicloxacillin ($R_1=R_2=Cl$) | |
| (v) Floxacillin ($R_1=F$, $R_2=Cl$) | |

(Continued)

(Continued)

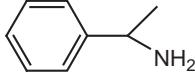
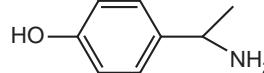
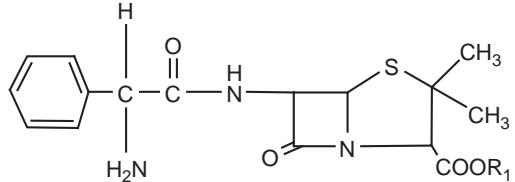
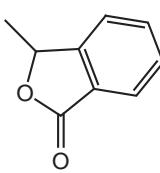
| Name | R |
|----------------|--|
| (vi) Nafcillin |  |

II. Penicillinase-resistant penicillins

General impact on antibacterial activity is as follows:

- Decreased susceptibility to many penicillinase.
- Active against microorganisms, resistant to early penicillin.
- Oxacillins offer good oral activity.

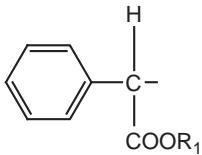
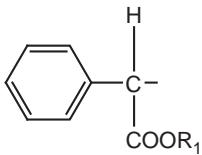
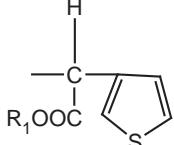
III. Aminopenicillins

| Name | R |
|--------------|--|
| Ampicillin |  |
| Amoxicillin |  |
| Talampicilin |  $\text{R}_1 =$  |

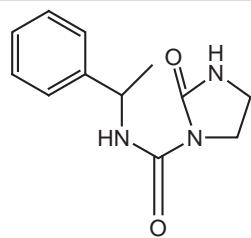
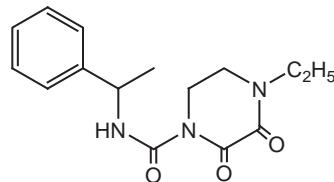
General impact on antibacterial activity is as follows:

- Extended spectrum of activity against some gram-negative bacteria and retention of gram-positive potency
- Ineffective against *Pseudomonas aeruginosa*

IV. Antipseudomonal penicillins (Carboxy Penicillins)

| Name | R |
|--|---|
| Carbenicillin ($R_1=H$) |  |
| Indanyl carbenicillin ($R_1=5\text{-indanol}$) |  |
| Ticarcillin ($R_1 = H$) |  |

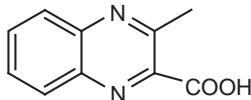
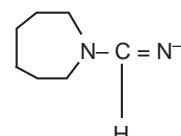
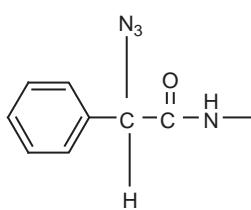
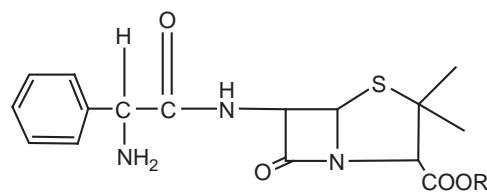
V. Ureidopenicillins

| Name | R |
|--------------|--|
| Aziocillin |  |
| Piperacillin |  |

General impact on antibacterial activity is as follows:

- Enhanced spectrum of activity against *P. aeruginosa* and expanded activity against *Klebsiella*.
- Good potency against gram-positive bacteria, but generally not effective against penicillinase producers.
- Good pharmacokinetic profile.
- Good activity against *Escherichia coli*, *Klebsiella*, *Shigella*, *Salmonella*, and many other resistant species.

VI. Miscellaneous penicillins

| Name | R |
|-----------------------------------|---|
| Quinicillin |  |
| Amidinopencillins (Mecillinam) |  |
| Azidocillin |  |
| Bacampicillin |  <p>$R_1 = \begin{array}{c} H \\ \\ -C-O-C(=O)-O-C_2H_5 \end{array}$</p> |

The chemical degradation of penicillins is depicted in Figure 4.1

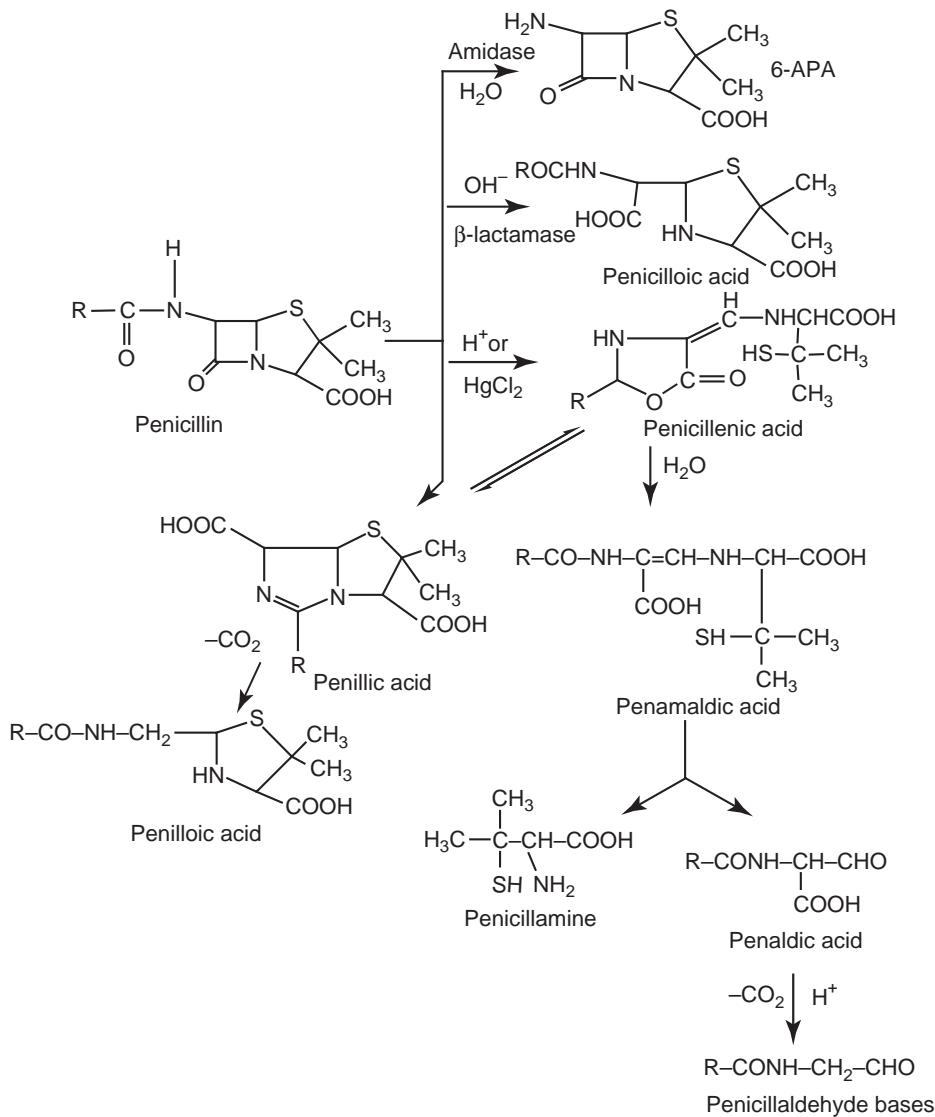


Figure 4.1 Chemical degradation of penicillins.

Inactivation of penicillins by acids, bases, and β -lactamases is as follows:

- The penicillins are very reactive due to the strained amide bond in the fused β -lactam of the nucleus.
- Penicillins undergo a complex series of reactions leading to a variety of inactive degradation products.

- They are extremely susceptible to nucleophilic attack by water or hydroxide ion to form the penicilloic acid. β -Lactamses also cleave the β -lactam ring to give penicilloic acid with a consequent loss of antibacterial activity.
- In strongly acidic solutions ($\text{pH} < 3$), penicillin is protonated at the β -lactam nitrogen, and this is followed by nucleophilic attack of the acyl oxygen atom on the β -lactam carbonyl carbon. The subsequent opening of the β -lactam ring destabilizes the thiazoline ring, which opens to form penicillenic acid that degrades into two major products penicillamine and penilloic acid. A third product, penicilloaldehyde is also formed.
- Acid-catalyzed degradation in the stomach contributes in a major way to the poor oral absorption of penicillin. Thus, efforts to obtain penicillins with improved pharmacokinetic and microbiologic properties have sought to find acyl functionalities that would minimize sensitivity of the β -lactam ring to acid hydrolysis and at the same time, maintain antibacterial activity.
- Substitution of an electron-withdrawing group for the α -position of the benzyl penicillin has stabilized the penicillin to acid catalyzed hydrolysis. The increased stability imparted by such electron-withdrawing groups has been attributed to a decrease in the reactivity of the side chain amide carbonyl oxygen atom towards participation in β -lactam ring opening to form the penicillenic acid.

Mode of action: The cell wall of bacteria is essential for the normal growth and development. Peptidoglycan is a heteropolymeric component of the cell wall that provides rigid mechanism for stability by virtue of its highly cross-linked lattice-wise structure. The peptidoglycan is composed of glycan chains, which are linear strands of two alternating amino sugars (*N*-acetyl glucosamine and *N*-acetylmuramic acid) that are cross-linked by peptide chains of an enzyme, transpeptidase. Penicillins inhibit the transpeptidase activity to the synthesis of cell walls. They also block cleavage of terminal D-alanine during the cell wall synthesis. The biosynthesis of peptidoglycan involves three stages (Fig. 4.2).

B-lactam antibiotics inhibit the last step in peptidoglycan synthesis. The transpeptidase enzyme that contains serine is probably acylated by β -lactam antibiotics with the cleavage of -CO-N-bond of the β -lactam ring. This renders the enzyme inoperative and inhibits peptidoglycan synthesis.

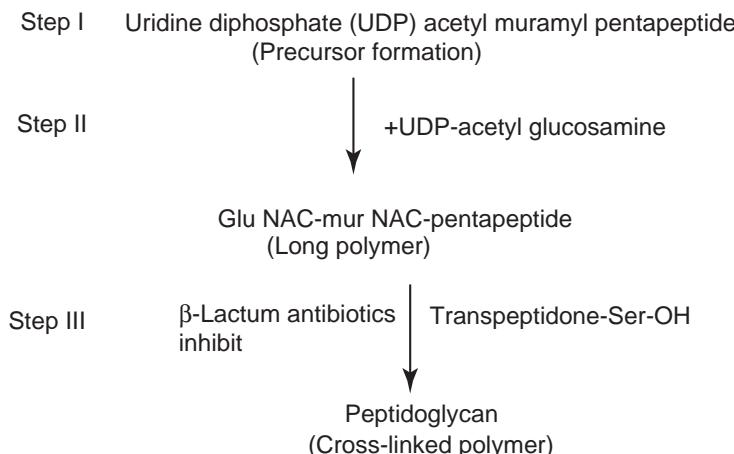
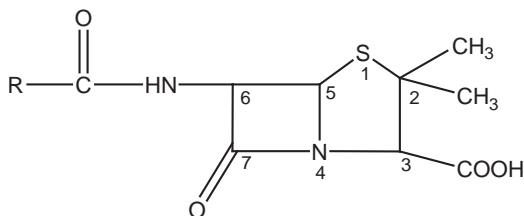


Figure 4.2 Stages involved in the biosynthesis of peptidoglycan.

SAR of Penicillins



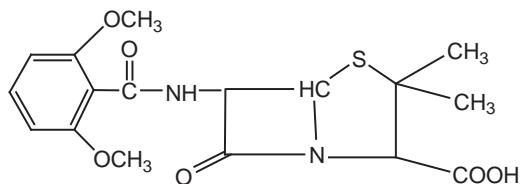
6-Acy side chain: The substitution of R on the primary amine with an electron withdrawing group decreases the electron density on the side chain and protects from acid degradation. Substituents on the α -carbon of the side chain, such as amino (ampicillin), chloro, and guanidine exerts good resistance to inactivation by acids. Benzyl penicillin undergoes acid and alkali degradation and is susceptible to all known β -lactamase. The increased latitude in varying the acyl amino side chain through acylation of 6-APA results with superior biological activity. Substitution of α -aryl of the alkyl group in the side chain gives increased stability and oral absorption.

1. Substitution of bulky groups on α -carbon of the side chain confers β -lactamase resistance. Examples: methicillin, nafcillin, oxacillin, etc. In all these penicillins, an aromatic ring is attached directly to the side chain amide carbonyl, and there is substitution at both positions ortho to the point of attachment. The size of the ring systems play an important role in determining the ability of the ortho substituent to confer penicillinase resistance.
2. The isomeric forms of penicillins differs in their activity. Example: D-isomer is 2–8 times more active than L-isomer of amoxicillin. The introduction of polar group or ionized molecule into the α -position of the side chain in the benzyl carbon atom of penicillin-G confers against the gram-negative bacilli. Amino, hydroxyl, carboxyl, and sulphonyl increases gram-negative activity. Example: ampicillin and carbenicillin.
3. Replacement of acyl side chain with hydroxymethyl groups shows improved gram-negative activity and introduction of C-6 α -methoxy group produces greater stability against β -lactamase. N-acylated ampicillins (ureidopenicillins) have increased activity against Pseudomonas.
4. Many esters of the carboxyl group attached to C-3 have been prepared as prodrugs to increase lipophilicity and acid stability. Example: Acetoxyethyl ester derivatives are used for preparing prodrugs.
5. The sulphur of the thiazolidine ring with O, CH_2 , and $\text{CH}-\beta\text{-CH}_3$ gives broad-spectrum antibacterial activity. The geminal dimethyl group at C-2 position is a characteristic of the penicillin. In general, derivatization of the C-3 carboxylic acid functionality is not tolerated unless the free penicillin carboxylic acid can be generated in vivo. Doubly activated penicillin esters, undergo rapid cleavage in vivo to generate active penicillin. Example: pivampicillin and becampicillin. The antibacterial activity is evidenced by N-4 atom at ring junction.
6. In vitro degradation is retarded by keeping the pH of the solution between 6.0 and 8.0. More lipophilic side chain increases the plasma protein binding. Example: Ampicillin: 25% plasma protein bound and phenoxy methyl penicillin: 75% plasma protein bound.

SYNTHESIS AND DRUG PROFILE

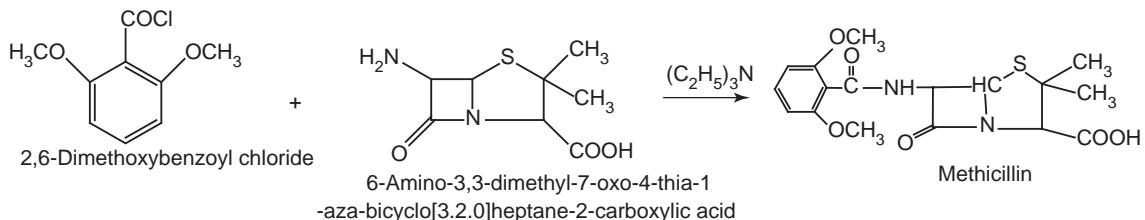
I. Penicillinase resistant penicillins

i. Methicillin



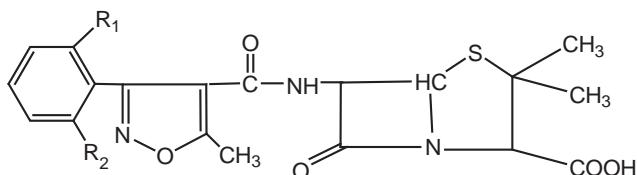
2,6-Dimethoxyphenyl penicillin

Synthesis

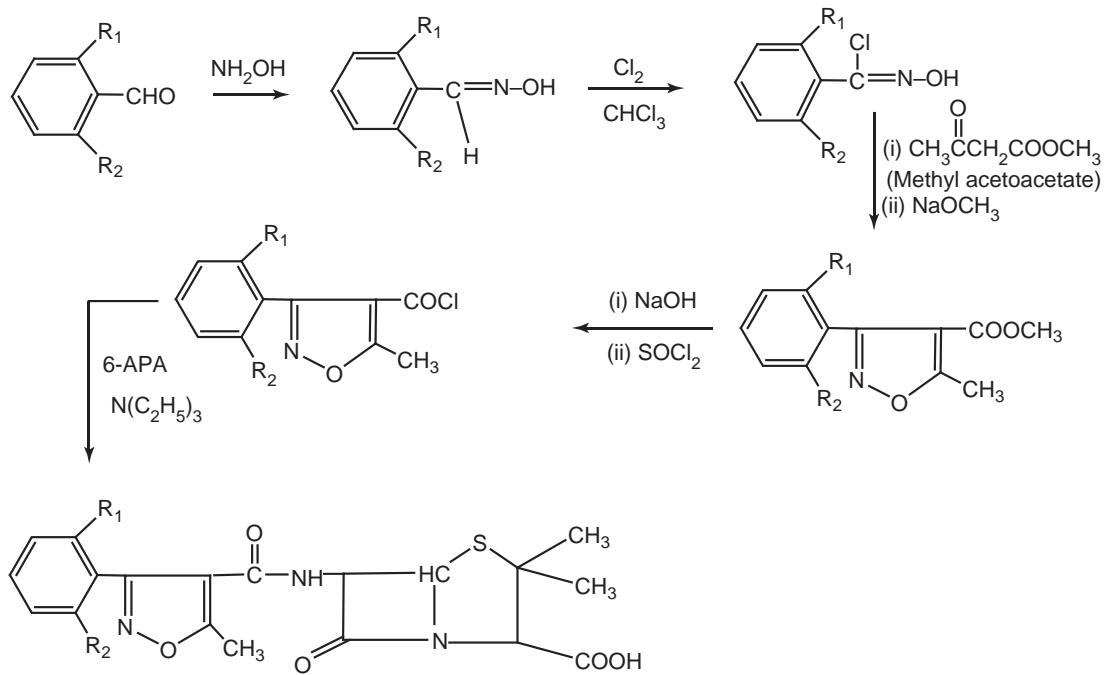


Properties and uses: Methicillin sodium is a white crystalline solid, odourless, soluble in water, slightly soluble in chloroform, but insoluble in ether. It is particularly resistant to inactivation by the penicillinase found in *Staphylococci* and somewhat more resistant than penicillin G to penicillinase from *Bacillus cereus*. Methicillin sodium has been introduced for use in the treatment of *Staphylococci* infections caused by the strains resistant to other penicillins. It is given by IM or by slow IV infusion every 4–6 h.

ii. Oxacillins (Isoxazolyl penicillins)



Properties and uses: Oxacillin sodium monohydrate is a white powder, soluble in water and methanol, insoluble in methylene chloride. The use of oxacillin and other isoxazolyl penicillins should be restricted to the treatment of infections caused by *Staphylococci* that are resistant to penicillin G, although their spectrum of activity is similar to that of penicillin G.

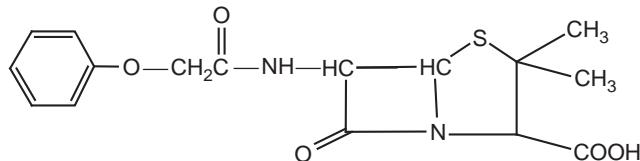
Synthesis

| Name | R_1 | R_2 |
|---------------|--------------|--------------|
| Oxacillin | -H | -H |
| Cloxacillin | -H | -Cl |
| Dicloxacillin | -Cl | -Cl |
| Floxacillin | -F | -Cl |

Assay: It is assayed by adopting liquid chromatography technique.

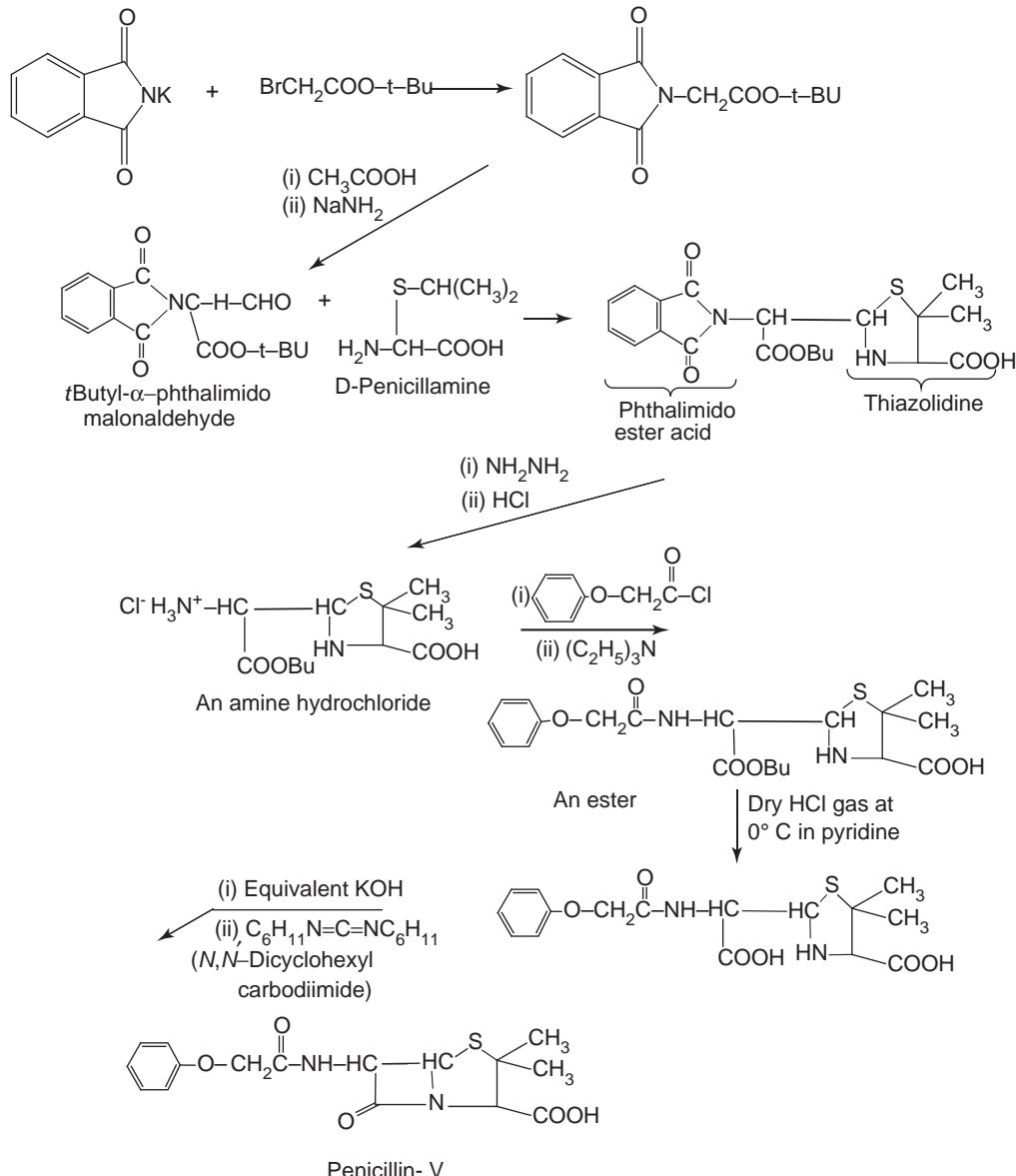
II. Penicillinase Susceptible Penicillins

i. Penicillin-V



3, 3-Dimethyl-7-oxo-6[(phenoxy acetylamo] -4-thia-1-azabicyclo(3.2.0) heptane-2-carboxylic acid

Synthesis



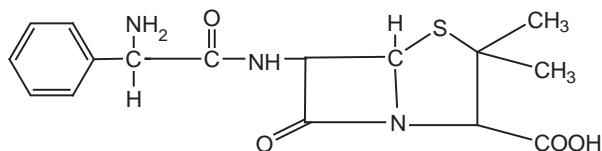
Properties and uses: Penicillin V is a white, odourless, crystalline powder with slightly bitter taste and soluble in water. It is more resistant to inactivation by gastric juice than penicillin G and better absorbed from the gastro intestinal (GI) tract. Equivalent oral doses provide two or five times greater plasma concentration than penicillin G. Penicillin V is given to treat 'trench mouth'. It is useful in the treatment of streptococcal pharyngitis, pneumonia, arthritis, meningitis, and endocarditis caused by *S. pyogenes*.

Dose: Dose of penicillin V by oral route is 125–500 mg six times daily for 10 days. For prophylaxis of rheumatic fever, the dose is 125–250 mg twice daily.

Assay: It is assayed by adopting liquid chromatography technique.

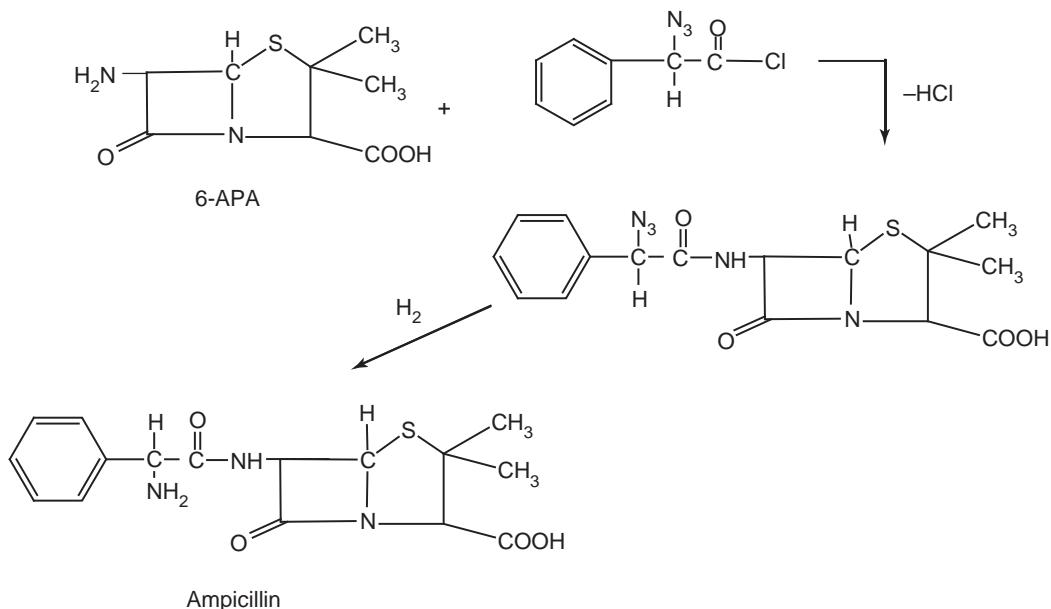
III. Amino penicillins

i. Ampicillin (Amcil, Omnipen)



6[D- α -Aminophenylacetamido] penicillanic acid

Synthesis



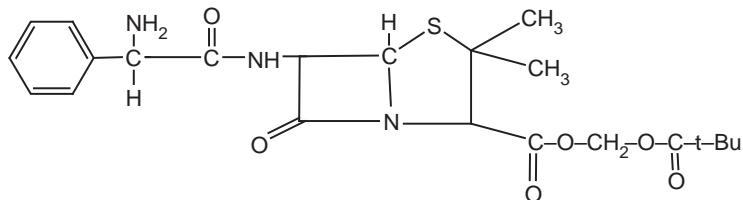
Properties and uses: Ampicillin is a white hygroscopic powder, freely soluble in water, sparingly soluble in acetone, practically insoluble in fatty oils and liquid paraffin. The corresponding product from acylation with 2-azido-4-hydroxyphenyl acetyl chloride is amoxicillin. The protonated α -amino group of ampicillin has a pK_a of 7.3 and is thus extensively protonated in acidic media, which explains ampicillin's stability towards acid hydrolysis and instability towards alkaline hydrolysis. The α -amino group plays an important role in the broader activity. It is used to treat urinary tract infections and respiratory tract infections.

Assay: It is assayed by adopting liquid chromatography technique.

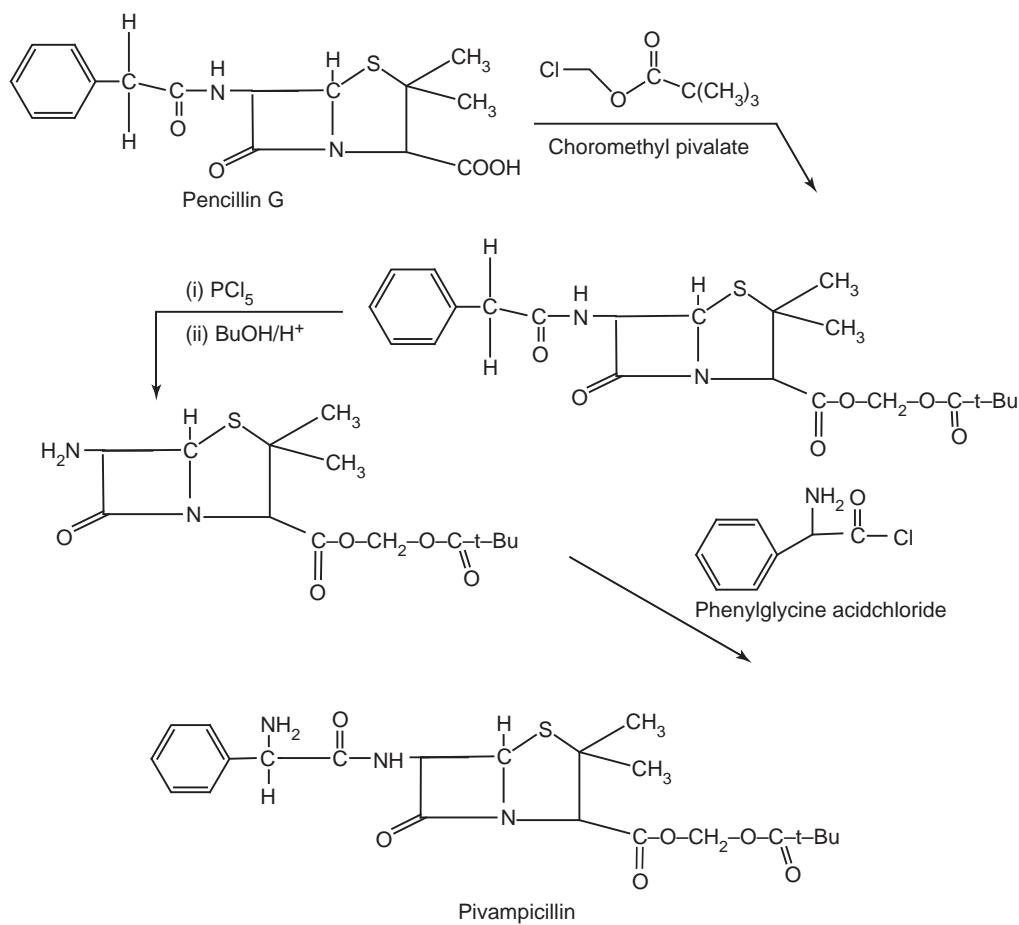
Dose: Available as capsules of 250 or 500 mg, as sodium salt for parenteral use, for oral suspension in strengths of 125–500mg/5ml, and in paediatric drops of 100 mg/ml. The consumption dose for adults is 1–4 g per day in divided dose for every 6 h, for children the dose is 100–200 mg/kg per day in three portions.

Dosage forms: Ampicillin capsules I.P., Ampicillin sodium injection I.P., Ampicillin injection B.P.

ii. Pivampicillin



Synthesis

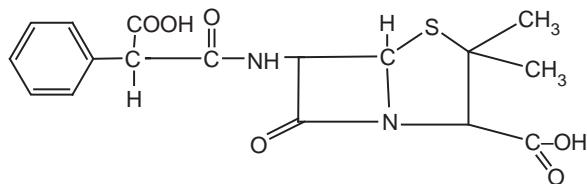


Properties and uses: Pivampicillin is a white crystalline powder, practically insoluble in water, soluble in methanol, ethanol, and dilute acids. It is a produg for ampicillin and in the in vivo esters hydrolyzes back to the parent ampicillin. It is used to treat urinary tract infections and respiratory tract infections.

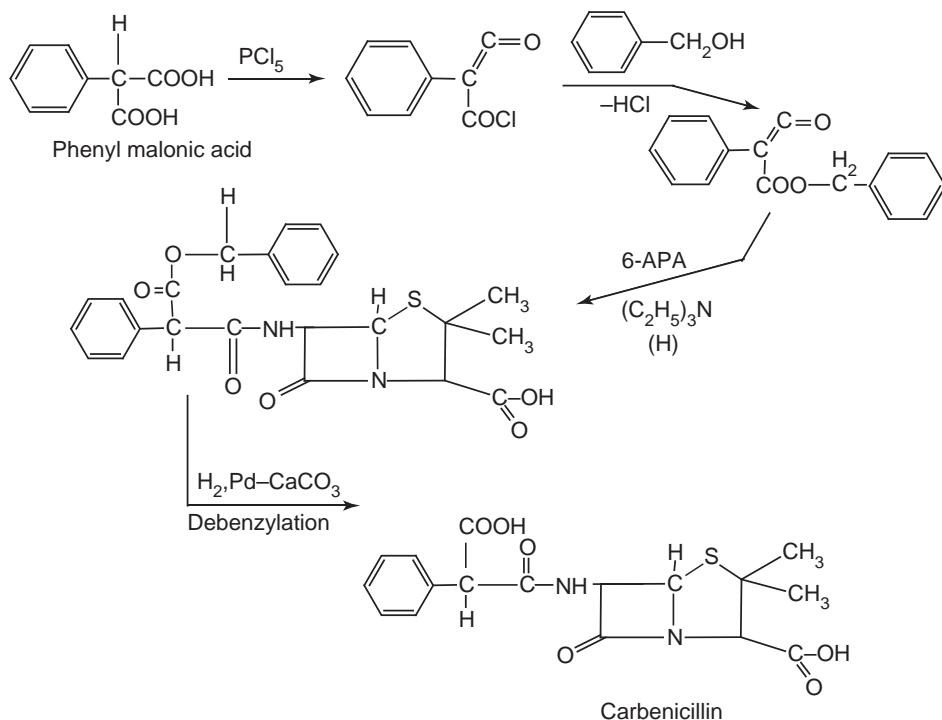
Assay: It is assayed by adopting liquid chromatography technique.

IV. Antipseudomonal penicillins

i. Carbenicillin



Synthesis

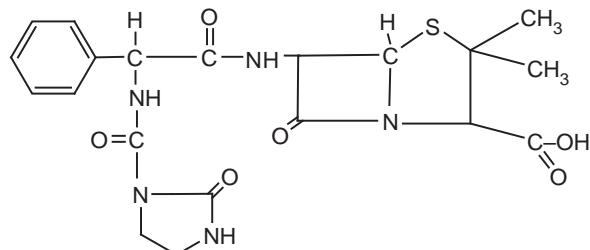


Properties and uses: It is a white to off white crystalline powder with bitter taste, hygroscopic in nature, soluble in water or alcohol, insoluble in chloroform or ether. It differs from ampicillin by having an ionizable carboxyl group substituted on the alpha carbon atom of the benzyl side chain rather than an amino group. The carboxyl group is thought to provide improved penetration of the molecule through the cell wall barriers of gram-negative bacilli as compared with other penicillins. A similar sequence starting with

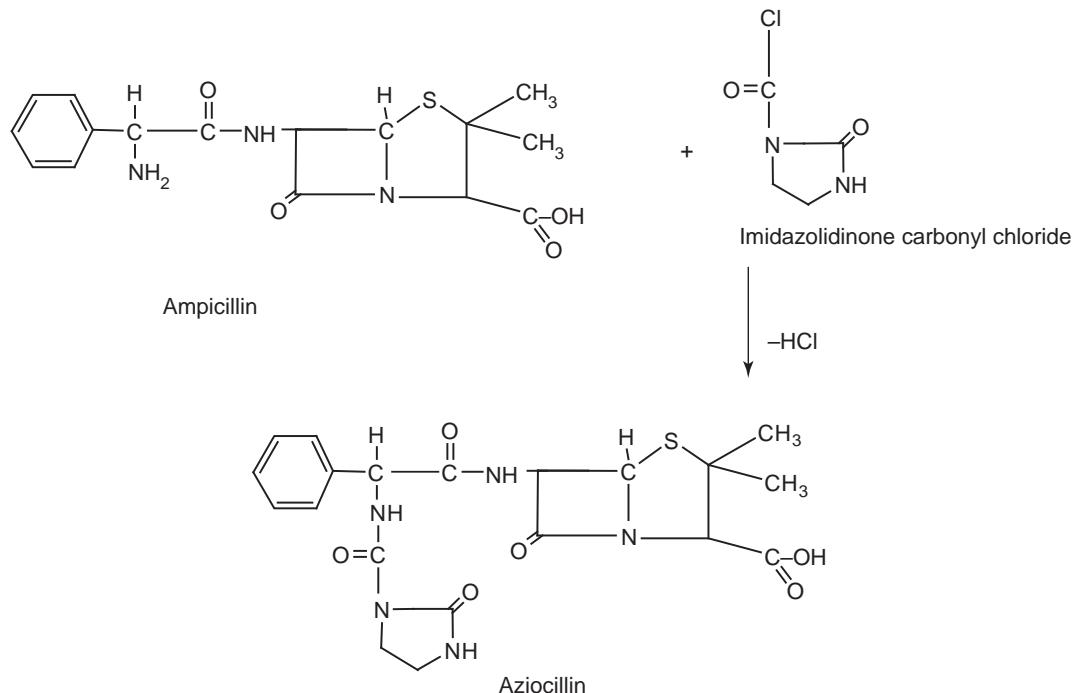
3-thiophenylmalonic acid leads to the ticarcillin. It is acid labile being a malonic acid derivative, it decarboxylates readily to penicillin G. It is effective in the treatment of systemic and urinary tract infections. It has low toxicity, except allergic sensitivity, and the drug interferes with platelet function resulting in bleeding.

V. Ureido penicillins

i. Aziocillin (Azlin)

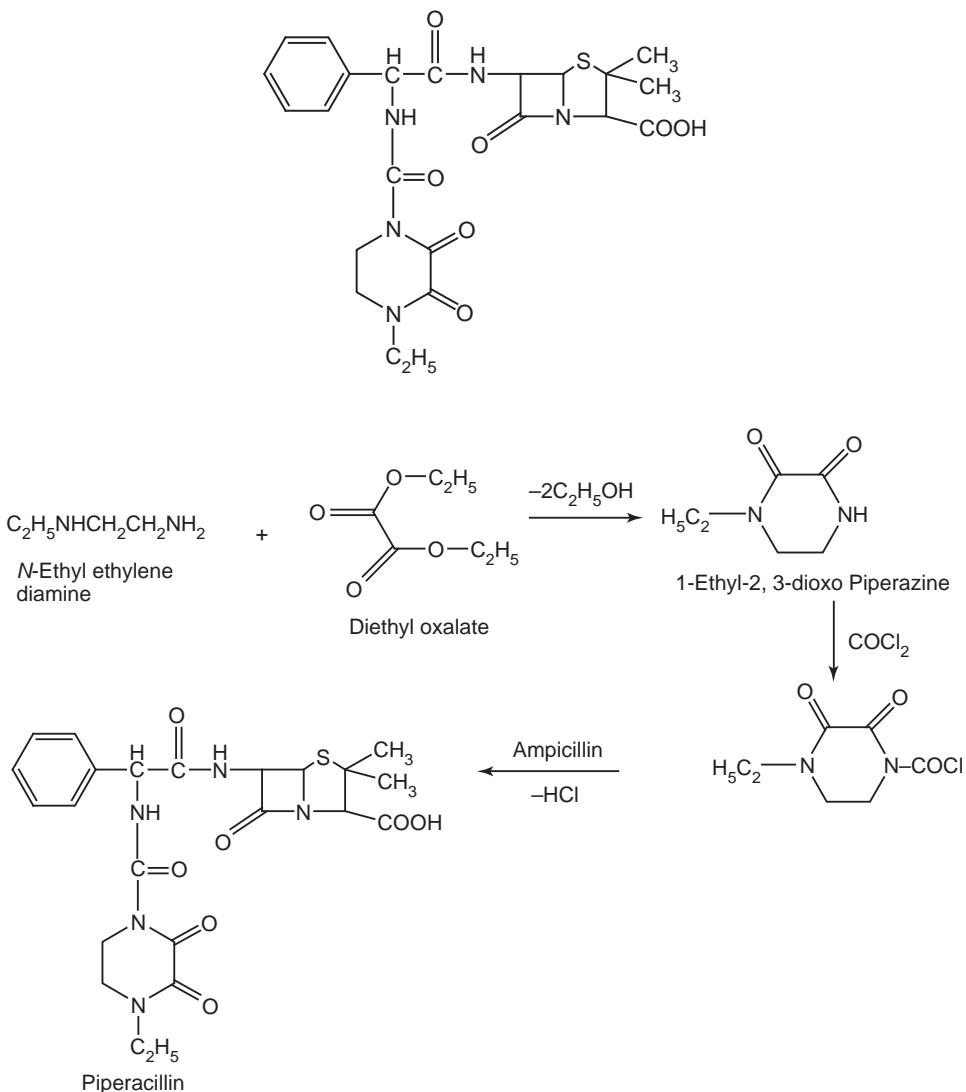


Synthesis



Properties and uses: It is the newest of ureidopenicillins, and is about 10 times more active than carbenicillin against *Pseudomonas* and *Streptococci*.

Dose: The dose is 8–18 g per day in 4–6 divided doses.

ii. Piperacillin (Pipracil, Pracil)**Synthesis**

Properties and uses: Piperacillin sodium is a white hygroscopic powder, soluble in water and methanol, practically insoluble in ethyl acetate. It is available as a powder for solubilization and injection. It is best given in combination with an aminoglycoside antibiotic.

Assay: It is assayed by adopting liquid chromatography technique.

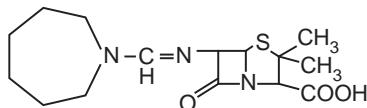
Dose: For serious and complicated infections: The adult dose as sodium is 200–300 mg/kg daily in divided doses or 3–4 g per day in divided doses of every 4 or 6 h. For life threatening conditions: especially those caused by *Pseudomonas* or *Klebsiella* spp, the dose is at least 16 g per day; usual maximum dose is 24 g per day. For children: 1 month–12 years, as sodium 100–300 mg/kg daily in 3–4 divided

doses. For neonates: The dose for less than 7 days or lesser than 2 kg, that is, 150 mg/kg daily in 3 divided doses; for more than 7 days and more than 2 kg, that is, 300 mg/kg in 3–4 divided doses, IV route is preferred for infants and children. Single dose more than 500 mg should not be given via IM injection.

Parenteral: For mild or uncomplicated infections: The adult dose as sodium is 100–125 mg/kg daily, the usual dose, if given via IV injection/infusion is 2 g every 6 or 8 h or 4 g every 12 h, if given via IM injection the dose is 2 g every 8 or 12 h. Prophylaxis of infection during surgery, for adults: as sodium the dose is 2 g just before the procedure or when the umbilical cord is clamped in caesarean section, followed by at least two doses of 2 g at intervals of 4 or 6 h within 24 h of procedure.

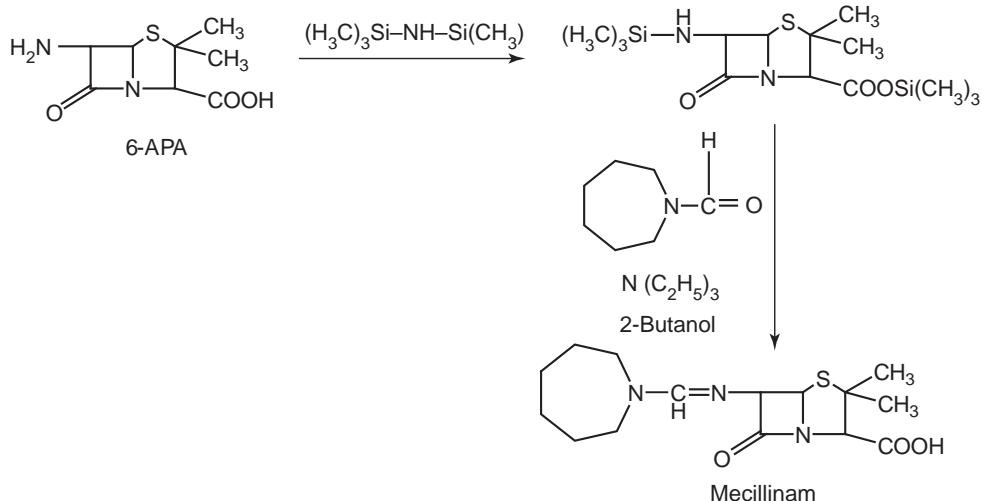
VI. Miscellaneous penicillins

i. Mecillinam (Amdinocillin)



6- β -(Hexahydro-1H-azepin-1-yl)-methylene aminopenicillanic acid

Synthesis



Properties and uses: Mecillinam is particularly active against enterobacteria including some ampicillin resistant strains and to treat urinary tract infections. It is structurally different from other penicillins, in that, it is not an acyl derivative, but rather alkylidene amino-(amidino) derivative of 6-APA, due to this difference, it has significant gram-negative antibacterial activity as compared to gram-positive antibacterial activity.

Cephalosporins

The cephalosporins were isolated from the fungus *Cephalosporium acremonium* in 1948 by Pro Tzu, Newton, and Abraham (1953). The main product being cephalosporin-C, the molecular modification of cephalosporin-C

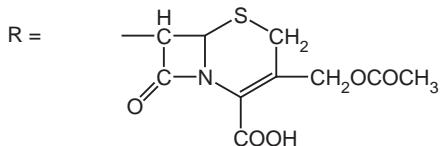
gave origin to semisynthetic substances. They are β -lactam antibiotics with same fundamental structural requirements as penicillins, the main difference between the two is that cephalosporins contain dihydromethiazine ring, while penicillin contains a tetrahydrothiazole (thiazolidine) ring. The cephalosporins are much more acid stable than the corresponding penicillins and also have a mechanism of action similar to that of penicillins; they mainly inhibit the cross-linking of the peptidoglycan units in bacterial cell walls by inhibiting transpeptidase enzyme. However, they bind in the target proteins other than penicillins binding proteins.

Cephalosporins can be divided into three classes:

1. *Cephalosporin N*: It has a penicillin-like structure being a derivative of 6-aminopenicillanic acid.
2. *Cephalosporin P*: An acidic antibiotic, which is steroid in nature.
3. *Cephalosporin-C*: It is a true cephalosporin and it is a derivative of 7 amino-cephalosporanic acid.

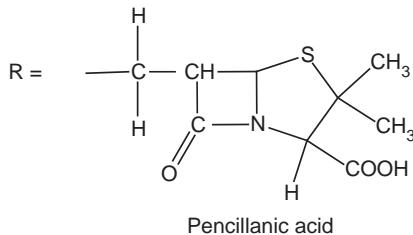
Generalized formula for cephalosporins

In cephalosporin C

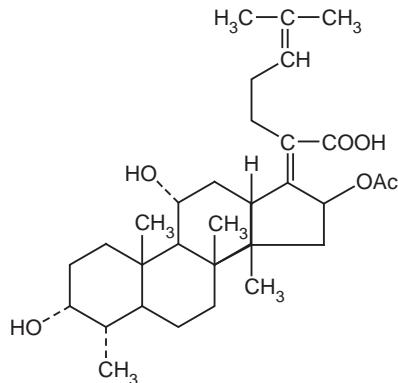


Cephalosporin C contains a side-chain derived from D- α -amino adipic acid, which is attached to 7-aminocephalosporanic acid

In cephalosporin N



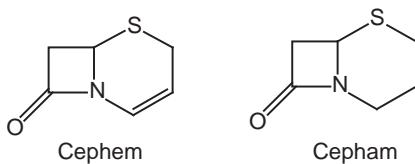
A compound structurally similar to cephalosporin P is called fusidic acid



Nomenclatures

Cephalosporins are named in the following ways:

1. *Chemical abstracts*: 5-Thia-1-azobicyclo (4.2.0) octanes. Accordingly, cephalothin is 3-(Acetoxy methyl)-8-oxo-7-(2-thienyl) acetamido-5thia-1-aza-bicyclo[4.2.0]-oct-2ene-2-carboxylic acid.
2. *Cephem derivatives*: Cephem is the name given to the unsubstituted bicyclic lactam.

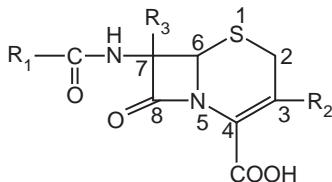


Classification

Cephalosporins are classified on the basis of their chemical structure, clinical pharmacology, antibacterial spectrum, or penicillinase resistance.

- a. Orally administered: cephalexin, cephadrine, and cefaclor
- b. Parentrally administered: cephalothin, cephapirin, cephacetrile, and cefazidone. These agents are sensitive to β -lactamase
- c. Resistant to β -lactamase and parentrally administered: cefuroxime, cefamandole, cefoxitin
- d. Metabolically unstable: cephalothin and cephapirin

Clinically used cephalosporins



I. First-generation cephalosporins

These drugs have the highest activity against gram-positive bacteria and the lowest activity against gram-negative bacteria (Table 4.1)

II. Second-generation cephalosporins

These drugs are more active against gram-negative bacteria and less active against gram-positive bacteria than first-generation members (Table 4.2).

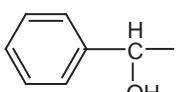
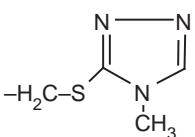
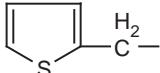
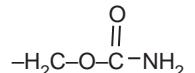
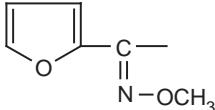
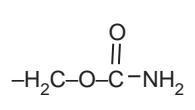
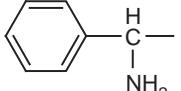
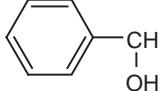
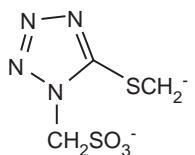
III. Third-generation cephalosporins

These drugs are less active than first-generation drugs against gram-positive organisms, but have a much-expanded spectrum of activity against gram-negative organisms (Table 4.3).

Table 4.1 First-generation cephalosporins.

| Name | R ₁ | R ₂ | R ₃ |
|----------------|----------------|----------------|----------------|
| Cephaloridine | | | -H |
| Cephalothin | | | -H |
| Cephapirin | | | -H |
| Cephalexin | | | -H |
| Cephaloglycine | | | -H |
| Cefadroxil | | | -H |
| Cephradine | | | -H |
| Cefazolin | | | -H |
| Cephradine | | | -H |

Table 4.2 Second-generation cephalosporins.

| Name | R ₁ | R ₂ | R ₃ |
|-------------|---|---|-------------------|
| Cefamandole |  |  | -H |
| Cefoxitin |  |  | -OCH ₃ |
| Cefuroxime |  |  | -H |
| Cefaclor |  | | -Cl |
| Cefonicid |  |  | -H |

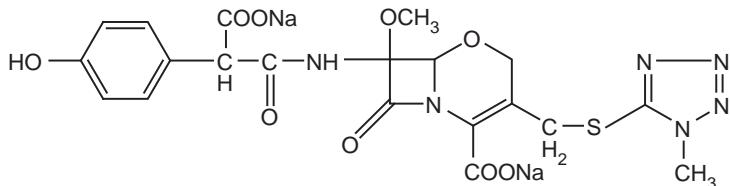
Moxalactam

Table 4.3 Third-generation cephalosporins.

| Name | R ₁ | R ₂ | R ₃ |
|-------------|----------------|---|----------------|
| Ceftizoxime | | -H | -H |
| Cefotaxime | | -H ₂ C-O-C(=O)-CH ₃ | -H |
| Ceftazidime | | | -H |
| Ceftriaxone | | | -H |
| Cefmenoxime | | | -H |

IV. Fourth-generation cephalosporins

Cefepime and cefpirome are new fourth-generation parenteral cephalosporins with a spectrum of activity which makes them suitable for the treatment of infections caused by a wide variety of bacteria (Table 4.4).

Table 4.4 Fourth-generation cephalosporins.

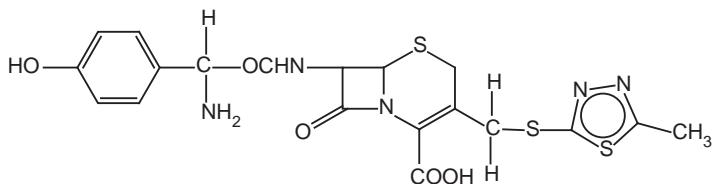
| Name | R ₁ | R ₂ | R ₃ |
|----------|----------------|----------------|--------------------------|
| Cefepime | | | -H <i>(Continued)</i> |

(Continued)

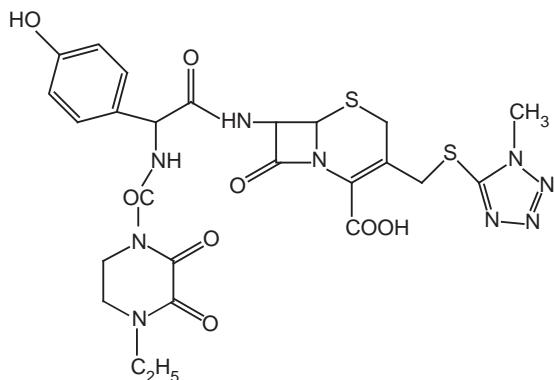
| Name | R ₁ | R ₂ | R ₃ |
|-----------|----------------|----------------|----------------|
| Cefpirome | | | -H |

V. Miscellaneous

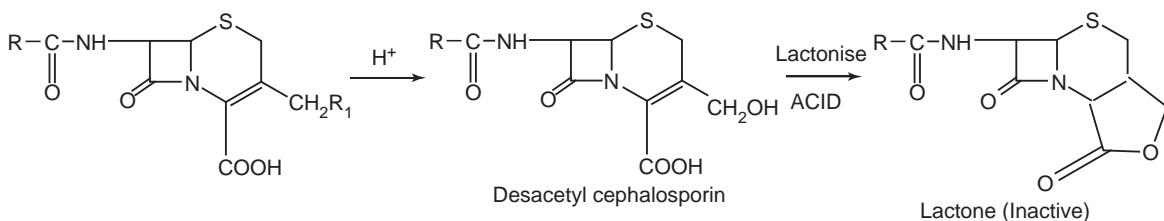
i. Cefaparole



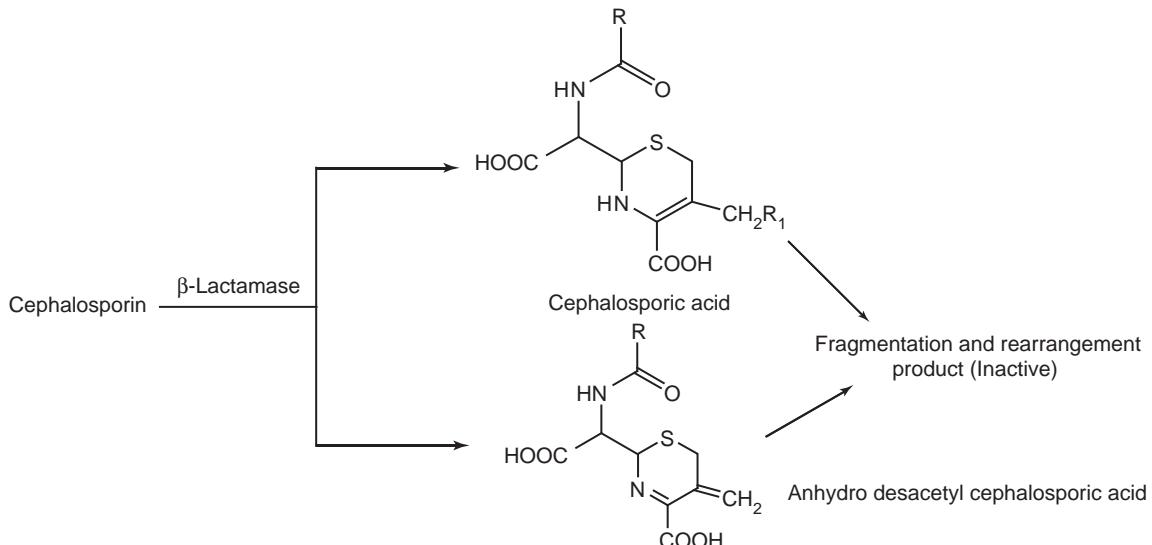
ii. Cefoperazone

**Degradation of Cephalosporins**

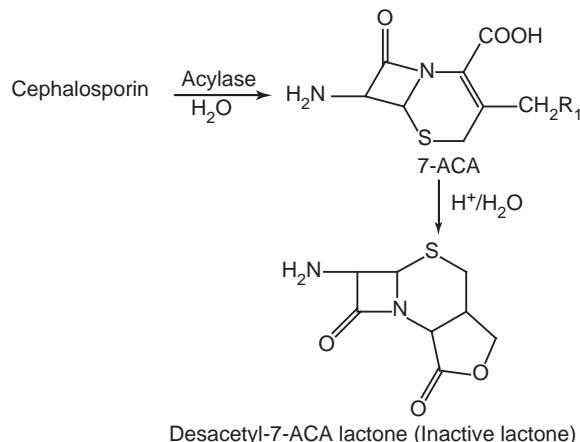
Cephalosporins experience a variety of hydrolytic degradation reactions.

In strong acid solutions

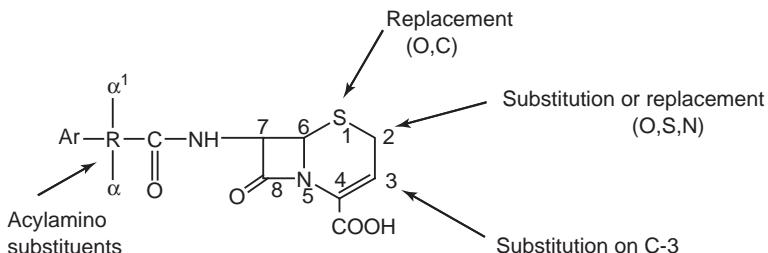
In the presence of β -lactamase



In the presence of acylase

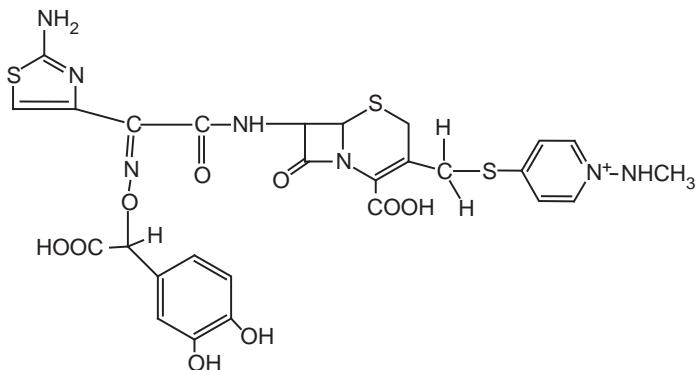


SAR of Cephalosporins



1. 7-Acylamino substitution

- The addition of amino group and a hydrogen to α and α_1 position produces basic compound, which is protonated under acidic conditions of stomach. The ammonium ion improves the stability of β -lactum of cephalosporins and make active orally. Activity against positive bacteria is increased and gram negative is decreased by acylation of amino group.
- When the new acyl groups are derived from carboxylic acids, it shows good spectrum of antibacterial action for gram-positive bacteria.
- Substitutions on the aromatic ring phenyl that increase lipophilicity provide higher gram-positive activity and generally lower gram-negative activity.
- The phenyl ring in the side chain can be replaced with other heterocycles with improved spectrum of activity and pharmacokinetic properties; these include thiophene, tetrazole, furan, pyridine, and aminothiazoles.
- The L-isomer of an α -amino α_1 -hydrogen derivative of cephalosporins was 30–40 fold stable than D-isomer. Addition of methoxy oxime to α and α_1 increases the stability to nearly 100-fold. The presence of catechol grouping can also enhance activity, particularly, against *Pseudomonas aeruginosa*, and also retain some gram-positive activity, which is unused for a catechol cephalosporin.



These compounds penetrate into the cell by utilizing the bacterial ion β -dependent ion transport system. There is a reduction of Gram negative activity when the lipophilicity of this side chain is increased and effects of polar α -substituents are enhanced (OH , NH_2 , SO_3H , COOH).

2. Modification in the C-3 substitution: The pharmacokinetic and pharmacodynamics depends on C-3 substituents. Modification at C-3 position has been made to reduce the degradation (lactone of desacetyl cephalosporin) of cephalosporins.

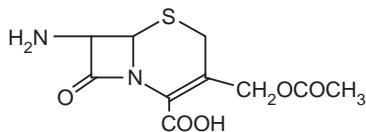
- The benzoyl ester displays improved gram-positive activity, but lowered gram-negative activity.
- Pyridine, imidazole replaced acetoxy group by azide ion yields derivative with relatively low gram-negative activity.
- Displacement with aromatic thiols of 3-acetoxy group results in an enhancement of activity against gram-negative bacteria with improved pharmacokinetic properties.
- Orally active compounds are produced by replacement of acetoxy group at C-3 position with CH_3 and Cl .

3. Other modifications

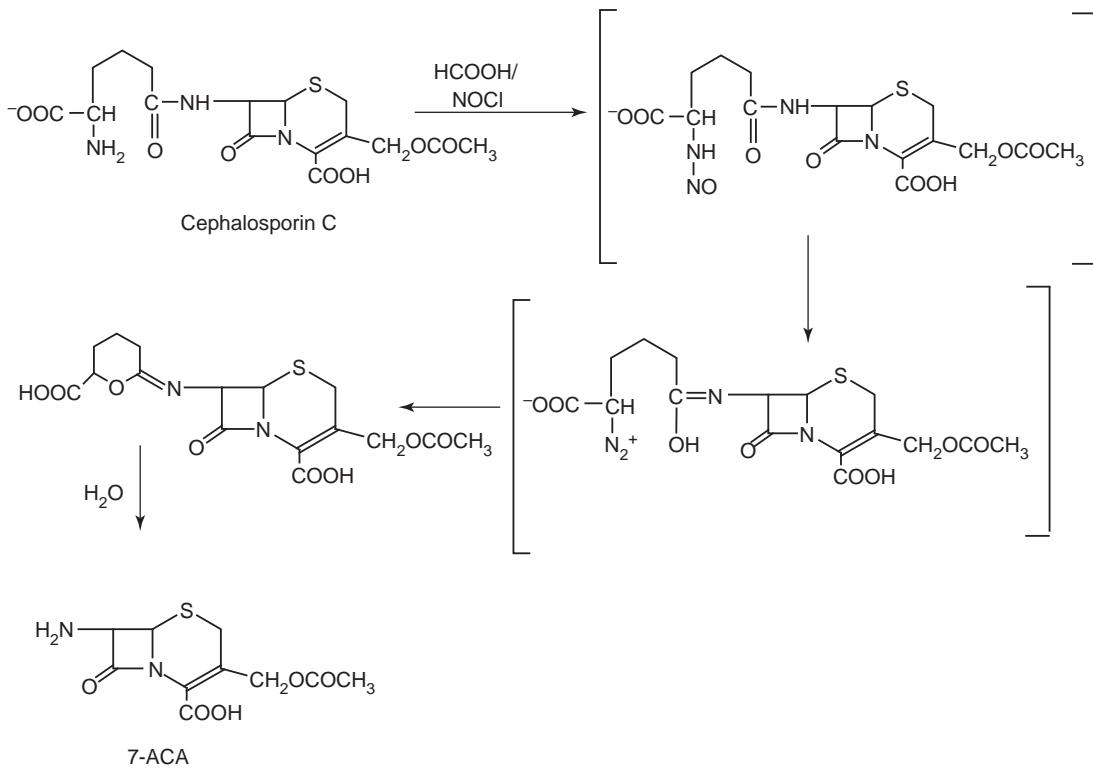
- Methoxy group at C-7, shows higher resistance to hydrolysis by β -lactamase.
- Oxidation of ring spectrum to sulfoxide or sulphone greatly diminishes or destroys the antibacterial activity.
- Replacement of sulphur with oxygen leads to oxacepam (latamoxet) with increased antibacterial activity, because of its enhanced acylating power. Similarly, replacement of sulphur with methylene group (loracavet) has greater chemical stability and a longer half-life.
- The carboxyl group position-4 has been converted into ester prodrugs to increase bioavailability of cephalosporins, and these can be given orally as well.
- The antibacterial activity depends on the olefinic linkage at C-3 and C-4 position and their activity is lost due to the ionization of double bond to 2nd and 3rd positions.

SYNTHESIS AND DRUG PROFILE

7-Aminocephalosporanic acid (7ACA)

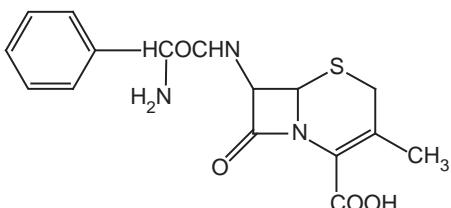


Synthesis

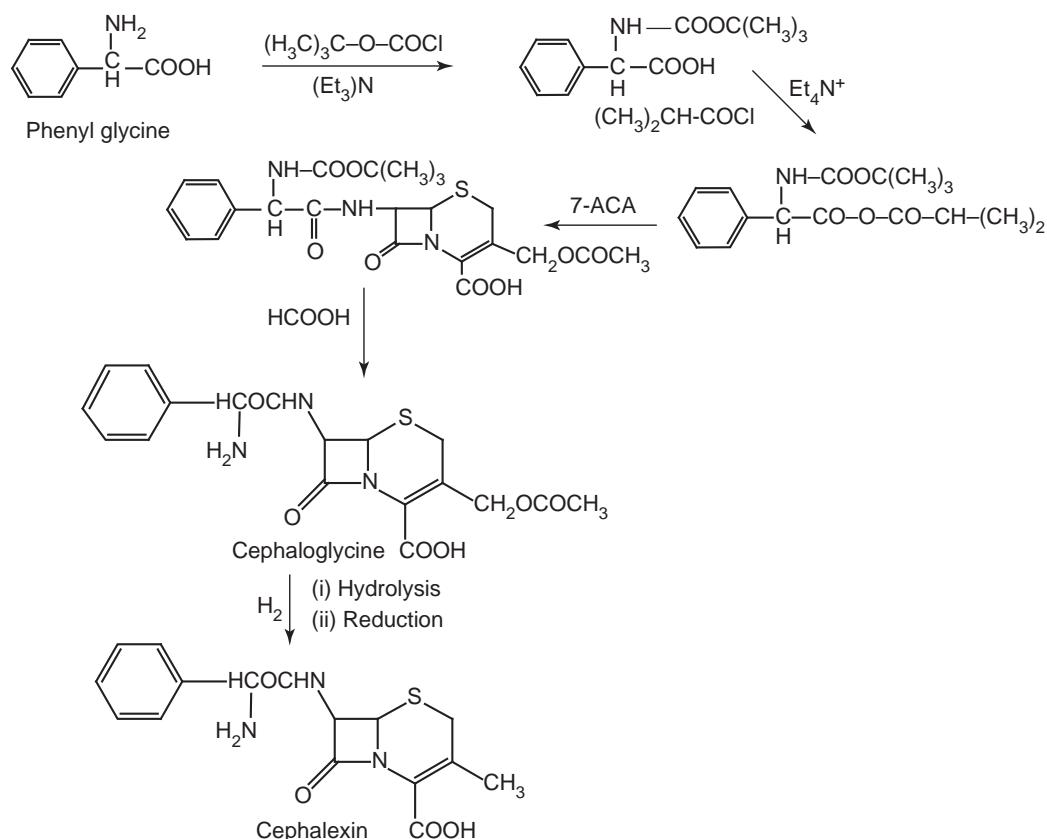


I. First-generation cephalosporins

i. Cephalexin (Keflex, Keforal)



Synthesis



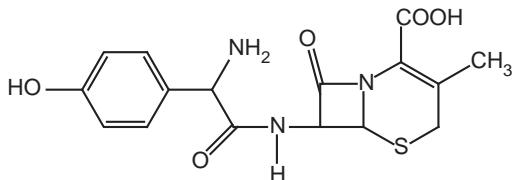
Properties and uses: Cephalexin monohydrate is a white crystalline powder, sparingly soluble in water, and practically insoluble in alcohol. The α -amino group of cephalexin renders it acid stable. The 3-methyl group is responsible for the metabolic stability. It is particularly recommended for urinary tract infection.

Dose: The oral dose for adults is 250–500 mg every 6 h, for children, the dose is 18–25mg/kg every 6 h.

Assay: It is assayed by adopting liquid chromatography technique.

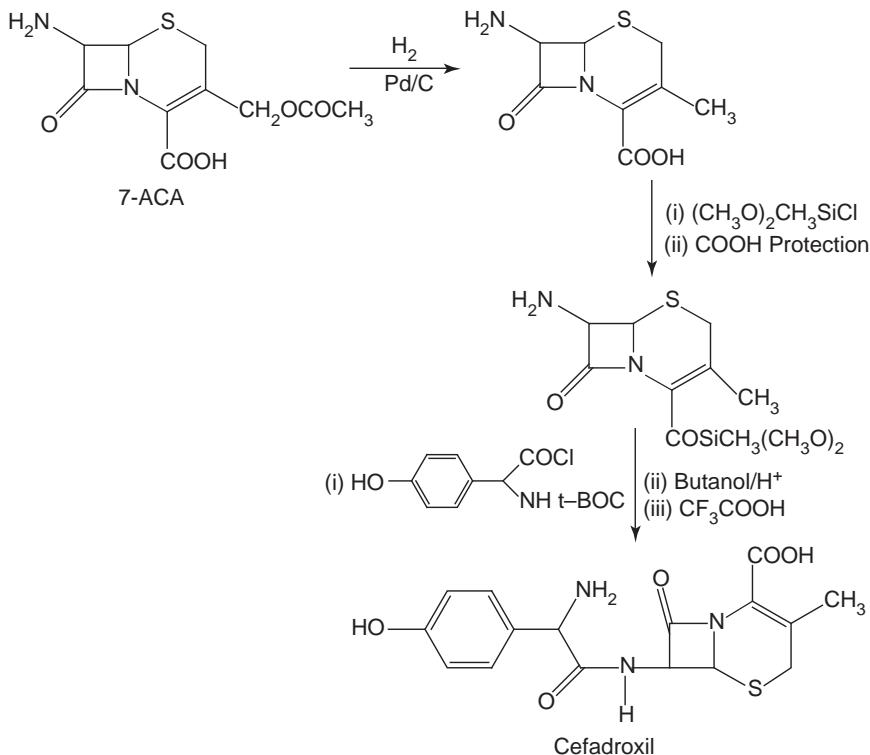
Dosage forms: Cefalexin capsules I.P., B.P., Cefalexin oral suspension I.P., B.P., Cefalexin tablets I.P., B.P.

ii. Cefadroxil (Cefadrox, Droxyl, Codroxil)



7-(2-Amino-2-(4-hydroxyphenyl)acetamido)-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Synthesis



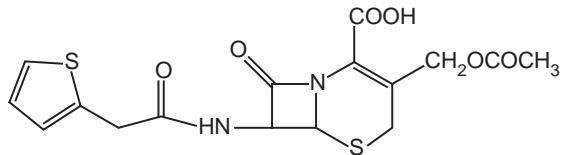
Properties and uses: Cefadroxil monohydrate is a white or almost white powder, slightly soluble in water, and sparingly soluble in ethanol. The antibacterial spectrum of action and therapeutic indications of cefadroxil are very similar to those of cephalexin and cephadrine. The D-p-hydroxyphenylglycyl isomer is much more active than the L-isomer.

Assay: It is assayed by adopting liquid chromatography technique.

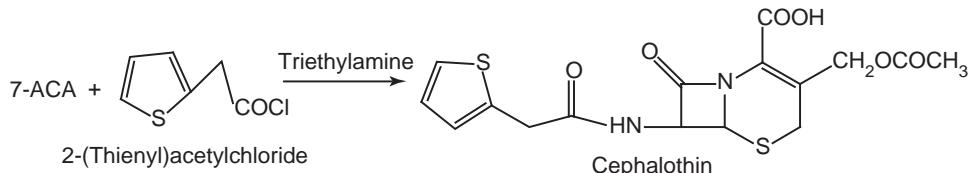
Dosage forms: Cefadroxil capsules I.P., B.P., Cefadroxil oral suspension I.P., B.P. Cefadroxil tablets I.P.

Dose: In the case of uncomplicated lower urinary tract infections: For adults, the dose is 1–2 g daily as a single or 2 divided doses. For children more than 6 years, the dose is 500 mg twice a day, that is, 1–6 years, 250 mg twice a day; for children less than 1 year, the dose is 25 mg/kg daily in divided doses. In the case of skin and skin structure infections: For adults, the dose is 1g per day in single or divided doses. For children, the dose is 30 mg/kg per day in equally divided doses every 12 h. In the case of pharyngitis and tonsilitis: For adults in the treatment of group A beta-haemolytic streptococcal pharyngitis and tonsilitis, the dose is 1 g per day in single or divided doses for 10 days. In the case of children, 30 mg/kg per day in equally divided doses every 12 h for at least 10 days.

iii. Cephalothin (Keflin)



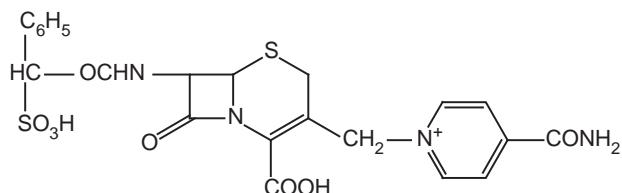
Synthesis

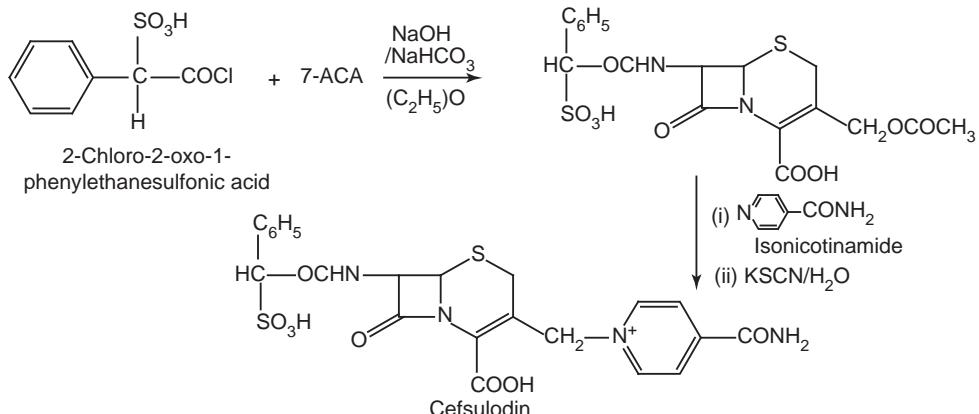


Properties: Cephalothin is a white, odourless, crystalline powder, insoluble in most organic solvents, soluble in organic solvents and it is acid stable. It is hygroscopic and decomposes on heating, and it has been described as broad-spectrum antibacterial compound, it is not in the same class as the tetracyclines. Its spectrum of activity is broader than that of penicillin G and more similar to that of ampicillin.

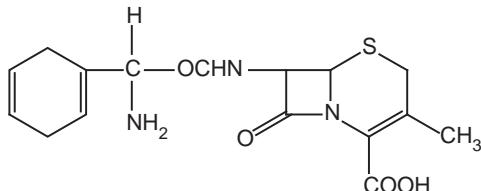
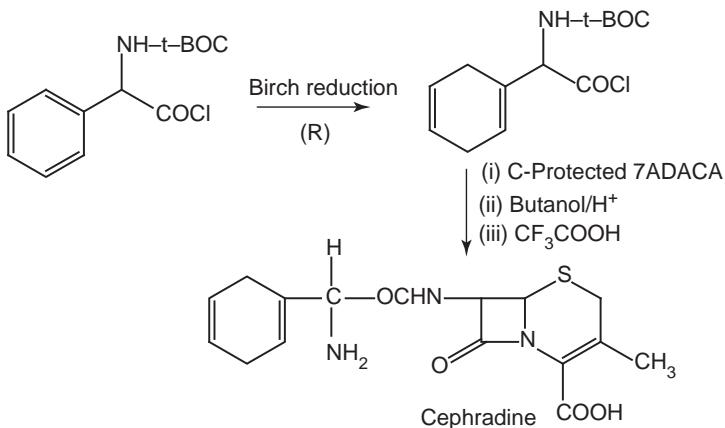
Dose: The dose for adults given IM or IV is equivalent to 500 mg–1 g every 4 to 6 h; children the dose is 13–26 mg/kg of body weight every 4 h.

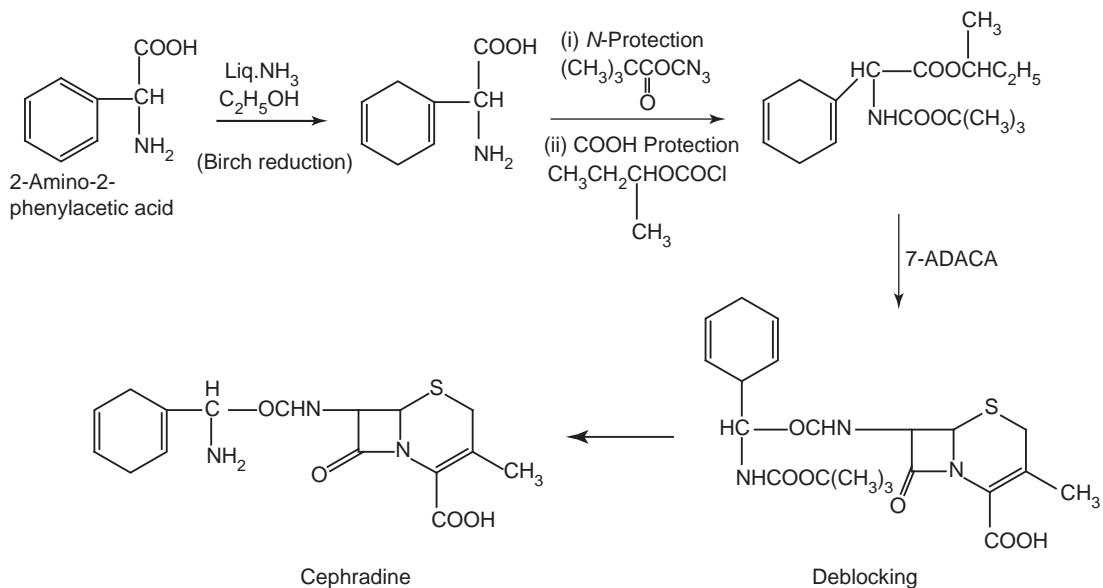
iv. Cefsulodin



Synthesis

Properties and uses: It is indicated for use in staphylococcal and pseudomonal infections.

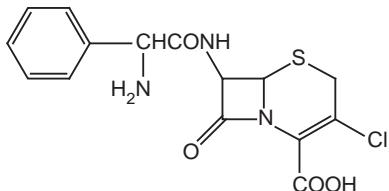
v. Cephradine**Synthesis****Route-I.**

Route-II. From: 2-Amino-2-phenylacetic acid


Properties and uses: Cephadrine exists as colourless crystals, soluble in propylene glycol, but slightly soluble in acetone or alcohol. Used as an antibacterial agent.

II. Second-generation cephalosporin

i. Cefaclor

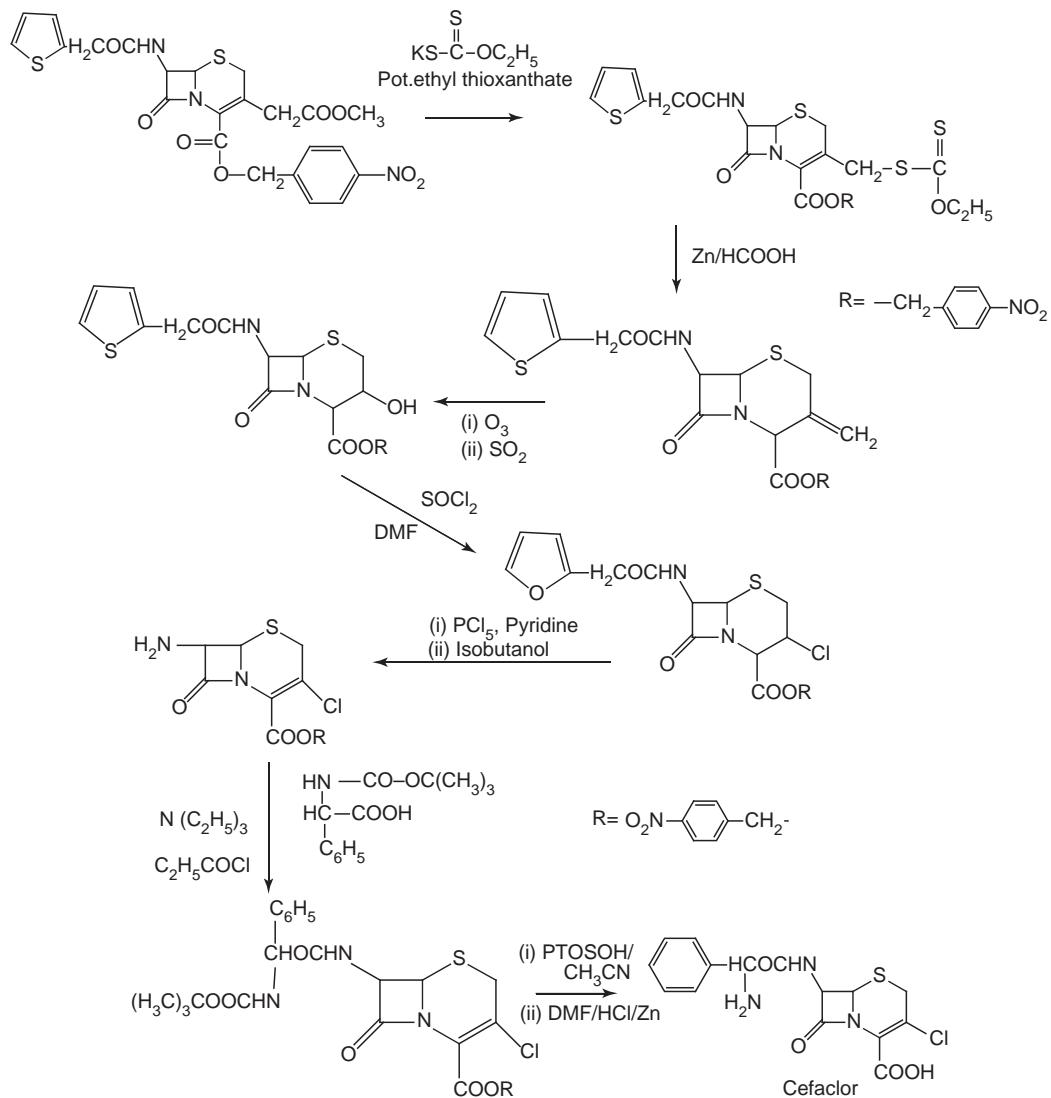
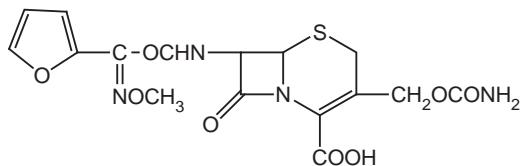


Properties and uses: Cefaclor is a white or slightly yellow powder, slightly soluble in water, practically insoluble in methanol and methylene chloride. It has chloro group at C-3 position, and hence, stable in acid and achieves sufficient oral absorption. Used in the treatment of upper respiratory tract infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

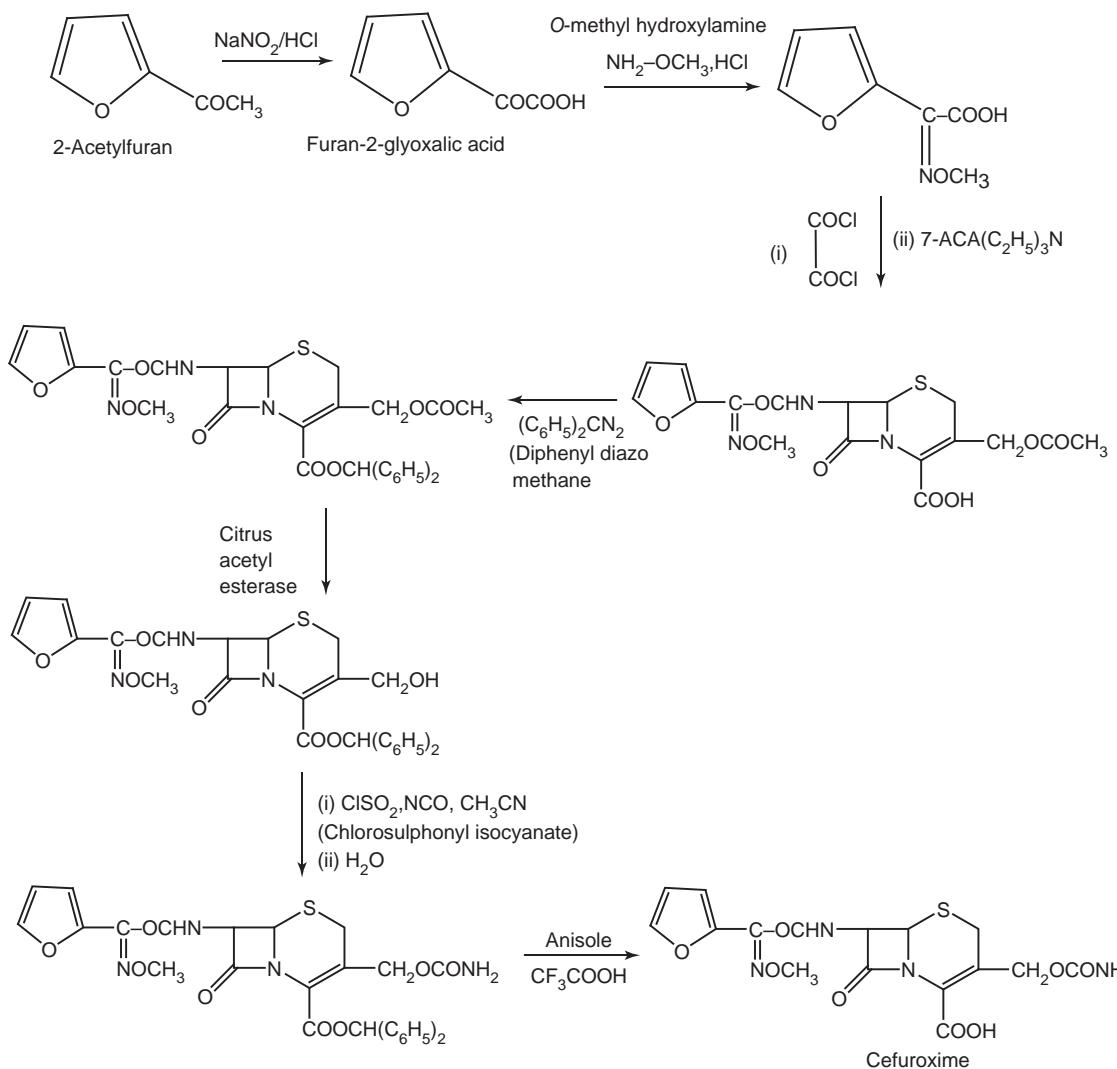
Dose: The dose orally for adults is 250–500 mg every 8 h.

Assay: It is assayed by adopting liquid chromatography technique.

Dosage forms: Cefaclor capsules B.P., Cefaclor oral suspension B.P., Prolonged-release Cefaclor tablets B.P.

Synthesis**ii. Cefuroxime (Zinacef, Kefurox)**

Synthesis

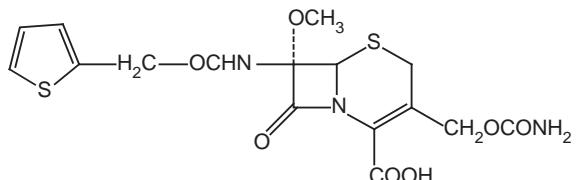
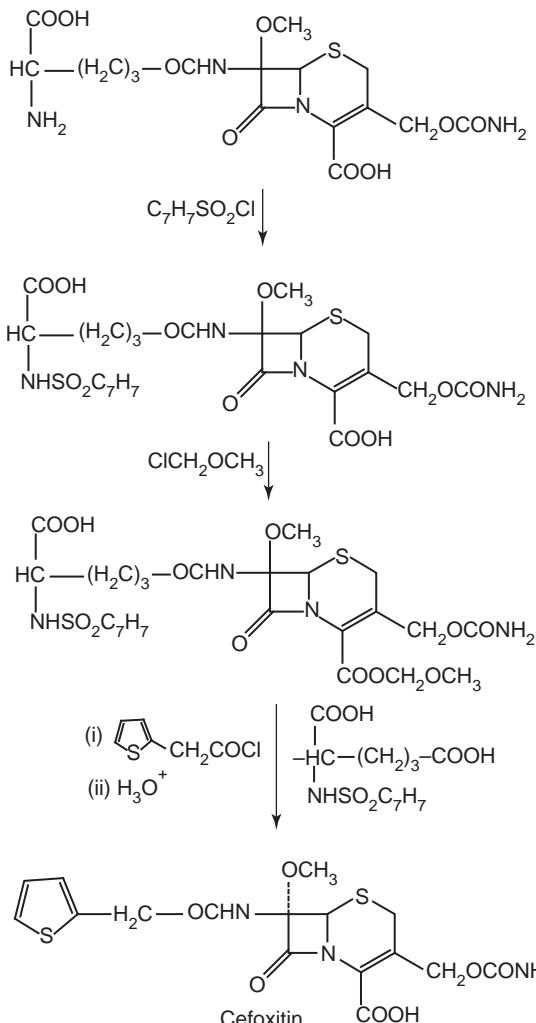


Properties and uses: Cefuroxime sodium is a white hygroscopic powder, freely soluble in water, and very slightly soluble in ethanol. It has excellent activity against all *gonococci*, hence, is used to treat gonorrhoea. It may be used to treat lower respiratory tract infections caused by *H. influenza* and *Para influenzae*, *Klebsiella* spp., *E. coli*, *Staphylococcus pneumoniae*, and pyrogens.

Assay: It is assayed by adopting liquid chromatography technique.

Dose: The dose is 1.5 g (IM) as a single dose and also available as powder for injection in strengths of 0.75 and 1.5 g.

Dosage forms: Cefuroxime sodium injection I.P., Cefuroxime injection B.P.

iii. Cefoxitin**Synthesis**

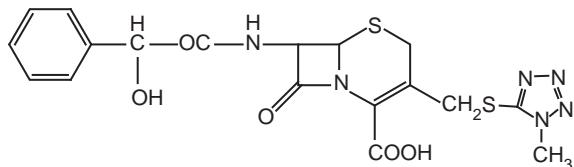
Properties and uses: Cefoxitin sodium is a white hygroscopic powder, soluble in water and sparingly soluble in alcohol. It is not the drug of choice for any infection, but it is an alternative drug for intra-abdominal infections, colorectal surgery, appendectomy, and ruptured viscus because it is active against most enteric

anaerobes, including *Bacteroides fragilis*. It is approved for use in the treatment of bone and joint infections caused by *Staphylococcus aureus*, gynecological and intra-abdominal infections by *Bacteroides* spp.

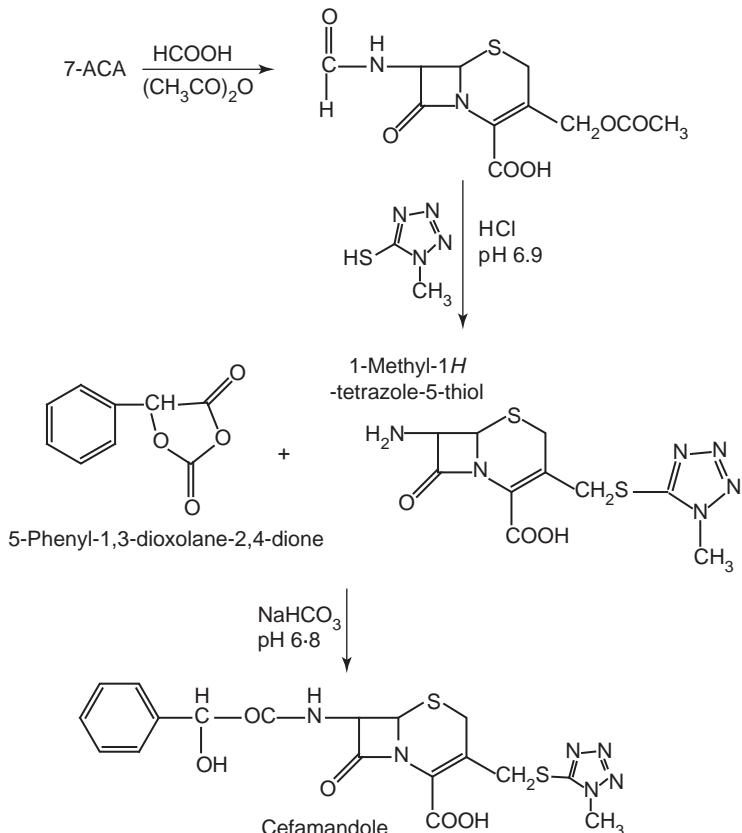
Assay: It is assayed by adopting liquid chromatography technique.

Dosage forms: Cefoxitin injection B.P.

iv. Cefamandole (Mandol, Kefadol)



Synthesis

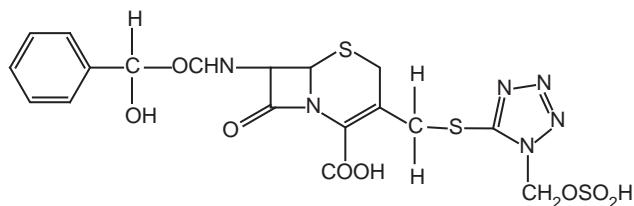


Properties and uses: Cefamandole nafate is a white powder, soluble in water, and sparingly soluble in methanol. It is the first compound of second-generation cephalosporin marketed in the United States. Cefamandole nafate is very unstable in solution and hydrolyzes rapidly to release cefamandole and formate. There is no loss of potency; however, these solutions are stored for 24 h at room temperature or up to 96 h by refrigeration.

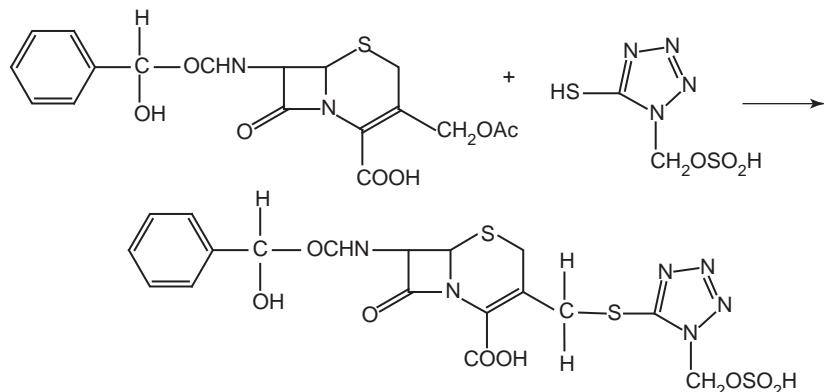
Assay: It is assayed by adopting liquid chromatography technique.

Dose: IV dose is 0.5–2 g every 4 to 6 h, also available as injection in strength of 0.5 and 1 mg/10ml.

v. Cefonicid



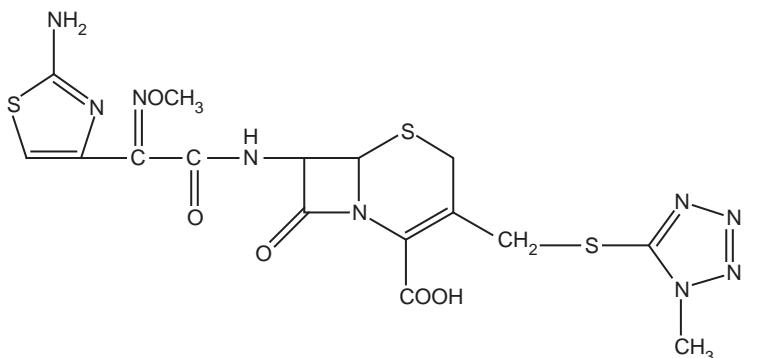
Synthesis



Properties and uses: Cefonicid is a second-generation cephalosporin that is structurally similar to cefamandole, except that it contains a methanesulphonic acid group attached to the N-1 position of the tetrazole ring. Used in the treatment of bacterial infections.

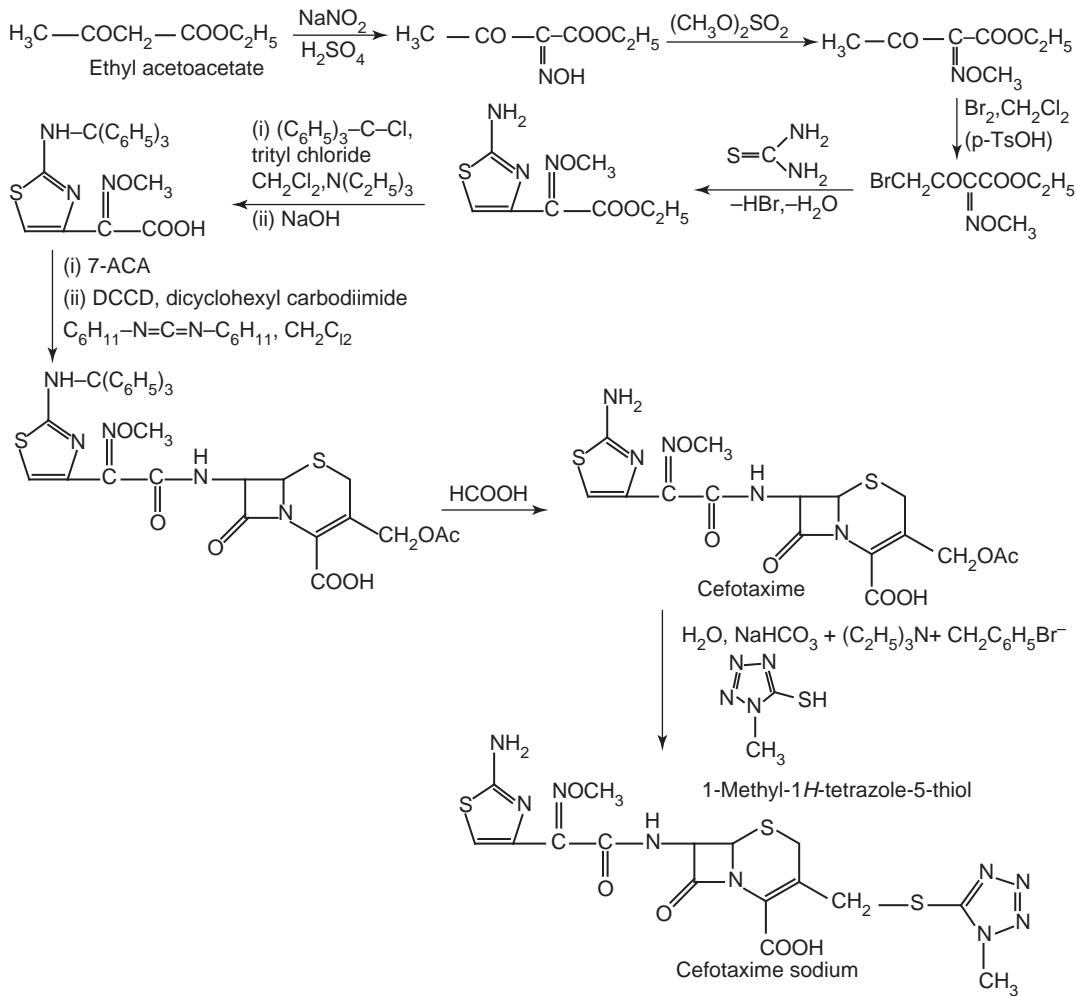
III. Third-generation cephalosporins

i. Cefotaxime Sodium



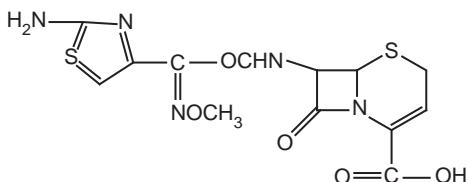
7-(2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((1-methyl-1*H*-tetrazol-5-ylthio)methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

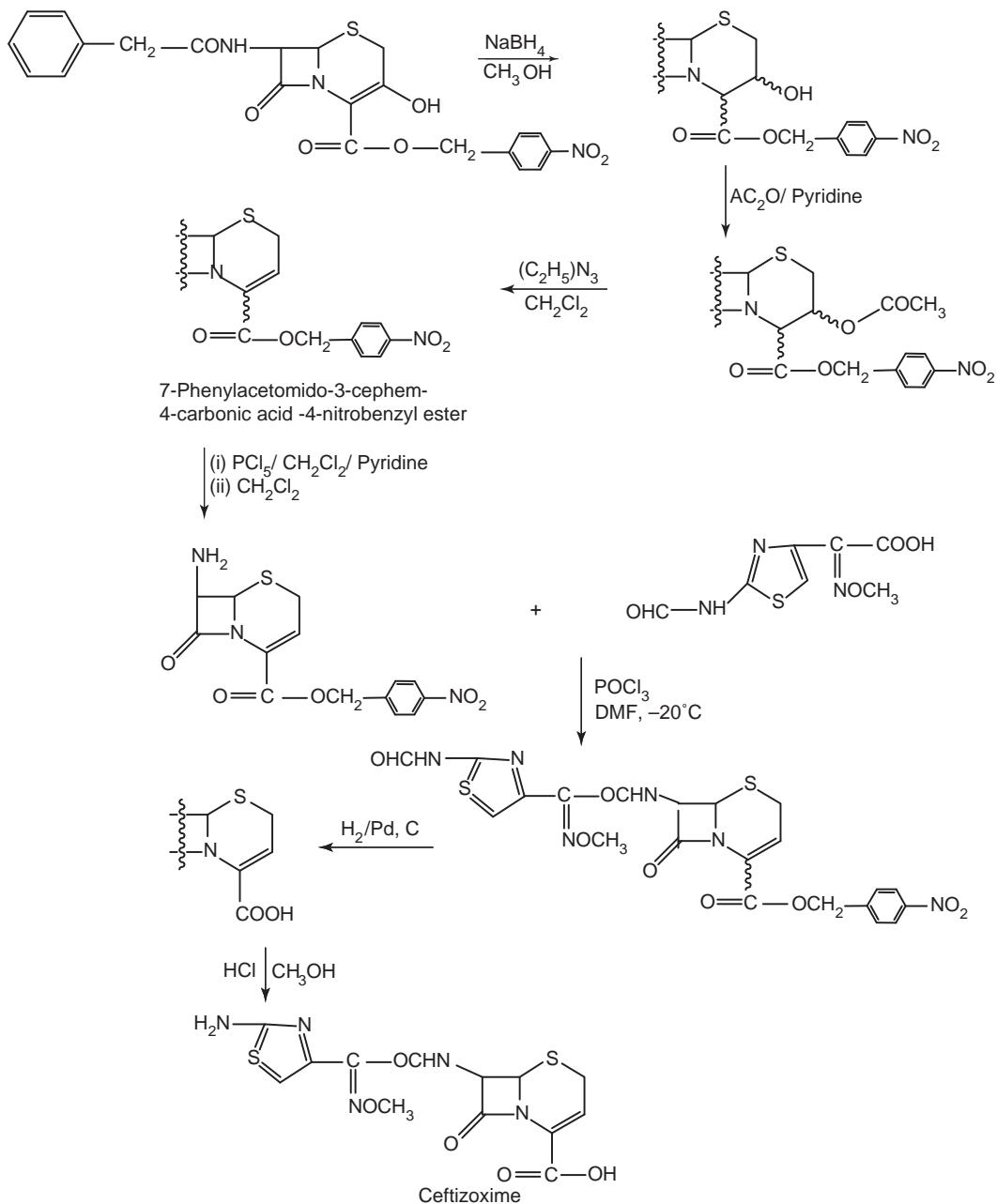
Synthesis



Properties and uses: Cefotaxime sodium exists as white solid and soluble in water, exhibits broad-spectrum activity against both gram-positive and gram-negative bacteria. Used in genitourinary infection and lower respiratory infection.

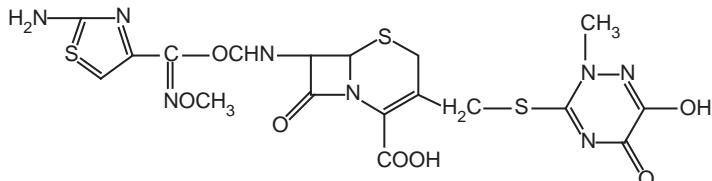
ii. Ceftizoxime sodium



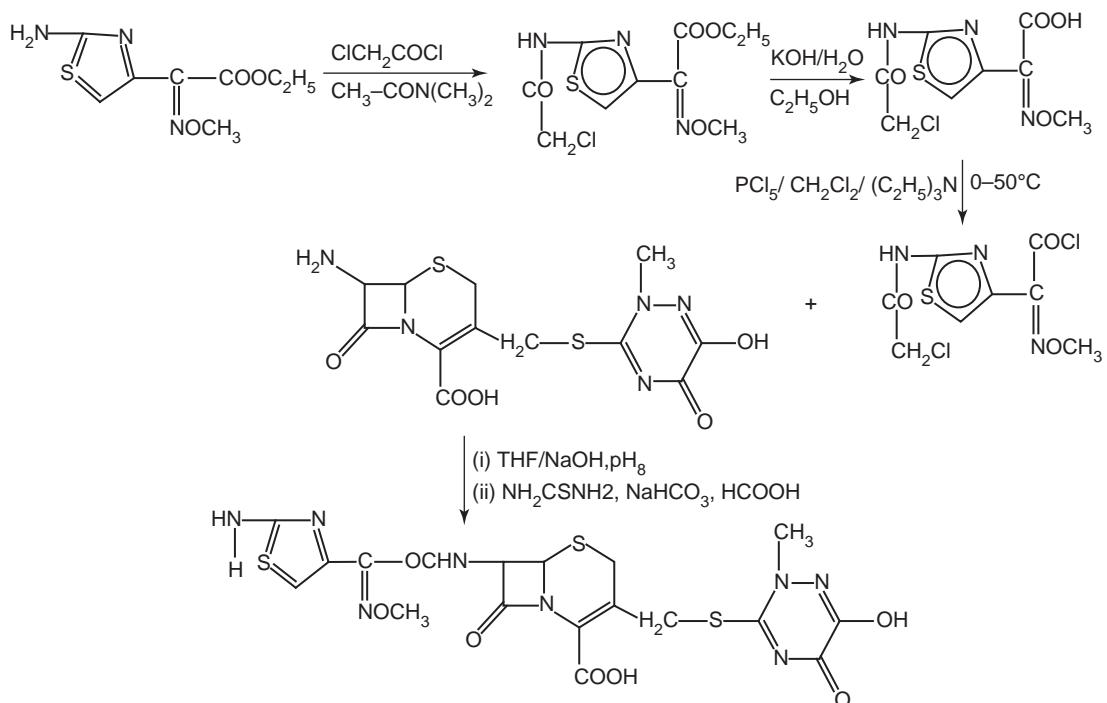
Synthesis

Properties and uses: It is a beta lactamase resistant cephalosporin, used in lower respiratory infection and meningitis.

iii. Ceftriazone disodium



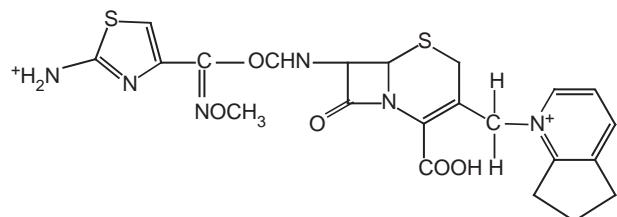
Synthesis



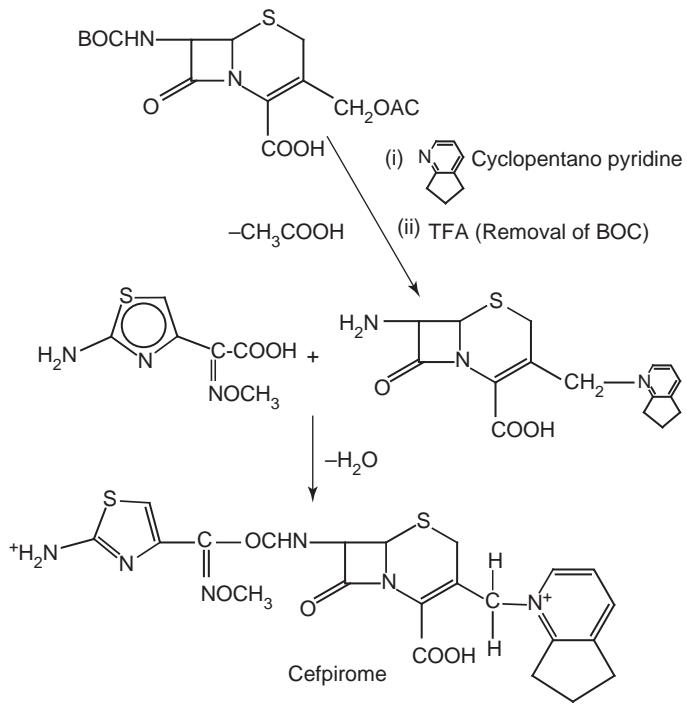
Properties and uses: It exists as white crystals, soluble in water, exhibits broad-spectrum activity against both gram-positive and gram-negative bacteria.

IV. Fourth-generation cephalosporin

i. Cefpirome (Ceform, Ominorm, Taform)



Synthesis

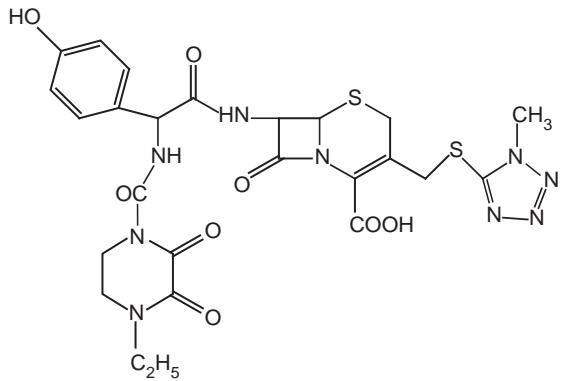


Properties and uses: Cefpirome is used to treat susceptible infections, including urinary and respiratory tract infections, skin infections, septicaemia, and infections in immuno-compromised patients.

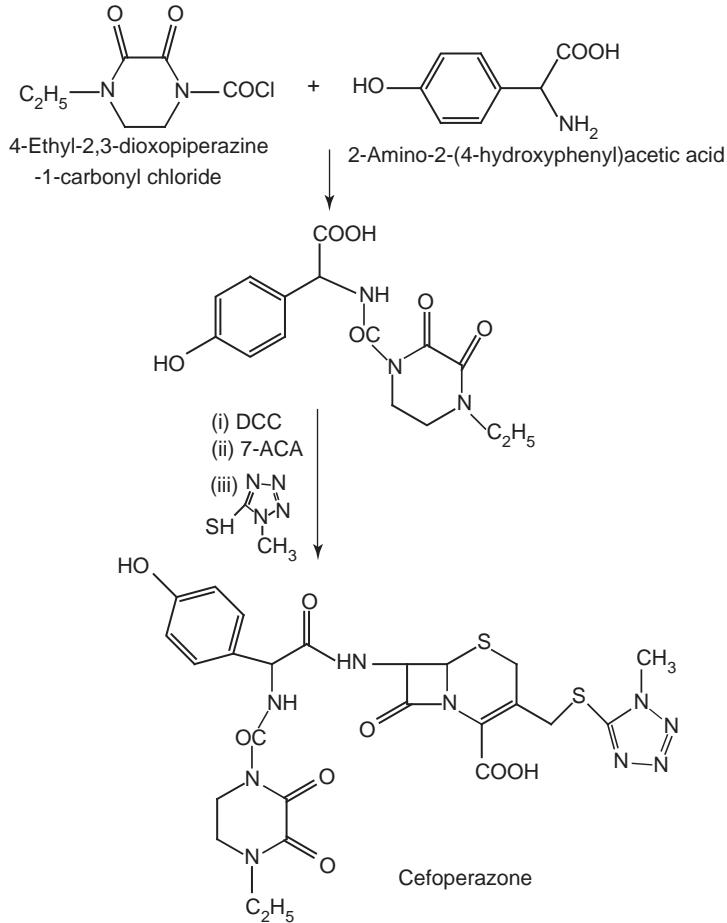
Dose: Intravenous dose for adults as sulphate is 1–2 g every 12 h over 3–5 min or infuse over 20–30 min.

V. Miscellaneous

i. Cefoperazone

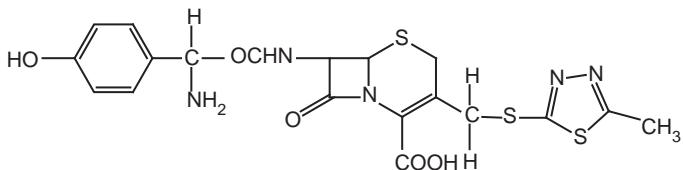


Synthesis

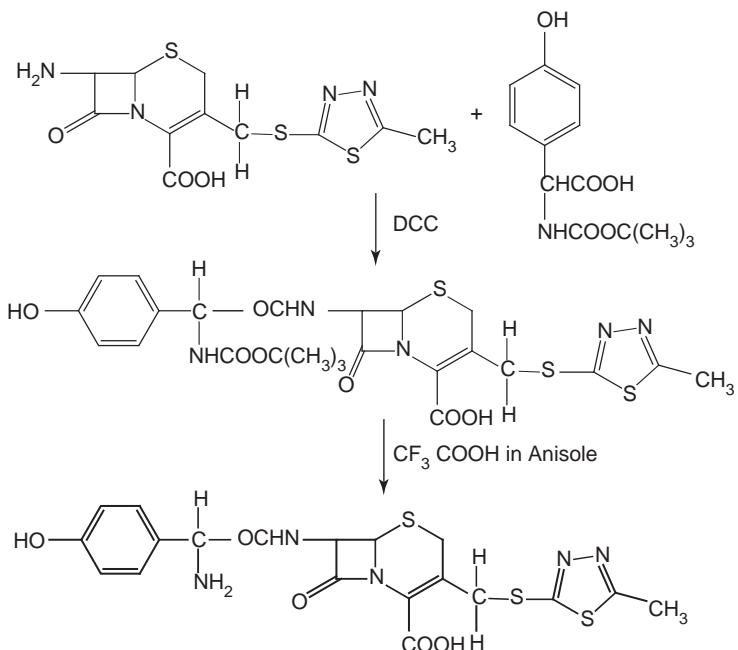


Properties and uses: Cefoperazone exists as white powder. It is a third-generation, antipseudomonal cephalosporin that resembles piperacillin, chemically and microbiologically. It is less active than cephalexin against gram-positive bacteria and less active than cefamandole against most of the enterobacteria.

ii. Cefoperazone



Synthesis



Adverse reactions of the cephalosporins

The cephalosporins produce a number of adverse effects. Examples are the following:

- Allergic manifestation:** The cephalosporins should be avoided or used with caution in individuals allergic to penicillins. When cefamandole or cefoperazone is ingested with alcohol, a disulphiram-like effect is seen, because these cephalosporins block the second step in alcohol oxidation, which results in the accumulation of acetaldehyde.
- Bleeding:** Bleeding can occur with cefamandole or cefoperazone because of antivitamin K effects. But the administration of the vitamin overcomes this problem.

2. Aminoglycoside antibiotics

The aminoglycoside antibiotics contain one or more amino sugars linked to an aminocytitol ring by glycosidic bonds. These are broad-spectrum antibiotics; in general, they have greater activity against gram-negative than gram-positive bacteria. The development of streptomycin, the first antibiotic of this group, was a well-planned work of Waksman (1944) and his associates, who isolated it from a strain of *Streptomyces griseus*.

The aminoglycoside can produce severe adverse effects, which include nephrotoxicity, ototoxicity, and neuro effects. These properties have limited the use of aminoglycoside chemotherapy to serious systemic indications. Some aminoglycosides can be administered for ophthalmic and topical purposes.

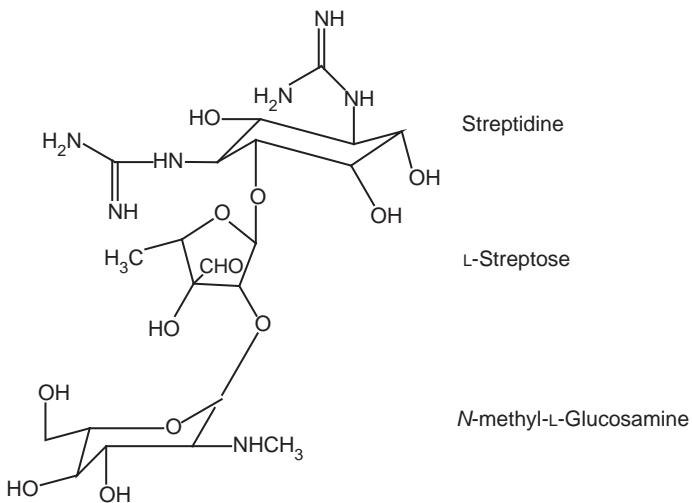
Mode of action: The aminoglycosides exhibit bactericidal effects as a result of several phenomena. Ribosomal binding on 30s and 50s subunits as well as the interface produces misreading; this disturbs

the normal protein synthesis. Cell membrane damage also plays an integral part in ensuring bacterial cell death. Some examples of aminoglycoside antibiotics are listed in Table 4.1.

Table 4.1 Examples of aminoglycoside antibiotics.

| Name | Source |
|-------------------------|---|
| Streptomycin | <i>Streptomyces griseus</i> |
| Neomycin | <i>S. fradiae</i> |
| Kanamycin | <i>S. kanamyeleticus</i> |
| Gentamycin | <i>Micromonospora purpura</i> |
| Netilmicin | <i>Micromonospora species</i> |
| Tobramycin (Nebramycin) | <i>S. tenebrarius</i> |
| Framycetin (Soframycin) | <i>S. decaris</i> |
| Paromomycin | <i>S. rimosus and S. paramomycinus</i> |
| Amikacin | It is 1-L-(-) 4-amino-2-hydroxy butyryl kanamycin |

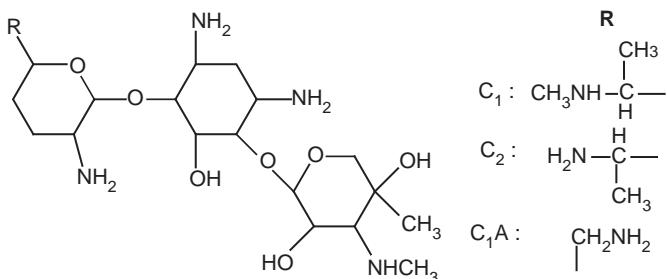
a. Streptomycin and dihydrostreptomycin



Properties and uses: Streptomycin sulphate is a white hygroscopic powder, very soluble in water, and practically insoluble in ethanol. The organism, *S. griseus*, releases the other substances, such as hydroxystreptomycin, mannisidostreptomycin, and cycloheximide, but do not reach up to the required activity/potency level. The development of resistant strains of bacteria and chronic toxicity constitutes major drawbacks of this category. It is an aminoglycoside antibacterial also used as an antitubercular drug.

Assay: It is assayed by microbiological method.

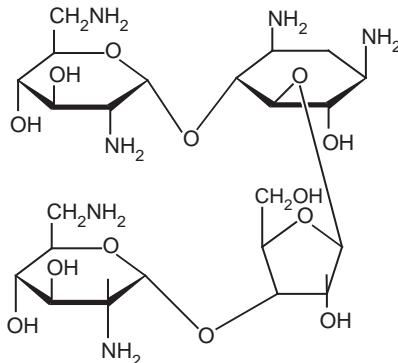
Dosage forms: Streptomycin injection B.P.

b. Gentamycins

Properties and uses: Gentamycin is a mixture of C_1 , C_2 , and C_1A compounds, obtained commercially from *Micromonospora purpurea*. Gentamycin sulphate exists as white hygroscopic powder, soluble in water, and practically insoluble in alcohol, although it is a broad-spectrum antibiotic. It is used in the treatment of infections caused by gram-negative bacteria of particular interest and has a high degree of activity against *P. aeruginosa*, where the important causative factor is burned skin. It is used topically in the treatment of infected bed-sores, pyoderma, burns, and in the eye infection.

Assay: It is assayed by microbiological method.

Dosage forms: Gentamicin cream B.P., Gentamicin ear drops B.P., Gentamicin and Hydrocortisone acetate ear drops B.P., Gentamicin eye drops B.P., Gentamicin injection B.P., Gentamicin ointment B.P.

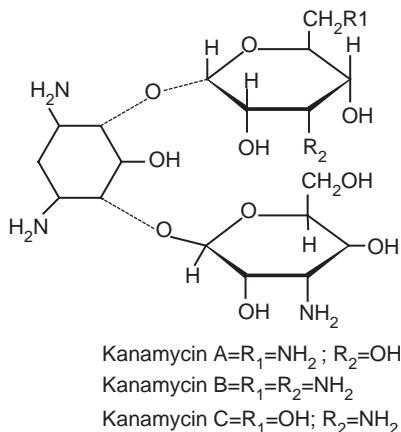
c. Neomycin

Properties and uses: Neomycin sulphate is a white or yellowish-white hygroscopic powder, very soluble in water, very slightly soluble in alcohol, and practically insoluble in acetone. Neomycin is a mixture of closely related epimers, neomycin B, and C. Neomycin B differ from neomycin C by the nature of the sugar attached terminally to D-ribose, this sugar called neosamine. B_1 differs from neosamine C in its stereochemistry. In neomycin B_1 , the neobiosamine moiety contains β -L-iodopyranosyl, whereas in neomycin C the configuration is inverted and it is 2-D-glucopyranosyl. It is photosensitive and its main use is in the treatment of the ear, eye, and skin infections; these include burns, wounds, ulcer, and infected dermatoses.

Assay: It is assayed by microbiological method.

Dosage forms: Dexamethasone and Neomycin ear spray B.P., Hydrocortisone and neomycin cream B.P., Hydrocortisone acetate and Neomycin ear drops B.P., Hydrocortisone acetate and Neomycin eye drops B.P., Neomycin eye drops B.P., Hydrocortisone acetate and Neomycin eye ointment B.P., Neomycin eye ointment B.P., Neomycin oral solution B.P., Neomycin tablets B.P.

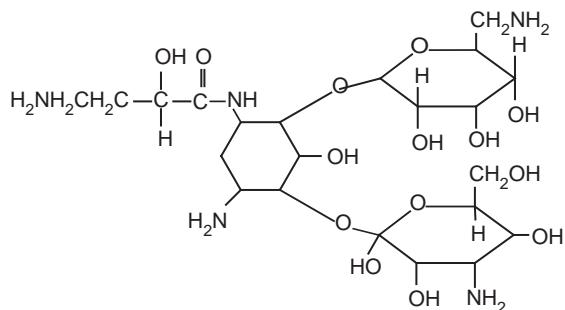
d. Kanamycin



Properties and uses: Kanamycin sulphate is a white crystalline powder, soluble in water, practically insoluble in acetone and in alcohol. The mixture consists of three related structures, that is, Kanamycin A, B, and C. The kanamycins do not possess D-ribose molecule that is present in neomycins and paramomycins. The use of kanamycins is restricted to infections of the intestinal tract and to systemic infections.

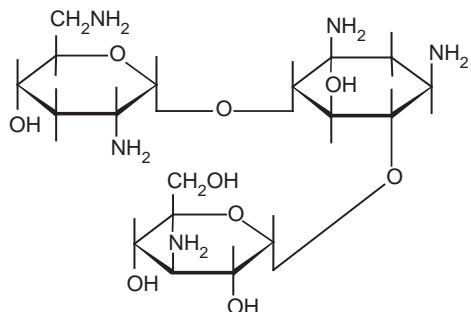
Assay: It is assayed by microbiological method.

e. Amikacin



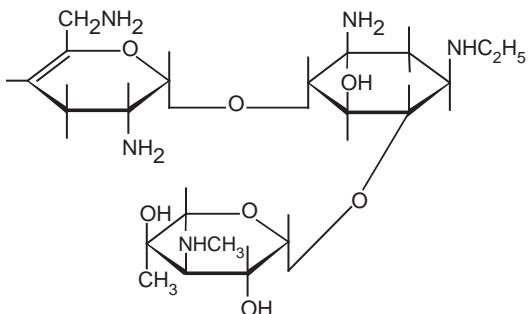
Properties and uses: Amikacin is a semisynthetic drug derived from kanamycin A. It retains 50% of the original activity of kanamycin A. L-Isomer is more active than D-isomer. It resists attack by most bacterial-inactivating enzymes. Therefore, it is very effective and less ototoxic than other aminoglycosides.

Dosage forms: Amikacin sulphate injection I.P.

f. Tobramycin

Properties and uses: Its activity is similar to gentamycin. The superior activity of tobramycin against *P. aeruginosa* may make it useful in the treatment of bacterial oesteromyelitis, and pneumonia caused by *P. species*.

Dosage forms: Tobramycin injection I.P.

g. Netilmicin (1-N-ethylsisomicin)

Properties and uses: Netilmicin sulphate is a white or yellowish-white hygroscopic powder, very soluble in water, practically insoluble in acetone and alcohol. It is similar to gentamycin and tobramycin. The majority of the aminoglycoside inactivating enzymes do not metabolize it. It is useful for the treatment of serious infections due to susceptible enterobacteria and other aerobic gram-negative bacilli.

Assay: It is assayed by microbiological method.

SAR of Aminoglycoside Antibiotics

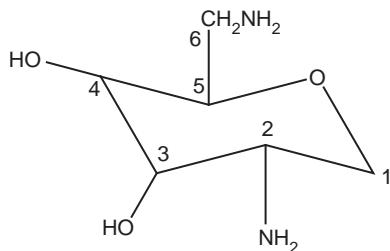
The aminoglycosides consist of two or more amino sugars joined in glycoside linkage to a highly substituted 1,3-diaminocyclo hexane (aminocyclitol), which is a centrally placed ring. The ring is a 2-deoxy streptamine in all aminoglycosides except streptomycin and dihydrostreptomycin, where it is streptidine.

Thus,

- In kanamycin and gentamycin families, two amino sugars are attached to 2-deoxy streptamine.
- In streptomycin, two amino sugars are attached to streptidine.
- In neomycin family, there are amino sugars attached to 2-deoxy streptamine.

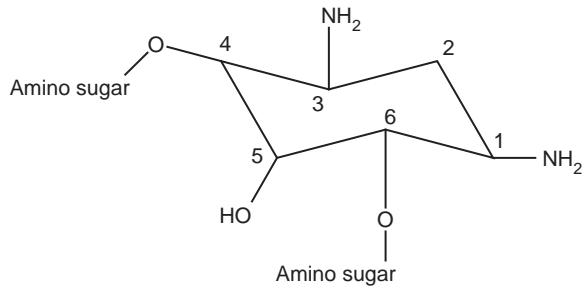
The aminoglycoside antibiotics contain two important structural features. They are amino sugar portion and centrally placed hexose ring, which is either 2-deoxystreptamine or streptidine.

1. Amino sugar portion



- i. The bacterial inactivating enzymes targets C-6 and C-2 position, and the substitution with methyl group at C-6 increases the enzyme resistance.
- ii. Cleavage of 3-hydroxyl or the 4-hydroxyl or both groups does not affect the activity.

2. Centrally placed hexose ring (aminocyclitol ring)



- i. Various modifications at C-1 amino group have been tested. The acylation (e.g. amikacyn) and ethylation (e.g. 1-N-ethylsisomycin) though does not increase the activity helps to retain the antibacterial potency.
- ii. In sisomicin series, 2-hydroxylation and 5-deoxygenation result in the increased inhibition of bacterial inactivating enzyme systems. Thus, very few modifications of the central ring are possible, which do not violate the activity spectrum of aminoglycosides.

3. Tetracycline antibiotics

Tetracyclines have a ring system of four linear annelated six-membered rings and are characterized by a common octahydronaphthalenes skeleton. They are potent, broad-spectrum antibacterial agents effective

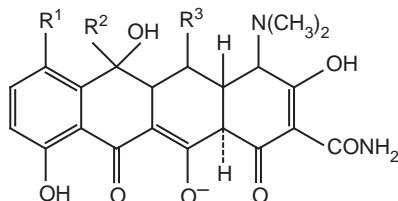
against gram-positive and gram-negative aerobic and anaerobic bacteria. As a result, the tetracyclines are drugs of choice or well-accepted alternatives for a variety of infectious diseases. Among these, they also play a role in the treatment of sexually transmitted and gonococcal diseases, urinary tract infections, bronchitis, and sinusitis remain prominent.

The majority of the marketed tetracyclines (tetracycline, chlorotetracycline, oxytetracycline, and demeclocycline) are naturally occurring compounds obtained by the fermentation of *Streptomyces spp.* broths. The semisynthetic tetracyclines (methacycline, doxycycline, minocycline) have the advantage of longer duration of antibacterial action. However, all these tetracyclines exhibit a similar profile in terms of antibacterial potency. In general, their activity encompasses many strains of gram-negative *E. coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Niesseria*, and *Serratia* spp., as well as gram-negative *Streptococci* and *Staphylococci* of particular interest is the potency of tetracyclines against *Haemophilus*, *Legionella*, *Chlamydia*, and *Mycoplasma*.

Classes of tetracyclines

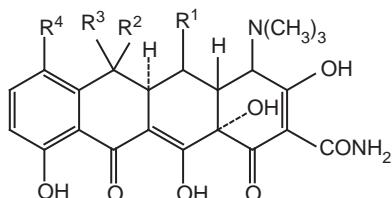
- I. Natural tetracyclines (biosynthetic)
- II. Semisynthetic tetracyclines
- III. Protetraacyclines

I. Natural tetracyclines



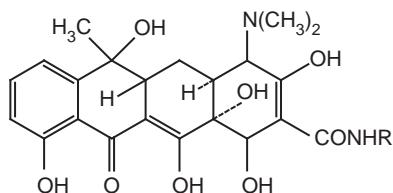
| S. No. | Drug | R¹ | R² | R³ |
|--------|-----------------------------|-----|------------------|-----|
| 1. | Tetracycline | -H | -CH ₃ | -H |
| 2. | Chlortetracycline | -Cl | -CH ₃ | -H |
| 3. | Oxytetracycline | -H | -CH ₃ | -OH |
| 4. | Bromotetracycline | -Br | -CH ₃ | -H |
| 5. | Dexamethyltetracycline | -H | -H | -H |
| 6. | Dexamethylchlortetracycline | -Cl | -H | -H |

II. Semisynthetic tetracyclines



| S. No. | Drug | R ¹ | R ² | R ³ | R ⁴ |
|--------|--------------|----------------|------------------|------------------|------------------------------------|
| 1. | Doxycycline | -OH | -H | -CH ₃ | -H |
| 2. | Minocycline | -H | -H | -H | -N-(CH ₃) ₂ |
| 3. | Methacycline | -OH | =CH ₂ | - | -H |
| 4. | Meclocycline | -OH | =CH ₂ | - | -Cl |
| 5. | Sencycline | -H | -H | -H | -H |

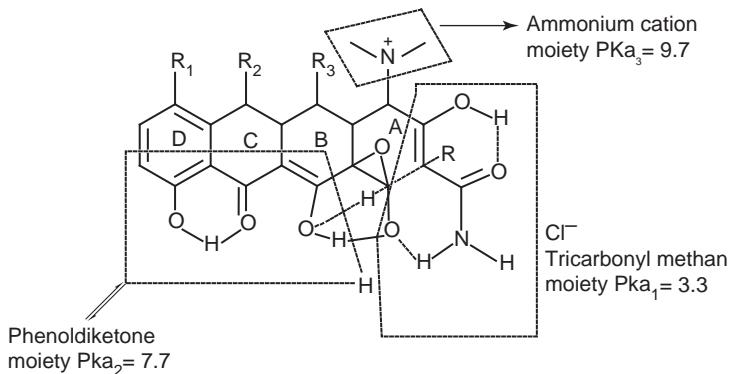
III. Pro-tetracyclines



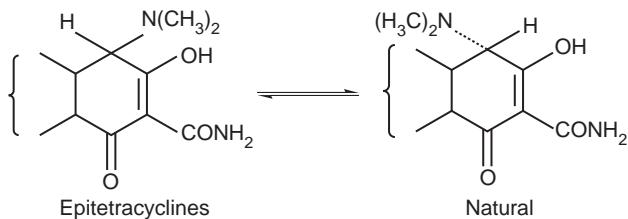
| S. No. | Drug | R |
|--------|------------------|---|
| 1. | Rolitetracycline | |
| 2. | Lymecycline | |
| 3. | Clomocycline | |
| 4. | Apicycline | |
| 5. | Pipacycline | |
| 6. | Guamecycline | |
| 7. | Meglucycline | |

General mode of action of tetracyclines: In bacterial protein synthesis, the messenger RNA attaches itself to 30S ribosomes. The initiation complex of mRNA starts the protein synthesis and polysome formation of the nascent peptide that is attached to 50S ribosomes. Its specific tRNA transports the next amino acid to the acceptor site of the ribosome, which is complementary to the base sequence of the next mRNA codon. The nascent peptide is transferred to the newly attached amino acid by peptide bond formation. Tetracyclines bind to 30S ribosomes and the attachment of aminoacyl tRNA to mRNA ribosome complex is interfered.

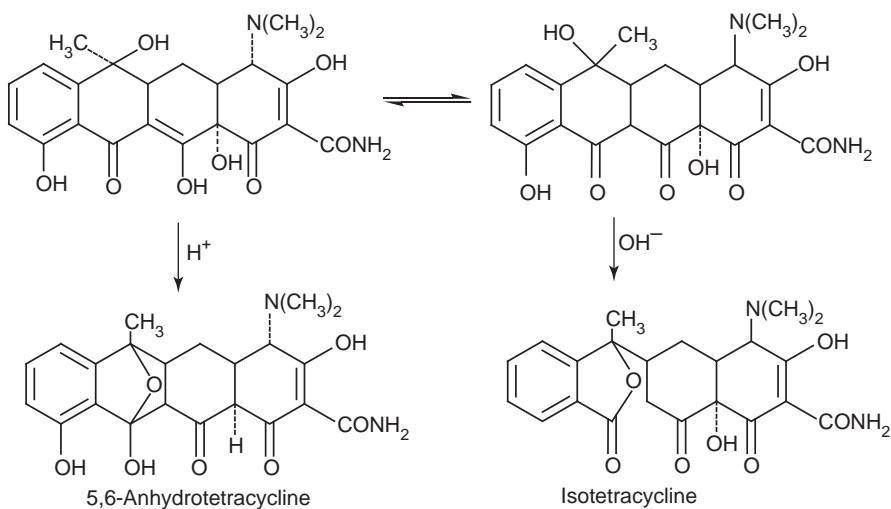
Physicochemical properties: These are amphoteric due to the acidic and the basic substituents, and have low solubility in water (0.5 mg/ml) with strong acids and bases. They form water-soluble salts in each tetracycline, there are three ionizable groups present: tricarbonyl methane moiety (pK_a 3.3), phenol diketone moiety (pK_a 7.7), and ammonium cation moiety (pK_a 9.7).



Effect of pH on tetracyclines: An interesting property of tetracyclines is their ability to undergo epimerization at C-4 position in solutions of intermediate pH range. These isomers are called epitetracyclines. Under the influence of the acidic conditions, equilibrium is established in about a day consisting of approximately equal amount of isomers. Epitetracyclines exhibit much less activity than natural isomers.



Strong acids and bases attack the tetracyclines having a hydroxyl group on C-6, causing a loss in activity through the modification of C-ring. Strong acids produce dehydration through a reaction involving the C-6 hydroxyl group and C-5a hydrogen. The double bond formed between the positions C-5a and C-6 induces a shift in the position of double bond between C-11a and C-12 to a position between C-11 and C-11a forming the more energetically favoured resonance of the naphthalene group found in the inactive anhydro tetracyclines.



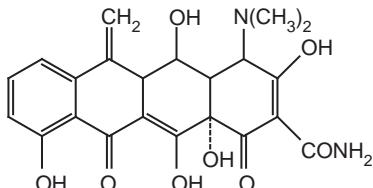
Bases promote a reaction between the C-6 hydroxyl group and the ketone group at the C-11 position, causing the bond between the C-11 and C-11a atoms to cleave and to form the lactone ring found in the isotetracycline.

Effect of metals on tetracyclines: Tetracyclines form stable chelate complexes with many metals, including calcium, magnesium, and iron. The chelates thus formed are insoluble in water accounting for the impairment in absorption of most of the tetracyclines in the presence of milk, calcium, magnesium, and aluminium containing antacids and iron salts.

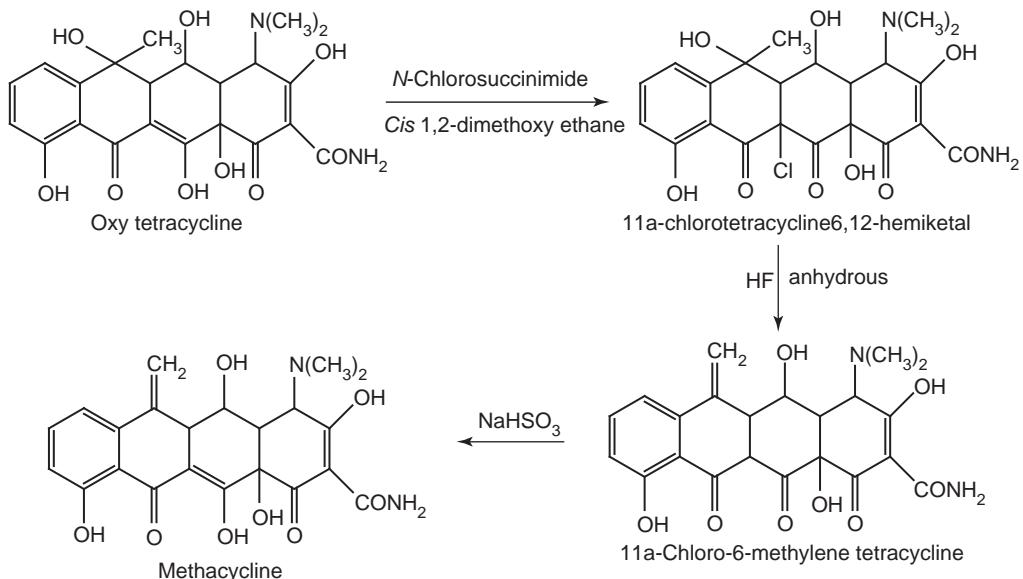
The affinity of tetracyclines for calcium causes them to be laid down in newly formed bones and teeth as tetracycline calcium orthophosphate complexes. Deposits of these antibiotics in tooth cause yellow discolouration that darkens because of photochemical reaction. Tetracyclines are distributed into the milk of lactating mothers and also cross the placenta into the foetus. The possible effect of these agents on bones and teeth of the child should be taken into consideration before they are used during pregnancy or in children under eight years of age.

II. Semisynthetic tetracyclines

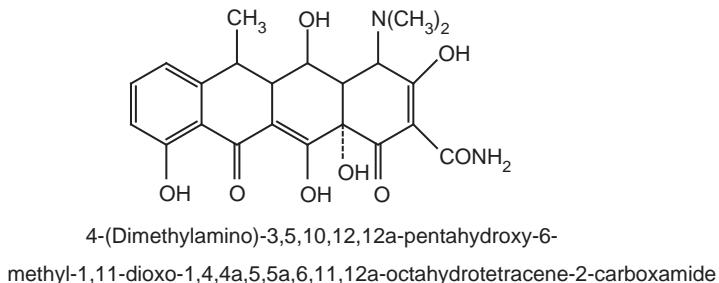
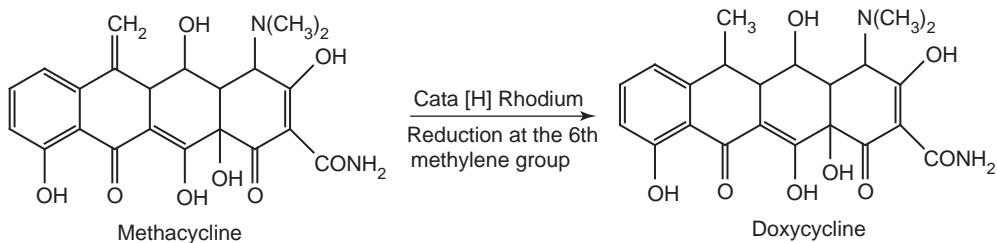
i. Methacycline



4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

Synthesis

Properties and uses: Methacycline is a yellow crystalline powder, sparingly soluble in water. It is obtained by the chemical modification of oxytetracycline. It has an antibiotic spectrum similar to tetracyclines, but greater potency; about 600 mg of methacycline is equivalent to 1 g of tetracycline.

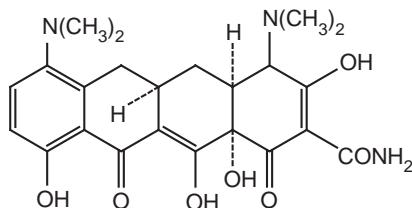
ii. Doxycycline (Vibramycin)**Synthesis**

Properties and uses: It was first obtained in small yields by a chemical transformation of oxytetracycline. The α -methyl epimer is more than three times as active as its β epimer.

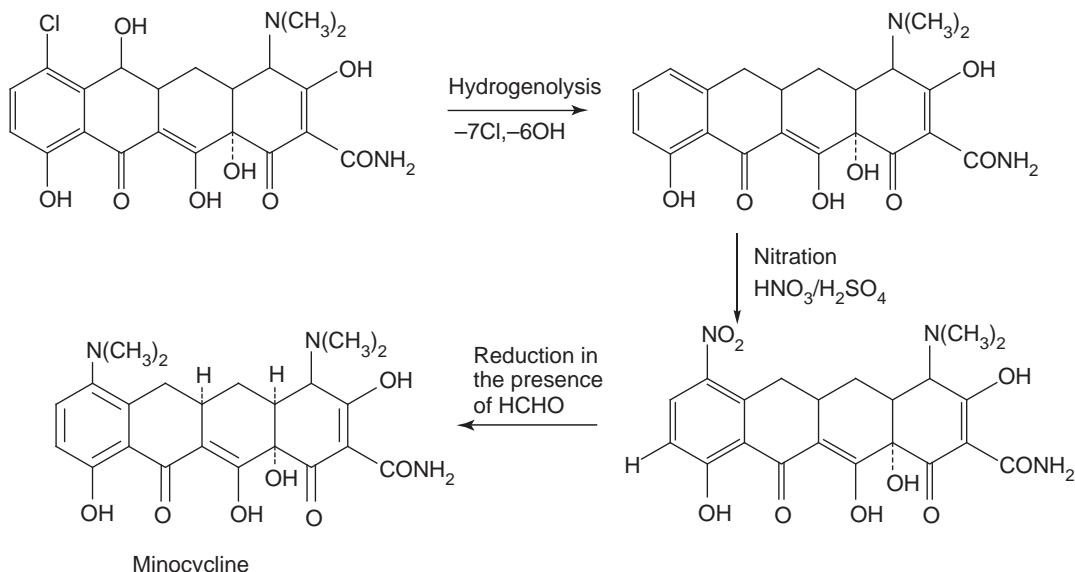
Dose: In adults, the oral dosage is 100 mg every 12 h.

Dosage forms: Doxycycline HCl capsules I.P., Doxycycline HCl tablets I.P.

iii. Minocycline (Cynomycin, Minolox)

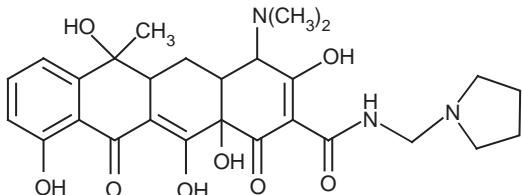
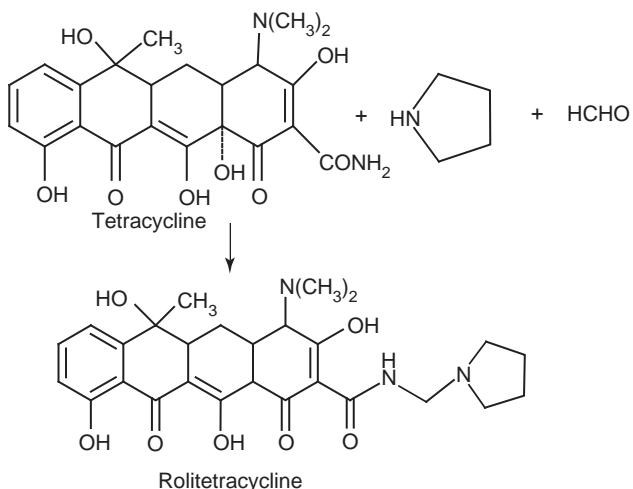
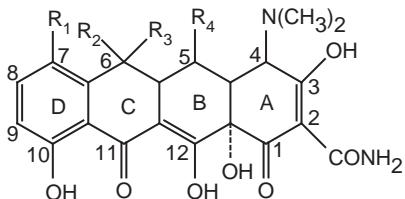


Synthesis



Properties and uses: It is a yellow crystalline powder with slightly bitter taste, soluble in water. It is very active against gram-positive bacteria. It is especially effective against *Mycobacterium marinum*. As a prophylactic against streptococcal infections, it is the drug of choice. It lacks the 6-hydroxyl group, therefore, it is stable to acids and does not dehydrate or rearrange to anhydro or lactone forms.

Dose: The dose orally for adults is 200 mg.

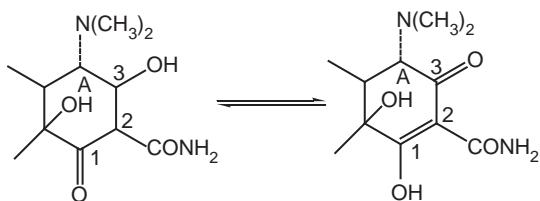
iv. Rolitetracycline**Synthesis****SAR of Tetracyclines**

The key structural feature is a linearly fused tetracyclic nucleus and each ring needs to be six membered and purely carbocyclic. A tetracyclic backbone skeleton is essential for activity.

- The D-ring needs to be aromatic and the A-ring must be appropriately substituted at each of its carbon atoms for notable activity.
- The B-ring and the C-ring tolerate certain substituent changes as long as the keto-enol systems (at C-11, 12, 12a) remain intact and conjugated to the phenolic D-ring.
- The D, C, B-ring phenol, keto-enol system is imperative and the A-ring must also contain a conjugated keto enol system.

- Specifically, the A-ring contains a tricarbonyl derived keto-enol array at positions C-1, 2, and -3. Other structural requirements for good antibacterial activity include a basic amine function at C-4 position of the A-ring.

Modification of C-1 and C-3 position: The keto-enol tautomerism of ring A in carbon atom 1 and 3 is a common feature to all biologically active tetracyclines, blocking this system by forming derivatives at C-1 and C-3 results in loss of antibacterial activity A-C = O, a function of C-1 and C-3 is essential for activity. In addition, equilibrium between non-ionized and Zwitterionic structure of tetracycline is essential for activity.



Modification of C-2 position: The antibacterial activity resides on the carboxamide moiety. The amide is best left unsubstituted or monosubstitution is acceptable in the form of activated alkylaminomethyl amide (Mannich bases). An example includes rolitetracycline large alkyl group on the carboxamide that may alter the normal keto-enol equilibrium of the C-1, 2, and 3 conjugated systems and diminishes inherent antibacterial activity. The replacement of carboxamide group or dehydration of carboxamide to the corresponding nitrile results in a loss of activity.

Modification of C-4 position: The keto-enolic character of the A-ring is due to the α -C-4 dimethyl amino substituent. Loss of activity is exerted when dimethyl amino group is replaced with hydrazone oxime or hydroxyl group.

Modification of C-4a position: The α -hydrogen at C-4a position of tetracyclines is necessary for useful antibacterial activity.

Modification of the C-5 and C-5a positions: Alkylation of the C-5 hydroxyl group results in loss of activity. Naturally occurring antibacterial tetracyclines have an unsubstituted methylene moiety at the C-5 position. However, oxytetracycline contains C-5 α -hydroxyl group, was found to be a potent compound, and has been modified chemically to some semisynthetic tetracyclines. Esterification is only acceptable if the free oxytetracycline can be liberated in vivo; only small alkyl esters are useful. Epimerization is detrimental to antibacterial activity.

Modification at the C-6 position: The C-6 methyl group contributes little to the activity of tetracycline. The C-6 position is tolerant to a variety of substituents. The majority of tetracyclines have α -methyl group and α , β -hydroxyl group at this position. Demeclocyclin is a naturally occurring C-6 demethylated chlorotetracycline with an excellent activity. Removal of C-6 hydroxyl group affords doxycycline, which exerts good antibacterial activity.

C-7 and C-9 substituents: The nature of the aromatic D-ring predisposes the C-7 position to electrophilic substitution. Substitution with electron withdrawing group such as nitro and halogen groups are introduced

in some C-7 tetracyclines, which produces the most potent of all the tetracyclines in vitro, but their compounds are potentially toxic and carcinogenic. The C-7 acetoxy, azido, and hydroxyl tetracyclines are inferior in terms of antibacterial activity.

C-10 substituents: The C-10 phenolic moiety is necessary for antibacterial activity. C-10 substitution with para or ortho hydrogen group activates the C-9 and C-7.

C-11 substituents: The C-11 carbonyl moiety is a part of one of the conjugated keto-enol system required for antibacterial activity.

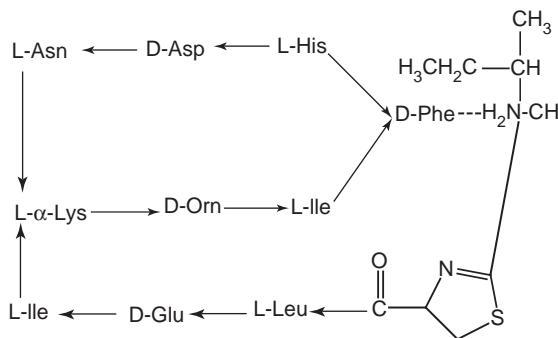
C-11a substituents: No stable tetracyclines are formed by modifications at the C-11a position.

C-12/12a substituents: Esterification of the hydroxyl group leads to the incorporation of drug with the tissues due to the enhanced lipophilicity and it should undergo hydrolysis to leave the active tetracycline with hydroxyl group at 12a position, which is necessary to produce good antibacterial action. The transport and binding of these drugs depends on keto-enol system.

4. Polypeptide antibiotics

The compounds have complex polypeptide structure. These are resistant to animal and plant proteases. These contain lipid moieties besides amino acids that are not found in peptides of animal and plant origins. Examples: bacitracin, polymycin, amphotomycin, tyrothricin, and vancomycin.

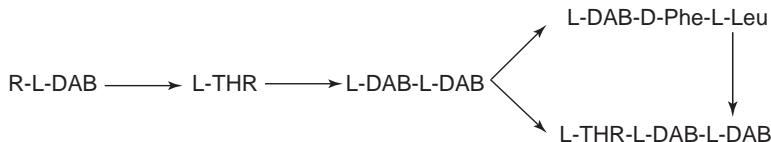
i. Bacitracin



Properties and uses: Bacitracin is a white hygroscopic powder, soluble in water and alcohol. Bacitracin antibiotic is isolated from the fermentation broth of a culture of tracyl-1 strain of *Bacillus subtilis*. It is found to be a complex mixture of at least 10 polypeptides (A, A₁, B, C, D, E, F₁, F₂, F₃, and G), of which bacitracin A fraction is believed to be the most abundant and the most potent. A divalent ion Zn⁺⁺ enhances its activity. Although bacitracin is occasionally employed for topical application (often in combination with neomycin, polymycin, and tyrothricin) for the treatment of burns, ulcer, and wounds, it can cause serious necrosis of the kidney tubules; if it is given systematically (i.e. I.V route) an oral administration is not feasible due to its lack of absorption from the GI tract. A variety of gram-positive cocci and bacilli are sensitive to bacitracin. It should be stored in airtight containers due to its hygroscopic nature.

Assay: It is assayed by microbiological method.

ii. Polymyxin



$\text{Polymyxin B}_1:\text{R} = (+)\text{-6-methyloctanoyl}$

$\text{Polymyxin B}_2:\text{R} = \text{6-methylpeptanoyl}$

DAB = $\alpha\text{-}\gamma\text{-Diaminobutyric acid}$

Properties and uses: Polymycin sulphate is a white hygroscopic powder, soluble in water, and slightly soluble in ethanol. The polymyxins are cyclic peptides holding a fatty acid side chain. This is a group of relatively simple basic, cationic, detergent peptides that are produced by *Bacillus polymyxia*. At least, five polymyxins (A, B, C, D, and E) are known, but only polymyxin B and polymyxin E are of clinical utility. Both polymyxin B and polymyxin E (colistin) are mixtures of two components and is used in the treatment of bacterial meningitis, urinary tract infection, burns, wounds, and gastroenteritis. Polymyxin may affect renal tubules and central nervous system (CNS), and because of their nephrotoxicity associated with their systemic use, they are primarily employed to treat topical infections.

Assay: It is assayed by adopting liquid chromatography technique.

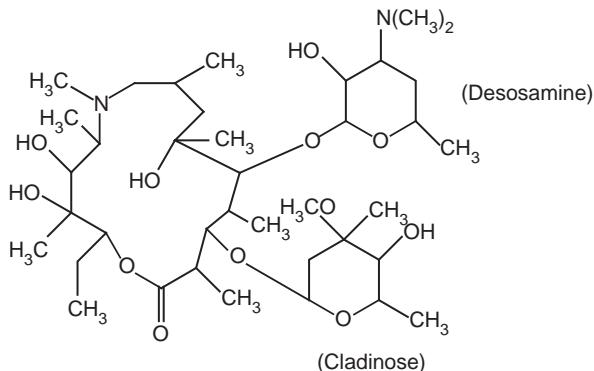
5. Macrolide antibiotics

The macrolide antibacterial agents are extremely useful chemotherapeutic agents for the treatment of a variety of infectious disorders and diseases caused by a host of gram-positive bacteria, both *cocci* and *bacilli*; they also exhibit useful effectiveness against gram-negative *cocci*, specially, *neisseria* spp. The macrolides are commonly administered for respiratory, skin, tissue, and genitourinary infections caused by these pathogens.

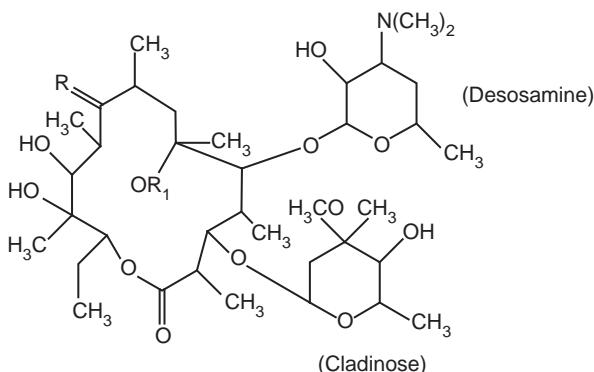
Chemistry: They are characterized by five common chemical features.

1. A macrocyclic lactone usually has 12–17 atoms, hence the name macrolide.
2. A ketone group.
3. One or two amino sugars glycosidically linked to the nucleus.
4. A neutral sugar linked either to amine sugar or to nucleus.
5. The presence of dimethyl amino moiety on the sugar residue, which explains the basicity of these compounds, and consequently the formation of salts. The antibacterial spectrum of activity of the more potent macrolides resembles that of penicillin. Examples: erythromycin, oleandomycin, clarithromycin, flurithromycin, dirithromycin, azithromycin.

i. Azithromycin



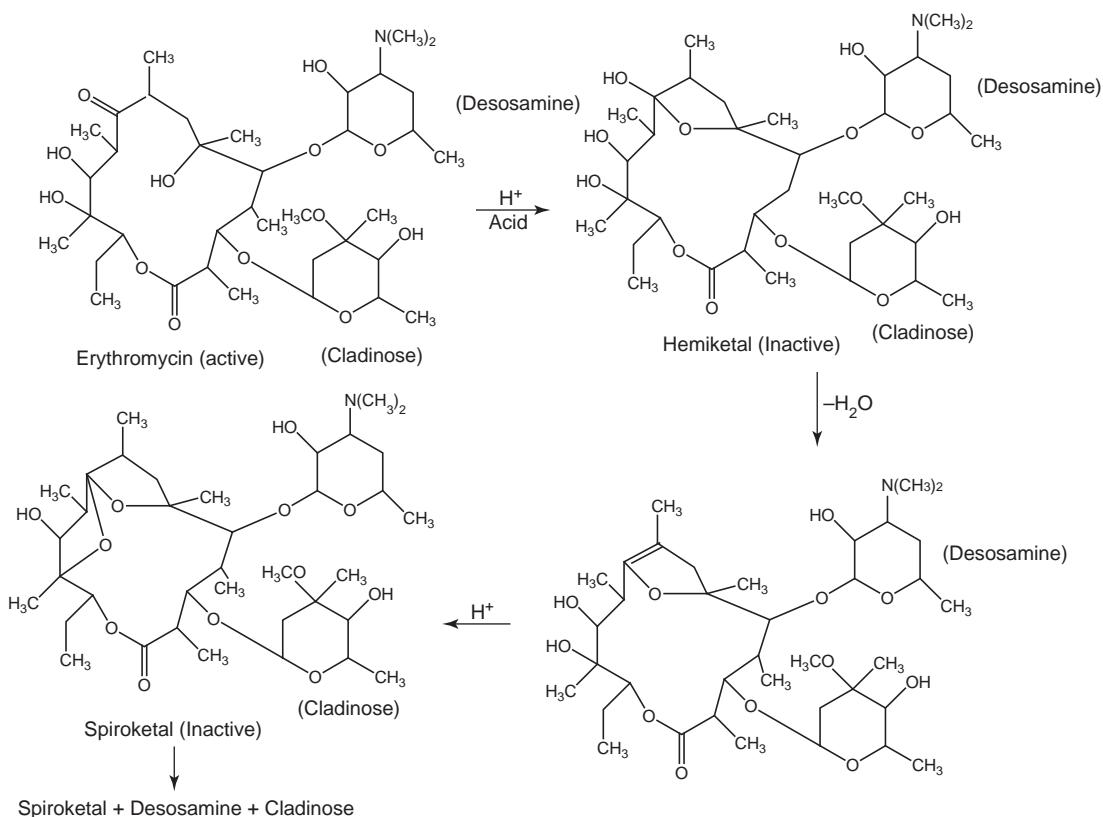
Properties and uses: Azithromycin is a white powder, practically insoluble in water, soluble in anhydrous ethanol and methylene chloride. It is very stable under acidic conditions, is less active against *Streptococci* and *Staphylococci* than erythromycin, and is far more active against respiratory infections due to *H. influenzae* and *Chlamydia trachomatis*.



| Name | R | R ₁ |
|----------------|--|------------------|
| Erythromycin | =O | -H |
| Roxithromycin | CH ₃ OCH ₂ CH ₂ OCH ₂ O- | -H |
| Clarithromycin | =O | -CH ₃ |

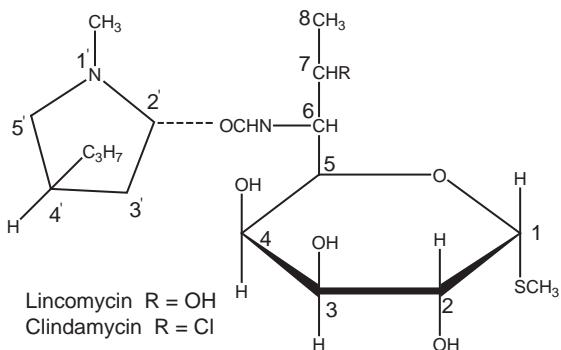
Acid degradation of erythromycin

Erythromycin is unstable in the acid media. The C-6 hydroxyl group reversibly attacks the C-9 ketone giving rise to a hemiketal intermediate. Dehydration prevents regeneration of the parent erythromycin and the C-12 hydroxyl group can subsequently add to produce a spiroketal species. The cladinose group is cleaved from the macrocycle and more harsh conditions lead to the release of desosamine. Useful antibacterial activity last till the dehydration of the hemiketal and the spiroketal is weakly active.



Mode of action: Macrolide antibiotics are bacteriostatic agents that inhibit protein synthesis by binding irreversibly to a site on the 50S subunits of the bacterial ribosome. Thus, inhibiting the translocation steps of protein synthesis at varying stages of peptide chain elongation (hinder the translocation of elongated peptide chain back from 'A' site to 'P' site). The macrolides inhibit ribosomal peptidyl transferase activity. Some macrolides also inhibit the translocation of the ribosome along with the mRNA template.

6. Lincomycins



Properties and uses: The antibiotic lincomycin is obtained from *Actinomycetes*, *Streptomyces*, and *Lincolnensis*. The ability of lincomycin to penetrate into bones, adds to its qualities and it gets promoted in the chemotherapy of bone and joint infections by penicillin resistant strains of *S. aureus*. Variation of the substituents on pyrrolidine portion and C-5 side chain affects the activity. Some of the examples are as follows:

- i. N-demethylation imparts activity against gram-negative bacteria.
- ii. Increase in the chain length of the propyl substituent at C-4 position in pyrrolidine moiety up to *n*-hexyl increase *in vivo* activity.
- iii. The thiomethyl ether of α -thiolincosamide moiety is essential for activity.
- iv. Structural modifications at C-7 position, such as introduction of 7S chloro or 7R-OCH₃, change the physiochemical parameters of the drug (i.e. partition coefficient), and thus, alter the activity spectrum and pharmacokinetic properties. The usual side effects include skin rashes, nausea, vomiting, and diarrhoea.

Dosage forms: Lincomycin HCl capsules I.P.

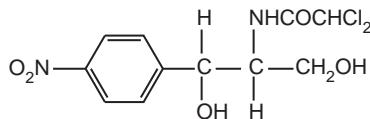
7. Other antibiotics

Examples of other antibiotics are chloramphenicol, rifampicin and mupirocin.

i. Chloramphenicol or chloromycetin

Chloramphenicol has a spectrum of activity resembling that of the tetracyclines except that it exhibits a bit less activity against some gram-positive bacteria. It is isolated from *Salmonella venezuelae* by Ehrlich et al in 1947. It contains chlorine and is obtained from an actinomycete, and thus, named as chloromycetin. It is specifically recommended for the treatment of serious infections caused by *H. influenzae*, *S. typhi* (typhoid), *S. pneumoniae*, and *N. meningitidis*. Its ability to penetrate into the CNS presents an alternative therapy for meningitis and exhibits antirickettsial activity.

Structure



N-(1,3-Dihydroxy-1-(4-nitrophenyl)propan-2-yl)dichloroacetamide

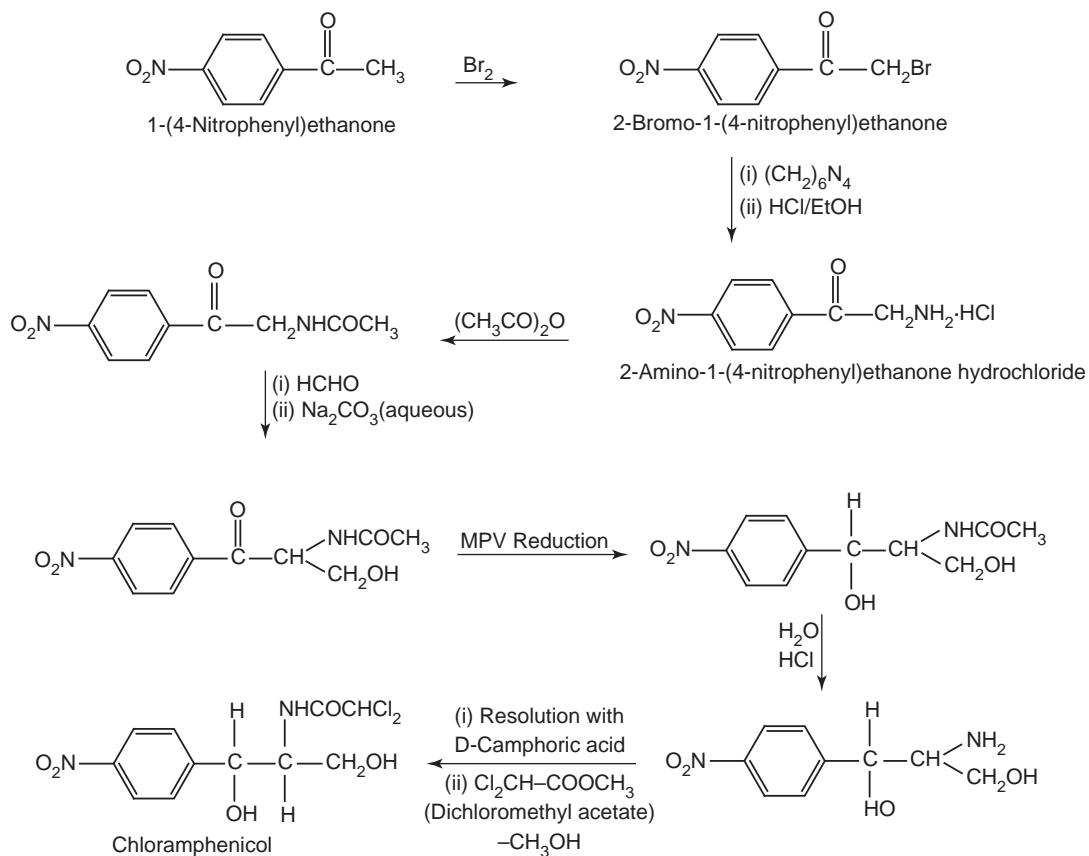
Properties and uses: Chloramphenicol is a white or greyish-white or yellowish-white crystalline powder or fine crystals, slightly soluble in water, soluble in alcohol and propylene glycol. It was the first, and still is the only therapeutically important antibiotic to be produced in competition with microbiological processes. It contains a nitrobenzene moiety and is a derivative of dichloroacetic acid. Since it has two chiral centres, four isomers are possible. The D-(-) threo is the biologically active form. It is used in the treatment of typhoid fever caused by *S. typhi*. The most serious adverse effect of chloramphenicol is bone marrow depression and fatal blood dyscrasias.

Assay: Dissolve the sample in water, dilute with the same solvent, and measure the absorbance at the maximum of 278 nm using ultraviolet spectrophotometer.

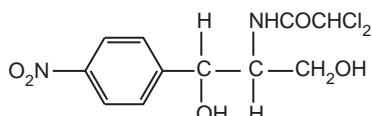
Dose: Usual adult dose is 500 mg every 6 h.

Dosage forms: Chloramphenicol capsules I.P., B.P., Chloramphenicol ear drops I.P., B.P., Chloramphenicol eye ointment I.P., B.P., Chloramphenicol eye drops B.P.

Synthesis



SAR of Chloramphenicol



- Modification of *p*-nitrophenyl group.
- Modification of dichloroacetamide side chain.
- Modification of 1, 3-propanediol.

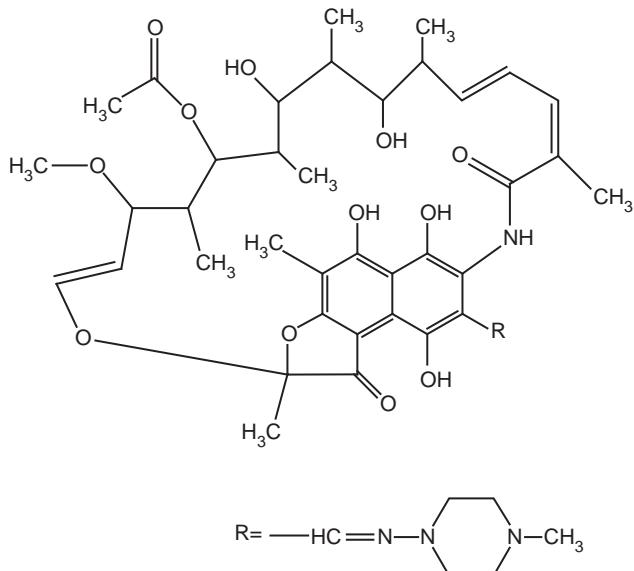
Modification of *p*-nitrophenyl group: The *p*-nitrophenyl group may be modified through the following ways:

- Replacement of the nitro group by other substituents leads to a reduction in activity.
- Shifting of the nitro group from the para position also reduces the antibacterial activity.
- Replacement of phenyl group by the alicyclic moieties results in less potent compounds.

Modification of dichloroacetamido side chain: Other dihalo derivatives of the side chain are less potent although major activities are retained.

Modification of 1,3-propanediol: If the primary alcoholic group on C-1 atom is modified, it results in a decrease in activity; hence, the alcoholic group seems to be essential for activity.

ii. Rifampicin



Properties and uses: Rifampicin is a reddish-brown or brownish-red crystalline powder, slightly soluble in water, acetone, and alcohol and soluble in methanol. It is a broad-spectrum bactericidal antibiotic, structurally similar to complex macrocyclic antibiotic obtained from *S. mediterranei*. They belong to a new class of antibiotics called as ansamycins. Five types, that is, rifampicin A, B, C, D, and E are present. It penetrates well into cerebrospinal fluid and is, therefore, used in the treatment of tuberculous meningitis.

Assay: Dissolve the sample in methanol and dilute it with the same solvent. Dilute the solution with phosphate buffer solution pH 7.4 and measure the absorbance at the maximum at 475 nm, using phosphate buffer solution pH 7.4 as blank.

PROBABLE QUESTIONS

1. What are penicillins? Classify with suitable examples and write the SAR of penicillins.
2. What are the cardinal requirements of a substance to be called as an antibiotic? Draw the structure, chemical name, and other names of the naturally occurring penicillins.
3. Explain the synthesis and the uses of phenoxy methyl penicillin and amoxycillin.
4. Draw the structure, chemical name, and uses of the following:
 - (a) Penicillins related to ampicillin
 - (b) Esters of ampicillin
5. Write short notes on the degradation of penicillins.
6. Write the structure, chemical name, uses, and synthesis of the given category of penicillins.
 - (a) Acid-resistant penicillins
 - (b) Betalactamase-resistant penicillins
7. What are cephalosporins? Explain how it differs from penicillins chemically. Write the SAR of cephalosporins in detail.
8. Write a comprehensive account of cephalosporins with suitable examples.
9. What are aminoglycoside antibiotics? Write the mode of action, structure, and uses of three potent drugs of this category.
10. Name any five aminoglycoside antibiotics and mention their source.
11. What are the reasons for recognizing chloramphenicol as a potent antibiotic? Write in detail about the SAR and stereochemistry of chloramphenicol. Describe the synthesis of chloramphenicol.
12. Explain the salient features of the tetracyclines. Write a brief account on the SAR of tetracyclines.
13. What are the five common characterized chemical features of macrolide antibiotics? Write its mode of action.
14. Write short notes on the semisynthetic tetracyclines.
15. Elaborate the characteristics of the tetracyclines with specific reference to their
 - (a) Effect on metals and
 - (b) Effect on strong acids and bases.

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Chapter 5

Antitubercular Agents

INTRODUCTION

Tuberculosis is the most prevalent infectious disease worldwide and a leading killer caused by a single infectious agent, that is, *Mycobacterium tuberculosis*. According to World Health Organization (WHO) report, *M. tuberculosis*, currently infects over 2 billion people worldwide, with 30 million new cases reported every year. This intracellular infection accounts for at least 3 million deaths annually. Common infection sites of the tuberculosis are lungs (primary site), brain, bone, liver, and kidney. The main symptoms are cough, tachycardia, cyanosis, and respiratory failure. Depending upon the site of infection, the disease can be categorized as follows:

- Pulmonary tuberculosis (respiratory tract).
- Genitourinary tuberculosis (genitourinary tract).
- Tuberculous meningitis (nervous system).
- Miliary tuberculosis (a widespread infection).

Drugs used in the treatment of tuberculosis can be divided into two major categories (Fig. 4.1):

1. First-line drugs: Isoniazid, streptomycin, rifampicin, ethambutol, and pyrazinamide.
2. Second-line drugs: Ethionamide, *p*-amino salicylic acid, ofloxacin, ciprofloxacin, cycloserine, amikacin, kanamycin, viomycin, and capreomycin.

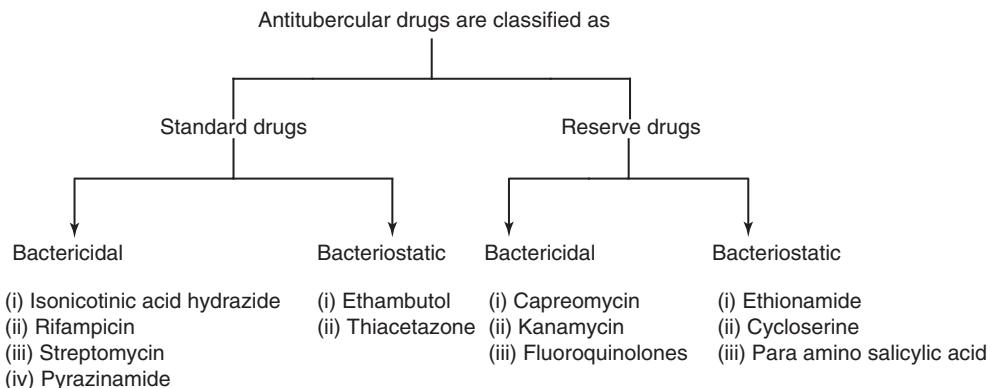


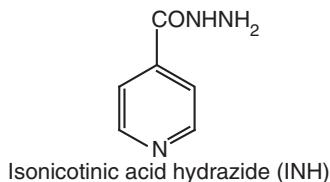
Figure 4.1 Classification of antitubercular drugs.

The majority of the patients with tuberculosis are treated with first-line drugs and shows excellent results with a 6-month course of treatment. For the first 2 months, isoniazid, rifampicin, and pyrazinamide are given, followed by isoniazid and rifampicin for the remaining 4 months. Second-line drugs are used mainly to treat multidrug resistant *M. tuberculosis* infections.

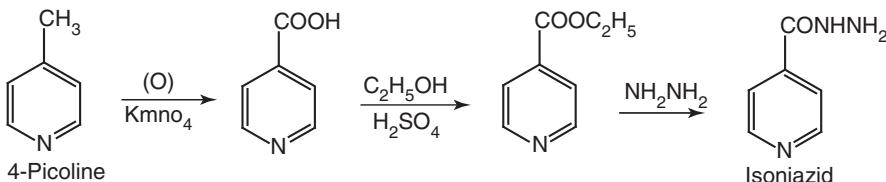
SYNTHESIS AND DRUG PROFILE

I. Standard drugs

i. Isoniazid (Continazin, Laniazid, Isonex, Ipcazide, INH, Isokin))



Synthesis

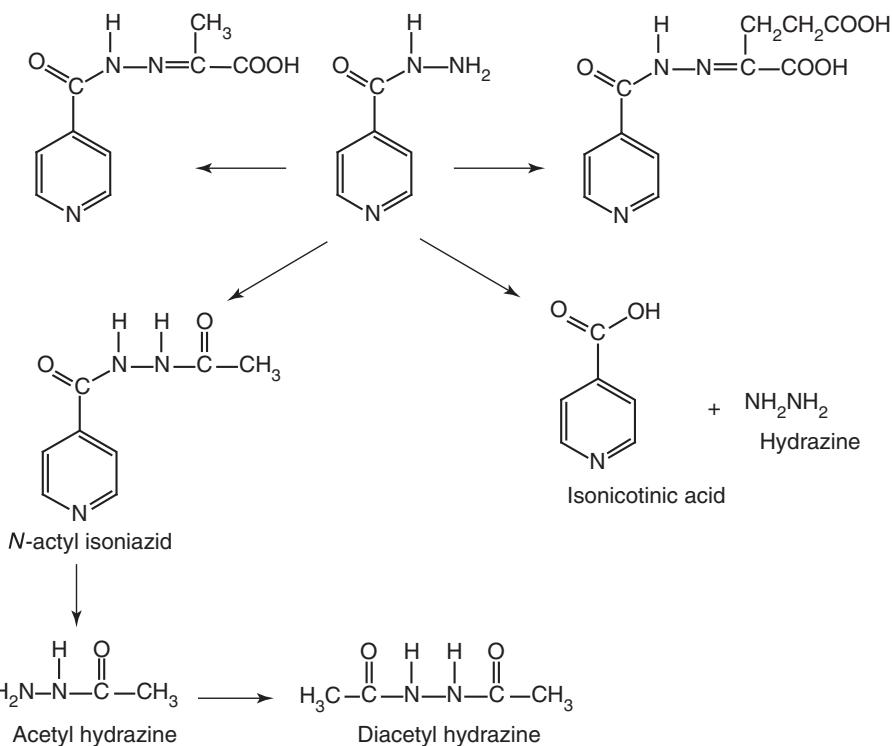


Mode of action: Isoniazid is a prodrug that is activated on the surface of *M. tuberculosis* by katG enzyme to isonicotinic acid. Isonicotinic acid inhibits the bacterial cell wall mycolic acid, thereby making *M. tuberculosis* susceptible to reactive oxygen radicals. Isoniazid may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The drug is active against susceptible bacteria only during bacterial cell division.

Metabolism: Isoniazid is extensively metabolized to inactive metabolites. The major metabolite is *N*-acetyl isoniazid. The enzyme responsible for acetylation is cytosolic *N*-acetyl transferase. Other metabolites include isonicotinic acid, which is found in the urine as a glycine conjugate and hydrazine. Isonicotinic acid also may result from hydrolysis of acetyl isoniazid, but in this case, the second product of hydrolysis is acetyl hydrazine. Acetyl hydrazine is acetylated by *N*-acetyl transferase to inactive diacetyl product. It has been suggested that a hydroxylamine intermediate is formed that results in an active acetylating agent.

Properties and uses: Isoniazid exists as white crystalline powder or colourless crystals, soluble in water, and sparingly soluble in alcohol. It is used as an antituberculosis drug.

Assay: Dissolve and dilute the sample with water, add hydrochloric acid, potassium bromide, and methyl red and titrate drop wise with 0.0167 M potassium bromate, shaking continuously, until the red colour disappears.

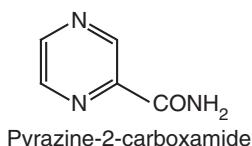


Dose: For the prophylaxis in case of adults is 5 mg/kg, with a maximum of 300 mg. For children: 10–20 mg/kg daily. Combination therapy Isoniazid, Rifampin and Pyrazinamide for 2 months followed by Isoniazid (15 mg/kg orally) with Rifampin (10 mg/kg upto 600 mg per dose) twice/week for 4 months.

Dose: For the prophylaxis in case of adults 5 mg/kg, with a maximum of 300 mg.

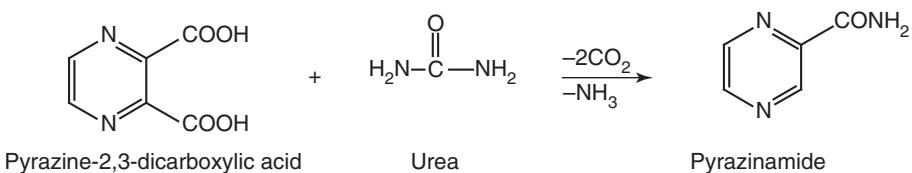
Dosage forms: Isoniazid tablets I.P., B.P. Isoniazid injection B.P.

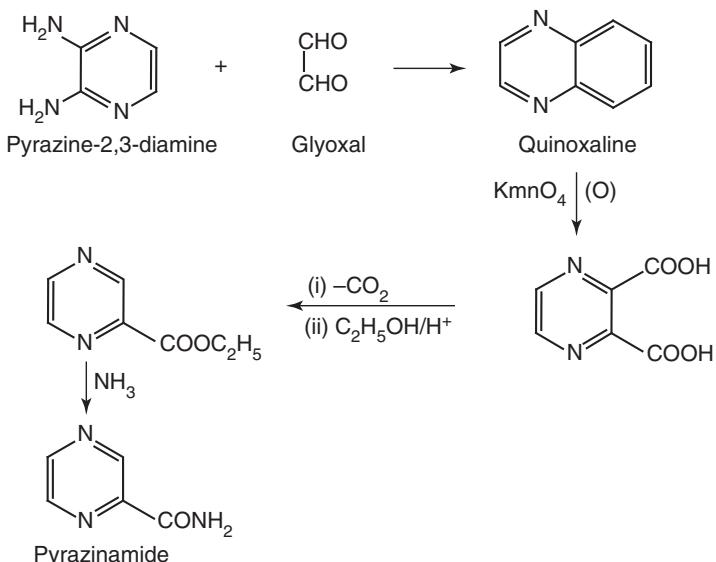
ii. Pyrazinamide



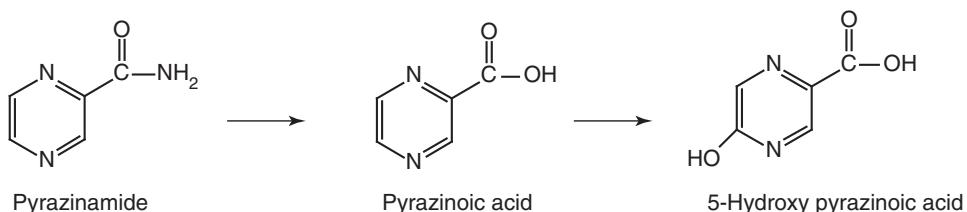
Synthesis

Route I. From: Pyrazine-2, 3-dicarboxylic acid



Route II. From: Pyrazine-2,3-diamine


Metabolism: The metabolic route constitutes of hydrolysis by hepatic microsomal pyrazinamidase into pyrazinoic acid, which may be then, oxidized by xanthine oxidase to 5-hydroxy pyrazinoic acid. The later compound may appear free either in the urine or as a conjugate with glycine.



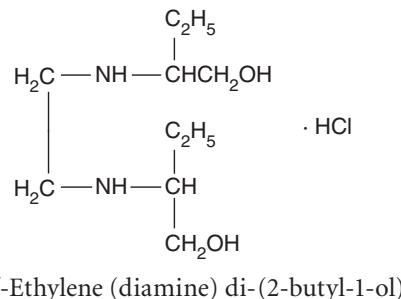
Properties and uses: Pyrazinamide is a white crystalline powder, sparingly soluble in water, slightly soluble in alcohol and in methylene chloride. It is a prodrug and is activated by *M. tuberculosis* amidase enzyme into pyrazine carboxylic acid, which has bactericidal activity. Pyrazinamide has recently been elevated to first-line status in the short-term treatment of tuberculosis regimens because of its tuberculocidal activity and comparatively less short-term toxicity. Pyrazinamide is maximally effective in the low pH environment that exists in macrophages (monocytes). It is used to treat tuberculosis and meningitis. The drug should be used with great caution in patients with hyperuricaemia or gout.

Assay: Dissolve the sample in acetic anhydride and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: Daily administered dose is 20–35 mg/kg in 3–4 equally spaced doses and maximum is 3 g daily.

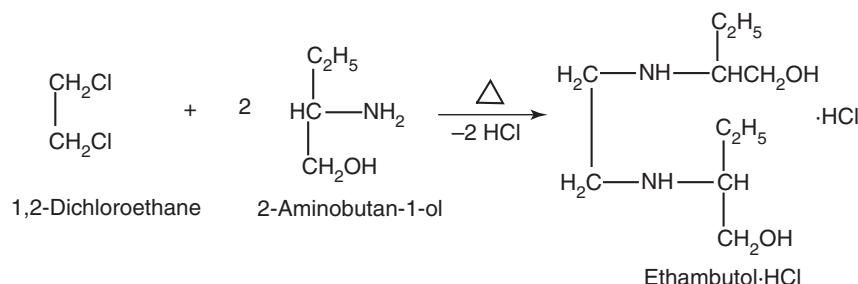
Dosage forms: Pyrazinamide tablets B.P.

iii. Ethambutol HCl (Myambutol)

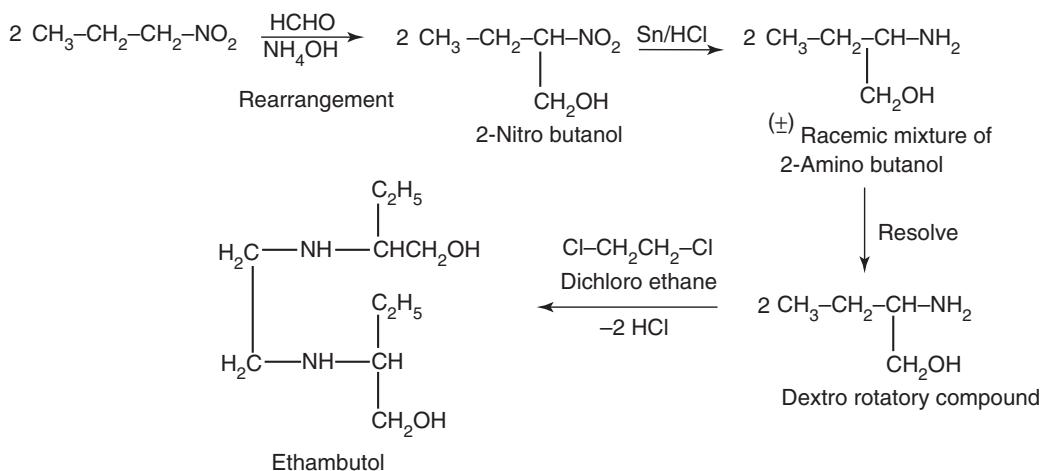


Synthesis

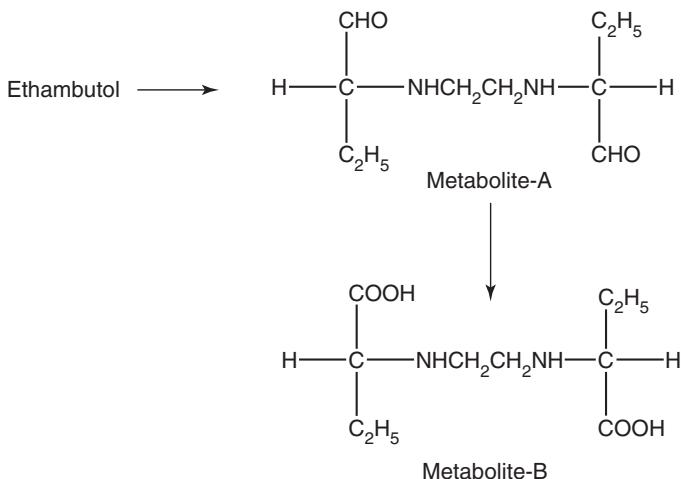
Route I. From: 1,2-Dichloroethane



Route II. From: Nitropropane



Metabolism: The majority of the administered ethambutol is excreted unchanged (73%), with not more than 15% appearing in the urine as a metabolite, which are devoid of biological activity.



Mode of action: It is a bacteriostatic drug that inhibits the incorporation of mycolic acid into the mycobacterium cell wall.

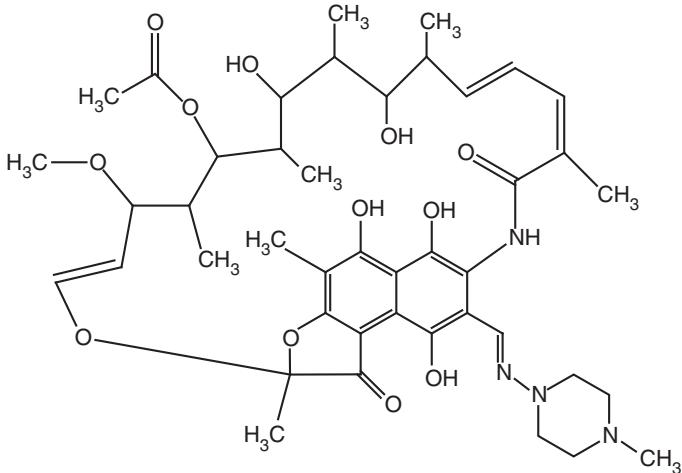
Properties and uses: Ethambutol hydrochloride is a white crystalline powder, soluble in water and in alcohol. It is not recommended for use as a single drug, but used in combinations with other antitubercular drugs in the chemotherapy of pulmonary tuberculosis.

Assay: Dissolve and dilute the sample with solution of dilute ammonia, copper sulphate solution, and dilute sodium hydroxide, and measure the angle of optical rotation of the solution at 436 nm.

Dose: The administered dose is 15–25 mg/kg once a day; low doses for new cases, and high doses for use in patients who have had previous antitubercular therapy.

Dosage forms: Ethambutol HCl tablets I.P., Ethambutol tablets B.P.

iv. Rifampicin



Mode of action: It is an antibiotic obtained from *Streptomyces mediterranei*. Rifampicin inhibits DNA-dependent RNA polymerase of mycobacteria by forming a stable drug enzyme complex, leading to suppression of initiation of chain formation in RNA synthesis and acts as a bactericidal drug.

Metabolism: The major metabolism of rifampicin and rifapentine is deacetylation, which occurs at the C-25 acetate. The resulting products, desacetyl rifampin, and desacetyl rifapentine are still active antibacterial agents. 3-Formylrifamycin has been reported as a second metabolite following both rifampicin and rifapentine administration.

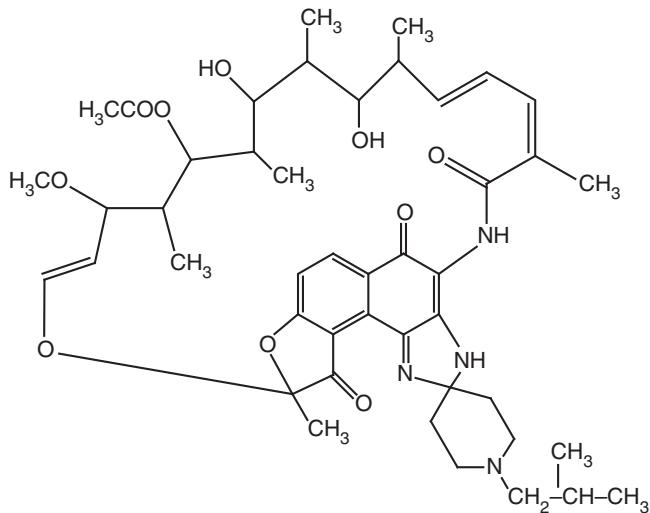
Properties and uses: Rifampicin is a reddish-brown or brownish-red crystalline powder, slightly soluble in water, acetone, alcohol, and soluble in methanol. Rifampicin is the most active agent in clinical use for the treatment of tuberculosis. It is used only in combination with other antitubercular drugs, and it is ordinarily not recommended for the treatment of other bacterial infections when alternative antibacterial agents are available.

Assay: Dissolve and dilute the sample in methanol. Dilute the solution with phosphate buffer solution pH 7.4 and measure the absorbance at the maxima of 475 nm, using phosphate buffer solution pH 7.4 as blank.

Dosage forms: Rifampicin tablets I.P, Rifampicin capsules I.P, B.P., Rifampicin oral suspension B.P.

v. Rifabutin

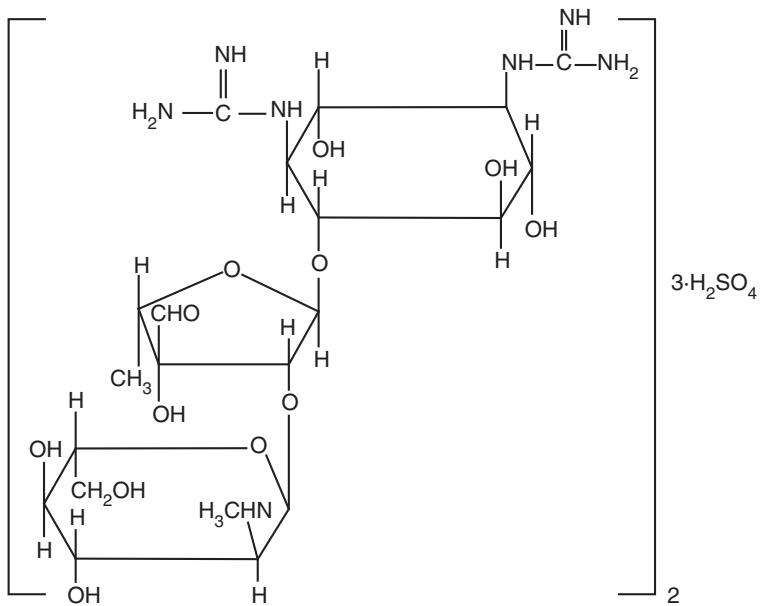
It is a semisynthetic rifamycin, structurally similar to rifampicin. It is used against *M. avium*, one of the most common causes of disseminated infections, with patients suffering with Human Immunodeficiency Virus (HIV). In vitro activity is attributed to rifabutin's lipophilic nature and its ability to penetrate the cell wall of the organism more effectively than other agents.



Properties and uses: Rifabutin is a reddish-violet amorphous powder, slightly soluble in water and alcohol, soluble in methanol. It is used as an antitubercular drug.

Assay: It is assayed by adopting liquid chromatography technique.

vi. Streptomycin sulphate



Metabolism: The enzymes responsible for inactivation are adenyltransferase, which catalyzes adenylation of the C-3 hydroxyl group in the N-methyl glucosamine moiety to give the O-3adenylated metabolite and phosphotransferase, which phosphorylates the same C-3 hydroxyl to give O-3 phosphorylated metabolite.

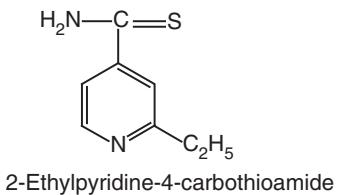
Properties and uses: Streptomycin is a white hygroscopic powder, very soluble in water, and practically insoluble in ethanol. It was the first effective drug for the treatment of tuberculosis. It is most often used in combination with other drugs, such as ethambutol and isoniazid, to treat pulmonary infections in patients with organisms that are known to be resistant. There has been an increasing tendency to reserve streptomycin products for the treatment of tuberculosis.

Assay: It is assayed by adopting microbiological assay method.

Dosage forms: Streptomycin sulphate injection I.P., Streptomycin sulphate tablets I.P., Streptomycin injection B.P.

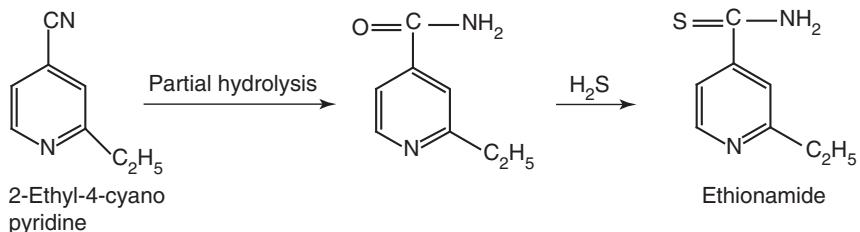
II. Reserve drugs

i. Ethionamide (Tridocin)

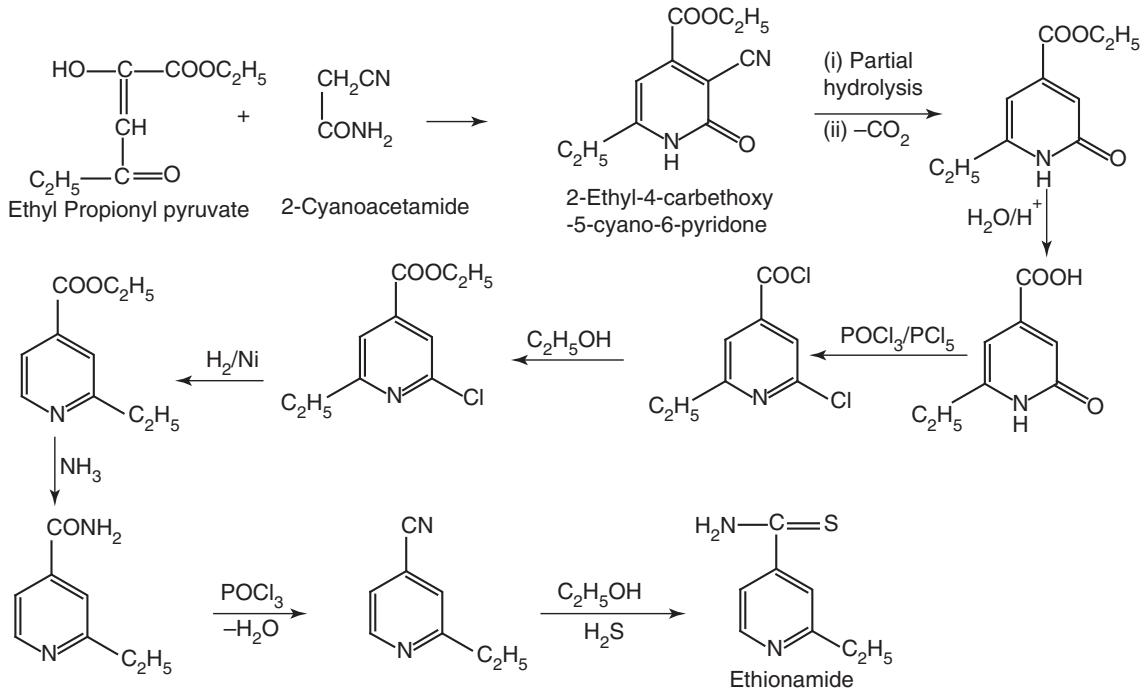


Synthesis

Route I. From: 2-Ethyl-4-cyanopyridine



Route II. From: Ethyl propionyl pyruvate



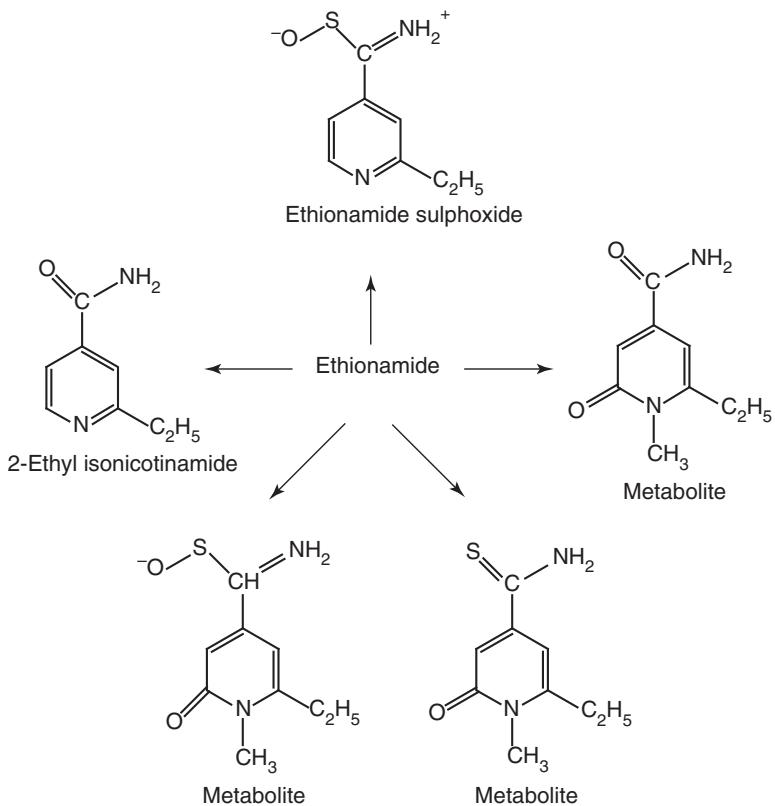
Mode of action: The antimycobacterial action of ethionamide seems to be due to an inhibitory effect on the mycolic acid synthesis.

Metabolism: Less than 1% of the drug is excreted in the free form, and remainder of the drug appear as six metabolites. Among the metabolites, ethionamide sulphoxide, 2-ethyl-isonicotinamide, and the N-methylated-6-oxo-dihydropyridines are the few.

Properties and uses: Ethionamide is a yellow crystalline powder or crystals, practically insoluble in water, soluble in methanol, and sparingly soluble in alcohol. It is used as antitubercular drug.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric. Determine the end point potentiometrically.

Dose: The dose to be administered is 500 mg–1 g per day in three or four divided doses with meals.



ii. Para-amino-salicylic acid (PAS, Tubacin)



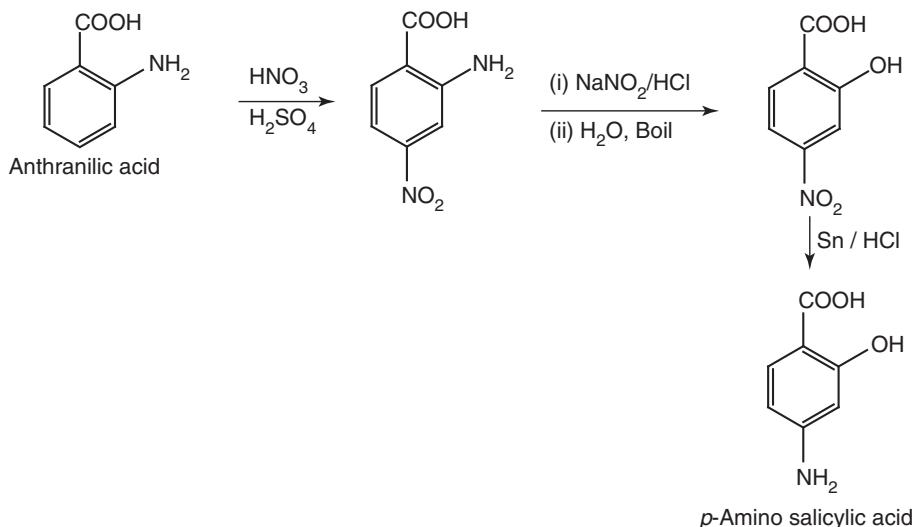
Mode of action: Aminosalicylic acid is an inhibitor of bacterial folate metabolism in a manner similar to the sulphonamide antibacterials.

Properties and uses: Aminosalicylic acid is bacteriostatic and highly specific for *M. tuberculosis*. Side effects are anorexia, nausea, epigastric pain, diarrhoea, and making poor compliance.

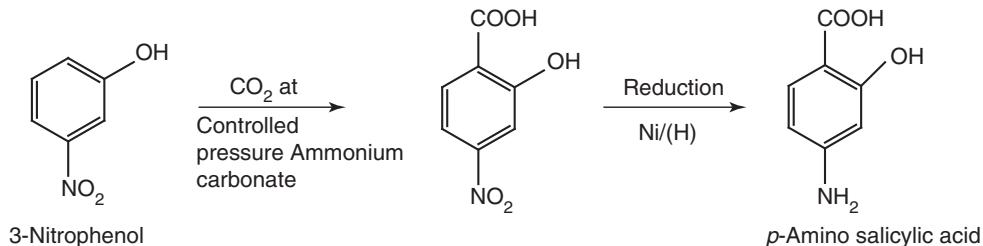
Dose: Dose administered orally 14–16 g daily after meals in three to four divided doses.

Synthesis

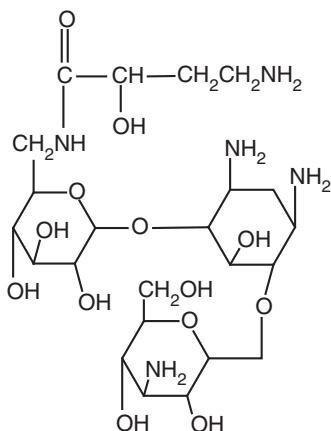
Route I. From: Anthranilic acid



Route II. From: m-Nitrophenol



iii. Amikacin

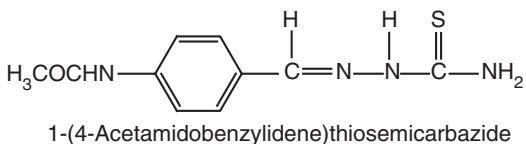


Properties and uses: Amikacin is a white powder, soluble in water, practically insoluble in acetone and in ethanol. It is a semisynthetic aminoglycoside that was first prepared in Japan. It is extremely active against several mycobacterial species, and may become the drug of choice for treatment of diseases caused by nontuberculous mycobacteria.

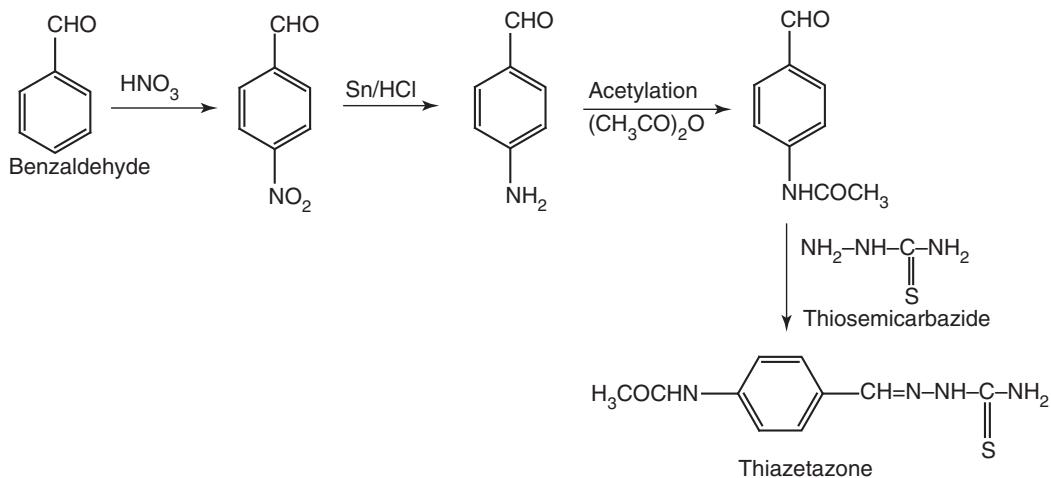
Assay: It is assayed by adopting liquid chromatography technique.

Dosage forms: Amikacin sulphate injection I.P., Amikacin injection B.P.

iv. Thiacetazone



Synthesis



Uses: It is used as an antitubercular agent.

PROBABLE QUESTIONS

- What is tuberculosis? How will you categorize it according to the site of infection? Define antitubercular drugs and classify them with suitable examples.
- Name the pyridine containing antitubercular agents. Outline the synthesis, mode of action, metabolism, dose, and dosage forms available for any one of them.
- Write the structure, chemical name, and uses of at least two most potent drugs from standard drugs and reserve drugs category.
- Write a detailed account on pyrazinamide along with its synthesis, mode of action, dosage forms available, and uses.

5. Write the following synthesis:
(a) Ethambutol (b) Thiacetazone (c) PAS
6. Write a note on antibiotics used in tuberculosis.

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Chapter 6

Antifungal Agents

INTRODUCTION

Human-fungi-parasitic relationship result in mycotic illnesses. Most fungal infections (mycoses) involve superficial invasion of the skin or mucous membrane of the body orifices. These diseases can usually be controlled by local application of the antifungal agents. Fungi have different shapes and sizes. Some are large while others are minute, parasitic, and saprophytic cells. They differ from the following organisms in some important aspects:

- Algae by lack of photosynthetic ability.
- Protozoa by the lack of motility, possession of chitinous cell wall, and ease of culture on simple media.
- Bacteria by greater size and having certain intracellular structure such as mitochondria and nuclear membrane.

CLASSIFICATION

On the basis of some differences, fungi may be classified as follows:

- a. Phyco myelitis (algae-like)
- b. Asco myelitis (sac-like)
- c. Basidio myelitis (mushrooms)
- d. Duetero myelitis

The potentially effective antifungal compounds are listed in Table 5.1.

Classification Based on the Chemical Structure, Action, and Source

The antifungal agents can be divided into the following classes, based on their chemical structure, mechanism of action, and source:

- I. Antibiotics: Amphotericin B, Nystatin, Griseofulvin
- II. Azoles (imidazole, triazole derivates)

Table 5.1 Potentially effective antifungal compounds.

| Disease | Compounds |
|------------------------|--|
| Dermatophytoses | Azoles (Butoconazole, Clotrimazole, Econazole, Itraconazole, Miconazole, Oxiconazole, Sulconazole), Griseofulvin, Naftifine, Terbinafine, Tolnaftate |
| Aspergillosis | Amphotericin B, 5-Fluorocytosin, Itraconazole |
| Blastomycosis | Amphotericin B, Itraconazole, Ketoconazole |
| Candidiasis | Amphotericin B, 5-Fluorocytosine, Nystatin Azoles (Butaconazole, Clotrimazole, Econazole, Fluconazole, Itraconazole, Ketoconazole, Miconazole, Terconazole, Tioconazole) |
| Chromomycosis | 5-Fluorocytosine, Itraconazole, Ketocanazole |
| Coccidiomycosis | Amphotericin B, Fluconazole, Itraconazole, Ketoconazole |
| Cryptococcosis | Amphotericin B, Fluconazole |
| Histoplasmosis | Amphotericin B, Itraconazole, Ketoconazole |
| Mucormycosis | Amyphotericin B |
| Paracoccidioidomycosis | Itraconazole, Ketoconazole |
| Pneumocytosis | Trimethoprim, Sulphamethoazole, Pentamidine, ecothionate |
| Pseudallescheriasis | Amphotericin B, Miconazole |
| Sporotrichosis | Amphotericin B, Itraconazole, Potassium iodide |

Triazoles—Fluconazole, Itraconazole, Terconazole

Imidazoles—Clotrimazole, Ketoconazole, Miconazole, Bifonazole, Butoconazole, and Zinoconazole

- III. Fluorinated pyrimidines: Flucytosine
- IV. Chitin synthetase inhibitors: Nikomycin Z
- V. Peptides/proteins: Cispentacin
- VI. Miscellaneous: Ciclopirox, Tolnaftate, Naftifine, and Terbinafine

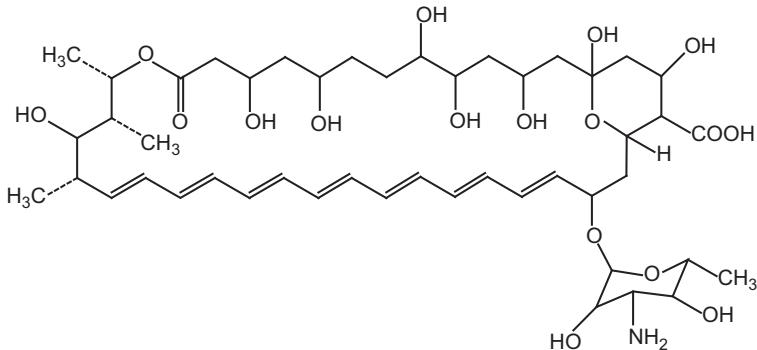
Classification Based on the Route of Administration

- I. Drugs for subcutaneous and systemic mycoses: Amphotericin B, Fluconazole, Flucytosine, Itraconazole, Ketoconazole.
- II. Drugs for superficial mycoses: Clotrimazole, Econazole, Griseofulvin, Miconazole, Nystatin.

SYNTHESIS AND DRUG PROFILE

I. Antibiotics

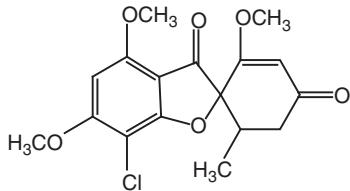
1. Amphotericin B



Mode of action: The antifungal activity of this drug depends, at least, in part, on its binding to a sterol moiety. Primarily, ergosterol that is present in the membrane of sensitive fungi, by virtue of their interaction with the sterols of cell membranes and polyenes, appear to form pores or channels. The result is an increase in the permeability of the membrane, allowing leakage of a variety of small molecules, such as intracellular potassium, magnesium, sugars, and metabolites leading to cellular death.

Properties and uses: It is polyene antibiotic obtained from *Streptomyces nodosus*. It is an amphoteric compound that consists of seven-conjugated double bond, an internal ester, a free carbonyl group, and a glycoside side chain with a primary amino group. The carbohydrate moiety is D-mycosamine. The conjugated systems are usually of all *trans* configurations, so that the ring contains a planner lipophilic segment and a less rigid hydrophilic portion. Amphotericin B is an amphoteric, forming soluble salts in both basic and acidic environments, and due to extensive unsaturation, it is unstable, primarily used as antifungal agents.

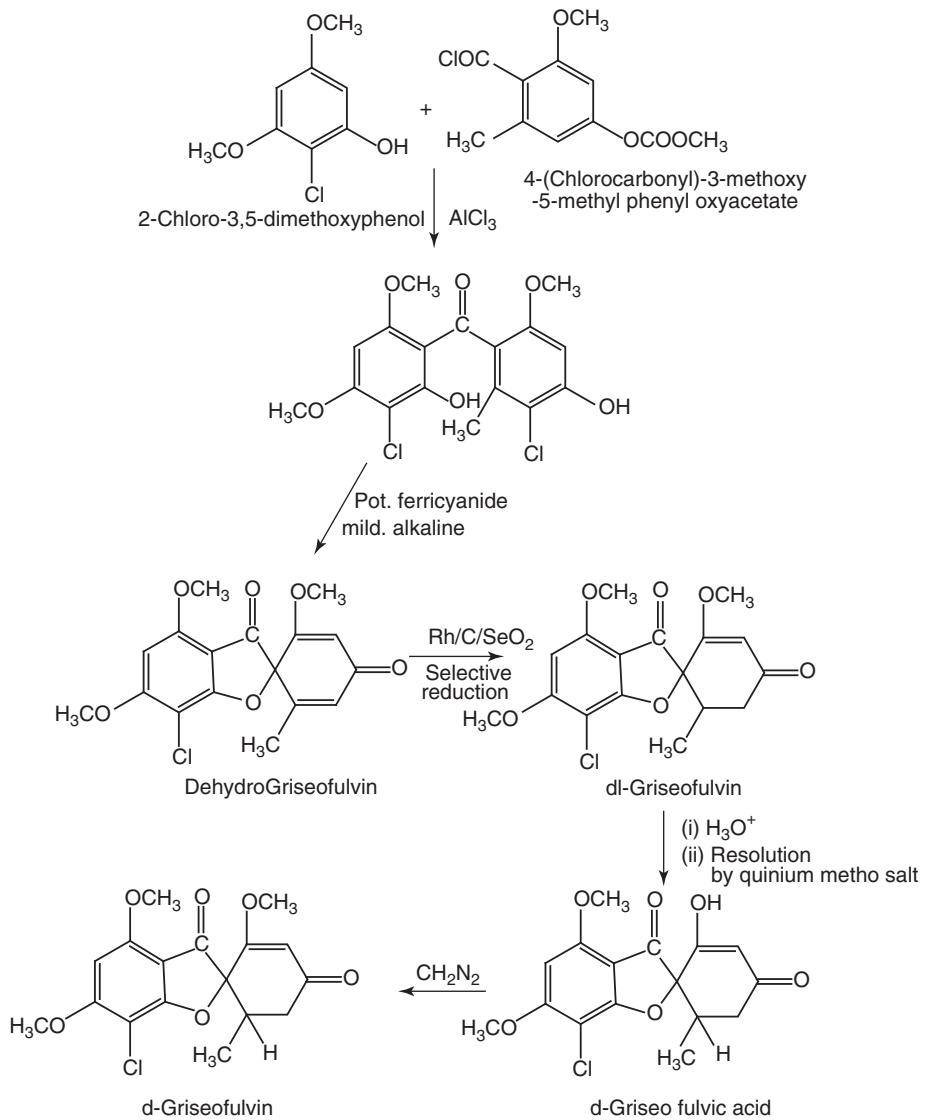
2. Griseofulvin (Fulvicin)



Mode of action: Griseofulvin is a fungi-static drug that causes disruption of the mitotic spindle by interacting with polymerized microtubules.

Properties and uses: Griseofulvin is a white or yellowish-white microfine powder, practically insoluble in water, freely soluble in dimethylformamide and tetrachloroethane, slightly soluble in ethanol and methanol. Used as an antifungal agent.

Synthesis

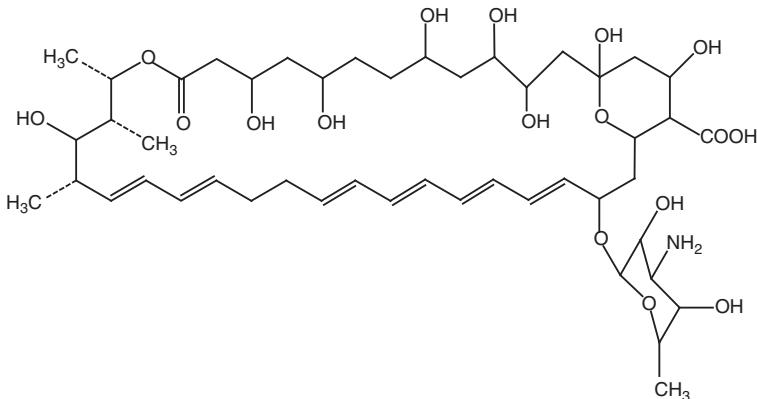


Assay: Dissolve the sample in ethanol and measure the absorbance after dilution with ethanol at the maxima of 291 nm using ultraviolet spectrophotometer.

Dose: As an oral suspension, the administered dose is 125 mg/5 ml; as capsules, 250 or 500 mg as tablets. For adults, in divided doses, the dose is 500 mg/day.

Dosage forms: Griseofulvin tablets I.P., B.P.

3. Nystatin



Mode of action: It is a polyene antibiotic isolated from *Streptomyces noursei*. It is structurally similar to amphotericin B and has the same mechanism of action.

Properties and uses: Nystatin is a yellow or slightly brownish hygroscopic powder, practically insoluble in water and in alcohol, freely soluble in dimethylformamide and in dimethyl sulphoxide, and slightly soluble in methanol. It is used as an antifungal agent.

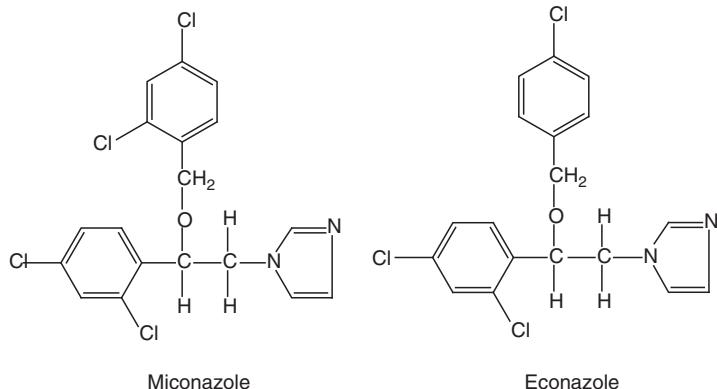
Assay: It is assayed by adopting microbiological assay method.

Dosage forms: Nystatin tablets I.P., B.P., Nystatin ointment I.P., B.P., Nystatin oral suspension B.P., Nystatin pastilles B.P., Nystatin pessaries B.P.

II. Azole antifungals

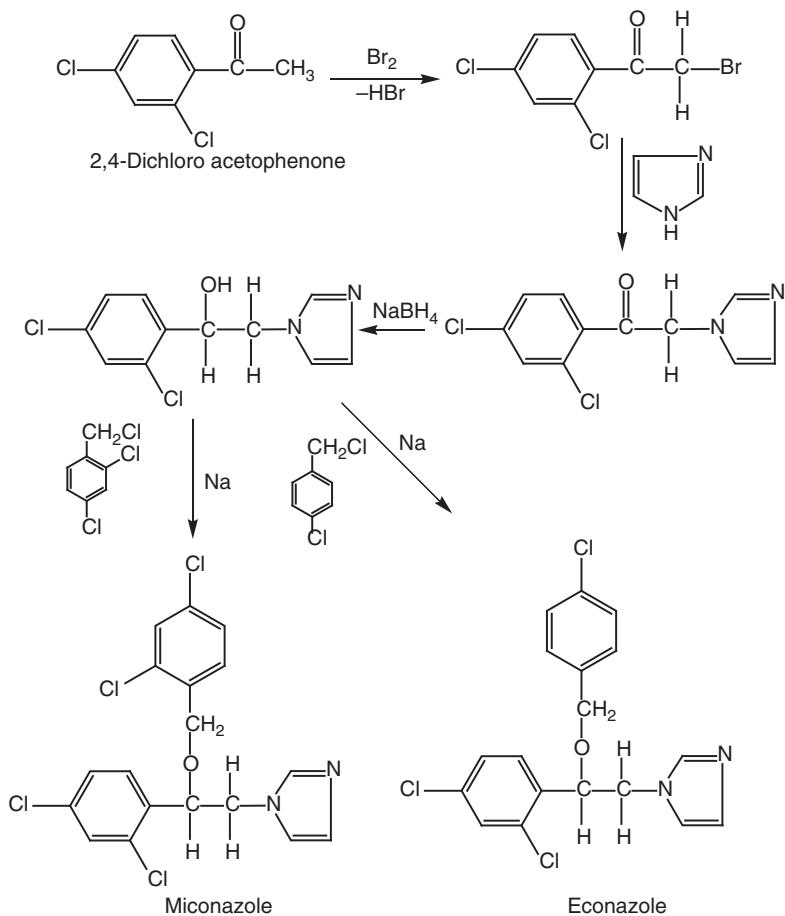
Mode of action: Azole antifungals inhibit sterol 14- α -demethylase, a microsomal cytochrome P450-dependent enzyme system, and thus, impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14- α -methyl sterols. These methylsterols may disrupt the packing of aryl chains of phospholipids, the functioning of certain membrane bound enzyme systems, such as ATPase and enzymes of the electron transport system, and thus, inhibiting the growth of fungi.

1. Miconazole (Micatin, Monistat) and Econazole



Synthesis

Synthesis of Miconazole and Econazole



Properties and uses of Miconazole: Miconazole is a white or almost white powder, very slightly soluble in water, sparingly soluble in methanol, and slightly soluble in alcohol. It is used as an antifungal agent.

Assay: Dissolve the sample in anhydrous acetic acid, with slight heating, if necessary, and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: It is to be applied in the vagina at bedtime for seven days, and 200 mg vaginal suppositories for three days therapy.

Dosage forms: Miconazole cream I.P., B.P., Miconazole pessaries I.P., Miconazole tablets I.P., Miconazole and Hydrocortisone cream B.P., Miconazole and Hydrocortisone acetate cream B.P., Miconazole and Hydrocortisone ointment B.P.

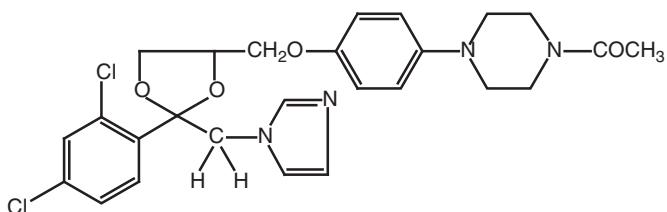
Properties and uses of Econazole: Econazole is white or almost white crystalline powder, very slightly soluble in water, soluble in methanol, sparingly soluble in methylene chloride, and slightly soluble in alcohol. It is used as antifungal agent.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

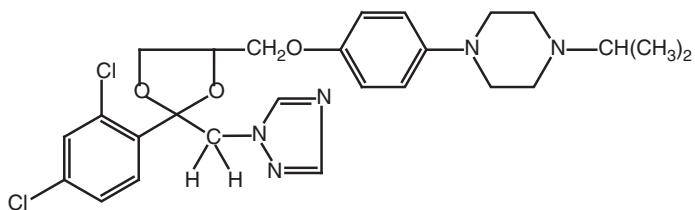
Dose: It is available as a water insoluble cream (1%) to be applied twice a day.

Dosage forms: Econazole cream B.P., Econazole pessaries B.P.

2. Ketoconazole (Nizoral) and Terconazole



Ketoconazole



Terconazole

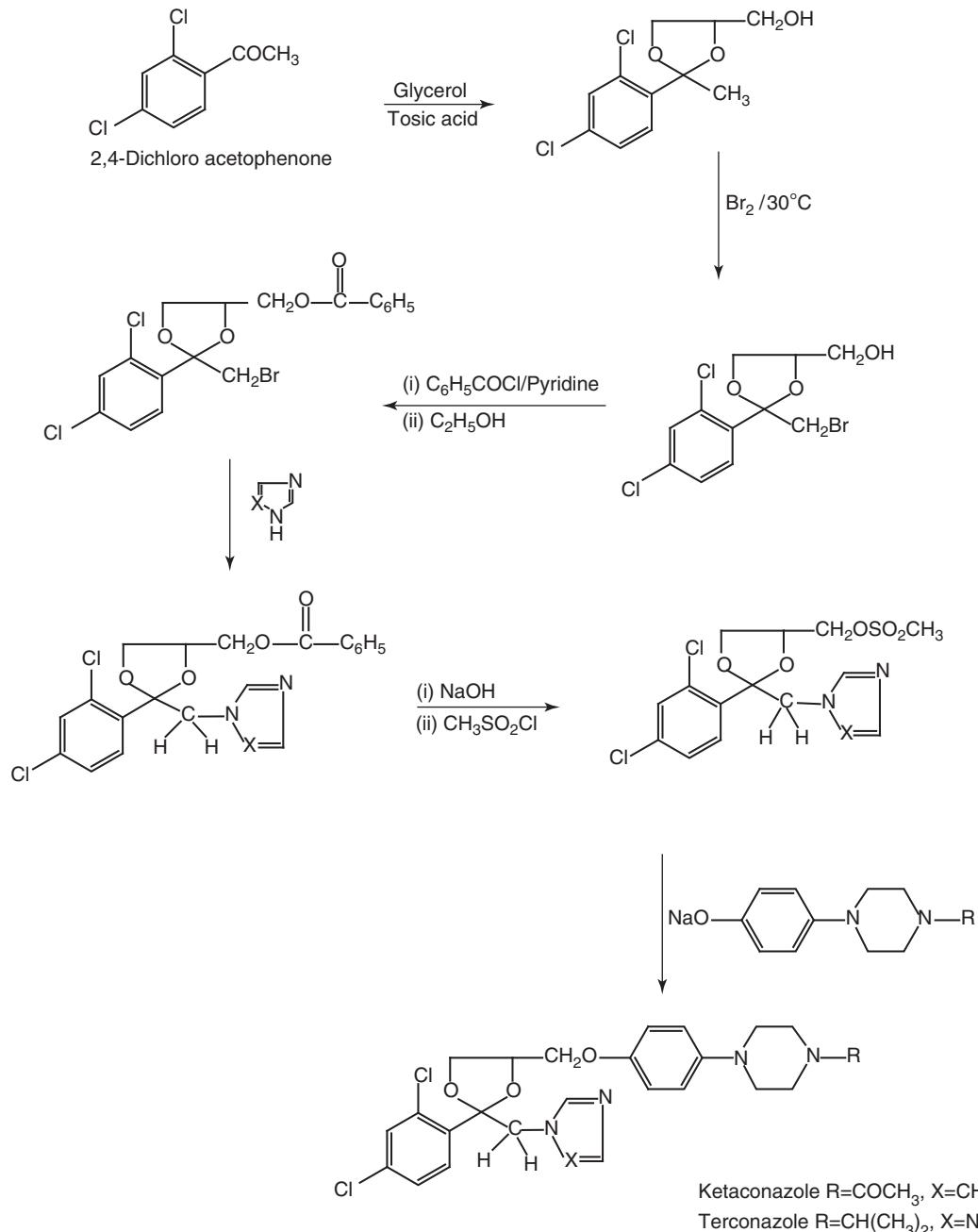
Metabolism of Ketoconazole: It is extensively metabolized by deacetylase of the microsomal enzymes and all the metabolites are inactive.

Properties and uses of Ketoconazole: Ketoconazole is a white powder, practically insoluble in water, soluble in methylene chloride and in methanol, sparingly soluble in alcohol. It is a racemic compound, consisting of the *cis*-2S, 4R, and *cis*-2R, 4S isomers. An investigation of the relative potencies of the four possible diastereomers of ketoconazole against rat lanosterol 1,4α-demethylase indicated that the 2S, 4R isomer was 2.5 times more active than its 2R, 4S enantiomer and the *trans* isomers, 2S, 4S, and 2R, 4R are much less active. Ketoconazole is an imidazole antifungal agent, which is a highly lipophilic compound. This property leads to high concentrations of ketoconazole in fatty tissues and purulent exudates. Ketoconazole is active against *Candida* spp and *Cryptococcus neoformans*.

Assay of Ketoconazole: Dissolve the sample in a mixture of anhydrous acetic acid and methyl ethyl ketone (1:7) and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: It is administered as 200 mg scored tablets and 2% topical cream.

Synthesis



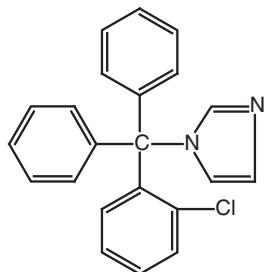
Metabolism of Terconazole: It is metabolized by CYP3A4 on oral administration.

Properties and uses of Terconazole: Terconazole is a white powder, practically insoluble in water, soluble in methylene chloride and in acetone, sparingly soluble in alcohol. It is a triazole derivative that is used exclusively for the control of *Vulvovaginal moniliasis* caused by *Candida albicans* and other *Candida spp.*

Assay of Terconazole: Dissolve the sample in a mixture of anhydrous acetic acid and volumes of methyl ethyl ketone (1:7) and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically at the second point of inflection.

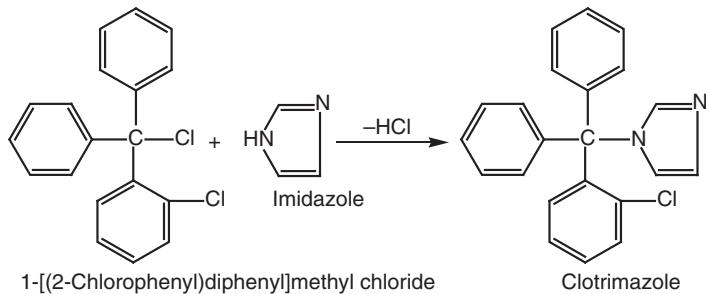
Dose: The administered dose is 80 gm vaginal suppository at bedtime for three days; and 0.4% as vaginal cream for seven days.

3. Clotrimazole (Clotrimin, Mycelex)



1-((2-Chlorophenyl)diphenylmethyl)-1*H*-imidazole

Synthesis



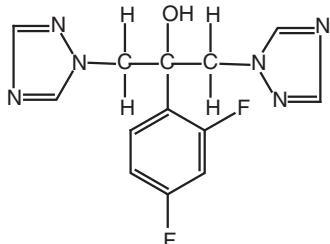
Properties and uses: Clotrimazole is a white or pale yellow crystalline powder, practically insoluble in water, soluble in alcohol and in methylene chloride. It is used as an antifungal agent.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid using naphtholbenzein as indicator until the colour changes from brownish-yellow to green.

Dose: The administered dose is usually as 100 mg tablet per day at bedtime for seven days for vaginal infection.

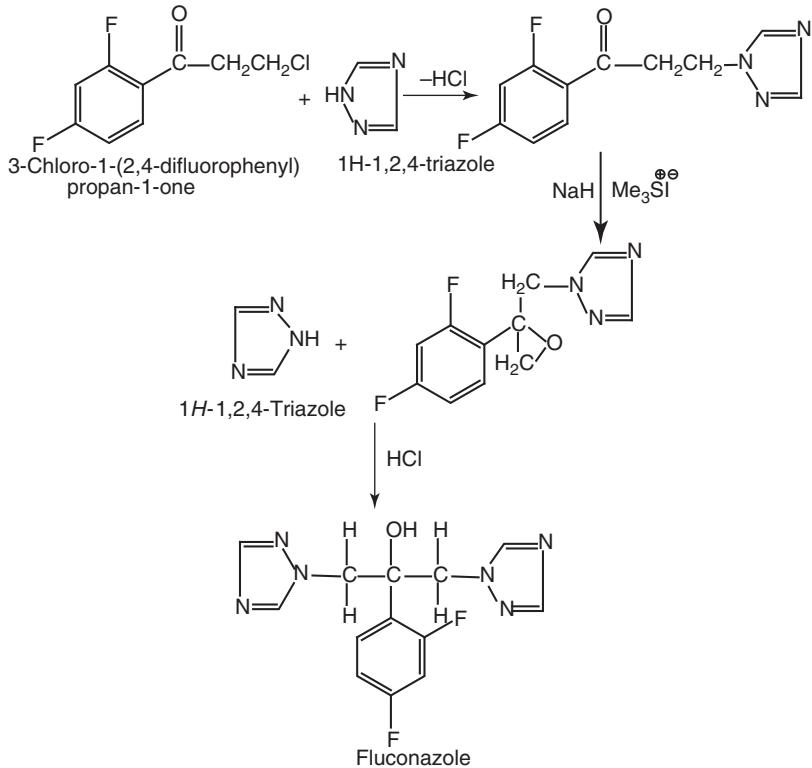
Dosage forms: Clotrimazole cream I.P., B.P., Clotrimazole pessaries I.P., B.P.

4. Fluconazole (Syscan, Zocon, Flucos)



2-(2,4-Difluorophenyl)-1,3-di(1*H*-1,2,4-triazol-1-yl)propan-2-ol

Synthesis



Properties and uses: Flucanazole is a white hygroscopic crystalline powder, slightly soluble in water, and soluble in methanol and in acetone. It is a widely used *bis*-triazole antifungal agent. It is generally considered to be a fungi-static agent, and it is principally active against *Candida* spp and *Cryptococcus* spp. Fluconazole has useful activity against *Coccidioides immitis*, and is often used to suppress the meningitis produced by the fungus.

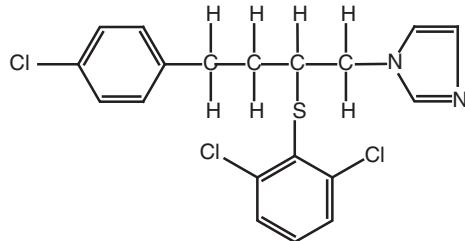
Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The administered dose for superficial mucosal candidiasis for adults is 50 mg daily, which is increased to 100 mg daily. Recommended treatment duration is 7–14 days; in the case of oropharyngeal candidiasis, 14 days for atrophic oral candidiasis associated with dentures, 14–30 days for other mucosal candidal infections, including oesophagitis. In the case of children, more than 4 weeks the loading dose is 6 mg/kg followed by 3 mg/kg daily.

The administered dose for dermatophytosis, pityriasis versicolor, and candida infections for adults is 50 mg daily for up to 6 weeks.

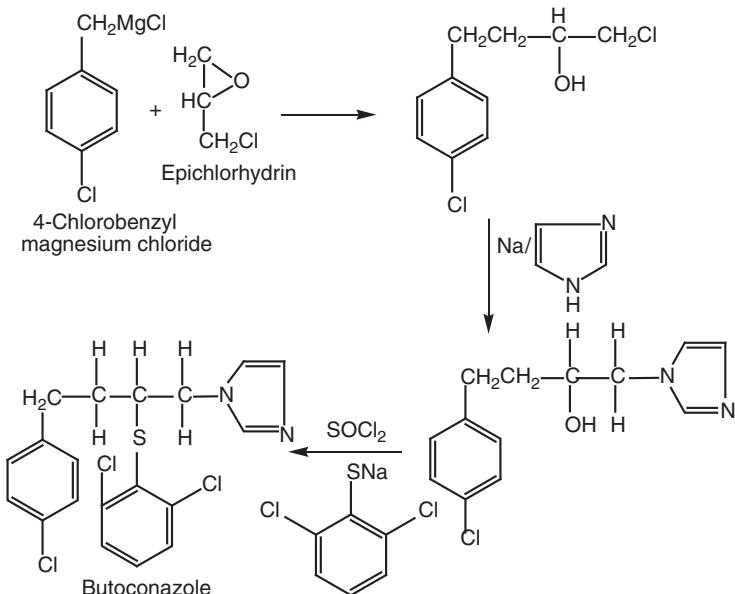
The administered dose for cryptococcal infections, including meningitis, systemic candidiasis for adults, initially is 400 mg followed by 200–400 mg daily; the maximum dose is 800 mg daily in the case of severe infections. In the case of cryptococcal meningitis, usual treatment duration is at least 6–8 weeks and may also be given via IV infusion. For children more than 4 weeks the dose is 6–12 mg/kg daily; same doses may be given every 72 h in neonates up to 2 weeks and every 48 h in neonates 2–4 weeks old; the maximum dose is 400 mg daily.

5. Butoconazole

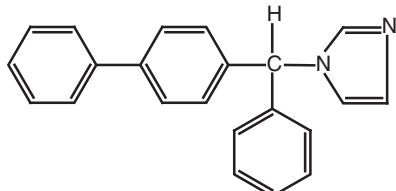


1-(4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)butyl)-1*H*-imidazole

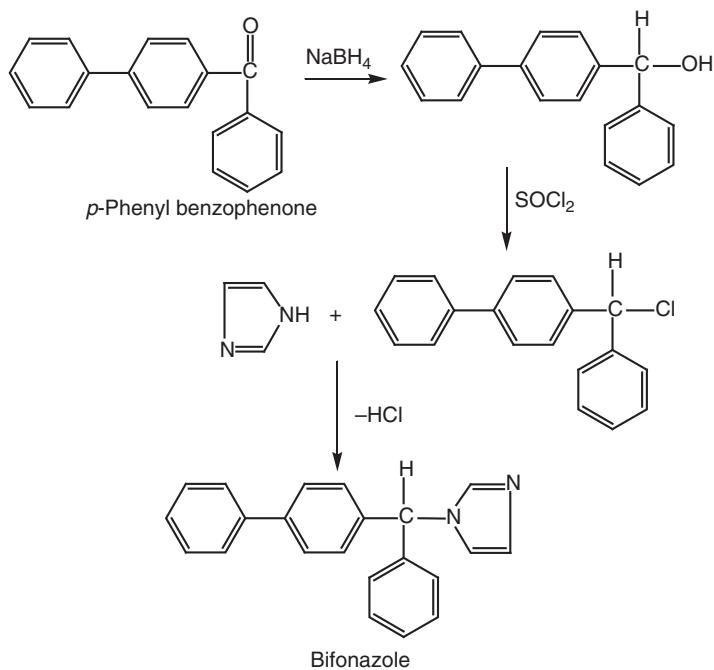
Synthesis



6. Bifonazole



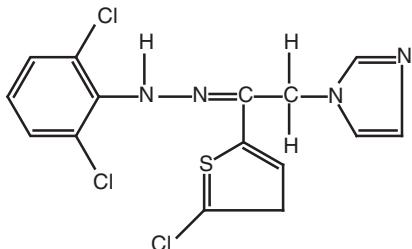
Synthesis

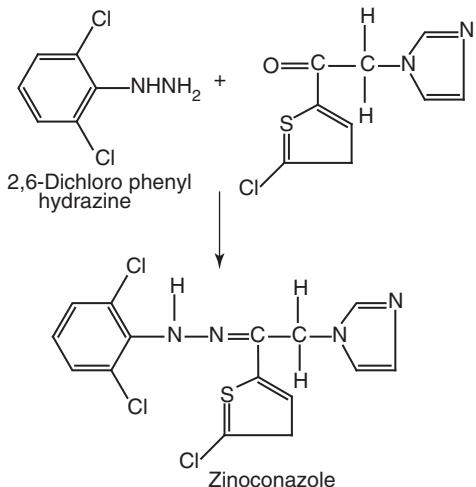
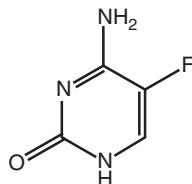
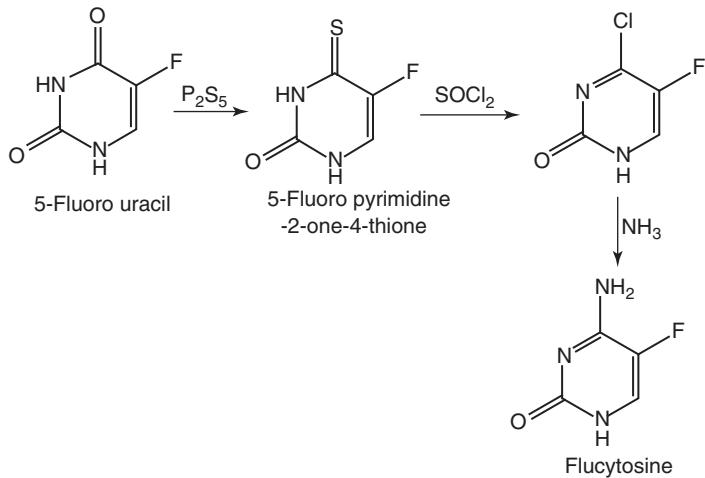


Properties and uses: Bifonazole is a white crystalline powder, practically insoluble in water, and sparingly soluble in anhydrous ethanol. It is used as an antifungal agent.

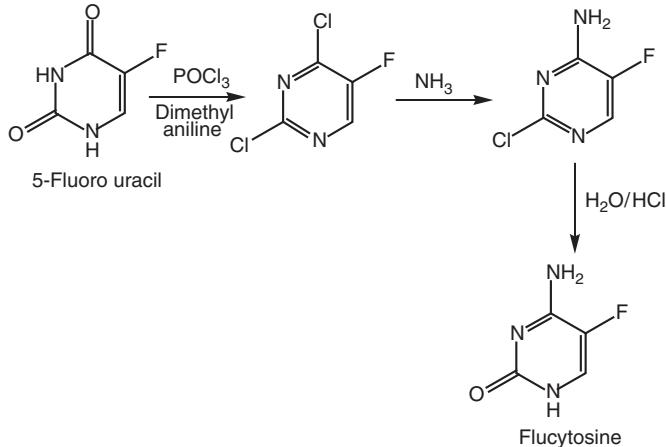
Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

7. Zinoconazole



Synthesis:**III. Fluorinated pyrimidines****1. Flucytosine**4-Amino-5-fluoropyrimidin-2(1*H*)-one**Synthesis****Route I. From: 5-Fluorouracil**

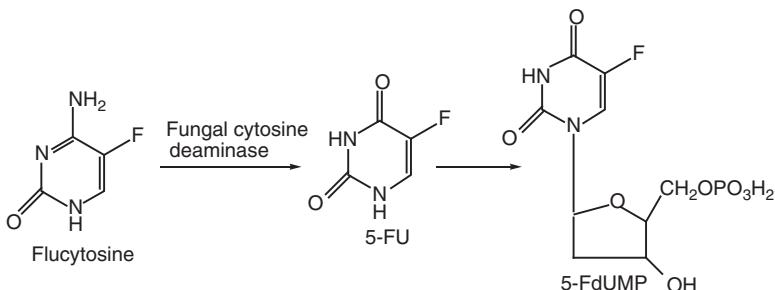
Route II. From: 5-Fluorouracil



Mode of action: Flucytosine is converted by cytosine deaminase into 5-fluorouracil (5-FU), then, 5-fluoro deoxyuridylic acid is formed. This false nucleotide inhibits thymidylate synthetase, thus, depriving the organism of thymidylic acid, an essential DNA component. It is a potent antimetabolite, which replaces uracil in the pyrimidine pool and thus, disrupts protein synthesis. Mammalian cells do not convert flucytosine to fluorouracil. This fact is crucial for the selective action of this compound. In addition, 5-fluorouracil is metabolized into 5-fluoro uridylic acid by the enzyme uridine monophosphate (UMP) pyrophosphorylase. It is either incorporated into the DNA (via synthesis of 5-fluorouridine triphosphate) or would be metabolized into 5-fluoro deoxyuridylic acid, which is a potent inhibitor of thymidylate synthetase.

Metabolism: It is metabolized to 5-FU by fungal cytidine deaminase.

Then 5-FU is converted into 5-fluorodeoxyuridine, which is a thymidylate synthase inhibitor and interferes with both protein and RNA biosynthesis.



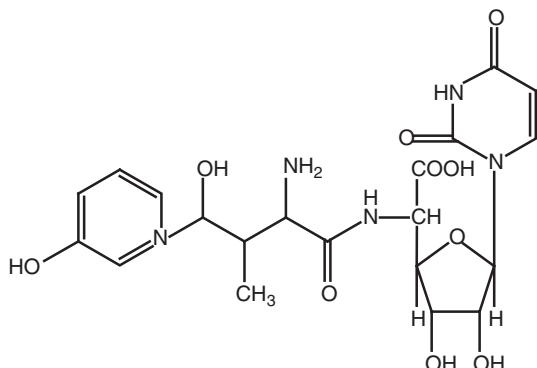
Properties and uses: Flucytosine is a white crystalline powder, sparingly soluble in water, and slightly soluble in ethanol. Flucytosine is the only available antimetabolite drug having antifungal activity.

Assay: Dissolve the sample in anhydrous acetic acid, add acetic anhydride, and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dosage forms: Flucytosine tablets B.P.

IV. Chitin synthetase inhibitors

1. Nikomycin



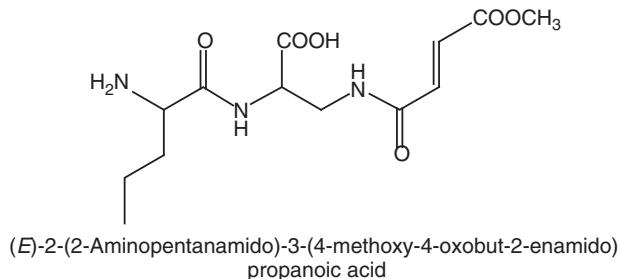
Mode of action: Nikomycin competitively inhibits the chitin synthase, mimicking its substrate uridine diphosphate-*N*-acetyl glucosamine of fungi with *C. albicans* as the primary target organism. The enzyme is an integral membrane protein. Nikomycin Z has shown to act synergistically in vitro with fluconazole, ketoconazole, and tioconazole against *C. albicans* at minimum inhibitory concentration (MIC) levels of azoles.

Properties and uses: Nikomycin is a nucleoside peptide antibiotic that is produced by soil strains of *Steptomyces tendae*. It is found to be more potent than most azoles in inhibiting highly chitinous, dimorphic fungal pathogens, such as *Coccidioides immitis* and *Blastomyces dermatididis*.

V. Peptides\proteins

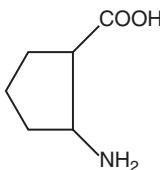
Examples—L-Norvalyl FMIP, Cispentacin

i. L-Norvalyl—FMIP



Mode of action: The inhibitors of glucosamine-6-phosphate synthase delivered through peptide transport systems have been reported as having anticandidal activity.

ii. *cis* Pentacin

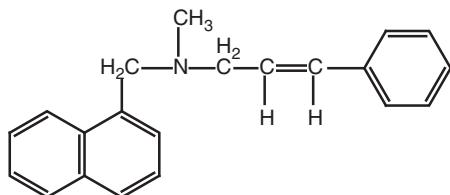


2-Aminocyclopentane carboxylic acid

Properties and uses: It is dipeptide analogue that is shown in vitro and in vivo activity against *C. albicans*.

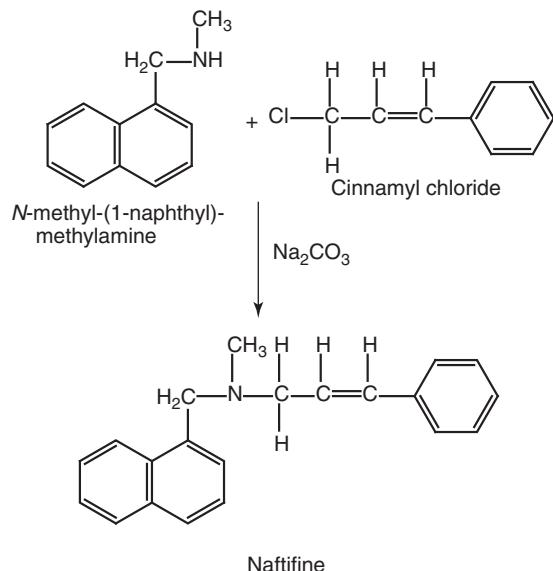
VI. Miscellaneous agents

1. Naftifine (Nabtin)



N-Methyl-N-(naphthalen-1-yl-methyl)-3-phenylprop-2-en-1-amine

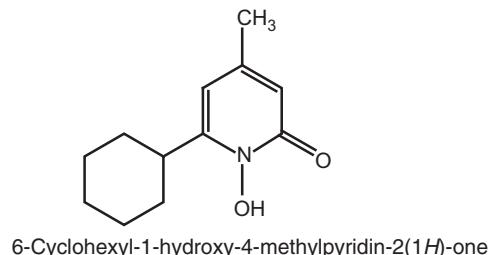
Synthesis



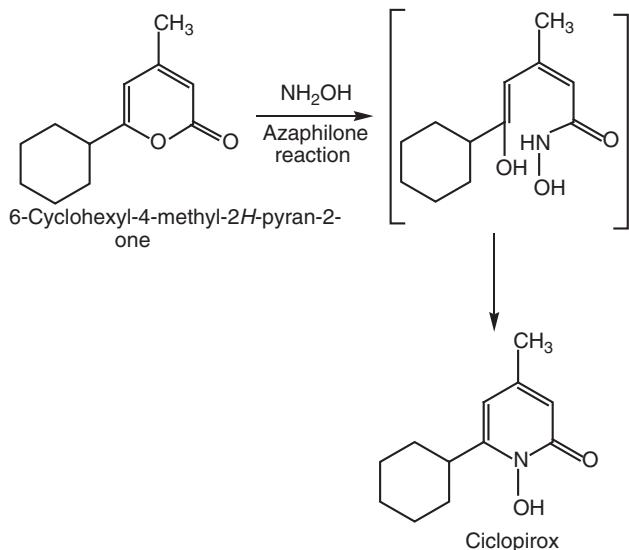
Mode of action: The drug has fungicidal activity against *Tinea cruris* and *Corporis* spp. This inhibits squalene 2,3-epoxidase and thus, inhibits fungal biosynthesis of ergosterol.

Dose: It is administered as 1% cream twice daily.

2. Ciclopirox



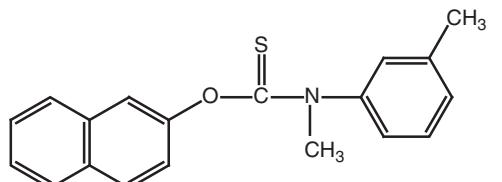
Synthesis



Properties and uses: Ciclopirox is a white or yellowish-white crystalline powder, slightly soluble in water, soluble in ethanol and in methylene chloride. It is available as 1% cream on cotton for the treatment of cutaneous candidiasis and for *Tinea corporis*, *T. cruris*, *T. pedis*, and *Pityriasis versicolour*.

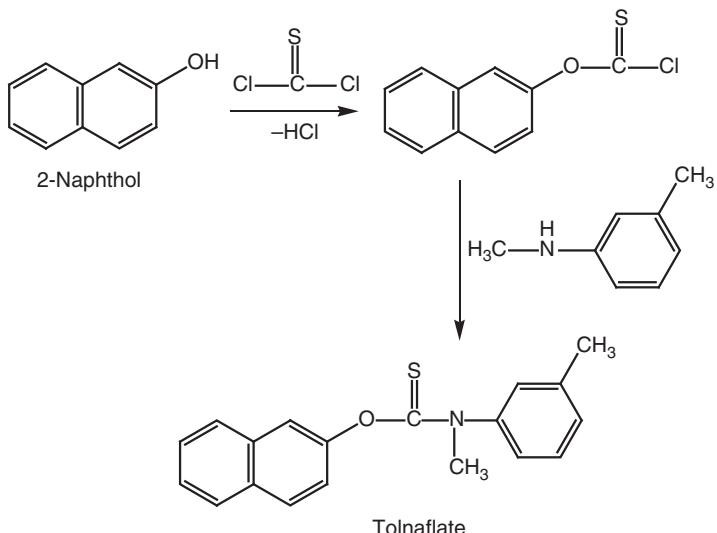
Assay: Dissolve the sample in methanol, add water, and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

4. Tolnaftate



O-(Naphthalen-2-yl)N-methyl(m-tolyl)carbamothioate

Synthesis

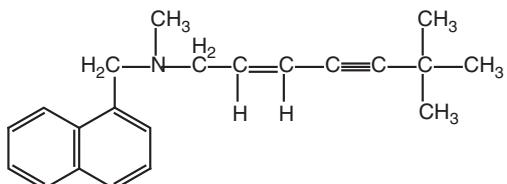


Properties and uses: Tolnaftate is a white or yellowish-white powder practically insoluble in water, soluble in acetone and in methylene chloride, and very slightly soluble in alcohol. It is effective for the treatment of most cutaneous mycoses, such as *Trichophyton rubrum* and *Microsporum canis*. Replacement of the aromatic methyl group by hydroxy or methoxy or its removal does not affect potency. Replacement of the complete tolyl group by a α -naphthyl or a β -naphthyl substituent does not decrease its potency. It is nontoxic.

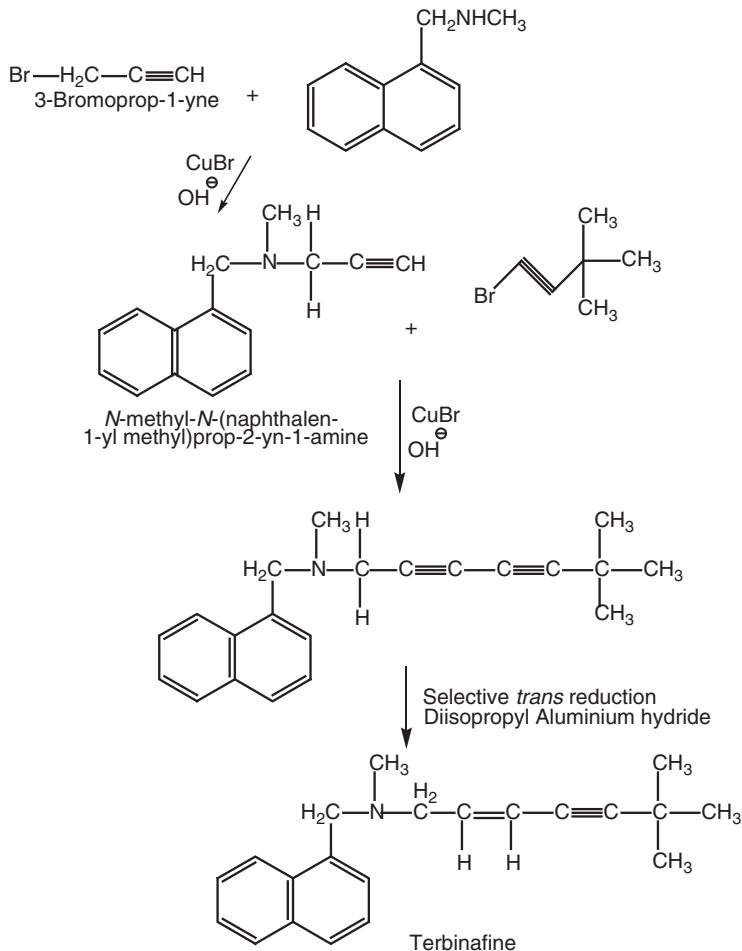
Dose: The administered dose is 1% as a cream, gel, powder, aerosol powder, and topical solution, applied locally twice a day.

Assay: Dissolve the sample in methanol, measure the absorbance, after its dilution with methanol, at the maxima at 257 nm, using ultraviolet spectrophotometer.

5. Terbinafine



N,6,6-Trimethyl-N-(naphthalen-1-yl methyl)hept-2-en-4-yn-1-amine

Synthesis

Mode of action: The uses and mechanism of action of terbinafine are the same as those of naffine. It is active by virtue of its ability to block squalene epoxidase.

Metabolism: Several CYP450 enzymes, including CYP1A₂, CYP2C1₉, CYP2C₉, CYP2C₈, CYP3A₄, and CYP2B₆, extensively metabolize it.

Properties and uses: Terbinafine hydrochloride is a white powder, slightly soluble in water and in acetone, soluble in anhydrous ethanol and in methanol. It is used as an antifungal agent.

Assay: Dissolve the sample in ethanol, add 0.01 M hydrochloric acid, and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

PROBABLE QUESTIONS

1. Define and classify antifungal agents. Write the synthesis and uses of any two of them.
2. Enumerate the various fungal diseases and mention the drugs used against those diseases.
3. Write a note on azoles used in fungal infection.
4. Write the synthesis and uses of tolnaftate, clotrimazole, and griseofulvin.

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12. Lyman CA and Walgh TJ. 'Systemically administered antifungal agents'. *Drugs* 44(1): 9–35, 1992.
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Chapter 7

Antiviral Agents

INTRODUCTION

Antiviral agents are substances used in the treatment and prophylaxis of diseases caused by viruses. Viral diseases include influenza, rabies, yellow fever, poliomyelitis, ornithosis, mumps, measles, ebola, human immuno deficiency virus (HIV), herpes, warts, and small pox. Viruses are not proper living things, but consists of a genome; they are smaller in size with simple chemical composition, sometimes a few enzymes stored in a capsule made up of protein and rarely covered with a lipid layer. The viruses only replicate within the host cell and the viral replication depends primarily on the metabolic processes of the invaded cell. Viruses does not possess cell wall, but they have RNA or DNA enclosed in a shell of protein known as capsid. The capsid is composed of several subunits known as capsomers. In certain cases, capsid may be surrounded by an outer protein or lipoprotein envelope. One group of RNA virus that deserves special mention are rteroviruses. They are responsible for acquired immuno deficiency syndrome (AIDS) and T-leukaemias. Reteroviruses contain reverse transcriptase (RT) enzyme activity that makes a DNA copy of the viral RNA template. Then, the DNA copy is integrated into the host genome, at which it is referred to as provirus and is transcribed into both the genomic RNA and mRNA for translocation into the viral proteins, giving generation to new virus particles. Viral life cycle varies according to the species, but they all share a general pattern that can be sequenced as follows (Fig. 7.1):

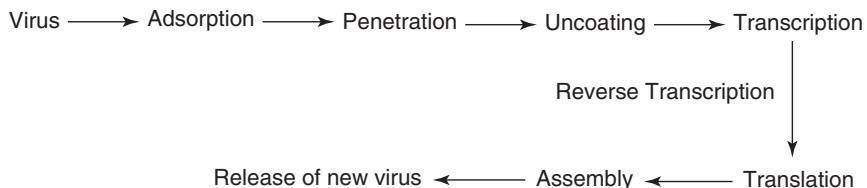


Figure 7.1 Life cycle of virus.

- **Adsorption:** Attachment of the virus to the host cell.
- **Penetration:** Penetration of virus into the cell.
- **Uncoating:** The genetic material or viral genome (DNA or RNA) passes into the host cell leaving the capsid covering outside the host cell.

- **Transcription:** Production of the viral mRNA from the viral genome.
- **Translation:** The viral genome enters the cytoplasm or the nucleoplasma and directs or utilizes the host nucleic acid machinery for the synthesis of the new viral protein and for the production of more viral genome. The viral protein modifies the host cell and allows the viral genome to replicate by using host and viral enzyme. This is often the stage at which the cell is irreversibly modified and eventually killed.
- **Assembly of the viral particle:** New viral coat protein assembles into capsid and viral genomes.
- Release of the mature virus from the cell and the budding process or rupture of the cell and repeat of the process, in a fresh host cell.

Since the host cell machinery is totally utilized for the production of new virions, the normal cell function is affected. Antiviral agents have been developed to act at various stages in the viral replication cycle, such as attachments, replication, and release of the virus.

Some virus types together with diseases that they cause are listed in Table 7.1.

Table 7.1 Examples of viruses with diseases.

| Virus | Diseases |
|--------------------|---|
| DNA viruses | |
| Pox virus | Small pox |
| Herpes virus | Chicken pox, Shingles herpes, Glandular fever |
| Adenovirus | Sore throat, Conjunctivitis |
| Papilloma virus | Warts |
| Parvo virus | Canine distemper |
| RNA viruses | |
| Orthomyxovirus | Influenza |
| Paramn virus | Measles, mumps, rabies |
| Rhabdo virus | Colds, meningitis |
| Picor virus | Poliomyelitis |
| Retrovirus | AIDS, T-cell leukaemia |
| Arena virus | Meningitis, Lassa fever |
| Hepadna virus | Serum hepatitis |
| Reo virus | Diarrhoea |
| Filo virus | Ebola, Marburg |
| Bunya virus | Encephalitis, haemorrhagic fever |

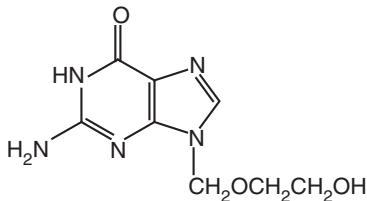
CLASSIFICATION

Classification According to its Mechanism of Action

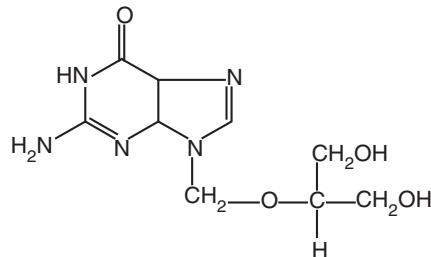
Antiviral drugs may be classified on the basis of its mechanism of action as follows:

I. Nucleoside RT inhibitors

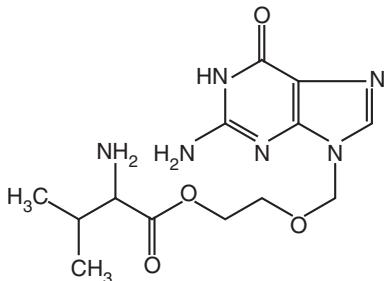
a. Purine nucleosides and nucleotides



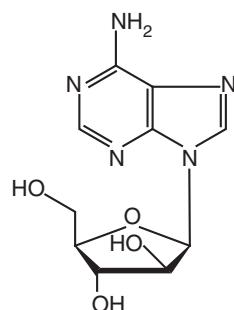
Aciclovir



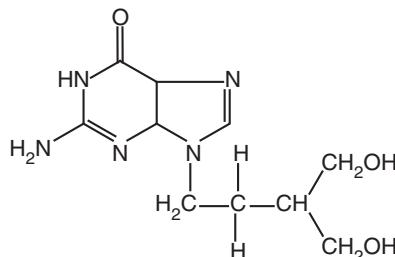
Ganciclovir



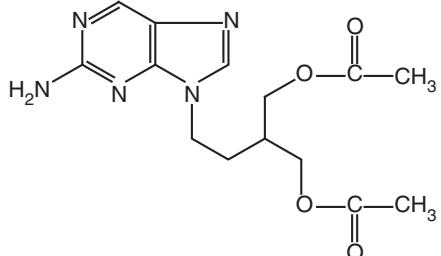
Valaciclovir



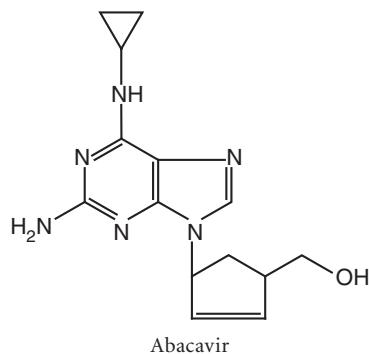
Vidarabine



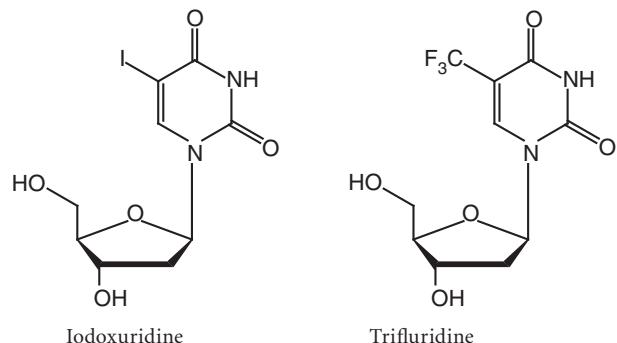
Penciclovir



Famciclovir

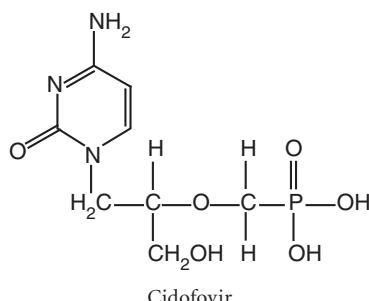


b. Pyrimidine nucleosides and nucleotides



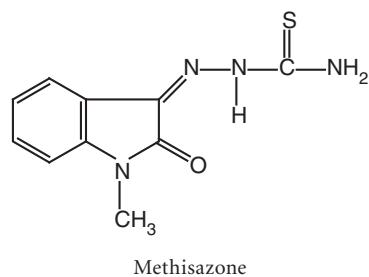
Iodoxuridine

Trifluridine



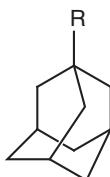
Cidofovir

c. Thiosemicarbazones



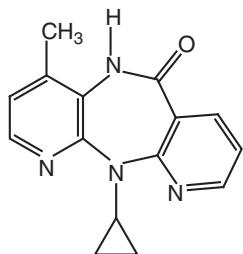
Methisazone

d. Adamantane amines

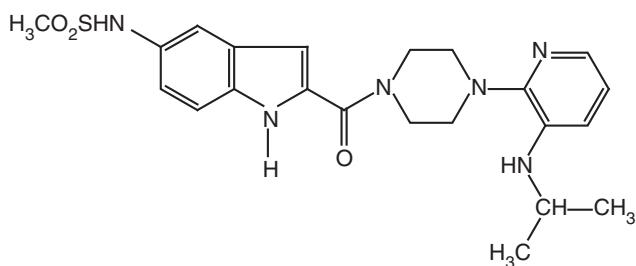


| Name | R |
|--------------|---|
| Amantadine | $-\text{NH}_2$ |
| Rimantadine | $\begin{array}{c} \text{H} \\ \\ -\text{C}-\text{CH}_3 \\ \\ \text{NH}_2 \end{array}$ |
| Somantadine | $\begin{array}{c} \text{H} \quad \text{CH}_3 \\ \quad \\ -\text{C}-\text{C}-\text{NH}_2 \\ \quad \\ \text{H} \quad \text{CH}_3 \end{array}$ |
| Tromantadine | $-\text{NHCOCH}_2\text{OCH}_2\text{CH}_2-\text{N}\begin{pmatrix} \text{CH}_3 \\ \\ \text{CH}_3 \end{pmatrix}$ |

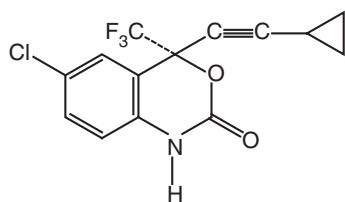
II. Non-nucleoside RT inhibitors



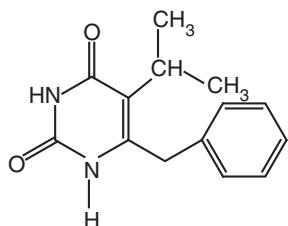
Nevirapine



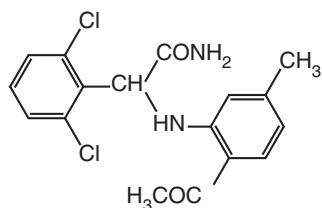
Delavirdine



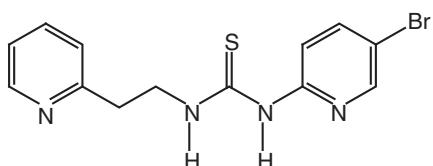
Efavirenz



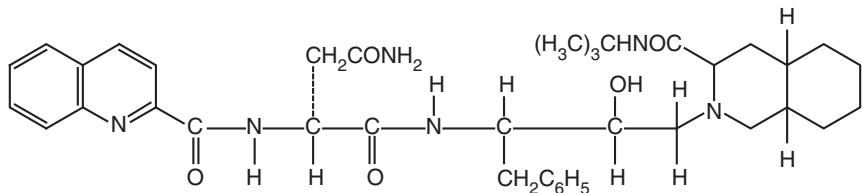
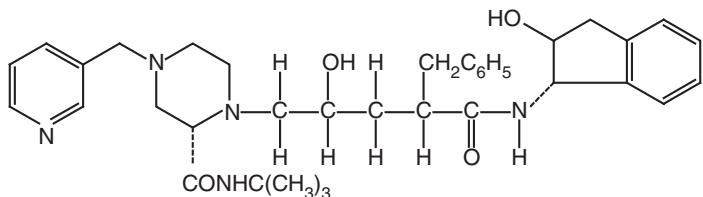
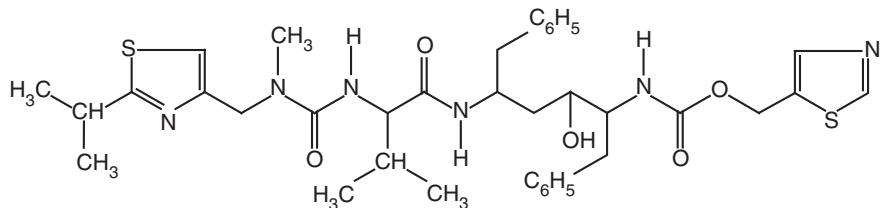
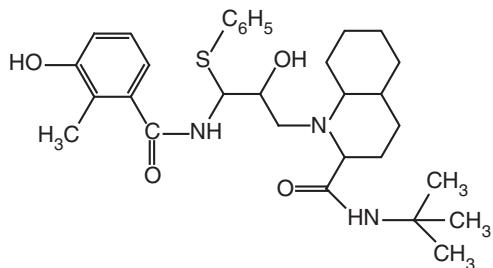
Emivirine



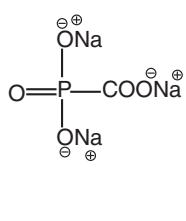
Loviride



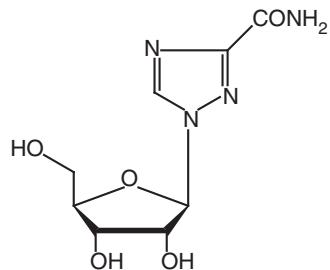
Trovirdine

III. HIV protease inhibitors**a. Saquinavir****b. Indinavir****c. Ritonavir****d. Nelfinavir**

IV. Miscellaneous



Foscarnet sodium

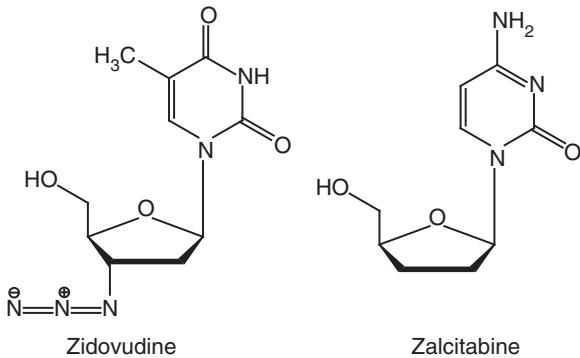


Ribavirin

Classification According to the Enzyme Inhibition

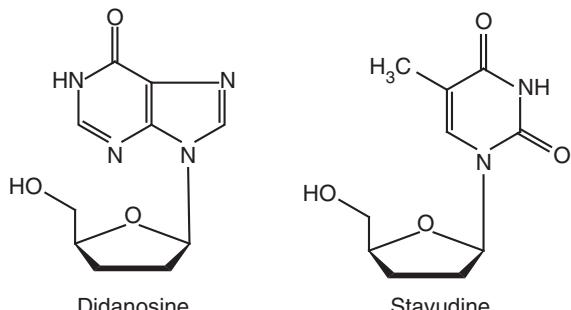
According to the enzyme inhibition, antiviral agents are classified as follows.

- i. DNA polymerase inhibitors: Idoxuridine, Trifluridine, Vidarabine
- ii. RT inhibitors:



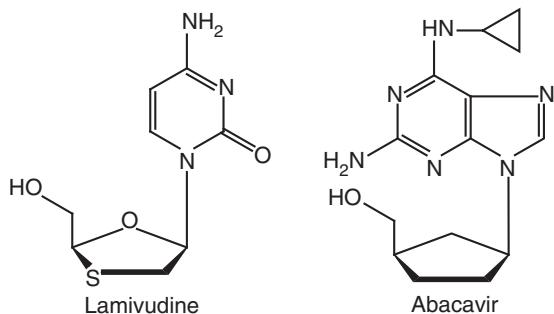
Zidovudine

Zalcitabine



Didanosine

Stavudine



Classification According to the Treatment Protocol

According to the treatment protocol antiviral agents are classified as follows:

I. Treatment of respiratory virus infection

Adamantane derivatives: Amantadine, Rimantadine

II. Treatment of herpes and cytomegalovirus infection.

- a. Purine nucleotides: Acyclovir, Ganciclovir, Vidarabine.
- b. Pyrimidine nucleosides: Trifluorouridine, Idoxuridine.
- c. Phosphorus derivatives: Foscarnet sodium.

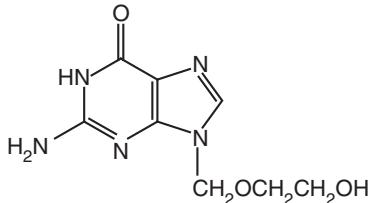
III. Treatment of HIV infections

- a. RT inhibition.
 - 1. Purine derivatives: Didanosine.
 - 2. Pyrimidine derivative: Zidovudine, Stavudine.
 - 3. Non-nucleosides: Nevirapine, Delavirdine, Efavirenz.
- b. Protease inhibition: Saquinavir, Indinavir, Ritonavir, Nelfinavir, Amprenavir, Lopinavir.
- c. Integration inhibition: Zintevir.

SYNTHESIS AND DRUG PROFILE

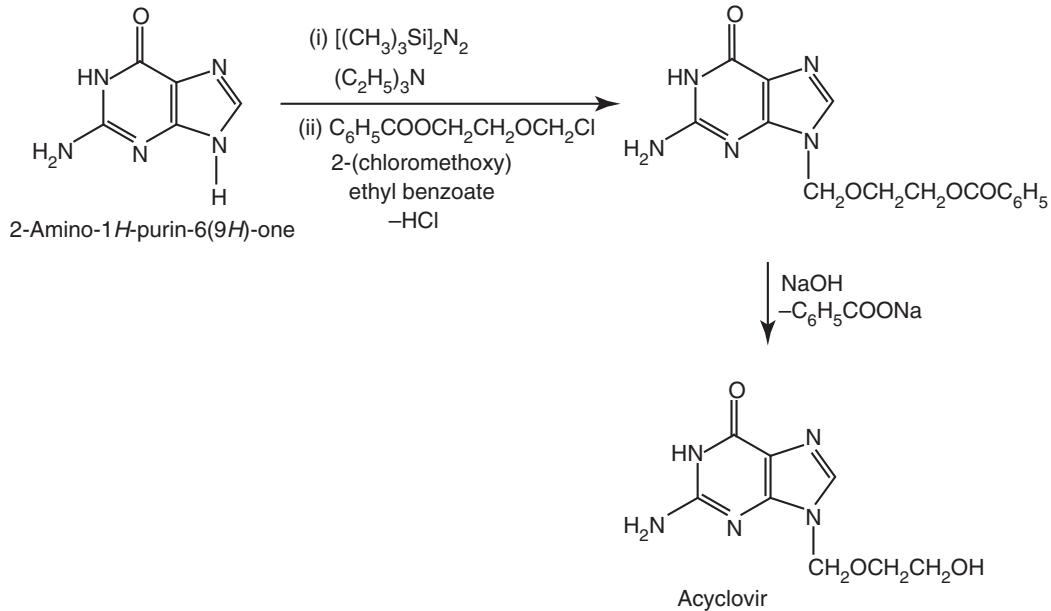
I. Nucleotide analogues

- a. Purine nucleosides and nucleotides
- i. Acyclovir (Ocuvir, Zovirax, Cyclovir)



2-Amino-9-((2-hydroxyethoxy)methyl)-1*H*-purin-6(9*H*)-one

Synthesis



Metabolism: The bioavailability of acyclovir is 15%–30 % and it is metabolized to 9-carboxy-methoxymethyl guanine, which is inactive.

Properties and uses: Acyclovir is a white crystalline powder, slightly soluble in water, soluble in dimethyl sulphoxide and in dilute mineral acids and alkali hydroxides, and very slightly soluble in ethanol. It is a purine nucleoside analogue, used as antiviral agent against herpes viruses.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically. Perform a blank titration.

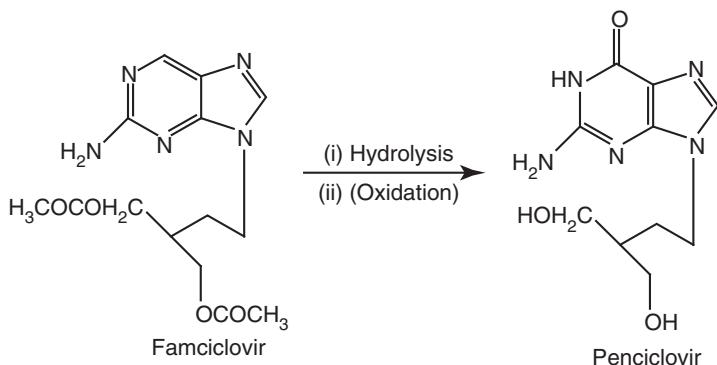
Dose: For herpes virus infections the administered dose for immuno-suppressed patients is up to 10 mg/kg body weight every 8 h.

Dosage forms: Acyclovir cream B.P., Acyclovir eye ointment B.P., Acyclovir intravenous infusion B.P., Acyclovir oral suspension B.P., Acyclovir tablets B.P., Dispersible acyclovir tablets B.P.

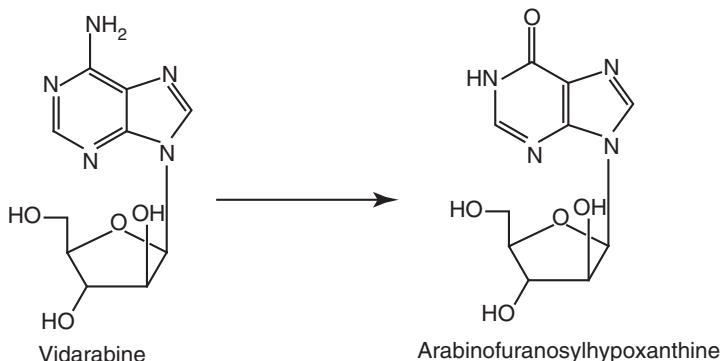
Metabolism of Valacyclovir: The related analogue 6-deoxy acyclovir is a prodrug form of acyclovir that is activated through metabolism by xanthine oxidase.

Metabolism of Cidofovir: It is metabolized by phosphorylation and it gives cidofovir diphosphate.

Metabolism of Famciclovir: It is a prodrug of penciclovir, which is formed in vivo by hydrolysis of acetyl groups and oxidation at the 6th position by the mixed function oxidase. Penciclovir and its metabolite penciclovir triphosphate possesses antiviral activity.

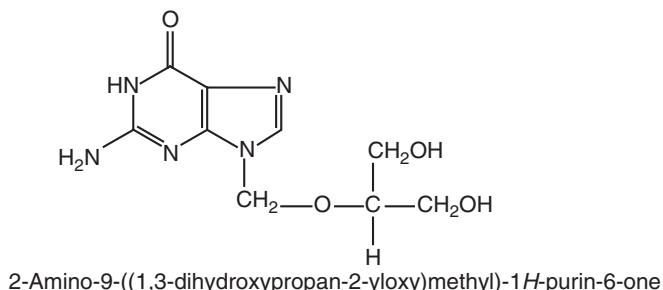


Metabolism of vidarabine: It is deaminated rapidly by adenosine deaminase enzyme, which is present in the serum and the red blood cells. The enzyme converts vidarabine to its principal metabolite, arabinosyl hypoxanthine, which has weak antiviral activity.

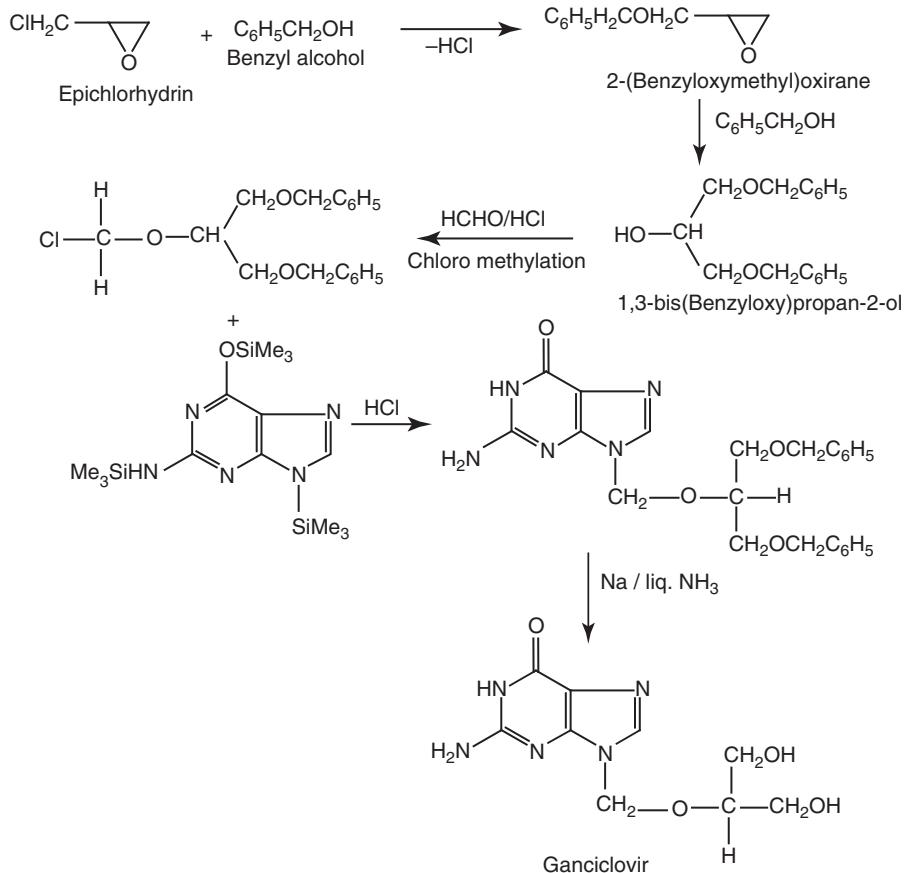


Uses: It is used for the short-term treatment of herpes simplex and chicken pox caused by varicella-zoster virus (VZV).

ii. Ganciclovir (Ganguard)



Synthesis

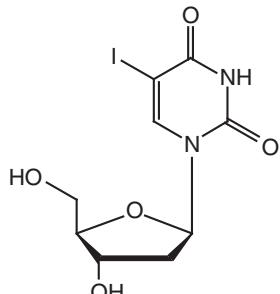


Properties and uses: Ganciclovir is a white powder, soluble in water and it is used as an antiviral agent.

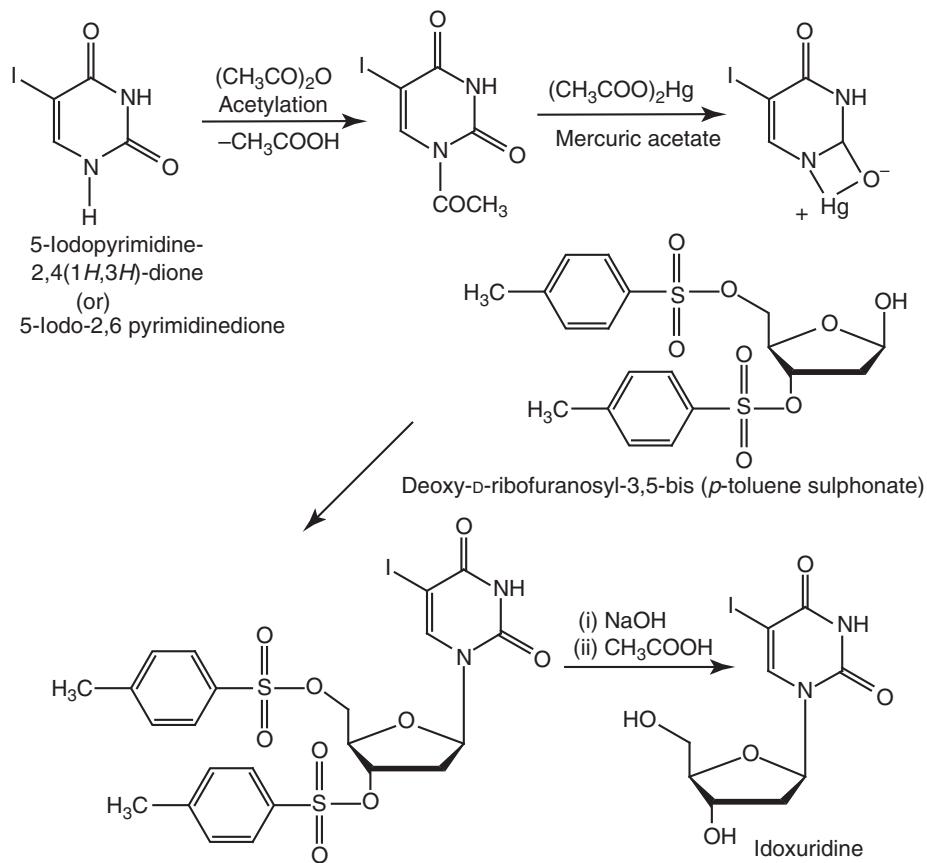
Dose: The recommended dose is 5 mg/kg 1 h for infusion every 12 h for 14 days.

I. b. Pyrimidine nucleoside and nucleotide inhibitors

iii. Idoxuridine (Antizona, Dendrid)



5-Iodo-2-deoxyuridine

Synthesis

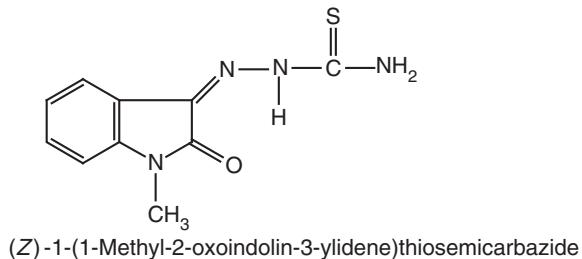
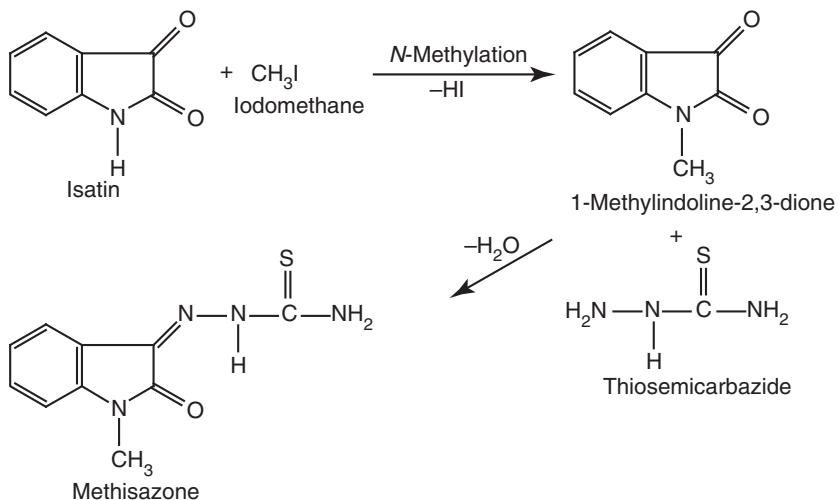
Metabolism: It has a plasma half-life of 30 min and it is rapidly metabolized in the blood to idoxuracil and uracil.

Properties and uses: Idoxuridine is a white crystalline powder, slightly soluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. It is a pyrimidine nucleoside analogue and used as an antiviral agent against herpes virus .

Assay: Dissolve the sample in dimethylformamide and titrate with 0.1 M tetrabutyl ammonium hydroxide. Determine the end point potentiometrically.

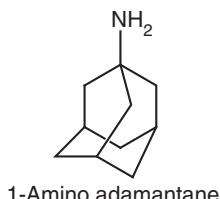
Dose: The administered dose topically as a ointment is 0.5%, 4–16 times a day or 0.1 ml of a 0.1% solution every 1 to 2 h into the conjunctiva.

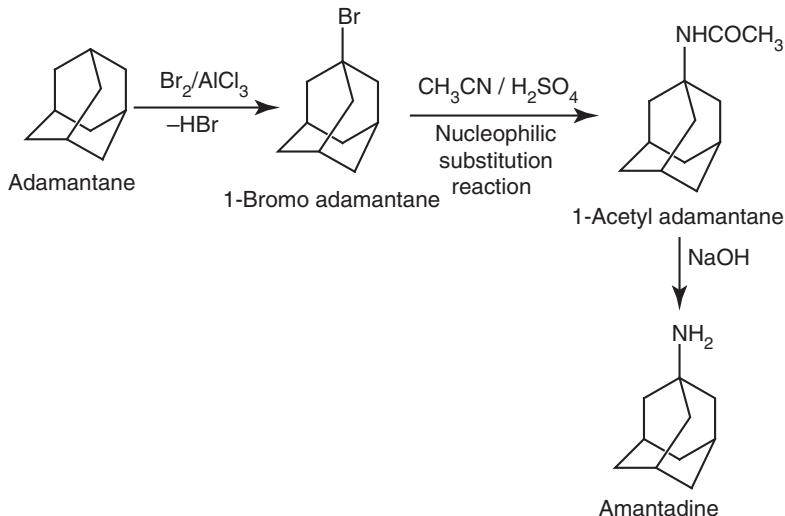
Dosage forms: Idoxuridine eye drops B.P.

I. c. Thiosemicarbazones**iv. Methisazone (Marboran)****Synthesis**

Dose: The recommended oral dose is 1.5–3.0 g twice daily for four days. As a prophylactic against small pox, it should be administered before the 8th or 9th day of the 12-day incubation period.

Uses: Used in the treatment of viral infection.

I. d. Adamantane amines**1. Amantadine (Symmetrel)**

Synthesis

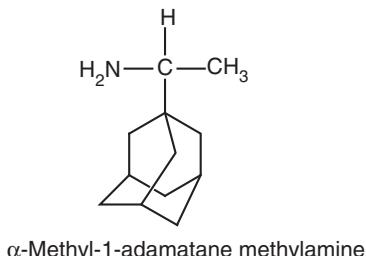
Metabolism: Approximately, 90% of the drug is excreted unchanged by the kidney, primarily through glomerular filtration and tubular secretion, and there are no reports of metabolic products. Acidification of urine increases the rate of amantadine excretion.

Properties and uses: Amantadine hydrochloride is a white crystalline powder, soluble in water and in alcohol. Amantadine is used in the treatment of Parkinson's disease. It is effective against influenza type-A virus, para influenza, and some RNA virus. It is also used as a dopamine receptor agonist.

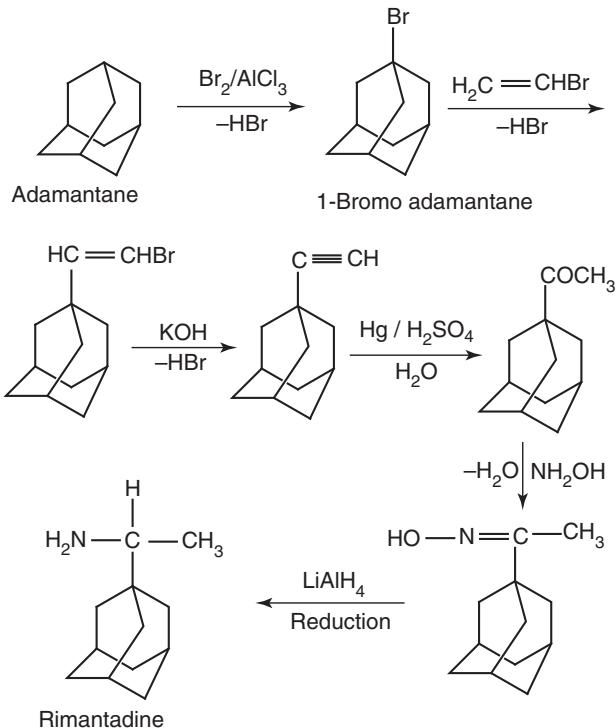
Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol (1:10) and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: The usual recommended dose is 100 mg twice daily. For children 1–9 years of age the administered dose is 4–9 mg/kg and 9–12 years of age 100 mg twice daily.

Dosage forms: Amantadine capsules I.P., B.P., Amantadine oral solution B.P.

2. Rimantadine

Synthesis



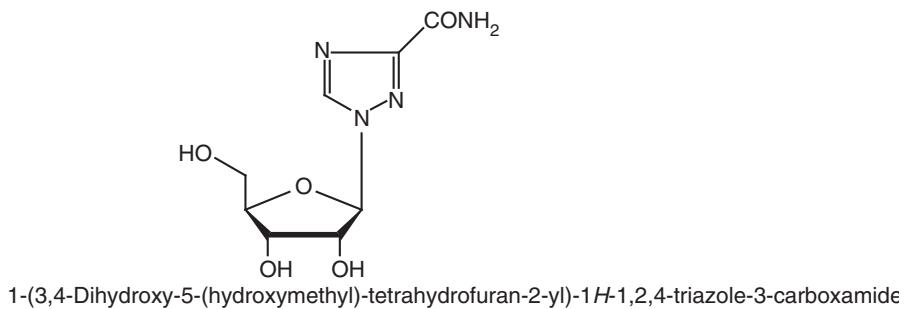
Metabolism: Rimantadine is metabolized in the liver and approximately 20% is excreted unchanged as hydroxylated compound.

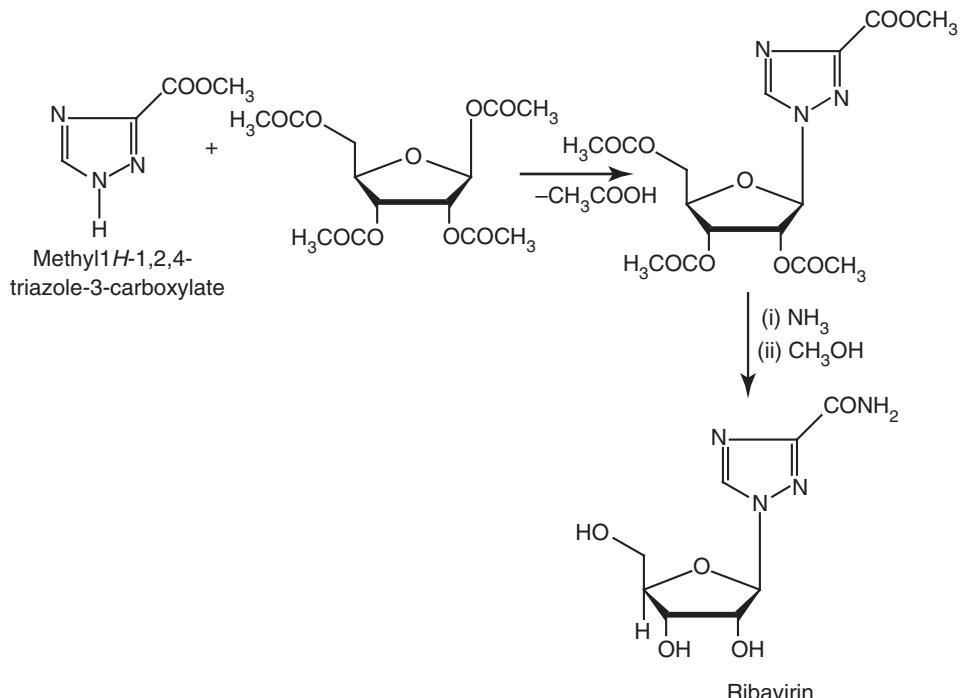
Properties and uses: Rimantadine is a white to off-white crystals, soluble in water. It is used for the prevention of infection caused by various strains of influenza virus-A.

Dose: The recommended dose usually is 300 mg.

Miscellaneous

i. Ribavirin (Virazole)



Synthesis

Properties and uses: Ribavirin is a white crystalline powder, soluble in water, slightly soluble in ethanol and in methylene chloride. It is used in the treatment of influenza type-A and -B, hepatitis, genital herpes, and Lassa fever.

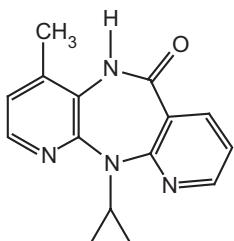
Assay: It is assayed by adopting liquid chromatography technique.

Dose: For viral hepatitis, influenza, and herpes virus infections, the recommended dose is up to 1g per day in divided doses.

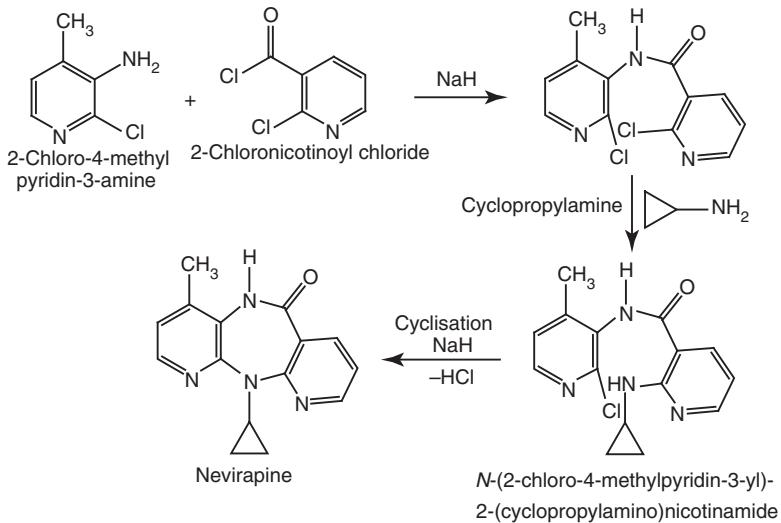
Dosage forms: Ribavirin nebulizer solution B.P.

II. Non-nucleoside RT inhibitors

i. Nevirapine (Neve, Nevipan, Nevimune)



Synthesis



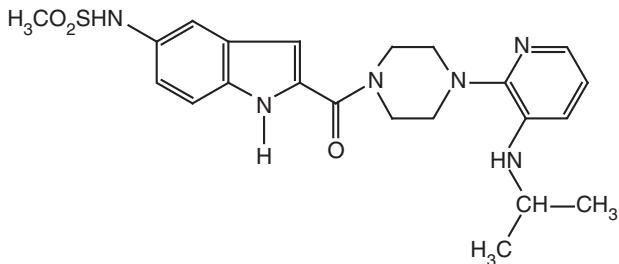
Metabolism: Nevirapine is metabolized as a glucuronide conjugation to form hydroxylated metabolites and excreted in urine.

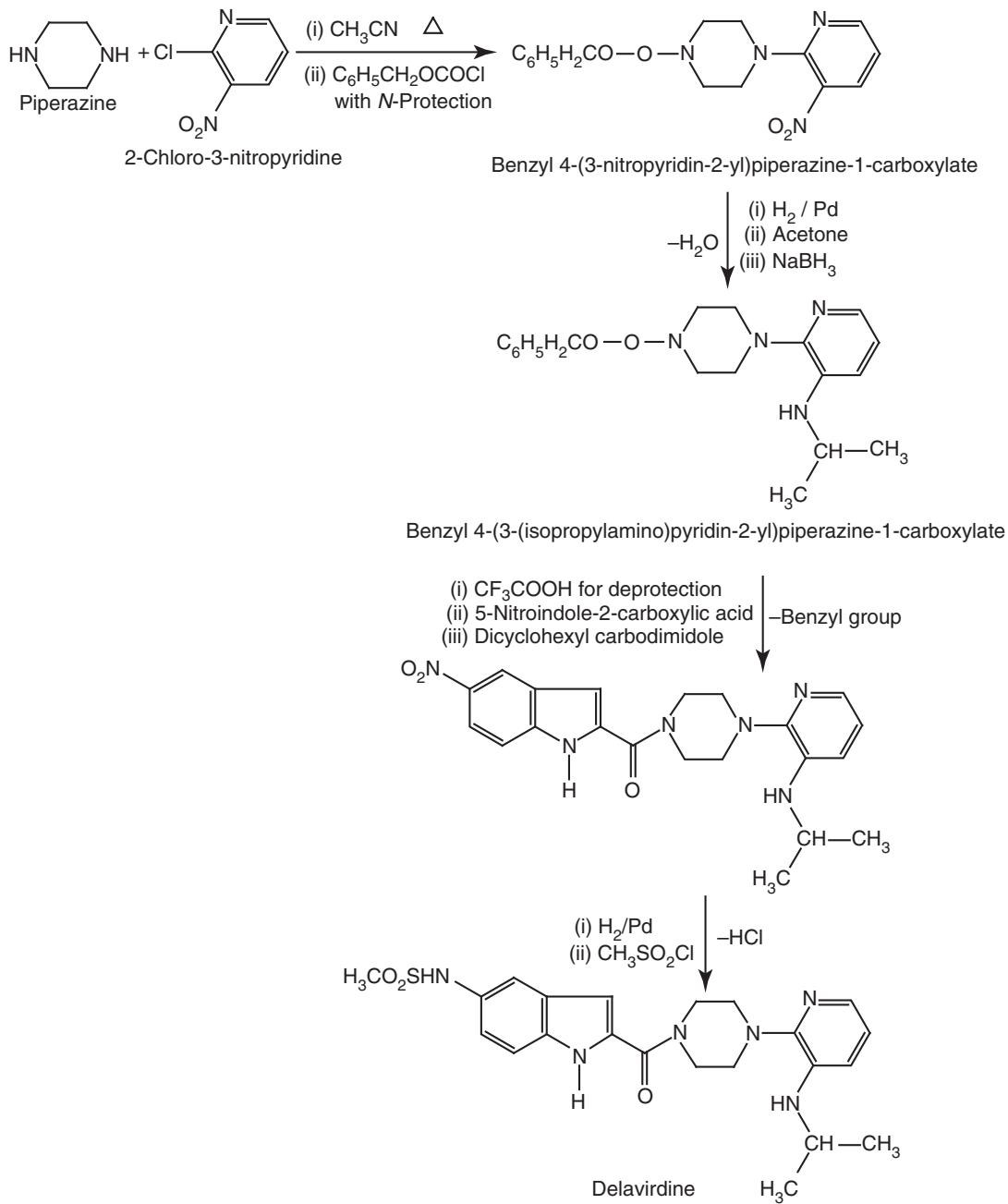
Properties and uses: Nevirapine is a white powder, practically insoluble in water, slightly soluble in methylene chloride and in methanol. It is a HIV non-nucleoside RT inhibitor, used as an anti-HIV agent. It causes rash fever, nausea, and headache.

Assay: It is assayed by adopting liquid chromatography technique.

Dose: The recommended dose for HIV infection combined with other antiretrovirals in the case of adults is 200 mg once daily for the first 14 days; then, to increase to 200 mg two times/day if rash does not develop. Interrupting the treatment for more than 7 days necessitates reintroduction of the medicine at a lower dose for the first 14 days. For children 2 months to 8 years the dose is 4 mg /kg once daily for the first 14 days, and increase to 7 mg/kg twice a day, if no rash is present. In the case of patients 8–16 years, the dose is 4 mg/kg once daily for 14 days followed by 4 mg/kg twice/day. Maximum dose that can be administered is 400 mg daily. Interrupting the treatment for more than 7 days necessitates reintroduction at a lower dose for the first 14 days.

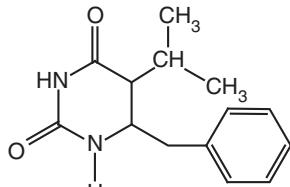
ii. Delavirdine



Synthesis

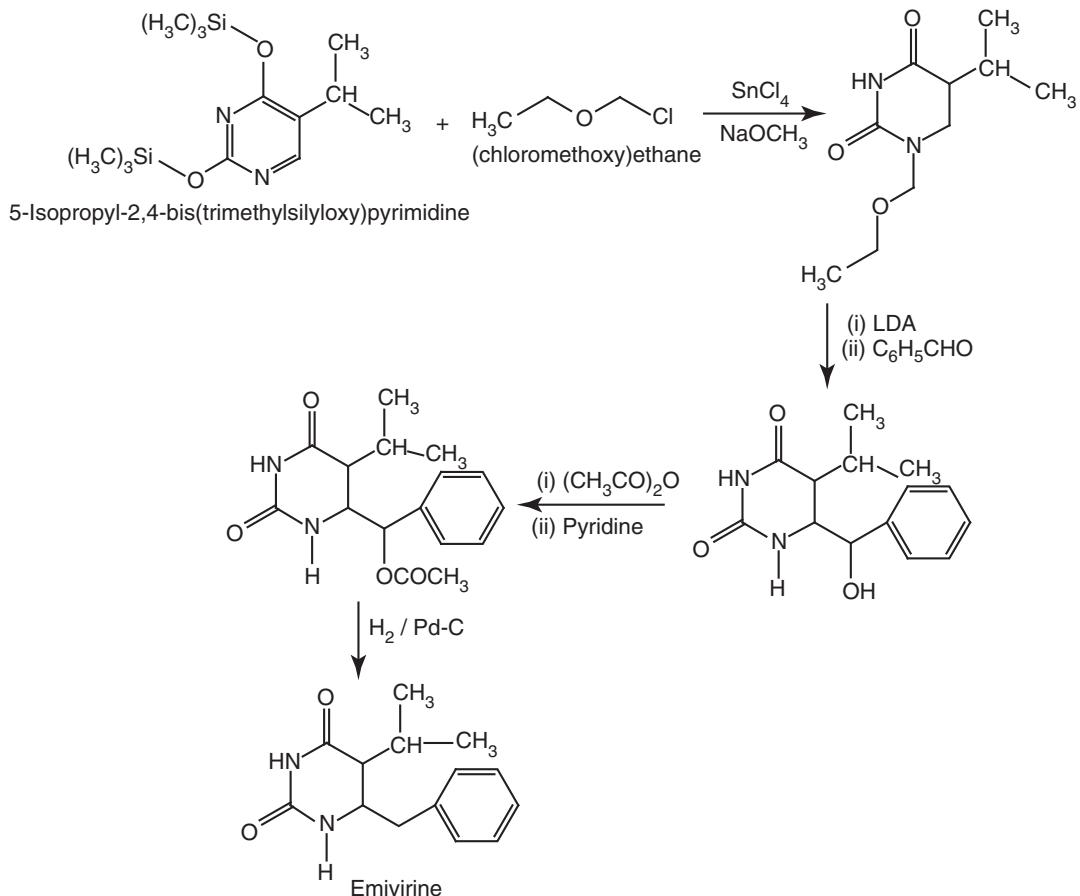
Metabolism: Delavirdine is metabolized to *N*-desisopropyl metabolite in the liver and the pharmacokinetics is nonlinear.

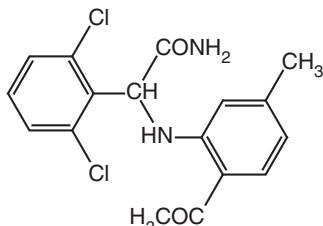
iii. Emivirine



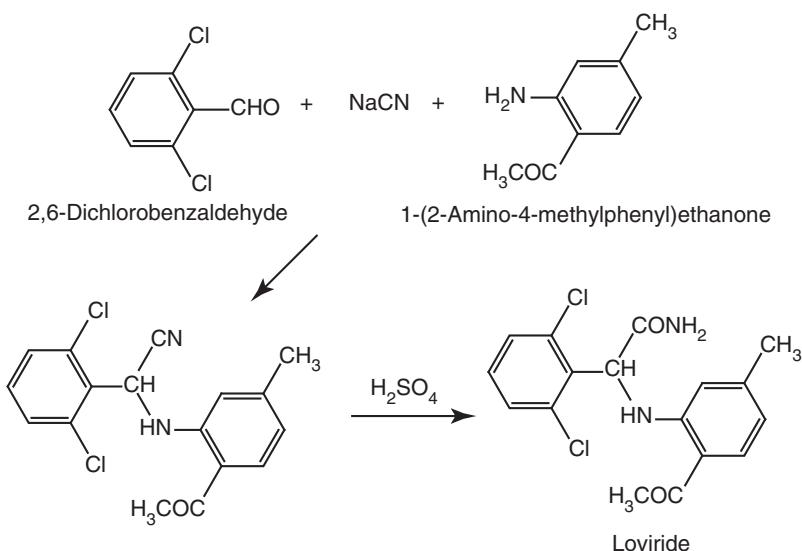
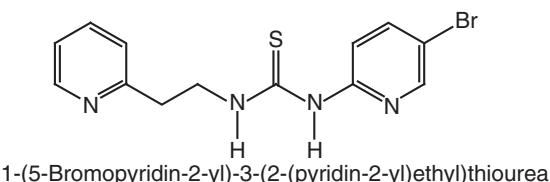
6-Benzyl-5-isopropyl-hexahydropyrimidine-2,4-dione

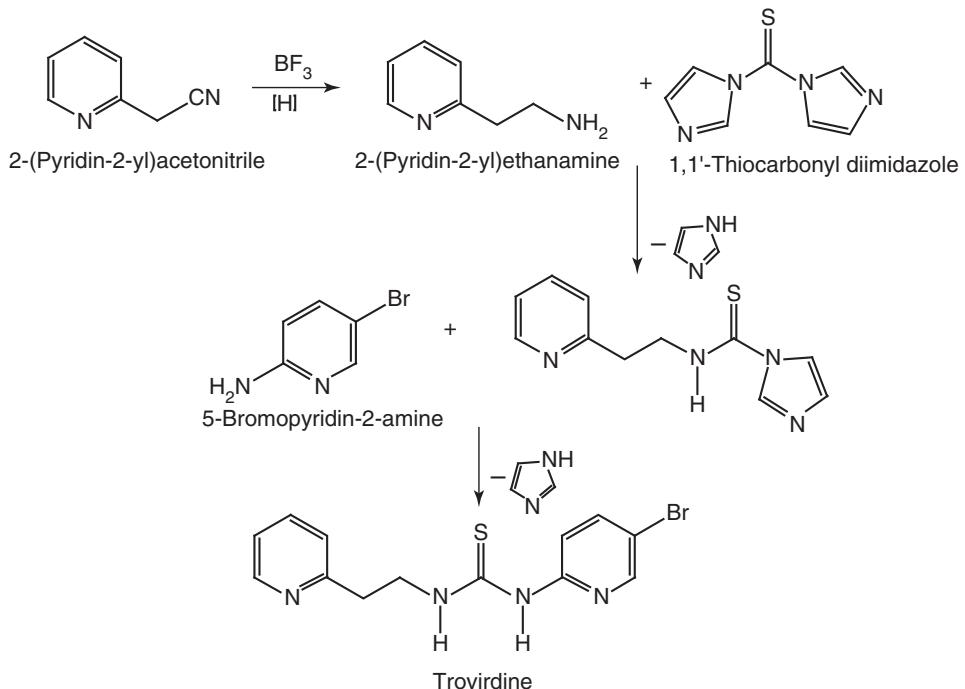
Synthesis



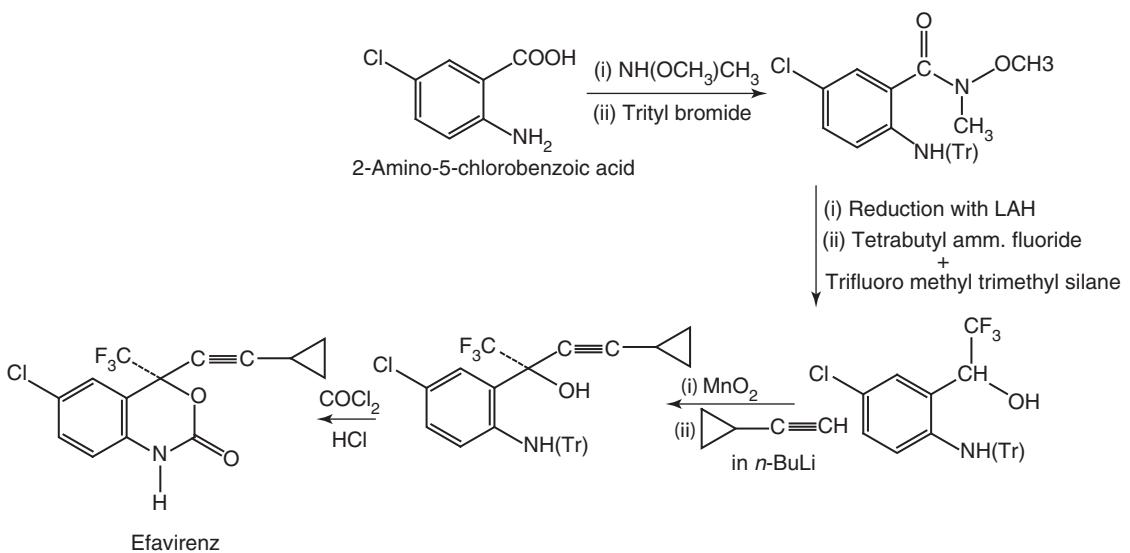
II. d. α -Anilinophenylacetamide**i. Loviride**

2-(2-Acetyl-5-methylphenylamino)-2-(2,6-dichlorophenyl)acetamide

Synthesis**II. e. Pyridyl ethyl thiourea****i. Trovirdine**

Synthesis:**II. f. Benzoxazinones**

Efavirenz (Efavir, Efferven, Evirenz)
Synthesis



Properties and uses: Efavirenz is a white to slightly pink crystalline powder, soluble in dilute hydrochloric acid and in ethanol, but insoluble in water. It is a non-nucleoside RT inhibitor used as a part of the combination therapy for the treatment of HIV infection.

Dose: The recommended oral dose for HIV infection combined with other antiretrovirals, in the case of adults is 600 mg, once daily. Dosing at bedtime recommended during first 2–4 weeks of therapy to improve tolerability. In a child above 3 years of age with 10–14 kg of body weight, the dose is 200 mg; for 15–19 kg, 250 mg; for 20–24 kg 300 mg; for 25–32.4 kg, 350 mg; for 32.5–39 kg, 400 mg \geq 40 kg; 600 mg to be taken once a day.

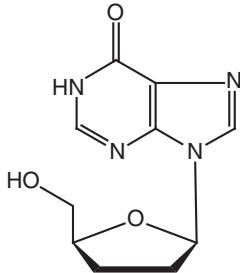
III. Anti-HIV agents

HIV virus is the cause of AIDS, both HIV-1 and HIV-2 cause AIDS. Anti-HIV agents are classified according to their mode of actions as follows:

III a. RT inhibitors

Reverse transcription is RNA dependent DNA polymerase. The drug inhibiting RT interferes with the replication of HIV and stops the synthesis of further viral particle. They are classified into nucleoside and non-nucleoside RT inhibitors.

Didanosine (2',3'-dideoxyinosine (DDI), Videx)



2',3'-Dideoxyinosine

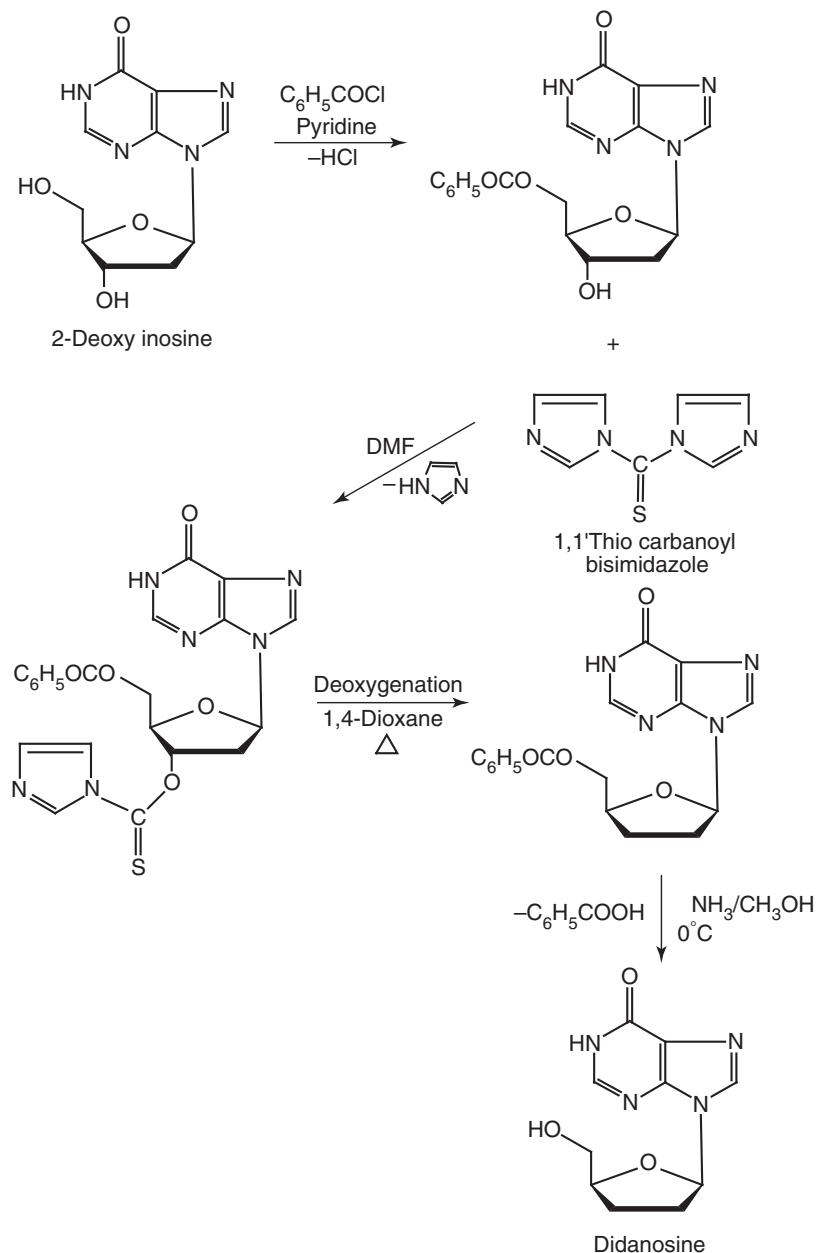
Metabolism: Didanosine is ultimately converted into hypoxanthine, xanthine, and uric acid through the usual metabolic pathways of purines. The latter is a nontoxic metabolic product.

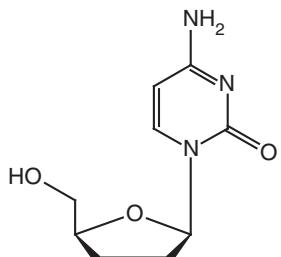
Properties and uses: Didanosine is a white crystalline powder, sparingly soluble in water, soluble in dimethyl sulphoxide, slightly soluble in methanol and ethanol. It is a nucleoside RT inhibitor recommended for the treatment of patients with advanced HIV infections.

Assay: Dissolve the sample in glacial acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The recommended dose for adults as tablets, which may be chewable and dispersible, for body weight more than 75 kg is 300 mg; for 50–74 kg body weight, 200 mg; for 35–49 kg body weight, 125 mg with antacids.

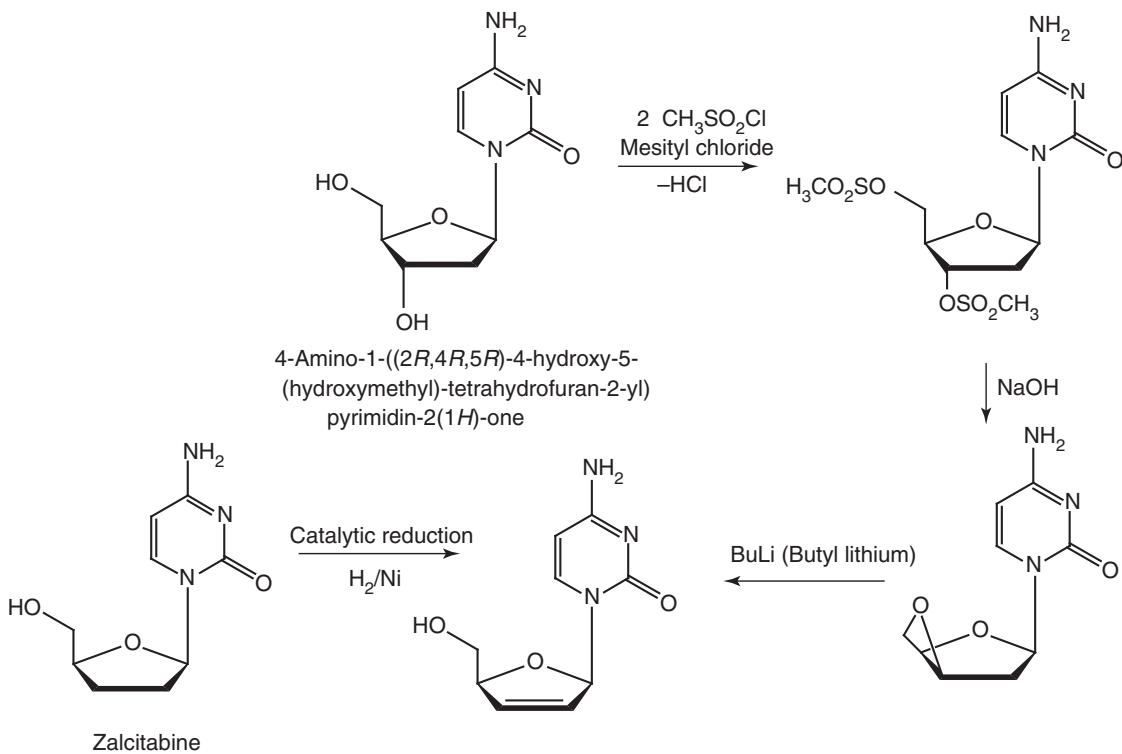
Synthesis

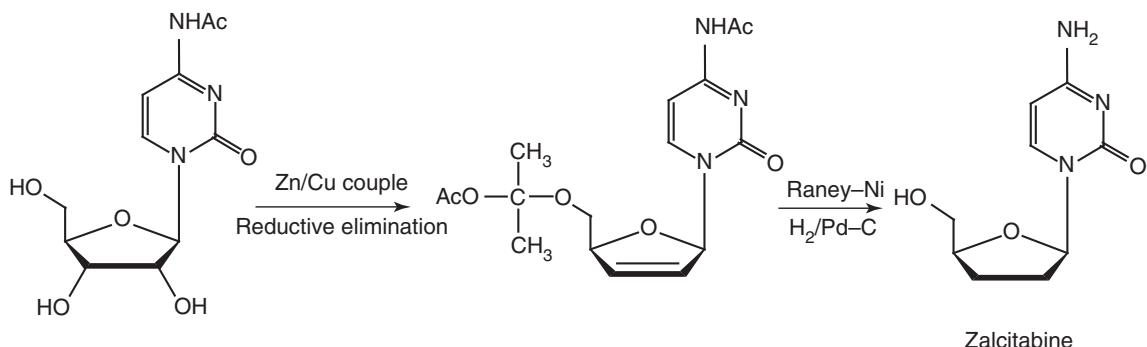
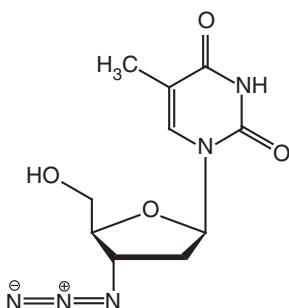


Zalcitabine (DDC, Hivid)4-Amino-1-((2*R*,5*S*)-5-(hydroxymethyl)-tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one

Properties and uses: Zalcitabine exists as white crystals. It is approved for combination therapy with zidovudine in advanced HIV infection, who has demonstrated significant clinical or immunological deterioration, showing intolerance to zidovudine.

Dose: Zalcitabine is administered with zidovudine at the dose level of 2–25 mg of zalcitabine and 600 mg of zidovudine per day.

Synthesis**Route I.**

Route II.**Zidovudine (ZDV)** [azido-deoxythymidine (AZT), Retrovir]

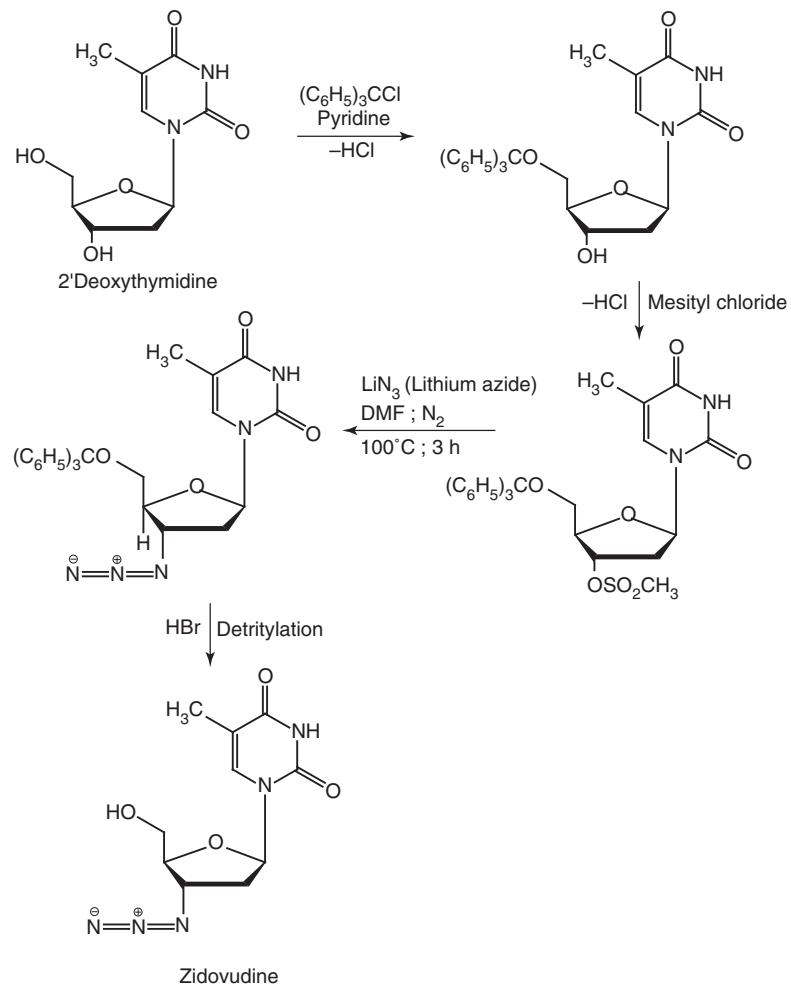
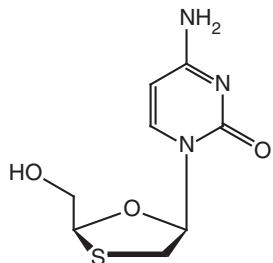
1-((2*R*,4*R*,5*S*)-4-azido-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione

Metabolism: Most of the administered drug is converted to its inactive glucuronide metabolite and it is excreted unchanged through urine.

Properties and uses: ZDV is a white or brownish powder, sparingly soluble in water and soluble in anhydrous ethanol. It is a nucleoside RT inhibitor, having activity against HIV, and hence, it is used for the treatment of AIDS and AIDS-related complex (ARC). It increases the survival and improves the quality of life of patients with complications, such as severe weight loss, fever, and pneumocytosis. As it crosses the blood brain barrier, it has favourable effect on the neurological symptoms of AIDS.

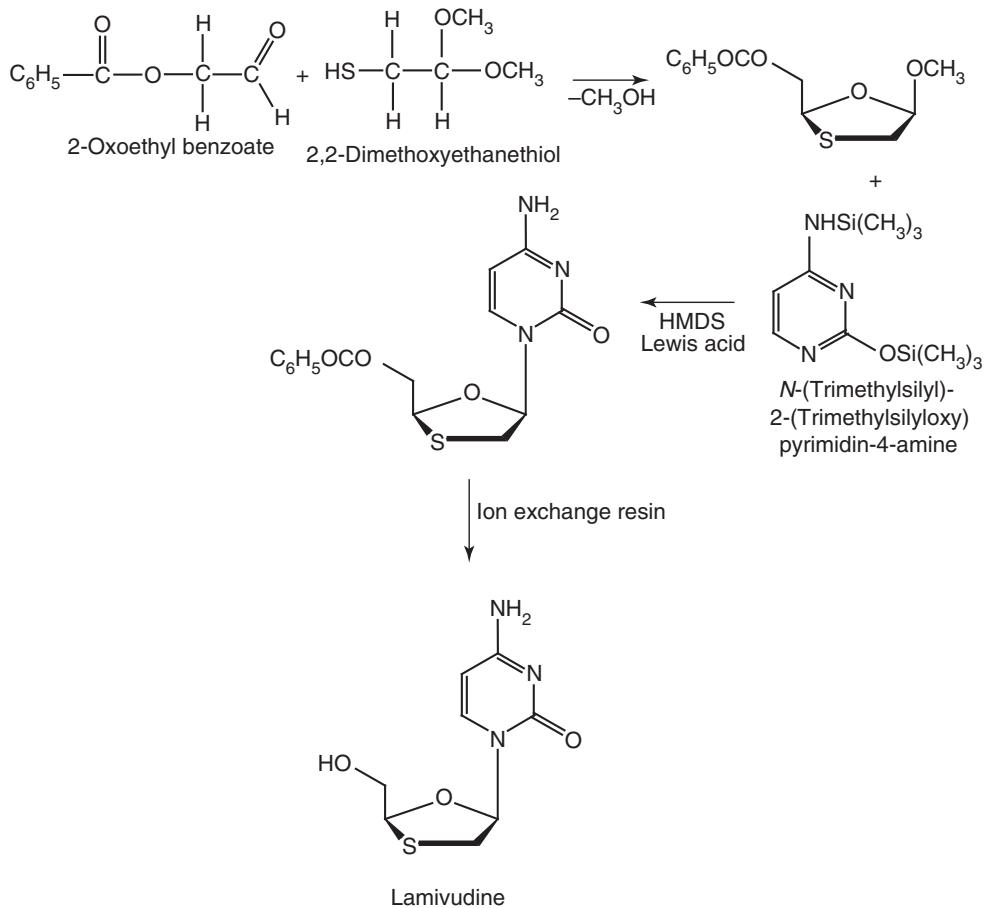
Assay: It is assayed by adopting liquid chromatography technique.

Dose: The recommended dose for adults in the case of oral asymptomatic HIV-infection initially is 100 mg every 4 h, while awake (500 mg a day), after 1 month, the dose may be reduced to 100 mg every 4 h. For intravenous infusion, the dose is 1–2 mg/kg infused over 1 h for every 4 h around the clock (6 times a day).

Synthesis**Lamivudine (Lamda, Rolam, Lamvir)**

4-Amino-1-((2*S*,5*R*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)pyrimidin-2(1*H*)-one

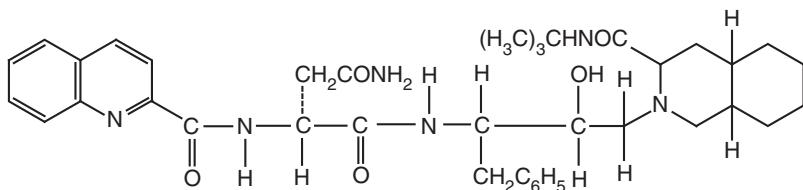
Synthesis



Properties and uses: Lamivudine is a white powder, soluble in water, sparingly soluble in methanol and slightly soluble in ethanol. It is a nucleoside RT inhibitor, used in combination with ZDV for the treatment of diseases caused by HIV infection.

Assay: It is assayed by adopting liquid chromatography technique.

Dose: The recommended dose for chronic hepatitis B in the case of adults is 100 mg once daily. For a child more than 2 years, the dose is 3 mg/kg once daily, maximum is 100 mg per day for HIV infection. The recommended dose for concomitant HIV and hepatitis B infection, in the case of adults is 150 mg twice a day or 300 mg once daily, in combination with other antiretrovirals. In the case of a child, 3 months–12 years, the dose is 4 mg/kg twice a day, maximum dose is 300 mg per day.

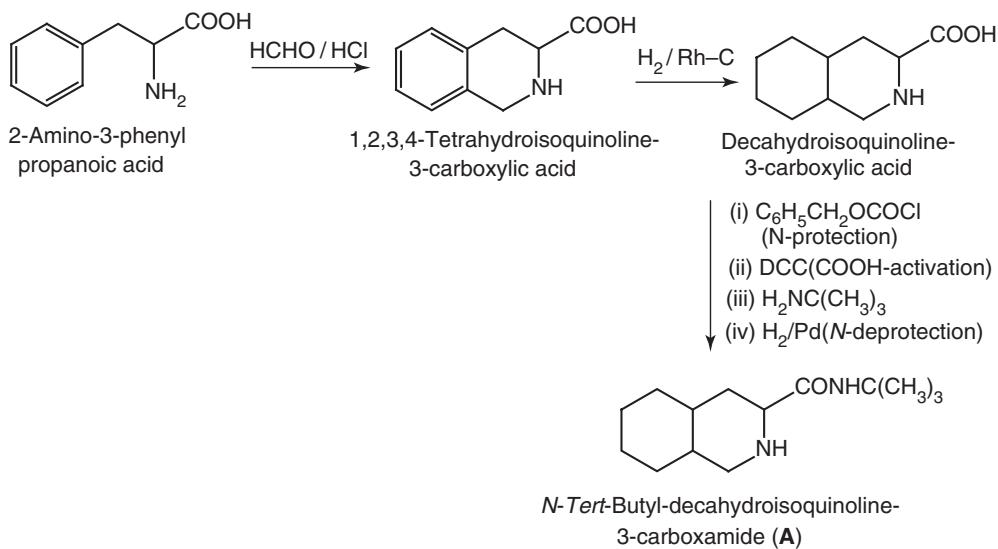
III. b. HIV protease inhibitors**i. Saquinavir (Saqquin)**

N-(*(S*)-1-(4-(3-(*tert*-butylcarbamoyl)-octahydroisoquinolin-2(*1H*)-yl)-3-hydroxy-1-phenylbutan-2-ylamino)-4-amino-1,4-dioxobutan-2-yl)quinoline-2-carboxamide

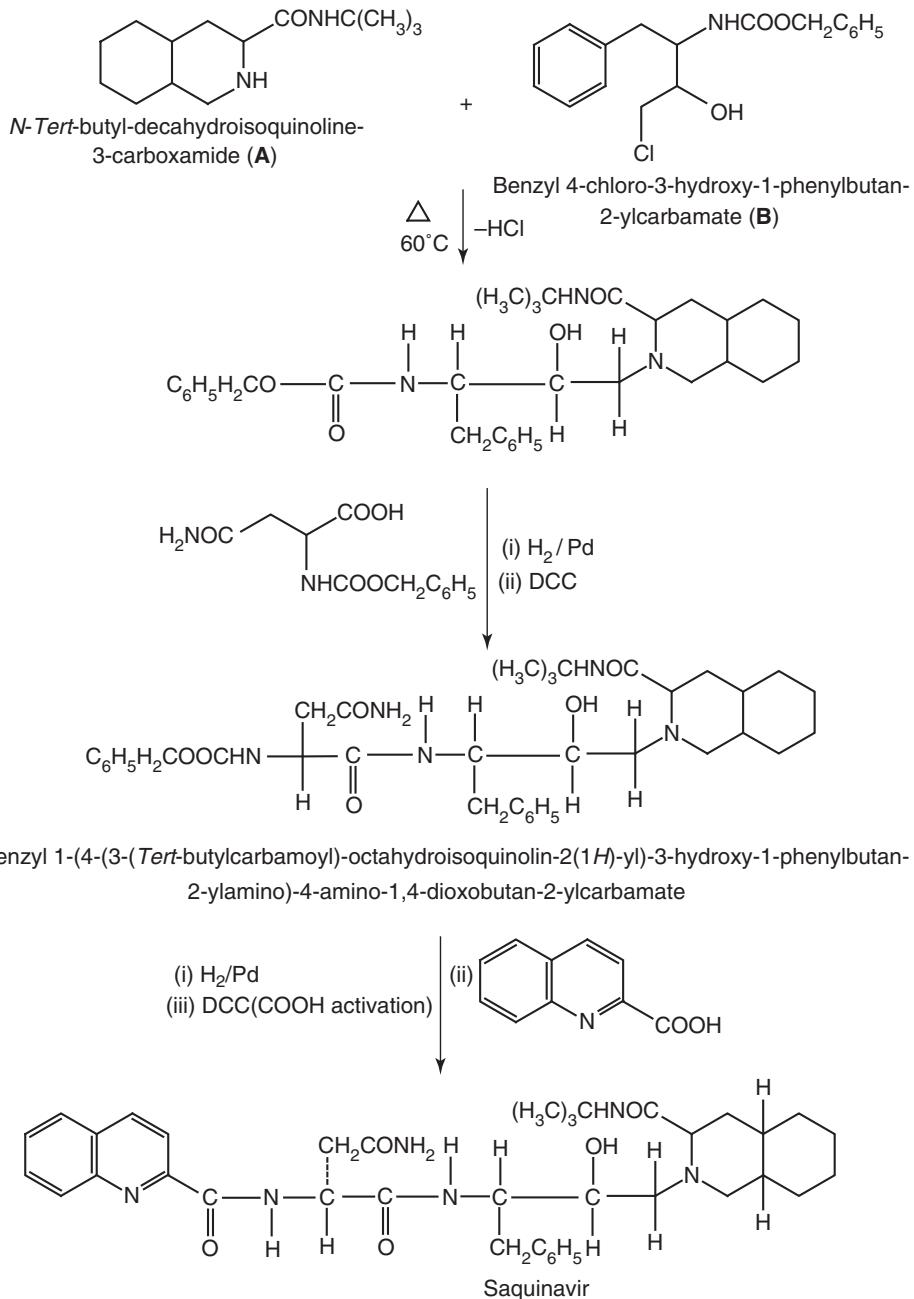
Metabolism: Metabolism of saquinavir is catalyzed by CYP3A₄ and possibly by CYP3A₅. The metabolites mono and dihydroxylated compounds are not active.

Properties and uses: It is a white to off-white fine powder, which is soluble in water. It is a synthetic peptide analogue and inhibitor of HIV-1 and HIV-2 proteases. It is used in combination with RT inhibitors, but it has less cross-resistance with other protease inhibitors.

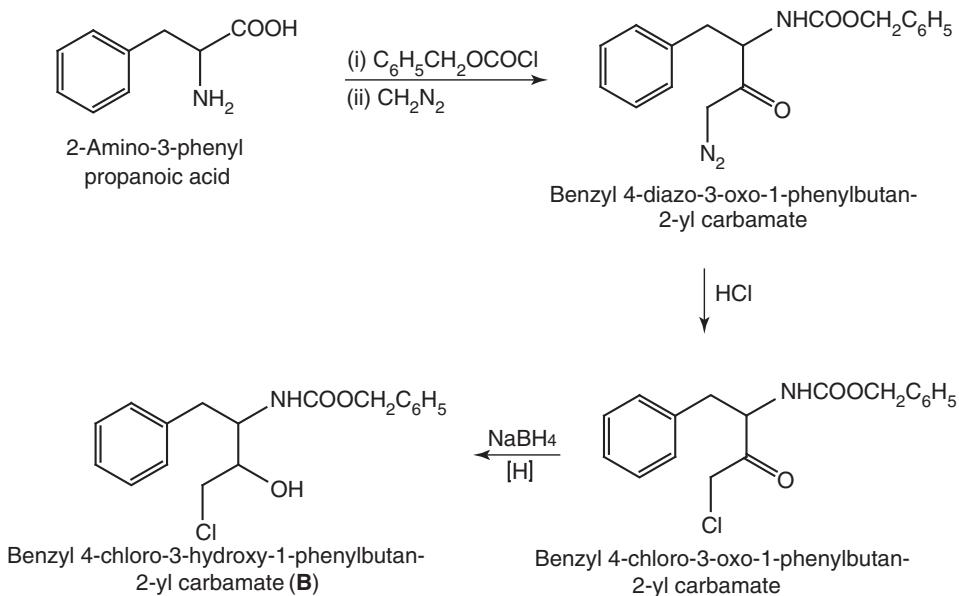
Dose: The recommended oral dose of saquinavir for HIV infection combined with other antiretrovirals, in the case of adults more than 16 years is 1 g twice a day, when taken with ritonavir 100 mg, it is twice a day. Alternatively, the administered dose of saquinavir could also be 400 mg twice a day with ritonavir 400 mg twice a day. In the case of postexposure prophylaxis, during occupational exposure to HIV, the dose for adults is 1 g of saquinavir twice a day with ritonavir 100 mg twice a day, combined with other antiretrovirals, and should be started as soon as possible and continued for 4 weeks, if tolerated.

Synthesis**Step I. Synthesis of *N*-*t*-butyl-decahydroisoquinoline-3-carboxamide (A)**

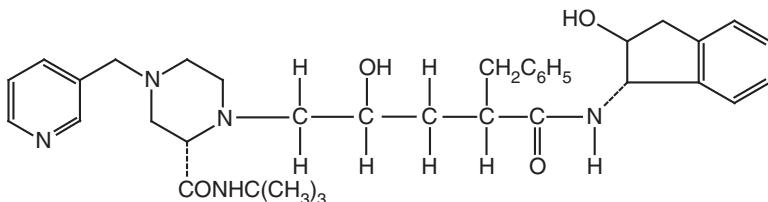
Step II. Condensation of (A) and (B)



Step III. Synthesis of Benzyl 4-chloro-3-hydroxy-1-phenylbutan-2-yl carbamate (**B**)



ii. Indinavir (Crixivan)



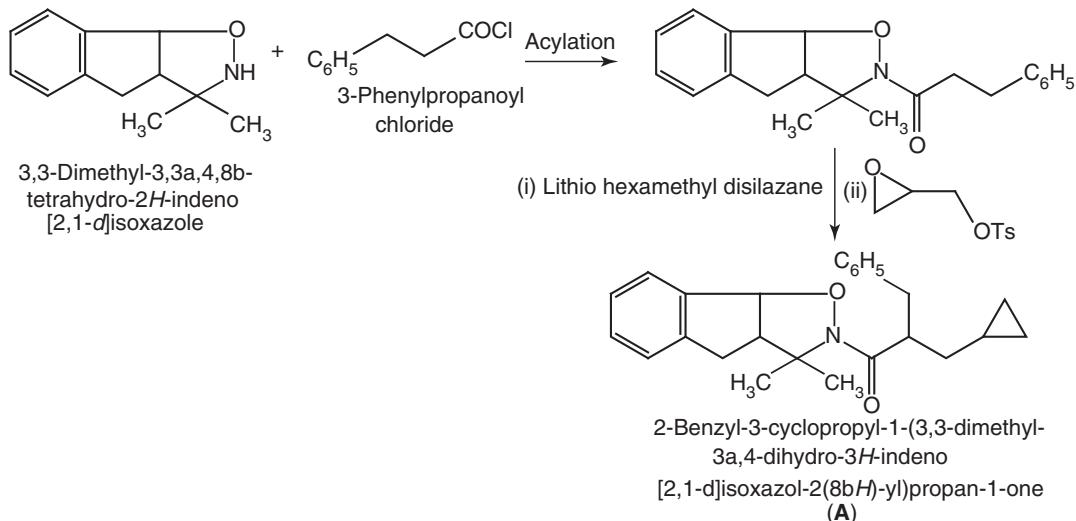
(*S*)-1-(4-benzyl-2-hydroxy-5-((1*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylamino)-5-oxopentyl)-*N*-*tert*-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide

Properties and uses: Indinavir is a white to off-white hygroscopic powder, soluble in water or in methanol. Used as anti-HIV agent.

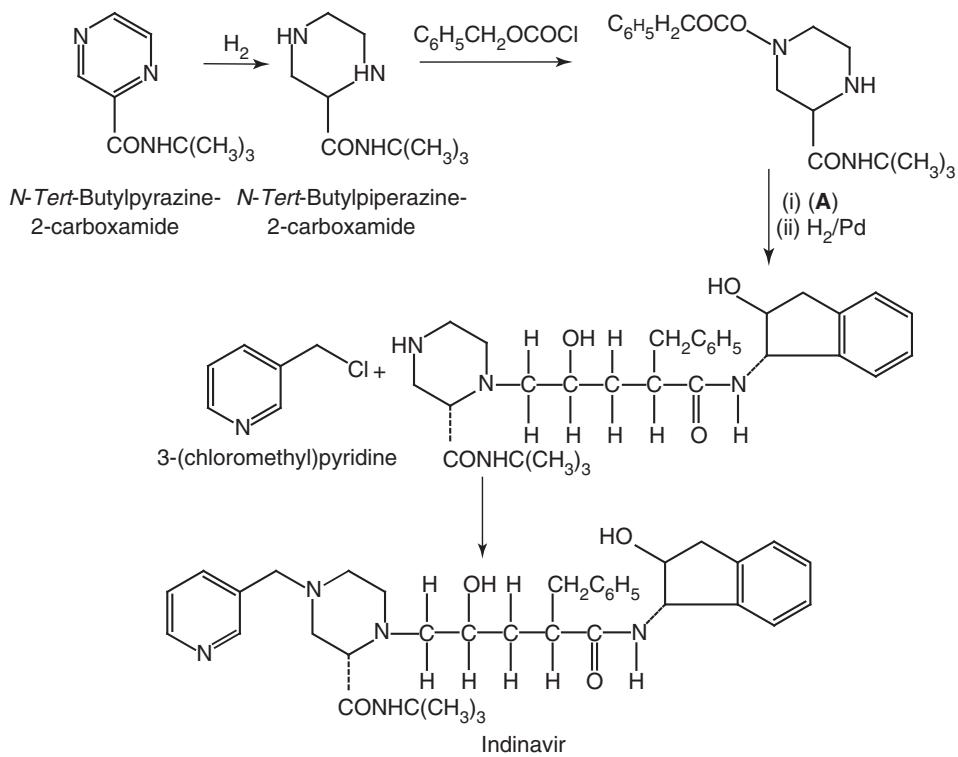
Dose: Indinavir is administered in multiple doses of 100–400 mg every 6 h for up to 10 days.

Synthesis

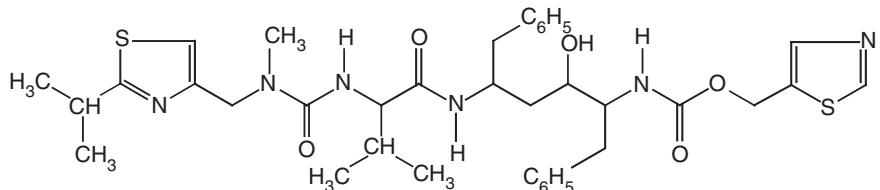
Step I: Synthesis of an intermediate (A)



Step II:

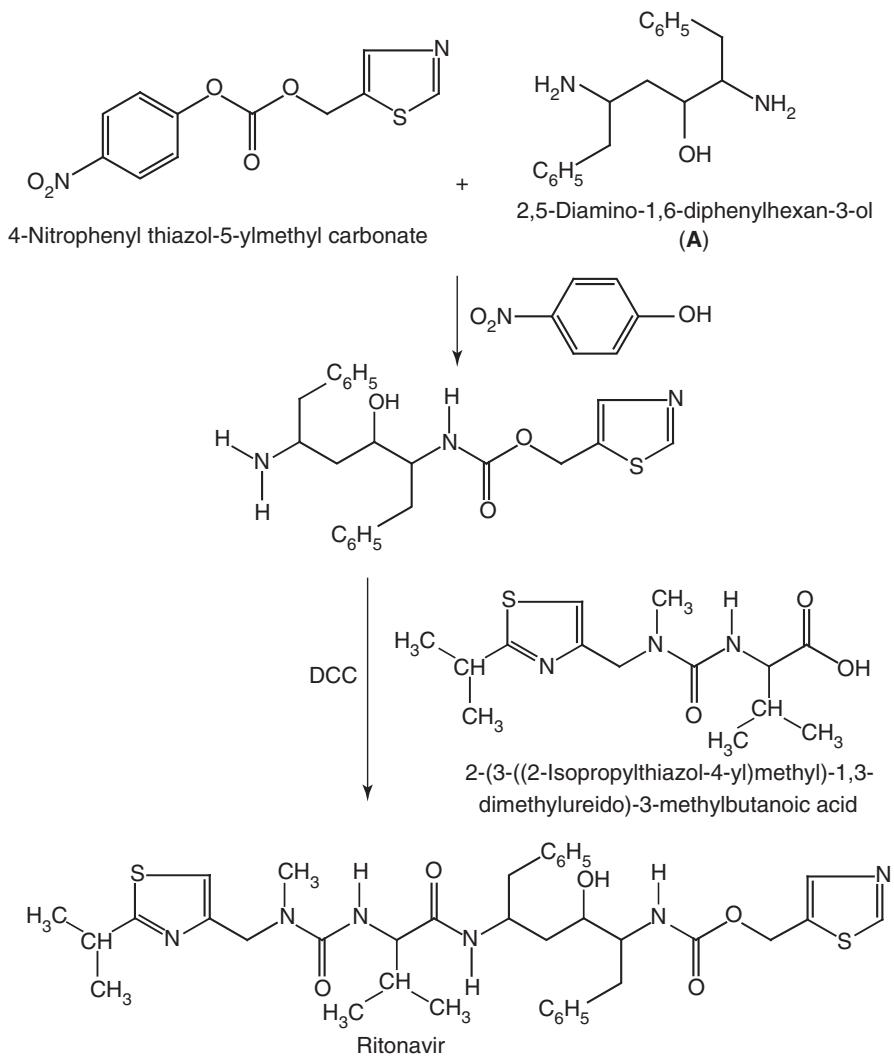


iii. Ritonavir (Empetus, Ritomax, Ritovir)

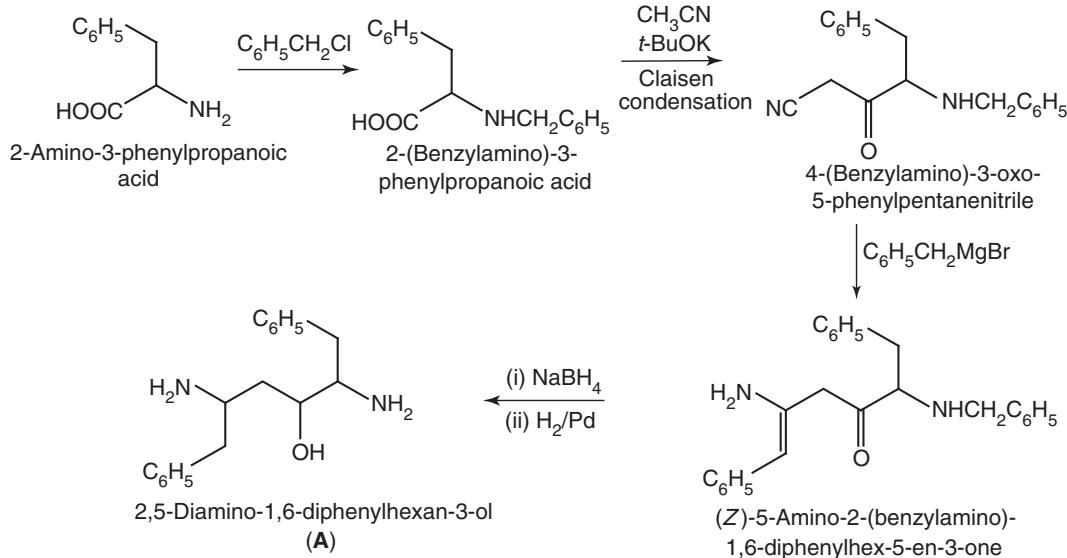


Synthesis

Step-I. Synthesis of Ritonavir



Step-II: Synthesis of (A)

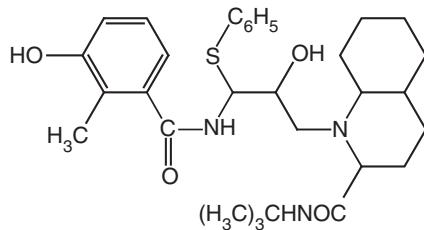


Metabolism: Ritonavir is metabolized by CYP3A4; the metabolites are isolated from urine. They are iso-propylthiazole oxidation products.

Properties and uses: Ritonavir is white to light tan powder with a bitter metallic taste. It is soluble in methanol and in isopropyl alcohol, but insoluble in water.

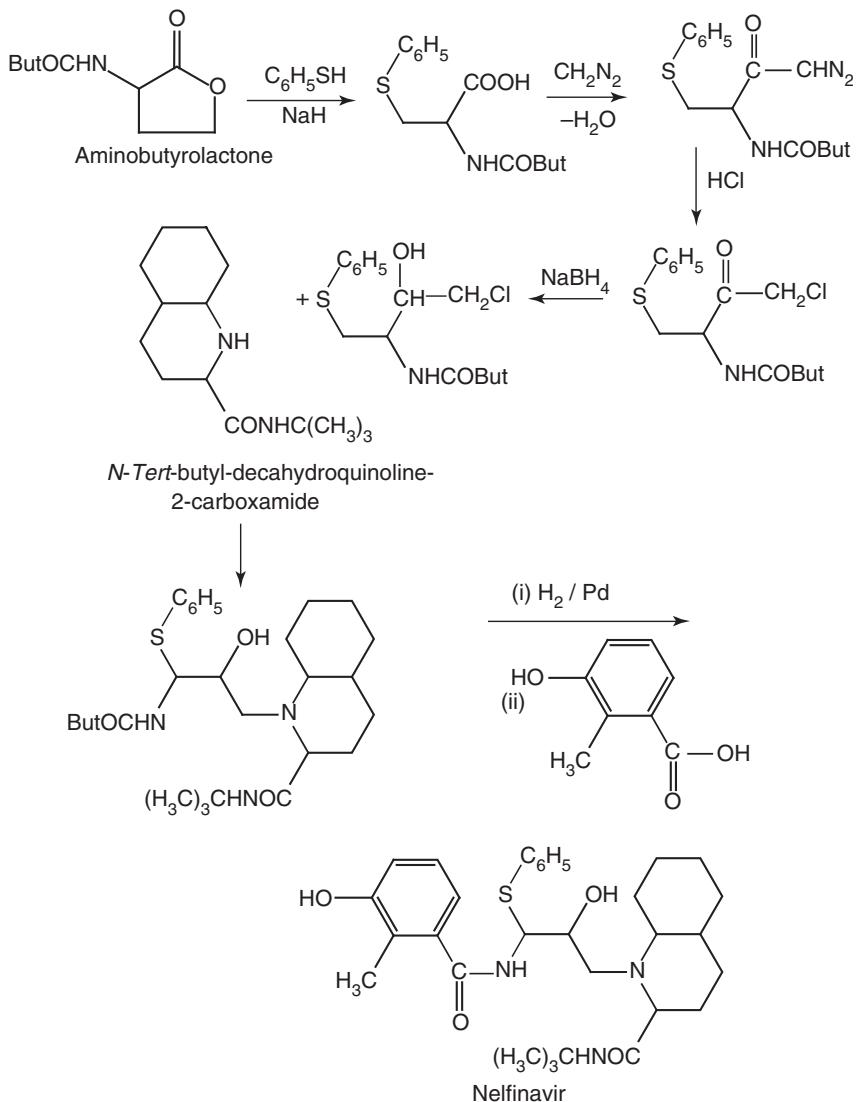
Dose: The recommended oral dose for HIV infection combined with other antiretroviral, in the case of adults, initially is 300 mg twice a day for the day one. The dose may be increased gradually by 100 mg twice a day and over a period of up to 14 days to 600 mg twice a day. In the case of a child more than 2 years, the recommended dose is 250 mg/m^2 twice a day. Increase the dose by 50 mg/m^2 twice a day, at 2–3 day intervals, up to 400 mg/m^2 twice a day. Maximum dose is 600 mg twice a day. As a pharmacokinetic enhancer, in the case of adults, to enhance the efficacy of other protease inhibitors the dose is 100–200 mg once or twice a day.

iv. Nelfinavir (Emnel, Nelvir, Retronel)



N-Tert-Butyl-1-(2-hydroxy-3-(3-hydroxy-2-methylbenzamido)-3-(phenylthio)propyl)-1,2,3,4-tetrahydroquinoline-2-carboxamide

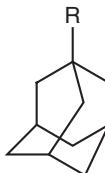
Synthesis



Properties and uses: It is a white to off-white amorphous powder, which is slightly soluble in water, soluble in methanol, ethanol, isopropyl alcohol, or propylene glycol. It is used as an anti-HIV agent.

Dose: The recommended dose for HIV infection combined with other antiretrovirals in the case of adults is 1.25 g twice a day or 0.75 g thrice a day. In the case of a child: For 2–13 years is 45–55 mg/kg twice a day or 25–35 mg/kg thrice a day. Maximum dose for a child is 0.75 g thrice a day.

SAR of Adamantane Amines



- α -methyl derivative of adamantane produced Rimantidine.
- α -methyl-1-adamantane methylamine is flumadine.
- N-Alkyl and N,N -dialkyl derivatives of adamantadine exhibit antiviral activity similar to that of adamantadine HCl.
- Except glycyldervatives, N-acyl derivatives show decreased antiviral action and tromantadine possesses efficacy against clinical *Herpes labialis* and *H. genitalis*.
- Replacement of the amino group with OH, SH, CN, or halogen produced inactive compounds.
- Optical isomers and the racemic mixtures of rimantadine are equally active.
- *Influenza A*₂ virus, is more susceptible to adamantanespiro-5-pyrrolidine derivative.

PROBABLE QUESTIONS

1. Enumerate a few DNA virus and RNA virus and mention the diseases produced by them. Classify the antiviral agents with suitable examples.
2. How will you synthesize the following:
(a) Amantadine HCl (b) Methisazone
3. Give the names of three important drugs that specifically interfere with viral nucleic acid replication. Discuss the synthesis of one such drug selected.
4. What are protease inhibitors? Mention a few examples and write the synthesis of indinavir.
5. Classify the antiviral drugs on the basis of their mode of action. Draw the structure, chemical name, and uses of at least one potent drug from each category.
6. Write the structure, chemical name, and uses of two important antiviral drugs that affect translation on cell ribosomes. Outline the synthesis of any one of them.
7. Enumerate the drugs used in HIV infection and write the synthesis of any one of them.
8. Discuss the following in detail:
(a) Important antiviral drugs (b) Mode of action of antiviral drugs.

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Chapter 8

Antiamoebic Agents

INTRODUCTION

Amoebiasis affects about 10% of the world's population, causing invasive diseases in about 50 million people and death in about 1,00,000 of these annually. This infection is, especially, common in lower socio-economic groups and institutionalized individuals living under crowded and poor hygienic conditions. Two morphologically identical, but genetically and biochemically distinct, species of *Entamoeba* (*E. histolytica* and *E. dispar*) are the causative organisms. Human beings are the only host for this organisms. Ingested amoebic cysts from contaminated food or water survive and form acid gastric contents and transform them into trophozoites that usually cause colitis which is either acute or chronic (dysentery). In some cases, they target the brain and the liver producing abscesses and systemic diseases.

This parasitic disease is one of the major causes of illness and death in many countries. World Health Organization (WHO) has classified this disease as follows:

1. Asymptomatic
2. Symptomatic
 - a. Intestinal Amoebiasis
 - i. Dysentery
 - ii. Nondysenteric colitis
 - iii. Amoeboma
 - iv. Amoebic appendicitis.
 - b. Extraintestinal amoebiasis
 - i. Hepatic acute nonsuppurative
 - ii. Liver abscesses
3. Cutaneous involvement of other organs

Lung, brain, and spleen without the obvious liver involvement are some examples under this category. Antiamoebic agents are drugs used to treat amoebiasis. The potential drug should be active within the bowel lumen, in the bowel wall, and particularly in the liver. Worldwide, nearly 480 million people are infected with *E. histolytica*, of whom 10% develop clinical disease. The infection is transmitted exclusively by the faecal—oral route; human beings are the only known hosts.

CLASSIFICATION OF AMOEVICIDES

I. Luminal amoebicides: Diloxanide furoate.

It is active only against intestinal forms of amoeba.

II. Systemic amoebicides: Dihydroemetin, Choroquine.

These agents have been employed primarily to treat severe amoebic dysentery or hepatic abscesses.

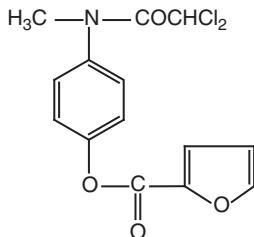
III. Mixed amoebicides: Metronidazole, tinidazole, and ornidazole.

These agents are active against both intestinal and systemic forms of amoeba.

SYNTHESIS AND DRUG PROFILE

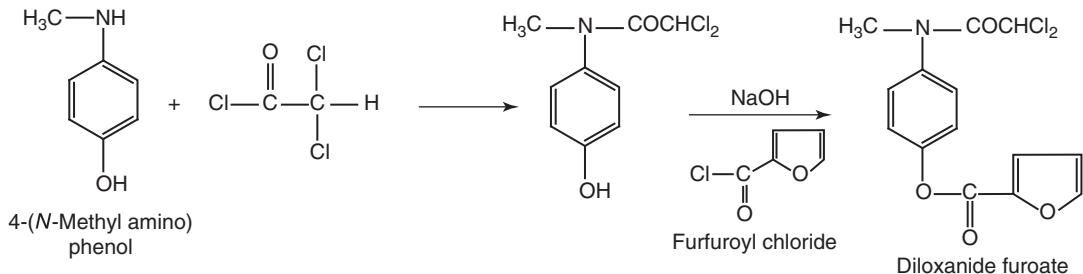
I. Luminal amoebicdes

i. Diloxanide Furoate (Furamide)

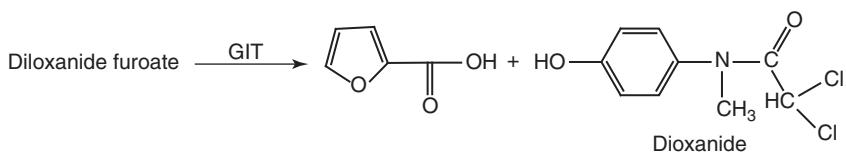


4-(2, 2-Dichloro-*N*-methylacetamido)phenyl furan-2-carboxylate

Synthesis



Metabolism: The diloxanide furoate is administered orally and is hydrolyzed in the gut to give diloxanide.



Properties and uses: Diloxanide furoate is a white crystalline powder, very slightly soluble in water, slightly soluble in ethanol and ether. It is dichloro acetamide derivative that is nontoxic, mainly used in the treatment of chronic amoebiasis. It is less effective in the treatment of acute intestinal amoebiasis.

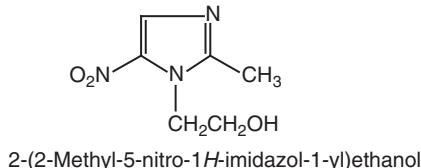
Assay: Dissolve the sample in anhydrous pyridine and titrate against 0.1 M tetrabutylammonium hydroxide. Determine the end point potentiometrically.

Dose: The recommended oral dose is 500 mg three times daily for 10 days (Diloxanide furoate 250 mg + Tinidazole 300 mg) two tablets daily. Diloxanide furoate 250 mg + Metronidazole 250 mg two tablets thrice daily for 10 days.

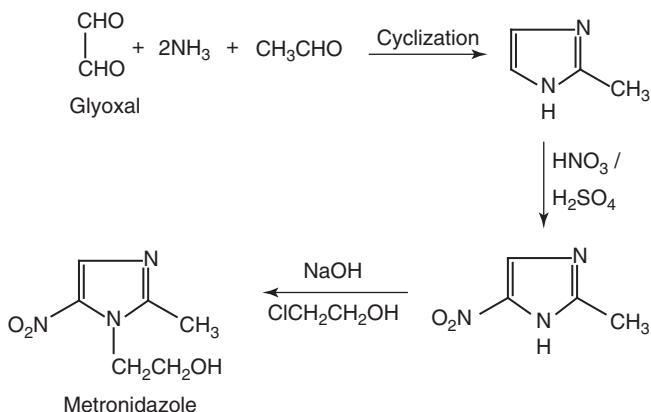
Dosage forms: Diloxanide tablets B.P.

III. Mixed amoebicides

1. Metronidazole (Flagyl, Metrogyll)

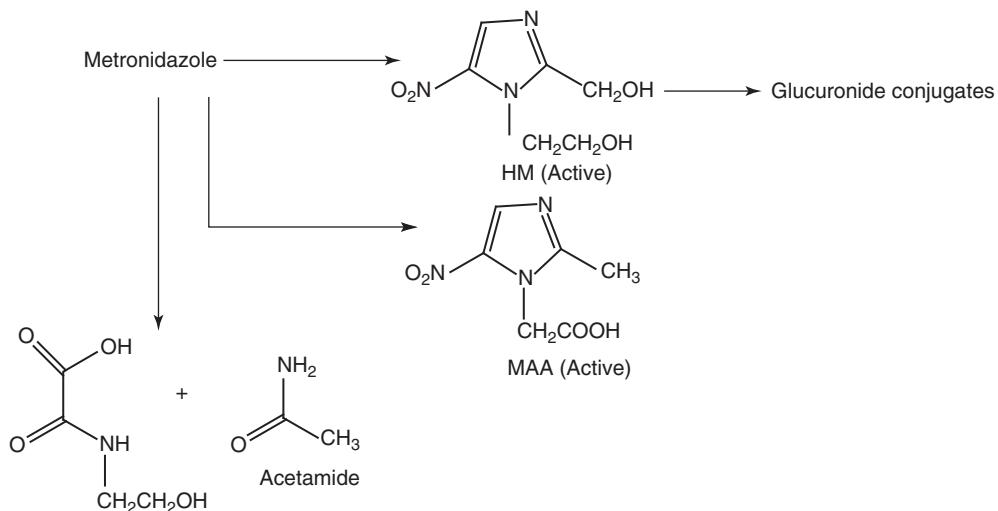


Synthesis



Mode of action: The reactive intermediate formed in the parasitai reduction of the 5-nitro group of metronidazole covalently binds to the DNA of the parasite and triggers the lethal effects. Potential reactive intermediates include the nitroxide, nitroso, hydroxylamine, and amine.

Metabolism: In the liver, metabolism of metronidazole leads to two major metabolites, hydroxylation of the 2-methyl group to 2-hydroxymethyl metronidazole and oxidation to metronidazole acetic acid (MAA).



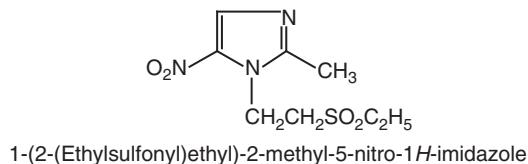
Properties and uses: Metronidazole is a white or yellowish crystalline powder, slightly soluble in water, acetone, alcohol, and methylene chloride. It is used in the treatment of intestinal and hepatic amoebiasis.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: For amoebiasis, the administered dose is 750 mg orally three times a day for 5–10 days. For trichomoniasis, the prescribed dose is 250 mg orally three times a day for 7 days. For giardiasis, the prescribed dose is 250 mg orally three times daily for 5–7 days.

Dosage forms: Metronidazole gel B.P., Metronidazole intravenous infusion B.P., Metronidazole suppositories B.P., Metronidazole tablets B.P.

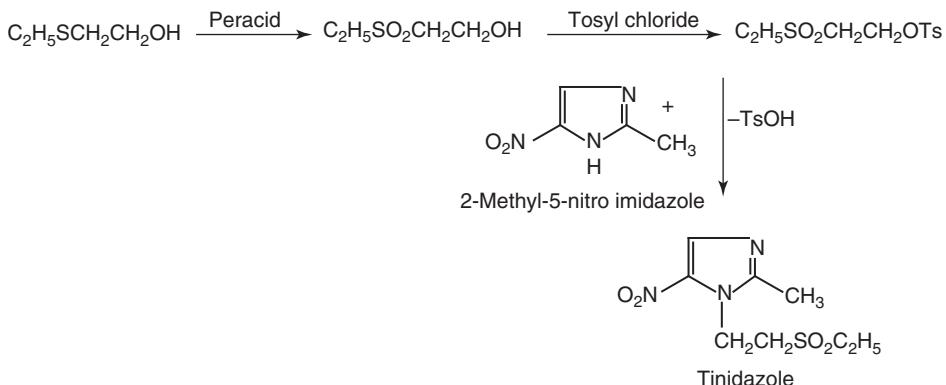
2. Tinidazole (Fasigyn)



Mode of action: Tinidazole's mechanism of action is similar to that of metronidazole. It is used in the treatment of intestinal and hepatic amoebiasis with a potential greater efficacy than metronidazole.

Metabolism: Tinidazole is metabolized by hydroxylation at the 2-methyl group and catalyzed by CYP3A4 to form inactive compound.

Synthesis

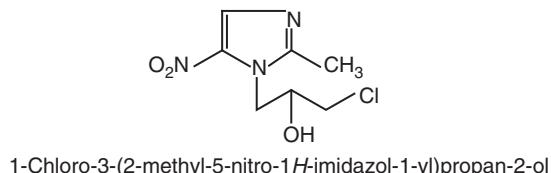


Properties and uses: Tinidazole is a white or pale yellow crystalline powder, practically insoluble in water, soluble in acetone and in methylene chloride, and sparingly soluble in methanol. Used as an antiprotozoal and antibacterial agent.

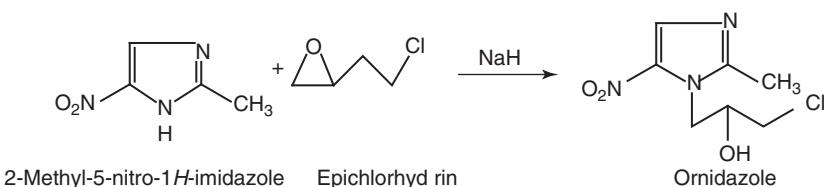
Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: For giardiasis, the administered dose is 2 mg as a single dose.

3. Ornidazole (Ornida, Dazolic, Onidaz)



Synthesis:

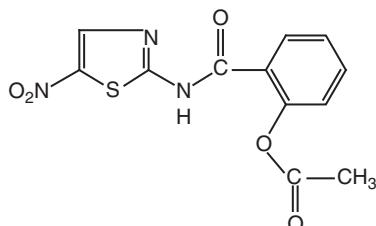


Properties and uses: It has a longer duration of action than metronidazole and used as an antiprotozoal.

Dose: The administered dose for amoebic dysentery in the case of adults is 1.5 g as a single daily dose for 3 days. Alternatively, for patients, whose weight is more than 60 kg, the dose is 1 g two times a day for 3 days. In the case of a child, the administered dose is 40 mg/kg daily. For amoebiasis, the recommended dose for adults is 5 g two times a day for 5–10 days. And in the case of a children, the dose is 25 mg/kg as a single daily dose for 5–10 days.

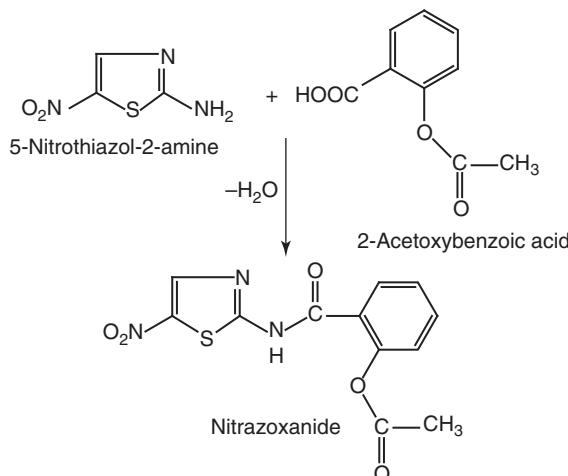
For giardiasis, in the case of adults, the dose is 1–1.5 g as a single daily dose for 1–2 days. In the case of a child, the dose is 30–40 mg/kg daily. In the case of trichomoniasis, the dose for adults is 1.5 g as a single daily dose or 0.5 g two times a day for 5 days. Treat sexual partners concomitantly. In the case of child, the dose is 25 mg/kg as a single dose. In the case of intravenous administration, during severe amoebic dysentery and amoebic liver abscess the prescribed dose for adults initially is 0.5–1 g infusion followed by 0.5 g every 12 h for 3–6 days. For a child, the dose is 20–30 mg/kg body weight daily.

4. Nitazoxanide



2-((5-Nitrothiazol-2-yl)carbamoyl)phenyl acetate

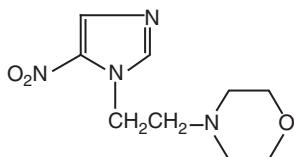
Synthesis



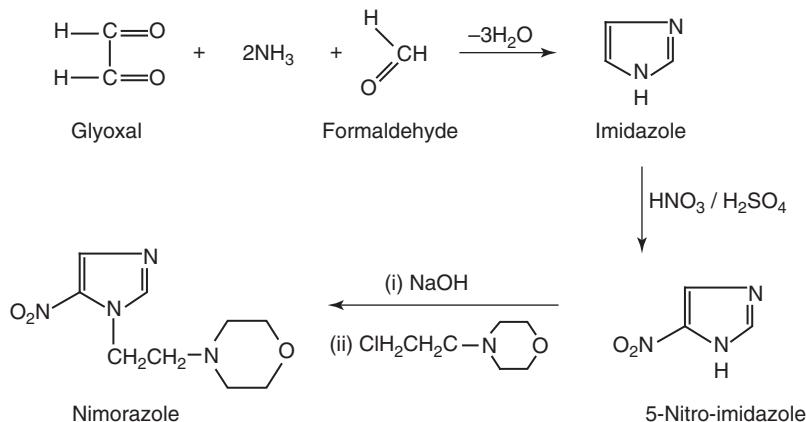
Mode of action: Nitazoxanide is a member of the 5-nitro heterocycles and is a prodrug forming a short-lived redox active intermediate. It appears to be more selective than metronidazole.

Uses: Used as an antiprotozoal agent.

5. Nimorazole (Nitroimidazole)



Synthesis



Properties and uses: It possesses antiamoebic activity, and hence, used against intestinal and hepatic amoebiasis.

PROBABLE QUESTIONS

1. Classify antiamoebic agents and write the synthesis of any three of them.
2. Write synthesis, metabolism, and uses of Diloxanide furoate, Metronidazole, and Tinidazole.

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Chapter 9

Antimalarials

INTRODUCTION

Antimalarial agents are drugs used for the treatment or prophylaxis of malaria. Malaria is caused by four species of *Plasmodium*, such as *Plasmodium falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Three of which produces the mild forms of malaria by destroying red blood cells in peripheral capillaries and thus, causing anaemia. The bouts of fever correspond to the reproductive cycle of the parasite. However, the most dangerous is the *P. falciparum*. In this case, the infected red blood cells become sticky and form lumps in the capillaries of the deep organs of the body and cause microcirculatory arrest. This disease still affects about 200 millions people and causes at least 2 million deaths per year.

LIFE CYCLE OF PLASMODIUM

The different stages of the reproductive cycle (Fig. 9.1) of the malarial parasite and the drugs acting at different stages of this cycle are given below:

- Stage-I: No drug is effective in this stage.
- Stage-II: Primaquine and pyrimethamine can block at this stage.
- Stage-III: Primaquine can only prevent because fever occurs at this stage.
- Stage-IV: Chloroquine, amodiaquine, santoquine, proguanil.
- Stage-V: Primaquine only.

Two important phases of the parasite life cycle are the following:

1. Asexual cycle—occurs in the infected host.
2. Sexual cycle—occurs in the mosquito.

After the insect bite, the parasite forms rapidly. They leave the circulation and localize in the hepatocytes whereby they transform, multiply, and develop into tissue schizonts. The primary asymptomatic tissue stage lasts for 15 days and the tissue schizonts rupture, each releasing thousands of merozoites. The released merozoites invade more erythrocytes to continue the cycle's synchronous rupture of erythrocytes to continue the cycle. Synchronous rupture of erythrocytes and release of merozoites into the circulation leads to

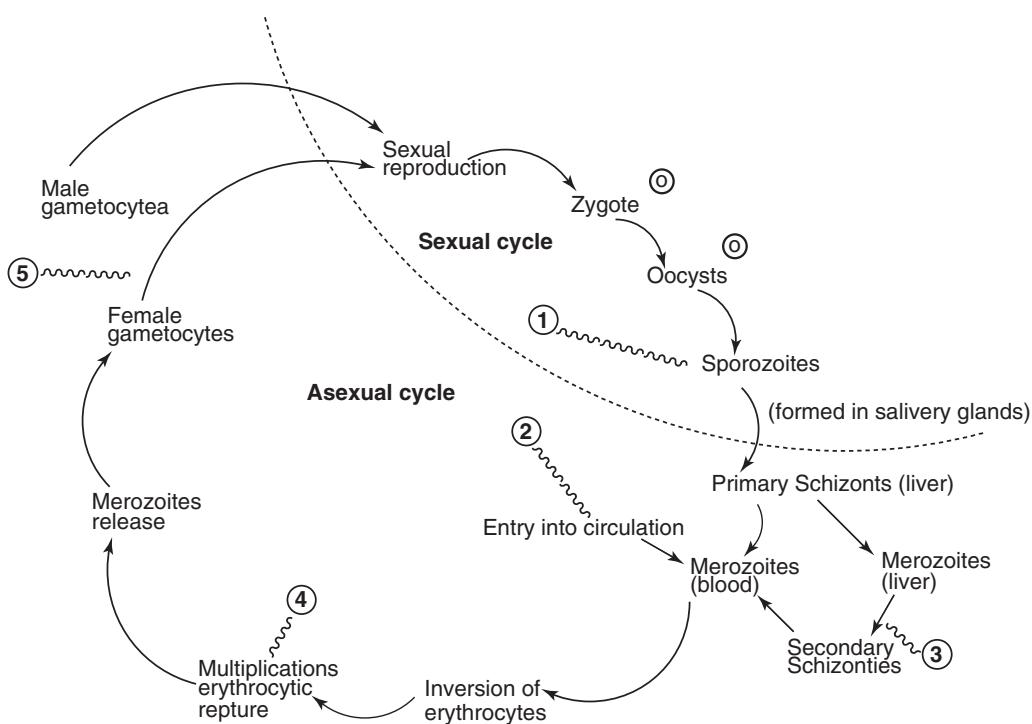
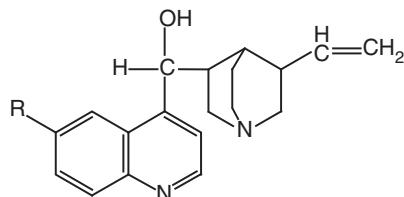


Figure 9.1 Life cycle of plasmodium.

febrile pattern attacks on day 1 and 3; hence, the designation is ‘tertian malaria’. Some erythrocyte parasites differentiate into several forms known as gametophytes. After infecting human blood, female mosquito ingests them. Then the exflagellation of male gametocyte is followed by the male gametogenesis and the fertilization of the female gametocytes in the insect’s guts. The resulting zygote, which develops as an oocyte in the gut wall, eventually gives rise to infective sporozoite, which invades the salivary glands of the mosquito. The insect then can infect another human by taking a blood meal.

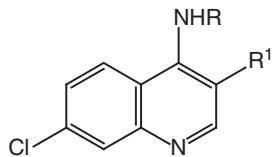
CLASSIFICATION

I. Cinchona alkaloids



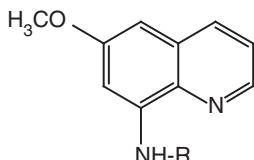
| Name | R |
|--------------|---|
| Quinine | -OCH ₃ (-) isomer |
| Quinidine | -OCH ₃ (+) isomer (used as antiarrhythmic) |
| Cinchonine | -H (+) isomer |
| Cinchonidine | -H (-) isomer |

II. 7-Chloro-4-Amino Quinolines



| Name | R | R ¹ |
|--------------------|---|------------------|
| Cholorquine | -CH(CH ₃)(CH ₂) ₃ -N(C ₂ H ₅) ₂ | -H |
| Amodiaquine | | -H |
| Hydroxychloroquine | | -H |
| Sontoquine | -CH(CH ₃)-(CH ₂) ₃ -N(C ₂ H ₅) ₂ | -CH ₃ |
| Amopyroquine | | -H |

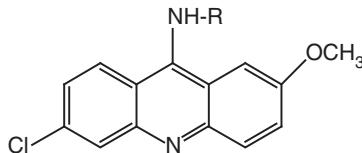
III. 8-Amino Quinolines



6-Methoxy-8-amino quinoline derivatives

| Name | R |
|----------------------|---|
| Primaquine | $-\text{CH}(\text{CH}_3)-\text{(CH}_2)_3-\text{NH}_2$ |
| Pamaquine | $-\text{CH}(\text{CH}_3)-\text{(CH}_2)_3-\text{N}(\text{C}_2\text{H}_5)_2$ |
| Pentaquine phosphate | $-(\text{CH}_2)_5-\text{NH}-\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}- \\ \\ \text{CH}_3 \end{array}$ |
| Isopentaquine | $-\text{CH}(\text{CH}_3)-\text{(CH}_2)_3-\text{NH}-\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}- \\ \\ \text{CH}_3 \end{array}$ |
| Quinocide HCl | $-(\text{CH}_2)_3-\text{CH}-\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CH}_3 \\ \\ \text{C}_2\text{H}_5 \end{array}$ |

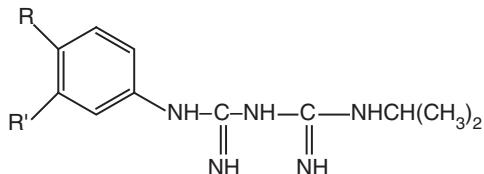
IV. Acridine derivatives (9-amino acridine derivatives)



| Name | R |
|------------|--|
| Quinacrine | $-\text{CH}(\text{CH}_3)-\text{(CH}_2)_3-\text{N}(\text{C}_2\text{H}_5)_2$ |
| Acriquine | $-(\text{CH}_2)_4-\text{N}(\text{C}_2\text{H}_5)_2$ |

V. Antifolates

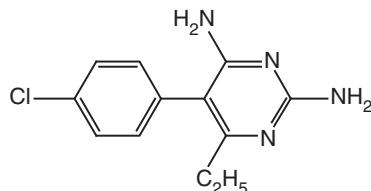
a. Biguanids



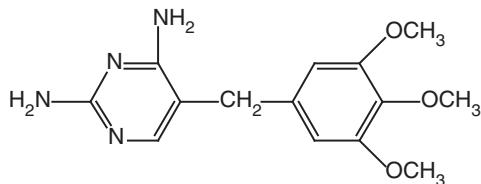
| Name | R | R' |
|------------------|------------------|-----|
| Proguanil | -Cl | -H |
| Chloro proguanil | -Cl | -Cl |
| Bromoguanil | -Br | -H |
| Nitroguanil | -NO ₂ | -H |

b. Diamino pyrimidines

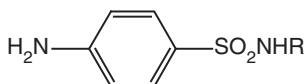
Pyrimethamine (Daraprim)



Trimethoprim



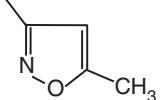
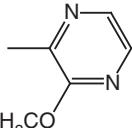
VI. Sulphonamides and Sulphones

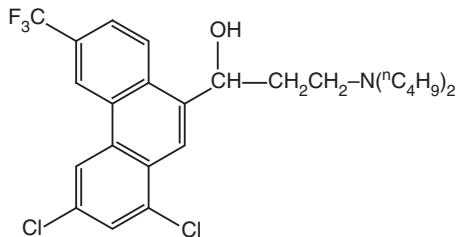
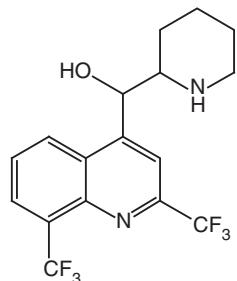
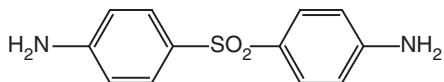


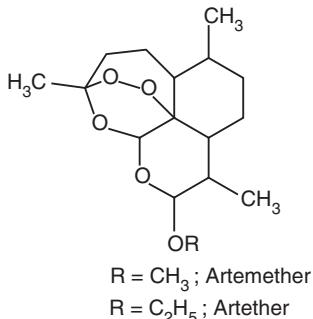
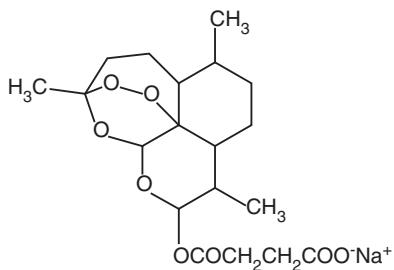
| Name | R |
|--------------|---|
| Sulphadoxine | |

| | |
|---------------|--|
| Sulphadiazine | |
| (Continued) | |

(Continued)

| Name | R |
|-------------------|---|
| Sulphamethoxazole |  |
| Sulphalene |  |

VII. Phenanthrine methanol**Halofentamine****VIII. Miscellaneous drugs****Halofantrine** (Hafan)**Mefloquine****Dapsone**

Artemether, Artemotil**Artesunate****SYNTHESIS AND DRUG PROFILE****I. 4-Substituted Quinolines**

Mode of Action: Three different mechanism of actions are suggested for these drugs:

DNA interaction: The mechanism of action for quinine is that the drug gets intercalated into the DNA of the parasite. It is based on the fact that the concentration required for the inhibition of nucleic acid synthesis is significantly higher than that necessary for the inhibition of the plasmodium parasite.

Ferriprotoporphyrin IX: The plasmodium parasite utilizes host haemoglobin as a source of amino acid. On digestion of the haemoglobin, the haem is released as ferriprotoporphyrins IX and it produces haemolysis of the erythrocyte parasites. Therefore, ferriprotoporphyrin that is released is converted into nontoxic products and they, in turn, to haemozoites by the polymerase enzyme. The steps involved in the conversion to haemozoites are inhibited by the chloroquine.

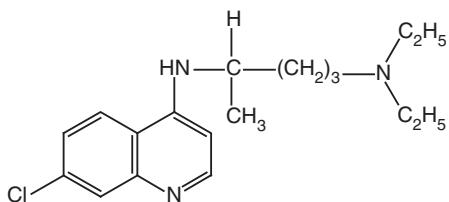
Weak base hypothesis: The 4-substituted quinolines have weak base and because of this pKa they are thought to accumulate in a location, which is acidic (parasite lysosome pH 4.8–5.2). As the extracellular fluid of the parasite is at pH 7.4, the weak base will move towards a more acidic pH of lysosome. Once the acid–base reaction occurs, elevating the pH in the lysosome, that in turn reduces the parasite's ability to digest haemoglobin, thus reducing the availability of amino acids.

Metabolism of Quinine: It is metabolized in the liver to 2-hydroxy derivative followed by additional hydroxylation on the quinoline ring with the 2,3-dihydroxy derivative, as the major metabolite. This metabolite has low activity and is rapidly excreted in urine.

Properties and uses: Quinine hydrochloride exists as fine, silky needles, often in clusters, colourless, soluble in water and in alcohol. It is used in the treatment of malaria.

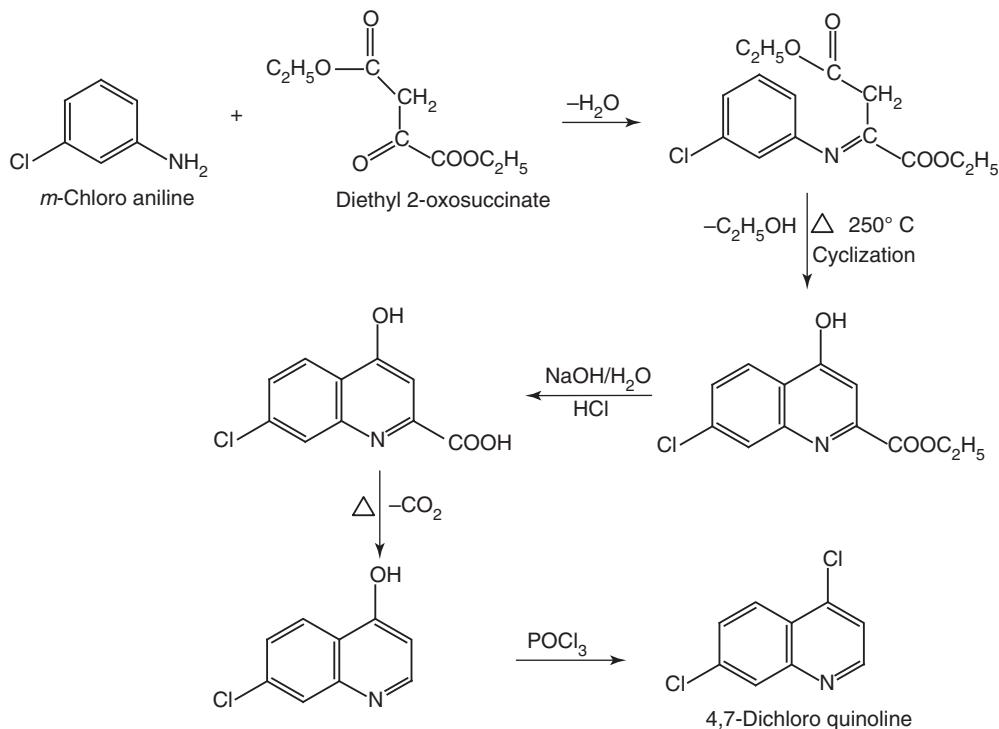
Assay: Dissolve the sample in alcohol, add 0.01 M hydrochloric acid, and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Chloroquine (Nivaquin, Aralen, Lariago)

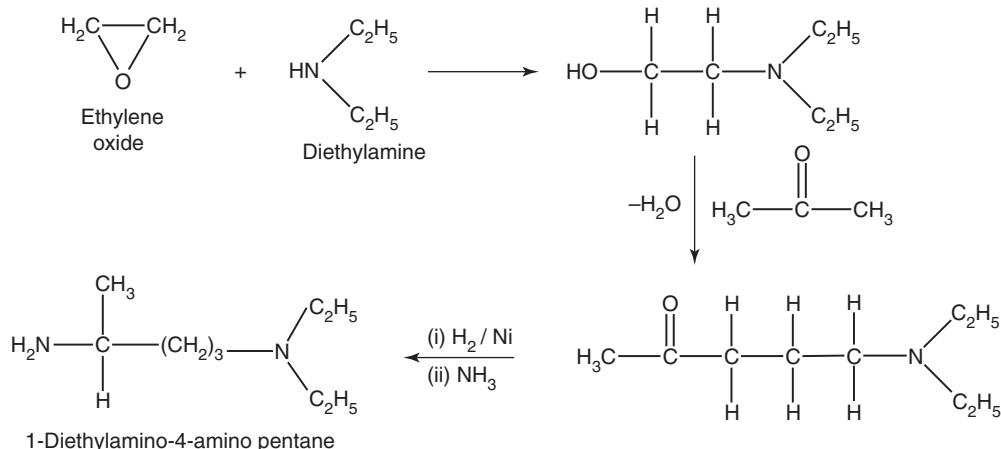


Synthesis

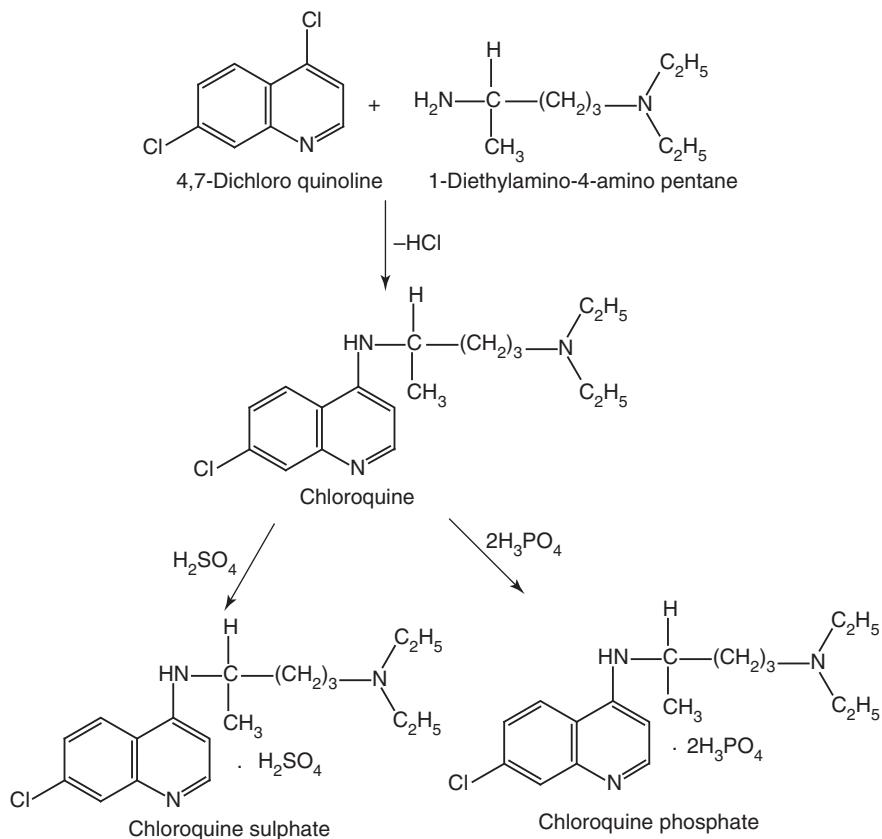
Step I. Synthesis of 4,7-dichloro quinoline



Step-II: Preparation of 1-diethyl amino-4-amino pentane



Step III. Condensation of the products of *Step I* and *Step II*



Metabolism: The drug is metabolized by *N*-dealkylation through CYP2D6, and CYP3A4 isoenzymes. It has been reported that the level of metabolism correlates closely with degree of resistance.

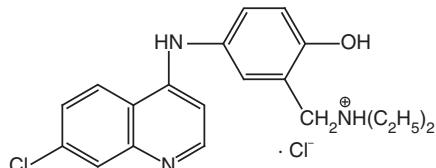
Properties and uses: Chloroquine exists as white or almost white crystalline powder, soluble in water and in methanol, very slightly soluble in ethanol. It is mainly used as an antimalarial. Chloroquine also has antihistaminic and antiinflammatory properties. It is used to treat hepatic amoebiasis, rheumatoid arthritis, discoid lupus erythematosus, cutanea tarda, solar urticaria, and polymorphous light eruptions. Chloroquine and other 4-amino quinolines are not effective against exoerythrocytic parasites. It is an example for poor selective toxicity. Adverse reactions include retinopathy, haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (same mutation that confers resistance against malaria), muscular weakness, exacerbation of psoriasis and porphyria, and impaired liver function.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

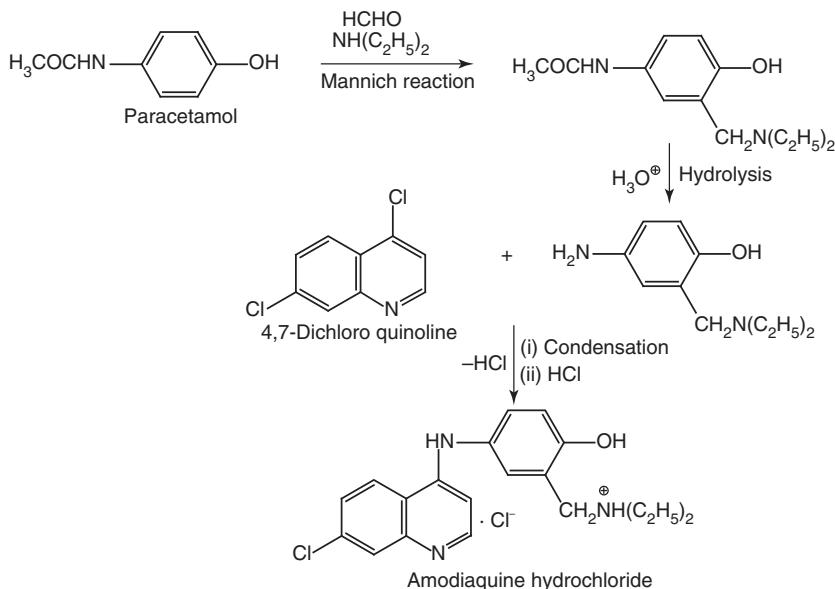
Dose: The recommended dose as a prophylactic and a suppressive is 500 mg once per week. As a therapeutic the dose , initially, is 1 g followed by 500 mg in 6 h, and 500 mg on the 2nd and 3rd day.

Dosage forms: Chloroquine sulphate injection I.P., B.P., Chloroquine sulphate tablets I.P., B.P.

Amodiaquine HCl (Camoquin)



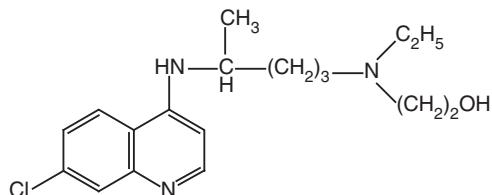
Synthesis



Properties and uses: It exists as yellow crystalline powder with a bitter taste, and is soluble in water. It is very similar to chloroquine and does not have any advantages over the other 4-amino quinoline drugs. It is used for suppressing *P. vivax* and *P. falciparum* infections being 3–4 times more active than quinine.

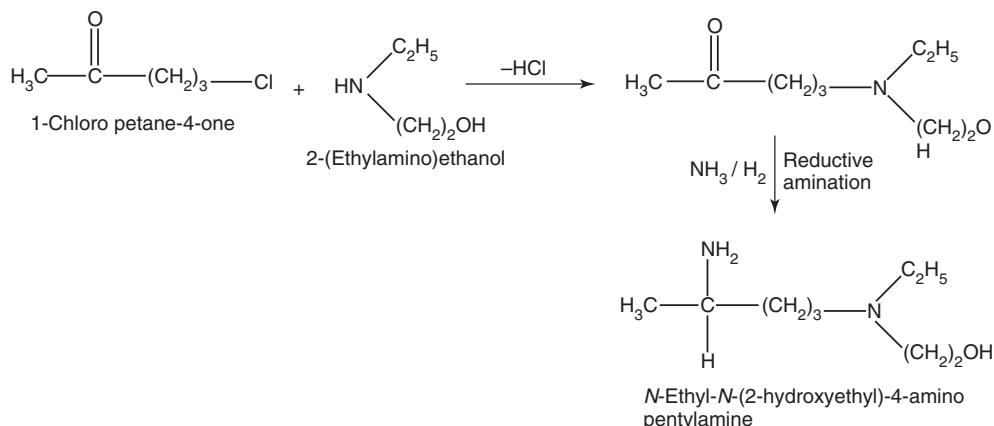
Dose: The recommended dose initially is 600 mg followed by 300 mg doses 6, 24, and 48 h later.

Hydroxy chloroquine (Plaquenil)

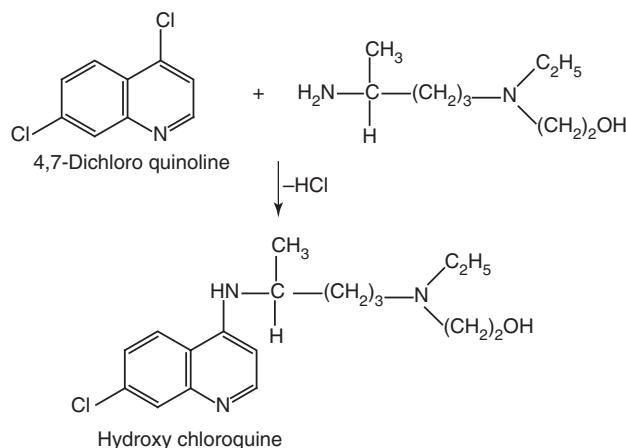


Synthesis

Step I. Preparation of side chain-*N*-ethyl-*N*-(2-hydroxyethyl)-4-amino pentyamine



Step II. Condensation of the product of *Step I* with 4,7-dichloro quinoline



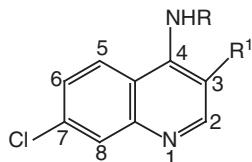
Properties and uses: Hydroxychloroquine is a white or almost white crystalline powder, soluble in water, practically insoluble in ethanol and in ether. It is equivalent to the chloroquine, but it is less toxic and used in the place of chloroquine against normally sensitive strains. It is mainly used as an antimalarial. It is also used for the treatment of rheumatoid arthritis and lupus erythematoses.

Assay: Dissolve the sample in water, add 1 M sodium hydroxide, and extract with dichloromethane. Combine the dichloromethane extracts and evaporate. Add anhydrous acetic acid and titrate against 0.1 M perchloric acid, using oracet blue B solution as indicator.

Dose: In *P. falciparum* infections, the dose is 1.25 g in a single dose or in two divided doses at 6 h intervals; in rheumatoid arthritis, 400 mg daily; in lupus erythematosus, 200 to 400 mg 1 or 2 times daily.

Dosage forms: Hydroxychloroquine tablets B.P.

STRUCTURE-ACTIVITY RELATIONSHIP

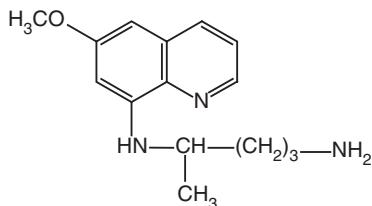


- At C-4 position, the dialkylaminoalkyl side chain has 2-5 carbon atoms between the nitrogen atoms, particularly the 4-diethylaminomethyl butyl amino side chain that is optimal for activity, as in chloroquine and quinacrine.
- The substitution of a hydroxyl group on one of the ethyl groups on the tertiary amine (hydroxy quinoline), reduces toxicity.
- Incorporation of an aromatic ring in the side chain (e.g. amodiaquine) gives a compound with reduced toxicity and activity.
- The tertiary amine in the side chain is important.
- The introduction of an unsaturated bond in the side chain was not detrimental to activity.
- The 7-chloro group in the quinoline nucleus is optimal, the methyl group in position 3 reduces activity, and an additional methyl group in position 8 abolishes activity.
- The D-isomer of chloroquine is less toxic than its L-isomer.

II. 8-Amino quinolines

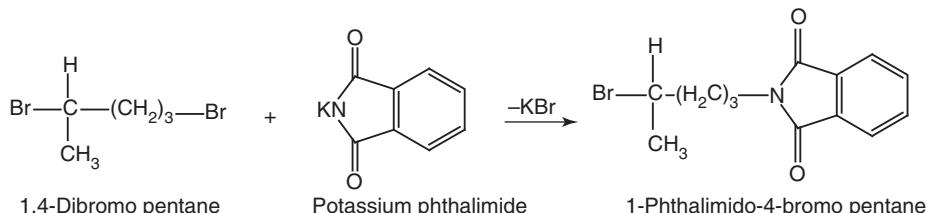
Mode of action: While the mechanism of action of the 8-amino quinolines is unknown, it is known that primaquine can generate reactive oxygen species via an autoxidation of the 8-amino quinoline group with the formation of radical anion. As a result, cell destructive oxidants, such as hydrogen peroxide, super oxide, and hydroxyl radical can be formed.

Primaquine (Primaquine Phosphate)

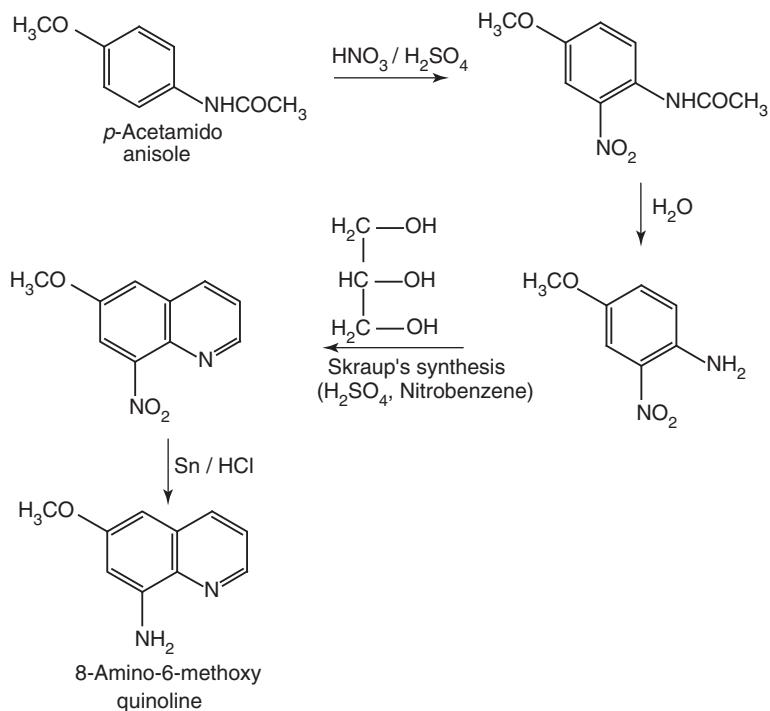


Synthesis

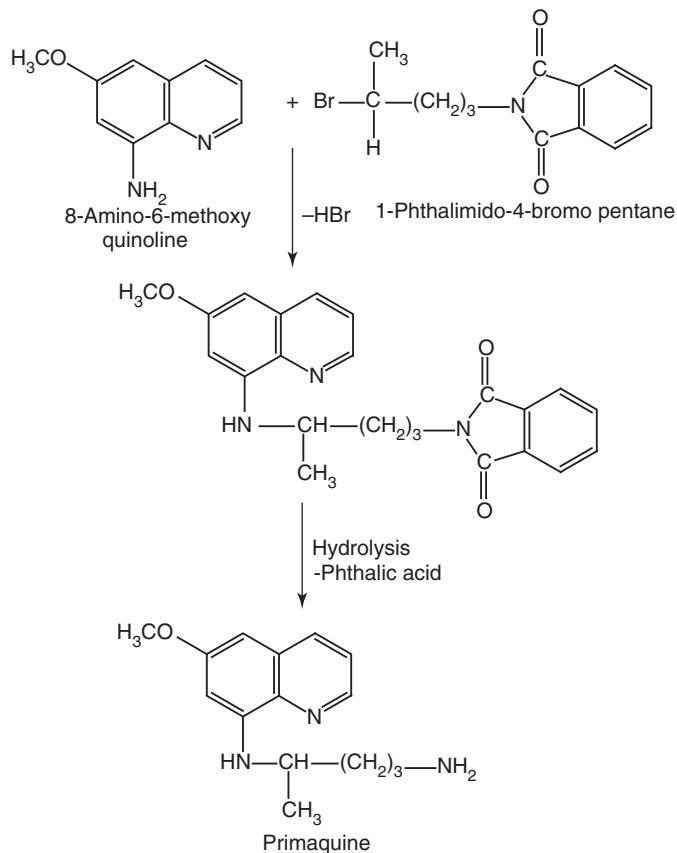
Step I. Preparation of 1-phthalimido-4-bromo pentane



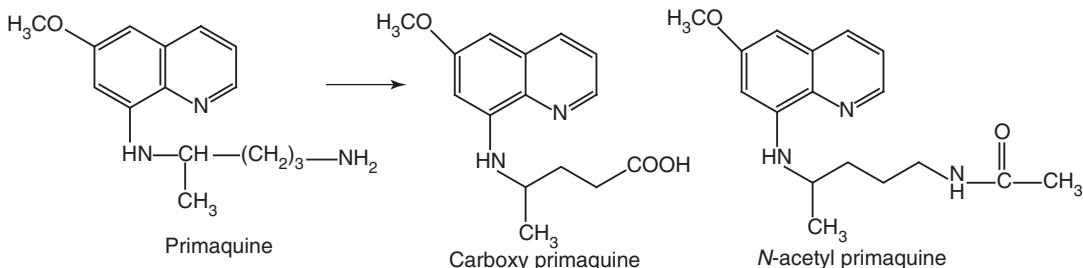
Step II. Synthesis of 8-amino-6-methoxy quinoline



Step III. Condensation of product of *Step I* and *Step II*



Metabolism: Primaquine is totally metabolized by CYP3A4 with primary metabolites having carboxy primaquine. Trace amounts of *N*-acetyl primaquine, aromatic hydroxylated products, and conjugation metabolites are seen.

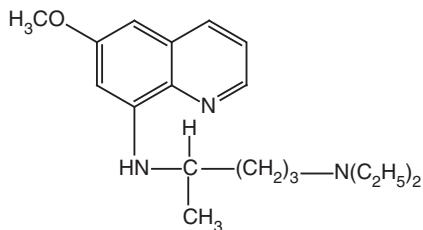


Properties and uses: Primaquine is a crystalline powder, soluble in water, and practically insoluble in alcohol. In vitro and in vivo studies indicate that the stereochemistry at the asymmetric carbon is not important for antimalarial activity. These appear to be less toxicity with the levorotatory isomer, but this is dose-dependent, and may not be of much importance as the doses used to treat exoerythrocytic *P. vivax* malaria. It is extensively used for the radical cure of relapsing *vivax* malaria, but it is not normally employed either for arresting the severe attacks of the disease or for the suppressive therapy. It invariably kills gametocytes of all the species, or inhibits their growth and development in the mosquito. It fails to produce any significant effect on other erythrocytic stages, and hence, it must not be employed alone for the treatment of malaria.

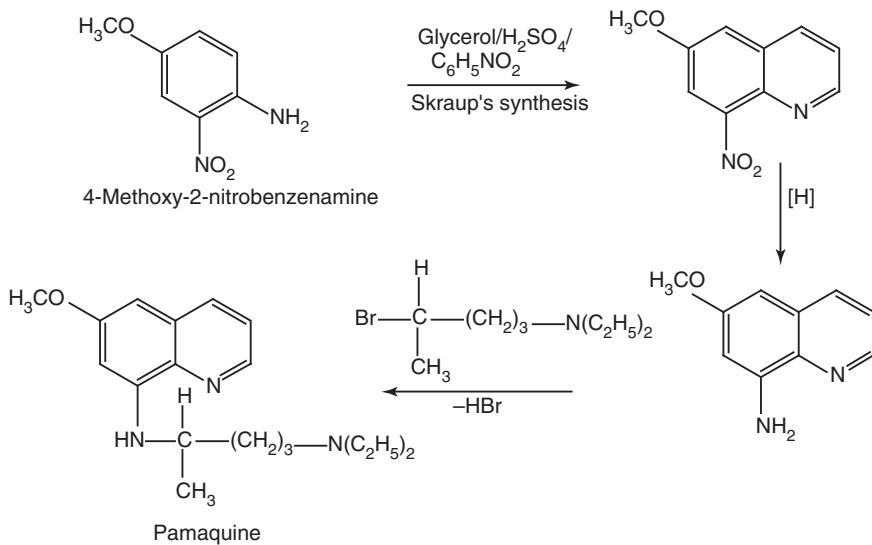
Assay: Dissolve the sample in anhydrous acetic acid and heat gently. Allow to cool and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The recommended dose for administration is 17.5–26.3 mg (10–15 mg of base) once daily for 14 days.

Pamaquine



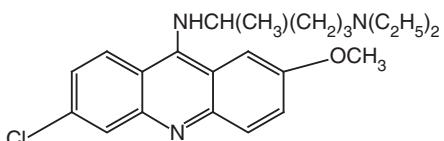
Synthesis



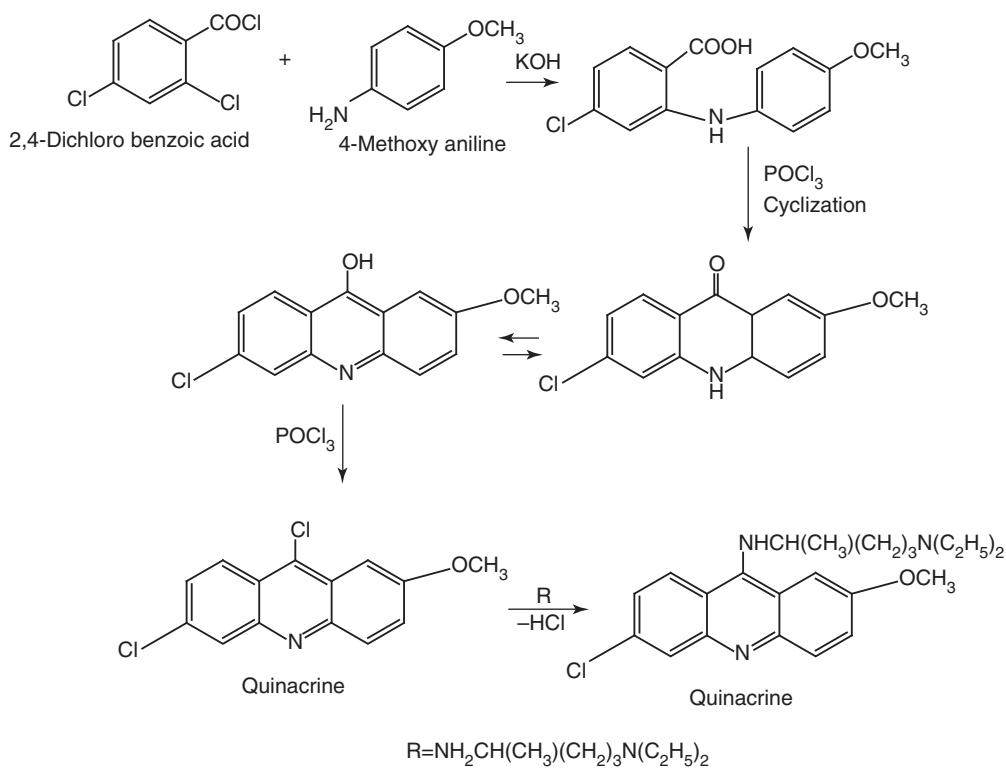
Properties and uses: It was the first 8-amino quinoline marketed, used as an antimalarial agent.

III. Acridine Derivatives

Quinacrine



Synthesis

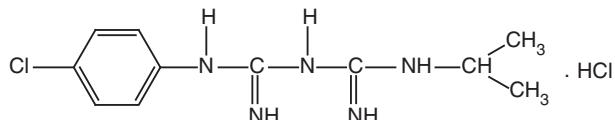


Mode of action: Quinacrine acts at many sites within the cell, including intercalation of DNA strands, succinic dehydrogenase, mitochondrial electron transport, and cholinesterase. It may be tumorigenic and mutagenic and has been used as a sclerosing agent. Because it is an acridine dye, quinacrine can cause yellow discolouration of the skin and urine.

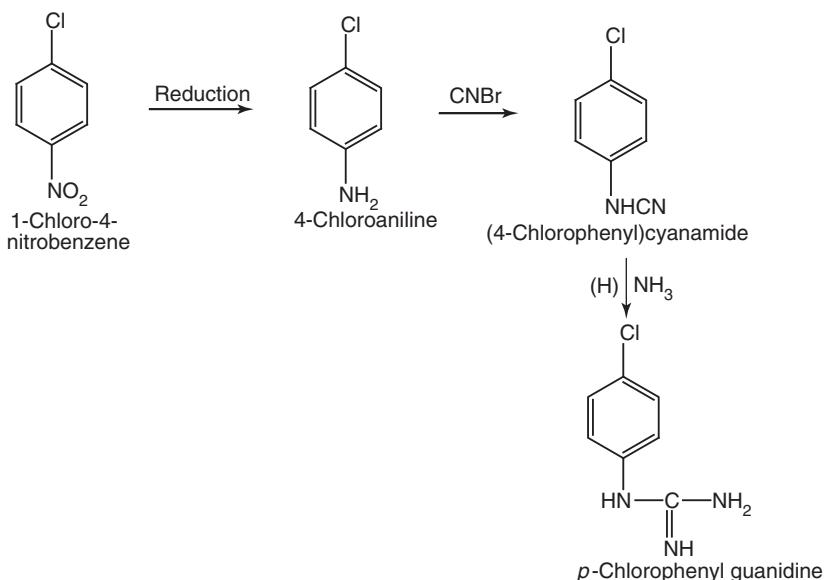
Properties and uses: It acts as a schizontocidal and now it is not used as an antimalarial agent. It is used in the treatment of leishmaniasis and some tape worm infestations.

IV. a. Biguanides

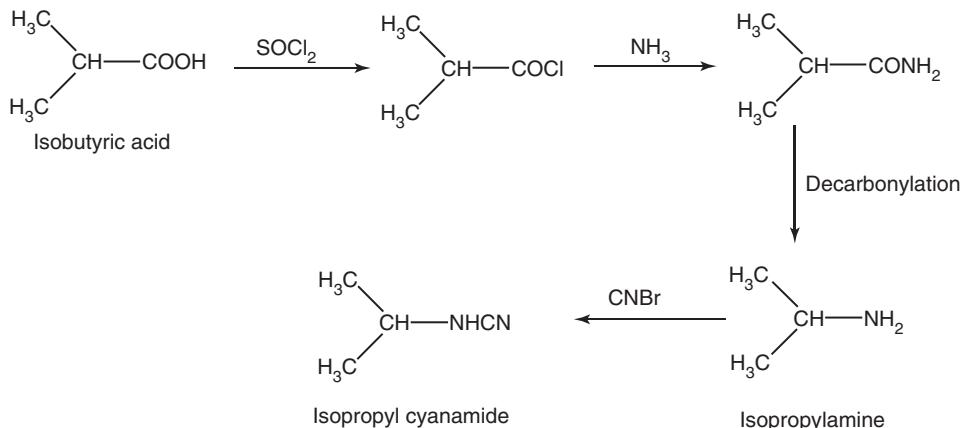
Mode of action: Biguanides inhibit dihydrofolate reductase enzyme and interfere in the folic acid metabolism. This leads to inhibition of the nuclear division in malarial parasites.

Proguanil HCl (Paludrine)**Synthesis**

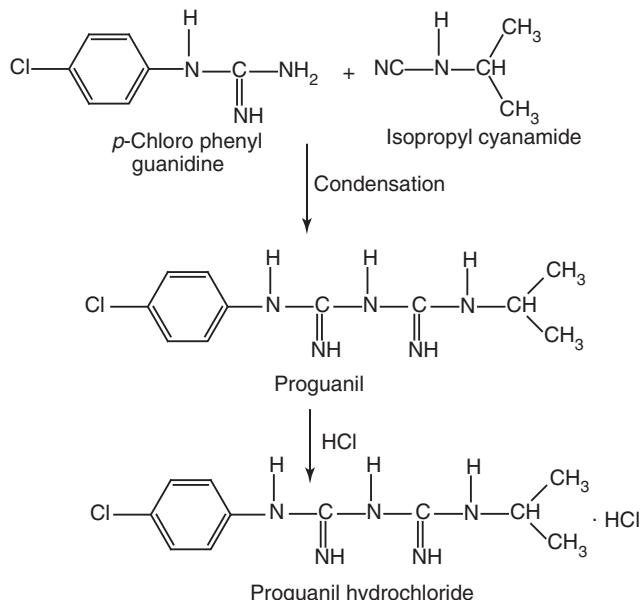
Step I. Synthesis of *p*-chloro phenyl guanidine



Step II. Synthesis of isopropyl cyanamide



Step III. Condensation of the products of *Steps I* and *II*



Metabolism: Proguanil is a prodrug, which is metabolized in the liver to diaminotriazine (cycloguanil) that acts as a dihydrofolate reductase inhibitor of *Plasmodium* species and inhibits DNA synthesis.

Properties and uses: Proguanil hydrochloride is a white crystalline powder, slightly soluble in water, sparingly soluble in ethanol, and practically insoluble in methylene chloride. It is used mainly for prophylactic treatment of malaria.

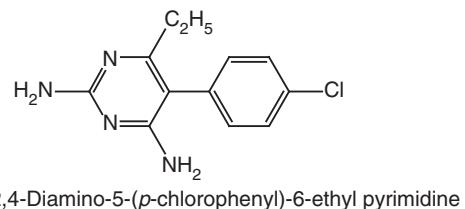
Assay: Suspend the sample in anhydrous acetic acid, shake and heat at 50°C for 5 min. Cool to room temperature, add acetic anhydride, and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The recommended dose as a prophylactic and a suppressant is 100 to 200 mg per day in nonimmune subjects; 300 mg/week or 200 mg twice/week in semi-immune subjects. In the case of acute *vivax* malaria, initial loading dose is 300 g–600 mg followed by 300 mg per day for 5–10 days. For the treatment of *falciparum* malaria, the dose is 300 mg two times daily for 5 days.

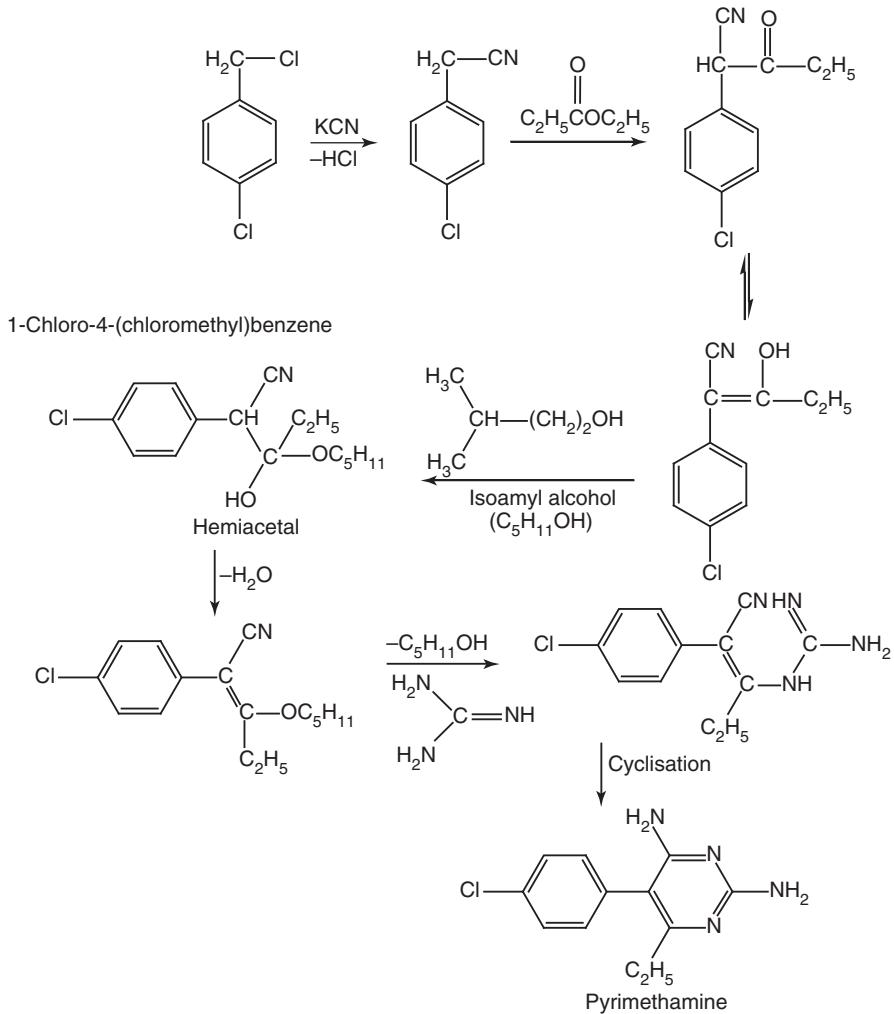
IV. b. Diaminopyrimidines

Mode of Action: It inhibits the reduction of folic acid and dihydrofolic acid to the active tetrahydrofolate coenzyme form.

Pyrimethamine (Daraprim)



Synthesis

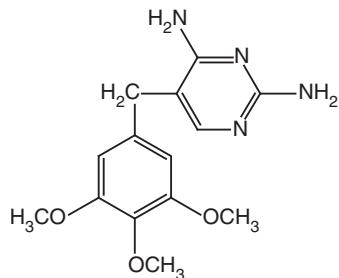
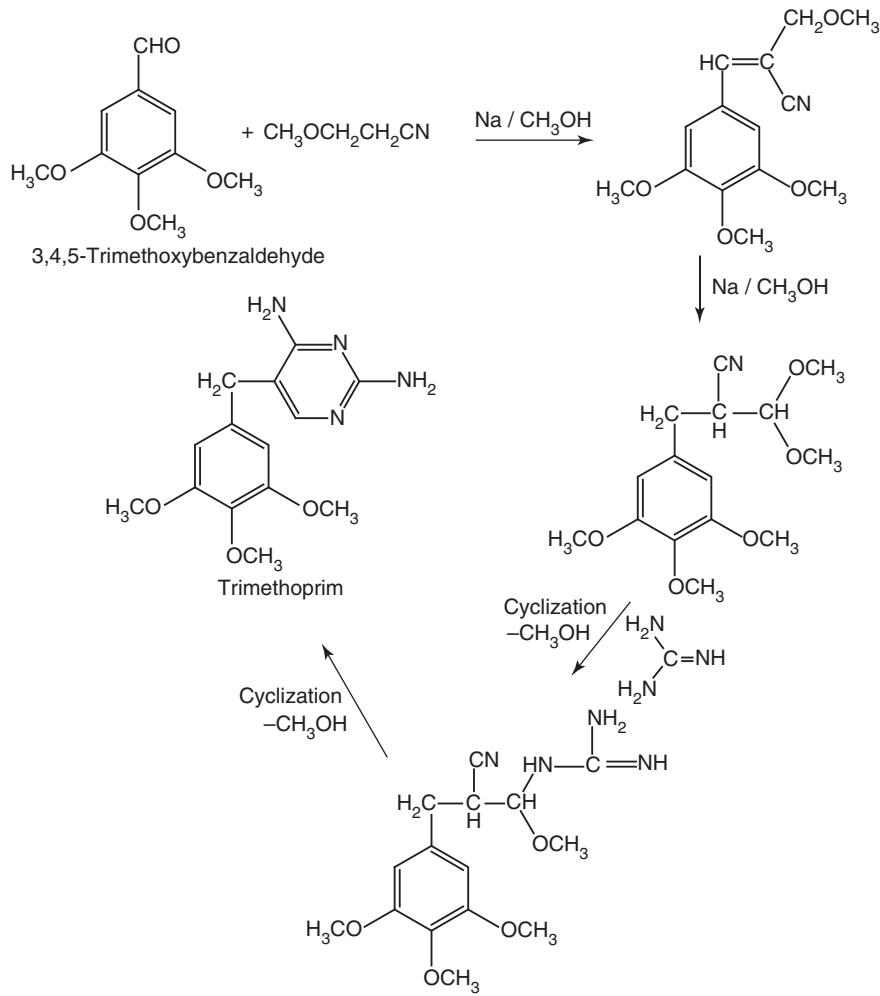


Properties and uses: Pyrimethamine exists as a white crystalline powder or colourless crystals, practically insoluble in water, and slightly soluble in alcohol. Pyrimethamine inhibits the reduction of folic acid and dihydrofolic acid to the active tetrahydrofolate coenzyme form. It finds its extensive use as a suppressive prophylactic for the prevention of severe attacks due to *P. falciparum* and *P. vivax*. It is also used in the treatment of toxoplasmosis and as an immuno suppressive agent.

Assay: Dissolve the sample in anhydrous acetic acid by heating gently. Cool and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The administered dose as a suppressive is 25 mg once a week, as a therapeutic 50–75 mg once a day for two days when used alone, otherwise 25 mg.

Dosage forms: Pyrimethamine tablets I.P., B.P.

Trimethoprim (Proloprim)**Synthesis**

Properties and uses: Trimethoprim exists as a white or yellowish-white powder, very slightly soluble in water, and slightly soluble in ethanol. It is a potent inhibitor of dihydrofolate reductase. It has been employed in conjugation with sulphamethopyrazine in the treatment of chloroquine-resistant malaria. It has also been used in conjugation with sulphonamides in the treatment of bacterial infections. Trimethoprim is an antibacterial, effective against malarial parasite.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The administered dose is 1.5 g with 1 g of sulphametopyrazine per day for 3 days.

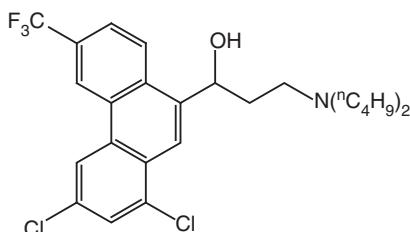
Dosage forms: Co-trimoxazole intravenous infusion B.P., Co-trimoxazole oral suspension B.P., Paediatric co-trimoxazole oral suspension B.P., Co-trimoxazole tablets dispersible B.P., Co-trimoxazole tablets paediatric B.P., Co-trimoxazole tablets B.P., Trimethoprim oral suspension B.P., Trimethoprim tablets B.P.

V. Sulphones and sulphonamides

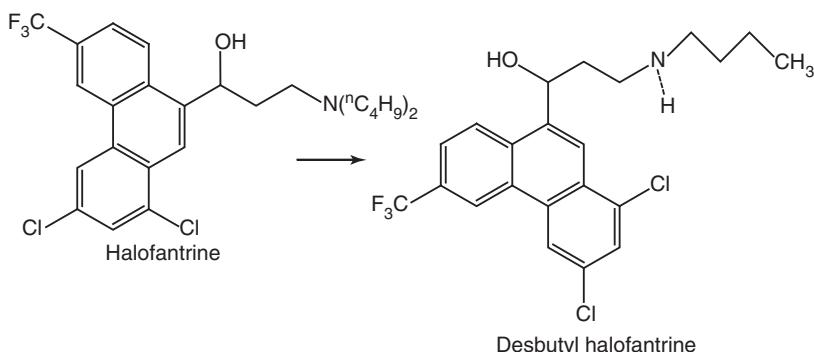
Mode of action: They only act against the erythrocytic stages of malaria parasite. The sulphadoxine interferes with the parasites ability to synthesize folic acid. Sulphonamides block the incorporation of *p*-amino benzoic acid (PABA) to form dihydropteroic acid. PABA is the central part of the folate structure. Sulphonamides exhibit significant toxicity because humans do not synthesize the vitamin folic acid. There are severe to fatal occurrences of erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis, and serum sickness syndromes attributed to the sulphadoxine.

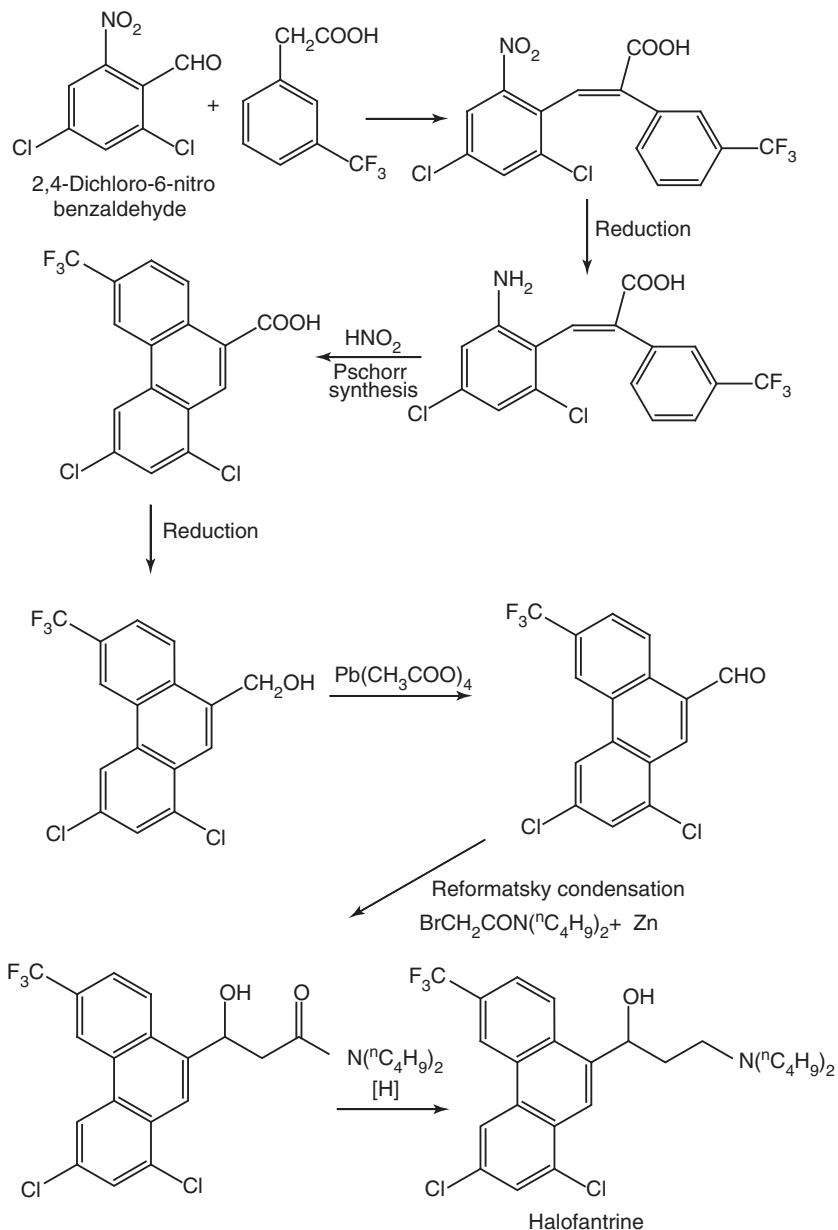
VI. Miscellaneous

Halofantrine



Metabolism: The drug is metabolized by *N*-dealkylation to desbutyl halofantrine by CYP3A4. The metabolites appear to be several folds more active than the parent drug.



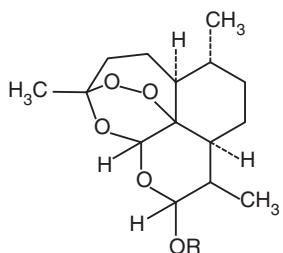
Synthesis

Properties and uses: Halofantrine is a white or almost white powder, practically insoluble in water, soluble in methanol, and sparingly soluble in alcohol. Structurally, halofantrine differs from all other antimalarial drugs and belongs to the latest generation of antimalarials. It is a good example of a drug design that

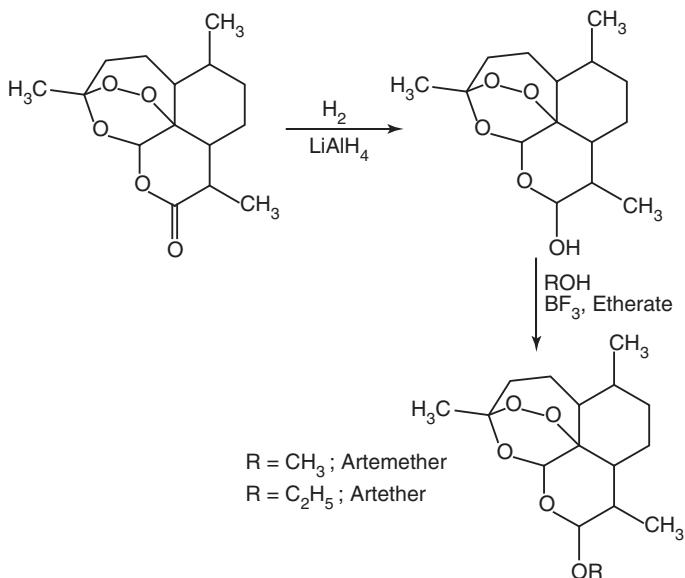
incorporates bioisosteric principles evidenced by the tri-fluoro methyl moiety. It is schizonticidal and has no effect on the sporozoite, gametocyte, or hepatic stages. It is effective in the treatment and prophylaxis of chloroquine and multidrug resistant *P. falciparum*.

Assay: It is assayed by adopting Liquid chromatography technique.

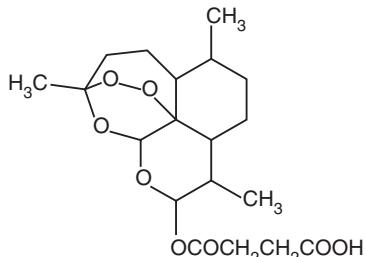
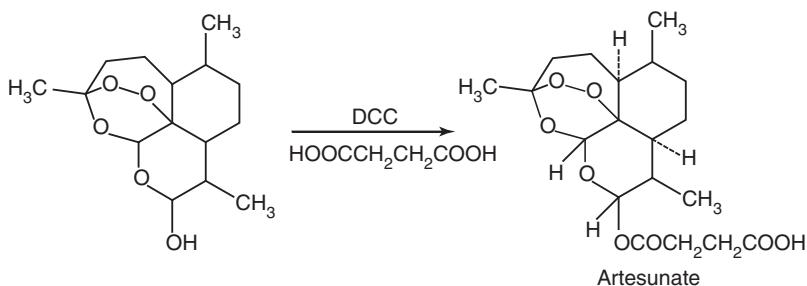
Artemether (Lariether, Paluther) and Artether



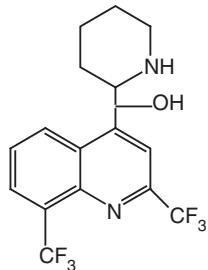
Synthesis



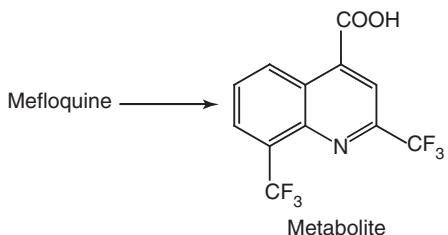
Dose: The administered dose for acute uncomplicated *falciparum* malaria in the case of adults is 80 mg daily to be taken with lumefantrine 480 mg daily. Doses to be taken at diagnosis and repeated after 8, 24, 36, 48, and 60 h. Total doses are six. For a child, the daily dose based on the body weight is as follows: 5–14 kg: 20 mg; 15–24 kg: 40 mg with lumefantrine 240 mg; 25–34 kg: 60 mg with lumefantrine 360 mg and more than 34 kg: 80 mg with lumefantrine 480 mg. Doses to be taken at diagnosis and repeated after 8, 24, 36, 48, and 60 h and the total doses are 6.

Artesunate (Asunate, Ultera, Falcigo)**Synthesis**

Dose: The dose in the case of *falciparum* malaria for adults is 2.4 mg/kg via IM or IV administration to be repeated after 12 h and 24 h later; then, once daily thereafter. For a child, the dose is 2.4 mg/kg via IM or IV administration and to be repeated after 12 h and 24 h later; then, once daily thereafter.

Mefloquine

Metabolism of mefloquine: It is metabolized through CYP3A4 oxidation to its major inactive metabolite called carboxy mefloquine and rest of the amount is excreted unchanged in urine.



Properties and uses: Mefloquine hydrochloride is a white or slightly yellow crystalline powder, very slightly soluble in water, soluble in methanol and in alcohol. It is used as an antimalarial agent.

Assay: Dissolve the sample in anhydrous formic acid, add acetic anhydride and titrate with 0.1 M perchloric acid. Determine the end-point potentiometrically.

PROBABLE QUESTIONS

- What are the casual organisms responsible for malaria? How do the antimalarials affect the life cycle of mosquito? Explain.
- Write the mode of action, synthesis, and metabolism of any one of the 4-amino quinoline derivatives.
- Discuss the synthesis of one important antimalarial drug belonging to the class:
(a) Diaminopyrimidines (b) Sulphones.
- Write the SAR of 4-amino quinolines.
- Classify the synthetic antimalarials based on their basic chemical nucleus. Provide examples of at least one of the two compounds from each class.
- Modifications of the side-chain at C-4 position on the 4-amino-7-chloroquinoline nucleus results in the following drugs:
(a) Chloroquine phosphate (b) Amodiaquine hydrochloride (c) Santoquin
- Outline the synthesis of proguanil hydrochloride from *p*-chlorophenyl guanidine and iso-propyl cyanamide. Write their structure, synthesis, and the dosage forms available.
- Name the three important antimalarials derived from 8-amino-6-methoxy quinoline nucleus, their structure, chemical name, uses, and the synthesis of any one drug.
- Elaborate the synthesis of mepacrine hydrochloride, the uses, and the dosage forms available.
- Proguanil hydrochloride is the wonder drug for malaria that gets metabolized to its active form cycloguanil *in vivo*. Explain its biotransformation.

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Chapter 10

Anthelmintics

INTRODUCTION

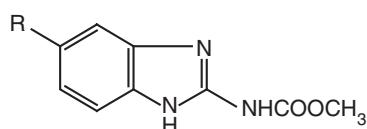
Anthelmintics are drugs used to treat parasitic infections due to worms. Worms that are pathogenic to human beings, namely, metazoa are conventionally classified into round worms (nematodes) and two types of flatworms, that is, flukes (trematodes) and tapeworms (cestodes). Anthelmintics act locally either to expel the worms from the gastrointestinal tract or systemically to eradicate the species and the developing forms of helminths that invade the organs and tissues. This class of agents have added significance due to their wide prevalence in third-world countries and it is estimated over 2 billion people are affected. No cheaper medicines are available for this disease, even now, although the primitive Chinese and Egyptians have started treating this disease 3500 years ago.

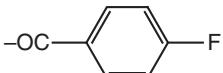
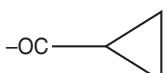
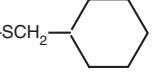
CLASSIFICATION

The anthelmintic agents comprise of drugs of chemically diverse structures and their mechanism of action differs from one agent to another.

I. Benzimidazoles

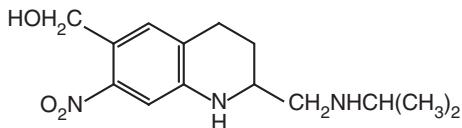
These are versatile anthelmintic agents particularly effective against gastrointestinal nematodes. These are highly effective against *ascaris*, *enterobius*, *trichuris*, and hookworm infections as single or mixed infections.



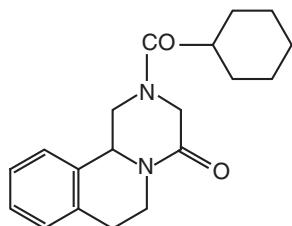
| S. No. | Drug | R |
|--------|----------------|---|
| 1 | Albendazole | —S—CH ₂ CH ₂ CH ₃ |
| 2 | Mebendazole | —COC ₆ H ₅ |
| 3 | Flubendazole | —OC—  |
| 4 | Cyclobendazole | —OC—  |
| 5 | Dribendazole | —SCH ₂ —  |
| 6 | Fenbendazole | —S—C ₆ H ₅ |
| 7 | Oxibendazole | —OCH ₂ CH ₂ CH ₃ |
| 8 | Parbendazole | —CH ₂ CH ₂ CH ₂ CH ₃ |

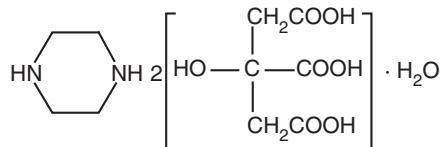
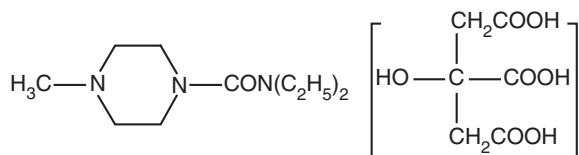
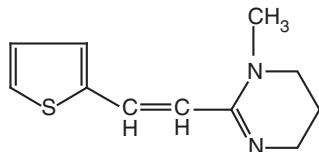
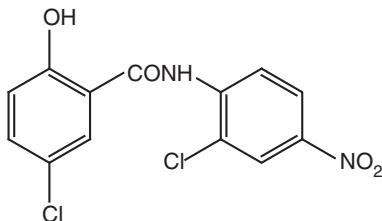
II. Quinolines and isoquinolines

Oxamniquine



Praziquantel



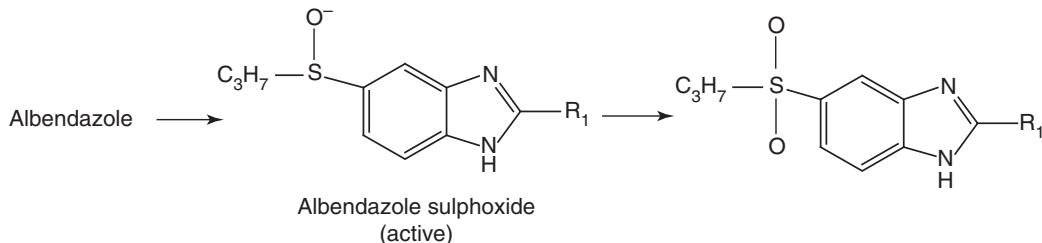
III. Piperazine derivatives**Piperazine citrate****Diethyl carbamazine****IV. Vinyl pyrimidines****Pyrantel pamoate****Oxantel****V. Amides****Niclosamide****VI. Natural products: Avermectins****VII. Organo phosphorus: Metrifonate****VIII. Imidazothiazoles: Levamisole****IX. Nitro derivatives: Niridazole.**

SYNTHESIS AND DRUG PROFILE

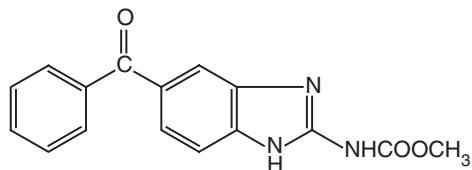
I. Benzimidazoles

Mode of action: These drugs act by blocking the glucose transportation in the parasites and lead to the depletion of glycogen storage of the intracellular microtubules in the cells of the worms, thereby arresting the nematodes and cell division in the metaphase. The major site of action is microtubular protein β tubulin of the parasite. These drugs are bound with β tubulin and inhibit the polymerization.

Metabolism: The parent compound is rapidly and almost completely metabolized by oxidative and hydrolytic processes.. The phase I oxidative reaction is commonly carried out by the cytochrome P450 catalyzed reaction, which may be followed by phase II conjugation.



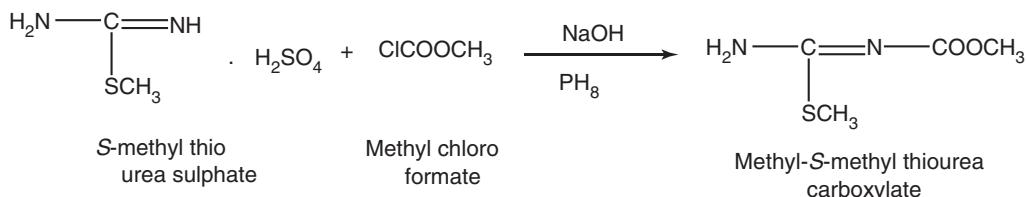
Mebendazole (Vermox)



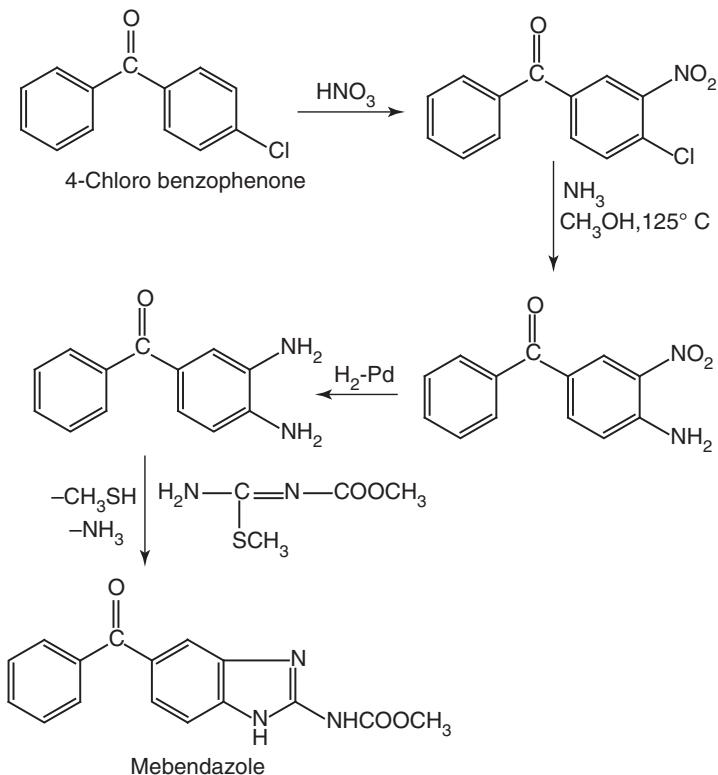
Methyl-5-benzoyl-2-benzimidazole carbamate

Synthesis

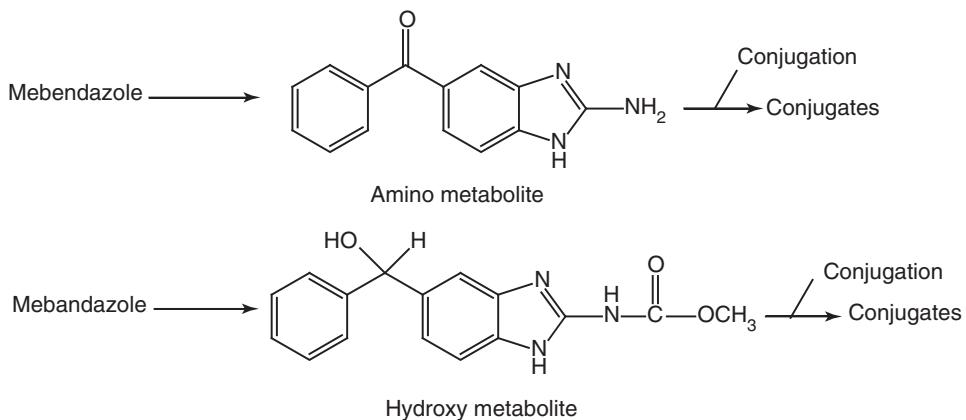
Step I. Synthesis of an intermediate-S-methyl thiourea arboxylate



Step II. Synthesis of Mebendazole



Metabolism: Mebendazole is metabolized by the reduction of the 5-carbonyl group to a secondary alcohol, which greatly increases the water solubility of this compound and thereby potentiates the excretion through urine. Secondary alcohol and amine are readily conjugated.

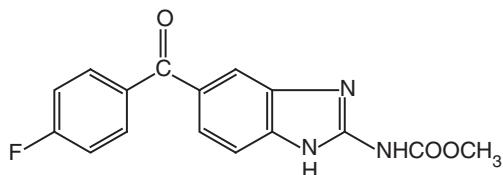


Properties and uses: Mebendazole is a white powder, practically insoluble in water, in alcohol, and in methylene chloride. It is used as an anthelmintic agent.

Assay: Dissolve the sample in anhydrous formic acid, add the mixture of anhydrous acetic acid and methyl ethyl ketone (1:7), and titrate against 0.1 M perchloric acid. Determine the end-point potentiometrically.

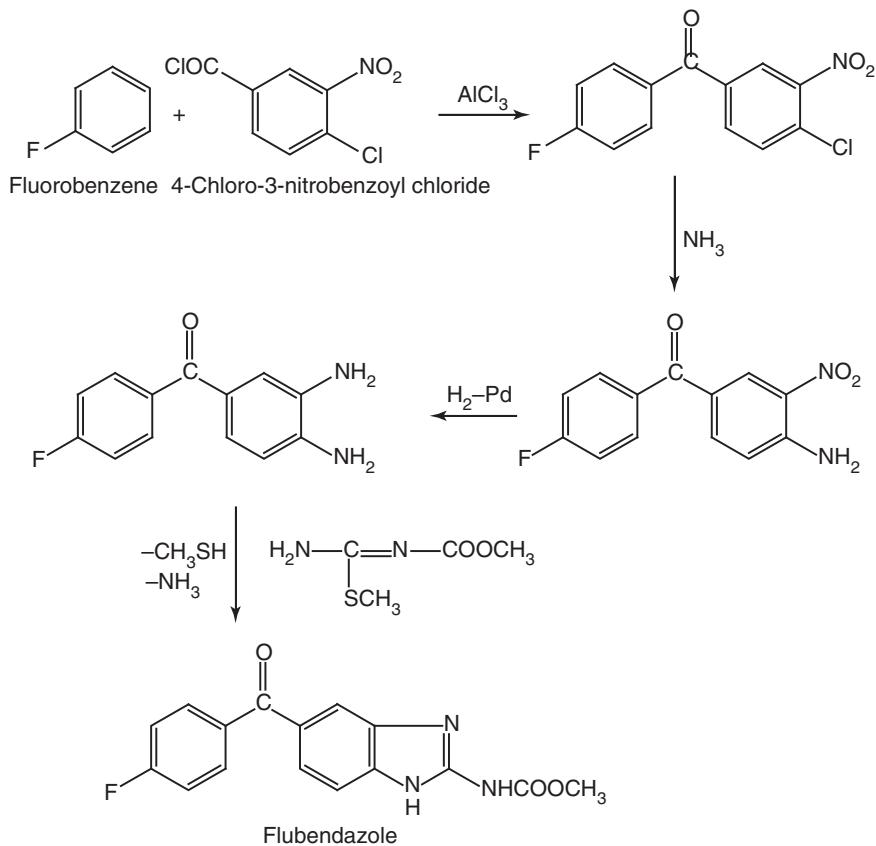
Dose: The administered oral dose is 100 mg tablets chewed daily.

Flubendazole



Methyl 5-(4-fluorobenzoyl)-1*H*-benzimidazol-2-yl-carbamate

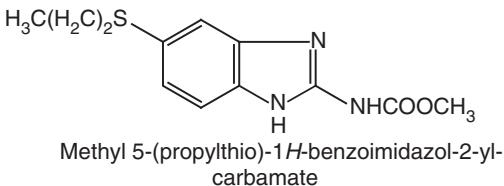
Synthesis



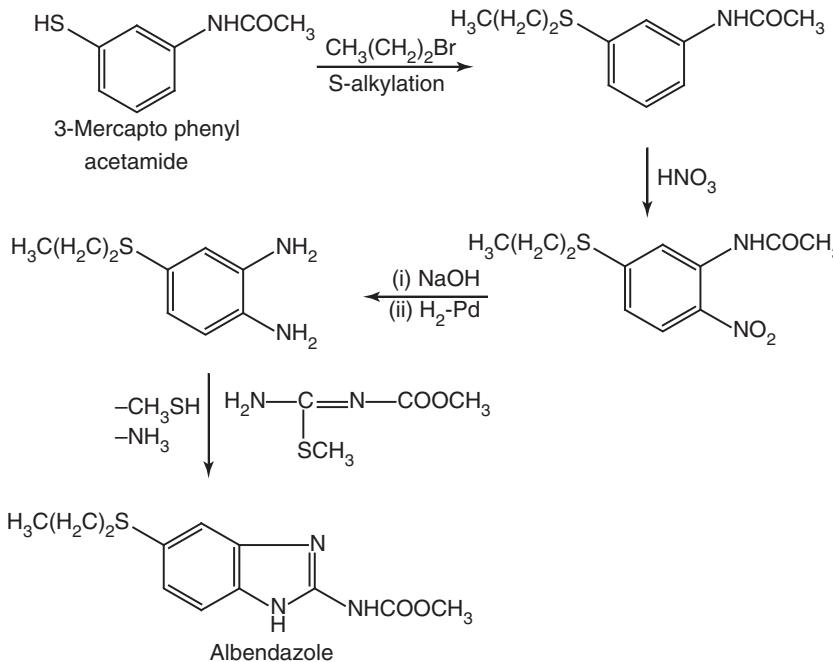
Properties and uses: Flubendazole is a white powder, practically insoluble in water, in alcohol, and in methylene chloride. It is used as an anthelmintic agent.

Assay: Dissolve the sample in anhydrous formic acid, add the mixture of anhydrous acetic acid and methyl ethyl ketone (1:7), and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Albendazole (Valbazen, Bentex, Zental)



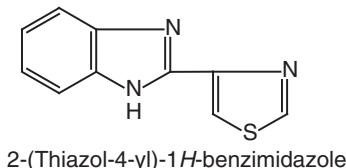
Synthesis



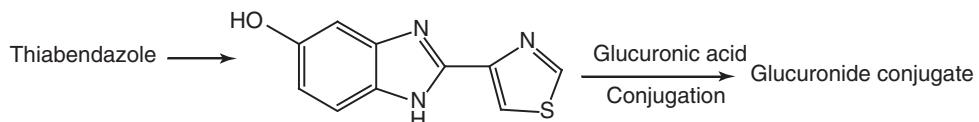
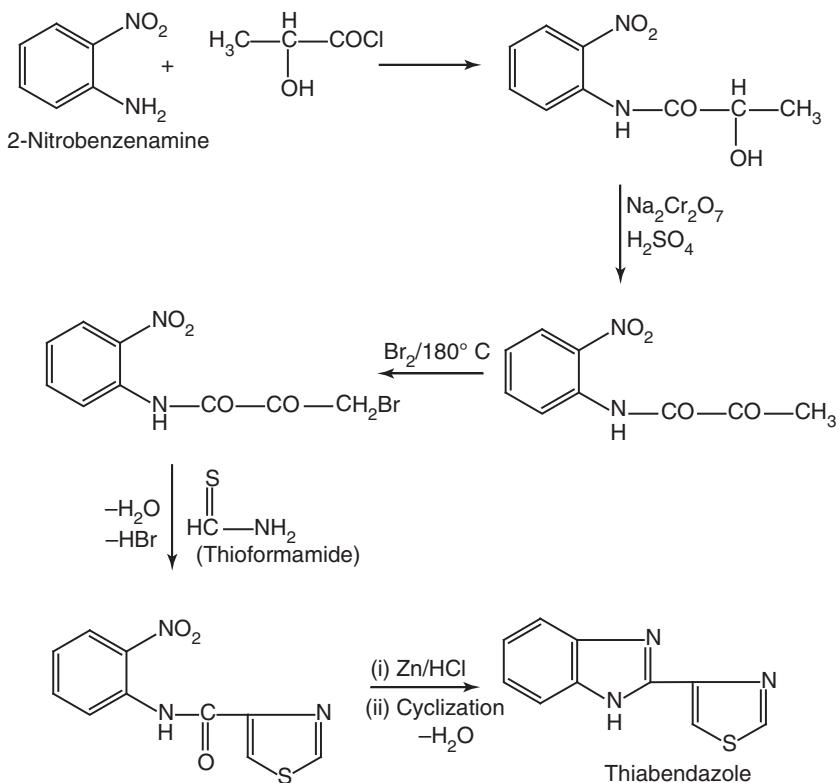
Properties and uses: Albendazole is a white or faintly yellowish powder, practically insoluble in water and alcohol, soluble in anhydrous formic acid, very slightly soluble in methylene chloride. It is used as an anthelmintic agent.

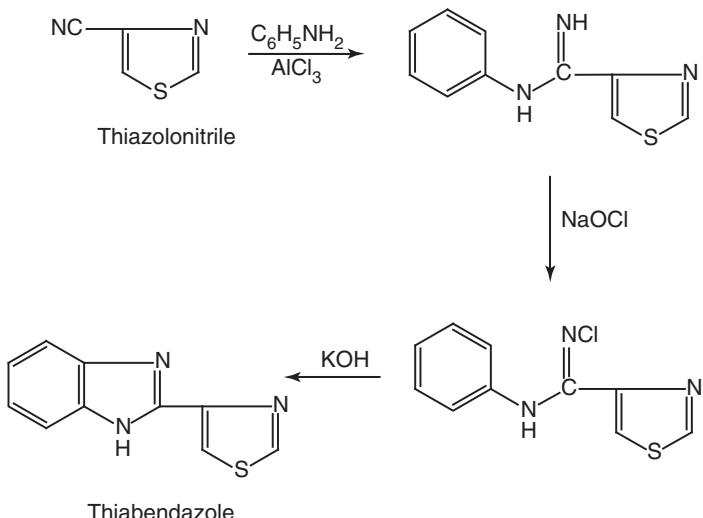
Assay: Dissolve the sample in anhydrous formic acid, add anhydrous acetic acid, and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The dose for controlling cysticercus cellulose is 5 mg/kg thrice daily for 30 days.

Thiabendazole (Mintezol)

Metabolism: Thiabendazole is metabolized through aromatic hydroxylation at the fifth position catalyzed by CYP1A2. The resulting phenol is conjugated to 5-hydroxythiabendazole glucuronide.

**Synthesis****Route I. From: *o*-Nitro aniline (or) 2-Nitrobenzenamine**

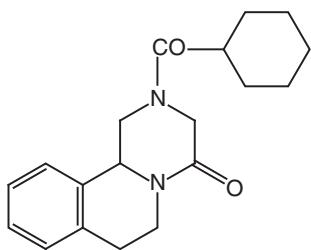
Route II. From: Thiazolo nitrile


Properties and uses: It is a white, odourless, and tasteless powder, insoluble in water, slightly soluble in acetone, chloroform, or ether. It is used as a anthelmintic.

Dose: The dose orally is 25 mg/kg twice daily to a maximum of 3 g after meals. The dose for chewable tablets is 500 mg and oral suspension is 500 mg/5ml.

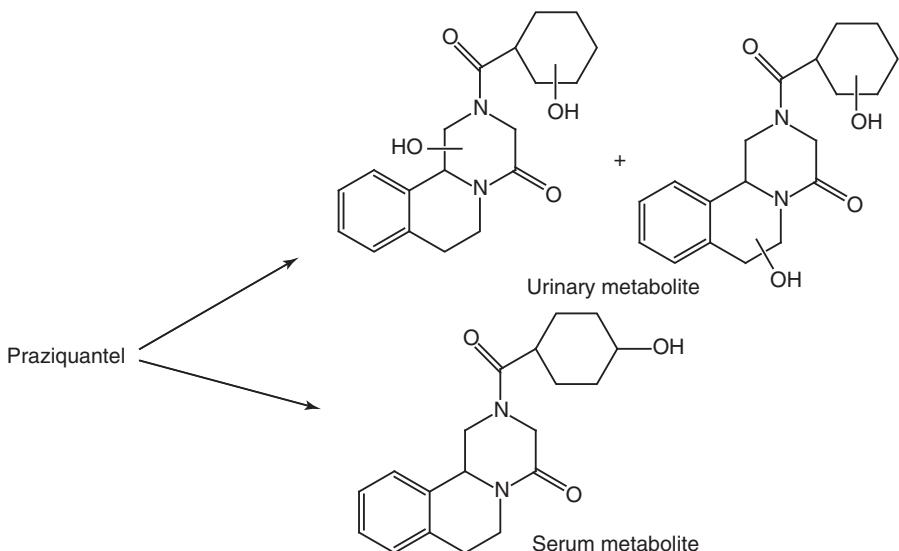
II. Quinoline and isoquinolines

Praziquantel (PZQ, Biltricide)

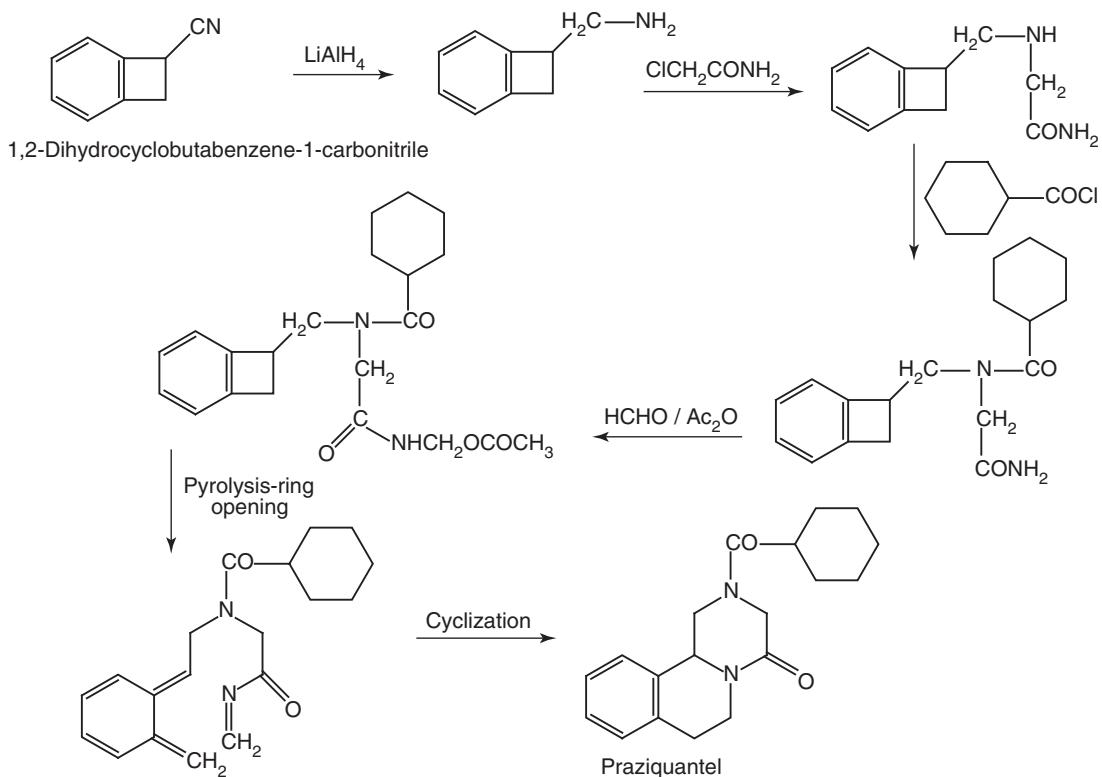


2-(Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11*b**H*)-one

Metabolism: In serum, the major metabolites are 4-hydroxycyclohexyl carboxylate, but in the urine, 50%–60% of the initial PZQ exist as dihydroxylated products. Hydroxylation reactions are catalyzed by CYP2B6 and CYP3A4.



Synthesis

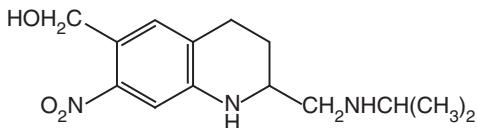


Properties and uses: PZQ is a white crystalline powder, very slightly soluble in water, soluble in alcohol, and in methylene chloride. It is used for the treatment of schistosomiasis and liver fluke infections. It causes legumental damage to the worms, which activates the host defence mechanisms and results in the destruction of the worms.

Assay: It is assayed by adopting liquid chromatography technique.

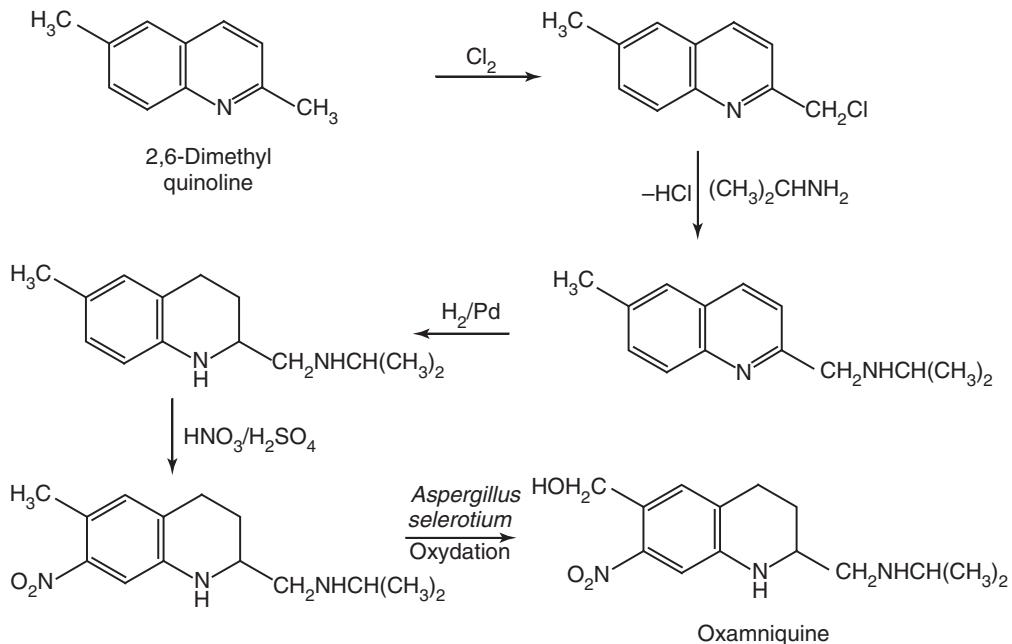
Dose: The oral dose is 600 mg tablet two to three times a day.

Oxamniquine (Vansil)



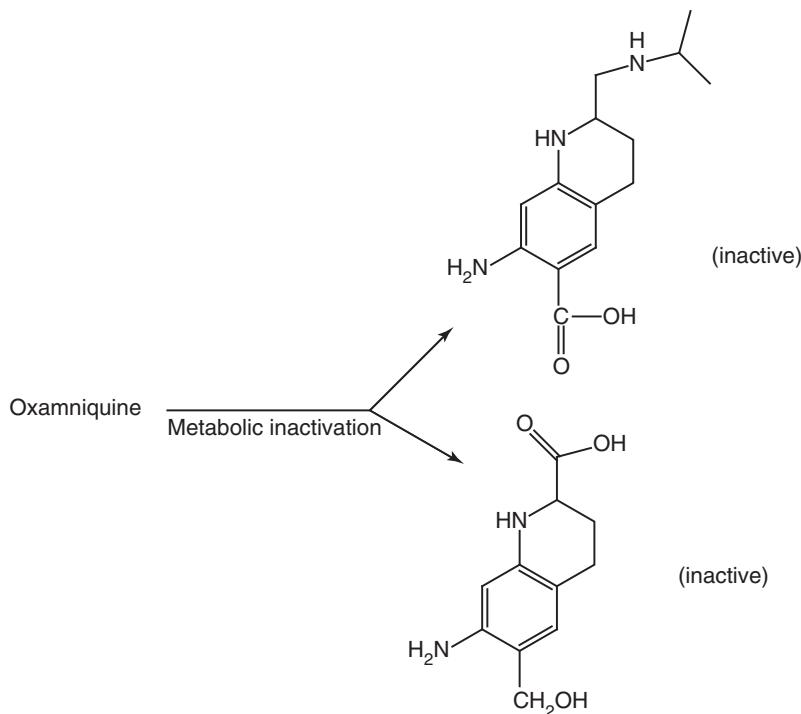
(2-((Isopropylamino)methyl)-7-nitro-1,2,3,4-tetrahydroquinolin-6-yl)methanol

Synthesis



Mode of action: *Schistosoma mansoni* is highly susceptible to oxamniquine. Adenosine-5'-triphosphate (ATP)-dependent enzymatic activation of the drug in susceptible schistosomes forms unstable phosphate esters, which disassociate to yield a chemically reactive carbocation this intermediate alkylates the DNA.

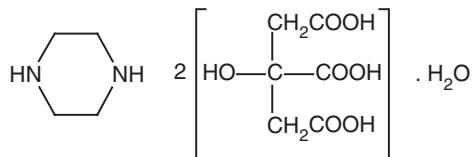
Metabolism: It is metabolized by oxidative reaction and it gives inactive metabolites of acid and alcohol derivatives.



Dose: The dose for oral route after meals depends upon geographical areas. In the western hemisphere, the dose is 15 mg/kg as a single dose, in Africa 15–60 mg/kg over 1–3 days.

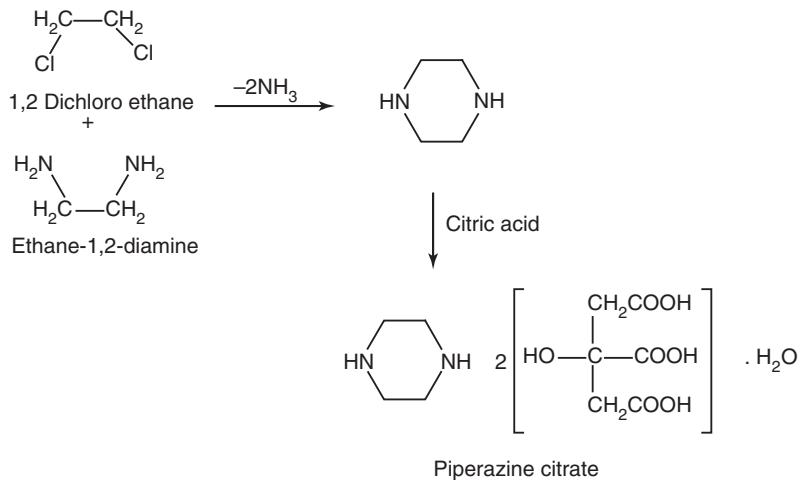
III. Piperazine derivatives

Piperazine Citrate (Vermizine, Antepar)



Mode of action: The drug is highly effective against both *Ascaris lumbricoides* and *Enterobius (oxyuris) vermicularis*. These drugs cause the hyperpolarization of the ascaris muscles by gamma-aminobutyric acid (GABA) agonistic action, opening Cl⁻ channels, which cause relaxation, depress responsiveness to the contractile action of acetylcholine, and produce the suppression of spontaneous spike potentials with peristalsis.

Synthesis



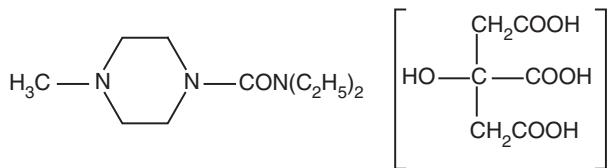
Properties and uses: Piperazine citrate is a white granular powder, soluble in water, and practically insoluble in alcohol, used as an anthelmintic. It can cause gastrointestinal and allergic reactions. It is contraindicated in epileptic patients.

Assay: Dissolve the sample in a mixture of anhydrous formic acid, acetic anhydride (2:3), and titrate quickly against 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The administered dose always orally in the case of *ascaris* is 3.5 g as single dose daily for two consecutive days. For *oxyuriasis* (thread worms) the dose is 2.5 g given for 7 days.

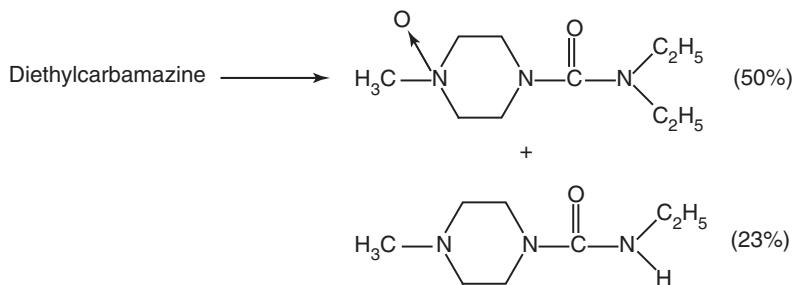
Dosage forms: Piperazine citrate syrup I.P., Piperazine citrate tablets I.P., Piperazine citrate elixir B.P.

Diethyl carbamazine citrate (Vanaide, Vellcome)



Mode of action: It selectively acts on the microflora, causes attraction, and therefore, is readily phagocytosed by the tissue fixed monocytes. It also has an effect on the muscular activity of the microflora and causes hyper-polarization to destroy the worms.

Metabolism: The metabolism of diethyl carbamazepine leads to the compounds of methyl piperazine and piperazine. Nearly, all of the metabolites appear in the urine.



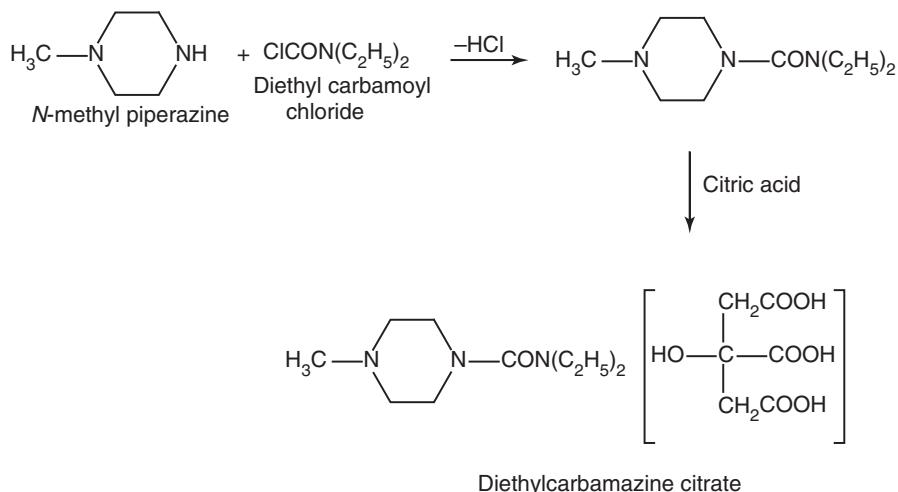
Properties and uses: Diethylcarbamazine citrate is a white crystalline slightly hygroscopic powder, very soluble in water, soluble in alcohol, and practically insoluble in acetone. It is the drug of choice for treating *filariasis* infections. In adequate dosage, it clears the blood rapidly of the microfilariae and appears to be curative. Antihistamines or corticosteroids may be needed to control the allergic reaction caused by the disintegration of microfilariae. It is active against microfilariae of *Loa loa*, but may cause encephalopathy.

Assay: Dissolve the sample in anhydrous acetic acid, add acetic anhydride, and titrate with 0.1 M perchloric acid using crystal violet as indicator, until a greenish-blue colour is obtained.

Dose: The dose in the case of oral route for *Brugia malayi*, *Loa loa*, and *Wuchereria bancrofti* is 2 mg/kg three times daily after meals for 10–30 days. For *Caecal volvulus*, the dose is 0.5 mg/kg once on the first day and twice on the second day and the adverse effects limit the use of this drug.

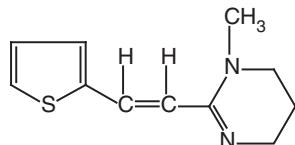
Dosage forms: Diethylcarbamazine tablets B.P.

Synthesis



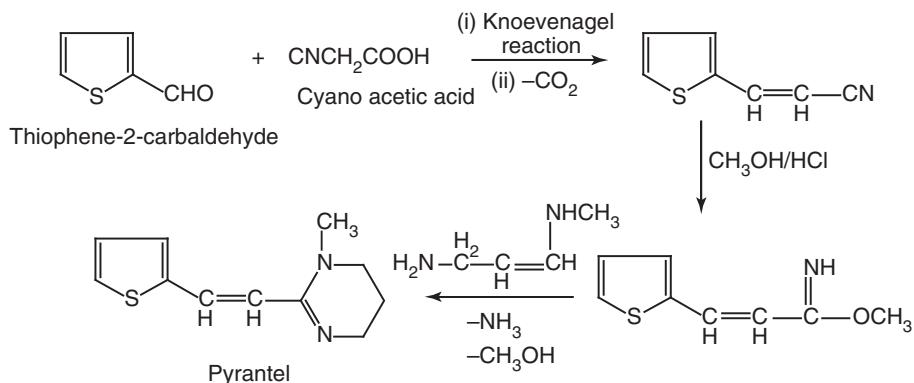
IV. Vinyl pyrimidines

Pyrantel (Antiminth, Combantrin)



1-Methyl-2-(2-(thiophen-2-yl)vinyl)-1,4,5,6-tetrahydropyrimidine

Synthesis



Mode of action: Pyrantel is a depolarizing neuromuscular blocking agent. It induces marked persistent activation of the nicotinic receptors, which result in spastic paralysis of the worm. It is an alternative to mebendazole in the treatment of ascariasis and enterobiasis.

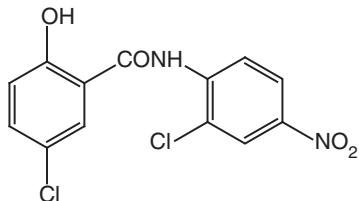
Properties and uses: It is a pale yellow or yellow powder, practically insoluble in water and in methanol, soluble in dimethyl sulphoxide. It is also as investigational drug for the treatment of hookworms, moniliformis, and trichostrongylus infections.

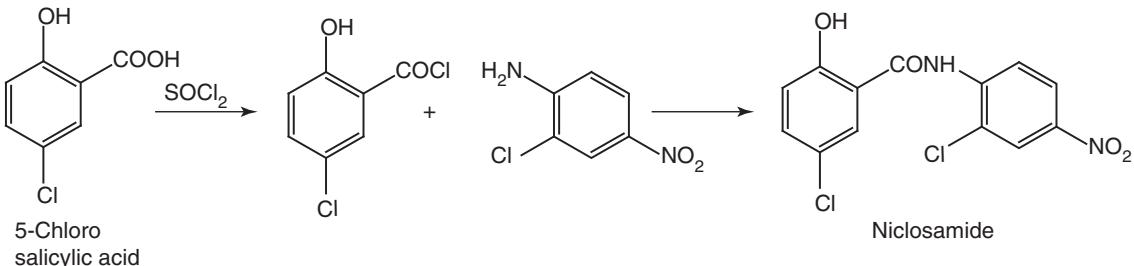
Assay: To the sample add acetic anhydride and glacial acetic acid, heat and stir. Allow to cool and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Doses: The dose for oral suspension or liquid is 50 mg/ml. A single dose of 11 mg/kg for ascariasis and enterobiasis.

V. Amides

Niclosamide (Niclocide)



Synthesis

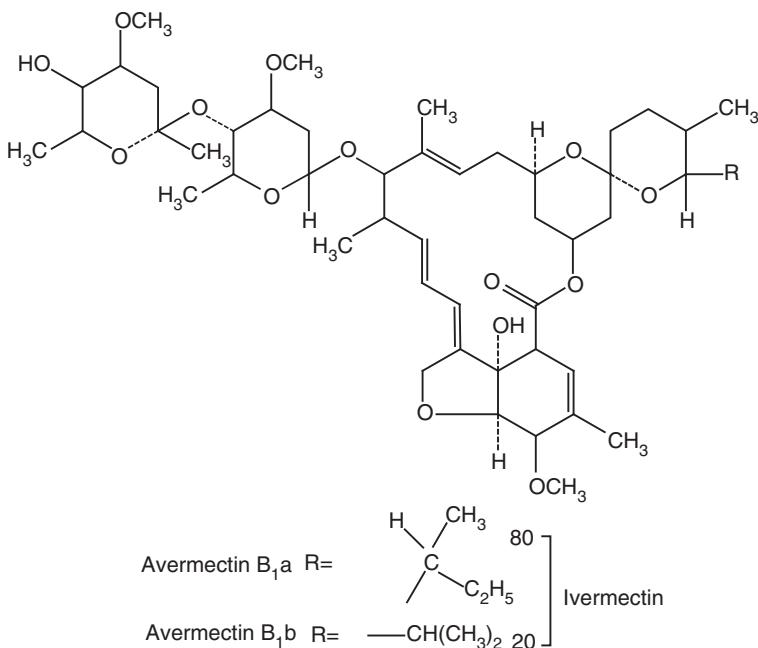
Mode of action: Niclosamide is also a potent molluscicide, which is effective against *Biomphalaria glabrata*, the principle action of the drug may be to inhibit anaerobic phosphorylation of adenosine diphosphate (ADP) by the mitochondria of the parasite, an energy producing process.

Properties and uses: Niclosamide exists as yellowish fine crystals, practically insoluble in water, sparingly soluble in acetone, and slightly soluble in ethanol. It is used as an anthelmintic.

Assay: Dissolve the sample in a mixture of equal volumes of acetone and methanol and titrate with 0.1 M tetrabutylammonium hydroxide. Determine the end point potentiometrically.

Dose: The dose orally to be taken after meals is 2 g chewable tablets.

Dosage forms: Niclosamide tablets B.P.

VI. Natural products**Avermectins (Mectizan)**

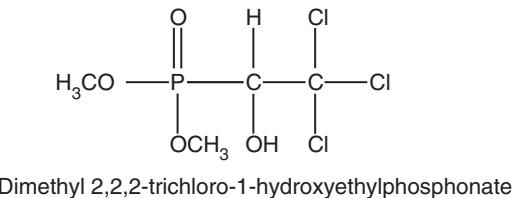
Mode of action: Avermectins specifically open the chloride channels in the invertebrate system distinct from the GABA-gated and glutamate-gated chloride channels.

Metabolism: It is metabolized and it gives 3-O-demethyl-22,23-dihydroavermectin B_{1a} monosaccharide.

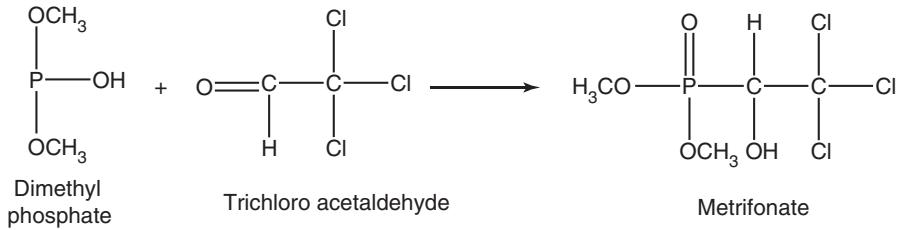
Properties and uses: Avermectins are macrocyclic lactones with broad antinematocidal activity. This class of compound was isolated from a fermentation broth of a soil actinomycetes (*Streptomyces avermitilis*). The drug avermectin is now effectively being used to treat and control *onchocerca volvulus*, the filarial infection responsible for liver blindness. Ivermectin is a mixture of B₁a and B₁b (80:20) and is prepared by catalytic reduction of ivermectin B₁ (Abamectin)

VII. Organophosphorus compounds

Metrifonate (Bilacil)



Synthesis

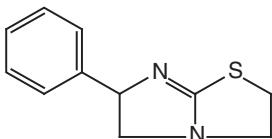
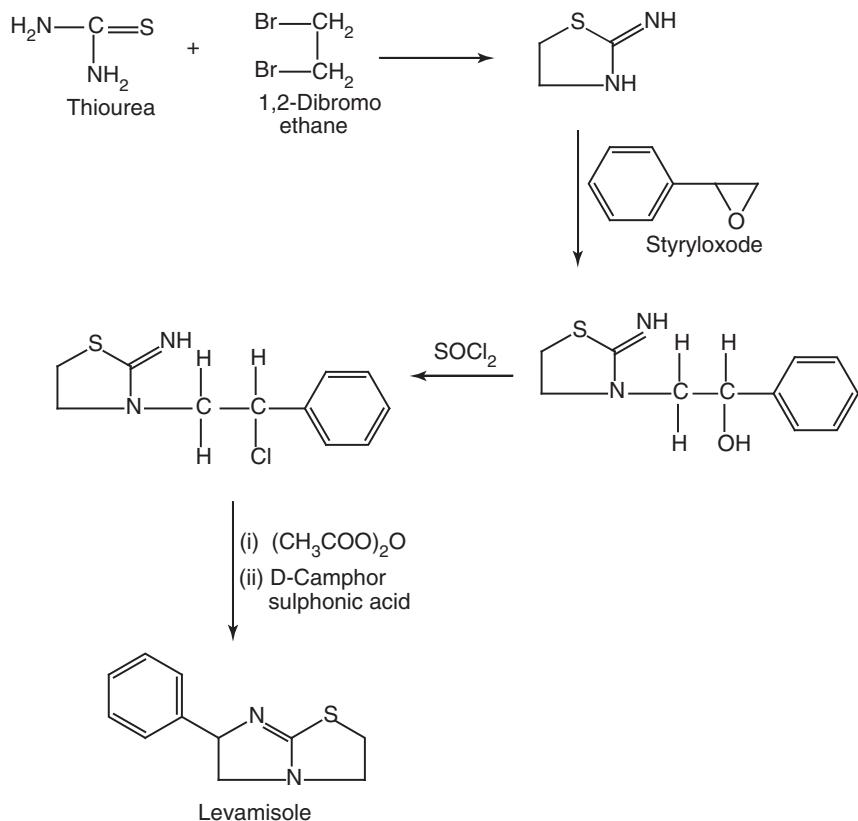


Mode of action: Metrifonate is metabolized and rearranged in vivo to dichlorvos, which inhibits acetyl cholinesterase.

Properties and uses: Metrifonate is a white crystalline powder, soluble in water, in acetone, and in alcohol, and very soluble in methylene chloride, used as an anthelmintic.

Assay: Dissolve the sample in alcohol, add ethanalamine, and allow to stand for 1 h at 20°C–22°C. Add chilled nitric acid maintaining the temperature of the mixture at 20°C–22°C and titrate with 0.1 M silver nitrate. Determine the end point potentiometrically.

Doses: The recommended dose is 7.5 to 10 mg/kg given orally three times at intervals of 2 weeks.

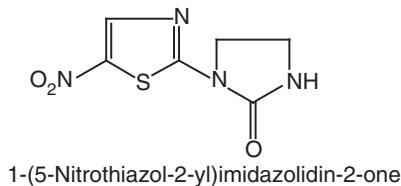
VIII. Midazothiazoles**Levamisole** (Bazole, Vermisol)6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole**Synthesis:**

Mode of action: It stimulates the ganglion in the worms, causes tonic paralysis, which results in the expulsion of live worms. These also interfere with the carbohydrate metabolism by inhibiting fumarate reductase.

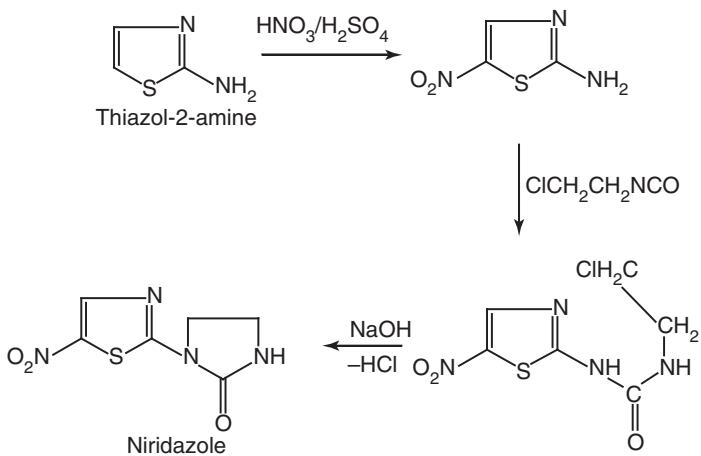
Dose: The administered dose is 15 mg as a single dose, repeated after 1 month to prevent recurrence.

IX. Nitro derivatives

Niridazole (Aambilhar)



Synthesis



Uses: Niridazole is used as an anthelmintic agent.

Dose: The recommended daily dose by oral route is 25 mg/kg daily in two divided doses.

PROBABLE QUESTIONS

1. Define anthelmintics and write the classification based on their chemical structure.
2. Write in detail about anthelmintics and provide suitable examples wherever necessary.
3. Outline the synthesis of the following drugs:
 - (a) Albendazole (b) Thiabendazole.
4. How will you classify anthelmintics on the basis of chemical structures? Write the structure, chemical name, and uses of two examples from each category.
5. Describe the synthesis, mode of action, and uses of oxaminquine.
6. Write a short note on the following:
 - (a) Pyrantel Pamoate (b) organophosphorus anthelmintic compounds.
7. What is avermectin? Describe its metabolism, mode of action, and uses.

8. Enumerate the various benzimidazoles derived from anthelmintics with their chemical structure, and write the synthesis, metabolism, and uses of mebendazole.
9. Mention an anthelmintic drug possessing quinoline nucleus, describe its synthesis, metabolism and uses.
10. Write a note piperazine derived anthelmintics

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Chapter 11

Antineoplastic Agents

INTRODUCTION

Antineoplastic agents are drugs used for the treatment of cancer, malignancy, tumour, carcinoma, sarcoma, leukaemia, or neoplasm (Greek neo = new, Plasm = formation). Neoplasm refers to a group of diseases caused by several agents, namely, chemical compounds and radiant energy. Cancer is characterized by an abnormal and uncontrolled, division of cells, which produces tumours and invades adjacent normal tissues. Often, cancer cells separate themselves from the primary tumour, and are carried by the lymphatic system to reach distant sites of the organs, where they divide and form secondary tumours (metastasis).

Cell Cycle Kinetics

Two key aspects of cellular life are the following:

1. DNA synthesis and mitosis to produce new cells.
2. Cell differentiation that produces specialized cells.

Limitations of Therapy

- Cancer cells very rapidly develop resistance to antineoplastic drugs.
- Differences between normal and neoplastic human cells are merely quantitative.
- Biochemical and morphological differences between normal and neoplastic cells are slight; therefore, antineoplastic agents are devoid of selective toxicity to tumour cells.
- Antineoplastic agents kill cells by first-order kinetics, that is, they kill a constant fraction of cells. However, some of the cancer cells elude killing and one of these cells may restabilize the tumour. It is extremely difficult to kill all the malignant cells.
- Most antineoplastic drugs are highly toxic to the patients.

Adverse Effects

The prominent adverse effects of antineoplastic drugs are exerted on rapidly proliferating normal tissues, in addition, to their chronic and cumulative toxicities.

- Bone marrow toxicity: Bleomycin, L-asparaginase.
- Hair follicle toxicity: Methotrexate, Vincristine, Cyclophosphamide, and Doxorubicin.
- Hepatotoxicity: Azathiopurine, Mercaptopurine, and L-asparaginase.
- Skin rashes: Vinca alkaloids, Nitrosourea, Anthracyclines, and Mitomycin C.
- Pulmonary toxicity: Bleomycin, Methotrexate, and Busulfan.
- Cardiac toxicity: Doxorubicin, Daunorubicin, and Anthracyclines.
- Other toxicities: Intestinal epithelium, central nervous system (CNS) toxicity, nephrotoxicity, immunosuppression, fever, anaphylaxis, cataracts, haemolytic anaemia, pancreatitis, pituitary insufficiency, adrenal insufficiency, coagulation problems, suppression of growth, and carcinogenicity.

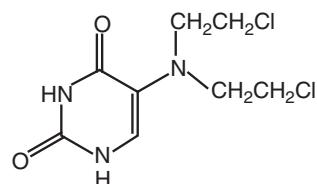
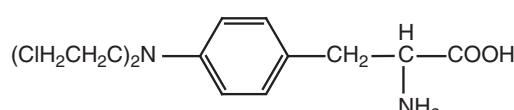
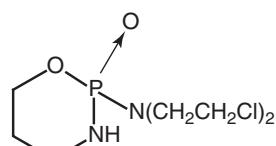
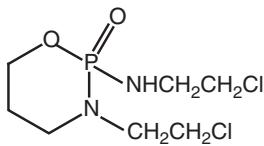
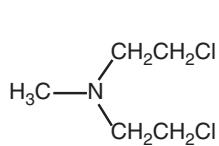
CLASSIFICATION

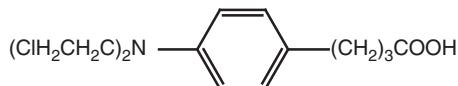
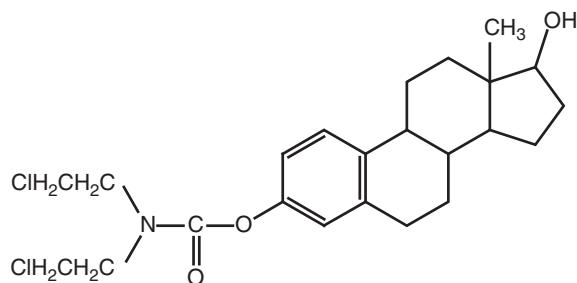
Antineoplastic agents are classified as follows:

- I. Alkylating agents
- II. Antimetabolites
- III. Antibiotics
- IV. Plant products
- V. Enzymes
- VI. Hormones
- VII. Immuno therapy
- VIII. Monoclonal antibodies
- IX. Radio-therapeutic agents
- X. Cyto-protective agents
- XI. Miscellaneous.

I. Alkylating agents

a. Nitrogen mustards

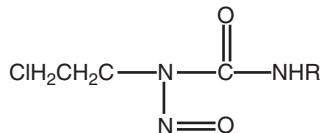


Chlorambucil**Estramustine**

Chloroquine nitrogen mustard

b. Alkyl Sulphonate

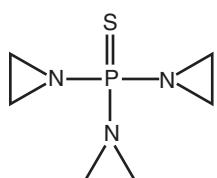
Busulfan

**c. Nitrosoureas**

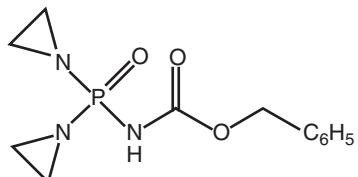
| Name | R |
|---------------|------------------------------------|
| Carmustine | $-\text{CH}_2\text{CH}_2\text{Cl}$ |
| Lomustine | |
| Semustine | |
| Chlorozotocin | Glucose |

d. Aziridines

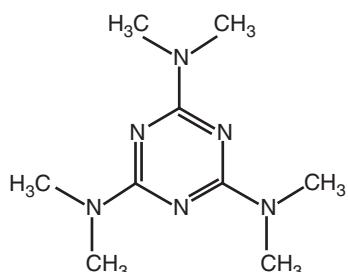
Thiotepa



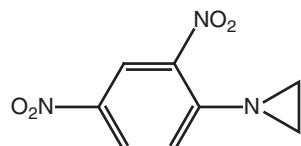
Benzo-tepa



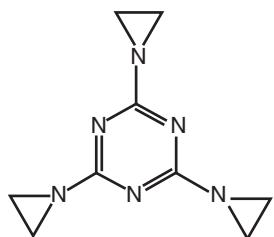
e. Altretamine



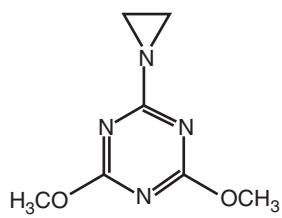
1,-(2,4-dinitro phenyl) aziridine



Triethylene melamine

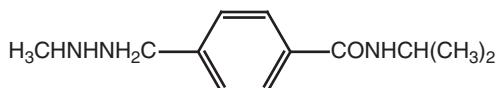


4 (1-aziridinyl)-2,6-dimethoxy triazine

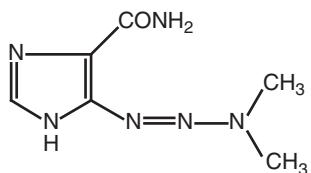


f. Methylhydrazines

Procarbazine

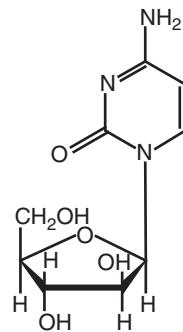
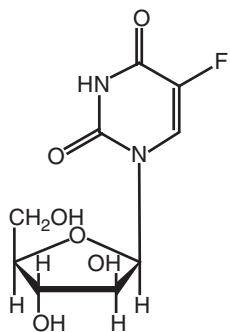
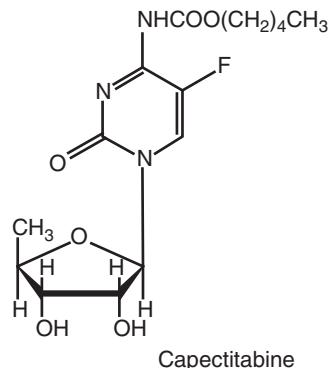
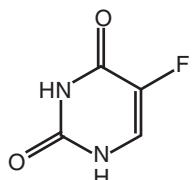


Dacarbazine

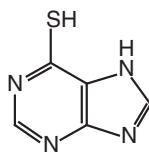


II. Antimetabolites

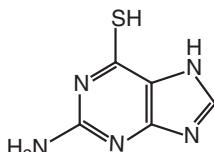
a. Pyrimidine analogues



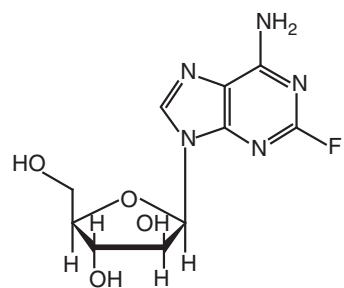
b. Purine Analogues



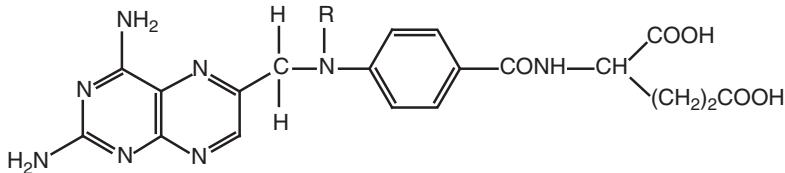
6-Mercaptapurine



6-Thioguanine

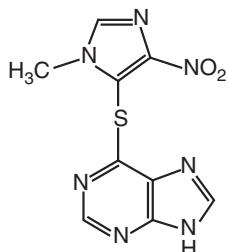


Fludarabine

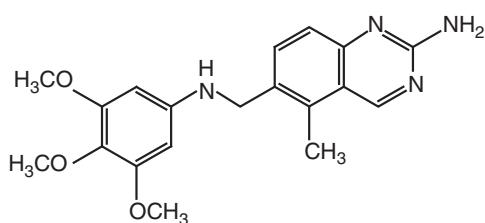
c. Folic acid analogues

R = H (Aminopterin)

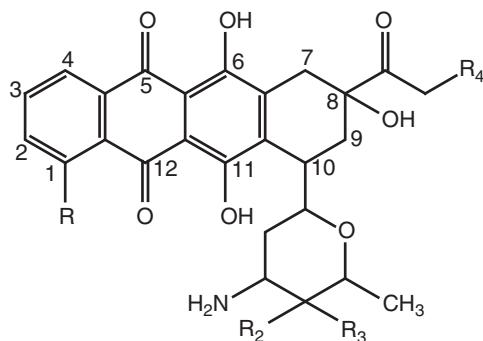
R = CH₃ (Methotrexate)



Azathiopurine



Trimetrexate

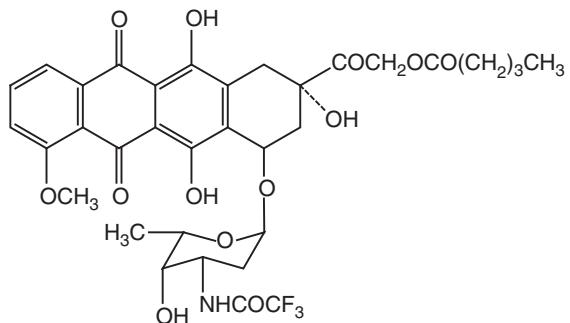
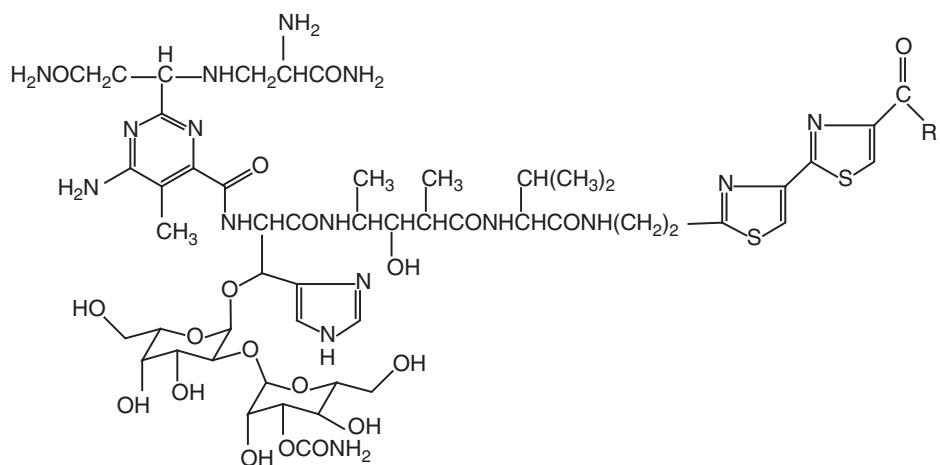
II. Antibiotics**a. Anthracyclines**

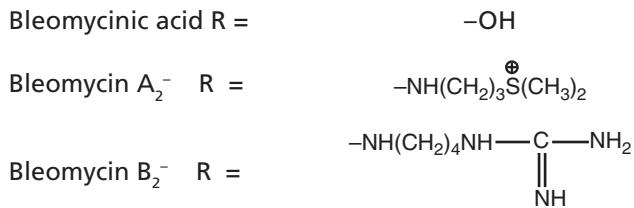
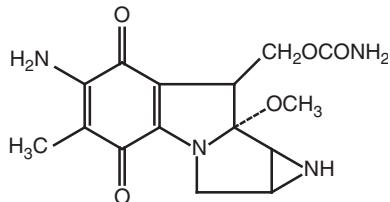
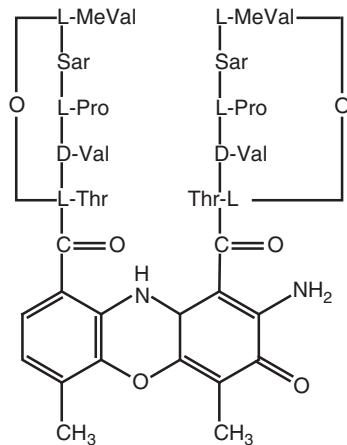
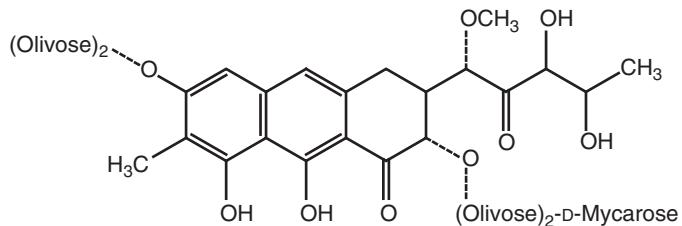
| Name | R ₁ | R ₂ | R ₃ | R ₄ |
|--------------|-------------------|----------------|----------------|----------------|
| Daunorubicin | -OCH ₃ | -H | -OH | -H |
| Doxorubicin | -OCH ₃ | -H | -OH | -OH |

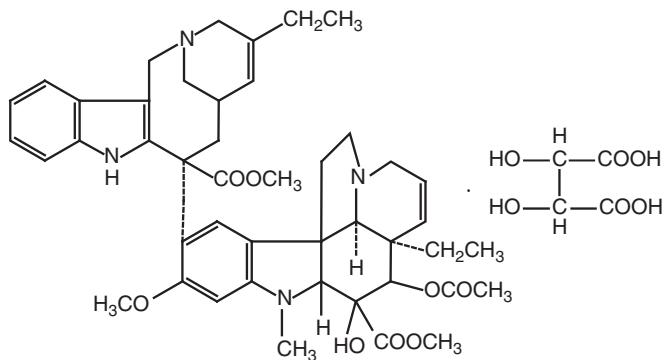
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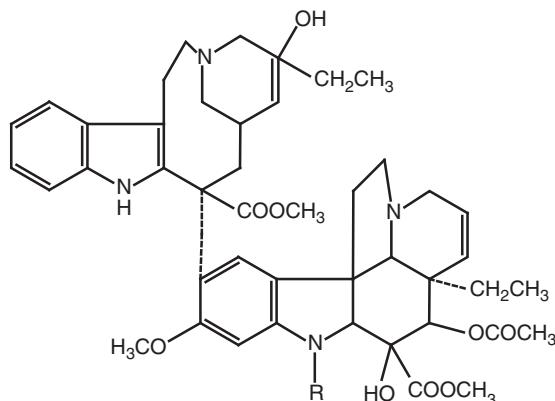
| Name | R ₁ | R ₂ | R ₃ | R ₄ |
|--------------|-------------------|----------------|----------------|----------------|
| Carminomycin | -OH | -H | -OH | -OH |
| Idarubicin | -H | -H | -OH | -H |
| Epirubicin | -OCH ₃ | -OH | -H | -OH |

Valrubicin**b. Bleomycins**

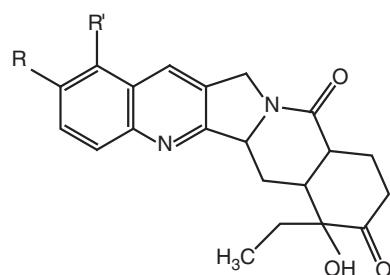
**c. Mitomycins****Mitomycin C****Dactinomycin C or Actinomycin D****Plicamycin or Mithramycin**

III. Plant products**a. Vinca alkaloids****Vinorelbine**

Vincristine, Vinblastine

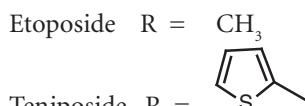
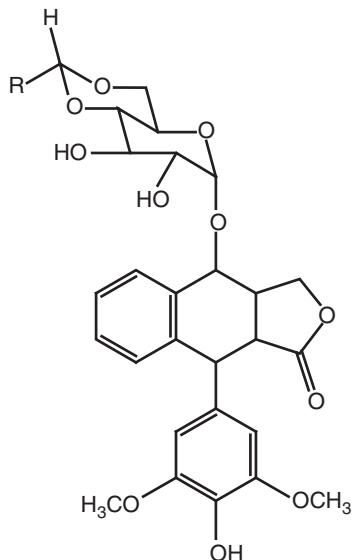


Vincristine R = CHO

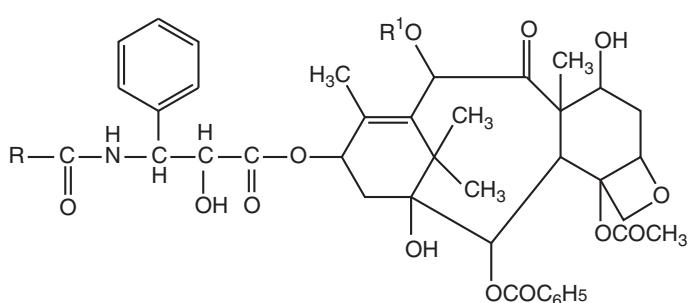
Vinblastine R = CH₃**b. Camptothecin Derivatives**

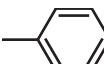
| Name | R | R' |
|--------------|------------------|------------------------------------|
| Camptothecin | -H | -H |
| Irinotecan | $-C_2H_5$ | $-OCO-N\left(C_6H_{11} \right)_2$ |
| Topotecan | $-CH_2N(CH_3)_2$ | -OH |

c. Epipodophyllo toxins



d. Taxol derivatives



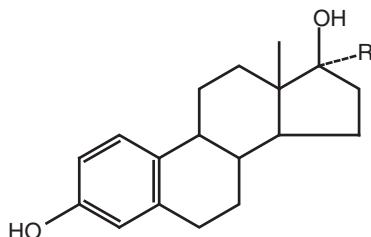
| Name | R | R^1 |
|------------|---|------------------|
| Paclitaxel |  | $-\text{COCH}_3$ |
| Docetaxel | $(\text{CH}_3)_3\text{CO}-$ | $-\text{H}$ |

IV. Enzymes

Examples—L-asparaginase, Pegaspargase

V. Hormones

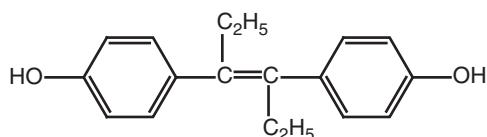
a. Estrogenic derivatives



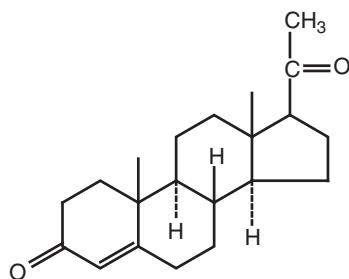
(i) 17β -Estradiol $\text{R} = \text{H}$

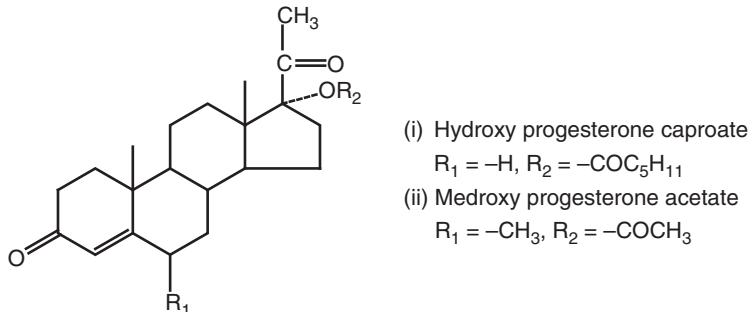
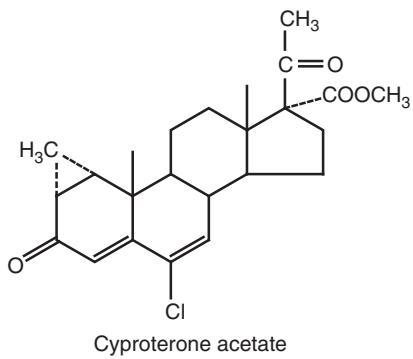
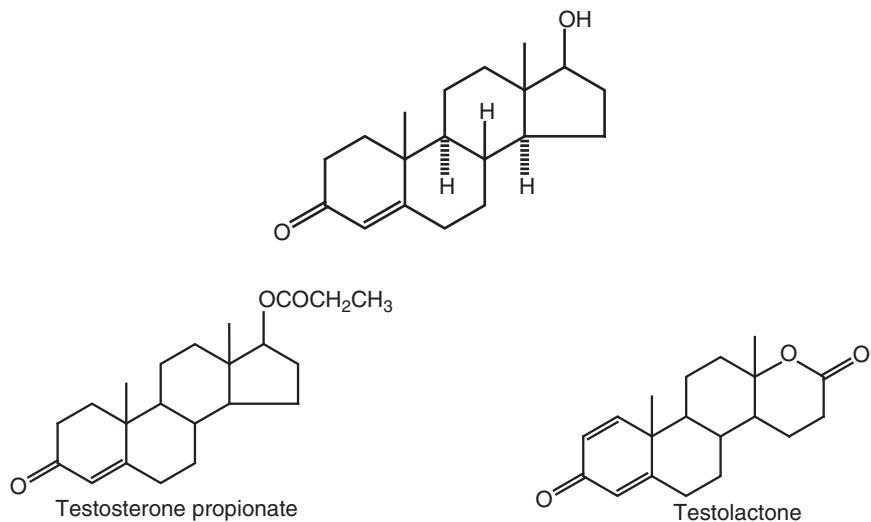
(ii) Ethynodiol diacetate $\text{R} = -\text{C}\equiv\text{CH}$

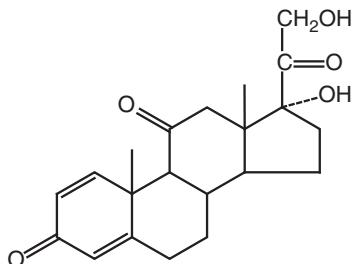
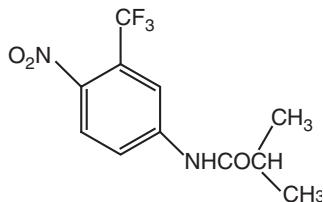
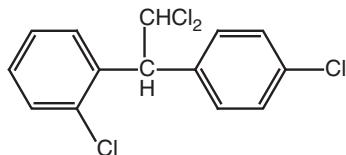
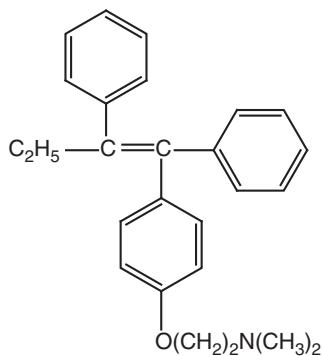
Diethylstilbestrol (nonsteroidal drug)

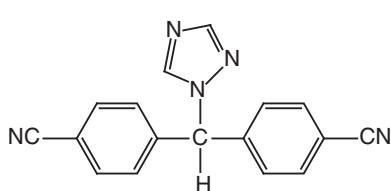
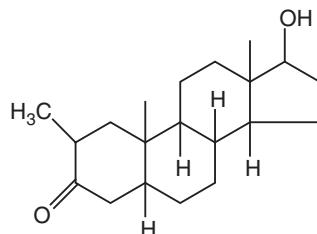
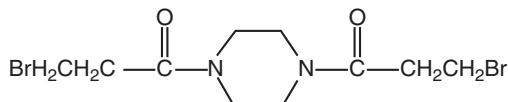
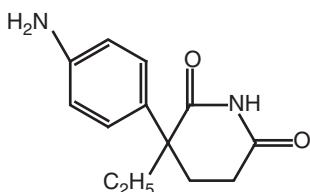


b. Progestin derivatives



Progesterone**Progestins****c. Testosterone derivatives****Testosterone**

d. Steroidal anti-inflammatory agents**Prednisone****Flutamide** (Nonsteroidal antiandrogen)**d. Miscellaneous agents****Mitotane****Tamoxifen**

Letrozole**Dromostanolone****Pipobroman****Aminoglutethimide****VI. Immuno therapy**

Interferon α -2a; Interferon-2b; Interferon α -n3; *Aldesleukin*, *Diftitox*, *Denileukin*; and *Bucillus calmette-Guerin* (BCG)

VII. Monoclonal Antibodies

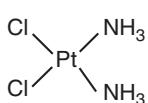
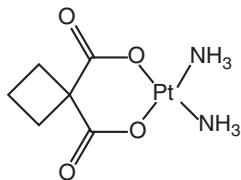
Rituximab, Gemtuzumab, Ozogamicin

VIII. Radio-therapeutic agents

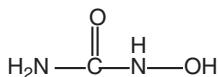
Chromic phosphate P-32; Sodium phosphate P-32; Sodium iodide I-131; Strontium-89 chloride; Samarium Sm 153 lexisronam

IX. Cytoprotective agents

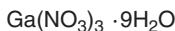
Mesna, Amifostine, Dexrazoxane

X. Miscellaneous**Cisplatin****Carboplatin**

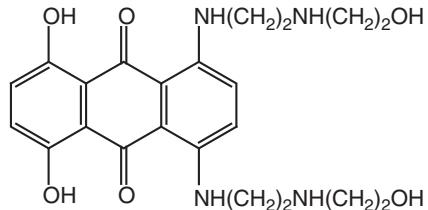
Hydroxy urea



Gallium nitrate



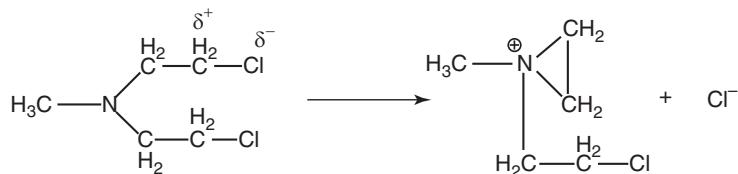
Mitoxantrone



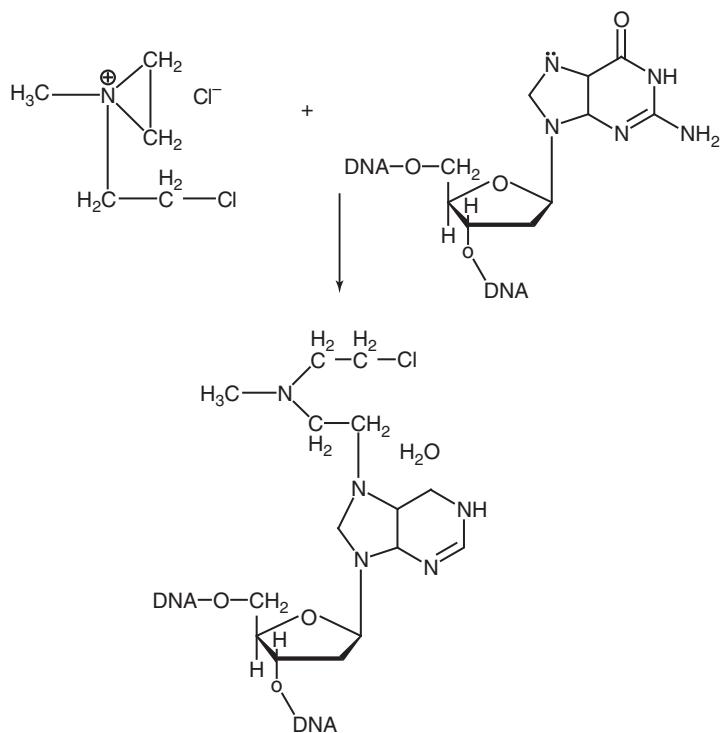
SYNTHESIS AND DRUG PROFILE

I. Alkylating agents

Step I: Intramolecular cyclization



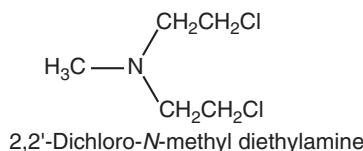
Step II: Nucleophilic attack of unstable aziridine



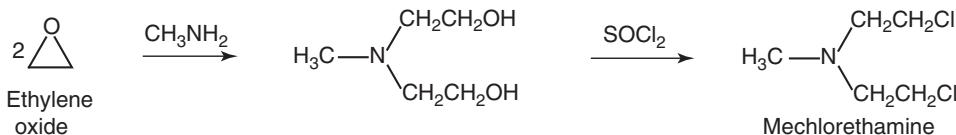
Mode of action: These compounds produce highly reactive carbonium ion intermediates that transfer alkyl group to cellular macromolecules by forming covalent bonds. It alkylates the 7th nitrogen atom of guanine residue in DNA, and results in cross-linking or abnormal base pairing. Initially, one of the 2-chloro ethyl side chain undergoes a first-order (SN_1) intramolecular cyclization with the release of Cl^- and formation of highly reactive ethyleniminium intermediate (Step I). By this reaction, tertiary amine is converted to an unstable quaternary ammonium compound, which react by forming carbonium ion. This precedes a second-order reaction (SN_2) nucleophilic substitution and alkylates the 7th N atom in guanine (Step II).

I. a. Nitrogen mustards

Mechlorethamine (Mustargen, Nitrogen mustard, Mustine)



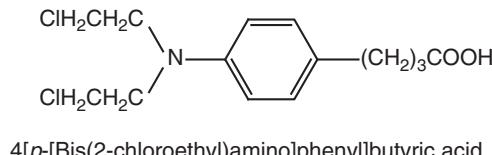
Synthesis



Properties and uses: It is a white crystalline hygroscopic powder, soluble in water and in alcohol. It is used in Hodgkin's disease in combination with vincristine, procarbazine, and prednisone. Most serious toxic reaction is bone marrow depression, which results in leukopenic and thrombocytopenia.

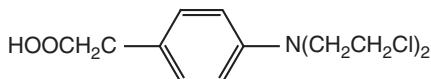
Dose: Single doses of 400 μg per kg body weight or a course of 4 daily doses of 100 μg per kg is normally administered by intravenous (IV) injection in a strength of 1 mg per ml in sodium chloride injection.

Chlorambucil (Leukaran)

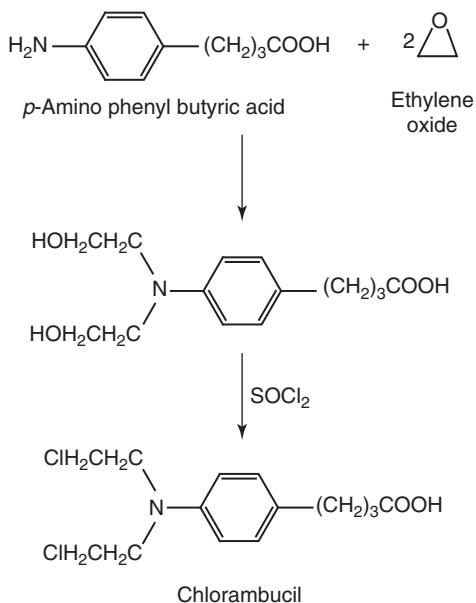


4-[*p*-(Bis(2-chloroethyl)amino)phenyl]butyric acid

Metabolism: This drug is active intact and also undergoes β -oxidation to provide an active phenylacetic acid mustard metabolite, which is responsible for some of the observed antineoplastic activity.



Synthesis



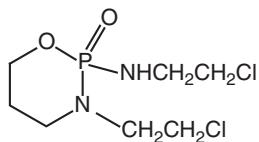
Properties and uses: Chlorambucil is a white crystalline powder, practically insoluble in water, and soluble in acetone and alcohol. It is used in the treatment of chronic lymphocytic leukaemia, macroglobulinaemia, lymphosarcoma, and Hodgkin's disease.

Assay: Dissolve the sample in acetone, add water, and titrate with 0.1 M sodium hydroxide, using phenolphthalein as indicator.

Dose: Usual oral doses are 100–200 μg per kg body weight daily (usually 4–10 mg as a single daily dose) for 4–8 weeks.

Dosage forms: Chlorambucil tablets I.P., B.P.

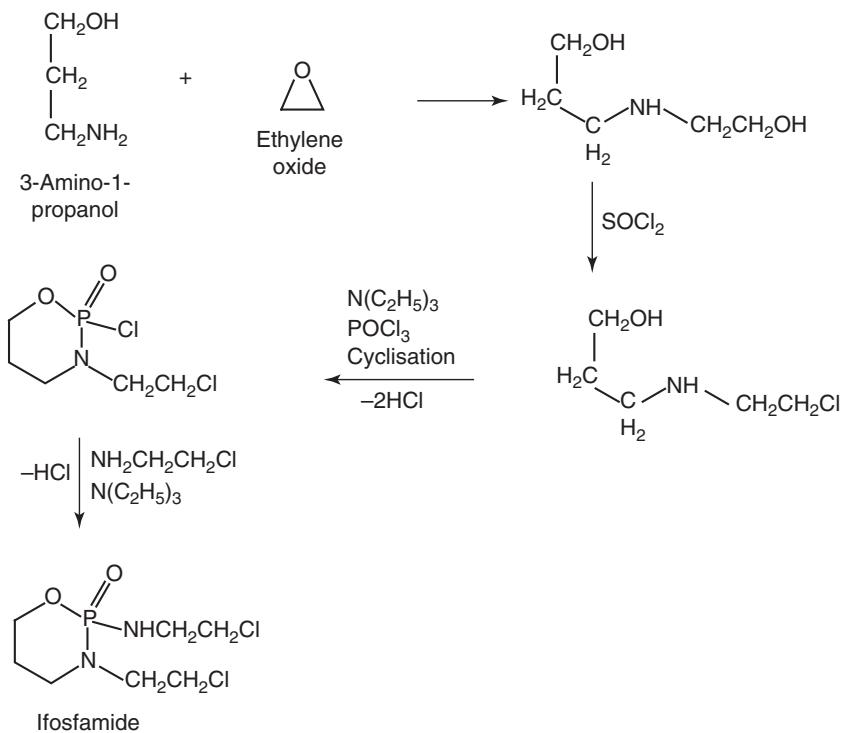
Ifosfamide (Holoxan)



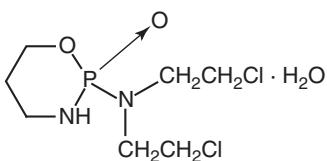
3-(2-Chloroethyl)-2-(2-chloroethyl)amino tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-oxide

Properties and uses: Ifosfamide is a white crystalline hygroscopic powder, soluble in water and methylene chloride. It is used for testicular cancer, leukaemia, ovarian, and breast carcinoma.

Assay: It is assayed by adopting liquid chromatography technique.

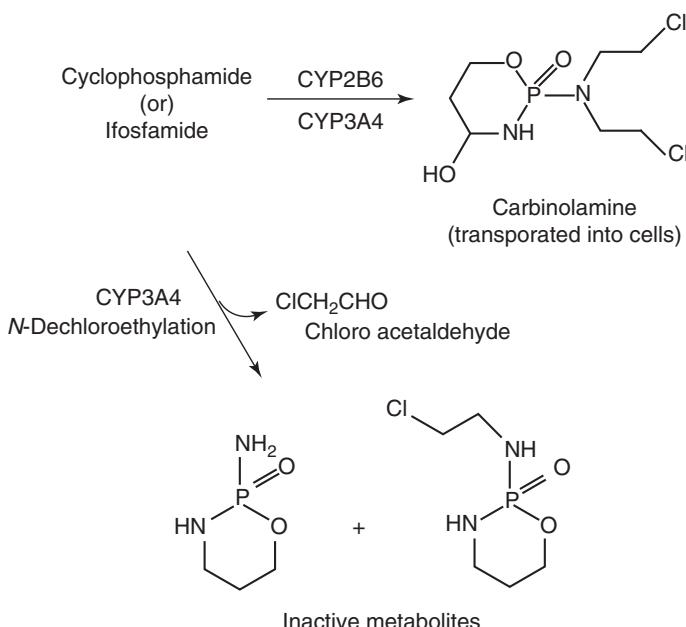
Synthesis

Dose: For the treatment of solid tumours of cervix, lungs, thymus, testes, and ovary; sarcoma; lymphoma of adults different licensed dosage regimens are available. Regimen 1: 8–12 g per m^2 divided over 3–5 days, repeat course every 2–4 weeks. Regimen 2: 6 g per m^2 divided over 5 days, repeat course every 3 weeks. Regimen 3: 5–6 g per m^2 (maximum, 10 g), given as a single 24 h infusion, repeat course every 3–4 weeks.

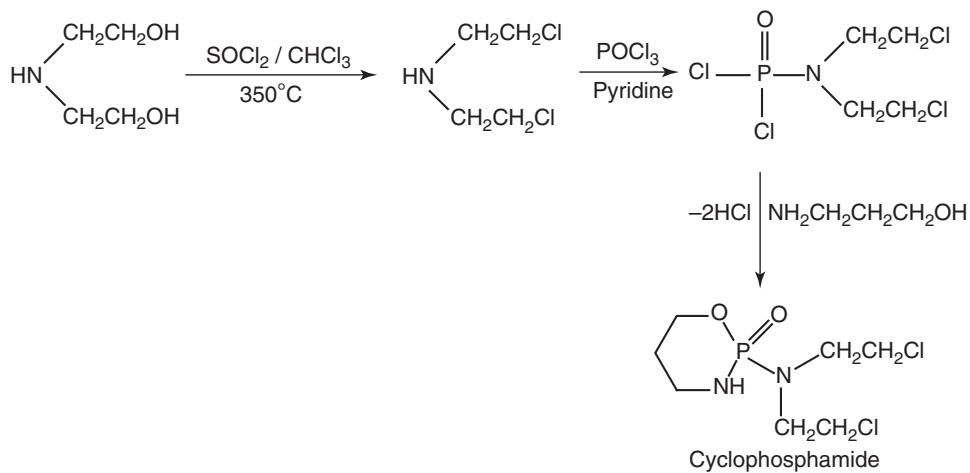
Cyclophosphamide (Cytoxin)

2-[Bis(2-chloroethyl)amino] tetrahydro-1, 3, 2-oxazaphosphorin-2-oxide monohydrate

Metabolism: The initial metabolic step is mediated primarily by CYP2B6 and involves hydroxylation of the oxazaphosphorine ring to generate a cabinolamine. CYP3A4 also catalyzes an inactivating *N*-dechloroethylation reaction, which yields nephrotoxic and neurotoxic chloroacetaldehyde.



Synthesis



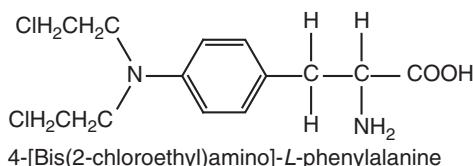
Properties and uses: Cyclophosphamide is a white crystalline powder, soluble in water and alcohol. It is one among the widely used anticancer drugs and it is superior to many alkylating agents. It is active against multiple myeloma chronic lymphocytic leukaemias, acute leukaemia of children, Hodgkin's disease, breast, ovarian cancer, and lung cancer.

Assay: Dissolve the sample in sodium hydroxide solution in ethylene glycol, boil under reflux, and rinse with water, add 2-propanol, dilute nitric acid, 0.1 M silver nitrate, and ferric ammonium sulphate solution and titrate with 0.1 M ammonium thiocyanate.

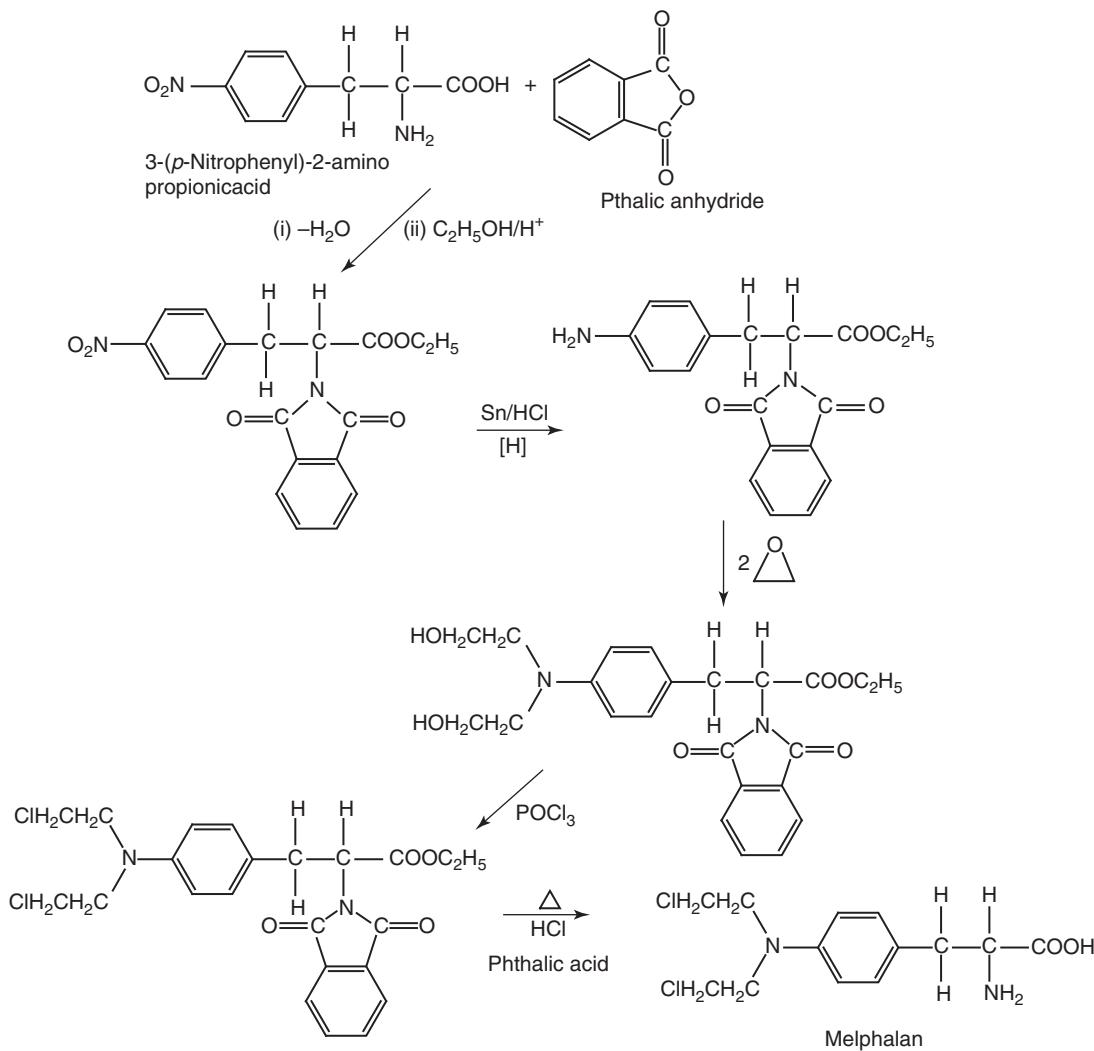
Dose: Initial adult dose of 40–50 mg per kg given intravenously in divided doses over 2–5 days and for children 2–8 mg per kg daily through IV injection.

Dosage forms: Cyclophosphamide injection I.P., B.P., Cyclophosphamide tablets I.P., B.P.

Melphalan (Alkeran)



Synthesis



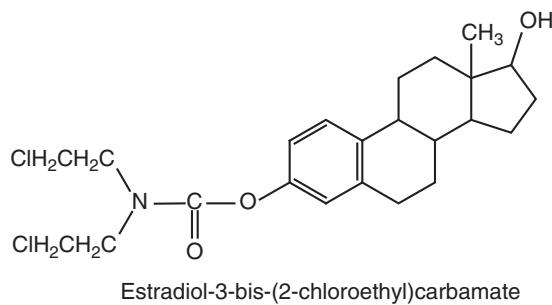
Properties and uses: Melphalan is a white powder, practically insoluble in water and ether, slightly soluble in methanol and dissolves in dilute mineral acids. Melphalan is active against multiple myeloma, breast, testicular, and ovarian carcinoma.

Assay: To the sample add 20% w/v solution of potassium hydroxide, heat on a water bath, add water and nitric acid, cool, and titrate with 0.1 M silver nitrate. Determine the end point potentiometrically.

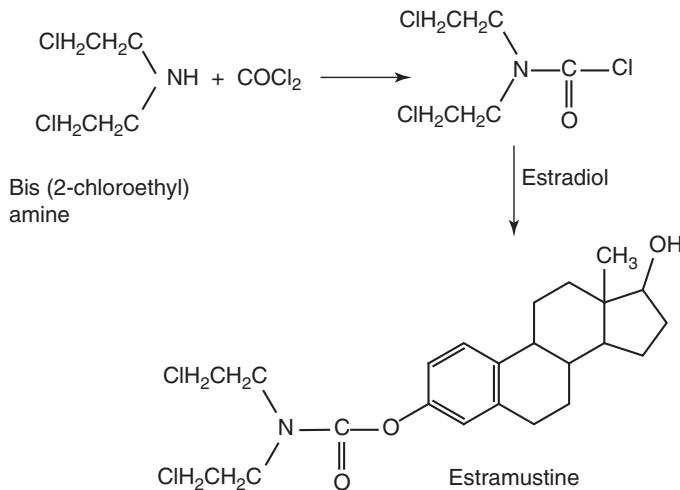
Dose: Dose orally is 150 µg per kg body weight daily for 4–7 days combined with prednisone 40–60 mg daily; 250 mg per kg daily for 4–5 days; or 6 mg daily by 2–3 weeks.

Dosage forms: Melphalan injection I.P., B.P., Melphalan tablets I.P., B.P.

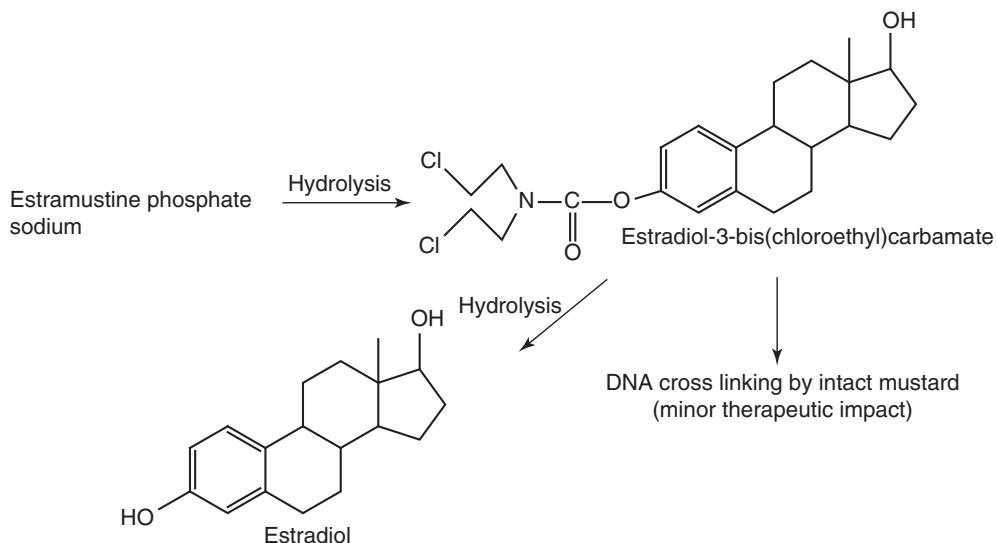
Estramustine



Synthesis



Metabolism: The resonance-stabilized mustard-like antineoplastic agent utilizes an oestradiol carrier to deliver to the steroid dependent prostate tissue selectively, and its use is limited to the palliative treatment of progressive prostate cancer. In estramustine sodium phosphate, the essential 17β -hydroxy group has been esterified with phosphoric acid, and the C-3 phenol has been carbamylated. The body still, however, transports the basic steroid pharmacophore into the cells. The ionized sodium phosphate ester of the active 17β -hydroxy group makes the compound water-soluble and to be able to distribute it in the blood. The ester is readily cleaved during absorption to provide the active 17β -hydroxy group.

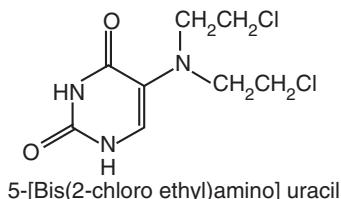


Properties and Uses: Estramustine sodium phosphate is a white powder, soluble in water and in methanol, and very slightly soluble in absolute ethanol. It is an alkylating agent, which is approved for metastatic/progressive cancer of the prostate, but is also active for advanced breast cancer. It causes nausea and vomiting, delayed bone-marrow depression, mild gynecomastia, thrombophlebitis, occasional myocardial infarction, hypertension, hypoglycaemia, and hepatotoxicity.

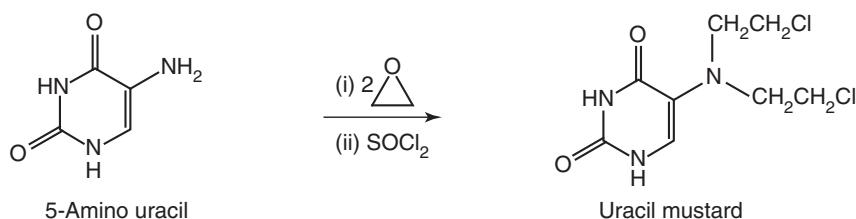
Assay: To the sample add 1M sodium hydroxide and boil under a reflux condenser. Cool and add 0.1 M silver nitrate and nitric acid dilute with water. Filter and titrate the excess of silver nitrate with 0.1 M ammonium thiocyanate using ammonium iron (III) sulphate as indicator.

Dosage forms: Estramustine phosphate capsules B.P.

Uracil Mustard



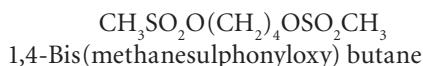
Synthesis



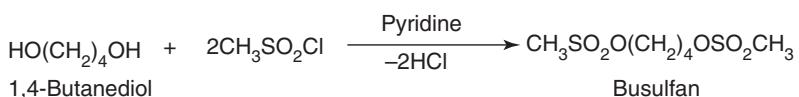
Properties and uses: It is an off-white crystalline powder, odourless, and soluble in water or alcohol. It is used for the treatment of prostate cancer.

I. b. Alkyl sulphones

Busulfan (mylearn)



Synthesis



Metabolism: Busulfan undergoes sulphur stripping due to interaction with thiol compounds such as glutathione or cysteine and leads to loss of two equivalents of methosulphonic acid and formation of cyclic sulphonium intermediates, which is then converted into a metabolite 3-hydroxythiolane-1, 1-dioxide.

Properties and uses: Busulfan is a white crystalline powder, very slightly soluble in water and alcohol, soluble in acetone and acetonitrile. It is used in the treatment of chronic granulocytic leukaemia.

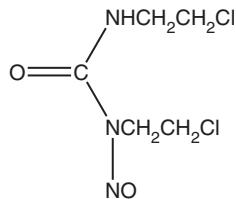
Assay: To the sample add water, boil under a reflux condenser, cool and titrate with 0.1 M sodium hydroxide using phenolphthalein as indicator until a pink colour is obtained.

Dose: For granulocytic leukaemia, the daily oral dose is 60 µg per kg body weight, up to a maximum single daily dose of 4 mg, and to be continued till the white cell count falls between 15,000 and 25,000 per mm³

Dosage forms: Busulfan tablets I.P., B.P.

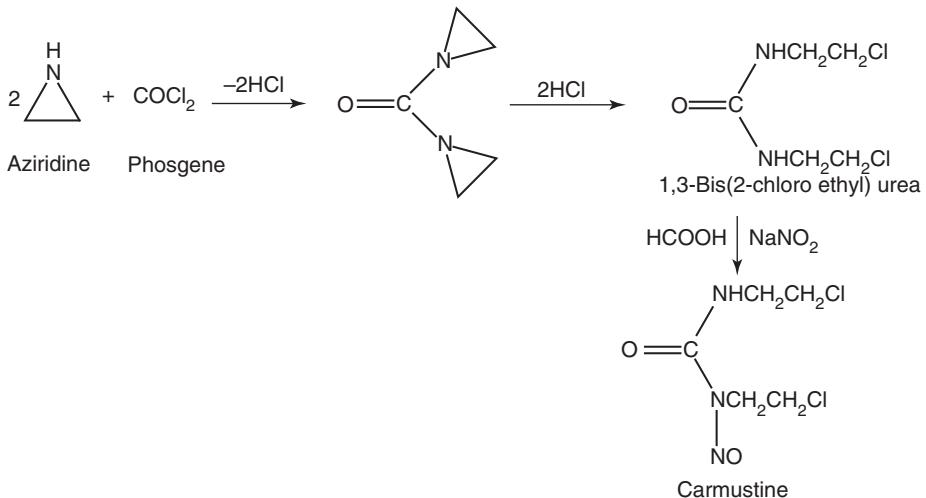
I.c. Nitrosourea

Carmustine



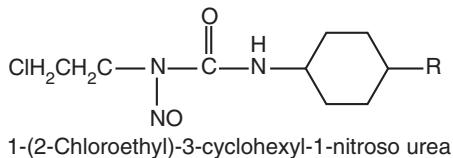
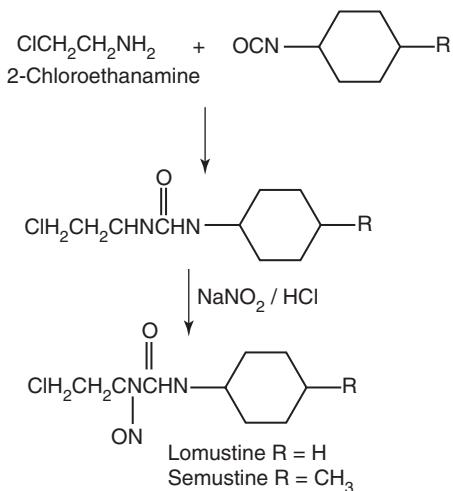
N,N'-Bis(2-chloro ethyl)-*N*-nitroso urea

Properties and uses: Carmustine is a yellowish granular powder, very slightly soluble in water, very soluble in methylene chloride, and soluble in ethanol. It is used against brain tumours and leukaemia, which have metastasized to the brain, and these multiple states respond to a combination of carmustine and prednisone.

Synthesis

Assay: Dissolve the sample in ethanol, dilute with water, and measure the absorbance at the maxima at 230 nm using ultraviolet spectrophotometer.

Lomustine and Semustine (Ceenu, Cinu)

**Synthesis**

Properties and uses: Lomustine is a yellow crystalline powder, practically insoluble in water, soluble in acetone, methylene chloride, and alcohol. It is used against both primary and metastatic brain tumours and as secondary therapy in relapsed Hodgkin's disease.

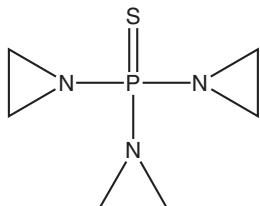
Assay: Dissolve the sample in alcohol, add potassium hydroxide, and boil under a reflux condenser. Add water and nitric acid, cool and titrate with 0.1 M silver nitrate. Determine the end point potentiometrically. Perform a blank titration.

Dose: Usual dose is 130 mg/m² orally every 6 weeks.

Dosage forms: Lomustine capsules B.P.

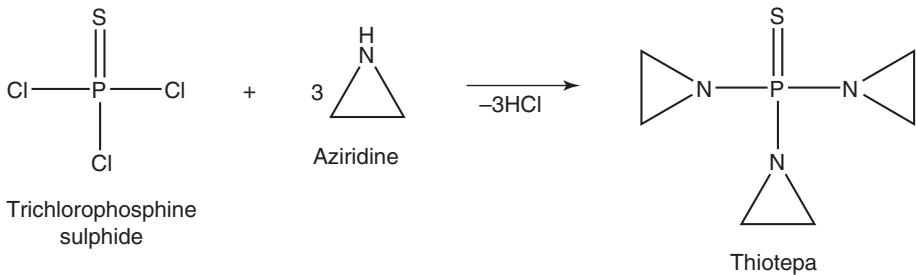
I. d. Aziridines

Thiotepa



Tri-(1-aziridyl) phosphine sulphide

Synthesis

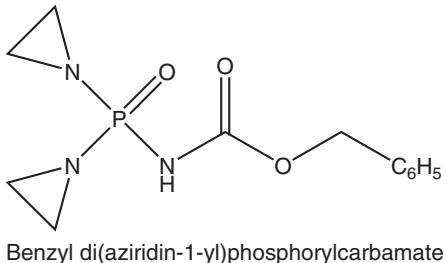
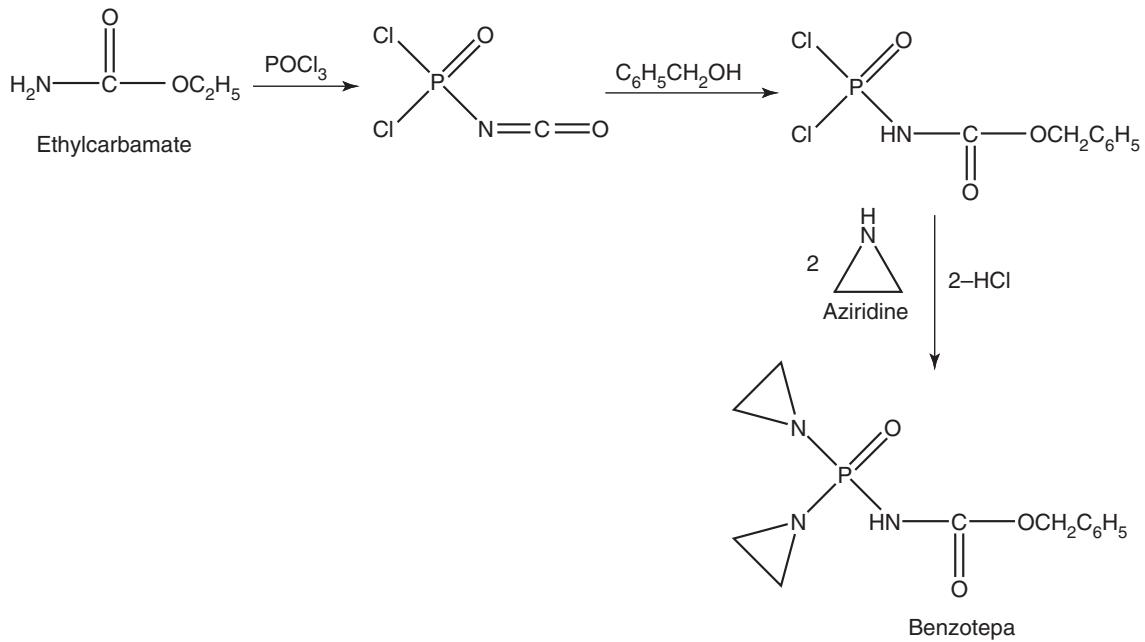
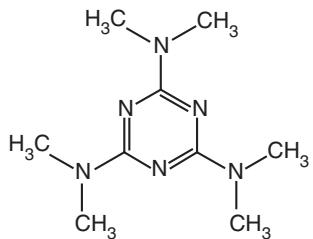


Metabolism: Thiotepa undergoes oxidative desulphuration forming an active cytotoxic metabolite known as Triethylene phosphoramide (TEPA). Aziridine metabolism occurs, with liberation of ethanolamine.

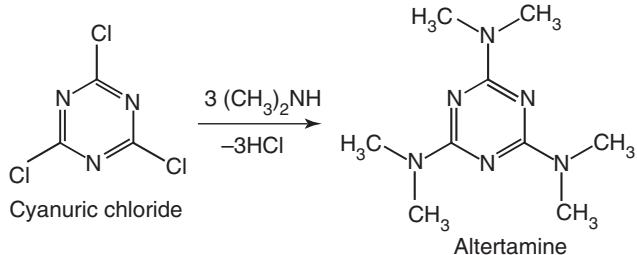
Properties and uses: Thiotepa exists as white crystalline flakes, freely soluble in water, chloroform, and ethanol. It is used as cytotoxic alkylating agent.

Assay: Transfer the sample to an iodine flask with the aid of 20% w/v solution of sodium thiosulphate and titrate immediately with 0.1 M hydrochloric acid, using methyl orange as indicator, until a faint red colour persists for 10 sec. Stopper the flask, allow to stand for 30 min, and titrate with 0.1 M sodium hydroxide using phenolphthalein as indicator. Subtract the volume of 0.1 M sodium hydroxide used from the volume of 0.1 M hydrochloric acid used.

Dosage forms: Thiotepa injection I.P., B.P.

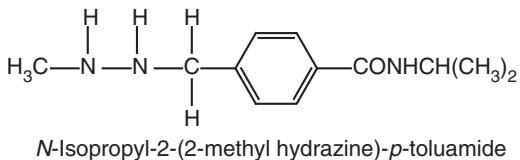
Benzotepa**Synthesis****Altretamine***N*²,*N*²,*N*⁴,*N*⁴,*N*⁶,*N*⁶-Hexamethyl-1,3,5-triazine-2,4,6-triamine

Synthesis



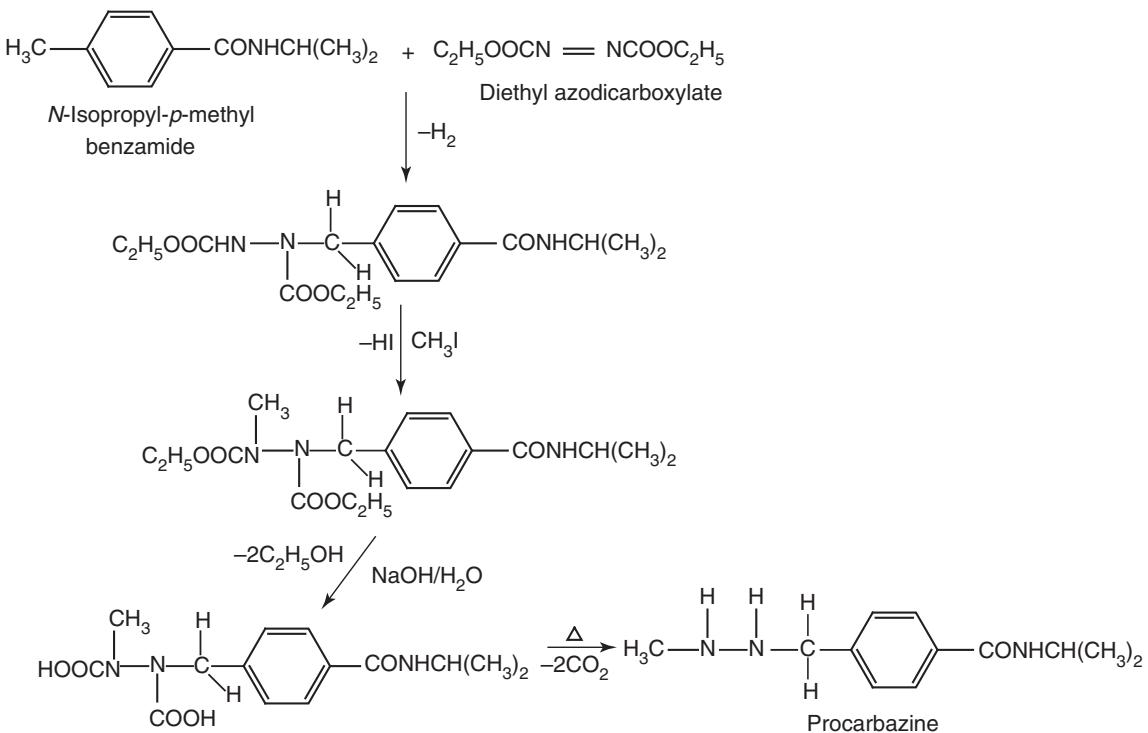
I.e. Methyl hydrazines

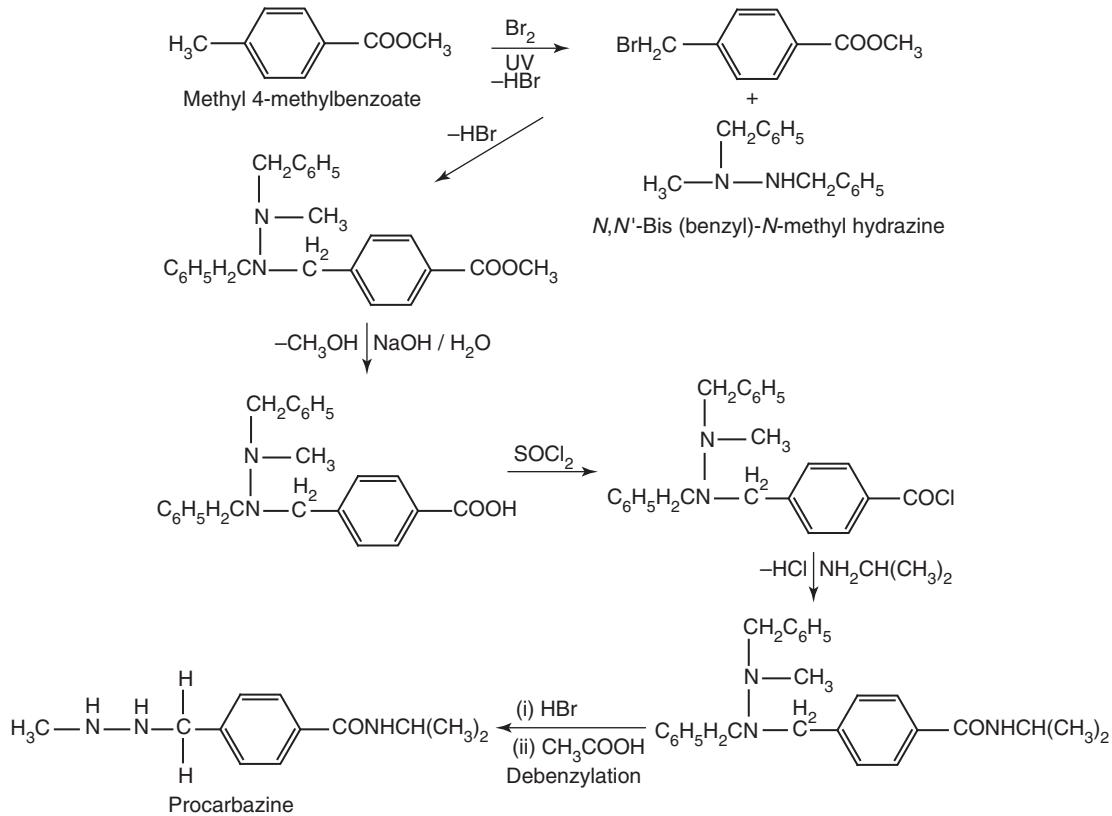
Procarbazine



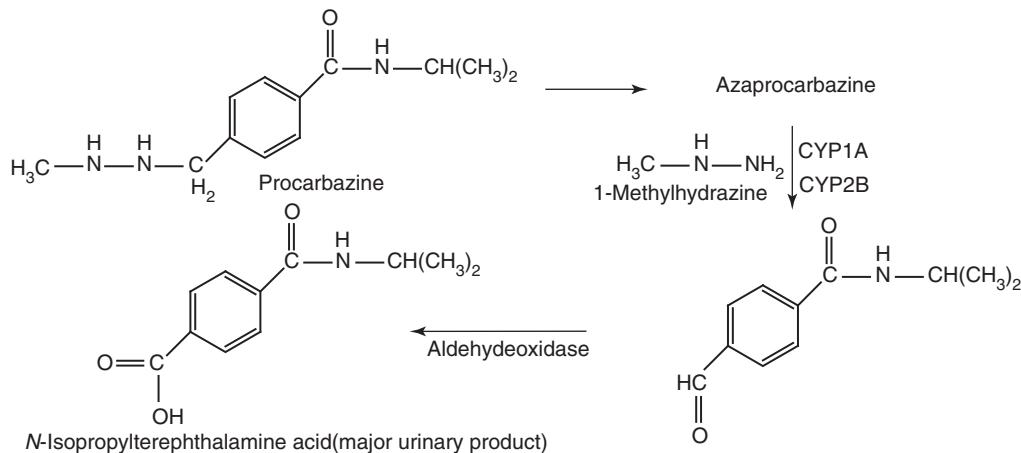
Synthesis

Route-I. From: *N*-Isopropyl-*p*-methyl benzamide



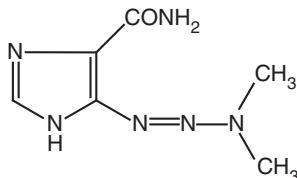
Route-II. From: Methyl-4-methylbenzoate

Metabolism: It is extensively metabolized in liver and 70% of the administered dose is excreted in the urine as *N*-isopropylterephthalamic acid.



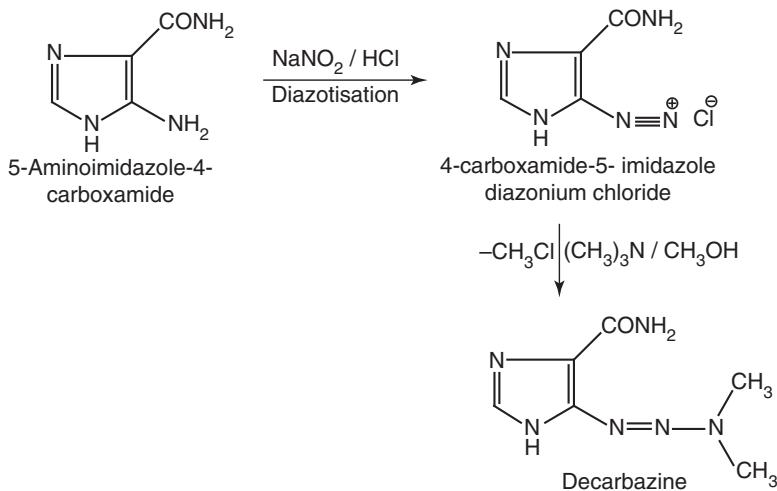
Properties and uses: It exists as white to pale yellow crystalline powder with a slight odour and a bitter taste, soluble in water or alcohol, slightly soluble in chloroform, but insoluble in ether. Solutions are acid to litmus, stable in light, slowly oxidized in air, and stable at room temperature (in the presence of oxygen, oxidation is accelerated by increased temperature).

Decarbazine

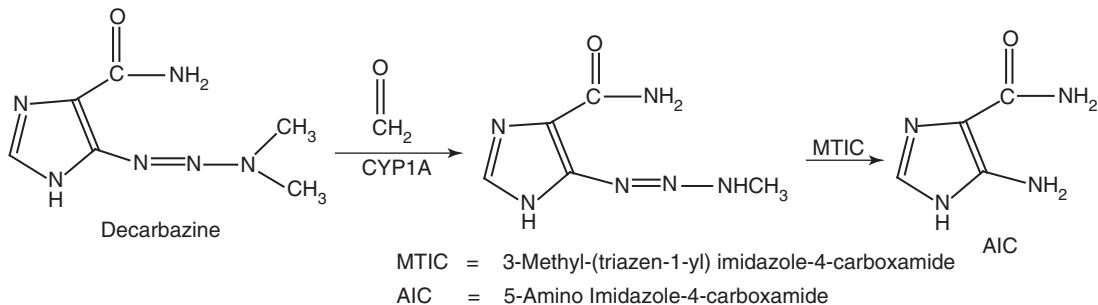


5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboxamide

Synthesis



Metabolism: Approximately 40% of the drug is excreted unchanged, but both the 5-amino imidazole-4-carboxamine and the carboxylic acid are seen in urine as metabolites.



Properties and uses: It is used as a cytotoxic agent, which is colourless to ivory coloured microcrystalline powder, soluble in water or alcohol.

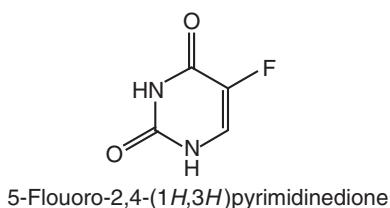
II. Antimetabolites

Mode of action: These are analogues that resemble normal compounds of co-enzymes, which participate in the DNA synthesis and competitively inhibit the utilization of normal substrate or incorporates to make dysfunction.

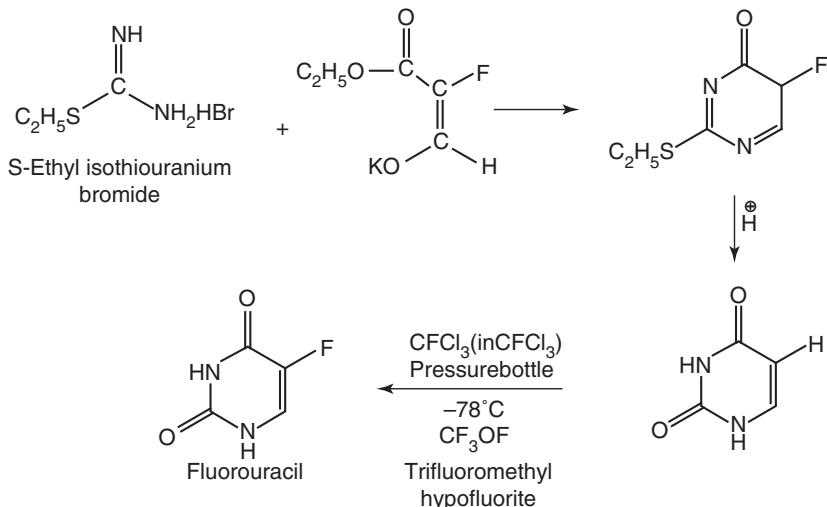
II. a. Pyrimidine analogues

The structural modification of these metabolites may be on the pyrimidine ring.

5-Fluorouracil



Synthesis



Mode of Action: It is converted into 5-fluoro-2-deoxy uridine monophosphate, which inhibits thymidilate synthetase and blocks the conversion of deoxy uridic acid to deoxy thymidilic acid. For binding to thymidilate synthetase, this fluorinated pyrimidine prodrug must be converted to its deoxyribonucleotide. The active form of fluorouracil differs from the endogenous substrate only by the presence of the 5-fluorogroup, which holds the key to the cytotoxic action of this drug.

Metabolism: 20% of drug is excreted unchanged in urine and rest undergoes metabolism by polymorphic dihydro pyrimidine dehydrogenase to produce 5-fluoro 5, 6, dihydrouracil, which is converted to α -fluorouridopropionic acid by dihydropyrimidinase and to α -fluoro β -alanine by β -ureidopropionase.

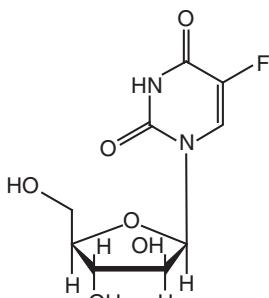
Properties and uses: Fluorouracil is a white crystalline powder, sparingly soluble in water, and slightly soluble in alcohol. It is used topically in the treatment of pancancerous dermatoses, especially actinic keratosis, for which it is the treatment of choice, if the lesions are multiple, even if the lesions that are not clinically discernable respond. For this reason, the drug is applied to the entire affected area. Healing

continues for 1 to 2 months after treatment. The drug does not affect nonkeratotic lesion. It is a secondary immuno-suppressive agent, and therefore, is not used in organ transplantation. It is the most active drug available for colorectal cancer. It is effective in the management of the breast, colon, pancreas, rectum, and stomach. It may have devastating bone marrow and gastrointestinal toxicity.

Assay: Dissolve the sample in dimethylformamide by gentle warming, cool and titrate with 0.1 M tetrabutylammonium hydroxide, using thymol blue as indicator.

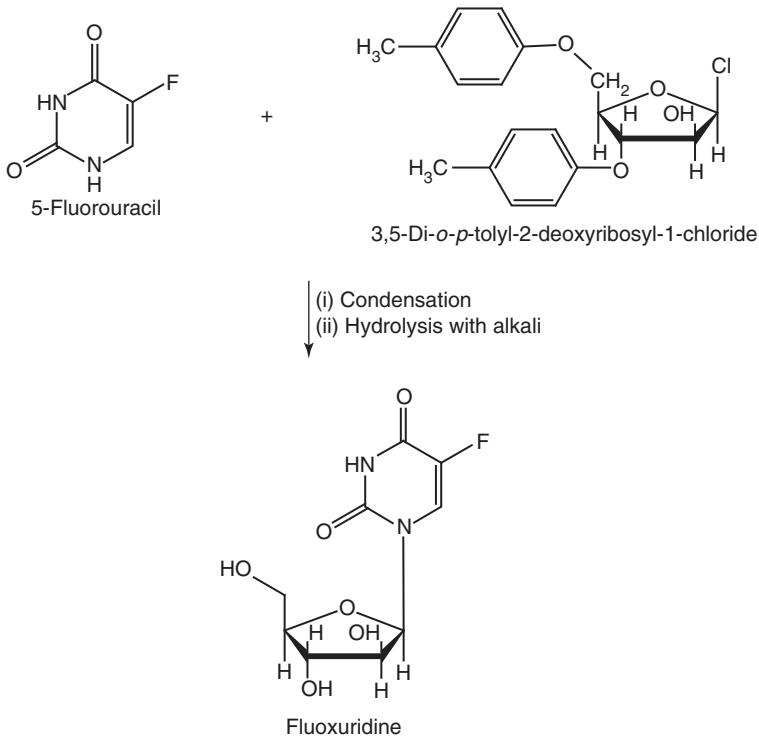
Dosage forms: Fluorouracil injection I.P., B.P., Fluorouracil cream B.P.

Fluoxuridine



1-(2-Deoxy-D-ribofuranosyl)-5-fluorouracil

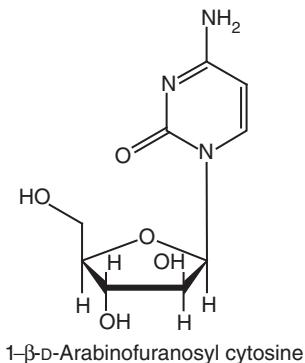
Synthesis



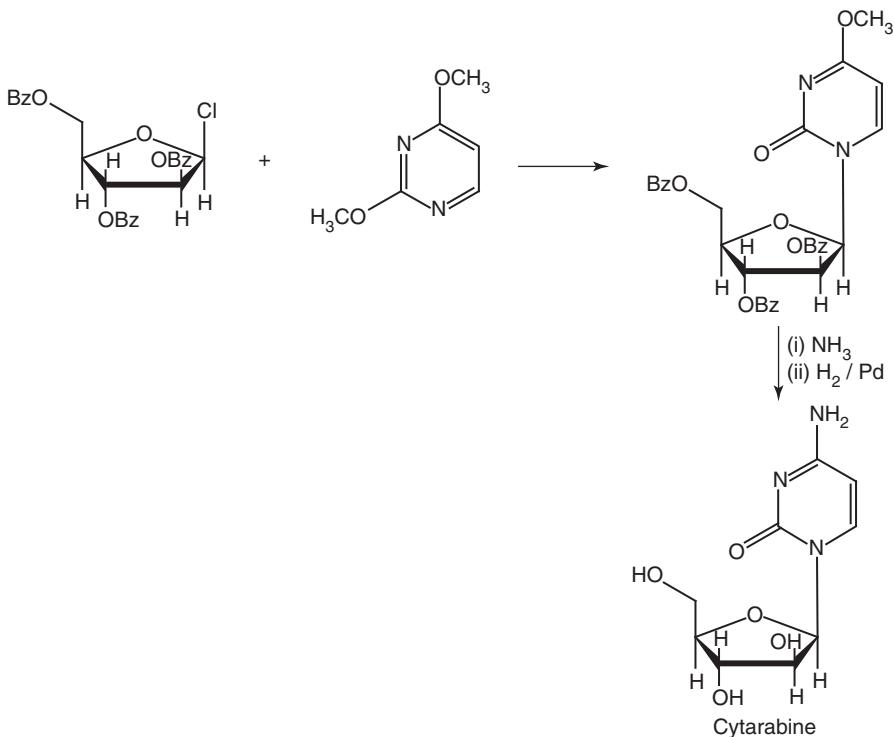
Metabolism: This deoxyribonucleoside prodrug is bioconverted via 2'-deoxyuridine kinase-mediated phosphorylation to the same active 5-fluoro-dUMP structure generated in the multistep biotransformation of fluorouracil.

Properties and uses: It is a white to off-white odourless powder, which is soluble in water, alcohol, or chloroform. Fluoxuridine is a prodrug of 5-fluorouracil. It is used for the palliation of gastrointestinal adenocarcinoma metastatic to the liver in patients who are considered incurable by surgery.

Cytarabine



Synthesis

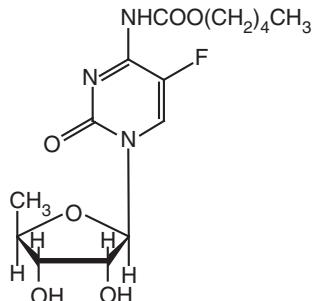


Properties and uses: Cytarabine is a white crystalline powder, soluble in water, very slightly soluble in alcohol and methylene chloride. It is used for acute leukaemia, chronic myelocytic leukaemia, meningeal leukaemia, acute lympholytic leukaemia, and chronic lympholytic leukaemia.

Assay: Dissolve the sample in anhydrous acetic acid, warm, if necessary, and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

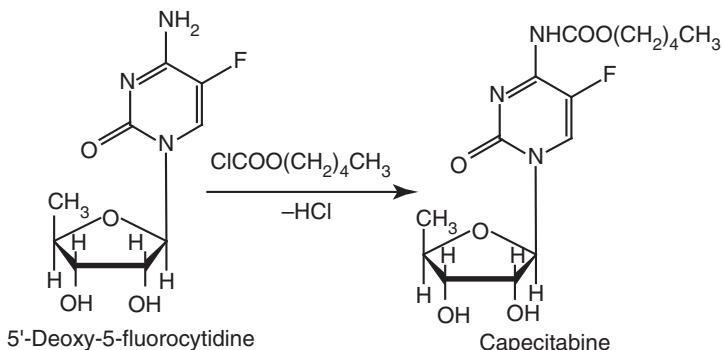
Dosage forms: Cytarabine injection I.P., B.P.

Capecitabine (Captabin, Capibine, Xabine)



5'-Deoxy-5-fluoro-N⁴-(pentyloxy carbonyl) cytidine

Synthesis



Metabolism: The drug is actually another 5-fluoro-deoxy uridine monophosphate prodrug. When given orally, it is extensively metabolized to fluorouracil, which is then converted to the active fluorinated deoxyribonucleotide.

Uses: It is used in acute granulocytic leukaemia of adults and children.

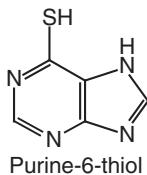
Dose: The dose for colorectal cancer and breast cancer for adults is 1.25 g per m² two times a day for 2 weeks followed by a 1-week rest period. Therapy is to be given in 3-week cycles. Recommended treatment duration for colorectal cancer is 6 months. May be used in combination with docetaxel at 75 mg per m² given as a 1 h IV infusion, once in every 3 weeks for the treatment of breast cancer.

Gastric cancer: The dose for adults, used in combination with platinum-based compound, 1 g per m² two times a day for 14 days followed by a 7-day rest period. First dose is given on the evening of day 1 and the last dose on the morning of day 15.

II. b. Purine analogues

Mode of action: These drugs are converted into appropriate mono-ribonucleotides, which inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides.

6-Mercaptopurine (Purinethol)



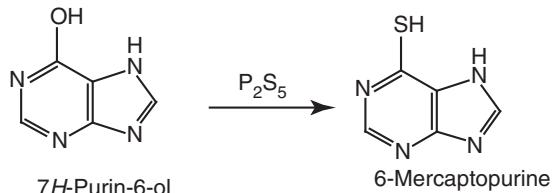
Properties and uses: Mercaptopurine is a yellow crystalline powder, practically insoluble in water, slightly soluble in alcohol, and dissolves in solutions of alkali hydroxides. It is used in the treatment of acute monocytic leukaemia.

Assay: Dissolve the sample in dimethylformamide and titrate with 0.1 M tetrabutylammonium hydroxide. Determine the end point potentiometrically.

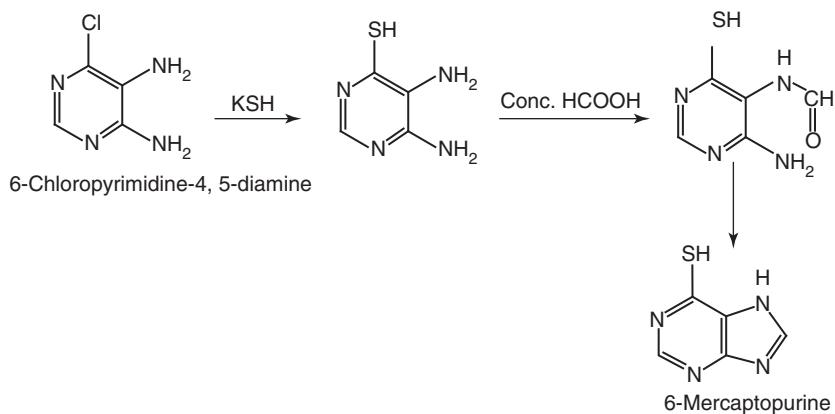
Dose: The usual initial oral dose for children and adults is 2.5 mg per kg body weight daily, but the dose varies as per individual response and tolerance.

Synthesis

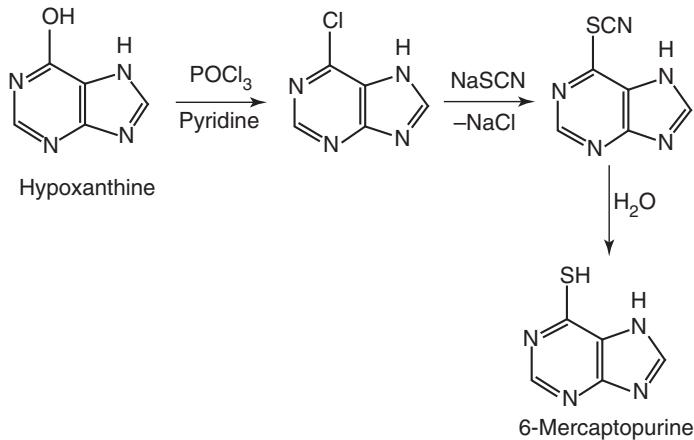
Route-I. From: 7H-Purin-6-ol



Route-II. From: 6-Chloropyrimidine-4,5-diamine

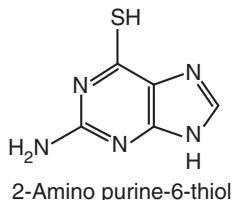


Route III. From: Hypoxanthine

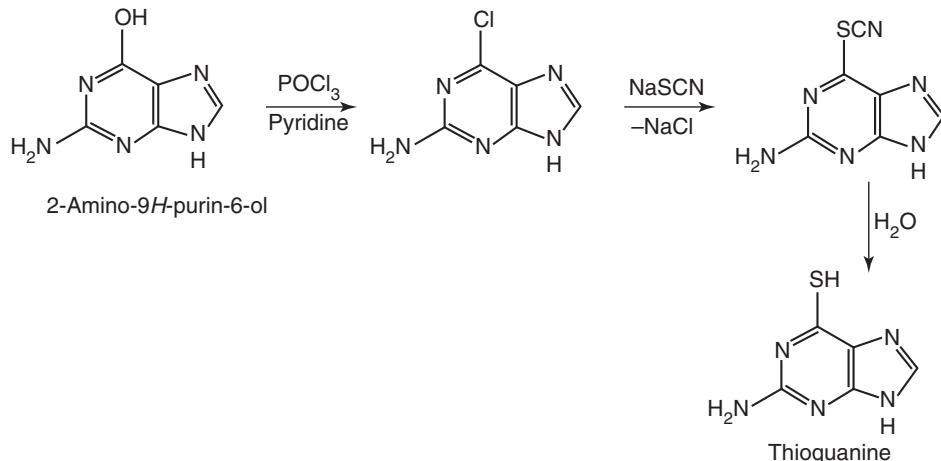


Dosage forms: Mercaptopurine tablets I.P., B.P, Mercaptopurine oral suspension B.P.

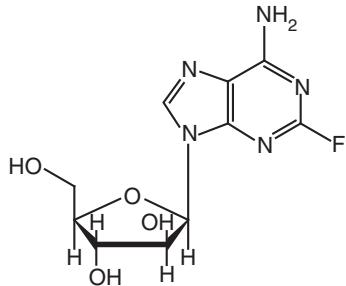
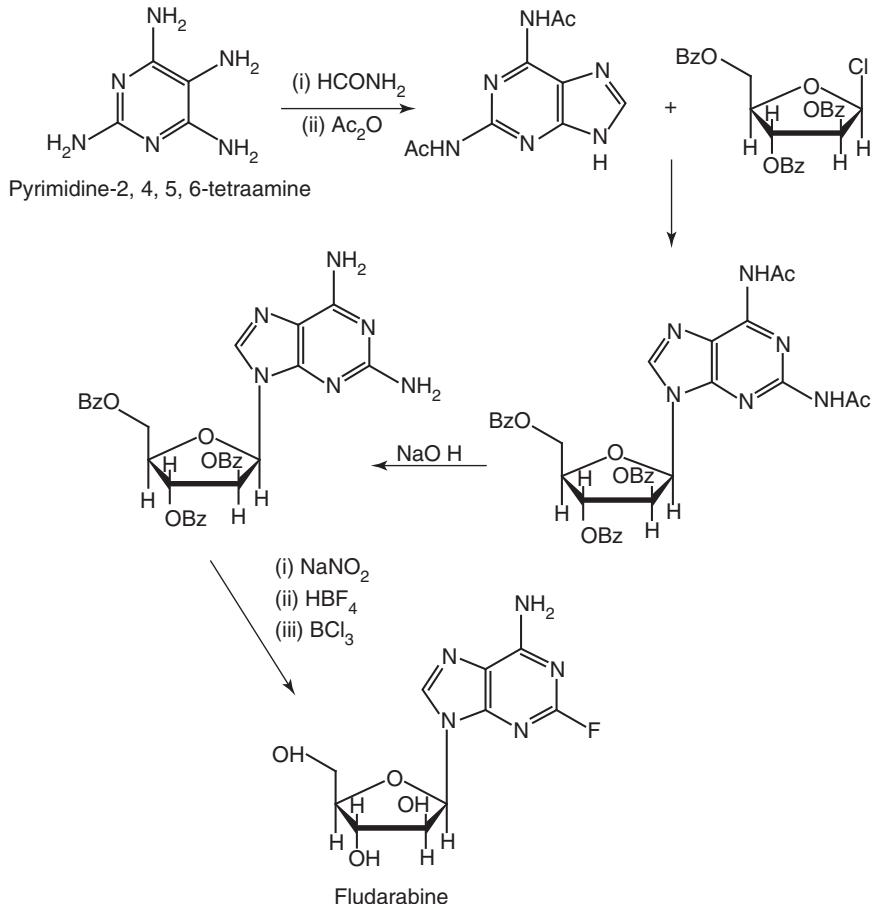
Thioguanine



Synthesis



Properties and uses: It is used in treating acute leukaemia, especially in combination with cytarabine. The adverse effects are bone marrow depression, leucopenia, thrombocytopenia, and bleeding.

Fludarabine**Synthesis**

Metabolism: This is a 3-halogenated adenosine based nucleoside, which undergoes conversion to active triphosphate nucleotides after active transport into the tumour cells.

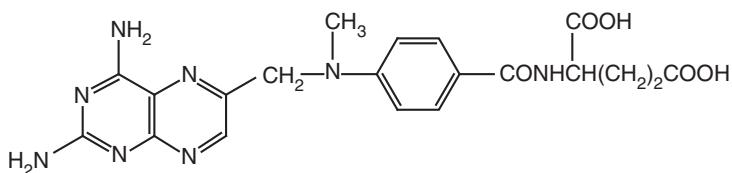
Properties and uses: Fludarabine phosphate is a white crystalline hygroscopic powder, slightly soluble in water, soluble in dimethylformamide, and very slightly soluble in anhydrous ethanol. It shows activity against low-grade lymphoma and mycosis fungoides.

Assay: It is assayed by adopting liquid chromatography technique.

II. c Folic Acid Analogues

Mode of action: These drugs inhibit dihydrofolate reductase (DHFRase), which converts the dihydrofolic acid to tetrahydro folic acid, the co-enzyme required for one carbon transfer reaction in de novo purine synthesis and amino acid interconversion.

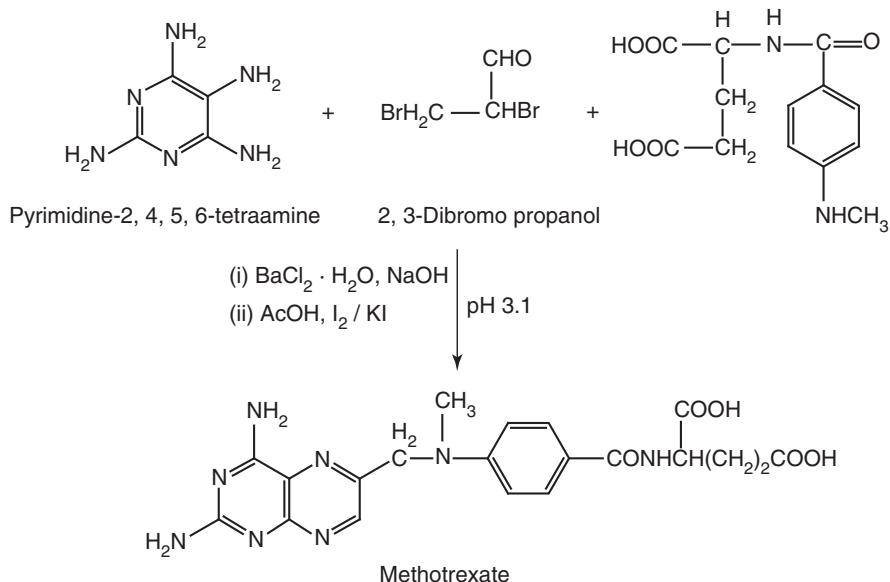
Methotrexate (Amethopterin)

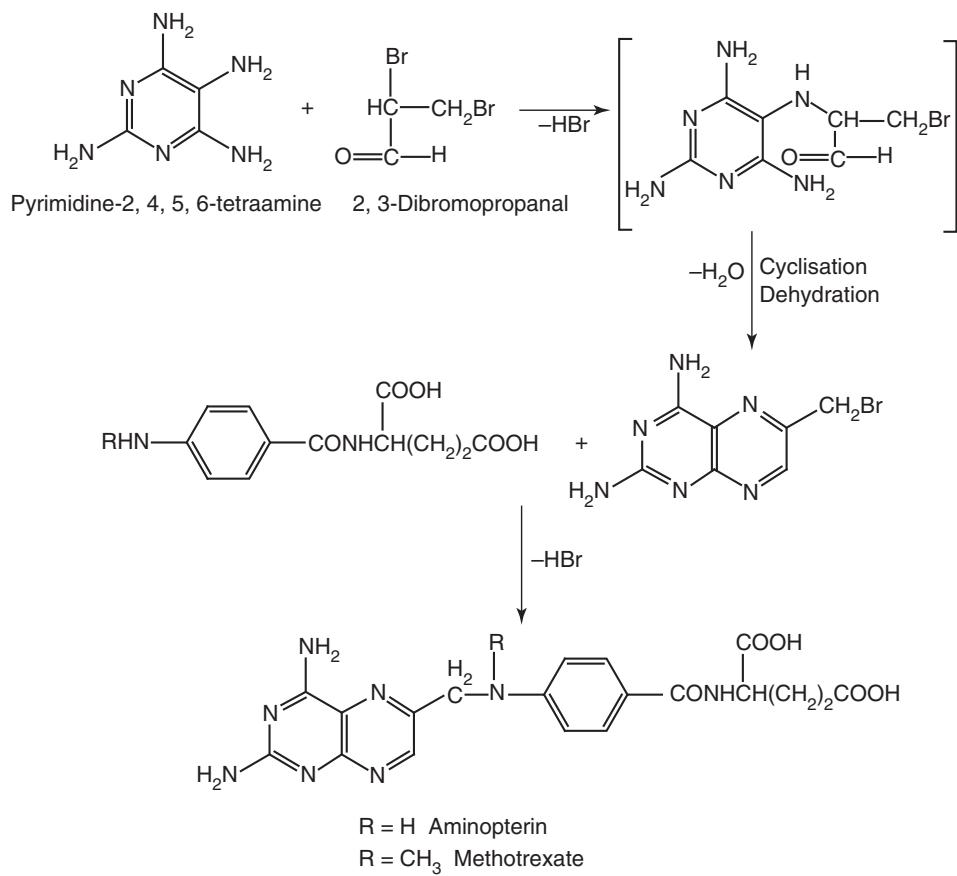


4-Amino-N¹⁰-methyl-pteroylglutamic acid

Synthesis

Route-I. From: Pyrimidine-2,4,5,6-tetraamine



Route-II. From: Pyrimidine-2,4,5,6-tetraamine

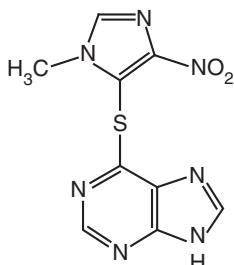
Properties and uses: Methotrexate is a yellow or orange crystalline hygroscopic powder, practically insoluble in water, ethanol, and methylene chloride. It dissolves in dilute mineral acids and dilute solutions of alkali hydroxides and carbonates. It is used for the treatment of acute lymphocytic leukaemia, acute lymphoblastic leukaemia, breast cancer, and epidermoid cancer of the head, neck, and lung cancer.

Assay: It is assayed by adopting liquid chromatography technique.

Dose: For the maintenance therapy of acute lymphoblastic leukaemia, the dose is 15–30 mg per m² body surface once or twice weekly either orally or intramuscularly, with other agents, such as mercaptopurine.

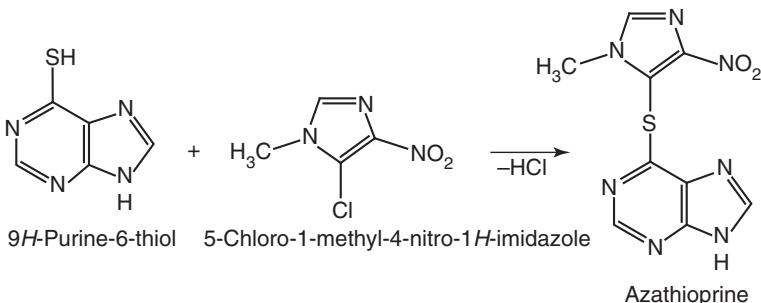
Dosage forms: Methotrexate injection I.P., B.P., Methotrexate tablets I.P., B.P.

Azathioprine



6-[(1-Methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine

Synthesis

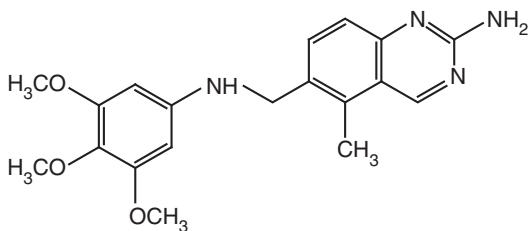


Properties and uses: Azathioprine is a pale-yellow powder, practically insoluble in water and alcohol. It is soluble in dilute solutions of alkali hydroxides and sparingly soluble in dilute mineral acids. It is used as an immuno-suppressant.

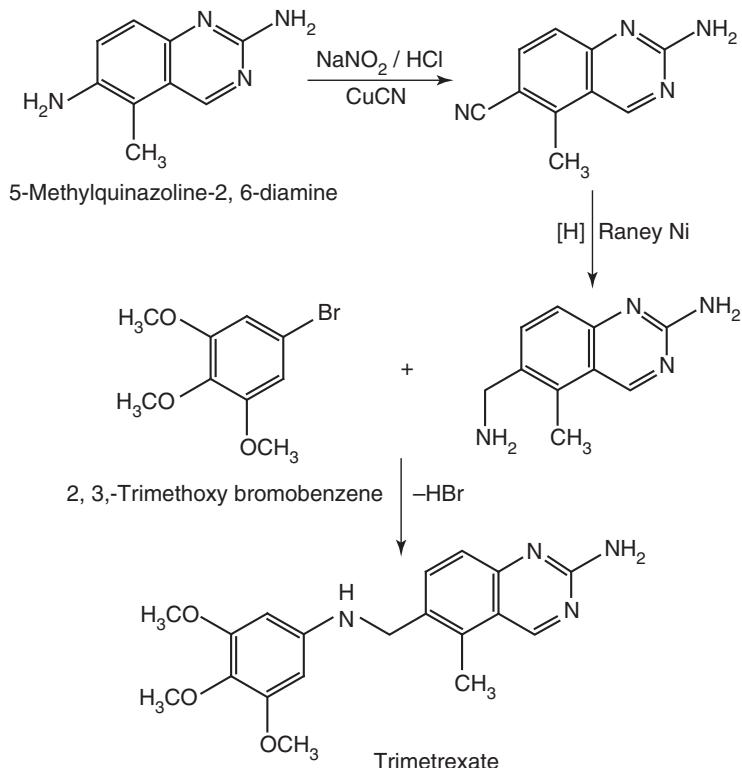
Assay: Dissolve the sample in dimethylformamide and titrate with 0.1 M tetrabutylammonium hydroxide. Determine the end point potentiometrically.

Dosage forms: Azathioprine tablets B.P.

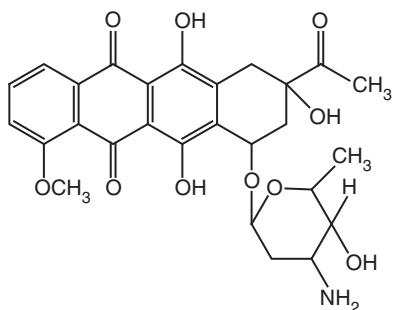
Trimetrexate



5-Methyl-6-((3, 4, 5-trimethoxyphenylamino)methyl)quinazoline-2, 4-diamine

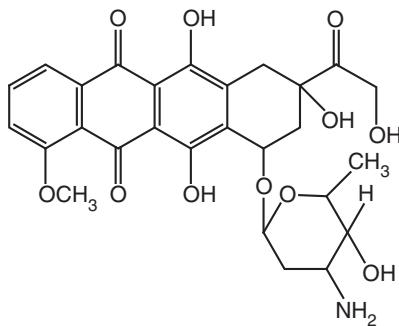
Synthesis**III. Antibiotics****III a. Anthracyclines**

Anthracyclines occur as glycosides of the anthracyclinone. The glycosidic linkage usually involves the-7-hydroxyl group of anthracyclinone and the β enantiomer of sugar with L-configuration. Anthracyclinone refers to an aglycone containing the anthraquinone chromophore within a linear hydrocarbon skeleton related to that of tetracycline.

Daunorubicin

Properties and uses: Daunorubicin is obtained from the fermentation of *Streptomyces peuetieus*. This drug bind to the DNA and inhibit nucleic acid synthesis, mitosis, and promote chromosomal aberration. These drugs are used for the treatment of acute myelocytic leukaemia, primary hepatocellular carcinomol, and ovarian endometrial carcinoma.

Doxorubicin

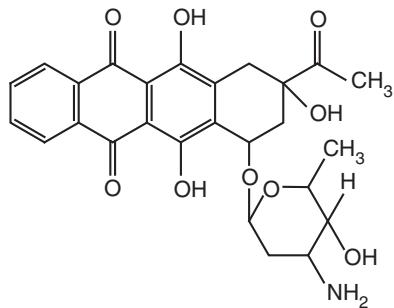


Properties and uses: Doxorubicin hydrochloride is an orange-red crystalline hygroscopic powder, soluble in water, and slightly soluble in methanol. Doxorubicin is 14-hydroxy daunorubicin obtained from the cultures of *Streptomyces peuetieus*. It is one of the most effective antitumour agent. It is used in the treatment of acute lymphocytic leukaemia, breast, lung, ovarian, thyroid, gastric carcinoma, and Hodgkin's disease.

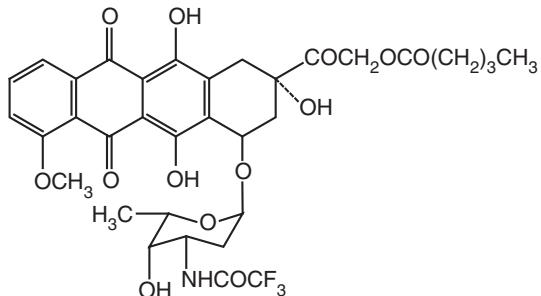
Assay: It is assayed by adopting liquid chromatography technique.

Dosage forms: Doxorubicin HCl injection I.P., Doxorubicin HCl tablets I.P., Doxorubicin injection B.P.

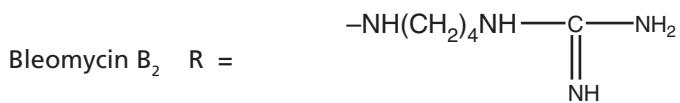
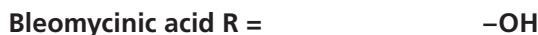
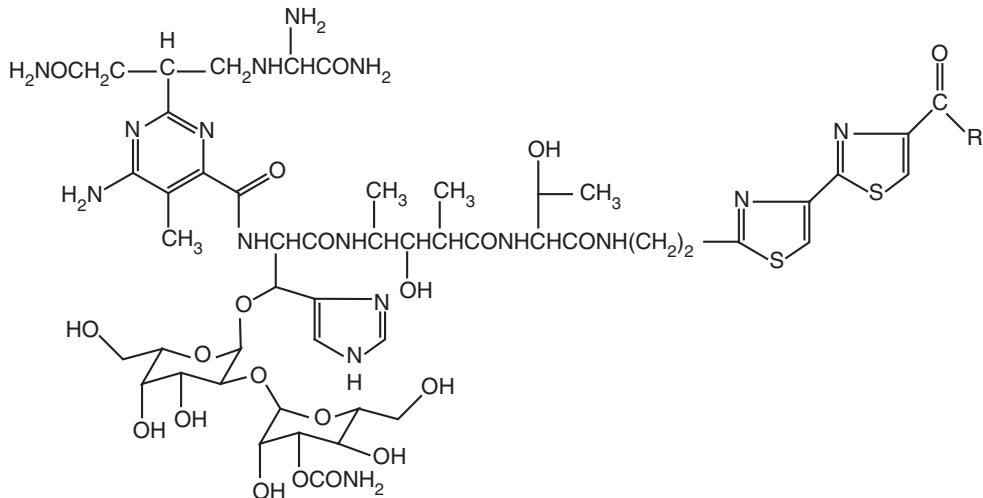
Idarubicin



Properties and uses: Idarubicin is demethoxy daunorubicin. It is a synthetic analogue of naturally occurring anthracyclines. It is used in acute myelogenous leukaemia and acute lymphocytic leukaemia.

Valrubicin

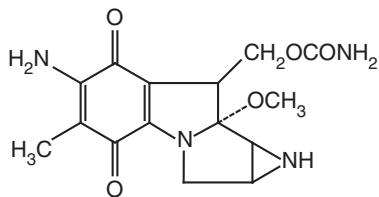
Properties and uses: Valrubicin is a derivative of doxorubicin in which the amino group has a trifluoroacetyl substituent and 14-hydroxy group is converted to valerate ester.

Bleomycin Sulphate

Properties and uses: Bleomycin sulphate is a mixture of cytotoxic glycopeptidase isolated from the strain of *Streptomyces verticillers*. It is a mixture of closely related compounds with bleomycin A₂ and B₂. Bleomycin occurs naturally as blue copper chelates. Inside the cell, bleomycin forms a complex with Fe (II), gives rise

to hydroxyl radical and superoxide radicals. These radicals cleave the phosphodiesterase bond of DNA. This degradation of DNA strands is thought to be a lethal event in cells. It is effective in the treatment of testicular carcinomas. It is also useful in the treatment of squamous cell carcinomas of the head, neck, oesophagus, skin, and the genito-urinary tract, including the cervix, vulva, scrotum, and penis.

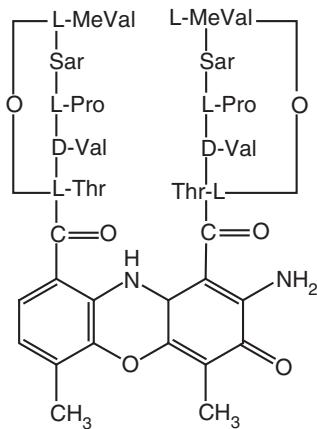
III. c. Mitomycin-C



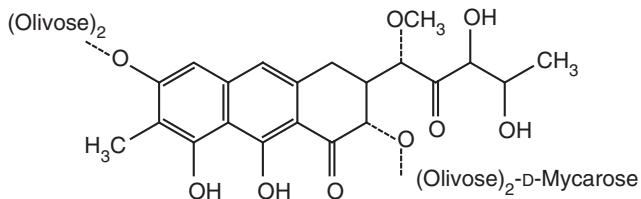
Properties and uses: Mitomycin exists as blue-violet crystals or crystalline powder, slightly soluble in water, freely soluble in dimethylacetamide, sparingly soluble in methanol, and slightly soluble in acetone. It is obtained from *Streptomyces equespitosus*; it contains three different carcinostatic functions, quinone, carbamate, and aziridine. The molecule is unreactive in its natural state. After intracellular enzymatic or spontaneous chemical reduction of the quinone and loss of the methoxy group, mitomycin becomes a bifunctional or trifunctional alkylating agent. The drug inhibits DNA synthesis at the O⁶ and N⁷ positions of guanine. In addition, single-strand breakage of DNA are caused by mitomycin. It is used in gastric and pancreatic carcinoma.

Assay: It is assayed by adopting liquid chromatography technique.

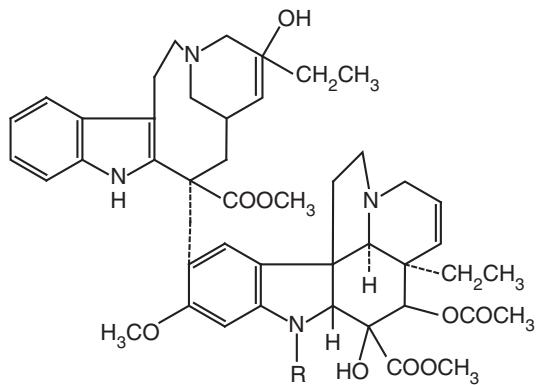
Dactinomycin or Actinomycin D



Properties and uses: It is obtained from the cultures of *Streptomyces antibioticus*. It consists of tricyclic phenoazone ring in the quinone oxidation state and two identical polypeptide and intercalates into the double helical DNA. The main biochemical consequence of the intercalation of actinomycin into DNA is the inhibition of DNA and RNA synthesis, which in turn leads to depletion of protein and cell death.

Plicamycin (Mithramycin)

Properties and uses: It is an aureolic acid derivative obtained from *Streptomyces plicatus* or *Streptomyces argilaceus*. It forms a complex with divalent metals, such as magnesium and calcium and such complex formation is required before binding with DNA. It inhibits DNA dependent RNA polymerase, which leads to cell death. It is used in the treatment of embryonal tumours of the testes and metastatic cancers.

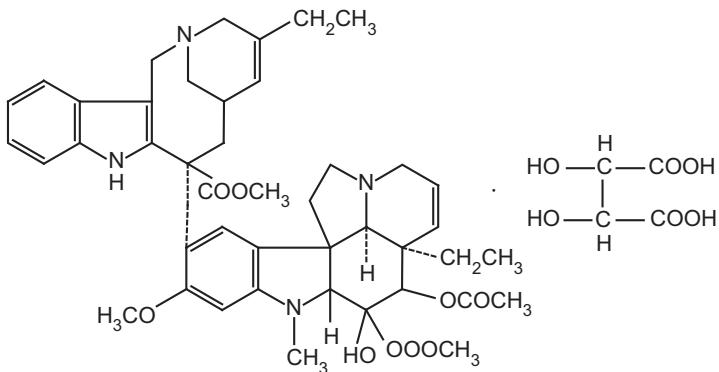
IV. Plant products**a. Vinca alkaloids**

Vincristine R = CHO

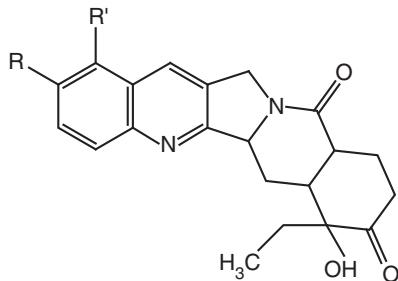
Vinblastine R = CH₃

Mode of action: It binds to microtubular protein tubulin, prevents polymerization and assembly of microtubules, and causes mitotic spindle destruction. The chromosomes fail to move apart during mitosis and lead to metaphase arrest.

Properties and uses: Vinca alkaloids are isolated from *Catharanthus roseus*. They have complex structures composed of a dimeric indole-containing moiety named catharanthine and an indoline-containing moiety named vindoline. Four closely related compounds have antitumour activity, that is, vincristine, vinblastine, vinrosidine, and vinleurosine. Semisynthetic derivative vinorelbine is also used as an antitumour agent.

Vinorelbine

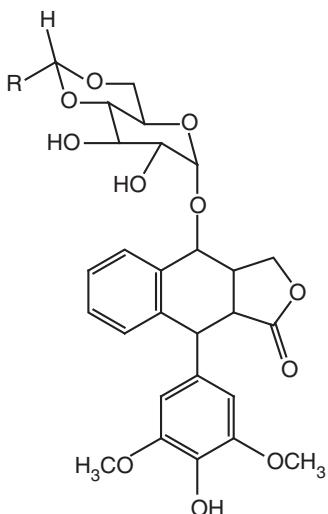
Properties and uses: They are used for the treatment of acute leukaemia, Hodgkin's disease, testicular cell tumour, lymphocytic lymphoma, histiocytic lymphoma, and carcinoma of the breast.

b. Camptothecin derivatives

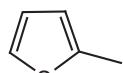
| Name | R | R' |
|--------------|---------------------------------------|---|
| Camptothecin | -H | -H |
| Irinotecan | $-\text{C}_2\text{H}_5$ | $-\text{OCO}-\text{N}(\text{C}_6\text{H}_{11})_2$ |
| Topotecan | $-\text{CH}_2\text{N}(\text{CH}_3)_2$ | -OH |

Properties and uses: Camptothecin is a pentacyclic alkaloid originally isolated from *Camptotheca acuminata*. These drugs are used for the treatment of colorectal and ovarian cancers.

c. Epipodophyllotoxins



Etoposide R = CH₃



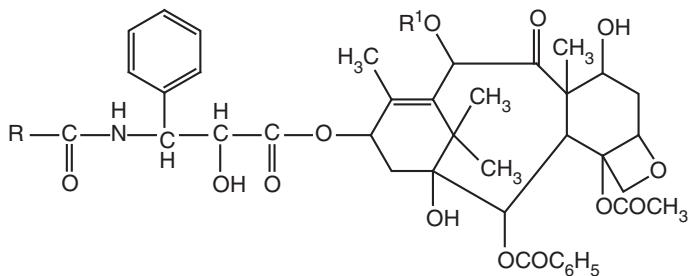
Teniposide R =

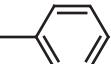


Mode of action: It arrests cells in G₂ phase and causes DNA breaks by affecting the DNA topoisomerase function and the resealing of DNA strand is prevented.

Properties and uses: Etoposide and teniposide are semi-synthetic derivatives of podophyllotoxin. It is obtained as extracts of May apple plant. It is effective in the treatment of lung cancer, testicular cancer, and Hodgkin's disease.

d. Taxol derivatives



| Name | R | R' |
|------------|---|--------------------|
| Paclitaxel |  | -COCH ₃ |
| Docetaxel | (CH ₃) ₃ CO— | -H |

Mode of action: This stabilizes the polymerization of tubulin and the depolymerization is prevented.

Properties and uses: The taxol derivative, paclitaxel, is isolated from the Western row tree, *Taxus brevifolia*. It is the first member of the taxane family used in cancer therapy. It is used for metastatic ovarian and breast cancer, lung, mouth, oesophageal, and bladder carcinomas.

V. Enzymes

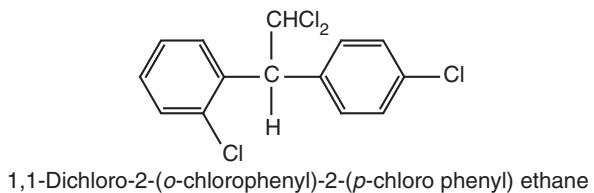
L-Asparaginase

It is an enzyme isolated from *Escherichia coli* and *Erwinia carotovora*. The enzyme has a molecular mass of 130,000. It consists of four equivalent subunits. It breaks down asparagine to aspartic acid and ammonia. It is active against tumour cells having lost the capacity to synthesize asparagine.

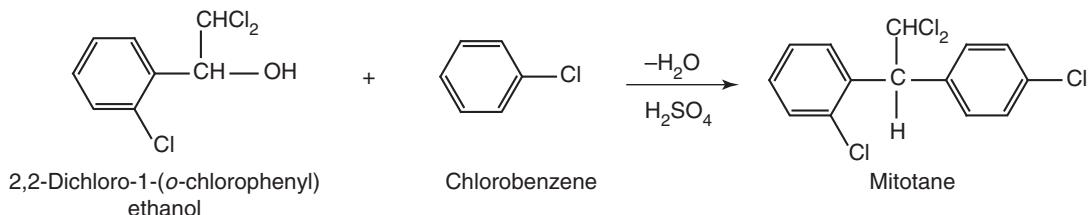
Properties and uses: It is used to treat childhood acute lymphocytic leukaemia in combination with vincristine and prednisone.

VI. Hormones

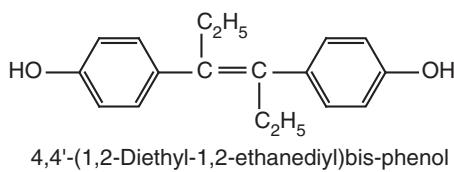
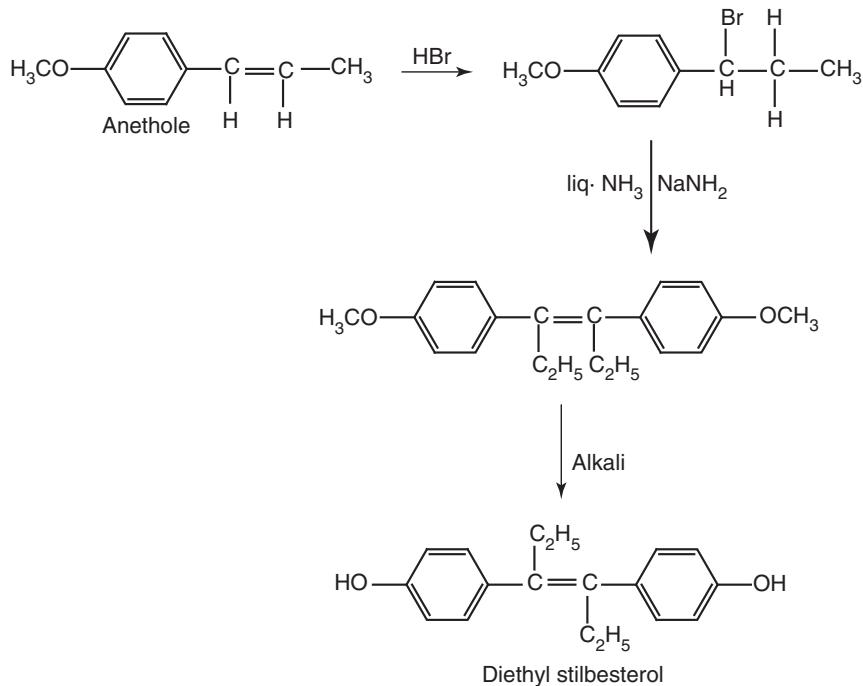
Mitotane



Synthesis



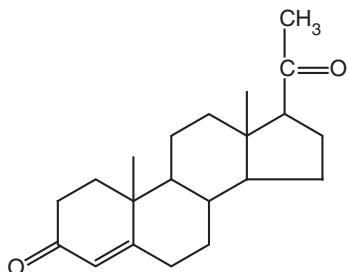
Properties and uses: It is indicated only for treating adrenal cortex carcinoma.

Diethylstilbestrol**Synthesis**

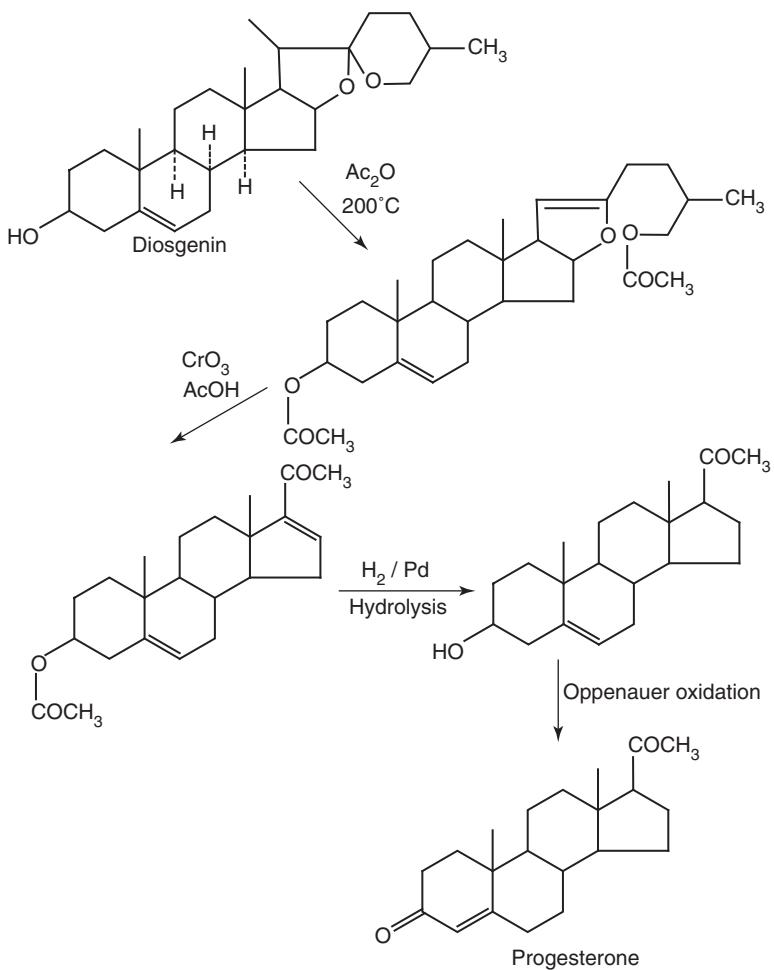
Properties and uses: Diethylstilbestrol is a white crystalline powder, practically insoluble in water, and soluble in alcohol and alkali hydroxides solutions. It is used for palliative therapy and produces relief in primary as well as metastatic prostrate carcinoma.

Assay: Dissolve the sample in ethanol and dilute with the same solvent. To the resulting solution, add dipotassium hydrogen phosphate solution. Prepare in the same manner, a reference solution using diethylstilbestrol reference standard. Irradiate with mercury lamp and measure the absorbance of the irradiated solutions at the maximum of 418 nm, using water as a blank.

Dosage forms: Diethylstilbestrol pessaries B.P., Diethylstilbestrol tablets B.P.

Progesterone

17-Acetyl-10,13-dimethyl-1,7,8,10,11,12,13,15,16,17-deahydro-2*H*-cyclopenta[*a*]phenanthren-3(6*H*,9*H*,14*H*)-one

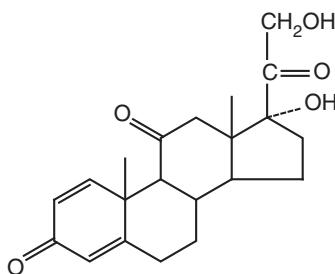
Synthesis

Properties and uses: Progesterone exists as white crystalline powder or colourless crystals, practically insoluble in water, soluble in ethanol, sparingly soluble in acetone and fatty oils. Progestins are palliative in 50% cases of advanced and metastatic endometrial carcinoma.

Assay: Dissolve the sample in alcohol, dilute with the same solvent, and measure the absorbance at 241 nm using ultraviolet spectrophotometer.

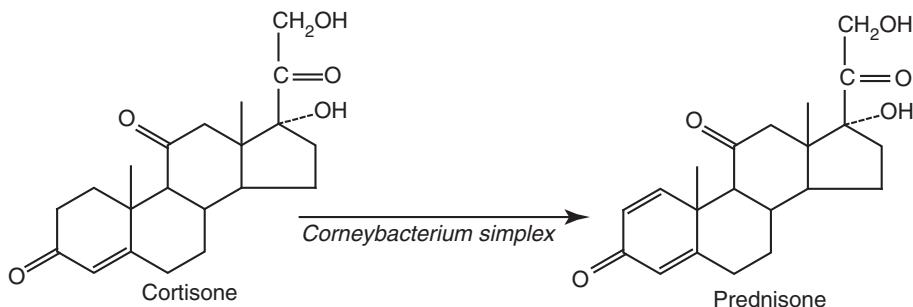
Dosage forms: Progesterone injection B.P.

Prednisone



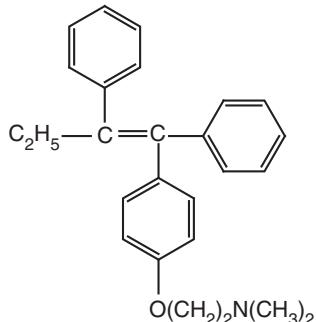
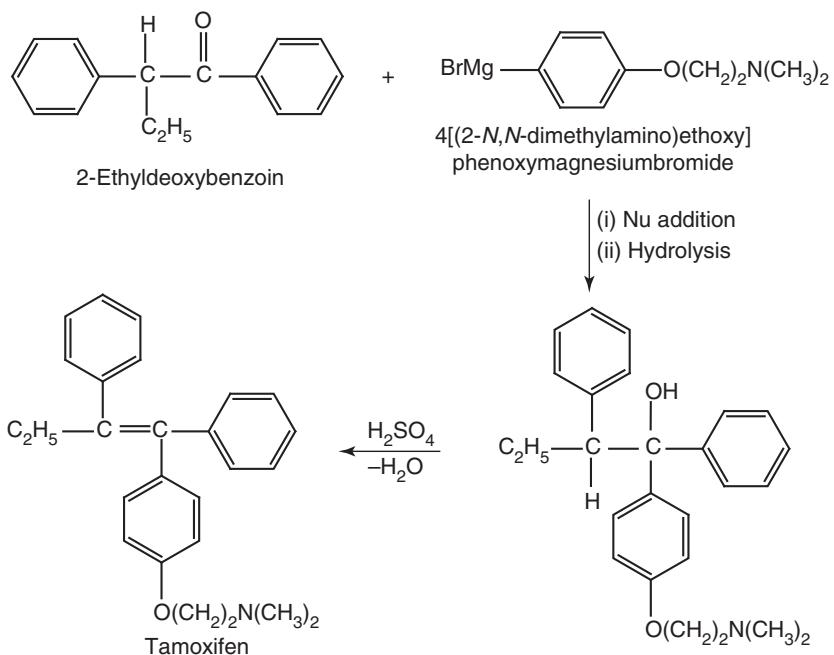
(17*R*)-17-Hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl
-7,8,13,15,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene-3,11(9*H*,10*H*,12*H*,14*H*)-dione

Synthesis



Properties and uses: Prednisone is a white crystalline powder, practically insoluble in water, slightly soluble in alcohol and methylene chloride. It is predominantly used in cancer chemotherapy, and in the treatment of acute exacerbations of multiple sclerosis. In paediatrics, it is widely used to treat nephrosis, rheumatic caslitis, leukaemia, and tuberculosis.

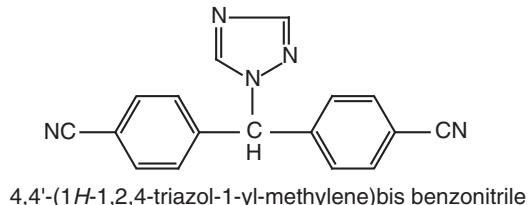
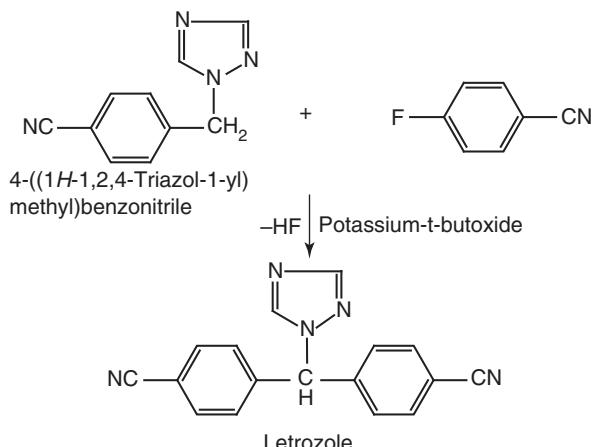
Assay: Dissolve the sample in alcohol, dilute with the same solvent, and measure the absorbance at 238 nm using ultraviolet spectrophotometer.

Tamoxifen2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-*N,N*-dimethyl ethamine**Synthesis**

Properties and uses: Tamoxifen citrate is a white crystalline powder, slightly soluble in water and acetone, but freely soluble in methanol. It is a nonsteroidal antiestrogen for palliative therapy of breast cancer in postmenopausal women. The drug competes with estrogens for cytosol estrogen receptors, and thus, blocks estrogens effects in the target tissue.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid using naphtholbenzein as indicator.

Dosage forms: Tamoxifen citrate tablets I.P., Tamoxifen tablets B.P.

Letrozole**Synthesis**

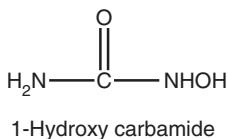
Properties and uses: Letrozole is a white or yellowish crystalline powder, practically insoluble in water, soluble in methylene chloride, and sparingly soluble in methanol. It is used for the treatment of breast carcinoma.

Assay: It is assayed by adopting liquid chromatography technique.

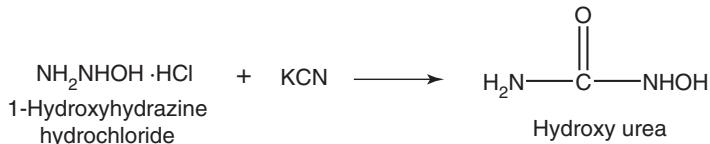
VII. Immunotherapy**Interferons**

The interferons are a family of cytokines with broad-spectrum antiviral and anticancer activity making them biological responsive modifiers. Three types of naturally occurring interferons have been found:

1. Leukocytic interferons: Interferons α produced by lymphocytes and macrophages.
2. Fibroblast interferons: Interferons β produced by fibroblast epithelial cell and macrophages.
3. Immune interferons: Interferons γ synthesized by CD4 $^{+}$, CD8 $^{+}$, and natural killer lymphocytes.

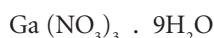
IX. Miscellaneous**Hydroxy Urea**

Synthesis



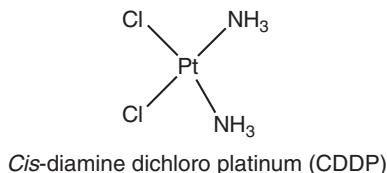
Uses: It is active against melanoma and chronic myelocytic leukaemia.

Gallium Nitrate

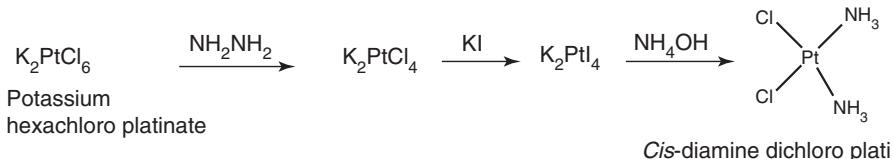


Uses: It is used to treat cancer-related hypocalcaemia.

Cisplatin



Synthesis

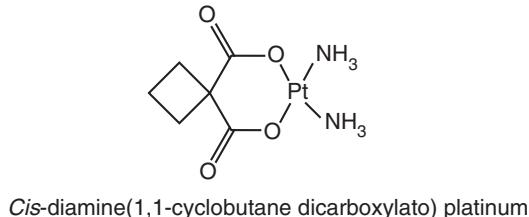


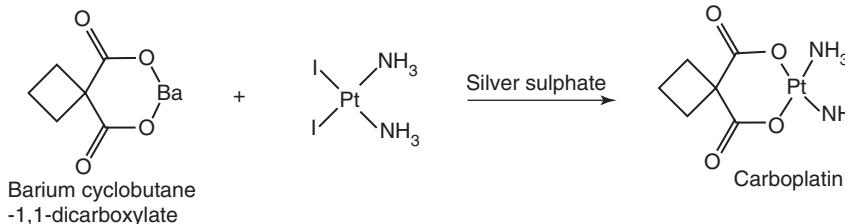
Properties and uses: Cisplatin is a yellow powder or yellow or orange-yellow crystals, slightly soluble in water, sparingly soluble in dimethylformamide, and practically insoluble in alcohol, used in testicular tumour.

Assay: It is assayed by adopting liquid chromatography technique.

Dosage forms: Cisplatin injection B.P.

Carboplatin



Synthesis

Properties and uses: Carboplatin is a colourless crystalline powder, sparingly soluble in water, very slightly soluble in acetone and alcohol. Food and Drug Administration (FDA) approved it for treatment of advanced ovarian cancer. It is cross-resistant with cisplatin in this tumour. Activity also has been reported in lung cancer, head and neck cancer, and testicular cancer. The usual dose-limiting toxicity is bone marrow suppression, especially, thrombocytopenia.

Assay: It is assayed by gravimetric method.

Dosage forms: Carboplatin injection B.P.

PROBABLE QUESTIONS

- What is a neoplasm? What are the causations of neoplasm? Write the structure, name, synthesis, and uses of at least two drugs from alkylating agents and antimetabolites.
- Describe in detail about the anticancer drugs obtained from plant source.
- Write a brief a note on Taxol derivatives and enzymes used in anticancer therapy.
- Write the structure, chemical name, mode of action, and metabolism and uses of any three anticancer drugs from different class.
- How will you classify the antineoplastic agents? Write the structure, chemical name, and uses of two agents from each class.
- Write an account on antibiotics used in anticancer therapy.
- Mustards, methanesulphonates, ethylenimines, and nitrosoureas constitute four vital categories of the alkylating agents employed for the treatment of neoplasms. Outline the synthesis, metabolism, and uses of the following drugs:
 - (a) Chlorambucil (b) Busulfan (c) Trithylene melamine (d) Carmustine
- Recognition of antibiotics as an important class of antineoplastic agents. Justify the statement with reference to the following drugs:
 - (a) Dactinomycin (b) Daunorubicin.
 - How would you classify 'antimetabolites'?
 - Give the structure, chemical name, and uses of the following:
 - (a) Methotrexate (b) Mercaptopurine (c) Fluorouracil (d) Azaserine.
 - Discuss the synthesis of any one of the drug stated above.
- Outline the synthesis of the following anticancer agents
 - (a) Methotrexate (b) Lomustine (c) Cytarabine.

10. Give a comprehensive account of hormones that are potent as antineoplastic agents. Support your answer with suitable examples.
11. Give a brief account of the following:
 - a. Immunotherapy in cancer
 - b. Pharmacokinetics, pharmacodynamic, and mode of action of antineoplastic agents
12. What are alkylating agents. Explain with the chemical reaction about alkylating mechanism in anticancer therapy. Enumerate the agents used in this category and describe the synthesis and uses of any two of them.
13. Write the synthesis, mode of action, metabolism, and uses of the following agents: Cyclophosphamide, Thiotepa, and Azathiapurine
14. Write a note on cytoprotective agents.
15. Discuss the following with regard to antineoplastic agents:
 - (a) Pteridines
 - (b) Acyclic tertiary amines
 - (c) Steroids

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Chapter 12

Antileprotic Drugs

INTRODUCTION

Leprosy is a chronic disease caused due to acid-fast bacillus called *Mycobacterium leprae* and produces nodules on the skin and causes loss of sensation. Once the organism enters into the body, it multiplies and produces antigen–antibody reaction and causes cell-mediated immunity, and produces allergic reaction by the metabolite of the microorganism and finally produces lepra reaction.

Categories of Leprosy

1. Tuberculoid leprosy
2. Lepromatous leprosy
3. Intermediate leprosy
4. Borderline leprosy

Lepromatous leprosy: Large number of organisms that are present in the affected area and induce lepra reaction.

Tuberculoid leprosy: Is characterized by skin molecules with clear centre and well-defined margin.

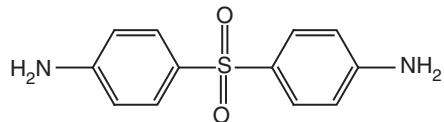
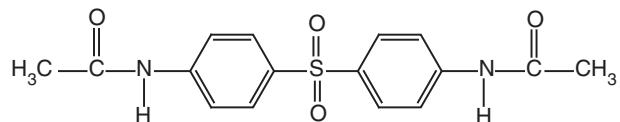
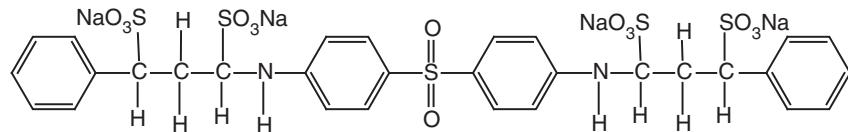
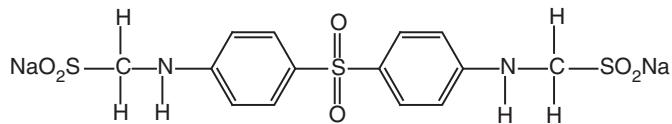
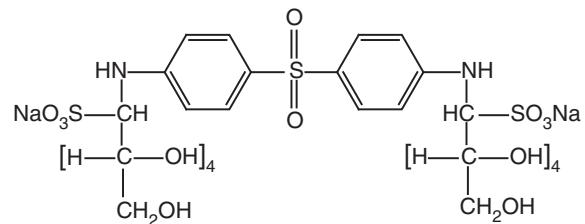
Intermediate leprosy: Is localized hypo-pigmentation with some sensory loss.

Borderline leprosy: It is an intermediate stage between tuberculoid leprosy and lepromatous leprosy.

CLASSIFICATION

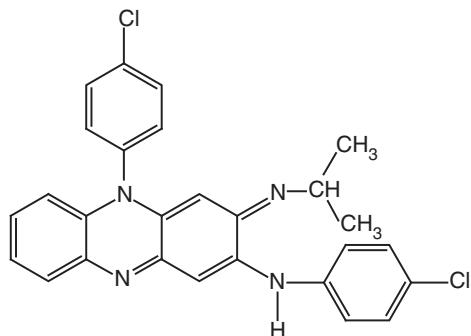
Antileprotic drugs are classified into the following:

- I. Sulphones
- II. Benzpyrazine derivatives: Clofazimine
- III. Plant drugs

I. Sulphones**Dapsone** (Diaminodiphenyl sulphone, DDS)**Acedapsone****Solapsone sodium****Sulfoxone sodium****Gluco sulfone sodium**

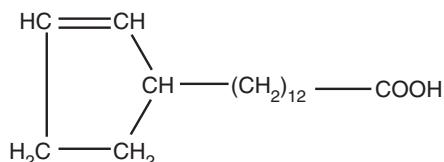
II. Dibenz pyrazine derivatives

Clofazimine (Lamprene)

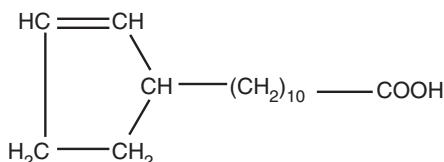


III. Plant drug

i. Chaulmaogric acid



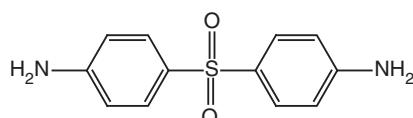
ii. Hydrocaprylic acid



SYNTHESIS AND DRUG PROFILE

I. Sulphones

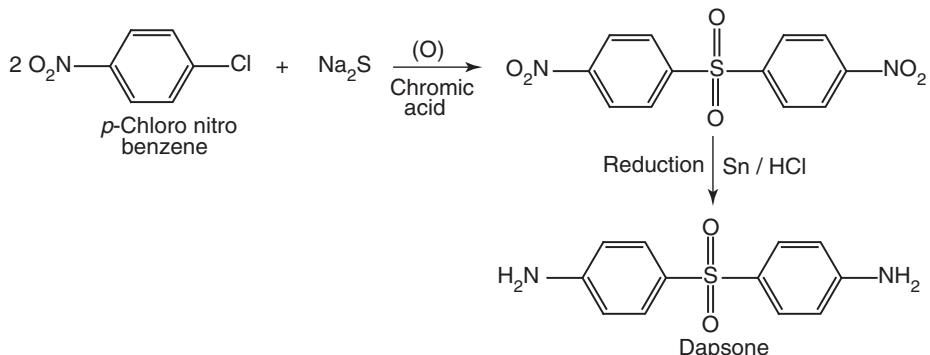
i. Dapsone (DDS, Diaminodiphenyl sulphone)



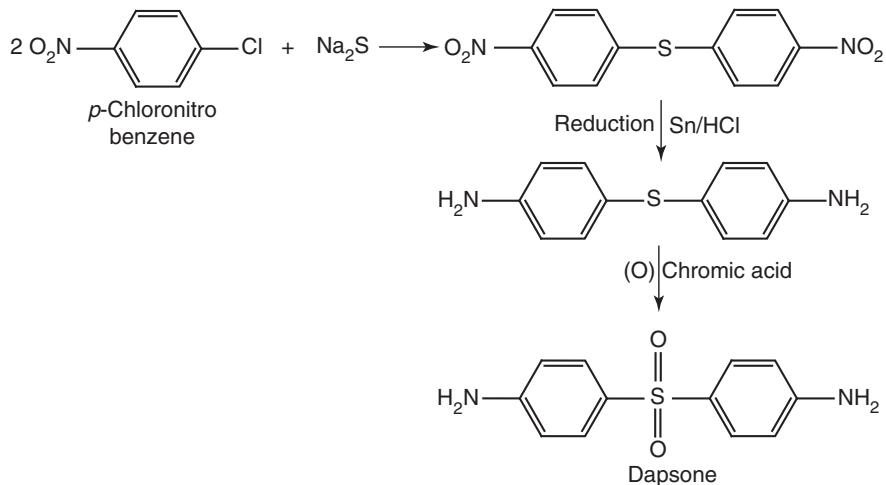
4-(4-Aminophenylsulfonyl)benzenamine

Synthesis

Route I. From: 4-chloro nitrobenzene

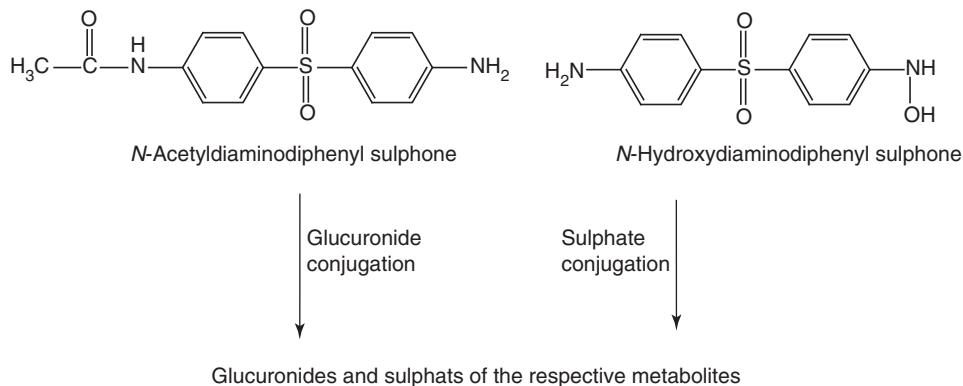


Route II. From: 4-Chloronitrobenzene



Metabolism: The major metabolic product of Dapsone results from *N*-acetylation in the liver by *N*-acetyltransferase. It also undergoes *N*-hydroxylation to hydroxylamine derivative. These metabolic reactions are catalyzed by CYP3A4 isoforms. Neither of these compounds possesses significant leprostatic activity, although *N*-acetyldiamino-diphenyl sulphone may be deacetylated back to Dapsone. Products found in

the urine consist of small amounts of Dapsone and the metabolites, that is, *N*-acetyldiamino-diphenyl sulphone and *N*-hydroxy-diamino-diphenyl sulfone, as well as glucuronide and sulphate of each of these substances.



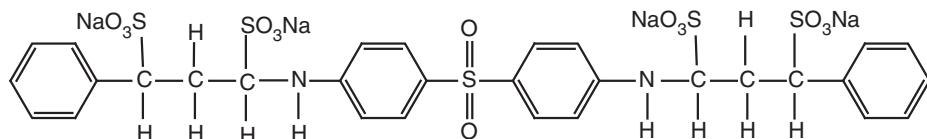
Properties and uses: Dapsone is a white or slightly yellowish-white crystalline powder, very slightly soluble in water, soluble in acetone and dilute mineral acids, but sparingly soluble in alcohol. It is a folic acid synthesis inhibitor used in both lepromatous and tuberculoid leprosy.

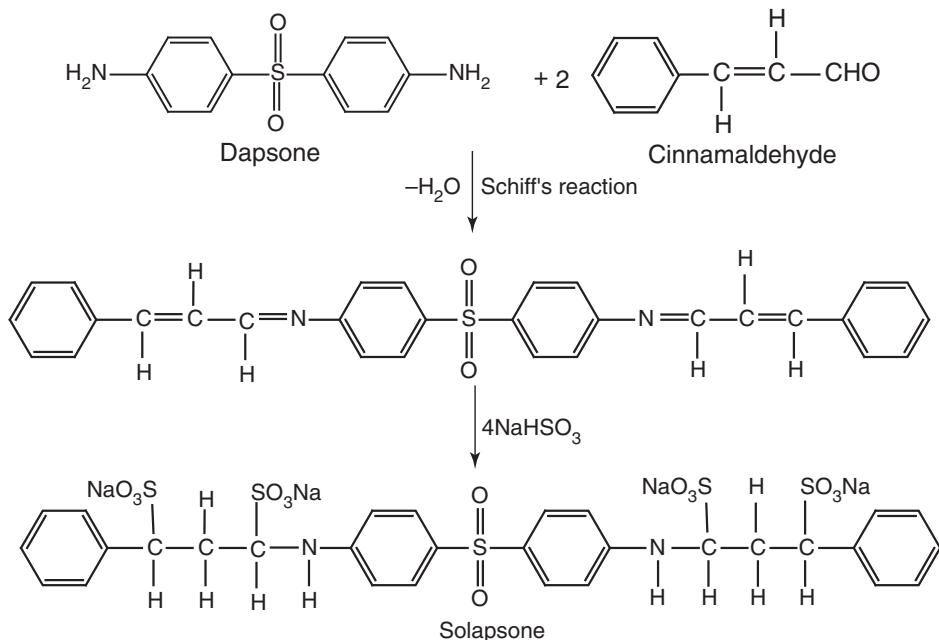
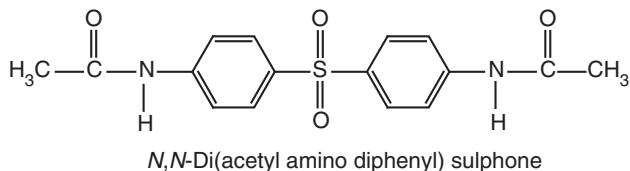
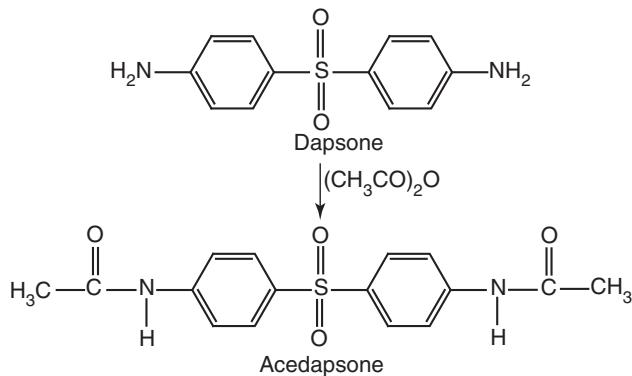
Assay: Dissolve the sample in dilute hydrochloric acid and add potassium bromide. Cool in ice and titrate against 0.1 N sodium nitrate. Determine the end point electrometrically.

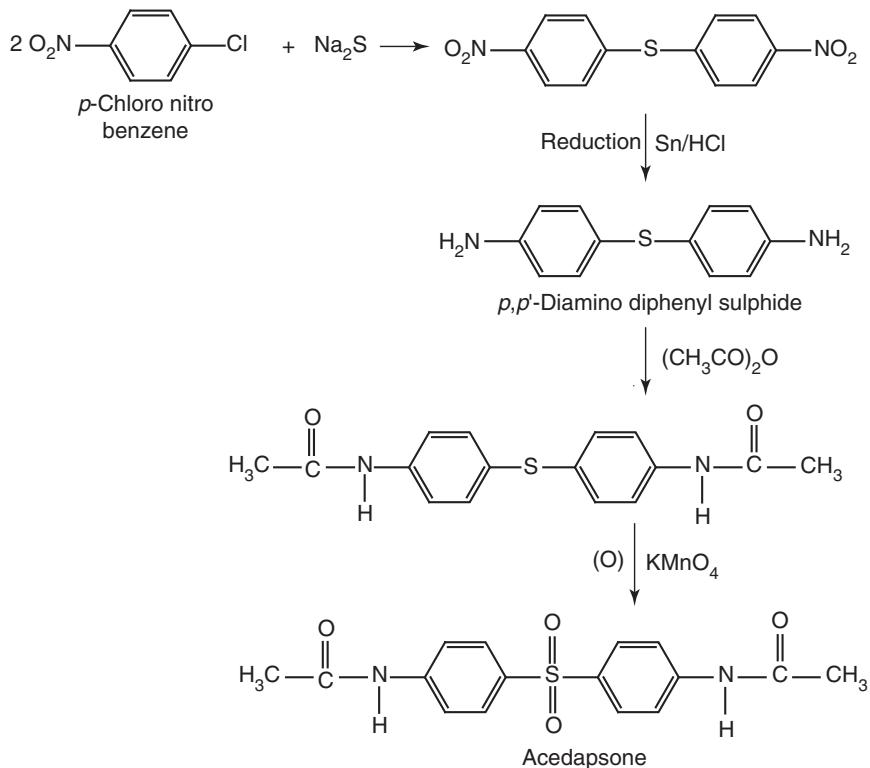
Dosage: The dose as tablets is 25 or 100 mg. For adults the dose consumed is 50 mg per day orally. For lepromatous leprosy, 100 mg Dapsone + 600 mg Rifampin and/or clofazimine 100 mg daily for at least 2 years followed by Dapsone monotherapy. For borderline tuberculoid disease, Dapsone 100 mg daily + Rifampin 600 mg once monthly for 6 months.

Dose : Dapsone tablets I.P., B.P.

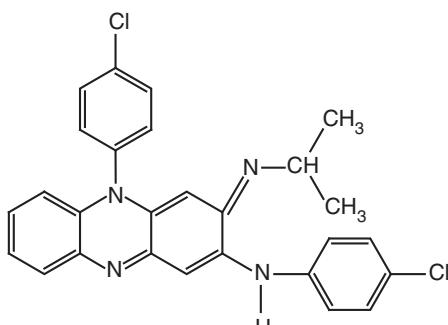
ii. Solapsone Sodium



Synthesis**Acedapsone****Synthesis****Route I: From Dapsone**

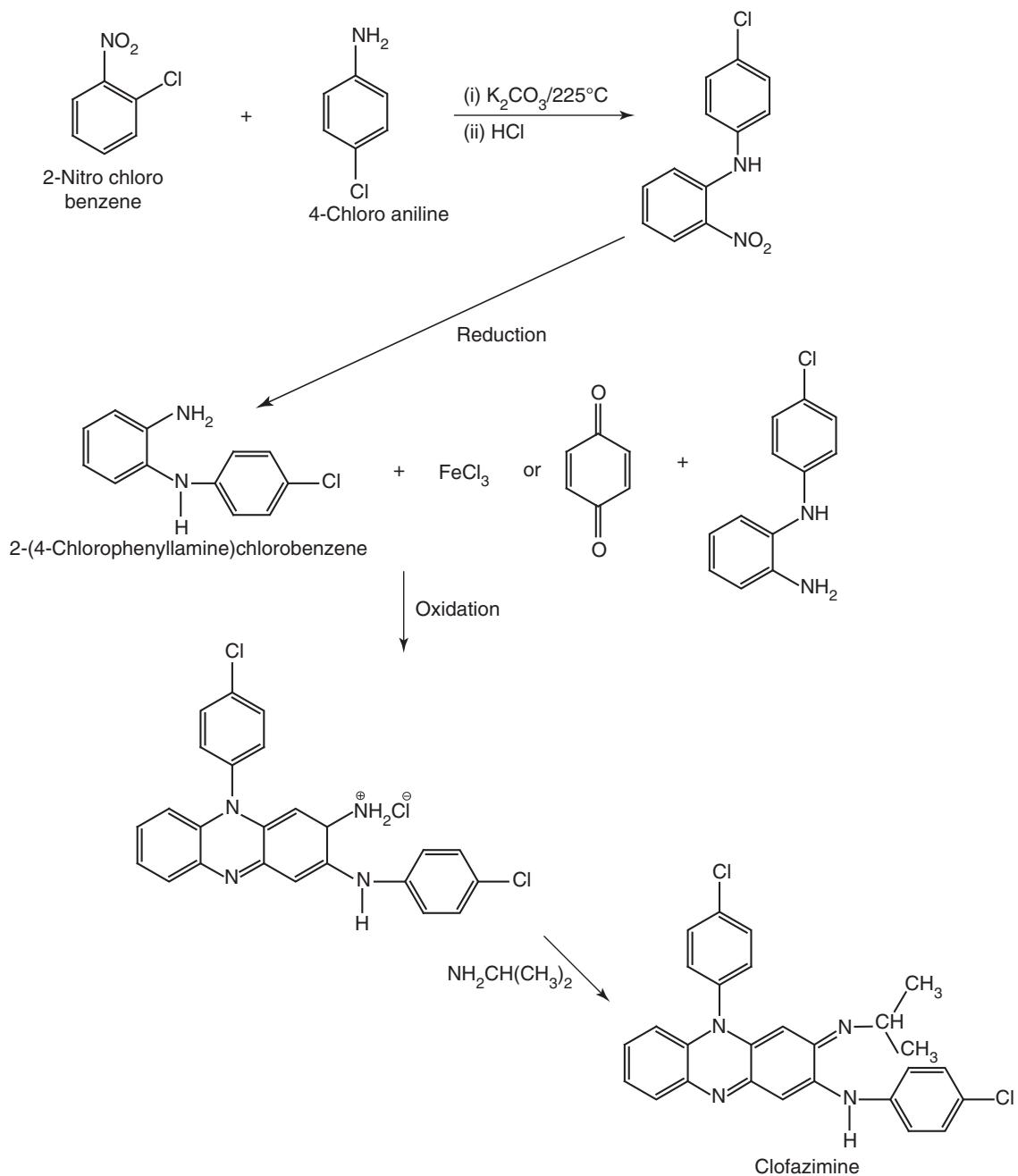
Route II: From 4-Chloro nitrobenzene

Properties and uses: Acedapsone (prodrug of Dapsone) is used in the treatment of both lepromatous and tuberculoid type of leprosy.

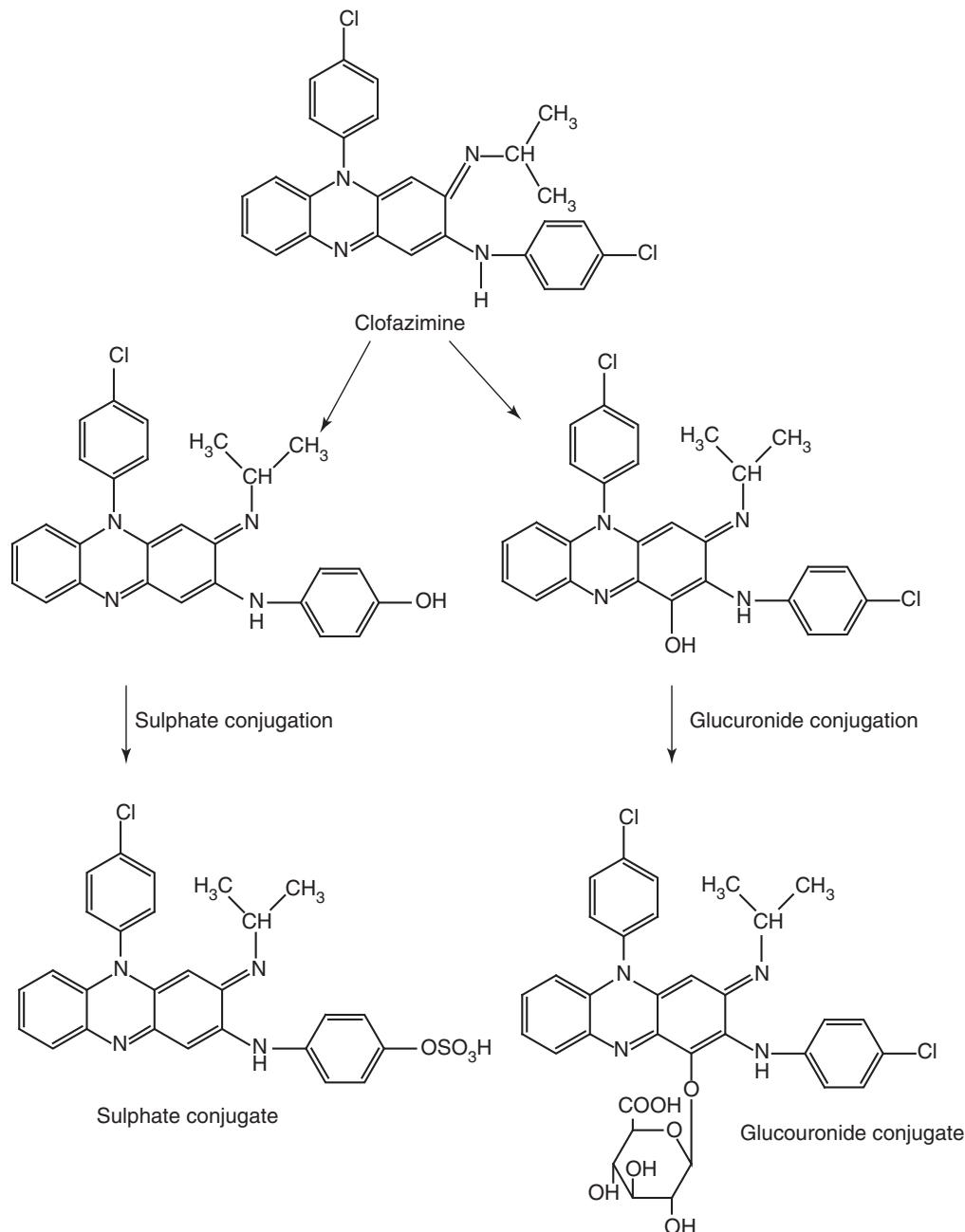
II. Benzpyrazine derivatives**iii. Clofazimine (Lamprene)**

(Z)-*N,N*-Bis(4-chlorophenyl)-3-(isopropylimino)-3,5-dihydrophenazin-2-amine

Synthesis



Metabolism: It is thought to undergo hydroxylic dehalogenation on the 4-chloroaniline, followed by sulphate conjugation. It also undergoes glucuronic acid conjugation.



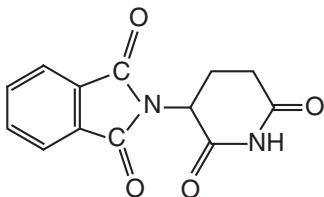
Properties and uses: Clofazimine is a reddish-brown fine powder, practically insoluble in water, soluble in methylene chloride, and very slightly soluble in ethanol. It is used as antileprotic drug.

Assay: Dissolve the sample in methylene chloride, add acetone and anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: The dose orally is 100 mg daily.

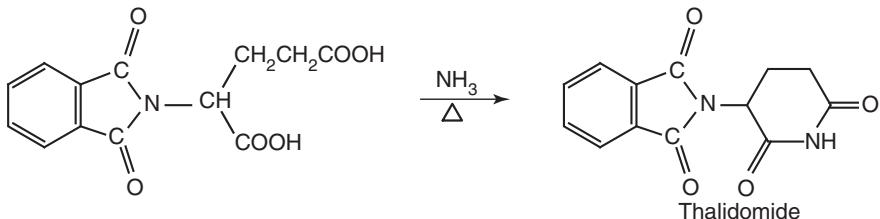
Dosage forms : Clofazimine capsules I.P., B.P.

iv Thalidomide (Thaloda, Thycad, Thalomid)



2-(2,6-Dioxopiperidin-3-yl)isoindoline-1,3-dione

Synthesis



Properties and uses: It is the drug of choice for *Erythema nodosum leprosum*. It must not be used in women during pregnancy because of its teratogenic activity.

Dose: Doses of 100–300 mg per day are effective.

PROBABLE QUESTIONS

1. Mention the different categories of leprosy, classify the drugs used, and outline the synthesis of any two of them.
2. Write a note on sulphones used in leprosy.
3. Outline the synthesis, metabolism, and uses of Clofazimine and Dapsone.

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