SECTION I

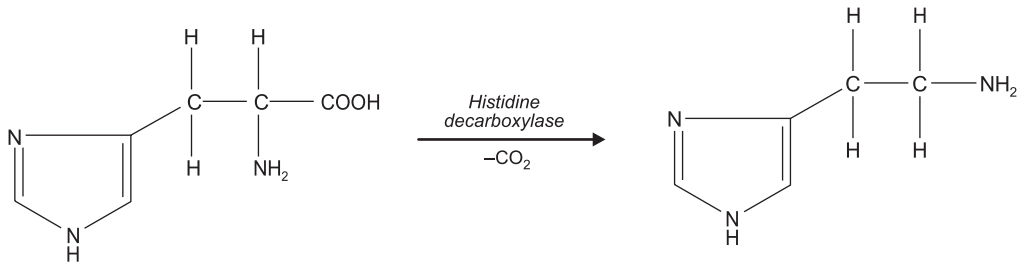
Drugs Acting on Inflammation/Allergy

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 (Table 1.1).



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 secretory 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 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 (H_1, H_2, and H_3) 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 causes vasodilation, low blood pressure, and increases the heart rate. It also causes symptoms such as itching, sneezing, watery eye, and running nose.

Histamine exerts its biological function by interacting with at least three distinctly specific receptors— H_1, H_2, and H_3. Historically, the term antihistamine has been used to describe a drug that

acts on H_1- and H_2-receptors. An antihistaminic agent should ideally prevent the production or release of these autacoids by inhibiting the response of sensitized mast cells and basophils to specific antigens.

1. Antihistamines are drugs that competitively block the H_1-receptors.
2. Antihistamines antagonize the stimulant action of histamine on the smooth muscles of gastrointestinal tract (GIT), uterus, and blood vessels, and inhibit histamine-augmented salivary secretion.
3. H_1-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 (Figure 1.1).

The release of histamine, in addition to the stimulation of IgE receptors, also activates the phospholipase A_2, leading to the production of host mediators, including platelet activating factors and metabolites of arachidonic acid. Leukotriene D_4 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 is 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 (Figure 1.2).

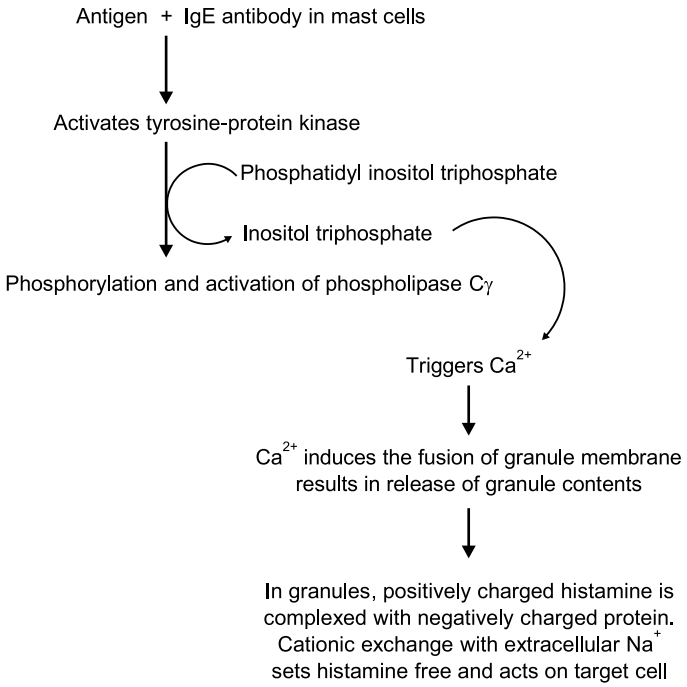


Figure 1.1: Steps involved in the release of histamine.

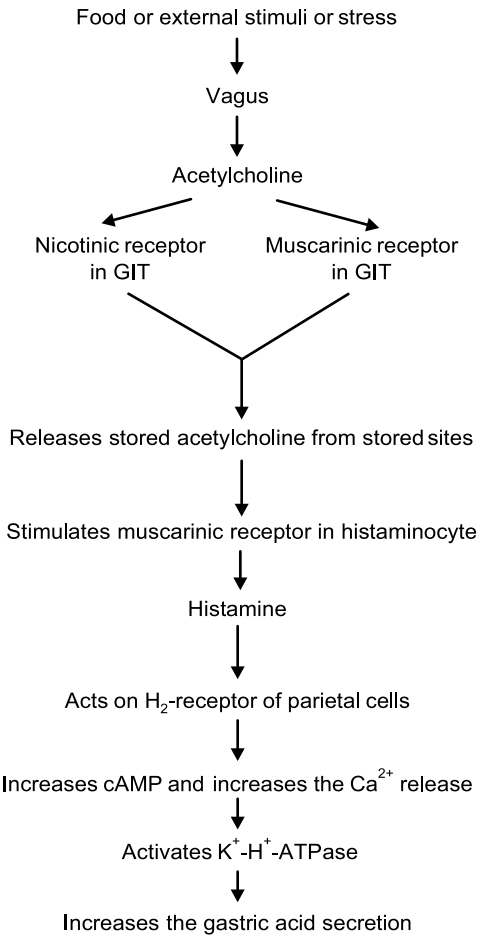


Figure 1.2: Histamine-induced gastric acid secretion.

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 A_2. The antihistaminergic drugs (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.

Table 1.1: Distribution of histamine receptors and the biological actions of histamine

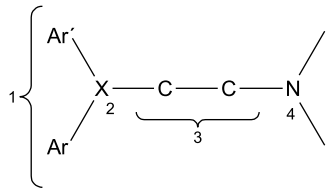
Recep-tor	***Location***	***Biological actions of histamine***		
		General	***In CNS***	***In allergy and immune modulation***
H_1	Widespread in the neuronal system, smooth muscles, endothelium	On stimulation: Itching, pain, vasodilation, tachycardia, broncho-constriction	Controls sleep–wake cycle, temperature regulation memory	Increases release of histamine, IgE production
H_2	Gastric mucosa, smooth muscle, heart, brain	Increased gastric acidity, increased airway mucous production, increased vascular permeability	Neuroendocrine regulation	Decreases neutrophil and eosinophil chemotaxis, suppresses cellular immunity
H_3	Histaminergic neurons and mysentric plexus	Prevent excessive broncho-constriction	Presynaptic hetero-receptor decreases histamine, NA, DA, 5-H, ACh release	–
H_4	Bone marrow and eosinophils, neutrophils	Differentiation of myeloblasts and promyelocytes	–	Increases eosinophills, chemotaxis and IL-16 production

STRUCTURE–ACTIVITY RELATIONSHIP—H_1-RECEPTOR ANTAGONISTS

Based on the pharmacological profile, the H_1-antihistamines are divided into two major groups:

1. First-generation or classical antihistamines
2. Second-generation or non-sedative antihistamines

The SAR of antihistamines is discussed with reference to the first-generation antihistamines. The structural requirements (pharmacophore) for H_1-antihistamines are shown below.



1. Aryl groups

- The diaryl substitution is essential for significant H_1-receptor 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. The active aryl substitutions are as follows:

  Ar: Phenyl, substituted phenyl and heteroaryl group like 2-pyridyl

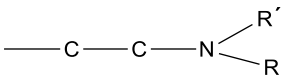
  Ar′: Aryl or aryl methyl group
- The majority of H_1-antihistamines possess substituents in one of the aryl rings (generally in phenyl ring), and this influences the potency of the compound. The two aryl rings may be linked, e.g. promethazine, cyproheptadine, and azatidine.

2. Nature of 'X'

- The X-connecting moiety of H_1-antihistamines may be simple carbon chain or saturated carbon–oxygen moiety, which serves as a spacer group for required pharmacophore.
- Antihistamines containing a carbon atom in the connecting moiety (example pheniramine series and carbinoxamine) exhibit chirality, which leads to stereoselective binding at the receptor. Among the enantiomers, the *S* isomer shows higher H_1-receptor-binding affinity.
- The active substitutions of X are as follows: X = oxygen (amino alkyl ether analogue), X = nitrogen (ethylene diamine derivative), X = carbon (mono amino propyl analogue).
- Based on the nature of this connecting moiety and the aryl moieties, H_1-antihistamines are further divided as ethylene diamines, amino alkyl ethers, mono amino propyl analogues, etc.

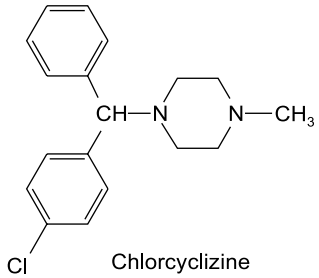
3. Alkyl chain $(CH_2)_n$

- The carbon chain consists of two or three atoms in H_1-antihistamines, which leads to the distance between the central point of the diaryl ring system and the terminal nitrogen atom in the extended conformation of these compounds in the range of 5–6 Å.



- Branching of this carbon chain leads to decrease in antihistaminic activity. (Exception is promethazine which is more potent than its non-branched counterpart.)
- If the carbon atom adjacent to the terminal nitrogen atom is branched, the possibility of asymmetry exists. However, it will not affect the binding affinity with the receptor.

4. Terminal nitrogen atom (NRR′): The terminal N-atom should be a 3° amine for maximum activity. The terminal nitrogen may be a part of heterocyclic ring, e.g. antazoline and chlorcyclizine which also retains high antihistaminic activity. The amino moiety deserves the protonation on interaction with H_1 -receptor due to the basicity with pK_a 8.5–10. For preparing stable solid dosage forms through salt formation the amino moiety is important.



Chlorcyclizine

Note: The antihistamines exhibit a range of pharmacological activities because of their interaction with H_1-receptors distributed throughout the body, and its pharmacophore is similar to that of pharmacophore required for binding to muscarinic as well as adrenergic and serotonergic receptors, which leads to the side effects like cardiac arrhythmia, dry mouth, etc., apart from sedation.

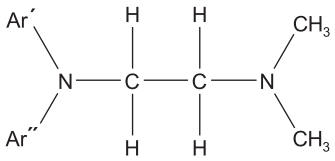
CLASSIFICATION

I. H_1-Antagonists with Classical Structures

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

a. Ethylene diamine derivatives
b. Amino alkyl ether analogues
c. Cyclic basic chain analogues or piperazine derivatives
d. Mono amino propyl analogues
e. Tricyclic ring system or phenothiazine derivatives
f. Dibenzocycloheptenes
g. Miscellaneous agents
h. Newer agents

a. Ethylene diamine derivatives



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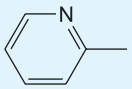
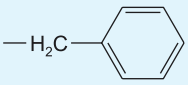
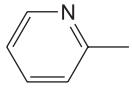
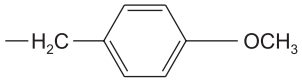
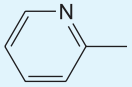
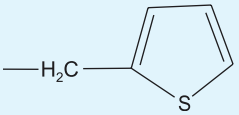
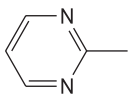
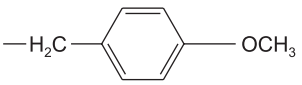
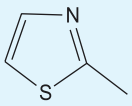
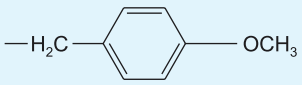
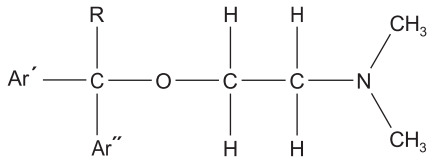
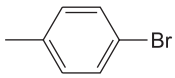
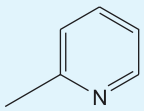
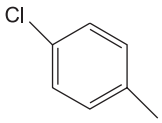
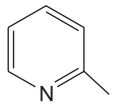
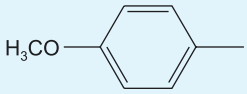
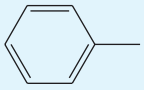
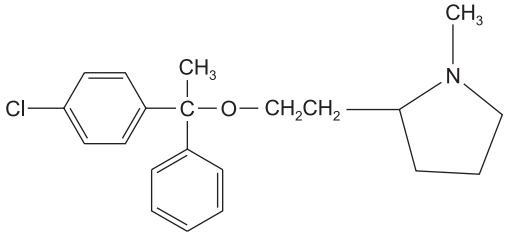
Tripelennamine		
Pyrilamine		
Methapyrilene		
Thonzylamine		
Zolamine		

b. Amino alkyl ether analogues

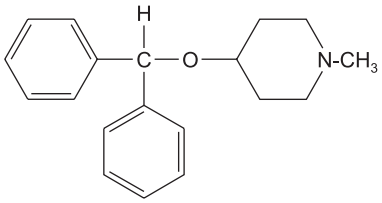


Name	*Ar'*	*Ar''*	*R*
Diphenhydramine	$-C_6H_5$	$-C_6H_5$	–H
Bromodiphenhydramine	$-C_6H_5$		–H
Doxylamine	$-C_6H_5$		$-CH_3$
Carbinoxamine			–H
Medrylamine			–H

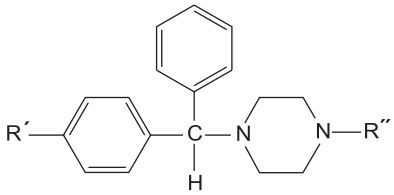
Clemastine



Diphenylpyraline



c. Cyclic basic chain analogues or piperazine derivatives



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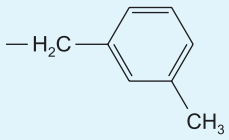
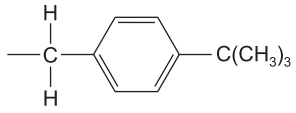
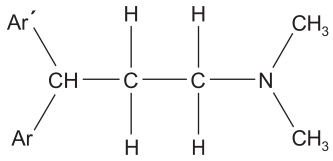
Chlorcyclizine	–Cl	$-CH_3$
Meclizine	–Cl	
Buclizine	–Cl	

d. Mono amino propyl analogues

i. Saturated analogues



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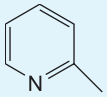
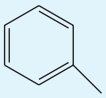
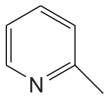
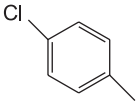
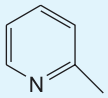
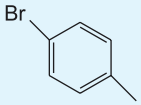
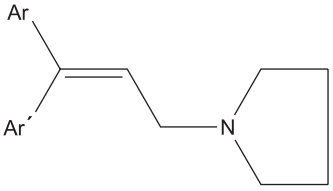
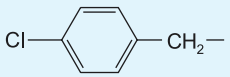
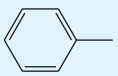
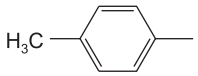
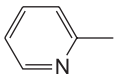
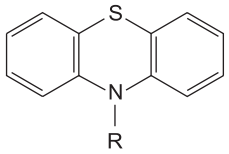
Pheniramine		
Chlorpheniramine		
Bromopheniramine		

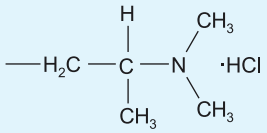
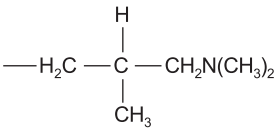
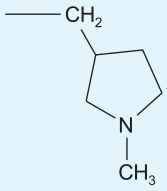
ii. Unsaturated analogues



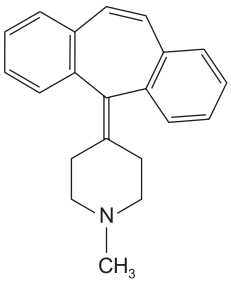
Name	*Ar*	*Ar′*
Pyrrobutamine		
Triprolidine		

e. Tricyclic ring system or phenothiazine derivatives

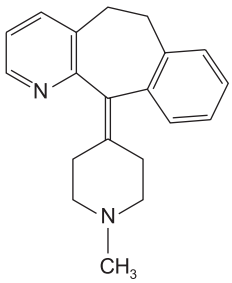


Name	*R*
Promethazine hydrochloride	
Trimeprazine	
Methdilazine	

f. Dibenzocycloheptenes

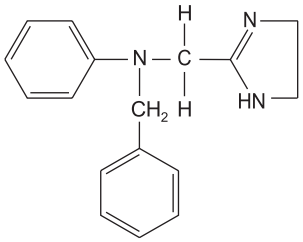


Cyproheptadine

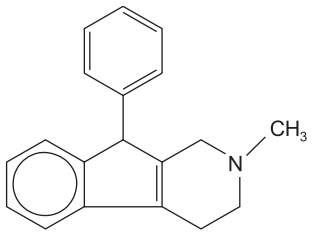


Azatadine

g. Miscellaneous agents

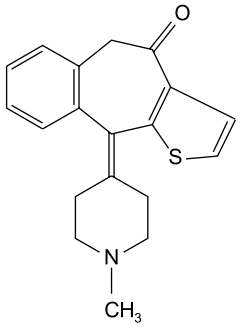


Antazoline

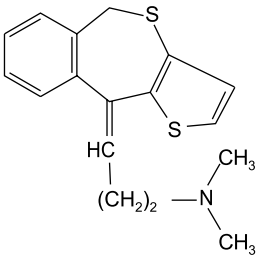


Phenindamine

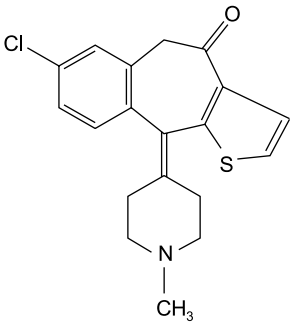
h. Newer agents



Ketotifene



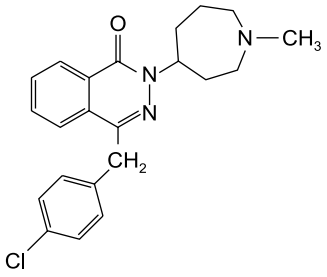
Dithiadene



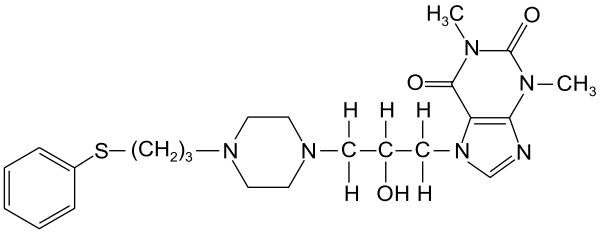
7-Chloroketotifene

II. H_1-Antagonists with Non-classical Structures

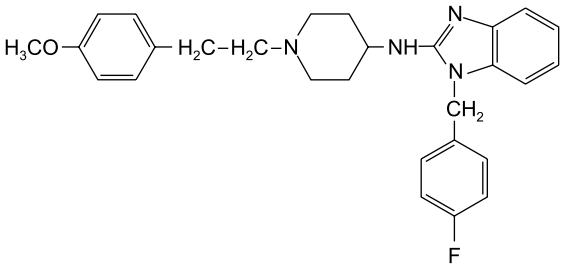
i. Azelastine



ii. Tazifylline



iii. Astemizole



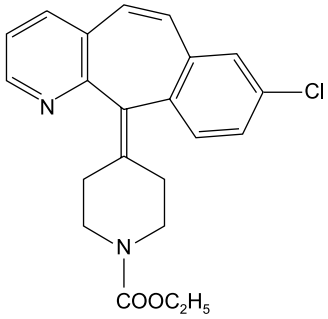
III. Non-sedative H_1-antihistamines

Non-sedative antihistamines bind only to peripheral H_1-receptors and produce with little or no sedation because of poor CNS penetration and lower affinity for central histaminic activity.

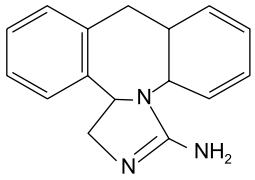
These are divided into two main classes:

1. Piperazine derivatives—cetirizine
2. Pyridine and piperidine derivatives—loratadine, fexofenadine, terfenadine, astemizole, acrivastine

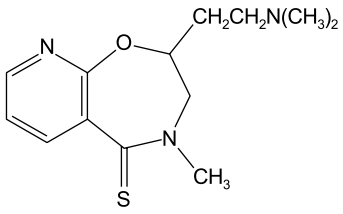
i. Loratadine



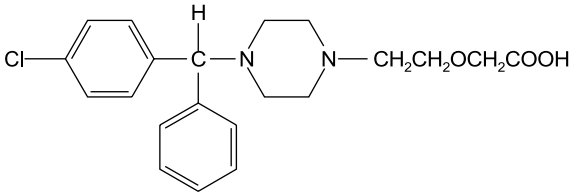
ii. Epinastine



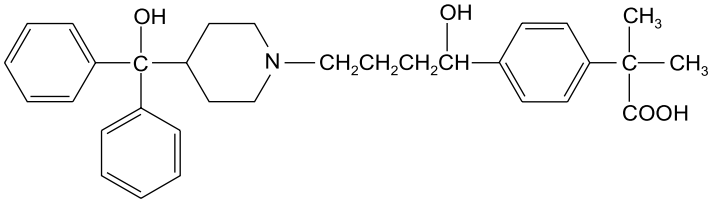
iii. Rocastine



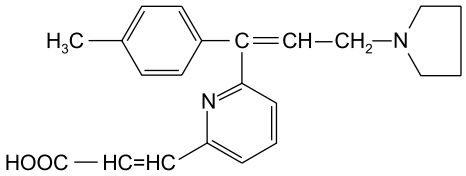
iv. Cetirizine



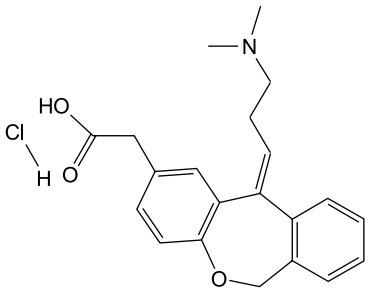
v. Fexofenadine



vi. Acrivastine

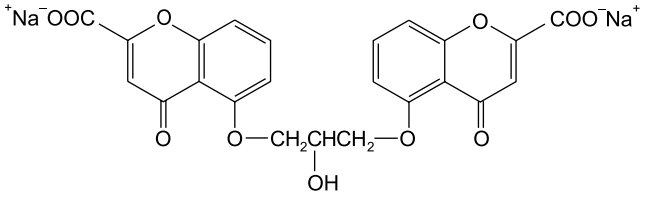


vii. Olopatadine hydrochloride

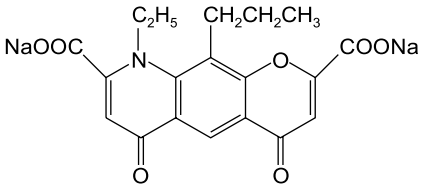


IV. Inhibition of Histamine Release (Mast Cell Stabilizers)

i. Cromolyn sodium



ii. Nedocromil sodium



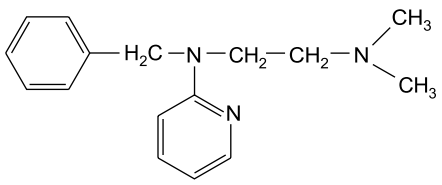
SYNTHESIS AND DRUG PROFILE

I. H_1-Antagonists with Classical Structure

a. Ethylene diamine derivatives

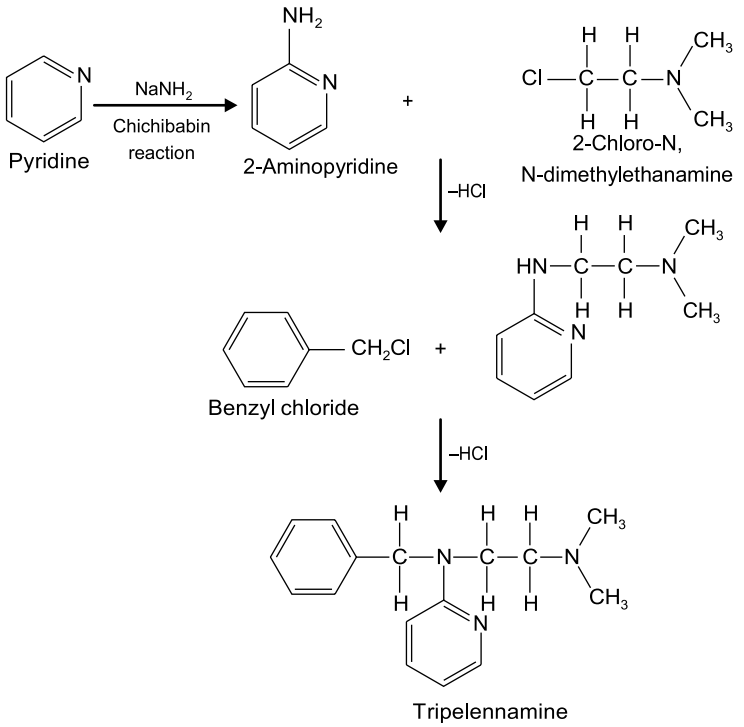
Metabolism of ethylene diamine derivatives: These antihistaminic drugs undergo N-demethylation and subsequent deamination. In addition, some compounds produce quaternary N-glucuronide as urinary metabolites, a process that occurs to some extent in many relatively unhindered tertiary aliphatic amines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

i. Tripelennamine (Pyribenzamine HCl)



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

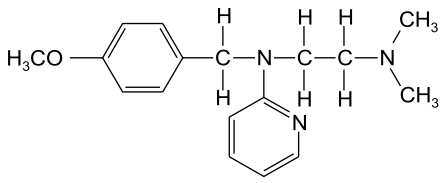
Synthesis



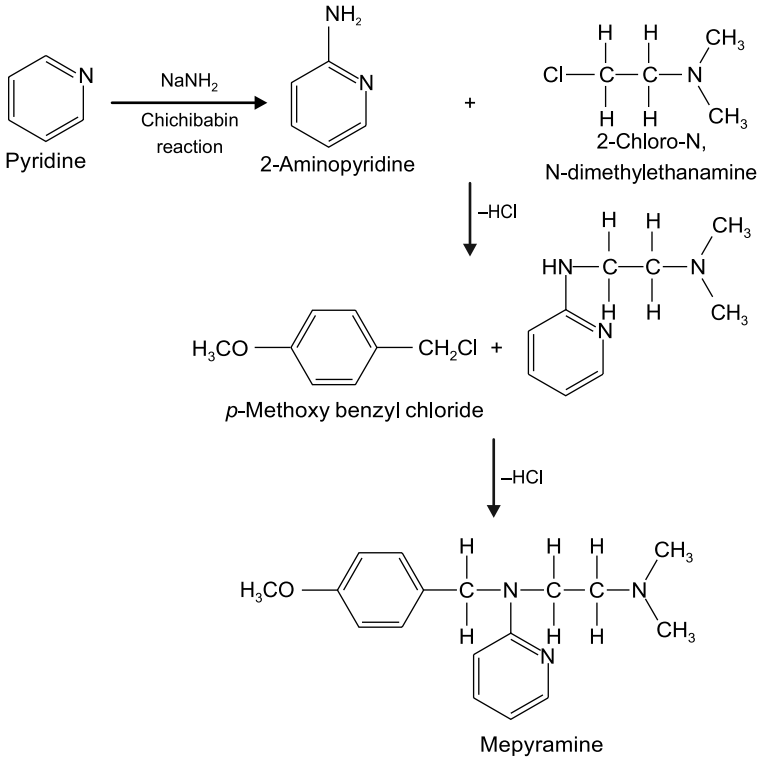
Properties and uses: It is a white, crystalline powder, soluble in water, freely soluble in alcohol and ether, but insoluble in chloroform or benzene. Tripelennamine is the first ethylenediamine developed in the American laboratories; it appears to be effective as diphenhydramine and may have the advantage 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)



Synthesis



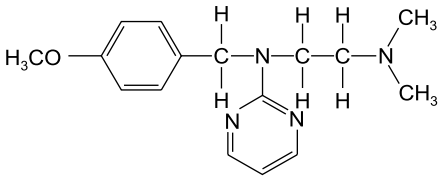
Properties and uses: Mepyramine maleate is a white or slightly yellowish crystalline powder, soluble in water and in ethanol. Pyrilamine differs structurally from tripelennamine having a methoxy group in the *para* position of the benzyl radical. It differs from its more toxic and less potent precursor 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.

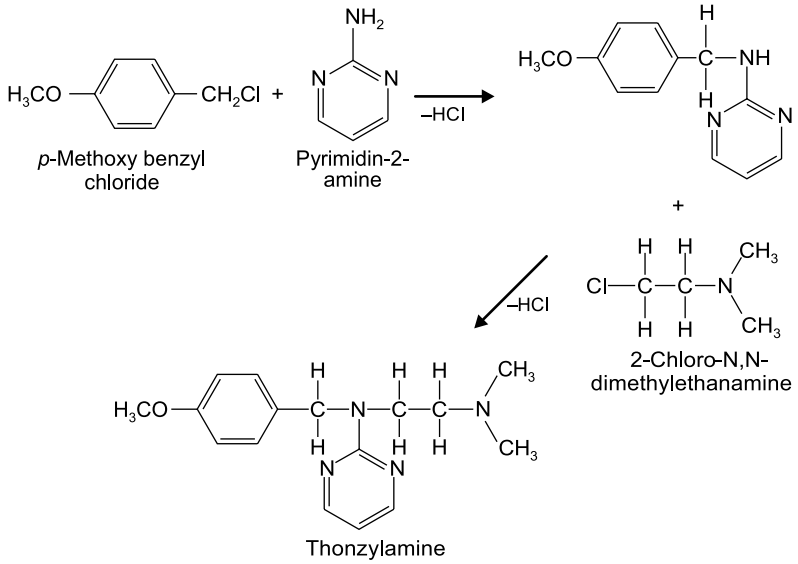
Dosage forms: Mepyramine tablets BP.

iii. Thonzylamine (Resistab)



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

Synthesis

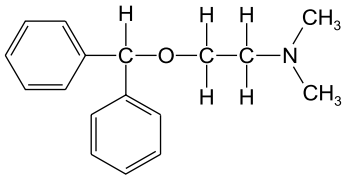


Properties and uses: It is recommended for use with streptomycin in exudative human tuberculosis. It is used in treating the symptoms of diseases, such as hay fever, urtricaria, and other mild allergic conditions.

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

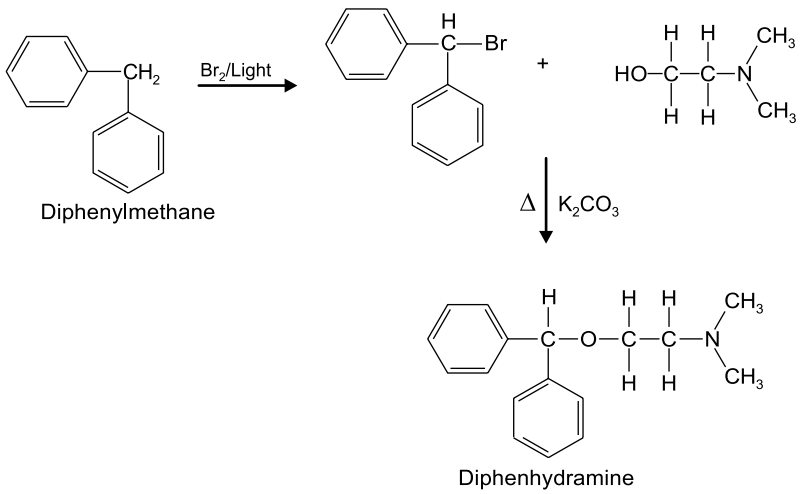
b. Amino alkyl ether analogues

i. Diphenhydramine (Benadryl, Bendylate)



2-(Benzhydryloxy)-N,N-dimethylethanamine

Synthesis



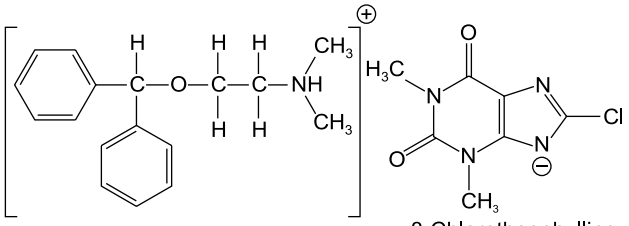
Properties and uses: Diphenhydramine hydrochloride is a white crystalline powder, soluble in water and in alcohol. In addition to antihistaminic activity, diphenhydramine exhibits antiemetic, antitussive, and sedative properties.

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.

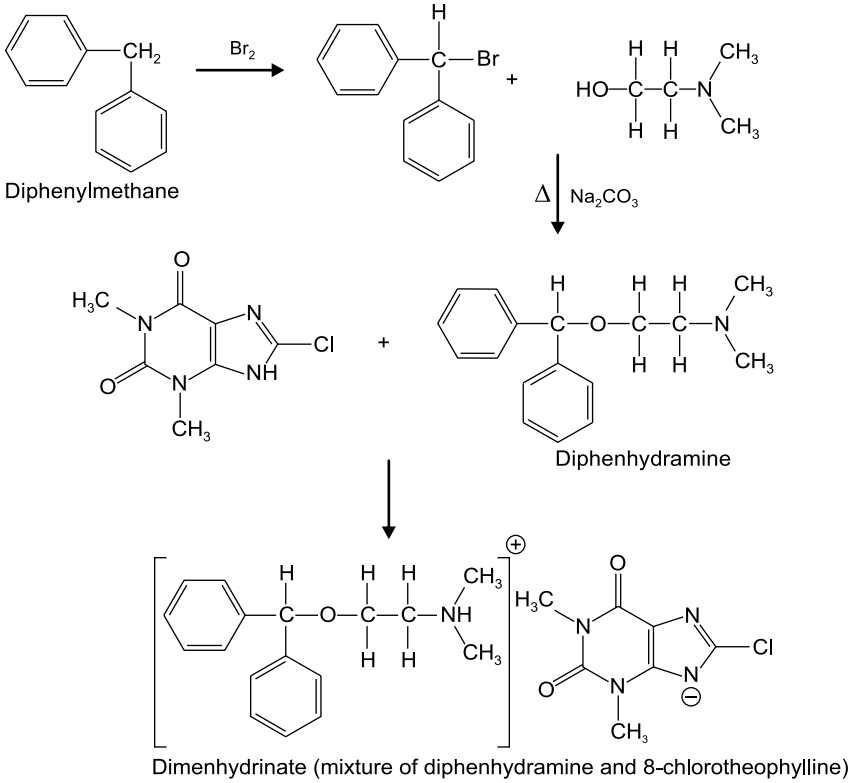
Dose: Usual dose is 25–50 mg for adult taken orally three to four times per day with maximum of 400 mg per day; for skin—used topically 2% of the cream three or four times per day.

Dosage forms: Diphenhydramine oral solution BP.

ii. Dimenhydrinate (Dramamine)



Synthesis



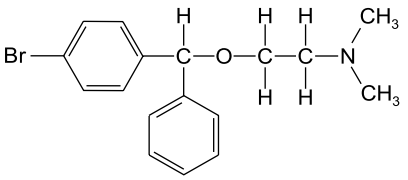
Properties and uses: Dimenhydrinate is a white crystalline powder or colourless crystals, slightly soluble in water and in alcohol. Used as histamine H_1-receptor antagonist, antinauseant, in motion sickness, radiation sickness, and also in the case of nausea during pregnancy.

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.

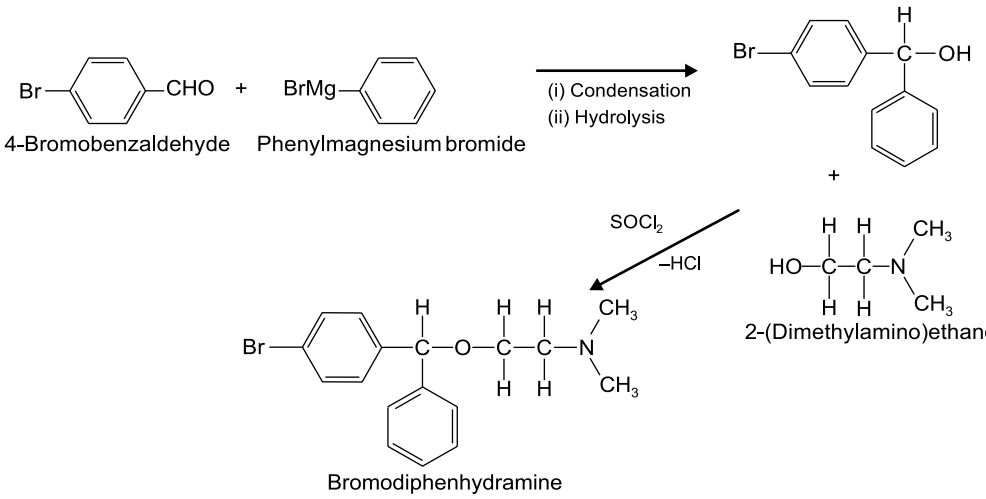
Dosage forms: Dimenhydrinate tablets BP.

iii. Bromodiphenhydramine (Ambodryl hydrochloride)



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

Synthesis



4-Bromobenzaldehyde Phenylmagnesium bromide

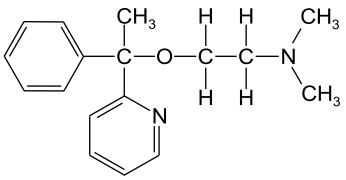
2-(Dimethylamino)ethanol

Bromodiphenhydramine

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

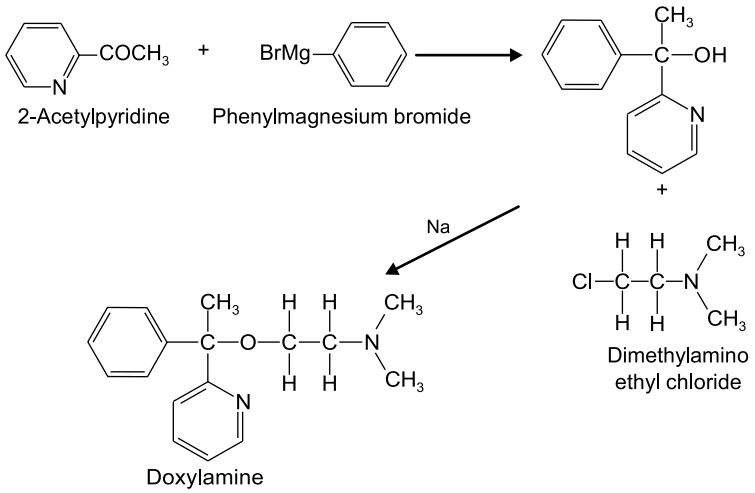
Dose: Usual dose is 25 mg three or four times per day.

iv. Doxylamine (Decapryn succinate)



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

Synthesis

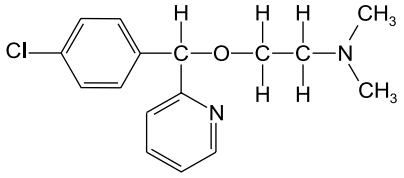


Properties and uses: Doxylamine succinate is a white powder, highly soluble in water and in alcohol. It is a relatively selective histamine H_1-receptor antagonist. *In vivo* studies have shown that concentrations dependent upon the inhibition of histamine-stimulated vascular permeability in the conjunctiva 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 per chloric acid. Determine the end point potentiometrically.

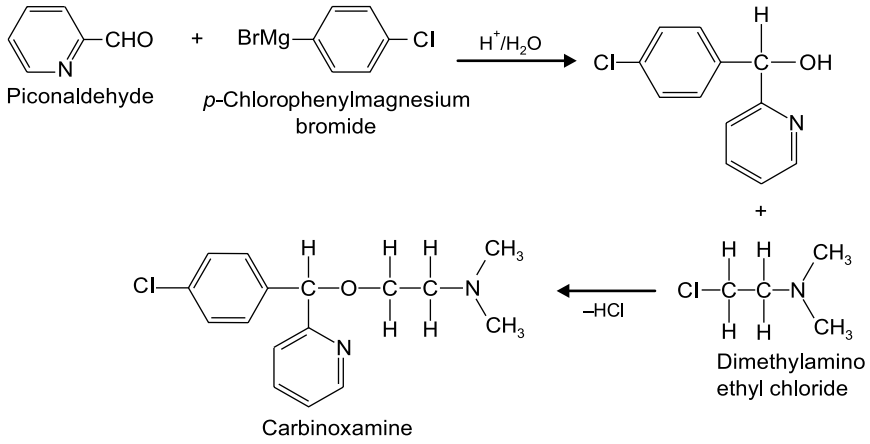
Dose: Usual dose is 12.5 to 25 mg for adult taken orally four to six times per day.

v. Carbinoxamine



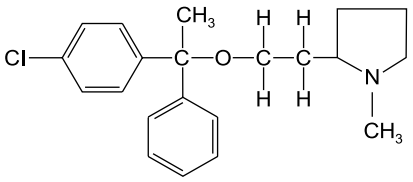
2-((4-Chlorophenyl)(pyridin-2-yl)methoxy)-N,N-dimethylethanamine

Synthesis



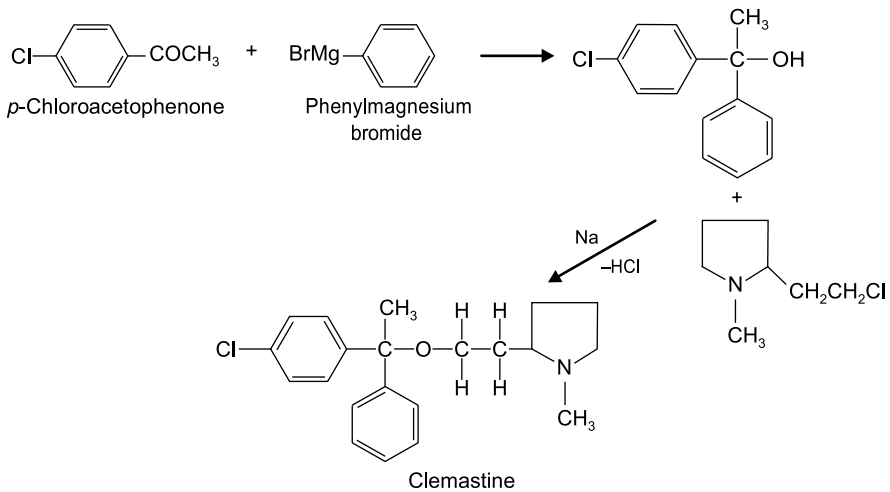
Properties and uses: Carbinoxamine is available as white, crystalline powder with no odour, soluble in water, alcohol, chloroform, or ether. It is a potent antihistaminic and is available as the racemic mixture. It differs structurally from chlorpheniramine only in having an oxygen atom separate from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

vi. Clemastine



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

Synthesis

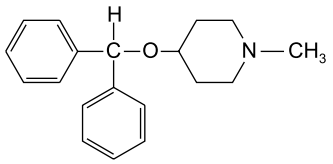


Properties and uses: Clemastine fumarate is a white crystalline powder, very slightly soluble in water, slightly soluble in alcohol and methanol. It has two chiral centres, each of which is (R) absolute configuration. A comparison of the activities of the antipodes indicates that the asymmetric centre 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.

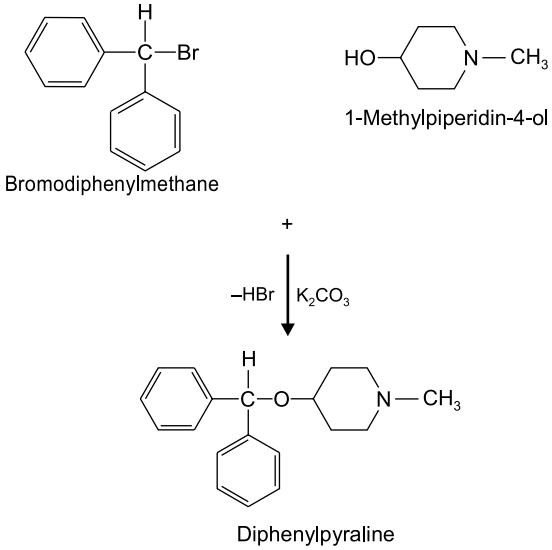
Dosage forms: Clemastine oral solution BP, clemastine tablets BP.

vii. Diphenylpyraline (Diaben)



4-(Diphenylmethoxy)-1-methylpiperidine

Synthesis

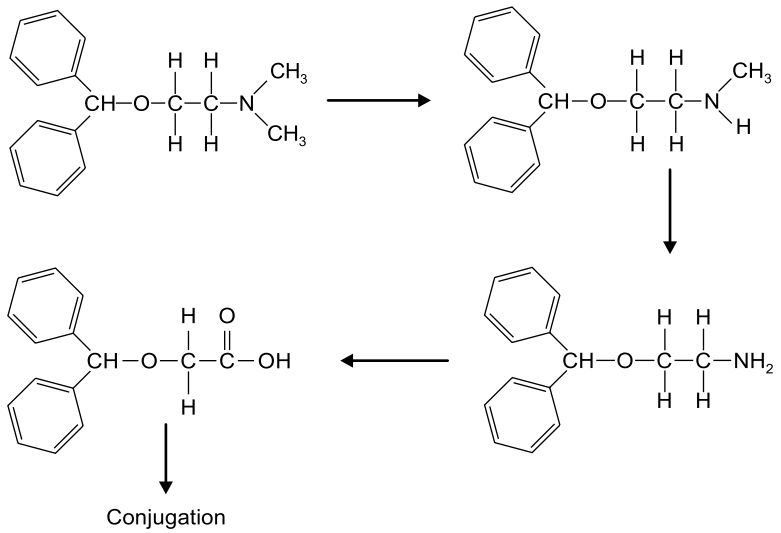


Bromodiphenylmethane

1-Methylpiperidin-4-ol

Diphenylpyraline

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.



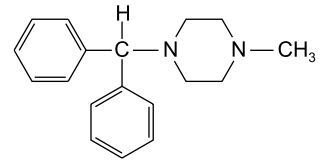
Properties and uses: Diphenylpyraline hydrochloride is a white powder, soluble in water and ethanol, practically insoluble in ether. It is structurally related to diphenhydramine with the aminoalkyl side chain incorporated in a piperidine ring. It is a potent antihistaminic agent.

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.

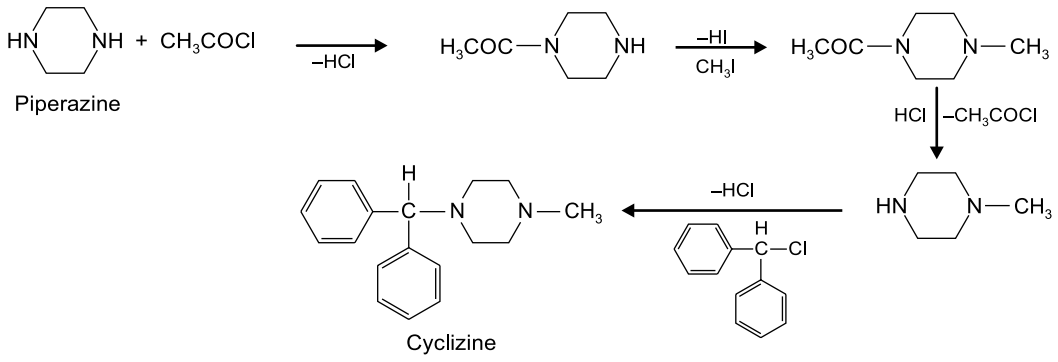
Dose: Usual dose for adults taken orally is 5 mg two times per day.

c. Piperazine derivatives

i. Cyclizine (Marezine)



Synthesis



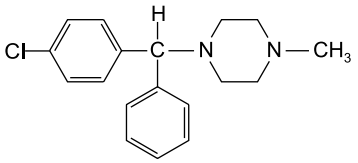
Properties and uses: Cyclizine hydrochloride is a white crystalline powder, slightly soluble in water and in alcohol. It is mostly employed as a prophylaxis and for the treatment of motion sickness.

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

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

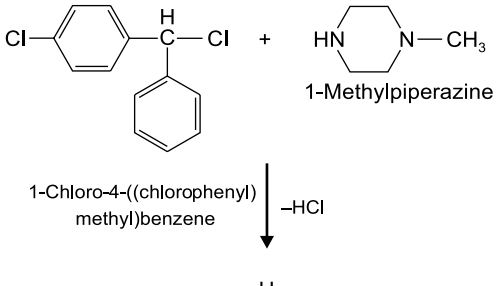
Dosage forms: Cyclizine HCl tablets IP, cyclizine injection BP, cyclizine tablets BP, dipipanone and cyclizine tablets BP.

ii. Chlorcyclizine (Diparalene)



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

Synthesis



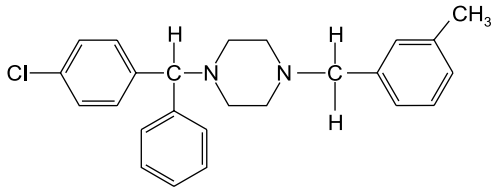
Chlorcyclizine

Properties and uses: Chlorcyclizine hydrochloride is a white crystalline powder, soluble in water, methylene chloride, and alcohol. Substitution of halogen in the second or third 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.

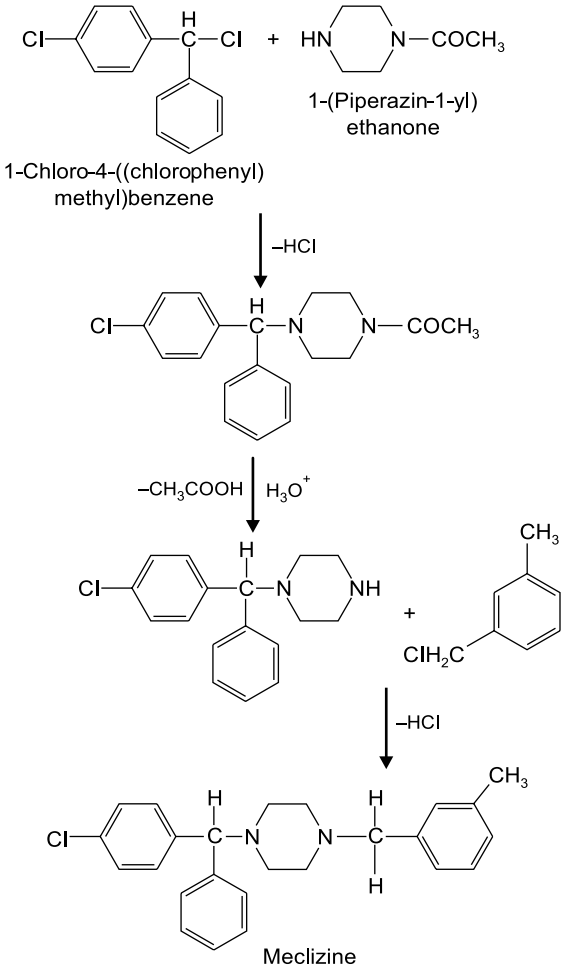
Dose: Usual dose is 50–200 mg per day.

iii. Meclizine (Antivert, Bonine)



1-(*p*-Chlorophenylbenzyl)-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.

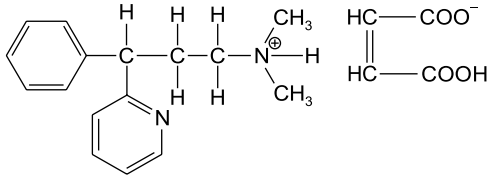
Assay: Dissolve the sample in alcohol and titrate against 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: Usual dose is 25–50 mg per day.

d. Monoamino propylamine derivatives

i. Saturated analogues

1. Pheniramine maleate (Avil, Polarmine)



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

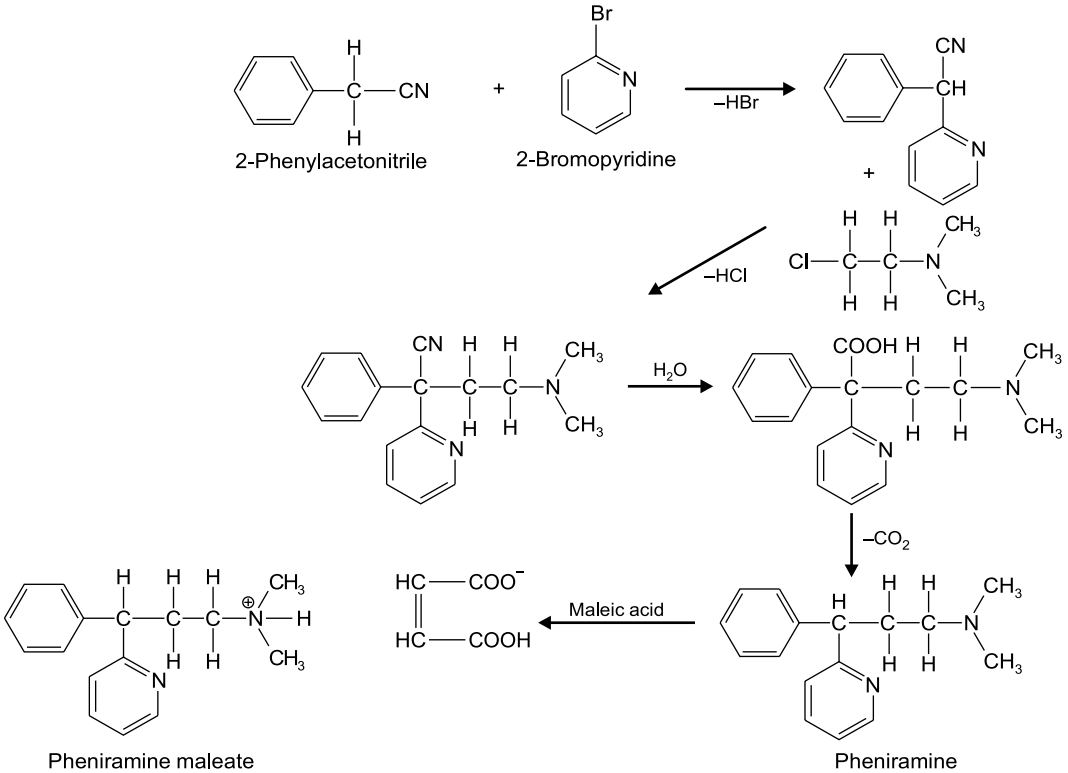
Properties and uses: Pheniramine maleate is a white crystalline powder, freely soluble in water, alcohol, methanol, and methylene chloride. This drug is the least potent member of the series and is marketed as the racemate.

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

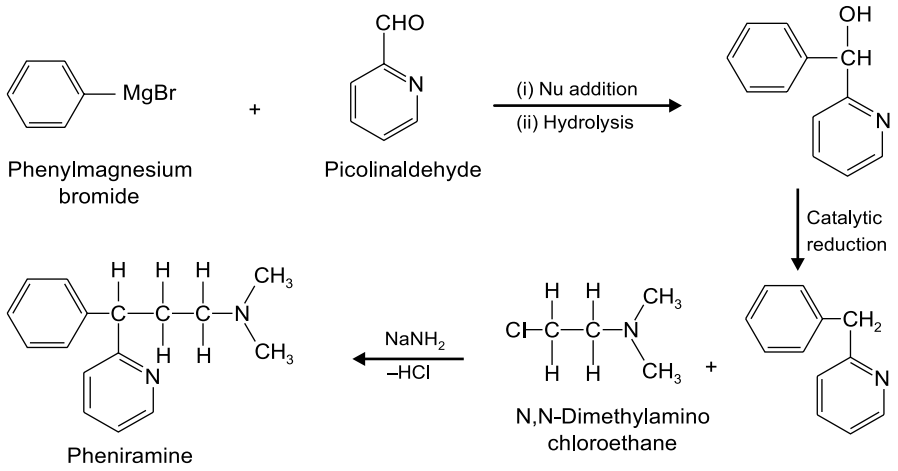
Dose: Usual dose is 25–30 mg per day in divided doses.

Synthesis

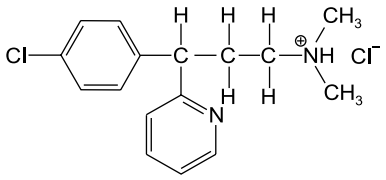
Route I. From: 2-Phenylacetonitrile



Route II. From: Picolinaldehyde



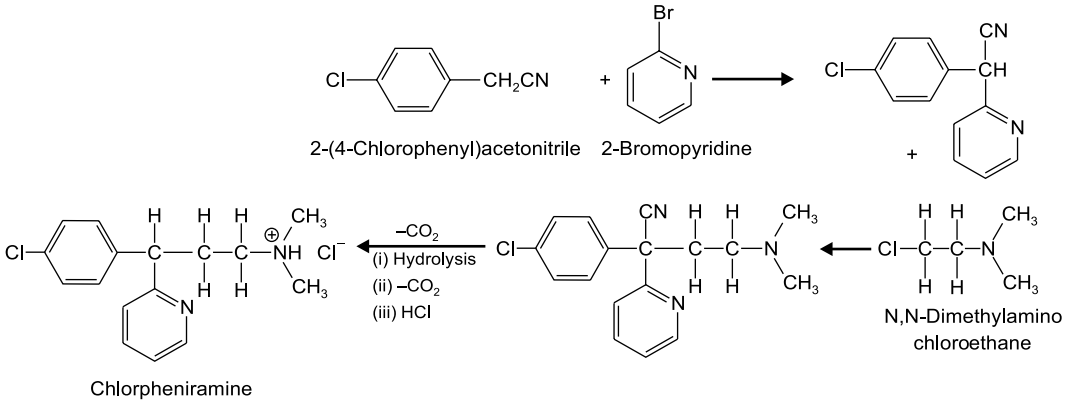
2. Chlorpheniramine HCl (Piriton, Alermine)



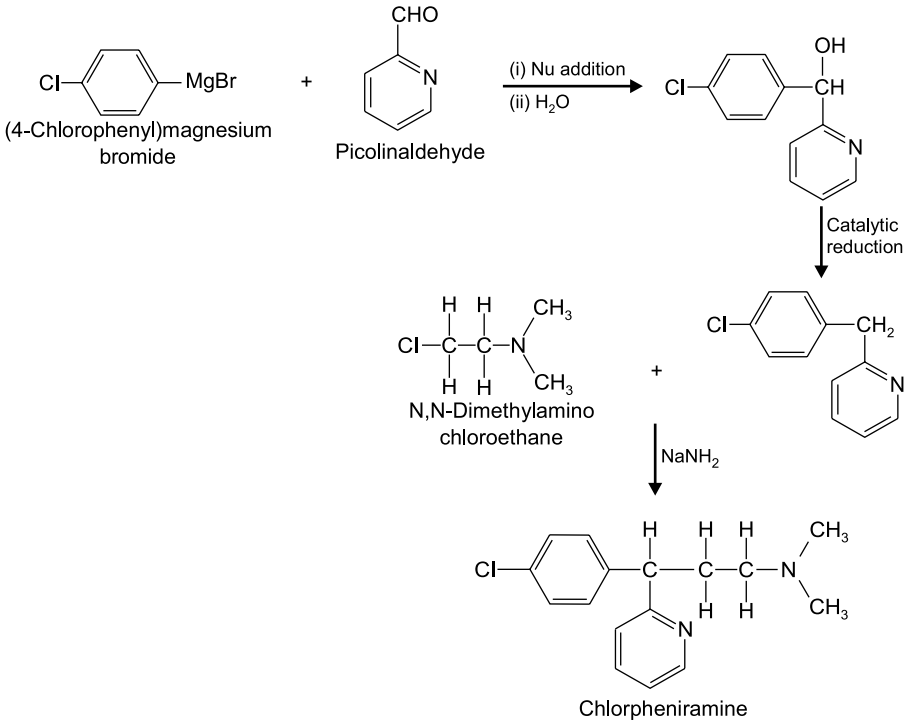
3-(4-Chlorophenyl)-N,N-dimethyl-3-(pyridin-2-yl)propan-1-amine

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.

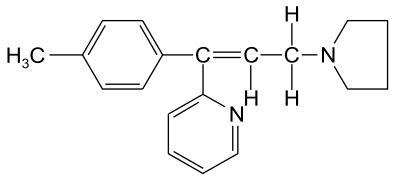
Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

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

Dosage forms: Chlorpheniramine maleate injection IP, BP, chlorpheniramine maleate tablets IP, BP, chlorpheniramine oral solution BP.

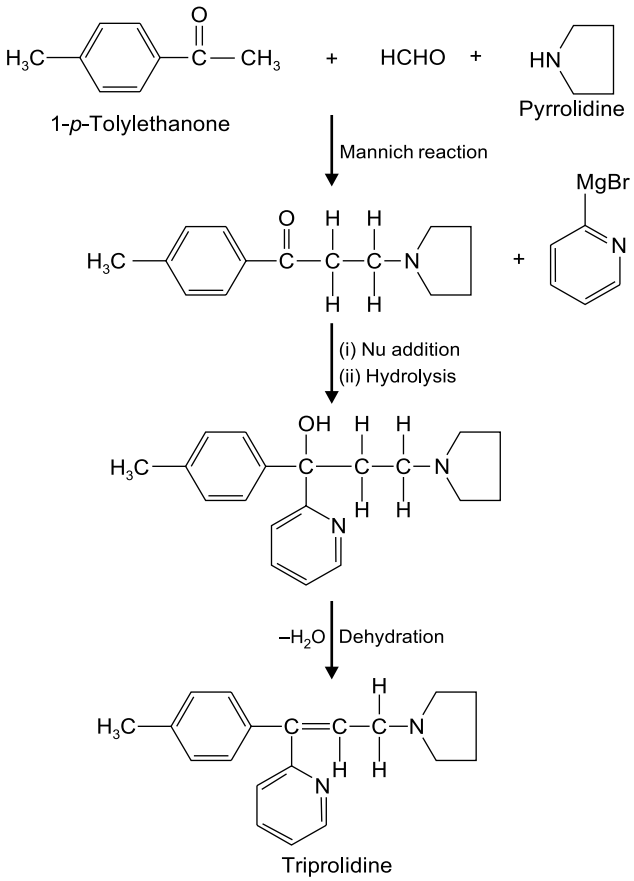
ii. Unsaturated analogues

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 H_1-antagonists. In guinea pig ileum sites, the affinity of triprolidine (E) for H_1-receptors was more than 1000 times the affinity of its (Z) partner.

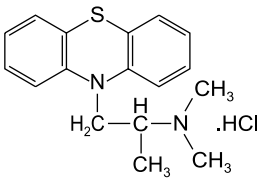
Assay: Dissolve the sample in a mixture of anhydrous acetic acid and acetic anhydride and titrate against 0.1 M perchloric acid using crystal violet solution as indicator.

Dose: Usual dose is 5–7.5 mg per day.

Dosage forms: Triprolidine HCl tablets IP, triprolidine tablets BP.

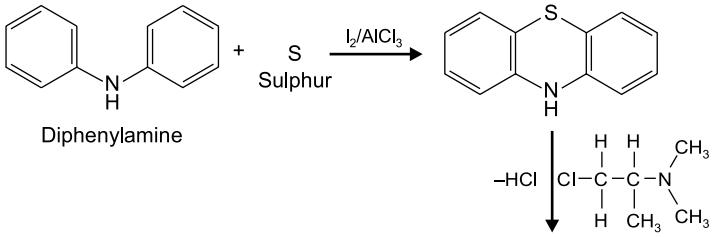
e. Tricyclic ring system or phenothiazines

1. Promethazine HCl (Phenargen)



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

Synthesis



Promethazine hydrochloride

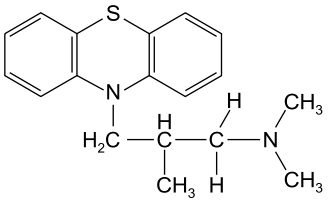
Properties and uses: Promethazine hydrochloride is a white or faintly yellowish crystalline powder, highly soluble in water, soluble in alcohol and in methylene chloride. It may be used effectively in perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant 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.

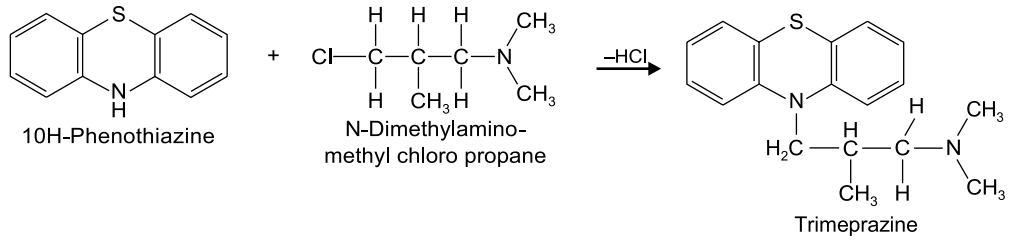
Dosage forms: Promethazine hydrochloride injection IP, promethazine hydrochloride tablets IP, BP, promethazine hydrochloride syrup IP, promethazine injection BP, promethazine oral solution BP.

2. Trimeprazine (Temaril)



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

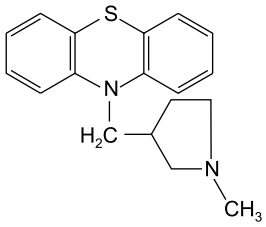
Synthesis



Properties and uses: It is a white crystalline powder, soluble in water. It is used as histamine H_1-receptor antagonist.

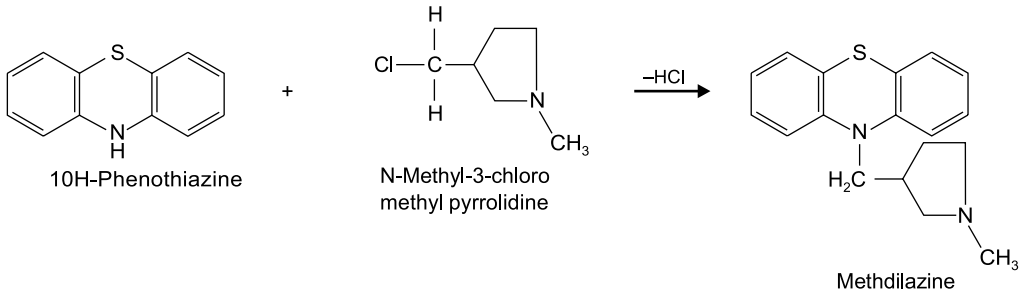
Dose: Usual dose for adults is 10–40 mg per day orally.

3. Methdilazine (Tacaryl HCl)



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

Synthesis

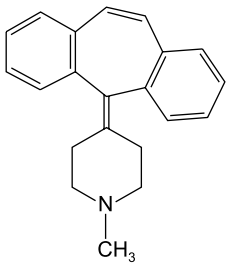


Properties and uses: It may be used for the symptomatic relief of urticaria. It has also been used successfully for the treatment of migraine headache.

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

f. Dibenzocycloheptene derivatives

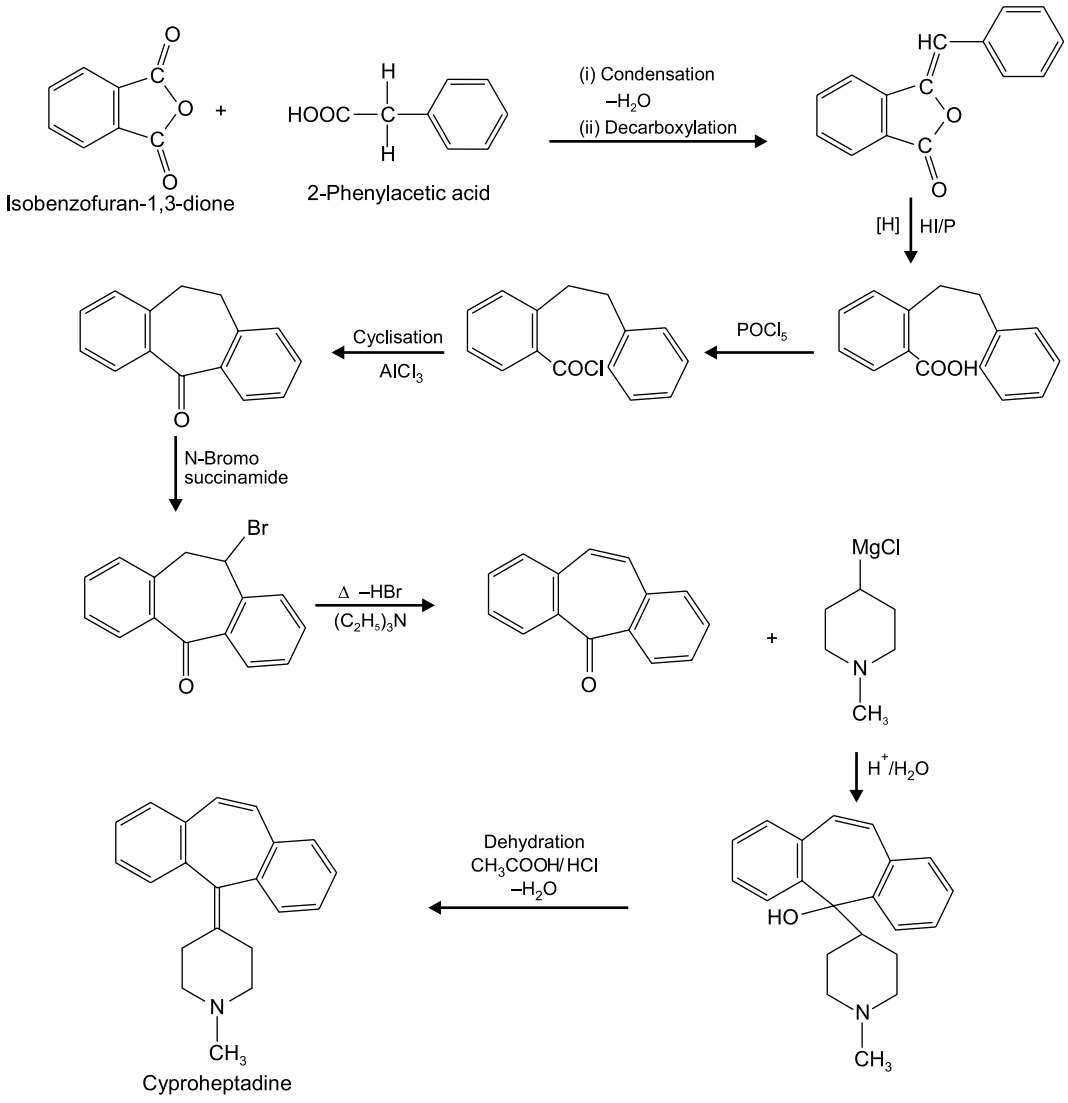
1. Cyproheptadine (Periacetin)



4-Dibenzo(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 antipruritic 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

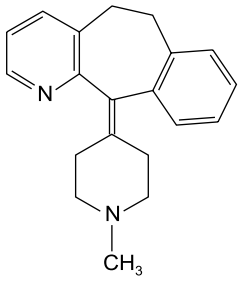


Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol and titrate against 0.1 M sodium hydroxide. Determine end point potentiometrically.

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

Dosage forms: Cyproheptadine HCl syrup IP, cyproheptadine HCl tablets IP, cyproheptadine tablets BP.

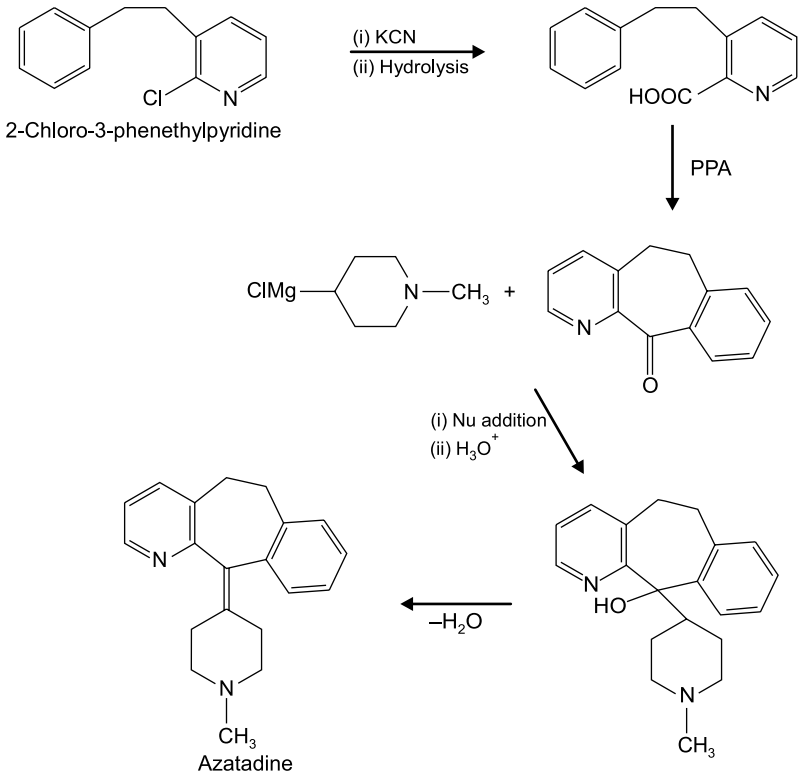
2. Azatadine



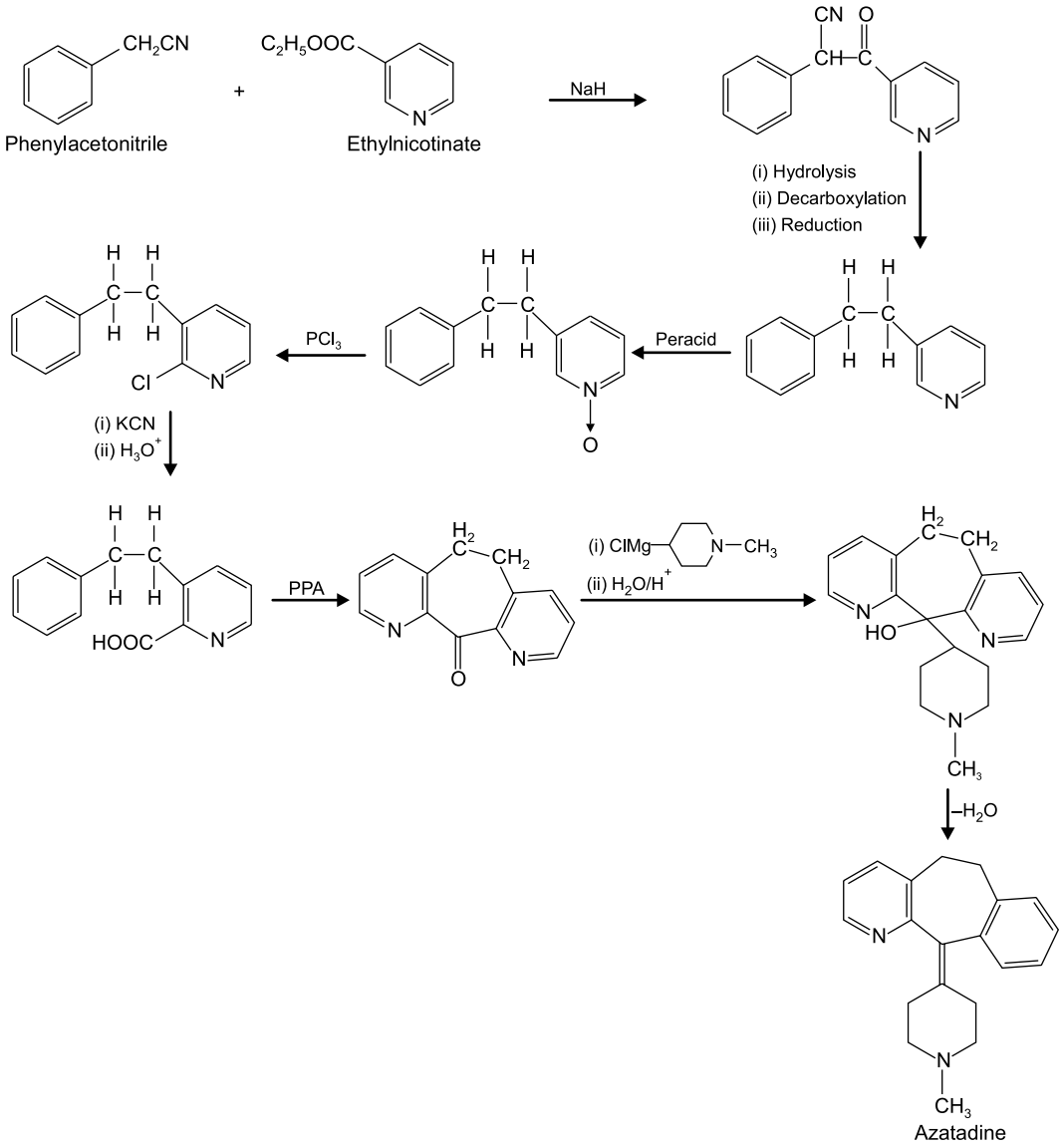
6,11-Dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo-[5,6]-cyclohepta-9-[1,2-6]pyridine

Synthesis

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



Route II. From: Phenylacetonitrile

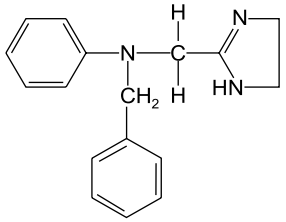


Properties and uses: Azatadine is a potent, long-acting antihistaminic with antiserotonin activity. In early testing, azatadine exhibited more than three times the potency of chlorpheniramine in the isolated guinea pig ileum screening and more than seven times the oral potency of chlorpheniramine in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

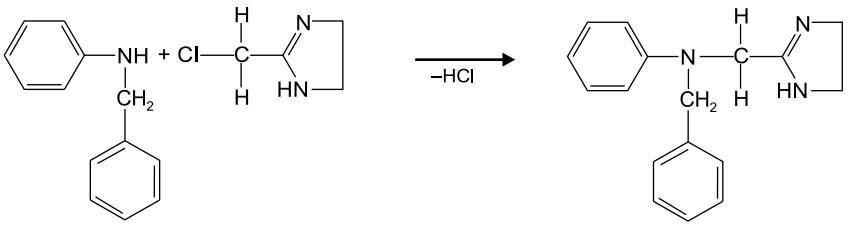
g. Miscellaneous

1. Antazoline (Antistine)



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

Synthesis



Benzyl aniline Antazoline

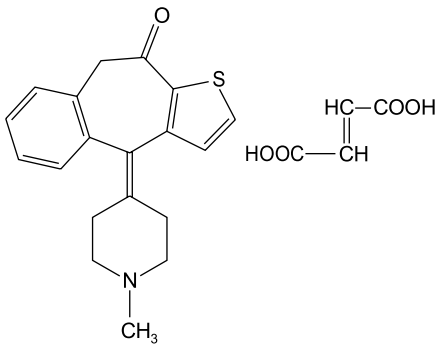
Properties and uses: Antazoline hydrochloride is a white crystalline powder, sparingly soluble in water, soluble in alcohol, and slightly soluble in methylene chloride. The phosphate salt is soluble in water, bitter taste. It is used for the treatment of rhinitis and conjunctivitis.

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.

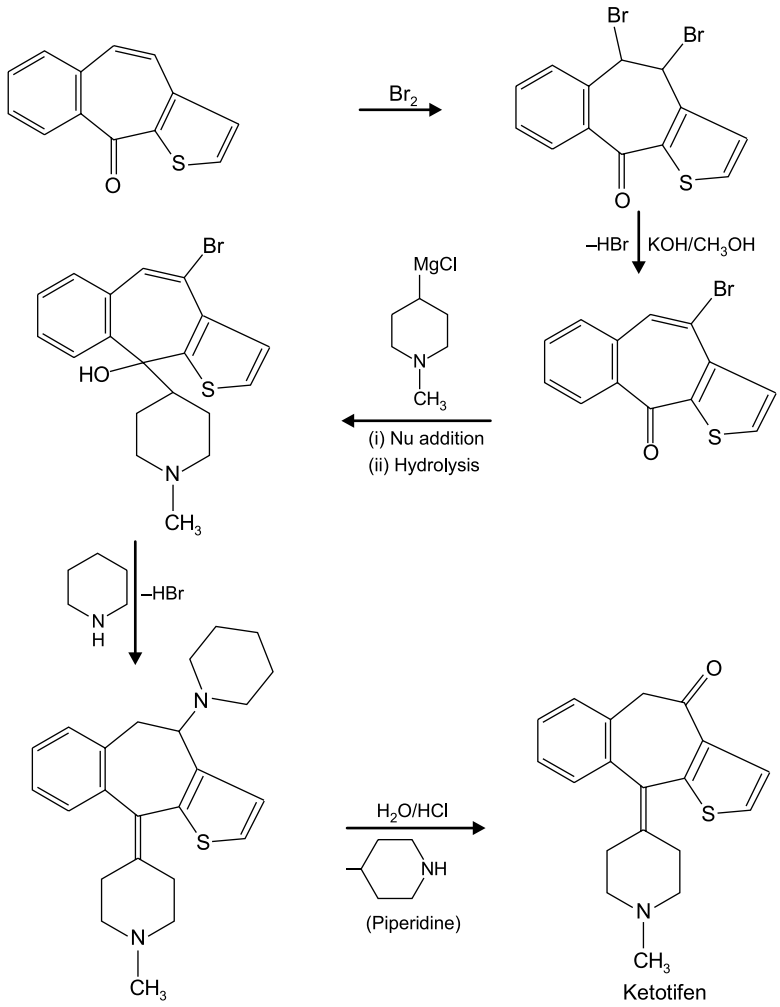
h. Newer agents

1. Ketotifen fumarate (Zaditen)



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

Synthesis



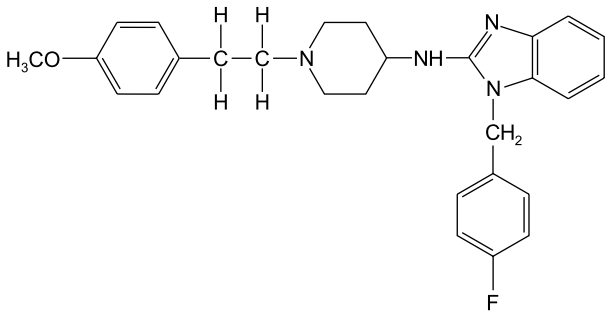
Properties and uses: Ketotifen fumarate is a white to brownish-yellow crystalline powder, sparingly soluble in water, slightly soluble in methanol and in acetonitrile. The recommended dose of ketotifen solution is one drop instilled into each affected eye every 8–12 hrs. Most frequently used for conjunctival 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.

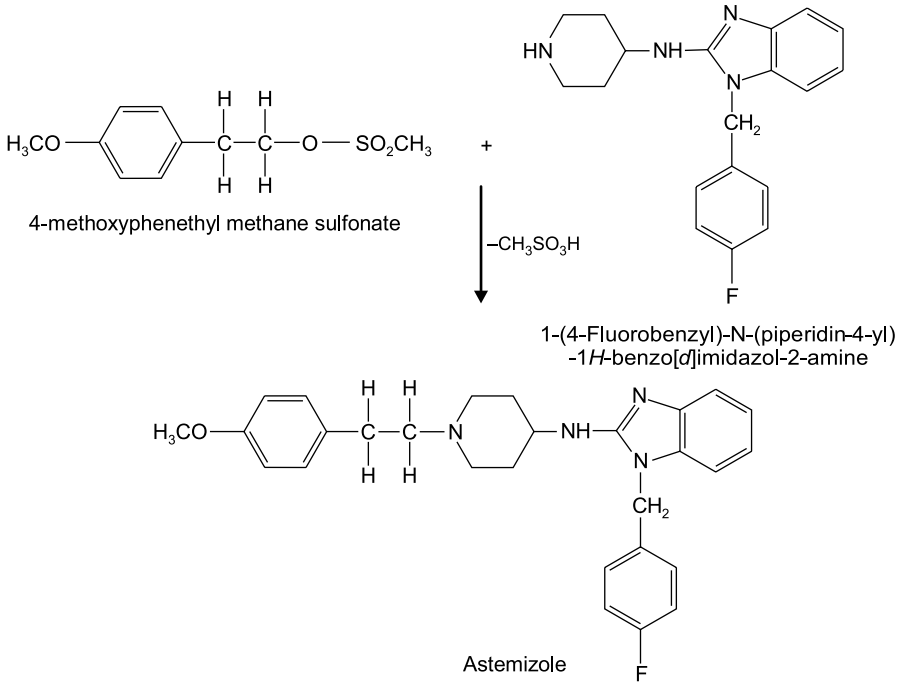
II. H_1-Antagonists with Non-classical Structure

1. Astemizole (Histalong)



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

Synthesis

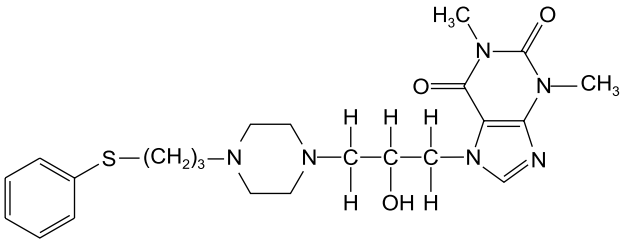


Properties and uses: Astemizole is a white powder, practically insoluble in water, soluble in methylene chloride, methanol, and alcohol. The drug is found to be more potent and possesses longer duration of action than the terfenadine. It has a slow onset, is long acting, and non-sedating piperidine antihistaminic 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.

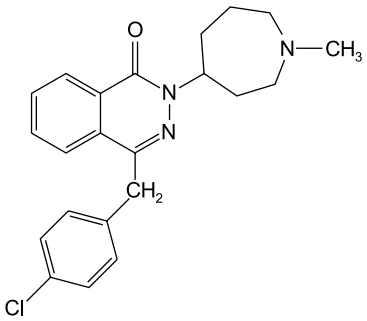
Dose: Usual dose is 10 mg (oral) increased, if required, to 30 mg per day for up to 7 days 1 hr before meals. It is not recommended for children below 6 years.

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.

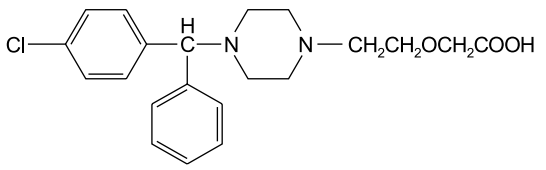
3. Azelastine



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 H_1-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. Non-sedative H_1-antihistamines (H_1-antagonists)

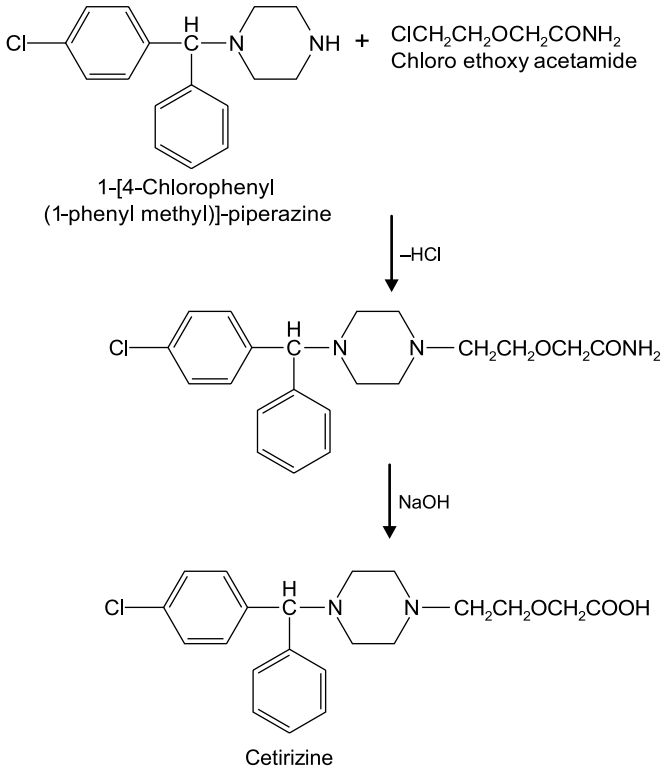
1. Cetirizine (Zirtin, Cetin, Cetzine)



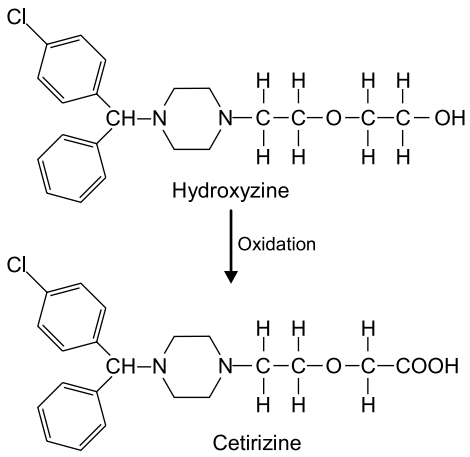
2-(2-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl) ethoxy)acetic acid

Synthesis

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



Route II. From: Hydroxyzine



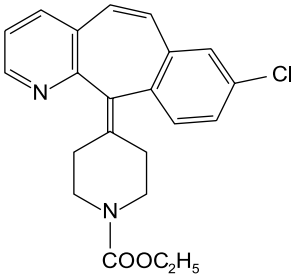
Cetirizine is an acid metabolite formed by the oxidation of primary alcohol of antihistamine hydroxyzine.

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 H_1-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 inflexion and determine the end point potentiometrically.

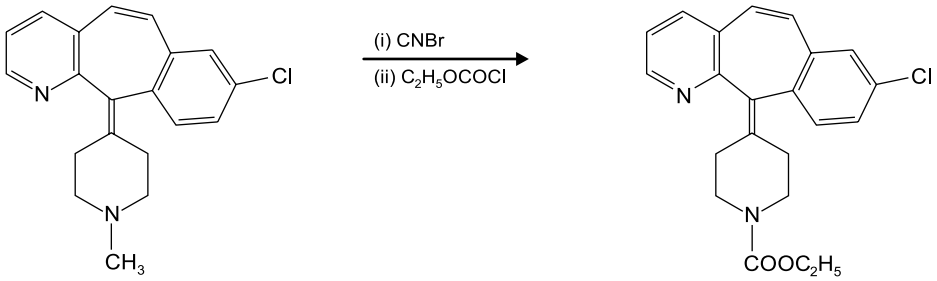
Dose: Usual dose is 5–10 mg thrice/day.

2. **Loratadine** (Alaspan, Lorfast)



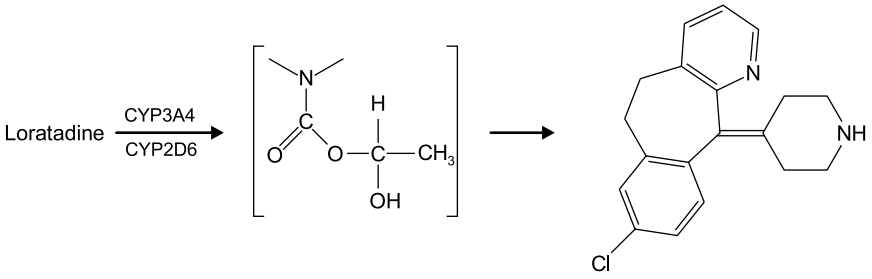
4-(8-Chlor-5,6-dihydro-benzocycloheptapyridin-11-ylidene)-1-piperidine carboxylic acid ethyl ester

Synthesis



8-Chloro azatidine Loratadine

Metabolism: It is a non-sedative antihistaminic drug. The metabolite is desloratidine (descarboethoxy loratidine) is associated with potentially cardiotoxic effect.

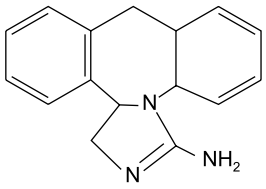


The metabolic conversion of loratidine to descarboethoxy loratidine occurs via oxidative process and not via hydrolysis, and both CYP2D6 and CYP3A4 are to be the isoenzymes catalysing this oxidative metabolism.

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 carbonate and introduction of 8-chloro substitution preserves the antihistaminic action and reduces the CNS effect. The potency of loratidine is comparable with that of astemizole and greater than of terfenadine.

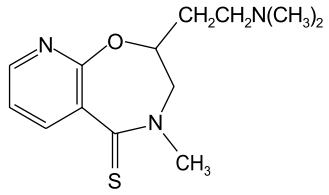
Assay: Dissolve the sample in glacial acetic acid and titrate against 0.1 M perchloric acid. Determine the end point potentiometrically.

3. Epinastine



Properties and uses: This is structurally related to the antidepressant and non-sedative H_1-receptor antagonist mianserin. Introduction of an amidine moiety preserves the antihistamine action and reduces the CNS effect (sedation).

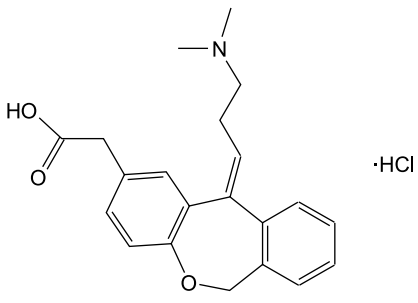
4. Rocastine



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

Properties and uses: It is a rapid acting, non-sedating H_1-antagonist. The R-enantiomer was at least 300 times more potent than S-enantiomer.

5. Olopatadine hydrochloride (Patanase)



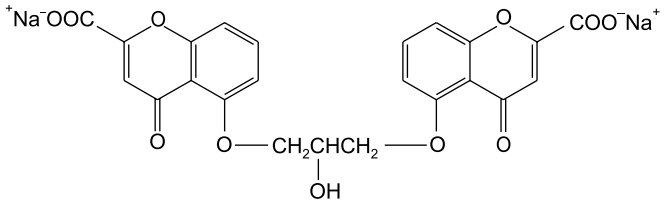
Mode of action: Olopatadine hydrochloride is an antihistamine with selective H_1-receptor antagonist activity. Its principal effects are mediated via inhibition of H_1-receptors. These drugs selectively bind to but do not activate histamine H_1-receptors, thereby blocking the actions of endogenous histamine. It inhibits the release of mast cell inflammatory mediators, i.e. histamine, tryptase, prostaglandin D_2 and TNFα. It is also an inhibitor of proinflammatory cytokine secretion from human conjunctival epithelial cells. Olopatadine acts as inhibitor of proinflammatory signal released from mast cells in response to allergic reactions or tissue damage from bronchi, capillaries, and other smooth muscles.

Properties and uses: Olopatadine hydrochloride is used for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. Adverse reactions associated with the use of olopatadine hydrochloride may include bitter taste, headache, epistaxis, pharyngolaryngeal pain, postnasal drip, cough, and urinary tract infection.

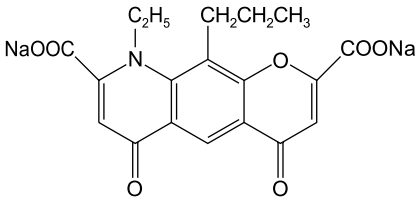
Dose: Olopatadine hydrochloride is supplied as a metered-dose manual spray pump designed for intranasal administration. The recommended initial dose of the drug is two sprays per nostril twice daily. Patanase must be primed before initial use and when it has not been used for more than 7 days.

IV. Inhibition of Histamine Release (Mast Cell Stabilizer)

i. Cromolyn sodium

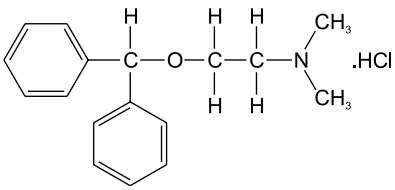


ii. Nedocromil sodium

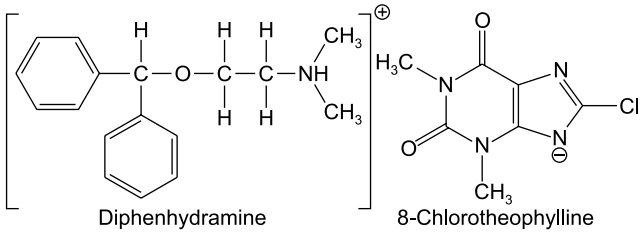


CLASSIFICATION BASED ON PCI SYLLABUS

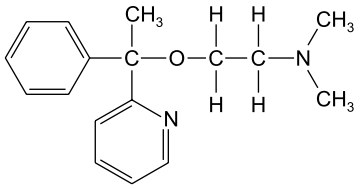
Diphenhydramine hydrochloride



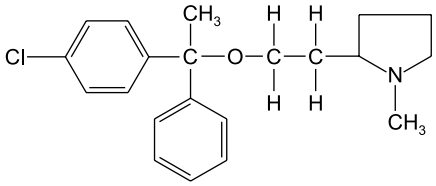
Dimenhydrinate [Diphenhydramine + 8-chlorotheophylline]



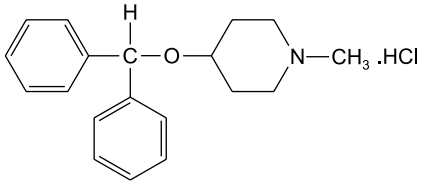
Doxylamine succinate



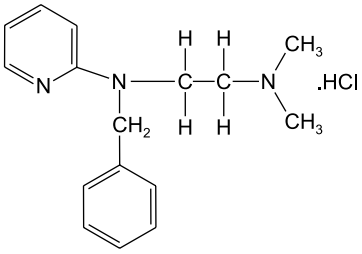
Clemastine fumarate



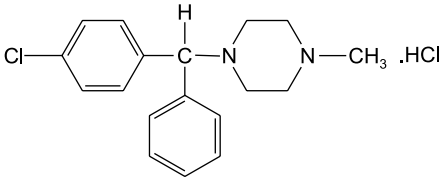
Diphenylphyraline hydrochloride



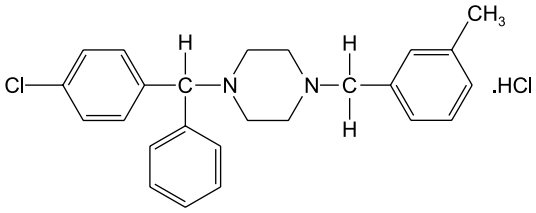
Tripelenamine hydrochloride



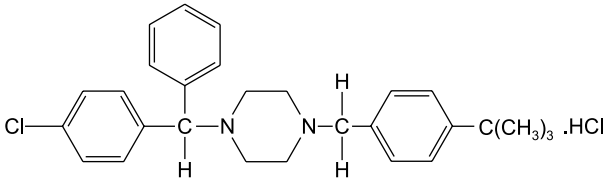
Chlorcyclizine hydrochloride



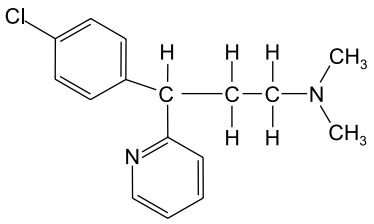
Meclizine hydrochloride



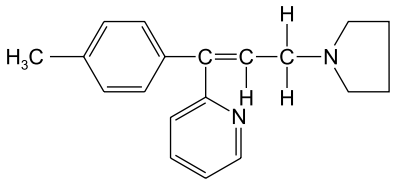
Buclizine hydrochloride



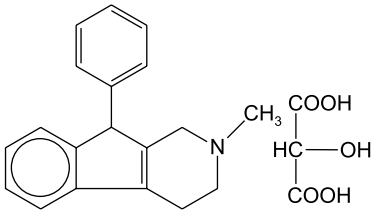
Chlorpheniramine maleate



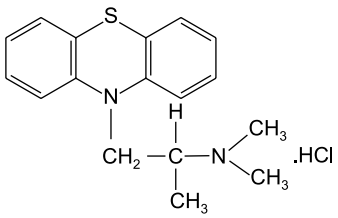
Triprolidine hydrochloride



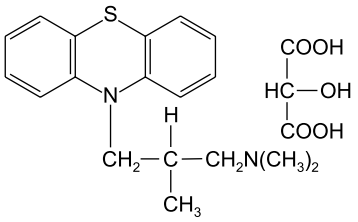
Phenindamine tartrate



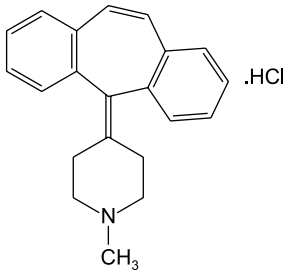
Promethazine hydrochloride



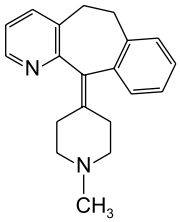
Trimeprazine tartrate



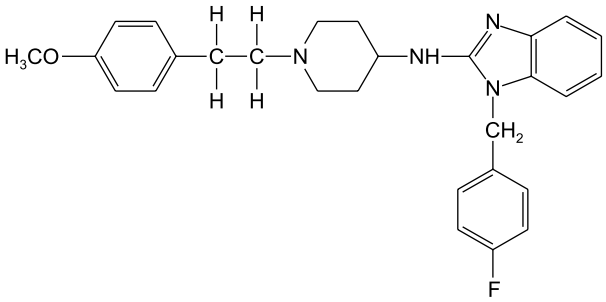
Cyproheptadine hydrochloride



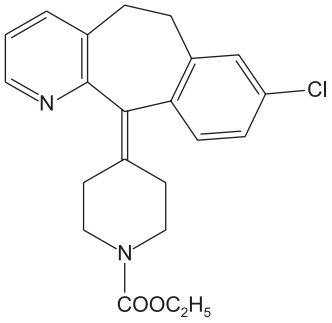
Azatidine maleate



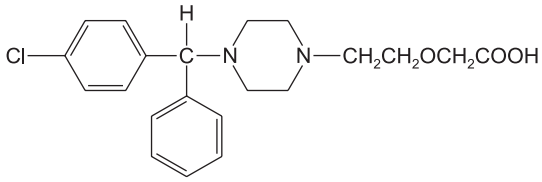
Astemizole



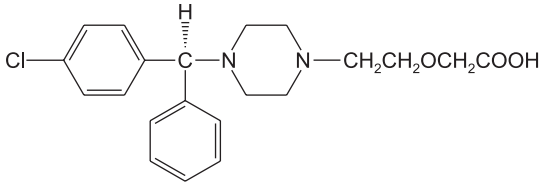
Loratadine



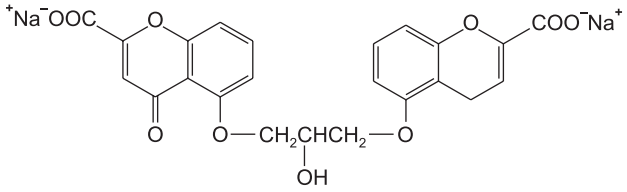
Cetirizine



Levocetrizine



Cromolyn sodium



Phenindamine tartrate: This is closely related to cyproheptadine. It is an anticholinergic and antihistaminic agent. It is used to treat allergies and common cold such as itching, sneezing, hives and rashes.

PROBABLE QUESTIONS

1. What is histamine? What are its biological effects? Mention the different histamine receptors.
2. What are allergens? What is the importance of antihistamines in combating various types of allergic conditions? Mention suitable examples to support your answer.
3. Classify the histamine H_1-receptor antagonists. Write the structure, chemical name, and uses of one drug from each category.
4. What are the side effects of classical antihistamines?
5. Outline the synthesis of the following: Diphenhydramine, chlorpheniramine maleate, and triprolidine.
6. Name any three ethylene diamines being used as antihistamines. Outline the synthesis of any one of them.

7. Write the chemical structure, chemical name, and uses of the following and describe the synthesis of any one drug.
   (a) Mepyramine maleate
   (b) Tripelenamine hydrochloride
8. Outline the synthesis of the following drugs and mention their uses:
   (a) Promethazine hydrochloride
   (b) Antazoline
   (c) Methdilazine hydrochloride
9. Phenindamine tartrate and chlorpheniramine maleate are two important antihistamines. Describe the synthesis of any one drug in detail.
10. Write a brief account of the following:
   (a) Drugs used in the prevention of histamine release
   (b) Newer antihistamines
11. Write a comprehensive account of the following:
   (a) SAR of H_1-receptor blockers
   (b) Mode of action of antihistamines
12. What are non-sedative antihistamines? Enumerate them with the chemical structure and write the synthesis of any one of them.

SUGGESTED READINGS

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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 non-steroidal anti-inflammatory drugs (NSAIDs) are due to their inhibitory effects on PG formation.

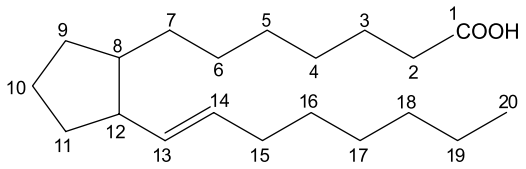
They are also reported to be present in significant quantities in the reproductive tissues, developing foetus and deciduals, umbilical cord, amniotic fluid, endometrium, menstrual fluid, epidermis, thymus, thyroid, and nerves. Further, in most of the organs, except for genital tissue, the PG is present as prostaglandin E (PGE) and prostaglandin F_2 (PGF_2). 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 (TXA_2) stimulates constriction and clotting of platelets. Conversely, PGI_2 have the opposite effect on the walls of blood vessels.
2. Certain PGs are involved in the induction of labour and other reproductive processes. PGE_2 causes uterine contractions and has been used to induce labour.

NOMENCLATURE

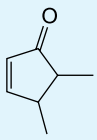
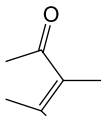
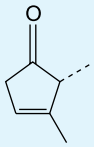
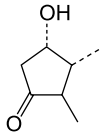
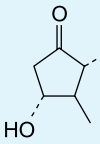
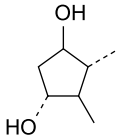


Prostanoic acid

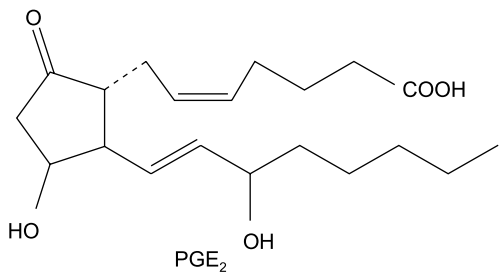
PGs are considered as analogues of polyunsaturated fatty acids. It is a 20-carbon carboxylic acid containing a five-member ring. The PGs (Table 2.1) are classified according to the nature of:

A. Cyclopentane ring.
B. Two side chains.
C. Configuration of newly introduced functional group.

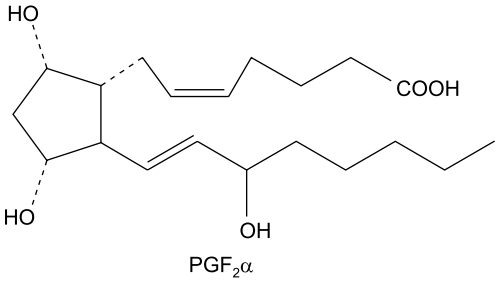
Table 2.1: Various types of PGs

A-type PGA		10,11-Unsaturated-9-keto function
B-type PGB		8,12-Unsaturated-9-keto function
C-type PGC		11,12-Unsaturated-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: PGE_2 and $PGF_2\alpha$.

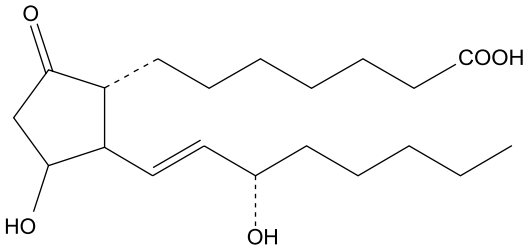


PGE_2

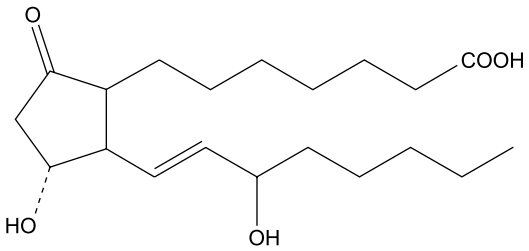


$PGF_2\alpha$

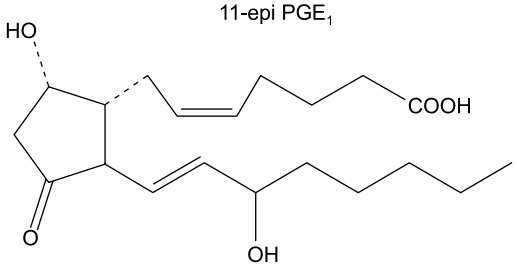
Two side chains are attached to the cyclopentane ring at C-8 and C-12. The upper chain, having a carboxylic acid group at the terminal, is α-side chain and the lower chain, having OH group at C-15 position, is a β-side chain. The α- and β-chains are in *trans* configuration in the prostanoic acid. The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



11-epi PGE_1



8-Isoprostaglandin



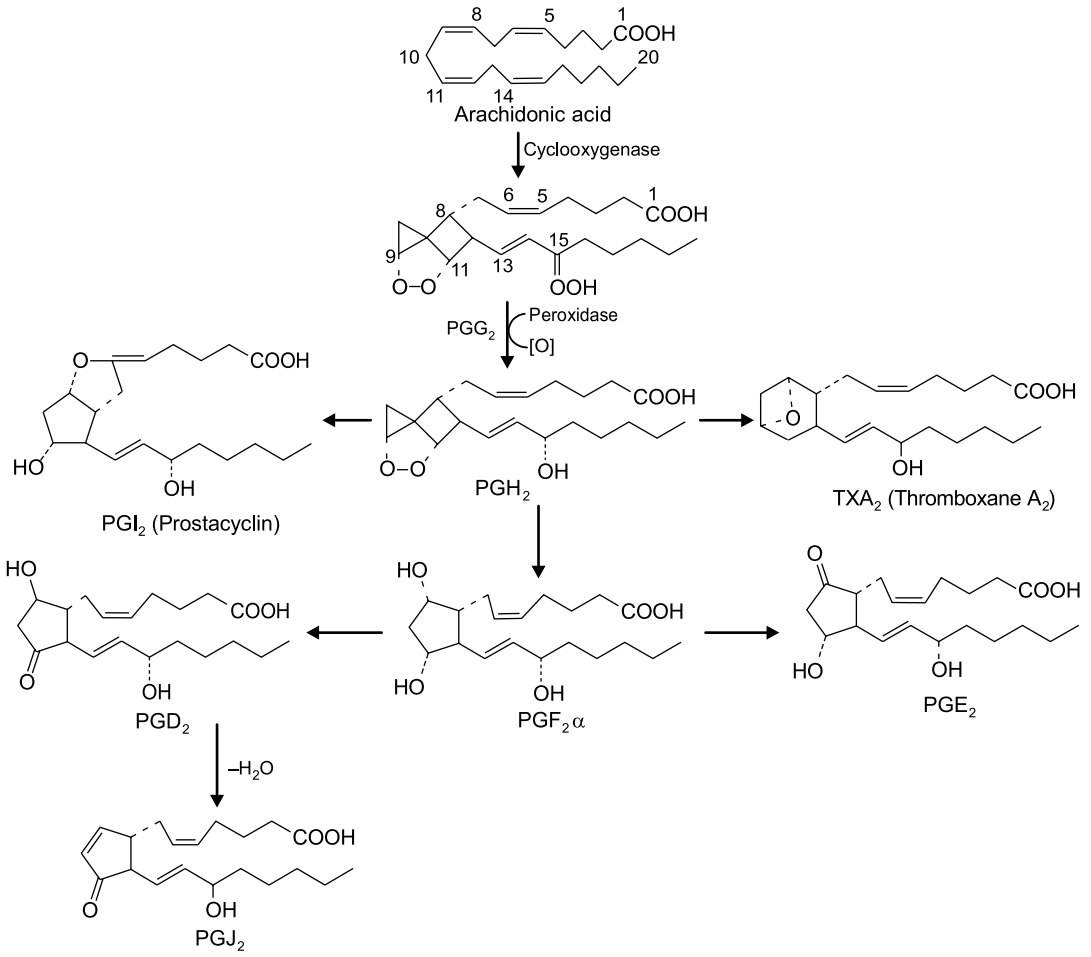
PGD_2

BIOSYNTHESIS

PGs are found virtually in 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

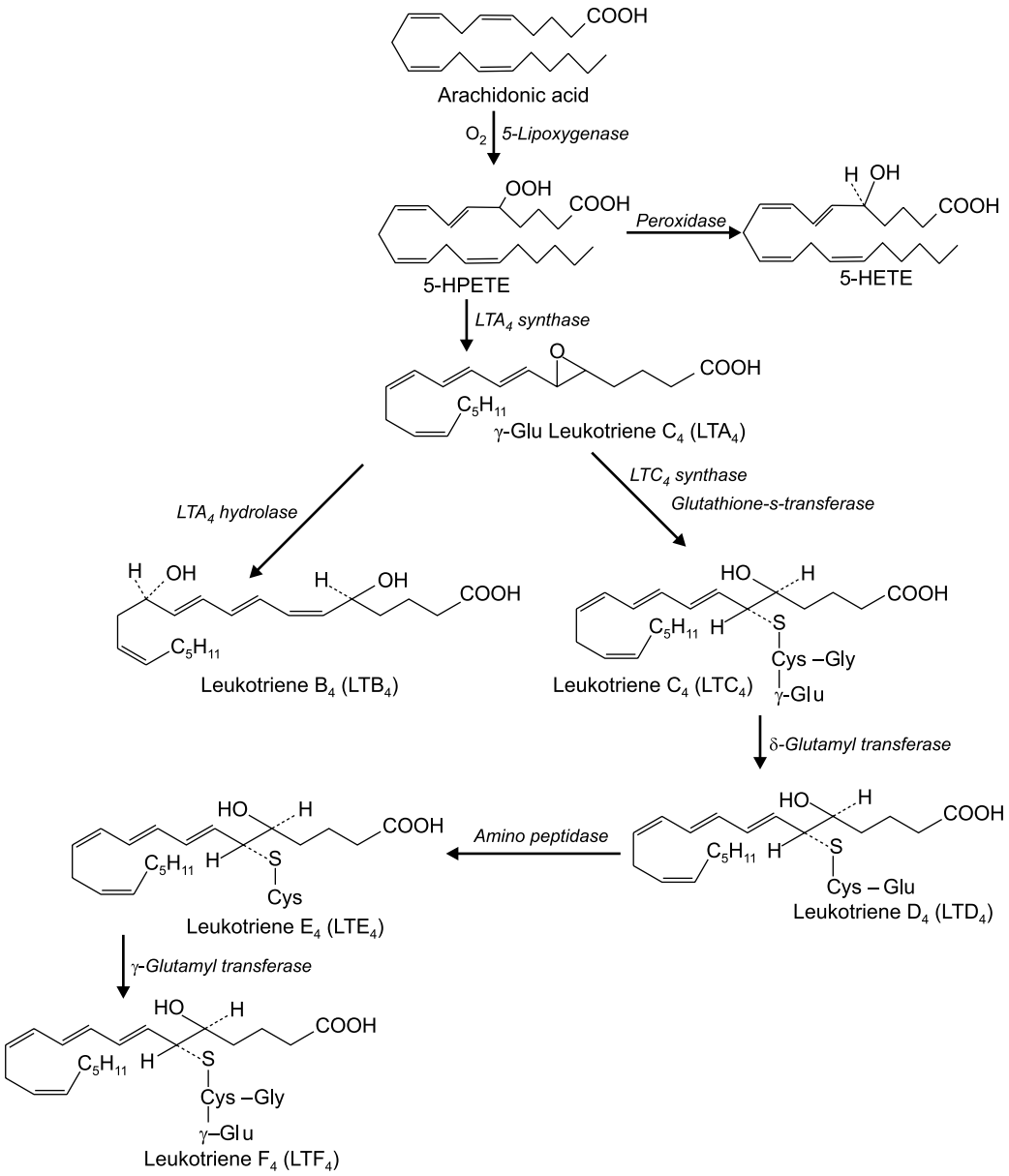
Cyclooxygenase Pathway



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 H_2 (PGH_2). PGH synthase is also called 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.

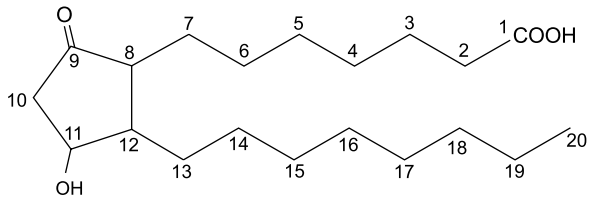
Lipoxygenase Pathway



Lipoxygenase are a group of enzymes that oxidize polyunsaturated fatty acid possessing two *cis* double bonds 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 eicosotetraenoic 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



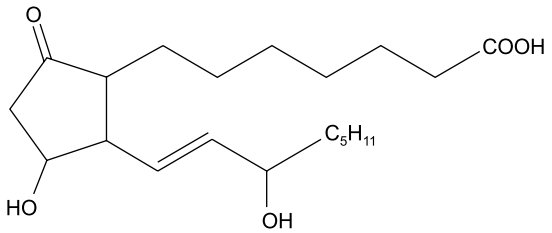
In the upper chain: Methyl esters (misoprostol), sulphonamide (sulprostone), and hydroxyl group (rioprost) possess greater activity than natural PGs.

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 $=CH_2$ 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 increases the leuteolytic activity.

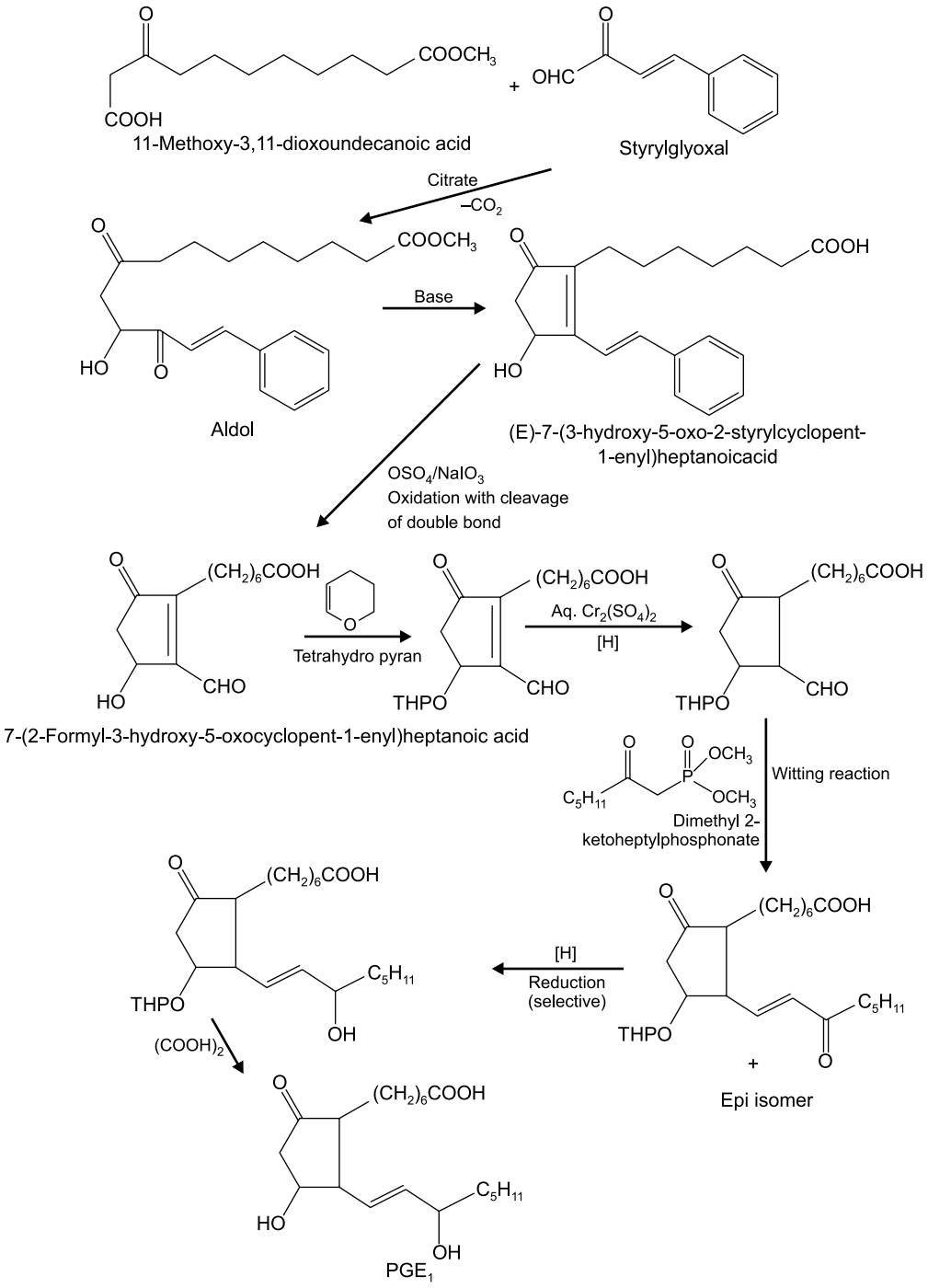
SYNTHESIS AND DRUG PROFILE

i. Prostaglandin E_1 (PGE_1)



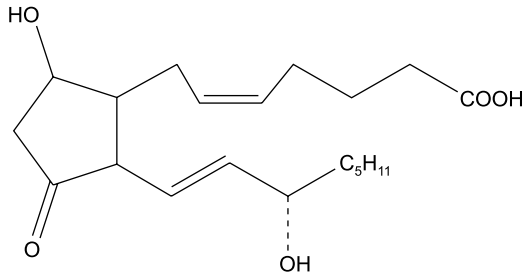
(E)-7-(3-hydroxy-2-(3-hydroxydec-1-enyl)-5-oxocyclopentyl)heptanoicacid

Synthesis



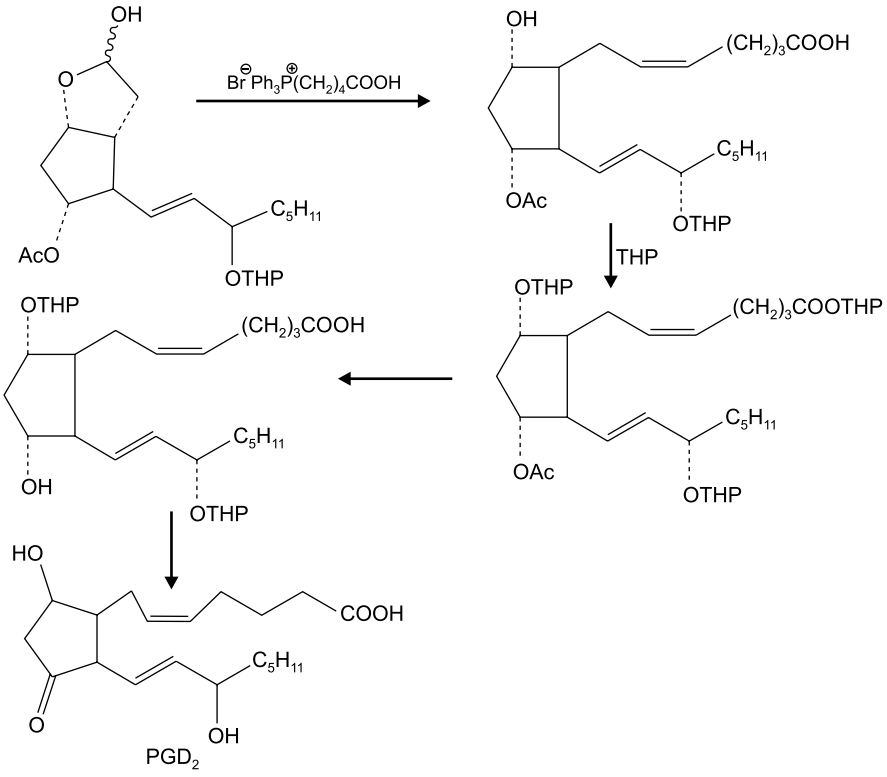
Dose: A dose of misoprostol, 200 µg three times a day for acute duodenal ulcer and comparable with cimetidine.

ii. Prostaglandin D_2 (PGD_2)

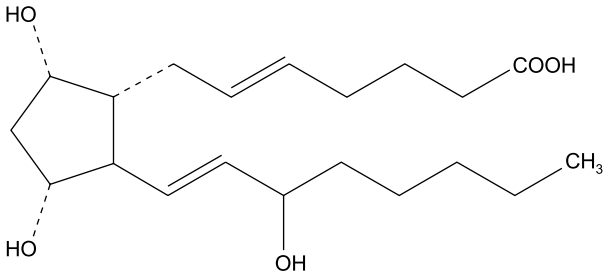


(Z)-7-(5-Hydroxy-2-((S,E)-3-hydroxyoct-1-enyl)-3-oxocyclopentyl)hept-5-enoic acid

Synthesis

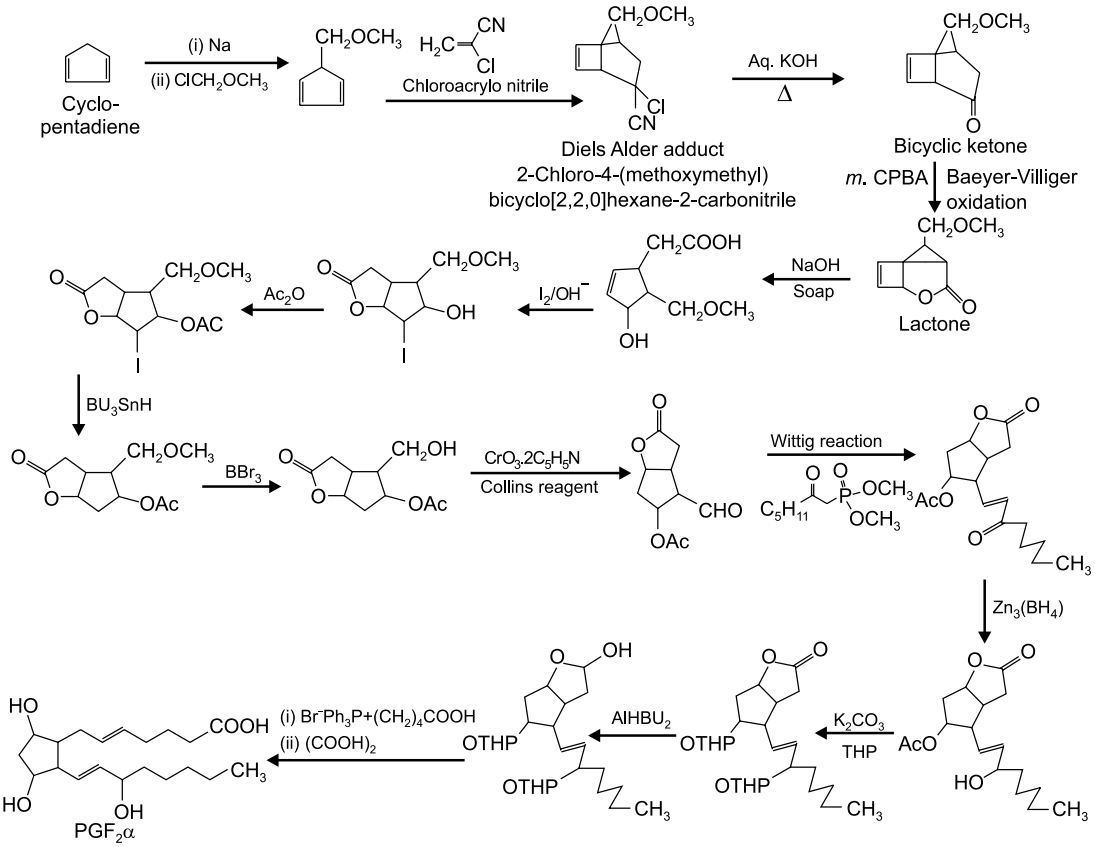


$PGF_2\alpha$



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

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 represents 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) PGE_1 and (b) PGD_2.
5. Explain the role of PGs and eicosanoids to combat the following diseases: (a) Gastric ulceration and (b) management of congenital heart disease.

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CHAPTER 3

Analgesics, Antipyretics and NSAIDs

INTRODUCTION

Non-steroidal 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 gastrointestinal 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 of 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 chickenpox 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 chickenpox 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 E_2 (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.

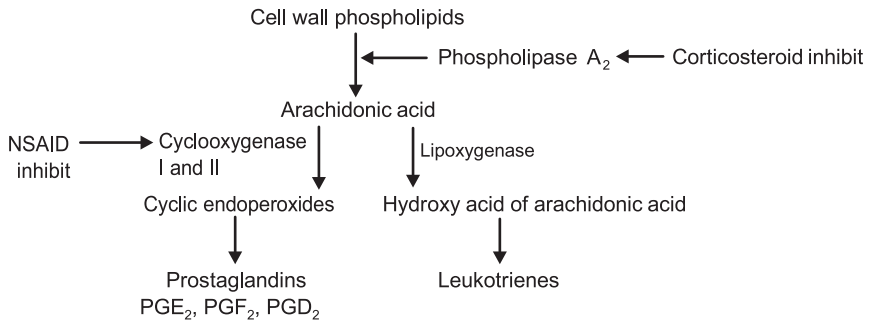
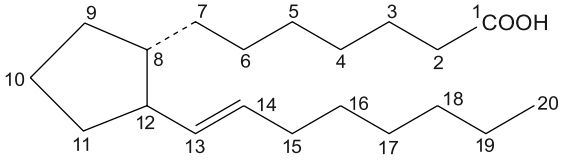


Figure 3.1: Biosynthetic pathway of PGs.

General Structure of PG

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



Mode of action: NSAIDs inhibit cycloxygenase (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 PGE_2 and PGI_2, 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 A_2 (TXA_2) in platelets, as TXA_2 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 PGF_2 in uterus. PGF_2 is a potent uterotropic 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. 3,5-Pyrazolidine dione derivatives: Phenyl butazone, oxyphenbutazone, sulphinpyrazone.
IV. Anthranilic acid derivatives (fonamates): 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, Ketoprofen, flurbiprofen, ketorolac, 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, sulphinpyrazone, febuxostat.

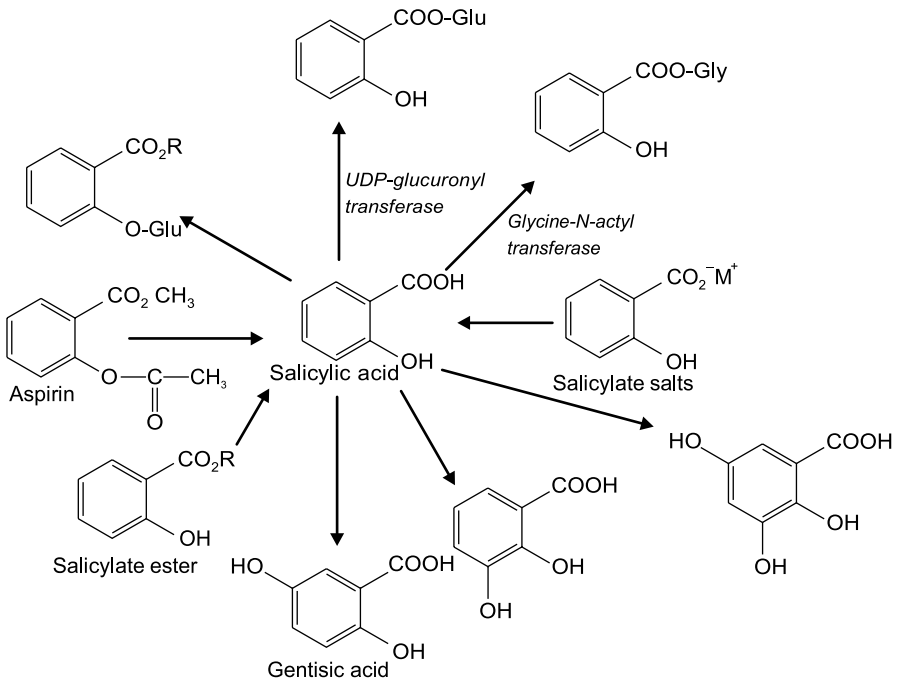
Salicylates

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.

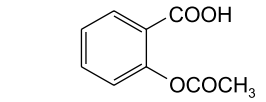
Structural–Activity Relationship (SAR) of Salicylates

- 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) retain 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 week 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 increases 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.

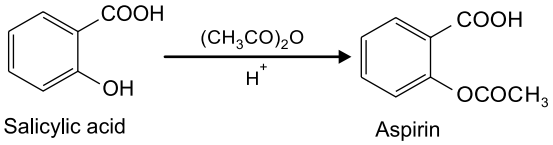


i. Aspirin (Emipirin, Bufferin)



2-Acetoxybenzoic acid or Acetyl salicylate

Synthesis



Salicylic acid Aspirin

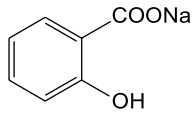
Properties and uses: Aspirin is a white crystalline powder, slightly soluble in water and soluble in alcohol, indicated for the relief of minor aches and mild-to-moderate pain in the conditions such as arthritis and related arthritic condition. Also used in myocardial infarction prophylaxis.

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 hrs orally or 650 mg to 1.3 g as the sustained-release tablet every 8 hrs; rectal, 200 mg to 1.3 g three or four times a day.

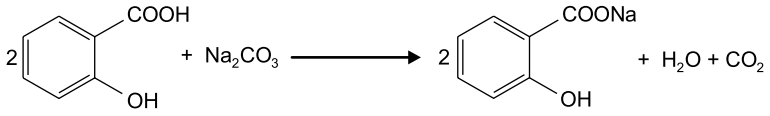
Dosage forms: Aspirin tablets IP, BP, dispersible aspirin tablets BP, effervescent soluble aspirin tablets BP, gastro-resistant aspirin tablets BP, aspirin and caffeine tablets BP, co-codaprin tablets BP, dispersible co-codaprin tablets BP.

ii. Sodium salicylate



Sodium 2-hydroxybenzoate

Synthesis

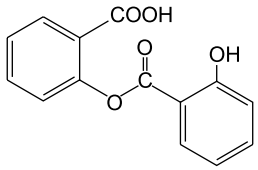


Salicylic acid Sodium carbonate Sodium salicylate

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.

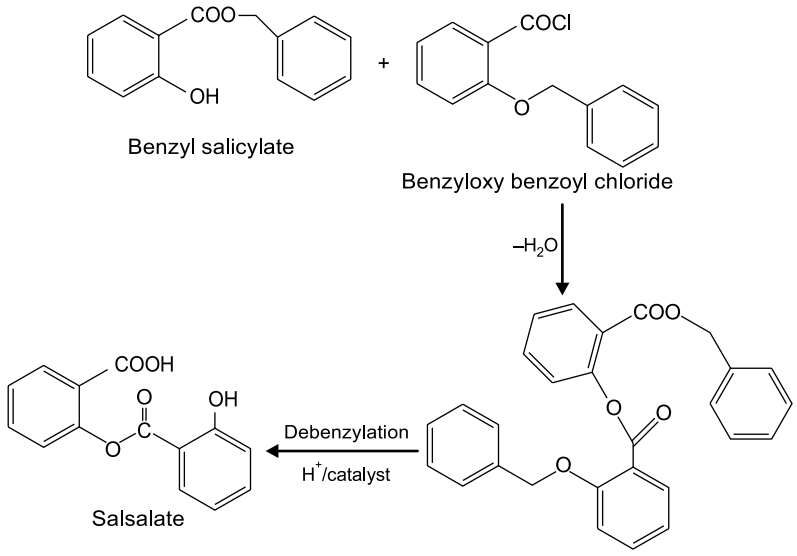
Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M per chloric acid. Determine the end point potentiometrically.

iii. Salsalate (Disalcid, Saloxium)



2-(2-Hydroxybenzoyloxy)benzoic acid

Synthesis



Benzyl salicylate

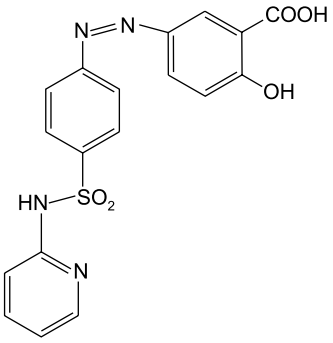
Benzyloxy benzoyl chloride

Salsalate

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.

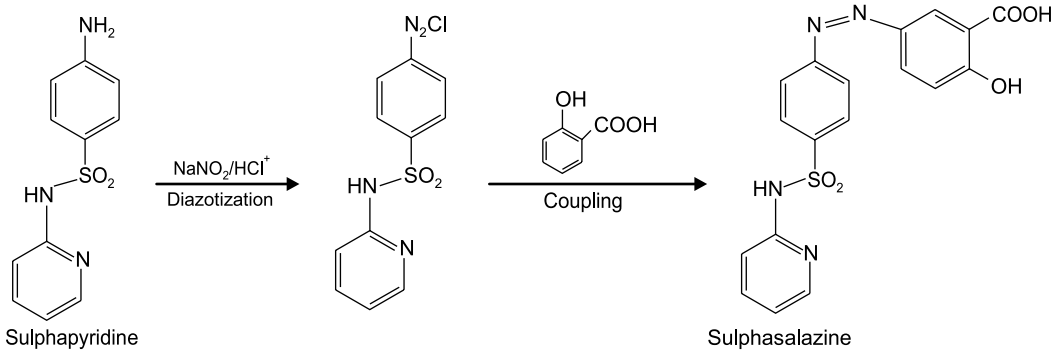
Dose: Usual adult dose is 325–1000 mg 2–3 times a day, orally.

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-aminosalicylic 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



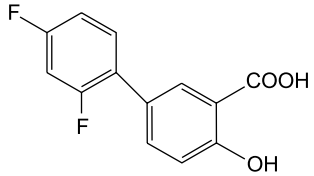
Sulphapyridine Sulphasalazine

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

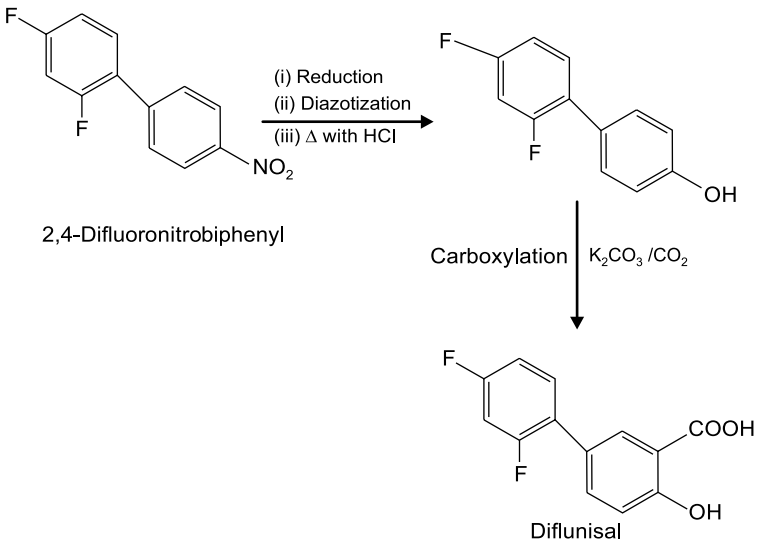
Dosage forms: Sulphasalazine tablets BP.

v. Diflunisal (Dolobid)



5-(2,4-Difluorophenyl) salicylic acid

Synthesis



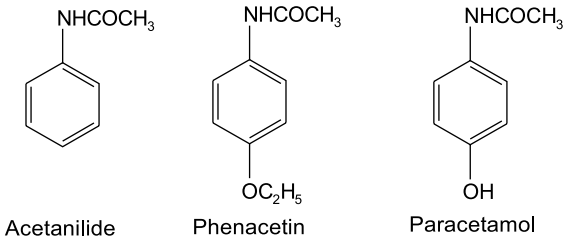
Properties and uses: Diflunisal is a white crystalline powder, practically insoluble in water, soluble in alcohol, and dilute solutions of alkali hydroxides. It is more potent than aspirin, but produces fewer side effects, and has a biological half-life 3–4 times greater than that of aspirin. It is a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

p-Amino Phenol Derivatives

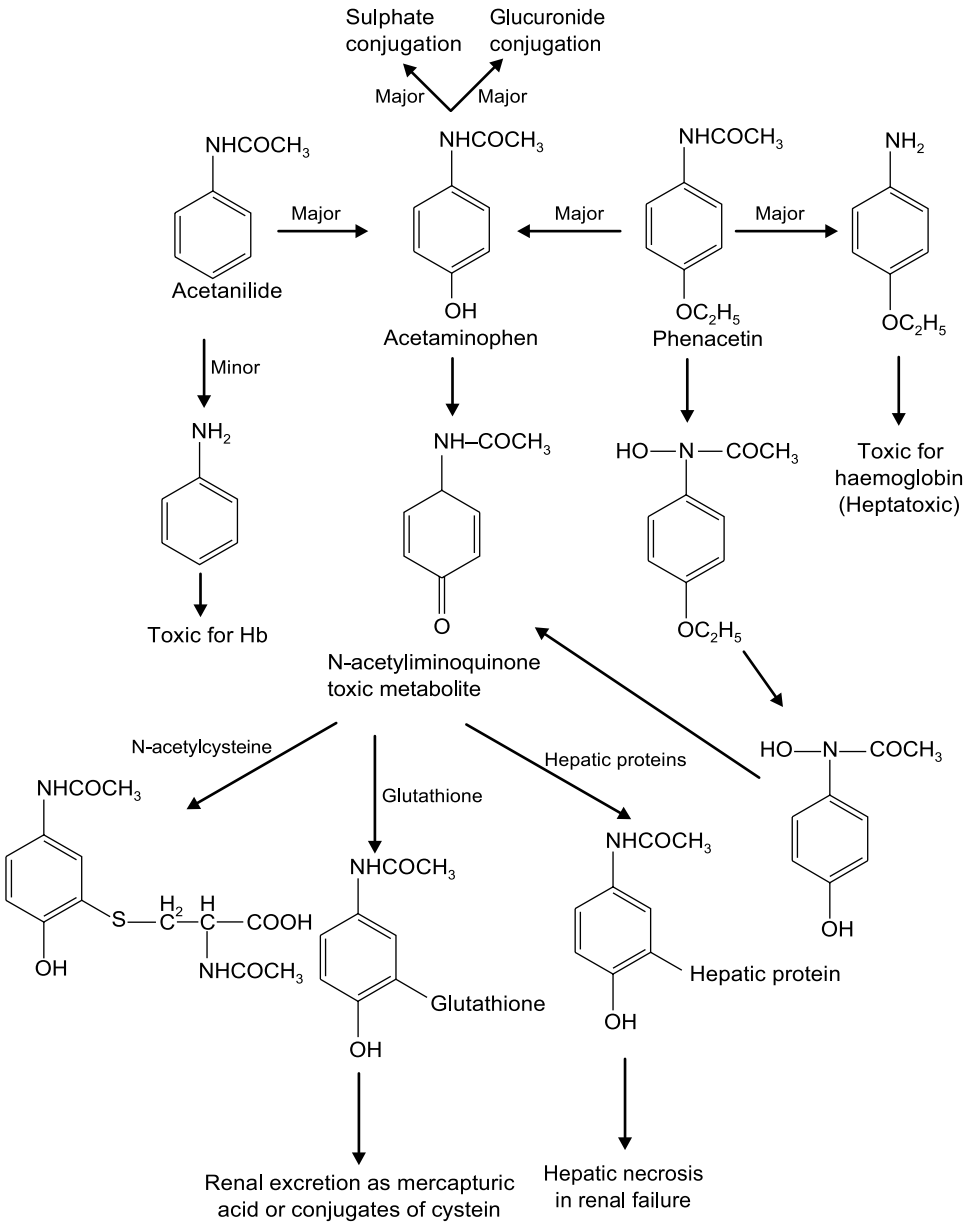
These derivatives possess analgesic and antipyretic action, but lack in anti-inflammatory effects. Acetanilide was introduced into the therapy in 1886 as an antipyretic–analgesic agent. However, it was subsequently found to be too toxic, having been associated with methemaglobinemia and jaundice.

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.



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

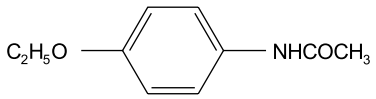
N-hydroxylamine is then converted into a reactive toxic metabolite, acetiminoquinone, which produces toxicity to the kidney and liver in conjugation with hepatic glutathione to form mercapturic acid or cysteine conjugates.



SAR of *p*-amino Phenol Derivatives

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

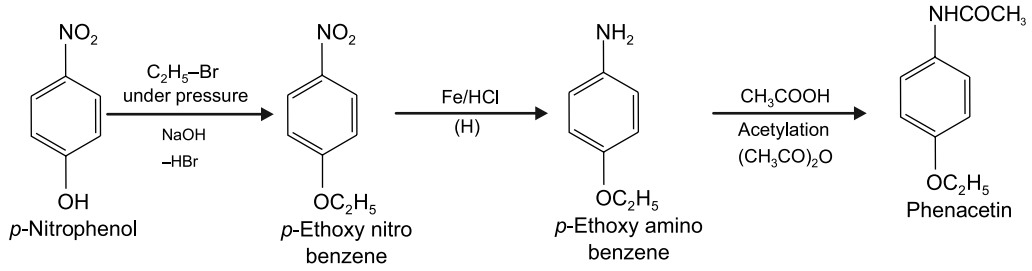
i. Phenacetin (Acetophenetidin)



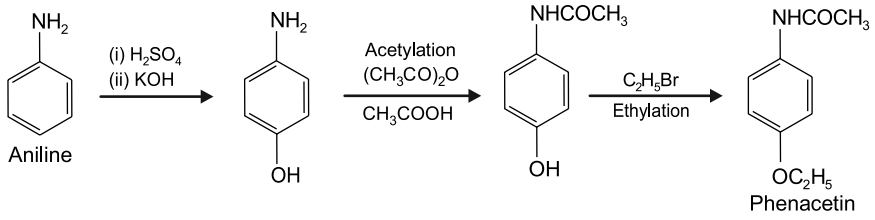
p-Ethoxy acetanilide

Synthesis

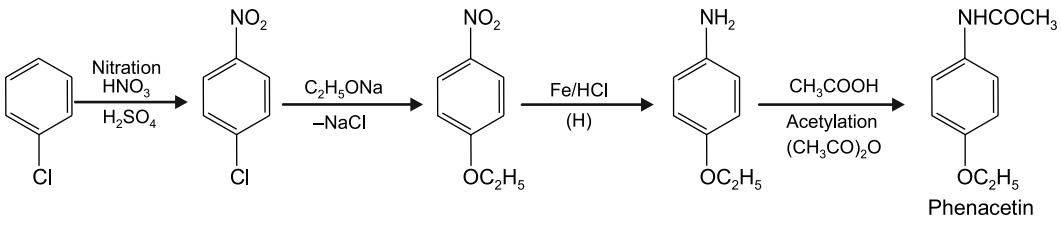
Route I. From: *p*-Nitrophenol



Route II. From: Aniline



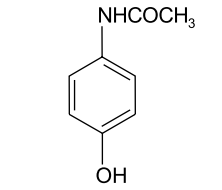
Route III. From: Chlorobenzene



Properties and uses: It exists as a white glistering 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 methemoglobinaemia) than paracetamol.

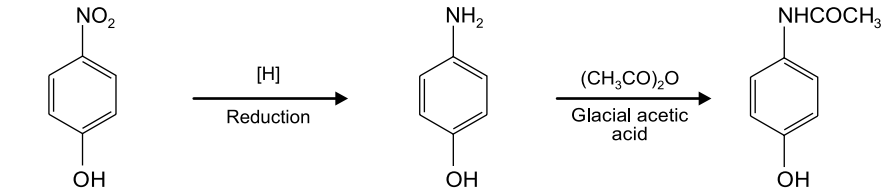
Dose: Usual dose as oral for adults is 300 mg to 2 g per day.

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



Para-acetaminophenol

Synthesis



Para-nitrophenol → *Para*-aminophenol → Paracetamol

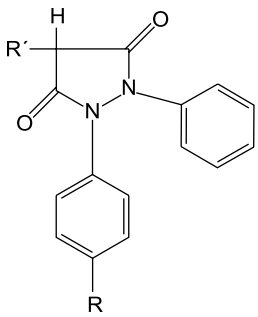
Properties and uses: Paracetamol exists as white crystalline powder, sparingly soluble in water, soluble in alcohol, and very slightly soluble in methylene chloride. Paracetamol produces antipyresis by acting on the hypothalamic heat-regulating centre and analgesia by elevating the pain threshold. Hepatic 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 IP, BP, paracetamol syrup IP, co-codamol tablets BP, effervescent co-codamol tablets BP, co-dydramol tablets BP, co-proxamol tablets BP, paracetamol capsules BP, paediatric paracetamol oral solution BP, paracetamol oral suspension BP, paracetamol suppositories BP, dispersible paracetamol tablets BP, soluble paracetamol tablets BP.

3,5-Pyrazolidinediones

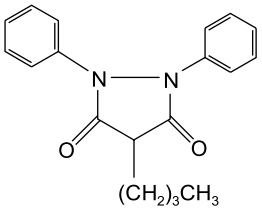


Name	*R*	*R'*
Phenyl butazone	–H	$-C_4H_9$
Oxyphenbutazone	–OH	$-C_4H_9$
Sulphin pyrazone	–H	$-(CH_2)_2SOC_6H_5$

SAR of 3,5-Pyrazolidinediones

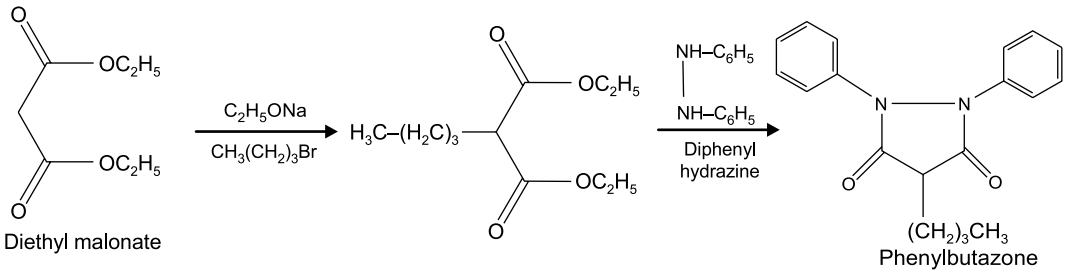
- Replacement of one of the nitrogen atom in the pyrazolidinediones with an oxygen atom yields isoxazole analogues, which are as active as pyrazolidinedione derivatives.
- In 3,5-pyrazolidinedione derivatives, pharmacological activities are closely related to their acidity, the dicarbonyl function at the 3rd and 5th positions enhances 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 phenylbutazone is replaced by substituents, such as a methyl group, anti-inflammation 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 gives mixed results. The γ-hydroxy-*n*-butyl derivative possesses pronounced uricosuric activity, but give fewer anti-inflammatory effects.
- Substitution of 2-phenyl thio ethyl group at the 4th position produces antigout activity (sulphin-pyrazone).
- 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)

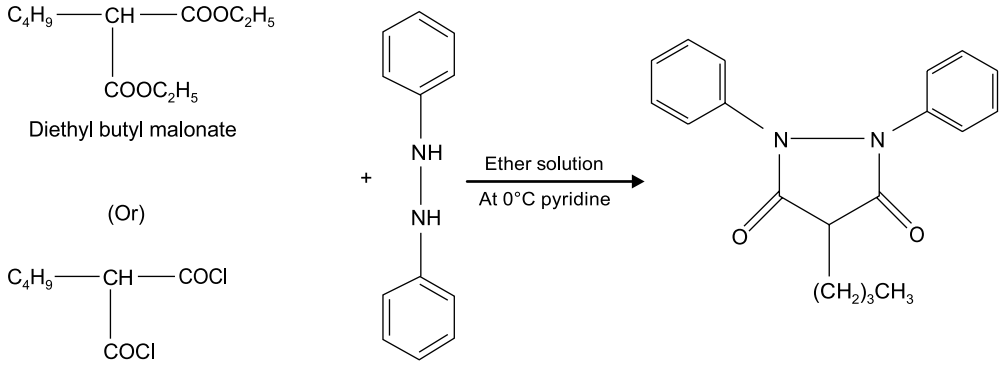


Synthesis

Route I. From: Diethylmalonate



Route II. From: Diethyl butyl malonate or butyl malonylchloride

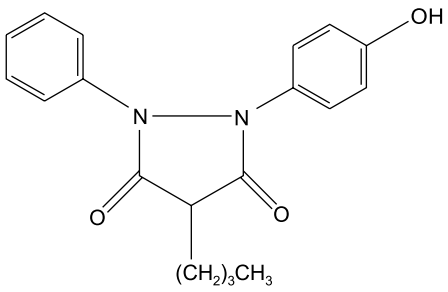


Properties and uses: Phenylbutazone is a white crystalline powder, practically insoluble in water, sparingly soluble in alcohol, and soluble in alkaline solutions. It is a pyrazole derivative that has antipyretic, analgesic, and anti-inflammatory actions, because of its toxicity it is not used as a general 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.

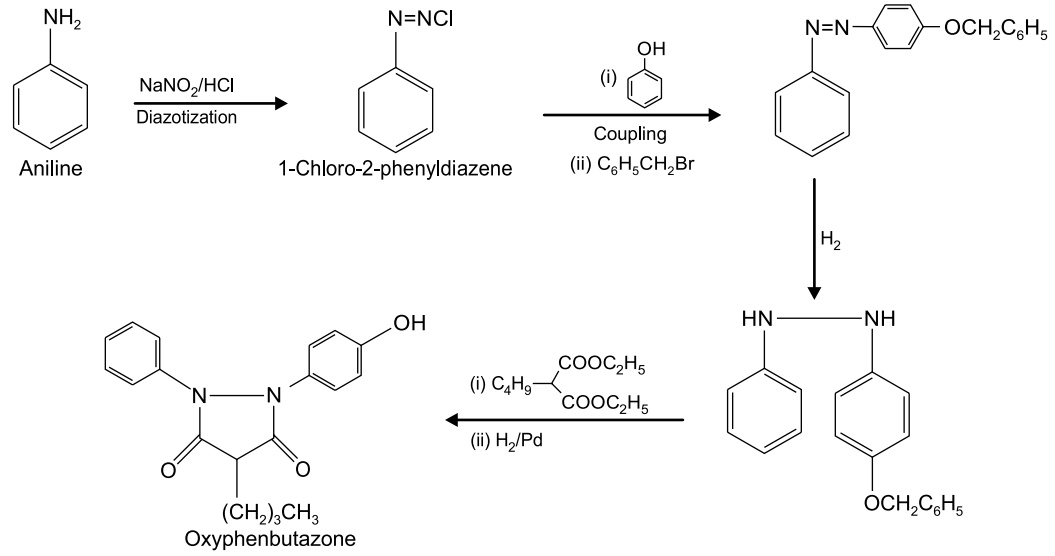
Dose: The usual dose is 100–600 mg per day.

ii. Oxyphenbutazone (Tandearil, Oxaril)

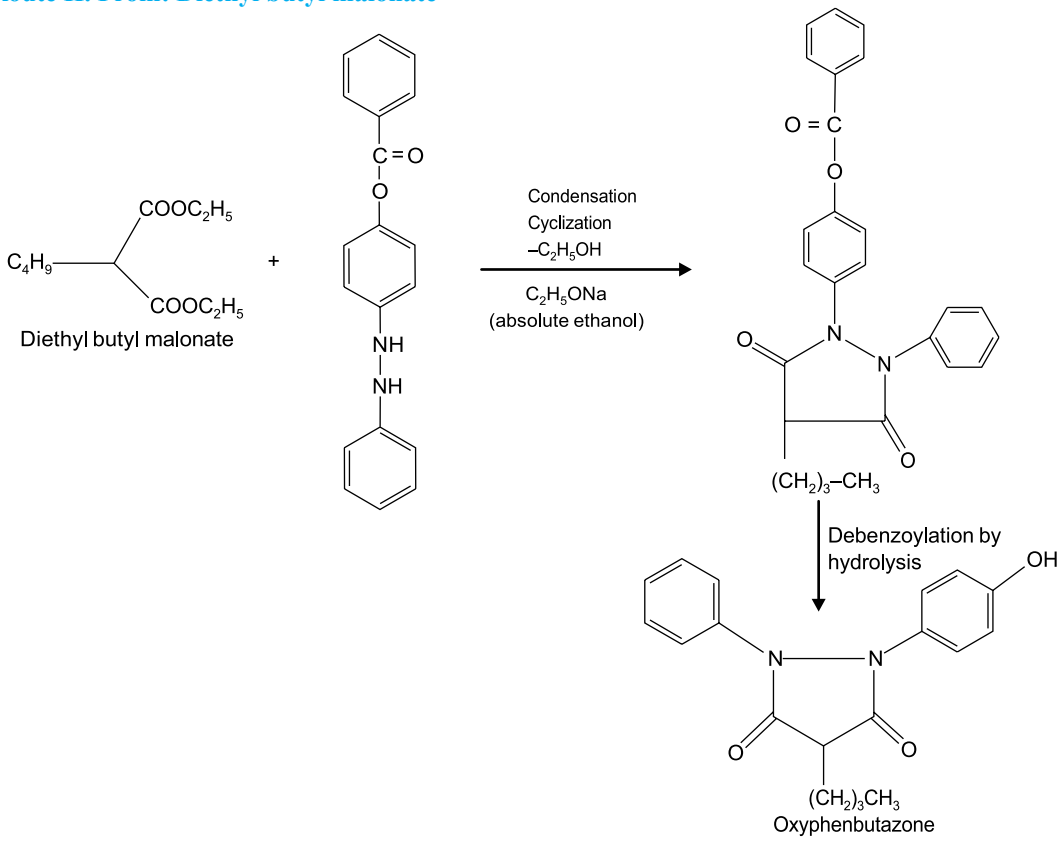


Synthesis

Route I. From: Aniline



Route II. From: Diethyl butyl malonate

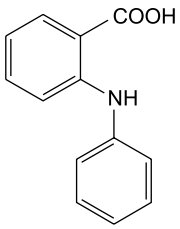


Properties and uses: It exists as a white to yellowish white, odourless, crystalline powder, soluble in water, alcohol, chloroform, and ether. Used as an analgesic and in arthritis.

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 hrs.

Anthranilic Acid Derivatives (Fenamates)

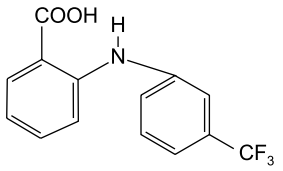
The anthranilic acid class NSAIDs result from the application of classic medicinal chemistry bioisosteric drug design concepts as these derivatives are nitrogen isoteres of salicylic acid.



SAR of Anthranilic Acid Derivatives (Fenamates)

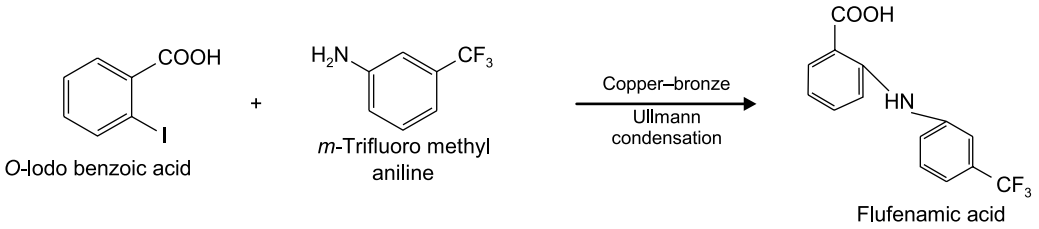
- The position of the carboxyl function is important for the activity of anthranilic acid derivatives that are active, whereas the 3- and 4-amino benzoic acid analogues are not active.
- Replacement of carboxylic acid function with the isosteric tetrazole results in the retention of anti-inflammatory 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′-Cl derivatives being more potent than 3′-Cl analogues.
- In disubstituted derivatives, where the nature of two substitutes is the same 2′,3′-disubstitution appears to be the most effective (mefenemic 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, N-CH_3, or $NCOCH_3$ functionalities significantly reduced the activity.

i. **Flufenamic acid** (Arlef, Tarlef)



N-(α,α,α-Trifluoro-*m*-tolyl) anthranilic acid

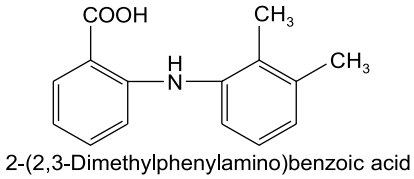
Synthesis



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.

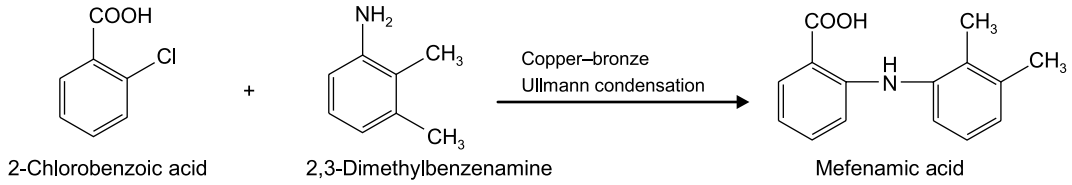
Dose: 400–600 mg per day in divided doses.

ii. Mefenamic acid



Synthesis

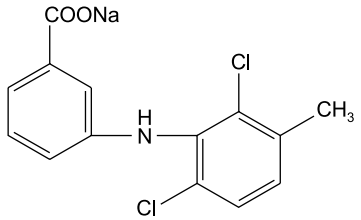
An analogues approach by reaction of *o*-chlorobenzoic acid with 2,3-dimethyl aniline.



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

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

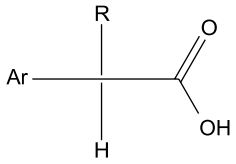
iii. Meclofenamate sodium



Sodium 3-(2,6-dichloro-3-methylphenylamino)benzoate

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

Aryl Alkanoic Acids



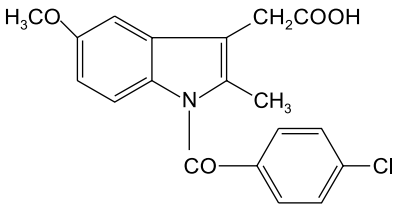
General structure

SAR of Aryl Alkanoic 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.

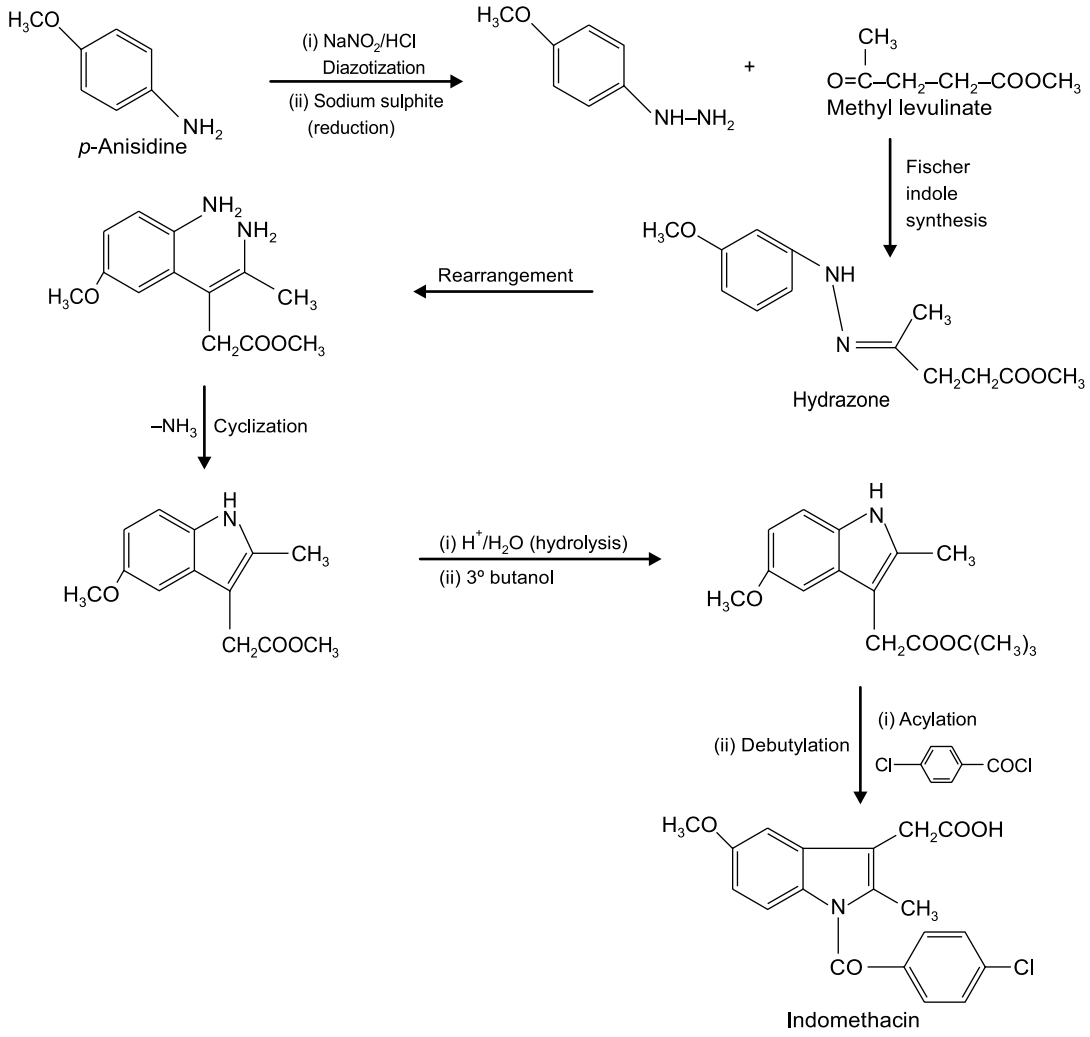
a. Indole acetic acid derivatives

i. Indomethacin (Indocin, Indocid)

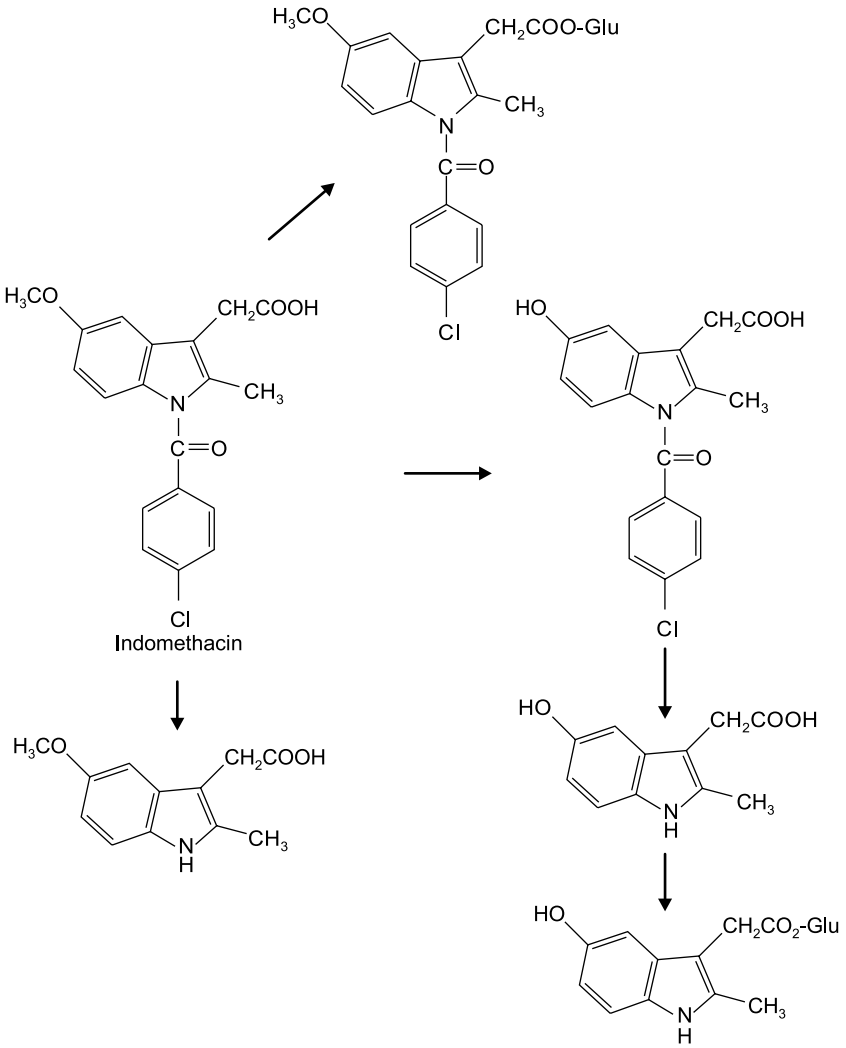


1-(*p*-Chlorobenzoyl)-5-methoxy-2 methylindole-3-acetic acid

Synthesis



Metabolism: It is converted into inactive metabolites, that is, 50% of single dose is 5-*o*-demethylated and 10% conjugated with glucuronic acid. Non-hepatic 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.

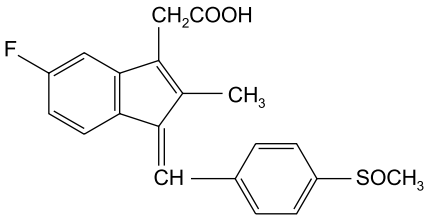
Assay: Dissolve the sample in acetone and pass nitrogen for 15 min and titrate with 0.1 M sodium hydroxide using phenolphthalein as indicator.

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: Indomethacin capsules IP, BP, indomethacin suppositories IP, BP.

b. Indeneacetic acid derivatives

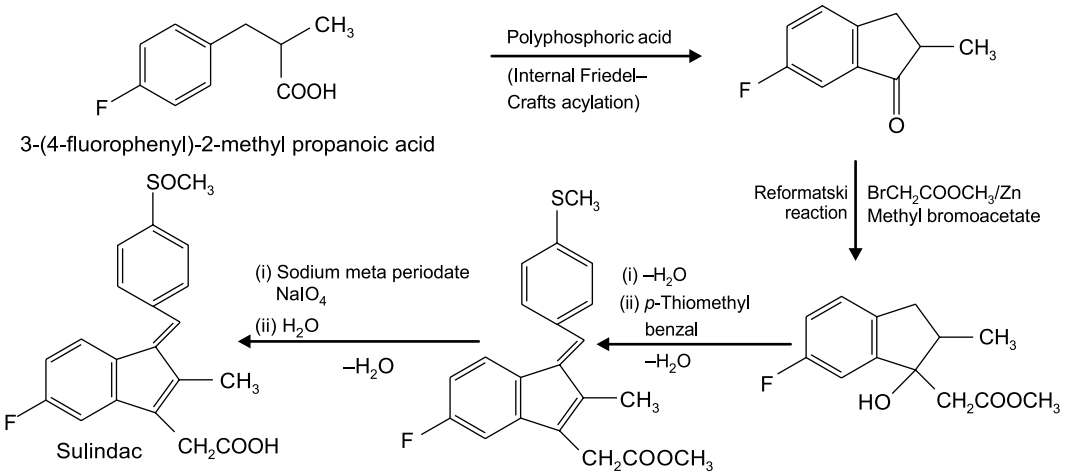
i. Sulindac (Clinoril)



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

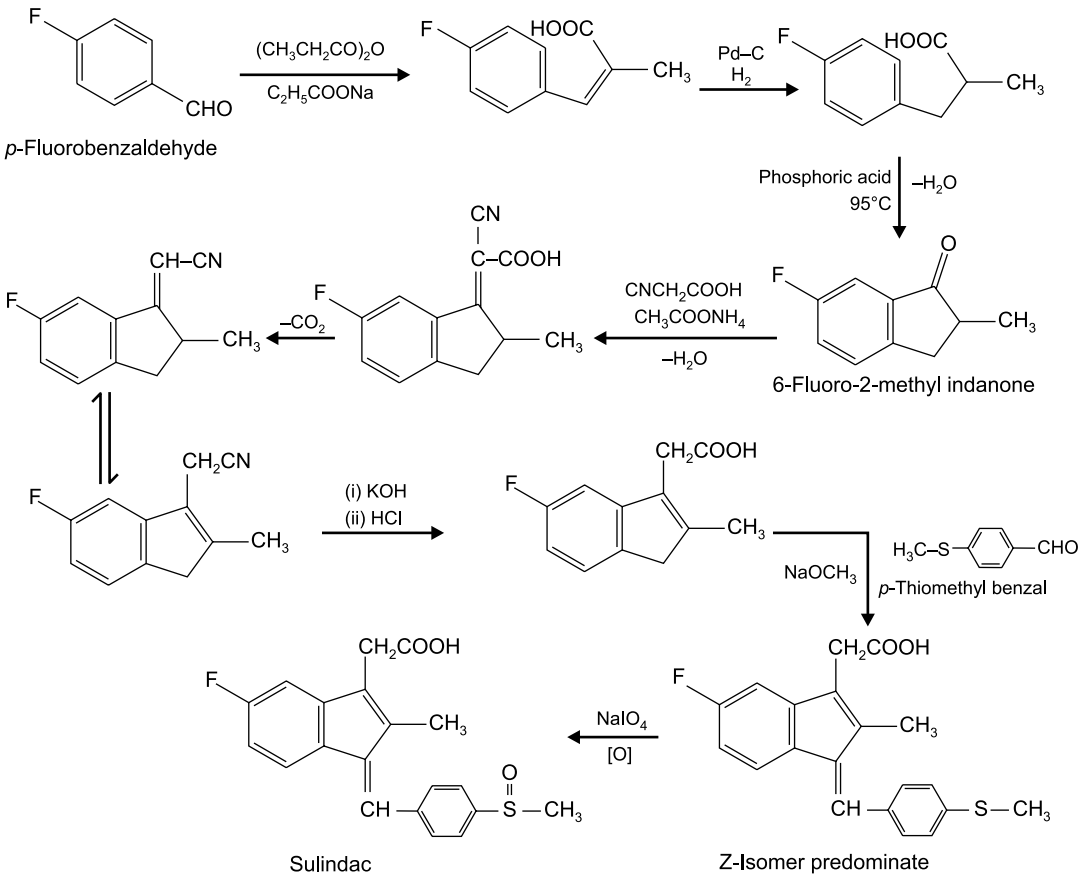
Synthesis

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



Synthesis

Route II. From: *p*-Fluorobenzaldehyde



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.

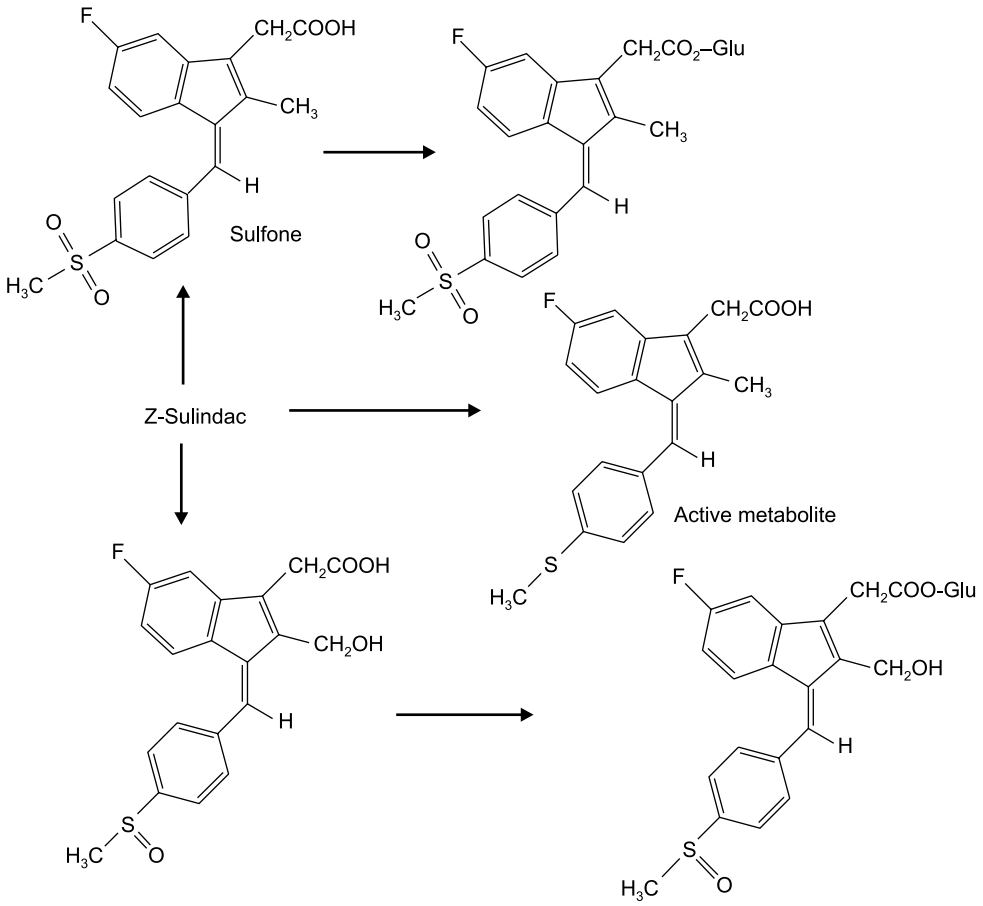
Properties and uses: Sulindac is a yellow crystalline powder, very slightly soluble in water, soluble in methylene chloride, and dilute solutions of alkali hydroxides, sparingly soluble in alcohol. The (Z)-isomer of sulindac showed much more potent anti-inflammatory activity than the corresponding (E)-isomer. The more polar and inactive sulphoxide 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.

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

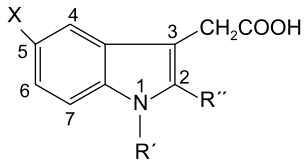
Dose: Usual adult oral dose is 150 mg twice a day with food.

Dosage forms: Sulindac tablets BP.

Metabolism of Sulindac



SAR of Indole Acetic Acid Derivatives



1. Placement of other acidic functionalities instead of the carboxyl group decreases activity and the amide derivatives are inactive.
2. Substituents of R′ useful for increasing anti-inflammatory activity are ranked as $C_6H_4CH_2$ > alkyl > H.
3. 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, CF_3, or S-CH_3 groups provide greatest activity.
5. The order of potency of activity of x substituents is: 5-OCH_3 > N $(CH_3)_2$ > CH_3 > H.

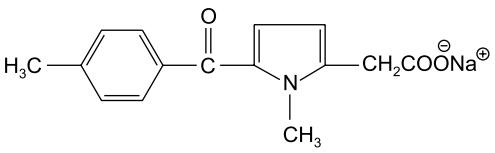
6. The presence of indole ring nitrogen is not essential for activity because the corresponding 1-benzylidenylindene analogue (sulindac) is also active.
7. Alkyl groups, especially, methyl group at second position is much active than aryl substituted analogues.
8. Substitution of a methyl group at the 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

c. Pyrrole acetic acid derivatives

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

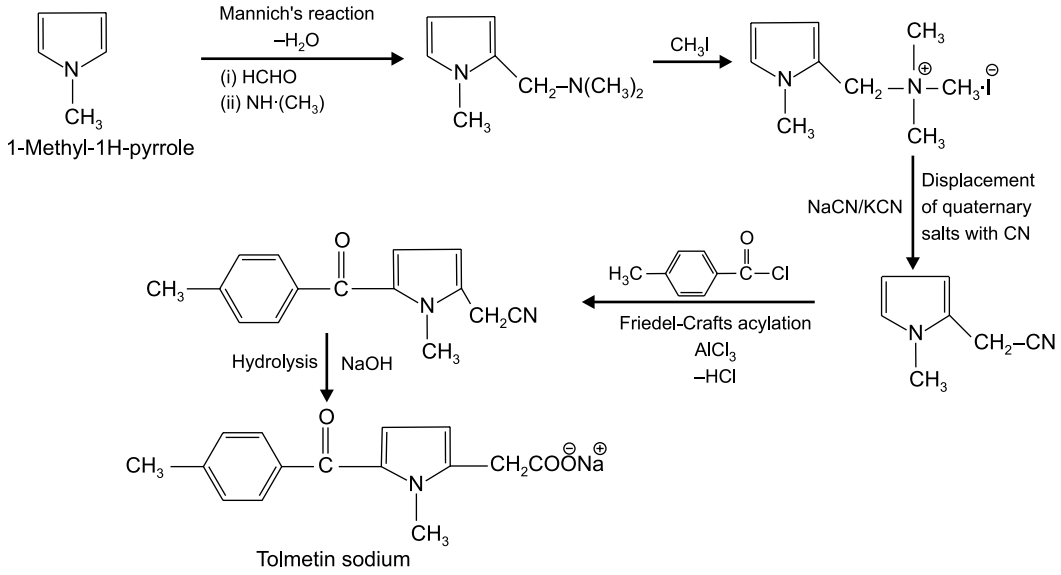
i. Tolmetin Sodium (Tolectin)



Sodium 2-(1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl)acetate

Synthesis

From: 1-Methyl-1H-pyrrole

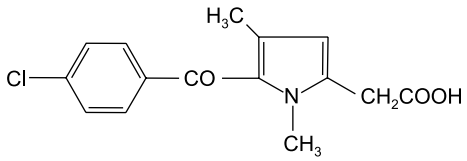


Metabolism: It is metabolized extensively first pass, involving hydroxylation of *p*-methyl group to primary alcohol, which is subsequently oxidized to dicarboxylic acid.

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.

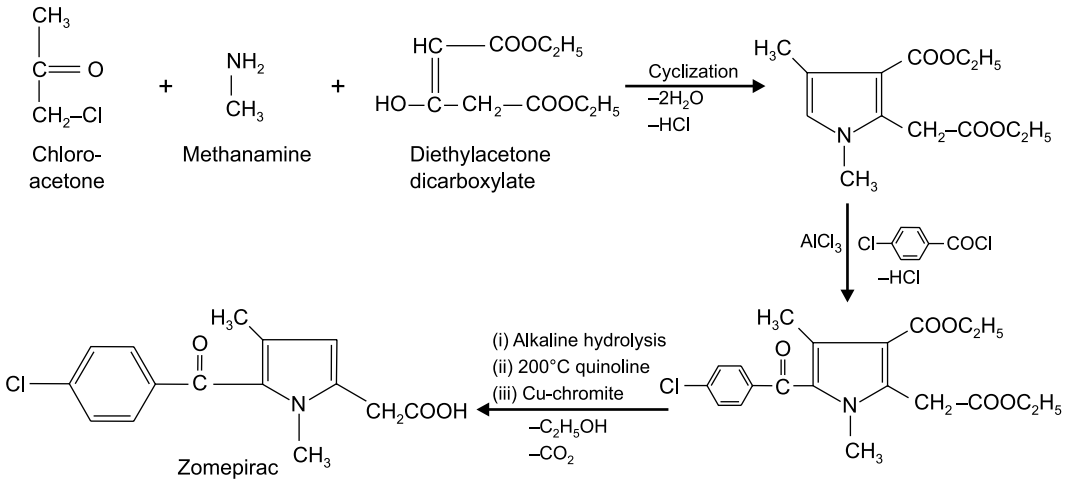
ii. Zomepirac (Zomax)



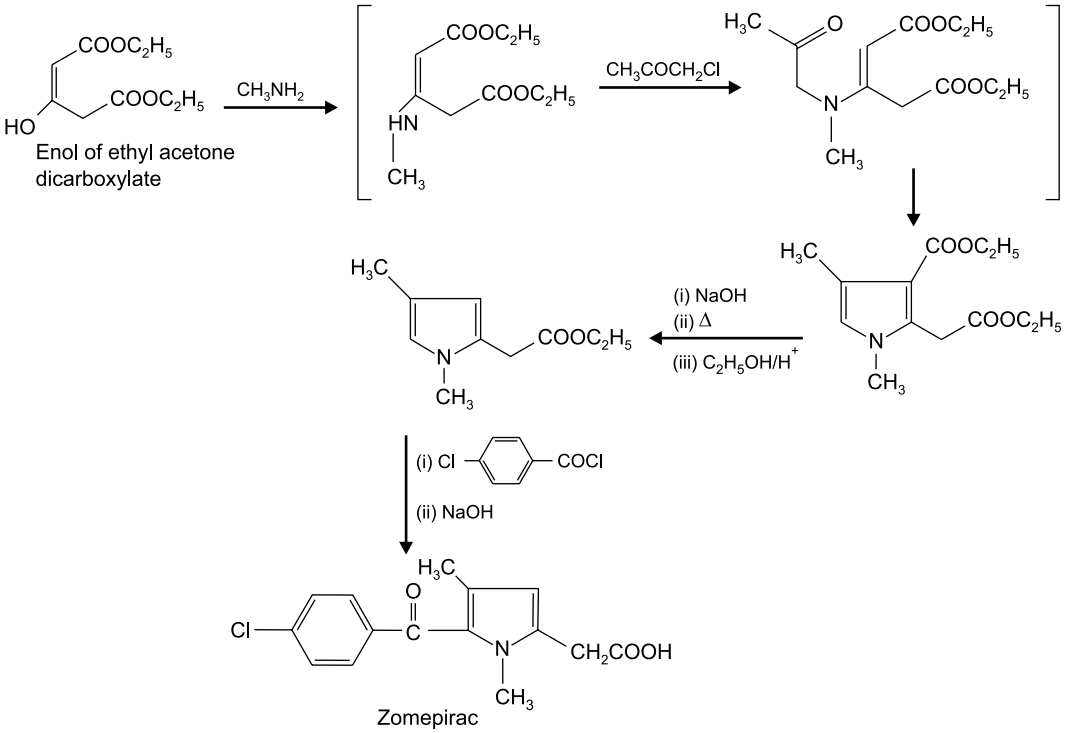
1,4-Dimethyl-5-(*p*-chlorobenzoyl) pyrrole-2-acetic acid

Synthesis

Route I. From: Chloroacetone



Route II. From: Enol of ethyl acetone dicarboxylate



Enol of ethyl acetone dicarboxylate

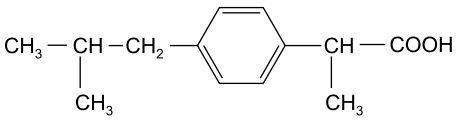
Zomepirac

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).

d. Aryl and heteroaryl acetic/propionic acid derivatives

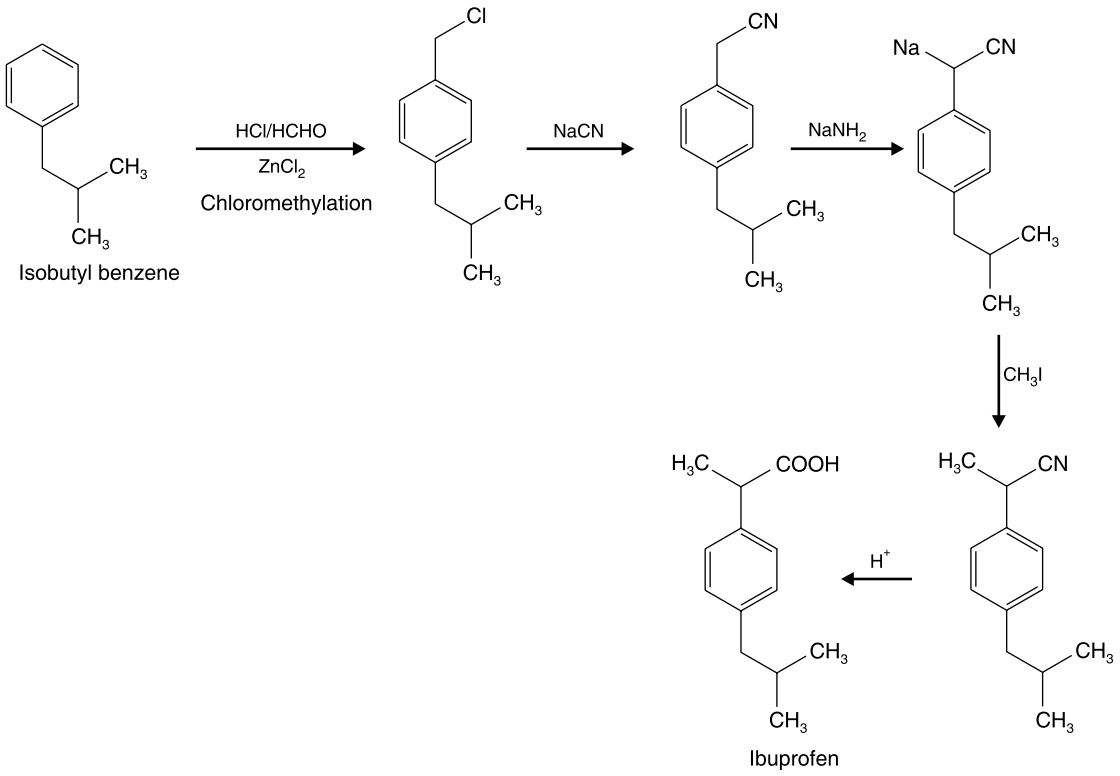
i. Ibuprofen (Brufen, Motrin)



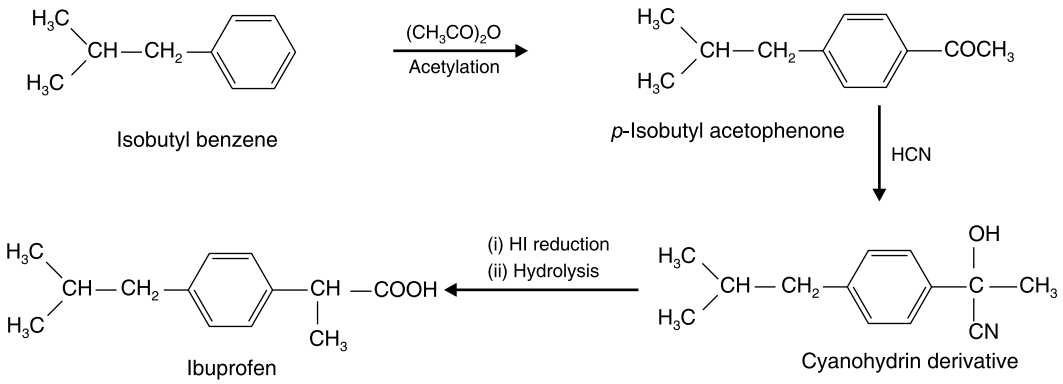
2-(4-Isobutyl phenyl) propionic acid

Synthesis

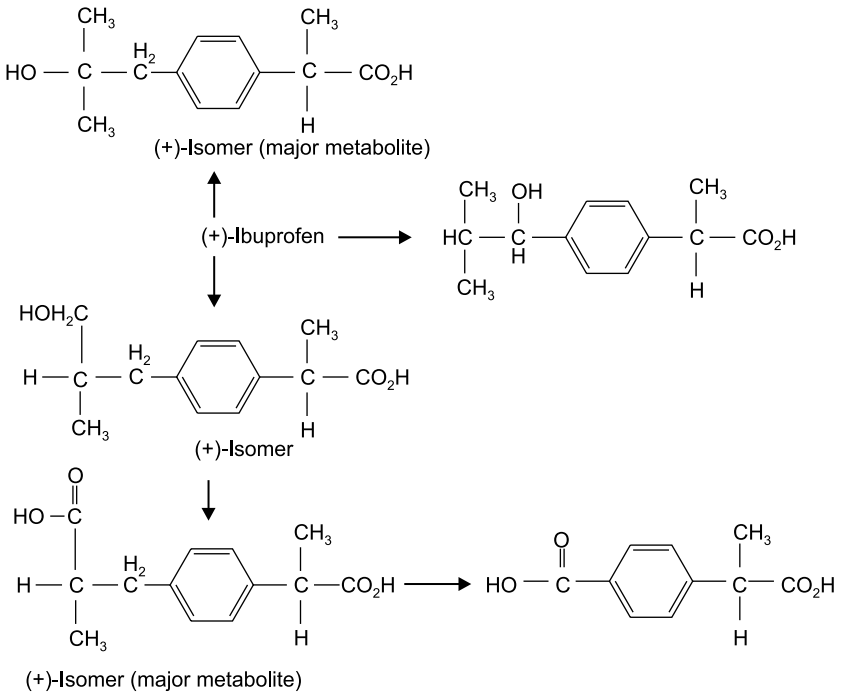
Route I. From: Isobutyl benzene



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.



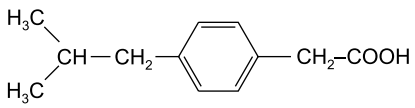
Properties and uses: Ibuprofen is a white crystalline powder or colourless crystals, practically insoluble in water, soluble in acetone, methanol, methylene chloride, and dilute solutions of alkali hydroxides and carbonates. The precursor ibufenac, which was abandoned owing to hepatotoxicity, was less potent. Moreover, the activity resides in the (s)-(+) isomer, not only in ibuprofen but also throughout the aryl acetic 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.

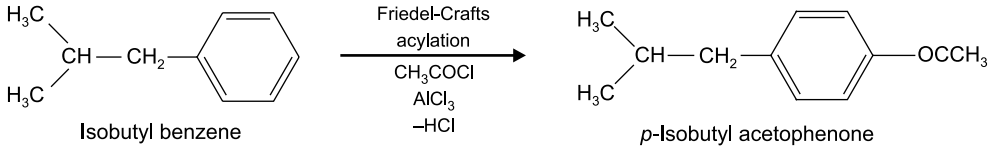
Dosage forms: Ibuprofen tablets IP, BP, ibuprofen cream BP, ibuprofen gel BP, ibuprofen oral suspension BP.

ii. Ibufenac



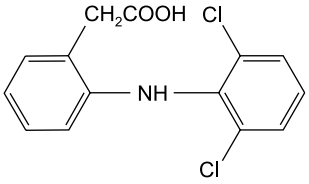
2-(*p*-Isobutyl-phenyl) acetic acid

Synthesis



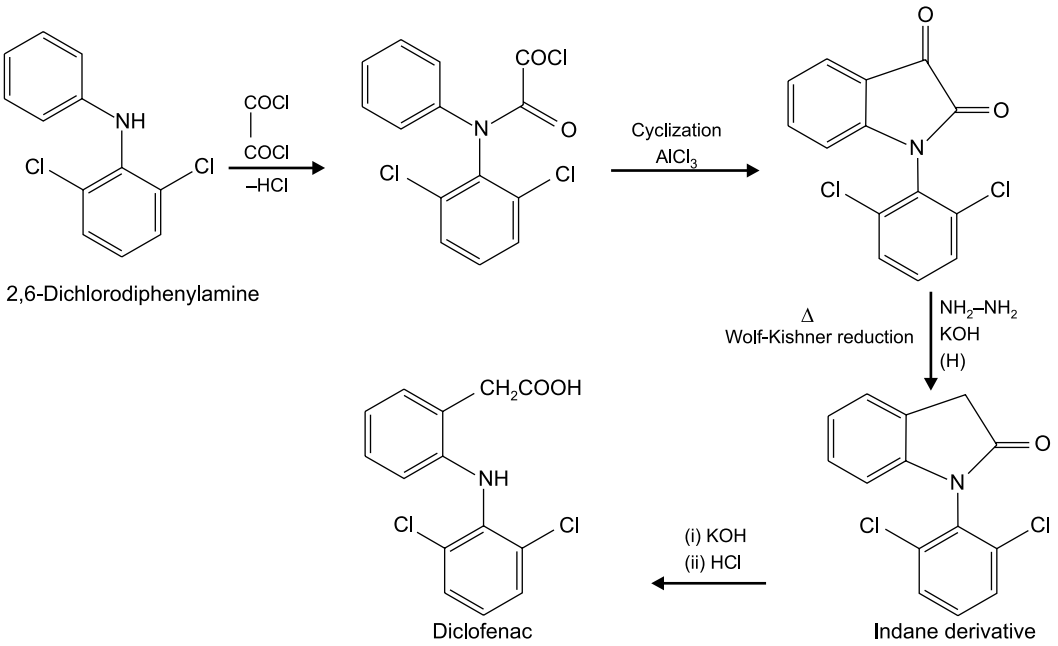
Properties and uses: It was formerly employed in the rheumatic conditions, but was found to cause hepatotoxicity. It has analgesic, antipyretic, and anti-inflammatory actions.

iii. Diclofenac (Voltaren, Voveran)



o-(2,6-Dichloro anilino) phenyl acetic acid

Synthesis



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

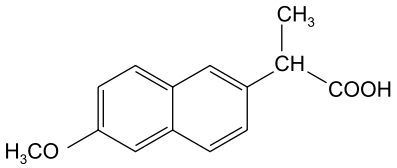
Properties and uses: Diclofenac sodium is a white or slightly yellowish crystalline slightly hygroscopic powder, sparingly soluble in water, soluble in methanol and alcohol, slightly soluble in acetone. Used in the treatment of rheumatic arthritis.

Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M per chloric 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.

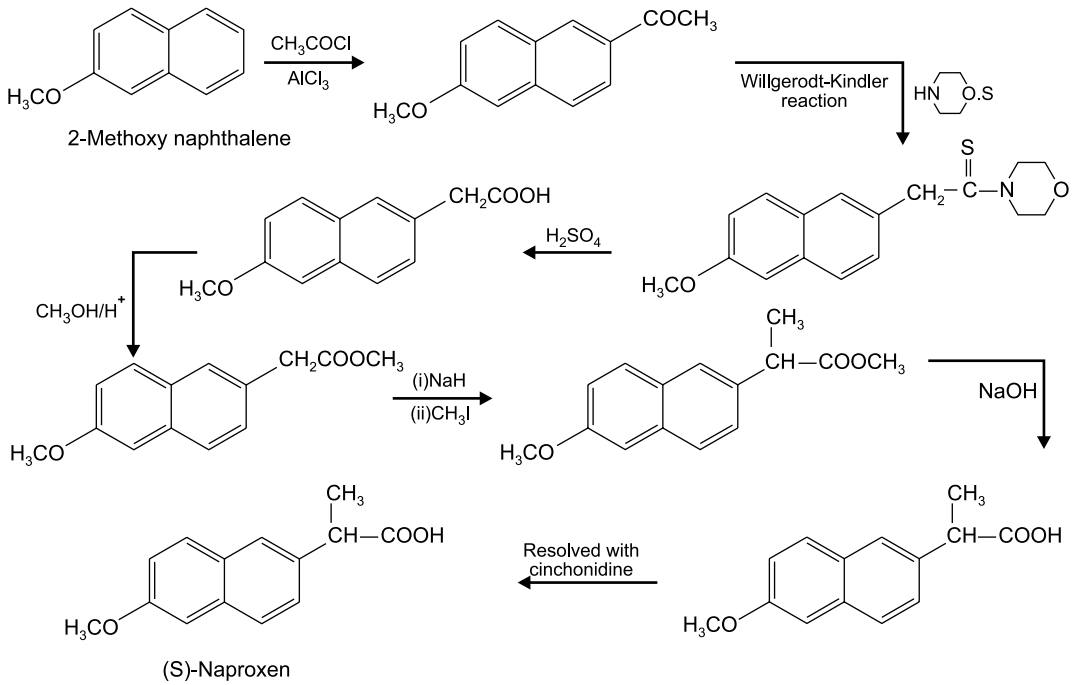
Dosage forms: Diclofenac tablets IP, diclofenac injection IP, prolonged-release diclofenac tablets BP, gastro-resistant diclofenac tablets BP, prolonged-release diclofenac injection BP, prolonged-release diclofenac capsules BP.

iv. Naproxen (Naprosyn)



(±)2-(6-Methoxy-2-naphthyl) propionic acid

Synthesis



2-Methoxy naphthalene

(S)-Naproxen

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

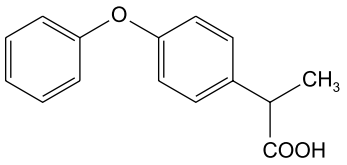
Properties and uses: Naproxen is a white crystalline powder, practically insoluble in water, soluble in ethanol and in methanol. The drug is fairly comparable to aspirin both in the management and control of disease symptoms. Nevertheless, it has relatively lesser frequency and severity of nervous system 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.

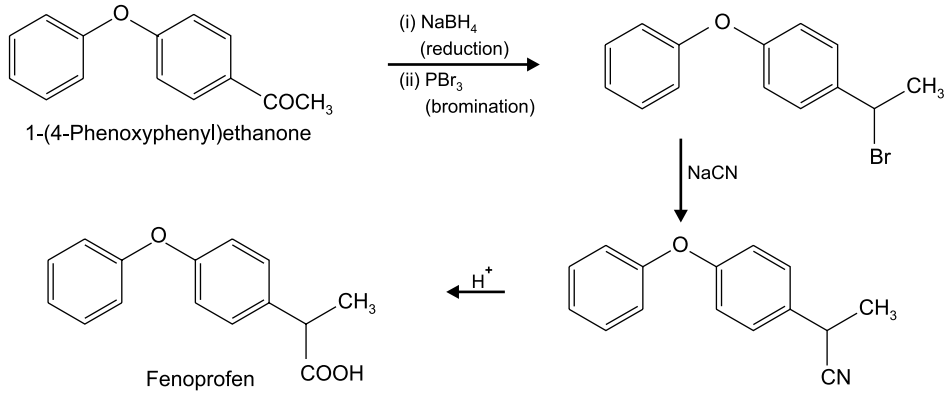
Dosage forms: Naproxen oral suspension BP, naproxen suppositories BP, naproxen tablets BP, gastro-resistant naproxen tablets BP.

v. Fenoprofen (Nalton)



2-(3-Phenoxyphenyl) propionic acid

Synthesis



1-(4-Phenoxyphenyl)ethanone

Fenoprofen

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

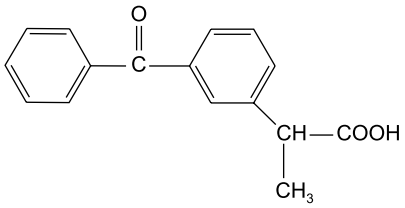
Properties and uses: Fenoprofen calcium is a white crystalline powder, slightly soluble in water and soluble in ethanol. Fenoprofen calcium has anti-inflammatory (antiarthritic) and analgesic properties. It has been shown to inhibit PG synthetase. It is known to reduce joint-swelling, decrease the duration 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 arhrtitis.

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 BP.

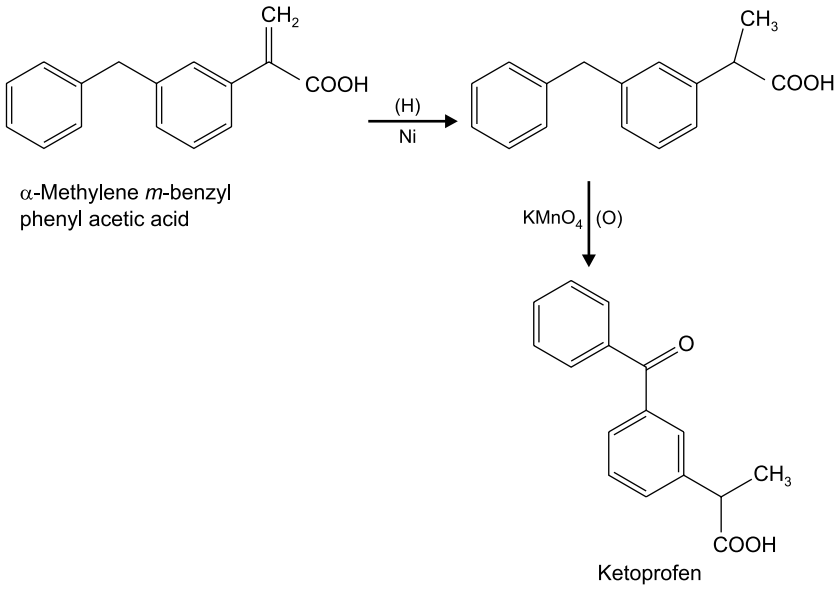
vi. Ketoprofen (Orudis)



2-(3-Benzoyl phenyl) propionic acid

Synthesis

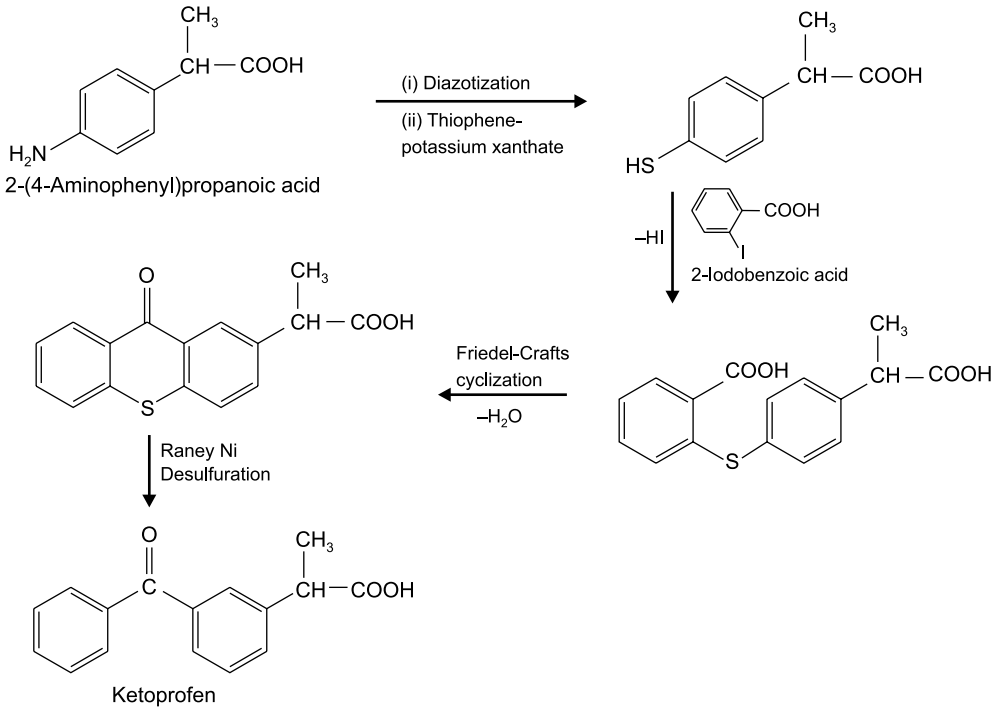
Route I. From: α-Methylene substituted *m*-benzyl phenyl acetic acid



α-Methylene *m*-benzyl phenyl acetic acid

Ketoprofen

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



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

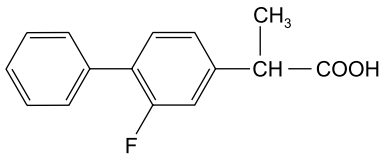
Properties and uses: Ketoprofen is a white crystalline powder, practically insoluble in water, soluble in acetone, in ethanol, and in methylene chloride. It is closely related to fenoprofen in structure, properties, and indications and has a low incidence of side effects and has been approved for counter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

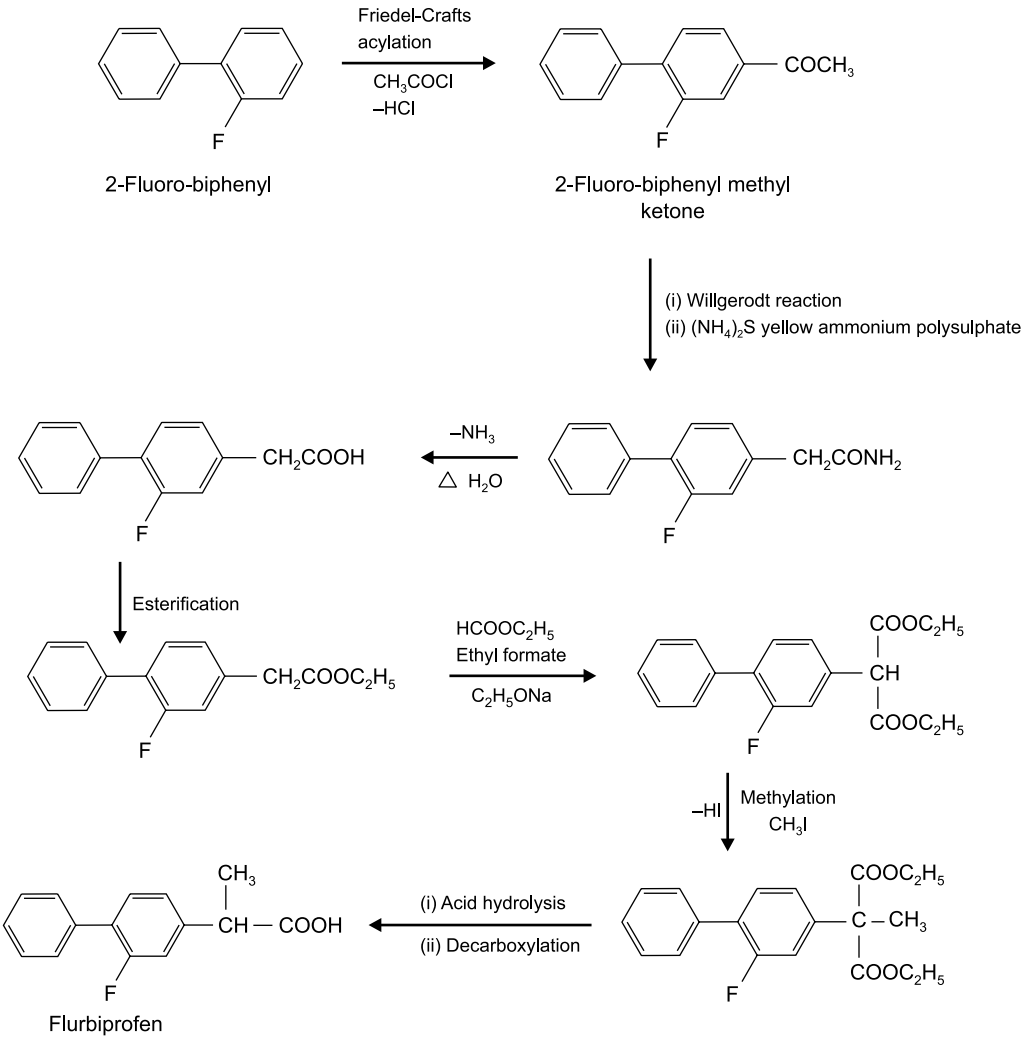
Dosage forms: Ketoprofen capsules IP, BP, ketoprofen gel BP.

vii. Flurbiprofen (Ansaid)



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

Synthesis



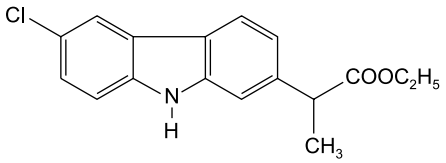
Properties and uses: Flurbiprofen is a white crystalline powder, practically insoluble in water, soluble in alcohol, in methylene chloride, and aqueous solutions of alkali hydroxides and carbonates. The drug is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen. Another hydrotropic acid analogue that is used in the acute or long-term management of rheumatoid arthritis and osteoarthritis, it posses 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 IP, BP, flurbiprofen suppositories BP.

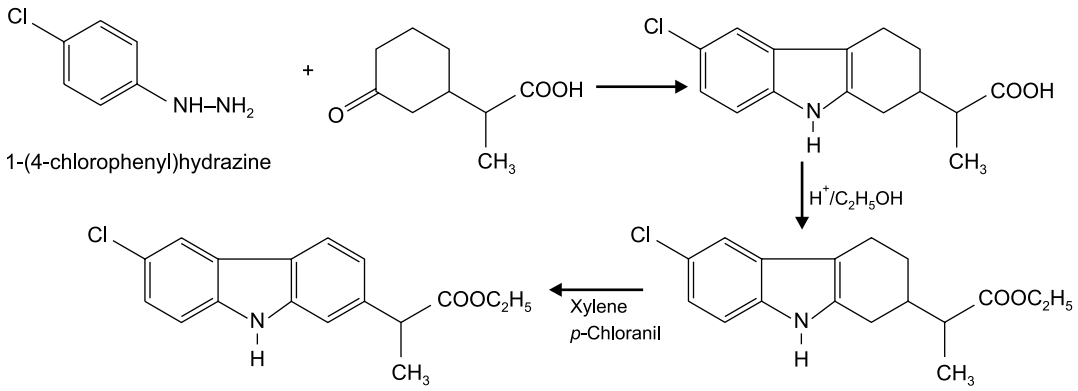
viii. Caprofen



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

Synthesis

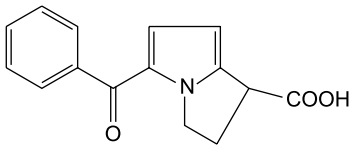
From: 1-(4-chlorophenyl) hydrazine



Caprofen

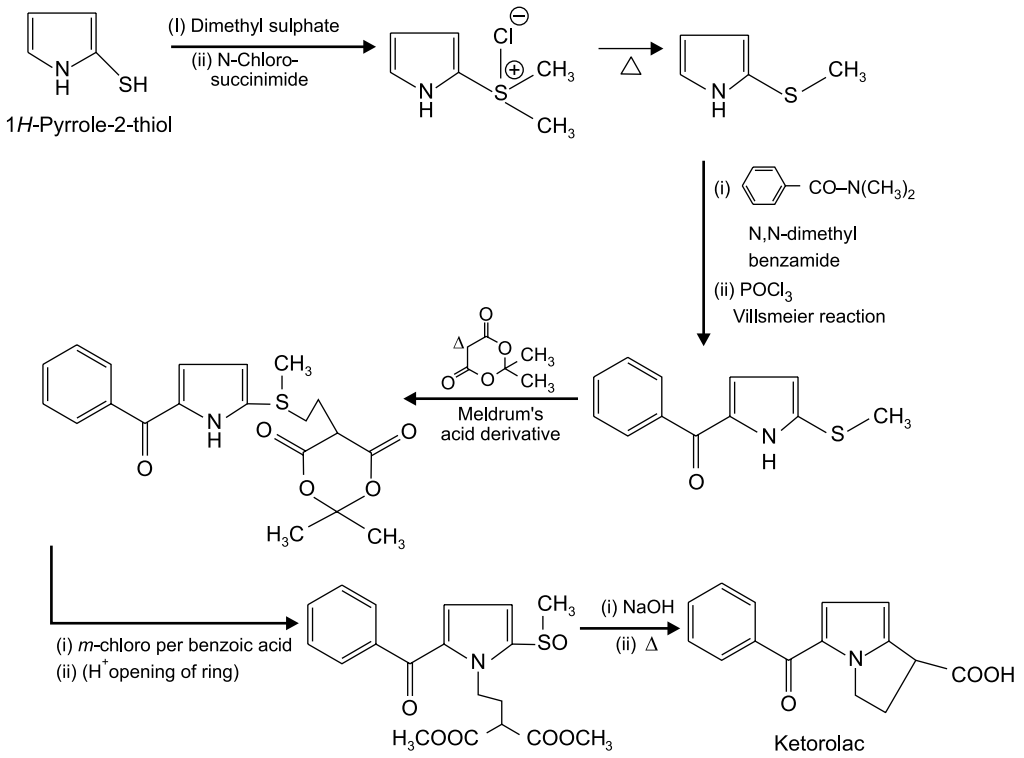
Uses: Used as an analgesic and anti-inflammatory agent.

ix. Ketorolac (Acular, Ketodrops, Ketlur)



5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid

Synthesis

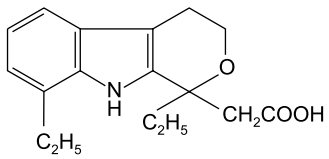


Properties and uses: Ketorolac is a white crystalline powder, soluble in water and in methanol, slightly soluble in ethanol, practically insoluble in methylene chloride. Ketorolac is a potent analgesic used for the treatment of moderately severe and acute pain.

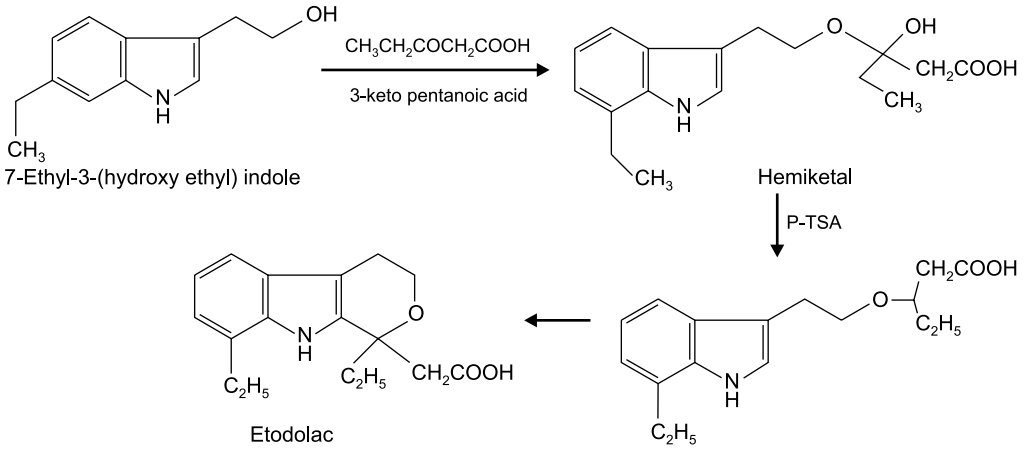
Assay: Dissolve the sample in anhydrous acetic acid and titrate against 0.1 M per chloric acid. Determine the end point potentiometrically.

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 sugery, instil one drop of 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.

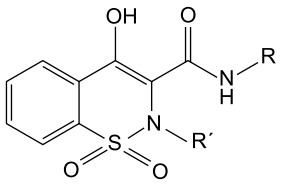
Properties and uses: Etodolac is a white crystalline powder, practically insoluble in water, soluble in acetone and in ethanol. It has anti-inflammatory activity and inhibits cyclooxygenase. It is used in the treatment of osteoarthritis and rheumatoid arthritis. Gastrointestinal irritation and ulceration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

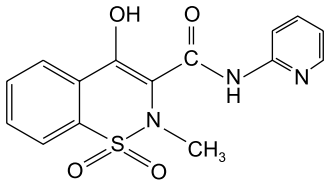
Dosage forms: Etodolac capsules BP, etodolac tablets BP.

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

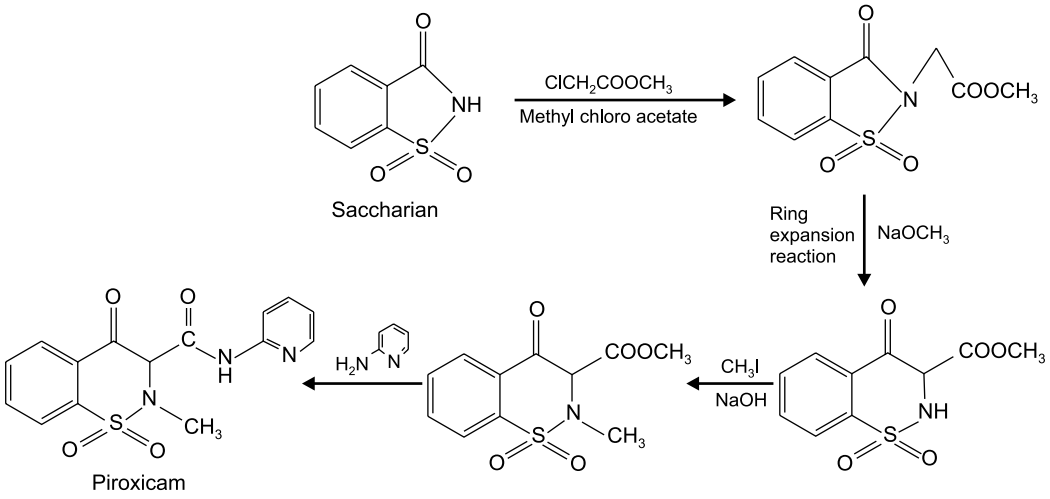
Properties and uses: Piroxicam is a white or slightly yellow crystalline powder, practically insoluble in water, soluble in methylene chloride, and slightly soluble in ethanol. It is employed for acute and long-term therapy for the relief of symptoms of osteoarthritis and rheumatoid arthritis. It also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

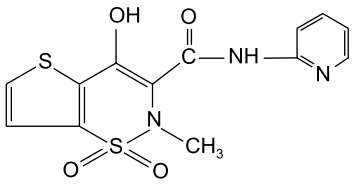
Dosage forms: Piroxicam capsules IP, BP, piroxicam tablets IP, piroxicam gel BP.

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)

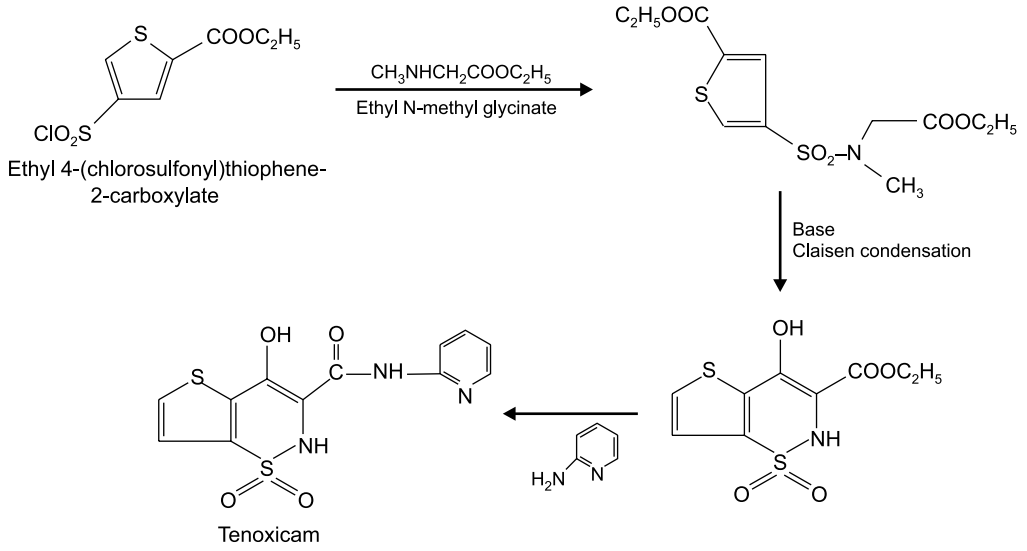


4-hydroxy-2-methyl-1,1-dioxo-pyridin-2-yl thieno [2,3-e] thiazine-3-carboxamide

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.

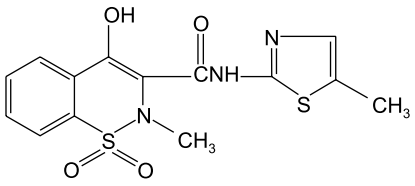
Synthesis



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 BP, tenoxicam tablets BP.

iii. Meloxicam (Mobic)



4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2*H*-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 BP.

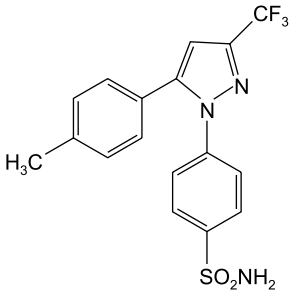
SAR of Oxicams

- 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 derivatives have acidities in the pK_a range of 6–8.

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)

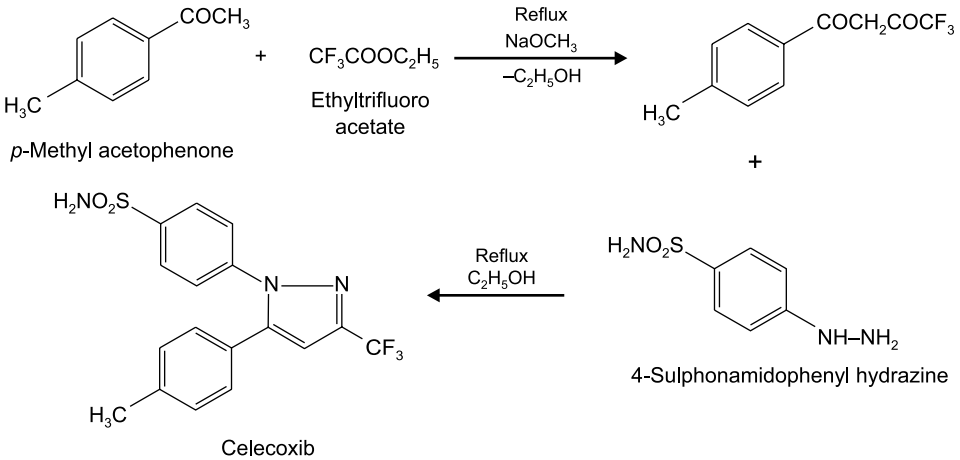


4-[5-(4-Methyl phenyl)-3-(trifluoro)-1*H*-pyrazo-lyl]-benzene sulphonamide

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.

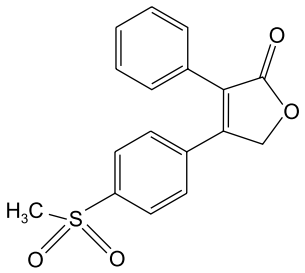
Properties and uses: It exists as pale yellow crystals, sparingly soluble in water. Celecoxib is used to treat arthritis, pain, menstrual cramps, and colonic polyps, and also for the relief of pain, fever, swelling, and tenderness caused by osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Synthesis



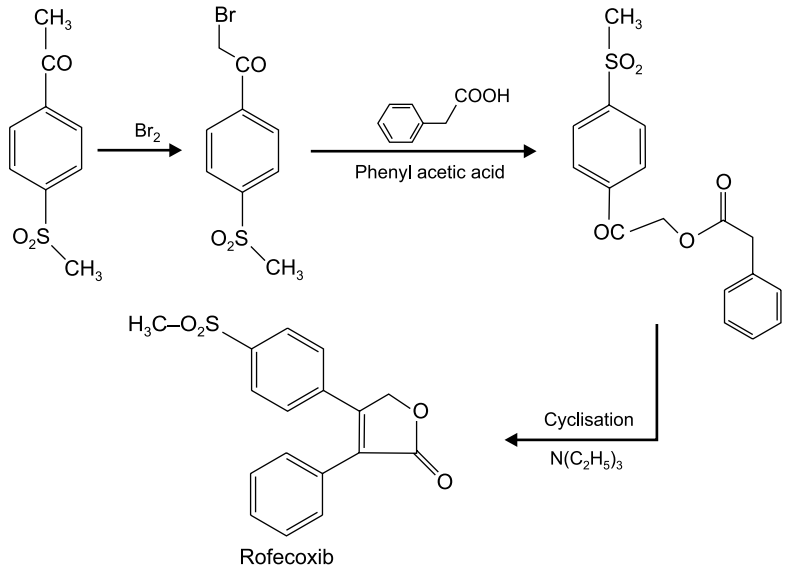
Dose: For osteoarthritis, the adult dose is 200 mg as a single dose or in two divided doses that may be increased to 200 mg two times a day, if necessary. For rheumatoid arthritis, the adult dose is 100–200 mg two times a day. For elderly people the dose is 100 mg two times a day. For dysmenorrhoea, 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 (Vioxx)



4-[4-(Methyl sulphinyl) phenyl]-3-phenyl-2-furanone

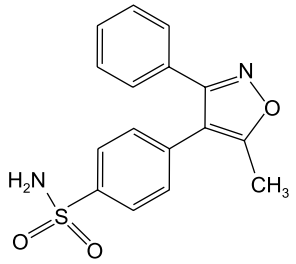
Synthesis



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

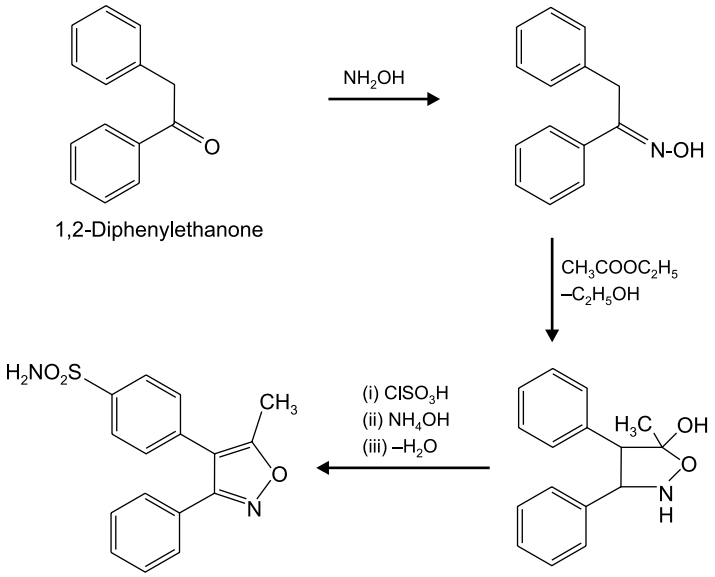
Properties and uses: It exists as white to light yellow powder, sparingly soluble in acetone, methanol, very slightly soluble in 1-octanol. It is a COX-2 inhibitor with greater potency and a longer half-life than celecoxib. Rofecoxib is used to relieve the pain, tenderness, inflammation (swelling), and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

iii. Valdecoxib (Bextra)



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

Synthesis



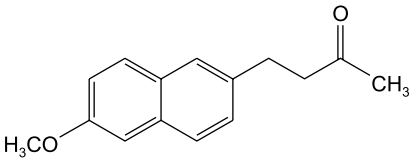
Metabolism: It is metabolized by hydroxylation of 5-methyl group and it is further metabolized to inactive carboxylate and *N*-Hydroxylation at the sulphonamide function, leading to the formation of corresponding sulphinic acid and suphomic metabolites.

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.

Miscellaneous

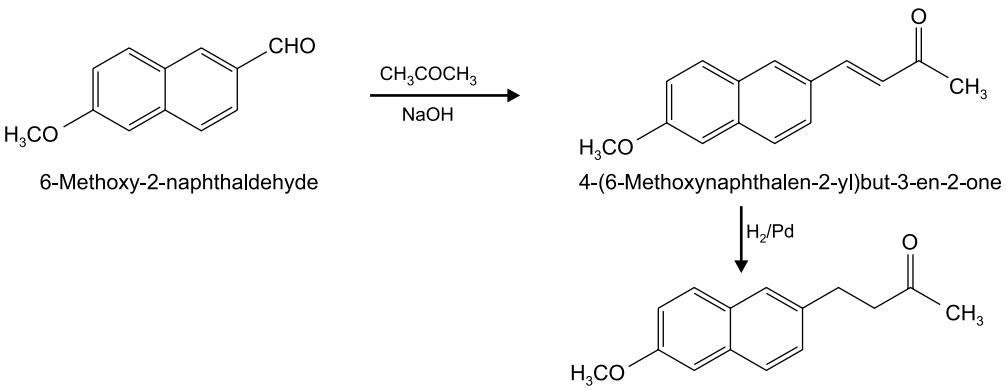
i. Nabumetone (Nabuflam, Niltis)



4-(6-Methoxy-2-naphthyl)-2 butanone

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 non-acidic 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



6-Methoxy-2-naphthaldehyde

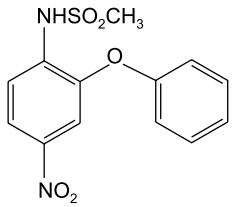
4-(6-Methoxynaphthalen-2-yl)but-3-en-2-one

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 BP, nabumetone tablets BP.

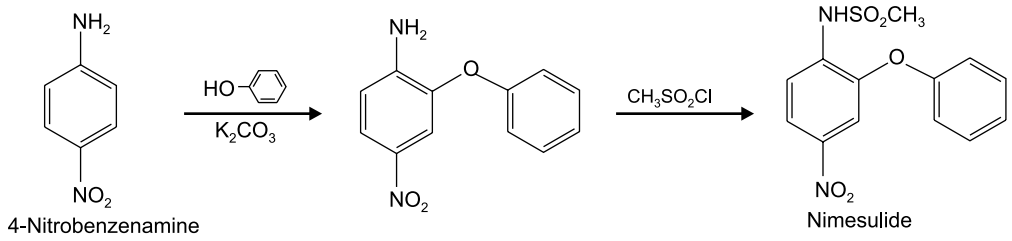
Assay: It is assayed by adopting liquid chromatography technique.

ii. Nimesulide (Auronim)



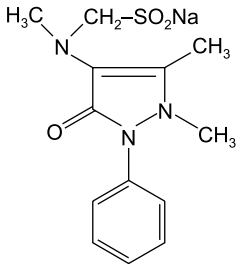
4-Nitro-2-phenoxy methane sulphonamide

Synthesis



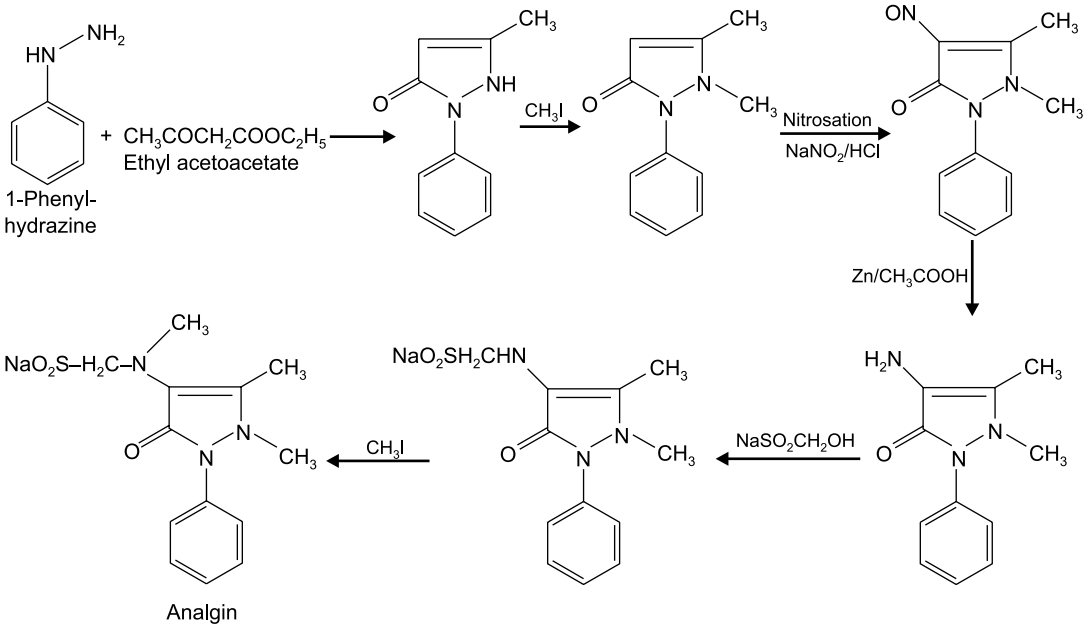
Properties and uses: Nimesulide is a yellowish crystalline powder, practically insoluble in water, soluble in acetone, and slightly soluble in anhydrous ethanol. It contains a sulphonamide moiety as an acidic group rather than a carbonic acid. It shows moderate incidence of gastric side effects because 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



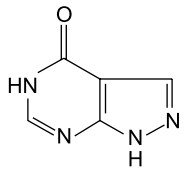
Uses: Used as an analgesic and anti-inflammatory agent.

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:

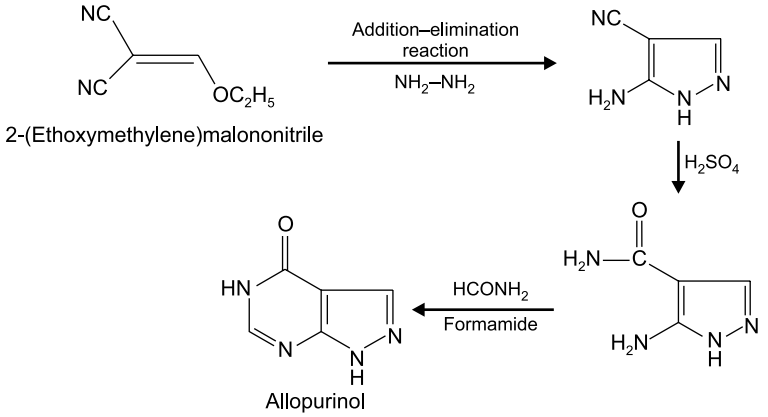
- By inhibiting uric acid synthesis: Allopurinol.
- By increasing uric acid excretion: Probenecid, sulphinpyrazone.
- Miscellaneous: Colchicines (alkaloid obtained from *Colchicum autumnale*).

i. Allopurinol (Zyloprim)

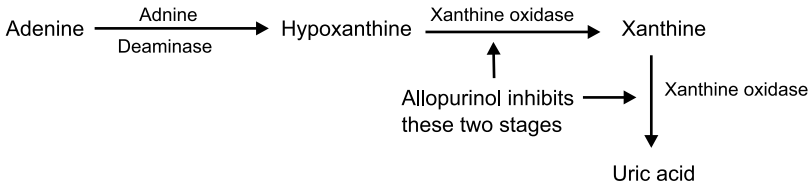


Pyrazolo pyrimidine-4-one

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 and competitive inhibitor of the enzyme at high concentrations; it is a non-competitive 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

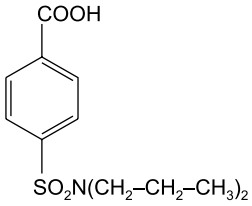
deposition in patients with leukaemia receiving anticancer drugs, which cause increasing serum uric acid levels.

Assay: It is assayed by adopting liquid chromatography technique.

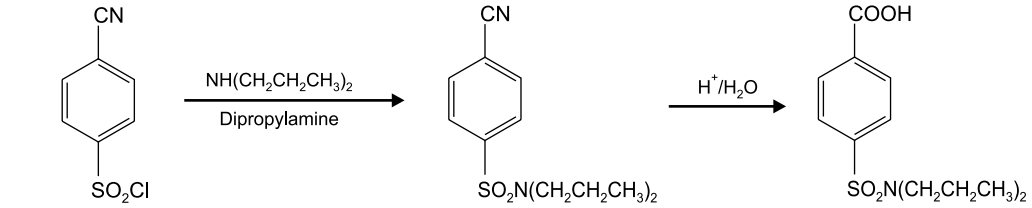
Dose: Usual adult oral dose for gout is 100–200 mg two or three times a day.

Dosage forms: Allopurinol tablets IP, BP.

ii. Probenecid (Benemid)



Synthesis



4-Cyanobenzene-1-sulfonyl chloride

Probenecid

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.

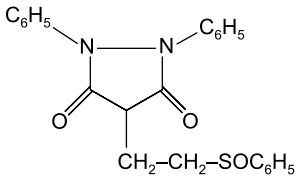
Properties and uses: Probenecid exists as white crystalline powder or small crystals, practically insoluble in water, soluble in acetone, and sparingly soluble in ethanol. Probenecid is uricosuric agent that increases the rate of excretion of uric acid and used in the treatment of chronic gout. The oral 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.

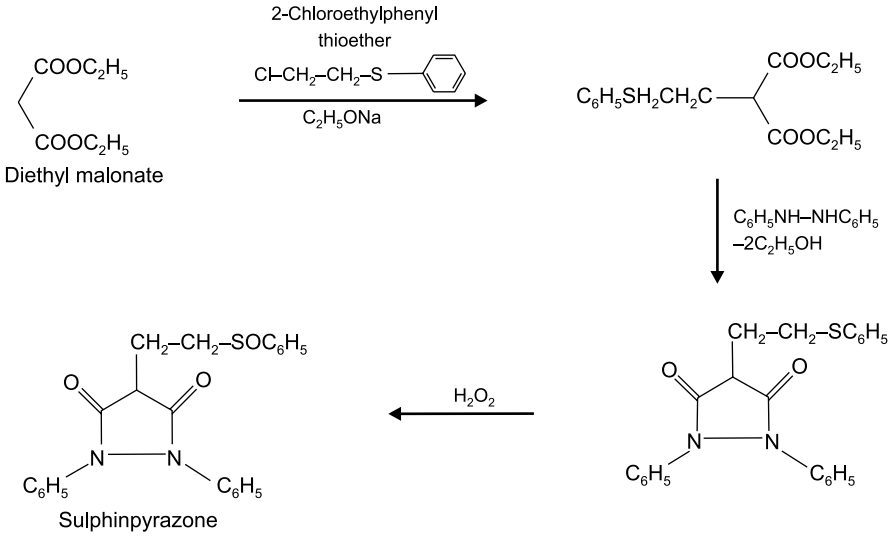
Dose: Adult oral dose is 500 mg–2 g per day; usually 250 mg two times a day for one week, then 500 mg twice a day thereafter.

Dosage forms: Probenecid tablets IP, BP.

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.

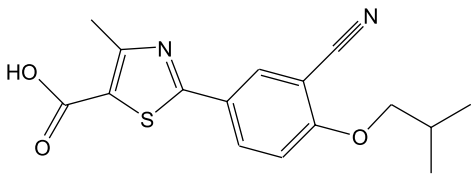
Properties and uses: Sulphinpyrazone is a white powder, very slightly soluble in water, sparingly soluble in alcohol, soluble in dilute solutions of alkali hydroxides and used as uricosuric agent.

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 BP.

iv. Febuxostat (Uloric)



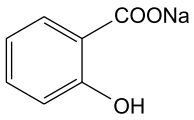
Mode of action: Febuxostat is a xanthine oxidase (XO) inhibitor. It achieves its therapeutic effect by decreasing serum uric acid. It is a non-purine selective XO inhibitor. Febuxostat inhibits both oxidized and reduced types of XO. It is not expected to inhibit other enzymes involved in synthesis and metabolism of purine and pyrimidine at therapeutic concentrations.

Properties and uses: Febuxostat is specifically used for the chronic management of hyperuricaemia in patients with gout. Adverse events associated with the use of febuxostat are liver function abnormalities, nausea, arthralgia, and rash.

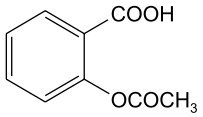
Dose: Febuxostat is supplied as a 40 mg tablet designed for oral administration. The recommended initial dose of the drug is 40 mg once daily. For patients who do not achieve a serumuric acid less than 6 mg per dL after the treatment for 2 weeks with 40 mg, uloric 80 mg is recommended.

CLASSIFICATION BASED ON PCI SYLLABUS

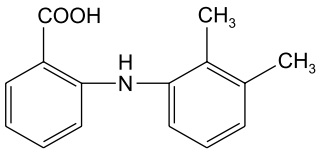
Sodium salicylate



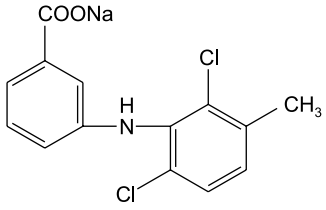
Aspirin



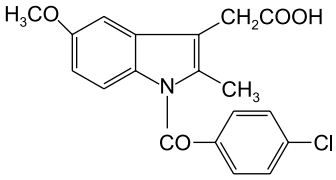
Mefenamic acid



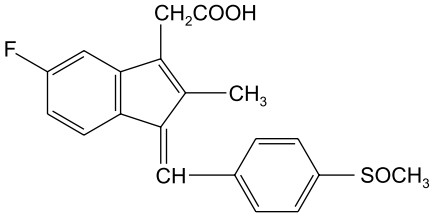
Meclofenamate



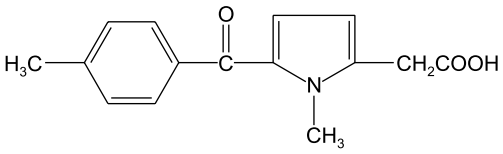
Indomethacin



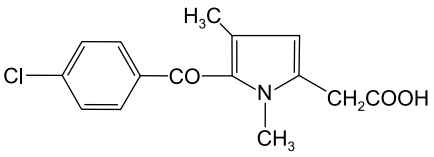
Sulindac



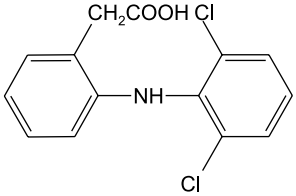
Tolmetin



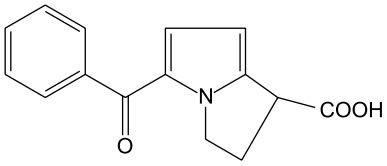
Zomepirac



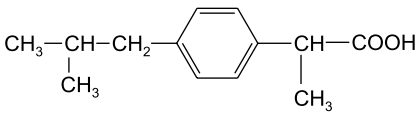
Diclofenac



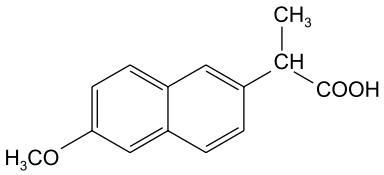
Ketorolac



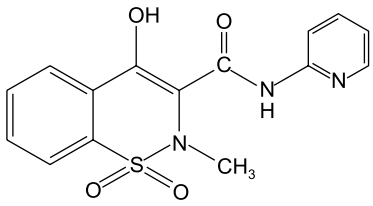
Ibuprofen



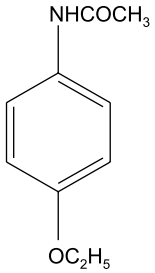
Naproxen



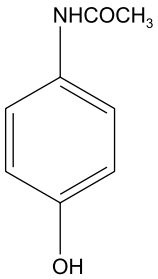
Piroxicam



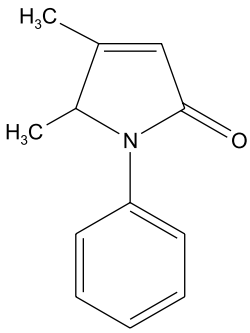
Phenacetin



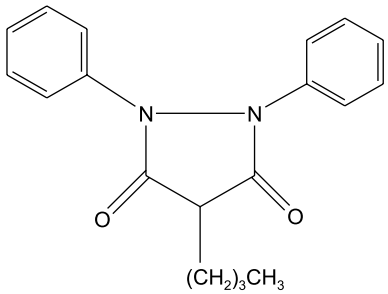
Acetaminophen



Antipyrine



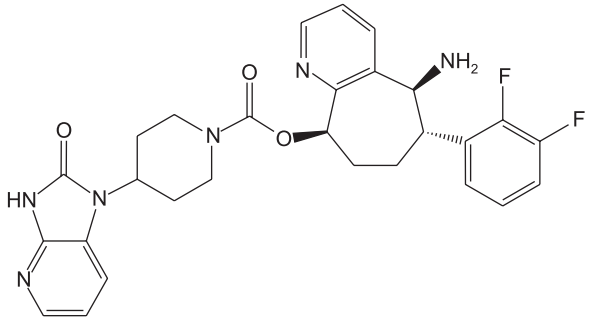
Phenylbutazone



Meclofenamate

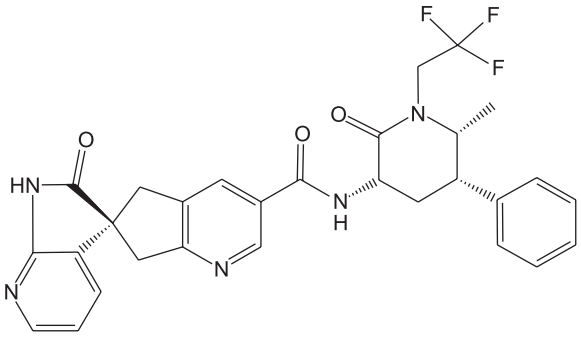
Properties and uses: It belongs to the category of anthranilic acid derivatives. It is a COX-inhibitor and used to treat joint and muscular pains, arthritis and dysmenorrhea.

Rimegepant



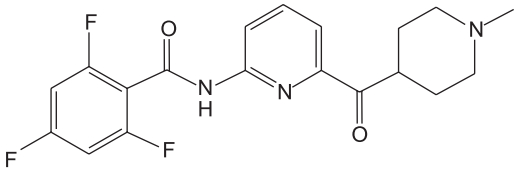
Uses: It is used to treat migraine.

Ubrogepant



Uses: It is used for the treatment of acute (immediate) treatment of migraine.

Lasmiditan



Uses: It is used for the treatment of migraine.

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 aryl acetic 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.

SUGGESTED READINGS

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2. *British Pharmacopoeia*. Medicines and Healthcare Products Regulatory Agency, London, 2008.
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6. Lemke TL and William DA. *Foye's Principle of Medicinal Chemistry* (6th edn). New York: Lippincott Williams and Wilkins, 2008.
7. Gennaro AR. *Remington's: The Science and Practice of Pharmacy* (21st edn). New York: Lippincot Williams and Wilkins, 2006.
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