Chapter

1

ANTIHISTAMINES

1. INTRODUCTION

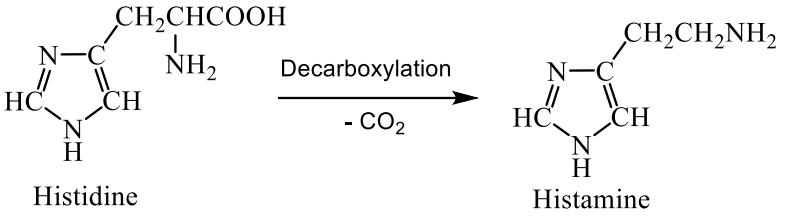
The term antihistamine implies to drug that reduces or eliminates the effects mediated by the chemical histamine. The term antihistamine refers only to H_1 receptor antagonist.

1.1 Histamine

Histamine is a neurotransmitter or chemical messenger that carries signals from one nerve to another, as well as performing several other important functions in various bodily tissues. Histamine is an autacoid, which means it acts similarly to a local hormone, near its site of synthesis. It is a β-imidazolyl ethylamine derivative, distributed in mast cells in all peripheral tissues of the body and basophils in the blood. It is produced naturally by immune system and released in response to tissue damage. It mediates immediate allergic and inflammatory response, causes gastric acid release and function as a central nervous system neurotransmitter. Systemically, histamine contracts smooth muscle of lungs and gastrointestinal system and cause vasodilatation, low blood pressure and increases heart rate. It causes symptoms such as itching, sneezing, watery eye and runny nose.

1.2 Biosynthesis of Histamine

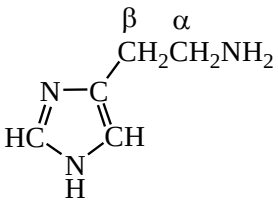
In the living organism, histamine is synthesized from the naturally occurring α-amino acid, histidine by the loss of a carboxyl group through bacteria or enzymatic decarboxylation. It is synthesized in the Golgi apparatus of mast cells and basophils. This conversion is catalyzed by *L-histidine decarboxylase*.



Histidine Histamine

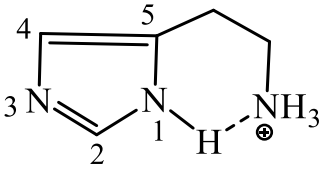
1.3 Chemistry of Histamine

Histamine is 4 - (2- Amino ethyl) imidazole, structurally composed of an imidazole and ethyl amine side chain. The methylene group of amino ethyl side chain is designated as α and β. The side chain attached via β-CH_2 to the 4th position of imidazole ring. The nitrogen at position 3 is designated as pros (π) and 1 is termed as (τ) tele.

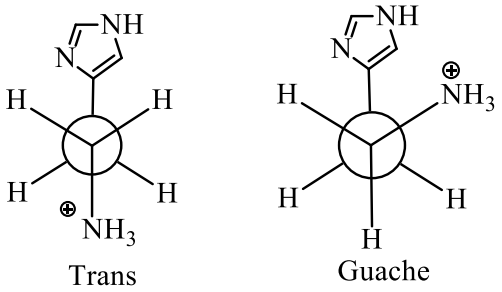


Histamine

At physiological pH, the amino nitrogen atom at the side chain is protonated. Histamine occurs therefore, as a monovalent cation, which forms an intramolecular hydrogen bond between side chain amino nitrogen and ring nitrogen.



Histamine is an achiral molecule, histamine receptors are stereo selective toward chiral ligand. Studies with conformational restricted histamine analogues suggest that *trans* rotamer possess affinity for both H_1 and H_2 histamine receptors, the Gauche conformer act at H_3 receptors



Histamine rotamers

1.4 Histamine Receptors

Histamine receptors belong to the G-protein coupled receptor family. These receptors are divided into four subtypes H_1, H_2, H_3 and H_4 according to their function, structure, distribution and their affinity to histamine.

i) H_1 receptors

It is found in smooth muscles of intestine, bronchi, blood vessels, adrenal medulla, endothelial cell and lymphocytes. The H_1-receptor protein is G-protein coupled, linked to intercellular Gq, which activates *phospholipase C* and increases intracellular Ca^{++} levels. All immediate hypersensitivity reactions, including symptoms observed in the skin, such as erythema, pruritus edema, broncho-constriction, motion sickness, smooth muscle relaxation and vasodilation may be due to activation of H_1 receptor. Antagonist of H_1 receptor are used as antiallergic and antiemetics.

ii) H_2 receptor

It is present in the tissues of parietal cells located in the stomach lining, myocardial cell, uterus and vascular smooth muscle cells. Histamine action at these receptors, stimulates the release of gastric acid, inhibit antibody and cytokine production. H_2antagonists are used as antiulcer.

iii) H_3 receptor

It is presynaptic receptor inhibit the synthesis and release of histamine in the histaminergic neurons in the central nervous system (CNS).

iv) H_4 receptor

The H_4 receptors found on immune cells and tissues including peripheral blood leukocytes, spleen, small intestine, bone marrow and thymus. Histamine action on these receptors, regulate the levels of white blood cell release from bone marrow. They have also been showing to direct mast cells.

Histamine antagonists are drugs that inhibit the effects of histamine by blocking or binding to H receptors. Histamine inhibitors are classified into

(A) **Histamine release inhibitors**

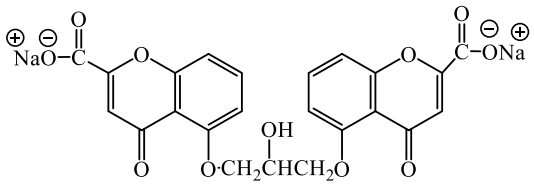
(B) **Released histamine inhibitors**

(i) H_1 antagonist- antihistamines (ii) H_2 antagonist - antiulcer

2. HISTAMINE RELEASE INHIBITORS - MAST CELL STABILIZERS

These agents stabilize mast cell and inhibit the release of histamine and other mediators of inflammation. Generally, the mast cell stabilizer inhibit activation and mediator release from a variety of inflammatory cell type associated with allergy and asthma, including eosinophils, neutrophils, macrophages, mast cell, monocytes and platelets.

A. Cromolyn sodium (Crolom)



Disodium - 1, 3 - bis - (2 - carboxychromon - 5 - yloxy) - 2 - hydroxy propane

Mechanism of action: It stabilizes mast cell and inhibits the release of histamine and anaphylaxis (SRS-A), a Type I allergic reaction. It may also reduce the release of inflammatory leukotrienes.

Use: It is used for bronchial asthma for prevention of induced bronchospasm and rhinitis (nasal solution). Topically used as eye drops for allergic conjunctivitis and keratitis.

3. RELEASED HISTAMINE INHIBITORS

(H_1 ANTAGONIST-ANTIHISTAMINES)

3.1 Introduction

Antihistamines are the drugs that inhibit the release of histamines at H_1 receptor. The first generation H_1 antihistamines are useful in the treatment of allergic response like hay fever, rhinitis, urticaria and food allergy. H_2 antagonists interact with H_2 receptors and primarily used in the treatment of peptic ulcer and other gastric hyper secretory states.

First-generation H_1 antihistamines readily cross the blood-brain barrier (BBB) and occupy H_1-receptors located on postsynaptic membranes of histaminergic neurons throughout the CNS. So, these agents act on adrenergic, cholinergic, dopaminergic and serotonergic receptor. This results in adverse effects like sedation, drowsiness, blurred vision, dry mouth, urinary retention, appetite stimulation, muscle spasm and CNS depression. This was overcome in second generation antihistamines, which do not cross the BBB and has less anticholinergic and CNS effect.

3.2 Mechanism of action of Antihistamines

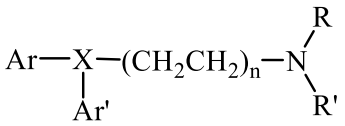
The antihistamines have been used extensively for the symptomatic treatment (sneezing, rhinorrhea and itching of eyes, nose, and throat) of allergic rhinitis, chronic idiopathic urticaria and a number of other histamine related diseases. These uses are due to their antagonism action for histamine at peripheral H_1 receptors. The histamine (H_1)

receptors like other G-protein coupled receptors exist as equilibrium between the inactive state and the active state. Histamine stabilizes the receptor in its active conformation, thus causing the equilibrium to swing to the 'on' position. H_1 antihistamines act as inverse agonists that combine with and stabilize the inactive conformation of the H_1-receptor, shifting the equilibrium towards the inactive state and produce the opposite effect. It prevents the action of histamine mainly in immediate hypersensitivity. They act in the bronchi, capillaries and some other smooth muscles and are used to relieve motion sickness, seasonal rhinitis and allergic dermatitis.

A number of the antihistamines, particularly the phenothiazines and amino alkyl ethers, have antiemetic actions and thus useful in the treatment of nausea, vomiting and motion sickness.It blocks the histamine receptors in the vomiting center and affects the medullary chemoreceptor trigger zone. Certain antihistamines block central muscarinic receptors as a result they have limited use in Parkinson-like syndromes.

3.3 Structure Activity Relationship

The essential pharmacophore for H_1 antagonistic activity is represented by a general structure of 2 aromatic groups linked through a short chain to a tertiary aliphatic amine:



- ✓ The Ar group may be phenyl, substituted phenyl or hetero aryl group such as 2- pyridyl Ar' is a second aryl or aryl methyl group.
- ✓ X is a connecting atom of O, C or N; Chemical classification of these agents are usually based on the unit X which may be saturated Carbon-Oxygen (amino alkyl ether),

nitrogen (ethylene diamine) or carbon (propylamine) Tricyclic derivative in which two aromatic rings are bridged. eg. Phenothiazine.

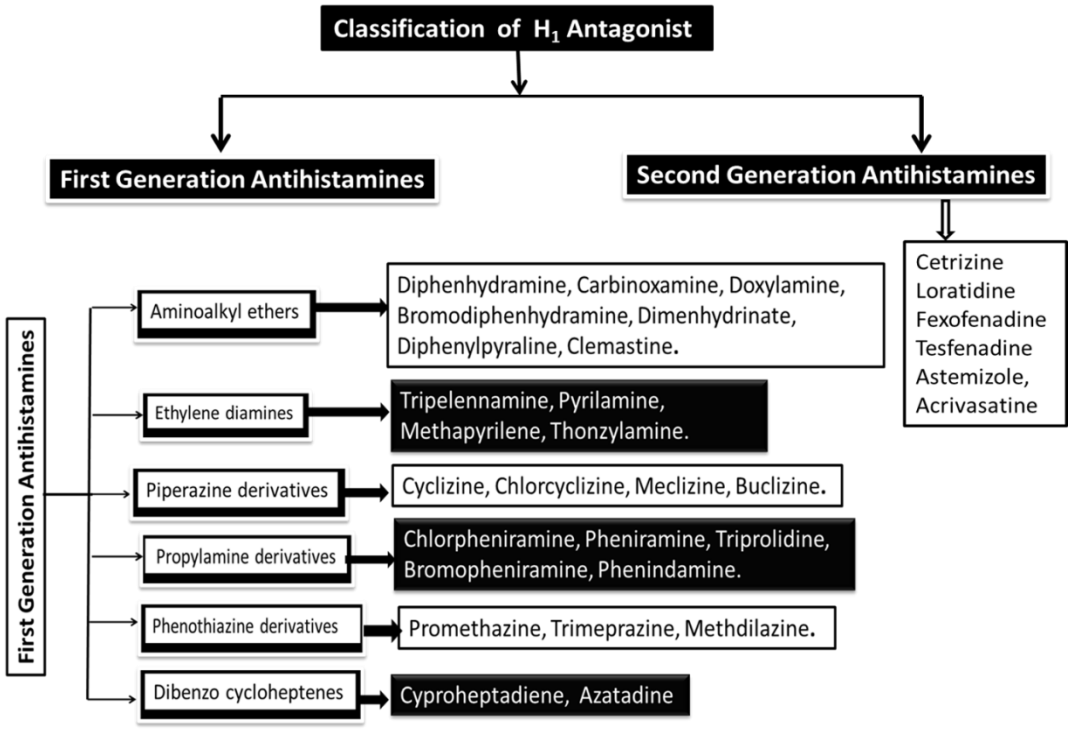
- ✓ $(CH_2)_n$ is a carbon chain usually ethyl.
- ✓ NRR' represents basic terminal amine function. The diaryl substitution is essential for significant H_1 affinity.
- ✓ The nitrogen should be 3˚ amine in nature for maximum antihistaminic activity. The 'N' may also form a part of heterocyclic moieties like piperidine or piperazine. The nitrogen should be separated by 5-6 A˚ from the aromatic or hetero aromatic group.
- ✓ The group present between nitrogen atom and group X may be saturated or unsaturated or substituted.
- ✓ Many antihistamines contain a carbon atom in the connecting atom (X) are chiral and exhibit stereo selective receptor binding. eg. S-configuration of Pheniramine series has more affinity for H_1 receptor.

3.4 Therapeutic Applications of Antihistamines

Antihistamines are in general used in various

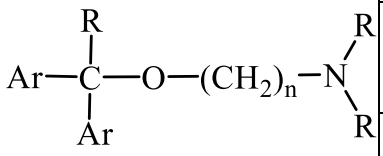
- ✓ allergic rhinitis (common cold),
- ✓ allergic conjunctivitis (pink eye),
- ✓ allergic dermatological conditions, urticaria (hives),
- ✓ angioedema (swelling of the skin),
- ✓ vertigo and Motion sickness,
- ✓ antiemetic and
- ✓ sedation (first generation H_1-antihistamines)

3.5 Classification

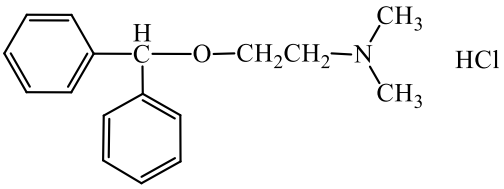


3.5.1 FIRST GENERATION H_1 ANTAGONISTS

3.5.1.1 Amino Alkyl Ethers

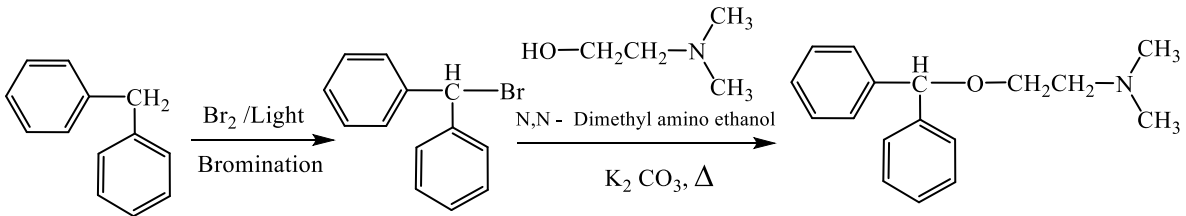
The best structure of amino-alkyl ethers 	Ar group may be phenyl or substituted phenyl or heterocyclic for good antihistaminic activity
	The R group may be methyl or hydrogen
	If double bond is introduced between α, β-carbon atoms of the propyl chain drowsiness is produced
	In compounds with asymmetric carbon atom, the dextroisomer is more active

A. Diphenhydramine hydrochloride (Allerdryl)



2 - (Diphenyl methoxy) - N, N' - dimethyl ethanamine hydrochloride

Synthesis



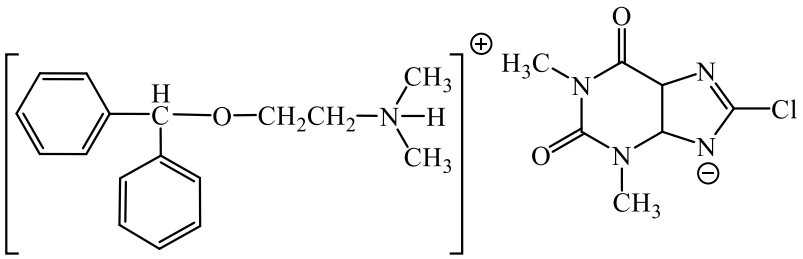
Diphenyl methane

Diphenhydramine

Mechanism of action: It acts as H_1 - receptor antagonist.

Use: In addition to antihistaminic activity, Diphenhydramine exhibits antiemetic, antitussive and sedative properties. It may be used as a nighttime sedative, for the control of drug induced Parkinsonism and in liquid form for control of cough.

B. Dimenhydrinate (Gravol)



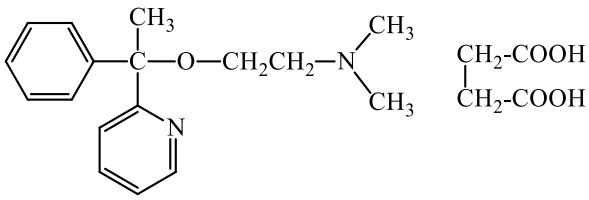
8 - Chloro - 3, 7 - dihydro - 1, 3 - dimethyl - 1H - purin - 2, 6 - dione compound with - 2 - (Diphenyl - N, N - dimethyl ethyl amine

Dimenhydrinate is 8-Chloro theophylline salt of Diphenhydramine. The salt of 8-chloro theophylline is used to overcome the common side effect (drowsiness and nervousness) of Diphenhydramine.

Mechanism of action: It is a H_1 - receptor antagonist.

Use: It is widely used to treat pregnancy and motion sickness induced nausea.

C. Doxylamine succinate (Aldex AN)

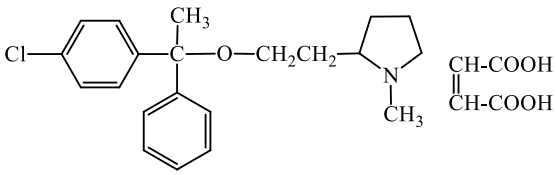


2 - [(1 - Phenyl) - 1 - (pyridin - 2 - yl) - ethoxy] - N, N - dimethyl ethanamine butanedioic acid

Mechanism of action: It is H_1 - receptor antagonist.

Use: It is an antihistaminic agent, but it has sedative property. It is also used with anti-tussive and decongestants for the relief of cough and cold.

D. Clemastine fumarate (Tavegyl)

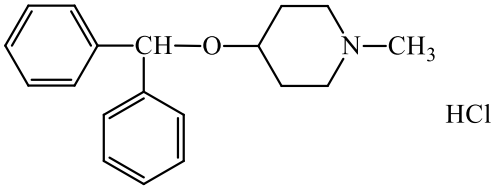


R - 2 - {2 - [1 - (p - Chloro phenyl) - 1 - phenyl ethoxy] ethyl} - 1 - methyl pyrrolidin but - 2 - enedioic acid

Mechanism of action: It is a H_1 – receptor antagonist.

Use: It has antihistaminic activity with anticholinergic and sedative effect. It is used for relief of allergic condition such as urticaria, rhinitis and conjunctivitis.

E. Diphenylpyraline hydrochloride (Corytab)



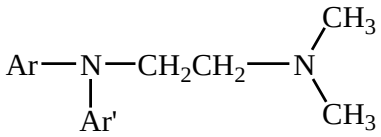
4 - (Diphenyl methoxy) -1- methyl piperidine hydrochloride

Structurally it is related to Diphenhydramine with the amino alkyl side chain incorporated in a piperidine ring.

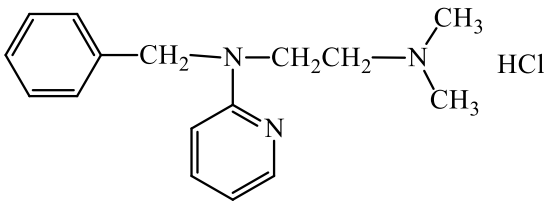
Mechanism of action: It is a H_1- receptor antagonist.

Use: It is a potent antihistaminic agent used in the treatment of allergic rhinitis, hay fever and allergic skin disorders.

3.5.1.2 Ethylenediamines

Basic structure of ethylenediamine derivatives of H_1antagonist 	Ar' group by 2 - pyridinyl system yield more significant antihistamine. Substitution by p-methoxy further enhances activity
	All the compounds of this series have two 3° nitrogen which are separated by a two-carbon chain
	Terminal amino group is required for H_1 blocking activity
	They are highly effective H_1 antagonist and are useful antihistamine. They also exhibit high frequency CNS depression and gastrointestinal effects.

A. Tripelennamine hydrochloride (Pyribenzamine)



2 - {Benzyl [2 - (dimethyl amino) ethyl] amino}
pyridine hydrochloride

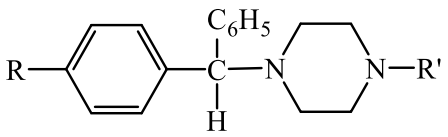
Mechanism of action: It is a H_1- receptor antagonist.

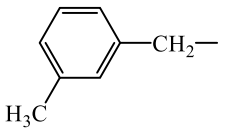
Use: It is used in the treatment of hay fever, urticaria and other mild allergic conditions.

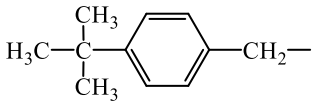
3.5.1.3 Piperazine Derivatives

Piperazine derivatives are moderately potent antihistaminic with a lower incident of drowsiness. These agents are used to treat motion sickness and vertigo. The general structure of piperazine derivatives with some examples are given in Table 1.2

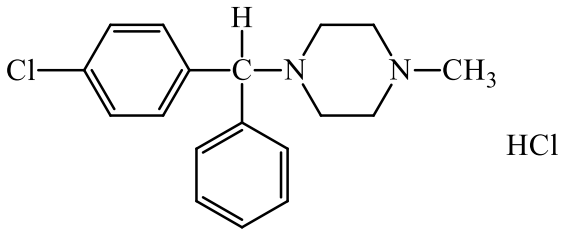
Table 1.2 Piperazine Derivatives



Name	R	R'
Chlorcyclizine	- Cl	- CH_3
Meclizine	- Cl	 3 - Methyl benzyl

Buclizine	- Cl	 4 - t - Butyl benzyl

A. Chlorcyclizine hydrochloride (Ahist)

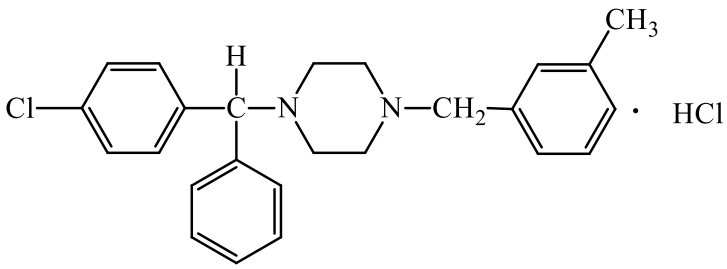


1 - [(4 - Chlorophenyl) phenyl methyl]- 4 - methyl piperazine hydrochloride

Mechanism of action: It acts as antihistamine by inhibiting the histamine at H_1 receptors. Chlorcyclizine also has some local anesthetic, anticholinergic and antiserotonergic properties and can be used as an antiemetic. It blocks the histamine receptors in the vomiting centre and affect the medullary chemoreceptor trigger zone.

Use: It is used in relief of urticaria, hay fever and certain other allergic conditions. It is also used as an antiemetic.

B. Meclizine hydrochloride (Antivert)

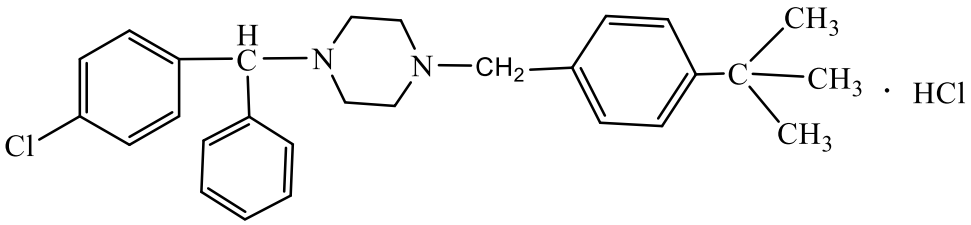


1- [(4 - Chloro phenyl) phenyl methyl] - 4 - (3 - methyl benzyl) piperazine hydrochloride

Mechanism of action: It acts as antihistamine by inhibiting the histamine at H_1 receptors. It blocks the histamine receptors in the vomiting center and affects the medullary chemoreceptor trigger zone.

Use: It is a moderate antihistamine. It is used to treat nausea and vomiting.

C. Buclizine hydrochloride (Longifene)



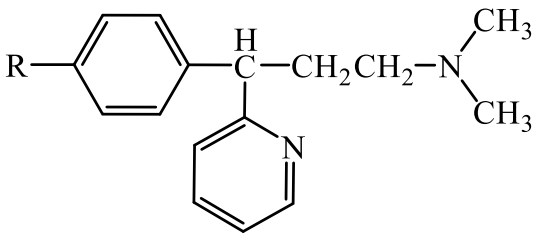
1- [(4 - t -Butyl phenyl) methyl] - 4 - [(4 - chloro phenyl) (phenyl) methyl] piperazine hydrochloride

Mechanism of action: It is an antihistamine with anti-muscarinic and moderate sedative properties. It is used mainly for its antiemetic activity. It is a potent H_1 receptor antihistaminic agent. It blocks the histamine receptors in the vomiting centre and thus affects the medullary chemoreceptor trigger zone. Furthermore, since Buclizine possesses anti-cholinergic properties as well, the muscarinic receptors are similarly blocked.

Use: It is used as an anti-vertigo and antiemetic agent.

3.5.1.4 Propylamine Derivatives

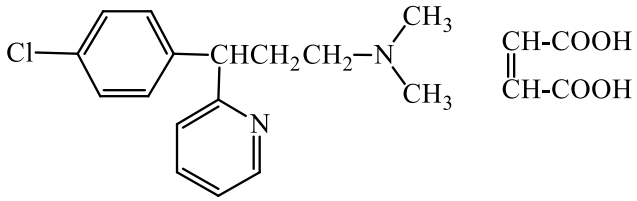
General structure of propylamine derivatives is



Propylamine derivatives contains an asymmetric carbon atom, the *dextro* rotatory isomer exhibit the greater potency. Introduction of chloro or bromo group in the benzene ring of Pheniramine increases its potency with no appreciable change in toxicity

Propylamine with connecting moiety include simple open chain alkene or cyclic alkene eg. Triprolidine, Phenindamine. In open chain double bond system appears to be an important factor for antihistaminic property. These compounds are asymmetric; E-isomer is more predominant than Z-isomer. The saturated member of this series are called Pheniramine. These agents produce less sedation than other classical antihistamines.

A. Chlorpheniramine maleate (Cadistin)

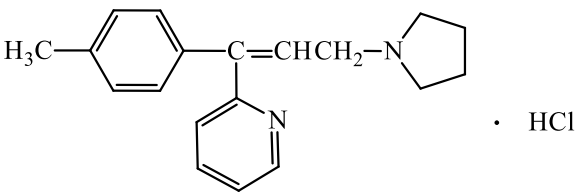


RS - 3 - (4 - Chloro phenyl) - 3 - (2 - pyridinyl) propyl dimethyl amine - but - 2 - enedioic acid

Mechanism of action: It competes with histamine for H_1 receptor sites on effectors cells in the gastrointestinal (GI) tract, blood vessels and respiratory tract. It provides effective temporary relief of sneezing, watery and itchy eyes and runny nose due to hay fever and other upper respiratory allergies.

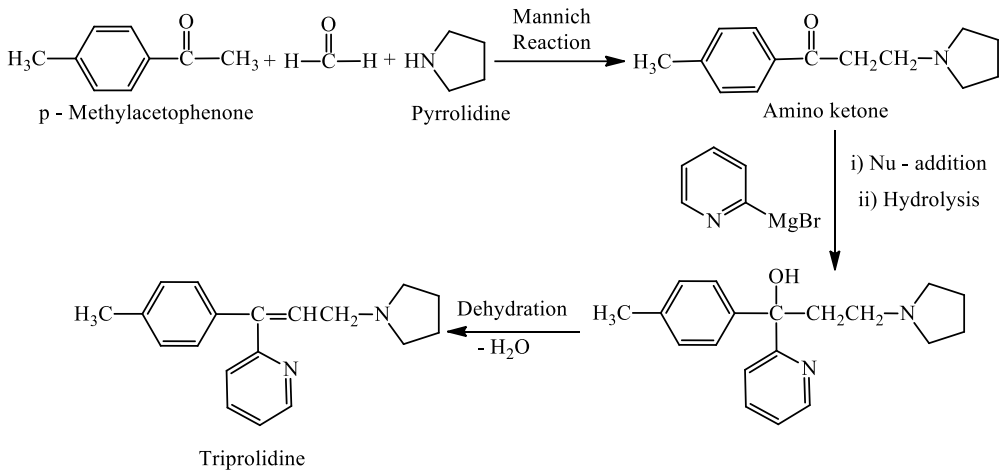
Use: It is used in symptomatic relief of hyper sensitive reaction like urticaria, rhinitis, conjunctivitis and angioedema.

B. Triprolidine hydrochloride (Histex)



E - 2 - [3 - (Pyrrolidin - 1- yl) - 1 - (4 - tolyl) propenyl] pyridine hydrochloride

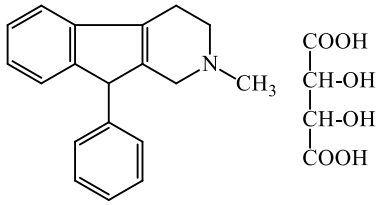
Synthesis



Mechanism of action: They compete with histamine for H_1-receptor sites on effector cells in the gastrointestinal (GI) tract, blood vessels, and respiratory tract.

Use: It is a potent antihistamine used for the relief of hypersensitivity including urticaria, rhinitis, conjunctivitis and skin disorders. It is used with Pseudo ephedrine for the treatment of cough and common cold.

C. Phenindamine tartrate (Nolahist)



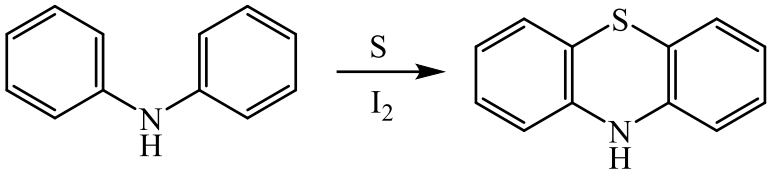
2 - Methyl - 9 - phenyl - 1, 3, 4, 9 - tetrahydro indeno [[2,1-c] - pyridine - 2, 3 - dihydroxy butanedioic acid

Mechanism of action: They compete with histamine for H_1- receptor sites and antagonize the effect of histamine.

Use: It is used in the treatment of common cold and allergies such as sneezing, itching and rashes.

3.5.1.5 Phenothiazine Derivatives

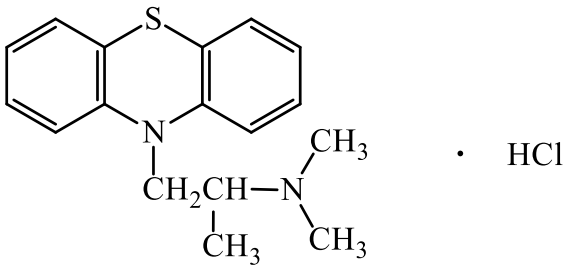
Phenothiazines possess tricyclic system. Phenothiazine derivatives possess two or three carbon chain bridge between basic phenothiazine nucleus and basic nitrogen. This differs from the phenothiazine antipsychotic series in which unbranched propyl chain is required. The phenothiazine ring is formed by treating the corresponding diphenylamine with a mixture of iodine and sulphur.



Diphenylamine Phenothiazine

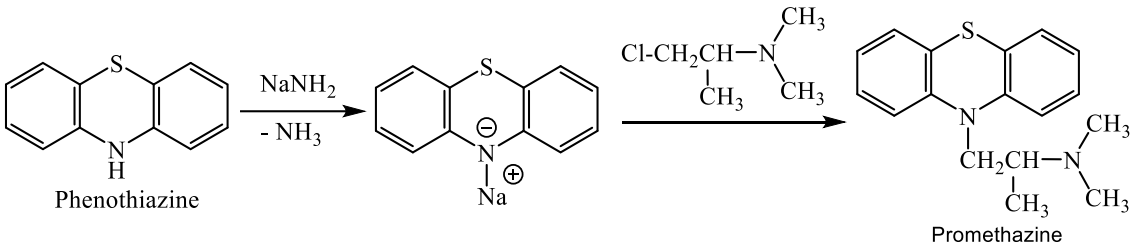
The proton on the nitrogen is weakly acidic, so a strong bases are required to form an anion in order to carry out the subsequent alkylation. Phenothiazine containing 2 or 3 carbon branched alkyl group between the ring and terminal nitrogen possess antihistaminic property. These derivatives with unbranched propyl chain exhibit antipsychotic activity.

A. Promethazine hydrochloride (Phenergan)



10 - [2 - (Dimethyl amino) propyl]
phenothiazine hydrochloride

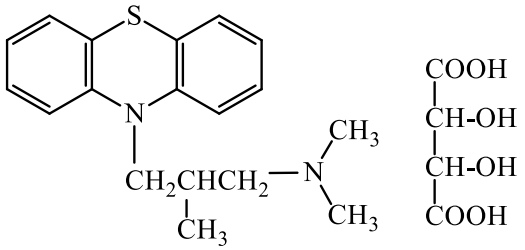
Synthesis



Mechanism of action: It competes with free histamine for binding at H_1 receptor sites in the GI tract, uterus, large blood vessel and bronchial muscle. The relief of nausea appears to be related to central anticholinergic actions and on the medullary chemoreceptor trigger zone.

Use: It is used as antihistaminic, antiemetic, tranquillizer, analgesic and sedative.

B. Trimeprazine tartrate (Alimemazine)



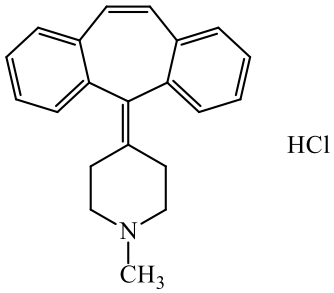
10 - [2 - (Dimethyl amino) propyl] phenothiazine - 2, 3 - dihydroxy butanedioic acid

Mechanism of action: It acts as antihistamine by inhibiting the histamine at H_1 receptors

Use: It is mainly used as antipruritic.

3.5.1.6 Dibenzo Cycloheptene Derivatives

A. Cyproheptadine hydrochloride (Apeplus)

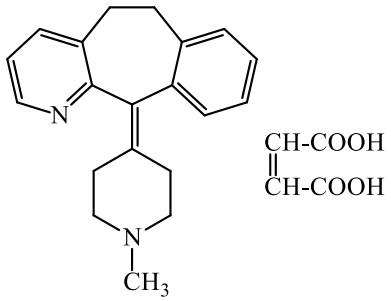


4 - (5H) - Dibenzo - [a, d] - cyclohepten - 5 - ylidene) - 1- methyl piperidine hydrochloride

Mechanism of action: It is a H_1-antagonists, act by competing with histamine for H_1-receptor sites on effector cells. It also has potent 5-HT (serotonin) antagonist activity through its 5-HT_{2A} receptor-blocking action. Antagonism of serotonin on the appetite center of the hypothalamus may account for its ability to stimulate appetite. In addition, it also has weak anticholinergic and central depressant properties.

Use: It possess both antihistaminic and anti-serotonin properties. It is also used as antipruritic agent, appetite stimulant, antiallergic and for the post gastrectomy dumping syndrome.

B. Azatadine maleate (Zadine)



1 1 - (1 - Methyl piperine - 4 - ylidene) - 6, 11 - dihydro - 5H - benzo - [5, 6] - cyclohepata [1, 2-b] - pyridine but - 2 - enedioic acid

It is an antihistamine, related to Cyproheptadine, with anti-serotonin, sedative and anticholinergic effects. It is an azo isomer of Cyproheptadine in which 10 and 11 double bond is reduced which gives a potent, low sedative compound.

Mechanism of action: It is a H_1 antagonists act by competing with histamine for H_1-receptor sites and reduces the intensity of allergic reactions and tissue injury response involving histamine release.

Use: It possess antihistaminic, anticholinergic, antiserotonin and sedative properties. It is used in the treatment of rhinitis, urticaria and other mild allergic conditions.

3.5.2 SECOND GENERATION ANTIHISTAMINES

Second-generation histamine H_1 receptor antagonists have been developed to reduce or eliminate the sedation and anticholinergic adverse effects that occur with older H_1 receptor antagonists.

Mechanism of action: Both first- and second-generation antihistamines are competitive antagonists to histamine at the H_1 receptor site. First generation antihistamines antagonize the acetylcholine at neuronal and neuromuscular muscarinic receptors. But second-generation antihistamine binds only to peripheral H_1 receptor and with no sedation. Because of poor CNS penetration and lower affinity for central histaminic, cholinergic and adrenergic receptors they have no central action like sedation. They are used for the treatment of allergic reactions.

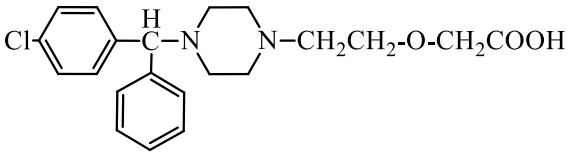
These classes of drugs are divided into two types:

(i) Piperazine derivative: eg. Cetirizine

(ii) Pyridine and piperidine derivatives: eg. Loratadine, Fexofenadine, Astemizole.

3.5.2.1 Piperazine Derivative

A. Cetirizine (Tancet, Oncet)



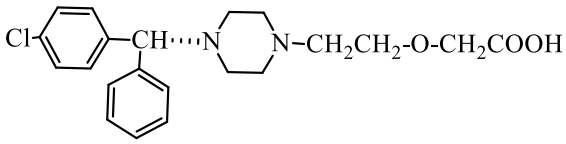
2 - {4 - [(4 - Chloro phenyl) phenyl methyl] - 1- piperazinyl ethoxy} acetic acid

This compound is a Zwitter ions and relatively polar and thus does not penetrate blood brain barrier. The advantage of this compound is once daily dosing, rapid onset of activity and minimal CNS effect. No cardio toxic effect when co-administered with imidazole antifungal and macrolide antibiotics. It is a racemic compound.

Mechanism of action: It is an orally active and selective second generation H1 receptor antagonist.

Use: It is used to relieve symptom such as itching, sneezing, runny nose and hives.

B. Levocetirizine (Levocet, Vozet)



2 - {4R- [(4 - Chloro phenyl) phenyl methyl] - 1- piperazinyl ethoxy} acetic acid

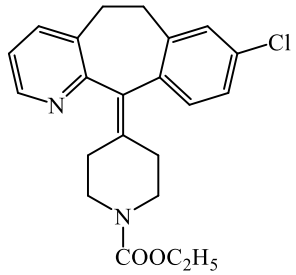
Levocetirizine is R-enantiomer of Cetirizine and display a better pharmacological profile than Cetirizine.

Mechanism of action: Cetirizine are competitive antagonists to histamine peripheral H_1 - receptor

Use: It is used as antihistamine to treat various allergic conditions.

3.5.2.2 Pyridine and Piperidine Derivatives

A. Loratadine (Alastin, Alaspan)



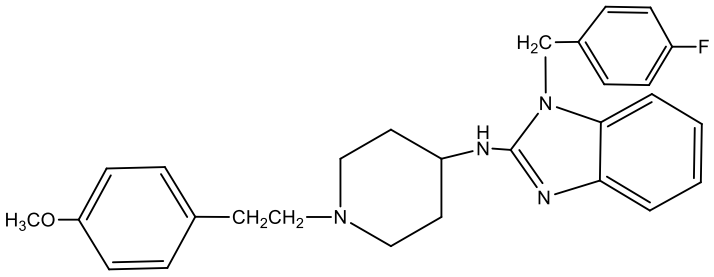
Ethyl 4 - (8 - Chloro - 5, 6 - dihydro -11H - benzo - [5,6] - cyclohepta - [1, 2-b] - pyridin -11 - ylidene) - 1 - piperidin carboxylate

Loratadine is an azo isomer of Cyproheptadine. It is structurally related to Azatadine. The replacement of methyl group of Azatadine (piperidine nitrogen) by corresponding carbamate and introduction of 8-chloro substitutes preserve the antihistaminic action and reduce the CNS effect (Sedative).

Mechanism of action: It binds to H_1 histamine receptors found on the surface of epithelial cells, endothelial cells, eosinophils, neutrophils, airway cells and vascular smooth muscle cells. It prevents severity of histamine mediated symptoms.

Use: It is a potent non-sedating antihistamine used in the treatment of seasonal allergic rhinitis, asthma, conjunctivitis and urticaria.

B. Astemizole (Acemiz, Acipax)



1- [(4 - Fluoro phenyl) methyl] - N - [1 - [2 - (4 -methoxy phenyl) ethyl] piperidin - 4 - yl] benzimidazol - 2 - amine

Mechanism of action: It acts as a reversible competitive inhibitor of histamine H_1-receptor, with less anticholinergic effects compared to related agents.

Use: It is a long-acting, non-sedative antihistamine used in the treatment of seasonal allergic rhinitis, asthma, allergic conjunctivitis and chronic idiopathic urticaria.

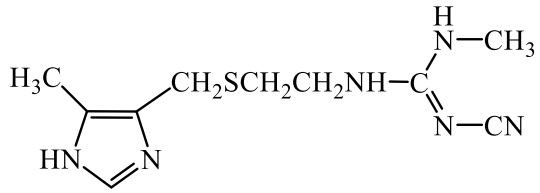
3.5.3 H_2 RECEPTOR ANTAGONIST

H_2 antagonists are a type of antihistamine, that block the action of histamine at the histamine H_2 receptors of the parietal cells in the stomach. This decreases the production of stomach acid. H_2 antagonists can be used in the treatment of dyspepsia, peptic ulcers and gastro esophageal reflux disease. They are also called as H_2 blockers. They include, Cimetidine imidazole derivative; Ranitidine substituted furans derivative, Famotidine is a member of the guanidine thiazole group and Roxatidine belongs to the aminoalkyl phenoxy series.

Mechanism of action

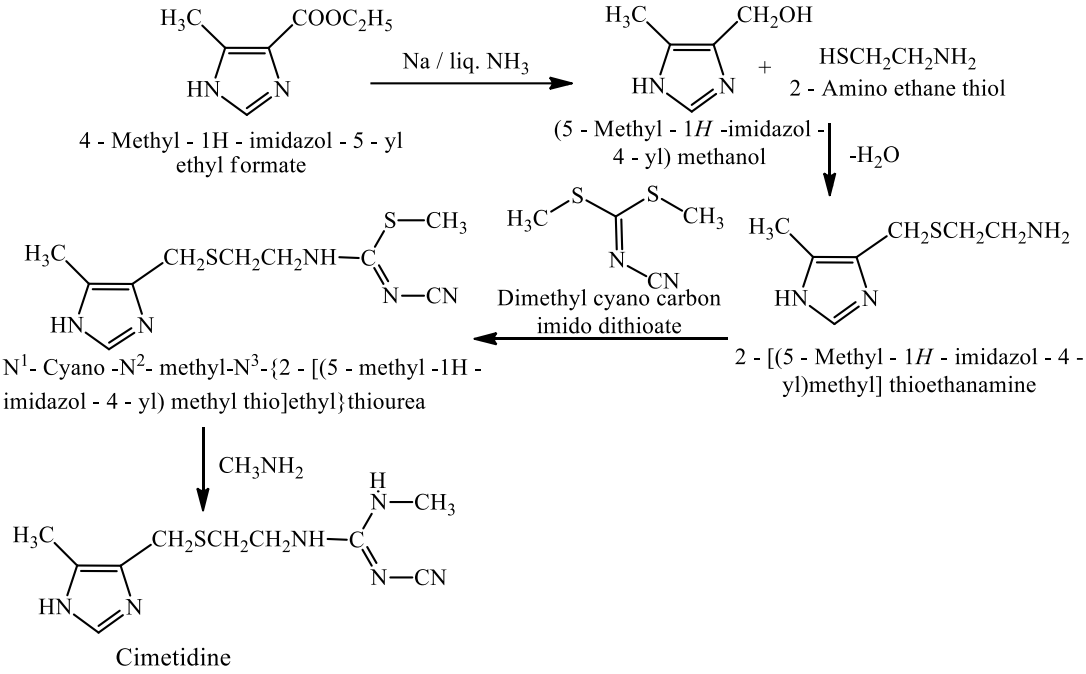
The principal stimulants for acid secretion are histamine, gastrin and acetylcholine released from postganglionic enteric neurons. Normally, after a meal, gastrin stimulates the release of histamine, which then binds to histamine H_2 receptors and leads to gastric acid release. H_2 blockers decrease gastric acid secretion by reversibly binding to histamine H_2 receptors located on gastric parietal cells, thereby inhibiting the binding and action of the histamine.H_2 blockers inhibit basal and nocturnal gastric secretion as well as secretion stimulated by food and pentagastrin. H_2 receptor antagonist are used in therapeutic application of acid peptic disorders ranging from heart burn to peptic ulcer disease, Zollinger-Ellison syndrome, gastro oesophageal reflux disease, acute stress ulcers and erosions.

A. Cimetidine (Tagamet)



N^1 - Cyano - N^2 - methyl - N^3- {2 - [[(5 - methyl - 1H - imidazol - 4 - yl) methyl]thio]ethyl}guanidine

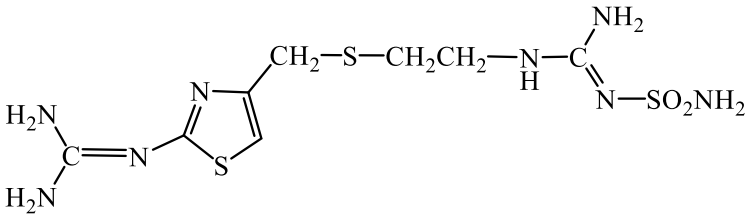
Synthesis



Mechanism of action: It decrease gastric acid secretion by reversibly binding to histamine H_2 receptors located on gastric parietal cells, thereby inhibiting the binding and action of the histamine. They inhibit basal and nocturnal gastric secretion as well as secretion stimulated by food and pentagastrin.

Use: It is used in gastric and duodenal ulcer.

B. Famotidine (Acilo, Fam)

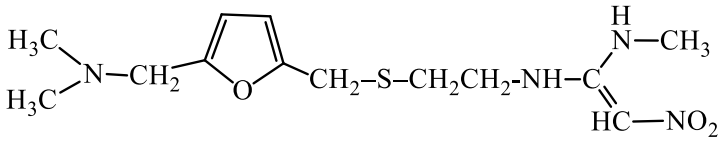


N' - (Amino sulfoxyl) - 3 - [[2 - (diamino methylene)amino]
- 4 - thiazolyl] methyl] thio] propionamide

Mechanism of action: It is a competitive inhibitor of histamine H_2 receptors and inhibits basal and nocturnal gastric secretion as well as secretion stimulated by food and pentagastrin.

Use: It is used in the treatment of duodenal and gastric ulcers, Zollinger- Ellison syndrome and heart burn.

C. Ranitidine (Rantac)



N - [2 -[[[5 - (Dimethyl amino) methyl] - 2 - furanyl] methyl] thio] ethyl]
- N' - methyl - 2 - nitro -1, 1 - ethenediamine

Mechanism of action: It decrease gastric acid secretion by reversibly binding to histamine H_2 receptors located on gastric parietal cells, thereby inhibiting the binding and action of the histamine. They inhibit basal and nocturnal gastric secretion as well as secretion stimulated by food and pentagastrin.

Use: It is used in treating duodenal ulcer.

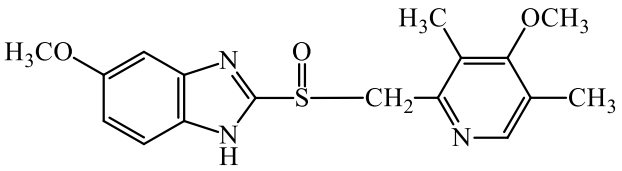
3.5.4 GASTRIC PROTON PUMP INHIBITORS

Gastric proton pump inhibitors (PPIs) are drugs that inhibit the hydrogen/potassium *adenosine triphosphatase* ($H^+K^+ATP_{ase}$) enzyme system of the gastric parietal cells. All PPIs give excellent healing of peptic ulcers and produce good results in reflux esophagitis. PPIs combined with antibiotics eradicate *Helicobacter pylori.*

Mechanism of action

The hydrogen/potassium *adenosine triphosphatase* ($H^+K^+ATP_{ase}$) enzyme normally catalyzes the exchange of H^+ for K^+ at the cell membrane. This is the final stage of acid secretory process, called the pump. Therefore, these drugs antagonize all stimulation (histamine, gastrin, Ach mediated) of the gastric secretion. Proton pump inhibitors are weak bases that act as prodrug and need an acidic environment in order to inhibit the $H^+K^+ATP_{ase}$. All these compounds share a common structure consisting of substituted pyridyl methyl sulfinyl benzimidazoles that varies in terms of the substitutions on either the pyridine or the benzimidazole rings. These drugs become protonated and converted into the active sulfonamide species, which forms disulfide bonds with cysteine residues in the α-subunit of the $H^+K^+ATP_{ase}$. This result in an inhibitory mechanism that is independent of histamine, acetylcholine or gastrin stimulus for acid secretion. Decreasing the acid in the stomach can aid the healing of duodenal ulcers and reduce the pain from indigestion and heartburn.

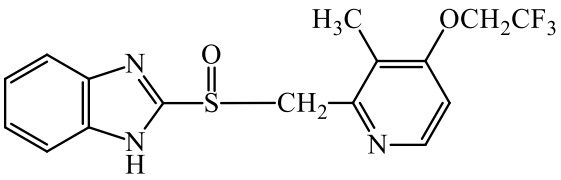
A. Omeprazole (Prilosec)



5 - Methoxy - 2 - (((4 - methoxy - 3, 5 - dimethyl - 2 - pyridinyl) methyl) sulfinyl) - 1H - benzimidazole

Use: It is used in the treatment of duodenal ulcer, gastric ulcer and pathological hypersecretory conditions.

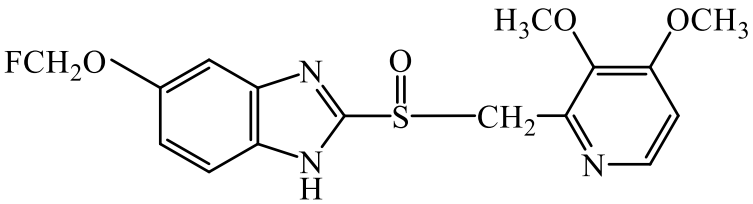
B. Lansoprazole (Prevacid)



2 - [[(3 - Methyl - 4 - (2, 2, 2 - trifluoro ethoxy) - 2 - pyridyl) methyl) sulfinyl] benzimidazole

Use: It is used in the treatment and prevention of NSAID-induced gastric ulcers as well as Zollinger-Ellison syndrome.

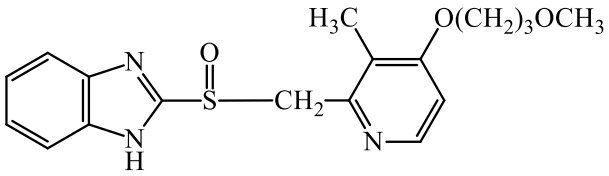
C. Pantoprazole (Protonix)



5 - (Difluoro methoxy) - 2 - [[3, 4 - dimethoxy - 2 - pyridinyl) methyl) sulfinyl] - 1H - benzimidazole

Use: It is used in the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome.

D. Rabeprazole (Aciphex)



2 - [[[4 - (3 - Methoxy propoxy) - 3 - methyl - 2 - pyridinyl] methyl] sulfinyl] - 1H - benzimidazole

Use: It is used in gastric hypersecretory disorder.