Antihistaminic Agents

Lecture notes of

Mangesh Mapari

Antihistaminic Agents

Introduction

Histamine

- Histamine, known trivially as 4(5-)(2-aminoethyl)imidazole, structurally is composed of an imidazole heterocycle and ethylamine side chain.
- The methylene groups of the amino ethyl side chain are designated alfa & Beta
- The methylene groups of the aminoethyl side chain are designated and The side chain is attached, via the -CH2 group, to the 4-position of an imidazole ring.
- The imidazole N at position 3 is designated the (pi) N, whereas the N at position 1 is termed the tele and the side chain N is distinguished as N alfa

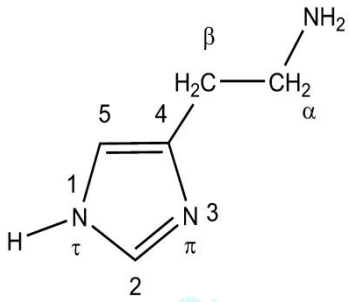


Fig: Structure Of Histamine

Chemistry of Histamine

- In unionized form, histamine has one neutral and two basic nitrogen atoms.
- The predominant form at pH 7.4 is the monocation, where the side- chain primaryamine is protonated and both imidazole nitrogen atoms are unionized.
- Histamine is achiral but can exist in multiple conformational states in solution.The trans conformation is believed to be preferred at H1 & H2 receptors.
- Histamine's imidazole ring is capable of tautomerization.

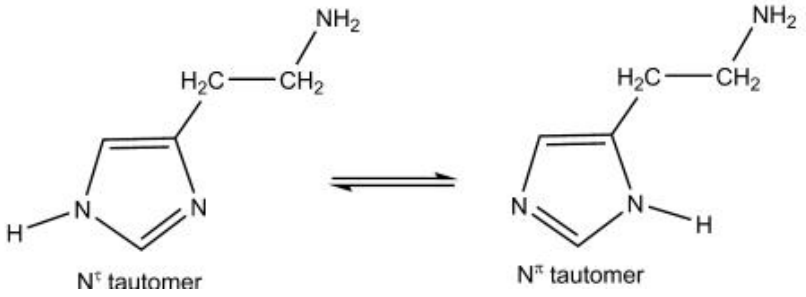
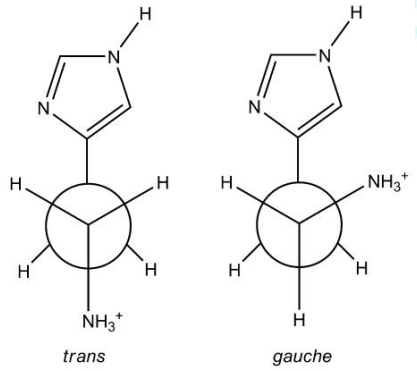


Fig : Histamine Tautomerization

- Tautomerization is essential for histamine activity at H1 receptors, with the N^{τ}-H tautomer important for initial receptor binding and the N^{π}-H tautomer important for receptor activation.
- Structure–activity relationship studies suggest that the NH3 monocation is important for agonist activity at histamine receptors and that transient existence of the more lipophilic uncharged histamine species may contribute to diffusion across cell membranes.
- Other studies support proposal that the N^{T} -H tautomer of the histamine monocation is the pharmacophoric species at the H1-receptor, while a 1,3-tautomeric system is important for selective H2-agonism.

Stereochemistry

- While histamine is an achiral molecule, histamine receptors exert high stereoselectivity toward chiral ligands.
- Molecular modeling and steric–activity relationship studies stated that trans-rotamer of histamine possesses affinity for both H1- and H2-receptors, and the gauche conformer is preferred for H3-receptors, but not H1- or H2-receptors.



Rotamer is
any of a set of conformers that arise from restricted rotation around a single

Fig : Histamine Rotomer

Biosynthesis and Distribution

- Histamine is synthesized in Golgi apparatus of its principal storage cells, mast cells, and basophils.
- Histamine is formed from the naturally occurring amino acid L-hisitidne (S-histidine) via the catalysis of either the pyridoxal phosphate dependent enzyme histidine decarboxylase (HDC) or L-aromatic amino acid decarboxylase (L-AAAD)
- Mast cells and histamine are in particularly high concentration in skin and the mucosal cells of the bronchi, intestine, urinary tract, and tissues adjacent to the circulation.
- It is found in higher concentrations in mammalian cerebrospinal fluid than in plasma and other body fluids.

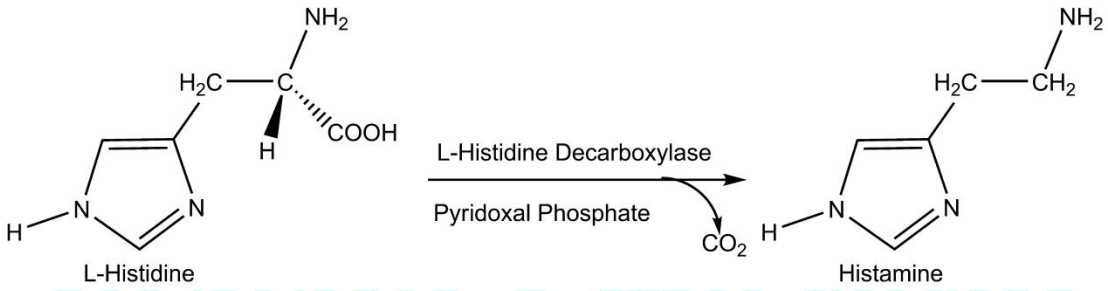


Fig: Synthesis of Histamine

Storage, Release, Metabolism

- Most histamine is biosynthesized and stored as protein complexes in mast cells (complexed with heparin) and basophilic granulocytes (complexed with chondroitin).
- Proteincomplexed histamine is stored in secretory granules and released by exocytosis in response to a wide variety of immune (antigen and antibody) and nonimmune (bacterial products, xenobiotics, physical effects, and cholinergic effects) stimuli.
- The release of histamine as one of the mediators of hypersensitivity reactions is initiated by the interaction of an antigen-IgE complex with the membrane of a histamine storage cell.

- This interaction triggers activation of intracellular phosphokinase C (PKC), leading to accumulation of inositol phosphates, diacylglycerol, and calcium.
- Exocytotic release of histamine follows the degranulation of histamine storage cells.
- Degranulation also results in the release of other mediators of inflammation including prostaglandins, leukotrienes, platelet-activating factor, kinins, etc.The release of mast cell mediators can be inhibited by several agents as described in the sections that follow.

- Histamine is released from mast cells in the gastric mucosa by gastrin and acetylcholine.
- Neurochemical studies also suggest that histamine is stored in and released from selected neuronal tracts in the CNS.
- Released histamine is rapidly inactivated by metabolism via two pathways as shown in Figure One pathway involves N-methylation via the enzyme histamine N-methyltransferase (HMT).

- This enzyme is widely distributed in mammalian tissues and catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to the ring tele-nitrogen of histamine, producing N - methylhistamine and S-adenosyl-L-homocysteine.

- The other pathway of catabolism involves oxidative deamination by diamine oxidase, yielding imidazole acetaldehyde, which is further oxidized to imidazole acetic acid by aldehyde dehydrogenases (ALD-DH).

- Similarly, N-methylhistamine is converted by both DAO and monoamine oxidase (MAO), followed by ALD-DH to Nmethyl imidazole acetic acid . All of these metabolites are devoid of histamine receptor agonist activity.

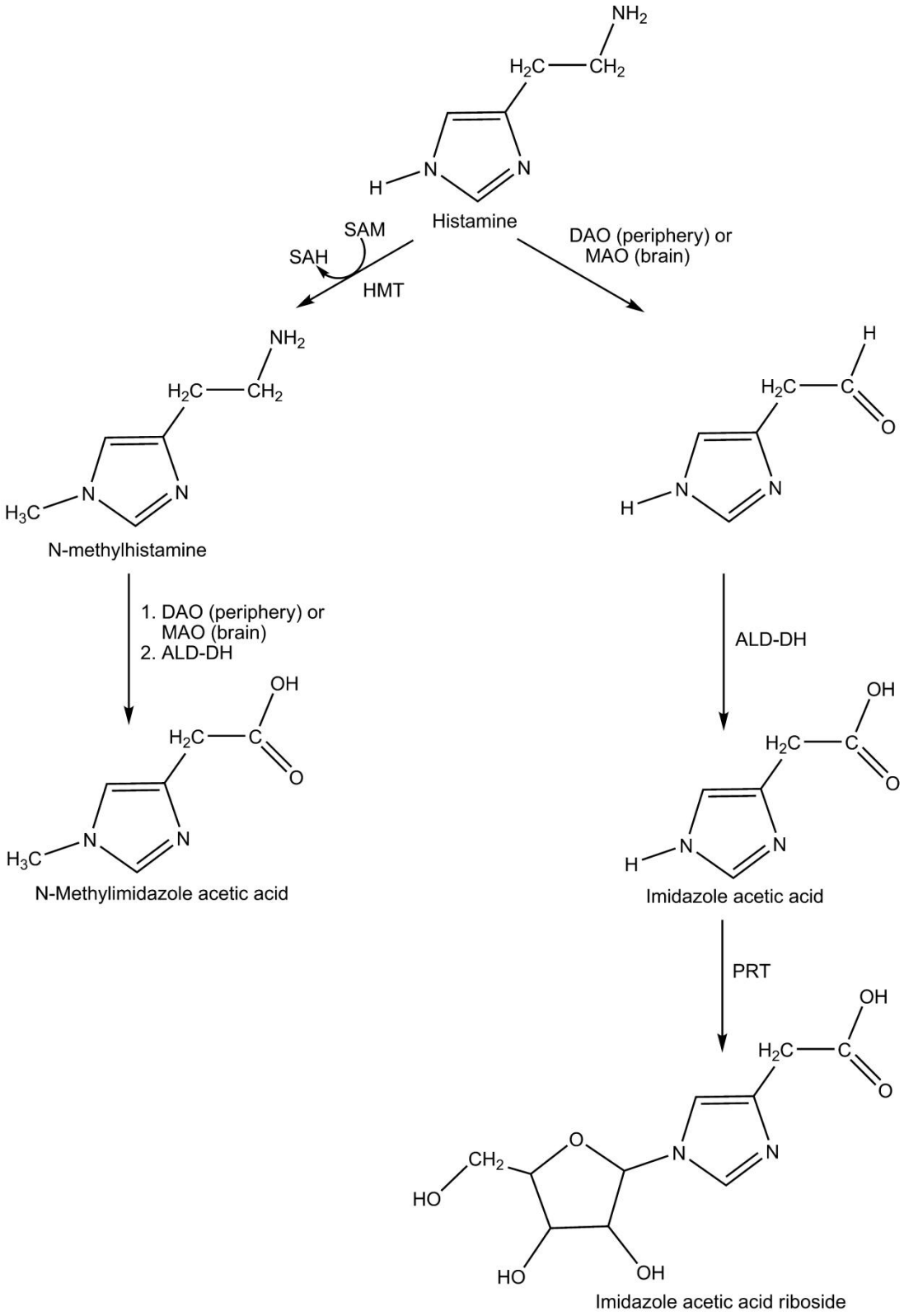


Fig: Histamine Metabolism

Histamine receptors

- There are four histamine receptor present H1, H2, H3, and H4.
- All four receptor subtypes have been cloned and belong to the G protein–coupled receptor superfamily.
- The histamine receptors can be distinguished on the basis of their post–receptor signal transduction mechanisms, tissue distribution, and sensitivities to various agonists and antagonists .
- Currently, only the H1- and H2-receptors are targets of clinical drug therapy.

Recptor	Tissue/Organ	Effect
H1	Brain, smooth muscle, heart, endothelium	Contaction Dilation -- Capillary Permiability Pain & Itching
H2	Brain, stomach, smooth muscle, heart, mast cells	Acid secreation Contaction Dilation -- Capillary Permiability Increased HR
H3	Brain, autonomic nerve endings, some endothelia	Decrease Histamine ACh NE Release Narrowing of the bronchial tubes Dilation -- Capillary Permiability
H4	Bone marrow, brain, peripheral leukocytes, lung	Immunomodulators Dilation -- Capillary Permiability

Antihistamine

- The term antihistamine historically has referred to drugs that block the actions of histamine at H1-receptors rather than other histamine receptor subtypes.

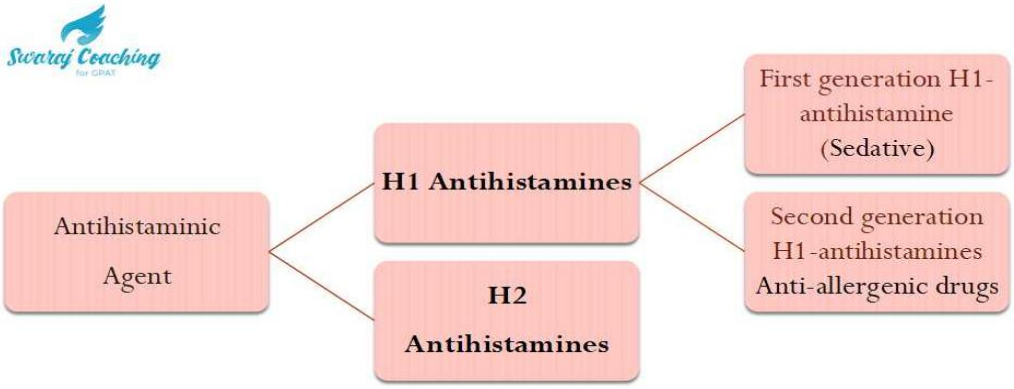


Fig: Classification of Antihistaminic agent

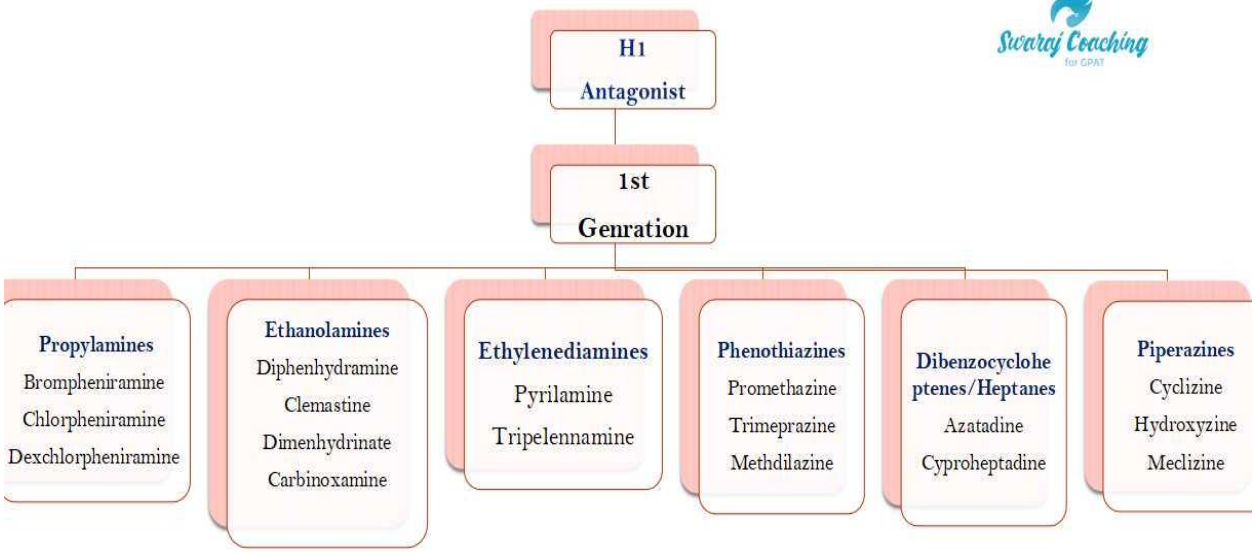


Fig: H1 Receptor antagonist classification

H1 Receptor antagonist

- H1 receptor is Gprotein coupled.
- The H1 receptor is found in smooth muscle of gut, bronchi, uterus, and vasculature.
- Stimulation results in relaxation and increased permeability of the vasculature and spontaneous contractions in the smooth muscle of the uterus, gut, and bronchi.

Structure–Activity Relationships at H1-Receptors

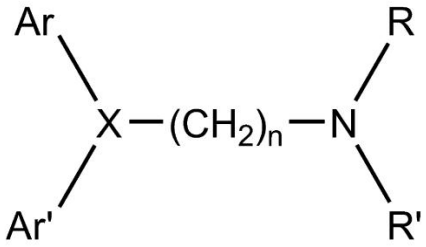


Fig: General Structure of H1 antihistaminic agent

The structural requirements for H1-antihistaminic action were identified as:

- Ar is aryl (including phenyl, substituted phenyl, and heteroaryl groups such as 2-pyridyl)
- Ar' is a second aryl or arylmethyl group;
- X is a connecting atom of O, C, or N
- (CH2)n represents a carbon chain, usually ethyl;
- NRR' represents a basic, terminal amine function.

- The nature of the connecting atom as well as the diaryl substitution pattern and amine moiety has been used to sub classify the first-generation antihistamines .

I. Diaryl substitution

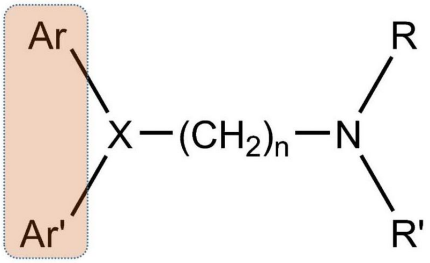


Fig: Diaryl groups

- This diaryl substitution pattern is present in both the first- and second-generation antihistamines and is essentially a significant H1-receptor affinity.
- The two aryl moieties must be able to adopt a noncoplanar conformation relative to each other for optimal interaction with the H1-receptor.
- The two aromatic systems may be linked, as in the tricyclic antihistamines (phenothiazines, dihenzocycloheptanes, and heptenes), but again they must be noncoplanar for effective receptor interaction.
- Most H1-antihistamines contain substituents in one of the aryl rings (usually benzene), and these influence histamine potency as well as biodisposition.

II. Terminal nitrogen atom

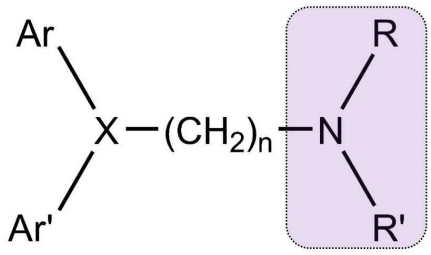


Fig: Terminal Nitrogen Groups

- In many of the first-generation, or classical, antihistamines, the terminal nitrogen atom is a simple dimethylmoiety
- The amino moiety is basic, with pKas ranging from 8.5 to 10, and thus is presumed to be protonated when bound on the receptor.

- The amine moiety is also important in the development of stable, solid dosage forms through salt formation

III. The carbon chain

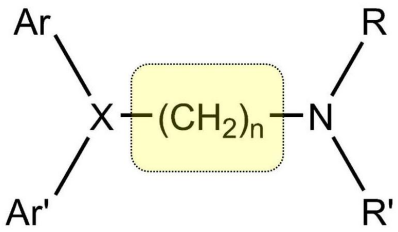


Fig: Carbon Chain

- The carbon chain of typical H1-antihistamines consists of two or three atoms.
- The distance between the central point of the diaryl ring system and the terminal nitrogen atom in the extended conformation of these compounds ranges from 5 to 6 angstroms (Å).
- Branching of the carbon chain results in reduced antihistaminic activity. (exceptions : promethazine)

IV. The X connecting moiety

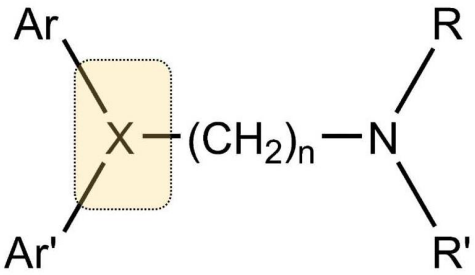


Fig : X connecting moiety

- The X connecting moiety of typical H1-antihistamines may be a saturated carbon–oxygen (C-O) moiety or simply a carbon atom (C-C).
- Many antihistamines containing a carbon atom in the connecting moiety are chiral and exhibit stereo selective receptor binding.
- Generally, the first- and second-generation antihistamines are substantially more lipophilic than the endogenous agonist, histamine (or the H2-antagonists).

First-Generation Antihistamine Classes

AMINOALKYL ETHERS (ETHANOLAMINES)

- The aminoalkyl ether antihistamines are characterized by the presence of a CHO connecting moiety (X) and a two- or three-carbon atom chain as the linking moiety between the key diaryl and tertiary amino groups.

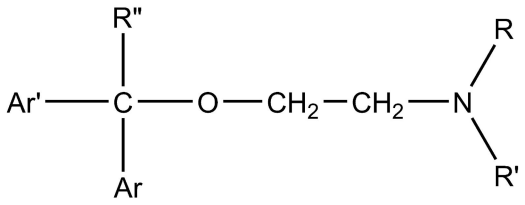
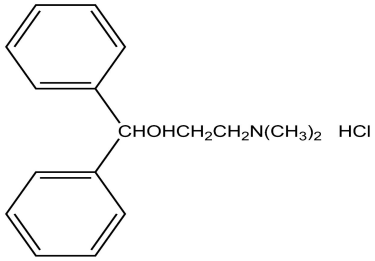


Fig: General structure of the aminoalkyl ethers.

- Most compounds in this series are simple N, N-dimethylethanolamine derivatives .
- The basic nitrogen in all of these compounds is not only essential for binding affinity, but also serves as a moiety for the formation of stable, solid salts.
- Asymmetrically substituted benzylic carbon, most of the aminoalkyl ethers are optically active.
- Most studies indicate indicate that the individual enantiomers differ significantly in antihistaminic activity, with activity residing predominantly in the S-enantiomers.
- Most members of this series appear to be extensively metabolized by pathways including N-oxidation
- and successive oxidative N-dealkylation followed by aldehyde oxidation and amino acid conjugation.

Diphenhydramine Hydrochloride

- IUPAC ; 2-(diphenylmethoxy)-N,N-dimethylethanamine hydrochloride



Diphenhydramine Hydrochloride

- **Diphenhydramine** Is an oily, lipid-soluble free base available as the bitter-tasting hydrochloride salt, which is a stable, white crystalline powder soluble in water (1:1), alcohol (1:2) and chloroform (1:2).
- It is a well known antihistamine. It is an amino alkyl ether derivative. As its main side effect is drowsiness, it is combined with 8-chlorotheophylline (Theoclate) as Dramamine'

Synthesis

- Firstly, diphenylmethane undergoes bromination in the presence of light to form diphenylbromomethane.
- Then, diphenylbromomethane, -dimethyl-aminoethanol, and sodium carbonate are heated in the presence of toluene to obtain diphenhydramine base.
- The purified diphenhydramine after distilling-off toluene converts into its hydrochloride form with hydrogen chloride.

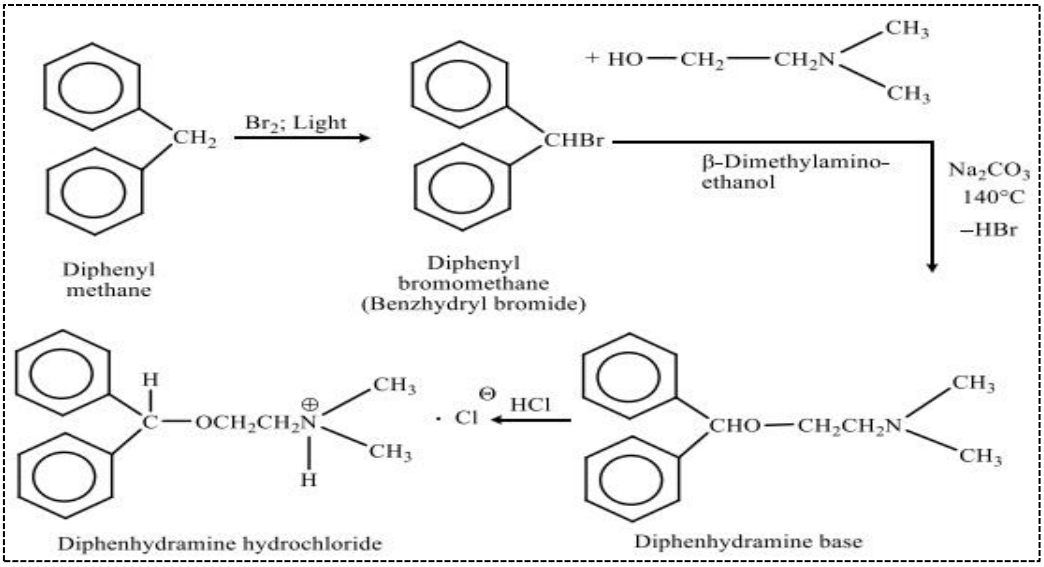


Fig : Synthesis of Diphenhydramine

Mechanism of Action

- Diphenhydramine works through the antagonism of H 1-receptors found on the respiratory smooth muscles, vascular endothelial cells, GIT, cardiac tissue, immune cells, uterus, and CNS neurons.
- On stimulating the H1-receptors in these tissues, they increase vascular permeability, stimulate vasodilation that leads to flushing, decrease the conduction time of atrioventricular (AV) node , stimulate the sensory nerves of a irways that leads to coughing, contract the smooth muscles of bronchi and GIT, and cause eosinophilic chemotaxis that enhances the allergic immune response.
- Diphenhydramine functions as an inverse agonist at H1-receptors, and then it converses the histamine effects on capillaries, and decreases the symptoms of allergic reaction

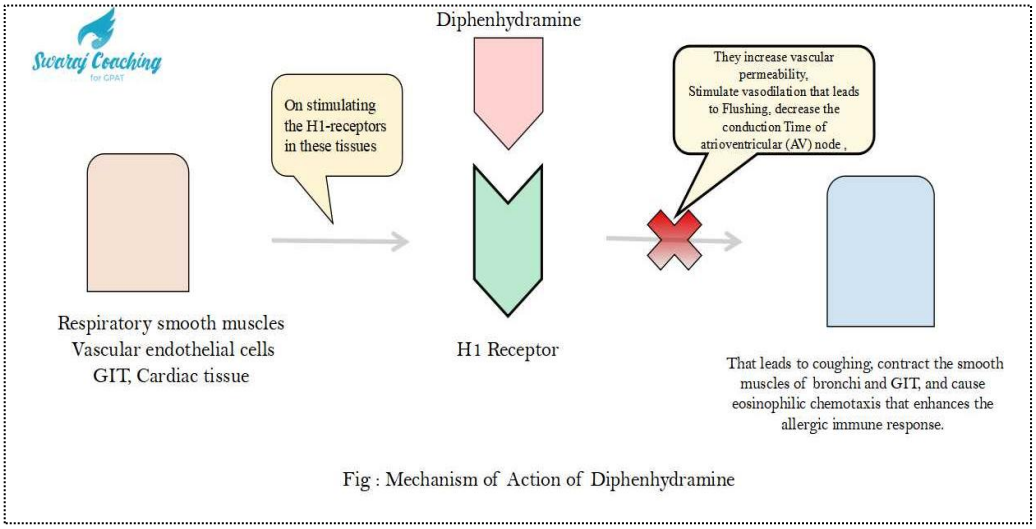


Fig : Mechanism of Action of Diphenhydramine

Uses

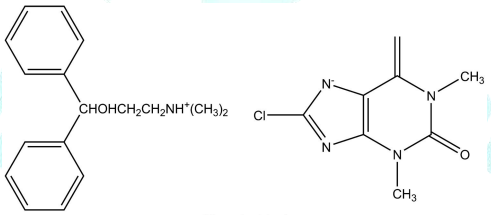
- It is used for preventing and curing nausea, vomiting and dizziness caused by motion sickness.
- It is used to relax and fall asleep.
- It is used for relieving the symptoms of a llergy, hay fever, common cold, rashes, itching, watery eyes, itchy eyes/nose/throat, cough, runny nose, and sneezing.

Preparations:

- ✓ Diphenhydramine HCI I.P.
- ✓ Diphenhydramine HCI Capsules I.P.
- ✓ Diphenhydramine HCI Tablets, Cough Sy*P, Expectorant (unofficial).
- ✓ Diphenhydramine Theoclate-Dramamine-(unofficial)'

Dimenhydrinate

- IUPAC: 8-chlorotheophylline 2-(diphenylmethoxy)-N,N-dimethylethylamine



Dimenhydrinate

- Dimenhydrinate is a combination drug as it comprises of diphenhydramine (53-55.5%) and 8-chlorotheophylline (not less than 44-47%) in a salt form.
- Dimenhydrinate is a white crystalline, odorless powder that is highly soluble in water and freely soluble in alcohol and chloroform.

Mechanism of Action

- Mechanism of some antihistamines producing antiemetic, anti-motion sickness and anti-vertigo effects is not known ; however, it can be related to their central anticholinergic actions. They reduce the vestibular stimulation and lower the labyrinthine function.

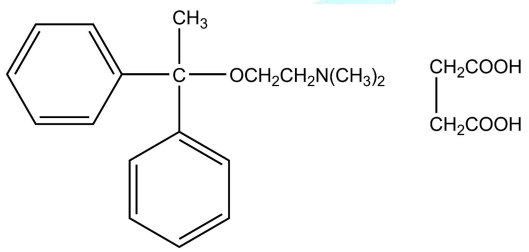
- The antiemetic effect may also be the result of a n action on the medullary chemoreceptive trigger zone.
- Dimenhydrinate is a competitive an tagonist of H1- receptors found in the human brain. It produces anti-emetic effect because of H1- antagonism in the vestibular system in the brain.

Uses

- It is used for preventing motion sickness, nausea, and vomiting.
- It helps in the treatment of ear congestion.
- It is used for relieving vertigo and vestibular disorder.

Doxylamine Succinate

- IUPAC: 2-[-[2-(dimethylamino)ethoxy]-methylbenzyl]pyridine bisuccinate



Doxylamine Succinate

- Doxylmine is a white to creamy-white powder with a characteristic odor. It is soluble in water (1:1), alcohol (1:2), and chloroform (1:2). A 1% solution has a pH of about 5.
- Doxylamine succinate is comparable in potency to diphenhydramine.

Mechanism of Action

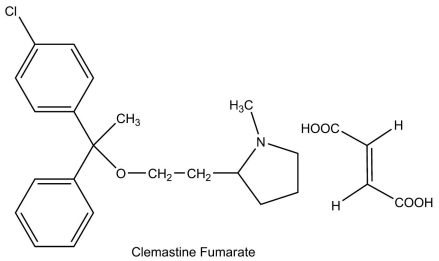
- Doxylamine competitively blocks the H1-receptor and controls t he allergic and anaphylactic responses, such as bronchoconstriction, vasodilation, increased capillary permeability, and spasmodic contraction of gastrointestinal smooth muscles caused by histamine actions on bronchial and gastrointestinal smooth muscles.

Uses

- It relieves the symptoms of allergy, hay fever, and common cold.
- It relieves sneezing, runny nose, watery eyes, hives, and skin rash.
- It is used for treating insomnia.
- It is used for preventing morning sickness in pregnant women in combination
- with vitamin B6 (pyridoxine).

Clemastine Fumarate

- IUPAC: R,R-2[2[1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1- methylpyrrolidine hydrogen furnarate



Clemastine Fumarate

- Clemastine has two chiral centers, each of which has the (R) absolute configuration. A comparison of the activities of the enantiomers indicates that the asymmetric center close to the terminal side chain nitrogen is of lesser importance to antihistaminic activity.

Mechanism of Action

- Clemastine is a se lective H1-antagonist. It binds to the H1-receptors and blocks the action of histamine, thus gives symptomatic relief of allergic conditions l ike rhinitis, urticaria, conjunctivitis, and pruritic (severe itching) skin conditions.

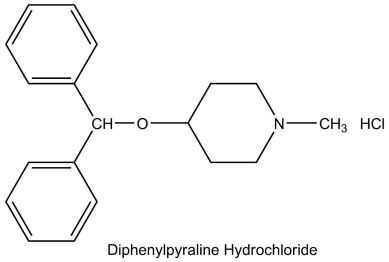
Uses

- It is used for relieving the symptoms of allergic rhinitis like sneezing, rhinorrhea, pruritus, and acrimation.
- It is used for the management of mild, uncomplicated allergic skin conditions of urticaria and angioedema.
- It is u sed as a self-medication for temporary relief of symptoms related to common cold.

➢

Diphenylpyraline Hydrochloride

➢ IUPAC: 4-(diphenylmethoxy)-1-methylpiperidine hydrochloride.



Diphenylpyraline Hydrochloride

➢ Diphenylpyraline is a white or slightly offwhite crystalline powder that is soluble in water or alcohol.

➢ Diphenylpyraline is structurally related to diphenhydramine with the aminoalkyl side chain incorporated in a piperidine ring

➢ It is a potent antihistaminic, and the usual dose is 2 mg 3 or 4 times daily.

Mechanism of Action

➢ Diphenylpyraline is used for treating allergy as it competes with histamine for binding on the H1-receptors on effector cells.

➢ After binding it suppresses the histamine effects, thus causing temporary relief of the allergic symptoms.

Uses

➢ It is used for treating allergic rhinitis.

➢ It is used for treating hay fever.

➢ It is used for treating allergic skin orders.

ETHYLENEDIAMINES

➢ The ethylenediamine antihistamines are characterized by the presence of a nitrogen-connecting atom (X) and a two-carbon atom chain as the linking moiety between the key diaryl and tertiary amino moieties

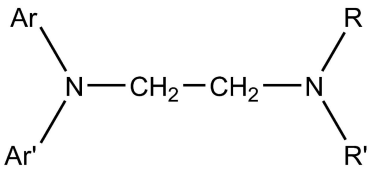
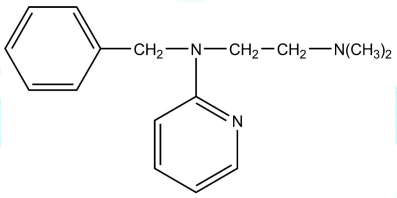


Fig: General structure of the ethylenediamines

- All compounds in this series are simple diarylethylenediamines except antazoline, in which the terminal amine and a portion of the carbon chain are included as part of an imidazoline ring system.
- Phenbenzamine was the first clinically useful member of this class and served as the prototype for the development of more effective derivatives.
- Ethylenediamine derivatives are metabolized in humans by N-glucuronidation, N-oxidation, and pyridyl oxidation followed by phenol glucuronidation.

Tripelennamine Citrate

- **IUPAC ;** 2-[benzyl[2-dimethylamino)-ethyl]amino]pyridine citrate



Triplennamine HCl or Citrate

- Tripelennamine monocitrate salt, which is a white crystalline powder freely soluble in water and in alcohol.
- For oral administration in liquid dose forms, the citrate salt is less bitter and thus more palatable than the hydrochloride.

Mechanism of Action

- Tripelennamine binds to the H1-receptor and blocks the action of endogenous histamine, thus temporarily relieving the negative symptoms caused by histamine.

Uses

- It treats the conditions of upper respiratory tract caused due to illnesses and hay fever.
- It relieves sneezing, runny nose, itching, watery eyes, hives, rashes, and other symptoms of allergies and common cold.

PIPERAZINES (CYCLIZINES)

- The piperazines or cyclizines can also be considered ethylenediamine derivatives or cyclic ethylenediamines (cyclizines).
- In this series, however, the connecting moiety (X) is a CHN group, and the carbon chain, terminal amine functionality, and the nitrogen atom of the connecting group are all part of a piperazine moiety.

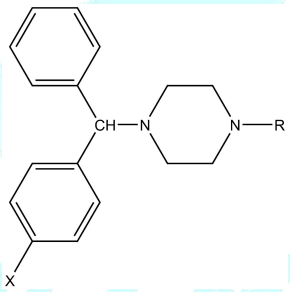


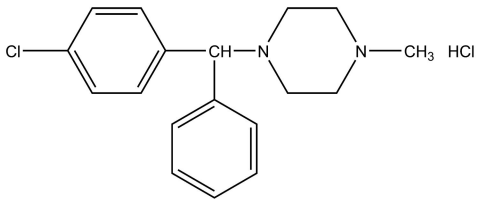
Fig: General structure of the piperazines.

- Both nitrogen atoms in these compounds are aliphatic and thus display comparable basicities.
- The primary structural differences within this series involve the nature of the para aromatic ring substituent (H or Cl) and, more importantly, the nature of the terminal piperazine nitrogen substituent
- The piperazines are moderately potent antihistaminics with a relatively high potential to cause drowsiness and psychomotor and cognitive dysfunction
- Some agents of these category diminish vestibular stimulation and act on the medullary chemoreceptor trigger zone.
- Thus, as a group, these agents have found significant use as antiemetics and antivertigo agents and in the treatment of motion sickness

- The primary pathways involve N-oxidation and N-demethylation, and both of these metabolites are devoid of antihistaminic activity.

Chlorcyclizine Hydrochloride

- IUPAC: 1-(p-chloro--phenylbenzyl)-4-methylpiperazine monohydrochioride



Chlorcyclizine Hydrochloride

- Chlorcyclizine is a light-sensitive, white crystalline powder that is soluble in water (1:2), in alcohol (1:11), and in chloroform (1:4).
- Disubstitution or substitution of halogen in the 2- or 3-position of the benzhydryl rings results in a much less potent compound.

Mechanism of Action

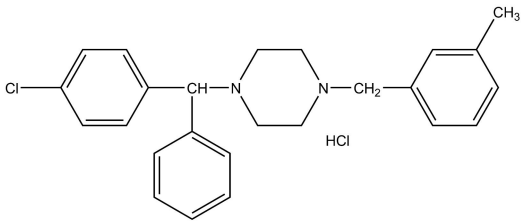
- Chlorcyclizine binds to the H1-receptor and blocks the action of endogenous histamine, thus temporarily relieving the negative symptoms caused by histamine.

Uses

- It is used for the treatment of allergic symptoms like rhinitis, urticaria, and pruritus.
- It is also used for treating hepatitis C.

Meclizine Hydrochloride

- IUPAC: 1-(p-chloro- -phenylbenzyl)-4-(m-methylbenzyl)piperazine dihydrochloride monohydrate.



Meclizine Hydrochloride

- Meclizine is a tasteless, white or slightly yellowish crystalline powder that is practically insoluble in water (1:1,000).
- It differs from chlorcyclizine in having an N-m-methylbenzyl group in place of the N-methyl group.

Mechanism of Action

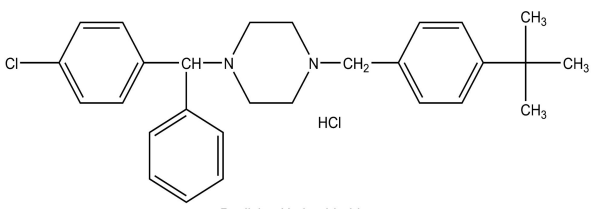
- Meclizine competitively blocks the H1-receptor and controls t he allergic and anaphylactic responses, such as bronchoconstriction, vasodilation, increased capillary permeability, and spasmodic contraction of gastrointestinal smooth muscles caused by histamine actions on bronchial and gastrointestinal smooth muscles.

Uses

- It is used for treating motion sickness.
- It is safely used in the treatment of nausea in pregnancy.
- It helps in relieving vertigo.

Buclizine Hydrochloride

- **IUPAC:** l- (p-tertbutylbenzyl)-4-(p-chloro- -phenylbenzyl)piperazine dihydrochloride
- Buclizine is a white to slightly yellow crystalline powder that is insoluble in water.



Buclizine Hydrochloride

Mechanism of Action

- Emesis (vomiting) is a protective mechanism as it removes irritant or harmful substances from the upper GIT. Emesis is regulated by the vomiting centre in the medulla region of brain.

- The vomiting centre has neurons which possess many muscarinic cholinergic and histamine-containing synapses. These neurons are involved in transmission from the vestibular apparatus to the vomiting centre.

- Motion sickness includes overstimulation of these pathways because of various sensory stimuli. Hence , buclizine blocks the histamine receptors in the vomiting centres and decreases the activity along these pathways. Buclizine also has anticholinergic properties and blocks the muscarinic receptors.

Use

- It is used as an anti-vertigo or antiemetic agent.
- It is used in the management of vertigo in diseases affecting the vestibular apparatus.
- It is used for treating nausea, vomiting and dizziness related to motion sickness.

PROPYLAMINES (MONOAMINOPROPYL OR ALKYLAMINE DERIVATIVES)

- The propylamine antihistamines are characterized structurally by an sp3 or sp2 carbon-connecting atom with a carbon chain of two additional carbons linking the key tertiary amino and diaryl pharmacophore moieties.

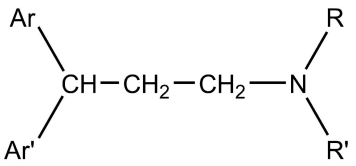
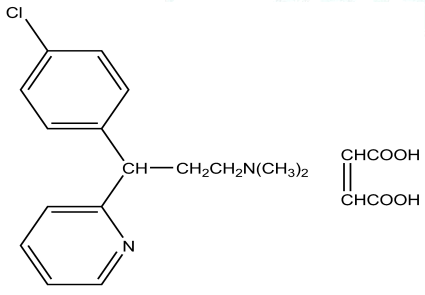


Fig: General structure of the propylamines.

- Those propylamines with a saturated carbon-connecting moiety are commonly referred to as the pheniramines.
- All of the pheniramines consist of a phenyl and a 2-pyridyl aryl group and a terminal dimethylamino moiety. These compounds differ only in the phenyl substituent at the para position: H (pheniramine), Cl (chlorpheniramine), and Br (brompheniramine).
- The halogenated pheniramines are significantly more potent (20–50 times) and have a longer duation of action than pheniramine.
- All pheniramines are chiral molecules, and the halogensubstituted derivatives have been resolved by crystallization of salts formed with d-tartaric acid.
- Antihistaminic activity resides almost exclusively in the S-stereoisomers (200–1,000 times higher H1-receptor binding affinities).
- The antihistamines in this group are among the most active H1-antagonists. But Oral bioavailability is relatively low (30%–50%) and may be limited by first-pass metabolism.
- The primary metabolites for this compound and other members of this series are the mono- and di-N-dealkylation products.

Chlorpheniramine Maleate.

- IUPAC: (+/-) 2-[p-chloro-[2-dimethylamino)ethyl]benzyl]pyridine bimaleate.



Chlorpheniramine Maleate
Dextrochlorpheniramine Maleate

- Chlorpheniramine is a white crystalline powder that is soluble in water (1:3.4), in alcohol (1:10), and in chloroform (1:10).
- Chlorination of pheniramine in the para position of the phenyl ring increases potency 10-fold with no appreciable change in toxicity.
- Most of the antihistaminic activity resides with the dextro isomer .

Mechanism of Action

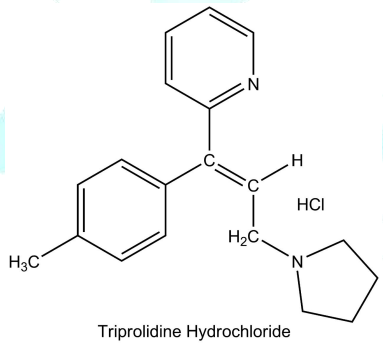
- Chloropheniramine binds to H 1-receptors and inhibits the action of histamine, thus temporarily relieving the negative symptoms produced by histamine.

Uses

- Chlorpheniramine is used for relieving the symptoms of allergy, hay fever, common cold, rashes, watery eyes, itchy eyes/nose/throat/skin, cough, runny nose, and sneezing

Triprolidine Hydrochloride

- IUPAC: (E)-2-[3-(1-pyrrolidinyl)-1-p-tolylpropenyl]pyridine mono-hydrochloride monohydrate.
- Triprolidine hydrochloride is a white crystalline powder with a slight, but unpleasant, odor. It is soluble in water and in alcohol, and its solutions are alkaline to litmus.



Triprolidine Hydrochloride

- The antihistaminic activity is confined mainly to the geometric isomer in which the pyrrolidinomethyl group is trans to the 2-pyridyl group.

Synthesis

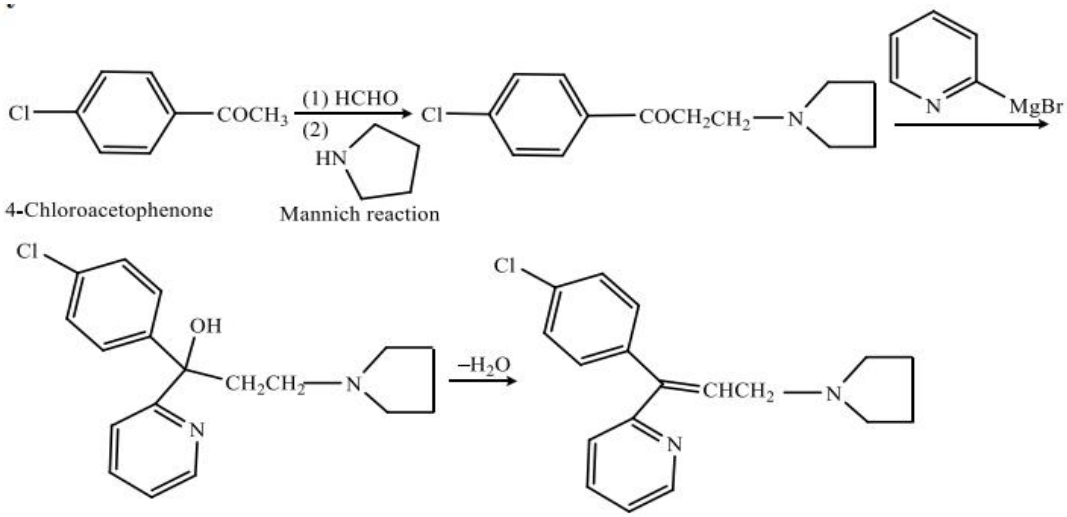


Fig: Synthesis of Triprolidine

Mechanism of Action

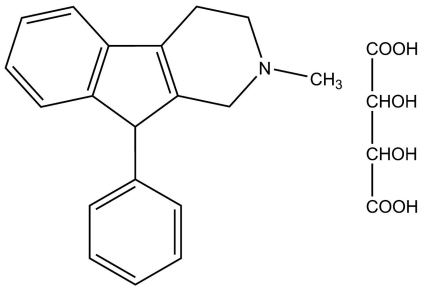
- Triprolidine hydrochloride binds to the H1-receptors and inhibits the action of histamine, thus temporarily relieving the negative symptoms of histamine.

Uses

- It is used for the symptomatic relief of seasonal or perennial allergic rhinitis or non -allergic rhinitis; allergic conjunctivitis; and mild, uncomplicated allergic skin conditions of urticaria and angioedema.
- It is used in combination with other agents for the symptomatic relief of symptoms related to common cold.

Phenindamine Tartrate

- IUPAC : 2,3,4,9-tetrahydro-2-methyl-9-phenyl-1H-indeno[2, 1-c] pyridine bitartrate.
- Phenindamine occurs as a creamy-white powder, usually with a faint odor and sparingly soluble in water (1:40).
- Oxidizing substances or heat may cause isomerization to an inactive form.



Phenindamine Tartrate

Mechanism of Action

- Phenindamine competes with histamine for H1-receptor sites on effector ce lls.
- It antagonises those pharmacological effects of histamine that are induced by the activation of H 1-receptor sites.
- Hence, it decreases the intensity of allergic reactions and tissue injury response that causes histamine release.

Uses

- It is used for relieving sneezing, runny nose, itching, watery eyes, hives, rashes, itching, and other symptoms of allergies and common cold.

PHENOTHIAZINES

- The phenothiazine derivatives that display therapeutically useful antihistaminic actions contain a two- or three-carbon, branched alkyl chain between the ring system and terminal nitrogen atom.

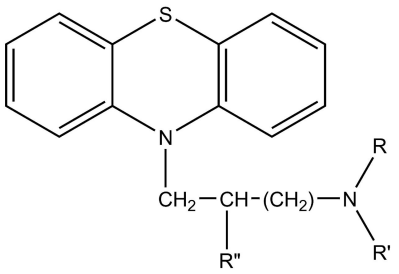


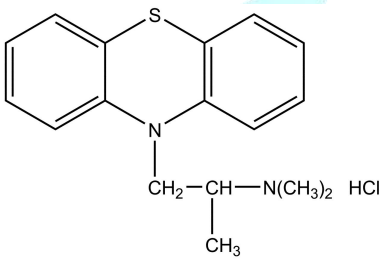
Fig: General structure of the phenothiazines.

- The phenothiazine antipsychotics series required unbranched propyl chain.

- The branched alkyl chain in phenothiazine antihistaminic derivatives contains a chiral carbon, giving rise to optical isomerism.
- This compound undergoes mono- and di-N-dealkylation, sulfur oxidation, aromatic oxidation at the 3-position to yield the phenol, and N-oxidation. Several of these metabolites, particularly the phenol, may yield glucuronide conjugates.

Promethazine Hydrochloride

- IUPAC: (+/-)10-[2-(dimethylamino)-propyl]phenothiazine monohydrochloride (Phenergan)
- Promethazine hydrochloride,occurs as a white to faint yellow crystalline powder that is very soluble in water, in hot absolute alcohol, and in chloroform. Its aqueous solutions are slightly acid to litmus.



Promethazine Hydrochloride

Synthesis

- Promethazine is formed by the alkylation of phenothiazine with 1-dimethylamino-2 chloropropane in the presence of sodium amide.

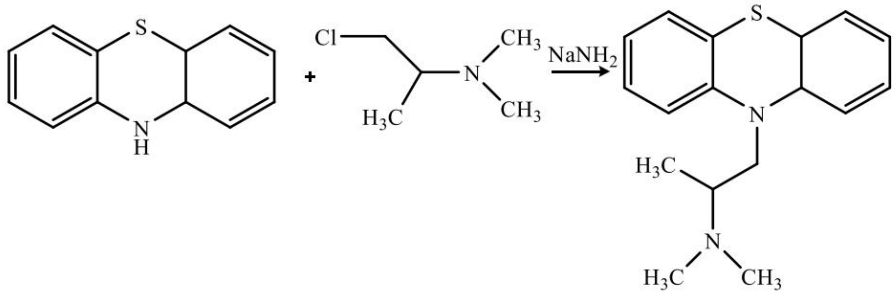


Fig: Synthesis of Promethazine

Mechanism of Action

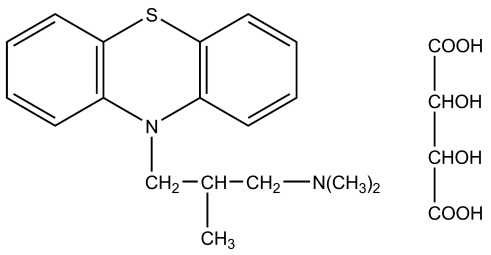
- Promethazine hydrochloride selectively inhibits the peripheral H 1-receptors, thus reduces the histamine effects on effector cells.
- It also inhibits the central histaminergic receptors, thus depresses the reticular system that causes sedative and hypnotic effects.
- It also exhibits centrally acting anticholinergic properties. It may control nausea and vomiting by acting on the medullary chemoreceptive trigger zone.

Uses

- It is used for preventing and curing vertigo and motion sickness. However, it shows marked and long antihistaminic activity.
- Due to its antiemetic properties, it is added in postoperative nausea and vomiting tablets, elixirs, syrups, suppositories, and injections.
- It is also used for anaest hetic premedication through intramuscular injection with atropine and meperidine.

Trimeprazine Tartrate.

- IUPAC : (+/-)10- [3-(dimethylamino)-2-methylpropyl] phenothiazine tartrate (Temaril),
- Trimeprazine tartrate, occurs as a white to off-white crystalline powder that is freely soluble in water and soluble in alcohol.
- Its antihistaminic action is reported to be from 1.5 to 5 times that of promethazine.
- Clinical studies have shown it has a pronounced antipruritic action that may be unrelated to its histamine-antagonizing properties.



Trimeprazine Tartrate

Mechanism of Action

- Trimeprazine acts by competing with free histamine for binding at H1-receptor sites. This antagonises histamine effects on H1 -receptors, thus reducing the negative symptoms caused by binding of histamine to H1-receptors.

Uses

- It is used alone or along with corticosteroids in controlling inflammatory and allergic problems.
- It is used for preventing and relie ving the allergic conditions that cause pruritus (itching) and urticaria (some allergic skin reactions).

DIBENZOCYCLOHEPTENES AND DIBENZOCYCLOHEPTANES

- The dibenzocycloheptene and dibenzocycloheptane antihistamines may be regarded as phenothiazine analogs in which the sulfur atom has been replaced by an isosteric vinyl group (cyproheptadine) or a saturated ethyl bridge (azatadine), and the ring nitrogen has been replaced by an sp2 carbon atom.
- The two members of this series are closely related in structure; azatadine is an aza (pyridyl) isostere of cyproheptadine in which the 10,11-double bond is reduced.

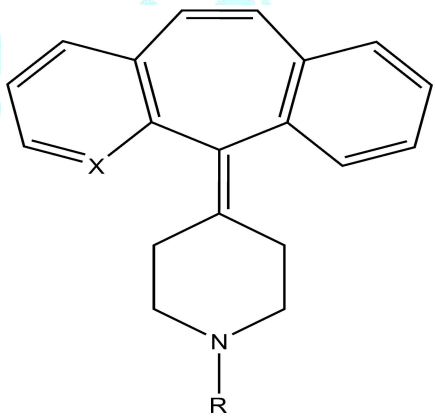
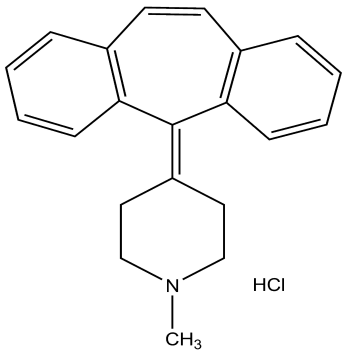


Fig: General structure of the dibenzocycloheptenes and dibenzocycloheptanes..

Cyproheptadine Hydrochloride.

- IUPAC : 4-(5H-dibenzo-[a,d]-cyclohepten-5-ylidine)-1-methylpiperidine hydrochloride sesquihydrate
- Cyproheptadine hydrochloride, is slightly soluble in water and sparingly soluble in alcohol.



Cyproheptadine Hydrochloride

Mechanism of Action

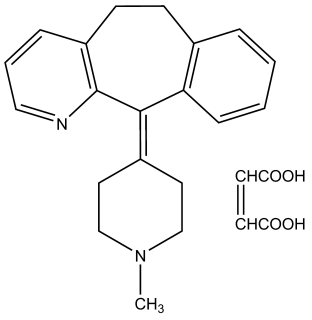
- Cyproheptadine acts by competing with free histamine for binding at H1-receptor sites.
- This antagonises histamine effects on H1-receptors, thus reducing the negative symptoms caused by binding of histamine to H1-receptors.
- It also competes with serotonin for binding to receptor sites in smooth muscle s in intestines and other locations.
- Antagonism of serotonin on the appetite centre of hypothalamus is responsible for cyproheptadine's ability to stimulate appetite.

Uses

- It is used for treating perennial and seasonal allergic rhinitis, vasomotor rhinitis,allergic conjunctivitis, mild uncomplicated allergic skin manifestations of urticarial and angioedema, amelioration of allergic reactions to blood or plasma, dermatographism, cold urticaria, and as a treatment for anaphylactic reactions adjuvant to epinephrine.

Azatadine Maleate

- IUPAC : 6,11-dihydro-11-(l-methyl-4-piperidylidene)-5H-benzo-[5,6]cyclo-hepta(1,2-b]pyridine maleate.
- Azatadine maleateis a potent, long-acting antihistaminic with antiserotonin activity.



Azatadine Maleate

Mechanism of Action

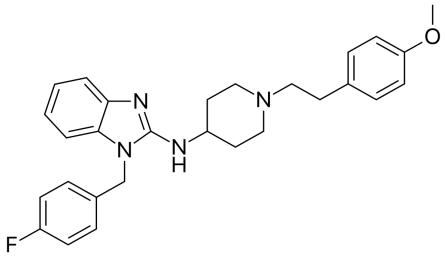
- Azatadine competes with histamine for H 1-receptor sites on effector cells.
- It antagonises those pharmacological effects of histamine that are induced by the activation of H 1-receptor sites.
- Hence, it decreases the intensity of allergic reactions and tissue injury response that causes histamine release.

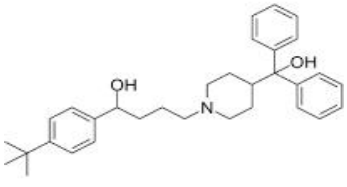
Uses

- It is used for treating the symptoms of upper respiratory mucosal congestion in perennial and allergic rhinitis.
- It is also used for treating nasal congestion and eustachian tube congestion.

Second-Generation Antihistamines

- Second-generation antihistamines focused on developing agents with a lower sedation potential and reduced binding affinities for non target proteins including muscarinic, adrenergic, and serotonergic receptors.
- The second-generation H1-antagonists are often referred to as nonsedating antihistamines.
- Astemizole and Terfenadine are first agent of second genration. Astemizole and Terfenadine Shows Cardiac toxicity (to QT prolongation).





Second-generation H1 antagonist Classification

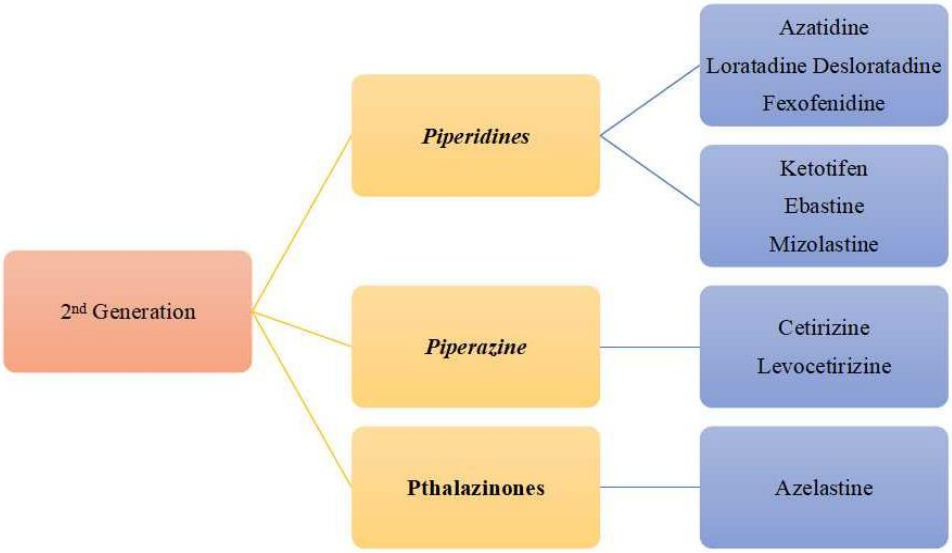
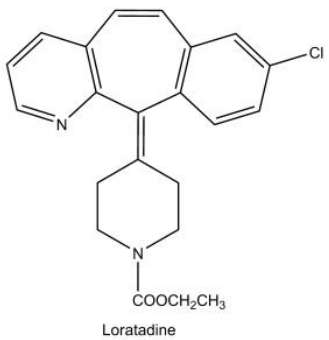


Fig: Classification of 2nd genration antihistamine agent

Loratadine

- 4-(8-chloro-5, 6-dihydro- 11Hbenzo[5,6]cyclohepta[1,2-b]pyridin-l 1-ylidene-1-carboxylic acid ethyl ester.
- Is a white to off-white powder insoluble in water but very soluble in acetone, alcohols, and chloroform.
- Loratadine is structurally azatadine and cyproheptadine.
- Loratadine is a selective peripheral H1-antihistamine.



Loratadine

Mechanism of Action

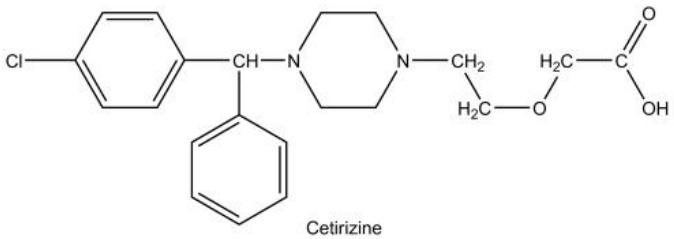
- Loratadine competes with free histamine. It shows specific and selective peripheral H 1-antagonistic activity, thus inhibits the action of histamine and temporarily relieves nasal congestion and watery eyes caused by histamine.
- It has a low affinity for cholinergic receptors and does not show any ap preciable in vitro α-adrenergic blocking activity.
- The clinical use of loratadine is unknown, but it s uppresses histamine and leukotrienes release from animal mast cells, and leukotrienes release from human lung fragments.

Uses

- It is a self-medication and is used alone or along with pseudoephedrine sulphate for the symptomatic treatment of seasonal allergic rhinitis.
- It is also used for the symptomatic relief of pruritus, erythema, and urticaria related to chronic idiopathic urticaria (it is not used in children below 6 years of age if not directed by a clinician).

Cetirizine

- IUPAC: (+/-) [2-[4-[(4-chlorophenyl)phenylmethyl]-1piperazinyl]ethoxy]acetic acid
- Is a racemic compound available as a white crystalline powder thatis water soluble.



Cetirizine

Mechanism of Action

- Cetirizine is an antihistamine drug and ahydroxyzine metabolite. It mainly acts by the selective inhibition of peripheral H 1-receptors.

Uses

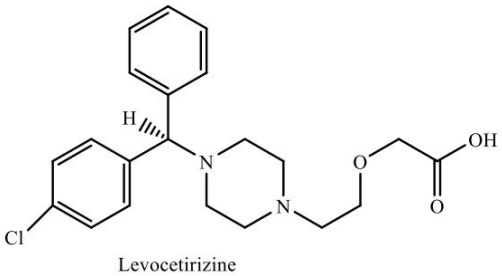
- **Seasonal Allergic Rhinitis:** It is used for treating symptoms related to seasonal allergic rhinitis caused by allergens (like ragweed, grass , and tree pollens) in adults and children of 2 years of age and above. Cetirizine is also used for treating sneezing, rhinorrhoea, nasal pruritus, ocular pruritus, tearing, and redness of eyes.

- **Perennial Allergic Rhinitis:** It is used for treating the symptoms related to perennial allergic rhinitis caused by dust mites, animal dander, and molds in adults and children of 6 months of age and above. Cetirizine is also used for treating sneezing, rhinorrhoea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.

- **Chronic Urticaria:** It is used for treating uncomplicated skin conditions of chronic idiopathic urticaria in adults and children of 6 months of age and above. Mainly, cetirizine decreases the occurrence, severity, and duration of hives and pruritus.

Levocetirizine

- Levocetirizine is a third generation non -sedative antihistamine.
- It is used for treating the symptoms related to seasonal and perennial allergic rhinitis and uncomplicated skin conditions of chronic idiopathic urticaria.



Levocetirizine

Mechanism of Action

- Levocetirizine is the active enantiomer of cetirizine. It produces its major effects by selective inhibiti on of H 1-receptors.

Uses

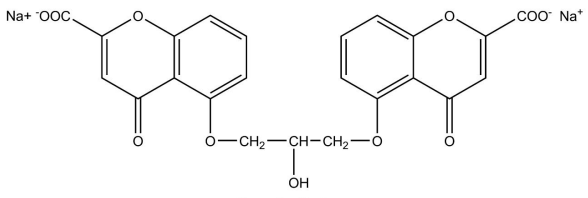
- It is used for treating the symptoms related to seasonal and perennial allergic rhinitis in adults and children of 6 years of age and above.
- It is used for treating the allergic symptoms like watery eyes, runny nose, itching eyes/nose, and sneezing.
- It is also used to treat itching and hives.

INHIBITION OF HISTAMINE RELEASE: MAST CELL STABILIZERS

- The first therapeutically significant member of this class was cromolyn sodium.
- Generally, the mast cell stabilizers inhibit activation of, and mediator release from, various inflammatory cell types associated with allergy and asthma, including eosinophils, neutrophils, macrophages; mast cells, monocytes, and platelets.
- In addition to histamine, these drugs inhibit the release of leukotrienes (C4, D4, E4) and prostaglandins.

Cromolyn Sodium

- IUPAC: 1,3- bis(2-carboxychromon-5-yloxy)-2-hydroxypropane.
- Cromolyn sodium is a hygroscopic, white, hydrated crystalline powder that is soluble in water (1:10). It is tasteless at first but leaves a very slightly bitter aftertaste.



Cromolyn Sodium

Mechanism of Action

Cromolyn sodium prevents the degranulation of mast cells, and thus prevents the release of h istamine and Slow-Reacting Substance of Anaphylaxis (SRS -A, mediators of type I allergic reactions). It may also suppress the release of inflammatory leukotrienes. It acts by inhibiting calcium influx.

Uses

- It used for the management of bronchial asthma.
- It is used for treating vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.
- It is used in the prophylactic treatment of asthma induced by allergy and exercise.
- On inhalation it prevents bronchial asthma attacks in adults and childre n of 2 years of age.

Histamine (H2) Receptor Blockers

- H2 receptors is G-Protein Coupled receptor
- Signal transducer involved is Gs and Gi
- The H2 receptor is found in the parietal cells of the stomach and in vascular smooth muscle, hepatocytes, and various blood cells.
- Stimulation of H2 receptors in the stomach leads to an increase in gastric acid secretion.

Histamine (H2) Receptor Distribution

Receptor	Organ	Function
H2	Gastric Glands	Acid secreation
	Blood Vessels	Dilation-- Capillary Permiability
	CNS- Neurotransmitter Sensoery Nerve	Pain & Itching
	Heart	HR increase

Fig: H2 receptor distribution

Histamine and Gastric Acid Secretion

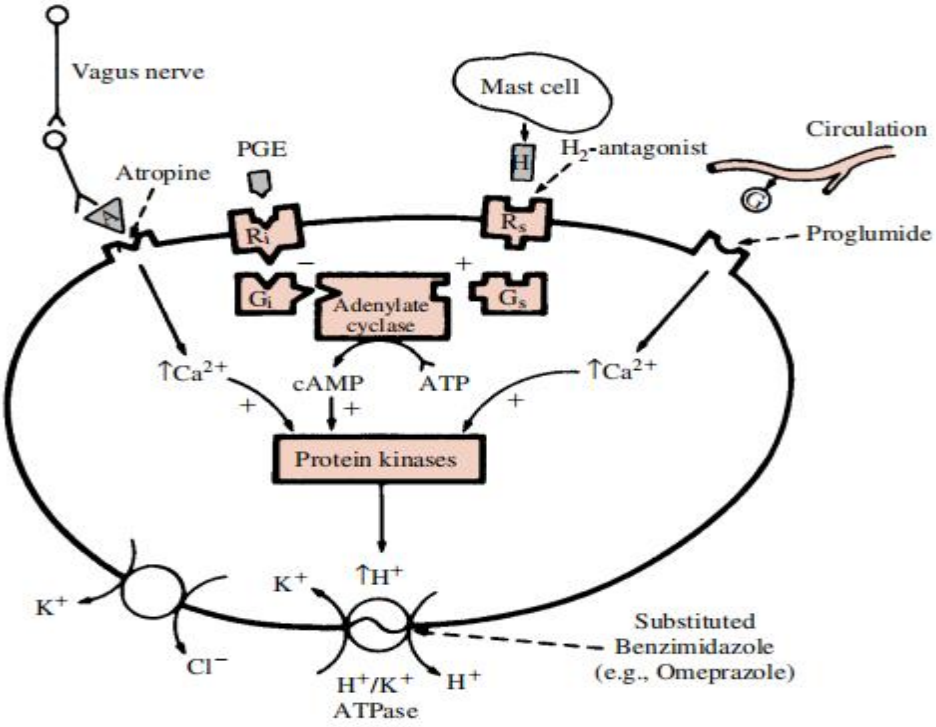


Fig: Molecular pathway for gastric acid secreation (Pareital cell)

Classification of H2 Antagonist

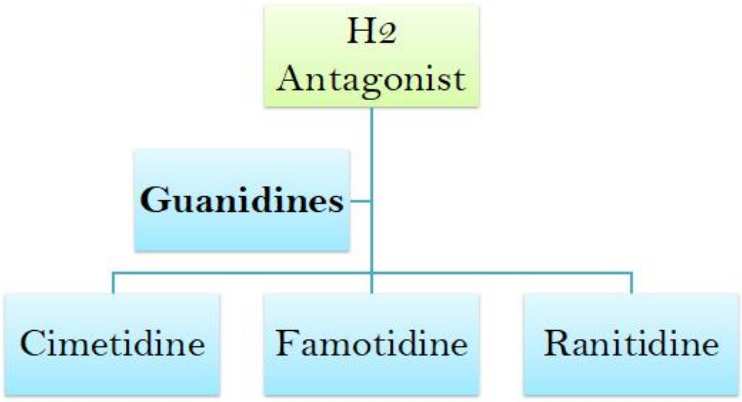
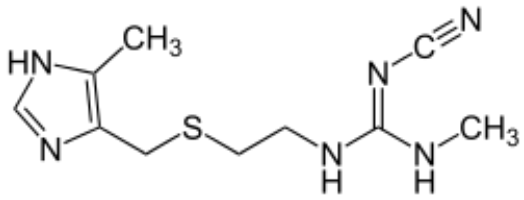


Fig: Classification of H2 Antagonist

Cimetidine

- Cimetidine is a member of the class of guanidines that consists of guanidine carrying a methyl substituent at position 1, a cyano group at position 2 and a 2-{[(5-methyl-1H-imidazol-4-yl)methyl]sulfanyl}ethyl group at position.



Cimetidine

- Cimetidine is a colorless crystalline solid that is slightly soluble in water (1.14% at 37°C).
- Cimetidine is a relatively hydrophilic molecule.

Mechanism of Action

- Cimetidine blocks the histamine effects by binding to the H2-receptors found on the baso lateral membrane of gastric parietal cell.
- Reduction in gastric acid secretion, gastric volume and acidity are the results of this competitive inhibition.

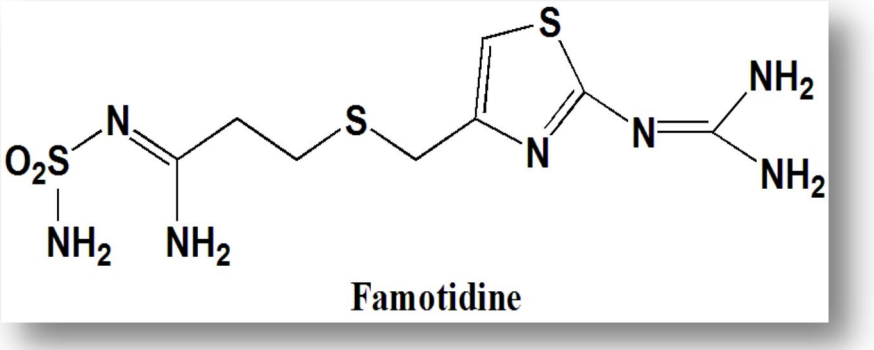
Uses

- It is used for treating certain types of ulcer.
- It is used for treating the conditions in which too much acid is secreted by the stomach.
- It is also used for treating acid-reflux disorders (like GERD), peptic ulcer disease, heartburn, and acid indigestion.

Famotidine

- IUPAC:N(aminosulfonyl)3[[[2[(diamnomethylene)amino]thiazolyl]methyl]thio]propanimidamide
- Is a white to pale-yellow crystalline compound that is very slightly soluble in water and practically insoluble in ethanol.

- It is a thiazole bioisotere of cimetidine that contains a guanidine substituent that may mimic the imizadole of cimetidine.



Famotidine

Mechanism of Action

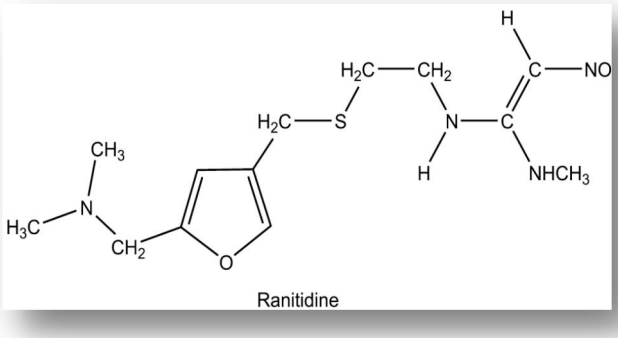
- Famotidine blocks the histamine effects by competitively binding to H2-receptors found on the basolateral membrane of gastric parietal cell.
- This competitive inhibition reduces basal and nocturnal gastric acid secretion, gastric volume, acidity, and amount of gastric acid produced in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin.

Uses

- It is used for treating and preventing stomach and intestinal ulcers.
- It is used in Zollinger-Ellison syndrome (in which excess amounts of acid is produced by the stomach).
- It is used for treating Peptic Ulcer Disease (PUD) and Gastroesophageal Reflux Disease (GERD).

Ranitidine

- Ranitidine, N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thiol] ethyl]-methyl-2- nitro-l,1-ethenediamine
- Is a white solid, which in its hydrochloride salt form is highly soluble in water.
- It is an aminoalkyl furan derivative



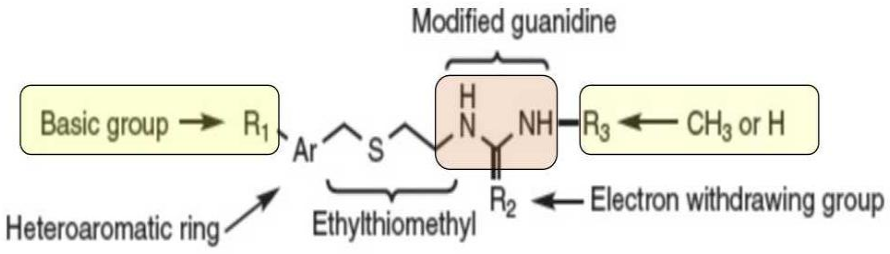
Mechanism of Action

- Ranitidine reduces the normal as well as the meal-stimulated secretion of acid by parietal cells by two mechanisms:
- Histamine is released by the ECL cells in stomach is prevented from binding to the H2-receptors on parietal cells that stimulate acid secretion.
- When H2-receptors are blocked, substances promoting acid secretion (**e.g.,** gastrin and acetylcholine) have a decreased effect on parietal cells.

Uses

- It is used for treating peptic ulcer disease and gastroesophageal reflux disease.
- It is used in gastric and duodenal u lcer and in conditions in which gastric juice secretion needs to be inhibited.
- It is given in combination with fexofenadine a nd other antihistamines for treating skin conditions like hives.

SAR of H_2 Blocker



- The molecules commonly called H_2 antagonists are inverse agonists that bind to and promote the inactive conformation of the H2 receptor. This decreases the basal level of histamine agonist action.
- The ethylthiomethyl spacer unit found in all H2-selective antihistamines is isosteric with a butyl group. The position of the sulfur atom in this spacer is important.
- The ethylthiomethyl moiety found on all H2-selective antihistamines binds hydrophobically to aromatic and aliphatic residues, including Val99 and Phe254.
- A modified guanidine moiety substituted with a powerful electron withdrawing group to destroy basicity is found in the same relative molecular area as histamine's primary amine.
- A heteroaromatic ring that either incorporates an ionizable basic center or has one as a substituent is required.

  Eg. Cimetidine's imidazole N^{π} is weakly basic.

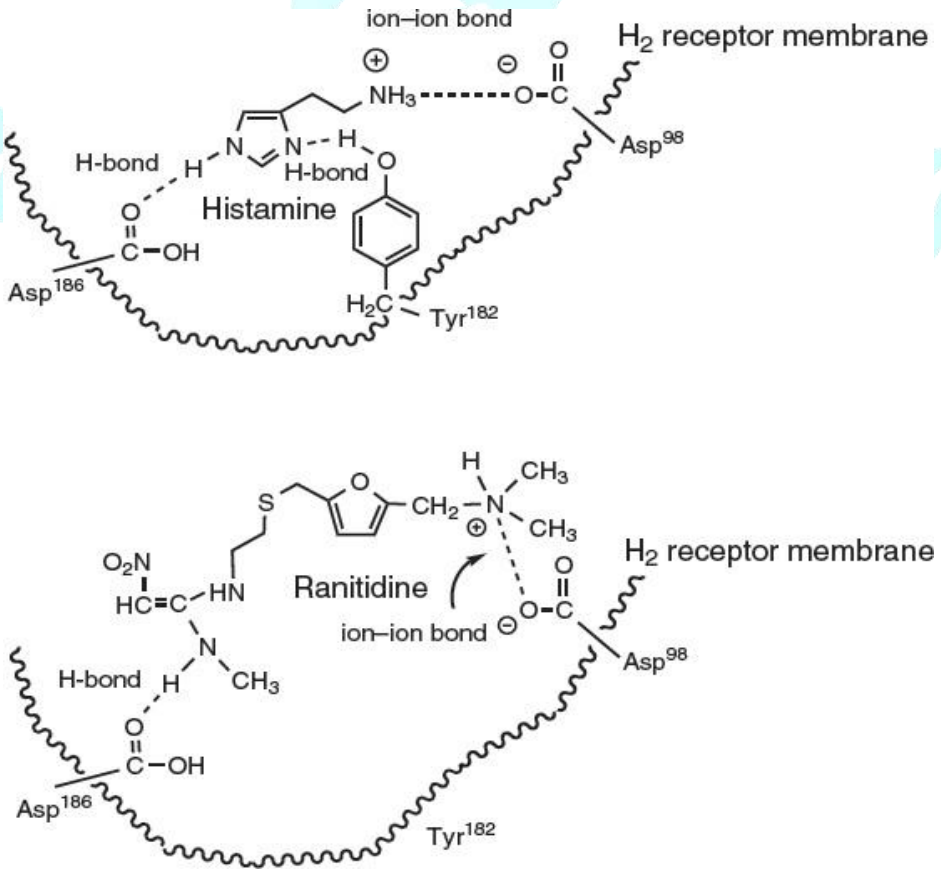


Figure: Histamine and antihistamine binding at H2 receptors