''बेटी बचाओ, बेटी पढ़ाओ''

JAYOTI VIDYAPEETH WOMEN'S UNIVERSITY, JAIPUR

FACULTY OF PHARMACEUTICAL SCIENCE

Faculty Name	**:**	JV'n Devendra Joshi
Course	**:**	B.Pharm (5rd sem.)
Session	**:**	**Medicinal chemistry – II** **M.O.A& S.A.R of Antihistamine drugs)**

Academic Day starts with–

- Greeting with saying **'Namaste'** by joining Hands together following by 2-3 Minutes Happy session, Celebrating birthday of any student of respective class and **National Anthem**

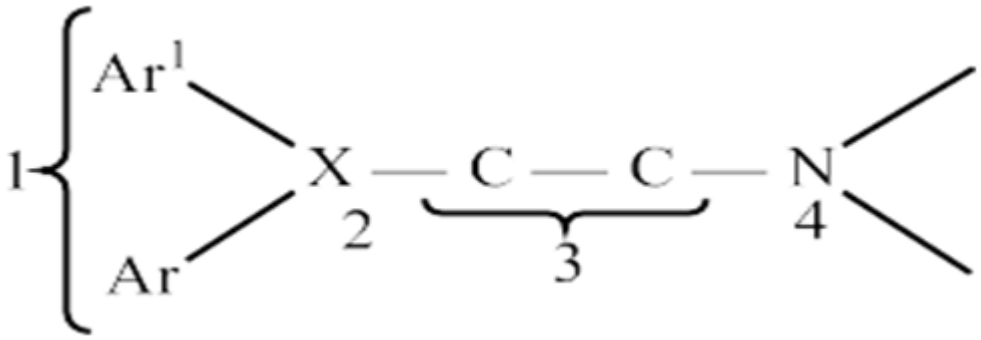
Mechanism of action Antihistamine drugs

After being released by the mast cells, histamine connects with the histaminergic receptors (H 1, H 2, and H 3). This binding initiates a cascade of activities that enable the typical responses of second messenger systems. G-protein coupled receptors make up histaminergic receptors. As a result, the H1-receptors are connected to phospholipase-C, and upon activation, they convert the phospholipids in the cell membrane into inositol phosphate (Ip 3) and diacylglycerol (DAG).Under the effect of Ip3, the endoplasmic reticulum quickly releases Ca2+ ions. DAG causes protein kinase C to become active. Thus, the Ca2+/calmodulin dependent protein kinase and phospholipase A 2 are

stimulated by the turnover of Ca 2+ ions and protein kinase C. The H 1-antagonist (anti-histaminergic) binds to the H 1-receptors and lowers the synthesis of IP3 and DAG are produced during activation of phospholipase-C. As a result, it prevents histamine's signature reaction. For a response to occur in the GIT, histamine generates cAMP-dependent protein kinase, commonly known as cyclic AMP or 3-5-cyclic adenosine monophosphate, on H2-receptors. Reversible binding between the H 2-antagonist and the H 2-receptors reduces cAMP synthesis. The proton pump is then turned on, which reduces the production of gastric acid in the GIT. Additionally, H3 receptors are G-protein coupled receptors. They lessen the influx of Ca2+ ions. Histamine and other neurotransmitters are inhibited by H 3-receptors as a result of their ability to lower calcium influx into CNS cells, lessen gastrin release from the GIT, and down-regulate histamine through auto-regulatory actions. The H3-receptors are blocked to counteract these effects. Whereas the clinical extendibility is narrow for H3.

Structure-ActivityRelationship (SAR)

H_1-ReceptorAntagonist



(1) Aryl Groups : Diaryl substitution is required for H_1 affinity, and is found infirst-generation and second -generation antihistamines. The co-planarity oftwo aryl substitutions in fluences the optimal antihistaminic activity. Activearyl substitutions are as follows:

(i) Ar isphenyl and hete ro aryl group (like 2-pyridyl).

(ii) Ar^1 is aryl or aryl methyl group.

(2) Nature of X : Antihistamines with X = carbon (pheniramine series) signifies the stereo selective receptor binding to the receptors because of its chirality. The active substitutions of X are as follows:

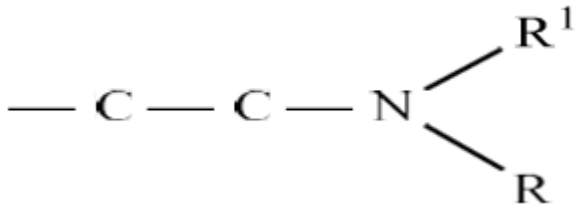
(iii) X= Oxygen (amino alkyl etheranalogue)

(iv) X= Nitrogen (ethylene-diamine derivative)

(v) X=Carbon (monoaminopropylanalogue)

(3) Alkyl Chain : Mostly antihista mines have ethylene chain, the branching of which forms a less active compound.

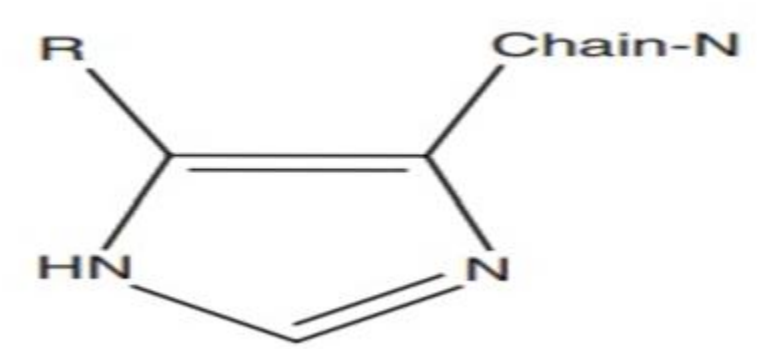
This general chain is present in all the antihistamines.



(4) Terminal Nitrogen Atom : The nitrogen atom at the terminal should be atertiary a mine for maximum activity. The terminal nitrogen can be the part of heterocyclic ring, **for example,** antazoline and chlorcyclizine have a high anti histaminic activity. The aminomoiety on interaction with H_1-receptors how sprotonation due to basicity with pka 8.5-10.

H_2-receptor SAR

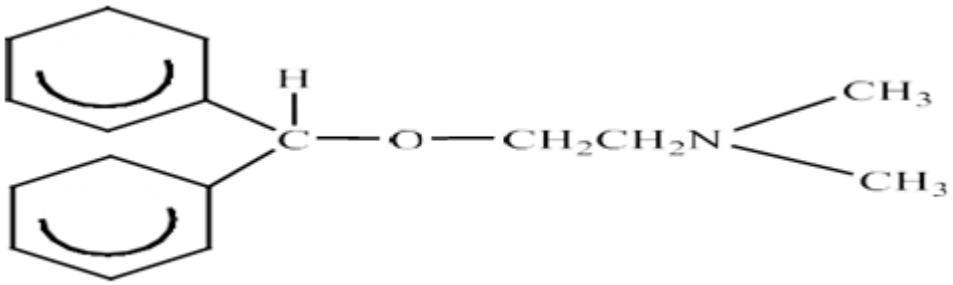
The international change of the histamine structure and the deliberate search for a chemically comparable molecule that would serve as a competitive inhibitor of the H2-receptors led to the development of the H2-receptor antagonists.



- Imidazole ring is not the sole necessary ring for histamine H2 receptors to compete with one another.
- Furan, thiophene, thiazole, and other heterocyclic rings can be utilized to increase the potency and selectivity of H2-receptor antagonism.
- For the best antagonistic activity, the ring and terminal nitrogen should be separated by four carbon atoms.
- There are certain medications that also have the is osteric thioether bond. For maximum antagonist effect, the terminal nitrogen group should be substituted with polar, non basic compounds.

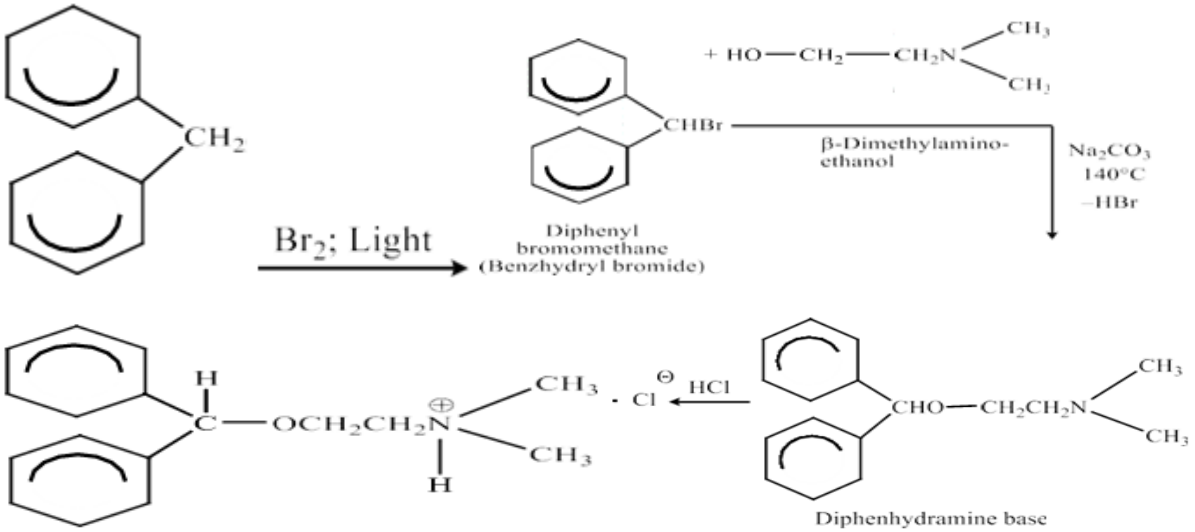
Study of Some Individual Drugs

(i) Diphenylhydramine hydrochloride



Diphenhydramine Hydrochloride

Synthesis of diphenhydramine hydrochloride



Mechanism of action :

Diphenhydramine works through the antagonism ofH_1-receptors found on the respiratory smooth muscles, vascular endothelial cells, GIT, cardiac tissue, immune cells, uterus, and CNS neurons. On stimulating the H_1-receptors in the set issues, they increase vascular permeability, stimulateva sodilation that leads to flushing, decrease the conduction time of atrioventricular (AV) node, stimulate the sensory nerves of airways that leads to coughing, contract the smooth muscles of bronchi and GIT, and cause eosinophilic chemo taxis that enhances the allergic immune response. Diphenhy dramine functions as an inverse agonist atH_1-receptors, and the nit converses the histamine effects on capillaries, and decreases the symptoms of allergic reaction.

Uses

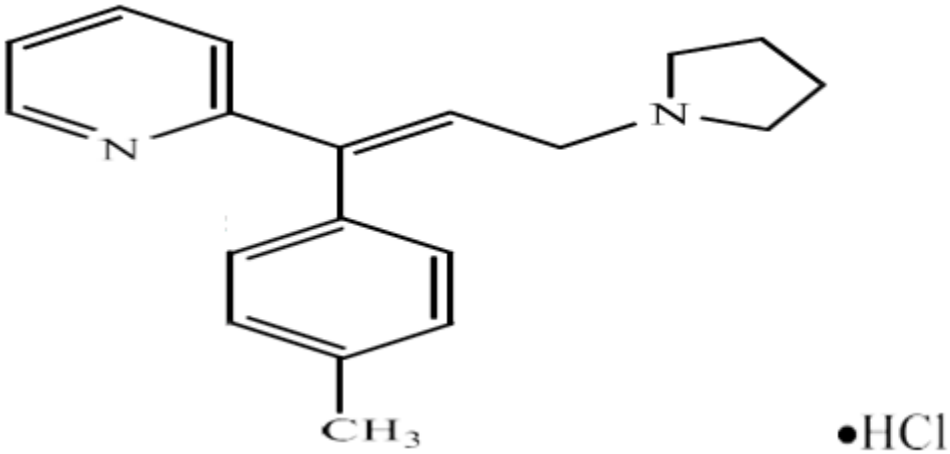
(i) It is used for preventing and curing nausea, vomiting and dizziness caused by motion sickness.

(ii) It is used to relax and fall asleep.

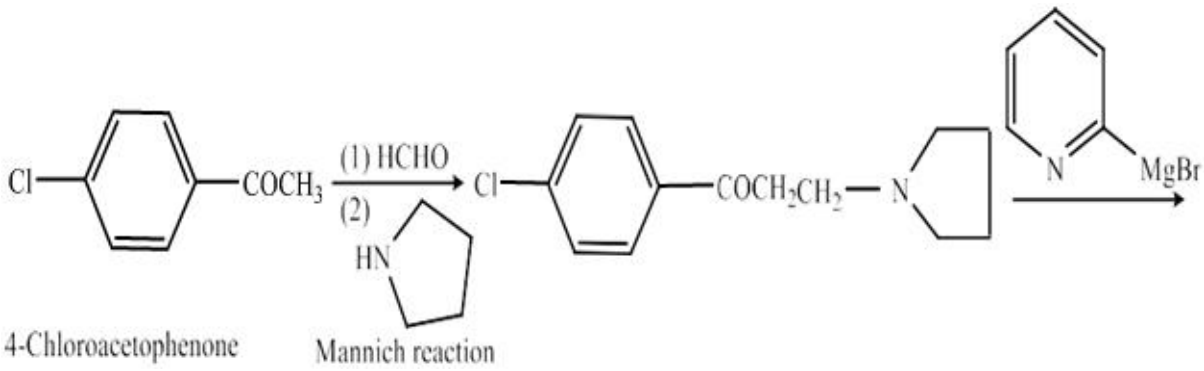
(iii) It is used for relieving the symptoms of allergy, hay fever, common cold,

rashes, itching, watery eyes, itchy eyes/nose/throat, cough, runny nose, and sneezing.

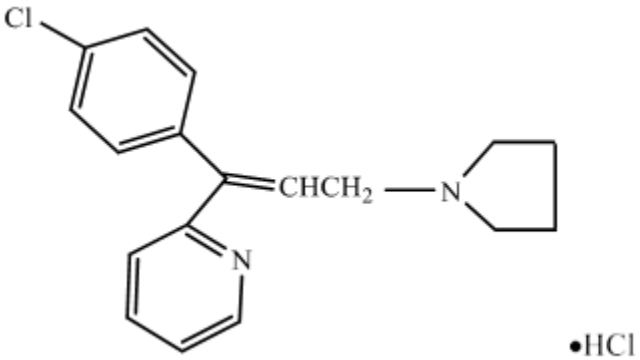
(ii) Triprolidine hydrochloride

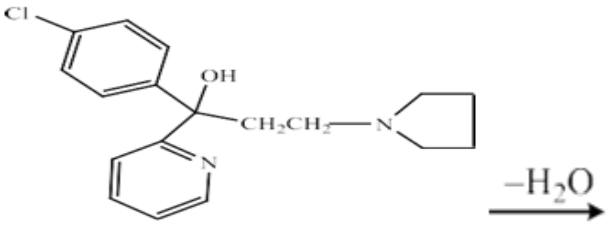


Triprolidine Hydrochloride



4-Chloroacetophenone Mannich reaction





Mechanism of action

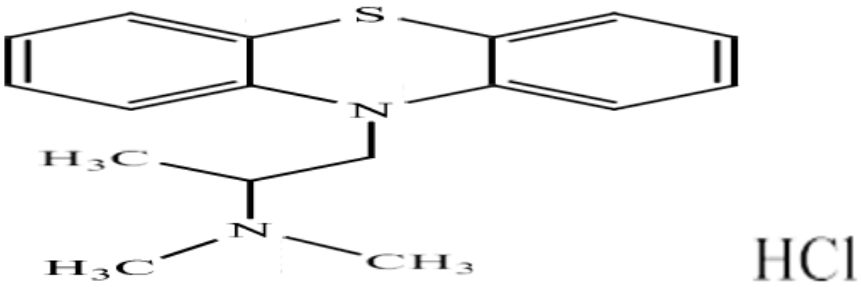
Triprolidine hydrochloride binds to the H_1-receptors and inhibits the action of histamine, thus temporarily relieving the negative symptoms of histamine

Uses :

(i) It is used for the symptomatic relief of seasonal or perennial allergic rhinitis or non-allergic rhinitis; allergic conjunctivitis; and mild, un complicated allergic skin conditions of urticaria and angioedema.

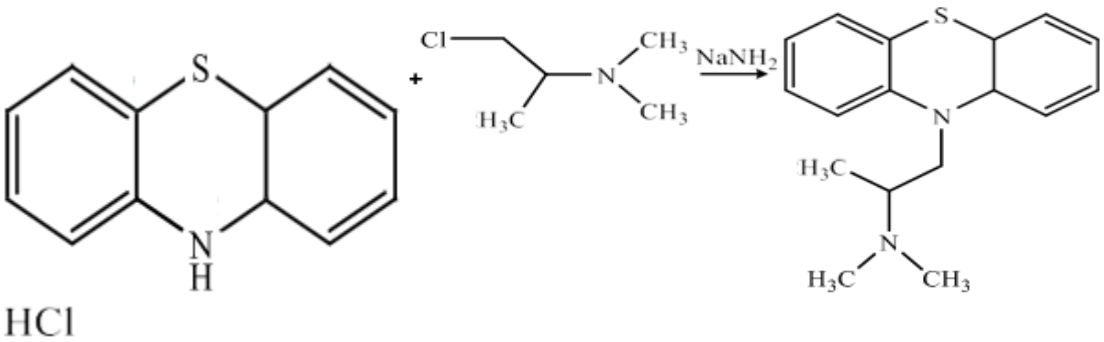
(ii) It is used in combination with other agents for the symptomatic relief of symptoms related to common cold.

(iii) Promethazine hydrochloride



Promethazine hydrochlorideis the hydrochloride salt form of promethazine, which is a phenothiazinederivative having antihistaminic, sedative and antiemetic properties.

Synthesis of promethazine hydrochloride



Phenothiazine dimethylamino-2-chloropropane

Promethazine Hydrochloride

Mechanism of action

Promethazine hydrochloride selectively inhibits the peripheral H_1-receptors, thus reduces the histamine effects on effect or cells. It also in hibits the central histaminergic receptors, thus depresses there ticular system that causess edativeandhyp notice effects. It also exhibits centrally acting anti cholinergic properties. it may control nausea and vomiting by acting on medullary chemoreceptive trigger zone.

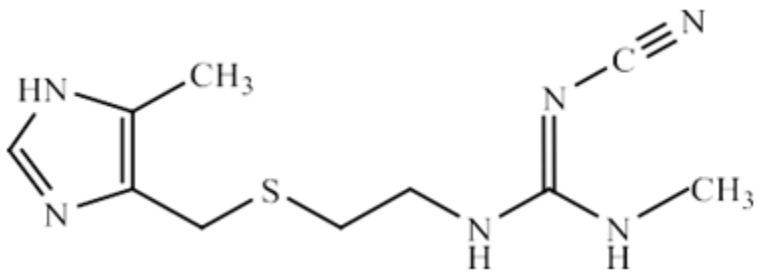
Uses

(i) It is used for preventing and curing vertigo and motion sickness. However, its hows marked and long antihistaminic activity.

(ii) Due to its antiemetic properties, it is added in postoperative nausea and vomiting tablets, elixirs, syrups, suppositories, and injections.

(iii) It is also used for anaesthetic pre medication throug hintramuscular injection with atropine and me peridine

(iv) Cimetidine

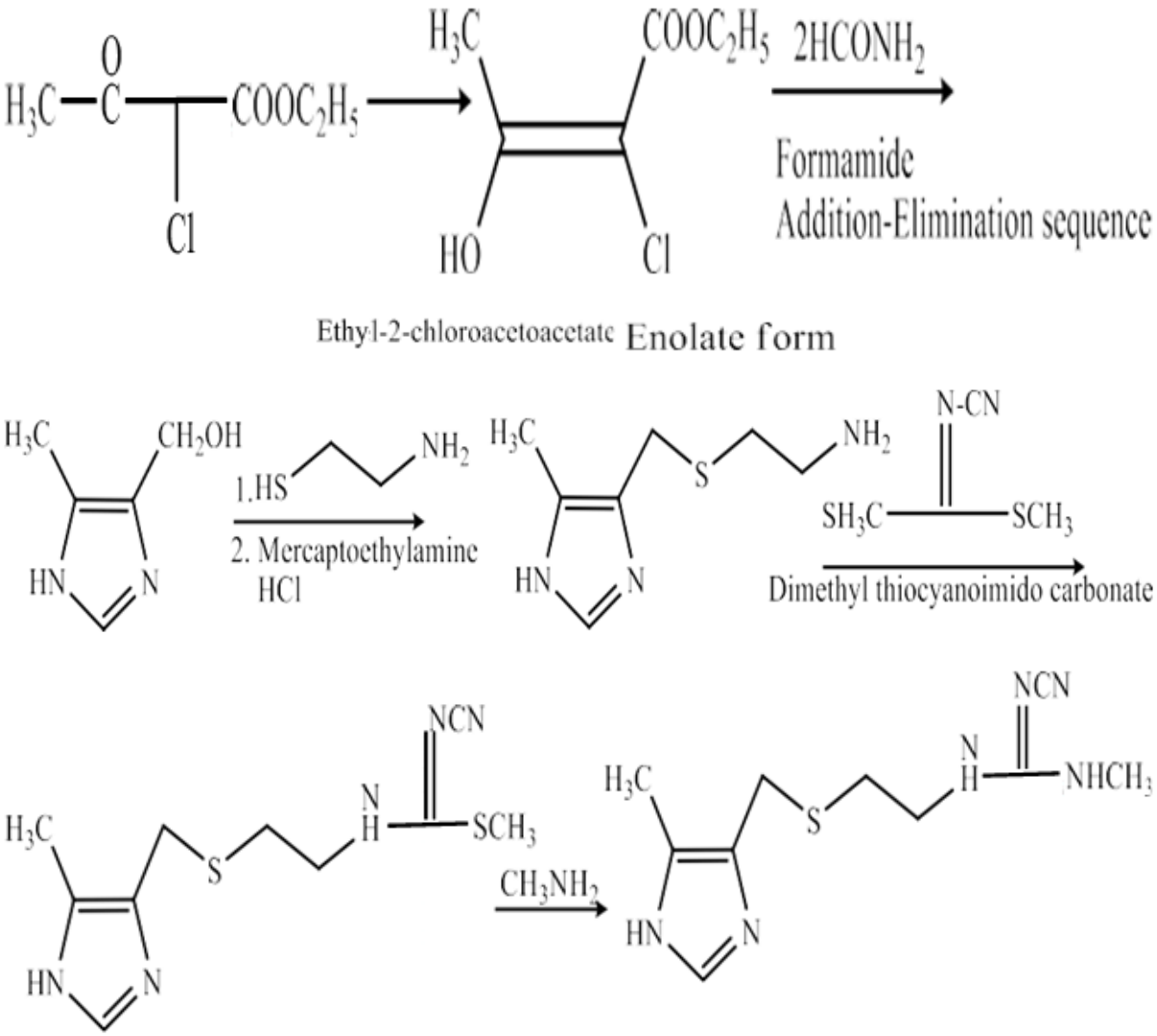


Cimetidine

Mechanism of action of cimetidine

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

Synthesis of Cimetidine



Cimetidine

Uses

(i) It is used for treating certain types of ulcer.

(ii) It is used for treating the conditions in which too much acid is secreted by the stomach.

(iii) It is also used for treating acid-reflux disorders (like GERD), peptic ulcer disease, heart burn, and acid indigestion

- **Next Topic-**

➢ Medicinal chemistry II – (Anti-neoplastic agent)

Acadmic Day ends with-

National song 'VandeMataram'

Reference :

Dr. Arora Pragi, Dr. Arora Varun, Kumar Davinder. A text book of medicinal chemistry-II S.Vikash and Company(medical publisher's) edition 2019 page no.1-23