ANTIHISTAMINIC AGENTS

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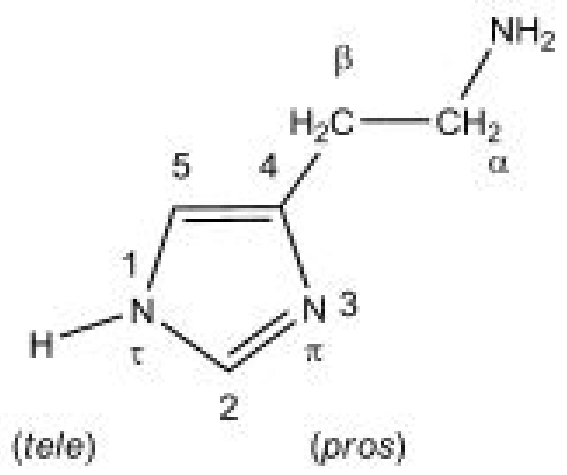
HISTAMINE CHEMISTRY

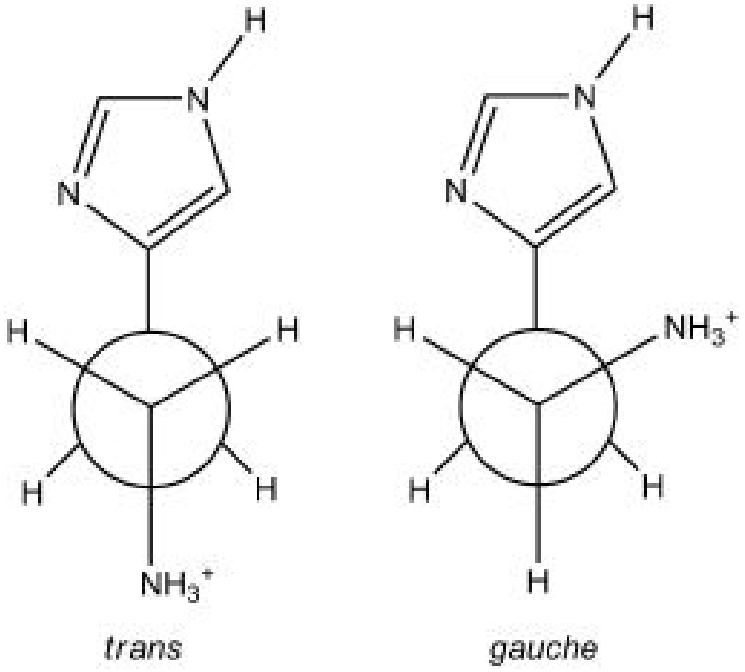
Histamine, 4-(2-aminoethyl) imidazole is composed of an imidazole heterocycle and ethylamine side chain.



Structure of Histamine

- Histamine is a basic organic compound.
- The imidazole N at position 3 is designated the pros (π) N, whereas the N at position 1 is termed the tele (τ) N.
- Histamine is an achiral molecule.

STEREOCHEMISTRY OF HISTAMINE

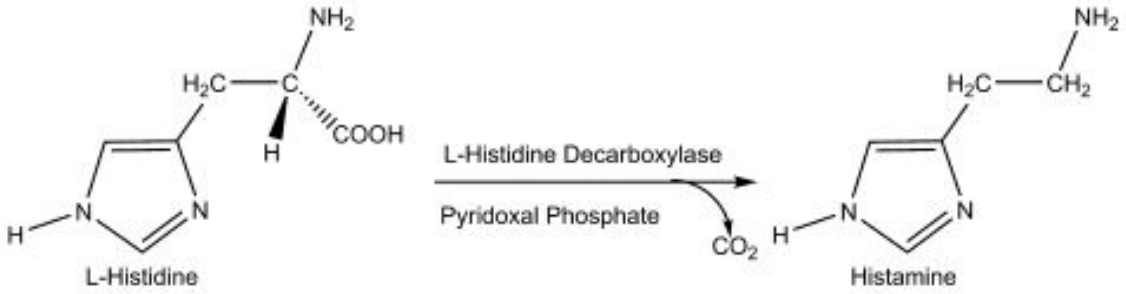


Rotamers of Histamine

- Trans rotamer of histamine possesses affinity for both H_1- and H_2-receptors.
- The gauche conformer is preferred for H_3-receptors, but not for H_1- and H_2-receptors.
- Rotamers are usually defined as low energy side chain conformations.

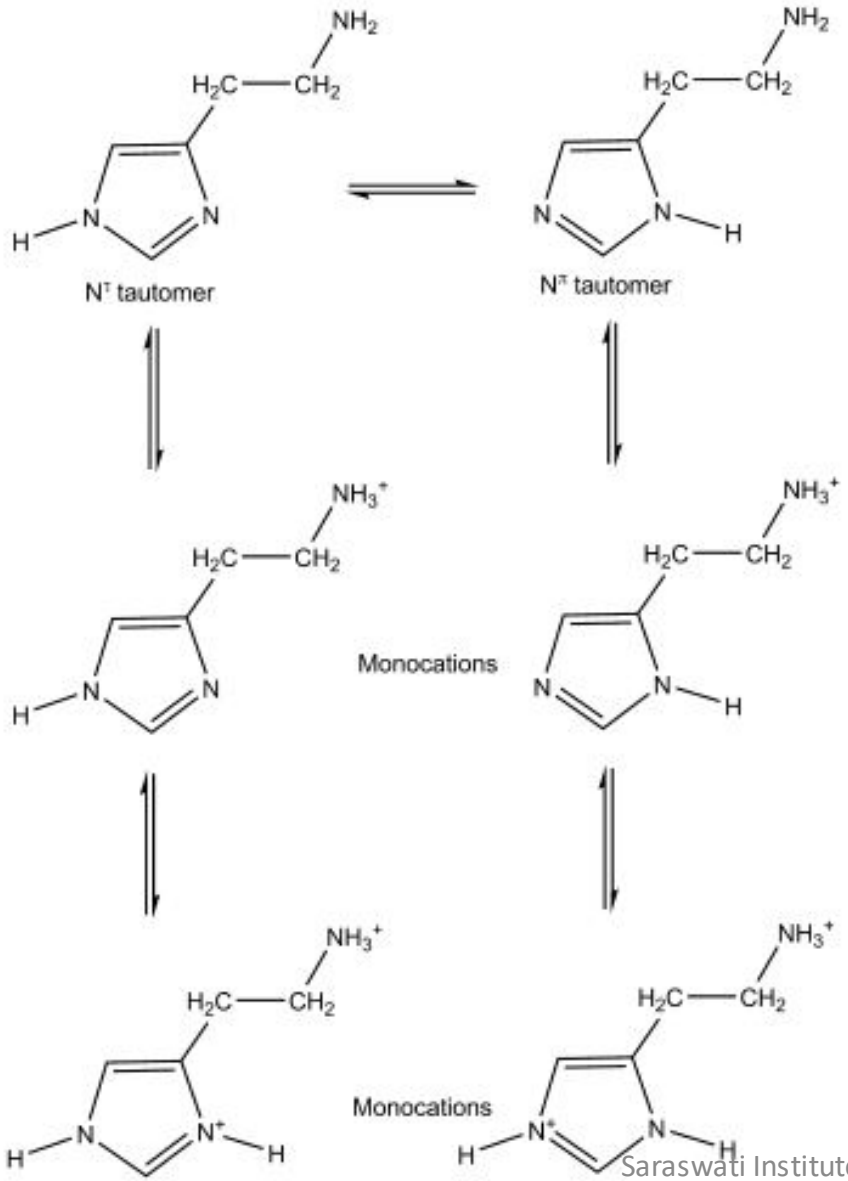
BIOSYNTHESIS OF HISTAMINE

- 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.
- 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.



Biosynthesis of Histamine

HISTAMINE TAUTOMERS AND CATIONS



- Histamine exists almost exclusively (96.6%) as the monocationic conjugate species (NH_3^+) at physiological pH (7.4).
- At lower pHs, a higher percentage of the dicationic species exists.
- Structure activity relationship studies suggest that the (NH_3^+) monocation is important for agonist activity at histamine receptors.
- The N^{τ}-H tautomer of the histamine monocation is the pharmacophoric species at the H_1-receptor.

HISTAMINE RECEPTORS LOCATION AND FUNCTIONS

Sr. No	Receptor Type	Location of Receptor	Functions
1	H_1-Histamine Receptor	▪ Smooth Muscle ▪ Endometrium ▪ CNS	▪ Causes vasodilation ▪ Bronchoconstriction ▪ Smooth muscle activation ▪ Primary receptor involved in allergic rhinitis symptoms and motion sickness.
2	H_2-Histamine Receptor	Parietal Cells	Regulate gastric acid secretion.
3	H_3-Histamine Receptor	--	Reduce neurotransmitter release of Acetylcholine, histamine, norepinephrine and serotonin
4	H_4-Histamine Receptor	Thymus, small intestine, spleen, colon, basophils and bone marrow	Unknown physiological role

FUNCTIONS OF HISTAMINE SUMMARY

Histamine exhibits a wide variety of both physiological and pathological functions in different tissues and cells.

(A) As a chemical mediator of hypersensitivity and allergic inflammatory reactions.

(B) A major role in the regulation of gastric acid secretion.

(c) An emerging role as a neurotransmitter in the CNS.

ANTIHISTAMINIC AGENTS (H_1-RECEPTOR ANTAGONIST)

- **Definition:** Antihistaminic agents are drugs used to reduce or eliminate effects produced by histamine.
- **Uses:** Antihistaminics are widely used in the palliative treatment in allergic conditions like hay fever, urticaria, some forms of pruritus, rhinitis, conjunctivitis, nasal discharge, mild asthma etc.
- A few antihistaminics possess potent antiemetic action and hence are frequently employed in the prevention and treatment of motion sickness, nausea in pregnancy and postoperative vomiting.
- **Side Effects:** In general, the most common side effect of antihistaminics is sedation which may be followed by drowsiness, impaired alertness and retarded ability to perform jobs.

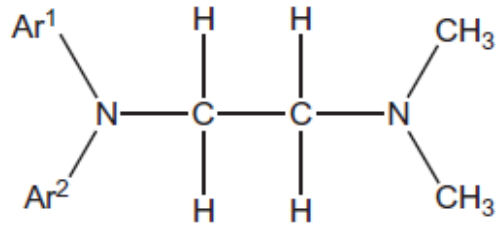
CLASSIFICATION OF H_1-ANTAGONISTS

First Generation H_1-Antagonist (Classical Antihistamines)

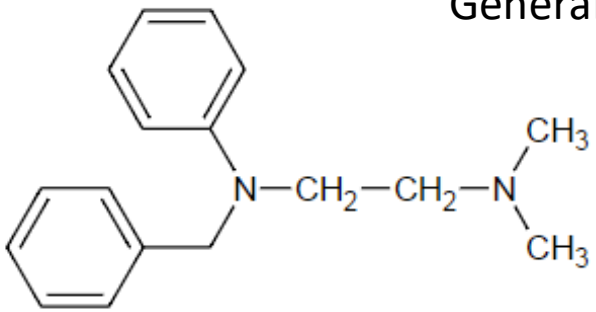
They are short to intermediate acting, more sedating and are likely to have more antimuscarinic side effects (blurred vision, dry mouth, urinary retention and constipation).

A) Ethylenediamines

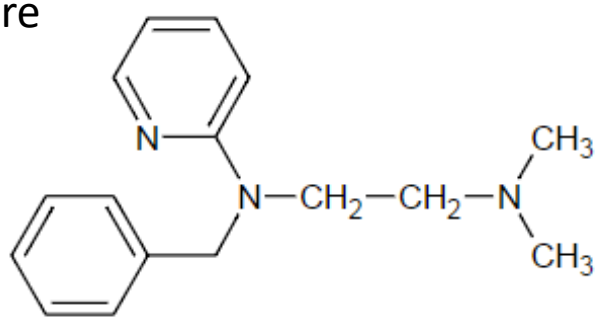
- It is the earliest series of H_1antihistamines.
- Sedation is very common among the agents in this class



General Structure



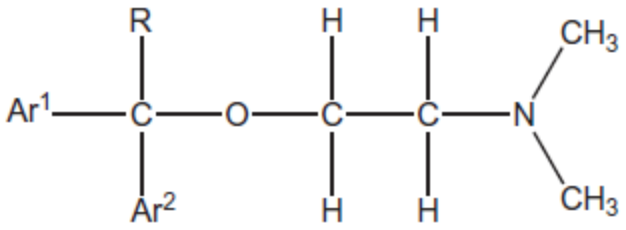
Phenbenzamine



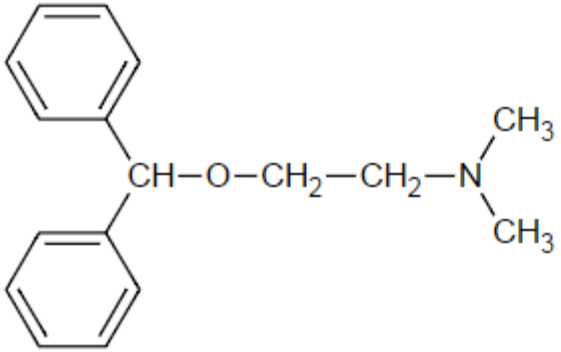
Pyribenzamine (Tripelenamine)

B) Ethanolamine Ethers or Aminoalkyl ethers

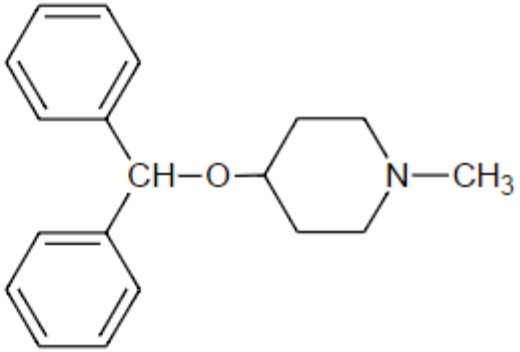
- Significant antimuscarinic side effects are observed among agents in this class.



General Structure

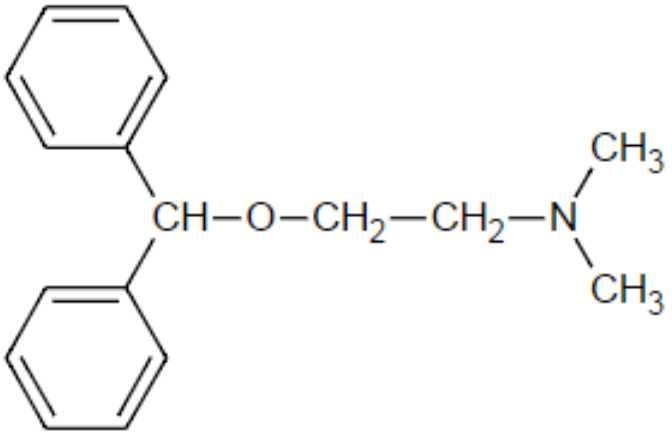


Diphenhydramine



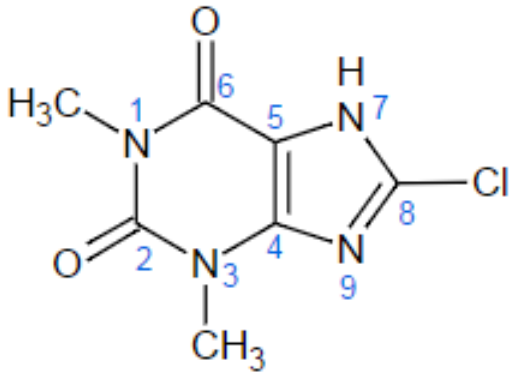
Diphenhylpyraline

- Diphenhydramine is the prototype of this class.
- It is used in treatment of Parkinsonism because of its central anticholinergic effect.



Diphenhydramine

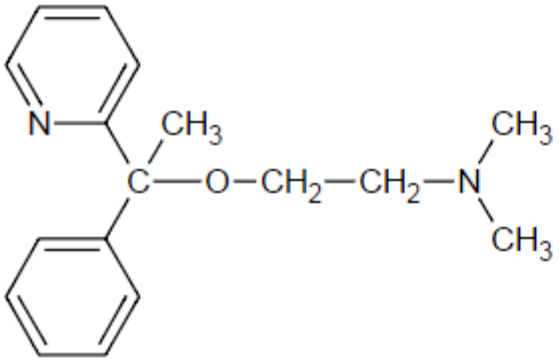
+



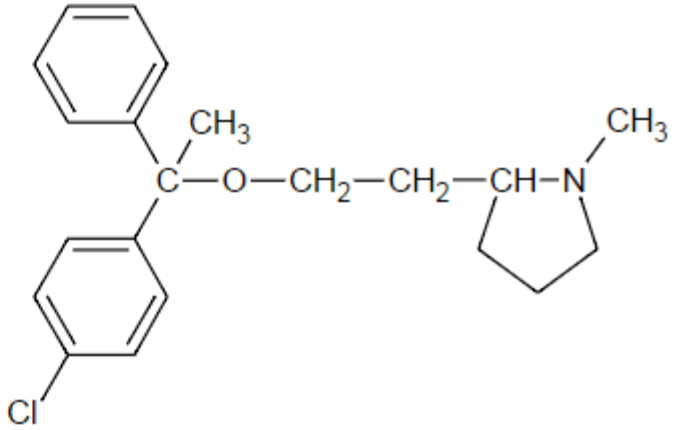
8-chlorotheophylline

Dimenhydrinate

- Dimenhydrinate is the combination of diphenhydramine and 8-chlorotheophylline.
- It is used for the treatment of motion sickness.
- 8-chlorotheophylline was added in order to counteract drowsiness caused by diphenhydramine.



Doxylamine

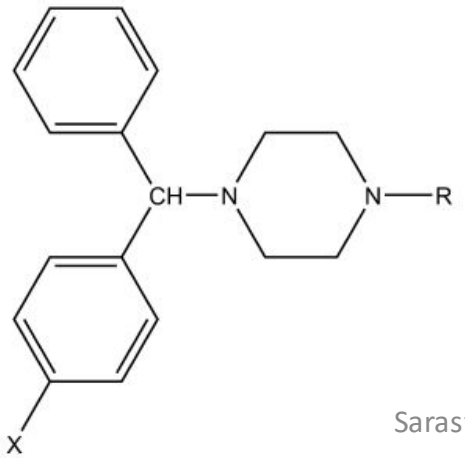


Clemastine

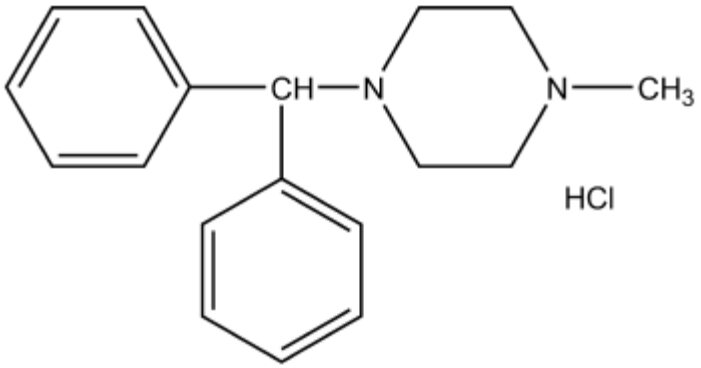
- In Clemastine, the spacer is three carbon chain.
- So it is not an ethanolamine ether but only an aminoalkyl ether.
- Amino group is incorporated into pyrrolidine ring using one carbon of spacer as a part of the ring.

C) PIPERAZINE (CYCLIZINE)

- The piperazines are moderately potent antihistaminics with a relatively high potential to cause drowsiness and psychomotor and cognitive dysfunction.
- The activity of the piperazine-type antihistaminics is characterized by a slow onset, but a long duration of action.
- Piperazine dervvatives act on the medullary chemoreceptor trigger zone.
- These agents have found significant use as antiemetics and antivertigo agents and in the treatment of motion sickness.
- Some members of this series have exhibited a strong **teratogenic potential (N-dealkylayed metabolites).**

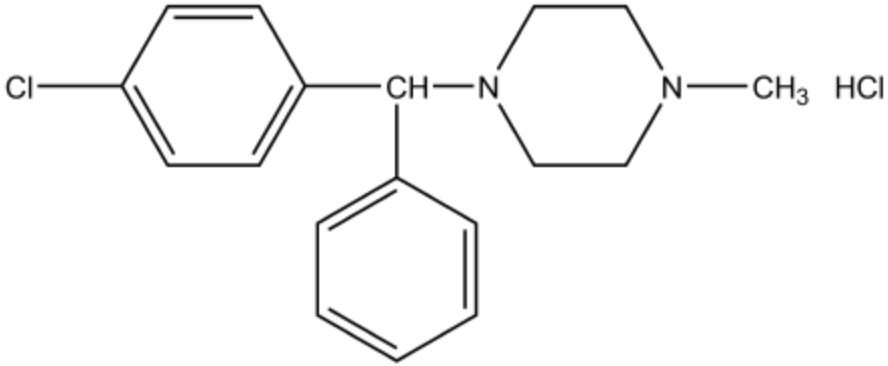


General structure of Piperazine as antihistaminic agents



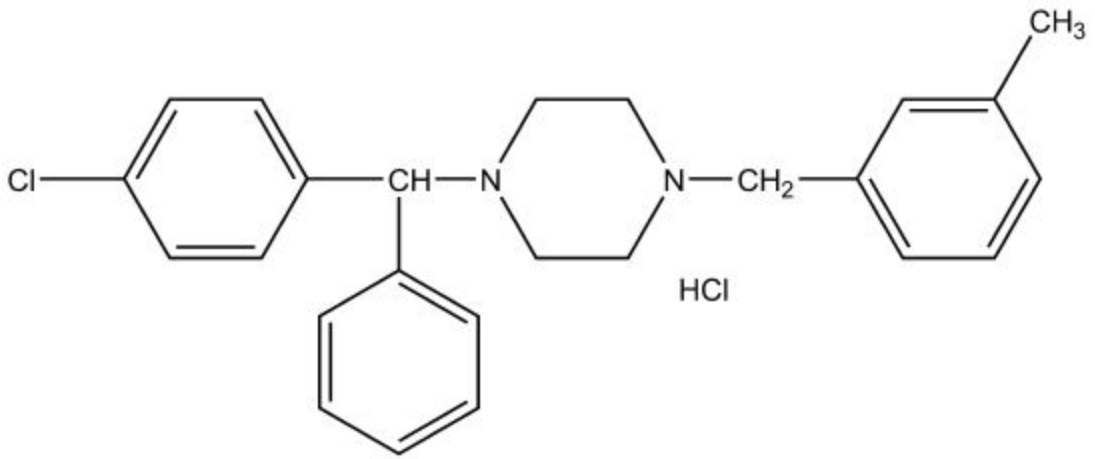
Cyclizine Hydrochloride or Lactate

1-(diphenylmethyl)-4-methylpiperazine



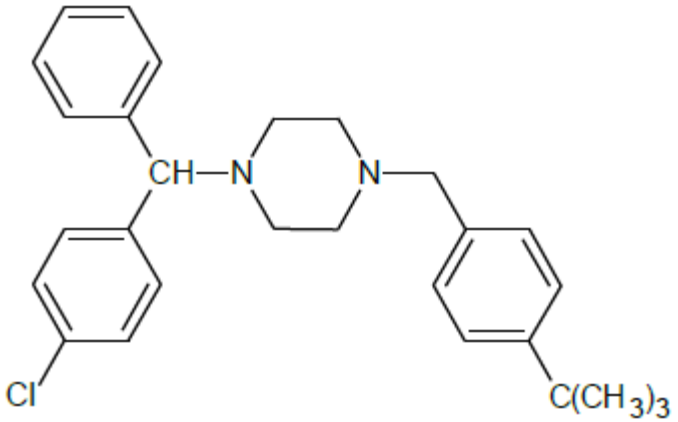
Chlorcyclizine Hydrochloride

1-(p-chloro-phenylbenzyl)-4-methylpiperazine



Meclizine Hydrochloride

1-(*p*-chloro--phenylbenzyl)-4-(*m*-methylbenzyl)piperazine

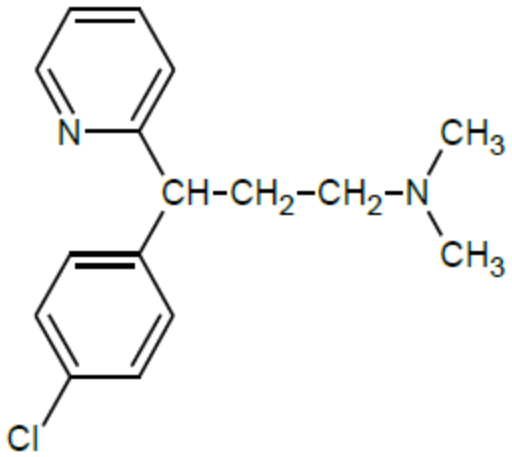


Buclizine

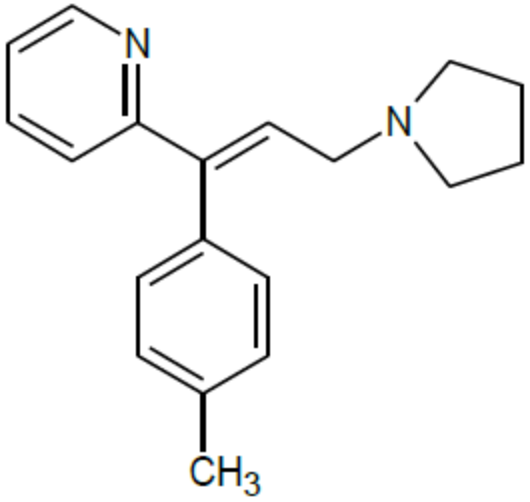
l-(*p*-tertbutylbenzyl)-4-(*p*-chloro--phenylbenzyl)piperazine

D) Alkyl Amines

These agents are characterized by a long duration of action and by a **decreased incidence of central sedative side effects** compared to the ethylenediamine and ethanolamine ether series.



Chlorpheniramine

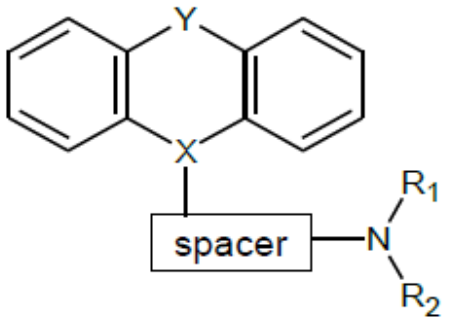


***E* - Triprolidine**

- IUPAC Name of Chlorpheniramine
  2-[p-Chloro-α-[2-(dimethylamino) ethyl] benzyl] pyridine
- Chlorpheniramine is widely used antihistamine for mild seasonal allergies.
- E-triprolidine is 1000 times more potent than its Z-isomer.

E) Tricyclic derivatives

The two aryl groups in the structure of antihistamines are bridged through a sulphur atom or through 2-carbon chain.



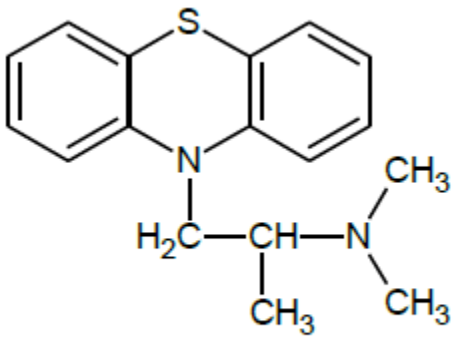
Y = S

X = C or N

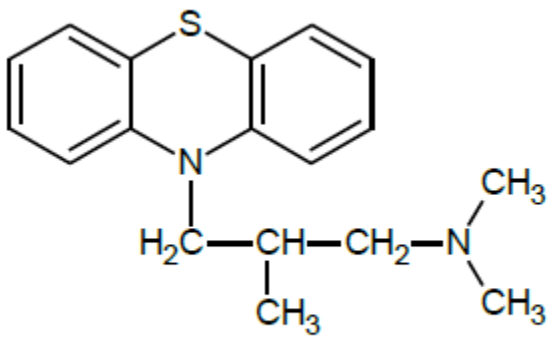
General Structure of tricyclic antihistamines

- The earliest potent tricyclic antihistamines were phenothiazines.
- Examples: Promethazine and Trimeprazine

a) Phenothiazine Type of Tricyclic Antihistamines



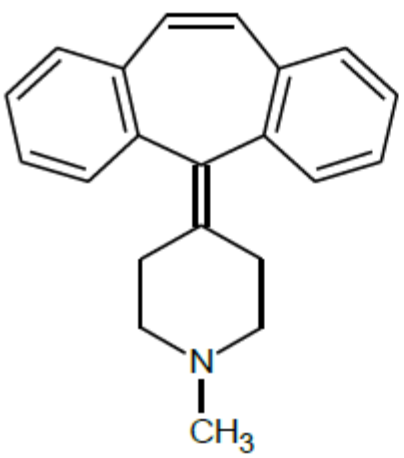
Promethazine



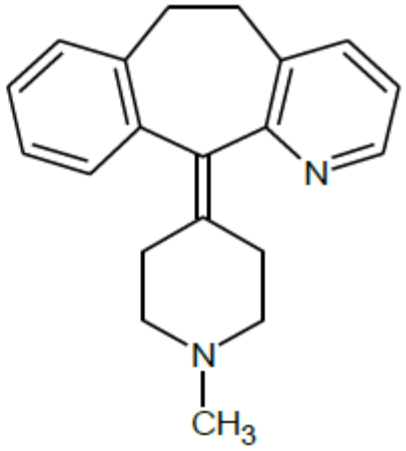
Trimeprazine

- **The antihistaminic phenothiazines contain a 2- or 3-carbon, branched alkyl chain as spacer. Whereas antipsychotic phenothiazines contain 3-carbon, unbranched alkyl chain as spacer.**
- Promethazine has significant antiemetic and anticholinergic properties. It also has sedative-hypnotic properties and has been used to potentiate the effects of analgesic drugs.
- Trimeprazine is used as antipruritic agents in the treatment of urticaria.

b) Other Tricyclic Antihistamines



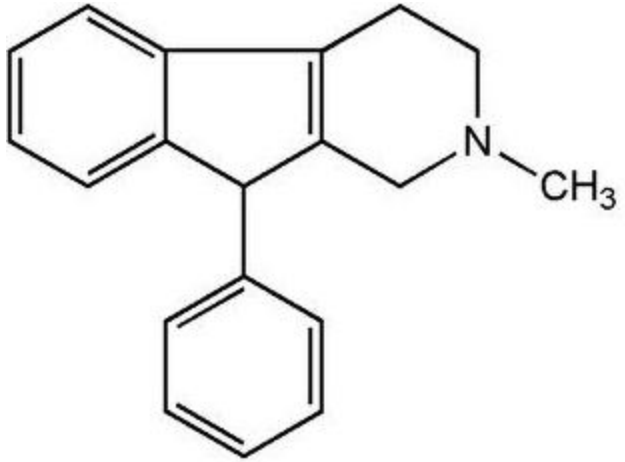
Cyproheptadine



Azatidine

- Cyproheptadine is an antihistamine used to relieve allergy symptoms such as watery eyes, runny nose, itching eyes, sneezing. It works by blocking a natural substance histamine that our body secretes during allergic reaction. This drug also blocks another natural substance serotonin.
- Azatidine is pyridine analogue of cyproheptadine. This drug has effects similar to cyproheptadine.

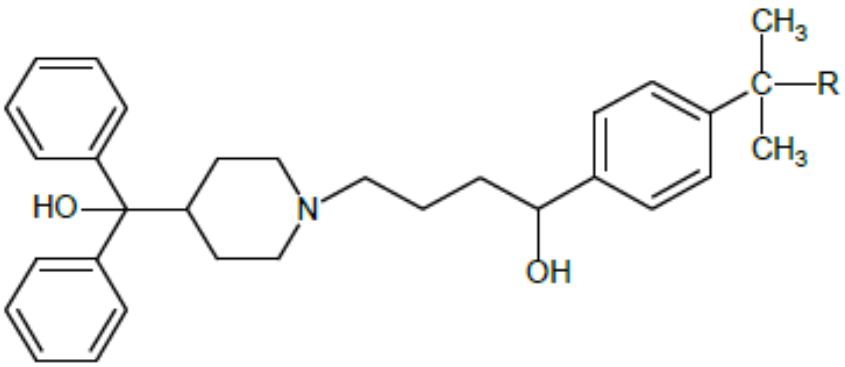
c) Miscellaneous Tricyclic Antihistamines



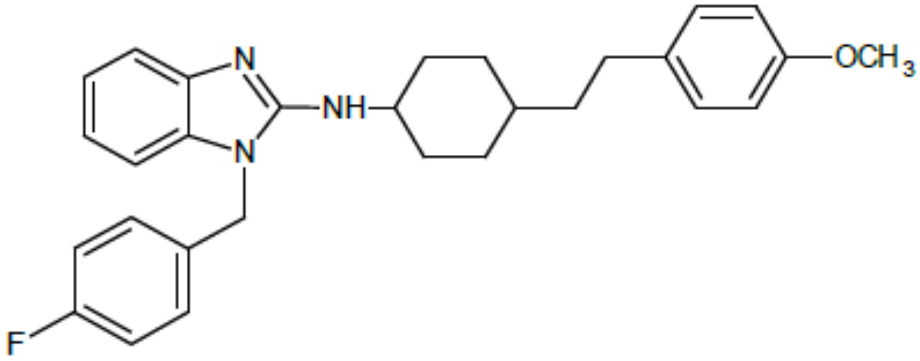
- Phenindamine is an indene.
- Phenindamine is an antihistamine. Phenindamine blocks the effects of the naturally occurring chemical histamine in human body.

Second Generation H_1-Antagonist (Non-Classical Antihistamines)

- They have improved H_1 selectivity in periphery and have little or no sedative effects.
- They usually have less anticholinergic, antiadrenergic and antiserotonergic activity.
- They vary widely in structure but less so in pharmacological properties.
- The parent drug or its active metabolites have sufficiently long half-lives to account for the long duration of action.
- Most of the drugs are administered once daily.
- Examples:
    a) Terfenadine
    b) Astemizole
    c) Loratidine
    d) Cetirizine

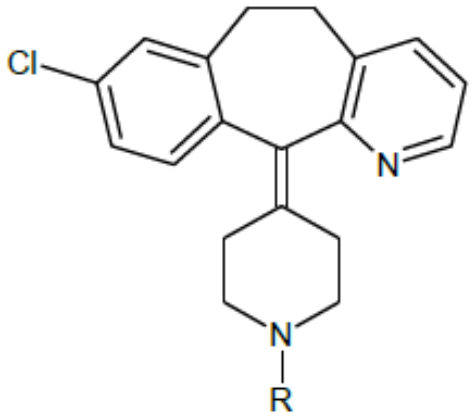


Terfenadine (R= -CH_3)
Fexofenadine (R= -COOH)



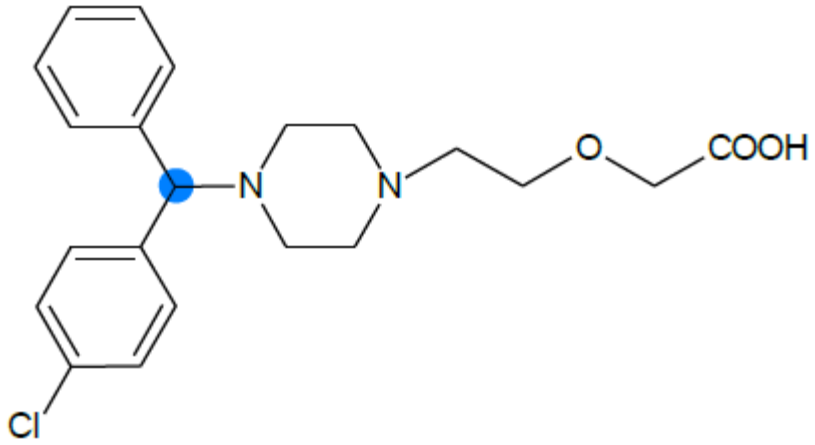
Astemizole

- Fexofenadine is acid metabolite of terfenadine.
- Terfenadine, fexofenadine and astemizole produce cardiac arrhythmias like cardiotoxic side effects.



Loratidine (R= -$COOCH_2CH_3$)
Desloratidine (R= -H)

- Loratidine and its metabolite desloratidine are devoid of cardiotoxic side effects.
- Desloratidine is more potent H_1 antagonist than loratidine.

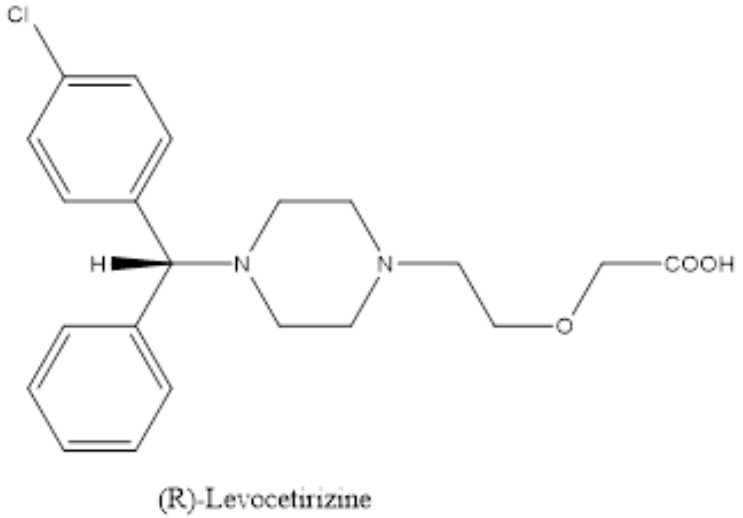


Cetirizine

- Cetirizine is acid metabolite of hydroxyzine (piperazine class of first generation H_1 antihistamines). It is widely used antihistamine.
- It is devoid of cardiotoxic side effects, but some drowsiness occurs.
- The Levo- isomer (Levocetirizine) has higher affinity than Dextro- isomer for the H_1 receptor. Thus, antihistaminic properties of cetirizine probably are accounted by its Levo-isomer.

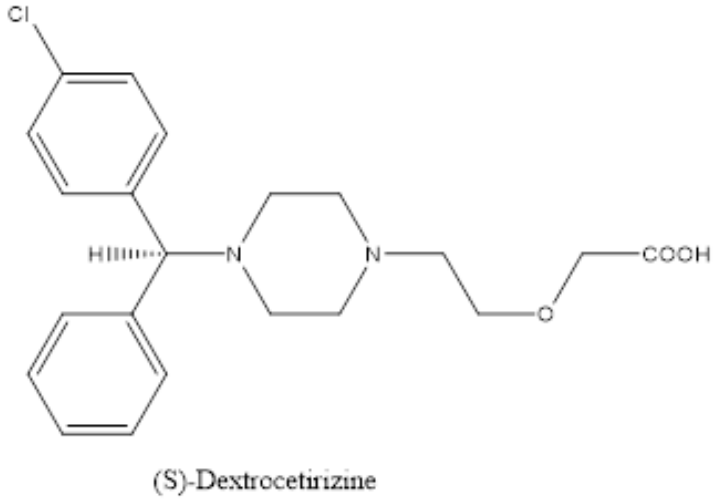
Third-generation H_1-antihistamines

They are second-generation antihistamines but labeled as third-generation because the active enantiomer (levocetirizine) or metabolite (desloratadine and fexofenadine) derivatives of second-generation drugs are intended to have increased efficacy with fewer adverse drug reactions.



(R)-Levocetirizine

Eutomer



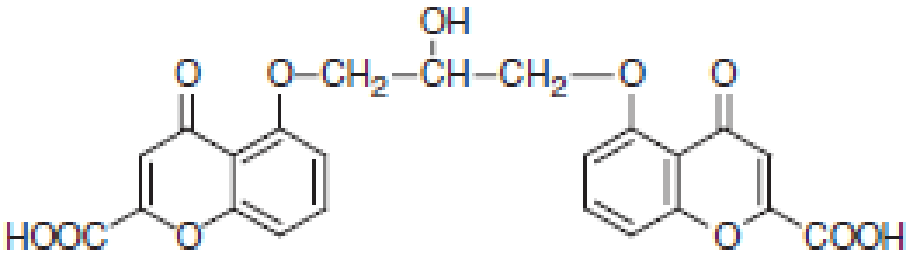
(S)-Dextrocetirizine

Distomer

The eutomer is the chiral enantiomer having the desired pharmacological activity, e.g., as an active ingredient in a drug. The distomer, on the other hand, is the enantiomer of the eutomer which may have undesired bioactivity or may be bio-inert.

Prevention of Histamine Release
Example: Cromonyl Sodium

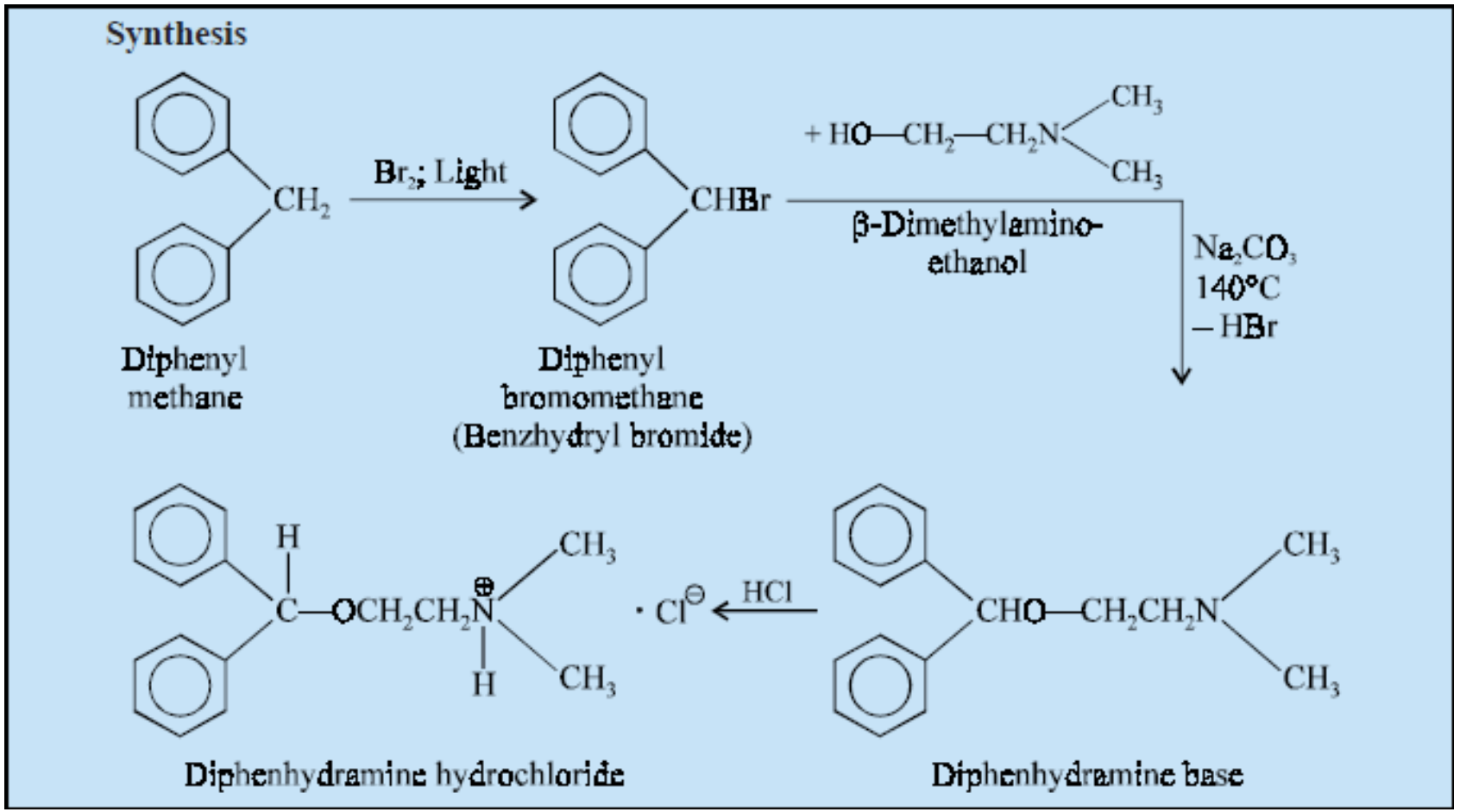
Sodium cromoglycate inhibits the release of histamine and SRS-A in allergic reactions. It is mostly employed in the prophylactic treatment of asthma.



It is used for bronchial asthma, as well as prevention of seasonal, constant, and physically caused asthma attacks and allergic rhinitis.

Synthesis of Diphenhydramine

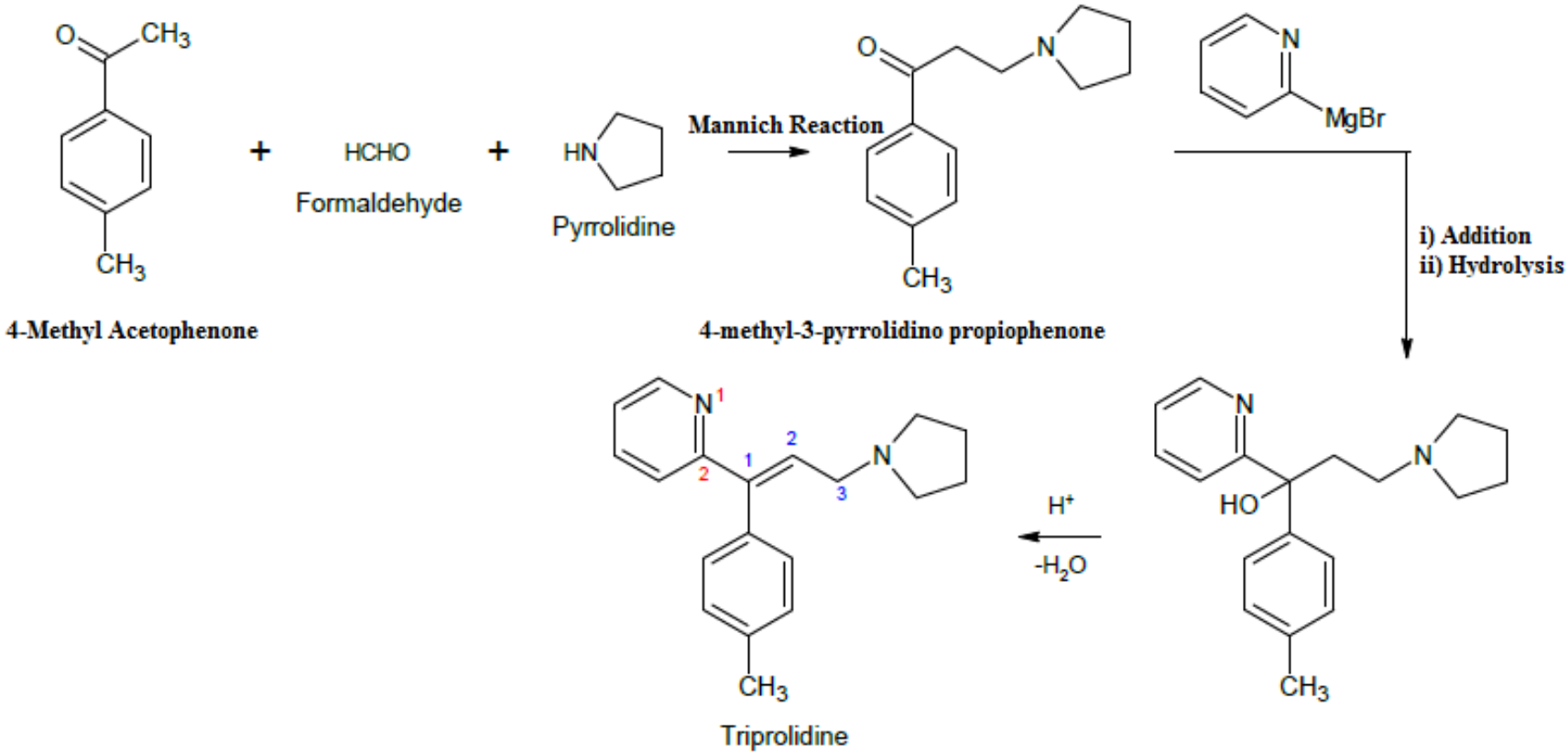
IUPAC Nomenclature: N,N-dimethyl-(diphenylmethoxy)ethylamine



Diphenhydramine is synthesized by the esterification of 2-dimethylaminoethanol with benzhydrylbromide

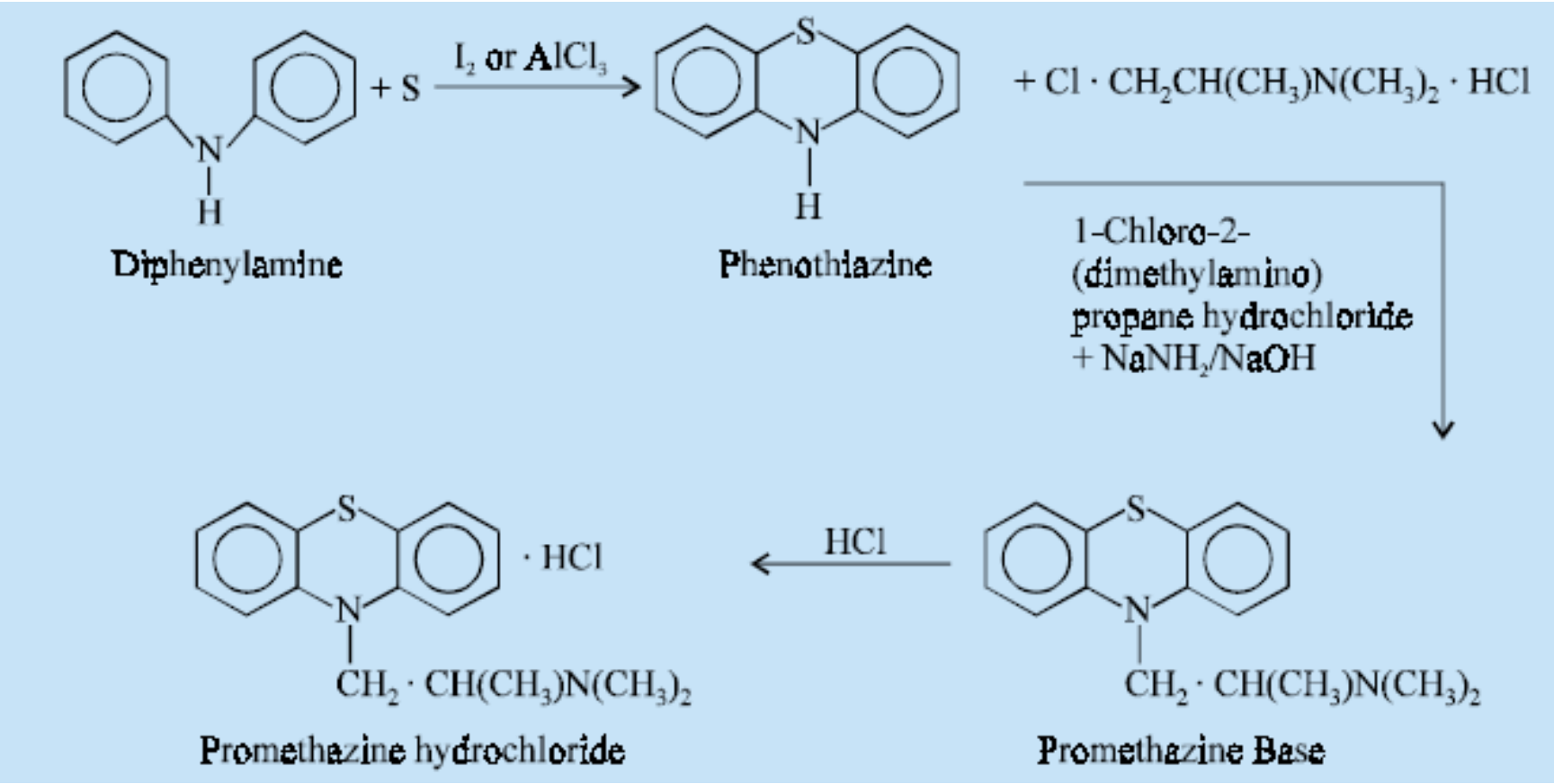
Synthesis of Triprolidine

IUPAC Nomenclature:
2-[(1E)-1-(4-methylphenyl)-3-(pyrrolidin-1-yl)prop-1-en-1-yl]pyridine



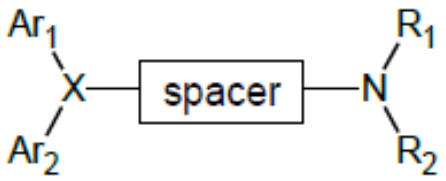
Synthesis of Promethazine

IUPAC Nomenclature:
10-[2-(Dimethylamino) propyl] phenothiazine monohydrochloride

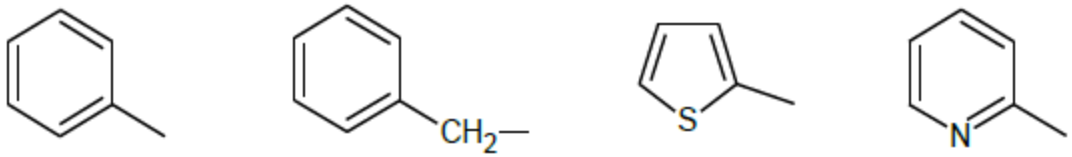


Structure-Activity Relationship of H_1-Antagonist

The large number of potent antihistaminic agents belong to various defined chemical categories. However, it is now possible to derive some important conclusions with respect to their structural requirements for optimal activity and pharmacological actions.



1) Two aromatic groups (Ar_1 and Ar_2) are linked through a short chain (spacer) to a tertiary aliphatic amine.
2) The aromatic groups usually are phenyl, benzyl, thienyl, or pyridyl.



Phenyl Benzyl Thienyl Pyridyl

3. For maximum activity the carbon-chain between the O and N atoms or the N and N atoms must be the ethylene moiety, i.e., $-CH_2CH_2-$. However, a long or branched chain combination gives rise to a less potent analog.

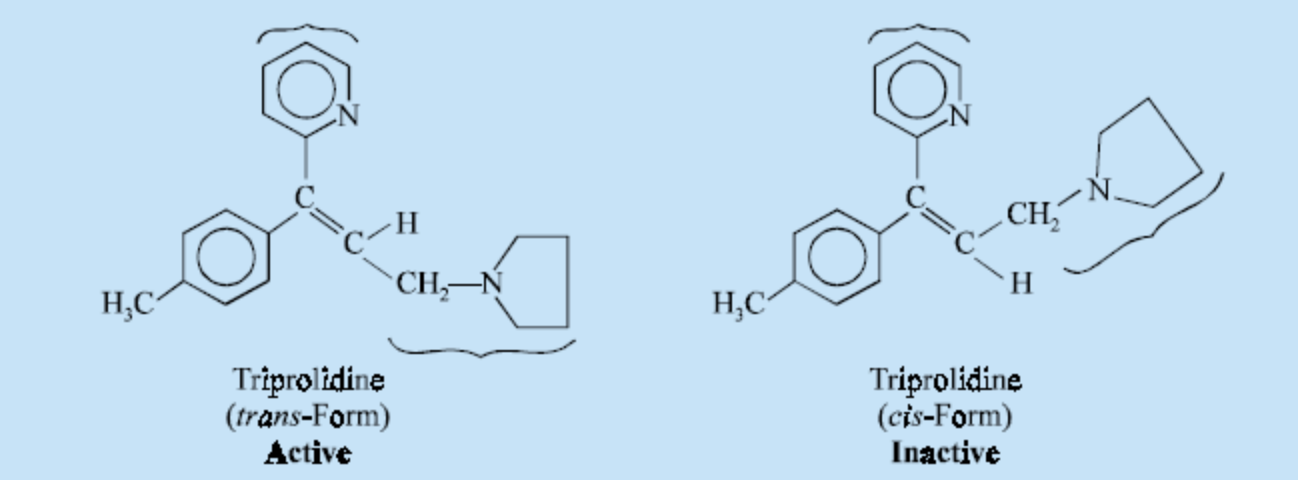
4. It is interesting to observe that in the promethazine hydrochloride molecule the two carbon chain is linked with an iso-propyl moiety, but the presence of the phenothiazine group might exert better therapeutic effect on the molecules as such.

5. Introduction of a halogen atom viz, Cl, Br at the para-position of the phenyl function improves the antihistaminic activity of the parent molecule, e.g., pheniramine compared with, chloropheniramine and brompheniramine.

6. Amongst the ethylenediamine analogs many potent compounds have evolved due to the inclusion of various groups on the second N of the chain. Such groups may be either heterocyclic aromatic rings.

7. The nucleus of an antihistaminic must bear a minimum of two alkyl or aryl functions or an equivalent embeded in a polycyclic ring.

8) Antihistaminics exhibiting optical isomerism revealed that the dextro-isomer supersedes the levo-in their potency, e.g., dexchlorpherniramine, dexbrompheniramine and E isomer in triprolidine



9) Introduction of basic-cyclic ring system by altering the position of dimethyl amino group also enhances the antihistaminic activity, e.g., cyclizine, chlorcyclizine, meclizine etc.