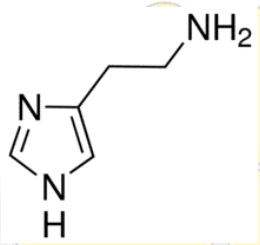
Chapter 1. Antihistamines

Syllabus:

- Histamine, Receptors, and their distribution in Human Body
- **H1R- Antagonists**: Diphenhydramine hydrochloride*, Dimenhydrinate, Doxylamine scuccinate, Clemastine fumarate, Diphenylphyraline hydrochloride, Tripelenamine hydrochloride, Chlorcyclizine hydrochloride, Meclizine hydrochloride, Buclizine hydrochloride, Chlorpheniramine maleate, Triprolidine hydrochloride*, Phenidamine tartarate, Promethazine hydrochloride*, Trimeprazine tartrate, Cyproheptadine hydrochloride, Azatidine maleate, Astemizole, Loratadine, Cetirizine, Levocetrazine Cromolyn sodium

1.1. HISTAMINE



2-(1H Imidazol-5-yl) ethyl amine

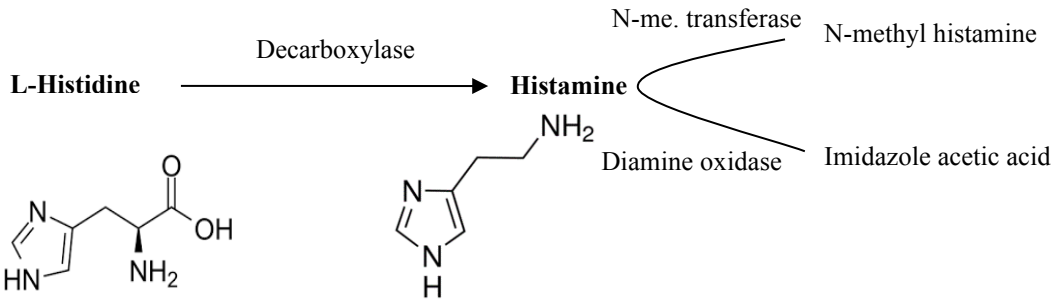
- It was first Identified by Barger and Dale in 1910 from plant fungus ergot and later in animal tissues (in 1911).
- In 20th century, Dale studied the allergic response of histamine.
- **Histamine** is an amine derivative autacoid also known as tissue amine, found in human, animals, and plants (Stinging Nettle)
- It is mainly stored in storage granules of the mast cells of skin, GI mucosa, lungs, liver, placenta (*slow turnover – synthesis and metabolism are slow), and in non-mast cells of neurons, epidermis, and vascular endothelial cells (*fast turnover – synthesis and metabolism are rapid).
- It is involved in local immune responses, as well as regulating various physiological function in the gut, vessels and smooth muscles, and acting as a neurotransmitter for the brain, spinal cord, and uterus
- Histamine receptors is classified into H1 R and H2 R in 1966 by Asch and Schild
- Sir James Black in 1972, showed the H2 blocking property of Burimamide
- In 1983, H3 R (auto receptor) was located in brain.

Physiological/Pharmacological Function

- **By H1-receptor**
  - Allergic & immunogenic Reaction
  - Contract the large vessels by IP3/DAG pathway and Dilation of small blood vessels by EDRF (NO)- dependent action
  - Smooth muscle contraction
  - Bronchoconstriction
  - Release the catecholamines
  - Neurotramsmi
- **By H2-Receptor**
  - Gastric acid secretion
  - Increase Cardiac Output and +chronotropic & +inotropic effects
  - Relaxation of uterus muscle
- **By H3 Receptor**
  - Decrease the release of histamine in brain and lungs, skin, and GI mucosa
  - Decrease the release of Acetylcholine in GI
  - Decrease the release of nordrenaline

Biosynthesis & Metabolism

- Hitamine is biosynthesised from L-histidine by the action of L-*histidine decarboxylase* and is stored within the mast cells and basophils along with the heparin-protein complex.



Classification of Histamine Receptors:

- H1 R: Inflammatory and Immune Response
- H2 R: Gastric Acid Secretions
- H3 R: Auto-receptor
- H4 R: Auto-receptor

Table 1.1. Histamine, Receptors, and their distribution in Human Body.

Molecule	Receptor	Pathways	Location	Agonist	Antagonist
Histamine	H1	GqPCR: activate IP3/DAG pathway	▪ Smooth muscles: intestine, bronchi, uterus, Blood Vessels ▪ Brain ▪ Ganglia ▪ Adrenal Medulla	2-methyl histamine, 2-pyridylethylamine	Mepyramine, Chlorpheniramine
	H2	GsPCR: activate cAMP/PKA pathway	▪ Stomach, ▪ Uterus, ▪ Heart	4-methylhistamine, Dimaprit, Impromidine	Ranitidine, Cimetidine, Famotidine
	H3	Gi/oPCR: inhibit cAMP/PKA, pathway activate K^+, and inhibit Ca^{2+} channel	▪ Brain	(R) α-methyl histamine, Imetit	Thioperamide, Clobenpropit,
	H4	Gq/iPCR: modulate IP3/DAG and cAMP/PKA pathways	▪ Brain	Clobenpropit, Imetit	JNJ777120

1.2. ANTIHISTAMINES

- These are the drugs which diminish or antagonize the actions of endogenously released histamine in the body (they do not prevent the formation of histamine).
- **Antihistamines are generally antagonists of H_1 receptor**.
- **These are used for the treatment of allergy and pruritis.**
- Antagonists of H_2 receptor are used to inhibit gastric acid secretion (treatment of peptic ulcer), however, antagonists of H_3 receptor are not used therapeutically.

Classification of Antihistamines (H1R-Blocker)

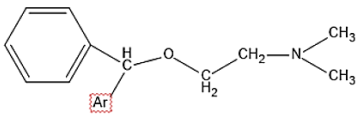
A. Based on Sedative Action

- H_1 antagonists are lipophilic, therefore, they cross blood brain barrier easily and produce sedation. Clinically H_1 antihistamines are classified into three categories depending on the use or degree of sedation they produce.

Sedative			Nonsedative	Antivertigo
Highly sedative	*Moderately Sedative*	*Mild Sedative*		
Diphenhydramine	Trimeprazine	Clemastine	Cetirizine	Cinnarizine
Dimenhydrinate	Meclizine	Methdilazine	Astemizole	
Promethazine	Buclizine	Chlorpheniramine	Terfenadine	
	Antazoline	Triprolidine		
	Pheniramine	Cyclizine		
	Cyproheptadine	Mepyramine		

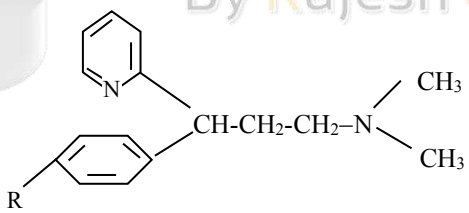
B. Based on Chemical Derivatives

1. **Amino alkyl ethers:** In addition to antihistamine property, drugs in this category possess anticholinergic property. Most active compounds have 2-carbon atom chain. These drugs are mainly used in motion and morning sickness as antiemetics.



Drugs: Diphenhydramine, Bromodiphenhydramine, Dimenhydrinate, Doxylamine, Clemastine

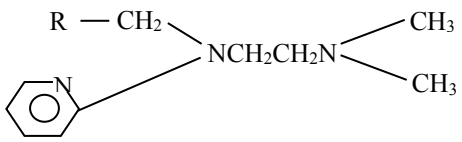
2. **Propylamines (Pheniramines):** Drugs in this category are chiral molecules, and mainly used in cold and cough



R = H Pheniramine
R = Cl Chlorpheniramine

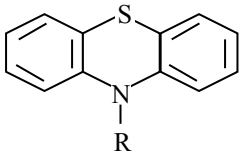
Drugs: Pheniramine, Chlorpheniramine, Triprolidine

3. **Ethylenediamine:** Mepyramine (Pyrilamine), Tripelennamine,



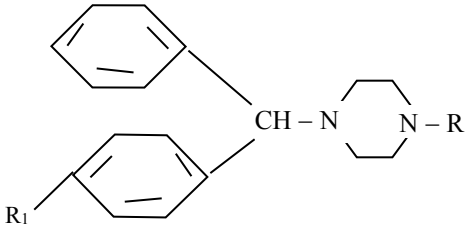
Mepyramine, R= $(CH_3\text{-}O\text{-}C_6H_5)$-; Tripelennamine, R= C_6H_5-

4. **Phenothiazines:** Used as antiemetics



Drugs: Promethazine, Methdilazine, Trimeprazine

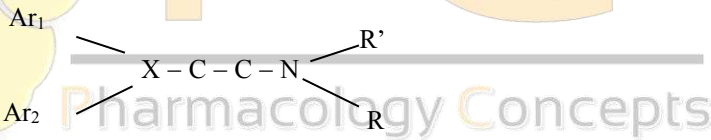
5. **Piperazines:** Cyclizine, Chlorcyclizine, Buclizine, Meclizine, Cinnarizine* (*antivertigo), Cetirizine$, l-cetirizine$ ($nonsedative antiallergic)



6. **Miscellaneous:** Cyproheptadine#, Azatadine#, (#Antiserotonin activity), Antazoline, Astemisole*, Terfenadine* (*Non sedative antihistamine)

Structure Activity Relationship (SAR) of H1 Blockers

Most of the H_1 antagonists have general structure:



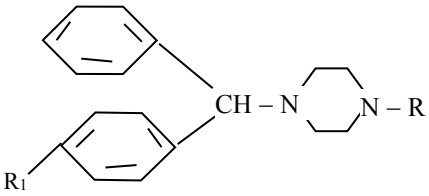
where Ar = Aryl group (phenyl, heterocyclic)

N-R- Basic terminal amino Alkyl group

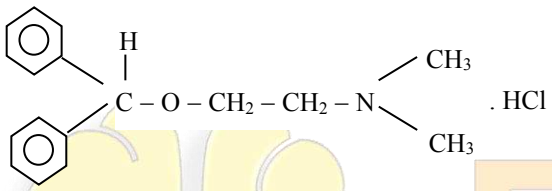
X= O, C, N

- **Aminoalkyl ethers** (X = saturated carbon-oxygen, CH-O-)
- **Propylamines** (X = carbon)
- **Ethylenediamine** (X = nitrogen)
- **Phenothiazines** (X = Bridged 2 aromatic rings)

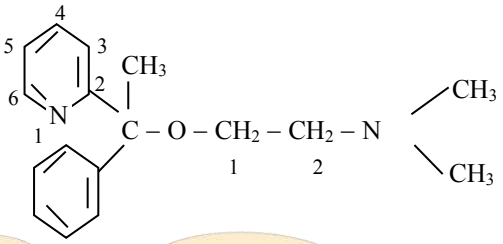
1. **Ethylene C-Chain**: Ethylene chain is required for maximum activity. Activity decreases by extention or branching of 2-aminoethyl side chain. E.g. **Piperazines** (Cyclazine, Chlorcyclizine)



2. **Nature of Aryl Groups:** Diaryl substituted is essemtial for H1 receptor affinity. Heterocyclic atom replaced to phenyl group may enhance the activity. E.g. Doxylamine

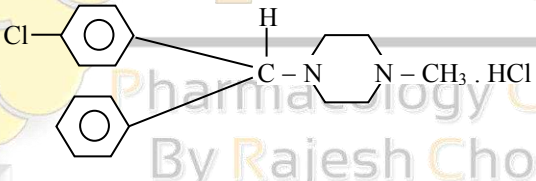


Diphenhydriamine



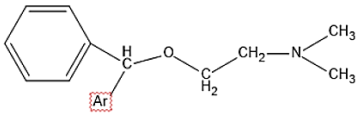
Doxylamine

3. **N-terminal**: Maximum activity is seen when the terminal atom is tertiary (N-atom may be part of a heterocyclic ring→ high potency e.g. Chlorcyclizine.

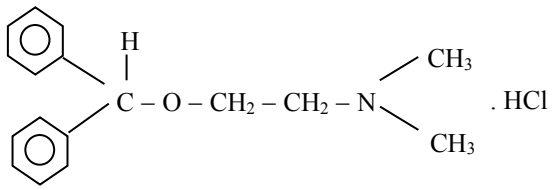


Medicinal Chemistry of Antihistamines

Aminoalkyl ethers



1. Diphenhydramine Hydrochloride,



2-(Diphenyl methoxy)-N, N-dimethyl ethyl amine hydrochloride

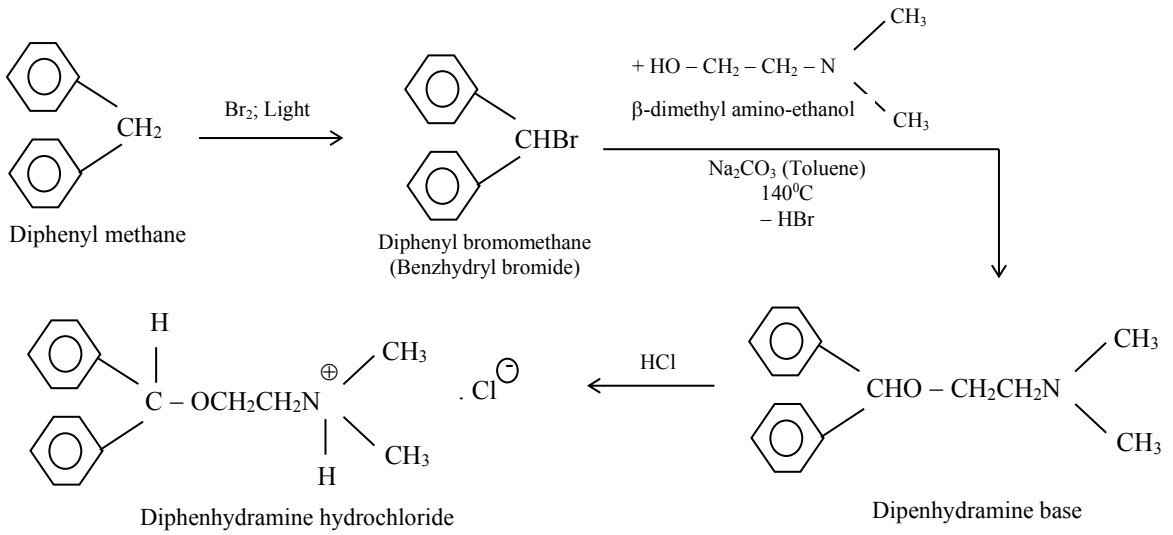
MAO: Peripheral and central H1 antagonist, also have antimuscarininic activity

** Central H1 antagonist shows sedation and have antimuscarininic activity*

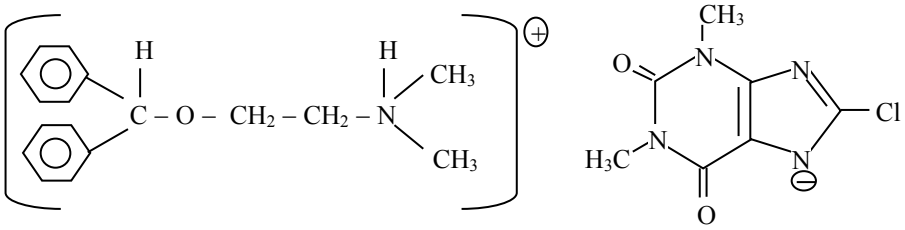
Uses:

- ✓ Allergy (urticaria, conjunctivitis, pruritic and rhinitis).
- ✓ Insomnia (due to sedation effects)
- ✓ Motion sickness (due to anticholinergic effcts)
- ✓ Parkinsonism (due to centrally anticholinergic effects)

Synthesis:



2. Dimenhydrinate



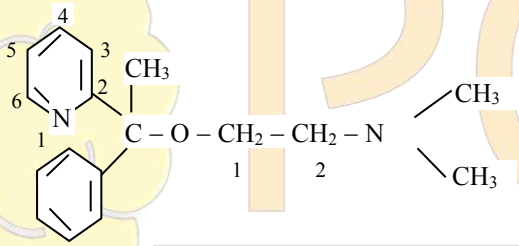
8-Chlorotheophylline, compound with 2-(diphenylmethoxy)-N, N-dimethyl-ethylamine (1:1)

MAO: H1 antagonist mainly vestibular system in the brain.

Uses:

- ✓ Used to treatment of nausea and vertigo caused by Meniere's diseases.
- ✓ In ear congestion.
- ✓ Primarily used to treat nausea, vomiting, and dizziness caused by motion sickness.

3. Doxylamine



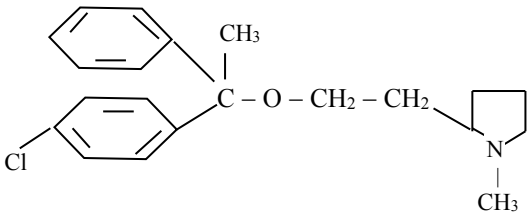
2-[α-(2-dimethyl amino ethoxy) α-methyl benzyl]-pyridine

MAO: H1 antagonist mainly

Uses:

- ✓ Antiemetic in pregnancy.
- ✓ Allergy and cold.
- ✓ Used as a short-term sedative
- ✓ Used along with paracetamol and codeine as an analgesic.

4. Clemastine



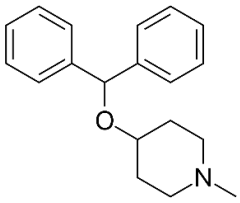
2-{2[1-(4-chlorophenyl)-l-phenylethoxy] ethyl} l-methyl-pyrrolidine

MOA: H1 antagonist and also having anticholinergic activity

Uses: Used in treatment of allergy, hay fever and cold.

Piperidine derivative

5. Diphenyl pyraline hydrochloride



4-benzhydryloxy-1-methyl piperidine

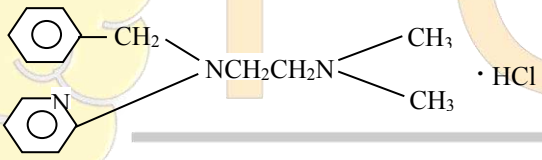
MOA: H1 antagonist and also having anticholinergic activity.

Uses:

- ✓ Used in treatment of allergy, hay fever, rhinitis, and pruritic
- ✓ Used as teoclate salt (piprinhydrinate) as an intgredient in the preparation of releaf of cough and common cold.
- ✓ Also useful in Parkinson disease

Ethylenediamines

6. Tripelenamine hydrochloride



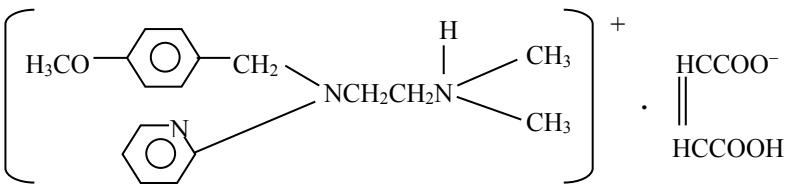
2-[Benzyl[2-(dimethylamino) ethyl] amino] pyridine monohydrochloride

MOA: H1 antagonist and also having anticholinergic activity and weak serotonin, noradrenaline, and dopamine reuptake inhibitor

Uses:

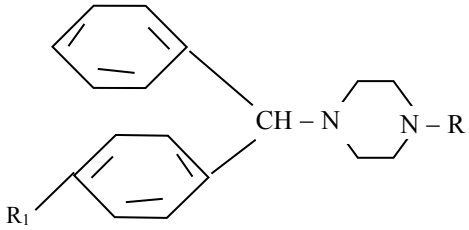
- ✓ Used in treatment of upper repiratory tract allergic condition like asthma, hay fever, rhinitis, and urticaria.
- ✓ Used in expectorant and decongestant formulation
- ✓ Also useful in Parkinson disease

7. Mepyramine Maleate, Pyrilamine Maleate, Mepyramine



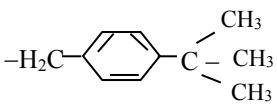
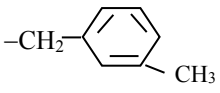
2-[[(2-(Dimethylamino) ethyl] (*p*-methoxybenzyl) amino] pyridine maleate (1:1)

Piperazines: Drugs of this category have **antiemetic activity** in addition to **antihistamine activity**. These drugs have slow onset but long duration of action.

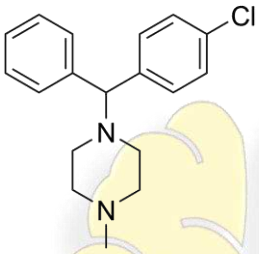


Diphenyl-methyl-piperazine derivatives

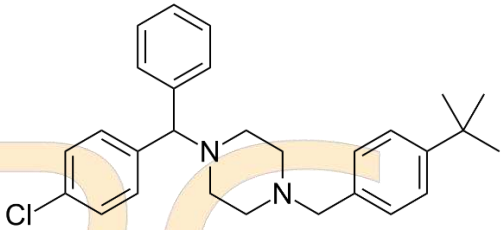
General structure of piperazine antihistamines

Compound	R1	R	Name	MOA & Uses
8. Cyclizine	-H	$-CH_3$	1-(diphenyl methyl)-4-methyl-piperazine	▪ Used in treatment of allergy, hay fever, rhinitis, and pruritic skin disease ▪ Antiemetic
9. Chlorcyclizine	-Cl	$-CH_3$	1-(p-chlorophenyl benzyl)-4 methyl-piperazine	▪ Anti-Histamines, AntiAch & Anti-5HT property ▪ Used in treatment of allergy, hay fever, rhinitis, and pruritic skin disease ▪ Antiemetic ▪ Local anesthetic property
10. Buclizine	-Cl		1-(p-chlorophenyl benzyl)-4 -(p-tert-butyl benzyl) piperazine	▪ Anti-Histamines, AntiAch property ▪ CNS depressant (high lipid soluble) ▪ Antivertigo
11. Meclizine	-Cl		l-(p-chlorophenyl benzyl)-4-(m-methylbenzyl) piperazine	▪ Anti Histamines, AntiAch & Anti-DA property ▪ Used in pruritic skin disease ▪ Long lasting Antiemetic effects ▪ Used for treatment of nausea and motion sickness or vertigo

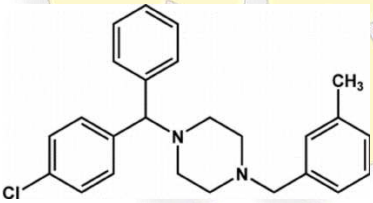
12. Cinnarizine	-H	– CH_2–CH=CH– 	1-(diphenyl methyl) 4-(3-phenyl-2-propenyl)-piperazine	▪ Anti-Histamines, AntiAch ▪ Antivertigo
13. Cetirizine (S, d-isomer) **14. Levocetirizine (R, l-isomer)**	-Cl	–CH_2–CH_2–O–CH_2.COOH	([2-[4[(4-chlorophenyl) benzyl] 1-piperazinyl] ethoxy])-acetic acid	▪ **Non-sedative anti Histamines** ▪ Used to relieve allergy symptoms like runny nose, itching, sneezing, etc. ▪ Common cold and cough



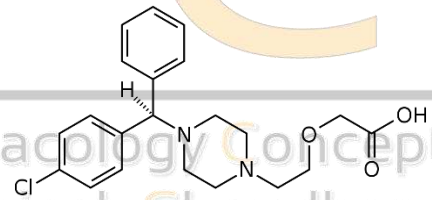
Chlorcyclizine



Buclizine



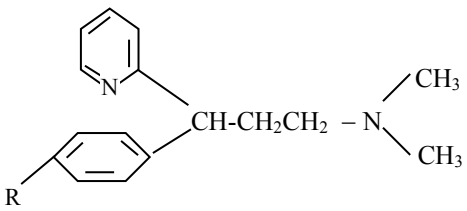
Meclizine



Levocetirizine

Propylamines (Pheniramines): Drugs in this category are chiral molecules.

15. Chlorpheniramine



R = H Pheniramine

R = Cl Chlorpheniramine

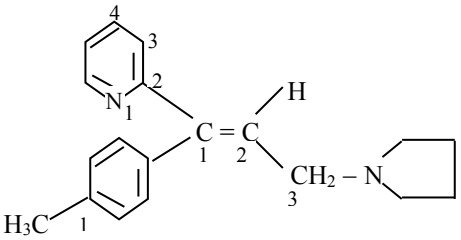
(±) 2-[1-(p-chlorophenyl)-3-dimethylamino) propyl)]-pyridine.

MOA: H1 antagonist

Uses:

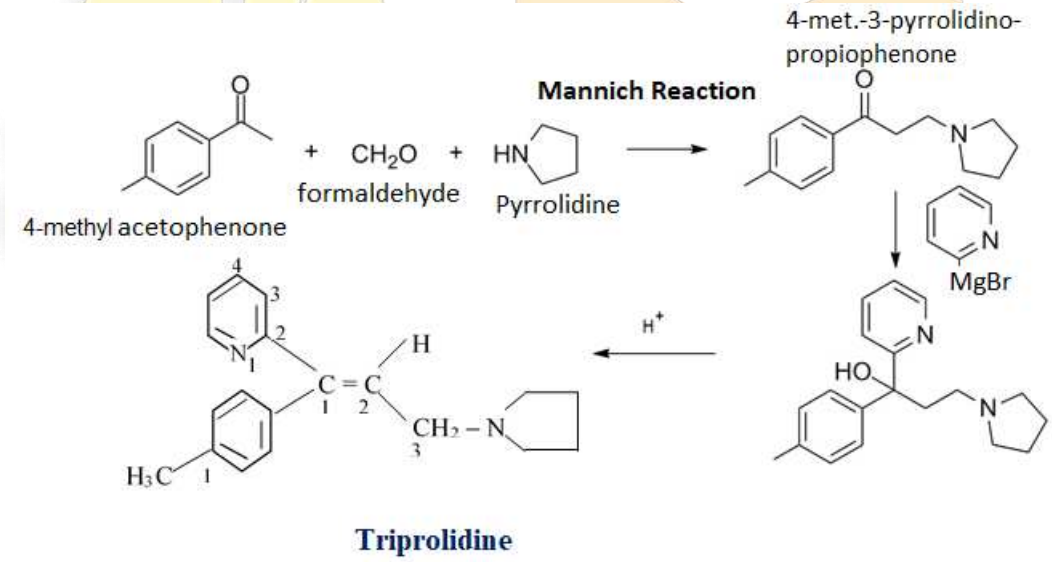
- ✓ Used in common cold and cough.
- ✓ Used along with phenylpropalamine for the treatment of allergy and decongestant
- ✓ Combination with hydrocodone (narcotic), used for cough and respiratory tract allergy.

16. Triprolidine



(±)-2-[3-(l-pyrrolidinyl)-l-p-tolylpropenyl] pyridine

Synthesis:

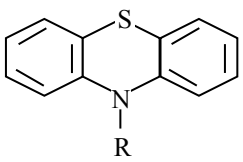


Triprolidine

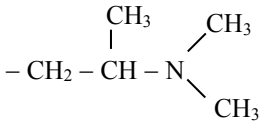
MOA: H1 antagonist

Uses: Used to control the symptoms of common cold, allergy, and flu

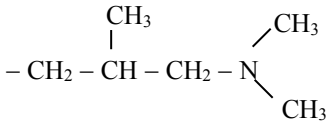
Phenothiazines



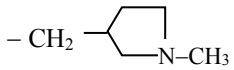
Promethazine:



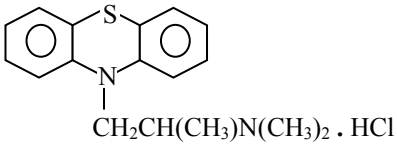
Trimeprazine:



Methdilazine:

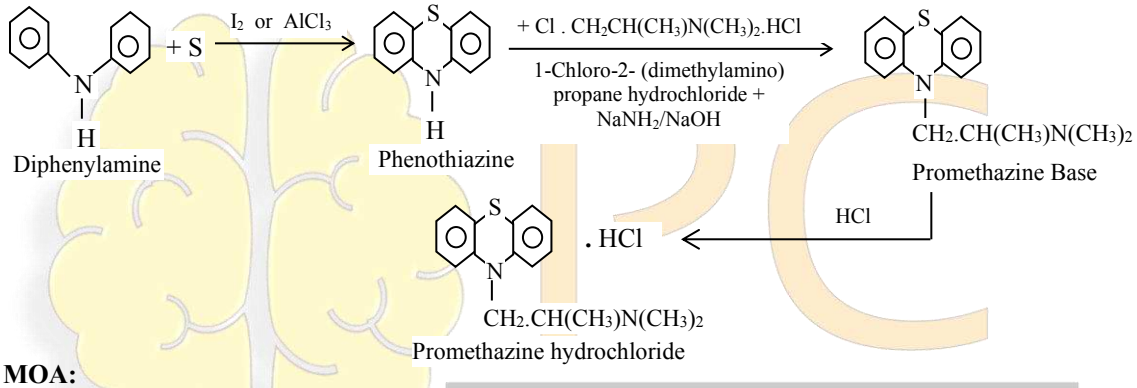


17. Promethazine hydrochloride



(±) 10-[2-(Dimethylamino) propyl] phenothiazine monohydrochloride

Synthesis:



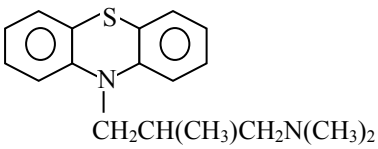
MOA:

- ✓ H1 antagonist and also have moderate anticholinergic activity
- ✓ It also shows weaker antagonistic activity on dopamine, 5HT, and alfa-1 receptor

Uses:

- ✓ Used in insomnia due to sedative action
- ✓ Used mainly in motion sickness.
- ✓ In allergic conditions.
- ✓ Used along with codeine to treat cough.

18. Trimeprazine



(±) 10-[3-dimethylamino-2-methyl propyl] phenothiazine

MOA: H1 antagonist and similar to promethazine

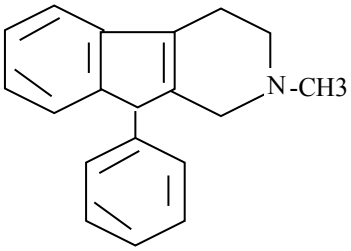
Uses:

- ✓ It acts as sedative-hypnotocs and antiemetic for motion sickness.

- ✓ In allergic conditions (pruritic)
- ✓ In Russia, it is also used in anxiety and mood disorders

Other Derivatives

19. Phenindamine

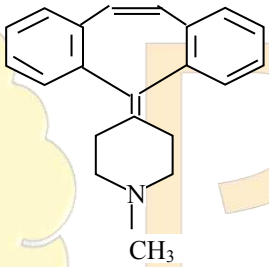


2, 3, 4, 9-tetrahydro-2-methyl-9-phenyl-1H-indeno-[2,1c] pyridine

MOA: H1 antagonist

Uses: Used to relieve allergy symptoms like runny nose, itching, sneezing, etc.

20. Cyproheptadine



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

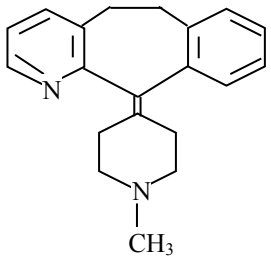
MOA:

- ✓ H1 antagonist and **Antiserotonergic** activity
- ✓ It also shows anticholinergic, antidopaminergic

Uses:

- ✓ In allergy
- ✓ **Used for increase appetite and weight gain**
- ✓ In migraine and movement disorders
- ✓ Antiemetic in cyclic vomiting syndrome

21. Azatadine



6,11-dihydro-11-(1-methyl piperid-4-ylidene)-5H-benzo[5, 6] cyclohepta [1, 2b] pyridine

MOA: H1 antagonist and **Antiserotonergic** activity

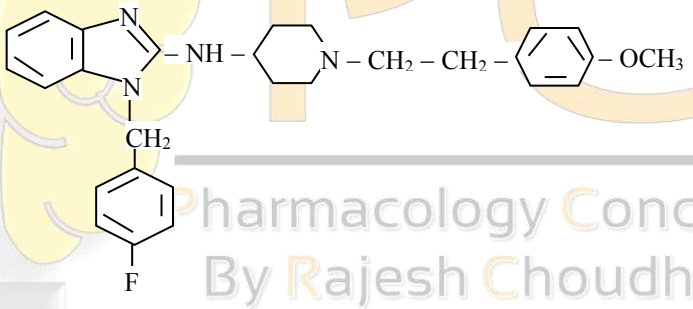
Uses: Used in upper respiratory mucosal decongest in allergy rhinitis condition.

Second Generation Non-Sedative Antihistamines

- These are the selective peripheral H1 receptor antagonist unlike the sedative 1st generation antihistamines, which also antagonise the centrally histaminergic and cholinergic action.
- Astemizole and Terfinadine were developed with larger N-tertiary amine substituents and produces serious cardiovascular side effects like arrhythmia. Terfinadine produces Torsades Depoint (arrhythmia).
- Later newer agent like Cetirizine, Levocetirizine, Rupatidine (also have PAF Antagonist), triprolidine, etc. were developed
- These drugs are used as antiallergy in cold, cough, and rhinitis condition, antivertigo, and preanesthetic medication.

Chemistry of Cetirizine and Levocetirizine are discussed above

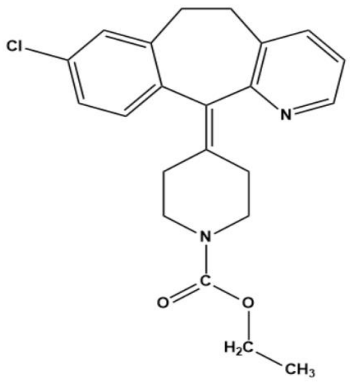
22. Astemizole



1-[(4-fluorophenyl)methyl]-*N*-[1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl]benzimidazol-2-amine

***No use longer due to cardiotoxicity**

23. Loratidine



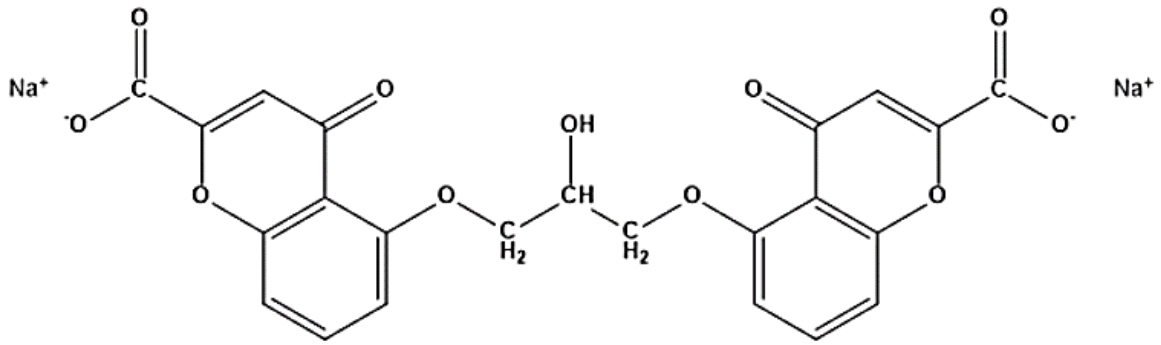
Ethyl 4-(8-chloro-5, 6-dihydro-11 H-benzo [5,6] cyclohepta [1,2-b] pyridine-11ylidine)-1-pipradine carboxylate

Uses: Used in rhinitis, pruritic, urticaria, and erythema single or in combination with pseudoephedrine.

MAST CELL STABILIZER

- These are the drugs, which stabilize the mast inhibit the degranulation and release of histamines and other inflammatory mediators like prostaglandins and leukotriens.
- These are the used in allergy and asthma

24. Cromolyn Sodium



1,3 bis (2-carboxychromon-5yl oxy)-2-hydroxy propane disodium salt

Uses:

- ✓ Nabulized cromlyn sod. used in the management of bronchial asthma and bronchospasm.
- ✓ Nasal solution for allergic rhinitis.
- ✓ Eye drops are used to treat allergy conjunctivitis and keratitis
- ✓ Also used in histamine related symptoms like flushing, vomiting, urticaria, and itching.

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