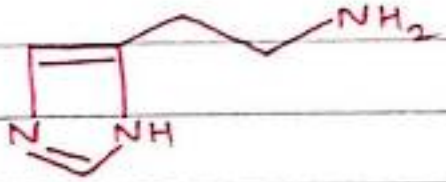
Unit - Ist

Antihistaminics Agents

Histamine is an amine that is produced as part of a local immune response to cause inflammation.

It also performs several important functions in the bowel and acts as a neurotransmitter (Chemical Messenger) that carries signals from one nerve to another.

Histamine, 4(5) - (2-Aminoethyl) - Imidazole



M.f = $C_5H_9N_3$

M.w = 111.15 g/mol

*Histamine is an amine derived of by enzymatic decarboxylation of histidine

Histidine is an alpha-amino acid with an imidazole functional group moiety. Most important "Histidine" is a precursor for histamine Synthesis.

Histamine is a major mediator of allergic and inflammatory processes.

Histamine is a member of the class of imidazoles that is 1H-imidazole substituted at position C-4 by a 2-aminoethyl group.

- Histamine is mainly found in many tissues including mast cells, basophils, lymphocytes, neurons and get widely distributed in connective tissues.

- It is an autacoid - Is a molecules secreted locally to increase or decreases that activity of nearby cells.

Histamine Receptors →

There are four types Histamine Receptors :-

	Receptor	location
(i)	H_1 →	Nasal mucosa, lung lymphy lymphocytes, monocytes neurons, gastric mucosa heart, CNS
(ii)	H_2 →	Gastric mucosa, lung, uterus heart, CNS
(iv)	H_3 →	Central and peripheral nervous system, GI tract, autonomic nerve terminals

H_4 → Hematopoietic Cells, Colon, heart lung, thymus, spleen, small bowel.

Pharmacological effects -

H_1 Histamine :- its release exerts effect on smooth muscles and glands by interacting with receptors.

H_1 receptors and H_1 Histamine interaction / interaction results in bronchoconstriction, contraction of gut vasodilation and increased vascular permeability H_1 Histamine is also involved in vomiting through its action on CNS.

H_2 Histamine :- Gastric acid Secretion, Vascular Permeability, hypotension, headache tachycardia, broncho-dilation and respiratory mucus production and therapeutically used as anti-ulcer drugs.

H_3 Histamine :- Adrenaline relay and autoreceptor of Histamine in CNS.

H_4 Histamine :- Differentiation of hematopoietic Cells.

HISTAMINE ANTAGONISTS

Drugs that inhibits or block the actions of histamine and its release.

"Antagonist" means, It is a type of receptor ligand or drug that blocks or inhibit the biological response by binding to and blocking a receptor, function opposite to an agonist.

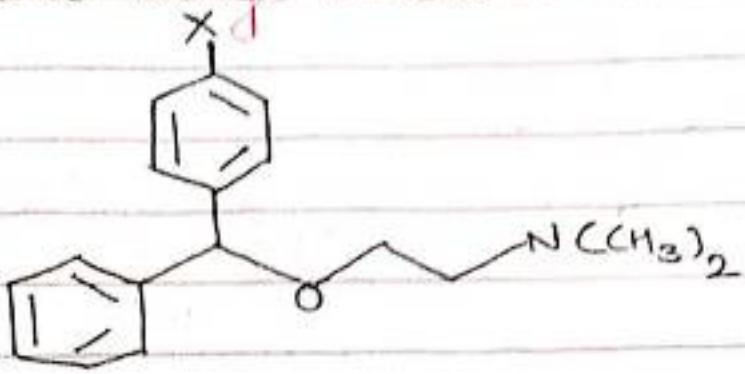
* Mechanism of Action *

The primary mechanism is to specific bind to ~~Cellular~~ Cellular receptor (H_1 receptor), which are present on nerve endings, smooth muscles and glandular cells to useful in treatment of allergic diseases, nausea and Vomiting.

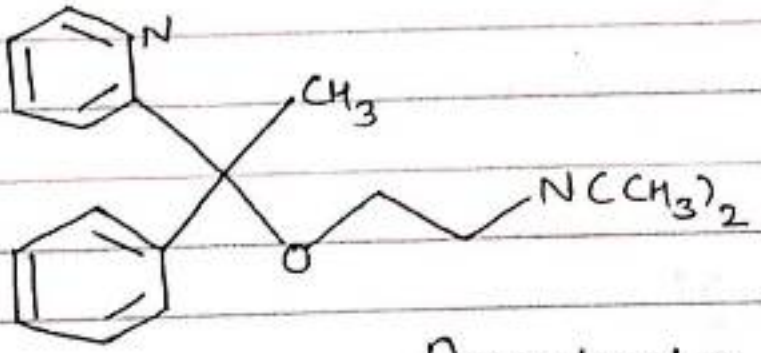
" Classification of H_1 Antagonist "

1) first Generation Drugs :-
   - Amino Alkyl ethers
   - Ethylenediamine derivatives
   - Propyl amine derivatives
   - Phenothiazine derivatives
   - Piperazine derivatives

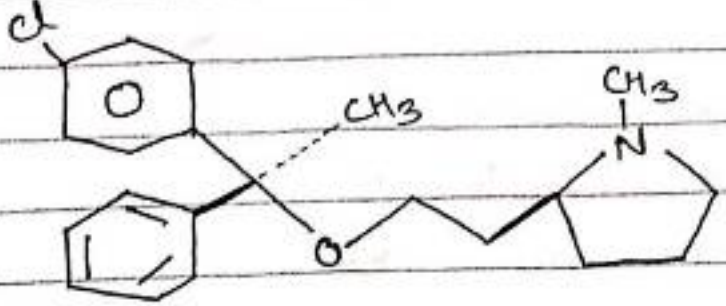
- Amino Alkyl Ethers (Ethanolamines)



Diphenhydramine X = H
Chlorodiphenhydramine X = Cl
Bromodiphenhydramine X = Br

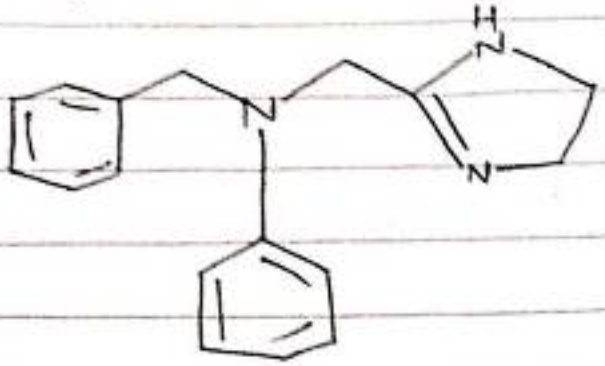


Doxylamine

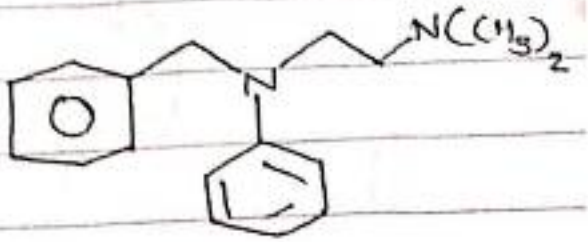


Clemastine

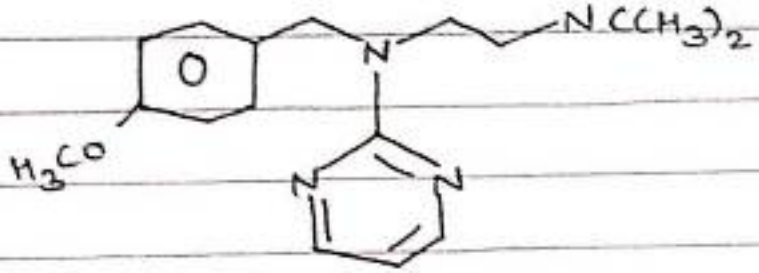
- Ethylenediamines



Antazoline

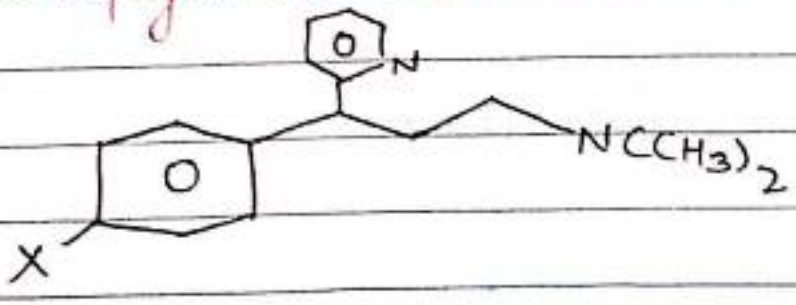


Phenbenzamine



Thonzylamine

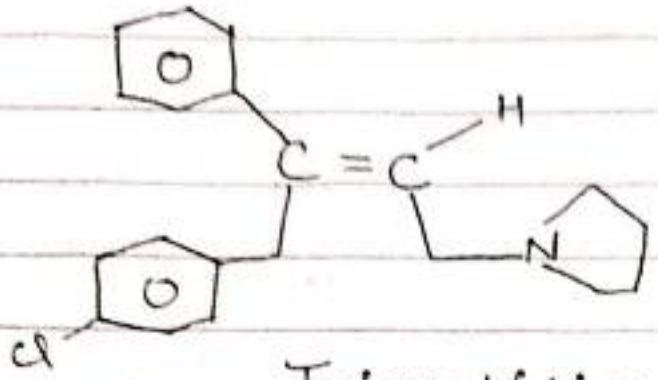
- Propylamines derivatives



Pheniramine X = H

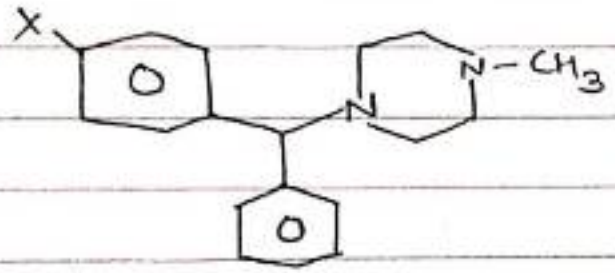
Chlorpheniramine X = Cl

brompheniramine X = Br



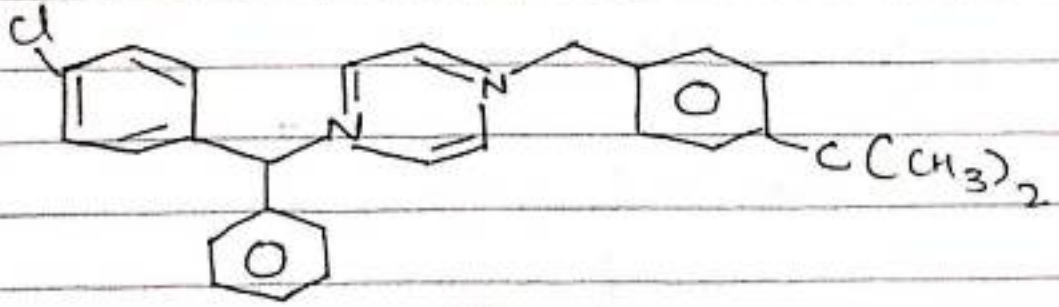
Triprolidine

- Piperazines derivatives



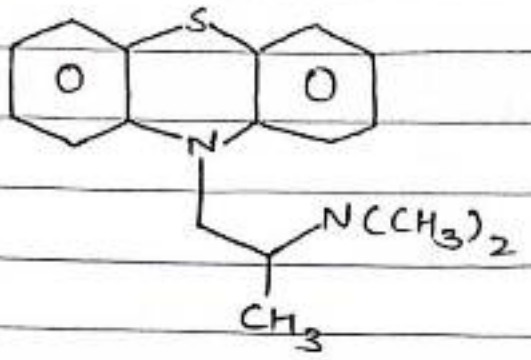
Cyclizine X = H

Chlorcyclizine X = Cl

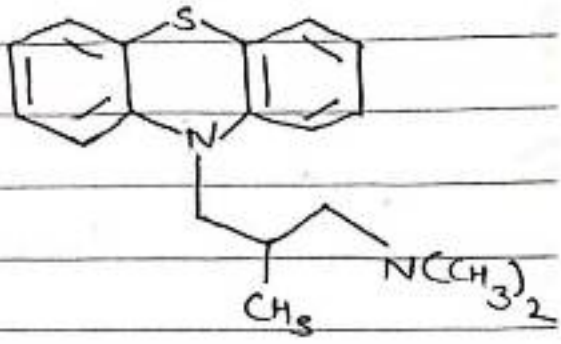


Buclizine

- Phenothiazine Derivatives:-

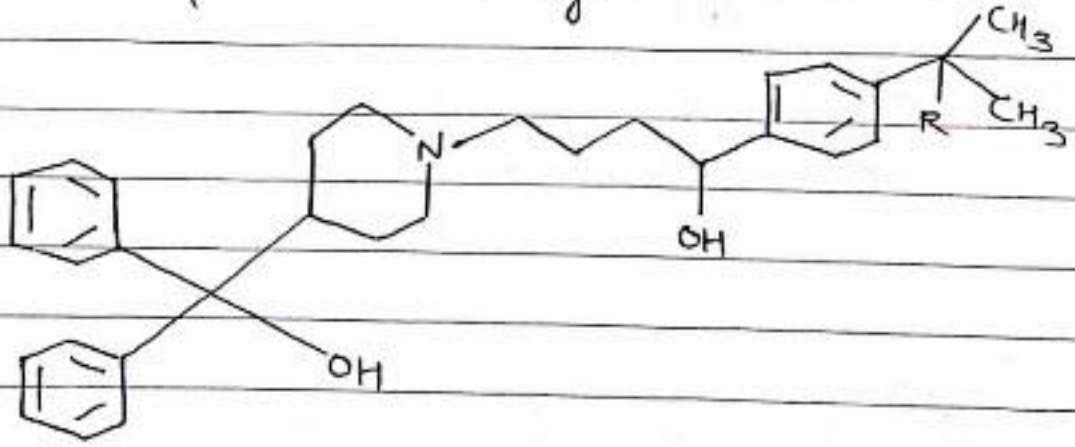


Promethazine

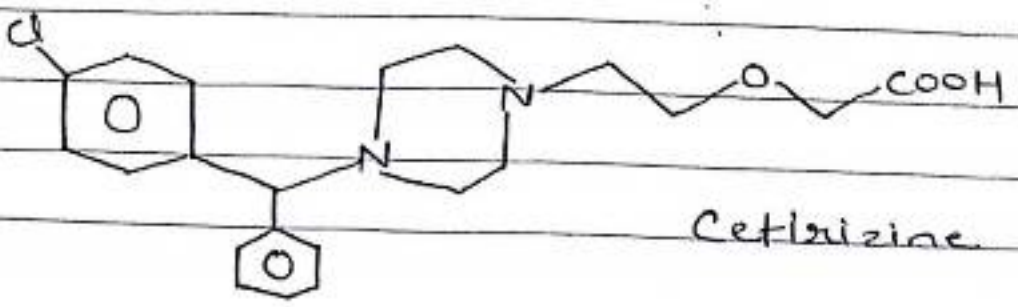


Trimeprazine

2) Second Generation Drugs :-



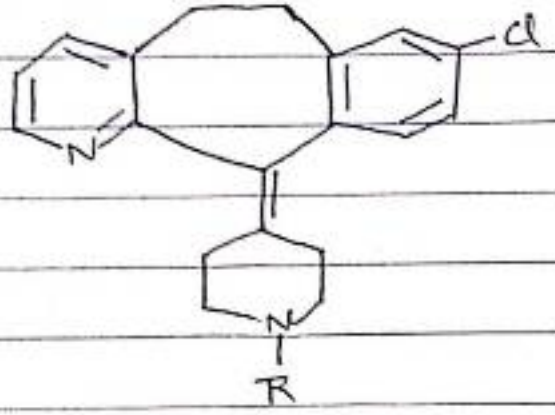
If R = CH_3 terfenadine
R = COOH fexofenadine



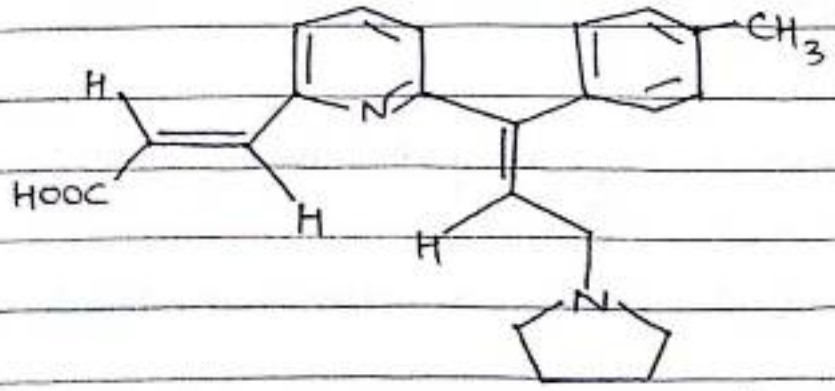
Cetirizine

- These have a relative low affinity for central H_1 receptors, largely free from sedation.
- The 2nd generation drugs have little affinity for muscarnic, adrenergic receptors.

3) Third Generation H_1 Antihistamines :-



R = $COOC_2H_5$ Loratidine



Acrivastine

Mechanism of Action of H_1 Antagonist

- H_1 Antagonist act by Competitively Inhibiting the effects of histamine at H_1 receptor.

- H_1 receptor blockade results in decreased Vascular permeability, reduction of pruritus, relaxation of Smooth Muscles in the respiratory, GIT.

Uses :-

→ These are clinically used in the treatment of histamine mediated allergic Conditions.

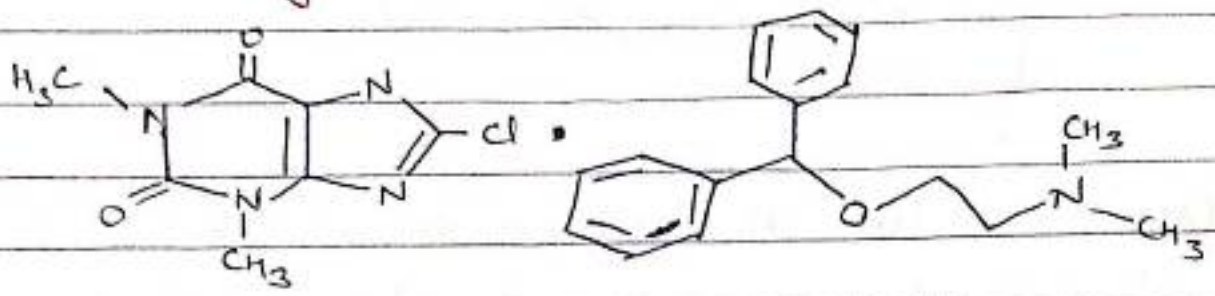
→ These are mainly used in allergic rhinitis, allergic Conjunctivitis, allergic dermatological Conditions.

Adverse Effect :-

- The main adverse effect of H_1 Antagonists is Sedation.
- It also Cause drowsiness, diminished ~~att~~ alertness.
- Relatively less selectively for the ~~pth~~ peripheral H_1 receptor.

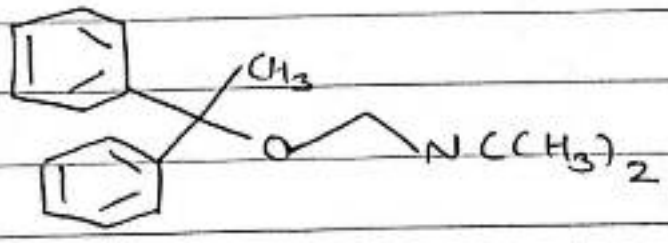
Structures of the Drugs belongs to H_1 Antagonists :-

1. Dimenhydrinate



Uses :- It is mainly used in treatment of nausea.

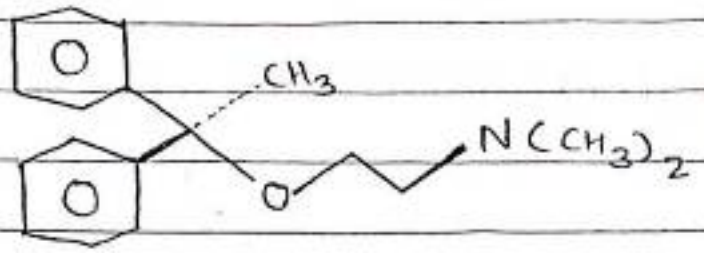
2. Doxylamines Succinate



Uses :-

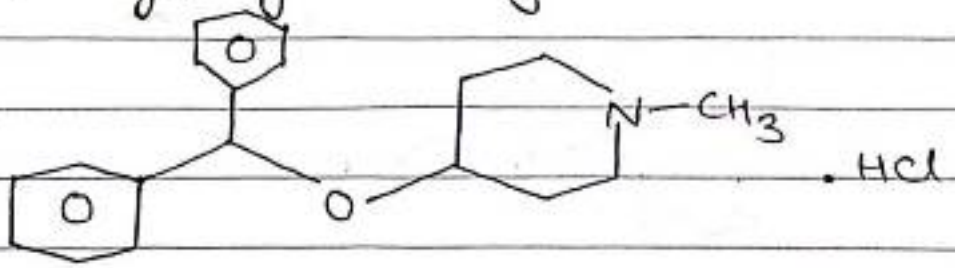
It is used to relieve symptoms of allergy hay fever and the Common Cold.

3. Clemastine fumarate.



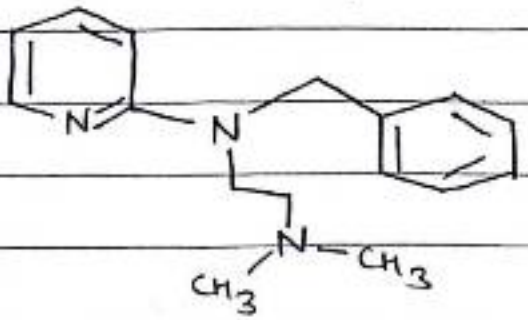
Uses :- Clemastine is an antihistamine used to relieve symptoms of allergy, hay fever and common cold.

4. Diphenylphyraline hydrochloride



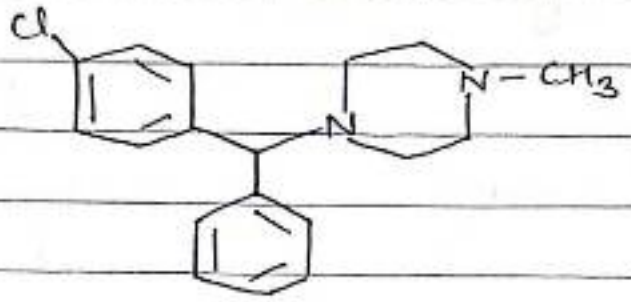
Uses :- It is widely used in treatment of motion Sickness because, it act as chemoreceptor trigger zone.

5. Tripelenamine hydrochloride

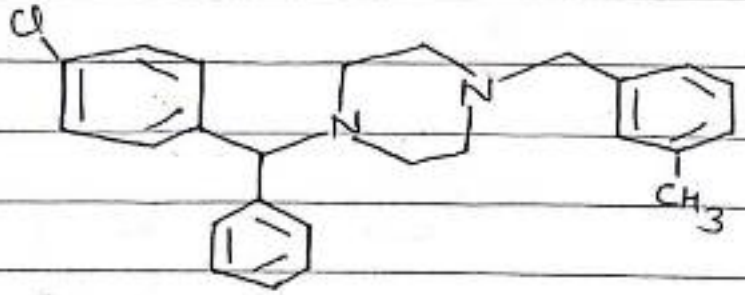


Uses :- It is used in treatment of Sneezing, runny nose, itching, watery eyes and rashes etc.

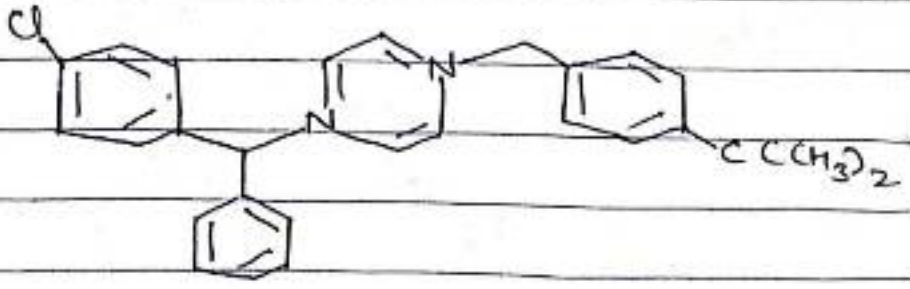
6. Chlorcyclizine Hydrochloride.



7. Meclizine Hydrochloride.



8. Buclizine hydrochloride.

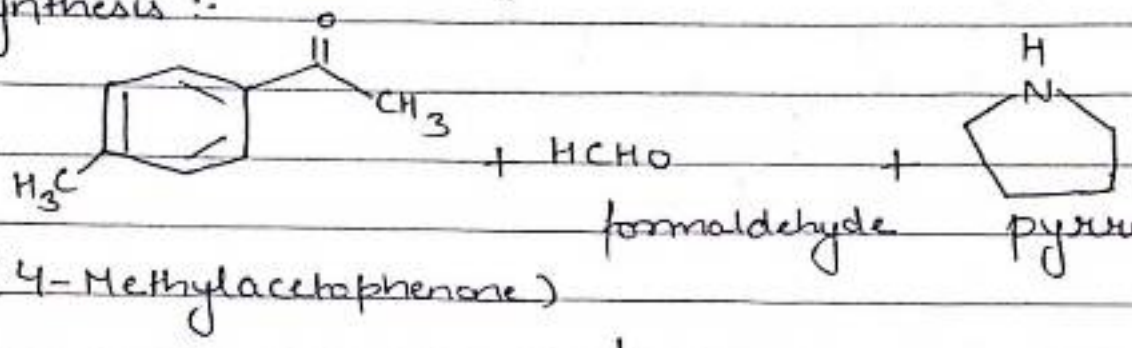


Uses :-

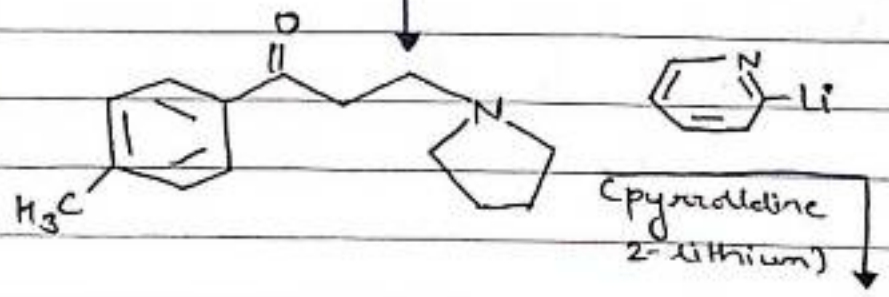
- Chlorcyclizine, meclizine & buclizine belongs to piperazine derivatives, useful as antiemetic and in the treatment of motion sickness.

9. Triprolidine Hydrochloride

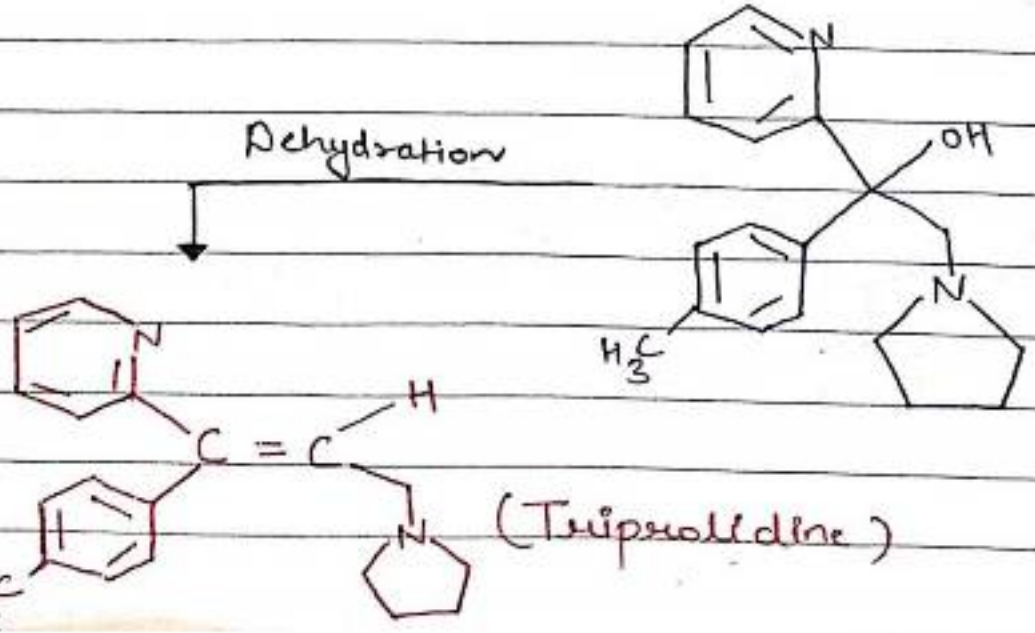
Synthesis :-



(4-Methylacetophenone)



Dehydration



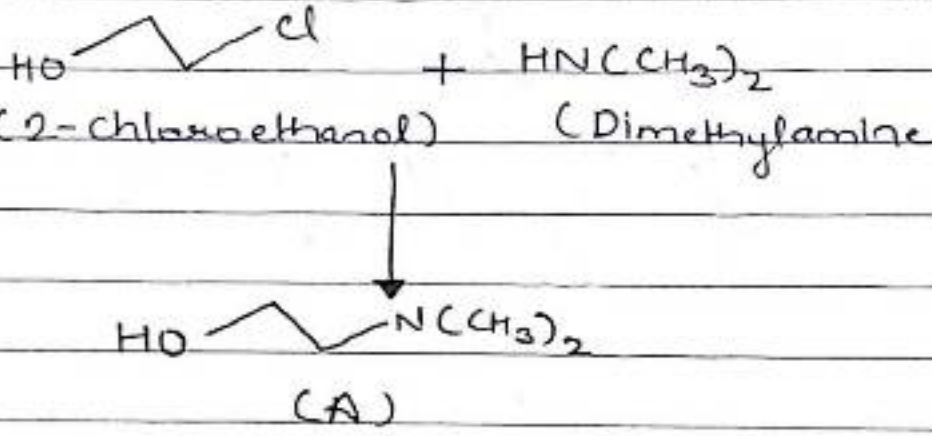
Uses :- This is clinically used in allergic reactions.

10. Diphenhydramine hydrochloride

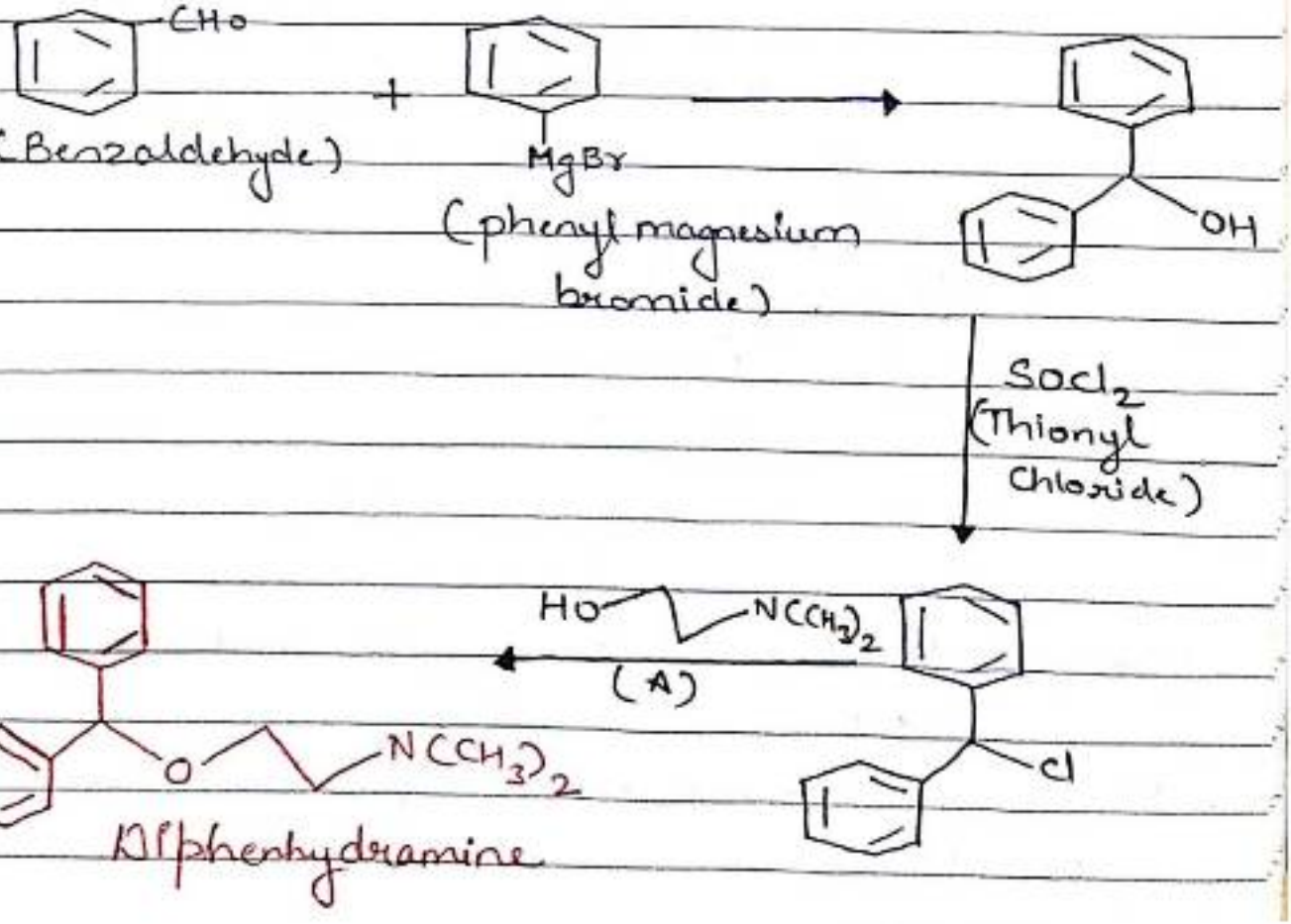
Synthesis :-

It is involves 2 steps :-

STEP 1 :→



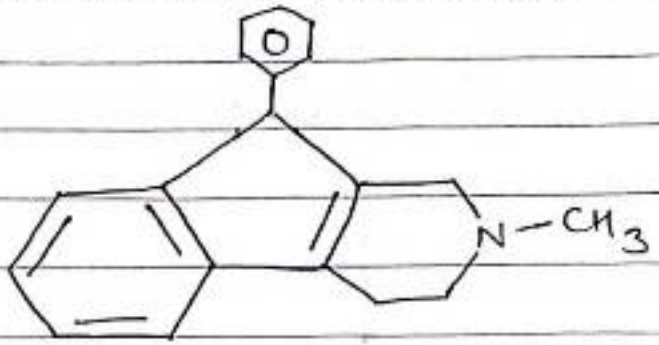
STEP 2 :→



Uses :- It is used as antiemetic, anti-tussive and sedative action.

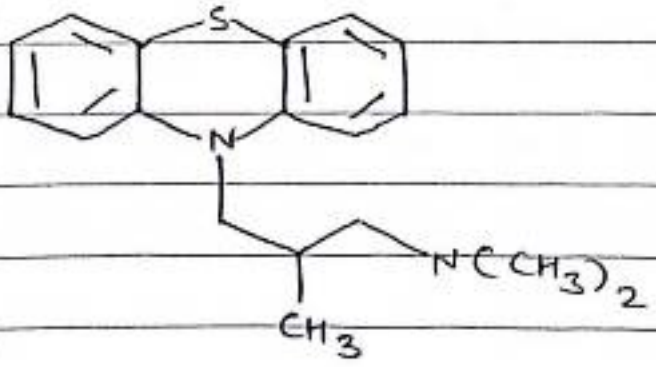
It is used in Various Allergic Condition.

11. Phenidamine tartarate



Uses!- It is used to treat Common cold and allergies such as Itching, rashes and Sneezing.

12. Trimeprazine tartrate

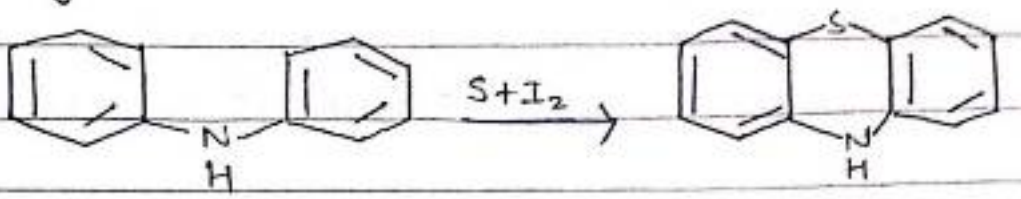


Uses!- • It posseses antiemetic and tranquillizing action.

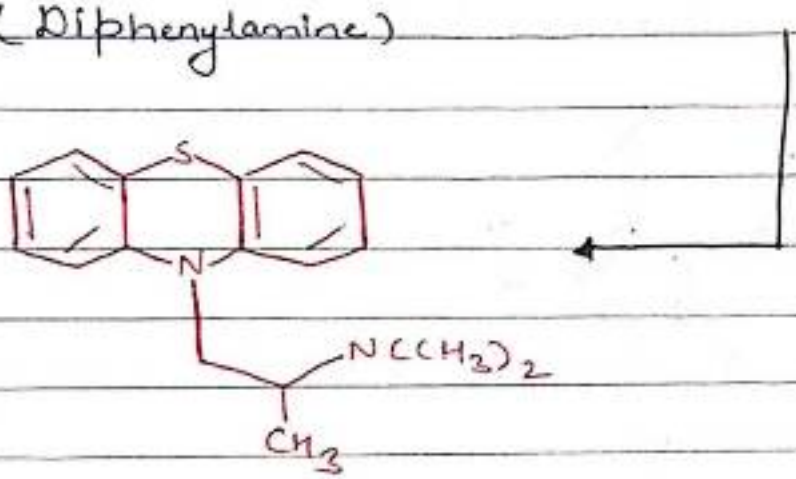
• It also produce potent action of analgesics and Sedatives.

13. Promethazine hydrochloride.

- Synthesis :-



(Diphenylamine)

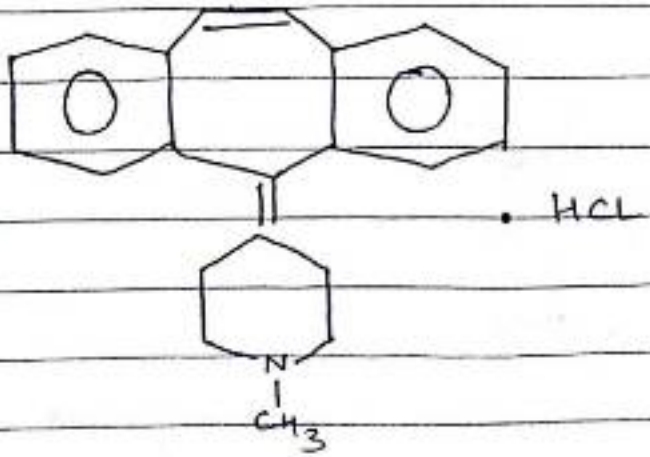


Promethazine

Uses :- It possesses antiemetic and tranquillizing action.

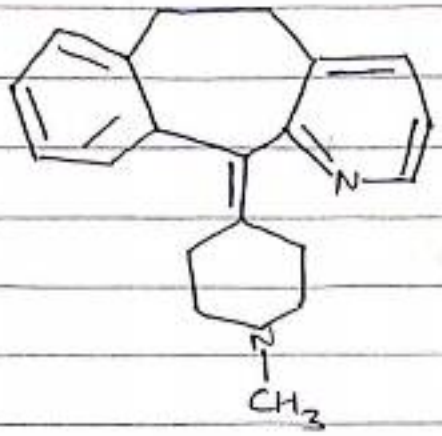
It also potent action of sedations.

14. Cyproheptadine hydrochloride.



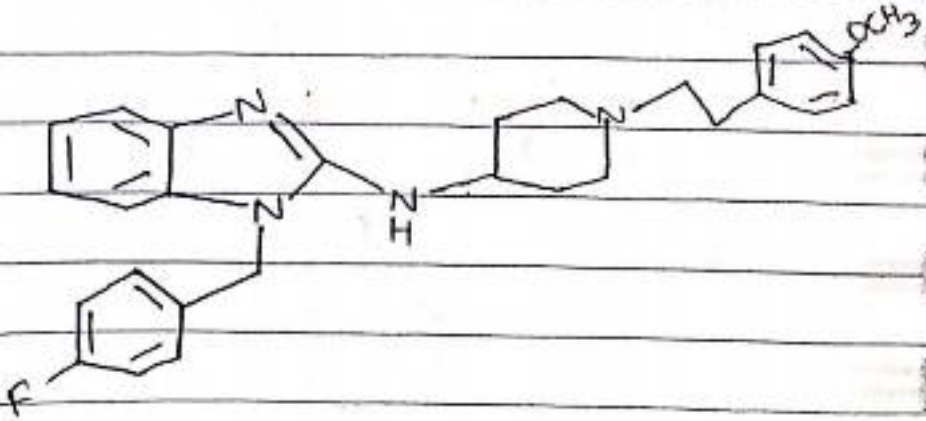
Uses :- It is widely used in allergic relief from watery eyes, itching, sneezing.
It is used in the treatment of perennial and seasonal allergic rhinitis, cold urticaria etc.

15. Azatidine Maleate :-



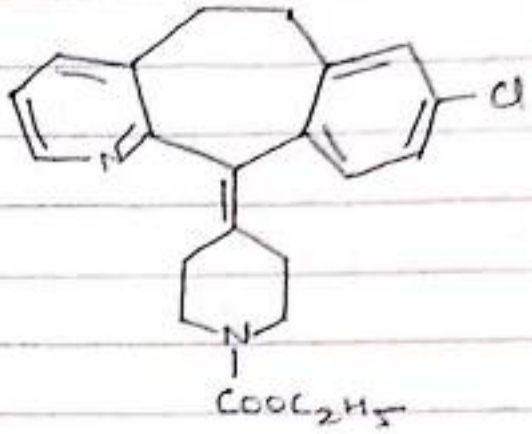
Uses :- It is a potent long acting antihistaminic and antiserotonin agents.

16. Astemizole



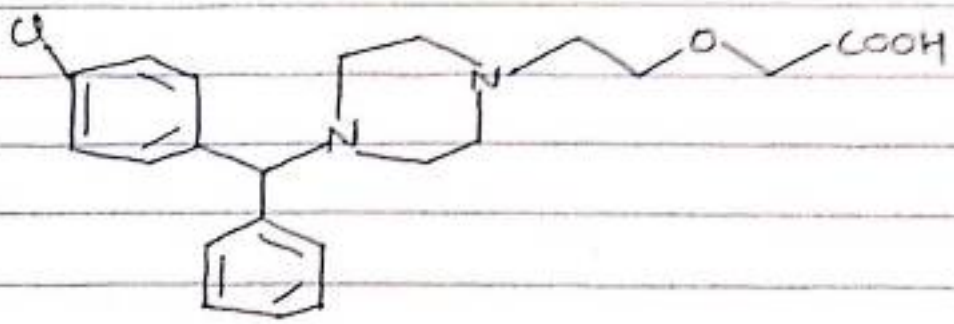
Uses :- It is potent selective H_1 antagonist without sedative effect.

17. Loratadine



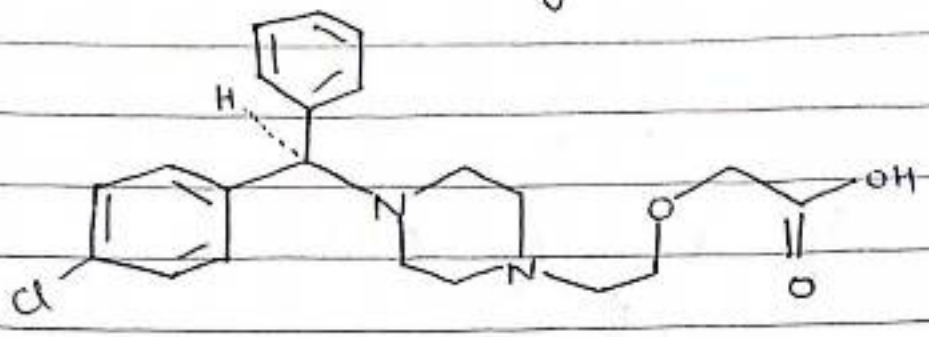
Uses:- It is similar to azatidine but due to presence of Cl⁻ group it has less CNS effect.

18. Cetirizine

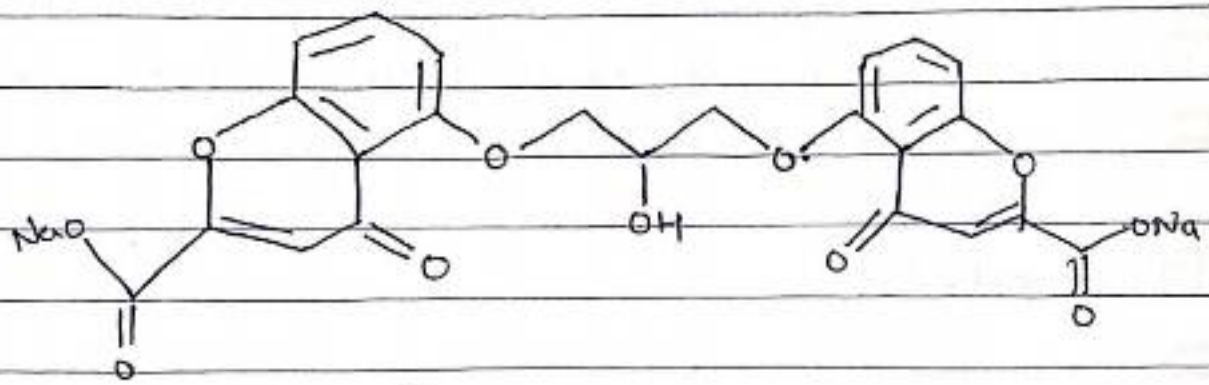


Uses:- It is highly selective H_1 antagonist without any central effects.

19. Levocetrazine Cromolyn Sodium



Levocetrazine

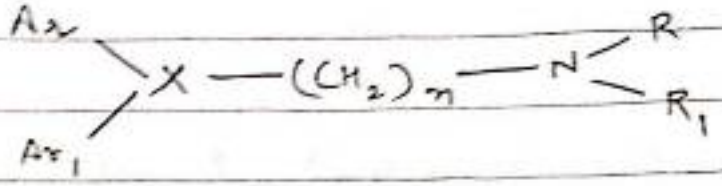


Cromolyn Sodium

Uses :- • Cromolyn Sodium, "mast-cell stabilizer"
• It helps prevent allergy symptoms.
• It is primarily used to prevent allergy induced asthma attacks.

Uses :- Levocetirizine is used to relief Itching Sneezing, redness, runny nose, seasonal-allergies and rashes etc.

SAR of H_2 Antagonist →



Ax is Aryl :- Phenyl, hetero aryl, 2-pyridyl
Ar_1 :- Secondary aryl (or) aryl methyl group.

X :- Connecting atom O, C and N
$(CH_2)_n$:- Carbon chain
N R R_1 :- Basic, terminal amine groups.

1. The diaryl substitution is essential for significant H_1 receptor affinity.
2. Mostly H_1 antihistamines possess substituents in one of the aryl rings (mainly phenyl rings), this influence the potency of the compound.
3. The X- Connecting moiety may be Carbon simply or Saturated C=O moiety, which Server as a spacer group for required pharmacophore.
4. Braching on the Carbon chain decrease in activity.
5. The terminal N-atom should be 3° amine for maxi-mum activity.

Reference :-

1. Rajasekaran VN, "Pharmaceutical Chemistry" CBS publisher & Distributor Pvt. Ltd, pg no = 267.

2. Yogeeswari P & Sriram D, "Medicinal chemistry" 2nd edition, published by pearson India

3. Razdan Balkishen, "Medicinal Chemistry", 2nd edition CBS publisher & Distributor Pvt. Ltd, pg no = 290.