Medicinal Chemistry | 02

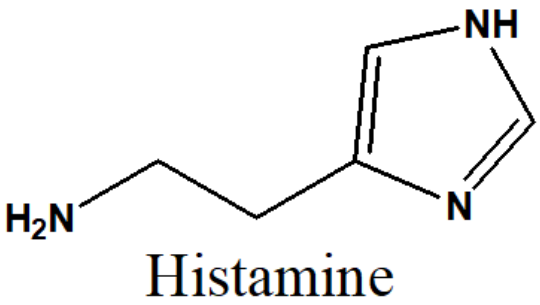
Antihistaminic agents

HISTAMINE

CHEMISTRY OF HISTAMINE:

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

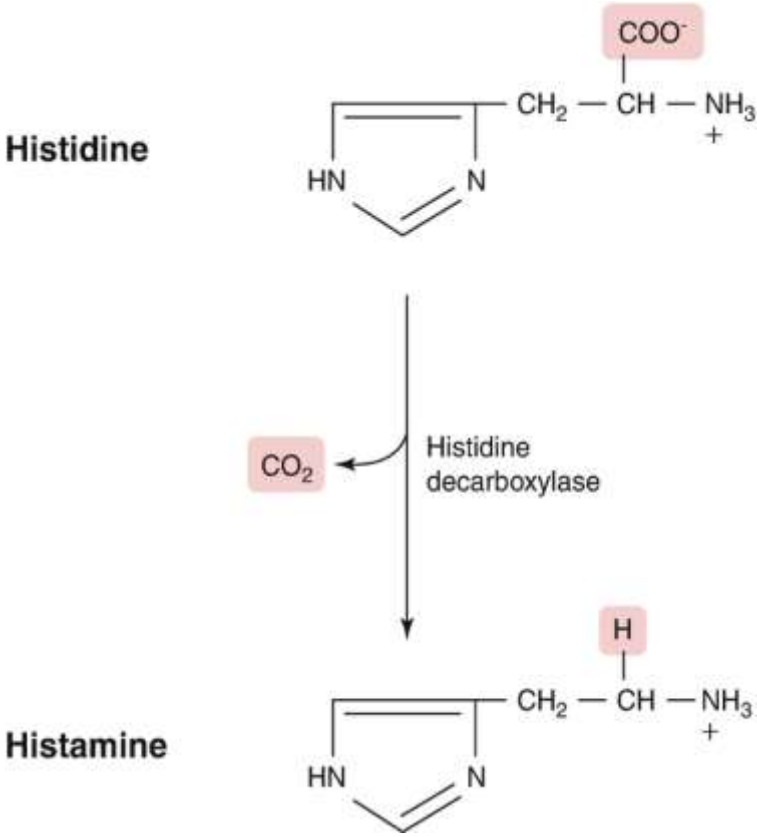
- Histamine is a basic organic compound.
- Histamine is an achiral molecule



Histamine

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.



HISTAMINE RECEPTORS LOCATION AND FUNCTIONS

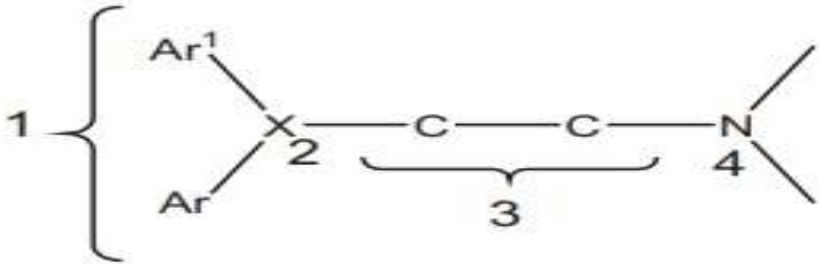
H1 receptors are linked to **allergic responses**, **H2** to **gastric acid regulation**, **H3** to **neurotransmitter release modulation**, and **H4** to **immune system function**.

There are four known histamine receptors:

H1 Receptors: These receptors are primarily located on smooth muscle cells, endothelial cells, and neurons.

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

STRUCTURE ACTIVITY RELATIONSHIP - H_1 RECEPTOR ANTAGONISTS



1. Aryl groups

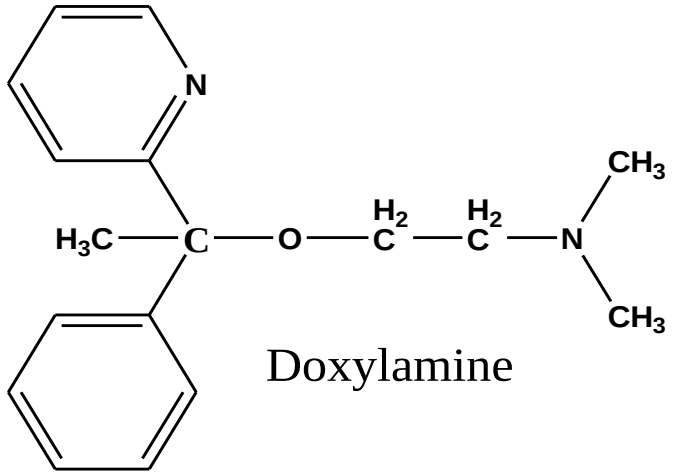
- The diaryl substitution is essential for significant H_1 affinity.
- It is present both in first generation and second generation antihistamines.
- The optimal antihistaminic activity depends on the co-planarity of two aryl substitutions.

Active aryl substitutions are as follows:

Ar is phenyl and hetero aryl group like 2-pyridyl

Ar^1-Aryl or aryl methyl group

- **Heterocyclic atom replaced to phenyl group may enhance the activity. E.g. Doxylamine**

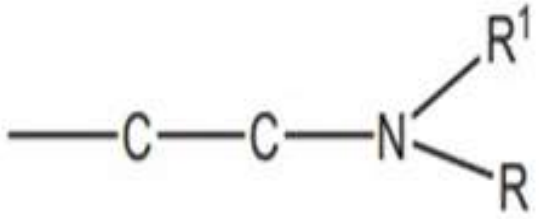


Doxylamine

2. Nature of X

- The X-connecting moiety of H1-antihistamines may be simple carbon, Oxygen, Nitrogen.
- Antihistamines with X = carbon (pheniramine series) represents the stereo selective receptor binding to the receptors due to its chirality.
- **The active substitutions of X are as follows:**

Where X = **oxygen** (amino alkyl ether analogue)
X = **nitrogen** (ethylene-diamine derivative)
X = **carbon** (mono amino propyl analogue)

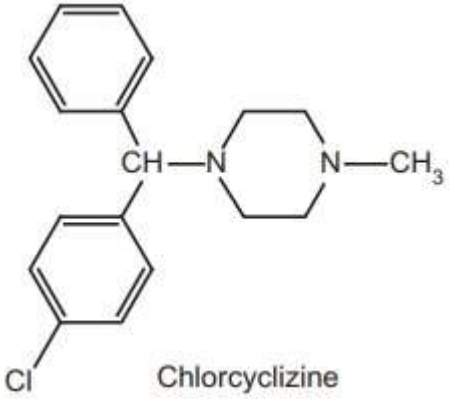


3. The Alkyl Chain

- Ethylene chain is required for maximum activity.
- The carbon chain consists of two or three atoms in H1-antihistamines, which leads to the distance between the central point of the diaryl ring system and the terminal nitrogen atom in the range of 5-6 Angstrom(Å).
- **All antihistamines contain this general chain.**
- Branching of this carbon chain leads decrease in antihistaminic activity.

4. Terminal nitrogen atom:

- The terminal N-atom should be a 3° amine for maximum activity.
- The terminal nitrogen may be a part of heterocyclic ring. For e.g: chlorcyclizine, retains high antihistaminic activity.
- The amino moiety deserves the protonation on interaction with H_1 recptor due to the basicity with pka 8.5-10.



Chlorcyclizine

CLASSIFICATION

A) Amino alkyl ethers (Ethanolamines)
Diphenhydramine,
Diphenhylpyraline,
Dimenhydrinate,
Doxylamine,
Clemastine

B) Ethylenediamine Derivatives.
Tripelenamine (Pyribenzamine)

C) Propyl amine Derivatives (Alkylamines).
Chlorpheniramine HCl,
Triprolidine HCl,

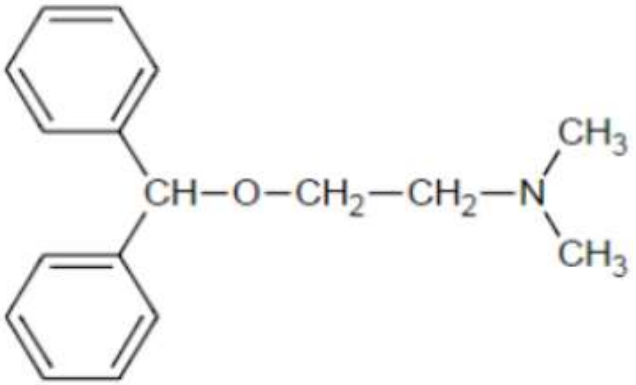
D) Phenothiazine Derivatives.
Promethazine HCl,
Trimeprazine HCl

E) Piperazine Derivatives.
Chlorcyclizine HCl,
Meclizine HCl,
Buclizine HCl

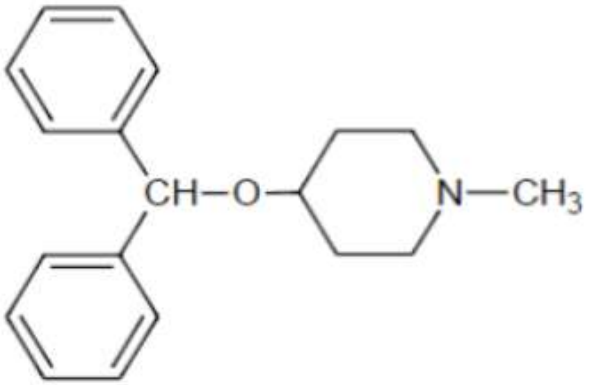
F) Tricyclic Derivatives
Cyproheptadine HCL
Azatidine Maleate
Phenidamine Tartarate

G) Second Generation H_1-Antagonist (Non-Classical Antihistamines)
Terfenadine
Astemizole
Loratidine
Cetirizine

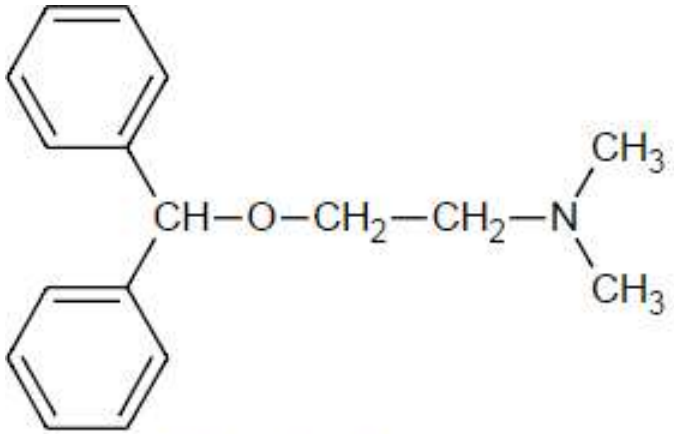
A. AMINO ALKYL ETHERS (ETHANOLAMINES)



Diphenhydramine



Diphenhylpyraline

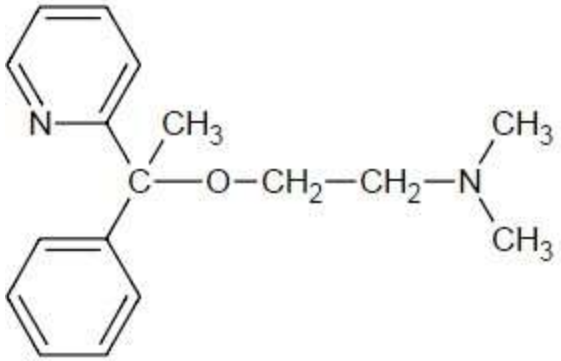


Diphenhydramine

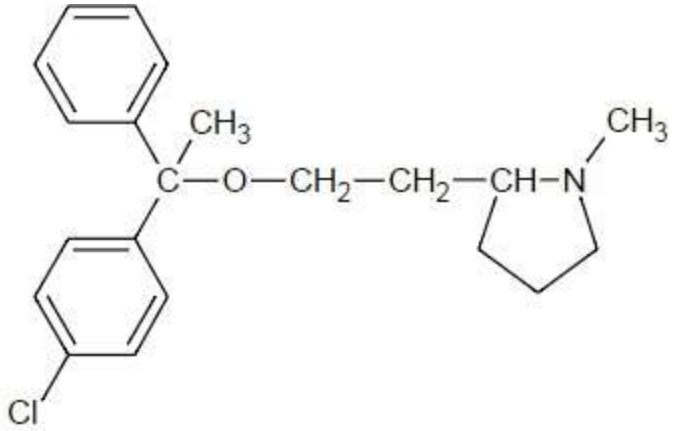
+

8-chlorotheophylline

Dimenhydrinate

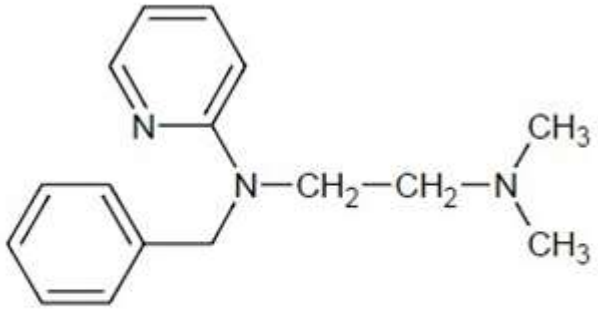


Doxylamine



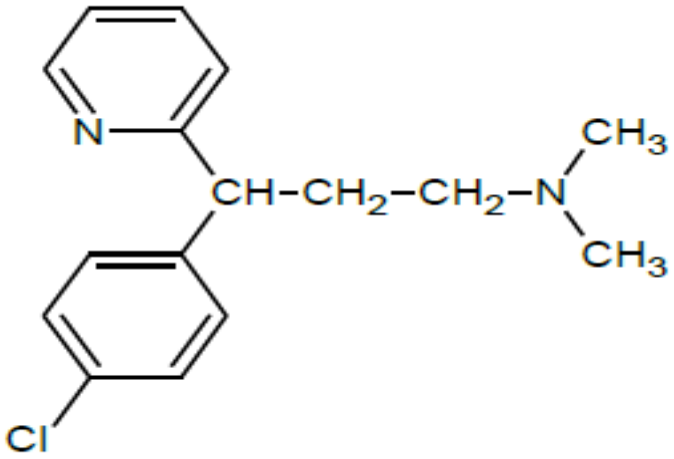
Clemastine

B) Ethylenediamine Derivatives

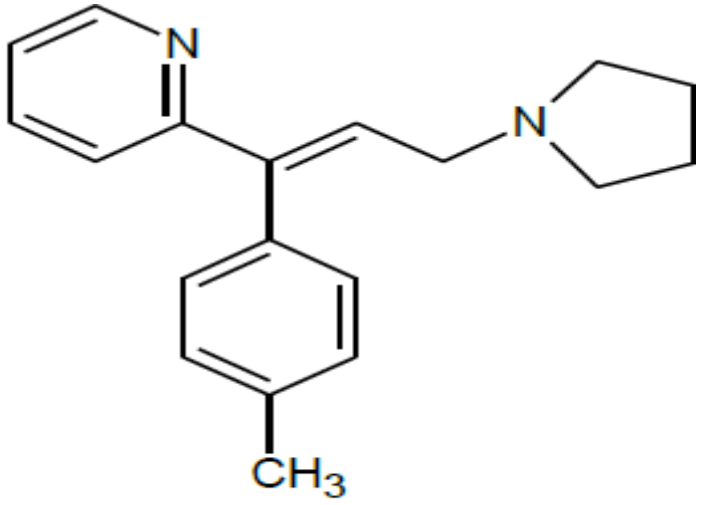


Pyribenzamine
(Tripelenamine)

C) Propyl amine Derivatives (Alkylamines)

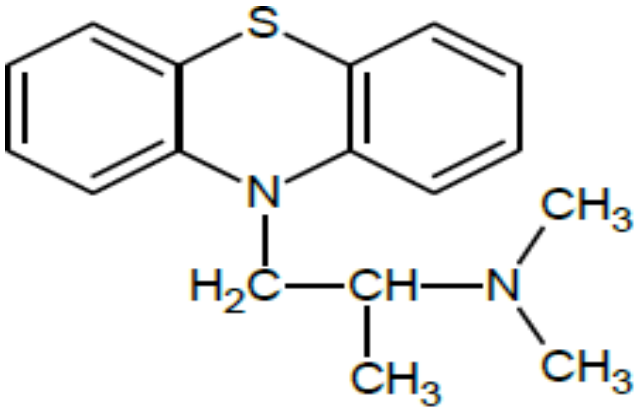


Chlorpheniramine

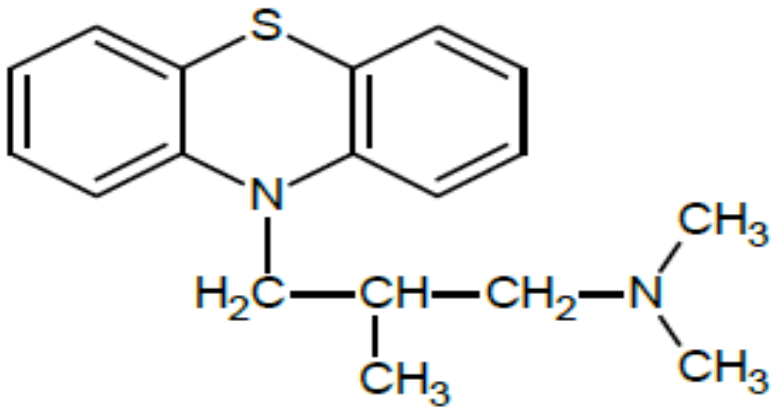


E - Triprolidine

D) Phenothiazine Derivatives

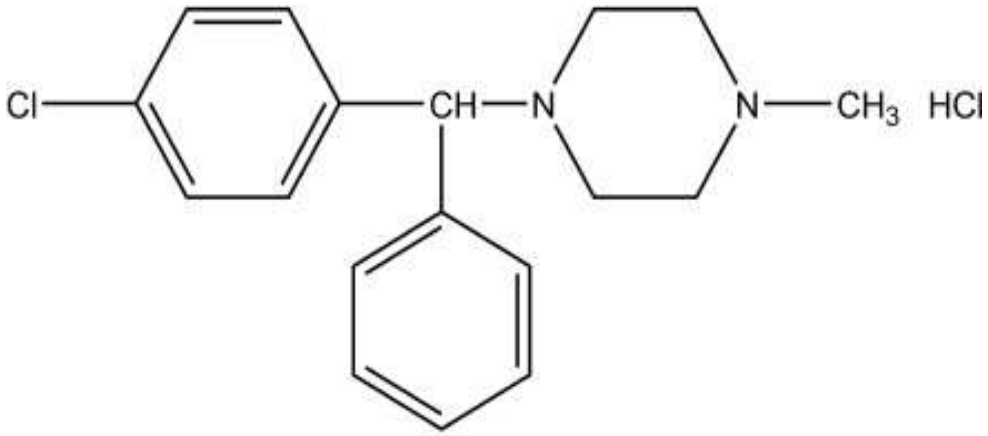


Promethazine

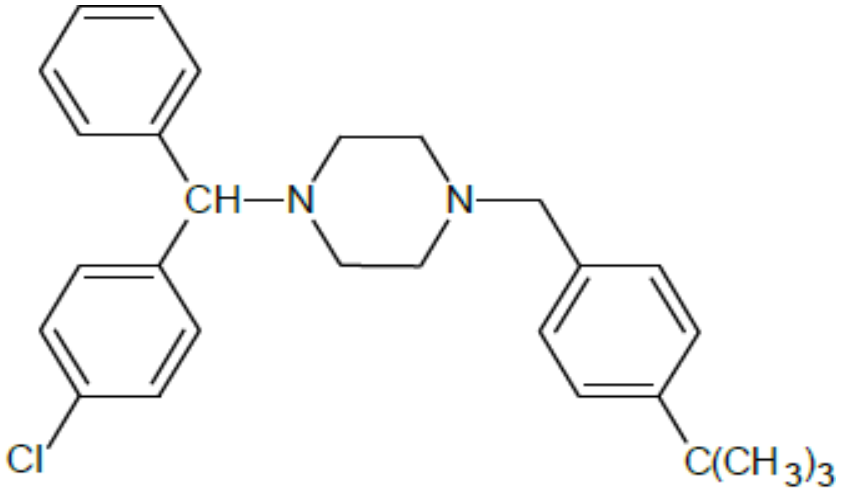


Trimeprazine

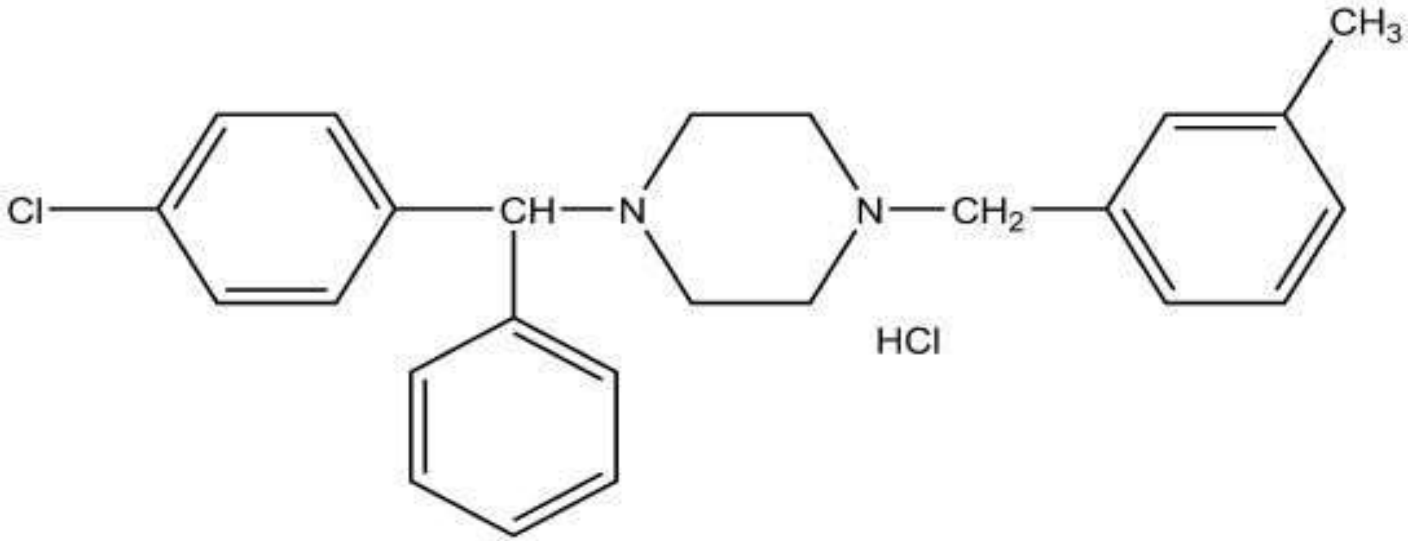
E) Piperazine Derivatives



Chlorcyclizine Hydrochloride

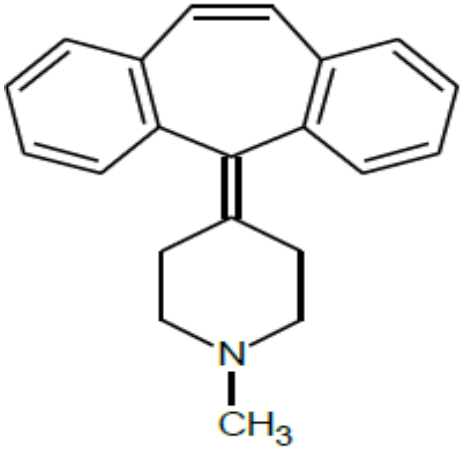


Buclizine

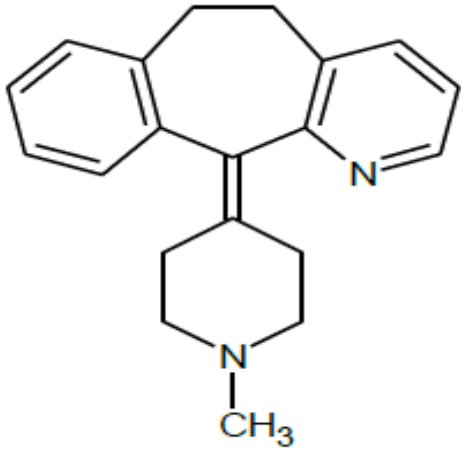


Meclizine Hydrochloride

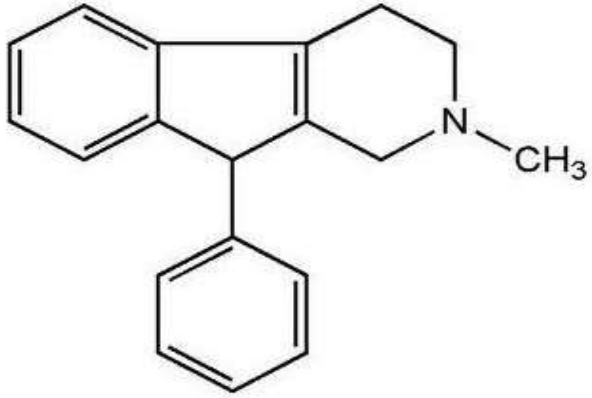
F) Tricyclic Derivatives



Cyproheptadine

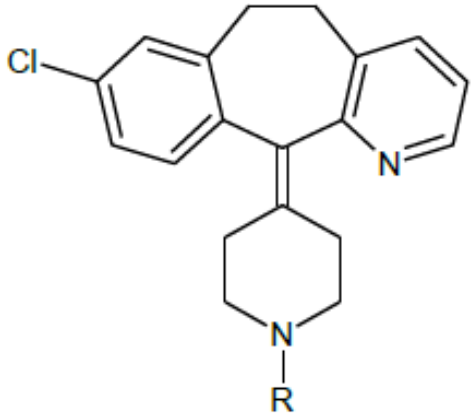


Azatidine

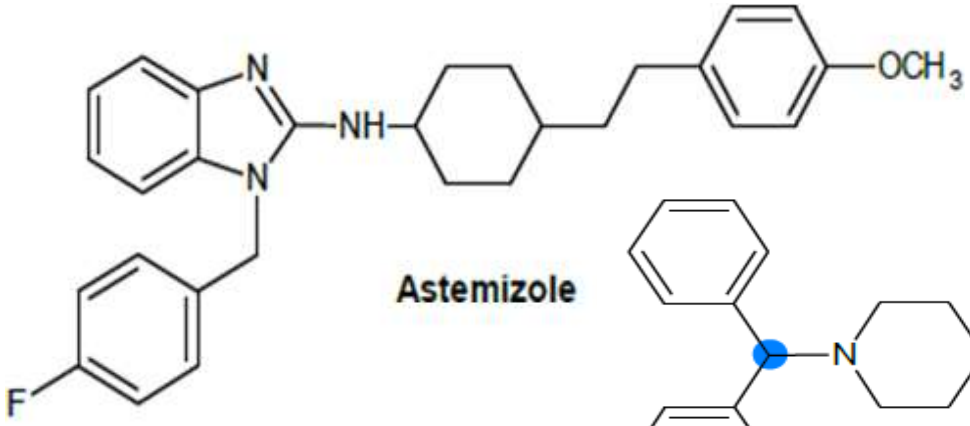


Phenidamine

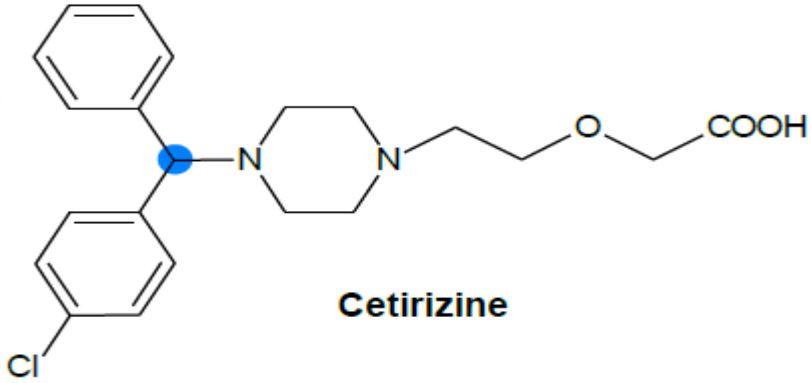
G) Second Generation H_1-Antagonist (Non-Classical Antihistamines)



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



Astemizole



Cetirizine

General Mechanism of Action of Antihistamines

- Blocks action of histamine at receptor
- Competes with histamine for binding
- Displaces histamine from receptor

Adverse effect

- Sedation,
- Diminished alertness and concentration,
- Light headedness,
- Motor incoordination,
- Fatigue and tendency to fall asleep
- Dryness of mouth,
- Alteration of bowel movement,
- Urinary hesitancy and blurring of vision

USES

1. Labyrinthine suppressants

(a) Antihistaminics (with anticholinergic action)—Cinnarizine, Dimenhydrinate, Diphenhydramine, Promethazine.

(b) Anticholinergics— Atropine, Hyoscine.

(c) Antiemetic phenothiazines— Prochlorperazine.

2. Vasodilators —Betahistine , Nicotinic acid.

3. Diuretics

—Acetazolamide, Thiazides, Furosemide.

4. Anxiolytics, antidepressants—Diazepam, Amitriptyline.

5. Corticosteroids.

6. Parenteral Prochlorperazine is the most effective drug for controlling violent vertigo and vomiting

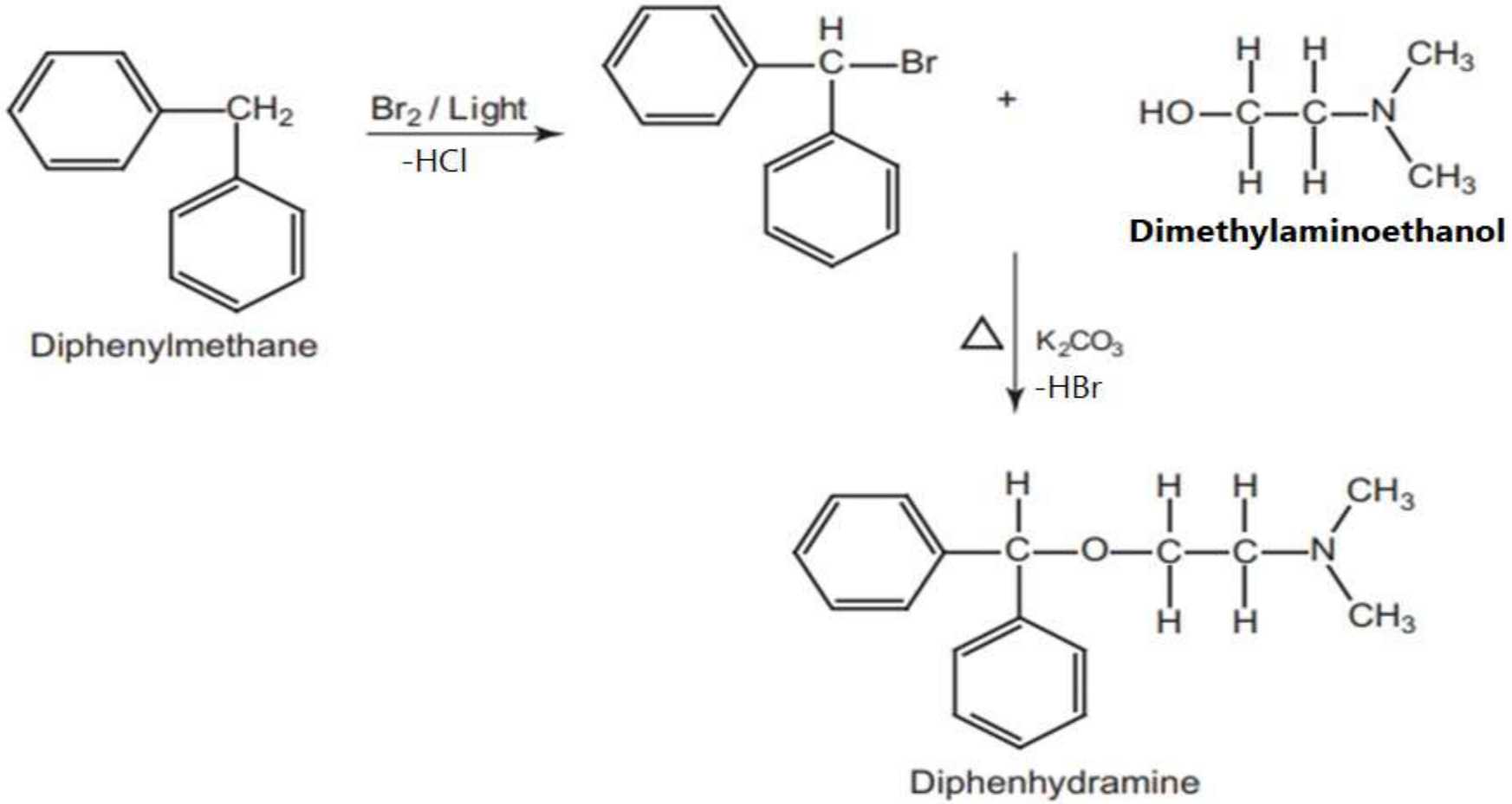
7. Preanaesthetic medication- Promethazine

8. Cough - Chlorpheniramine, Diphenhydramine and Promethazine

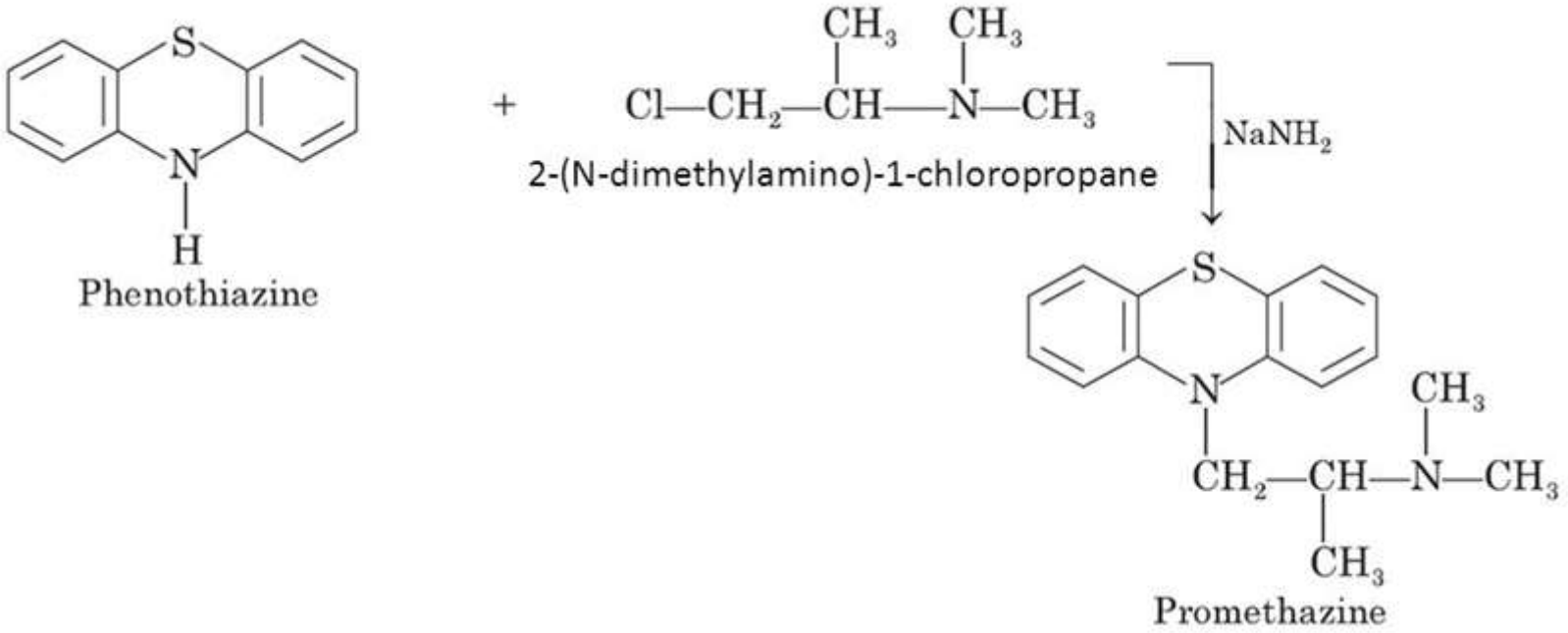
9. Parkinsonism- Promethazine

10. Acute muscle dystonia- Promethazine, Diphenhydramine

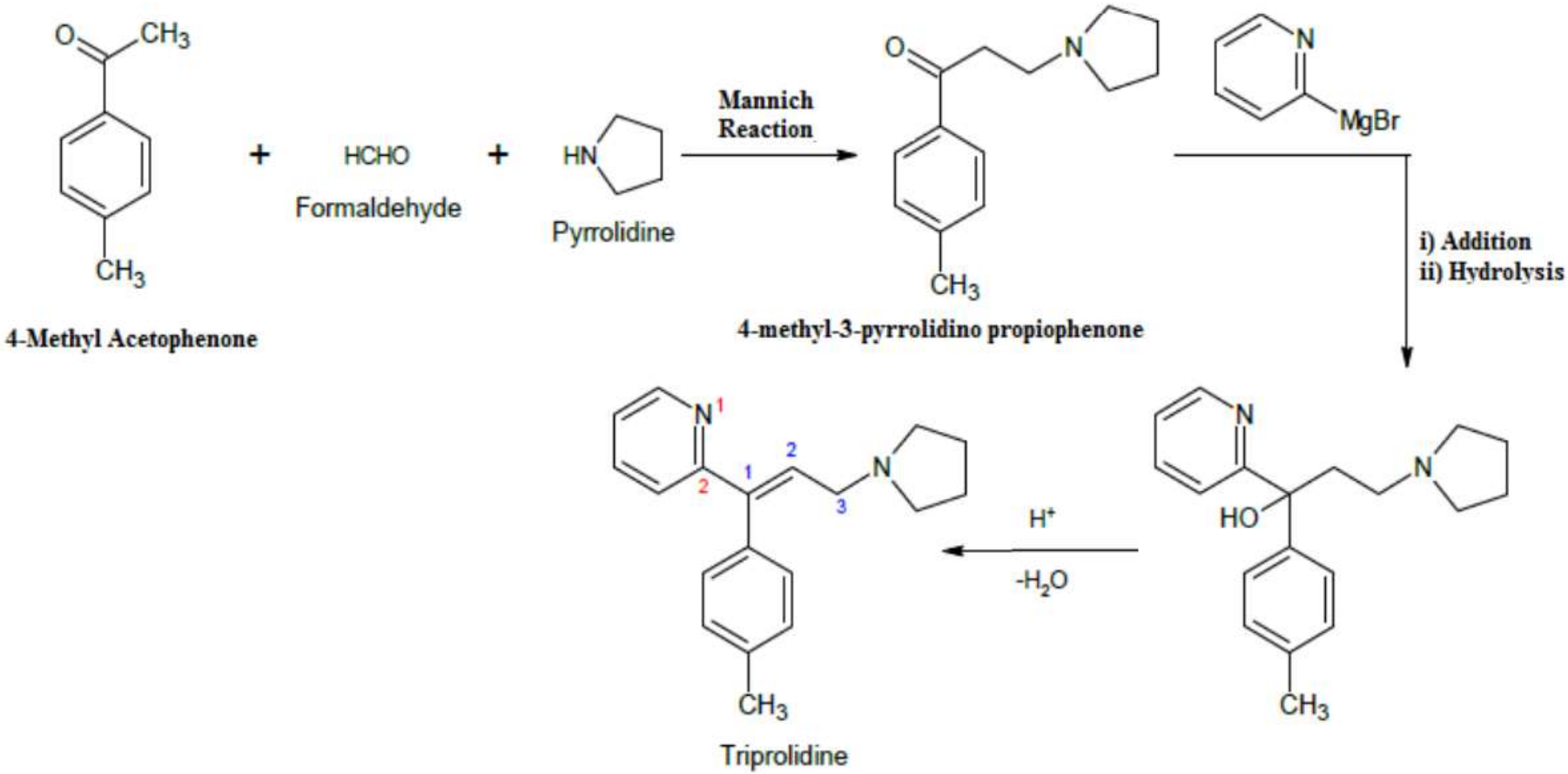
SYNTHESIS OF DIPHENHYDRAMINE



SYNTHESIS OF PROMETHAZINE



SYNTHESIS OF TRIPROLIDINE



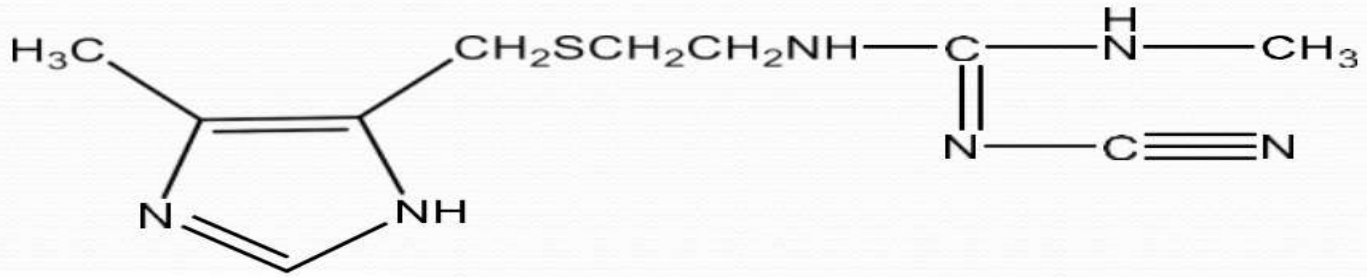
H_2 receptor antagonists

1. Cimetidine (tagamet)
2. Rantidine (zantac)
3. Famotidine (pepcid)

H2 receptor antagonists (HRAs), also called **H2 blockers,** are a class of drugs that **reduce stomach acid production by blocking histamine** from binding to **H2 receptors** in the stomach.

HRAs are often used to treat acid-peptic diseases, such as:
Duodenal ulcers, Gastric ulcers, Gastroesophageal reflux disease, Heartburn, and Mild to moderate erosive esophagitis.

Cimetidine

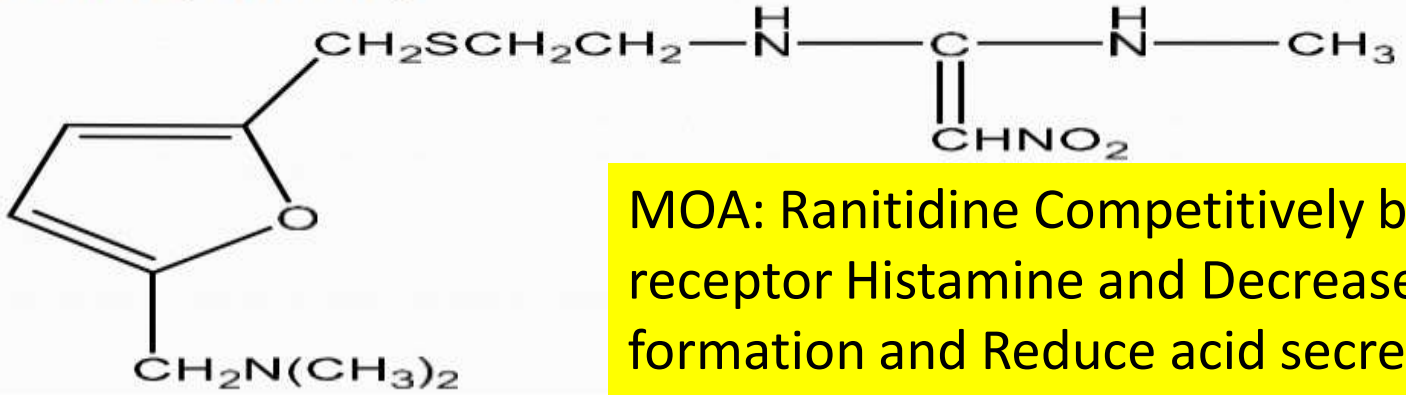


Uses:

To treat ulcer

Used to treat gastro esophagel reflux disease (GERD)

Ranitidine (Zantac):



MOA: Ranitidine Competitively block H2 receptor Histamine and Decrease cAMP formation and Reduce acid secretion

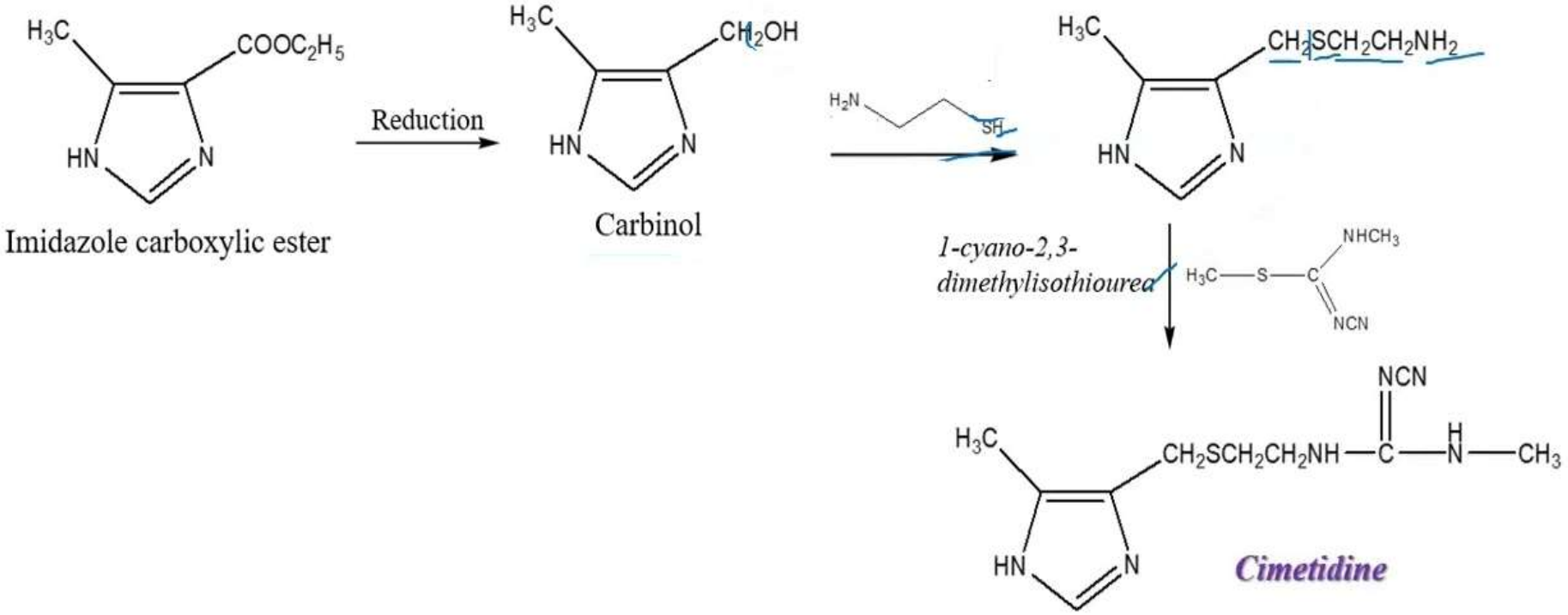
Uses:

To treat ulcer

Used to treat gastro esophagel reflux disease (GERD)

Zollengers-Ellison Syndrome

Synthesis of Cimetidine




Thank
you