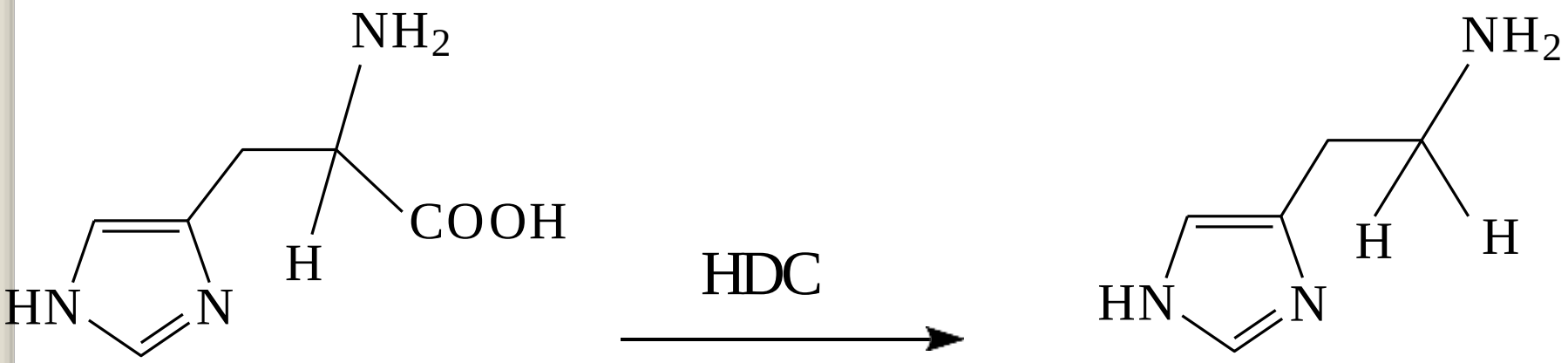
HISTAMINE

- Histamine is a β-imidazolylethylamine derivative present in all mammalian tissues.
- It was first discovered by SIR HENRY DALE.
- Its synthesis occurs in mast cells,parietal cells of gastric mucosa, CNS, periphery.
- It functions as an autocoid & one of the mediator involved in the allergic inflammatory responses.
- It has an important role in the regulation of gastric acid secretion.

BIOSYNTHESIS OF HISTAMINE



S-HISTIDINE

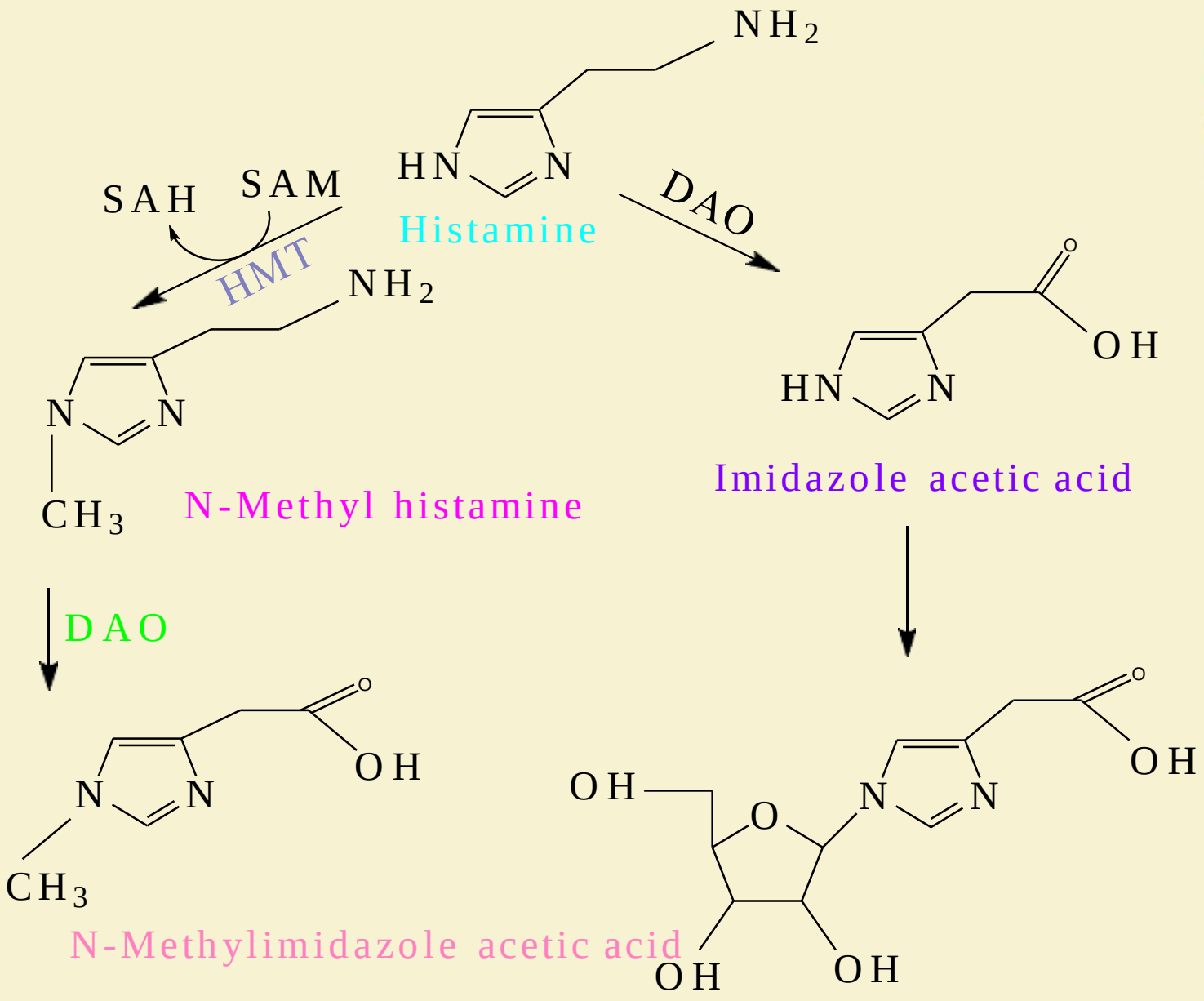
HISTAMINE

BIOSYNTHESIS OF HISTAMINE

- Histamine is synthesized in cytoplasmic granules of its storage cells, mast cells & basophils.
- It is formed from naturally occurring amino acid, S-histidine, via the catalysis of the pyridoxal phosphate – dependent enzyme histidine decarboxylase/ aromatic decarboxylase.

INHIBITORS OF HISTIDINE DECARBOXYLASE

- α-fluoromethyl histidine
- Certain flavonoids


NH2
HN
N
Histamine
SAH
SAM
HMT
DAO
NH2
N
N
CH3
N-Methyl histamine
OH
O
HN
N
Imidazole acetic acid
DAO
OH
O
N
N
CH3
N-Methylimidazole acetic acid
OH
O
N
N
OH
OH
OH
Imidazole acetic acid
riboside

METABOLISM OF HISTAMINE

- Metabolism of histamine takes by the enzymatic inactivation.
- Enzymes that involve in the metabolism are:

1. Histamine N-methyl transferase(HMT)
2. Diamine oxidase.

- Histamine is metabolized as N- methylimidazole acetic acid , imidazole acetic acid riboside. Both are excreted through urine.

IMPORTANCE OF HISTAMINE

- It is not used therapeutically but in the past it has been used to test acid secreting capacity of stomach.
- To test bronchial hyperactivity in asthmatics.
- For diagnosis of pheochromocytoma , but these pharmacological tests are risky.
- In pulmonary laboratories, histamine aerosol has been used as a provocative test of bronchial hyperactivity.
- To distinguish between real & pseudoanesthesia.

RECEPTORS

- Histamine receptors are belonging to the family of G-Protein coupled receptors.
- The sub types of histamine receptors are:
  - H_1
  - H_2
  - H_3
  - H_4

RECEPTOR	H_1	H_2	H_3	H_4
LOCATION	Brain,GIT,CVS Lymphocytes.	Myocardial cells,parietal cells	CNS,myentric plexus, gastric mucosa	Spleen,thymus ,T-cells, eosinophils.

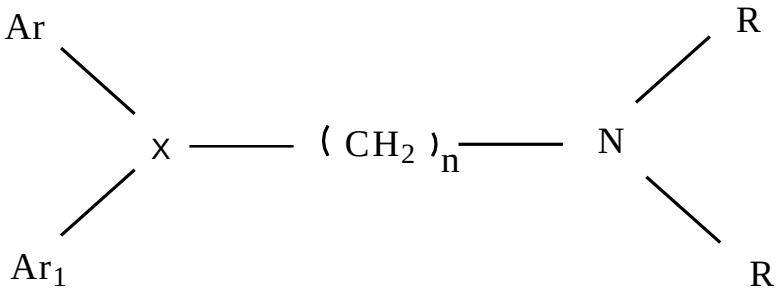
HISTAMINE ANTAGONISTS

- Drugs that block the action of histamine at H_1,H_2,H_3,H_4 receptors
- The development of antihistamines began by the discovery of PIPEROXAM.

1. Drugs that inhibits the histamine release.
2. Drugs that inhibits the action of released histamine
    a. H_1 antagonists(first,second&third generations)
    b. H_2 antagonists
    c. H_3 antagonists

3.Drugs having dual action

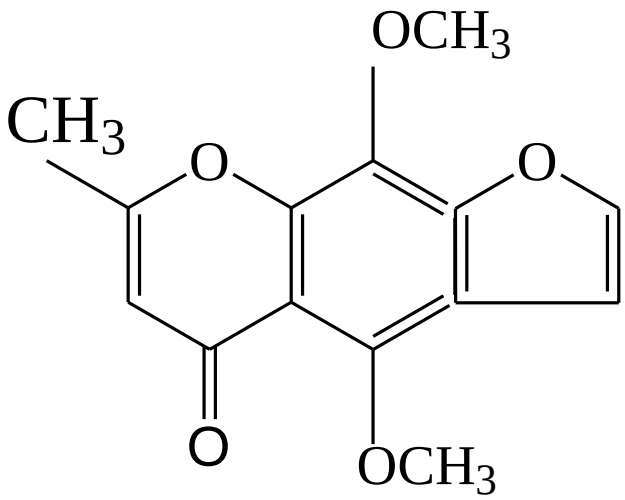
GENERAL STRUCTURE OF ANTIHISTAMINES



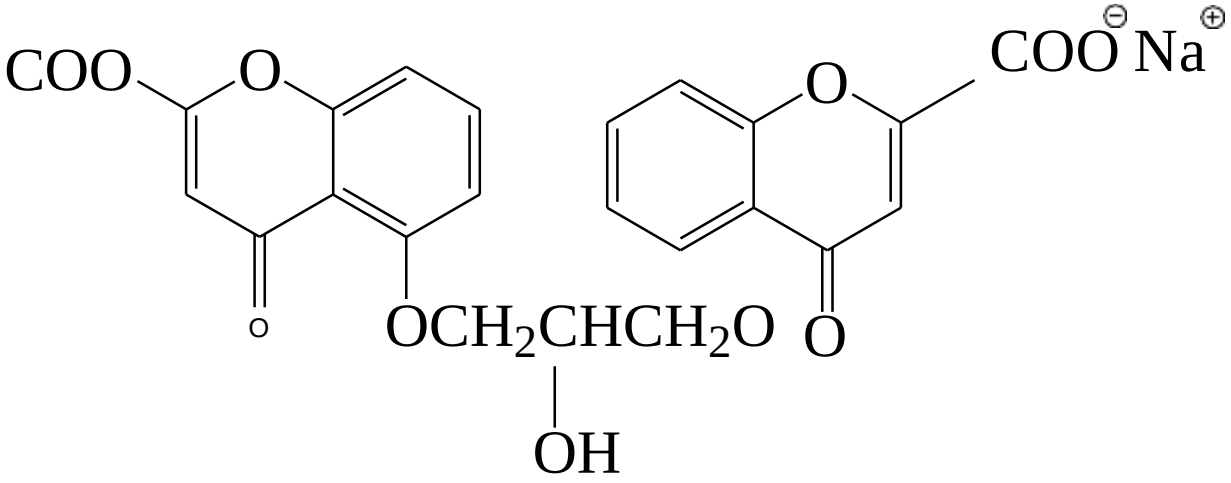
STRUCTURAL REQUIREMENTS:

- Ar is aryl: Phenyl, substituted phenyl,hetero aryl groups like 2- pyridyl.
- Ar_1: Second aryl (or) aryl methyl group.
- X: Connecting atom of O, C, (or) N.
- $(CH_2)n$: Carbon chain usually ethyl.
- NRR_1: Basic, terminal amine functional group.

DRUGS THAT BLOCK THE HISTAMINE RELEASE



KHELLIN



CROMOLYN SODIUM

- These drugs act by stabilizing the mast cells & inhibit the release of histamine & other mediators of inflammation.
- Natural product KHELLIN led to the development of bis compounds.
- CROMOLYN nasal solution used for the prevention & treatment of allergic rhinitis.
- Oral concentrate used to treat the histaminic symptoms of mastocytosis.

DRUGS THAT BLOCK THE RELEASED HISTAMINE

a) H_1 ANTAGONISTS(FIRST GENERATION DRUGS):

- These are classical antihistamines.
- These are clinically used in the treatment of histamine mediated allergic conditions like allergic rhinitis, allergic conjuctivitis etc.,

CLASSIFICATION:

a) Amino alkyl ethers.

b) Ethylenediamine derivatives.

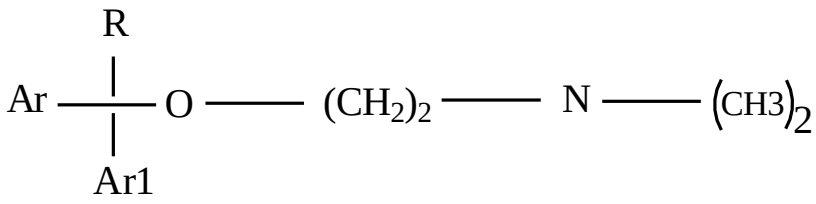
c) Propyl amine derivatives.

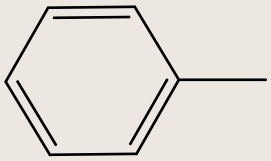
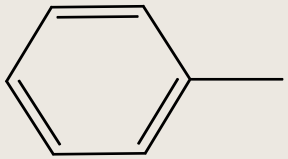
d) Phenothiazine derivatives.

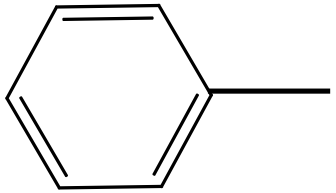
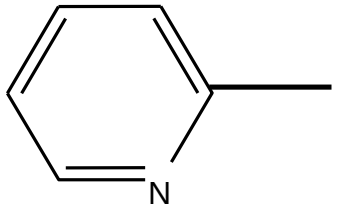
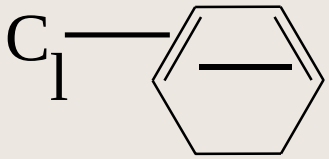
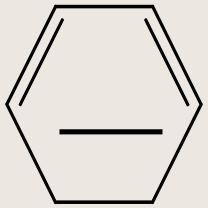
e) Piperazine derivatives.

a) AMINO ALKYL ETHERS (ETHANOLAMINES)

General structure:



DRUG	Ar	Ar1	R	CHEMICAL NAME
DIPHENHYDRAMINE			H	N,N-Dimethyl ethanamine.

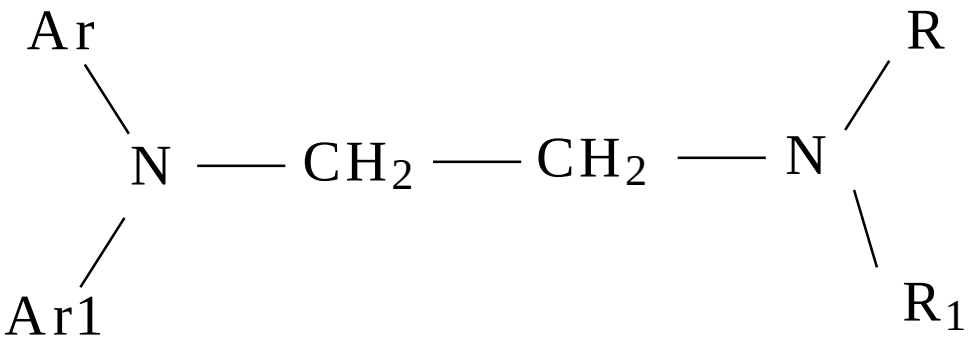
DOXYLAMINE.			CH_3	2-[α-[2-(dimethylamino)ethoxy]-α-methylbenzyl pyridine.
CLEMASTINE.			CH_3	2-[2-[1-(4-Chlo Ro phenyl)-1-Phenyl-ethoxy] Ethyl]1-Methyl pyrrol Idine.

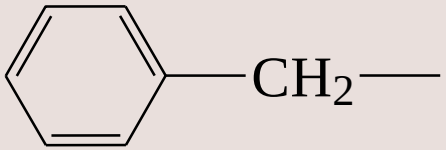
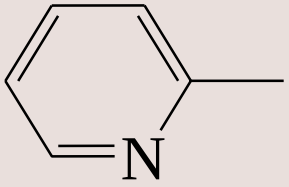
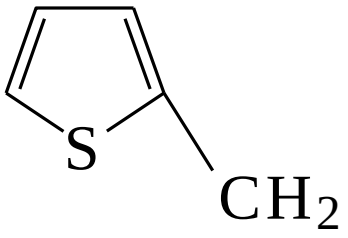
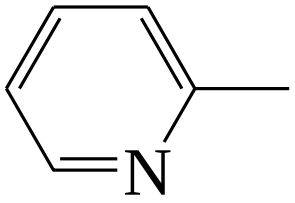
STRUCTURE ACTIVITY RELATIONSHIP

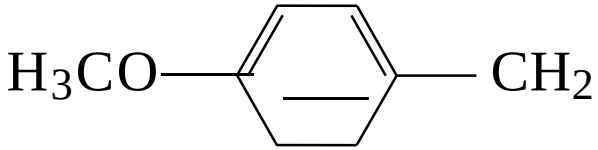
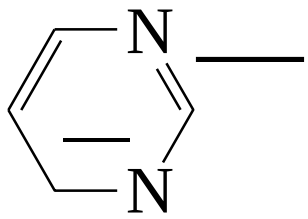
- These are characterized by presence of OXYGEN connecting moiety.
- Most compounds in this series are simple N,N-dimethyl ethanolamine derivatives.
- CLEMASTINE differs from basic structural pattern.
- Most amino alkyl ethers are optically active.
- The drugs in this group possess significant anticholinergic activity, which may enhance the H_1 blocking action on exocrine secretion.
- This amino alkyl ethers have to penetrate the BBB and occupy central H_1 receptor resulting the DROWSINESS.

b) ETHYLENEDIAMINE DERIVATIVES:

GENERAL STRUCTURE:



DRUG	Ar	Ar1	CHEMICAL NAME
TRIPELENNAMINE			2-[Benzyl[2-(dimeThylamino)ethyl]-Amino]pyridine
METHAPYRILENE			2-[2-(Dimethyl Amino)ethyl]2-Thienylamino Pyridine.

THONZYL AMINE			2-[2-Dimethylamino Ethyl](p-methoxy Benzyl amino] pyrimidine

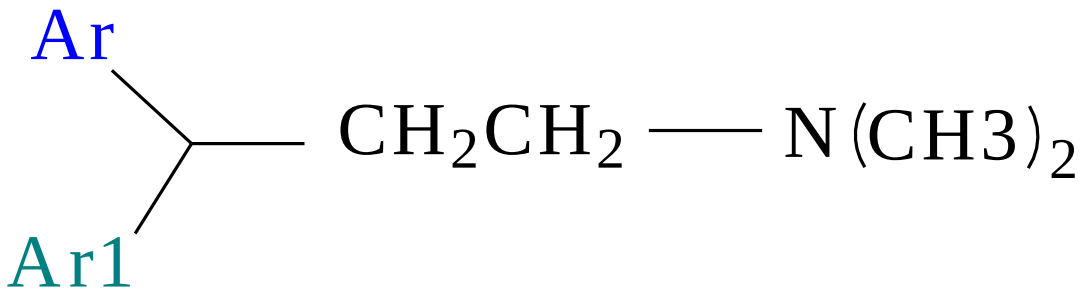
SAR:

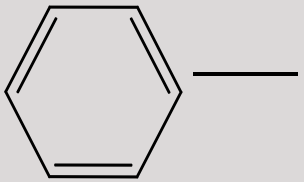
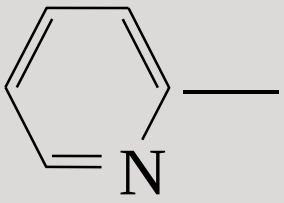
- These are characterized by NITROGEN connecting atom.
- Phenbenzamine was first clinically useful member.
- Replacement of phenyl moiety of Phenbenzamine with a 2-pyridyl system yielded "tripelennamine"
- Replacement of benzyl group of tripelennamine with a 2-thienylmethyl group provided methapyriline.
- Replacement of tripelennamine with -2-pyridyl group with a pyrimidinyl moiety yields thonzylamine.
- The anticholinergic & antiemetic action of these compounds are low.

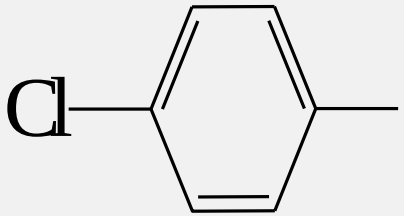
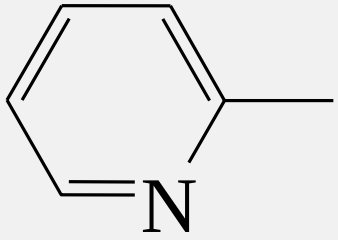
C) PROPYLAMINE DERIVATIVES:

1. SATURATED ANALOGUES:

GENERAL STRUCTURE:



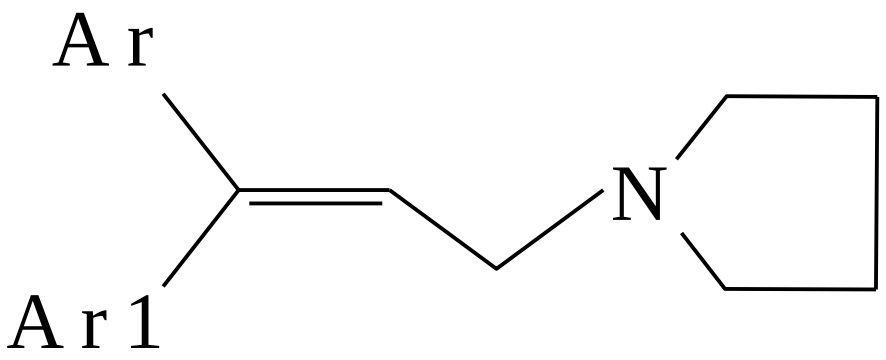
DRUG	Ar	Ar1	CHEMICAL NAME
PHENIRAMINE			2-[α-[2-Dimethyl Amine ethyl] Benzyl]pyridine.

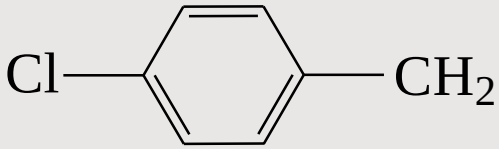
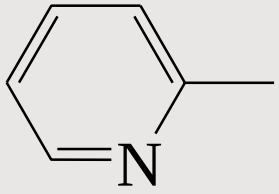
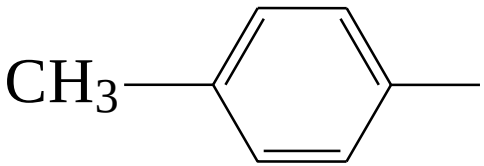
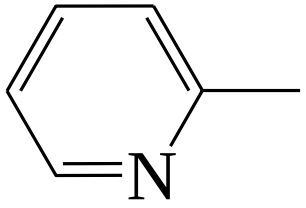
CHLORPHE R INAMINE			2-[P-Chloro-α[2-Dimethyl amino) Ethyl]benzyl]-pyridine

SAR:

- Phenyl substituent at P-position replaces with "Cl" is chlorpheniramine & "Br" is bromopheniramine.
- These halogenated pheniramines are more potent & have a longer duration of action.
- The agents in this class produce less sedation than the other classical antihistamines.

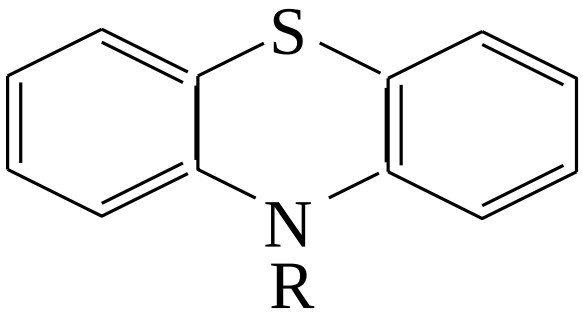
2) UNSATURATED ANALOGUES:

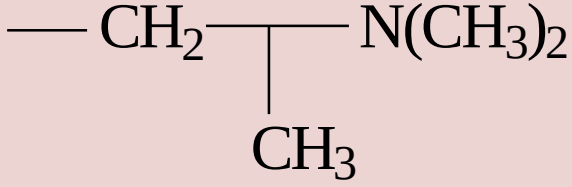
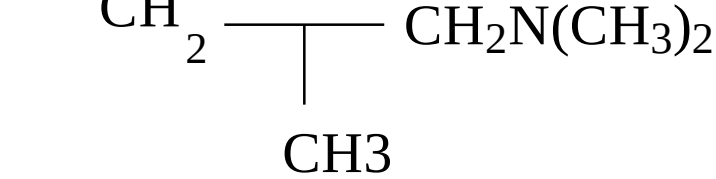


DRUG	Ar	Ar1
PYRROBUTAMINE		
TRIPROLIDINE		

d) PHENOTHIAZINE DERIVATIVES:

GENERAL STRUCTURE:



DRUG	R	CHEMICAL NAME
PROMETHAZINE		(±)10-[2-(Dimethylamino)propyl]phenothiazine
TRIMEPRAZINE		(±)10-[3-(Dimethylamino)-2-methylpropyl]phenothiazine.

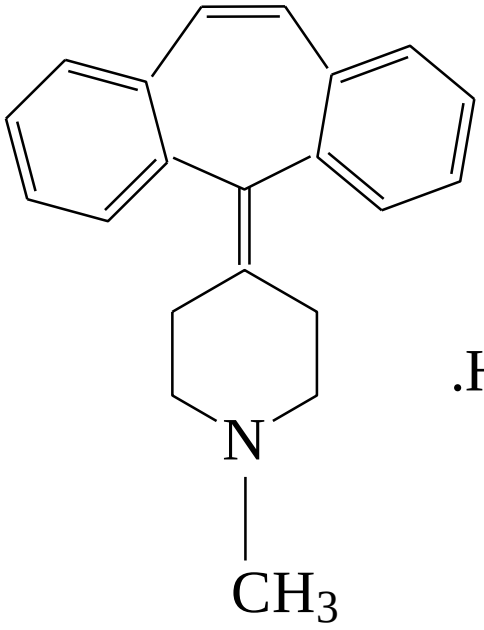
SAR

- Phenothiazine derivatives that contain a 2/3 carbon branched alkyl chain between alkyl chain between the ring system and terminal nitrogen atom.
- This differs the phenothiazine's from antipsychotic series in which an unbranched propyl chain is required.
- PROMETHAZINE, the parent member of this series is moderately potent & with prolonged action & pronounced sedative side effects.
- The combination of lengthening of side chain & substitution of lipophilic groups in 2nd position of aromatic ring results in compounds with decreased antihistaminic activity & increased psychotherapeutic properties.

METABOLISM:

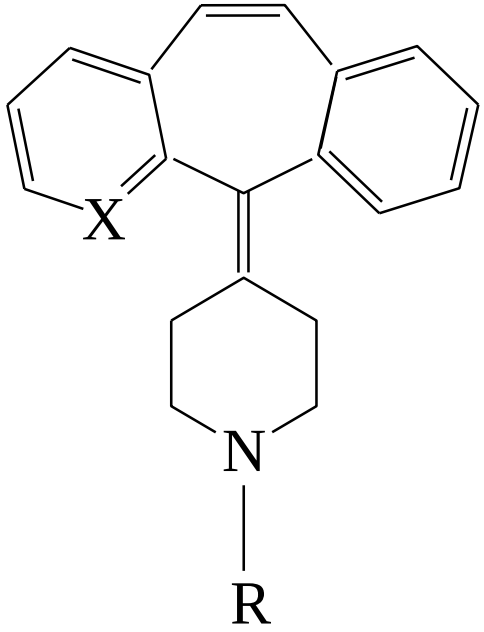
- These compounds undergo mono-di & N-dealkylation,sulfur oxidation, aromatic oxidation at 3rd position to yield phenol & N-oxidation.

DIBENZOCYCLOHEPTANES & DIBENZOCYCLOHEPTENES



.HCl

CYPROHEPTADINE

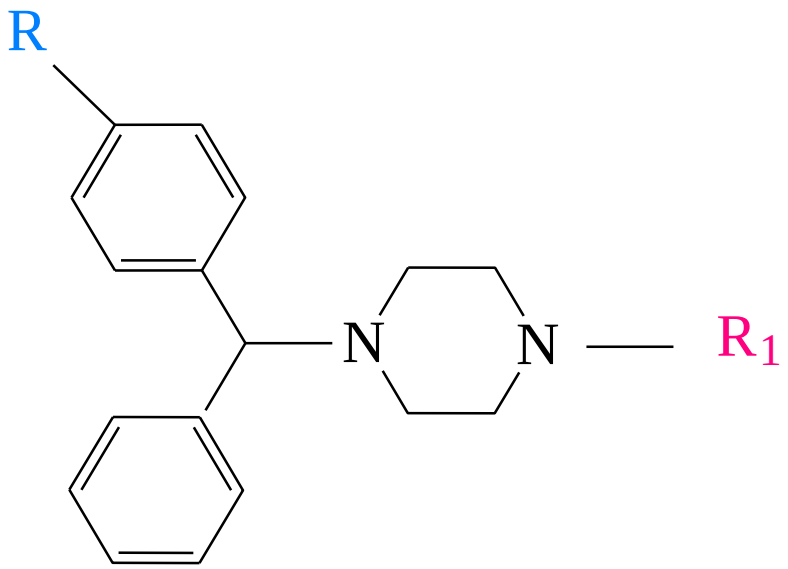


AZATIDINE

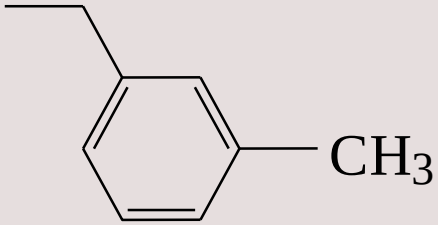
- These are the phenothiazine analogues in which sulfur atom is replaced by an isosteric vinyl group (cyproheptadine) or saturated ethyl bridge (AZATIDINE).

e) PIPERAZINE DERIVATIVES:

GENERAL STRUCTURE:



DRUG	R	R_1	CHEMICAL NAME
CYCLIZINE	H	CH_3	1-(Diphenylmethyl)-4-methyl piperazine.

CHLORCYCLINE	Cl	CH_3	1-(P-Chloro-α-phenylbenzyl)-4-methyl piperazine
MECLIZINE	Cl		1-(P-Chloro-α-Phenyl benzyl) -4-(m-methyl Benzyl)piperazine.

SAR:

- These are ETHYLENE DIAMINE derivatives.
- Connecting moiety(X) is CHN group.
- These are moderatly potent, with low incidence of drowsiness. slow onset of action & exhibit peripheral & central antimuscarnic activity.
- Primary structural difference is nature of para aromatic ring substituent.

MECHANISM OF ACTION

- H_1 antagonists 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 muscle in the respiratory, GIT.

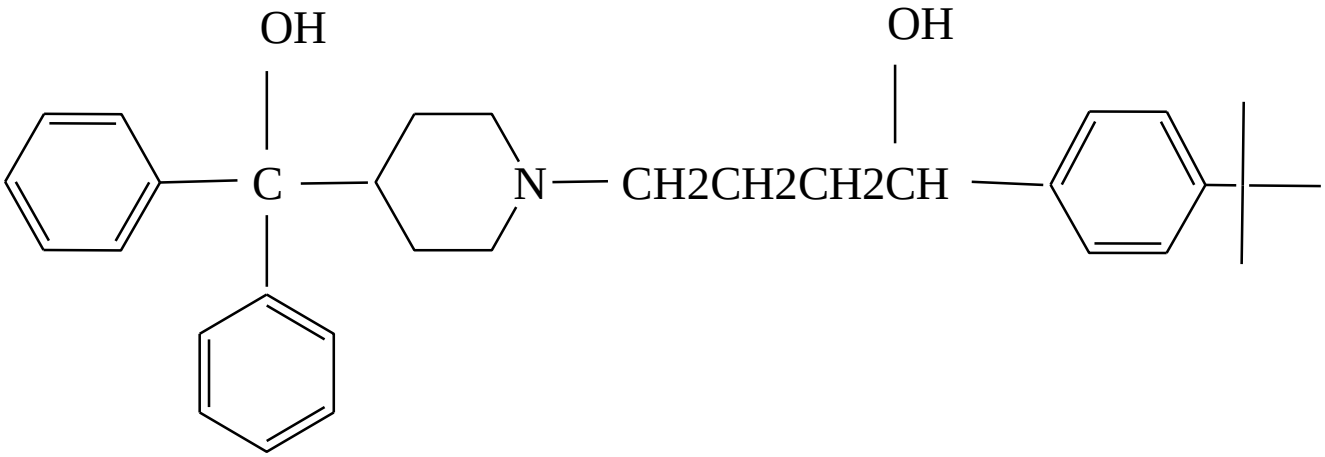
H_1 ANTAGONISTS (FIRST GENERATION)

- These are classical antihistamines.
- These are clinically used in the treatment of histamine mediated allergic conditions.
- These are mainly used in allergic rhinitis, allergic conjunctivitis, allergic dermatological conditions.

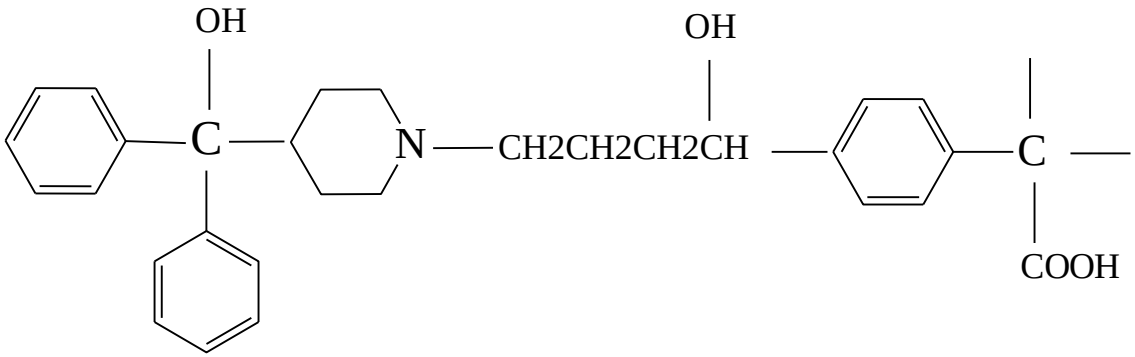
ADVERSE EFFECTS:

- The main adverse effect of H_1 antagonists first generation is SEDATION.
- This is evidenced by drowsiness, diminished alertness.
- This is due to their relative lack of selectivity for the PERIPHERAL H1 RECEPTOR,.

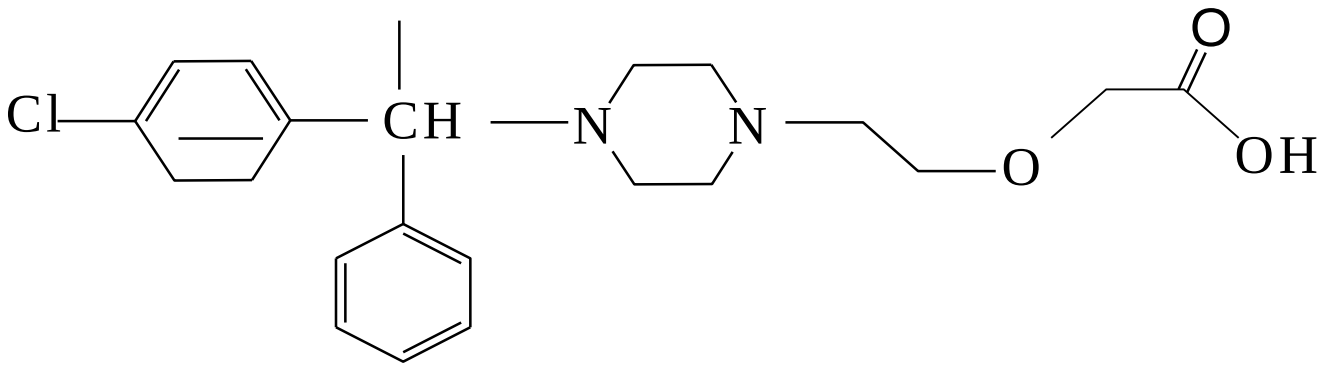
SECOND GENERATION H_1 ANTAGONISTS(NON-SEDATIVE)



TERFENADINE



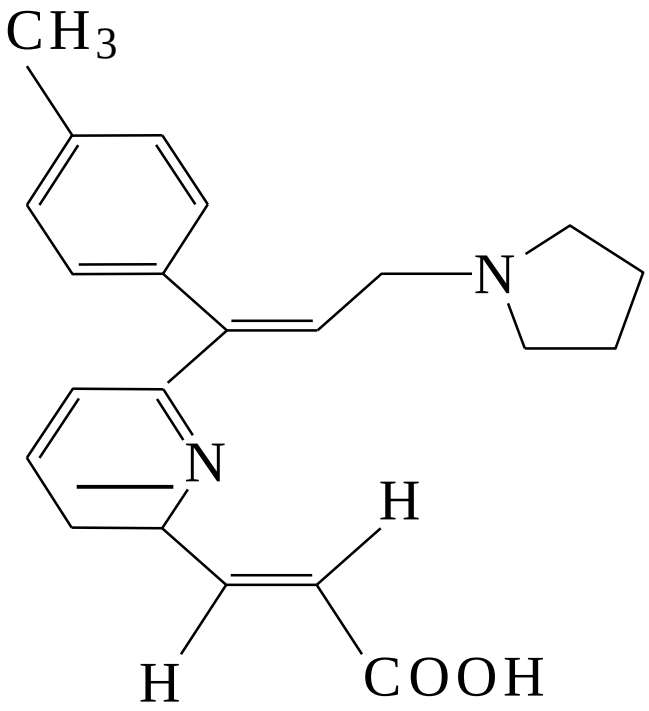
FEXOFENADINE



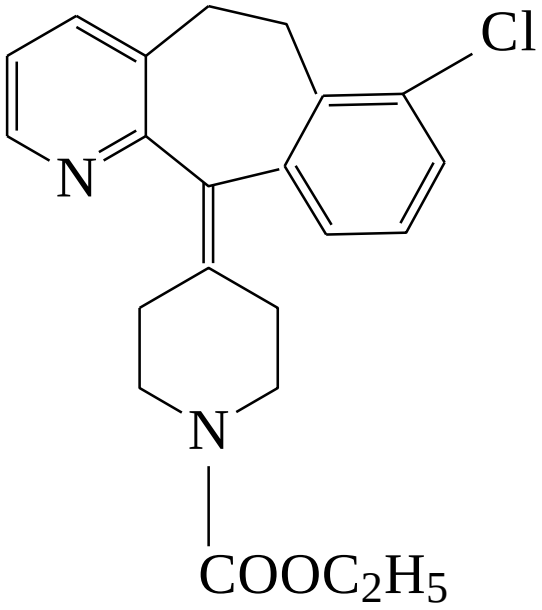
CETIRIZINE

- 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.
- TERFENADINE is a long acting H_1 antagonist.
- FEXOFENADINE is a primary oxidative metabolite of TERFENADINE& does not cross the BBB.

THIRD GENERATION H_1 ANTIHISTAMINES



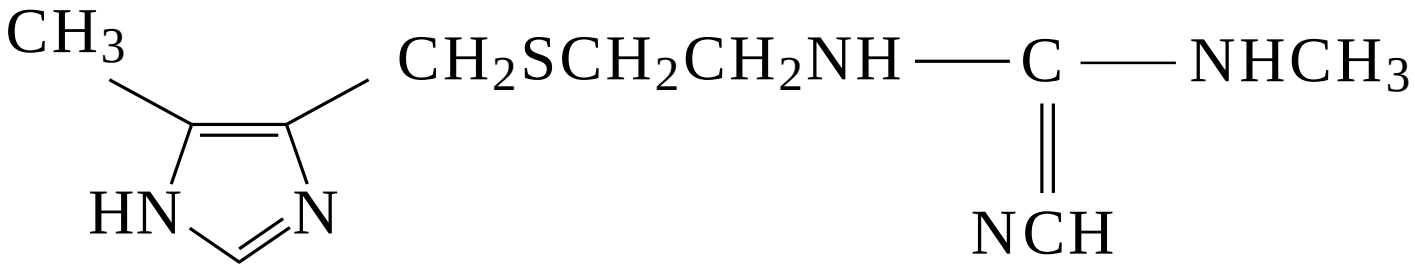
ACRIVASTINE



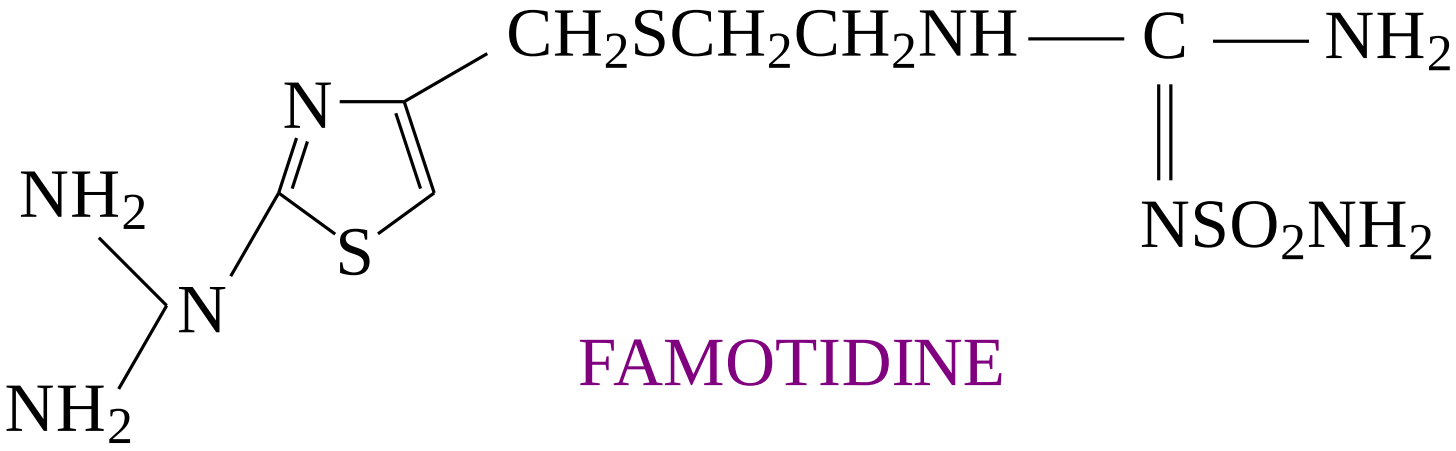
LORATIDINE

- These are active metabolite derivatives of second generation drugs intended to have increased efficacy with fewer adverse drug reactions.

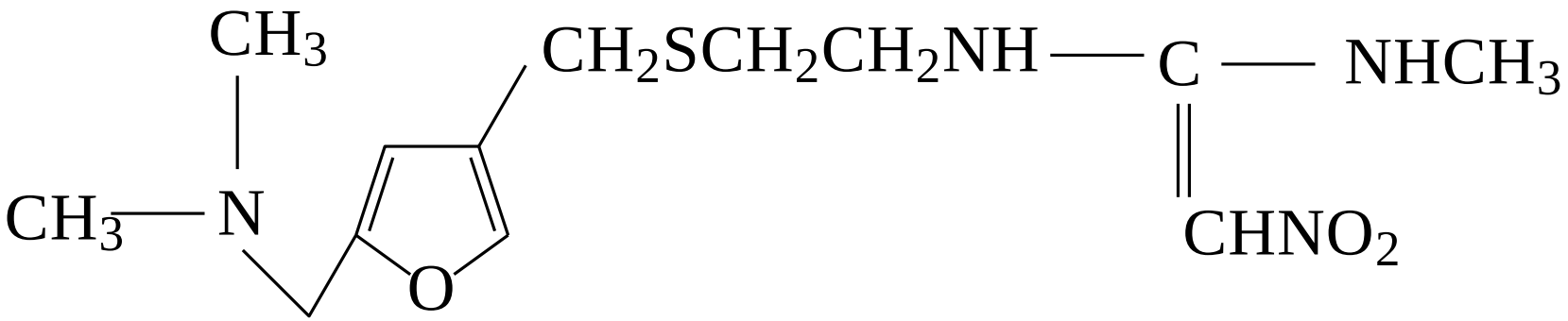
H_2 ANTAGONISTS



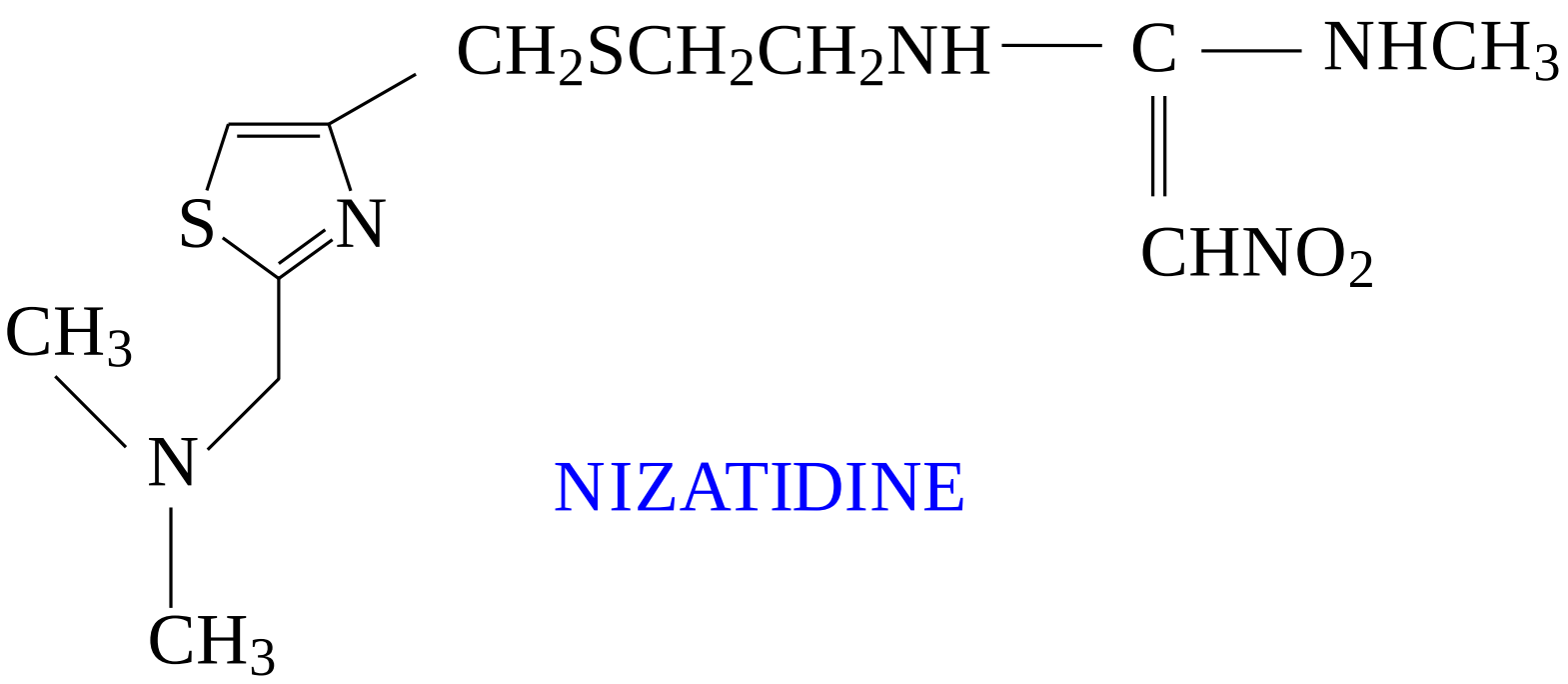
CIMETIDINE



FAMOTIDINE



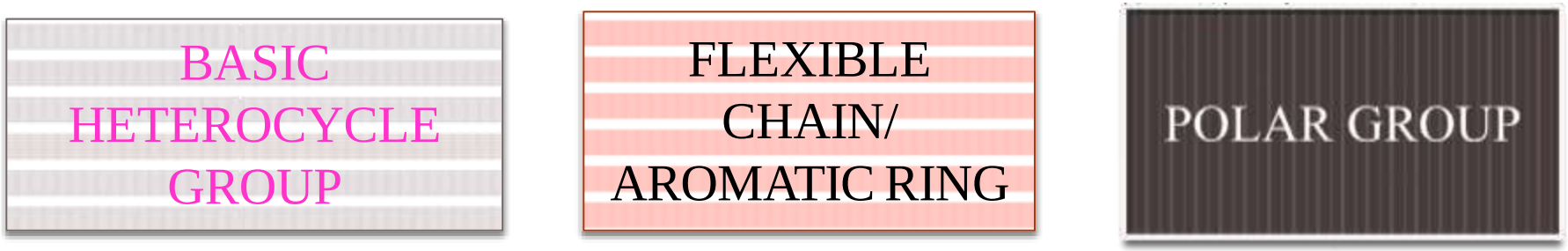
RANITIDINE



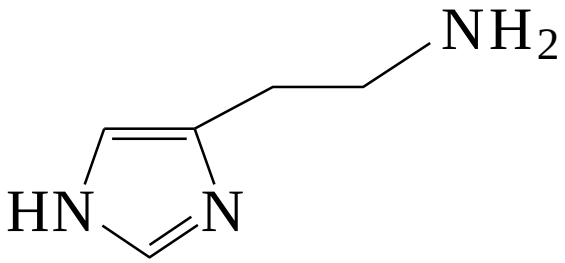
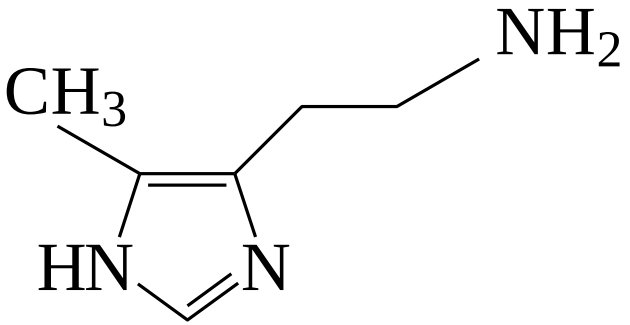
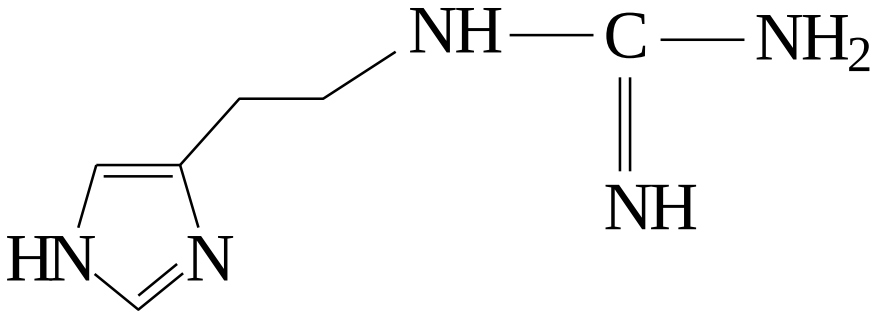
NIZATIDINE

SAR & STRUCTURAL REQUIREMENTS:

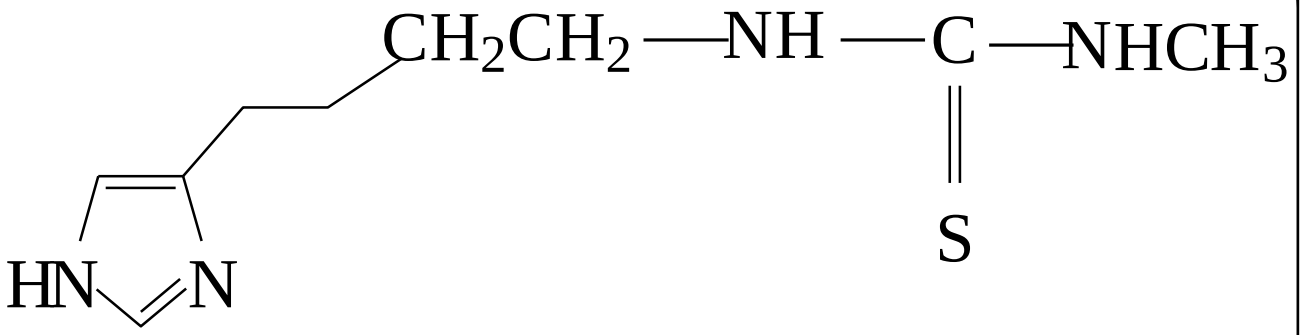
GENERAL FORMULA FOR H_2 ANTAGONISTS:



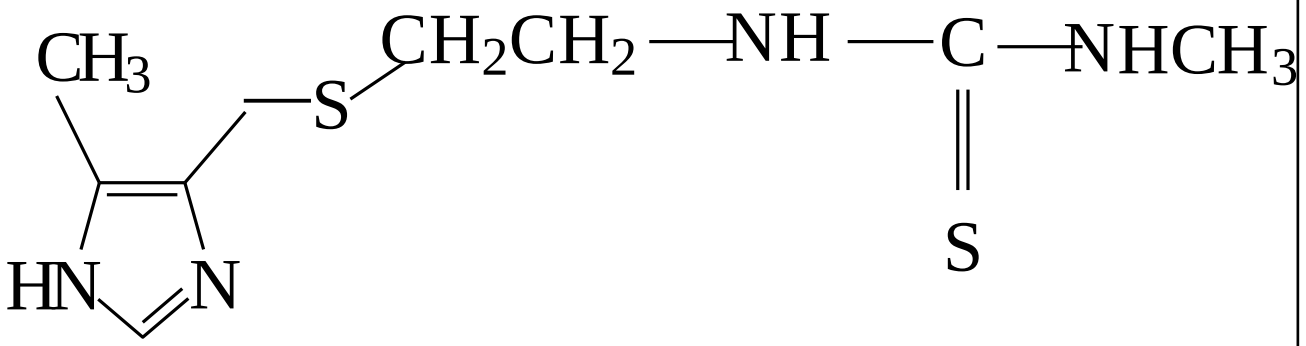
- These are the result of modification of histamine structure.
- The imidazole ring of histamine is not required for competitive antagonism of histamine at H_2
- Separation of ring & nitrogen group with the equivalent of 4 carbon chain is necessary for optimum antagonist activity.
- The terminal nitrogen group should be polar,non-basic substituents for maximal activity.

SAR	STRUCTURE
HISTAMINE:H_1=H_2 Agonism	
5-Methylhistamine:H_2>H_1 Agonism	
N-Guanylhistamine:Partial H_2 agonist (weak – antagonist)	

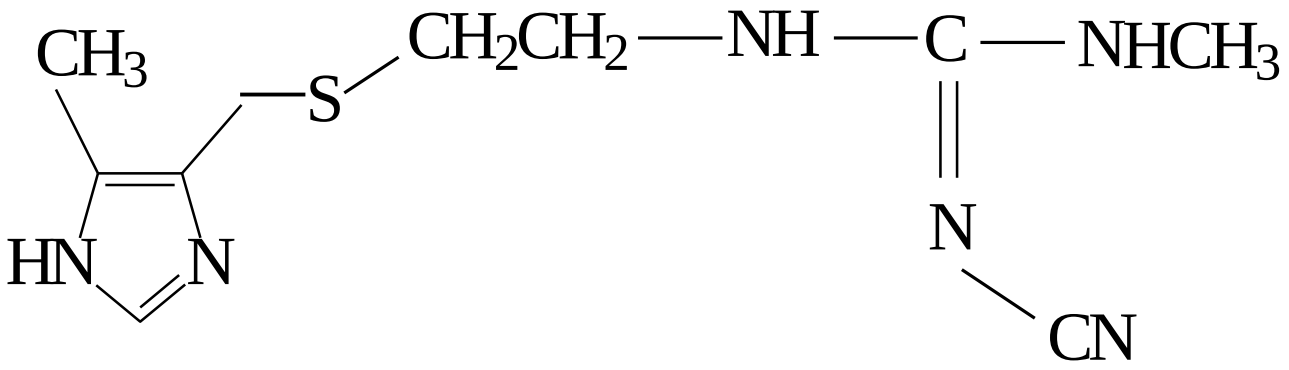
Burimamide:
Full H2 Antagonist.
low potency



Metiamide:
Full H2 antagonist.
Higher potency

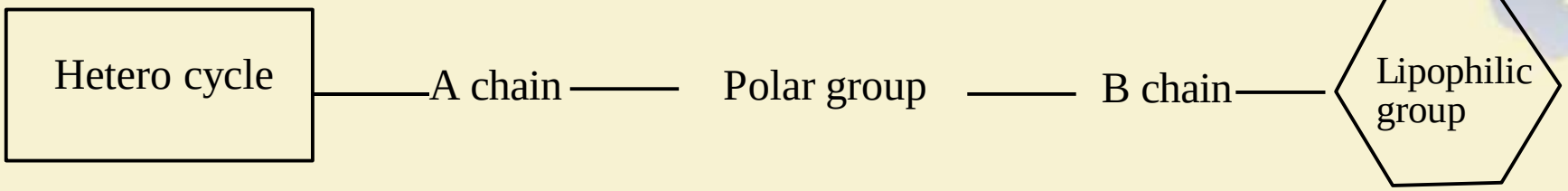


Cimetidine:
Full H2 antagonist
Higher potency

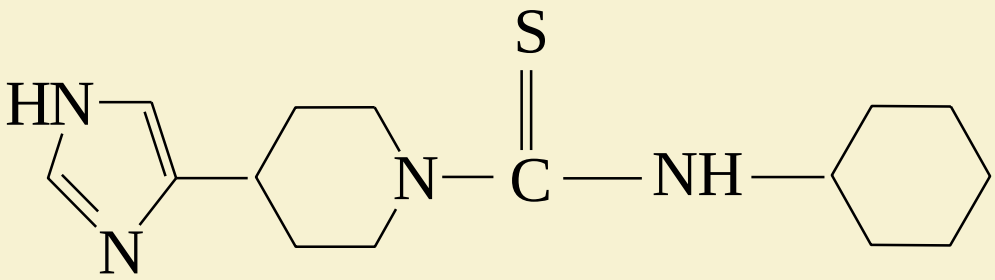


H_3 ANTAGONISTS

General structure:



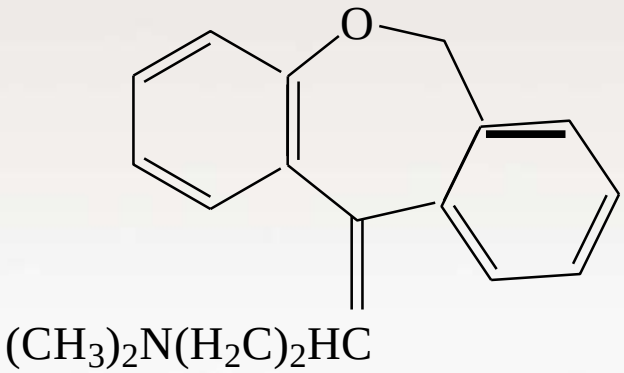
DRUGS:



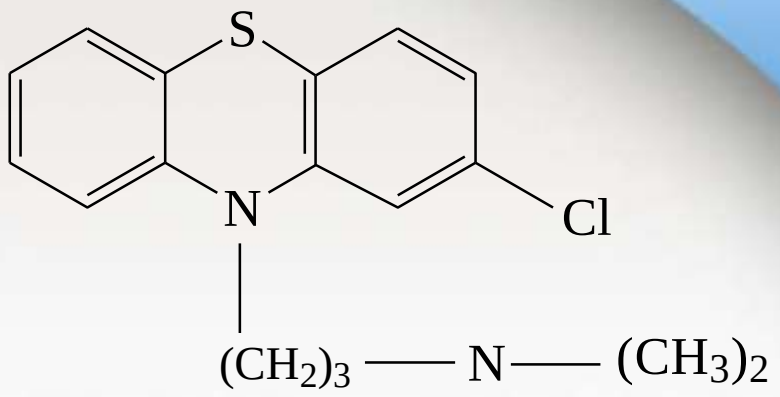
THIOPERAMIDE

- This THIOPERAMIDE was first potent H3 antagonist used to treat sleep disorders.

H_4 ANTAGONISTS



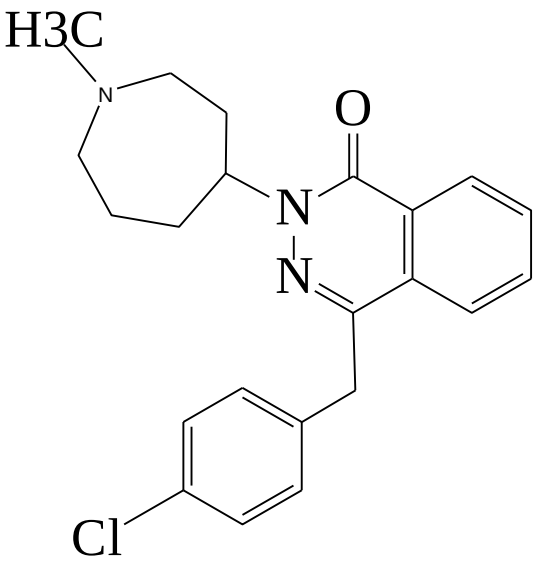
DOXEPINE



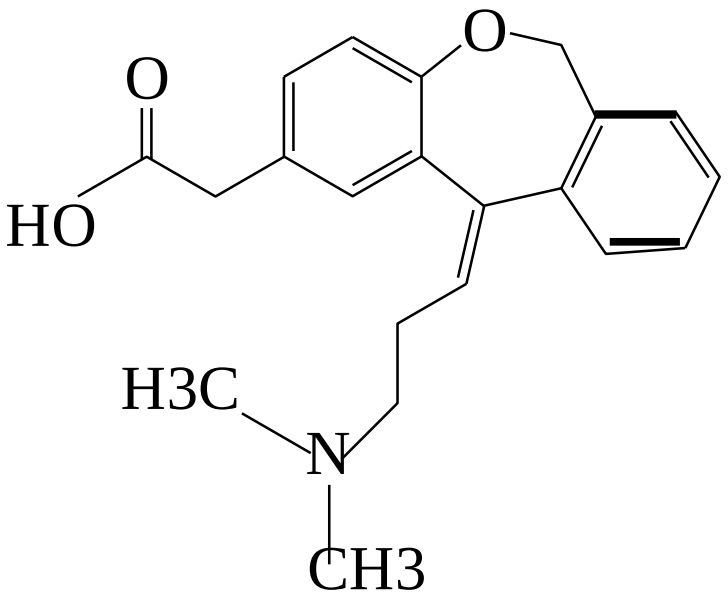
CHLORPROMAZINE

- This DOXEPINE, CHLORPROMAZINE are bind to the H_4 receptor with high affinity.

DRUGS HAVING DUAL ACTION



AZELASTINE



OLOPAT
IDINE

- Both the drugs having the action of antihistaminic & mast cell stabilization.
- Both are used in allergic conjunctivitis.

USES OF ANTIHISTAMINES

ALLERGIC DISORDERS:

- They effectively control certain immediate type of allergies like itching, urticaria, seasonal hay fever, allergic conjunctivitis & angioedema of lips eyelids etc.,
- CETIRIZINE have adjuvant role in seasonal asthma.

PRURITIS:

- Antihistamines are first choice of drugs for idiopathic pruritus.

COMMON COLD:

- They donot effect the illness but may afford sympatomatic relief by anticholinergic & sedative actions.

  As hypnotics eg: diphenhydramine & promethazine.

- As “anti-tussives” Eg: diphenhydramine.
- As “anti-emetic” Eg: meclizine
- In “parkinsonism” Eg: promethazine , diphenhydramine.
- In drug induced “acute dystonias” Eg: diphenhydramine, promethazine.
- To treat “motion & morning sickness” Eg: cyclizine, promethazine.
- To treat “vertigo” conditions Eg: cinnarizine.


Thank you!