H_1 AND H_2 RECEPTOR ANTAGONIST

CONTENTS:

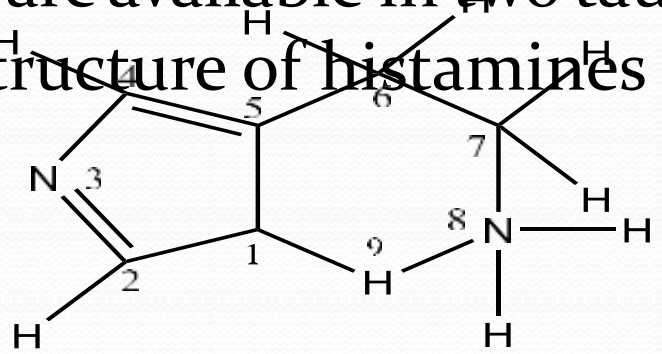
- Brief introduction about **Histamine.**
- Antihistamine introduction and classification.
- H1 receptors antagonist
- H2 receptor antagonist
- Reference books

INTRODUCTION:

Histamine is a chemical messenger which are synthesized in the mast cells.

Structurally histamines is 4-(2-amino ethyl)-immidazole.

The histamines are available in two tautomeric forms. The general structure of histamines looks like.



Generally histamines are found in theanimal tissue, venoms of insect, bacteria and plant.

Pharmacologically histamine causes the **vasodilatation of capillaries** and which **increase the rate of flow and this cause edema**, **increase heart rate**, **stimulate gastric fluids and which lead to the formation of ulcers**.

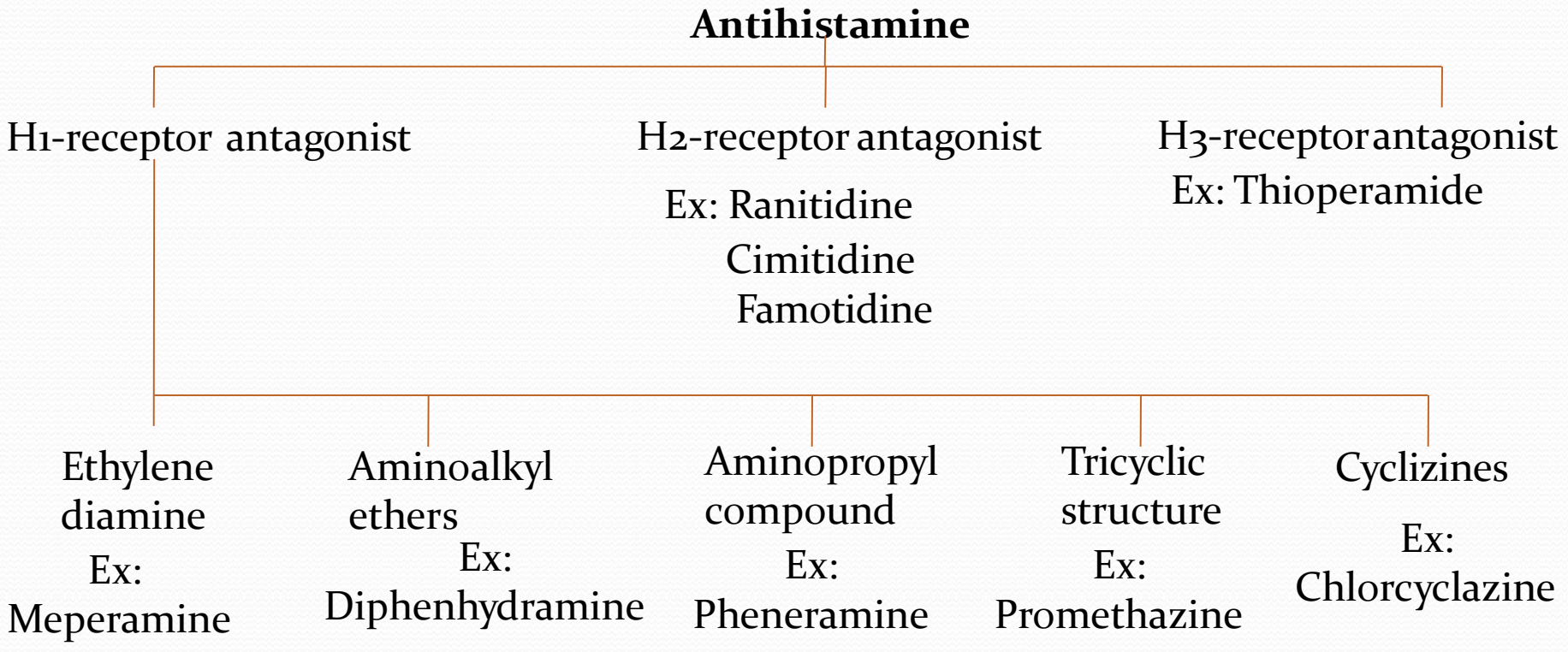
The human body contains histaminic receptor and are divided into three different types upon their action.

1. **H1-receptors**
2. **H2-receptors**

NAME OF RECEPTOR	PLACE WHRE IT PRESENT IN OUR BODY	ATAGONIST FOR RECEPTOR
H1 Receptor	Smooth muscle, Intestine, Bronchi & Blood vessel	Mepyrmine
H2 Receptor	T-lymphocyte, Basophile & Mast cell	Cimitidine,Ranitidine
H3 Receptor	Neuron (This receptor help to release the histamine and other transmitters).	Thioperamide

ANTIHISTAMINES: These are the agents which block the action of histamines.

Classification:



H1 receptor antagonist (Classical histamine):

INTRODUCTION:

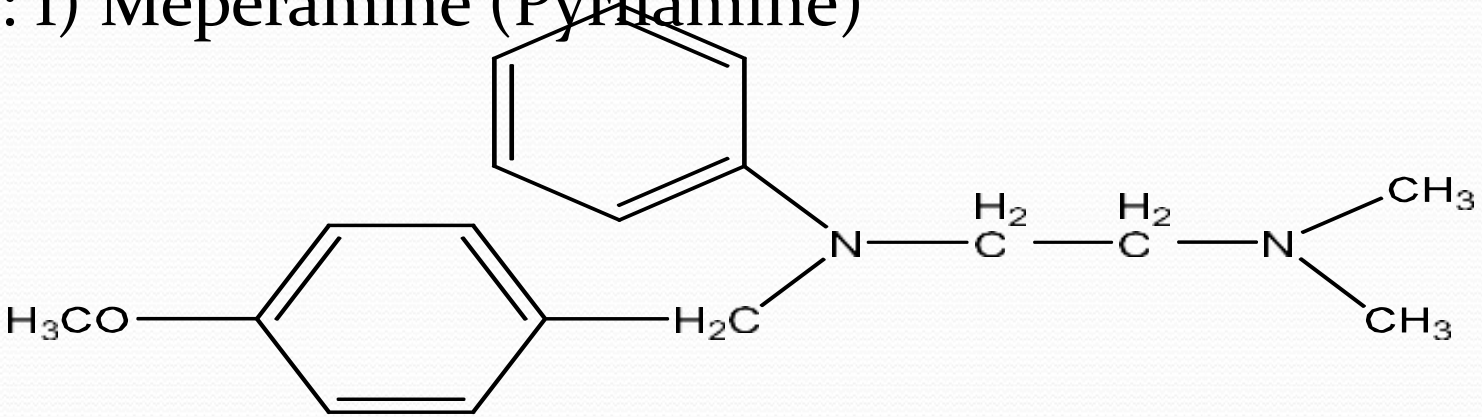
In the year 1933 the first drug **Piperoxan** invented by **Bovet** & **Furnease**. This drug can protect the animal from **bronchial spasm**. This drug is the inititation for the discovery of the H1-receptorantagonist.

In the year 1942, **Halpen** researched and reported about 24 derivatives of ethylene diamine in which **Phenbenzamine** was found to be most potent and

Classification:

- Ethylene diamine derivatve

  Ex: 1) Meperamine (Pyrilamine)

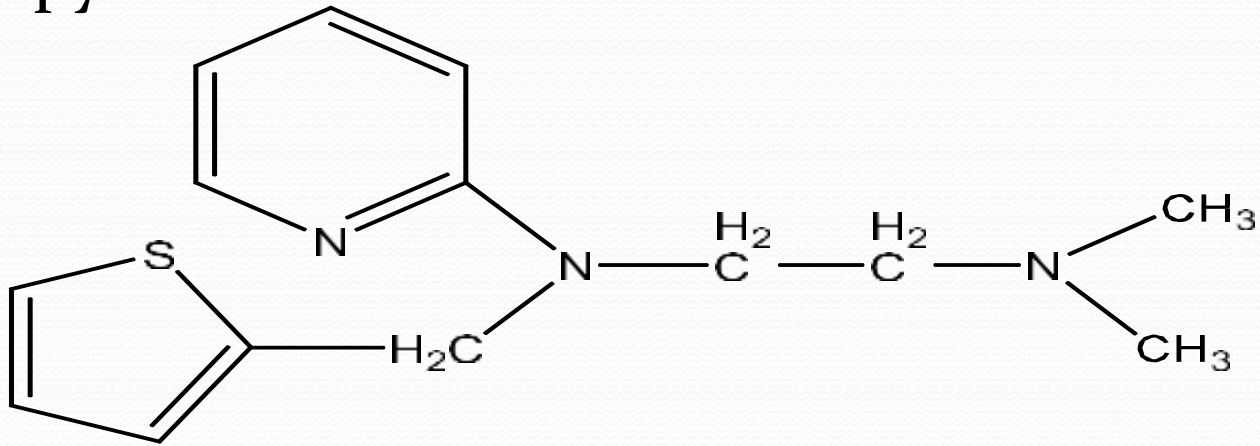


Solubility: Freely soluble in **water** & **alcohol** ; **Melting point**: 98-101°C

Uses: Antihistaminic,

Antitussive,

2) Methapyrilene:



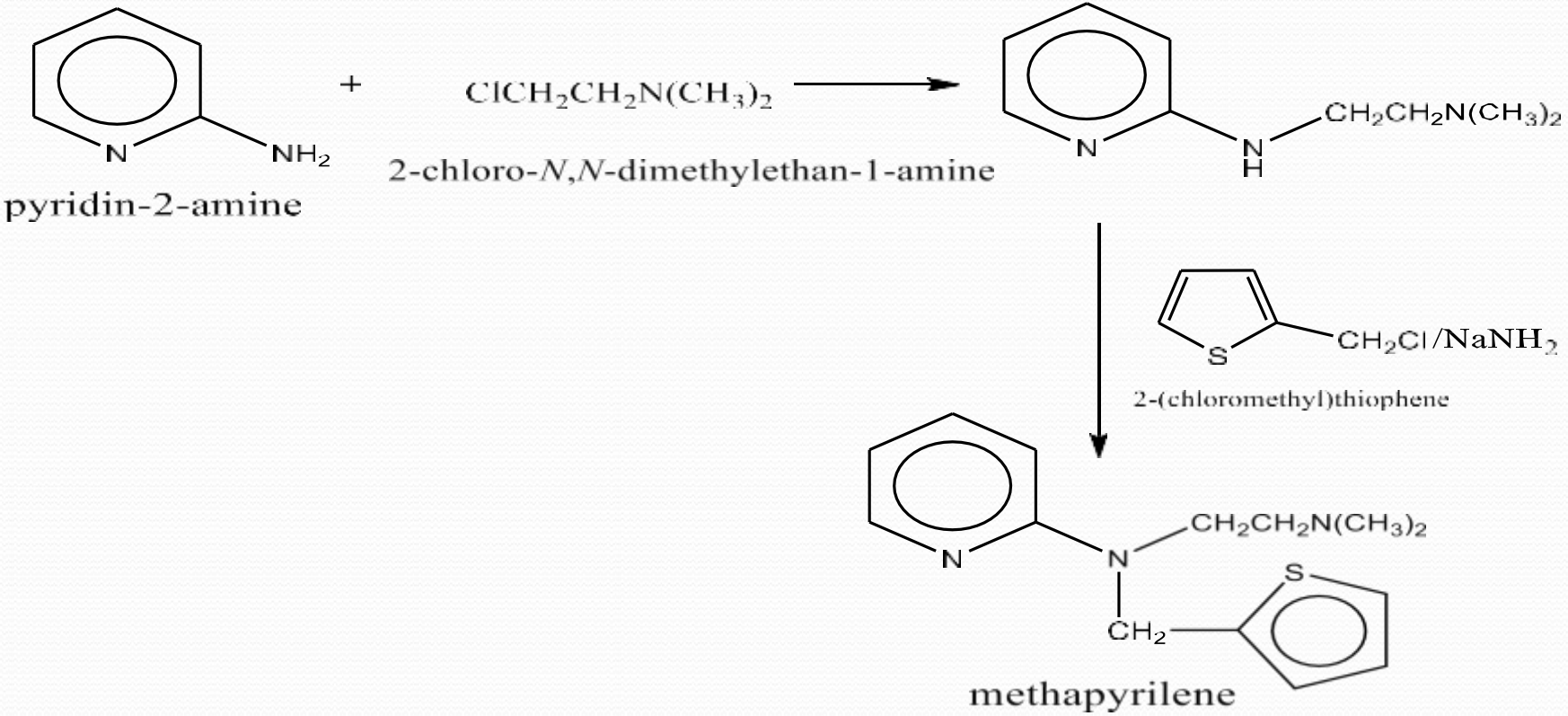
Melting point: 324°F

Uses: Antihistamine

Anticholinergic

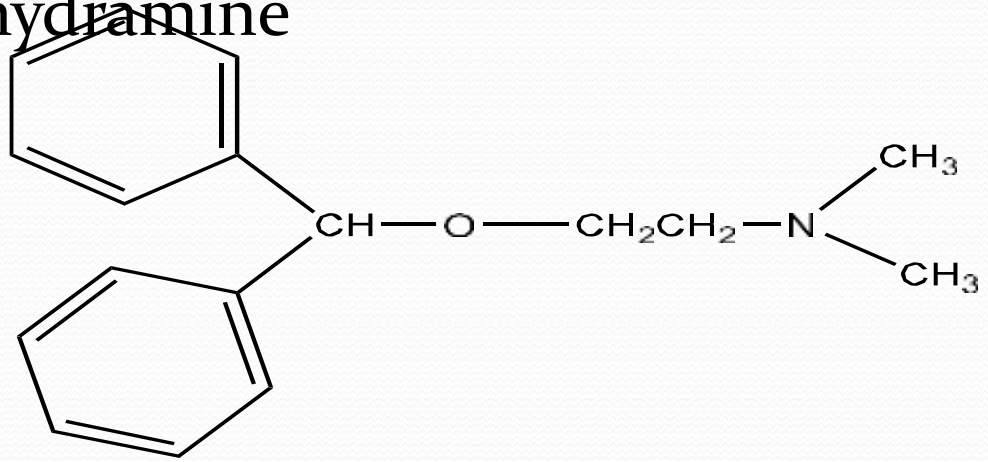
Strong sedative

Synthesis:


N
NH2
pyridin-2-amine
+
ClCH2CH2N(CH3)2
2-chloro-N,N-dimethylethan-1-amine
N
N
H
CH2CH2N(CH3)2
S
CH2Cl/NaNH2
2-(chloromethyl)thiophene
N
N
CH2CH2N(CH3)2
CH2
S
methapyrilene

- Aminoalkyl ethers

Ex: 1) Diphenhydramine



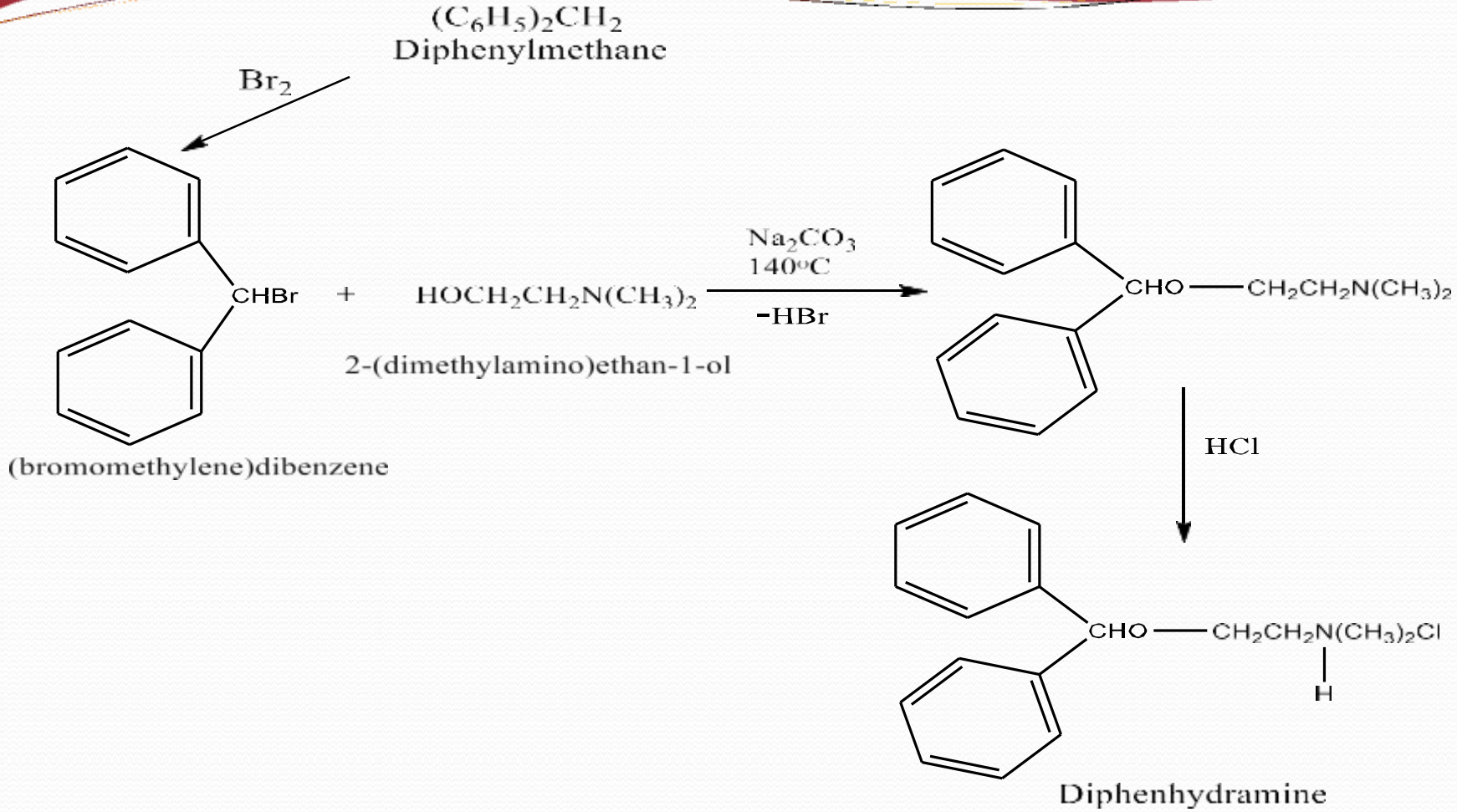
Solubility: Freely soluble in **water & alcohol** ; **Melting point**:168-172°C

Uses: Anticholinergic

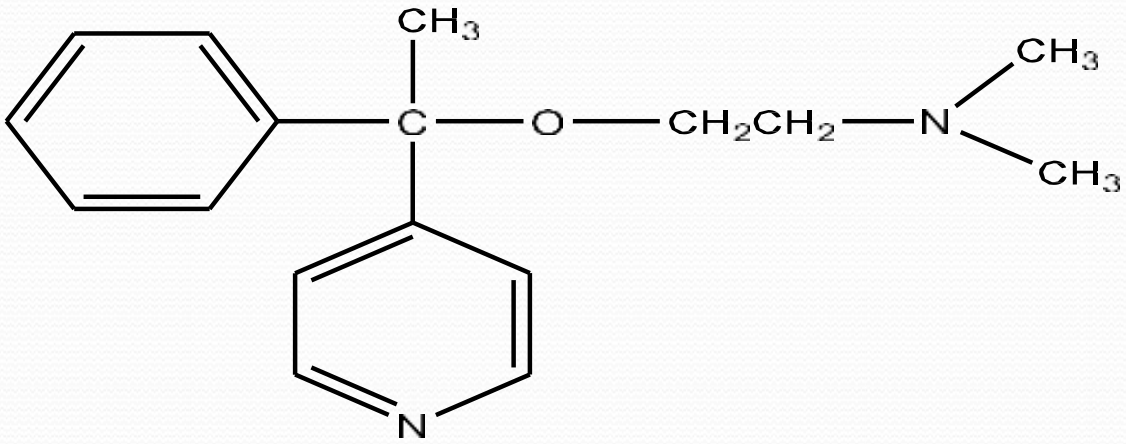
Sedative

Treat motion sickness

Synthesis:


(C6H5)2CH2
Diphenylmethane
Br2
CHBr
+
HOCH2CH2N(CH3)2
Na2CO3
140°C
-HBr
2-(dimethylamino)ethan-1-ol
CHO
CH2CH2N(CH3)2
HCl
CHO
CH2CH2N(CH3)2Cl
H
(bromomethylene)dibenzene
Diphenhydramine

2) Doxylamine:



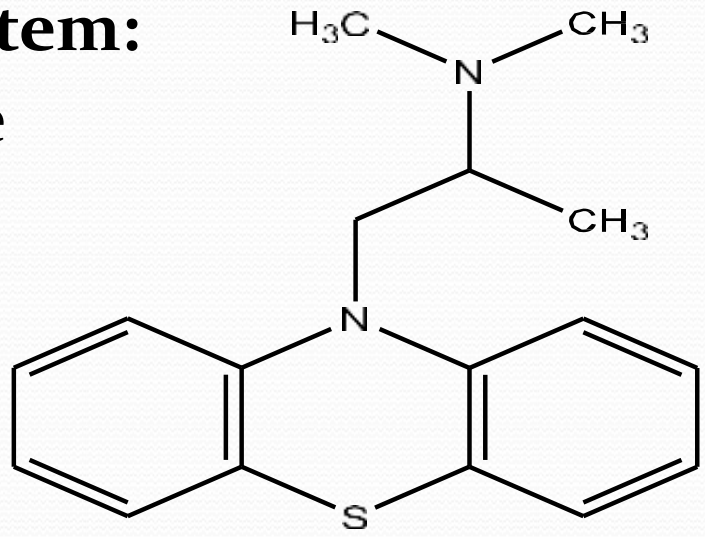
Melting point: 100-104℃

Uses: Antihistamine

Short-term sedative

- **Tricyclic ring system:**

Ex: 1) Promethazine



promethazine

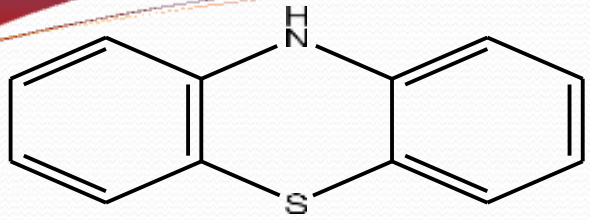
Melting point: 446-450°F

Uses : Anti emetic effect

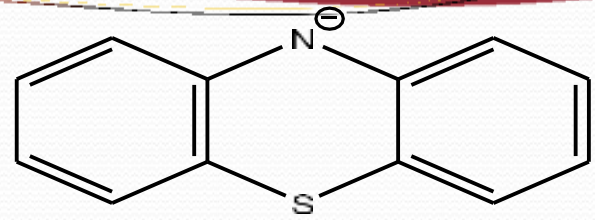
Tranquilizing action

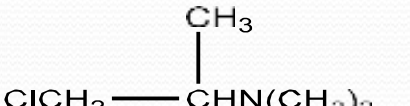
Analgesic and Sedativeeffect

Synthesis:

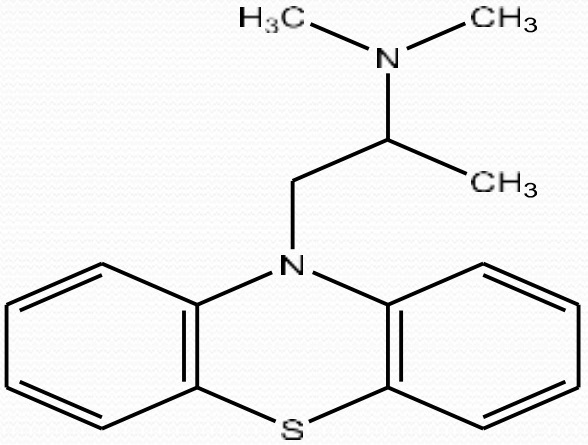


phenothiazine



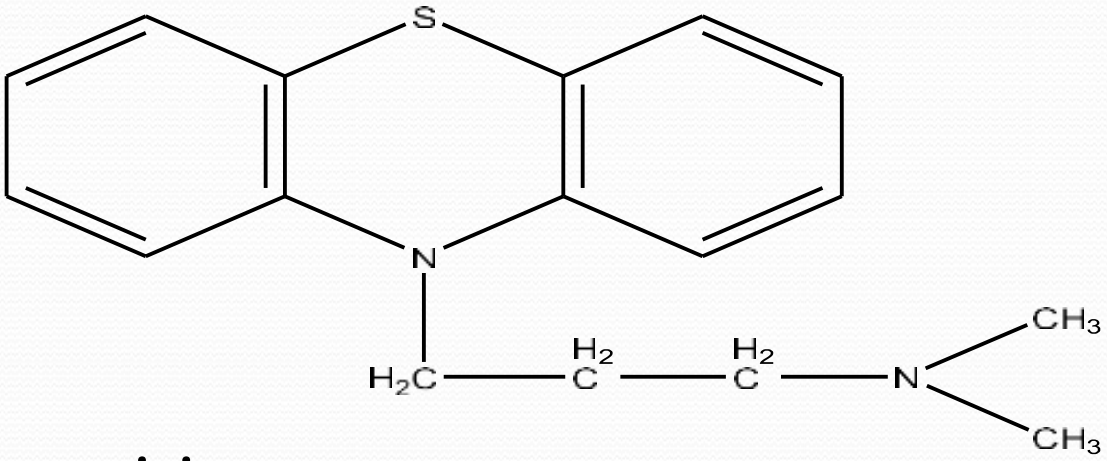


1-chloro-*N*,*N*-dimethylpropan-2-amine



PROMETHAZINE

2)Trimeprazine (Alimemazine):



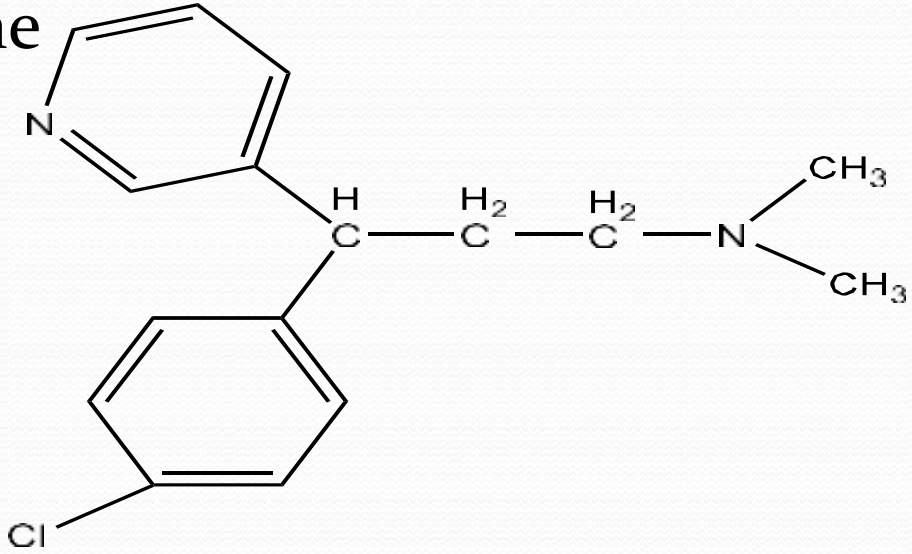
Uses: Antipruritic

Antiemetic

Sedative and Hypnotic

- **Propylamine derivative**

Ex: Chloropheneramine



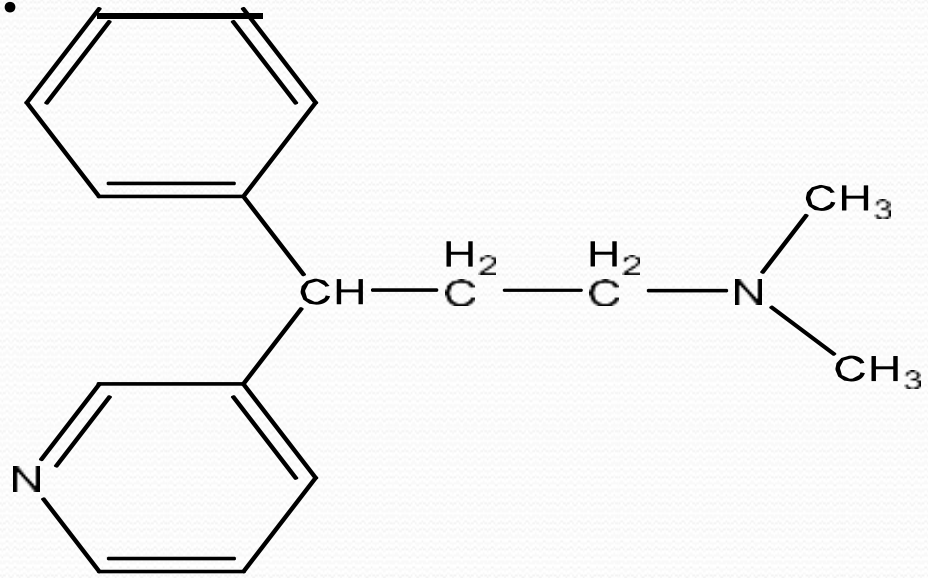
Melting point: 130-135°C

Uses : Effective in **allergic** and **vasomotorrhinitis**.

Adjunct therapy in **anaphylactic shock**.

Antitussive .

2) Pheniramine:

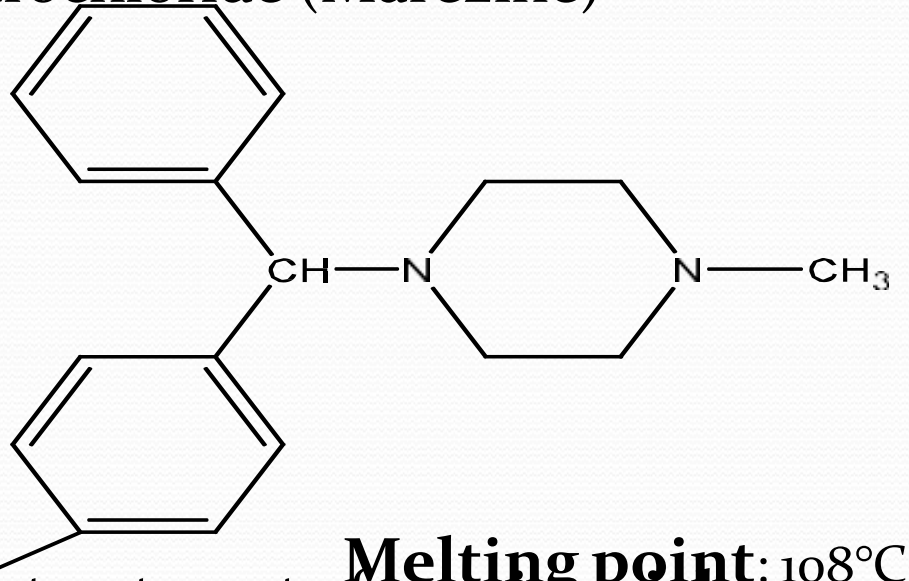


Melting point: 104-108°C

Uses: Antihistamine

- **Cyclic basic chain analogues:**

Ex: Cyclizine Hydrochloride (Marezine)

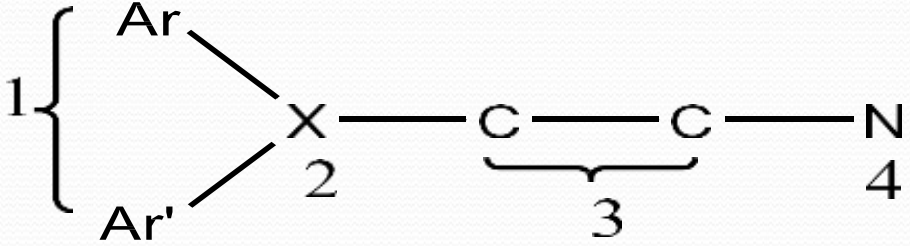


Melting point: 108°C

Uses: Used in the treatment of **motionsickness**.

Prophylaxix.

SAR of H1 receptors



- In the above general structure, **Ar** is aryl group and **Ar'** is **aryl** or **aryl methyl** group
- In the general structure the **X** part determines the **class of drug** to which that belongs I.e. if X=O (amino alkyl analogue), X=N (Ethylene diamine derivative).

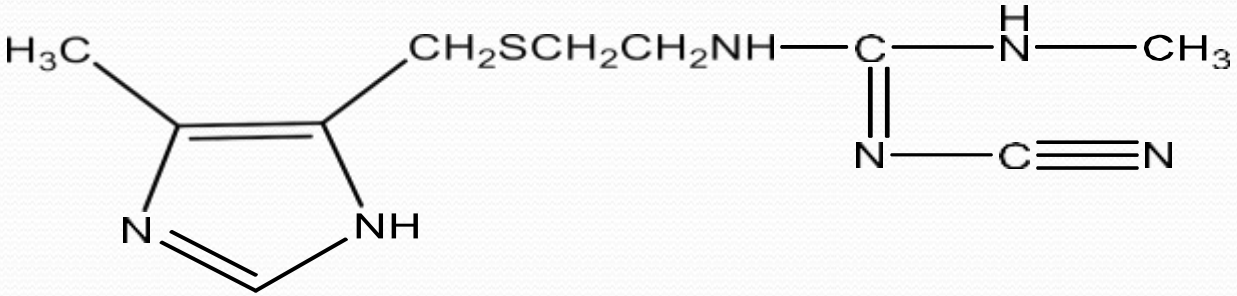
•Most of the H1 antagonist have ethylene chain, extension of this chain or branching of thischain lead to reduce the activity of the compound.

•Homologation played to improve the drug like **tricyclic anti-depressents**, **neruroleptics** .

•Due to the closeresemblance of **antihistamine structure** to the **cholinergic blocking agent**, most of the antihistamines **show the activity of anti-cholinergic activity** .

H2 receptor antagonist:

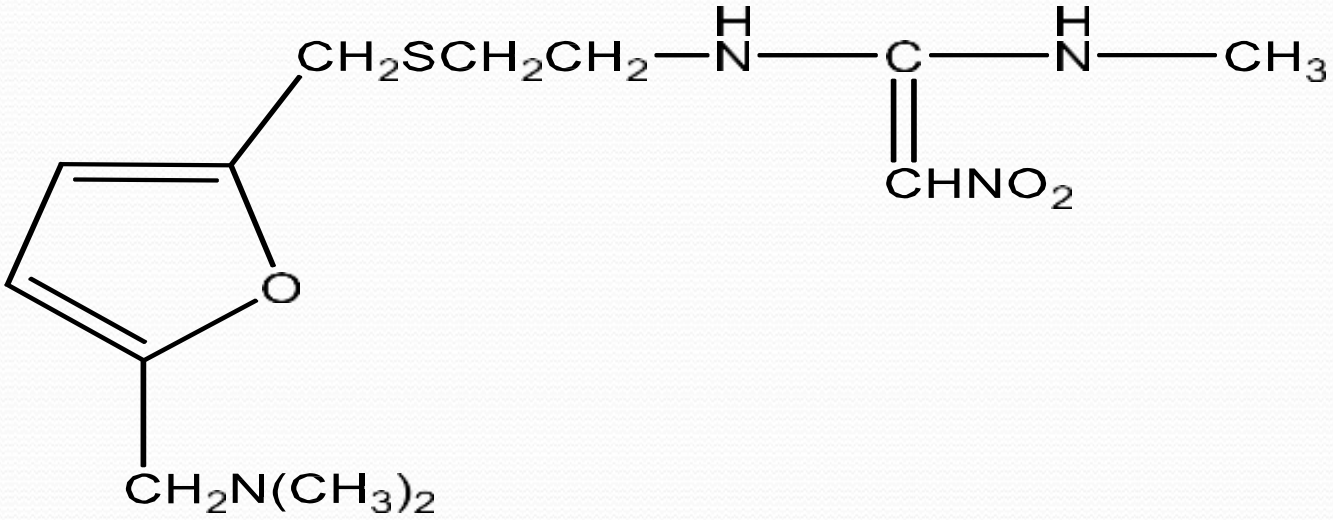
- Cimetidine



Uses: To treat ulcer

Used to treat gastroesophagel reflux disease (GERD)

2) Ranitidine (Zantac):

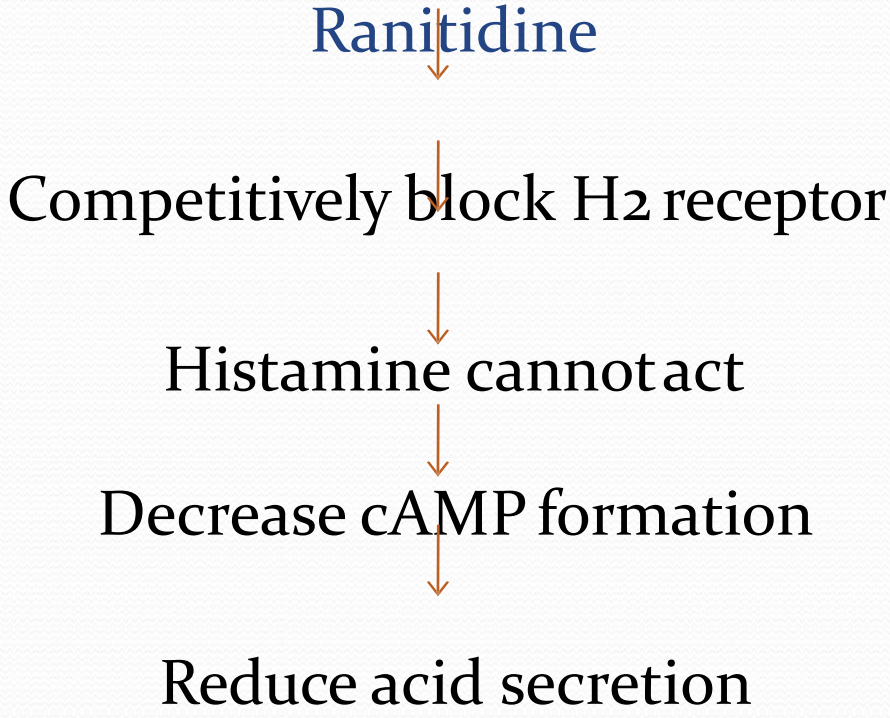


Uses: To treat ulcer

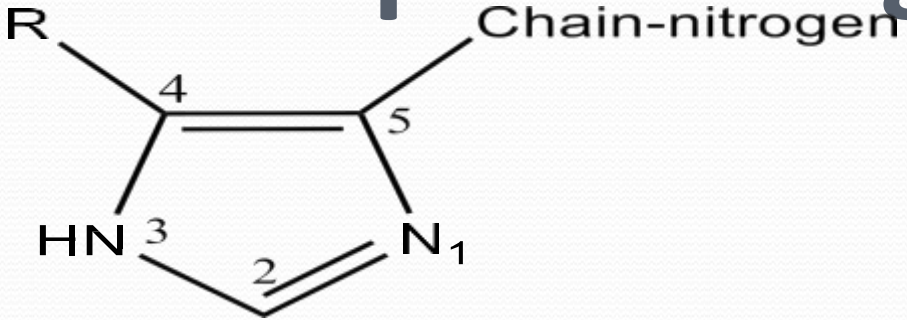
Used to treat gastroesophagel reflux disease (GERD)

Zollengers-Ellison Syndrome

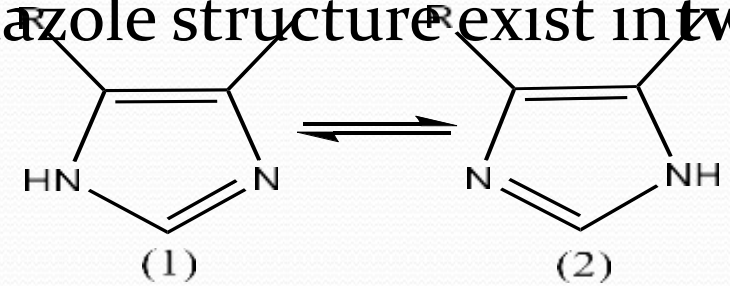
- **Mechanism of action:**



SAR of H2 receptor antagonist:



- In the H2 receptor, **immidazole structure** believed to be **important for receptor action**.
- The immidazole structure exist in **two** forms.



- The **form (1)** seems to be necessary for **maximal H2-antagonist activity**. Where the **R** is substituted **with CH_3** the **activity becomes potent**.
- Chain of **four carbon atom is optional for the activity**, **shorter chain drastically lowers the activity**. The **presence** of **thioether (-S-)** in the **methylene place** (-CH_3-) lead to **more activity**.
- The presence of **terminal N** group **increase the activity**.

Reference:

- A text book of Medicinal chemistry (vol-1) by Suresh N. Pandeya.
- Principles of Medicinal Chemistry (vol-2) by Kadam.
- Medicinal chemistry by Ashutosh Kar.
- Internet

THANK YOU