H₁ AND H₂ 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-aminoethyl)-immidazole.
The histamines are available in two tautomeric forms. The general structure of histamines looks like.
Generally histamines are found in the animal 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
3. H3 receptors
<table>
<thead>
<tr>
<th>NAME OF RECEPTOR</th>
<th>PLACE WHERE IT PRESENT IN OUR BODY</th>
<th>ATAGONIST FOR RECEPTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 Receptor</td>
<td>Smooth muscle, Intestine, Bronchi &amp; Blood vessel</td>
<td>Mepyrmine</td>
</tr>
<tr>
<td>H2 Receptor</td>
<td>T-lymphocyte, Basophile &amp; Mast cell</td>
<td>Cimitidine, Ranitidine</td>
</tr>
<tr>
<td>H3 Receptor</td>
<td>Neuron (This receptor help to release the histamine and other transmitters)</td>
<td>Thioperamide</td>
</tr>
</tbody>
</table>
ANTIHISTAMINES: These are the agents which block the action of histamines.

Classification:

- H1-receptor antagonist
  - Ex: Meperazine
  - Ethylene diamine
  - Ex: Diphenhydramine
  - Aminoalkyl ethers
  - Ex: Phenerazine

- H2-receptor antagonist
  - Ex: Ranitidine
  - Cimetidine
  - Famotidine
  - Aminopropyl compound
  - Ex: Promethazine
  - Tricyclic structure
  - Ex: Chlorcyclazine

- H3-receptor antagonist
  - Ex: Thioperamide
  - Cyclizines
  - Ex: Chlorcyclazine
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 initiation for the discovery of the H1-receptor antagonist.

In the year 1942, Halpen researched and reported about 24 derivatives of ethylene diamine in which Phenbenzamine was found to be most potent and this is used the first H1-antagonist used clinically.
Classification:
- Ethylene diamine derivative
  Ex: 1) Meperamine (Pyrilamine)

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

Uses: Antihistaminic, Antitussive, Less sedative
2) Methapyrilene:

Melting point: 324°F

Uses: Antihistamine
Anticholinergic
Strong sedative
Synthesis:

\[
\text{pyridin-2-amine} + \text{ClCH}_2\text{CH}_2\text{N(CH}_3)_2 \rightarrow \text{methapyrilene}
\]

2-chloro-\( N,N \)-dimethylmethan-1-amine

2-(chloromethyl)thiophene
Aminoalkyl ethers

Ex: 1) Diphenhydramine

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

Uses: Anticholinergic
      Sedative
      Treat motion sickness
Synthesis:

\[
\text{(bromomethylene)dibenzenene + HOCH}_2\text{CH}_2\text{N(CH}_3\text{)}_2 \xrightarrow{\text{Na}_2\text{CO}_3, 140^\circ\text{C}} \xrightarrow{-\text{HBr}} \text{CHO} \xrightarrow{\text{HCl}} \text{CHO} \xrightarrow{\text{H}} \text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2\text{Cl}
\]

\[
\text{(C}_6\text{H}_5\text{)}_2\text{CH}_2 \quad \text{Diphenylmethane}
\]

2-(dimethylamino)ethan-1-ol
2) Doxylamine:

Melting point: 100-104°C

Uses: Antihistamine
Short-term sedative
• **Tricyclic ring system:**
  
  Ex: 1) Promethazine

  Melting point: 446-450°F
  Uses: Anti emetic effect
  Tranquilizing action
  Analgesic and Sedative effect
Synthesis:

\[
\text{phenothiazine} \rightarrow \text{NaNH}_2 \rightarrow \text{1-chloro-}N,N\text{-dimethylpropan-2-amine} \rightarrow \text{promethazine}
\]
2) Trimeprazine (Alimemazine):

**Uses:** Antipruritic  
Antiemetic  
Sedative and Hypnotic
• Propylamine derivative
  Ex: Chloropheneramine

  Melting point: 130-135°C

  Uses: Effective in allergic and vasomotor rhinitis.
  Adjunct therapy in anaphylactic shock.
  Antitussive.
2) Pheniramine:

Melting point: 104-108°C

Uses: Antihistamine
Cyclic basic chain analogues:
Ex: Cyclizine Hydrochloride (Marezine)

Uses: Used in the treatment of motion sickness.

Melting point: 108°C

Prophylaxis.
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).

Sometimes two aromatic rings are bridged that...
Most of the H₁ antagonist have ethylene chain, extension of this chain or branching of this chain lead to reduce the activity of the compound.

Homologation played to improve the drug like tricyclic anti-depressants, neuroleptics.

Due to the close resemblance 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 gastroesophageal reflux disease (GERD)
2) Ranitidine (Zantac):

Uses: To treat ulcer
Used to treat gastroesophageal reflux disease (GERD)
Zollengers-Ellison Syndrome
Mechanism of action:

- Ranitidine
  - Competitively block H₂ receptor
    - Histamine cannot act
      - Decrease cAMP formation
        - Reduce acid secretion
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 CH₃ 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 (-CH₃-) 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