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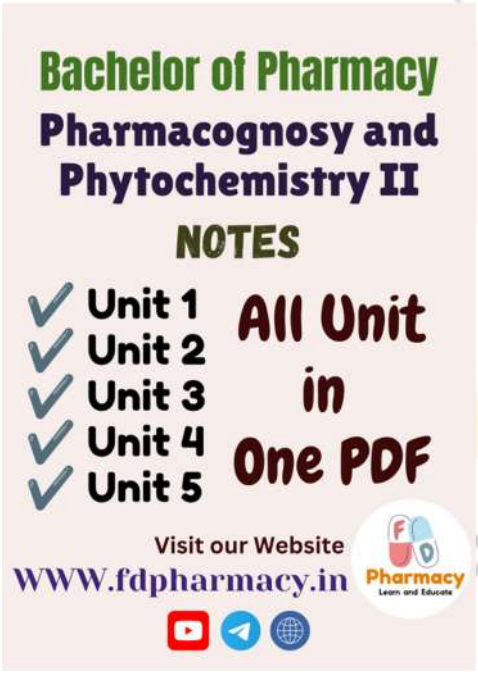
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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **H2-antagonists :** Cimetidine*, Famotidine, Ranitidin.

H_2 Antagonists (H_2 Blockers)

H_2 antagonists, also called H_2 blockers, are a class of drugs that reduce gastric acid secretion by blocking histamine H_2 receptors on parietal cells of the stomach lining.

Histamine normally binds to H_2 receptors on parietal cells, stimulating gastric acid production. By blocking these receptors, H_2 antagonists decrease basal and stimulated acid secretion, helping manage acid-related disorders.

Mechanism of Action

1. H_2 antagonists act as competitive antagonists of histamine at H_2 receptors on parietal cells.
2. By binding to H_2 receptors, they prevent histamine from activating the receptor.
3. Without histamine stimulation, parietal cells do not secrete gastric acid, leading to a reduction in overall acid production.

Structure-Activity Relationship (SAR) of H□ Antagonists

H_2 receptor antagonists were developed through structural modifications of histamine to find competitive inhibitors of H_2 receptors.

Key SAR points:

1. Heterocyclic ring:
    - Imidazole is classical, but other heterocycles (furan, thiophene, thiazole) can enhance potency and selectivity.
2. Terminal nitrogen group:
    - Should be basic for optimal antagonistic activity.
    - For some compounds, non-basic substitutions can reduce activity.
3. Distance between ring and terminal nitrogen:
    - Optimal spacer of at least two atoms is required for maximum receptor binding and antagonist effect.

Examples :

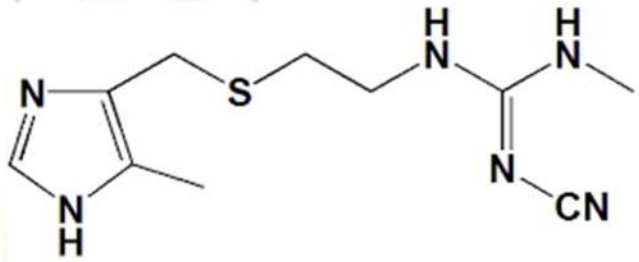
- Cimetidine
- Famotidine
- Ranitidine

Cimetidine

- Cimetidine is a histamine H_2 receptor antagonist (H_2 blocker).
- It is used to reduce gastric acid secretion in conditions such as peptic ulcer, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and stress ulcers.
- It selectively blocks H_2 receptors on gastric parietal cells without affecting H_1-mediated allergic responses.
- It was the first clinically successful H_2 antagonist, discovered by Sir James Black in the 1970s.

Chemical Structure

- IUPAC Name: N-cyano-N-methyl-1-[2-[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]guanidine
- Molecular Formula: $C_{10}H_{15}N_7S$
- Molecular Weight: 252.34 g/mol
- Chemical Structure



Cimetidine

Mechanism of Action

- H_2 Receptor Antagonism:
  - Cimetidine selectively binds to H_2 receptors on gastric parietal cells.
  - Inhibits histamine-mediated activation of adenylate cyclase, reducing cAMP formation and proton pump activity.
  - Leads to decreased secretion of gastric acid, pepsin, and intrinsic factor.
- No significant H_1 receptor activity:
  - Does not affect allergic responses mediated by H_1 receptors.
- Additional effects:
  - Mild inhibition of basal and nocturnal acid secretion.

Synthesis of Cimetidine

1. Imidazole Preparation:
    - Start with 4-methylimidazole as the core ring system.
2. Side Chain Attachment:
    - React 4-methylimidazole with 2-chloroethyl thioether to introduce the thioether linkage.
3. Guanidine Formation:
    - The terminal amine is converted to N-cyano-N-methylguanidine, forming the active Cimetidine molecule.

Uses

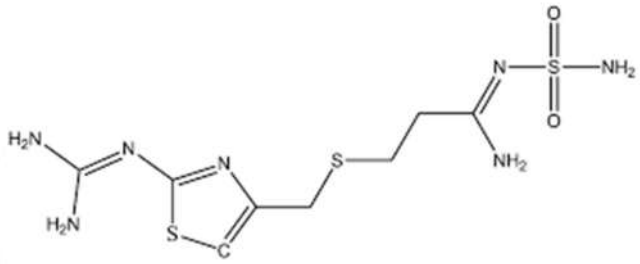
1. Peptic ulcer disease:
    - Treatment and maintenance therapy for duodenal and gastric ulcers.
2. Gastroesophageal reflux disease (GERD):
    - Reduces acid reflux and heartburn.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. Stress ulcers and prophylaxis:
    - Reduces gastric acidity in hospitalized patients.
5. Other:
    - Sometimes used off-label for allergic conditions due to weak H_1 and H_2 combined effects.

Famotidine

- Famotidine is a histamine H_2 receptor antagonist (H_2 blocker).
- It is used to reduce gastric acid secretion in conditions such as peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and stress ulcers.
- Famotidine is more potent and longer-acting than cimetidine and has fewer drug interactions because it does not inhibit cytochrome P450 enzymes significantly.
- It is available in oral tablets, suspensions, and intravenous formulations.

Chemical Structure

- IUPAC Name: 3-[[2-(diaminomethyleneamino)thiazol-4-yl]methylthio]-N-sulfamoylpropanimidamide
- Molecular Formula: $C_8H_{15}N_7O_2S_3$
- Molecular Weight: 337.43 g/mol
- Chemical Structure



Mechanism of Action

- H_2 Receptor Antagonism:
  - Famotidine selectively binds to H_2 receptors on gastric parietal cells.
  - Inhibits histamine-induced activation of adenylate cyclase, reducing cAMP formation and proton pump activity.
  - Results in reduced gastric acid secretion, pepsin secretion, and basal/meal-stimulated acid output.
- CNS Effects:
  - Minimal central effects; does not cause sedation.
- Other Effects:
  - Rapid onset and longer duration of action compared to cimetidine.
  - Minimal drug interactions due to lack of significant CYP450 inhibition.

Synthesis of Famotidine

1. Thiazole Formation:
    - Prepare the thiazole ring with a diaminomethylene substituent at position 2.
2. Side Chain Introduction:
    - Introduce the thioether-linked 3-guanidino-propyl group via nucleophilic substitution.
3. Sulfonamide Formation:
    - Attach the sulfonamide group to the guanidine moiety, forming the final Famotidine molecule.

Uses

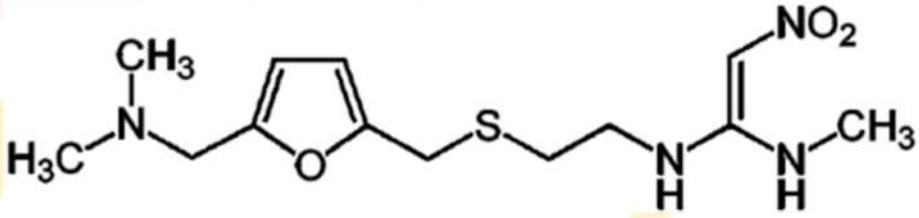
1. Peptic ulcer disease:
    - Treatment and maintenance therapy for duodenal and gastric ulcers.
2. Gastroesophageal reflux disease (GERD):
    - Reduces acid reflux, heartburn, and esophagitis.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. Stress ulcer prophylaxis:
    - Reduces gastric acidity in critically ill patients.
5. Safe in elderly and patients with liver disease:
    - Minimal hepatic metabolism, reducing the risk of drug interactions.

Ranitidine

- Ranitidine is a histamine H_2 receptor antagonist (H_2 blocker).
- It was widely used to reduce gastric acid secretion in peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and stress ulcers.
- Ranitidine selectively blocks H_2 receptors on gastric parietal cells, thereby decreasing acid and pepsin secretion.
- Compared to cimetidine, ranitidine has higher potency, fewer drug interactions, and longer duration of action.
- Note: Many countries have withdrawn ranitidine due to NDMA contamination, a probable carcinogen.

Chemical Structure

- IUPAC Name: N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N-methyl-2-nitroethene-1,1-diamine
- Molecular Formula: $C_{13}H_{22}N_4O_3S$
- Molecular Weight: 314.42 g/mol
- Chemical Structure



Mechanism of Action

- H_2 Receptor Antagonism:
  - Ranitidine selectively binds to H_2 receptors on gastric parietal cells.
  - Inhibits histamine-induced adenylate cyclase activation, reducing cAMP levels and proton pump activity.
  - Results in decreased secretion of gastric acid and pepsin, reducing ulcer formation and acid reflux symptoms.
- Other Effects:
  - Reduces basal and meal-stimulated gastric acid secretion.
  - Minimal CNS effects and low sedation.

Synthesis of Ranitidine

1. Furan Derivative Preparation:
    - 2-furaldehyde is reacted with dimethylaminoethylthiol to form the thioether intermediate.
2. Nitroethyl Substitution:
    - The intermediate is reacted with nitroethylenediamine to introduce the H_2 antagonistic nitroethyl moiety.
3. Methylation:
    - Terminal amine is methylated to yield ranitidine base, which is then purified.

Uses

1. Peptic ulcer disease:
    - Treatment and maintenance therapy for duodenal and gastric ulcers.
2. Gastroesophageal reflux disease (GERD):
    - Reduces acid reflux, heartburn, and esophagitis.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. Stress ulcer prophylaxis:
    - Reduces gastric acidity in critically ill patients.
5. Adjunct therapy:
    - Sometimes used with antibiotics in H. pylori eradication regimens.