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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 :

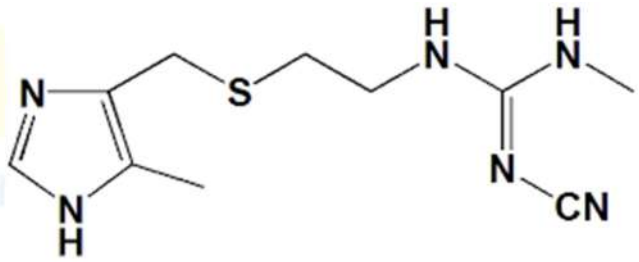
- Cimetidine
- Famotidine
- Ranitidine

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

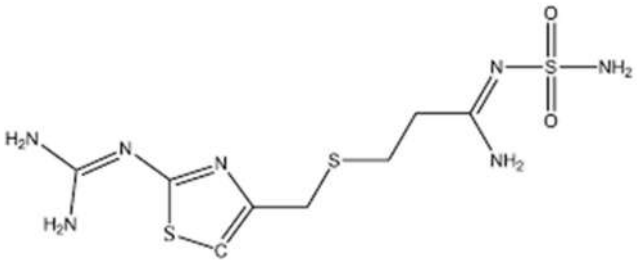
1. **Peptic ulcer disease:**
   - Treatment and maintenance therapy for **duodenal and gastric ulcers**.
2. **Gastroesophageal reflux disease (GERD):**
   - Reduces **acid reflux and heartburn**.
3. **Zollinger-Ellison syndrome:**
   - Controls **gastric acid hypersecretion**.
4. **Stress ulcers and 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

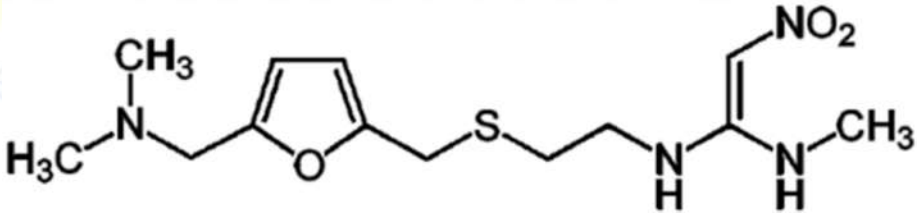
1. **Peptic ulcer disease:**
   - Treatment and maintenance therapy for **duodenal and gastric ulcers**.
2. **Gastroesophageal reflux disease (GERD):**
   - Reduces **acid reflux, heartburn, and esophagitis**.
3. **Zollinger-Ellison syndrome:**
   - Controls **gastric acid hypersecretion**.
4. **Stress 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**.