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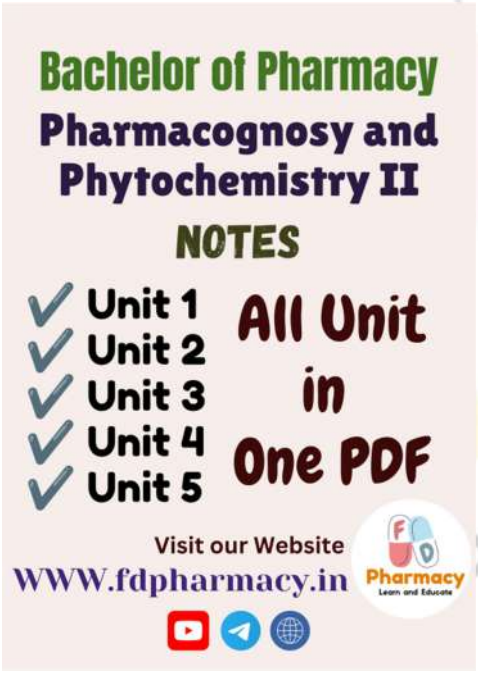
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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **Gastric Proton pump inhibitors :** Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole

Gastric Proton Pump Inhibitors (PPIs)

Proton Pump Inhibitors (PPIs) are a class of drugs that suppress gastric acid secretion by directly inhibiting the proton pump (H^+/K^+ ATPase enzyme) in the gastric parietal cells.

By reducing stomach acid, PPIs are effective in treating acid-related disorders such as:

- Gastroesophageal reflux disease (GERD)
- Peptic ulcer disease (PUD)
- Zollinger-Ellison syndrome
- Stress-related gastritis

Mechanism of Action

1. PPIs are prodrugs, initially inactive when administered orally.
2. After absorption into the bloodstream, they accumulate in the acidic canaliculi of parietal cells and are converted to their active sulfenamide form.
3. The active form binds covalently to the H^+/K^+ ATPase enzyme, blocking the exchange of hydrogen ions (H^+) with potassium ions (K^+).
4. This inhibits gastric acid secretion effectively.
5. Since proton pumps need to be resynthesized by parietal cells, PPIs have a prolonged duration of action, often allowing once-daily dosing.

Classification

PPIs are sulfur-containing prodrugs. Their activity is influenced by substitutions on the benzimidazole and pyridine rings.

Common PPIs and their structures:

Drug	Substituents (R)	Remarks
Omeprazole	Methoxy ($-OCH_3$) on benzimidazole; methyl ($-CH_3$) on pyridine	First marketed PPI
Lansoprazole	Fluoro (-F) on pyridine; methyl ($-CH_3$) on benzimidazole	More acid-stable; longer half-life
Rabeprazole	Methoxy ($-OCH_3$) on benzimidazole; CF_3 on pyridine	Rapid onset; high potency
Pantoprazole	Difluoromethoxy ($-OCHF_2$) on benzimidazole	Acid-stable; IV formulation available

Advantages of PPIs

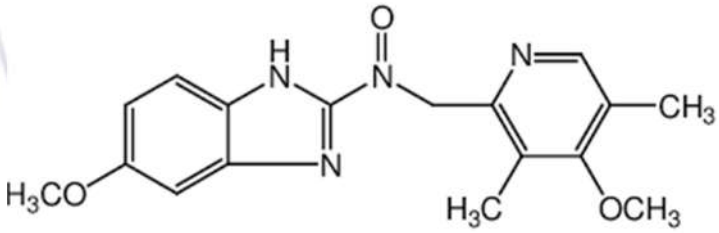
- More potent and longer-lasting acid suppression than H_2 blockers
- Effective for healing erosive esophagitis and refractory ulcers
- Minimal side effects with short-term use
- Can be combined with antibiotics for H. pylori eradication therapy

Omeprazole

- Omeprazole is a proton pump inhibitor (PPI).
- It is used to suppress gastric acid secretion in conditions such as peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and erosive esophagitis.
- Omeprazole irreversibly inhibits the H^+/K^+ ATPase (proton pump) in gastric parietal cells, providing long-lasting acid suppression.
- It is administered orally in enteric-coated tablets or capsules to prevent degradation in the stomach.

Chemical Structure

- IUPAC Name: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1H-benzimidazole
- Molecular Formula: $C_{17}H_{19}N_3O_3S$
- Molecular Weight: 345.42 g/mol
- Chemical Structure



Mechanism of Action

- Proton Pump Inhibition:
  - Omeprazole is a prodrug activated in the acidic environment of parietal cell canaliculi.
  - Converts to a sulfenamide, which covalently binds to cysteine residues of the H^+/K^+ ATPase enzyme, irreversibly inhibiting it.
  - Results in marked reduction of gastric acid secretion, both basal and stimulated.
- Duration of Action:
  - Acid suppression lasts up to 24 hours despite short plasma half-life, due to irreversible pump inhibition.
- No significant H_2 receptor activity:
  - Does not block histamine receptors; works directly at the proton pump.

Synthesis of Omeprazole

1. Benzimidazole Formation:
    - Condense 2-chlorobenzimidazole with appropriate substituted pyridine methyl sulfide to form the benzimidazole-sulfur intermediate.
2. Oxidation to Sulfoxide:
    - Oxidize the sulfur atom to sulfoxide (S=O) using mild oxidizing agents.
3. Purification and Formulation:
    - Purified omeprazole is formulated as enteric-coated tablets or capsules to prevent acid degradation.

Uses

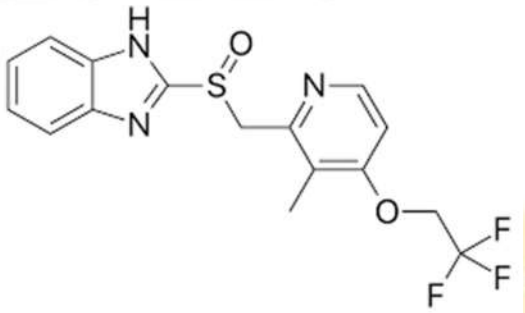
1. Peptic ulcer disease:
    - Effective in duodenal and gastric ulcers, including H. pylori eradication therapy.
2. Gastroesophageal reflux disease (GERD):
    - Reduces heartburn, regurgitation, and esophagitis.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. NSAID-induced ulcers:
    - Prevents and treats ulceration in long-term NSAID users.
5. Other uses:
    - Part of triple or quadruple therapy for H. pylori infection.

Lansoprazole

- Lansoprazole is a proton pump inhibitor (PPI) used to suppress gastric acid secretion.
- It is employed in peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and erosive esophagitis.
- Like other PPIs, it irreversibly inhibits the H^+/K^+ ATPase enzyme in gastric parietal cells, providing long-lasting acid suppression.
- Administered orally in enteric-coated capsules or orally disintegrating tablets to prevent degradation in the acidic stomach environment.

Chemical Structure

- IUPAC Name: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole
- Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
- Molecular Weight: 369.36 g/mol
- Chemical Structure



Mechanism of Action

- Proton Pump Inhibition:
  - Lansoprazole is a prodrug activated in the acidic environment of parietal cell canaliculi.
  - Forms a sulfenamide intermediate that irreversibly binds to cysteine residues of the H^+/K^+ ATPase, inhibiting gastric acid secretion.
- Duration of Action:
  - Provides up to 24 hours of acid suppression, despite a short plasma half-life, due to irreversible inhibition.
- No H_2 receptor activity:
  - Works directly at the proton pump rather than histamine receptors.

Synthesis of Lansoprazole

1. Benzimidazole Formation:
    - Condensation of 2-chlorobenzimidazole with a pyridine methyl sulfide derivative to form the benzimidazole-sulfide intermediate.
2. Oxidation to Sulfoxide:
    - The sulfur atom is oxidized to sulfoxide (S=O) using mild oxidizing agents.
3. Purification and Formulation:
    - Purified lansoprazole is formulated as enteric-coated capsules or orally disintegrating tablets to protect from stomach acid.

Uses

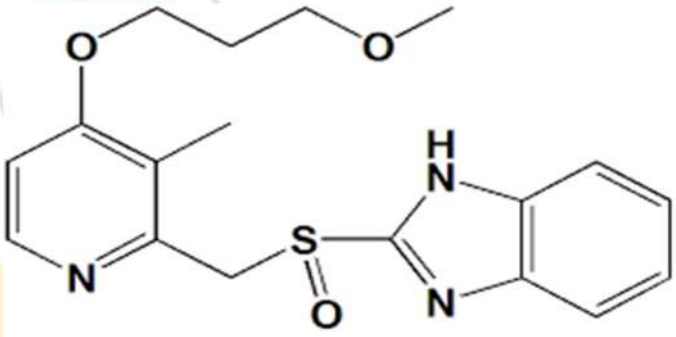
1. Peptic ulcer disease:
    - Effective in duodenal and gastric ulcers, including H. pylori eradication therapy.
2. Gastroesophageal reflux disease (GERD):
    - Reduces heartburn, acid reflux, and esophagitis.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. NSAID-induced ulcers:
    - Prevents and treats ulcers in long-term NSAID therapy.
5. Other uses:
    - Part of triple therapy for H. pylori eradication.

Rabeprazole

- Rabeprazole is a proton pump inhibitor (PPI) used to suppress gastric acid secretion.
- It is employed in peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and erosive esophagitis.
- Like other PPIs, it irreversibly inhibits the H^+/K^+ ATPase enzyme in gastric parietal cells, providing long-lasting acid suppression.
- Administered orally as enteric-coated tablets or capsules to prevent degradation by stomach acid.

Chemical Structure

- IUPAC Name: 2-[[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfinyl]-1H-benzimidazole
- Molecular Formula: $C_{18}H_{20}N_3O_3S$
- Molecular Weight: 359.44 g/mol
- Chemical Structure



Rabeprazol

Mechanism of Action

- Proton Pump Inhibition:
  - Rabeprazole is a prodrug activated in the acidic environment of parietal cell canaliculi.
  - Forms a sulfenamide intermediate that irreversibly binds to cysteine residues of the H^+/K^+ ATPase, inhibiting gastric acid secretion.
- Duration of Action:
  - Provides up to 24 hours of acid suppression, despite a short plasma half-life.
- No H_2 receptor activity:
  - Acts directly on the proton pump, not on histamine receptors.

Synthesis of Rabeprazole

1. Benzimidazole Formation:
    - Condense 2-chlorobenzimidazole with a substituted pyridine methyl sulfide to form the benzimidazole-sulfide intermediate.
2. Oxidation to Sulfoxide:
    - Oxidize the sulfur atom to sulfoxide (S=O) using mild oxidizing agents.
3. Purification and Formulation:
    - Purified rabeprazole is formulated as enteric-coated tablets or capsules to prevent degradation in the acidic stomach.

Uses

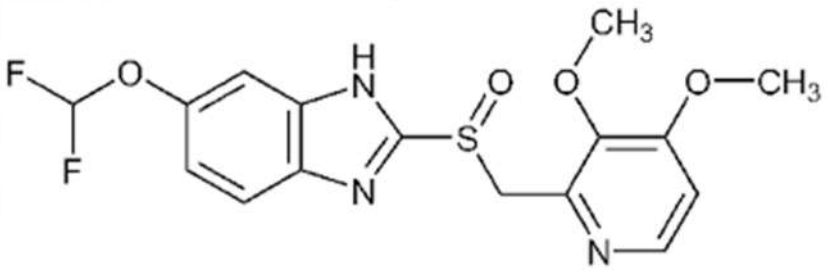
1. Peptic ulcer disease:
    - Treatment and maintenance of duodenal and gastric ulcers, including H. pylori eradication therapy.
2. Gastroesophageal reflux disease (GERD):
    - Reduces heartburn, acid reflux, and esophagitis.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. NSAID-induced ulcers:
    - Prevents ulcer formation in long-term NSAID therapy.
5. Other uses:
    - Part of triple therapy for H. pylori eradication.

Pantoprazole

- Pantoprazole is a proton pump inhibitor (PPI) used to suppress gastric acid secretion.
- It is effective in peptic ulcer disease, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and erosive esophagitis.
- Pantoprazole irreversibly inhibits the H^+/K^+ ATPase enzyme in gastric parietal cells, leading to long-lasting acid suppression.
- Administered orally as enteric-coated tablets or intravenously for rapid acid control.
- It has high oral bioavailability and fewer drug interactions due to limited metabolism by CYP2C19.

Chemical Structure

- IUPAC Name: 6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzimidazole
- Molecular Formula: $C_{16}H_{14}F_2N_3O_4S$
- Molecular Weight: 383.31 g/mol
- Chemical Structure



Mechanism of Action

- Proton Pump Inhibition:
  - Pantoprazole is a prodrug that is activated in the acidic canaliculi of parietal cells.
  - Forms a sulfenamide intermediate that covalently binds to cysteine residues of the H^+/K^+ ATPase, irreversibly inhibiting gastric acid secretion.
- Duration of Action:
  - Provides up to 24 hours of acid suppression, despite a short plasma half-life.
- No H_2 receptor activity:
  - Directly inhibits proton pumps, not histamine receptors.

Synthesis of Pantoprazole

1. Benzimidazole Formation:
    - Condensation of 2-chlorobenzimidazole with a 3,4-dimethoxypyridine methyl sulfide derivative forms the benzimidazole-sulfide intermediate.
2. Oxidation to Sulfoxide:
    - Oxidize the sulfur atom to sulfoxide (S=O) using mild oxidizing agents.
3. Purification and Formulation:
    - Purified pantoprazole is formulated as enteric-coated tablets or IV injection to protect from stomach acid.

Uses

1. Peptic ulcer disease:
    - Effective for duodenal and gastric ulcers, including H. pylori eradication therapy.
2. Gastroesophageal reflux disease (GERD):
    - Reduces heartburn, acid reflux, and esophagitis.
3. Zollinger-Ellison syndrome:
    - Controls gastric acid hypersecretion.
4. NSAID-induced ulcers:
    - Prevents ulcer formation in long-term NSAID therapy.
5. Other uses:
    - Safe for long-term maintenance therapy in chronic acid-related disorders.