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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	Rapid onset; high

	benzimidazole; CF_3 on pyridine	potency
Pantoprazole	Difluoromethoxy (-$OCHF_2$) on benzimidazole	Acid-stable; IV formulation available

Advantages of PPIs

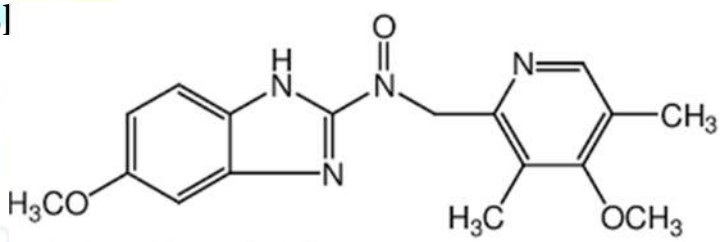
- More potent and longer-lasting acid suppression than H_2 blockers
- Effective for **healing erosive esophagitis** and **refractory ulcers**
- Minimal side effects with short-term use
- Can be combined with antibiotics for **H. pylori eradication therapy**

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

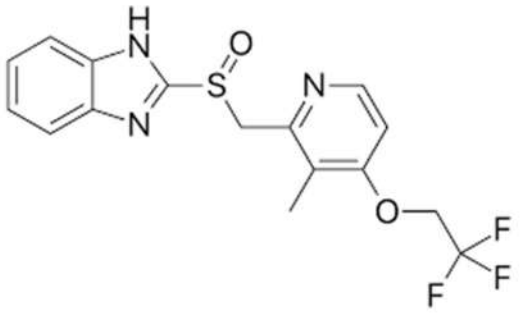
1. **Peptic ulcer disease:**
   - Effective in **duodenal and gastric ulcers**, including **H. pylori eradication therapy**.
2. **Gastroesophageal reflux disease (GERD):**
   - Reduces **heartburn, regurgitation, and esophagitis**.
3. **Zollinger-Ellison syndrome:**
   - Controls **gastric acid hypersecretion**.
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

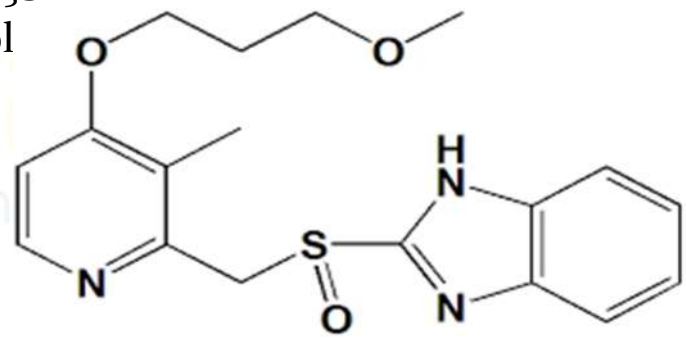
1. **Peptic ulcer disease:**
   - Effective in **duodenal and gastric ulcers**, including **H. pylori eradication therapy**.
2. **Gastroesophageal reflux disease (GERD):**
   - Reduces **heartburn, acid reflux, and esophagitis**.
3. **Zollinger-Ellison syndrome:**
   - Controls **gastric acid hypersecretion**.
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

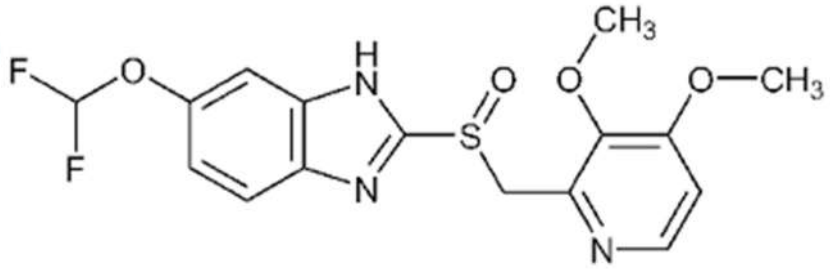
1. **Peptic ulcer disease:**
   - Treatment and maintenance of **duodenal and gastric ulcers**, including **H. pylori eradication therapy**.
2. **Gastroesophageal reflux disease (GERD):**
   - Reduces **heartburn, acid reflux, and esophagitis**.
3. **Zollinger-Ellison syndrome:**
   - Controls **gastric 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.