Chapter 2. Anti-Gastric Drugs

Syllabus

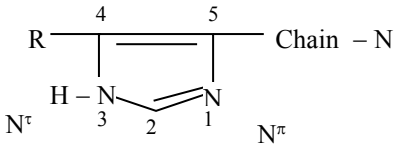
- **H2 R Antagonist**: Cimetidine*, Fomatidine, Ranitidine
- **Gastric Proton Pump Inhibitors**: Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole

These are the drugs which are used in the treatment of gastric ulcer by reducing the gastric acid (HCl) secretion and volume

2.1. H2 RECEPTOR ANTAGONISTS

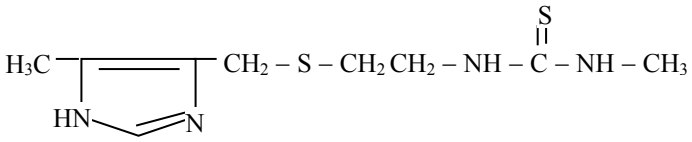
- The histamine H_2 receptor antagonists act on H_2 receptors in the stomach, blood vessels and other sites.
- They are competitive antagonists of histamine and are fully reversible.
- These agents completely inhibit gastric acid secretion induced by histamine, or gastrin. However, they only partially inhibit gastric acid secretion induced by acetylcholine or bethanechol.
- They have some common side effects like hypotension, dizziness, headach, diarrhoea, and constipation.
- They are highly hydrophilic, therefore they can't cross blood brain barrier and do not produce any sedative effect.
- Cimetidine is not used nowadays due to antiandrogenic side effects
- Drugs: Burimamide, Cimetidine, Famotidine, Piratidine, Ranitidin.

SAR of H_2 Receptor Antagonists

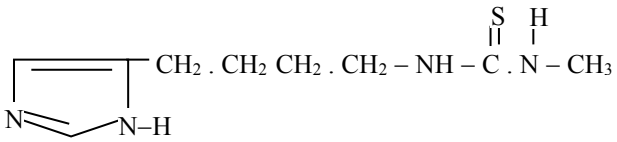


General structure of H_2 antagonist

- H_2 antagonists possess imidazole ring capable of undergoing 1, 3-prototropic tautomerism. $N^{\tau}H$ tautomer is necessary for maximal H_2 antagonistic activity. When R-group is electron donating ($-CH_3$) the $N^{\tau}H$ tautomer is favoured.



Metiamide (*favour $N^{\tau}H$ tautomer*)

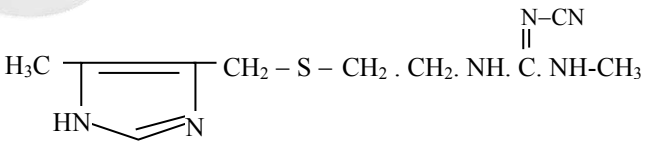


Burimamide (*favour $N^{\pi}H$ tautomer*)

- Metiamide, which favours the $N^{\tau}H$ tautomer is 5 times more potent than burimamide (which favours $N^{\pi}H$ tautomer).
- For optimal activity the ring should be separated by the equivalent of 4C-chain from N-group in side chain. A shorter chain lowers antagonistic activity. An isosteric thioether (–S–) link in place of a methylene group ($–CH_2$) give more active compounds (e.g. cimetidine).
- An Imidazole nucleus is not necessary for H_2 antagonist activity. Compounds containing furan (e.g. Ranitidine) or thiazole ring (e.g. Famotidine and Nizatidine) are more active than Cimetidine (contain an imidazole nucleus).

Medicinal Chemistry of H2-Blockers

1. Cimetidine

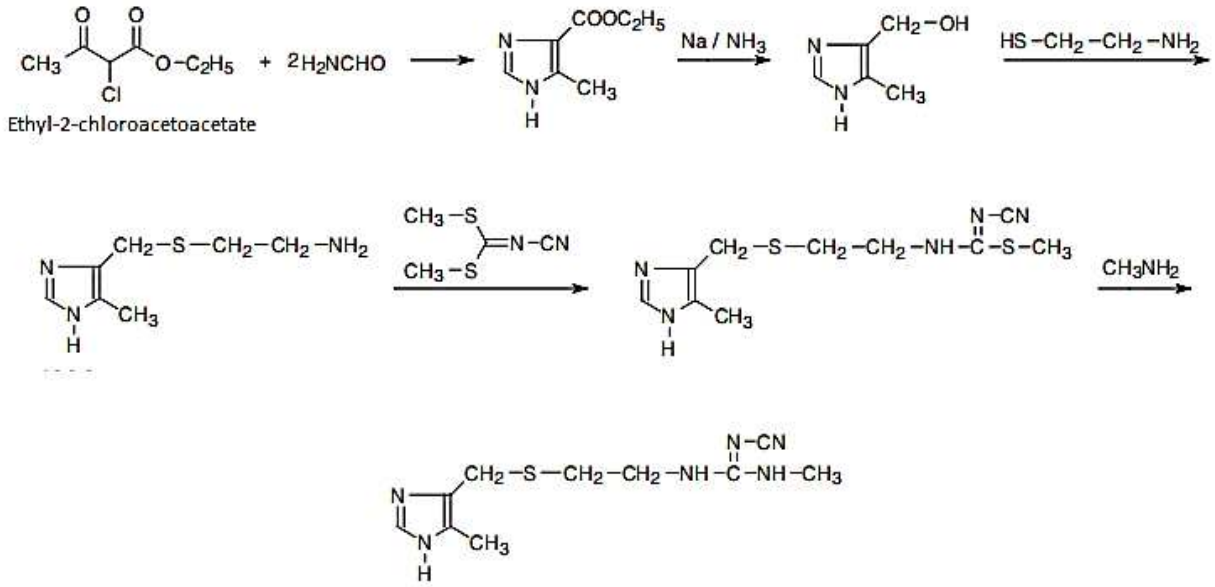


2-cyano-l-methyl-3-[2-(5-methyl imidazol-4-yl-methylthio) ethyl] guanidine

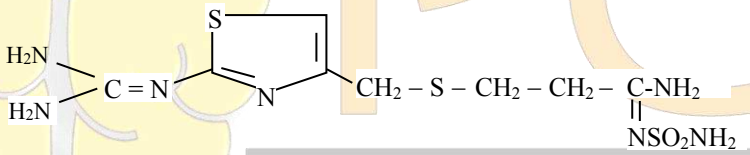
MOA: H2 Receptor Blocker

Uses: Used in gastric and duodenal ulcers.

Synthesis:



2. Famotidine

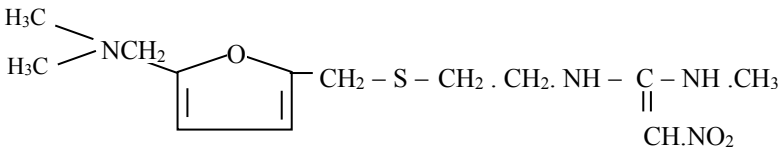


3-[[[2-[(diamino methylene) amino]-4-thiazolyl] methyl] thio]-N-(aminosulfonyl) propan-imidamide

MOA: H2 Receptor Blocker

Uses: Used in gastric and duodenal ulcers.

3. Ranitidine

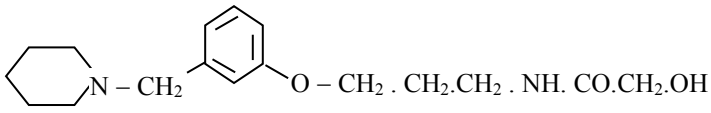


Dimethyl-{5-[2-(1-methylamino-2-nitrovinylamino) ethyl-thiomethyl] furfuryl} amine.

MOA: H2 Receptor Blocker

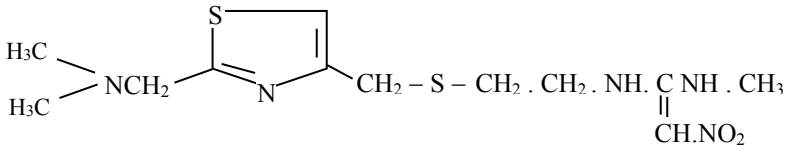
Uses: Used in gastric and duodenal ulcers.

4. Roxatidine



N-(3[3-(1-piperidinylmethyl)-phenoxy]-propyl) acetoxyacetamide

5. Nizatidine

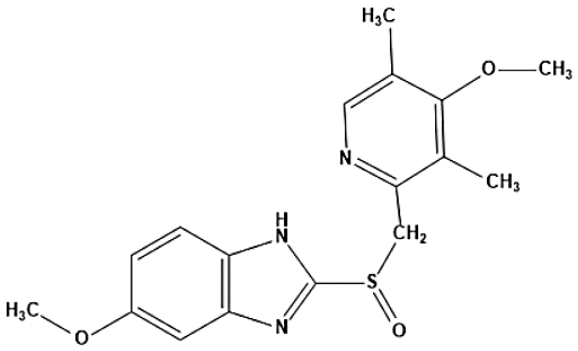


N-[2-[[[2-[(dimethylamino) methyl]-4-thiazolyl] methyl] thio]ethyl]-N'-methyl-2-nitro-l, l, ethenediamine

2.2. GASTRIC PROTON PUMP INHIBITORS

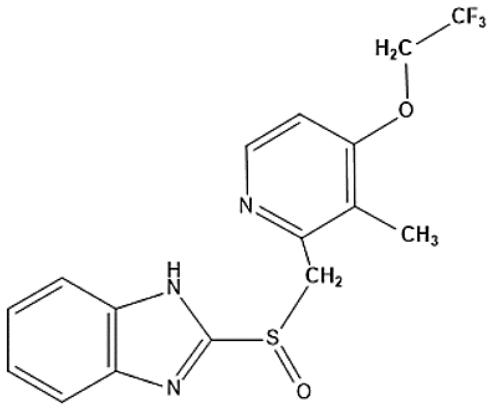
- These the newer class of antiulcer drug which frequently used clinically
- These are the **benzimidazole** derivatives.
- **MOA:** They binds to the H^+K^+-ATPase enzyme (proton pump) of the parietal cell, suppressing secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid.
- **Uses**
  - ✓ Ulcer
  - ✓ Zollinger-Ellison Syndrome (tumors in stomach which cause ulcer)
  - ✓ Gastroesophageal reflex diseases (GERD)

1. Omeprazole



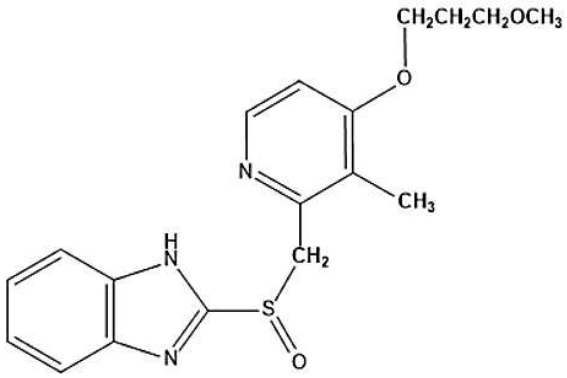
6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl sulfinyl]-1H-benzimidazole

2. Lansoprazole



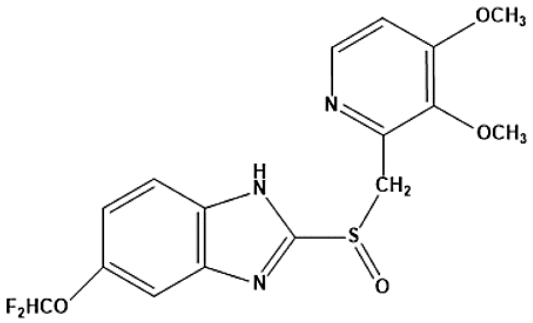
2-[[3-methyl-4-(2,2,2-trifluoro ethoxy)pyridin-2-yl]methyl sulfinyl]-1*H*-benzimidazole

3. Rabeprazole



2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methyl sulfinyl]-1*H*-benzimidazole

4. Pantoprazole



6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methyl sulfinyl]-1H-benzimidazole

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