HISTAMINE H_2-ANTAGONIST

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HISTAMINE H_2-ANTAGONISTS

- Drugs whose pharmacological action primarily involves antagonism of the action of histamine at its H_2-receptors.
- Therapeutic application in the treatment of acid-peptic disorders including heartburn, gastroesophageal reflux disease (GERD), erosive esophagitis, gastric and duodenal ulcers, and gastric acid pathologic hypersecretory diseases such as Zollinger-Ellison syndrome.
- They are also useful in combination with H_1-antihistamines for the treatment of chronic urticaria and for the itching of anaphylaxis and pruritis.
- Classification of H_2-Antagonist

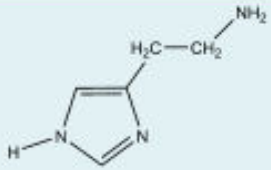
  a) Imidazole ring analogue (Cimetidine)

  b) Furan ring analogue (Ranitidine)

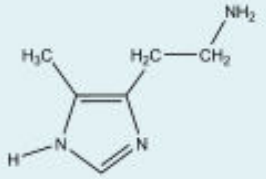
  c) Thiazole ring analogue (Famotidine & Nizatidine)

SAR of H_2-Antagonist

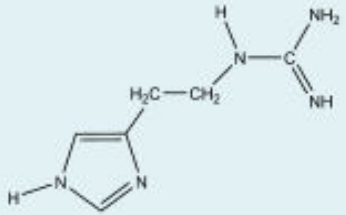
Histamine: Nonselective histamine receptor agonist ($H_1 = H_2$)



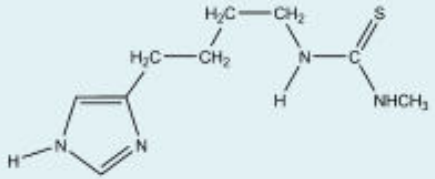
5-Methylhistamine: Selective H_2-agonist ($H_2 > H_1$)



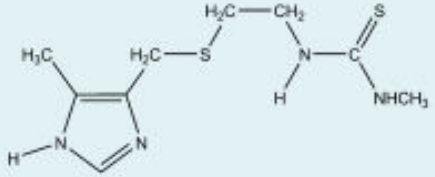
N^{α}-Guanylhistamine: Partial H_2-receptor agonist (weak antagonist)



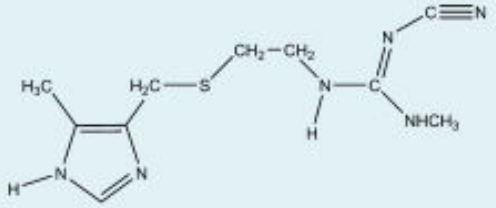
Burimamide: Full H_2-receptor antagonist; but low potency and poor oral bioavailability



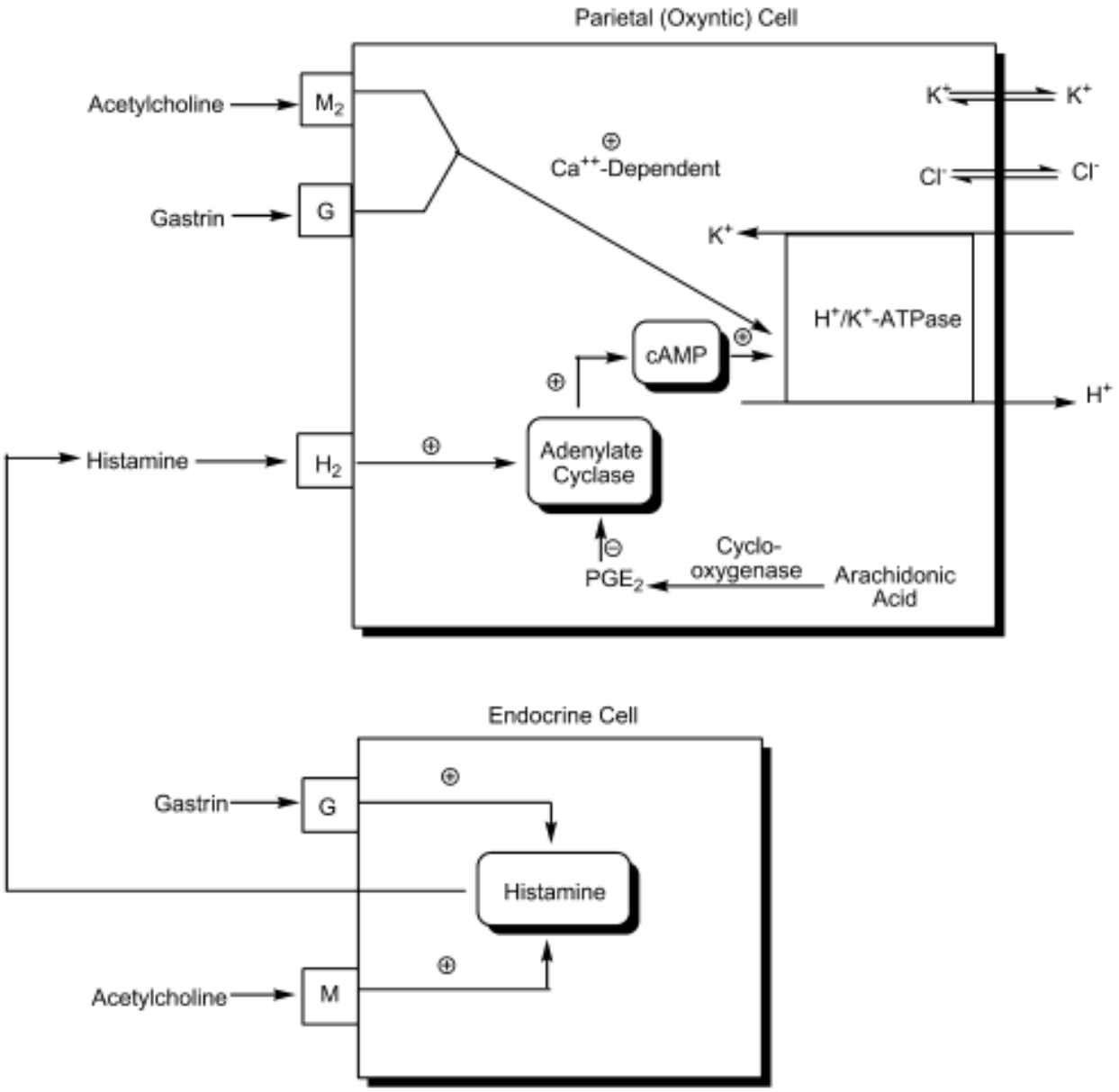
Metiamide: Full H_2-receptor antagonist with higher potency and improved oral bioavailability; but toxicity resulting from the thiourea



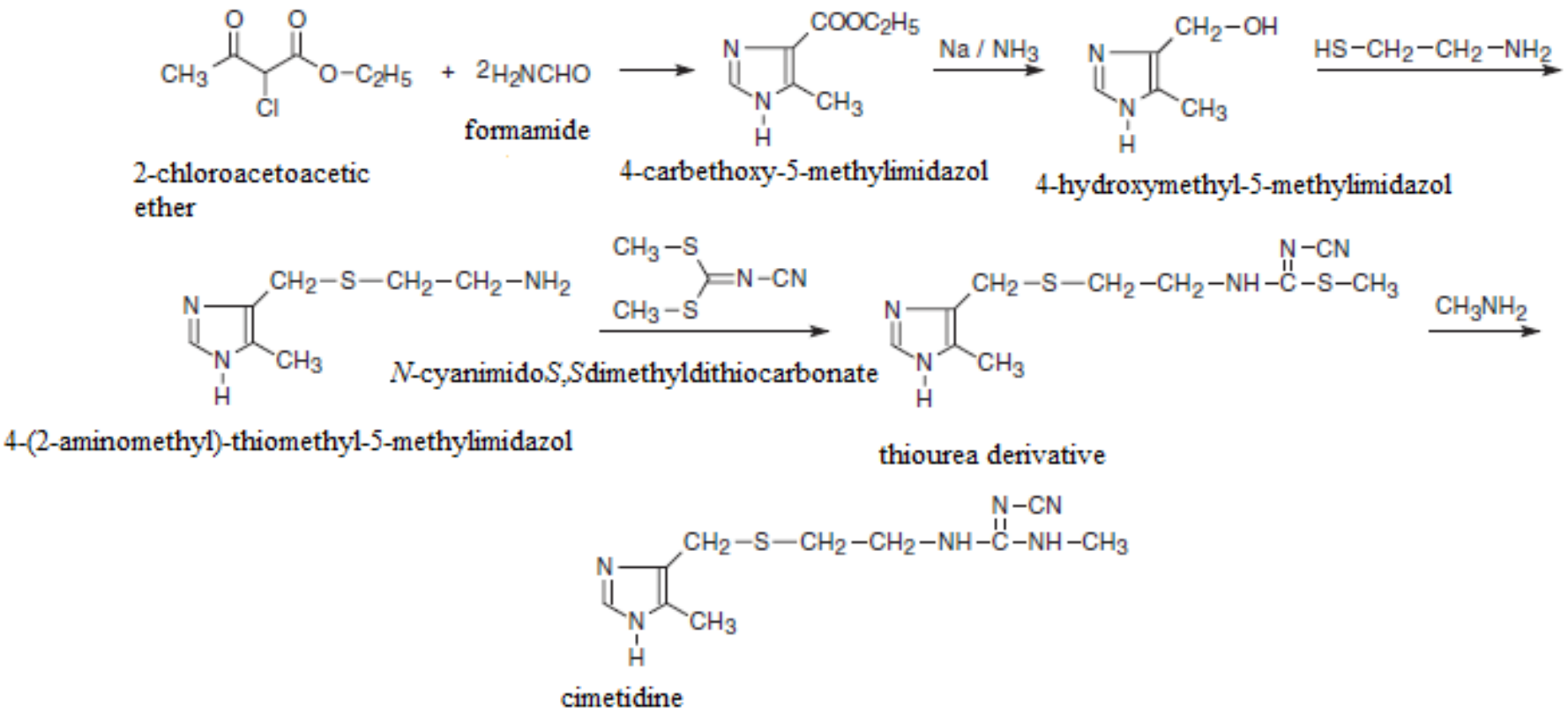
Cimetidine: Full H_2-receptor antagonist with higher potency and improved oral bioavailability and low systemic toxicity



Hormonal Regulation of Acid Secretion by Parietal Cell

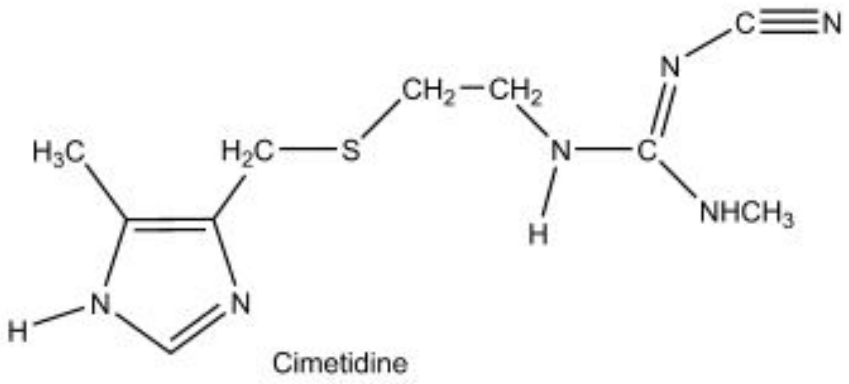


Synthesis of Cimetidine



IUPAC Name:
1-cyano-2-methyl-3-[2-[[5-[[methylimidazol-4-yl)methyl]thio]ethyl] guanidine

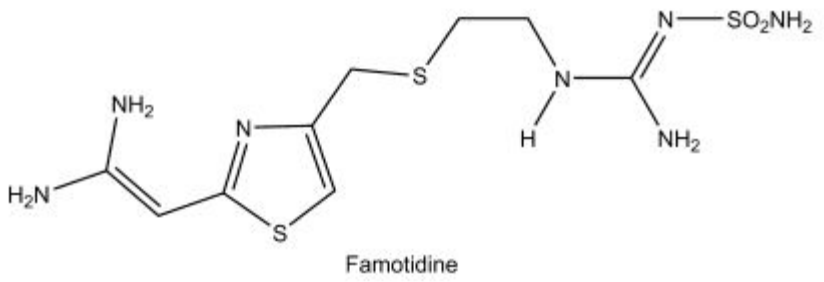
Structures of H_2-Receptor Antagonist



Cimetidine

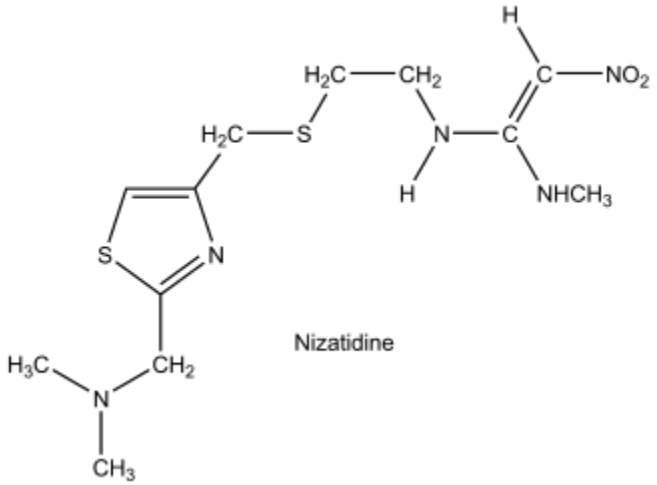
Cimetidine exhibits relatively good bioavailability (60% - 70%)

Side Effect: Cimetidine has a weak antiandrogenic effect, and it may cause gynecomastia in patients treated for 1 month or more.



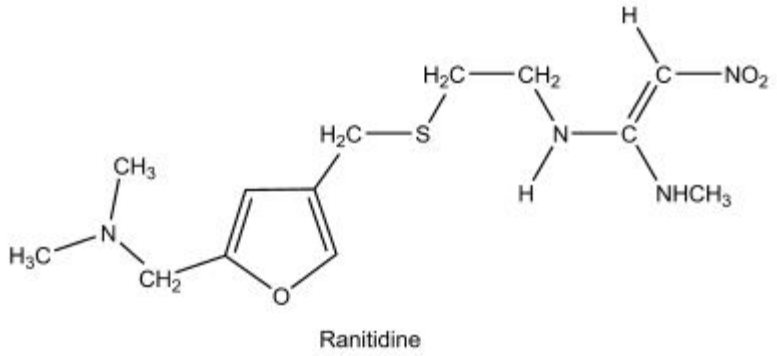
Famotidine

Famotidine is a competitive inhibitor of histamine H_2-receptors with a potency significantly greater than cimetidine.



Nizatidine

Nizatidine has excellent oral bioavailability (90%).
Nizatidine is more potent than Cimetidine



Ranitidine

IUPAC Name:
N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thiol]ethyl]-N-methyl-2-nitro-1,1 ethenediamine
Ranitidine is more potent than cimetidine, but less potent than famotidine. Like other H_2-antagonists, it does not appear to bind to other receptors.