Anti-ulcer Drugs

Pharmaceutical Chemistry IV

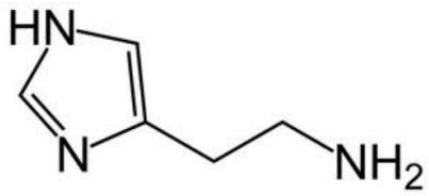
PHA 482

Anti-ulcer Drugs

1) Neutralization of gastric acid (Antacids)
   - Systemic: Sodium bicarbonate, Sodium citrate
   - Non-systemic (Local): MgOH, Al(OH)3, CaCO3
2) Reduction of gastric acid secretion
   - H_2 antihistamine: Cimetidine, ranitidine, famotidine,roxantidine
   - Proton Pump Inhibitors (PPIs): Omeprazole, pantoprazole, rabeprazole, esmoprazole
   - Anticholinergics: Pirenzepine,propantheline,oxyphenonium
   - Prostaglandin analogues: Misoprostol, enprostil, rioprostil
3) Ulcer protectives: Sucralfate, CBS (Colloidal Bismuth Subcitrate)
4) Ulcer healing Drugs: Carbenoxolone sodium
5) Anti-H. pyloric drugs: Amoxicillin, clarithromycin, metronidazole, tinidazole, tetracycline

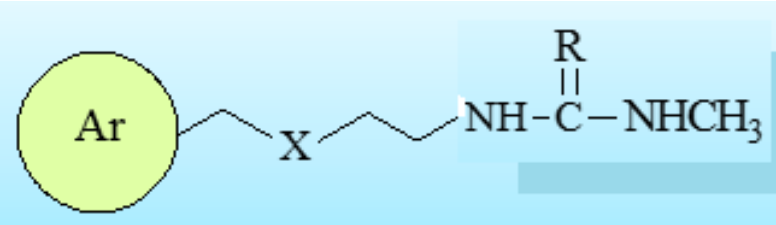
H_2 Histamine Antagonists

- Histamine is released from mast cell in gastric mucosa by gastrin and acetylcholine
- MOA- Histamine acts on H_2 receptor and stimulates proton pump through the cAMP pathway which leads to acid secretion. These drug antagonize H_2 receptor and block Histamine mediated acid secretion
- They are associated with libido loss or erectile dysfunction



Histamine

SAR of H_2 Histamine antagonists

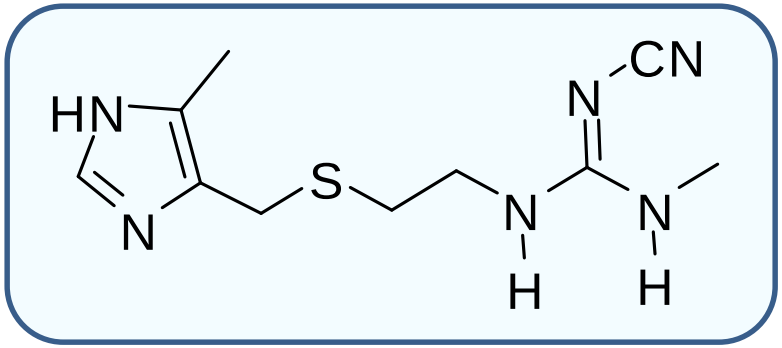


1) Need an aromatic/hetero-aromatic ring. The imidazole ring is not required but if it is present there must be electron donors at position 5 to promote the first tautomer.

2) The terminal nitrogen group should be polar but not basic. Electron withdrawing groups like cyano (CN), nitro (NO_2), sulfamoyl (SO_2NH_2) are preferable as substituent.

3) Separation of the ring from the nitrogen group by 4 atoms gives maximal potency. Shorter chain drastically lowers the activity. The presence of thioether (-S-) in the methylene place (X) lead to more activity.

Cimetidine

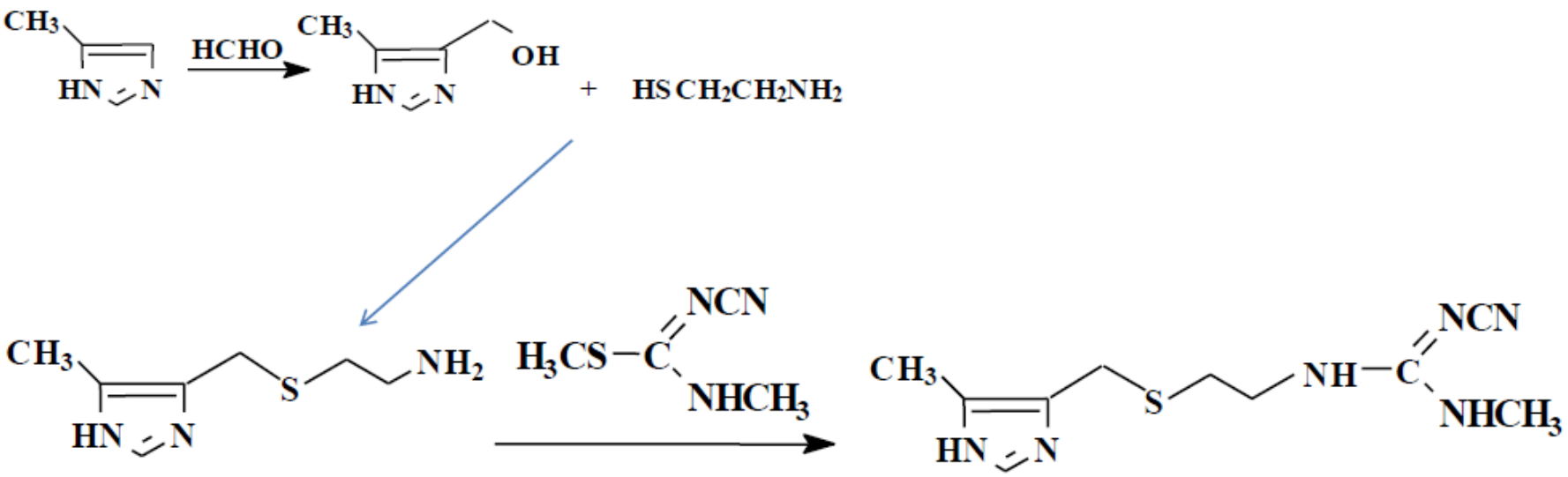


1-cyano-2-methyl-3-[2-[(5-methyl-1*H*-imidazol-4- yl)methylsulfanyl]ethyl]guanidine

2-cyano-1-methyl-3-(2-((5-methyl-1*H*-imidazol-4-yl)methylthio)ethyl)guanidine

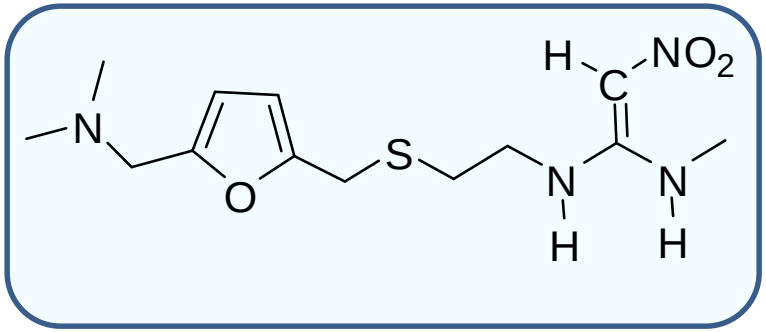
- It is an imidazole derivative H_2 -antagonist
- It **inhibits CYP, which leads to many drug–drug** interactions.
- It exhibits **antiandrogenic action** and can cause **gynecomastia** if used for more than 1 month.
- It has **63-78% bioavailability**
- Uses;
  - Peptide ulcer, Heartburn, Zollinger–Ellison syndrome, GERD (Gastroesophageal reflux disease)

Synthesis of Cimetidine



(E)-methyl N'-cyano-N-methylcarbamimidothioate

Ranitidine



(*E*)-1-*N*'-[2-[[5-[(dimethylamino)methyl]furan-2-yl]methylsulfanyl]ethyl]-1-*N*-methyl-2-nitroethene-1,1-diamine

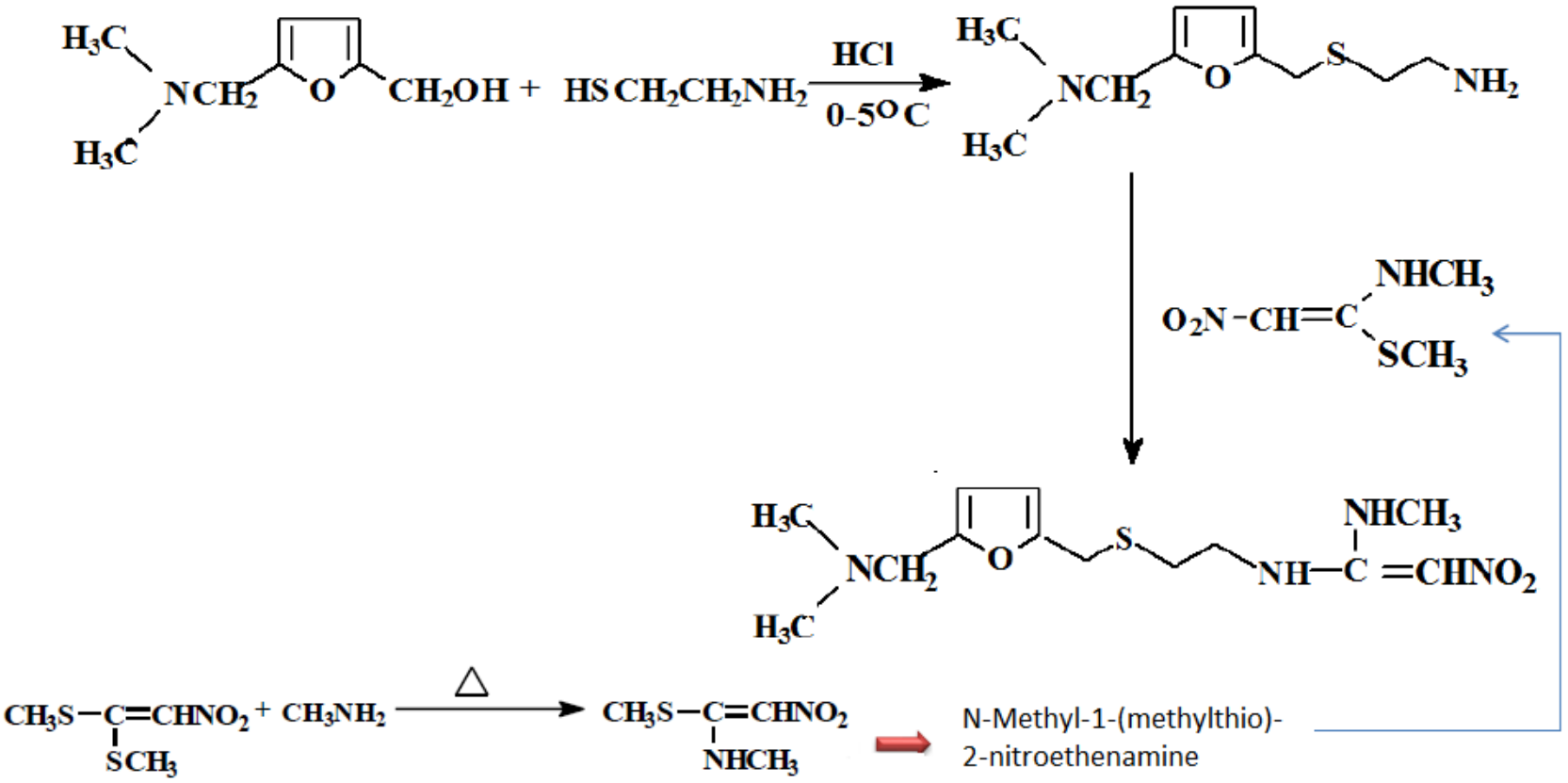
(E)-N-(2-((5-((dimethylamino)methyl)furan-2-yl)methylthio)ethyl)-N-methyl-2-nitroethene-1,1-diamine

- It is a furan derivative H_2-antagonist, which is an isostere of the imidazole ring.
- It is a **weaker CYP inhibitor** than cimetidine and has **no antiadrogenic effect**
- It is about **6 times** more potent than Cimetidine with a **longer duration of action.**
- It's **bioavailability is 52%.**
- Uses;

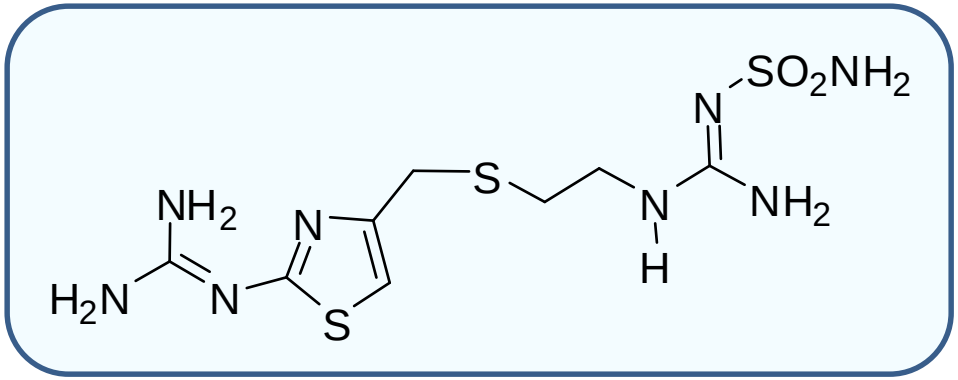
  -Peptide Ulcer, heartburn

Synthesis of Ranitidine

I-



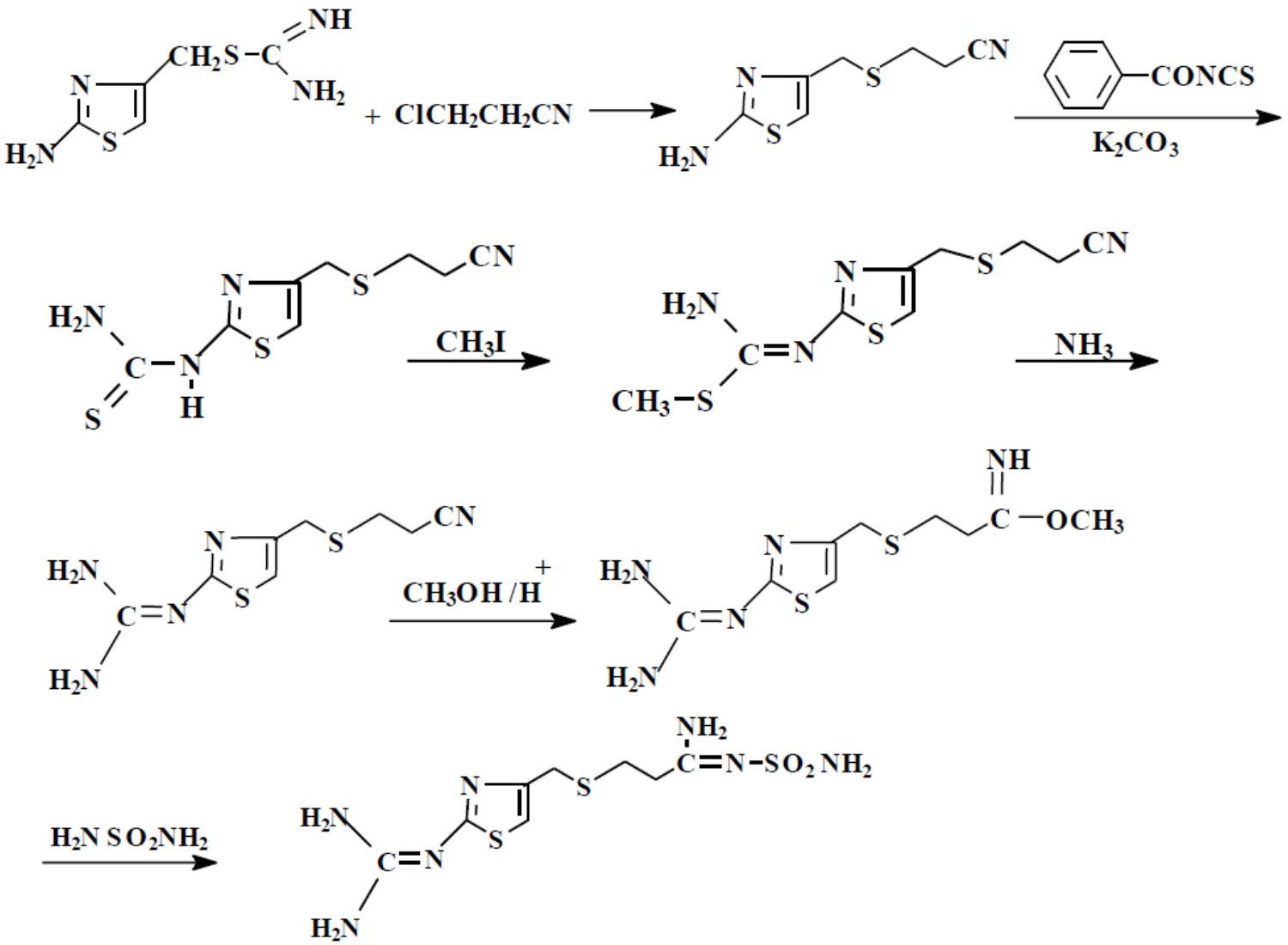
Famotidine



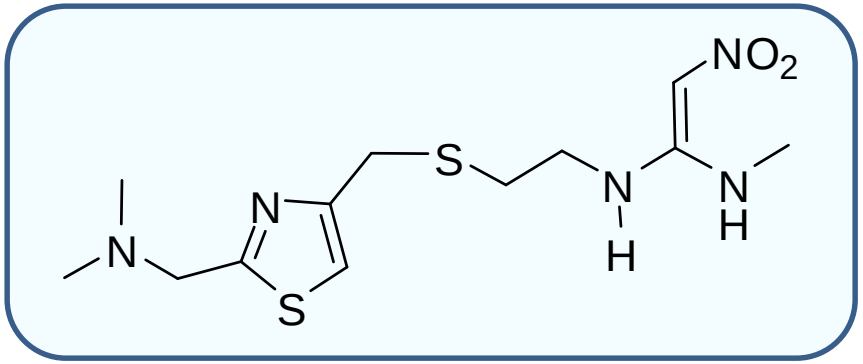
3-[[2-(diaminomethylideneamino)-1,3-thiazol-4-yl]methylsulfanyl]-*N*'-sulfamoylpropanimidamide

- It is a thiazole derivative H_2-anatgonist.
- It does **not cause gynecomastia** and is a **weak inhibitor of CYP.**
- It is **40 times more potent than Cimetidine but it has** only **37 to 45% bioavailability.**
- Uses;
  - Peptide Ulcer, heartburn, GERD

Synthesis of Famotidine



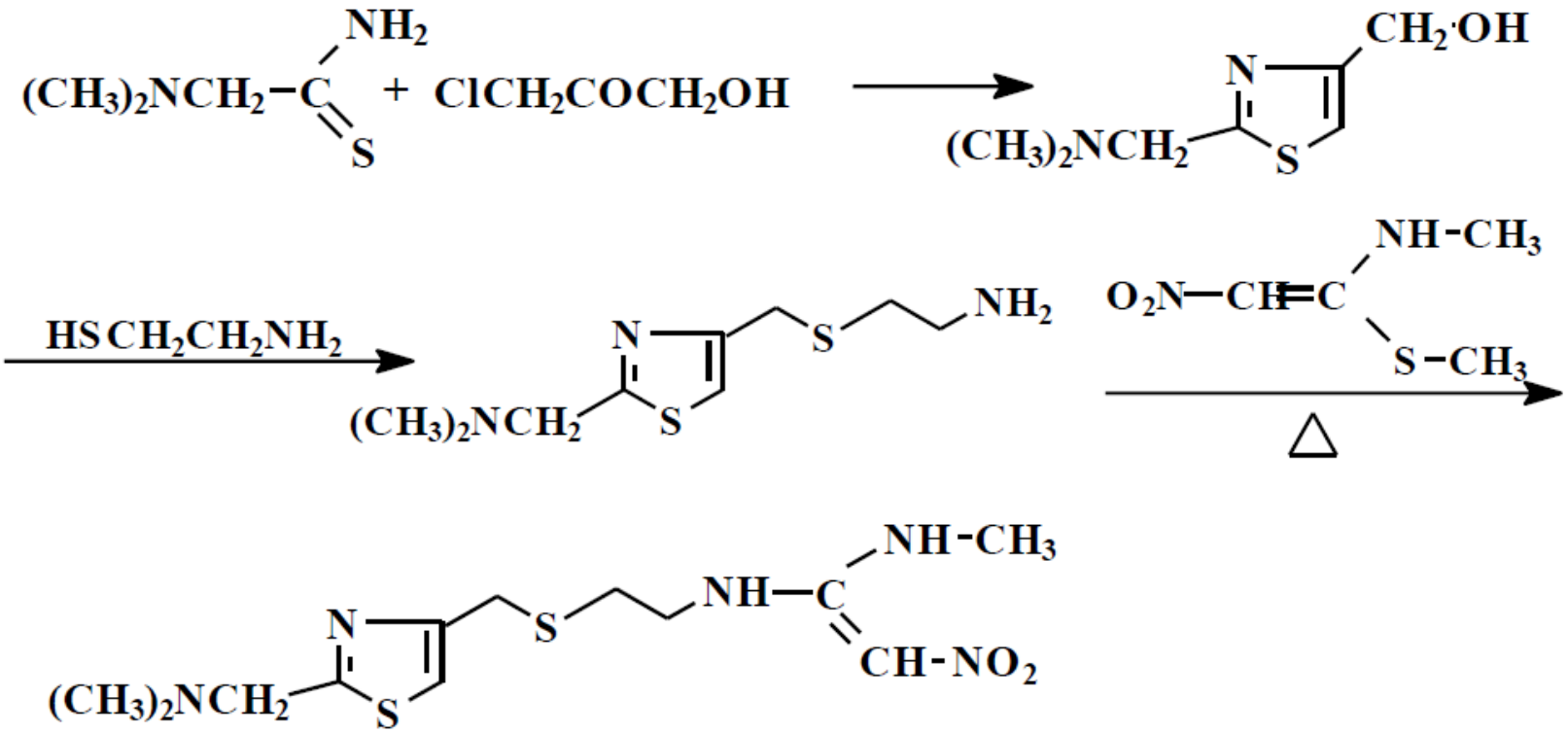
Nizatidine



(*E*)-1-*N*'-[2-[[2-[(dimethylamino)methyl]-1,3-thiazol-4-yl]methylsulfanyl]ethyl]-1-*N*-methyl-2-nitroethene-1,1-diamine
(*E*)-*N*-(2-((2-((dimethylamino)methyl)thiazol-4-yl)methylthio)ethyl)-*N*-methyl-2-nitroethene-1,1-diamine

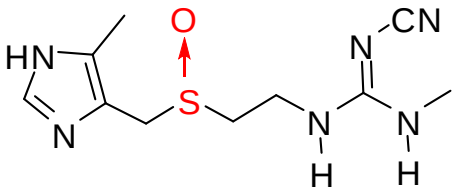
- It is a thiazole derivative similar to Ranitidine.
- It does **not inhibit CYP** and has **no antiandrogenic effect.**
- It is **10 times more potent than Cimetidine** and it has **more than 98% bioavailability**
- Uses
  - Peptide Ulcer, heartburn,GERD

Synthesis of Nizatidine

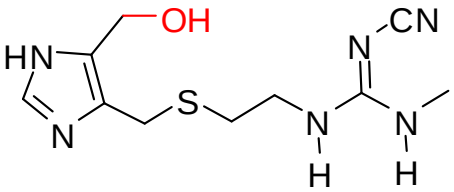


Metabolism

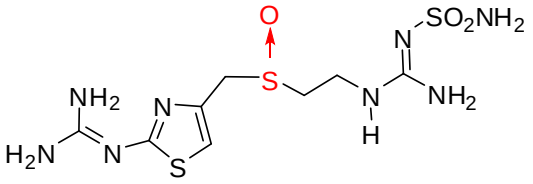
Cimetidine, ranitidine, and famotidine are subject to first-pass metabolism, and each has oral bioavailability of about 50%. The oral bioavailability of nizatidine is about 90%. All have half-lives of 1.5 to 4 hours, with that of nizatidine being the shortest. Significant amounts of each of these H_2 antihistamines are excreted unchanged, with small amounts of urinary products of sulfoxidation being a common metabolic feature. As expected, hydroxylation of the imidazole C-4 methyl group of cimetidine occurs. Ranitidine is excreted largely unchanged, but minor metabolic pathways include *N*-demethylation and *N*- and *S*-oxidation. The metabolites are not thought to contribute to the therapeutic properties of the parent drugs, with the exception of nizatidine from which the *N*-desmethyl metabolite retains H_2 antihistamine activity.



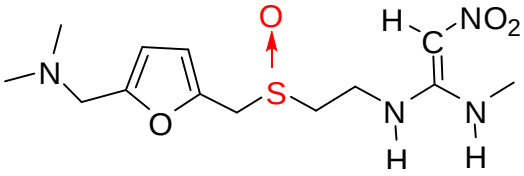
Cimetidine S-oxide



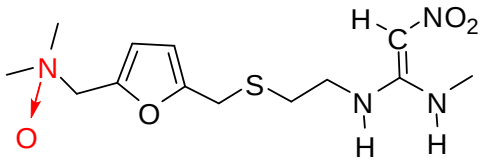
4-Hydroxymethyl-cimetidine



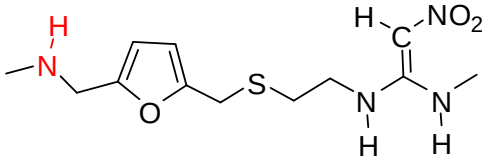
Famotidine S-oxide



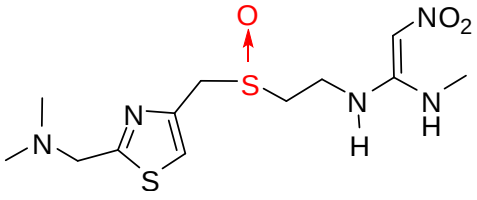
Ranitidine S-oxide



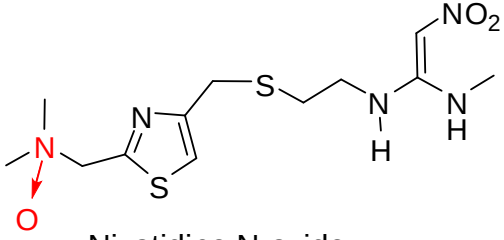
Ranitidine N-oxide



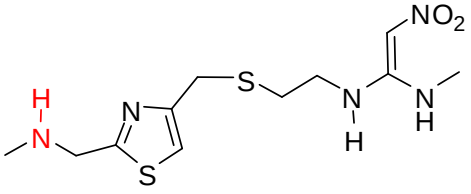
Monodesmethylranitidine



Nizatidine S-oxide



Nizatidine N-oxide



Monodesmethylnizatidine (has activity)