

HISTAMINE H₂-ANTAGONISTS, PROTON PUMP INHIBITORS AND OTHER DRUGS THAT ALTER GASTRIC ACIDITY

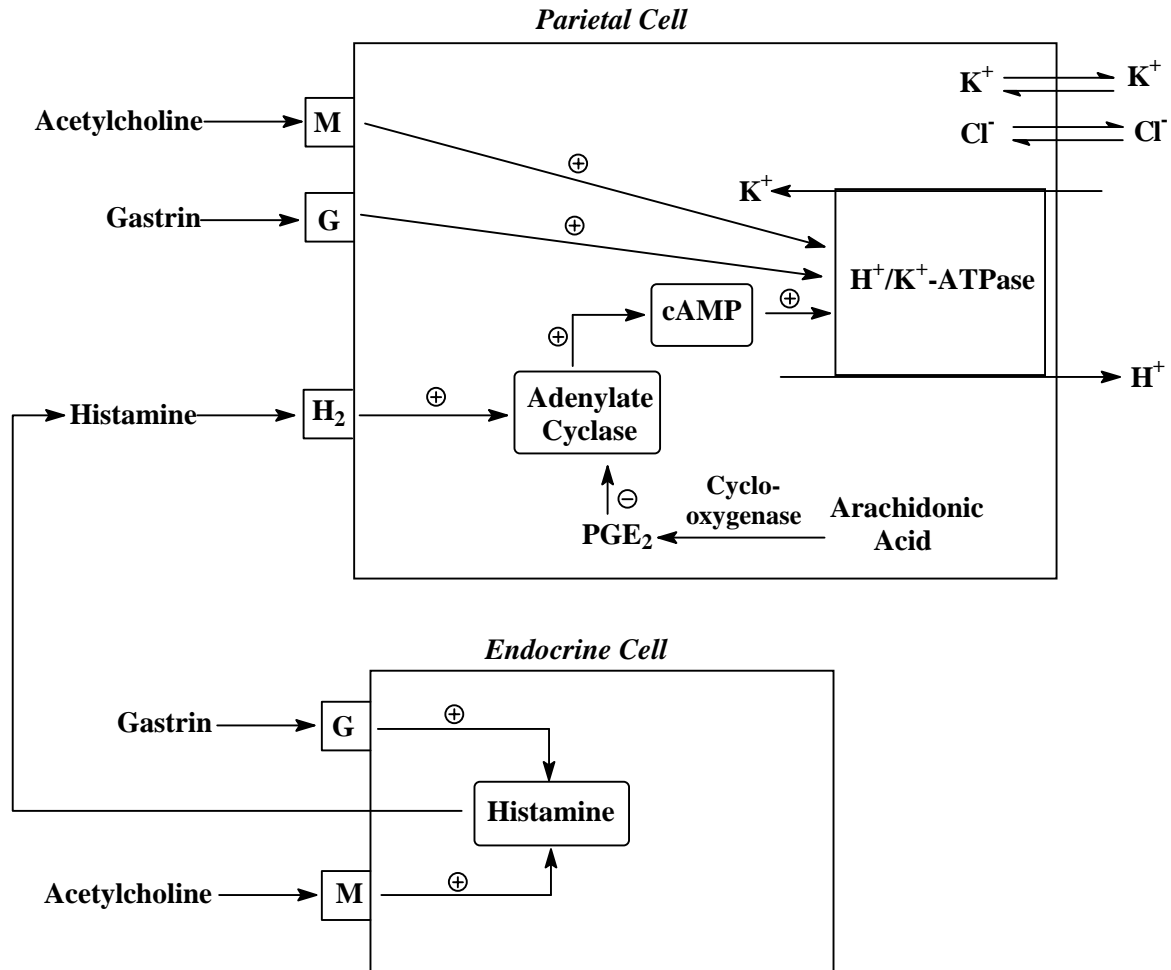
I. Introduction

Peptide ulcer disease (PUD) is a group of upper gastrointestinal tract disorders that result from the erosive action of acid and pepsin. Duodenal ulcer (DU) and gastric ulcer (GU) are the most common forms although PUD may occur in the esophagus or small intestine. Factors that are involved in the pathogenesis and recurrence of PUD include hypersecretion of acid and pepsin and GI infection by *Helicobacter pylori*, a gram-negative spiral bacterium. *H. Pylori* has been found in virtually all patients with DU and approximately 75% of patients with GU. Some risk factors associated with recurrence of PUD include cigarette smoking, chronic use of ulcerogenic drugs (e.g. NSAIDs), male gender, age, alcohol consumption, emotional stress and family history.

The goals of PUD therapy are to promote healing, relieve pain and prevent ulcer complications and recurrences. Medications used to heal or reduce ulcer recurrence include antacids, antimuscarinic drugs, histamine H₂-receptor antagonists, protective mucosal barriers, proton pump inhibitors, prostaglandins and bismuth salt/antibiotic combinations.

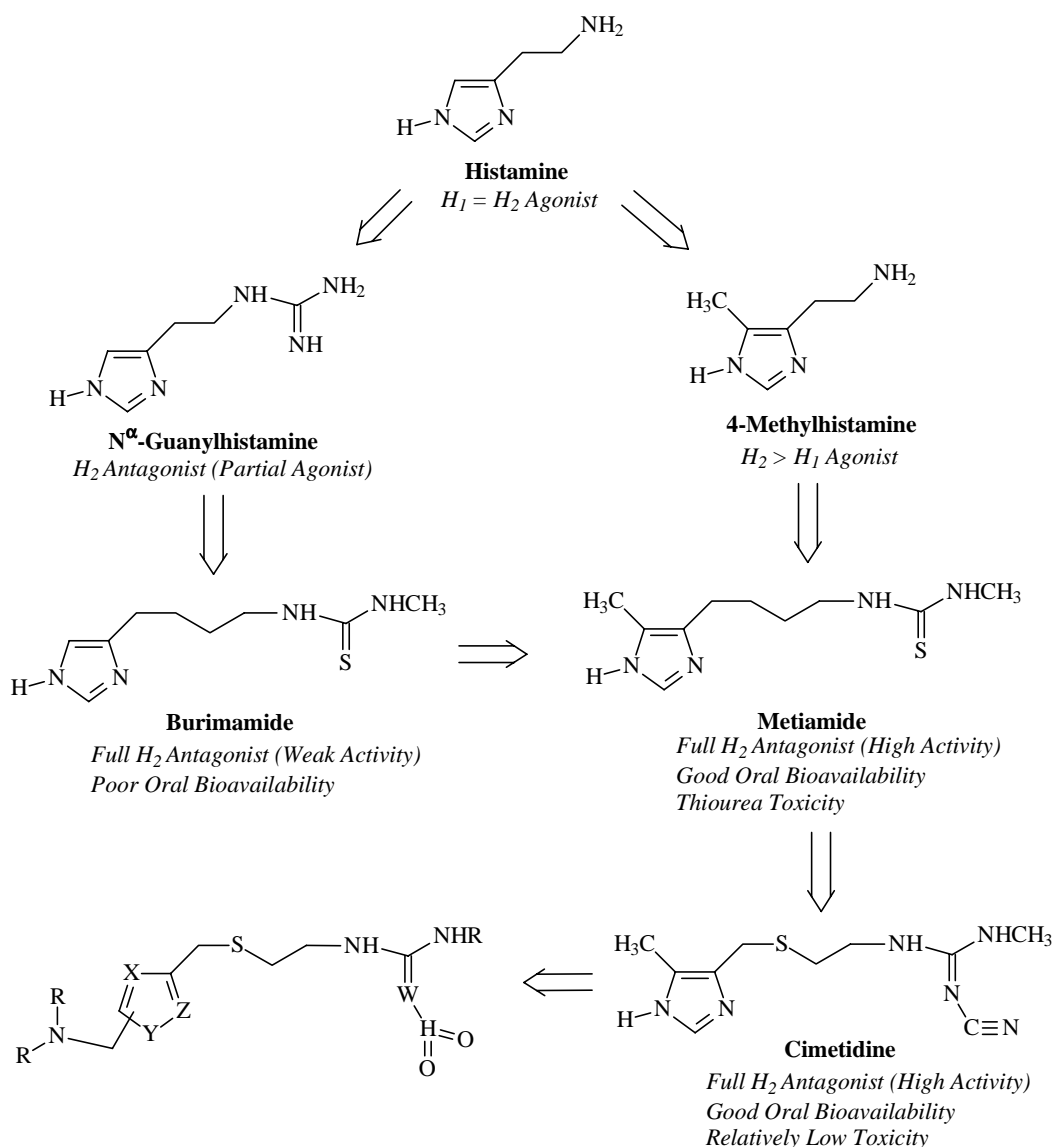
A characteristic feature of the stomach is its ability to secrete acid as part of its involvement in digesting food for absorption later in the intestine. The presence of acid and proteolytic pepsin enzymes, whose formation from pepsinogen is facilitated by the low gastric pH, is generally assumed to be required for the hydrolysis of proteins and other foods. The acid secretory unit of the gastric mucosa is the parietal (oxyntic) cell. Parietal cells contain a hydrogen ion pump, a unique H₃O⁺-K⁺-ATPase system that secretes H₃O⁺ in exchange for the uptake of K⁺ ion. Secretion of acid by gastric parietal (oxyntic) cells is regulated by the actions of various mediators at receptors located on the basolateral membrane including histamine agonism of H₂-receptors (cellular), gastrin activity at G-receptors (blood) and acetylcholine at M₂-muscarinic receptors (neuronal) as shown in the Figure on the next page

Drugs whose pharmacological action primarily involves antagonism of the action of histamine at its H₂-receptors find therapeutic application in the treatment of acid-peptic disorders ranging from heartburn to peptic ulcer disease, Zollinger-Ellison syndrome, gastroesophageal reflux disease (GERD), acute stress ulcers and erosions. Antimuscarinic drugs may generally express similar activities, but usually are less effective. Drugs that directly inhibit the hydrogen or proton pump (PPIs) are reportedly more effective in the short term than the H₂-blockers in healing duodenal ulcers and erosive esophagitis and can heal esophagitis resistant to treatment with the H₂-blockers. In addition, the benzimidazole PPIs have antimicrobial activity against *H. pylori* and therefore possess efficacy in treating gastric ulcers or with one or more antimicrobials in eradicating infection by this organism. The chemistry and basic activity of drugs that antagonize histamine or inhibit the proton pump are described in the sections that follow.



II. Histamine-2 Receptor Antagonist Development

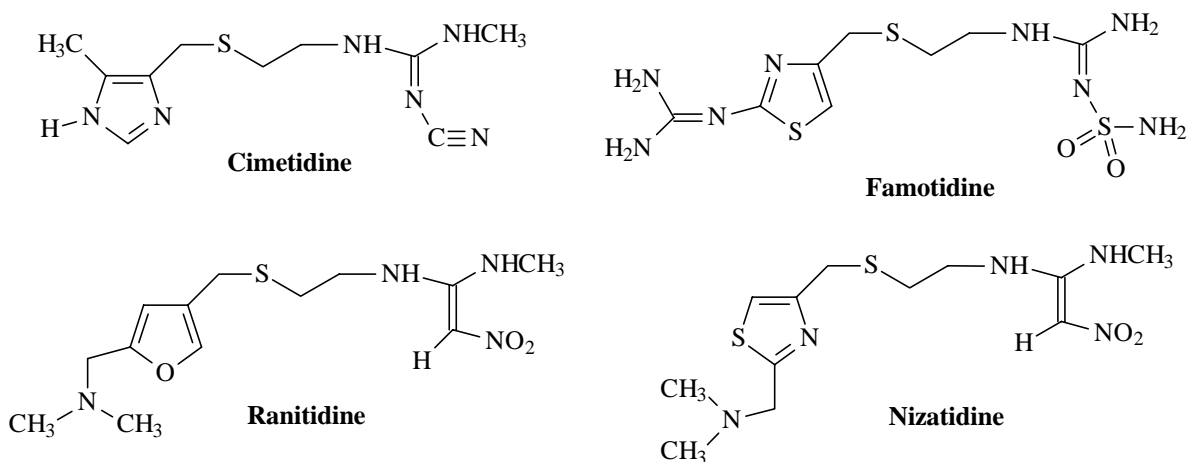
Structural evolution of the first discovered, clinically-useful H₂-antagonist, cimetidine, is depicted in the Figure below. Methylation of the 5-position of the imidazole heterocycle of histamine produces a selective agonist at atrial histamine receptors (H₂). The guanidino analogue of histamine possesses a small degree of antagonist activity to the acid-secretory actions of histamine. Increasing the length of the side chain from two to four carbons coupled with replacement of the strongly basic guanidino group by the neutral methyl thiourea function leads to burimamide, the first antagonist to be developed lacking detectable agonist activity in laboratory assays. The low potency of burimamide is postulated to be related to its nonbasic, electron-releasing side chain which favors the non-pharmacophoric N π -H imidazole tautomer compared to the basic, electron-withdrawing side chain in histamine which predominantly presents the higher affinity N τ -H imidazole tautomer to the receptor. Insertion of an electronegative thioether function in the side chain in place of a methylene group favors the N τ -tautomer and introduction of the 5-methyl group favors H₂-receptor selectivity leads to metiamide, a H₂-blocker of higher potency and oral bioavailability compared to burimamide. Toxicity associated with the thiourea structural feature is eliminated by replacing the thiourea sulfur with a cyano-imino function to produce cimetidine.



Cimetidine has proven to be an effective antisecretory agent, promoting the healing of duodenal ulcers. However, cimetidine is not without a number of limitations. Because it is short-acting it requires a frequent dosing schedule and its selectivity is poor. Cimetidine has antiandrogenic activity which can lead to gynecomastia and it inhibits the cytochrome P-450 mixed function oxygenase metabolizing enzyme system in the liver, an action which potentiates the effects of drugs whose clearance also depends upon biotransformation by this system. Cimetidine also causes confusional states in some elderly patients. Subsequent development of additional drugs of this class indicate that a great deal of structural latitude is available in the design of H₂-antagonists.

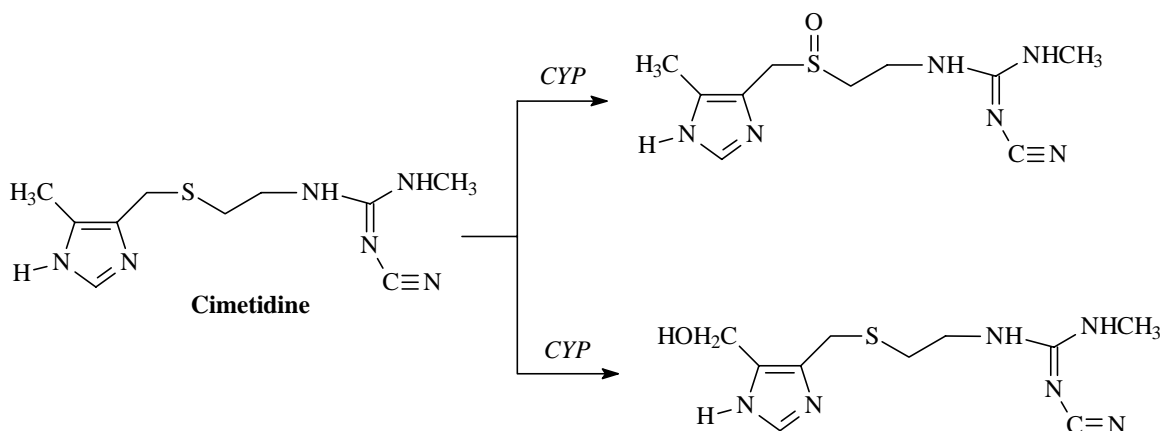
Examination of the structural features of H₂-antagonists that came after cimetidine (see general structure above) makes it obvious that the imidazole ring of histamine is not required for competitive antagonism of histamine at H₂-receptors. Other heterocycles may be used and may, in fact, enhance both potency and selectivity of H₂-receptor antagonism. However, if the imidazole ring is used, the

Nt-H tautomer should be the predominant species for maximal H₂-antagonist activity. The electronic effects of the ring substituents and side chain structural feature determine the tautomerism. Separation of the ring and the nitrogen group with the equivalent of a four-carbon chain appears to be necessary for optimal antagonist activity. The isosteric thioether link is present in the four agents currently marketed in the US. The terminal nitrogen-containing functionality should be a polar, nonbasic substituent for maximal antagonist activity; positively charged terminal nitrogen substituents (at physiologic pH) appear to confer agonist activity.



A. Properties of Cimetidine:

- Cimetidine exhibits high oral bioavailability (60 to 70%) and an plasma half-life of ~2 hours which is increased in renal and hepatic impairment and in the elderly. Approximately 30 to 40% of a cimetidine dose is metabolized (S-oxidation, 5-CH₃ hydroxylation) and the parent drug and metabolites are eliminated primarily by renal excretion.



- Cimetidine has a weak antiandrogenic effect resulting in gynecomastia in some patients.
- Reversible CNS effects (eg, mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation) have occurred with cimetidine, predominantly in severely ill patients.

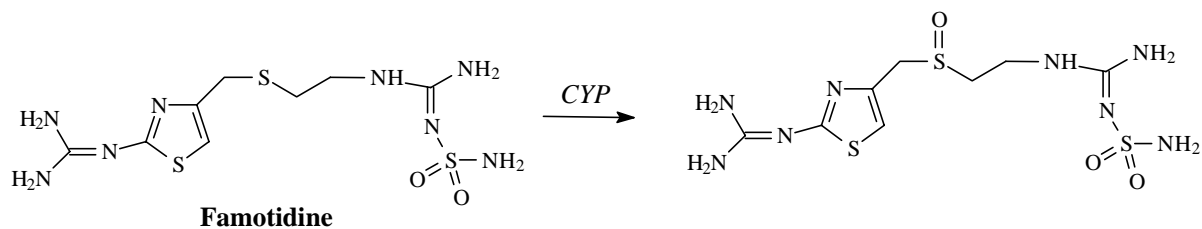
- Cimetidine Inhibits the hepatic metabolism of drugs biotransformed by the cytochrome P-450 mixed oxidase system delaying elimination and increasing serum levels of these drugs. Concomitant therapy of patients with cimetidine and drugs metabolized by hepatic microsomal enzymes, particularly those of low therapeutic ratio or in patients with renal or hepatic impairment, may require dosage adjustment. The following table provides a compilation of drugs whose combination therapy with cimetidine may result in their increased pharmacologic effects or toxicity. Antacids interfere with cimetidine absorption and should be administered at least one hour before or after a cimetidine dose.

Cimetidine Drug Interactions

Benzodiazepines	Metronidazole	Tacrine
Caffeine	Moricizine	Theophylline
Calcium channel blockers	Pentoxifylline	Triamterene
Carbamazepine	Phenytoin	Tricyclic antidepressants
Chloroquine	Propafenone	Valproic acid
Labetalol	Propranolol	Warfarin
Lidocaine	Quinidine	
Metoprolol	Quinine	
	Sulfonylurea	

B. Properties of Famotidine

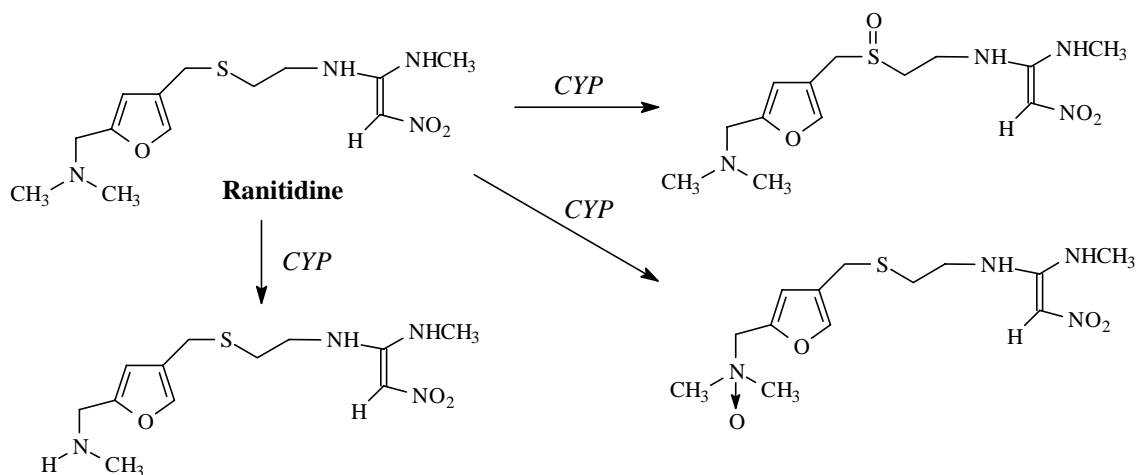
- Thiazole bioisostere of the imidazole heterocycle in cimetidine; the basic guanidine side chain may mimic the basic imidazole of cimetidine
- Famotidine is incompletely absorbed (40–45% bioavailability) due to its higher polarity (>cimetidine). The drug is eliminated by renal (65–70%) and metabolic (30–35%) routes. Famotidine sulfoxide is the only metabolite identified in humans. The effects of food or antacid on the bioavailability of famotidine are not clinically significant.



- No cases of gynecomastia, increased prolactin levels, or impotence have been reported, even at the higher dosage levels used in patients with pathologic hypersecretory conditions. Studies with famotidine in humans, in animal models, and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes (e.g., cytochrome P-450 system).

C. Properties of Ranitidine:

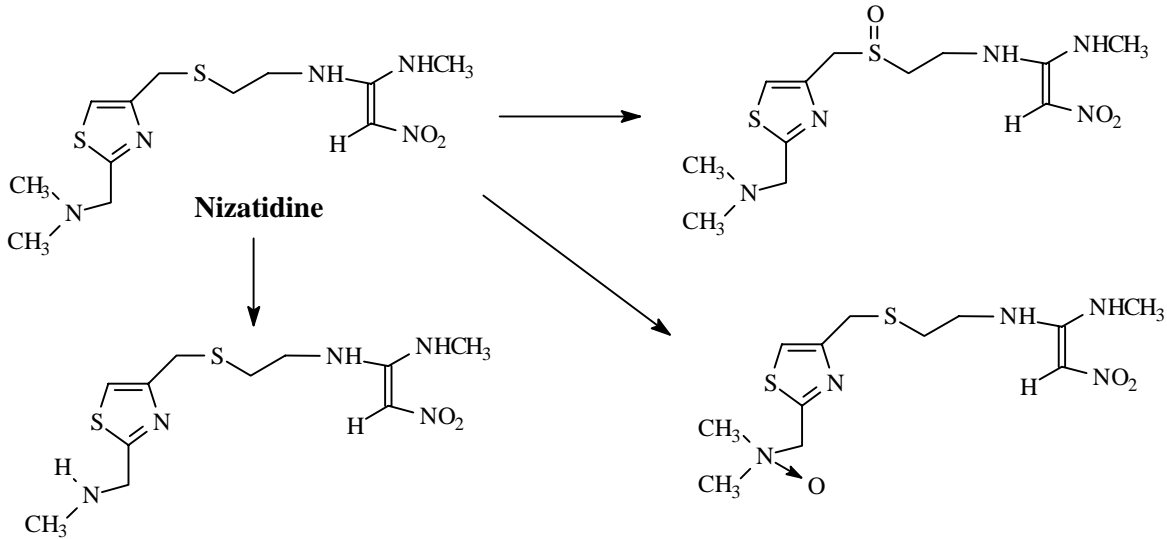
- An aminoalkyl furan with a dimethylaminomethyl side chain and a 1,1-diaminonitroethene substituent on the terminal nitrogen. The dimethylamino side chain may mimic electronically the imidazole ring of cimetidine. It has pKa values of 2.7 (side chain) and 8.2 (dimethylamino). Bioavailability of an oral dose of ranitidine is »50 to 60% and is not significantly affected by the presence of food. Some antacids may reduce ranitidine absorption and should not be taken within one hour of administration of the H₂-blocker. The plasma half-life of the drug is 2–3 hours and it is excreted along with its metabolites in the urine. Three metabolites, ranitidine N-oxide, ranitidine S-oxide and desmethyl ranitidine, have been identified.



- In addition to being available in a variety of dosage forms as the hydrochloride salt, ranitidine is also available as a bismuth citrate salt for use with the macrolide antibiotic clarithromycin in treating patients with an active duodenal ulcer associated with *Helicobacter pylori* infection. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence.
- Ranitidine is only a weak inhibitor of hepatic cytochrome P-450 mixed function oxidase system and does not appear to have antiandrogenic activity

D. Properties of Nizatidine:

- Has a thiazole ring system with a dimethylaminomethyl side chain and a 1,1-diaminonitroethene substituent on the terminal nitrogen. The dimethylamino side chain may mimic electronically the imidazole ring of cimetidine. Nizatidine has excellent oral bioavailability (>90%). The effects of antacids or food on its bioavailability are not clinically significant. The elimination half-life is 1-2 hours. It is excreted primarily in the urine (90%) and mostly as unchanged drug (60%). Metabolites include nizatidine sulfoxide (6%), N-desmethylnizatidine (7%) and nizatidine N₂-oxide (dimethylaminomethyl function).
- Nizatidine has no demonstrable antiandrogenic action or inhibitory effects on cytochrome P-450-linked drug-metabolizing enzyme system.



Key Properties of the H-2 Antagonists

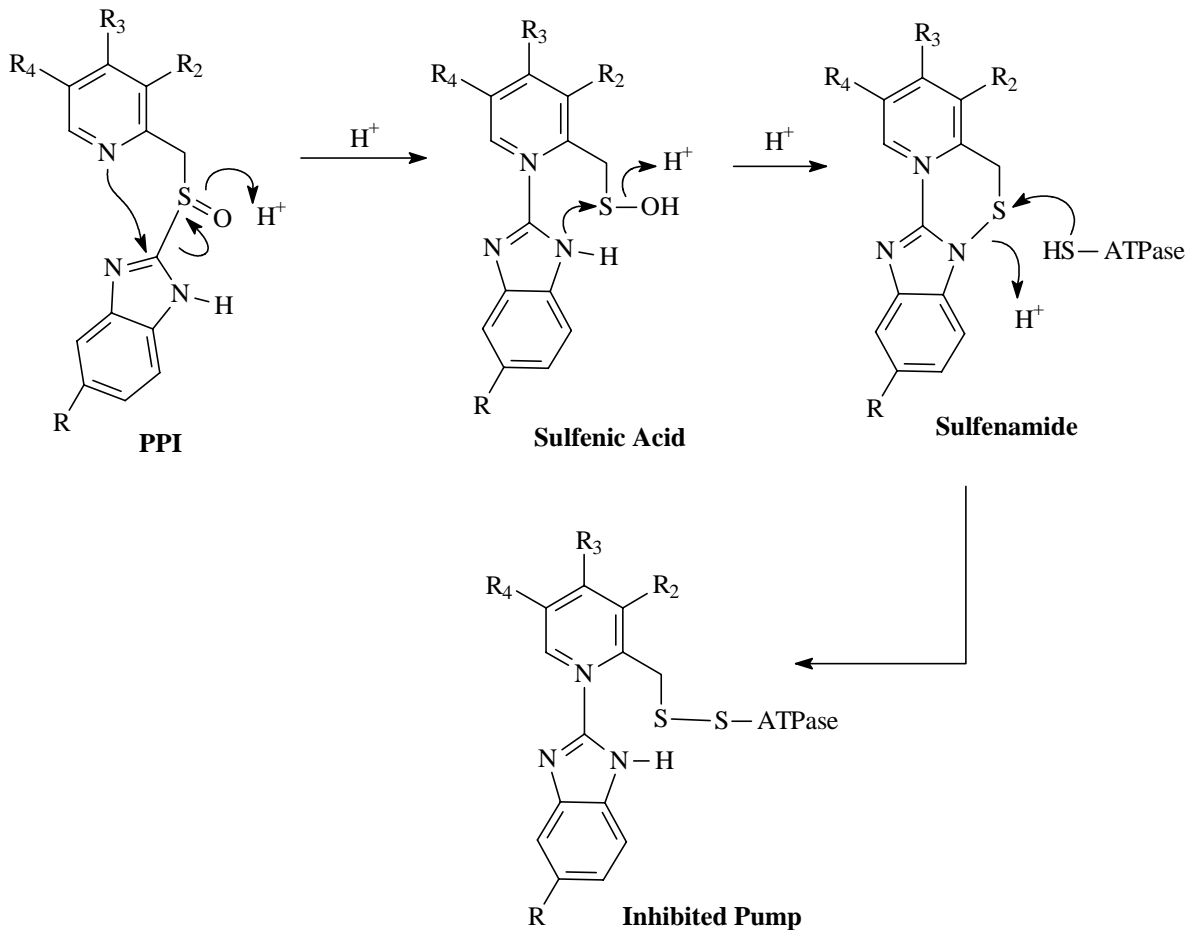
Parameter	Cimetidine	Famotidine	Nizatidine	Ranitidine
% Oral Bioavailability	60-70	40-45	>90	50-60
Tmax, hrs	0.75-1.5	1-3	0.5-3	1-3
Half-life, hrs	2	2.5-3.5	1-2	2-3
PPB	13-25	15-20	35	15
Vd, L/Kg	0.8-1.2	1.1-1.4	0.8-1.5	1.2-1.9
%Metabolism	30-40	30-35	<18	<10
%Parent Drug in Urine	48	25-30	60	30-35
CYP Inhibition	Potent	NO	NO	Weak
Antiandrogenic Activity	Yes	NO	NO	NO

III. The Proton Pump Inhibitors (PPIs)

The final step in acid secretion in the parietal cell is the extrusion ("pumping") of protons. The membrane pump, a H^+/K^+ -ATPase, catalyzes the exchange of hydrogen ions for potassium ions. Inhibition of this proton pump acts beyond the site of action of second messengers, e.g. calcium ion and cyclic AMP, and is independent of the action of secretagogues histamine, gastrin, and acetylcholine. Thus, acid or proton pump inhibitors (PPIs) block basal and stimulated secretion.

In 1972, a group of Swedish medicinal chemists discovered that certain pyridylmethyl benzimidazole sulfides possessed potent gastric acid (proton) pump inhibitory (PPI) activity. The benzimidazole PPIs are not the active inhibitor of the H^+/K^+ -ATPase but are transformed within the acid compartment of the parietal cell to an inhibitor molecule which reacts covalently with an essential thiol (SH) function on the enzyme. *In vitro*, the benzimidazoles are reversibly transformed in acidic media to a sulfenamide which can react with thiols to establish a disulfide link between inhibitor and pump enzyme. This is a transient covalent which can be cleaved eventually to regenerate and active pump.

PPI Mechanism of Action (Parietal Cell)



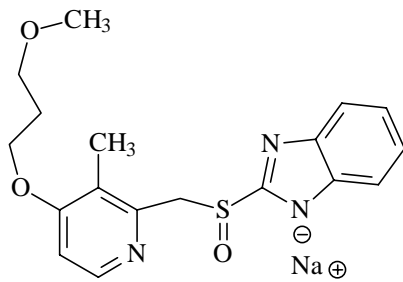
The PPIs inhibit both basal and stimulated gastric acid secretion. Unlike the H_2 -blockers, the PPIs inhibit daytime and nocturnal acid secretion regardless of whether they are administered in the morning or the evening. Gastric acid inhibition is also similar when these drugs are administered before or after a meal. The PPIs have no effect on postprandial digestive function or gastric emptying. The PPIs are more effective in the short term than the H_2 -blockers in healing duodenal ulcers and erosive esophagitis and can heal esophagitis resistant to treatment with the H_2 -blockers. In addition, the benzimidazole PPIs have antimicrobial activity against *H. pylori* and therefore possess efficacy in treating gastric ulcers or with one or more antimicrobials (tetracyclines, metronidazole, etc.) in eradicating infection by this organism.

Because of the normal physiologic effect caused by the inhibition of gastric acid secretion, blood flow in the antrum, pylorus, and duodenal bulb decreases. These agents increase serum pepsinogen levels and decrease pepsin activity. As with other agents that elevate intragastric pH, increases in gastric pH are associated with increases in nitrate-reducing bacteria and elevation of nitrate concentration in gastric juice in patients with gastric ulcer. Long term PPI therapy reportedly results in significant (2- to 3-fold) increases in serum gastrin levels and an associated moderate increase in enterochromaffin-like cell (ECL-cell) density. This is of concern since such changes in gastric histology may be associated with

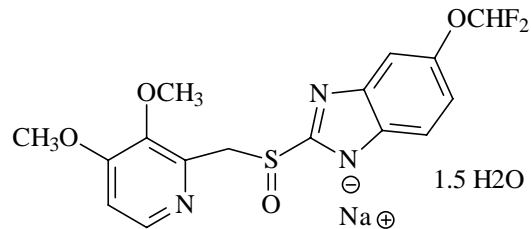
increased risk of ECL-cell hyperplasia, gastrointestinal carcinoids and colorectal adenocarcinoma. However, in animal and human studies to date there appears to be no increased risk of development of GI neoplasms secondary to PPI-induced hypergastrinemia. Also while serum gastrin levels increase parallel with inhibition of acid secretion. No further increase in serum gastrin occurs with continued treatment. Gastrin values usually returned to pretreatment levels within several weeks to months after discontinuation of therapy.

The pharmacologic actions of the PPIs appear to be relatively specific. To date no significant deleterious effects on cardiovascular, respiratory, ophthalmic, or central nervous system function have been noted with these drugs. Also, they do not appear to effect levels of neurotransmitters or key hormones including cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

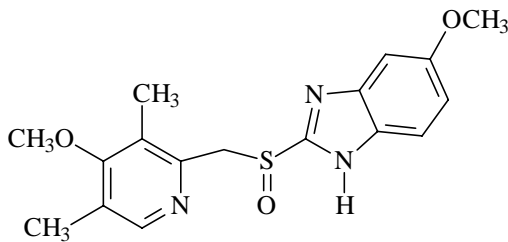
Currently five benzimidazole PPIs are available in the US including omeprazole (*Losec*[®]), the single enantiomer of omeprazole, esomeprazole (*Nexium*[®]), lansoprazole (*Prevacid*[®]), rabeprazole (*Aciphex*[®]) and pantoprazole (*Protonix*[®]). All of these drugs are very similar structurally as shown below and have the same mechanism of action. The structural differences between PPIs results in modest differences in metabolic, pharmacokinetic and pharmacodynamic properties.



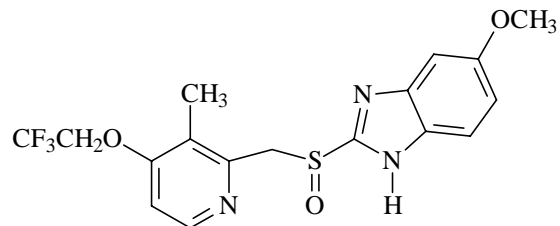
Rabeprazole Sodium (Aciphex)



Pantoprazole Sodium (Protonix)



**Omeprazole (Losec)
Esomeprazole (Nexium)**



Lansoprazole (Prevacid)

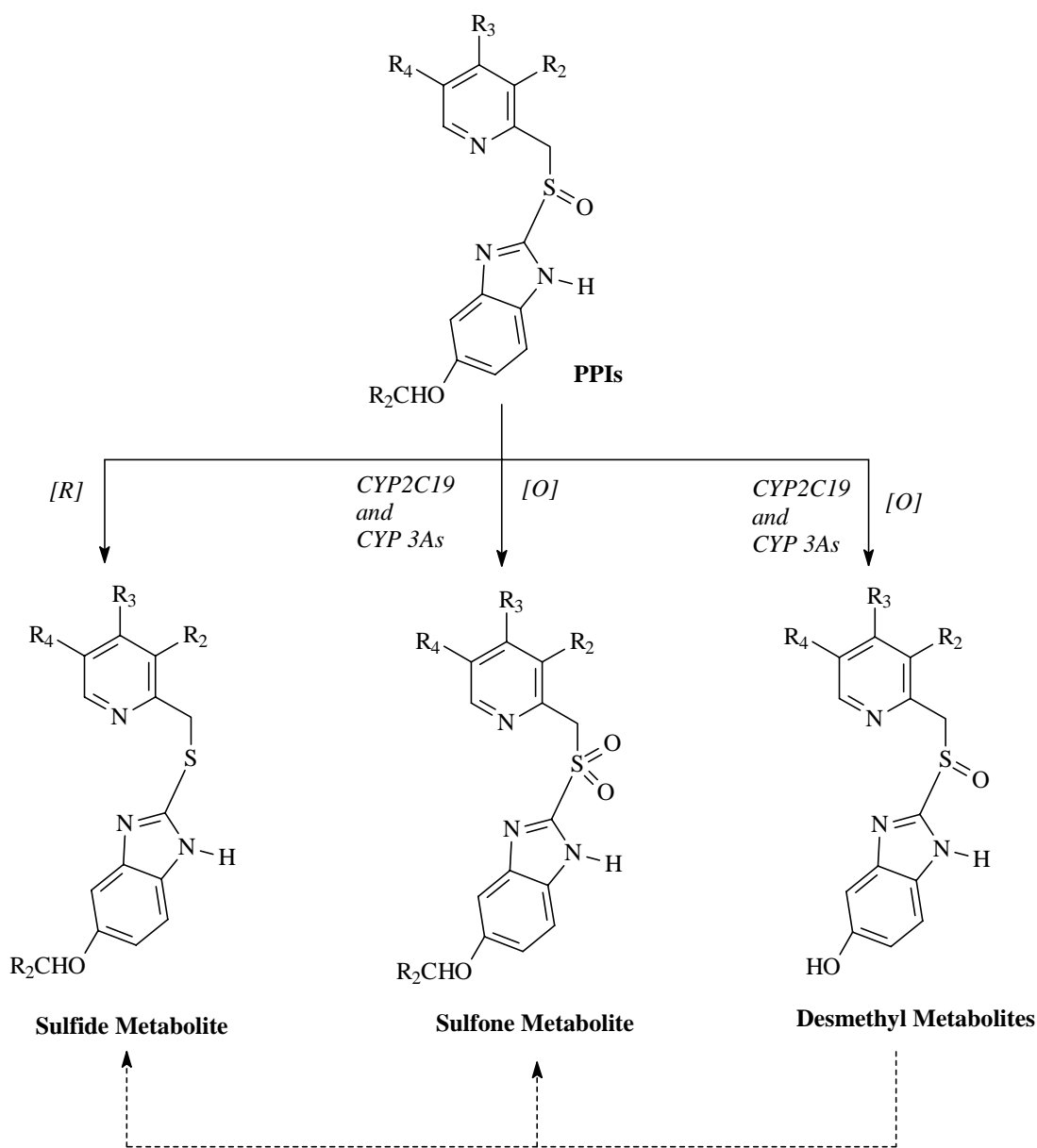
- Pharmacologic Properties:
 - Duration of acid suppression: Lansop>rabepr, pantop>omep
 - Onset of acid suppression: Rabepr>lansop>omep>pantop

- General Efficacy: Comparable to each other and > H₂-Antagonists in providing relief and promoting ulcer healing.
- Esomeprazole undergoes less first pass metabolism and has a lower clearance rate than the racemate, omeprazole

Pharmacokinetic Properties of the PPIs

Parameters	Omepr	Esomepr	Lansopr	Rabepr	Pantopr
Dosage form	Oral	Oral	Oral	Oral	Oral/IV
Bioavailability	35%–60%	50-70%	85%	52%	77%
Tmax	0.5-3.5 hr	1.6 hr	1.7 hr	2-5 hr	2.4 hr
Half-life	0.5–1.0 hr	1.25 hr	1.5 hr	1-2 hr	1.0 hr
Duration	>24 hrs	>24 hrs	>24 hrs	>24 hrs	>24 hrs
Protein binding	95%	97%	99%	96%	98%
Clearance	Liver	Liver	Liver	Liver	Liver
Renal Elim	80%	80%	33%	90%	71%

PPI Metabolism



- **PPI Drug Interactions:**

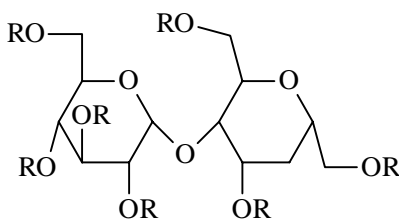
- Proton pump inhibitors cause a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole, omeprazole, pantoprazole, and rabeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, ampicillin, iron salts, and digoxin. Because of effects on gastric acid secretion, PPIs may also decrease digestion and the absorption of some essential nutrients such as vitamin B12 (cyanocobalamins).
- P450 system: Omeprazole may interact with other drugs also metabolized via the cytochrome P450 system. There are clinical reports of interaction with other drugs metabolized via the cytochrome P450 (CYP450) system (eg, cyclosporine, warfarin, disulfiram, benzodiazepines). While the other PPIs are also metabolized through the CYP450 system (usually CYP3A and CYP2C19 isoenzymes), they do not appear to produce clinically significant inhibition or interactions with other drugs metabolized by the CYP450 system.

IV. Chemical Complexation Agents

The sulfate esters and sulfonate derivatives of polysaccharides and lignin form chemical complexes with the enzyme pepsin. These complexes have no proteolytic activity. Because polysulfates and polysulfonates are poorly absorbed from the gastrointestinal tract, specific chemical complexation appears to be a desirable mechanism of pepsin inhibition. Unfortunately, these polymers are also potent anticoagulants.

The properties of chemical complexation and anticoagulant action are separable by structural variation. In a comparison of selected sulfated saccharides of increasing number of monosaccharide units, from disaccharides through starch-derived polysaccharides of differing molecular size, three conclusions are supported by the data: (1) the anticoagulant activity of sulfated saccharide is positively related to molecular size; (2) anticoagulant activity is absent in the disaccharides; and (3) the inhibition of pepsin activity and the protection against experimentally induced ulceration is dependent on the degree of sulfation and not on molecular size.

The readily available disaccharide, sucrose, has been used to develop a useful antiulcer agent, sucralfate (Carafate[®]). Sucralfate is the aluminum hydroxide complex of the octasulfate ester of sucrose. It is practically insoluble in water and soluble in strong acids and bases. It has a pKa value between 0.43 and 1.19.



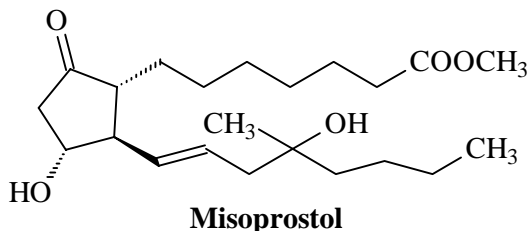
Sucralfate: $R=SO_3[Al_2(OH)_5 \cdot (H_2O)_2]$

Sucralfate is minimally absorbed from the gastrointestinal tract and thus exerts its antiulcer effect through local rather than systemic action. It has negligible acid-neutralizing or buffering capacity in therapeutic doses. Its mechanism of action has not been established, however, studies suggest that sucralfate binds preferentially to the ulcer site to form a protective barrier that prevents exposure of the lesion to acid and pepsin. In addition, it adsorbs pepsin and bile salts. Either would be very desirable modes of action.

The product labeling states that the simultaneous administration of sucralfate may reduce the bioavailability of certain agents (e.g., tetracycline, phenytoin, digoxin, or cimetidine). It further recommends restoration of bioavailability by separating administration of these agents from that of sucralfate by two hours. Presumably sucralfate binds these agents in the gastrointestinal tract. The most frequently reported adverse reaction to sucralfate is constipation (2.2%). Antacids may be prescribed as needed, but should not be taken within one-half hour before or after sucralfate.

V. Prostaglandins

The prostaglandins are endogenous 20 carbon unsaturated fatty acids biosynthetically derived from arachidonic acid. These bioactive substances and their synthetic derivatives have been of considerable research and development interest as potential therapeutic agents because of their widespread physiologic and pharmacologic actions on the cardiovascular system, gastrointestinal smooth muscle, the reproductive system, the nervous system, platelets, kidney, the eye, etc. Prostaglandins of the E, F and I series are found in significant concentrations throughout the gastrointestinal tract. The gastrointestinal actions of the prostaglandins include inhibition of basal and stimulated gastric acid and pepsin secretion in addition to prevention of ulcerogen or irritant-induced gross mucosal lesions of the stomach and intestine (termed *cytoprotection*). The prostaglandins are capable of both stimulation (PGFs) and inhibition (PGEs and PGI₂s) of intestinal smooth muscle contractility and accumulation of fluid and electrolytes in the gut lumen (PGEs). Therapeutic application of the natural prostaglandins in the treatment of gastrointestinal disorders is hindered by their lack of pharmacologic selectivity coupled with a less than optimal biodisposition



profile.

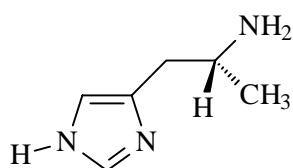
Misoprostol, (±)-methyl 11a, 16-dihydroxy-16-methyl-9-oxoprost-13*E*-en-1-oate, is a semisynthetic derivative of PGE₁ that derives some pharmacologic selectivity as well as enhanced biostability from its 16-methyl, 16-hydroxy structural features. Misoprostol exhibits both antisecretory and cytoprotectant effects characteristics of the natural prostaglandins along with a therapeutically acceptable biodisposition profile. While the antisecretory effects of misoprostol are thought to be related to its agonistic actions at parietal cell prostaglandin receptors, its cytoprotective actions are

proposed to be related to increases in gastrointestinal mucus and bicarbonate secretion, increases in mucosal blood flow and/or prevention of back diffusion of H_3O^+ into the gastric mucosa.

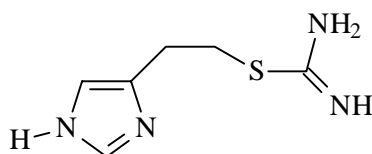
Misoprostol is rapidly absorbed following oral administration and undergoes rapid deesterification to the pharmacologically-active free acid with a terminal half-life of 20 to 40 minutes. Misoprostol is commonly used to prevent NSAID-induced gastric ulcers in patients at high risk of complications from a gastric ulcer such as elderly patients and patients with a history of ulcer. Misoprostol has also been used in treating duodenal ulcers unresponsive to histamine H_2 -antagonists; however, the drug does not prevent duodenal ulcers in patients on NSAIDS. Misoprostol can cause miscarriage, often associated with potentially dangerous bleeding.

HISTAMINE H_3 -RECEPTOR LIGANDS

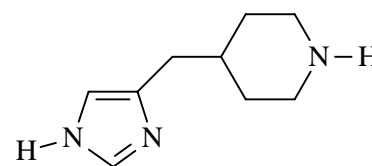
The histamine H_3 receptor has been described to play a role as a general regulatory receptor system, modulating not only the release and synthesis of histamine but also the release of other neurotransmitters. In order to characterize the physiologic and potential therapeutic roles of histamine H_3 -receptors, medicinal chemists have been actively seeking structural features associated with selective agonism and antagonism of these sites. Structural alterations of histamine itself have resulted in development of the potent and selective H_3 -agonist (*R*)- α -methylhistamine. Replacement of the amino group with other polar cationic groups has yielded the potent and selective H_3 -agonist, imetit. Immepip, which has an aminobutylene chain incorporated in a piperidine ring, is comparable in agonist potency to (*R*)- α -methylhistamine.



(R)- α -Methylhistamine

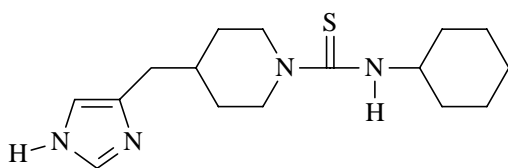


Imetit

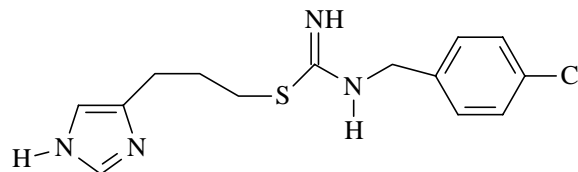


Immepip

The classical H_1 -antagonists are not very active at the H_3 -receptor but several compounds which are active antagonists at the H_2 -receptor, such as burimamide, display moderate H_3 -antagonistic activity. Thioperamide, a cyclohexylthiourea derivative of immepip, is a potent, competitive H_3 -antagonist both *in vitro* and *in vivo*. Thioperamide has become an important tool for the pharmacological characterization of possible H_3 -receptor-mediated effects. Clobenpropit, a benzylthiourea homolog of histamine, is also a frequently used pharmacological tool for the study of histamine H_3 -receptors.



Thioperamide



Clobenpropit

Studies with these experimental agents suggest that H_3 -receptor agents might provide new therapeutics for CNS, airway and gastrointestinal disorders.