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Review

Recent advances in proton pump inhibitors and management of acid-peptic disorders

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Abstract—Acid-peptic ulcers and diseases have been increasingly on rise in today's era of globalization, which is characterized by hurry, worry, and curry. This review summarizes various disorders associated with increased gastric acid secretion and various therapeutic strategies to control them. The emphasis has been laid, in particular, on the role of proton pump inhibitors (PPIs) widely used nowadays for the treatment of gastric acid diseases. The medicinal chemistry aspects and mechanism of action of irreversible PPIs and APAs have been discussed at molecular levels. The ongoing research status in this field has also been covered. Further, biological evaluation methods that can be used for screening of PPIs are also discussed in short.

Contents

Keywords: Acid-peptic disorders; Therapeutic strategies; Gastric H^+/K^+-ATPase (proton pump); Proton pump inhibitors (PPIs); Acid pump antagonist (APAs).
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1. Introduction

'Hurry, Worry & Curry' are the causes of many disorders in today's world of globalization. Of these acid-peptic ulcers and diseases have assumed a distinctly high proportion. The pathophysiology of acid-peptic disease is attributed to the imbalance between aggressive factors (like acid, pepsin, and *Helicobacter pylori* infection) and local mucosal defenses (like secretion of bicarbonate, mucus, and prostaglandins). Although treatment is often directed at reduction of aggressive factors, it can also be directed at strengthening mucosal defenses of stomach and duodenum.[1]

The inhibition of gastric acid secretion is a key therapeutic target for the ulcer diseases (viz., peptic, duodenal ulcers or that through *H. pylori* infection), gastro esophageal reflux disease (GERD), Zollinger–Ellison syndrome (Z-E), and gastritis. Currently this is achieved by blocking the acid secretary effect of histamine (HA) through the use of H_2-receptor antagonists or the irreversible H^+/K^+-ATPase inhibitors, popularly referred to as proton pump inhibitors (PPIs). The incidence of ulcer diseases shows global variation and their treatment should be designed to alleviate the symptoms, while keeping the risk of adverse effects to minimum. In western countries duodenal ulcers are more common, whereas in eastern countries gastric ulcers predominate. These differences are attributed to factors like diet and genetic make up. As a result the therapeutic strategies also differ from east to west. In western countries, the conventional therapy for duodenal and gastric ulcer is eradication of *H. pylori*. Whereas, in Japan unlike the west, H_2-antagonists are commonly used for maintenance therapy along with the PPIs.[2]

The discovery of the gastric acid was the first step to understand the role of the stomach in digestion and

Table 1. Some landmarks in the therapy of acid-peptic disorders in past 35 years[2]

Year	Company/discoverer	Event/discovery
1972	James Black et al.[5]	Discovery of H_2-receptor and H_2-receptor antagonists
1973	A. Ganser & J. Forte.[6]	Discovery of H^+/K^+-ATPase (The Proton Pump)
1976	SmithKline & French.[7]	Cimetidine launched (H_2-receptor antagonist)
1982	Allen & Hanburys Ltd[8]	Ranitidine launched (H_2-receptor antagonist)
1988	AstraZeneca.[9]	Omeprazole launched (PPI)
1995	Takeda-Abbott[10]	Lansoprazole launched (PPI)
1997	Eisai Co. (licensed to Janssen)[11]	Rabeprazole launched (PPI)
2001	AstraZeneca[12]	Esomeprazole launched (PPI)

the diseases associated with hypersecretion of acid.[3,4] The drug discovery process linked with the gastric acid secretion involving H_2-receptor antagonists and PPIs is summarized in Table 1. It indicates the gradual change in the focus in the treatment of gastric acid secretion disorders.[2]

In this review, various disorders related with increased gastric acid secretion and therapeutic strategies to control them have been summarized. Furthermore, emphasis has been laid on the role of PPIs in particular for the treatment of gastric acid disorders. The medicinal chemistry aspects of this particular class of compounds are also discussed.

1.1. Mechanism of gastric acid secretion

Stomach is a primary site of digestion. Presence of food stimulates release of acids and enzymes in stomach. The chemo- and mechanosensitive receptors present in stomach are triggered by presence of food to produce specific responses.[2] The acid secreting parietal cell is the principle cell in gastric glands. The physiological regulation of acid secretion by the parietal cells is thus an important factor behind the rationale of use of various agents to reduce gastric acidity. Three major pathways activating parietal acid secretion include: (1) neuronal stimulation via the vagus nerve, (2) paracrine stimulation by local release of histamine from enterochromaffin-like (ECL) cells, and (3) endocrine stimulation via gastrin released from antral G cells. In neuronal pathway, acetylcholine (Ach) released by vagal nerve directly stimulates gastric acid secretion through muscarinic M_3 receptors located on the basolateral membrane of parietal cells. The CNS is considered to be the chief contributor for initiating gastric acid secretion in response to the anticipation of food. Ach indirectly stimulates release of histamine from enterochromaffin-like (ECL) cells in the fundus and gastrin from the G cells in the gastric antrum. ECL cells, the sole source of gastric histamine involved in acid secretion, are present in close proximity to parietal cells. Histamine released from ECL cells activates parietal cells in paracrine fashion by binding to H_2 receptors. Gastrin is primarily present in antral G cells. Release of gastrin is under regulation of central neural activation, local distension, and chemical composition of gastric content. Gastrin stimulates parietal cells by binding with gastrin receptors. Gastrin also exerts its action in an indirect manner by causing the release of histamine from ECL cells.[1] Binding to respective G-protein coupled receptors by Ach, gastrin, and histamine results in activation of second-messenger systems.[2] Vagal stimulation and the action of gastrin (from duodenal and antral G cells) stimulate release of histamine from paracrine-ECL cells or mast cells. Increased levels of both intracellular Ca^{2+} by gastrin/Ach and cyclic AMP by histamine finally cause acid secretion.[13] The final step in acid secretion is mediated by H^+/K^+-ATPase, also called as gastric proton pump.[14] Activation of either the cAMP or Ca^{2+}-dependent pathway or both causes stimulation of H^+/K^+-ATPase on parietal cells[15] (Fig. 1).

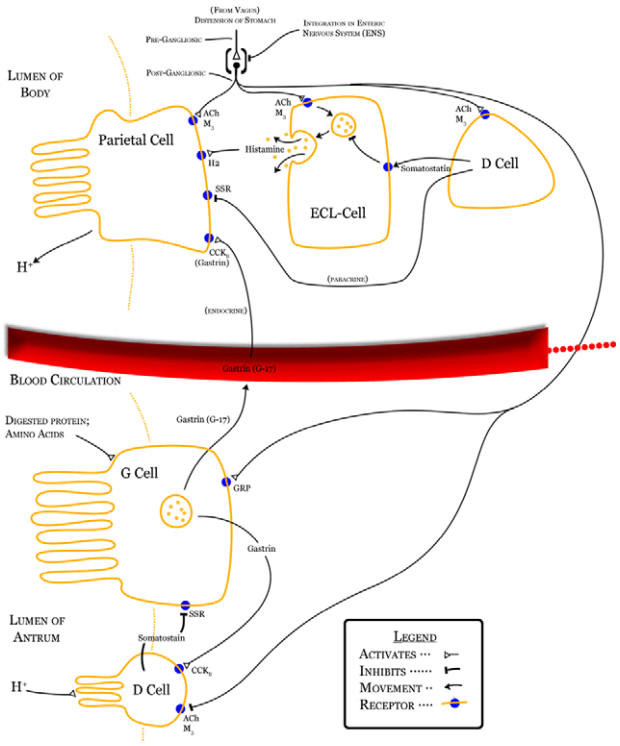


Figure 1. Mechanism of gastric acid secretion.[16]

1.2. Disorders associated with elevated secretion of gastric acid

(a) *Peptic ulcers*: Neuropeptide Y, corticotrophin-releasing factor, bombesin, calcitonin, neurotensin, interlukin 1, along with somatostatin, prostaglandins, bicarbonates, and mucin act as mucosal defense factors. Imbalance between these mucosal defense factors and aggressive factors (acid and pepsin) is involved in peptic ulcers[2] (Fig. 2). Their rational treatment is aimed at restoring this balance. In case of duodenal ulcers (DU), there is increase in basal acid secretion. In gastric ulcers (GU), however, there is weakening of mucosal defenses that can lead to injury in spite of low acid secretion. Differences between DU and GU are summarized in Table 2. *H. pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) play important role in ulcer induction.[1] Particularly NSAIDs inhibit production of prostaglandins from arachidonic acid by inhibiting enzyme cyclooxygenase (COX). Chronic NSAID users are at 2–4% risk of developing a symptomatic ulcer, gastrointestinal bleeding or associated perforation. In ulcer patients, NSAIDs increase the risk of probable complications fourfold. Further, these complications may remain undetected because of reduction in pain, thereby worsening the condition. Co-administration of Misoprsotol, the synthetic prostaglandin analog or acid suppression therapy may be beneficial. Proton pump inhibitors are superior to H_2-receptor antagonist in promoting healing and preventing recurrence of both GU and DU[1] (see Fig. 3).

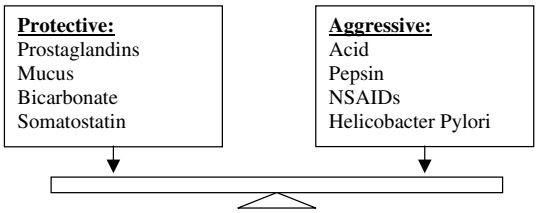


Figure 2. Factors involved in maintaining acid balance.

(b) *Zollinger–Ellison (Z-E) syndrome*: In this disease, a non-β cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate the secretion of gastric acid to life-threatening levels. This can lead to severe gastroduodenal ulcerations and other consequences of the uncontrolled hyerchlorhydria. The therapy is aimed at reducing gastric acid secretion. In this the proton pump inhibitors being surely the drugs of choice.[2] ECL-cells carcinoids are rare events that have been described in association with Z-E syndrome.[19]

(c) *Helicobacter pylori (H. pylori) infection*: Around 40% of patients over 40 years age and with peptic ulcer disease are infected with *H. pylori* infection. *H. pylori* is a gram-negative rod-shaped bacteria and has clearly been associated with gastritis, peptic ulcers, gastric adenocarcinoma, and gastric β-cell lymphoma. Up to 80–90% of ulcers may be associated with *H. pylori* infection of stomach. This infection may lead to impaired production of somatostatin by D cells. This results into increased gastric acid secretion along with impaired duodenal bicarbonate production.[1] *H. pylori* infection is now proven to be a risk factor for gastric cancer and the organism was classified as group-I carcinogen by WHO.[20] *H. pylori* infection also causes inflammation of the antral gastric mucosa. Bacterial products and inflammatory cytokines may produce changes in the endocrine function.[21] It has now became a standard care procedure to eradicate the infection in patients with gastric and duodenal ulcers. This strategy is almost successful in eliminating the risk of ulcer recurrence (Fig. 4).[1]

(d) *Gastro esophageal reflux disease (GERD)*: It is a disorder of defense mechanism at the esophageal junction, caused by regurgitation of the gastric contents, especially of gastric acid. GERD is associated with decreased gastric emptying and/or increased incidence of transient lower esophageal relaxation (T-LESR).[23] Smoking and obesity increase the incidence of GERD symptoms like heartburn, belching, and bloating. GERD is not life-threatening, but can cause significant discomfort and increased risk of Barrett's esophagus.[2] Relationship between GERD symptoms and incidence of esophageal adenocarcinoma has also been suggested. It has also been linked to tracheopulmonary symptoms like laryngitis and asthma. Besides disturbed gastrointestinal motility, injurious effects of the acid-peptic refluxate on the esophageal epithelium are also responsible for GERD symptoms. Hence along with prokinetic drugs, suppression of gastric acid is the current pharmacotherapeutic approach for its treatment.[1] *H. pylori* infection does not necessarily correlate with GERD, although a reduction in acid secretion reduces chances of reflux.[23]

Table 2. Distinguishing features of the two major forms of peptic ulcers[18]

Serial No.	Features	Duodenal ulcer	Gastric ulcer
1	Incidence	Four times common than gastric ulcers	Less common than duodenal ulcers
		Usual age 25–50 years	Usually beyond 6th decade
		More common in males than in females (4:1)	More common in males than in females (3.5:1)
2	Etiology	Most commonly as a result of *Helicobacter pylori* infection	Gastric colonization with *H. pylori* asymptomatic but higher chances of development of duodenal ulcers. Disruption of mucus barrier most important factor. Association with gastritis, bile reflux, drugs, alcohol, and tobacco
		Other factors are hypersecretion of acid-pepsin, association with alcoholic cirrhosis, tobacco, hyperparathyroidism, chronic pancreatitis, blood group O, genetic factors, etc.	
3	Pathogenesis	Mucosal digestion from hyperacidity most significant factor	Usually normal-to-low acid levels: hyperacidity if present is due to high serum gastrin
		Protective gastric mucus barrier may be damaged	Damage to mucus barrier is a significant factor
4	Pathological changes	Most common in the first part of duodenum	Most common along the lesser curvature and pyloric antrum
		Often solitary, 1–2.5 cm in size, round to oval, punched out	Grossly similar to duodenal ulcers
5	Complications	Commonly hemorrhage, perforation, sometimes obstruction, are observed. However, malignant transformation never occurs	Perforation, hemorrhage and at times obstruction, are common. Malignant transformation less than 1% cases
6	Clinical features	Pain food relief pattern	Food pain pattern
		Night pain common	No night pain
		No vomiting	Vomiting common
		Melaena more common than hematemsis	Hematemsis more common
		No loss of weight	Significant loss of weight
		No particular choice of diet	Patients choose bland diet devoid of fried food, curries etc.
		Marked seasonal variation	No seasonal variation
		Occurs more commonly in people at greater stress	More often in laboring groups

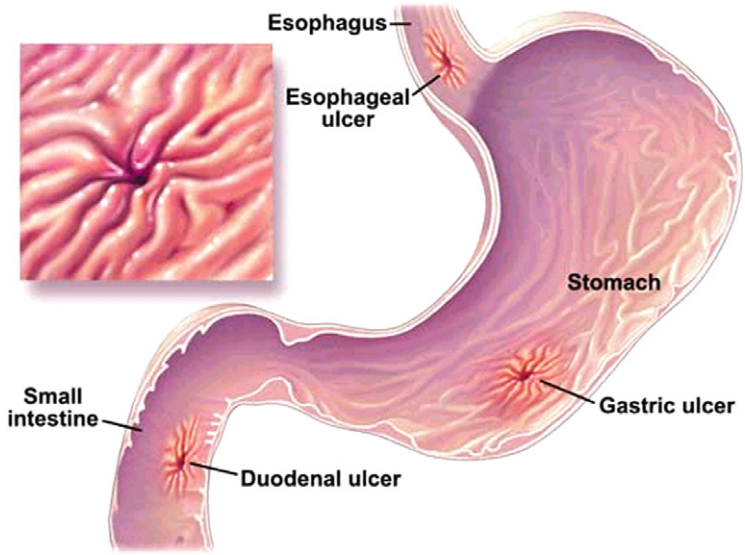


Figure 3. Peptic ulcer.[17]

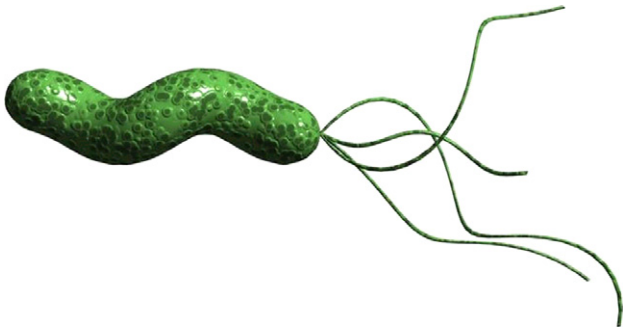


Figure 4. *Helicobacter pylori*.[22]

(e) *Stress–related ulcers*: These are the ulcers of stomach and duodenum that usually occur as a result of severe systemic or CNS illness or trauma. Both acid and mucosal ischemia are involved in the etiology of stress ulcers. Similarly, stress due to physiological factors like septicemia, intracranial lesions, alcohol intake, and smoking can also appreciably contribute to ulcer induction. Intravenous H_2-receptor antagonist and intravenous PPIs are preferred agents for its treatment.[1]
(f) *Non-ulcer dyspepsia*: It refers to ulcer-like symptoms in patients who are without overt gastroduodenal ulceration. Though pathogenesis of this syndrome remains unclear, it may occur because of gastritis or use of NSAIDs. Empirical treatment with acid-suppressive agents is used routinely.[1]

1.3. Complications arising from the disorders associated with elevated secretion of gastric acid[18]

1.3.1. Obstruction. Development of fibrous scar at or near the pylorus results in pyloric stenosis.

1.3.2. Hemorrhage. Minor bleeding by erosion of small blood vessels in the base of an ulcer occurs in all the ulcers and can be detected by testing the stool for occult blood.

1.3.3. Malignant transformation. The dictum '*cancers ulcerate but ulcers rarely cancerate*' holds true for most peptic ulcers. A chronic duodenal ulcer never turns malignant, while less than 1% of chronic gastric ulcers may transform into carcinoma.

1.3.4. Perforation. Perforation occurs more commonly in chronic duodenal ulcers than chronic gastric ulcers. Following sequel may result.

(i) On perforation the contents escape into the lesser sac or into the peritoneal cavity, causing acute peritonitis.
(ii) Air escapes from the stomach and lies between the liver and the diaphragm giving the characteristic radiological appearance of air under the diaphragm.
(iii) Perforation may extend further to involve adjacent organs (liver and pancreas).

2. Therapeutic strategies

Acid secretion is a physiologically important process of the stomach as:

1. Acid induces pepsinogen activation to initiate digestive process and
2. It kills bacteria and other microbes ensuring a stable intragastric environment. However, under certain circumstances secretion of large excess of gastric acid and pepsinogen injures the gastroduodenal mucosa and causes serious and fatal ulcerations.[15] Hence, there is a need of good gastric acid secretion inhibitors.

The secretion of gastric acid occurs at the level of parietal cells of oxyntic glands in the gastric mucosa, producing 2–3 L of gastric juice per day (HCl of pH 1).[24]

Based on the understanding of the mechanisms contributing to ulcer development and particularly to gastric acid secretion, a variety of therapeutic strategies exist. These include suppressing the aggressive factors with use of antacids, specific antagonists of muscarinic $-M_1$ receptors, gastrin receptors, histamine-H_2 receptors, proton pump inhibitors (PPIs), eradication of *H. pylori*, and agonists of prostaglandins/somatostatin receptors.[1,15] These overall strategies are discussed below in terms of specific therapeutic agents.

2.1. Antacids

Naturally occurring carbonates, potash, bismuth were used as antacids more than century ago. Since then, they have been developed and are widely used.[25] Antacids are compared quantitatively in terms of their acid neutralizing capacity. This is defined as the quantity of 1 N HCl (expressed in milli equivalents), that can be brought to pH 3.5 in 15 min. Antacids neutralize HCl to form water and carbon dioxide. Hydroxides of aluminum and magnesium are the most common constituents of antacid preparations. Sodium bicarbonate, calcium carbonate are also used, as are other carbonates, silicates, and phosphates. Some antacid preparations combine $Al(OH)_3$ and $NaHCO_3$ to achieve both, the rapid effect of carbonate and sustained effect of $Al(OH)_3$. Simethicone, a surfactant that may decrease foaming and thus, esophageal reflex, is also included in many antacid preparations. Common side effects include alkalosis, belching, nausea, abdominal distension, flatulence, diarrhea, and constipation.[1]

2.2. Muscarinic antagonists

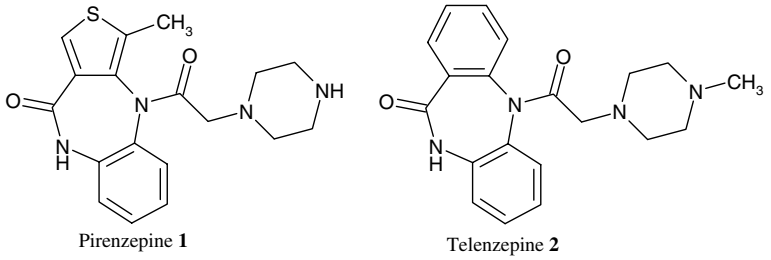
The secretion of acid, mucus, and pepsinogen in the gastric mucosa is stimulated via muscarinic receptors. Overexpression of M_3 receptors in DU patients is proved by autoradiographic techniques. Thus, blockade of this receptor subtype can reduce the pain by decreasing the duodenal motility and provide an effective anti-secretory therapy.[26] Based on its high affinity to block the muscarinic receptors on the intramural ganglia of stomach wall, pirenzepine **1** was developed as an anti-secretory drug, which was followed by telenzepine **2**, a more potent derivative with improved healing rates.[27] Parasympathetic side effects of these agents include dry mouth, blurred vision, and constipation. These side effects along with their incomplete inhibition of gastric acid secretion limit their clinical utility[28] (see Fig. 5).

2.3. H_2 receptor antagonists

H_2 receptor antagonists completely inhibit the interaction of histamine **3** with H_2 receptors, thereby reducing both volume and H^+ ion concentration of the gastric juice. They are selective and have little or no effect on H_1 receptors. They also inhibit acid secretion elicited by gastrin, muscarinic agonists, food, sham feeding, fundic distension, as well as other pharmacological agents. They also inhibit basal and nocturnal acid secretion. This effect contributes in a major way to their clinical efficacy.[1]

Black et al.,[5] identified H_2-receptor and prototype H_2-receptor antagonist, burimamide **4**. The potency of burimamide at inhibiting gastric acid secretion far exceeded anticholinergic drugs and was devoid of side effects. However, it had poor bioavailability. It was subsequently replaced by metiamide **5**, which also because of its side effects like agranulocytosis was withdrawn from the clinical trials.[29,30] Cimetidine[7] **6** was the third H_2 receptor antagonist to be tested in humans and was similar to metiamide in its pharmacological profile, but did not cause agranulocytosis. Discovery of this molecule reduced the necessity of surgical procedures for peptic acid diseases. Further, ranitidine[8] **7** was introduced as more potent drug in 1981 with a much superior safety profile.[2] Third and most potent antagonist was Famotidine[31] **8** available for clinical use, being 20–50 times more potent than cimetidine and 6–10 times more potent than ranitidine.[32] nizatidine[33] **9** and roxatidine[34] **10** followed famotidine. Each of these drugs are rapidly absorbed and eliminated after oral administration.[35] H_2 receptor antagonists are histamine congeners that contain a bulky cysteamine side chain in place of ethylamine moiety of histamine. Earlier representatives of these groups such as burimamide, metiamide, and cimetidine retained the imidazole ring of histamine. This ring was further replaced by furan in ranitidine, by thiazole in famotidine nizatidine, and by piperidylbenzyloy as in roxatidine.[1] This helped to avoid unwanted cytochrome P_{450} interactions[36] (Fig. 6).

H_2 receptor antagonists are generally extremely safe drugs with incidence of adverse effect of cimetidine less than 3%. Adverse effects include dizziness, nausea, skin-rashes, somnolence, confusion, impotence, gynecomastia, hematological effects, and altered function of immune system. Rarely they may cause bone marrow depression, hepatitis, and anaphylaxis.[1] Cimetidine



Pirenzepine **1** Telenzepine **2**

Figure 5. Structures of muscarinic antagonists.

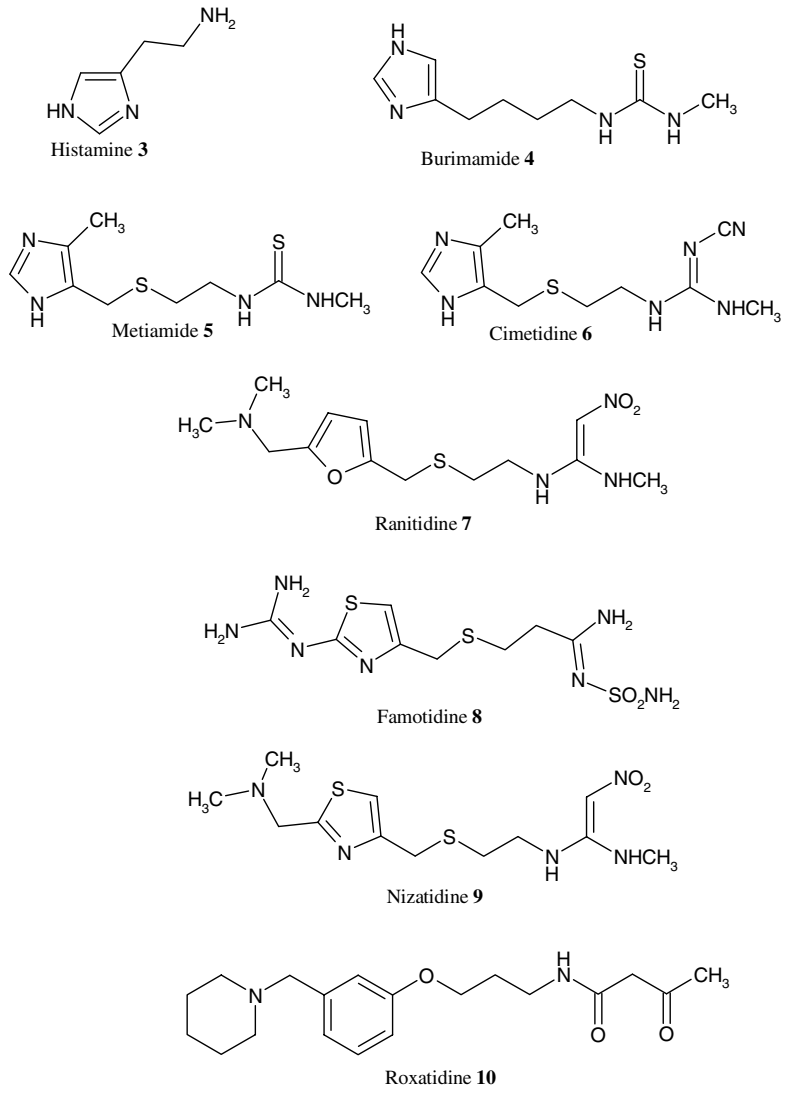


Figure 6. Structures of H_2-receptor antagonists.

selectively showed anti-androgen properties in a small number of patients.[37]

2.4. Eradication of *H. pylori* infections

Helicobacter pylori is a gram-negative rod-shaped bacilli that colonizes in the mucus on the luminal surface of gastric epithelium. *H. pylori* infection causes inflammatory gastritis and is a putative contributor to peptic ulcer disease, gastric lymphoma, and adenocarcinoma.[1]

Infection may not always be causative as ulcers may recur in patients who have undergone successful eradication treatment.[38] Double or triple antimicrobial therapies, in combination with antisecretory drugs, are being used successfully to treat peptic ulcers. Bismuth compounds are also been included in regimen probably due to their cytoprotective action. Triple therapy with metronidazole, a bismuth compound and either tetracycline or amoxycillin for two weeks is recommended to treat *H. pylori* infections. However, therapeutic limitations of this triple therapy include complex regimen and related nausea, diarrhea, and dizziness.[1]

2.5. Other agents used

Carbenoxolone **11**, an olendane derivative of glycyrrhizic acid, a compound found naturally in licorice, is also useful in the treatment of peptic ulcer. Mechanism of action is not clear, but appears to alter the composition and quantity of mucus. It is not approved for use in U.S., but is being used in Europe since 1962 for the treatment of peptic ulcer. Being a steroid analog, it exhibits substantial mineralocorticoid activity like hypertension, hypokalemia, fluid retention, etc.[1]

Sucralfated polysaccharides inhibit pepsin mediated protein hydrolysis. The octasulfate of sucrose was observed to inhibit peptic hydrolysis in vitro. Reaction of sucrose octasulfate with $AI(OH)_3$ forms a viscous substance, sucralfate **12**. A variety of mechanisms have been proposed to account for the cytoprotective and healing

effects of sucralfate, including stimulation of prostaglandin synthesis, absorption of pepsin, and stimulation of local production of epidermal growth factor.[39]

Prostaglandins PGE_2 **13** and PGI_2 **14** are synthesized by gastric mucosa and stimulate the secretion of mucus and bicarbonate. Because the administration of prostaglandins protects the gastric mucosa of animals against various ulcerogenic insults, a number of slowly metabolized prostaglandin analogs have been developed and tested in human beings. Example includes misoprostol **15**, which is currently approved for prevention of gastric ulcers. Side effects of misoprostol include diarrhea, abdominal cramps, and abortifacient in pregnant women[40] (Fig. 7).

2.6. The proton pump inhibitors (PPIs)

Proton pump is the ultimate mediator of gastric acid secretion by parietal cells. With the identification of H^+/K^+-ATPase as the primary gastric proton pump, it was proposed that activation of H^+ secretion occurred by incorporation of H^+/K^+-ATPase-rich tubulovesicles into the apical plasma membrane and that the pumps were re-sequestered back into the cytoplasmic compartment on return to the resting state.[41] Inhibition of the protons pumping H^+/K^+-ATPase as a means of controlling gastric pH has attracted considerable attention in recent years with the discovery of benzimidazole sulfoxide class of anti-secretory agents. Ruwart et al.[42] identified timoprazole **16** as one of the first well-defined inhibitor of gastric proton pump. Timoprazole was followed by more potent picoprazole **17** (1976) and omeprazole **18** (1979).[43] Chemically, the basic structure consists of substituted benzimidazole ring and a substituted pyridine ring connected to each other by a methylsulfinyl chain. Clinically used PPIs include omeprazole **18**, lansoprazole **19**, rabeprazole **20**, pantoprazole **21**, and esomeprazole **22** (see Fig. 8).

These compounds have proved to be effective in clinic for the treatment of acid-related gastrointestinal disorders. They bind to the gastric proton pump on the parietal cell membrane, inhibiting the release of hydrogen ions from the parietal cells into the lumen of the gastric glands and hence stomach.[44] Some of the adverse effects of PPIs include nausea, diarrhea, dizziness,[45] hypergastrinemia,[46] enteric infections,[2] etc. It has been demonstrated that irreversible inhibition of H^+/K^+-ATPase occurs following acid activation of these compounds within the acidic compartments in the parietal cells and covalent binding of the reactive intermediate to one or more critical thiol groups on the enzymes present in apical membrane[47] as in Figure 9. Acid secretion is therefore blocked at the final step of its production independent of the different kind of its stimulation.[48]

3. Structure of the proton pump

The gastric H^+/K^+-ATPase is a member of the P2-type ATPase family and undergoes a cycle of phosphorylation and dephosphorylation coupled to the outward and inward transport of hydrogen and potassium ions, respectively, in the secretory canaliculus of the parietal cells. Conformations of the enzyme that bind ions for outward transport are defined as E1, whereas those that bind luminal ions for inward transport are termed E2.

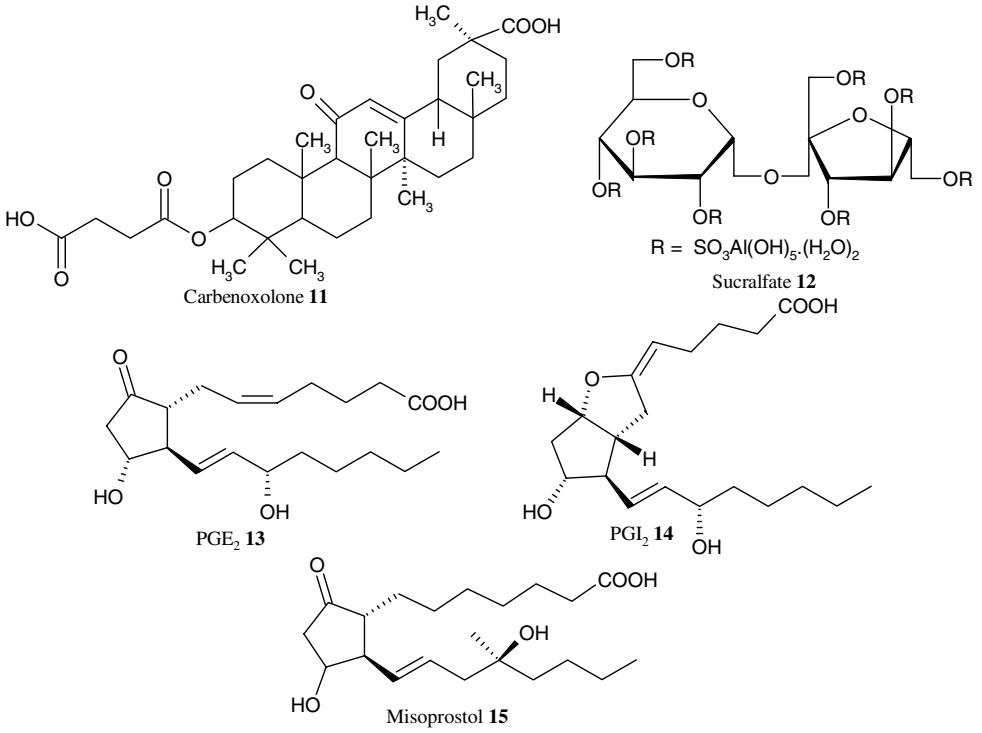


Figure 7. Structures of the other classes of drugs used in treatment of peptic ulcers.

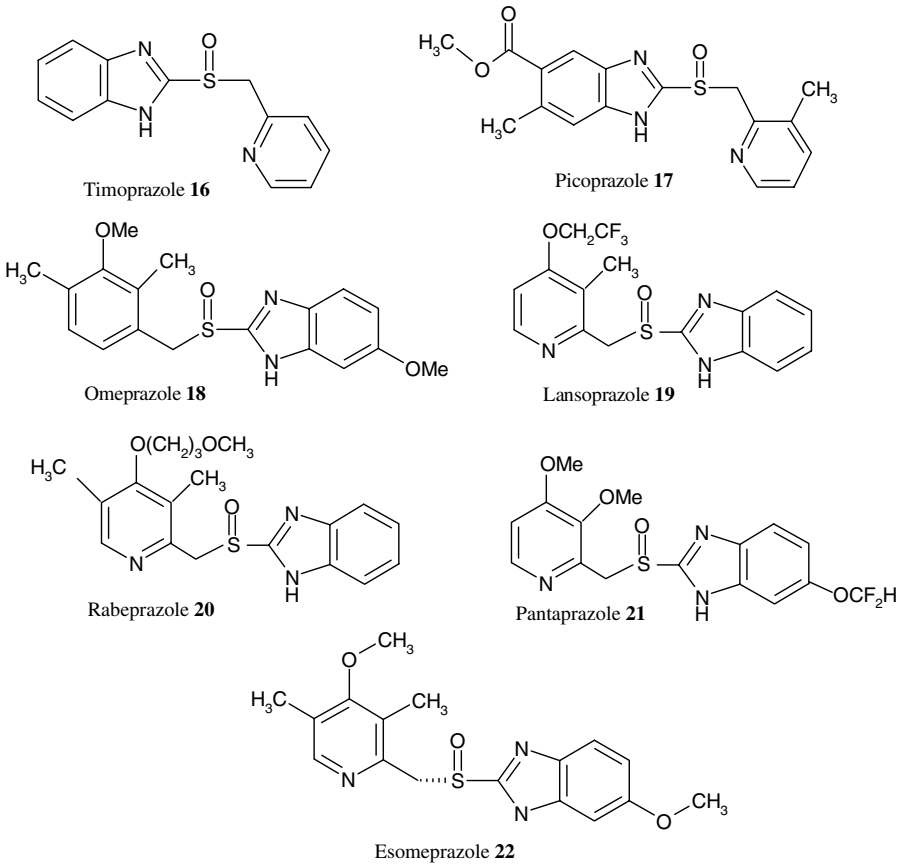


Figure 8. Structures of proton pump inhibitors.

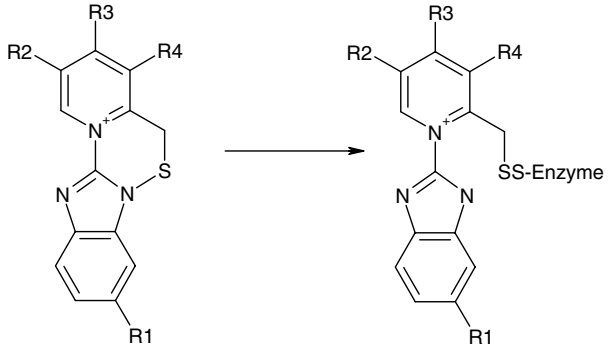


Figure 9. Covalent binding of sulfenamide with thiol group of proton pump.

Ion binding to E1 activates phosphorylation from MgATP to form the intermediate E1-P, which then converts to E2-P in the acid transporting step. In the gastric H^+/K^+-ATPase as well as the Na^+/K^+-ATPases, K^+ binding to E2-P stimulates dephosphorylation to give the occluded form $E2 \cdot K^+_{occ}$ followed by conversion to $E1{\cdot}K^+$ and release of K^+ to the cytoplasm. The gastric H^+/K^+-ATPase sustains a 10-fold inward potassium gradient (150 K^+ in, 15 mM K^+ out) and a transmembrane outward hydrogen ion gradient of greater than 1 million-fold to generate a luminal pH of 0.8. This is the largest ion gradient generated by a P2-type ATPase. The exported ions are presumed to be hydronium rather than protons partly because of the ability of Na^+ to act as a competent surrogate for H^+ at pH 8. Hence, there is a functional similarity to the Na^+/K^+-ATPase at this pH. The primary structure of the gastric H^+/K^+-ATPase (HK R1) shows significant homology to the Na^+/K^+-ATPase (62%) and the sr Ca-ATPase 1 (29%). The ion binding sites of the H^+/K^+-ATPase are homologous to these, and other, P2-type ATPases in that they have only carboxylate side chains as the counter charge species.

It is known that all PPIs bind to cysteine 813, resulting in covalent inhibition of the enzyme via formation of this disulfide that stabilizes the enzyme in the E2 conformation (Fig. 10). The acid pump antagonists (APAs), such as SCH28080 **23** (Fig. 11), represent a second class of inhibitors now under development. These are reversible, K^+ competitive inhibitors with a substituted 1,2-R-imidazo[1,2-*a*]pyridine core structure, that also binds to the E2 form of the ATPase.[49]

4. Classification of PPIs

4.1. Irreversible gastric PPIs

Three main structural features of this class of compounds are the substituted pyridine ring; the substituted benzimidazole ring, and the methylsulfinyl linking group. Irreversible PPIs lacking one or more of these features are rare. They are further classified according to their chemical structure as follows.

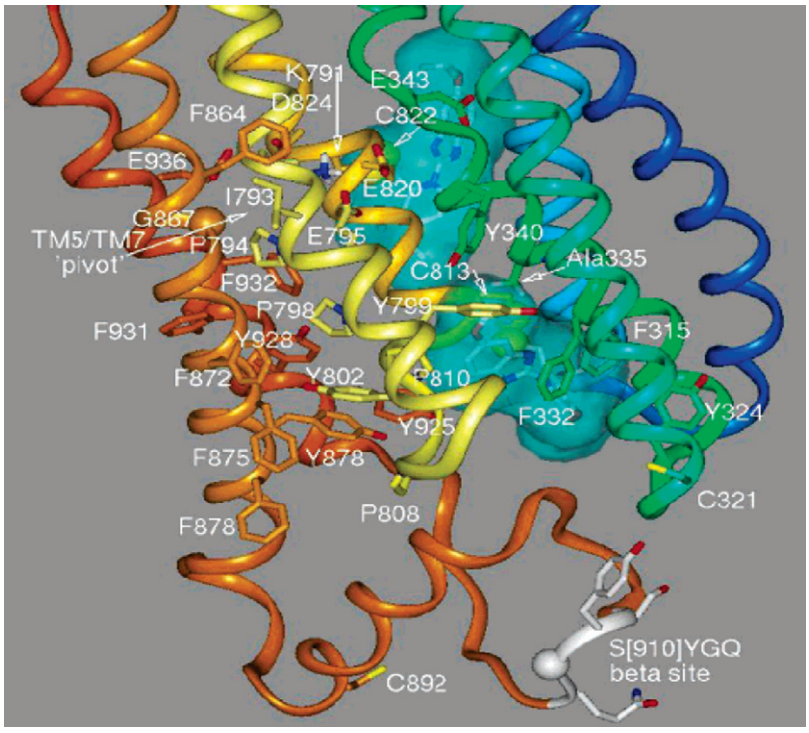
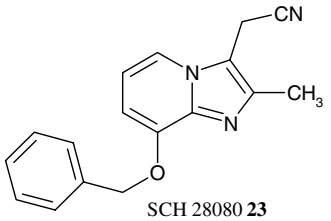


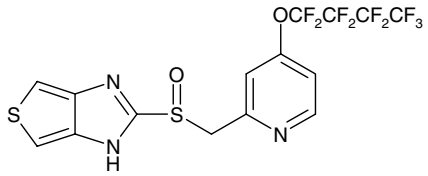
Figure 10. Membrane domain of the H,K-ATPase E2-P model with pantoprazole, bound at Cys813 and Cys822 (stick with Connolly surfaces in cloud). A known site of *a* subunit interaction (*36*, *37*), S[910]YGQ, is highlighted (white ribbon) in the TM7/TM8 loop.Cys813, Cys892, and Cys321 are labeled (38) by various proton pump inhibitors (all at Cys813, omeprazole at Cys892, and lansoprazole at Cys321) and are solvent-accessible in the model. Labeling at the latter two sites is not correlated with inhibition (3). The crossover point ('pivot') between TM5 near Ile793 and TM7 near Gly867 (gold sphere) is apparently conserved in the P2-type ATPases. An extensive array of aromatic side chains (in stick form) replaces non-aromatic sr Ca-ATPase residues and affects the spacing between helices. TM9 and TM10 are omitted for clarity. Reprinted with permission from *Biochemistry* **2005**, *44*, 5267.



SCH 28080 **23**

Figure 11. Acid–pump antagonist.

4.1.1. Pyridinylmethylsulfinyl benzimidazoles. The same chemical features are retained by clinically used PPIs, differing only in the substituents present on the benzimidazole and pyridine ring. Examples of this class include omeprazole **18**, lansoprazole **19**, rabeprazole **20**, pantoprazole **21**, and esomeprazole **22**.



Saviprazole **24**

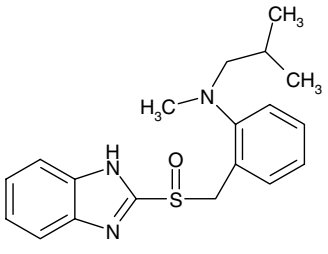
Figure 12. Structures of thienoimidazole as irreversible gastric proton pump inhibitors.

4.1.2. Pyridylmethylsulfinyl thienoimidazoles. In this class, the benzene ring of imidazole is replaced by thiophene, keeping other structural features same. Examples include Saviprazole **27** (see Fig. 12).

4.1.3. Aminobenzylsulfinyl benzimidazoles. Here, pyridine ring is replaced by substituted aminobenzyl ring. Examples include leminoprazole **25** (see Fig. 13).

4.2. Reversible gastric PPIs

To overcome the drawbacks associated with the use of irreversible PPIs, research has been directed toward discovery of reversible inhibitors. Examples include



Leminiprzole **25**

Figure 13. Structures of 2-[(2-aminobenzyl) sulfinyl]-1*H*-benzimidazole as a irreversible gastric proton pump inhibitors.

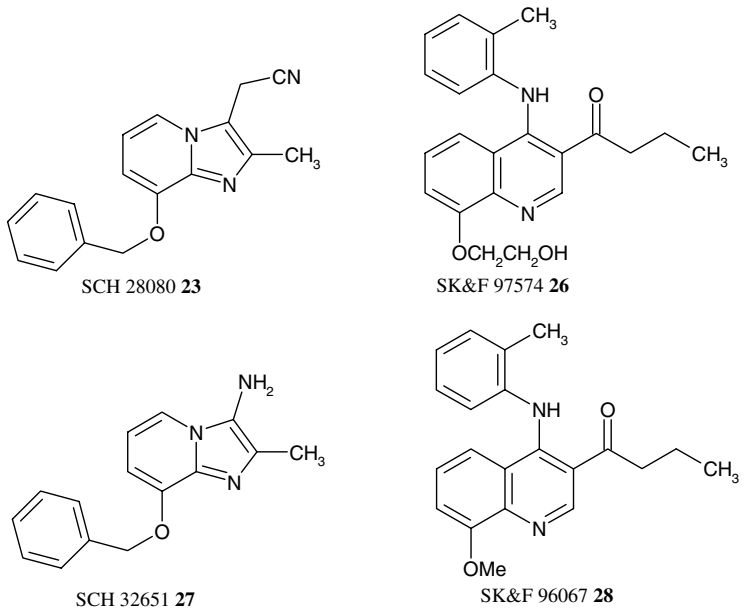


Figure 14. Structures of some reversible gastric proton pump inhibitors.

SCH28080 **23**, SK& F 97574 **26**, SCH 32651 **27**, and SK& F 96067 **28** (see Fig. 14).

5. Irreversible proton pump inhibitors

5.1. Introduction

In early 1970s, anti-secretory activity of the analogs of the pyridylthioacetamide (CMN) **29** was studied. This led to the discovery of a class of extremely efficacious inhibitors of gastric acid secretion, with a novel mode of action, of which the pyridylmethyl benzimidazole sulfoxide, Timoprazole **16**, is the archetypal structure. Meanwhile H^+/K^+-ATPase enzyme was also discovered by other research group that enabled the demonstration that compounds related to timoprazole were non-competitive inhibitors of the enzyme. This led to the synthesis of picoprazole **17** and omeprazole **18**, new drugs for the treatment of peptic-ulcer and related diseases. This work also helped in generating and understanding the way in which this enzyme operates[50] (see Fig. 15).

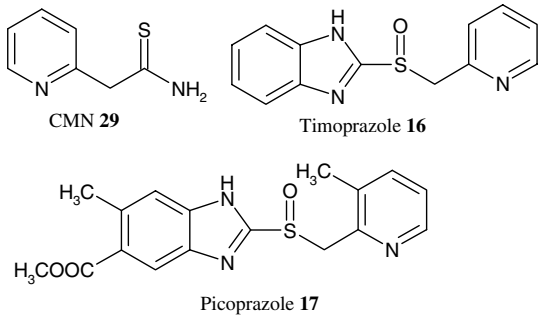


Figure 15. Structure of some initial PPIs.

5.2. Mechanism of action

On studying the mechanism of action of these inhibitors of the H^+/K^+-ATPase, several salient features of their action became apparent like; (a) the weak basicity of the compounds ($pK_a \approx 4$), allowing them to accumulate in the acid space adjacent to their site of action (i.e., secretory canaliculus of the parietal cells); (b) the sulfoxides themselves have no intrinsic activity, but under the influence of acid undergo a chemical rearrangement to an active species; (iii) the active species is thiophillic in nature and covalently binds to thiol functions like cysteinyl residues generating disulfide bridges to the enzymes, thereby causing its inactivation.[50]

The reaction mechanism proposed for the acid transformation of pyridinylmethylsulfinyl benzimidazoles **30** to the sulfenamide **30c** isomers is outlined in Figure 16. The reaction is reversible and goes via a spiro intermediate, **30a**, and the sulfenic acid **30b**. The reversibility was firmly proved by kinetic measurements in both directions for example starting from **30** and **30c**. The formation of the spiro intermediate **30a** via Smile's rearrangement[50] is a rate-limiting step supported by kinetic measurements. The rate constant obtained for omeprazole analogs is strongly dependent on substituents in the pyridine ring, indicating that a positive charge is created in the pyridine nitrogen atom in the rate-limiting step. The spiro intermediate **30a** is dihydrobenzimidazole with a pronounced tendency to undergo aromatization, thus forming the sulfenic acid **30b** by a C–S bond cleavage. The subsequent formation of the sulfenamide **30c** is in accordance with known reaction between sulfenic acids and amines. This sulfenamide **30c** represents the active enzyme inhibitor and binds covalently to sulfhydryl groups of cysteines of proton pump.[15] Likewise, the reaction of **30c** with β-mercaptoethanol or the cysteine 813 residue of H^+/K^+-ATPase

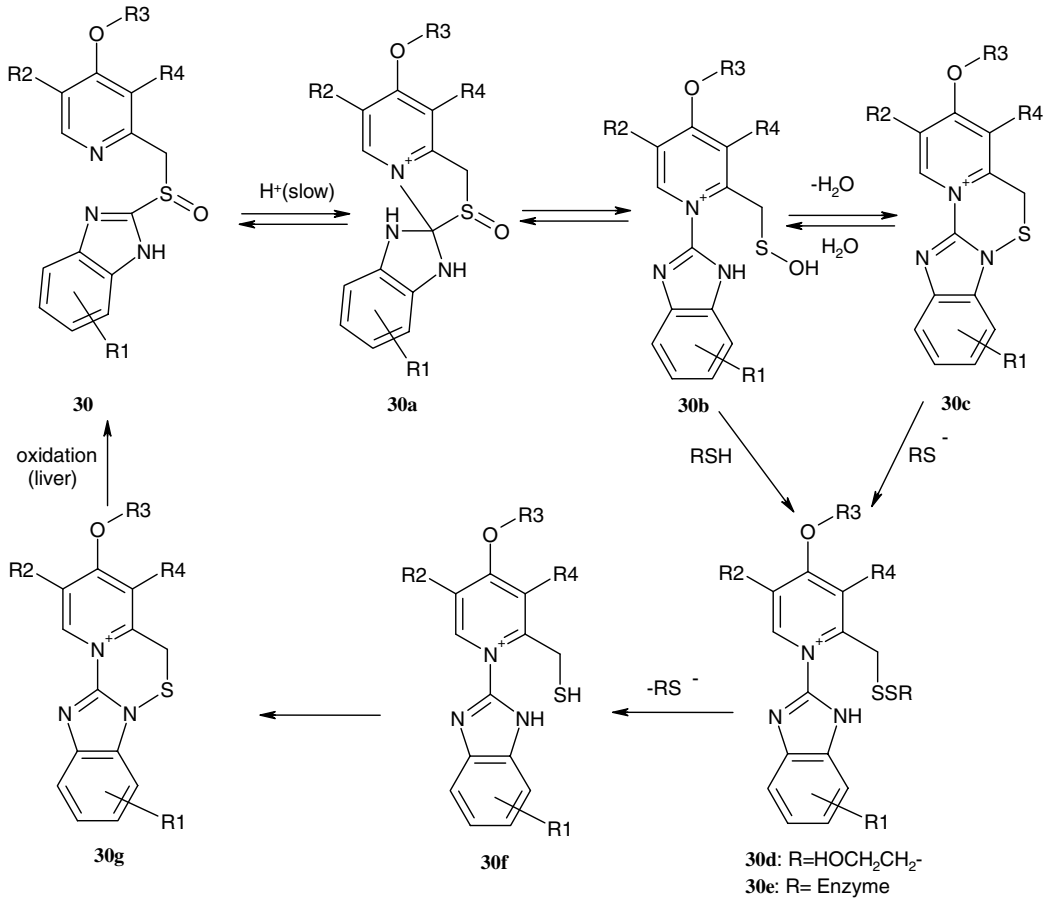


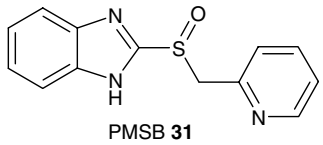
Figure 16. Reaction mechanism proposed for the acid transformation of pyridinylmethylsulfinyl benzimidazoles **30** (PMSBs) to sulfenamide.

to form adducts **30d** and **30e**, respectively, is now easily understood, since sulfenamides or sulfenic acid derivatives in general are known to react with mercaptanes to form disulfides. The adduct **30d** may then react with endogenous thiols or a free thiol group of the enzyme and may react with second molecule of β-mercaptoethanol (or enzyme) in base catalyzed Smiles' reaction to form a sulfide **30g**, probably via the unstable mercaptan **30f**, resulting from S–S bond cleavage during simultaneous formation of disulfide of the β-mercaptoethanol. This sulfide, **30g**, corresponds to original sulfoxide. Sulfides of this type are known to be oxidized by liver to parent sulfoxides, which raises the intriguing possibility of catalytic drug action in which cyclization occurs as shown in Figure 14 for pyridinylmethylsulfinyl benzimidazoles **30** (PMSBs). The recovery of enzymes' activity requires de novo synthesis of enzyme which is consistent with the long duration of action of the drug.[50,51]

The introduction of methyl group in the 6th position of the pyridine ring of the omeprazole analogs results in compounds stable in acid solutions. This supports the suggested mechanism. Also, the space filling models show that 6-methyl group will experience a strong steric interference with the imidazole ring, which prevents the formation of spiro intermediate **30a**.[51]

5.3. Structure–activity relationships

The pyridinylmethylsulfinyl benzimidazole (prototype) **31** (PSMB) can be considered to possess three structural elements: the pyridine ring, the benzimidazole ring system, and the linking chain. Replacement of $SOCH_2$ of the linking chain, by a variety of other groups like $–SCH_2$, $–SO_2CH_2$, $–SCH_2CH_2$, and various carbon and oxygen containing chains, leads to loss of activity in vitro. Extending the length of chain by $–SOCH_2CH_2$ gives rise to inactive acid stable compound. In the pyridine ring system, degree of nucleophilicity (rather than basicity) of nitrogen atom reflects the ease of spiro intermediate formation. For example, substitution in 6′-position of the ring results in loss of activity as disfavoring steric interaction. When significant steric effects are absent, a pK_a value of $\geqslant 4$ is probably optimal for activity. Weak bases like timoprazole and 4′-CO_2CH_3 derivatives show greatly reduced activity, as 4′-methyl compound is several times less active than 4′-alkoxy analogs. In case of omeprazole ($pK_a = 4$), the 4′-methyl substitution has little effect on pK_a, as it is bent out of plane by the two flanking methyl groups. The substitution in benzimidazole ring does not change the activity to a great extent. Introduction of electron withdrawing substituents like 5-NO_2, 5-MeSO, 5-CF_3 and leads to decreased enzyme inhibition[50] (see Fig. 17).



PMSB **31**

Figure 17. General structure of classical irreversible PPIs.

With respect to the sulfinyl group, gastric proton pump inhibitors exist as a racemic mixture of both enantiomers. Although chirality is lost in corresponding pyridinium sulfenamide formation, it is unclear whether one enantiomer is more susceptible toward acid activation than the other. Both enantiomers of lansoprazole inhibit dbcAMP-induced aminopyridine uptake in isolated canine parietal cells, as well as H^+/K^+-ATPase activity in canine gastric microsomes with equal activity.[15]

5.4. Drawbacks of irreversible proton pump inhibitors

Extreme acid suppression some times leads to achlorohydria at recommended doses and that may produce enteric infections like typhoid, cholera, and dysentery. Significant drug interactions can lead to decreased absorption of some drugs like griseofulvin, ketoconazole, vit.B_{12}, iron salts, etc. Unpredictable action and variation in individual responsiveness can cause hypergastrinemia, gastric polips, and carcinoma.[52] Other side effects include abdominal pain, diarrhea, nausea, and headache. Acute interstitial nephritis progressing to acute renal failure has also been reported to be associated with the use of PPIs.[53]

5.5. Pharmacological properties of the PPIs

Anti-secretory effect of PPIs seems to depend on the presence of *H. pylori* infection because eradication of *H. pylori* has negative consequences on the efficacy of anti-secretory drugs.[54,55] Acid secretion can be restored only through endogenous synthesis of H^+/K^+-ATPase, which has a half-life of production of approximately 50 h.[56] Rabeprazole shows faster rate of inhibition and a shorter duration of action.[57] Esomeprazole has least bioavailability, whereas, lansoprazole being the most bioavailable.[58] The PPIs are clearly more potent than H_2-receptor antagonists with clinically their doses being 15 times lower than those of H_2 receptor antagonists in the treatment of duodenal ulcers.[59]

Further, Becker et al.[60] evaluated a unique pathway for gastro-protective activity of PPIs demonstrating that both omeprazole and lansoprazole protect human gastric epithelial and endothelial cells against oxidative stress. The antioxidant defense protein heme oxygenease (HO-1) is a target of PPIs in both endothelial and gastric epithelial cells. HO-1 induction might account for the gastroprotective effects of PPIs independently of acid inhibition. Concentration-dependent hydroxy radical scavenging activity of PPIs has also been reported suggesting their possible anti-inflammatory activity.[61] As lansoprazole and rabeprazole are known to increase plasma adrenocorticotropic hormone (ACTH) and cortisol levels, they are under study for the treatment of psychiatric disorders involving dysregulation of appetite.[62]

The currently available PPIs have similar pharmacological properties, which are detailed in Table 3.

6. Reversible proton pump inhibitors

6.1. Introduction

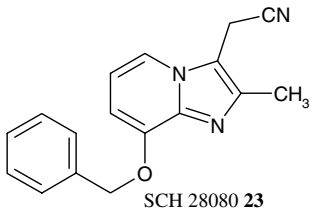
Prolonged suppression of gastric acid secretion produced by both H_2 receptor antagonists and PPIs produces extended periods of hypergastrinemia, which has been associated with the formation of precancerous changes in human gastric mucosa and gastric carcinoids in long-term animal studies. However, research efforts are currently targeted at obtaining reversible proton pump inhibitors often referred to as acid pump antagonists (APAs). Several research groups have progressed APAs into development though currently none is marketed.[2]

The imidazopyridine based compound SCH28080 **23** was the prototype of this class.[68] Anti-secretory effect of this compound is mediated through gastric proton pump and this has been further demonstrated by its ability to antagonize the binding of omeprazole[69] (see Fig. 18).

Table 3. Pharmacological properties of the different proton pump inhibitors

Generic name	Half-life (h)	Peak effect (h)	Duration of effect (h)	pK_a	Bioavailability (%)	Metabolism	Excretion (%)
Omeprazole[63]	0.7	2	24–72	~4	30–40	Extensively Hepatic	$U = 77$ $F = 23$
Pantoprazole[64]	1	2.5	24–72	~4	77	Extensively Hepatic	$U = 71$ $F = 18$
Lansoprazole[65]	2	1.7	>24	~4	80	Extensively Hepatic	$U = 35$ $F = 65$
Rabeprazole[66]	1	2–5	24	~5	52	Extensively Hepatic	$U = 90$ $F = 10$
Esomeprazole[67]	1.3	1.5	24-27	~4	64	Extensively Hepatic	$U = 80$ $F = 20$

U, urine; pK_a, dissociation constant; F, faeces.



SCH 28080 **23**

Figure 18. Prototype acid pump antagonist.

6.2. Mechanism of action

Omeprazole **18** and SCH 28080 **23** differ in inhibition kinetics for their proton pump inhibitory activity. In contrast to omeprazole, SCH 28080 **23** is a competitive inhibitor of high affinity luminal K^+ site of the gastric proton pump. In contrast to Na^+/K^+-ATPase, it is highly selective to H^+/K^+-ATPase activity. SCH 28080 is a protonable weak base ($pK_a = 5.6$), hence like omeprazole it accumulates in the acidic compartments of the parietal cells in its protonated form.[70] SCH 28080 is chemically stable and after protonation, is itself active and does not need an acid-induced transformation, as required by omeprazole and its congeners.[71]

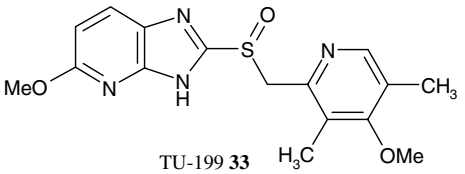
6.3. Structure–activity relationships

Totally 81 derivatives of imidazo[1,2-*a*]pyridines **32a** and **32b**, related to SCH 28080 **23**, were synthesized and studied, based on which following observations were made: (1) a small alkyl group at C-2 (methyl or ethyl) favored activity; (2) cyano methyl or amino group at C-3 was a requirement for maintaining both anti-secretory and cytoprotective activity; (3) activity at 8-position was maximized with benzyloxy, 3-thienylmethoxy or phenylmethylamino substitution; (4) replacement of C-7 by N leads to retention of activity. Surprisingly little work has been reported on these reversible inhibitors of H^+/K^+-ATPase. Although, highly efficacious drugs could emerge from research on APAs[50] (see Fig. 19).

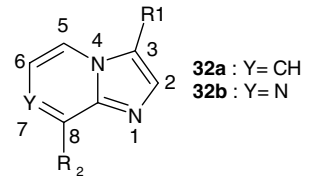
7. Reports on the ongoing research and development on different PPIs as well as other agents

7.1. Irreversible inhibitors, related structurally to pyridinylmethylsulfinyl benzimidazole

Uchiyama et al.[72] have reported the synthesis of (+/−) 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methylsulfinyl]-1*H*-imidazo[4,5-*b*]pyridine,(TU-199) **33**, and its effect on histamine, carbachol, and tetragastrin stimulated gastric acid secretion. They have claimed it to be having more potent and long lasting effects on gastric acid secretion via inhibition of H^+/K^+-ATPase than imeprazole.



TU-199 **33**

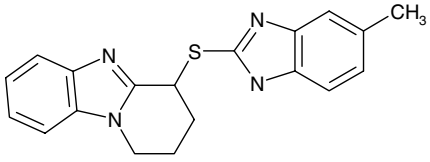


32a : Y= CH
32b : Y= N

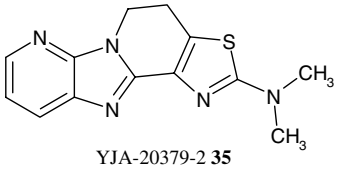
Figure 19. General structure of reversible PPIs to describe SAR.

7.1.1. Changes made on/in the benzimidazole nucleus. Changes have been made on the benzimidazole nucleus without loss of activity. Following are some reports:

Woo et al.[73] have reported the biological evaluation of 2-[3-(2,3-dihydro-1*H*-pyrolo [1,2-*a*]benzimidazolyl)sulfinyl]-5-methyl-1*H*-benzimidazoles, (YJA20379-4) **34**, having marked inhibitory effect on H^+/K^+-ATPase. YJA20379-4 also exhibited anti-*H. pylori* activity 3 times higher than omeprazole along with the enhancement of mucosal defense, thus, indicating a wide spectrum of anti-ulcer activities. In another related work, Kim et al.[74] modified **34** by fusing imidazopyridines with thiazolopyridines to get YJA-20379-2, **35**. This compound not only suppressed H^+/K^+-ATPase activity, but also had significant reinforcing activity on the defensive factors.

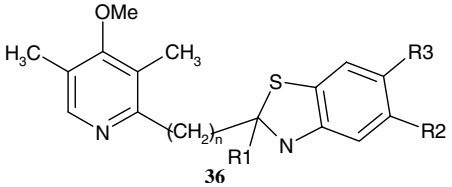


YJA20379-4 **34**



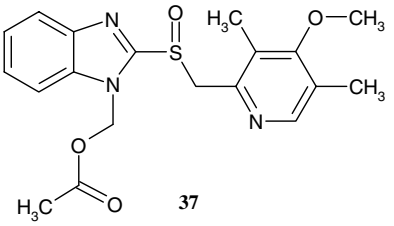
YJA-20379-2 **35**

Yoon et al.[75] have replaced the conventional benzimidazole ring system with the bioisosteric benzothiazolidine ring system. They have reported the synthesis of derivatives of 2-[(3,5-dimethyl-4-methoxypyridylalkyl]-benzothiazolidine **36** which were found to be more potent in vitro inhibitors of H^+/K^+-ATPase. The methylsufinyl linkage has also been replaced by methylene linkages.



36

N-alkylation/acylation of the benzimidazole ring nitrogen leads to the biolabile N-substituted benzimidazole derivatives (prodrugs) of Timoprazole. The parent N–H compound is liberated either by in vivo esterase hydrolysis or requires an acidic environment. *N*-(acyloxy)alkyl-substituted benzimidazoles showed improved chemical stability of which **37** proved twice as potent as omeprazole. Similarly **38** was found to be twice active as timoprazole.[76]



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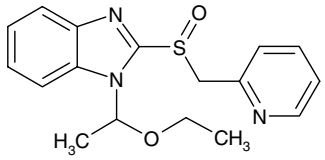
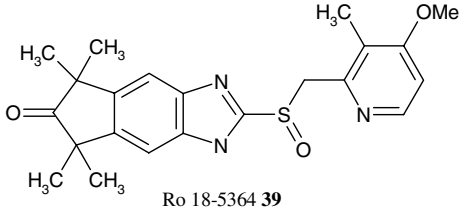


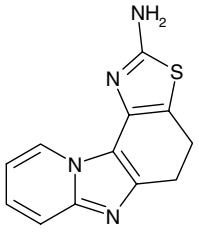
38

Fusion of one more ring on the benzimidazole nucleus has been shown to be beneficial. Sigrist-Nelson et al.[77] have reported the synthesis and evaluation of 5,7-dihydro-2{[(4-methoxy-3-methyl-2-pyridyl)methyl]sulfinyl}-5,5,7,7-tetramethylindeno-[5,6-*d*]imidazol-6-(1*H*)-one (Ro 18-5364) **39** as an extremely effective inhibiting agent. Ro 18-5364 produced almost complete inhibition of the H^+/K^+-ATPase activity, as well as associated proton translocation. The activity of the inhibitor appeared to be independent of its stereochemistry. However, sulfide analog of Ro 18-5364 was devoid of any significant inhibitory activity.



Ro 18-5364 **39**

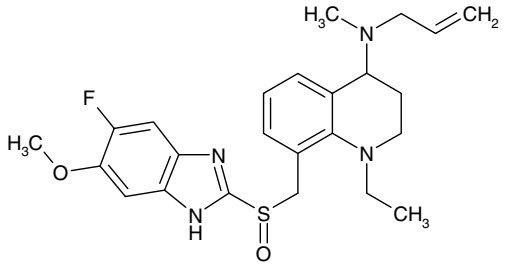
Yoon et al.[78] have synthesized imidazopyridines fused with benzothiazole moiety **40**. These novel compounds not only showed potent inhibitory activity against H^+/K^+-ATPase but also showed significant cell protective activity.



40

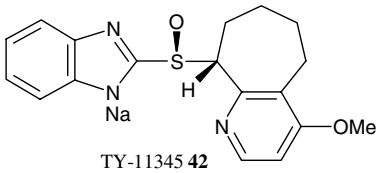
7.1.2. Changes made on the pyridine nucleus. The pyridine ring has been annulated to one more ring or its bioisosteric replacement is done or has been replaced by an aromatic carbocycle, without loss of potency.

Uchida et al.[79] have quinoline analogs of PMSBs. A series of some 4-substituted 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline, has exhibited H^+/K^+-ATPase inhibitory and anti-secretory activities against histamine-induced gastric acid secretion. Of these, 4-(*N*-allyl-*N*-methylamino)-1-ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl)sulfinylmethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline **41** was found to have potent anti-ulcer activity. Further, many of the derivatives showed cytoprotective activities. Notably, the methyl sulfinyl side chain is not attached to the pyridine nucleus but to the benzene ring.



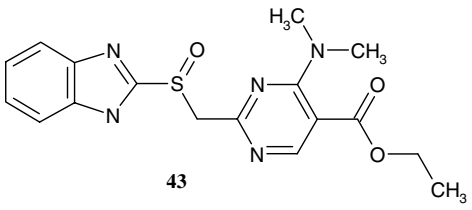
41

Annulations of pyridine ring to a alicycle has also been tried. Yamada et al.[80] have synthesized a series of 2-[(cycloalka[*b*]pyridinyl)sulfinyl]-1*H*-benzimidazoles and tested for the inhibition of pentagastrin-induced gastric acid secretion. A novel benzimidazole derivative containing a cyclohepta[*b*]pyridine moiety was found to be the most potent among the congeners, which included five- to eight-membered cycloalka[*b*]pyridine ring system. Of them 2-[(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)-sulfinyl]-1*H*-benzimidazole analogs having various substituents on aromatic rings were found to be superior than Omeprazole. Compound TY-11345 **42** was selected for further evaluation. Notably, the methylsulfinyl linkage has also been modified.



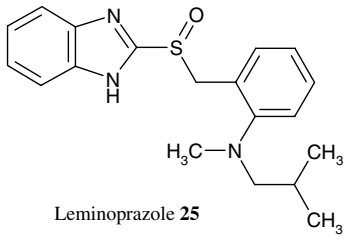
TY-11345 **42**

Replacement of the pyridine ring with less basic isosteric pyrimidine ring has also been reported by Japanese workers.[81] They have evaluated 2-(1*H*-benzoimidazole-2-sulfinylmethyl)-4-dimethylamino-pyrimidine-5-carboxylic acid ethyl ester **43** for its proton pump inhibition. It was found to have marked proton pump inhibitory activity with IC_{50} of 7.5 μm as compared to omeprazole IC_{50} of 5.8 μm.



43

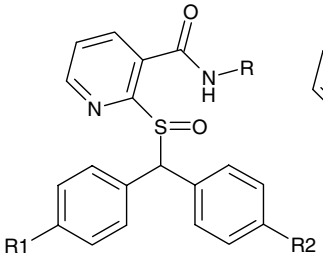
Replacement of the heterocyclic pyridine ring with aromatic carbocycles has also been attempted. Tsukahara et al.[82] synthesized [2-(1*H*-benzoimidazole-2-sulfinylmethyl)-phenyl]-isobutyl-methyl-amine (leminoprazole) **25** which was found to be a potent PPI.



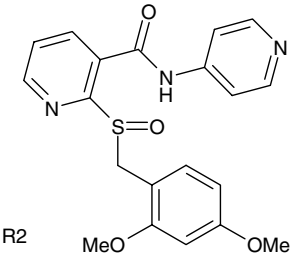
Leminoprazole **25**

7.2. Irreversible inhibitors, not related structurally to pyridinylmethylsulfinyl benzimidazole

Terauchi et al.[83] have reported the synthesis and evaluation of N-substituted 2-(benzhydryl)nicotinamides **44** and N-substituted 2-(benzylsulfinyl)nicotinamides **45**, which upon acid activation were converted to their active forms, 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines **46** responsible for gastric H^+/K^+-ATPase inhibition.[55] Of these, **45** showed in vivo and in vitro inhibitory activities equivalent to omeprazole and was more stable than omeprazole, lansoprazole, and pantoprazole at neutral and weakly acidic pH. Further, these parent nicotinamides were devoid of any in vitro H^+/K^+-ATPase inhibitory activity of themselves.



44



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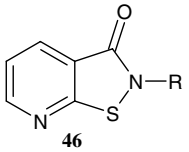
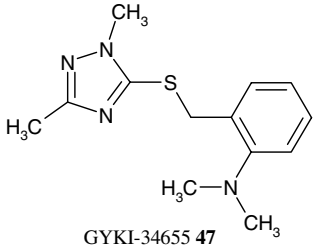


46

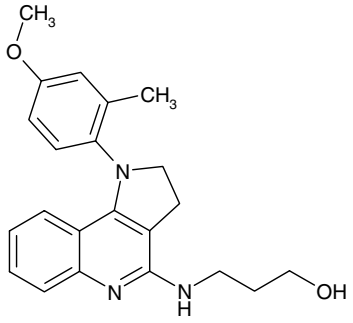
Berzsenyi et al.[84] have synthesized and tested [2-(2,5-dimethyl-2*H*-[1,2,4]triazol-3-ylsulfanylmethyl)phenyl]dimethylamine,(GYKI-34655) **47**, as irreversible inhibitor. It was found to be a potent gastric anti-secretory, anti-ulcer, and cytoprotective agent.



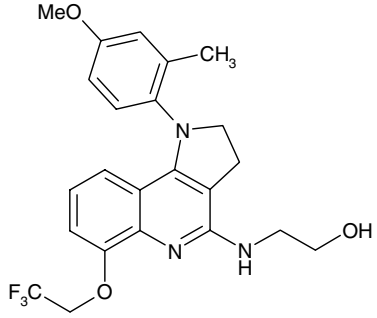
GYKI-34655 **47**

7.3. Reversible inhibitors (acid pump antagonists)

Cheon et al.[85] have reported the activity of 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (DBM-819) **48** as potential reversible inhibitor. DBM-819 successfully reduced histamine and pentagastrin stimulated gastric acid secretion and protected against gastric lesions induced by ethanol, NaOH, indomethacin, and aspirin, suggesting that DBM-819 acts as an effective anti-ulcer agent in vivo. The same workers have also evaluated 1-(2-methyl-4-methoxyphenyl)-4-[(2-hydroxyethyl)amino]-6-trifluoroethoxy-2,3-dihydropyrrolo[3,2-*c*] quinoline (AU-461) **49**, which was found to be reversible and competitive inhibitor with respect to the activating K^+ cation.[86]

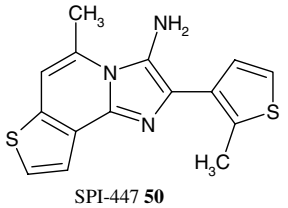


DBM-819 **48**



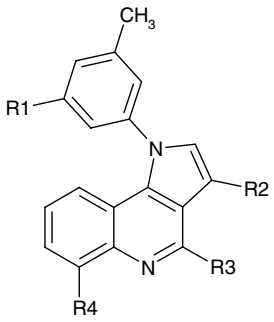
AU-461 **49**

3-Amino-5-methyl-2(2-methyl-3-theinyl)-imidazo[1,2-*a*]thieno[3,2-*c*]pyridine (SPI-447) **50** has also been studied as a reversible inhibitor of proton pump. SPI-447 had no effect on Na^+/K^+-ATPase activity and was K^+ competitive inhibitor of H^+/K^+-ATPase similar to SCH28080 **23.**[69]



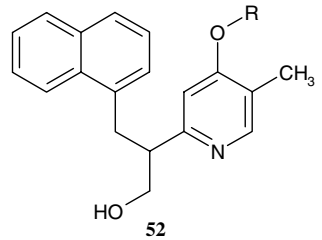
SPI-447 **50**

A series of 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines **51** have been found to be inhibitor of H^+/K^+-ATPase. In vitro H^+/K^+-ATPase inhibitory activity was dependent on the substituents at the 3-position of the pyrrolo[3,2-*c*]quinolines, whereas 1-aryl substituents affected the in vivo gastric acid secretion.[87]



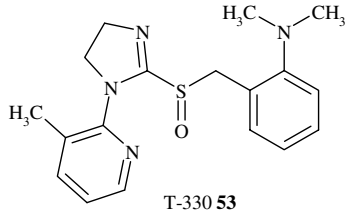
51

Niiyama et al.[88] have synthesized novel 4-substituted pyridine derivatives like 4-alkoxy-, 4-alkylthio, and 4-aryloxy-5-methyl-2-[1-(hydroxymethyl)-2-(1-naphthyl)-ethyl(ethenyl)]pyridine **52** which were found to have reversible inhibitory activity against H^+/K^+-ATPase.



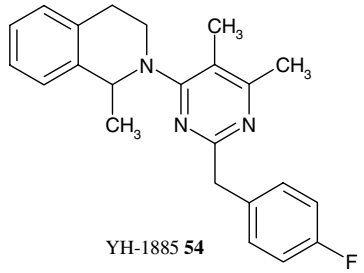
52

Kinoshita et al.[89] have reported a novel reversible PPI, 2-[(2-dimethyl-aminobenzyl)sulfinyl]-1-(3-methylpyridine-2-yl-)imidazole **53** (T-330), which was found to possess anti-secretory activity more potent than omeprazole and ranitidine.



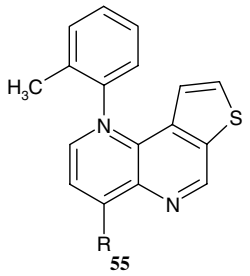
T-330 **53**

Kim et al.[90] have reported the synthesis and proton pump inhibitory activity of YH-1885 **54** which is now one of the most clinically advanced APAs.



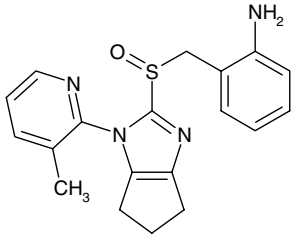
YH-1885 **54**

Condensed naphthyridines have also been reported as possible reversible proton pump inhibitors, for example, 4-substituted-1-(2-methylphenyl) thieno [2,3-*c*]-1,5-naphthyridines **55**. These compounds were evaluated for their H^+/K^+-ATPase and anti-secretory activity. However, in vitro activity of these substituted naphthyridines was not high enough to be of further interest.[91]



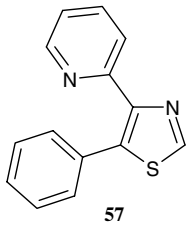
55

Yamada et al.[92] reported the reversible H^+/K^+-ATPase inhibitory activity of 2-[(2-aminobenzyl)sulfinyl]-1-(2-pyridyl)-1,4,5,6-tetrahydrocyclopenta[*d*]imidazoles. Acid degradation study of **56** indicates mechanism of action different from omeprazole.



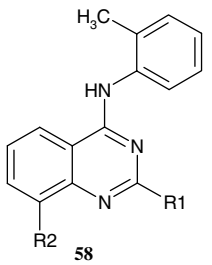
56

Ife et al.[93] have reported 4-(2-pyridyl)-5-phenylthiazoles **57** as reversible, K^+-competitive gastric H^+/K^+-ATPase inhibitors.

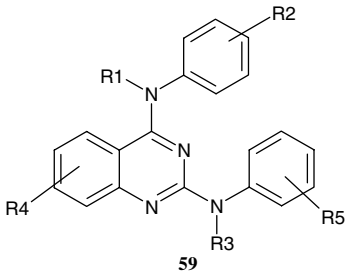


57

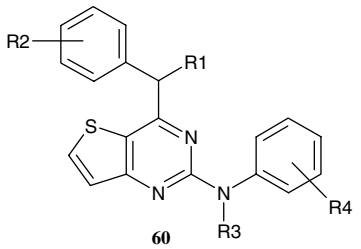
They have further reported reversible proton pump inhibitory activity of 4-(arylamino) quinazolines **58**, 2,4-bis (arylamino) quinazolines **59**, and 2,4-bis (arylamino)thieno-pyrimidines **60**. In case of the theinopyrimidines, the [3,2-*d*] isomers proved to be more effective than [2,3-*d*].[94]



58

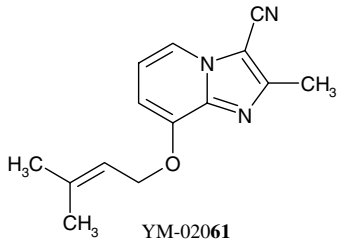


59



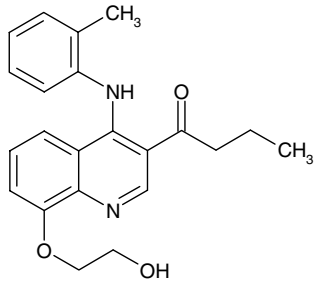
60

Yuki et al.[95] have reported proton pump inhibitory activity of 2-methyl-8-(3-methyl-but-2-enyloxy)-imidazo[1,2-*a*]pyridine-3-carbonitrile (YM-020) **61**.



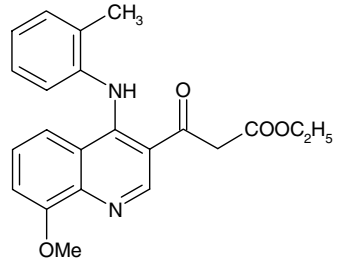
YM-020**61**

Leach et al.[96] have reported H^+/K^+-ATPase inhibitory activity of 3-butyryl-4-[(2-methylphenyl)amino]-8-(2-hydroxyethoxy)quinoline, SK& F 97574 **62**.[68] It was found to be well tolerated and efficacious in phase-I studies.



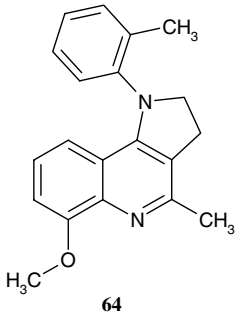
SK & F97574 **62**

Similar derivatives, 3-[3-(ethoxycarbonyl)propionyl]-8-methoxy-4-[(2-methylphenyl)amino]quinolines, (CP-113411) **63**, have also been reported. Besides being reversible inhibitors of gastric proton pump, they also inhibited bone absorption by osteoclasts.[97]



CP-113,411 **63**

Ife et al.[98] have reported the synthesis and evaluation of a series of 1-arylpyrrolo[3,2-*c*]quinolines as inhibitors of H^+/K^+-ATPase. Unsaturation in the five-membered ring of this nucleus made little difference, but introduction of heteroatom in the same ring reduced the activity drastically. Of the series, compound **64** showed reversible K^+ competitive binding to the enzyme.[99] Further, modification of same nucleus by Leach et al.[100] led to discovery of SK&F 96356 **65**, a potent inhibitor of gastric acid secretion. Ife et al.[98] studied 3-substituted-4-(phenylamino)quinolines as reversible inhibitors of H^+/K^+-ATPase. From this series, SK&F 96067 **28** was found to be potent inhibitor of histamine stimulated gastric acid secretion.



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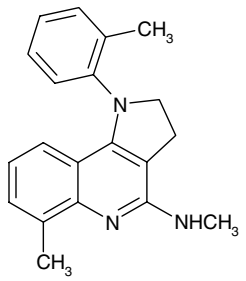
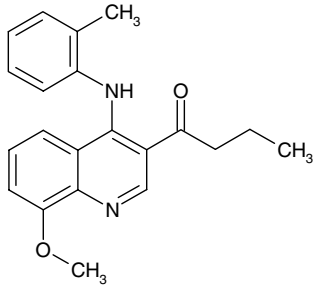
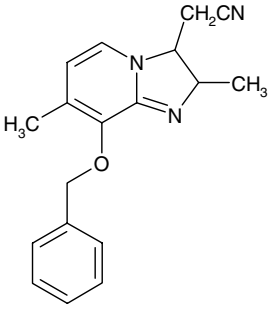


SK&F 9635**65**

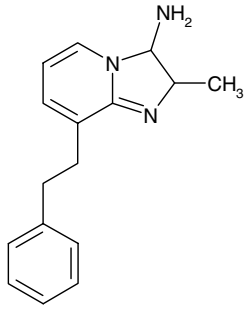


SK&F 9606**728**

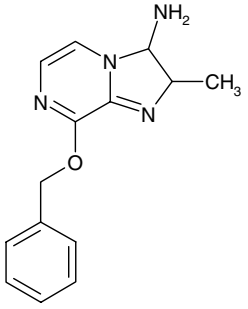
Kaminski et al.[101] identified 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo [1,2-*a*]pyridine **66**, 3-amino-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine **67**, and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine, Sch-32651 **68**. These analogs exhibit anti-secretory and cytoprotective activity, particularly, Sch 32651 was mentioned as a promising candidate.



66



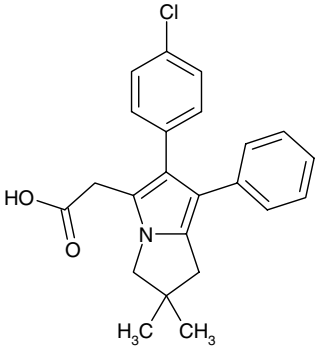
67



Sch 32651 **68**

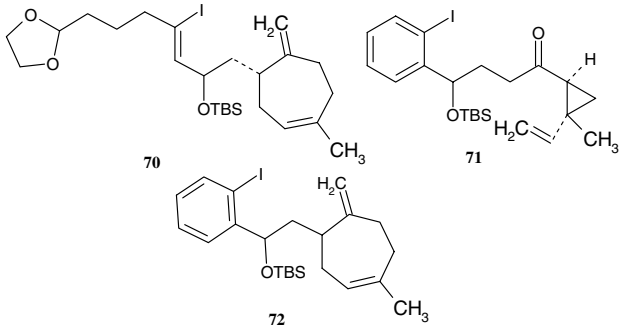
7.4. Other proton pump inhibitors under investigation

Smolka et al.[102] have reported the synthesis and evaluation of the pyrrolizine derivatives of the type ML 3000, **69**, which along with the inhibition of H^+/K^+-ATPase also inhibited 5-lipoxygenase.



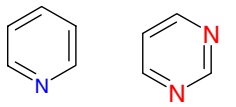
ML 3000, **69**

Hayashi et al.[103] have reported the proton pump inhibitory effects of synthetic compounds with the scopadulan ring system, which have ether linkages at C-6, C-13, and/or C-18 positions. *tert*-Butyldimethylsilyl ethers of 5-methylenecycloheptene and related compounds **70**–**72** were shown to be novel proton pump inhibitors.



Jain et al.[104] have designed a variety of novel mononuclear and condensed pyrimidine analogs of omeprazole replacing the pyridine heterocycle of conventional PSMBs with its 3-aza isoster, pyrimidine. The rationale behind their work is that the weakly basic nature of pyrimidine (pK_a 1.31) as compared to pyridine (pK_a 5.2) as the N_1 and N_3 atoms of pyrimidine less electron donating than the pyridine nitrogen.[105] This makes the formation of sulfenamide intermediate difficult (Fig. 20).

A review of a basic literature on organic and the heterocyclic chemistry reveals that indeed pyrimidine ring is the ring of choice.



Pyridine pKa :5.2 Pyrimidine pKa :1.31

The weekly basic nature of pyrimidine (pK_a 1.31) is striking in relation to pyridine (pK_a 5.2). It is understandable due to the depletion of π-electrons caused by insertion of the avidly electron-attracting second nuclear nitrogen atom. Pyrimidine may therefore be likened more to β-nitropyridine (pK_a 0.8), which contains the equally strongly electron-attracting nitro group, making it less basic than parent pyridine. A cursory review of the literature does reveal successful use of this logic. Replacement of the pyridine ring with less basic isosteric pyrimidine ring has also been reported by Japanese workers.[81] They have evaluated 2-(1*H*-benzoimidazole-2-sulfinylmethyl)-4-dimethylamino-pyrimidine-5-carboxylic acid ethyl ester **43** for its proton pump inhibition. It was found to have marked proton pump inhibitory activity with IC_{50} of 7.5 μm as compared to omeprazole IC_{50} of 5.8 μm.

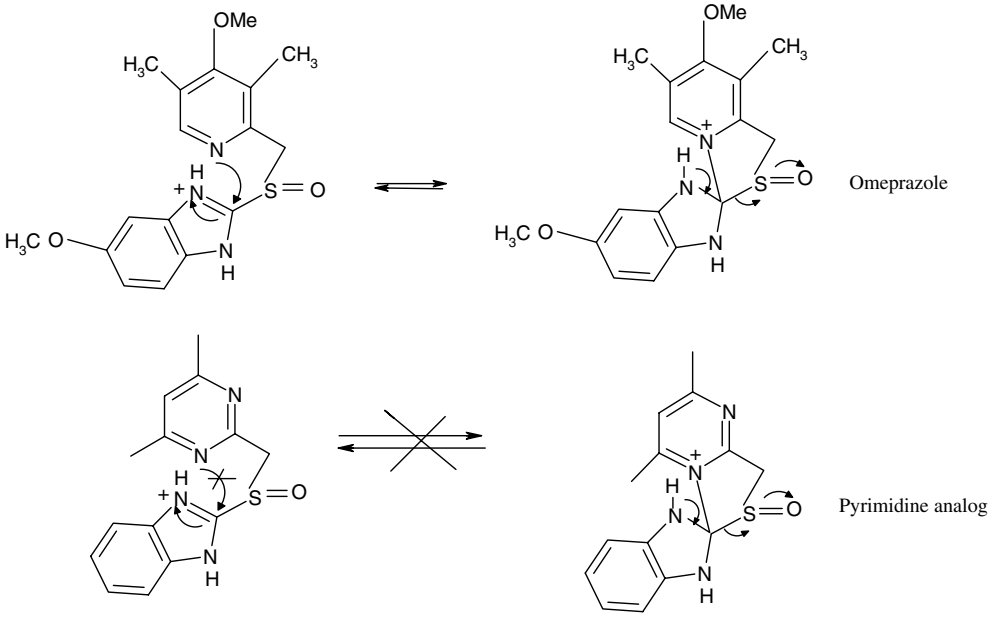
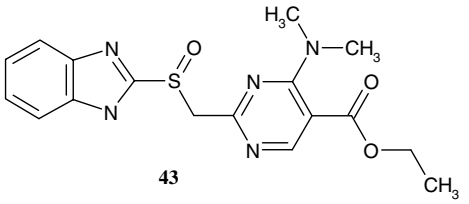


Figure 20. Inability of pyrimidine analog of omeprazole to form sulfenamide intermediate.

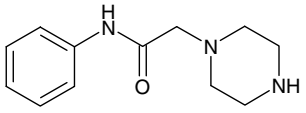


43

It really appears difficult that in this system the formation of the disulfide intermediate is likely. This is owing to the poor availability of electrons on pyrimidine and its nitrogens.

7.5. Some more literature reports

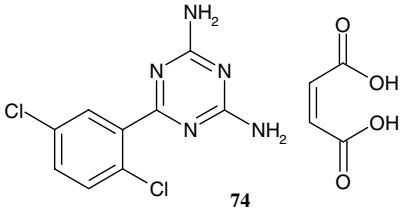
Corvi-Mora[106] has synthesized derivatives of piperazinylacetamides **73** possessing anti-ulcer and anti-secretion properties. These compounds were entirely free from anticholinergic activity. Though mechanism of action is not clear, anti-ulcer activity was evaluated successfully in different models like rats with reserpine induced ulcer, as well as phenylbutazone-histamine induced ulcer.



73

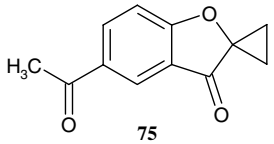
Murai et al.[107] have reported the anti-ulcerative activity of benzoguanamine derivatives **74**.

74.



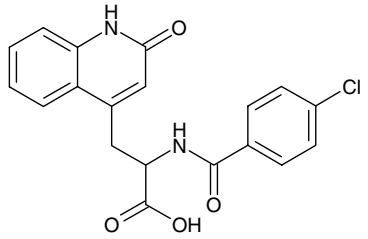
74

Hirosada et al.[108] have reported gastric secretion inhibiting activity of spiro compounds with novel skeleton **75**. These compounds were found to be of value as anti-ulcer, anti-inflammatory, and as analgesic agents.



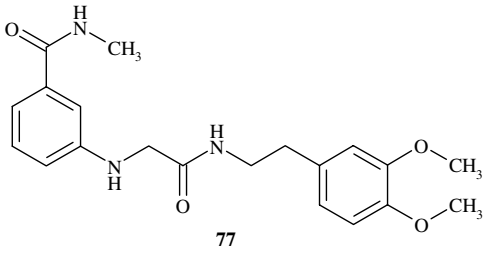
75

Otsubo et al.[109] have synthesized the enantiomers of 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid **76**, new anti-ulcer agent that enhances mucosal resistance. The (+) isomer, rebamipide, was about 1.7 times as potent as the (−)-isomer in anti-ulcer activity against ethanol-induced gastric ulcers.



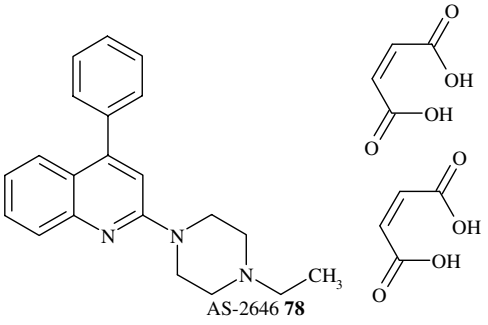
76

Miki et al.[110] have synthesized derivatives of benzamide, **77**, which have exhibited excellent inhibitory effects on several gastric models such as alcohol ulcer, indomethacin ulcer, aspirin ulcer, and stress ulcer. Also, these compounds exhibited an inhibitory effect on duodenal ulcer models such as cysteamine ulcer and dulcerozine ulcer.



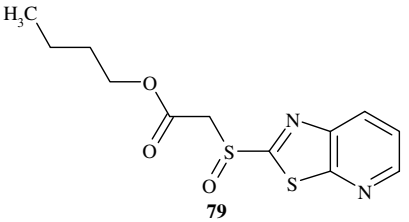
77

Hino et al.[111] have synthesized a novel class of anti-ulcer agents, substituted 4-phenyl-2-(1-piperazinyl)quinolines. These compounds can be classified into three groups; first, that is effective on stress-induced ulcers, second, that is effective on both stress-induced and ethanol-induced ulcer, and third, that is selectively effective on the ethanol-induced ulcer. Among the compounds evaluated, AS-2646 **78** (fumarate salt) showed potent inhibition of stress-induced ulcer and gastric acid secretion.



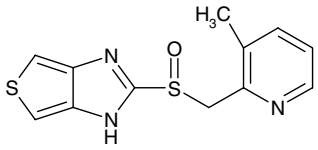
AS-2646 **78**

Katano et al.[112] have reported the anti-ulcer activity of some pyridothiazole derivatives **79** which exhibited both, strong effect of inhibiting the secretion of gastric acid, as well as an enhanced effect on protecting the gastrointestinal mucosa.

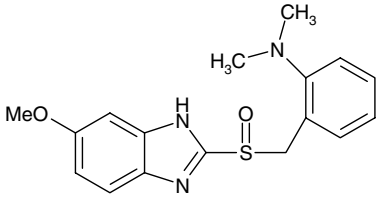


79

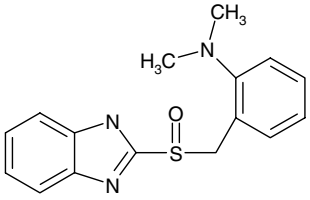
Herling et al.[113] had synthesized structural analogs of PSMBs by replacing benzimidazole heterocycle by theinoimidazole to get S 1924, **80**. Similarly, aminobenzyl ring has also been tried as a replacement to pyridine ring of PSMBs as in **81** and **82**.



S 1924 (Hoechst) **80**



NC-1300-B(Nippon Chemiphar) **81**



NC-1300-(Nippon Chemiphar) **82**

7.5.1. CCK_2/gastrin-receptor antagonists. Gastrin is the only peptide hormone released from the stomach. It mediates the gastric acid secretion. Gastrin stimulated secretion of gastric acid is produced directly by stimulation of cholecystokinin-2 (CCK_2)/gastrin receptors on parietal cells or indirectly after CCK_2/gastrin receptor-mediated HA releases from ECL cells. The regulation of gastrin and HA-stimulated gastric acid secretion are key therapeutic targets in controlling acid-peptic disorders. Inhibition of acid secretion through H_2-receptor antagonists and PPIs has positive feedback effect on the release of gastrin.[114,115] Numbers of chemically diverse CCK_2/gastrin receptor antagonist have been studied for their anti-secretory effects or as inhibitors of panic attacks including L-365260 (Merck) **83**, CR2194 (Rotta) **84**, and JB95008 (James Black Foundation) **85**.[116] However, until date, none has been marketed[2] (see Fig. 21)

8. Biological evaluation of PPIs

8.1. Studies on isolated guinea pig mucosa[117]

8.1.1. Preparation of tissue and solution. Isolated guinea pig mucosa is mounted on a plastic funnel with the mucosal surface facing the tube lumen. Each preparation is immersed in an organ bath containing 40 ml of serosal solution having the different compositions.

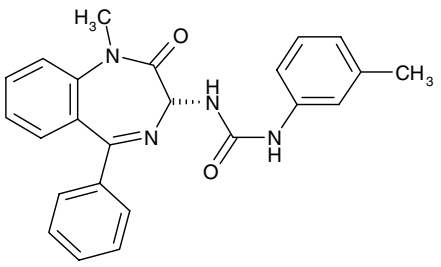
8.1.2. Measurement of H^+ secretion. This is performed by continuous titration using a radiometer (Copenhagen, Denmark), pH-stat (pHM 82, TTT 80), and Autoburette (ABU 80).

8.1.3. Measurement of K^+ secretion. K^+ content of mucosal solution is determined on a flame-emission photometer.

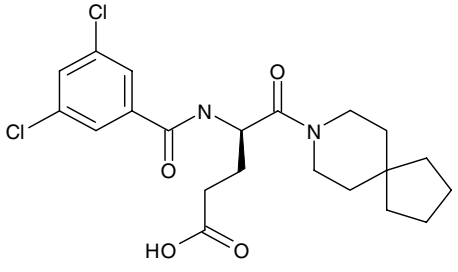
8.1.4. Experiments with simultaneous measurements of K^+ and H^+ secretion. Histamine is added to serosal solutions followed by sample solutions and secretion rates are calculated.

8.2. Effect of H+/K+ ATPase inhibitors on serum gastrin levels[118]

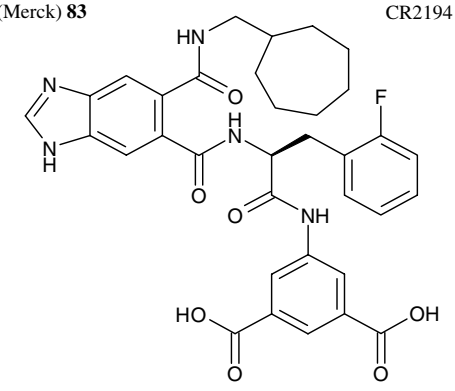
Female Wistar rats are treated with the H^+/K^+-ATPase inhibitors to cause gastric inhibition. Blood samples are



L-365,260 (Merck) **83**



CR2194 (Rotta) **84**



JB95008 (James Black Foundation) **85**

Figure 21. Structures of CCK_2/gastrin receptor antagonists.

collected and gastrin is determined by radio-immunoassay using a commercially available kit. At the end of the study of 10 weeks, the animals are studied for their gastric acid output using pylorus ligation (Shay technique).

8.3. Pylorus Ligation in rats (Shay et al.)[118]

A simple and reliable method for production of gastric ulceration in the rat based on the ligature of the pylorus has been published by Shay et al.[118] The ulceration is caused by accumulation of acidic gastric juice in the stomach. The intensity of ulceration is expressed in terms of ulcer index.

9. Conclusion

In 19th century, light diet consisting of food not stimulating gastric acid secretion was recommended for treating peptic ulcer-related disorders. From then a number of strategies have been designed to control these disorders related to the hypersecretion of acid. These therapeutic strategies extend from simple conventional antacids to the use of more complex and effective proton pump inhibitors (PPIs). Associated effects of antacids like constipation or diarrhea limit their patient compliance and are today mainly used for fast symptomatic relief. Muscarinic antagonists like pirenzepine inhibit gastric acid secretion as well as decrease gastric motility, but clinical use of these drugs is now limited because of availability of more effective anti-secretory medications. A new era in the treatment of acid-peptic disorders dawned with the launch of H_2-receptor antagonist, cimetidine, in 1976. This class of drugs, however, have a short duration of action. Peptic ulcers caused by *H. pylori* can be treated by combination of antibiotics and anti-secretory medications. However, complex drug regimen and associated side effects may limit usefulness. Launch of omeprazole in 1988 introduced a conceptually new approach of inhibition of proton pump in the management of acid-related disorders. PPIs proved to be superior to any of the previously used drugs including H_2-antagonists.

Today, almost two decades after introduction of the first PPI, the apparent drawbacks of irreversible proton pump inhibitors, mainly because of their prolonged acid suppression, are becoming a cause of concern. Hence, the researchers worldwide have been attracted toward designing reversible, shorter, and rapid acting acid pump antagonists (APAs). Thus, APAs are the conceivable future drugs for the treatment of acid-peptic disorders.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.07.068.

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