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PROTON PUMP INHIBITORS: PRESENT AND FUTURE A REVIEW

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ABSTRACT

Proton pump inhibitors (PPIs) are very effective drugs used largely in acid related disorders. Since their introduction into clinical practice almost two decades ago, PPIs have revolutionized the medical treatment of acid related disorders. Oesophageal mucosal healing has made PPIs the first choice treatment not only for reflux disease but also for other acid related diseases. This review includes physiology of acid secretion, acid related disorders which are arise due to excessive released of gastric acid, proton pump, PPIs and its classification, pharmacology of PPIs, Clinical significance of PPIs, adverse effect of PPIs and advancement in different PPIs. Although PPIs are very effective drugs they are still far from the ideal antisecretory compound and display a number of shortcomings. A number of new drugs are currently being investigated to vide a significant advance on current treatments. Some of them have already reached clinical testing while some other are still in preclinical development and need the proof of concept in human beings. In this connection, new formulations, novel compounds and better acid-suppressing regimens are welcome.

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Key words: *Proton pump, Proton pump inhibitors, Acid secretion, Acid related disorders*

INTRODUCTION

The discovery of gastrin by John Edkins initiated the scientific examination of the regulation of gastric acid secretion and led to elucidation of the pathogenic basis of peptic ulcer and its subsequent cure **[1]**. During the course of the century after this breakthrough, the identification of the cellular regulators of acid secretion culminated in the development of novel pharmaco-therapeutic agents, namely histamine-2 (H_2) receptor antagonists and proton pump inhibitors (PPIs) **[2]**. The efficacy of PPIs is superior to H_2-receptor antagonists **[3-6]** and their use is recommended in current guidelines for the treatment of gastro-esophageal reflux disease **[7]**, peptic ulcer prevention in patients receiving NSAIDs, **[8]** Helicobacter pylori eradication protocols **[9]**.

Moreover, PPIs are often used for the prevention of stress ulcer **[10]**.

DISORDERS DUE TO HYPERSECRETION OF GASTRIC ACID

Ulcer Disease

Peptic ulcers arise because of an imbalance of acid secretory mechanisms and mucosal-protective factors and the rationale for their treatment is aimed at restoring that balance. The loss of balance between acid secretion and mucosal-protective factors varies among peptic ulcer types. The causes of gastric ulcers include H. pylori infection, non-steroidal anti-inflammatory drugs, environmental factors, and malignancy. Duodenal ulcers can result from hypersecretion of gastrin. Proton pump inhibitors are superior to H_2-receptor antagonist in promoting healing and preventing recurrence of both gastric ulcers and duodenal ulcers.

Zollinger-Ellison Syndrome

In this disease, a non-beta-cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate secretion of gastric acid to life-threatening levels. This can lead to severe gastro-duodenal ulcerations. The development of H^+/K^+ ATPase inhibitors has enabled adequate inhibition of gastrin-stimulated acid secretion to be achieved for longer periods. Infection of Helicobacter pylori (H. Pylori) occurs in approximately 40% of patients over 40 years age and with peptic ulcer disease is infected with H. pylori infection. 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. H. pylori infection also causes inflammation of the antral gastric mucosa. Bacterial products and inflammatory cytokines may produce changes in the endocrine function **[11]**. H. pylori is a gram-negative rod-shaped bacteria and has clearly been associated with gastritis, peptic ulcers, gastric adenocarcinoma, and gastric B-cell lymphoma. Gastric enterochromaffin-like (ECL) cell carcinoids are rare events that have been described in association with pernicious anemia and Zollinger-Ellison syndrome. They usually relate to marked hypergastrinemia, atrophic gastritis, or a genetic defect, rather than the presence or absence of acid. Regression or disappearance of ECL-cell carcinoids may occur either spontaneously or after removal of gastrin. H. pylori infection is now proven to the a risk factor for gastric cancer and the organism was classified as a Group 1 carcinogen by the International Agency for Research on Cancer sponsored by the World Health Organization in 1994 **[12]**.

Gastro esophageal reflux disease (GERD)

This international group defined GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications”. Troublesome symptoms are defined by the patient to effect their quality of life. Mild symptoms occurring two or more days a week, or moderate to severe symptoms occurring more than one day a week, is often considered troublesome by patients. GERD is the most common esophageal disease and one of the most common diseases seen in practice. Heartburn occurs on a daily or a monthly basis in anywhere from 7% to 36% of control subjects **[13]**. A population-based study with a validated questionnaire found that heartburn and/or acid regurgitation are experienced at least weekly in 19.8% and less frequently intermittently in 58.7%of responders **[14]**. The typical symptoms of GERD are heartburn, regurgitation, and dysphagia. It can also have atypical presentations such as odynophagia, hypersalivation, nausea, and globus sensation, as well as extra-esophageal manifestations like chest pain and cough.

Helicobacter pylori (H. pylori)

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 B-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. H.

pylori infection is now proven to the a risk factor for gastric cancer and the organism was classified as a Group 1 carcinogen by the International Agency for Research on Cancer sponsored by the World Health Organization in 1994 **[15]**.

PHYSIOLOGY OF ACID SECRETION

Presence of food stimulates release of acids and enzymes in stomach. The chemo- and mechano-sensitive receptors present in stomach are triggered by presence of food to produce specific responses **[16]**. The acid secreting parietal cell is the principle cell in gastric glands. Three major pathways activating parietal acid secretion include:

- neuronal stimulation via the vagus nerve
- paracrine stimulation by local release of histamine from ECL-cells
- endocrine stimulation via gastrin released from antral G cells.

The parietal cell contains receptors for gastrin, histamine (H_2), and acetylcholine (muscarinic, M_3). When acetylcholine or gastrin bind to the parietal cell receptors, they cause an increase in cytosolic calcium, which in turn stimulates protein kinases that stimulate acid secretion from a H^+/K^+ ATPase (the proton pump) on the canalicular surface. In close proximity to the parietal cells are gut endocrine cells called ECL cells. ECL cells have receptors for gastrin and acetylcholine and are the major source for histamine release. Histamine binds to the H_2 receptor on the parietal cell, resulting in activation of adenylyl cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP). cAMP activates protein kinases that stimulate acid secretion by the H^+/K^+ ATPase.

From the knowledge of physiology of acid secretion, a variety of therapeutic treatments are available. 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.

DISCOVERY OF PROTON PUMP INHIBITORS (PPIs)

The discovery and development of H_2-receptor antagonists was the beginning of a novel therapeutic approach to diseases associated with the hypersecretion of gastric acid. During the 1980, H_2-antagonists became first-line therapy in peptic ulcer disease and negated the necessity of surgery for a large number of patients. It soon became apparent that H_2-receptor antagonist therapy had some drawbacks. In a small but significant number of patients, the disease was resistant or recurred after maximal H_2-antagonist therapy **[17]**. In another small group of patients, H_2-receptor antagonists were particularly poor when it came to inhibiting the nocturnal secretion of gastric acid **[18]**. **A** further problem was that acid rebound (elevated acid secretory response) occurred after cessation of H_2-antagonist therapy **[19]**. In some patients, tolerance to H_2-antagonist therapy also appeared to develop when long-term treatment was necessary **[20]**. In 1977, a year after the launch of cimetidine, Astra reported on the first PPI, H83/88, a benzimidazole derivative.

STRUCTURE OF THE PROTON PUMP

The H^+/K^+ ATPase enzyme, present in tubulovesicular and canalicular membranes of the gastric parietal cell, consists of two subunits, a 114 kDa α-subunit and a 34-kDa β-subunit. The α-subunit has been shown to contain 10 transmembrane helices, with the β-subunit possessing only a single transmembrane helix **[21]**. 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. The α-subunit carries out the catalytic and transport functions of the enzyme because it contains both ATP and cation binding sites; it also contains the sequences responsible for apical membrane localization. When the parietal cell transforms from an active to resting state, the heavily glycosylated

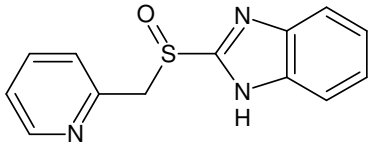
β-subunit is required for endocytic retrieval of the H^+/K^+ ATPase from the canalicular membranes.

H^+/K^+ ATPASE (PROTON PUMP) INHIBITION

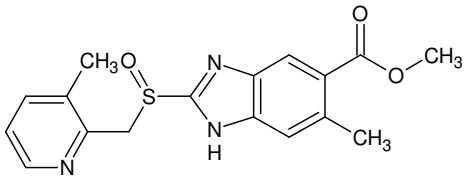
The enzyme H^+/K^+ ATPase, or proton pump, regulates the final stage in the cellular cascade that terminates in the secretion of gastric acid. When the parietal cell transforms from a resting to a stimulated state, cytoskeletal rearrangement occurs and H^+/K^+ ATPase relocates to the apical plasma membrane. Potassium and chloride ions move across the apical cell membrane together with secreted protons. Potassium is recycled, whereas the hydrochloric acid of gastric juice is formed by chloride ions together with secreted protons. Neuronal, hormonal, and enzymic pathways influence the secretion of gastric acid. The most potent inhibitor of gastric acid secretion is produced by inhibiting H^+/K^+ ATPase.

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 **[22]**. Ruwart et al. identified timoprazole **[23]** as one of the first well-defined inhibitor of gastric proton pump. Timoprazole was followed by more potent picoprazole (1976) and omeprazole (1979) **[24]**. 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, lansoprazole, rabeprazole, pantoprazole and esomeprazole.



Timoprazole



Picoprazole

MECHANISM OF ACTION OF PROTON-PUMP INHIBITORS

PPIs are both more potent and of longer duration than H_2-receptor antagonists and therefore are frequently the drug of choice for the treatment of diseases associated with the secretion of gastric acid. PPIs inhibit gastric acid secretion by inhibiting the enzyme H^+/K^+ ATPase, which is located on the luminal surface of gastric parietal cells. Like omeprazole, the other commercially available PPIs, lansoprazole, rabeprazole, pantoprazole, and esomeprazole are inactive prodrugs that are activated in the acid environment of the gastric glands. The inactive PPI diffuses from the bloodstream into the parietal cells and subsequently into the acid environment of the secretory canaliculi, where it rearranges to form a sulfenic acid in equilibrium with a sulfenamide. Either chemical entity is then able to interact covalently with thiol groups at cysteine residues located on the luminal surface of the α-subunit of the H^+/K^+ ATPase. This covalent binding results in specific and essentially irreversible inactivation of the enzyme, leading to long-lasting inhibition of gastric acid secretion. Unlike omeprazole and lansoprazole, which bind to two (cyst413 and cys892) and three (cys813, cys892, and cys321) cysteine residues, respectively, rabeprazole is reported to bind to a single cysteine residue located at position 322 between transmembrane domain H3 and the lumen.

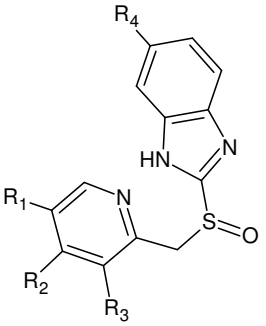
CLASSIFICATION OF PROTON-PUMP INHIBITORS

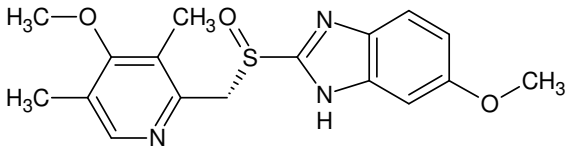
A) Irreversible gastric PPIs

Three main structural features of this class of compounds are the substituted pyridine ring;

the substituted benzimidazole ring, and the methylsulfinyl linking group. They are further classified according to their chemical structure as follows:

Pyridinylmethylsulfinyl benzimidazoles

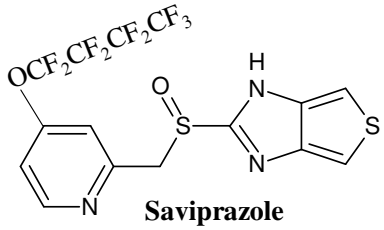




Esomeprazole

Pyridylmethylsulfinyl thienoimidazoles

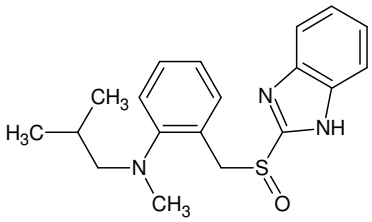
The benzene ring of imidazole is replaced by thiophene, keeping other structural features same. e.g. Saviprazole



Saviprazole

Aminobenzylsulfinyl benzimidazoles

The pyridine ring is replaced by substituted aminobenzyl ring. e.g. leminoprazole.



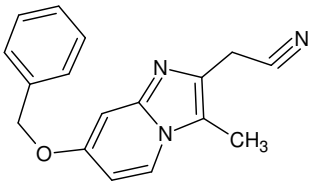
Leminiprazole

B) Reversible gastric PPIs

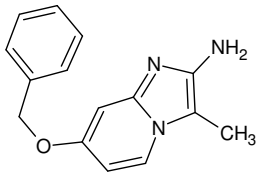
The drawbacks associated with the use of irreversible PPIs, some reversible inhibitors

The substitution takes place present on the benzimidazole and pyridine ring. e.g. omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

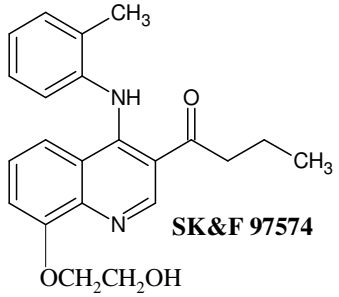
were discovered. e.g. SCH 28080, SK& F 97574, SCH 32651, and SK& F 96067.



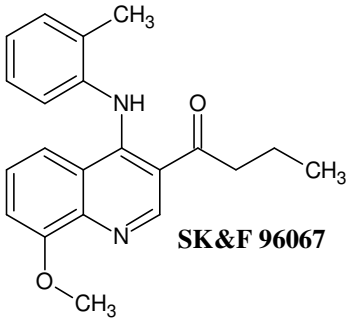
SCH 28080



SCH 32651



SK&F 97574



SK&F 96067

PHARMACOLOGY OF THE PROTON-PUMP INHIBITORS

Omeprazole is a potent and irreversible inhibitor of H^+/K^+ ATPase. Subsequently developed compounds (lansoprazole, pantoprazole, esomeprazole and rabeprazole) have a similar mechanism of action, although small differences in bioavailability,

potency, and metabolism have been reported. Rabeprazole shows faster rate of inhibition and a shorter duration of action **[25]**. Esomeprazole has least bioavailability, whereas, lansoprazole being the most bioavailable **[26]**. Comparative studies with lansoprazole and pantoprazole suggest that they have potency similar to that of omeprazole. Compared with lansoprazole, the onset of action of rabeprazole was faster and its duration of action was shorter, as determined by measuring acid output and microsomal enzyme activity **[27]**. 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 **[28]**.

TABLE 1: Pharmacokinetic profile of commonly used PPIs

PPIs	A	C	D	E	F	G	H	I	J
Omeprazole **[29]**	22-72	0.6-1	54	95	0.31-0.34	9	30-40	U-77 F-33	Mostly hepatic
Pantoprazole **[30]**	22-72	0.9-1.9	77	98	0.13-0.17	8.6	77	U-71 F-18	Mostly hepatic
Lansoprazole **[31]**	>24	0.9-1.6	85	97-99	0.39-0.46	9	80	U-35 F-65	Mostly hepatic
Rabeprazole **[32]**	24	1	52	95-98	-	-	52	U-90 F-10	Mostly hepatic
Esomeprazole **[33]**	24-27	0.8-1.2	90	97	-	9	64	U-80 F-20	Mostly hepatic

A= Duration of effect (hr), **B=** Half Life (hr), **C=** Half Life (hr),
D= Oral Absorption%, **E=** Plasma protein binding %, **F=** Vol. of distribution (l/kg), **G=** Pk_b (In-vitro), **H=** Bio-availability %, **I=** Excretion (%), **J=** Metabolism

CLINICAL SIGNIFICANCE OF PROTON PUMP INHIBITORS [34]

- Proton pump inhibitors are the most potent medications available to reduce gastric acid secretion.
- With the widespread use of PPIs, the long-term safety issues need to be considered.
- The collective body of information overwhelmingly suggests increased risk of infectious complications and nutritional deficiencies.
- Data on the risk of increased gastric and colon malignancy, despite a physiologic theoretic basis, is less convincing.
- The long-term need for PPIs must be reassessed frequently.

ADVERSE EFFECTS OF PROTON PUMP INHIBITORS

Gastric polyps

PPIs long term treatments have been associated with the development of fundic glands polyps. These polyps are frequent in patients with familial adenomatous polyposis but might also occur sporadically **[35,36]**. Their occurrences have been related to PPIs use longer than 12 months and regression of polyps have been described after PPIs withdrawal **[37]**.

Gastric cancer

Mowat et al. investigated the effects of a four week course of 40 mg of omeprazole on gastric juice concentration of vitamin-C in 20 healthy volunteers. They showed that omeprazole increase the levels of nitrites and reduce those of vitamin-C. The reduced ascorbate/nitite ratio induced by PPI, may increase the risk of gastric cancer. This effect was more marked in H. Pylori positive patients, probably because the acid suppressive effect of PPIs is more pronounced in these patients **[38,39]**.

Bone fractures

HCl is believed to be an important mediator of calcium absorption in the small intestine, therefore without an appropriate acid environment, calcium might be retained in food reducing its absorption. A decrease in calcium absorption has been shown in rats treated with PPIs. Few studies evaluated the

effects of PPIs administration on calcium absorption, only two are randomized placebo controlled and directly measured intestinal calcium absorption **[40,41]**. The first showed a decreased intestinal calcium absorption (an average of 41%) in women treated with omeprazole, the second did not show differences in intestine calcium absorption in healthy people treated with omeprazole.

Enteric infections

The gastrointestinal tract has many defence mechanisms, such as the integrity of the membranes and mucous layer, the gastrointestinal microflora and gastric acidity. A decrease in gastric acidity may induce changes in the normal microbial flora with bacterial overgrowth. Diarrhoea is the most frequent adverse event in the long term PPI use and the most frequent cause of PPI withdrawal, with reported incidence ranging between 3.7% and 4.1% **[42,43]**.

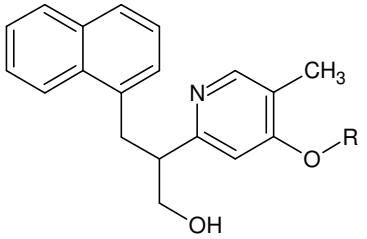
Vitamin B_{12} deficiency and hypomagnesaemia

Marcuard et al. evaluated vitamin-B_{12} absorption before and after a short term omeprazole therapy in ten healthy male volunteers (age range 22–50 years). Five patients were randomized to receive 20 or 40 mg of omeprazole daily for two weeks. At the end of the therapy in patients receiving omeprazole 20 mg, cyanocobalamin absorption decreased from 3.2% to 0.9%, and in patients receiving 40 mg, cyanocobalamin absorption decreased from 3.4% to 0.4% **[44]**. Recent reports described the cases of seven patients developing hypomagnesaemia while on long term PPI, with resolution after PPI withdrawal **[45,46]**. The incidence and the mechanism of hypomagnesaemia development in long term PPI users have still to be determined by specific studies.

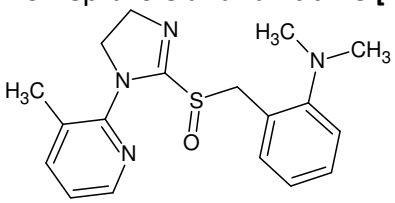
ADVANCEMENT IN DIFFERENT PROTON PUMP INHIBITORS

Reversible inhibitors

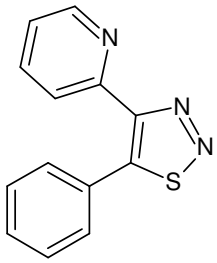
Niiyama et al. have synthesized novel 4-substituted pyridine derivatives like 4-alkoxy-, 4-alkylthio, and 4-aryloxy-5-methyl-2-[1-(hydroxymethyl)-2-(1-naphthyl)- ethyl (ethenyl)] pyridine which were found to have reversible inhibitory activity against H^+/K^+ ATPase **[47]**.



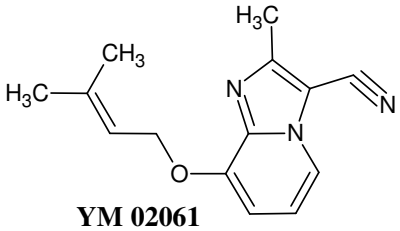
Kinoshita et al. have reported a novel reversible PPI, 2-[(2-dimethyl aminobenzyl)sulfinyl]-1-(3-methylpyridine- 2-yl-)imidazole (T-330), which was found to possess anti-secretory activity more potent than omeprazole and ranitidine **[48]**.



Ife et al. have reported 4-(2-pyridyl)-5-phenylthiazoles as reversible, K+-competitive gastric H^+/K^+ ATPase inhibitors **[49]**.

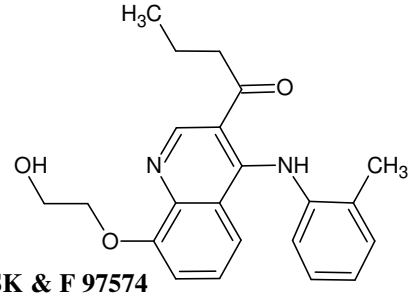


Yuki et al. have reported proton pump inhibitory activity of 2-methyl-8-(3-methyl-but 2-enyloxy)-imidazo[1,2-a]pyridine-3-carbonitrile (YM-0201) **[50]**.



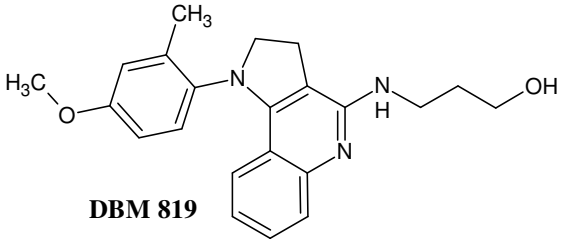
YM 02061

Leach et al. have reported H^+/K^+ ATPase inhibitory activity of 3-butyryl-4-[(2 methylphenyl)amino]-8-(2- hydroxyethoxy)quinoline, SK& F 97574. It was found to be well tolerated and efficacious in phase-I studies **[51]**.



SK & F 97574

Cheon et al. 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) as potential reversible inhibitor **[52]**.

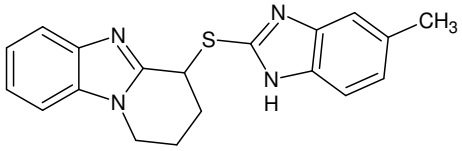


DBM 819

Irreversible inhibitors

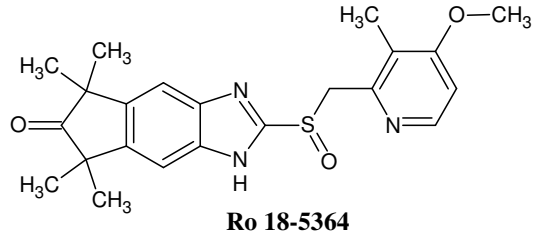
Substitution at benzimidazole nucleus

Woo et al. have reported the synthesis and biological evaluation of 2-[3-(2,3-dihydro-1H-pyrolo[1,2 a] benzimidazolyl)sulfinyl]-5-methyl-1H-benzimidazoles,(YJA20379-4). YJA20379-4 having marked inhibitory effect on H^+/K^+ ATPase and also exhibited anti-H. pylori activity three times higher than omeprazole along with the enhancement of mucosal defense **[53]**.



YJA 20379-4

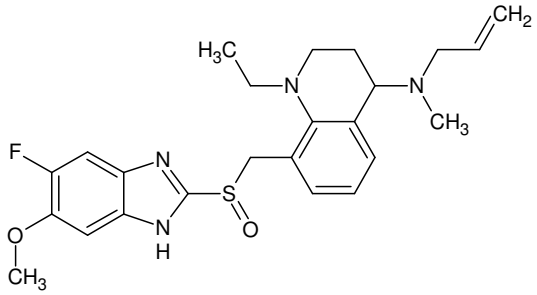
Sigrist-Nelson et al. have reported the synthesis and evaluation of 5,7-dihydro- 2{[(4 methoxy-3-methyl-2-pyridyl)methyl]sulfinyl}-5,5,7,7-tetramethylindeno-[5,6d]imidazole 6-(1H)-one (Ro18-5364) as an extremely effective H^+/K^+ ATPase inhibitors. Ro 18-5364 produced almost complete inhibition of the H^+/K^+ ATPase activity **[54]**.



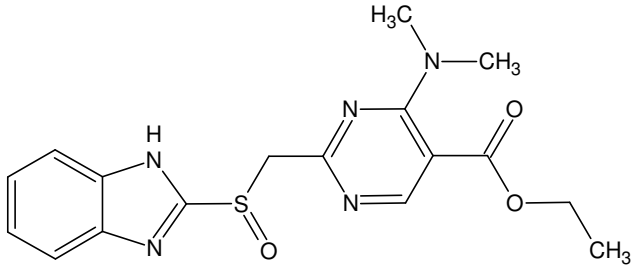
Ro 18-5364

Substitution at pyridine nucleus

Uchida et al have reported the synthesis and evaluation of 4-(N-allyl-N-methylamino)-1 ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl) sulfinylmethyl]-1-ethyl-1,2,3,4 tetra hydroquinoline and was found to have potent anti-ulcer activity **[55]**.

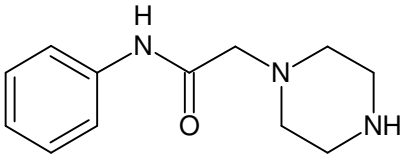


Japanese workers replace pyridine ring with pyrimidine ring and have evaluated 2-(1H benzoimidazole-2-sulfinylmethyl)- 4-dimethylamino-pyrimidine-5-carboxylic acid ethyl ester for its proton pump inhibition. It was found to have marked proton pump inhibitory as compared to omeprazole **[56]**.

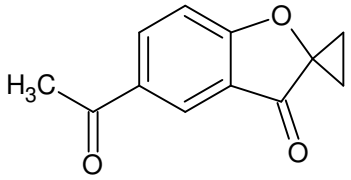


PROTON PUMP INHIBITORS AND ITS FUTURE

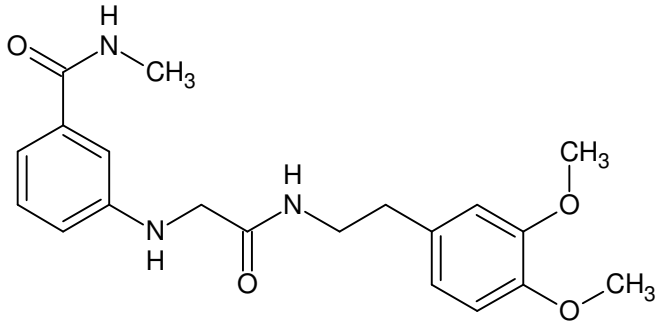
Corvi-Mora has synthesized derivatives of piperazinylacetamides possessing anti ulcer and anti-secretion properties **[57]**.



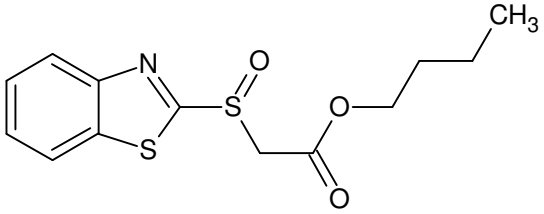
Hirosada et al. have reported gastric secretion inhibiting activity of spiro compounds with novel skeleton **[58]**.



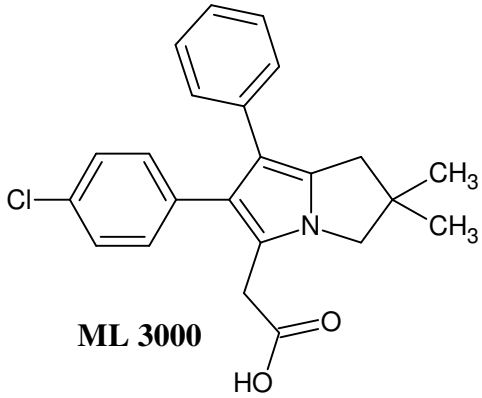
Miki et al. have synthesized derivatives of benzamide, which have exhibited excellent inhibitory effects on several gastric models such as alcohol ulcer, indomethacin ulcer, aspirin ulcer, and stress ulcer **[59]**.



Katano et al. have reported the anti-ulcer activity of some pyridothiazole derivatives which exhibited both, strong effect of inhibiting the secretion of gastric acid, as well as an enhanced effect on protecting the gastrointestinal mucosa **[60]**.

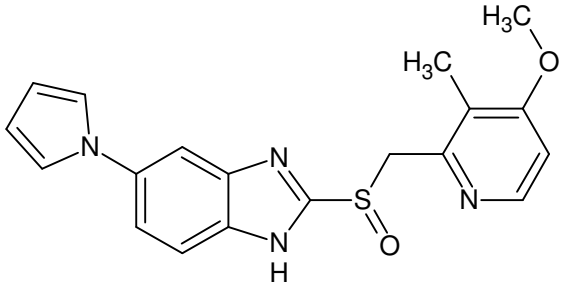


Smolka et al. have reported the synthesis and evaluation of the pyrrolizine derivatives of the type ML 3000, which along with the inhibition of H^+/K^+ ATPase also inhibited 5-lipoxygenase **[61]**.



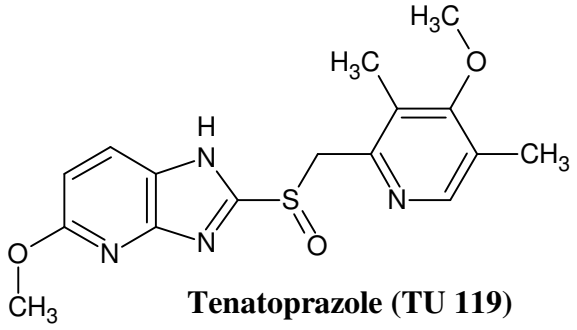
ML 3000

Ilaprazole is a benzimidazole compound synthesized at Il-Yang (South Korea) and presently developed by TAP Pharmaceuticals. Its antisecretory activity proved to be two to three times higher and its half-life two to three times longer than that of omeprazole. Although the drug is already on the market in South Korea, a phase II clinical trials is ongoing in USA **[62]**.



Ilaprazole (IY 81149)

Tenatoprazole has been developed by Mitsubishi Pharma in Japan and is now under active development by Negma-Gild (France). Conversely from all the other PPIs, this compound is not a benzimidazole derivative, consisting of one imidazopyridine ring connected to a pyridine ring by a sulfinylmethyl chain. Like the other PPIs, tenatoprazole is a prodrug, which is converted to the active sulfenamide or sulfenic acid by acid in the secretory canaliculus of the stimulated parietal cell of the stomach **[63]**.



Tenatoprazole (TU 119)

CONCLUSIONS

PPIs are highly effective drugs that have revolutionized the management of acid-related disorders during the last two decades. 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 H2 antagonists. A number of new drugs are currently being investigated to vide a significant advance on current treatments. Some of them have already reached clinical testing while some other are still in preclinical development and need the proof of concept in human beings. Although acid suppression therapy has stood the test of time, the new targets for pharmacological manipulation of gastric secretion will likely bring us a step forward.

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