INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

# REVIEW ON IMIDAZOPYRIDINE DERIVATIVES AS POTENT REVERSIBLE INHIBITORS OF THE GASTRIC $H^+$, $K^+$-ATPASE

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**ARTICLE INFO**

**Article history**

Received 04/07/2017

Available online

04/08/2017

**Keywords**

Gastric Acid Secretion,
Gastric Disorders,
Proton Pump Inhibitors,
Acid Pump Antagonist,
Imidazopyridine,
Biological Activity.

**ABSTRACT**

The gastric $H^+$, $K^+$-ATPase is the preferred target for acid suppression. PPIs are acid-activated prodrug that requires acid protection. Once acid-activated, PPIs bind to cysteine of the ATPase, resulting in covalent, long-lasting inhibition. The currently available PPIs require around 3–5 days to achieve maximum acid inhibition at existent therapeutic doses, primarily due to their chemical structures and irreversible inhibition of $H^+$,$K^+$-ATPase. Therefore, many novel strategies to address the unmet needs of PPI therapy have been investigated, and acid pump antagonists (APAs) could play a promising role, as they provide faster onset and longer duration of action than irreversible PPIs by virtue of their ability to reversibly bind to the proton pump. They are active in absence of acid secretion and bind to specific sites in the membrane domain of the $H^+/K^+$-ATPase. The imidazopyridine based compound was the prototype of this class. Comparison was made between to the classic PPIs and P-CABs. SAR of imidazo [1,2-a]pyridines related to SCH 28080 is described. Various modifications were done on imidazopyridine nucleus, to search for lead molecule is also described. Some of the potent compounds are SCH28080, Soraprazan, Revaprazan, Linaprazan, Vonoprazan, Tak-438-1, AZD 0865, BY841.

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*Please cite this article in press as **Ravindra S. Sonawane** et al. Review on Imidazopyridine Derivatives as Potent Reversible Inhibitors of the Gastric $H^+$, $K^+$-Atpase. Indo American Journal of Pharmaceutical Research.2017:7(07).*

## INTRODUCTION

Physiological processes, such as digestion, sterilization of food and absorption of calcium and iron are very much governed by presence of gastric acid. Gastric acid is involved in the etiology of peptic ulcer disease (PUD) and gastroesophagal reflux disease (GERD). Erossion of the inner lining of the stomach or the first part of the small intestine by gastric acid and other digestive juices causes Peptic Ulcer Diseases. When the barrier breaks down, the lining is exposed to the destructive potential of the digestive juices. From many years, it is believed that acidic foods and stress causes peptic ulcers. But the research conducted in the 1980s shown that along with these factors infection by bacteria *Helicobacter pylori*, which can survive in the acidic environment of the stomach also responsible. Such bacteria can produce a change in the mucous barrier, which results in ulcers. Other factors associated with recurrence of PUD includes cigarette smoking, chronic consumption of ulcerogenic drugs like NSAID, consumption of alcohol for prolonged periods, age, emotional stress and family history.

The common symptom of peptic ulcer is mild to moderate severe pain just below the breastbone may last for once or a few times daily typically after eating. It generally lasts from one to several weeks and may be then disappears. Other symptoms include heartburn and nausea and vomiting. If untreated, ulcers continuing to corrode GI lining and may lead to serious complications.
Inhibition of the $H^+/K^+$-ATPase, therefore, blocks the basal and stimulated acid secretion. Many benzimidazole sulfoxide pyridine classes as proton pump inhibitors (PPIs), significantly progressed in this field. Starting from 1974, timoprazole, picoprazole, omeprazole, Pantoprazole, Rabeprazole were discovered.

Extreme acid suppression also shown achlorohydria and that may produce enteric infections like typhoid, cholera, and dysentery. Some time drug interactions leads to decreased absorption of some drugs like griseofulvin, ketoconazole, vit.B12, iron salts, etc. Unpredictable action shows hypergastrinemia, gastric polips, and carcinoma. Other side effects include abdominal pain, diarrhea, nausea, and headache, acute interstitial nephritis etc [1-3].

The currently available PPIs requires long time to achieve maximum acid inhibition at therapeutic doses, primarily due to their chemical structural modification and irreversible inhibition of $H^+,K^+$-ATPase. Therapy failed to control sustained acid inhibition throughout the day and night, in spite of twice daily administration. Therefore, many novel strategies are used to solve the unmet needs of PPI therapy. Acid pump antagonists (APAs) could play a promising role, due to their faster onset and longer duration of action than irreversible PPIs by their ability to reversibly bind to the proton pump. Many researchers worked to find out novel APAs but currently none is marketed. The imidazopyridine based compound SCH28080 was the prototype of this class. In comparison to omeprazole, SCH 28080 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, hence like omeprazole it accumulates in the acidic compartments of the parietal cells in its protonated form. SCH 28080 is chemically stable and after protonation, is itself active and does not need an acid-induced transformation, as required by PPIs as shown in figure 1 [4,5].

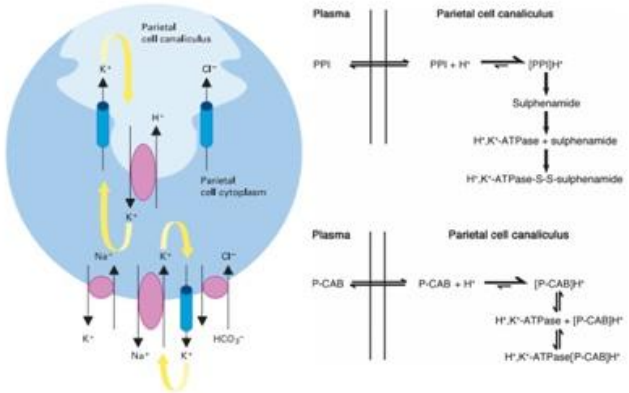


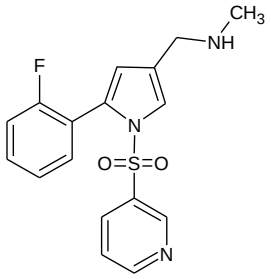

**Figure 1: Comparison between to the classic PPIs and P-CABs.**

Derivatives of imidazo [1,2-a] pyridines related to SCH 28080, were synthesized by many researchers and studied, based on which the observations are made as a small alkyl group at C-2 (methyl or ethyl) favored activity, cyano methyl or amino group at C-3 was a requirement for anti-secretory and cytoprotective activity, 8-position was maximized with benzyloxy, 3-thienylmethoxy or phenylmethylamino substitution, 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. APAs are weak bases and lipophilic that have diverse structures such as, imidazopyridines, pyrimidines, imidazonaphthyridines, quinolines, etc. The APAs class mostly rely on substituted imidazo [1, 2-a] pyridine derivatives. And they were shown to inhibit the gastric acid secretion by reversible and $K^+$ competitive binding to $H^+,K^+$-ATPase, and they also displayed excellent antisecretory properties [6].

Thus the development of another class of compounds targeting the $H^+/K^+$-ATPase tries to combine the advantages of both PPIs and $H_2$RAs and are active in absence of acid secretion. They bind to specific sites in the membrane domain of the $H^+/K^+$-ATPase. This prevents $H^+$ ion transport. Treatment with APAs should provide a more rapid elevation of gastric pH than is found with PPIs, and the elevation of pH should be greater than with oral PPIs at least as long as the APA is present in blood above threshold. Further prolongation of the acid suppressing effect might be caused by high affinity of the drug to the enzyme, and tolerance is not to be expected. Therefore APAs should provide excellent control of intragastric pH, hence faster symptom remission and perhaps better clinical results in gastric acid related diseases, symptom relief and in combination therapy for *Helicobacter pylori* eradication. Various modifications were done on imidazopyridine nucleus, to search for lead molecule as described below.

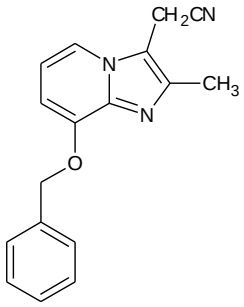
**SUBSTITUTION ON IMIDAZOPYRIDINE NUCLEUS AND EFFECT ON ANTIULCER ACTIVITY:**

*Mitsuyo Kondo et al* discovered a novel class of PPIs, screened a low-molecular-weight compounds library and identified two prospective acid blockers that were pyrrole derivatives. Both compounds inhibited $H^+/K^+$-ATPase in a reversible and potassium-competitive manner. These compounds led to the development of TAK-438 (1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate), which was identified as a novel potassium-competitive acid blocker for the treatment of acid-related diseases [7].



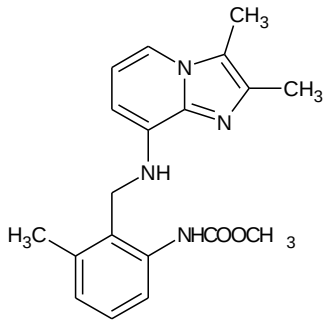

**TAK-438.**

*Ene M. D. et al* reported SCH 28080 (2-methyl-8-(phenyl methoxy) imidazo-(1-2-a) pyrine-3-acetonitrile) as a novel anti-ulcer agents. Antisecretory activity of SCH 28080 was confirmed in various screening. SCH 28080 is found four to ten times more potent than cimetidine while screened in rats [4].



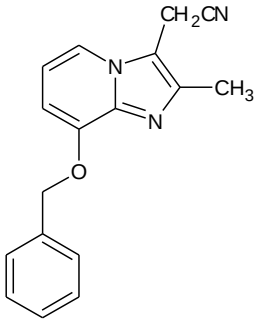

**SCH-28080.**

*Wilhelm Wursta and Manfred Hartmann et al* reported the introduction of $H_2$-receptor antagonists first time for acid-related diseases for their short duration of action and single receptor targeting. BY841 one of the imidazopyridines derivative as possible class of APAs chemically a (8-(2-methoxy carbonyl amino-6-methyl-phenyl methyl amino)-2, 3-dimethyl-imidazo [1, 2-a]-pyridine). In pharmacological experiments BY841 proved to be superior to both ranitidine and omeprazole by rapidly elevating intragastric pH up to a value of 6. In comparison with the standard dose of omeprazole, BY841 administered at a various doses and found potent as omeprazole following repeated daily administration [8].

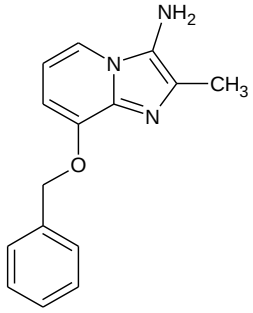


**BY-841.**

*James J. Kaminski et al* reported the four compounds which exhibit pharmacologic profiles similar to compound Sch 28080. Three compounds are potential successors with an amino group functions as a surrogate for the 3-cyanomethyl substituent of the prototype. These studies have shown that Sch 28080 is well-absorbed and metabolized as thiocyanate anion. A similar study performed on 3-amino analogue of Sch 28080 and found same antisecretory and cytoprotective profile comparable to that of Sch 28080. Metabolized as thiocyanate anion, but occurs via a different mechanism. In the chemistry of the amino compounds protonation of the 3-amino analogue and the structurally related imidazo [1, 2-a] pyrazine is also discussed. It was found that N1 is the site of protonation and confirmed by X-ray crystal structue analysis [6].

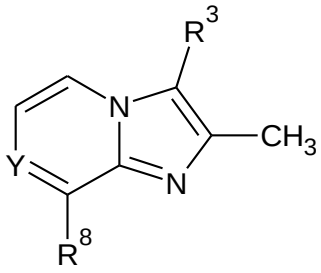


**Sch 28080**

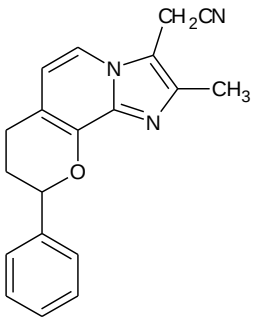


**3-amino analogue of Sch 28080**

*James J. Kaminski and f Bjorn Wallmark et al* reported biochemical characterization study of many imidazo [1, 2-a] pyridines analogues for $H^+/K^+$-ATPase and the intact gastric gland. The good correlation observed between the in vitro and in vivo models suggested that these compounds are gastric proton pump inhibitors in vivo. A molecular modeling study of these compounds were done. Hypothetical description of the pharmacophore of compounds like 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy) imidazo [1, 2-a] pyridine, Sch 28080 and its analogues is described [9].

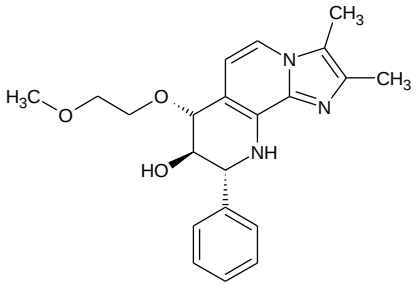


Y = N
Active analogue



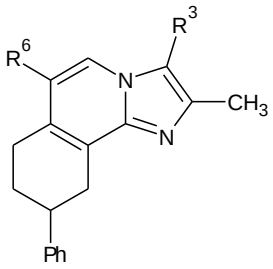
(2-methyl-9-phenyl-8,9-dihydro-7*H*-imidazo[1,2-*a*]pyrano[2,3-*c*]pyridin-3-yl)acetonitrile

*Simon W. A. et al* reported unmet medical needs such as rapid and reliable pain reliever. He introduced and characterized the biochemistry and pharmacology of the potassium-competitive acid blocker (P-CAB) **soraprazan**, a novel, reversible, and fast-acting inhibitor of gastric $H^+/K^+$-ATPase. Inhibitory and binding properties of soraprazan were studied. Soraprazan is 2000 times selective for $H^+/K^+$-ATPase over $Na^+$,$K^+$-and Ca-ATPases. Soraprazan is superior than $H^+/K^+$-ATPase inhibitors. Soraprazan is one of the potent P-CABs for therapy of GERD [10].



**Soraprazan**

*Andreas Marc Palmer et al* reported a series of novel tetrahydroimidazo [2, 1-a] isoquinolines. He established a structure–activity relationship focussing on the influence of the substitution pattern in position 3 and 6 of the heterocycle on antisecretory activity, lipophilicity, and pKa value. Potent inhibitors of the gastric acid pump were identified [11].

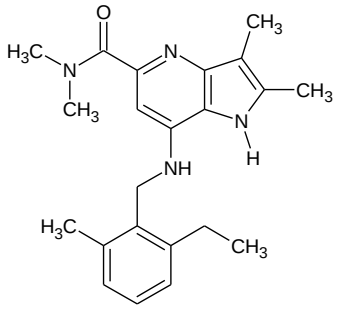


$R^3$ = H, $CH_3$, Br, $CH_2OH$

$R^6$ = carboxylic acid amide

**Potent Inhibitors**

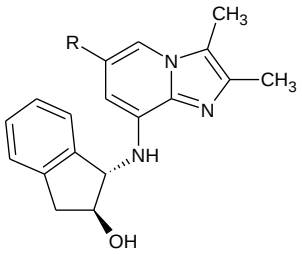
*Andreas Marc Palmer et al* reported a series of novel 1H-pyrrolo [3, 2-b] pyridines, A structure–activity relationship was established focusing on the influence of the substitution pattern in position 1, 3, and 5 of the heterocycle on anti-secretory activity, lipophilicity, and pKa value. Some of the compounds proved to be potent inhibitors of the gastric acid pump [12].



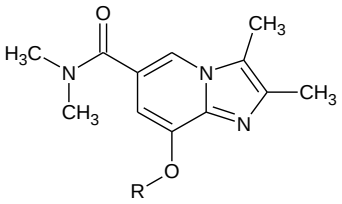
7-((2-ethyl-6-methylbenzyl)amino)-*N*,*N*,2,3-tetramethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxamide

**Potent Inhibitor**

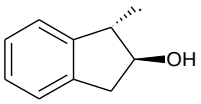
*Peter Jan Zimmermann et al* reported a series of novel 8-indanyl amino- and 8-indanyloxy-substituted imidazo [1, 2-a] pyridines. The anti-secretory activity of these compounds was tested against $H^+/K^+$-ATPase. Some of the compounds proved to be potent inhibitors of the gastric acid pump [13].

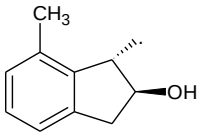


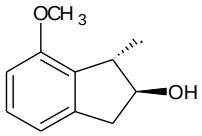
R = -CONH 2, -CONHCH 3, -CON(CH 3)2,
-CONHCH 2CH2OCH 3



R =

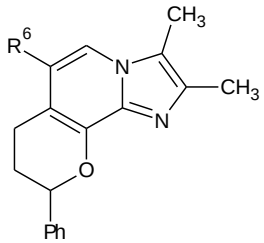






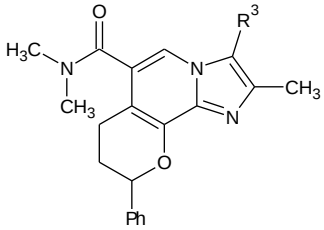
**Potent Inhibitors**

*Andreas M. Palmer et al* reported the synthesis of 7*H*-8, 9-Dihydropyrano [2, 3-*c*] imidazo [1, 2-*a*] pyridines based on Claisen rearrangement/cross-metathesis reaction or on the (asymmetric) reduction of prochiral ketones as interesting candidates for further development as potassium competitive acid blockers (P-CABs). The effect of substituents R3, R6, and Ar on the biological activity and the physicochemical properties of the target compounds were examined. A carboxamide residue showed improved in vivo activity. Whereas variation of R3 is useful for modification in basicity and lipophilicity and strong inhibition of the $H^+/K^+$-ATPase. Small modifications of the aryl group are responsible for the gastric acid secretion inhibiting action, whereas the enantiomers are virtually inactive [14].

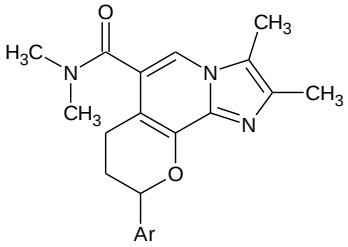


$R^6$ = -CON(CH 3)2, -CONH 2, -CONHCH 3,

substituted aziridine, azitidine,pyrrolidine



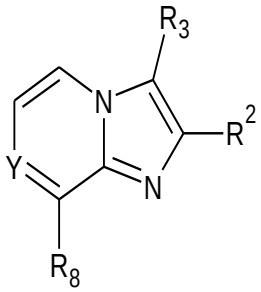
R3 = -CH 3, -CH 2OH, -CON(CH 3)2, Br, -CH 2CH 3, CH 3COCH 3



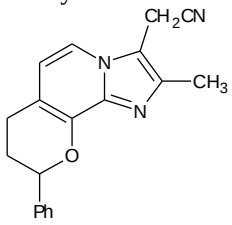
Ar = 2CH 3 C6H5, 2 FC 6H5, 4 F C 6H5

**Potent Inhibitors**

*James J. Kaminski et al* reported comparative molecular field analysis (CoMFA) and hypothetical active site lattice (HASL) methodologies study of substituted imidazo [1, 2-a] pyridines. Furthermore, the steric and electrostatic effects also studied by these two independent methods and their influence on determining biological activity were identified [15].

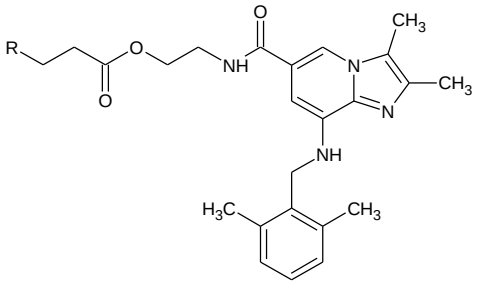



Potent Analogue



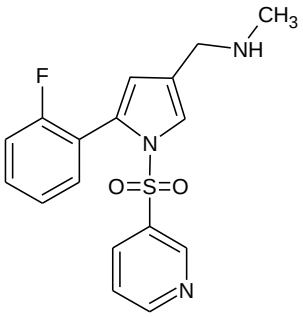

(2-methyl-9-phenyl-8,9-dihydro-7*H*-imidazo[1,2-*a*]pyrano[2,3-*c*]pyridin-3-yl)acetonitrile

*Dahlstrom and Mikael et al* reported the synthesis of Imidazo [1, 2-a] pyridines Where R-$CH_2COOH$ or COOH used against gastric acid secretion [16].



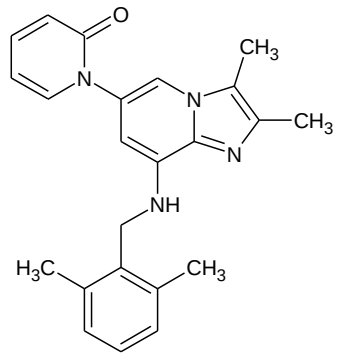

**Potent Inhibitors**

*Scott D. R. et al* reported a new alternative to PPIs is the pyrrolo-pyridine, vonoprazan (TAK-438), a potassium-competitive acid blocker (PCAB) that does not require acid protection. In contrast to other PCABs, vonoprazan has a long duration of action, resulting in 24-h control of acid secretion [17].



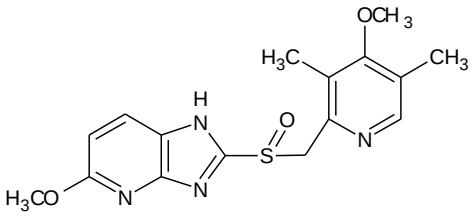

**Vonoprazan**

*Nick Bailey et al* reported AZD-0865 an acid pump antagonists which have proven efficacious at low oral doses in acid related gastric disorders. He described broader SAR in this class of molecule and discovery of an imidazo [1, 2-a] pyridine. The discovery strategy focused on use of heteroaryl and heterocyclic substituents at the C-6 position [18].



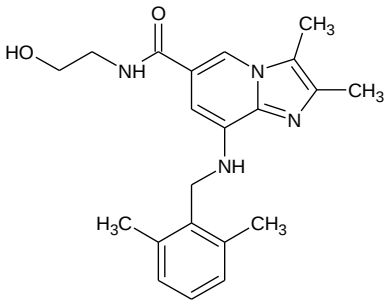
**Analogue of AZD-0865.**

*Kazuyuki Uchiyama et al* reported the study of 5-methoxy-2-{[(4-methoxy-3, 5-dimethylpyrid-2-yl) methyl] sulphinyl}-1**H**-imidazo [4, 5-**B**] pyridine (TU-199) as an Acid Pump Antagonist (APA). The effect of TU-199 on gastric acid secretion was found more potent than $H^+/K^+$-ATPase inhibitors. Study also suggested that TU-199 might have potent and long-lasting effects on gastric acid secretion and act as APA [19].



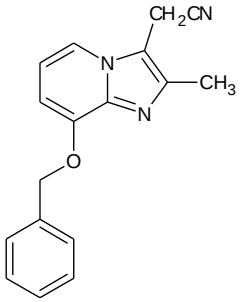
**TU-199**

*Karin Gedda et al* reported AZD0865 as a member of a drug class that inhibits gastric $H^+/K^+$-ATPase by $K^+$-competitive binding. The objective of these experiments was to characterize the mechanism of action, selectivity and inhibitory potency of AZD0865 in vitro. Finally it was concluded that AZD0865 potently with $K^+$ competitively, and selectively inhibits gastric $H^+/K^+$-ATPase activity and acid formation in vitro, with a fast onset of action [1].



**AZD 0865**

*James J. Kaminski et al* described conformational studies of substituted imidazo- [1, 2-a] pyridines with their antiulcer activity and investigated by using a variety of experimental and theoretical methods. The results was the identification of two distinctly different candidates, designated the 'folded" and the "extended" conformation, to represent the two possible minimum-energy conformations of compound SCH-28080. Gastric antisecretory activity was found to only in the trans isomers, which mimic the "extended" conformation. This observation led to the construction of 8, 9-dihydro-2-methyl-9-phenyl-7H-imidazo [l, 2-a] pyrano [2, 3 pyridine-3-acetonitrile, a rigid tricyclic analogue that is effectively locked in the "extended" conformation and that exhibited an antiulcer profile comparable to that of prototype compound. These results demonstrated that, in accord with expectation for a drug operating at a specific receptor, the conformational characteristics of the molecule have a substantial effect in determining its antiulcer activity. More precisely, also demonstrated that the "extended" conformation of prototype compound that represents the "bioactive" form of the drug. These results on the basis of molecular probe confirmed these compounds as gastric proton pump inhibitors [20].




**SCH-28080**

*Yao-Kuang Wang et al* studied that proton pump inhibitors are the most potent acid suppressant and provides good eficacy in esophagitis healing and symptom relief, but with poor response to standard doses of PPIs. Many other drugs as Antacids, alginate, histamine type-2 receptor antagonists, and prokinetic agents are usually used as add-on therapy to PPI in clinical practice. It was concluded that novel therapeutic agents should be with lower esophageal sphincter relaxation, motility disorder, mucosal protection, and esophageal hypersensitivity. Newer PPIs with faster and longer duration of action and potassium-competitive acid blocker, acid suppressant, have also been investigated in clinical trials [2].

*Kjell Andersson and Enar Carlsson et al* studied current therapies to treat gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and other acid-related diseases either prevent stimulation of the parietal cell or inhibit gastric $H^+/K^+$-ATPase. These drugs block gastric $H^+/K^+$-ATPase by reversible and $K^+$-competitive ionic binding. In animal studies comparison of P-CABs with PPIs suggested some important pharmacodynamic differences. [3].

*Olga Vagin et al* reported that the gastric $H^+/K^+$-ATPase is inhibited selectively and $K^+$ competitively from its luminal surface by protonated imidazo [1, 2R] pyridines (e.g., SCH28080). Identification of the amino acids in the membrane domain that affect SCH28080 inhibition should provide a template for modeling a luminally directed vestibule in this enzyme, based on the crystal structure of the sr Ca-ATPase. Five conserved carboxylic residues, Glu343, Glu795, Glu820, Asp824, Glu936, and unique Lys791 in the $H^+/K^+$-ATPase were mutated, and the effects of mutations on the Ki for SCH28080, Vmax, and Km, app [$NH4^+$] were measured. A kinetic analysis of the ATP hydrolysis data indicated that all of these residues significantly affect the interaction of $NH4^+$ ions with the protein but only three of them, Glu795, Glu936, and Lys791, greatly affected SCH28080 inhibition. Mutation of Lys791 to Ser, the residue present in the SCH28080-insensitive $Na^+/K^+$-ATPase, resulted in a 20-fold decrease in SCH28080 affinity, suggesting an important role of this residue in SCH28080 selectivity of the $H^+/K^+$-ATPase versus $Na^+/K^+$-ATPase. It is suggested that the imidazopyridine moiety of SCH28080 in the protonated state interacts with residues near the negatively charged residues of the empty ion site from the luminal side. The possibility of the SCH28080 binding site depends on the presence of Lys791, Glu936, and Glu795 of H,K-ATPase [21].

## CONCLUSION

We identified several imidazo [1, 2-a] pyridine scaffold derivatives with excellent physicochemical and pharmacological properties that represent interesting candidates for further development as potassium-competitive acid blockers. Reversible proton pump inhibitors or antagonists are the future prospectives in the treatment of ulcer with greater activity and minimum side effects. Some of the potent compounds are SCH28080, Soraprazan, Revaprazan, Linaprazan, Vonoprazan, Tak- 438-1, AZD 0865, BY841.

## ACKNOWLEDGMENTS

We are thankful to the Principal, Smt. S. S. Patil College of Pharmacy, Chopda, for providing the research facility and guidance.

**Conflict of interests:**

Authors declare that they have no conflict of interest.

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