A SYSTEMATIC REVIEW OF BENZIMIDAZOLE DERIVATIVES AS AN ANTIULCER AGENT

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ABSTRACT

A series of benzimidazole derivatives have proven anti-ulcer activity as potential inhibitors of H^+/K^+ - ATPase. Therapeutic significance of these clinically useful drugs in treatment of peptic ulcer and associated gastrointestinal diseases encouraged the development of some more potent and significant compounds. The pathophysiology of disease, different disorders associated with gastric acid secretion, physiology of gastric acid secretion, structural and molecular chemistry of the benzimidazole derivatives, possible mode of action are discussed. This comprehensive study summarizes the different derivatives of substituted benzimidazole along with their biological evaluation and factors that make benzimidazole more specific for proton pump inhibitors.

Keywords: *Gastric acid secretion, Acid gastric disorders, Therapeutic strategies, Substituted benzimidazoles, Biological activity*.

INTRODUCTION

The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux-oesophagitis and nonsteroidal anti-inflammatory drug-induced lesions[1].Many issues responsible for the imbalance between aggressive factors (like acid, pepsin, *H.pylori* infection) and local mucosa defense (secretion of bicarbonates, mucus and prostaglandin) results in acid-peptic and duodenal ulcer, gastroesophagal reflux disease, Zolinger-ellision syndrome and gastritis[2]. This disease seems to have very prominent share in health disorder in current scenario of globalization.

Treatment of ulcer diseases is prominently focused on reduction of aggressive factors and strengthening mucosal defense of stomach and duodenum. These are all treated by blocking acid secretion through proton pump inhibitors such as benzimidazole derivatives**.** The discovery of benzimidazole derivatives as proton pump inhibitors may be traced back to the 1960 when Fort *et al*, Sachs and Hirschowitz[3] described K^+ stimulated phosphatase activity in the gastric mucosa. It was shown later that a K^+ dependent ATPase acidifies a vesicular compartment in the dog gastric mucosa, subsequently attributed to an electroneutral H^+/K^+ exchange. This biochemical work coincided with synthetic work focusing on gastric acid inhibition by substituted benzimidazoles.These derivatives potently inhibit gastric proton pump by converting into active metabolite, that is, thiophilic cyclic sulphenamides. This transformation takes place in the luminal compartment of secreting parietal cell.

Almost all benzimidazole derivatives with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of these drugs. Tissue selectivity of this type of antiulcer drugs is based on both their pH dependent accumulation, as weak bases in the acidic compartment of secreting

parietal cell, and the subsequent acid-induced rearrangement of the parent compound to the pharmacologically active principle[3]. The enzyme H^+/K^+ATPase is responsible for gastric acid production and is located in the secretary membranes of the parietal cell[4]. Gastric acid secretion is regulated by interaction of basolateral parietal cell receptors with their physiological stimulants gastrin, acetylcholine, and histamine[5]. The irreversible inhibition of the H^+/K^+ATPase, a means of controlling gastric pH has attracted considerable attention in recent years with the discovery of the benzimidazole sulfoxide class of antisecretory agents. Synthesis and utility of novel substituted benzimidazole derivatives is evaluated by their ability to inhibit gastric H^+/K^+ATPase and by blocking the gastric acid secretion[6].

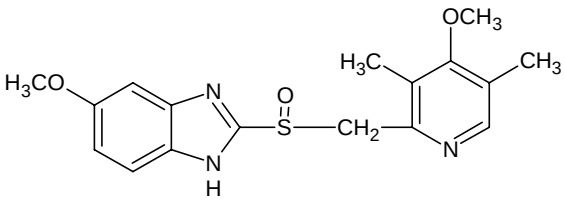
The macroaerophilic bacterium *Helicobacter pylori* has been recognized as the major cause of gastritis, a significant determinant in peptic and duodenal ulcer disease and gastric cancer. Benzimidazole class of many substituted compounds such as 2-[[(2-pyridyl) methyl] thio]-1-H benzimidazole has shown selective activities against gastric pathogen *Helicobacter pylori,* the probable mechanism being as inhibitor of *H.pylori*[7,8].

Various therapeutics strategies have been utilized for the acid induced ulcer, such as acid neutralizing agents, acid inhibitory agents, antigastrin agents, ulcer insulators and promoters of ulcer healing agents[9]. Various irreversible acting pyridinyl methyl sulfinyl benzimidazole derivatives have been synthesized but only few of them are potent and are in current use[2].(Fig.1.) This review concentrates on recent benzimidazole derivatives and their biological activity as antiulcer agents from the year 1990-2005.

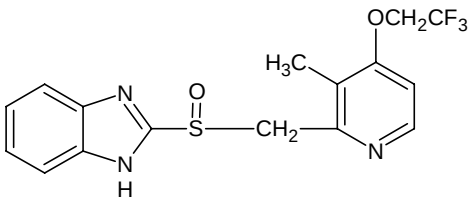
SUBSTITUTION ON BENZIMIDAZOLE NUCLEUS AND EFFECT ON ANTIULCER ACTIVITY

In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity[10-13]. It was also showed that substitution on pyridine by electron donating group increases activity. In 1991 benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl acetamido thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity[14-17]. Subsequently in 1992 Katsura *et al*[19] prepared compounds with substitution of dimethyl imidazopyridine at sixth position of benzimidazole showing strong antisecretory activity. Pantoprazole synthesis by Bernhard *et al* [20] explained role of methoxy group of pyridine for maximum biological activity. Introduction of rigid ring with benzimidazole and their conversion to biological active sulfenamide in acidic media has been verified by Shin-ichi *et al* [21] in 1994. Kohl *et al* [22] substituted pyridine by triazole 3-yl 1-3 dithiane and reported promising results when biologically evaluated against *H.Pylori.*

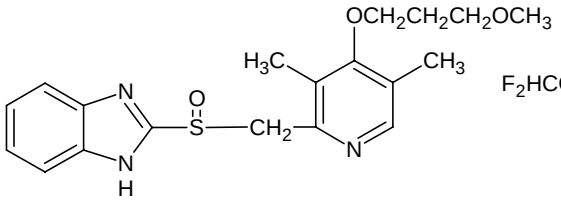
One more approach was applied to reduce the basicity of ring nitrogen of pyridine and to reduce irreversibility of compound with enzyme by using pyrimidine as ring substituent by Shimamura *et al* [23] in 1995. Synthesis of Leminiprazole was carried out by replacing pyridine with phenyl isobutyl methyl amine reported by Tsukahara *et al*[26] in 1996 showing potent proton pump inhibitory activity. Further in 1997 Yum *et al* [27]replaced pyridine by 2,2 dimethyl pyrranopyridine ring. Yoo *et al*[28] synthesized 2- dimethyl amino thiazo cyclobenzene benzimidazole showed good proton pump inhibitory activity. Woo T *et al*[26] in 1998 replaced pyridine with pyrrolobenzimidazolyl moiety, which showed proton pump inhibitory activity. Synthesis of Esomeprazole by asymmetric oxidation of prochiral sulfide of omeprazole showed potent antiulcer activity reported by Hanna *et al* [29]in 2000.



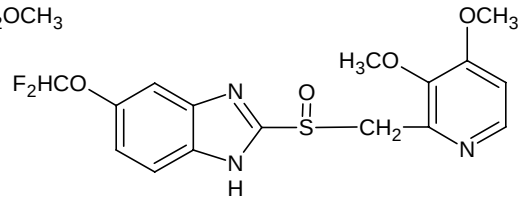
Omeprazole 1



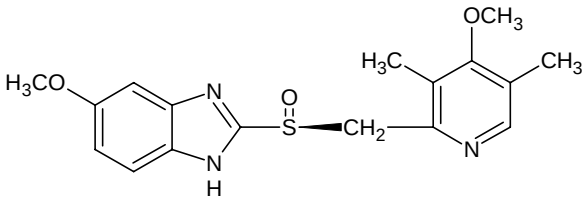
Lansoprazole 2



Rabeprazole 3



Pantoprazole 4

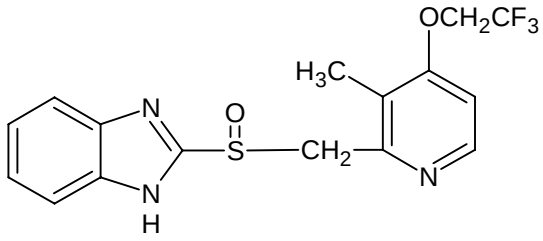


Esomeprazole 5

Figure 1: Established antiulcer agents in clinical practice

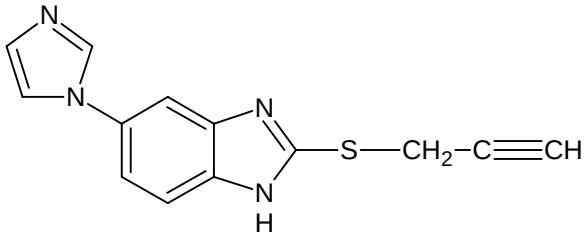
In 2002 pyridine substituted by phenyl sulfanyl ethanol, carbamates and benzimidazole substituted by methyl acetate showed high stability, absorption and good antiulcer activity[1,31]. Grast *et al* [32] in 2003 substituted benzimidazole at first position by pyridyl sulfinyl and resulted in potentially active compounds. Recently substitution was carried out by n- propyl and N-(1 cyclohex-3-enylmethyl) piperidin-4-yl)-5-carboxamide and resulted in significant antiulcer activity, explained by shrinivasulu *et al* [33] in 2005**.**

In 1990 it was known that introduction of fluorine to a molecule increases both thermal and oxidative stability, alters chemical reactivity and/ or enhances the rate of absorption and transport. Keiji Kubo *et al* [10] reported the synthesis of 2-[(3-methyl , 4- trifluro ethoxy) 2-pyridyl) methyl , sulfinyl] benzimidazole **6** which showed antisecretory, antiulcer , cytoprotective activity. After examining the pharmacological and toxicological properties Lansoprazole **6** was selected as a promising antiulcer agent.



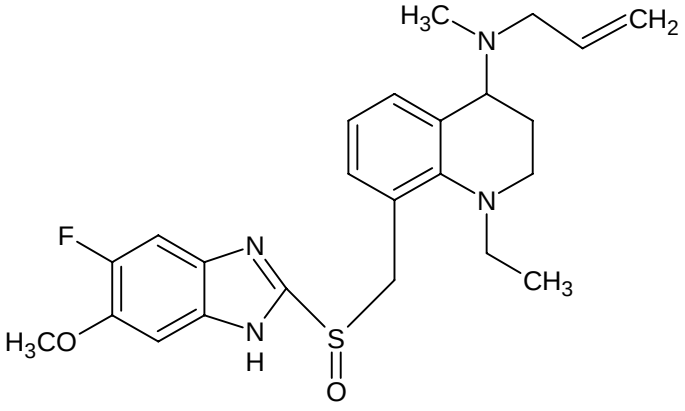
6

Brumagniez *et al* [11] reported the synthesis of 2-(thiopropyne)- 5- (imidazole -1-yl.) benzimidazole **7** which exhibited moderate antiulcer activity against ulcer induced by anti inflammatory agents in rats orally.



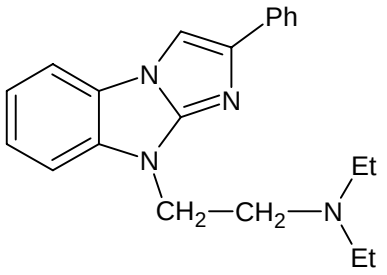
7

The synthesis of 2-[[(1- ethyl , 4- N-methyl –N – (1 propene) 1,2,3,4 tetrahydro quinoline- 8 yl) methylsulfinyl] 5- fluro , 6- methoxy benzimidazole **8** by Minoru Uchida *et al* [12] showed high activity. It appears from these results that the presence of basic amino group may be an important contributing factor in activity of the molecule.



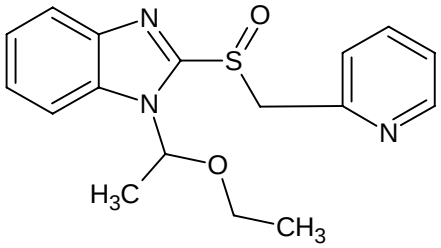
8

Kovalev *et al* [13] reported the synthesis of 9-(diethyl amino ethylene) 2 – phenyl imidazo [1,2-a] benzimidazole **9** which was found to be more potent than omeprazole.



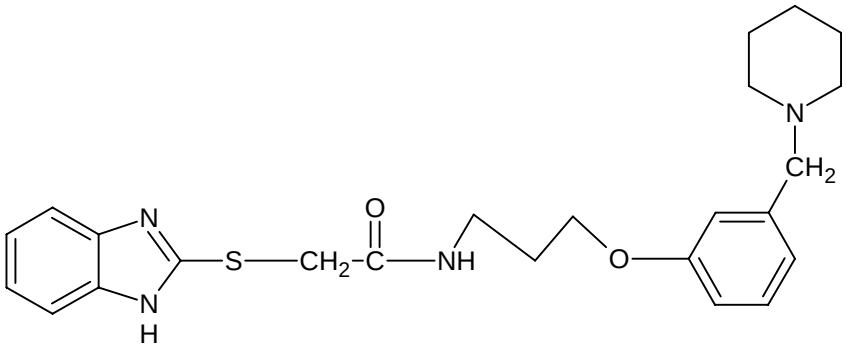
9

It has been found that many omeprazole like compounds undergo decomposition by rapid purple coloration in aqueous solution, limited shelf life and tend to colorize during storage. Omeprazole is effective in enteric coated capsule, otherwise the drug will be destroyed in acidic compartment of stomach. The chemical instability and biological activity of omeprazole appear to be associated with behavior of N-H substituent of benzimidazole ring and its transformation to sulfenamide. It was thought that derivatization at N-H position would render omeprazole more chemically stable for storage, handling and formulation for oral and parentral formulation and could make it more bioavailable. Many N-H substituted derivatives were synthesized such as N-hydroxy methyl and N-hydroxy ethyl ester, N-carbalkoxy, N-carbaryloxy, N-carbobenzyloxy ester which showed greater chemical stability and good *in vivo* antisecretory, gastroprotective and proton pump inhibitory activity than parent N-H compound. Sih *et al* [6] reported the synthesis of 1- (diethyl ether 2-yl) 2- pyridyl, methyl, sulfinyl benzimidazole **10** which showed good antiulcer activity.



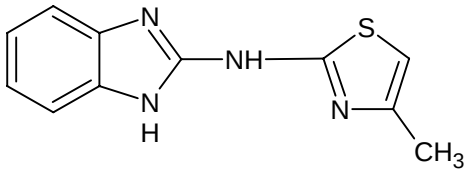
10

Endo *et al* [14] reported the synthesis of 2- [[(3- piperido methyl phenoxy) propyl] acetamido thio] benzimidazole **11** which however did not show much activity.



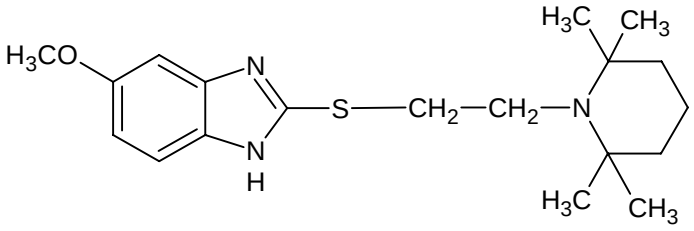
11

Compound 2-(2′-benzimidazolyl)-amino-4-methyl-thiazol showed good gastroprotective and antisecretory effect than other standard drugs in many experimental ulcer models reported by Alessandro *et al*[15], and it was thought that the sulphur in thiazole ring **12** may be implicated in gastroprotective action.



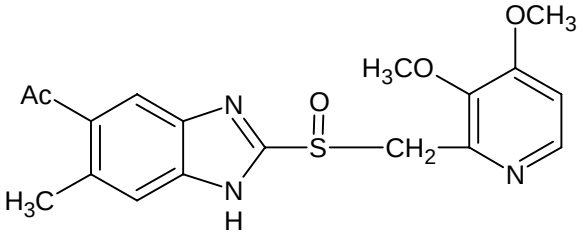
12

Katano *et al*[16] reported the synthesis of 2 - [(2, 2, 6, 6 tetramethyl piperidine) ethyl thio] 5-methoxy benzimidazole **13** which showed moderate activity.



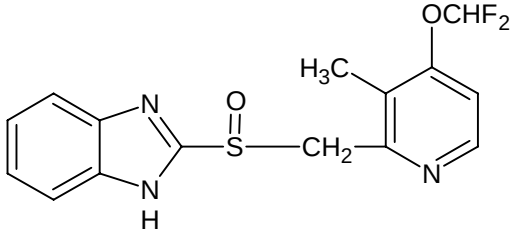
13

Braendstroem *et al* [17] reported the synthesis of 2- [(3, 4 dimethoxy, 2 –pyridyl) methyl, sulfinyl] 5- acetyl, 6-methyl benzimidazole **14** which inhibited gastric acid secretion in dogs.



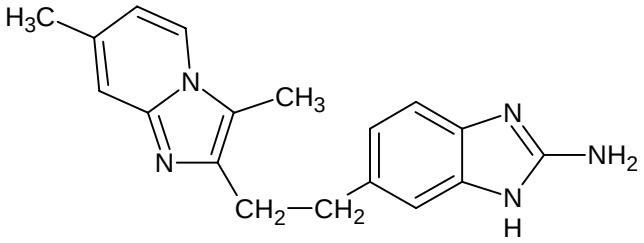
14

2- [(3-methyl, 4-difluromethoxy, 2-pyridyl) methyl, sulfinyl] benzimidazole **15** inhibited ethanol induced ulcers in rats orally studied by Sohda *et al* [18].



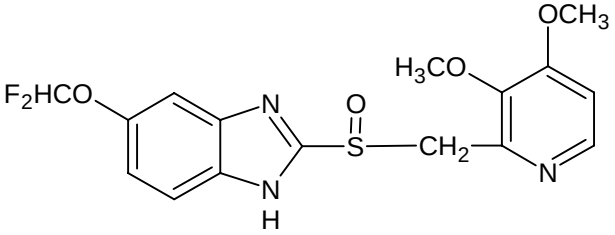
15

2 amino 6- [[2-(3, 6 dimethyl imidazo) (1, 2- α) pyridine 2-yl] ethyl] benzimidazole 16 synthesized by Katsura *et al* [19] exhibited strong antisecretory activity.



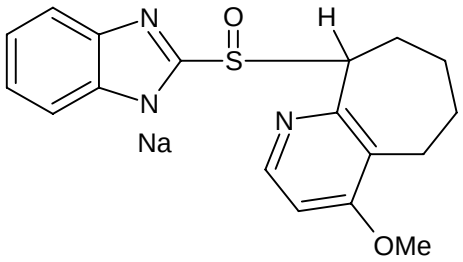
16

The introduction of 3- methoxy group produced inhibitors possessing a combination of high potency, similar to omeprazole and lansoprazole and increased stability. As a result of these studies, Pantoprazole **17** was selected as drug for further clinical studies reported by Bernhard *et al* [20]. The design of selective inhibitors was guided by modulating the pyridine basicity by substituent in 3 & 5 positions.



17

Shin-ichi *et al* [21] reported the synthesis of 2- [(4- methoxy , 6,7,8,9- tetra hydro- 5H – cyclohepta (b) pyridine –9-yl) sulfinyl] 1-H benzimidazole sodium salt **18** which showed promising antiulcer activity and stability on isolated H^+/K^+-ATPase of rabbit gastric mucosa. Introduction of a rigid ring system was expected to influence a process of chemical transformation in acidic medium to biologically active sulfenamide from parent compound.



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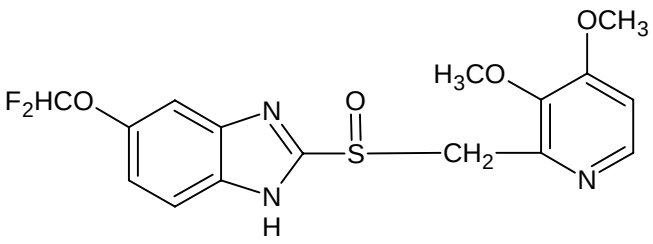
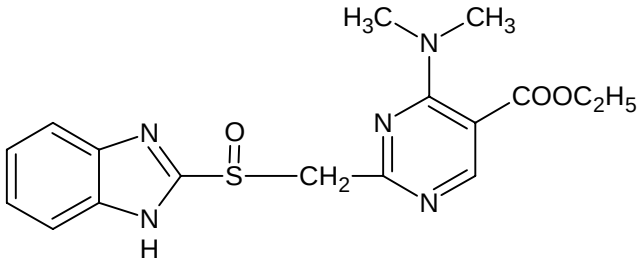
18

Bernhard *et al* [22] showed that 2-[(difluro methoxy-2-pyridyl)methyl sulfinyl] 5- difluromethoxy benzimidazole **19** was highly active against H^+/K^+-ATPase.



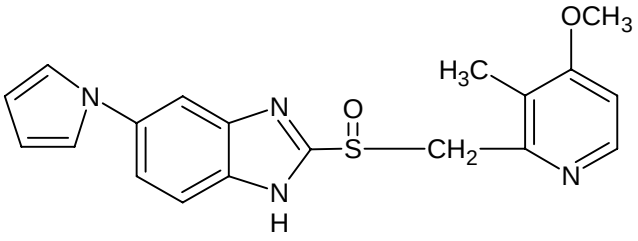
19

The synthesis of 2-[(4-dimethyl amino, 5 carboxylate 2 pyrimidinyl) methyl sulfinyl] benzimidazole **20** in which the pyridine nucleus of omeprazole is replaced by ethyl 4- dimethyl amino-5- pyrimidine carboxylate reported by Shimamura *et al* [23] showed good antiulcer , gastroprotective and antisecretory activity.



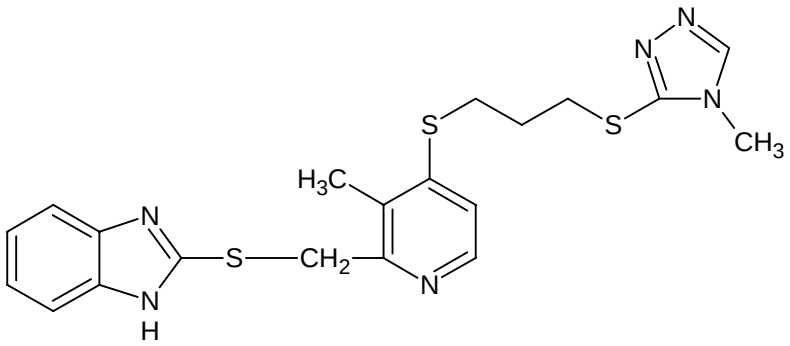
20

Kim *et al* [24] reported the synthesis of 2-[(3-methyl, 4-methoxy, 2-pyridyl) methyl, sulfinyl 5- (1-pyrrolyl) benzimidazole **21** which showed moderate activity against H^+/K^+ATPase with low toxicity.



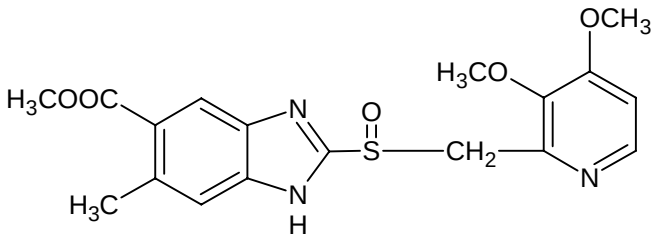
21

Kohl *et al* [22] reported the synthesis of 2-[3-methyl,4 (N-methyl, 1,2,4 triazole 3 yl, 1,3 dithiane,) 2 pyridyl] methyl thio benzimidazole **22** which showed high activity against *Helicobacter Pylori.*



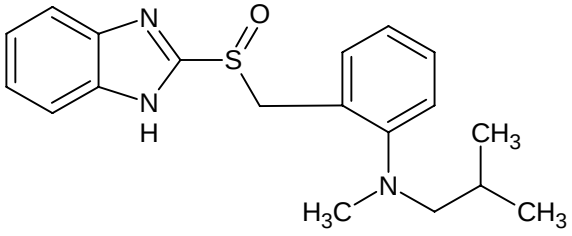
22

Braendstroem *et al* [25] reported the synthesis of Methyl 2- ((3,4-dimethoxypyridin-2-yl) methylsulfinyl)-6-methyl-1H-benzimidazole-5-carboxylate **23** which showed high activity in dog & rat.



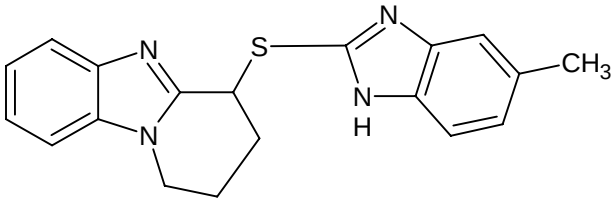
23

The synthesis of 2- (1-H benzimidazole 2-sulfinyl methyl) phenyl isobutyl methyl amine **24** reported by Tsukahara *et al* [26] showed good antiulcer activity.



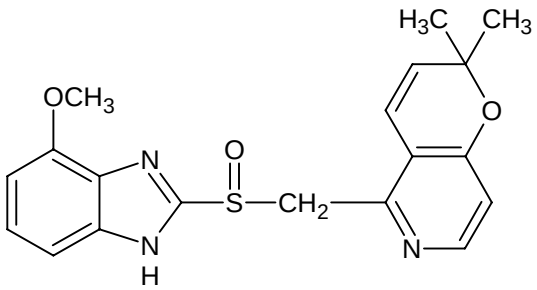
24

2- [3 (2,3 dihydro 1- H pyrrolo [1,2-a] benzimidazolyl) sulfinyl] 5-methyl benzimidazole (YJA 20379-4) **25** showed effect on H^+/K^+ATPase, *H.Pylori* ,mucosal defense and antiulcer activity reported by Woo T. *et al* [26].



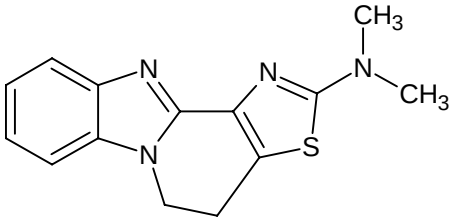
25

Yum *et al* [27] reported the synthesis of 2- [[2,2 dimethyl 2-H pyrrano (3,2,c) 2- pyridyl] methyl, sulfinyl] 4- methoxy benzimidazole **26** which showed high activity against H^+ / K^+ ATPase.



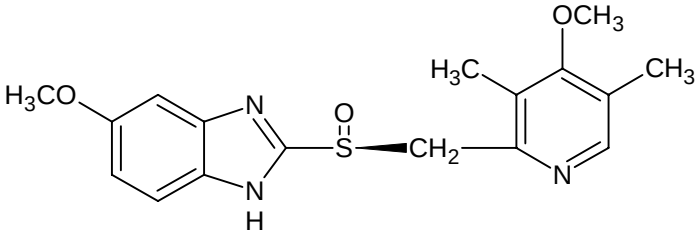
26

Yoo *et al* [28] reported the synthesis of 2-dimethyl amino thiazo [4,5] cyclobenzene [1,2] benzimidazole **27** which showed moderate activity.



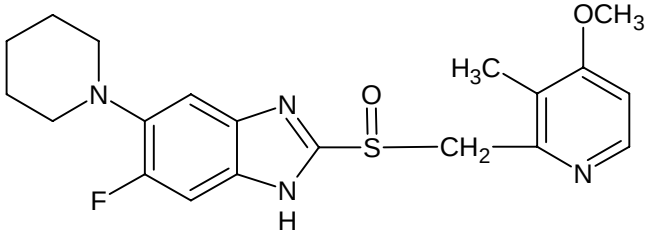
27

Efficient synthesis of Esomeprazole **28** was carried out by Hanna *et al* [29] in 2000 by asymmetric oxidation of prochiral sulphide of omeprazole. It was achieved by titanium mediated oxidation with cumene hydroperoxide in presence of (S-S) diethyltartrate. Further it was believed that N-H group of imidazole is important for the enantioselectivity.



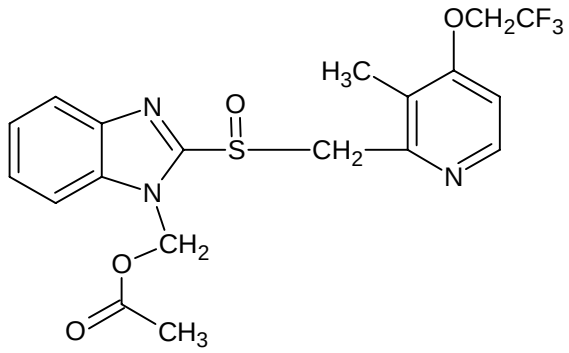
28

Lohray *et al* [30]reported the synthesis of 2- [(3-methyl, 4-methoxy, 2 pyridyl) methyl, sulfinyl] 5-piperidine, 6-fluro benzimidazole **29** showed high activity.



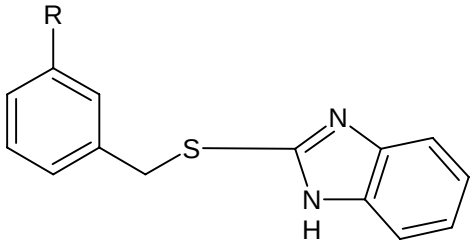
29

Kamiyama *et al* [31] reported the synthesis of 1- methyl acetate, 2- [(3-methyl,4- trifluro ethoxy 2-pyridyl) methyl, sulfinyl] benzimidazole **30** showed excellent antiulcer, gastric acid secretion inhibitory, mucosa protecting, anti *H pylori* effect in *vivo*. This compound also showed low toxicity, high stability to acid, higher absorption rate than enteric preparation and long lasting effect.



30

The 2-[{ 3-[(1-H benzimidazole -2-yl sulfanyl) methyl] –phenyl] sulfanyl) -1- ethanol **31a** and 2-({3-[(1-H benzimidazole 2-yl sulfanyl) methyl]-2-methyl phenyl]}sulfanyl) ethyl carbamates **31b** derived successfully by Daniel *et al*[1] displayed potent and selective activities against *H.Pylori*. The substitution of hydrogen with sulphur in 3 position of phenyl ring of these structures proved to be beneficial in improving potency. Tolerance was also observed by larger substitution such as isobutyl, ----(CH_2CH_2O)$_3$ CH_3, ----(CH_2CH_2O)$_5$$CH_3$, ---$CH_2CH_2$--and 4-morpholinyl groups.

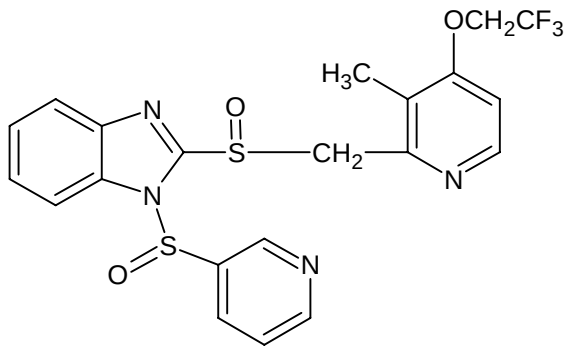


a R== ---S--CH_2--CH_2--OH

b R== --S--CH_2 CH_2 OC ONH Ph

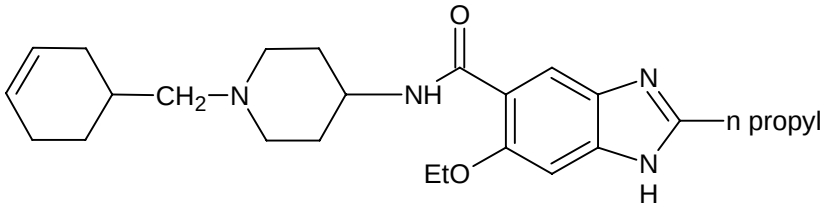
31

Garst *et al* [32] reported the synthesis of 1- (3-pyridyl sulfinyl) –2 [(3-methyl, 4 trifluroethoxy, 2 pyridyl) methyl, sulfinyl] benzimidazole **32** which exhibited proton pump inhibitory activity and was highly effective in treatment of diseases caused by gastric acid secretion.



32

Shrinivasulu *et al* [33] reported the synthesis of 2- n propyl, 5 (N methyl 3, 4 cyclo hexane, 4 amino piperidine) keto, 6 ethoxy, benzimidazole **33** which exhibited good antiulcer activity.



33

CONCLUSION

In the treatment of acid peptic disorders a landmark event in the history of therapeutics was introduction of H_2 receptor antagonist, cimetidine in 1976. The condition in which H_2 blockers lacked efficacy narrated the development of proton pump inhibitors such as Omeprazole, with its ability to induce prolong acid suppression in 1988.

In the benzimidazole derivatives degree of nucleophilicity of pyridine nitrogen is important for formation of sulfenamide intermediate which is the active molecule. Factors such as steric effect, pka value and degree of nucleophilicity are optimal for antiulcer activity of benzimidazole derivatives. Electron donating and withdrawing group of pyridine & benzimidazole and linking chain plays important role in structure activity relationship and stability of benzimidazole derivatives. The long lasting inhibition of gastric secretion by proton pump inhibitors showed an indirect pharmacodynamic consequence i.e. ECL- cell hyperplasia and some apparent drawbacks such as extreme irreversible gastric acid suppression, achlorhydria, hypergastrenemia, carcinoma and affinity for cytochrome 450. Hence researchers have been attracted toward designing of reversible, shorter, and rapid acting acid pump antagonist. Thus, acid pump antagonists are the important future drugs for treatment of acid-peptic disorders.

REFERENCES

1. D. Carcanague, Y.K.Shue, M.A.Wuonola, M.U.Nickelsen, C.Joubran, J.K.Abedi, J.Jones and T.C.Kuhler, *J. Med. Chem.*, **45**, 4300-4309 (2002).
2. S.Robert, I.M. McDonald, Burger's Medicinal Chemistry & Drug Discovery, 6th ed; John Wiley and Sons, New Jersey, Page No.86-121 (2003).
3. W.Kromer, *Digestion*, **56,** 443-454 (1995).

4. P.Lindberg,P. Nordberg,T. Alminger, A. Bradstrom, B. Wallmark, *J. Med. Chem.,* **29**, 1327-1329 (1986).
5. R.J.Ife, C.A.Dyke, D.J.Keeling, E.Meemam, M.L.Meesoon, M.E.Parson, C.A.Price, C.J.Theobald and A.H.Underwood, *J.Med. Chem.,* **32**, 1970-1977 (1989).
6. J.C.Sih, W.B.Im, A.Robert, D.R.Graber, D.P.Blackmann, *J.Med. Chem.*, **34**, 1049 - 1062(1991).
7. T.C.Kuhler, J.Fryklund, N.Bergman, J.Weilitz, A.Lee, and H. Larsson, *J.Med. Chem.* ,**38**,4906-4916 (1995).
8. D.Carcanague,Y.K.Shue,M.A.Wuonola,M.U.Nickelsen,C.Joubran,J.K.Abedi,J.Jo nes,T.C.Kuhler, *J. Med. Chem.* ,**45**,4300-4309 (2002).
9. S.D.Seth, Text Book of Pharmacology, 2nd ed; Elsevier, New Delhi, Page No. 390-391(1999).
10. K.Kubo, K.Oda, T Kaneko, H.Satoh, A.Nohara, *Chem. Pharm. Bull*., **38** (10), 2853-2858 (1990).
11. B.Nicole,G.Timur, L.Jean, L.Michele, T.J. Marie, Eur. Patent No. 385850 (1990).
12. M.Uchida, M.Chihiro, S.Morita, H.Yamashita, *Chem.Pharm.Bull*., **38**(6)1575-1586 (1990).
13. G.V.Kovalev, A.A.Spasor, P.A.Bakumov, M.E.Reshetov, V.A.Anisimova, *Himiko-Farmatsevticheskii Zhurnal*, **24**(2) 127-30 (1990).
14. E.Isamu, O.Tadashi, M.Masazumi, K.Shingo, T.Takaaki, Japanese Patent No. 03148263 (1991).
15. Grassi, J.Ippen, M.Bruno and G.Thomas, *Eur.J.Pharmacology*,**195**,251-259 (1991).
16. K.Kiyoaki, T.Tamaka, O. Hiroko, H.Fumiya, Y.Yasukatsu, K. Fukio, Eur Patent No.457331 (1991).
17. Braendstroem, A.E.Lindberg, P.Lennart, Sunden, G. Elisabeth, World Patent No. 9119712 (1991).
18. S.Takashi, I.Nobuhiro, Eur Patent No.481764 (1992).
19. K.Yousuke,I.Yoshikazu, N.Shigetaka, T.Massaaki, T. Hisashi, *Chem.Pharm.Bull.,* **40**(7) ,1818-22 (1992).
20. B.Kohl, E.Sturm, J.S.Blifinger,W.Alexander,S.V. Kruger, *J. Med. Chem.,* **35**, 1049-1057 (1992).
21. S.Yamada,T.Goto , E.Shimanuki and S. Narita , *Chem. Pharm. Bull*., **42** (3), 718—20 (1994).
22. K.Bernhard, G.Gerhard, S.B.Joerg, O.Wolfgang, World Patent No.9501351 (1995).
23. S.Hiroshi,T.Koji, K.Akito, I.Yasuhiro, K.Isami, K.Asyoshi, K.Mikiko, S. Makota, *Chem. Pharm. Bull*., **43** (1) ,166-168 (1995).
24. K.S.Ung, K.D.Yeon, C.G.JU, H.S.Kol, P.S.Jun, N.S. Hoon, L.Y. Suk, World Patent No. 9523140 (1995).
25. B.A.Elof, S.I.Kerstin, T.Hijelte, L.Inaera, World Patent No. 9515962 (1995).
26. K.S.Jain,A.K.Shah,J.Bariwal,S.M.Shelke,A.P.Kale,J.R.Jagtap,A.V.Bhosale, *Bioorg. Med. Chem.*, **15**, 1181-1205 (2007).
27. Y.E.Kaun, C.J.Kwon, C.S.Yun, K.S.Kyu, World Patent No. 9700875 (1997).
28. Y.H.Yong, C.K.Jong, C.Mansik, K.S.Gyu, C.W.Soo, World Patent No.9703077 (1997).
29. H.Cotton, T. Elebring, M. Larsson, L. Li, *Tetrahedron Asymm.*, **11**, 3819-3825 (2000).

30. B.B.Lohray, V.B.Lohray, G.P.Kommireddi, US Patent No. 6051570 (2000).
31. K.Keiji, S. Fumihiko, World Patent No. 2002030920 (2002).
32. G. Michael, S. George, S.J. Moo, US Patent No.6559167 (2003).
33. S.G. Reddy, P.P. Hegde, P.C.Ranjan, *Het. Comm.*, **11**(1), 23-28 (2005).

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An expert is a man who has made all the mistakes, which can be made in a very narrow field.
-Niels Bohr