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REVIEW ARTICLE

Biology and Chemistry of Benzimidazole Derivatives as Antiulcer Agents: A Review

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Clinical drugs

ABSTRACT: A flexible heterocyclic moiety found in many synthetic and natural compounds is benzimidazole. Because of its wide-ranging effects, it has drawn interest from researchers all around the world for the treatment of many illnesses. Many proton pump inhibitors that have received clinical approval have been available in the market since the discovery of Omeprazole in 1988, which was the first inhibitor based on benzimidazole. But the primary focus of research is on the necessity of pursuing specific goals in order to lessen the adverse effects of proton pump inhibitors. In order to achieve these goals, numerous different proton pump inhibitor medication combinations have also been tested. At the moment, clinical trials are being conducted on a few novel and inventive formulations. In order to set the stage for future investigations, a thorough analysis of antiulcer benzimidazoles was conducted. Researchers and academicians would find this review paper useful in their efforts to create less hazardous and more therapeutically active benzimidazoles. To the best of our knowledge, this study is the first attempt to compile important developments on benzimidazoles that have been suggested as antiulcer drugs.

INTRODUCTION

The benzimidazole moiety sparked popular interest in 1944 when Woolley's research revealed that it shared structural similarities with biotin and purines, meaning it could function similarly to purines in inducing certain biological reactions [1]. However, Brink later identified 5, 6-dimethylbenzimidaozle as a vitamin B12 degradation product and discovered that several of its derivatives had activity similar to that of vitamin B12. Despite this breakthrough, it was not taken seriously [2,3]. Certain compounds of substituted benzimidazoles have notable antifungal activity [4].

Due to its structural similarities to several moieties found in vitamins, proteins, and nucleic acids, the benzimidazole structure has drawn and continues to draw a great deal of interest from medicinal chemists. Benzimidazoles have a significant role in both synthetic and biological medicinal chemistry approaches. Periodically, a number of review publications on the benzimidazole moiety and its many biological actions are released [5-12].

The disorders Zolinger-ellision syndrome, duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, and peptic ulcer are becoming more common worldwide, especially in poorer nations. Approximately 10% of the global population is impacted, and a survey conducted in 2015 revealed 267,500 deaths [13,14].

The initial discovery on H. pylori was the cause of peptic ulcers as reported in [15]. Peptic ulcers and chronic

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gastritis are caused by the gram-negative bacterium Helicobacter pylori, which grows in the mucous layer of the stomach epithelium. Because urease enzyme activity is inhibited, benamidazoles are effective against H. pylori [16,17]. According to certain published reports, a PPI should be taken in addition to two or three antibiotics for a synergistic effect that will be more successful than H2RAs in eliminating H. pylori [18,19].

The stomach secretes a digestive fluid called gastric acid, which is primarily made up of sodium chloride (NaCl), potassium chloride (KCl), and hydrochloric acid (HCl). An essential component of digestion is gastric acid. The mucous secreted by mucous cells creates a protective layer on the stomach cells, preventing the stomach from eroding, and is one of the natural defense mechanisms of the stomach. Moreover, the pancreas generates bicarbonate to counteract stomach acid. However, an imbalance between these two variables leads to Zolinger-ellision syndrome, gastroesophageal reflux disease, duodenal ulcers, peptic ulcers, and stomach ulcers [20].

The primary component of gastric juice, hydrochloric acid, is generated by parietal cells. Parietal cells are made up of a vast network of secretory structures called canaliculi, from which hydrochloric acid is secreted into the stomach lumen. Proton pump inhibitors, or PPIs, are medications that block the proton pump H^+/K^+ ATPase (Hydrogen-Potassium Adenosine Triphosphatase), which is primarily responsible for maintaining acidity [21]. The last stage of acid secretion is proton transport by the gastric (H^+/K^+)-ATPase. Because they create an irreversible covalent bond between the enzyme and the cysteine disulphide (-S-S-) bond of H^+/K^+-ATPase (a proton pump) at the secretary surface of the gastric parietal cell, it was estimated that drugs that inhibit this step could be more effective inhibitors. The only way to start secreting gastric acid again is if new enzymes start to form [22]. The physiological stimulants gastrin, acetylcholine, and histamine interact with basolateral parietal cell receptors to regulate gastric acid secretion [23].

The primary working mechanism of proton pump inhibitors (PPIs) is dependent upon three factors. They are firstly weakly basic (pKa 3.8-4.5) because they contain a pyridine group. They are able to accumulate selectively in the highly acidic secretary canaliculus of the parietal cell due to their weak basic nature. The second is the parietal cells' need for an acidic pH. The third step involves the PPIs' activation into their active forms, sulphenic acid and sulfonamide, within the acidic canaliculus environment. The production of gastric acid is inhibited by these active forms because they form disulfide bonds with the cysteins of the H^+ K^+-ATPase [24–26]. PPIs are unable to block every gastric pump because not all pump enzymes are always active. They are rapidly metabolized by the liver, giving them short half-lives of 60 to 90 minutes. Only roughly 70% of pumps are inhibited due to their short half-lives and the fact that not all pump enzymes are activated [27]. Because of this, achieving maximum acid suppression requires some time—roughly three days [28]. The slow action of gastric acid pumps is caused by the activation of the three previously mentioned factors and the conversion of inactive pumps to active states [29]. Because the PPIs that are currently on the market have issues with chemical instability and half-lives. Thus, there are numerous efforts underway to find novel PPI prodrugs [30]. A number of novel PPIs and their combinations, as well as other benzimidazole derivatives like extended release, are undergoing clinical trials. PPIs, Prokinetic PPIs and P-CABs are also in market which are shown in (Figure 1).

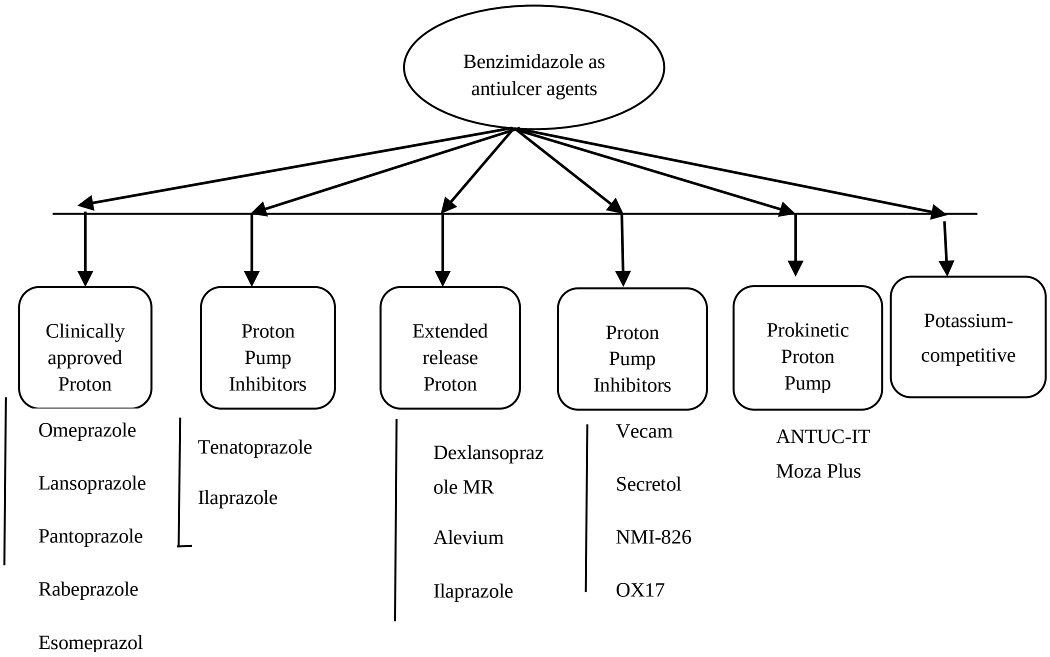


Figure 1. Benzimidazole derivatives as antiulcer agents.

For acid-induced ulcers, a variety of therapeutic approaches have been used, including ulcer insulators, anti-gastric agents, neutralizing and inhibiting agents, and promoters of ulcer healing agents [31].

The focus of this review is on the biological activity of benzimidazole derivatives as antiulcer agents between 2000 and till present date.

Chemistry of Benzimidazole

A class of heterocyclic, aromatic chemicals known as benzimidazole shares a basic structural feature: six-membered benzene fused to a five-membered imidazole [32]. It contains hydrogen bound to nitrogen at the 1-position, which causes hydrogen to tautomerise in benzimidazole (Figure 2(a-b).

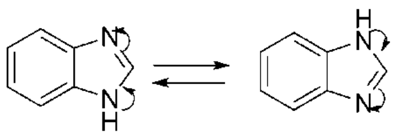


Figure 2(a). Tautomerism in Benzimidazole.

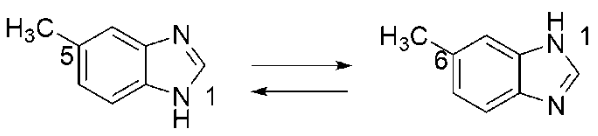


Figure 2(b). Tautomerism in 5(or 6)-methylbenzimidazole.

These two are tautomers even though they appear to be isomers. A tautomer of 6-methylbenzimidazole is 5-methylbenzimidazole. Ring nitrogens are important because they use a range of forces to interact with different types of receptors and enzymes in biological systems [33–35]. In benzimidazole, the NH group at position 1 has a weak basicity and is comparatively strongly acidic [36].

Benzimidazole derivatives for ulcer treatment

Benzimidazole derivatives as clinically approved/established drugs

The majority of benziimidazole derivatives with antiulcer properties are in the class of proton pump inhibitors. In the realm of antiulcer medications, PPIs offer a novel strategy for the efficient suppression of stomach acid production [37]. The first was omeprazole, which was released in 1988. With their SAR study, pantoprazole **5**, rabeprazole **6**, lansoprazole **3**, and omeprazole **4** are now well-established proton pump inhibitors in clinical practice [38] as depicted in (Figure 3).

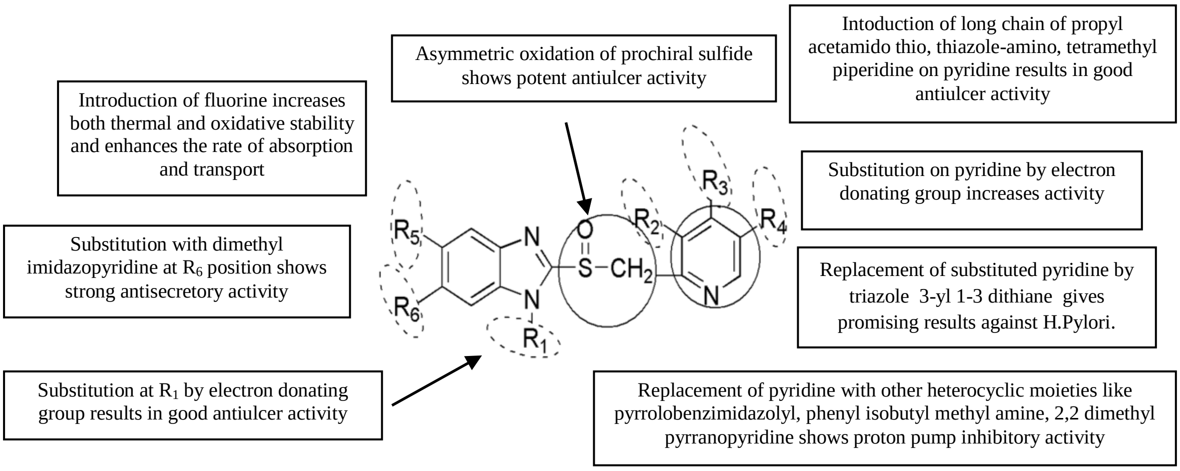
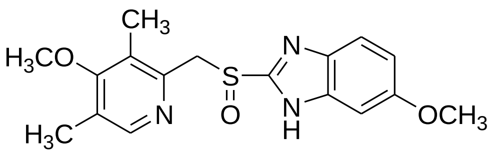


Figure 3. Benzimidazoles as clinically approved proton pump inhibitors (PPIs) with their SAR study.

According to the structure-activity relationship study, strong antiulcer agents have been produced by substituting different substituents at positions 1, 2, 5, and 6 of the benzimidazole nucleus. On the other hand, the nucleus's positions 3, 4, and 7 are empty (Figure-3). Benzimidazole's 1-position can be left unsubstituted or can have aryl or heteroaryl moieties suitably substituted with groups that donate electrons. Similarly, good antiulcer activity is obtained by introducing a long chain of propyl, acetamido, thio, thiazole-amino, and tetramethyl piperidine on the pyridine ring at position 2. PPI activity is observed when pyridine is substituted with other heterocyclic compounds such as pyrrolobenzimidazolyl or phenyl isobutyl methylamine. Dimethylimidazopyridine has a potent antisecretory effect. The nucleus's 5 or 6 positions may be unsubstituted, or substituents may come from functional groups like halogens. Omeprazole (3) was a breakthrough drug discovered in 1979. It was reported to be the most potent substance and did not cause any significant side effects in the initial animal repeat-dose toxicity studies. Its effectiveness in humans was initially documented in 1983. Literature review shows that in an acidic environment, omeprazole is converted to its sulfenic acid and sulfenamide derivatives, which then form a covalent disulfide bond with the Cys 813 sulfhydral group [39,40]. Additionally, it was discovered to be beneficial in the management of persistent Zollinger-Ellison syndrome. The most promising antiulcer drug, lansoprazole **4**, was discovered by Kubo et al. in 1990. It possesses cytoprotective, antisecretory, and antiulcer properties that outperform those of omeprazole [42]. The drug pantoprazole (5) was produced by substituting certain functional groups on the pyridine ring, such as methyl and trifluoroalkoxy with methoxy. This resulted in a drug with increased stability and potency comparable to omeprazole **3** and lansoprazole **4** [43]. All benzimidazoles as clinically approved drugs are shown in Figure 4.



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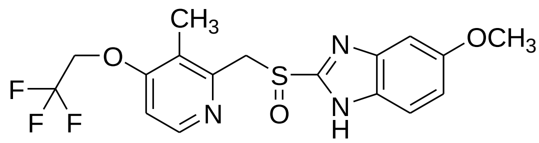

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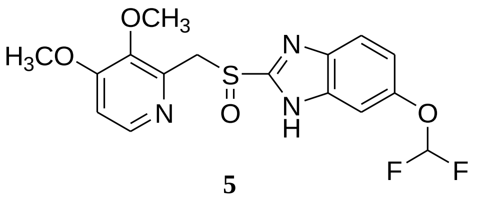

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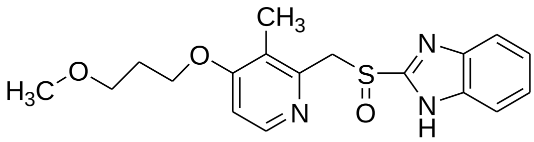

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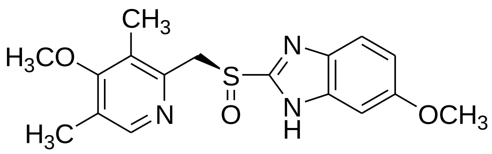

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Figure 4. Benzimidazoles as clinically approved drugs.

2007 saw the introduction of Rabeprazole **6**, a medication that functions more quickly and effectively thanks to additional pyridine nucleus modification [42] To enhance the pharmacokinetic characteristics of omeprazole **3**, esomeprazole **7**, which is the S-enantiomer of omeprazole, demonstrated greater acid inhibition potency when compared to other proton pump inhibitors [44].

Through a distinct mode of action, substituted benzimidazoles block the H^+/K^+ ATPase, the proton pump of the parietal cell. When certain stimuli are present, these substituted benzimidazoles have the ability to prevent the secretion of stomach acid. A study of the relationship between structure and activity has revealed that the sulfoxide group, a heterocyclic methylene group, is crucial for activity [45] as shown in Figure 3.

PPIs are acknowledged as the best treatments currently on the market for conditions linked to acidity. Compared to H2RAs, they offer improved rates of healing and symptom control for both PUD (Peptic Ulcer Disease) and GERD (Gastroesophagal Reflux Disease). However, the drawbacks of a delayed acute effect onset and a slow full effect development led to the adoption of several alternative therapeutic approaches to meet the goal [46]. Among these, the combination of PPIs with other medications, P-CABs, and extended release proton pump inhibitors are being processed, as indicated in Table 1.

Table 1. PPIs and Combination of PPIs in clinical Trials.

Group	Drug	Clinical trials
PPIs	Ilaprazole	Phase II. Randomized multicenter study
	Tenatoprazole	Phase III
PPIs combinations	NMI 826	Phase II
	OX17	Phase II
	Vecam Omeprazole + lansoprazole	Phase I
	PPI + alginate	Phase III

Extended release proton pump inhibitors

The controlled and prolonged drug release of these PPI formulations with extended release makes them popular. Takeda Pharmaceuticals sells the dual delayed-release formulation of dexlansoprazole (the R-enantiomer of lansoprazole), known as Dexlansoprazole MR 8 (Figure 5). The medication comes in capsule form, each containing two different kinds of granules with a coating that dissolves at a different pH of 6.8 and 5.5, respectively [47,48]. Unlike other delayed PPIs, it can be taken without consideration for meals [49].

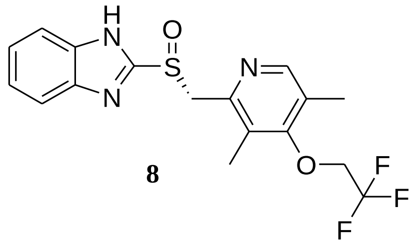

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Figure 5. Dexlansoprazole MR.

AGN201904-Z (Alevium)

The omeprazole prodrug AGN201904-Z (Alevium) **9** (Figure 6) is acid-stable. It therefore has a long plasma half-life and does not need an enteric coating to protect itself from acid. It is quickly hydrolyzed to omeprazole in vivo [50].

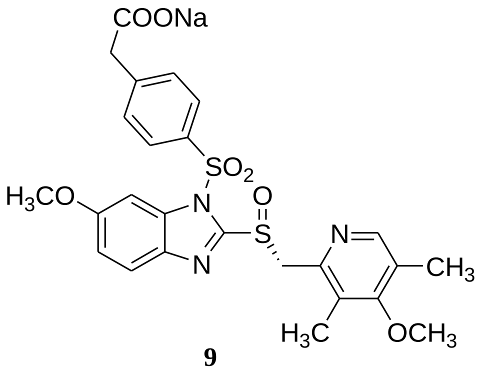

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Figure 6. Alevium.

Ilaprazole

Ilaprazole **10** (Figure 7), also known as compound IY-81149, shares chemical similarities with lansoprazole and omeprazole [51, 52] as shown in Figure 7. It undergoes extensive metabolism to produce ilaprazole sulfone as the main metabolite. The patent license for ilaprazole in China (license ID: CN 1121714 A) is held by Livzon Pharmaceutical Group Inc. (China), who is currently developing the drug after Il-Yang (South Korea) synthesizes it.

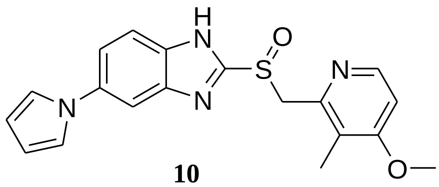

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Figure 7. Ilaprazole.

PPI combinations

Proton pump inhibitor-VB101 (Vecam)

Omeprazole and succinic acid are combined to create the combination medication Vecam, which causes the parietal cells' proton pumps to open. The administration of PPI without consideration for food is the primary goal. Succinic acid activates proton pumps, which increases PPI's effectiveness [53].

Secretol

Omiprazole and lansoprazole are combined in the medication known as secretol. Phase II trials are being conducted to compare it to esomeprazole in terms of healing and symptom control for patients with EE (Eosinophilic esophagitis).

NMI-826

Nitric oxide (NO) and PPI are combined to form NMI-826. It has been discovered that the combination heals stomach ulcers more effectively than a PPI by itself [54].

OX17

OX17 is omeprazole and famotidine combined. Compared to omeprazole alone, this combination has been shown to be 60% more effective at maintaining intragastric pH levels above 4. Recently, a novel tenatoprazole and H2RA combination was patented [55].

Prokinetic PPI

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The medication contains itopride (prokinetic action) and rabeprazole (PPI). Rabeprazole inhibits the acid secretion's last stage. Itopride is a derivative of prokinetic benzamide that has gastrokinetic effects and inhibits dopamine [56].

***Moza* plus**

Combination of pantoprazole plus mosapride is marketed under the name Moza *Plus [57]*.

Potassium-competitive acid blockers

A novel class of medication known as potassium-competitive acid blockers, or P-CABs, functions similarly to proton pump inhibitors (PPIs). Nonetheless, they bind to the K^+-binding region of the H^+, K^+-ATPase because of their structural specificity. P-CABs are medications that lower stomach acid by inhibiting ATPase K^+-competitively. It has been reported that certain new benzimidazole carboxamides function as P-CABs **11** (Figure 8). They have lower pKb values and are very stable both chemically and metabolically. They have dose-dependent pharmacokinetics that are linear and rapidly reach high plasma concentrations after oral administration. Their quick start of action will undoubtedly determine this new class's role in treating illnesses linked to acidity [58-60].

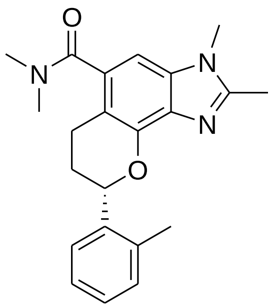

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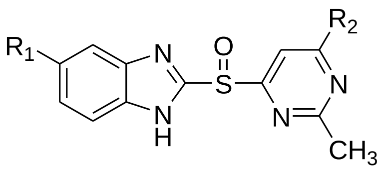
Figure 8. Potassium competitive acid blocker.

Other benzimidazole analogs as Antiulcer agents

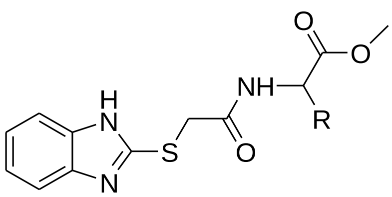
Authors created new substituted benzimidazole derivatives (Figure 9) and used pharmacological screening to look for their H^+/ K^+ ATPase inhibitors and antiulcer properties. Comparing certain compounds to the standard drug, such as **12c** (74.03%), 12f (72.87%), and **12i** (75.15%), they demonstrated highly significant antiulcer activity; similarly, compound **12c** (88.88%), **12d** (91.03%), **12f** (86.48%), and **12g** (84.21%) demonstrated highly significant anti-secretory activity [61].



12c=R_1=H, R_2=C_3H_7
12d=R_1=CH_3, R_2=CH_3
12f=R_1=CH_3 , R_2=C_3H_7
12g=R_1=NO_2, R_2=CH_3
12i=R_1=NO_2 , R_2=C_3H_7

Figure 9. 2,5- substituted benzimidazole derivatives.

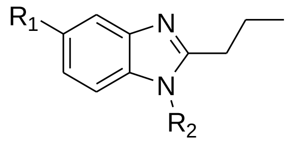
2-mercaptobenzimidazole amino acid conjugates (Figure 10) were synthesized and assessed for their anti-secretory activity. Compounds **13f** and **13j** demonstrated a noteworthy anti-ulcer effect, while compounds **13g** and **13k** demonstrated an anti-secretory effect [62].



13f = R = Phe
13g = R = Ala
13j = R = Ser
13k = R = Tyr

Figure 10. 2-mercaptobenzimidazole derivatives.

New methanesulphonamido-benzimidazole derivatives (Figure 11) were prepared by combining anti-inflammatory and antiulcer drugs. In order to achieve this, the methanesulphonamido function from anti-inflammatory drugs (nimesulide and rofecoxib) and the benzimidazole nucleus from antiulcer medications (lansoprazole, omeprazole, and ilaprazole) were combined to create novel compounds with properties and activities from both categories. The compounds **14**, **15**, and **16** were found in the study to be gastro-sparing anti-inflammatory agents [63].



14 R_1= -$NHSO_2CH_3$, R_2= -C_4H_9
15 R_1= -$NHSO_2CH_3$, R_2= -C_5H_{11}
16 R_1= -$NHSO_2CH_3$, R_2= -C_6H_{13}

Figure 11. Methanesulphonamido-benzimidazole derivatives.

In order to test for acute ulcerogenic activity,A number of novel 1, 2, and 3-substituted benzimidazole derivatives (Figure 12) were synthesized. Compound **17** stood out among the series as a noteworthy compound that lacked any irritating qualities for the stomach [64].

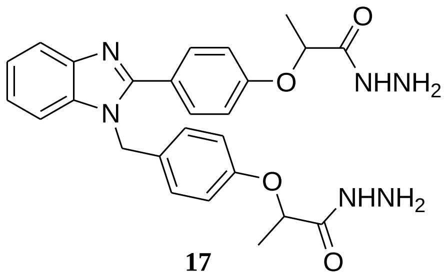


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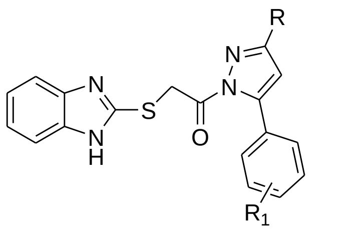
Figure 12. 1,2,3-substituted benzimidazole derivatives.

Six unique benzimidazole-pyrazole hybrids (Figure 13) **18a**, **18b**, **18c**, **18d**, **18e**, and **18f** were created and tested for their anti-ulcer properties. The outcomes showed strong antiulcer activity when compared to Omeprazole, the typical medication. The antiulcer activity was proposed by SAR research in connection with the substitution pattern on the two aromatic rings that are joined to the pyrazole ring. In order to determine how well these novel hybrid molecules interacted with the target H^+/K^+ ATPase compared to omeprazole, docking studies were also conducted. The Lipinski rule of five was used to evaluate the drug-likeness of molecules [65].



18a =R=C_6H_5, R_1=2-OH
18b =R=2-OHC_6H_5, R_1=2-OH
18c =R=2-OHC_6H_5, R_1=3-OH, 4-OCH_3
18d =R=4-OHC_6H_5NH, R_1=2-OH
18e =R=C_6H_5, R_1=H
18f =R=3-OH, 4-OCH_3, R_1=H

Figure 13. Benzimidazole-Pyrazole hybrids.

Recently, some hybrid benzimidazole derivatives (Figure 14) were created by combining pyridine derivative with 1-methyl-2-mercapto-5-nitro-1H-benzimidazole, and then tested for their' anti-ulcer properties biologically. The gastro-protective potential of compound **19** was demonstrated by the results and SAR study. This is believed to be because the compound has hydrophobic moieties and less steric hindrance surrounding the pyridine ring [66].

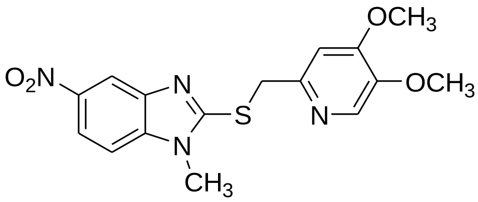


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Figure 14. 2- Mercaptobenzimidazole hybrids.

A novel benzimidazole derivative (Figure 15) was reported and evaluated for its impact on the development of ulcers and the release of gastric acid in rats. The importance of compound **20**, which offers defense against ulcers brought on by pylorus ligation, was demonstrated by the results [67].

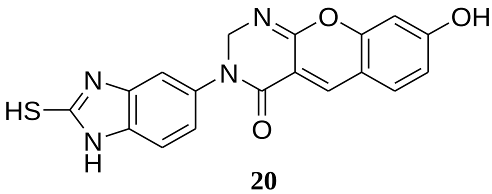

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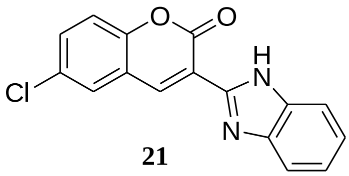
Figure 15. Benzimidazole derivative.

Some newcoumarin-benzimidazole derivatives (Figure 16) were designed by taking into consideration the anti-inflammatory properties of 3-substituted coumarins and the antiulcer activity of 2-substituted benzimidazole. An assessment of the ulcer index revealed that substances **21** and **22** are safe for the stomach mucosa [68].



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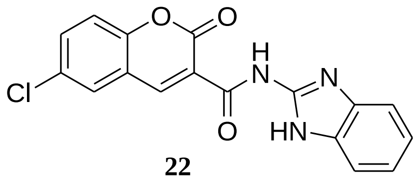

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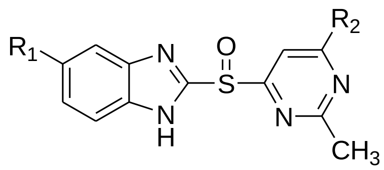
Figure 16. Coumarin-Benzimidazole derivatives.

A number of substituted 2-(pyrimidinylsulfinyl) benzimidazole derivatives (Figure 17) were reported and assessed for their antiulcer and anti-secretory properties. Early investigations revealed that compounds **23c** and **23d** demonstrated strong anti-secretory activity, while compounds **23a**, **23b**, and **23d** had good antiulcer activity with decreased toxicity [69].



23a =R_1=H, R_2=CH_3
23b =R_1=H, R_2=C_2H_5
23c =R_1=H, R_2=C_3H_7
23d =R_1=NO_2, R_2=C_3H_7

Figure 17. 2-(pyrimidinylsulfinyl) benzimidazole derivatives.

Analogs of benzoimidazole piperazine conjugated compounds (Figure 18) were reported and their in vivo antiulcer activity was evaluated. Out of all the synthesized analogs, compound **24** exhibited the strongest antiulcer properties. To determine the function of various functional groups accountable for increased activity, SAR research was also conducted. It was revealed that the activity of the 4-methoxy phenyl substituted for piperazine and attached to the benzimidazole moiety was caused by its electron-donating property [70].

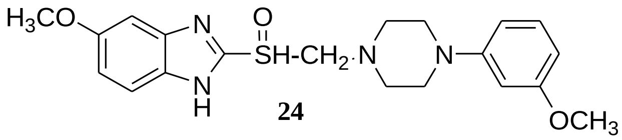


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Figure 18. Benzimidazole-Piperazine conjugated compounds.

A group of 3,4,5-trimethoxybenzylbenzimidazole derivatives with anti-H. pylori activity were reported by Chang et al. Compound 2-fluorophenyl-5-methyl-1-(3,4,5-trimethoxybenzyl)benzimidazole (FMTMB) **25** (Figure 19), the most potent of the series, was found. Additionally, an in vitro investigation revealed its mode of action, which involved FMTMB preventing H. pylori from adhering to and invading gastric epithelial cells [71].

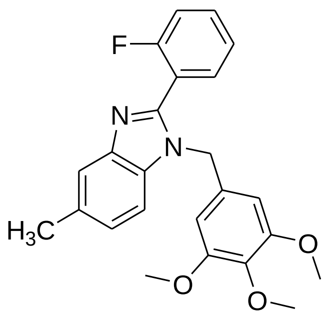

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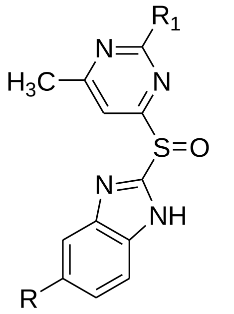
Figure 19. 2-fluorophenyl-5-methyl-1-(3,4,5-trimethoxybenzyl)benzimidazole.

By inhibiting stomach H^+ /K^+ - ATPase, derivatives made from pyrimidine and benzimidazoles (Figure 20) were assessed for their antiulcer and anti-secretory properties. The control dose was acetylsalicylic acid. When compared to the standard medication pentaprozole, sulfoxides **26(a-d)** demonstrated good antiulcer activity with lower toxicity, and compound **26(c,d)** demonstrated good anti-secretory activity [72].



26(a-c) R=H; d) $R=NO_2$
R_1=a) Methyl, b)Ethyl, c,d) Propyl

Figure 20. Benzimidazoles- Pyrimidine hybrids.

A new series of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives (Figure 21) were reported for the H^+ /K^+ -ATP enzyme inhibiton . Compound **27** showed notable in vitro activity within the series, with an IC50 value within the range of 1.6 × 10−5 M when compared to the reference medication, omeprazole [73].

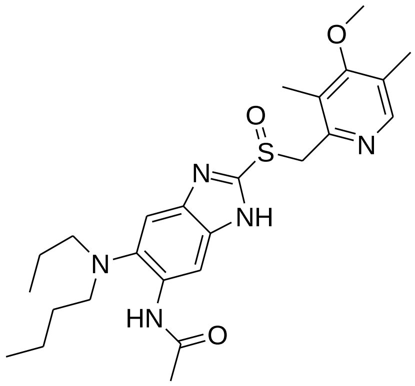


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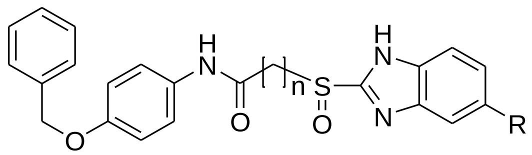
Figure 21. 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives.

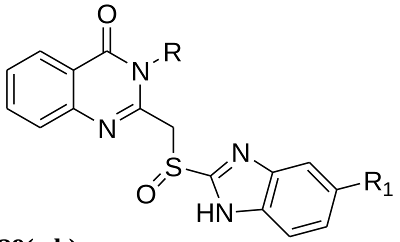
Six novel 2-substituted mercaptobenzimidazole derivatives (Figure 22.) were synthesized and assessed for their antiulcer activity. Of these, it was discovered that compounds **28a**, **28b**, and **28c** had significantly lower pH, gastric secretion volume, ulcer score, and free and total acidity [74].



28a = n=1, R=H
28b = n=3, R=H
28c = n=3, $R=OCH_3$

Figure 22. 2-substituted mercaptobenzimidazole derivatives.

Using the benzimidazole and quinazoline moieties, some novel compounds (Figure 23) were created, and their antiulcer activity was assessed against ulcers caused by pylorus ligation, aspirin, and ethanol in rat models. A study comparing compounds **29(a,b)** to the medicine Omeprazole at doses of 10 and 20 mg kg^{-1} demonstrated the compounds' strong activity. Remarkably, the SAR study stated that the dimethoxy phenyl with difluromethoxy and the benzimidazole sulfinyl methyl quinazoline substituted with 3-N pyrazine had the highest activity [75].



29(a,b)
a) R=3,4-Dimethoxy Phenyl, R_1=$OCHF_2$
b) R=2-Pyrazine, R_1= $OCHF_2$

Figure 23. Benzimidazole-Quinazoline hybrid derivatives.

As proton pump inhibitor prodrugs, Shin et al. (2009) synthesized 1-Arylsulfonyl-2-(Pyridylmethylsulfinyl) Benzimidazoles (Figure 24). Due to compounds' longer chemical stability in neutral and acidic environments—which eliminates the need for enteric coating—they were found to be more effective than PPIs. An additional benefit is that compounds can be dissolved in phosphate-buffered saline solution and then injected intravenously. Compound **30** was discovered to be the most effective series. In conclusion, their extended stability may prevent acid secretion in vivo for an extended period of time [76].

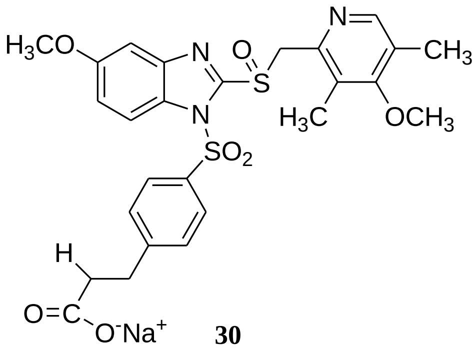


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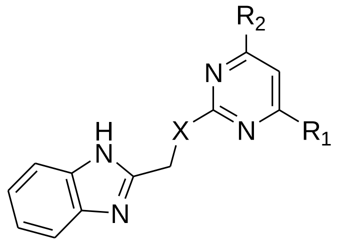
Figure 24. 1-Arylsulfonyl-2-(Pyridylmethylsulfinyl) Benzimidazoles.

Rat pylorus ligation was used by authors to test the antiulcer activity of a novel series of pyrimidylthiomethyl benzimidazoles **31(a-c)** and pyrimidylsulfinylmethyl benzimidazoles **32(a-c)** (Figure 25). Similar to omeprazole, compounds **31a** and **32a** significantly decreased the amount of gastric acid secreted, the amount of free acidity, and the number of gastric ulcers in the pylorus-ligated rats. Additional research revealed some new information about the superiority of thio analogs over sulfinyl derivative [77].

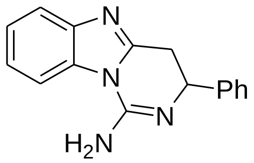


31(a-c), 32(a,c)

31: X=S a) R_1=CH_3, R_2=CH_3
32: X=SO b) R_1= CH_3, R_2=C_6H_5
c) R_1=OH, R_2= CH_3

Figure 25. Pyrimidylthiomethyl benzimidazoles.

Several novel benzimidazole derivatives (Figure 26) with strong antiulcer activity were reported. It was discovered that compounds **33**, **34** and **35** exhibited stronger antiulcer properties than the common medication, omeprazole [78].



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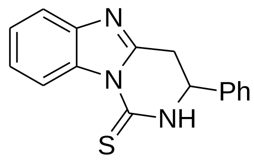

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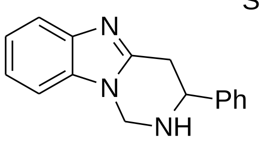

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Figure 26. Benzimidazole derivatives.

A novel benzimidazole derivative (Figure 27) with gastric antisecretory and anti-ulcer properties, ME3407 **36**, was described. The compound was structurally similar to leminoprazole and omeprazole (it contained a heteroaromatic sulfoxide moiety). However, since it only demonstrated activity upon oral administration and not upon parenteral administration, it was thought to operate via a different mechanism [79].

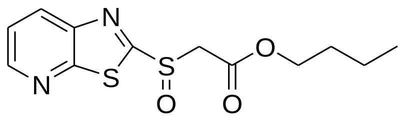

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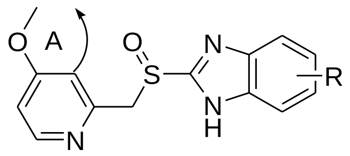
Figure 27. 2-substituted benzimidazole derivative.

The inhibitory and anti-secretory effects of oxycyclic pyridine-containing benzimidazole derivatives (Figure 28) on gastric H+/K+-ATPase were examined. While compounds containing furo [3,2-c]pyridine (37(h-i)) expressed nearly the same ATPase inhibitory and anti-secretory effect as that of 6-membered oxycyclicpyridines, compounds containing pyranopyridines **37(a-g)** demonstrated notable biological activities [80].

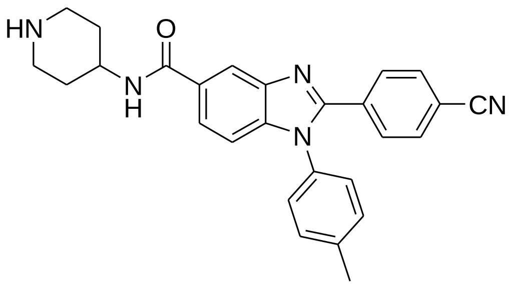


37(a-d): OA=OC$(CH_3)_2$CH=CH; a) R_1=H; b) R_2=4-OCH_3;c)5-OCH_3; d)4-Cl
37(e-g): OA=OC$(CH_3)_2CH_2CH_2$; e) H ; f) 4-OCH_3; g) 5-OCH_3
37(h-i): OA=OC=$(CH_3)_2$; h) 5-OCH_3; i) H

Figure 28. Oxycyclic pyridine-containing benzimidazole derivatives.

The anti-secretory activity of rival Omeprazole and proton pump inhibitors (lansoprazole, pantoprazole, and rabeprazole) for the treatment of ulcer disease was compared by authors. In order to compare their respective efficacies in suppressing acid secretion and preventing the accumulation of aminopyrine (AP) in isolated gastric glands, this study compared them. The superiority of lansoprazole and pantoprazole over other medications was shown by the result reports. But in isolated gastric glands, lansoprazole (4) seemed to be the most effective at preventing AP accumulation [81].

Using vonoprazan as the lead compound, a series of 1,2,5-substituted benzimidazole derivatives (Figure 29) were designed and synthesized using skeleton hopping and conformational restriction techniques. **38** (IC_{50} = 9.32 μM) and **39** (IC_{50} = 5.83 μM) compounds exhibited superior inhibition at the enzyme (H^+, K^+-ATPase) level among the synthesized compounds. The findings demonstrated that **38** and **39** compounds significantly inhibited basal gastric acid secretion. Furthermore, compounds **38** and **39** showed good stability and minimal toxicity [82].



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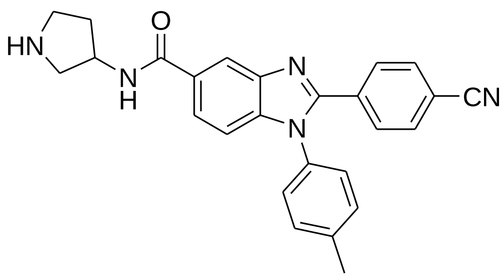

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Figure 29. 1,2,5 substituted benzimidazole derivatives.

Future directions

The discovery and development of drugs using benzimidazole scaffolds has attracted the interest of many academics and researchers to this field. Numerous benzimidazole derivatives are being investigated for the treatment of a variety of diseases in various clinical trials. With its undiscovered new powerful chemical entities, the benzimidazole scaffold combined with other potent moieties has the potential to revolutionize the field of medicine.

Even though there has been a lot of progress, there is still work to be done and it will continue until humanity survives because as time goes on, more and more diseases that are resistant to treatment or completely fatal will emerge. To propose in the following areas in relation to the benzimidazole moiety, some work is required. Acid-borne illnesses such as gastric ulcers, peptic ulcers, and GERD are prevalent in today's world. PPIs are primarily used to treat these conditions. It is necessary to enhance the PPI's activation mechanism and blood residence time.

A few more Changes must also be made to address issues with benzimidazole derivative toxicity, resistance, and low bioavailability. In recent times, the prodrug concept has been employed to enhance bioavailability. Gaining a thorough understanding of the mechanism underlying resistance development may help with resistance issues. The idea of bioisosterism can be applied to reduce toxicity. It's also necessary to investigate a few more substitution sites, such as benzimidazole's positions 4, 6, and 7.

CONCLUSIONS

Even though significant progress has been made in understanding the pathways leading to the release of acid secretion, new antiulcer drugs with minimal side effects have not yet been found. To treat disorders linked to acid secretion, a variety of clinically approved antiulcer medications (PPIs) and their creative combinations with other medications are being marketed. There is ongoing research that could result in novel and effective pharmaceutical discoveries.

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Conflict of interest

The author confirm that this article content has no conflicts of interest.

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