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Development of drugs based on Benzimidazole Heterocycle: Recent advancement and insights

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Abstract
Benzimidazole rings are the most important nitrogen-containing heterocycles, which are widely explored and utilized by the pharmaceutical industry for drug discovery. Due to their special structural features and electron-rich environment, Benzimidazole containing drugs bind to a variety of therapeutic targets, thereby exhibiting a broad spectrum of bioactivities. Numerous benzimidazole based drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potential.
Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms.
Due to their enormous medicinal value, the research and development of benzimidazole-containing drugs is an increasingly active and attractive topic of medicinal chemistry. This review enlightens about the chemistry of different derivatives of substituted benzimidazoles along with their pharmacological activities.
Furthermore, the present review also provides the recent advances in the development of benzimidazole-based drugs along with new perspectives. We hope that this paper will open up new opportunities for researchers to design future generation novel and potent benzimidazole containing drugs.

Keywords: Substituted Benzimidazoles, Chemistry, Pharmacological activities

1. Introduction
Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Heterocyclic compounds occupy a central position in medicinal chemistry and are of particular interest and significant importance in the search for new bioactive molecules in the pharmaceutical industry (GABA *et al.*, 2014) [46]. The nitrogen-containing heterocycles, in particular, exhibit diverse range of biological activities due in part to their similarities with many natural and synthetic molecules with known biological activities (DeSimone *et al.*, 2004) [31]. The benzimidazole rings have been commonly used as privileged scaffolds for the development of therapeutic molecules of pharmaceutical or biological interest.
Benzimidazole is a six membered bicyclic heteroaromatic compound in which benzene ring is fused to the 4- and 5-positions of imidazole ring. In 1872, Hoebrecker reported the first benzimidazole synthesis of 2, 5- and 2, 6-dimethylbenzimidazole by ring closure reaction of benzene-1,2-diamine derivatives (Wright, 1951) [93] and more interest in the area of benzimidazole based chemistry was developed in the 1950s, when 5,6-dimethyl-1-(a-D-ribofuranosyl) benzimidazole was found as an integral part of the structure of vitamin B12 (Barker *et al.*, 1960) [3]. Moreover in 1882, Radziszewski reported the first synthesis of highly substituted imidazoles by condensing 1, 2-diketones with different aldehydes in the presence of ammonia (Radziszewski, 1882) [94]. Afterward, the related research and drug discovery in this class of compounds are rapidly developing and have achieved great progress.
Benzimidazole ring contain two nitrogen atoms with amphoteric nature, i.e., possessing both acidic and basic characteristics. These rings exist in two equivalent tautomeric forms, in which the hydrogen atom can be located on either of the two nitrogen atoms (Fig. 1). Furthermore, the electron-rich nitrogen heterocycles could not only readily accept or donate protons, but also form diverse weak interactions easily.

These special structural features of benzimidazole rings with desirable electron rich characteristic is beneficial for benzimidazole derivatives to readily bind with a variety of therapeutic targets, thereby exhibiting broad pharmacological activities (Wright, 1951; Bhatnagar *et al.*, 2011; Ingle and Magar, 2011; Gaba *et al.*, 2010 [93,10, 69, 45]; Fig. 2). From the last decade, a diverse range of biological activities based on benzimidazole derivatives has been reviewed by several authors (Narasimhan *et al.*, 2011; Yadav and Ganguly, 2015; GABA Et Al., 2015) [95, 96, 47]. Their ubiquitous properties and important role in different diseases has attracted special interest in benzimidazole based medicinal chemistry. The work embodied in this article relates to the clinically useful benzimidazole containing drugs with their discovery and development. Moreover, the mechanism of action, SAR points as well as some opinions have been presented to help medicinal chemist and chemical biologist in designing invaluable novel drugs with benzimidazole cores for the treatment of different disorders. It is anticipated that this review will be helpful for new thoughts in the quest for rational design of more active and potent drugs in future research.

1.1 Benzimidazole-based drugs in the service of humankind

The benzimidazole scaffolds are extremely versatile and have featured a number of clinically used drugs such as antihistaminic, antiulcer, antihypertensive, antibacterial, antifungal, antiparasitic, antiemetic, anti- cancer, antiviral, and other therapeutic agents with high therapeutic potency and market value. Therefore, it is worthwhile to get insight into the discovery and development of benzimidazole containing drugs along with their mechanism of action for future endeavors.

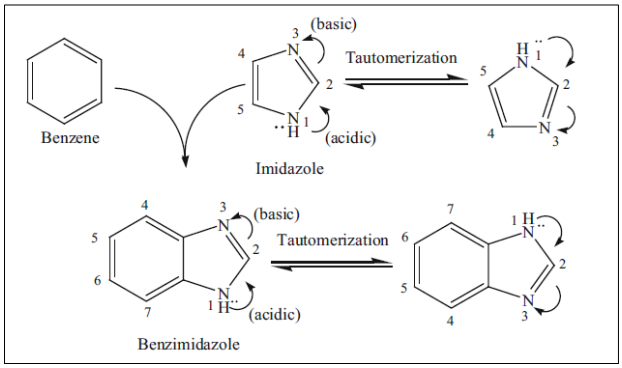

Fig 1: Benzene and imidazole ring fusion and imidazole–benzimidazole tautomerism

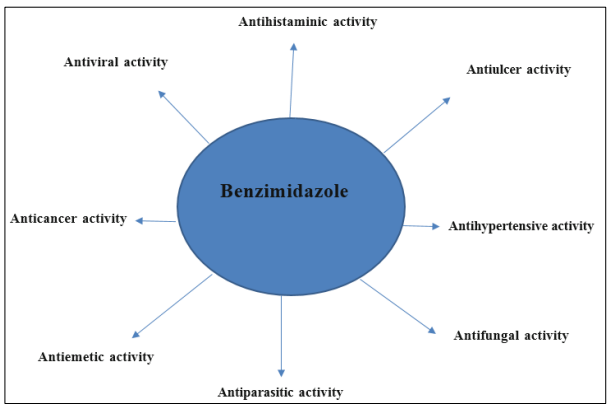

Fig 2: Imidazole and benzimidazole derivatives encompassing a diverse range of biological activities.

1.2 Antihistaminic drugs

Histamine is an important chemical mediator and neuro-transmitter that influences a variety of physiological and pathophysiological processes in the body via stimulation of a class of G protein-coupled histamine receptor subtypes, i.e., H1, H2, H3, and H4 (Hough, 2001) [67]. The biogenic amine, histamine, is known to participate in allergic and inflammatory reactions, gastric acid secretion, and immunomodulation, as well as in neurotransmission. Antihistaminic drugs or histamine receptor antagonists that were the first to be introduced are ones that bind at H1-receptor sites and block the action of histamine. They are therefore designated as H1-receptor antagonists and are used for the treatment of allergic conditions (Parsons and Ganellin, 2006). [97] The benzimidazole-containing drugs, i.e., bilastine, astemizole, mizolastine, emedastine, and clemi- zole, are playing a vital role as H1-receptor antagonists (Fig. 3). Bilastine was developed by FAES Farma as a selective and potent antagonist at H1 receptor sites for the treatment of allergic rhinoconjunctivitis and urticaria (Corcostegui *et al.*, 2005) [27]. Astemizole, a second-generation H1-receptor antagonist, was discovered in 1977 by Janssen Pharmaceutica. It was developed from a series of diphenylbutylpiperidine antihistamines in an effort to extend the duration of action. The piperidino-aminobenzimidazole moiety appears to be required for H1-receptor affinity and contributes significantly for persistent receptor binding that result in prolonged action. But it has been withdrawn from the market because of side effects like QT interval prolongation and arrhythmias (Zhou *et al.*, 1999 [98]. Mizolastine, structurally resembling astemizole, is fast- acting non-sedating antihistaminic drug. It does not prevent the actual release of histamine from mast cells, just prevents it binding to receptors. It has not been shown to increase the QT interval and considered as an effective antihistaminic in the management of allergic rhinitis and chronic idiopathic urticarial (Prakash and Lamb, 1998) [99]. Emedastine is also a second-generation H1-receptor antagonist with high affinity and specificity for H1-receptors. It is used in the form of eye drops to treat allergic conjunctivitis (Bielory *et al.*, 2005) [12], whereas clemizole is first-generation antihistamine used to treat itching and allergic reactions.

Histamine has a physiological role in regulating the secretion of acid in the stomach, where it stimulates the parietal cells to produce hydrochloric acid. In the 1970s a new class of drugs was invented that blocked the action of histamine at its H2-receptors so-called as H2-receptor antagonists. These drugs were shown to be extremely effective in antagonizing the action of histamine on parietal cells (specifically H2-receptors) in the stomach and decrease the production of acid by these cells. The discovery of first H2-receptor antagonist, i.e., cimetidine is strongly associated with Sir James Black and coworkers. The scientists at GlaxoSmithKline initiated a program of systematic research of H2-receptor antagonists starting from the structure of histamine. The first breakthrough was the *Na*-guanylhistamine that possessed weak antagonistic activity against the gastric secretion induced by histamine. The lengthening of the side chain of this compound increased the H2-receptor antagonistic activity, but a residual agonist effect remained. Therefore, the basic guanidino group was replaced by a neutral thiourea that eventually led to the development of burimamide, a specific competitive antagonist of H2-receptor 100-times more potent than *Na*-guanylhistamine, proved the existence of the H2-receptor. But it was not suitable for progression to clinical

trials because its antagonist activity was too low for oral administration. Further, modification of the structure of burimamide was done by inserting an electronegative atom, i.e., sulfur instead of the methylene group into the side chain and a methyl group at five-position on imi-dazole ring that obtained metiamide with enhanced H2-receptor antagonistic activity as compared to burimamide. Metiamide was an effective agent; however, it was associated with unacceptable nephrotoxicity and agranulocytosis. The toxicity was proposed to arise from the thiourea group, so further structure modification was carried out by replacing the thiourea group in metiamide with an *N*- cyanoguanidine group that led to the ultimate discovery of cimetidine with potent antagonistic activity (Scheinfeld, 2003) [100]. Cimetidine is a prototypical H2-receptor antagonist, developed at GlaxoSmithKline by Black and coworkers, and has established new vistas for the effective treatment of gastric ulcers, heartburn, and gastritis (Black *et al.*, 1972) [14]. It reached the clinic at the end of 1976, as the pioneer drug which revolutionized the medical treatment of peptic ulcer disease. Indeed, in many countries, it became the best-selling prescription medicine and was the first of the ‘‘blockbuster’’ products (billion dollar annual sales; Freston, 1982) [42].

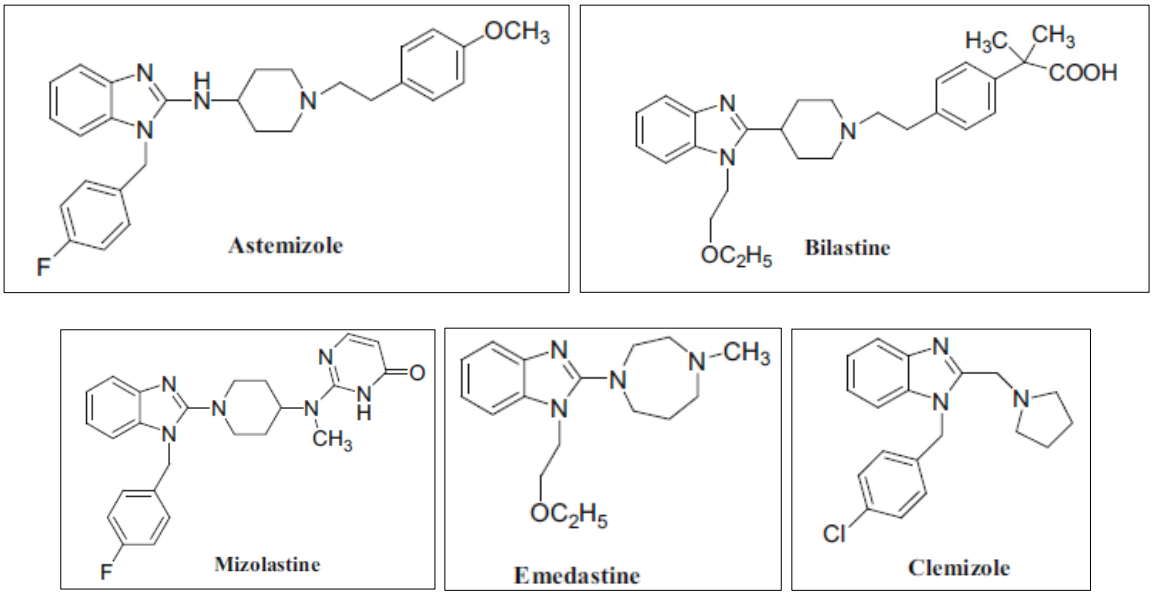

Fig 3: Benzimidazole-based H1-receptor antagonists

1.3 Antiulcer drugs

Gastric acid has been known to be a key factor in normal upper gastrointestinal functions, including protein digestion, iron or calcium absorption as well as provide some protection against bacterial infection. However, inappropriate level of acid underlies several pathological condi-tions, including gastroesophageal reflux disease (GERD), heartburn, and peptic ulcers (Olbe *et al.*, 2003) [101]. Gastric damage or gastrointestinal toxicity represents an important medical and socioeconomic problem, which can be treated by blocking acid secretion through proton pump inhibitors (PPIs). These drugs have emerged as the treatment of choice for acid-related diseases, which act irreversibly by blocking the H+-K+-ATPase of the gastric parietal cells and thereby reducing the gastric acid secretion (Zajac *et al.*, 2013) [103].

The vast majority of these drugs are benzimidazole derivatives and their discovery as PPIs may be traced back to the 1968 when George Sachs and his collaborators described an H+-K+-ATPase as the proton pump that moves acid across the gastric mucosa and gastric parietal cells (Sachs *et al.*, 1968; Blum *et al.*, 1971; Chang *et al.*, 1977; Sachs and Wallmark, 1989) [104, 15, 23,105]. Further, it was discovered that H+-K+-ATPase is the final step of gastric acid secretion, and blockade of this enzyme could lead to potent inhibitors of acid secretion irrespective of external or endogenous signals. This biochemical work was coincided with synthetic work by focusing on gastric acid inhibition. In the mid-1970s, the search for drugs that might to control acid secretion began by the Astra Pharmaceuticals. From the literature it is found that the 2-(pyridin-2-yl) ethanethioamide developed by the Servier exhibited antisecretory activity; this compound, however, showed toxicity due to thioamide group, and further research into this compound was cancelled (Fig. 5; Lindberg and Carlsson, 2006) [91]. Therefore, based on the structure of cimetidine, a benzimidazole ring was added to 2-(pyridin-2-yl) ethanethioamide by the Astra group along with modification of the sulfide (2-(pyridin-2-yl-methylthio)-benzimidazole) to a sulfoxide that led to the introduction of 2-(2-pyridinylmethylsulfinyl)-benzimidazole (timoprazole) with a surprisingly high level of antisecretory activity (Fig. 5; Olbe *et al.*, 2003; Shin *et al.*, 2008) [101,102]. Later on, studies on timoprazole revealed an enlargement of the thyroid gland due to inhibition of iodine uptake as well as atrophy of the thymus gland, so it could not be used in humans. Moreover, it was found that some substituted mercaptobenzimidazoles have no effect on iodine uptake and the introduction of such substituents into timoprazole resulted in elimination of the toxic effects, without reducing the antisecretory effects (Lindberg and Carlsson, 2006) [91]. A variety of analogs of timoprazole were synthesized, and picoprazole was found to have antisecretory action without iodine blockage activity. SAR studies on analogs of picoprazole showed that electron-donating groups on the pyridine ring, which increased the p*K*a of the pyridine ring, also increased the potency as an inhibitor of H+-K+-ATPase (Fig. 4). As a result the best analog was omeprazole that is substituted with two methoxy groups, one at 6-position of the benzimidazole, other at 4-position of the pyridine, and two methyl groups at 3 and 5-positions of pyridine. It is the first PPI discovered by AstraZeneca in 1978 that controlled the acid secretion in the stomach also clinically

superior than H2-receptor antagonists (Shin *et al.*, 2008; Fellenius *et al.*, 1981; Munson *et al.*, 2005) [102, 38, 106]. In 1996, omeprazole became the world's biggest ever selling pharmaceutical, and by 2004 over 800 million patients had been treated with this drug worldwide. After that a number of analogs of omeprazole were studied by pharmaceutical companies with different substitutions on benzimidazole as well as pyridine ring which led to the discovery of lansoprazole, pantoprazole, esomeprazole (i.e., *S*-enantiomer of omeprazole) and rabeprazole all claiming to share a flourishing market, after their development (Fig. 5; Shin *et al.*, 2008; Sachs *et al.*, 2007) [102,107]. Esomeprazole was discovered in 1987 by AstraZeneca having faster onset of antisecretory action and higher bioavailability than the *R*-enantiomer, i.e., omeprazole. It is used to treat peptic ulcers and GERD, which became one of the most widely prescribed drugs, with sales of about $5 billion in 2009 (Sachs *et al.*, 2007) [107]. Lansoprazole was the second PPI discovered in 1984 by Takeda and reached in the market in 1991. It has no substitutions at the benzimidazole ring, but two substituents are present on the pyridine ring, i.e., a methyl group at 3-position and a trifluoroethoxy group at 4-position. Dexlansoprazole (*R*- enantiomer of lansoprazole) was launched as a follow up of lansoprazole in 2009. Moreover, both enantiomers have similar effects on the proton pump (Emerson and Marzella, 2010) [35], whereas rabeprazole was discovered by Eisai Co. and it is similar to lansoprazole in having no substituents on its benzimidazole part, whereas a methyl group is present at 3-position of pyridine, and the only difference is the methoxy- propoxyphene substitution at 4-position instead of the trifluoroethoxy group on lansoprazole. Pantoprazole was the third PPI introduced into the German market in 1994 that was discovered by Byk-Gulden. It has a difluoroalkoxy side group on the benzimidazole ring and two methoxy groups in 3- and 4-positions on the pyridine ring (Senn-Bilfinger and Sturm, 2006) [108]. Ilaprazole, a pyrrole-substi-tuted benzimidazole, was synthesized at IL-Yang Pharmaceutical. Its antisecretory activity is proved to be two to three times higher and its half-life two to three times longer than that of omeprazole (Scarpignato and Hunt, 2008), [109] whereas tenatoprazole, consisting of one imidazopyridine ring connected to a pyridine ring by a sulfinylmethyl chain, represents a new chemical entity developed by Mitsubishi Pharma in Japan and is now under active development by Sidem (France). The inhibitory activity of this novel compound on gastric H+-K+-ATPase has been thoroughly characterized (Fig. 5; Shin *et al.*, 2008) [102]. Like other PPIs, tenatoprazole is a prodrug (p*K*a = 4.04), which is con-verted to the active sulfenamide or sulfenic acid in the acidic secretory canaliculus of the stimulated parietal cell.

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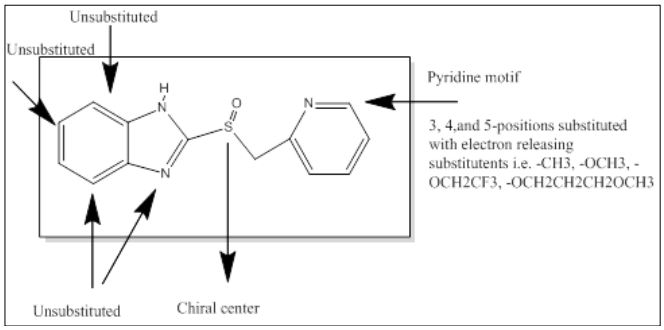
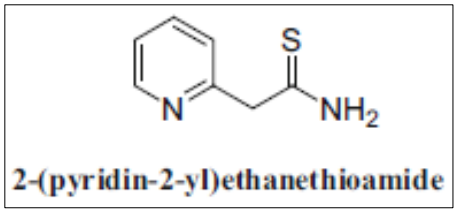
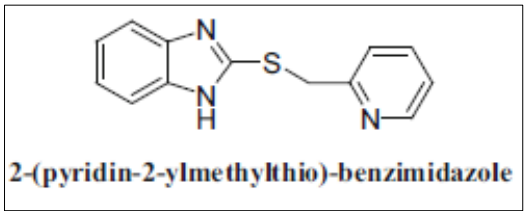
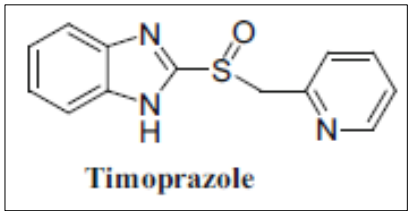
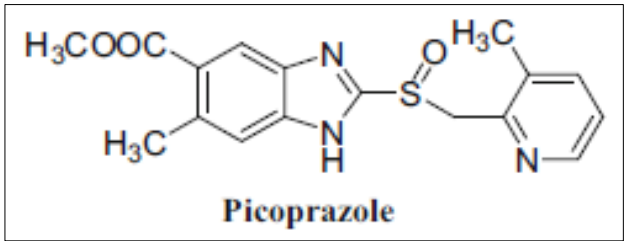


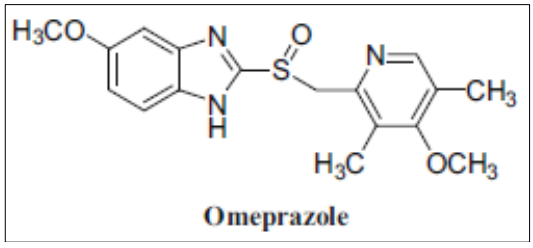
Fig 4: Structural features required for PPI activity

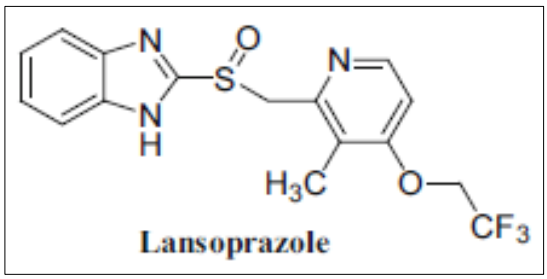


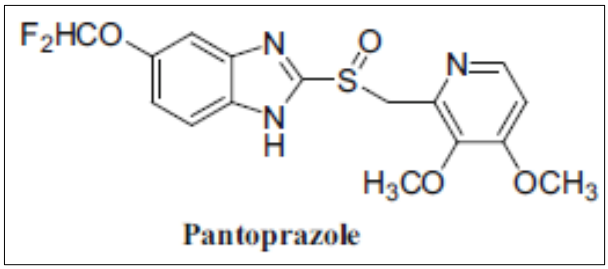












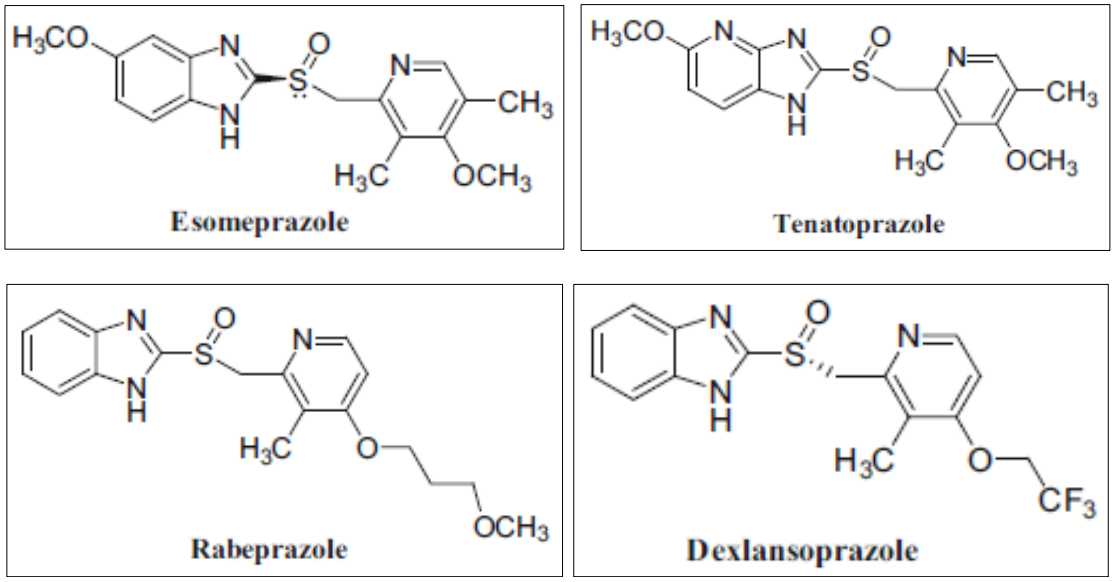


Fig 5: Benzimidazole-based PPIs

1.4 Angiotensin II type 1 (AT1) receptor antagonists

High blood pressure is one of the most common health problems worldwide, which can lead to heart attack, heart failure, and peripheral arterial disease. Thus, there is a continuing need for the development of potent antihypertensive drugs with higher curative effects and lower side effects. Several benzimidazole-based compounds have been well explored as antihypertensive drugs acting by interrupting an important hormone pathway, i.e., renin–angiotensin system, which plays a pivotal role in the regulation of blood pressure and fluid and electrolyte homeostasis.

Angiotensinogen, a polypeptide, is cleaved by renin to produce a decapeptide, Angiotensin I (Ang I), which is further acted upon by angiotensin-converting enzyme (ACE) to generate Angiotensin II (Ang II) an octapeptide which acts on G protein-coupled AT1 receptors resulting in vasoconstriction, sodium retention, and aldosterone release to cause hypertensive action. The various strategies to control these actions of Ang II include blocking the production of Ang II through the use of renin and ACE inhibitors or blocking the binding of Ang II to AT1 receptors. The major breakthrough in the understanding of the renin– angiotensin system was triggered by the development of ACE inhibitors. However, the inhibition of ACE produces an increase in the plasma bradykinin level and contributes to the side effects of ACE inhibitors, e.g., angioedema. To overcome several of the deficiencies of ACE inhibitors, the specific Ang II receptor antagonists were discovered and developed (Naik *et al.*, 2010; Burnier, 2001) [110, 20]. The concept of treating hypertension by a specific blockade of the renin–angiotensin system was first established with the use of saralasin, a nonselective antagonist of Ang II receptors. Although, saralasin reduced the arterial pressure in hypertensive patients with high circulating plasma renin activity, its therapeutic potential remained limited, since due to its peptidic nature, it has a very short plasma half- life, is not orally bioavailable, and also possesses signifi- cant Ang II-like agonistic properties.

Further, potent AT1 receptor antagonists have also been obtained by replacing the imidazole ring with fused heterocyclic moiety, i.e., benzimidazole. Candesartan cilexetil is a benzimidazole ester carbonate prodrug, which was developed by Takeda. In vivo, it is rapidly converted to the much more potent corresponding 7-carboxylic acid, candesartan. The carboxyl group of the benzimidazole ring in candesartan plays an important role in binding with AT1 receptors. Candesartan and its prodrug have a stronger blood pressure lowering effect than losartan. Telmisartan is also an orally active potent AT1-selective antagonist that was discovered and developed in 1991 by Boehringer Ingelheim. It is unusual in that it contains benzimidazole with a second benzimidazole attached at 6-position signi- fying a bulky lipophilic group and a carboxylic acid at the 2-position of the biphenyl-methyl group which is more potent than the tetrazole analog (Fig. 6; Burnier and Brunner, 2000) [19]. Among all AT1 receptor antagonists, it is the most lipophilic compound and showed excellent oral absorption and tissue penetration. Both, candesartan and telmisartan are successfully prescribed for lowering of blood pressure. Azilsartan, developed as a result of the medicinal chemistry effort by Takeda group, is the most recently announced benzimidazole-containing AT1 recep- tor antagonist for the treatment of hypertension. It is the eighth AT1 receptor antagonist in clinical use worldwide, which was discovered by modification of the tetrazole ring in candesartan, and has a unique moiety, 5-oxo-1, 2, 4-oxadiazole, instead of tetrazole ring. The biphenyl-5-oxo- 1, 2, 4-oxadiazole moiety may increase the lipophilicity and bioavailability compared with candesartan (Kohara *et al.*, 1996) [86]. Azilsartan medoxomil, a prodrug of azilsartan, was approved in the USA by the FDA in 2011 for the treatment of hypertension. Azilsartan medoxomil and azilsartan both have shown greater antihypertensive effects than other AT1 receptor antagonists (Miura *et al.*, 2013) [111].

For benzimidazole-based AT1 receptor antagonism, the 1-position should also contain biphenyl-methyl group along with acidic groups. Incorporation of acidic groups like tetrazole or COOH produced orally active antagonists. The 2-position should be substituted with alkyl or alkoxy chain. The 3- and 5-positions should be unsubstituted, whereas 4- and 6-positions remain unsubstituted or should bear alkyl or bulky lipophilic groups, respectively. A car- boxyl group at 7-position of benzimidazole provides potent compounds (Fig. 7). Esterification of the acidic function (ester prodrugs e.g., candesartan cilexetil and olmesartan medoxomil) improves the oral bioavailability.

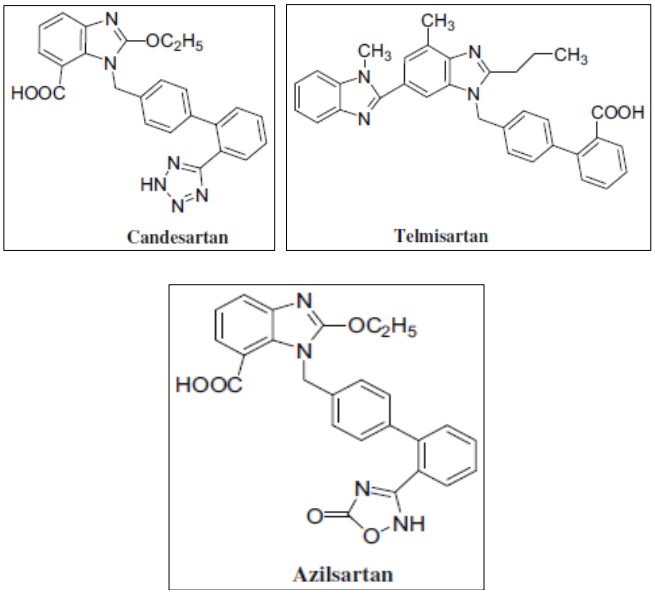


Fig 6: Benzimidazole-based Ang II receptor antagonists

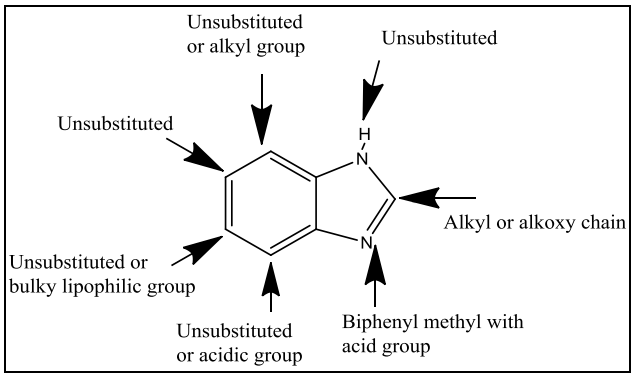


Fig 7: Structural features required around benzimidazole scaffolds for Ang II receptor antagonists

1.5 Antifungal drugs

Fungal infections pose a continuing and serious threat to human health and life. These infections are estimated to occur in billions of people each year, and recent evidence suggests the rate is increasing. As a result, serious attention has been directed toward the discovery and development of antifungal drugs. This chemical group has well represented with numerous clinically useful drugs that act by inhibiting cytochrome P-450-dependent 14a-lanosteroldemethylase enzyme which is required for fungal ergosterol biosynthesis (Rezaei *et al.*, 2011) [112]. The first report of antifungal activity of an azole compound, benzimidazole, was described in 1944 by Woolley, who was studying biotin deficiency in animals and microbes (Woolley, 1944) [113]. At that time, mycotic diseases were of minimal interest so Woolley's initial discovery was largely ignored. Thirty years later, Vanden Bossche observed that phenethylimidazole, another azole moiety with antifungal activity, inhibited the uptake of purines in yeast form *Candida* species by interference at the cell membrane (Vanden Bossche, 1974) [114]. In, Jerchel *et al.*, 1952 [76] revived Woolley's work and reported that certain substituted benzimidazole compounds had significant antifungal activity (Jerchel *et al.*, 1952) [76]. This publication encouraged other investigators to screen this group of chemicals in search of clinically useful antifungal agents.

The introduction of ketoconazole in 1981 by Janssen Pharmaceutica represented the nadir in the search for new safe and effective agents. For nearly a decade, it was the only oral agent available for the treatment of systemic fungal infections and considered to be the ''gold standard'' (Heeres *et al.*, 1979) [61]. Over the years, a number of clinically relevant shortcomings of this compound appeared like dose-related gastrointestinal side effects, unpredictable drug interactions (e.g., cyclosporine), largely fungistatic, proved to be less effective in immunocompromised patients, and intravenous formulation is not available.

Moreover, benzimidazole containing systemic fungicide, e.g., benomyl was introduced in 1968 by DuPont, and carbendazim, metabolite of benomyl, was developed in 1973 by BASF, Hoeschst (now part of Bayer) and DuPont (Fig. 8). Due to toxicity as well as prevalence of resistance of parasitic fungi, these drugs are withdrawn from the market (Stringer and Wright, 1976). [93]

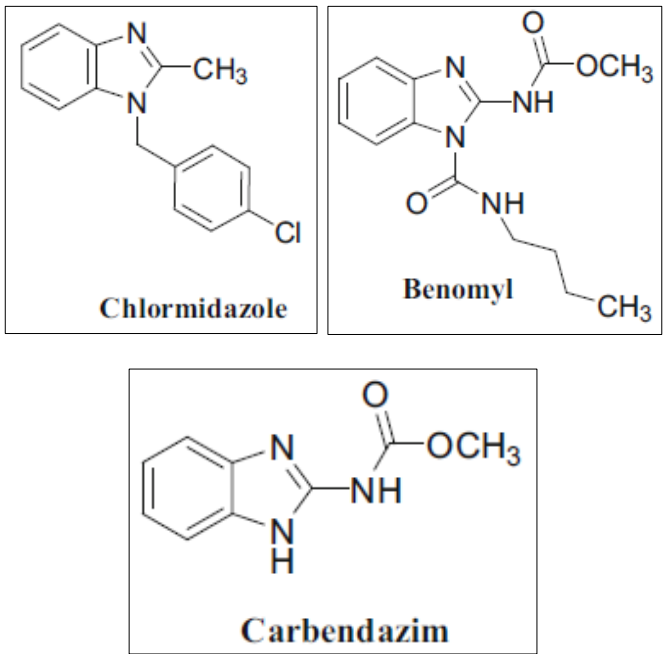


Fig 8: Benzimidazole-based antifungal drugs

1.6 Antiparasitic drugs

Parasites are microorganisms that live on or inside another organism (the host) and produce harmful effects by growing, reproducing, or giving off toxins to the host that result in parasitic infection. Such organisms may include helminths (nematodes, cestodes, and trematodes etc.) or protozoa, (amoeba). Parasitic infections can spread through contaminated water, waste, fecal matter, blood, or through food and constitute one of the most widespread human health problems, mainly in tropical and subtropical regions. Since parasites are eukaryotic, they share many common features with their mammalian host; therefore, the development of effective and selective drugs against parasites is a challenging task. Antiparasitics are a class of drugs which are indicated for the treatment of parasitic infections. Among heterocycles, benzimidazole-based drugs have played a major role to combat such infections. The nitroimidazole-based drugs, i.e., metronidazole, ornidazole, secnidazole, nimorazole, and tinidazole are well-established drugs in widespread clinical use to treat diseases caused by protozoa and anaerobic bacteria. Particularly, structurally simple metronidazole is an effective synthetic compound introduced in 1960 and possesses strong inhibitory effect against anaerobic bacteria such as *Helicobacter pylori* and protozoa such as *Giardia*, *Lamblia*, and *Entamoeba histolytica* (Khabnadideh *et al.*

2007) [84]. Although metronidazole is a product of synthetic chemistry, its origin goes back to the discovery of azomycin (2-nitroimidazole) in 1953, by Nakamura at the prolific laboratory of Hamao Umezawa in Tokyo, and its structure was solved in 1955 (Nakamura 1955) [115]. Azomycin, produced from the extract of soil *Streptomyces* cultures, was the first 2-nitroimidazole to exhibit activity against several protozoans, specifically *Trichomonas*. Azomycin itself turned out to be too toxic to be used clinically, but it inspired the synthesis of a series of analogs by the French team that led to the emergence of metronidazole, an important drug for treating protozoal and trichomonas infections (Cosar and Julou, 1959) [29]. Serendipitously, it was found to be active against ulcerative gingivitis, bacterial infection of gums, and this led to the realization of its broader antibacterial activity. It is especially active against anaerobic bacteria such as *Bacteroides fragilis* and is approved for a number of indications which involve this pathogen (Shinn, 1962) [116]. Azomycin became the chemical lead in extensive synthetic development of over hundred compounds. Benznidazole is another 2-nitroimidazole-based drug and find its therapeutic use in Chagas disease due to trypanosomiasis infection.

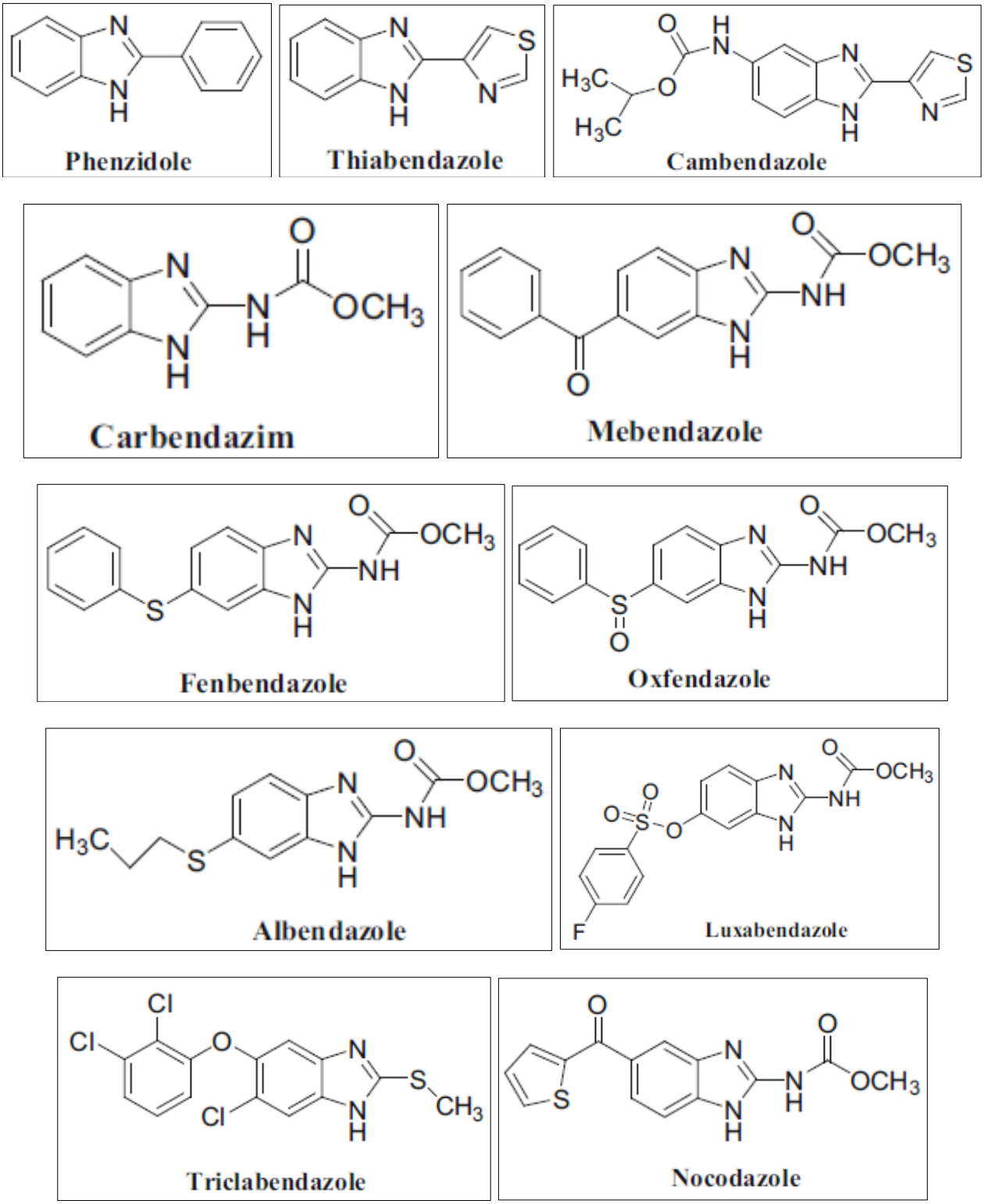


Fig 9: Benzimidazole-based antiparasitic drugs

1.7 Anthelmintics

The therapeutic potential of benzimidazole in parasite chemotherapy was recognized after the introduction of phenzidole as a sheep anthelmintic by Imperial Chemical Industry in the early sixties (McFarland, 1972) [117]. In 1961, Brown and his team at Merck Sharp & Dohme Laboratories discovered thiabendazole as a broad-spectrum anthelmintic (Brown *et al.*, 1961) [17]. The introduction of thiabendazole against parasite infections of both humans and domestic animals provided a major breakthrough that opened up a new era to design further potent anthelmintics. Thiabendazole is the first benzimidazole to be marketed over 50 years ago to combat helminthic infections. Although, it shows broad-spectrum activity against different helminths, it suffers from the limitation of being readily metabolized into inactive 5-hydroxythiabendazole, with very short half-life (Fisher, 1986) [41]. To prevent enzymatic hydroxylation of thiabendazole at 5-position, Merk scientists synthesized a variety of 5-substituted thiabendazoles, of which cambendazole showed promising activity with a longer half-life (Hoff *et al.*, 1970; Hoff, 1982) [66, 65]. Another milestone in the SAR of benzimidazoles was achieved at SmithKline Laboratory, where replacement of the thiazole ring of thiabendazole by thiocarbamate led to the discovery of parbendazole with high anthelmintic activity (Actor *et al.*, 1967) [1]. The discovery of parbendazole stimulated a vigorous search for better benzimidazole anthelmintics in different pharmaceutical companies of the world. A number of benzimidazole-based broad-spectrum anthelmintics as derivatives of carbendazim came into the market that act by inhibiting the microtubule formation, such as mebendazole, flubendazole, cyclobendazole, fenbendazole, oxfendazole (or fenbendazole sulfoxide), oxibendazole, nocodazole, albendazole, ricobendazole, (albendazole sulfoxide), and luxabendazole (Townsendand and Wise, 1990; Martin, 1997; Fig. 9) [118, 119]. Albendazole, fenbendazole, and oxfendazole are the first benzimidazoles to be successfully used for the treatment of all growth stages of gastroin- testinal nematodes. These drugs may also be used in the treatment of lungworms, tapeworms, and adult stages of liver fluke. The noncarbamate benzimidazole, triclaben- dazole, was later introduced as antihelmenthic agents for treatment of all stages of liver fluke, but it is ineffective against nematodes. Luxabendazole is a benzimidazole sulfide used in the treatment of food-producing animal. The low solubility of benzimidazole sulfides and sulfoxides leads to their low absorption from gut, resulting in low bioavailability. Therefore, netobimin and febantel, which are the prodrugs of albendazole and fenbendazole, respectively, have greater water solubility resulting in improved absorption and increased bioavailability, whereas other pro-benzimidazoles such as benomyl and thiophanate, have found widespread use as fungicidal agents, which are precursors of carbendazim (Ozkay *et al.*, 2010) [120]. It is found that various benzimidazole-based drugs for parasitic chemotherapy have been developed by carrying out structure modifications at 2, 5(6)-positions of the benzimidazole nucleus. The presence of hydrogen atom at 1-position of benzimidazole is essential for anthelmintic activity, as all 1-substituted benzimidazoles led to lowering or loss of activity except for benomyl (prodrug). The presence of substituents on 2- and 5(6)-positions of benzimidazole plays a significant role in determining the anthelmintic profile, whereas the 1-, 4- and 7-positions should be unsubstituted. Although, benzimidazole-2-carbamates possess broad-spectrum activity against different gastrointestinal helminths, virtually all of them suffer from the limitation of being highly insoluble, due to which these have poor and inconsistent gastrointestinal drug absorption making them weakly active and ineffective. In an attempt to improve the solubility of benzimidazole-2-carbamates, a large number of 2-alkyl/aryl carbonylaminobenzimidazoles and 2-benzimidazolylureas have been synthesized. Further, to improve biological response a variety of 5-alkylthio and 5-arylthiobenzimi-dazole-2-carbamates have been prepared. The demonstration of higher-order anthelmintic activity by thiabendazole and cambendazole possessing a 4-thiazolyl group at 2-position of benzimidazole may be explained by electronic and structural congruence of the thiazolyl pharmacophore with the methoxycarbonylamino function (McCracken and Lipkowitz, 1990; Fig. 10) [123].

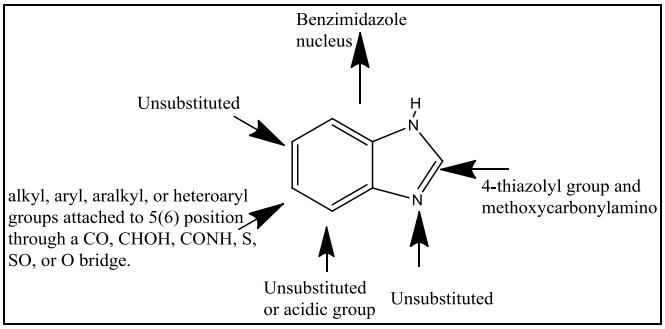


Fig 10: Structural features required around benzimidazole scaffold for anthelmintic activity

1.8 Anticancer drugs

Cancer is one of the most serious threats to human health, which has drawn unusual attention all over the world. Extensive research has been devoted toward the development of effective anticancer therapeutics, involving radia- tion therapy and chemotherapy (Grasso *et al.*, 2012) [55].

Indimitecan has been demonstrated to inhibit topoisomerase-I enzyme by intercalating between the DNA base pairs and to stabilize a ternary complex. Additionally, they produce a unique pattern of DNA cleavage sites relative to camptothecins and therefore may target genes differently, which could result in a different spectrum of anticancer activities (Beck *et al.*, 2014) [7], whereas bendamustine (Fig. 11) Is also a bifunctional alkylating agent, synthesized in the 1960s by Ozegowski and Krebs in East Germany with the aim of combining the alkylating properties of 2-chloroethylamine and the antimetabolite properties of a benzimidazole ring (Tageja and Nagi, 2010) [121]. It is believed to act as an alkylating agent that induces interstrand DNA cross-linking and is used in the treatment of chronic lymphocytic leukemia and lym- phomas (Hartmann and Zimmer, 1972; Kath *et al.*, 2001) [57, 83]. It has a nitrogen mustard moiety, a benzimidazole ring, and an alkane carboxylic acid side chain, which all may be responsible for its cytotoxic activity. The benzimidazole ring may be responsible for the purine analog activity of bendamustine (Weide, 2008) [122].

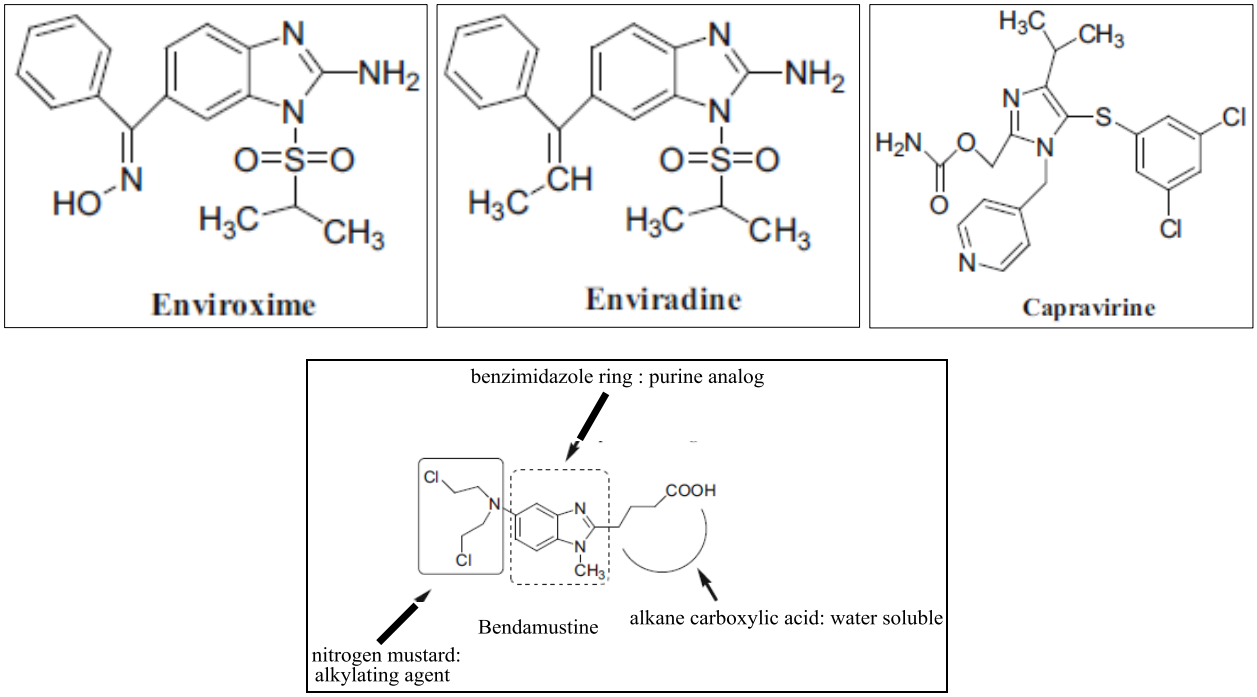


Fig 11: Benzimidazole-based antiviral & anticancer drugs

1.9 Antiviral drugs

Viral infections are common obligate parasites, which severely threaten the health of human beings. Much research has been carried out toward the development of benzimidazole-based drugs against human cytomegalovirus (HCMV), human herpes simplex virus, human immunodeficiency virus, and hepatitis B and C virus. Nucleoside analogs are currently in clinical use for the treatment of such infections act by inhibiting viral replication. In the late 1980, Leroy B. Townsend and John C. Drach at the University of Michigan discovered antiviral activity in a series of benzimidazole derivatives. The two compounds, TCRB and 2-bromo analog (BDCRB), were found to be potent and selective inhibitors of HCMV replication. The most exciting aspect of this new chemical series was the mode of action that involves the inhibition of viral DNA synthesis and viral egress. Unfortunately, their clinical development potential was limited because of rapid metabolic cleavage of the sugar from the heterocycle. Through a collaborative partnership with Burroughs Wellcome, they conducted SAR studies on benzimidazole series that led to the emergence of two clinical candidates, i.e., the pyranoside of BDCRB and maribavir, each novel but with distinct modes of action. Maribavir is a selective, orally bioavailable ribosyl benzimidazole, which is introduced for the prevention and treatment of HCMV disease in hematopoietic stem cell/bone marrow transplant patients (Biron *et al.*, 2002) [13]. A ribosyl moiety at 1-position proved to be very important for the activity (Chodosh *et al.*, 1989; Fig. 11) [25]. However, nucleoside analogs are associated with solubility problems, so extensive work has been done in exploring non-nucleoside compounds as antiviral agents. This led to the discovery of enviroxime and enviradine which are the non-nucleoside analogs and came into clin- ical use in the early 1980s as potent broad-spectrum inhi- bitors of RNA viruses. Enviroxime and related compounds inhibit the replication of rhinoviruses and enteroviruses (Heinz and Vance, 1995) [62].

1.10 Miscellaneous

In addition to the above discussed therapeutic areas, benzimidazole-based drugs have also been approved for clinical use such as anticonvulsants, antithyroids, antidiabetics, sedative and hypnotics, Anesthetics, immunosuppressants, anticoagulants, retinoic acid metabolism blockers, thromboxane synthetase inhibitors, and analgesics.

1.11 Future directions

The benzimidazole-based drug discovery and development is an attractive topic and draws more and more researchers to engage in this research area. An increasing number of benzimidazole derivatives have been explored and related research is ongoing with infinite potentiality. There are currently adequate numbers of drug candidates in different stages of clinical trials which are discovered by various pharmaceutical companies.

In future research, novel as well as potent chemical entities can be explored by combining benimidazole scaffolds with enormous potentiality for the treatment of diverse diseases. This may revolutionize the world of medicine in the next century. Due to the problems like resistance, toxicity, or poor bioavailability, there is a need for modification of existing agents that will bring about a big change for improvement of activity or change in activity. Prodrug concept can also be utilized to improve bioavailability of existing drugs. Benzimidazole derivatives have attracted considerable attention in recent years. Combination of the modifications at positions 1, 2 and 5 of the molecule has provided the most active drugs. However, the 4-, 6-, and 7-positions of benzimidazole need to be explored further for novel entities with exciting biological activities.

As discussed above acid-related diseases, such as peptic ulcers and GERD are an extremely common set of human ailments and PPIs are mainstay of therapy. Improvements in PPIs can be made by altering the mechanism of activation of PPIs. What may be amenable to future research is to generate PPIs with a much longer residence time in the blood so that

more pumps can be inhibited and also bedtime dosing can be achieved.

Thus, the benzimidazole nucleus can be optimized to generate new, safer, and more effective drugs that satisfy the increasing need of patients afflicted with fungal infections. In recent years much effort has been devoted toward triazole-based antifungal drugs as these possess superior antifungal activity. Therefore, in our opinion novel drugs can be discovered by combining benzimidazole–trizole-based heterocycles. This concept can represent the next major step forward in the development of broad-spectrum, more potent, and less toxic antifungal drugs. We are hopeful that these perspectives could provide the impetus to investigate novel and more efficacious drugs in future.

2. Conclusion

The structurally simple bioactive heterocycles, benzimidazole have played an imperative role in drug discovery and development. A large amount of effort has been invested toward benzimidazole-based medicinal chemistry with outstanding achievements that resulted in various drugs for the treatment of many diseases with great therapeutic utility. Benzimidazole-based medicinal chemistry as well as designing of drugs will continue to be an overwhelmingly attractive topic in quite a long time. The successful strategies as well new perspectives have been discussed to discover novel drugs in the future. We hope this paper will form a comprehensive foundation and reference source that will open up new opportunities for researchers interested in benzimidazole-based medicinal chemistry and drug designing.

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