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An updated review on benzimidazole derivatives as potential antihypertensive agents

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***Abstract*---**A growing number of researchers in the field of medicinal chemistry are focused on nitrogenous heterocyclic compounds. Benzimidazole scaffolds appear often in this group of heterocyclic compounds. Benzimidazole derivatives are important chemotherapeutic drugs because of their isostructural pharmacophore of naturally occurring active biomolecules. Many benzimidazole derivatives have been produced in the recent few decades, and many of these compounds have shown high bioactivity against a wide range of diseases and have bioavailability, safety, and stability profiles that are among the best in the industry. Here, we've included data on the antihypertensive properties of benzimidazole derivatives that have appeared in recent studies (2010–2022), along with a structure-activity link for each. Human studies are underway for a number of intriguing therapeutic candidates, and some of them will be authorized for use in clinical settings. In order to gather the information on proposed topic all the scientific search engines and publisher sites were used such as Google scholar, Science direct, Bentham science, PubChem, PubMed, Tayler and Francis, Hindawi, Springer nature, and ACS websites. The present review provides a detailed insight of benzimidazole derivatives reported as antihypertensive agents. We believe this data can effectively guide researchers to select potential lead nucleus for the further development of antihypertensive agents.

***Keywords*---**Benzimidazole, hypertension, 1*H*-benzimidazole, antihypertensive agents, Telmisartan.

Introduction

Benzimidazole, also known as 1*H*-benzimidazole and 1,3-benzodiazole, is a significant heterocyclic pharmacophore composed of a benzene ring fused with a five-membered imidazole ring. Heterocyclic chemistry consider benzimidazole to be a "privileged structure" because of the vast variety of biological activities(Alaqeel, 2017; Barot et al., 2013). There were a few theories in the 1940s about benzimidazole's role in biology, and the first study on benzimidazole nucleus' biological activity was published in 1944(Woolley, 1944). When Brink et al.(Brink & Folkers, 1949) discovered that 5,6-dimethylbenzimidazole was a breakdown product of vitamin B12 and several of its derivatives also exhibited vitamin B12-like action, interest among researchers in the synthesis technique of benzimidazole and its derivatives increased. Researchers were inspired by these early findings to investigate the nucleus of benzimidazole for a variety of purposes. Because of its presence in a wide range of biologically active compounds, including antiparasitics, antimicrobials, antivirals, antifungals, anticonvulsants, antihypertension medications and analgesics, anti-inflammatory drugs, anticancer drugs and anticoagulant agents, benzimidazole has emerged as an important heterocyclic system over the course of many years of research (Figure 1)(Fei & Zhou, 2013; Wang et al., 2015).

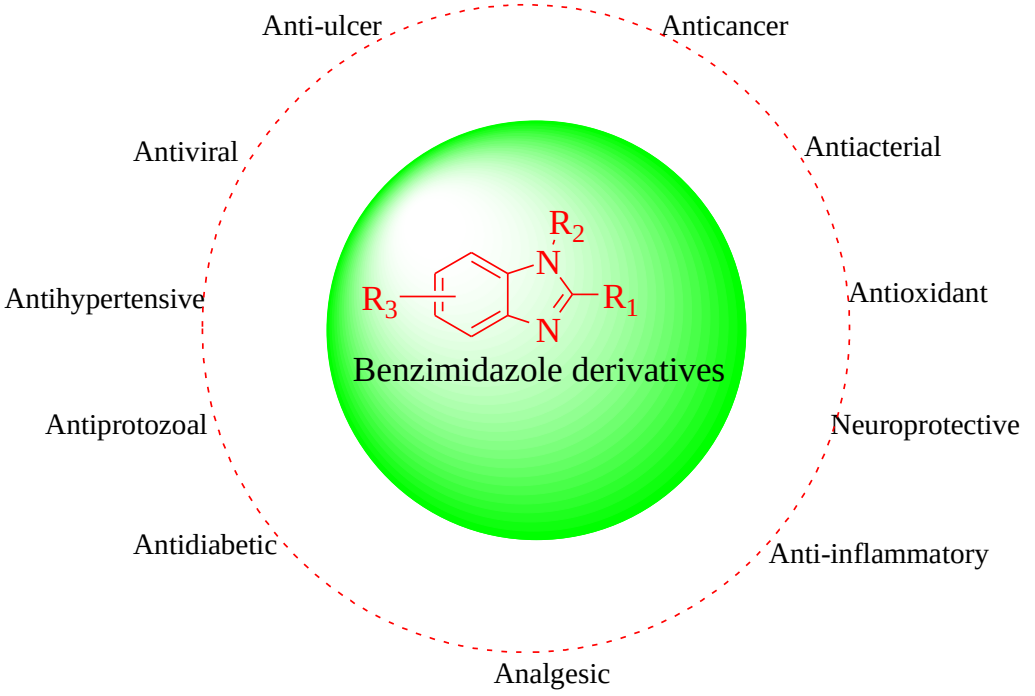


Fig. 1. Wide range of biological applications for benzimidazole derivatives

Many drugs with diverse therapeutic lines have been developed as a result of substituent changes around the core structure, including albendazole, mebendazole, and thiabendazole as antihelmintics; enviradine as antiviral; carbendazim as fungicidal; omeprazole, lansoprazole, and pantoprazole as proton pump inhibitors; candesartan cilexitil and telmisartan as antihypertensives, and

astemizole as antihistaminic agent (Figure 2)(Alaqeel, 2017; Bansal & Silakari, 2012). Medical chemists have been motivated to synthesize various new therapeutic compounds containing the benzimidazole moiety due to the excellent therapeutic potential of benzimidazole-related therapeutics(S. Khan et al., 2021; S. L. Khan et al., 2020; Mayura et al., 2019; Morais et al., 2017; Shntaif et al., 2021; Siddiqui et al., 2021). Recently, Khan et al. synthesized and analyzed pyrimidine-linked benzimidazole hybrids and identified their antibacterial and antifungal activity *in vitro*, as well as their capacity to inhibit the main protease and spike glycoprotein of SARS-CoV-2(S. Khan et al., 2021). The chemistry, structure-activity relationship, and biological activity of many benzimidazole-based compounds have been the subject of several studies in the last few years. Many benzimidazole analogues have been designed and synthesized as a result of the wide range of biological activity shown by molecules containing the benzimidazole moiety. Table 1(Brishty et al., 2021) lists a few recent patents on the benzimidazole moiety. Several review papers have been published that highlight the role of the benzimidazole nucleus in biological activity, such as anticancer, analgesic, antiinflammatory, antibacterial, antiviral, antitubercular, antiulcer, antihypertensive, and antidiabetic properties(Morais et al., 2017). To the best of our knowledge, there is no review article in the literature that focuses on the most recent information on benzimidazole derivatives' antihypertensive properties. The current analysis provides a detailed overview of the antihypertensive properties of benzimidazole derivatives, including data from recent research published up to 2022. Although this review is focused on literature, it also includes an in-depth look at current research on benzimidazole derivatives.

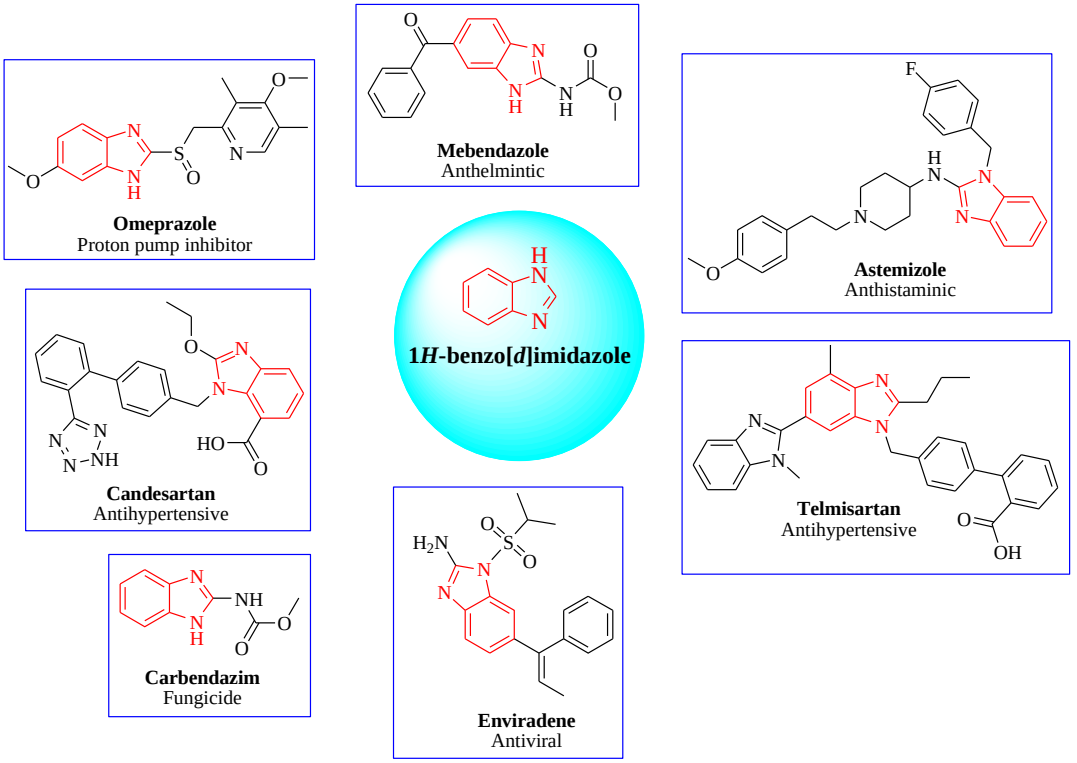


Fig. 2. The structure of 1*H*-benzo[*d*]imidazole and benzimidazole containing drugs approved by USFDA

Table 1
Patents on benzimidazole derivatives have recently been published

Sr. No.	Patent No.	Country	Patent title	Publication date
01	ES2807191T3	Spain	Benzimidazole derivatives as dual ligands of the histamine H1 receptor and the histamine H4 receptor	Feb 22, 2021
02	AU2017382436A1	Australia	Compounds and methods for the targeted degradation of Rapidly Accelerated Fibrosarcoma polypeptides	Jan 28, 2021
03	US10835488B2	United States	Stable orally disintegrating pharmaceutical compositions	Nov 17, 2020
04	US10787420B2	United States	Benzimidazole compound and preparation method thereof	Sep 29, 2020
05	US20190322671A1	United States	Cxcr4 inhibitors and uses thereof	Oct 24, 2019
06	CA3079081A1	Canada	Benzimidazole derivatives and their uses	April 25, 2019
07	AU2020104192A4	Australia	Process of synthesis of	Dec 20,

			benzimidazole derivatives against M.tb	2018
08	WO2018057810A1	France	Benzimidazole derivatives and their use as phosphatidylinositol 3-kinase inhibitors	Mar 29, 2018
09	US8372987B2	United States	2-{(R)-2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide crystalline form 1	Sep 13, 2013
10	US20150361032A1	United States	Benzimidazole inhibitors of the sodium channel	Dec 17, 2015
11	US20150336967A1	United States	Novel Benzimidazole Derivatives as Kinase Inhibitors	Nov 26, 2015

Search Method and Keywords used to collect the information

In order to gather the information on proposed topic all the scientific search engines and publisher sites were used such as Google scholar, Science direct, Bentham science, PubChem, PubMed, Tayler and Francis, Hindawi, Springer nature, and ACS websites. Different keywords like benzimidazole as antihypertensive agents; benzimidazole derivatives as ACE inhibitors; recent update on benzimidazole derivatives as antihypertensive agents; benzimidazole derivatives as potential cardiovascular agents; recent patents on benzimidazoles; diverse biological activities of benzimidazoles etc.

Benzimidazole derivatives as Antihypertensive Agents

Candesartan cilexetil and Telmisartan are two well-known examples of antihypertensive medications that have a benzimidazole moiety (Figure 2). In treating hypertension, these drugs act as angiotensin II receptor antagonists(Keri et al., 2015). Benzimidazole-based new antihypertensive medications have been developed in recent years by a number of scientists, with comparable or even superior effectiveness than traditional antihypertensive treatments. Substituted benzimidazole derivatives were produced by Sharma et al.(Sharma et al., 2010) and tested as angiotensin II receptor antagonists or sartans in Wister rats. When compared to losartan, compounds 1 and 2 (Figure 3) seemed to be the most effective antihypertensive compounds in the series.

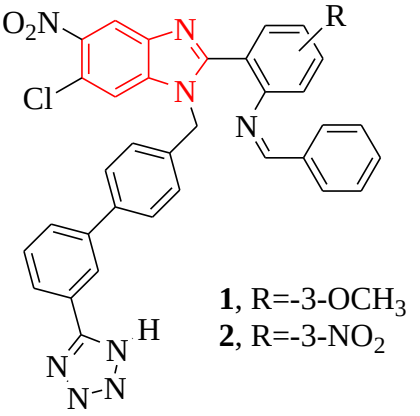
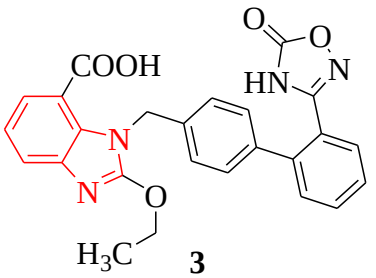


Fig. 3. Structures of compounds 1 and 2 reported by Sharma et al.

Azilsartan medoxomil and its active metabolite azilsartan (3, Figure 4) were studied in rats and dogs by Kusumoto et al.(Kusumoto et al., 2011) and found to be a new, long-lasting, and powerful AT1 blocker. Researchers found that administering 0.1–1 mg/kg of azilsartan medoxomil to spontaneously hypertensive rats (SHRs) and renal hypertensive dogs had a superior impact on blood pressure reduction at all levels than the conventional treatment, olmesartan medoxomil. Abou-Seri et al.(Abou-Seri et al., 2011) have created a series of 2-alkoxy-4-aryl-6-(1*H*-benzimidazol-2-yl)-3-pyridinecarbonitrile derivatives. There were substantial vasodilator characteristics in all of the molecules in the series. It was shown that compounds 4–7 (Figure 4, IC_{50}=0.145, 0.202, 0.210, and 0.214 mM, respectively) were the most active in comparison to normal prazosin hydrochloride (IC_{50}=0.487 mM).



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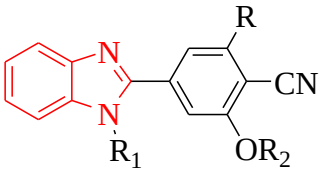
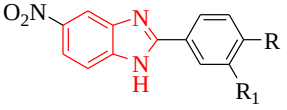


4, R=-4-Clphenyl, R1, R2=-Me
5, R=-5-methyl-2-furanyl, R1= -H, R2=-Me
6, R=-4-Mephenyl, R1, R2=-Me
7, R=-2,4-diClphenyl, R1, R2=-Me

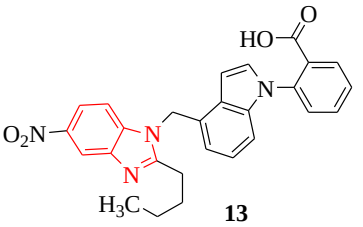
Fig. 4. The structures of compounds reported by Kusumoto et al. and Abou-Seri et al.

After synthesized twenty 5-nitrobenzimidazole analogues, Datani et al.(Datani et al., 2012) tested them for *ex vivo* vasorelaxant properties in pre-contracted rings of pre-stressed rats. With an EC_{50} lesser than 30 µM, the compounds 8–12 (Figure 5) demonstrated significant vasorelaxant action. With an IC_{50} value of 1.03±0.26 nM, compound 13 (Figure 5) was shown to be the most potent against AT1 among a new series of 5-nitro benzimidazole derivatives(Zhu et al., 2014). The inclusion of a butyl chain on the 2-position of the benzimidazole moiety (13) allowed the derivative to engage and bind firmly with the receptor's lipophilic

pocket. It was found that compound 14 (Figure 5) had strong AT1 receptor antagonism as demonstrated by IC_{50} value (0.006 mM), among many benzimidazole derivatives having indazole moiety prepared by Lamotte et al.(Lamotte et al., 2014).



8, R=-OCH_3, R1=-OCH_3
9, R=-OCH_3, R1=-H
10, R=-$N(CH_3)_2$, R1=-H
11, R=-OH, R1=-H
12, R=-OH, R1=-OCH_3



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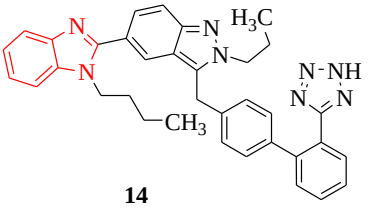

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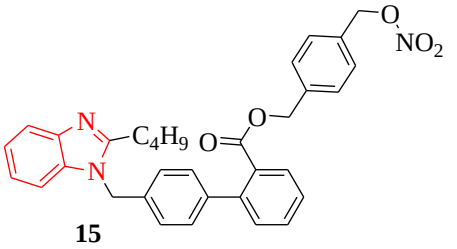
Fig. 5. The structures of benzimidazole derivatives reported by Datani et al. and Lamotte et al.

The benzimidazole biphenyl skeleton was coupled with nitro ester and furoxan NO-donor moieties to produce two series of nitric oxide (NO) releasing benzimidazole derivatives, and compounds 15–16 (Figure 6) were shown to have activity equivalent to that of the positive control losartan. When Hao et al.(Hao et al., 2015) developed and synthesized a series of 4′-[(benzimidazol-1-yl)methyl]biphenyl-2-sulphonamide derivatives with IC_{50} values of 28 and 10 nM, they discovered that compound 17 (Figure 6) was the most powerful AT1 and Endothelin ET_A antagonist. Compound 18 (Figure 6), a mineralocortinoid receptor antagonist discovered by high-throughput screening, demonstrated equal effectiveness to the conventional medicine spironolactone at a dosage of 100 mg/kg (p.o) in the rat natriureis model(C. Yang et al., 2015).



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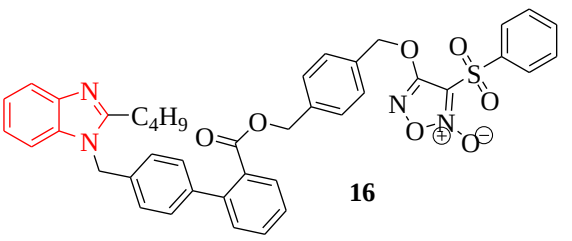

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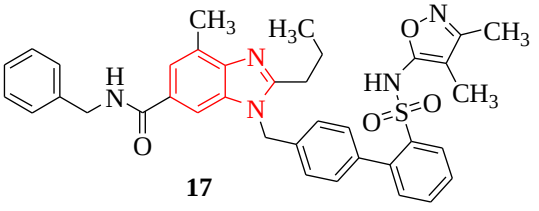

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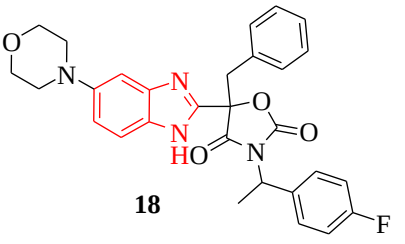

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Fig. 6. The structures of benzimidazole derivatives reported as antihypertensive agents (15, 16, 17, and 18)

An investigation by Bao et al.(Bao et al., 2017) found that the blood pressure of spontaneously hypertensive rats could be lowered by a series of benzimidazole derivatives. At 5 mg/kg and 10 mg/kg, compound 19 had the longest-lasting effect on lowering blood pressure, going from a maximum response of 35.82±6.20 mmHg to 55.98±4.74 mmHg. The IC_{50} value of the compound was 1.13±1.68 nM for AT1 receptor, compared to conventional telmisartan. The antihypertensive properties of compound 20 in spontaneously hypertensive rats were proven to be superior to those of conventional losartan in a separate investigation conducted by Khan et al.(M. T. Khan et al., 2018), who synthesised a series of 2-phenyl substituted benzimidazoles and tested their antihypertensive efficacy using the tail cuff technique. Compound 21 was shown to have a promising pulmonary hypotensive impact and a favourable pharmacokinetic profile when compared to tadalafil, according to a recent study(Y. Yang et al., 2020). These compounds 22–23 were shown to be superior to losartan and telmisartan in blocking the AT1 receptor (IC_{50} (mean±SEM): 0.8±0.1 and 2.3±0.7, respectively) in terms of AT1 receptor inhibition(Wu et al., 2020).

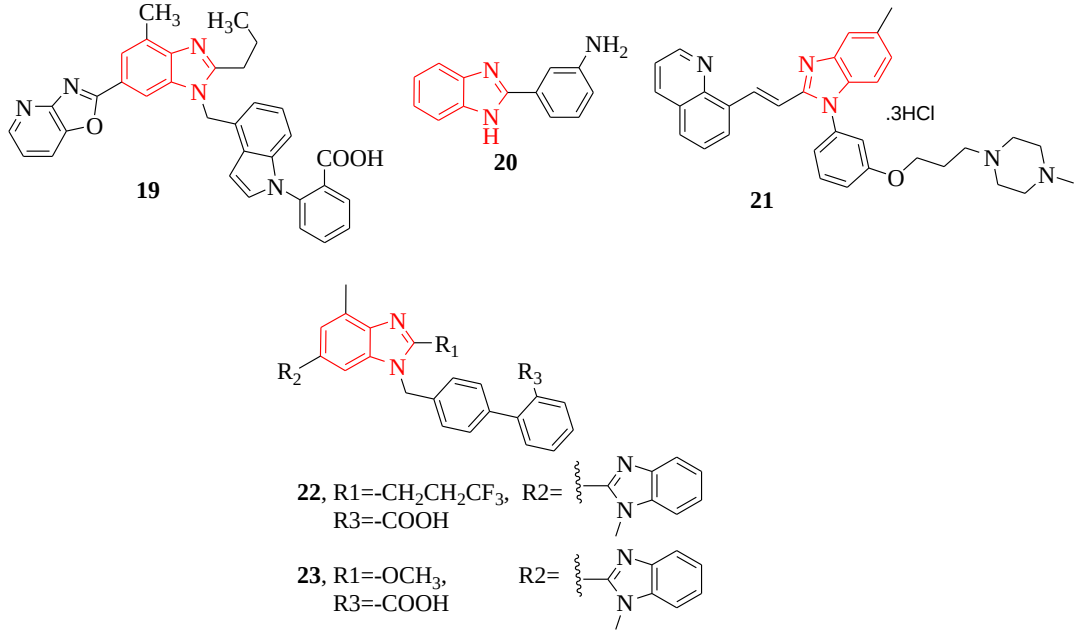

Fig. 7. The structures of benzimidazole derivatives reported by Bao et al. and Khan et al.

Conclusion

When it comes to heterocyclic compounds, the pioneering role of benzimidazole derivatives has been particularly prominent during the previous several decades. There are numerous natural substances whose benzimidazole nucleus is comparable to that of the benzimidazole, therefore benzimidazole derivatives may readily interact with a wide range of biomacromolecules or target proteins. Hypertension, for example, may be treated well by molecules with benzimidazole ring systems, which have broad-spectrum anti-disease properties. There are several therapeutically useful molecules that contain the nitrogen-containing

heterocyclic component benzimidazole. In the past few years, there has been a noticeable increase in the number of researchers interested in developing novel therapeutically active benzimidazole derivatives to treat a variety of diseases. It's not an easy task to introduce the many synthetic compounds that have been shown to have useful pharmacological qualities via various investigations into clinical trials, and then secure their availability in the market and in clinical care. However, this sector has several challenges. The present review provides a detailed insight of benzimidazole derivatives reported as antihypertensive agents. We believe this data can effectively guide researchers to select potential lead nucleus for the further development of antihypertensive agents.

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