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Abstract: Hypertension is a major cause of death worldwide as well as one of the main causes of death in Saudi Arabia. The prevalence of this disease is increasing in all age groups throughout the world which advocates that there is a need for more research in the field of hypertension. The renin angiotensin system (RAS) is implicated in the pathogenesis of hypertension. The renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor (AT$_1$) antagonists are the drugs that affect renin angiotensin system to control hypertension. Recently, benzimidazole derivatives have emerged as an important scaffold for the development of angiotensin II, Type I (AT$_1$) receptor antagonists for the treatment of hyp. Three benzimidazole derivatives, namely, candesrtan, telmisartan, and azilsartan, have already been approved by the USFDA for the treatment of hypertension and related cardiac conditions. Based on the reported structure activity relationship studies and literature, newer benzimidazole derivatives as AT$_1$ receptor antagonists are being developed to tackle the issues related to hypertension and related cardiac conditions with emphasis to maintain their potency, duration of action, and bioavailability. Many reviews have been published that provide the importance of benzimidazole derivatives in medicinal chemistry and in the development of medicinal compounds for clinical use. However, this review highlights the development of newer benzimidazole derivatives as potential AT$_1$ receptor antagonists that may be able to see the light of future as approved drugs for the treatment of hypertension.

Keywords: Benzimidazole derivatives; Angiotensin receptor (AT$_1$) antagonists; Hypertension.
بحث مرجعي

مشتقات البينزيميدازول: دعامة مهمة لتطوير مضادات جديدة لمستقبلات الأنجيوتنسين

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ملخص البحث:
إن ارتفاع ضغط الدم هو أحد المسببات الرئيسية للوفاة بالعالم، وكذلك في المملكة العربية السعودية، كما أن انتشار هذا المرض في تزايد مستمر عند جميع الفئات العمرية في جميع أنحاء العالم، مما يحفز بضرورة القيام بالعديد من البحوث العلمية في هذا المجال. فقد وُجد أن نظام الرينين أنجيوتنسين هو المتسبب في ارتفاع مستوى ضغط الدم، وأن هذا النظام يمكن أن يتأثر بالعديد من الأدوية ومنها مثبطات الرينين، ومثبطات الإنزيمات المحولة للأنجيوتنسين، ومستقبلات الأنجيوتنسين. وظهر حديثاً بعض المركبات الكيميائية من مشتقات البينزيميدازول التي يمكن أن تشكل داعمًا أساسياً لتطوير مضادات مستقبلات الأنجيوتنسين لعلاج ضغط الدم. وبالمقابل فقد أجابت الهيئة الأمريكية للغذاء والدواء ثلاثة مركبات من مشتقات البينزيميدازول، وكادكسبر وتيلميسارتان وأزيلسارتان، بهدف علاج مرض ضغط الدم والأمراض المتعلقة بالقلب. واعتماداً على الدراسات السابقة وبيانات الأبحاث العلمية الحديثة التي تتناول مشتقات البينزيميدازول كمضادات لمستقبلات الأنجيوتنسين فقد تم بفضل أثرها على علاج ضغط الدم والأمراض المتعلقة به، كما تم التأكيد على الحفاظ على قابلية هذه الأدوية ودورة استمرارها واحتياجات الجدوى. وتضررت أيضاً العديد من البحوث التي توضح أهمية مشتقات البينزيميدازول في الكيمياء الطبية في تطوير هذه المركبات للاستخدام السريري. وسيتم في هذه الورقة العلمية تسليط الضوء على تطوير المشتقات الجديدة لبيئزيميدازول كمضادات لمستقبلات الأنجيوتنسين التي لها المقترح في المستقبل لتكون من الأدوية المعتمدة لعلاج ارتفاع ضغط الدم.

كلمات المفتاحية: مشتقات البينزيميدازول؛ مضادات مستقبلات الأنجيوتنسين؛ ضغط الدم.

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المستقبلات: المشتقات البينزيميدازول؛ مضادات مستقبلات الأنجيوتنسين؛ ضغط الدم.

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1. INTRODUCTION

Hypertension is a major cause of death worldwide as well as one of the main causes of death in the Saudi population (Imran & Abida, 2016; Gaetano, 2013; Al-Sieni, Baghdadi, & Al-Abbasi, 2014). This disease is no longer an old age disease as it is also affecting adults and children. Accordingly, it has been recommended to establish well-equipped hospitals for the care of hypertensive children in many countries, including the Kingdom of Saudi Arabia (Al-Mendalawi, 2010). Researchers have also advised that there is a need for further research in the field of hypertension as the prevalence of this disease is increasing in all age groups throughout the world (Temilolu & Miller, 2009; Reddy, 2002). Therefore, researchers have started exploring new approaches for the treatment of hypertension (Oparil & Schmieder, 2015). The current treatment of hypertension that involves the use of drugs belonging to the class of Angiotensin-converting enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Thiazide and Thiazide-like Diuretics, Calcium Channel Blockers (CCB), β-Blockers, α-Blockers, Centrally Acting Agents, Direct Vasodilators, and Mineralocorticoid Receptor Antagonists (Weber, Schiffrin, White, Mann, Lindholm, Kenerson, Flack, Carter, Materson, Ram, Cohen, Cadet, Jean-Charles, Taler, Kountz, Townsend, Chalmers, Ramirez, Bakris, Wang, Schutte, Bisogmanno, Touyz, Sica, & Harrap, 2014). The ACEIs and ARBs act by interfering with the renin angiotensin system (RAS), which is implicated in the pathogenesis of hypertension (Naik, Murumkar, Giridhar, & Yadav, 2010). The renin angiotensin system (RAS) is a hormonal cascade which produces angiotensin peptides. The circulating renin converts angiotensinogen to Angiotensin I, which is rapidly converted to Angiotensin II by the action of Angiotensin Converting Enzyme (ACE). Angiotensin II causes vasoconstrictor through its interaction with the AT1 receptor. Therefore, drugs that prevent the generation of Angiotensin II from Angiotensin I by inhibiting the enzyme Angiotensin Converting Enzyme (ACE) as well as Angiotensin Receptor Blockers (ARBs), are clinically used as antihypertensive agents, for example, captopril, enalapril and Lisinopril (ACE inhibitors) and telmisartan, candesartan, olmesartan and azilsartan (ARBs) (Naik et al., 2010).

Telmisartan, candesartan, olmesartan and azilsartan are benzimidazole derivatives, potent ARBs, that are approved by the FDA and commonly used for the management of hypertension. This review highlights the development of recent and important benzimidazole derivatives as potential angiotensin II, Type-I (AT1) receptor antagonists that may be able to see the light of the future as approved drugs for the treatment of hypertension.

Initially, the medicinal importance of the core structure of benzimidazole and various related groups of drugs are mentioned briefly. Then, the structure-activity relationship of benzimidazole derivatives approved by the US FDA for the treatment of hypertension is described, followed by a rather comprehensive review of newer benzimidazole derivatives that are angiotensin receptor antagonists and have the potential for the development of antihypertensive drugs.

2. BENZIMIDAZOLE DERIVATIVES AS ANGIOTENSIN RECEPTOR ANTAGONISTS

Benzimidazole has the following general formula (Figure 1) and this heterocyclic moiety has an important place in medicinal chemistry (Wright, 1951).

![Figure 1: General structure of benzimidazole.](image_url)

Many review articles have been published that provide the importance of benzimidazole derivatives in medicinal chemistry and their role in the development of medicinal compounds for clinical use (Rajasekhar, Maiti, Balamurali, & Chanda, 2017; Ajani, Aderohunmu, Ikpo, Adedapo, & Olanrewaju, 2016; Keri, Hiremathad, Budagumpi & Nagaraja, 2015; Barot, Nikolova, Ivanov, & Ghate, 2013; Gaba & Mohan, 2016; Bansal & Silakari, 2012; Yadav & Ganguly, 2015). Besides the benzimidazole derivatives clinically used as antihypertensive agents mentioned above, benzimidazole derivatives have been approved for other clinical applications, for example, irtemazole (uricosuric agent); astemizole (antihistaminic);
omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole (proton pump inhibitor); pimobendan (cardiotonic agent); lobendazole, mebendazole, oxibendazole, albendazole, thibendazole, and oxfendazole (anthelmintic agent); enviroxime and enviradine (antiviral agent); bendamustine, veliparib, dovitinib, (anticancer agent).

In 2010, Vyas and Ghate reviewed benzimidazole derivatives as antagonists of AT₁ receptor (Vyas & Ghate, 2010). They highlighted some important benzimidazole derivatives, such as telmisartan, candesartan, TCV-116, CV-11974 (Figure 2), CV-11194 (Figure 3), BIBR-277 (Figure 4), and TAK-536 as AT₁ receptor antagonist.

2.1 US FDA Approved Benzimidazole Derivatives as Angiotensin II Receptor Antagonists

2.1.1. Candesartan cilexetil

Candesartan cilexetil (ATACAND) (Figure 5), a prodrug of candesartan (Figure 6), was approved by the US FDA on Jun 4, 1998 and was first disclosed in the United States Patent Number 5,196,444. The chemical name of this drug is (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(1H-tetrazol-5ylphenyl)]benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester). Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexylcarboxynolox ethyl ester group. Following an oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral. It is a selective AT₁ receptor antagonist that is indicated for the treatment of hypertension and is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg, or 32 mg of candesartan cilexetil (Ardiana, Lestari, & Indrayanto, 2012; Joost, Schunkert, & Radke, 2011).
2.1.2. Telmisartan

Telmisartan (MICARDIS) (Figure 7) is a non-peptide AT₁ receptor antagonist. It was approved by the US FDA for the treatment of hypertension on April 4, 2000 and was first disclosed in the European Patent Number 0502314 B1. Telmisartan is chemically described as 4’-[(1,4’-dimethyl-2’-propyl [2,6’-bi-1H-benzimidazol]-1’-yl)methyl]-[1,1’-biphenyl]-2-carboxylic acid and is available as tablets for oral administration, containing 20 mg, 40 mg or 80 mg of telmisartan (Bakheit, Abd-Elgalil, Mustafa, Haque, & Wani, 2015; Frampton, 2011; Destro, Cagnoni, Dognini, Galimberti, Taietti, Cavalleri, & Galli, 2011).

![Figure 7: The chemical structure of Telmisartan.](image)

2.1.3. Azilsartan medoxomil

Azilsartan medoxomil (EDARBI) (Figure 8), a prodrug, is hydrolyzed to azilsartan (Figure 9) in the gastrointestinal tract during absorption, which is a selective AT₁ receptor antagonist. It is also known as azilsartan kamedoxomil as it is marketed as a potassium salt and has the chemical name as (5Methyl-2-oxo-1,3-dioxol-4-yl)methyl-2-ethoxy-1-[(2’-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4yl)methyl]-1H-benzimidazole-7-carboxylate monopotassium salt. This drug was first disclosed in the United Patent Number 7,157,584 B2. Edarbi was approved by the USFDA for the treatment of hypertension on February 25, 2011 and is available for oral use as tablets which contain 42.68 or 85.36 mg of azilsartan kamedoxomil equivalent to 40 mg or 80 mg, respectively, of azilsartan medoxomil (Angeloni, 2016; Perry, 2012; Zaiken & Cheng, 2011).

![Figure 8: The chemical structure of Azilsartan medoxomil.](image)

![Figure 9: The chemical structure of Azilsartan (TAK-536).](image)

2.2. Recent Benzimidazole Derivatives as Angiotensin II Receptor Antagonist

The in vitro and in vivo activity evaluation of 6-substituted benzimidazoles as angiotensin II receptor antagonists are described (Zhu, Bao, Ren, Da, Wu, Li, Yan, Wang, & Chen, 2016). Many synthesized benzimidazoles exhibited high affinities for AT₁ receptor when compared with telmisartan. The compound 2-[4-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazole-1-y1] methyl]-1H-indol-1-yl]benzoic acid (Figure 10) was found to cause a significant decrease in blood pressure. The toxicity study of this compound revealed that this had a low acute toxicity and further studies have been recommended for its therapeutic application.
Some AT$_1$ blockers having 6-substituted carbamoylbenzimidazoles were evaluated for their ability to displace [125I] Sar(1) Ile(8)-Ang II, which was specifically bound to the AT$_1$ receptor (Han, He, Wang, Xu, Hao, Liang, Zhang, & Zhou, 2015). The radio ligand binding assays showed that several compounds have a nanomolar affinity for the AT$_1$ receptor. It was also observed that the IC$_{50}$ values of some compounds for binding with AT$_1$ receptor were comparable with Losartan (IC$_{50}$ = 28.6 nM). The compound 1 (Figure 11) having IC$_{50}$ value of 1.1 nM was identified as a lead compound with good AT$_1$ receptor antagonistic activity and low toxicity.

A series of 5-nitrobenzimidazoles as ARB has been reported (Zhu, Da, Wu, Zheng, Zhu, Wang, Yan, & Chen, 2014). The compound, 2-(4-((2-butyl-5-nitro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)benzoic acid (Figure 12), exhibited a high affinity for the angiotensin II type 1 receptor with IC$_{50}$ value of 1.03±0.26 nM. It was concluded that this compound could be an effective and durable antihypertensive agent and must be further investigated for its therapeutic benefits.

A novel series of substituted benzimidazoles was designed and its ADMET (absorption, distribution, metabolism, excretion and toxicity) was predicted using in silico methods (Vyas, Gupta, Ghate, & Patel, 2014; Vyas, Ghate, Chintha, & Patel, 2013). It was reported that some key features in substituted benzimidazole derivatives, such as lipophilicity and H-bonding at the 2- and 5-positions of the benzimidazole nucleus, respectively, for the AT$_1$ receptor antagonist activity play an important role.

A series of 6-substitutedaminocarbonyl as well as acylamino benzimidazoles was prepared as nonpeptidic AT$_1$ receptor antagonists (Zhang, Wang, Yu, Zhou, Tao, Wang, Xue, Xu, Hao, Han, Fei, Liu, & Liang, 2013). Some compounds showed good binding affinity for the AT$_1$ receptor. Two compounds of this series, namely compound 2 (AT$_1$ IC$_{50}$ = 3 nM, AT$_2$ IC$_{50}$ > 10,000 nM, PA$_2$ = 8.51) (Figure 13) and compound 3 (Figure 14) (AT$_1$ IC$_{50}$ = 0.1 nM, AT$_2$ IC$_{50}$ = 149 nM, PA$_2$ = 8.43) displayed good antagonistic activity with the additional advantage of being orally active.
A series of benzimidazole derivatives bearing sulfonamide group was synthesized and tested for their antihypertensive activity with respect to losartan (Figure 15) (Bai, Wei, Liu, Xie, Yao, Wu, Jiang, Wang, & Xu, 2012). The compound 4 (Figure 16) was identified as the most active compound (IC$_{50}$ = 8.5 nM) that antagonized AT$_1$ receptor and showed more potency than losartan (IC$_{50}$ = 95 nM).

Wang et al. reported a series of 6-substitutedaminocarbonyl benzimidazoles as nonpeptidic AT$_1$ receptor antagonists (Wang, Zhang, Zhou, Li, Xue, Xu, Hao, Han, Fei, Liu, & Liang, 2012). The preliminary screening revealed that all compounds of this series were potent, whereas the compound 5 (Figure 17) was found to be an orally active, potent AT$_1$ receptor antagonist with a low toxicity; this requires further investigation.

A study focused on the replacement of the tetrazole moiety by other acidic groups to improve the oral bioavailability and also solve the synthetic and metabolic problems has been performed (Kohara, Kubo, Imamiya, Inada, & Naka, 1996). The reported benzimidazole 7-carboxylic acids containing acidic heterocyclic rings as novel tetrazole bioisostreres were checked for their AT$_1$ antagonistic activity, wherein the biososteres of tetrazole compounds of chemical formula 6-11 were found more potent than their tetrazole counterpart of chemical formula 12 (Figure 18).

Novel (6-oxo-3-pyridazinyl)-benzimidazole derivatives obtained by the derivatization of pimobendan have been prepared as AT$_1$ receptor antagonists (Dorsch, Mederski, Beier, Lues, Minck, & Schelling, 1994). Pimobendan (Figure 19), an inhibitor of phosphodiesterase III showed significant
binding with the AT$_1$ receptor having IC$_{50}$ value of 1.7 µmol. The compound 13 (Figure 20) having an IC$_{50}$ value of 1.6 µmol was found to have a better affinity to the receptor than pimobendan.

A research group (Palkowitz, Steinberg, Zimmerman, Thrasher, Hauser, & Boyd, 1995) reported a series of 5-aryl benzimidazole derivatives, wherein the compound 14 (Figure 21) was obtained as the most potent AT$_1$ receptor antagonist.

A study of 5-nitrobenzimidazole derivatives (Bali, Bansal, Sugumaran, Saggu, Balakumar, Kaur, Bansal, Sharma, & Singh, 2005) describes the synthesis of substituted benzimidazole by varying substitutions on C-2 of benzimidazole ring. These compounds were designed by a computer aided drug design with respect to losartan with the expectation of having more potent AT$_1$ receptor antagonists. The study concluded that the compound 15 (Figure 22) having the nitro group at C-5 and n-butyl side chain at the C-2 of benzimidazole moiety was more potent than candesartan.

Similarly, the biphenyl tetrazole moiety was replaced with (phenylpyrrole) tetrazole moiety in a series of 2-alkyl benzimidazoles (Xu et al., 2007). The synthesized compounds were subjected for their AT$_1$ antagonistic activity and it was revealed that this bioisosteric replacement produced extremely potent compounds 19 and 20 (Figure 24).
Substituted carboxamido benzimidazole derivatives with C-5 amino group on benzimidazole nucleus with different alkyl or aryl carbonyl chains as AT\textsubscript{1} antagonists were developed (Shah, Sharma, Bansal, Bansal, & Singh, 2008). It was observed that the compounds 21-24 (Figure 25) were non-competitive antagonists, whereas the compounds 25-27 (Figure 25) were competitive antagonists. It was also suggested that a methyl group can be accommodated in the AT\textsubscript{1} receptor pocket, that a suitable alkyl group may increase the antihypertensive activity, and that an increase in the bulk of the alkyl or aryl moieties retards the activity.

Some benzimidazoles have been synthesized by replacing the tetrazole ring of biphenyl moiety with imidazole, 5- chloroimidazole, 1,2,4-triazol and imidazoline ring system with an additional methyl benzimidazole moiety at C-6 of benzimidazole (Guo, Lin, Rui, Xiao-Xiao, Bo-Gang, & Xiao-Xia, 2008). These compounds were subjected for their AT\textsubscript{1} receptor antagonistic activity. The in vitro and in vivo results revealed that imidazoline derivative 30 (Figure 27) having an IC\textsubscript{50} value of 2.6 x 10\textsuperscript{-7} \textmu M had an almost equipotent activity to that of telmisartan.
3. DISCUSSION

The Renin Angiotensin System (RAS) is implicated in the pathogenesis of hypertension. Three types of antihypertensive drugs are used that affect this system. These are renin inhibitors, for example, aliskiren, remikiren, enalkiren, and zankiren; Angiotensin Converting Enzyme (ACE) inhibitors, such as lisinopril, capttopril, enalapril, ramipril, and fosinopril; and angiotensin II receptor antagonists, for example, losartan, valsartan, irbesartan, telmisartan, olmesartan, and candesartan. Recently, benzimidazole derivatives have emerged as an important scaffold for the development of angiotensin II receptor antagonists as antihypertensive agents. Some of these benzimidazole derivatives, for example, candesartan, telmisartan, and azilsartan, have already been approved by the USFDA for the treatment of hypertension and related cardiac conditions. Based on the relationship between the AT$_1$ receptor and blood pressure regulation as well as the structure activity relationship studies of benzimidazole derivatives, newer benzimidazole derivatives as the AT$_1$ receptor antagonists are being developed for the treatment of hypertension. This is evident by the filing of recent patent applications related to benzimidazole derivatives as AT$_1$ receptor antagonists, such as United States Patent Application Number 20120172401 A1, United States Patent Application Number 2009054502 A1, PCT Publication Number WO 2009/076288 A1, PCT Publication Number WO 2008/153857 A1, PCT Publication Number WO 2004/082621 A1, Russian Patent Number 002501798, Chinese Patent Publication Number 10276534, and Japan Patent Application Number 2011101381. It has been suggested by researchers that the alkyl group at C-2 position of benzimidazole moiety is essential for lipophilic interaction with the receptor and an ionized acidic group, such as a tetrazole or carboxyl group, on biphenyl moiety is responsible for ionic interaction with the AT$_1$ receptor (Vyas & Ghate, 2010; Bergsma, Ellis, Kumar, Nuthulaganti, Kersten, Elshourbagy, Griffin, Stadel, & Aiyar, 1992; Underwood, Strader, Rivero, Patchett, Greenlee, & Prendergast, 1994; Carini, Duncia, Aldrich, Chiu, Johnson, Pierce, Price, Snatella, Wells, Wexler, Wong, Yoo, & Timmermans, 1991; Kubo, Yasuhisa, Imamiya, Yoshihiro, Inada, Furukawa, & Nishikawa, 1993; Ries, Mihm, Narr, Hasselbach, Wittneben, Entzeroth, Van Meel, Wienen, & Hauel, 1993). The N-3 of benzimidazole is likewise important as it also interacts with these receptors through hydrogen bonding. Besides these essential features, other possible variations have also been reported by the researchers mentioned above. A carboxyl group at C-7 position, a small alkoxy group at C-2 position, and an acylamino group at C-6 position of benzimidazole nucleus have been reported for better AT$_1$ receptor antagonistic activity. Accordingly, scientists are working to develop newer AT$_1$ receptor antagonists that contain a benzimidazole nucleus with emphasis in order to maintain their potency, duration of action, and bioavailability.

CONCLUSION & RECOMMENDATION

It is evident from the literature, that benzimidazole derivatives are an important scaffold for the development of clinically used drugs. Many researchers and scientist have published and established important structure activity relationship studies related to the diverse pharmacological activities of this chemical moiety. A complete knowledge and understanding of the structure activity relationship studies of benzimidazole derivatives as angiotensin receptor antagonists is helping the scientists to develop novel benzimidazole derivative as angiotensin receptor antagonists. In this review, the authors have tried to highlight the potential development of novel benzimidazole derivatives as AT$_1$ receptor antagonists that may be helpful to the medicinal chemist fraternity for a target oriented and comprehensive information. Further, it would be interesting to see how many newer benzimidazole derivatives will be able to see the light of future as approved drugs for the treatment of hypertension.

Keeping in mind the potential of benzimidazole derivatives as an important scaffold for the development of newer angiotensin receptor antagonists for the treatment of hypertension. It is recommended to design, synthesize, and develop newer molecules containing this chemical moiety as angiotensin receptor antagonists. It is also recommended to perform in silico toxicity studies, drug likeliness prediction studies, and molecular
docking studies of already reported and established benzimidazole derivatives which have already been screened for other types of biological activities. This may also result in the identification of a safe, potent, and efficacious benzimidazole derivative as an angiotensin receptor antagonist.

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