Substituted Benzimidazole Derivatives as Angiotensin II -AT_1 Receptor Antagonist: A Review

V.K. Vyas* and M. Ghate

Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad, 382 481 Gujarat, India

Abstract: The renin angiotensin system (RAS) plays an important role in regulation of blood pressure and fluid-electrolyte homeostasis. The renin-angiotensin system consists of a cascade of enzymatic reactions producing angiotensin II (Ang II). Ang II is a vasoconstrictive peptide hormone that exerts a wide variety of physiological actions on cardiovascular, renal, endocrine and central nervous systems. The RAS can be inhibited at various points to control pathogenesis of hypertension. Renin inhibitors and angiotensin-converting enzyme (ACE) inhibitors were the earliest RAS blocking agents. A relatively new class of compounds known as Ang II receptor antagonists (SARTANs) is developed for the treatment of hypertension. They exert their action by blocking the binding of Ang II on AT_1 receptor. Angiotensin converting enzyme (ACE) inhibitors are associated with incident of side effects such as cough and angioedema while clinical trials with Ang II receptor antagonists have confirmed that these drugs are safe and efficacious for the treatment of hypertension. Based upon the understanding of molecular interaction of Ang II receptor antagonists with AT_1 receptor some of the common structural features have been identified, such as a heterocyclic (nitrogen atom) ring system, an alkyl side chain and an acidic tetrazole group. Research efforts for development of new molecules with similar structural features have led to the discovery of various non-peptidic Ang II receptor antagonists with different substituted heterocylic such as imidazole (losartan) and benzimidazole (candesartan and telmisaratn). In this study we have critically reviewed various benzimidazole substituted compounds as Ang II- AT_1 receptor antagonists and explored other potential clinical uses for this class of compounds.

Keywords: Angiotensin II, AT_1 receptor, AT_2 receptor, ACEIs, Ang II receptor blockers, substituted benzimidazole derivatives.

1. INRODUCTION

The renin-angiotensin system (RAS) plays an essential role in blood pressure regulation, fluid and electrolyte homeostasis in human beings for management of hypertension [1-3]. The linear octapeptide Ang II (Asp^1-Arg^2-Val^3-Tyr^4-Ile/Val^5-His^6-Pro^7-Phe^8) is a potent vasoconstrictor produced by the renin-angiotensin cascade which regulates blood pressure homeostasis, fluid volume and electrolyte balance. Ang II interacts with specific cellular receptors causing aldosterone secretion, renal sodium retention, vasoconstriction, and other biological effects [4-6]. Ang II interacts primarily with two definite receptor proteins, AT_1 and AT_2 [1]. AT_1 is the primary vascular receptor linked with regulation of blood pressure. It is responsible for virtually all the well-known physiological actions of Ang II in cardiovascular, neuronal, renal, hepatic, endocrine, and other target cells [7]. Several types of drugs are available which can block the RAS at any site within the system and can be useful in the treatment of hypertension [8]. Renin inhibitors and angiotensin-converting enzyme (ACE) inhibitors were the earliest of RAS blocking agents to have broad therapeutic success, with numerous clinical trials indicating their effectiveness in the treatment of congestive heart failure, renovascular hypertension and essential hypertension [9-12]. Ang II receptor antagonists, a class of RAS blockers, have recently proved to be safe and effective antihypertensive agents both in animal and human studies [13-27]. This review provides an opportunity for researchers to design highly potent Ang II-AT_1 receptor antagonists in the future.

*Address correspondence to this author at the Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, S.G. Highway, Chharodi, Ahmedabad, 382 481, Gujarat, India;
Tel: +91 9624931060; Fax: +91 2717 241916;
E-mail: vicky_1744@yahoo.com, vivekvyas@nirmauni.ac.in

2. RENIN-ANGIOTENSIN SYSTEM (RAS)

RAS is a complex, highly regulated pathway that is integral in the regulation of blood volume, electrolyte balance and arterial blood pressure [1, 2]. It consists of two enzymes, renin and angiotensin converting enzyme (ACE), whose purpose is to release octapeptide Ang II, from its endogenous 452 amino acid precursor angiotensinogen, a single obligate precursor protein. Angiotensinogen is the source of all angiotensin peptides (Fig. **1**). Circulating angiotensinogen (from liver) is primarily cleaved by protease renin (from kidney) to yield 10 amino acid peptide angiotensin I (Ang I), which in turn is processed by angiotensin converting enzyme (ACE) (in lungs) to produce the active octapeptide angiotensin II (Ang II). Renin is an aspartyl protease; its secretion is mediated by multiple signals, afferent glomerular arterioles stimulate the juxtaglomerular (JG) cells to increase or decrease renin release. An increase in the stretch implies a raised blood pressure and results in reduced release of renin, where as decrease in the stretch increases renin secretion. Adrenergic receptors in the

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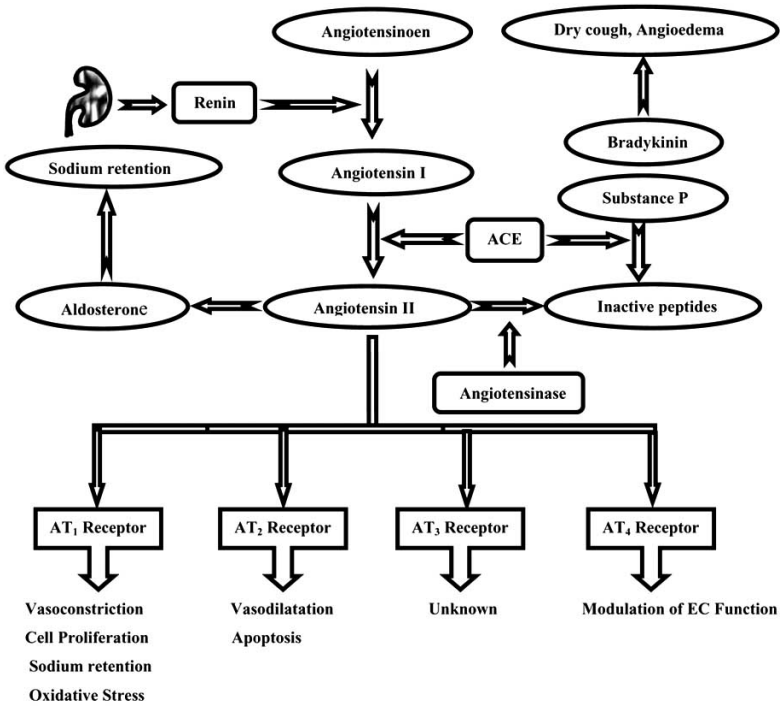


Fig. (1). Renin-angiotensin system (RAS).

JG cells react to neurogenic signals conveyed either directly by renal nerves or circulating catecholamines. P-Adrenergic receptor stimulation is mainly responsible for renin secretion. Renin is also synthesized in other tissues, including ovary, adrenal gland, brain, visceral adipose tissue, heart and vascular tissue [28-32]. Angiotensin converting enzyme (ACE) is a zinc protease, a membrane-bound exopeptidase and is localized on plasma membranes of various cell types, including vascular endothelial cells, microvillar brush border epithelial cells (e.g., renal proximal tubule cells) and neuroepithelial cells. ACE also exists in soluble form in plasma, but this form may simply reflect turnover and clearance of membrane-bound ACE. ACE metabolizes a number of other peptides, including vasodilator peptides bradykinin and kallidin, to inactive metabolites. Thus, functionally, the enzymatic actions of ACE potentially result in increased vasoconstriction and decreased vasodilation [33, 34]. Ang II is the primary active product of RAS and there is evidence that other metabolites of Ang I and II may have significant biological activity, particularly in tissues. Inactive peptides are formed by the sequential removal of amino acids from the N-terminus of Ang II by the action of angiotensinase (Fig. **1**).

Ang II increases blood pressure through various mechanisms on different organ systems. In vascular smooth muscle, it induces vasoconstriction, in the adrenal cortex, acts on the zona glomerulosa and stimulates aldosterone biosynthesis and secretion; it also modulates fluid balance by affecting tubular sodium reabsorption, besides constriction of both efferent arterioles and the glomerular mesangium. The effect of Ang II on the glomerular mesangium influences regulation of renal blood flow and glomerular filtration, thereby inhibiting renin release. Ang II stimulates catecholamine release by acting on adrenal medulla and facilitates neurosynaptic transmission and stimulates autonomic ganglia. In the central nervous system, Ang II increases circulating volume by increasing the secretion of corticotrophin and vasopressin, increasing sympathetic activity, and augmenting appetite and thirst [35-37]. The development of specific nonpeptide Ang II-AT_1 receptor antagonists has led to major advances in the pathophysiology of the RAS.

3. ANGIOTENSIN II RECEPTORS

Ang II exhibits its effects by binding with specific receptors in plasma membrane of various tissues. Ang II binds with high affinity to two distinct receptors, the type 1 and type 2 angiotensin receptors (AT_1 and AT_2) both are 7-transmembrane spanning receptors that belong to the G protein-coupled receptor (GPCR) superfamily. The AT_1 receptor is composed of 359 amino acids where as AT_2 receptor has 363. It is observed that angiotensin receptors can be differentiated into two distinct subtypes by radio-ligand-receptor binding studies by using the specific, non-peptide antagonist's losartan (DuP 753) and PD12317736-38 [38-40]. The AT_1 receptor found in virtually all vascular tissue predominates in the kidney glomeruli [41] and mediates most of the established physiological and pathophysiological effects by coupling to a transmembrane G protein [42, 43] and it can be inhibited by guanine nucleotides [44]. Pharmacological actions of Ang II appear to be mediated via the AT_1 receptor which is a major targets for drug development and the non-peptide antagonists of AT_1 (the "sartans") led therapeutics in the treatment of hypertension and cardiovascular diseases. AT_2 receptor is abundant during foetal life in the brain, kidney and other sites. It is less in adult tissues. Its signal pathways include serine and tyrosine phosphatases, phospholipase A2, nitric oxide and cGMP. AT_2 receptor mediates vasodilation and antiproliferative effects. A recent study suggested the implications of AT_2 receptor in programmed cell death

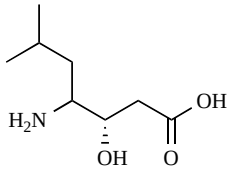
apoptosis [45-46]. Activation of AT_2 receptors in kidney, may influence proximal tubule sodium reabsorption and stimulate the conversion of renal prostaglandin E2 to prostaglandin F2α. [47-49]. Function of the type-3 (AT_3) receptors is unknown. Type-4 (AT_4) receptors specifically binds Ang IV (Ang 3-8), located in brain and kidney and are associated with the release of plasminogen activator inhibitor 1 by Ang II and by N-terminal truncated peptides (Ang III and Ang IV). Its signal mechanisms are unknown [50]. In other tissues Ang II receptor subtypes exhibit different distributions. For example, in rat brain AT_1 receptor is present in pituitary and periventricular organs, but AT_2 receptors are found in thalamus, locus coeruleus and cerebellum [51-53]. A current hypothesis proposes that Ang-AT_1 receptor and Ang-AT_2 receptors have opposing effects suggesting physiological antagonism between the two receptors [54].

4. INHIBITORS OF RENIN ANGIOTENSIN SYSTEM (RAS)

RAS is recognized for its pathological role in hypertension, mediated by AT_1 receptor. RAS can be inhibited at various points (Fig. **2**). Inhibition of RAS is an effective way to control pathogenesis of cardiovascular and renal disorders. Earlier studies showed that β blockers reduce the release of renin from juxtaglomerular apparatus by reducing plasma renin levels and blocking sympathetically (β_1) mediated renin release resulting in lower blood pressure [55]. Inhibitors of angiotensin-converting-enzyme (ACE) reduce conversion of Ang I to Ang II [56]. It is not a rate-limiting step in the production of Ang II. ACE inhibitors also inhibit inactivation of bradykinin and an increased level of bradykinin which was thought to contribute as side-effects of ACE inhibitors, like cough [57] and angiooedema [58]. Angiotensin-receptor blockers (ARBs) specifically interfere with the interaction of Ang II with AT_1 receptor.

4.1. Renin Inhibitors

Inhibition of catalytic activity of renin at the point of activation of RAS results in decreased formation of Ang II. The earliest studies on block of RAS were based upon antibodies raised against renin [59, 60]. Immunological inhibition of renin results in lowering of blood pressure in volume depleted normotensive marmosets [61] and gave evidence of renin inhibition. Pepstatin [62] (N-isovaleryl-Val-Val-Sta-Ala-Sta) is a naturally occurring inhibitor of renin. The activity of pepstatin is due to the central statine residue (Fig. **3**). A new clinical drug candidate enalkiren is extensively studied in preclinical and clinical experiments. It has shown to be efficacious, if given intravenously; however, it lacks significant bioavailability [63].



Statine

Fig. (3). Chemical structure of statine.

Lipophilic analog, **A-72517** (zankiren) has demonstrated increased oral bioavailability and efficacy but it has been withdrawn from clinical trials for undisclosed reasons. The clinical utility of this class of agents were challenged by poor pharmacokinetic properties such as low oral bioavailability. In spite of this, other orally active non-peptidic renin inhibitors are still under development. The most recent class of agents that block RAS to be introduced are direct renin inhibitors (Fig. **4**) represented by aliskiren [64] is recently approved for treatment of hypertension. Renin inhibitors may be clinically indicated in combination therapy with other antihypertensive agents such as diuretics, ACEIs inhibitors and ARBs.

4.2. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

ACEIs prevent conversion of Ang I into vasoconstricting octapeptide Ang II, by blocking action of ACE and thereby reducing circulation and local levels of Ang II. They are widely used for the treatment of patients with high blood pressure, cardiac failure and diabetic nephropathy. ACE cleaves the C-terminal dipeptide of various oligopeptides, including bradykinin and Ang I. ACE regulates balance between the vasodilatory and natriuretic properties of bradykinin and vasoconstrictive and salt-retentive properties of Ang II. ACEIs alter this balance by decreasing formation of Ang II and degradation of bradykinin [65, 66]. In a search for orally active inhibitors of ACE; the first of these, captopril, was designed, which is a prototype of the sulfhydryl-containing ACE inhibitors. Sulfhydryl-containing amino acids serve as ligand for zinc moiety and attributed to many undesirable effects, such as free-radical scavenging effects on prostaglandins, proteinuria, skin rashes and altered taste [67, 68]. Successive work led to the development of ACEIs replacing sulfhydryl group with carboxyl group. A majority of the other ACE inhibitors contain a carboxyl reactive moiety (e.g., lisinopril, benazepril, quinapril, ramipril, perindopril, cilazapril, trandolapril) and fosinopril (Fig. **5**) the only FDA-approved ACE inhibitor that contains phosphinyl group as its moiety [69-72]. The majority of ACE inhibitors are administered as prodrugs that remain inactive until esterified in the liver [73, 74].

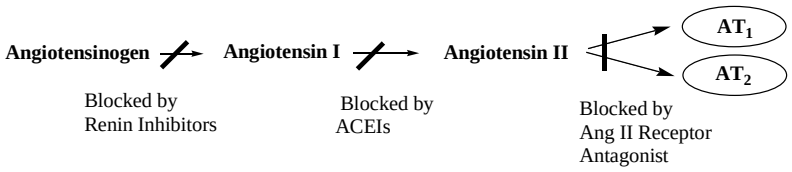


Fig. (2). Block of Renin Angiotensin System (RAS) at various points.

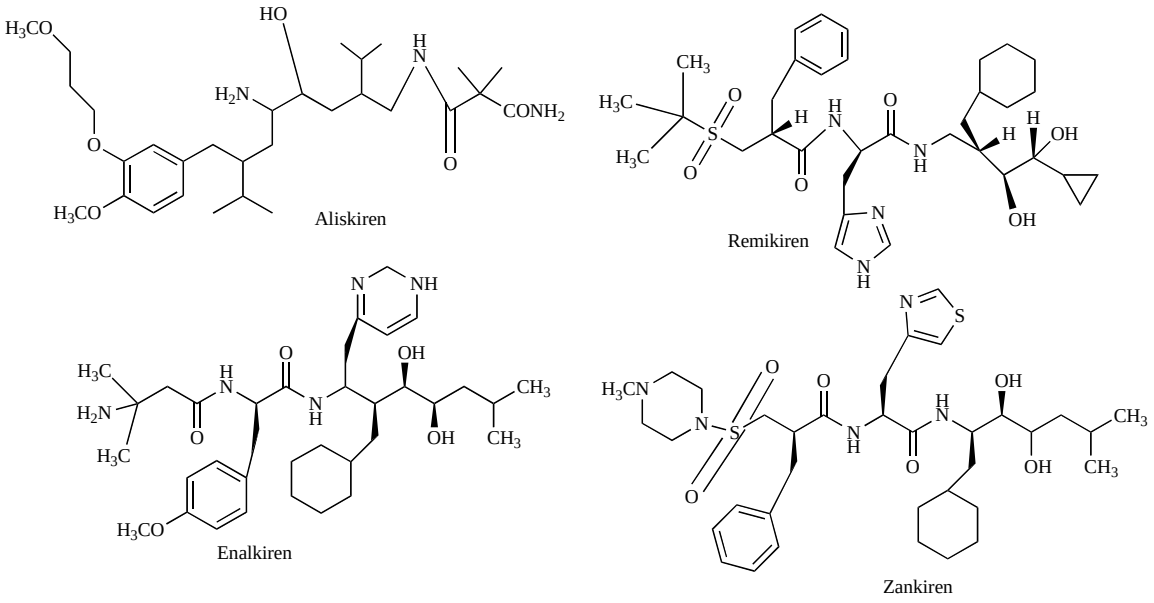


Fig. (4). Chemical structure of orally active renin inhibitors.

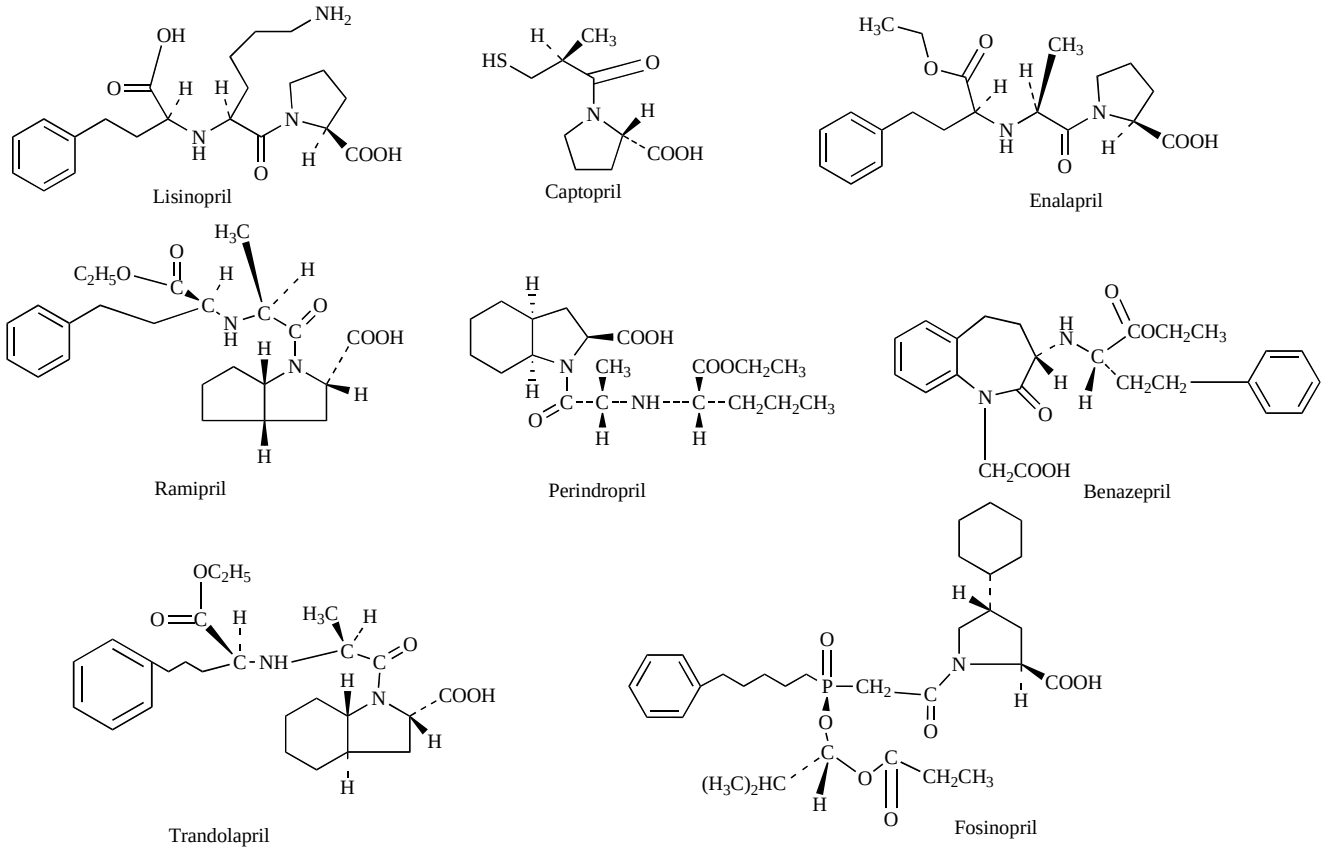


Fig. (5). Chemical structure of angiotensin converting enzyme inhibitors (ACEIs).

ACEIs are generally well tolerated by most patients and have proved effective in the treatment of hypertension but they are associated with some significant side effects like dry cough and angioedema [57, 58]. ACEIs along with other antihypertensive agents such as beta-blockers and calcium channel blockers are generally found potent in reducing blood pressure.

4.3. Angiotensin II Receptor Blockers (ARBs)

Saralasin (Fig. **6**), the first non-selective, specific peptide antagonist of Ang II discovered, was reported to decrease blood pressure in both animals and human beings with systemic hypertension [75-77].

On the other hand, saralasin's clinical efficacy as antihypertensive agent was restricted by its short half-life,

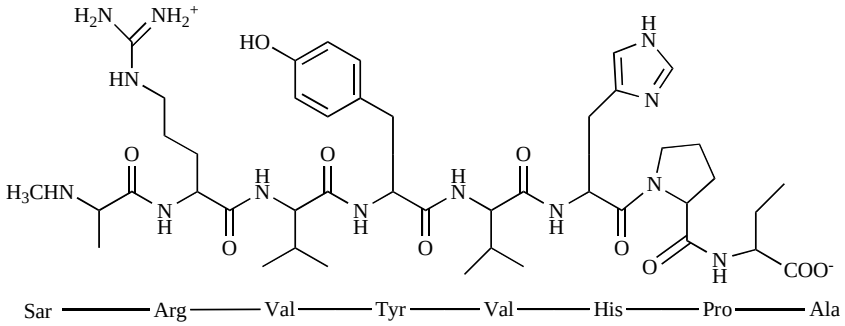


Fig. (6). Chemical structure of saralasin.

significant agonistic properties, poor oral bioavailability and intravenous administration [78, 79]. Later, simple benzyl-substituted imidazoles derivatives were synthesized as a series of low molecular weight nonpeptide analogues that possess weak but selective, competitive AT_1 receptor blocking property [80, 81]. Their bioavailability is poor and the duration of action is short [82]. These compounds with synthetic modifications, led to increasingly potent and orally active nonpeptide AT_1 receptor blockers i.e., losartan, telmisartan, valsartan, tasosartan, milfasartan, zolasartan, candesartan, olmesartan irbesartan, and saprisartan (Fig. **7**) that were evaluated for their affinity, potency and antihypertensive effects.

Non-peptide antagonists and peptide antagonists block the action of Ang II on AT_1 binding site in a competitive and reversible manner but display non-classical patterns of antagonism [83]. ARBs act by inhibiting Ang II actions at the receptor level, rather than inhibiting its synthesis. They must antagonize AT_1 mediated effects of Ang II no matter the way it is synthesized. Optimization of these compounds led to discovery of orally active, most potent, losartan (2-N-Butyl-4-chloro-5-hydroxymethyl- 1-(2'-(l*H*-tetrazole-5-yl) biphenyl-4-yl) imidazole, potassium salt) [84], a novel Ang II receptor antagonist [85]. Pharmacophore of Ang II (Asp_1-Arg_2-Val_3-Tyr_4-Ile_5-His_6-Pro_7-Phe_8) (Fig. **8**) consists of phenolic group of Tyr_4, His_6 residue, aromatic ring of Phe_8 and C-terminal carboxylate. His_6 residue is important for receptor recognition, while the other three groups are essential for agonist activity. The remaining groups in Ang II appear to have only supportive roles [86]. As a result, the structural requirements for binding to either or both AT_1 and AT_2 of Ang II have been defined.

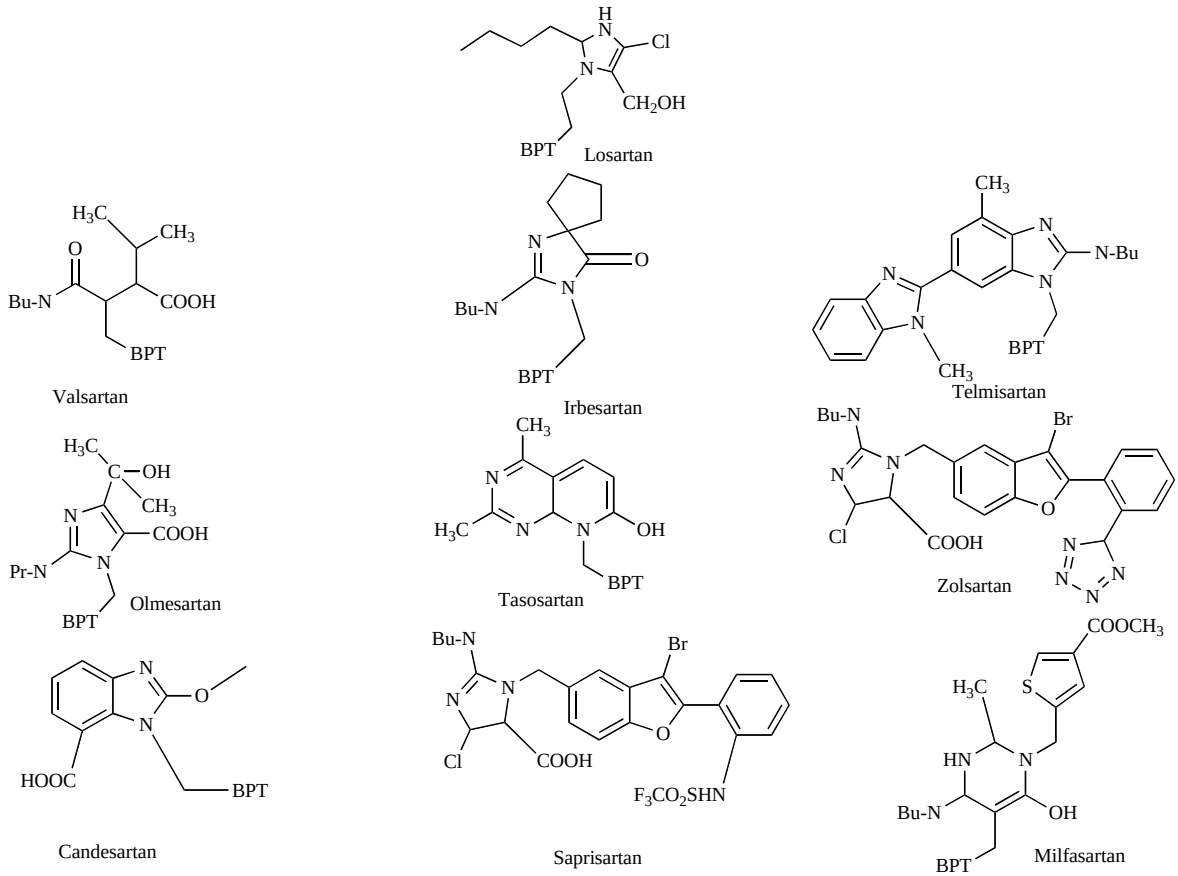


Fig. (7). Chemical structure of currently approved Ang II receptor blockers (ARBs).

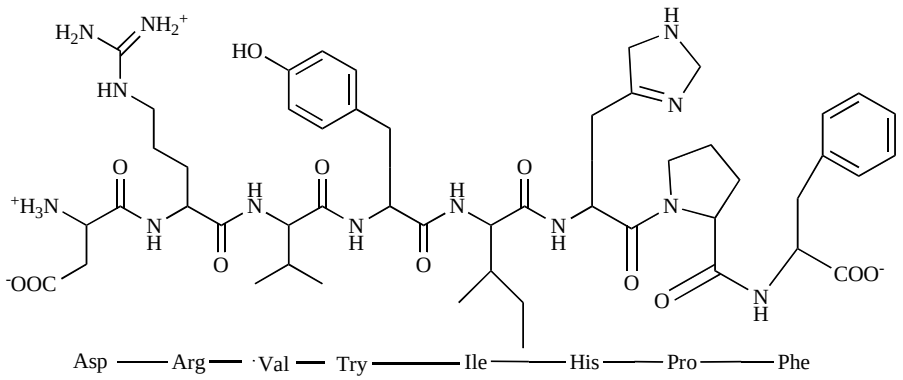


Fig. (8). Chemical structure of Angiotensin II.

This discovery has led to explosion of a number of new oral, nonpeptide, Ang II receptor antagonists similar to losartan with similar or improved pharmacological activity. The therapeutic effect of ARBs has demonstrated that these drugs are safe and efficacious for the treatment of hypertension and have improved side effect profile over ACEIs.

5. MEDICINAL CHEMISTRY OF SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS ANGIOTENSIN II-AT$_1$ RECEPTOR ANTAGONIST

Primary sequence data for human AT_1 receptor [87] is available which led to the development of a 3D receptor model [88] used to rationalize structure- activity relationship (SAR) for selective Ang II antagonists. Carini *et al.* [89] proposed a SAR of Ang II receptor antagonists, a biphenyl group of losartan (imidazole nucleus), able to fit into third hydrophobic pocket and presence of acidic group on biphenyl is very important like tetrazole group or an acidic isostere at ortho position of the biphenyl group able to show good oral activity, and tetrazole containing compound have good binding affinity. Tetrazole group have four heteroatom and they support negative charge. The tetarzole require electronic distribution to interact better with the positive charge on Ang II receptor. Heterocyclic ring confirmed the need of alkyl chain at C2. Hydrogen on α- carbon shows high reactivity and unsaturation in the side chain increases binding affinity. C5 of imidazole ring generally prefers hydrogen bonding substitution such as alcohol, aldehydes or carboxylic acid but a wide range of substitution can be allowed. The literature regarding ARBs reveals exhaustive reviews on the methods for improving pharmacological activity, increase in potency, duration of action, binding affinity, oral bioavailability and selectivity. The available data from the literature has explained the extensive SAR work based upon replacement of imidazole with other heterocyclic and modification of acidic functional group. For this purpose, different substitutions in benzimidazole nucleus are studied. Among the different substituents, a carboxylic group at C7 and ethoxy group at C2, (candesartan) [90] and a acylamino at C6 with linear butyl chain at C2 (telmisartan) [91] of benzimidazole nucleus have been found to be favorable for Ang II antagonism.

5.1. Discovery of Candesartan and Telmisartan

Keiji Kubo and colleagues at Takeda Chemical Industries of Osaka in Japan [90] were the first to discover a series of 2-substituted benzimidazole bearing biphenyl moiety derivatives such as, **CV-11194** (Fig. **9**) and **CV-11974** (candesartan). They evaluated Ang II receptor antagonistic activity (Inhibition of specific binding of [^{125}I] Ang II to bovine adrenal cortex: IC_{50} = 1.1X 10^{-7} M). Keiji Kubo *et al.* studied SAR for a series of 2-substituted benzimidazole on binding affinity and inhibition of Ang II induced pressor response and suggested that ethoxy group and ethyl group were the best substitutes on C2 of benzimidazole nucleus and carboxyl group at C7 and tetrazole ring at C2' position. They are the most important for potency and oral activity of compounds. Most extensive variations were applied to C2 position of benzimidazole nucleus. An ethoxy group at C2 benzimidazole moiety of lead candesartan was considered essential for Ang II antagonistic. The importance of position of carboxyl group **1-3** (Fig. **10**) was demonstrated in inhibition of Ang II induced contraction in rabbit aortic strips (IC_{50} of **1** =450 X 10^{-7} M, IC_{50} of **2** = 130 X 10^{-7} M and IC_{50} of **3** = 9.3 X 10^{-7} M).

The inhibitory effect of 7- carboxylic acid **4 (CV-11974)** (Fig. **10**) was more potent than other carboxylic acids. Ang II antagonistic activity of substituted benzimidazole was investigated by *in vitro* assay. It includes Ang II receptor binding assay and Ang II induced vasoconstrictor assay as well as *in vivo* assay such as Ang II induced pressor response in rat. Further it was found that **4** abolish Ang II induced pressor response in conscious normotensive rat and reduced mean arterial blood pressure (MABP) in hypertensive rats in a dose dependent manner. A single dose of **CV-11974** at 1mg/kg intravenous reduce MABP by more than 50 mmHg with a duration of action exceeding 24 hr. QSAR study (Hansch-Fuzita) was performed to gain insight into the nature of interaction compounds with Ang II-AT_1 receptor and to explore the effects of substitution on C2 of benzimidazole ring on binding affinity. It suggested a need for substituent that is small as well as lipophilic to certain degree for optimal binding affinity. QSAR study could not estimate electronic effect of substituent at C2 due to great contribution of steric effect. The nitrogen atom contributed to antagonist-receptor complex formation by acting as an electron donor in hydrogen bonding. The study identified common features responsible for Ang II antagonist. An ethoxy group was found to be the best substitution at 2-position and 2-ethoxy derivative (**4**: **CV-11974**) selected for further evaluation. Candesartan is demonstrated for a

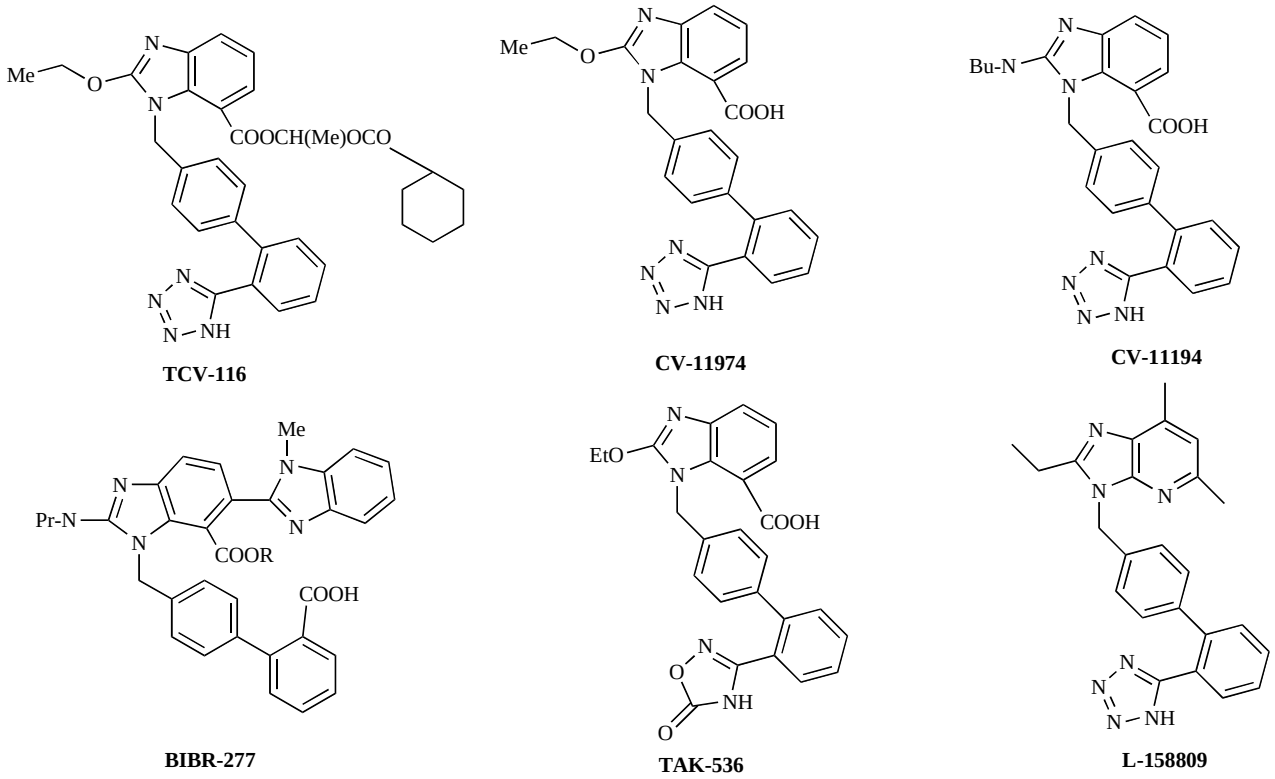
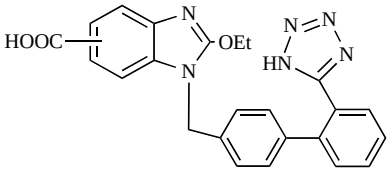


Fig. (9). Chemical structure of substituted benzimidazole derivatives as Ang II-AT1 receptor antagonist.



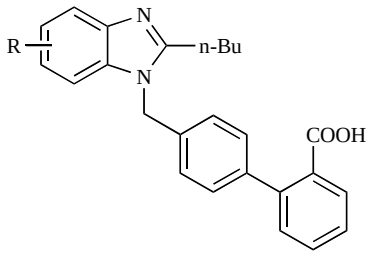
1: 4-COOH, **2**: 5-COOH, **3**: 6-COOH, 4:**7**-COOH

Fig. (10). Chemical structure of 4, 5, 6, and 7-carboxylic acid substituted benzimidazole.

selective and competitive antagonist of AT_1 receptors [92]. Candesartan is administered as an ester carbonate prodrug **TCV-116** (Candesartan cilexetil) [93] (Fig. **9**) that undergoes activation during gastrointestinal absorption. See S. and Stirling A.L. [94] reviewed mechanism of action, pharmacokinetics, pharmacodynamics, clinical efficacy and adverse effects of candesartan cilexetil. It was found that candesartan cilexetil is an effective antihypertensive drug that can be used alone or in combination with other antihypertensive drugs and it is beneficial drug over ACEIs with no drug interaction.

Extensive investigation on Ang II antagonists, particularly focusing on substitution at C6 of the benzimidazole has resulted in compound 6-(benzimidazol-2-yl) benzimidazole **BIBR-277** (telmisartan) by Uwe J. Ries [91] and colleagues. New Ang II antagonists were explored in this study with the replacement of imidazole ring by benzimidazole ring in the main skeleton.

A series of benzimidazole analogs were synthesized in which a set of substituents was systematically varied along the four phenylene ring positions C4-C7. SAR study revealed that receptor affinity is not influenced significantly by small methyl and amino substituents, regardless of their positions. Binding model study suggested that formation of a



5: R= 6-$NHCOCH_3$, **6**: R= 6-$NHCONHC_6H_{11}$, **7**: R= 5-$NHCOCH_3$, **8**: R= 5-$NHCOCH_3$,
9: R= 5-$NHCONHC_6H_{11}$,**10**: R= 7-$NHCONHC_6H_{11}$, **11**: R=H, **12**: R= 6-$NHCONHC_6H_{11}$

Fig. (11). Chemical structure of benzimidazole, substituted at phenylene ring positon 4-7.

hydrogen bond from the receptor to N-3 of the benzimidazole moiety is important for receptor affinity. Substituents in C6 (**5** and **6**) (Fig. **11**) seem to contribute additional binding energy. The IC_{50} (for specific binding of [^{125}I] Ang II to rat lung membrane preparation) values of the compounds **7** (460 nM), **8** (1800 nM) (Fig. **11**), **9** (800 nM) and **10** (160 nM) (Fig. **11**) were fairly similar to that of the unsubstituted benzimidazole **11** (400 nM) which indicate that there are areas at the receptor binding site tolerating these substituents. Compound **12** (IC_{50} = 26 nM) is approximately 16-fold more potent as compared to unsubstituted benzimidazole compound **11** (IC_{50} = 400 nM). In contrast to the amino compounds **13** (390 nM) and **14** (160 nM), the acylated analogs **15** (86 nM), **16** (24 nM) and **17** (26 nM) (Fig. **12**) showed increased potency by about 1 order of magnitude.

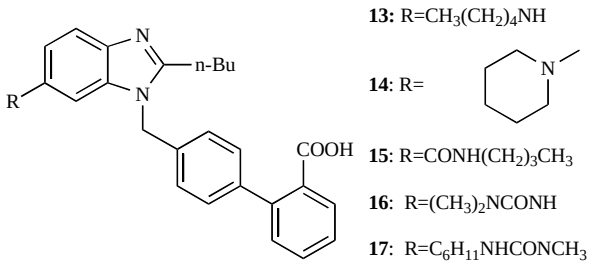
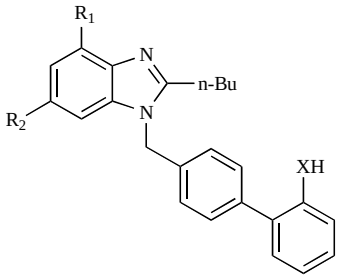


Fig. (12). Benzimidazole substituted with alkylamino and acylamino residues at position 6.

The increased binding energy is probably a result of an additional hydrogen bond with carbonyl oxygen of carboxamide group which functions as a hydrogen acceptor. Substitution with an additional benzimidazole (**18-21),** an imidazopyridine (compound **22** and **23),** or a pyridine



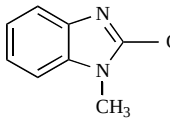
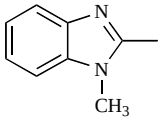
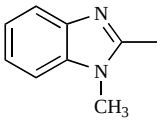
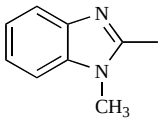
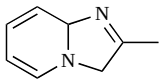
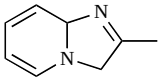
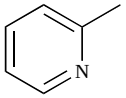
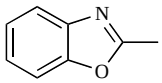
Comp.	R1	R2	XH	IC_{50} X 10^{-7}M
18	CH_3		COOH	3
19	H		COOH	3
20	CH_3		Tetrazole	13
21	H		Tetrazole	5
22	CH_3		COOH	4
23	CH_3		Tetrazole	3
24	CH_3		Tetrazole	5
25	CH_3		Tetrazole	11

Fig. (13). Chemical structure and IC50 values of benzimidazole, substituted with nitrogen-containing heterocycles at position 6.

(compounds **24** and **25)** led to highly active antagonists with IC_{50} (Fig. **13**) values in a low nanomolar range.

Compound **18** (**BIBR-277**: telmisartan) is a representative compound for a series of 6-substituted benzimidazole. It incorporates carboxylic acid as the biphenyl ionized acidic group. Positioning and nature of the substituents exhibit a strong influence on potency. 6-position is superior to 4, 5 and 7-position of benzimidazole nucleus. Compounds **13-25** were tested for Ang II antagonism in normotensive rats. After intravenous (iv) administration, they exhibited strong inhibition of Ang II pressor response corresponding to their *in vitro* activity. On the basis of conformational analysis and molecular modeling, SAR study was proposed which revealed that substituents with additional hydrogen bond strongly increase affinity and contribute to receptor binding, *n-Bu* and *n-Pr* side chain at C2. They are advantageous for lipophylic interaction with receptor and carboxylate or tetrazole attached to biphenyl are also advantageous for ionic interaction with receptor. **BIBR-277** was evaluated [95] for Ang II antagonism in conscious chronically-instrumented renovascular hypertensive rats and disclosed that it was three times more potent than losartan. Telmisartan is effective in transgenic hypertensive rat model and improved glomerulosclerosis and proteinuria present in untreated animals [96]. Recently, it was found that telmisartan act as a partial agonist of peroxisome proliferator-activated receptor-gamma (PPARγ), a well-known target for insulin-sensitizing, antidiabetic drugs [97-99].

5.2. 2-Alkyl Benzimidazole Derivatives

The concept of incorporating an alkyl side chain at C2 position of benzimidazole to improve potency has been extensively explored [100]. In this study, molecular mechanism calculation was carried out on imidazole analogue and conformationally restricted analogues were synthesized as Ang II antagonist. On the basis of key structural element of imidazole, the authors turned their attention to the contribution of benzimidazole **26** (IC_{50}= 2.3 μM) (Fig. **14**) to the binding affinity. From binding assay, it was concluded that chlorine and hydroxyl-methyl group were not critical for binding. The high impact of nitrogen of benzimidazole was explored in **27** (IC_{50}= 51 μM) and **28 (**IC_{50}= 7.4 μM) (Fig. **14**).

The basic N-3 nitrogen play an important role in binding affinity by 25 fold drop in binding affinity of indole **27** as compared to benzimidazole **26**, where as the moderate fall in binding affinity shown by imidazopyridine **28** indicate a less critical contribution of N-1 nitrogen. Replacement of carboxylic group of **26** with tetrazole group of **29** (IC_{50}= 0.096 μM) led to 20 fold improvement in the affinity. An acidic group attached to biphenyl ring is able to ionize at physiological pH and important for good binding. It was suggested that it binds to some positively charged site on the receptor. From SAR and binding affinity analysis, it was postulated that benzimidazole binds to the receptor in similar manner as 2-alkyl group of benzimidazole binds to hydrophobic pocket of the receptor. Synthesized compounds were tested for Ang II antagonistic activity by *in vivo* evaluation in normotensive rat model and it showed antagonism of

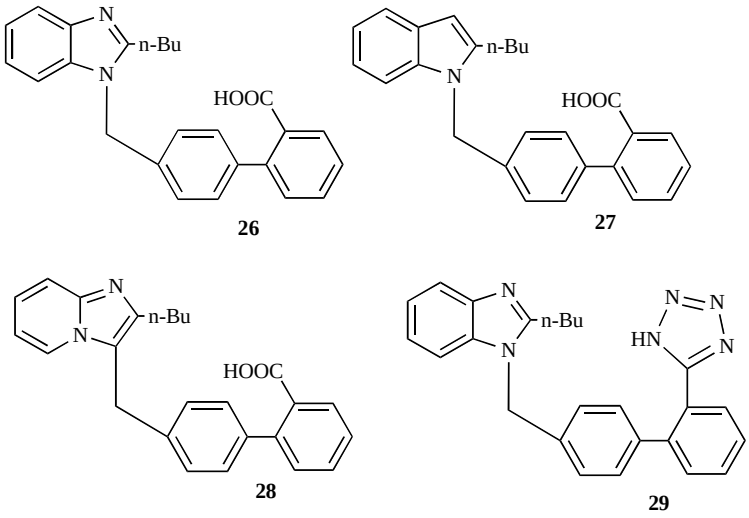
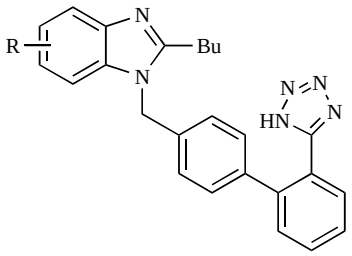


Fig. (14). Chemical structure of 2-alkyl substituted ARBs.



30: R= 4-COOH **31**: R= 5-COOH
32: R= 6-COOH **33**: R= H
34: R= 7-COOH **35**: R= 7-COOMe
36: R= 7-CH_2COOEt **37**: R= 7-Me
38: R= 7-CH_2OH **39**: R= 5-Me 7-COOH
40: R= 5-Cl 7-COOH **41**: R= 6-Me 7-COOH

Fig. (15). Chemical structure of 4, 5, 6 and 7 substituted benzimidazole analogs.

hypertensive effect of the Ang II in the dose range of 5-20 mg/kg. In this study it was found that oral activity of synthesized compounds was poor only marginal effects being seen at a dose of 50 mg/kg.

Potent Ang II receptor antagonists are also obtained [101] by substituting C7 of benzimidazole by carboxyl or an ester group. IC_{50} value of synthesized compounds were determined by inhibition of specific binding of [^{125}I] Ang II (0.2 nM) to bovine adrenal cortex (inhibit 50% of bound [^{125}I] Ang II). A study suggested that substitution at C4 (**30**), C5 (**31**) and C6 (**32**) of benzimidazole (Fig. **15**) reduce affinity (IC_{50} of **30**, **31** and **32** is >100 X 10^{-7} M, 55 X 10^{-7} M and 90 X 10^{-7} M respectively) relative to unsubsitituted compound **33 (**IC_{50} = 9.0 X 10^{-7} M**)** and carboxyl substituent at C7 of benzimidazole nucleus **34** is found to be conducive showing good binding affinity (IC_{50}= 0.5 X 10^{-7} M) than losartan (IC_{50}= 1.5 X 10^{-7} M).

SAR study of 4, 5, 6 and 7 substituted benzimidazole suggested that substitution with carboxyl **34**, methoxy-carbonyl **35** (IC_{50}= 3.2 X 10^{-7} M), ethyl acetate **36**(IC_{50}= 2.5 X 10^{-7} M), methyl **37**(IC_{50}= 3.3 X 10^{-7} M), and hydroxyl methyl **38** (IC_{50}= 4.5 X 10^{-7} M) group at C7 of benzimi-dazole increase the affinity relative to unsubsitituted **33**. Substitution at C4, C5 and C6 of benzimidazole (**30-32**) de-crease the affinity. Additional substitution at 5- or 6- position of 7-carboxylic acid **39-41** have no significant effect on bind-ing affinity. In an *in vivo* assay orally administered **34** caused long lasting inhibition of Ang II induced pressor response.

5.3. Prodrugs of Benzimidazole 7-carboxylic Acids (Candesartan Cilexetil)

Closely related compounds of **CV- 11194** and **CV-11974** (candesartan) (Fig. **9**) were synthesized as prodrug (**TCV-116**) [102] to improve oral bioavailability by tritylation of tetrazole ring. Treatment of N-tritylated benzimidazole 7-carboxylic acids with a variety of alkyl

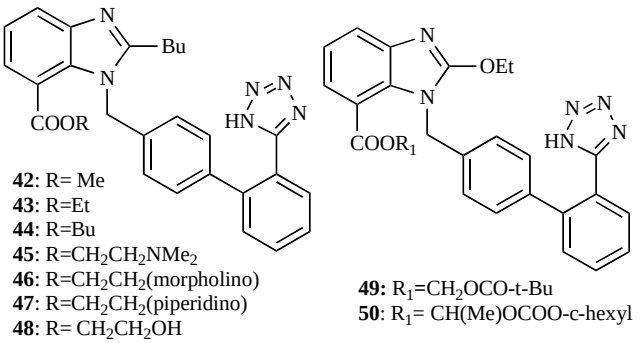


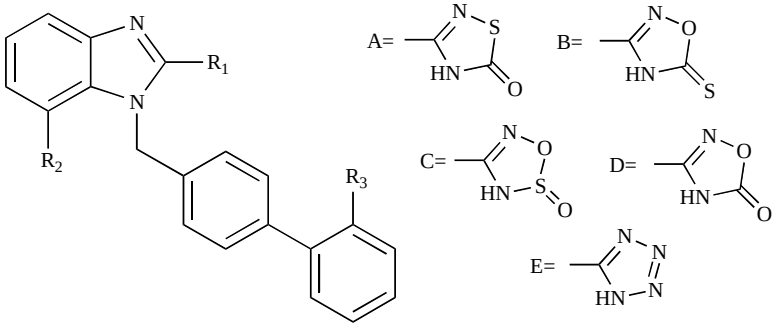
Fig. (16). Chemical structure of 7- substituted benzimidazole derivatives (prodrugs).

halides and 1-(acyloxy)alkylester and 1-[(alkoxycarbonyl) oxy]alkyl esters, double ester derivatives were synthesized. Inhibitory effects of synthesized compound on Ang II induced pressor response in rats and oral bioavailability was calculated from the ratio of the area under the plasma concentration- time curve (AUC) from 0 to infinity after oral dose (10mg/kg equivalent to **CV- 11194**) of the test compound, and after iv administration of **CV- 11194** at a dose of 1mg/kg in rats. Keji Kubo *et al.* [102] successfully performed chemical modification of **CV- 11194** and **CV-11974** to improve oral absorption.

Bioavailability and Ang II antagonistic potency of simple alkyl ester **42(**BA=10.9%), **43**(BA=2.4%), **44** (BA=0.4%) and β-substituted ethyl ester (**45-48**) was very poor but double esters **49 (**BA=34.9%) and **50** [102] (**TVC-116**: BA=33.4%) were found to be very effective prodrugs of **CV-11194** and **CV- 11974**. **TVC-116** (candesaratan cilexetil) was selected as a candidate for clinical evaluation.

5.4. Benzimidazole Bearing Novel Tetrazole Bioisosteres

Within a series of substituted benzimidazole Ang II antagonists, considerable efforts are placed for identifying a



Comp.	R_1	R_2	R_3	IC_{50} X 10^{-7}M
49	Bu	H	A	7.2
50	Bu	H	B	7.6
51	Bu	H	D	6.2
52	Bu	H	E	5.5
53	EtO	H	A	2.5
54	EtO	H	D	> 10
55	EtO	H	E	1.1

Fig. (17). Chemical structure of substituted benzimidazole derivatives bearing a novel tetrazole bioisosteres.

bioisosteres of biphenyl tetrazole. Yasihisa Kohara *et al.* at Takeda Chemical Industries at Osaka in Japan [103] designed, synthesized and evaluated benzimidazole 7-carboxylic acids bearing acidic heterocycles, **TAK-536** (Fig. **9**) **55** as a novel tetrazole bioisostreres. Reported compound were evaluated for their binding affinity to Ang II receptor with respect to inhibition of [^{125}I] Ang II (0.2 nM) binding to bovine adrenal cortical membrane. The 5-oxo-1, 2, 4 thiadiazole, 5-thioxo-1, 2, 4 oxadiazole, 5-oxo-1, 2, 4 oxodiazole were found more potent as tetrazole (**49**, **50**, **51** Vs 52, **53**, **54** Vs **55**) (Fig. **17**). The effect of varying side chain R_1 at the C2 of benzimidazole on binding affinity were also examined and it was found that the length of R_1 seemed to be two or three carbon atom regardless of the nature of R_1 and R_3. This study was mainly focused on replacement of the tetrazole ring by other important lipophilic acidic groups to improve oral bioavailability and also solve synthetic and metabolic problems.

5.5. 6-Oxo-3-Pyridazinyl-Benzimidazole Derivatives

Dieter Dorsch *et al.* [104] disclosed novel (6-oxo-3-pyridazinyl)-benzimidazole derivatives as potent Ang II receptor antagonist and synthesized compounds screened for their ability to displace Ang II from its receptor in bovine adrenal cortex membrane. Pimobendan (**56**), an inhibitor of phosphodiesterase III showed significant binding with IC_{50} of 1.7μmol. The authors reported synthesis and Ang II antagonistic properties of (6-oxo-3-pyridazinyl)-benzimidazole related to pimobendan.

SAR of this series of compounds suggested that replacement of methoxyphenyl group of **56** with butyl **57** (**IC_{50}** > 10 μmol). The introduction of biphenyl tetrazol (BPT) moiety at pyridazinone amide nitrogen **58** (IC_{50} = 5.4 μmol) have no effect on the binding affinity. Compound **59** (IC_{50} = 5.5 μmol) with BPT on residue at imidazole nitrogen showed improved binding. Introduction of both butyl and BPT on (6-oxo-3-pyridazinyl)-benzimidazole provided compounds **60** (IC_{50} = 7 μmol), **61** (IC_{50} = 2.2 μmol) and **62** (IC_{50} = 1.6 μmol) with improved affinity to the receptor (Fig. **18**).

5.6. Hetero-substituted Benzimidazole Derivatives

K.H. Gibson and colleagues at Zeneca Pharmaceuticals, Cheshire England [105] have disclosed a series of heterosubstituted benzimidazole derivatives as potent Ang II receptor antagonist. The findings showed that introduction of nitrogen atom at C4 of benzimidazole nucleus **L-158809** (IC_{50} = 0.006 μM and ED_{50}= 0.22 mg/kg iv) (Fig. **9**) is highly beneficial for Ang II antagonistic activity which is determined by a conventional ligand binding assay based on displacement of monoiodinated Ang II of a washed membrane fraction prepared from guinca-pig adrenal gland and ED_{50} values were determined by measuring inhibition of pressor response induced by infusion Ang II in male adrenal park wister rats after a single iv dose of compounds. Additional heteroatom in benzimidazole moiety has provided very potent Ang II-AT_1 receptor antagonist.

5.7. 5- Aryl Benzimidazole Derivatives

Alan D. Palkowitz *et al.* [106] reported discovery of polysubstituted 4-aminoimidazole derivative **63** as a novel nonpeptide antagonist of the Ang II. As an elaboration of this work, the authors replaced the imidazole-4-benzoyl-amide moiety of **63** with a 5-aryl benzimidazole **64** (Fig. **19**) and studied the effect of this modification on biological activity both, before and after incorporating phenoxyproline side chain.

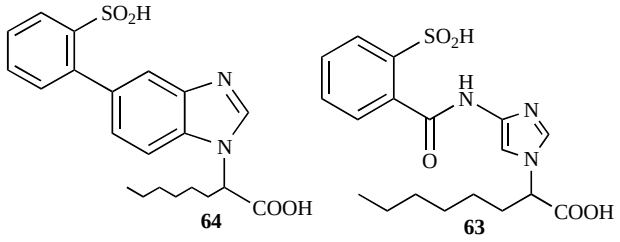


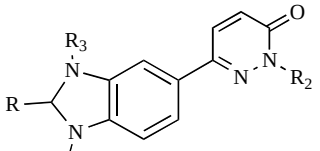
Fig. (19). Chemical structure of 5- aryl benzimidazole derivatives.

This modification would result in molecules with increased affinity for AT_1 receptor. Antagonism of Ang II *in vitro* was determined in isolated rabbit thoracic aorta and *in vivo* evaluation was carried out for their ability to block pressor response to Ang II in pithed rats by oral administration. Compounds from both the series were equipotent *in vitro*.

5.8. 5-Nitro Benzimidazole Derivatives

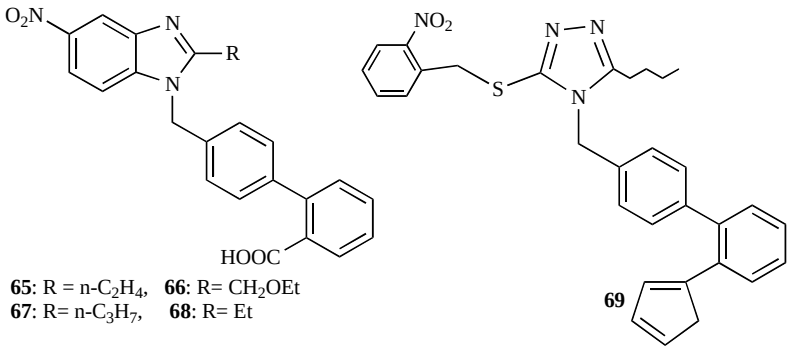
Incorporating nitro group at C5 of benzimidazole moiety has led to a series of 5-nitrobenzimidazole derivatives. Paper [107] describes design and synthesis of a series of substituted benzimidazole by varying substitutions on C2 **65-68** (Fig. **20**) and proposed a drug receptor interaction model. Compounds **65-68** were designed with nitro group at C5 of benzimidazole by correlating relative conformation of nitro and carboxylate group determined with the distance between O^1 and N^4 of **69** (4.638Å) and O^1 and C^4 of **65** (4.236 Å) in their energy minimized conformations**.**

The distance is found to be very similar and it was expected that these compounds have higher potency than losartan. Synthesized compound were tested for Ang II



56: R = 4-Methoxyphenyl, R_1 = H, R_2 = H, R_3 = H
57: R = Bu, R_1 = H, R_2 = H, R_3 = H
58; R = 4-Methoxyphenyl, R_1 = H, R_2 = BPT, R_3 = H
59: R = 4-Methoxyphenyl, R_1 = BPT, R_2 = H, R_3 = H
60: R = Bu, R_1 = H, R_2 = BPT, R_3 = H
61: R = Bu, R_1 = H, R_2 = H, R_3 = BPT
62: R= Bu, R_1 = BPT, R_2= H, R_3 = H

Fig. (18). Chemical structure of 6-oxo-3-pyridazinyl-benzimidazole derivatives.



65: R = n-C_2H_4, **66**: R= CH_2OEt
67: R= n-C_3H_7, **68**: R= Et

Fig. (20). Chemical structure of 5-nitro benzimidazole derivatives

receptor antagonism on endothelium removed isolated rat aortic ring using force transducer and BIOPAC four channel recorder. The activity was expressed as PA_2. The study revealed that nitro group at C5 and n-butyl side chain at C2 of benzimidazole nucleus **68** (PA_2 = 7.0) is found to be more potent than candesartan (PA_2 = 8.02).

5.9. 2- Alkyl Benzimidazole Based on N-Substituted (Phenyl-Amino) Phenyl-Acetic Acid Derivatives

The "spacer" phenyl ring is replaced by fused ring heterocycles (phenylamino) phenylacetic acid [108] that led to the design and synthesis of series of 2- alkyl benzimidazole derivatives based on imidazo [5,4 -b] pyridine **70**. The study showed synthesis and pharmacological evaluation of 2-alkylsubstituted benzimidazole derivatives in which a new analogue of biphenyl tetrazole was introduced as (phenyl-amino) phenylacetic acid **71-73** (Fig. **21**).

The synthesized compounds were evaluated for their antagonism of Ang II induced contraction in rabbit thoracic aortic ring with isolated rabbit aortic strip. The assay results showed that synthesized compounds **71** (pA_2 = 8.1), **72** (pA_2 = 8.3) and **73** (pA_2 = 8.1) exhibit potent antagonistic activity of AT_1 receptor, which were more potent than losartan (pA_2 = 7.9).

5.10. 2-Alkyl-Benzimidazoles Bearing N-Phenyl-pyrrole

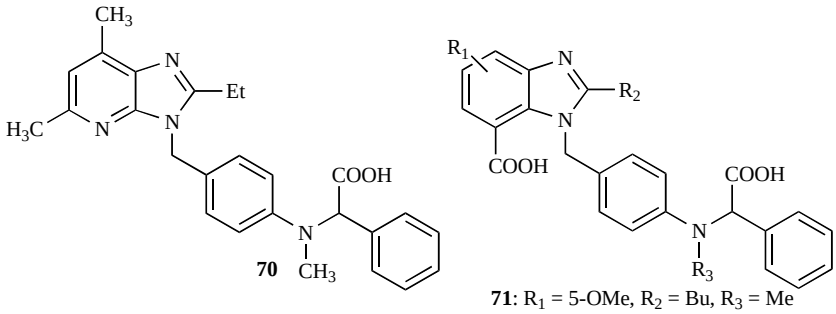
Replacement of biphenyl tetrazole (BPT) with phenyl-pyrole tetrazole moiety is a result in the series of 2-alkyl benzimidazole substituted derivatives bearing *N*-phenyl-pyrrole moiety **74** [109] (Fig. **22**). The authors were interested in exploring new surrogates for the BPT. The Study was focused on introduction of phenyl-pyrrole instead of BPT moiety. Molecular modeling techniques were used to explore structural parameters in comparison to related biphenyl system of some potent compounds.

Energy minimized conformation of most active compound **74** and losartan are similar and their structural parameters (bond angles, distance and dihedral angle) are very close, indicating that the two molecules have similar electronic characters. Synthesized compounds were evaluated for their ability to competitively inhibit Ang II binding to AT_1 receptor by a ligand-binding assay using a bovine adrenal cortex and for antagonism of Ang II induced pressor response by oral administration. The result of this study showed that the bioisosteric replacement of biphenyl tetrazole with N-phenylpyrrole-2-tetrazole (**74:** IC_{50} = 9.8 ± 0.2 nM) and N-phenylpyrrole-2-carboxylic acid (**75:** IC_{50} = 33 ± 2.4 nM), produced extremely potent novel analogues.

5.11. Substituted Carboxamido and 5-Sulfamoyl Benzimidazole Derivatives

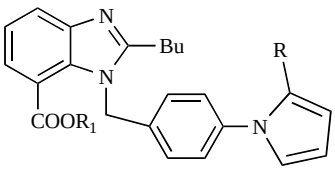
Recently, Gulshan Bansal *et al.* [110] have disclosed a series of substituted carboxamido benzimidazole derivatives as Ang II-AT_1 receptor antagonists **75-81** (Fig. **23**). Amino group at C5 of benzimidazole nucleus with diverse alkyl/aryl carbonyl chains produce AT_1 antagonists with extensive activities.

Ang II antagonistic activity of synthesized compounds was determined on isolated rat aortic ring using force transducers and BIOPAC four channel recorder systems. The antagonistic activity was expressed as pA_2 values. The pA_{10} values were also determined to establish the mode of antagonism. Comparison of the pA_2 and pA_{10} values



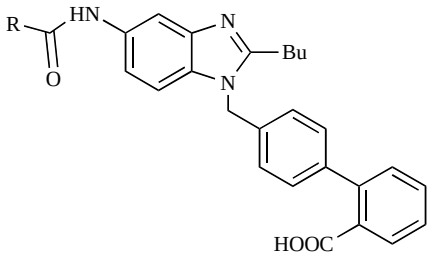
71: R_1 = 5-OMe, R_2 = Bu, R_3 = Me
72: R_1 = H, R_2 = Bu, R_3 = Et
73: R_1 = 6-OMe, R_2 = Bu, R_3 = Me

Fig. (21). Chemical structure of 2-alkyl benzimidazole based on N-substituted (phenylamino) phenylacetic acid derivatives.



74:R = Tetrazole, R_1 = Me
75: R = COOH, R_1= H

Fig. (22). Chemical structure of 2-butyl benzimidazole bearing N-phenylpyrrole ring.



75: R = CH_3, **76**: R= CH_2CH_3 **77**: R= nC_3H_7, **78**; R = nC_4H_9
79: R =C_6H_5, **80**: R= (2-Cl) C_6H_4, **81**:R = (4-Cl) C_6H_4

Fig. (23). Chemical structure of substituted carboxamido and 5-sulfamoyl benzimidazole derivatives.

indicates that **75-78** are non-competitive antagonists (pA2 - pA10 > 1) whereas the other compounds **79-81** are competitive antagonists (pA2 - pA10 < 1).

The authors suggested that an alkyl group not longer than methyl can be accommodated in the receptor pocket, an appropriate alkyl group can increase antihypertensive activity, increase in bulk of the alkyl/aryl residues decrease activity. The second approach is to design and synthesize 5-sulfamoyl benzimidazole derivatives [111] as novel Ang II receptor antagonists based on isosteric replacement of nitro group at C5 of benzimidazole with sulfonyl group and extending the latter with alkylamino group **82-89** (Fig. **24**).

It was hypothesized that sulfonyl group mimics nitro group, alkylamino can interact with H-bond acceptor group and alkyl group (R) can form a stronger drug–receptor complex. SAR study suggested that unsubstituted sulfonamide derivative **82** (pA_2 = 6.7) was found least active and equipotent to sulfonic acid derivative **91** (pA_2 = 6.6). Both **82** and **91** were significantly less active than lead compound **90** (pA_2 = 8.5). It indicated that nitro group interacts with the receptor more strongly than isosteric sulfonyl group. The activity of alkyl substituted sulfonamide analogs increased with increasing size of alkyl group at sulfonamide moiety except for compound **87** where activity was decreased. Synthesized compounds were evaluated for *in vitro* Ang II antagonism and for *in vivo* antihypertensive activity on isolated rat aortic ring. Difference in pA_2 and pA_{10} values of compounds **82-87** indicated that they were competitive inhibitors while the compounds **88** and **89** were non-competitive ones similar to **91** and candesartan. The authors have proposed receptor binding model on the basis of SAR study which revealed that the *tert*-butylsulfamoyl **88** analog has emerged as maximally active compound during *in vitro* studies but cyclohexyl-sulfamoyl analog **89** has maximum decrease in MABP in hypertensive rats.

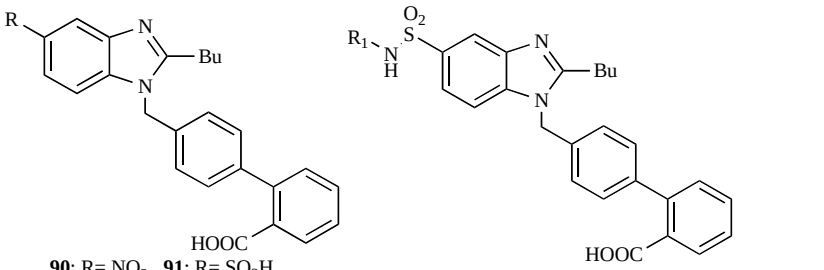
5.12. Double Benzimidazole Derivatives

Xing-Zhou Guo *et al.* [112] synthesized a series of benzimidazole derivatives by replacing tetrazole ring with imidazole, 5- chloroimidazole, 1, 2, 4-triazol and imidazoline ring system and an introduction of additional methyl benzimidazole at C6 of benzimidazole (double benzimidazole) **92-95** (Fig. **25**). Synthesized compounds were evaluated for their activity to competitively inhibit [^{125}I] Ang II binding to AT_1 receptor by a conventional ligand-binding assay using a bovine adrenal cortex and measurement of antagonism of Ang II-induced pressor response.

SAR study revealed that acidity of imidazole **92** can be increased through substitution with electron-withdrawing group, such as -Cl **93**, as compared to 5-chloroimidazole derivative, and then the binding affinity surpasses those of the corresponding imidazole derivatives. It was confirmed by *in vitro* and *in vivo* results that imidazoline derivative (**95**: IC_{50} = 2.6 X 10^{-7} M) displayed almost equal antihypertensive activity to that of telmisartan, where as the imidazole derivatives (**92**: IC_{50} = 14 X 10^{-7} M, **93**: IC_{50} = 6.8 X 10^{-7} M) and the triazole derivative (**94**: IC_{50} = 15 X 10^{-7} M) showed weak or no antihypertensive activity.

5.13. Docking Studies with Novel Substituted Benzimidazole

Mitchell A. Avery *et al.* [113] discovered benzimidazole derivatives have dual Ang II antagonist and PPARγ agonist activity for the treatment of metabolic syndrome. The paper describes design, synthesis and docking study of two classes of benzimidazole based compounds as potential dual PPARγ



90: R= NO_2, **91**: R= SO_3H

82: R_1= H, **83**: R_1 = CH_3, **84**: R_1= CH_2CH_3
85: R_1 = n-C_3H_7, **86**:R_1 = iso-C_3H_7, **87**:R_1 = n-C_4H_9,
88: R_1= tert-C_4H_9, **89**:R_1 = cyclohexyl

Fig. (24). Chemical structure of 5-sulfamoyl benzimidazole derivatives.

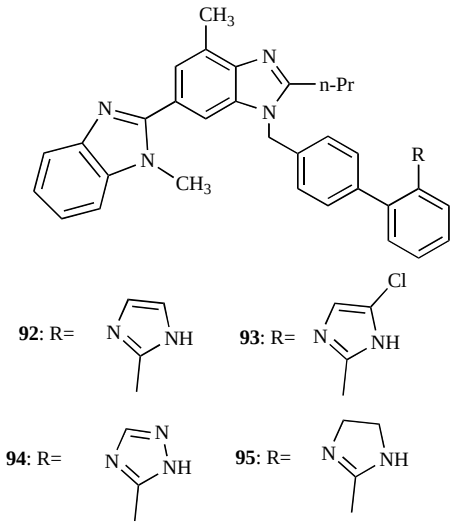


Fig. (25). Chemical structure of double benzimidazole derivatives.

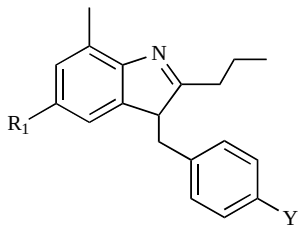
agonists/Ang II antagonists. Some of the benzimidazole derivatives also exhibited moderate activity against PPARα. The binding affinity of synthesized compounds for Ang II-AT_1 receptor antagonism were measured by their ability to compete with Ang II binding to rat liver membrane and evaluated for the activation of PPARγ using human PPARγ-GAL-4 cell-based trans activation assay. The authors synthesized several telmisartan like analogues with mono- and bis-benzimidazole moieties with tetrazole and carboxylate substitutions. SAR study revealed that some of the tetrazole containing molecules **96-99** showed better activity in an AT_1 receptor radioligand binding assay as compared to corresponding acid and ester analogues, supported by comparing with the binding affinities of ester analogue **100**, (IC50>10 μM), and corresponding tetrazole analogue **95** (Ki=2.84 μM) (Fig. **26**).

In mono-benzimidazole series, elongation of spacer between nitrogen of proximal benzimidazole nucleus and aryl ring by three atoms did not improve the affinity for AT_1 receptor. For example compounds **101** with one methylene and **102** with two methylenes and one oxygen spacer were inactive in AT_1 receptor assay, whereas the same compounds showed moderate activity against PPARγ. Interesting key features of this SAR study is derivatives bearing bis-benzimidazole moiety showing better activity in AT_1 receptor than the corresponding mono-benzimidazoles. This result is supported by the comparing AT_1 receptor affinities of mono-benzimidazoles **96** (Ki=2.84 μM) and **103** (IC50>10 μM) with bis-benzimidazole derivatives **97** (Ki=13 nM) and **104** (Ki=2.53 μM). These results further suggest that bis-benzimidazole unit is crucial pharmacophore for maintaining AT_1 receptor affinity.

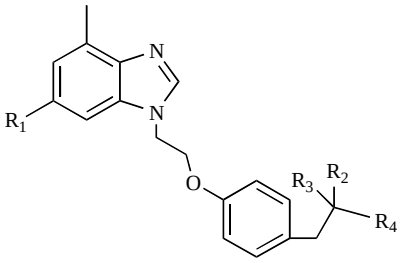
6. SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS ANTIHYPERTENSIVE AGENTS

6.1. 2-Phenyl-Amino-Phenyl-Methyl Benzimidazole Derivatives

Mukesh C. Sharma *et al.* [114] synthesized new 4'-{5-amino-2-[2-substituted-phenylamino)-phenyl-methyl]-benzi-

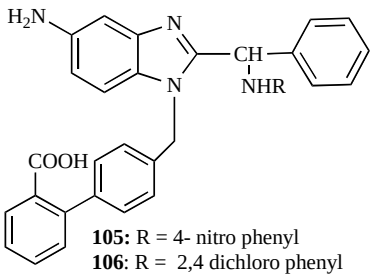


96: R_1 = H, Y = CH_2CH_2-(5-1*H*-tetrazole)
97: R_1 = N -Me -2 -benzimidazole, Y = CH_2CH_2-(5-1*H*-tetrazole)
99: R_1 = H, Y = O-CH_2-(5-1*H*-tetrazole)
100: R_1 = H, Y = $CH_2CH_2CO_2Et$
101:R_1 = H, Y = O-C -(Me_2)CO_2Et



98: R_1 = N - Me -2-benzimidazole, R_2 = R_3 = H, R_4 = (5-1*H*-tetrazole)
102: R_1 = H, R_2 = R_3 = CH_3, R_4 = CO_2Et
103:R_1 = H, R_2 =OPh, R_3 = CH_3, R_4 = CO_2Et
104: R_1 = N - Me -2 - benzimidazole, R_2 = R_3 = H, R_4 = (5-1*H*-tetrazole)

Fig. (26). Chemical structure of mono and aryloxy-carboxy benzimidazole derivatives.



105: R = 4- nitro phenyl
106: R = 2,4 dichloro phenyl
107: R = 2,5 dinitro phenyl
108: R = 2,4 dinitro phenyl

Fig. (27). Chemical structure of 2-phenylamino-phenyl-methyl benzimidazole derivatives.

midazol-1-ylmethyl}-biphenyl-2-carboxylic acid derivatives **105-108 (**Fig. **27**) and screened for their antihypertensive activity by tail cuff method and direct method measurement of blood pressure.

On the basis of SAR study it was suggested that the presence of amino group at C5 of benzimidazole nucleus increases the antihypertensive activity, it was postulated that there are some sites in the receptor pocket which can interact with the phenylamino-phenyl-methyl at C2 of benzimidazole nucleus.

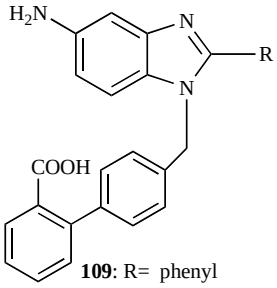
6.2. 6-Chloro-5-Nitro Benzimidazoles Derivatives

Nitro group in benzimidazole ring has high impact on antihypertensive potency as demonstrated by Mukesh C. Sharma *et al.* [115]. The authors synthesized some 6-chloro-5-nitro-benzimidazole derivatives and screened for their antihypertensive activity. Pharmacological evaluation of synthesized compounds was carried out using rat blood

pressure measurement experiment. It was suggested that derivatives with nitro group at C5 and aryl group at C2 of benzimidazole nucleus is found more potent than losartan. In addition to that, a novel and simple method for synthesis of tetrazole biphenyl moiety is devised. Their SAR studies showed that the presence of nitro group at C5 of benzimidazole increases antihypertensive activity.

6.3. 5-Amino-2-Phenyl/Ethyl-Benzimidazoles

Concept of incorporating amino group at C5 of benzimidazole along with phenyl group at C2 **109, 110** (Fig. **28**) explored by Jat Rakesh Kumar *et al.* [116]. In this study, it was found that compound with ethyl group at C2 of benzimidazole **110** was more active (MABP=109.6±0.67) than C2 phenyl **109** (MABP=113.0±0.83).



109: R= phenyl
110: R= ethyl

Fig. (28). Chemical structure of 5-amino-2-phenyl/ethyl-benzimidazole.

Presence of biphenyl carboxylic acid and amino group at C5 of benzimidazole is necessary for antihypertensive activity of compounds activity.

7. QSAR MODELING OF SUBSTITUTED BENZIMIDAZOLE AS ARBS

QSAR study [117] was performed on reported work of Keiji Kubo *et al.* [101] in order to gain insight into the structural requirement of 4, 5, 6 and 7 substituted benzimidazoles as Ang II receptor antagonist. Fujita-ban analysis suggested importance of -CH_2COOH group at C7 of benzimidazole nucleus for better Ang II antagonistic activity. QSAR study indicates that electronic (LUMO and total energy), thermodynamic (bend energy) and steric (ovality) descriptors govern the Ang II antagonistic activity. Another QSAR study [118, 119] on reported work of Kohara, Y. *et al*. [103] and Uwe Ries *et al.* [91] respectively demonstrated the importance of geometrical, structural and shape descriptors for governing Ang II antagonistic activity.

8. CONCLUSION AND PERSPECTIVE

The fundamental role of Ang II in physiological processes including cardiovascular, neuronal, renal, endocrine and central nervous system has emerged Ang II as attractive targets for the treatment of hypertension. The strategy for controlling hypertension is focused on AT_1 receptor antagonists (SARTANs) which represent the last generation of drugs for management of hypertension. Utilizing the relationship between AT_1 receptor and the control of blood pressure various AT_1-selective Ang II antagonists have emerged in the last two decades. Candesartan and telmisaratn (with benzimidazole as heterocyclic ring) is nonpeptide Ang II antagonist to be approved by the FDA. Substituted benzimidazole as ARBs appears to provide an opportunity as better therapeutic agents for treatment of hypertension and related cardiovascular disorders. Progress is made in understanding the critical binding sites on the AT_1 receptor. Molecular modeling and computational tools helped medicinal chemist to identify structure of the target receptor and have assisted in design of new Ang II antagonist. Within a series of substituted benzimidazole Ang II antagonists, considerable efforts are placed to maintain the potency, duration of action and bioavailability of related compounds. Based upon various experimental finding discussed above it was suggested that most extensive variations were applied to 2, 7 and 6-position of benzimidazole. Alkyl group (n- butyl) at the C2 of benzimidazole moiety of lead telmisaratn was considered to be essential group for lipophilic interaction with the receptor and ionized acidic group (tetrazole/ carboxyl) on biphenyl moiety is responsible for ionic interaction with AT_1 receptor. According to these investigations important pharmacophoric groups were identified, among them lone pair of electron on N-atom in benzimidazole acts as hydrogen acceptor which is responsible for hydrogen bonding with receptor site, *n-bu* and *n-pr* side chain at 2-position of benzimidazole nucleus for lipophilic van der Waals interaction, carboxylate/tetrazole attached to biphenyl moiety for ionic interaction and biphenyl ring system for aromatic hydrophobic interaction with AT_1 receptor. Beyond these findings several other important substituents are identified which would improve the potency of benzimidazole derivatives. A strong hydrogen bonding is possible for heteroatom (N or O) on 6-position of benzimidazole. Positioning of carboxyl group on benzene ring of benzimidazole moiety is of primary importance and was reconfirmed by comparison of Ang II antagonistic activity which proved that 7-position is best position for this group. Binding profile studies confirmed that an increase in activity with appropriate substituent at 5-position. Main chemical variations at 5-position of benzimidazole comprise of nitro, amino, carboxamido and sulfamoyl which can interact with receptor pocket through van der Waal and/or H-bonding interactions. On the basis of quantum mechanical calculations it was hypothesized that interaction of nitro group with receptor surface is stronger and further extension at nitrogen atom of nitro group with substituents like alkyl amino group may strengthen binding interactions. Replacement of tetrazole ring often yields moderately active compounds. Replacement of phenyl group of biphenyl ring system with pyrole and pyrimidine moiety retained potency. The effects of spacer between the benzimidazole nitrogen and biphenyl ring fragments were approximately equipotent to losartan. Concept of bis-benzimidazole is explored; important common feature of bis-benzimidazole is a relatively high electron density at their nitrogen atom. SAR studies on different substituted benzimidazole would guide medicinal chemistry efforts for the structural modifications for targeting Ang II- AT_1 receptor to optimize molecular selectivity. Several structural features necessary for AT_1 receptor affinity are reviewed in present communication. These advances around the substituted

benzimidazole provide structural insights into development of novel nonpeptide ARBs.

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LIST OF ABBREVIATIONS

RAS = Renin Angiotensin System

Ang II = Angiotensin II

AT_1 = Angiotensin type 1 Receptor

AT_2 = Angiotensin type 2 Receptor

AT_3 = Angiotensin type 3 Receptor

AT_4 = Angiotensin type 4 Receptor

ACE = Angiotensin-Converting-Enzyme

ACEIs = Angiotensin-Converting-Enzyme Inhibitors

ARBs = Angiotensin II Receptor Blockers

SAR = Structure- Activity Relationship

PPAR = Peroxisome proliferator-activated receptor

BPT = Biphenyl tetrazole

BPC = Biphenyl carboxylic acid

MABP = Mean arterial blood pressure

LUMO = Lowest unoccupied molecular orbital

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