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Design, Synthesis, and Biological Evaluation of AT1 Angiotensin II Receptor 2 Substituted phenyl-(phenyl-{1- [2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-5-ylamine

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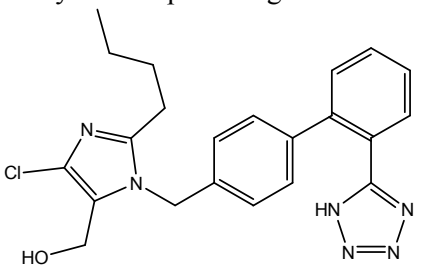
Abstract: Synthesis of a series of novel substituted benzimidazole derivatives by the condensation of *o*-phenylenediamine **(**OPDA,**)** with Mandlic acid and subsequent reactions of the benzimidazole with different amino substituted is reported with reaction biphenyl tetrazole. All the compounds synthesized were screened for their potential anti-hypertensive properties,

Keywords: 2-(α-hydroxy benzyl) benzimidazole, AngII, Blood Pressure, biphenyl tetrazole, Antihypertensive agents.

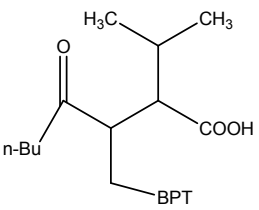
Introduction

The discovery of potent and orally active nonpeptide Ang II antagonists such as losartan and eprosartan has encouraged the development of a large number of similar compounds.[1]Among them, irbesartan, candesartan, valsartan, telmisartan, tasosartan, and olmesartan are on the market. Most of the developed AT_1 receptor antagonists are characterized by the presence in their structure of the biphenyl fragment bearing an acidic moiety and differ in the nature of the pendent heterocyclic system (valsartan lacks the heterocyclic moiety) connected to the para position of the proximal phenyl.Hypertension is one of the most important cardiovascular risk factor but its control is still Challenge for physicians all around the world. Antihypertensive are a class of drugs that are used in medicine and pharmacology to treat hypertension (high blood pressure). All Hypertensive drugs cause dizziness, ankle swelling, headache, fatigue, chest discomfort and cough. This review focus on the adverse effects of Antihypertensive drugs, severity of these adverse effects and attempts made to prevention and treatment of hypertension by non-pharmacological intervention. The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure through the actions of angiotensin II (AII) (vasoconstriction, aldosterone secretion, renal sodium re-absorption, and nor epinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension. The renin-angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis and electrolyte/ fluid balance in normotensive and hypertensive subjects.[2]Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of the octapeptide angiotensin II (AII), which then interacts with specific receptors present in different tissues.[3] Two basic types of receptors, both having a broad distribution, have been characterized so far: the AT1 receptor, responsible for the majority of effects attributed to this peptide, and the AT2 receptor, with a functional role yet uncertain.[4] The main effects of AII are the regulation of blood pressure through

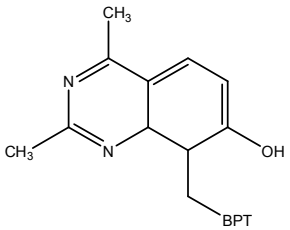
vasoconstriction, thereby effecting an increase in vascular resistance, the regulation of volemia through the stimulated release of vasopressin and aldosterone, which induces saline retention, and the regulation of the adrenocorticotropic hormone (ACTH). Thus, reducing the levels of AII by inhibition of one of the RAS enzymes or directly blocking the AII receptors is in theory a good approach for treating hypertension, confirmed by the success of angiotensin-converting enzyme (ACE) inhibitors as antihypertensives.[5] Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported.[6]The discovery of potent and orally active nonpeptide Ang II antagonists such as losartan and eprosartan has encouraged the development of a large number of similar compounds.[7] No less effort has been devoted to finding AII antagonists, which besides being the most direct way of controlling the RAS could have the additional advantage of lacking the side effects, such as cough and angioedema, observed with ACE inhibitors, as these are probably caused by partial inhibition of the cleavage of bradykinin and substance P. Starting from the initial leads reported by Takeda,[8] researchers at DuPont discovered losartan, the first orally active AT1 selective nonpeptide AII antagonist that reached the market for the treatment of hypertension (1994, Cozaar). Whereas reports on effective replacements of the biphenyl tetrazole "tail" of losratan are scarce, the imidazolic "head" of the molecule, postulated to act mainly to link the required functionalities, has been successfully replaced by a wide variety of cyclic and acyclic structures, leading to a number of compounds currently in clinical trials.[9]AngII receptor antagonists are expected to have similar therapeutic effects and indications as the ACE inhibitors without unwanted side effects associated inhibition of other ACE mediated pathways, such as bradykinin metabolism.Intial research in this area led to the discovery of peptide analog such as saralasin ([sar1-Ala8]-AngII) which displayed potent and selective AngII receptor antagonist activity both *in vivo and in vitro*.However, these peptides had limited therapeutic utility due to partial agonist activity short duration of action and lack of appreciable oral bioavailability[10].Only in recent years a number of non peptides AngII antagonists that show promise as inhibitors of the RAS been reported[11].All these antagonists possess a central aromatic nucleus bearing the pharmacophores indispensable for activity and notably a polar function adjustant to biphenyl substituents while a polar function in this area of molecule seems to be necessary to maintain activity[12]. Sartans are appropriately substituted heterocyclic head coupled through a methylene linker to pendent biphenyl system bearing an acidic function; viz. candesartan is an effective competitive Ang II antagonist with benzimidazole nucleus as the heterocyclic head [13]. The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity[14]. Compounds containing tetrazole nucleus are also reported as AT_1 receptor antagonists and their protypical derivative 3 exhibits non-competitive antagonism[15] and amino group attach with carboxylic group given good biological activity [16 ,17] In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives as a source of new antimicrobial agents. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocycles, which are the structural isosters of nucleotides owing fused heterocyclic nuclei in their structures that allow them to interact easily with the biopolymers, possess potential activity with lower toxicities in the antihypertensive activity approach in man[18]. Benzimidazole derivatives are an important class of nitrogen containing heterocycles and were reported to possess a wide spectrum of biological properties such as antihypertensive, antibacterial, analgesic, anti-inflammatory, antifungal and antimalarial activities. Although a number of drugs are available in the market, thirst for discovering new antihypertensive, drugs with better pharmacokinetic profile, and lesser toxicity has become main objectives in the field of medicinal chemistry due to fast development of microbial resistance towards the existing molecules.



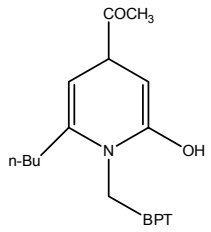
Losartan



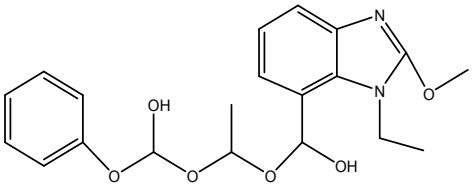
Valsartan



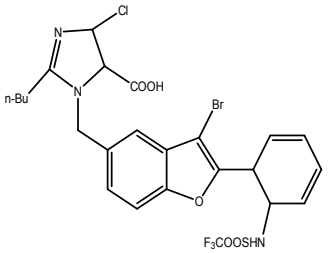
Tasosartan



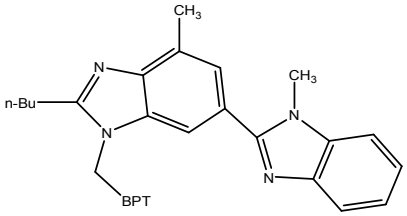
Candesartan



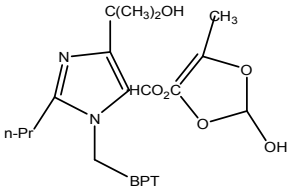
Milfasartan



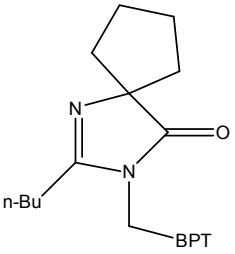
Saprisartan



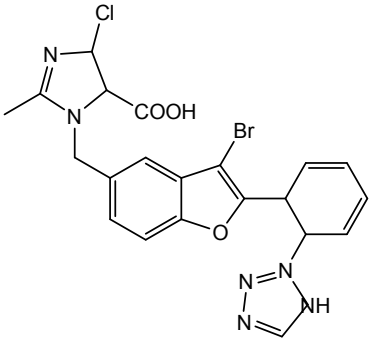
Telmisartan



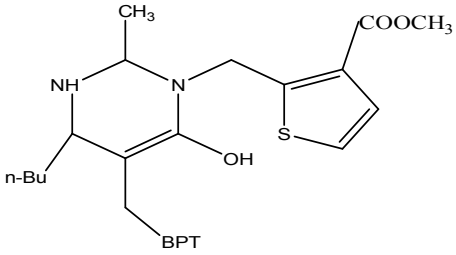
Olmesartan



Irbesartan



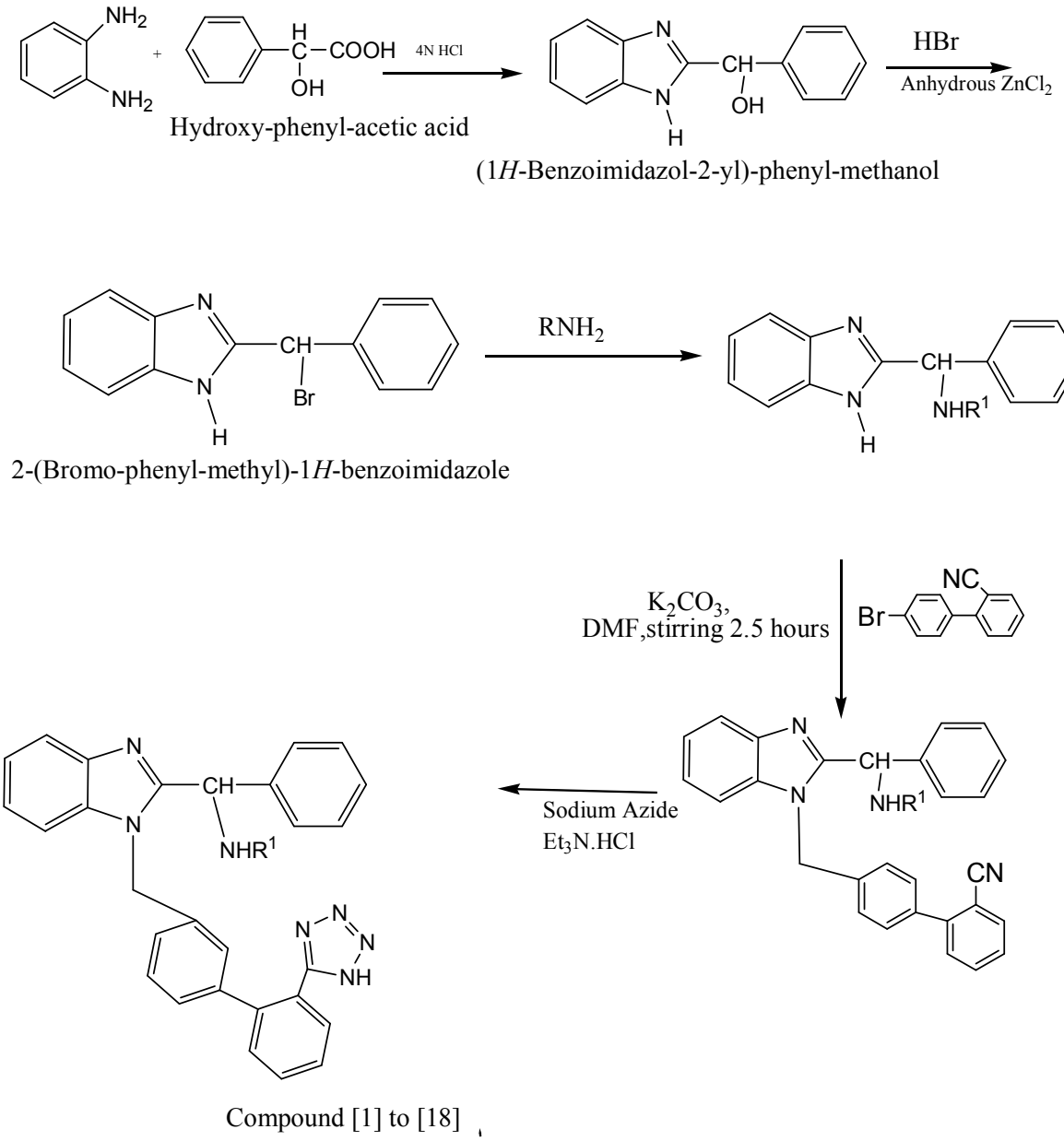
Zolzsartan



Eprosartan

Angiotensin II selective antagonists

SCHEME



Compound [1] to [18]

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. The time required for completion of the reaction was monitored by TLC using Silica gel-G plates and spots were exposed in iodine chamber. IR spectra were recorded on a Perkin Elmer 1800 (FTIR) spectrometer 1^H NMR spectra (DMSO) were taken on a DRX-300 spectrometer (300 MHz) using TMS as internal standard and chemical shifts are expressed in δ ppm.

2-(α-hydroxy benzyl) benzimidazole[19,20]

In a 500ml of round bottom flask, equimolar amount of o-phenylene diamine (0.01 mol) and Mandelic acid (0.01 mol) were placed. 18 ml of 4n HCL was than added followed by a few porcelain chips and the mixture was refluxed gently on an oil-bath at 135-140°C for 2 hours. The reaction mixture was then allowed to cool to room temperature, which was further neutralized with 20% Na2CO3 solution and was kept overnight. The crude product filtered at the vacuum pump, was recrystallized from ice-cold water or acetone. The formation of 2-(**α** -hydroxy benzyl) benzimidazole was confirmed by comparing its melting point with that reported in the literature, by thin layer chromatography and spectral analysis.

Synthesis of 2-(α-bromo benzyl) benzimidazole[21-25]

In a 250 ml round bottom flask fitted with a reflux condenser, (the top of which is connected to a device

for absorbing hydrogen chloride gas) Zinc chloride (o.5 mole) and HBr (3ml) were placed and 2-(α – hydroxy benzyl) benzimidazole (0.25 mol) was added. The mixture was refluxed gently at 125-130^{o}C for 3 hours on an oil bath. The reaction mixture was then allowed to cool and the resulting bromide compound was separated. Refrigerated overnight and recrystallized successively from ice-cold water or acetone.

Yield: 72 %, m.p. =133^{0}-135^{0}C. Anal.Calcd for $C_{14}H_{13}N_3$:C,75.68;H, 5.46 ;N,18.91 %;IR(KBr):1923,1562,1437,1353,1870,1933.^{1}HNMR(300Hz,CDCl3):2.89(s,2H,NH)5.22(m,1H,C-H),7.10-8.23(m,10H,ArH),FAB-MS, 222.11

Step-3 -2-(α-bromo benzyl) benzimidazole (0.01mole) was dissolved in anhydrous dioxane (45 ml) and excess of various substituted aromatic amines were added. The reaction mixtures were allowed to stand overnight at room temperature, the solutions were evaporated to dryness and gummy solid obtained was washed with cold water. The solids were then extracted with 2M HCl. The acidic extracts were made alkaline with NH4OH and the resultant products were recrystallized from ice-cold water or acetone. Some of these final derivatives were characterized as picrates. The melting points of all the title compounds were recrystallized by open capillary method and were found to be uncorrected. The compounds were obtained in comparatively good yield of 50-70%.

MCS-03-4`-{2-[2-chloro-phenylamino)-phenyl-methyl]-benzoimidazol1ylmethyl}biphenyl-2-carbonitrile

To a solution of 1.5 g (10.12 mmol) compound substitute -03 65 mL of DMF was added potassium carbonate 2.8 g (8.43 mmol), the mixture was stirred for 1.3 hours at room temperature, and 4-(bromomethyl) biphenyl-2'-nitrile 5.0 g (20.12 mmol) was added. After stirring for 18 hours the mixture was poured into distilled water (120 mL) and extracted with diethyl ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated.

MCS-04-(2-Subsituted-phenyl)-(phenyl-{1-[2'(1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}methyl)-amine

A mixture of different substituted 4`-{2-[2-chloro-phenylamino)-phenyl-methyl]-benzoimidazol1ylmethyl} biphenyl-2-carbonitrile (2.5 g, 3.08 mmol), sodium azide (1.21 g, 13.43 mmol), and Et3N·HCl (2.1 g, 10.05 mmol) in NH_4Cl (15 mL) is stirred at 160°C for 15 hours. After cooling, the mixture is diluted with distilled water (50 mL), acidified to pH 4.5with 4N HCl, and extracted with EtOAc (3 × 50 mL). The organic layer was washed with H_2O (3 × 50 mL), then the combined extracts were dried (MgSO4) and evaporated and the solid residue was purified by silica gel column chromatography eluting with ethyl acetate/ethanol (80:20/v: v) to give solid. Compounds.

[1] (2-chloro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine

Yield:78%,m.p.=134-136^{0}C.Mol.wt 543.17, Anal. Calcd for $C_{34}H_{26}ClN_7$:C,71.86;H, 4.61;N,17.26 %; IR (KBr): 3587, 3498,3115, 1519,1648,665 ^{1}HNMR (300 MHz,$CDCl_3$)^{1}HNMR(300Hz,CDCl3).10.06 (s,1H,tetrazole-NH),4.89(s,2H,CH_2),6.65 8.52(m,21H,ArH),4.03(s,2H,aromatic C-NH).^{13}CNMR ($CDCl_3$)δ:54.1, 110.1, 111,112,114.2, 118.3, 123.5, 167.5, FAB-MS, 568.07

[2] (3-chloro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine

Yield:69%,m.p.=130-132^{0}C.Mol.wt 543.17, Anal. Calcd for $C_{34}H_{26}ClN_7$: C,71.86;H, 4.61;N,17.26 %; %; IR (KBr): 3566, 3478,3132, 1511,1621,654 ^{1}HNMR(300Hz,CDCl3).10.11(s,1H,tetrazole-NH),4.80(s,2H,CH_2),6.77 8.61(m,21H,ArH),4.12 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ:54.1, 110.1, 111,112,114.2, 118.3, 123.5, 148.2, FAB-MS, 568.32

[3] (4-chloro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine

Yield:82%,m.p.=142-145^{0}C.Mol.wt 543.17, Anal. Calcd for $C_{34}H_{26}ClN_7$: C,71.86;H, 4.61;N,17.26 %; IR (KBr): 3543-3243,3476,3104, 1544,1639,649 ^{1}HNMR (300 MHz, $CDCl_3$)^{1}HNMR(300Hz,CDCl3).10.14 (s,1H,tetrazole-NH),4.97(s,2H,CH_2),6.73 8.54(m,21H,ArH),4.16 (s,2H,aromatic C-NH). ^{13}CNMR($CDCl_3$)δ:52.5,111.1,112,114,115.2,119.3,124.5,126.0,127.2,127.5,127.9,133.2,142.1 FAB-MS, 567.85

[4] (2, 3-Dichloro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine

Yield:82%,m.p.=166-168^{0}C.Mol.wt 601.15, Anal. Calcd for $C_{35}H_{25}ClN_7$: C,67.78;H, 4.18;N,16.27 %; IR (KBr): 3575-3285,3496,3133, 2937, 1575,1649,649 ^{1}HNMR (300 MHz, $CDCl_3$)^{1}HNMR (300Hz,CDCl3). 9.77(s,1H,tetrazole-NH),4.97(s,2H,CH_2),6.71-8.34 (m,20H,ArH),4.16(s,2H,ar-NH). ^{13}CNMR($CDCl_3$)δ:52.5,111.1,112,114,115.2,119.3,124.5,126.0,127.2,127.5,127.9,133.2,140,FAB-MS, 602.51

[5](2, 4-Dichloro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:70%,m.p.=154-157^{0}C.Mol.wt 601.15, Anal. Calcd for $C_{35}H_{25}ClN_7$: C,67.78;H, 4.18;N,16.27 %; IR (KBr): 3587-3265,3486,3121, 2932, 1575,1649,654 ^{1}HNMR (300 MHz, $CDCl_3$)^{1}HNMR (300Hz, CDCl3).9.79(s,1H,tetrazole-NH),4.87(s,2H,CH_2),6.77-8.44(m,20H,ArH),4.10(s,2H,ar-NH). ^{13}CNMR($CDCl_3$)δ: 52.5,111.1,112,114.2,115.1,116.6,120.1,122.5,122.9,133,133.5,147, FAB-MS, 601.32

[6] (2, 5-Dichloro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:59%,m.p.=173-177^{0}C.Mol.wt 601.15, Anal.Calcd for $C_{35}H_{25}ClN_7$: C,67.78;H, 4.18;N,16.27 %; IR (KBr): 3557-3264,3448,3133, 2937, 1559, 1640,642, ^{1}HNMR (300 MHz, $CDCl_3$)^1 HNMR (300Hz,CDCl3).9.96(s,1H,tetrazole-NH),4.92 (s,2H,CH_2),6.62-8.54(m,20H,ArH),4.40(s,2H,ar-NH). ^{13}CNMR($CDCl_3$)δ: 52.5,111.1,112, 114.2,115.1,116.6, 120.1,122.5,122.9,133.135.1,141.5, FAB-MS, 602.5

[7](2, 6-Dichloro-phenyl)- (phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:66%,m.p.=157-163^{0}C.Mol.wt 601.15, Anal. Calcd for $C_{35}H_{25}ClN_7$: C,67.78;H, 4.18;N,16.27 %; IR (KBr): 3550-3285,3486,3165, 2976, 1565,1649,652.8. ^{1}HNMR(300Hz,CDCl3).9.92(s,1H,tetrazole-NH),4.86(s,2H,CH_2),6.69-8.63(m,20H,ArH), 4.46(s,2H,ar-NH). ^{13}CNMR($CDCl_3$)δ: 52.5,111.1,112, 114.2,115.1,116.6,120.1,122.5,122.9,133.135.1,141.5, FAB-MS, 602.5

[8] (2-Nitro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:69%,m.p.=117-119^{0}C.Mol.wt 578.21, Anal. Calcd for $C_{34}H_{26}N_8O_2$: C,70.58;H, 4.53;N,17.26 %; %; IR (KBr): 3576-3586,3465,3154, 1565,1659, ^{1}HNMR(300Hz,CDCl3).10.21(s,1H,tetrazole-NH),4.99(s,2H,CH_2),6.84-8.43(m,21H,ArH),4.26 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: 47,111.1, 115.3,119.5,121.2,127.5,129.3,133.2,145.6, FAB-MS, 578.12

[9] (3-Nitro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:58%,m.p.=114-116^{0}C.Mol.wt 578.21, Anal. Calcd for $C_{34}H_{26}N_8O_2$: C,70.58;H, 4.53;N,17.26 %; %; IR (KBr): 3556-3280,3496,3175, 2998, 1587,1675, ^{1}HNMR(300Hz,CDCl3).10.07(s,1H,tetrazole-NH), 5.04(s,2H,CH_2),6.78-8.36(m,21H,ArH),4.21 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: 55.4,111.1,115.3,119.5,121.2,127.5,129.3,133.2,141, FAB-MS, 577.12

[10] (4-Nitro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:73%,m.p.=113-115^{0}C.Mol.wt 578.21, Anal. Calcd for $C_{34}H_{26}N_8O_2$: C,70.58;H, 4.53;N,17.26 %; %; IR (KBr): 3551-3285,3432,3121, 2998, 1587,1675, ^{1}HNMR(300Hz,CDCl3).10.12(s,1H,tetrazole-NH),4.94(s,2H,CH_2),6.65-8.40(m,21H,ArH),4.26 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: 47,111.1,115.3,119.5,121.2,127.5,129.3,133.2,145.6, FAB-MS, 578.53

[11](2, 4-Dinitro -phenyl)- (phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:73%,m.p.=134-137^{0}C.Mol.wt 623.20, Anal. Calcd for $C_{34}H_{25}N_9O_4$: C,65.48;H, 4.04;N,10.26 %; %; IR (KBr): 3571-3205,3487,3143, 2995, 1565,1615, ^{1}HNMR(300Hz,CDCl3).10.01(s,1H,tetrazole-NH),4.94(s,2H,CH_2),6.60-8.47(m,20H,ArH),4.20 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ:55.4, 112.1,113.4,114.1,116.3,119.2,128.2,134.2,139.7,142.7,FAB-MS, 624.06

[12](2, 5-Dinitro -phenyl)- (phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:73%,m.p.=142-145^{0}C.Mol.wt 623.20, Anal. Calcd for $C_{34}H_{25}N_9O_4$: C,65.48;H, 4.04;N,10.26 %; %; IR (KBr): 3576-3226,3481,3132, 2965, 1560,1611, ^{1}HNMR(300Hz,CDCl3).10.04(s,1H,tetrazole-NH),4.97(s,2H,CH_2),6.67-8.39(m,20H,ArH),4.23 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ:55.4, 112.1,113.4,114.1,116.3,119.2,128.2,134.2,139.7,142.7,FAB-MS, 624.06

[13] (2-chloro-4-nitro -phenyl)- (phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:73%,m.p.=142-145^{0}C.Mol.wt 612.178, Anal. Calcd for $C_{34}H_{25}ClN_8O_2$: C,66.61;H, 4.04;N,10.26 %; IR (KBr): 3559-3287,3493,3155, 2923, 1543,1676,643. ^{1}HNMR (300Hz,CDCl3) .9.64 (s,1H,tetrazole-NH),4.88(s,2H,CH_2),6.61 8.65(m,20H,ArH),4.27 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ:55.4, 112.1,113.4, 114.1,116.3, 119.2, 128.2,134.2,139.7,142.7,FAB-MS, 613.06

[13](2-chloro-5-nitro -phenyl)- (phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:70%,m.p.=152-155^{0}C.Mol.wt 612.178, Anal.Calcd for $C_{34}H_{25}ClN_8O_2$: C,66.61;H, 4.04;N,10.26 %; IR (KBr): 3559-3287,3493,3155, 2923, 1543,1676,643. ^{1}HNMR(300Hz,CDCl3) .9.72(s,1H,tetrazole-NH),4.95(s,2H,CH_2),6.61-8.65(m,20H,ArH),4.27(s,2H,aromaticC-NH). ^{13}CNMR ($CDCl_3$)δ:55.4,112.110.8,112.3,114.2,123.2,124.2, 129.2, 139.3,143.6,FAB-MS, 614.2

[14] (2-Methoxy-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:73%,m.p.=125-127^{0}C.Mol.wt 563.24, Anal. Calcd for $C_{35}H_{29}N_8O$: C,74.58;H, 5.19;N,17.39 %,IR (KBr): 3535-3246,3476,3154, 2965, 1533,1653, ^{1}HNMR(300Hz,CDCl3).10.14(s,1H,tetrazole-NH),4.99(s,2H,CH_2),6.78-8.60(m,21H,ArH), 3.24(s,3H,CH_3),4.13 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: δ:58.2,111.0,115.1, 119.2,121.1,124.1, 133.4,134.0,148.1, FAB-MS, 564.11

[15] (3-Methoxy-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:64%,m.p.=132-135^{0}C.Mol.wt 563.24, Anal. Calcd for $C_{35}H_{29}N_8O$: C,74.58;H, 5.19;N,17.39 %,IR (KBr): 3530-3211,3464,3134, 2974, 1598,1661. ^{1}HNMR(300Hz,CDCl3).10.23(s,1H,tetrazole-NH),4.92(s,2H,CH_2),6.71-8.66(m,21H,ArH), 3.28(s,3H,CH_3),4.18 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: δ:13,52.3,112.3, 113.1,115.2,123.1, 130.4, 135.1,138.1,141.2,143.2,148.1, FAB-MS, 562.87

[16] (4-Methoxy-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:73%,m.p.=136-13^{0}C.Mol.wt 563.24, Anal.Calcd for $C_{35}H_{29}N_8O$: C,74.58;H, 5.19;N,17.39 %,IR (KBr): 3535-3246,3476,3154, 2965, 1533,1653,645. ^{1}HNMR (300Hz,CDCl3).10.16(s,1H,tetrazole-NH),4.96(s,2H,CH_2),6.71-8.56(m,21H,ArH), 3.20(s,3H,CH_3),4.17 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: δ:20,42.4,50.2,58.3,60.1,75.3,112.7,114.5,116.1,119.1, 123.1,136.2,139., FAB-MS, 563.03

[17] (2-fluoro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:53%,m.p.=127-129^{0}C.Mol.wt 551.22, Anal. Calcd for $C_{34}H_{26}FN_7$:C,74.03;H, 4.75;N,17.77 %; IR (KBr): 3554-3199, 3456,3143, 1544,1616,678 ^{1}HNMR (300 MHz, $CDCl_3$)9.95(s,1H,tetrazole-NH),4.99 (s,2H,CH_2),6.95 8.43(m,21H,ArH),4.86 (s,2H,aromatic C-NH). ^{13}CNMR ($CDCl_3$)δ: 50.2,111.,113.1, 115.2,123.1,130.4,135.1,138.1,141.2,FAB-MS, 552.05

[18] (3-fluoro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:53%,m.p.=127-129^{0}C.Mol.wt 551.22, Anal. Calcd for $C_{34}H_{26}FN_7$:C,74.03;H, 4.75;N,17.77 %; IR (KBr): 3554-3199, 3456,3143, 1544,1616,678 ^{1}HNMR (300 MHz, $CDCl_3$).9.99(s,1H,tetrazole-NH),4.89(s,2H,CH_2),6.90-8.45(m,21H,ArH),4.97 (s,2H,aromatic C-NH).^{13}CNMR ($CDCl_3$)δ: 50.2,111., 113.1,115.2,123.1,130.4,135.1,138.1,141.2, FAB-MS, 552.95

[19] (4-fluoro-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:53%,m.p.=127-129^{0}C.Mol.wt 551.22, Anal. Calcd for $C_{34}H_{26}FN_7$:C,74.03;H, 4.75;N,17.77 %; IR (KBr): 3559-3156, 3476,3198, 1574,1656,671 ^{1}HNMR(300Hz,CDCl3).9.98(s,1H,tetrazole-NH),4.89(s,2H,CH_2),6.87 8.54(m,21H,ArH),4.80 (s,2H,aromatic C-NH).^{13}CNMR ($CDCl_3$)δ: 50.2,111.,113.1,115.2,123.1,130.4,135.1,138.1,149.4, FAB-MS, 550.76

[20] (2-Iodo-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:61%,m.p.=187-189^{0}C.Mol.wt 659.12, Anal. Calcd for $C_{34}H_{26}IN_7$:C,61.92;H, 3.97;N,17.77 %; IR (KBr): 3559-3156, 3476,3198, 1574,1656,671 ^{1}HNMR(300Hz,CDCl3).10.13(s,1H,tetrazole-NH),5.05(s,2H,CH_2),6.60- 8.34(m,21H,ArH),4.89 (s,2H,aromatic C-NH).^{13}CNMR ($CDCl_3$)δ: 50.2,111.,113.1,115.2,123.1,130.4,135.1,138.1,154, FAB-MS, 660.132

[21] (3-Iodo-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine
Yield:66%,m.p.=193-196^{0}C.Mol.wt 659.12, Anal. Calcd for $C_{34}H_{26}IN_7$:C,61.92;H, 3.97;N,17.77 %; IR (KBr): 3565-3132, 3487,3111, 1576,1636,1088. ^{1}HNMR(300Hz,CDCl3).10.02(s,1H,tetrazole-NH),5.12(s,2H,CH_2),6.88- 8.73(m,21H,ArH),4.83 (s,2H,aromatic C-NH).^{13}CNMR ($CDCl_3$)δ: 50.2,111.,113.1,115.2,123.1,130.4,135.1,138.1,154, FAB-MS, 659.06

[22] (4-Iodo-phenyl)-(phenyl-{1-[2' (1-H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl} methyl)-amine

Yield:60%,m.p.=199-204^{0}C.Mol.wt 659.12, Anal. Calcd for $C_{34}H_{26}IN_7$:C,61.92;H, 3.97;N,17.77 %; IR (KBr): 3576-3185, 3470,3321, 1563,1680,1092 ^{1}HNMR (300 MHz, $CDCl_3$)^{1}HNMR (300Hz,CDCl3).10.0(s,1H,tetrazole-NH),4.98(s,2H,CH_2),6.62- 8.47(m,21H,ArH),4.89 (s,2H,aromatic C-NH).^{13}CNMR ($CDCl_3$)δ: 50.2,111.,113.1,115.2,123.1,130.4,135.1,138.1,154, FAB-MS, 660.25

Antihypertensive Activity

Procedure for development of hypertensions for normotensive rats [26--]Albino normotensive rats (Wistar Strain) were taken and they were hypertensized by cholinomimetic agents for screening of all the synthesized benzimidazole derivatives for there anti-hypertensive activity. Suspension of test compounds was prepared in 1% w/v sodium carboxy methyl cellulose (sodium CMC) and was administered at dose level of 50 and 100 microgram/kg animal body weight to different groups of five rats each. After administration of dose to animal blood pressure was measured by normotensive tail and cuff method using pressure meter. Measurements were done after one hour and three hours interval in step-wise manner as follows: Screening Methods for Anti-hypertensive Activity:

(a) Angiotensin II induced Hypertension: [27](i) Invasive method (Direct method). (ii) Non-invasive Tail cuff method (Indirect method).

(b) In-vitro determination of vasodilator activity by aortic rings.

(i) Invasive Method (Direct Method):**[28-29]** Male albino wistar (150-250 gm) rats were used and housed at 28±1^{0}C room temperature. The rats were anaesthetized with sodium chloride 0.9% solution, Drug solution 10-µg/100ml, and Heparin 500 I.U.solution urethane hydrochloride 50% w/v solution 80 mg/kg i.p. To set up the instrument firstly the level of mercury in the left arm of manometer was adjusted to 90-100 mm of Hg (normal blood pressure of rat).this was done in steps of 10mm at a time and the physiograph so obtained was used as calibration graph for calculations. The Jugular vein and carotid artery were surgically cannulated for drug administration for recording the blood pressure respectively. The trachea was cannulated in order to provide artificial respiration to rat during the experiment. By means of three way stop cock and a stainless steel needle at the end of P.E. tubing was attached to arterial cannula for B.P., Transducers and the venus cannula to a syringe. Then both the cannulas were filled by heparinized saline before the administration. Arterial cannula was connected via transducer to physiograph recorder. Several baseline readings of systolic and diastolic pressures were recorded. The physiograph shows the reduction of the blood pressure with compare to losratan. Synthesized compounds were screened in presence of Angiotensin II induced hypertension (0.5 µg/kg i.v.). Observations are given in the table 3, 4.

(ii) Non-invasive Tail cuff Method (Indirect Method):**[28-29]** Albino rats weighing 200-250 gm were used to screening for all the synthesizes benzimidazole derivatives for antihypertensive activity. Suspension of test compound was prepared in 1% w/v sodium carboxy methyl cellulose and administered at dose level of 50 mg/kg animal body weight to different of six rats each group.Contorl group received an equal quantity of 1% w/v sodium carboxy methyl cellulose suspension. After administration of dose to animal, blood pressure was measured by Non-invasive Tail cuff Method using pressure meter.Measurment were done after 1 hour and 3 hour time interval intensive stepwise. One hour after administration of drug sample, animal was shifted to the restrainer, which restricts the movement of animal. The tail was cleaned with moist cotton to remove the dirty matter and talcum powder was sprayed on tail to make its surface smooth. A tail cuff and pulse transducer was fixed around the tail. Initially animal shows particular pulse level, when the pulse rate is within the normal range. 'STRAT' switch is put on and the recorder records the blood pressure as SBP (systolic blood pressure). DBP (Diastolic blood pressure) and MABP (mean arterial blood pressure), which is displayed on monitor. The pressure can be easily read from the pre-calibrated monitor. Once all the values are displayed the recorder is switched off and for next measurement. Some procedures are allowed once when sufficient pulse level is attained. Observations are given in the table 1, 2.

Table 1. Hypertension induced in normotensive rat

Comp.	Exp. Animal Albino (Wistar) Rat	After 1hour			After 3 hour		
		SBP	DBP	MA BP	SBP	DBP	MABP
[1]	1	141	110	126	140	108	124
	2	138	105	122	139	109	124
	3	132	104	118	142	106	124
	4	142	103	123	140	106	123
	5	141	110	121	143	115	124
[2]	1	140	110	125	134	105	119
	2	141	104	123	138	104	121
	3	139	111	125	135	103	119
	4	140	101	121	136	103	119
	5	142	103	122	134	102	118
[3]	1	140	106	123	138	101	119
	2	138	104	121	140	106	123
	3	141	109	125	143	106	124
	4	136	112	124	141	103	122
	5	142	112	127	140	103	121
[4]	1	143	110	127	134	102	118
	2	137	102	124	135	102	118
	3	139	107	123	140	101	120
	4	143	109	126	137	104	120
	5	141	109	125	139	102	120
[5]	1	140	110	125	134	105	119
	2	141	104	123	138	104	121
	3	139	111	125	135	103	119
	4	140	101	121	136	103	119
	5	142	103	122	134	102	118
[6]	1	140	104	122	141	103	122
	2	138	106	123	140	106	123
	3	133	114	124	139	101	120
	4	142	105	124	135	107	121
	5	141	102	121	139	103	121
[7]	1	143	101	122	140	110	125
	2	134	112	123	135	107	121
	3	140	105	122	137	103	120
	4	141	106	124	141	101	121
	5	143	105	124	143	105	124
[8]	1	142	112	127	140	102	121
	2	144	116	130	141	101	122
	3	142	110	126	139	104	123
	4	146	106	126	144	104	124
	5	144	104	124	140	100	120
[9]	1	143	102	121	142	103	122
	2	133	117	124	143	102	121
	3	137	105	123	140	104	122
	4	140	105	124	139	104	120
	5	143	108	123	138	103	121

[10]	1	144	112	127	141	102	121
	2	142	114	128	144	101	122
	3	146	110	126	142	100	120
	4	140	108	124	138	102	120
	5	142	108	125	138	100	119
[11]	1	136	105	123	142	104	119
	2	135	102	122	140	97	119
	3	146	103	125	139	105	120
	4	149	101	125	143	101	121
	5	144	109	131	140	100	120
[12]	1	142	115	127	135	98	118
	2	140	106	123	142	101	121
	3	142	108	125	141	102	120
	4	139	110	125	143	101	120
	5	146	105	126	142	101	118
[13]	1	142	102	124	143	101	122
	2	145	105	125	145	100	121
	3	136	113	124	142	101	121
	4	139	113	122	140	100	120
	5	139	105	123	138	198	118
[14]	1	141	106	125	144	99	119
	2	140	111	124	139	97	120
	3	144	114	126	141	100	120
	4	141	112	123	139	96	117
	5	140	103	124	145	98	119
[15]	1	135	116	125	142	104	120
	2	139	112	124	146	102	121
	3	144	116	126	144	101	121
	4	142	114	123	142	103	122
	5	139	105	126	146	106	120
[16]	1	148	106	127	142	106	124
	2	151	109	130	146	104	125
	3	146	104	125	142	104	123
	4	144	106	125	140	102	121
	5	148	104	126	142	106	124
[17]	1	143	106	125	139	104	121
	2	146	110	128	140	104	122
	3	149	111	130	143	106	124
	4	152	112	133	145	103	124
	5	150	111	131	146	104	125
[18]	1	144	114	129	146	106	126
	2	142	108	125	146	104	125
	3	146	106	126	142	104	123
	4	142	110	126	140	116	128
	5	148	102	125	144	106	125
[19]	1	144	112	127	142	104	123
	2	142	114	127	140	101	122
	3	148	104	126	144	104	124
	4	154	108	132	144	102	123
	5	148	104	126	142	100	121

[20]	1	142	113	125	143	100	121
	2	136	105	123	142	104	119
	3	135	102	122	140	97	119
	4	146	103	125	139	105	120
	5	144	109	131	140	100	120
[21]	1	142	113	125	142	102	122
	2	141	109	123	144	101	121
	3	144	114	129	141	104	120
	4	146	104	132	142	100	121
	5	148	104	125	145	102	123
[22]	1	140	106	123	138	101	119
	2	138	104	121	140	106	123
	3	141	109	125	143	106	124
	4	136	112	124	141	103	122
	5	142	112	127	140	103	121
Control	**Losartan**	114	-	-	-	-	-
	Telmisartan	118	-	-	-	-	-

Table 2. Reduction in blood pressure (mm Hg) at a dose of 50 µgm/kg animal body weight.

Comp.	**Exp. Animal Albino (Wistar) Rat**	**After 1hour**			**After 3 hour**		
		SBP	**DBP**	**MABP**	**SBP**	**DBP**	**MABP**
[1]	1	124	101	112	122	102	114
	2	128	105	114	121	103	112
	3	126	100	113	124	101	112
	4	123	102	112	123	102	111
	5	124	102	113	125	102	112
[2]	1	126	101	113	125	100	113
	2	131	105	118	125	100	115
	3	128	104	116	123	101	112
	4	125	105	115	126	104	115
	5	126	106	116	122	100	111
[3]	1	126	103	114	126	96	111
	2	129	101	115	119	104	111
	3	123	107	115	121	99	110
	4	127	105	119	123	103	113
	5	123	101	113	124	103	112
[4]	1	131	105	118	124	101	115
	2	126	103	114	128	106	117
	3	124	106	115	127	104	116
	4	127	105	116	125	105	115
	5	132	96	114	130	101	116
[5]	1	129	108	119	124	104	114
	2	122	112	117	122	103	112
	3	126	114	124	128	107	117
	4	124	111	121	123	104	113
	5	126	104	115	127	107	117

[6]	1	127	105	122	126	105	115
		129	108	121	124	104	114
	3	122	112	117	122	103	112
	4	126	114	120	128	107	117
	5	124	111	118	123	104	113
[7]	1	122	100	111	126	102	115
	2	124	102	112	126	102	111
	3	126	101	113	124	104	114
	4	128	102	115	126	104	115
	5	125	105	115	122	100	112
[8]	1	124	100	112	128	101	113
	2	130	104	117	128	102	115
	3	125	105	115	124	101	112
	4	122	100	111	126	104	115
	5	128	102	115	130	103	116
[9]	1	128	105	114	121	103	112
	2	126	100	113	124	101	112
	3	123	102	112	123	102	111
	4	122	101	111	126	102	114
	5	124	102	113	125	102	112
[10]	1	123	102	113	128	103	112
	2	121	101	113	123	102	111
	3	126	102	111	124	101	112
	4	121	100	110	125	102	111
	5	126	103	115	122	103	112
[11]	1	126	101	117	123	102	112
	2	131	100	123	121	106	110
	3	129	103	124	122	100	111
	4	133	105	118	127	104	114
	5	130	108	113	123	102	113
[12]	1	127	103	117	127	102	112
	2	122	102	119	124	102	113
	3	126	104	118	125	102	114
	4	125	101	113	128	102	115
	5	123	103	116	126	100	113
[13]	1	123	101	112	122	106	116
	2	124	102	113	124	102	113
	3	122	102	112	126	100	111
	4	124	102	113	128	100	114
	5	128	102	115	129	101	115
[14]	1	130	104	117	128	102	115
	2	125	105	115	124	101	112
	3	122	100	111	126	104	115
	4	125	100	112	121	107	114
	5	128	102	115	130	103	116
[15]	1	129	101	115	119	104	111
	2	123	107	115	121	99	110
	3	127	105	119	123	103	113
	4	129	100	111	126	104	115
	5	123	101	113	124	103	112

[16]	1	126	104	115	125	105	115
	2	124	104	114	121	100	110
	3	125	102	112	128	100	114
	4	120	100	120	130	95	112
	5	130	104	117	126	101	113
[17]	1	126	103	115	128	103	116
	2	131	109	120	121	105	113
	3	129	102	116	124	101	113
	4	133	103	117	127	105	116
	5	130	108	118	124	100	112
[18]	1	127	105	122	126	105	115
	2	129	108	121	124	104	114
	3	122	112	117	122	103	112
	4	126	114	120	128	107	117
	5	124	111	118	123	104	113
[19]	1	128	107	117	127	101	114
	2	126	103	114	125	104	113
	3	132	105	119	121	102	110
	4	131	106	118	119	103	107
	5	136	107	121	129	101	115
[20]	1	124	96	110	124	106	115
	2	127	101	114	123	102	112
	3	121	103	112	121	97	109
	4	120	100	115	128	100	114
	5	128	98	113	131	99	115
[21]	1	126	103	114	128	106	117
	2	124	106	115	127	104	116
	3	127	105	116	125	105	115
	4	130	102	115	132	102	117
	5	132	96	114	130	101	116
[22]	1	124	101	112	122	102	114
	2	128	105	114	121	103	112
	3	126	100	113	124	101	112
	4	123	102	112	123	102	111
	5	124	102	113	125	102	112
Control	**Losartan**	103	-	-	-	-	-
	Telmisartan	107	-	-	-	-	-

Table: 3 Blood Pressure values for synthesized compounds over duration of 90 minutes

Comp. No.	Mean Arterial Pressure After									
	0 min.	10 min.	20 min.	30 min.	40 min.	50 min.	60 min.	70 min.	80 min.	90 min.
Losartan	168	164	157	147	140	133	125	120	116	112
1	177	172	169	161	155	149	142	138	131	127
2	182	176	170	164	158	151	146	139	131	125
3	176	170	165	157	151	142	137	130	122	117
4	179	173	168	160	152	144	135	126	121	115
5	175	168	161	156	150	142	136	127	120	113
6	180	174	169	161	154	148	141	135	130	126
7	175	169	161	154	146	140	134	128	121	116
8	170	164	159	152	145	138	130	123	116	110
9	173	166	160	153	146	139	132	127	121	117
10	169	153	149	144	141	137	132	128	125	121
11	179	172	165	157	150	143	135	125	117	107
12	177	169	161	156	150	144	138	130	124	115
13	181	176	170	165	159	151	143	137	130	125
14	174	168	160	155	149	141	134	129	125	120
15	184	175	168	162	156	150	145	139	133	128
16	172	167	163	158	151	146	141	135	131	125
17	174	168	163	157	152	148	142	137	129	123
18	169	160	154	146	142	134	127	120	114	111
19	177	170	167	161	156	148	142	137	131	128
20	178	171	163	157	151	145	138	131	126	119
21	174	166	162	156	148	141	138	131	126	120
22	173	168	159	148	142	135	129	122	117	112

Table: 4 Antihypertensive Activity of synthesized compounds

Compound. No	Minimum Blood pressure value(mm Hg)	Duration of hypertension effect(min.)
Losratan	112	90
1	114	106
2	115	113
3	111	99
4	108	96
5	110	95
6	115	114
7	109	100
8	110	90
9	112	95
10	113	100
11	107	90
12	110	95
13	116	115
14	113	105
15	115	120
16	116	110
17	117	103
18	111	90
19	120	100
20	114	95
21	112	107
22	108	95

Results and discussion

The synthesized compounds were characterized on the basis of chemical and spectral data.To date, many orally available sartans have been developed and are used in the treatment of both hypertension and damage associated with diseases like atherosclerosis and diabetes. In particular, the good properties of new non peptide AngII antagonists, such as losartan, have stimulated the design of many different congeners. All these drugs contain some common Structural features represented by a biphenyl fragment bearing an acidic moiety (i.e.: tetrazole, carboxylic- or sulphonamidocarboxyl- group), linked to a heteroaromatic or acyclic system by means of a methylene group. Almost all of the chemical manipulations within the fundamental skeleton of sartans concerned the substitution of the benzimidazole ring of losartan with several variously substituted heteroaromatic groups or acyclic structures. In the present work, *ortho* phenylene diamine was condensed with mandallic acid. The resulting 2-(α-hydroxy benzyl) benzimidazole was converted to 2-(α –bromo benzyl) benzimidazole by reacting with HBr and Anhydrous $ZnCl_2$. Further attempts were made to synthesize synthesis compounds reacts with different substituted amines and biphenyl tetrazole ring(to increase biological activity) of with react sodium azide and potassium carbonate which were characterized by physical and instrumental analysis like recording their melting points in Open capillary tubes and by spectral studies such as IR, NMR and Mass spectroscopy. The present work was mainly intended to establish the moieties which are responsible for Angiotension-II inhibition. Presence of amino substituted has increased the activity substantially over the substituted [1] to [22]. The maximum activity has been observed with nitro group (Compound 3, 4, 5, 8, 11, 13, 18, and 22). Substituted benzimidazole nucleus coupled to biphenyl tetrazole group has been designed, synthesized and evaluated for angiotensin II antagonism. Compound with amine substituted compounds. The higher activity of amine derivatives may be ascribed to the ability of group to act as H-bond acceptor, hydrophobic, vanderwall and hydrogen acceptor with respect to the receptor site. Hence a new binding profile has been proposed where an additional receptor pocket in the binding site can accommodate bulky but H-bond acceptor group and this pocket may not be accessible to natural ligands and even losartan and Telmisartan. Additionally a novel and simple method for synthesis of pendant biphenyl moiety has been devised to improve safety and yield.

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