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Benzimidazoles derivatives with (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl)-(substituted-benzylidene)-amine with potential angiotensin II receptor antagonists as antihypertensive activity

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Abstract

In this study we have synthesized some Benzimidazole derivatives (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl)-(Substituted-benzylidene)-amine and screened for their antihypertensive activity. 4-chloro-o-Phenylenediamine was condensed with anthranilic acid in presence of Polyphosphoric acid and different aryl aldehydes compounds with biphenyl tetrazole ring. The presence of specific functional group were analysed by IR spectroscopy, The determination of structure for the synthesized compounds by NMR and Mass spectroscopy ^{13}C NMR, ^{1}H NMR, FAB Mass. All the synthesized compounds showed significant antihypertensive activity.

Keywords: Benzimidazole; Antihypertensive; 4-chloro-o-Phenylenediamine; Biphenyl tetrazole; Blood pressure.

Introduction

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 chemotherapeutic approach in man [1,2] . Moreover, these fused heterocylces were distinctively studied for their antitumor, antiviral and antimicrobial activities as the new nonnucleoside topoisomerase I poisons, human immunodeficiency virus-1 reverse transcriptase inhibitors and /or potent DNA gyrase inhibitors [3-5]. In addition, benzimidazole derivatives have played a crucial role in theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis. The rennin-angiotensin system (RAS) plays a major role in the regulation of blood pressure and electrolyte homeostasis [6]. RAS is a cascade of proteolytic enzymes (rennin and angiotensin converting enzyme (ACE)) that result in the production of the systemic hormone angiotensin II (AII).The blockade of RAS with inhibitors of ACE has demonstrated the effectiveness of the reduction of levels of AII on cardiovascular and kidney heamodynamics, aldosterone production and release, and the absorption of sodium. Antagonists of AII constitute an alternative method blocking the RAS. Several peptidic and nonpeptidic AII receptor antagonists are known. The therapeutic availability is less for the peptidic AII antagonist due to their poor bioavailability; short plasma half-life and partial agonist activity but the nonpeptidic AII receptors

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antagonist lack the defect of peptidic antagonist [7].The therapeutic profile of AII receptor antagonist is thought to be similar to that of angiotensin converting enzyme (ACE) inhibitors such as captopril, enalapril, and lisinopril. In addition, since AII receptor antagonist does not affect the metabolism of bradykinin so they may not have the side effect of ACE inhibitors, such as dry cough and angiodema. 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 antihypertensive [8]. Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported [9].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 [10-12].

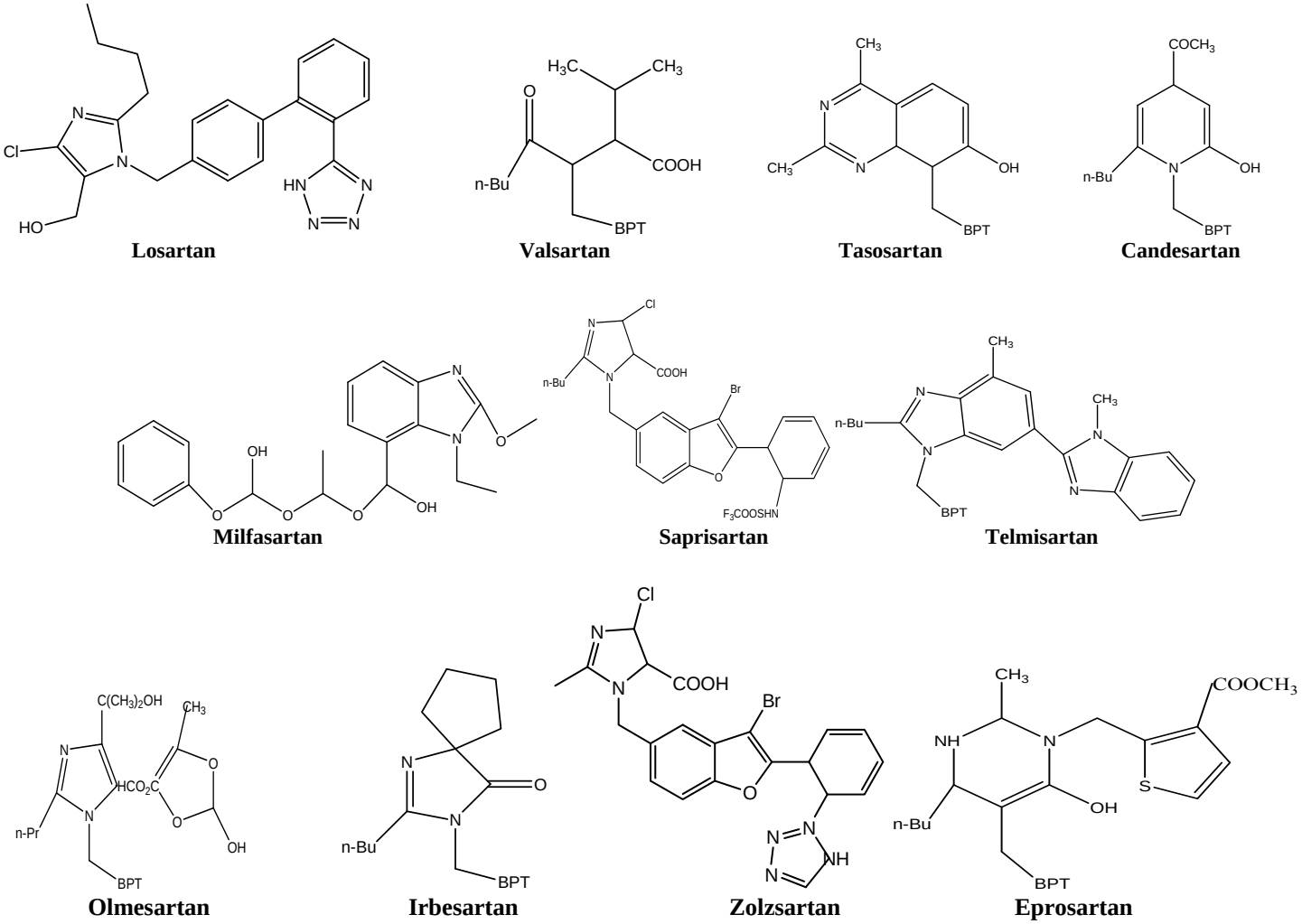

Figure 1. Angiotensin II selective antagonists

Material and methods

Experimental

All melting points were taken in open capillaries and are uncorrected. FT-IR spectra were recorded on

perkin-Elmer-157 spectrophotometer instrument using KBr discs. ^{1}HNMR were taken on a Bruker WN-400 FTMHz NMR instrument using DMSO/$CDCl_3$ solvent and TMS as a internal standard.

[MCS 01] -2-(2- aminophenyl) benzimidazole

4-Chloro-benzene-1, 2-diamine was condensed with anthranilic acid in poly phosphoric acid at 168-172 ^{0}C for 7 hrs. The reaction mixture was poured into crushed ice. Filtered, washed, dried and recrystalized. The product 2-(2-aminophenyl) benzimidazole was obtained.

[MCS-02] 2-(5-Nitro-1H-benzimidazole-2-yl)-phenyl amine

12.5 ml of concentrated nitric acid was placed in three necked flask and equal quantity of concentrated sulphuric acid (1:1) was added slowly. The mixture was kept in the ice cold water then compound MCS-01 (1.5 gm) was mixed in portions during 5 hours under room temperature. After stirred continuously for 2.5 hours 15 minutes and then the reaction mixture was poured slowly over crushed ice with stirring. The precipitated product was filtered out and washes with cold water. The final product MCS-02 was formed. Product was 2-(5-Nitro-1H-benzimidazole-2-yl)-phenyl amine then treated with various aromatic aldehydes to obtain the Schiff bases compounds MCS-03.

MCS-04- 4!-{2-[2-(Benzylidene-amino)-phenyl]-6-chloro-5-nitro-benzimidazol-1-ylmethyl}-biphenyl-2-carbonitrile

To a solution of 1.5 g (10.12 mmol) compound aryl 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-05- (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl)-(Substitued-benzylidene)-amine

A mixture of different substituted 4!-{2-[2-(Benzylidene-amino)-phenyl]-6-chloro-5-nitro-benzimidazol-1-ylmethyl}-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 ($MgSO_4$) 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.

Data

[1] (2-Chloro- benzylidene)- (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl) - amine

Yield:70%,m.p.=104-106^{0}C.Mol.wt 645.0, Anal.Calcd for$C_{34}H_{22}ClN_8O_2$:C,63.26;H, 3.44;N,17.36 %; IR (KBr): 3514-3106,3486,1544,1621, 1543-1332 (N-O str., NO2), 1178 (C-N str.), 815.8 (1,4 disub. Benz.Ring). 647(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$)10.13(s,1H,tetrazole-NH),4.97(s,2H,CH_2),7.08-8.66(m,19H,ArH).^{13}CNMR ($CDCl_3$)δ:55.8, 113.4,114.1,116.3,119.2,128.2,134.2,139.7, FAB-MS, 646.05

[2] (3-Chloro- benzylidene)-(2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl) - amine

Yield:64%,m.p.=117-119^{0}C.Mol.wt 645.0, Anal.Calcd for$C_{34}H_{22}ClN_8O_2$:C,63.26;H, 3.44;N,17.36 %; IR (KBr): 3522-3114,3489,1542,1625, 1540-1339 (N-O str., NO2), 1175 (C-N str.), 811.0 (1,4 disub. Benz.Ring). 651(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$)10.10(s,1H,tetrazole-NH),4.99(s,2H,CH_2),7.01-8.48(m,19H,ArH).^{13}CNMR ($CDCl_3$)δ:55.8,110.1,111.6,113.1,117.3, 123.1,130.3,131.3,139.1, FAB-MS, 644.3

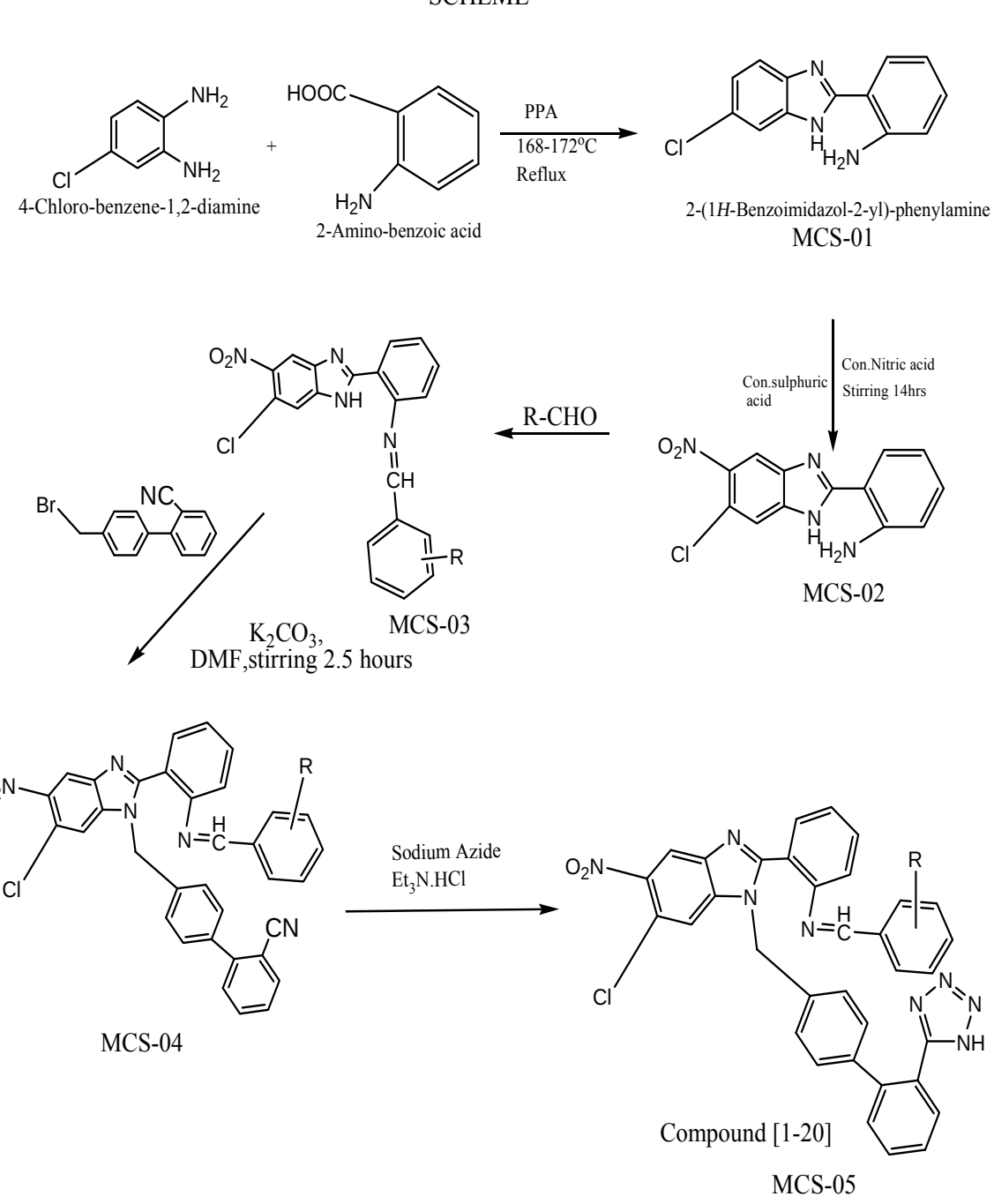

Figure 2. Synthesis of fifteen analogs compounds

[3] (4-Chloro- benzylidene)-(2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl) – amine

Yield:67%,m.p.=114-116^{0}C.Mol.wt 645.0, Anal.Calcd for$C_{34}H_{22}ClN_8O_2$:C,63.26;H, 3.44;N,17.36 %; IR (KBr): 3517-3109,3494,1537,1613, 1546-1328 (N-O str., NO2), 1184 (C-N str.), 809.5 (1,4 disub. Benz.Ring). 650(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$)10.15(s,1H,tetrazole-NH),4.93(s,2H,CH_2),6.98-8.35(m,19H,ArH).^{13}CNMR ($CDCl_3$)δ:55.8,110.1,111.6,113.1,117.3,123.1,130.3,131.3,139.1,139.7,FAB-MS, 645.76

[4] 2-[2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenylimino)-methyl]phenol

Yield:60%,m.p.=155-158^{0}C.Mol.wt 627.0, Anal.Calcd for$C_{34}H_{23}ClN_8O_3$:C,65.12;H, 3.70;N,17.87 %; IR (KBr): 3548-3132,3486,3075,1527,1644, 1538-1359 (N-O str., NO2), 1180 (C-N str.), 816.2 (1,4 disub. Benz.Ring). 645(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$)9.98(s,1H,tetrazole-NH),5.03(s,2H,CH_2),6.98-8.35(m,19H,ArH),5.37(arm OH).^{13}CNMR($CDCl_3$)δ:59.2, 112.8,113.4,116.2,117.2,126.5,130.1,132.133.8,135.1,136.3,136.2,139.4,140.3,142.4,FAB-MS, 626.7

[5] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2-methoxy-benzylidene)-amine

Yield: 52%, m.p. =144-146^{0}C.Mol.weight 641.0, Anal.Calcd for $C_{35}H_{25}ClN_8O_3$: C,65.57; H, 3.93; N,17.48 %. IR (KBr): 3524-3112, 3075, 2941.1 (C-H str.,CH_3), 2895.7 (C-H str.,CH_2), 1640-1518 (C=N and C=Cstr.), 1565-1301 (N-O str., NO2), 1178 (C-N str.), 897.1(1,4 disub. Benz.Ring) 651.8(C-Cl). ^{1}HNMR (300 MHz,$CDCl_3$)10.08(s,1H,tetrazole-NH),5.08(s,2H,CH_2), 6.98-8.35(m,19H,ArH),3.31(m,3H-OCH_3). ^{13}CNMR ($CDCl_3$) δ:14.0,49, 111.3,115.1,117.8,120.2,129.2, 139.2,149.7,FAB-MS, 641.2

[6] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(3-methoxy-benzylidene)-amine

Yield: 56%, m.p. =149-154^{0}C.Mol.weight 641.0, Anal.Calcd for $C_{35}H_{25}ClN_8O_3$: C,65.57; H, 3.93; N,17.48 %. IR (KBr): 3520-3116, 3069, 2928.6 (C-H str.,CH_3), 2898 (C-H str.,CH_2), 1647-1510 (C=N and C=Cstr.), 1562-1314 (N-O str., NO2), 1173 (C-N str.), 885.0(1,4 disub. Benz.Ring) 648.8(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$) 10.16 (s,1H,tetrazole-NH), 5.00 (s,2H,CH_2),7.03-8.52(m,19H,ArH),3.35(m,3H-OCH_3). ^{13}CNMR($CDCl_3$)δ: 17.0,51.4,110.6, 111.3,112.3,115.1, 117.8,120.2, 129.2,139.2,143.1,FAB-MS, 640.5

[7] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(4-methoxy-benzylidene)-amine

Yield: 50%, m.p. =138-142^{0}C.Mol.weight 641.0, Anal.Calcd for $C_{35}H_{25}ClN_8O_3$: C,65.57; H, 3.93; N,17.48 %. IR (KBr): 3514-3110, 2933.0 (C-H str.,CH_3), 2884.0(C-H str.,CH_2), 1645-1511 (C=N and C=Cstr.), 1554-1318 (N-O str., NO2), 1166 (C-N str.), 896.3(1,4 disub. Benz.Ring) 643.5(C-Cl). ^{1}HNMR (300 MHz,$CDCl_3$)10.03(s,1H,tetrazole-NH),5.05(s,2H,CH_2), 7.09-8.46(m,19H,ArH),3.37(m,3H-OCH_3). ^{13}CNMR($CDCl_3$)δ:14.0,49,110.8,112.3,114.2,123.2,124.2,129.2,134.9,140.3,FAB-MS, 641.6

[8] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2,3-dichloro-benzylidene)-amine

Yield: 59%, m.p. =125-128^{0}C.Mol.weight 680.0, Anal.Calcd for $C_{34}H_{21}Cl_3N_8O_3$: C,60.06; H, 3.11; N,16.48 %. IR (KBr): 3514-3110, 2887.3(C-H str.,CH_2), 1640-1516 (C=N and C=Cstr.), 1538-1343 (N-O str., NO2), 1186 (C-N str.), 890.0(1,4 disub. Benz.Ring) 647.6(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$)9.81(s,1H,tetrazole-NH),4.89(s,2H,CH_2),7.22-8.53(m,18H,ArH).^{13}CNMR($CDCl_3$)δ:56.7,110.8,112.3, 114.1,116.8,124.2,129.2,139.5,144.2,148.7,FAB-MS, 681.0

[9] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2,4-dichloro-benzylidene)-amine

Yield: 64%, m.p. =131-134^{0}C.Mol.weight 680.0, Anal.Calcd for $C_{34}H_{21}Cl_3N_8O_3$: C,60.06; H, 3.11; N,16.48 %. IR (KBr): 3508-3126, 2887.3(C-H str.,CH_2), 1640-1519 (C=N and C=Cstr.), 1532-1349 (N-O str., NO2), 1180 (C-N str.), 898.0(1,4 disub. Benz.Ring) 649.2(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$)9.95(s,1H,tetrazole-NH),4.93(s,2H,CH_2),7.17-8.41(m,18H,ArH).^{13}CNMR($CDCl_3$)δ:54.3,110.1,111.5, 117.2,124.7,127.4,133.1,138.2,FAB-MS, 679.7

[10] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2,5-dichloro-benzylidene)-amine

Yield: 60%, m.p. =130-133^{0}C.Mol.weight 680.0, Anal.Calcd for $C_{34}H_{21}Cl_3N_8O_3$: C,60.06; H, 3.11; N,16.48 %. IR (KBr): 3501-3118, 2896(C-H str.,CH_2), 1647-1510 (C=N and C=Cstr.), 1530-1341 (N-O str., NO2), 1183 (C-N str.), 899.0(1,4 disub. Benz.Ring) 650.7(C-Cl). ^{1}HNMR (300 MHz, $CDCl_3$) 9.99(s,1H,tetrazole-NH),4.96(s,2H,CH_2),7.15-8.47 (m,18H,ArH).^{13}CNMR($CDCl_3$)δ:54.3,110.1,111.5,117.2,124.7,127.4,133.1,138.2,139.3,141.2,FAB-MS, 680.4

[11] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2-nitro -benzylidene)-amine

Yield:76%, m.p. =151-155^{0}C.Mol.weight 656.049, Anal.Calcd for $C_{34}H_{22}ClN_9O_4$: C,62.25; H, 3.38; N,19.22 %. IR (KBr): 3532-3143, 2899.6 (C-H str.,CH_2), 1647-1510 (C=N and C=Cstr.), 1566-1316 (N-O str., NO2), 1189 (C-N str.), 891.0(1,4 disub. Benz.Ring) 655(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.25(s,1H,tetrazole-NH),5.15(s,2H,CH_2),7.35-8.67(m,19H,ArH).^{13}CNMR($CDCl_3$)δ:57.6,111.4,111.8, 112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,143.0 ,FAB-MS, 655.74

[12] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(3-nitro -benzylidene)-amine

Yield:73%, m.p. =156-159^{0}C.Mol.weight 656.049, Anal.Calcd for $C_{34}H_{22}ClN_9O_4$: C,62.25; H, 3.38; N,19.22 %. IR (KBr): 3538-3144, 2906.0 (C-H str.,CH_2), 1654-1513 (C=N and C=Cstr.), 1560-1319 (N-O str., NO2), 1195 (C-N str.), 893.6(1,4 disub. Benz.Ring) 659.6(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.20(s,1H,tetrazole-NH),5.11(s,2H,CH_2),7.40-8.53(m,19H,ArH).^{13}CNMR($CDCl_3$)δ:57.6,111.4,111.8, 112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,143.5 ,143.8,FAB-MS, 656.59

[13] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(4-nitro -benzylidene)-amine

Yield:70%, m.p. =161-164^{0}C.Mol.weight 656.049, Anal.Calcd for $C_{34}H_{22}ClN_9O_4$: C,62.25; H, 3.38; N,19.22 %. IR (KBr): 3535-3140, 2901.4 (C-H str.,CH_2), 1651-1508 (C=N and C=Cstr.), 1553-1331 (N-O str., NO2), 1187.8 (C-N str.), 895.2(1,4 disub. Benz.Ring) 660.5(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.17(s,1H,tetrazole-NH),5.10(s,2H,CH_2),7.37-8.61(m,19H,ArH).^{13}CNMR($CDCl_3$)δ:57.6,111.4,111.8, 112.0,114.2,115.1,116.6,120.1,122.5,122.9,127.9,134.6 137.6,140.9,141.3,FAB-MS, 657.0

[14] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(3-fluoro -benzylidene)-amine

Yield:65%, m.p. =211-214^{0}C.Mol.weight 629.04, Anal.Calcd for $C_{34}H_{22}ClFN_8O_2$: C,64.92; H, 3.53; N,17.81 %. IR (KBr): 3526-3111, 2889 (C-H str.,CH_2), 1654-1519 (C=N and C=Cstr.), 1543-1365 (N-O str., NO2), 1195.9 (C-N str.), 890.0(1,4 disub. Benz.Ring) 653.3(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.32(s,1H,tetrazole-NH),5.02(s,2H,CH_2),7.00-8.69(m,19H,ArH).^{13}CNMR($CDCl_3$)δ:49.6,112.5,113.6, 114.2,124.7,124.1,126.4,128.0,134.1,139.8,142.9,143.7 ,FAB-MS, 628.6

[15] (2-{6-Chloro-5-nitro-1-[4-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(4- fluoro -benzylidene)-amine

Yield:62%, m.p. =217-221^{0}C.Mol.weight 629.04, Anal.Calcd for $C_{34}H_{22}ClFN_8O_2$: C,64.92; H, 3.53; N,17.81 %. IR (KBr): 3528-3115, 2885(C-H str.,CH_2), 1650-1522 (C=N and C=Cstr.), 1549-1360(N-O str., NO2), 1189.9 (C-N str.), 892.1(1,4 disub. Benz.Ring) 648.3(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.37(s,1H,tetrazole-NH),5.06(s,2H,CH_2),7.05-8.61(m,19H,ArH).^{13}CNMR($CDCl_3$)δ: 59.8,110.7,111.5,112.3,115.4,117.8,120.1,126.1,129.5, 131.3,133.4,136.4,138,140.1,143.7,FAB-MS, 628.8

[16] (2-{6-Chloro-5-nitro-1-[4-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2-methyl-benzylidene)-amine

Yield:62%, m.p. =217-221^{0}C.Mol.weight 625.07, Anal.Calcd for $C_{35}H_{25}ClN_8O_2$: C,67.25; H, 4.03; N,17.93 %. IR (KBr): 3520-3133, 2943.6(C-H str.,CH_3), 2898.8(C-H str.,CH_2), 1666-1513 (C=N and C=Cstr.), 1540-1333(N-O str., NO2), 1194 (C-N str.), 887.5(1,4 disub. Benz.Ring) 644.7(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.56(s,1H,tetrazole-NH),5.00(s,2H,CH_2), 2.21(m,3H,CH_3),7.22-8.51(m,19H,ArH).^{13}CNMR($CDCl_3$)δ: 19.4,52.3,112.3,114.1,116.2,117.1, 118.1,119.2,120.1,123.1,128,144.2,FAB-MS, 624.17

[17] (2-{6-Chloro-5-nitro-1-[4-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(3-methyl-benzylidene)-amine

Yield:67%, m.p. =232-235^{0}C.Mol.weight 625.07, Anal.Calcd for $C_{35}H_{25}ClN_8O_2$: C,67.25; H, 4.03; N,17.93 %. IR (KBr): 3526-3139, 2949(C-H str.,CH_3), 2890(C-H str.,CH_2), 1660-1508 (C=N and C=Cstr.), 1532-1365(N-O str., NO2), 1188.7 (C-N str.), 891.3(1,4 disub. Benz.Ring) 645.3(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.62(s,1H,tetrazole-NH),5.04(s,2H,CH_2), 2.24(m,3H,CH_3),7.18-

8.48(m,19H,ArH).^{13}CNMR($CDCl_3$)δ: 18.1,54.2,112.4,113.2,116.1,123.5,129.1,130.6,133.7,138.2,142.9,FAB-MS, 625.32

[18] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(2,3-dimethoxy-benzylidene)-amine

Yield:58%, m.p. =265-268^{0}C.Mol.weight 671.104, Anal.Calcd for $C_{35}H_{27}ClN_8O_4$: C,64.43; H, 4.06; N,16.70%. IR (KBr): 3526-3139,3087, 2973.6(C-H str.,CH_3), 2883.2(C-H str.,CH_2), 1644-1536 (C=N and C=Cstr.), 1554-1306(N-O str., NO2), 1199.5 (C-N str.), 885.2(1,4 disub. Benz.Ring) 652.8(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.86(s,1H,tetrazole-NH),4.96(s,2H,CH_2), 3.77(m,6H,CH_3),7.11-8.79(m,18H,ArH).^{13}CNMR($CDCl_3$)δ: 18.1, 19.8,52.3,112.3,113.1,115.2,123.1,130.4,135.1,138.1,141.2,143.2,145,FAB-MS, 670.79

[19] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(3,4-dimethoxy-benzylidene)-amine

Yield:58%, m.p. =251-254^{0}C.Mol.weight 671.104, Anal.Calcd for $C_{35}H_{27}ClN_8O_4$: C,64.43; H, 4.06; N,16.70%. IR (KBr): 3520-3133,3097, 2970.0(C-H str.,CH_3), 2899.8(C-H str.,CH_2), 1665-1531 (C=N and C=Cstr.), 1507-1319(N-O str., NO2), 1194.0(C-N str.), 888.5(1,4 disub. Benz.Ring) 650.4(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.82(s,1H,tetrazole-NH),4.98(s,2H,CH_2), 3.75(m,6H,CH_3),7.24-8.76(m,18H,ArH).^{13}CNMR($CDCl_3$)δ: 18.1, 19.8,52.3,112.3,113.1,115.2,123.1,130.4,135.1,138.1,141.2,143.2,145,FAB-MS, 671.08

[20] (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H benzoimidazol-2-yl}-phenyl)-(3,4,5-trimethoxy-benzylidene)-amine

Yield:70%, m.p. =287-290^{0}C.Mol.weight 701.13, Anal.Calcd for $C_{37}H_{29}ClN_8O_5$: C,63.38; H, 4.16; N,15.98%. IR (KBr): 3555-3114, 2991.2(C-H str.,CH_3), 2894.1(C-H str.,CH_2), 1665-1531 (C=N and C=Cstr.), 1522-1343(N-O str., NO2), 1187.0(C-N str.), 890.8(1,4 disub. Benz.Ring) 646.5(C-Cl).^{1}HNMR(300 MHz, $CDCl_3$)10.95(s,1H,tetrazole-NH),4.92(s,2H,CH_2), 3.79 (m,9H,CH_3),7.24-8.76(m,17H,ArH).^{13}CNMR($CDCl_3$)δ: 14.5,18.1,19.8,52.3,112.7,114.5,116.1,119.1,123.1,136.2,139.1,142.1,143.6,146.8,FAB-MS, 701.54

Antihypertensive Activity

Invasive Method (Direct Method) [13-16]

Male albino wistar (160-250 gm) rats were used and housed at 26±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 physiogram 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 1, 2.

Results and discussion

All the synthesized benzimidazole incorporated antihypertensive activity with standard drug compared all synthesized compounds [synthesis compounds 1-20]. Almost all the newly synthesized substituted 6-Chloro-5-nitro-benzimidazole showed good antihypertensive activity with the goal of investigating the structure–activity relationships of benzimidazole, based molecules, fifteen analogs compounds were synthesized (Figure 2). Synthesis has been carried out of selected benzimidazole derivatives having electron donor and acceptor substituents at 5-position nitro group and 2-postions different aryl groups and their authencity and purity have been established through appropriate spectral and chromatographic techniques.

Table 1. 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	**172**	**169**	**161**	**154**	**148**	**140**	**136**	**128**	**119**	**113**
1	177	170	167	161	156	148	143	138	130	124
2	178	172	166	159	151	144	137	130	125	120
3	174	166	162	156	148	141	138	131	126	122
4	173	168	159	148	142	135	129	122	117	110
5	180	176	170	166	161	154	148	141	136	130
6	177	171	167	159	151	145	138	128	119	108
7	170	166	160	154	148	140	133	124	119	112
8	181	177	170	162	153	147	138	130	126	120
9	175	170	164	156	150	143	138	130	124	118
10	175	169	162	157	150	144	135	126	121	116
11	174	170	161	152	144	139	135	129	124	117
12	177	170	164	157	149	140	131	122	116	109
13	176	170	164	158	151	144	138	130	122	112
14	181	176	170	165	159	151	143	137	130	122
15	174	168	160	155	149	141	134	129	125	119
16	184	175	168	162	156	150	145	139	133	128
17	178	173	167	159	150	143	136	127	120	114
18	176	170	165	158	153	147	139	131	126	120
19	179	174	168	160	154	145	140	131	123	116
20	181	177	170	164	157	151	145	136	125	118

The synthesized compounds were characterized on the basis of chemical and spectral data. Synthetic scheme for target compounds was divided into two steps. Step I involved synthesis of different aryl aldehydes substituents benzimidazoles by condensation reaction of o-phenylenediamine with the respective anthranilic acid then corresponding react with PPA 170-172^{o}C and react with 5-postion nitro group with biphenyl tetrazole . Our initial efforts of optimizing the benzimidazole structures were focused on either replacing the 2-substituted 5-nitro groups on different substituents at different positions of the benzimidazole derivatives. We recently determined the significance of the 5 position of the benzimidazole ring for inhibitory activity. We also investigated the possible effect of any change in the linker between both aromatic rings upon the bioactivity. The structures of the synthesized compounds were confirmed using IR, NMR and elemental analysis methods. The higher activity of 4-chloro-5-nitro-benzimidazole derivatives may be ascribed to the ability of nitro group to act as H-bond acceptor with respect to the receptor site. Moreover, the bulk of nitro group may optimally "fill up" the receptor pocket and hence results in closer proximity to the interacting surface of the receptor. It may consequently increase their affinity to the receptor site. The present work was mainly intended to establish the moieties which are responsible for Angiotension-II inhibition. Presence of Nitro group has increased the activity substantially over the substituted one [1] to [20]. The maximum activity has been observed with nitro group (Compound 4, 6, 7, 12, 13, 17) [Table 1 and 2]. Biological activity of synthesized compounds was carried out using rat blood pressure measurement experiment; the maximum fall blood pressure produced by standard drug compare with our synthesis molecule Losartan is from value 172mm Hg to 113 mm Hg over a period 90 minutes.

Table 2. Antihypertensive activity of synthesized compounds.

Compound. No	Minimum Blood pressure value(mm Hg)	Duration of hypertension effect(min.)
Losratan	**113**	**90**
1	117	100
2	114	105
3	116	100
4	110	90
5	115	110
6	108	90
7	112	90
8	114	100
9	112	95
10	110	95
11	113	95
12	109	90
13	112	90
14	116	100
15	113	95
16	118	105
17	114	90
18	115	95
19	110	98
20	115	95

Conclusion

Different aryl groups reaction with Substituted 4-chloro-5-nitro-benzimidazole derivatives nucleus coupled to tetrazole biphenyl group have been designed synthesized and evaluated for angiotensin II antagonism. Compound with nitro group at 5-position and aryl groups chain at 2- position have been found to be less potent than standard drug. Additionally a novel and simple method for synthesis of tetrazole biphenyl moiety has been devised to improve safety and yield.

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