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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4'-(5-AMINO-6-CHLORO-2-SUBSTITUTED-BENZOIMIDAZOL-1-YLMETHYL)]-BIPHENYL-2-CARBOXYLIC ACID AS ANTIHYPERTENSIVE AGENTS

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A series of 4`-(5-Amino-6-chloro-2-substituted-benzoimidazol-1-ylmethyl)]-biphenyl-2-carboxylic acid side chain in the 2 position have been synthesized from substituted compounds [1-14] compounds aromatic aldhyde,ayl,alkyl groups and tested for antihypertensive activity in induced hypertensive rats. All the compounds have been found to be less active than Losartan, Telmisartan their structures were assigned with elemental analysis, melting point and spectral analysis like ^{1}R, 1H NMR, ^{13}C NMR and EI MS

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1. Introduction

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 reabsorption, and nor epinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension.[1]The renin-angiotensin system (RAS) is known to play an important role in the regulation of blood pressure and electrolyte balance.[2] Inhibitors of the RAS would be effective for the treatment of hypertension and congestive heart failure. Although angiotensin-converting enzyme (ACE) inhibitors are highly effective and their use has become well-established for the treatment of hypertension and congestive heart failure, they suffer from some side effects such as dry cough and angioedema caused by the nonspecific action of ACE.[3] On the other hand, angiotensin II (AII) (the primary effector component of the RAS) receptor antagonists block the RAS at the AII receptor level and are expected to be more specific and effective agents than ACE inhibitors.Angiotensin II (Ang II)*a* type 1 (AT1) receptor belongs to the G protein-coupled receptor superfamily and mediates virtually all the known physiological actions of Ang II through interaction with heterotrimeric G-protein and subsequent activation of several effector systems (phospholipases C, D, A2, adenyl cyclase, etc.). AT1 receptor shows the seven hydrophobic transmembrane domains forming R-helices in the lipid bilayer of the cell membrane and plays a key role in the reninangiotensin system involved in the regulation of cardiovascular functions and pathophysiology of hypertension.[4,5] 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.[6] Amongthem, irbesartan, candesartan, valsartan, telmisartan, tasosartan,and olmesartan are on the market. Most of the developed AT1 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.Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported.[7]

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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,[9] researchers at DuPont discovered losartan, the first orally active AT1 selective nonpeptide AII antagonist that reached the market for the treatment of hypertension (1994, Cozar). 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.[10]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[11].Only in recent years a number of non peptides AngII antagonists that show promise as inhibitors of the RAS been reported[12].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[13]. 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 [14]. The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity[15]. Compounds containing tetrazole nucleus are also reported as AT_1 receptor antagonists and their protypical derivative 3 exhibits non-competitive antagonism[16] and amino group attach with carboxylic group given good biological activity [17,18]

2. Experimental

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 1H 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.

MCS-6-chloro-2-substitued -1H-benzoimidazole

4-chloro-benzene-1,2-diamine(5.0 gm) was dissolved in a mixture of methanol/water (200 ml, v/v 1:1).To this, different aromatic aldehyde,alkyl and aryl compound (1.1gm) in absolute ethanol (25ml) and Cu $(OAc)_2$ H_2O (3.1 gm in water (100ml) were added sequentially while stirring the solution. The reaction mixture was then heated to reflux under vigorous stirring for three hours after this a white precipitate was formed. The mixture was filtered hot and then washed with water to afford a yellow solid. The precipitate was again dissolved in ethanol (150ml) and to this, HCl (15 ml) and solution of Na_2SxH_2O was added in water (100 ml).At this stage, the reaction mixture was heated at reflux for 2.5 hour, resulting in the formation of black slurry. Reaction mixture was allowed to cool to room temperature and filtered through a pad of celite to remove the precipitated CuS.The filtrate was treated with ammonia solution to *p*H 8-9 and then concentrated to yield a reddish pale precipitate. After filtration and vacuum evaporation, compound obtained as reddish solid.

MCS-02: 6-chloro-5-nitro-2-substitued -1H-benzoimidazole

65.0 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(different R-methyl, ethyl, butyl) (15.10 gm) was mixed in portions during 2 hour under room temperature. After stirred continuously for 14 hours 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 recrystillzed from absolute ethanol.

MCS 03: (Biphenyl Carboxylic acid)

35 gm of potassium hydroxide was heated at 170°-192 °C in a three necked flask until fusion. 12.5gm of finely powdered of 9H-Fluorenone was added in five portions over one and half hour with vigorous stirring and the temperature was maintained at 170°-192°C for further one half hour. The fusion mixture was then poured in ice cold water with stirring. The obtained suspension was filtered at vacuum pump and then filtrate was acidify with HCl to pH-5.3 resulting in precipitation of by product which was filtered under suction wash with distilled water and the filtrate was again acidify with Con.HCl. The precipitated product was filtered under suction and dried in air. The product was recrystallized from Absolute ethanol. Product MCS-03 was formed.

Yield:72%.m.p.=152-155°C.IR(KBr):3573-3112(O-Hstr),1711.6(C=OCarboxylic,str), 1331, 1303(C-O-H in-plane bend).^{1}H-NMR(CDCl3):9.59(1H,s,COOH),7.33-8.16(1H,m,9H),^{13}CNMR($CDCl_3$)δ:111.2,112.1,115.8,127.5,139.8,FABMS,198.08(100%),199.06(14.5%),200.12(1.%).Anal. Calcd for $C_{13}H_{10}O_2$: Found: C, 78.77; H, 5.07%.

MCS-04: (4' Acetylamino methyl biphenyl-2-caboxylic acid)

5 gm of MCS 03 was dissolved in 25 ml of concentrated H_2SO_4.After that acetamide (2.15 gm) and Paraform aldehyde (0.560) gm were added subsequently. The solution was heated at 70°C along with stirring for 4.5 hours. The hot mixture was poured over ice and cold water. The precipitated product was filtered under suction and dried in air. The product was recrystallized from Absolute ethanol. The resulting solid was filtered out.

Yield: 58% m.p.-165^{o}-169^{o}C IR (KBr) (cm^{-1}): 3397.4 (N-H str.), 3262.7(O-H, str), 2986 (C-H str), 2945 (aliphatic C-H str), 1675.2 (C=O str of), 1587.5 (N-H bend of amide), 1495.9(C-N str) 784.6(Benz. Ring); ^{1}H NMR (300 MHz, $CDCl_3$) δ:2.03(s,3H,CH_3), 9.76(1H,s,COOH),4.32(2H,s,CH_2),7.98(s,1H,-NH);7.09 8.24(m,8H,ArH).^{13}CNMR($CDCl_3$)δ:19.5(CH_3),53.7(CH_2)112.4,116.1,122.1,125.7,133.5,139.2,144 .1,155.7,170.2,FAB-MS, 269.12(100%), 270.03(18.6),271.07 (2.2%).Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20%; Found: C, 71.27; H, 5.54; N, 5.12

MCS 05: (4'bromomethylbiphenyl-2-carboxylic acid)

1.4gm of MCS-04 was taken in a RBF. 1.598 gm of phosphorus oxy chloride was added to 4ml of DMF and further addition of xylene (4ml). The reaction mixture was refluxed for 7 ½ hours. The cold solution was washed with water and evaporated to give a light yellow crystalline product. Yield: 52 % m.p.-133^{o}-136^{o}C IR (KBr) (cm-1): IR (KBr): 3354 (O-H str.), 2902(C-H str., CH_2), 1679.4 (Carboxylic, C=O str.), 1676-1413 (C=N, C=C str.), 1189 (C-O str), 854.2 (.benz. ring), 598.7(C-Cl str.) ^{1}H NMR (300 MHz, $CDCl_3$)10.07(s,1H,OH),7.118.05(m,8H,ArH),4.64(s,2H,CH_2)..^{13}CNMR($CDCl_3$)δ:33.8(CH_2)115.9, 117.2,123.4,128.2,136.1,139.2,142.4,151.2,,FABMS,289.12(100%)291.14(97.11%),270.03(18.6), 271.07 (2.2%).Anal.Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81; %; Found: C, 57.71; H, 3.80; %.

MCS06:4-(6-chloro-2-substitued-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

0.4612gm of MCS-02 was dissolved in 20ml of DMF (dimethyl formamide) and stirred vigorously with 1.5gm of potassium carbonate at 27^{0}C for one hour. To the resulting mixture 0.482gm of MCS-05 first dissolved in 20 ml of DMF and then was added drop wise with dropping funnel in 1 hour the reaction was allowed to proceed for further 11 hours at room temperature and solvent removed under vacuum. Residue was treated with 20ml of dilute HCl and extracted with ethyl acetate. The organic layer was washed with brine solution, distilled water and dried over anhydrous sodium sulphate. (MCS-06) was obtained.

(1)4-(6-chloro-2-methyl-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield: 72%, m.p. = 179^{0}-182^{0}C. Anal.Calcd for $C_{22}H_{16}ClN_3O_4$: Found: C,62.64;H, 4.82;N,9.96 %;IR (KBr): 3398(Broad O-H str.), 2912 (C-H str., CH_3), 2812.0 (C-H str.,

CH_2),1706.2 (carboxylic, C=O str.),1602,1549(C=N and C=Cstr.), 1532-1313 (N-O str., NO2), 1141 (C-N str.), 795.29(ben.Ring),654.4(C-Cl str).1^H NMR (300 MHz, $CDCl_3$) 10.23(s,1H,COOH),7.26-8.42(m,10H,ArH),2.87(s,3H,CH_3),5.12(s,2H,CH_2).^{13}CNMR($CDCl_3$)δ:24.4,58.3,111.3,112.1,116.2, 127.1,131.4,133.1,139.1,142.2,147.2,150.4,FAB-MS, 421.082

(2)4-(6-chloro-2-ethyl-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:59%,m.p.=158-163^{0}C.Mol.weight435.09,Anal.Calcd for $C_{23}H_{18}ClN_3O_4$:C,63.38;H, 4.16;N,9.64 %. IR (KBr): 3294.1(Broad O-H str.), 2994 (C-H str., CH_3), 2902 (C-H str., CH_2), 2853.6 (C-H str,CH_2),1703(carboxylic,C=O str.),1642.3,1532.1 (C=N and C=Cstr.), 1512-1327 (N-O str., NO2), 1123 (C-N str.), 782 (1,4 disub. Benz.Ring) 647.1(C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 9.72(s, 1H, COOH), 7.12-8.19(m, 10H, ArH),2.42(s,3H,CH_3),4.99(s,2H,CH_2),3.26(s,2H,CH_2),.^{13}CNMR($CDCl_3$)δ:21,53.1,60.3,111.4,113. 1,115.3,118.2,127.2,136.2,142.2,144.1,FAB-MS, 435.03(100%)

(3)4-(6-chloro-5-nitro-2-propyl-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:59%,m.p.=158-163^{0}C.Mol.weight449.11,Anal.Calcd for $C_{24}H_{20}ClN_3O_4$:C,64.08;H, 4.46;N,9.34 %. IR (KBr): 3311(Broad O-H str.), 2942 (C-H str., CH_3), 2956 (C-H str.,CH_2), 2821 (C-H str,CH_2), 2123.1 (C-H str,CH_2),1711(carboxylic,C=O str.),1622,1532 (C=N and C=Cstr.), 1521-1317 (N-O str., NO2), 1125 (C-N str.), 793 (1,4 disub. Benz.Ring) 657(C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 10.12(s, 1H, COOH), 7.02-8.23(m,10H,ArH),2.41(s,3H,CH_3),4.90(s,2H,CH_2),3.26(s,2H,CH_2),1.69(s,2H,CH_2).^{13}CNMR($CDCl_3$)δ:20,50.1,53.3,65.1,73.7,112.4,114.1,116.1,117.1,122.2,130.2,141.1,145.1,FAB-MS, 449.12(100%)

(4)4-(2-butyl-6-chloro-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:50%,m.p.=163-166^{0}C.Mol.weight463.12,Anal.Calcd for $C_{25}H_{22}ClN_3O_4$:C,64.78;H, 4.76;N,9.06 %. IR (KBr): 3349.5(Broad O-H str.), 2923 (C-H str., CH_3), 2921 (C-H str., CH_2), 2801 (C-H str,CH_2), 2103.0 (C-H str,CH_2),1698(carboxylic,C=O str.),1627-1540 (C=N and C=Cstr.), 1503-1311 (N-O str., NO2), 1117 (C-N str.), 801 (1,4 disub. Benz.Ring) 654(C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 10.22(s, 1H, COOH), 7.09-8.13(m,10H,ArH),2.53(s,3H,CH_3),5.04(s,2H,CH_2),3.22(s,2H,CH_2),1.53(s,2H,CH_2),1.31(s,2H,CH_2) .^{13}CNMR($CDCl_3$)δ:22,46.4,53.2,55.3,67.1,71.3,112.2,113.5,117.1,118.1,124.1,132.2,134.1,140.0, FAB-MS, 464.02.

(5)4-(6-chloro-5-nitro-2-pentyl-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:50%,m.p.=188-194^{0}C.Mol.weight477.15,Anal.Calcd for $C_{26}H_{24}ClN_3O_4$:C,65.38;H, 5.06;N,8.76 %. IR (KBr): 3357(Broad O-H str.), 2913.5 (C-H str.,CH_3), 2874.3 (C-H str., CH_2), 2846.5 (C-H str,CH_2), 2103.0-2153.6 (C-H str,CH_2),1718(carboxylic,C=O str.),1627-1517 (C=N and C=Cstr.), 1511-1303 (N-O str., NO2), 1123(C-N str.), 812 (1,4 disub. Benz.Ring) 648.3(C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 9.48(s,1H,COOH), 7.31-8.29(m,10H,ArH),2.74(s,3H,CH_3),5.13(s,2H,CH_2),3.31(s,2H,CH_2),1.65(s,2H,CH_2),1.38(s,4H,CH_2) .^{13}CNMR($CDCl_3$)δ:21,43.4,51.2,53.3,62.1,73.8,112.8,113.4,116.2,117.2,126.5,130.1,132.1,142.4, FAB-MS, 476.02.

(6)4-(6-chloro-2-(2-chloro-phenyl)-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:57%,m.p.=223-226^{o}C. Anal.Calcd for $C_{27}H_{17}Cl_2N_3O_4$:C,62.51;H,3.30;N,8.11 %; IR (KBr): 3491.2(Broad O-H str.), 2947 (C-H str., CH_2), 1704 (carboxylic, C=O str.),1640,1581 (C=N and C=Cstr.),1530-1302 (N-O str., NO_2), 1184(C-N str.), 797.8(Benz.Ring)628.0(C-Clstr),651.3(C-Clstr), ^{1}HNMR(300MHz,$CDCl_3$)9.56(s,1H,COOH),7.18 - 8.23(13H,ArH),5.16(s,2H,CHCl),3.51(s,1H,CHCl)^{13}CNMR($CDCl_3$)δ:42.2,112.3,113.5,117.2,119. 2,125.5,127.1,136.1,139.4,FAB-MS, 517

(7)4-(6-chloro-2-(3-chloro-phenyl)-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:64%,m.p.=233-236^{o}C. Anal.Calcd for $C_{27}H_{17}Cl_2N_3O_4$:C,62.56;H,3.32;N,8.13 %; IR (KBr): 3499.2(Broad O-H str.), 2944 (C-H str., CH_2), 1700 (carboxylic, C=O str.),1643,1587 (C=N and C=Cstr.),1532-1312(N-O str., NO_2), 1198(C-N str.), 790.8(Benz.Ring)621.1(C-

Clstr),656.8(C-Clstr), ^{1}HNMR(300MHz,$CDCl_3$)9.51(s,1H,COOH),7.16-8.09(13H,ArH),5.18(s,2H,CHCl),3.63(s,1H,CHCl)^{13}CNMR($CDCl_3$)δ:42.2,112.3,113.5,117.2,119.2,125.5,127.1,136.1,139.4,FAB-MS, 518

(8) 4-(6-chloro-2-(4-chloro-phenyl)-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:57%,m.p.=248-250^{o}C. Anal.Calcd for $C_{27}H_{17}Cl_2N_3O_4$:C,62.56;H,3.32;N,8.13 %; IR (KBr): 3503(O-H str.), 2936 (C-H str., CH_2), 1712 (carboxylic, C=O str.),1649,1582 (C=N and C=Cstr.),1524-1302(N-O str., NO_2), 1184(C-N str.), 798(Benz.Ring)626.2(C-Clstr),657.8(C-Clstr), ^{1}HNMR(300MHz,$CDCl_3$)9.51(s,1H,COOH),7.31- 7.98 (13H,ArH),5.11(s,2H,CHCl),3.74(s,1H,CHCl)^{13}CNMR($CDCl_3$)δ:42.2,112.3,113.5,117.2,119.2,125.5,127.1,136.1,139.4,FAB-MS, 518

(9) 4-[6-chloro-2-(2-fluoro-phenyl)-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:53%,m.p.=256-259^{o}C. Anal.Calcd for $C_{27}H_{17}Cl\,FN_3O_4$:C,64.62;H,3.42;N,7.06 %; IR (KBr): 3515(O-H str.), 2914 (C-H str., CH_2), 1702 (carboxylic, C=O str.),1665,1532 (C=N and C=Cstr.),1549-1324(N-O str., NO_2), 1156(C-N str.), 791(Benz.Ring)626.2(C-Clstr). ^{1}HNMR(300MHz,$CDCl_3$)10.16 (s,1H,COOH),7.14- 8.22 (14H,ArH),5.11(s,2H,CH_2),3.51(s,1H,CHCl).^{13}CNMR($CDCl_3$)δ:58.2,111.0,115.1,119.2,121.1,124.1,133.4,134.0,138.5,FAB-MS, 501.08

(10) 4-[6-chloro-2-(2-hydroxy-phenyl)-5-nitro-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

Yield:53%,m.p.=236-239^{o}C. Anal.Calcd for $C_{27}H_{18}Cl\,N_3O_5$:C,64.87;H,3.63;N,8.41 %; IR (KBr): 3475(O-H str.), 2947 (C-H str., CH_2), 1698 (carboxylic, C=O str.),1613,1554 (C=N and C=Cstr.),1519-1335(N-O str., NO_2), 1130(C-N str.), 797(Benz.Ring) 642.4(C-Clstr). ^{1}HNMR(300MHz,$CDCl_3$)10.02 (s,1H,COOH),7.36- 8.51 (10H,ArH),5.11(s,2H,CH_2),3.51(s,1H,CHCl),3.18(s,3H,CH_3),5.07(s,1H,OH),.^{13}CNMR($CDCl_3$)δ:23.2,48.2,112.3,114.1,117.2,120.1,123.1,128,144.2,147.5,FAB-MS, 499.90

MCS-4`-(5-Amino-6-chloro-2-substituted-benzoimidazol-1-ylmethyl)]-biphenyl-2-carboxylic acid

2.5 gm of compound was placed in three necked RBF and dissolved in absolute ethanol and heated to 60^{0}C under reflux. To this, 1.2 gm stannous chloride dihydrate was added with slow stirring during 1.5hours and reaction conditions were maintained for further 12 hours. The mixture was cooled to room temperature and pH adjusted to 7.6 with 5% sodium hydroxide solution. The organic layer was washed with brine, distilled water then dried over anhydrous sodium sulphate. Solvent removed under vacuum and product was obtained.

MCS[1]:4`-(5-Amino-6-chloro-2-methyl-benzoimidazol-1-ylmethyl)]-biphenyl-2-carboxylic acid

Yield: 64%, m.p. = 211^{0}-214^{0}C. Anal.Calcd for $C_{22}H_{18}ClN_3O_2$: Found: C, 67.44; H, 4.62; N, 10.76 %; IR (KBr): 3412.3(Broad O-H str.), 2943 (C-H str., CH_3), 2854 (C-H str., CH_2), 1718 (carboxylic, C=O str.), 1615, 1519(C=N and C=Cstr.), 812 (Ben. Ring),632.4(C-Clstr).1^{H}NMR(300MHz,$CDCl_3$)9.54(s,1H,COOH),7.06-8.22 (m,10H,ArH),2.42(s,3H,CH_3),5.00(s,2H,CH_2),4.08(s,2H,NH),.^{13}CNMR($CDCl_3$)δ:13,52.3,112.3,113.1,115.2,123.1,130.4,135.1,138.1,141.2,143.2,145.1,FAB-MS, 391.10

MCS [2]:4`-(5-Amino-6-chloro-2-ethyl -benzoimidazol-1-ylmethyl)]-biphenyl-2-carboxylic acid

Yield:61%,m.p.=219^{0}-223^{0}C. Anal.Calcd for $C_{22}H_{20}ClN_3O_2$:Found:C,68.04;H,4.95;N,10.36 %;IR (KBr): 3453(Broad O-H str.), 2903 (C-H str., CH_3), 2825 (C-H str., CH_2),1710 (carboxylic, C=O str.),1602,1532(C=N and C=Cstr.), 802 (ben.Ring),645(C-Clstr).1^{H}NMR(300MHz,$CDCl_3$)9.72(s,1H,COOH),7.11-8.02 (m,10H,ArH),2.34(s,3H,CH_3),5.04(s,2H,CH_2),4.82(s,2H,NH),2.64(s,2H,CH_2),.^{13}CNMR($CDCl_3$)δ:14,58.0,112.9,113.4,116.2,121.1,128.4,135.5,137.2,140.1,142.5,145.9,FAB-MS, 405.21

MCS [3]:4`-(5-Amino-6-chloro-2-propyl -benzoimidazol-1-ylmethyl)]-biphenyl-2-carboxylic acid

Yield:52%,m.p.=231-235^{0}C.Mol.weight449.11,Anal.Calcd for $C_{23}H_{22}ClN_3O_2$:C,68.68;H, 5.26;N,10.04 %. IR (KBr): 3392(Broad O-H str.), 2931 (C-H str., CH_3), 2909 (C-H str., CH_2), 2865 (C-H str,CH_2), 2154 (C-H str,CH_2),1701(carboxylic,C=O str.),1654,1513 (C=N and C=Cstr.), 1114 (C-N str.), 799.5 (1,4 disub. Benz.Ring) 651(C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 10.00(s, 1H, COOH), 7.12-8.20(m,10H,ArH),2.48(s,3H,CH_3),4.95(s,2H,CH_2),4.89(s,2H,NH),2.96(s,2H,CH_2),1.69(s,2H,CH_2). ^{13}CNMR($CDCl_3$)δ:17,53.1,55.3,61.1,70.7,111.4,113.1,113.5,114.1,121.2,132.2,145.1,148.1,FAB-MS, 419.14

MCS[4]:4`-(5-Amino-2-butyl-6-chloro-benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:47%,m.p.=163-166^{0}C.Mol.weight463.12,Anal.Calcd for $C_{23}H_{24}ClN_3O_4$:C,69.21;H, 5.57;N,9.66 %. IR (KBr): 3352.3(Broad O-H str.), 2934.5(C-H str., CH_3), 2902 (C-H str., CH_2), 2862 (C-H str,CH_2), 2143.2 (C-H str,CH_2),1692(carboxylic,C=O str.),1620-1518 (C=N and C=Cstr.), 1154 (C-N str.), 805 (1,4 disub. Benz.Ring) 650(C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 9.52(s, 1H, COOH), 4.49(s,2H,NH), 7.19-8.10(m,10H,ArH),2.59(s,3H,CH_3),5.00(s,2H,CH_2),3.58(s,2H,CH_2),1.66(s,2H,CH_2),1.38(s,2H,CH_2) .^{13}CNMR($CDCl_3$)δ:20,42.4,50.2,58.3,60.1,75.3,112.7,114.5,116.1,119.1,123.1,136.2,139.1,145.0, FAB-MS, 434.11.

MCS[5]:4`-(5-Amino-6-chloro-2-pentyl-benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:54%,m.p.=237-240^{0}C. Anal.Calcd for $C_{26}H_{26}ClN_3O_2$:C,69.71;H, 5.86;N,9.38 %. IR (KBr): 3376(Broad O-H str.), 2919(C-H str.,CH_3), 2846 (C-H str.CH_2), 2898 (C-H str,CH_2), 2132 (C-H str,CH_2),1714(carboxylic,C=O str.),1607-1500 (C=N and C=Cstr.), 1129(C-N str.), 810 (1,4 disub. Benz.Ring) 658 (C-Cl str). ^{1}HNMR (300 MHz, $CDCl_3$) 9.87(s,1H,COOH),7.35-8.58(m,10H,ArH), 4.69 (s,2H,NH), 2.56(s,3H,CH_3),5.06(s,2H,CH_2),3.54(s,2H,CH_2),1.72(s,2H,CH_2),1.62(s,4H,CH_2).^{13}CNMR($CDCl_3$) δ:20,40.4,57.2,59.3,68.1,74.8,113.8,115.4,118.2,119.2,127.5,132.1,134.1,145.4,FAB-MS, 446.16.

MCS[6]:4`-[5-Amino-6-chloro-2-(2-chloro-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:64%,m.p.=245-247^{o}C. Anal.Calcd for $C_{27}H_{19}Cl_2N_3O_2$:C,66.41;H,3.92;N,8.61 %; IR (KBr): 3416.1(Broad O-H str.), 2922 (C-H str., CH_2), 1713 (carboxylic, C=O str.),1623,1512 (C=N and C=Cstr.), 1184(C-N str.), 802.8(Benz.Ring)649.3(C-Clstr), ^{1}HNMR(300MHz,$CDCl_3$)9.93(s,1H,COOH),7.18-8.23(14H,ArH),5.16(s,2H,CH Cl),4.24(s,2H,NH)^{13}CNMR($CDCl_3$)δ:47,111.1,115.3,119.5,121.2,127.5,129.3,133.2,142.0,FAB-MS, 488.02

MCS[7]:4`-[5-Amino-6-chloro-2-(3-chloro-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:67%,m.p.=247-250^{o}C. Anal.Calcd for $C_{27}H_{19}Cl_2N_3O_2$:C,66.41;H,3.92;N,8.61 %; IR (KBr): 3421(Broad O-H str.), 2925 (C-H str., CH_2), 1710 (carboxylic, C=O str.),1620,1518 (C=N and C=Cstr.), 1181(C-N str.), 799.2(Benz.Ring)652.1(C-Clstr), ^{1}HNMR(300MHz,$CDCl_3$)9.98(s,1H,COOH),7.20-8.13(14H,ArH),5.06(s,2H,CH Cl),4.28(s,2H,NH)^{13}CNMR($CDCl_3$)δ:47,111.1,115.3,119.5,121.2,127.5,129.3,133.2,142.0,FAB-MS, 487.11

MCS[8]:4`-[5-Amino-6-chloro-2-(4-chloro-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:55%,m.p.=241-244^{o}C. Anal.Calcd for $C_{27}H_{19}Cl_2N_3O_2$:C,66.41;H,3.92;N,8.61 %; IR (KBr): 3414.2(Broad O-H str.), 2925.6 (C-H str., CH_2), 1711 (carboxylic, C=O str.),1620,1516 (C=N and C=Cstr.), 1180(C-N str.), 811(Benz.Ring)647.2(C-Clstr), ^{1}HNMR(300MHz,$CDCl_3$)10.04(s,1H,COOH),7.25-8.11(14H,ArH),4.96(s,2H,CHCl),4.33(s,2H,NH)^{13}CNMR($CDCl_3$)δ:47,112.1,113.3,115.5,122.2,124.5,127.3,131.2,140.2,FAB-MS, 488.02

MCS[9]:4`-[5-Amino-6-chloro-2-(2-fluoro-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:55%,m.p.=261-264^{o}C. Anal.Calcd for $C_{27}H_{19}ClFN_3O_2$:C,68.71;H,4.06;N,8.91 %; IR (KBr): 3427.4(Broad O-H str.), 2915.3 (C-H str., CH_2), 1700.6 (carboxylic, C=O str.),1629,1510 (C=N and C=Cstr.), 1174(C-N str.), 801(Benz.Ring). ^{1}HNMR(300MHz,$CDCl_3$)10.19(s,1H,COOH),7.15-8.26(14H,ArH),4.99(s,2H,CH Cl),4.86(s,2H,NH)^{13}CNMR($CDCl_3$)δ:42,113.0,114.1,116.2,120.1,122.5,124.3,133.5,142.5,FAB-MS, 470.155

MCS[10]:4`-[5-Amino-6-chloro-2-(3-fluoro-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:67%,m.p.=266-269^{o}C. Anal.Calcd for $C_{27}H_{19}ClFN_3O_2$:C,68.71;H,4.06;N,8.91 %; IR (KBr): 3422.1(Broad O-H str.), 2918.6 (C-H str., CH_2), 1702.4 (carboxylic, C=O str.),1622,1516 (C=N and C=Cstr.), 1179(C-N str.), 806(Benz.Ring). ^{1}HNMR(300MHz,$CDCl_3$)10.13(s,1H,COOH),7.19-8.21(14H,ArH),5.09(s,2H,CH Cl),4.92(s,2H,NH)^{13}CNMR($CDCl_3$)δ:42,113.0,114.1,116.2,120.1,122.5,124.3,133.5,142.5 ,FAB-MS, 469.125

MCS[11]:4`-[5-Amino-6-chloro-2-(4-fluoro-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:55%,m.p.=262-2647^{o}C. Anal.Calcd for $C_{27}H_{19}ClFN_3O_2$:C,68.71;H,4.06;N,8.91 %; IR (KBr): 3416.1(Broad O-H str.), 2922.6(C-H str., CH_2), 1698 (carboxylic, C=O str.),1654,1521 (C=N and C=Cstr.), 1154(C-N str.), 798.1(Benz.Ring). ^{1}HNMR(300MHz,$CDCl_3$)9.99(s,1H,COOH),7.10-8.16(14H,ArH),4.90(s,2H,CH Cl),4.64(s,2H,NH)^{13}CNMR($CDCl_3$)δ:42,113.0,114.1,116.2,120.1,122.5,124.3,133.5,142.5,FAB-MS, 471.03

MCS[12]:4`-[5-Amino-6-chloro-2-(2-hydroxy-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:55%,m.p.=281-284^{o}C. Anal.Calcd for $C_{27}H_{20}ClN_3O_3$:C,69.01;H,4.29;N,7.54 %; IR (KBr): 3356.8(Broad O-H str.), 2986(C-H str., CH_2), 1699.6 (carboxylic, C=O str.),1614,1501 (C=N and C=Cstr.), 1133(C-N str.), 804(Benz.Ring). ^{1}HNMR(300MHz,$CDCl_3$)10.26(s,1H,COOH),7.24-8.62(14H,ArH),4.96(s,2H,CH Cl),4.75(s,2H,NH),4.08(s,1H,OH),^{13}CNMR($CDCl_3$)δ:56.8,111.3,115.1,117.2,122.1,127.5, 125.1,131.8,140.9,FAB-MS, 469.13

MCS[13]:4`-[5-Amino-6-chloro-2-(3-hydroxy-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:63%,m.p.=283-285^{o}C. Anal.Calcd for $C_{27}H_{20}ClN_3O_3$:C,69.01;H,4.29;N,7.54 %; IR (KBr): 3351.2(Broad O-H str.), 2980(C-H str., CH_2), 1702.2 (carboxylic, C=O str.),1619,1512 (C=N and C=Cstr.), 1139(C-N str.), 800(Benz.Ring). ^{1}HNMR(300MHz,$CDCl_3$)10.21(s,1H,COOH),7.20-8.71(14H,ArH),4.90(s,2H,CH Cl),4.82(s,2H,NH),4.16(s,1H,OH),^{13}CNMR($CDCl_3$)δ:56.8,111.3,115.1,117.2,122.1,127.5,125.1,13 1.8,140.9,FAB-MS, 470.10

MCS[14]:4`-[5-Amino-6-chloro-2-(4-hydroxy-phenyl)benzoimidazol-1-ylmethyl)]-biphenyl-2 carboxylic acid

Yield:55%,m.p.=278-281^{o}C. Anal.Calcd for $C_{27}H_{20}ClN_3O_3$:C,69.01;H,4.29;N,7.54 %; IR (KBr): 3362.0(Broad O-H str.), 2989(C-H str., CH_2), 1695.0 (carboxylic, C=O str.),1632,1520 (C=N and C=Cstr.), 1139(C-N str.), 794(Benz.Ring). ^{1}HNMR(300MHz,$CDCl_3$)10.11(s,1H,COOH),7.24-8.62(14H,ArH),4.96(s,2H,CH Cl),4.79(s,2H,NH),4.32(s,1H,OH),^{13}CNMR($CDCl_3$)δ:56.8,111.3,115.1,117.2,122.1,127.5,125.1,13 1.8,140.9,FAB-MS, 469.13

3. Pharmacological activity

Procedure for development of hypertention for normotensive rats [22]

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: [23](i) Invasive method (Direct method). (ii) Non-invasive Tail cuff method (Indirect method).

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

4. Experimental techniques

(i) Invasive Method (Direct Method):[23-25] Male albino wistar (150-250 gm) rats were used and housed at 24±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.

(ii) Non-invasive Tail cuff Method (Indirect Method):[24-25] 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 table1, 2.

5. Results and discussion

First we synthesized 2-phenyl Benzimidazole. In this method the reactants are condensed in the presence of an oxidant such as cupric acetate. An improvement on the conventional method is the use of sodium bisulfite addition adduct of the aldehyde12.The reactions are carried out in boiling ethanol, yields are good [e.g. 2-phenyl (90%), 2-(3- pyridyl) (97%)] and there is little risk

of decomposition of liable substituents. Synthetic scheme (Fig. 2) for target compounds was divided into two steps. Step I involved synthesis of 2- aryl, alkyl, aldehyde benzimidazoles by condensation reaction of 4-chlor-o-phenylenediamine with the respective. The corresponding 5-nitro derivatives were prepared by nitration under controlled temperature conditions.[19] Step II include the novel sequential combination of three routine reactions to synthesize 2'-carboxybiphenyl methylene chloride. Biphenyl –2-carboxylic acid was prepared by potash fusion of 9H flourenone[20] which was then subjected to aromatic substitution reaction using paraformaldehyde and acetamide in conc. sulphuric acid[20] to affect intermediate,4-acetamidomethyl biphenyl-2'-carboxylic acid. The required component was identified as third fraction which was subjected to substitution reaction with phosphorus oxychloride in xylene and dimethyl formamide[21] to produce the pendant moiety 4-(bromomethyl) biphenyl-2'-carboxylic acid and synthesis biphenyl with carboxylic compound[26]. The synthesized compounds were characterized on the basis of chemical and spectral data. The present work was mainly intended to establish the moieties which are responsible for Angiotension-II inhibition. Ang II antagonism by compounds with same functional group at 2 position has been found to be a function of substituent at 5-position. Presence of amino group has increased the activity substantially over the substituted one ([1] to [14]). The maximum activity has been observed with nitro group (Compound 2, 4, 6, 7, 9, 10, 12, 13, and 14). This suggests that there are some sites in the receptor pocket, which can interact with the functional groups at position 5. Substituted benzimidazole nucleus coupled to carboxylbipheny methyl group has been designed, synthesized and evaluated for angiotensin II antagonism. Compound with amino group at 5-position and aromatic, aryl, alkyl compounds at 2-position have been found to be more potent than losratan and Telmisartan. Higher activity of Compound 2, 4, 6, 7, 9, 10, 12, 13, and 14suggests that this group at 2-position should be either H-bond acceptor and hydrophobic. The higher activity of 5-amino derivatives may be ascribed to the ability of group to act as H-bond acceptor, hydrophobic with respect to the receptor site. The noncompetitive mode of antagonism of further suggests that such receptor pocket may not be accessible to the natural ligand, Ang II.

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Table 1. Hypertension induced in normotensive rat.

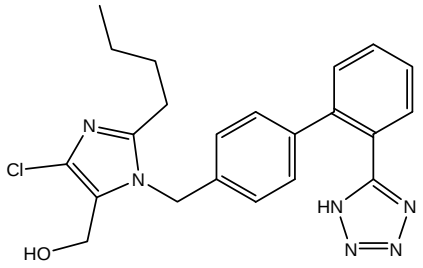
Comp.	Exp. Animal Albino (Wistar) Rat	After 1hour			After 3 hour		
		SBP	DBP	MABP	SBP	DBP	MABP
[1]	1	145	106	126	141	112	122
	2	141	112	127	144	114	126
	3	142	111	124	140	106	123
	4	147	108	129	142	102	122
	5	142	112	127	143	106	123
	6	141	116	128	142	112	122
[2]	1	145	111	128	140	107	123
	2	143	115	129	138	106	122
	3	147	107	127	141	102	123
	4	152	110	131	142	106	124
	5	148	106	127	141	104	122
	6	144	110	127	138	104	121
[3]	1	144	108	126	142	104	123
	2	148	106	127	142	106	124
	3	151	109	130	146	104	125
	4	146	104	125	142	104	123
	5	144	106	125	140	102	121
	6	148	104	126	142	106	124
[4]	1	140	116	128	139	104	122
	2	148	106	126	144	104	124
	3	145	113	129	144	100	122
	4	141	111	126	140	112	126
	5	146	114	130	142	104	123
	6	144	116	130	140	106	123
[5]	1	146	108	127	142	106	124
	2	143	106	125	139	104	121
	3	146	110	128	140	104	122
	4	149	111	130	143	106	124
	5	152	112	133	145	103	124
	6	150	111	131	146	104	125
[6]	1	148	112	130	144	102	123
	2	144	114	129	146	106	126
	3	142	108	125	146	104	125
	4	146	106	126	142	104	123
	5	142	110	126	140	116	128
	6	148	102	125	144	106	125
[7]	1	140	106	123	142	106	124
	2	141	114	128	142	104	123
	3	146	108	127	144	104	124
	4	148	114	130	144	102	123
	5	144	112	132	142	104	123
	6	146	114	12	143	101	122

[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	148	106	127	146	102	124
	6	144	104	124	140	100	120
[9]	1	140	106	123	138	102	120
	2	144	112	127	142	104	123
	3	142	114	127	140	101	122
	4	148	104	126	144	104	124
	5	154	108	132	144	102	123
	6	148	104	126	142	100	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	144	106	125	142	101	123
	6	142	108	125	138	100	119
[11]	1	140	104	122	144	106	125
	2	142	106	124	140	106	121
	3	146	104	125	144	104	120
	4	140	114	127	136	100	121
	5	148	108	126	144	102	123
	6	151	112	133	146	101	124
[12]	1	144	114	129	142	102	121
	2	139	114	127	135	103	119
	3	142	106	124	140	102	123
	4	144	108	126	142	100	121
	5	148	104	126	145	104	124
	6	143	106	124	141	101	122
[13]	1	141	110	129	142	108	125
	2	138	105	125	139	107	123
	3	132	104	128	142	102	122
	4	142	103	123	140	102	121
	5	141	110	124	143	105	123
	1	140	105	128	138	104	121
	6	139	108	124	141	103	122
[14]	1	142	113	128	142	104	123
	2	141	109	125	144	103	124
	3	144	114	128	141	102	121
	4	146	104	125	142	102	122
	5	144	112	127	141	106	123
	6	148	104	126	145	105	125
Control	**Losartan**	116	-	-	-	-	-
	Telmisartan	114	-	-	-	-	-

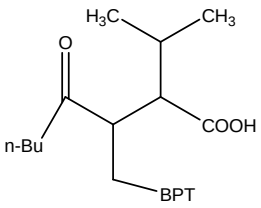
Table 2. Reduction in blood pressure (mm Hg) at a dose of 50 µgm/kg animal body weight.

Comp.	Exp. Animal Albino (Wistar) Rat	After 1hour			After 3 hour		
		SBP	DBP	MABP	SBP	DBP	MABP
[1]	1	123	101	112	122	101	113
	2	127	105	112	121	102	115
	3	124	104	114	122	102	112
	4	121	104	113	123	104	115
	5	123	101	112	121	104	112
	6	122	103	113	120	100	111
[2]	1	120	100	110	122	102	112
	2	122	102	112	121	101	111
	3	121	100	111	124	103	113
	4	122	103	114	121	104	112
	5	120	101	111	120	102	111
	6	118	104	111	123	101	112
[3]	1	120	102	111	125	102	113
	2	122	106	114	122	100	111
	3	123	101	113	126	102	113
	4	121	107	114	127	103	115
	5	122	102	112	123	107	115
	6	121	106	113	126	102	114
[4]	1	126	106	112	128	102	115
	2	124	106	115	123	103	113
	3	126	104	115	124	104	114
	4	124	108	116	122	102	112
	5	123	100	113	125	105	115
	6	122	114	114	123	103	114
[5]	1	124	111	115	122	102	112
	2	127	109	123	124	102	113
	3	125	110	122	127	101	114
	4	124	112	118	121	102	112
	5	126	105	116	127	101	114
	6	126	109	117	122	106	114
[6]	1	124	103	115	125	101	113
	2	128	105	114	127	102	114
	3	133	107	120	122	102	112
	4	131	108	123	124	104	114
	5	126	102	114	127	102	115
	6	128	104	115	122	102	111
[7]	1	126	105	116	121	104	113
	2	129	104	117	124	104	114
	3	127	102	115	127	102	115
	4	126	108	118	122	107	113
	5	124	106	115	126	106	116
	6	130	114	122	128	104	117
[8]	1	123	103	113	124	102	113

	2	125	104	115	122	103	112
	3	124	105	116	126	104	115
	4	125	101	113	123	104	116
	5	132	104	118	127	107	117
	6	135	105	120	129	102	116
[9]	1	123	103	113	124	103	114
	2	122	106	114	123	107	115
	3	127	101	114	126	106	116
	4	125	105	130	123	105	114
	5	128	109	119	124	102	113
	6	131	103	117	128	103	115
[10]	1	134	102	118	125	106	116
	2	132	105	119	129	105	117
	3	127	103	115	125	104	114
	4	124	101	113	123	104	112
	5	128	105	116	125	101	113
	6	124	103	117	122	100	111
[11]	1	124	102	113	126	104	115
	2	121	101	111	129	103	116
	3	124	105	115	123	106	115
	4	135	102	119	124	101	112
	5	136	101	118	122	104	113
	6	134	100	117	126	104	115
[12]	1	122	102	112	122	100	111
	2	123	103	116	124	110	117
	3	125	104	115	125	106	116
	4	122	105	116	131	106	118
	5	134	105	119	120	105	113
	6	125	103	114	126	102	114
[13]	1	127	104	116	124	105	114
	2	125	108	117	122	108	115
	3	124	105	115	125	106	116
	4	122	109	116	126	106	116
	5	125	104	114	122	106	114
	6	123	111	118	128	104	116
[14]	1	127	105	116	126	105	115
	2	129	108	119	124	104	114
	3	122	112	117	122	103	112
	4	126	114	120	128	107	117
	5	124	111	118	123	104	113
	6	126	104	115	127	107	117
Control	**Losartan**	116	-	-	-	-	-
	Telmisartan	114	-	-	-	-	-



Losartan



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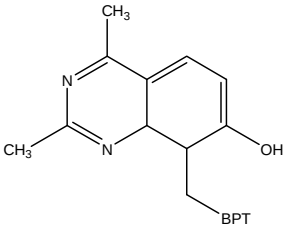

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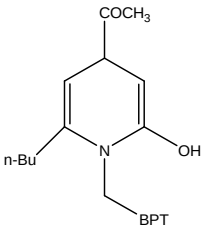

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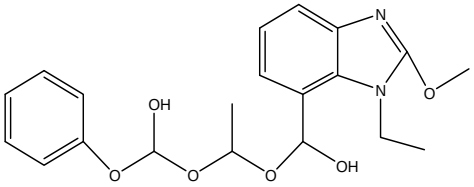
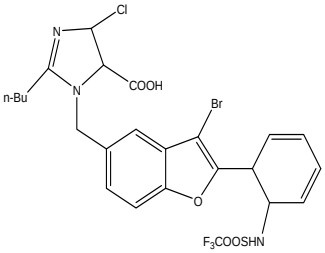


Milfasartan



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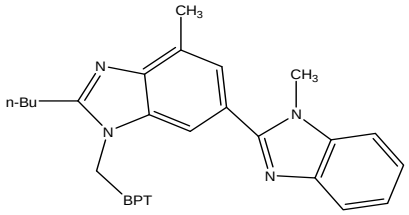

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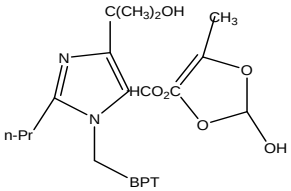
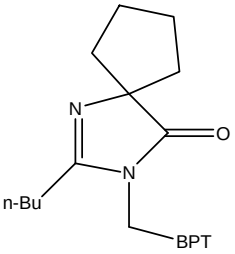
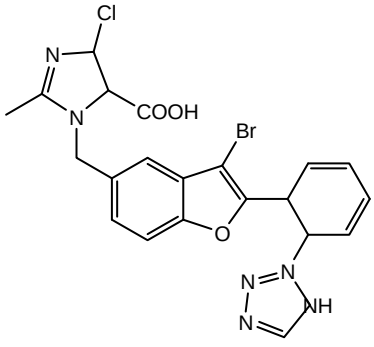


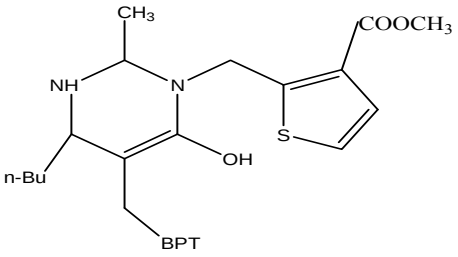
Olmesartan



Irbesartan



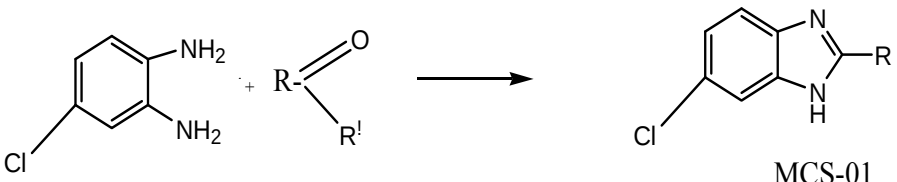
Zolzsartan



Eprosartan

Fig. Angiotensin II AT_1 selective antagonists

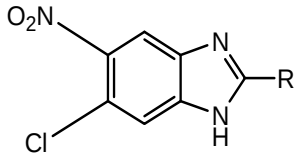
SCHEM-



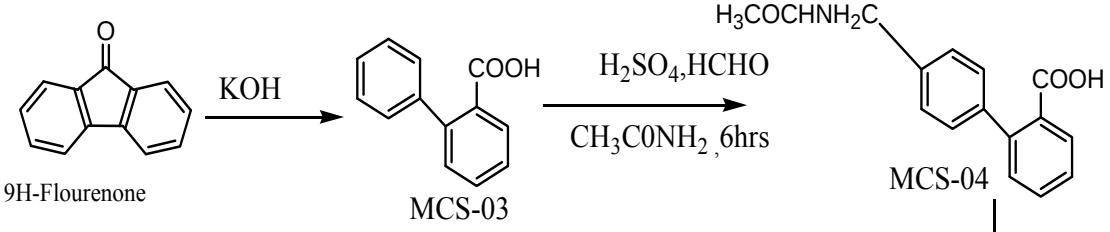
R=Alkyl,Aryl
R^{I}=Aldehyde,Acid

MCS-01

Con.sulphuric acid
Con.Nitric acid
Stirring 14hrs



6-Chloro-2-substiued -5-nitro-1*H*-benzoimidazole



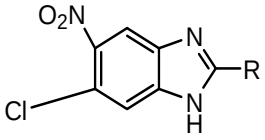
9H-Flourenone

MCS-03

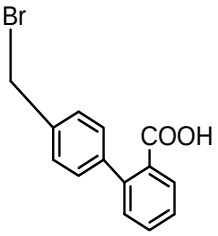
H_2SO_4,HCHO
CH_3C0NH_2 ,6hrs

MCS-04

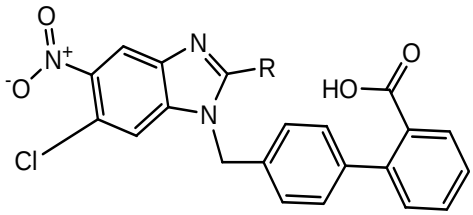
$POCl_3$



DMF,K_2CO_3

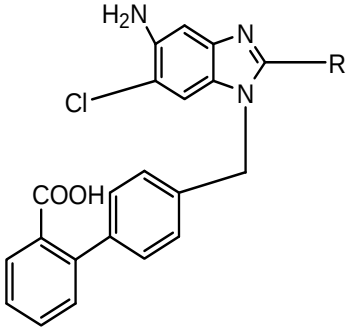


MCS-05



4'-(6-Chloro-2-substiued -5-nitro-benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid

$SnCl_2$.$2H_2O$
EtOH



4'-(5-Amino-6-chloro-2-substitued -benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid

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