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Synthesis and antihypertensive activity of some new benzimidazole derivatives of 4'-(6-methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid in the presences of $BF_3 \cdot OEt_2$

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ABSTRACT

A series of 4'-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid were synthesized expeditiously in good yields from 4-methoxy-1, 2-phenylenediamine and different substituted carboxylic acids in the presence of $BF_3 \cdot OEt_2$ as a catalyst with biphenyl carboxylic acid have been confirmed by IR,^{1}H NMR,MS and elemental analysis. The title compounds have been evaluated for antihypertensive activity direct and indirect methods. Some of these compounds have been found to exhibit excellent antihypertensive activity.

Key words: $BF_3 \cdot OEt_2$, angiotensin II, biphenyl-2-carboxylic acid.

INTRODUCTION

The renin-angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis and electrolyte/ fluid balance in normotensive and hypertensive subjects.[1]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[2]. 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[3] 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 [4]. It also stimulates the release of vasopressin luteinizing hormone oxytocin and corticotropin. ANG II further induces vagus suppression and α-adrenergic potentiation and increases inotropy and chronotropy. Stimulation of the cardiac

fibroblast matrix formation has also been described[3-5]. ANG II stimulates synthesis of prostaglandin [6] endothelin[7] and elicits procoagulatory effects by activating the plasminogen activator (PA) plasmin system[8-11]. The beneficial effect of a chronic RAS blockade was first shown for inhibitors of the angiotensin converting enzyme (ACE) such as captopril quinapril enalapril and ramipril in patients with ischemic heart disease congestive heart failure [12-14] the development of potent drugs that interfered with the RAS: the angiotensin receptor type 1 (AT_1) antagonists. To find a more specific blockade of ANG II at its AT_1 receptor highly selective non-peptidic AT1-receptor antagonists were designed and developed as competitive antagonists with virtually no agonistic effect at the receptor level. Losartan was described as the first non-peptide AT_1 receptor antagonist and the coined group name was sartans[15-16]. All major pharmaceutical companies embarked on a fast follower program immediately thereafter. Today irbesartan candesartan and valsartan are all established in the market and others e.g. tasosartan and telmisartan are following closely. Some further 20 compounds are in development. Most of these compounds share the biphenyl tetrazole unit or replacements thereof with the original advanced lead losartan [17]. Some variations of the parent biphenyl tetrazole alone were reported in the meantime excluding the obvious variation of the biphenyl spacer. The carboxylic acid another common moiety of the sartans appears to establish another important interaction with the receptor but it often hampers oral absorption. Therefore several prodrug concepts had to be realized to mask the carboxylic acid as either a labile ester or an oxidatively labile precursor that delivers the acid after absorption. Recent findings [18-19] indicate the involvement of this peptide also in situations concerning tissue remodelling, such as cardiac hypertrophy and cancer. All these responses are mediated by two distinct subtypes of Ang II receptors [type 1 (AT1) and type 2 (AT2)]. In particular, AT1 receptors mediate all of the known effects associated to Ang II that constitutes the principal target of an effectiveness therapy against the cardiovascular pathology. The Ang II effects may be reduced by inhibiting almost partially the enzyme responsible of biosynthesis of Ang II or through the interaction with AT1 receptor. 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 Ang II 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 imidazole ring of losartan with several variously substituted heteroaromatic groups or acyclic structures[20].All these antagonists possess a central aromatic nucleus bearing the pharmacophores indispensable for activity and notably a polar function adjustant to biphenyl subsistent while a polar function in this area of molecule seems to be necessary to maintain activity[21] 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 [22]. The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity [23] compounds containing tetrazole nucleus are also reported as AT1 receptor antagonists and their protypical derivative exhibits non-competitive antagonism[24] amino group attach with carboxylic group given good biological activity [25-27].In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives as a source of new antihypertensive agents. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, 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 [28-29]. In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives as a source of new antihypertensive agents.Benzimidazole structures are classified under several classes of drugs[30], based on the possible substitution at different positions of the benzimidazole nucleus.Methods of benzimidazole synthesis include the condensation of *o*-aryldiamines and aldehyde in refluxing nitrobenzene [31] the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid or mineral acids .

MATERIALS AND METHODS

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. Moreover, most of the methods have not been found to be quite accessible from the viewpoints of both yield and economics of the reaction. Thus, in order to cater the needs associated with synthetic aspects, herein, we would like to present unique approach to synthesize benzimidazole derivatives. $BF_3{\cdot}OEt_2$ is a Lewis acid catalyst used in a wide variety of applications, such as, in mild dehydration of tertiary alcohols to alkenes, in Diels-Alder reaction, in cleavage of ethers, in THP protection of alcohols, in rearrangement of epoxides to carbonyl compounds, in reaction of ally tin reagents with aldehydes and ketones *etc*. However, there are examples of the use of $BF_3{\cdot}OEt_2$ as a catalyst for the preparation of benzimidazoles[33]. Herein, protocol for the rapid synthesis of a variety of biologically significant benzimidazoles using a catalytic amount of $BF_3{\cdot}OEt_2$ under extremely mild solvent-free conditions (**Scheme**).

MCS-01-General Procedure for the Synthesis of Benzimidazoles
A mixture of 4-methoxy-1, 2-phenylenediamine (1.0 mmol, 0.55gm), different substitute carboxylic acid (1.5 mmol), in the presence of $BF_3{\bullet}OEt_2$ (0.5 mmol) to this reaction mixture, CH_2Cl_2 (50 mL) was added and washed with water. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to get the crude compound. The crude compounds were purified by silica gel column chromatography using ethyl acetate: chloroform (99:1) as eluent. Given product MCS-01(6-Methoxy-2-substituted-1H-benzimidazol).

MCS-02 Synthesis of (Biphenyl Carboxylic acid) [34]
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 4.5 resulting in precipitation of by product which was filtered under suction wash with distilled water and the filtrate was again acidify with Conc.HCl. The precipitated product was filtered under suction and dried in air. The product was recrystallized from Absolute ethanol. Product was formed.

Yield: 81%, m.p.=145-148°C. IR(KBr): 3598-3069(O-Hstr),1675.4(C=O Carboxylic, str), 1393, 1364.3(C-O-H in-plane bend); 1H NMR(CDCl3): 10.03(1H, s, COOH), 7.4-8.2(m, 9H), ^{13}CNMR($CDCl_3$)δ: 112.4, 116.8, 126.8, 133.5, 162.8, FABMS, 198.08.

MCS-03-Synthesis of (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), 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-04-Synthesis of 4'-chloromethylbiphenyl-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): 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), 7.11-8.05(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 %.

MCS-05- Synthesis of 4-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid

50 mg of Schiff (different substituted carboxylic acid MCS-01) was dissolved in 75ml of DMF (dimethyl formamide) and stirred vigorously with 2.5 gm of potassium carbonate at 42^{0}C for 2.5 hours. To the resulting mixture 0.250 gm of MCS-04(4'-chloro methylbiphenyl-2-carboxylic acid) first dissolved in 30 ml of DMF and then was added drop wise with dropping funnel in 1.5 hours the reaction was allowed to proceed for further 12 hours at room temperature and solvent removed under vacuum. Residue was treated with 20 ml of Conc. HCl and extracted with ethyl acetate. The organic layer was washed with water, distilled water and dried over anhydrous sodium sulphate. The solvent was evaporated and solid (MCS-05) was obtained.

Compounds with spectral data
[a].**4'-(6-Methoxy-2-methyl-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 70 %, m.p. = 266-268^{0}C. Anal. Calcd for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25%; IR (KBr): 3450, 3398, 3241, 3050, 2854, 1708, 1670, 1643, 1527-1590, 1439, 1310, 1277, 740 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$) 12.14(1H, s, -NH-Benzimidazole), 10.13(s, 1H, COOH), 4.96(s, 2H, CH_2), 6.96-8.51(m, 14H, Ar-H), 2.35(s, 3H, CH_3), 3.74(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 55.8, 110.1, 121.32, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28, 149.11, FAB-MS, 448.17.

[b].**4'-(6-Methoxy-2-ethyl-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 74 %, m.p. = 277-278^{0}C. Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.05%; IR (KBr): 3450, 3398, 3241, 3143, 2822, 1713, 1670, 1643, 1527-1343, 1439, 1277, 740cm-1. ^{1}HNMR (300 MHz, $CDCl_3$) 12.65(1H, s, -NH-Benzimidazole), 10.11(s, 1H, COOH), 7.1-8.6(m, 14H, Ar H), 4.98(s, 2H, CH_2), 2.61(s, 2H, CH_2), 2.38(s, 3H, CH_3) 3.77(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 16.3, 17.9, 55.2, 110.1, 113.4, 116.2, 121.1, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28, 149.11, FAB-MS, 462.19.

[c].**4'-(2-Isopropyl-6-methoxy-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 66 %, m.p. = 283-285^{0}C. Anal. Calcd for $C_{31}H_{28}N_2O_3$: C, 78.13; H, 5.92; N, 5.88%; IR (KBr): 3456, 3390, 3242, 3113, 3071, 2853, 1718, 1672, 1649, 1527-1328, 1439, 1277, 765 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 12.43(1H, s, -NH-Benzimidazole), 10.28(s, 1H, COOH), 7.1-8.6(m, 15H, ArH), 5.08(s, 2H, CH_2), 1.34(d, 6H, CH_3), 3.72(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 15.3, 16.5, 20.1, 55.6, 110.1, 113.4, 116.2, 121.1, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28, 149.11, FAB-MS-476.21.

[d].**4'-(6-Methoxy-2-phenyl-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 59 %, m.p. = 223-235^{0}C. Anal. Calcd for $C_{28}H_{22}N_2O_3$: C,77.41; H, 5.10; N, 6.45%; IR (KBr): 3452, 3394, 3381, 3253, 3144, 2838, 1712, 1649, 1637, 1526-1396, 1277, 1141, 763 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.12(1H, s, -NH-Benzimidazole), 10.21(s, 1H, COOH), 7.11-8.57(m, 15H, Ar H), 5.02(s, 2H, CH_2), 3.73(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 20.6, 55.6, 110.1, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 148.48, 149.18, FAB-MS, 434.16.

[e].**4'-[2-(3-Carboxy-5-hydroxy-phenyl)-6-Methoxy-benzimidazole-1-ylmethyl)-biphenyl -2-carboxylic acid**
Yield: 62 %, m.p. = 204-207^{0}C. Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22%; IR (KBr): 3473, 3387, 3376, 3255, 3137, 2876, 1702, 1649, 1637, 1526-1396, 1277, 1141, 766 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.27(1H, s, -NH-Benzimidazole), 10.29(s, 1H, COOH), 7.21-8.52(m, 14H, Ar H), 5.01(s, 2H, CH_2), 3.71(s, 3H, CH_3), 5.11(s, 1H, arm-OH). ^{13}CNMR ($CDCl_3$)δ: 18.2, 55.6, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.11, 149.10, FAB-MS.450.15.

[f].**4'-[2-(3-Carboxy-5-chloro-phenyl)-6-Methoxy-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 77 %, m.p. = 188-191^{0}C. Anal. Calcd for $C_{28}H_{21}ClN_2O_3$: C, 71.72; H, 4.51; N, 5.97%; IR (KBr): 3449, 3352, 3372, 3255, 3137, 2876, 1707, 1643, 1637, 1526-1390, 1253, 1121, 765 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.18(1H, s, -NH-Benzimidazole), 10.54(s, 1H, COOH), 7.21-8.52(m, 14H, Ar H), 5.00(s, 2H, CH_2), 3.72(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 19.43, 50.1, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.11, 149.52, FAB-MS.468.124.

[g].**4'-[2-(3-Carboxy-5-bromo-phenyl)-6-Methoxy-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 71 %, m.p. = 215-218^{0}C. Anal. Calcd for $C_{28}H_{21}BrN_2O_3$: C, 65.51; H, 4.12; N, 5.46%; IR (KBr): 3442, 3315, 3327, 3244, 3137, 2876, 1714, 1647, 1635, 1526-1363, 1253, 1121, 765 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.14(1H, s, -NH-Benzimidazole), 10.59(s, 1H, COOH), 7.1-8.5 (m, 14H, Ar H), 4.98(s, 2H, CH_2), 3.76(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 17.3, 52.6, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.11, 149.0, FAB-MS.512.07.

[h].**4'-[2-(3-Carboxy-5-iodo-phenyl)-6-Methoxy-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 67 %, m.p. = 272-274^{0}C. Anal. Calcd for $C_{28}H_{21}IN_2O_3$: C, 60.01; H, 3.78; N, 5.00%; IR (KBr): 3430, 3311, 3322, 3264, 3126, 2876, 1714, 1647, 1635, 1526-1363, 1253, 1121, 760 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.16(1H, s, -NH-Benzimidazole), 10.45(s, 1H, COOH), 7.0-8.47 (m, 14H, Ar H), 4.99(s, 2H, CH_2), 3.74(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 17.6, 56.9, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.11, 148.43, FAB-MS.560.06.

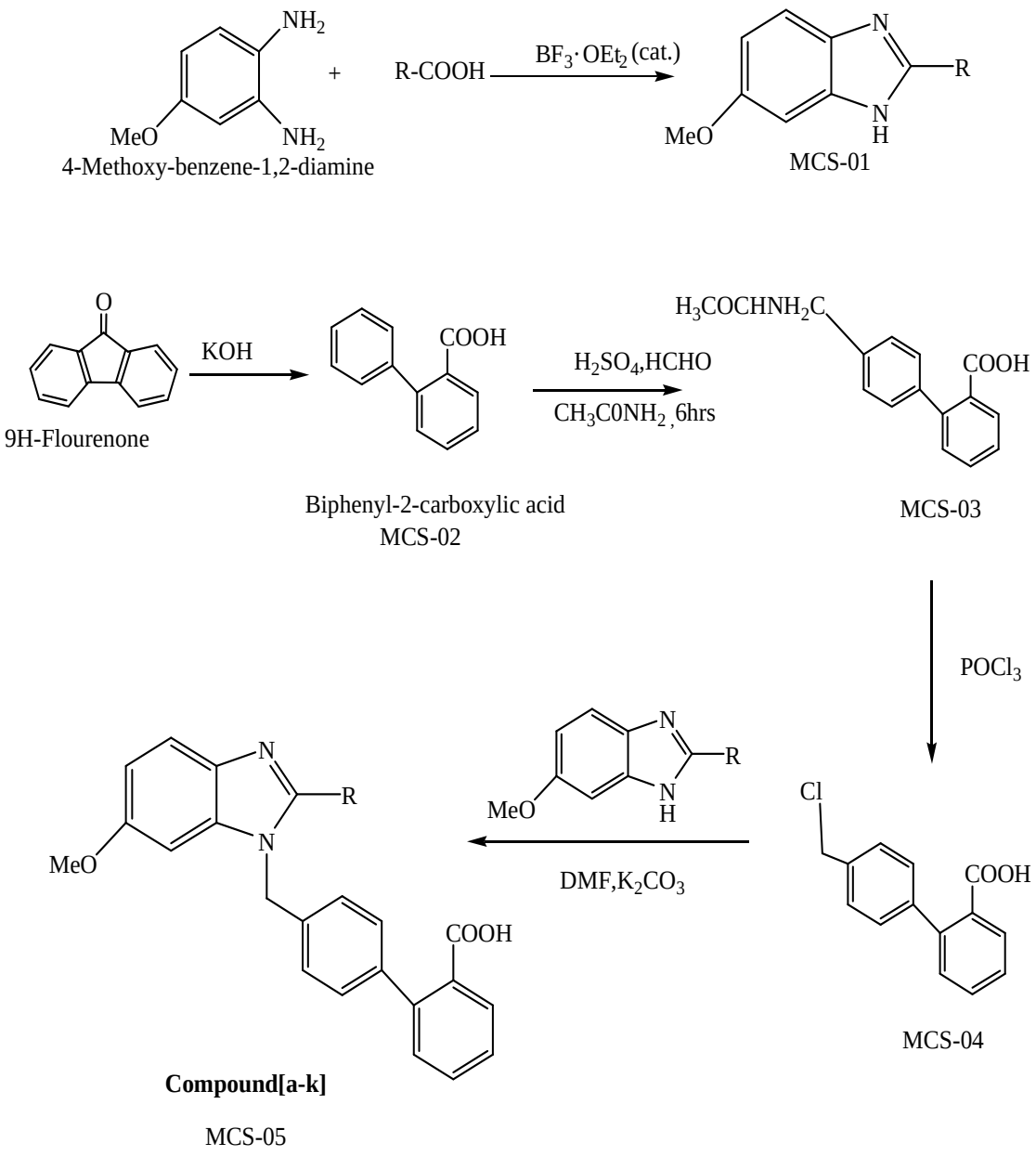
[i].**4'-[2-(3-Carboxy-2-chloro-phenyl)-6-Methoxy-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 82 %, m.p. = 194-196^{0}C. Anal. Calcd for $C_{28}H_{21}ClN_2O_3$: C, 71.72; H, 4.51; N, 5.97%; IR (KBr): 3449, 3352, 3372, 3255, 3137, 2876, 1707, 1643, 1637, 1526-1390, 1253, 1121, 765 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.18(1H, s, -NH-Benzimidazole), 10.54(s, 1H, COOH), 7.21-8.52(m, 14H, Ar H), 5.00(s, 2H, CH_2), 3.72(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 19.43, 50.1, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.11, 149.52, FAB-MS.469.54.

[j].**4'-[2-(4-Amino-phenyl)-6-Methoxy-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 73 %, m.p. = 215-217^{0}C. Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35%; IR (KBr): 3432, 3359, 3372, 3255, 3137, 2876, 1707, 1643, 1637, 1526-1369, 1248, 1126, 758 cm-1.^{1}HNMR (300 MHz, $CDCl_3$), 12.94(1H, s, -NH-Benzimidazole), 10.38(s, 1H, COOH), 7.01-8.63(m, 14H, Ar H), 4.67(s, 2H, arm-NH_2), 5.03(s, 2H, CH_2), 3.73(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 20.04, 51.1, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.0, FAB-MS.449.174.

[k] **4'-(6-Methoxy-2-(4-nitro-phenyl-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid**
Yield: 81 %, m.p. = 233-236^{0}C. Anal. Calcd for $C_{28}H_{21}N_3O_5$: C, 70.14; H, 4.41; N, 8.76%; IR (KBr): 3426, 3343, 3313, 3285, 3130, 2871, 1718, 1451, 1675, 1526-1361, 1248, 1126, 767 cm-1. ^{1}HNMR (300 MHz, $CDCl_3$), 13.11(1H, s, -NH-Benzimidazole), 10.19(s, 1H, COOH), 7.23-8.68(m, 14H, Ar H), 5.06(s, 2H, CH_2), 3.69(s, 3H, CH_3). ^{13}CNMR ($CDCl_3$)δ: 20.04, 51.1, 112.9, 113.4, 116.2, 121.1, 128.4, 135.5, 138.2, 142.6, 148.0, FAB-MS.479.18.

Pharmacological Activity: [35-40]
Non-invasive Method (Indirect Method) Albino rats weighing 150-250 gm were used to screening for all the synthesized benzimidazoles 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 five 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. Measurements were done after 1 hour and 3 hour time interval intensive stepwise. One hour after administration of drug sample, animal was shifted to the restrainers, 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. [Table1, 2]

SCHEME



Invasive Method (Direct Method): 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 cannula 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.)Table 3, 4.

Table 1. Hypertension induced in normotensive rat

Comp.	Exp. Animal Albino (Wistar) Rat	After 1hour			After 3 hour		
		SBP	DBP	MABP	SBP	DBP	MABP
[a]	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
[b]	1	138	106	122	141	103	122
	2	132	110	121	143	105	124
	3	141	111	126	139	104	121
	4	144	105	124	139	103	122
	5	140	113	127	142	107	124
[c]	1	141	104	123	137	106	121
	2	135	101	118	136	107	121
	3	140	110	125	138	112	125
	4	141	103	122	135	109	122
	5	134	106	120	143	114	129
[d]	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
[e]	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
[f]	1	140	106	123	142	101	121
	2	142	108	125	141	102	120
	3	139	110	125	143	101	120
	4	146	105	126	142	101	118
	5	142	102	124	143	101	122
[g]	1	140	105	122	137	103	120
	2	141	106	124	141	101	121
	3	143	105	124	143	105	124
	4	142	112	127	140	102	121
	5	144	116	130	141	101	122
[h]	1	152	112	133	145	103	124
	2	150	111	131	146	104	125
	3	144	114	129	146	106	126
	4	142	108	125	146	104	125

	5	146	106	126	142	104	123
[i]	1	143	123	136	103	119	137
	2	149	125	138	105	122	140
	3	146	114	12	143	101	122
	4	142	112	127	140	102	121
	5	144	116	130	141	101	122
[j]	1	150	123	136	103	119	137
	2	147	125	138	105	122	140
	3	146	114	12	143	101	122
	4	136	112	124	141	103	122
	5	142	112	127	140	103	121
[k]	1	139	107	123	140	101	120
	2	132	104	128	142	102	122
	3	142	103	123	140	102	121
	4	133	113	123	141	109	125
	5	141	110	126	140	108	124
Control	**Losartan**	123	-	-	-	-	-

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
[a]	1	124	102	113	126	100	113
	2	122	101	112	126	103	112
	3	126	104	115	124	102	113
	4	128	102	115	126	104	115
	5	131	103	117	124	102	113
[b]	1	126	103	114	122	109	115
	2	124	107	115	127	106	117
	3	127	104	116	124	95	109
	4	129	108	118	130	102	116
	5	126	101	117	123	97	110
[c]	1	128	103	115	120	103	112
	2	124	96	110	124	106	115
	3	127	101	114	123	102	112
	4	121	103	112	121	97	109
	5	120	100	115	128	100	114
[d]	1	127	105	118	126	102	114
	2	124	106	122	122	101	111
	3	123	102	119	127	101	110
	4	122	104	118	124	98	113
	5	127	108	119	126	103	109
[e]	1	128	106	117	123	100	112
	2	127	101	116	125	105	110
	3	124	102	119	128	102	111
	4	129	104	117	124	101	112
	5	133	103	118	126	100	110

[f]	1	125	101	113	121	101	110
	2	123	107	115	125	100	112
	3	126	103	114	126	96	111
	4	129	101	115	119	104	111
	5	123	107	115	121	99	110
[g]	1	126	103	114	125	104	113
	2	132	105	119	121	102	110
	3	131	106	118	119	103	107
	4	122	104	112	125	101	113
	5	123	102	113	128	103	112
[h]	1	126	104	110	123	106	116
	2	122	106	114	129	101	113
	3	124	106	115	127	102	114
	4	126	104	115	125	105	115
	5	124	104	114	121	100	110
[i]	1	129	102	116	124	101	113
	2	133	103	117	127	105	116
	3	130	108	118	124	100	112
	4	132	105	118	120	102	111
	5	129	111	120	123	101	112
[j]	1	125	101	113	121	101	110
	2	123	107	115	125	100	112
	3	126	103	114	126	96	111
	4	129	101	115	119	104	111
	5	123	107	115	121	99	110
[k]	1	126	114	124	128	107	117
	2	124	111	121	123	104	113
	3	126	104	115	127	107	117
	4	127	105	114	126	105	115
	5	129	108	118	124	104	114
Control	**Losartan**	106		-	-	-	-

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	**158**	**152**	**148**	**140**	**132**	**127**	**122**	**116**	**113**	**107**
[a]	176	170	164	159	154	149	143	137	133	129
[b]	165	159	155	148	144	138	136	132	129	127
[c]	163	158	151	145	140	138	134	131	128	123
[d]	169	164	158	152	147	140	137	132	129	126
[e]	166	163	158	151	146	141	138	133	128	124
[f]	164	160	156	151	146	140	133	129	126	123
[g]	175	170	166	162	159	153	148	143	138	135
[h]	167	164	159	155	151	147	143	139	136	132
[i]	169	164	159	152	147	141	137	132	129	126
[j]	173	167	163	160	152	148	142	136	132	129
[k]	180	177	170	162	153	147	142	139	134	130

Table: 4 Antihypertensive Activity of synthesized compounds

Compound. No	Minimum Blood pressure value(mm Hg)	Duration of hypertension effect(min.)
Losratan	**107**	**90**
[a]	121	101
[b]	120	105
[c]	117	95
[d]	122	102
[e]	114	100
[f]	116	105
[g]	123	110
[h]	121	106
[i]	119	100
[j]	121	102
[k]	118	110

RESULTS AND DISCUSSION

Synthesis compounds were screened for their antihypertensive activity by methods using 150-250 gm male either sex.the rats having hypertension more than 160 mm of Hg were taken for the experiment. All the eleven compounds synthesized [a-k] showed good antihypertensive activity.copmounds c,e,f,i,j shown the good antihypertensive activity with compared the standard drug.

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