Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2010, 1 (1): 111-123

Studies in the Presences of $BF_3 \cdot OEt_2$ Catalysts of Some Benzimidazole Derivatives [2-(substituted-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazole] with Potent antihypertensive agents

M. C. Sharma*[a], D. V. Kohli [a], Smita Sharma[b] and A. D. Sharma[c]

[a]*Department of Pharmaceutical Sciences, Dr. Hari Singh Gaur University, Sagar(M.P), India*
[b]*Department of Chemistry, Yadhunath Mahavidyalya, Bhind (M.P), India*
[c]*Oriental College of Pharmacy, Indore(M.P), India*

ABSTRACT

Series of substituted benzimidazole derivatives [2-(substituted-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H benzimidazole] 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 tetrazole.Synthesis compounds have been evaluated for antihypertensive activity direct and indirect methods and confirmed by IR,^{1}H NMR,MS and elemental analysis.

Keywords: $BF_3 \cdot OEt_2$, angiotensin II, antihypertensive agents, biphenyl tetrazole.

INTRODUCTION

Antihypertensive are a class of drugs that are used in medicine and pharmacology to treat hypertension (high blood pressure).It is now 100 years since renin was described by R Tigerstedt and P G Bergmann as a pressure system originating in the kidney and more than 60 years since H Goldblatt's group demonstrated that hypertension could be generated in dogs by the constriction of one renal artery, a procedure which in 1940 was shown to stimulate renin (angiotensin) production by the ischaemic kidney. Then the elements of the enzymatic cascade representing the renin-angiotensin system were progressively elucidated (figure 1). In the 1970s came the first observations that angiotensin II harms the heart and kidney and that patient with high levels of plasma-renin activity are at increased risk of stroke or myocardial infarction. The development of pharmacological agents that block the renin-angiotensin system specifically have helped to define the contribution of this system to blood-pressure control and to the pathogenesis of hypertension, congestive heart failure, and chronic renal failure. The concept of treating hypertension and heart failure via this route was first established in the 1970s with saralasin, a peptidic antagonist of angiotensin II receptors[1–3].Angiotensin II receptor blockade with saralasin, alone or in combination with salt depletion, lowered blood pressure in hypertensive patients and improved haemodynamics in congestive heart failure. However, saralasin had to be administered intravenously and at higher doses it had some partial agonist, angiotensin-II like

effects.The renin-angiotensin system (RAS) is recognized as a key element in blood pressure regulation and electro-lyte/fluid homeostasis [4] As outlined in Figure 1, the RAS constitutes a proteolytic cascade in which angio-tensinogen from the liver is cleaved by the aspartyl protease renin to produce the decapeptide angiotensin I (Ang I). Biologically inactive Ang I is cleaved by the metalloprotease angiotensin-converting enzyme (ACE) to produce the endogenous octapeptide hormone angio-tensin II (Ang II). The clinical and commercial success of ACE inhibitors[5] such as captopril[6] and enalapril[7] for the treatment of hypertension and congestive heart failure has initiated substantial interest in the exploration of novel ways to interfere with the RAS cascade[8-9]. Despite the fact that ACE inhibitors have met with a high degree of success, ACE is a nonspecific protease which is also responsible for the degradation of brady-kinin as well as other peptides such as substance P and enkephalins. The dry cough that occurs in 5-10% of the population treated with ACE inhibitors and the rare instances of angioedema have been proposed to be the result of the lack of specificity of ACE; more specifically these side effects have been attributed to bradykinin potentiation [10]. In the search for novel methods of intervention, inhibitors of renin have also been extensively investigated. However, to date, poor oral bioavailability, rapid biliary excretion, and the structural complexity of most renin inhibitors have hampered their development as drugs [11]. While progress has been made toward eliminating these liabilities, the pharmaceutical industry has been unsuccessful in bringing a renin inhibitor to market. Inhibition of the terminal step in the RAS, i.e., Ang II receptor blockade, offers a highly specific approach to inhibition of the system regardless of the source of Ang II. Also, since ACE would not be affected by such agents, potentiation of bradykinin and hence cough or angioedema by this mechanism would not be expected during therapy with an Ang II blocker [12]. All Hypertensive drugs cause dizziness, ankle swelling, headache, fatigue, chest discomfort and cough. This review focus on the adverse effects of Antihypertensive drugs, severity of these adverse effects and attempts made to prevention and treatment of hypertension by non-pharmacological intervention. Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported[13].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[14]. Among them, irbesartan, candesartan, valsartan, telmisartan, tasosartan, and olmesartan are on the market. Most of the developed AT_1 receptor antagonists are characterized by the presence in their structure of the biphenyl fragment bearing an acidic moiety and differ in the nature of the pendent heterocyclic system (valsartan lacks the heterocyclic moiety) connected to the para position of the proximal phenyl. Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported[15]. 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 substanceP.Starting from the initial leads reported byTakeda, [16]researchers at DuPont discovered losartan, the first orally active AT1 selective nonpeptide AII antagonist that reached the market for the treatment of hypertension (1994, Cozaar). The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity[17]. Compounds containing tetrazole nucleus are also reported as AT1 receptor antagonists and their protypical derivative exhibits non-competitive antagonism[18] and amino group attach with carboxylic group given good biological activity [19-21]. 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.

MATERIALS AND METHODS

Benzimidazoles are being recognized as a drug of choice in the current drug design scenario. The advent of high throughput screening technologies has impacted significantly on the methodologies that are used for the synthesis of a number of medicinal compounds. The implementation in the laboratory of these synthetic technologies to increase the number of molecules generated by chemists is now a prerequisite to competitive advantage in the field. However, most of the existing methods to design benzimidazole skeleton requires the insertion of a carbon into a precursor with ortho heteroatom on a benzene ring. 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. Benzimidazole structures are classified under several classes of drugs[22], 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 [23-24], the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid[25] or mineral acids[26] .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 aldehyde 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.

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 4'-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carbonitrile

To a solution of 250 mg (10.12 mmol) compound carboxylic acid substitute MCS-01 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 14 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-03-Synthesis of 2-(substituted-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole

A mixture of different substituted 4'-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carbonitrile (1.0 g), sodium azide (1.5 g, 10.mmol), and Et3N·HCl (5.5 g, 14.12 mmol) in NH_4Cl (35 mL) is stirred at 40°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/chloroform (80:20/v: v) to give solid Compounds.

Compounds and spectral data-

[1] 6-methoxy-2-phenyl -1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl] -1H-benzoimidazole

Yield: 65 %, m.p. = 211-213^0 c. Anal.Calcd for $C_{28}H_{22}N_6O$:C,73.36;H, 4.89;N,18.35%; IR (KBr): 3428, 3365,3291, 3076,2850, 1653, 1613,1533-1598, 1277, 1234, 899, 765 cm-1.^{1}HNMR(300MHz,$CDCl_3$) 13.04(1H,s,-NH-Benzimidazole), 10.04(s,1H,tetrazole-NH),4.99(s,2H,CH_2),6.58-8.21(m,15H,Ar-H), 3.74(s,3H,CH_3). ^{13}CNMR ($CDCl_3$)δ: 18.6,54.1, 113.5, 120.32, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28,149.0,FAB-MS.458.16

[2] 6-Methoxy-2-methyl-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl] -1H-benzoimidazole

Yield: 58 %, m.p. = 203-205^0 c. Anal.Calcd for $C_{23}H_{20}N_6O$:C,69.68;H, 5.08;N,21.20%; IR (KBr): 3419, 3339,3265, 3070,2858, 1632, 1695,1530-1591, 1276, 1233, 896, 761cm-1.^{1}HNMR(300MHz,$CDCl_3$) 13.01(1H,s,-NH-Benzimidazole), 10.09(s,1H,tetrazole-NH),4.95(s,2H,CH_2),6.65-8.20(m,10H,Ar-H), 3.70(s,3H,CH_3), 2.42 (s,3H,CH_3). ^{13}CNMR ($CDCl_3$)δ: 16.7,18.1,54.7, 113.0, 120.32, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28,149.65,FAB-MS.396.177

[3] 6-Methoxy-2-ethyl-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl] -1H-benzoimidazole

Yield: 61 %, m.p. = 196-197^0 c. Anal.Calcd for $C_{24}H_{22}N_6O$:C,70.23;H, 5.40;N,20.47%; IR (KBr): 3424, 3335,3261, 3075,2852, 1636, 1693,1535-1589, 1276, 1233, 896, 768.^{1}HNMR(300MHz,$CDCl_3$);13.00(s,1H,-NH-Benzimidazole), 10.06(s,1H,tetrazole-NH),4.97(s,2H,CH_2), 2.57(s,2H,CH_2),6.65-8.20(m,10H,Ar-H), 3.70(s,3H,CH_3), 2.42 (s,3H,CH_3). ^{13}CNMR ($CDCl_3$)δ: 16.7,18.1,54.7, 113.0, 120.32, 122.34, 122.36, 124.59, 137.43, 148.48, 149.28,149.60,150.22,150.57,FAB-MS.410.186

[4] 2-Isopropyl-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl] -1H-benzoimidazole

Yield: 55 %, m.p. = 166-169 ^{0} c. Anal.Calcd for $C_{25}H_{24}N_6O$:C,70.73;H, 5.70;N,19.80%; IR (KBr): 3433, 3315,3263, 3071,2885, 1642, 1690,1532-1554, 1270, 1233, 893, 761.^{1}HNMR(300MHz,$CDCl_3$);13.05(s,1H,-NH-Benzimidazole), 10.11(s,1H,tetrazole-NH),4.91(s,2H,CH_2), 6.76-8.43(m,11H,Ar-H), 3.70(s,3H,CH_3), 1.27(s,6H,CH_3). ^{13}CNMR ($CDCl_3$)δ: 16.7,18.1, 58.0,112.9,113.4,116.2,121.1,128.4,135.5,138.2,148.1, 150.22,151.15,FAB-MS.424.20

[5]2-{6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole-2-yl}-phenol

Yield: 60 %,m.p. = 179-184 ^{0} c. Anal.Calcd for $C_{28}H_{22}N_6O_2$:C,70.88;H, 4.67;N,17.80%; IR (KBr): 3448, 3310,3269, 3043,2881, 1654, 1643,1511-1550, 1270, 1233, 887, 769.^{1}HNMR(300MHz,$CDCl_3$);13.09(s,1H,-NH-Benzimidazole), 10.19(s,1H,tetrazole-NH),4.90(s,2H,CH_2), 6.97-8.50(m,14H,Ar-H), 3.72(s,3H,CH_3), 5.10(s,1H,O-H). ^{13}CNMR ($CDCl_3$)δ: 18.7, 58.0,112.9, 112.9,113.4,116.2,121.1,128.4,135.5,138.2,148.0, 150.65, FAB-MS.474.06

[6] 2-(2-chloro-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole

Yield: 80 %,m.p. = 156-159 ^{0} c. Anal.Calcd for $C_{28}H_{21}ClN_6O$:C,68.22;H, 4.27;N,17.06%; IR (KBr): 3464, 3317,3226, 3033,2844, 1632, 1665,1517-1520, 1211, 1236, 886,

766.^{1}HNMR(300MHz,$CDCl_3$);13.15(s,1H,-NH-Benzimidazole), 10.15(s,1H,tetrazole-NH),4.96(s,2H,CH_2), 6.9-8.4 (m,14H,Ar-H), 3.77(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 21.1, 55.2,111.5, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.0, 152.05, FAB-MS.492.13

[7]2-(3-chloro-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield: 86 %,m.p. = 163-165 ^{0}c. Anal.Calcd for $C_{28}H_{21}ClN_6O$:C,68.22;H, 4.27;N,17.06%; IR (KBr): 3464, 3317,3226, 3033,2844, 1632, 1665,1517-1520, 1211, 1236, 886, 766.^{1}HNMR(300MHz,$CDCl_3$);13.15(s,1H,-NH-Benzimidazole), 10.15(s,1H,tetrazole-NH),4.96(s,2H,CH_2), 6.9-8.4 (m,14H,Ar-H), 3.77(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 21.1, 55.2,111.5, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.0, 152.05, FAB-MS.493.17

[8]2-(4-chloro-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield: 84 %,m.p. = 151-153 ^{0}c. Anal.Calcd for $C_{28}H_{21}ClN_6O$:C,68.22;H, 4.27;N,17.06%; IR (KBr): 3464, 3317,3226, 3033,2844, 1632, 1665,1517-1520, 1211, 1236, 886, 766.^{1}HNMR(300MHz,$CDCl_3$);13.15(s,1H,-NH-Benzimidazole), 10.15(s,1H,tetrazole-NH),4.96(s,2H,CH_2), 6.9-8.4 (m,14H,Ar-H), 3.77(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 21.1, 55.2,111.5, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.0, 152.05, FAB-MS.491.65

[9]2-(2-fluoro-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield: 76%,m.p. = 185-187 ^{0}c. Anal.Calcd for $C_{28}H_{21}FN_6O$:C,70.58;H, 4.45;N,17.64%; IR (KBr): 3465, 3312,3226, 3033,2844, 1632, 1665,1517-1520, 1211, 1236, 897, 760.^{1}HNMR(300MHz,$CDCl_3$);13.19(s,1H,-NH-Benzimidazole), 10.18(s,1H,tetrazole-NH),4.99(s,2H,CH_2), 7.3-8.6 (m,14H,Ar-H), 3.74(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 21.6, 55.1,111.7, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.0, 152.05, FAB-MS.476.178

[10]2-(2-bromo-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield:76%,m.p.= 227-230 ^{0}c. Anal.Calcd for $C_{28}H_{21}BrN_6O$:C,62.58;H, 3.94;N,15.64%; IR (KBr): 3460, 3317,3222, 3039,2853, 1660,1515-1520, 1211, 1236, 1175,1043,894,765.^{1}HNMR(300MHz,$CDCl_3$);13.12(s,1H,-NH-Benzimidazole), 10.24(s,1H,tetrazole-NH),4.96(s,2H,CH_2), 7.2-8.64 (m,14H,Ar-H), 3.73(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 20.5, 55.9,112.5, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.5, 151.0, FAB-MS.536.09

[11]2-(2-iodo-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield: 68%,m.p. = 244-247 ^{0}c. Anal.Calcd for $C_{28}H_{21}IN_6O$:C,57.55;H, 3.64;N,14.38%; IR (KBr): 3468, 3311,3226, 3033,2859, 1655,1528-1529, 1242, 1258, 1171,1049,895,760.^{1}HNMR(300MHz,$CDCl_3$);13.24(s,1H,-NH-Benzimidazole), 10.43(s,1H,tetrazole-NH),4.93(s,2H,CH_2), 7.2-8.4 (m,14H,Ar-H), 3.73(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 19.5, 50.3,112.1, 113.7,115.3,116.9,121.6,128.4,135.5,138.2,148.1, 151.31, FAB-MS.584.084

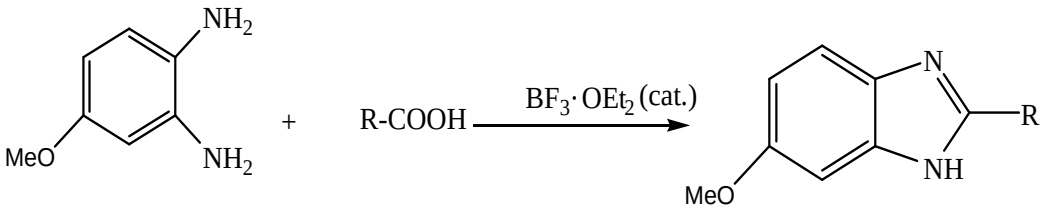
[12]2-(4-fluoro-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield: 72%,m.p. = 183-185 ^{0}c. Anal.Calcd for $C_{28}H_{21}FN_6O$:C,70.58;H, 4.45;N,17.64%; IR (KBr): 3465, 3312,3226, 3033,2844, 1632, 1665,1517-1520, 1211, 1236, 897, 760.^{1}HNMR(300MHz,$CDCl_3$);13.19(s,1H,-NH-Benzimidazole), 10.18(s,1H,tetrazole-NH),4.99(s,2H,CH_2), 7.3-8.6 (m,14H,Ar-H), 3.74(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 21.6, 55.1,111.7, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.0, 152.05, FAB-MS.478.02

[13]2-(4-bromo-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield:76%,m.p.= 227-230 ^{0}c. Anal.Calcd for $C_{28}H_{21}BrN_6O$:C,62.58;H, 3.94;N,15.64%; IR (KBr): 3460, 3317,3222, 3039,2853, 1660,1515-1520, 1211, 1236, 1175,1043,894,765.^{1}HNMR(300MHz,$CDCl_3$);13.12(s,1H,-NH-Benzimidazole), 10.24(s,1H,tetrazole-

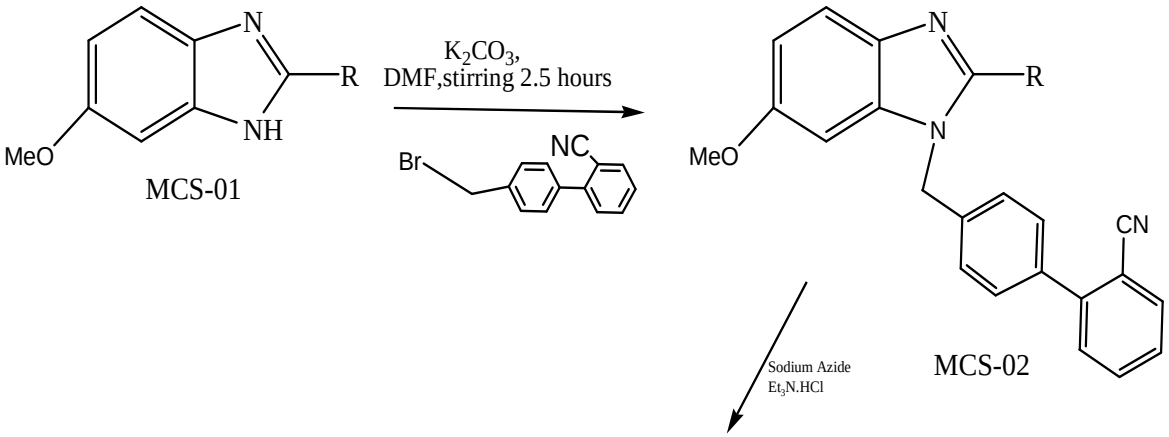
NH),4.96(s,2H,CH_2), 7.2-8.64 (m,14H,Ar-H), 3.73(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 20.5, 55.9,112.5, 113.2,115.4,116.2,121.1,128.4,135.5,138.2,148.5, 151.0, FAB-MS.535.24

[14]2-(4-iodo-phenyl)-6-methoxy-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazole
Yield: 68%,m.p. = 244-247 ^{0} c. Anal.Calcd for $C_{28}H_{21}IN_6O$:C,57.55;H, 3.64;N,14.38%; IR (KBr): 3468, 3311,3226, 3033,2859, 1655,1528-1529, 1242, 1258, 1171,1049,895,760.^{1}HNMR(300MHz,$CDCl_3$);13.24(s,1H,-NH-Benzimidazole), 10.43(s,1H,tetrazole-NH),4.93(s,2H,CH_2), 7.2-8.4 (m,14H,Ar-H), 3.73(s,3H,CH_3), ^{13}CNMR ($CDCl_3$)δ: 19.5, 50.3,112.1, 113.7,115.3,116.9,121.6,128.4,135.5,138.2,148.1, 151.31, FAB-MS.583.17

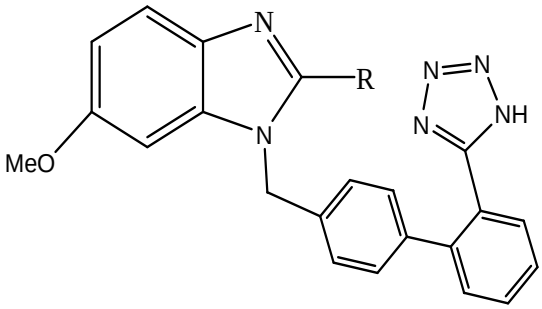
SCHEME



4-Methoxy-benzene-1,2-diamine MCS-01



MCS-01 MCS-02



Compound-1-14

MCS-03

Biological Activity: [21, 28-34]

Non-invasive Method (Indirect Method)

Albino rats weighing 150-250 gm were used to screening for all the synthesizes 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]

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
[1]	1	142	102	124	143	101	122
	2	145	105	125	145	100	121
	3	136	113	124	142	101	121
	4	139	113	122	140	100	120
	5	139	105	123	138	198	118
[2]	1	141	106	125	144	99	119
	2	140	111	124	139	97	120
	3	144	114	126	141	100	120

	4	141	112	123	139	96	117
	5	140	103	124	145	98	119
[3]	1	135	116	125	142	104	120
	2	139	112	124	146	102	121
	3	144	116	126	144	101	121
	4	142	114	123	142	103	122
	5	139	105	126	146	106	120
[4]	1	148	106	127	142	106	124
	2	151	109	130	146	104	125
	3	146	104	125	142	104	123
	4	144	106	125	140	102	121
	5	148	104	126	142	106	124
[5]	1	143	106	125	139	104	121
	2	146	110	128	140	104	122
	3	149	111	130	143	106	124
	4	152	112	133	145	103	124
	5	150	111	131	146	104	125
[6]	1	140	104	122	141	103	122
	2	138	106	123	140	106	123
	3	133	114	124	139	101	120
	4	142	105	124	135	107	121
	5	141	102	121	139	103	121
[7]	1	136	105	123	142	104	119
	2	135	102	122	140	97	119
	3	146	103	125	139	105	120
	4	149	101	125	143	101	121
	5	144	109	131	140	100	120
[8]	1	142	115	127	135	98	118
	2	140	106	123	142	101	121
	3	142	108	125	141	102	120
	4	139	110	125	143	101	120
	5	146	105	126	142	101	118
[9]	1	136	113	124	142	101	121
	2	142	112	127	140	103	121
	3	140	110	125	139	107	123
	4	138	106	122	141	103	122
	5	132	110	121	143	105	124
[10]	1	140	108	124	138	102	120
	2	144	106	125	142	101	123
	3	143	110	127	134	102	118
	4	138	107	128	143	101	121
	5	140	108	125	141	104	120
[11]	1	144	111	126	143	112	116
	2	144	106	125	144	109	128
	3	145	112	126	139	100	124
	4	142	109	126	143	111	126
	5	140	102	123	140	100	120
[12]	1	144	111	126	143	112	116

	2	144	106	125	144	109	128
	3	145	112	126	139	100	124
	4	142	109	126	143	111	126
	5	140	102	123	140	100	120
[13]	1	144	111	126	143	112	116
	2	144	106	125	144	109	128
	3	145	112	126	139	100	124
	4	142	109	126	143	111	126
	5	140	102	123	140	100	120
[14]	1	144	111	126	143	112	116
	2	144	106	125	144	109	128
	3	145	112	126	139	100	124
	4	142	109	126	143	111	126
	5	140	102	123	140	100	120
Control	**Losartan**	123	-	-	-	-	-
	Telmisartan	122	-	-	-	-	-

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	102	113	128	103	112
	2	121	101	113	123	102	111
	3	126	102	111	124	101	112
	4	121	100	110	125	102	111
	5	126	103	115	122	103	112
[2]	1	126	101	117	123	102	112
	2	131	100	123	121	106	110
	3	129	103	124	122	100	111
	4	133	105	118	127	104	114
	5	130	108	113	123	102	113
[3]	1	127	103	117	127	102	112
	2	122	102	119	124	102	113
	3	126	104	118	125	102	114
	4	125	101	113	128	102	115
	5	123	103	116	126	100	113
[4]	1	123	101	112	122	106	116
	2	124	102	113	124	102	113
	3	122	102	112	126	100	111
	4	124	102	113	128	100	114
	5	128	102	115	129	101	115
[5]	1	130	104	117	128	102	115
	2	125	105	115	124	101	112
	3	122	100	111	126	104	115
	4	125	100	112	121	107	114
	5	128	102	115	130	103	116
[6]	1	129	101	115	119	104	111

	2	123	107	115	121	99	110
	3	127	105	119	123	103	113
	4	129	100	111	126	104	115
	5	123	101	113	124	103	112
[7]	1	123	102	113	128	103	112
	2	144	114	129	142	102	121
	3	139	114	127	135	103	119
	4	142	106	124	140	102	123
	5	144	108	126	142	100	121
[8]	1	148	104	126	145	104	124
	2	144	106	125	144	100	122
	3	145	112	126	139	100	120
	4	142	109	126	143	97	120
	5	140	102	123	140	100	120
[9]	1	137	101	124	146	100	123
	2	129	108	119	124	104	114
	3	122	112	117	122	103	112
	4	125	105	115	122	100	112
	5	124	100	112	128	101	113
[10]	1	130	104	117	128	102	115
	2	125	105	115	124	101	112
	3	122	100	111	126	104	115
	4	128	102	115	130	103	116
	5	123	102	113	128	103	112
[11]	1	121	101	113	123	102	111
	2	126	102	111	124	101	112
	3	121	100	110	125	102	111
	4	126	103	115	122	103	112
	5	123	102	113	128	103	112
[12]	1	127	101	114	122	103	112
	2	125	106	117	127	101	112
	3	123	104	114	125	104	111
	4	129	102	119	121	102	110
	5	130	104	118	119	103	104
[13]	1	132	102	121	129	101	111
	2	123	101	119	122	101	113
	3	127	103	117	127	102	112
	4	122	102	119	124	102	113
	5	126	104	118	125	102	114
[14]	1	125	101	113	128	102	115
	2	123	103	116	126	100	113
	3	126	102	113	123	103	113
	4	123	101	112	122	106	116
	5	124	102	113	124	102	113
Control	**Losartan**	102	-	-	-	-	-
	Telmisartan	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	170	164	157	152	148	143	136	129	119	110
1	173	167	162	156	149	142	139	133	129	127
2	174	170	166	162	158	152	147	141	136	132
3	179	172	165	159	154	149	145	137	131	128
4	177	169	165	159	153	146	141	136	133	130
5	181	176	173	168	162	157	149	143	138	135
6	174	168	160	155	149	143	137	131	127	123
7	184	175	167	161	156	152	147	142	137	131
8	173	169	164	159	153	148	142	138	133	126
9	174	168	163	157	152	148	142	137	131	128
10	178	171	167	160	155	149	141	137	133	129
11	174	169	164	158	151	147	140	135	130	124
12	176	173	168	162	157	151	147	141	135	132
13	179	173	168	164	159	152	147	142	137	131
14	180	174	169	161	154	148	141	135	130	127

Table: 4 Antihypertensive Activity of synthesized compounds

Compound. No	Minimum Blood pressure value(mm Hg)	Duration of hypertension effect(min.)
Losratan	110	90
1	116	111
2	114	120
3	119	105
4	117	115
5	115	120
6	113	105
7	117	110
8	110	115
9	115	110
10	120	105
11	118	95
12	120	100
13	121	105
14	115	102

RESULTS AND DISCUSSION

4-methoxy-1, 2-phenylenediamine (1.0 mmol, 0.55gm), different substitute carboxylic acid (1.5 mmol), in the presence of BF_3•OEt_2 (0.5 mmol) to this reaction mixture, CH_2Cl_2 (50 mL) was added and washed with water then compound carboxylic acid substitute MCS-01 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. Different substituted 4'-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carbonitrile (1.0 g), sodium azide (1.5 g, 10.mmol), and Et3N·HCl (5.5 g, 14.12 mmol) in NH_4Cl (35 mL) is stirred at 40°C for 15 hours. 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 forteen compounds synthesized [1-14] showed antihypertensive activity. with compared the standard drug.

Acknowledgement
The authors are thankful to Head of Department School of Pharmacy D.A.V.V Indore to providing the facilities for IR spectra.

REFERENCES

[1] Brunner HR, Gavras H, Laragh JH, Keenan R.*Lancet*, **1973**, 1045–48.
[2] Brunner HR, Gavras H, Laragh JH.*Prog. Cardiovasc. Dis*, **1974**, 17, 87–98.
[3] Gavras H, Flessas A, Ryan TJ, Brunner HR, Faxon DP, Gavras I.*JAMA*, **1977**,238: 880–92.
[4] Sealey JE, Laragh, JH, Laragh, JH, Brenner BM. In *Hypertension Patho-physiology, Diagnosis and Management*; Eds.; Raven Press: New York, 1287-1317,**1990**
[5] McAreavey, D, Robertson JIS. *Drugs*, **1990**, 40, 326-345.
[6] Ondetti MA, Rubin A,Cushman DW.*Science*, **1977**, *196*, 441-444.
[7] Patchett A, Harris E, Tristram E, Wyvratt MJ, Wu MT, Taub D, Peterson E R, Ikeler TJ,Broeke J, Payne LG, Ondekya DL, Thorsett ED, Greenlee WJ, Lohr NS, Hoffsommer RD,Joshua H,Ruyle WJ, Rothrock JW, Aster SD,Maycock A L, Robinson F M,Hirschmann R,Sweet CS, Ulm EH, Gross DM, VassilTC, Stone A.*Nature*, **1980**, *288*, 280-283.
[8] VallottenM B. *Trends Pharamacol. Sci*, **1987**, *8*, 69-74.
[9] Erdoes EG, Skidgel RA.*Hypertension*, **1986**, *8*, 40-48.
[10] Nahmias C, Strosberg A. D, *Trends Pharmacol. Sci*, **1995**, 16, 223-225.
[11] Lindgren BR, Andersson RGG.*Med. Toxicol.Adverse Drug Exp*, **1989**, *4*, 369-380.
[12] Greenlee WJ, Renin inhibitors. *Med. Res. Rev*, **1990**, 10, 173-236.
[13] Timmermans PBMWM, Wong PC, Chiu AT, Herblin W F. *Trends Pharmacol. Sci*, **1991**, *12*, 55-62.
[14] Kleinert HD. *Exp. Opin. Invest. Drugs***, 1994**,3, 1087-1104.
[15] Dutta AS, Testa B, Ed.Academic Press: London, 21, 147-286, **1991**.
[16] McEwan JR, FullerRW. *J. Cardiovasc. Pharmacol*, **1989**,13 (Suppl. 3), S67-S69.
[17] Furukawa Y, Kishimoto S, Nishikawa S. *U.S. Patent* 4340598,(**1982**).
[18] Carini DJ, Duncia JV, Aldrich PE, Chiu AT, Johnson AL, Pierce ME, Price WA, Santella JB, Wells GJ, Wexler RR, Wong PC, Yoo SE, Timmermans PBMWM, *J. Med. Chem*, **1991**,34, 2525-2547.
[19] Bali A, Bansal Y, Sugumaran M, Saggu J.S, Balakumar P, Kaur G, Bansal G, Sharma A, Singh M, *Bioorg. Med. Chem. Lett*, **2005,** 15, 3962-3965.
[20] Dhvanit I S, Sharma M, Bansal Y,Bansal G, M. Singh, *European Journal of Medicinal Chemistry*, **2008**,43, 1808-1812.
[21] Jat RK, Jat JL, Pathak DP, *Euro. Journal. of Chemistry*., **2006**,3:(13), 278-285.
[22] Velik J, Baliharova V, Fink-GremmelsJ. *Res. Vet. Sci*, **2004**, *76*, 95.
[23] YadagiriB , Lown JW. *Synth. Commun*, **1990**, *20*, 955.
[24] Sun Q, YanB.*Bioorg. Med. Chem. Lett*, **1998**, *8*, 361.
[25] PrestonPN. Benzimidazoles and Congeneric Tricyclic Compounds, In The Chemistry of Heterocyclic Compounds, Eds. Weissberger, A. Taylor, E. C, Wiley: NewYork, Part 1, Vol. 40, **1981**, 6-60.
[26] GrimmettMR. Imidazoles and their Benzo Derivatives, In Comprehensive Heterocyclic Chemistry, Vol. 5, Eds.: Pergamon: Oxford, **1984**, 457-487
[27] Rahul RNagawade, Devanand B Shinde.*Chinese Chemical Letters* ,17,4, 453-456, **2006**.
[28] Shanmugapandiyan P, Denshing KS, R. Ilavarasan N Anbalagan, Nirmal R, *Int. J. of Pharma. Scienc and Drug Research*, **2010**; 2(2): 115-119
[29] Badyal DK, Lata H, Dadhich AP, *Indian J of Pharmacology*, **2003**, 35(66), 349-362.
[30] Bunag RD, McCubbin JW, Page IH, *Cardiovasc.Res*,**1971**,5(1): 24-31.

[31] Gupta SK, Drug Screening methods, Jaypee Brothers Medical Publisher, New Delhi, **2004,** pp 236-246.
[32] Shreenivas MT, Chetan BP, Bhat AR, *J. of Pharma.Sci. And Technology*, **2009**, 1 (2), 88-94.
[33] Siddiqui AA, Wani M.S, *Indian.J.Chemistry*, **2004**, 43B,pp. 1574-1579.
[34] Vogel G.H.Drug Discovery and Evaluation, Pharmacological Assay, **2002**; (Springer. Berlin), 122. 24-31.