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A rational approach for synthesis, characterization and antihypertensive activity evaluation of 1-(4-{5-amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(substituted -phenyl)-azetidin-2-ones

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ABSTRACT

A new series of 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(Substituted -phenyl)-azetidin-2-one derivatives MCS 06[1-15] has been synthesized and subjected to evaluate their antihypertensive activity. All the synthesized compounds of the series elicit remarkable activity in comparison to standard drug (Losartan). Structures of the synthesized compounds have been elucidated on the basis of their elemental analyses and spectral data.

Keywords: azetidin-2-one, Angitotensin II, Losartan, antihypertensive agents.

INTRODUCTION

Ang II receptor antagonists have proved to lower blood pressure effectively, and they are better tolerated than other classes of drugs. 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]. The octapeptide angiotensin II (Ang II) produced by the rennin angiotensin system (RAS) is a potent vasoconstrictor and thus plays an integral role in the pathophysiology of hypertension. This directed many researchers toward designing drugs to block the effects of Ang II either by inhibiting the angiotensin converting enzyme (ACE) or renin or by blocking the Ang II receptors. 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 affecting an increase in vascular resistance, the regulation of volemia through the stimulated release of vasopressin and

aldosterone, which induces saline retention, and the regulation of the adrenocorticotropic hormone (ACTH). Thus, reducing the levels of AII by inhibition of one of the RAS enzymes or directly blocking the AII receptors is in theory a good approach for treating hypertension, confirmed by the success of angiotensin-converting enzyme (ACE) inhibitors as antihypertensives [4]. Hypertension is one of the most important cardiovascular risk factor but its control is still Challenge for physicians all around the world. Antihypertensive are a class of drugs that are used in medicine and pharmacology to treat hypertension (high blood pressure). All Hypertensive drugs cause dizziness, ankle swelling, headache, fatigue, chest discomfort and cough. This review focus on the adverse effects of Antihypertensive drugs, severity of these adverse effects and attempts made to prevention and treatment of hypertension by non-pharmacological intervention. Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported[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]. Among them, 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]. 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[8] 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, Cozaar). The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity[10]. Compounds containing tetrazole nucleus are also reported as AT1 receptor antagonists and their protypical derivative exhibits non-competitive antagonism11 and amino group attach with carboxylic group given good biological activity [11-12]. In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives as a source of new antimicrobial agents. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocycles, which are the structural isosters of nucleotides owing fused heterocyclic nuclei in their structures that allow them to interact easily with the biopolymers, possess potential activity with lower toxicities in the antihypertensive activity approach.

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.

MS-01- Synthesis of 4-(6-fluoro-1H-benzoimidazol-2-yl)-phenyl amine

A solution of 4-fluoro-1,2-phenylenediamine dihydrochloride (0.45 g, 2.5 mmol) in 5 ml of water was cooled to 0°C and treated with a solution of cyanogen bromide (0.60 ml, 5 M in acetonitrile, 3.0 mmol) and solid $NaHCO_3$ (0.41 mg, 4.9 mmol). The solution was stirred at ambient temperature for 40-45 h. The mixture was made basic with 1 M aqueous Na_2CO_3 and

the solution was concentrated under reduced pressure. The residue was triturated with hot ethanol, and the ethanolic solution was filtered and concentrated under reduced pressure to obtain the compound 1 in appreciable yield.

MS-02- 4-(6- fluoro -5-nitro-1H-benzoimidazol-2-yl)-phenyl amine

Thirty five 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. After stirred continuously for 14 hrs minutes and then the reaction mixture were 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.

MS-03- [4-(6-Fluoro-5-nitro-1H-benzoimidazol-2-yl)-phenyl]-(2-substituted-benzylidene)-amine

Dissolve 4-(6-Chloro -5-nitro-1H-benzoimidazol-2-yl)-phenyl amine (1.5 g, 0.01 mole) in absolute ethanol (100 mL) and acetyl chloride (1.5 g, 0.01 mole) was added drop wise with then compound (different R-aryl groups) (15.10 gm) was mixed in portions during 2 hour under room temperature. The reaction mixture was stirred for 6 hrs. The excess solvent was distilled off and the solid product was filtered, dried and recrystallised from ethanol to give compound yield

MS-04- 3-Chloro-1-[4-(6-fluoro-5-nitro-1H-benzoimidazol-2-yl)-phenyl]-4-substituted-azetidin-2-one

Chloroacetyl chloride (0.01mol) was added drop wise to a mixture of Schiff base (0.01mol) and triethylamine (0.02 mol) in dioxane (25 ml) at room temperature. The mixture was stirred for 8 h and allowed to stand at room temperature for 3 days. The contents were poured on crushed ice and the precipitate obtained was filtered, washed with 10 % w/v sodium bicarbonate solution, vacuum dried and recrystallised using absolute ethanol.

MS-05- 4'-{2-[4-(3-Chloro-2-oxo-4-substituted-azetidin-1-yl)-phenyl]-6-fluoro-5-nitro-1H-benzo imidazol-1-ylmethyl}-biphenyl-2-carbonitrile

To a solution of 260 mg (1.0 mmol) compound aryl substitute 50 mL of DMF was added potassium carbonate 2.0 g (7.5 mmol), the mixture was stirred for 2.5 hours at room temperature, and 4-(bromomethyl) biphenyl-2'-nitrile 1.5 g (15.10 mmol) was added. After stirring for 14 hours the mixture was poured into distilled water (150 mL) and extracted with diethyl ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated.

MS-06- 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimida zol-2-yl}-phenyl)-3-chloro-substituted-azetidin-2-one

A mixture of different substituted 4'-{2-[4-(3-Chloro-2-oxo-4-substituted-azetidin-1-yl)-phenyl]-6-fluoro-5-nitro-1H-benzoimidazol-1-ylmethyl}-biphenyl-2-carbonitrile (65 mg, 1.00 mmol), sodium azide (4.5 g, 15.0 mmol), and $Et_3N{\cdot}HCl$ (4.0 g, 16.0 mmol) in NH_4Cl (70 mL) is stirred at 35°C for 8 hours. After cooling, the mixture is diluted with distilled water (50 mL), acidified to pH 4.5 with 4N HCl, and extracted with EtOAc (3 × 50 mL). The organic layer was washed with ether (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.

Then 2.5 gm of compound was placed in three necked RBF and dissolved in absolute ethanol and heated to 60^0C 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.

Compounds and Spectral data

[1] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(2-chloro-phenyl)-azetidin-2-one

Yield: 80%, m.p. = 243-247^{o}C. Anal. Calcd for $C_{36}H_{25}Cl_2FN_8O$: Found: C, 64.01; H, 3.73; N, 16.59%; IR (KBr): 3662, 3470, 3351, 3241, 3095, 2911, 1645, 1517, 1558-1318, 654. ^{1}HNMR(300MHz, $CDCl_3$), 13.12(1H, s, -NH Benzimidazole), 10.77(s, 1H, tetrazole-NH), 4.98(s, 2H, CH_2), 6.7-8.5(m, 19H, Ar-H), 5.10(s, 2H, arm-NH_2), ^{13}CNMR($CDCl_3$)δ: 58.2, 112.1, 113.3, 115.5, 122.2, 124.5, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.6, FAB-MS, 674.15.

[2] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(3-chloro-phenyl)-azetidin-2-one

Yield: 73%, m.p. = 254-257^{o}C. Anal. Calcd for $C_{36}H_{25}Cl_2FN_8O$: Found: C, 64.01; H, 3.73; N, 16.59%; IR (KBr): 3662, 3470, 3351, 3241, 3095, 2911, 1645, 1517, 1558-1311, 654. ^{1}HNMR(300MHz,$CDCl_3$), 13.12(1H, s, -NH Benzimidazole), 10.77(s, 1H, tetrazole-NH), 4.98(s, 2H, CH_2), 6.7-8.5(m, 19H, Ar-H), 5.10(s, 2H, arm-NH_2). ^{13}CNMR($CDCl_3$)δ: 58.2, 112.1, 113.3, 115.5, 122.2, 124.5, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.6, FAB-MS, 675.63.

[3] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(4-chloro-phenyl)-azetidin-2-one

Yield: 73%, m.p. = 254-257^{o}C. Anal. Calcd for $C_{36}H_{25}Cl_2FN_8O$: Found: C, 64.01; H, 3.73; N, 16.59%; IR (KBr): 3662, 3470, 3351, 3241, 3095, 2911, 1645, 1517, 1558-1308, 654. ^{1}HNMR(300MHz, $CDCl_3$), 13.12(1H, s, -NH Benzimidazole), 10.77(s, 1H, tetrazole-NH), 4.98(s, 2H, CH_2), 6.7-8.5(m, 19H, Ar-H), 5.10(s, 2H, arm-NH_2), ^{13}CNMR($CDCl_3$)δ: 58.2, 112.1, 113.3, 115.5, 122.2, 124.5, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.6, FAB-MS, 676.87.

[4] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -4-(2-Bromo-phenyl)-3-chloro-azetidin-2-one

Yield: 66%, m.p. = 277-279^{o}C. Anal. Calcd for $C_{36}H_{25}BrClFN_8O$: Found: C, 60.05; H, 3.53; N, 15.56%; IR (KBr): 3697, 3446, 3321, 3242, 3187, 3065, 2966, 1648, 1512, 1531-1319, 651. ^{1}HNMR(300MHz, $CDCl_3$), 13.16(1H, s, -NH-Benzimidazole), 10.95(s, 1H, tetrazole-NH), 4.99(s, 2H, CH_2), 6.72-8.59(m, 19H, Ar-H), 5.15(s, 2H, arm-NH_2), ^{13}CNMR($CDCl_3$)δ: 54.6, 111.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.3, 141.97, FAB-MS, 719.04.

[5] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -4-(3-Bromo-phenyl)-3-chloro-azetidin-2-one

Yield: 60%, m.p. = 279-282^{o}C. Anal. Calcd for $C_{36}H_{25}BrClFN_8O$: Found: C, 60.05; H, 3.53; N, 15.56%; IR (KBr): 3697, 3446, 3321, 3242, 3065, 2966, 1648, 1512, 1531-1399, 651. ^{1}HNMR(300MHz, $CDCl_3$), 13.16(1H, s, -NH-Benzimidazole), 10.95(s, 1H, tetrazole-NH), 4.99(s, 2H, CH_2), 6.72-8.59(m, 19H, Ar-H), 5.15(s, 2H, arm-NH_2). ^{13}CNMR($CDCl_3$)δ: 54.6, 111.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.3,141.9, FAB-MS, 718.11.

[6] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -4-(4-Bromo-phenyl)-3-chloro-azetidin-2-one

Yield: 56%, m.p. = 269-271^{o}C. Anal. Calcd for $C_{36}H_{25}BrClFN_8O$: Found: C, 60.05; H, 3.53; N, 15.56%; IR (KBr): 3697, 3446, 3321, 3242, 3065, 2966, 1648, 1512, 1531-1339, 651. ^{1}HNMR(300MHz, $CDCl_3$), 13.16(1H, s, -NH-Benzimidazole), 10.95(s, 1H, tetrazole-NH), 4.99(s, 2H, CH_2), 6.72-8.59(m, 19H, Ar-H), 5.15(s, 2H, arm-NH_2), ^{13}CNMR($CDCl_3$)δ: 54.6,

111.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.3, 141.9, FAB-MS, 719.86.

[7] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(2-hydroxy-phenyl)-azetidin-2-one
Yield: 66%, m.p. = 194-196^{o}C. Anal. Calcd for $C_{36}H_{26}ClFN_8O_2$: Found: C, 65.81; H, 3.99; N, 17.06%; IR (KBr): 3618, 3473, 3397, 3242, 3022, 2942, 1664, 1510, 1539-1359, 651. ^{1}HNMR(300MHz, $CDCl_3$), 13.10(1H, s, -NH-Benzimidazole), 10.85(s, 1H, tetrazole-NH), 4.95(s, 2H, CH_2), 6.7-8.6(m, 19H, Ar-H), 4.99(s, 2H, arm-NH_2), 5.02(s, 1H, armomatic-OH). ^{13}CNMR($CDCl_3$)δ: 48.9, 110.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.38, FAB-MS, 719.86.

[8] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(3-hydroxy-phenyl)-azetidin-2-one
Yield: 61%, m.p. = 186-188^{o}C. Anal. Calcd for $C_{36}H_{26}ClFN_8O_2$: Found: C, 65.81; H, 3.99; N, 17.06%; IR (KBr): 3618, 3473, 3397, 3242, 3022, 2942, 1664, 1510, 1539-1359, 651. ^{1}HNMR(300MHz,$CDCl_3$), 13.10(1H, s, -NH-Benzimidazole), 10.85(s, 1H, tetrazole-NH), 4.95(s, 2H, CH_2), 6.7-8.6(m, 19H, Ar-H), 4.99(s, 2H, arm-NH_2), 5.02(s, 1H, armomatic-OH). ^{13}CNMR($CDCl_3$)δ: 48.9, 110.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.38, FAB-MS, 719.66.

[9] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(4-hydroxy-phenyl)-azetidin-2-one
Yield: 55%, m.p. = 191-193^{o}C. Anal. Calcd for $C_{36}H_{26}ClFN_8O_2$: Found: C, 65.81; H, 3.99; N, 17.06%; IR (KBr): 3618, 3473, 3397, 3242, 3022, 2942, 1664, 1510, 1539-1359, 651. ^{1}HNMR(300MHz, $CDCl_3$), 13.10(1H, s, -NH-Benzimidazole), 10.85(s, 1H, tetrazole-NH), 4.95(s, 2H, CH_2), 6.7-8.6(m, 19H, Ar-H), 4.99(s, 2H, arm-NH_2), 5.02(s, 1H, armomatic-OH). ^{13}CNMR($CDCl_3$)δ: 48.9, 110.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.38, FAB-MS, 720.02.

[10] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-*o*-tolyl-azetidin-2-one;
Yield: 77%, m.p.=203-206^{o}C. Anal. Calcd $C_{36}H_{28}ClFN_8O$: Found: C, 67.83; H, 4.31; N, 17.10%; IR(KBr): 3603, 3529, 3430, 3375, 3202, 3086, 2911, 1660, 1557, 1519, 1322. ^{1}HNMR(300MHz, $CDCl_3$), 13.34(1H, s, NH-Benzimidazole), 10.58(s, 1H, tetrazole-NH), 4.99(s, 2H, CH_2), 6.8-8.5(m, 19H, ArH), 4.99(s, 2H, NH_2), 2.33(s, 3H, CH_3). ^{13}CNMR($CDCl_3$)δ: 18.86, 49.6, 110.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.65, FAB-MS, 719.66.

[11] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-*m*-tolyl-azetidin-2-one
Yield: 61%, m.p.=199-203^{o}C. Anal. Calcd $C_{36}H_{28}ClFN_8O$: Found: C, 67.83; H, 4.31; N, 17.10%; IR(KBr): 3603, 3529, 3430, 3375, 3202, 3086, 2911, 1660, 1557, 1519, 1322. ^{1}HNMR(300MHz, $CDCl_3$), 13.34(1H, s, NH-Benzimidazole), 10.58(s, 1H, tetrazole-NH), 4.99(s, 2H, CH_2), 6.8-8.5(m, 19H, ArH), 4.99(s, 2H, NH_2), 2.33(s, 3H, CH_3). ^{13}CNMR($CDCl_3$)δ: 18.86, 49.6, 110.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.65, FAB-MS, 718.42.

[12] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-*p*-tolyl-azetidin-2-one
Yield: 63%, m.p.=210-212^{o}C. Anal. Calcd $C_{36}H_{28}ClFN_8O$: Found: C, 67.83; H, 4.31; N, 17.10%; IR(KBr): 3603, 3529, 3430, 3375, 3202, 3086, 2911, 1660, 1557, 1519, 1322. ^{1}HNMR(300MHz, $CDCl_3$), 13.34(1H, s, NH-Benzimidazole), 10.58(s, 1H, tetrazole-NH), 4.99(s, 2H, CH_2), 6.8-

8.5(m, 19H, ArH), 4.99(s, 2H, NH_2), 2.33(s, 3H, CH_3). ^{13}CNMR($CDCl_3$)δ: 18.86, 49.6, 110.1, 112.3, 114.5, 120.2, 126.7, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8, 139.65, FAB-MS, 720.11.

[13] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(2-methoxy-phenyl)-azetidin-2-one

Yield: 66%, m.p.=233-236^{o}C. Anal. Calcd $C_{37}H_{28}ClFN_8O_2$: Found: C, 66.22; H, 4.21; N, 16.70%; IR(KBr): 3609, 3531, 3439, 3345, 3272, 3026, 2961, 1643, 1517, 1586, 1321. ^{1}HNMR(300MHz, $CDCl_3$), 13.31(1H, s, NH-Benzimidazole), 10.21(s, 1H, tetrazole-NH), 4.92(s, 2H, CH_2), 6.9-8.7(m, 19H, ArH), 4.91(s, 2H, NH_2), 3.75(s, 3H, CH_3). ^{13}CNMR($CDCl_3$)δ: 19.21, 53.1, 112.1, 113.3, 113.5, 121.2, 122.7, 125.3, 133.2, 133.1, 134.3, 135.2, 137.8, 139.22, 140.21, FAB-MS, 670.05.

[14] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(3-methoxy-phenyl)-azetidin-2-one

Yield: 60%, m.p.=227-229^{o}C. Anal. Calcd $C_{37}H_{28}ClFN_8O_2$: Found: C, 66.22; H, 4.21; N, 16.70%; IR(KBr): 3609, 3531, 3439, 3345, 3272, 3026, 2961, 1643, 1517, 1586, 1321. ^{1}HNMR(300MHz, $CDCl_3$), 13.31(1H, s, NH-Benzimidazole), 10.21(s, 1H, tetrazole-NH), 4.92(s, 2H, CH_2), 6.9-8.7(m, 19H, ArH), 4.91(s, 2H, NH_2), 3.75(s, 3H, CH_3). ^{13}CNMR($CDCl_3$)δ: 19.21, 53.1, 112.1, 113.3, 113.5, 121.2, 122.7, 125.3, 133.2, 133.1, 134.3, 135.2, 137.8, 139.22, 140.21, FAB-MS, 672.42.

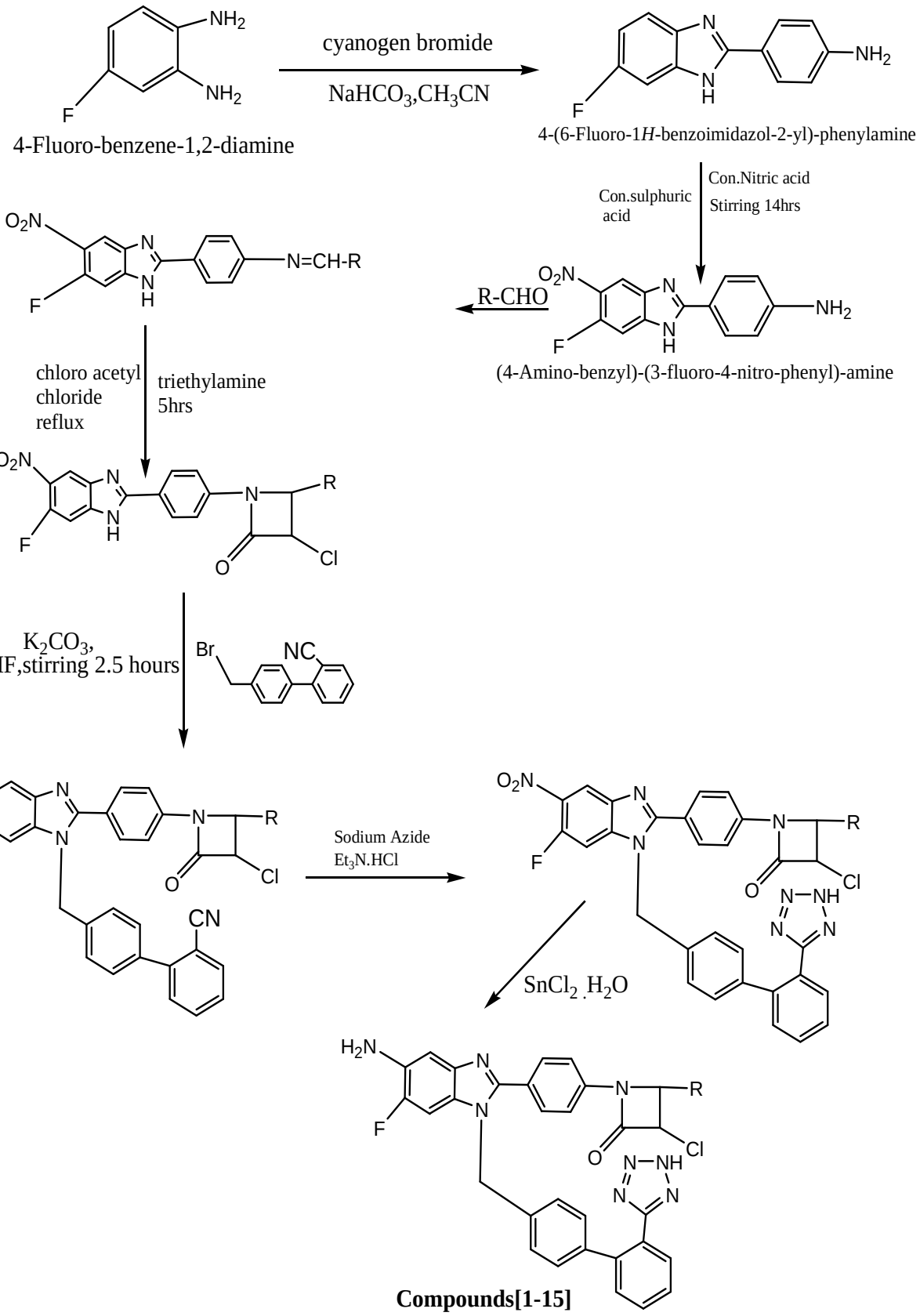
[15] 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-3-chloro-4-(4-methoxy-phenyl)-azetidin-2-one

Yield: 61%, m.p.=230-232^{o}C. Anal. Calcd $C_{37}H_{28}ClFN_8O_2$: Found: C, 66.22; H, 4.21; N, 16.70%; IR(KBr): 3609, 3531, 3439, 3345, 3272, 3026, 2961, 1643, 1517, 1586, 1321. ^{1}HNMR(300MHz, $CDCl_3$), 13.31(1H, s, NH-Benzimidazole), 10.21(s, 1H, tetrazole-NH), 4.92(s, 2H, CH_2), 6.9-8.7(m, 19H, ArH), 4.91(s, 2H, NH_2), 3.75(s, 3H, CH_3). ^{13}CNMR($CDCl_3$)δ: 19.21, 53.1, 112.1, 113.3, 113.5, 121.2, 122.7, 125.3, 133.2, 133.1, 134.3, 135.2, 137.8, 139.22, 140.21, FAB-MS, 671.02.

Pharmacological Activity [12-18]

Non-invasive Tail cuff Method: Albino rats weighing 200-250 gm were used to screening for all the synthesized 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.

SCHEME



Compounds[1-15]

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	144	109	131	140	100	120
	2	142	113	125	142	102	122
	3	141	109	123	144	101	121
	4	144	114	129	141	104	120
	5	146	104	132	142	100	121
[2]	1	143	111	125	143	100	121
	2	141	114	126	139	102	120
	3	140	112	126	143	100	122
	4	144	116	130	145	98	119
	5	144	106	125	144	100	122
[3]	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
[4]	1	142	108	125	138	100	119
	2	140	104	122	144	106	125
	3	142	106	124	140	106	121
	4	146	104	125	144	104	120
	5	140	114	127	136	100	121
[5]	1	148	108	126	144	102	123
	2	151	112	133	146	101	124
	3	144	114	129	142	102	121
	4	139	114	127	135	103	119
	5	142	106	124	140	102	123
[6]	1	144	108	126	142	100	121
	2	148	104	126	145	104	124
	3	143	106	124	141	101	122
	4	141	110	129	142	108	125
	5	138	105	125	139	107	123
[7]	1	132	104	128	142	102	122
	2	142	103	123	140	102	121
	3	141	110	124	143	105	123
	4	140	105	128	138	104	121
	5	139	108	124	141	103	122
[8]	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
[9]	1	140	102	121	140	103	121
	2	138	104	122	137	104	120
	3	142	112	127	139	102	121
	4	140	108	124	143	101	122

	5	137	104	121	140	103	121
[10]	1	138	106	122	137	101	119
	2	143	110	127	134	102	118
	3	137	102	124	135	102	118
	4	139	107	123	140	101	120
	5	143	109	126	137	104	120
[11]	1	141	109	125	139	102	120
	2	143	103	123	141	103	122
	3	140	106	123	138	101	119
	4	138	104	121	140	106	123
	5	141	109	125	143	106	124
[12]	1	136	112	124	141	103	122
	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
[13]	1	141	111	126	139	104	121
	2	144	105	124	139	103	122
	3	140	113	127	142	107	124
	4	138	104	121	143	103	123
	5	138	105	122	143	107	123
[14]	1	139	112	122	142	108	125
	2	135	109	124	138	102	120
	3	140	106	121	137	102	120
	4	144	106	125	142	104	123
	5	146	108	124	140	103	120
[15]	1	138	112	125	138	100	119
	2	139	102	122	143	100	121
	3	148	104	124	143	102	122
	4	146	112	128	137	101	118
	5	143	108	126	140	103	121
Control	**Losartan**	121	-	-	-	-	-

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	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
[2]	1	125	105	115	127	101	114
	2	120	102	111	123	101	112
	3	125	103	114	126	100	113
	4	122	100	111	128	103	114
	5	125	101	113	121	101	110
[3]	1	123	107	115	125	100	112

	2	126	103	114	126	96	111
	3	129	101	115	119	104	111
	4	123	107	115	121	99	110
	5	127	105	119	123	103	113
[4]	1	121	100	110	125	102	111
	2	126	103	115	122	103	112
	3	124	102	113	126	100	113
	4	122	101	112	126	103	112
	5	126	104	115	124	102	113
[5]	1	128	102	115	126	104	115
	2	131	103	117	124	102	113
	3	128	104	118	122	106	114
	4	129	103	119	129	104	111
	5	126	101	117	123	102	112
[6]	1	131	100	123	121	106	110
	2	129	103	124	122	100	111
	3	133	105	118	127	104	114
	4	130	108	113	123	102	113
	5	127	105	118	126	102	114
[7]	1	124	106	122	122	101	111
	2	123	102	119	127	101	110
	3	122	104	118	124	98	113
	4	127	108	119	126	103	109
	5	128	102	116	125	101	106
[8]	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
[9]	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
[10]	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
[11]	1	122	102	112	126	100	111
	2	124	102	113	128	100	114
	3	128	102	115	129	101	115
	4	128	106	117	123	100	112
	5	127	101	116	125	105	110
[12]	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	130	99	115	126	98	112
[13]	1	126	101	117	123	97	110
	2	128	103	115	120	103	112
	3	124	96	110	124	106	115
	4	127	101	114	123	102	112
	5	121	103	112	121	97	109
[14]	1	120	100	115	128	100	114
	2	128	98	113	131	99	115
	3	131	105	118	124	101	115
	4	126	103	114	128	106	117
	5	124	106	115	127	104	116
[15]	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
Control	**Losartan**	104	-	-	-	-	-

RESULTS AND DISCUSSION

Synthesis compounds were screened for their antihypertensive activity by methods using 200-250 gm male either sex.the rats having hypertension more than 160 mm of Hg were taken for the experiment. All the fifteen compounds synthesized [1-15] showed antihypertensive activity and with compared the standard drug. Substitution with chlorine, methoxy, hydroxyl, bromo in benzimidazole ring also changes biological activity. When amino group was substituted at position 5; it increased the force of contraction of aantihypertensive activity.

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