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Efficient Synthesis and Pharmacological Evaluation of 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(substituted) - thiazolidin-4-one as Potent Antihypertensive Agents

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ABSTRACT

Several substituted-benzimidazole 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(substituted)- thiazolidin-4-one were synthesized by condensation of various steps with various substituted aryl aldehydes reaction. Elemental analysis, IR, 1HNMR and mass spectral data confirmed the structure of the newly synthesized compounds. Synthesized and subjected to evaluate their antihypertensive activity. All the synthesized compounds of the series elicit remarkable activity in comparison to standard drug (Losartan).

Keywords: thiazolidin-4-one, Angitotensin II, antihypertensive agent.

INTRODUCTION

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. 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 re-absorption, and nor epinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension. 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 antihypertensives[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 prostag-landin[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 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 AT_1-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. 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 12 000 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 (AT_1) and type 2 (AT_2)]. In particular, AT_1 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 AT_1 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 AT_1 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]. Moreover, these fused heterocyclic were distinctively studied for their antihypertensive activity, antitumor, antiviral and antimicrobial activities as the new nonnucleoside topoisomerase I poisons, human immunodeficiency virus-1 reverse transcriptase inhibitors and or potent DNA gyrase inhibitors[30-31]. 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 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. 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.

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 ethanol solution was filtered and concentrated under reduced pressure to obtain the compound **1** in appreciable yield.

MS-02- Synthesis of 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- Synthesis of [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- Synthesis of 2-(Substituted-phenyl)-3-[4-(6-Fluoro-5-nitro-1H-benzoimidazol-2-yl)-phenyl]-thiazolidin-4-one

To a mixture of Schiff base (1.0 mol) and mercaptoacetic acid (0.15 mol) dissolved in dioxane (50 ml), anhydrous zinc chloride (0.8 mol) was added and refluxed for 12 hrs. The reaction mixture was cooled, filtered, washed with 10 % w/v sodium bicarbonate solution, vacuum dried and recrystallised using absolute ethanol. Compounds [7a-7l].

MS-05- Synthesis of 4'-{2-[4-(2-(substituted-phenyl)-4-oxo-thiazolidin-3-yl]-phenyl}-6-fluoro-5-nitro-benzoimidazol -1-ylmethyl}-biphenyl-2-carbonitrile

To a solution of 110 mg (1.5 mol) compound aryl substitute 50 mL of DMF was added potassium carbonate 5.0 g (11.5 mmol), the mixture was stirred for 4 hours at room temperature, and 4-(bromomethyl) biphenyl-2'-nitrile 2.25 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- Synthesis of 3-(4-{6-fluoro-5-nitro-1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-substituted- thiazolidin-4-one

A mixture of different substituted 4'-{2-[4-(2-(substituted-phenyl)-4-oxo-thiazolidin-3-yl]-phenyl}-6-fluoro-5-nitro-benzoimidazol -1-ylmethyl}-biphenyl-2-carbonitrile (80 mg, 1.65 mmol), sodium azide (3.8 g, 15.0 mmol), and $Et_3N{\cdot}HCl$ (5.0 g, 11.0 mmol) in NH_4Cl (50 mL) is stirred at 35°C for 10hours. 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.

MS-07- 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimi-dazol-2-yl}-phenyl) -2-(substituted)- thiazolidin-4-one

1.02 gm of substituted compounds 3-(4-{6-fluoro-5-nitro-1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl)-substituted- thiazolidin-4-one was placed in three necked RBF and dissolved in absolute ethanol and heated to 55^0 C under reflux. To this, 3.5 gm stannous chloride dihydrate was added with slow stirring during 3 hours and reaction conditions were maintained for further 10 hours. The mixture was cooled to room temperature and pH adjusted to 7.6 with 25% 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 analysis

[7a]3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimida-zol-2-yl}-phenyl) -2-(2-chloro-phenyl)- thiazolidin-4-one; Yield: 84%, m.p.=211-215°C. Anal. Calcd for $C_{36}H_{26}ClFN_8OS$: Found: C, 64.22; H, 3.89; N, 16.64%; IR(KBr): 3617, 3549, 3427,

3194, 3066, 2883, 2785, 1615, 1553, 1418, 1186, 885. ^{1}HNMR(300MHz,$CDCl_3$): 13.3(1H, s, NH Benzimidazole), 10.13(s, 1H, tetrazole-NH), 6.6- 8.66(m, 19H, ArH), 3.98(*d*, 2H, arm NH_2), 3.31(s, 2H, CH_2), 5.87(s, 1H, CH): ^{13}CNMR($CDCl_3$)δ: 47.3, 50.8, 111.1, 112.5, 114.1, 121.2, 123.5, 128.2, 130.2, 133.1, 134.3, 137.1, 138.4, FAB-MS, 672.19.

[7b] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(4-chloro-phenyl)- thiazolidin-4-one

Yield: 79%, m.p.=218-220^{o}C. Anal. Calcd for $C_{36}H_{26}ClFN_8OS$: Found: C, 64.22; H, 3.89; N, 16.64%; IR(KBr): 3617, 3549, 3427, 3194, 3066, 2883, 2785, 1615, 1553, 1418, 1186, 885. ^{1}HNMR(300MHz, $CDCl_3$), 13.3(1H, s, NH Benzimidazole), 10.13(s, 1H, tetrazole-NH), 6.6-8.66(m, 19H, ArH), 3.98(*d*, 2H, arm NH_2), 3.31(s, 2H, CH_2), 5.87(s, 1H, CH), ^{13}CNMR($CDCl_3$)δ: 48.3, 50.8, 111.1, 112.5, 114.1, 121.2, 123.5, 128.2, 130.2, 133.1, 134.3, 137.1, 138.4, FAB-MS, 673.51.

[7c] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(2-iodo-phenyl)- thiazolidin-4-one

Yield: 65%, m.p.=266-269^{o}C. Anal. Calcd for $C_{36}H_{26}IFN_8OS$: Found: C, 56.55; H, 3.43; N, 14.65%; IR(KBr): 3661, 3519, 3494, 3144, 3060, 2853, 2730, 1632, 1522, 1439, 1176, 889. ^{1}HNMR(300MHz, $CDCl_3$); 13.17(1H, s, NH Benzimidazole), 10.49(s, 1H, tetrazole-NH), 6.7-8.60(m, 19H, ArH), 4.06(*d*, 2H, arm NH_2), 3.36(s, 2H, CH_2), 5.94(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 56.2, 59.7, 112.8, 113.4, 116.2, 117.2, 126.5, 130.1, 132, 133.8, 135.1, 136.3, 139.95, 140.4, FAB-MS, 764.054.

[7d] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(4-iodo-phenyl)- thiazolidin-4-one

Yield: 63%, m.p.=273-276^{o}C. Anal. Calcd for $C_{36}H_{26}IFN_8OS$: Found: C, 56.55; H, 3.43; N, 14.65%; IR(KBr): 3661, 3519, 3494, 3144, 3060, 2853, 2730, 1632, 1522, 1439, 1176, 889; ^{1}HNMR(300MHz, $CDCl_3$) 13.17(1H, s, NH Benzimidazole), 10.49(s, 1H, tetrazole-NH), 6.7-8.60(m, 19H, ArH), 4.06(*d*, 2H, arm NH_2), 3.36(s, 2H, CH_2), 5.94(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 52.3, 55.7, 112.8, 113.4, 116.2, 117.2, 126.5, 130.1, 132.133.8, 135.1, 136.3, 139.95, 140.4, FAB-MS, 765.632.

[7e] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(2-bromo-phenyl)- thiazolidin-4-one

Yield: 58%, m.p.=293-296^{o}C. Anal. Calcd for $C_{36}H_{26}BrFN_8OS$: Found: C, 60.25; H, 3.65; N, 15.62%; IR(KBr): 3668, 3514, 3499, 3165, 3068, 2857, 2721, 1602, 1584, 1449, 1163, 883; ^{1}HNMR(300MHz, $CDCl_3$): 13.28(1H, s, NH Benzimidazole), 10.66(s, 1H, tetrazole-NH), 6.78-8.63(m, 19H, ArH), 4.01(*d*, 2H, arm NH_2), 3.38(s, 2H, CH_2), 5.90(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 50.2, 52.5, 111.1, 112, 114, 115.2, 119.3, 124.5, 126.0, 127.2, 127.5, 127.9, 133.2, 134.2, 138, 141.51, FAB-MS, 716.118.

[7f] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(4-bromo-phenyl)- thiazolidin-4-one

Yield: 68%, m.p.=291-293^{o}C. Anal. Calcd for $C_{36}H_{26}BrFN_8OS$: Found: C, 60.25; H, 3.65; N, 15.62%; IR(KBr): 3668, 3514, 3499, 3165, 3068, 2857, 2721, 1602, 1584, 1449, 1163, 883; ^{1}HNMR(300MHz, $CDCl_3$): 13.28(1H, s, NH Benzimidazole), 10.66(s, 1H, tetrazole-NH), 6.78-8.63(m, 19H, ArH), 4.01(*d*, 2H, arm NH_2), 3.38(s, 2H, CH_2), 5.90(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 49.2, 52.5, 111.1, 112, 114, 115.2, 119.3, 124.5, 126.0, 127.2, 127.5, 127.9, 133.2, 134.2, 138, 141.51, FAB-MS, 717.218.

[7g] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(2-hydroxy-phenyl)- thiazolidin-4-one
Yield: 73%, m.p.=244-246^{o}C. Anal. Calcd for $C_{36}H_{27}FN_8O_2S$: Found: C, 66.05; H, 4.15; N, 17.13%; IR(KBr): 3661, 3518, 3479, 3135, 3041, 2844, 2728, 1642, 1580, 1469, 1161, 881; ^{1}HNMR(300MHz, $CDCl_3$): 13.22(1H, s, NH Benzimidazole), 10.61(s, 1H, tetrazole-NH), 6.71-8.53(m, 19H, ArH), 5.12(s, 1H OH), 4.04(*d*, 2H, arm NH_2), 3.38(s, 2H, CH_2), 5.90(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 51.5, 56.7, 111.1, 112, 114.2, 115.1, 116.6, 120.1, 122.5, 122.9, 133.2, 134.2, 136, 139.7, 140.2, FAB-MS, 654.194.

[7h] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(4-hydroxy-phenyl)- thiazolidin-4-one
Yield: 70%, m.p.=249-252^{o}C. Anal. Calcd for $C_{36}H_{27}FN_8O_2S$: Found: C, 66.05; H, 4.15; N, 17.13%; IR(KBr): 3661, 3518, 3479, 3135, 3041, 2844, 2728, 1642, 1580, 1469, 1161, 881; ^{1}HNMR(300MHz, $CDCl_3$): 13.22(1H, s, NH Benzimidazole), 10.61(s, 1H, tetrazole-NH), 6.71-8.53(m, 19H, ArH), 5.12(s, 1H OH), 4.04(*d*, 2H, arm NH_2), 3.38(s, 2H, CH_2), 5.90(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 51.5, 56.7, 111.1, 112, 114.2, 115.1, 116.6, 120.1, 122.5, 122.9, 133.2, 134.2, 136, 139.7, 140.2, FAB-MS, 655.35.

[7i] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-*o-tolyl*- thiazolidin-4-one
Yield: 59%, m.p.=221-225^{o}C. Anal. Calcd for $C_{36}H_{29}FN_8O_2S$: Found: C, 68.06; H, 4.47; N, 17.17%; IR(KBr): 3669, 3512, 3471, 3133, 3027, 2839, 2711, 1682, 1530, 1419, 1152, 887; ^{1}HNMR(300MHz, $CDCl_3$), 13.28(1H, s, NH Benzimidazole), 10.67(s, 1H, tetrazole-NH), 6.8-8.5 (m, 19H, ArH), 2.36(s, 3H CH_3), 4.07(*d*, 2H, arm NH_2), 3.33(s, 2H, CH_2), 5.97(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 21.6, 48.4, 55.4, 112.1, 113.4, 114.1, 116.3, 119.2, 128.2, 134.2, 139.7, 140.1, 142.4, 142.5, FAB-MS, 651.65.

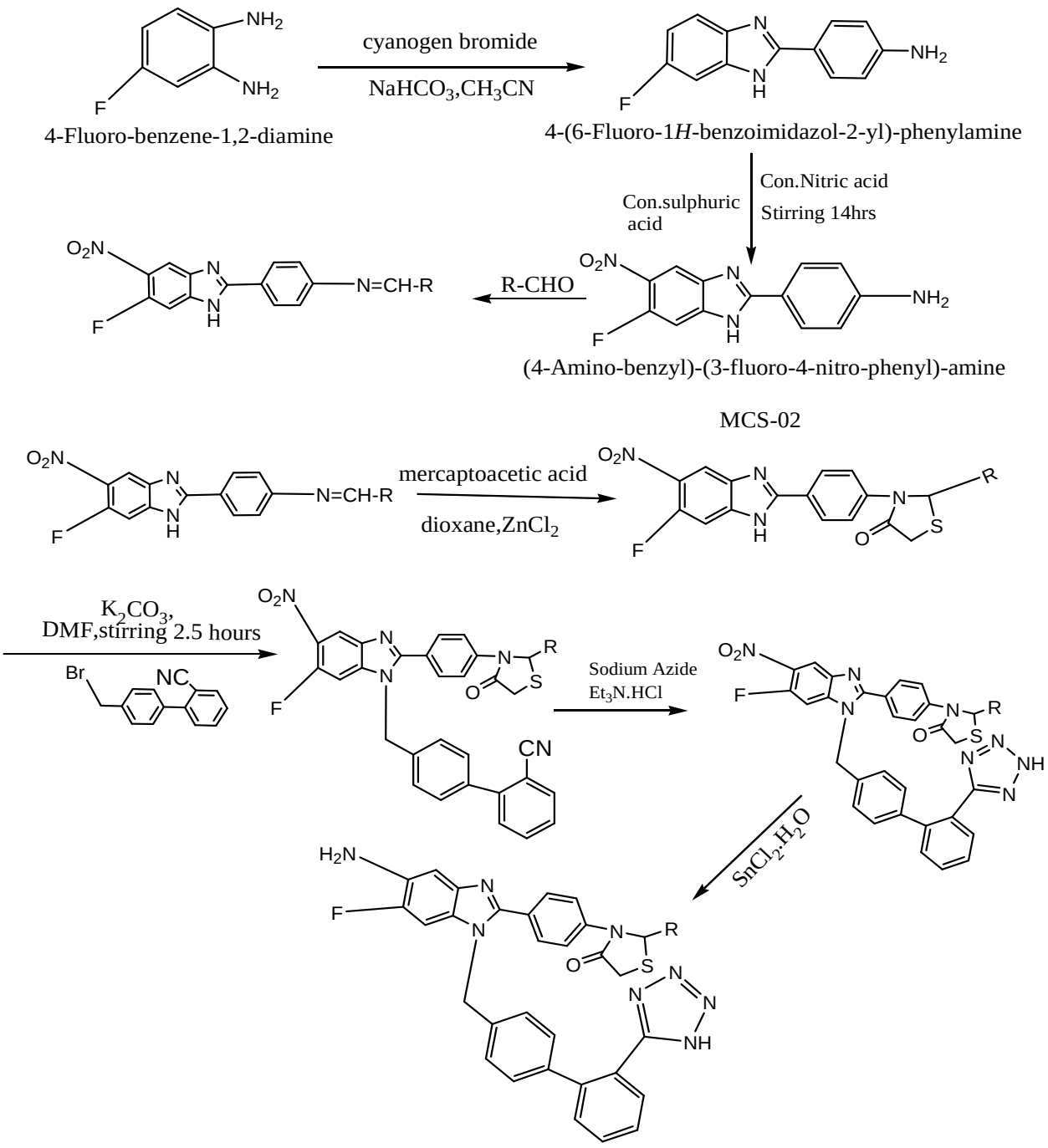
[7j] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-*p-tolyl*- thiazolidin-4-one
Yield: 65%, m.p.=227-229^{o}C. Anal. Calcd for $C_{36}H_{29}FN_8OS$: Found: C, 68.06; H, 4.47; N, 17.17%; IR(KBr): 3669, 3512, 3471, 3133, 3027, 2839, 2711, 1682, 1530, 1419, 1152, 887; ^{1}HNMR(300MHz, $CDCl_3$), 13.28(1H, s, NH Benzimidazole), 10.67(s, 1H, tetrazole-NH), 6.8-8.5 (m, 19H, ArH), 2.36(s, 3H CH_3), 4.07(*d*, 2H, arm NH_2), 3.33(s, 2H, CH_2), 5.97(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 21.6, 48.4, 55.4, 112.1, 113.4, 114.1, 116.3, 119.2, 128.2, 134.2, 139.7, 140.1, 142.4, 142.5, FAB-MS, 651.65.

[7k] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(2-methoxy-phenyl)- thiazolidin-4-one
Yield: 60%, m.p.=202-204^{o}C. Anal.Calcd for $C_{36}H_{29}FN_8O_2S$: Found: C, 66.46; H, 4.37; N, 16.77%; IR(KBr): 3639, 3502, 3451, 3130, 3097, 2832, 2744, 1626, 1538, 1411, 1143, 884. ^{1}HNMR(300MHz, $CDCl_3$), 13.41(1H, s, NH Benzimidazole), 10.43(s, 1H, tetrazole-NH), 6.8-8.5 (m, 19H, ArH), 3.75(s, 3H OCH_3), 4.01(*d*, 2H, arm NH_2), 3.28(s, 2H, CH_2), 5.93(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 20.2, 54.4, 60.3, 112.1, 113.5, 115.1, 119.1, 126, 133.1, 139.3, 141.3, 141.8, 142.4, 142.9, FAB-MS, 668.22

[7l] 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(2-methoxy-phenyl)- thiazolidin-4-one
Yield: 60%, m.p.=202-204^{o}C. Anal.Calcd for $C_{36}H_{29}FN_8O_2S$: Found: C, 66.46; H, 4.37; N, 16.77%; IR(KBr): 3639, 3502, 3451, 3130, 3097, 2832, 2744, 1626, 1538, 1411, 1143, 884.^{1}HNMR(300MHz, $CDCl_3$); 13.41(1H, s, NH Benzimidazole), 10.43(s, 1H, tetrazole-NH),

6.8-8.5(m, 19H, ArH), 3.75(s, 3H, OCH_3), 4.01(*d*, 2H, arm NH_2), 3.28(s, 2H, CH_2), 5.93(s, 1H, CH); ^{13}CNMR($CDCl_3$)δ: 20.2, 54.4, 60.3, 112.1, 113.5, 115.1, 119.1, 126, 133.1, 139.3, 141.3, 141.8, 142.4, 142.9, FAB-MS, 669.54.

SCHEME



Compounds[7a-l]

Biological Activity

Non-invasive Method: 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[32-36]. Some procedures are allowed once when sufficient pulse level is attained. Observations are given in the table1, 2.

Table 1. Hypertension induced in normotensive rat

Comp.	Exp. Animal Albino (Wistar) Rat	After 1hour			After 3 hour		
		SBP	DBP	MABP	SBP	DBP	MABP
[7a]	1	146	108	124	140	103	120
	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
[7b]	1	136	113	124	142	101	121
	2	139	113	122	140	100	120
	3	146	116	127	143	101	122
	4	143	105	124	139	104	121
	5	141	101	126	143	104	120
[7c]	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	139	102	122	143	100	121
[7d]	1	144	109	131	140	100	120
	2	140	106	123	138	102	120
	3	144	112	127	142	104	123
	4	142	114	127	140	101	122
	5	148	104	126	144	104	124
[7e]	1	144	105	124	139	103	122
	2	140	113	127	142	107	124
	3	141	104	123	137	106	121
	4	135	101	118	136	107	121
	5	140	110	125	138	112	125
[7f]	1	146	114	130	142	104	123

	2	144	116	130	140	106	123
	3	146	108	127	142	106	124
	4	143	106	125	139	104	121
	5	139	102	122	143	100	121
[7g]	1	141	114	128	142	104	123
	2	148	104	126	144	104	124
	3	154	108	132	144	102	123
	4	148	104	126	142	100	121
	5	144	112	127	141	102	121
[7h]	1	139	114	127	135	103	119
	2	142	106	124	140	102	123
	3	140	105	128	138	104	121
	4	139	108	124	141	103	122
	5	142	113	128	142	104	123
[7i]	1	139	111	125	138	101	119
	2	142	104	123	141	104	122
	3	138	104	121	140	106	123
	4	141	109	125	143	106	124
	5	136	112	124	141	103	122
[7j]	1	141	105	123	135	100	117
	2	142	103	123	140	103	122
	3	134	110	122	140	102	121
	4	137	108	123	136	103	119
	5	140	110	125	138	105	122
[7k]	1	143	105	124	143	105	124
	2	140	108	124	140	104	122
	3	141	104	123	137	106	121
	4	135	101	118	136	107	121
	5	140	110	125	138	112	125
[7l]	1	141	103	122	135	109	122
	2	134	106	120	143	114	129
	3	133	113	123	141	109	125
	4	141	110	126	140	108	124
	5	138	105	122	139	109	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
[7a]	1	125	105	115	126	104	115
	2	121	104	112	123	104	112
	3	126	106	116	122	100	111
	4	118	104	111	115	103	114
	5	125	105	115	124	102	113
[7b]	1	128	102	115	127	104	115
	2	126	101	112	124	100	111
	3	125	103	114	122	103	116

	4	127	103	115	130	102	115
	5	124	100	112	128	101	113
[7c]	1	129	108	119	124	104	114
	2	122	112	117	122	103	112
	3	126	114	120	128	107	117
	4	124	111	118	123	104	113
	5	126	104	115	127	107	117
[7d]	1	120	102	111	123	101	112
	2	125	101	113	121	101	110
	3	123	107	115	125	100	112
	4	126	103	114	126	96	111
	5	129	101	115	119	104	111
[7e]	1	124	106	115	127	102	114
	2	126	104	115	125	105	115
	3	124	104	114	121	100	110
	4	129	102	116	124	101	113
	5	133	103	117	127	105	116
[7f]	1	122	104	112	125	101	113
	2	123	102	113	128	103	112
	3	121	101	113	123	102	111
	4	126	102	111	124	101	112
	5	126	103	115	122	103	112
[7g]	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
[7h]	1	144	106	125	144	100	122
	2	145	112	126	139	100	120
	3	142	109	126	143	97	120
	4	140	102	123	140	100	120
	5	137	101	124	146	100	123
[7i]	1	123	101	112	125	100	112
	2	122	100	111	126	102	115
	3	124	102	112	126	102	111
	4	126	101	113	124	104	114
	5	128	102	115	126	104	115
[7j]	1	136	107	121	129	101	115
	2	126	103	114	122	109	115
	3	124	107	115	127	106	117
	4	127	104	116	124	95	109
	5	129	108	118	130	102	116
[7k]	1	130	99	115	126	98	112
	2	126	101	117	123	97	110
	3	136	107	121	129	101	115
	4	140	103	122	141	101	121
	5	138	114	126	138	100	119
[7l]	1	128	106	117	123	100	112

	2	127	101	116	125	105	110
	3	126	105	116	127	101	114
	4	126	109	117	122	106	114
	5	124	103	115	125	101	113
Control	**Losartan**	117	-	-	-	-	-

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 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.).

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	**165**	**160**	**156**	**151**	**146**	**140**	**134**	**129**	**125**	**121**
[7a]	177	173	167	159	154	147	144	139	136	134
[7b]	169	165	160	155	149	144	139	136	133	129
[7c]	172	167	163	158	154	148	143	138	133	130
[7d]	170	165	159	154	149	144	139	136	133	131
[7e]	174	168	160	155	150	146	141	136	132	127
[7f]	177	172	166	161	156	151	146	142	138	134
[7g]	175	168	159	150	146	141	136	132	129	127
[7h]	176	172	167	163	158	153	147	142	139	136
[7i]	168	165	160	156	150	146	141	136	133	131
[7j]	166	160	156	152	148	142	139	135	130	128
[7k]	170	166	163	158	153	147	143	138	135	131
[7l]	169	163	160	155	149	145	140	137	133	129

Table: 4 Antihypertensive Activity of synthesized compounds

Compound. No	Minimum Blood pressure value(mm Hg)	Duration of hypertension effect(min.)
Losratan	121	90
[7a]	120	111
[7b]	121	108
[7c]	120	115
[7d]	122	100
[7e]	125	103
[7f]	120	120
[7g]	119	107
[7h]	122	110
[7i]	121	100
[7j]	119	105
[7k]	116	110
[7l]	121	100

RESULTS AND DISCUSSION

The biological activity and medicinal importance of Tetrazoles and schiff bases, we synthesized some schiff bases of 3-(4-{5-Amino-6-fluoro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2-yl}-phenyl) -2-(2-substituted -phenyl)- thiazolidin-4-one by reaction of with different aromatic aldehydes. The compounds of the type substituted (7 a-l) were studied for the antihypertensive activity. The relationship between structure and different biological activities was studied. Other derivatives of Tetrazole containing chloro, bromo and 4-hydroxy, methoxy benzaldehyde are also expected to exhibit good antihypertensive activity. Hence amino group was substituted at position 5; it increased the force of contraction of antihypertensive activity. These compounds are recommended for the screening of antihypertensive activity. 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 twelve compounds synthesized [7a-l] showed antihypertensive activity and with compared the standard drug.

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