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Synthesis and pharmacological activity of 2-(2-substituted-phenyl)-3-(4-{1-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1*H*-benzoimidazol-2-yl}-phenyl)-thiazolidin-4-ones

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ABSTRACT

An easy and efficient method to obtain Schiff bases of [2-(2-substituted-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H benzoimidazol-2-yl}-phenyl)- thiazolidin-4-one] using different aromatic aldehydes. Reaction mixture of Schiff base (0.01 mol) and mercaptoacetic acid (0.05 mol) dissolved in dioxane (50 ml), anhydrous zinc chloride (0.008 mol) was added and refluxed for 12 hrs. The reaction mixture was cooled, filtered, washed with 10 % w/v sodium bicarbonate solution. After reactions with compounds sodium azide (1.50 g, 13.43 mmol), and Et3N·HCl (4.2 g, 16.31 mmol) in NH4Cl (30 mL) is stirred at 40◦C for 8 hours [A-O]. The compounds obtained were identified by spectral data and were subjected to a prediction of biological activities. All synthesis compounds screened for Angiotension (A II) Receptor Antagonist antihypertensive activity with biphenyl tetrazole Schiff bases Thiazoldine-4-one shows good activity compared with losartan.

Keywords: Biphenyl tetrazole, Angiotensin II, antihypertensive drug, Losartan.

INTRODUCTION

Hypertension is the most common cardiovascular diseases and constituents a major factor for several cardiovascular pathologies including atherosclerosis, coronary artery disease, and myocardium infract, heart failure, renal insufficiency, stroke and dissecting aneurysm of aorta. 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 antihypertensive [4].It also stimulates the release of vasopressin luteinizing hormone oxytocin and corticotropin. ANG II further induces vagus suppression and α-adrenergic potentiation and increases inotropy and chronotropy. Stimulation of the cardiac fibroblast matrix formation has also been described[3-5]. ANG II stimulates synthesis of prostaglandin [6] endothelin[7] and elicits procoagulatory effects by activating the plasminogen activator (PA) plasmin system[8-11]. The beneficial effect of a chronic RAS blockade was first shown for inhibitors of the angiotensin converting enzyme (ACE) such as captopril quinapril enalapril and ramipril in patients with ischemic heart disease congestive heart failure [12-14] the development of potent drugs that interfered with the RAS: the angiotensin receptor type 1 (AT_1) antagonists. To find a more specific blockade of ANG II at its AT_1 receptor highly selective non-peptidic AT1-receptor antagonists were designed and developed as competitive antagonists with virtually no agonistic effect at the receptor level. Losartan was described as the first non-peptide AT_1 receptor antagonist and the coined group name was sartans[15-16]. All major pharmaceutical companies embarked on a fast follower program immediately thereafter. Today irbesartan candesartan and valsartan are all established in the market and others e.g. tasosartan and telmisartan are following closely. Some further 20 compounds are in development. Most of these compounds share the biphenyl tetrazole unit or replacements thereof with the original advanced lead losartan [17]. Some variations of the parent biphenyl tetrazole alone were reported in the meantime excluding the obvious variation of the biphenyl spacer. The carboxylic acid another common moiety of the sartans appears to establish another important interaction with the receptor but it often hampers oral absorption. Therefore several prodrug concepts had to be realized to mask the carboxylic acid as either a labile ester or an oxidatively labile precursor that delivers the acid after absorption. Recent findings [18-19] indicate the involvement of this peptide also in situations concerning tissue remodelling, such as cardiac hypertrophy and cancer. All these responses are mediated by two distinct subtypes of Ang II receptors [type 1 (AT1) and type 2 (AT2)]. In particular, AT1 receptors mediate all of the known effects associated to Ang II that constitutes the principal target of an effectiveness therapy against the cardiovascular pathology. The Ang II effects may be reduced by inhibiting almost partially the enzyme responsible of biosynthesis of Ang II or through the interaction with AT1 receptor. To date, many orally available sartans have been developed and are used in the treatment of both hypertension and damage associated with diseases like atherosclerosis and diabetes. In particular, the good properties of new non peptide Ang II antagonists, such as losartan, have stimulated the design of many different congeners. All these drugs contain some common structural features represented by a biphenyl fragment bearing an acidic moiety (i.e.: tetrazole, carboxylic- or sulphonamidocarboxyl- group), linked to a heteroaromatic or acyclic system by means of a methylene group. Almost all of the chemical

manipulations within the fundamental skeleton of sartans concerned the substitution of the imidazole ring of losartan with several variously substituted heteroaromatic groups or acyclic structures[20].All these antagonists possess a central aromatic nucleus bearing the pharmacophores indispensable for activity and notably a polar function adjustant to biphenyl subsistent while a polar function in this area of molecule seems to be necessary to maintain activity[21] Sartans are appropriately substituted heterocyclic head coupled through a methylene linker to pendent biphenyl system bearing an acidic function; viz. candesartan is an effective competitive Ang II antagonist with benzimidazole nucleus as the heterocyclic head [22]. The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity [23] compounds containing tetrazole nucleus are also reported as AT1 receptor antagonists and their protypical derivative exhibits non-competitive antagonism[24] amino group attach with carboxylic group given good biological activity [25-27].In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives as a source of new antihypertensive agents. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, which are the structural isosters of nucleotides owing fused heterocyclic nuclei in their structures that allow them to interact easily with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in man [28-29].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].

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.

Synthesis of 1H-benzimidazol-2-amine-

A solution of 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 NaHCO3 (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 Na2CO3 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. Yield 85%; mp 135-136 0C; Anal Calcd for C7H7N3 (R=H): C, 63.14; H, 5.30; N, 31.56%; Found: C, 63.10; H, 5.28; N, 31.53%; IR (υ cm-1): 3045 (C-H, sp2), 3210 (NH, bonded), 3175 (NH, free), 1654 (C=N), 1626, 1586, 1444 (C…C, ring str) 958, 859, 742 (sub. phenyl); 1H NMR (300 MHz, CDCl3) δ: 4.0 (s, 2H, NH2), 5.0 (s, NH), 7.6-7.9 (m, 4H, Ar-H); 13C NMR (CDCl3) δ: 117.41, 124.34, 136.66, 158.62; FAB-MS: 134 (M+H)+.

Synthesis of 4-(1H-Benzimidazole-2-yl)-phenyl]-benzylidene-amine)

A mixture of 2-(4-aminophenyl) Benzimidazole (0.01 mol), substituted Benzaldehyde (0.01 mol) and a drop of acetic acid was dissolved in ethanol (25 ml) and heated on a steam bath for 45-60 min. The reaction mixture was allowed to stand at room temperature for 24 h; the product separated out was filtered, dried under vacuum and recrystallized by using warm Absolute ethanol.

Synthesis of 3-[4-(1H-Benzimidazole-2-yl)-phenyl]-substituted -phenyl-thiazolidin-4-one

To a mixture of Schiff base (0.01 mol) and mercaptoacetic acid (0.05 mol) dissolved in dioxane (50 ml), anhydrous zinc chloride (0.05 mol) was added and refluxed for 10 hrs. The reaction mixture was cooled, filtered, washed with 10 % w/v sodium bicarbonate solution, vacuum dried and recrystallised using absolute ethanol. Compounds [1-15].

Synthesis of 4'-{2-[4-(2-substituted-phenyl)-4-oxo-4-thiazolidin-3-yl)-phenyl} benzoimidazol-1-ylmethyl}-biphenyl-2-carbonitrile

To a solution of 150 mg (2.5 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 (MgSO4) and evaporated.

Synthesis of 2-(2-substituted-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H-benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

A mixture of different substituted 4'-{2-[4-(2-substituted-phenyl)-4-oxo-4-thiazolidin-3-yl)-phenyl} benzoimidazol-1-ylmethyl}-biphenyl-2-carbonitrile (165 mg, 1.08 mmol), sodium azide (1.50 g, 13.43 mmol), and Et3N·HCl (4.2 g, 16.31 mmol) in NH4Cl (30 mL) is stirred at 40◦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 H2O (3 × 50 mL), then the combined extracts were dried (MgSO4) and evaporated and the solid residue was purified by silica gel column chromatography eluting with ethyl acetate/ethanol (80:20/v: v) to give solid Compounds.

[A] 2-(2-hydroxy-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:59%,m.p.=263-2660C.Molecular weight 621.71 Anal.Calcd for C36H27N7O2S:C,69.55;H,4.38; N,15.77;S,5.16 %; IR (KBr): 3687,3553, 3426, 3086,2875,1645, 1570,1288, 897, 774, .1HNMR (300 MHz, CDCl3) 10.03(s,1H,tetrazole-NH),4.93(s,2H,CH2),6.93-8.65(m,20H,Ar-H), 3.43(s,2H,CH2) 5.15(s,1H,arm-OH),5.98(s,1H-CH).13CNMR (CDCl3)δ: 54.7, 58.2, 112.1, 113.3, 115.5, 122.2, 124.5, 127.3, 131.2, 133.1, 134.3, 135.2, 137.8,FAB-MS, 621.14

[B] 2-(3-hydroxy-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:55%,m.p.=274-2760C.Molecular weight 621.71 Anal.Calcd for C36H27N7O2S:C,69.55;H,4.38; N,15.77;S,5.16 %; IR (KBr): 3687,3553, 3426, 3086,2875,1645, 1570,1288, 897, 774, .1HNMR (300 MHz, CDCl3) 10.03(s,1H,tetrazole-NH),4.93(s,2H,CH2),6.93-8.65(m,20H,Ar-H), 3.43(s,2H,CH2) 5.15(s,1H,arm-OH),5.98(s,1H-CH).13CNMR (CDCl3)δ: 54.7, 58.2, 112.1, 113.3, 115.5, 122.2, 124.5, 127.3, 131.2, 133.1, 134.3, 135.2,137.9,FAB-MS, 622.46

[C] 2-(4-hydroxy-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:62%,m.p.=269-2720C.Molecular weight 621.71 Anal.Calcd for C36H27N7O2S:C,69.55;H,4.38; N,15.77;S,5.16 %; IR (KBr): 3687,3553, 3426, 3086,2875,1645, 1570,1288, 897, 774, .1HNMR (300 MHz, CDCl3) 10.03(s,1H,tetrazole-NH),4.93(s,2H,CH2),6.93-8.65(m,20H,Ar-H), 3.43(s,2H,CH2) 5.15(s,1H,arm-OH),5.98(s,1H-CH).13CNMR (CDCl3)δ: 54.7, 58.2, 112.1, 113.3, 115.5, 122.2, 124.5, 127.3, 131.2, 133.1, 134.3, 135.2, 137.5, FAB-MS, 620.88

[D] 2-(2-Chloro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:70%,m.p.=231-2340C.Molecular weight 640.16 Anal.Calcd for C36H26ClN7OS:C,67.54;H,4.09;N,15.32;S,5.01 %; IR (KBr): 3671,3508, 3338, 3063,1754, 1276, 873, 727.1HNMR (300 MHz, CDCl3) 10.14(s,1H,tetrazole-NH),5.03(s,2H,CH2),6.98-8.69(m,20H,ArH), 3.34(s, 2H, CH2) 5.94(s, 1H, CH). 13CNMR (CDCl3)δ: 55.7,110.1,111.6,113.1,117.3,123.1,130.3,131.3,139.1,139.5,140.9,FAB-MS, 639.16

[E] 2-(3-Chloro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:70%,m.p.=231-2340C.Molecular weight 640.16 Anal.Calcd for C36H26ClN7OS:C,67.54;H,4.09;N,15.32;S,5.01 %; IR (KBr): 3671,3508, 3338, 3063,1754, 1276, 873, 727.1HNMR (300 MHz, CDCl3) 10.14(s,1H,tetrazole-NH),5.03(s,2H,CH2),6.98-8.69(m,20H,ArH), 3.34(s, 2H, CH2) 5.94(s, 1H, CH). 13CNMR (CDCl3)δ: 53.6,110.1,111.6,113.1,117.3,123.1,130.3,131.3,139.1,139.5,143.2,FAB-MS, 641.07

[F] 2-(4-Chloro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:72%,m.p.=237-2390C.Molecular weight 640.16 Anal.Calcd for C36H26ClN7OS:C,67.54;H,4.09;N,15.32;S,5.01 %; IR (KBr): 3671,3508, 3338, 3063,1754, 1276, 873, 727.1HNMR (300 MHz, CDCl3) 10.11(s,1H,tetrazole-NH),5.03(s,2H,CH2),6.98-8.69(m,20H,ArH), 3.34(s, 2H, CH2) 5.94(s, 1H, CH). 13CNMR (CDCl3)δ: 50.8,110.1,111.6,113.1,117.3,123.1,130.3,131.3,139.1,139.5,144,FAB-MS, 641.65

[G] 2-(2-nitro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:77%,m.p.=212-2160C.Molecular weight 652.04 Anal.Calcd for C36H26N8O3S:C,66.45;H,4.06;N,17.22;S,4.94 %; IR (KBr): 3630,3557, 3324, 3050,1748, 1511,1209, 898.1HNMR (300 MHz, CDCl3) 10.34(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.97-8.62(m,20H,ArH), 3.37(s, 2H, CH2) 5.86(s, 1H, CH). 13CNMR (CDCl3)δ: 51.2,55.8, 110.1,111.6,113.1,117.3,123.1,130.3,131.3,137.8, FAB-MS, 650.24

[H] 2-(3-nitro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:82%,m.p.=219-2230C.Molecular weight 652.04 Anal.Calcd for C36H26N8O3S:C,66.45;H,4.06;N,17.22;S,4.94 %; IR (KBr): 3630,3557, 3324, 3050,1748, 1511,1209, 898.1HNMR (300 MHz, CDCl3) 10.31(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.97-8.62(m,20H,ArH), 3.37(s, 2H, CH2) 5.86(s, 1H, CH). 13CNMR (CDCl3)δ: 52.5,55.8, 110.1,111.6,113.1,117.3,123.1,130.3,131.3,137.1, 140.3,FAB-MS, 653.31

[I] 2-(4-nitro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:77%,m.p.=210-2120C.Molecular weight 652.04 Anal.Calcd for C36H26N8O3S:C,66.45;H,4.06;N,17.22;S,4.94 %; IR (KBr): 3630,3557, 3324, 3050,1748, 1511,1209, 898.1HNMR (300 MHz, CDCl3) 10.37(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.97-8.62(m,20H,ArH), 3.37(s, 2H, CH2) 5.86(s, 1H, CH). 13CNMR (CDCl3)δ: 49.3,55.8, 110.1,111.6,113.1,117.3,123.1,130.3,131.3,137.3, FAB-MS, 653.79

[J] 2-(2-bromo-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:64%,m.p.=288-2890C.Molecular weight 684.60 Anal.Calcd for C36H26BrN7OS:C,63.15;H,3.83;N,14.32;S,4.64 %; IR (KBr): 3674,3533, 3305, 3059,1721, 1518,1229, 896.1HNMR (300 MHz, CDCl3) 10.54(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.82-8.48(m,20H,ArH), 3.31(s, 2H, CH2) 5.95(s, 1H, CH). 13CNMR (CDCl3)δ: 58.0,112.9,113.4,116.2,121.1,128.4,135.5,138.2,FAB-MS, 683.110

[K] 2-(3-bromo-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:61%,m.p.=282-2840C.Molecular weight 684.60 Anal.Calcd for C36H26BrN7OS:C,63.15;H,3.83;N,14.32;S,4.64 %; IR (KBr): 3674,3533, 3305, 3059,1721, 1518,1229, 896.1HNMR (300 MHz, CDCl3) 10.50(s,1H,tetrazole-NH),4.94(s,2H,CH2),6.82-8.48(m,20H,ArH), 3.35(s, 2H, CH2) 5.95(s, 1H, CH). 13CNMR (CDCl3)δ: 58.0,112.9,113.4,116.2,121.1,128.4,135.5,138.2,FAB-MS, 685.86

[L] 2-(4-bromo-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield:68%,m.p.=292-2950C.Molecular weight 684.60 Anal.Calcd for C36H26BrN7OS:C,63.15;H,3.83;N,14.32;S,4.64 %; IR (KBr): 3674,3533, 3305, 3059,1721, 1518,1229, 896.1HNMR (300 MHz, CDCl3) 10.57(s,1H,tetrazole-NH),4.92(s,2H,CH2),6.82-8.48(m,20H,ArH), 3.39(s, 2H, CH2) 5.95(s, 1H, CH). 13CNMR (CDCl3)δ: 53.1,55.3,61.1,70.7,111.4,113.1,113.5,114.1,121.2, 135.5,137.2,140.9,FAB-MS, 685.23

[M] 2-(2-Fluoro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield: 55%,m.p.=251-2540C.Molecular weight 623.702 Anal.Calcd for C36H26FN7OS:C,69.33;H,4.23;N,15.70;S,5.14 %; IR (KBr): 3603,3528,3311, 3057,1701, 1547,1234, 899.1HNMR (300 MHz, CDCl3) 10.54(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.82-8.48(m,20H,ArH), 3.31(s, 2H, CH2) 5.95(s, 1H, CH). 13CNMR (CDCl3)δ: 58.0,112.9,113.4,116.2,121.1,128.4,135.5,138.2,FAB-MS, 623.19

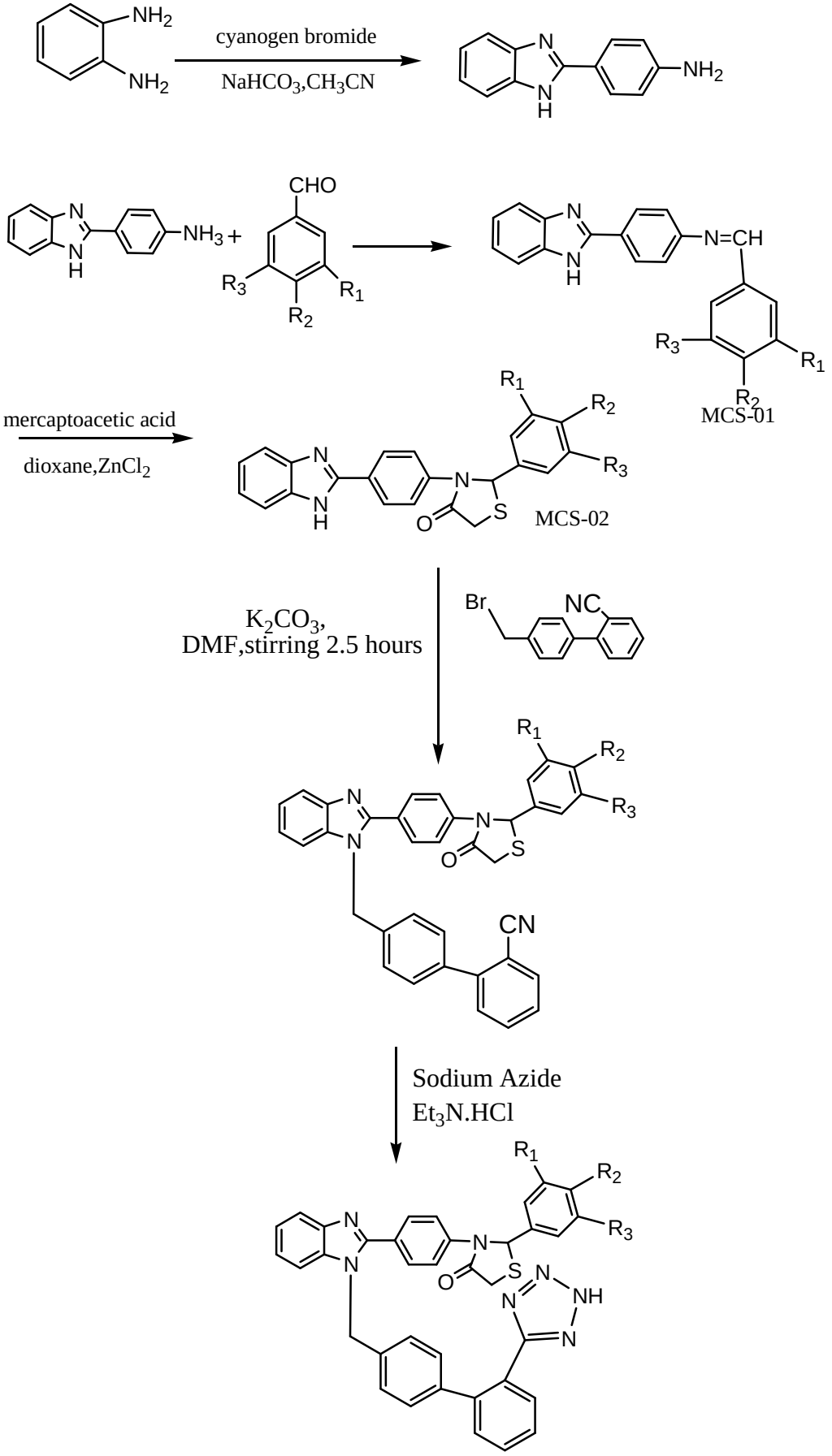
[N] 2-(3-Fluoro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield: 52%,m.p.=246-2480C.Molecular weight 623.702 Anal.Calcd for C36H26FN7OS:C,69.33;H,4.23;N,15.70;S,5.14 %; IR (KBr): 3603,3528,3311, 3057,1701, 1547,1234, 899.1HNMR (300 MHz, CDCl3) 10.54(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.82-8.48(m,20H,ArH), 3.31(s, 2H, CH2) 5.95(s, 1H, CH). 13CNMR (CDCl3)δ: 58.0,112.9,113.4,116.2,121.1,128.4,135.5,138.2,FAB-MS, 622.54

[O] 2-(4-Fluoro-phenyl)-3-(4-{1-[2-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl])-1H- benzoimidazol-2-yl}-phenyl) - thiazolidin-4-one

Yield: 57%,m.p.=251-2540C.Molecular weight 623.702 Anal.Calcd for C36H26FN7OS:C,69.33;H,4.23;N,15.70;S,5.14 %; IR (KBr): 3603,3528,3311, 3057,1701, 1547,1234, 899.1HNMR (300 MHz, CDCl3) 10.54(s,1H,tetrazole-NH),4.99(s,2H,CH2),6.82-8.48(m,20H,ArH), 3.31(s, 2H, CH2) 5.95(s, 1H, CH). 13CNMR (CDCl3)δ: 58.0,112.9,113.4,116.2,121.1,128.4,135.5,138.2,FAB-MS, 624.66

SCHEME



Compounds[A-O]

Biological Activity:

Non-invasive Method (Indirect Method) [23, 31-35] Albino rats weighing 150-200 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.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 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]

Table 1. Hypertension induced in normotensive rat

Comp.	Exp. Animal Albino (Wistar) Rat	After 1hour			After 3 hour		
		SBP	DBP	MABP	SBP	DBP	MABP
[A]	1	144	103	124	141	103	122
	2	141	111	126	140	104	122
	3	142	103	124	144	102	123
	4	142	108	125	146	104	125
	5	146	106	126	142	104	123
[B]	1	142	105	124	135	107	121
	2	141	102	121	139	103	121
	3	140	105	123	141	105	124
	4	143	101	122	140	110	125
	5	145	105	125	145	100	121
[C]	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
[D]	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
[E]	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

[F]	1	152	112	133	145	109	124
	2	139	102	122	143	107	126
	3	148	104	124	143	109	128
	4	146	112	128	137	106	126
	5	143	108	126	140	109	127
[G]	1	146	103	125	139	105	120
	2	144	109	131	140	100	120
	3	140	106	123	138	102	120
	4	144	112	127	142	104	121
	5	142	114	127	140	101	126
[H]	1	146	108	127	142	109	123
	2	143	106	125	139	107	129
	3	139	102	122	143	106	124
	4	148	104	124	143	113	126
	5	146	112	128	137	101	118
[I]	1	151	112	133	146	101	124
	2	144	114	129	142	102	121
	3	139	114	127	135	103	119
	4	142	106	124	140	102	123
	5	140	105	128	138	104	121
[J]	1	144	105	124	139	103	128
	2	140	113	127	142	107	122
	3	141	104	123	137	106	129
	4	144	101	118	136	107	125
	5	140	110	125	138	112	125
[K]	1	140	108	124	138	102	120
	2	144	106	125	142	101	123
	3	143	110	127	134	102	118
	4	137	102	124	135	102	118
	5	139	107	123	140	101	120
[L]	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	146	116	127	143	101	122
[M]	1	143	105	124	139	104	121
	2	141	101	126	143	104	120
	3	141	110	126	143	104	119
	4	142	102	125	141	102	121
	5	139	111	124	138	102	120
[N]	1	139	109	123	142	102	123
	2	140	101	125	140	101	124
	3	138	107	128	143	101	121
	4	140	108	125	141	104	120
	5	144	111	126	143	100	119
[O]	1	141	102	121	139	103	126
	2	140	105	123	141	105	123
	3	143	101	122	140	117	129

	4	139	107	123	140	106	124
	5	143	109	126	137	108	127
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
[A]	1	126	106	116	122	100	111
	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
[B]	1	123	101	113	124	103	112
	2	131	105	118	124	101	115
	3	126	103	114	128	106	117
	4	124	106	115	127	104	116
	5	127	105	116	125	105	115
[C]	1	132	96	114	130	101	116
	2	129	108	119	124	104	114
	3	122	112	117	122	103	112
	4	126	114	124	128	107	117
	5	124	111	121	123	104	113
[D]	1	122	106	114	122	103	112
	2	128	107	117	127	101	114
	3	126	103	114	125	104	113
	4	132	105	119	121	102	110
	5	131	106	118	119	103	107
[E]	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
[F]	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
[G]	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
[H]	1	129	108	119	124	104	114
	2	122	112	117	122	103	112
	3	125	105	115	122	100	112
	4	124	100	112	128	101	113
	5	130	104	117	128	102	115

[I]	1	125	105	115	124	101	112
	2	122	100	111	126	104	115
	3	128	102	115	130	103	116
	4	123	102	113	128	103	112
	5	121	101	113	123	102	111
[J]	1	126	102	111	124	101	112
	2	121	100	110	125	102	111
	3	126	103	115	122	103	112
	4	123	102	113	128	103	112
	5	125	100	112	121	107	114
[K]	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
[L]	1	127	105	118	126	102	114
	2	124	106	122	122	101	111
	3	123	102	119	127	101	110
	4	122	104	118	124	98	113
	5	127	108	119	126	103	109
[M]	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
[N]	1	126	102	113	123	103	113
	2	123	101	112	122	106	116
	3	124	102	113	124	102	113
	4	122	102	112	126	100	111
	5	124	102	113	128	100	114
[O]	1	128	102	115	126	104	115
	2	125	105	115	122	100	112
	3	124	101	112	124	100	112
	4	122	100	111	121	103	112
	5	124	102	113	124	106	115
Control	**Losartan**	107		-	-	-	-

RESULTS AND DISCUSSION

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 NaHCO3 (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 Na2CO3 and the solution was concentrated under reduced pressure. 2-(4-aminophenyl) Benzimidazole (0.01 mol), substituted Benzaldehyde (0.01 mol) and a drop of acetic acid was dissolved in ethanol (25 ml) and heated on a steam bath for 45-60 min, To a mixture of Schiff base (0.01 mol) and mercaptoacetic acid (0.05 mol) dissolved in dioxane (50 ml), anhydrous zinc chloride (0.008 mol) was added and refluxed for 12 hrs. The reaction mixture was cooled, filtered, washed with 10 % w/v sodium bicarbonate

solution. After reactions with compounds sodium azide (1.50 g, 13.43 mmol), and Et3N·HCl (4.2 g, 16.31 mmol) in NH4Cl (30 mL) is stirred at 40◦C for 8 hours. Tail-cuff non-invasive blood pressure measurements can be consistent, accurate and reproducible when studying awake and anesthetized mice and rats. Care must be exercised to properly handle the animals. Training the animals and monitoring the animal's temperature may also be beneficial. The volumetric pressure recording method provides the highest degree of correlation with telemetry and direct blood pressure and is clearly the preferred tail-cuff sensor technology. The main advantages are: (1) they require no surgery; (2) they are significantly less expensive than other blood pressure equipment, such as telemetry; (3) they can screen for systolic and diastolic BP changes over time in large numbers of animals; and (4) they provide the researcher with the ability to obtain accurate and consistent blood pressure measurements over time in long-term studies. In view of the pharmacological and medicinal importance of benzimidazoles derivatives in different disciplines of medicines the present study has been carried out antihypertensive activity.A series of newly synthesized benzimidazoles derivatives (A-O) has been evaluated for hypertensive activity in normotensive anesthetized rats at the doses of 0.5µg/kg taking. The compounds B, D, E, G, I, K, L, M, O showed mild hypertensive activity while compound A,C,F,H,J, and N were found active at that dose level. In conclusion, among the tested compounds, six of them produced mild hypertension. This study is the preliminary investigation that can further be extended to explore the potentials of these compounds leading potent antihypertensive and/or hypotensive agents.

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