Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2010, 1 (1): 92-105

Design, Synthesis and Biological Activity of Some Benzimidazoles Derivatives 3-Chloro-4-(Substituted--phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-ones

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

A novel method for the synthesis of novel 3-Chloro-4(4-chloro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one derivatives have been reported. Structures of all the synthesized compounds have been corroborated on the basis of elemental IR, ^{1}H NMR, ^{13}C NMR and Mass spectro-analytical data. Many Schiff bases were prepared by condensation reaction of nitro compound containing biphenyl tetrazole with aromatic aryl aldehydes derivatives with azetidin-2-one. The synthesized compounds were screened for AT_1 Angiotension (A II) Receptor Antagonist activity. The nitro, chlorine, hydroxy, florine, iodo compound containing biphenyl tetrazole Schiff bases azetidin-2-one shows good activity compared with losartan and Telmisartan.

Keywords: Schiff base, Biphenyl tetrazole, azetidin-2-one, Angitotensin II, Losartan, Telmisartan.

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).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. 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], RAS constitutes a proteolytic cascade in which angiotensinogen 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).

MATERIALS AND METHODS

Now a days in view of the affinity displayed by them toward a variety of enzymes and protein receptors, 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 heteroatoms 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. 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 $NaHCO_3$ (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. Yield 85%; mp 135-136 ^{0}C; Anal Calcd for $C_7H_7N_3$ (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, sp^2), 3210 (NH, bonded), 3175 (NH, free), 1654 (C=N), 1626, 1586, 1444 (C⋯C, ring str) 958, 859, 742 (sub. phenyl); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.0 (s, 2H, NH_2), 5.0 (s, NH), 7.6-7.9 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 117.41, 124.34, 136.66, 158.62; FAB-MS: 134 $(M+H)^+$.

Synthesis of 4-(1H-Benzimidazole-2-yl)-phenyl]-benzylidene-amine)[22]

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 4-(1H-Benzimidazole-2-yl)-phenyl]-3-chloro-4-phenyl-azetidine-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.

Synthesis of 4'-{2-[4-(3-Chloro-2-oxo-4-subsituted-azetidin-1-yl)-phenyl] benzoimidazol-1-ylmethyl}-biphenyl-2-carbonitrile

To a solution of 1.5 g (10.12 mmol) compound aryl substitute -03 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 18 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.

Synthesis of 3-Chloro-4(Substituted--phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

A mixture of different substituted 4'-{2-[4-(3-Chloro-2-oxo-4-subsituted-azetidin-1-yl)-phenyl] benzoimidazol-1-ylmethyl}-biphenyl-2-carbonitrile (2.5 g, 3.08 mmol), sodium azide (1.21 g, 13.43 mmol), and Et3N·HCl (2.1 g, 10.05 mmol) in NH_4Cl (15 mL) is stirred at 160°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/ethanol (80:20/v: v) to give solid Compounds.

[1] 3-Chloro-4(2-chloro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:74%,m.p.=221-224^{0}C.Molecular weight 643.51 Anal.Calcd for $C_{36}H_{25}Cl_2N_7O$:C,67.29;H,3.92;N,15.26 %; IR (KBr): 3643,3542, 3343, 3052,1706, 1255, 873, 721, 539.^{1}HNMR (300 MHz, $CDCl_3$) 9.87(s,1H,tetrazole-NH),5.00(s,2H,CH_2),6.94-8.65(m,20H,ArH), 5.39(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 49, 111.3,115.1,117.8,120.2,129.2,139.2,142, FAB-MS, 642.72

[2] 3-Chloro-4(3-chloro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:70%,m.p.=226-228^{0}C.Molecular weight 643.51 Anal.Calcd for $C_{36}H_{25}Cl_2N_7O$:C,67.29;H,3.92;N,15.26 %; IR (KBr): 3646,3557, 3361, 3023,1701, 1258, 873, 721, 539.^{1}HNMR (300 MHz, $CDCl_3$) 9.84(s,1H,tetrazole-NH),5.00(s,2H,CH_2),6.94-8.65(m,20H,ArH), 5.39(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 55.8,110.1,111.6,113.1,117.3,123.1,130.3,131.3,139.1,139.5,140.2,FAB-MS, 644.105

[3] 3-Chloro-4(4-chloro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:65%,m.p.=231-234^{0}C.Molecular weight 643.51 Anal.Calcd for $C_{36}H_{25}Cl_2N_7O$:C,67.29;H,3.92;N,15.26 %; IR (KBr): 3647,3537, 3365, 3077,1721, 1250, 879, 726, 555.3.^{1}HNMR (300 MHz, $CDCl_3$) 9.82(s,1H,tetrazole-NH),5.06(s,2H,CH_2),6.97-8.60(m,20H,ArH), 5.31(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 55.8, 113.4,114.1,116.3,119.2,128.2,137.2, FAB-MS, 644.04

[4] 3-Chloro-4(2-nitro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:77%,m.p.=212-216^{0}C.Molecular weight 652.04 Anal.Calcd for $C_{36}H_{25}ClN_8O$:C,66.21;H,3.86;N,17.16 %; IR (KBr): 3638,3586, 3394, 3057,1729, 1543,1221, 865, 728, 568.6.^{1}HNMR (300 MHz, $CDCl_3$) 10.03(s,1H,tetrazole-NH),4.96(s,2H,CH_2),6.65-8.58(m,20H,ArH), 5.36(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 55.8, 110.1,111.6,113.1,117.3,123.1,130.3,131.3,137.8, FAB-MS, 653.13

[5] 3-Chloro-4(3-nitro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:74%,m.p.=206-208^{0}C.Molecular weight 652.04 Anal.Calcd for $C_{36}H_{25}ClN_8O$:C,66.21;H,3.86;N,17.16 %; IR (KBr): 3689,3581, 3394, 3057,1729, 1654-1543,1221, 865, 728, 568.6.^{1}HNMR (300 MHz, $CDCl_3$) 10.08(s,1H,tetrazole-NH),4.96(s,2H,CH_2),6.65-8.58(m,20H,ArH), 5.36(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 49, 110.8,112.3,114.2,123.2,124.2,129.2,134.9,140.8, FAB-MS, 653.65

[6] 3-Chloro-4(4-nitro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:70%,m.p.=212-216^{0}C.Molecular weight 652.04 Anal.Calcd for $C_{36}H_{25}ClN_8O$:C,66.21;H,3.86;N,17.16 %; IR (KBr): 3638,3586, 3394, 3057,1729, 1654-1595,1221, 865, 728, 568.6.^{1}HNMR (300 MHz, $CDCl_3$) 10.03(s,1H,tetrazole-NH),4.96(s,2H,CH_2),6.65-8.58(m,20H,ArH), 5.36(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 57.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,142.3 FAB-MS, 651.053

[7] 3-Chloro-4(2-flouro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:62%,m.p.=244-246^{0}C.Molecular weight 626.08 Anal.Calcd for $C_{36}H_{25}ClFN_7O$:C,69.06;H,4.06; N,15.66 %; IR (KBr): 3613,3551, 3364, 3077,1763, 1590,1265, 895, 774, 552.1.^{1}HNMR (300 MHz, $CDCl_3$) 10.24(s,1H,tetrazole-NH),4.97(s,2H,CH_2),6.93-8.52(m,20H,ArH), 5.41(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 57.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,143.5,145.1,FAB-MS, 625.12

[8] 3-Chloro-4(3-flouro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:62%,m.p.=256-257^{0}C.Molecular weight 626.08 Anal.Calcd for $C_{36}H_{25}ClFN_7O$:C,69.06;H,4.06; N,15.66 %; IR (KBr): 3613,3551, 3364, 3077,1763, 1590,1265, 895, 774, 552.1.^{1}HNMR (300 MHz, $CDCl_3$) 10.28(s,1H,tetrazole-NH),4.97(s,2H,CH_2),6.93-8.52(m,20H,ArH), 5.41(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 57.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,143.5,145.1,FAB-MS, 626.16

[9] 3-Chloro-4(4-flouro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:62%,m.p.=241-242^{0}C.Molecular weight 626.08 Anal.Calcd for $C_{36}H_{25}ClFN_7O$:C,69.06;H,4.06; N,15.66 %; IR (KBr): 3613,3551, 3364, 3077,1763, 1590,1265, 895, 774, 552.1.^{1}HNMR (300 MHz, $CDCl_3$) 10.21(s,1H,tetrazole-NH),4.97(s,2H,CH_2),6.93-8.52(m,20H,ArH), 5.41(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 57.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,143.5,144.8,FAB-MS, 624.99

[10] 3-Chloro-4(2-iodo-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:48 %,m.p.=274-276^{0}C.Molecular weight 733.97 Anal.Calcd for $C_{36}H_{25}ClIN_7O$:C,58.91;H,3.83; N,13.36 %; IR (KBr): 3674,3527, 3392, 3035,1693, 1571,1231, 890, 779, 547.3.^{1}HNMR (300 MHz, $CDCl_3$) 10.15(s,1H,tetrazole-NH),4.90(s,2H,CH_2),7.15-8.59(m,20H,ArH), 5.45(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 52.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,142.1,144.0,FAB-MS, 734.36

[11] 3-Chloro-4(3-iodo-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:54%,m.p.=279-281^{0}C.Molecular weight 733.97 Anal.Calcd for $C_{36}H_{25}ClIN_7O$:C,58.91;H,3.83; N,13.36 %; IR (KBr): 3674,3530, 3393, 3037,1693, 1571,1231, 890, 779, 547.3.^{1}HNMR (300 MHz, $CDCl_3$) 10.18(s,1H,tetrazole-NH),4.90(s,2H,CH_2),7.15-8.59(m,20H,ArH), 5.45(s, 2H, CH-Cl). ^{13}CNMR

($CDCl_3$)δ: 52.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,142.1,143.6,FAB-MS, 732.42

[12] 3-Chloro-4(4-iodo-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:51%,m.p.=271-273^{0}C.Molecular weight 733.97 Anal.Calcd for $C_{36}H_{25}ClIN_7O$:C,58.91;H,3.83; N,13.36 %; IR (KBr): 3674,3538, 3396, 3037,1693, 1571,1231, 890, 779, 547.3.^{1}HNMR (300 MHz, $CDCl_3$) 10.12(s,1H,tetrazole-NH),4.90(s,2H,CH_2),7.15-8.59(m,20H,ArH), 5.45(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 52.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,142.1,144.8,FAB-MS, 734.51

[13]3-Chloro-4(2-hydroxy-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:50%,m.p.=289-291^{0}C.Molecular weight 624.09 Anal.Calcd for $C_{36}H_{26}ClN_7O_2$:C,69.28;H,4.23; N,15.71 %; IR (KBr): 3637,3512, 3396, 3037,1693, 1571,1231, 890, 779, 547.3.^{1}HNMR (300 MHz, $CDCl_3$) 10.65(s,1H,tetrazole-NH),4.95(s,2H,CH_2),7.10-8.48(m,20H,ArH), 5.40(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 49.6,112.5,113.6,114.2,124.7,124.1,126.4,128.0,134.1,139.8,142.9,143.8,FAB-MS, 623.86

[14]3-Chloro-4(3-hydroxy-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:54%,m.p.=286-288^{0}C.Molecular weight 624.09 Anal.Calcd for $C_{36}H_{26}ClN_7O_2$:C,69.28;H,4.23; N,15.71 %; IR (KBr): 3637,3512, 3396, 3037,1693, 1571,1231, 890, 779, 547.3.^{1}HNMR (300 MHz, $CDCl_3$) 10.76(s,1H,tetrazole-NH),4.95(s,2H,CH_2),7.10-8.48(m,20H,ArH), 5.40(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 52.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,130.6,142.1,143.1,FAB-MS, 625.38

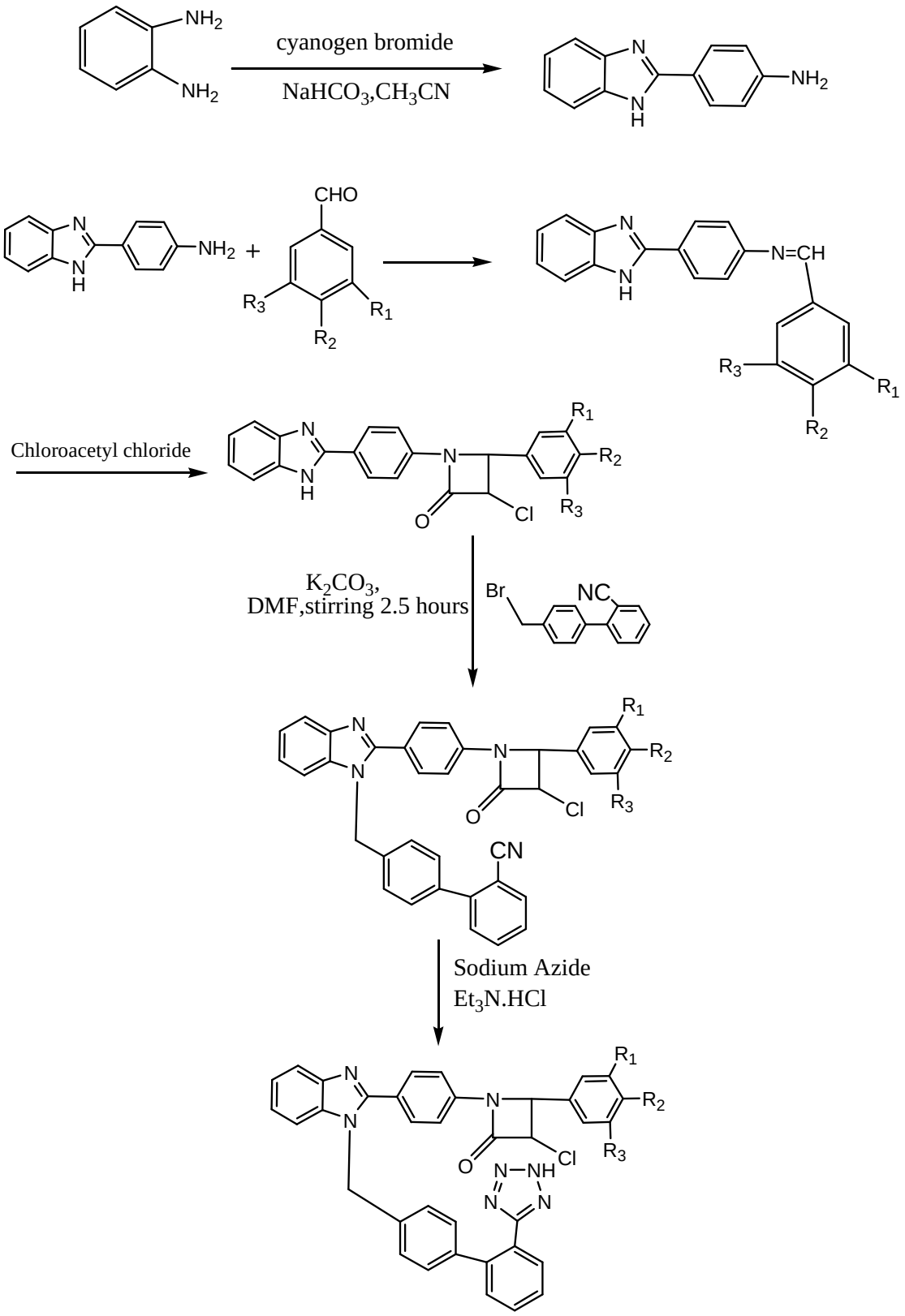
[15]3-Chloro-4(4-hydroxy-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:60%,m.p.=289-291^{0}C.Molecular weight 624.09 Anal.Calcd for $C_{36}H_{26}ClN_7O_2$:C,69.28;H,4.23; N,15.71 %; IR (KBr): 3637,3512, 3396, 3037,1693, 1571,1231, 890, 779, 547.3.^{1}HNMR (300 MHz, $CDCl_3$) 10.82s,1H,tetrazole-NH),4.95(s,2H,CH_2),7.10-8.48(m,20H,ArH), 5.40(s, 2H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ:
57.6,111.4,111.8,112.0,114.2,115.1,116.6,120.1,122.5,122.9,127.9,134.6137.6,140,144.6,FAB-MS, 625.27

[16]3-Chloro-4-phenyl-1-(4-{1-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazol-2yl}-phenyl)-azetidin-2-one

Yield:65%,m.p.=195-197^{0}C.Molecular weight 608.21 Anal.Calcd for $C_{36}H_{26}ClN_7O$:C,71.11;H,4.31;N,16.12 %; IR (KBr): 3624,3512, 3304, 3043,1712, 1232, 885, 732, 721, 532.^{1}HNMR (300 MHz, $CDCl_3$) 9.65(s,1H,tetrazole-NH),5.02(s,2H,CH_2),6.94-8.65(m,22H,ArH), 5.34(s, 1H, CH-Cl). ^{13}CNMR ($CDCl_3$)δ: 17.0, 51.4, 110.6, 111.3, 112.3, 115.1, 117.8, 120.2, 129.2, 139.2, FAB-MS, 607.401

SCHEME



COMPOUND 1-16

Biological Activity: [21-28]

Method [A]

Albino rats weighing 200-250 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.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. Observations are given in the table1, 2.

Method [B]

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.). Observations are given in the 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	138	105	122	139	109	124
	2	132	104	118	142	106	124
	3	142	103	123	140	106	123
	4	141	110	121	143	115	124
	5	140	110	125	134	105	119
[2]	1	142	112	127	140	103	121

	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
[3]	1	140	110	125	134	105	119
	2	141	104	123	138	104	121
	3	139	111	125	135	103	119
	4	140	101	121	136	103	119
	5	142	105	124	135	107	121
[4]	1	141	102	121	139	103	121
	2	140	105	124	139	104	120
	3	143	108	123	138	103	121
	4	144	112	127	141	102	121
	6	142	114	128	144	101	122
[5]	1	146	110	126	142	100	120
	2	150	111	131	146	104	125
	3	144	114	129	146	106	126
	4	142	108	125	146	104	125
	5	146	106	126	142	104	123
[6]	1	142	110	126	140	116	128
	2	146	103	125	139	105	120
	3	144	109	131	140	100	120
	4	142	113	125	142	102	122
	5	141	109	123	144	101	121
[7]	1	144	114	129	141	104	120
	2	143	105	124	143	105	124
	3	149	101	125	143	101	121
	4	144	109	131	140	100	120
	5	142	102	124	143	101	122
[8]	1	145	105	125	145	100	121
	2	140	113	124	143	100	121
	3	142	105	122	142	101	120
	4	139	111	126	141	102	119
	5	142	109	126	143	97	120
[9]	1	140	102	123	140	100	120
	2	148	104	125	145	102	123
	3	140	106	123	138	101	119
	4	138	104	121	140	106	123
	5	141	109	125	143	106	124
[10]	1	136	112	124	141	103	122
	2	144	106	125	142	101	123
	3	143	108	126	140	103	121
	4	145	106	123	136	97	116
	5	152	112	133	145	103	124
[11]	1	139	102	122	143	100	121
	2	140	106	123	142	106	124
	3	146	114	130	142	104	123
	4	144	116	130	140	106	123

	5	146	108	127	142	106	124
[12]	1	140	106	123	142	101	121
	2	144	112	127	142	104	123
	3	142	114	127	140	101	122
	4	148	104	126	144	104	124
	5	141	110	126	143	104	119
[13]	1	142	102	125	141	102	121
	2	139	111	124	138	102	120
	3	144	106	125	140	102	121
	4	132	110	121	143	105	124
	5	141	111	126	139	104	121
[14]	1	144	106	125	142	101	123
	2	143	110	127	134	102	118
	3	141	109	123	144	101	121
	4	144	114	129	141	104	120
	5	146	104	132	142	100	121
[15]	1	148	104	125	145	102	123
	2	140	106	123	142	101	121
	3	141	106	124	141	101	121
	4	143	105	124	143	105	124
	5	142	112	127	140	102	121
[16]	1	144	116	130	141	101	122
	2	152	112	133	145	103	124
	3	146	104	132	142	100	121
	4	148	104	125	145	102	123
	5	150	111	131	146	104	125
Control	**Losartan**	123	-	-	-	-	-
	Telmisartan	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	126	100	113	124	101	112
	2	123	102	112	123	102	111
	3	124	102	113	125	102	112
	4	126	101	113	125	100	113
	5	131	105	118	125	100	115
[2]	1	128	104	116	123	101	112
	2	125	105	115	126	104	115
	3	126	106	116	122	100	111
	4	131	105	118	124	101	115
	5	126	103	114	128	106	117
[3]	1	129	108	119	124	104	114
	2	122	112	117	122	103	112
	3	126	114	124	128	107	117
	4	125	105	115	127	101	114

	5	120	102	111	123	101	112
[4]	1	125	101	113	121	101	110
	2	123	107	115	125	100	112
	3	126	103	114	126	96	111
	4	129	101	115	119	104	111
	5	123	107	115	121	99	110
[5]	1	126	103	114	125	104	113
	2	132	105	119	121	102	110
	3	131	106	118	119	103	107
	4	124	107	115	127	106	117
	5	127	104	116	124	95	109
[6]	1	124	111	118	123	104	113
	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
[7]	1	123	102	112	123	102	111
	2	122	101	111	126	102	114
	3	124	102	113	125	102	112
	4	124	111	121	123	104	113
	5	126	104	115	127	107	117
[8]	1	127	105	119	123	103	113
	2	129	100	111	126	104	115
	3	123	101	113	124	103	112
	4	126	104	115	125	105	115
	5	122	112	117	122	103	112
[9]	1	122	102	112	123	107	115
	2	121	106	113	126	102	114
	3	126	106	112	128	102	115
	4	124	106	115	123	103	113
	5	126	104	115	124	104	114
[10]	1	124	108	116	122	102	112
	2	123	100	113	125	105	115
	3	122	114	114	123	103	114
	4	136	101	118	122	104	113
	5	134	100	117	126	104	115
[11]	1	122	102	112	122	100	111
	2	123	103	116	124	110	117
	3	125	104	115	125	106	116
	4	124	102	113	124	102	113
	5	122	102	112	126	100	111
[12]	1	124	102	113	128	100	114
	2	123	101	113	124	103	112
	3	126	104	115	125	105	115
	4	124	104	114	121	100	110
	5	125	102	112	128	100	114
[13]	1	125	105	115	124	101	112
	2	122	100	111	126	104	115

	3	125	100	112	121	107	114
	4	128	102	115	130	103	116
	5	125	105	115	127	101	114
[14]	1	125	105	115	124	101	112
	2	122	100	111	126	104	115
	3	125	100	112	121	107	114
	4	128	102	115	130	103	116
	5	125	105	115	127	101	114
[15]	1	126	100	113	121	101	111
	2	124	101	112	122	102	114
	3	126	106	116	122	100	111
	4	118	104	111	115	103	114
	5	125	105	115	124	102	113
[16]	1	122	100	111	121	103	112
	2	124	103	111	125	102	113
	3	122	102	114	123	100	111
	4	120	103	112	119	101	110
	5	127	103	115	125	102	114
Control	**Losartan**	102	-	-	-	-	-
	Telmisartan	104	-	-	-	-	-

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	**163**	**160**	**156**	**150**	**143**	**135**	**127**	**120**	**115**	**109**
1	180	172	169	163	158	151	146	142	137	132
2	175	170	165	158	152	148	143	139	135	130
3	177	168	157	152	147	143	139	136	133	129
4	165	162	158	154	151	146	142	139	136	133
5	170	166	164	157	152	148	144	138	135	131
6	174	171	165	159	150	146	143	139	135	132
7	166	163	160	155	149	142	138	134	130	124
8	168	163	157	150	143	138	134	129	126	124
9	166	164	159	153	149	144	139	135	133	129
10	178	173	169	163	158	152	147	143	137	134
11	174	167	164	158	151	148	142	137	134	129
12	170	164	158	152	147	144	139	133	129	127
13	167	163	158	151	146	141	138	134	130	125
14	165	160	156	151	146	140	133	129	127	123
15	176	170	164	158	151	144	138	134	130	128
16	175	170	166	159	150	144	137	131	127	125

Table: 4 Antihypertensive Activity of synthesized compounds

Compound. No	**Minimum Blood pressure value(mm Hg)**	**Duration of hypertension effect(min.)**
Losratan	109	90
1	116	115
2	122	100
3	121	100
4	119	110

5	117	100
6	122	110
7	115	100
8	110	100
9	117	103
10	117	105
11	118	102
12	115	100
13	117	106
14	112	111
15	120	100
16	116	105

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 $NaHCO_3$ (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. 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 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. Step II solution of 1.5 g (10.12 mmol) compound aryl aldehydes 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 was added. After stirring for 18 hours the mixture was poured into distilled water and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated. A mixture of different substituted react with sodium azide and Et3N·HCl in NH_4Cl (15 mL) is stirred at 160°C for 15 hours. Almost all the newly synthesized substituted aryl group showed good antihypertensive activity with the goal of investigating the structure–activity relationships of benzimidazole and purity have been established through appropriate spectral and chromatographic techniques. The present work was mainly intended to establish the moieties which are responsible for Angiotension-II inhibition. Ang II antagonism by compounds with same functional group at 2 positions has been found to be a function of substitute aryl groups chlorine, nitro, fluoro, iodo groups showing good antihypertensive activity [table-1, 2, 3, 4]. The present work was mainly intended to establish the moieties which are responsible for Angiotension-II inhibition. The benzimidazole derivatives were able to increases Angiotensin-II induced hypertension and also vasoconstriction, compared with Losartan. The similar results were noticed with synthesized Schiff bases and azetidine-2-one. From the preliminary screening the synthesized molecules shows good Angiotensin II induced anti hypertension activity and above molecules can be taken as a lead molecule for Angiotensin II induced hypertension. Therefore we conclude in our preliminary screening that it may not to be necessary to go for a synthesis of big molecule. Further study of these molecules and its analogues under progress in our laboratory.

Acknowledgement
The authors are thankful to Prof.Pratibha Sharma School of Chemical Sciences DAVV Indore, to given valuable suggestion to experimental work, authors also thankful to Dr.Rajesh Sharma 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] Shanmugapandiyan P, Denshing KS, R. Ilavarasan N Anbalagan, Nirmal R, *Int. J. of Pharma. Scienc and Drug Research*, **2010**; 2(2): 115-119
[23] Badyal DK, Lata H, Dadhich AP, *Indian J of Pharmacology*, **2003**, 35(66), 349-362.
[24] Bunag RD, McCubbin JW, Page IH, *Cardiovasc.Res*,**1971**,5(1): 24-31.
[25] Gupta SK, Drug Screening methods, Jaypee Brothers Medical Publisher, New Delhi, **2004,** pp 236-246.
[26] Shreenivas MT, Chetan BP, Bhat AR, *J. of Pharma.Sci. And Technology*, **2009**, 1 (2), 88-94.
[27] Siddiqui AA, Wani M.S, *Indian.J.Chemistry*, **2004**, 43B,pp. 1574-1579.
[28] Vogel G.H.Drug Discovery and Evaluation, Pharmacological Assay, **2002** ;(Springer. Berlin), 122. 24-31.