1.1 Hypertension

As the thesis pertains to research work carried out for the development of multitargeted ligands as potential antihypertensive agents, it is in order to introduce the reader about hypertension and related aspects. Hypertension is recognized as one of the leading risk factors for human morbidity and mortality. On a worldwide basis hypertension has been ranked on the top as a cause of disability adjusted life years.[1] Recently, the global prevalence of hypertension (systole/diastole ≥140/90 mmHg) was estimated for the year 2000 and the data was used to predict the global prevalence of hypertension by 2025 (Fig. 1).[2] More than 25% of the world's adult population was hypertensive by the afore-mentioned criteria in 2000. The estimated total number of people with hypertension in 2000 was 972 million, and this is projected to increase by 60% to a total of 1.56 billion by 2025, i.e., 29% of the worldwide adult population.[3]

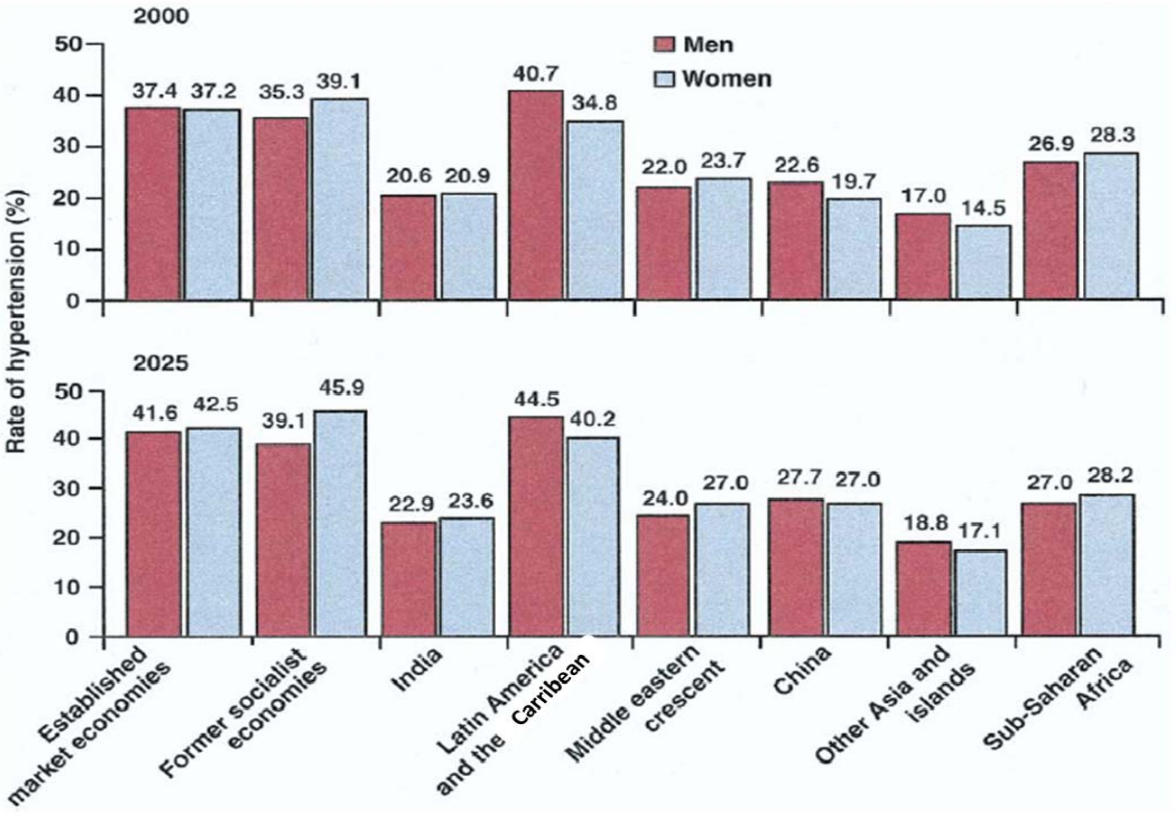


Figure 1: Frequency of hypertension in people of ages 20 years and older in the world regions and genders in 2000 (upper panel) and projected to be in 2025 (lower panel).

Hypertension is a major risk factor for myocardial infarction, congestive heart failure, stroke and end-stage renal disease.[4] Blood pressure is derived from the hemodynamic properties of closed systemic circulation. Therefore the tension on the walls of blood vessels depends on several factors, like:

(a) The pumping function of the heart

(b) The total blood volume

(c) The size, structure and distensibility of the vascular tree and

(d) Other factors like reflex and neurohumoral feedback systems which in turn may interfere with a, b and c.

Thus, hypertension is influenced by both, function and structure of blood vessels. As a consequence of elevated blood pressure arterial elasticity is reduced and wall damage appears that can lead to cholesterol and fat deposition on these lesions and eventually to obstruction of the vessels. This is the basis of most of the target organ damages induced by hypertension. Another consequence can be an increase in vascular resistance which forces the pumping activity of the heart to maintain nutrients and oxygen distribution. This work overload for the heart may induce the development of cardiac hypertrophy, an increase in cardiac mass and thickness.[5]

Some patients may "inherit" abnormalities that make them prone to the development of hypertension as well as a complex series of cardiovascular disease risk factors. These include elevated lipids, increased left ventricular hypertrophy (LVH), arterial stiffening, insulin resistance, renal function abnormalities and neuroendocrine changes. Studies assessing both arterial structure and function have shown reduced arterial compliance in normotensive subjects with a family history of hypertension.[6,7] Insulin resistance has been shown to occur in approximately 50% of hypertensive patients.[8] Elevated blood pressure has been implicated as a cause for renal dysfunction in hypertensive patients. The sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) are believed to be pivotal in the pathogenesis of hypertension. Interruptions of these systems effectively reduce blood pressure.[9]

The difficulty in controlling hypertension is related, at least in part, to the complex pathogenesis of hypertension and related cardiovascular diseases. Multiple signaling pathways and redundant feedback mechanisms, both positive and negative, contribute to the hypertensive disease process, which is further confounded by the interrelationship of hypertension with associated diseases such as diabetes and renal dysfunction.

1.2 Drug targets for the management of hypertension

Hypertension is, by definition, a hemodynamic disorder. The major hemodynamic finding associated with higher levels of blood pressure is a rise in peripheral vascular resistance. This observation led to the discovery and development of increasingly complex and targeted vasodilators, although many of the earlier antihypertensive drugs, by virtue of their actions blocking the sympathetic nervous system, had a vasodilator component to their mode of action. The first non-specific vasodilator was hydralazine.[10] Approaches made in the search of effective antihypertensive agents revealed more systems and newer targets as discussed below[11-13]:

- The sympathetic nervous system (SNS) (since 1954) was then explored for the treatment of hypertension. SNS is involved in the homeostatic regulation of a wide variety of functions such as heart rate, force of contraction of the heart, vasomotor tone and ultimately blood pressure. The sympathetic nervous system is subdivided into the α and β subsystems. β_1 Receptor blockade results into decreased cardiac output while α receptor blockade caused peripheral vasodilatation.
- Diuretics provide a means of forced diuresis to increase the excretion of water from body. Kidney is a vital organ in the maintenance of fluid volume. There are many classes of diuretics like thiazides, loop and potassium sparing etc.
- Calcium Channel Blockers (CCBs) (1980) are very effective antihypertensive agents that reduce blood pressure primarily through arteriolar vasodilatation.
- Renin Angiotensin System (RAS) is an important target for renal and cardiovascular protection. Angiotensin converting enzyme inhibitors (ACEIs) were successfully developed in mid 1980. Later on, angiotensin receptor blockers

(ARBs) were developed (1990). Now a days, renin inhibitors are also available (2010).

The search for the effective control of blood pressure revealed more targets like:

- Aldosterone is a potent mineralocorticoid which promotes Na^+ reabsorption causing increase in water level. Aldosterone receptor antagonists (ARA) act at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding while Aldosterone Synthase Inhibitor (ASIs) inhibit the action of aldosterone synthase.[14]
- Endothelin 1 (ET_1) is a twenty one amino acid vasoactive peptide that is released predominantly from vascular endothelium[15] and is synthesized by a variety of cell types including vascular smooth muscles, cardiomyocytes and cardiac fibroblasts.[16] Endothelin stimulates potent vasoconstriction and cell proliferation through activation of endothelin A receptor. Endothelin receptor antagonists are useful in treatment of pulmonary hypertension.[17]
- Prostacyclin, a metabolite of arachidonic acid, has vasoprotective effects including vasodilation, platelet antiaggregation, and inhibition of smooth cell proliferation.[18, 19] Prostacyclin analogues are antagonists useful for the treatment of pulmonary hypertension.[20]
- The nitric oxide (NO)/soluble guanylate cyclase (sGC)/cyclic guanosine-3',5'-monophosphate (cGMP) pathway plays an important role in cardiovascular regulation by producing vasodilation and inhibiting platelet aggregation, and vascular smooth muscle proliferation. Soluble guanylate cyclase activators increase intracellular cGMP concentrations resulting in relaxation of the smooth muscle of the vasculature.[21]
- Phosphodiestarase (PDE) inhibitors can prolong or enhance the effects of physiological processes mediated by cAMP or cGMP by inhibition of their degradation by PDE. These phosphodiesterase inhibitors are used primarily as remedies for erectile dysfunction and have medical applications such as treatment of pulmonary hypertension.[20]

1.3 Monodrug therapy

A great deal of clinical research over the past few decades has attempted to answer the seemingly critical question, "What is the best drug for hypertension?" Long-term clinical trials have successfully demonstrated the efficacy of different classes of drugs including angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), β_1-blockers (BBs), α_1-blockers, aldosterone antagonists and diuretics. The report of JNC VII provided a list of oral antihypertensive agents (**Table 1**).[23]

Table 1. Oral antihypertensive agents

Sr. No.	Class	Drugs
1	ARBs	Losartan, Valsartan, Olmesartan, Telmisartan, Candesartan, Irbesartan, Eprosartan
2	ACEIs	Captopril, Ramipril, Benzapril, Enalapril, Fosinopril, Lisinopril, Trandolapril, Perindopril, Quinapril, Moexipril,
3	CCBs	Amlodipine, Felodipine, Nicardipine, Nifedipine, Nisoldipine Diltiazem, Verapamil
4	β_1- Blockers	Atenolol, Betaxolol, Bisprolol, Metoprolol, Nadolol, Propranolol, Timolol
5	α_1- Blockers	Prazosin, Doxazosin, Terazosin
6	Aldosterone antagonists	Eplerenone, Spironolactone
7	Diuretics	Hydrochlorothiazide, Chlorothiazide, Chlorthalidone, Polythiazide, Indapamide, Metolazone, Bumetamide, Furosemide, Torsemide, Amiloride, Triamterene
8	Direct vasodilators	Hydralazine, Minoxidil
9	Combined α and β blockers	Carvedilol, Labetalol
10	Central α_2 agonists	Clonidine, Methyldopa, Reserpine, Guanfacine

Hypertension is a risk factor and may associate with several disorders or conditions. The current antihypertensive therapy is able to treat the hypertension in patients with different disorders or conditions. Many drugs are reported to be effective in

treating hypertensive patients with different disorders or conditions. The systems, their targets and benefits in treating hypertension associated with other disorders or conditions are discussed below.

1.3.1 Sympathetic Nervous System (SNS)

The sympathetic nervous system is involved in the homeostatic regulation of a wide variety of functions such as heart rate, force of contraction of the heart, vasomotor tone and ultimately blood pressure. The sympathetic nervous system is subdivided into the α and β subsystems. The hyperactivity of this system leads to various cardiovascular disturbances such as hypertension, shock, cardiac failure and arrythmias, asthma, allergy and anaphylaxis. α_1 Receptor causes peripheral vasoconstriction. Commonly used antagonists are prazosin, doxazosin and terazosin. In V-HeFT 1 study, men with chronic congestive heart failure and cardiac dilatation (CT ratio > 0.55) or LVEF <45% in association with reduced exercise tolerance were treated with prazosin or placebo. Prazosin reduced all cause deaths by 6%. [24]

β_1 Receptor blockade results into decreased cardiac output. β Blockers have an important dual role to play in the management of patients with diabetic kidney disease - to help achieve target BP and to provide optimal cardioprotection in those patients who are at high risk for cardiac events. β Blockers clearly have a role in reducing CV risk in the treatment of patients with diabetic or nondiabetic kidney disease.[25]

1.3.2 Diuretics

Diuretics are effective antihypertensive drugs. Treatment with a diuretic such as hydrochlorothiazide results in a dose-dependent blood pressure reduction that levels off with higher dosages.[26] In long-term trials diuretics have been shown to reduce the incidence of stroke, congestive heart failure, coronary artery disease and total mortality from cardiovascular diseases.[27]

1.3.3 Calcium Channel Blockers (CCBs)

Calcium channel blockers are very effective antihypertensive agents that reduce blood pressure primarily through arteriolar vasodilatation. CCBs have also been shown to improve the CV risk profile to a greater degree than that expected by their BP-lowering effects alone and to provide additional advantages in terms of renal and vascular protection, reduction in new-onset diabetes cases and lack of effect on metabolic parameters.[28]

1.3.4 Renin-Angiotensin System (RAS)

RAS is an important target for renal and cardiovascular protection. A hormonal cascade regulates blood volume and arterial pressure to maintain adequate organ perfusion. Chronic RAS activation results in vascular and cardiac hypertrophy, vasoconstriction, and salt and water retention. The RAS cascade starts with the release of renin into the circulation from the juxtaglomerular cells of the kidney. Active renin in the plasma cleaves angiotensinogen (produced by the liver) to angiotensin I (ang I), which is then converted by circulating and locally expressed angiotensin converting enzyme (ACE) to angiotensin II (ang II). Most of the effects of ang II are exerted by its binding to angiotensin II type 1 receptor (AT_1). Therapeutic agents that block RAS via different mechanisms include ACEIs, ARBs and direct renin inhibitors.[29]

ARBs are an effective class of antihypertensive agents. They showed effects beyond blood pressure control. Mega-trials of ARBs in patients with hypertension have confirmed that blood pressure (BP) control with these agents reduced cardiovascular disease (CVD) morbidity and mortality in a range of patients, including those with diabetes mellitus, heart failure or left ventricular hypertrophy (LVH) and those at risk of developing heart failure following myocardial infarction.[30] The ARBs have demonstrated renoprotective efficacy in several large trials in patients with nephropathy associated with type 2 diabetes.[31-40]

ACEIs have been demonstrated to be similar to conventional standard therapy (β-blockers, diuretics or calcium channel blockers) in patients with hypertension or high risk patients with evidence of vascular disease or diabetes plus other cardiovascular risk factors.[41-45] In a systematic review of five long-term trials involving 12,763 patients with left ventricular (LV) dysfunction or heart failure (HF), treatment with ACEIs significantly reduced mortality and rates of readmission for HF and/or reinfarction versus placebo.[46]

Renin inhibitors represent a new class of drugs that suppress renin-angiotensin system (RAS) by blocking the action of renin on angiotensinogen to produce angiotensin I (**Table 2**). Aliskiren is the first direct renin inhibitor available for the treatment of hypertension. Available evidence shows that aliskiren is a potent and safe antihypertensive agent when used alone and in combination with other antihypertensive agents. To date, aliskiren has been shown to be effective in patients with stage 1 and 2 hypertension, diabetes, left ventricular hypertrophy, proteinuria or heart failure.[47-49]

Table 2. Renin inhibitors and their clinical status[50]

Sr. No.	Compound	Company	Phase of Development
1	Aliskiren	Novartis and Speedel Pharmaceuticals	Approved 2007
2	SPP635	Speedel Pharmaceuticals	Phase I
3	SPP676	Speedel Pharmaceuticals	Phase I
4	SPP1148	Speedel Pharmaceuticals	Phase I
5	VTP2799	Vitae Pharmaceuticals	Phase I
6	SPP1234	Speedel Pharmaceuticals	Preclinical

SPP635, another molecule from this category of drugs showed the safety and efficacy in male and female patients with mild-to-moderate hypertension monitored by measuring office and ambulatory blood pressure.[51]

1.3.5 Aldosterone receptor antagonists

Aldosterone, independent of ang II, has been implicated in the pathogenesis of progressive cardiovascular[52, 53] and renal disease.[54] Aldosterone antagonists have proved to be as effective as other antihypertensive drugs in the treatment of high BP [55-62] and useful in reducing a variety of cardiovascular[52] and renal[60] endpoints.

Eplerenone was found at least non-inferior to amlodipine,[63] enalapril[64] and losartan[65] in reducing blood pressure. In addition, eplerenone lowers blood pressure in patients with hypertension[66] and reduces all cause mortality in patients with heart failure when added to conventional therapy.[67] In EMPHASIS-HF study, the efficacy of eplerenone was again proved in patients with New York Heart Association class II heart failure with an ejection fraction of no more than 35%.[68]

1.3.6 Vasopressin receptor antagonists

One of the hormones that is increased in chronic heart failure is vasopressin. Vasopressin reduces free water excretion and at high concentrations, causes vasoconstriction in the peripheral vasculature. Subsequently, vasopressin acts on the renal collecting duct to cause retention of free water and a subsequent increase in blood pressure.[69-71] Out of the two receptors, V_1 subtype receptor appears primarily responsible for vasopressor activity while the V_2 subtype receptor appears to regulate the antidiuretic effects of vasopressin. The V_1 subtype receptor can be further distinguished into V_{1A} and V_{1B} (also called V_3) receptors.[72-76] Few compounds have been reported to possess V_{1A} selective (Relcovaptan, OPC-21268), V_{1B} selective (SR 121463A, SR121463B, OPC-31260, Tolvaptan, Lixivaptan, VPA-343) or both V_{1A} and V_{1B} selective (Clonivaptan, YM-471) antagonism.[77]

Two identical prospective randomized double-blind placebo-controlled trials were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST). Patients hospitalized with heart failure and congestion were studied. In patients hospitalized with heart failure, oral

tolvaptan in addition to standard therapy including diuretics improved many, though not all, heart failure signs and symptoms, without serious adverse events.[78]

1.3.7 Endothelin receptor antagonists

Endothelin 1 is a 21 amino acid vasoactive peptide that is released predominantly from vascular endothelium[79] and is synthesized by a variety of cell types including vascular smooth muscles, cardiomyocytes, and cardiac fibroblasts.[80] Endothelin causes potent vasoconstriction and cell proliferation through activation of endothelin A receptors on vascular smooth muscle cells, whereas endothelin B receptors are primarily involved in the mediation of vasodilatation through effects on the clearance of endothelin, inhibition of endothelial apoptosis, release of nitric oxide and prostacyclin, and inhibition of endothelin converting enzyme 1 expression.[81] The inhibitors of endothelin receptors (A or A/B), such as bosentan, darusentan, sitaxsentan, and tezosentan, represent a newer class of antihypertensive drugs in treating pulmonary arterial hypertension.[82]

In a trial, the blood-pressure-lowering effects of darusentan revealed additional benefit of reduction in blood pressure in patients who had not attained their treatment goals with three or more antihypertensive drugs.[83]

1.3.8 Prostacyclin analogues

Prostacyclin, a metabolite of arachidonic acid, has vasoprotective effects including vasodilation, platelet antiaggregation and inhibition of smooth cell proliferation.[84, 85] Prostacyclin analogues epoprostenol, reprostinil and iloprost are useful for the treatment of pulmonary hypertension.[86] The trial on epoprostenol (FIRST) for patients with class IIIb/IV congestive heart failure and decreased LVEF did not reveal effectiveness of the drug.[87]

1.3.9 Soluble guanylate cyclase activators

The nitric oxide/soluble guanylate cyclase/cyclic guanosine-3',5'-monophosphate

pathway plays an important role in cardiovascular regulation by producing vasodilation and inhibiting platelet aggregation and vascular smooth muscle proliferation.

Soluble guanylate cyclase activators increase intracellular cGMP concentrations resulting in relaxation of the smooth muscle of the vasculature. Soluble guanylate cyclase is pharmacologically activated on binding nitric oxide at a heme site bound to the protein, and then catalyses the conversion of guanosine triphosphate (GTP) to cGMP.[21]

Cinaciguat (BAY-58-2667, Bayer AG) is currently in developmental stage. In clinical trials in patients with acute decompensated heart failure, cinaciguat potently unloaded the heart, increased cardiac output and renal blood flow, and preserved renal function and sodium and water excretion without further neurohumoral activation.[88] Riociguat (BAY 63-2521) another molecule in phase III trials, possessed rapid, potent and prolonged efficacy and good tolerability in different types of pulmonary hypertension.[89]

1.3.10 Phosphodiestarase (PDE)

Phosphodiestarase can prolong or enhance the effects of physiological processes mediated by cAMP or cGMP by inhibition of their degradation by PDE. Sildenafil, vardenafil and the newer udenafil and avanafil selectively inhibit PDE_5, which is cGMP-specific and responsible for the degradation of cGMP in the corpus cavernosum.[86]

Nitric oxide is a potent vasodilator that also inhibits platelet adhesion and smooth muscle cell proliferation. Its inhalation has been shown to improve hemodynamics with pulmonary selectivity and improves exercise capacity in patients with pulmonary hypertension.[90]

1.4. Combination therapy

In spite of the availability of variety of antihypertensive agents, BP control in the general population is at best inadequate. Because of its multifactorial nature, simply

interfering with one of its pathophysiologic mechanisms by monotherapy is usually insufficient to control it. Treatment with a single antihypertensive agent will generally control BP in less than half of the patients and more than 60% of the patients require combination therapy with two or more drugs of different classes to achieve target BP, as has been observed in a number of large clinical trials [for example, ALLHAT (63%); PROGRESS (58%), INVEST (70%), INCLUSIVE (70%), LEAAD (60%) and SHIELD (74%)].[91-97] Blood pressure control is very important, as a large meta-analysis of one million hypertensive patients showed that a 2 mmHg reduction in systolic BP is associated with 7% and 10% reductions in the risk for cardiovascular and stroke deaths, respectively.[97]

Increasingly, it is being recognized that a balanced modulation of several targets can provide a superior therapeutic effect profile compared to the action of a selective ligand. The goal of antihypertensive treatment is to maximize therapeutic efficacy without significant adverse effects. Therefore, antihypertensive therapy has been directed toward improving BP control in treating patients with the available drugs by using the right combinations at optimum doses. New clinical trials are needed to determine optimal drug combinations that will also confer target-organ protection in addition to and independent of their BP lowering effects. Some poor or troublesome combinations that have been reported are β-blockers with ACEIs/ARBs or with verapamil/diltizem.[98]

Using two separate drugs with complementary mechanisms of action for the treatment of hypertension has long been accepted by physicians. Fixed-dose combinations of two complementary drugs are gaining acceptance. Such low-dose combination therapy has resulted in better BP control, fewer adverse effects, prolonged duration of the antihypertensive effect due to different half lives of component drugs, lower cost of care and increased patient compliance.[94] Several dose strengths of fixed dose combinations are available which give dosing flexibility.

1.4.1 Combination of β blockers and diuretics

The addition of diuretics has been shown to improve the antihypertensive efficacy of β_1-blockers in African-American patients and other populations with low-renin hypertension. However, both of these drug classes have been shown to have similar adverse effects in that they increase the risk of glucose intolerance, the development of new-onset diabetes, fatigue and sexual dysfunction. Outcome studies have shown a morbidity and mortality reduction with diuretics and β_1-blockers in combination.[10]

Combinations listed in JNC VII are atenolol/chlorthalidone, bisoprolol fumarate/ HCTZ, propranolol LA (long acting)/HCTZ, metoprolol tartrate/HCTZ, nadolol/ bendro-flumethiazide and timolol maleate/HCTZ.[23]

1.4.2 Diuretic combinations

The JNC VII-reported diuretic combinations are amiloride HCl/HCTZ, spironolactone/HCTZ, triamterene/HCTZ.[23]

Combination therapy has been attempted with a potassium-sparing diuretic and a thiazide diuretic to reduce the risk of adverse metabolic effects. Combination therapy does not obviate the need for serial monitoring of serum electrolyte levels, but it does decrease the incidence of thiazide-induced hypokalemia without an increased risk of hyperkalemia.[99]

1.4.3 Targeting CCBs

1.4.3.1 Dual calcium channel blockade

The combination of a dihydropyridine CCB with either verapamil or diltiazem has been shown in a recent metaanalysis to have an additive effect on blood pressure lowering without significantly increasing adverse events. Dual CCB blockade may be useful in patients with documented angioedema on RAS inhibitors or in patients with advanced renal failure at risk for hyperkalaemia. However, no outcome data are available with dual CCB therapy and long-term safety remains undocumented.[100]

1.4.3.2 Combination of CCBs and diuretics

Most physicians are somewhat reluctant to combine a CCB with a diuretic. However, in the VALUE trial, hydrochlorthiazide was added as a second step in patients randomized to amlodipine. The diuretic/CCB combination was found to be well tolerated, although there was a higher risk of new onset diabetes and hyperkalaemia when compared with the valsartan arm.[101] The use of diuretics plus calcium channel blockers for hypertension may be associated with a higher risk of myocardial infarction but not stroke, compared with a combination of diuretics and β blockers.[102]

1.4.4 Targeting RAS

1.4.4.1 RAS and diuretic combination

Data from randomized double-blind placebo-controlled clinical trials have shown that an ARB in combination with hydrochlorothiazide is significantly more efficacious than either of the agents alone and the combination has an excellent adverse event profile. Fixed-dose combinations of an ARB and low-dose hydrochlorothiazide provide a convenient and effective treatment option for patients who do not achieve blood pressure targets on monotherapy, without compromising the placebo-like tolerability of ARBs.

The combinations of ACEIs and diuretics listed in JNC VII are benazepril/HCTZ, captopril/HCTZ, enalapril maleate/HCTZ, lisinopril/HCTZ, moexipril HCl/HCTZ and quinapril HCl/HCTZ.[23] An international randomized controlled trial has shown that antihypertensive therapy using perindopril and indapamide significantly reduces the recurrence of stroke; 62.8% of the patients achieved the blood pressure goal. The incidence of adverse events was significantly higher in the combination therapy group than in the perindopril monotherapy group. If adequate care of compromised renal function is taken, perindopril plus diuretic combination therapy exerts potent hypotensive effects without posing significant safety problems in patients with a history of stroke.[103]

1.4.4.2 Combination of ARBs and ACEIs

Current treatment regimens with ACEIs and ARBs may not completely suppress

the RAS. Combinations of ACEIs and ARBs have been shown to be superior to either of the agents alone for some, but certainly not for all composite cardiovascular and kidney

Table 3. Effect of combination therapy with ACEIs and ARBs

Study	Patient No.	Patient Characteristics	Results	Outcome
ValHeFT[38] [8]	5,010	Class II–IV CHF	Addition of valsartan to ACE inhibitor was superior to placebo in lowering BP	Addition of valsartan to ACE inhibitor significantly decreased mortality and morbidity
RESOLVD [106]	426	Class II–IV CHF	Trend toward lower systolic BP with candesartan plus enalapril	Combination of candesartan plus enalapril was significantly superior to either drug alone in improving cardiac ejection fraction
CHARM-added [107]	2,548	Class II–IV CHF and ejection fraction ≤40%	Addition of candesartan to ACE inhibitor resulted in significantly greater BP reductions than addition of placebo	Combination of candesartan plus an ACE inhibitor significantly decreased risk versus placebo plus an ACE inhibitor for primary composite outcome of cardiovascular death or hospitalization for HF
CHARM-overall [108]	7,601	Class II–IV CHF and ejection fraction ≤40%	Not reported	Combination of candesartan plus an ACE inhibitor significantly decreased all-cause mortality
Cice [109]	80	CHF and ejection fraction <40%	Not reported	Addition of telmisartan to ACE inhibitor significantly decreased the risks for CHF hospitalization, all-cause mortality, and cardiovascular death
VALIANT [37]	4,909	Recent myocardial infarction	Addition of valsartan to captopril was significantly superior to placebo in lowering BP	No significant differences between treatment groups with regard to the primary outcome measure, death from any cause
CALM [110]	199	Diabetes mellitus, hypertension, and proteinuria	Combination of lisinopril and candesartan was significantly superior to either drug alone in lowering BP	Combination of lisinopril and candesartan was significantly superior to either drug alone in decreasing the albumin/ creatinine ratio
CALM II [111]	75	Diabetes mellitus plus hypertension	Combination of candesartan and low-dose lisinopril was not significantly superior to high-dose lisinopril in lowering BP	Combination of candesartan and lowdose lisinopril was not significantly superior to high-dose lisinopril placebo in lowering the albumin/ creatinine ratio
COOPER ATE [112]	263	Chronic non-diabetic nephropathy	Reductions in BP similar to losartan, trandolapril, and the combination	Losartan plus trandolapril was signi-ficantly superior to either drug alone for decreasing risk for the composite endpoint of doubling of serum creatinine level or progression to end-stage renal disease

outcomes. The RAS blockade with ACEIs and ARBs has antihypertensive and pleiotropic effects conferring cerebral, cardiac and renal target-organ protection. In clinical trials, ACEIs and ARBs have demonstrated reno- and cardioprotection (**Table 3**). [104, 105]

1.4.5 Combination of RAS inhibitors and CCBs

CCBs have been shown to be amenable to combination with other antihypertensive drugs including ARBs and ACE inhibitors. The additive effect observed with combination therapy most likely occurs because of differing modes of action providing synergistic or complementary effects.

Complementary action of dihydropyridine CCBs with ARBs results from arteriolar dilation and natriuresis by the CCB and counteraction of the effects of stimulated angiotensin II by the ARBs. Another benefit of this combination is the alleviation of pedal edema associated with dihydropyridine CCB monotherapy.[113-116] The first approved ARB-CCB combination of valsartan and amlodipine was supported by a study[113] that evaluated the efficacy and safety of different amlodipine and valsartan dose combinations over an 8-week period in 1911 patients with hypertension. The next approved ARB/CCB combination, olmesartan medoxomil and amlodipine, was supported in a study by Chrysant et al[114] that evaluated the efficacy and safety of different amlodipine and olmesartan medoxomil dose combinations over an 8-week period in 1940 patients with hypertension. The third ARB/CCB combination, telmisartan and amlodipine, was investigated in a study by Littlejohn et al.[117] that evaluated the efficacy and safety of different amlodipine and telmisartan dose combinations over an 8-week period in 1461 patients with hypertension.[118]

Regarding the combination of dihydropyridine **CCBs with ACEIs**, some of the combinations listed in JNC VII are amlodipine/benazepril hydrochloride, enalapril maleate/felodipine and trandolapril/verapamil.[23] Amlodipine/benazepril combinations were well tolerated and resulted in significant BP reductions and better BP responder

rates than amlodipine monotherapy. Addition of benazepril at high doses to amlodipine monotherapy significantly reduced office and ambulatory BP, and increased the BP responder rate. The results of the study suggest that high dose amlodipine/benazepril combination therapy is an effective, safe and well-tolerated treatment option for hypertensive patients who do not respond adequately to amlodipine alone or who have experienced unacceptable edema.[119]

In conclusion, the combination of RAS inhibitors with DHP-CCBs may provide more intensive BP control to currently recommended targets and cardiovascular protective effects that lead to more global risk-factor reduction in patients with hypertension. Given their excellent and complementary tolerability profiles, the combination therapy of an ARB or ACEI with a long-acting DHP-CCB is a rational choice for patients requiring two or more antihypertensive agents.[120]

Now a days the combinations of ARBs, CCBs and diuretic are in the market. Amlodipine-valsartan-hydrochlorothiazide (approved in 2009) is a fixed dose combination of the well established antihypertensive agents. In patients with moderate or severe hypertension, triple combination therapy with amlodipine, valsartan and HCTZ produced significantly greater reductions from baseline in mean sitting systolic and diastolic BP than the combinations of either valsartan and HCTZ, amlodipine and HCTZ or amlodipine and valsartan in a large 8-week randomized double-blind multinational phase III trial.[121]

In several clinical trials, α_1 blockers were allowed or were specified as add-on therapy. Usefulness of the α_1 blocker doxazosin as a third-line antihypertensive drug has been checked with combination of CCBs and ARBs/ACEIs. Results suggest that addition of a low dose of the α_1 blocker doxazosin effectively reduces BP in patients.[122] In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) nine patients received extended-release doxazosin as a third drug if they did not reach their goal blood pressure with either the combination of amlodipine plus perindopril or atenolol plus

bendroflumethiazide. It suggested doxazosin as safe and effective addition.[123] The review of reported clinical trials of doxazosin in different groups of hypertensive patients such as diabetics, the elderly, patients with benign prostatic hyperplasia or hypercholesterolaemia, the obese or Afro-Americans and in combination with all major groups of antihypertensive drugs such as CCBs, diuretics, β_1 receptor antagonists, ACEIs and ARBs, doxazosin showed its efficiency. A large proportion of patients demonstrated a favorable blood pressure response with relatively few treatment-associated side effects showing that this drug appears to be a valuable add-on antihypertensive treatment option.[124]

1.4.6 Other combinations

Although aldosterone is a product of the renin-angiotensin system, its production is not inhibited by treatment with either ACEIs or ARBs.[125, 126] This phenomenon is known as aldosterone escape. Combining of ACEIs/ARBs and ARA has been suggested to provide substantial inhibition of entire RAS.

Soluble guanlyate cyclase activators caused vasodilation which might be countered by the effects of reflex up-regulation of the RAS. ACEIs can inhibit this reflex. This synergy may be more than an additive acute effect or a reduced propensity to the development of tolerance following repeated dosing.[127] Prostacyclin analogues were found to be effective in combination with CCBs in the treatment of pulmonary hypertension.[22]Agents interrupting RAS like ARBs and ACEIs are reported to be used in combination.

1.5 Development of multitargeted ligands

Treatment with a fixed dose drug combination (FDC) is a good option as two or more drugs can be co-formulated in a single dosage form simplifying dosing regimens and thereby improving patient compliance[128, 129] However, complications may arise due to highly complex PK/PD relationships of the drugs requiring sophisticated formulations.

Potential drug-drug interactions could have a significant impact on the risks and costs of developing FDCs[130]

An alternative strategy with a different risk - benefit profile is to develop a single chemical entity capable of modulating multiple biological targets simultaneously[131]. A lower risk of drug-drug interactions in comparison to cocktails or fixed drug combinations is a clear advantage of this strategy. Although the development of such multiple-acting ligands can be challenging due to increased complexity in the design and optimization of such ligands, these difficulties are associated with an early and therefore less expensive stage of the drug discovery process. The risks and costs of developing multiple targeted ligands are in principle no different to the development of any other single entity. A number of clinically used drugs have been found to have activity at more than one target, which in some cases is associated with increased efficacy, in others with side effects. In most cases these are historical drugs for which the multiple activity profile was not designed but serendipitously discovered. The rational design of ligands, that act selectively on specific multiple targets of therapeutic interest termed Designed Multiple Ligands (DML), is a more recent trend.

1.5.1 Lead Generation Strategies

Two fundamentally different methods for discovering DML lead compounds have been reported in the literature: *screening* approach and *knowledge-based* approach that exploit information either from the general literature or from proprietary sources.

1.5.1.1 Screening approach

The screening of compound libraries appears to be the most commonly reported approach to DML lead generation (Fig. 2). Interestingly, the predominant screening strategy so far reported is focussed screening rather than high throughput screening (HTS). This helps to simplify the logistics of screening against multiple targets and improves screening hit rates. In focussed screening, compound classes that are already

known to be active against one of the targets of interest are screened against another target. This is a particularly favoured strategy for kinase targets where DMLs are usually

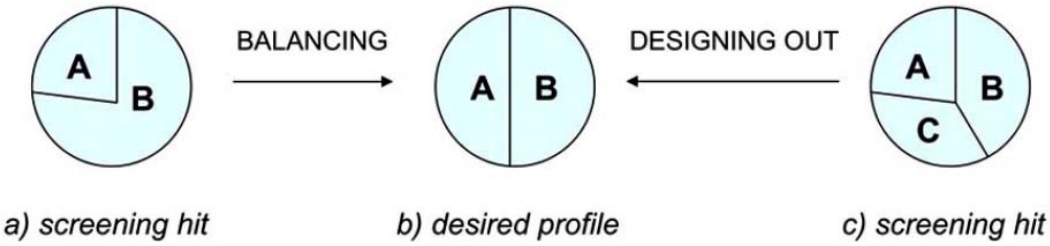


Figure 2: Screening approaches

discovered through the cross-screening of ligands from selective kinase programmes against other kinases. Although DML lead compounds produced by either of these screening approaches would normally have all desired biological activities, it is highly unlikely they would have the desired activity profile. Leads often require "*balancing"*, since one of the biological activities would need a greater improvement during the optimization in order to achieve the desired DML profile. In addition to the desired activities, screening hits frequently bind to other targets. To minimize the risk of side effects these undesired activities will need to be "designed out".

1.5.1.2 Knowledge-based approach

The knowledge-based approach, also referred to as *framework combination*, is another lead generation strategy frequently reported in the literature (**Fig. 3**). This approach is based on a combination of frameworks and the underlying pharmacophores of two molecules, each selective for different target of interest into a single molecule to "design in" both activities. The resulting DMLs are termed *linked, fused or merged,* depending upon the extent to which frameworks of the selective ligands have been integrated (**Fig. 3**). At one end of the whole spectrum of possible degrees of integration reported in the literature are linked DMLs, or conjugates, whose molecular frameworks

are in fact not integrated but connected through a distinct linker group not found in either of the starting selective ligands. In some cases linked DMLs contain a metabolically cleavable linker designed to release two ligands *in vivo* that would then interact independently with each target. This could be seen as a half-way scenario between a true DML and a fixed dose combination. However, in most cases the linker is intended to be metabolically stable yielding a single compound capable of interacting with both targets,

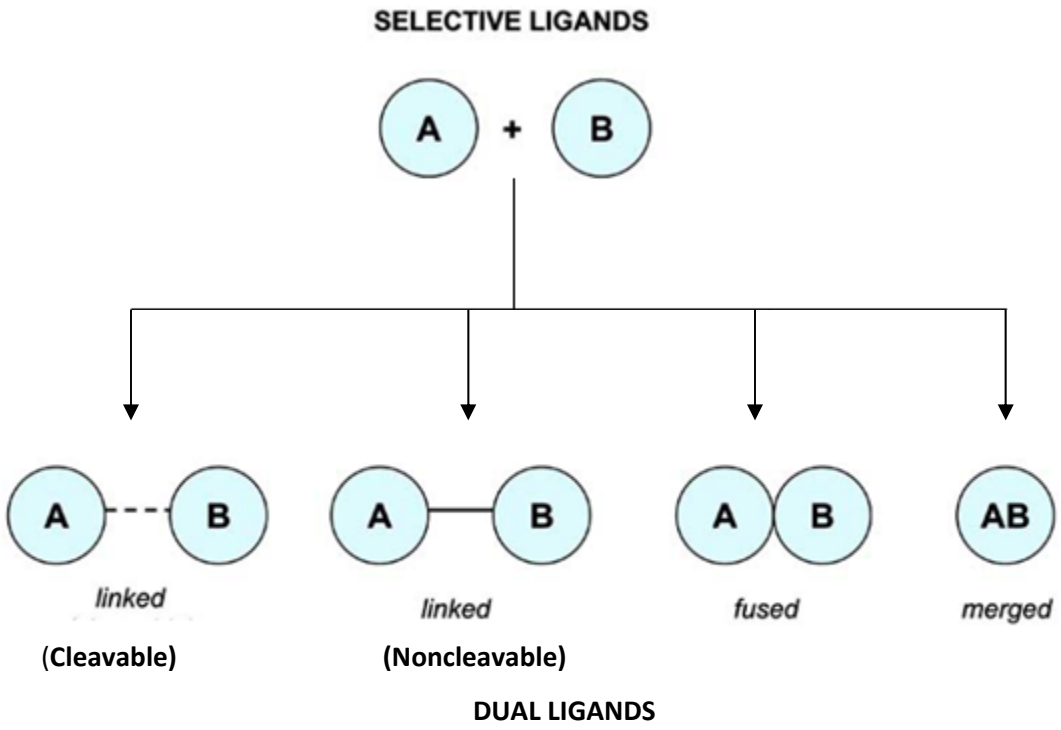


Figure 3: Knowledge-based approaches

albeit different ends of the molecule may be responsible for the activity at the different targets.[132, 133] Medicinal chemists generally aspire to maximize the degree of framework overlap in order to produce smaller and simpler molecules with favorable physicochemical properties. Hence, the most common and most sought after are *merged* DMLs, where the frameworks are integrated by taking advantage of commonalities in the structures of the starting compounds. The screening and knowledge-based approaches can be viewed as complementary strategies. One of the main advantages of the

framework combination approach is a potentially rapid access to a DML starting point, which can be greatly assisted by leveraging the in-depth structure-activity relationship (SAR) knowledge from historical selective ligand projects. Over the recent years efforts have been made to synthesize agents which modulate multiple biological targets simultaneously.[131, 134, 135]

1.5.2 Dual α_1 and β_1 antagonists

Dual inhibition of α_1 and β_1 receptors was considered beneficial as it can decrease pheripheral resistance and cardiac output. The dual acting α and β-blockers may be useful in the management of hypertension. Some dual acting blockers are adimolol, bucindolol, carvedilol, labetalol, medroxalol and primidolol. In experimental studies and in patients with diabetes and hypertension, carvedilol has demonstrated improvements in endothelial vasodilatory and anti-inflammatory functions and in platelet antiaggregation activity.[136] In the GEMINI trial, patients on carvedilol also showed improved insulin resistance and reduced progression to microalbuminuria.[137] Carvedilol helps to produce a desirable hemodynamic profile and facilitates appropriate blood pressure and heart rate responses to exercise. Carvedilol does not appear to adversely affect left ventricular systolic function and in selected patients with heart failure, has been shown to increase the ejection fraction in elderly patients.[138]

1.5.3 β-Blockers with NO vasodilator/β_2-stimulants

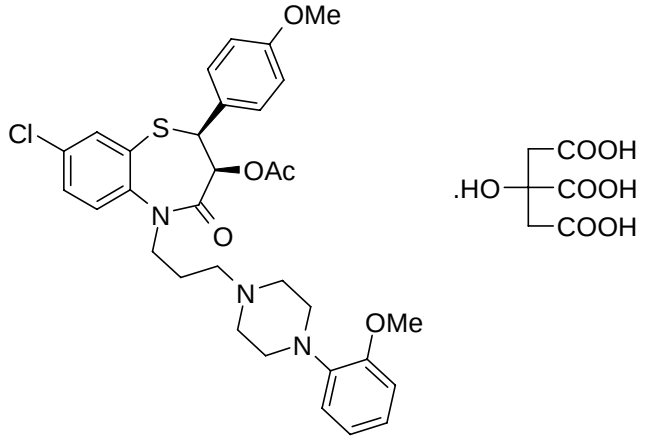
The third generation β_1 blockers are used for the treatment of hypertensive patients, especially with diastolic or systolic dysfunction. Nevibolol (approved in 2007), a highly selective β_1 blocker with an NO-mediated vasodilating effect, looks promising in controlling hypertension[139-142] because it acts by dual mechanisms.[143] The vasodilator effect of nevibolol on the renal artery involves 1) activation of the endothelial β_2-adrenoceptor, 2) participation of Ca^{2+}, 3) increase in NO (by preventing its oxidative degradation) and eNO_S, and 4) activation of Ca^{2+}-activated K^+ channels.[144] SENIORS was conducted to observe the effects of nevibolol in older patients with heart failure

independent of LV ejection fraction (LVEF). A primary outcome showed nevibolol group representing a significant 14% relative risk ratio compared to the placebo group.[145]

Celiprolol, a cardioselective β-blocker with a stimulant effect on β_2 receptors, is as effective an antihypertensive agent as other β-blockers.[146, 147] Celiprolol is useful in treating hypercholesterolemic hypertensive patients because it improves lipid profile (decrease in total cholesterol, low density lipoprotein cholesterol and triglycerides, and increase in high density lipoprotein cholesterol).[148]

1.5.4 Dual CCB and α_1 antagonists

S-2150 (**I**) also inhibited [^{3}H] WB4101 binding to rat cerebral cortical membrane with a mean K_i value of 0.021 μM. It produced relaxation with an IC_{50} of 190 nM in rat



(**I**)

thoracic aorta rings without endothelium, precontracted with KCl (18 mM). S-2150 (**I**) exerted a clear hypotensive effect in spontaneously hypertensive rats (SHR), two-kidney one-clip renal hypertensive rats (RHR) and normotensive rats (NR).[149]

1.5.5 Dual RAS and neutral endopeptidase (NEP) inhibitors

The physiologic interaction of the renin-angiotensin, the kallikrein-kinin and the natriuretic peptide systems in the regulation of body fluid volume and arterial blood pressure provide a rationale for simultaneously modulating these systems in the treatment of disorders such as hypertension and congestive heart failure. The RAS, kallikrein-kinin

system and the natriuretic peptides are important modulators of cardiovascular homeostasis. These systems alter in conditions such as hypertension and CHF, leading to the rationale of simultaneously blocking these systems.[150]

The dual inhibition of AT_1 and NEP could provide clinical benefits in a range of cardiovascular diseases including hypertension and heart failure. LCZ696 (Novartis; East Hanover, NJ, USA) is a dual acting ARB and neprilysin inhibitor. Treatment with LCZ696 provided significant reductions in blood pressure compared to valsartan. This shows that dual inhibition of the ang II receptor and neprilysin have complementary effects.[151] LCZ696 is in the phase II of development. There are two more molecules namely daglutril (phase II) and VNP489 (phase I) which are based on the same concept.[77] In Ruilope study, patients with mild to moderate hypertension were effectively treated by LCZ696 compared to placebo.[152]

1.5.5.1 Dual vasopeptidase (ACE and NEP) inhibitors

Combined inhibition of NEP and ACE produces cardiovascular effects greater than those elicited by selective inhibition of either of the enzymes alone. Moreover, renin-angiotensin, the kallikrein-kinin and the natriuretic peptide systems, all converge at two key regulatory enzymes which are now known to have structurally similar active sites, ACE and NEP. The development of dual metalloprotease inhibitors (**Table 4**), which inhibit both ACE and NEP, exploit this fortuitous complementarity between the active sites and the physiologic roles of these two enzymes and provides a novel approach to the treatment of cardiovascular diseases[153-158] The simultaneous inhibition of both NEP and ACE in animal models of hypertension and heart failure produces hemodynamic or renal effects which are more than additive when compared with those caused by inhibition of either one of these enzymes alone[159-164]

Early studies with vasopeptidase inhibitors were encouraging. Omapatrilat reduced blood pressure in stroke-prone spontaneously hypertensive rats[165] and salt sensitive rats[166] as well as in individuals with mild to moderate hypertension.[167] Larger

trials of omapatrilat, such as OVERTURE,[168] and OCTAVE,[169] confirmed that combined ACE and NEP inhibition might be effective in the treatment of hypertension and heart failure, but also validated concerns about the higher incidence of angioedema with combined therapy than with ACE inhibition alone. Clinically omapatrilat produced great-

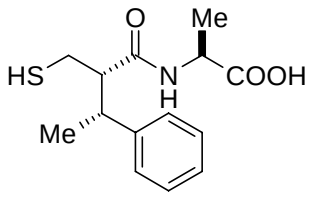
Table 4. Selected vasopeptidase inhibitors[77, 154]

Sr. No.	Compound	Company	Phase of development
1	Omapatrilat	Bristol- Mayers squibb	Phase III
2	Sampatrilat	Roberts	Phase II
3	Gemopatrilat	Bristol- Mayers squibb	Phase I/II
4	MDL-100240	Aventis	Phase II/III
5	Fasidopril	Eli Lilly	Phase II
6	Z-13752A	Zambon/Glaxo Smithkline	Phase II

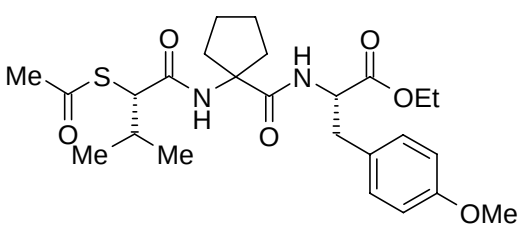
er reductions in peripheral and central pulse pressure in association with a pressure-independent reduction in proximal aortic stiffness. These findings are consistent with a favorable effect of natriuretic peptides on central conduit vessel function.[170] Sampatrilat was shown to lower blood pressure in patients with hypertension.[171] Some researchers have reported molecules which possessed dual antagonism as discussed below.

S21402 (**II**) is a sulfhydryl-containing inhibitor of both NEP (K_i = 1.7 nM) and ACE (K_i = 4.2 nM). S21402 has been tested with purified rabbit kidney NEP and with mouse lung membrane as a source of ACE. The K_i value for NEP is 1.7 nM with ^{3}H-D-Ala-Leu enkephalin as a substrate, and the K_i for ACE is 4.8 nM with NCbz-Phe-His-Leu as a substrate. Oral S21402 reduces systolic blood pressure in an ACE inhibition-sensitive model (SHR) and in a NEP inhibition-sensitive model (DOCA-salt rats).[172]

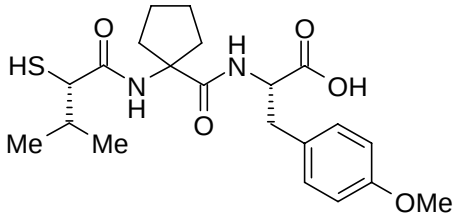
CGS 30440 (**III**) is a thioacetyl-containing dipeptide, which is believed to be metabolized *in vivo* to its biologically active form CGS 30008 (**IV**). CGS 30440 (**III**) had IC_{50} values of 19 nM for ACE and 2.2 nM for NEP. CGS 30440 (**III**) blocked ang I pres-



(**II**)



(**III**)



(**IV**)

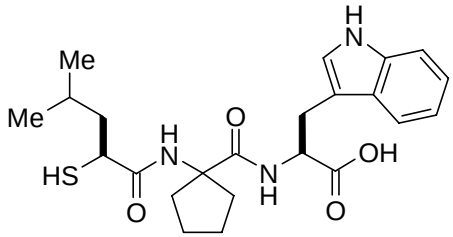
sor responses and increased plasma ANP immunoreactivity during the infusion of exogenous ANP to Sprague-Dawley rats. *In vivo,* CGS 30440 reduced plasma and lung ACE activity and kidney NEP activity in Sprague-Dawley rats for 24 h following a single administration.[173]

1.5.5.2 Triple vasopeptidase inhibitors

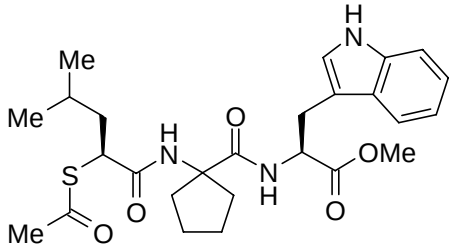
One potential limitation of the ACE/NEP dual inhibition approach is an increase in plasma levels of endothelin 1 (ET-1), a vasoconstricting peptide similar to ang II that is degraded by NEP. This might be overcome by additionally inhibiting endothelin converting enzyme (ECE-1). CGS 35601 (**V**), a triple vasopeptidase inhibitor (VPI), may represent a novel class of antihypertensive drugs and may have the potential to reduce morbidity and mortality from cardiovascular disorders, diabetes and subsequent renal complications. CGS 35601 (**V**) is one of a few single molecules capable of inhibiting the activities of ACE, NEP and ECE simultaneously, with IC_{50} values of 22, 2 and 55 nM, respectively. In order to improve the oral bioavailability of CGS 35601, the S-acetyl,

methyl ester prodrug CGS 37808 (**VI**) was synthesized. At an oral dose of 10 mg Eq/kg, it inhibited the ang I-induced pressor response by an average of 49% for 4 h and potentiated the plasma ANP levels by 103% when compared with vehicle-treated rats.[174]

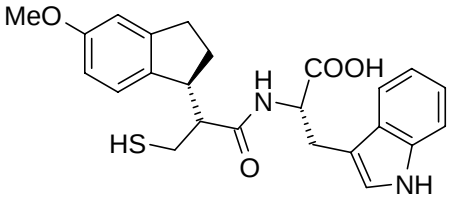
Researchers reported a series of compounds for triple inhibition of ACE, NEP and ECE-1. One of the best compounds derived from this approach was the indanyl analogue (**VII**) displaying binding affinity toward ACE, NEP and ECE-1 with 1.3, 24 and 10 nM respectively.[175]



(V)



(VI)



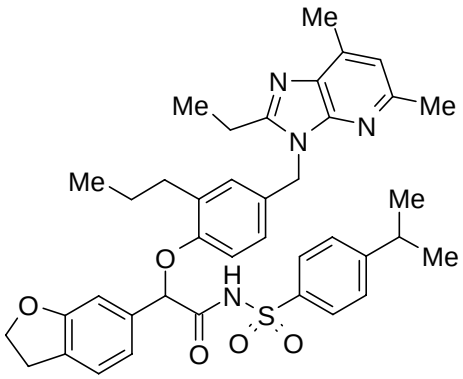
(VII)

1.5.6 Miscellaneous

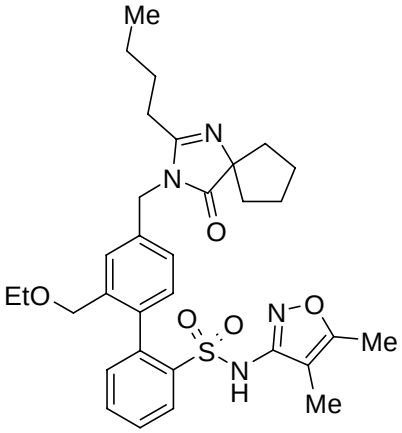
1.5.6.1 Dual ARB and endothelin receptor antagonists

A combination of the AT_1 selective antagonist losartan and the ET_A/ET_B selective antagonist SB-290670 produced an additive reduction in blood pressure compared to either of the drugs alone, prompting groups at Merck and BMS to develop simultaneous blockers of AT_1 and ET_A receptors. Merck and BMS worked on to develop simultaneous blockers of AT_1 and ET_A receptors that resulted into compound (**VIII**) which exhibited balanced activity at all four receptors (AT_1- 0.013, AT_2 -0.032, ET_A- 0.024 and ET_B- 0.06 uM).[176] Another work carried out using the same strategy resulted into balanced antagonist (**IX**) with binding affinity of 0.8 and 9.3 nM for AT_1 and ET_A

respectively.[177] PS433540 (Pharmacopeia) is in the phase II of development possessing dual antagonism of AT_1 and ET_A. The investigators reported PS433540 to be safe and well tolerated.[178]



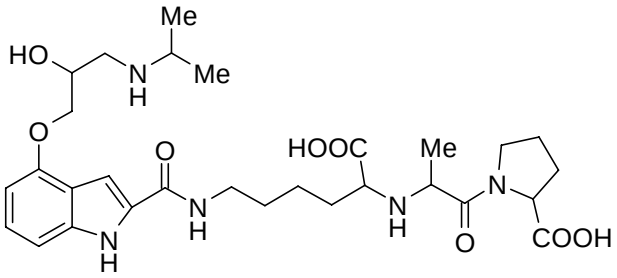
(**VIII**)



(**IX**)

1.5.6.2 Dual ACE and β receptor antagonists

BW A385C (**X**) originated from a programme of research with the objective of developing a novel hybrid drug incorporating both ACE inhibitory and β-receptor blocking properties. The agent produces a competitive blockade of heart rate responses to isoprenaline in a guinea pig right atrial preparation with a pK_b of 6.7 (β receptor blocking properties) and (IC_{50}) of 1.2 ± 0.18 nM (ACE inhibition*). In vitro* and *in vivo*



(**X**)

studies have shown that BW A385C possesses both ACE inhibitory and β receptor blocking properties. BW A385C reduces blood pressure, after acute administration without elevating heart rate and without compromising either cardiac or renal function.[179]

1.5.6.3 Dual ARB antagonists and PPARγ agonists

Telmisartan was later on found to be a multitargeted ligand. ARBs possess partial agonism of peroxisome proliferator-activated receptor gamma (PPARγ) receptor. Data provides a novel insight that telmisartan inhibits AT_1 receptor gene expression through PPARγ activation. The dual inhibition of ang II function by telmisartan – AT_1 receptor blockade and its downregulation – would contribute to more complete inhibition of the RAS. Telmisartan, an ARB and a partial agonist of PPARγ, may be quite useful for the treatment of patients with hypertension with complications such as diabetes and atherosclerosis.[180] A DML may be more useful for microalbuminuria reduction than ARBs with no PPARγ agonistic action. Telmisartan achieved more microalbuminuria reduction than an ARB with no PPARγ agonistic action, possibly through suppression of the inflammatory state in metabolic hypertensive patients.[181] Two more molecules azilsartan and PF-03838135 are reported to possess AT_1 receptor antagonism and a partial agonism of PPARγ.[77]

2.1 AT_1 and α_1 receptors and their antagonism

Hypertension is a hemodynamic disorder arising predominantly due to increase in peripheral vascular resistance.[10] There are two important contributors to the regulation of vascular tone:

- ✓ The sympathetic nervous system (SNS)
- ✓ The renin-angiotensin aldosterone system (RAAS).

Over the years, a number of experimental and clinical investigations have shed light on the key role exerted by RAAS and SNS in the homeostatic control of blood volume and blood pressure.[182, 183] Straightforward evidence has been provided that these two systems do not operate independently but interact mutually with each other in accomplishing their cardiovascular regulatory functions[184, 185] as shown in Fig. 4 below. Stimulation of SNS results into vasoconstriction and increased inotropic and

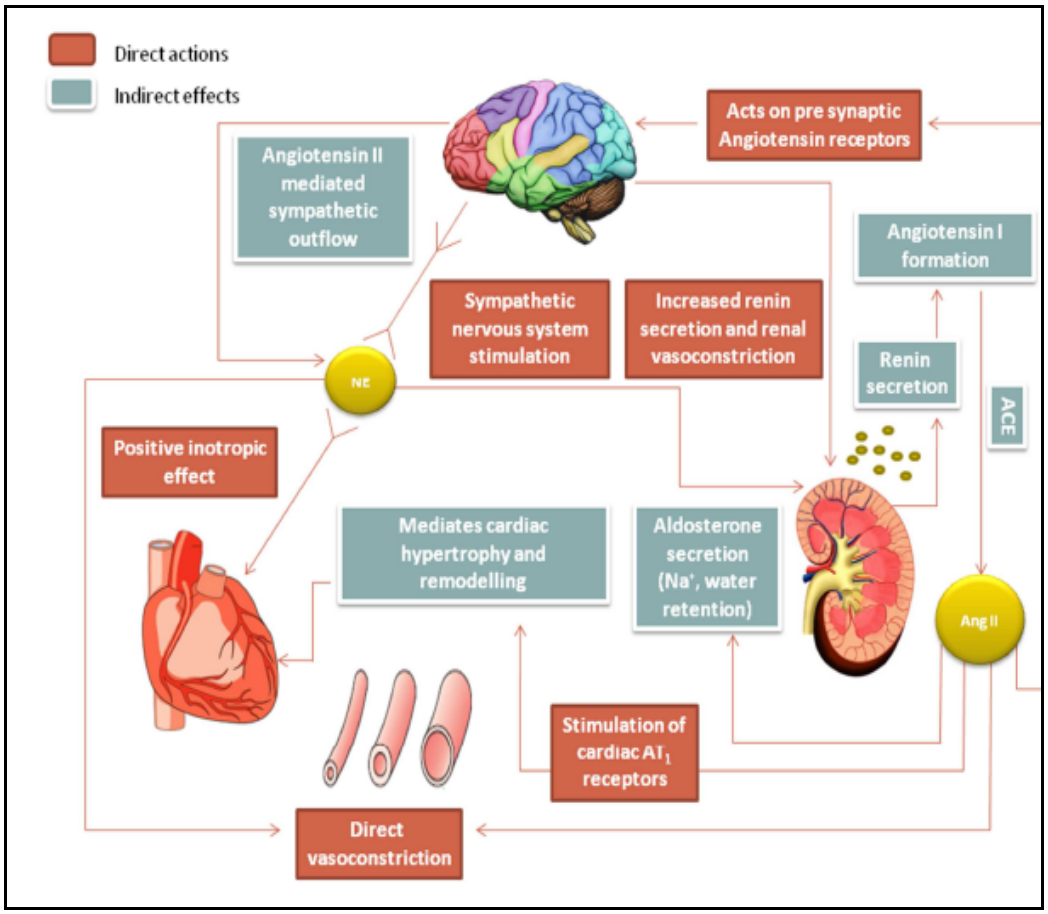


Figure 4: Coordination between Sympathetic Nervous System and Renin Angiotensin System

chronotropic effect of heart, while stimulation of RAAS results in increased production of active hormone ang II, which raises blood pressure in two ways: firstly, ang II is a potent vasoconstrictor that raises systemic vascular resistance and secondly, it indirectly influences blood pressure through release of aldosterone and noradrenaline. Both, SNS and RAAS also appear to modulate fluid volume through kidney. Kidney is a vital organ involved in long term control of blood pressure. The renal-body fluid feedback mechanism couples the long-term regulation of arterial pressure to extracellular volume homeostasis (sodium and water) via pressure natriuresis, whereby the kidneys respond to changes in arterial pressure by altering urinary sodium and water excretion.[186] Both SNS and RAAS systems are primary modulators of renal effects on circulating blood volume. α-Adrenergic receptors are involved only when associated renal hemodynamic changes occur with decrease in renal blood flow (RBF), glomerular filtration rate (GFR) and urinary sodium excretion. Renal α_1-receptors mediate renal (including preglomerular) vasoconstriction and tubular gluconeogenesis. These effects are coupled to tubular Na^+ reabsorption. The direct effect of renal nerve stimulation through renal tubular α_1-adrenergic receptors were observed *in vivo* in the dog[187] and rabbit [188] and *in vitro* in isolated buffer-perfused kidney preparation of the rat.[189-191] On the other hand ang II causes vasoconstriction and diminishes blood flow through the kidneys, thereby increasing the reabsorption of salt and water retention.[192]

Information on the renin-angiotensin-sympathetic interactions has also been extended to the possible sites of these interactions:

- Stimulation of the sympathetic nervous system leads to renin secretion and ang II formation[193]
- It has been shown that released norepinephrine negatively regulates ang II receptors in cultured brain neurons[194]and in vascular tissue through its interactions with α_1-receptor.[195] In neonatal rat cardiac myocytes ang II selectively down-regulates α_1A-receptor subtype mRNA and its corresponding receptors.[196]

Evidence has also been provided that ang II:

- Triggers a sympathetically mediated blood pressure rise associated with systemic vasoconstriction when dosed intracerebrally. It suggested a central facilitatory effect of ang II on sympathetic outflow.[191, 192, 197]
- Plays a facilitatory role on the neuroadrenergic transmission across sympathetic ganglia.[197-199]
- Potentiates norepinephrine release from sympathetic nerve terminals via stimulation of presynaptic angiotensinergic receptors[197, 198, 200] and
- Amplifies the α-receptor mediated vasoconstrictor responses to exogenously administered or endogenously produced norepinephrine. Furthermore, ang II has been shown to exert inhibitory effects on baroreceptor reflex control of heart rate and sympathetic nerve traffic.[197, 198]

The renin-angiotensin-sympathetic interactions have physiological, as well as pathophysiological relevance; a reciprocal reinforcement of the favorable as well as unfavorable cardiovascular, renal, metabolic and reflex effects of the two systems have been reported in a variety of cardiovascular conditions like hypertension.[197-199]

SNS and RAAS become important targets in order to control the blood pressure as both the systems work in coordination. Simultaneous blockade of both systems would be beneficial. Two important targets that emerge out of this study are α_1 and AT_1 receptors.

2.1.1 α_1 Receptor[201]

The α_1 receptor play a pivotal role in the regulation of a variety of physiological processes (**Table 5**), particularly within the cardiovascular system. The main subtypes of α adrenoreceptors (α-adrs) are α_1 and α_2. The occurrence of α_1/ α_2-adrs throughout the vascular bed is not uniform. The initial sub-classification of α_1 adr is into α_1A, α_1B and α_1D subtypes. The α_1A is the predominant receptor causing vasoconstriction in many vascular beds, including the arteries of mammary, mesenteric, splenic, hepatic, omental, renal, pulmonary and epicardial coronary. It is also the predominant subtype in the vena cava and the saphenous and pulmonary veins. Together with the α_1B receptor subtype, it promotes cardiac growth and

structure. The α_1B receptor subtype is the most abundant type in the heart, whereas the α_1D receptor subtype is the predominant receptor causing vasoconstriction in the aorta. α_1A, α_1B & α_1D adr isoforms differ in their biochemical properties, although their tissue distribution is distinct.

Table 5. Distribution, location and function of α_1-adrenergic receptors

Receptor	Location	Action
α_1	Blood vessels (postsynaptic)	Contraction
	Smooth muscle (postsynaptic)	Contraction
	Heart (postsynaptic)	Positive inotropy/chronotropy
	Eyes (postsynaptic)	Mydriasis, ocular hypertension
	Liver (postsynaptic)	Glycogen phosphorylase activation
	CNS (postsynaptic)	Stimulation, inhibition of baroreceptors afferent inputs
	Sympathetic neurons (presynaptic)	Inhibition of nor adrenaline release

2.1.2 AT_1 Receptor[202]

Most of the pressor and tissue destructive mechanisms of ang II are carried out through AT_1 receptor. The circulatory ang II through AT_1 receptor induces vasoconstriction, sympathetic nervous system activation and aldosterone secretion, all of which act in concert to raise blood pressure. Ang II is a potent vasoconstrictor that causes vasoconstriction mainly in the arterioles, thereby increasing the total peripheral resistance. Through its vasoconstrictor properties, ang II diminishes blood flow through the kidneys causing increase in the reabsorption of salt and water. In addition, ang II causes increased sodium reabsorption at the proximal tubules. Ang II also stimulates the release of aldosterone from the zona glomerulosa of the adrenal gland. Aldosterone causes marked increase in sodium reabsorption by the kidney tubules, increasing the extracellular fluid sodium. This in turn causes water retention, which also increases extracellular fluid volume, leading to elevated arterial pressure.

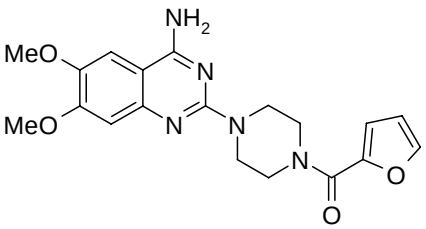
Table 6. Ang II Receptors, their locations and functions

Receptor	Location	Action
AT_1	Vessels	Vasoconstriction
	Brain	Activate sympathetic activity
	Heart	Promote myocyte hypertrophy, Stimulate vascular and cardiac fibrosis, Increase myocardial contractility, Induce arrhythmias
	Kidney	Increase sodium retention Suppress renin secretion
	Adrenal gland	Increase endothelin secretion Increase vasopressin release,
	Nerves	Activate sympathetic activity, Stimulate superoxide formation

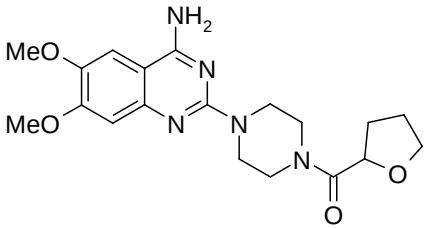
Since the aim of the current work was designing of dual α_1 and AT_1 antagonists, it is in order to survey literature on the α_1 blockers of prazosin category and the AT_1 antagonists.

2.2 α_1 Receptor antagonists[201]

Prazosin (**AP1**) is the prototype α_1 receptor blocker. Other antagonists include terazosin (**AP2**) doxazosin (**AP3**), alfuzosin (**AP4**) bunazosin (**AP5**), tiodazosin (**AP6**), naphazoline (**AP7**) and mephendioxan (**AP8**). 6,7-Dimethoxyquinazoline constitutes the main pharmacophore present in currently marketed drugs as discussed below.



(**AP1**)



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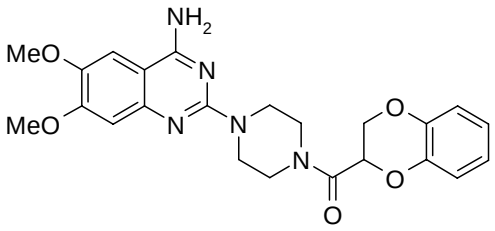
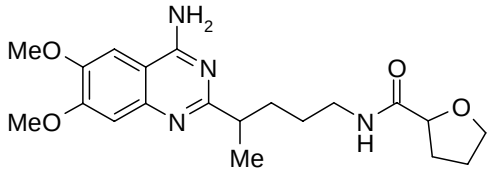
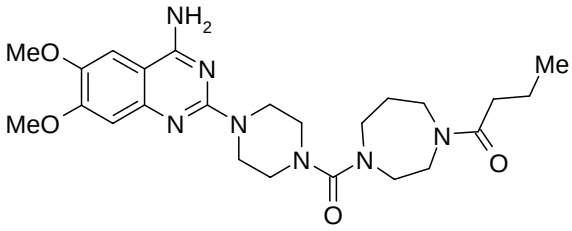


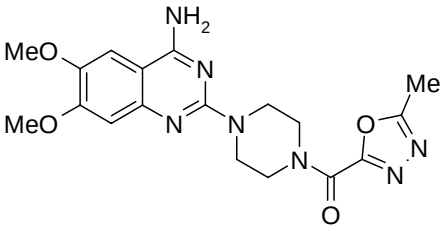
(**AP3**)



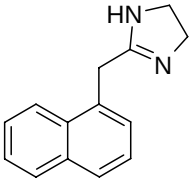
(**AP4**)



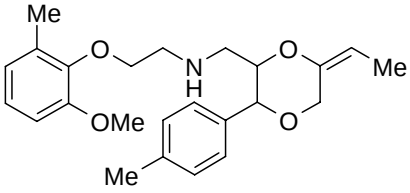
(**AP5**)



(**AP6**)



(**AP7**)



(**AP8**)

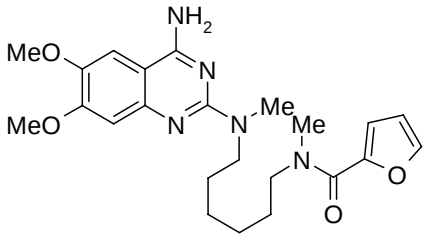
A variety of nuclei has been reported for α_1 receptor antagonistic activity such as five membered rings like imidazolines, fused imidazolines, indoles and fused indoles, six membered rings like quinazolines, pyrimidines, dihyropyrimidines, pyridines, dihydropydridines, pyridazinones, fused pyrimidinediones and *N*-aryl indoles.

2.2.1 Quinazolines reported as α_1 antagonists

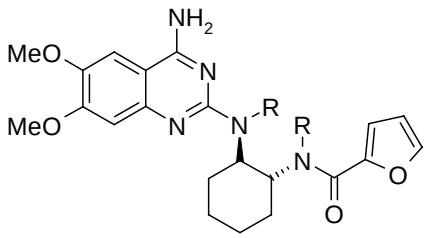
Quinazoline nucleus seems to be essential for α_1 receptor antagonistic activity as is found in marketed drugs like prazosin (**AP1**), terazosin (**AP2**), doxazosin (**AP3**), alfuzosin (**AP4**) and bunazosin (**AP5**). These derivatives have a very high index of α_1-/α_2-adr affinity that triggered off a renaissance of interest in the treatment of hypertension using these drugs.[203] Prazosin (**AP1**) and its analogues such as terazosin (**AP2**),[204] doxazosin (**AP3**),[205] alfluzosin (**AP4**)[206] and bunazosin (**AP5**)[207] are vasodilators with strong action in the arteriolar vascular bed. Researchers working on quinazoline nucleus of prazosin have revealed some key features like importance of

2,4-diaminoquinazoline moiety, particularly N_1 atom. N_1 atom is essential for activity while N_3 can be replaced.[208]

The piperazine moiety at position 2 has been substituted successfully with different groups. Studies reported by Italian workers[209] have indicated that compound (**AP9**), bearing a 1,6-hexamethylenediamine moiety, was the most active of the series, being more potent than prazosin in both in *vivo* and in *vitro* evaluations.

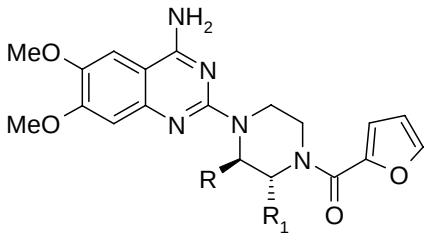


(**AP9**)

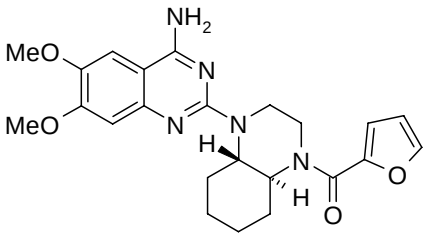


(**AP10**)

A series of compounds were designed in which the polymethylene chain at the position 2 is incorporated partially or completely into constrained structures (**AP10** and **AP11**). The quinoxalinyl derivative cyclazosin **(AP12)** proved to be not only a potent and selective α_1-adr antagonist, but also an effective antihypertensive agent.[210]



(**AP11**)

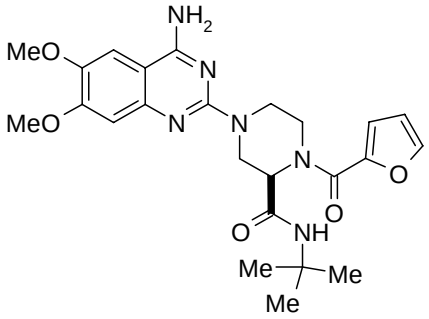


(**AP12**)

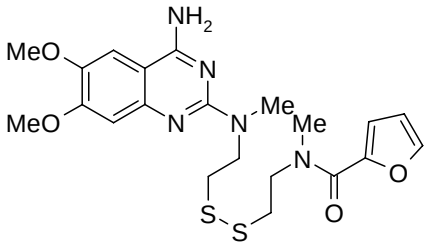
Substituents were introduced at position 5 of the 2-furoyl moiety and its replacement with classical isosteric rings was investigated. The 5-methylfuryl derivative [(+)-metcyclazosin], improved the pharmacological properties of the progenitor, displaying a competitive antagonism, and an 11-fold increase in selectivity for α_1B over α_1A receptor, while maintaining a similar selectivity for the α_1B relative to the α_1D receptor.[211]

Another approach consisted of incorporating new structural elements into the piperazine subunit. Moderate α_1B receptor selectivity was induced by incorporating a

(*s*)-*tert*.butylcarboxamido group at the C_3 of the piperazine moiety, as shown in compound (**AP13**).[212]



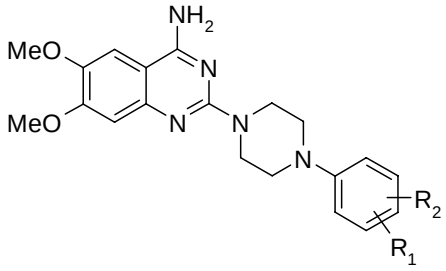
(**AP13**)



(**AP14**)

A novel series of quinazolines related to prazosin and its open chain amino analogue, cystazosin **(AP14)** were synthesized and evaluated for antagonistic activity on α_1 receptor subtypes. The cystamine bearing quinazoline (**AP14**) of this series has a reversed affinity profile relative to (+)-cyclazosin, owing to its higher affinity for α_1D receptor and a significantly lower affinity for the α_1A and α_1B receptor subtypes.[213]

In order to clarify further the importance and the function of the furoyl π system, synthesis and pharmacological properties of a series of 2-(4-heterocyclylpiperazin-1-yl)quinazolines (**AP15**) are reported.[214] Results demonstrate that the heteroaryl moieties in this series provide effective replacement for the carbonyl function present in prazosin.



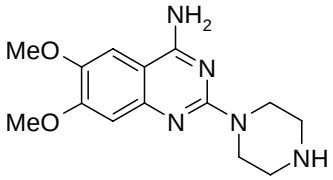
R^1 = H, 4-OCH_3, 4-C_3H_7, 4-CH_3, 4-C_6H_5, 4-NH_2

R^2 = H, 6-OCH_3, 6-NH_2

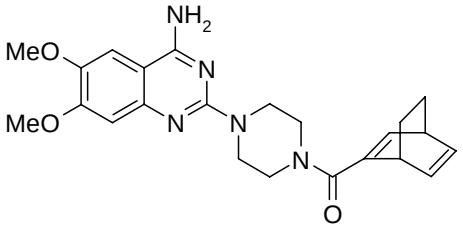
(**AP15**)

A new series of prazosin analogues comprising *N*-acyl derivatives of N^1-(4-amino-6,7-dimethoxyquinazolinyl)piperazine (**AP16**) was prepared and the nature of their binding to α_1 receptor was investigated. A very high affinity and irreversible

binding was observed with the bicyclo[2.2.2]octa-2,5-dien-2-ylcarbonyl derivative, SZL-4945 (**AP17**).[215]

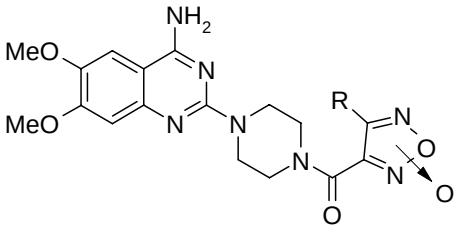


(**AP16**)



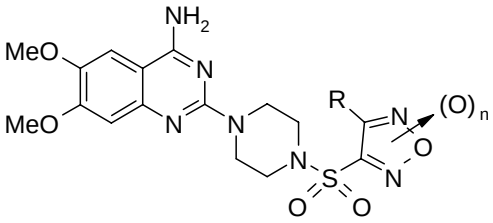
(**AP17**)

Synthesis of furoxan analogues of prazosin, in which the phenyl (or methyl) furoxanylcarbonyl system was substituted for the 2-furonylcarbonyl moiety, was carried out. [216] The design and synthesis of prazosin analogues (**AP18** and **AP19**) was undertaken. Both series of compounds exhibited same potency.[217]



R = C_6H_5, $COOCH_3$, $CONH_2$, CN

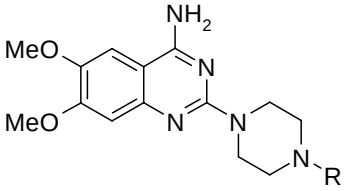
(**AP18**)



R = C_6H_5 and n = 0, 1

(**AP19**)

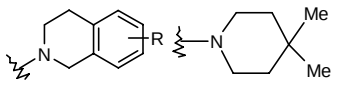
A novel series of piperazine and non-piperazine derivatives of 2,4-diamino-6,7-dimethoxyquinazoline (**AP20** and **AP21**) were synthesized and evaluated for their



(**AP20**) R = COR^1, COAr, $COCH_2NHCOR^1$, $CO(CH_2)_n$-OAr

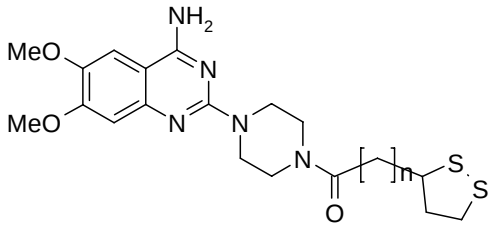
(R^1 = Alkyl and Ar = Disubstituted aryl)

(**AP21**) R = $NHCH_2NHC_6H_5$, NH-$(CH_2)_n$-$CH(C_6H_5)$,

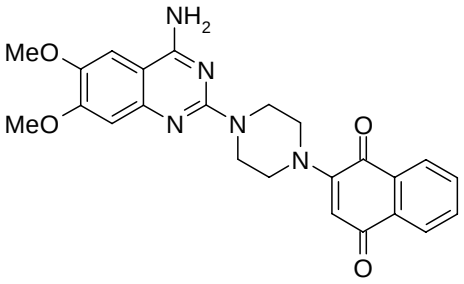


binding affinities toward α_1 receptors.[218] Compounds (**AP20**) showed moderate selectivity toward α_1B receptor subtype, whereas compounds (**AP21**) showed *in vivo* potency close to that of prazosin.[219]

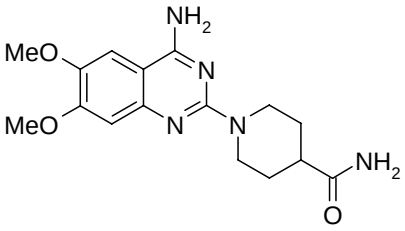
The furoyl moiety of prozosin was replaced with the lipoyl fragment of lipoic acid in compound **(AP22)** and with 1,4-naphthoquinone in compound **(AP23)**.[220] All of the compounds were effective α_1 receptor antagonists when tested by both functional and binding assays.



(**AP22**) n = 0, 1, 4

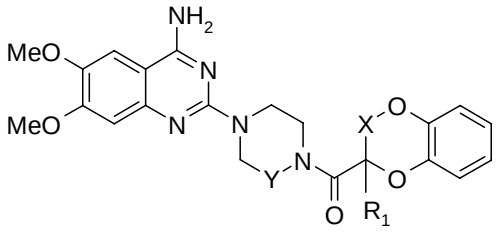


(**AP23**)



(**AP24**)

The piperazine ring at the 2-position has been replaced by its 4-deaza analogue (**AP24**) resulting into the piperidine ring system bearing a carboxamide moiety on its 4th position. It has been observed that increase or decrease in the activity is rather related to the substitutions on the 4-carboxamido moiety.[221] Replacement of this carboxamido system with ethylenedioxyalkyl groups led to an increase in the α_1-adr affinity and potency compared to prazosin.[222]



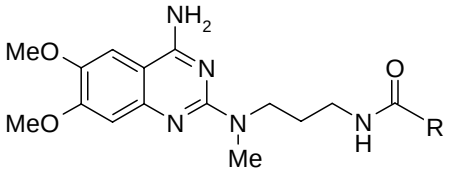
Y = CH_2, $(CH_2)_2$, $CH(CH_3)$; R_1 = H, CH_3; X = $CH(CH_3)$, $(CH_2)_2$, CH_2

(**AP25**)

Simultaneous replacement of piperazine and furyl moiety was reported by researchers. Many derivatives of doxazosin were synthesized in which the 1,4-benzodioxan moiety was explored with the aim to preserve the α_1 receptor affinity and

selectivity, and to prolong the duration of antihypertensive activity. Most of the members of this series (**AP25**) displayed high affinity for α_1 receptors and none of the compounds showed any significant activity at α_2 receptor sites.[223, 224]

The synthesis and biological activity of some *N*-[(acylamino)alkyl]-6,7-dimethoxy-2,4-quinazolinediamines was carried out and it was found that the anti-hypertensive properties of these new molecules appeared to strongly depend on the length of the alkylamine chain. Maximum activity was observed in compounds having a propyl chain between the two nitrogen atoms. Compounds (**AP26 - AP28**) were found to be the most potent derivatives as antihypertensive agents form this study.[225]

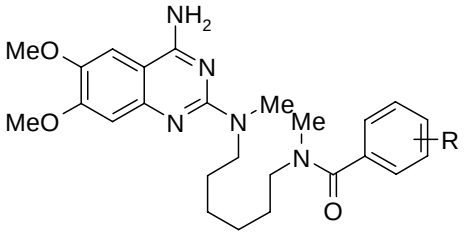


(**AP26**) R = C_6H_5

(**AP27**) R = Tetrahydro-2-furyl

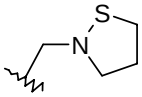
(**AP28**) R = Cyclopentyl

Simultaneous replacement of both piperazine and furan ring of prazosin gave (**AP29 - AP32**), which resulted in a potent and selective α_1B receptor antagonist (85-



(**AP29**) R = H

(**AP30**) R = 2-$CH_2NH(CH_2)_4NH_2$

(**AP31**) R = 

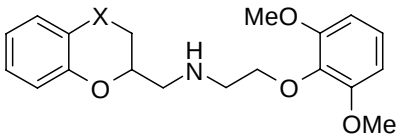
(**AP32**) R = 3-$CH_2N(CH_3)(CH_2)_4NHCH_3$

and 15-fold more potent than prazosin, at the α_1A and α_1D receptor subtypes, respectively).[226]

2.2.2 Benzodioxan containing antagonists

Benzodioxans represent one of the oldest and the best known class of $\alpha_1$dr antagonists which involve chemical structures incorporating a 1,4-benzodioxan-2-yl

moiety as the main structural feature responsible for the α_1 receptor antagonist activity. Compound, WB 4101 (**AP33**) is the prototype of α_1 receptor antagonists bea-

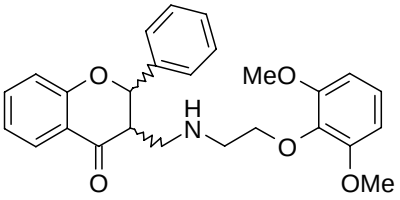


(**AP33**) X = O

(**AP34**) X = S

ring a benzodioxan moiety. Both the benzodioxan-2-yl and (2,6-dimethoxy phenoxy) ethylamino moieties are reported to be essential for the activity. As a result, a variety of analogues have been studied involving modifications at the benzodioxan ring, the amine function or the (2,6-dimethoxyphenoxy)ethyl moiety.[227, 228]

Replacement of ring oxygen at position 4 of the benzodioxan ring of WB 4101 (**AP33**) with sulfur atom in the benoxathian (**AP34**) did not modify the biological profile, but rather gave a potent and highly selective α_1 receptor antagonist.[229-230] Various structural modifications performed on the benzodioxan ring system include replacement of hydrogens at 2- or 3-position with a variety of substituents.[231] Replacement with methyl, isopropyl, cyclohexyl, phenyl or *p*-substituted phenyl groups at position 3 either in *cis* or *trans* relationship relative to the side chain at position 2 led to compounds having better α_1/α_2 selectivity; but except for the derivatives bearing the phenyl and *p*-methylphenyl substitutions at position 3, none of them showed selectivity for the α_1 receptor subtype. These results imply that the 3-substitution endows a significant role in the modulation of selectivity for α_1 receptor subtypes.



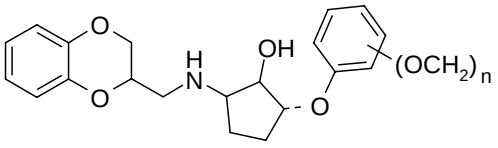
(**AP35**)

Subtle variations at positions 1 and 4 have been made to assess affinity and selectivity for α_1 receptor subtypes. These modifications however, did not improve the

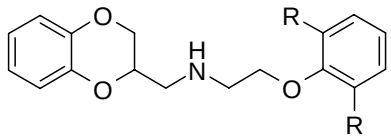
biological profile of these molecules with the exception of compound (**AP35**). Compound (**AP35**) is more selective to α_1A adr subtype than to the α_1B and α_1D receptor subtypes.

Further modifications in WB 4101 (**AP33**) to optimize the activity by fusion of cyclohexane or an additional benzene ring with benzodioxan were tried and evaluated for possible modulations in activity and selectivity.[232] Opening of the dioxan ring of compound (**AP33**) through the cleavage of C_2 and C_3 bonds gave a very potent ligand at α_1 receptor. This structural modification also resulted in an inversion of the selectivity profile, as the resulting compound was more potent at α_1D-adr than at α_1A and α_1B receptor subtypes.[233]

A series of WB410155-related benzodioxans were synthesized by replacing the ethylene chain separating the amine and the phenoxy units of **AP33** with a cyclopentanol moiety. Compound (**AP36**) displayed a significant affinity toward the α_1D receptor. The stereochemistry of cyclopentane unit had a great influence on the affinity.



(**AP36**)



R = F, Cl, *t*-Bu, OCH_3, CH_3, C_2H_5, CH_2CH_2Cl, *i*-Pr

(**AP37**)

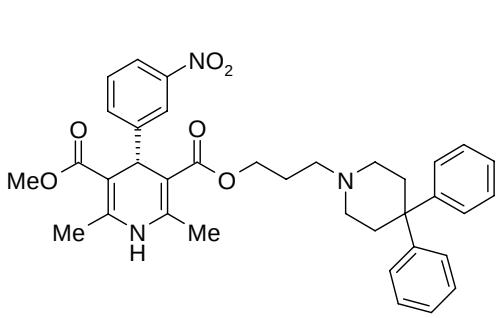
A number of ortho-disubstituted analogues of 2-[(2-phenoxyethyl)amino methyl]-1,4-benzodioxan were designed and synthesized in both the enantiomeric forms and tested in binding assays on the same receptors. The affinity values of the new compounds (**AP37**) were compared with the enantiomers of WB 4101 and of the ortho-monosubstituted derivatives, suggesting some distinctive aspects of the interaction of the phenoxy moiety, in particular with the α_1A and the 5-HT_{1A} receptors of the monosubstituted and the disubstituted compounds.[234]

To evaluate a possible role of p electrons, the dehydrodioxan ring of **AP33** was replaced by phenyl, indole and tetrahydronaphthalene rings. Low activity of all

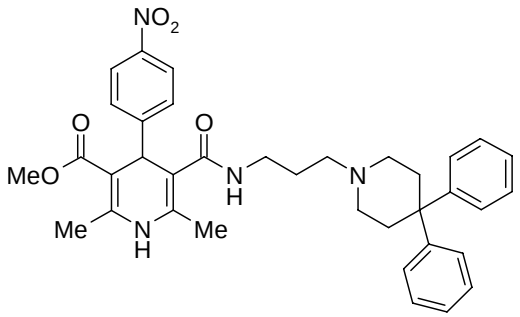
these compounds indicates that the 1,4-benzodioxane ring system is an integral pharmacophore for the activity, and rings like naphthalene, indole, tetrahydronaphthalene may have misfit planarity with the α_1 receptor.[235]

2.2.3 Dihydropyridine and dihydropyrimidine containing antagonists

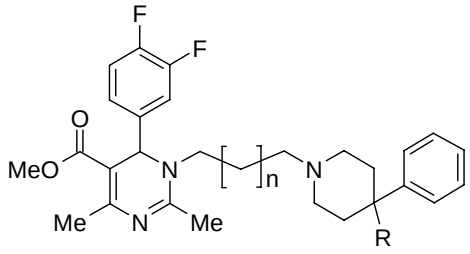
In contrast to the prazosin analogues, the 1,4-dihydropyridine, (*S*)-(+)-niguldipine (**AP38**) exhibits 340 to 630-fold selectivity in binding to the cloned human α_1A receptor relative to the α_1B and α_1D receptors.[236] Another compound belonging to dihydropyridine class of compounds is SNAP 5089 (**AP39**), which is closely related to niguldipine a known Ca^{2+} channel blocker. Analogues of (*S*)-(+)-niguldipine were synthesized with the aim of achieving greater selectivity and affinity for the human α_1A receptor and reducing Ca^{2+} channel affinity.[201]



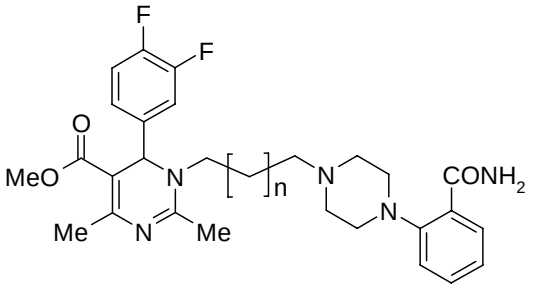
(**AP38**)



(**AP39**)



(**AP40**) n = 2, 3 etc.; R = $CONH_2$, CN

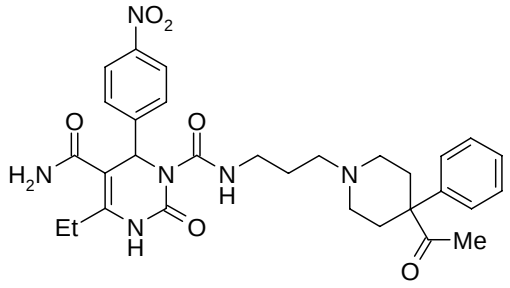


(**AP41**) n = 2, 3 etc.

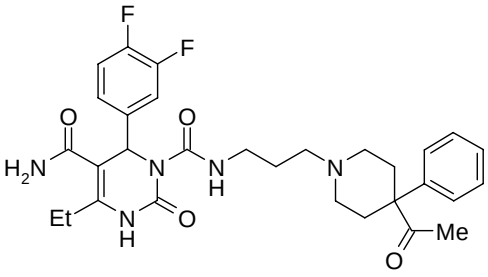
In an effort to optimize the pharmacokinetic parameters by replacing the dihydropyridine moiety with a dihydropyrimidine template, a number of dihydropyrimidines (**AP40** and **AP41**) showed good binding affinity (>300-fold) and selectivity for α_1A-adr over α_1B, α_1D, and α_2 receptors. A number of modifications on the dihydropyrimidine template, linker chain, and piperidine or piperazine side chains

are well tolerated. Although, all these modifications yielded compounds with good binding affinity and selectivity for α_1A receptors, their pharmacokinetic profile was found to be poor with low bioavailability and short plasma half-lives.[237]

Dihydropyrimidinone would not undergo oxidative metabolism shown by dihydropyrimidine nucleus and therefore, might exhibit a better pharmacokinetic pro-



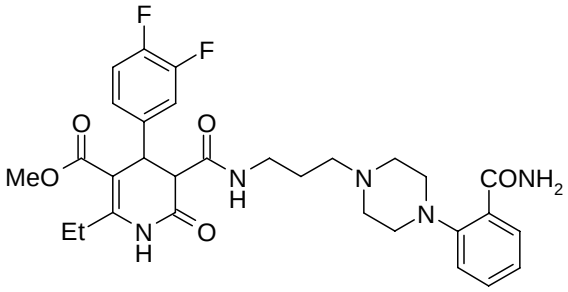
(**AP42**)



(**AP43**)

file. Thus, new compounds (**AP42** and **AP43**) were synthesized. These compounds showed good binding affinity and subtype selectivity for α_1A receptor.[238]

Working on similar lines, new derivatives of dihydropyrimidinone containing substituted 4-phenylpiperazines were synthesized. *Dextro* isomer of compound (**AP44**) was identified as a lead compound with a binding and functional profile comparable to the standard.[239]

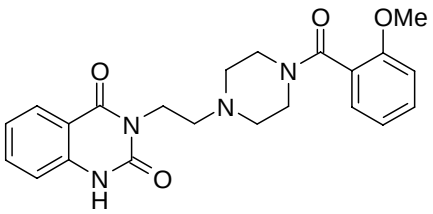


(**AP44**)

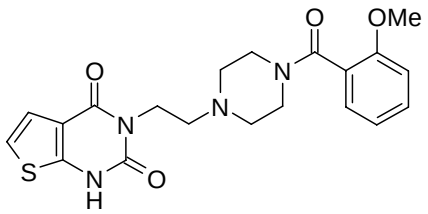
2.2.4 Fused pyrimidinedione containing antagonists

The prototype of this type of compounds is shown by the general structure, the quinazoline-2,4-dione derivative, SGB 1534 (**AP45**), which exhibits potent α_1 adr inhibiting activity.[240] The quinazoline-2,4-dione part has been replaced with a variety of heterocycles like thienopyrimidine-2,4-dione (**AP46**), exhibiting effective α_1 receptor blocking properties.[241]

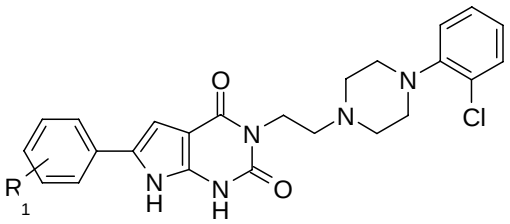
A new series of selective and high-affinity α_1-adr ligands, characterized by a 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)dione system, was synthesized. Compounds (**AP47**-**AP49**) displayed affinity in the nanomolar range for α_1 receptor.



(**AP45**)



(**AP46**)

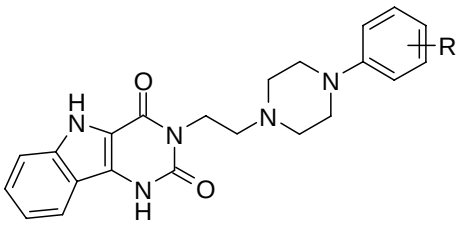


(**AP47**) R_1 = 2-Me

(**AP48**) R_1 = 2-OMe

(**AP49**) R_1 = 4-Cl

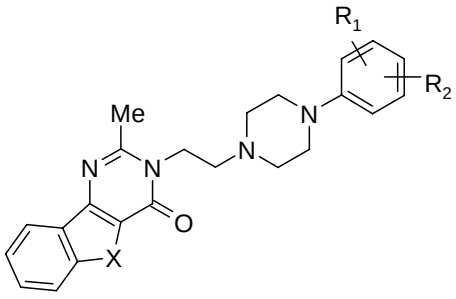
On similar lines a tricyclic 3-substituted pyrimido[5,4-*b*]indole-2,4-dione system was coupled by means of an alkyl chain to the phenylpiperazine moiety to



(**AP50**) R = 2-OMe

(**AP51**) R = 4-*i*.Pr

(**AP52**) R = 4-*tert*.butyl



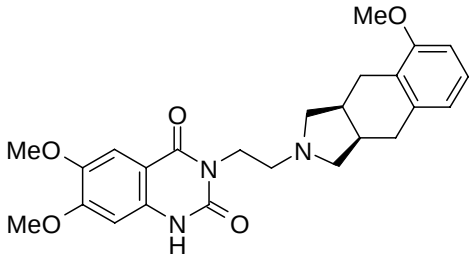
(**AP53**) X = NH, R_1 = 2- OMe, R_2 = 5-Cl

(**AP54**) X = S, R_1 = 2- OMe, R_2 = H

develop selective α_1-adr binding ligands. In this series, compound (**AP50**) emerged as the most interesting candidate showing higher affinity and selectivity for α_1-adr on rat cortical membranes over α_2, β_2, and 5-HT_1A receptors. Compounds (**AP51** and **AP52**), bearing 4-*iso*.propyl and 4-*tert*.butyl substituents respectively, when tested in

the binding assays on the three human cloned α_1 receptor (α_1A, α_1B, and α_1D) subtypes, exhibited very good α_1D receptor selectivity.[242]

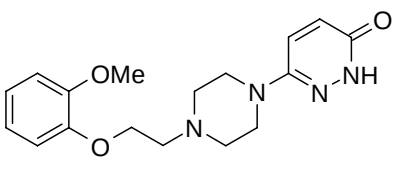
A number of new pyrimido[5,4-*b*]indole and benzothieno[3,2-*d*]pyrimidine derivatives were synthesized and evaluated for their binding and functional properties at α_1 receptor subtypes. In binding assays on human cloned receptors, some new compounds such as (**AP53** and **AP54**) showed very high affinity and a slight preference for the α_1D-adr subtype.[243] Further, modifications in this series involving replacement of tricyclic pyrazinothienopyrimidine-2,4-dione part with various azaquinazoline-2,4-diones, diazaquinazolin- 2,4-diones, pyrrolopyrimidine-2,4-diones and various thienopyrimidine-2,4-diones gave a diverse series of compounds. The dimethoxyquinazoline-2,4-dione has also been used to replace the tricyclic pyrazinothienopyrimidine-2,4-dione part as in **AP55**. Compound (**AP55**) was found to be the most potent with highest degree of selectivity in the radioligand-binding assays (57-fold). The overall conclusion from the various modifications is that, the selectivity is manifested only with the quinazolinediones of which the 6,7-dimethoxyquinazolinediones are found to be the best.[244]



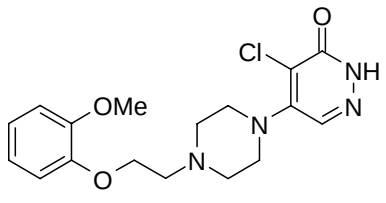
(**AP55**)

2.2.5 Pyridazinone ring containing antagonists

The literature search reveals pyridazinones as a class of compounds with a potential for selective α_1 receptor antagonist activity. The pyridazinone derivatives



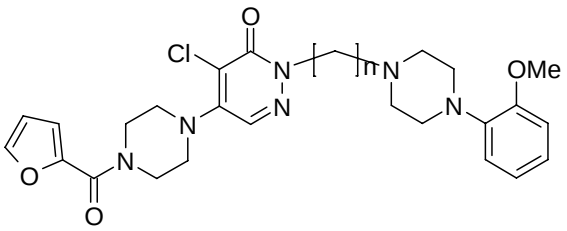
(**AP56**)



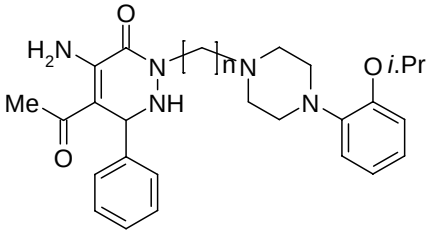
(**AP57**)

(**AP56** and **AP57**) have been reported as biologically active antihypertensives.[245-246]

Barbaro et al.,[247] in order to increase the selectivity of these compounds, developed a three dimensional model of the pharmacophoric features responsible for the α_1 receptor antagonistic activity. On this basis, a new series of pyridazin-3(2*H*)-one derivatives was evaluated for its *in vitro* affinity toward both α_1 and α_2 receptors. Compound (**AP58**) showed a very high selective affinity for the α_1 receptor, which was 274 times higher than that for α_2 receptor. The effect of alkoxy substitution at the o-position was studied and it was found that the bulkier alkoxy substitution at this position increased the affinity by 4 to 5-folds. The optimum activity was obtained in compound (**AP59**) bearing an *iso.*propoxy substituent.[248]



(**AP58**)



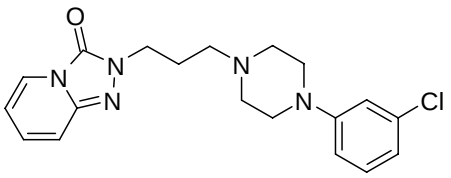
(**AP59**)

4,5-Disubstituted-6-phenylpyridazinones (**AP59**) having an arylpiperazinyl alkyl side chain at position 2 and carrying an ethylenic spacer between the protonated arylpiperazine and the pyridazinone groups showed slight α_1D/a_1A, high α_1D/a_1B, and very high $\alpha_1A/5\text{-}HT_1A$ and $\alpha_1D/5\text{-}\ HT_1A$ receptor selectivities.[249]

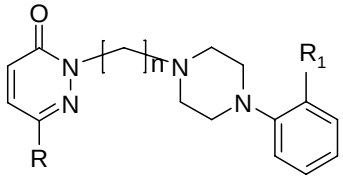
Using a rational design approach, compounds bearing a benzimidazolyl or imidazolyl substituent on the pyridazinone moiety have been synthesized and evaluated for α_1 receptor affinity and blocking activities. The most active compound of the series showed 1.1 nM affinity toward α_1 receptor.[250] The importance of substituents on the pyridazinone ring was further studied by synthesizing a series of derivatives having arylpiperazinylalkyl chain at different positions of the ring. Most of the synthesized compounds showed high potency in all the assays and some degree of selectivity for α_1A and α_1D receptor subtypes.[251]

In order to increase the affinity and selectivity for α_1-adr and its subtypes, new series of compounds containing benzimidazolylpyridazinone, indolylpyridazinone, and imidazolylpyridazinone moieties were prepared by modifying the structure of trazodone (**AP60**). The SAR studies of these compounds suggested that the presence

of a methoxy group at the *o*-position of the phenylpiperazine moiety led to the best α_1 receptor affinity and selectivity profile. Lengthening of the spacer chain to three- or four-carbon atoms afforded compounds with an increased affinity toward α_1 adrs.



(**AP60**)



(**AP61**) R = 1- Benzimidazolyl, n = 4, R_1 = OMe

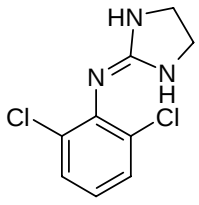
(**AP62**) R = 1- Imidazolyl, n = 7, R_1 = Cl

(**AP63**) R = 1- Indolyl, n = 4, R_1 = OMe

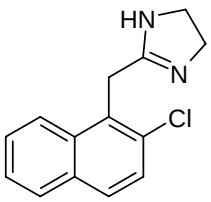
Further, elongation of the spacer to five- and six-carbon atoms led to slight decrease in the activity. These experimental results suggested that the long alkyl spacer, mainly based on its conformational flexibility, could assume a size and shape that influenced the affinity (and selectivity) of compounds to α_1 and α_2 receptors. Compounds (**AP61**-**AP63**) were found to be the most active in this study.[252]

2.2.6 Imidazolines and fused imidazoline containing antagonists

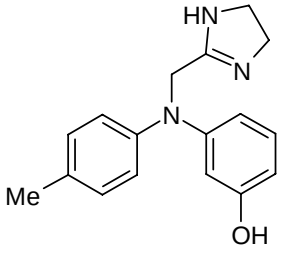
Since a long time imidazoline derivatives have been considered as one of the major class of drugs interacting with α_1 receptor. Compounds like clonidine (**AP64**) and naphazoline (**AP65**), which contain a 2-iminoimidazolidine and imidazoline rings, respectively, show α_1- and α_2 receptor antagonist activities.[253] Furthermore, specifically phentolamine (**AP66**), which contains an imidazoline ring, is a well known α_1 adr antagonist.[254]



(**AP64**)



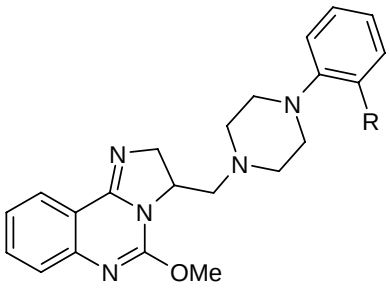
(**AP65**)



(**AP66**)

Conformationally restricted analogues have been synthesized to check their selectivity for α_1A receptor. Compounds (**AP67** and **AP68**) were the most potent

compounds of this series that showed better affinity than that of prazosin and SGB 1534.[255]

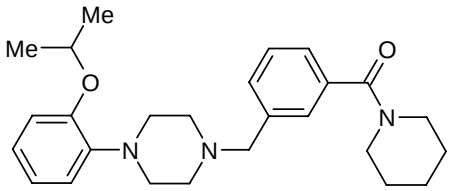


(**AP67**) R = OMe

(**AP68**) R = Cl

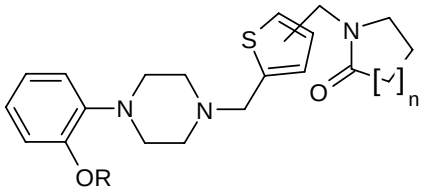
2.2.7 N-Aryl and N-heteroaryl piperazine derivatives

Synthesis and activity of RWJ-37796 (**AP69**), an arylpiperazine derivative, which binds with high affinity (K_i < 4 nM) to 5-HT_1A and α_1A receptors, have been reported.[256] α_1-Adr binding has been broken into α_1A (0.20 nM) and α_1B receptor (47 nM) components by competition experiments with the α_1A receptor ligand WB 4101.

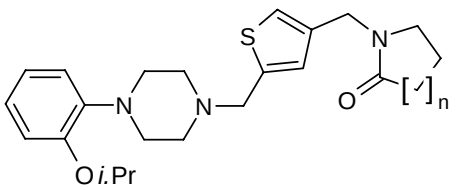


(**AP69**)

Screening of a chemical library against α_1-adr in a radioligand binding assay has led to the discovery of a new series of compounds with the general structure of **AP70**. Further, modifications in the structure of these compounds were done with an aim to improve their affinity and selectivity. Compounds (**AP71)** are highly potent against a_1A receptor and very selective for it than other subtypes.[257]



(**AP70**) n = 1-3



(**AP71**) n = 1-3

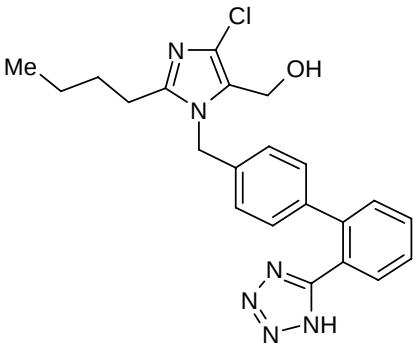
A new series in which the thiophene ring was replaced by other five-embered heterocyclic ring systems like isoxazole, oxazole and thiazole was synthesized and

evaluated for α_1-adr subtypes binding affinities. Binding affinities of these derivatives clearly indicated that these heterocyclic ring systems were not well tolerated for the potency, as well as selectivity for the α_1A receptor subtypes.[258]

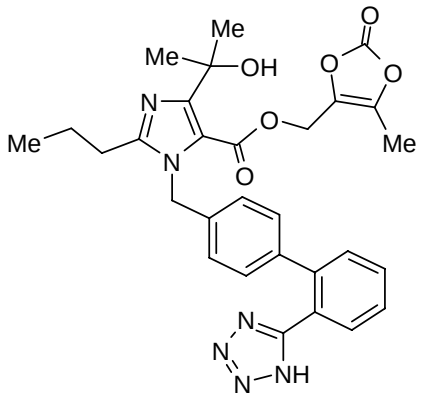
A new class of piperazine derivatives was designed, synthesized and biologically tested for the α_1 receptor antagonistic activity. Biological data showed an interesting profile for the phenylpiperazine subclass which was found to have nanomolar affinity toward α_1 receptor and less pronounced affinity for α_2 and the 5-HT_1A serotoninergic receptors.[259]

2.3 AT_1 receptor antagonists[202]

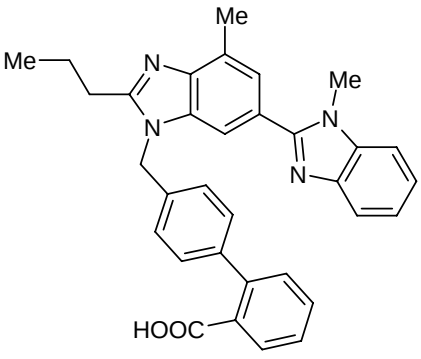
Some of the marketed AT_1 receptor antagonists are shown below. Losartan (**AT1**) is the prototype for this class of antagonists. Other antagonists are olmesartan (**AT2**), telmisartan (**AT3**), valsartan (**AT4**), candesartan (**AT5**) and irbesartan (**AT6**)



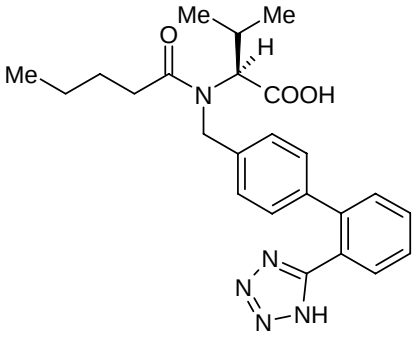
(**AT1**)



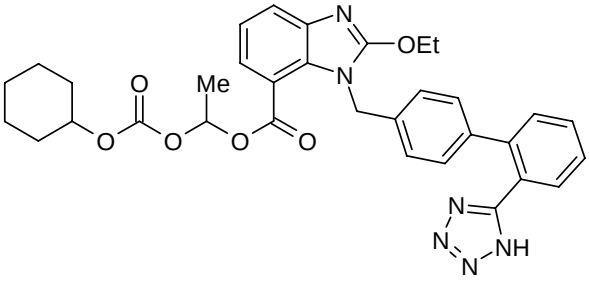
(**AT2**)



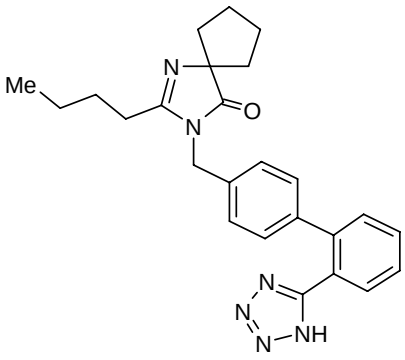
(**AT3**)



(**AT4**)



(**AT5**)



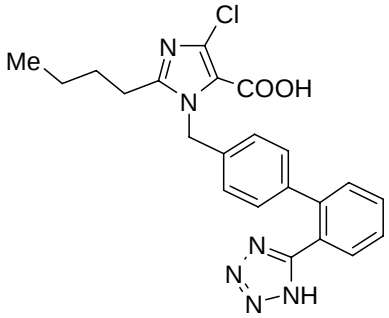
(**AT6**)

Variety of nuclei have been reported as AT_1 antagonists which are categorized on the basis of type of nuclei like five membered triazoles, imidazoles, pyrroles, dihydropyrazolones; six membered quinolines, isoquinolines, quinazolines, quinazolinones, pyridazines, piperazines and fused five and six membered ones as reported below.

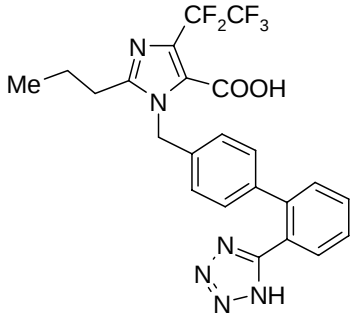
2.3.1 Imidazole containing antagonists

The Structure Activity Relationship (SAR) studies of the substituted imidazole ring of losartan (**AT1**) and EXP3174 **(AT7)** have been carried out. At C_2 position of imidazole, an alkyl chain of 3-4 carbon atoms in length is required. Introduction of unsaturation in the alkyl chain at C_2 position slightly increased the binding affinity while branched alkyl, cycloalkyl and aromatic substituents lowered binding affinity. At C_4 and C_5 positions, the exact steric or electronic properties did not appear critical for binding.[260]

At C_5 position, hydroxymethyl, carboxaldehyde, or carboxamido groups yielded potent antagonists. Acidic group at C_5 is also advantageous as seen in case of



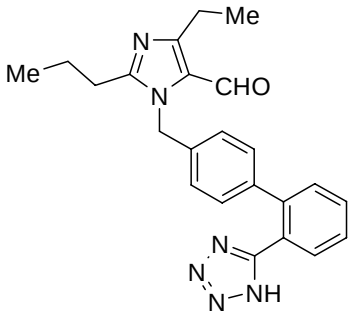
(**AT7**)



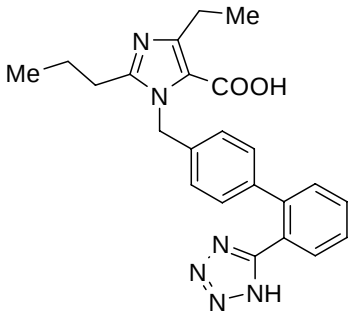
(**AT8**)

EXP3174 (**AT7**).[261] Acylsulfonamides as non-tetrazole analogs of EXP3174 have been reported by Naylor et al. The most potent compound of the series showed equal or slightly higher potency than EXP3174.[262]

Substitution at C_4 position of imidazole does not appear critical for binding to the enzyme. Halogens, alkyl, aryl and heteroaryl groups are successfully substituted at this position. Within the series of 4-halo derivatives, the SAR depends in part on acidic functional group present at biphenyl ring. A large lipophilic and electron withdrawing group is favored at this position as supported by good binding affinity shown by the compound having CF_3 group at C_4 position. A series of 4-(perfluoroalkyl)imidazoles have been reported as AT_1 antagonists with the most potent compound DuP 532 **(AT8)** possessing 4-pentafluoroethyl substituent. Compound (**AT8**) has an IC_{50} value of 3.1 nM (rat adrenal) and decreased blood pressure with ED_{30} of 0.02 mg/kg (i.v.) and 0.21 mg/kg (p.o.) in RHR.[263, 264] Aliphatic groups at C_4 position of imidazole afforded increased *in vitro* and *in vivo* potency. DMP 581 (**AT9**) is reported to be a potent antagonist having IC_{50} value of 2.1 nM in rat adrenal membrane preparation and it decreased blood pressure with an ED_{30} value of 0.027 mg/kg (p. o.) in the RHR.[265, 266] Compound (**AT9**) was metabolized to its more active diacidic metabolite DMP 811 (**AT10**) (IC_{50} 6 nM, rat adrenal).



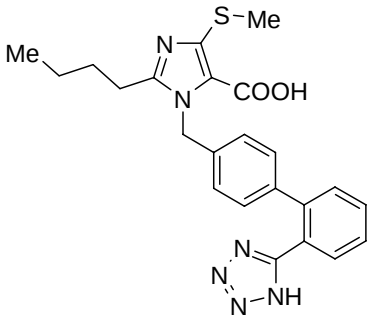
(**AT9**)



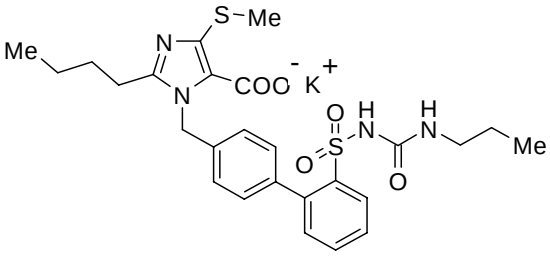
(AT10)

There are reports indicating that the hydroxymethyl substituent at C_4 position along with carboxyl substituent at the C_5 position of imidazole nucleus is favorable for the antagonistic activity.[267] The concept of substituting C_4 position with differently substituted alkylthio groups resulted into development of potent RU 56184[268] (**AT11**) having IC_{50} value of 0.2 nM with an ID_{50} of 0.05 mg/kg (i.v.) and 0.4 mg/kg (p.o.).

Replacement of the tetrazole moiety of compound (**AT11**) with alkyl substituted sulphonylureas resulted in HR 720 (**AT12**),[269] an insurmountable antagonist (IC_{50} 0.48 nM, rat liver). In pithed normotensive rats compound (**AT12**) inhibited the ang II induced pressor response when dosed intravenously (ID_{50} 0.11 mg/kg) and orally (ID_{50} 0.7 mg/kg).

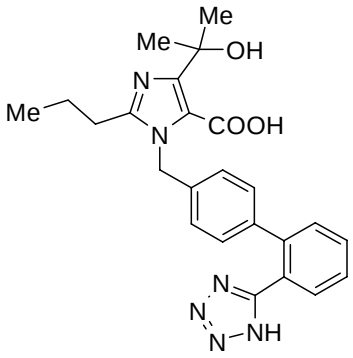


(**AT11**)

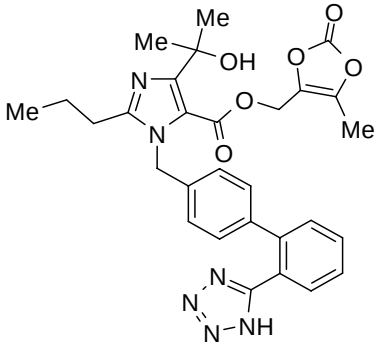


(AT12)

Sankyo's CS-866 (**AT14**) (Olmesartan) is completely and rapidly hydrolysed to the active acid, RNH 6270 (**AT13**). Compound (**AT13**) with IC_{50} of 8.1 nM in bovine adrenal cortex (ID_{50} 0.0079 mg/kg) is the most potent derivative of C_4 (alkyl, alkenyl and hydroxymethyl) substituted imidazole-5-carboxylic acid series.[270]

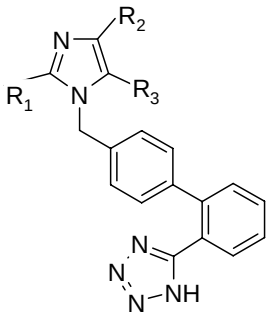


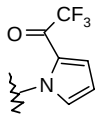
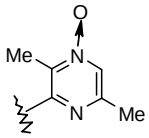
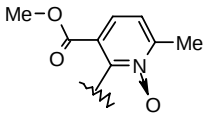
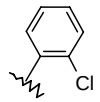
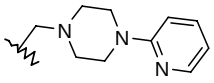
(AT13)



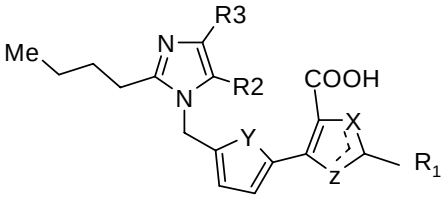
(**AT14**)

Tolerance of a large group at C_4 position is demonstrated by the high binding affinity of imidazoles which carry bulky aryl or heteroaryl substituents (**AT15-AT19**). Various heterocyclic or carbocyclic groups are successfully substituted at C_4 position of the imidazole ring.[271-276]



	R_1	R_2	R_3
(**AT15**)	*n*.propyl		COOH
(**AT16**)	*n*.butyl		H
(**AT17**)	*n*.butyl		H
(**AT18**)	*n*.butyl		COOH
(**AT19**)	*n*.propyl		COOH

The biphenyltetrazole moiety of losartan was considered to be essential for AT_1 receptor antagonistic activity. However, it has been successfully substituted for its tetrazole, spacer and terminal phenyl groups. This could best be summarized through compounds (**AT20-AT29**) which are potent ang II antagonists.[277-291]

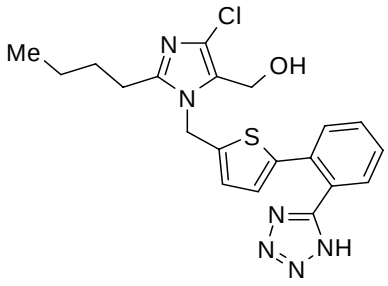


X = O, S, CH=CH, N= CH

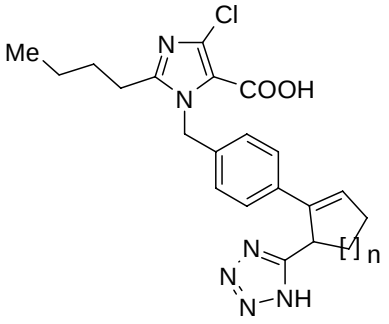
Y = O, S, CH=CH

Z = CH, N, N=CH

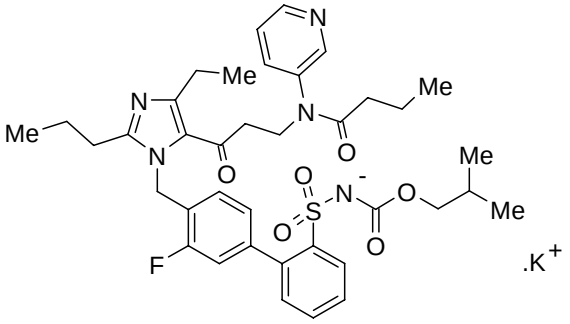
(**AT20**)



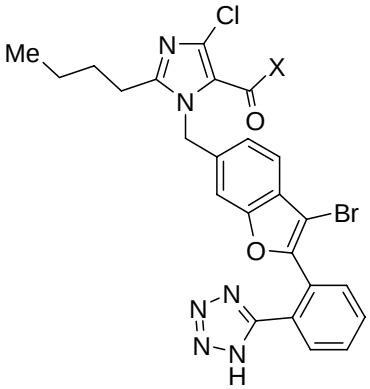
(**AT21**)



(**AT22**) n = 1-3

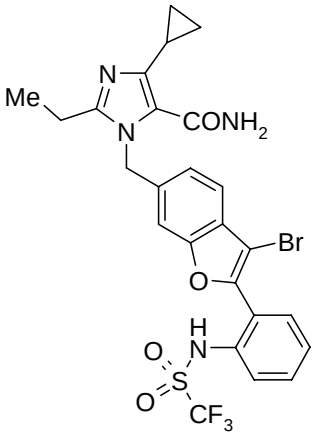


(**AT23**)

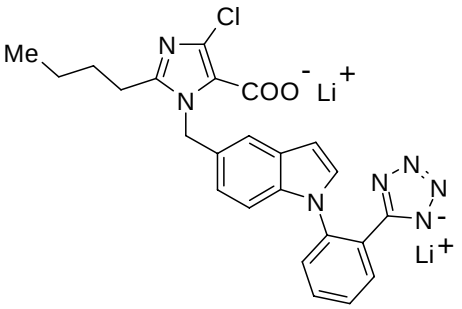


(**AT24**) X = OH

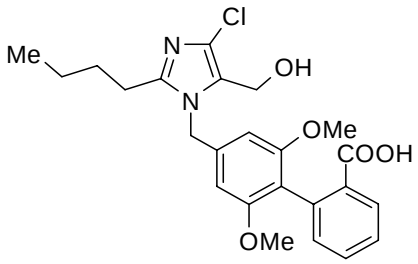
(**AT25**) X = $NHCH_2COOEt$



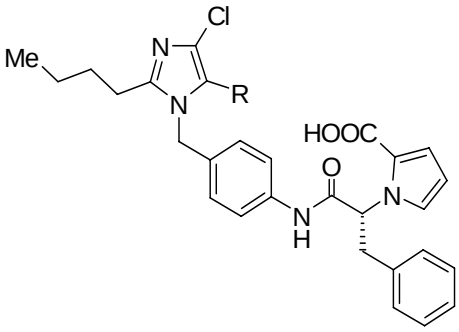
(**AT26**)



(**AT27**)



(**AT28**)

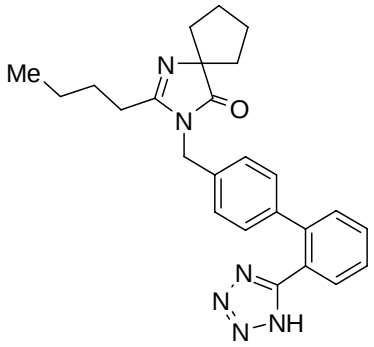


R = COOH, CH_2COOH, CH_2CH_2COOH

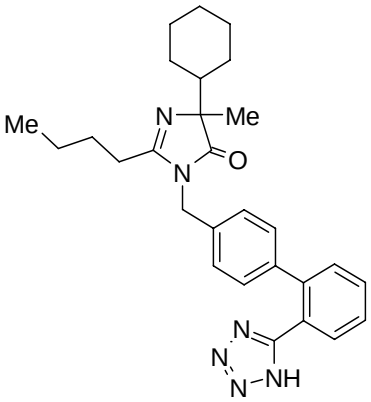
(**AT29**)

2.3.2 Dihydroimidazol-4-one containing antagonists

Bernhart et al. have reported SR 47436 (Irbesartan) [292] (**AT30**), a potent AT_1 selective (IC_{50} 1.3 nM, rat liver) antagonist which antagonized the pressor response to ang II in a dose-dependent manner (0.1-3 mg/kg, i.v. and 0.3-30 mg/kg, p.o.).[293]



(**AT30**)

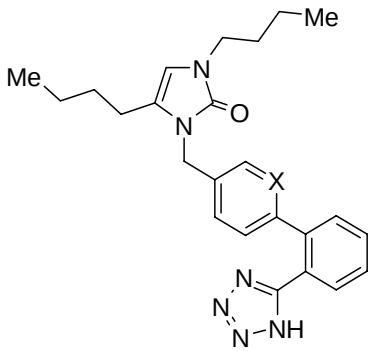


(**AT31**)

Perream et al. reported the importance of sterochemistry at the 5th position in dihydroimidazol-4-one 5,5-disubstituted biphenylcarboxylic acid and biphenyltetrzaole series, which were evaluated in *in vitro* studies. The results showed that *dextro* isomer of compound (**AT31**) (IC_{50} 5.2 nM, rat liver membrane and IC_{50} 0.77 nM, rabbit aortic rings) is 20 times more potent than the *leavo* isomer (IC_{50} 110 nM, rat liver membrane).[294]

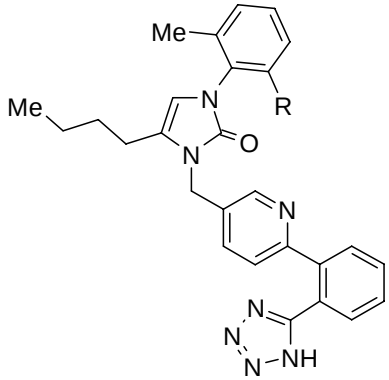
Non-tetrazole analogues of compound (**AT30**) were also reported but none of these compounds showed the same or a better activity than the parent tetrazole analogue.[295]

Repositioning of one of the ring nitrogen atoms led to the development of imidazol-2-one derivatives having comparable activity with the parent compounds.[296] Substitutions at the N_1 position of dihydroimidazolone ring were reported for SC-51895 (**AT32**).[297-298] A subsequent investigation into nitrogen containing biphenylmethyl compounds, phenylpyridinylmethyl and pyridinylphenylmethyl analogues of 2*H*-imidazol-2-one showed consistent doubling of binding potencies (IC_{50}) in phenylpyridinylmethyl analogue SC-52892 (**AT33**) (IC_{50}= 6.5 nM, pA_2 8.68) relative to the parent biphenyl analogue (**AT32**) (IC_{50} 12 nM, pA_2 8.65).[299] Aromatic group present at C_3 position of imidazolone has been substituted at its C_2 position resulting into potent, surmountable AT_1 antagonist SC 54628 (**AT34**). Further substitution converted it to the insurmountable (noncompetitive) receptor antagonist SC 54629 (**AT35**) because of steric hindrance.[300]



(**AT32**) X= CH

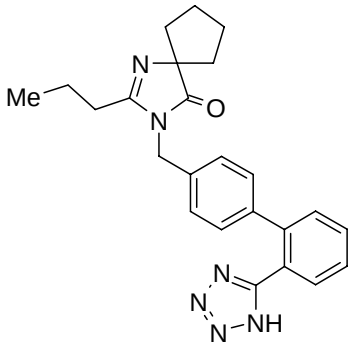
(**AT33**) X= N



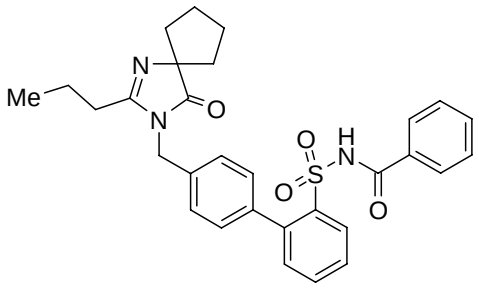
(**AT34**) R= H

(**AT35**) R= Me

Quan et al. worked on the tetrazolylbiphenyl of imidazolinone derivatives. The *n*.propyl/butyl group at position C_2 was found to be optimum (e.g. **AT36**). Substitution at C_2 position with phenyl moiety resulted in decreased potency. At posi-



(**AT36**)



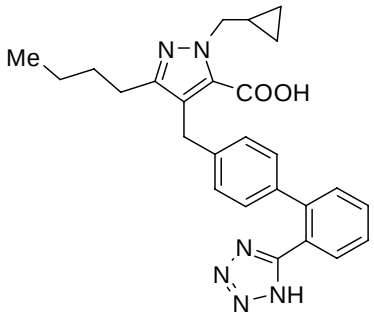
(**AT37**)

tion C_4, cyclopentyl substitution was found to be the most potent. The imidazolinones were selective for the AT_1 site; when the acylsulfonamide was used, the AT_2 affinities (**AT37**) were significantly enhanced. Both the tetrazoles and sulfonamides were very active in lowering blood pressure in RHR following intravenous administration.[301]

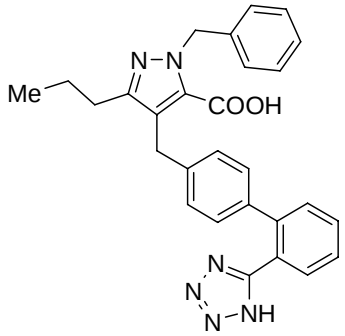
2.3.3 Pyrazole containing antagonists

Pyrazole containing antagonists arise from transposition of N_1 and C_4 in the imidazole ring. Watson et al. have reported novel series of pyrazole carboxylic acids with *n*.butyl at C_3 and cyclopropylmethyl at N_1 position. From this series, compound (**AT38**) was effective at 1 mg/kg (p.o.) in lowering blood pressure for 48 hr in renal ligated antihypertensive rats and was highly potent *in vitro.*[302]

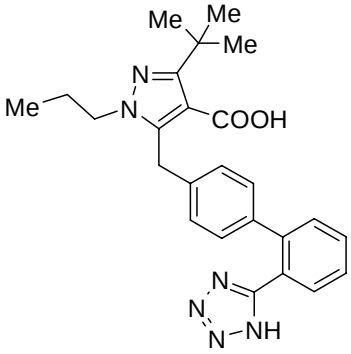
Ashton et al. carried out similar type of work at the Merck Lab. The most potent compound (**AT39**) showed IC_{50} of 0.42 nM in rabbit aorta and inhibited 90%



(**AT38**)



(**AT39**)



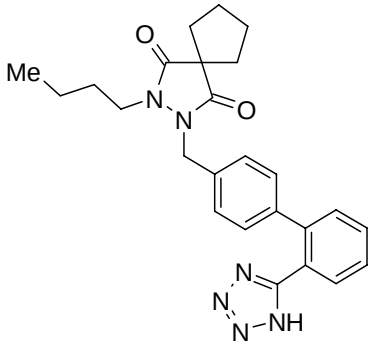
(**AT40**)

of the pressor response for more than 24 hr in conscious normotensive rats. Various lipophilic groups like benzyl, phenethyl, 2-pyridyl and phenyl were tried at N_1 position. For C_3 position, *n*.propyl group was found to be optimum.[275] Almansa et al.

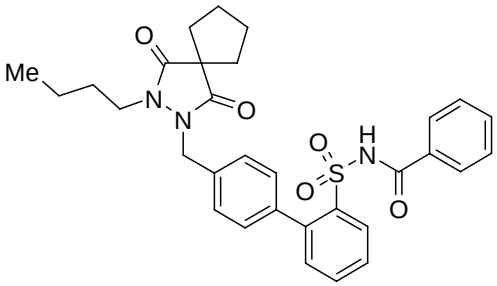
reported UR 7280 (**AT40**) as a selective AT_1 antagonist which showed high potency both *in vitro* (IC_{50} 3 nM) and *in vivo* assays (0.3 mg/kg) and inhibited more than 60% pressor response of ang II.[202]

2.3.4 Pyrazolidine-3,5-dione containing antagonists

On the basis of the structure of SR 47436 (**AT30**) Bourdonnec et al. reported a new series of AT_1 antagonists. The central imidazolone nucleus of irbesartan was replaced by pyrazolidine-3,5-dione and these compounds were evaluated for binding and antagonistic activities. Two compounds (**AT41** and **AT42**) of the series possessed good affinity (K_i 25 and 10 nM, respectively) to displace [^{3}H]ang II in PLC-PRF-5 human hepatoma cell line. Ang II antagonistic activity for compounds (**AT41** and **AT42**) in terms of IC_{50} values were 22 nM and 12 nM, respectively. Both of these compounds are less potent than SR 47436 (**AT30**).[303]



(**AT41**)



(**AT42**)

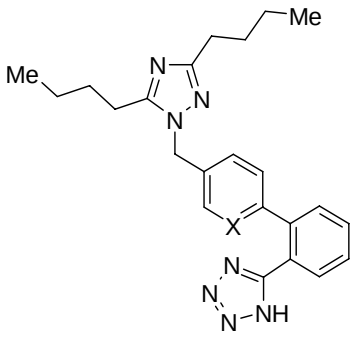
2.3.5 Triazole containing antagonists

1,2,4-Triazole system having similar geometry as the imidazole moiety is considered to be a reasonable candidate for AT_1 receptor antagonistic activity. The additional nitrogen atom in the 1,2,4-triazole ring was expected to exert an electron withdrawing effect similar to the C_4 chloro substituent in imidazole ring of losartan.

Reitz et al. have investigated N-biphenylmethyl substituted 1,2,4-triazoles and discovered that the 3,5-dibutyl analogue SC-50560 (**AT43**) is a highly potent (IC_{50}= 5.6 nM, pA_2 = 8.7), orally active AT_1 receptor antagonist.[304, 305] A subsequent investigation, in which CH was systematically replaced with N at each position of both of the aromatic rings of the biphenyl i.e. N-phenylpyridinylmethyl and N-

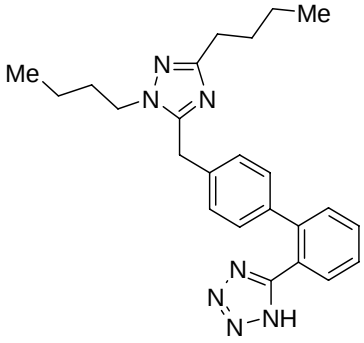
pyridinylphenylmethyl was conducted to determine the pharmacological effects of such substitutions. The most active compound in the series SC-52458 (**AT44**) showed IC_{50} value of 6.9 nM, pA_2 value of 8.2, and was found to have superior *in vivo* properties than SC-50560.[306]

The N_1 biphenylmethyl group and the C_5 butyl groups of potent, orally active compound (**AT43**) were interchanged to give the isomeric "C-linked" 1,2,4-triazole analogue SC-51757 (**AT45**). Compound (**AT45**) with IC_{50} value of 16 nM and pA_2 of 8.5 showed decreased potency.[307]



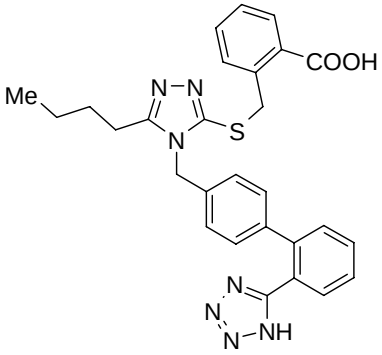
(**AT43**) X = CH

(**AT44**) X = N



(**AT45**)

A group form Merck Laboratory worked on the 5th position of the triazole with different substituents like phenyl, benzyl, pyridyl, furyl, perfluroalkyl, thiobenzyl, thioether etc. Amongst these, thioether diacidic derivative (**AT46**) showed high potency (*in vitro*, IC_{50} 1.4 nM).[308]

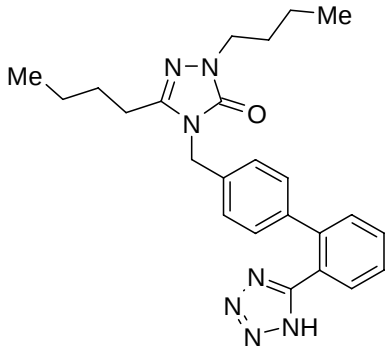


(**AT46**)

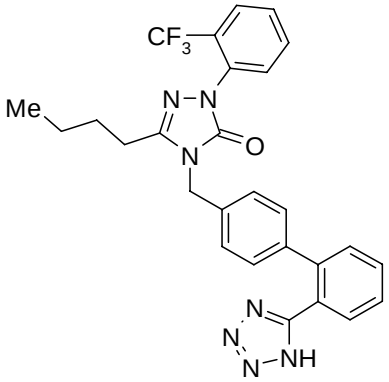
2.3.6 Triazolone containing antagonists

Hydrogen bond accepting groups at the C_5 position may enhance the binding affinity to the AT_1 receptor. Triazolone is one of the heterocycles that can

accommodate this structural feature. Huang et al. in 1993 reported SC 51316 (**AT47**) as orally active and selective antagonist with IC_{50} value of 5.1 nM in rat uterine membrane. Compound (**AT47**) showed competitive and reversible antagonism of ang II mediated contraction of rabbit aortic rings with pA_2 value of 8.86. The 2nd position



(**AT47**)



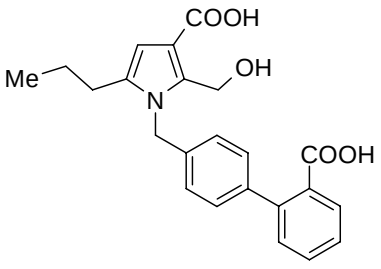
(**AT48**)

of triazole was further explored with unbranched and branched groups like alkyl, phenyl, benzyl etc. but none of the compounds was found to be active.[309]

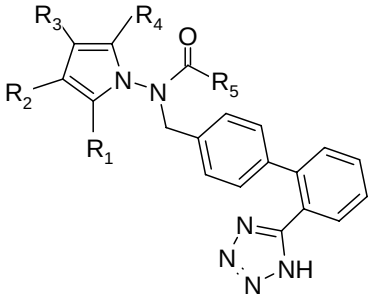
Aryl substituted compound (**AT48**) effectively displaced (IC_{50} 1.2 nM) ^{125}I Sar^1Ile^8 Ang II from rabbit aortic membranes. The tetrazole moiety of (**AT48**) was replaced by other carboxylic acid bioisosteres such as acylsulfonamides (L-159,913). It is a AT_1 selective, reversible and competitive antagonist with K_i value of 1.7 nM.[310]

2.3.7 Pyrrole and pyrrolidin-2-one containing antagonists

Compounds with pyrrole ring and hydroxymethyl and carboxylic groups have been reported and evaluated for *in vivo* and *in vitro* activities. Pyrroles (e.g. **AT49**)



(**AT49**)

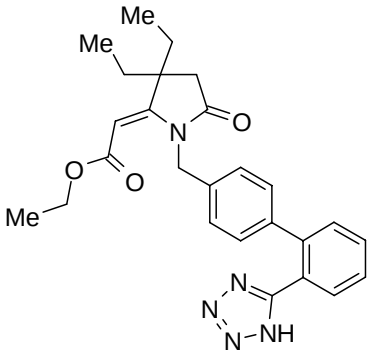


(**AT50**)

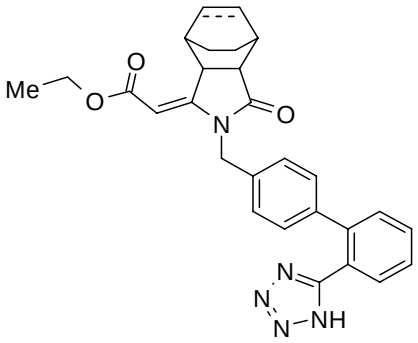
showed weak antagonistic activities. Pyrroles were predicted to be weak antagonists in comparison to imidazoles because of the lack of a nitrogen atom at the C_3 position

of the imidazole ring.[267] Biphenyltetrazole derivatives of 1-aminopyrroles (e.g. **AT50**) were synthesized. All of the compounds in this series were found to be inactive.[311]

Murray et al. reported a novel series of substituted pyrrolidin-2-ones (e.g. **AT51**, **AT52**). The most potent inhibitor (**AT51**) from the series antagonized ang II induced contractions in rabbit aortic strip with pA_2 value as high as 7.9 and exhibited



(**AT51**)

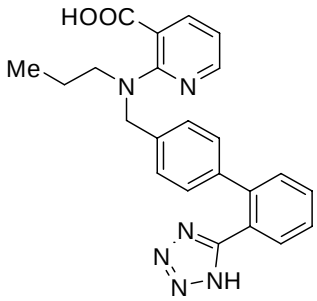


(**AT52**)

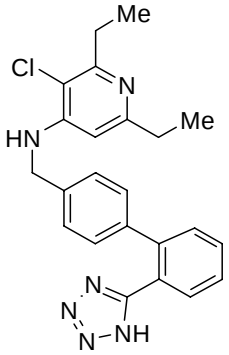
IC_{50} as low as 100 nM (rabbit adrenal cortex). Some of the compounds from this series were found to be orally active in SHR.[312]

2.3.8 Pyridine and pyridinone containing antagonists

Abbott Laboratories discovered pyridine derivatives as a novel class of orally active, non-peptide AT_1 antagonists. Abbott's A-81988[313] (**AT53**) (K_i 0.76 nM, rat liver; pA_2 10.1-10.7, rabbit aorta)[314] was found to be a surmountable antagonist. A series of 3-substituted 4-amino-2,6-dialkylpyridines **(**e.g. **AT54)** was developed and



(**AT53**)

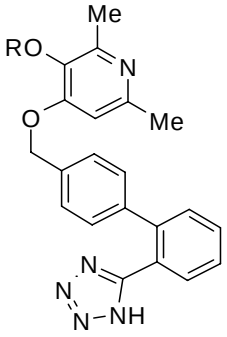


(**AT54**)

compounds from this series showed potent *in vitro* antagonistic activity. The most potent compound of the series (**AT54**) showed significant inhibition (66%) of the ang

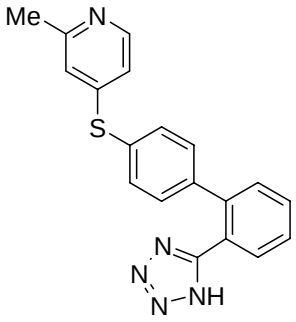
II pressor response for 5 hours after dosing at 1.0 mg/kg. It showed high oral absorption with an ED_{50} of 0.06 mg/kg.[315]

Derivatives containing pyridine ring connected to biphenyl portion through oxymethylene linker were synthesized and evaluated for AT_1 receptor antagonistic activity. Nagura et al. (Meiji Seika) reported ME 3221 (**AT55**) as a competitive AT_1 selective antagonist (pK_i 8.7, rat liver).[316] Repeated administration of compound (**AT55**) to SHR showed a stable and long lasting antihypertensive effect without influencing heart rate. It showed faster onset of action and got metabolized to EF 2831 (**AT56**).[317] EF2831 (**AT56**), a metabolite of compound (**AT55)** is also a surmountable AT_1 receptor antagonist. Compound (**AT55**) was found to be less potent



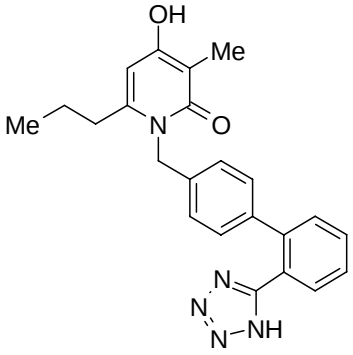
(**AT55**) R= Me

(**AT56**) R=H



(**AT57**)

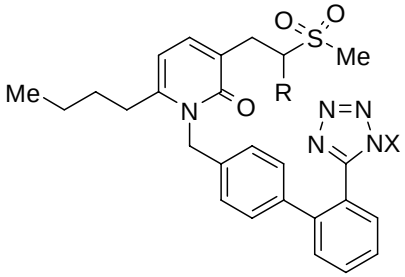
in vitro and *in vivo* than EF2831.[307] Pyridine ring connected to biphenyl moiety through sulphur linker (**AT57**) was also synthesized and evaluated for AT_1 receptor antagonistic activity but it showed weak AT_1 antagonistic activity (IC_{50} 1.5 uM, rat liver membrane).[318]



(**AT58**)

Bantick et al. have reported a series of biphenyl 2(1*H*)-pyridinones. 4-Substituted pyridinones, particularly 4-OH, 4-SH and 4-COOH showed activity in *in vitro* and *in vivo* evaluation studies. Compound (**AT58**) showed potent antagonistic activity, and ID_{50} value in the range of 0.02 mg/kg in normotensive rats.[139] The same research group evaluated AT_1 receptor antagonistic activity of fused bicyclic analogues of 2-pyridinones. Potent antagonist activity was found in the 2-quinolinone, thieno[2,3-*b*]pyridine and imidazo[*c*]pyridine series of compounds.[319]

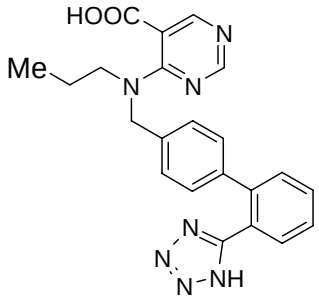
Research group at E Merck worked on a series of dihydropyridin-2-ones. Some of the potent compounds (**AT59** and **AT60**) in the series displayed potencies in nanomolar range (1.9 nM and 1.2 nM) and their inhibitory effect on ang II pressor response in pithed rat was superior to that of losartan.[320] Another derivative (**AT61**) also showed promising *in vivo* activity.[321]



(**AT59**) R = *i*.Propyl, X = H
(**AT60**) R = Me, X = H
(**AT61**) R = Methylcyclopropyl, X = K

2.3.9 Pyrimidine containing antagonists

Abbott Laboratory was the first to report novel & potent (pA_2 9.93, isolated rabbit-aorta) pyrimidine derivative A-81080 (**AT62**). When administered intravenously at a dose of 0.3-1 mg/ kg as disodium salt, compound (**AT62**) lowered



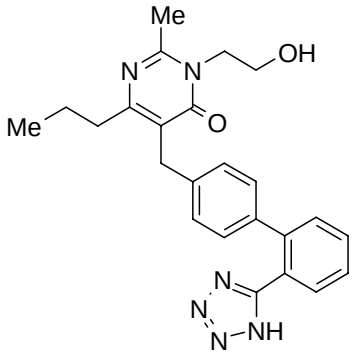
(**AT62**)

MABP in a dose-dependent manner in the renal artery-ligated (RAL) hypertensive rats. However, the oral response in the RAL rats (1-10 mg/kg, p.o.) was poor, both in

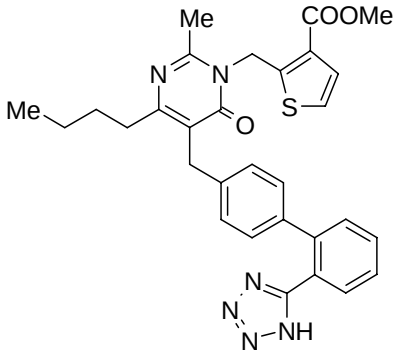
terms of the antihypertensive effect and the duration of action.[313] Heterocyclic analogues of A-81080 were synthesized and evaluated for AT_1 antagonistic activity and were found to be less potent.[322]

2.3.10 Pyrimidinone containing antagonists

Nicolai et al. reported UP 243-38 (**AT63**) a C-C linked AT_1 antagonist. C-Linked pyrimidinones showed maximal decrease in MAP of 60.8 mm Hg, with longer duration of action and faster onset of action at a dose of 3 mg/kg (p.o.). Compound (**AT63**) is equipotent to losartan with a slightly different pharmacokinetic pattern.[323] Subissi et al. reported LR B081 (Lusofarmaco) (**AT64**), an N_3-heteroaryl substituted and C-linked insurmountable pyrimidinone antagonist. Compound (**AT64**) showed selective (Ki 0.9 nM, rat adrenal cortical membrane) and competitive antagonism.[324]

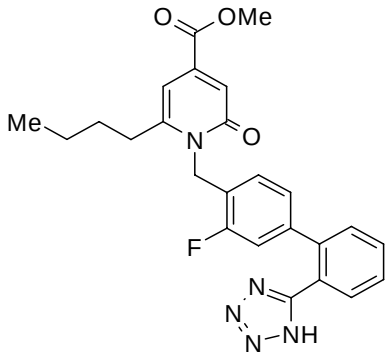


(**AT63**)

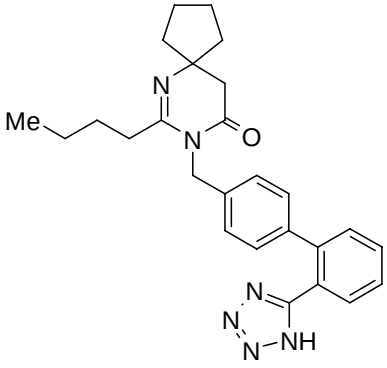


(**AT64**)

BAY 10-6734 (Embusartan) (**AT65**) is an orally active AT_1 antagonist containing dihydropyridinone nucleus. BAY 10-6735 is a therapeutically active moie-



(AT65)



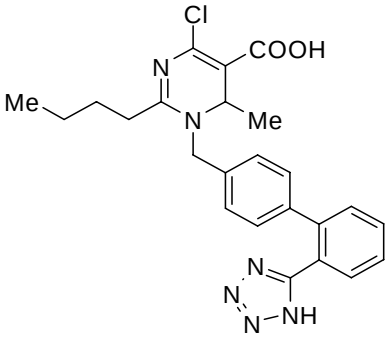
(**AT66**)

ty produced by the hydrolysis of of BAY 10-6234. BAY 10-6734 showed competitive whereas BAY 10-6735 exhibited a noncompetitive mode of antagonism. Compound (**AT65**) is a well tolerated and long lasting antagonist (24hr).[325]

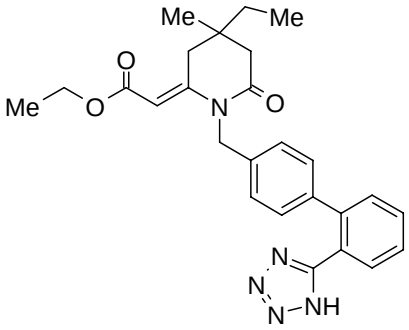
A novel series of homologues (e.g. **AT66**) of SR 47436 (**AT30**), substituted 3*H*-dihydropyrimidinones were identified as AT_1 receptor antagonists. The best compound (**AT66**) in the series showed high affinity for the AT_1 receptor with IC_{50} in the nanomolar range. It was equipotent to SR 47436 (**AT30**) in conscious normotensive rat, but was inactive in normotensive cynomolgus monkeys.[326]

2.3.11 Dihydropyrimidine containing antagonists

Bristol Myers Squibb successfully replaced the imidazole ring with the dihydropyrimidine ring. The most potent compound **(AT67)** of the series showed good binding affinity (K_i 1 nM) as well as functional antagonism (K_b 0.45 nM).[327]



(**AT67**)



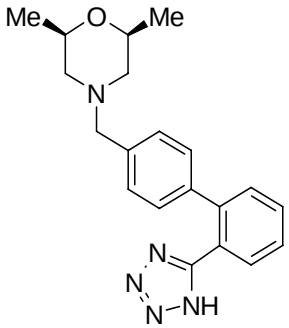
(**AT68**)

2.3.12 Piperidinone containing antagonists

RWJ 46458 (**AT68**) (Johnson & Johnson) showed moderate *in vitro* activity (IC_{50} 250 nM, bovine adrenal) but proved potent insurmountable antagonist (pA_2 9.0, rabbit aorta) in the functional assay.[328]

2.3.13 Morpholine containing antagonists

Morpholine derivative RWJ 47639 (**AT69**) showed a pA_2 value of only 6.9. It showed a rapid onset of action with duration of action of more than 12 h. in SHR.[329]

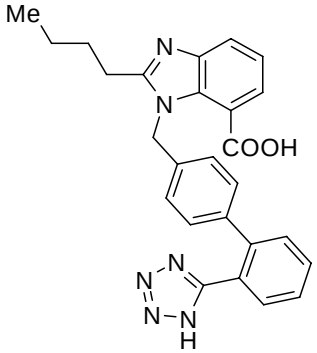


(**AT69**)

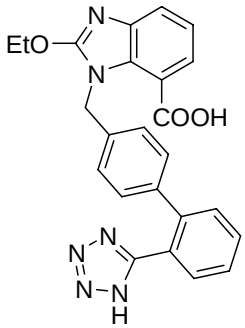
2.3.14 Benzimidazole containing antagonists

The ability of imidazole ring to tolerate a variety of substituents at the C_4 and C_5 positions while maintaining high binding affinity to the AT_1 receptor indicated that these substituents could be joined internally to yield a variety of ring-fused imidazoles.

Benzimidazoles have been investigated by several groups to find potent antagonists. Kubo et al. from Takeda Chemical Industeries reported CV-11194 **(AT70)** as inhibitor of specific binding of [^{125}I]ang II to bovine adrenal cortical membrane with an IC_{50} value of 0.55 μM.[330]

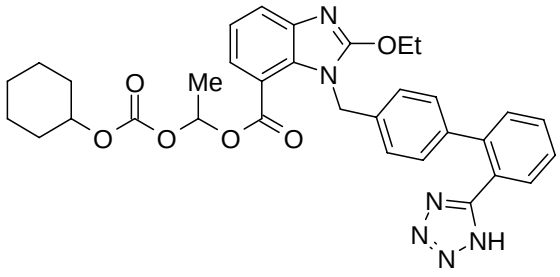


(AT70)



(AT71)

In order to improve potency, numbers of substituents were explored at C_2 position of benzimidazole and the most potent compound of the series was CV-11974 **(AT71)**. Compound (**AT71**) is a long acting, selective (0.11 μM) antagonist.[331] In or-

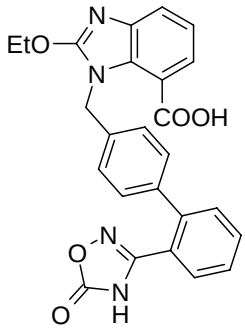


(**AT72**)

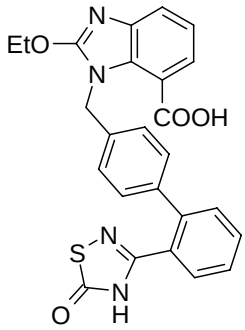
der to improve the oral bioavaibility, different esters of compound (**AT71**) were prepared and evaluated. The most potent compound of the series TCV-116 **(AT72)** (Candesartan cilexetil) is an orally active nonpeptide antagonist of AT_1 receptor. Compound (**AT72**) is a highly potent and long lasting antagonist of AT_1 receptor in

man.[332] Compound (**AT72**) blocked the ang II pressor response with an ED_{50} value of 0.069 mg/kg (p.o.).[333]

Kohara et al. from Takeda Chemical Industeries further explored bioisosteres for tetrazole moiety of compound (**AT71**)[334] and successfully replaced it with two moieties as seen in TAK-536 (**AT73**) and compound (**AT74**). Binding affinity to bovine adrenal cortical membrane of both of the compounds, TAK-536 (**AT73**) and



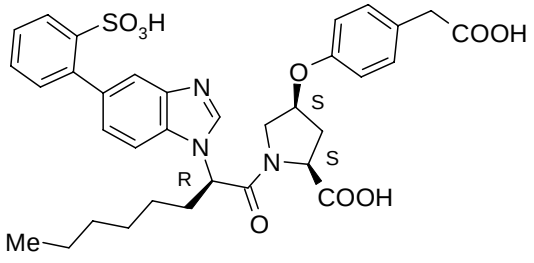
(AT73)



(AT74)

AT74 showed slightly lower affinity (4.2 nM and 2.5 nM, respectively) than compound (**AT71**).[334]

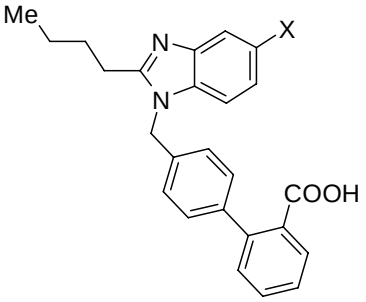
A novel series of heterocyclic compounds bearing two acidic functionalities, a carboxyl group and a tetrazole ring, was prepared and evaluated for *in vitro* and *in vivo* activities. These derivatives showed significantly more potent AT_1 receptor antagonistic activities than the parent compounds which were without the carboxylic groups. This structure-activity relationship study revealed the importance of the carboxyl group attached to the heterocyclic moieties especially for insurmountable antagonism and enhancement of *in vivo* (p.o.) activity.[335]



(AT75)

Palkowitz et al. reported a novel series of benzimidazoles **(**e.g. **AT75)** with phenoxyprrolidine side chain for ang II antagonistic activity. All of these benzimidazole analogues were found to be equipotent *in vitro*.[336]

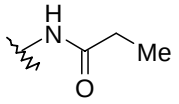
Bansal et al. worked on the 5th position of the benzimidazole nucleus with nitro, alkylcarboxamido and alkylsulfamoyl subtituents and reported potent AT_1 antagonists **(AT76 – AT79)**.[337-339]



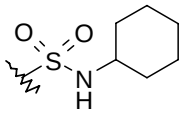
X

(AT76) NO_2

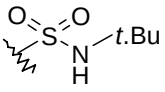
(AT77)



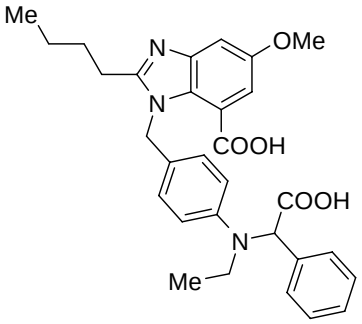
(AT78)



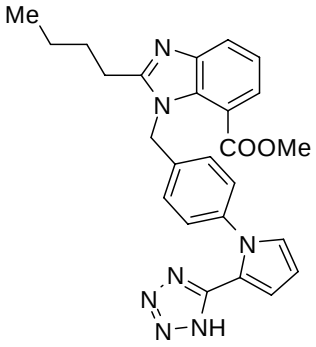
(AT79)



Xu et al. reported benzimidzoles with differently substituted groups. Compounds **(AT80** and **AT81)** showed functional antagonism (pA_2 8.3 and 8.4 respectively, rabbit thoracic aortic rings) more potently than losartan (pA_2 7.9). In conscious normotensive rats, they showed more potent and long lasting effects than losartan at a dose of 1 mg/kg (p.o.).[340]



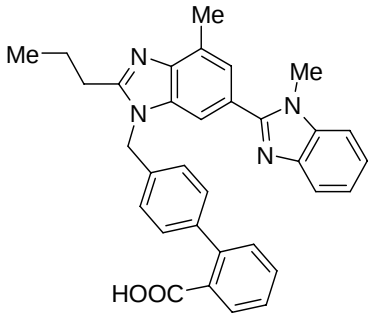
(**AT80**)



(**AT81**)

BIBR 277 (Telmisartan) (**AT82**) is a selective (K_i 3.7 nM, rat lung) and potent insurmountable antagonist. Compound (**AT82**) produced a dose-dependent decrease

in MABP in conscious RHR (0.3 and 1 mg/kg, p.o.) and SHR (1 and 3 mg/kg). Its hypertensive effect was observed for 24 hr, when dosed orally (3 mg/ kg).[341, 342]

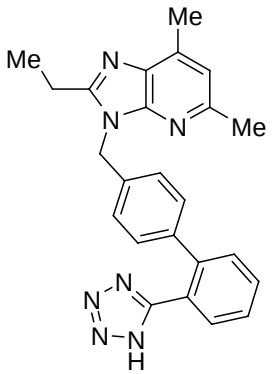


(AT82)

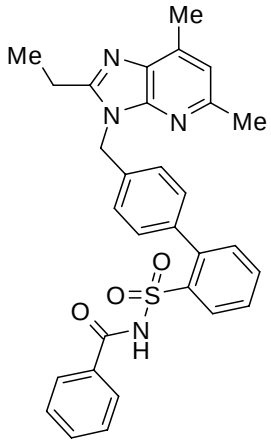
2.3.15 Imidazopyridine containing antagonists

An imidazopyridine heterocycle ring could replace the imidazole ring as it contains common imidazole elements and the pyridine nitrogen is capable of mimicking the hydrogen-bond forming capability of the polar 5-substituent. This strategy is employed in the designing of Merck's L-158,809 (**AT83**), a potent (IC_{50} 0.3 nM, rabbit aorta) and competitive antagonist. It inhibited pressor response of ang II for 24 h, when dosed intravenously 0.1 mg/kg and orally 0.3 mg/kg to conscious normotensive rats.[343, 344]

Tetrazole moiety in the biphenyl portion undergoes N-glucuronidation. Replacement of tetrazole moiety of L-158,809 (**AT83**) with acylsulfonamide group



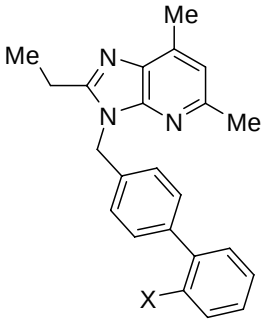
(AT83)

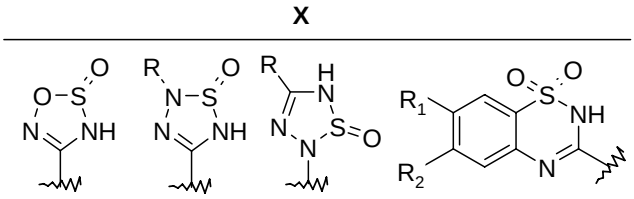


(AT84)

resulted into MK-996 (**AT84**). Compound (**AT84**) is selective (IC_{50} 0.2 nM, rabbit aorta) and insurmountable antagonist (pA_2 10.3). [345]

Replacement of the acidic tetrazole functionality by various heterocyclic acid equivalents such as oxathiadiazole, thiatriazole and dioxobenzothiadiazine **(AT85)** were tried. The most potent compound of this series **AT85a** (L-161,177, IC_{50} 0.7 nM, rabbit aorta), bearing oxathiadiazole ring exhibited excellent *in vivo* activity profile after intravenous as well as oral administration to conscious rats.[346]

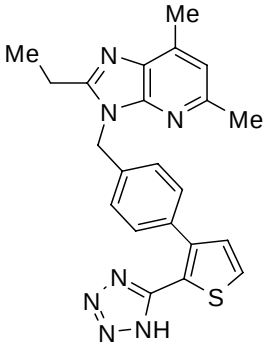




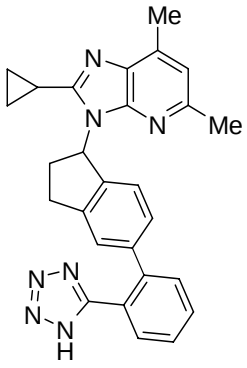
(a) **(b)** **(c)** **(d)**

(**AT85 a-d**)

The biphenyl fragment of the potent AT_1 receptor antagonist (**AT83**) was replaced by phenylthiophene and phenylfuran moieties. Replacement of the central phenyl ring by a 2,5-disubstituted thiophene resulted in a thousand fold loss of poten-



(**AT86**)



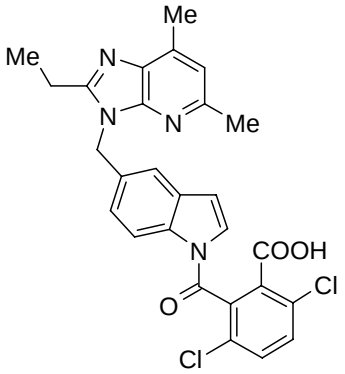
(**AT87**)

cy while replacement of the tetrazole-bearing phenyl group by a thiophene **(**e.g. L-159,827, **AT86**) resulted in a small loss in binding affinity (< 3X) with an IC_{50} of 2.3 nM. Replacement of tetrazole with benzoylsulfonamide group dramatically increased

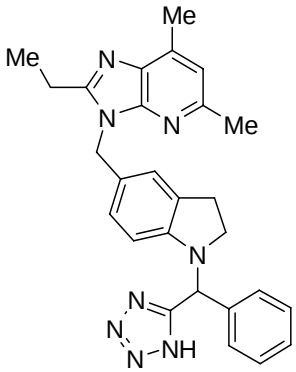
AT_2 affinity. Substitution at the 5th position of thiophene ring also imparted higher AT2 binding. [347,348]

Carpino et al. reported a conformationally restrained series of derivatives of compound (**AT83**). The benzyl linker in L-158,809 (**AT83**) was replaced by a series of bicyclic rings such as dihydroindanyl, tetrahydronaphthyl, tetrahydrobenzo-cycloheptenyl or naphthyl rings. The optimal bicyclic ring was found to be a dihydroindanyl ring. Such a modification resulted in the discovery of a rigid analog (**AT87**) as a potent (IC_{50} 0.2 nM) compound.[349]

The biphenyl moiety of L-158,809 (**AT83**) was replaced with N-substituted indoles and dihydroindoles. Two most potent compounds of the series are **AT88** (AT_1 IC_{50} = 0.8 nM, rabbit aorta) and **AT89** (AT_1 IC_{50} = 1 nM, rabbit aorta). Compound (**AT88**) blocked the ang II induced pressor response for only 0.5 hr after intravenous



(AT88)



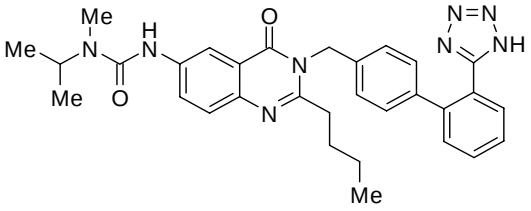
(AT89)

administration of 1.0 mg/kg to conscious normotensive rats. This compound also showed affinity for AT_2 receptor.[350]

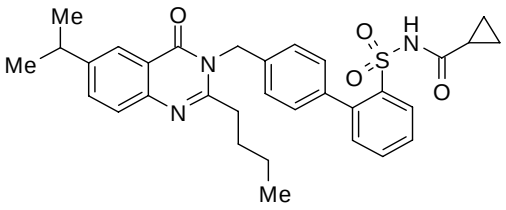
2.3.16 Quinazolinone containing antagonists

Quinazoline ring possessed the same arrangement of nitrogens (1 and 3 positions) as found in imidazole ring and can accommodate the requisite side chain at position C_2. Merck's L-159,093 (**AT90**) is an orally active, highly potent AT_1 (0.1 nM, rabbit aorta) antagonist. Compound (**AT90**) inhibited ang II pressor response at 3 mg/kg (p.o.) in conscious normotensve rhesus monkeys for more than 3 hr.[351] The acylsulfonamide group was used as a substitute for tetrazole function. The most potent compound of the series was L-161,021 (**AT91**). This antagonist displayed

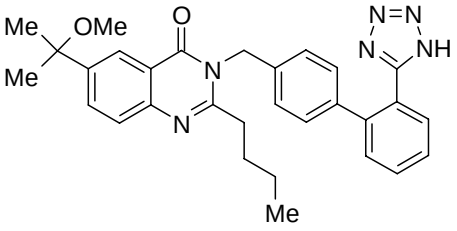
excellent *in vivo* activity in conscious rats after intravenous (ED_{50}= 0.25 mg/kg) and oral administration (ED_{50} 0.68 mg/kg).[352]



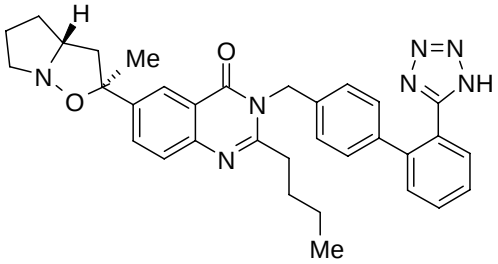
(**AT90**)



(**AT91**)

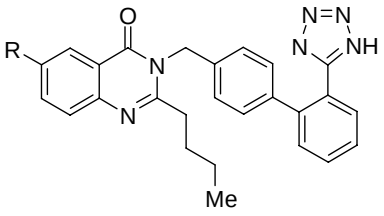


(**AT92**)

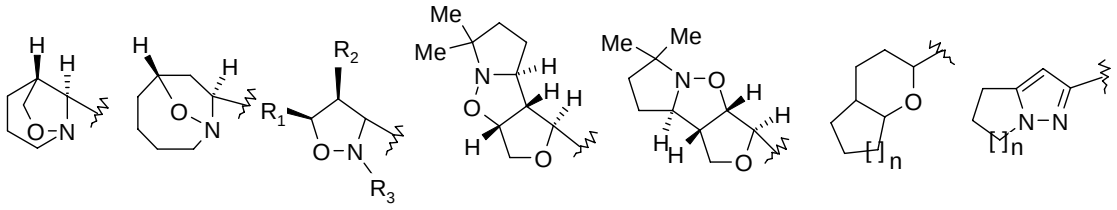


(**AT93**)

A series of 2,3,6-trisubstituted-4(3*H*)-quinazolinones is reported. The most potent compound of the series is Lederle's CL 329,167 (**AT92**), a selective ($IC_{50,}$ 6 nM) and competitive antagonist (pA_2 8.01, rabbit aortic rings).[353] In order to further improve the potency, isoxazoline and isoxazolidine analogs of CL329,167 (**AT92**) were synthesized. CL l90,133 (**AT93**) was found to be specially potent, orally active,



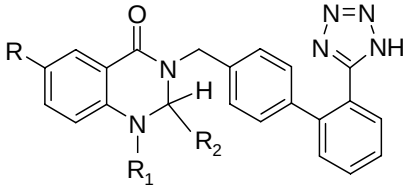
(AT94) R



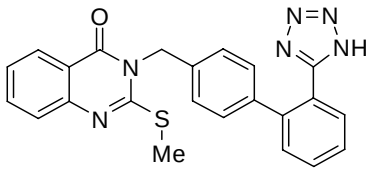
non-competitive AT_1 receptor antagonist with an apparent pA_2 of 10.9. CL 332,877, sodium salt of CL 329,167 (**AT92**) is a potent, long-acting, noncompetitive antagonist (pA_2 10.9).[354] In order to search other heterocycles which not only exceed the oral

potency of CL 332,877 but also remain robust under physiological conditions, position-6 substituted bridged analogues of isoxazolidine, like substituted isoxazolidine, dihydrofuran, tetrahydropyran and fused pyrazole analogues (**AT94**) were synthesized and evaluated for AT_1 receptor antagonistic activity. But, none of them increased the oral potency level.[355]

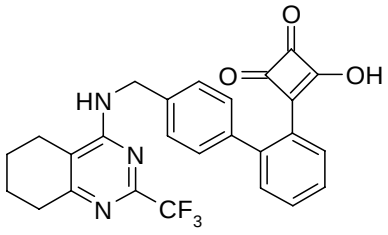
A series 2,3-dihydro-4(1*H*)-quinazolinone analogues (**AT95**) related to CL 329,167 (**AT92**) were synthetized and evaluated. But these compounds were devoid of any significant oral activity.[356] Ismail et al. have reported a series of novel quinazolin-4-ones. The most active compound (**AT96**) of the series decreased the BP effectively in both normotensive and hypertensive male SD rats.[357]



(**AT95**)



(**AT96**)



(**AT97**)

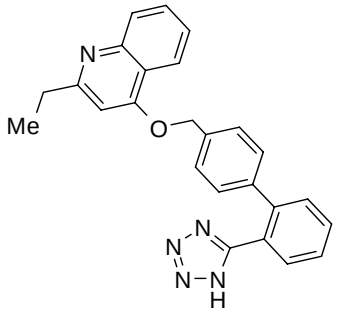
A novel analogue (**AT97**) containing bioisostere of tetrazole, 3-hydroxy-3-cyclobutene-1,2-dione was synthesized and evaluated. It showed less potency than parent tetrazole analogue.[358]

2.3.17 Quinoline containing antagonists

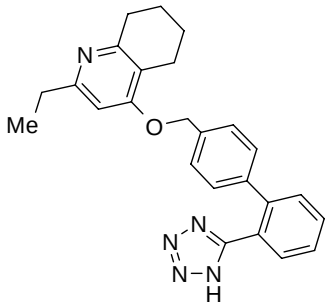
Oldham et al. reported ICI-8731 **(AT98)** an orally active, potent (IC_{50} 30 nM, guinea pig adrenal) and competitive (pA_2 8.3, rabbit aorta) AT_1 antagonist.[359]

ZENECA's ICI-6888 (**AT99**) showed higher binding affinity (IC_{50} 5 nM, guinea pig adrenal) and more *in vitro* potency (pA_2 10.3, rabbit aorta) than ICI D8731 (**AT98**). But both of them possessed similar oral efficacy in RHR.[360] Synthetic analogues of ICI-6888 are reported. Several of these compounds showed comparable

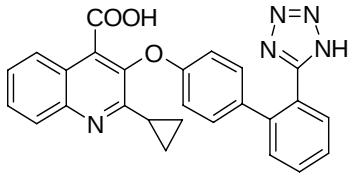
or superior activity to ICI-6888 in binding assay and in inhibition of the ang II induced pressor response in normotensive rats. Compounds bearing substituents in the C_3 position showed comparable or better activity than the parent ICI-6888 (**AT99**) in



(**AT98**)



(**AT99**)

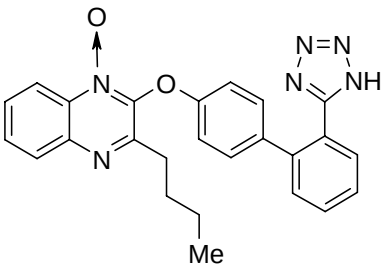


(**AT100**)

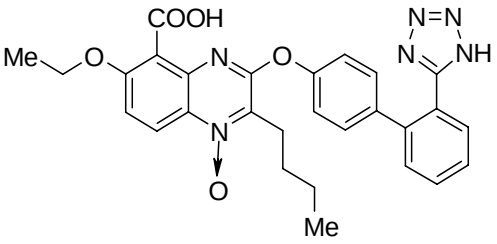
an acute dosed rat model (i.v.).[361] Lloyd et al. reported BMS-183920 (**AT100**) as a potent (K_i 2.9 nM, rat adrenal cortex) AT_1 antagonist. It is an insurmountable antagonist.[362]

2.3.18 Quinoxaline containing antagonists

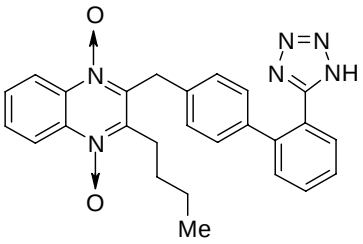
Bristol Meyers Squibb Pharma reported a new class of N_1 (**AT101**) and N_4 (**AT102**) quinoxaline oxide derivatives as AT_1 antagonists. Compound (**AT101**) possessed good binding affinity (K_i 4.5 nM) and showed functional antagonism, but its *in vivo* activity was found to be low. As compared to N_1-oxide derivative, the N_4-oxide derivative (**AT102**) showed higher potency in *in vitro* and *in vivo* preparations. But this compound (**AT102**) also possessed low oral activity. To improve the oral acivity, its ester derivative was synthesized, which showed improved oral activity and longer duration of action, as seen in SHR.[363] The same group reported a bis N-oxide derivative (**AT103**), which showed potent ang II receptor antagonistic activities, both in binding (K_i 2.6 nM, rat adrenal cortical membrane) and functional assays (K_b 2.1 nM, rat aorta).[364]



(**AT101**)



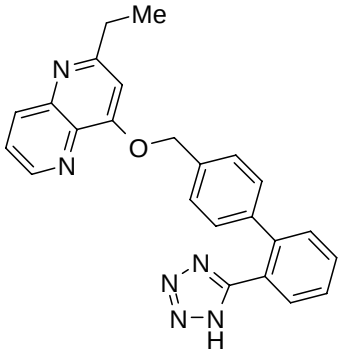
(AT102)



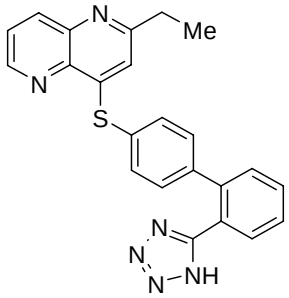
(**AT103**)

2.3.19 Naphthyridine containing antagonists

Naphthyridine derivatives connected to biphenyl moiety with oxymethylene and sulfide linkers were synthesized and evaluated fot AT_1 receptor antagonistic activity. Both of the compounds (**AT104** and **AT105**) possessed activity in the nanomolar range. Compound (**AT104**) showed good affinity for AT_1 receptors (IC_{50}



(**AT104**)

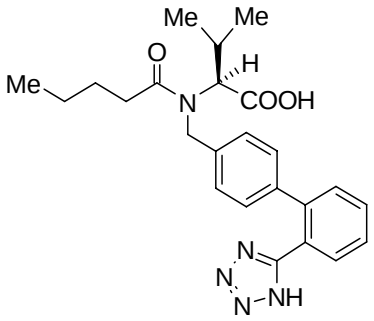


(**AT105**)

value of 0.024 uM, guinea pig adrenal membrane). When dosed intravenously, compound (**AT104**) inhibited ang II induced pressor response with an ED_{50} of 0.86 mg/kg. Compound (**AT105**) also showed high level of bioactivity (IC_{50} 0.020 uM, rat liver membrane).[318, 360]

2.3.20 Antagonists having acyclic replacements of imidazole

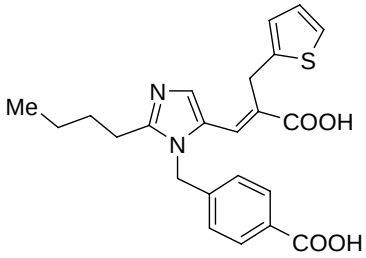
Buhlmayer et al. reported valsartan (CGP 48933) (**AT106**) as a potent, selective AT_1 antagonist (IC_{50} 2.7 nM, rat aorta). When dosed orally (3 and 10 mg/kg) in RHR, compound (**AT106**) decreased systolic blood pressure (SBP) dose dependently. Its antihypertensive effect lasted for 24 hr.[365, 366]



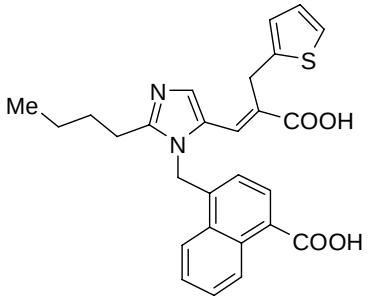
(**AT106**)

2.3.21 Modifications to eprosartan

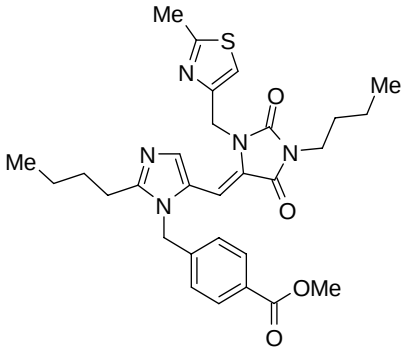
Efforts were also made by researchers to develop novel AT_1 antagonists by taking eprosartan (**AT107**) as a prototype and replacing its acrylic acid moiety with a



(**AT107**)



(**AT108**)



(**AT109**)

hydantoin nucleus. SB 203220 (**AT108**), the naphthyl analog of eprosartan (**AT107**)

is a potent, long-acting and partially insurmountable antagonist. It inhibited the pressor effect of ang II at a dose 10 mg/kg (p.o.) for up to 20 hours.[367] Edmunds et al. reported a series of 5-substituted hydantoins as AT_1 antagonists. The most potent compound (**AT109**) of the series (3.8 nM, rabbit aorta) reduced the MABP of RHR by 40% at 30 mg/kg p.o. and by 25% at 10 mg/kg p.o. In addition, this compound (**AT109**) was efficacious in the salt-depleted normotensive monkey model decreasing blood pressure by 27% at 10 mg/kg (p.o.).[368]

Patients suffering from hypertension need multidrug therapy for effective control of blood pressure. Multidrug therapy poses certain pharmacokinetic problems. So it was planned to design and synthesize compounds bearing dual, α_1 and AT_1 receptor antagonistic properties.

A key challenge in the design of multiple target ligands is attaining a balanced activity at each target of interest while simultaneously achieving a higher selectivity and suitable pharmacokinetic profile. Rational designing approaches involve selection of structural features from selective ligands combined into one single entity to produce multiple targeted ligands. Dual antagonists have been designed by considering the two different approaches, screening and knowledge-based approaches as discussed earlier.

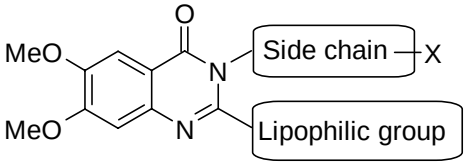
Knowledge–based approach was used for designing of dual α_1 and AT_1 antagonists. This approach is based on combining of frameworks and underlying pharmacophores of two drug molecules, each selective for one particular target of interest, into a single chemical entity possessing both of the activities of the parent molecules. The resulting dual acting ligands could have linked, fused or merged pharmacophores. In order to design dual α_1 and AT_1 antagonists, a thorough survey of literature for α_1 and AT_1 antagonists was performed as discussed earlier. The molecules were designed by considering the structure activity relationships of both categories of compounds. The following points emerged from the study of the structures of the α_1 antagonists:

- α_1 Antagonists could be categorized distinctly into two categories: prazosin and related compounds which bear quinazoline moiety, and phenoxybenzamine and phentolamine type of compounds which can not be clubbed under one chemical category.
- All quinazoline derivatives possessed 6,7-dimethoxyquinazoline ring which was reported to be essential for α_1 antagonistic activity.
- Substitution at C_2 position did not appear to be critical for activity.
- Substitution at N_3 is not essential for activity.

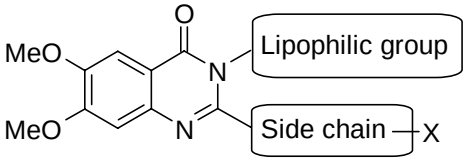
- The amino function at 4-position is highly favorable for activity although it could be effectively substituted by keto function.

  Following generalizations could be made for AT_1 receptor antagonists:
- Imidazole ring in losartan could be easily substituted by other five- or six-membered heterocyclic rings or even by simple open chain moieties containing nitrogen.
- *n*.Alkyl groups in the heterocyclic ring give more active compounds but it is not an essential structural feature.
- A suitably placed hydrogen bond acceptor either in the heterocyclic ring or part of an open chain moiety provides active molecule.
- An aromatic ring system possessing an acidic functionality as a side chain is required for activity. A biphenylmethyl group containing an acidic tetrazole affords the most potent ang II antagonists however, various types of ring systems have been reported to provide active compounds.

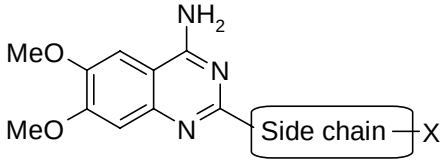
After studying the structural features of both of the classes of compounds it was felt that it should be possible to design dual α_1 and AT_1 receptor antagonists. It was envisaged to synthesize the following three categories of compounds:



(**I**)



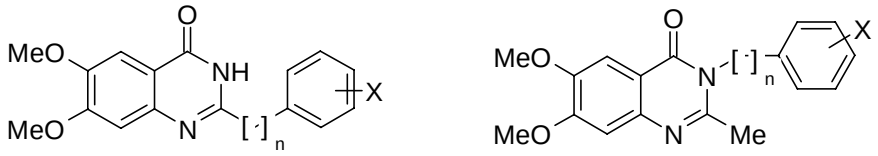
(**II**)



(**III**)

X = Neutral/acidic/basic groups

To explore the synthetic feasibility, preliminary work was started in this laboratory with the synthesis of simple 2/3-substituted phenyl-6,7-dimethoxyquinazoline-4(3*H*)-ones (**IV** and **V**) bearing neutral groups like methyl, halo, nitriles etc.

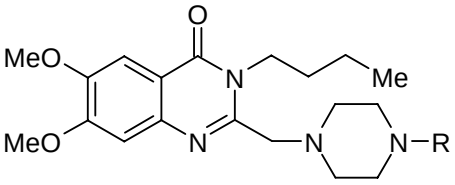


(**IV**) n = 0, 1 (**V**)

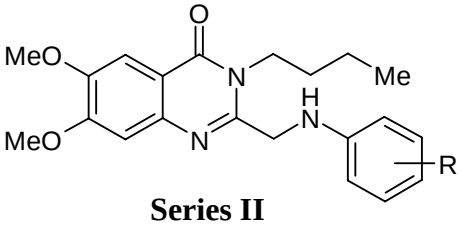
The synthesized compounds were evaluated for *in vivo* blockade of pressor response of phenylephrine (α_1) and ang II in rat model. To our astonishment, almost all of the synthesized compounds showed significantly good blockade of responses of both of the agonists. But, unfortunately, majority of these compounds showed poor aqueous solubility which could be because of their neutral character.

As all of the above evaluated compounds had 6,7-dimethoxyquinazoline motif, we got suspicious of the existence of the dual α_1 and AT_1 inhibiting activity even in a drug like prazosin, a well documented α_1 inhibitors. When prazosin was evaluated for its AT_1 antagonistic activity, it showed high AT_1 antagonistic activity. However, losartan, a clinically used AT_1 antagonist did not show any α_1 antagonistic activity.[369]

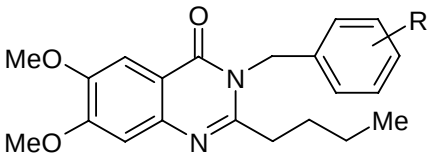
Encouraged by these results, it was planned by this investigation to synthesize compounds which could have better aqueous solubility and more structural variations. The following six series of compounds were aimed to be synthesized and their biological activity evaluated:



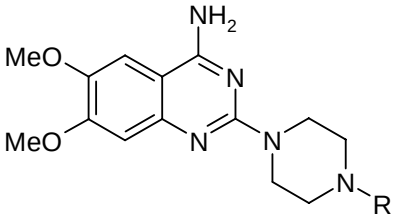
Series I



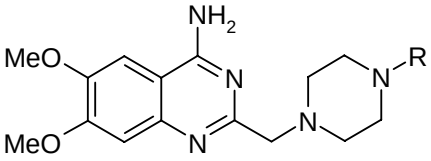
Series II



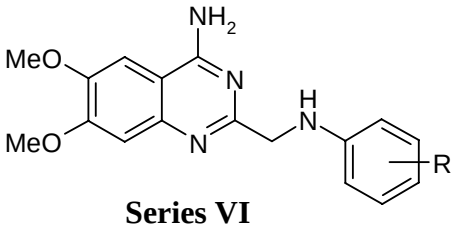
Series III



Series IV



Series V



Series VI

The work carried out towards achieving the proposed plan has been discussed under the following two main headings :

4.1 Chemical studies

4.2 Biological studies

4.1 Chemical studies

The synthetic work has been divided into the following heads:

4.1.1 Synthesis of starting materials and intermediates

- Synthesis of 6-nitroveratric acid
- Synthesis of 2-amino-4,5-dimethoxybenzonitrile
- Synthesis of substituted anilines
- Synthesis of substituted benzyl bromides

4.1.2 Synthesis of 3-*n*.butyl-2-chloromethyl-6,7-dimethoxyquinazolin-4(3*H*)-one

- Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substituted piperazin-1-yl) methyl] quinazolin-4(3*H*)-ones (**Series I**)
- Synthesis of 2-[(3/4-Substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-ones (**Series II**)

4.1.3 Synthesis of 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinzolin-4(3*H*)-ones (**Series III**)

4.1.4 Synthesis of 2-chloro-6,7-dimethoxyquinazolin-4-amine

- Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (**Series IV**)

4.1.5 Synthesis of 2-chloromethyl-6,7-dimethoxyquinazolin-4-amine

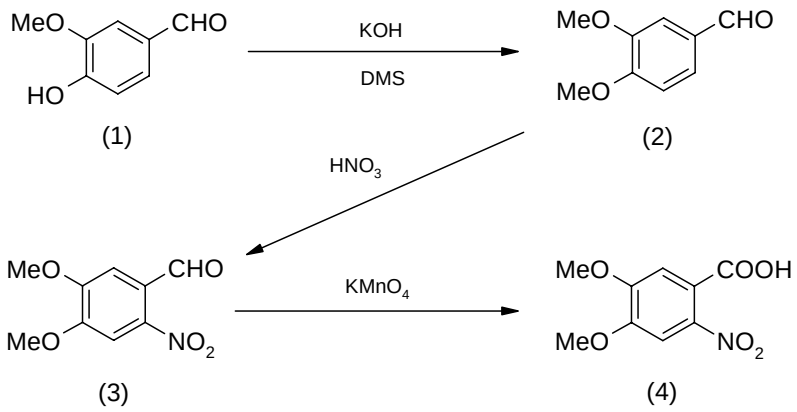
- Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (**Series V**)
- Synthesis of 2-[(aryl(alkyl)amino/heteroaryl)methyl]-6,7-dimethoxyquinazolin-4-amines (**Series VI**)

4.1.1 Synthesis of starting materials and intermediates

- **Synthesis of 6-nitroveratric acid** (**4**)

Vanillin (**1**) was methylated using dimethyl sulfate (DMS) under basic conditions to give verateraldehyde (**2**) as per the reported procedure.[370, 371](**Scheme 1**) Nitration of verateraldehyde (**2**) with concentrated nitric acid yielded 6-

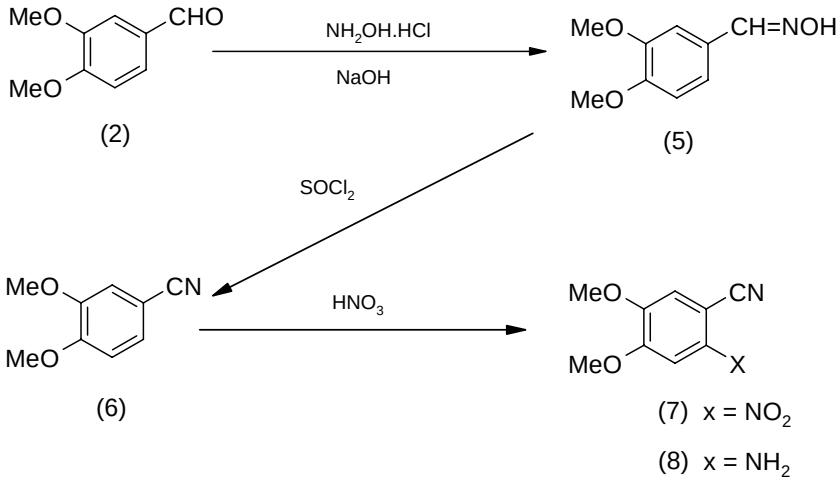
nitroverateraldehyde (**3**)[372] Its IR spectrum showed strong peaks at 1523 (N=O asym. str), 1336 (N=O sym. str) and 1686 cm^{-1} (C=O str). 6-Nitroveratraldehyde was subjected to potassium permanganate oxidation to obtain 6-nitroveratric acid (**4**).[373] 6-Nitroveratric acid (**4**) showed a broad peak of O-H around 3300 cm^{-1} and a shift in the peak of C=O stretching to 1703 cm^{-1} from 1686 cm^{-1} of 6-nitroveratraldehyde.



Scheme 1

- **Synthesis of 2-amino-4,5-dimethoxybenzonitrile**

Veratraldoxime (**5**) was prepared from veratraldehyde (**2**) by reacting it with hydroxylamine. Compound (**5**) showed characteristic broad peak at 3458 (O-H str) and absence of aldehydic (C=O) peak around 1670 cm^{-1} in its IR spectrum. Veratral-



Scheme 2

doxime (**5**) was dehydrated with thionyl chloride to get 3,4-dimethoxybenzonitrile (**6**)[374], which showed characteristic peak at 2221cm^{-1} (-C≡N) and absence of broad peak of O-H in its IR spectrum. Nitration of 3,4-dimethoxy benzonitrile (**6**) with conc.

nitric acid gave 4,5-dimethoxy-2-nitrobenzonitrile (**7**)[375]. Molecular ion peak was observed at m/z 208.06 in its mass spectrum. Its IR spectrum showed characteristic peaks at 2226 (-C≡N str), 1570 (N=O asym str) and 1397 cm^{-1} (N=O sym str). 4,5-Dimethoxy-2-nitrobenzonitrile (**7**) was reduced with tin and concentrated hydrochloric acid to yield 2-amino-4,5-dimethoxybenzonitrile[376] (**8**). Molecular ion peak was observed at m/z 178 in its mass spectrum. Its IR spectrum displayed characterisitic peaks at 3452 (N-H str) and 2210 cm^{-1} (-C≡N str).

- **Synthesis of substituted anilines**

Substituted anilines required for the synthesis of titled compounds were either procured from commercial sources or prepared in the laboratory. 3/4-Aminobenzoic acids were refluxed in methanol with continuously passing hudrogen chloride gas through them in order to get methyl 3/4-aminobenzoates. IR spectra showed peaks of C=O group at (1723 and 1714 cm^{-1}) respectively. The 3/4-Nitroanilines were acetylated to get 3/4-nitroacetanilides. Upon reduction with iron powder and ammonium chloride in aq methanol they yielded 3/4-acetamidoanilines respectively. IR spectra of these compounds showed peaks of N-H and C=O group for 3-acetamidoaniline (3413 and 1674 cm^{-1}) and 4-acetamidoaniline (3370 and 1664 cm^{-1}).

Methylsulfonation of 3/4-nitroanilines afforded 3/4-methanesulfonamido nitrobenzenes respectively, which upon reduction with iron powder and ammonium chloride in aq methanol afforded the corresponding amines. IR spectra of these compounds showed peaks of N-H and SO_2 group for 3-methanesulfonamidoaniline (3406, 1317 and 1147 cm^{-1}) and 4-methanesulfonamidoaniline (3414, 1397 and 1146 cm^{-1}).

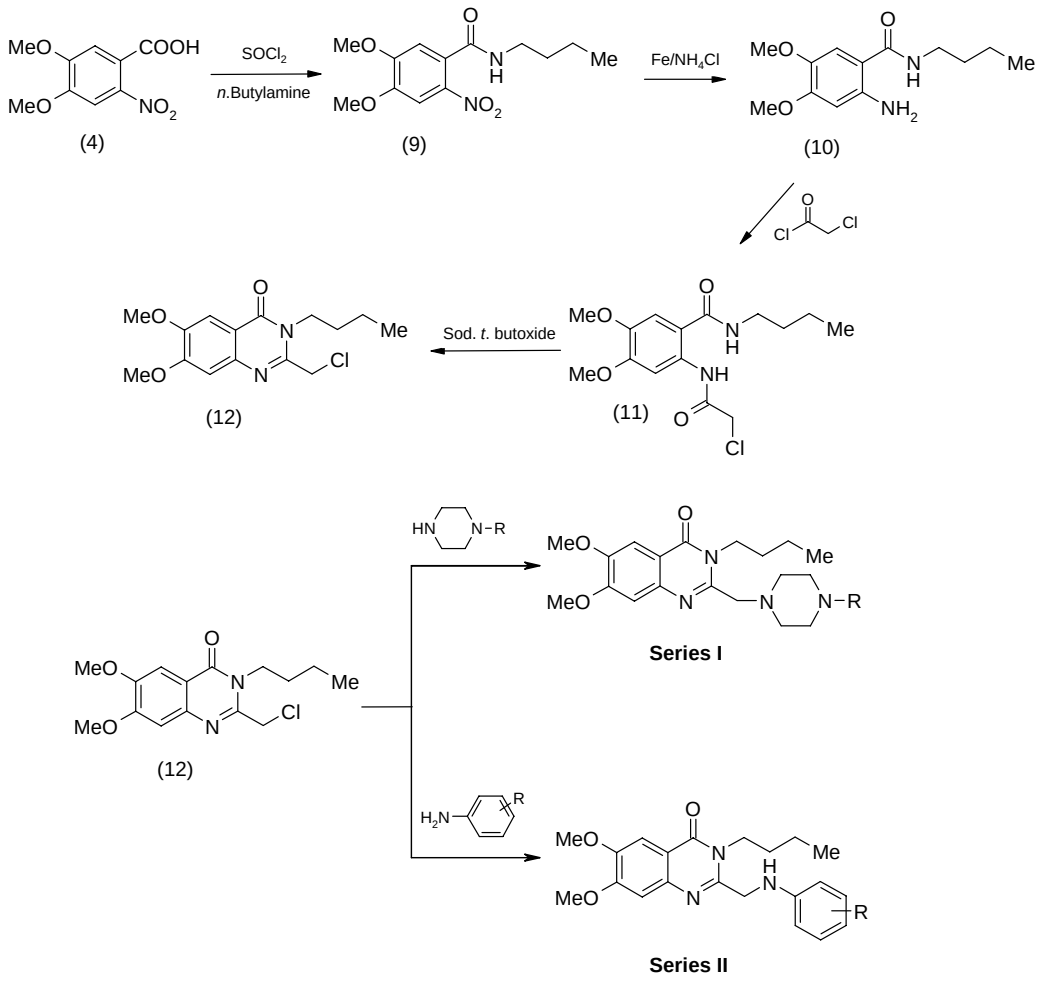
5-(3/4-Aminophenyl)-1*H*-tetrazoles were prepared in four steps from *m* and *p*-nitrobenzaldehydes. Aldoximes of 3/4-nitrobenzaldehydes were prepared by using hydroxylamine hydrochloride. The aldoximes were further dehydrated with thionyl chloride to afford the 3/4-nitrocyanobenzenes. IR spectra of these compounds confirmed the presence of the CN group (2236 and 2232 cm^{-1}). The cyano function was then converted to tetrazole moiety by using sodium azide. The corrsponding 5-(3/4-nitrophenyl)-1*H*-tetrazoles were further reduced to the 5-(3/4-aminophenyl)-1*H*-tetrazoles by iron powder and ammonium chloride in aq methanol.

- **Synthesis of substituted benzyl bromides**

Substituted benzyl bromides were prepared from substituted toluenes. 3-Tolunitrile, 3/4-methyl benzoates and 3-nitrotoluene were brominated by following a common preocedure. Substituted toluenes *were* brominated by using *N*-bromosuccinimide and benzoyl peroxide in DCM. The reaction mixture was refluxed until the reaction completed. This way 3-cyanobenzyl bromide, methyl 3/4-bromomethylbenzoate and 3-nitrobenzyl bromide were prepared.

4.1.2 Synthesis of 3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (12)

The acid chloride of 6-nitroveratric acid (**4**) prepared by its treatment with thionyl chloride was treated with *n*.butylamine in tetrahydrofuarn (THF) in presence



Seheme 3

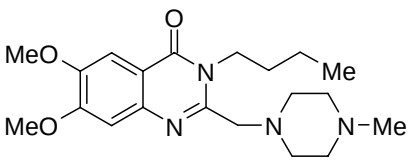
of triethylamine (TEA) to obtain *N*-*n*.butyl-4,5-dimethoxy-2-nitrobenzamide (**9**)

(**Scheme-3**). Compound (**9**) showed characteristic IR peaks at 3270 (N-H str), 1640 (C=O str), 1519 (N=O asym) and 1349 cm^{-1} (N=O sym). Reduction of *N*-*n*.butyl-4,5-dimethoxy-2-nitrobenzamide (**9**) with iron powder and ammonium chloride in aq. ethanol gave 2-amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (**10**). Peaks were observed at 3409 (N-H str) and 1637 cm^{-1} (C=O str) in its IR spectrum. 2-Amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (**10**) was then reacted with chloroacetyl chloride to form 2-(2-chloroacetamido)-*N*-*n*.butyl-4,5-dimethoxybenzamide (**11**). Its IR spectrum showed peaks at 3404 (N-H str), 1666 (C=O str), 1262 (C-N str) and 1212 cm^{-1} (Ar-O str). Molecular ion peak was obtained at m/z 329 in its mass spectrum. 2-(2-Chloroacetamido)-*N*-*n*.butyl-4,5-dimethoxybenzamide **(11)** was cyclised in presence of sodium *t*.butoxide and ethylene glycol to form 3-*n*.butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (**12**). The IR peaks were observed are 1669 (C=O str), 1260 (Ar-O str) and 1039 cm^{-1} (O-CH_3 str). Its mass spectrum showed molecular ion peak at m/z 311.

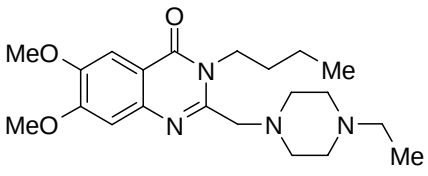
- **Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substituted piperazin-1-yl)methyl] quinazolin-4(3*H*)-ones (Series I)**

Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substitutedpiperazin-1-yl)methyl]quinazolin-4(3*H*)-ones were accomplished by following **Scheme 3**. Compound (**12**) and substituted amines in DMF were stirred at 60°C until the reaction was complete.

3-*n*.Butyl-6,7-dimethoxy-2-[(4-methylpiperazin-1-yl)methyl]quinazoline-4(3 *H*)-one (**I-1**) displayed characteristic peaks at 1662 (C=O str), 1242 (Ar-O str) and 1012 cm^{-1} (O-CH_3 str) in its IR spectrum.



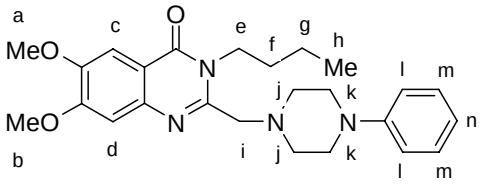
(**I-1**)



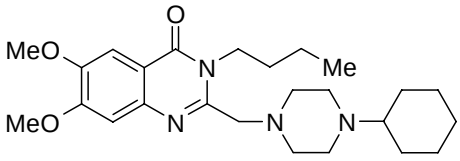
(**I-2**)

3-*n*.Butyl-2-[(4-ethylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-2**) showed characteristic peaks at 1663 (C=O str), 1266 (Ar-O str) and 1019 cm^{-1} (O-CH_3 str) in its IR spectrum.

3-*n*.Butyl-6,7-dimethoxy-2-[(4-phenylpiperazin-1-yl)methyl]quinazolin-4(3*H*)-one (**I-3**) displayed characteristic peaks at 1667 (C=O str), 1266 (Ar-O str) and 1053 cm^{-1} (O-CH_3 str) in its IR spectrum. Signals appeared at δ 7.43 (s, 1H, Ar-H_c), 7.22-7.15 (m, 3H, Ar-H_l and Ar-H_d), 6.93-6.91 (m, 2H, Ar-H_m), 6.79-6.75 (m, 1H, Ar-H_n), 4.15-4.11 (t, 2H, CH_{2e}), 3.90 (s, 3H, OC$H_{3a/3b}$), 3.87 (s, 3H, OC$H_{3a/3b}$), 3.69 (s, 2H, CH_{2i}), 3.12 (b, 4H, 2 × CH_{2k}), 2.63 (m, 4H, 2 × CH_{2j}), 1.72-1.69 (m, 2H, CH_{2f}), 1.41-1.35 (m, 2H, CH_{2g}) and 0.94-0.92 (t, 3H, CH_{3h}) in its NMR spectrum.



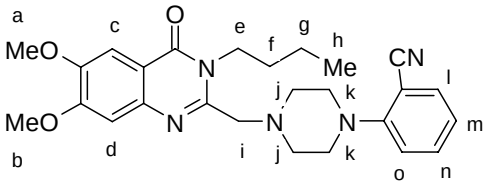
(**I-3**)



(**I-4**)

3-*n*.Butyl-2-[(4-cyclohexylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-4**) displayed characteristic peaks at 1660 (C=O str), 1271 (Ar-O str) and 1051 cm^{-1} (O-CH_3 str) in its IR spectrum.

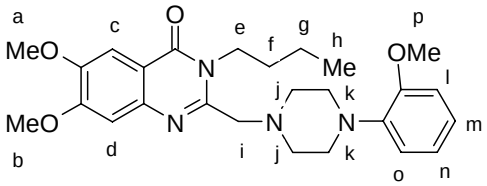
IR spectrum of 2-[4-((3-*n*.butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2-yl)methyl)piperazin-1-yl]benzonitrile (**I-5**) displayed characteristic IR peaks at 2220 (C≡N str), 1669 (C=O str), 1265 (Ar-O str) and 1016 cm^{-1} (O-CH_3 str). Its NMR spectrum showed signals at δ 7.72-7.69 (m, 1H, Ar-H_l), 7.62-7.57 (m, 1H, Ar-H_n), 7.44 (s, 1H, Ar-H_c), 7.17 (s, 1H, Ar-H_d), 7.14-7.08 (m, 2H, Ar-$H_{n,o}$), 4.16-4.12 (t, 3H, N-CH_{2e}), 3.90 (s, 3H, O-C$H_{3a/b}$), 3.87 (s, 3H, O-C$H_{3a/b}$), 3.71 (s, 2H, CH_{2i}), 3.14 (b, 4H, CH_{2k}), 2.68 (b, 4H, CH_{2j}), 1.73-1.69 (m, 2H, CH_{2f}), 1.42-1.37 (m, 2H, CH_{2g}) and 0.96-0.93 (t, 3H, CH_{3h})



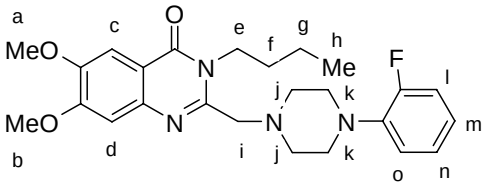
(**I-5**)

3-*n*.Butyl-6,7-dimethoxy-2-[(4-(2-methoxyphenyl)piperazin-1-yl)methyl]quinazolin-4-(3*H*)-one (**I-6**) displayed characteristic peaks at 1669 (C=O str), 1238 (Ar-O str) and 1053 cm^{-1} (O-CH_3 str) in its IR spectrum. Its gave signals at δ 7.42 (s, 1H, Ar-

H_c), 7.14 (s, 1H, Ar-H_d), 6.92-6.85 (m, 4H, Ar-$H_{o\text{-}l}$), 4.13 (m, 2H, N-CH_{2e}), 3.90 (s, 3H, O-C$H_{3a/b}$), 3.86 (s, 3H, O-C$H_{3a/b}$), 3.76 (s, 3H, O-CH_{3p}), 3.68 (s, 2H, -CH_{2i}), 2.95 (b, 4H, CH_{2k}), 2.61 (b, 4H, CH_{2j}), 1.73 (m, 2H, CH_{2f}), 1.39-1.37 (m, 2H, CH_{2g}) and 0.95-0.92 (t, 3H, CH_{3h}) in its NMR spectrum.



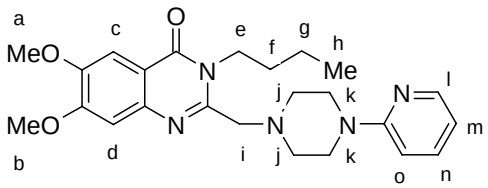
(**I-6**)



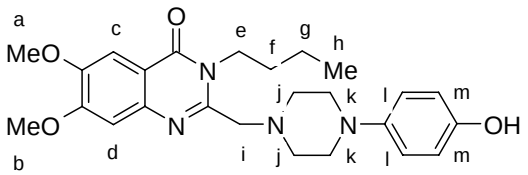
(**I-7**)

3-*n*.Butyl-2-[(4-(2-fluorophenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-(3*H*)-one (**I-7**) displayed characteristic peaks at 1666 (C=O str), 1237 (Ar-O str) and 1052 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR peaks were obtained at δ 7.42 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 7.13-7.07 (m, 2H, Ar-H_n and H_l), 7.03-6.95 (m, 2H, Ar-H_o and H_m), 4.15-4.11 (m, 2H, N-CH_{2e}), 3.90 (s, 3H, O-C$H_{3a/b}$), 3.87 (s, 3H, O-C$H_{3a/b}$), 3.69 (s, 2H, CH_{2i}), 3.00 (s, 4H, CH_{2k}), 2.65 (s, 4H, CH_{2j}), 1.73-1.69 (m, 2H, CH_{2f}), 1.44-1.34 (m, 2H, CH_{2g}) and 0.96-0.92 (t, 3H, CH_{3h}). Molecular ion peak was observed at m/ z 467.45 in its mass spectrum.

IR spectrum of 3-*n*.butyl-6,7-dimethoxy-2-[(4-(pyridin-2-yl)piperazin-1-yl)methyl]quinazolin-4(3*H*)-one (**I-8**) showed characteristic peaks at 1668 (C=O str), 1244 (Ar-O str) and 1052 cm^{-1} (O-CH_3 str). Its NMR showed signals at δ 8.1 (m, 1H, Ar-H_l), 7.55-7.50 (m, 1H, Ar-H_m), 7.43 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 6.82-6.80



(**I-8**)

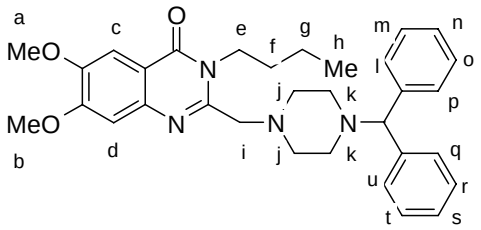


(**I-9**)

(m, 1H, Ar-H_o), 6.66-6.63 (m, 1H, Ar-H_n), 4.17-4.13 (t, 2H, N-CH_{2e}), 3.90 (s, 3H, OC$H_{3a/b}$), 3.87 (s, 3H, OC$H_{3a/b}$), 3.68 (s, 2H, CH_{2i}), 3.46 (b, 4H, 2 × CH_{2k}), 2.57 (b, 4H, 2 × CH_{2j}), 1.73-1.69 (m, 2H, CH_{2f}), 1.42- 1.35 (m, 2H, CH_{2g}) and 0.97-0.93 (t, 3H, CH_{3h}).

3-*n*.Butyl-2-[(4-(4-hydroxyphenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-(3*H*)-one (**I-9**) gave characteristic peaks at 1660 (C=O str), 1272 (Ar-O str) and 1020 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR showed signals at δ 8.85 (s, 1H, O*H*), 7.43 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 6.77-6.75 (d, 2H, Ar-H_m), 6.64-6.62 (d, 2H, Ar-H_l), 4.14-4.10 (t, 2H, N-CH_{2e}), 3.90 (s, 3H, OC$H_{3a/b}$), 3.86 (s, 3H, OC$H_{3a/b}$), 3.67 (s, 2H, CH_{2i}), 2.95 (bs, 4H, 2 × CH_{2k}), 2.60 (bs, 4H, 2 × CH_{2j}), 1.72-1.68 (m, 2H, CH_{2f}), 1.40- 1.33 (m, 2H, CH_{2g}) and 0.94-0.90 (t, 3H, CH_{3h}).

2-[(4-Benzhydrylpiperazin-1-yl)methy]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-10**) displayed characteristic peaks at 1668 (C=O str), 1268 (Ar-O str) and 1005 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR signals appeared at δ 7.40-7.10 (m, 12H, Ar-$H_{c,\ d}$ and $_{l-u}$), 4.07-4.04 (t, 2H, N-CH_{2e}), 3.88 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3a/b}$), 3.68 (s, 2H, CH_{2i}), 2.69 (b, 4H, 2 × CH_{2k}), 2.08 (b, 4H, 2 × CH_{2j}), 1.67 (b, 2H, CH_{2f}), 1.36-1.33 (m, 2H, CH_{2g}) and 0.92-0.88 (t, 3H, CH_{3h}).



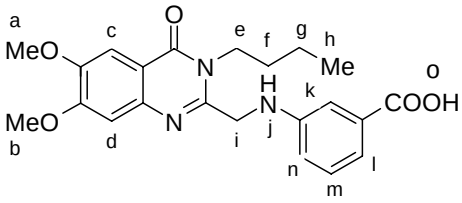
(**I-10**)

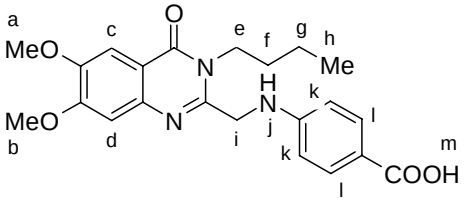
- **Synthesis of 2-[(3/4-substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (Series II)**

Synthesis of 2-[(3/4-substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxy quinazolin-4(3*H*)-ones were accomplished by **Scheme 3** as discussed above. 3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (**12**) was reacted with different 3/4-substituted anilines in presence of flame dried cesium carbonate in dry DMF to obtain corresponding 2-[(3/4-substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one.

3-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2-yl)methylamino] benzoic acid (**II-1**) displayed characterstic peaks at 3360 (broad O-H str), 1717 and 1662 (C=O str), 1226 (Ar-O str) and 1098 cm^{-1} (O-CH_3 str) in its IR spectrum. Signals appeared at δ 7.61 (s, 1H, Ar-H_c), 7.49-7.47 (m, 1H, Ar-H_l), 7.39-7.38 (m, 1H, Ar-

H_k), 7.28-7.21 (m, 1H, Ar-H_m), 7.08 (s, 1H, Ar-H_d), 6.91-6.88 (m, 1H, Ar-H_n), 5.39 (s, 2H, CH_{2i}), 4.12-4.08 (t, 2H, N-CH_2), 4.01 (s, 3H, OC$H_{3a/3b}$), 4.00 (s, 3H, OC$H_{3a/3b}$), 1.78-1.72 (m, 2H, CH_{2f}); 1.43-1.37 (m, 2H, CH_{2g}) and 0.93-0.89 (t, 3H, CH_{3h}) in its NMR spectrum. Molecular ion peak was observed at m/z 410.9 in its mass spectrum.

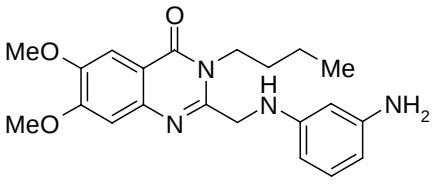


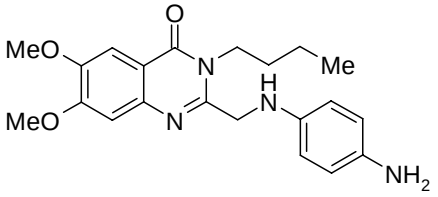


(**II-1**) (**II-2**)

4-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino] benzoic acid (**II-2**) showed characteristic peaks at 1700, 1657 (C=O str), 1272 (Ar-O str) and 1028 cm^{-1} (O-CH_3 str) in IR spectrum. Its NMR spectrum gave signals at δ 7.91-7.89 (d, 2H, Ar-H_l), 7.61 (s, 1H, Ar-H_c), 7.09 (s, 1H, Ar-H_d), 6.66-6.64 (d, 2H, Ar-H_k), 5.37 (s, 2H, NH-CH_2), 4.14-4.04 (t, 2H, N-CH_{2e}), 4.00 (s, 3H, OC$H_{3a/3b}$), 3.98 (s, 3H, OC$H_{3a/3b}$), 1.77-1.74 (m, 2H, CH_{2f}), 1.42-1.36 (m, 2H, CH_{2g}) and 0.91-0.88 (t, 3H, CH_{3h}). Molecular ion peak was observed at 410.9 (m/z) in its mass spectrum.

2-[(3-Aminophenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**II-3**) showed characteristic IR peaks at 3131 (N-H str), 1663 (C=O str), 1210 (Ar-O str) and 1167 cm^{-1} (O-CH_3 str). Mass spectrum of the compound (**II-3**) showed molecular ion peak at m/z 382.13.

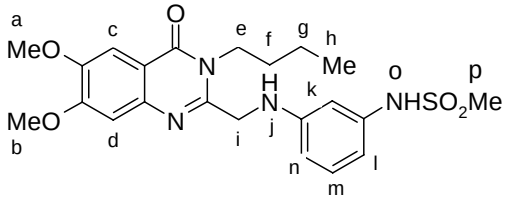




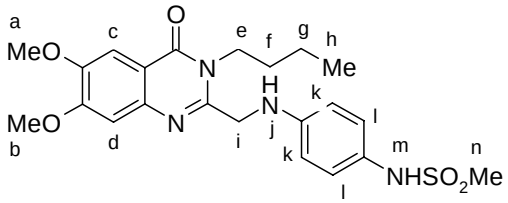
(**II-3**) (**II-4**)

2-[(4-Aminophenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**II-4**) showed characteristic peaks at 3127 (N-H str), 1678 (C=O str), 1261 (Ar-O str) and 1095 cm^{-1} (O-CH_3 str) in its IR spectrum. Molecular ion peak was observed at m/z 381.20 in its mass spectrum.

IR apectrum of *N*-[3-[(3-*n*.butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino]phenyl]methanesulfonamide (**II-5**) showed characteristic peaks at 3444 and 3361 (N-H str), 1678 (C=O str), 1331 and 1147 (SO_2 str) and 1082 cm^{-1} (O-CH_3 str). Peaks were observed at δ 7.57 (s, 1H, Ar-H_c), 7.13-7.09 (m, 1H, Ar-H_m), 6.93 (s, 1H, Ar-H_d), 6.92-6.88 (m, 2H, Ar-H_n and H_l), 6.60-6.58 (m, 1H, Ar-H_k), 4.99 (s, 2H, CH_{2i}), 4.14-4.11 (t, 2H, N-CH_{2e}), 3.98 (s, 6H, OC$H_{3a/b}$), 3.73 (b, 1H, NH_o), 3.23 (s, 3H, CH_{3p}), 1.71-1.67 (m, 2H, CH_{2f}), 1.47-1.41 (m, 2H, CH_{2g}) and 0.99-0.95 (t, 3H, CH_{3h}) in its NMR spectrum. Molecular ion peak was observed at 460.10 (m/z) in its mass spectrum.



(**II-5**)

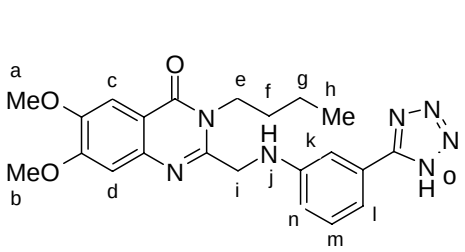


(**II-6**)

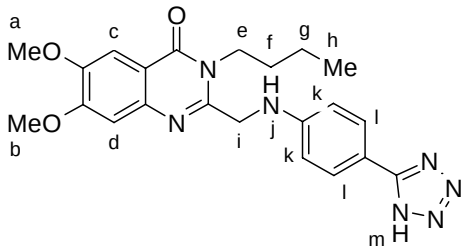
N-[4-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino]phenyl]methanesulfonamide (**II-6**) displayed characteristic peaks at 3462 and 3366 (N-H str), 1655 (C=O str), 1338 and 1145 (SO_2 str), 1272 (Ar-O str) and 1078 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR spectrum gave signals at δ 7.56 (s, 1H, Ar-H_c) 7.31-7.28 (d, 2H, Ar-H_k), 6.94 (s, 1H, Ar-H_d), 6.60-6.58 (d, 2H, Ar-H_l), 4.96 (s, 2H, CH_{2i}), 4.16-4.12 (t, 2H, N-CH_{2e}), 3.99 (s, 3H, OC$H_{3a/3b}$), 3.98 (s, 3H, OC$H_{3a/3b}$), 3.16 (s, 3H, CH_{3n}), 1.68-1.61 (m, 2H, CH_{2f}), 1.46-1.41 (m, 2H, CH_{2g}) and 0.99-0.95 (t, 3H, CH_{3h}). Molecular ion peak was observed at 460.09 (m/z) in mass spectrum.

Characteristic peaks at 3416 (N-H str), 1665 (C=O str), 1262 (Ar-O str) and 1038 cm^{-1} (O-CH_3 str) were obsereved in IR spectrum for 2-[(3-(1*H*-tetrazol-5-yl)phenylaminomethyl)-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**II-7**). Its NMR spectrum showed signals at δ 7.52 (s, 1H, Ar-H_c), 7.45 (s, 1H, Ar-H_k), 7.40-7.38 (m, 1H, Ar-H_n), 7.22-7.18 (m, 1H, Ar-H_m), 6.91 (s, 1H, Ar-H_d) 6.78-6.77 (d, 1H, Ar-H_l), 6.14 (s, 2H, N*H*), 4.21-4.13 (t, 2H, N-CH_{2e}), 3.95 (s, 3H, OC$H_{3a/b}$), 3.90 (s, 3H, OC$H_{3a/b}$), 1.66-1.59 (m, 2H, CH_{2f}), 1.51-1.43 (h, 2H, CH_{2g}) and 0.88-0.85 (t, 3H, CH_{3h}). Molecular ion peak was obsereved at m/z 434.98 in mass spectrum.

2-[(4-(1*H*-Tetrazol-5-yl)phenylaminomethyl]-3-*n*.butyl-6,7-dimethoxyquinazo -lin-4(3*H*)-one (**II-8**) showed characteristic peaks at 3359 (N-H str), 1664 (C=O str), 1270 (Ar-O str) and 1037 cm^{-1} (O-CH_3 str) in its IR spectrum. Signals appeared in its NMR spectrum at δ 7.80-7.78 (d, 2H, Ar-H_l), 7.49 (s, 1H, Ar-H_c), 6.89 (s, 1H, Ar-H_d),



(**II-7**)

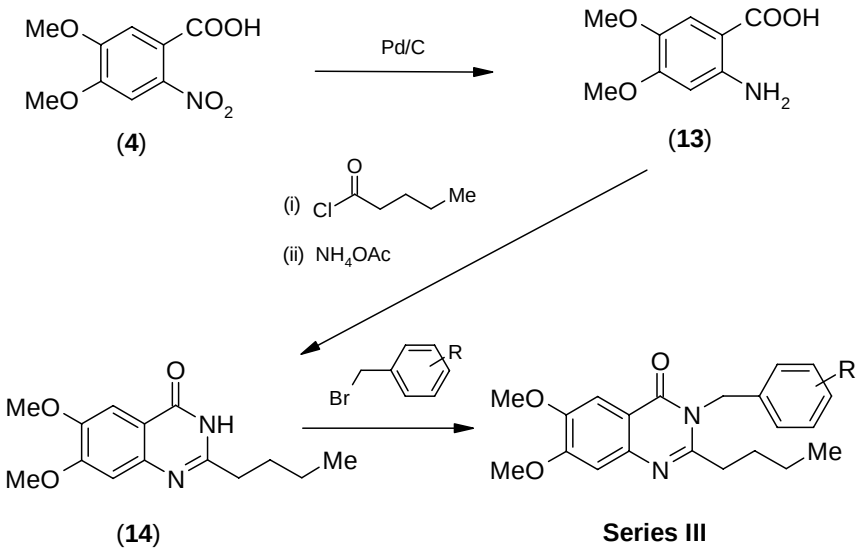


(**II-8**)

6.72-6.69 (d, 2H, Ar-H_k), 6.14 (s, 2H, N*H*), 4.19-4.15 (t, 2H, NCH_{2i}), 3.98 (s, 3H, OC$H_{3a/b}$), 3.92 (s, 3H, OC$H_{3a/b}$), 1.62-1.55 (m, 2H, CH_{2f}), 1.48-1.42 (m, 2H, CH_{2g}) and 0.99-0.84(t, 3H, CH_{3h}). Molecular ion peak was observed at m/z 435.17 in mass spectrum.

4.1.3 Synthesis of 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-ones (Series III)

Reduction of 6-nitroveratric acid (**4**) with palladium charcoal afforded 4,5-dimethoxyanthranilic acid (**13**) which showed characteristic peak at 3374cm^{-1}. A solu-

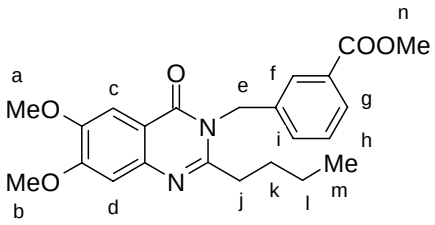


Scheme 4

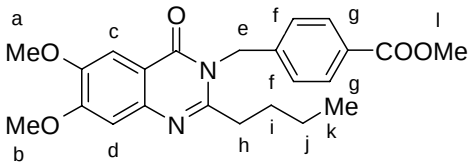
tion of 4, 5-dimethoxyanthranilic acid (**13**) and valeroyl chloride in DMF was heated

to afford the cyclised compound 2-*n*.butyl-6,7-dimethoxy-benz[1,3-*d*]-4*H*-oxazin-4-one. It was isolated and characterized through IR. Its IR spectrum showed peak at 1746 (C=O str.) cm^{-1}. However, this compound was sensitive to moisture and therefore it was treated *in situ* with ammoniun acetate to afford the desired compound 2-*n*.Butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**14**) as solid. Its IR spectrum showed peaks at 3157 (N-H str.) and 1670 (C=O str.) cm^{-1}. The molecular ion peak was observed at m/z 262.06 in its mass spectrum. Compound (**14**) was thenreacted with different substituted benzyl bromides in acetone at RT in order to get 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin- 4(3*H*)-ones (**Scheme 4**).

Methyl 3-[(2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl) benzoate (**III-1**) displayed characteristic peaks at 1669 (C=O str.), 1273 (Ar-O str.) and 1032 cm^{-1} (O-CH_3 str.) in its IR spectrum.



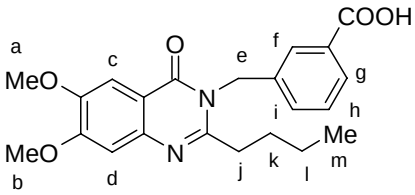
(**III-1**)



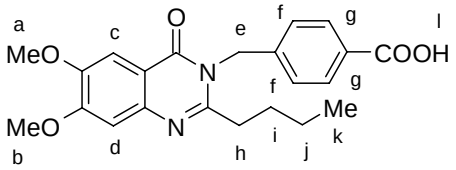
(**III-2**)

Methyl 4-[(2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzo-ate (**III-2**) showed characteristic peaks at 1720, 1654 (C=O str.), 1283, (Ar-O str.) and 1012 cm^{-1} (O-CH_3 str.) in its IR spectrum. NMR signals were appeared at δ 7.94- 7.92 (d, 2H, Ar-H_g), 7.46 (s, 1H, Ar-H_c), 7.29-7.27 (d, 2H, Ar-H_f), 7.11 (s, 1H, Ar-H_d), 5.46 (s, 2H, CH_{2e}), 3.92 (s, 3H, OC$H_{3a/b}$), 3.87 (s, 3H, OC$H_{3a/b}$), 3.83 (s, 3H, OCH_{3l}), 2.68-2.65 (t, 2H, CH_{2h}), 1.67-1.59 (m, 2H, CH_{2i}), 1.33-1.24 (m, 2H, CH_{2j}) and 0.82-0.79 (t, 3H, CH_{3k}).

3-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoic acid (**III-3**) displayed characteristic peaks at 3130 (O-H str.), 1703, 1660 (C=O str.) and 1288 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum exhibited signals at δ 7.86-7.84 (d, 1H, Ar-H_g), 7.68 (s, 1H, Ar-H_f), 7.51-7.43 (m, 3H, Ar-$H_{c, h, i}$), 7.11 (s, 1H, Ar-H_d), 5.77 (s, 2H, N-CH_{2e}), 3.92 (s, 3H, OC$H_{3a/b}$), 3.88 (s, 3H, OC$H_{3a/b}$), 2.71-2.67 (m, 2H, CH_{2j}), 1.64-1.60 (m, 2H, CH_{2k}), 1.31-1.27 (m, 2H, CH_{2l}) and 0.84-0.77 (t, 3H, CH_{3m}).



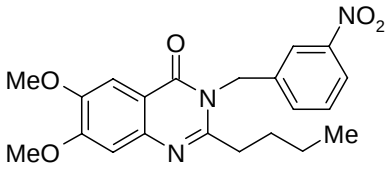
(**III-3**)



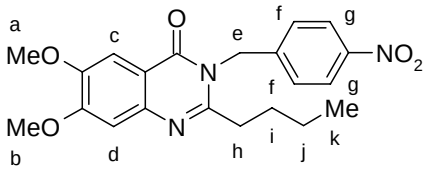
(**III-4**)

4-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoic acid (**III-4**) displayed characteristic peaks at 3413 (O-H str.), 1670, 1638 (C=O str.), 1254 (Ar-O str.) and 1058 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals were obtained at δ 8.23-8.21 (d, 2H, Ar-H_g), 7.46 (s, 1H, Ar-H_c), 7.43-7.41 (d, 2H, Ar-H_f), 7.12 (s, 1H, Ar-H_d), 5.51 (s, 2H, N-CH_{2e}), 3.93 (s, 3H, OC$H_{3a/b}$), 3.88 (s, 3H, OC$H_{3a/b}$), 2.70-2.66 (m, 2H, CH_{2h}), 1.69-1.62 (m, 2H, CH_{2i}), 1.35-1.23 (m, 2H, CH_{2j}) and 0.87-0.83 (t, 3H, CH_{3k}) in its NMR spectrum.

2-*n*.Butyl-6,7-dimethoxy-3-(3-nitrobenzyl)quinazolin-4(3*H*)-one (**III-5**) displayed characteristic peaks at 1664 (C=O str.), 1530 (N=O asym.), 1351 (N=O sym.) and 1228 cm^{-1} (Ar-O str.) in its IR spectrum.



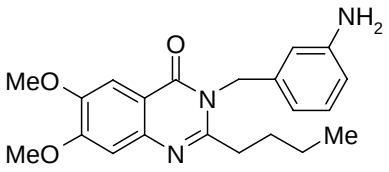
(**III-5**)



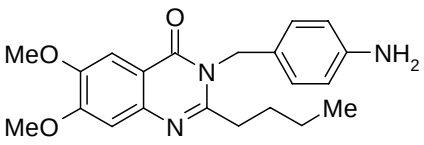
(**III-6**)

2-*n*.Butyl-6,7-dimethoxy-3-(4-nitrobenzyl)quinazolin-4(3*H*)-one (**III-6**) showed characteristic peaks at 1657 (C=O str.), 1520 (N=O asym.), 1345 (N=O sym.) and 1230 cm^{-1} (Ar-O str.) in its IR spectrum. Its ^{1}NMR spectrum showed signals at 8.20-8.18 (d, 2H, Ar-H_g), 7.50 (s, 1H, Ar-H_c), 7.44-7.41 (d, 2H, Ar-H_f) 7.10 (s, 1H, Ar-H_d), 5.29 (s, 2H, NCH_2), 3.97 (s, 3H, OC$H_{3a/b}$), 3.92 (s, 3H, OC$H_{3a/b}$), 2.71-2.67 (t, 2H, CH_{2h}), 1.73-1.67 (m, 2H, CH_{2i}), 1.39-1.33 (m, 2H, CH_{2j}) and 0.90-0.86 (t, 3H, CH_{3k}).

3-(3-Aminobenzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one(**III-7**) displayed characteristic peaks at 3413, 3115 (N-H str.), 1664 (C=O str.) and 1271 (Ar-O str.) in its IR spectrum.



(**III-7**)



(**III-8**)

3-(4-Aminobenzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**III-8**) displayed characteristic peaks at 3413, 3159 (N-H str.), 1658 (C=O str.), 1266 cm^{-1} (Ar-O str.) in its IR spectrum.

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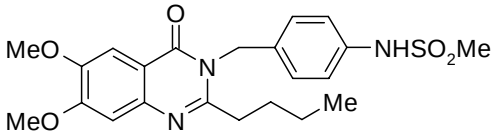
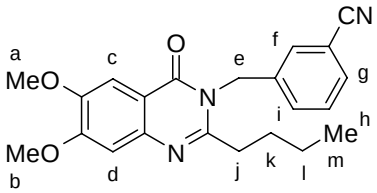
IR spectrum of *N*-[4-((2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl)phenyl]methanesulfonamide (**III-9**) displayed characteristic peaks at 3414 and 3143 (N-H str.), 1659 (C=O str.), 1335 (S=O str.), 1247 (Ar-O str.), 1152 (S=O str.) and 1013 cm^{-1} (O-CH_3 str.) in its IR spectrum.

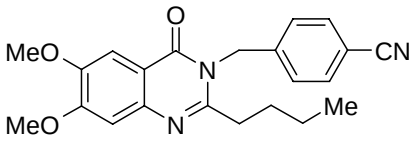


(**III-9**)

3-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzonitrile (**III-10**) displayed characteristic peaks at 2230 (C≡N str.), 1660 (C=O str.), 1245 (Ar-O str.) and 1012 cm^{-1} (O-CH_3 str) in its IR spectrum. Peaks were observed at δ 7.63-7.62 (m, 1H, Ar-H_g), 7.56-7.51 (m, 4H, Ar-$H_{c, f, h, i}$), 7.20 (s, 1H, Ar-H_d), 5.46 (s, 2H, NCH_{2e}), 4.00 (s, 3H. O-C$H_{3a/b}$), 3.97 (s, 3H, O-C$H_{3a/b}$), 2.81-2.77 (t, 2H, CH_{2j}), 1.74-1.68 (m, 2H, CH_{2k}), 1.43-1.38 (m, 2H, CH_{2l}) and 0.92-0.88 (t, 3H, CH_{3m}). Molecular ion peak was observed at m/z 377.90 in its mass spectrum.



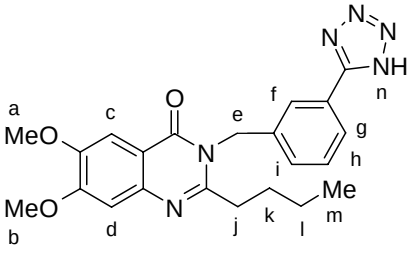
(**III-10**)



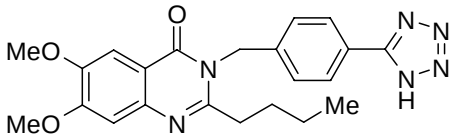
(**III-11**)

4-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzonitrile (**III-11**) displayed characteristic peaks at 2228 (C≡N str.), 1658 (C=O str.), 1245 (Ar-O str.) and 1013 cm^{-1} (O-CH_3 str.) in its IR spectrum.

2-*n*.Butyl-6,7-dimethoxy-3-[3-(1*H*-tetrazol-5-yl)benzyl]quinazolin-4(3*H*)-one (**III-12**) displayed characteristic peaks at 3132 (N-H str.), 1638 (C=O str.), 1245 (Ar-O str.) and 1024 cm^{-1} (O-CH_3 str.) in its IR spectrum. NMR signals appeared at 7.96-7.94 (d, 1H, Ar-H_g), 7.82 (s, 1H, Ar-H_c), 7.61-7.57 (t, 1H, Ar- H_h), 7.48 (s, 1H, Ar-H_f), 7.42-7.40 (d, 1H, Ar-H_i), 7.12 (s, 1H, Ar-H_d), 5.48 (s, 2H, CH_{2e}), 3.92 (s, 3H, O-C$H_{3a/b}$), 3.88 (s, 3H, O-C$H_{3a/b}$), 2.74-2.71 (t, 2H, CH_{2j}), 1.69-1.61 (m, 2H, CH_{2k}), 1.32-1.26 (m, 2H, CH_{2l}), 0.84-0.80 (t, 3H, CH_{3m}).



(**III-12**)

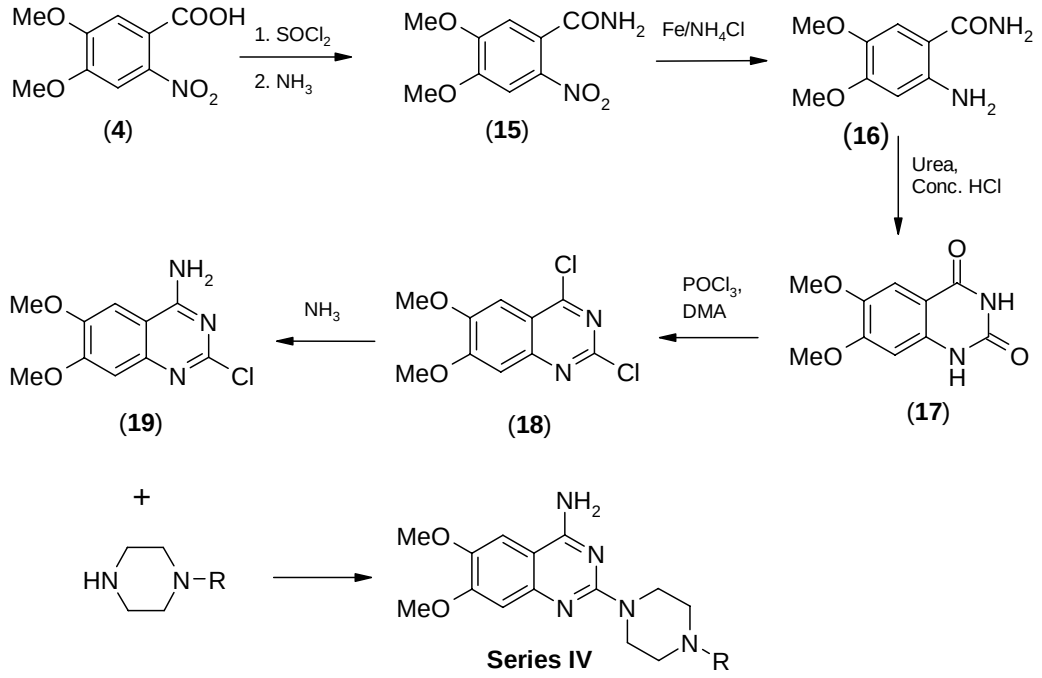


(**III-13**)

2-*n*.Butyl-6,7-dimethoxy-3-[4-(1*H*-tetrazol-5-yl)benzyl]quinazolin-4(3*H*)-one (**III-13**) displayed characteristic peaks at 3418, 3013 (N-H str.), 1649 (C=O str.), 1252 (Ar-O str.) and 1067 cm^{-1} (O-CH_3 str.) in its IR spectrum.

4.1.4 Synthesis of 2-chloro-6,7-dimethoxyquinazolin-4-amine (19)

The acid (**4**) was converted into amide (**15**) by treatment of its acid chloride with ammonia. Nitro group of the amide (**15**) was reduced to amino using iron-ammonium chloride to obtain 2-amino-4,5-dimethoxybenzamide (**16**). The amide (**16**) was condensed with urea in presence of catalytic amount of hydrochloric acid to afford 6,7-dimethoxy-1,2,3,4-tetrahydroquinazoline-2,4-dione (**17**).[377] Compound (**17**) was treated with phosphorus oxychloride in presence of catalytic amount of *N*,*N*-dimethylaniline (DMA) to yield 2,4-dichloro-6,7-dimethoxyquinazoline (**18**)[378]. In light of the reported[379] susceptibility of 4-chloroquinazoline towards moisture, compound (**18**) was used immediately after its preparation. Compound (**18**) was treated with dry ammonia gas in THF for 36 hours to obtain 4-amino-2-chloro-6,7-dimethoxyquoinazoline (**19**). IR spectrum for compound (**19**) showed characteristic peaks at 3409 & 3326 (N-H str.), 1279 (C-N str.), 1250 (Ar-O str.) and 1026 cm^{-1} (O-CH_3 str.). Its mass apectrum showed M+H peak at m/z 240.

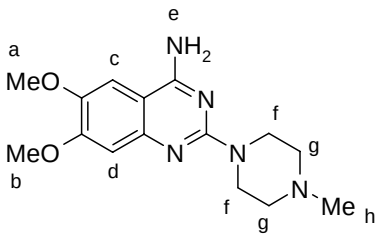


Scheme 5

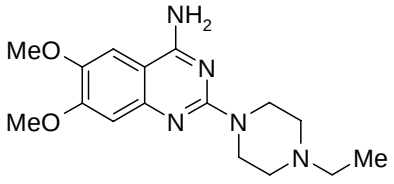
- **Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (Series IV)**

6,7-Dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines were prepared by reacting substituted piperazines with compound (**19**). Compound (**19**) and substituted piperazines in DMF were stirred at 100° C in sealed tube until the reaction was complete (**Scheme 5**).

6,7-Dimethoxy-2-(4-methylpiperazin-1-yl)quinazolin-4-amine (**IV-1**) showed characteristic peaks at 3555 and 3334 (N-H str.), 1280 (C-N str.), 1244 (Ar-O str.) and



(**IV-1**)

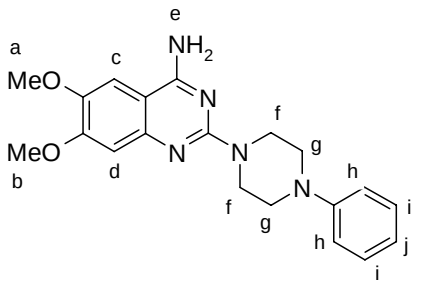


(**IV-2**)

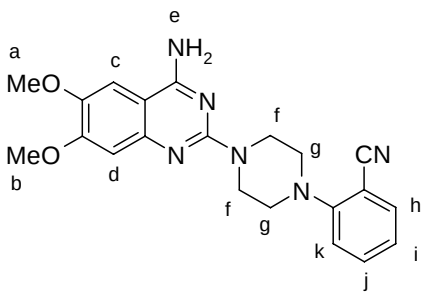
1002 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.40 (s, 1H, Ar-H_d), 7.09 (b, 2H, NH_{2e}), 6.70 (s, 1H, Ar-H_c), 3.82 (s, 3H, O$CH_{3a/b}$), 3.77 (s, 3H, O$CH_{3a/b}$), 3.68 (b, 4H, 2 × CH_{2f}), 2.33 (b, 4H, 2 × CH_{2g}) and 2.19 (s, 3H, CH_{3h}).

2-(4-Ethylpiperazin-1-yl)-6,7-dimethoxyquinazolin-4-amine (**IV-2**) displayed characteristic peaks at 3291 and 3086 (N-H str.), 1294 (C-N str.) and 1248 (Ar-O str.) in its IR spectrum.

IR spectrum of 6,7-dimethoxy-2-(4-phenylpiperazin-1-yl)quinazolin-4-amine (**IV-3**) displayed characteristic peaks at 3456 and 3262 (N-H str.), 1288 (C-N str.), 1235 (Ar-O str.) and 1033 cm^{-1} (O-CH_3 str.). Its NMR showed signals at δ 7.42 (s, 1H, Ar-H_d), 7.25-7.21 (m, 2H, Ar-H_i), 7.15 (b, 2H, NH_{2e}), 7.01-6.99 (d, 2H, Ar-H_h), 6.82-6.78 (m, 1H, Ar-H_j), 6.74 (s, 1H, Ar-H_c), 3.83 (s, 6H, OCH_{3a} and OCH_{3b}), 3.17-3.15 (m, 8H, 4 × CH_{2f} and CH_{2g}) in its NMR spectrum.



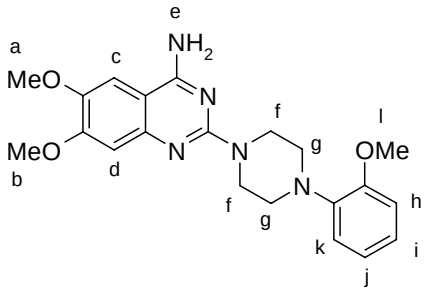
(**IV-3**)



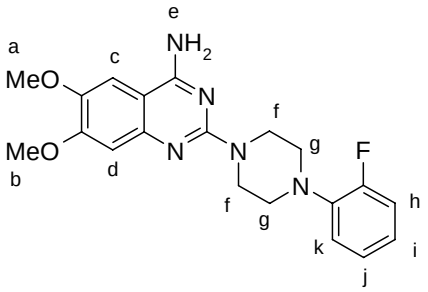
(**IV-4**)

2-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-y]benzonitrile (**IV-4**) showed characteristic peaks at 3491 and 3321 (N-H str.), 2218 (C≡N str.), 1284 (C-N str.), 1217 (Ar-O str.) and 1034 cm^{-1} (O-CH_3 str.) in its IR spectrum. Peaks were observed at δ 7.75-7.73 (dd, 1H, Ar-H_h), 7.73-7.60 (m, 1H, Ar-H_j), 7.43 (s, 1H, Ar-H_d), 7.23-7.06 (m, 4H, Ar-H_k, Ar-H_i and NH_{2e}), 6.75 (s, 1H, Ar-H_c), 3.90-3.88 (m, 4H, 2 × CH_{2g}), 3.84 (s, 3H, $OCH_{3a/3b}$), 3.79 (s, 3H, O$CH_{3a/3b}$) and 3.19-3.17 (m, 4H, 2 × CH_{2f}) in its NMR spectrum. Molecular ion peak was observed at m/z 390.21 in its mass spectrum.

IR spectrum of 6,7-dimethoxy-2-[4-(2-methoxyphenyl)piperazin-1-yl]quinazolin-4-amine (**IV-5**) displayed characteristic peaks at 3412 and 3211 (N-H str.), 1291 (C-N str.), 1247 (Ar-O str.) and 1028 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.42 (s, 1H, Ar-H_d), 7.13 (b, 2H, NH_{2e}), 6.97-6.85 (m, 4H, Ar H_h-H_k), 6.73 (s, 1H, Ar-H_c), 3.85-3.83 (b, 7H, 2 × CH_{2g} and OCH_{3l}), 3.80 (s, 3H, O$CH_{3a/b}$), 3.78 (s, 3H, O$CH_{3a/b}$) and 2.98-2.96 (t, 4H, 2 × CH_{2f}).



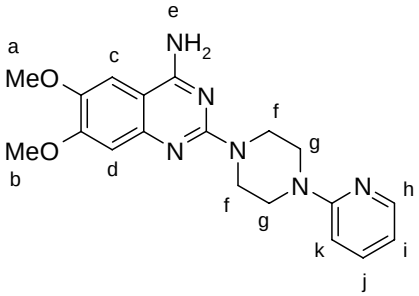
(**IV-5**)



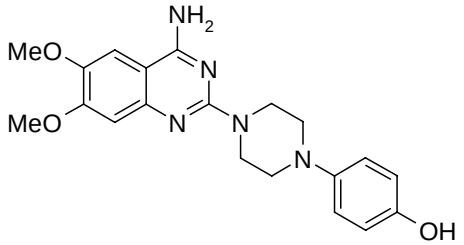
(**IV-6**)

2-[4-(2-Fluorophenyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine (**IV-6**) displayed characteristic peaks at 3484 and 3371 (N-H str.), 1281 (C-N str.), 1235 (Ar-O str.) and 1033 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals appeared at δ 7.42 (s, 1H, Ar-H_d), 7.18-6.98 (m, 6H, Ar H_h-H_k and NH_{2e}), 6.74 (s, 1H, Ar-H_c), 3.88-3.86 (t, 4H, 2 × CH_{2g}), 3.83 (s, 3H, OC$H_{3a/b}$), 3.78 (s, 3H, OC$H_{3a/b}$) and 3.04-3.02 (t, 4H, 2 × CH_{2f}) in its NMR spectrum.

6,7-Dimethoxy-2-(4-(pyridin-2-yl)piperazin-1-yl)quinazolin-4-amine (**IV-7**) showed characterristic peaks at 3433 and 3189 (N-H str.), 1277 (C-N str.), 1235 (Ar-O str.) and 1033 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 8.13-8.12 (dd, 1H, Ar-H_h), 7.57-7.53 (m, 1H, Ar-H_i), 7.42 (s, 1H, Ar-H_d), 7.18 (b, 2H, NH_{2e}), 6.89-6.87 (d, 1H, Ar-H_k), 6.76 (s, 1H, Ar-H_c), 6.67-6.64 (m, 1H, Ar-H_j), 3.83-3.78 (m, 10H, 2 × CH_{2g} and 2 × OCH_3) and 3.55-3.52 (t, 4H, 2 × CH_{2f}).



(**IV-7**)

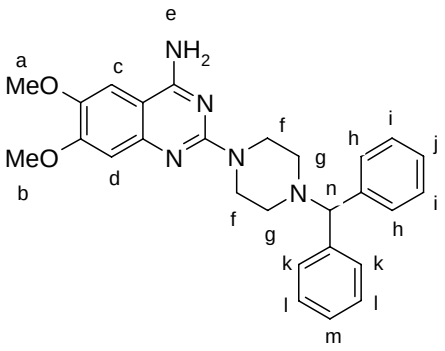


(**IV-8**)

IR spectrum of 4-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]phenol (**IV-8**) displayed characterristic peaks at and 3357 (N-H str.), 3145 (broad O-H str.), 1279 (C-N str.) and 1230 cm^{-1} (Ar-O str.).

2-(4-Benzhydrylpiperazin-1-yl)-6,7-dimethoxyquinazolin-4-amine (**IV-9**) showed characterristic peaks at 3438 and 3330 (N-H str.), 1277 (C-N str.), 1239 (Ar-

O str.) and 1030 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.46-7.09 (m, 13H, 11 Ar-H_d, H_{h-m} and NH_{2e}), 6.68 (s, 1H, Ar-H_c), 4.30 (s, 1H, CH_n), 3.80 (s, 3H, OC$H_{3a/b}$), 3.76 (s, 3H, OC$H_{3a/b}$), 3.70 (s, 4H, 2 × CH_{2f}) and 2.36-2.33 (b, 4H, 2 × CH_{2g}).

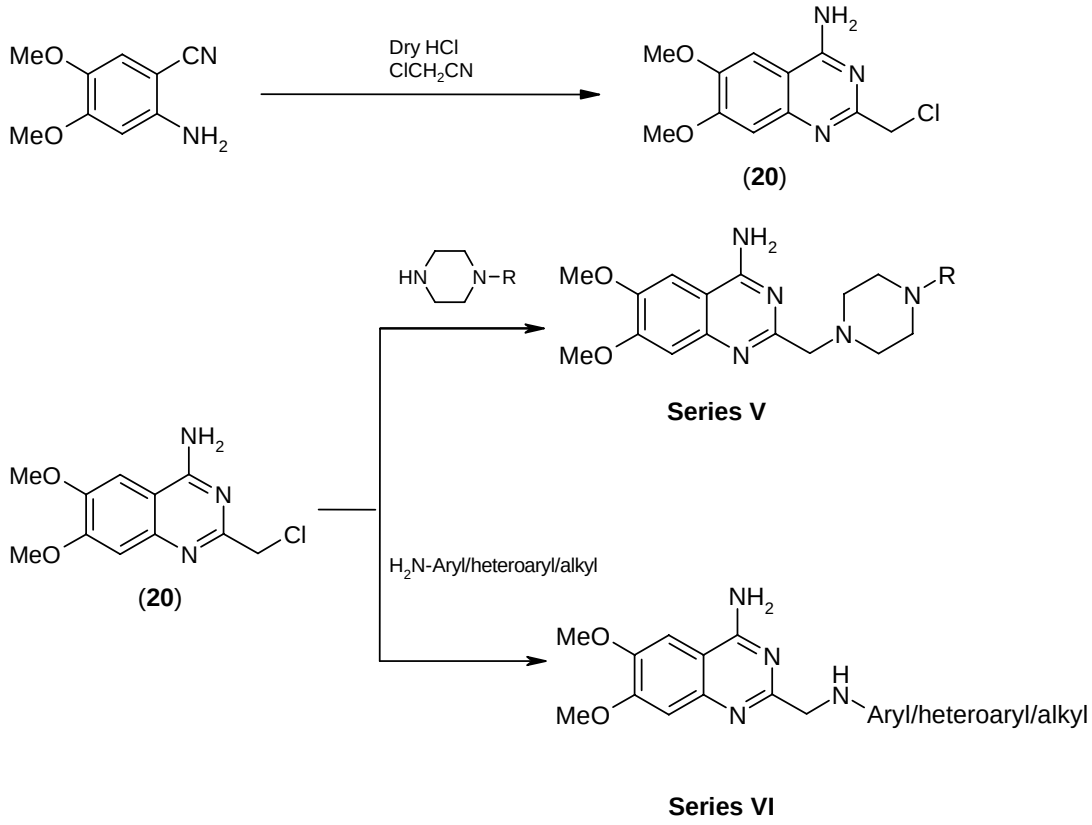


(**IV-9**)

4.1.5 Synthesis of 2-(chloromethyl)-6,7-dimethoxyquinazolin-4-amine (20)

2-(Chloromethyl)-6,7-dimethoxyquinazolin-4-amine (**20**) was required to prepare the desired 4-aminoquinazoline derivatives. It was prepared by reacting compound (**8**) with chloroacetonitrile in presence of dry hydrogen chloride in dioxane. Reaction was controlled and monitored regularly to prevent the formation of unwanted 2-(chloromethyl)-4-chloro-6,7-dimethoxyquinazolin. IR spectrum of compound (**20**) showed absence of peak of nitrile group around 2210 cm^{-1}. Peaks were observed at m/z 252.98 (M^+) and 254.99 (M+2) in its mass spectrum (**Scheme 6)**.

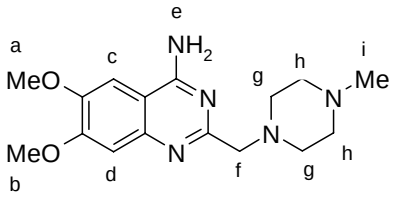
Synthesis of compounds belonging to Series V and Series VI were accomplished by following **Scheme 6**. Compound (**20**) and substituted amines were stirred at 60°C until the reaction was complete.



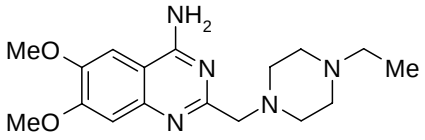
Scheme-6

- **Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (Series V)**

6,7-Dimethoxy-2-[(4-methylpiperazin-1-yl)methyl]quinazolin-4-amine (**V-1**) displayed characteristic peaks at 3131 (N-H str.), 1261 (C-N str.) and 1225 (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals δ 7.53 (s, 1H, Ar-H_d), 7.41 (b, 2H, NH_{2e}), 7.07 (s, 1H, Ar-H_c), 3.87 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3s/3b}$), 3.40 (s, 2H, CH_{2f}), 2.50 (b, 4H, 2 × CH_{2g}), 2.28 (b, 4H, 2 × CH_{2h}) and 2.12 (s, 3H, CH_{2i}).



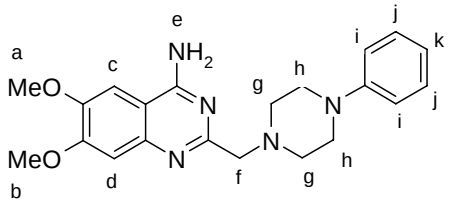
(**V-1**)



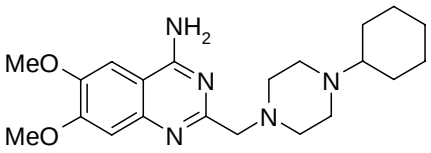
(**V-2**)

2-[(4-Ethylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-2**) showed characteristic peaks at 3306 and 3146 (N-H str.), 1279 (C-N str.), 1248 (Ar-O str.) and 1016 cm^{-1} (O-CH_3 str.) in its IR spectrum.

6,7-Dimethoxy-2-[(4-phenylpiperazin-1-yl)methyl]quinazolin-4-amine (**V-3**) displayed characteristic peaks at 3313 and 3151 (N-H str.), 1281 (C-N str.), 1222 (Ar-O str.) and 1015 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals appeared at δ 7.55 (s, 1H, Ar-H_d), 7.44 (b, 2H, NH_{2e}), 7.21-7.17 (t, 2H, Ar-H_j), 7.09 (s, 1H, Ar-H_c), 6.92-6.90 (d, 2H, Ar-H_i), 6.77-6.73 (t, 1H, Ar-H_k), 3.89 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3a/3b}$), 3.49 (s, 2H, CH_{2f}), 3.10-3.09 (t, 4H, CH_{2h}) and 2.64- 2.62 (t, 4H, CH_{2g}) in its NMR spectrum.



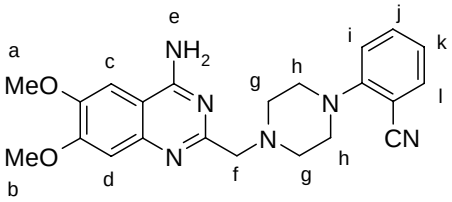
(**V-3**)



(**V-4**)

2-[(4-Cyclohexylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-4**) displayed characteristic peaks at 3387 and 3171 (N-H str.), 1223 (Ar-O str.) and 1017 cm^{-1} (O-CH_3 str.) in its IR spectrum.

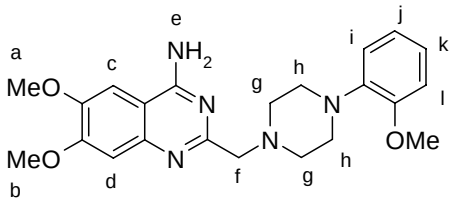
IR spectrum of 2-[4-((4-amino-6,7-dimethoxyquinazolin-2-yl)methyl) piperazin-1-yl]benzonitrile (**V-5**) displayed characteristic peaks at 3382 and 3132 (N-H str.), 2223 (C≡N str), 1265 (C-N str.) and 1221 cm^{-1} (Ar-O str.) in its IR spectrum. Peaks were observed at δ 7.57-7.50 (m, 3H, Ar- H_d , H_j and H_l), 7.19 (b, 2H, NH_{2e}), 7.13 (s, 1H, Ar-H_c), 7.07-7.00 (m, 2H, Ar-H_i and H_k), 3.93 (s, 6H, OCH_{3a} and OCH_{3b}), 3.63 (s, 2H, CH_{2f}), 3.24 (b, 4H, CH_{2h}) and 2.77 (b, 4H, CH_{2g}) in its NMR spectrum.



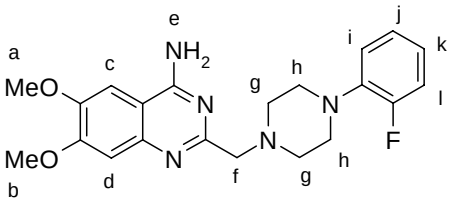
(**V-5**)

6,7-Dimethoxy-2-[(4-(2-methoxyphenyl)piperazin-1-yl)methyl]quinazolin-4-amine **(V-6)** displayed characteristic peaks at 3299 and 3145 (N-H str.), 1275 (C-N str.), 1241 (Ar-O str.) and 1017 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum displayed signals at δ 7.58 (s, 1H, Ar-H_d), 7.17 (s, 1H, Ar-H_c), 6.95-6.84 (m,

4H, Ar- $H_{i\text{-}l}$), 3.96 (s, 6H, OC$H_{3a,\ 3b}$), 3.83 (s, 3H, OCH_3), 3.67 (s, 2H, CH_{2m}), 3.10 (b, 4H, CH_{2h}) and 2.79 (b, 4H, CH_{2g}). Molecular ion peak was observed at m/z 404.8 in its mass spectrum.



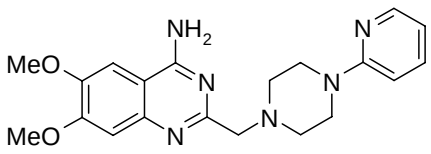
(**V-6**)



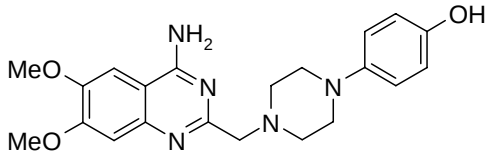
(**V-7**)

2-[(4-(2-Fluorophenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-7**) showed characteristic peaks at 3324 and 3161 (N-H str.), 1279 (C-N str.), 1233 (Ar-O str.) and 1014 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals appeared at δ 7.59 (s, 3H, Ar-H_d and NH_{2e}), 7.27 (s, 1H, Ar-H_c), 7.07-6.89 (m, 4H, Ar-$H_{i\text{-}l}$), 4.00 (s, 6H, OCH_{3a} and OCH_{3b}), 3.74 (s, 2H, CH_{2f}), 3.17 (b, 4H, CH_{2h}) and 2.81 (b, 4H, CH_{2g}) in its NMR spectrum.

IR spectrum of 6,7-dimethoxy-2-[(4-(pyridin-2-yl)piperazin-1-yl)methyl] quinazolin-4-amine (**V-8**) displayed characteristic IR peaks at 1272 (C-N str.) and 1240 cm^{-1} (Ar-O str.).



(**V-8**)

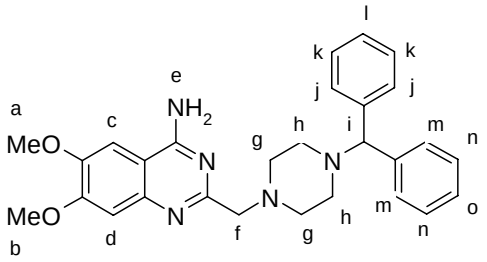


(**V-9**)

4-[4-((4-Amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl]phenol (**V-9**) displayed characteristic peaks at 3419 (N-H str.), broad 3190 (O-H str.), 1255 (C-N str.) and 1226 cm^{-1} (Ar-O str.) in its IR spectrum.

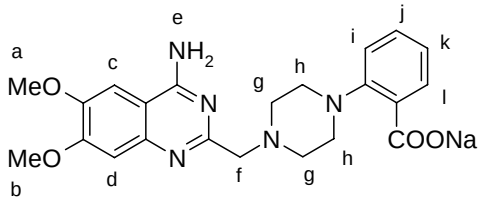
2-[(4-Benzhydrylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-10**) displayed characteristic peaks at 3490 and 3297 (N-H str.), 1279 (C-N str.), 1252 (Ar-O str.) and 1078 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum exhibited signals at δ 7.55 (s, 1H, Ar-H_d), 7.41-7.22 (m, 9H, Ar-H), 7.16-7.11 (m, 4H,

Ar-*H* and NH_{2e}), 4.22 (s, 1H, CH_i), 3.93 (s, 6H, OCH_{3a} and OCH_{3b}), 3.59 (s, 2H, CH_{2f}), 2.64 (b, 4H, CH_{2h}) and 2.42 (b, 4H, CH_{2g}).



(**V-10**)

Sodium 2-[4-((4-amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl] benzoate (**V-11**) displayed molecular ion peak at 423.9 (M/Z) in mass spectrum. Its NMR spectrum showed signals at δ 7.44 (s, 1H, Ar-H_d), 7.24-7.21 (m, 2H, Ar-*H*), 7.13 (s, 1H, Ar-H_c), 7.05-6.90 (m, 4H, Ar-*H* and NH_{2e}), 3.95 (s, 3H, OC$H_{3a/b}$), 3.91 (s, 3H, OC$H_{3a/b}$), 3.55 (s, 2H, CH_{2f}), 3.02 (b, 4H, CH_{2h}) and 2.61 (b, 4H, CH_{2g}).



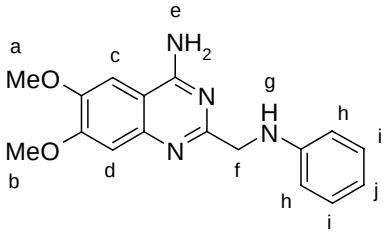
(**V-11**)

- **Synthesis of 2-[(aryl(alkyl)amino/heteroaryl)methyl]-6,7-dimethoxyquinazolin-4-amines (Series VI)**

Syntheses of 2-[(aryl(alky)amino/heteroaryl)methyl]-6,7-dimethoxy quinazoline-4-amines were accomplished by following the above described general **Scheme 6** in which 2-(chloromethyl)-6,7-dimethoxyquinazolin-4-amine (**20**) was reacted with different amines in presence of flame dried potassium carbonate in dry DMF at 60°C to obtain corresponding 2-[(aryl(alky)amino/heteroaryl)methyl]-6,7-dimethoxyquinazolin-4-amines.

N-[(4-Amino-6,7-dimethoxyquinzaolin-2-yl)methyl]aniline (**VI-1**) displayed characteristic peaks at 3384 and 3126 (N-H str.), 1254 (C-N str.) and 1216 (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.57 (s, 1H, Ar-H_d), 7.37 (b,

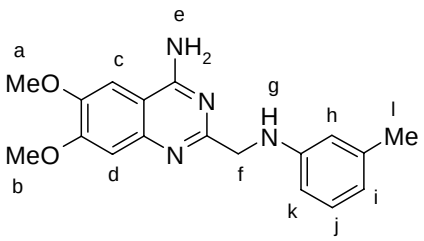
2H, NH_{2e}), 7.10-7.07 (m, 3H, Ar-H_h and H_c), 6.67- 6.65 (m, 2H, Ar-H_i), 6.58-6.54 (m,



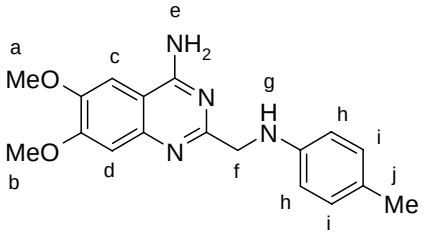
(**VI-1**)

1H, Ar-H_j), 5.69 (b, 1H, NH_g), 4.21-4.20 (d, 2H, CH_{2f}) and 3.93 (s, 3H, OC$H_{3a/b}$) and 3.91 (s, 3H, OC$H_{3a/b}$). M+H peak was observed at m/z 310.5 in its mass spectrum.

2-[(3-Toluidino)-*N*-methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-2**) displayed characteristic peaks at 3396 and 3119 (N-H str.), 1270 (C-N str.) and 1242 (Ar-O str.) in its IR spectrum. Peaks were observed at δ 7.52 (s, 1H, Ar-H_d), 7.28 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 6.93-6.89 (m, 1H, Ar-H_j), 6.43-6.39 (m, 2H, Ar-H_h and H_k), 6.34-6.32 (m, 1H, Ar-H_i), 5.52 (b, 1H, NH_g), 4.13-4.12 (d, 2H, CH_{2f}), 3.87 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3a/b}$) and 2.16 (s, 3H, CH_{3l}) in its NMR spectrum.



(**VI-2**)



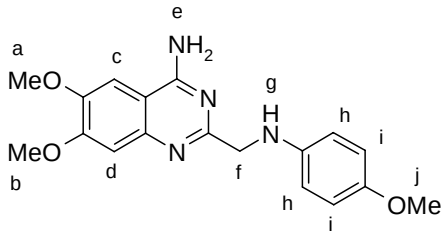
(**VI-3**)

2-[(4-Toluidino)-*N*-methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-3**) displayed characteristic peaks at 3414 and 3126 (N-H str.), 1254 (C-N str.), 1222 (Ar-O str.) and 1014 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.58 (s, 1H, Ar-H_d), 7.47 (b, 2H, NH_{2e}), 7.11 (s, 1H, Ar-H_c), 6.91-6.88 (d, 2H, Ar-H_i), 6.59-6.57 (d, 2H, Ar-H_h), 5.57 (b, 1H, NH_g), 4.18 (s, 2H, CH_{2f}), 3.93 (s, 3H, OC$H_{3a/b}$), 3.90 (s, 3H, OC$H_{3a/b}$) and 2.17 (s, 3H, CH_{3j}). M+H peak was obsereved at m/z 324.9 in its mass spectrum.

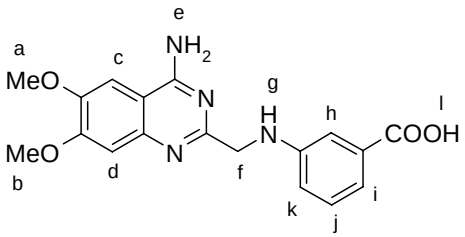
6,7-Dimethoxy-2-[(4-methoxyphenylamino)methyl]quinazolin-4-amine (**VI-4**) displayed characteristic peaks at 3444 and 3124 (N-H str), 1250 (Ar-O str) and 1030

cm^{-1} (O-CH_3 str) in its IR spectrum. Signals were observed at δ 7.97-7.97 (b, 2H, NH_{2e}), 7.69-7.67 (d, 2H, Ar-H_i), 7.53 (s, 1H, Ar-H_d), 7.05 (s, 1H, Ar-H_c), 6.63-6.60 (d, 2H, Ar-H_h), 6.50 (b, 1H, NH_g), 4.25-4.24 (d, 2H, CH_{2f}), 3.89 (s, 3H, OC$H_{3a/b}$), 3.86 (s, 3H, OC$H_{3a/b}$) and 3.71 (s, 3H, OCH_{3j}) in its NMR spectrum.

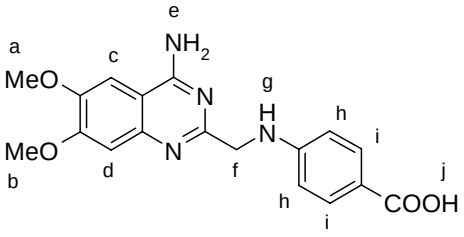
IR spectrum of 3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino] benzoic acid (**VI-5**) displayed characteristic peaks at 3444 and 3322 (N-H str.), 3122 (broad O-H str.), 1705 (C=O str.), 1279 (C-N str.) and 1235 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.56 (s, 1H, Ar-H_d), 7.35-7.27 (m, 4H, Ar-H_h, Ar-H_i and NH_{2e}), 7.15-7.11 (m, 1H, Ar-H_j), 7.01 (s, 1H, Ar-H_c), 6.85-6.83 (m, 1H, Ar-H_k), 5.23 (s, 2H, CH_{2f}), 4.92 (b, 1H, NH_g) and 3.93 (s, 6H, 2 × OCH_{3a} and OCH_{3b}).



(**VI-4**)



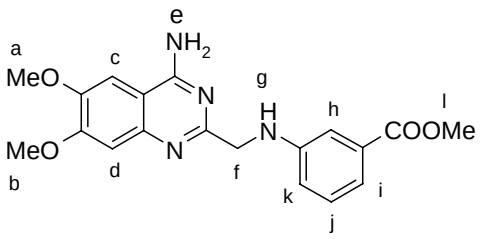
(**VI-5**)



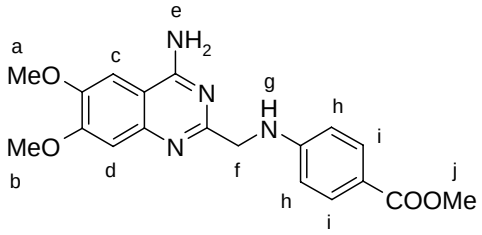
(**VI-6**)

Characteristic peaks were observed for 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoic acid (**VI-6**) displayed peaks at 3425 and 3369 (N-H str.), 3120 (broad O-H str.), 1673 (C=O str.), 1279 (C-N str.), 1218 (Ar-O str.) and 1018 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.75-7.73 (d, 2H, Ar-H_i), 7.57 (s, 1H, Ar-H_d), 7.39 (b, 2H, NH_{2e}), 7.04 (s, 1H, Ar-H_c), 6.61-6.58 (d, 2H, Ar-H_h), 5.69 (b, 2H, NH_g and OH_j), 5.16 (s, 2H, CH_{2f}) and 3.93 (s, 6H, 2 × OCH_{3a} and OCH_{3b}). M+H peak was observed at m/z 354.9 in its mass spectrum.

Methyl 3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoate (**VI-7**) displayed characteristic peaks at 3343 and 3202 (N-H str.), 1715 (C=O str.), 1293 (C-N str.), 1228 (Ar-O str.) and 1031 cm^{-1} (O-CH_3 str) in its IR spectrum. Peaks were observed at δ 7.52 (s, 1H, Ar-H_d), 7.35 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 6.99-6.95 (m, 1H, Ar-H_j), 6.60 (s, 1H, Ar-H_h), 6.54-6.52 (m, 1H, Ar- H_i), 6.46-6.44 (m, 1H, Ar-H_k), 6.08 (b, 1H, NH_g) 4.14 (b, 2H, CH_{2f}) and 3.86 (s, 3H, OC$H_{3a/b}$) 3.84 (s, 3H, OC$H_{3a/b}$) in its NMR spectrum.



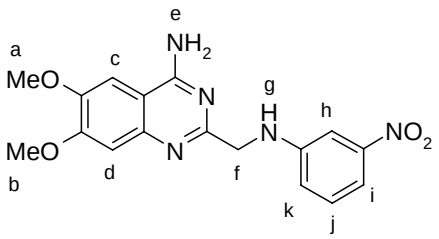
(**VI-7**)



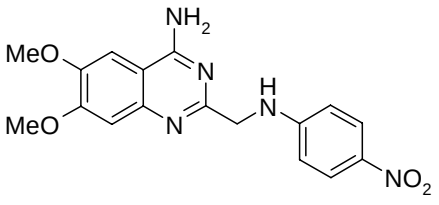
(**VI-8**)

Methyl 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoate (**VI-8**) displayed characteristic peaks at 3419 and 3133 (N-H str.), 1684 (C=O str.), 1276 (C-N str.) and 1227 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.51 (s, 1H, Ar-H_d), 7.28-7.18 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 6.68-6.65(d, 2H, Ar-H_i), 6.60-6.56 (d, 2H, Ar-H_h), 5.20 (b, 1H, NH_g), 4.11 (s, 2H, CH_{2f}), 3.90 (s, 3H, OC$H_{3a/b}$), 3.86 (s, 3H, OC$H_{3a/b}$) and 3.61 (s, 3H, COOCH_{3j}).

Characterisitics peaks were observed for 2-[(3-nitrophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-9**) at 3374 and 3125 (N-H str.), 1518 (N=O asym.), 1347 (N=O sym.) and 1244 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.54 (s, 1H, Ar-H_d), 7.45 (s, 1H, Ar-H_h), 7.33- 7.31(m, 3H, Ar-*H* and NH_2), 7.26-7.22 (m, 1H, Ar-H_j), 7.05 (s, 1H, Ar-H_c), 7.04-7.01 (m, 1H, Ar-*H*), 6.57-



(**VI-9**)

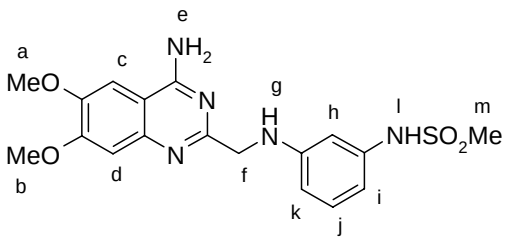


(**VI-10**)

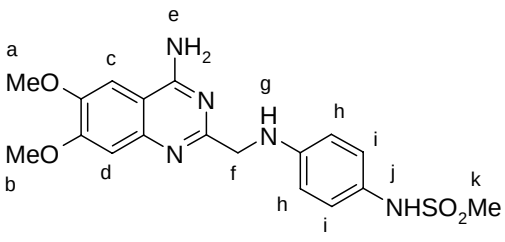
6.55 (t, 1H, N*H*), 4.26-4.25 (d, 2H, CH_{2f}), 3.90 (s, 3H, OC$H_{3a/b}$) and 3.84 (s, 3H, OC$H_{3a/b}$).

IR spectrum. of 2-[(4-nitrophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-10**) showed characteristic peaks at 3367 and 3128 (N-H str.), 1527 (N=O asym.), 1345 (N=O sym.) and 1247 (Ar-O str.) cm^{-1} in its IR spectrum.

N-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]methane sulfonamide (**VI-11**) displayed characteristic peaks at 3450 and 3361 (N-H str.), 1319 (S=O asym.), 1147 (S=O sym.) 1249 (Ar-O str.) and 1031 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals were seen at δ 7.57 (s, 1H, Ar-H_d), 7.39 (b, 2H, NH_{2e}), 7.01 (s, 1H, Ar-H_c), 6.93-6.89 (m, 1H, Ar-H_j), 6.75-6.74 (t, 1H, Ar-H_h), 6.58-6.56 (dd, 1H, Ar-H_k), 6.46-6.44 (dd, 1H, Ar-H_i), 4.95-4.93 (d, 2H, NH_g and NH_i), 4.76 (s, 2H, CH_{2f}), 3.92 (s, 6H, OCH_{3a} and OCH_{3b}) and 3.30 (s, 3H, CH_{3m}) in its NMR spectrum. Molecular ion peak was observed at m/z 403.8 in its mass spectrum



(**VI-11**)

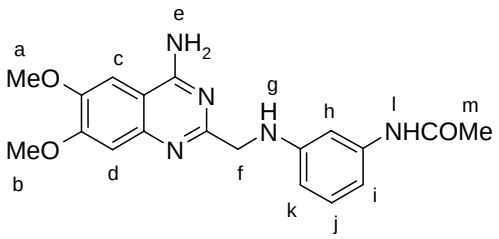


(**VI-12**)

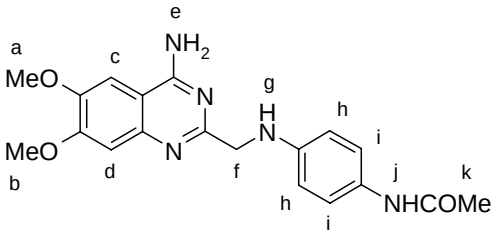
. IR spectrum of *N*-[4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino] phenyl]methane sulfonamide **(VI-12)** displayed characteristic peaks at 3417and 3144 (N-H str.), 1320 (S=O asym.) and 1153 cm^{-1} (S=O sym.). Its NMR spectrum gave signals at δ 7.57 (s, 1H, Ar-H_d),7.40 (b, 2H, NH_{2e}), 7.05 (s, 1H, Ar-H_c), 7.03-7.01 (d, 2H, Ar-H_i), 6.47-6.45 (d,2H, Ar-H_h), 4.90 (b, 2H, NH_g and NH_i), 4.69 (s, 2H, CH_{2f}), 3.92 (s, 3H, OC$H_{3a/3b}$), 3.91 (s, 3H, OC$H_{3a/3b}$) and 3.28 (s, 3H, CH_{3k}). Molecular ion peak was observed at m/z 403.4 in its mass spectrum.

N-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]acetamide (**VI-13**) displayed characteristic peaks at 3450, 3396 and 3124 (N-H str.), 1663 (C=O str.), 1248 (Ar-O str.) and 1032 cm^{-1} (O-CH_3 str.) in its IR spectrum. Peaks were obtained at δ 7.54 (s, 1H, Ar-H_d), 7.34 (b, 2H, NH_{2e}), 7.07 (s, 2H, Ar-H_c and H_h), 6.97-6.93 (t, 1H, Ar-H_j), 6.70-6.68 (m, 1H, Ar-H_i), 6.33-6.31 (m, 1H, Ar-H_k), 5.62 (b, 1H, NH_g), 4.16 (s, 2H, CH_{2f}), 3.93 (s, 3H, OC$H_{3a/b}$), 3.90 (s, 3H, OC$H_{3a/b}$) and 2.00 (s, 3H, CH_{3m}) in its NMR spectrum.

N-[4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]acetamide (**VI-14**) displayed characteristic peaks at 3362 and 3131 (N-H str.), 1656 (C=O str.), 1239 (Ar-O str.) and 1028 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 9.39 (b, 1H, NH_j), 7.54 (s, 1H, Ar-H_d), 7.32-7.20 (m, 4H, Ar-H_i and NH_{2e}), 7.06 (s, 1H, Ar-H_c), 6.58-6.56 (d, 2H, Ar-H_h), 5.49 (b, 1H, NH_g), 4.15 (s, 2H, CH_{2f}), 3.90 (s, 3H, OC$H_{3a/b}$), 3.88 (s, 3H, OC$H_{3a/b}$) and 1.96 (s, 3H, CH_{3k}).

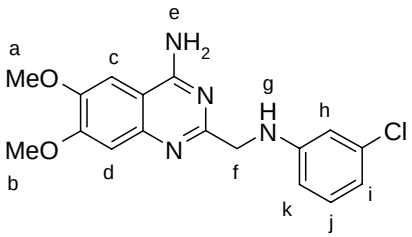


(**VI-13**)

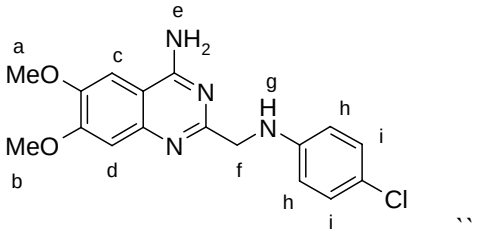


(**VI-14**)

2-[(3-Chlorophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-15**) displayed characteristic peaks at 3502, 3388 and 3125 (N-H str.) and 1258 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 10.61 (b, 1H, NH_g), 8.39 (s, 1H, Ar-H_d), 8.09-8.07 (m, 1H, Ar-H_i), 7.69-7.67 (m, 2H, Ar-H_k), 7.64 (s, 2H, NH_{2e}), 7.44-7.40 (t, 1H, Ar-H_j), 7.27 (s, 1H, Ar-H_c), 3.92 (s, 3H, OC$H_{3a/b}$), 3.91(s, 3H, OC$H_{3a/b}$) and 3.84 (s, 2H, CH_{2f}).



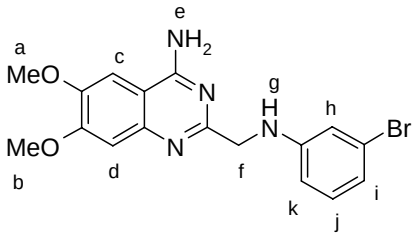
(**VI-15**)



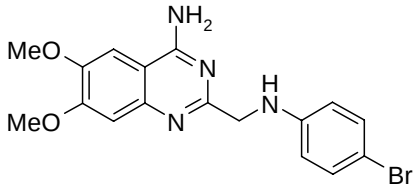
(**VI-16**)

2-[(4-Chlorophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-16**) showed characteristic peaks at 3482, 3389 and 3316 (N-H str.), 1256 (Ar-O str.) and 1013 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.51 (s, 1H, Ar-H_d), 7.29 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 7.02-6.99 (d, 2H, Ar-H_i), 6.60-6.58 (d, 2H, Ar-H_h), 5.84 (b, 1H, NH_g), 4.14-4.13 (d, 2H, CH_{2f}), 3.87 (s, 3H, OC$H_{3a/b}$) and 3.85 (s, 3H, OC$H_{3a/b}$).

3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]bromobenzene (**VI-17**) displayed characteristic peaks at 3421 and 3122 (N-H str.) and 1229 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR showed sigmals at 7.57 (s, 1H, Ar-H_d), 7.47 (s, 2H, NH_{2e}), 7.07 (s, 1H, Ar-H_c), 7.69-7.67 (t, 1H, Ar-H_j), 6.80-6.79 (t, 1H, Ar-H_i), 6.65-6.61 (m, 2H, Ar-H_h and H_k), 3.88 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3a/b}$) and 3.17 (s, 2H, CH_{2f}).



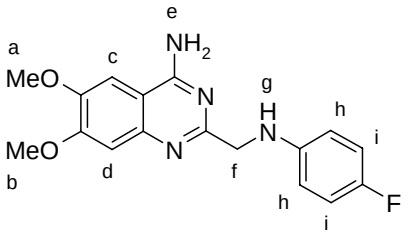
(**VI-17**)



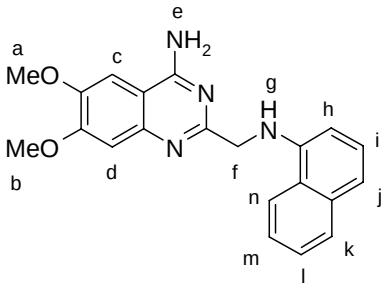
(**V1-18**)

IR spectrum of 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino] bromobenzene (**VI-18**) displayed characteristic peaks at 3380 and 3127 (N-H str.), and 1239 cm^{-1} (Ar-O str.).

4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]fluorobenzene (**VI-19**) displayed characteristic peaks at 3383 and 3123 (N-H str.) and 1247 cm^{-1} (Ar-O str.) in its IR spectrum. Signals appeared at δ 7.53 (s, 1H, Ar-H_d), 7.27 (b, 2H, NH_{2e}), 7.05 (s, 1H, Ar-H_c), 6.84-6.79 (m, 2H, Ar-H_i), 6.63-6.58 (m, 2H, Ar-H_h), 5.54 (b, 1H, NH_g), 4.14 (s, 2H, CH_{2f}) and 3.90 (s, 3H, OC$H_{3a/b}$), 3.88 (s, 3H, OC$H_{3a/b}$) in its NMR spectrum.



(**VI-19**)

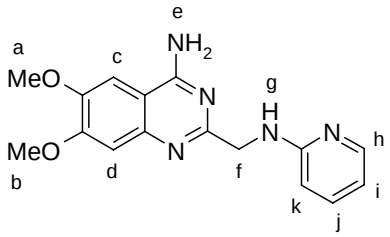


(**VI-20**)

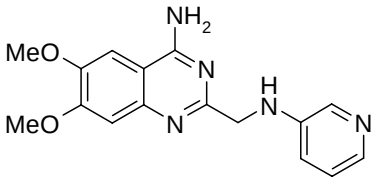
1-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]naphthalene (**VI-20**) displayed characteristic peaks at 3390 and 3129 (N-H str.) and 1245 cm^{-1} (Ar-O str.)

in its IR spectrum. Its NMR spectrum gave signals at δ 8.16-8.14 (d, 1H, Ar-H_n), 7.76-7.75 (d, 1H, Ar-H_k), 7.60 (s, 1H, Ar-H_d), 7.49-7.41 (m, 2H, Ar-H_m, H_h), 7.30-7.26 (t, 1H, Ar-H_i), 7.15-7.11 (m, 2H, Ar-H_c and H_j), 6.56-6.54 (d, 2H, NH_2), 4.40-4.39 (d, 2H, CH_{2f}), 3.98 (s, 3H, OC$H_{3a/b}$) and 3.93 (s, 3H, OC$H_{3a/b}$). Molecular ion peak was observed at m/z 360.6 in its mass spectrum.

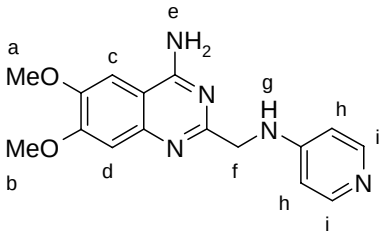
6,7-Dimethoxy-2-[(pyridin-2-ylamino)methyl]quinazolin-4-amine (**VI-21**) showed characteristic peaks at 3343 and 3134 (N-H str) and 1249 cm^{-1} (Ar-O str) in its IR spectrum. Its NMR spectrum showed signals at δ 7.97 (b, 1H), 7.74 (b, 2H), 7.59 (s, H, Ar-H_d), 6.99-6.96 (d, 1H, Ar-*H*), 6.85 (s, 1H, Ar-H_c), 6.72 (s, 1H), 5.31 (s, 2H, CH_{2f}) and 3.85 (s, 6H, OC$H_{3a, 3b}$).



(**VI-21**)



(**VI-22**)

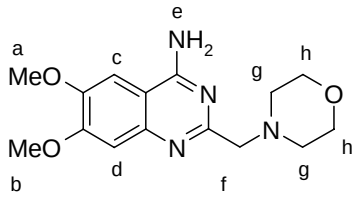


(**VI-23**)

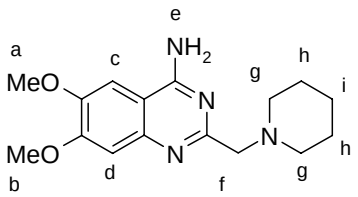
6,7-Dimethoxy-2-[(pyridin-3-ylamino)methyl]quinazolin-4-amine (**VI-22**) displayed characteristic peaks at 3339 and 3190 (N-H str) and 1250 cm^{-1} (Ar-O str) in its IR spectrum.

IR apectrum of 6,7-dimethoxy-2-[(pyridin-4-ylamino)methyl]quinazolin-4-amine (**VI-23**) displayed characteristic IR peaks at 3221, 3110 (N-H str) and 1256 cm^{-1} (Ar-O str). Its ^{1}H-NMR spectrum gave signals at δ 8.16-8.14 (m, 2H, Ar-H_i), 7.59 (s, 1H, Ar-H_d), 6.93 (m, 3H, Ar-H_c and H_h), 5.32 (s, 2H, CH_{2f}), 3.90 (s, 6H, OCH_{3a} and OCH_{3b}) and 3.33 (b, 3H, NH_{2e} and NH_g).

6,7-Dimethoxy-2-(4-morpholinomethyl)quinazolin-4-amine (**VI-24**) displayed characteristic peaks at 3310, 3132 (N-H str) and 1249 cm^{-1} (Ar-O str) in its IR spectrum. Peaks were observed at δ 7.86 (s, 1H, Ar-H_d), 7.14 (s, 1H, Ar-H_c), 7.05 (b, 2H, NH_{2e}), 3.95 (s, 6H, OCH_{3a} and OCH_{3b}), 3.71-3.69 (t, 4H, CH_{2h}), 3.57 (s, 2H, CH_{2f}) and 2.58-2.57 (b, 4H, 2 × CH_2) in ^{1}H-NMR spectrum.



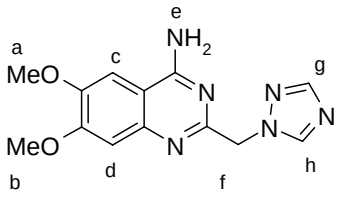
(**VI-24**)



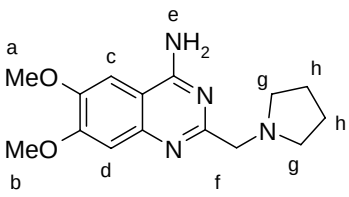
(**VI-25**)

6,7-Dimethoxy-2-[(piperidin-1-yl)methyl]quinazolin-4-amine (**VI-25**) displayed characteristic peaks at 3316 (N-H str) and 1245 cm^{-1} (Ar-O str) in its IR spectrum.

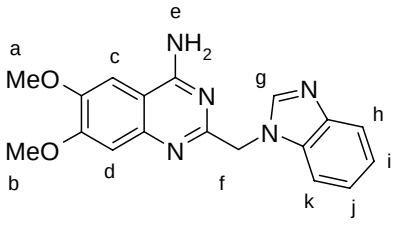
6,7-Dimethoxy-2-[(1*H*-1,2,4-triazol-1-yl)methyl]quinazolin-4-amine (**VI-26**) displayed characteristic peaks at 3401 and 3338 (N-H str) and 1233 cm^{-1} (Ar-O str) in its IR spectrum. Its NMR spectrum gave signals δ 8.52 (s, 1H, Ar-H_g), 7.89 (s, 1H, Ar-H_h), 7.62 (s, 1H, Ar-H_d), 7.10 (s, 1H, Ar-H_c), 5.45 (s, 2H, CH_{2f}) and 3.97 (s, 3H, OC$H_{3a/b}$) and 3.95 (s, 3H, OC$H_{3a/b}$).



(**VI-26**)



(**VI-27**)



(**VI-28**)

6,7-Dimethoxy-2-[(pyrrolidin-1-yl)methyl]quinazolin-4-amine (**VI-27**) displayed characteristic peaks 1245 cm^{-1} (Ar-O str) in its IR spectrum. Signals were

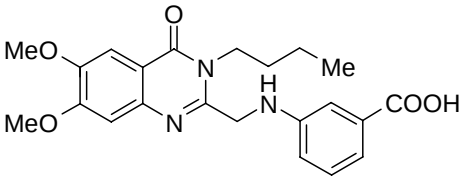
observed at 7.53 (s, 1H, Ar-H_d), 7.37 (b, 2H, NH_{2e}), 7.06 (s, 1H, Ar-H_c), 3.87 (s, 3H, OC$H_{3a/b}$), 3.84 (s, 3H, OC$H_{3a/b}$), 3.54 (s, 2H, CH_{2f}) 2.51-2.50 (m, 4H, 2 × CH_2) and 1.67-1.64 (m, 4H, CH_{2h}) in its NMR spectrum.

2-[(1*H*-Benzimidazol-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-28**) displayed characteristic peaks at 3295 and 3122 (N-H str), and 1256 cm^{-1} (Ar-O str) in its IR spectrum. Its NMR spectrum gave signals at δ 8.33 (s, 1H, Ar-H_g), 7.68-7.66 (m, 3H, Ar-*H*, and NH_{2e}), 7.59 (s, 1H Ar-H_d), 7.49-7.46 (m, 1H, Ar-*H*), 7.21-7.19 (m, 2H, Ar-*H*), 7.05 (s, 1H, Ar-H_c), 5.46 (s, 2H, CH_{2f}), 3.93 (s, 3H, OC$H_{3a/b}$) and 3.90 (s, 3H, OC$H_{3a/b}$).

4.2 Biological activity

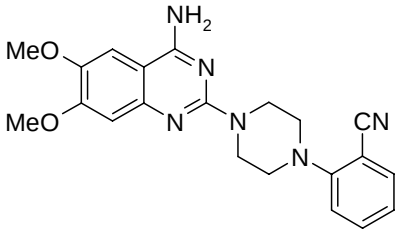
As determination of pA_2 values is a time consuming job, preliminary screening of the synthesized compounds was performed by observing the effects of the compounds on the modulation of responses of nonadrenaline and ang II on the rat blood pressure. Compounds showing significant changes in the responses of the two agonists were chosen for *in vitro* studies. Compounds of **Series I** and **III** did not show noticeable changes, hence were not selected for determination of pA_2 values.

Table 7 shows the pA_2 values for the compounds for both of the receptor types. Compound (**II-1**) showed the highest potency on both the receptors in **Series-II**. Both of the tetrazoles (**II-7** & **II-8**) showed low potency in blocking both the receptor types (α_1 and AT_1). The *p*-amino group bearing compound (**II-4**) was almost inactive.



$\alpha_1 = 7.45$ $AT_1 = 6.14$

(**II-1**)



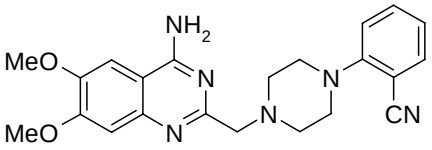
$\alpha_1 = 8.59$ $AT_1 = 9.04$

(**IV-4**)

Only one compound (**IV-4**) was used for determination of pA_2 values in the **Series-IV**. This compound (**IV-4**) showed very high antagonistic potency on both the

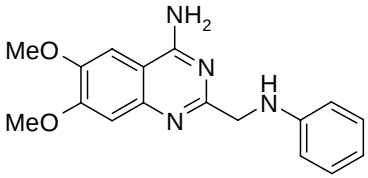
types of receptors. The activity is comparable to prazosin (**AP1**) and losartan (**AT1**).

Series V proved to be the most friutful one. Compound (**V-5**) in the series surpassed tha activity of the standerd drugs. None of the compounds could match compound (**V-5**) in potency against both of these receptors.



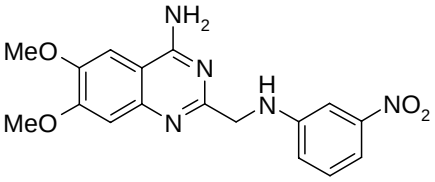
$\alpha_1 = 10.1$ $AT_1 = 8.83$

(**V-5**)



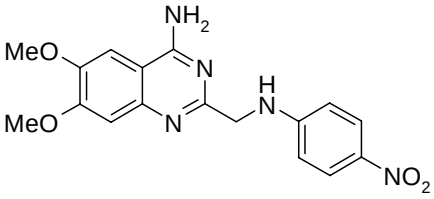
$\alpha_1 = 9.87$ $AT_1 = 8.37$

(**VI-1**)



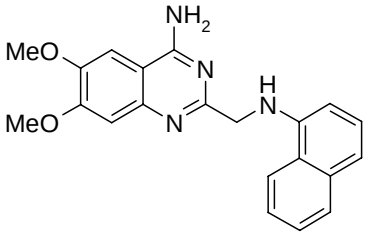
$\alpha_1 = 9.38$ $AT_1 = 7.64$

(**VI-9**)



$\alpha_1 = 8.09$ $AT_1 = 9.04$

(**VI-10**)



$\alpha_1 = 8.37$ $AT_1 = 7.07$

(**VI-20**)

Series VI offered four potent compounds, two of them have non-substituted aryl rings (**VI-1** and **VI-20**) while the remaining two have electron withdrawing nitro groups at *m*- and *p*-positions (**VI-9** and **VI-10**). Remaining compounds did not show promising activity.

As in evident from the structures of compounds, various groups like acidic, basic, neutral, bulky, non-bulky, aromatic, aliphatic and heteroaromatic have been attached to the quinazoline motif. Activity has been shown by compounds having aromatic rings in the side chain. Certain interesting observations were made as given below:

- 6,7-Dimethoxyquinazoline has proved to be a very good motif for development of dual acting α_1 and AT_1 receptor antagonists.
- 4-Amino group provides much more potent dual antagonists than compounds of 4-oxo group.
- Attachment of a basic nitrogen to the quinazoline ring through one carbon linker gives more potent compounds.
- Attachment of an aromatic ring to the basic nitrogen provides better dual acting compounds.
- Small-sized electron withdrawing groups like CN, NO_2 provide more potent derivatives.
- Presence of an acidic group in the side chain is not a must to exhibit AT_1 antagonistic activity unlike losartan.
- Unsubstituted aromatic rings (**VI-1**, **VI-20**) or neutral groups (**IV-4**, **V-5**, **VI-9**, **VI-10**) are ideal for dual α_1-and AT_1-antagonist activities.

This work has proved beyond doubt that dual α_1 and AT_1 antagonists are a reality and not a figment of imagination. Further optimization of the lead structures is in progress in the laboratory.

Table 7: The pA_2 values of synthesized compounds

Compound	pA_2 values		Compound	pA_2 values	
	α_1	AT_1		α_1	AT_1
II-1	**7.45**	**6.14**	**VI-2**	6.16	5.38
II-2	5.27	5.75	**VI-3**	5.28	3.45
II-4	5.48	5.28	**VI-5**	5.52	4.87
II-5	6.06	5.13	**VI-6**	4.49	6.43
II-6	5.69	5.62	**VI-9**	**9.38**	**7.64**
II-7	5.63	4.9	**VI-10**	**8.09**	**9.04**
II-8	4.53	5.19	**VI-11**	4.48	3.41
IV-4	**8.59**	**9.04**	**VI-12**	NA	4.38
V-1	6.79	5.1	**VI-15**	7.02	6.27
V-2	4.19	3.22	**VI-16**	4.89	4.65
V-3	6.49	6.78	**VI-20**	**8.37**	**7.07**
V-4	4.90	3.01	**VI-23**	5.86	4.68
V-5	**10.1**	**8.83**	**VI-24**	5.26	6.15
V-6	7.45	6.34	**VI-25**	3.01	3.70
V-7	6.76	6.09	**VI-27**	3.49	3.63
V-8	5.47	3.65	**VI-28**	4.05	4.15
V-10	5.32	6.36	**Prazosin**	8.91	8.26
V-11	3.64	6.28	**Losartan**	5.46	8.08
VI-1	**9.87**	**8.37**			

All the reagents and solvents required for synthesis were purified by general laboratory techniques before use. Compounds were purified by passing them through silica gel H (100-200 mesh) purifying column using mixture of chloroform and methanol or chloroform alone as eluent. Melting points were determined using a Veego make silicon oil bath-type melting point apparatus and are uncorrected. Purity of the compounds and completion of reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}; Merck), visualizing with ultraviolet light or iodine vapors. The yields reported here are un-optimized. The IR spectra were recorded using KBr disc method on a Bruker FT-IR, model alpha. The ^{1}H-NMR spectra (on a Bruker 300/400 MHz spectrometer) were recorded in DMSO-d_6 (chemical shifts in δ ppm) or otherwise stated. The assignment of exchangeable protons was confirmed by the D_2O exchange studies wherever required. Mass spectral data were obtained on a Thermo Scientific mass spectrometer (DSQ II). Microwave reactions were performed in CEM-Discovery, USA microwave reactor.

5.1 Chemical work

5.1.1 Synthesis of starting materials and intermediates

- **Synthesis of 6-nitroveratric acid (4)**

Veratraldehyde (**2**)

In a three-neck round bottom (Rb) flask (100 mL) equipped with two dropping funnels, vanillin (**1**) (1.0 g, 6.57 mmol) was fused at 100 °C. Addition of an aqueous solution of potassium hydroxide (0.55 g, 9.81 mmol in 0.8 ml water) was started at a rate of 1-2 drops per second while the external heating was continued. After about one-fourth of potassium hydroxide solution was added, addition of dimethyl sulfate (DMS) (1.03 g, 8.61 mmol) was started at the same rate as that of potassium hydroxide solution. The *p*H of the solution was always maintained basic by adjusting the rate of addition of the two reagents. The external heating was switched off after 5 min of the start of the addition and the solution was allowed to reflux by the heat of the reaction. Yellow colored oil separated out in the reaction mixture at the end of the addition. The solution was stirred for another 30 min after the addition of both of the reagents was completed. The reaction

mixture was kept at 10-12 °C for 18 h. The solid mass so obtained was triturated with cold water, filtered, washed with water and dried under vacuum to give white colored veratraldehyde (**2**) (0.9 g, 82 %) m.p. 44-46 °C (lit.[370]43-44.5 °C).

Anal.:

TLC : R_f 0.45 (Benzene)

IR : 1683, 1590, 1512, 1272, 1138 and 1019 cm^{-1}

6-Nitroveratraldehyde (**3**)

In an Rb flask (50 mL), concentrated nitric acid (5.0 mL) was cooled to 5 °C and veratraldehyde (**2**) (1.0 g, 6.02 mmol) was added to it portion-wise over a period of 10 min, keeping the temperature of the reaction mixture between 5-10 °C. The reaction mixture was stirred at RT for another 2 h and quenched into crushed ice (30 g). As the product is light sensitive, enough care was taken to prevent the product from light exposure from this point onwards. The solid so formed was filtered, washed with cold water and dried under vacuum to get compound (**3**) as yellow colored solid (0.88 g, 70 %) m.p. 128-29 °C (lit.[371]129-31 °C).

Anal.:

TLC : R_f 0.75 (Benzene)

IR : 1686, 1523, 1336, 1288, 1227 and 1060 cm^{-1}

6-Nitroveratric acid (4)

6-Nitroveratraldehyde (**3**) (5.0 g, 23.69 mmol) was dissolved in aldehyde-free acetone (25 mL) in an Rb flask (250 mL). An aqueous solution of potassium permanganate (15.0 g, 94.78 mmol in 25 ml water) was added drop-wise to the above solution through a pressure equalizing dropping funnel (PEDF) over a period of 20 min. The reaction mixture was stirred at RT for another 2 h, filtered through filtering aid (hiflosupercel) and washed with hot water. The filtrate was concentrated to remove acetone and acidified with dilute sulfuric acid (5 %). The precipitated material so obtained was filtered, washed with cold water and dried under vacuum to give compound (**4**) as yellow colored solid (3.76 g, 70 %) m.p. 193-95 °C (lit.[380] 192-95 °C).

Anal.:

TLC : R_f 0.1 (Chloroform: Methanol, 18:2)

IR : 3300, 2854, 1703, 1599, 1530, 1419, 1364, 1286, 1219 and 1054 cm^{-1}

- **Synthesis of 2-amino-4,5-dimethoxybenzonitrile (8)**

3,4-Dimethoxybenzaldoxime (5)

Method A: Veratraldehyde (5 g, 30.08 mmol) (**2**) was dissolved in warm methanol (10 mL) in an Rb flask (100 mL). An aqueous solution of hydroxylamine hydrochloride (2.51g, 36.10 moles in 5ml water) was added and mixed thoroughly. A solution of sodium hydroxide (1.8 g, 45.13 mmol in 5ml water) was added drop-wise through dropping funnel with constant stirring. The reaction mixture was allowed to stand for 2.5 h and quenched into crushed ice (25 g).The solution was saturated with CO_2. Aldoxime was separated as oil. The mixture was allowed to stand for 12-24 h in refrigerator. When the oil was solidified, crystalline aldoxime was filtered off through vaccume pumpand dried in air (5.2 g, 95 %) m.p. 88-90 °C.

Anal:

TLC : R_f 0.24 (Chloroform: Methanol, 19:1)

IR : 3458, 1584, 1511, 1460, 1337, 1267, 1141, 1020, 970, 905, 860 and 757 cm^{-1}

3,4-Dimethoxybenzonitrile (**6**)

Method B: 3,4-Dimethoxybenzaldoxime (**5**) (5 g, 27.62 mmol) was dissolved in diethyl ether (20 mL) in an Rb flask (100 mL). Thionyl chloride (5 mL) was added dropwise through dropping funnel with constant stirring. Hydrogen chloride gas produced during reaction was trapped through sodium hydroxide trap. The reaction mixture was allowed to stirr for 2 h and poured drop-wise into ice-cold water.The precipitates so obtained were filtered, washed with cold water and dried under vacuum to obtain the product (3.8 g, 85 %) m.p. 65-67 °C (lit.[374] 67 °C).

Anal:

TLC : R_f 0.8 (Chloroform: methanol, 19:1)

IR : 2221, 1598, 1514, 1269, 1243, 1137, 1017, 875, 810 and 762 cm^{-1}

4,5-Dimethoxy-2-nitrobenzonitrile (7)

In an Rb flask (50 mL), concentrated nitric acid (10 mL) was cooled to 10 °C and 3,4-dimethoxybenzonitrile (**6**) (5 g, 30.66 mmol) was added to it portion-wise. After complete addition, the mixture was allowed to stir for 1 h and then quenched into ice cold water. The solid product so formed was filtered, washed with saturated solution of sodium bicarbonate and followed by ice cold water to remove excess nitric acid.The solid was dried under vacuum to obtain the desired product (**7**) (5.98 g, 94.62 %) m. p. 164-66 °C (lit.[375]164-66 °C).

Anal:

TLC : R_f 0.41(Chloroform: methanol, 19:1)

IR : 2226, 1570, 1523, 1458, 1397, 1292, 1229, 1058, 978 and 886 cm^{-1}

MS : m/z 208.06 (M^+ peak)

2-Amino-4,5-dimethoxybenzonitrile (**8**)

4,5-Dimethoxy-2-nitrobenzonitrile (**7**) (5 g, 24 mmol) was taken in an Rb flask (250 mL). Concentrated hydrochloric acid (30 mL) and granulated tin (4.25 g, 36 mmol) were added into it. The reaction mixture was allowed to reflux for 2 h. The reaction mixture was poured in ice-cold water (50 mL) and basified with sodium hydroxide until the precipitated tin oxide residue got dissolved. Thereaction mixture was filtered and washed with water.The solid thus obtained was recrystallized from methanol to get 2-amino-4,5-dimethoxybenzonitrile(**8**) (2.2g, 51.28 %) m.p. 96-99°C (lit.[376] 96-101°C).

Anal:

TLC : R_f 0.24(Chloroform: methanol, 19:1)

IR : 3452, 3230, 2210, 1658, 1621, 1581, 1513, 1464, 1268, 1132, 1003 and 838 cm^{-1}

MS : m/z 178 (M^+ peak)

- **Synthesis of substituted amines**

Methyl 3-aminobenzoate

Method C: 3-Aminobenzoic acid (5 g) was dissolved in methanol (50 mL) saturated initially with dry hydrogen chloride gas. The solution was refluxed under anhydrous

conditions on water bath for 2 h and the reaction mixture was concentrated to half of its original volume. The solution was quenched into cold water (50 mL) to get a clear solution which was neutralized with solid sodium bicarbonate to get a precipitate which was filtered, washed with cold water and dried to obtain the desired compound as white colored solid (4.9 g, 89.0 %) m.p. 49-50 °C (lit.[381]50-54°C).

Anal:

TLC : R_f 0.58 (Chloroform: Methanol, 19:1)

IR : 3415, 3131, 1723, 1619, 1401, 1090 and 745 cm^{-1}

Methyl 4-aminobenzoate

Following **Method C**, butusing 4-aminobenzoic acid (5 g), the desired compound methyl 4-aminobenzoate was obtained as a solid (4.7 g, 84.7 %) m.p. 111-13 °C (lit.[382] 110-113 °C).

Anal:

TLC : R_f 0.58 (Chloroform: Methanol 19:1)

IR : 3416, 3120, 1714, 1608, 1400, 1113 and 857 cm^{-1}

3-Acetamidoaniline

3-Acetamidonitrobenzene

Method D: 3-Nitroaniline (5.0 g, 36.0 mmol) was dissolved in glacial acetic acid (15 mL) and acetic anhydride (6.85 mL, 72.4 mmol) was added to it. The reaction mixture was refluxed under anhydrous conditions on an oil bath for 1 h and quenched into crushed ice (30 g). The precipitate was filtered, washed with cold water and dried to afford3-acetamidonitrobenzene (5.8 g, 89.2 %), m.p. 151-53 °C. (lit.[383] 151-53 °C).

Anal:

TLC : R_f 0.35 (Chloroform: Methanol 19:1)

3-Acetamidoaniline

Method E: A solution of 3-acetamidonitrobenzene (5.0 g, 27.5 mmol) in methanol (50 mL) was refluxed on a water bath. Iron powder (12 g, 220 mmol) and a solution of ammonium chloride (11.7 g, 220 mmol) in water (15 mL) were added portion-wise (in 4

parts at an interval of 45 min) to the refluxing solution. Refluxing was continued for 7-8 h and the solution was filtered through filtering aid and washed with hot methanol (2 x 10 mL). The filtrate was concentrated under reduced pressure to remove excess of methanol and the resulting aqueous solution was diluted with water (25 mL), basified with sodium bicarbonate (10 % aq solution) and extracted with chloroform (3 x 50 mL). The combined chloroform layer was dried and concentrated to get brown colored residue which was dried under vacuum to afford 3-acetamidoaniline (3.0 g, 72 %) m.p. 84-86 °C (lit.[384] 86-88 °C).

Anal:

TLC : R_f 0.16 (Chloroform: Methanol, 19:1)

IR : 3413, 1674, 1611, 1370, 1259, 1163 and 850 cm^{-1}

4-Acetamidoaniline

4-Acetamidonitrobenzene

Following **Method D**, but using 4-nitroaniline (5.0 g, 36.0 mmol), 4-acetamidonitrobenzene was obtained as a solid (5.8 g, 89.2 %) m.p. 215-17 °C (lit.[385] 215-17 °C).

Anal.:

TLC : R_f 0.35 (Chloroform: Methanol 19:1)

4-Acetamidoaniline

4-Acetamidonitrobenzene (5.0 g, 27.5 mmol) was reduced with iron powder and sodium chloride in aqueous methanol using **Method E** to afford 4-acetamidoaniline (0.45 g, 54.2 %) m.p. 164-67 °C (lit.[386] 164-67 °C).

Anal.:

TLC : R_f 0.12 (Chloroform: Methanol 19:1)

IR : 3370, 1664, 1512, 1265, 1089 and 827 cm^{-1}

3-Methanesulfonamidoaniline

3-Methanesulfonamidonitrobenzene

Method F: A solution of 3-nitroaniline (1.0 g, 7.24 mmol) in dry pyridine (4 mL) in a

two-neck Rb flask (50 mL) was cooled to 0 °C. Methanesulfonyl chloride (0.84 mL, 10.86 mmol) was added to it drop-wise over a period of 10 min maintaining the temperature at 0-5 °C. The reaction mixture was stirred at RT for another 1 h and quenched into a mixture of hydrochloric acid (5 mL) and ice (50 g). The solid so formed was filtered, washed with cold water and dried to give 3-methanesulfonamido-nitrobenzene (1.38 g, 88.0 %) m.p. 136-38 °C.

Anal.:

TLC : R_f 0.23 (Chloroform: Methanol 19:1)

3-Methanesulfonamidoaniline

3-Methanesulfonamidonitrobenzene (0.1 g, 0.54 mmol) as obtained above was reduced with iron powder and aq. ammonium chloride in methanol using **Method E** to provide 3-methanesulfonamidoaniline (0.06 g, 73.2 %) m.p. 122-24 °C.

Anal:

TLC : R_f 0.44 (Chloroform: Methanol 19:1)

IR : 3406, 3337. 3118, 1607, 1401, 1317, 1147, 987 and 876 cm^{-1}

4-Methanesulfonamidoaniline

4-Methanesulfonamidonitrobenzene

Following **Method F**, but using 4-nitroaniline (1.0 g, 7.24 mmol), 4-methanesulfonamidonitrobenzene was obtained as a solid (1.34 g, 85.7 %) m.p. 166-68 °C.

Anal.:

TLC : R_f 0.35 (Chloroform: Methanol, 19:1)

4-Methanesulfonamidoaniline

4-Methanesulfonamidonitrobenzene (0.1 g, 0.54 mmol) was reduced with iron powder and aq. ammonium chloride in methanol using **Method E** to provide 4-methanesulfonamidoaniline (0.05 g, 68.8 %) m.p. 118-20 °C.

Anal.:

TLC : R_f 0.51 (Chloroform: Methanol, 19:1)

IR : 3414, 3256, 1634, 1512, 1397, 1279, 1146 and 1017 cm^{-1}

5-(3-Aminophenyl)-1*H*-tetrazole

3-Nitrobenzaldoxime

Following **Method A**, but using 3-nitrobenaldehyde (5 g, 33.11 mmol), 3-nitrobenzaldoxime was obtained as a solid (4.94 g, 90 %) m.p.119-21°C (lit[387] 123-25 °C).

Anal.:

TLC :R_f 0.33 (Chloroform: Methanol, 19:1)

3-Nitrobenzonitrile

3-Nitrobenzaldoxime (4 g, 24.09 mmol) was converted to 3-nitrobenzonitrile using **Method B** (3.1 g, 87 %) m.p. 114-16 °C (lit[388] 115-19 °C).

Anal.:

TLC :R_f 0.73 (Chloroform: Methanol, 19:1)

IR : 2236, 1619, 1534, 1356, 1200 and 1101 cm^{-1}

5-(3-Nitrophenyl)-1*H*-tetrazole

Method G: In an Rb flask (10 mL) equipped with a guard tube, 3-nitrobenzonitrile (2 g, 13.51 mmol), was dissolved in DMF (1 mL). Sodium azide (2.63 g, 40.57 mmol) and ammonium chloride (3.58 g, 67.5 mmol) were added to the above solution and the reaction mixture was heated at 100 °C with stirring for 6 h. The reaction mixture was quenched with water and acidified with dilute hydrochloric acid. The precipitate so formed was filtered, washed with water and dried (1.6 g, 62 %) m.p. 210 dec.

Anal.:

TLC :R_f 0. 21 (Chloroform: Methanol, 19:1)

5-(3-Aminophenyl)-1*H*-tetrazole

5-(3-Nitrophenyl)-1*H*-tetrazole (1 g, 0.54 mmol) as obtained above was reduced with iron powder and aq. ammonium chloride in methanol using **Method E** (0.6 g, 71 %) m.p. 197-99 dec. (lit [389] 202-05 dec.).

Anal.:

TLC :R_f 0. 15 (Chloroform: Methanol 19:1)

IR : 3119, 1628, 1523, 1399, 1056 and 1006 cm^{-1}

5-(4-Aminophenyl)-1*H*-tetrazole

4-Nitrobenzaldoxime

Following **Method A**, but using 4-nitrobenaldehyde (5 g, 33.11 mmol), 4-nitrobenzaldoxime was obtained as a solid (4.83 g, 88%) m.p. 122-24 °C (lit[390] 126-31 °C).

Anal.:

TLC : R_f 0. 33(Chloroform: Methanol, 19:1)

4-Nitrobenzonitrile

4-Nitrobenzaldoxime (4 g, 24.09 mmol) was converted to 4-nitrobenzonitrile using **Method B** (3.15 g, 88 %) m.p. 144-47 °C (lit[391] 146-49 °C).

Anal.:

TLC : R_f 0. 69 (Chloroform: Methanol, 19:1)

IR : 2232, 1603, 1527, 1349, 1293 and 1104 cm^{-1}

5-(4-Nitrophenyl)-1*H*-tetrazole

5-(4-Nitrophenyl)-1*H*-tetrazole was prepared from 4-nitrobenzonitrile (2 g, 13.51 mmol) by following **Method G** (1.75 g, 67 %) m.p. 218 °C dec (lit[392] 223 dec.).

Anal.:

TLC : R_f 0. 21 (Chloroform: Methanol 19:1)

5-(4-Aminophenyl)-1*H*-tetrazole

5-(4-Nitrophenyl)-1*H*-tetrazole (1 g, 0.54 mmol) as obtained above was reduced with iron powder and aq. ammonium chloride in methanol using **Method E** (0.67 g, 79 %) m.p. 272-74 °C (lit[393] 275-77 °C).

Anal.:

TLC : R_f 0. 15 (Chloroform: Methanol 19:1)

IR : 3129, 1620, 1500, 1400 and 1263 cm^{-1}

- **Synthesis of substituted benzyl bromides**

3-Cyanobenzyl bromide

Method H: 3-Tolunitrile (2 mL, 1.7 mmol), *N*-bromosuccinimide (3.65 g, 2.04 mmol) and benzoyl peroxide (0.1 g) in dichloromethane (DCM) were taken in an Rb flask (50 mL). The reaction mixture was refluxed on water bath. The orange color disappeared after 2-3 h. Reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to get precipitate of the*N*-succinimide. The reaction mixture was filtered and the filtrate was concentrated to get solid compound (1.49 g, 45 %) m.p. 90-92 °C (lit.[394]93-96 °C).

Anal.:

TLC : R_f 0.60 (Hexane: Ethyl acetate, 18:2)

IR : 3060, 2227, 1713, 1449, 1268, 1178 and 1025 cm^{-1}

3-Nitrobenzyl bromide

Following **Method H**, but using 3-nitrotoluene (2 mL), compound 3-nitrobenzyl bromide was obtained as a solid (1.68 g, 54 %) m.p. 54-56 °C (lit.[395]58-59 °C).

Anal.:

TLC : R_f 0.56 (Hexane: Ethyl acetate, 18:2)

IR : 1528, 1350, 1224 and 808 cm^{-1}

Methyl 3-(bromomethyl)benzoate

Following **Method H**, but using methyl 3-toluate (2 mL), the desired compound methyl 3-(bromomethyl)benzoate was obtained as a solid (1.66 g, 55 %) m.p. 44-46 °C (lit.[396] 46-47 °C).

Anal.:

TLC : R_f 0.53 (Hexane: Ethyl acetate, 18:2)

IR : 1723, 1605, 1433, 1289, 1203, 1107 and 987 cm^{-1}

Methyl 4-(bromomethyl)benzoate

Following **Method H**, but using methyl 4-toluate (2 mL), the desired compound methyl 4-(bromomethyl)benzoate was obtained as a solid (1.84 g, 61 %) m.p. 54-56 °C (lit.[397] 56-58 °C).

Anal.:

TLC : R_f 0.53 (Hexane: Ethyl acetate, 18:2)

IR : 1726, 1610, 1435, 1280, 1111, 1018 and 859 cm^{-1}

5.1.2 Synthesis of 3-*n*.butyl-2-chloromethyl-6,7-dimethoxyquinazolin-4(3*H*)-one (12)

2-Nitro-*N*-*n*.butyl-4,5-dimethoxybenzamide (9)

Method I: A mixture of 6-nitroveratric acid (**4**) (5.0 g, 22.0 mmol) and thionyl chloride (10 mL) was refluxed under anhydrous conditions for 2 h. Excess of thionyl chloride was removed under reduced pressure and the residue was dissolved in anhydrous tetrahydrofuran (THF, 10 mL). In a separate two-neck Rb flask (100 mL) a solution of *n*.butylamine (2.6 mL, 26.4 mmol) and triethylamine (TEA, 9.2 mL, 66.0 mmol) in THF (15 mL) was cooled to 0-5 °C. The acid chloride solution prepared above was added drop-wise to this solution over a period of 10 min, maintaining the temperature below 10 °C. The reaction mixture was stirred for further 2 h at RT and quenched in cold water (75 mL). The precipitate so formed was filtered, washed with cold water and dried. The solid thus obtained was recrystallized from methanol to get yellow colored crystals for 2-nitro-*N*-*n*.butyl-4,5-dimethoxybenzamide (**9**) (4.8 g, 77.4 %) m.p. 130-32 °C.

Anal.:

TLC : R_f 0.38 (Chloroform: methanol, 19:1)

IR : 3270, 1640, 1519, 1349, 1277, 1224, 1077 and 1036 cm^{-1}

2-Amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (10)

2-Nitro-*N*-*n*.butyl-4,5-dimethoxybenzamide (**9**) (1.0 g, 3.5 mmol) was reduced with iron powder and sodium chloride in aqueous methanol using **Method E** to afford 2-amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (**10**) (0.84 g, 95.0 %) m.p. 110-11 °C.

Anal.:

TLC : R_f 0.35 (Chloroform: methanol, 19:1)

IR : 3409, 3317, 1637, 1512, 1462, 1260, 1220, 1178 and 860 cm^{-1}

2-(2-Chloroacetamido)-*N*-*n*.butyl-4,5-dimethoxybenzamide (11)

In a two neck Rb flask (150 mL), 2-amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (**10**) (5 g, 19.84 mmol) and TEA (2.40 mL, 23.80 mmol) were dissolved in dry THF and cooled to 5-10°C. Chloroacetyl chloride (1.88 ml, 23.80 mmol) was added drop-wise to this solution through pressure equalizing funnel, while maintaining the temperature of the reaction mixture between 5-10 °C and allowed the reaction mixture to stir for 1 h at RT. The reaction mixture was then poured in the ice cold water (50 mL). The precipitate so formed was filtered, washed with water and dried to get the compound (**11**) (4.6 g, 70%) m.p. 130-32 °C.

Anal:

TLC : R_f 0.31 (Chloroform: Methanol, 9:1)

IR : 3404, 3298, 1666, 1604, 1527, 1460, 1113 and 1034 cm^{-1}

MS : m/z 329 (M^+ peak)

3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (12)

2-(2-Chloroacetamido)-*N*-*n*.butyl-4,5-dimethoxybenzamide (**7**) (3 g, 9.12 mmol) and sodium *t*.butoxide (1.75 g, 18.24 mmol) was dissolved in ethylene glycol (10 mL). The reaction mixture was stirred for 1 h and quenched in cold water (50 mL). The reaction mixture was extracted several times with chloroform (3 × 25 mL). The organic layer was collected and dried over sodium sulphate to remove traces of water andremoved to afford the compound (**12**) (2 g, 72 %) m.p. 128-30 °C.

Anal:

TLC : R_f 0.36 (Chloroform: Methanol, 9:1)

IR : 1669, 1503, 1260, 1039 and 792 cm^{-1}

MS : m/z 311 (M^+ peak)

- **Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substituted piperazin-1-ylmethyl]) quinazolin-4(3*H*)-ones (Series I)**

3-*n*.Butyl-6,7-dimethoxy-2-[(4-methylpiperazin-1-yl)methyl]quinazolin-4(3*H*)-one (I-1)

Method J: 3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (**12**) (0.15 g, 0.48 mmol), *N*-methylpiperazine (0.08 mL, 0.72 mmol), flame dried potassium carbonate (0.28 g, 2.41 mmol) and dry DMF (1 mL) were taken in an Rb flask (50 mL). The reaction mixture was stirred overnight at 60° C and poured in ice cold water (20 mL) and precipitates so obtained were washed several times with water and filtered. The solid thus obtained was recrystallized from DCM-methanol to afford compound (**I-1**) (0.12 g, 65 %) m.p. 153-55 °C.

Anal.:

TLC : R_f 0.5 (DCM: methanol, 19:1)

IR : 1662, 1501, 1242, 1160, 1012 and 836 cm^{-1}

3-*n*.Butyl-2-[(4-ethylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (I-2)

Compound (**I-2**) was prepared by reacting *N*-ethylpiperazine (0.093 mL, 0.72 mmol) with compound (**12**) (0.15 g, 0.48 mmol) following **Method J** (0.12 g, 64 %) m.p.157-59 °C.

Anal.:

TLC : R_f 0.53 (DCM: methanol, 19:1)

IR : 1663, 1500, 1266, 1162, 1019 and 837 cm^{-1}

3-*n*.Butyl-6,7-dimethoxy-2-[(4-phenylpiperazin-1-yl)methyl]quinazolin-4(3*H*)-one (I-3)

Compound (**I-3**) was prepared by reacting *N*-phenylpiperazine (0.11 mL, 0.72 mmol) with compound (**12**) (0.15 g, 0.48 mmol) following **Method J** (0.15, 72 %) m.p. 162-64 °C.

Anal.:

TLC : R_f 0.43 (Hexane: ethyl acetate, 10:10)

IR : 1667, 1606, 1498, 1266, 1235, 1139, 1053 and 1009 cm^{-1}

NMR : δ 7.43 (s, 1H, Ar-*H*), 7.22-7.15 (m, 3H, Ar-*H*), 6.93-6.91 (m, 2H, Ar-*H*), 6.79-6.75 (m, 1H, Ar-*H*), 4.15-4.11 (t, 2H, C*H*$_2$), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OC*H*$_3$), 3.69 (s, 2H, CH_2), 3.12 (b, 4H, 2 × C*H*$_2$), 2.63 (b, 4H, 2 ×C*H*$_2$), 1.72-1.69 (m, 2H, C*H*$_2$), 1.41-1.35 (m, 2H, C*H*$_2$) and 0.94-0.92 (t, 3H, C*H*$_3$)

3-*n*.Butyl-2-[(4-cyclohexylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-4**)

Reaction of *N*-cyclohexylpiperazine (0.12 g, 0.72 mmol) and compound (**12**) (0.15 g, 0.48 mmol) under the set of conditions described in **Method J** afforded compound (**I-4**) (0.19 g, 60 %) m.p. 154-56 °C.

Anal.:

TLC : R_f 0.1 (Hexane: ethyl acetate, 10:10)

IR : 1660, 1611, 1502, 1400, 1341, 1271, 1160, 1051 and 1019 cm^{-1}

2-[4-((3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2-yl)methyl)piperazin-1-yl]benzonitrile (**I-5**)

Reaction of 1-(2-cyanophenyl)piperazine (0.12 mL, 0.72 mmol) and compound (**12**) (0.15 g, 0.48 mmol) under a set of conditions described in **Method J** afforded compound (**I-5**) (0.15 g, 66 %) m.p. 171-73°C.

Anal.:

TLC : R_f 0.5 (Hexane: ethyl acetate, 10:10)

IR : 2220, 1669, 1593, 1496, 1265, 1237, 1053, 1016 and 759 cm^{-1}

NMR : δ 7.72-7.69 (m, 1H, Ar-*H*), 7.62-7.57 (m, 1H, Ar-*H*), 7.44 (s, 1H, Ar-*H*), 7.17 (s, 1H, Ar-*H*), 7.14-7.08 (m, 2H, Ar-*H*), 4.16-4.12 (t, 3H, N-C*H*$_2$), 3.90 (s, 3H, O-C*H*$_3$), 3.87 (s, 3H, O-C*H*$_3$), 3.71 (s,2H, C*H*$_2$), 3.14 (b, 4H, C*H*$_2$), 2.68 (b, 4H, C*H*$_2$), 1.73-1.69 (m, 2H,CH_2), 1.42-1.37 (m, 2H, C*H*$_2$) and 0.96-0.93 (t, 3H, C*H*$_3$)

3-*n*.Butyl-6,7-dimethoxy-2-[(4-(2-methoxyphenyl)piperazin-1-yl)methyl]quinazolin-4(3*H*)-one (I-6)

Compound (**I-6**) was obtained by the reaction of 1-(2-methoxyphenyl)piperazine (0.12 mL, 0.72 mmol) and compound (**12**) (0.15 g, 0.48 mmol) as per general **Method J** (0.17 g, 75 %) m.p. 160-62 °C.

Anal.:

TLC : R_f 0.26 (Hexane: ethyl acetate, 10:10)

IR : 1669, 1607, 1500, 1458, 1238, 1053, 1022 and 749 cm^{-1}

NMR : δ 7.42 (s, 1H, Ar-*H*), 7.14 (s, 1H, Ar-*H*), 6.92-6.85 (m, 4H, Ar-*H*), 4.13 (m, 2H, N-C*H*$_2$), 3.90 (s, 3H, O-C*H*$_3$), 3.86 (s, 3H, O-C*H*$_3$), 3.76(s, 3H, O-C*H*$_3$),3.68 (s, 2H, -C*H*$_2$), 2.95 (b, 4H, C*H*$_2$), 2.61(b, 4H,C*H*$_2$), 1.73 (m, 2H, CH_2), 1.39-1.37 (m, 2H, C*H*$_2$) and 0.95-0.92 (t, 3H, C*H*$_3$)

MS : m/z 467.43 (M^+ peak)

3-*n*.Butyl-2-[(4-(2-fluorophenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (I-7)

Compound (**I-7**) was prepared by reacting 1-(2-flurophenyl)piperazine (0.09 mL, 0.72 mmol) with compound (**12**) (0.15, 0.48 mmol) following **Method J** (0.15 g, 68 %) m.p. 189-91 °C.

Anal.:

TLC : R_f 0.5 (Hexane: ethyl acetate, 10:10)

IR : 1666, 1613, 1500, 1456, 1237, 1138, 1052, 1018 and 757 cm^{-1}

NMR : δ 7.42 (s, 1H, Ar-*H*), 7.15 (s,1H,Ar-*H*), 7.13-7.07 (m, 2H, Ar-*H*), 7.03-6.95 (m, 2H, Ar-*H*), 4.15-4.11 (m, 3H, N-C*H*$_2$), 3.90 (s, 3H, O-C*H*$_3$), 3.87 (s, 3H, O-C*H*$_3$), 3.69 (s, 2H,C*H*$_2$), 3.00 (s, 4H,C*H*$_2$), 2.65 (b, 4H, C*H*$_2$), 1.73-1.69 (m, 2H, CH_2), 1.44-1.34 (m, 2H, C*H*$_2$) and 0.98-0.94 (t, 3H, C*H*$_3$)

3-*n*.Butyl-6,7-dimethoxy-2-[(4-(pyridin-2-yl)piperazin-1-yl)methyl]quinazolin-4(3*H*)-one (I-8)

1-(2-Pyridyl)piperazine(0.11 mL, 0.72 mmol) was reacted with compound (**12**) (0.15 g, 0.48 mmol) as per **Method J** to get compound (**I-8**) (0.14 g, 64 %) m.p. 186-88 °C.

Anal.:

TLC : R_f 0.23 (Hexane: ethyl acetate, 10:10)

IR : 1668, 1638, 1500, 1268, 1244, 1166, 1052 and 1013 cm^{-1}

NMR : δ 8.1 (m, 1H, Ar-*H*), 7.55-7.50 (m, 1H, Ar-*H*), 7.43 (s, 1H, Ar-*H*), 7.15 (s, 1H, Ar-*H*), 6.82-6.80 (m, 1H, Ar-*H*), 6.66-6.63 (m, 1H, Ar-*H*), 4.17- 4.13 (t, 2H, CH_2), 3.90 (s, 3H, O-CH_3),3.87 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2), 3.46 (b, 4H, 2 × CH_2), 2.57 (b, 4H, 2 × CH_2), 1.73-1.69 (m, 2H, CH_2), 1.42- 1.35 (m, 2H, CH_2) and 0.95 (t, 3H, CH_3)

3-*n*.Butyl-2-[(4-(4-hydroxyphenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (I-9)

Reaction of 1-(4-hydroxyphenyl)piperazine (0.12 g, 0.72 mmol) and compound (**12**) (0.15 g, 0.48 mmol) under a set of conditions described in **Method J**afforded compound (0.15 g, 66 %) m.p. 204-06 °C.

Anal.:

TLC : R_f 0.13 (Hexane: ethyl acetate, 10:10)

IR : 3146, 1660, 1614, 1501, 1406, 1272, 1179, 1020 and 836 cm^{-1}

NMR : δ 8.85 (s, 1H, O*H*), 7.43 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 6.77-6.75 (d, 2H, Ar-*H*), 6.64-6.62 (d, 2H, Ar-*H*), 4.14-4.10 (t, 2H, N-CH_2), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2), 2.95 (bs, 4H, 2 × CH_2), 2.60 (bs, 4H, 2 × CH_2), 1.72-1.68 (m, 2H, CH_2), 1.40- 1.33 (m, 2H, CH_2) and 0.94-0.90 (t, 3H, CH_3).

2-[(4-Benzhydrylpiperazin-1-yl)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (I-10)

Compound (**I-10**) was prepared by reacting 1-benzhydrylpiperazine (0.15 g, 0.72

mmol) with compound (**12**) (0.15 g, 0.48 mmol) following **Method J** (0.18 g, 72 %) m.p. 130-32°C.

Anal.:

TLC : R_f 0.5 (Hexane: ethyl acetate, 10:10)

IR : 1668, 1603, 1498, 1459, 1400, 1268, 1139, 1005 and 704 cm^{-1}

NMR : δ 7.40-7.10 (m, 12H, Ar-*H*), 4.07-4.04 (t, 2H, N-CH_2), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2), 2.69 (b, 4H, 2 × CH_2), 2.08 (b, 4H, 2 × CH_2), 1.67 (b, 2H, CH_2), 1.36-1.33 (m, 2H, CH_2) and 0.92-0.88 (t, 3H, CH_3).

- **Synthesis of 2-[(3/4-substituted phenylamino)methyl)-3-*n*.butyl-6,7-dimethoxy-quinazoline-4(3*H*)-ones (Series II)**

3-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino)benzoic acid (II-1)

Method K: 3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (**12**) (0.2 g, 0.64 mmol), 3-aminobenzoic acid (0.13 g, 0.96 mmol), flame dried cesium carbonate (0.31 g, 0.64 mmol) and dry DMF (10 mL) were taken in Rb flak (50 mL). The reaction mixture was stirred overnight and poured in ice cold water (20 mL). The precipitates so obtained were washed several times with water and filtered. The solid residue was recrystallized from methanol to afford compound (**II-1**) (0.16 g, 60 %) m.p. 192-94°C.

Anal.:

TLC : R_f 0.52 (Chloroform: Methanol, 19:1)

IR : 3455, 3360, 1717, 1662, 1503, 1226 and 1098 cm^{-1}

NMR : δ 7.61 (s, 1H, Ar-*H*), 7.49-7.47 (m, 1H, Ar-*H*), 7.39-7.38 (m, 1H, Ar-*H*), 7.28-7.21 (m, 1H, Ar-*H*), 7.08 (s, 1H, Ar-*H*), 6.91-6.88 (m, 1H, Ar-*H*), 5.39 (s, 2H, CH_2), 4.12-4.08 (t, 2H, N-CH_2), 4.01 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 1.78-1.72 (m, 2H, CH_2), 1.43-1.37 (m, 2H, CH_2) and 0.93-0.89 (t, 3H, CH_3).

MS : m/z 410.90 (M^+ peak)

4-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2-yl)methylamino]benzoic acid (II-2)

Compound (**II-2**) was prepared by reacting 4-aminobenzoic acid (0.13 g, 0.96 mmol) with compound (**12**) (0.2 g, 0.64 mmol) as per **Method K** (0.17 g, 68 %) m.p. 122-24°C.

Anal.:

TLC : R_f 0. 33(Chloroform: Methanol, 19:1)

IR : 3466, 3352, 1700, 1657, 1604, 1503, 1272, 1111 and 1028 cm^{-1}

NMR : δ 7.91-7.89 (d, 2H, Ar-*H*), 7.61 (s, 3H, Ar-*H*), 7.09 (s, 3H, Ar-*H*), 6.66 6.64 (d, 2H, Ar-*H*), 5.37 (s, 2H, CH_2), 4.14-4.08 (m, 2H, N-CH_2), 4.00 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 1.77-1.74 (m, 2H, CH_2), 1.42-1.36 (m, 2H, CH_2) and 0.91-0.88 (t, 3H,CH_3).

MS : m/z 410.96 (M^+ peak)

2-[(3-Aminophenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (II-3)

Compound (**II-3**) was prepared by reacting 3-phenylenediamine (0.10 g, 0.96 mmol) with compound (**12**) (0.2 g, 0.64 mmol) as per **Method K** (0.18 g, 69 %) m.p. 98-102 °C.

Anal.:

TLC : R_f 0.59 (Chloroform: Methanol, 9:1)

IR : 3131, 1663, 1608, 1499, 1400, 1210 and 1167 cm^{-1}

MS : m/z 382.13 (M^+ peak)

2-[(4-Aminophenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (II-4)

4-Phenylenediamine (0.10 g, 0.96 mmol) was reacted with compound (**12**) (0.2 g, 0.64 mmol) as per the **Method K** to get compound (**II-4**) (0.16 g, 65 %) m.p. 135-38 °C.

Anal.:

TLC : R_f 0.56 (Chloroform: Methanol, 19:1)

IR : 3127, 1668, 1608, 1504, 1447, 1261, 1095 and 801 cm^{-1}

MS : m/z 381.20 (M^+ peak)

***N*-[3-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino] phenyl]methanesulfonamide (II-5)**

Reaction of 3-methanesulfonamidoaniline (0.179 g, 0.96 mmol) and compound (**12**) (0.2 g, 0.64 mmol) under a set of conditions described in **Method K** afforded compound (**II-5**) (0.17 g, 60 %) m.p. 160 °C dec.

Anal.:

TLC : R_f 0.39 (Chloroform: Methanol, 19:1)

IR : 3444, 3361, 1678, 1607, 1501, 1331, 1272, 1147 and 1082 cm^{-1}

NMR : δ 7.57 (s, 1H, Ar-*H*), 7.13-7.09 (m, 1H, Ar-*H*), 6.93 (s, 1H, Ar-*H*), 6.92-6.88 (m, 2H, Ar-*H*), 6.60-6.58 (m, 1H, Ar-*H*), 4.99 (s, 2H, CH_2), 4.14-4.11 (t, 2H, N-CH_2), 3.98 (s, 6H, 2 × OCH_3), 3.73 (b, 1H, N*H*), 3.23 (s, 3H, CH_3), 1.71-1.66 (m, 2H, CH_2), 1.47-1.41 (m, 2H, CH_2) and 0.99-0.95 (t, 3H, CH_3)

MS : m/z 460.10 (M^+ peak)

***N*-[4-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazoline-2yl)methylamino]-*N*-phenyl]methanesulfonamide (II-6)**

Reaction of 4-methanesulfonamidoaniline (0.179 g, 0.96 mmol) and compound (**12**) (0.2 g, 0.64 mmol) under a set of conditions described in **Method K** afforded compound (**II-6**) (0.17 g, 62 %) m.p. 172 °C dec.

Anal.:

TLC : R_f 0.37 (Chloroform: Methanol, 19:1)

IR : 3462, 3366, 1655, 1607, 1508, 1338, 1272, 1145 and 1078 cm^{-1}

NMR : δ 7.56 (s, 1H, Ar-*H*), 7.31-7.28 (d, 2H, Ar-*H*), 6.94 (s, 1H, Ar-H_d), 6.60-6.58 (d, 2H, Ar-*H*), 4.96 (s, 2H, CH_2), 4.16-4.12 (t, 2H, N-CH_2), 3.99 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.16 (s, 3H, CH_3), 1.68-1.61 (m, 2H, CH_2), 1.46-1.41 (m, 2H, CH_2) and 0.99-0.95 (t, 3H, CH_3).

MS : m/z 460.09 (M^+ peak)

5-[3-((3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino)-phenyl]-1*H*-tetrazole (**II-7**)

Compound (**II-7**) was prepared by reacting 5-(3-aminophenyl)-1*H*-tetrazole (0.19 g, 0.96 mmol) with compound (**12**) (0.2 g, 0.64 mmol) as per **Method K** (0.13 g, 46 %) m.p. 167-70 °C.

Anal.:

TLC : R_f 0.78(Chloroform: Methanol, 18:2)

IR : 3416, 1665, 1611, 1501, 1400, 1262, 1210, 1171, 1038 and 788 cm^{-1}

NMR : δ 7.52 (s, 1H, Ar-*H*), 7.45 (s, 1H, Ar-*H*), 7.40-7.38 (m, 1H, Ar-*H*), 7.22-7.18 (m, 1H, Ar-*H*), 6.91 (s, 1H, Ar-*H*), 6.78-6.77 (m, 1H, Ar-*H*), 6.14 (s, 2H, N-CH_2), 4.21-4.13 (t, 2H, N-CH_2), 3.95 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 1.66-1.59 (m, 2H, CH_2), 1.51-1.43 (m, 2H, CH_2) and 0.88-0.85 (t, 3H, CH_3)

MS : m/z 434.98 (M+ peak)

5-[4-((3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino)-phenyl]-1*H*-tetrazole (**II-8**)

Compound (**II-8**) was prepared by reacting 5-(4-aminophenyl)-1*H*-tetrazole (0.19 g, 0.96 mmol) with compound (**12**) (0.2 g, 0.64 mmol) as per **Method K** (0.12 g, 44 %) m.p. 90-92 °C.

Anal.:

TLC : R_f 0.78 (Chloroform: Methanol, 18:2)

IR : 3359, 3133, 1664, 1611, 1502, 1465, 1270, 1207, 1174 and 1037 cm^{-1}

NMR : δ 7.80-7.78 (d, 2H, Ar-*H*), 7.49 (s, 1H, Ar-*H*), 6.89 (s, 3H, Ar-*H*), 6.72-6.69 (d, 2H, Ar-*H*), 6.14 (s, 2H, CH_2), 4.19-4.15 (t, 2H, N-CH_2), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 1.62-1.55 (m, 2H, CH_2), 1.48-1.42 (m, 2H, CH_2) and 0.99-0.84 (t, 3H, CH_3)

MS : m/z 435.17 (M^+ peak)

5.1.3 Synthesis of 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinzolin-4(3*H*)-ones (Series III)

4,5-Dimethoxyanthranilic acid (13)

Method L: 6-Nitroveratric acid (**4**) (5 g) was dissolved in methanol (50 mL) in a three-neck Rb flask (100 mL) equipped with a hydrogen balloon. Palladium-charcoal (0.1 g, 10 %) was added to the above solution and the reaction mixture was stirred under an atmosphere of hydrogen gas for 4 h. The reaction mixture was filtered through filtering aid, washed with hot methanol and the filtrate was concentrated under reduced pressure to afford 4,5-dimethoxyanthranilic acid (**13**) as brown colored solid (3.6 g, 85 %), m.p. 154-56 °C (lit[398] 155-58 °C).

Anal.:

TLC : R_f 0.2 (Chloroform: Methanol, 18:2)

IR : 3487, 3373, 1705, 1652, 1550, 1386, 1180 and 1033 cm^{-1}

2-*n*.Butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (14)

In a Rb flask (10 mL), a solution of 4,5-dimethoxyanthranilic acid (**13**) (1 g, 5.1 mmol), *n*.valeroyl chloride (1.4 mL, 11.16 mmol) in DMF (2 mL) was taken and heated on an oil bath for 2 h under anhydrous conditions. Few dropsof acetic anhydride wereadded in order to complete the reaction.The black colored sticky residue thus obtained was triturated with hexane to give free flowing solid which was filtered and dried to afford 2-*n*.butyl-6,7-dimethoxybenz[1,3-*d*]-4*H*-oxazin-4-one (1.0 g, 89.3 %) m.p. 182-84 °C.

Anal.:

TLC : R_f 0.73 (Chloroform: Methanol, 17:3)

IR : 1746, 1605, 1509, 1459, 1260, 1093, 1024 and 801cm^{-1}

2-*n*.Butyl-6,7-dimethoxy-4*H*-benz[1,3-*d*]oxazin-4-one prepared as above was treated with ammonium acetate and the reaction mixture heated at 100°C until the reaction completed. The reaction mixture was poured in ice-cold water (20 mL), filtered and washed several times with water. The dried residue was recrystallized from DCM and methanol to afford the desired product.

Anal.:

TLC : R_f 0.36 (Chloroform: Methanol, 17:3)

IR : 3157, 3057, 1670, 1614, 1496, 1393, 1260, 1217, 995 and 864 cm^{-1}

MS : 262.06 (M^+ peak)

Methyl 3-[(2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoate (III-1)

Method M: Compound (**14**) (0.2 g, 0.76 mmol), methyl 3-(bromomethyl)benzoate (0.35 g, 1.52 mmol) and K_2CO_3 (0.21 g, 1.52 mmol) were taken in dry acetone. The reaction mixture was stirred at RT and monitored by TLC. After completion of the reaction, it was poured in ice-cold water (20 mL). The precipitate so formed were filtered and washed several times with water. The residue was recrystallized from DCM-methanol to afford the solid compound (**III-1**) (0.18 g, 57 %) m.p. 178-80 °C.

Anal.:

TLC : R_f 0.5 (Hexane: ethyl acetate, 12:8)

IR : 1669, 1611, 1500, 1403, 1273, 1168, 1138, 1032 and 870 cm^{-1}

Methyl4-[(2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoate (III-2)

Compound (**III-2**) was obtained by the reaction of methyl 4-(bromomethyl)benzoate (0.35 g, 1.52 mmol) and compound (**14**) (0.2 g, 0.76 mmol) as per general **Method M** (0.17 g, 55 %) m.p. 186-89 °C.

Anal.:

TLC : R_f 0.46 (Hexane: ethyl acetate 12:8)

IR : 1720, 1654, 1611, 1503, 1435, 1283, 1059, 1012 and749 cm^{-1}

NMR : δ 7.94- 7.92 (d, 2h, Ar-*H*), 7.46 (s, 1H, Ar-*H*), 7.29-7.27 (d, 2H, Ar-*H*), 7.11 (s, 1H, Ar-*H*), 5.46 (s, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.68-2.65 (t, 2H, CH_2),1.67-1.59 (m, 2H, CH_2), 1.33-1.24 (m, 2H, CH_2) and 0.82-0.79 (t, 3H, CH_3)

3-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoic acid (**III-3**)

Method N: Compound (**III-1**) (0.1 g, 0.23 mmol) was suspended in methanol (5 mL) in an Rb flask (10 mL) and aq sodium hydroxide solution (30 %, 0.5 mL) was added to it. The reaction mixture was refluxed for 30 min and excess of methanol was recovered. The residue was quenched in cold water (20 mL) and carefully neutralized (*p*H 5.5-6.0) with dilute hydrochloric acid. The precipitate so formed was filtered under suction, washed with cold water and dried. The solid thus obtained was subjected to recrystallization from a mixture of chloroform and methanol to afford compound (**III-3**) (0.067 g, 70 %) m.p. 198-200 °C.

Anal.:

TLC : R_f 0.2 (Hexane: ethyl acetate 12:8)

IR : 3130, 1703, 1660, 1617, 1506, 1400, 1288, 1167 and 1003cm^{-1}

NMR : δ 7.86-7.84 (d, 1H, Ar-*H*), 7.68 (s, 1H, Ar-*H*), 7.51-7.43 (m, 3H, Ar-*H*), 7.11 (s, 1H, Ar-*H*), 5.77 (s, 2H, N-CH_2), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.71-2.67 (m, 2H, CH_2), 1.64-1.60 (m, 2H, CH_2), 1.31-1.27 (m, 2H, CH_2) and 0.84-0.77 (t, 3H, CH_3)

4-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoic acid (**III-4**)

Compound (**III-4**) was obtained from compound (**III-2**) (0.1 g, 0.23 mmol) as per general **Method N** (0.071g, 74 %) m.p. 240-42 °C dec.

Anal.:

TLC : R_f 0.18 (Hexane: ethyl acetate, 12:8)

IR : 3413, 1670, 1638, 1616, 1502, 1402. 1348, 1254, 1058 and 1013 cm^{-1}

NMR : *δ* 8.23-8.21 (d, 2H, Ar-*H*), 7.46 (s, 1H, Ar-*H*), 7.44-7.41 (d, 2H, Ar-*H*), 7.12 (s, 1H, Ar-*H*), 5.51 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.70-2.66 (m, 2H, CH_2), 1.69-1.62 (m, 2H, CH_2), 1.35-1.23 (m, 2H, CH_2) and 0.87-0.83 (t, 3H, CH_3)

2-*n*.Butyl-6,7-dimethoxy-3-(3-nitrobenzyl)quinazolin-4(3*H*)-one (**III-5**)

Compound (**III-5**) was prepared by reacting 3-nitrobenzyl bromide (0.33 g, 1.52 mmol) with compound (**14**) (0.2 g, 0.76 mmol) as per **Method M** (0.18 g, 61 %) m.p. 160-62 °C.

Anal.:

TLC : R_f 0.33 (Hexane: ethyl acetate, 12:8)

IR : 1664, 1612, 1571, 1530, 1443, 1351, 1228, 1000 and 780 cm^{-1}

2-*n*.Butyl-6,7-dimethoxy-3-(4-nitrobenzyl)quinazolin-4(3*H*)-one (**III-6**)

Compound (**III-6**) was prepared by reacting 4-nitrobenzyl bromide (0.33 g, 1.52 mmol) with compound (**14**) (0.2 g, 0.76 mmol) as per **Method M** (0.19 g, 63 %) m.p. 178-80 °C.

Anal.:

TLC : R_f 0.36 (Hexane: ethyl acetate, 12:8)

IR : 1657, 1610, 1520, 1501, 1401, 1345, 1230, 1002, 850 and 733 cm^{-1}

NMR : δ 8.20-8.18 (d, 2H, Ar-*H*), 7.50 (s, 1H, Ar-*H*), 7.44-7.41 (d, 2H, Ar-*H*), 7.10 (s, 1H, Ar-H), 5.29 (s, 3H, N-CH_2), 3.97 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.71-2.67(t, 2H, N-CH_2), 1.73-1.67 (m, 2H, CH_2), 1.39-1.33 (m, 2H, CH_2) and 0.90-0.86 (t, 3H, CH_3)

3-(3-Aminobenzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**III-7**)

Compound (**III-7**) was prepared from compound (**III-5**) (0.15 g, 0.37 mmol) with iron powder and ammonium chloride by following **Method E** (0.11 g, 76 %) m.p. 224-26 °C.

Anal:

TLC : R_f 0.2 (Hexane: ethyl acetate, 12:8)

IR : 3413, 3115, 1664, 1614, 1530, 1503, 1400, 1351, 1271, 1208, 999 and 780 cm^{-1}

3-(4-Aminobenzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**III-8**)

Compound (**III-8**) was prepared from compound (**III-6**) (0.15 g, 0.37 mmol) with iron powder and ammonium chloride by following **Method E** (0.11, 80 %) m.p. > 280°C.

Anal.:

TLC : R_f 0.23 (Hexane: ethyl acetate, 12:8)

IR : 3413, 3159, 3006, 1658, 1614, 1496, 1400, 1266, 1138 and 1001 cm^{-1}

***N*-[4-((2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl)phenyl]methane sulfonamide (III-9)**

Compound (**III-9**) was prepared by methylsulfonation of compound (**III-8**) (0.1 g, 0.27 mmol) by following **Method F** (0.083 g, 69 %) m.p. 154-56 °C.

Anal.:

TLC : R_f 0.26 (Hexane: ethyl acetate, 12:8)

IR : 3414, 3143, 1659, 1612, 1500, 1401, 1335, 1247, 1210, 1152, 1013 and 781cm^{-1}

3-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzonitrile (III-10)

Reaction of 3-(bromomethyl)benzonitrile (0.30 g, 1.52 mmol) and compound (**14**) (0.2 g, 0.76 mmol) under a set of conditions described in **Method M** afforded compound (**III-10**) (0.16 g, 58 %) m.p. 215-17 °C.

Anal.:

TLC : R_f 0.56 (Hexane: ethyl acetate, 12:8)

IR : 2230, 1660, 1611, 1501, 1400, 1269, 1245, 1141 and 1012 cm^{-1}

NMR : δ 7.63-7.62 (m, 1H, Ar-*H*), 7.56-7.51 (m, 4H, Ar-H), 7.20 (s, 1H, Ar-*H*), 5.46 (s, 2H, N-CH_2), 4.00 (s, 3H. O-CH_3), 3.97 (s, 3H, O-CH_3), 2.81-2.77 (t, 2H, N-CH_2), 1.74-1.68 (m, 2H, CH_2), 1.43-1.38 (m, 2H, CH_2) and 0.92-0.88 (t, 3H, CH_3)

MS : m/z 377.90 (M^+ peak)

4-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzonitrile (III-11)

Reaction of 4-(bromomethyl)benzonitrile (0.30 g, 1.52 mmol) and compound (**14**) (0.2 g, 0.76 mmol) under a set of conditions described in **Method M** afforded compound (**III-11**) (0.17 g, 60 %) m.p. 214-16 °C.

Anal.:

TLC : R_f 0.56 (Hexane: ethyl acetate, 12:8)

IR : 2228, 1658, 1610, 1502, 1402, 1245, 1232, 1013, 846 and 784 cm^{-1}

2-*n*.Butyl-6,7-dimethoxy-3-[3-(1*H*-tetrazol-5-yl)benzyl]quinazolin-4(3*H*)-one (**III-12**)

Compound **III-12** was prepared from compound (**III-10**) (0.12 g, 0.32 mmol) by following **Method G** (0.073 g, 55 %) m.p. 260 °C dec.

Anal.:

TLC : R_f 0.2 (Hexane: ethyl acetate, 12:8)

IR : 3132, 1638, 1608, 1501, 1403, 1294, 1245, 1212, 1173, 1024 and 860 cm^{-1}

NMR : δ 7.96-7.94 (d, 1H, Ar-*H*), 7.82 (s, 1H, Ar-*H*), 7.61-7.57 (t, 1H, Ar-*H*), 7.48(s, 1H, Ar-*H*), 7.42-7.40 (d, 1H, Ar-*H*), 7.12 (s, 1H, Ar-*H*), 5.48 (s, 2H, CH_2), 3.92 (s, 3H, O-CH_3), 3.88 (s, 3H, O-CH_3), 2.74-2.71 (t, 2H, CH_2), 1.69-1.61 (m, 2H, CH_2), 1.32-1.26 (m, 2H, CH_2) and 0.82 (t, 3H, CH_3)

2-*n*.Butyl-6,7-dimethoxy-3-[4-(1*H*-tetrazol-5-yl)benzyl]quinazolin-4(3*H*)-one (**III-13**)

Compound (**III-13**) was obtained from compound (**III-11**) (0.12 g, 0.32 mmol) as per general **Method G** (0.076 g, 57 %). m.p. 195-97 °C.

Anal.:

TLC : R_f 0.17 (Hexane: ethyl acetate 12:8)

IR : 3148, 1649, 1613, 1502, 1403, 1292, 1252, 1167, 1067 and 999 cm^{-1}

5.1.4 Synthesis of 2-chloro-6,7-dimethoxyquinazolin-4-amine (19)

3,4-Dimethoxy-6-nitrobenzamide (**15**)

A solution of 6-nitroverateric acid (**4**) (5.0 g, 22.0 mmol) in thionyl chloride (10 mL) was refluxed under anhydrous conditions for 2 h in an Rb flask (50 mL). The excess of thionyl chloride was removed under reduced pressure. The residue so obtained was dissolved in anhydrous tetrahydrofuran (THF) (25 mL) and cooled to 5 °C. Aqueous ammonia (15 mL) was added to this solution drop-wise over a period of 15 min, keeping the temperature of the reaction mixture between 5-10 °C. The reaction mixture was stirred for further 2 h at RT and quenched in cold water (100 mL). The precipitate thus formed was filtered, washed with cold water and dried. The solid so obtained was

recrystallized from methanol to get yellow colored crystals of 3,4-dimethoxy-6-nitrobenzamide (**15**) (3.0 g, 60.2 %), m.p. 192-95 °C (lit.[399] 192-95 °C).

Anal.:

TLC : R_f 0.5 (Chloroform: methanol, 18:2)

IR : 3423, 1663, 1576, 1525, 1512, 1343, 1276, 1226 and 1050 cm^{-1}

2-Amino-4,5-dimethoxybenzamide (**16**)

Compound (**16**) was prepared from compound (**15**) (1.0 g, 4.4 mmol) with iron powder and ammonium chloride by following **Method E** (0.45 g, 51.9 %), m.p. 144-46 °C (lit.[400] 145-47 °C).

Anal.:

TLC : R_f 0.45 (Chloroform: methanol, 18:2)

IR : 3450, 3341, 1671, 1631, 1548, 1394, 1258, 1178 and 1078 cm^{-1}

6,7-Dimethoxy-1,2,3,4-tetrahydroquinazoline-2,4-dione (**17**)

Compound (**16**) (1.0 g, 5.10 mmol) was dissolved in pyridine (3 mL) in an Rb flask (10 mL) and to the clear solution urea (0.06 g, 10.20 mmol) and 2 drops of dilute hydrochloric acid were added. The reaction mixture was refluxed with stirring for 8 h, cooled to RT and the precipitate so formed was filtered, washed with diethyl ether and dried. The solid thus obtained was subjected to recrystallization from a mixture of chloroform and methanol to afford 6,7-dimethoxy-1,2,3,4-tetrahydroquinazoline-2,4-dione (**17**) (0.60 g, 57 %) m.p. > 280 °C.

Anal.:

TLC : R_f 0.13 (Chloroform: methanol, 18:2)

IR : 3176, 1706, 1657, 1625, 1509, 1426, 1264, 1101 and 1039 cm^{-1}

2,4-Dichloro-6,7-dimethoxyquinazoline (**18**)

A mixture of 6,7-dimethoxy-1,2,3,4-tetrahydroquinazoline-2,4-dione (**17**) (1.0 g, 4.50 mmol), phosphorus oxychloride (3.0 mL) and *N*,*N*-dimethylaniline (2 drops) was refluxed with stirring in an Rb flask (10 mL) for 16 h. The reaction mixture was cooled to RT and cautiously quenched in crushed ice (50 g) with vigorous stirring. The precipitate

so formed was filtered and immediately dissolved in chloroform (25 mL) which was dried and concentrated to give yellow colored solid of 2,4-dichloro-6,7-dimethoxyquinazoline (**18**), which was immediately used as such for the next step (0.52 g, 44.5 %) m.p. > 280 °C.

Anal.:

TLC : R_f 0.88 (Chloroform: methanol, 18:2)

IR : 1612, 1543, 1480, 1445, 1372, 1340, 1268, 1153 and 1110 cm^{-1}

4-Amino-2-chloro-6,7-dimethoxyquinazoline (**19**)

2,4-Dichloro-6,7-dimethoxyquinazoline (**18**) (1.0 g, 3.86 mmol) was dissolved in THF (15 mL) and dry ammonia gas was bubbled through this solution for 36 h. The solid precipitate formed was filtered after every 16 h and at the end of the reaction the reaction mixture was concentrated to get an additional crop. The solid thus obtained was recrystallized from a mixture of chloroform and methanol to afford 4-amino-2-chloro-6,7-dimethoxyquinazoline (**19**).(0.27 g, 30 %) m.p. 260-62 °C dec. (lit.[401] 262-66 °C dec.).

Anal.:

TLC : R_f 0.18 (Hexane: ethyl acetate, 10:10)

IR : 3409, 3326, 1658, 1585, 1498, 1279, 1250, 1087 and 1026 cm^{-1}

MS : m/z 240 $(M + 1)^+$

- **Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amine** (**Series IV**)

6,7-Dimethoxy-2-(4-methylpiperazin-1-yl)quinazolin-4-amine (**IV-1**)

Method O: Potassium carbonate was flame dried under vacuum. To a solution of 4-amino-2-chloro-6,7-dimethoxyquinazoline (**19**) (0.1 g, 0.41 mmol) and *N*-methyl piperazine (0.139 mL, 1.25 mmol) potassium carbonate in dry DMF was added. The reaction mixture was stirred overnight at 120°C in sealed tube. The reaction mixture was poured in ice cold water and the precipitates so obtained were filtered and washed with water. The residue was recrystallized from DCM-methanol to afford the desired compound (**IV-1**) (0.07 g, 58 %) m.p. 132-34°C.[402]

Anal.:

TLC : R_f 0.9 (DCM: methanol, 19:1)

IR : 3555, 3334, 1644, 1485, 1443, 1374, 1280, 1244, 1143, 1002 and 836 cm^{-1}

NMR : δ 7.40 (s, 1H, Ar-*H*), 7.09 (b, 2H, NH_2), 6.70 (s, 1H, Ar-*H*), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.68 (b, 4H, 2 × CH_2), 2.33 (b, 4H, 2× CH_2) and 2.19 (s, 3H, CH_3)

2-(4-Ethylpiperazin-1-yl)-6,7-dimethoxyquinazolin-4-amine (**IV-2**)

Reaction of *N*-ethylpiperazine (0.15 mL, 1.25 mmol) and compound (**19**) (0.1 g, 0.41 mmol) under a set of conditions described in **Method O** afforded compound (**IV-2**) (0.08 g, 60%) m.p. 187-89 °C.

Anal.:

TLC : R_f 0.33 (DCM: methanol, 19:1)

IR : 3291, 3086, 1666, 1580, 1494, 1382, 1294, 1248, 1212, 1180, 993 and 844 cm^{-1}

6,7-Dimethoxy-2-(4-phenylpiperazin-1-yl)quinazolin-4-amine (**IV-3**)

Reaction of *N*-phenylpiperazine (0.19 mL, 1.25 mmol) and compound (**19**) (0.1g, 0.41 mmol) as per **Method O** afforded compound (**IV-3**) (0.1 g, 70%) m.p. 230-32 °C.[403]

Anal.:

TLC : R_f 0.36 (Hexane: ethyl acetate, 15:5)

IR : 3456, 3362, 1628, 1570, 1440, 1379, 1288, 1235, 1166, 1103, 1033 988 and 840 cm^{-1}

NMR : δ 7.42 (s, 1H, Ar-*H*), 7.25-7.21 (m, 2H, Ar-*H*), 7.15 (b, 2H, NH_2), 7.01-6.99 (d, 2H, Ar-*H*), 6.82-6.78 (m, 1H, Ar-*H*), 6.74 (s, 1H, Ar-H), 3.83 (s, 6H, 2 × OCH_3), 3.17-3.15 (m, 8H, 4 × CH_2).

2-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]benzonitrile (**IV-4**)

1-(2-Cyanophenyl)piperazine (0.20 mL, 1.25 mmol) was reacted with compound

(**19**) (0.1g, 0.41 mmol) as per **Method O** to get compound (**IV-4**) (0.1 g, 65%) m.p. 127-29 °C.

Anal.:

TLC : R_f 0.46 (Hexane: ethyl acetate, 15:5)

IR : 3491, 3321, 2218, 1638, 1571, 1485, 1379, 1284, 1253, 1217, 1149, 1106, 1034, 995 and 850 cm^{-1}

NMR : δ 7.75-7.73 (dd, 1H, Ar-*H*), 7.73-7.60 (m, 1H, Ar-*H*), 7.43 (s, 1H,Ar-*H*), 7.23-7.06 (m, 4H, Ar-*H* and NH_2), 6.75 (s, 1H, Ar-*H*), 3.90-3.88 (m, 4H, 2× C*H*$_2$), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, OC*H*$_3$) and 3.19-3.17 (m, 4H, 2× C*H*$_2$)

MS : m/z 390.21 (M^+ peak)

6,7-Dimethoxy-2-[4-(2-methoxyphenyl)piperazin-1-yl]quinazolin-4-amine (**IV-5**)

Compound (**IV-5**) was prepared by reacting 1-(2-methoxyphenyl)piperazine (0.22 mL, 1.25 mmol) with compound (**19**) (0.1g, 0.41 mmol) as per **Method O** (0.11 g, 72%) m.p. 122-24 °C.[404]

Anal.:

TLC : R_f 0.3 (Hexane: ethyl acetate, 15:5)

IR : 3412, 3211, 1639, 1557, 1501, 1442, 1404, 1291, 1247, 1146, 1112, 1028, 846 and 750 cm^{-1}

NMR : δ 7.42 (s, 1H, Ar-*H*), 7.13 (b, 2H, N*H*$_2$), 6.97-6.85 (m, 4H, Ar- *H*), 6.73 (s, 1H, Ar-*H*), 3.85-3.83 (bs, 7H, 2 × C*H*$_2$ and OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$) and 2.98-2.96 (t, 4H, 2 × C*H*$_2$)

2-[4-(2-Fluorophenyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine (**IV-6**)

Reaction of 1-(2-flurophenyl)piperazine (0.19, 1.25 mmol) andcompound (**19**) (0.1g, 0.41 mmol) under a set of conditions described in **Method O** afforded compound (**IV-6**) (0.1 g, 62 %) m.p. 202-04 °C.

Anal.:

TLC : R_f 0.53(Hexane: ethyl acetate, 15:5)

IR : 3484, 3371, 1626, 1573, 1435, 1371, 1281, 1235, 1168, 1098, 1033, 993, 839 and 745 cm^{-1}

NMR : δ 7.42 (s, 1H, Ar-*H*), 7.18-6.98 (m, 6H, Ar-*H* and NH_2), 6.74 (s, 1H, Ar-H), 3.88-3.86 (t, 4H, 2 × CH_2), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3) and 3.04-3.02 (t, 4H, 2 × CH_2)

6,7-Dimethoxy-2-[4-(pyridin-2-yl)piperazin-1-yl]quinazolin-4-amine (**IV-7**)

Reaction of 1-(2-pyridyl)piperazine (0.19 mL, 1.25 mmol) and compound (**19**) (0.1 g, 0.41 mmol) under conditions described in **Method O** afforded compound (**IV-7**) (0.08 g, 52%) m.p. 226 °C dec.

Anal.:

TLC : R_f 0.3 (Hexane: ethyl acetate 15:5)

IR : 3433, 3189, 1646, 1562, 1490, 1436, 1374, 1277, 1235, 1165, 1099, 1033, 982, 836 and 773 cm^{-1}

NMR : δ 8.13-8.12 (dd, 1H, Ar-*H*), 7.57-7.53 (m, 1H, Ar-*H*), 7.42 (s, 1H, Ar-*H*), 7.18 (b, 2H, NH_2), 6.89-6.87 (d, 1H, Ar-*H*), 6.76 (s, 1H, Ar-*H*),6.67-6.64 (m, 1H, Ar-*H*), 3.83-3.78 (m, 10H, 2 × CH_2 and 2 × OCH_3) and3.55-3.52 (t, 4H, 2 × CH_2)

4-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]phenol (**IV-8**)

Compound (**IV-8**) was prepared by reacting 1-(4-hydroxyphenyl)piperazine (0.22 g, 1.25 mmol) and compound (**19**) (0.1g, 0.41 mmol) using **Method O** (0.09 g, 56%) m.p. > 280 °C (lit[405])

Anal.:

TLC : R_f 0.2 (Hexane: ethyl acetate 15:5)

IR : 3357, 3145, 1631, 1510, 1279, 1230, 1176 and 1031 cm^{-1}

2-(4-Benzhydrylpiperazin-1-yl)-6,7-dimethoxyquinazolin-4-amine (**IV-9**)

Compound (**IV-9**) was obtained by the reaction of benzhydryl piperazine (0.26 g, 1.25 mmol) and compound (**19**) (0.1g, 0.41 mmol) as per general **Method O** (0.12 g, 68 %) m.p. 270-72 °C (lit[406] 273-74 °C).

Anal.:

TLC : R_f 0.46 (Hexane: ethyl acetate 15:5)

IR : 3438, 3330, 1654, 1562, 1490, 1441, 1277, 1239, 1146, 1107, 1030, 997, 850 and 749 cm^{-1}

NMR : δ 7.46-7.09 (m, 13H, 11 Ar-*H* and NH_2), 6.68 (s, 1H, Ar-*H*), 4.30 (s, 1H, C*H*), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.70 (b, 4H, 2 × CH_2) and 2.36-2.33 (b, 4H, 2× CH_2)

5.1.5 Synthesis of 2-(chloromethyl)-6,7-dimethoxyquinazolin-4-amine

2-(Chloromethyl)-6,7-dimethoxyquinazolin-4-amine (**20**)

Chloroacetonitrile (0.42 ml, 6.74 mmol) and dioxane (5 mL) saturated with dry HCl gas (0.82 g, 22.47 mmol) were taken in Rb flask (50 mL) and allowed to stir for half an hour. 2-Amino-4,5-dimethoxybenzonitrile (**8**) (1 g, 5.61 mmol) was dissolved in dry dioxane and addedto the above reaction mixture. The reaction mixture was allowed to stir for 24 hour. The reaction mixture was quenched in ice cold water (15 mL). The suspension so formed was filtered and the precipitate rejected. The filtrate was basified with ammonia solution. The precipitates so obtained were filtered and dried under vaccum to obtain the product (**20**) (0.9g, 63.38%) m.p. 250 °C dec.

Anal.:

TLC : R_f 0.21(Ethyl acetate: hexane, 14:6)

IR : 3479, 3330, 3136, 1657, 1583, 1508, 1434, 1254, 1216, 1170, 1001 and 841 cm^{-1}

MS : m/z 252.98 (M^+ peak), 254.99 $(M + 2)^+$

- **Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amine** (**Series V**)

6,7-Dimethoxy-2-[(4-methylpiperazin-1-yl)methyl]quinazolin-4-amine (**V-1**)

Reaction of *N*-methylpiperazine (0.26 mL, 2.37 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under a set of conditions described in **Method J** afforded compound (**V-1**) (0.16 g, 63%) m.p. 253-55 °C.

Anal.:

TLC : R_f 0.1 (DCM: Methanol, 18:2)

IR : 3131, 1672, 1582, 1489, 14011261, 1225 and 1142 cm^{-1}

NMR : δ 7.53 (s, 1H, Ar-*H*), 7.41 (b, 2H, NH_2), 7.07 (s, 1H, Ar-*H*), 3.87 (s, 3H, OCH_3), 3.84(s, 3H, OCH_3), 3.40 (s, 2H, CH_2), 2.50 (b, 4H), 2.28 (b, 4H, CH_2) and 2.12 (s, 3H)

2-[(4-Ethylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-2**)

Reaction of *N*-ethylpiperazine (0.3 mL, 2.37 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under the conditions described in **Method J** afforded compound (**V-2**) (0.17 g, 64%) m.p. 241-43 °C.

Anal.:

TLC : R_f 0.1 (DCM: Methanol, 18:2)

IR : 3306, 3146, 1666, 1580, 1491, 1279, 1248, 1165, 1016 and 869 cm^{-1}

6,7-Dimethoxy-2-[(4-phenylpiperazin-1-yl)methyl]quinazolin-4-amine (**V-3**)

Compound (**V-3**) was prepared by reacting *N*-phenylpiperazine (0.36 mL, 2.371 mmol) with compound (**20**) (0.2 g, 0.79 mmol) as per **MethodJ** (0.22 g, 74%) m.p. 230-32 °C.

Anal.:

TLC : R_f 0.73 (DCM: Methanol, 18:2)

IR : 3313, 3151, 1666, 1579, 1323, 1281, 1222, 1133, 1015 and 862 cm^{-1}

NMR : δ 7.55 (s, 1H, Ar-*H*), 7.44 (b, 2H, NH_2), 7.21-7.17 (t, 2H, Ar-*H*), 7.09 (s, 1H, Ar-*H*), 6.92-6.90 (d, 2H, Ar-*H*), 6.77-6.73 (t, 1H, Ar-*H*), 3.88(s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2), 3.10-3.09 (t, 4H, CH_2) and 2.64-2.62 (t, 4H, CH_2)

2-[(4-Cyclohexylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-4**)

Compound (**V-4**) was obtained by the reaction of *N*-cyclohexylpiperazine (0.39 g, 2.371 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.18, 60 %) m.p. 234-36 °C.

Anal.:

TLC : R_f 0.1 (DCM: Methanol, 19:1)

IR : 3387, 3171, 1647, 1511, 1401, 1259, 1223, 1171, 1017 and 993 cm^{-1}

2-[4-((4-Amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl]benzonitrile (V-5)

Reaction of 1-(2-cyanophenyl)piperazine (0.40 mL, 2.371 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under conditions as described in **Method J** afforded compound (**V-5**) (0.21 g, 68 %) m.p. 137-39 °C.

Anal.:

TLC : R_f 0.76 (DCM: Methanol, 18:2)

IR : 3382, 3132, 2223, 1630, 1513, 1481, 1400, 1265, 1221 and 773 cm^{-1}

NMR : δ 7.57-7.50 (m, 3H, Ar-*H*), 7.19 (b, 2H, NH_2), 7.13 (s, 1H, Ar-*H*), 7.07-7.00 (m, 2H, Ar-*H*), 3.93 (s, 6H, 2 × OCH_3), 3.63 (s, 2H, CH_2), 3.24 (b,4H, CH_2) and 2.77 (b, 4H, CH_2)

MS : m/z 404.8 (M^+ peak)

6,7-Dimethoxy-2-[(4-(2-methoxyphenyl)piperazin-1-yl)methyl]quinazolin-4-amine (V-6)

Compound (**V-6**) was obtained by the reaction of 1-(2 methoxyphenyl)piperazine (0.41 mL, 0.2371 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.22 g, 71 %) m.p. 236-38 °C.

Anal.:

TLC : R_f 0.73 (DCM: Methanol, 19:1)

IR : 3299, 3145, 1661, 1581, 1507, 1334, 1275, 1241, 1138, 1017 and 744 cm^{-1}

NMR : δ 7.58 (s, 1H, Ar-*H*), 7.17 (s, 1H, Ar-*H*), 6.95-6.84(m, 4H, Ar-*H*), 3.96 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2), 3.10 (b, 4H, CH_2) and 2.79 (b, 4H, CH_2)

2-[(4-(2-Fluorophenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (V-7)

Compound (**V-7**) was obtained by the reaction of 1-(2-fluorophenyl)piperazine (0.39 mL, 2.371 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.21 g, 70%) m.p. 217-20 °C dec.

Anal.:

TLC : R_f 0.8 (DCM: Methanol, 18:2)

IR : 3324, 3161, 1654, 1577, 1506, 1408, 1279, 1233, 1134, 1014, 854 and 757 cm^{-1}

NMR : δ 7.59 (s, 3H, Ar-*H* and NH_2), 7.27 (s, 1H, Ar-*H*), 7.07-6.89 (m, 4H, Ar-*H*), 4.00 (s, 6H, 2 × OCH_3), 3.74 (s, 2H, CH_2), 3.17 (b, 4H, CH_2) and 2.81 (b, 4H, CH_2).

6,7-Dimethoxy-2-[(4-(pyridin-2-yl)piperazin-1-yl)methyl]quinazolin-4-amine (V-8)

1-(2-pyridyl)piperazine (0.36 mL, 2.371 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under set of reaction conditions as described in **Method J** to yield compound (**V-8**) (0.19g, 64%) m.p. > 280 °C.

Anal.:

TLC : R_f 0.53 (DCM: Methanol, 18:2)

IR : 3008, 1603, 1553, 1432, 1272, 1240, 1166, 990 and 731 cm^{-1}

4-[4-((4-Amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl]phenol (V-9)

Reaction of 1-(4-hydroxyphenyl)piperazine (0.42g, 2.371 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under a set of conditions described in **Method J** afforded compound (**V-9**) (0.2 g, 63%) m.p. > 280 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 18:2)

IR : 3419, 3190, 1638, 1583, 1510, 1401, 1328, 1255, 1226, 1135 and 987 cm^{-1}

2-[(4-Benzhydrylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-10**)

Compound (**V-10**) was obtained by the reaction of benzhydrylpiperazine (0.5 g, 2.371 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.28, 78%) m.p. 246-48 °C.

Anal.:

TLC : R_f 0.4 (DCM: Methanol, 18:2)

IR : 3490, 3297, 1646, 1572, 1480, 1279, 1252, 1163, 1078, 1001, 856 and 702 cm^{-1}

NMR : δ 7.55 (s, 1H, Ar-*H*), 7.41-7.22 (m, 9H, Ar-*H*), 7.16-7.11 (m, 4H,Ar-*H* and NH_2), 4.22 (s, 1H, C*H*), 3.93 (s, 6H, OCH_3), 3.59 (s, 2H, CH_2),2.64 (b, 4H, CH_2) and 2.42 (b, 4H, CH_2)

Sodium 2-[4-((4-amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-y]benzoate (**V-11**)

Compound (**V-5**) (0.1 g, 0.24 mmol) and aq. solution of conc. H_2SO_4 (5 mL, 60%) were taken in an Rb flask (10 mL). The reaction mixture was heated on water bath. The reaction was monitored by TLC. The reaction mixture was poured in water and basified with sodium hydroxide to get its sodium salt. In order to get the precipitated salt, the reaction mixture was mixed with acetone. The precipitated salt was filtered. The solid residue was then refluxed in methanol. The solution was filtered and filtrate was concentrated to obtain solid compound.m. p. > 280 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 18:2)

MS : m/z 423.48 (M^+ peak)

NMR : δ 7.44 (s, 1H, Ar-*H*), 7.24-7.21 (m, 2H, Ar-*H*), 7.13 (s, 1H, Ar-*H*), 7.05-6.90 (m, 4H, Ar-*H* and NH_2), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2), 3.02 (b, 4H, 2 × CH_2) and 2.61 (b, 4H, 2 × CH_2).

- **Synthesis of 2-[(aryl(alky)amino/heteroaryl)methyl]-6,7-dimethoxyquinazo-lin-4-amine** (**Series VI**)

***N*-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methyl]aniline** (**VI-1**)

Compound (**V1-1**) was obtained by the reaction of aniline (0.32 mL, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.16 g, 65 %) m.p. 181-83 °C.

Anal.:

TLC : R_f 0.53 (DCM: Methanol, 19:1)

IR : 3384, 3126, 1665, 1579, 1510, 1483, 1404, 1254, 1216, 867 and 745 cm^{-1}

NMR : δ 7.57 (s, 1H, Ar-*H*), 7.37 (b, 2H, NH_2), 7.10-7.07 (m, 3H, Ar-*H*), 6.67-6.65 (m, 2H, Ar-*H*), 6.58-6.54 (m, 1H, Ar-*H*), 5.69 (b, 1H, N*H*), 4.21-4.20 (d, 2H, CH_2),3.93 (s, 3H, OCH_3)and3.91 (s, 3H, OCH_3)

MS : m/z 310.5 (M^+ peak)

2-[(3-Toluidino)-*N*-methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-2**)

3-Toluidine (0.54 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under set of reaction conditions described in **Method J** to yield compound (**VI-2**) (0.16 g, 64 %) m.p. 160-62 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3396, 3119, 1644, 1615, 1578, 1506, 1477, 1402, 1270, 1242, 1168, 1132 and 848 cm^{-1}

NMR : δ 7.52 (s, 1H, Ar-*H*), 7.28 (b, 2H, NH_2), 7.03 (s, 1H, Ar-*H*), 6.93- 6.89 (m, 1H, Ar-*H*), 6.43-6.39 (m, 2H, Ar-*H*), 6.34-6.32 (m, 1H, Ar-*H*), 5.52 (b, 1H, N*H*), 4.13-4.12 (d, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3) and 2.16 (s, 3H, CH_3)

2-[(4-Toluidino)-*N*-methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-3**)

4-Toluidine (0.54 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under set of reaction conditions described in **Method J** to yield compound (**VI-3**) (0.17 g, 68%) m.p. 204-207 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3414, 3126, 1668, 1620, 1580, 1518, 1486, 1401, 1254, 1222, 1173, 1014 and 803 cm^{-1}

NMR : δ 7.58 (s, 1H, Ar-*H*), 7.47 (b, 2H, Ar-*H*), 7.11 (s, 1H, Ar-H), 6.91-6.88 (d,2H, Ar-*H*), 6.59-6.57 (d, 2H, Ar-H), 5.57 (s, 1H, N*H*), 4.18 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3) and 2.17 (s, 3H, CH_3)

MS : m/z 324.9 (M^+ peak)

6,7-Dimethoxy-2-[(4-methoxyphenylamino)methyl]quinazolin-4-amine (VI-4)

Reaction of 4-anisidine (1.48 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under set of conditions described in **Method J** afforded compound (**VI-4**) (0.19 g, 72 %) m.p.173-75 °C.

Anal.:

TLC : R_f 0.44 (DCM: Methanol, 19:1)

IR : 3444, 3124, 1659, 1624, 1509, 1402, 1250, 1127, 1030 and 851 cm^{-1}

NMR : δ 7.97-7.97 (b, 2H, NH_2), 7.69-7.67 (d, 2H, Ar-*H*), 7.53 (s, 1H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 6.63-6.60 (d, 2H, Ar-*H*), 6.50 (b, 1H, N*H*), 4.25- 4.24 (d, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3) and 3.71(s, 3H, OCH_3)

3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoic acid (VI-5)

Compound (**V1-5**) was obtained by the reaction of 3-aminobenzoic acid (0.54 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.17 g, 62%) m.p. 249-52 °C.

Anal.:

TLC : R_f 0.2 (DCM: Methanol, 19:1)

IR : 3444, 3322, 3122, 1705, 1662, 1584, 1490, 1279, 1235, 1110, 982, 861 and 749 cm^{-1}

NMR : δ 7.56 (s, 1H, Ar-*H*), 7.35-7.27 (m, 4H, Ar-*H* and NH_2), 7.15-7.11 (m, 1H, Ar-*H*), 7.01 (s, 3H, Ar-*H*), 6.85-6.83 (m, 1H, Ar-*H*), 5.23 (s, 2H, CH_2), 4.92 (b, 1H, N*H*) and 3.93 (s, 6H, 2 × OCH_3)

4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoic acid (**VI-6**)

Compound (**V1-6**) was obtained by the reaction of 4-aminobenzoic acid (0.54 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.18 g, 64%) m.p. 275-80 °C.

Anal.:

TLC : R_f 0.18 (DCM: Methanol, 19:1)

IR : 3425, 3369, 3120, 1673, 1607, 1516, 1493, 1279, 1218, 1169, 1114, 1081, 1018, 873 and 769 cm^{-1}

NMR : δ 7.75-7.73 (d, 2H, Ar-*H*), 7.57 (s, 1H, Ar-*H*), 7.39 (b, 2H, NH_2), 7.04(s, 1H, Ar-*H*), 6.61-6.58 (d, 2H, Ar-*H*), 5.69 (b, 2H, N*H* and O*H*), 5.16 (s, 2H, CH_2) and 3.93 (s, 6H, 2 × OCH_3)

MS : m/z 354.8 (M^+ peak)

Methyl 3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoate (**VI-7**)

Methyl 3-aminobenzoate (0.5 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under set of reaction conditions described in **Method J** to yield compound (**VI-7**) (0.20 g, 69 %) m.p. 146-49 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3343, 3204, 1715, 1650, 1588, 1546, 1511, 1445, 1293, 1228, 1031 and 752 cm^{-1}

NMR : δ 7.52 (s, 1H, Ar-H_d), 7.35 (b, 2H, NH_2), 7.03 (s, 1H, Ar-H), 6.99-6.95 (m, 1H, Ar-H_j), 6.60 (s, 1H, Ar-*H*), 6.54-6.52 (m, 1H, Ar- *H*), 6.46-6.44 (m, 1H, Ar-*H*), 6.08 (b, 1H, N*H*) 4.14 (b, 2H, CH_2), 3.86 (s, 3H, OCH_3) and 3.84(s, 3H, $COOCH_3$).

Methyl 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoate (**VI-8**)

Methyl4-aminobenzoate (0.5 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under reaction conditions as described in **Method J** to yield compound (**VI-8**) (0.20 g, 69 %). m.p. 148-50 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3419, 3133, 1684, 1669, 1603, 1513, 1406, 1321, 1276, 1227, 1175, 1111 and 774 cm^{-1}

NMR : δ 7.51 (s, 1H, Ar-*H*), 7.28-7.18 (b, 2H, NH_2), 7.03 (s, 1H, Ar-H), 6.68-6.65(d, 2H, Ar-*H*), 6.60-6.56 (d, 2H, Ar-*H*), 5.20 (b, 1H, N*H*), 4.11 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3) and 3.61 (s, 3H, COOCH_3)

2-[(3-Nitrophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-9**)

Reaction of 3-nitroaniline (0.54 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under the conditions as described in **Method J** afforded compound (**VI-9**) (0.14g, 52 %) m.p. 223-25 °C.

Anal.:

TLC : R_f 0.53 (DCM: Methanol, 19:1)

IR : 3374, 3125, 1624, 1518, 1400, 1347, 1244 and 1127 cm^{-1}

NMR : δ 7.54 (s, 1H, Ar-*H*), 7.45 (s, 1H, Ar-*H*), 7.33-7.31(m, 3H, Ar-*H* and NH_2), 7.26-7.22 (m, 1H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 7.04-7.01 (m, 1H, Ar-*H*), 6.57-6.55 (t, 1H, N*H*), 4.26-4.25 (d, 2H, CH_2), 3.90 (s, 3H, OCH_3) and 3.84 (s, 3H, OCH_3)

2-[(4-Nitrophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-10**)

Reaction of 4-nitroaniline (0.54 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under the conditions described in **Method J** afforded compound (**VI-10**) (0.15 g, 54 %) m.p. 214 °C dec.

Anal.:

TLC : R_f 0.53 (DCM: Methanol, 19:1)

IR : 3367, 3128, 1623, 1527, 1481, 1405, 1345, 1247, 1168, 990 and 852 cm^{-1}

***N*-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]methane sulfonamide (VI-11)**

Compound (**VI-11**) was prepared by reacting 3-methanesulfonamidoaniline (0.73 g, 3.95 mmol) with compound (**20**) (0.2 g, 0.79 mmol) as per **Method J** (0.18 g, 59 %) m.p. > 280 °C.

Anal.:

TLC : R_f 0.28 (DCM: Methanol, 19:1)

IR : 3450, 3361, 3045, 1673, 1624, 1584, 1489, 1319, 1249, 1147, 1031, 857 and 779 cm^{-1}

NMR : δ 7.57 (s, 1H, Ar-*H*), 7.39 (b, 2H,NH_2), 7.01 (s, 1H, Ar-*H*), 6.93-6.89 (m, 1H, Ar-*H*), 6.75-6.74 (t, 1H, Ar-*H*), 6.58-6.56 (dd, 1H, Ar-*H*), 6.46-6.44 (dd, 1H, Ar-*H*), 4.95-4.93 (d, 2H, 2 × N*H*), 4.76 (s, 2H, CH_2), 3.92 (s,6H, 2 × OCH_3) and 3.30 (s, 3H, CH_3)

MS : m/z 403.8 (M+ peak)

***N*-[4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]methane sulfonamide (VI-12)**

Compound (**VI-12**) was prepared by reacting 4-methanesulfonamidoaniline (0.73 g, 3.95 mmol) with compound (**20**) (0.2 g, 0.79 mmol) as per **Method J** (0.18 g, 59 %) m.p. 206-09 °C.

Anal.:

TLC : R_f 0.31 (DCM: Methanol, 19:1)

IR : 3417, 3144, 1637, 1512, 1401, 1320 and 1153 cm^{-1}

NMR : δ 7.57 (s, 1H, Ar-*H*), 7.40 (b, 2H, NH_2), 7.05 (s, 1H,Ar-*H*), 7.03-7.01 (d, 2H, Ar-*H*), 6.47-6.45 (d,2H, Ar-*H*), 4.90 (b, 2H, 2 × N*H*), 4.69(s, 2H,), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3) and 3.28 (s, 3H, CH_3)

MS : m/z 403.4 (M^+ peak)

***N*-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]acetamide (VI-13)**

Compound (**VI-13**) was obtained by the reaction of 3-acetamidoaniline (0.65 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.15 g, 54 %) m.p. 235-37 °C.

Anal.:

TLC : R_f 0.46 (DCM: Methanol, 19:1)

IR : 3450, 3396, 3124, 1663, 1616, 1511, 1480, 1334, 1276, 1248, 1167, 1032 and 990 cm^{-1}

NMR : δ 7.54 (s, 1H, Ar-*H*), 7.34 (b, 2H, NH_2), 7.07 (s, 2H, Ar-H), 6.97-6.93 (t, 1H, Ar-*H*), 6.70-6.68 (m, 1H, Ar-*H*), 6.33-6.31 (m, 1H, Ar-*H*), 5.62 (b, 1H, N*H*), 4.16 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3)3.90 (s, 3H, OCH_3)and 2.00 (s, 3H, CH_3)

***N*-[4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]acetamide (VI-14)**

Compound (**VI-14**) was obtained by the reaction of 4-acetamidoaniline (0.65 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.16 g, 57 %) m.p. 239 °C dec.

Anal.:

TLC : R_f0.46 (DCM: Methanol, 19:1)

IR : 3362, 3131, 1656, 1622, 1515, 1401, 1373, 1312, 1239, 1165, 1028 and 850 cm^{-1}

NMR : δ 9.39 (b, 1H, N*H*), 7.54 (s, 1H, Ar-*H*), 7.32-7.25 (m, 4H, Ar-H and NH_2), 7.06 (s, 1H, Ar-*H*), 6.58-6.56 (d, 2H, Ar-H), 5.49 (b, 1H, N*H*), 4.15 (s, 2H, CH_2), 3.90(s, 3H, OCH_3), 3.88 (s, 3H,OCH_3) and 1.96 (s, 3H, CH_3)

2-[(3-Chlorophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (VI-15)

4-Chloroaniline (0.41 mL, 3.95 mmol) was reacted with compound (**20**) (0.2 g,

0.79 mmol) under set of reaction conditions described in **Method J** to yield compound (**VI-15**) (0.17 g, 63 %) m.p. 219-21 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3502, 3388, 3321, 1657, 1583, 1509, 1482, 1313, 1258, 1211, 1126 and 864 cm^{-1}

NMR : δ 10.61 (b, 1H, N*H*), 8.39 (s, 1H, Ar-*H*), 8.09-8.07 (m, 1H, Ar-*H*), 7.69-7.67 (m, 2H, Ar-*H*), 7.64 (s, 1H, Ar-*H*), 7.44-7.40 (t, 1H, Ar-*H*), 7.27 (s, 1H, Ar-*H*), 3.92 (s, 3H, OCH_3) 3.91 (s, 3H, OCH_3) and 3.84 (s, 2H, CH_2)

2-[(4-Chlorophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-16**)

4-Chloroaniline (0.5 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under set of reaction conditions described in **Method J** to yield compound (**VI-16**) (0.18 g, 66 %) m.p. 230-32 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3482, 3389, 3316, 1653, 1578, 1507, 1402, 1314, 1256, 1216, 1171, 1091and 1013 cm^{-1}

NMR : δ 7.51 (s, 1H, Ar-*H*), 7.29 (b, 2H, NH_2), 7.03 (s, 1H, Ar-H), 7.02-6.99 (d, 2H, Ar-*H*),6.60-6.58 (d, 2H, Ar-*H*), 5.84 (b, 1H, N*H*), 4.14-4.13 (d, 2H, CH_2), 3.87 (s, 3H, OCH_3) and 3.85 (s, 3H, OCH_3).

3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]bromobenzene (**VI-17**)

Compound (**VI-17**) was obtained by the reaction of 3-bromoaniline (0.41 mL, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.184 g, 60 %) m.p. 234-36 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3421, 3122, 1656, 1611, 1502, 1400, 1344, 1289, 1229, 1167 and 1055 cm^{-1}

NMR : 7.57 (s, 1H, Ar-*H*), 7.47 (s, 2H, NH_2), 7.07 (s, 1H, Ar-*H*), 7.69-7.67 (t, 1H, Ar-*H*), 6.80-6.79 (t, 1H, Ar-*H*), 6.65-6.61 (m, 2H, Ar-*H*), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3) and 3.17 (s, 2H, CH_2).

4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]bromobenzene (**VI-18**)

Compound (**VI-18**) was obtained by the reaction of 4-bromoaniline (0.67 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.18 g, 58 %) m.p. 217-19 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3380, 3127, 1672, 1588, 1493, 1371, 1239, 1168, 1022 and857 cm^{-1}

4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]fluorobenzene (**VI-19**)

Reaction of 4-fluoroaniline (0.44 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under the conditions as described in **Method J** afforded compound (**VI-19**) (0.14 g, 56 %) m.p. 214 °C dec.

Anal.:

TLC : R_f 0.50 (DCM: Methanol, 19:1)

IR : 3383, 3123, 1606, 1506, 1402, 1247, 1214, 992 and 856 cm^{-1}

NMR : δ 7.53 (s, 1H, Ar-*H*), 7.27 (b, 2H, NH_2), 7.05 (s, 1H, Ar-*H*), 6.84- 6.79 (m, 2H, Ar-*H*), 6.63-6.58 (m, 2H, Ar-*H*), 5.54 (b, 1H, N*H*), 4.14 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3) and 3.88 (d, 3H, OCH_3)

1-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]naphthalene (**VI-20**)

1-Naphthylamine (0.56 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under reaction conditions as described in **Method J** to yield compound (**VI-20**) (0.22 g, 80 %) m.p. 235-37 °C.

Anal.:

TLC : R_f 0.40 (DCM: Methanol, 19:1)

IR : 3390, 3129, 1659, 1580, 1510, 1405, 1245, 1167, 1131 and 768 cm^{-1}

NMR : δ 8.16-8.14 (d, 1H, Ar-*H* and N*H*), 7.76-7.75 (d, 1H, Ar-*H*), 7.60 (s, 1H, Ar-*H*), 7.49-7.41 (m, 2H, Ar-*H*), 7.30-7.26 (t, 1H, Ar-*H*), 7.15-7.11 (m, 2H, Ar-*H*), 6.56-6.54 (m, 2H, NH_2), 4.40-4.39 (d, 2H, CH_2), 3.98 (s, 3H, OCH_3) and 3.93 (s, 3H, OCH_3)

MS : m/z 360.6 (M^+ peak)

6,7-Dimethoxy-2-[(pyridin-2-ylamino)methyl]quinazolin-4-amine (VI-21)

Compound (**VI-21**) was obtained by the reaction of 2-aminopyridine (0.37 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.13 g, 52 %) m.p. 210-14 °C dec.

Anal.:

TLC : R_f 0.13 (DCM: Methanol, 19:1)

IR : 3343, 3134, 1673, 1586, 1516, 1486, 1435, 1249, 1207, 1170, 1034, 866 and 775 cm^{-1}

NMR : δ 7.97 (b, 1H), 7.74 (b, 2H), 7.59 (s, 1H, Ar-*H*), 6.99-6.96 (d, 1H, Ar-*H*), 6.85 (s, 1H, Ar-*H*), 6.72 (s, 1H), 5.31 (s, 2H, CH_2) and 3.85 (s, 6H, 2 × OCH_3).

6,7-Dimethoxy-2-[(pyridin-3-ylamino)methyl]quinazolin-4-amine (VI-22)

Compound (**VI-22**) was obtained by the reaction of 3-aminopyridine (0.37 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.10 g, 44 %) m.p. 220-24 °C dec.

Anal.:

TLC : R_f 0.13 (DCM: Methanol, 19:1)

IR : 3339, 3190, 1635, 1585, 1511, 1403, 1250, 1208, 1118 and1028 cm^{-1}

6,7-Dimethoxy-2-[(pyridin-4-ylamino)methyl]quinazolin-4-amine (VI-23)

Compound (**VI-23**) was obtained by the reaction of 4-aminopyridine (0.37 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.15 g, 56 %) m.p. > 280 °C.

Anal.:

TLC : R_f 0.13 (DCM: Methanol, 19:1)

IR : 3221, 3110, 1675, 1587, 1514, 1481, 1395, 1256, 1216, 1094, 995 and 849 cm^{-1}

NMR : δ 8.16-8.14 (m, 2H, Ar-*H*), 7.59 (s, 1H, Ar-*H*), 6.93 (m, 3H, Ar-*H*), 5.32 (s, 2H, CH_2), 3.90 (d, 6H, 2 ×OCH_3) and 3.33 (b, 3H, N*H* and NH_2)

6,7-Dimethoxy-2-(4-morpholinomethyl)quinazolin-4-amine (**VI-24**)

Reaction of morpholine (0.31 mL, 3.95mmol) and compound (**20**) (0.2 g, 0.79 mmol) under the conditions as described in **Method J** afforded compound (**VI-24**) (0.17 g, 72 %) m.p. 231-33 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3310, 3132, 1670, 1620, 1482, 1323, 1249, 1211, 1113 and 852 cm^{-1}

NMR : δ 7.86 (s, 1H, Ar-*H*), 7.14 (s, 1H, Ar-*H*), 7.05 (b, 2H, NH_2), 3.95 (s, 6H, 2 × OCH_3), 3.71-3.69 (t, 4H, CH_2), 3.57 (s, 2H, CH_2) and 2.58-2.57 (b, 4H, 2 × CH_2)

6,7-Dimethoxy-2-[(piperidin-1-yl)methyl]quinazolin-4-amine (**VI-25**)

Reaction of piperidine (0.39 mL, 3.9 mmol) and compound (**20**) (0.2 g, 0.79 mmol) under the conditions as described in **Method J** afforded compound (**VI-25**) (0.16 g, 67 %) m.p. 232-34 °C.

Anal.:

TLC : R_f 0.16 (DCM: Methanol, 19:1)

IR : 3316, 3133, 1670, 1579, 1508, 1433, 1244, 1209, 1167, 1115, 860 and 781 cm^{-1}

6,7-Dimethoxy-2-[(1*H*-1,2,4-triazol-1-yl)methyl]quinazolin-4-amine (**VI-26**)

Compound (**VI-26**) was obtained by the reaction of 1,2,4-triazole (0.27 g, 3.95

mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.13 g, 56 %) m.p. 235-40 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3401, 3338, 1671, 1588, 1492, 1422, 1266, 1233, 1215, 1036 and 846 cm^{-1}

NMR : δ 8.52 (s, 1H, Ar-*H*), 7.89 (s, 1H, Ar-*H*), 7.62 (s, 1H, Ar-*H*), 7.10 (s, 1H, Ar-*H*), 5.45 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3) and 3.95 (s, 3H, OCH_3)

6,7-Dimethoxy-2-[(pyrrolidin-1-yl)methyl]quinazolin-4-amine (**VI-27**)

Compound (**VI27**) was obtained by the reaction of pyrrolidine (0.28 g, 3.95 mmol) and compound (**20**) (0.2 g, 0.79 mmol) as per general **Method J** (0.13 g, 56 %) m.p. 201-03 °C.

Anal.:

TLC : R_f 0.23 (DCM: Methanol, 19:1)

IR : 1685, 1562, 1510, 1415, 1340, 1245, 1163 and 1130 cm^{-1}

NMR : δ 7.53 (s, 1H, Ar-*H*), 7.37 (b, 2H, NH_2), 7.06 (s, 1H, Ar-*H*), 3.87(s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.54 (s, 2H, CH_2), 2.51-2.50 (m, 4H, CH_2) and 1.67-1.64 (m, 4H, CH_2)

2-[(1*H*-Benzimidazol-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine(**VI-28**)

Benzimidazole (0.46 g, 3.95 mmol) was reacted with compound (**20**) (0.2 g, 0.79 mmol) under set of reaction conditions described in **Method J** to yield compound (**VI-28**) (0.14 g, 54 %) m.p. 234-36 °C.

Anal.:

TLC : R_f 0.56 (DCM: Methanol, 19:1)

IR : 3295, 3122, 1680, 1585, 1495, 1416, 1256, 1203, 997, 868 and 742 cm^{-1}

NMR : δ 8.33 (s, 1H, Ar-H), 7.68-7.66 (m, 3H, Ar-*H* and NH_2), 7.59 (s, 1H, Ar-*H*), 7.49-7.46 (m, 1H, Ar-H), 7.21-7.19 (m, 2H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 5.46 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3)and3.90(s, 3H, OCH_3)

5.2 Biological work

General

The study was conducted on healthy wistar rats of either sex weighing 200-250 g. The animals were housed in an air-conditioned room (22±2°C) in polypropylene cages in groups of 3 each. The animals were maintained on commercial pelleted rat chow and tapwater *ad libitum*. They were housed in 12 hr light/12 hr dark cycle. The study protocol was approved by the Institutional Animal Ethics Committee of the Pharmacy Dept., The Maharaja Sayajirao University of Baroda. All the experiments were carried out in accordance with the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India. The work has been carried out in the pharmacology section of the department and not by the candidate himself.

In vitro study

Animals were sacrificed by cervical dislocation.Descending thoracic aortas were removed immediately and placed in ice-cold Kreb's bicarbonate solution of the following composition (mM): NaCl 112, $NaHCO_3$ 12, glucose 11.1, KCl 5.0, $MgSO_4$ 1.2, KH_2PO_4 1.0 and $CaCl_2$ 2.5. The tissue was aerated with 95% O_2 and 5% CO_2. Peri-adventitious tissue was removed, taking care not to stretch the tissue. A spinal needle was inserted in the tissue and rotated gently to denude the endothelium. Following this, the tissue was cut spirally into a helical strip (20 mm × 3 mm) using a surgical blade. The strip was tied at both ends using a cotton thread and suspended in a 25 ml organ tube under an initial resting tension of 2 g. The *p*H of the Kreb's solution was 7.4 and maintained at 37°C using a thermostat. The Kreb's solution in the organ tube was changed every 10 mins during an equilibration period of about 90 mins. Denudation of the endothelium was confirmed by observing the "absence of relaxation" on strips precontracted with phenylephrine. Isometric contractions were recorded using a force transducer (UGO BASILE, Italy) coupled to a Gemini 7070 recorder (UGO BASILE, Italy).Contractions were induced in rat aortic strips with graded, cumulative concentrations of phenylephrine or ang II. Test compounds (10 μM) or vehicle were added to the organ tubes atleast 30

mins prior to the addition of either phenylephrine or ang II. pA_2 Values were calculated by the method described by Arunlakshana and Schild, 1959.[407]

1. WHO guideline Global health risks: mortality and burden of disease attributable to selected major risks, **2009**.
2. Kearney, P. M.; Whelton, M.; Reynolds, K.; Muntner, P.; Whelton, P. K.; He, J., *Lancet*, **2005**, 365, 217–23.
3. Williams, B., *JACC*, **2006**, 48, 1698.
4. Carey, R. M., AT_1 Receptors, Angiotensin Receptor Blockade, and Clinical Hypertensive Disease. In Renin Angiotensin System and Cardiovascular Disease, Contemporary Cardiology; DeMello, W. C., Frohlich, Eds; Humana Press, **2009**; pp. 59–79.
5. Cohuet, G.; Struijker-Boudier, H., *Pharmacol. Ther.*, **2006**, 111, 81.
6. Taddei, S.; Virdis, A.; Mattei, P.; Arzilli, F.; Salvetti, A., *J. Cardiovasc. Pharmacol.*, **1992**, 20 (Suppl 12), S193.
7. Safar, M. E.; Laurent, S.; Pannier, B. M.; London, G. M., *J. Clin. Hypertens.*, **1987**, 3, 360.
8. Kaplan, N. M. Treatment of hypertension: drug therapy. in Clinical Hypertension, Williams & Wilkins, **1994**
9. Neutel, J. M.; Smith, D. H., *Am. J. Hypertens.*, **1999**, 12, 164S.
10. Sever, P. S.; Messerli, F. H., *European Heart J.*, **2011**doi:10.1093/eurheartj/ehr177.
11. Fries, E. D., Historical development of antihypertensive treatment. In Hypertension: pathophysiology, diagnosis and management, Eds; Raven press **1995**; pp. 2741-2751.
12. Bakris, G.; Frohlich, E. D., *JACC*, **1989**, 14, 1595.
13. Schlaich, M. P.; Krum, H.; Esler, M. D., *Curr. Hypertens. Rep.*, **2010**, 12, 296.
14. Grandi, A. M., *Curr. Pharm. Design*, **2005**, 11, 2235.
15. Yanagisawa, M.; Kurihara, H.; Kimura, S., *Nature*, **1988**, 332, 411.
16. Fujisaki, H.; Ito, H.; Hirata, Y. Tanaka, M.; Hata, M.; Lin, M.; Adachi, S.; Akimoto, H.; Marumo, F.; Hiroe, M., *J. Clin. Invest.*, **1995**, 96, 1059.
17. Ergul, A., *Expert. Opin. Ther.*, **2003**, 13, 33.
18. Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R., *Nature*, **1976**, 263, 663.
19. Moncada, S.; Vane, J. R., *N. Engl. J. Med.*, **1979**, 300, 1142.
20. Nagaya, N., *Am. J. Cardiovasc. Drugs*., **2004**, 4, 75.
21. UP John Co., US Patent, 20050059660A1, **2005**.

22. Hasuda, T.; Satoh, T.; Shimouchi, A.; Sakamaki, F.; Kyotani, S.; Matsumoto, T.; Goto, Y.; Nakanishi, N., *Circulation*, **2000**, 101, 2066.
23. The JNC Seventh Report: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, **2003**.
24. Cohn, J. N.; Archibald, D. G.; Ziesche, S.; Franciosa, J. A.; Harston, W. E.; Tristani, F. E.; Dunkman, W. B.; Jacobs, W.; Francis, G. S.; Flohr, K. H., *N. Engl. J. Med.*, **1986**, 314, 1547.
25. Bakris, G. L., *Am. J. Hypertens.*, **2003**, 16, 7S.
26. Neutel, J. M., *Am. J. Med.*, **1996**, 101, 71S.
27. http://www.aafp.org/afp/20000515/3049.html
28. Alcocer, L.; Bendersky, M.; Acosta, J.; Urina-Triana, M., *Am. J. Cardiovasc. Drugs*, **2010**, 10, 143.
29. Prisantmd, L. M., *Clin. Cardiol.*, **2009**, 32, 4.
30. Maggioni, A. P.; Anand, I.; Gottlieb, S. O.; Latini, R.; Tognoni, G.; Cohn, J. N., *J. Am. Coll. Cardiol.*, **2002**, 40, 1414.
31. Brenner, B. M.; Cooper, M. E.; de Zeeuv, D.; Keane, W. F.; Mitch, W. E. Parving, H. H.; Remuzzi, G.; Snapinn, S. M.; Zhang, Z.; Shahinfar, S., *N. Engl. J. Med.*, **2001,** 345, 861.
32. Lewis, E. J.; Hunsicker, L. G.; Clarke, W. R.; Berl, T.; Pohl, M. A. Lewis, J. B.; Ritz, E. ; Atkins, R. C.; Rohde, R.; Raz, I., *N Engl J. Med*, **2001**, 345, 851.
33. Pitt, B.; Poole-Wilson, P. A.; Segal, R.; Martinez, F. A.; Dickstein, K. Camm, A. J.; Konstam, M. A.; Riegger, G.; Klinger, G. H.; Neaton, J.; Sharma, D.; Thiyagarajan, B., *Lancet*, **2000**, 355, 1582.
34. Yusuf, S.; Granger, C. B.; McMurray, J. J.; Held, P.; Michelson, E. L. Yusuf, S.; Pfeffer, M. A.; Swedberg, K.; Granger, C. B.; Held, P.; McMurray, J. J.; Michelson, E. L.; Olofsson, B.; Ostergren, J., *Lancet*, **2003**, 362, 777.
35. Lithell, H.; Hansson, L.; Skoog, I.; Elmfeldt, D.; Hofman, A. Olofsson, B.; Trenkwalder, P.; Zanchetti, A., *J. Hypertens.*, **2003**, 21, 875.
36. Dickstein, K.; Kjekshus, J., *Lancet*, **2002**, 360, 752.
37. Pfeffer, M. A.; McMurray, J. J.; Velazquez, E. J.; Rouleau, J. L.; Kober, L. Maggioni, A. P.; Solomon, S. D.; Swedberg, K.; Vande Werf, F.; White, H.;

Leimberger, J. D.; Henis, M.; Edwards, S.; Zelenkofske, S.; Sellers, M. A.; Califf, R. M., *N. Engl. J. Med.*, **2003**, 349, 1893.

38. Cohn, J. N.; Tognoni, G., *N. Engl. J. Med.*, **2001**, 345, 1667.
39. Julius, S.; Kjeldsen, S. E.; Weber, M.; Brunner, H. R.; Ekman, S.; Hansson, L. Hua, T.; Laragh, J.; McInnes, G. T.; Mitchell, L.; Plat, F.; Schork, A.; Smith, B.; Zanchetti, A., *Lancet*, **2004**, 363, 2022.
40. Schrader, J.; Luders, S.; Kulschewski, A.; Hammersen, F.; Plate, K. Plate, K.; Berger, J.; Zidek, W.; Dominiak, P.; Diener, H. C., *Stroke*, **2005**, 36, 1218.
41. Hansson, L.; Lindholm, L. H.; Ekbom, T.; Dahlof, B.; Lanke, J.; Schersten, B. Wester, P. O.; Hedner, T.; de Faire, U., *Lancet*, **1999**, 354, 1751.
42. Hansson, L.; Lindholm, L. H.; Niskanen, L.; Lanke, J.; Hedner, T.; Niklason, A. Luomanmäki, K.; Dahlöf, B.; de Faire, U.; Mörlin, C.; Karlberg, B. E.; Wester, P. O.; Björck, J. E., *Lancet*, **1999**, 353, 611.
43. Yusuf, S.; Sleight P.; Poque J. Bosch, J.; Davies, R.; Dagenais, G., *N. Engl. J. Med.*, **2000**, 342, 145.
44. PROGRESS Collaborative Group, *Lancet*, **2001**, 358, 1033.
45. Wing, L. M. H.; Reid, C. M.; Ryan, P.; Beilin, L. J.; Brown, M. A.; Jennings, G. L. Johnston, C. I.; McNeil, J. J.; Macdonald, G. J.; Marley, J. E.; Morgan, T. O.; West, M. J., *N. Engl. J. Med.*, **2003**, 348, 583.
46. Flather, M. D.; Yusuf, S.; Kober, L.; Pfeffer, M.; Hall, A. Murray, G.; Torp-Pedersen, C.; Ball, S.; Pogue, J.; Moyé, L.; Braunwald, E., *Lancet*, **2000**, 355, 1575.
47. Barrios, V.; Escobar, C., *Am J Cardiovasc Drugs*, **2010**, 10, 349.
48. Stanton, A.; Jensen, C.; Nussberger, J. O'Brien, E., *Hypertension*, **2003**, 42, 1137.
49. Gradman, A. H.; Schmieder, R. E.; Lins, R. L., *Circulation*, **2005**, 111, 1012.
50. Zaman, M. A.; Oparil, S.; Calhoun, D. A., *Nat. rev. drug disc.*, **2002,** 1, 621.
51. file:///F:/Paper/Designed%20Multiple%20Agents/Clinical%20trial/Drug/Speedel%20Reports%20Successful%20SPP635%20Phase%20IIa%20Trial%20in%20Hypertension%20-%20Drugs _com %20MedNews.htm)
52. MacFadyen, R. J.; Barr, C. S.; Struthers, A. D., *Cardiovasc Res.*, **1997**, 35, 30.
53. Grandi, A. M.; Imperiale, D.; Santillo, R. Barlocco, E.; Bertolini, A.; Guasti, L.; Venco, A., *Hypertension*, **2002**, 40, 647.

54. Chrysostomou, A.; Becker, G., *N. Engl. J. Med.*, **2001**, 345, 925.
55. Weinberger, M. H.; Roniker, B.; Krause, S. L. Weiss, R. J., *Am J Hypertens.*, **2002**, 15, 709.
56. Burgess, E. D.; Lacourciere, Y.; Ruilope-Urioste, L. M. Oparil, S.; Kleiman, J. H.; Krause, S.; Roniker, B.; Maurath, C., *Clin. Ther.*, **2003**, 25, 2388.
57. Pitt, B.; Reichek, N.; Willenbrock, R. Zannad, F.; Phillips, R. A.; Roniker, B.; Kleiman, J.; Krause, S.; Burns, D.; Williams, G. H., *Circulation.*, **2003**, 108, 1831.
58. Grandi, A. M., *Curr. Pharmaceut Design*, **2005**, 11, 2235.
59. Magni, P.; Motta, M., *Curr. Hypertens. Rep.*, **2005**, 7, 206.
60. Pratt-Ubunama, M. N.; Nishizaka, M. K.; Calhoun, D. A., *Curr. Hypertens. Rep.*, **2005**, 7, 186.
61. Reyes, A. J.; Leary, W. P.; Crippa, G., *Eur. J. Intern. Med.*, **2005**, 16, 3.
62. Burgess, E., *Expert. Opin. Pharmacother.*, **2004**, 5, 2573.
63. White, W. B.; Duprez, D.; St Hillaire, R.; Krause, S.; Roniker, B.; Kuse-Hamilton, J.; Weber, M. A., *Hypertension*, **2003**, 41, 1021.
64. Williams, G. H.; Burgess, E.; Kolloch, R. E.; Ruilope, L. M.; Niegowska, J.; Kipnes, M. S.; Roniker, B.; Patrick, J. L.; Krause, S. L., *Am. J. Cardiol.*, **2004**, 93, 990.
65. Weinberger, M. H.; White, W. B.; Ruilope, L. M.; MacDonald, T. M.; Davidson, R. C.; Roniker, B.; Patrick, J. L.; Krause, S. L., *Am. Heart J.*, **2005**, 150, 426.
66. Krum, H.; Nolly, H.; Workman, D.; He, W.; Roniker, B.; Krause, S.; Fakouhi, K., *Hypertens.*, **2002**, 40, 117.
67. Pitt, B. White, H.; Nicolau, J.; Martinez, F.; Gheorghiade, M.; Aschermann, M.; van Veldhuisen, D. J.; Zannad, F.; Krum, H.; Mukherjee, R.; Vincent, J., *J. Am. Coll. Cardiol.*, **2005**, 46, 425.
68. Zannad, F.; McMurray, J. J.; Drexler, H.; Krum, H.; van Veldhuisen, D. J.; Swedberg, K.; Shi, H.; Vincent, J.; Pitt, B., *Eur. J. Heart Fail.*, **2010,** 12, 617.
69. Francis, G. S.; Benedict, C.; Johnstone, D. E. Kirlin, P. C.; Nicklas, J.; Liang, C. S.; Kubo, S. H.; Rudin-Toretsky, E.; Yusuf, S., *Circulation*, **1990**, 82, 1724.
70. Szatalowicz, V. L.; Arnold, P. E.; Chaimovitz, C. Bichet, D.; Berl, T.; Schrier, R. W., *N. Engl. J. Med.*, **1981,** 305, 263.

71. Goldsmith, S. R.; Francis, G. S.; Cowley, A. W. Cowley, A. W. Jr.; Levine, T. B.; Cohn, J. N., *J. Am. Coll. Cardiol.*, **1983**, 1, 1385.
72. Bichet, D. G., *Kidney Int.*, **1996**, 49, 1706.
73. Thibonnier, M.; Conarty, D. M.; Preston, J. A. Wilkins, P. L.; Berti-Mattera, L. N.; Mattera, R., *Adv. Exp. Med. Biol.*, **1998,** 449, 251.
74. Walker, B. R.; Childs, M. E.; Adams, E. M., *Am. J. Physiol.*, **1988**, 255, H261.
75. Jard, S., *Kidney Int. suppl.*, **1988**, 26, S38.
76. Russell, S. D.; DeWald, T., *Am. J. Cardiovasc. Drugs*, **2003**, 3, 13.
77. Paulis, L.; Unger, T., *Nat. Rev. Cardiol.*, **2010**, 7, 431.
78. Gheorghiade, M.; Konstam, M. A.; Burnett, J. C. Jr. Grinfeld, L.; Maggioni, A. P.; Swedberg, K.; Udelson, J. E.; Zannad, F.; Cook, T.; Ouyang, J.; Zimmer, C.; Orlandi, C., *JAMA.*, **2007**, 297, 1332.
79. Yanagisawa, M.; Kurihara, H.; Kimura, S., *Nature*, **1988**, 332, 411.
80. Fujisaki, H.; Ito, H.; Hirata, Y. Tanaka, M.; Hata, M.; Lin, M.; Adachi, S.; Akimoto, H.; Marumo, F.; Hiroe, M., *J. Clin. Invest.*, **1995**, 96, 1059.
81. Spieker, L. E.; Noll, G.; Ruschitzka, F. T., *J. Am. Coll. Cardiol.*, **2001**, 37, 1493.
82. Ergul, A., *Expert. Opin. Ther. pat.*, **2003**, 13, 33.
83. Weber, M. A.; Black, H.; Bakris, G. Krum, H.; Linas, S.; Weiss, R.; Linseman, J. V.; Wiens, B. L.; Warren, M. S.; Lindholm, L. H., *Lancet.*, **2009**, 374, 1423.
84. Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R., *Nature*, **1976**, 263, 663.
85. Moncada, S.; Vane, J. R., *N. Engl. J. Med.*, **1979,** 300, 1142.
86. Nagaya, N., *Am. J. Cardiovasc. Drugs*, **2004,** 4, 75.
87. Califf, R. M.; Adams, K. F.; McKenna, W. J., *Am. Heart J.*, **1997**, 134, 44.
88. Tamargo, J.; Duarte, J.; Caballero, R. Delpón, E., *Curr. Opin. Investig. Drugs*, **2010**, 11, 1039.
89. Schermuly, R. T.; Janssen, W.; Weissmann, N., *Expert Opin. Investig. Drugs*, **2011**, 20, 567.
90. Hasuda, T.; Satoh, T.; Shimouchi, A.; Sakamaki, F.; Kyotani, S.; Matsumoto, T.; Goto, Y.; Nakanishi, N., *Circulation*, **2000**, 101, 2066.
91. Segura, J.; Praga, M.; Campo, C. Rodicio, J. L.; Ruilope, L. M., *J. Renin Angiotensin Aldosterone Syst.*, **2003**, 4, 43.

92. Ruzicka, M.; Leenen, F. H., *Can. J. Cardiol.*, **2002**, 18, 1317.

93. Fox, J. C.; Leight, K.; Sutradhar, S. C. Demopoulos, L. A.; Gleim, G. W.; Lewin, A. J.; Bakris, G. L., *J. Clin. Hypertens.* (Greenwich), **2004**, 6, 437.

94. Cooper-Dehoff, R. M.; Zhou, Q.; Pepine, C. J., *Am. J. Hypertens.*, **2005**, 18, 104A.

95. Weber, M. A., *Am. J. Hypertens.*, **2005**, 18, 96A.

96. Abbott, K. C.; Bakris, G. L., *Med. Clin. North. Am.*, **2004**, 88, 189.

97. Bakris, G. L., *Am. J. Hypertens.*, **2005**, 18, 267A.

98. Chrysant, S. G., *Clin. Drug Investig.*, **2008**, 28, 713.

99. Hollenberg, N. K.; Mickiewicz, C. W., *Am. J. Cardiol*., **1990**, 63, 37B.

100. Alviar, C. L.; Devarapally, S.; Romero, J.; Benjo, A. M.; Nadkarni, G.; Javed, F., *ASH*, **2010**

101. Julius, S.; Kjeldsen, S. E.; Brunner, H.; Hansson, L.; Platt, F., *Am. J. Hypertens.*, **2003**, 7, 544.

102. Cooper-DeHoff, R. M.; Pepine, C. J., *Evid. Based Med.*, **2010**, 15, 92.

103. Hasegawa, Y.; Shimada, K.; Yamaguchi, T. (J-PADOC), **2010**, 19, 10.

104. Cohn, J. N.; Goldman, J. M., *Am. J. Hypertens.*, **2008**, 21, 248.

105. Mogensen, C. E.; Neldam, S.; Tikkanen, I.; Oren, S.; Viskoper, R.; Watts, R. W.; Cooper, M. E., *BMJ*, **2000**, 321, 9.

106. McKelvie, R. S.; Rouleau, J. L.; White, M.; Afzal, R.; Young, J. B.; Maggioni, A. P.; Held, P.; Yusuf, S., *Eur. Heart J.*, **2003**, 24, 1727.

107. McMurray, J. J.; Ostergren, J.; Swedberg, K.; Granger, C. B.; Held, P.; Michelson, E. L.; Olofsson, B.; Yusuf, S.; Pfeffer, M. A., *Lancet*, **2003**, 362, 767.

108. Pfeffer, M. A.; Swedberg, K.; Granger, C. B.; Held, P.; McMurray, J. J.; Michelson, E. L.; Olofsson, B.; Ostergren, J.; Yusuf, S.; Pocock, S., *Lancet*, **2003**, 362, 759.

109. Cice, G.; Di Benedetto, A.; D'Isa, D.; D'Andrea, A.; Bonanno, D.; Pacchiano, G.; d'Amato, R.; Marcelli, D.; Gatti, E.; Calabrò, R., The XLII ERA/EDTA Congress. Istanbul, Turkey, **2005**.

110. Mogensen, C. E.; Neldam, S.; Tikkanen, I.; Oren, S.; Viskoper, R.; Watts, R. W.; Cooper, M. E., *BMJ*, **2000**, 321, 1440.

111. Andersen, N. H.; Poulsen, P. L.; Knudsen, S. T.; Poulsen, S. H.; Eiskjaer, H.; Hansen, K. W.; Helleberg, K.; Mogensen, C. E., *Diabetes Care*, **2005**, 28, 273.

112. Rossing, K.; Jacobsen, P.; Pietraszek, L.; Parving, H. H., *Diabetes Care*, **2003**, 26, 2268.
113. Chrysant, S. G., *Drugs Today*, **2008**, 44, 443.
114. Chrysant, S. G., *J. Clin. Hypertens.* (Greenwich), **2008**, 10, 716.
115. Fogari, R.; Zoppi, A.; Derosa, G. Mugellini, A.; Lazzari, P.; Rinaldi, A.; Fogari, E.; Preti, P., *J. Hum. Hypertens.*, **2007**, 21, 220.
116. Messerli, F. H., *Am. J. Hypertens.*, **2001**, 14, 978.
117. Littlejohn, T. W. IIIrd ; Majul, C. R.; Olvera, R., *J. Clin. Hypertens.* (Greenwich), **2009**, 11, 207.
118. Chrysant, S. G., *Am. J. Cardiovasc. Drugs*, **2010**, 10, 315.
119. Chrysant, S. G.; Sugimoto, D. H.; Lefkowitz, M.; Salko, T.; Khan, M.; Arora, V.; Shi, V., *Blood Press suppl.*, **2007**, (Suppl 1), 10.
120. Dahlof, B., *J. Hum. Hypertens.*, **2009**, 23, 77.
121. Solomon, S. D.; Appelbaum, E.; Manning, W. J.; Verma, A.; Berglund, T.; Lukashevich, V.; Cherif Papst, C.; Smith, B. A.; Dahlof, B., *Circulation*, **2009**, 119, 530.
122. Ohta, Y.; Tsuchihashi, T.; Onaka, U.; Eto, K.; Ueno, M., *Hypertens. Res.*, **2007**, 30, 301.
123. Chapman, N.; Chang, C. L.; Dahlof, B.; Sever, P. S.; Wedel, H.; Poulter, N. R., *Circulation*, **2008**, 118, 42.
124. Wykretowicz, A.; Guzik, P.; Wysocki, H., *Expert. Opin. Pharmacother.*, **2008**, 9, 625.
125. Staessen J. Lijnen, P.; Fagard, R.; Verschueren, L. J.; Amery, A., *J. Endocrinol.*, **1981**, 91, 457.
126. Borghi, C.; Boschi, S.; Ambrosioni, E., *J. Clin. Pharmacol.*, **1993**, 33, 40.
127. Pharmacia and Upjohn Co., US Patent, 20050059660A1, **2005**.
128. Skolnik, N. S.; Beck, J. D.; Clark, M., *Am. Fam. Physician*, **2000**, 61, 3049.
129. Glass G., *Nat. Rev. Drug Discov.*, **2004**, 3, 731.
130. Edwards, I. R.; Aronson, J. K., *Lancet*, **2000**, 356, 1255.
131. Morphy, R.; Key, C.; Rankovic, Z., *Drug Discov. Today*, **2004**, 9, 641.
132. Portoghese, P. S., *J. Med. Chem.*, **2001**, 44, 2259.

133. Buijsman, R. C.; Basten, J.E.; van Dinther, T. G.; van der Marel, G. A.; van Boeckel,C. A.; van Boom, J. H., *Bioorg. Med. Chem. Lett.*, **1999**, 9, 2013.
134. Morphy, R.; Rankovic, Z., *Curr. Pharmaceut. Design*, **2009**, 15, 587.
135. Morphy, R.; Rankovic, Z., *J. Med. Chem.*, **2005**, 48, 6524.
136. Giugliano, D.; Marfella, R.; Acampora, R. Giunta, R.; Coppola, L.; D'Onofrio, F., *Diabetes Care*, **1998**, 21, 631.
137. Bakris, G. L.; Fonseca, V.; Katholi, R. E. McGill, J. B.; Messerli, F. H.; Phillips, R. A.; Raskin, P.; Wright, J. T. Jr., Oakes, R.; Lukas, M. A.; Anderson, K. M.; Bell, D. S., *JAMA*, **2004**, 292, 2227.
138. Lessem, J. N.; Weber, M. A., *J. Hypertens. Suppl*, **1993**, 11, S29.
139. Mazza, A.; Gil-Extremera, B.; Maldonato, A. Toutouzas, T.; Pessina, A. C., *Blood Press*, **2002**, 11, 182.
140. Czuriga, I.; Riecansky, I.; Bodnar, J. Fulop, T.; Kruzsicz, V.; Kristof, E.; Edes, I., *Cardiovasc. Drugs Ther.*, **2003**, 17, 257.
141. Rosei, E. A.; Rizzoni, D.; Comini, S. Boari, G., *Blood Press. Suppl*., **2003**, 1, 30.
142. Zanchetti, A., *Blood Press. Suppl.*, **2004**, 1, 17.
143. Weiss, R. J.; Weber, M. A.; Carr, A. A., *Am. J. Hypertens*., **2005**, 18, 96A.
144. Georgescu, A.; Pluteanu, F.; Flonta, M-L. Badila, E.; Dorobantu, M.; Popov, D., *Eur. J. Pharmacol.*, **2005**, 508, 159.
145. Flather, M. D.; Shibata, M. C.; Coats, A. J.; Van Veldhuisen, D. J.; Parkhomenko, A.; Borbola, J.; Cohen-Solal, A.; Dumitrascu, D.; Ferrari, R.; Lechat, P.; Soler-Soler, J.; Tavazzi, L.; Spinarova, L.; Toman, J.; Böhm, M.; Anker, S. D.; Thompson, S. G.; Poole-Wilson, P. A., *Eur. Heart J*., **2005**, 26, 215.
146. Jacob, S.; Balletshofer, B.; Henriksen, E. J Volk, A.; Mehnert, B.; Löblein, K.; Häring, H. U.; Rett, K., *Blood Press.*, **1999**, 8, 261.
147. Cleophas, T. J.; vdMey, N.; Meulen, J. Niemeyer, M. G., *Am. J. Ther*., **1997**, 4, 117.
148. Erley, C. M.; Klass, M.; Kramer, D. Berger, E.; Heyne, N.; Braun, N.; Wolf, S.; Risler, T., *Int. J. Clin. Pharmacol. Ther.*, **1996**, 34, 504.
149. Iwaki, K.: Nakashima, M.; Kishi, M., *Cardiovascular Drug Reviews*, **1997**,15, 299
150. Worthley, M. I.; Corti, R.; Worthley, S. G., *Brit. J. Clinical Pharmacol.*, **2003**, 57, 27.

151. Segura, J.; Ruilope, L. M., *Curr. Hypertens. Rep.*, **2011**, 13, 74.
152. Ruilope, L. M.; Dukat, A.; Bhm, M.; Lacourcire, Y.; Gong, J.; Lefkowitz, M. P., *Lancet*, **2010**, 375, 1255.
153. Trippodo, N. C.; Robl, J. A.; Asaad, M. M. Bird, J. E.; Panchal, B. C.; Schaeffer, T. R.; Fox, M.; Giancarli, M. R.; Cheung, H. S., *J. Pharmacol. Exp. Ther.*, **1995**, 275, 745.
154. French, J. F.; Anderson, B. A.; Downs, T. R.; Dage, R. C., *J. Cardiovasc. Pharmacol.*, **1995**, 26, 107.
155. Fournie-Zaluski, M. C.; Coric, P.; Thery, V. Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J. B.; Roques, B. P., *J. Med. Chem.*, **1996**, 39, 2594.
156. Fink, C. A.; Carlson, J. E.; McTaggart, P. A. Qiao, Y.; Webb, R.; Chatelain, R.; Jeng, A. Y.; Trapani, A. J., *J. Med. Chem.*, **1996**, 39, 3158.
157. Gonzalez, W.; Fournie-Zaluski, M. C.; Turcaud, S., *Cardiovasc. Drug Rev.*, **1996**, 14, 166.
158. Weber, M. A., *Lancet*, **2001**, 358, 1525.
159. Seymour, A. A.; Swerde, J. N.; Abboa-Offei, B., *J. Cardiovasc. Pharmacol.*, **1991**, 17, 456.
160. Margulies, K. B.; Perrella, M. A.; McKinley, L. J.; Burnett, J. C. Jr., *J. Clin. Invest.*, **1991**, 88, 1636.
161. Pham, I.; Gonzalez, W.; Amrani, A. I.; Fournié-Zaluski, M. C.; Philippe, M.; Laboulandine, I.; Roques, B. P.; Michel, J. B., *J. Pharmacol. Exp. Ther.*, **1993**, 265, 1339.
162. Seymour, A. A.; Asaad, M. M.; Lanoce, V. M., *J. Pharm. Exper. Ther.*, **1993**, 266, 872.
163. Trippodo, N. C.; Fox, M.; Natarajan, V. Panchal, B. C.; Dorso, C. R.; Asaad, M. M., *J. Pharmacol. Exp. Ther.*, **1993**, 267, 108.
164. Trippodo, N. C.; Robl, J. A.; Asaad, M. M.; Fox, M.; Panchal, B. C.; Schaeffer, T. R., *Am. J. Hypertens.*, **1998**, 11, 363.
165. Intengan, H. D.; Schiffrin, E. L., *Hypertens*., **2000**, 35, 1221.
166. d'Uscio, L. V.; Quaschning, T.; Burnett, J. C. Jr.; Lüscher, T. F., *Hypertens*., **2001**, 37, 28.

167. Ruilope, L. M., *Am. J. Hypertens*., **2000**, 13, 134A.
168. Packer, M. Califf, R. M.; Konstam, M. A.; Krum, H.; McMurray, J. J.; Rouleau, J. L.; Swedberg, K., *Circulation*, **2002**, 106, 920.
169. Kostis, J. B.; Packer, M.; Black, H. R. Schmieder, R.; Henry, D.; Levy, E., *Am J Hypertens*, **2004**, 17, 103.
170. Mitchell, G. F.; Lacourcie`re, Y.; Ouellet, J-P.; Izzo, J.; Neutel, J.; Qian, C.; Kerwin, L. J.; Block, A. J.; Pfeffer. M. A., *Am. J. Hypertens.*, **2002**, 105, 2955.
171. Norton, G. R. Woodiwiss, A. J.; Hartford, C.; Trifunovic, B.; Middlemost, S.; Lee, A.; Allen, M. J., *Am. J. Hypertens.*, **1999**, 12, 563.
172. Gonzalez, W.; FourniC-Zaluskit, M-C.; Turcaudt, S.; Roquest, B-P.; Michel, J-B., *Cardiovascular Drug Reviews*, **1996**, 14, 161.
173. Cohen, D. S.; Fink, C. A.; Trapani, A. J.; Webb, R. L.; Zane, P. A.; Chatelain, R. E., *Cardiovascular Drug Reviews*, **1999**, 17, 16.
174. Battistini, B.; Daull, P.; Jeng, A. Y., *Cardiovascular Drug Reviews*, **2005**, 23, 317.
175. Inguimbert, N.; Poras, H.; Meudal, H.; Teffo, F.; Beslot, F.; Selkti, M.; Tomas, A.; Scalbert, E.; Bennejean, C.; Renard, P.; Fournie- Zaluski, M.-C.; Roques, B. P., *Bioorg. Med. Chem. Lett.*, **2002**, 12, 2001.
176. Walsh, T.; Fitch, K.; Williams, D.; Murphy, K.; Nolan, N.; Pettibone, D.; Chang, R.; O'Malley, S.; Clineschmidt, B.; Veber, D.; Greenlee, W., *Bioorg. Med. Chem. Lett.*, **1995**, 5, 1155.
177. Murugesan, N.; Tellew, J.; Gu, Z.; Kunst, B.; Fadnis, L.; Cornelius, L.; Baska, R.; Yang, Y.; Beyer, S.; Monshizadegan, H.; Dickinson, K.; Panchal, B.; Valentine, M.; Chong, S.; Morrison, R.; Carlson, K.; Powell, J.; Moreland, S.; Barrish, J.; Kowala, M.; Macor, J., *J. Med. Chem.*, **2002**, 45, 3829.
178. Teutel, J. M.; Germino, F. W.; Punzi, H. American Society of Hypertension Annual Meeting; May 16, **2008**; New Orleans, LA.
179. Allan, G.; Cambridge, D.; Follenfant, M. J.; Hardy, G. W., *Cardiovascular Drug Review*, **1988**, 6, 84.
180. Imayama, I.; Ichiki, T.; Inanaga, K.; Ohtsubo, H.; Fukuyama, K.; Ono, H.; Hashiguchi, Y.; Sunagawa, K., *Cardiovasc. Res.*, **2006**, 72, 184.

181. Yano, Y.; Hoshide, S.; Ishikawa, J.; Noguchi, C.; Tukui, D.; Takanori, H.; Tada, M.; Kanemaru, Y.; Yano, A.; Ishikawa, S.; Shimada, K.; Kario, K., *Am. J. Hypertens.*, **2007**, 20, 565.
182. Sealey, J. E.; Laragh, J. H. The renin-angiotensin-aldosterone system for the normal regulation of blood pressure and sodium and potassium homeostasis. In Hypertension: Pathophysiology, Diagnosis and Management; Laragh, J. G., Brenner, B. M., Eds; New York: Raven Press, **1995**; pp 1763-1797.
183. Shepherd, J. T.; Mancia, G., *Rev. Physiol. Biochem. Pharmacol.*, **1986**, 105, 1.
184. Grassi, G. J., *J. Hypertens.*, **2001**, 19, 1713.
185. Rang, H. P.; Dale, M. M.; Ritter, J. M.; Flower, R. J. *Pharmacology*. Philadelphia, USA: Churchill Livingstone Publisher. **2007**.
186. Cowley, A. W., *Physiol Rev.*, **1992**, 72, 231.
187. Summers, R. J., *Fed Proc.*, **1984**, 43, 2917.
188. Wolff, P. W.; Gesek, F. A.; Strandhoy, J. W., *Fed Proc.*, **1985**, 44, 76.
189. Drew, G. M.; Whiting, S. B. *Br. J. Pharmacol.*, **1979**, 67, 207.
190. Horn, P. T.; Kohl, J. D.; Listinsky, J. J.; Goldberg, L. I., *Naunyn Schmiedebergs Arch Pharmacol*., **1982**, 318, 166.
191. Wolff, P. W.; Buckalew, V. M.; Strandhoy, J. W., *J. Cardiovasc. Pharmacol.*, **1984**, 6, S793.
192. Hall, R. A., *Semin Cell Div Biol*., **2004**, 15, 281.
193. DiBona, G. F., *Am. J. Hypertens.*, **1989**, 2, 119S.
194. Mancia, G., Saino, A., Grassi, G. Interactions between the sympathetic nervous system and the renin-angiotensin system. In Hypertension: Pathophysiology, Diagnosis and Management, Laragh, J. G. Brenner, B. M.; Eds.: New York, Raven Press, **1995**, 399.
195. Du, Y.; Qiu, J.; Nelson, S. H., *Am. J. Physiol.*, **1997**, 273, R1224.
196. Li, H. T.; Long, C. S.; Gray, M. O., *Circ. Res*., **1997**, 81, 396.
197. Zimmerman, B. G.; Sybertz, E. J.; Wong, P. C., *J. Hypertens.*, **1984**, 2, 581.
198. Reid, I. A., *Am. J. Physiol.*, **1992**, 262, E763.
199. Reit, E., *Fed. Proc.*, **1972**, 31, 1338.
200. Starke, K., *Rev. Physiol. Biochem. Pharmacol.*, **1977**, 77, 1.

201. Jain, K. S.; Bariwal, J. B.; Kathiravan, M. K.; Phoujdar, M. S.; Sahne, R. S.; Chauhan, B. S.; Shah, A. K.; Yadav, M. R., *Bioorg. Med. Chem.*, **2008**, 16, 4759.
202. Naik, P. P.; Murumkar, P. R.; Giridhar, R.; Yadav, M. R., *Bioorg. Med. Chem.*, **2010**, 18, 8418.
203. Pieter, B.; Timmermans, M. W. M.; Chiu, A. T.; Thoolen, M. J. M. C. In Comprehensive Medicinal Chemistry; Hansch, C., Eds.; Pergamon Press, Oxford, 2005, pp 141–145.
204. Kynel, J. J.; Hollinger, R. E.; Oheim, K. W.; Winn, M., *Pharmacologist*, **1980**, 22, 272.
205. Timmermans, P. B. M. W. M.; Kwa, H. Y.; Ali, F. K.; Van Zwieten, P. A., *Arch. Int. Pharmacodyn. Ther.*, **1980**, 245, 218.
206. Cavero, I.; Lefevre-Borg, F.; Manoury, P. H., *Br. J. Pharmacol.*, **1984**, 81, 13P.
207. Kawasaki, T.; Uezono, I.; Abe, I.; Nakamura, M.; Ueno, N.; Kawazoe, N.; Amae, T., *Eur. J. Clin. Pharmacol.*, **1981**, 20, 399.
208. Campbell, S. F.; Hardstone, J. D.; Palmer, M. J., *J. Med. Chem.*, **1988**, 31, 1031.
209. Giardina, D.; Brasilli, L.; Gregori, M.; Massi, M.; Picchio, M. T.; Quaglia, W.; Melchiorre, C., *J. Med. Chem.*, **1989**, 32, 50.
210. Giardini, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rafaiani, G.; Michiorre, C., *J. Med. Chem.*, **1993**, 36, 690.
211. Sagratini, G.; Angeli, P.; Buccioni, M.; Gulini, U.; Marucci, G.; Melchiorre, C.; Leonardi, A.; Poggesic, E.; Giardina, D., *Bioorg. Med. Chem.*, **2007**, 15, 2334.
212. Patane, M. A.; Scott, A. L.; Broten, T. P.; Chang, R. S. L.; Ransom, R. W.; Di Salvo, J.; Forray, C.; Bock, M. G., *J. Med. Chem.*, **1998**, 41, 1205.
213. Minarini, A.; Budriesi, R.; Chiarini, A.; Leonardi, A.; Melchiorre, C., *Bioorg. Med. Chem. Lett.*, **1998**, 8, 1353.
214. Campbell, S. F.; Plews, R. M., *J. Med. Chem.*, **1987**, 30, 1794.
215. Pitha, J.; Szabo, L.; Szurmai, Z.; Buchowiecki, W.; Kusiak, J. W., *J. Med. Chem.*, **1989**, 32, 96.
216. Di Stilo, A.; Fruttero, R. R.; Boschi, D.; Gasco, A. M.; Sarba, G.; Gasco, A.; Orsetti, M., *Med. Chem. Res.*, **1993**, 3, 554.
217. Fruttero, R.; Boschi, D.; Stilo, D. A.; Gasco, A., *J. Med. Chem.*, **1995**, 38, 4944.

218. Menziani, M. C.; DeBenidetti, P. G.; Karelson, M., *Bioorg. Med. Chem.*, **1998**, 6, 535.
219. Leonardi, A.; Motta, G.; Boi, C.; Testa, R.; Pogessi, D.; Benedetti, P. G.; Menziani, M. C., *J. Med. Chem.*, **1999**, 42, 427.
220. Antonello, A.; Hrelia, P.; Leonardi, A.; Marucci, G.; Rosini, M.; Tarozzi, A.; Tumiatti, V.; Melchiorre, C., *J. Med. Chem.*, **2005**, 48, 28.
221. Valerie, A. A.; Simon, F. C.; John, C. D.; Colin, W. G.; Rhona, M. P., *J. Med. Chem.*, **1987**, 30, 999.
222. Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M., *J. Med. Chem.*, **1988**, 31, 516.
223. Campbell, S. F., *Drug Des. Delivery*, **1986**, 1, 83.
224. Campbell, S. F.; Davey, M. J. J.; Hardstone, D.; Lewis, B. N.; Palmer, M. J., *J. Med. Chem.*, **1987**, 30, 49.
225. Manoury, P. M.; Binet, J. L.; Dumas, A. P.; Lefevre- Borg, F.; Cavero, I., *J. Med. Chem.*, **1986**, 29, 19.
226. Giardiana, D.; Crucianelli, M.; Gulini, U.; Marucci, G.; Melchiorre, C.; Spampinato , S., *Eur. J. Med. Chem.*, **1997**, 32, 9.
227. Melchiorre, C.; Giardiana, D.; Gallucci, P.; Brasili, L., *J. Pharm. Pharmacol.*, **1982**, 34, 683.
228. Giardiana, D.; Angeli, P.; Brasili, G. U.; Melchiorre, C.; Strappeghetti, G., *J. Med. Chem.*, **1984**, 19, 411.
229. Melchiorre, C.; Brasili, L.; Giardinti, D.; Pigini, M.; Strappaghetti, G., *J. Med. Chem.*, **1984**, 27, 1535.
230. Cassinelli, A.; Quaglia, W.; Brasili, L.; Giardini, D.; Gulini, U.; Melchiorre, C., *Eur. J. Med. Chem.*, **1987**, 22, 83.
231. Stillings, M. S.; Chapleo, C. B.; Butler, R. C.; Davis, J. A.; England, C. D.; Myers, P. L.; Tweddle, N.; Welbourn, A. P.; Doxey, J. C.; Smith, C. F., *J. Med. Chem.*, **1985**, 28, 1054.
232. Bolchi, C.; Catalano, P.; Fumagalli, L.; Gobbi, M.; Pallavicini, M.; Pedretti, A.; Villa, L.; Vistoli, G.; Valoti, E., *Bioorg. Med. Chem.*, **2004**, 12, 4947.

233. Quaglia, W.; Pigini, M.; Piergentili, A.; Giannella, M.; Maruccisi, G.; Poggesi, E.; Leonardi, A.; Melchiorre, C., *J. Med. Chem.*, **1999**, 42, 2961.
234. Pallavicini, M.; Fumagalli, L.; Gobbi, M.; Bolchi, C.; Colleoni, S.; Moroni, B.; Pedretti, A.; Rusconi, C.; Vistoli, G.; Valoti, E., *Eur. J. Med. Chem.*, **2006**, 41, 1025.
235. Pigini, M.; Brasili, L.; Giannella, M.; Giardin, D.; Gulini, U.; Quaglia, W.; Melchiorre, C., *J. Med. Chem.*, **1988**, 31, 2300.
236. Boer, R.; Grasseger, A.; Schudt, C.; Glossman, H., *Eur. Pharmacol., Mol. Pharmacol. Sect.*, **1989**, 172, 131.
237. Wong, W. C.; Sun, W.; Lagu, B.; Tian, D.; Marzabadi, M. R.; Zhang, F.; Nagarathnam, D.; Miao, S. W.; Wetzel, J. M.; Peng, J.; Forray, C.; Chang, R. S. L.; Chen, T. B.; Ransom, R. W.; O'Malley, S.; Broten, T. P.; Kling, P.; Vyas, K. P.; Zhang, K.; Gluchowski, C., *J. Med. Chem.*, **1999**, 42, 4804.
238. Nagarathnam, D.; Miao, S. W.; Lagu, B.; Chiu, G.; Fang, J.; Murali Dhar, T. G.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F.; Wong, W. C.; Sun, T. D.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; FSchorn, T. W.; Chen, T. B.; O'Malley, S.; Kling, P.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Vyas, K. P.; Gluchowski, C., *J. Med. Chem.*, **1999**, 42, 4764.
239. Lagu, B.; Tian, D.; Nagarathnam, D.; Marzabadi, M. R.; Wong, W. C.; Miao, S. W.; Zhang, F.; Sun, W.; Chiu, G.; Fang, J.; Forray, C.; Chang, R. S. L.; Ransom, R. W.; Chen, T. B.; O'Malley, S.; Zhang, K.; Vyas, K. P.; Gluchowski, C., *J. Med. Chem.*, **1999**, 42, 4794.
240. Imagawa, J.; Sakai, K., *Eur. J. Pharmacol.*, **1986**, 131, 257.
241. Ronald, K.; Russell, J. B.; Press, R. A.; Rampulla, J. J.; McNally, R.; Falotico, J. A.; Keiser, D. A.; Bright, A. T., *J. Med. Chem.*, **1988**, 31, 1786.
242. Romeo, G.; Materia, L.; Manetti, F.; Cagnotto, A.; Mennini, T.; Nicoletti, F.; Botta, M.; Russo, F.; Minneman, K. P., *J. Med. Chem.*, **2003**, 46, 2877.
243. Romeo, G.; Materia, L.; Marucci, G.; Modica, M.; Pittala, V.; Salerno, L.; Siracusa, M. A.; Buccioni, M.; Angeli, P.; Minneman, K. P., *Bioorg. Med. Chem. Lett.*, **2006**, 16, 6200.

244. Meyer, M. D.; Altenbach, R. J.; Bai, H.; Basha, F. Z.; Carroll, W. A.; Kerwin, J. F., Jr.; Lebold, S. A.; Lee, E.; Pratt, J. K.; Sippy, K. B.; Tietje, K.; Wendt, M. D.; Brune, M. E.; Buckner, S. A.; Hancock, A. A.; Drizin, I., *J. Med. Chem.*, **2001**, 44, 1971.

245. Carsano, S.; Strappaghetti, G.; Codagnone, A.; Scapicchi, R.; Murucci, G., *Eur. J. Med. Chem.*, **1992**, 27, 545.

246. Carsano, S.; Scapicchi, R.; Strappaghetti, G.; Marucci, G.; Paparelli, F., *Eur. J. Med. Chem.*, **1993**, 28, 647.

247. Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S., *J. Med. Chem.*, **2001**, 44, 2118.

248. Betti, L.; Floridi, M.; Giannaccini, G.; Manetti, F.; Strppaghrtti, G.; Tafi, A.; Botta, M., *Bioorg. Med. Chem. Lett.*, **2003**, 13, 171.

249. Montesano, F.; Barlocco, D.; Piaz, V. D.; Leonardi, A.; Poggesi, E.; Fanelli, F.; Benedetti, P. G. D., *Bioorg. Med. Chem.*, **1998**, 6, 925.

250. Betti, L.; Botta, M.; Corelli, F.; Floridi, M.; Fossa, P.; Giannaccini, G.; Manetti, F.; Strappaghetti, G.; Corsano, S., *Bioorg. Med. Chem. Lett.*, **2002**, 12, 437.

251. Barlocco, D.; Cignarella, G.; Montesano, F.; Leonardi, A.; Mella, M.; Toma, L., *J. Med. Chem.*, **1999**, 42, 173.

252. Betti, L.; Botta, M.; Corelli, F.; Floridi, M.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Tafi, A.; Corsano, S., *J. Med. Chem.*, **2002**, 45, 3603.

253. Amemiya, Y.; Hong, S. S.; Venkataraman, B. V.; Patil, P. N.; Shams, G.; Romstedt, K.; Feller, D. R.; Hsu, F. L.; Miller, D. D., *J. Med. Chem.*, **1992**, 35, 750.

254. Ford, A. P. D. W.; Williams, T. J.; Blue, D. D. R.; Clarke, E., *Trends Pharmacol. Sci.*, **1994**, 15, 167.

255. Chern, J. W.; Tao, P. L.; Yen, M. H.; Lu, G. Y.; Shiau, C. Y.; Lai, Y. J.; Chan, C. H., *J. Med. Chem.*, **1993**, 36, 2196.

256. Reitz, A. B.; Bennett, D. J.; Blum, P. S.; Codd, E. E.; Maryanoff, C. A.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. P.; Vaught, J. Ln., *J. Med. Chem.*, **1994**, 37, 1060.

257. Khatuya, H.; Pulito, V. L.; Jolliffe, L. K.; Li, X.; Murray, W. V., *Bioorg. Med. Chem. Lett.*, **2002**, 12, 2145.

258. Khatuya, H.; Hutchings, R. H.; Kuo, G. H.; Pulito, V. L.; Jolliffe, L. K.; Li, X.; Murray, W. V., *Bioorg. Med. Chem. Lett.*, **2002**, 12, 2443.

259. Betti, L.; Floridi, M.; Giannaccini, G.; Manetti, F.; Paparelli, C.; Strappaghetti, G.; Botta, M., *Bioorg. Med. Chem.*, **2004**, 12, 1527.

260. Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans P. B. M. W. M., *J. Med. Chem.*, **1991**, 34, 2525.

261. Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M., *Med. Res. Rev.*, **1992**, 12, 149.

262. Naylor, E. M.; Chakravarty, P. K.; Costel1o, C. A.; Chang, R. S.; Chen, T.-B.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Zingaro, G. J.; Siegl, P. K. S.; Wong, P. C.; Carini, D. J.; Wex1er. R. R.; Patchett, A. A.; Greenlee, W. J., *Biorg. Med. Chem. lett.*, **1994**, 4, 69.

263. Chiu, A. T.; Carini, D. J.; Duncia, J. V.; Leung, K. H.; McCall, D. E.; Price, W. A.; Wong, P. C.; Smith R. D.; Wexler, R. R.; Timmermans, P. B. M. W. M., *Biochem. Biophys. Res. Commun.*, **1991**, 177, 209.

264. Wong, P. C.; Hart, S. D.; Chiu, A. T.; Herblin, W. F.; Carini, D. J.; Smith, R. D.; Wexler, R. R.; Timmermans, P. B. M. W. M., *J. Pharmacol. Exp. Ther.*, **1991**, 259, 861.

265. Carini, D. J.; Ardecky, R. J.; Ensinger, C. L.; Pruitt, J. R.; Wexler, R. R.; Wong, P. C.; Huang, S.- M.; Aungst, B. J.; Timmermans, P. B. M. W. M., *Biorg. Med. Chem. Lett.*, **1994**, 4, 63.

266. Wong, P. C.; Huang, S.-M.; Ardecky, R. J.; Carini, D. J.; Chiu, A. T.; Price, W. A., Jr.; Agra, A. M.; Wexler, R. R.; Timmermans, P. B. M. W. M., *Clin. Exp. Hypertens.*, **1995**, 17, 1233.

267. Yanagisawa, H.; Amemiya, Y.; Kanazaki, T.; Fujitnoto, K.; Shimoji, Y.; Fujimoto, Y.; Sada, T.; Mizuno, M.; Koike, H., *Biorg. Med. Chem. lett.*, **1994**, 4, 177.

268. Caille, J. C.; Corbier, A.; Fortin, M.; Jouquey, S.; Vevert, J.-P. Eur. Patent, 0 465 368 A1, 1992 ; *Chem. Abstr.*, **1992,** 116, 214499g.

269. Deprez, P.; Guillaume, J.; Becker, R.; Corbier, M.; Didierlaurent, S.; Fortin, M.; Frechet, D.; Hamon, G.; Heckmann, B.; Heitsch, H.; Kleemann, H.-W.; Vevert, J.-P.; Vincent, J.-C.; Wagner, D.; Zhang. J., *J. Med. Chem.*, **1995**, 38, 2357.

270. Yanagisawa, H.; Amemiya, Y.; Kanazaki, T.; Shimoji, Y.; Fujimoto, K.; Kitahara, Y.; Sada, T.; Mizuno, M.; Ikeda, M.; Miyamoto, S.; Furukawa, Y.; Koike H., *J. Med. Chem.*, **1996**, 39, 323.

271. Sircar, I.; Hodges, J. C.; Quin, J. III; Bunker, A. M.; Winters, R. T.; Edmunds, J. J.; Kostlan, C. R.; Connolly, C.; Kesten, S. J.; Hamby, J. M.; Topliss, J. G.; Keiser, J. A.; Panekt, R. L., *J. Med. Chem.*, **1993**, 36, 2253.

272. Keiser, J. A.; Ryan, M. J.; Panek, R. L.; Hodges, J. C.; Sircar, I., *J. Pharmacol. Exp. Ther.*, **1995**, 272, 963.

273. Keiser, J. A.; Olszewski, B.; Hicks, G.; Ryan, M. J.; Hodges, J., *FASEB J.*, **1993**, 7, A654.

274. Harmat, N. J. S.; Giorgi, R.; Bonaccorsi, F.; Cerbai, G.; Colombani, S. M.; Renzetti, A. R.; Cirillo, R.; Subissi, A.; Alagona, G.; Ghio, C.; Arcamone, F.; Giachetti, A.; Palearil, F.; Salimbeni, A., *J. Med. Chem.*, **1995**, 38, 2925.

275. Ashton, W. T.; Hutchins, S. M.; Greenlee, W. J.; Doss, G. A.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S., *J. Med. Chem.*, **1993**, 36, 3595.

276. Olson, R. E.; Liu, J.; Lalka, G. K.; VanAtten, M. K.; Wexler, R. R.; Chiu, A. T.; Nguyen, T. T.; McCall, D. E.; Wong, P. C.; Timmermans, P. B. M. W. M., *Biorg. Med. Chem. Lett.*, **1994**, 4, 2229.

277. Salimbeni, A.; Canevotti, R.; Paleari,F.; Bonaccorsi, F.; Renzetti, A. R.; Belvisi, L.;Bravi, G.; Scolastic, C., *J. Med. Chem.*, **1994**, 37, 3928.

278. Estenne, G.; Dodey, P.; Renaut, P.; Leclerc, G., *Biorg. Med. Chem. Lett.*, **1995**, 5, 15.

279. Lin, H.-S.; Rampersaud, A. A.; Zimmerman, K.; Steinberg, M. I.; Boyd, D. B., *J. Med. Chem.*, **1992**, 35, 2658.

280. Quan, M. L.; Olson, R. E.; Carini, D. J.; Ellis, C. D.; Hillyer, G. L.; Lalka, G. K.; Liu, J.; VanAtten, M. K.; Chiu, A. T.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M., *Biorg. Med. Chem. Lett.*, **1994**, 4, 2011.

281. Quan, M. L.; Chiu, A. T.; Ellis, C. D.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M., *J. Med. Chem.*, **1995**, 38, 2938.

282. Robertson, M. J.; Barnes, J. C.; Drew, G. M.; Clark, K. L.; Marshall, F. H.; Michel, A.; Middlemiss, D.; Ross, B. C.; Scopes, D.; Dowle, M. D., *Br. J. Pharmacol.*, **1992**, *107*, 1173.

283. Middlemiss, D.; Drew, G. M.; Ross, B. C.; Robertson, M. J.; Scopes, D. I. C.; Dowle, M. C.; Akers, J.; Cardwell, K.; Clark, K. L.; Coote, S.; Eldred, C. D.; Hamblett, J.; Hilditch, A.; Hirst, G. C.; Jack, T.; Montana, J.; Panchal, T. A.; Paton, J. M. S.; Shah, P.; Stuart, G.; Travers, A., *Biorg. Med. Chem. Lett.*, **1991**, 1, 711.

284. Hilditch, A.; Hunt, A. A. E.; Gardner, C. J.; Twissell, D. J.; Polley, J.; Travers, A.; Drew, G. M.; Middlemiss, D.; Ross, B. C.; Robertson, M. J., *Br. J. Pharmacol.*, **1994**, 111, 137.

285. Middlemiss, D.; Watson, S. P.; Ross, B. C.; Dowle, M. D.; Scopes, D. I. C.; Montana, J. G.; Hirst, G. C.; Panchal, T. A.; Paton, J. M. S.; Hubbard, T.; Stuart, G.; Drew, G. M.; Hilditch, A.; Travers, A.; Robertson, M. J.; Hunt, A. A. E.; Palmer, E.; Manchee, G. R., *Biorg. Med. Chem. Lett.*, **1993**, 3, 2043.

286. Judd, D. B.; Dowle, M. D.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Jack, T. I.; Pass, M.; Tranquillini, E.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Paton, J. M. S.; Hubbard, T.; Hilditch, A.; Drew, G. M.; Robertson, M. J.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Polley, J.; Eddershaw, P. J.; Bayliss, M. K.; Manchee, G. R.; Donnelly, M. D.; Walker, D. G.; Richards, S. A., *J. Med. Chem.*, **1994**, 37, 3108.

287. Dowle, M. D.; Judd, D. B.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Pass, M.; Tranquillini, E.; Jack, T. I.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Drew, G. M.; Robertson, M. J.; Hilditch, A.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Manchee, G. R.; Walker, D. G.; Eddershaw, P. J.; Donnelly, M. D.; Bayliss, M. K., *Biorg. Med. Chem. Lett.*, **1993**, 3, 2047.

288. Hilditch, A.; Hunt, A. A.; Travers, A.; Polley, J., Drew, G. M.; Middlemiss, D., Judd, D. B.; Ross, B. C.; Robertson, M. J. Pharmacol. Expt. Ther. 1995, 272, 750.

289. Dickinson, K. E. J.; Cohen, R. B.; Skwish, S.; Delaney, C. L.; Serafino, R. P.; Poss, M. A.; Gu, Z.; Powell, J. R., *Br. J. Pharmacol.*, **1994**, 113, 179.
290. Poss, M. A.; Gu, Z.; Ryono, D. E.; Reid, J. A.; Sieber-McMaster, E.; Spitzmiller, E. R.; Dejneka, T.; Dickinson, Kenneth, E. J.; Williams, S. B.; Moreland, S.; Delaney, C. L.; Bird, J. E.; Waldron, T. L.; Schaeffer, T. R.; Hedberg, S. A.; Petrillo, E. W., *Biorg. Med. Chem. Lett.*, **1994**, 4, 145.
291. Bovy, P. R.; Collins, J J. T.; Olins, G. M.; McMahon, E. G.; Hutton, W. C., *J. Med. Chem.*, **1991**, 34, 2410.
292. Bernhart, C. A.; Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J.-L. A.; Clement, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E.; Vignal, M.-A.; Gougat, J.; Guiraudou, P. R.; Lacour, C. A.; Roccon, A.; Cazaubon, C. F.; Breliere, J.-C.; Le Fur, G.; Nisato, D., *J. Med. Chem.*, **1993**, 36, 3371.
293. Cazaubon , C.; Gougat, J.; Bousquet, F.; Guiraudou, P.; Gayraud, R.; Lacour, C.; Roccon, A.; Galindo, G.; Barthelemy, G.; Gautret, B.; Bernhart, C.; Perreaut, P.; Breliere, J.-C.; Le Fur, G.; Nisato, D., *J. Pharmacol. Exp. Ther.*, **1993**, 265, 826.
294. Perream, P,; Clement, J.; Muneaux, C.; Muneaux, Y.; Cazaubon, C.; Gougat, J.; Guiraudou, P.; Lacour, C.; Nisato, D.; Le Fur, G.; Brehere, J-C., *Biorg. Med. Chem. Lett.*, **1994**, 4, 163.
295. Ferrari, B.; Taillades, J.; Perreaut, P.; Bernhart, C.; Gougat, J.; Guiraudou, P.; Cazaubon, C.; Roccon, A.; Nisato, D.; Fur, L.; Brelibe, J. C., *Biorg. Med. Chem. Lett.*, **1994**, 4, 45.
296. Reitz, D. B.; Garland, D. J.; Norton, M. B.; Collins, J. T. Reinhard, E. J.; Manning, R. E., *Biorg. Med. Chem. Lett.*, **1993**, 3, 1055.
297. Reitz, D.B.; Garland, D. J.; Norton, M. B.; Chen, B. K.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M.A.; Koepke, J. P.; Moore, G. K.; Smits, G. J.; McGraw, D. E.; Blaine, E. H.; Manning, R. E. 204th ACS National Meeting, **1992**, MEDI-31.
298. Reitz, D. B.; Manning, R. E. US Patent, 5087634, **1992**.
299. Reitz, D. B.; Manning, R. E. US Patent, 5164403, **1992**.
300. Reitz D. B.; Garland, D. J., *Biorg. Med. Chem. Lett.*, **1994**, 4, 111.

301. Quan, M. L.; DeLucca, I.; Boswcll, G. A.; Chiu, A. T.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B.M.W.M., *Biorg. Med. Chem. Lett.*, **1994**, 4, 1527.
302. Middlemiss, D.; Ross, B. C.; Eldred, C.; Montana, J. G.; Shah, P.; Hirst, G. C.; Watson, S. P.; Panchal, T. A.; Paton, J. M. S.; Hubbard, T.; Drew, G. M.; Robertson, M. J.; Hilditch, A.; Clark, K. L., *Biorg. Med. Chem. Lett.*, **1992**, 2, 1243.
303. Bourdonnec, B. L.; Meulon, E.; Yous, S.; Goossens, J.-F.; Houssin, R.; Henichart, J.-P., *J. Med. Chem.*, **2000**, 43, 2685.
304. Reitz, D. B.; Penick, M. A.; Brown, M. S.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Koepke, J. P.; Moore, G. K.; Smits, G. J.; McGraw, D. E.; Blaine, E. H., 203rd ACS National Meeting, **1992**, MEDI-189.
305. Reitz, D. B. US Patent, 5098920, **1992**.
306. Reitz, D. B.; Penick, M. A.; Reinhard, E. J.; Cheng, B. K.; Olins, G. M.; Corpus, V. M.; Palomo, M. A.; McGraw, D. E.; McMahon, E. G., *Biorg. Med. Chem. Lett.*, **1994**, 4, 99.
307. Reitz, D. B.; Penick, M. A.; Norton, M. B.; Reinhard, E. J.; Olins, G. M.; Corpus, V. M.; Palomo, M. A.; McGraw, D. E.; McMahon, E. G., *Biorg. Med. Chem. Lett.*, **1994**, 4, 105.
308. Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchine, S. M.; Strelitz R. A.; MacCoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S., *J. Med. Chem.*, **1993**, 36, 591.
309. Huang; H.-C.; Reitz, D. B.; Chamberlain, T. S.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Koepke, J. P. Smits, G. J.; McGraw, D. E.; Blaine, E. H.; Manning, R. E., *J. Med. Chem.*, **1993**, 36, 2172.
310. Chang, L.L.; Ashton, W. T.; Flanagan, K. L.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Bendesky, R. J.; Chen, T. -B.; Faust, K. A.; Kling, P. J.; Schaffer, L. W.; Schorn, T. W.; Zingaro, G. J.; Chang, R. S. L.; Lotti, V. J.; Kivlighn, S. D.; Siegl, P. K. S., *Biorg. Med. Chem. Lett.*, **1994**, 4, 115.
311. Attanasi, O. A.;, Colombani, S. A.; , Crescentini, L. D.; Giorgi, R.; Monti, S.; Perrone, A.; Perrulli, F. R.; Renzetti, A. R.; Santeusanio, S., *IL Farmaco*, **1999**, 54, 64.

312. Murray, W. V.; Lalan, P.; Gill, A.; Addo, M. F.; Lewis, J. M.; Lee, D. K. H.; Wachter, M. P.; Rampulla, R.; Underwood, D. C., *Biorg. Med. Chem. Lett.*, **1993**, 3, 369.

313. De, B.; Winn, M.; Zydowsky, T. M.; Kerkman, D. J.; Debernardis, J. F.; Lee, J.; Buckner, S.; Warner, R.; Brune, M.; Hancock, A.; Opgenorth, T.; Marsh, K., *J. Med. Chem.*, **1992**, 35, 3714.

314. Winn, M.; De, B.; Zydowsky, T. M.; Altenbach, R. J.; Basha, F. Z.; Boyd, S. A.; Brune, M. E.; Buckner, S. A.; Crowell, D.; Drizin, I.; Hancock, A. A.; Jae, H.-S.; Kester, J. A.; Lee, J. Y.; Mantei, R. A.; Marsh, K. C.; Novosad, E. I.; Oheim, K. W.; Rosenberg, S. H.; Shiosaki, K.; Sorensen, B. K.; Spina, K.; Sullivan, G. M.; Tasker, A. S.; VonGeldern, T. W.; Warner, R. B.; Opgenorth, T. J.; Kerkman, D. J.; Debernardis, J. F., *J. Med. Chem.*, **1993**, 36, 2676.

315. Bradbury, R. H.; Edwards, M. P.; Fisher, E.; Girdwood, J. A.; Major, J. S.; Oldham, A. A.; Patel, M. L.; Pearce, R. J.; Revill, J.; Ratcliffe A. H., *Biorg. Med. Chem. Lett.*, **1994**, 4, 139.

316. Nagura, J.; Fujishima, K.; Kawano, K.; Yasuda, S.; Hachisu, M.; Konno, F., *J. Hypertens.*, **1994**, 12 (Suppl.3), S99.

317. Nagura, J.; Yasuda, S.; Fujishima, K.; Yamamoto, M.; Hui, C.; Kawano, K.-I.; Katano, K.; Konno, F., *Eur. J. Pharmacol.*, **1995**, 274, 201.

318. Norman, M. H.; David Smith, H.; Andrews, W.; Tang, F. L. M.; Cowan, C. L.; Steffen, R. P., *J. Med. Chem.*, **1995**, 38, 4670.

319. Bantick, J. R.; Beaton, H. G.; Cooper, S. L.; Hill, S.; Hirst, S. C.; McInally, T.; Spencer, J.; Tinker, A. C.; Willis, P. A., *Biorg. Med. Chem. Lett.*, **1994**, 4, 127.

320. Osswald, M. Mederski, W. W. K. R.; Schwarz, M.; Beier, N.; Lues, I.; Minck, K.-O., *Biorg. Med. Chem. Lett.*, **1994**, 4, 683.

321. Koppe, T.; Mederski, W. W. K. R.; Osswald, M.; Schwarz, M., *Tetrahedron Lett.*, **1995**, 36, 377.

322. Zydowsky, T. M.; Winn, M.; De, B.; Condon, S. L.; Altenbach, R. J.; Basha, F. Z.; Boyd, S. A.; Buckner, S. A.; Hancock, A. A.; Lee, J. Y.; Mantei, R. A.; Novosad, E. I.; Sorensen, B. K.; Tasker, A. S.; Shiosaki, K.; Kerkman, D. J.; Opgenorth, T. J; DeBernardis, J. F., *Biorg. Med. Chem. Lett.*, **1994**, 4, 173.

323. Nicolai, E.; Curk, G.; Goyard, J.; Kirchner, M.; Teulon, J. M.; Versigny, A.; Cazes, M.; Virone-Oddos, A.; Caussade, F.; Cloarec A., *Eur. J. Med. Chem.* **1995**, 30, 365.

324. Subissi, A.; Renzetti, A. R.; Cucchi, P.; Guelfi, M.; Caliari, S.; Giachetti, A., *J. Hypertens.*, **1994**, 12 (Suppl. 3), 595.

325. Aulakh, G. K.; Sodhi, R. K.; Singh, M., *Life Sci.*, **2007**, 81, 615.

326. Bernhart, C. A.; Haudricourt, F. B.; Assens, J. L.; Gougat, J.; Lacour, C.; Roccon, A.; Cazaubon, C.; Breliere. J. C.; Le Fur, L.; Nisato, D., *Biorg. Med. Chem. Lett.*, **1994**, 4, 157.

327. Atwal, K. S.; Ahmed, S. Z.; Bird, J. E.; Delaney, C. L.; Dickinson, K. E. J.; Ferrara, F. N.; Hedberg, A.; Miller, A. V.; Moreland, S.; O'Reilly, B. C.; Schaeffer, T. R.; Waldron, T. L.; Weller, H. N., *J. Med. Chem.*, **1992**, 35, 4761.

328. Murray, W. V.; Lalan, P.; Gill, A.; Addo, M. F.; Lewis, J. M.; Lee, D. K. H. Rampulla, R.; Wachter, M. P.; Hsi, J. D.; Underwood, D. C., *Biorg. Med. Chem. Lett.*, **1992**, 2, 1775.

329. Hsi, J. D.; Murray, W. V.; Gill, A., *Biorg. Med. Chem. Lett.*, **1993**, 3, 1523.

330. Kubo, K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukawa, Y.; Nishikawa, K.; Nakat, T., *J. Med. Chem.*, **1993**, 36, 1772.

331. Kubo, K.; Kohara, Y.; Imamiya, E.; Sugiura, Y.; Inada, Y.; Furukawa, Y.; Nishikawa, K.; Naka, T., *J. Med. Chem.*, **1993**, 36, 2182.

332. Ogihara, T.; Nagano, M.; Higaki, J.; Kohara, K.; Mikami, H., *J. Cardiovasc. Pharmacol.*, **1995**, 26, 490.

333. Kubo, K.; Kohara, Y.; Yoshimura, Y.; Inada, Y.; Shibouta, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T., *J. Med. Chem.*, **1993**, 36, 2343.

334. Kohara, Y.; Imamiya, E.; Kubo, K.; Wada, T.; Inada, Y.; Naka, T., *Biorg. Med. Chem. Lett.*, **1995**, 5, 1903.

335. Cho, N.; Kubo, K.; Furuya, S.; Sugiura, Y.; Yasuma, T.; Kohara, Y.; Ojima, M.; Inada, Y.; Nishikawa, Y.; Naka, T., *Biorg. Med. Chem.Lett.*, **1994**, 4, 3540.

336. Palkowitz, A. D.; Steinberg, M. I.; Zimmerman, K. M.; Jeff Thrasher, K.; Hauser, K. L.; Boyd, D. B., *Biorg. Med. Chem. Lett.*, **1995**, 5, 1015.

337. Bali, A.; Bansal, Y.; Sugumaran, Y.; Saggu, J. G.; Balakumar, P.; Kaur, G.; Bansal, G.; Sharma, A.; Manjeet Singh., *Biorg. Med. Chem. Lett.*, **2005**, 15, 3962.

338. Shah, D. I.; Sharma, M.; Bansal, Y.; Bansal, G.; Manjeet singh., *Eur. J. Med. Chem.*, **2008**, 43, 1808.

339. Kaur, N.; Kaur, A.; Bansal, Y.; Shah, D. I.; Bansal, G.; Manjeet singh., *Biorg. Med. Chem.*, **2008**, 16, 10210.

340. Xu, J. Y.; Ran. Q., Hua, W. Y.; Wu, X. M.; Wang, Q.J. Zhang, J., *Chin. Chem. Lett.*, **2007**, 18, 251.

341. Ries, U. J.; Mihm, G.; Narr, B.; Hasselbach, K. M.; Wittneben, H.; Entzeroth, M.; VanMeel, J. C. A.; Wienen, W.; Hauel, N. H., *J. Med. Chem.*, **1993**, 36, 4040.

342. Wienen, W.; Hauel, N.; Van Meel, J. C. A.; Narr, B.; Ries, U. J.; Entzeroth, M., *Br. J. Pharmacol.*, **1993**, 110, 245.

343. Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J., *J. Med. Chem.*, **1991**, 34, 2919.

344. Chang, R. S. L.; Siegl, P. K. S.; Clineschmidt, B. V.; Mantlo, N. B.; Chakravarty, P. K.; Greenlee, W.J.; Patchett, A. A.; Lotti, V. J., *J. Pharmacol. Exp. Ther.*, **1992**, 262, 133.

345. Chakravarty, P. K.; Naylor, E. M.; Chen, A.; Chang, R. S. L.; Chen, T.-B.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Gable, R. A.; Zingaro, G. J.; Schorn, T. W.; Schaffer, L. W.; Broten, T. P.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J., *J. Med. Chem.*, **1994**, 37, 4068.

346. Rim, D.; Mantlo, N. B.; Chang, R. S. L.; Kivlighn, S. D.;Greenlee, W .J, *Biorg. Med. Chem. Lett.*, **1994**, 4, 41.

347. Rivero, R. A.; Kevin, N. J.; Allen, E. E., *Biorg. Med. Chem. Lett.*, **1993**, 1119

348. Kevin, N. J.; Rivero, R. A.; Greenlee, W. J.; Chang, R. S. L.; Chen, T. B., *Biorg. Med. Chem. Lett.*, **1994**, 4, 189.

349. Carpino, P. A.; Sneddon, S. F.; Jardine, P. S.; Magnus-Ayritey, G. T. ; Rauch, A. L.; Burkard, M. R., *Biorg. Med. Chem. Lett.*, **1994**, 4, 93.

350. Dhanoa, D. S.; Bagley, S. W.; Chang, R. S. L.; Lotti, V. J.; Chen, T-B.; Kivlighn, S. D.; Zingaro, G. J.; Siegl, P. K. S.; Patchett, A. A.;Greenleet, W. J., *J. Med. Chem.*, **1993**, 36, 4230.

351. de Laszlo, S. E.; Allen, E. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Nachbar, R. B.; Siegl, P. K. S.; Chang, R. S.; Kivlighn, S. D.; Schorn, T. S.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Lotti, V. J., *Biorg. Med. Chem. Lett.*, **1993**, 3, 1299.

352. Chakravarty, P. K.; Strelitz, R. A.; Chen, T.-B.; Chang, R. S. L.; Lott, V. I.; ;Zingaro, G. J.; Schom, T. W.; Kivlighn, S. D.; Siegl, P. K. S.; Patchettt, A. A.; Greenlee, W. J., *Biorg. Med.Chem. Lett.*, **1994**, 4, 75.

353. Levin, J. I.; Venkatesan, A. M.; Chan, P. S.; Baker, J. S.; Francisco, G.; Bailey, T.; Vice, G.; Katocs, A.; Lai, F.; Coupet, J., *Biorg. Med. Chem. Lett.*, **1994**, 4, 1135.

354. Levin, J. I.; Chan, P. S.; Coupet, J.; Thibault, L.; Venkatesan, A. M.; Bailey, T. K.; Vice, G.; Cobuzzi, A.; Lai, F.; Mellish, N., *Biorg. Med. Chem. Lett.*, **1994**, 4, 1709.

355. Levin, J. L.; Venkatesan, A. M.; Ghan. P. S.; Bailey, T. K.; Vice, G.; Coupet, J., *Biorg. Med. Chem. Lett.*, **1994**, 4, 1819.

356. Levin, J. L.;, Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M., *Biorg. Med. Chem. Lett.*, **1994**, 4, 1141.

357. Ismail, M. A. H.; Barker, S.; Dalal A. Abou El Ella, Abouzid, K. A. M.; Toubar, R. A.; Todd, M. H., *J. Med. Chem.*, **2006**, 49, 1526.

358. Soll, R. M.; Kinney, W. A.; Primeauj, J.; Ganick, L.; McCaully, R. J.; Colatsky, T.; Oshii, G.;Park, C. H.; Harmpee; D.; White; V.; McCallum, J.; Russo, A.; Dinish, J., *Biorg. Med. Chem. Lett.*, **1993**, 3, 757.

359. Oldham, A. A.; Allott, C. P.; Major, J. S.; Pearce, R. J.; Roberts, D. A.; Russell, S., T. *Br. J. Pharmacol.*, **1992**, 105, 83P.

360. Allott, C. P.; Bradbury, R. H.; Dennis, M.; Fisher, E.; Luke, R. W. A.; Major, J. S.; Oldham, A. A.; Pearce, R. J.; Reid, A. C.; Roberts, D. A.; Rudge, D. A.; Russell, S. T., *Biorg. Med. Chem. Lett.*, **1993**, 3, 899.

361. Thomas, A. P.; Roberts, D. A.; Thomason, D. A., *Biorg. Med. Chem. Lett.*, **1994**, 4, 2615.

362. Lloyd, J.; Ryono, D. E.; Bird, J. E.; Buote, J.; Delaney, C. L.; Dejneka, T.; Dickinson, K. E. J.; Moreland, S.; Normandin, D. E.; Skwish, S.; Spitzmiller, E. R.; Waldron, T. L., *Biorg. Med. Chem. Lett.*, **1994**, 4, 195.

363. Kim, K. S.; Qian, L.; Bird, J. E.; Dickinson, K. E. J.; Moreland, S.; Schaeffer, T. R.; Waldron, T. L.; Delaney, C. L.; Weller, H. N.; Miller, A. V., *J. Med. Chem.*, **1993**, 36, 2335.

364. Kim, K. S.; Qian, L.; Dickinson, K. E. J.; Delaney, C. L.; Bird, J. E.; Waldron, T. L.; Moreland, S., *Biorg. Med. Chem. Lett.*, **1993**, 3, 2667.

365. Buhlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J., *Biorg. Med. Chem. Lett.*, **1994**, 4, 29.

366. Criscione, L.; de Gasparo, M.; Buhlmeyer, P.; Whitebread, S.; Ramjou, H. P.; Wood, J. M., *J. Hypertens.*, **1992**, 10, 196.

367. Weinstock, J.; Hill, D. T.; Keenan, R. M.; Franz, R. G.; Gaitan~poulos, D. E.; Girard, G. R.; Eggleston, D. S.; Aiyar, N.; Griffin, E.; Ohlstein, E.; Brooks, D. P.; Gellai, M.; Frederickson, T. A.; Weidley, E. F.; Edwards, R. M., *Biorg. Med. Chem. Lett.*, **1994**, 4, 23.

368. Edmunds, J. J.; Klutchko, S.; Hamby, J. M.; Bunker, A. M.; Connolly, C. J. C.; Winters, T.; Quin, J. III; Sircar, I.; Hodges, J. C.; Panek, R. L.; Keiser, J. A,; Doherty, A. M., *J. Med. Chem.*, **1995**, 38, 3759.

369. Yadav, M. R.; Gandhi, H. P.; Naik, P. P., *Pharmaceutical Biology*, 2011, accepted in press

370. Buck, J. S., *Organic Syntheses Collective Volume II*, John Willey and sons. **1943**, p 619.

371. Fetscher, C. A., *Organic Syntheses Collective Volume IV*, John Willey and Sons, Inc. **1963**, p 735.

372. Althuis, T. H., Hess, H.–J., *J. Med. Chem.*, **1977**, 20, 146.

373. Zentmyer, D. T., Wagner, E. C., *J. Org. Chem.*, **1949**, 14, 967.

374. Furniss, B. S.; Hannford, A. J.; Smith, P. G. S.; Tatchell, A. E.; Vogel's Textbook of practical organic chemistry, Pearson education, **2007**, 1084.

375. Aldrich Research Chemicals Catalogue **2009-2010**, 1103.

376. Aldrich Research Chemicals Catalogue **2009-2010**, 119.

377. Lange, N. A., Sheibley F. E. *Organic Syntheses Collective Volume II*, John Willey and Sons, **1963**, 79.

378. Baddiley, T., *J. Chem. Soc.*, **1944**, 678.

379. Tomisek, C., *J. Am. Chem. Soc.*, **1945**, 67, 2112.
380. Lancaster Research Chemicals Catalogue, **2002-2003**, 1352.
381. Aldrich Research Chemicals Catalogue, **2009-2010**, 1828.
382. Aldrich Research Chemicals Catalogue, **2009-2010**, 1828.
383. Lancaster Research Chemicals Catalogue, **2002-2003**, 1319.
384. Aldrich Research Chemicals Catalogue, **2009-2010**, 94.
385. Lancaster Research Chemicals Catalogue, **2002-2003**, 1320.
386. Aldrich Research Chemicals Catalogue, **2009-2010**, 94.
387. http://www.chemicalbook.com/ProductChemicalPropertiesCB6164340_EN.htm
388. http://www.chemicalbook.com/ProductMSDSDetailCB2689005_EN.htm
389. http://www.chemicalbook.cn/ChemicalProductProperty_EN_CB0733568.htm
390. http://www.chemblink.com/products/1129-37-9.htm
391. http://www.chemicalbook.com/ChemicalProductProperty_EN_CB1776654.htm
392. http://www.apolloscientific.co.uk/display_item.asp?id=15500
393. http://www.chemspider.com/Chemical-Structure.920357.html?rid=c9f33767-a50b-4043-a3b8-6c591a169da4
394. Aldrich Research Chemicals Catalogue, **2009-2010**, 522.
395. Aldrich Research Chemicals Catalogue, **2009-2010**, 2017.
396. Aldrich Research Chemicals Catalogue, **2009-2010**, 1844.
397. Aldrich Research Chemicals Catalogue, **2009-2010**, 1844.
398. Lancaster Research Chemicals Catalogue, **2002-2003**, 73.
399. Curd, F. H. S., Landquist, J. K., Rose, F. L., *J. Chem. Soc.*, **1948**, 1759.
400. Hess, H.–J. US Patent 3511836, **1970**.
401. Aldrich Research Chemicals Catalogue **2000-2001**, 70.
402. Bristol-Meyer Company, US 4138561, **1979**.
403. Alexandra, F.; Charles, Z. WO Patent 2005007672A2, **2005**.
404. *Bollettino Chimico Farmaceutico,* **1989**, 128, 129.
405. Koho, K. T., JPN Patent 2000281660, **2000**, 12.
406. Leonardi, A.; Motta, G.; Boi, C.; Testa, R.; Poggesi, E.; De Benedetti, P. G.; Menziani, C., *J. Med. Chem.*, **1999,** 42, 427.
407. Arunlakshana, O.; Schild, H. O., *Br. J. Pharmacol.*, **1959**, 14, 48.

CONTENTS

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CERTIFICATE

This is to certify that the thesis entitled "**Design and synthesis of some multitargeted ligands as potential antihypertensive agents**" submitted for the Ph. D. Degree in Pharmacy by Mr Prashant Prakash Naik incorporates the original research work carried out by him under my supervision.

Supervisor
(Prof. M. R. Yadav)

HEAD
Pharmacy Department

DEAN
Faculty of Technology & Engineering,
The M.S. University of Baroda,
Vadodara -390 001

DECLARATION

I hereby declare that the topic entitled **"Design and synthesis of some multitargeted ligands as potential antihypertensive agents**" submitted herewith to The Maharaja Sayajirao University of Baroda, Vadodara for the fulfilment of the award of the degree of **DOCTOR OF PHILOSOPHY IN PHARMACY** is the result of the work carried out by me in Pharmacy Department, Faculty of Technology and Engineering, The M. S. University of Baroda, Vadodara.

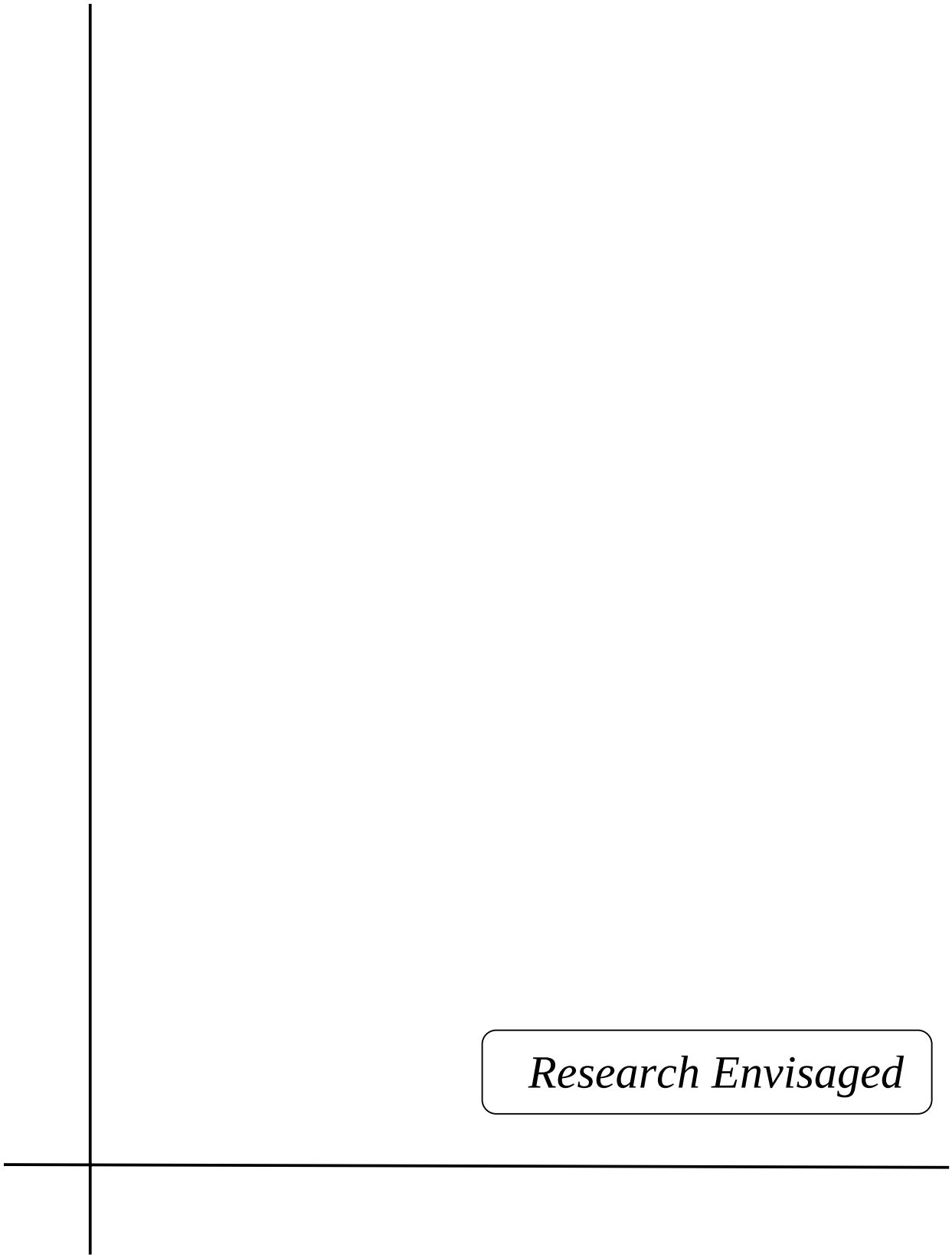
The result of this work has not been previously submitted for any degree/fellowship.

Date:

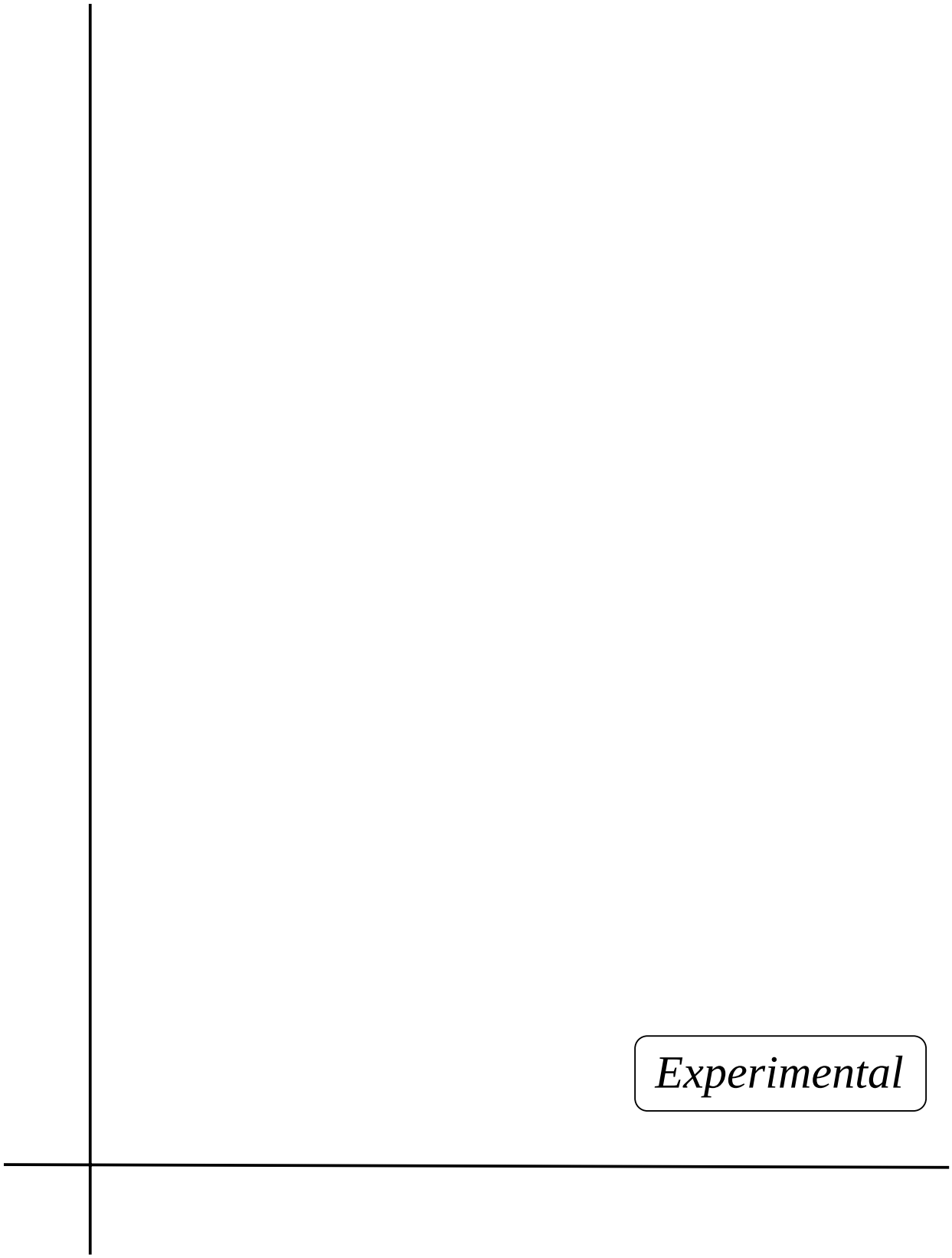
Place: Vadodara **Prashant P. Naik**

Introduction

Literature Survey


Research Envisaged

Resume' and Discussion


Experimental

Reference

Summary

DESIGN AND SYNTHESIS OF SOME MULTI-TARGETED LIGANDS AS POTENTIAL ANTIHYPERTENSIVE AGENTS

A THESIS SUBMITTED TO
THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA
FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY
IN
PHARMACY

BY

PRASHANT P. NAIK

UNDER THE GUIDANCE OF

PROF. M. R. YADAV

Pharmacy Department
Faculty of Technology and Engineering
The M. S. University of Baroda
Vadodara-390 001

DECEMBER 2011

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Faculty of Technology and Engineering
The M. S. University of Baroda
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DECEMBER 2011

Dedicated to my beloved family

Hypertension is recognized as one of the leading risk factors for human morbidity and mortality. On a worldwide basis hypertension has been ranked on the top as a cause of disability adjusted life years. The estimated total number of people with hypertension in 2000 was 972 million, and this is projected to increase by 60% to a total of 1.56 billion by 2025, i.e., 29% of the worldwide adult population.

This observation led to the discovery and development of increasingly complex and targeted vasodilators, although many of the earlier antihypertensive drugs. In spite of the availability of variety of antihypertensive agents, BP control in the general population is at best inadequate. Because of its multifactorial nature, simply interfering with one of its pathophysiologic mechanisms by monotherapy is usually insufficient to control it. Treatment with a single antihypertensive agent will generally control BP in less than half of the patients and more than 60% of the patients require combination therapy with two or more drugs of different classes to achieve target BP, as has been observed in a number of large clinical trials. Increasingly, it is being recognized that a balanced modulation of several targets can provide a superior therapeutic effect profile compared to the action of a selective ligand. The goal of antihypertensive treatment is to maximize therapeutic efficacy without significant adverse effects. Therefore, antihypertensive therapy has been directed toward improving BP control in treating patients with the available drugs by using the right combinations at optimum doses.

Treatment with a fixed dose drug combination is a good option as two or more drugs can be co-formulated in a single dosage form simplifying dosing regimens and thereby improving patient compliance. However, complications may arise due to highly complex PK/PD relationships of the drugs requiring sophisticated formulations. Potential drug-drug interactions could have a significant impact on the risks and costs.

An alternative strategy with a different risk - benefit profile is to develop a single chemical entity capable of modulating multiple biological targets simultaneously. A

lower risk of drug-drug interactions in comparison to cocktails or fixed drug combinations is a clear advantage of this strategy.

A key challenge in the design of multiple target ligands is attaining a balanced activity at each target of interest while simultaneously achieving a higher selectivity and suitable pharmacokinetic profile. Rational designing approaches involve selection of structural features from selective ligands combined into one single entity to produce multiple targeted ligands.

Hypertension is a hemodynamic disorder arising predominantly due to increase in peripheral vascular resistance.[10] There are two important contributors to the regulation of vascular tone:

- ✓ The sympathetic nervous system (SNS)
- ✓ The renin-angiotensin aldosterone system (RAAS).

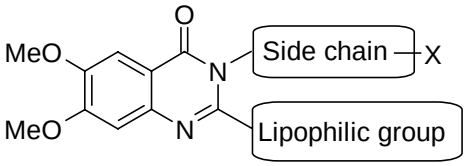
Over the years, a number of experimental and clinical investigations have shed light on the key role exerted by RAAS and SNS in the homeostatic control of blood volume and blood pressure. Straightforward evidence has been provided that these two systems do not operate independently but interact mutually with each other in accomplishing their cardiovascular regulatory functions.

Patients suffering from hypertension need multidrug therapy for effective control of blood pressure. Multidrug therapy poses certain pharmacokinetic problems. So it was planned to design and synthesize compounds bearing dual, α_1 and AT_1 receptor antagonistic properties.

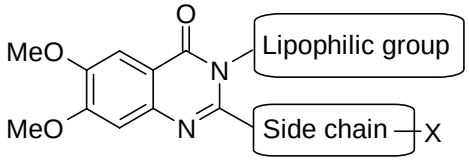
Knowledge–based approach was used for designing of dual α_1 and AT_1 antagonists. This approach is based on combining of frameworks and underlying pharmacophores of two drug molecules, each selective for one particular target of interest, into a single chemical entity possessing both of the activities of the parent

molecules. The resulting dual acting ligands could have linked, fused or merged pharmacophores. In order to design dual α_1 and AT_1 antagonists, a thorough survey of literature for α_1 and AT_1 antagonists was performed as discussed earlier. The molecules were designed by considering the structure activity relationships of both categories of compounds.

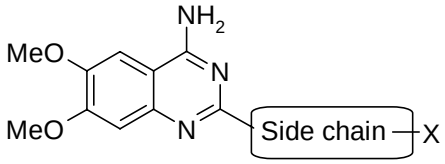
After studying the structural features of both of the classes of compounds it was felt that it should be possible to design dual α_1 and AT_1 receptor antagonists. It was envisaged to synthesize the following three categories of compounds:



(**I**)



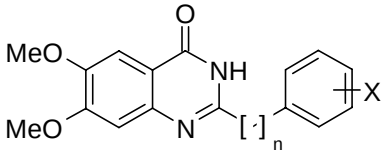
(**II**)



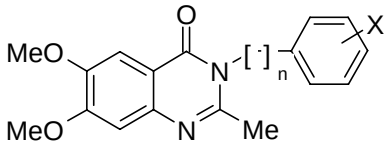
(**III**)

X = Neutral/acidic/basic groups

To explore the synthetic feasibility, preliminary work was started in this laboratory with the synthesis of simple 2/3-substituted phenyl-6,7-dimethoxyquinazoline-4(3*H*)-ones (**IV** and **V**) bearing neutral groups like methyl, halo, nitriles etc.



(**IV**) n = 0, 1

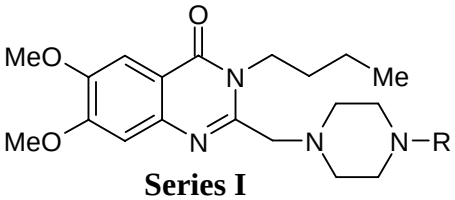


(**V**)

The synthesized compounds were evaluated for *in vivo* blockade of pressor response of phenylephrine (α_1) and ang II in rat model. To our astonishment, almost all of

the synthesized compounds showed significantly good blockade of responses of both of the agonists. But, unfortunately, majority of these compounds showed poor aqueous solubility which could be because of their neutral character.

Encouraged by these results, it was planned by this investigation to synthesize compounds which could have better aqueous solubility and more structural variations. The following six series of compounds were aimed to be synthesized and their biological activity evaluated.



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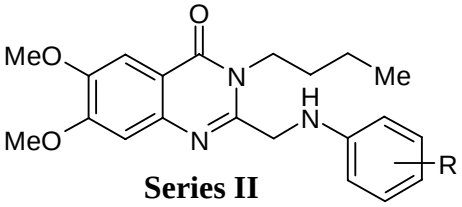

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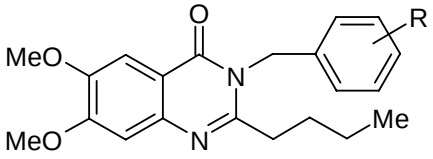
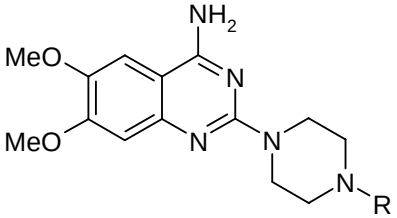


Series III



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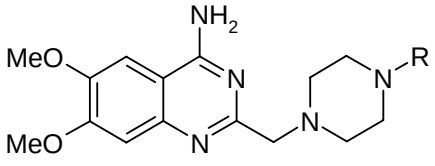

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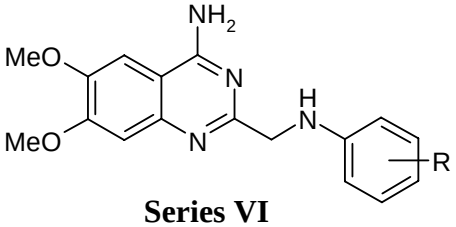

Series VI

All of the synthesized derivatives were characterized on the basis of their spectral data. Synthetic methods for preparing these new chemical entities, spectral (IR, PMR and Mass spectrometry) data and biological activity of these compounds have been discussed in detail in the thesis.

Synthesized compounds were subjected to screening for their *in vitro* antagonism at α_1 and AT_1 receptors in rat arota. Compound (**II-1**) showed highest potency on the both receptors amongst **Series II**. Compound (**IV-4**) was found to be potent against both α_1 and AT_1 receptors which even surpassed the activity of standard drugs. Compound (**V-5**) proved to be the most fruitful dual antagonist possessing pA_2 values of 10.1 (α_1 receptor) and 8.83 (AT_1 receptor).

None of the other compounds could match compound (**V-5**) in potency against both of these receptors. Four more compounds (**IV-4**, **VI-1**, **VI-9**, **VI-10** and **VI-20**) were found to possess good dual inhibitory properties. They have equal or even higher potency than standered drugs on both the types of receptors.

These results could serve as basis for designing of more potent dual α_1 and AT_1 receptor antagonists. Further optimization of the activity for the compounds is in progress in the laboratory.