# *Literature Survey*

## 2.1 $AT_1$ and $\alpha_1$ 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

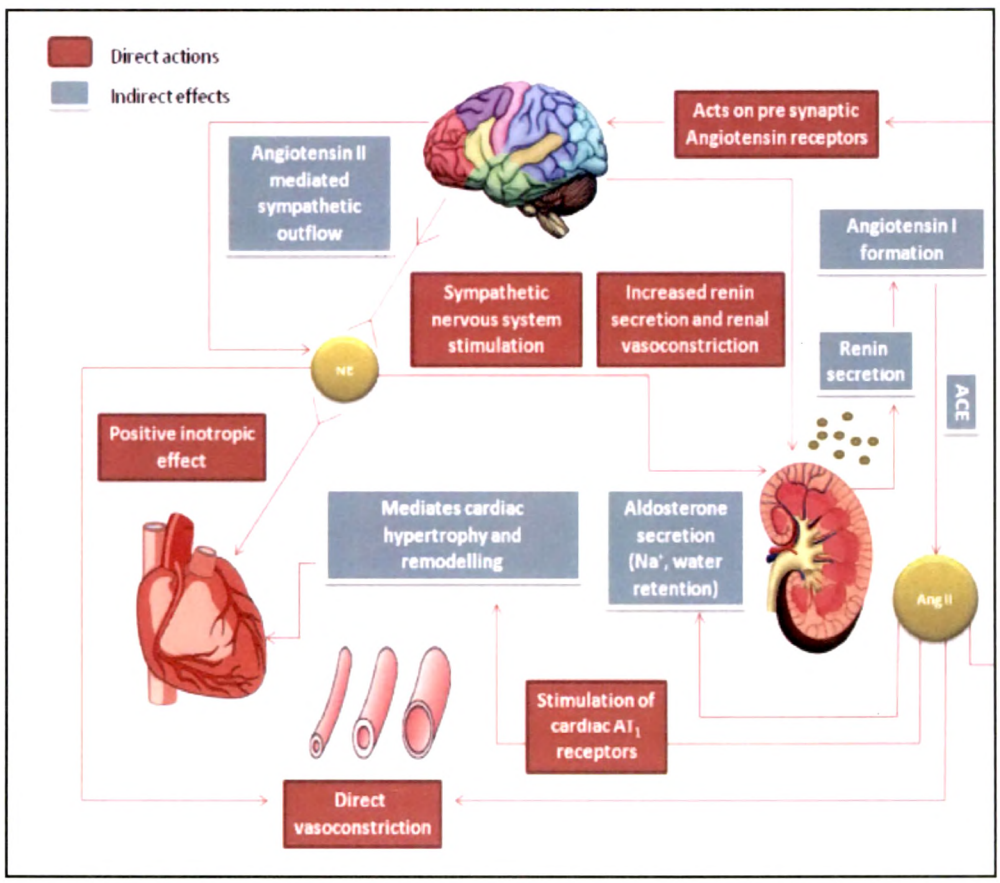



**Figure 4:** Coordination between Sympathetic Nervous System and Renin Angiotensin System

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 $\alpha_1$-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 $\alpha_1$-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 $\alpha_1$-receptor.[195] In neonatal rat cardiac myocytes ang II selectively down-regulates $\alpha_1$A-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 $\alpha_1$ and $AT_1$ receptors.

### 2.1.1 $\alpha_1$ Receptor[201]

The $\alpha_1$ 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 $\alpha_1$ and $\alpha_2$. The occurrence of $\alpha_1$/ $\alpha_2$-adrs throughout the vascular bed is not uniform. The initial sub-classification of $\alpha_1$ adr is into $\alpha_1A$, $\alpha_1B$ and $\alpha_1D$ subtypes. The $\alpha_1A$ 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 $\alpha_1B$ receptor subtype, it promotes cardiac growth and

structure. The $\alpha_1B$ receptor subtype is the most abundant type in the heart, whereas the $\alpha_1D$ receptor subtype is the predominant receptor causing vasoconstriction in the aorta. $\alpha_1A$, $\alpha_1B$ & $\alpha_1D$ adr isoforms differ in their biochemical properties, although their tissue distribution is distinct.

**Table 5**. Distribution, location and function of $\alpha_1$-adrenergic receptors

| Receptor | Location | Action |
|---|---|---|
| $\alpha_1$ | 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.

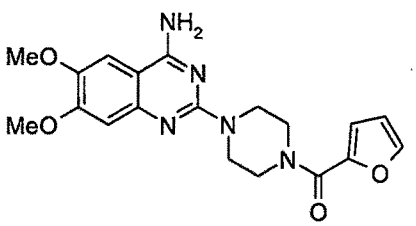
**Table 6.** Ang II Receptors, their locations and functions

| 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 |

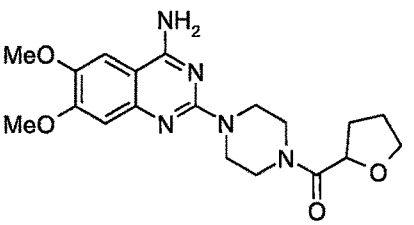
Since the aim of the current work was designing of dual $\alpha_1$ and $AT_1$ antagonists, it is in order to survey literature on the $\alpha_1$ blockers of prazosin category and the $AT_1$ antagonists.

## 2.2 $\alpha_1$ Receptor antagonists[201]

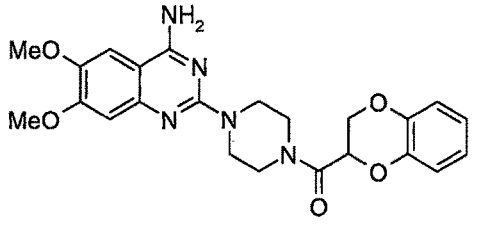
Prazosin (**AP1**) is the prototype $\alpha_1$ receptor blocker. Other antagonists include terazosin (**AP2**) doxazosin (**AP3**), alfuzosin (**AP4**) bunazosin (**AP5**), tiodazosin (**AP6**), naphazoline (**AP7**) and mephendioxan (**AP8**). 6,7-Dimethoxyquinazoline constitutes the main pharmacophore present in currently marketed drugs as discussed below.



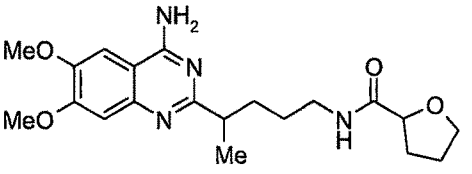

**(AP1)**



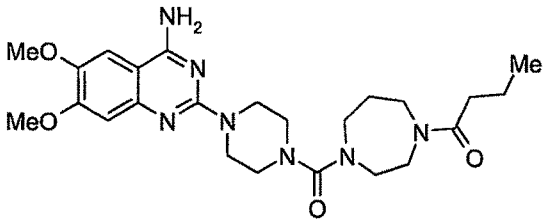

**(AP2)**



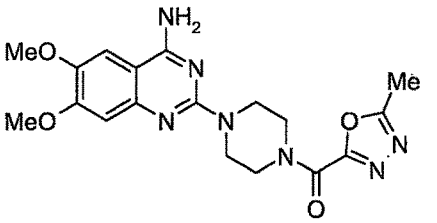
(AP3)



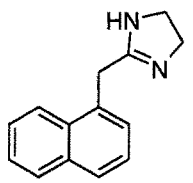
(AP4)



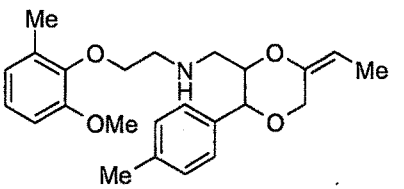
(AP5)



(AP6)



(AP7)



(AP8)

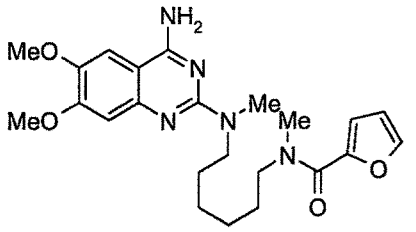
A variety of nuclei has been reported for $\alpha_1$ receptor antagonistic activity such as five membered rings like imidazolines, fused imidazolines, indoles and fused indoles, six membered rings like quinazolines, pyrimidines, dihyropyrimidines, pyridines, dihydropydridines, pyridazinones, fused pyrimidinediones and *N*-aryl indoles.

### 2.2.1 Quinazolines reported as $\alpha_1$ antagonists

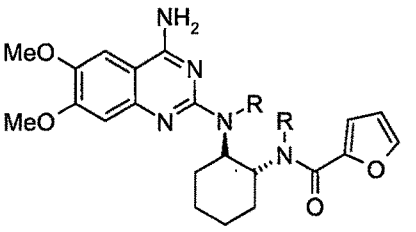
Quinazoline nucleus seems to be essential for $\alpha_1$ receptor antagonistic activity as is found in marketed drugs like prazosin (**AP1**), terazosin (**AP2**), doxazosin (**AP3**), alfuzosin (**AP4**) and bunazosin (**AP5**). These derivatives have a very high index of $\alpha_1$-/$\alpha_2$-adr 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.

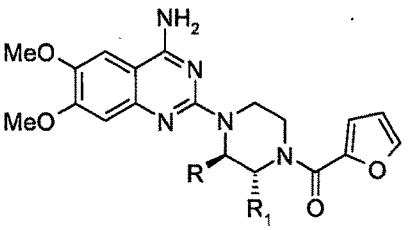


(**AP9**)

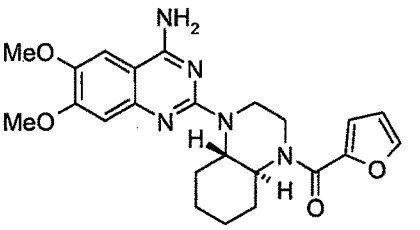


(**AP10**)

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 $\alpha_1$-adr antagonist, but also an effective antihypertensive agent.[210]



(**AP11**)

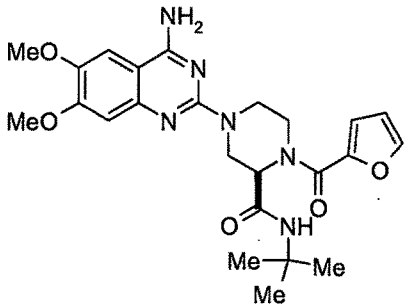


(**AP12**)

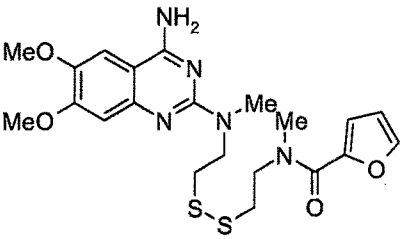
Substituents were introduced at position 5 of the 2-furoyl moiety and its replacement with classical isosteric rings was investigated. The 5-methylfuryl derivative [(+)-metcyclazosin], improved the pharmacological properties of the progenitor, displaying a competitive antagonism, and an 11-fold increase in selectivity for $\alpha_1$B over $\alpha_1$A receptor, while maintaining a similar selectivity for the $\alpha_1$B relative to the $\alpha_1$D receptor.[211]

Another approach consisted of incorporating new structural elements into the piperazine subunit. Moderate $\alpha_1$B 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]



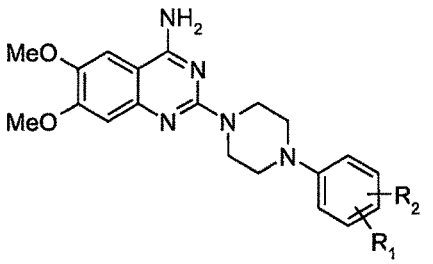
(**AP13**)



(**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 $\alpha_1$ receptor subtypes. The cystamine bearing quinazoline (**AP14**) of this series has a reversed affinity profile relative to (+)-cyclazosin, owing to its higher affinity for $\alpha_1$D receptor and a significantly lower affinity for the $\alpha_1$A and $\alpha_1$B 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.



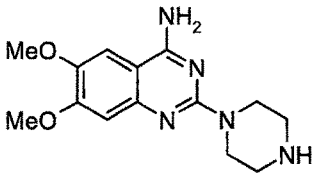
$R^1$ = H, 4-$OCH_3$, 4-$C_3H_7$, 4-$CH_3$, 4-$C_6H_5$, 4-$NH_2$

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

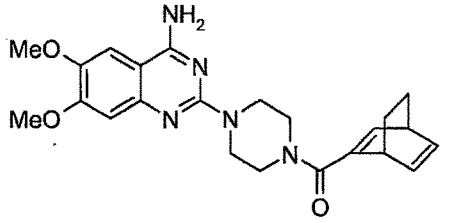
(**AP15**)

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 $\alpha_1$ 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]

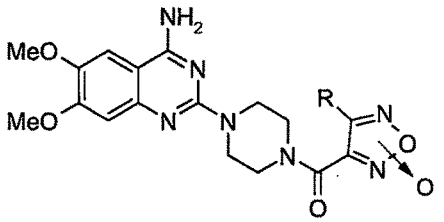


**(AP16)**



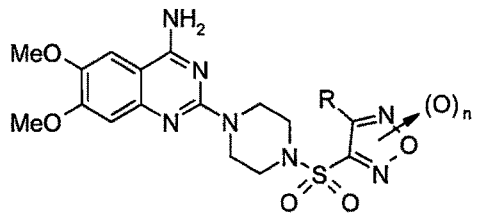
**(AP17)**

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

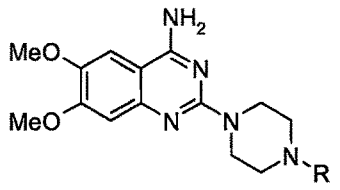
**(AP18)**



$R = C_6H_5$ and n = 0, 1

**(AP19)**

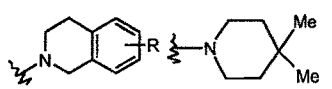
A novel series of piperazine and non-piperazine derivatives of 2,4-diamino-6,7-dimethoxyquinazoline (**AP20** and **AP21**) were synthesized and evaluated for their



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

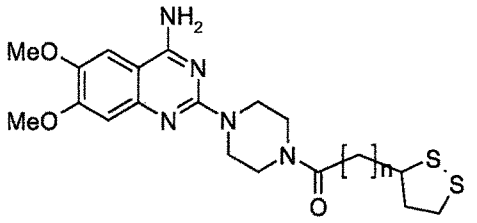
($R^1$ = Alkyl and Ar = Disubstituted aryl)

**(AP21)** $R = NHCH_2NHC_6H_5$, $NH\text{-}(CH_2)_n\text{-}CH(C_6H_5)$,

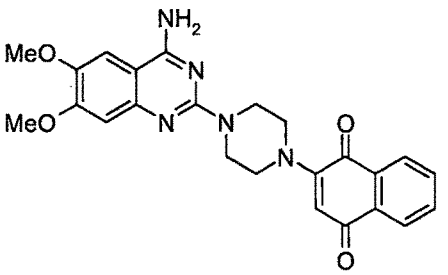


binding affinities toward $\alpha_1$ receptors.[218] Compounds (**AP20**) showed moderate selectivity toward $\alpha_1$B receptor subtype, whereas compounds (**AP21**) showed *in vivo* potency close to that of prazosin.[219]

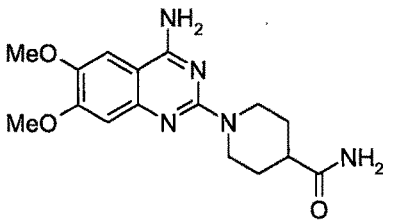
The furoyl moiety of prozosin was replaced with the lipoyl fragment of lipoic acid in compound **(AP22)** and with 1,4-naphthoquinone in compound **(AP23)**.[220] All of the compounds were effective $\alpha_1$ receptor antagonists when tested by both functional and binding assays.



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

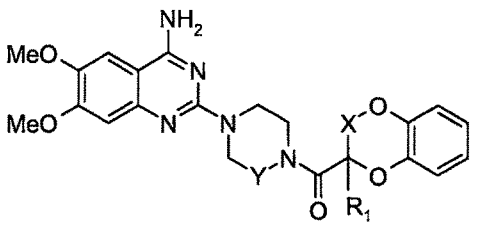


**(AP23)**



**(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 4$^{th}$ 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 $\alpha_1$-adr affinity and potency compared to prazosin.[222]



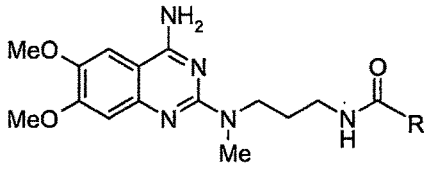
Y = $CH_2$, $(CH_2)_2$, $CH(CH_3)$; $R_1$ = H, $CH_3$; X = $CH(CH_3)$, $(CH_2)_2$, $CH_2$

**(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 $\alpha_1$ receptor affinity and

selectivity, and to prolong the duration of antihypertensive activity. Most of the members of this series (**AP25**) displayed high affinity for $\alpha_1$ receptors and none of the compounds showed any significant activity at $\alpha_2$ 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]

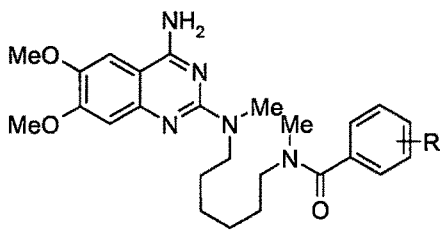


(**AP26**) R = $C_6H_5$

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

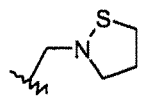
(**AP28**) R = Cyclopentyl

Simultaneous replacement of both piperazine and furan ring of prazosin gave (**AP29 - AP32**), which resulted in a potent and selective $\alpha_1$B receptor antagonist (85-



(**AP29**) R = H

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

(**AP31**) R = 

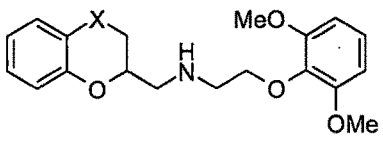
(**AP32**) R = 3-$CH_2N(CH_3)(CH_2)_4NHCH_3$

and 15-fold more potent than prazosin, at the $\alpha_1$A and $\alpha_1$D 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 $\alpha_1$ receptor antagonist activity. Compound, WB 4101 (**AP33**) is the prototype of $\alpha_1$ receptor antagonists bea-

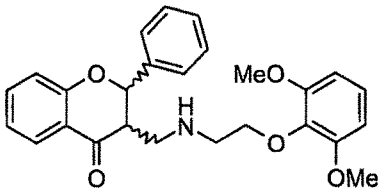



(**AP33**) X = O

(**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 $\alpha_1$ 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 $\alpha_1/\alpha_2$ selectivity; but except for the derivatives bearing the phenyl and *p*-methylphenyl substitutions at position 3, none of them showed selectivity for the $\alpha_1$ receptor subtype. These results imply that the 3-substitution endows a significant role in the modulation of selectivity for $\alpha_1$ receptor subtypes.



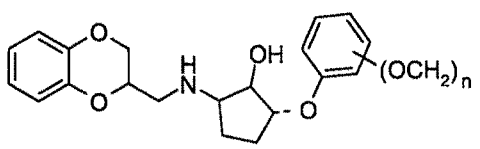

(**AP35**)

Subtle variations at positions 1 and 4 have been made to assess affinity and selectivity for $\alpha_1$ receptor subtypes. These modifications however, did not improve the

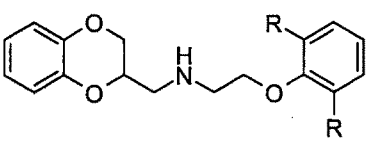
biological profile of these molecules with the exception of compound (**AP35**). Compound (**AP35**) is more selective to $\alpha_1$A adr subtype than to the $\alpha_1$B and $\alpha_1$D receptor subtypes.

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 $\alpha_1$ receptor. This structural modification also resulted in an inversion of the selectivity profile, as the resulting compound was more potent at $\alpha_1$D-adr than at $\alpha_1$A and $\alpha_1$B 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 $\alpha_1$D 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)**

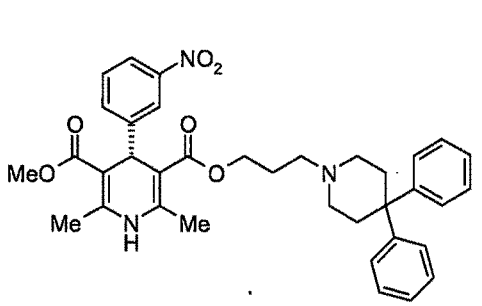
A number of ortho-disubstituted analogues of 2-[(2-phenoxyethyl)amino methyl]-1,4-benzodioxan were designed and synthesized in both the enantiomeric forms and tested in binding assays on the same receptors. The affinity values of the new compounds (**AP37**) were compared with the enantiomers of WB 4101 and of the ortho-monosubstituted derivatives, suggesting some distinctive aspects of the interaction of the phenoxy moiety, in particular with the $\alpha_1$A 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

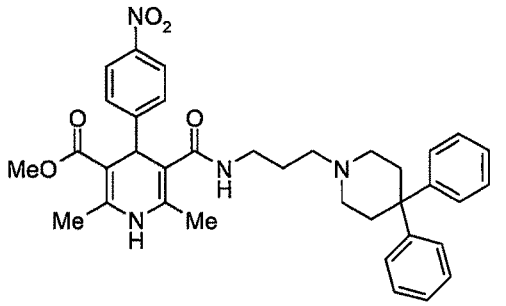
these compounds indicates that the 1,4-benzodioxane ring system is an integral pharmacophore for the activity, and rings like naphthalene, indole, tetrahydronaphthalene may have misfit planarity with the $\alpha_1$ receptor.[235]

### 2.2.3 Dihydropyridine and dihydropyrimidine containing antagonists

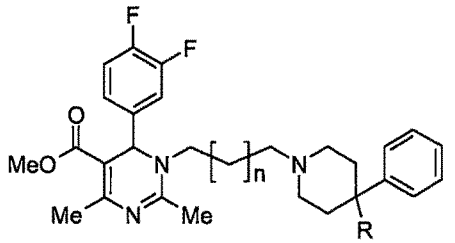
In contrast to the prazosin analogues, the 1,4-dihydropyridine, (*S*)-(+)-niguldipine (**AP38**) exhibits 340 to 630-fold selectivity in binding to the cloned human $\alpha_1$A receptor relative to the $\alpha_1$B and $\alpha_1$D receptors.[236] Another compound belonging to dihydropyridine class of 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 $\alpha_1$A receptor and reducing $Ca^{2+}$ channel affinity.[201]



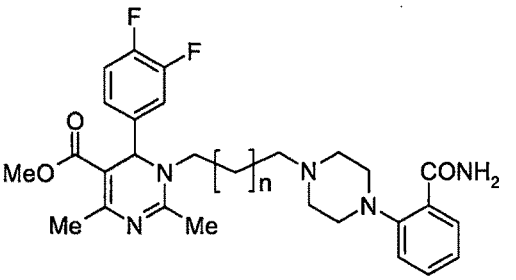
**(AP38)**



**(AP39)**



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

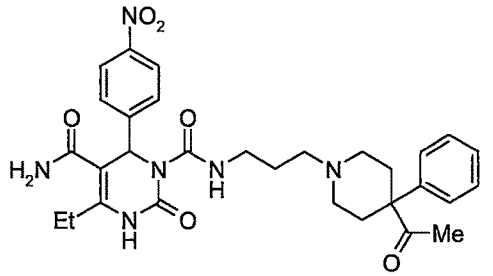


**(AP41)** n = 2, 3 etc.

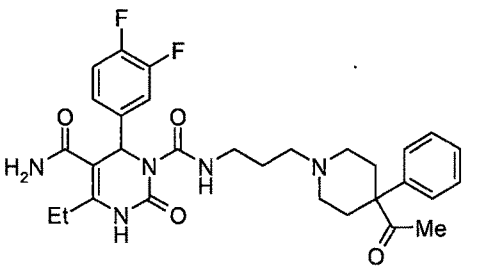
In an effort to optimize the pharmacokinetic parameters by replacing the dihydropyridine moiety with a dihydropyrimidine template, a number of dihydropyrimidines (**AP40** and **AP41**) showed good binding affinity (>300-fold) and selectivity for $\alpha_1$A-adr over $\alpha_1$B, $\alpha_1$D, and $\alpha_2$ 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 $\alpha_1$A 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-



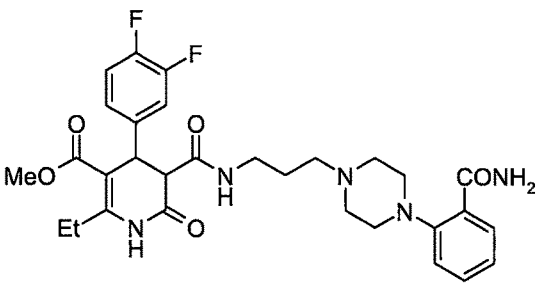
**(AP42)**



**(AP43)**

file. Thus, new compounds (**AP42** and **AP43**) were synthesized. These compounds showed good binding affinity and subtype selectivity for $\alpha_1$A 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]

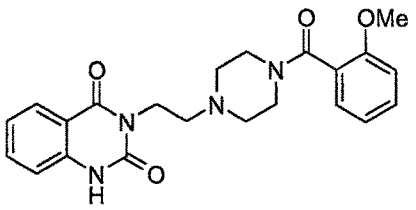


**(AP44)**

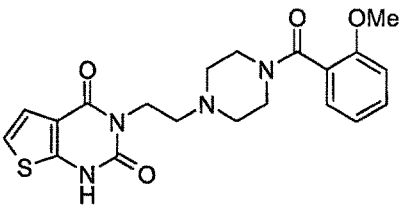
### 2.2.4 Fused pyrimidinedione containing antagonists

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 $\alpha_1$ 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 $\alpha_1$ receptor blocking properties.[241]

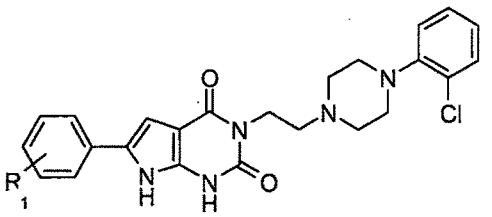
A new series of selective and high-affinity $\alpha_1$-adr ligands, characterized by a 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)dione system, was synthesized. Compounds (**AP47-AP49**) displayed affinity in the nanomolar range for $\alpha_1$ receptor.



**(AP45)**



**(AP46)**

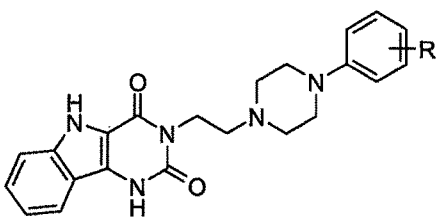


**(AP47)** $R_1$ = 2-Me

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

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

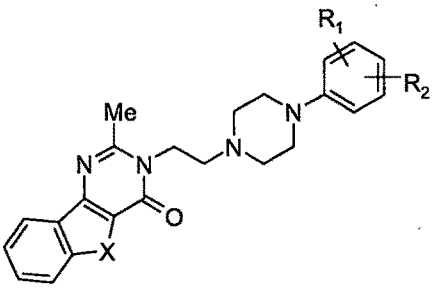
On similar lines a tricyclic 3-substituted pyrimido[5,4-*b*]indole-2,4-dione system was coupled by means of an alkyl chain to the phenylpiperazine moiety to



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

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

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



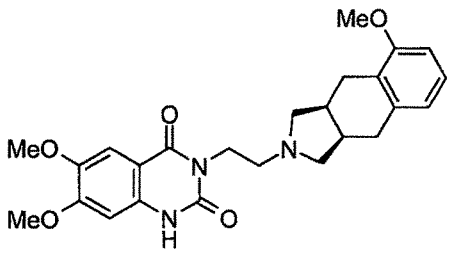
**(AP53)** X = NH, $R_1$ = 2- OMe, $R_2$ = 5-Cl

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

develop selective $\alpha_1$-adr binding ligands. In this series, compound (**AP50**) emerged as the most interesting candidate showing higher affinity and selectivity for $\alpha_1$-adr on rat cortical membranes over $\alpha_2$, $\beta_2$, and 5-$HT_1$A 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 $\alpha_1$ receptor ($\alpha_1A$, $\alpha_1B$, and $\alpha_1D$) subtypes, exhibited very good $\alpha_1D$ receptor selectivity.[242]

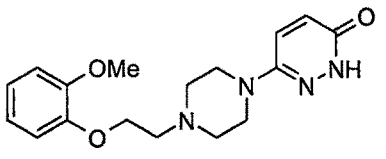
A number of new pyrimido[5,4-*b*]indole and benzothieno[3,2-*d*]pyrimidine derivatives were synthesized and evaluated for their binding and functional properties at $\alpha_1$ receptor subtypes. In binding assays on human cloned receptors, some new compounds such as (**AP53** and **AP54**) showed very high affinity and a slight preference for the $\alpha_1D$-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]



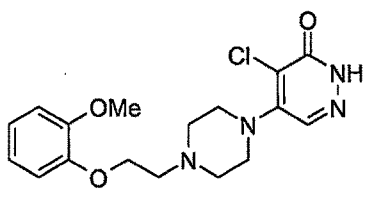

**(AP55)**

### 2.2.5 Pyridazinone ring containing antagonists

The literature search reveals pyridazinones as a class of compounds with a potential for selective $\alpha_1$ receptor antagonist activity. The pyridazinone derivatives



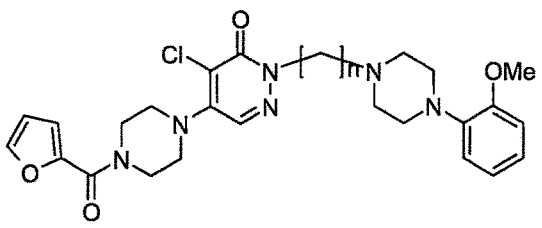

**(AP56)**



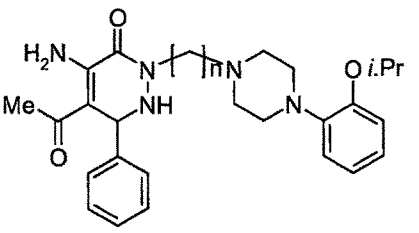

**(AP57)**

(**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 $\alpha_1$ 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 $\alpha_1$ and $\alpha_2$ receptors. Compound (**AP58**) showed a very high selective affinity for the $\alpha_1$ receptor, which was 274 times higher than that for $\alpha_2$ 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**)



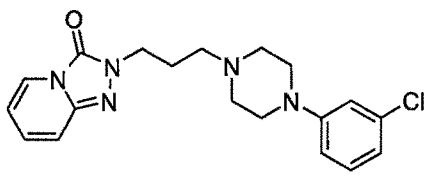
(**AP59**)

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 $\alpha_1D/a_1A$, high $\alpha_1D/a_1B$, and very high $\alpha_1A/5\text{-}HT_1A$ and $\alpha_1D/5\text{-}HT_1A$ receptor selectivities.[249]

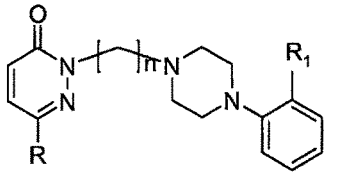
Using a rational design approach, compounds bearing a benzimidazolyl or imidazolyl substituent on the pyridazinone moiety have been synthesized and evaluated for $\alpha_1$ receptor affinity and blocking activities. The most active compound of the series showed 1.1 nM affinity toward $\alpha_1$ receptor.[250] 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 $\alpha_1A$ and $\alpha_1D$ receptor subtypes.[251]

In order to increase the affinity and selectivity for $\alpha_1$-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 $\alpha_1$ receptor affinity and selectivity profile. Lengthening of the spacer chain to three- or four-carbon atoms afforded compounds with an increased affinity toward $\alpha_1$ 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

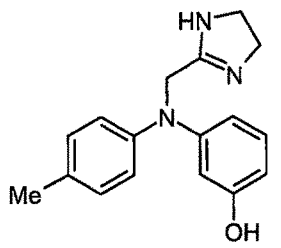
Further, elongation of the spacer to five- and six-carbon atoms led to slight decrease in the activity. These experimental results suggested that the long alkyl spacer, mainly based on its conformational flexibility, could assume a size and shape that influenced the affinity (and selectivity) of compounds to $\alpha_1$ and $\alpha_2$ 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 $\alpha_1$ receptor. Compounds like clonidine (**AP64**) and naphazoline (**AP65**), which contain a 2-iminoimidazolidine and imidazoline rings, respectively, show $\alpha_1$- and $\alpha_2$ receptor antagonist activities.[253] Furthermore, specifically phentolamine (**AP66**), which contains an imidazoline ring, is a well known $\alpha_1$ adr antagonist.[254]

**(AP64)**

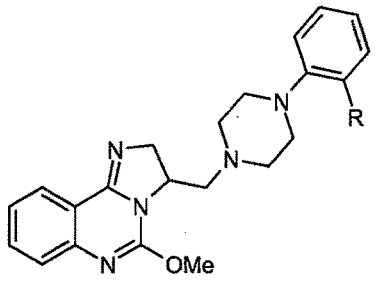
**(AP65)**



**(AP66)**

Conformationally restricted analogues have been synthesized to check their selectivity for $\alpha_1$A 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]

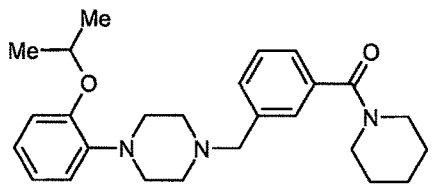


**(AP67)** R = OMe

**(AP68)** R = Cl

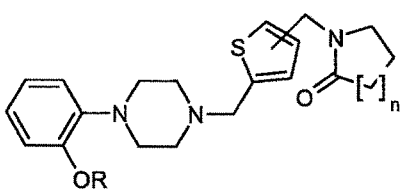
### 2.2.7 N-Aryl and N-heteroaryl piperazine derivatives

Synthesis and activity of RWJ-37796 **(AP69)**, an arylpiperazine derivative, which binds with high affinity ($K_i$ < 4 nM) to 5-$HT_1$A and $\alpha_1$A receptors, have been reported.[256] $\alpha_1$-Adr binding has been broken into $\alpha_1$A (0.20 nM) and $\alpha_1$B receptor (47 nM) components by competition experiments with the $\alpha_1$A receptor ligand WB 4101.

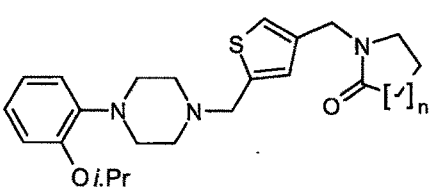


**(AP69)**

Screening of a chemical library against $\alpha_1$-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 $a_1$A receptor and very selective for it than other subtypes.[257]



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



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

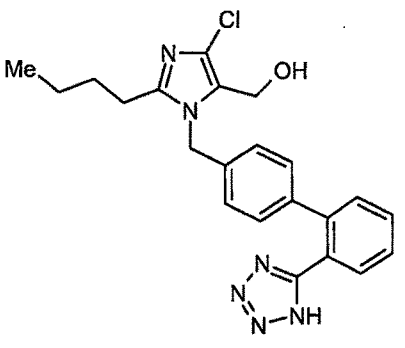
A new series in which the thiophene ring was replaced by other five-embered heterocyclic ring systems like isoxazole, oxazole and thiazole was synthesized and

evaluated for $\alpha_1$-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 $\alpha_1$A receptor subtypes.[258]

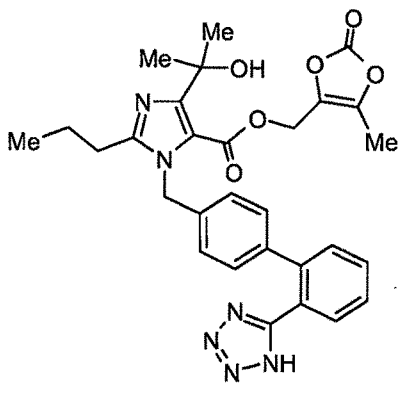
A new class of piperazine derivatives was designed, synthesized and biologically tested for the $\alpha_1$ receptor antagonistic activity. Biological data showed an interesting profile for the phenylpiperazine subclass which was found to have nanomolar affinity toward $\alpha_1$ receptor and less pronounced affinity for $\alpha_2$ and the 5-$HT_1$A serotoninergic receptors.[259]

### 2.3 $AT_1$ receptor antagonists[202]

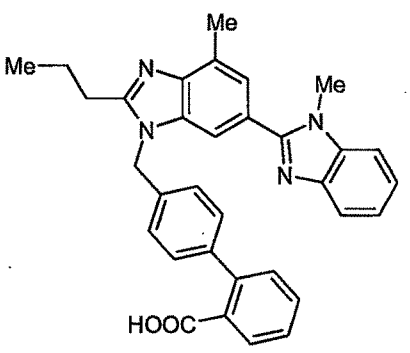
Some of the marketed $AT_1$ receptor antagonists are shown below. Losartan (**AT1**) is the prototype for this class of antagonists. Other antagonists are olmesartan (**AT2**), telmisartan (**AT3**), valsartan (**AT4**), candesartan (**AT5**) and irbesartan (**AT6**)



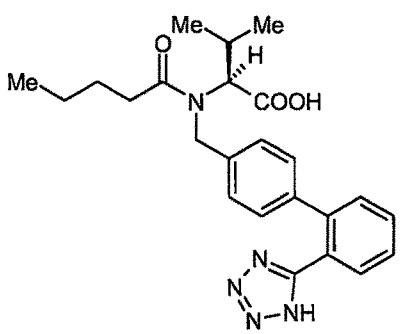

(**AT1**)



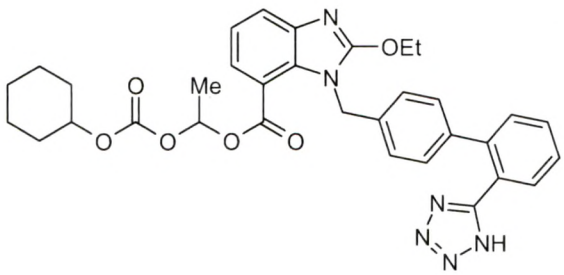

(**AT2**)



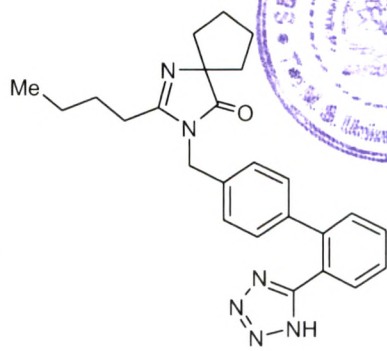

(**AT3**)




(**AT4**)



(**AT5**)



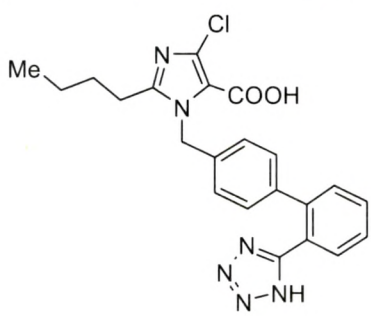
(**AT6**)

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.

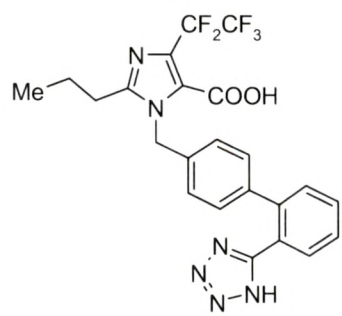
### 2.3.1 Imidazole containing antagonists

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



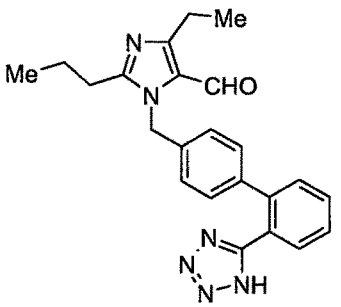
(**AT7**)



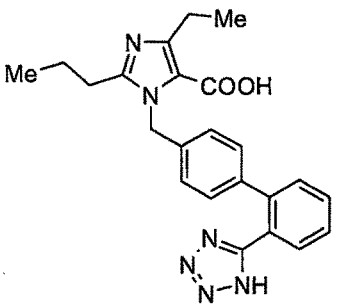
(**AT8**)

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).



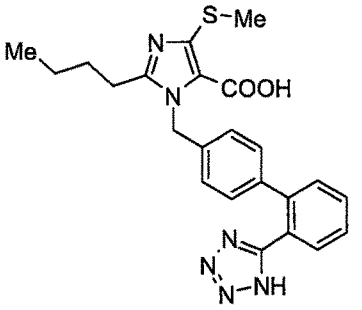

**(AT9)**



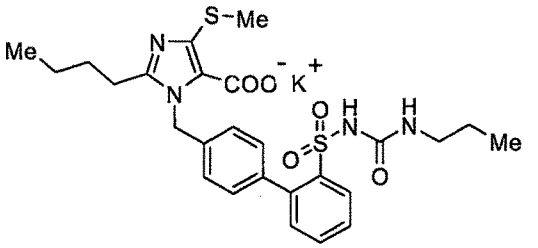

**(AT10)**

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).

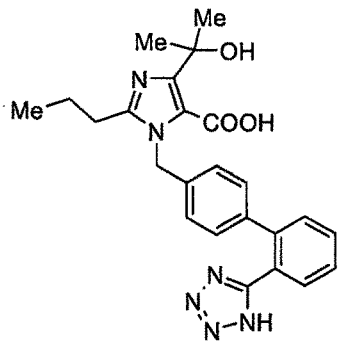


**(AT11)**

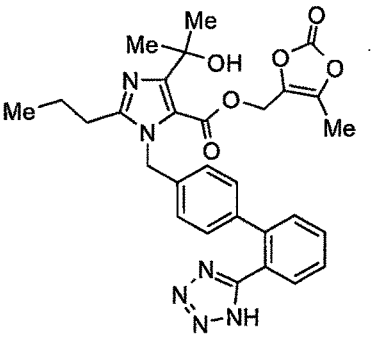


**(AT12)**

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]

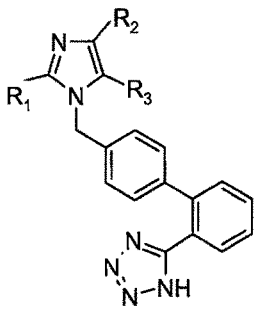


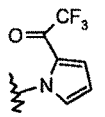
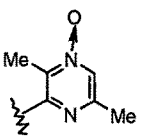
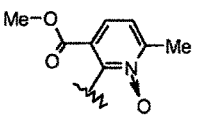
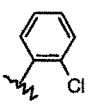
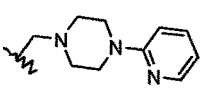
**(AT13)**



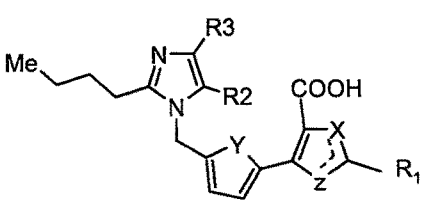
**(AT14)**

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]

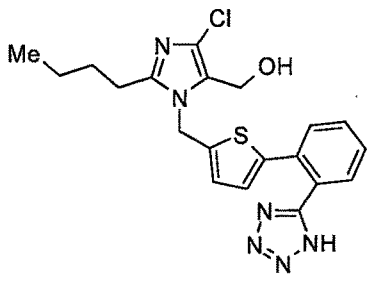


X = O, S, CH=CH, N= CH

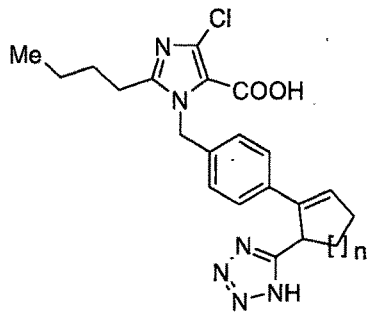
Y = O, S, CH=CH

Z = CH, N, N=CH

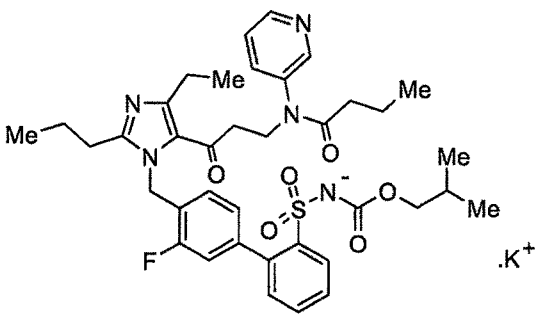
**(AT20)**



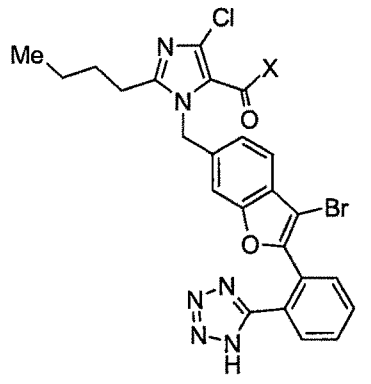
**(AT21)**



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

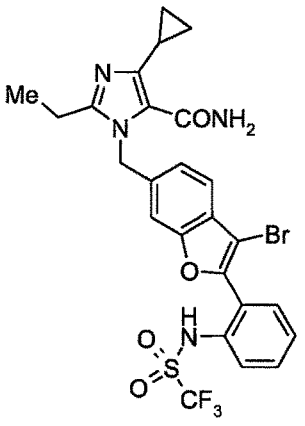


**(AT23)**

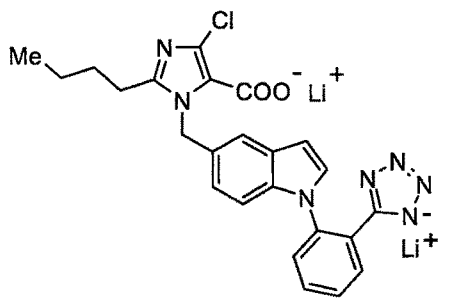


**(AT24)** X = OH

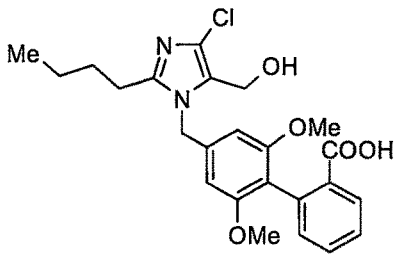
**(AT25)** X = $NHCH_2COOEt$



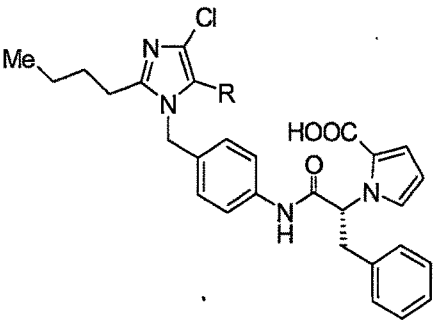
**(AT26)**



**(AT27)**



(AT28)

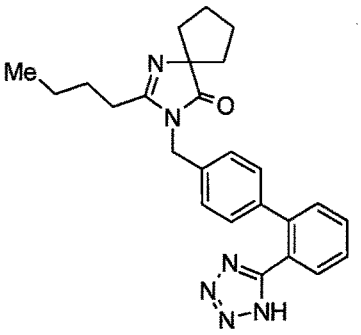


R = COOH, $CH_2COOH$, $CH_2CH_2COOH$

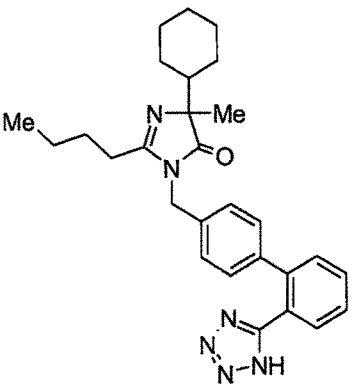
(AT29)

### 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)

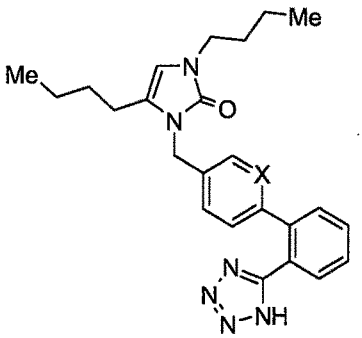


(AT31)

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]

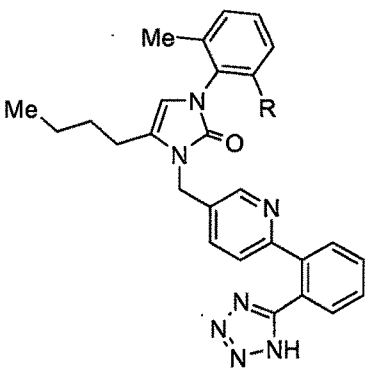
Non-tetrazole analogues of compound (**AT30**) were also reported but none of these compounds showed the same or a better activity than the parent tetrazole analogue.[295]

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

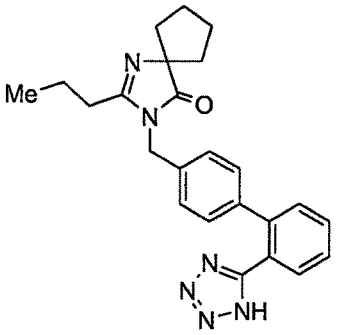
(**AT33**) X= N



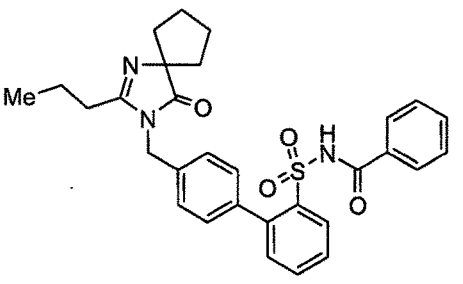
(**AT34**) R= H

(**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**)



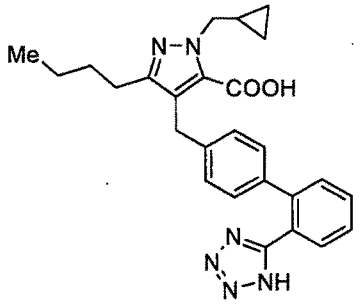
(**AT37**)

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]

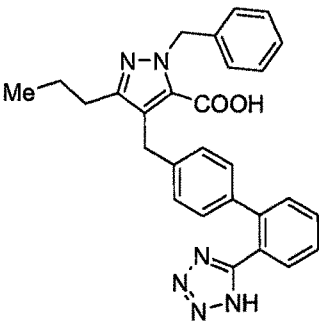
### 2.3.3 Pyrazole containing antagonists

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]

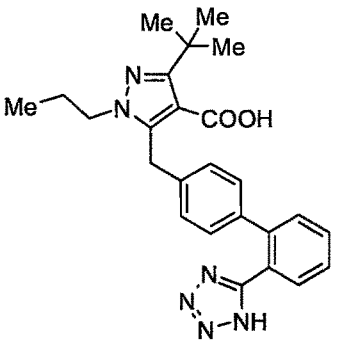
Ashton et al. carried out similar type of work at the Merck Lab. The most potent compound (**AT39**) showed $IC_{50}$ of 0.42 nM in rabbit aorta and inhibited 90%




(**AT38**)




(**AT39**)



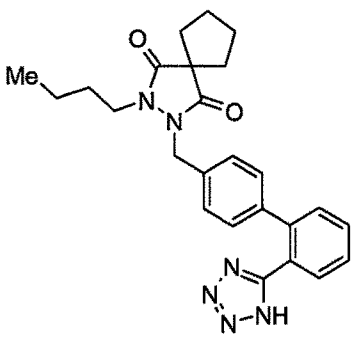

(**AT40**)

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.

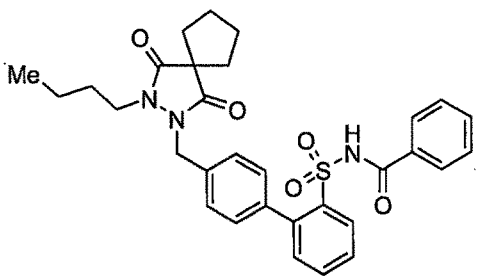
reported UR 7280 (**AT40**) as a selective $AT_1$ antagonist which showed high potency both *in vitro* ($IC_{50}$ 3 nM) and *in vivo* assays (0.3 mg/kg) and inhibited more than 60% pressor response of ang II.[202]

### 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)**

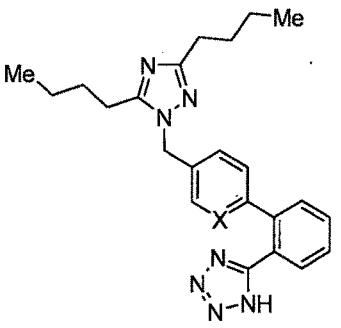
### 2.3.5 Triazole containing antagonists

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-

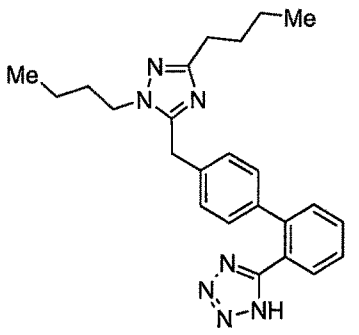
pyridinylphenylmethyl was conducted to determine the pharmacological effects of such substitutions. The most active compound in the series SC-52458 (**AT44**) showed $IC_{50}$ value of 6.9 nM, $pA_2$ value of 8.2, and was found to have superior *in vivo* properties than SC-50560.[306]

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]



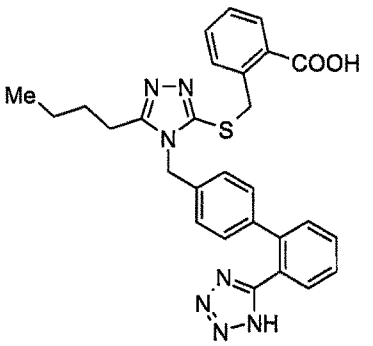
(**AT43**) X = CH

(**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]

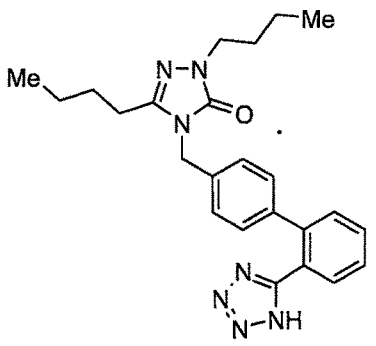


(**AT46**)

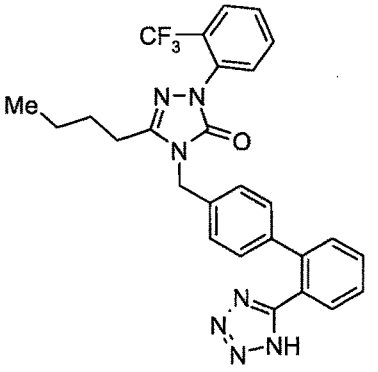
### 2.3.6 Triazolone containing antagonists

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)**



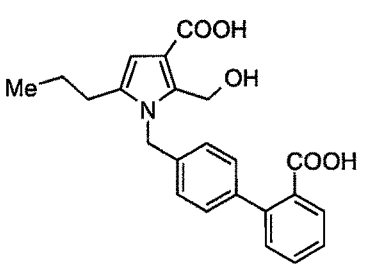
**(AT48)**

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]

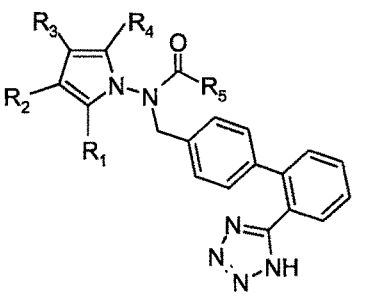
Aryl substituted compound (**AT48**) effectively displaced ($IC_{50}$ 1.2 nM) $^{125}I$ $Sar^1Ile^8$ Ang II from rabbit aortic membranes. The tetrazole moiety of (**AT48**) was replaced by other carboxylic acid bioisosteres such as acylsulfonamides (L-159,913). It is a $AT_1$ selective, reversible and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

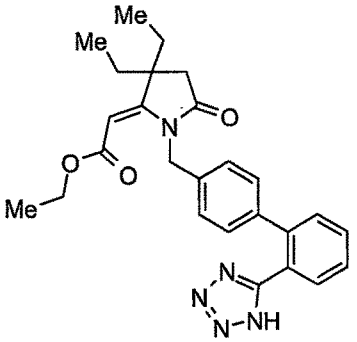


**(AT50)**

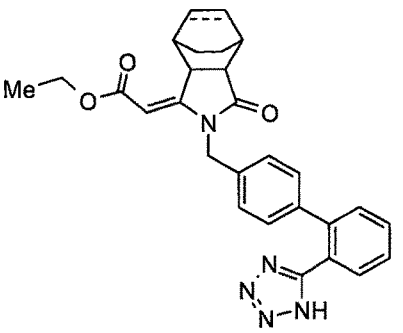
showed weak antagonistic activities. Pyrroles were predicted to be weak antagonists in comparison to imidazoles because of the lack of a nitrogen atom at the $C_3$ position

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)**

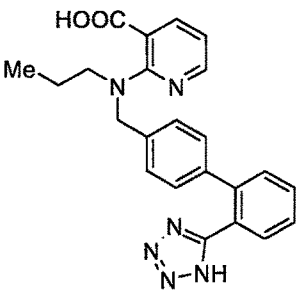


**(AT52)**

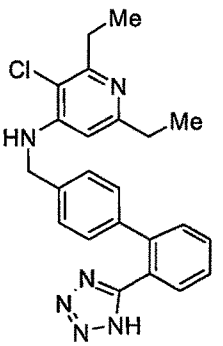
$IC_{50}$ as low as 100 nM (rabbit adrenal cortex). Some of the compounds from this series were found to be orally active in SHR.[312]

### 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)**

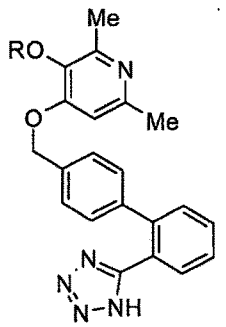


**(AT54)**

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

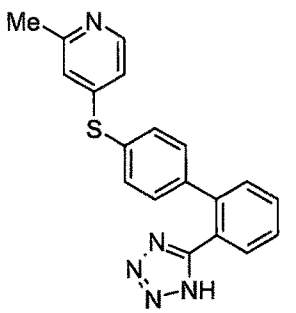
II pressor response for 5 hours after dosing at 1.0 mg/kg. It showed high oral absorption with an $ED_{50}$ of 0.06 mg/kg.[315]

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



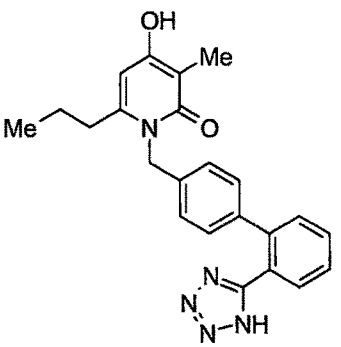

(**AT55**) R= Me

(**AT56**) R=H




(**AT57**)

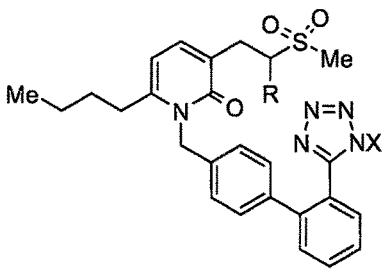
*in vitro* and *in vivo* than EF2831.[307] Pyridine ring connected to biphenyl moiety through sulphur linker (**AT57**) was also synthesized and evaluated for $AT_1$ receptor antagonistic activity but it showed weak $AT_1$ antagonistic activity ($IC_{50}$ 1.5 uM, rat liver membrane).[318]




(**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]

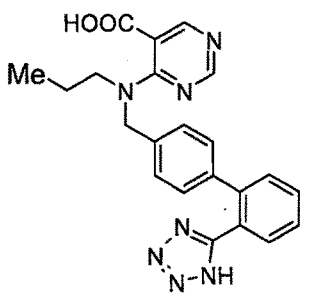
Research group at E Merck worked on a series of dihydropyridin-2-ones. Some of the potent compounds (**AT59** and **AT60**) in the series displayed potencies in nanomolar range (1.9 nM and 1.2 nM) and their inhibitory effect on ang II pressor response in pithed rat was superior to that of losartan.[320]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



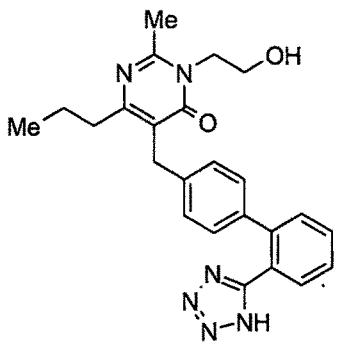
(**AT62**)

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

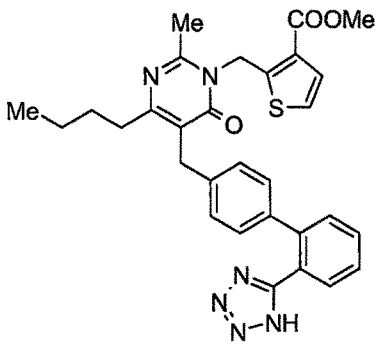
terms of the antihypertensive effect and the duration of action.[313] Heterocyclic analogues of A-81080 were synthesized and evaluated for $AT_1$ antagonistic activity and were found to be less potent.[322]

### 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]

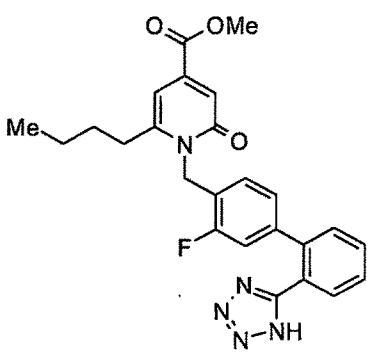



**(AT63)**

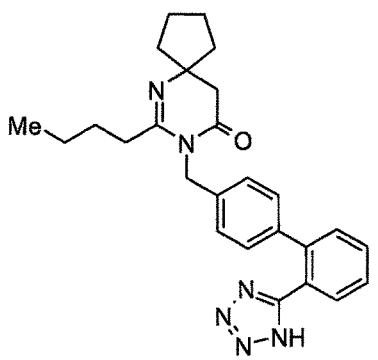



**(AT64)**

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




**(AT65)**



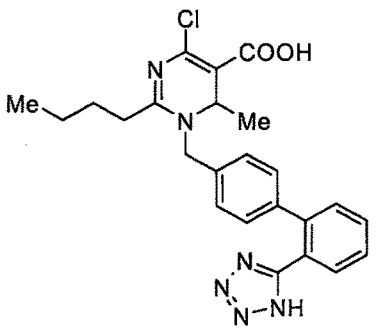

**(AT66)**

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]

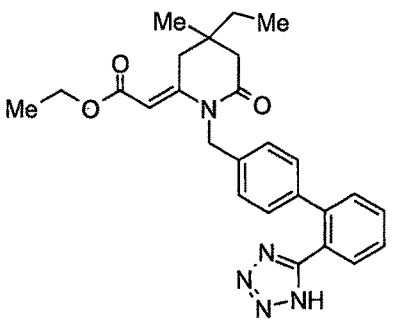
A novel series of homologues (e.g. **AT66**) of SR 47436 (**AT30**), substituted 3*H*-dihydropyrimidinones were identified as $AT_1$ receptor antagonists. The best compound (**AT66**) in the series showed high affinity for the $AT_1$ receptor with $IC_{50}$ in the nanomolar range. It was equipotent to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



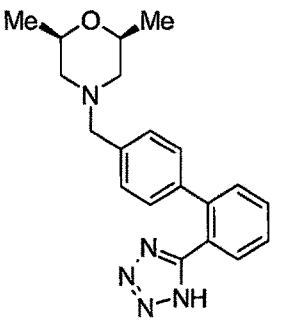
**(AT68)**

### 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]

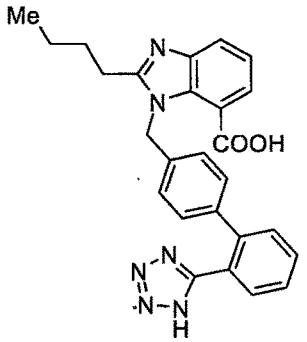


**(AT69)**

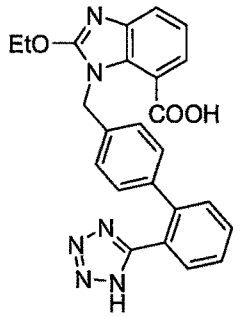
### 2.3.14 Benzimidazole containing antagonists

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]

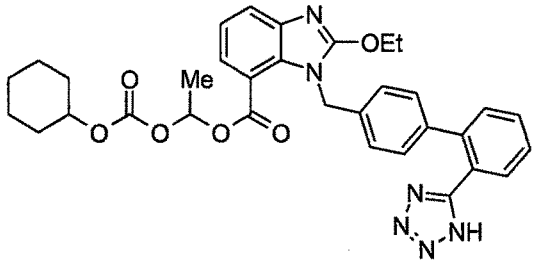


**(AT70)**



**(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-

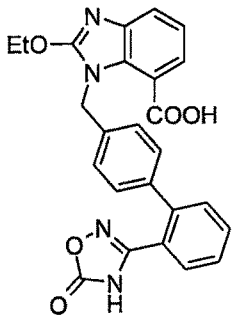


**(AT72)**

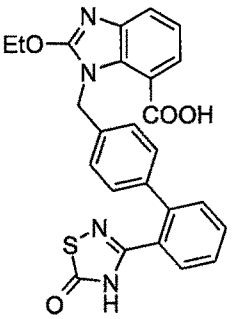
der to improve the oral bioavaibility, different esters of compound **(AT71)** were prepared and evaluated. The most potent compound of the series TCV-116 **(AT72)** (Candesartan cilexetil) is an orally active nonpeptide antagonist of $AT_1$ receptor. Compound **(AT72)** is a highly potent and long lasting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



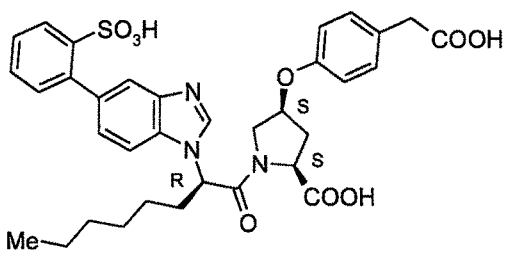
**(AT73)**



**(AT74)**

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

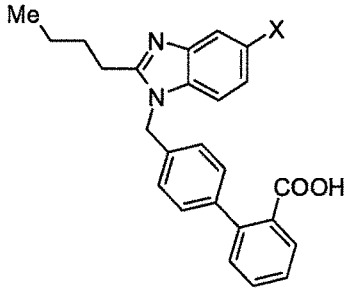
A novel series of heterocyclic compounds bearing two acidic functionalities, a carboxyl group and a tetrazole ring, was prepared and evaluated for *in vitro* and *in vivo* activities. These derivatives showed significantly more potent $AT_1$ receptor antagonistic activities than the parent compounds 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)**

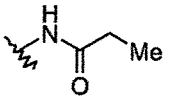
Palkowitz et al. reported a novel series of benzimidazoles (e.g. **AT75)** with phenoxyprrolidine side chain for ang II antagonistic activity. All of these benzimidazole analogues were found to be equipotent *in vitro*.[336]

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]

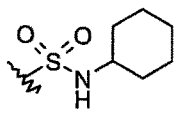


**X**

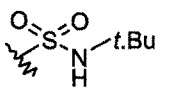
**(AT76)** $NO_2$



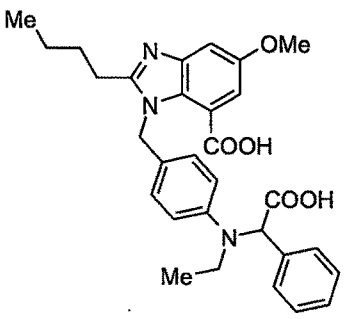
**(AT77)**



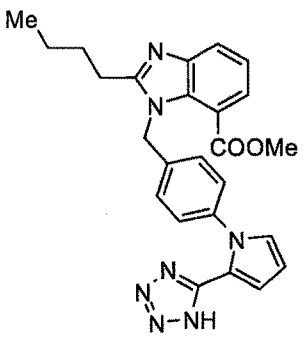
**(AT78)**



**(AT79)**



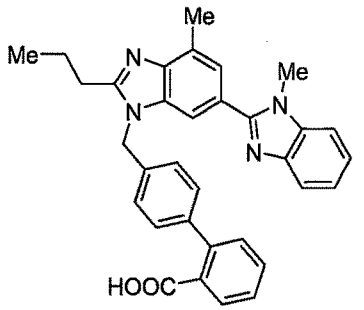
**(AT80)**



**(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]

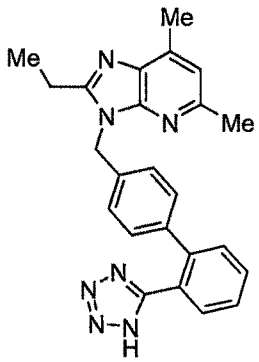


**(AT82)**

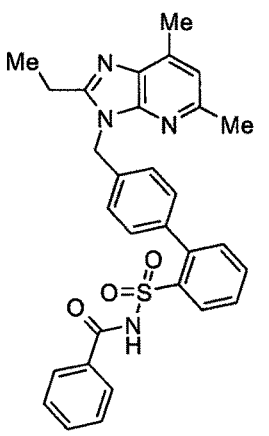
### 2.3.15 Imidazopyridine containing antagonists

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



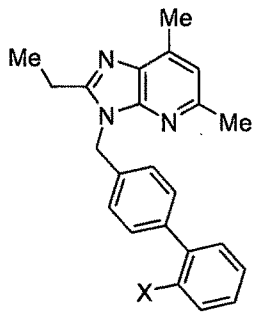
**(AT83)**



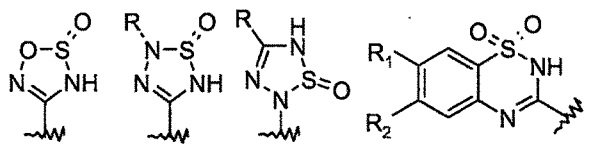
**(AT84)**

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]



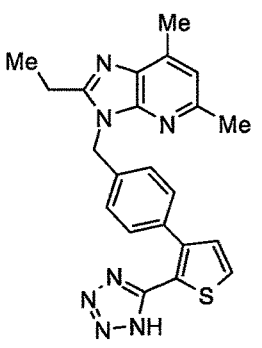
**X**



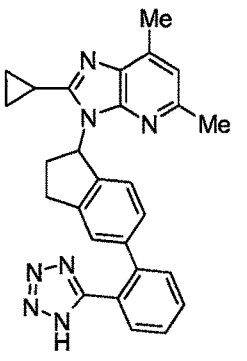
**(a)** **(b)** **(c)** **(d)**

**(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)**



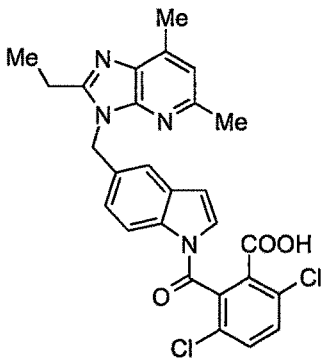
**(AT87)**

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

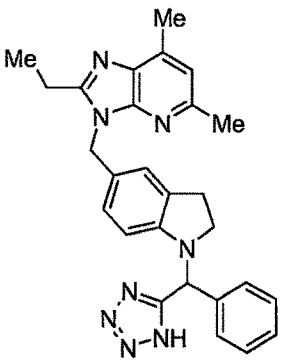
$AT_2$ affinity. Substitution at the 5th position of thiophene ring also imparted higher AT2 binding. [347,348]

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)**



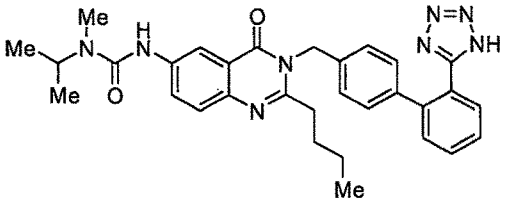
**(AT89)**

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

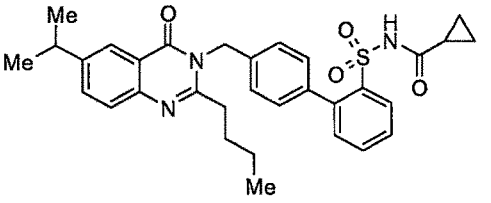
### 2.3.16 Quinazolinone containing antagonists

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

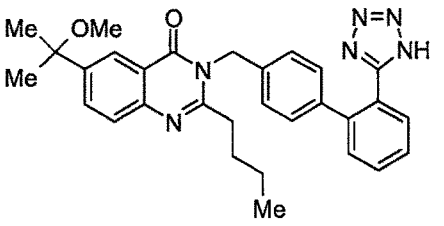
excellent *in vivo* activity in conscious rats after intravenous ($ED_{50}$= 0.25 mg/kg) and oral administration ($ED_{50}$ 0.68 mg/kg).[352]



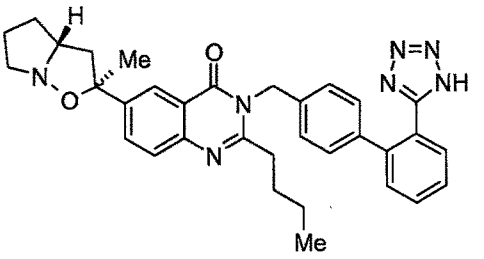
**(AT90)**



**(AT91)**

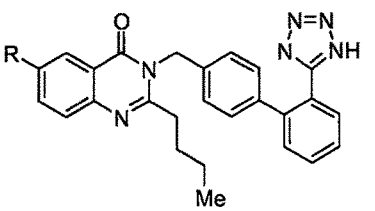


**(AT92)**

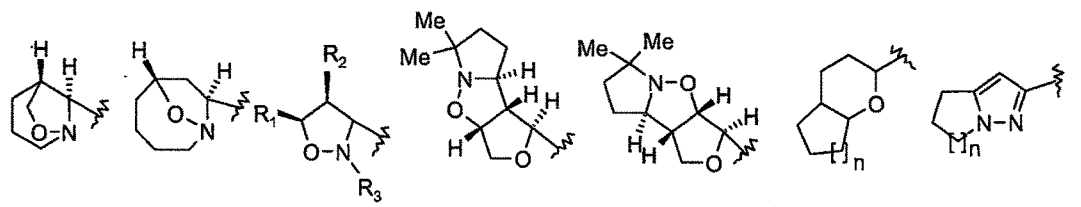


**(AT93)**

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 190,133 (**AT93**) was found to be specially potent, orally active,



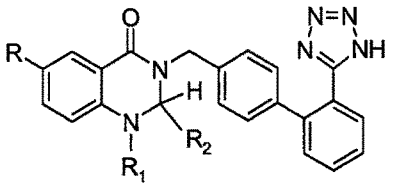
**(AT94)** R



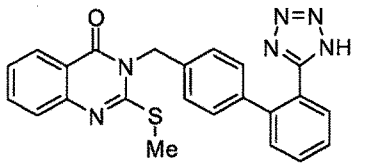
non-competitive $AT_1$ receptor antagonist with an apparent $pA_2$ of 10.9. CL 332,877, sodium salt of CL 329,167 (**AT92**) is a potent, long-acting, noncompetitive antagonist ($pA_2$ 10.9).[354] In order to search other heterocycles which not only exceed the oral

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]

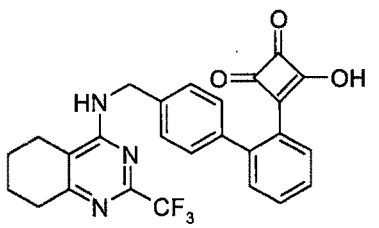
A series 2,3-dihydro-4(1*H*)-quinazolinone analogues (**AT95**) related to CL 329,167 (**AT92**) were synthetized and evaluated. But these compounds were devoid of any significant oral activity.[356] Ismail et al. have reported a series of novel quinazolin-4-ones. The most active compound (**AT96**)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



**(AT95)**



**(AT96)**



**(AT97)**

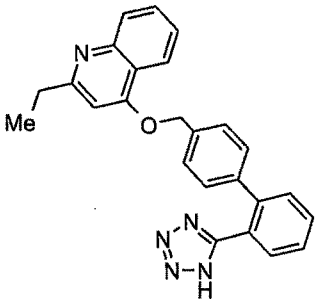
A novel analogue (**AT97**) containing bioisostere of tetrazole, 3-hydroxy-3-cyclobutene-1,2-dione was synthesized and evaluated. It showed less potency than parent tetrazole analogue.[358]

### 2.3.17 Quinoline containing antagonists

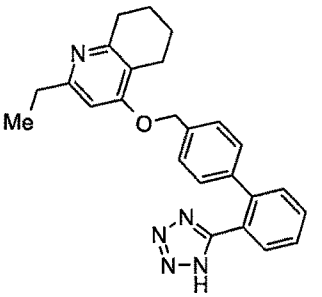
Oldham et al. reported ICI-8731 (**AT98**) an orally active, potent ($IC_{50}$ 30 nM, guinea pig adrenal) and competitive ($pA_2$ 8.3, rabbit aorta) $AT_1$ antagonist.[359]

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

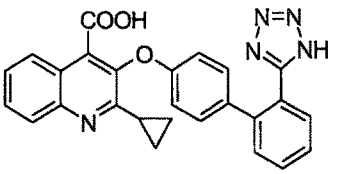
or superior activity to ICI-6888 in binding assay and in inhibition of the ang II induced pressor response in normotensive rats. Compounds bearing substituents in the $C_3$ position showed comparable or better activity than the parent ICI-6888 (**AT99**) in



**(AT98)**



**(AT99)**

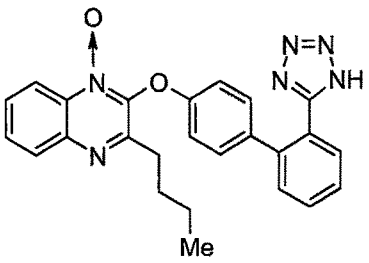


**(AT100)**

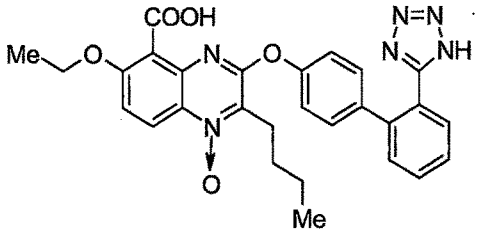
an acute dosed rat model (i.v.).[361] Lloyd et al. reported BMS-183920 (**AT100**) as a potent ($K_i$ 2.9 nM, rat adrenal cortex) $AT_1$ antagonist. It is an insurmountable antagonist.[362]

### 2.3.18 Quinoxaline containing antagonists

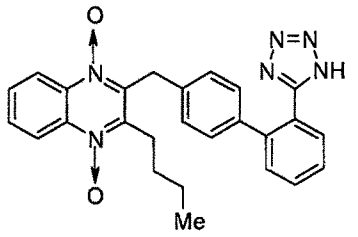
Bristol Meyers Squibb Pharma reported a new class of $N_1$ (**AT101**) and $N_4$ (**AT102**) quinoxaline oxide derivatives as $AT_1$ antagonists. Compound (**AT101**) possessed good binding affinity ($K_i$ 4.5 nM) and showed functional antagonism, but its *in vivo* activity was found to be low. As compared 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)



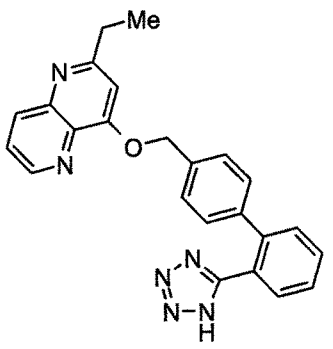
(AT102)



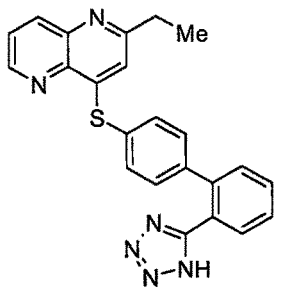
(AT103)

### 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)

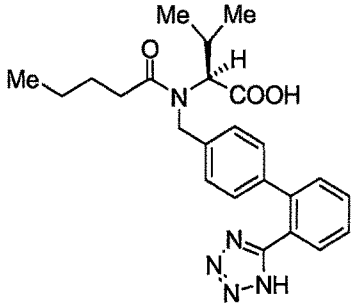


(AT105)

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

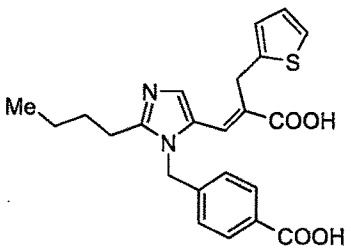
Buhlmayer et al. reported valsartan (CGP 48933) (**AT106**) as a potent, selective $AT_1$ antagonist ($IC_{50}$ 2.7 nM, rat aorta). When dosed orally (3 and 10 mg/kg) in RHR, compound (**AT106**) decreased systolic blood pressure (SBP) dose dependently. Its antihypertensive effect lasted for 24 hr.[365,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



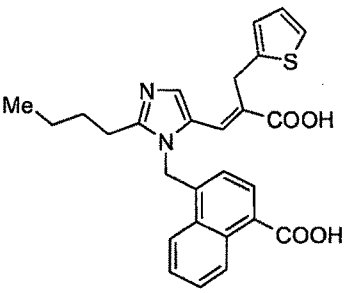
**(AT106)**

### 2.3.21 Modifications to eprosartan

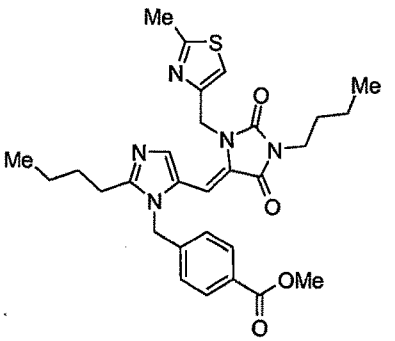
Efforts were also made by researchers to develop novel $AT_1$ antagonists by taking eprosartan (**AT107**) as a prototype and replacing its acrylic acid moiety with a



**(AT107)**



**(AT108)**



**(AT109)**

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