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Review

# Angiotensin II receptor type 1 ($AT_1$) selective nonpeptidic antagonists—A perspective

Prashant Naik, Prashant Murumkar, Rajani Giridhar, Mange Ram Yadav *

*Pharmacy Department, Faculty of Tech. and Engg., The M. S. University of Baroda, Vadodara 390 001, Gujarat, India*

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ABSTRACT

Hypertension is a major risk factor for human morbidity and mortality through its effects on target organs like heart, brain and kidneys. More intensive treatment for the effective control of blood pressure significantly reduces the morbidity and mortality. The renin angiotensin system (RAS) is a coordinated hormonal cascade of major clinical importance in the regulation of blood pressure. The principal effector peptide of RAS is angiotensin II, which acts by binding to one of the two major angiotensin II receptors $AT_1$ and $AT_2$. Angiotensin II through $AT_1$ receptor mediates vast majority of biologically detrimental actions. Nonpeptidic angiotensin II ($AT_1$) antagonists are the most specific means to block the renin angiotensin enzymatic cascade available presently. Majority of $AT_1$ antagonists are based on modifications of losartan structure, the first clinically used $AT_1$ antagonist. In this review, a comprehensive presentation of the literature on $AT_1$ receptor antagonists has been given.



**Contents**



* Corresponding author. Tel.: +91 265 2434187; fax: +91 265 2418927.
*E-mail addresses:* mryadav11@yahoo.co.in, mryadav-phar@msu.ac.in (M.R. Yadav).

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## 1. Introduction

Hypertension is recognized as one of the leading risk factors for human morbidity and mortality. On a worldwide basis hypertension has been ranked third as a cause of disability adjusted life years.[1] The enormity of the problem of hypertension is underscored by the fact that one-quarter of the world's adult population had hypertension in the year 2000 and this number is predicted to increase in the coming few years.[2] Despite the huge burden of the disease and the availability of several different classes of antihypertensive pharmacological agents, relatively few patients achieve the targeted blood pressure (BP) level. Hypertension is a major risk factor for myocardial infarction, congestive heart failure, stroke, and end-stage renal disease as shown in Figure 1,[3] all of which convey risk of significant morbidity and mortality.[1]

Hypertension is defined as an elevated blood pressure. The individual blood pressure is derived from the hemodynamic properties of the systemic circulation. The systemic circulation is a closed system that aims at providing adequate supply of oxygen and nutrients to the body as well as carrying metabolic products to be eliminated. The tension on the walls of blood vessel depends on several factors like:

(a) The pumping function of the heart;
(b) The total blood volume;
(c) The size, structure, and distensibility of the vascular tree; and
(d) Other factors like reflex and neurohumoral feedback systems, which in turn may interfere with a, b, and c.

Thus, hypertension is influenced by both, function and structure of blood vessels. As a consequence of elevated blood pressure, arterial elasticity is reduced and wall damage appears that can lead to cholesterol and fat deposition on these lesions and eventually to obstruction of the vessels. This is the basis of most of the target organ damages induced by hypertension. Another consequence can be the increase in vascular resistance, which forces the pumping activity of the heart to maintain its role in nutrients and oxygen distribution. This work overload for the heart may induce the development of cardiac hypertrophy, an increase in cardiac mass and thickness.[4]

The difficulty in controlling hypertension is related, at least in part, to the complex pathogenesis of hypertension and related cardiovascular diseases. Multiple signaling pathways and redundant feedback mechanisms, both positive and negative, contribute to the hypertensive disease process, which is further confounded by the interrelationship of hypertension with associated diseases such as diabetes and renal dysfunction. The renin angiotensin system (RAS) plays an important role not only in the control of BP but in the pathogenesis of diabetes and kidney diseases. While it has been difficult to demonstrate in vivo activation of the RAS in early or established hypertension in humans, there is no question that inhibition of the RAS is effective in lowering BP in patients with primary hypertension. The results of multiple clinical trials demonstrate that blocking the RAS with angiotensin-converting enzyme (ACE) inhibitors or Ang II ($AT_1$) receptor blockers (ARBs) not only lower BP and BP variability but also reduces cardiovascular events and total morbidity and mortality.[1,5]

Sufficient evidence exists convincing the central role of RAS, and particularly its key mediator Ang II, in pathophysiology of cardiovascular disease. Both clinical and animal studies indicate that RAS blockade and interruption of Ang II activity have protective effects on the heart, vasculartur and kidneys that appear to lead to the positive clinical outcomes observed in ACE inhibitors and ARB trials. Investigations have identified Ang II receptor subtypes with important but differing contributory roles in the pathophysiology of CV and renal diseases. Selective blockade of the $AT_1R$ by ARBs may prevent the negative effects of Ang II associated with stimulation of this receptor while allowing the positive effects, mediated through the $AT_2R$. Treatment with an ARB was demonstrated to reduce CV events and heart failure progression, improve renal disease and prevent new-onset diabetes through pleiotropic effects independent of the effect on blood pressure.[6] The outcome of the clinical trials conducted by different organizations for Ang II antagonists have been summarized in Table 1.[6–10]

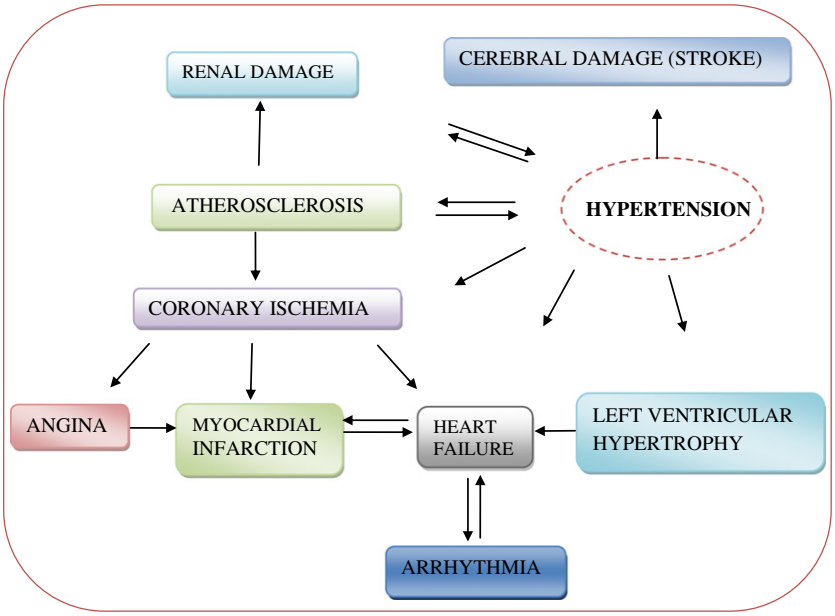



**Figure 1.** Hypertension as risk factor.[3]

**Table 1**
Clinical outcomes of Ang II ($AT_1$) receptor blockers[6–10]

| Disease | Drug | Trial name | No. of patients | End points | Key outcomes |
|---|---|---|---|---|---|
| **A. Patients with cardiovascular disorder** | | | | | |
| *Patients with hypertension* | | | | | |
| With Left ventricular hypertrophy | Losartan | LIFE | 9194 | Mortality, MI, stroke | Losartan-based regimen reduced risk of combined end point of cardiovascular (CV) death, stroke and myocardial infarction significantly compared to atenolol<br>Losartan reduced incidence of fatal and nonfatal stroke more significantly than atenolol |
| With high CV Risk | Valsartan | VALUE | 15,245 | CV mortality | Post-hoc analysis of value's population showed that CV events and incidence of new onset diabetes tend to be fewer in valsartan group compared to amlodipine |
| In elderly | Candensartan | SCOPE | 4400 | CV mortality, Stroke, Myocardial infarction | Candensartan effectively reduced nonfatal stroke |
| *Patients with heart failure* | | | | | |
| | Losartan | ELITE I | — | CV mortality | Reduction in all cause mortality with losartan compared to captopril in elderly patients with sympathomimetic heart failure |
| | | ELITE II | 3121 | CV mortality | Losartan is slightly superior to captopril |
| | Valsartan | Val-HeFT | 5200 | All cause mortality | Valsartan is superior to placebo on combined mortality and morbidity in ACE and diuretic treated patients, most benefits in ACE intolerant patients |
| LVEF $\leqslant$0.40 | Candensartan | CHARM I | 1700 | All cause mortality | Candensartan reduced risk of CV death or CHF hospitalization in all cases |
| LVEF $\leqslant$0.40 and ACE intolerant | | CHARM II | — | | |
| LVEF >0.40 | | CHARM III | — | | |
| *Patients with post myocardial infarction* | | | | | |
| | Losartan | OPTIMAAL | 5000 | All cause mortality | No significant difference when compared to ACE inhibitor |
| | Valsartan | VALIANT | 14,500 | All cause mortality | Equally effective to captopril for preventing mortality and composite end point of fatal and nonfatal CV events |
| **B. Patients with diabetes/renal disorder** | | | | | |
| *Patients with type II diabetes* | | | | | |
| With nephropathy | Irbesartan | IDNT | 1650 | Mortality, Doubling of creatinine, ESRD | Irbesartan significantly reduced progression of nephropathy |
| With nephropathy | Losartan | RENAAL | 1520 | | Losartan significantly reduced progression of nephropathy |
| With microalbuminuria | Irbesartan | IRMA II | 590 | Microalbuminuria | A greater proportion of patients reverted to nonmicroalbuminuria in irbesartan group than amlodipine group |

### 1.1. Renin angiotensin system (RAS) in hypertension

The RAS is a coordinated hormonal cascade which creates angiotensin peptides and operates not only at circulatory/systemic (endocrine) level, but also at tissue (paracrine) level like heart, blood vessels, brain and kidneys, which is of major significance for blood pressure regulation with proliferation, growth and inflammatory processes.[11]

During the period of more than last ten decades, science has accumulated rich information about the angiotensin peptides that are created by renin and some other enzymes involved in the renin angiotensin cascade as outlined in Figure 2. Recently the chronological details about the RAS have been described.[12,13]

### 1.2. Angiotensin II (Ang II)

In 1898, Tiegerstedt et al.[14] demonstrated that injection of kidney extracts into rabbits elicited a pressor effect. They named the unknown pressor substance renin, and it was later shown to be a protease enzyme. From that time we can trace the slow realization that the product of renin activity has a major role in human physiology and cardiovascular disease. It took 40 years after the discovery of renin to elucidate that the active pressor substance was an octapeptide, Ang II (Fig. 3). Studies from labs in Argentina (Buenos Aires) and United State (Cleveland clinic) in 1939, independently named the same pressor substance 'hypertensin' and 'angiotonin', respectively, which became by agreement, 'angiotensin'. Ang II is potent vasoconstrictor and major effector peptide of RAS.[15]

The circulatory (systemic) RAS appears to be responsible for acute effects including short-term homeostatic reactions, whereas the tissue RAS seems to be involved in the long-term control of BP,

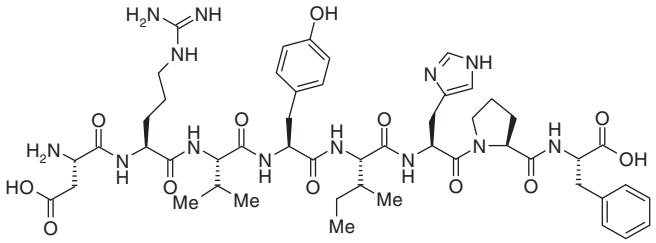


**Figure 3.** Structure of Ang II.

and organ growth and function.[16] Ang II is generated at both circulatory and tissue level (Fig. 4).[17] At circulatory level, renin (small protein enzyme from the juxtaglomerular cells in the kidney) circulates through the bloodstream and converts substrate angiotensinogen (from liver) into Angiotensin I (Ang I), which is rapidly converted to Ang II by the Angiotensin Converting Enzyme (ACE) in the endothelium of the lung vessels. In addition to its role as a circulating hormone, Ang II is secreted at the tissue level by local pathways in the heart, brain, kidney and arteries. In these tissues, enzymes other than ACE, such as cathepsin G and chymase cleave Ang I to Ang II. Ang II (circulatory and tissue level) mediates biological response through two principle receptor subtypes namely, Ang II type one receptor ($AT_1$) and Ang II type two receptor ($AT_2$). The response depends upon their expression pattern in tissues as shown in Table 2.[10]

The potential detrimental effects of the Ang II, at both circulatory/systemic (endocrine) and tissue (paracrine) levels, are outlined in Figure 5.[1] Almost all of these effects are mediated by $AT_1$ receptor.

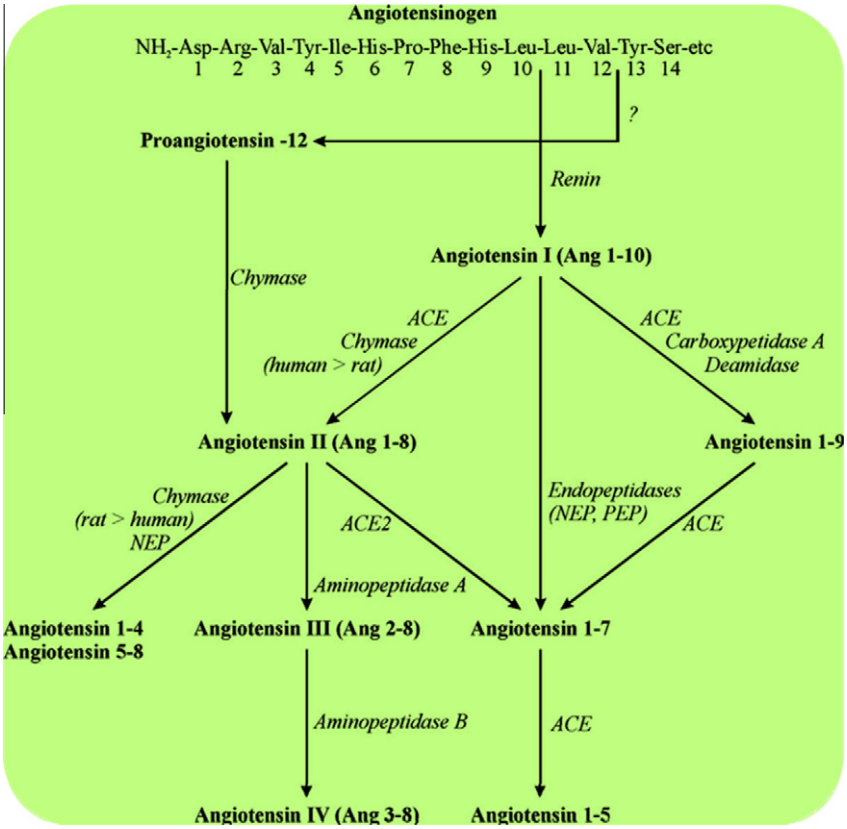



**Figure 2.** Angiotensin peptides generated from renin angiotensin cascade.[12,13]

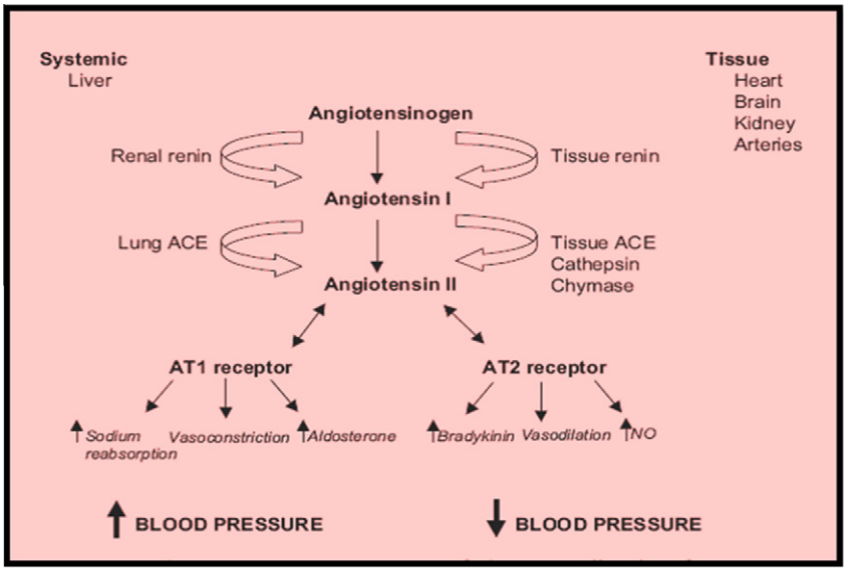



**Figure 4.** Generation of Ang II (systemic and tissue level) and their actions.[17]

**Table 2**
Ang II receptors, their functions and location[10]

| Receptor | Actions | Location |
|---|---|---|
| $AT_1$ | Vasoconstriction | Vessels |
| | Increase sodium retention | Brain |
| | Suppress renin secretion | Heart |
| | Increase endothelin secretion | Kidney |
| | Increase vasopressin release | Adrenal gland |
| | Activate sympathetic activity | Nerves |
| | Promote myocyte hypertrophy | |
| | Stimulate vascular and cardiac fibrosis | |
| | Increase myocardial contractility | |
| | Induce arrhythmias | |
| | Stimulate plasminogen activator inhibitor 1 | |
| | Stimulate superoxide formation | |
| $AT_2$ | Antiproliferation/inhibition of cell growth | Adrenal gland |
| | Cell differentiation | Heart |
| | Tissue repair | Brain |
| | Apoptosis | Myometrium |
| | Vasodilation (NO mediated) | Fetus |
| | Kidney and urinary tract development | Injured tissue |
| | Control of pressure/natriuresis | |
| | Stimulate renal prostaglandins | |
| | Stimulate renal bradykinin and NO | |

### 1.3. Activity of Ang II through $AT_1$ receptor

#### 1.3.1. Systemic level Ang II

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 BP. Ang II is a potent vasoconstrictor and cause vasoconstriction mainly in the arterioles, thereby increasing the total peripheral resistance. Through its vasoconstrictor properties, Ang II diminishes blood flow through the kidneys, thereby increasing the reabsorption of salt and water. In addition, Ang II causes increased sodium reabsorption at the proximal tubulus. 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.[18]

#### 1.3.2. Tissue level Ang II

Tissue Ang II is helpful in maintaining the vascular structure and tone. Ang II is secreted at the tissue level by local pathways in the heart, brain, kidney, and arteries, thereby exerting autocrine

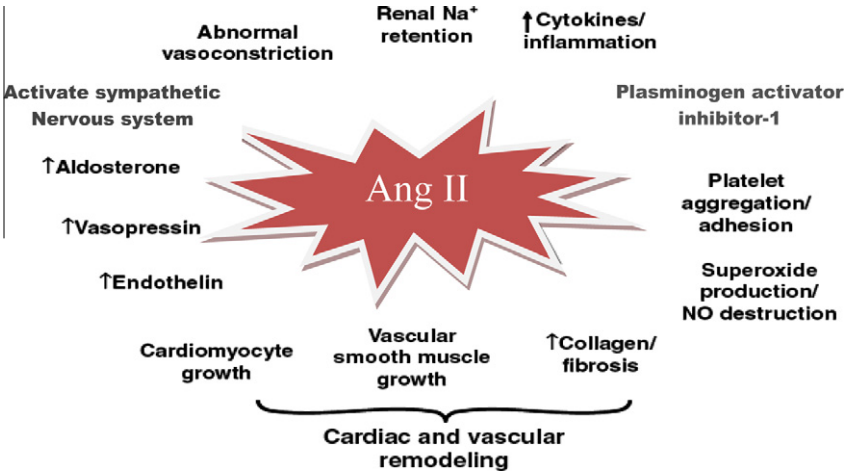



**Figure 5.** Deleterious actions of Angiotensin II.[1]

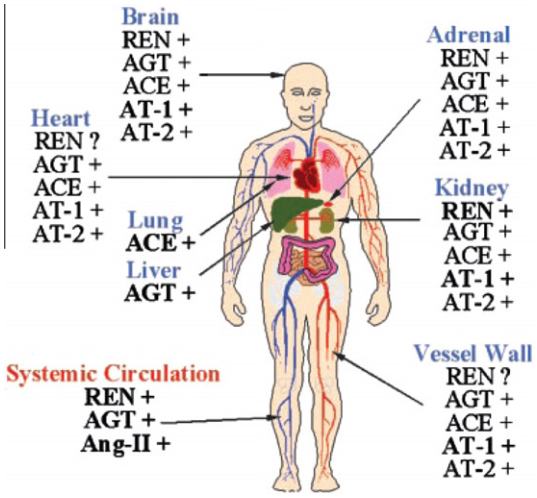



**Figure 6.** Sites of expression of the different components of the RAS.[16]

and paracrine effects through $AT_1$ receptor.[15] There is increasing evidence that points to the role of tissue Ang II in the primary consequence of chronic hypertension, namely end-organ damage.

- Local tissue Ang II exerts a direct influence on endothelial function. Normal endothelial function is dependent on the cell redox state, determined by the homeostatic balance between NO and reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide.[19] The endothelium is responsible for regulating vessel tone, coagulation, cell growth and death, and leukocyte migration, all of which are dependent on the balance between vasodilators such as nitric oxide (NO) and vasoconstrictors such as Ang II. Elevated levels of Ang II in the endothelium cause oxidative stress to generate ROS.[20] This leads to endothelial dysfunction, cell growth and inflammation via the activation of nuclear factor-B (NF-B), monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule (VCAM), and the release of the cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNF).[21,22] The action of VCAM and cytokines increases the adhesiveness of the endothelium and the binding of inflammatory cells to its surface, leading to vascular inflammation and thrombosis.[23] Ang II contributes to the process of lesion formation by stimulating the release of endothelin-1 (ET-1), the proliferation of smooth muscle cells and the formation of foam cells, which are the initial stages of formation of atherosclerotic plaques.
- Ang II is also involved in vascular remodeling by inducing the expression of autocrine growth factors such as platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor and transforming growth factor-1 in vascular smooth muscle cells.[24]
- Ang II can also stimulate the production of matrix metalloproteinase (MMP) enzymes, which are associated with atherosclerotic plaque stability and disruption.[25] The MMPs can break down the extracellular matrix, increasing the probability of plaque rupture. Ang II can also alter the balance between fibrinolytic and coagulation systems through its effect on the endothelium. Ang II induces the formation of plasminogen activator inhibitor type 1 (PAI-1), that is mediated by specific angiotensin receptors on endothelial cells, thereby promoting the development of a prothrombotic state.[26,27]

These detrimental actions of Ang II can be offset to some extent by $AT_1$ receptor mediated short-loop negative feedback suppression of renin biosynthesis and secretion at renal juxtaglomerular cells.

### 1.4. Activity of Ang II through $AT_2$ receptor

In contrast to the pressor and tissue destructive mechanisms of Ang II via $AT_1$ receptors, Ang II activation induces opposite effects via $AT_2$ receptors, including vasodilation of both resistance and capacitance vessels, natriuresis and inhibition of cellular proliferation and growth.[27,28] However, the relative balance between $AT_1$ and $AT_2$ receptors functions may be influenced by receptor expression patterns in tissues. Whereas $AT_1$ receptors are highly expressed in the cardiovascular, renal, endocrine, and nervous systems in adults, $AT_2$ receptor expression is quantitatively less and its tissue distribution is more limited than that of $AT_1$ receptor. The RAS components' expression is outlined in Figure 6.[16]

It is widely accepted that the $AT_1$ receptor accounts for a majority of the cardiovascular effects evoked by Ang II. All Ang II antagonists currently available in the market, like losartan (**1**), olmesartan (**13**), irbesartan (**33**), candensartan (**103**), telmisartan (**114**) and valsartan (**187**) are $AT_1$ selective. Majority of the reported compounds in literature were screened for $AT_1$ selectivity.

## 2. Losartan and eprosartan, prototypes of nonpeptidic Ang II antagonists

The origin of potent nonpeptide Ang II receptor antagonists with high $AT_1$ selectivity, of which losartan is the prototype, can be traced back to the Takeda series of 1-benzylimidazol-5-acetic acid derivatives like S-8307 and S-8308, that are selective but weak antagonists.[29–32]

Losartan (DuP 753)[33] (**1**) and eprosartan (SK&F 108566)[34] (**2**) were derived from the benzylimidazole series using two different molecular models of putative active conformations of Ang II to align the Takeda derivatives, with the C-terminal region of Ang II. Dupont and Smith Kline Beecham researchers worked on Takeda lead by using different strategies. Wexler et al. have reported the discovery of losartan and eprosartan (Fig. 7) in detail in their review.[35]

### 2.1. Losartan as a selective $AT_1$ receptor antagonist

Losartan (**1**) is selective and competitive ($pA_2$ 8.48, rabbit aorta) antagonist for $AT_1$ receptor.[36] It displaced radiolabeled Ang II from its specific binding sites affording $IC_{50}$ values of approximately 19 and 20 nM in rat adrenal cortex and rat vascular smooth muscle, respectively. Losartan showed antihypertensive effects, when dosed intravenously ($ED_{30}$ 0.78 mg/kg) and when dosed orally ($ED_{30}$ 0.59 mg/kg) without affecting heart rate in renal hypertensive rats (RHR). In RHR, the antihypertensive effect of losartan (3 mg/kg po) lasted for more than 24 h.[37] In furosemide-treated conscious dogs with high renin levels, losartan caused a dose-dependent but transient decrease in blood pressure.[38]

Losartan has high selectivity for Ang II receptors as it did not inhibit the contractions or radioligand bindings of endothelin, neurotensin, substance P, opioids, glycine (strychnine insensitive), dopamine-2, serotonin-2, phencyclidine, acetylcholine agonists and basic fibroblast growth factor, but blocked the contraction of Ang II.[39]

Losartan potassium (MK 954) does not readily cross the blood–brain barrier. It crossed the blood–brain barrier when administered chronically (po). The effects of chronic administration of losartan (po) were observed at 3 mg/kg per day.[40] MK 954 markedly

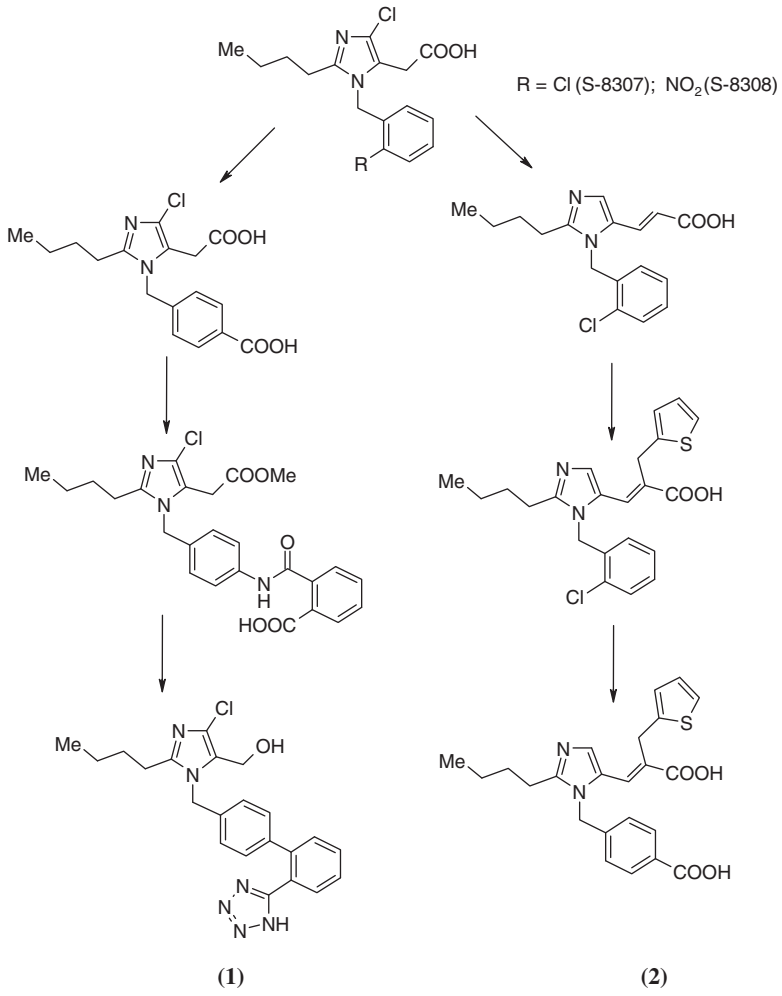
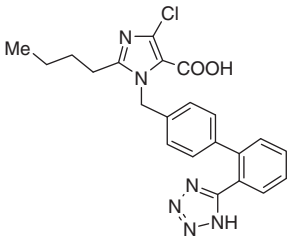



**Figure 7.** Development of Losartan and Eprosartan.[35]

reduced blood pressure in Spontaneously Hypertensive Rats (SHR) but not in Wistar Kyoto rats (WKY). Plasma renin activity, Ang I and Ang II levels were increased, while plasma aldosterone level decreased in both strains.[41]

Xu et al. have briefly reviewed the chemical structure of losartan and its pharmacological effects along with its use in renal diseases.[42] Ono et al. have reported the structural basis for platelet anti-aggregation activity of losartan via glycoprotein VI (GPVI). This study indicated that the phenyl group with the tetrazole ring in losartan plays a crucial role in interaction with GPVI. Losartan inhibited in vitro and in vivo collagen-stimulated platelet adhesion and aggregation.[43]

Biphasic antihypertensive response was observed after administration of losartan (1 mg/kg, iv) to RHR.[37] The finding of lower or at least comparable oral $ED_{30}$ to the intravenous $ED_{30}$ in RHR (oral bioavailability of losartan in rats is 33%) suggested the involvement of one or more active metabolites. EXP3174 (**3**), the imidazole-5-carboxylic acid resulting from oxidation of the imidazole's 5-hydroxymethyl group, was identified in rat plasma as the major metabolite of losartan.[44] The low bioavailability of losartan was mainly attributable to first pass metabolism. After intravenous or oral administration of losartan, the conversion of losartan to the metabolite EXP3174 was 14%.[45]



(**3**)

EXP3174 (**3**) possesses comparable binding affinity to Ang II receptors, lacks agonistic activity and shows a similar high selectivity as losartan. It displaced Ang II from its specific binding sites in rat adrenal cortical membranes with an $IC_{50}$ of 0.37 nM. In the isolated rabbit aorta, EXP3174 caused nonparallel shifts to the right of the Ang II concentration contractile response curves and reduced the maximal response by 30–40% with an apparent $pA_2$ value of 10.09 and a $K_B$ value of $10^{-10}$ M. In the spinal pithed rat, EXP3174 inhibited the pressor responses of Ang II at 0.03–0.3 mg/kg (iv). This demonstrates that EXP3174 is a selective and noncompetitive Ang II receptor antagonist and lacks agonistic effect. In conscious renal artery ligated rats, EXP3174 showed $ED_{30}$

(decrease in mean arterial blood pressure by 30 mm of Hg) of 0.038 mg/kg (iv) and 0.66 mg/kg (po). In contrast to losartan (**1**), EXP3174 behaves as a noncompetitive antagonist and is approximately 20 times more potent as an antihypertensive agent, with a long duration of action.[44]

### 2.2. Eprosartan as selective $AT_1$ receptor antagonist

The Smith Kline Beecham group designed eprosartan (**2**)[34,46–48] independently from the Takeda benzylimidazoles, based on their initial design strategy of a combination of molecular modeling and a knowledge of the peptide structure–activity relationship (SAR). Eprosartan is $AT_1$ selective and potent antagonist ($IC_{50}$ 1.5 and 9.2 nM, rat mesenteric artery and adrenal cortical membranes, respectively). In the normotensive rat, it exhibited potent inhibition of the pressor response to Ang II ($ID_{60}$ 0.08 mg/kg iv). Dose-dependent inhibition of the pressor response to Ang II was observed with an $ID_{50}$ value of 5.5 mg/kg when administered intraduodenally, and at the highest dose (10 mg/kg) significant inhibition was observed for 3 h after dosing. In dogs this compound at 3 mg/kg iv or 10 mg/kg po lowered blood pressure substantially.

## 3. Development of Ang II $AT_1$ selective antagonists from losartan

Majority of selective Ang II $AT_1$ antagonists have resulted from the strategy of modifying or replacing the imidazole ring of losartan. Replacement of imidazole ring of losartan with five-membered, six-membered, fused and acyclic moieties (Fig. 8) have resulted in potent $AT_1$ selective antagonists like olmesartan, candensartan, telmisartan, valsartan, etc. Till date compounds containing a variety of heterocyclic nuclei (Fig. 8) with ortho substituted biphenyls, mainly biphenyl tetrazole, have been synthesized and evaluated for $AT_1$ antagonistic activity. Further substitutions on both of the phenyl rings of the biphenyl moiety have been carried out. In some cases, ortho substituted biphenyl moiety has been replaced successfully with different other groups.

### 3.1. Antagonists having substituted five-membered heterocyclic rings

Imidazoles, dihydroimidazol-4-ones, pyrazoles, pyrazolidine-3,5-diones, triazoles, triazolones, pyrroles, pyrrolidines, acyliminothiadiazolines, thiazoles, thiadiazoles and some other derivatives have all demonstrated $AT_1$ antagonistic activity as discussed below.

#### 3.1.1. Imidazole derivatives

The structure–activity relationship (SAR) studies of the substituted imidazole ring of losartan and EXP3174 (**3**) 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

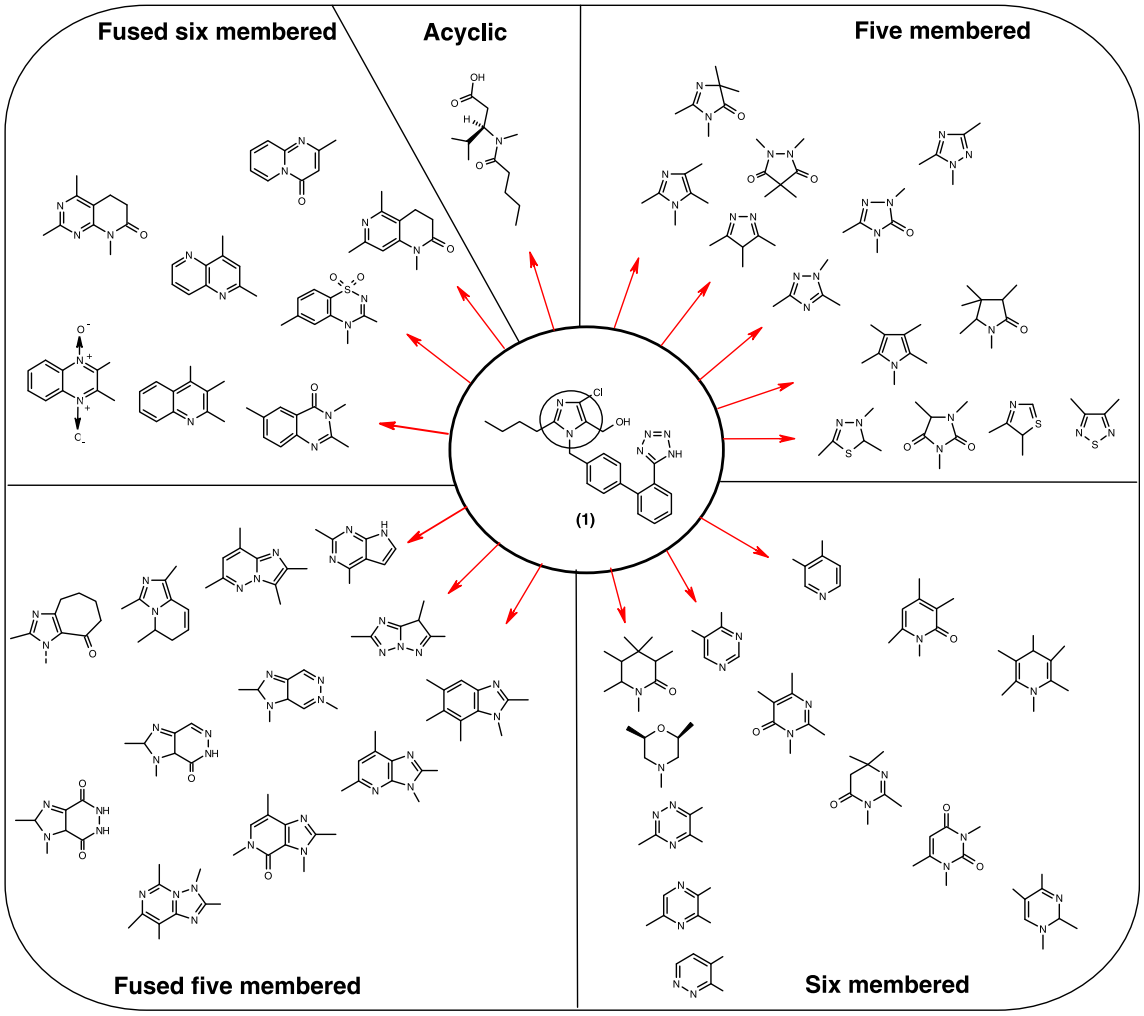
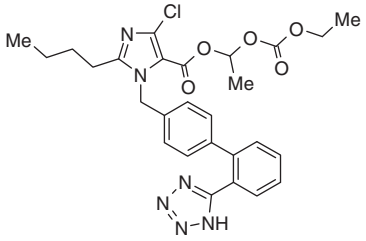



**Figure 8.** Ang II receptor antagonists.

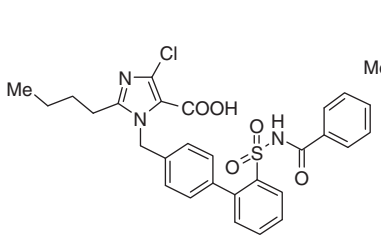
properties did not appear critical for binding. Biphenyltetrazole moiety is important but can be replaced for its tetrazole and substituted for spacer and terminal phenyl groups.[49] After the discovery of losartan, the role of imidazole nucleus and biphenyl moiety present in losartan were explored by number of groups.[50–98]

The imidazole nucleus was explored for substitutions at $C_4$ and $C_5$ positions. A variety of substituents at these positions are acceptable. At $C_5$ position, hydroxymethyl, carboxaldehyde, or carboxamido groups yielded potent antagonists.[49] Acidic group at $C_5$ is also advantageous as seen in case of EXP3174 (**3**).[50] However, the diacid EXP 3174 showed poor bioavailability due to binding to the plasma proteins. To improve the poor bioavailability, its ester prodrug HN-65021 (**4**) was synthesized at Hafslund Nycomed. Full inhibition was achieved, when compound **4** was administered orally to conscious rats (1 mg/kg). Significant inhibition was observed even after 24 h. Compound **4** decreased the pressor response dose dependently with an $ED_{50}$ of 0.5 mg/kg.[51]



(4)

Acylsulfonamides as non-tetrazole analog of EXP3174 have been reported by Naylor et al. The most potent compound **5** of the series showed equal or slightly higher potency than EXP3174. In normotensive rats, compound **5** displayed good inhibition of the Ang II pressor response. However, compound **5** showed shorter duration of action when compared to its tetrazole analog EXP3174. Replacement of tetrazole by either acylsulfonamide or sulfamide led to an enhancement in $AT_2$ potency.[52]



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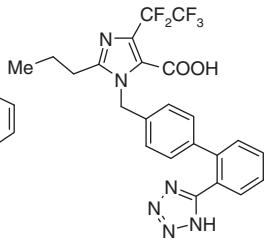


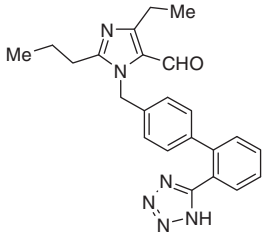
(6)

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. Substituents at $C_4$ position, although not required for $AT_1$ binding, often increase potency and have also shown favorable effects on in vivo properties. Within the series of 4-halo derivatives, the SAR depends in part on acidic functional group present at biphenyl ring. In biphenylcarboxylic acids, binding affinity appeared in the order I > Br > Cl. It is different for biphenyltetrazole series, in which Cl and I are equipotent. 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. $CF_3$ group was found to give the most potent compounds in biphenyl carboxylic acid and biphenyl tetrazole series.[49]

A series of 4-(perfluoroalkyl)imidazoles have been reported as $AT_1$ antagonist with the most potent compound DuP 532[53] (**6**) possessing 4-pentafluoroethyl substituent. Compound **6** has an $IC_{50}$ value of 3.1 nM (rat adrenal) and decreased blood pressure with $ED_{30}$ of 0.02 mg/kg (iv) and 0.21 mg/kg (po) in RHR.[54,55] In conscious SHR and conscious furosemide treated dogs, compound **6** lowered blood pressure in a dose-dependent fashion at 0.3–3.0 mg/kg (iv or po).[55] Compound **6** caused a marked and long lasting drop when administered orally to RHR. Compound **6** was extensively bound in human plasma. Although compound **6** and EXP3174 (**3**) both have similar $AT_1$ receptor potency but plasma concentrations of compound **6** were found to be much greater than losartan/EXP3174.[56]

Aliphatic groups at $C_4$ position of imidazole afforded increased in vitro and in vivo potency. DMP 581 (**7**) 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 (po) in the RHR.[57,58] Compound **7** metabolized to its more active diacidic metabolite DMP 811 (**8**) ($IC_{50}$ 6 nM, rat adrenal). In conscious RHR, DMP 811 (**8**) decreased blood pressure with $ED_{30}$ values of 0.005 and 0.03 mg/kg, (iv and po, respectively). It is 20 times more potent than losartan ($ED_{30}$ 0.59 mg/kg) orally. However, like other diacids the oral bioavailability of compound **8** is moderate.[57,58]

Santella et al. reported the substituted esters and amides of compound **8** with sulfonylcarbamate acid isostere having increased affinity for $AT_2$ receptor. Some of the esters bind well to both receptor subtypes $AT_1$ and $AT_2$ in the nanomolar range. Substitution of spacer phenyl with fluorine at ortho position increased $AT_2$ affinity.[59]



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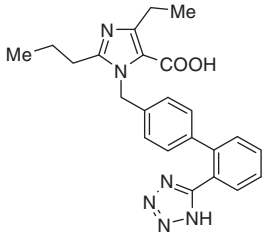
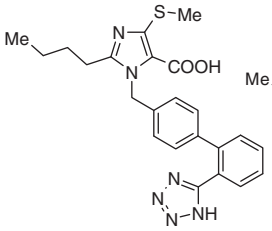


(8)

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.[60] The concept of substituting $C_4$ position with differently substituted alkylthio groups resulted into development of potent RU 56184[61] (**9**) having $IC_{50}$ value of 0.2 nM with an $ID_{50}$ of 0.05 mg/kg (iv) and 0.4 mg/kg (po). This suggests that receptor accepts more bulky substituents at this position (more active in in vitro assay) than the chloro analog EXP3174 (**3**). Glucouronidation of tetrazole moiety of losartan resulted in rapid elimination and shorter in vivo duration of action in monkeys. Considering this fact Hoechst Marion Roussel group successfully replaced the tetrazole moiety of compound **9** with alkyl substituted sulfonylureas resulting in HR 720 (**10**),[62] an insurmountable antagonist ($IC_{50}$ 0.48 nM, rat liver).[34] In pithed normotensive rats, compound **10** inhibited the Ang II induced pressor response when dosed intravenously ($ID_{50}$ 0.11 mg/kg) and orally ($ID_{50}$ 0.7 mg/kg). In RHR, compound **10** lowered blood pressure (BP) significantly for >24 h at a dose of 1 mg/kg and above. This orally active compound **10** produced a markedly long lasting decrease in blood pressure in high renin animal model and proved superior in comparison to the corresponding tetrazole (**9**) analog.[62] During this period, concerted efforts were made in synthesizing balanced $AT_1$ and $AT_2$ antagonists in order to suppress the stimulation of $AT_2$ receptor. Pharmacology of $AT_2$ receptor was not completely understood at that time. Chronic blockade of $AT_1$ receptor by $AT_1$ selective antagonists caused accumulation of large quantities of Ang II in blood. So, in order to avoid further consequences of overstimulation of $AT_2$ receptor by the accumulated Ang II,



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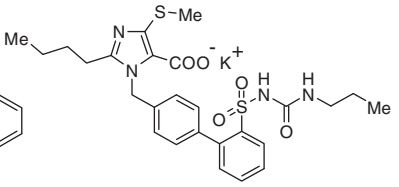
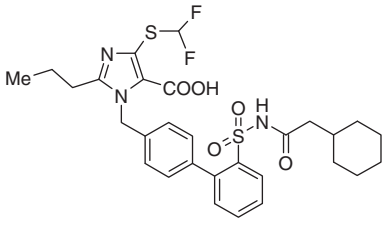


(10)

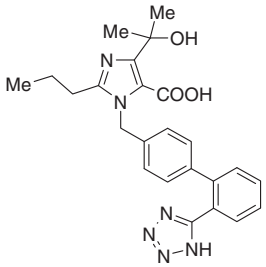
many attempts were made to prepare the balanced $AT_1$ and $AT_2$ antagonists. However, stimulation of $AT_2$ receptor is now proving to be advantageous.[1] Hoechst Marion Roussel group worked on making of balanced analogs of compound **10** by substituting different positions of imidazole ring and alkyl chain of sulfonylurea. Substitution of sulfonylurea with cyclohexylmethyl, cyclopentylmethyl and benzyl groups along with $C_4$ position of imidazole ring with difluoromethyl sulfide group increased the binding affinity for the $AT_2$ receptor [RU 65868 (**11**)].[63] Substitution at the $C_5$ position of the imidazole ring with α-hydroxyacid moiety (RU 63455) also resulted into enhanced $AT_2$ binding affinity.[64] β-Ketosulfoxide, β-ketosulfone and β-ketoester groups proved to be effective substituents



(11)

with nanomolar affinities to both of the receptor ($AT_1$ and $AT_2$) subtypes. β-Ketosulfoxide derivative (RU 64276) is also a potent Ang II inhibitor with high affinity for both of the receptor subtypes.[65] Selenium containing analog of compound **10** was reported as Ang II antagonist. Results revealed that this selenium containing analog retained the biological activity of the parent compound.[66]

Sankyo's CS-866 (**13**) (Olmesartan) is completely and rapidly hydrolyzed to the active acid, RNH 6270 (**12**). Compound **12** 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. It works selectively by binding to $AT_1$ receptor.[67] Compound **12** inhibited [$^{125}$I] Ang II binding to bovine adrenal cortical membrane ($AT_1$ receptors) with an $IC_{50}$ value of 7.7 nM, but did not inhibit [$^{125}$I] Ang II binding to bovine cerebellar membranes ($AT_2$ receptors), indicating the selectivity of the compound for $AT_1$ receptors. In guinea pig aorta, compound **12** reduced the maximal response in the dose–response curve of Ang II (sensitivity to Ang II, i.e., p$D_2$ 9.9). In conscious rats, intravenous injection of compound **12** inhibited Ang II induced pressor response in a dose-dependent manner.[68] Compound **12** is several times more potent than losartan in in vitro and in vivo experiments but, it showed poor bioavailability. In order to improve its bioavailability, different substituents were tried at $C_5$ that resulted in the development of medoximil ester (**13**)[66], an ester prodrug which gets deesterified to the parent compound **12**. A single oral dose of 10–20 mg of compound **13** resulted in maximal effects.[69] Compound **13** on oral administration produced a long-lasting inhibition of Ang II pressor responses.[68]



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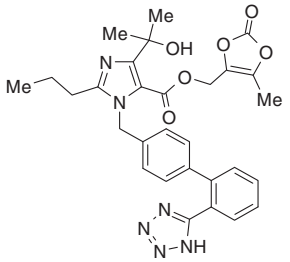
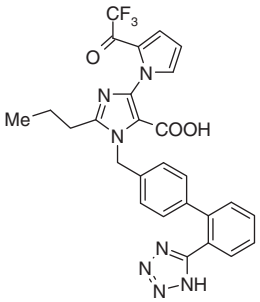


(13)

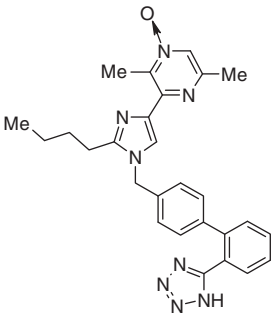
Tolerance of a large group at $C_4$ position is demonstrated by the high binding affinity of imidazoles which carry bulky aryl or heteroaryl substituents (**14**–**18**). Various heterocyclic or carbocyclic groups are successfully substituted at $C_4$ position of the imidazole ring.

$C_4$ position of the imidazole ring was successfully substituted with the 1*H*-pyrrol-l-yl substituent by Sircar et al. CI-996 (**14**) (Warner–Lambert) is a potent $AT_1$ receptor antagonist. In rat liver membranes, compound **14** displaced specifically the bound [$^{125}$I] Ang II, with an $IC_{50}$ of 0.8 nM. In isolated rabbit aorta, compound **14** produced dose-dependent inhibition of Ang II induced contraction and decreased the maximal contractile response to Ang II. In anesthetized ganglionic-blocked rats, compound **14** produced dose-dependent inhibition of the Ang II pressor dose–response curve with an $IC_{50}$ of 6.2 mg/kg (iv). When orally administered, compound **14** dose-dependently lowered mean arterial blood pressure (MABP) in conscious renal hypertensive rats, conscious sodium-depleted dogs, conscious sodium-depleted monkeys and conscious renal hypertensive monkeys.[70,71] In RHR, compound **14** (1–30 mg/kg, po) lowered MABP in a dose-dependent manner with a duration of $\geqslant$24 h.[72]



(14)

Harmat et al. reported a series of compounds containing variously substituted diazine or pyridine moieties either as free bases or as their N-oxides at $C_4$ position of imidazole ring. The N-oxide derivatives showed slightly more binding affinity (adrenal cortex membrane) and decreased Ang II induced-pressor response to a higher extent in conscious normotensive rats as compared to their free bases. Only those compounds (**15**, **16**) showed potent activity in the $AT_1$ binding assay in which the ring nitrogen was adjacent to the imidazole ring.[73]



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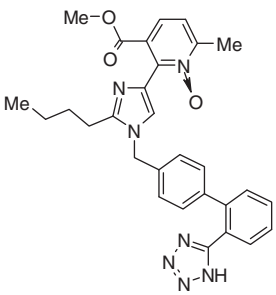
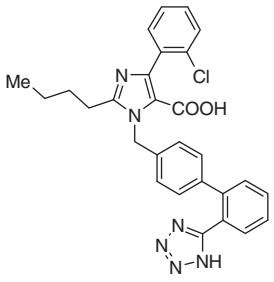
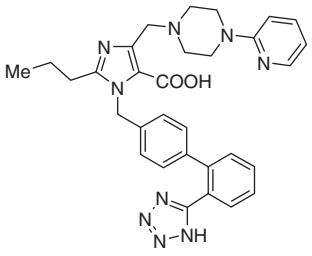


(16)

Merck's L-158,854 (**17**) showed potent antagonistic activity ($IC_{50}$ 0.55 nM, rabbit aorta) and inhibited pressor response of Ang II at a dose of 0.1 mg/kg by 88%, with a duration of >6 h in conscious normotensive rats.[74]



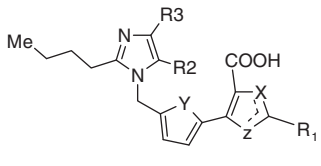
(**17**)



(**18**)

The introduction of aminomethyl [e.g., XH148 (**18**)] and acylaminomethyl substituents at the $C_4$ position of imidazole imparts affinity for the $AT_2$ receptor. Replacement of tetrazole with substituted sulfonamide increased the $AT_2$ affinity. Compound **18** showed significant and prolonged antihypertensive activity after oral administration at 3 mg/kg. It reduced BP in RHR with an $ED_{50}$ value of 0.18 mg/kg (iv) and 1.65 mg/kg (po).[75]

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 (**20**–**27**) which are potent Ang II antagonists. With the aim of finding the influence of structural changes in the biphenyl moiety on the biological activity, a series of *N*-(heterobiaryl)methylimidazoles (**19**) were synthesized. The compounds were synthesized by replacing either the central or the terminal phenyl rings with a heterocyclic one, such as furan, thiophene, thiazole or pyridine. Compared to the reference DuPont compound (**1**), all the heterobiaryl derivatives showed reduced potency, both in receptor binding (rat adrenal capsular membrane) studies as well as in the functional assays (contraction of rabbit aorta strip). This loss of potency is attributed to the altered conformational and electrostatic features. The reduced activity could be justified by almost plane disposition of biphenyl moiety. Central aromatic ring of the biaryl moiety works as a spacer, disposing the terminal aromatic ring, whose electronic distribution is crucial for fitting well into a lipophilic pocket of the receptor site, into suitable orientation.[76]

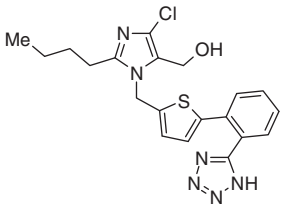


(**19**)

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

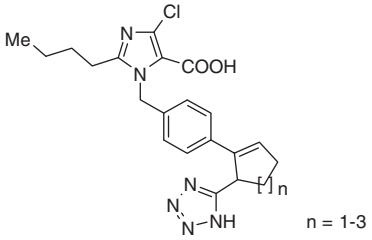
Y = O, S, CH=CH

Z = CH, N, N=CH



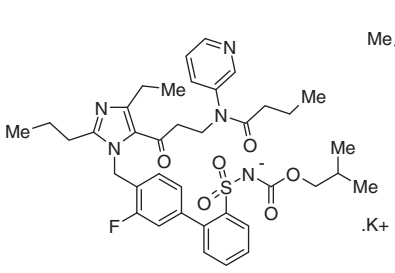
(**20**)

An arylthiophene analog (**20**) of compound **1**, showed decreased potency in its in vitro (rabbit aorta) evaluation.[77] A series of compounds (e.g., **21**), in which the terminal phenyl group was substituted with cycloalkenyls (five- to seven-membered rings), was synthesized and evaluated. The effects of lipophilicity, steric bulk and the amount of π electron density of the terminal ring, and the relative spatial proximity of the tetrazolyl and the middle phenyl groups were explored in terms of their binding affinity to $AT_1$ receptors in rat adrenal glomerulosa and rabbit aorta. Potency at the $AT_1$ receptors got maximized when the terminal ring is six-membered. An aromatic ring binds better than a cycloalkenyl ring. Compounds with cycloalkenyl rings are unable to interact with $AT_1$ receptor sites as well as those with a phenyl rings (however, those with phenyl rings are preferred one). Thus, it was summarized that the planar terminal ring system with rich π electrons increased affinity to $AT_1$ receptors.[78] Ortho substitution to the inner phenyl ring of the biphenyl system afforded compounds having higher $AT_2$ affinity. When combined with a sulfonylcarbamate as the acid isostere this further increased the affinity for $AT_2$. Chloro and fluoro substituents on the spacer phenyl group produced high affinity for $AT_2$.[79] Some

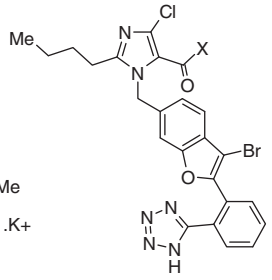


(**21**)

compounds exhibited nanomolar affinities for both the receptors with prolonged antihypertensive effects in renal hypertensive rats. XR510 (**22**) is highly active in lowering blood pressure in renal hypertensive rats and furosemide treated dogs following its oral administration. It exhibited nanomolar affinity for both the receptor sites.[80]



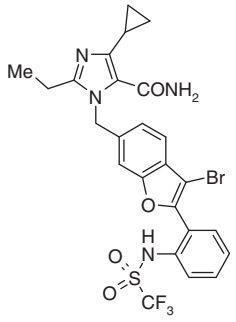
(**22**)



(**23**) X = OH; (**24**) X = $NHCH_2COOEt$

Compound (**23**, GR117289, Glaxo) belongs to a new class of $AT_1$ antagonist in which the "spacer" phenyl ring of EXP3174 (**3**) is replaced by a bromobenzofuran. The 3-bromo substituent was found to be essential for high potency and correlated well with its increased inductive strength. Compound **23** was a potent competitor with [$^3$H] Ang II for $AT_1$ binding sites ($pK_i$ 8.7). In rabbit isolated aortic strips, compound **23** (0.3, 1 and 3 nM) caused a concentration-related insurmountable suppression of the concentration–response curve to Ang II.[81,82] Intra-arterial (0.3–3 mg/kg) and oral (1–10 mg/kg) administration of compound **23** for 6 days to left Renal Artery-Ligated Hypertensive (RALH) rats [diastolic blood pressure (DBP) >140 mmHg] produced significant dose related reductions in DBP with apparently little effect on heart rate (<15%). The antihypertensive effect of compound **23** developed progressively over several hours and with some doses it persisted for 24–48 h after administration. Systemic or oral administration of compound **23** (3 mg/kg) inhibited the pressor responses produced by Ang II, resulting in parallel, rightward displacements of Ang II dose–response curve. Maximal displacement of Ang II dose–response curve occurred at 1 h and 1–7 h after systemic and oral administration, respectively.[83]

Development of a hybrid of compound **23** and Eprosartan (**2**) led to the synthesis of a series of amino acid-amides. These compounds showed moderate to good $AT_1$ selective antagonistic in vitro activity. The possibility that the amino acid-amide element of these molecules mimics the C-terminus of Ang II is counted. One of these compounds, glycine ethyl ester (**24**), exhibited good oral activity in the RHR, caused large and sustained fall in BP at a dose of l mg/kg, but showed poor pharmacokinetic profile in the dog.[84] GR138950 (**25**) resulted from a strategy aimed at enhancing the bioavailability of bromobenzofuran diacid (**23**).[85] Replacement of the carboxyl group at $C_5$ position with carboxamide group along with replacement of the tetrazole ring with a triflamide resulted into a compound **25**



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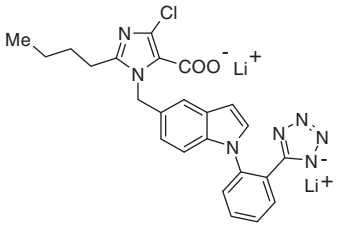
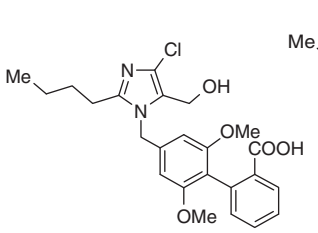


(26)

with increased absorption on oral administration.[86] Compound **25** is a potent, selective and specific $AT_1$ receptor antagonist which is orally active.[87] It showed high affinity for $AT_1$ binding sites in rat liver ([$^3$H] p$K_i$ = 9.3) with potent antagonistic activity (p$K_b$ 9.0, rabbit aorta). Oral bioavailability of compound **25** in rats and dogs is high, confirming that the compound **25** is absorbed well after oral administration. It is a potent antagonist of Ang II in vitro and causes marked and sustained fall in blood pressure in RHR at 0.3 mg/kg (po).[86] Compound **25** (1 mg/kg ia and po) inhibited pressor responses of Ang II in conscious normotensive rats. It showed parallel displacements in Ang II dose–response curves. The antagonistic activity of compound **25** lasted for up to 24 h. It significantly reduced DBP in renal artery ligated hypertensive rats (>0.03 mg/kg ia, >0.3 mg/kg, po) with little effect on heart rate.

Replacement of the "spacer" benzofuran ring in GR117289 (**23**) with indole resulted in a new series of compounds at Bristol Myers Squibb. BMS-180560 (**26**) is a potent, specific, predominantly competitive, reversible $AT_1$ receptor antagonist, displaying insurmountable receptor antagonism.[88,89] Compound **26** as $AT_1$ receptor antagonist, selectively inhibited [$^{125}$I]-Sar$_1$Ile$_8$ Ang II binding to rat aortic smooth muscle (RASM) cells, and rat adrenal cortical membrane ($K_i$ 7.6 and 18.4 nM, respectively). Compound **26** inhibited Ang II stimulated contraction of rabbit aorta. It antagonized the pressor response to Ang II in conscious Sprague–Dawley rats (SD rats) at doses as low as 0.03 μM/kg ($ED_{50}$ 0.22 μM/kg) when administered intravenously. When administered orally (30 μM/kg) to salt depleted SHR, compound **26** caused a sustained reduction in blood pressure which extended up to 72 h. The maximum percent reduction in MAP was 39% at the 30 μM/mg dose.[89]

In order to increase activity through conformational rigidity, research group at Searle explored 2′,6′-disubstitution on the spacer phenyl group. Compound **27** resulting from such a change was evaluated for specific binding to the Ang II to $AT_1$ and $AT_2$ receptors ($IC_{50}$) and for antagonism of Ang II induced contraction of rabbit aorta rings (p$A_2$). Compound **27** was found to be selective antagonist for $AT_1$ subclass of Ang II receptors. It proved to be a moderately potent competitive antagonist.[90]



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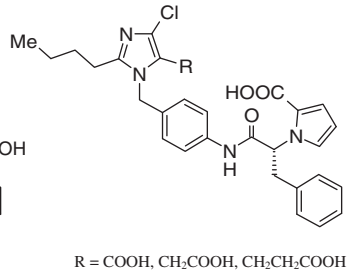


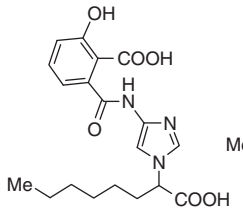
R = COOH, $CH_2COOH$, $CH_2CH_2COOH$

(28)

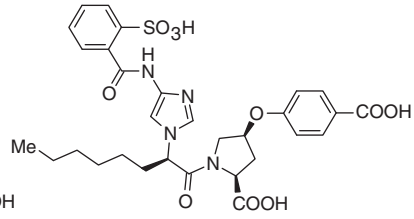
The biphenyl moiety has been reported to be replaced with number of other moieties (e.g., compounds **28–31**), but this modification met with little success. Ciba geigy group replaced biphenyl with 6/7-substituted naphthalene and tetrahydronaphthalene rings. These derivatives showed weaker potency in receptor binding assays and in functional tests which could be due to increased rigidity of the spacer, that did not allow conformational adjustments needed at the receptor site.[91] On the basis of three dimensional conformation of biphenyltetrazole, Merck group designed dibenzobicyclo[2.2.2]octane scaffold, Rebek's cleft and fluorene scaffolds. Two of the compounds showed good blood pressure lowering profile but were devoid of oral activity.[92]

A novel series of compounds (**28**), without biphenylyltetrazole as $AT_1$ receptor antagonist, was synthesized. 1*H*-Pyrrol-1-ylacetyl residue was utilized to replace the imidazole nucleus. The receptor binding affinity of several members of this new series was to the order of $10^{-8}$ M. Few of the compounds showed potency in functional assays in the range of nanomoles.[93]

A series of polysubstituted 4-aminoimidazole derivatives (e.g., **29**) as novel structural antagonists of the $AT_1$ receptor have been synthesized. These compounds possess only modest in vitro potency (p$A_2$ 7.0, rabbit aorta strip).[94] In order to take advantage of the structural novelty of the series, it has been further elaborated resulting into increased potency. The most potent compound **30** of the series showed selective, insurmountable antagonism in rabbit aorta.[95] Further refinement in the series resulted into compounds

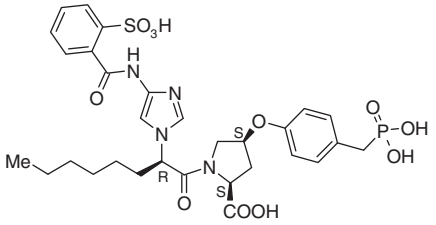


(29)



(30)

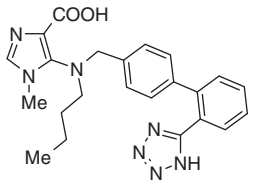
with increased potency. The most potent compound (in vivo $K_b$ 1.8 mg/kg) of the series, a phosphonic acid derivative **31**, produced a dose-dependent antihypertensive effect in the



(31)

Lasix-pretreated conscious SHR with a long duration of action (12 h) when administered orally (10 mg/kg). Compound **31** inhibited the pressor response of Ang II for periods up to 8 h (po).[96]

Biphenyltetrazole portion of the losartan has been reported to be replaced with biphenylaldoximic and phenylsalicylaldoximic moieties.[97] Novel imidazole analogs connected to biphenyl moiety through nitrogen (e.g., **32**) were reported to show weak potency.[98]

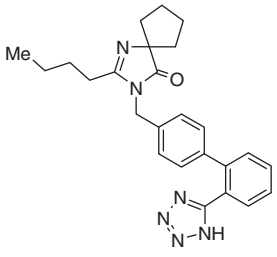


(32)

### 3.1.2. Dihydroimidazol-4-one containing antagonists

Bernhart et al. have reported SR 47436 (Irbesartan)[99] (**33**), 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, iv and 0.3–30 mg/kg, po).[100,101] Compound **33** was found to be 10-fold more potent than losartan ($IC_{50}$ 20.8 nM). When dosed orally (10 mg/kg), it inhibited the Ang II induced pressor response and maintained reduced blood pressure up to 28 h. Compound **33** was highly effective to lower blood pressure in high renin dependent hypertensive models such as two-kidney one-clip renal hypertensive rats and renal artery-ligated hypertensive rats.[102] In pithed rat, it produced a non-parallel shift to the right of Ang II dose–response curve.[103]

Perream et al. reported the importance of configuration of the 5th position in dihydroimidazol-4-one 5,5-disubstituted biphenylcarboxylic acid and biphenyltetrzaole series, which were evaluated in vitro. The results showed that dextro isomer of compound **34** ($IC_{50}$ 5.2 nM, rat liver membrane and $IC_{50}$ 0.77 nM, rabbit aortic rings) is 20 times more potent than the levo isomer ($IC_{50}$ 110 nM, rat liver membrane).[104]



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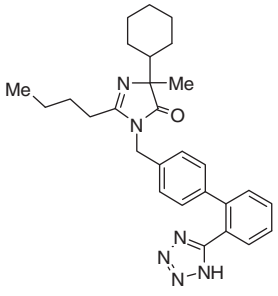
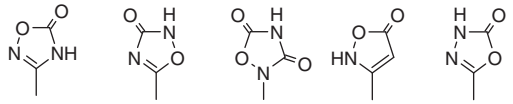


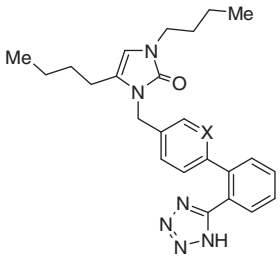
(34)

Non-tetrazole analogs (**a**–**e**) of compound **33** were also reported but none of these compounds showed the same or a better activity than the parent tetrazole analog.[105]

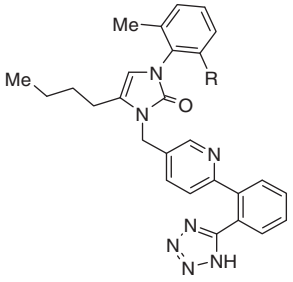


(a) (b) (c) (d) (e)

Repositioning of one of the ring nitrogen atoms led to the development of imidazol-2-one derivatives having comparable activity with the parent compounds.[106] Substitutions at the $N_1$ position of dihydroimidazolone ring were reported for SC-51895 (**35**).[107,108] A subsequent investigation into nitrogen containing biphenylmethyl compounds, phenylpyridinylmethyl and pyridinylphenylmethyl analogs of 2*H*-imidazol-2-one showed consistent doubling of binding potencies ($IC_{50}$) in phenylpyridinylmethyl analog SC-52892 (**36**) ($IC_{50}$ = 6.5 nM, $pA_2$ 8.68) relative to the parent biphenyl analog **35** ($IC_{50}$ 12 nM, $pA_2$ 8.65).[109] Aromatic group has been substituted at its $C_2$ position resulting into potent, surmountable $AT_1$ antagonist SC 54628 (**37**). Further substitution converted it to the



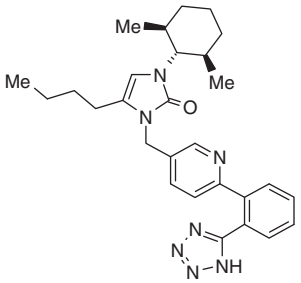
(35) X= CH; (36) X= N



(37) R= H; (38) R= Me

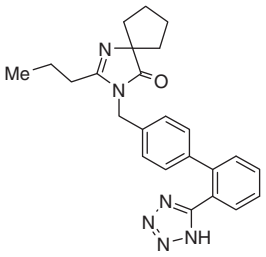
insurmountable (noncompetitive) receptor antagonist SC 54629 (**38**) because of steric hindrance.[110]

$N_1$- *trans*, *trans*-2,6-Dimethylcyclohexyl analog SC-55634 (**39**) of SR 47436 (**33**) was synthesized and reported as insurmountable antagonist with an $IC_{50}$ value of 4.9 nM and $pA_2$ 9.3.[106]



(39)

Quan et al. worked on the tetrazolylbiphenyl of imidazolinone. The propyl/butyl group at position $C_2$ was found to be optimum (e.g., **40**). Substitution at $C_2$ position with phenyl moiety resulted in decreased potency. At position $C_4$, cyclopentyl substitution was found to be most potent. The imidazolinones were selective for the $AT_1$ site; when the acylsulfonamide was used, the $AT_2$ affinities (**41**) were significantly enhanced. Both the tetrazoles and sulfonamides were very active in lowering blood pressure in RHR following intravenous administration.[111]



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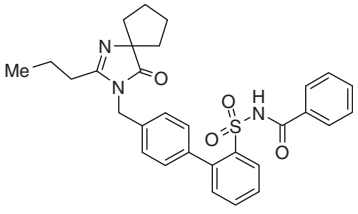
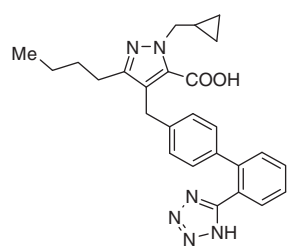


(41)

### 3.1.3. 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 **42** was effective at 1 mg/kg (po) in lowering blood pressure for 48 h in renal ligated antihypertensive rats and was highly potent in vitro.[112] Compound **42** exhibited a long plasma half-life, low plasma clearance and high volume of distribution.[113]

Ashton et al. carried out similar type of work at the Merck Lab. The most potent compound **43** showed $IC_{50}$ of 0.42 nM in rabbit aorta and inhibited 90% of the pressor response for more than 24 h in conscious normotensive rats. Various lipophilic groups like benzyl, phenethyl, 2-pyridyl and phenyl were tried at $N_1$. For $C_3$ position, propyl group was found to be optimum.[74] Almansa et al. reported UR 7280 (**44**) 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. It showed long duration of action. Compound **44** produced long lasting dose dependent decrease in blood pressure in furosemide treated sodium depleted rats, and RHR and conscious furosemide treated sodium depleted dogs. Compound **44** showed good pharmacokinetic profile in rats (half-life 7.4 h, 45% bioavailability) and in rhesus monkeys (half-life 15 h, 49% bioavailability).[114] Binding studies in rat liver membranes showed that compound **44** is an apparently competitive antagonist. In rabbit aorta this compound antagonized the Ang II-induced contractile response in an insurmountable way, causing a significant reduction of the maximal response[115] and thus acting as competitive, slowly reversible antagonist. Novel pyrazole



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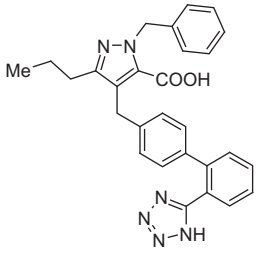

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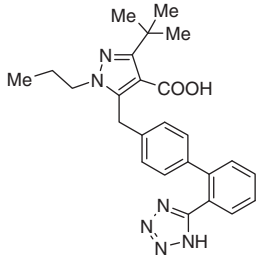

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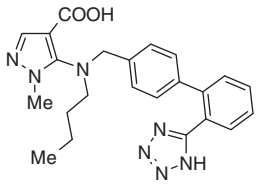
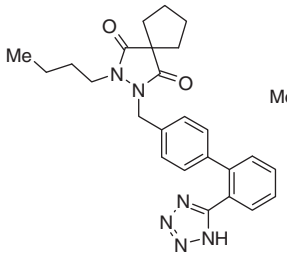


(45)

analog **45** connected to biphenyl moiety through nitrogen has also been reported but it has shown weak potency.[98]

### 3.1.4. Pyrazolidine-3,5-dione containing antagonists

On the basis of the structure of SR 47436 (**33**) Bourdonnec et al. reported a new series of $AT_1$ antagonist. 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 (**46** and **47**) 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. Both of the compounds showed good selectivity for $AT_1$ over $AT_2$. Ang II antagonistic activity for compounds **46** and **47** in terms of $IC_{50}$ values were 22 and 12 nM, respectively. Both of these compounds are less potent than SR 47436 (**33**). The difference in affinity between SR 47436 and compounds (**46** and **47**) suggests that the second carbonyl function in the pyrazolidinedione $C_5$ position is not positioned in the optimal direction to mimic the basic nitrogen of irbesartan.[116]



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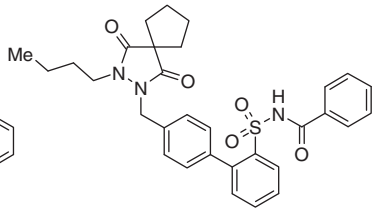


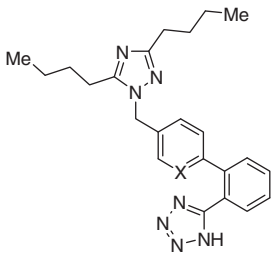
(47)

### 3.1.5. Triazole containing antagonists

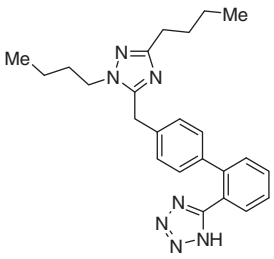
1,2,4-Triazole system having similar geometry to the imidazole moiety is considered to be a reasonable candidate for $AT_1$ receptor antagonistic activity. The additional nitrogen atom in the 1,2,4-triazole ring was expected to exert an electron withdrawing effect similar to the $C_4$ chloro substituent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

Reitz et al. have investigated *N*-biphenylmethyl substituted l*H*-1,2,4-triazoles and discovered that the 3,5-dibutyl analog SC-50560 (**48**) is a highly potent ($IC_{50}$ = 5.6 nM, p$A_2$ = 8.7), orally active $AT_1$ receptor antagonist.[117,118] A subsequent investigation, in which CH was systematically replaced with N at each position of both aromatic rings of the biphenyl, that is, *N*-phenylpyridinylmethyl and *N*-pyridinylphenylmethyl, was conducted to determine the pharmacological effects of such substitutions. The *N*-pyridinylphenylmethyl analog showed clear detrimental effect on potency while *N*-phenylpyridinylmethyl analog appeared to have little effect on the in vitro properties of compound **48**. The most active compound in the series SC-52458 (**49**) showed $IC_{50}$ value of 6.9 nM, p$A_2$ value of 8.2, and was found to have superior in vivo properties than SC-50560.[119] Compound **49** was a potent inhibitor of [$^{125}$I] Ang II ($IC_{50}$ values of 2.8, rat adrenal cortex). SC-52458 is an orally active, competitive $AT_1$ receptor antagonist. In conscious dogs when dosed orally (30 mg/kg), it blocked the pressor response of Ang II with maximal inhibition (91%) up to 2 h and the effects persisted for 24 h.[119,120]

The $N_1$ biphenylmethyl group and the $C_5$ butyl groups of potent, orally active compound **48** were interchanged to give the isomeric 'C-linked' 1,2,4-triazole analog SC-51757 (**50**). Compound **50** showed $IC_{50}$ value of 16 nM and p$A_2$ of 8.5. At a dose of 3 mg/kg compound **50** inhibited the Ang II induced pressor response in rats. A good activity was observed only when *n*-butyl group was adjacent to the *C*-biphenylmethyl group and not to the *C*-butyl group. The antagonist with *n*-butyl group adjacent to the *C*-butyl group showed decreased potency.[121]



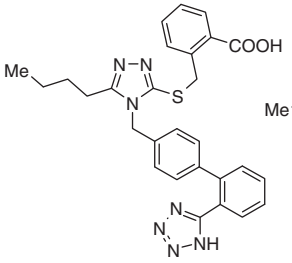
(48) X = CH; (49) X = N



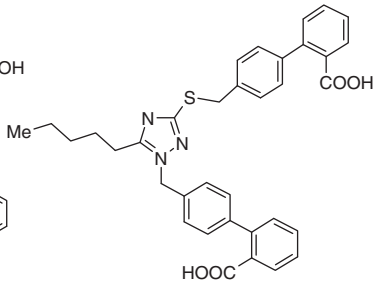
(50)

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. Among these,

thioether diacidic derivative **51** showed high potency (in vitro, $IC_{50}$ 1.4 nM) and blocked the Ang II pressor response in conscious rats at 0.3 mg/kg (iv) with duration of action of approximate 6 h. Upon oral administration at 3 mg/kg, compound **51**



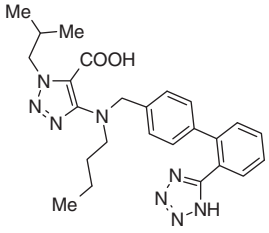
**(51)**



**(52)**

displayed moderate activity with more than 6 h duration of action. $C_2$ Position was also evaluated for thioether groups but it did not show any enhancement in potency.[122]

Bandurco et al. reported a novel series of substituted 1,3 and 1,5-bisbiphenyl mercaptotriazoles as potent antagonists of $AT_1$ receptor. These compounds were tested in rabbit aortic rings and in a high renin rat model. The best compound **52** of the series showed potent antagonism of Ang II contraction in rabbit aortic rings ($pA_2$ 8.4) and reduced blood pressure for more than 24 h in high renin rat (5 mg/kg).[123] A compound containing triazole

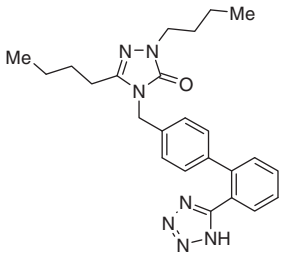


**(53)**

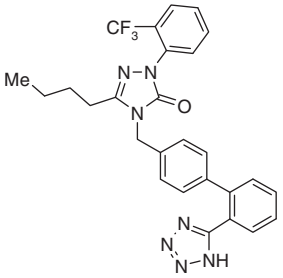
nucleus connected to biphenyl moiety through nitrogen (**53**) was synthesized and evaluated for $AT_1$ receptor antagonistic activity ($pA_2$ 9.3).[98]

### 3.1.6. 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 (**54**) as orally active and selective antagonist with $IC_{50}$ value of 5.1 nM in rat uterine membrane. Compound **54** showed competitive and reversible antagonism of Ang II mediated contraction of rabbit aortic rings with $pA_2$ value of 8.86. It has also showed dose dependent inhibition of Ang II induced pressor response. The $ID_{50}$ value was found to be 2.1 mg/kg. The 2nd position of triazole was further explored with unbranched and branched groups like alkyl, phenyl, benzyl, etc. but none of them was found to be active.[124] Chang et al. worked on $N_2$ position of triazol-3-one.

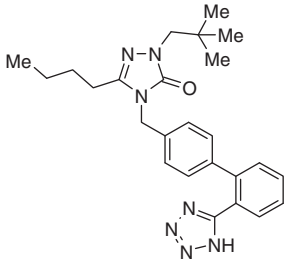


**(54)**



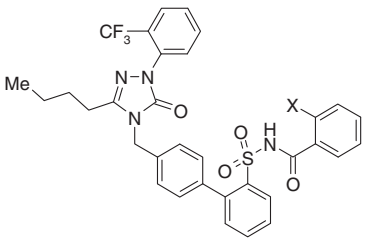
**(55)**

Aryl substituted compound **55** was effective to inhibit Ang II pressor response by 70% at a dose of 1 mg/kg (iv) in conscious normotensive rats. It effectively displaced ($IC_{50}$ 1.2 nM) $^{125}I$ $Sar^1Ile^8$ Ang II from rabbit aortic membranes. Alkyl substituents were also tried and the most potent compound **56** showed $IC_{50}$ value of 1.2 nM in rabbit aortic membrane. It effectively blocked the Ang II pressor response in conscious rats with a significant duration of 2.5 h at 1 mg/kg (po).[125]

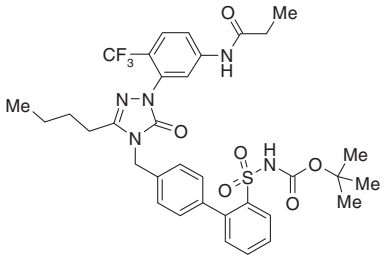


**(56)**

In order to improve the in vitro and/or in vivo properties of this class of $AT_1$ antagonists, the same group from the Merck Lab replaced the tetrazole by other carboxylic acid bioisosteres such as acylsulfonamides. L-159,913 (**57**) an $AT_1$ selective, reversible and competitive antagonist with $K_i$ value of 1.7 nM resulted from replacement of tetrazole moiety of compound **55** with acylsulfonamide. Compound **57** showed increased in vivo activity. At 1 mg/kg, it inhibited Ang II pressor response with good duration of action orally in conscious rats and dogs. In the rhesus monkey, at 10 mg/kg po, it showed 76% peak inhibition of the pressor response with 4–24 h of duration of action. The oral bioavailability of compound **57** was reported to be 44% in the rat, which compared favorably with losartan (33%).[126] Substitution in aromatic ring of the sulfonamide group further increased the $AT_2$ affinity. The benzoylsulfonamide analog L-162,223 (**58**)[127] displayed

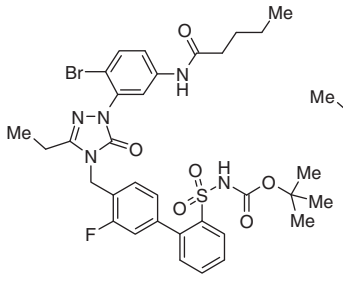


**(57)** X = H; **(58)** X = Cl



**(59)**

approximately 80-fold increase in $AT_2$ affinity relative to the corresponding tetrazole. Analogs L-163,007 (**59**)[127], L-163,958 (**60**) and (**61**)[128] also showed increased $AT_2$ potency. Upon replacement of tetrazole by a lipophilic acylsulfonamide, enhancement in $AT_2$ binding affinity was observed in compounds belonging to other heterocyclic series also.



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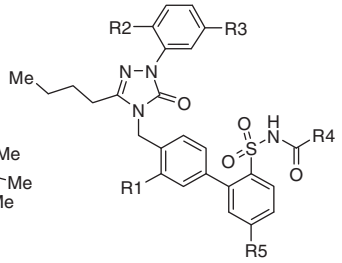
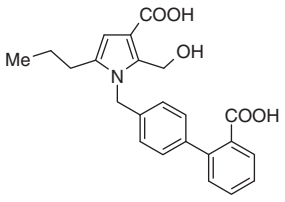


(61)

### 3.1.7. Pyrrole containing antagonists

Compounds with pyrrole ring, and hydroxymethyl and carboxylic groups, have been reported and evaluated for in vivo and in vitro activities. In vivo activity ($ID_{50}$) was determined by suppression of the pressor response induced by Ang II in conscious normotensive rats (iv) while in vitro activity $IC_{50}$ was determined by inhibition of specific binding of [$^{125}$I] Ang II to bovine adrenal cortex. Pyrroles (e.g., **62**) showed weak antagonistic activities. Pyrroles would be 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.[58] Biphenyltetrazole derivatives of 1-aminopyrroles (e.g., **63**) were synthesized. All of the compounds in this series were found to be inactive.[129]



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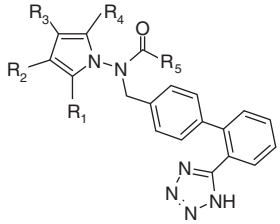
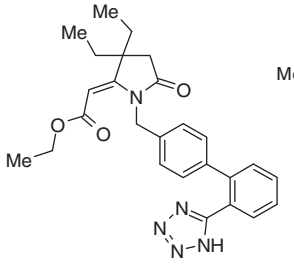


(63)

### 3.1.8. Pyrrolidin-2-one containing antagonists

Murray et al. reported a novel series of substituted pyrrolidin-2-ones (e.g., **64**, **65**). The most potent inhibitor **64** from the series antagonized Ang II induced contractions in rabbit aortic strip with $pA_2$ value as high as 7.9 and exhibited $IC_{50}$ as low as 100 nM (rabbit adrenal cortex). Some of the compounds from this series were found to be orally active in SHR.[130]



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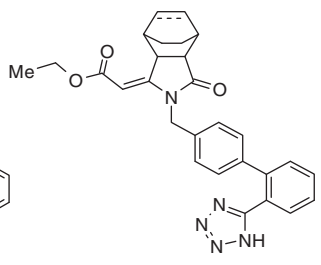
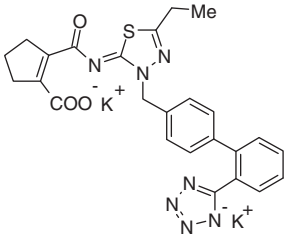


(65)

### 3.1.9. Acyliminothiadiazoline containing antagonists

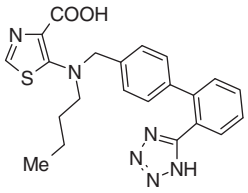
Hirata et al. reported a novel series of Ang II antagonists having acyliminothiadiazoline nucleus. The most potent compound of the series KRH-594 (**66**) is $AT_1$ selective antagonist with $IC_{50}$ of 0.4 nM. When dosed orally, compound **66** showed strong antihypertensive action in RHR. It showed 10 times higher potency than losartan.[131]



(66)

### 3.1.10. Thiazole and thidiazole containing antagonists

Pratt et al. reported novel thiazole (**67**, **68**) and thiadiazole (**69**, **70**) analogs and evaluated their $AT_1$ antagonistic activity. Compounds **67–70** showed weak activity in antagonism assay using rabbit aorta.[98]



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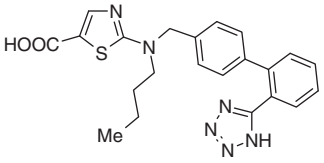

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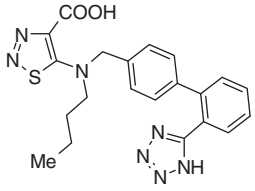

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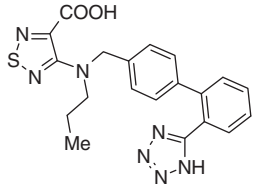
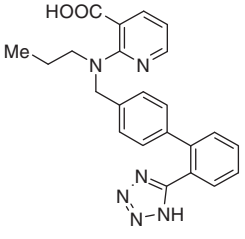


(70)

## 3.2. Substituted six-membered antagonists

### 3.2.1. Pyridine containing antagonists

Abbott Laboratories discovered pyridine derivatives as a novel class of orally active, non-peptide $AT_1$ antagonists. Abbott's A-81988[132] (**71**) ($K_i$ 0.76 nM, rat liver; $pA_2$ 10.1–10.7, rabbit aorta)[133] was found to be a surmountable antagonist. In conscious RHR, A-81988 lowered MABP after oral administration (0.3 mg/kg), with duration of action exceeding 24 h.[134] It showed high oral bioavailability (>50%) in rats, dogs and cynomolgus monkeys. It reduced blood pressure significantly in both furosemide treated SHR (0.1 mg/kg, po) and untreated SHR (3 mg/ kg, po), and in renal artery ligated hypertensive rats (0.03 mg/kg).[133,135]



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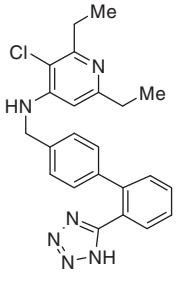
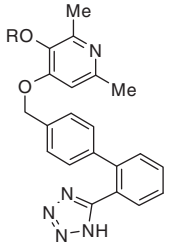


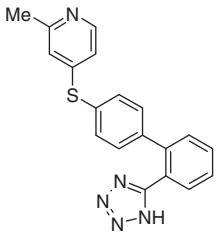
(72)

A series of 3-substituted 4-amino-2,6-dialkylpyridines (e.g., **72**) was developed and compounds from this series showed potent in vitro antagonistic activity. The most potent compound of the series (**72**) showed significant inhibition (66%) of the Ang II pressor response for 5 h after dosing at 1.0 mg/kg. It showed high oral absorption with an $ED_{50}$ of 0.06 mg/kg.[136]

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 (**73**) as a competitive $AT_1$ selective antagonist ($pK_i$ 8.7, rat liver).[137,138] Compound **73** antagonized Ang II induced contraction in the rabbit aorta with a $pA_2$ value of 8.82.[139] Given orally or intravenously it inhibited the pressor response to Ang II in conscious normotensive rats dose-dependently. Compound **73** lowered BP in both SHR and RHR for 24 h with $ED_{50}$ values of 0.48 and 2.5 mg/kg, po, respectively but, did not lower the blood pressure in DOCA salt rats and normotensive rats. Repeated administration of compound **73** 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(**74**).[140] EF2831 (**74**), a metabolite of compound **73**, is also a



(**73**) R= Me; (**74**) R=H



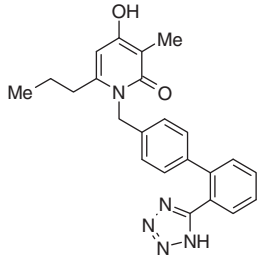
(**75**)

surmountable $AT_1$ receptor antagonist, whose potency is 1/30 of compound **73**, when evaluated in vitro, and equal to or 1/30 of compound **73**, when evaluated in vivo.[117] Compound **74** has long lasting antihypertensive effect. It inhibited pressor effect of Ang II in a dose dependent manner, when administered orally (po) or intravenously (iv) to conscious normotensive rats and common marmosets.[141]

Pyridine ring connected to biphenyl moiety through sulfur linker (**75**) was also synthesized and evaluated for $AT_1$ receptor antagonistic activity but it showed weak antagonistic activity ($IC_{50}$ 1.5 μM rat liver membrane).[142]

### 3.2.2. Pyridinone containing antagonists

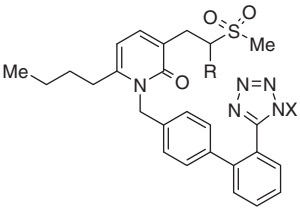
Bantick et al. have reported a series of biphenyl 2(1*H*)-pyridinones. 4-Substituted pyridinones, particularly 4-OH, 4-SH and 4-COOH showed activity in in vitro and in vivo evaluation studies. Compound **76** showed potent antagonistic activity and $ID_{50}$ value in the range of 0.02 mg/kg in normotensive rats. When dosed orally in SHR, it lowered blood pressure for more than 6 h duration.[143] Compounds sharing different substituents at 3rd



(**76**)

position were evaluated showing good tolerance with small decrease in potency. The same research group evaluated $AT_1$ receptor antagonistic activity of fused bicyclic analogs of 2-pyridinones. Potent antagonist activity was found in the 2-quinolinone, thieno [2,3-*b*]pyridine and imidazo[*c*]pyridine series of compounds.[144]

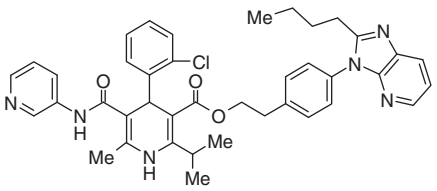
Research group at E. Merck worked on a series of dihydropyridin-2-ones. Some of the potent compounds (**77**, **78**) in the series displayed potencies in nanomolar range (1.9 and 1.2 nM) and their inhibitory effect on Ang II pressor response in pithed rat was superior to that of losartan.[145] Another derivative (**79**) also showed promising in vivo activity.[146]



(**77**) R = *i*.Propyl, X = H;
(**78**) R = Me, X = H;
(**79**) R = Methylcyclopropyl, X = K

### 3.2.3. Dihydropyridine containing antagonist

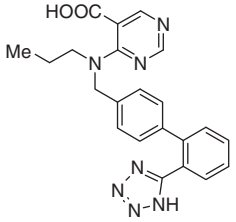
Pfizer reported a new class of dihydropyridine antagonists. UK77778 (**80**), a selective $AT_1$ receptor antagonist showed $IC_{50}$ value of 0.6 nM in rat adrenal cortex. Modifications of UK77778 increased both binding affinity and selectivity for $AT_1$ receptor.[147]



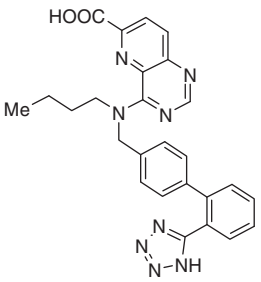
(**80**)

### 3.2.4. Pyrimidine containing antagonists

Abbott Laboratory was the first to report novel & potent ($pA_2$ 9.93, isolated rabbit aorta) pyrimidine derivative A-81080 (**81**). When administered intravenously at a dose of

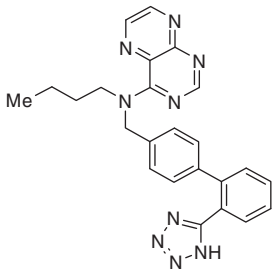


(**81**)



(**82**)

0.3–1 mg/ kg as disodium salt, compound **81** lowered MABP in a dose-dependent manner in the renal artery-ligated (RAL) hypertensive rats. However, the oral response in the RAL rats



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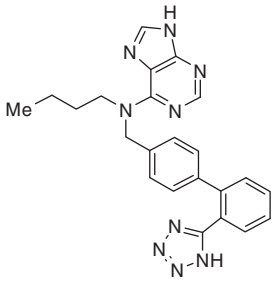
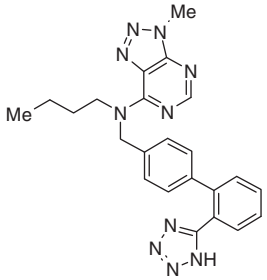


(84)

(1–10 mg/kg, po) was poor, both in terms of the antihypertensive effect and the duration of action.[132]

Heterocyclic analogs (**82**–**86**) of A-81080 were synthesized and evaluated for antagonistic activity and were found to be less potent.[148]



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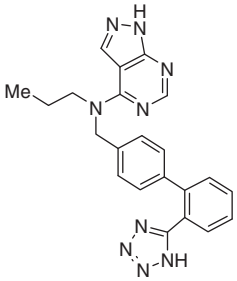
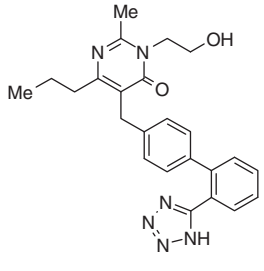


(86)

### 3.2.5. Pyrimidinone containing antagonists

Nicolai et al. reported UP 243-38 (**87**). 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 (po). It showed high affinity for rat adrenal membrane $AT_1$ receptor with displacement of more than 60% of radiolabeled Ang II at nanomolar range. Compound **87** is equipotent to losartan with a slightly different pharmacokinetic pattern.[149]



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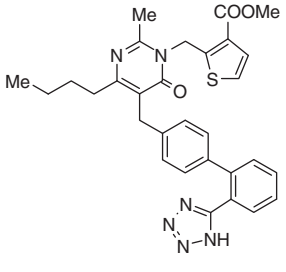
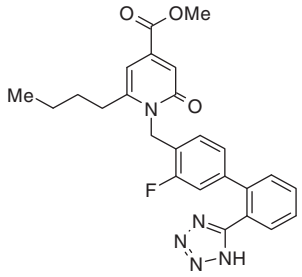


(88)

Subissi et al. reported LR B081 (Lusofarmaco) (**88**), an $N_3$-heteroaryl substituted and C-linked pyrimidinone insurmountable antagonist. Compound **88** showed selective ($K_i$ 0.9 nM, rat adrenal cortical membrane) and competitive antagonism. Compound **88** showed long-lasting antihypertensive activity when dosed orally in RHR and SHR. It is a well-tolerated, orally active compound.[150] A series of selenophene analogs of the thiophene containing compound **88** were prepared and tested for $AT_1$ receptor antagonist properties. These selenides were as effective as the sulfur containing parent compounds in blocking $AT_1$ receptor mediated responses. The study revealed that the replacement of sulfur with selenium in thiophene containing SARTANs did not interfere with SARTAN activity.[151]

BAY 10-6734 (Embusartan) (**89**) is an orally active $AT_1$ antagonist containing dihydropyridinone nucleus. BAY 10-6735 is a therapeutically active moiety produced by the hydrolysis of BAY 10-6234. BAY 10-6734 showed competitive whereas BAY 10-6735 exhibited a noncompetitive mode of antagonism. Compound **89** is a well tolerated and long lasting antagonist (24 h).[152]



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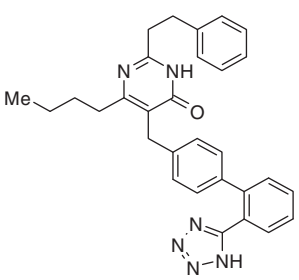
Synthelabo's SL 910102 (**90**), a potent antagonist reduced Ang II pressor effects in anesthetized rats and lowered blood pressure after chronic administration in SHR.[34]



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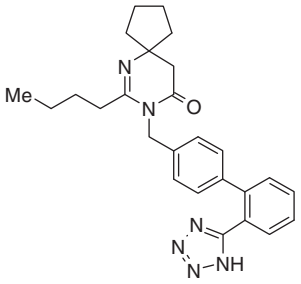
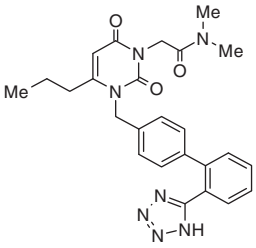


(91)

A novel series of homologs of SR 47436 (**33**), substituted 3-*H*-dihydropyrimidinones were identified as $AT_1$ receptor antagonists. The best compound **91** in the series showed high affinity for the $AT_1$ receptor with $IC_{50}$ in the nanomolar range. It was equipotent to SR 47436 (**33**) in conscious normotensive rat, but was inactive in normotensive cynomolgus monkeys.[153]

E. Merck explored pyrimidinedione nucleus for Ang II antagonistic activity. The most potent compound **92** of the series showed strong affinity for bovine adrenal cortex (9.3 nM, losartan 11.6 nM) and rat adrenal cortex (0.65 nM, losartan 0.82 nM).[149] Further annellation of the ring gave two uracil derivatives **93** and **94**. When evaluated for Ang II binding affinity, both of them were found to be less active.[154]



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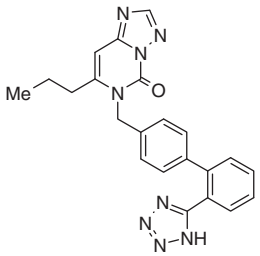

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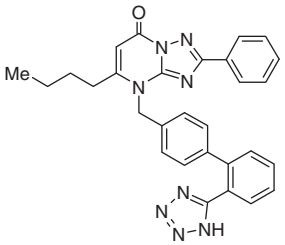
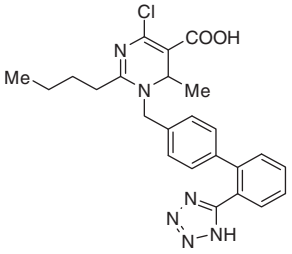


(94)

### 3.2.6. Dihydropyrimidine containing antagonists

Bristol Myers Squibb successfully replaced the imidazole ring with the dihydropyrimidine ring. The most potent compound (**95**) of the series showed good binding affinity ($K_i$ 1 nM) as well as functional antagonism ($K_b$ 0.45 nM). It showed 10 times more



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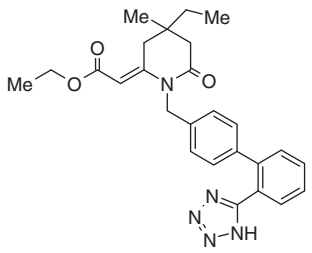


(96)

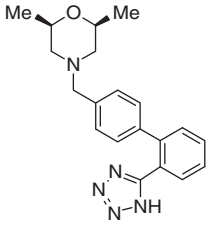
potency in binding and 25 times more antagonism than losartan. It effectively lowered blood pressure in SHR ($ED_{50}$ 0.08 μmol/kg) with its potency being 20-fold higher than that of losartan.[155]

### 3.2.7. Piperidinone containing antagonists

RWJ 46458 (**96**) (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. In SHR compound **96** produced a maximum antihypertensive effect at 30 mg/kg, po with duration of action exceeding 24 h. In high renin rat model, it produced maximum effect with a rapid onset of action (dose 30 mg/kg, po).[156,157]

### 3.2.8. Morpholine containing antagonists

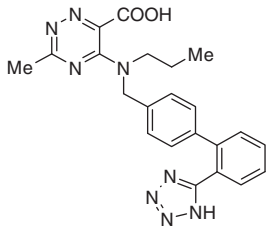
Morpholine derivative RWJ 47639 (**97**) showed a $pA_2$ value of only 6.9. It showed a rapid onset of action with a duration of action >12 h. in SHR.[158]



(97)

### 3.2.9. Triazine, pyrazine and pyridazine containing antagonists

A series of six-membered ring heterocycles like triazine (e.g., **98**), pyrazine (e.g., **99**) and pyridazine (e.g., **100**) connected to a biphenyltetrazole through nitrogen were synthesized and evaluated for $AT_1$ receptor antagonistic activity. All of these compounds showed weak potency as $AT_1$ receptor antagonists.[133]



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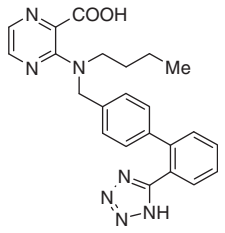

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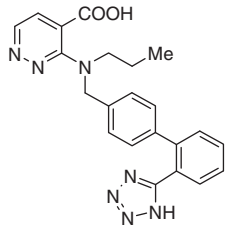


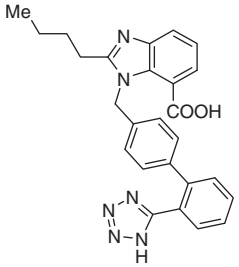
(100)

## 3.3. Antagonists with fused five-membered heterocyclic ring

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.

### 3.3.1. Benzimidazole containing antagonists

Benzimidazoles have been investigated by several groups to find potent antagonists. Kubo et al. from Takeda Chemical Industeries reported CV-11194 (**101**) as inhibitor of specific binding of $^{125}$I Ang II to bovine adrenal cortical membrane with an $IC_{50}$ value of



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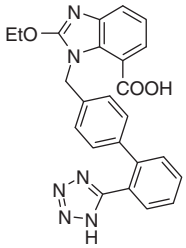


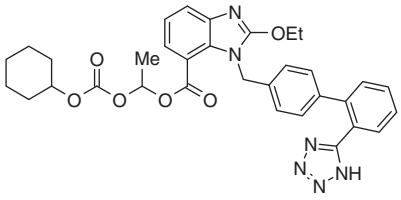
(102)

0.55 μM. The compound **101** showed potent antagonism in rabbit aortic strips with $IC_{50}$ value of 0.055 nM. Orally administered compound **101** inhibited the Ang II induced pressor response in rats and dogs dose-dependently (0.3–10 mg/kg). Compound **101** reduced blood pressure in SHR at 1 mg/kg (po). At 10 mg/kg po it completely inhibited the pressor response to Ang II for at least 7 h.[159]

In order to improve potency, number of substituents were explored at $C_2$ position of benzimidazole and the most potent compound of the series was CV-11974 (**102**). Compound **102** is a long acting, selective (0.11 μM) and competitive ($pD_2$ 9.97) antagonist. In conscious normotensive rats, orally dosed compound **102**

(1 mg/kg) inhibited Ang II induced pressor response with long duration of action. Compound **102** at 0.1–1 mg/kg (iv) reduced blood pressure dose-dependently in SHR. A single dose of compound **102** at 1 mg/kg (iv) reduced the MABP for more than 24 h.[160] The affinity of the compound **102** to the $AT_1$ receptors was approximately 80 and 10 times higher than that of losartan and EXP3174 (**3**), respectively. In the in vitro functional study, a dose of 1 mg/kg (po) blocked the Ang II pressor response in conscious rats for more than 24 h.[161] At a dose of 20 mg/kg (iv), compound **102** decreased vasopressor response to Ang II in a non-competitive manner.[162] The insurmountable antagonism of compound **102** was observed due to its slow dissociation from angiotensin $AT_1$ receptors.[163]

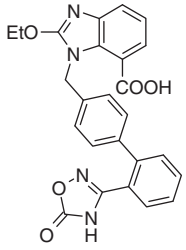
In order to improve the oral bioavailability, different esters of compound **102** were prepared and evaluated. The most potent compound of the series TCV-116 (**103**) (Candensartan cilexetil) is an orally active nonpeptide antagonist of $AT_1$ receptor. Compound **103** is a highly potent and long lasting antagonist of $AT_1$ receptor in man.[164] Compound **103** blocked the Ang II pressor response with an $ED_{50}$ value of 0.069 mg/kg (po).[165] In both renal and genetic hypertensive rats it produced long acting Ang II antagonism and antihypertensive effects without affecting heart rate. The oral bioavailability



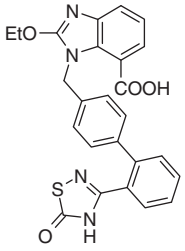
(**103**)

of compound **103** in rats is 28–33%.[165–167] The inhibitory effects were observed in conscious normotensive rat for longer duration of action at doses of 0.3 and 0.03 mg/kg (po) when compared with parent compound. In isolated rabbit aortic strips, it inhibited $AT_1$ induced contraction with $IC_{50}$ values of 0.2 μM.[165]

Kohara et al. from Takeda Chemical Industeries further explored bioisosteres for tetrazole moiety of compound **102**[168,169] and successfully replaced it with two moieties as seen in TAK-536 (**104**) and (**105**).[169] Binding affinity to bovine adrenal cortical membrane



(**104**)

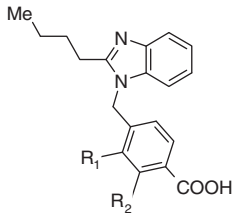


(**105**)

of both of the compounds, TAK-536 (**104**) and (**105**) showed slightly lower affinity (4.2 and 2.5 nM, respectively) than compound **102**. At 0.01 mg/kg po, compound **104** produced dose dependent inhibition which lasted for 24 h and its $ID_{50}$ value (0.04 mg/kg) was comparable to compound **103** (0.06 mg/kg) in conscious rats.[168,169]

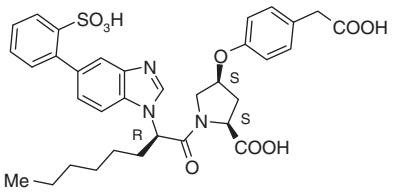
The importance of the carboxyl group attached to the heterocyclic moieties for insurmountable antagonism and enhancement of in vivo (po) activity was evaluated. A novel series of heterocyclic compounds bearing two acidic functionalities, a carboxyl group and a tetrazole ring, was prepared and evaluated for in vitro and in vivo activities. These compounds showed significantly more potent $AT_1$ receptor antagonistic activities than the parent compounds which were without the carboxylic groups. This structure–activity relationship (SAR) study revealed the importance of the carboxyl group attached to the heterocyclic moieties especially for insurmountable antagonism and enhancement of in vivo (po) activity.[170]

Thomas et al. evaluated a series of toluic acids (**106**) of benzimidazole for biphenylacids and found out their in vitro binding affinities to be in the range of $10^{-5}$–$10^{-7}$ M. Compound **106** antagonized the hypertensive effects in the range of 5–20 mg/kg (iv) in vivo. However, oral activity of these compounds was poor; only marginal effects were observed at a dose of 50 mg/kg.[171]



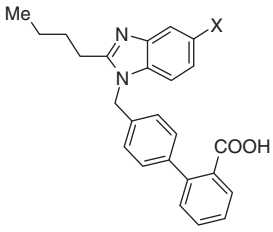
(**106**)

Palkowitz et al. reported a novel series of benzimidazoles (e.g., **107**) with phenoxyproline side chain for Ang II antagonistic activity. All of these benzimidazole analogs were found to be equipotent in vitro.[172]



(**107**)

Bansal et al. worked on the 5th position of the benzimidazole nucleus with nitro, alkylcarboxamido and alkylsulfamoyl substituents and reported potent $AT_1$ antagonists (**108–111**).[173–175]

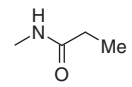


(**108-111**)

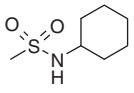
**X =**

(**108**) X = -$NO_2$

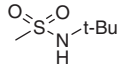
(**109**) X =



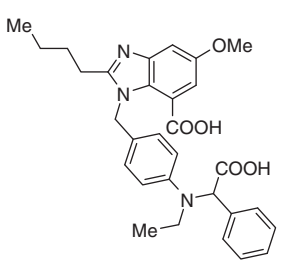
(**110**) X =



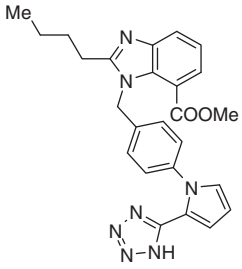
(**111**) X =



Xu et al. reported benzimidzoles with differently substituted groups. Compounds (**112** and **113**) showed functional antagonism ($pA_2$ 8.3 and 8.4, respectively, rabbit thoracic aortic ring) more potently than losartan ($pA_2$ 7.9). In conscious normotensive rats, they showed more potent and long lasting effects than losartan at dose of 1 mg/kg (po).[176,177]

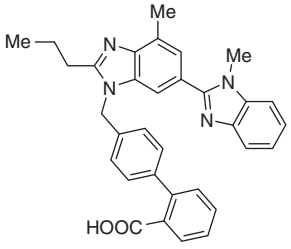


**(112)**

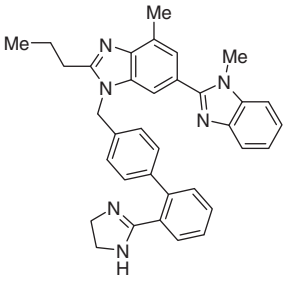


**(113)**

BIBR 277 (Telmisartan) (**114**) is a selective ($K_i$ 3.7 nM, rat lung) and potent insurmountable antagonist.[178] Compound **114** produced a dose-dependent decrease in MABP in conscious RHR (0.3 and 1 mg/kg, po) and SHR (1 and 3 mg/kg).[179,180] Its hypertensive effect was observed for 24 h, when dosed orally (3 mg/kg). It showed somewhat less affinity for $AT_2$.



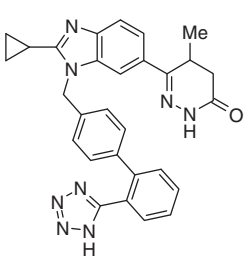
**(114)**



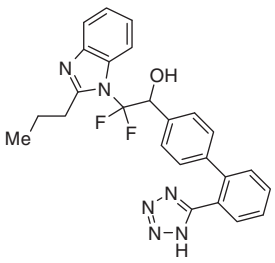
**(115)**

An orally active compound **115** competitively inhibited the binding of radiolablled Ang II to bovine adrenal cortex. The compound **115** was found to be equipotent to losartan ($IC_{50}$ 2.9 nM). In spontaneously hypertensive dogs, it showed significant inhibition of Ang II pressor response which was equivalent to standard telmisartan (**114**).[181]

The synthesis and Ang II antagonistic activities of novel (6-oxo-3-pyridazinyl)-6-benzimidazole derivatives are reported. The most active compound **116** ($IC_{50}$ 1.8 nM) in the series showed excellent inhibition (80%) of the Ang II induced pressure response in a pithed rat model after intraduodenal administration.[182]



**(116)**

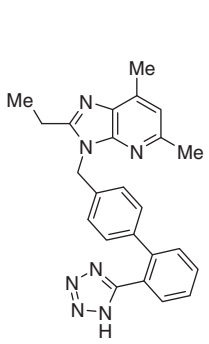


**(117)**

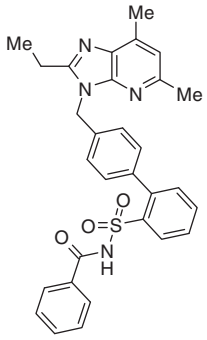
Yagupolskii et al.[183] synthesized and evaluated a series of 2-alkyl-1-(2-aryl-1,1-difluoro-2-hydroxyethyl)benzimidazoles. The most potent compound of the series was **117**. BIBS-39 ($AT_1$ $K_i$ 29 nM; $AT_2$ $K_i$ 480 nM) and BIBS-222 ($AT_1$ $K_i$ 20 nM; $AT_2$ $K_i$ 730 nM), benzimidazoles have been reported by Zhang et al.[184] to possess modest binding affinity for both $AT_1$ and $AT_2$ receptors. Both antagonists lowered blood pressure in renal hypertensive rats with an $ED_{30}$ value of 2 mg/kg (iv).

### 3.3.2. Imidazopyridine containing antagonists

An imidazopyridine heterocycle ring could replace the imidazole ring as it contains common imidazole element 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 (**118**). L-158,809 (**118**) is a potent ($IC_{50}$ 0.3 nM, rabbit



**(118)**



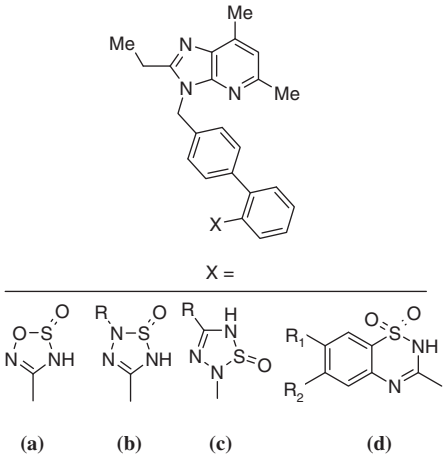
**(119)**

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. In rat with high renin levels, it reduced the MABP to normotensive levels with duration of 48 h at single doses of 0.1 and 0.3 mg/kg (po).[185–187]

Tetrzole moiety in the biphenyl portion undergoes N-glucuronidation. So, considerable efforts were made for identifying an isostere of tetrazole which maintained the potency, duration of action and bioavailability of losartan and other related biphenyltetrazoles. Replacement of tetrazole moiety of L-158,809 (**118**) with acylsulfonamide group resulted into MK-996 (**119**). Compound **119** is selective ($IC_{50}$ 0.2 nM, rabbit aorta)[188] and insurmountable antagonist ($pA_2$ 10.3). This benzoylsulfonamide analog showed excellent in vitro and in vivo properties.[189,190] It inhibited the Ang II pressor response in conscious animals with oral $ED_{50}$ values of 0.067 (rat), 0.035 (dog) and 0.1 mg/kg (rhesus monkeys).[191] Compound **119** (1 mg/kg) blocked the Ang II-induced pressor response in anaesthetized chimpanzees. Similar prolonged duration of action was observed in conscious dogs at a dose of 1 mg/kg (po).

The 5th position of terminal phenyl ring was explored and these compounds showed increased $AT_2$ affinity. L-162,389 in which benzoyl sulfonamide acid group was replaced by *n*-butylsulfonylcarbamate having a propyl chain at the 5th position of the terminal phenyl showed increased $AT_2$ antagonistic activity.[192]

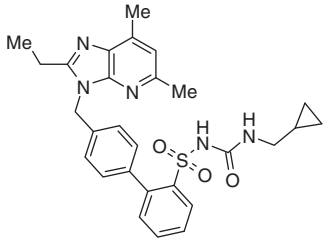
Replacement of the acidic tetrazole functionality by various heterocyclic acid equivalents such as oxathiadiazole, thiatriazole and dioxobenzothiadiazine (**120**) were also tried. The most potent compound of this series **120a** (L-161,177, $IC_{50}$ 0.7 nM, rabbit aorta),




**120 (a-e)**

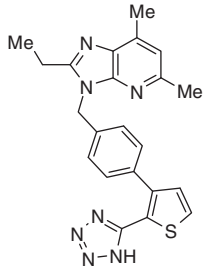
bearing the oxathiadiazole, exhibited excellent in vivo activity profile after intravenous as well as oral administration to conscious rats. Compound **120a** inhibited the pressor response to Ang II in conscious normotensive rats at dose of 0.1 mg/kg (iv). Compared to compound **118**, it showed slightly shorter duration of action.[193]

Heitsch et al. reported a series of imidazo[4,5-*b*]pyridine biphenylsulfamylureas and carbamates as highly potent $AT_1$ selective compounds. The most potent compound **121** of the series showed $IC_{50}$ value of 1 μM in rat liver membrane. Compound **121** showed $ED_{50}$ of 14 μg/kg on iv and 12 μg/kg on intraduodenal (id) administration in pithed rats.[194]



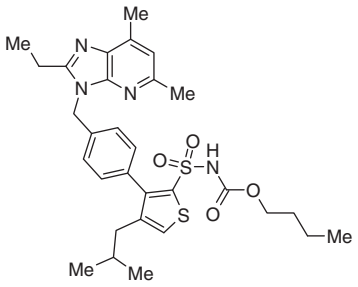
**(121)**

The biphenyl fragment of the potent $AT_1$ receptor antagonist **118** was replaced by phenylthiophene and phenylfuran moieties. Replacement of the central phenyl ring by a 2,5-disubstituted thiophene resulted in a 1000-fold loss of potency while replacement of the tetrazole-bearing phenyl group by a thiophene (e.g., L-159,827, **122**) resulted in a small loss in binding affinity (<3×) with an $IC_{50}$ of 2.3 nM. Compound **122** showed 90% peak



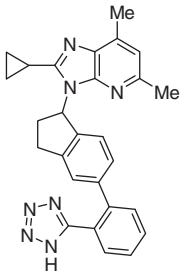
**(122)**

inhibition of Ang II pressor response for more than 6 h in conscious rat (1 mg/kg, iv).[195] Replacement of tetrazole with benzoylsulfonamide dramatically increased $AT_2$ affinity. Substitution at the 5th position of thiophene ring also imparted higher $AT_2$ binding.[196] Replacement of the acidic tetrazole moiety with a substituted sulfonamide made the derivative (**123**) an agonist for $AT_1$ and $AT_2$ receptors.[197]



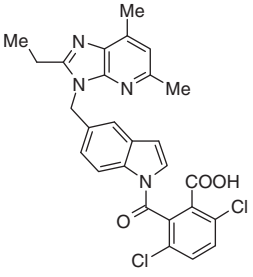
**(123)**

Carpino et al. reported a conformationally restrained series of derivatives of compound **118**. The benzyl linker in L-158,809 (**118**) was replaced by a series of bicyclic rings such as dihydroindanyl, tetrahydronaphthyl, tetrahydrobenzocycloheptenyl 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 **124** that was as potent ($IC_{50}$ 0.2 nM) as compound **118**.[198]

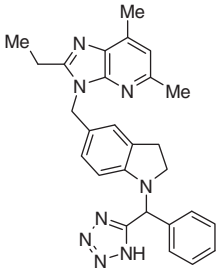


**(124)**

The biphenyl moiety of L-158,809 (**118**) was replaced with N-substituted indoles and dihydroindoles. Two most potent compounds of the series are **125** ($AT_1$ $IC_{50}$ = 0.8 nM, rabbit aorta) and **126** ($AT_1$ $IC_{50}$ = 1 nM, rabbit aorta). Compound **125** blocked



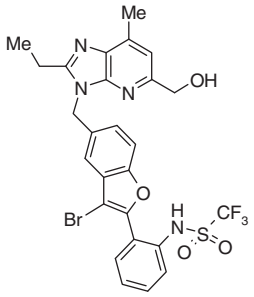
**(125)**



**(126)**

the Ang II induced pressor response for only 0.5 h after intravenous administration of 1.0 mg/kg to conscious normotensive rats. This compound also showed affinity for $AT_2$ receptor.[199]

A strategy to increase oral bioavailability of GR138950 (**25**) by replacement of the imidazole ring with the 7-methylimidazopyridine resulted in GR159763 (**127**). In renal hypertensive rats, it decreased blood pressure for more than 24 h. Compound **127** showed excellent bioavailability in rat with low plasma clearance.[200,201]



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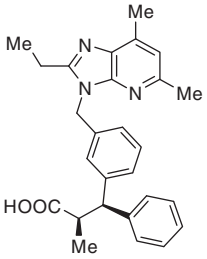

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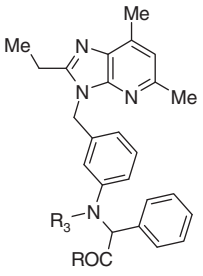
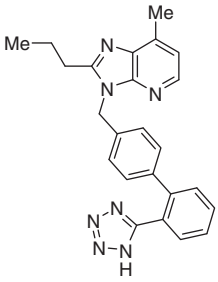
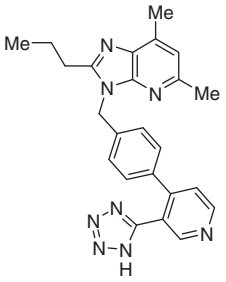


(132) R = OH, $NHSO_2Ph$

L-158,338 (**128**), 5-desmethyl analog of compound **118** showed increased affinity for $AT_2$ receptor.[185–187] Pyridine isostere of L-158,338 has been prepared. The 4-phenyl-3-tetrazolylpyridyl derivative **129** exhibited low nanomolar binding affinity to the $AT_1$ receptor. Compound **129** is orally active in rats at 1 mg/kg, but the iv versus po activities indicated a somewhat poor oral bioavailability in comparison to that of L-158,338 (**128**). Substitution in the 6th position of the pyridyl moiety in compound **129** led to increased $AT_2$ affinity of the resulting derivatives.[202]

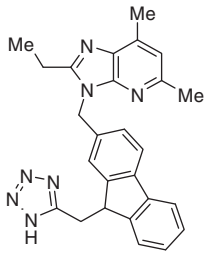


(128)



(129)

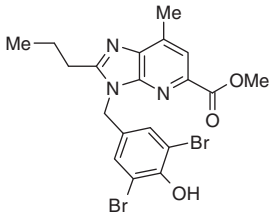
Ishikawa et al. (Kyowa Hakko) reported KW-3433 (**129**) ($IC_{50}$ 11 nM, bovine adrenal) as a competitive Ang II antagonist ($pA_2$ 9.2, rabbit aorta). In conscious rats, compound **130** blocked the Ang II pressor response with a duration of action of >7 h at dose (3 mg/kg, po). Compound **130** reduced blood pressure dose dependently with a >10 h duration of action in RHR and SHR (1–10 mg/kg, po).[203]



(130)

Almansa et al. reported UR-7198 (**131**) as a competitive antagonist with selectivity for the $AT_1$ receptor (0.069 μM, rat liver). The oral antihypertensive activity of the most potent compounds was evaluated in a furosemide-treated sodium depleted rat model where in compound **131** produced a dose dependent decrease in blood pressure, with maximum values of 39 mmHg at 10 mg/kg and 24 mmHg at 3 mg/kg. It showed a rapid onset and acceptable duration of action, in accordance with its good pharmacokinetic profile in rats (91% bioavailability and half-life of 9.1 h).[204]

A new class of highly potent non-peptide $AT_1$ receptor antagonists derived from N-substituted (phenylamino)phenylacetic acids and acylsulfonamides exhibited a high selectivity for the $AT_1$ receptor. These compounds (e.g., **132**) showed affinity for both $AT_1$ and $AT_2$.[205] Dhanoa et al. reported a series of imidazo [4,5-*b*]pyridine based acidic phenols (e.g., **133**) and the most potent compound ($IC_{50}$ 5 nM, rabbit aorta) exhibited good in vivo potency after both iv and po administration to conscious rats. In vivo potency of L-161,816 (potassium salt of **133**) was determined by assessing the inhibition of pressor response to Ang II in conscious normotensive rats. L-161,816 produced a dose related inhibition of the Ang II pressor response when administered intravenously.[206]



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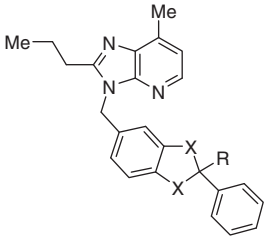
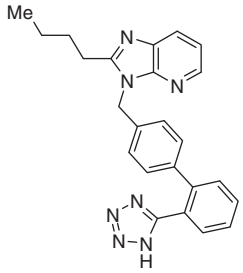


(134) R = COOH, tetrazole; X = O, S

In vitro $AT_1$ receptor binding affinity of substituted 1,3-benzodioxole-2-carboxylates and 1,3-benzodithiole-2-carboxylates, and their tetrazole analogs (**134**) is reported as quite high. The $IC_{50}$ of the benzodioxole carboxylate and the benzodithiole carboxylate in the $AT_1$ receptor binding assay was 56 and 34 nM.[207]

Series of nonpeptidic $AT_1$ selective antagonists containing a phenoxyphenylacetic acid element as a replacement of biphenyl tetrazole have been prepared. Replacement of both of the phenyl rings, terminal phenyl[208] and the spacer phenyl[209] have been explored. Final outcome of the series resulted into a compound L-746,072, which showed potent antagonistic activity (13 nM) for $AT_1$ receptors but unfortunately it showed strong affinity for $AT_2$ receptors also.[210]

FK739 (Fujisawa) (**135**), is a selective and competitive ($IC_{50}$ 0.6 nM, rat aorta; $pA_2$ 8.45, rabbit aorta) $AT_1$ antagonist. When dosed orally (32 and 100 mg/kg, po) it reduced blood pressure in a dose-dependent manner in SHR. Compound **135** effectively blocked the Ang II induced pressor response in normotensive rats and dogs. When dosed orally, compound **135** caused decrease in blood pressure in RHR and renal hypertensive dogs at a dose of 10 mg/kg.[211]



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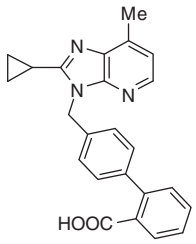
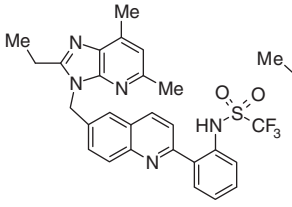


(136)

E4177 (Eisai) (**136**) is a selective ($IC_{50}$ 52 nM, rat adrenal cortex) and competitive ($pA_2$ 8.7, rabbit aorta) antagonist. When administered intraduodenally to anesthetized dogs, compound **136** showed a strong and long lasting inhibition of Ang II-induced pressor response at 0.3 mg/kg (i.d.).[34,212]

Quinoline ring was successfully substituted with spacer phenyl of biphenyl moiety and it resulted into GA0113 (**137**). In RHR, compound **137** (0.01–1 mg/kg) reduced BP with $ED_{25}$ value of 0.015 mg/kg. It showed excellent oral bioavailability (94%) and a long circulating half-life (12 h) in rats.[213]



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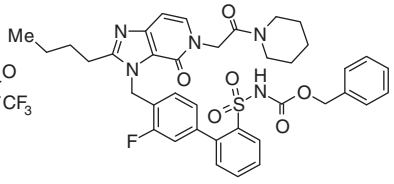
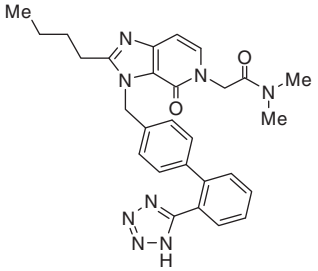


(138)

A series of $AT_1$ selective 4,5-dihydro-4-oxo-3-imidazo[4,5-*c*]pyridines was synthesized. The most potent compound **138** of the series showed affinity for both $AT_1$ ($IC_{50}$ 4.7 nM) and $AT_2$ ($IC_{50}$ 3.5 nM) with a ratio of 0.74. After oral administration of 3 mg/kg to cynomolgus monkeys, EMD 90423 (potassium salt of **138**) demonstrated good efficacy and a long duration of action as an antihypertensive agent.[214]

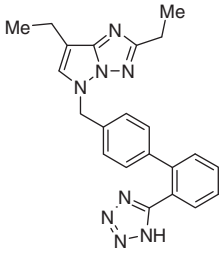
A series of novel nonpeptide $AT_1$ receptor antagonists containing a 2,3,5-trisubstituted 4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine was synthesized. The most potent compound of the series EMD 66,684 (**139**) showed selective ($IC_{50}$ 0.7 nM, rat cortical membrane) and potent ($IC_{50}$ 0.2 nM, rabbit aorta) antagonism. When dosed orally, compound **139** reduced blood pressure dose dependently in SHR. Compound **139** is found to be superior to losartan. It caused a dose-related and long lasting fall in blood pressure in furosamide treated rat model.[215]



(139)

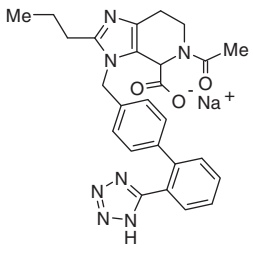
### 3.3.3. Miscellaneous five-membered fused antagonists

A number of antagonists have been reported in which different five-membered ring heterocycles replace the substituted imidazole ring of losartan. Yamanouchi's YM 358 (**140**) is a potent, competitive and $AT_1$ selective antagonist. It lowered blood pressure after a single oral administration (1–30 mg/kg) in conscious rats. The rank order of potency of compound **140** in conscious rats was 2-kidney 1-clip RHR > SHR > normotensive rats on the basis of lowering of blood pressure. Compound **140** showed potent antagonism ($pA_2$ 8.82, isolated rabbit aorta). In conscious normotensive rats, compound **140** at 3–30 mg/kg (po) inhibited the Ang II-induced presser response in a dose-dependent manner.[216,217]

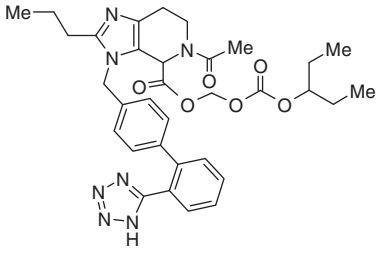


(140)

4,5,6,7-Tetrahydroimidazo[4,5-*c*]pyridine derivatives like 606A (**141**) has been reported as $AT_1$ receptor antagonist. Its prodrug form TA-606 (**142**) lowered the blood pressure with an $ED_{30}$ values of 0.14 and 0.21 mg/kg (iv and po, respectively).[218]



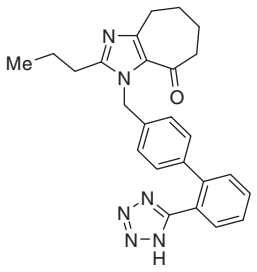
(141)



(142)

Yanagisawa et al. reported KT 3-671 (Kotobuki Seiyaku) (**143**) as a potent ($IC_{50}$ 0.8 nM, rat liver) and insurmountable antagonist ($pA_2$ 10.04, isolated rabbit aorta). In RHR, compound **143** reduced blood pressure dose-dependently at doses of 1 and 3 mg/kg (po).[219] In rabbit isolated smooth muscles, compound **143** was most effective in reducing the maximal contraction induced by Ang II.[220]

Kotobuki's KT 3-866 (**144**) is a potent ($IC_{50}$ 5.5 nM, rat liver) and noncompetitive antagonist ($pD_2$ 9.91, rabbit aorta). Compound **144** blocked the Ang II pressor response in rats at dose of 0.3 mg/kg (po) for 24 h of duration. Compound **144** is five times more potent than compound **144**.[221]



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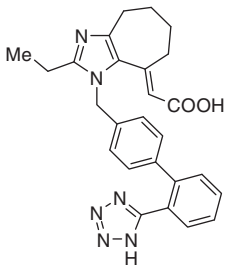
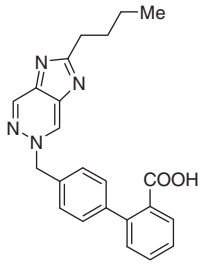


(144)

Gibson et al. reported imidazo[4,5-*d*]pyridazines (**145** and **146**), imidazo[4,5-*d*]pyridazinone (**147**) ($IC_{50}$ 0.022 μM, $ED_{50}$ 0.62 mg/kg, iv) and imidazo[4,5-*d*]pyridazo-4,7-dione (**148**) ($IC_{50}$ 0.017 μM, $ED_{50}$ 0.04 mg/kg, iv). $ED_{50}$ values for these compounds



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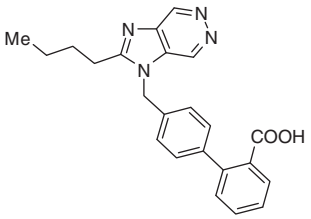

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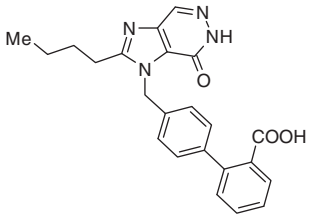

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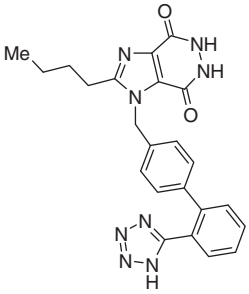
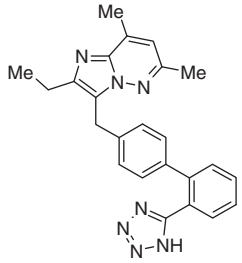


(148)

were obtained by measuring inhibition of the pressor response induced by Ang II in male Wistar rats after an intravenous dose.[222]

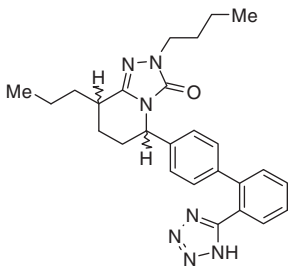
L-158,809 (**118**) undergoes metabolic hydroxylation at the benzylic methylene group followed by cleavage of the heterocyclic moiety, which might inactivate the compound. Therefore, to overcome this problem, a new class of imidazo[1,2-*b*]pyridazine antagonists were synthesized wherein the biphenylmethyl side chain was attached to the heterocyclic ring through carbon–carbon bond. The imidazo[1,2-*b*]pyridazine L-161,719 (**149**) displayed potent $AT_1$ selective antagonistic activity. In conscious normotensive rats, compound **149**



(149)

provided more than 90% inhibition of Ang II pressor response at a dose of 1.0 mg/kg (iv) for duration of action exceeding 6 h. The tetrazole moiety was substituted for carboxyl, benzoylsulfonamide and trifluoromethylsulfonamide, but none of them was found active.[223]

A series of potent, selective and conformationally restricted analogs of triazolone-based and imidazole-based biphenyl derivatives (e.g., **150**, **151**) were prepared. The most active compound in the series, has an $IC_{50}$ of 11 nM and $pA_2$ value of 8.8.[224]



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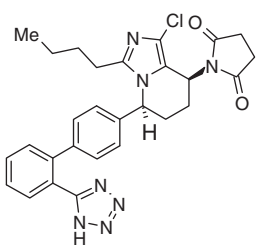
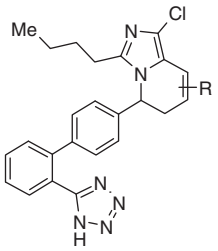


(151)

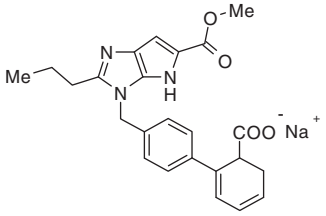
Synthesis of two conformationally restricted analogs of losartan and their evaluation have been reported. The potency of compounds **152** ($IC_{50}$ 10 and 50 nM, respectively) was found to be similar to that of losartan.[225]



(152) R= 7-COOH, 8-COOH

Akhavan et al. reported 2-alkyl-*N*-biphenyl fused imidazoles. The potency of the synthesized compounds was evaluated on guinea-pig ileum. The most potent compound **153** of the series ($pA_2$ 7.6) showed comparable activity with losartan ($pA_2$ 7.8) in isolated perfused rat kidney.[226]

Cappelli et al. reported CR3210 (**154**) as a selective and potent $AT_1$ receptor antagonist. Compound **154** possessed $IC_{50}$ value of 0.4 nM compared to losartan (6.7 nM) in rat hepatic membrane. It was slightly more active than losartan in inhibiting Ang II induced contraction in rabbit aortic ring.[227]



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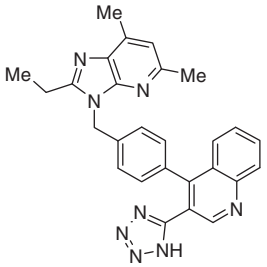
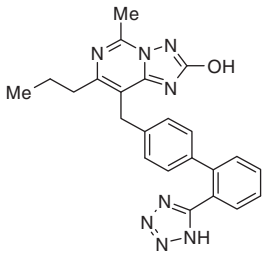


(154)

Nicolai et al. reported UP 269-6 (**155**) (UPSA), a triazolopyrimidine, as selective ($K_i$ 24 nM) and insurmountable $AT_1$ antagonist. Compound **155** produced sustained antihypertensive effect that lasted for at least 16 h in hypertensive renal artery-ligated rats (1 and 3 mg/kg, po). It showed rapid onset of action. Compound **155** caused dose-dependent and long-lasting inhibition of the Ang II-induced pressor response in conscious normotensive rats and dogs when dosed orally 0.1–30 mg/kg. In conscious furosemide pretreated dogs, compound **155** maximally decreased MABP at 1 and 10 mg/kg (po).[228,229]



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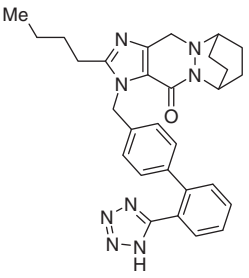


(156)

U-97018 (**156**) showed insurmountable ($pK_b$ 10.6) and selective ($IC_{50}$ 1.3 nM, rat mesenteric artery) antagonism. U-97018 inhibited the Ang II induced pressor response with an $ED_{50}$ of 0.28 mg/kg (iv).[230]

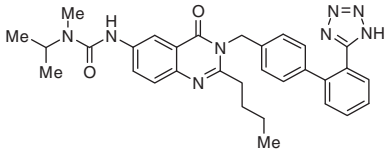
### 3.4. Fused six-membered Antagonists

Incorporation of a variety of functionality at $C_4$ and $C_5$ positions of imidazole ring in losartan suggested that six-membered rings can also be fused to yield a variety of potent $AT_1$ antagonist.

#### 3.4.1. Quinazolinone containing antagonists

Quinazoline ring possessed the same arrangement of nitrogens (1,3) as found in imidazole ring and can accommodate the requisite side chain at position $C_2$. Merck's L-159,093 (**157**) is an orally active, highly potent $AT_1$ (0.1 nM, rabbit aorta) antagonist. Compound **157** inhibited Ang II pressor response at 3 mg/kg (po) in conscious normotensive rhesus monkeys for more than 3 h.[231] Despite good in vitro potency of compound **157** and its other analog, many of these antagonists displayed short duration of action in conscious normotensive rats and rhesus monkeys after intravenous administration. This may be attributed to glucuronidation of tetrazole function which caused their rapid clearance. Therefore, an alternative acidic group acylsulfonamide was incorporated for tetrazole function. The most potent compound of the series is L-161,021 (**157**). 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). Compound **158** blocked Ang II pressor response in normotensive conscious dogs for more than 5 h when dosed orally (3.0 mg/kg). However, L-161,021 (**158**) showed increased $AT_2$ receptor binding affinity.[232]

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 (**159**), a selective ($IC_{50}$ 6 nM) and competitive antagonist ($pA_2$ 8.01, rabbit aortic rings). At 5 mg/kg (po) it produced a rapid decline in MABP which was sustained for over 24 h.[233,234] In order to further improve the potency, isoxazoline and isoxazolidine analogs of CL329,167 (**159**) were synthesized. CL l90,133 (**160**) was found to be specially potent, orally active, non-competitive $AT_1$ receptor antagonist with an apparent $pA_2$ of 10.9. Compound **160** completely blocked the vasopressor response to Ang II for over 5 h (5 mg/kg po). In the renin-dependent aorta-coarcted rat model of hypertension, a l mg/kg po dose produced a rapid (55 mm/Hg) decrease in MABP which was sustained for over 5 h.[234] CL 332,877, sodium salt of CL 329,167 is a potent, long-acting, non-competitive antagonist ($pA_2$ 10.9).[235] Although, CL 332,877 was potent, orally active and long-lasting, the isoxazolidine ring was found to undergo metabolism. 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 analogs (**161**) of isoxazolidine, like substituted isoxazolidine, dihydrofuran, tetrahydropyran and fused pyrazole analogs were synthesized and evaluated for $AT_1$ receptor antagonistic activity. But, none of them increased the oral potency level.[236]



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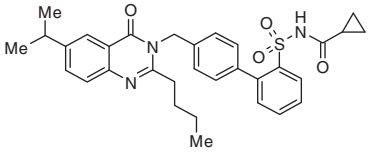

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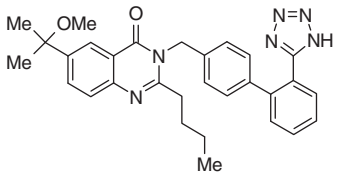

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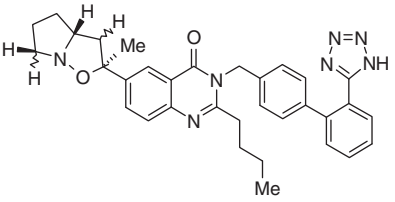

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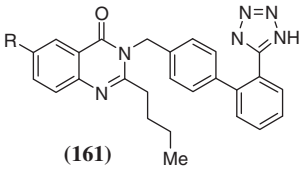

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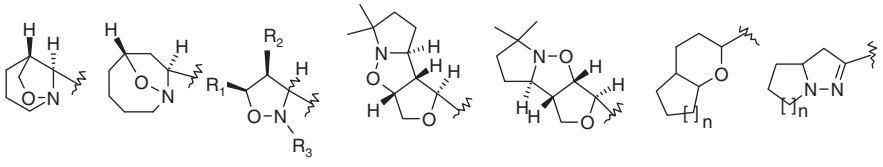
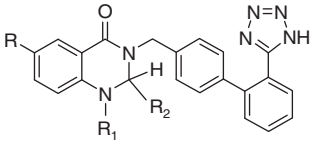


A series 2,3-dihydro-4(1*H*)-quinazolinone analogs (**162**) related to CL 329,167 (**159**) were synthesized and evaluated. But these compounds were devoid of any significant oral activity.[237] Ismail et al. have reported a series of novel quinazolin-4-ones. The most active compound **163** of the series decreased the BP effectively in both normotensive and hypertensive male SD rats.[238]



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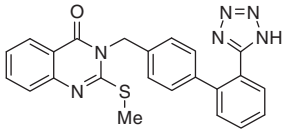

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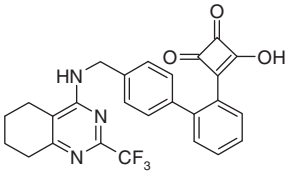


(164)

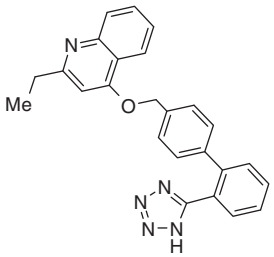
Novel analog (**164**) containing bioisostere of tetrazole, 3-hydroxy-3-cyclobutene-1,2-dione was synthesized and evaluated. It showed less potency than parent tetrazole analog.[239] The presence of lipophilic substituents at 6th position of quinazoline decides the affinity of a compound for both $AT_1$ and $AT_2$ as seen in L-159,689[240] (**165**) and L-161,638[241] (**167**) ($AT_1/AT_2$, 1:3000). The incorporation of a sulfonylcarbamate group in place of tetrazole along with 6th substitution provides further enhancement in the $AT_2$ binding affinity as observed in L-162,393[242] (**166**) and L-163,579,[243] (**168**) ($AT_1$:$AT_2$ nearly 1:2).

Compound (**169**) having quinazoline ring connected to the biphenyl ring through sulfur was synthesized and evaluated for $AT_1$ receptor antagonistic activity. It showed moderate antagonistic potency ($IC_{50}$ 0.35 μM rat liver membrane).[142]

### 3.4.2. Quinoline containing antagonists

Oldham et al. reported ICI-8731 (**170**) an orally active, potent ($IC_{50}$ 30 nM, guinea pig adrenal) and competitive ($pA_2$ 8.3, rabbit aorta) $AT_1$ antagonist.[244] Compound **170** showed a rapid and sustained lowering of BP at a dose of 5 mg/kg in RHR. At doses of 1-10 mg/kg, compound **170** exhibited a dose related inhibition of the pressor response in normotensive rats and showed sufficiently good duration of action at the higher doses.[245]

ZENECA's ICI-6888 (**171**) 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 (**170**). But both of them possessed similar oral efficacy in RHR.[246,247] Synthetic analogs 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 (**171**) in an acute dosed rat model (iv).[248]



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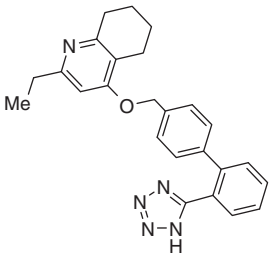

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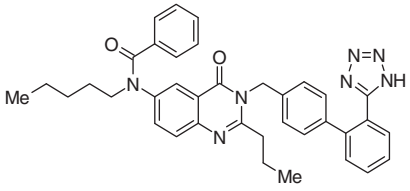

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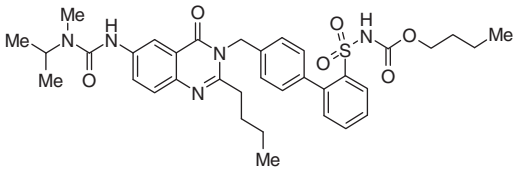

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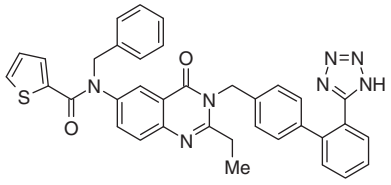

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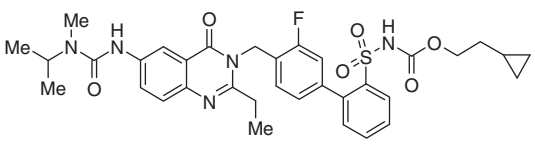
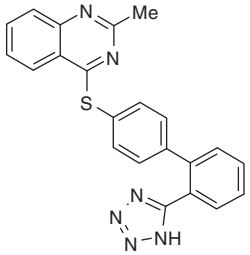
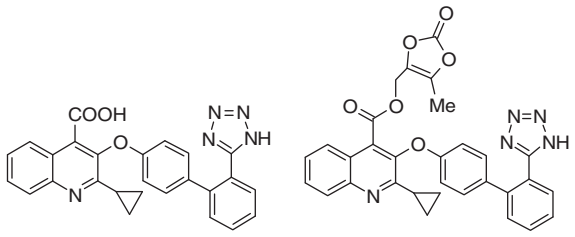


(168)



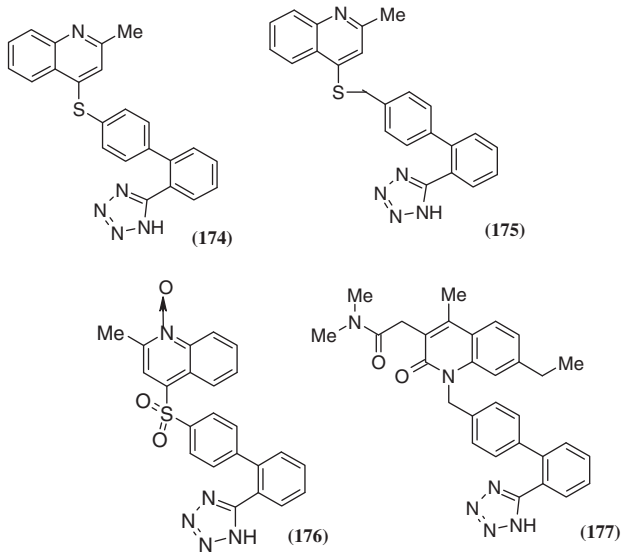
(169)

Lloyd et al. reported BMS-183920 (**172**) as a potent ($K_i$ 2.9 nM, rat adrenal cortex) antagonist. It is an insurmountable antagonist.[249] Compound **172** is more potent than losartan in blocking the pressor response of Ang II in the normotensive rat. However, it possessed moderate oral activity and to overcome this deficiency, ester of a dioxolenone BMS-184698 (**173**) was synthesized. In SHR, at a dose of 30 μM/kg (once for 7 days) compound **173** reduced blood pressure to a greater extent than losartan at the same dose. Compound **173** showed an oral bioavailability of 27% in rats compared to 11% for BMS-183920 (**172**), the parent compound.[250]



(172) (173)

Quinoline derivative (**174**) in which the heterocyclic ring is connected to the biphenyl moiety through sulfur bridge was synthesized. A fourfold increase in receptor binding affinity ($IC_{50}$ 0.096 μM, rat liver membrane) was obtained compared to a methylenethio ($IC_{50}$ 0.37 μM, guinea pig adrenal membrane) linking unit (e.g., **175**) suggesting

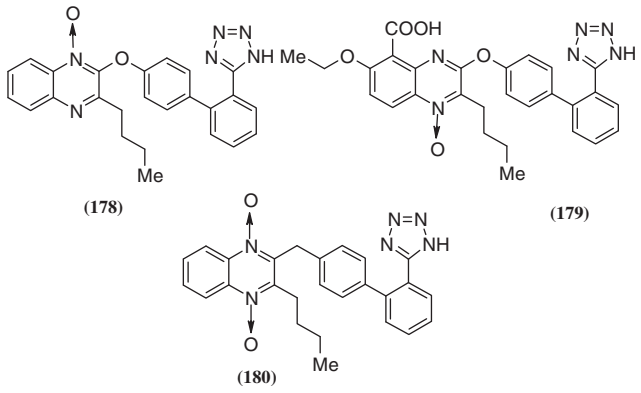


(174) (175) (176) (177)

that a shorter distance from the nitrogen of the quinoline to the tetrazole pharmacophore was beneficial for in vitro binding affinity. But this compound **174** was found to be less potent when compared to oxymethylene containing analog ICI-8731 (**170**) ($IC_{50}$ 30 nM, guinea pig adrenal). Fused pyridine oxide derivative **176** showed less affinity for rat liver membrane.[142] Beier et al. reported quinolone derivative (**177**) as a potent Ang II receptor antagonist.[251]

### 3.4.3. Quinoxaline containing antagonists

Bristol Myers Squibb Pharma reported a new class of $N_1$ (**178**) and $N_4$ (**179**) quinoxaline oxide derivatives as $AT_1$ antagonists. Compound **178**, 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 **179** showed higher potency in in vitro and in vivo preparations. But this compound **179** also possessed low oral activity. To improve the oral activity, its ester derivative was synthesized, which showed improved oral activity and longer duration of action, as seen in SHR.[252] The same group

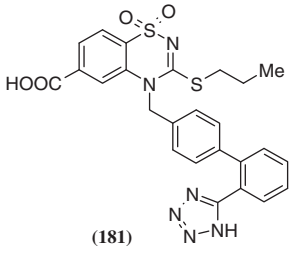


(178) (179) (180)

reported a bis N-oxide derivative (**180**), 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).[253]

### 3.4.4. Benzothiadiazine dioxide containing antagonists

Bristol Myers Squibb Pharma reported new class of benzothiadiazine dioxides as $AT_1$ antagonist. The most potent compound **181** of the series showed high activity in functional

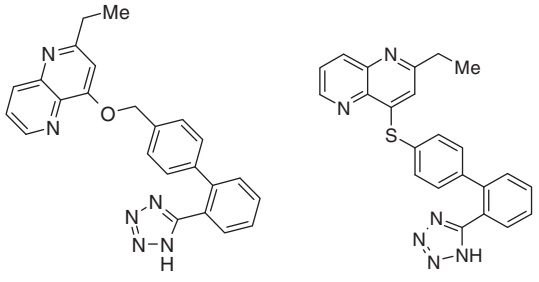


(181)

($K_b$ 0.08 nM, rabbit aorta) and binding assays (8.5 nM, rat adrenal cortical membrane).[254]

### 3.4.5. Naphthyridine containing antagonists

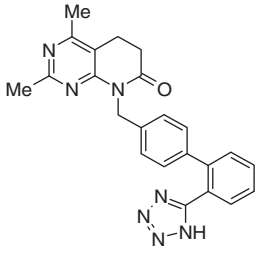
Naphthyridine derivatives connected to biphenyl moiety with oxymethylene and sulfide linkers were synthesized and evaluated for $AT_1$ receptor antagonistic activity. Both of the compounds (**182**, **183**) possessed activity in the nanomolar range. Compound **182** showed good affinity for $AT_1$ receptors ($IC_{50}$ value of 0.024 μM, guinea pig adrenal membrane). When dosed intravenously, compound **182** inhibited Ang II induced pressor response with an $ED_{50}$ of 0.86 mg/kg. Compound **183** also showed increased bioactivity ($IC_{50}$ 0.020 μM, rat liver membrane).[142,246]



(182) (183)

### 3.4.6. Miscellaneous fused six-membered antagonists

Ellingboe et al. (Wyeth Ayerst) reported ANA-756 (tasosartan) (**184**)[255] a selective ($IC_{50}$ 5.2 nM, rat liver) and competitive ($pA_2$ 8.4, rabbit aorta) $AT_1$ antagonist.[256] Compound



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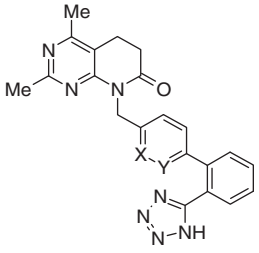
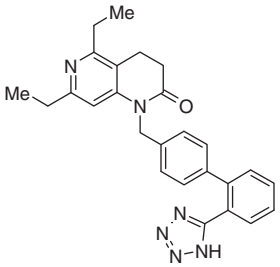


(185) X; Y =C/ N, N/C

**184** lowered blood pressure for more than 24 h in RHR at a dose of 1 mg/kg (po). In SHR, compound **184** at a dose of 3 mg/kg/day for 5 days, produced a sustained drop in blood pressure similar to that seen with losartan at a dose 10 times higher. Compound **184** caused a dose related decrease in MABP for 24 h ($ED_{60}$ 0.58 mg/kg, po) in conscious Goldblatt hypertensive rats.[256] The introduction of nitrogen into the biphenyl ring portion (e.g., **185**) decreased the binding activity.

Zeneca's ZD-7155 (**186**)[257] is a selective antagonist with $IC_{50}$ of 3.8 nM in guinea pig adrenal. In conscious rats, ZD-7155 inhibited Ang II induced pressor response with an $ED_{50}$ of 0.19 mg/kg (iv). When dosed orally (3 mg/kg), compound **186** lowered blood pressure up to 24 h in RHR.[258]



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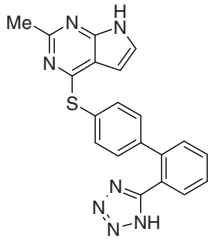

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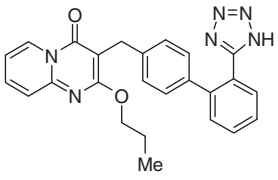


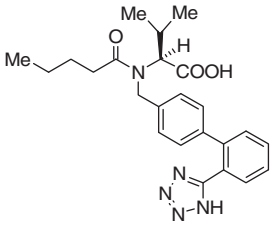
(188)

Pyrrolopyrimidine derivatives (e.g., **187**) connected to biphenyl moiety through sulfide linker were synthesized and evaluated for biological activity. These compounds showed less affinity for rat liver membrane.[142]

4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones have been synthesized and investigated as potential Ang II receptor antagonists. The most potent compound **188** of the series was found to be equipotent to losartan in in vitro assay (0.25 μM). However, these compounds are less active than losartan when evaluated in vivo.[259]

### 3.5. Antagonists having acyclic replacements of imidazole

Buhlmayer et al. reported valsartan (CGP 48933) (**189**) 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 **189** decreased systolic blood pressure (SBP) dose dependently. The antihypertensive effect lasted for 24 h.[260–262]

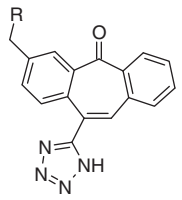


(189)

Extensive molecular modeling studies, including conformational analysis and the comparison of molecular electrostatic potential distributions were used to evaluate structural parameters of new antagonists containing acyclic replacements of the N=C–N imidazole region. The newly synthesized compounds were examined in vitro as $AT_1$ receptor antagonists by evaluating their ability to displace [$^3$H] Ang II from rat adrenal cortical membranes (RACM). Compared to the reference losartan or valsartan, all the acyclic derivatives showed a significantly reduced binding affinities.[263]

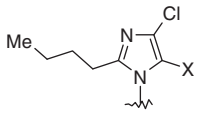
### 3.6. Miscellaneous

Novel $AT_1$ antagonists with dibenzo[*a*,*d*]cycloheptene or dibenzo[*b*,*f*]oxepin nuclei were designed and synthesized. The receptor binding affinity ($K_i$) for several members of **190** was found up to $10^{-10}$ M.[264]

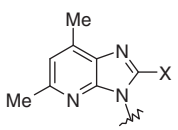


(190)

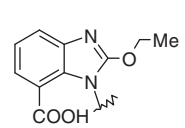
R =

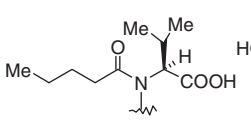


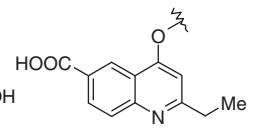
X = CHO, COOH

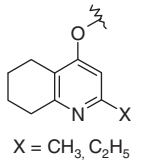


X = $C_2H_5$, $C_3H_7$, c-$C_3H_5$

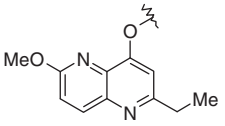


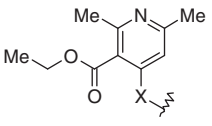




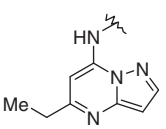


X = $CH_3$, $C_2H_5$

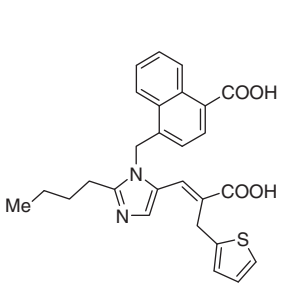




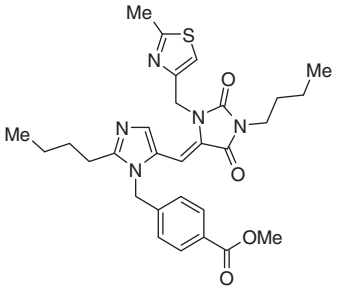
X = O, NH



Efforts were also made by researchers to develop novel $AT_1$ antagonists by taking eprosartan (**2**) as a prototype and replacing its acrylic acid moiety with a hydantoin nucleus. SB 203220 (**191**), the naphthyl analog of eprosartan (**2**) is a potent, long-acting and partially




(**191**)




(**192**)

insurmountable antagonist. It inhibited the pressor effect of Ang II at a dose 10 mg/kg (po) for up to 20 h.[265] Edmunds et al. reported a series of 5-substituted hydantoins as $AT_1$ antagonists. The most potent compound (**192**) of the series (3.8 nM, rabbit aorta) reduced the MABP of RHR by 40% at 30 mg/kg po and by 25% at 10 mg/kg po In addition, this compound **192** was efficacious in the salt-depleted normotensive monkey model decreasing blood pressure by 27% at 10 mg/kg (po).[266] Selenophene analog of the thiophene containing antihypertensives eprosartan (**2**) has been reported to be equipotent to the parent compound.[151]

## 4. Molecular modeling studies

Direct drug designing is considered to be a promising tool in the designing of novel drug molecules. But due to non-availability of the crystal structure of $AT_1$ receptor, ligand based approach is considered to be an acceptable tool for the designing and development of many $AT_1$ receptor antagonists.

### 4.1. Ligand based approach

In past few years, several 3D-QSAR and pharmacophore studies have been performed for the designing of $AT_1$ receptor antagonists which have been reported in the literature.[267–273] In 2004, a 3D-QSAR study of $AT_1$ receptor antagonists was reported on the basis of receptor surface analysis. A hypothetical receptor model was constructed for a set of 38 $AT_1$ antagonists using activity data of each molecule as a weight in the building of the receptor surface. The best model was derived by optimizing various parameters such as atomic partial charges, surface fit and the manner of representation of electrostatics on the surface. Descriptors like van der Waals energy, electrostatic energy and total nonbonded energy were used individually or in combination to derive quantitative structure–activity relationship equations.[269] In 2002, Datar et al. applied two 3D-QSAR methods, CoMFA and CoMSIA to develop models for $AT_1$ receptor antagonists. In this study diversity of structures belonging to the imidazole, pyrazole, imidazopyridine, triazole and imidazotriazole containing compounds were considered.[272]

In 1994 Prendergast et al. developed a 3D pharmacophore model for the $AT_1$ receptor. A systematic search was used to derive a hypothesis for the receptor-bound conformation of Ang II antagonist for $AT_1$ receptor. The pharamacophore model so developed during this study contained the pharmacophoric features as shown in Figure 9. These are, an acidic group (A), an aromatic N (functioning as an H-bond acceptor) (B) and an alkyl side chain (C). The alkyl group must minimally be an ethyl group for a compound to exhibit $AT_1$ antagonism, and the biphenyl spacer (D) provides an aromatic recognition element for the receptor for showing the $AT_1$ antagonistic activity.[273]

In 1996 Belvisi et al. developed 3D-QSAR CoMFA model to study non-peptide $AT_1$ receptor antagonists. CoMFA descriptors and approaches were applied to study 3D-QSARs in a series of structurally different and conformationally flexible non-peptide Ang II antagonists using binding affinities to the Ang II receptor obtained from the literature.[274] Hirata et al. have reported a QSAR studies of Benzoylthiazoline derivatives as $AT_1$ receptor antagonists.[275] This QSAR study led to the identification of certain given structural

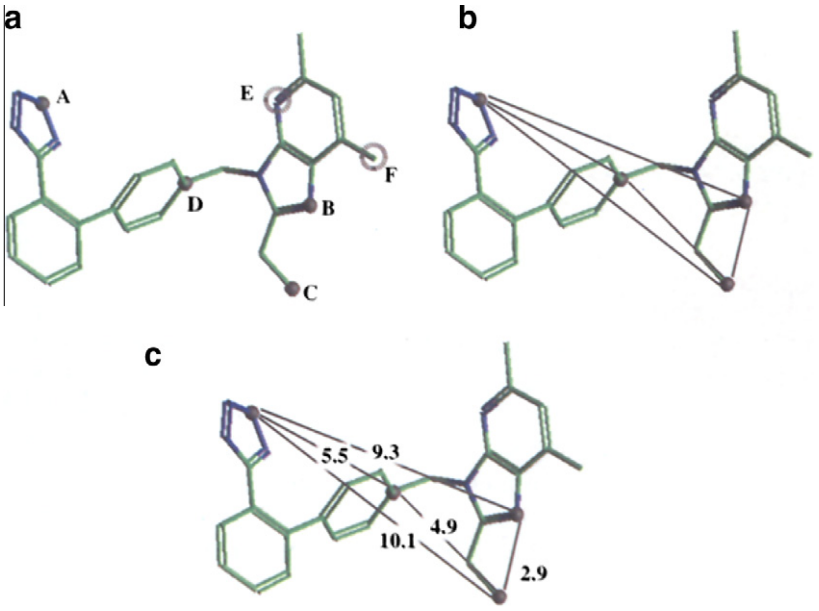



**Figure 9.** (a) Illustration of the Ang II pharmacophore model used in systematic search. The pharmacophore points are represented as gray spheres on the atomic centers of L-158809 (117). (b) Distances used to define the A-II pharmacophore and monitored during search, illustrated on L-158809. (c) Final distances located by systematic search (in A), illustrated on L-158809.

requirements for good binding to the $AT_1$ receptor. The contributions of substituent $R_1$ on benzene ring in the benzoyl moiety and 5-position substituent $R_2$ on the 1,3,4-thiadiazololine ring (Fig. 10) were quantitatively investigated in this study. Application of these QSAR studies led to active compound KRH-594 (**66**).

In 2006, Su et al. used multiple linear regression (MLR) and artificial neutral networks (ANN) for QSAR of a set of 113 $AT_1$ receptor antagonists. The ANN model showed better performance with a 6-6-1 architecture than MLR. The results obtained from this study indicated that three descriptors, that is, hydration energy (EH), *n*-octanol/water partition (log *p*) and LUMO play an important role for $AT_1$ receptor antagonist activity with biphenyltetrazole structures.[276]

### 4.2. Structure based approach

Knowledge of 3D structure of the $AT_1$ receptor could have been of great help in the task of understanding antagonist's interaction, and in the rational design of specific ligands; however, GPCRs are membrane-bound proteins, high resolution structural characterization is still an extremely difficult task. For this reason, great importance has been attached to the molecular modeling studies and in particular, to homology modeling techniques. Several studies have been undertaken to construct a homology model of the human $AT_1$ receptor by molecular modeling procedures. An excellent review appeared in 2007 which covers all the computational results concerning the construction of the 3D structure of $AT_1$ receptor.[277]

Tuccinardi et al.[278] have developed a three-dimensional model of the $AT_1$ receptor by using a homology modeling procedure, using the X-ray structure of bovine rhodopsin determined at 2.2 Å (IU19) as the template. Docking of losartan and its active metabolite EXP3174 (**3**) suggested a different binding orientation for these antagonists. Furthermore, on the basis of the information derived from an $AT_1$ receptor homology model, the docking of several non-peptide antagonists was used as an alignment tool for the development of 3D-QSAR model. Figure 11 shows the binding site of losartan in the $AT_1$ receptor.

Some references[279–282] based on mutagenesis studies suggested a fundamental role for the residues Asp 74, Asn 111, Ser 115, Asn 294 and Asn 295 in the process of activation of the receptor. As per the study of Tuccinardi et al. these residues were not directly involved in the interaction with losartan, but as shown in Figure 12, they interacted with each other, creating a H bond network system able to connect TM2, TM3 and TM7, probably controlling the inactive-active state of the receptor. The results obtained from the docking of the active metabolite (EXP3174) (**3**) of losartan showed that the binding disposition of the ligand was similar to that of losartan with the biphenyl ring located in the lipophilic pocket delimited by Val 108, Val 179, Thr 253, His 256, Ile 288,

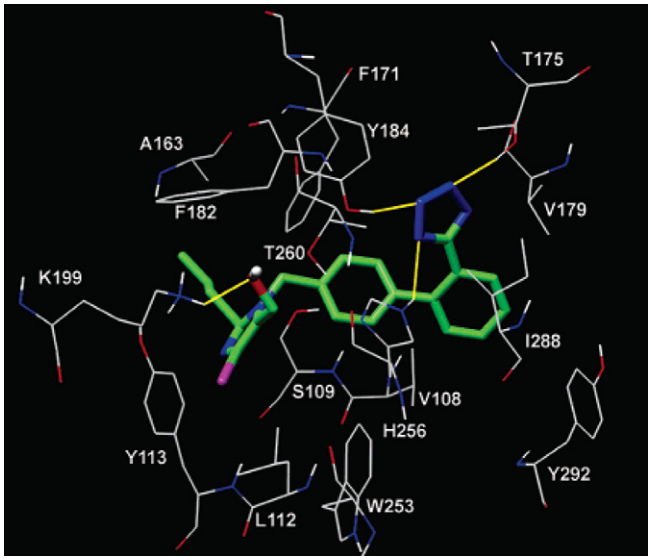



**Figure 11.** Losartan docked in the $AT_1$ binding site. Interatomic distances between H-bonded atoms are indicated in yellow.

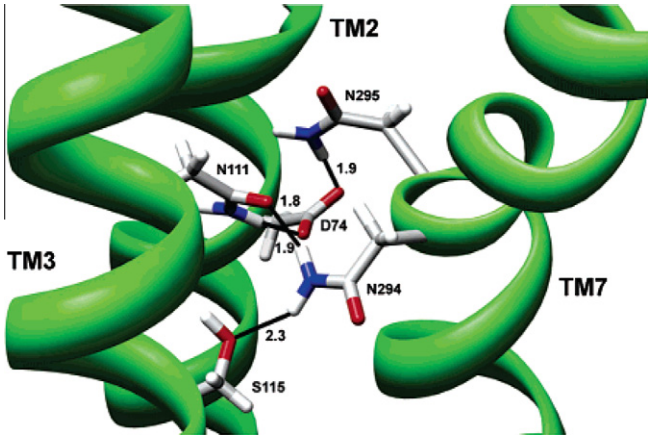
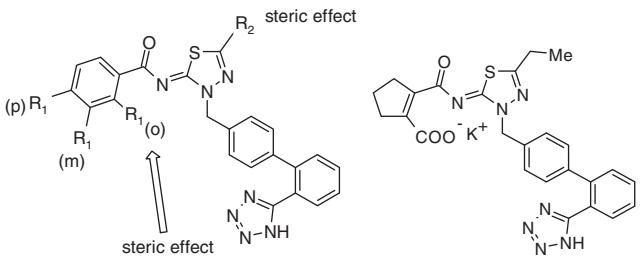



**Figure 12.** H bond network system among TM2, TM3, and TM7 of the $AT_1$ receptor model.[213]

Tyr 113, Ala 163, Phe 171 and Phe 182. However, as shown in Figure 13, with respect to losartan, EXP3174 was shifted about 2.7 Å towards TM5. This disposition determined the loss of H-bond of tetrazole with Thr 175, which proved to be too distant (5.3 Å from the tetrazole ring), while the interaction with Tyr 184 and His 256 was maintained. As regards the imidazole ring, it exhibited




**(66)**

**Figure 10.** Structural requirements of benzoyliminothiadiazoline derivatives for good binding to the $AT_1$ receptor.

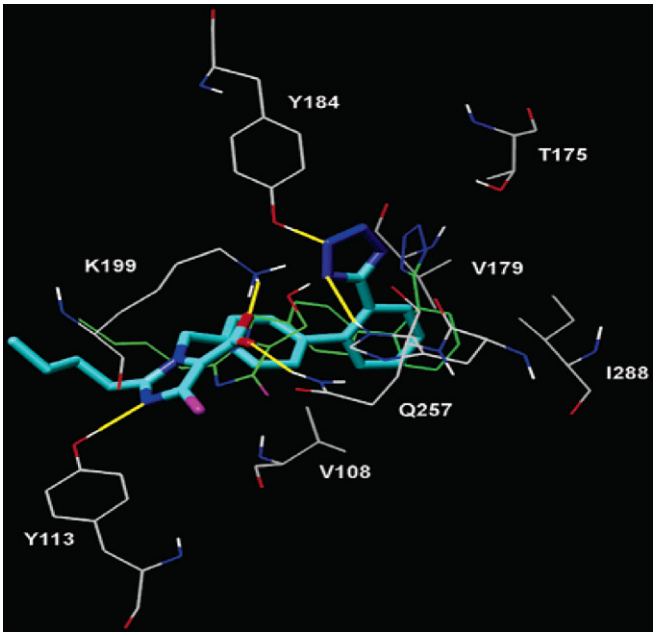



**Figure 13.** Superimposition between EXP3174 (sky blue) and losartan (green) docked in the $AT_1$ binding site.

a new H-bond with Tyr 113, while the carboxylate group interacted with Lys 199 and also formed a second H bond with Gln 257. The carboxylate group formed an ionic interaction with Lys 199, which should be stronger than the H bond interaction of the hydroxymethyl group of losartan. Overall, it was concluded with this docking study that the EXP3174-$AT_1$ binding interaction was stronger than losartan-$AT_1$ interaction. These observations were in agreement with the hypothesis that unlike surmountable antagonists, insurmountable antagonists could bind tightly and dissociate slowly, causing the functional loss of the occluded receptors.

Klabunde et al.[283] have also reported a 3D-homology model for the $AT_1$ receptor in complex with losartan using the MOBILE (MOdeling Binding sites Including Ligand information Explicitly) approach. $\beta_2$-Adrenergic receptor was used as a template structure for homology modeling (Fig. 14). The topological interaction model for the molecular recognition of losartan (**1**) in the $AT_1$ receptor is shown in Figure 14a along with the proposed binding site of losartan in the $AT_1$ receptor.

## 5. Studies related to conformational analysis of Ang II, $AT_1$ peptide and nonpeptide antagonists

The relationship between the spatial arrangement of atoms and the conformational properties of bioactive molecules with their pharmacological profile has been well documented in medicinal chemistry. For the regulation of hypertension, research efforts are focused either in blocking Ang II release or its action on $AT_1$ receptors. Hence efforts were made to understand the molecular basis of action of Ang II, its derivatives and the $AT_1$ antagonists belonging to SARTAN class of molecules.[284]

There are different schools of thought regarding the active conformation of Ang II with opinions ranging from a fully extended to

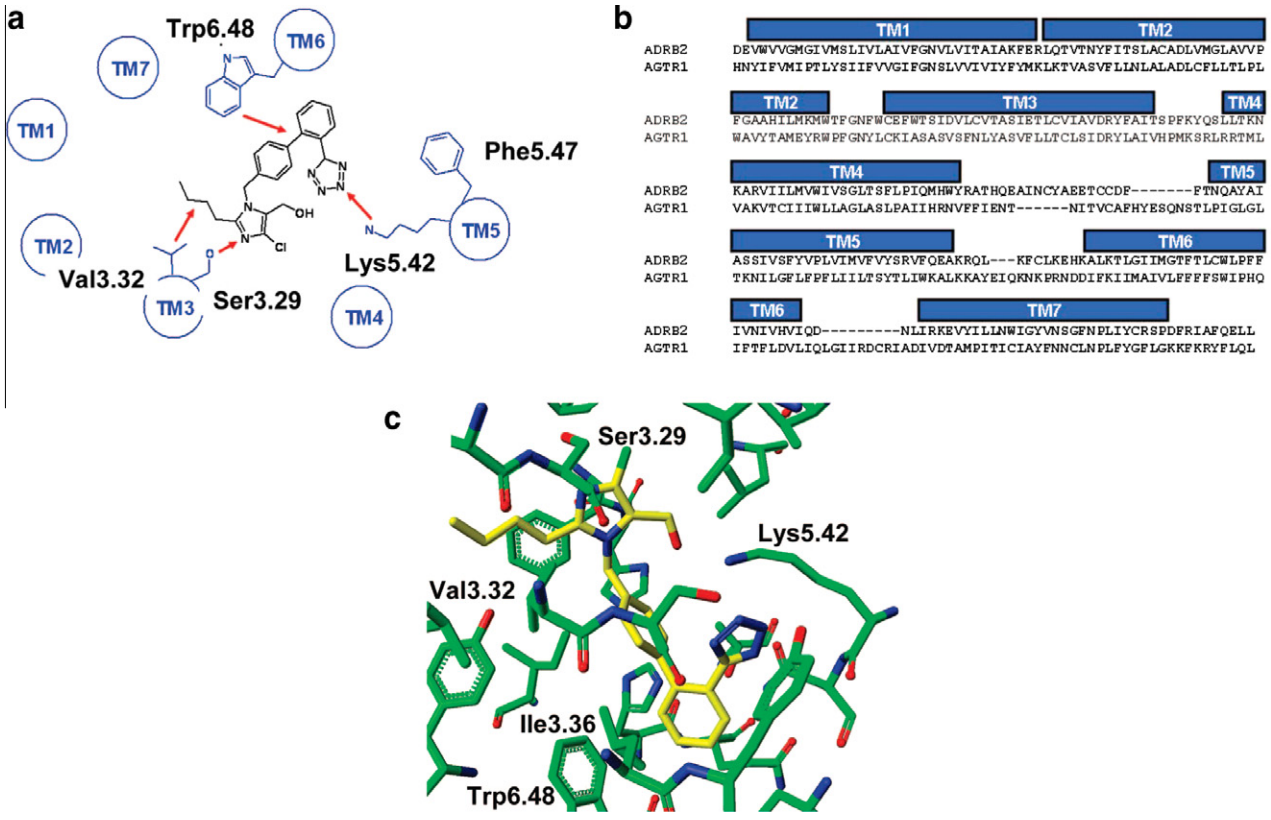



**Figure 14.** Generation of 3D-homology model for the $AT_1$ receptor in complex with losartan using the MOBILE approach: (a) topological interaction model for the molecular recognition of losartan in the $AT_1$ receptor; (b) sequence alignment between the $AT_1$ and the $\beta_2$-adrenergic receptor used as template structure for homology model generation; (c) proposed 3D-model of the binding site of losartan in the $AT_1$ receptor.

folded structures hence, the active conformation of Ang II has remained controversial.[281,285–291]

Conformational analysis of Ang II was carried out by Mavromoustakos et al.[284] The proposed bioactive conformation of Ang II is shown in Figure 15. The proposed model is characterized by a backbone bend at the Tyr-Ile-His, clustering of aromatic rings $Tyr^4$-$His^6$-$Phe^8$, and a charge relay system involving the triad phenolic hydroxyl group of $Tyr^4$ imidazole of $His^6$ and carboxylate of $Phe^8$. It was reported in this study that clustering was the result of the backbone bend which brought the aromatic rings into spatial proximity. $Arg^2$ was also protruding towards the cluster by interacting with $Tyr^4$. The key amino acids $Tyr^4$, $His^6$ and $Phe^8$ form a relay system through electrostatic interactions. This form of a relay system is energetically favoured and could be a key requirement of Ang II to interact productively with the active site of the receptor. As claimed this model was also supported by Carpenter et al.[287] who performed conformational analyses in micelle and phospholipid bilayers. Dimethyl sulfoxide (DMSO) might simulate the amphoteric environment of membrane bilayer. Other models described in different environments using physio-chemical methods and theoretical calculations have also been reported in the literature.[273,286,292–309]

Preto et al. performed MD simulations with the objective of finding stable conformation of Ang II in aqueous and DMSO environments.[285] Experimentally proposed models for the structure of Ang II in both the environments were not consensual. In this study, N-terminal of Ang II in the aqueous environment has been found to be associated with a considerably larger flexibility than the corresponding C-terminus, but this was not the case in DMSO environment. This study was consistent with the assumption that the biological activity of Ang II was associated with its C-terminal residue remaining embedded in the hydrophobic environment of $AT_1$ receptor. Other features detected in DMSO environment were an H($His^6$ imidazole)-O($Phe^8$ carboxylate) hydrogen bond and a salt-bridge structure involving $Asp^1$ and $Arg^2$ side chains.[285]

To comprehend the stereoelectronic requirements that may lead to better understanding of the basis of hypertension, the stereochemical features of Ang II, its peptide antagonists sarmesin and sarilesin, synthetic peptide analogs and $AT_1$ non-peptide antagonists have been explored.[286,310,311] $AT_1$ antagonists were designed to mimic the C-terminal part of Ang II. It was proposed that the butyl chain of losartan might mimic the isopropyl chain of Ile of Ang II, the tetrazole ring the C-terminal carboxylate group and the imidazole ring the corresponding imidazole ring of $His^6$.[47,310,311]

The conformations of three Ang II peptide antagonists ([Sar1]-AII(1-7)-NH2, [Sar1,Val5,Ala8]-AII and [Glu1,Gly2,Val5, Val8]-AII) were assessed in a lipid medium by Wilkes et al. A common backbone turn was identified through modeling and spectroscopic studies. As per this study, the $His^6$ residue acted as a pivoting point beyond which each peptide adopted two distinct conformations. One principal conformer resembled the previously determined one for Ang II while, the other was designated as an Ang II antagonist-like conformer. A computational overlay between the nonpeptide antagonist, losartan, and both of the Ang II-like and Ang II antagonist-like conformations of [Sar1,Val5,Ala8]-AII revealed common pharmacophoric points with RMS deviations between 1 and 1.5 Å. Both the Ang II conformer and the Ang II antagonist-like conformer of [Sar1,Val5,Ala8]-AII were docked into a model of the $AT_1$ receptor. Receptor residues Phe289 and Asp281 provided good contact points for both the peptides. Some differences were also noted. The terminal carboxyl of AII contacted Lys199 of the receptor while carboxyl of [Sar1,Val5,Ala8]-AII bridged Arg23 at the top of helix 1. The Asp1 side chain of Ang II interacted with His183 of the receptor. As per the authors' claim, this study could serve as a novel starting point for determination of active conformation of $AT_1$ receptor antagonists from C-terminal.[312]

Based on superimposition studies of losartan with the model proposed for sarmesin, attempts have been made to design and synthesize novel compounds MM1 (**193**), MMK2 (**194**) and MMK3 (**195**). These are the examples of synthetic nonpeptidic antagonists devoid the classical templates of SARTANs. Docking studies showed that MM1 acts on the same site of receptor as losartan.[313,314]

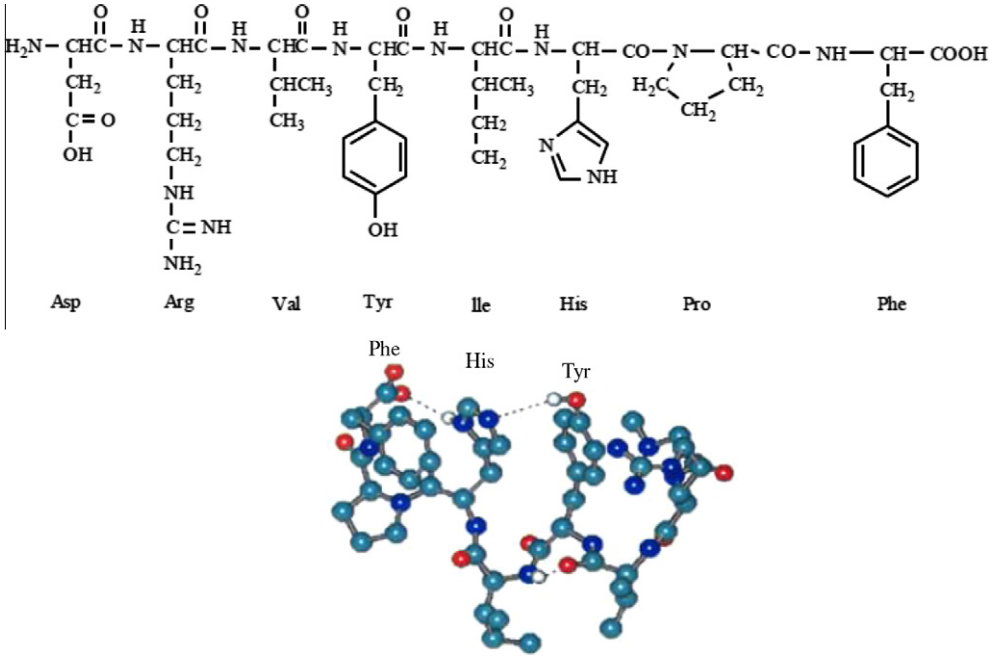
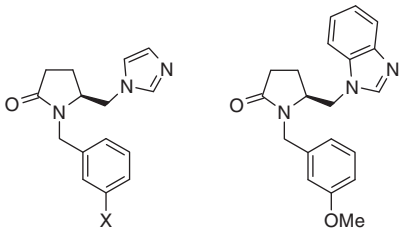



**Figure 15.** Chemical structure of Ang II and its proposed bioactive conformation.[284] The major conformational feature of the molecule is the cluster and relay system between the side groups of $Tyr^4$-$His^6$-$Phe^8$.




**(193)** X = H (MM1) **(195)** MMK3
**(194)** X = OME (MMK2)

Conformations of $AT_1$ antagonist valsartan (**189**) in solution and at the binding site of the receptor have been analyzed by Potamitis et al. In this study low energy conformations of valsartan (**189**) in solution were explored by NMR spectroscopy and molecular modeling studies. The NMR results showed the existence of two distinct and almost isoenergetic conformations of valsaratan (cis:trans ratio around the amide bond ~40:60). Docking and molecular dynamics studies were used by this group to study binding of valsartan at the $AT_1$ receptor site, explicitly solvated and embedded in lipid bilayers and solvent molecules. These studies confirmed that majority of the docked poses adopted a trans (major) conformation. MD simulations results showed that the two acidic groups of valsartan are bridged through Lys199 enabling it for multiple hydrogen bond interactions. In a lipid bilayer environment these interactions are enhanced, emphasizing the important role played by the lipid bilayer for a better binding of valsartan and its stabilization at the active site.[315] Although the studies reported by Potamitis et al. have been performed in artificial biological conditions which might not reflect the true biological environment, but outcome of these studies might provide valuable data for the molecular basis of hypertension and could contribute to the rational designing of novel analogs.[315]

Yoo et al. synthesized conformationally restricted analogs of losartan as Ang II antagonists. This study revealed the importance of a particular three dimensional arrangement of pharmacophoric elements for good binding activity.[316] The same research group worked on synthesis and conformational analysis of benzofuran derivatives as Ang II antagonist. The relation between the conformational and antagonistic activity was studied to define structural and conformational requirements of compounds. The molecular mechanics-based conformational analysis of these compounds were carried out and the resulting low energy conformations were further evaluated with geometrical constraints obtained from the NMR NOE experiments. To illustrate the conformational similarity, the most active and the least active conformers in this series of benzofurans were overlapped with losartan (**1**). The conformations of compounds with good binding affinities were found to be quite similar to the active conformer of losartan. This study proved that the potent benzofuran derivatives also bind to the same site of Ang II receptor as losartan.[317,318]

## 6. Conclusion

Selective blockade of $AT_1$ receptor effectively reduces blood pressure. When $AT_1$ receptor is blocked, renin secretion and Ang II formation is increased. Consequently, Ang II is free to activate unblocked $AT_2$ receptor with potential beneficial effects. Many clinical trials have demonstrated the efficacy and safety of Ang II ($AT_1$) blockers in hypertension. The efficacy of Ang II ($AT_1$) blockers proved comparable to calcium channel and β-blockers in treating hypertension. Evidence from both animal and clinical studies indicate that RAS blockade and interruption of Ang II activity have protective effects on the heart, vasculature and kidney that appear to lead to the positive clinical outcomes observed in trials on $AT_1$ receptor blockade. Treatment with $AT_1$ receptor blockers has been demonstrated to significantly reduce CV events and heart failure progression, improve renal diseased-condition, and prevent new onset of diabetes through pleiotropic effects independent of the effect on blood pressure.

Researchers across the globe have reported number of $AT_1$ selective antagonists. Compounds belonging to different chemical classes have been synthesized and reported as selective $AT_1$ receptor antagonists. An overview of literature has thrown open an array of scaffolds having imidazole, dihydroimidazol-4-one, pyrazole, triazole, pyridine, pyrimidine, benzimidazole, imidazopyridine and other heterocycle/acycle-containing antagonists. Taking losartan as the lead molecule, large number of its congeners have been synthesized resulting into olmesartan (imidazole series), irbesartan (dihydroimidazol-4-one), candensartan, telmisartan (benzimidazole) and valsartan (acyclic moiety), etc. as clinically used Ang II inhibitors. To understand the interaction of Ang II and its antagonists with $AT_1$ receptor, molecular modeling studies and computational analysis have been performed. These studies have thrown new light on the molecular requirements for compounds to possess $AT_1$ antagonistic activity. Outcome of these studies could provide valuable information for the proper understanding of molecular basis of hypertension and contribute to the rational designing of novel and potent selective $AT_1$ antagonists.

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**Mr. PRASHANT NAIK** is born on 20 July 1983 in Maharashtra, India. He studied for his undergraduate degree (2004) in Pharmacy from North Maharashtra University, India. He post graduated in Pharmaceutical Chemistry from University of Pune, India in 2006.

Currently he is pursuing his Ph.D. in Pharmacy at Pharmacy Department, The M.S. University of Baroda, Vadodara, India. He joined research group of Professor M. R. Yadav at Pharmacy Department, The Maharaja Sayajirao University of Baroda, Vadodara, India in 2007 for his doctoral work. His topic for doctoral research is 'Design and Synthesis of Some Multitargeted Ligands as Potential Antihypertensive Agents'.

His research interests include computational and conventional design and synthesis of dual acting antagonist of $AT_1$ and $\alpha_1$-receptor for better control of hypertension.

**PRASHANT R. MURUMKAR** is a Ph.D. research scholar at Pharmacy Department, The M. S. University of Baroda, Vadodara, India. Born on 10th October 1980 in Maharashtra, India, he studied for his undergraduate and postgraduate degree (Pharm. Chemistry) from the North Maharashtra University, India. In 2006, he joined the research group of Professor M. R. Yadav at Pharmacy Department, The M. S. University of Baroda, for pursuing his Ph.D. in Pharmaceutical Sciences. His topic for doctoral research is 'Designing of Some Novel Enzyme Inhibitors'.

He has been awarded a National Doctoral Fellowship by AICTE, New Delhi, Government of India for the period of 2006-2009 for his doctoral work. He has also been awarded Young Scientist Travel Grant from various government agencies like Department of Science & Technology, Council of Scientific and Industrial Research (CSIR), Government of India for presenting his research work at 235$^{th}$ and 237$^{th}$ American Chemical Society (ACS) National meeting in New Orleans and Salt Lake City, USA in 2008 and 2009 respectively.

He was a visiting research scholar at The University of Utah, Salt Lake City, USA, in the year 2009 where he worked with research group of Prof. Thanh N. Troung. His current research interest includes virtual screening of databases, pharmacophore designing and 3D-QSAR studies for anti-inflammatory and anticancer drugs. Mr. Prashant has twelve research publication and one book chapter to his credit. He is a life Member of Association of Community Pharmacists of India.

**Ms. RAJANI GIRIDHAR** is presently working as Professor, Pharmaceutical Chemistry at Pharmacy Department, Faculty of Tech. & Engg., The M. S. University of Baroda, Vadodara, Gujartat, India.

She has 35 years of teaching experience. She obtained the Doctoral degree in Pharmacy from The M. S. University of Baroda, Vadodara in 1987 and the M. Pharm. degree in Medicinal Chemistry in 1975 from B.I.T.S., Pilani, Rajasthan. She graduated with the B. Pharm. degree from Madras University in 1973 and was awarded two gold medals for being an outstanding student securing the first rank. Prof. Rajani Giridhar has guided 5 research students and around 32 students for M. Pharm. Presently, she is guiding 5 doctoral students and 3 M. Pharm. students. Her research areas include design and synthesis of reverse transcriptase inhibitors, PTP1B inhibitors for antidiabetic activity, antiplatelet agents and heterocyclic systems (seven membered) for CNS activity etc.

She has obtained one Indian Patent and applied for four more. She has published around 65 research papers in National and International journals and also a book chapter to her credit. A few papers were presented by her research team in international conferences also. She has been funded for research projects from various funding agencies of the Indian government like AICTE, New Delhi and UGC, New Delhi.

**Dr. M. R. YADAV** is a distinguished pharmaceutical scientist and an academician of high distinction. Presently he is working as Professor of Pharmaceutical Chemistry and Head of Pharmacy Department, The M.S. University of Baroda, Vadodara, India.

Born in September 1954, he had his schooling at Delhi and graduated from the University of Delhi, India. He obtained his postgraduate degree in Pharm. Chemistry from Banaras Hindu University, Varanasi, and Ph.D. in Pharmaceutical Chemistry from Panjab University, Chandigarh, where he remained a teaching faculty also for 6 years. He also had a brief stint of 4 years as Assistant Professor at the College of Pharmacy (now DIPSAR), University of Delhi, Delhi.

He has a research experience of almost 25 years with more than 90 national and international research publications and eight Indian patents to his credit. A few papers have been presented by his research team in international conferences also. His research interests include synthesis and molecular modeling studies in designing of medicinally active compounds in the fields of enzyme inhibitors like TACE and aromatase, anti-inflammatory, anti-hypertensive and anticancer agents. Ten students have been awarded Ph.D. under his supervision. Presently eight Ph.D. and four M. Pharm. students are working under his guidance. He is a Member of Editorial Advisory Board of 'The Open Drug Discovery Journal'.

He has successfully organized GPAT-2010 Examination as Co-ordinator, for the first time in India.

Recently he has been awarded 'Pharmacy Teacher of the Year 2010' award by Association of Pharmacy Teachers of India. Presently he is a member of National Board of Accreditation for Management and Technology, AICTE, New Delhi; Regional Committee, South Central Regional office, AICTE, Hyderabad for three years from 26th Feb. 2010; Board of Studies of Pharmacy, The M.S. University of Baroda, Vadodara and Devi Ahilya Vishwavidyalaya, Indore, India. He is a chairman of National Monitoring Committee-GPAT, AICTE, New Delhi for the year 2009–2010.