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Perspective

Nonpeptide Angiotensin II Receptor Antagonists: The Next Generation in Antihypertensive Therapy

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1. Introduction

The renin−angiotensin system (RAS) is recognized as a key element in blood pressure regulation and electrolyte/fluid homeostasis.[1] As outlined in Figure 1, the RAS constitutes a proteolytic cascade in which angiotensinogen from the liver is cleaved by the aspartyl protease renin to produce the decapeptide angiotensin I (Ang I). Biologically inactive Ang I is cleaved by the metalloprotease angiotensin-converting enzyme (ACE) to produce the endogenous octapeptide hormone angiotensin II (Ang II). The clinical and commercial success of ACE inhibitors[2] such as captopril[3] and enalapril[4] for the treatment of hypertension and congestive heart failure has initiated substantial interest in the exploration of novel ways to interfere with the RAS cascade.[5,6] Despite the fact that ACE inhibitors have met with a high degree of success, ACE is a nonspecific protease which is also responsible for the degradation of bradykinin as well as other peptides such as substance P and enkephalins.[7] The dry cough that occurs in 5−10% of the population treated with ACE inhibitors and the rare instances of angioedema have been proposed to be the result of the lack of specificity of ACE; more specifically these side effects have been attributed to bradykinin potentiation.[8]

In the search for novel methods of intervention, inhibitors of renin have also been extensively investigated. However, to date, poor oral bioavailability, rapid biliary excretion, and the structural complexity of most renin inhibitors have hampered their development as drugs.[9] While progress has been made toward eliminating these liabilities, the pharmaceutical industry has been unsuccessful in bringing a renin inhibitor to market. Inhibition of the terminal step in the RAS, i.e., Ang II receptor blockade, offers a highly specific approach to inhibition of the system regardless of the source of Ang II. Also, since ACE would not be affected by such agents, potentiation of bradykinin and hence cough or angioedema by this mechanism would not be expected during therapy with an Ang II blocker.[10] Although potent peptide Ang II receptor antagonists such as Phe[4]-Tyr[8]-Ang II and saralasin (Sar[1]-Ala[8]-Ang II) have been used as pharmacological tools for the past

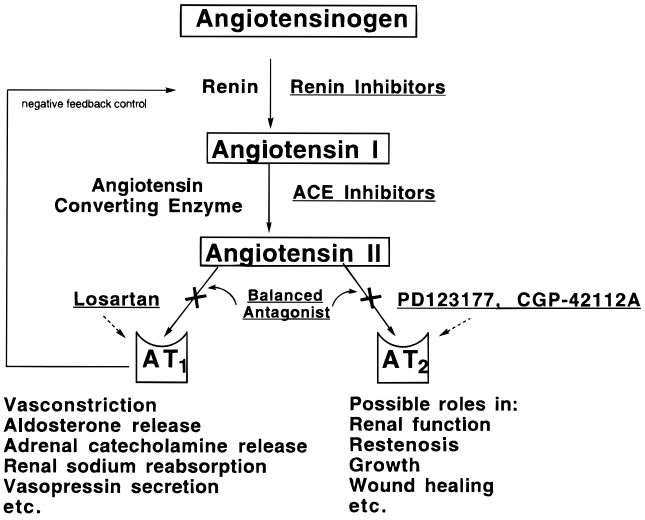

Figure 1. Renin−angiotensin system: targets for intervention.

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2−3 decades, these peptides have limited therapeutic value because of their poor oral bioavailability, short duration of action, and significant agonist properties.[11,12]

The concept that nonpeptide Ang II antagonists would lack the disadvantages of the peptide Ang II receptor antagonists was an attractive but elusive strategy until 1982, when Furukawa and co-workers at Takeda Chemical Industries disclosed a series of 1-benzylimidazole-5-acetic acid derivatives.[13,14] In these early patent publications, several compounds from this series were reported to inhibit the Ang II-induced contractile response in rabbit aorta and the pressor response in the Ang II-infused rat, but no information was given on the selectivity of these compounds. Two compounds from the Takeda series, S-8307 (CV2947) and S-8308 (CV2961), were prepared and studied thoroughly by the DuPont group and confirmed to be weak but selective competitive Ang II receptor antagonists lacking agonist properties.[15,16] These early compounds demonstrated the feasibility of nonpeptide Ang II receptor antagonists and served as the starting point which culminated in the discovery of losartan (COZAAR, also designated as DuP 753 and MK-954), which is the prototype of this new class of potent, orally active, nonpeptide Ang II receptor antagonists.[17−19]

2. Angiotensin II Receptor Subtypes

The discovery of losartan and nonpeptide spinacine-derived compounds such as PD-123,177[20] and PD-123,-319[21] along with peptides such as CGP-42112A[22] (section 4) led to the confirmation of earlier suggestions of the existence of Ang II receptor heterogeneity. Chiu et al.[23] and Whitebread et al.[22] independently showed that losartan is bound to the majority of receptors in most tissues but not in others such as the adrenal medulla or uterus. The losartan insensitive sites could be occupied by PD-123,177 or CGP-42112A. The Ang II receptor subtypes inhibited by losartan have been designated AT_1 and those inhibited by the spinacine derivatives such as PD-123,177 and CGP-42112A as AT_2. The distribution of these receptor subtypes has been shown to vary from species to species and from tissue to tissue within the same species.[24,25] Although the AT_1 site predominates in most tissues, the AT_2 site is widely expressed in fetal tissue and localized in discrete parts of the brain of various species including man (see reviews[26−30]).

Losartan and other AT_1-selective nonpeptide antagonists block virtually all of the well-known functional effects of Ang II including vasoconstriction, aldosterone release, and cardiovascular growth, and hence most of the pharmaceutical effort toward developing nonpeptide Ang II antagonists has focused on AT_1-selective agents.[26,28−30] The AT_1 receptor is G-protein coupled, and activation leads to inhibition of adenylate cyclase and decreased cAMP or to stimulation of phospholipase C with formation of IP_3 and the release of intracellular calcium.[31] Much less is known about the function and intracellular functional response coupling of the AT_2 receptor. The AT_2 receptor has now been cloned and shares 32−34% homology with the AT_1 receptor.[32,33] The report that the AT_2 site is coupled to cGMP formation has not been confirmed.[32,33] Further, these authors have described opposite effects of Ang II on protein tyrosine phosphatase in PC12W cells that express only

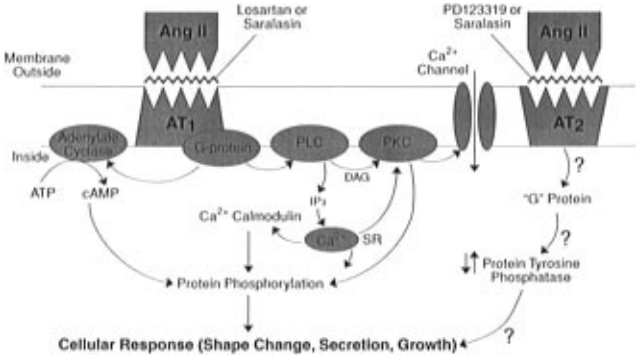


Figure 2. Ang II receptor−cellular response coupling. ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; G-protein = guanosine protein; PLC = phospholipase C; DAG = diacetylglycerol; PKC = protein kinase C; SR = sarcoplasmic reticulum.

AT_2 sites.[33,34] There have been a number of reports that have shown that either the combination of losartan and PD-123,177 (or CGP-42112A) or only the AT_2 antagonists attenuate certain responses to Ang II.[26−30] Thus, a role of the AT_2 site cannot be ruled out even though the majority of data points to the inactivity of selective AT_2 receptor ligands at reasonable doses (concentrations).

Nonselective blockade of both AT_1 and AT_2 receptors can be accomplished by using ACE inhibitors to block the availability of Ang II at both receptor subtypes, by using the peptide antagonists (e.g., saralasin), by combining nonpeptide antagonists, or by studying the effects of newly identified nonpeptide antagonists that have high affinity for both AT_1 and AT_2 receptor subtypes. Each of these approaches has its own limitations. The comparisons to date show that inhibiting the RAS with ACE inhibitors or nonpeptide AT_1-selective Ang II receptor antagonists gives quite similar results in a variety of *in vitro* and *in vivo* settings.[30] Where differences are observed, usually only one dose of each compound was compared so the comparability of the blockade of the RAS is difficult to evaluate. Experiments with saralasin-like nonselective antagonists are limited by their peptide nature and partial agonist activity. The use of combination treatments (e.g., losartan plus PD-123,177) is complicated by the high protein binding of the individual agents. The apparent additive effects of these agents may actually reflect enhancement of the free drug concentration, e.g., losartan, due to displacement from binding sites.[35] The recent discovery of nonselective antagonists provides a simpler way to address the functional role of the AT_2 site. To date, however, such compounds have not indicated a clear physiological (or pathological) role for this receptor.

3. AT_1-Selective Nonpeptidic Antagonists

Due to the clear link between the AT_1 receptor and the control of blood pressure, numerous AT_1-selective antagonists have emerged in the past several years. With the exception of SK&F 108566[36,37] and related imidazole-5-acrylic acids, and the more recent Lilly antagonists,[38] these nonpeptide antagonists are based on modifications to one or more fragments of losartan. The majority of these compounds have resulted from the strategy of modifying or replacing the imidazole moiety of losartan. AT_1-selective antagonists have been exten-

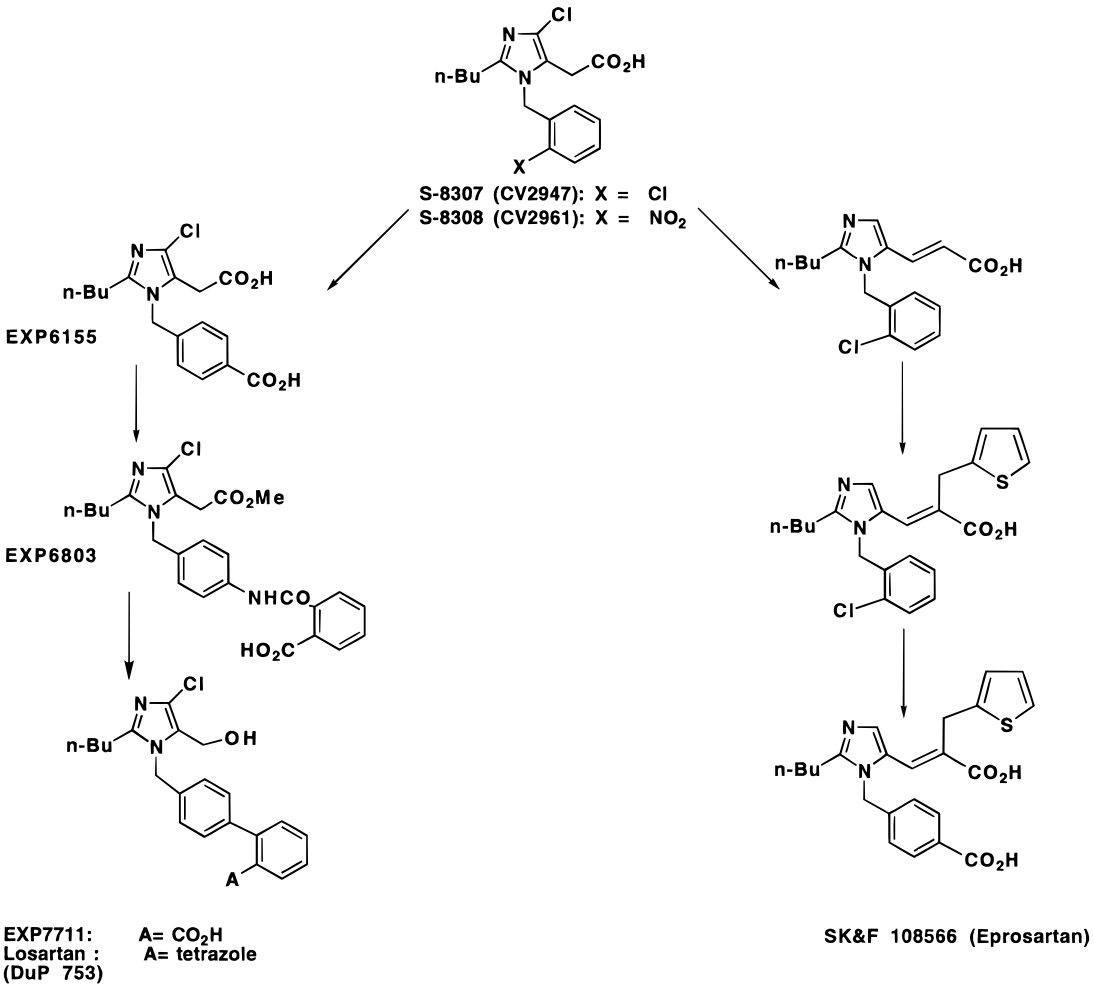


Figure 3. Discovery of losartan and SK&F 108566.

sively reviewed in several books and review articles in the last 2 years, and these reviews should be consulted for an in-depth account of the innovative contributions of the many research groups who have contributed to this endeavor.[26,27,29,30,39−52]

This Perspective article highlights the AT_1-selective compounds which have been chosen for clinical evaluation, the AT_2-selective antagonists, the AT_1/AT_2 balanced antagonists that have been reported on to date, and the impact computer modeling has had on the design of these antagonists. We also have attempted to give a clinical perspective on the AT_1 antagonists and the expected therapeutic impact of losartan and other AT_1-selective antagonists vs nonselective Ang II antagonists. Lastly, new therapeutic strategies for the treatment of hypertension are discussed.

3. 1. Development of Losartan and SK&F 108566 from the Takeda Benzimidazole Leads. As mentioned previously, 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-benzylimidazole-5-acetic acid derivatives like S-8307 and S-8308 that are selective but weak antagonists (Figure 3).[13−16] Losartan[17] and SK&F 108566[36] 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 (see section 7 for a summary of the models employed).

The DuPont modeling strategy gave rise to EXP6155, which showed a 10-fold increase in binding affinity (IC_{50} = 1.6 μM, rat adrenal; pA_2 = 6.54, rabbit aorta) over S-8307.[53,54] Although the compound did not show an antihypertensive effect when dosed orally (100 mg/kg) to renal hypertensive rats (RHR), it did lower blood pressure when dosed intravenously (ED_{30} = 10 mg/kg).

From this starting point, a series of progressively more potent (higher affinity for the AT_1 receptor) phthalamic acids and related compounds were synthesized, exemplified by EXP6803, which produced another 10-fold enhancement in binding affinity (IC_{50} = 120 nM, rat adrenal; pA_2 = 7.20, rabbit aorta).[17,54−56] In RHR, EXP6803 reduced blood pressure with an ED_{30} = 11 mg/kg but was inactive when dosed orally at 100 mg/kg. A series of compounds was synthesized where the amide group was replaced by a linking group containing zero to three atoms.[57,58] This series of compounds lacked oral activity until the amide linker was replaced with a single bond, which resulted in EXP7711.[57] The biphenyl derivative, while orally active (ED_{30} = 11 mg/kg), was slightly less potent than EXP6803 in inhibiting [^{3}H]Ang II binding (IC_{50} = 0.23 μM compared with 0.12 μM) and in antagonizing Ang II-induced contractions in rabbit aorta. In conscious RHR, EXP7711 dosed intravenously had an ED_{30} value of 3.7 mg/kg compared to 11 mg/kg for EXP6803.[59] To further improve the oral activity of the biphenyl compounds, a number of acidic groups were systematically evaluated as bioisosteric replacements for the carboxyl group. This effort culminated in the identification of losartan as a clinical candidate. In

losartan, the carboxylic acid moiety was replaced with a tetrazole, which gave a significant improvement in potency and good oral antihypertensive activity. More detailed accounts of the discovery of losartan have appeared.[17,18,26,39,60−62]

Losartan is a selective AT_1 antagonist having IC_{50} values of 19 and 20 nM in rat adrenal cortex and rat vascular smooth muscle, respectively, and essentially no affinity for the AT_2 receptor subtype.[63] It is a competitive antagonist of Ang II ($pA_2 = 8.48$, rabbit aorta) and does not possess the partial agonist properties characteristic of the peptide receptor antagonists like saralasin.[64] In RHR, losartan showed antihypertensive effects at 0.1 mg/kg when dosed intravenously ($ED_{30} = 0.78$ mg/kg) and at 0.3 mg/kg or greater when dosed orally ($ED_{30} = 0.59$ mg/kg), without affecting heart rate and with antihypertensive efficacy comparable to that of ACE inhibitors. No further drop in blood pressure was seen with the administration of a large dose of captopril at the time of peak losartan activity.[65] In RHR, the antihypertensive effect of losartan (3 mg/kg orally) lasted for more than 24 h.[65] Losartan administered orally or intravenously also reduced arterial pressure of conscious spontaneously hypertensive rats but was inactive in Wistar−Kyoto normotensive rats and in the DOCA (deoxycorticosterone acetate) hypertensive rat, a renin-independent model.[65−67]

Intravenous administration of losartan to RHR (1 mg/kg) produced a biphasic antihypertensive response.[65] This suggested the involvement of one or more active metabolites. Also in support of this suggestion was the finding that the oral ED_{30} value of losartan is lower or at least comparable to the intravenous ED_{30} value in RHR even though the oral bioavailability of losartan in rats is 33%. EXP3174,[68] the imidazole-5-carboxylic acid resulting from oxidation of the imidazole 5-hydroxymethyl group, was identified in rat plasma as the major metabolite of losartan.[69] Unlike losartan, in functional assays EXP3174[68] was found to be a noncompetitive antagonist (apparent $pA_2 = 10.09$, rabbit aorta).[68] However, similar to losartan, EXP3174 maintained high selectivity in Ang II receptor blockade *in vitro* ($IC_{50} = 1.3$ nM, rat adrenal cortical microsomes). Similar to the earlier nonpeptide Ang II antagonists, losartan and EXP3174 do not possess the partial agonist properties characteristic of the peptide antagonists, e.g., saralasin, and did not increase heart rate.[68] Oral bioavailability of EXP3174 in rats is 12% compared to 33% for losartan.[69,70] Given intravenously, EXP3174 is ca. 20 times more potent than losartan ($ED_{30} = 0.04$ vs 0.78 mg/kg, respectively). Given orally, EXP3174 is slightly less potent than losartan ($ED_{30} = 0.66$ vs 0.59 mg/kg, respectively).[68] Not only does EXP3174 show enhanced intrinsic potency relative to losartan, but it also shows prolonged duration of action. In animal models and man, it has been shown that losartan owes much if its *in vivo* activity and duration of action to this carboxylic acid metabolite.[68−70] Like losartan, EXP3174 has served as a starting point for the development of many novel AT_1 antagonists.

The antihypertensive effects of losartan have been demonstrated in experimental models of renal and genetic hypertension[30] that support the primary antihypertensive indication. In the SHR model of "normal" renin essential hypertension, losartan and other AT_1-selective antagonists lower blood pressure and reduce cardiac and vascular hypertrophy.[30,71] The maximum effect is the same as with ACE inhibitors. No tolerance to the blood pressure-lowering effects and no rebound hypertension on withdrawal of treatment were noted.[72]

Positive results in experimental models of renal failure, cardiac failure, and stroke suggest additional indications for losartan and other AT_1-selective antagonists. Losartan has been shown to have blood pressure-lowering and antiproteinuric effects in models of renal failure produced by partial nephrectomy,[73] uninephrectomy,[74] streptozotocin,[75] and puromycin.[76]

In models of "cardiac failure", losartan or related AT_1 antagonists have been shown to have beneficial hemodynamic effects in mice,[77] rats,[78,79] dogs,[80] and sheep.[81] Although consistent effects of AT_1 receptor blockade have been demonstrated in rats with aortocaval shunt, less consistent effects have been noted in rats with failure induced by coronary artery ligation.[82] Additional studies will be required to define the role of Ang II and antagonists in heart failure.

In the stroke-prone SHR, losartan has been shown to have significant effects on morbidity. Although blood pressure is not normalized, cardiac, vascular, renal, and cerebral changes are markedly reduced by losartan treatment.[83−85] The similar effects observed with ACE inhibitors[86] suggest that Ang II is the pathological factor involved. The pioneering studies with losartan are now being confirmed with other AT_1-selective antagonists in each of the experimental models of hypertension and other disease states.[87−89]

As mentioned above, the SmithKline Beecham clinical candidate (SK&F 108566) is representative of one of the few series of Ang II antagonists to date designed independently from the Takeda benzylimidazoles and not from losartan. Like the DuPont group, the SmithKline Beecham group also based their initial design strategy (see section 7) on a combination of molecular modeling and a knowledge of the peptide structure−activity relationship (SAR) (reviewed in detail in several recent references).[36,37,90,91] A 15-fold enhancement in binding affinity was realized by chain extension at the imidazole-5-position via a *trans*-5-acrylic acid group followed by addition of an α-benzyl group which appeared to better mimic the Phe^8 side chain. Replacement of the α-benzyl group with a 2-thienylmethyl group followed by replacement of the 2-chlorobenzyl group with a 4-carboxybenzyl group to better mimic the phenolic moiety of Tyr^4 afforded SK&F 108566 (eprosartan). SK&F 108566 is a potent, AT_1-selective antagonist that exhibits competitive inhibition of [^{125}I]Ang II binding to rat mesenteric artery and adrenal cortical membranes ($IC_{50} = 1.5$ and 9.2 nM, respectively).[36,37,92] In conscious normotensive rats, SK&F 108566 administered via bolus intravenous injection produced a dose-dependent inhibition of pressor responses to Ang II (250 ng/kg) with an $ID_{50} = 0.08$ mg/kg. When administered intraduodenally, a dose-dependent inhibition of the pressor response to Ang II was observed with an ID_{50} value of 5.5 mg/kg, and at the highest dose (10 mg/kg), significant inhibition was observed 3 h after dosing.[92] In conscious normotensive dogs infused with Ang I (100 ng/kg/min, iv), SK&F 108566 (3 mg/kg, iv, or 10 mg/kg, po) lowered mean arterial pressure from 160 to ca. 100 mmHg with a duration of >6 h at this dose.[93]

3. 2. Imidazole Biphenyltetrazole Antagonists Related to Losartan. Studies of the SAR around the substituted imidazole ring of losartan (and EXP3174) carried out at DuPont have been published.[18,19,62] At the imidazole C2 position, a linear alkyl or alkenyl group is preferred, which is optimal at three to four carbon atoms. A variety of substituents at the imidazole C4 and C5 positions are acceptable, the exact steric or electronic properties of which do not appear critical for binding. The high potency of EXP3174 demonstrated that an acidic group at C5 is particularly advantageous. Other hydrogen bond-accepting substituents at C5 such as a hydroxymethyl, carboxaldehyde, or carboxamido group also yield potent antagonists.

While not required for AT_1 binding, a substituent at C4 often increases potency and has also shown favorable effects on *in vivo* properties. Within a series of 4-haloimidazole derivatives, the binding affinity showed a small increase in affinity with the increasing size of the halogen (I > Br > Cl).[57] Subsequent introduction of perfluoroalkyl substituents to pursue the possibility that the Ang II receptor could accommodate a large lipophilic and electron-withdrawing group resulted in a series of 4-(perfluoroalkyl)imidazoles, the most potent of which possessed a 4-pentafluoroethyl substituent.[94] DuP 532 was prepared to capitalize on the enhanced binding affinity of the 4-pentafluoroethyl group and the observation that diacid EXP3174 is a potent Ang II antagonist, with good antihypertensive activity and long duration of action. DuP 532 has an IC_{50} value of 3.1 nM (rat adrenal) and an ED_{30} value in RHR of 0.02 and 0.21 mg/kg for intravenous and oral administration, respectively.[95,96] The antihypertensive effect of 0.3, 1.0, or 3.0 mg/kg doses given orally lasted for >24 h. In conscious spontaneously hypertensive rats and conscious furosemide treated dogs, DuP 532 administered either intravenously or orally (0.3−3.0 mg/kg) lowered blood pressure in a dose-dependent fashion.[96]

More recently, simple 4-alkyl substituents (e.g., 4-ethyl) have been found to yield antagonists with high *in vitro* and *in vivo* potency. In fact, DMP 581 and DMP 811 (AT_1 IC_{50} = 2.1 and 6 nM, rat adrenal) represent the most potent oral antihypertensives prepared in the DuPont Ang II program, with ED_{30} values following oral administration in the RHR of 0.027 and 0.03 mg/kg, respectively.[98,99] DMP 581 is 60−70% absorbed when administered as a neat powder to rats and dogs and completely absorbed in both species when administered in solution. Like losartan, it is metabolized to its more active diacidic metabolite DMP 811 which contributes significantly to the antihypertensive effect and duration of action of DMP 581. In conscious RHR, DMP 811 decreased blood pressure with iv and po ED_{30} values of 0.005 and 0.03 mg/kg, respectively. Hence, it is 20-fold more potent orally than losartan (po ED_{30} for losartan is 0.59 mg/kg).[99] However, like other diacids the oral bioavailability of DMP 811 is moderate, ca. 8% and 13% when administered as a neat powder to rats and dogs, respectively, which is similar to that of DuP 532.[62,97−99]

Like losartan, DMP 581 (an imidazolecarboxaldehyde) is a competitive antagonist, while DMP 811 and other diacids such as DuP 532 and EXP3174 behave as noncompetitive antagonists,[96,99] that is, these compounds cause nonparallel rightward shifts of the Ang II concentration−contractile response curves and reduce

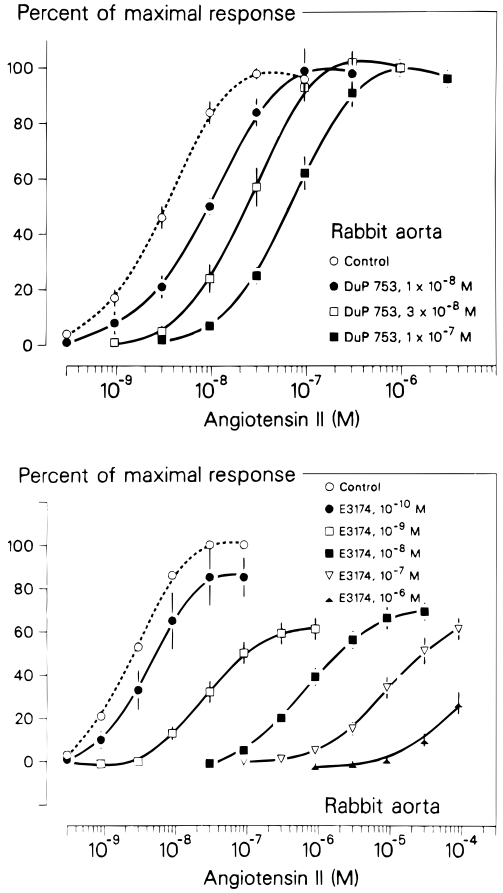


Figure 4. Losartan (DuP 753) produces a "surmountable" blockade of the contractile response of rabbit aortic strips to Ang II. EXP3174, the active metabolite of losartan, produces an "insurmountable" blockade (a nonparallel shift of the concentration−response curve with a decreased maximum response). Values are the mean ± SE (N = 5−6) (refs 64 and 68).

the maximal contractile response to Ang II by 30−40%[68,99] in the functional assay (isolated rabbit aorta). This phenomenon may be the result of a slow off-rate of bound antagonist from the receptor. Compounds which behave like losartan showing parallel shifts to the right without a suppression of the maximal response to Ang II have been termed *surmountable* antagonists, while the diacids like EXP3174 which show a nonparallel shift with a suppression of the maximal response have been termed *insurmountable* antagonists.[68,100]

These diacidic compounds have been found to bind tightly to plasma proteins, including bovine serum albumin (BSA) commonly used to reduce nonspecific binding in Ang II receptor antagonist assays. This led to a discrepancy between *in vitro* binding to membrane preparations and potency in functional (aortic contraction) assays of up to 3 orders of magnitude. For example, removal of BSA from the binding assays enhanced the binding affinity of DuP 532 by 1500-fold and EXP3174 by 20-fold.[95] Although diacidic antagonists show more of an effect of BSA, a high degree of plasma binding may prove to be an important characteristic of other antagonist series as well.

Due to the moderate oral bioavailability of the diacids, several groups have evaluated prodrugs of the diacids. One prodrug currently undergoing clinical investigation is HN-65021 (Hafslund Nycomed). HN-65021 is a prodrug ester of EXP3174 and is currently in phase II

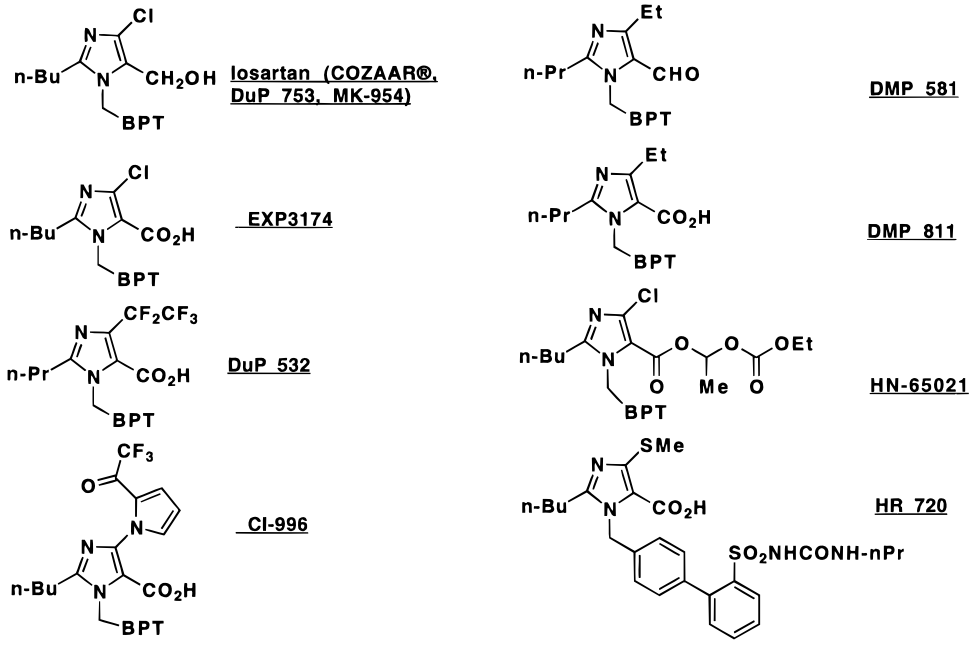


Figure 5. Imidazole antagonists.

trials. This prodrug, when administered to conscious rats, dose-dependently decreased the pressor response with an oral ED_{50} value of 0.5 mg/kg. When dosed at 1 mg/kg, po, full inhibition was achieved and significant inhibition was still observed 24 h postdose.[101] Comparable results were obtained in conscious beagle dogs; however, a shorter duration of action was reported.[101]

Returning to the SAR at the C4 position, the tolerance of a large group at this position is demonstrated by the high binding affinity of imidazoles which carry bulky 4-aryl[102,103] or heteroaryl[104] substituents. An example of a heteroaryl derivative is CI-996 (Warner-Lambert). CI-996 is a potent AT_1 receptor antagonist (AT_1 IC_{50} = 0.58 nM, rat liver) that was selected from a series of 1-pyrrolylimidazoles.[104,105] CI-996 is an insurmountable antagonist like many of the other imidazole-5-carboxylic acids. In RHR, CI-996 (1−30 mg/kg, po) lowered mean arterial blood pressure (MABP) in a dose-dependent manner with a duration ≥24 h.[106] CI-996 (1 mg/kg, iv) was more effective than losartan at the same dose in blocking the Ang II pressor response in sodium-replete anaesthetized dogs.[107] In renal hypertensive monkeys (10 mg/kg, po), CI-996 dosed daily for 3 days reduced blood pressure by ca. 10 mmHg for ≥24 h.[106]

Other 4-substituted imidazoles which have been exploited include the 4-(alkylthio)imidazole which has been successfully employed in HR720,[108,109] which incorporates a sulfonylurea replacement for the tetrazole moiety. HR720 is in phase II trials by Hoechst Marion Roussel. In binding assays, HR720 has an AT_1 IC_{50} = 0.48 nM (rat liver) and an AT_2 IC_{50} = 920 nM (rabbit uterus).[108] It is an insurmountable antagonist as are many of the other imidazole-5-carboxylic acid derivatives (pD'_2 = 10.15, rat portal vein). In pithed normotensive rats, HR720 inhibited the Ang II pressor response with ED_{50} values of 0.11 mg/kg, iv, and 0.7 mg/kg, po.[109] In RHR, at a dose of 1 mg/kg and above, the compound lowered BP significantly for >24 h. In sodium-depleted dogs, HR720 at a dose of 0.3 mg/kg produced a decrease in blood pressure which reached a plateau at 6 h and was sustained for up to 24 h.[109]

3. 3. Fused Imidazole Antagonists. The ability to incorporate a variety of functionality at the imidazole C4 and C5 positions of antagonists in the losartan series suggested that these substituents could be joined to yield ring-fused imidazoles. 1-(Arylmethyl)benzimidazoles have been investigated by several groups, and potent antagonists have been reported including three compounds currently undergoing clinical investigation: TCV-116, BIBS 39, and BIBR 277.

TCV-116 (candesartan cilexetil; Takeda), currently undergoing phase III trials, is an ester carbonate prodrug which is rapidly converted *in vivo* to CV-11974.[110] Benzimidazole CV-11974 is a potent inhibitor *in vitro* (K_i = 0.64 nM; AT_1 IC_{50} = 28 nM, rabbit aorta) which bears a C7 carboxy substituent positioned to mimic the carboxyl group of EXP3174.[110,111] CV-11974 noncompetitively inhibited Ang II-induced contraction (IC_{50} = 0.3 nM, rabbit aorta).[110,111] A dose of 1 mg/kg, po, blocked the Ang II pressor response in conscious rats for greater than 24 h. By intravenous administration to conscious rats, CV-11974 was ca. 10 times more potent than EXP3174.[112] The prodrug TCV-116, dosed orally, blocked the Ang II pressor response with an ED_{50} value of 0.069 mg/kg.[112,113] TCV-116 produced long-acting Ang II antagonism and antihypertensive effects in both renal and genetic hypertensive rats (in SHR, 1 mg/kg, po, lowered BP for over 24 h with no effect on heart rate).[87,112−115] TCV-116 showed no effect on blood pressure in DOCA/salt hypertensive rats (10 mg/kg, po) or in normotensive rats (1.0 mg/kg, po).[115,116] The oral bioavailability of TCV-116 in rats is 28−33%.[113,115] In an additional study of chronic TCV-116 in spontaneous hypertensive rats, regression of cardiac hypertrophy was observed.[117,118] TCV-116 (10 mg/kg/day) also prevented intimal thickening and impairment of vascular function after carotid artery balloon injury in rats.[119]

The Thomae group has carried out extensive inves-

tigation on benzimidazole antagonists particularly focusing on substitution at the 6-position of the heterocycle. BIBS 39 and BIBS 222 were the first compounds Thomae reported on in detail.[120,121] As BIBS 39 and BIBS 222 were the first Ang II antagonists described with substantial binding affinity for both the AT_1 and AT_2 receptors, they will be discussed in the section on balanced AT_1/AT_2 antagonists (section 5). A follow-up compound, 6-(benzimidazol-2-yl)benzimidazole BIBR 277 (telmisartan; Boehringer Ingelheim/Thomae), is currently reported to be in phase II clinical trials.[120−122] BIBR 277 incorporates a carboxylic acid as the biphenyl acidic group. Unlike the case in other series of antagonists, the biphenylcarboxylic acid BIBR 277 was more potent than its tetrazole analog.[120] BIBR 277 is a potent (K_i = 3.7 nM, rat lung) and selective insurmountable antagonist (K_B = 0.33 nM, rabbit aorta). BIBR 277 produced a dose-dependent decrease in MABP in conscious RHR (0.3 and 1 mg/kg, po; daily dose each day for 4 days) and SHR (1 and 3 mg/kg; daily dose for 4 days) following oral administration.[122] The hypertensive effect lasted for up to 24 h following a single 3 mg/kg, po, dose. BIBR 277 was also effective in a transgenic hypertensive rat model and improved the glomerulosclerosis and proteinuria present in untreated animals.[123] In conscious, sodium-depleted cynomolgus monkeys, BIBR 277 was similar in potency to EXP3174 and 100-fold more potent than losartan in decreasing blood pressure.[124]

The concept of incorporating a nitrogen atom in place of the benzimidazole C7 to include a functional group capable of hydrogen bonding to improve potency has been extensively explored. The most thoroughly studied is Merck's imidazol[4,5-*b*]pyridine series, which resulted in an exceedingly potent antagonist, L-158,809 (AT_1 IC_{50} = 0.3 nM, rabbit aorta).[125,126] In rat adrenal cortical cells, L-158,809 shifted the concentration−response curve for Ang II-induced aldosterone release to the right without altering the maximal response (pA_2 = 10.5), indicating that it is a competitive antagonist.[126] L-158,-809 inhibited the Ang II pressor response in conscious rats (ED_{50} = 0.029 mg/kg, iv, and 0.023 mg/kg, po), and at doses of 0.1 mg/kg, iv, and 0.3 mg/kg, po, the duration of action exceeded 24 h.[127] In rats with high renin hypertension (aortic coarctation), single oral doses of 0.1 and 0.3 mg/kg L-158,809 reduced the MABP to normotensive levels (reductions of 60 and 80 mmHg, respectively) with the decrease in BP lasting up to 48 h.[126] In both the coarcted rat model and volume-depleted rhesus monkeys, L-158,809 elicited a peak hypotensive response similar to that of enalaprilat. In the conscious spontaneously hypertensive rats, L-158,809 is also a potent antihypertensive agent with a duration of action exceeding 24 h.[127] L-158,809 did not elicit a hypotensive response in animals with low renin hypertension (DOCA salt rats). The oral bioavailability of L-158,809 was found to be 100% in rats and 32% in rhesus monkeys.[128]

Within the series of imidazole and fused imidazole Ang II antagonists, considerable effort has been placed on identifying an isostere for tetrazole which maintains the potency, duration of action, and bioavailability of losartan and other related biphenyl tetrazoles. To this end, replacement of the tetrazole moiety of L-158,809 with a benzoylsulfonamide group led to the discovery of MK-996 (L-159,282), which is currently in phase II clinical trials (AT_1 IC_{50} = 0.2 nM, rabbit aorta).[129] This acylsulfononamide group was selected because it does not undergo the N2 glucuronidation which was seen with the tetrazole L-158,809. Excellent *in vitro* and *in vivo* properties were observed for this benzoylsulfonamide analog of L-158,809.[129−131] MK-996 is an insurmountable antagonist with a pA_2 of 10.3. MK-996 inhibited the Ang II pressor response in conscious animals with oral ED_{50} values of 0.067 (rat), 0.035 (dog), and 0.1 (rhesus monkeys) mg/kg.[132] MK-996 (1.0 mg/kg, iv) also blocked the Ang II pressor response in anesthetized chimpanzees with a duration of action exceeding 24 h. In aortic coarcted (high renin) rats, MK-996 (3.0 mg/kg, po) reduced blood pressure to the normotensive level with duration of action exceeding 6 h, similar to enalapril at 3.0 mg/kg, po. Both iv and po potencies of MK-996 in rats and monkeys were similar to those of L-158,809 but significantly greater than those of losartan. The po/iv ED_{50} ratios indicate good oral bioavailability for MK-996 in rats, dogs, and rhesus monkeys.

Two additional imidazopyridines, FK739 and E4177, were placed into clinical evaluation in Japan. FK739 (Fujisawa) is a selective and competitive AT_1 antagonist (AT_1 IC_{50} = 0.6 nM, rat aorta; pA_2 = 8.45, rabbit aorta).[133] FK739 dosed at 10 mg/kg, po, was effective in blocking the Ang II-induced pressor response in normotensive rats and dogs and in decreasing blood pressure in RHR and renal hypertensive dogs. In SHR, FK739 at 32 and 100 mg/kg, po, reduced BP in a dose-dependent manner. In studying whether FK739 would cause side effects which are caused by ACE inhibitors, it was found that FK739 (10 and 32 mg/kg, po) did not affect the capsaicin-induced bronchial edema, while captopril (10 mg/kg) produced a significant enhancement.

E4177 (Eisai), a biphenylcarboxylic acid derivative, is also a selective, competitive antagonist (AT_1 IC_{50} = 52 nM, rat adrenal cortex; pA_2 = 8.7, rabbit aorta).[134,135] E4177 blocked the Ang II pressor response at 0.3 mg/kg, id (more efficacious than captopril), and exhibited a long duration of action. E4177 was studied in the Goldblatt 2-kidney, 1-clip rat (renin-dependent model) and shown to be beneficial in the treatment of hypertension associated with myocardial hypertrophy and renal lesion.[136] In a rat model of postangioplasty restenosis, E4177 (10 mg/kg) almost completely prevented neointima formation following vascular injury, whereas an ACE inhibitor had only a slight effect, suggesting that an Ang II antagonist may have an advantage over an ACE inhibitor in preventing vascular restenosis.[137] The ineffectiveness of the ACE inhibitor was attributed to local generation of Ang II by chymase.

Another fused ring imidazole antagonist currently undergoing clinical investigation contains a seven-membered ring fused to the imidazole. KT3-671 (Kotobuki Seiyaku), currently in phase I trials in Japan, shows excellent AT_1 binding potency (IC_{50} = 0.8 nM, rat liver) and functional activity (pA_2 = 10.04, isolated rabbit aorta). Oral administration of KT3-671 to renal hypertensive rats (1 and 3 mg/kg) gave a dose-dependent reduction in blood pressure.[138] The 3 mg/kg dose produced a maximal hypertensive action 2−3 h after administration, and a significant hypotensive effect remained after 24 h. In SHR, KT3-671 (10 mg/kg/day)

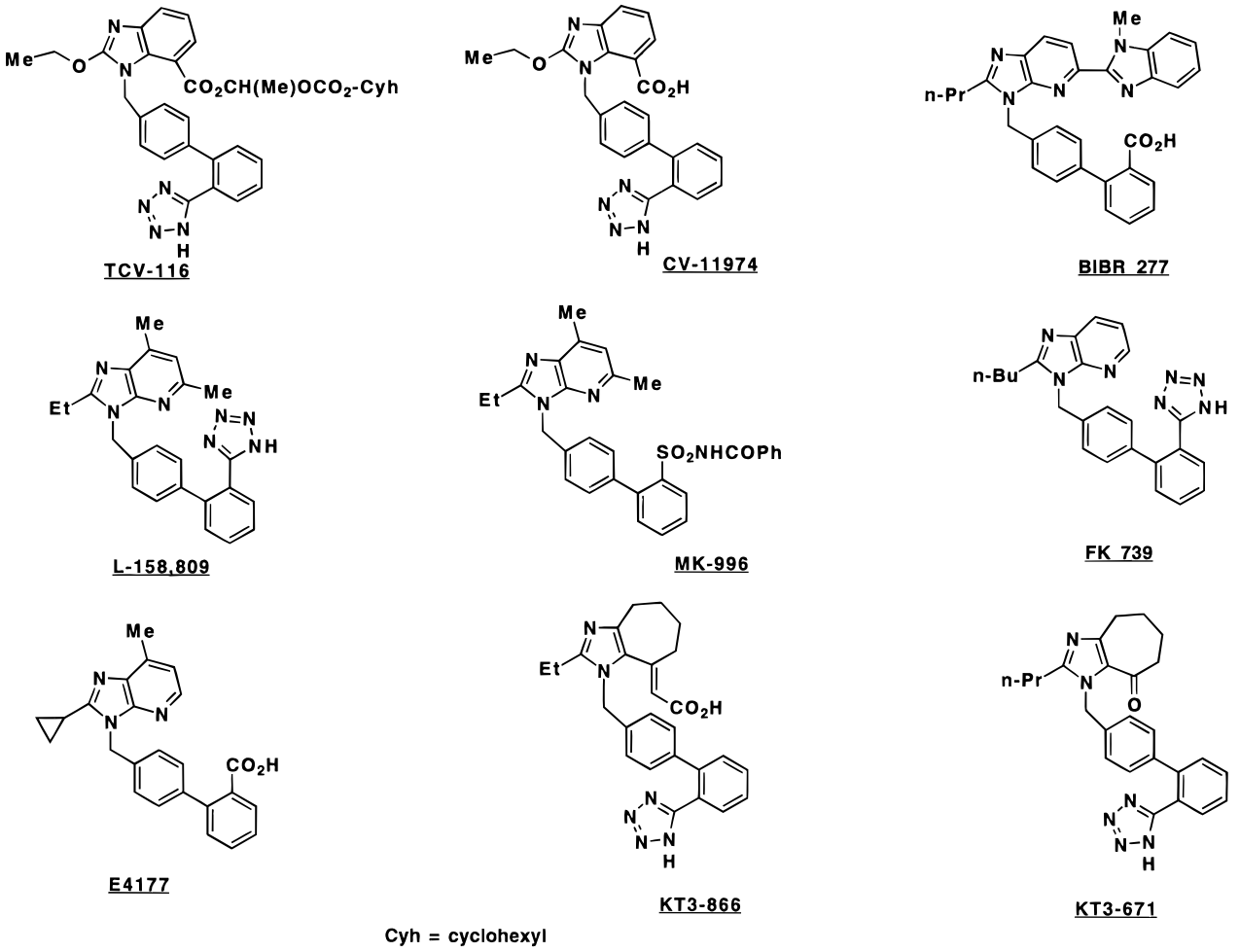


Figure 6. Fused imidazole antagonists.

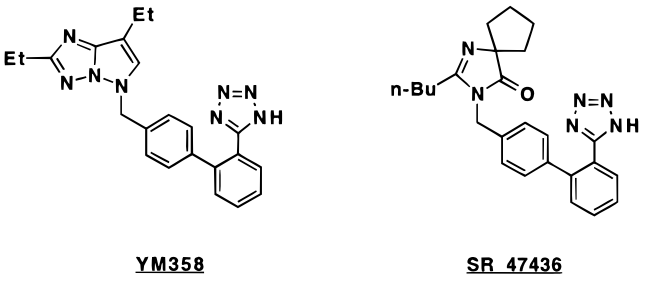


Figure 7. Additional five-membered ring heterocycles.

produced a sustained hypotensive effect for a 3-week period (mean blood pressure ca. 160 mmHg). A carboxymethylidene derivative, KT3-866 (AT_1 IC_{50} = 5.5 nM, rat liver), has recently been disclosed by Kotobuki.[139] Unlike KT3-671, this compound is a noncompetitive antagonist (pD'_2 = 9.91, rabbit aorta). It was ca. 5 times more potent than KT3-671 in blocking the Ang II pressor response in rats (0.3 mg/kg, po) and had a duration of action ≥24 h.[139]

3. 4. Additional Five-Membered Ring Antagonists. A number of additional antagonist designs have been reported in which various five-membered ring heterocycles replace the substituted imidazole found in losartan. Yamanouchi's lead Ang II antagonist YM358 (AT_1 IC_{50} = 1.7 nM; pA_2 = 8.65, rabbit aorta) is reported to be in phase I clinical trials in Japan.[140−142] YM358 is a substituted pyrazolotriazole in which the biphenylmethyl moiety is N-linked to the pyrazole ring but, unlike in losartan-like structures, is not adjacent to the alkyl chain. YM358 caused a dose-dependent decrease in BP in RHR (1−30 mg/kg, po) with a duration of effect which was >24 h.[140−142] In 2-kidney, 1-clip hypertensive (2K1C) rats, YM358 (1−30 mg/kg, po) produced a dose-dependent decrease in BP with a duration of >10 h. In 1-kidney, 1-clip hypertensive (1K1C) rats, YM358 (dosed at 30 mg/kg, po) caused a long-acting antihypertensive effect with normal PRA levels.[143] In furosemide-treated dogs, YM358 (10 and 30 mg/kg, po) decreased mean blood pressure dose-dependently, with a duration of action >8 h.[142]

The potent antagonist SR 47436 (AT_1 IC_{50} = 1.3 nM, rat liver) reported by Sanofi incorporates an imidazolinone ring in which a carbonyl group functions as a hydrogen bond acceptor in place of the C5 hydroxymethyl group of losartan.[144,145] This 4-spirocyclopentaneimidazolin-5-one is currently in phase III clinical trials and is being developed by Bristol Myers Squibb and Sanofi/Sterling (irbesartan, SR 474361/BMS-186295). In isolated rabbit aorta, the compound inhibited Ang II-induced contractions (IC_{50} = 4 nM). SR 47436 and losartan blocked the Ang II-induced proliferation of human aortic smooth muscle cells in a dose-dependent manner (IC_{50} = 0.32 μM, 0.71 μM for losartan) and hence may have beneficial effects in the development and regression of vascular hypertrophy.[146] In conscious rats, SR 47436 antagonized the pressor response to Ang

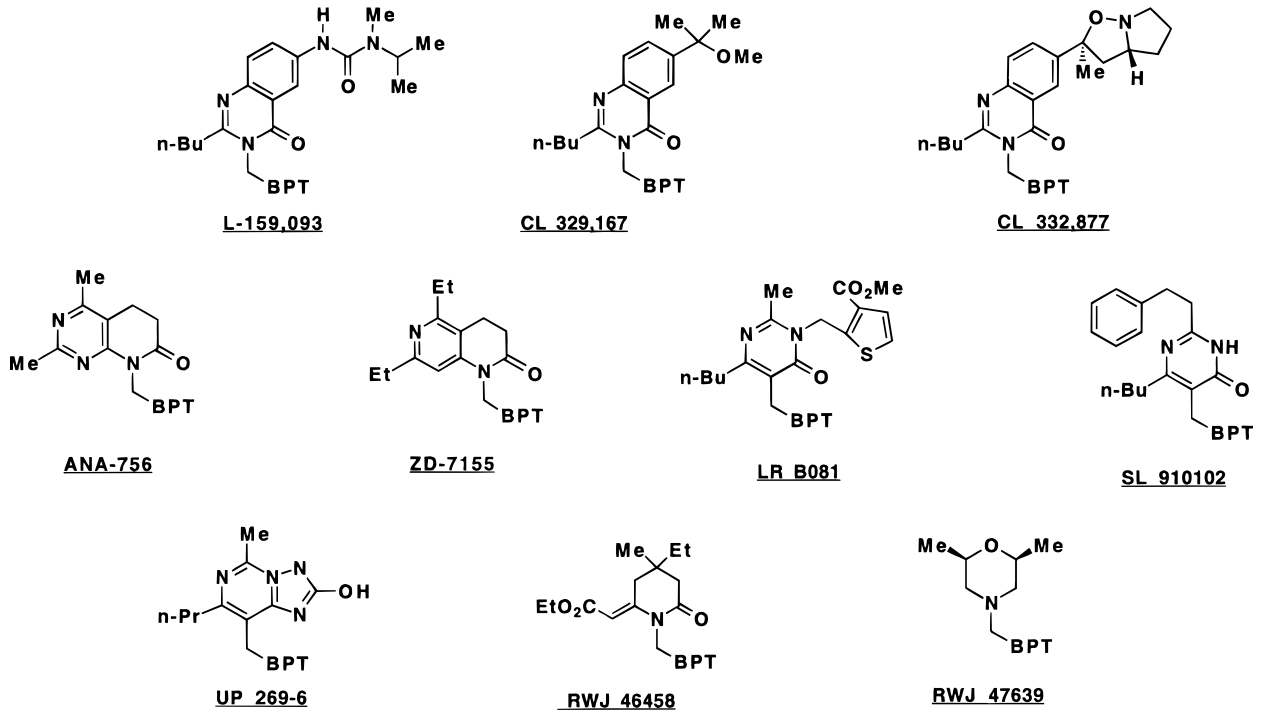


Figure 8. Six-membered ring antagonists.

II in a dose-dependent manner (0.1−3 mg/kg, iv, and 0.3−30 mg/kg, po). At these same dosages, DuP 753 produced equivalent inhibition; however, the maximal effect was delayed (3 h vs 15 min for SR 47436). SR 47436 blocks the pressor response to Ang II in cynomolgus monkeys after oral administration at a dose 10 times less than that required of losartan to give a similar response; SR 47436 dosed at 1 mg/kg antagonized the Ang II-induced hypertension by 89% after intravenous administration and 66% after oral administration. Under similar conditions, losartan dosed at 10 mg/kg antagonized hypertension by 83% when administered intravenously and 20% when administered orally.[145] However, losartan is not efficiently metabolized to EXP3174 in cynomolgus monkeys.[145] In conscious cynomolgus monkeys, a 10 mg/kg, po, dose of SR 47436 showed a maximal decrease in MABP of 20 mmHg (1−6 h postdose) but still showed a 12 mmHg decrease after 28 h ($t_{1/2}$ is ca. 20 h).[147]

3. 5. Six-Membered Ring Antagonists. Potent antagonists have also been obtained by replacing the imidazole of losartan with six-membered ring and fused six-membered ring heterocycles. The quinazolinone ring system has the same 1,3-arrangement of nitrogens found in losartan and can accommodate the requisite lipophilic side chain at position 2. Additionally the carbonyl of the quinazolinone can serve as a mimic of the hydroxymethyl group of losartan. Hence quinazolinones have proven to be a rich source of exceptionally potent Ang II antagonists. Quinazolinone antagonists have been disclosed by MRL, Lederle, Ciba, and Takeda. Early work by the Merck group showed the 6-position of the benzo ring to be a favorable attachment point for a variety of potency-enhancing substituents. An example is the potent urea analog L-159,093 (AT_1 IC_{50} = 0.1 nM, rabbit aorta).[148] In conscious rats, L-159,093 at 1 mg/kg, po, produced 84% peak inhibition of the Ang II pressor response, with a duration of >5 h. The quinazolinone work at Lederle Laboratories resulted in CL 329,167 (AT_1 IC_{50} = 6 nM) which is reported to be in phase II clinical trials.[149,150] CL 329,167 is a competitive antagonist with a pA_2 of 8.01 in rabbit aortic rings. In RHR, CL 329,167 dosed orally (5 mg/kg) produced a decrease of 65 mmHg in MABP and the antihypertensive effect was sustained for >24 h. More recently, the Lederle group reported on CL 332,877, an isoxazolidinyl-substituted quinazolinone, which is a potent, long-acting, noncompetitive antagonist (apparent pA_2 = 10.9).[151] However, synthetic difficulties and the need to develop a synthesis to the enantiomers of CL 332,877, both of which were subsequently achieved, presented barriers to the timely development of the compound.

Wyeth Ayerst's ANA-756[152,153] (tasosartan, AT_1 IC_{50} = 5.2 nM, rat liver) is a competitive antagonist[154] (pA_2 = 8.4, rabbit aorta). In RHR, ANA-756 at 1 mg/kg, po, was at least as effective as 30 mg/kg losartan in lowering blood pressure and had a duration of action >24 h.[154] In conscious Goldblatt hypertensive rats, ANA-756 caused a dose-related decrease in MABP for 24 h with an ED_{60} value of 0.58 mg/kg, po. In SHR, ANA-756 dosed at 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.[155] ANA-756 is currently in phase III clinical trials. Zeneca's ZD-7155[156] (AT_1 IC_{50} = 3.8 nM, guinea pig adrenal) is closely related in structure to ANA-756. When administered intravenously to conscious rats, ZD-7155 inhibited AII-induced pressor response with an ED_{50} value of 0.19 mg/kg. In RHR, a dose of 3 mg/kg, po, of ZD-7155 lowered blood pressure for up to 24 h.[157]

Two C-linked pyrimidinone Ang II antagonists have recently entered clinical trials. LR B081 (Lusofarmaco),[158] the lead compound in a series of N3 heteroaryl-

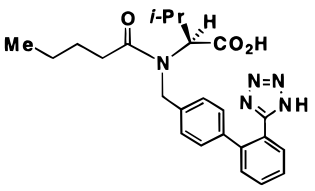
substituted pyrimidinones (K_i = 0.9 nM; pk_b = 9.5, rabbit aorta) is reported to be in phase II clinical trials. LR B081 is an insurmountable antagonist which shows long-lasting antihypertensive activity when dosed orally in RHR and SHR.[159] Synthelabo is reported to be in phase I clinical trials in Europe with SL 910102.[160,161] SL 910102 antagonized angiotensin-induced pressor effects in anesthetized rats and lowered BP after chronic administration in SHR.

Carbon-linked triazolopyrimidine UP 269-6 (UPSA), a selective AT_1 antagonist (AT_1 K_i = 24 nM),[162] has entered phase II clinical trials. UP 269-6 inhibited Ang II-induced contraction of isolated rabbit aortic strips in an insurmountable manner (K_B = 0.29 nM).[163] On the basis of the calculated K_B values, UP 269-6 (0.29 nM) was as potent as L-158,809 (0.28 nM) and considerably more potent than losartan (22 nM). Oral administration of UP 269-6 (0.1−30 mk/kg) resulted in a dose-dependent and long-lasting inhibition of the Ang II-induced pressor response in conscious normotensive rats and dogs. Both UP 269-6 and losartan (1 and 3 mg/kg) when given orally to hypertensive renal artery-ligated rats produced a similar sustained antihypertensive effect lasting for at least 16 h (decrease of 40, 65, 30, and 60 mmHg, respectively), but UP 269-6 exhibited a more rapid onset than losartan.[164] In conscious furosemide-pretreated dogs, UP 269-6 at 1 and 10 mg/kg, po, maximally decreased MABP by 30 mmHg at both doses.[163]

Other six-membered ring heterocycles reported recently include piperidinone RWJ 46458 in which the heterocycle bears an acrylic ester moiety in place of the butyl group of losartan[165,166] and morpholine derivative RWJ 47639.[167] RWJ 46458 (Johnson & Johnson) shows modest *in vitro* activity (AT_1 IC_{50} = 250 nM, bovine adrenal) but is a potent insurmountable antagonist (pA_2 = 9.0, rabbit aorta) in the functional assay.[165,166] In SHR, dosed at 30 mg/kg, po, RWJ 46458 produced a maximum antihypertensive effect similar to that of losartan, with a duration of action which exceeds 24 h. While RWJ 47639 had a pA_2 value of only 6.9, it is active in SHR at 10 and 30 mg/kg, po, and shows a rapid onset of action with a duration of action >12 h.[167]

3. 6. Acyclic Imidazole Replacements. Ciba has disclosed novel nonheterocyclic antagonists in which the imidazole of losartan is replaced with an acylated amino acid.[168] Valsartan (CGP 48933), a diacidic compound like EXP3174 (active metabolite of losartan), was selected from this series and is currently undergoing clinical evaluation (phase II trials). CGP 48933 is a potent selective AT_1 antagonist *in vitro* (IC_{50} = 2.7 nM, rat aorta; IC_{50} = 1.4 nM, rabbit aorta contraction).[168−170] In RHR after single oral dosing (3 and 10 mg/kg) of CGP 48933, systolic blood pressure (SBP) decreased dose-dependently. The maximum effect was achieved 2−4 h after dosing, and the antihypertensive effect lasted for 24 h.[169,170] In sodium-depleted marmosets, blood pressure was reduced at doses of 0.3, 1.0, and 3.0 mg/kg, po, for >6 h.[170] In this model, CGP 48933 (10 mg/kg/day) lowered BP by 25 mmHg, and blood pressure remained down over the 8 days of treatment.

3. 7. Biphenyl Modifications. 3. 7. 1. Heteroatom-Linked Biphenyl. A number of novel heterocyclic designs have been reported in which a biphenyl substituent is linked to the heterocycle through an oxymethylene or aminomethylene linker rather than having a biphenylmethyl moiety directly attached to a nitrogen or carbon atom on the heterocyclic ring. These antagonists achieve high binding potency despite the fact that their novel linking elements may result in different orientations of the biphenyl acid relative to the plane of the heterocycle. The potent quinoline ZD-8731,[171,172] the related tetrahydroquinoline ZD-6888,[173] and the pyridine[174] and naphthyridines[173,175] reported by the Zeneca group make use of the oxymethylene linker connecting the heterocycle to the biphenyltetrazole. ZD-8731 is a competitive antagonist of Ang II which has moderate *in vitro* potency (AT_1 IC_{50} = 30 nM, guinea pig adrenal; pA_2 = 8.3, rabbit aorta contraction).[171,172] When dosed orally at 5 mg/kg, ZD-8731 reduced Ang II-induced hypertension in conscious rats by 70% at 1 h and 50% at 5 h after dosing. In this model the effectiveness of the compound was maintained when given once daily at 5 mg/kg/day for 10 days.[171] ZD-6888 with greater binding affinity and *in vitro* potency (AT_1 IC_{50} = 5 nM, guinea pig adrenal; pA_2 = 10.3, rabbit aorta contraction) but similar oral efficacy in renal hypertensive rats was also placed in clinical development.[173,174]



CGP-48933 (Valsartan)

Figure 9. Acyclic imidazole replacements.

A closely related pyridine derivative, ME 3221 (Meiji Seika), a competitive AT_1-selective antagonist (AT_1 pK_i = 8.7, rat liver; pA_2 = 8.82, rabbit aorta), is reported to be in phase II clinical trials.[176,177] ME 3221 given po or iv dose-dependently inhibited the pressor response to Ang II in conscious normotensive rats and marmosets.[178] ME 3221 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 BP in DOCA salt rats and normotensive rats. ME 3221 was found to be a more potent antihypertensive than losartan and enalapril when evaluated orally in aged stroke-prone SHR (SHRSP).[179]

Abbott has successfully employed an aminomethylene linker to connect substituted pyrimidines and pyridines to the biphenyltetrazole. The most potent of these is aminopyridine A-81988[180] (AT_1 K_i = 0.76 nM, rat liver; pA_2 = 10.1−10.7, rabbit aorta) in which it appears that the *N*-propyl substituent plays the role of the imidazole 2-substituent in losartan and the carboxylic acid substituent mimics that of EXP3174.[180−182] A-81988 was found to be a surmountable antagonist despite its diacidic nature. In conscious RHR, A-81988 lowered MABP after oral administration (0.3 mg/kg), with a duration of action exceeding 24 h.[183] Furosemide-treated SHR (0.1 mg/kg, po) and untreated SHR (3 mg/kg, po) also showed significant BP reduction.[184] Once daily dosing with A-81988 in SHR (3 mg/kg, po) caused regression of ventricular hypertrophy in addition to reduction of blood pressure.[185] Surprisingly, in spite of the diacidic nature of the compound, A-81988 showed

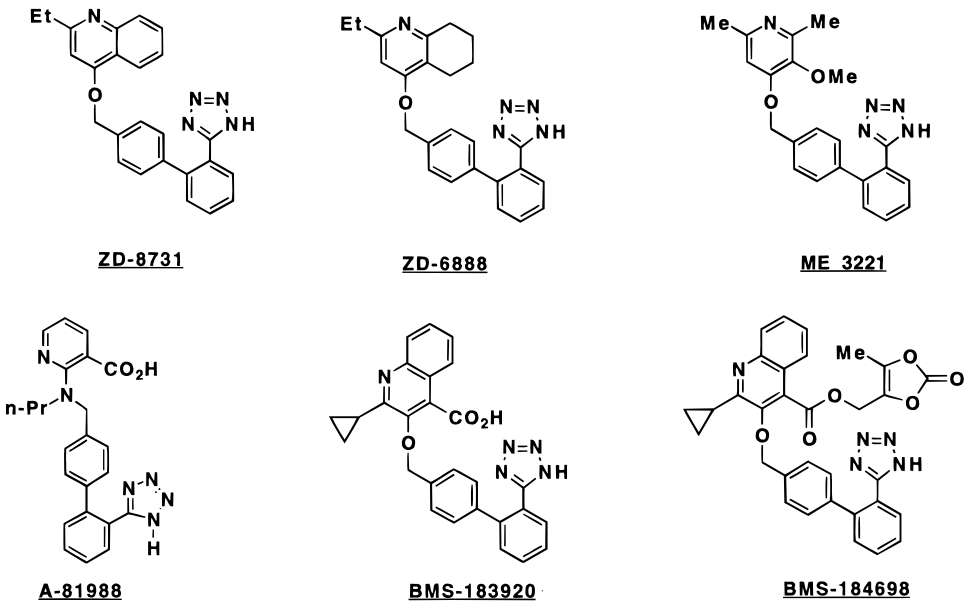


Figure 10. Heteroatom-linked biphenyl antagonists.

high oral bioavailability (>50%) after oral administration to rats, dogs and cynomolgus monkeys.[184]

BMS-183920 (Bristol-Myers Squibb), a quinoline-4-carboxylic acid, contains an oxymethylene as an isosteric replacement for the methylene bridging the biphenyl moiety and the heterocycle. BMS-183920 has a K_i value of 2.9 nM in the rat adrenal cortex binding assay and a K_B value of 0.061 nM in the rabbit aorta functional assay (insurmountable antagonist).[186] While it is more potent than losartan in blocking the pressor response to Ang II challenge in the normotensive rat, as a diacid, perhaps it is not surprising that the oral activity and bioavailability were more moderate. BMS-184698, a dioxolenone ester was put forward to overcome this deficiency.[187] BMS-184698 dosed at 30 μmol/kg, po, to SHR once daily for 7 days reduced blood pressure to a greater extent than losartan at the same dose. BMS-184698 has an oral bioavailability of 27% in rats compared to 11% for BMS-183920, the parent compound.

3. 7. 2. Heterocyclic Replacement of "Spacer" Phenyl Ring. The number of antagonists in development that do not contain the biphenyl fragment of losartan has been more limited. In early work leading up to the discovery of losartan, a number of designs were explored in which the phenyl rings were connected by one-atom (-O-, -S-, -CO-), two-atom (-NHCO-, -CONH-, -OCH_2-), and three-atom (-NHCONH-) linkages. However, the biphenyl design was unique in providing compounds (EXP7711, losartan) with oral activity. Recently, the "spacer" phenyl ring has been replaced by several fused ring heterocycles, including indoles, benzothiophenes, and benzofurans.[188] The corresponding indoles and benzothiophenes are comparable in potency *(in vitro)* to the benzofurans, but are less active *in vivo*. In GR117289 (zolarsartan), Glaxo Wellcome's first clinical candidate, the "spacer" phenyl ring of EXP3174 is replaced by a bromobenzofuran. In this compound, as well as the subsequent benzofurans, the 3-bromo substituent is essential for high potency and has been correlated with increased inductive electron-withdrawing strength. In contrast to the biphenyl series, GR117289 and its corresponding 2′-carboxyphenyl analog are equipotent. GR117289 is a potent and slowly reversible competitor for the AT_1 binding sites in the rat liver in competition binding studies using [^{125}I]Sar^1-Ile^8-Ang II (pK_i = 9.0).[189,190] In a functional assay (rabbit aorta), GR117289 causes insurmountable suppression of the Ang II-induced contraction with a pK_B of 9.8. In normotensive rats, dogs, and marmosets, GR 117289 (3 mg/kg, po) blocked the Ang II pressor response for up to 24 h.[191] In renal artery-ligated hypertensive rats, GR117289 (0.3−3 mg/kg, ia, or 0.3−10 mg/kg, po) caused dose-dependent, long-lasting decreases in diastolic blood pressure with minimal effects on heart rate. A single oral dose of 10 mg/kg, po, GR 117289 normalized blood pressure for more than 24 h.[191]

GR138950, Glaxo Wellcome's second clinical candidate, resulted from a strategy aimed at enhancing the bioavailability of bromobenzofuran diacid GR117289.[192] The proposal was that a monoacid would be better absorbed after oral administration and have enhanced oral bioavailability. Toward this end, the imidazole-carboxylic acid was replaced by a neutral imidazole-5-carboxamide. This was combined with replacement of the tetrazole with a triflamide, which the Glaxo Wellcome group had previously found to provide better absorption than the tetrazole.[193] GR138950 has high affinity for AT_1 binding sites (pK_i = 9.3, rat liver) and is a potent antagonist of Ang II-induced contractions (pK_B is ca. 9.0, rabbit aorta). This compound when dosed at 1 mg/kg, po, to RHR showed a significant decrease in diastolic blood pressure which lasted for >7 h. Good oral bioavailability was observed in rats and dogs (79% in rats compared to 3% for GR117289 and complete absorption in dogs), confirming that it is well absorbed after oral administration. Additionally, plasma clearance was low in both rats and dogs. Preliminary data from clinical studies indicate that the high bioavailability of GR138950 in rats and dogs also translates to man.[192]

Following the strategy of preparing monoacidic compounds to enhance oral absorption led to the replacement of the imidazole ring with the 5,7-dimethylimidazopyridine employed in the Merck compound L-158,809. This resulted in a potent benzofuran (pK_B

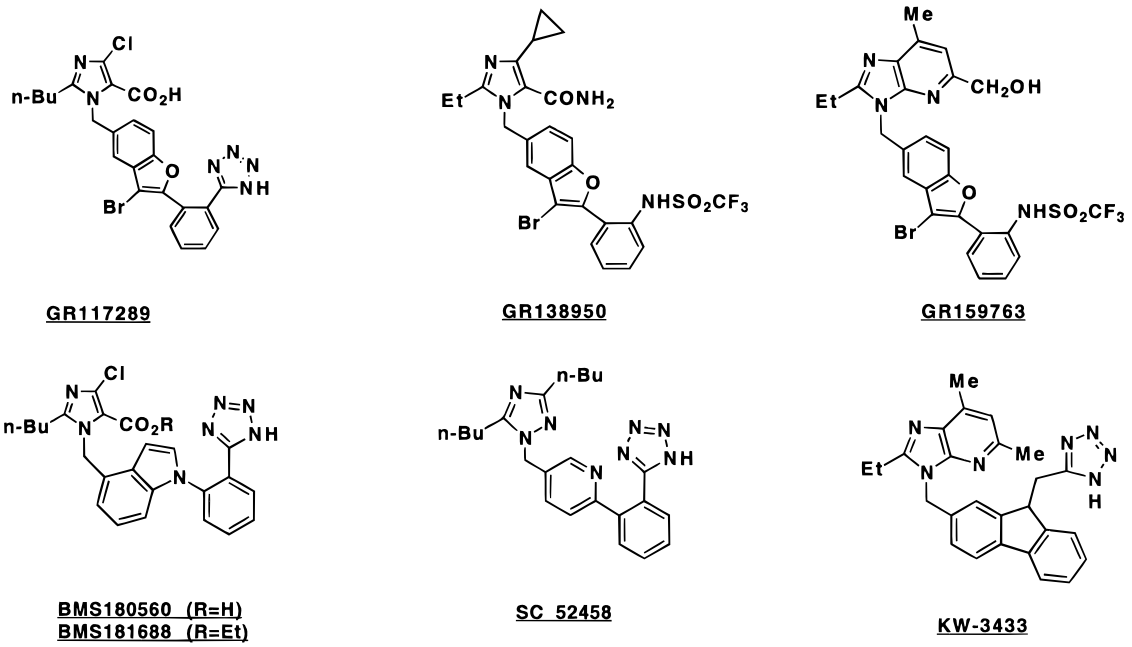


Figure 11. Antagonists with a heterocycle replacing the "spacer" phenyl ring.

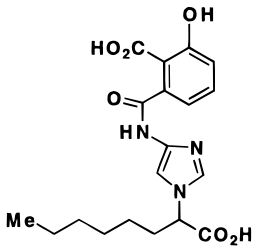
= 9.3, rabbit aorta) with a duration of action of >50 h when dosed orally at 1 mg/kg in renal artery-ligated hypertensive rats.[194] Oral bioavailability in rats was 70%, and plasma clearance was low. Evaluation of the metabolites of this compound resulted in the preparation of the 5-hydroxymethyl derivative GR159763 (pK_B = 8.6, rabbit aorta).[194,195] This compound when dosed at 1 mg/kg, po, to RHR showed a significant decrease in blood pressure which lasted for more than 24 h. HPLC analysis showed that GR159763 was not metabolized to the corresponding 5-carboxylic acid in contrast to losartan. Pharmacokinetic studies showed GR159763 to have excellent bioavailability in the rat and a low value for plasma clearance which is indicative of high metabolic stability.[195]

A closely related compound to GR117289 is BMS-180560 in which the "spacer" phenyl ring has been replaced by an indole ring. BMS-180560 is a potent, selective, insurmountable antagonist of Ang II (AT_1 K_i = 0.8 nM, rat adrenal; K_B = 0.068 nM, rabbit aorta functional assay).[188,196] BMS-180560 antagonizes the pressor response to Ang II in conscious Sprague–Dawley rats following iv administration (ED_{50} = 0.22 μM/kg). The ethyl ester prodrug BMS-181688 caused a sustained drop in blood pressure after oral administration (10 μM/kg), more effective than the parent at the same dose, and the duration of action exceeded 72 h.[196]

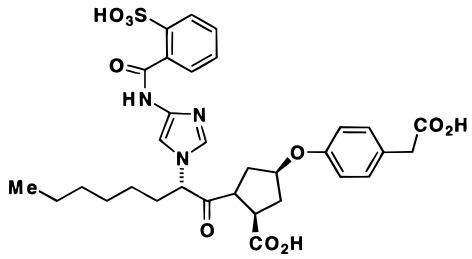
Another compound in which the "spacer" phenyl ring is replaced by a heterocycle is SC-52458 (Searle),[197] a 1,2,4-triazole in which a pyridine replaced the inner phenyl ring and which is currently in phase II trials. *In vitro*, SC 52458 inhibited binding of Ang II to the AT_1 receptor with an IC_{50} value of 2.8 nM (rat adrenal), and in rabbit aortic rings it competitively and reversibly inhibited Ang II-induced contractions (pA_2 = 8.18).[197,198] Treatment of conscious sodium-deficient dogs with 10, 30, and 50 mg/kg, po, caused a dose-dependent reduction in blood pressure.[199] Daily treatment with SC-52458 at 20, 30, and 50 mg/kg either intravenously or by gavage for 4 days decreased BP in conscious SHR.[198] In conscious dogs, 30 mg/kg, po, blocked the pressor response to Ang II with maximal inhibition (91%) at 2 h, and the effects persisted for 24 h.[199]

In Kyowa Hakko's KW-3433 (AT_1 IC_{50} = 11 nM, bovine adrenal), which bears the imidazopyridine head group contained in L-158,809, the biphenyl side chain is replaced by a tricyclic system on which the tetrazole has been repositioned so that it is pendant to the central ring. KW-3433 is a competitive antagonist (pA_2 = 9.2, rabbit aorta).[200,201] In conscious rats (3 mg/kg, po), KW-3433 blocked the Ang II pressor response (73% peak inhibition) with a duration of action of >7 h. KW-3433 when dosed to RHR and SHR (1–10 mg/kg, po) dose-dependently reduced blood pressure with a duration of action >10 h.[201]

3. 8. (Benzoylamino)imidazoles. Lilly has disclosed a series of compounds with an entirely new structure. LY235656 is reported to bind to rat adrenal with a K_i = 4.4 μM. LY235656 inhibits Ang II-induced contraction of rabbit aortic strips with a K_B = 0.078 μM (pA_2 = 7.1) and inhibited the pressure response to Ang II in pithed rats (10 mg/kg iv, 1 h).[202,203] Additional (benzoylamino)imidazole compounds were prepared to try to improve the potency and bioavailability. LY301875[38,204,205] noncompetitively inhibited the Ang II-induced contraction of isolated rabbit aorta with a pK_B value of 9.1–9.9, compared to losartan which had a pK_B value of 8.2 in this assay. In SHR, LY301875 (10 mg/kg, po) was shown to lower BP for up to 24 h, which is somewhat surprising due to the triacidic nature of the compound.[205] On the basis of molecular modeling, the Lilly group has proposed a structural overlay of LY301875 with losartan in which the alkyl chain, proline carboxylic acid, and sulfonic acid are aligned with the butyl group, hydroxyl methyl group, and tetrazole, respectively. The (carboxymethyl)phenoxy group of LY301875 stereospecifically accesses a receptor binding site which is not reached by losartan.[206]



LY235656



LY301875

Figure 12. (Benzoylamino)imidazoles.

4. AT_2-Selective Antagonists

Ligands which bind to the AT_2 receptor have been reviewed.[40,207] Peptides which show high selectivity for binding to the AT_2 receptor include CGP-42112A (AT_2 IC_{50} = 0.5 nM; AT_1 IC_{50} = 3 μM)[22] and [*p*-NH_2Phe]^6-Ang II (AT_2 IC_{50} = 12 nM; AT_1 IC_{50} = 8.6 μM).[208] A radioiodinated analog of CGP-42112A has been developed as a potent radioligand for the AT_2 receptor.[209] The first nonpeptide AT_2-selective ligands were a series of tetrahydroimidazopyridines, including PD-123,177 (AT_2 IC_{50} = 66 nM), PD-121,981 (WL-19) (AT_2 IC_{50} = 70 nM), and PD-123,319 (AT_2 IC_{50} = 34 nM).[20] These selective ligands (all have AT_1 IC_{50} > 100 μM) have been important tools for defining Ang II receptor subtypes in tissues from various species, including man.[210] Radioiodinated, fluorescent, and biotinylated analogs of PD-123,319 with high affinity for the AT_2 receptor have been reported.[211]

A series of potent AT_2-selective diacylpiperazines has been reported of which L-162,686 (AT_2 IC_{50} = 1.5 nM; AT_1 IC_{50} >100 μM) has the best potency and selectivity for the AT_2 receptor. This ligand has high aqueous solubility as the potassium salt and promising oral bioavailability (50%) and plasma half-life (>6 h) in rats.[212] Potent tetrahydroisoquinolines with high AT_2 selectivity have been reported, including PD-126,055 (AT_2 IC_{50} = 0.6 nM; AT_1 IC_{50} >100 μM)[213] and EXP801 (AT_2 IC_{50} = 30 nM; AT_1 IC_{50} >10 μM).[214] Substituted quinazolinones, developed as AT_1-selective[148,215] and dual (AT_1/AT_2) antagonists (section 5), have been modified to give potent AT_2-selective ligands such as L-162,-638 (AT_2 IC_{50} = 0.06 nM; AT_1 IC_{50} = 200 nM).[216] This quinazolinone has good oral bioavailability (53%) and plasma half-life in rats ($t_{1/2}$ = 3 h), increasing its potential usefulness as a pharmacological tool for determination of possible roles for the AT_2 receptor. Benzolactams have also been disclosed[217] which are claimed as AT_2-selective binding inhibitors.

5. Balanced Angiotensin II Antagonists

The potential role of the AT_2 receptor in mediating important *in vivo* functional responses to Ang II has resulted in efforts to design antagonists which are highly potent in blocking both AT_1 and AT_2 receptors ("balanced antagonists"). The possibility exists that such an antagonist might be more effective than an AT_1-selective antagonist in the treatment of hypertension, especially if AT_2 receptors were important in preventing long-term growth responses to Ang II (e.g., vascular hypertrophy, cardiac fibrosis). However, to date, it has been exceeding difficult to clearly define a pathophysiological role of this receptor. Nonetheless, concern has arisen that the increase in Ang II levels (up to 10-fold) seen during treatment of healthy human subjects with losartan[218] could result in unanticipated responses. Blockade of both receptors might more closely mimic the effects of an ACE inhibitor. Due to the lack of a direct pharmacological readout of an AT_2-mediated effect *in vivo*, studies directed toward mixed AT_1/AT_2 antagonists to date have focused on compounds with approximately equal affinity at the two receptor subtypes. Raising the dose of an antagonist with higher affinity for AT_1 in order to block AT_2 receptors is not feasible due to the potential for hypotension to result.

The existence of nonpeptidic receptor antagonists which are selective for either the AT_1 or AT_2 subtypes has provided an opportunity for medicinal chemists to create hybrid structures with dual activity. Surprisingly, only a modest effort has been reported in this area to date, despite the structural similarity between AT_2 ligands such as PD-123,319 and AT_1 antagonists like losartan. The hybrid structure L-162,132 (AT_1 IC_{50} = 15 nM; AT_2 IC_{50} = 180 nM), which incorporates elements of the AT_2-selective ligand L-159,686 (section 4) and losartan, has modest binding affinity for both receptors and blocks Ang II pressor response in rats (80% inhibition at 3 mg/kg, po).[219] Interestingly, the related hybrid structure **1** has only AT_1 affinity, while its desbutyl analog **2** is AT_2-selective.[220]

The second approach to balanced antagonists has been to modify AT_1-selective antagonists to enhance their AT_2 receptor binding potency. This approach appears to be that which led to the discovery of 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 reported to have modest binding affinity for both AT_1 and AT_2 receptors.[121] Both antagonists lower blood pressure in renal hypertensive rats (ED_{30} ~ 2 mg/kg, iv), similar in potency to losartan.[221] The benzimidazole antagonists demonstrated for the first time that addition of appropriate substituents to the heterocycle of an AT_1-selective antagonist series could yield balanced antagonist leads. A related study in which substituents were incorporated into imidazopyridine antagonists resulted in analogs such as **3** (AT_1 IC_{50} = 0.6 nM; AT_2 IC_{50} = 140 nM) with substantially increased AT_2 affinity.[222] A series of imidazoles incorporating a variety of 4-substituents yielded near-balanced antagonists such as XH148 (AT_1 IC_{50} = 4.2 nM; AT_2 IC_{50} = 60 nM).[223] An imidazopyridinone analog, **4** (AT_1 IC_{50} = 5.7 nM; AT_2 IC_{50} = 300 nM), reported recently also incorporates a heterocyclic substituent.[224]

Quinazolinone biphenyltetrazoles developed as AT_1-selective antagonists[148,215] showed modest AT_2 receptor

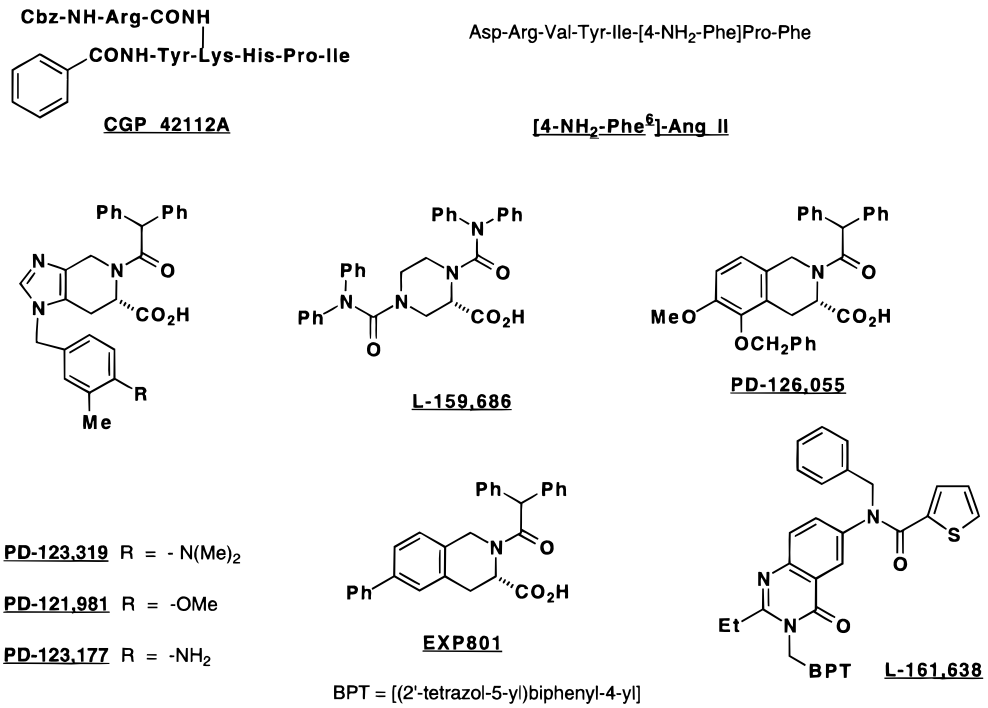


Figure 13. AT_2-selective Ang II binding inhibitors.

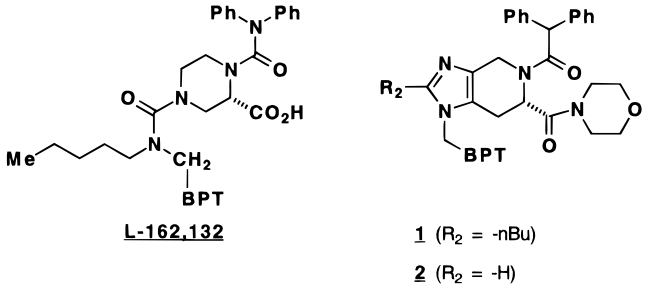


Figure 14. Hybrid Ang II antagonists.

affinity when a carbamate substituent is present at the C6 position of the quinazolinone, as in **5** (AT_1 IC_{50} = 2.5 nM; AT_2 IC_{50} = 2.2 μM).[225] Shortening the quinazolinone 2-substituent from *n*-butyl to *n*-propyl and incorporation of an *N*-alkylcarbamate or -amide substituent at C6 resulted in the first potent, balanced Ang II antagonists, including L-159,689 (AT_1 IC_{50} = 1.7 nM; AT_2 IC_{50} = 0.7 nM). This antagonist showed blockade of Ang II pressor response in conscious rats for >6 h after oral administration (3 mg/kg).[225] Although there was no direct pharmacological readout of an AT_2 effect *in vivo*, radioligand assays of plasma samples withdrawn from rats dosed with L-159,689 indicated that equivalence of AT_1 and AT_2 binding was maintained for >8 h. Although L-159,689 showed an excellent *in vivo* profile in rats, no oral activity was demonstrated in dogs, possibly due to rapid *in vivo* glucuronidation of the tetrazole moiety in this species.[226] Quinazolinones with high selectivity for the AT_2 receptor have also been reported (section 4). Several additional types of modifications of AT_1-selective antagonists have yielded series with enhanced AT_2 binding affinity. These include replacement of the tetrazole with sulfonamide-based acidic groups, addition of appropriate substituents to the biphenyl moiety, and replacement of the biphenyl with other groups. The use of these modifications, either alone or in combination, to yield potent, balanced Ang II antagonists is described below.

The enhanced AT_2 affinity observed for antagonists such as MK-996 (AT_1 IC_{50} = 0.2 nM; AT_2 IC_{50} = 2.9 μM)[129] and L-159,913 (AT_1 IC_{50} = 0.5 nM; AT_2 IC_{50} = 450 nM)[226] relative to their tetrazole analogs demonstrated that acylsulfonamide groups can enhance AT_2 affinity. That this effect is general is illustrated by the near-balanced activity of the imidazopyridine L-159,894 (AT_1 IC_{50} = 0.05 nM; AT_2 IC_{50} = 18 nM),[227] the quinazolinone L-159,958 (AT_1 IC_{50} = 3 nM; AT_2 IC_{50} = 80 nM),[228] and the triazolinone L-162,234 (AT_1 IC_{50} = 0.45 nM; AT_2 IC_{50} = 17 nM),[229] which were derived from AT_1-selective heterocyclic biphenyltetrazole antagonist series. The imidazole **6** (AT_1 IC_{50} = 1.9 nM; AT_2 IC_{50} = 500 nM)[230] and the related sulfonylurea analog S0029 (AT_1 IC_{50} = 0.3 nM; AT_2 IC_{50} = 775 nM)[231] provide additional examples.

Progress toward truly balanced (non-tetrazole) antagonists was achieved during optimization of the acylsulfonamide group and heterocyclic substituents.[223,232,233] Particularly useful is the sulfonylcarbamate group present in the quinazolinone L-162,393 (AT_1 IC_{50} = 0.24 nM; AT_2 IC_{50} = 2.4 nM).[232] L-162,393 was orally active with a long duration of action in pressor response assays in rats (1 mg/kg), dogs (3 mg/kg), and rhesus monkeys (3 mg/kg). The sulfonylcarbamate group also allowed near-balanced binding potency to be achieved in the imidazopyridine series with L-162,620 (AT_1 IC_{50} = 0.33 nM; AT_2 IC_{50} = 0.94 nM). This antagonist blocked the pressor response to Ang II for more than 6 h in conscious rats (0.3 mg/kg) and dogs (1 mg/kg).[233]

An hypothesis that the acylsulfonamide group and the heterocyclic substituent of antagonists such as L-162,393 lie close to one another in their AT_1 receptor-bound conformation has been put forward on the basis of a conformational model for nonpeptidic AT_1 receptor antagonists.[234] This hypothesis led to the design of macrocyclic antagonists such as **7**, in which these two groups are joined.[235] Interestingly, **7** has high binding

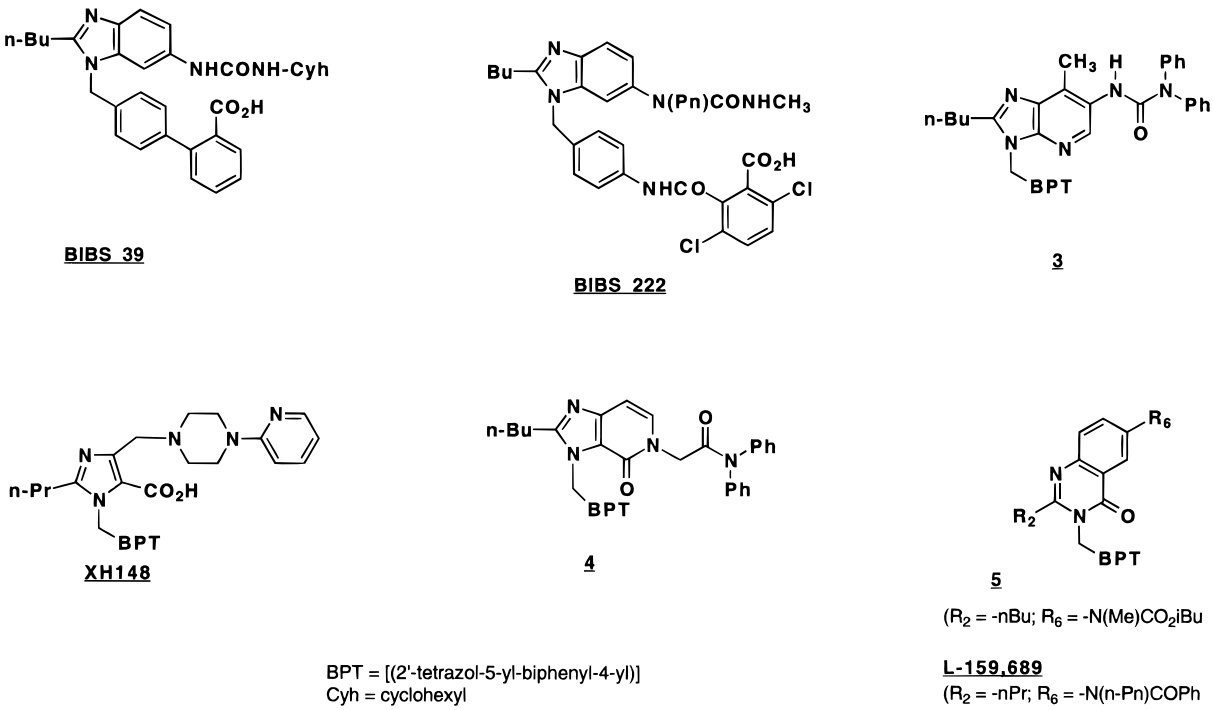


Figure 15. Near-balanced and balanced affinity Ang II antagonists.

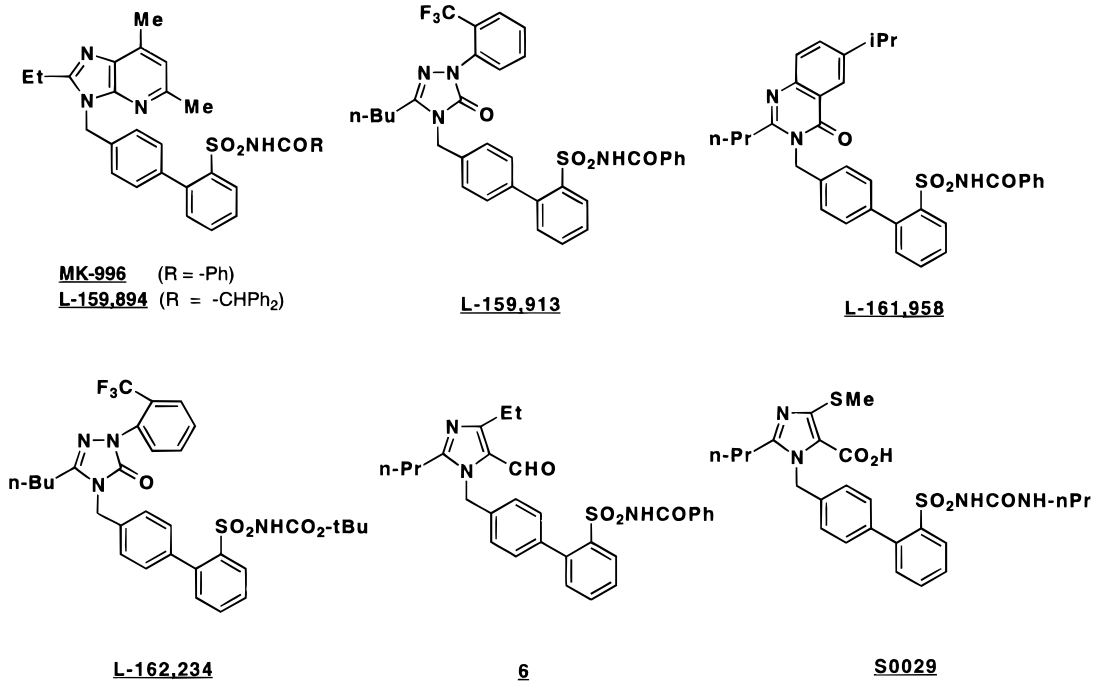


Figure 16. Acidic sulfonamide analogs with AT_1 and AT_2 binding affinity.

affinity for both AT_1 and AT_2 receptors (AT_1 IC_{50} = 4 nM; AT_2 IC_{50} = 24 nM) suggesting that a single conformation (or related conformations) of this antagonist binds to both receptor subtypes.

Incorporation of a biphenyl 5′-alkyl substituent into the potent AT_1-selective antagonist L-158,809[125] led to analogs such as **8** (AT_1 IC_{50} = 0.3 nM; AT_2 IC_{50} = 2 μM) with improved AT_2 receptor affinity.[236] Combining the 5′-substituent with acylsulfonamide groups led to potent, balanced biphenyl analogs such as L-162,389 (AT_1 IC_{50} = 1.5 nM; AT_2 IC_{50} = 6.1 nM).[237] Unexpectedly, *in vivo* AT_1 agonist activity (section 6) has been discovered in this series.[238,239]

A substantial contribution to AT_2 binding potency of biphenyl 2-substituents was revealed when EXP332 (AT_1 IC_{50} = 3 nM; AT_2 IC_{50} = 80 nM), a brominated analog of DuP 532, was found to have substantially enhanced AT_2 receptor affinity.[240] The optimal substituent, a 2-fluoro group, was found to enhance AT_2 affinity by 10-fold or more in the imidazole series. Imidazole antagonists such as EXP970 and EXP408 which incorporate both a sulfonylcarbamate group and a 2-fluoro substituent were found to achieve nanomolar affinities for both the AT_1 and AT_2 receptors.[240,241] Both EXP970 (AT_1 IC_{50} = 1 nM; AT_2 IC_{50} = 3 nM) and EXP408 (AT_1 IC_{50} = 1 nM; AT_2 IC_{50} = 1 nM) were highly effective in lowering blood pressure in the renal hypertensive rats (ED_{30} = 0.48 and 0.67 mg/kg, po; duration of action > 24 h).[241]

Enhanced AT_2 binding potency has also been reported

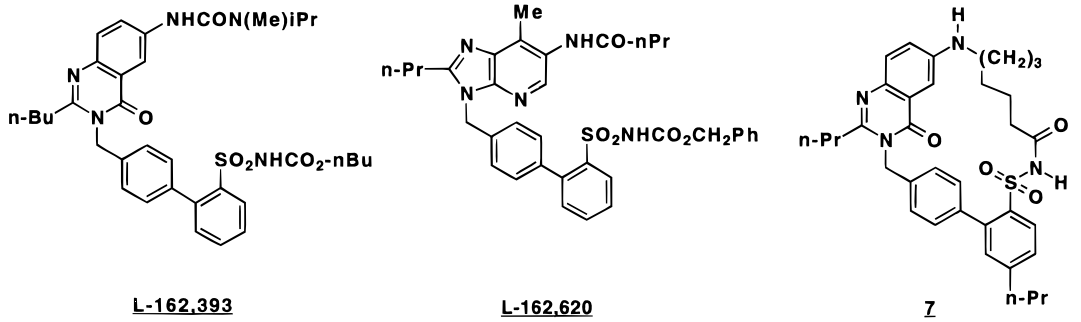


Figure 17. Acidic sulfonylcarbamate analogs with AT_1 and AT_2 binding affinity.

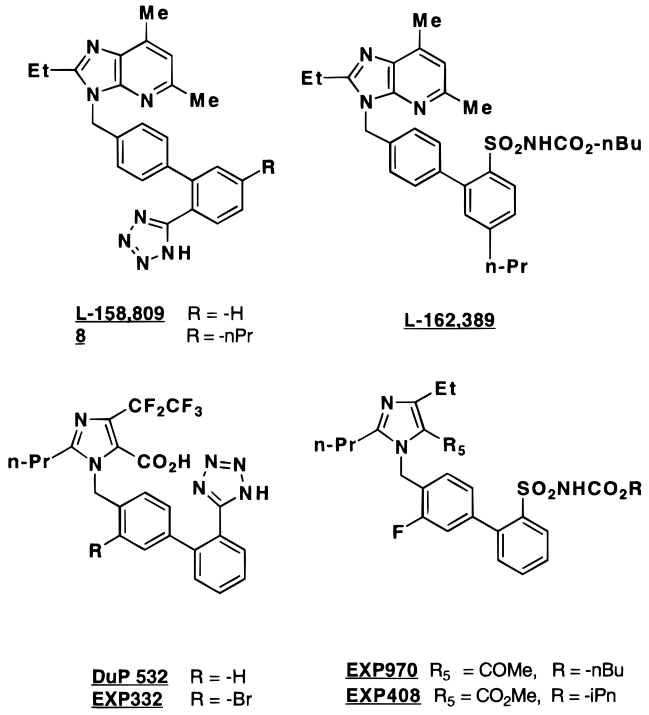


Figure 18. Antagonists incorporating a substituted biphenyl element.

in AT_1-selective antagonist series in which the biphenyltetrazole moiety is replaced by a phenoxyphenylacetic acid (**9**: AT_1 IC_{50} = 19 nM; AT_2 IC_{50} = 240 nM),[242,243] related (phenylamino)phenylacetic acid (**10**: AT_1 IC_{50} = 5.3 nM; AT_2 IC_{50} = 490 nM),[244] or a substituted indole element (**11**: AT_1 IC_{50} = 5 nM; AT_2 IC_{50} = 130 nM).[245]

Optimization of heterocyclic and sulfonylcarbamate substituents has resulted in antagonists from several heterocyclic biphenylsulfonylcarbamate series which show potent and equivalent binding to both AT_1 and AT_2 receptors. The imidazopyridine antagonist L-163,017 (AT_1 IC_{50} = 0.24 nM; AT_2 IC_{50} = 0.29 nM), balanced against rat adrenal receptors, also has balanced affinity in several human tissues, including human aorta, kidney, and adrenal.[246] This antagonist demonstrated a long duration of action in conscious rats (1 mg/kg, po) and dogs (3 mg/kg, po). In aortic coarcted rats, the antihypertensive efficacy of L-163,017 was comparable to that of the ACE inhibitor enalapril. The oral bioavailability of L-163,017 was determined to be 45% in rats and 34% in dogs. Equivalence of AT_1 and AT_2 receptor binding was maintained for >6 h following oral administration to rats or dogs, as determined by radioligand assay of plasma samples.[247] In the imidazole series, placing a large lipophilic ester on the imidazole 5-position resulted in the balanced antagonist EXP597 (AT_1 IC_{50} = 0.57 nM; AT_2 IC_{50} = 0.69 nM).[248] This compound was effective in reducing blood pressure in renal hypertensive rats (ED_{30} = 0.05, iv, and 0.9 mg/kg, po; duration of action > 8 h at 1, 3, and 10 mg/kg).[248,249] Replacement of the ester substituent at C5 of the imidazole with a β-ketoamide moiety resulted in XR510 (AT_1 IC_{50} = 0.26 nM; AT_2 IC_{50} = 0.28 nM).[250,251] The imidazole XR510 showed potent, balanced antagonist potency and potent oral activity in renal hypertensive rats (ED_{30} = 0.27 mg/kg) with a duration of action >24 h.[252] Given orally to furosemide-treated dogs (1 and 3 mg/kg), XR510 decreased blood pressure by ca. 30% with a duration of >8 h. The oral bioavailability of XR510 was determined to be 100% in rats and 25% in dogs. The quinazolinone L-163,579 (AT_1 IC_{50} = 0.57 nM; AT_2 IC_{50} = 0.39 nM) is orally active in rats and dogs (3 mg/kg) with duration exceeding 6 h.[253] Bioavailability was found to be 23% in rats and 17% in dogs. The triazolinone L-163,958 (AT_1 IC_{50} = 0.20 nM; AT_2 IC_{50} = 0.12 nM) also achieves balanced antagonist potency and produces long-lasting blockade of Ang II pressor response in conscious rats (>6 h) after

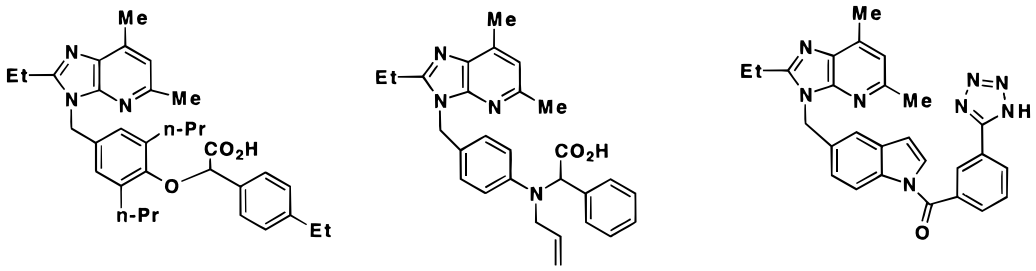


Figure 19. Balanced antagonists with biphenyl replacements.

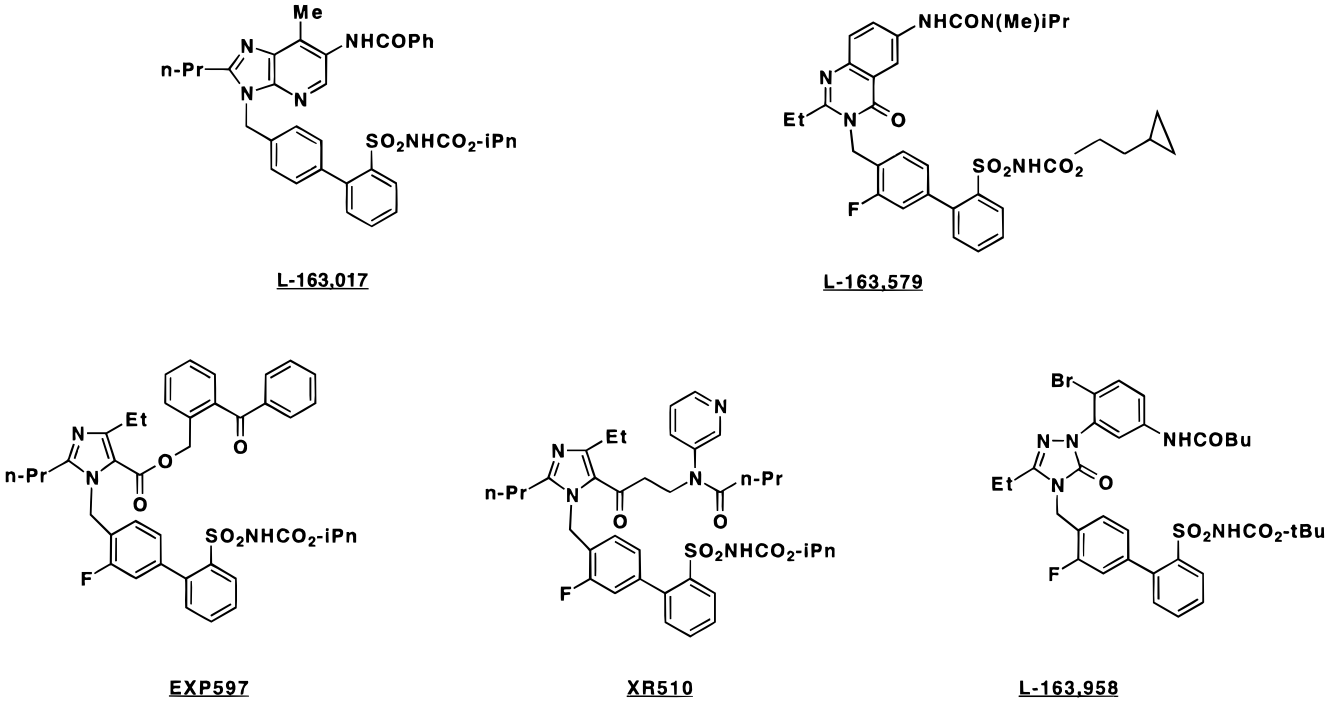


Figure 20. Balanced antagonists.

oral administration (3 mg/kg).[254] The excellent *in vivo* properties of these antagonists make them useful tools for *in vivo* pharmacology studies for determination of potential differences between AT_1-selective and balanced antagonists.

6. Nonpeptidic Angiotensin II Agonists

Recently, the first nonpeptidic angiotensin II AT_1 receptor agonist L-162,313 (AT_1 IC_{50} = 1.1 nM; AT_2 IC_{50} = 2.0 nM) was reported.[238,239] This agonist raises blood pressure to the same extent as Ang II but has prolonged duration of action (>3 h after 1 mg/kg, iv) and is active after oral administration. The action of L-162,313 to raise blood pressure in conscious rats is blocked by the AT_1 antagonist L-158,809 but not by the ACE inhibitor enalaprilat. The structure of L-162,313 is similar to those of AT_1 antagonists such as L-162,389 (section 4), suggesting that subtle interactions with the AT_1 receptor can determine the agonist/antagonist properties of nonpeptidic ligands. Since L-162,313 also has high affinity for AT_2 receptors, it will be interesting to learn whether it may be an agonist of the AT_2 receptor. Recently, a related agonist, L-163,491 (AT_1 IC_{50} = 1.4 nM; AT_2 IC_{50} = 101 nM), with modest selectivity for the AT_1 receptor was reported.[255]

7. Molecular Modeling

The first modeling study in the area of Ang II antagonist design arose from considerations of how to improve the potency of the Takeda 1-benzylimidazole-5-acetic acid derivative S-8307.[17] Using the Fermandjian model of Ang II conformation as a guide for possible receptor contacts, the Takeda derivative was hand-aligned to the peptide.[256] From peptide SAR, the C-terminal segment of Ang II was known to be the critical element in receptor binding, and it was hypothesized that the small molecule mimicked the interactions made by this portion of the peptide via the acetic acid carboxyl group. The nucleus of the superposition

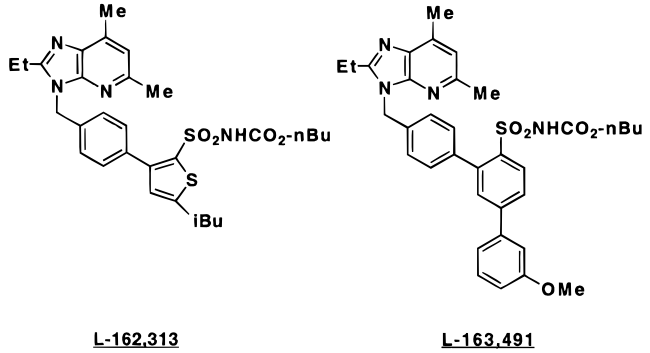


Figure 21. Ang II AT_1 agonists.

was overlap between the imidazole group of S-8307 with His^6 of Ang II. The lipophilic *n*-butyl group at the imidazole 2-position was pointed at the Ile^5 side chain of Ang II (Figure 22, top left). As a result, the benzyl group of S-8307 extended toward the N-terminus of ANG II and suggested that elongation of the compound via functionalization at the para position would enhance potency by building toward the Ang II Tyr^4 site. The exercise resulted in the identification of EXP6155, which was 10-fold more potent than the original lead.[53] This initial success led to an intensive medicinal chemistry effort around EXP6155, ultimately leading to losartan and clearly demonstrating the utility of simple structural models in molecular design.

An alternate hypothesis for the superposition between Ang II and the Takeda benzimidazole antagonists was offered by workers at SK&F. This model also included extensive rationalization of parallels between peptide and nonpeptide SAR to generate an initial guess at the superimposition. Working from the Fermandjian model for the solution conformation of Ang II, the 2-chlorobenzyl substituent of the Takeda lead was positioned to be spatially equivalent to the Tyr^4 position of Ang II. The butyl group aligned with the Ile^5 side chain and the 5-carboxymethyl group was directed toward the C-terminus of Ang II. However, due to the ability to

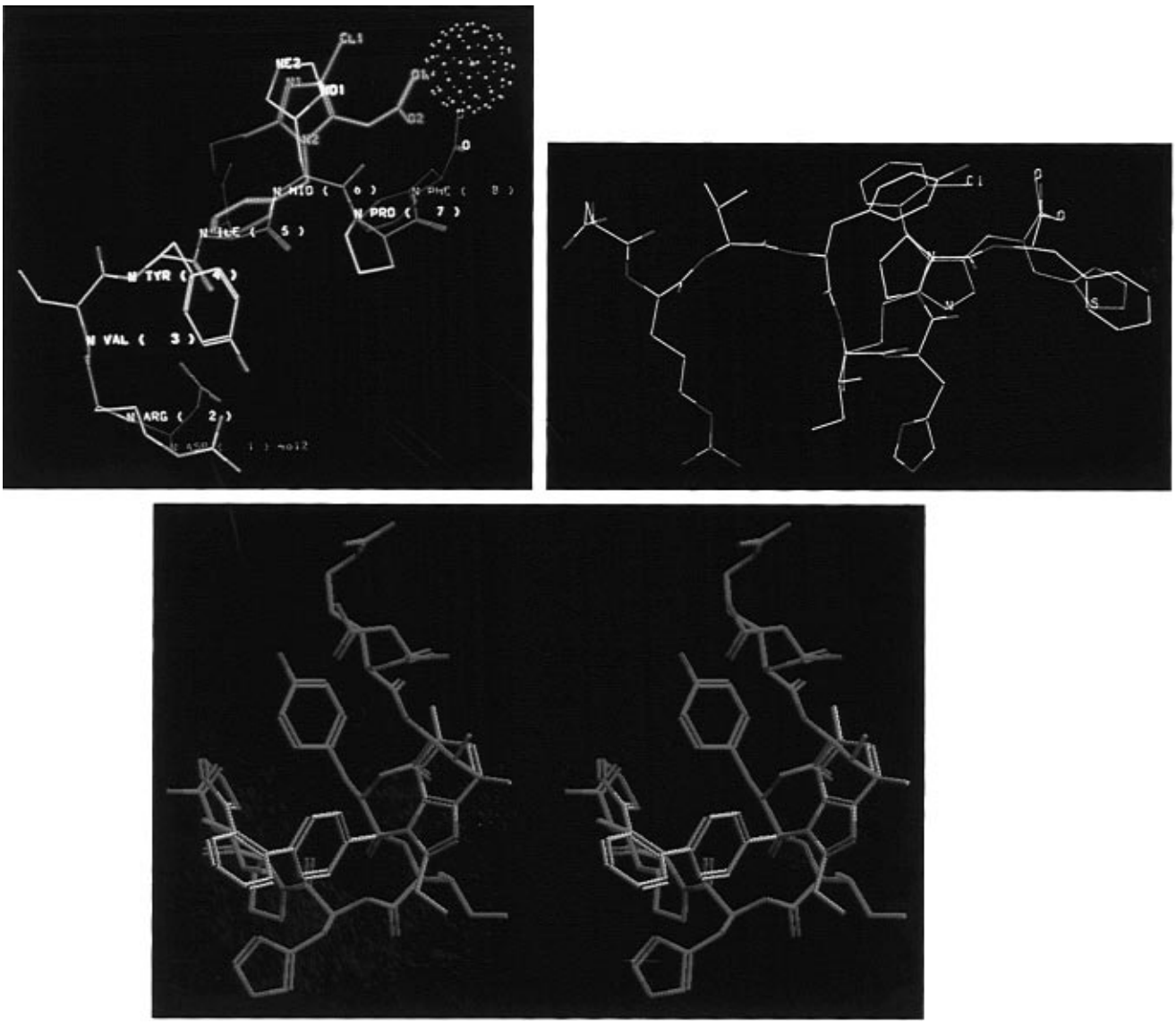


Figure 22. (Top left) DuPont overlay. (Top right) SK&F overlay. (Bottom) Superposition of L-158,809 and IIe[8] Ang II resulting from 3D pharmacophore mapping. The conformation of L-158,809 is described in Figure 23.

add substituents to the imidazole in the Takeda lead, the equivalence between His[6] and the imidazole was not assumed as it had been in the DuPont study. Rather, the imidazole of S-8307 was viewed as a scaffold for correct positioning of pendant groups toward the receptor. This model suggested that an improved mapping to the C-terminus of Ang II could be achieved by refining the presentation of the acid and better filling the binding pocket for the Phe[8] side chain. The end point of extensive medicinal chemistry efforts originating from this model was SK&F 108566 which is 40 000-fold more potent than S-8307 (Figure 22, top right).[36] The fact that two different models for the correspondence between peptides and nonpeptides led in productive directions was fortuitous, since, barring multiple binding modes for the Takeda series, only one mapping can be correct. A refinement of the SK&F model was recently presented to account for new data on constrained peptide analogs.[90] By iterating on the peptide conformation as new data emerged, the SK&F superposition continued to evolve and retains its value as a predictive tool today.

While these two modeling studies led to successful drug development, neither had carefully considered the likely shapes of the small molecules which elicit antagonism. To progress away from assuming the molecular shapes, computational attempts to predict the bioactive conformation of small molecule antagonists have been made.[257] A novel methodology, molecular shape comparison (MSC), was developed at Zeneca and applied to *de novo* prediction of the bioactive conformation of both the (biphenyl-4-ylmethyl)imidazoles and the *N*-(biphenyl-4-ylmethoxy)quinolines. Multiple low-energy conformers of the two classes were generated, and a comparison of molecular volumes resulted in a small subset of shapes which were common to both series.[258] Using a conceptually similar technique, the active analog approach[259] was used to identify a single receptor-bound presentation of the antagonist pharmacophore which was a subset of the structural families identified by MSC.[234] Sixteen potent and structurally diverse ligands were used to filter out a common presentation of the antagonist pharmacophore. The resulting small molecule conformation (Figure 23) was used in a comparative molecular (CoMFA) study of 50 diverse antagonists spanning 4 orders of magnitude in activity. A cross-validated R^2 of 0.64 reflects the good predictive ability of this model and provides some

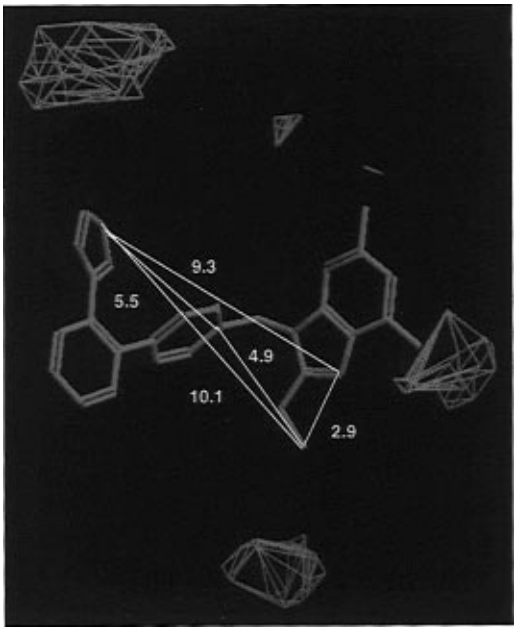


Figure 23. 3D pharmacophore for Ang II nonpeptide antagonists. The indicated distances resulted from pharmacophore mapping as described in the text and are common to all active analogs. The colored regions are CoMFA fields and reflect the steric and electrostatic interactions that contribute to binding. Green indicates regions where negatively charged groups are preferred. Red contours indicate the presence of a steric wall in the receptor, and blue indicates regions which require steric bulk for maximum potency.

statistical validation of the structural hypothesis from which it was derived. A successful *experimental* test of this 3D pharmacophore model was offered by preparation of macrocyclic antagonists, i.e., **7**.[235] The design of this antagonist was guided by the CoMFA analyses and is the first conformationally restricted small molecule to retain high potency on the AT_1 receptor. Using this 3D description of the pharmacophore geometry, a refined peptide to nonpeptide superposition was produced. The peptide conformation was built and minimized to be consistent with available data on constrained peptide analogs, such as [Sar[1],(3,5-hCys),Ile[8]]-Ang II.[260,261] Again, hand alignment between the small molecule and the C-terminus of Ang II was used to probe for 3D similarity. The biphenyl acid was overlapped with the C terminal acid allowing part of the terminal aromatic ring to fill the Ile[8] side chain binding site. The 2-substituent of the heterocycle mapped to Ile[5] and the central phenyl of the biphenyl was positioned roughly in the region of Pro[7] (Figure 22, bottom). This superposition benefits from the inclusion of carefully derived conformations for both the peptide and nonpeptide, in addition to the incorporation of SAR amassed during years of medicinal chemistry efforts.

On the basis of multiple successes using peptide to nonpeptide superpositions in small molecule design, one may ask whether these compounds are peptide mimetics. For a small molecule to mimic the action of Ang II peptides, one would expect to see simple transformations in structure that would lead to agonism and antagonism at other types of G-protein-coupled receptors. In fact, these criteria are met and have been discussed in this review. However, there is not a close correspondence between the chain tracing of the peptide and that of the small molecules in *any* overlay hypothesis. Rather, the various classes of Ang II antagonists

Table 1. Sequence of Human AT_1[a]

```
                                          ----------TM1---------
  1 MILNSSTEDGIKRIQDDCPKAGRHNYIFVMIPTLYSIIFVVGIFGNSLVV

                      ----------TM2---------------
 51 IVIYFYMKLKTVASVFLLNLALADLCFLLTLPLWAVYTAMEYRWPFGNYL

    ----------TM3-----------              --------TM4---
101 CKIASASVSFNLYASVFLLTCLSIDRYLAIVHPMKSRLRRTMLVAKVTCI

    -------------                                 ---TM5-
151 IIWLLAGLASLPAIIHRNVFFIENTNITVCAFHYESQNSTLPIGLGLTKN

    ----------------                          ----TM6---
201 ILGFLFPFLIILTSYTLIWKALKKAYEIQKNKPRNDDIFKIIMAIVLFFF

    ---------------                 ---------TM7----
251 FSWIPHQIFTFLDVLIQLGIIRDCRIADIVDTAMPITICIAYFNNCLNPL

    ----------
301 FYGFLGKKFKRYFLQLLKYIPPKAKSHSNLSTKMSTLSYRPSDNVSSSTK


351 KPAPCFEVE
```

[a] Sites that have been discussed explicitly in the text are underlined.

seem to mimic the essential side chain arrangement on Ang II, while they do not track the peptide backbone itself. Nikiforovich and Marshall have come to similar conclusions based on their extensive work with constrained peptide analogs.[262,263] Their careful analysis indicates the backbone conformation around the central Tyr[4] position in Ang II can vary while still exhibiting potent binding and agonism. Molecular recognition by the AT_1 receptor must be accomplished *primarily* by the arrangement of the peptide's side chain groups, and the small molecule mimetics can achieve this placement from several varied core scaffolds. In summary, the small molecules are thought to mimic parts of the Tyr-Ile-His-Pro-Phe sequence of Ang II, and the essential carboxylic acid is thought to be equivalent to the C-terminal carboxylate. While Ile[5] and Phe[8] are pharmacophoric elements presented by both losartan and eprosartan, identity between other features of these structures is not probable.

The availability of primary sequence data for the human AT_1 receptor[264] (Table 1) led to the development of a 3D receptor model[265] which was used to rationalize SAR for selective and balanced antagonists and to interpret site-directed mutagenesis data. Coordinates for the AT_1 receptor were generated from a homology model of the β_2-adrenergic receptor, positioning the helices as found in bacteriorhodopsin. Mutation analysis of the AT_1 receptor had identified Lys[199] in transmembrane helix 5 (TM5) as the counterion for Ang II's C-terminal carboxylate.[266] Docking Ang II into the AT_1 receptor maintained this contact. Due to the strong requirement of an acid (tetrazole, carboxylate, acylsulfonamide) in small molecule antagonists and the overlay hypotheses equating the biphenyl acid to Phe[8]-COOH of Ang II, docking of losartan *assumed* the involvement of Lys[199] as a counterion for the tetrazole. Orientation of these ligands in the transmembrane helices was based on SAR and employed the 3D conformations derived from prior modeling (Figure 24).[267]

While initial mutagenesis studies were used to argue for nonoverlapping binding sites between peptides and nonpeptides,[268] the accumulation of experimental data strengthens the modeling proposal of a partially overlapping antagonist binding site centered around Lys[199]. On the basis of its proximity to Lys[199] in the docked

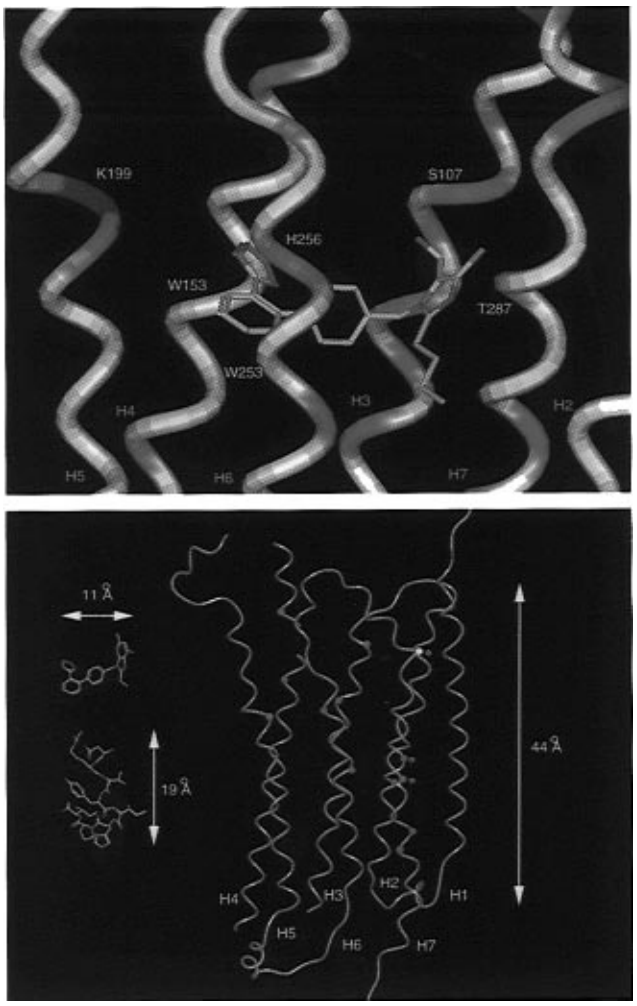


Figure 24. (Top) Model of losartan docked in the proposed small molecule binding site of the AT_1 receptor. The receptor is shown as a Cα trace, with residues colored according to the following key: red = acidic, blue = basic, green = polar, white = hydrophobic, and yellow = sulfur. (Bottom) Full scale view of the AT_1 receptor. The residues which have been shown to perturb small molecule antagonist binding are red, those that affect peptide binding are yellow, and sites which perturb both peptide and nonpeptide are green. Starred sites have been shown to affect signal transduction by Ang II.

model, His^{256} was postulated to form part of the floor on which the biphenyl rests. Subsequent site directed mutagenesis experiments confirmed that both Lys^{199} and His^{256} are in direct contact with small molecule antagonists. Interestingly, His^{256} acts in concert with Lys^{199} to recognize tetrazole derivatives.[269] His^{256} also participates in recognition of eprosartan analogs which are unaffected by Lys^{199} mutation.[270]

A role for Ser^{107} in subtype-selective binding of losartan to the AT_1 receptor was proposed based on the 3D model. Parallel mutagenesis studies confirmed this region of helix 3 was important to subtype selectivity but not as described in the original model: No *single* helix 3 mutant can account for the specificity of losartan for AT_1 over AT_2. Rather, combinations of point mutations are required to perturb losartan binding to the AT_1 receptor.[271]

Using the model, several conserved residues (Lys^{102}, Arg^{167}, Asp^{263}, Asp^{281}) were identified as possible sites for interaction with the N-terminal Asp^1 and Arg^2 of Ang II. Recently, all of these residues have been subject to site-directed mutagenesis.[269,272,273] By studying a series of Ang II variants against receptor mutants, Feng et al.[274] confirmed that Asp^{281} interacts directly with Arg^2 of Ang II. The binding of Asp^1 of Ang II by His^{183} in the second extracellular loop (EC2) was not predicted by this model.[274] Asp^{263}, Lys^{102}, and Arg^{167} mutants also perturb peptide binding.[273] Losartan would not be expected to contact Asp^{281}, Asp^{263}, Lys^{102}, or Arg^{167} since it is substantially smaller than Ang II, but Lys^{102} and Arg^{167} mutants do change nonpeptide binding. These residues may exert their effects by providing structure to the ligand-binding site and stabilizing a particular receptor conformation. Recent work postulates at least two conformational states of the AT_1 receptor.[275]

Whether the nonpeptide agonist L-162,313 binds to the same region of the receptor as the peptide agonist Ang II or the small molecule antagonists is unclear. Mutations known to affect Ang II, losartan, or L-158,809 *binding* have been shown to have *no* effect on the binding of the nonpeptide agonist L-162,313.[274,276] At least three sites that contribute to peptide *signaling* have been identified,[274,277,278] Asp^{74}, Tyr^{292}, and Asp^{281}, but the effect of mutating Tyr^{292} and Asp^{74} on the efficacy of the small molecule agonist L-162,313 is unknown. The binding and signal transduction of both classes of agonists have been studied against the Asp^{281} mutation and indicate that the interaction between Arg^2 of Ang II and Asp^{281} of the receptor appears necessary for full agonism. These workers[274] propose the *partial* agonism exhibited by the nonpeptide agonist L-162,313 may be due to the inability of this ligand to interact with Asp^{281}.

The receptor model provides a convenient framework for design and interpretation of mutagenesis studies. Ongoing experimental results will raise many questions regarding the precise interactions important to molecular recognition and signal transduction in peptide, nonpeptide, antagonist, and agonist interaction with the AT_1 receptor. Continued integration of these data into refinement of the receptor model could help further understanding of these complex phenomena.

8. Clinical Investigations of Angiotensin II Antagonists

Losartan is the first nonpeptide Ang II receptor antagonist to be studied in humans. Since losartan was established as an Ang II antagonist in humans,[279] it and a number of other such compounds have entered clinical trials with the objective of providing a safe and selective treatment for hypertension and other cardiovascular disorders. Table 2 summarizes the status of these agents from the published accounts available at the time of this review.[279−298] In humans, these antagonists block responses to exogenous Ang II with a time course of blockade which generally parallels plasma drug concentrations.[291,292,298,299] Antihypertensive activity with once or twice daily administration has been reported for several compounds,[281,282,284−286,289] with an acceptable safety profile.

The clinical investigation of Ang II antagonists includes establishing the mechanism's unique properties, with the overall objective being to differentiate the class of compounds from other agents, particularly ACE inhibitors, which also inhibit the renin−angiotensin−aldosterone system. As in preclinical studies,[26,52,300] Ang II antagonists can be differentiated from ACE

Table 2. Angiotensin II Antagonists Undergoing Clinical Investigation: Summary of Published Clinical Reports

compound	phase	oral dose[a] (mg)	sponsor	refs
losartan (DuP 753)	III+	50	DuPont/Merck	279−282
eprosartan (SK&F 108566)	II−III	150−350	SmithKline Beecham	283, 284
candesartan (TCV 116)	III	5−10	Takeda/Astra	285, 286
irbesartan (SR 47436)	III	10−50	Sanofi/Bristol-Myers Squibb	287−289
zolarsartan (GR 117289 C)	II; development suspended		Glaxo	290
telmisartan (BIBR 0277 SE)	II−III	40−80	Boeringer Ingelheim	291
tasosartan (ANA 756)	III	>100	Wyeth Ayerst	292
valsartan (CGP 48933)	II−III	>100	Ciba Geigy	293−296
ZD-8731	I; development suspended	>100	ICI	297
SC 52458	I	>100	Searle	298

[a] Based on antagonism of Ang II pressor effects and/or (if available) antihypertensive activity.

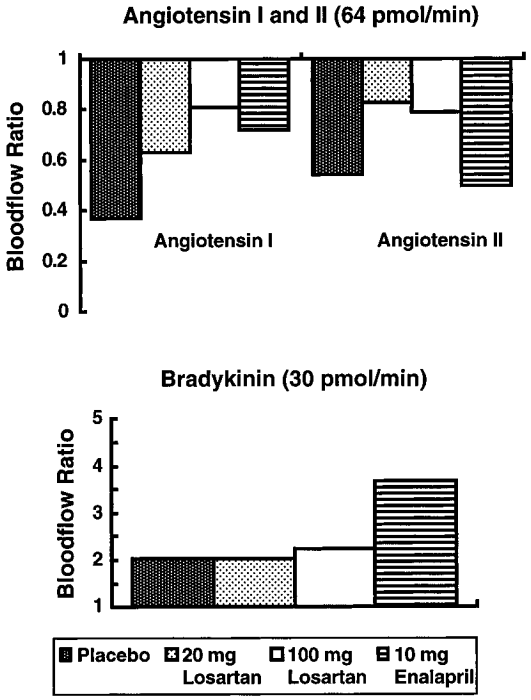


Figure 25. Effects of losartan and enalapril on forearm blood flow responses to intraarterial infusions of Ang I, Ang II, and bradykinin (data from ref 280). Values shown are the ratios of forearm blood flow measurements during infusion of agonist to measurements during infusion of saline, prior to agonist (e.g., a ratio of 0.5 indicates a 50% reduction of forearm blood flow).

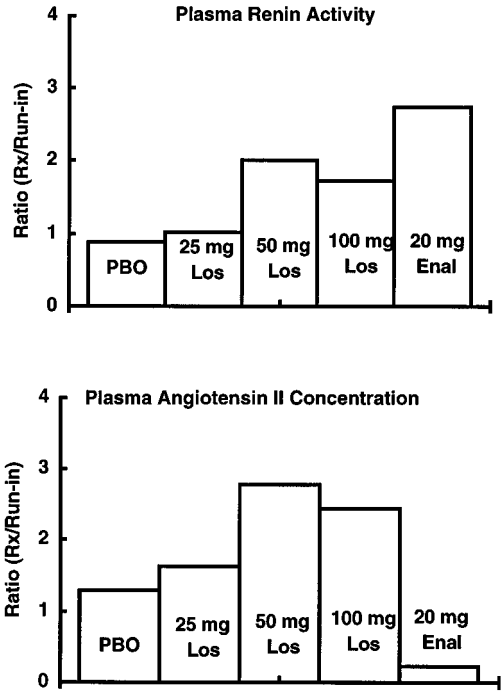


Figure 26. Effects of losartan and enalapril on plasma renin activity and Ang II concentrations (HPLC-RIA assay) in patients with mild to moderate hypertension (N = 11−13/group). Values are the ratio of measurements after 6 weeks of treatment to those during a single-blind placebo run-in day, with samples collected 4 h after dosing (a ratio of 2 indicates a doubling). (Data from ref 281 and Merck Research Laboratories, data on file.)

inhibitors in humans in pharmacodynamic,[280] biochemical,[281] and clinical[301] models.

In the human forearm,[280] it can be shown that an Ang II antagonist, losartan, blocks vasoconstrictor responses due to Ang II (i.e., those to Ang I and II) without modification of vasodilator responses to the peptide bradykinin. In contrast, an ACE inhibitor, enalapril, does not modify effects of Ang II but inhibits vasoconstrictor responses to Ang I and enhances vasodilator responses to bradykinin. Responses to a single infusion rate of each of these agonists 5 h after placebo, 20 and 100 mg of losartan, and 10 mg of enalapril are summarized in Figure 25. Both losartan and enalapril blocked vasoconstrictor responses to Ang I, whereas only losartan blocked responses to Ang II. Vasodilator responses to bradykinin were not altered by losartan and were significantly enhanced by 10 mg of enalapril.

In contrast to ACE inhibitors which increase plasma renin activity (PRA) without increasing Ang II, Ang II receptor antagonists are expected to increase both PRA and Ang II. This effect has been shown in healthy subjects[218,279] and in patients with hypertension.[281] The effects of 25, 50, and 100 mg of losartan and 20 mg of enalapril[281] (M. R. Goldberg, unpublished observations) on PRA and plasma Ang II concentrations 4 h after dosing, after 6 weeks of once daily administration to patients with mild-to-moderate hypertension, are summarized in Figure 26. Losartan (50 and 100 mg) and enalapril (20 mg) increase PRA to comparable degrees; however, losartan modestly increases Ang II, and enalapril reduces Ang II.

Losartan has been dosed to several hundred patients for more than 1 year with no loss of blood pressure control or unexpected effects.[302,303] Reports of comparative trials of losartan and a calcium channel blocker or β-blocker are very encouraging.[304,305]

Dry cough is the most commonly reported characteristic adverse effect of ACE inhibitors which, in some patients, may limit their clinical utility. On the basis of the known effects of ACE inhibitors to inhibit the metabolism of kinins (and other peptides), it has been postulated that cough is unrelated to blockade of the RAS by ACE inhibitors. Rather, potentiation of brady-

kinin may be the underlying pathophysiologic mechanism of ACE inhibitor-associated cough. If true, examination of cough in clinical trials of Ang II receptor antagonists will provide a third differentiating feature of these compounds. In support of this, a recent study[301] has documented that an enriched population of hypertensive patients who coughed during ACE inhibitor treatment shows a high incidence of cough (72%) when rechallenged a third time with an ACE inhibitor, lisinopril. The incidence of cough during losartan and hydrochlorothiazide was less than one-half the incidence during lisinopril (about 30%). The observed incidence of cough during losartan and hydrochlorothiazide in this study is attributed to the use of a study population known to have a history of cough and likely represents the background of cough in a population enriched for ACE-induced cough. This has been confirmed in a placebo-controlled study in a similar patient population (Merck Research Laboratories, data on file). Similarly, in trials in patients without a history of ACE-induced cough, the incidence of spontaneously reported cough during losartan and placebo was about 3%, compared to nearly 9% with ACE inhibitors (Merck Research Laboratories, data on file). It is also postulated that the more serious, but lower incidence, ACE inhibitor-associated adverse event angioedema is also related to potentiation of bradykinin or other peptides by ACE inhibitors. However, differentiation of Ang II receptor antagonists in this regard will be very difficult to demonstrate in a controlled study.

In patients with congestive heart failure and renal disease, preliminary results with losartan suggest that acutely blocking the Ang II receptor has effects similar to those observed with ACE inhibitors.[306,307] It will take some time to determine if all of the benefits of ACE inhibition can be attributed to a decrease in Ang II availability at the AT_1 receptor. It is important to remember, however, that Ang II can be generated by non-ACE pathways, e.g., human heart chymase, and blocking Ang II at its receptor independent of its source may provide superior protection against the pathologic effects of Ang II.

Thus, clinical studies have shown a variety of structurally diverse nonpeptide Ang II receptor antagonists to block responses to Ang II and to have antihypertensive activity. Using losartan, the first of these agents to enter clinical trials, as an example, these compounds can be shown to be differentiable from ACE inhibitors and specific in their clinical actions. Clinically useful antihypertensive efficacy with acceptable safety[308] has been demonstrated for losartan. It remains to be seen how other Ang II antagonists compare with respect to their efficacy and safety profiles.

9. Future Perspectives

Nonpeptide Ang II receptor antagonists have rekindled the exploration of the physiological and pathophysiological roles of Ang II. What has emerged is an amazing amount of new information on the structure of the cloned receptor subtypes from several species, the unique localization of these receptors, and the many species and intraspecies differences in the structure and function of these receptors. What seems clear is that virtually all of the well-known effects of Ang II (vasoconstriction, aldosterone release, drinking, norepinephrine release, renin release) are blocked by losartan and are, therefore, by definition AT_1 mediated. Losartan is the first nonpeptide Ang II antagonist to be approved by the FDA. It is the first antihypertensive agent with a novel mechanism of action to be introduced to the market in over a decade. While losartan is the first of this new class of nonpeptide antagonists, studies with a rapidly increasing number of new AT_1-selective nonpeptide antagonists have confirmed the early work with losartan and underscored the functional importance of the AT_1 receptor.

Modeling of the natural ligand Ang II provided the primary guidance for the synthetic program which led to the discovery of losartan from the early Takeda antagonists. Disclosure of the structure of the cloned receptors (AT_1 or AT_2) has, however, not yet led to the design of unique nonpeptide antagonists. Some progress has been made in understanding the critical binding sites on the external domain of the receptor, but translation of this knowledge into the design of novel antagonists has not taken place. As discussed above, the most important open question is the role of the AT_2 site.[309] Since the function of this site is largely unknown, new synthetic approaches have been limited. However, great progress has been made in synthesizing molecules that have high affinity for both AT_1 and AT_2 sites. These compounds appear to provide an opportunity for the possible therapeutic significance of the AT_2 site to be determined. The clinical testing of such a compound is unlikely if the AT_1-selective compounds continue to show efficacy and safety. It is clear that Ang II levels rise during treatment with AT_1-selective antagonists, and possible actions on the unblocked AT_2 site cannot be ruled out. It has been suggested that this site might belong to the family of seven transmembrane receptors which includes somatostatin and dopamine D_3 receptors[31] and that Ang II may not be the natural ligand.

The therapeutic impact of losartan and other AT_1-selective antagonists hinges on (1) their comparable efficacy alone and in combination with other antihypertensive agents in patients with all degrees of hypertension and (2) their superior tolerability when compared to ACE inhibitors and other antihypertensive agents. It seems clear that losartan can be differentiated from ACE inhibitors pharmacodynamically and in relation to the incidence of cough and from many other antihypertensive agents in relation to other adverse effects such as headache and edema. It may be possible to show that Ang II receptor blockade results in less first-dose hypotension and less hypokalemia than ACE inhibitors. It will be much more difficult to demonstrate the absence of the rarer "bradykinin" effects, angioedema and rash.

The future of this new class of cardiovascular agents rests on both therapeutic usefulness, which is still being evaluated, and health economic issues of cost effectiveness and reimbursement. These latter concerns can be separated from the cutting-edge chemistry and biology that culminated in these agents. New and exciting molecular biological and computer modeling tools have helped us understand the structure of the target receptor and have assisted in the design of new drugs. Clearly, the discovery of losartan has heralded in a new era of Ang II research and has allowed medicinal

chemists to forge ahead in the design of a nonpeptide, small molecular antagonist of an important natural mediator. With the new tools, the biologists have then given us an even broader understanding of the pathophysiological role of Ang II. If the initial clinical trials are confirmed, the efforts of these medicinal chemists and biologists will result in an important new class of therapeutic agents.

Beyond Ang II receptor antagonists, the potential for renin inhibitors to reach clinical practice should be considered. Although a number of renin inhibitors have been shown to lower blood pressure in hypertensive patients, their oral bioavailability and duration of action are limited.[9,310] Ro425892 has been shown to be orally active, but it is unclear whether it has sufficient efficacy in hypertension to offer benefit over Ang II receptor antagonists or ACE inhibitors.[311] Patents and applications describing novel renin inhibitors (primarily transition state peptidomimetics) continue to appear. Each of the reviewed molecules had a molecular weight >500,[312] suggesting that they may share the bioavailability and duration of action problems characteristic of this class of agents.[313]

Renin is the rate-limiting enzyme in the generation of Ang II, and it may be possible to regulate renin gene expression either at the transcriptional level or by the design of antisense oligonucleotides to inhibit post-transcriptionally.[314] Although the study of the regulation of the human gene expression has been limited by the absence of an immortalized cell line expressing renin, progress has been made in identifying the cAMP response element of the renin gene in secondary culture of human chorionic cells.[315] Such understanding of the regulation of renin gene expression prompts drug targeting of these sites.

Dipharmacophores, that is, molecules with affinity for two distinct sites, have been described in preclinical studies. These include dual inhibitors of neutral endopeptidase and ACE[316] and ACE and thromboxane synthesis.[317] A synergistic effect on blood pressure in rats following coadministration of a renin inhibitor or an ACE inhibitor with an Ang II receptor antagonist has been reported[318] which supports the theoretical benefit of such combinations. The clinical importance of such synergy, if confirmed in man, is unknown.

The most far-reaching speculative look at the future of the treatment of hypertension involves the possibility of (1) pulse dosing of antihypertensive drugs during a critical, presumably early period of development or (2) gene therapy. Short-term dosing of SHR has been shown to produce long-lasting reduction is blood pressure.[319,320] Captopril dosed to pregnant SHR prevented the development of hypertension in the offspring.[319] Can the hypertensive phenotype be identified early and changed without affecting the genetic material and other aspects of development? Are neurohumoral mediators (in this case Ang II or bradykinin) capable of influencing development plasticity to effect this change?[321] If the "critical period" could be identified in individuals at risk for hypertension, a significant change in therapeutic strategy can be envisioned. Identifying the individuals at risk and overcoming the special issues of treating the fetus,[322] however, pose significant hurdles to such a strategy.

Gene therapy represents the most exciting but challenging new therapeutic strategy for the therapy of hypertension. Gene therapy has been proposed for both systemic (e.g., atherosclerosis or hypercoagulable states) and local (e.g., restenosis after angioplasty or angiogenesis) gene therapy, and the techniques of local gene transfer have now been demonstrated.[323] Before the gene therapy of hypertension can be approached, however, the target gene or genes must be identified. The RAS is an important candidate system, but blood pressure and hypertension are the results of interacting systems including the sympathetic nervous system and locally released vasoactive substances such as nitric oxide. A review of linkage studies in families and sibling pair studies has suggested that renin and ACE are not candidate genes for hypertension. The angiotensinogen gene appears to be genetically linked to hypertension in some patients,[324] but the association with an increased risk of hypertension is not clear. The frequency of the 325T and 174M alleles of the angiotensinogen gene, for example, have been associated with hypertension in Caucasians and Japanese, but the 235T allele has recently been shown to be very common in populations of West African origin with no evidence of an increased risk of hypertension.[325] Ongoing studies with other RAS genes including those for the Ang II receptor subtypes and the associated G-proteins are needed to tie the findings at the genomic level to risk of cardiovascular disease in the essential hypertensive population. Whether single-gene deficits can be identified and separated from the environmental factors which can significantly affect the adult phenotype[326] remains conjectural. Health economics may also impact the progress of this search. With effective and inexpensive drugs available, is the search for the gene therapy of hypertension necessary or even desirable?

With all of the scientific and other problems not withstanding, future advances in hypertension therapy are likely to come from the current exploration of the human genome. If the "hypertensive" phenotype of every patient can be identified and the treatment tailored to that phenotype, a significant advance will have been made. Likewise, if new protein mediators of hypertension can be identified, novel molecules can be designed to correct the abnormal function. At the present time, however, it would appear that truly new antihypertensive drug discovery and therapy must await the future advances in the molecular biology of hypertension.

Biographies

Willam J. Greenlee completed his Ph.D. degree in chemistry at Harvard with Professor R. B. Woodward. Following postdoctoral work at Columbia University with Professor Gilbert Stork, he joined Merck Research Laboratories, Rahway, in 1977 where he was a Senior Director in Basic Medicinal Chemistry. In 1995, he joined the Schering-Plough Research Institute, as Senior Director, Cardiovascular and CNS Chemistry.

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