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Articles

A Novel Series of Selective, Non-Peptide Inhibitors of Angiotensin II Binding to the AT_2 Site

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The availability of peptide and non-peptide Ang II receptor antagonists has permitted the study of Ang II receptor heterogeneity. It is now widely recognized that there are at least two distinct Ang II receptor subtypes. AT_1 receptors are selective in their recognition of agents such as losartan, DuP 532, L-158,809, SK&F108566, and similar non-peptides. To date, all of the well-known actions of Ang II in mammals are blocked by the AT_1 selective antagonists such as losartan and are thus designated as being mediated by the AT_1 receptor. Although there have been reports of functional activity mediated through AT_2 sites, the pharmacological role for the AT_2 receptor has not yet been elucidated. Herein, we report the chemistry and SAR on a novel series of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids which have selective affinity for AT_2 receptors. The most potent of which (**19**) has an IC_{50} of 30 nM for the AT_2 receptor in the rat adrenal radioligand binding assay.

Introduction

The renin–angiotensin system (RAS) has long been known to play a role in the regulation of cardiovascular functions such as arterial pressure and sodium balance.[1] The RAS cascade begins with the enzyme renin which converts angiotensinogen to angiotensin I (Ang I), see Figure 1. This is in turn cleaved by angiotensin converting enzyme (ACE) to produce angiotensin II (Ang II). Ang II in turn acts on its receptors to cause vasoconstriction.

Hypertension can be blunted by reducing the amount of Ang II that is available to bind to its receptor. This was first accomplished by ACE inhibitors. ACE inhibitors moderate the amount of Ang II available by blocking the conversion of Ang I to Ang II. There are many known ACE inhibitors, and they are used extensively to regulate high blood pressure in patients.[2] Much effort has been made to find an inhibitor of renin.[3] By blocking renin, the levels of Ang I decrease and, consequently, the levels of Ang II decrease. The stumbling block in the search for a renin inhibitor has been the oral bioavailability of the inhibitors. Most recently, Ang II receptor antagonists have been used to block the vasoconstrictive effects caused by the binding of Ang II to its receptor. The discovery of an orally active, non-peptide, Ang II receptor antagonist, losartan (DuP 753, see Figure 2),[4] has led to a large effort

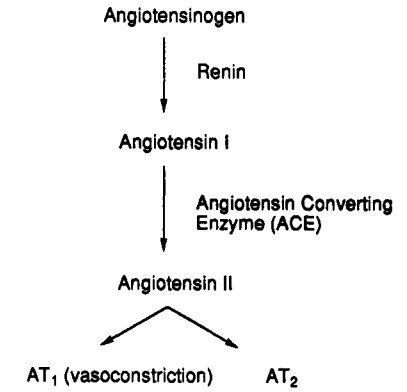

Figure 1. The renin angiotensin system.

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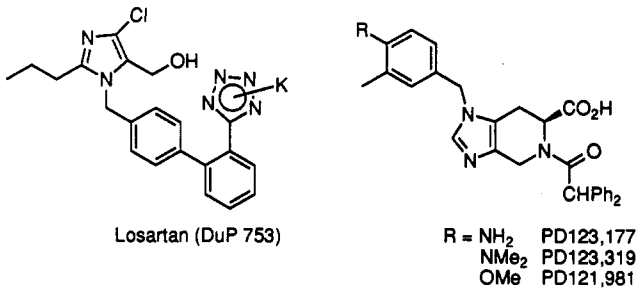


Figure 2. Inhibitors of angiotensin II binding.

in the pharmaceutical industry to find other Ang II antagonists.[5]

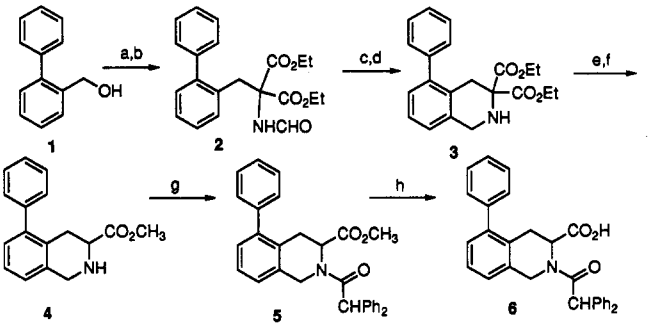
The Parke-Davis group discovered a series of 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acids that bind to the Ang II receptor in a rat adrenal preparation that contained dithiotreitol (DTT). Examples of their series are PD123,177, PD123,319, and PD121,981 (see Figure 2).[6] Even though these compounds were found to bind to the Ang II receptor, they did not lower blood pressure. It is now known that DTT, added to stabilize the peptides in the assay, actually deactivates the AT_1 receptor without affecting the AT_2 subtype. Therefore, the addition of DTT to their receptor preparation abolished the inhibitory effect of losartan on Ang II binding, but it enhanced the inhibitory effect of PD123,177.[7,8] This result eventually led to the discovery of a second subtype of the Ang II receptor. Convention for the nomenclature of Ang II receptor subtypes has recently been published and is based primarily on the selective displacement of Ang II with binding inhibitors.[9] This second Ang II receptor has been labeled the AT_2 receptor. It is inhibited by PD123,177 and related analogs[6] as well as peptides such as CGP 42112A.[10] The Ang II receptor that is inhibited by losartan has been labeled the AT_1 receptor. Besides losartan, a few of its ligands are DuP 532,[11] L-158,-809,[12-14] and SK&F 108566,[15,16] to name just a few. The natural peptides, Ang I and Ang II, exhibit a slight preference for binding to the AT_2 site over the AT_1.[17]

To further confuse the whole question of Ang II heterogeneity, the AT_1 and the AT_2 receptors exhibit heterogeneity among themselves; namely AT_{1A}, AT_{1B},[18-21] AT_{2A}, and AT_{2B}.[22] There is no evidence that the non-peptide inhibitors can distinquish between the different sub-subtypes.

The distribution, affinity and relative properties of the AT_1 and AT_2 receptor subtypes vary greatly between tissues and species. Tissues such as kidney, liver, lung, placenta, urinary bladder, gastrointestinal tract, and vascular smooth muscle cells express only the AT_1 receptor, [23] while other tissues such as adrenal medulla, pancreas, human uterus, and ovarian granulosa express predominantly the AT_2 receptor subtype.[23] Both receptor subtypes are expressed in adrenal cortex, heart, renal arteries, rat uterus, and brain.[23] Generally, the AT_1 subtype is associated with tissues involved in regulation of blood pressure and fluid electrolyte balance, whereas the distribution of the AT_2 subtype is more difficult to correlate with a particular function. So far, no consistent physiological effect has been observed with compounds that inhibit binding to the AT_2 receptor.[24]

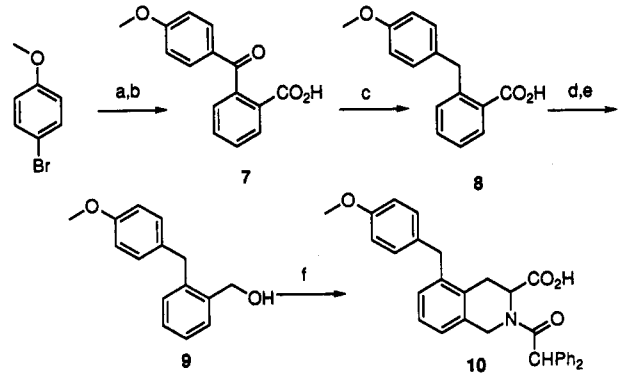
Herein, we would like to report a novel series of substituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids which inhibit the binding of Ang II to the AT_2 receptor.

Scheme I[a]



[a]Method A: (a) MsCl; (b) sodium diethyl formamidomalonate; (c) P_2O_5, toluene; (d) $NaCNBH_3$, glacial acetic acid; (e) KOH, MeOH; (f) H^+, MeOH; (g) diphenylacetyl chloride; (h) NaOH.

Scheme II[a]



[a]Method B: (a) Mg, ether; (b) phthalic anhydride; (c) 20 atm of H_2, Pd/C; (d) H^+, MeOH; (e) $LiBH_4$; (f) see Scheme I.

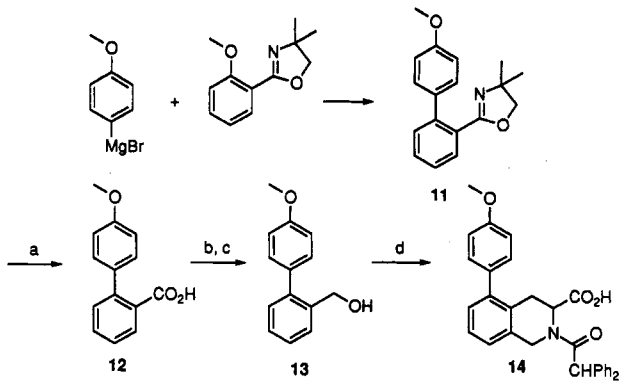
Chemistry

1,2,3,4-Tetrahydroisoquinolines have typically been prepared by using either a Pictet–Spengler[25,26] or a Bischler–Napieralski[27] reaction. We have found the Bischler–Napieralski reaction to be more convenient in the synthesis of the 5-substituted tetrahydroisoquinolines. For the 6-substituted tetrahydroisoquinolines, the Pictet–Spengler reaction was used.

The 5-substituted tetrahydroisoquinolines were constructed by the method shown in Scheme I, employing the appropriately substituted benzyl alcohol, such as **1**. The alcohol was converted to the mesylate by treatment with methanesulfonyl chloride in the presence of triethylamine. The mesylate was then displaced with the sodium salt of diethyl formamidomalonate to yield **2**. The formamide was then subjected to the Bischler–Napieralski conditions of phosphorus pentoxide in refluxing toluene, to yield the dihydroisoquinoline.[27] The dihyroisoquinoline was reduced with sodium cyanoborohydride in the presence of glacial acetic acid to yield the tetrahydroisoquinoline, **3**. Attempts to acylate **3** failed. It was found that the diester must first be converted to the monoester in order for the acylation to proceed. In one pot, the diester was hydrolyzed to the diacid using potassium hydroxide in methanol and then decarboxylated by the addition of acid. Finally, refluxing in methanol produced the monoester, **4**. The amine was then acylated by reacting with the appropriateacid chloride to yield **5**, which was then hydrolyzed to the acid, **6**.

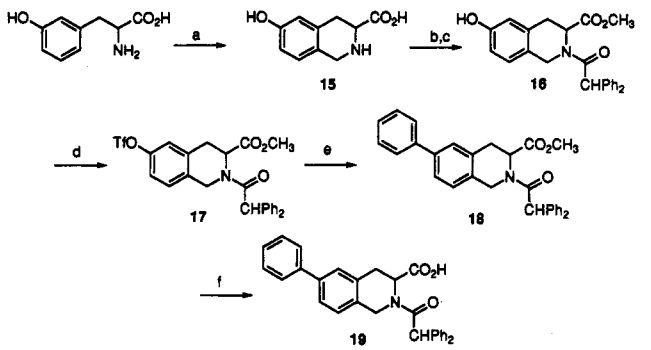
Several of the substituted benzyl alcohols were commercially available. Those not available were prepared using the procedures described in Schemes II and III. Substituted 2-benzylbenzyl alcohols such as **9** were pre-

Scheme III[a]



[a]Method C: (a) 4.5 N HCl; (b) H^+, MeOH; (c) $LiBH_4$; (d) see Scheme I.

Scheme IV[a]



[a]Method D: (a) HCHO; (b) HCl, MeOH; (c) diphenylacetyl chloride; (d) triflic anhydride, pyridine; (e) $PhSnMe_3$, $(Ph_3P)_4Pd$; (f) KOH, MeOH.

pared by following the method of Fouche.[28] Substituted phenylmagnesium bromide was reacted with phthalic anhydride to yield the 2-benzoylbenzoic acid, **7**. The ketone was reduced by high pressure hydrogenation at 70 °C to yield **8**. The carboxylic acid moiety was then reduced by first converting it to the ester and then reacting it with lithium borohydride to produce the benzyl alcohol. This substituted benzyl alcohol **9** was then converted to the corresponding tetrahydroisoquinoline **10** using the same method as was described in Scheme I. This method was used to prepare all of the substituted 2-benzylbenzyl alcohols and their corresponding tetrahydroisoquinoline-3-carboxylic acids.

Substituted 2-phenylbenzyl alcohols such as **13** were prepared as illustrated in Scheme III, using the chemistry initially described by Meyers.[29] The substituted phenylmagnesium bromide was added to the (2-methoxyphenyl)-oxazoline to yield **11**. The oxazoline was then hydrolyzed to the carboxylic acid, **12**, by refluxing in 4.5 N HCl. The acid was then converted to the alcohol, **13**, by esterification and subsequent reduction. Then **13** was converted to the corresponding tetrahydroisoquinoline **14** by using the same method as shown in Scheme I. This method was used to prepare both substituted 5-phenyl- and 5-alkyltetrahydroisoquinolines.

The 6-substituted tetrahydroisoquinolines were obtained by the method described by Ornstein[30] (see Scheme IV). In this procedure, *m*-tyrosine was converted to the tetrahydroisoquinoline **15** via the Pictet–Spengler reaction, employing formaldehyde in dilute acid. The carboxylic acid was then esterified in refluxing HCl/methanol. This was followed by acylation of the amine with the appropriate acid chloride to yield **16**. The 6-position was then functionalized using the Stille coupling method.[31] The phenol was first converted to triflate **17**, followed by reaction with trimethylphenyltin(IV) in the presence of palladium catalyst to yield the 6-phenyltetrahydroisoquinoline **18**, which was then hydrolyzed to the corresponding carboxylic acid **19**.

Discussion

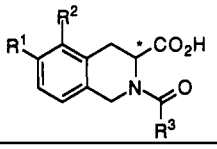
The Parke-Davis group prepared a large number of 4,5,6,7-tetrahydro[4,5-*c*]imidazopyridine-6-carboxylic acid analogs and have described the structure–activity relationships for this series.[6] Two of their most potent compounds are PD123,177 and PD121,981. We prepared these compounds as a benchmark and found them to be potent selective inhibitors of Ang II binding to the AT_2 receptor (IC_{50} = 40 and 10 nM, respectively, in the rat adrenal).

The unsubstituted tetrahydroisoquinoline **20** (Table I) was first prepared to test whether the imidazole ring in the tetrahydroimidazopyridine is necessary for good binding to the AT_2 receptor. We speculated that the imidazo ring might act as an electron-rich group which participates in hydrogen bonding to the receptor or, alternatively, was merely serving as a template for holding the key pharmacophores (the N-2 amide group, the C-3 carboxylic acid, and the N-5 benzyl substituent) a certain distance from each other. The diphenylacetyl group was employed at the 2-position because it resulted in excellent binding in the tetrahydroimidazopyridine series. The unsubstituted compound **20** proved to be a modest AT_2 receptor inhibitor (IC_{50} = 2.5 μM). This result was an indication to us that the imidazole was just acting as a template and that the imidazole was not binding to the receptor through a hydrogen bond.

Several analogs of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid were prepared to see if the same or better potency could be obtained as was achieved in the tetrahydroimidazopyridine series. Substitution at the R^1 position led to an increase in the binding affinity (see Table I). The 5-benzyl substituent, **21**, improved the binding to 90 nM, an increase of 30 times over the binding affinity of **20**. Substitution on the benzyl substituent improved the binding in the tetrahydroimidazopyridine series. In the tetrahydroisoquinoline series, the presence of a 4-methoxy on the benzyl (**10**) yielded the same affinity as the unsubstituted compound (**21**). The further addition of a 3-methyl group, as in compound **26**, led to a decrease in the binding affinity. This result differs from that obtained in the tetrahydroimidazopyridine series in which electron donating substituents had benefit in either the meta or para position. Combination of groups at both positions afforded compounds with binding affinity in the 30–50 nM range.[5] In that series, the optimum binding was obtained when the N_1-benzyl was substituted with a *m*-methyl group and either a *p*-methoxy, -amino, or -dimethylamino group, as in PD121,981, PD123,177, and PD123,319.

To our knowledge, the 5-phenyl analog **6** does not have a counterpart which has been reported in the tetrahydroimidazopyridine series. The use of a phenyl group instead of a benzyl moiety increased the affinity to the AT_2 site to 40 nM, an increase of 60 fold over the unsubstituted compound, **20**. Substitution of a 4-methoxy group on the phenyl group (**14**) yielded the same affinity

Table I. Effect of Substituents on AT_2 Binding



compd	R^1	R^2	R^3	$[\alpha]_D$, deg[a]	IC_{50} AT_1 (μM)	IC_{50} AT_2 (μM)
PD123, 177					>10	0.04
20	H	H	$CHPh_2$	*	>30	2.5
21[b]	H	$PhCH_2$	$CHPh_2$	*	10	0.09
22[b]	H	$PhCH_2$	$CHPh_2$	+10.7, *c* 0.75 EtOH	5	0.07
23[b]	H	$PhCH_2$	$CHPh_2$	−8.5, *c* 0.94 EtOH	4	0.08
24[b]	H	CH_3	$CHPh_2$	*	>10	0.3
30[d]	H	pentyl	$CHPh_2$	*	>10	0.04
6[b]	H	Ph	$CHPh_2$	*	>10	0.04
10[c]	H	4-$MeOC_6H_4CH_2$	$CHPh_2$	*	7	0.09
26[c]	H	3-Me-4-$MeOC_6H_4CH_2$	$CHPh_2$	*	5	0.1
14[d]	H	4-$MeOC_6H_4$	$CHPh_2$	*	10	0.04
27[d]	H	3-Me-4-$MeOC_6H_4$	$CHPh_2$	*	>10	0.07
28[b]	PhO	H	$CHPh_2$	*	>10	0.06
29[e]	OH	H	$CHPh_2$	*	>10	0.6
19[e]	Ph	H	$CHPh_2$	*	>10	0.03
31[c]	H	4-$MeOC_6H_4CH_2$	NPh_2	*	10	0.2
32[c]	H	4-$MeOC_6H_4CH_2$	$NPh(CH_3)$	*	>10	0.4
33[b]	PhO	H	$NPh(CH_3)$	*	>10	0.3

[a] An asterisk denotes racemic compound. [b] This substitution pattern was prepared using method A. [c] This substitution pattern was prepared using method B. [d] This substitution pattern was prepared using method C. [e] This substitution pattern was prepared using method D.

as for the unsubstituted compound. As before, the addition of the 3-methyl group (**27**) lowered the binding affinity.

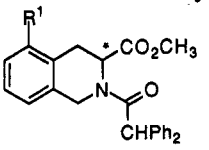
When an alkyl group is substituted at the 5-position, the binding affinity is also improved over the unsubstituted analog. The 5-methyl compound **24** shows enhanced affinity of 1 order of magnitude over the unsubstituted compound, **20**. The 5-pentyl compound, **30**, showed an increase of 2 orders of magnitude over the unsubstituted compound. This analog, **30**, yielded the same binding affinity as the 5-phenyl compound **6**. This result parallels that found with the tetrahydroimidazopyridine ring system in which groups of a reasonable size were required for good activity. In that series, similar potencies were achieved with a variety of subtituents including benzyl, aliphatic, and heterocycloalkyl groups.[6]

The compounds that are substituted at the 6-position also do not have a direct correlate in the tetrahydroimidazopyridine series. The addition of a 6-hydroxy group as in compound **29** increased the binding to the AT_2 site by a factor of 4 over that of the unsubstituted compound. Further, the addition of either a phenoxy (**28**) or a phenyl group (**19**) at the 6-position increased the binding affinity to 60 and 30 nM, respectively. The 6-phenyltetrahydroisoquinoline-3-carboxylic acid (**19**) exhibited the best affinity to the AT_2 receptor of the compounds prepared in this series.

So far, all of the analogs discussed contain the diphenylacetyl moiety at the 2-position. The other variants that were tried at that position were the *N*,*N*-diphenylurea and the *N*-phenyl-*N*-methylurea. In both of these cases, the binding affinity is decreased from the corresponding diphenylacetyl compound. When the diphenylacetyl group on **10** is replaced with diphenylurea (**31**) the binding affinity is decreased by a factor of 2. The use of *N*-methyl-*N*-phenylurea in compound **32** decreases the affinity by factor of 4 compared to the affinity of **10**.

The compounds described were prepared as racemic mixtures. To test the effect of the individual enantiomers, **21** was separated by chiral HPLC to yield the two isomers.[32] The (+) isomer was eluted off the column first and was therefore the more pure of the two isomers. The (−) isomer was contaminated with approximately 20% of the other isomer. The purity was also seen in the optical rotations of the corresponding enantiomers. When the binding affinity of these enantiomers was obtained, it was shown that they exhibit essentially the same affinity. This is in contrast to the result found for the tetrahydroimidazopyridine series in which the *R*-isomer was 3 times less potent than the *S*-isomer for both the N_1-benzyl compound and PD123,317. In PD123,317, the *S*-isomer had an AT_2 affinity of 34 nM while the *R*-isomer had an affinity of 97 nM.[6]

Table II. Binding Affinities of C-3 Methyl Esters



compd	R^1	IC_{50} AT_1 (μM)	IC_{50} AT_2 (μM)
34	CH_3	>10	5.0
35	$PhCH_2$	>10	7.0
5	Ph	>10	2.0
36	4-$CH_3OC_6H_4CH_2$	>10	>10
37	4-$CH_3OC_6H_4$	>10	2.0

As can be seen in Table II, the C-3 carboxylic acid is not essential for binding to the AT_2 site. However, it is necessary for optimal binding. The presence of a methyl ester at the 3-position lowers the binding affinity between 1 and 2 orders of magnitude over the binding affinity for the corresponding carboxylic acid. In comparing the binding affinities of compounds **6** and **5**, the binding is decreased from 40 to 2000 nM. Less potent compounds, such as **24** do not show as large of a decrease in binding affinity when compared with the requisite C-3 carboxylic acid for compound **34**.

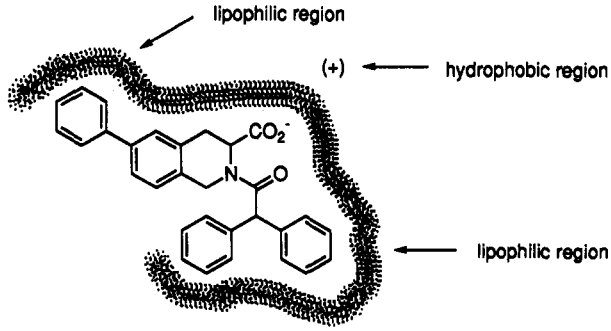


Figure 3. Representation of the AT_2 receptor.

Conclusion

We have discovered a series of potent inhibitors of Ang II binding to the AT_2 receptor subtype. The 1,2,3,4-tetrahydroisoquinoline appears to be acting as a scaffold, holding two lipophilic moieties a fixed distance apart with respect to the carboxylic acid (see Figure 3). The lipophilic pocket on the "top" of the receptor is large because it can accommodate substantial substitutents at either the 5- or 6-position of the 1,2,3,4-tetrahydroisoquinoline. The lipophilic pocket on the "bottom" of the receptor prefers the diphenylacetyl moiety. The pocket with the positive charge appears to be large and nonspecific as it accepts either enantiomer of the carboxylic acid.

Experimental Section

Melting points were determined in an open capillary with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1600 series FTIR. NMR spectra were determined with a Varian VXR-300a. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter. Microanalyses were performed by Quantatitve Technologies and were within ±0.4% of the calculated values. Mass spectra were obtained on a HP 5988A MS/HP Particle Beam Interface. Chromatography was done using EM Science Silica Gel 60. Radiolabeled [^{125}I]Ang II was obtained from Du Pont NEN Products (Boston, MA).

Radioligand–Receptor Binding. The binding to the AT_1 receptor subtype was determined using rat isolated adrenal cortical microsomes, and the binding to the AT_2 receptor subtype was determined using rat isolated adrenal medullary microsomes. Procedures for the preparation of the adrenal cortical microsomes and details of the binding assays are described in the literature.[33] This receptor preparation produces approximately 80% AT_1 receptors in the assay. The same procedures and conditions were used for adrenal medullary microsomes.[8] This receptor preparation produces approximately 90% AT_2 receptors in the assay. Aliquots of a freshly prepared particulate fraction (13000–102000g) were incubated with 0.05 nM [^{125}I]Ang II and varying concentrations of inhibitor in a final volume of 0.5 mL of assay buffer containing 5 mM $MgCl_2$ and 50 mM Tris base, pH 7.2 at 25 °C. After 60 min of incubation, the reaction was terminated by addition of cold assay buffer. The bound and free radioactivity were rapidly separated through glass-fiber filters, and the trapped radioactivity was determined by γ counting. All data presented are specific binding, which is defined as that which is displaced by 1 μM unlabled Ang II added to the mixture. Intraassay variability is 5%, and interassay variability is 20%. All compounds were tested in duplicate and were compared with an internal standard such as DuP 753 and saralasin.

Synthesis: Method A. Ethyl 3-(Biphenyl-2-yl)-2-carbethoxy-2-(formylamino)propanoate (2). A solution of 2-biphenylmethanol (6.07 g, 33.0 mmol) and triethylamine (9.2 mL, 66 mmol) in 125 mL of dichloromethane was added dropwise into an ice bath-cooled solution of methanesulfonyl chloride (5.1 mL, 66 mmol) in 150 mL of dichloromethane. After 1 h, the solution was washed with 10% sodium bicarbonate solution, dried over $MgSO_4$, and evaporated to yield the crude mesylate.

NaH (80% by weight, 1.02 g, 34.0 mmol) was carefully added to 200 mL of ethanol. Diethyl formamidomalonate (6.92 g, 34.1 mmol) was then added. After 5 min, the crude mesylate was added. The reaction mixture was then stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in dichloromethane, washed with 1.0 N NaOH solution, dried over $MgSO_4$, and evaporated to yield an oil (9.65 g, 26.2 mmol) which solidified on standing. NMR ($CDCl_3$): ∂ 7.1–7.6 (m, 11H), 4.12 (m, 2H), 3.95 (m, 2H), 3.88 (s, 2H), 1.13 (t, 6H). MS: 370 (M + H).

Diethyl 5-Phenyl-3,4-dihydroisoquinoline-3,3-dicarboxylate. The malonate derivative, 2, was dissolved in 300 mL of toluene. P_2O_5 (~10 g) was added. The reaction mixture was heated to reflux for 4 h. After cooling, the reaction was carefully quenched with water. The water layer was made basic with concentrated NaOH and then separated. It was then extracted twice with dichloromethane. The combined toluene and dichloromethane extracts were dried over $MgSO_4$ and evaporated to yield product (8.18 g, 23.3 mmol) as a brown oil. NMR ($CDCl_3$): ∂ 8.58 (s, 1H), 7.5–7.0 (m, 8H), 4.18 (m, 4H), 3.89 (s, 2H), 1.18 (m, 6H). MS: 352 (M + H).

Diethyl 5-Phenyl-1,2,3,4-tetrahydroisoquinoline-3,3-dicarboxylate (3). The cyclized product was dissolved in 100 mL of glacial acetic acid. $NaCNBH_3$ (8.18 g, 23.3 mmol) was slowly added. After the addition was complete, the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with water, and then the reaction was quenched carefully with concentrated NaOH and extracted with dichloromethane. The combined extracts were dried over $MgSO_4$ and evaporated to yield crude diethyl 5-phenyltetrahydroisoquinoline-3,3-dicarboxylate. MS: 354 (M + H).

Methyl 2-(Diphenylacetyl)-5-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5). The crude diester, 3, was dissolved in 300 mL of methanol. Approximately 2 equiv of KOH (4.94 g, 88.2 mmol) was added. The reaction mixture was heated to reflux for 4 h. After the mixture was cooled to room temperature, concentrated sulfuric acid (15 mL) was carefully added. The reaction mixture was heated to reflux for 4 more h. The solvent was evaporated. The residue was taken up in water, neutralized with 10% K_2CO_3, and extracted with dichloromethane. The extracts were dried over $MgSO_4$ and evaporated to yield methyl 5-phenyltetrahydroisoquinoline-3-carboxylate, 4 (6.45 g, 22.8 mmol), as a yellow oil.

The crude methyl ester was dissolved in 300 mL of dry THF. Diisopropylethylamine (2.9 mL, 23 mmol) was added. After 5 min, diphenylacetyl chloride (5.30 g, 23.0 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in dichloromethane, washed with water, dried over $MgSO_4$, and evaporated. The product was then purified by flash chromatography (1% methanol/dichloromethane) and subsequently by HPLC (silica fireplug, 5% glyme and 95% butyl chloride gradient to 25% glyme and 75% butyl chloride) to yield a solid, which was then recrystallized from methanol. Mp: 149–150 °C. NMR ($CDCl_3$): ∂ 7.5–7.1 (m, 17H), 6.87 (d, 1H), 5.39 (s, 1H), 5.22 (t, 1H), 4.78 (d, 1H), 4.61 (d, 1H), 3.40 (s, 3H), 3.21 (dd, 1H), 3.04 (dd, 1H). MS: 462.3 (M + H). IR: 1743, 1641, 1600. Anal. ($C_{31}H_{27}NO_3 \cdot 0.5H_2O$) C, H, N.

2-(Diphenylacetyl)-5-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6). The above methyl ester, 5 (0.60 g, 1.3 mmol), was dissolved in 20 mL of methanol and 7 mL of THF; 1.0 N NaOH (2.0 mL) was added, and the reaction mixture was heated to reflux for 4 h. The solvent was evaporated. The residue was taken up in water and extracted with ether, and these extracts were discarded. The aqueous was acidified with 6 N HCl and extracted with ether. These ether extracts were dried and evaporated to yield the solid product (0.55 g, 1.2 mmol), mp 216–221 °C. NMR (acetone-d_6), two amide isomers present: ∂ 7.5–7.0 (m, 18H), 5.73 and 5.57 (2 s, 1H), 5.23 and 5.12 (2 t, 1H), 5.03 (d, 1H), 4.89 and 4.62 (2 d), 3.4–3.0 and 2.75 (m, 2H). MS: 448.3 (M + H). IR (KBr): 1716, 1649, 1638. Anal. ($C_{30}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

Method B. 2-(4-Methoxybenzoyl)benzoic Acid (7). Freshly cleaned magnesium ribbon (1.6 g) was suspended in 150 mL

of ether. *p*-Bromoanisole (7.5 mL, 60 mmol) was added. A trace of iodine and 1,2-dibromoethane was added to initiate the reaction, and the reaction mixture was heated to reflux for 1 h. In another flask, phthalic anhydride (8.79 g, 59.4 mmol) was placed in 50 mL of ether and 90 mL of benzene. The Grignard solution was then transferred via cannula slowly into the phthalic anhydride solution. The reaction mixture was then heated to reflux overnight. The reaction was carefully quenched with sataturated NH_4Cl solution. The mixture was then extracted three times with ether, dried over $MgSO_4$, and evaporated to yield a yellow foam (10.71 g, 41.8 mmol) in 70% yield. NMR (acetone-d_6): ∂ 8.08 (d, 1H), 7.70 (m, 4H), 7.39 (d, 1H), 6.99 (d, 2H), 3.87 (s, 3H). MS: 257.0 (M + H).

2-[(4-Methoxyphenyl)methyl]benzoic Acid (8). The above keto-acid, 7, was dissolved in 50 mL of methanol along with 5% palladium on carbon (2.48 g). The solution was maintained under 20 atm of hydrogen, at 70 °C, for 12 h. The reaction mixture was filtered through Celite. The Celite was washed well with methanol. The combined methanol was evaporated to yield 8 as a white solid (8.09 g, 33.4 mmol) in 85% yield. NMR (acetone-d_6): ∂ 7.95 (d, 1H), 7.48 (t, 1H), 7.30 (m, 2H), 7.12 (d, 2H), 6.81 (d, 2H), 4.36 (s, 2H), 3.75 (s, 3H). MS: 260.2 (M + NH_4).

Methyl 2-[(4-Methoxyphenyl)methyl]benzoate. The above benzoic acid was dissolved in 250 mL of methanol. Concentrated H_2SO_4 (5 mL) was added. The reaction mixture was heated to reflux for 4 h. The solvent was evaporated. The residue was partitioned between water and dichloromethane, and the water was extracted three times with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and evaporated to yield the benzoic ester as an oil (8.37 g, 33.4 mmol) in 98% yield. NMR ($CDCl_3$): ∂ 7.89 (d, 1H), 7.42 (t, 1H), 7.28 (t, 1H), 7.21 (d, 1H), 7.08 (d, 2H), 6.82 (d, 2H), 4.32 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H). MS: 274.2 (M + NH_4).

2-[(4-Methoxyphenyl)methyl]benzyl Alcohol (9). The benzoic ester was dissolved in 250 mL of ether. An excess of $LiBH_4$ (2.95 g, 134 mmol) was added. The reaction mixture was stirred at room temperature overnight. The ether was evaporated. Methanol was carefully added to destroy the $LiBH_4$. The reaction mixture was then diluted with water and extracted with dichloromethane. The combined dichloromethane extracts were dried over $MgSO_4$ and evaporated to yield the benzyl alcohol in 84% yield (6.28 g, 27.5 mmol). NMR ($CDCl_3$): δ 7.38 (m, 1H), 7.22 (m, 2H), 7.10 (m, 1H), 7.02 (d, 2H), 6.80 (d, 2H), 4.58 (s, 2H), 3.99 (s, 2H), 3.75 (s, 3H). MS: 228.1 (M + H).

Methyl 2-(Diphenylacetyl)-5-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (36). This product was prepared from **9** as an amorphous solid in a similar manner as was described in method A. NMR ($CDCl_3$) two amide isomers present: ∂ 7.6–6.8 (m, 17H), 5.44 and 4.85 (2 m, 1H), 5.37 and 5.14 (2 s, 1H), 5.02 and 4.75 (2 d, 1H), 4.60 and 4.57 (2 d, 1H), 3.92 and 3.78 (2 s, 3H), 3.52 and 3.41 (2 s, 3H), 3.30 (dd, 1H), 2.87 and 2.50 (2 dd, 1H). MS: 506.2 (M + H). IR (KBr): 1743, 1656, 1610. Anal. ($C_{33}H_{31}NO_4$) C, H, N.

2-(Diphenylacetyl)-5-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (10). This product was prepared from **36** as an amorphous solid in a similar manner as was described in method A for the preparation of **6**. NMR (acetone-d_6) two amide isomers present: ∂ 7.4–6.8 (m, 17H), 5.70 and 5.59 (2 s, 1H), 5.41 and 5.19 (2 m, 1H), 5.03 and 4.95 (2 d, 1H), 4.70 and 4.53 (2 d, 1H), 3.97 and 3.89 (2 s, 2H), 3.76 and 3.74 (2 s, 3H), 3.4 (m, 1H), 2.90 and 2.48 (2 dd, 1H). MS: 492.2 (M + H). IR (KBr): 3420, 1739, 1652, 1510, 1496. Anal. ($C_{32}H_{29}NO_4$) C, H, N.

Method C. 2-[2-(4-Methoxyphenyl)phenyl]oxazoline (11). A THF solution of *p*-bromoanisole was prepared in a similar manner as was described for the preparation of **7**. The Grignard solution was then carefully added to a solution of (*o*-methoxyphenyl)oxazoline (6.16 g, 30 mmol) in 50 mL of THF. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution. The solution was extracted with ethyl actate. The combined organic extracts were dried over $MgSO_4$ and evaporated. The material was then chromatographed using 25–50% ethyl acetate in pentane to yield product (6.65 g, 23.7 mmol) in 79% yield. NMR ($CDCl_3$): ∂ 7.71 (d, 1H), 7.45 (d, 1H), 7.36 (m, 4H), 6.93 (d, 2H), 3.83 (s, 3H), 3.80 (s, 2H), 1.31 (s, 6H). MS: 282.4 (M + H).

2-(4-Methoxyphenyl)benzoic Acid (12). The above product, 11, was placed in methanol (250 mL) with concentrated H_2SO_4 (5 mL). The reaction mixture was heated to reflux for 4 h. The methanol was evaporated. The residue was partitioned between CH_2Cl_2 and brine. The aqueous was extracted twice more with CH_2Cl_2. The organics were dried over $MgSO_4$ and evaporated to produce the amide. This amide was then suspended in 150 mL of 4.5 N HCl. The reaction mixture was heated to reflux overnight. The reaction mixture was extracted three times with ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to yield the benzoic acid as a white solid (4.08 g, 17.9 mmol) in 75% yield. NMR (acetone-d_6): ∂ 7.80 (dd, 1H), 7.56 (td, 1H), 7.43 (m, 2H), 7.30 (d, 2H), 6.96 (d, 2H), 3.83 (s, 3H). MS: 229.2 (M + H).

Methyl 2-(Diphenylacetyl)-5-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (37). This product was prepared as an amorphous solid in a similar manner to that described in methods A and B. NMR ($CDCl_3$) two amide isomers present: ∂ 7.4-7.2 (m, 14H), 7.0–6.8 (m, 3H), 5.39 (s, 1H), 5.22 (t, 1H), 4.77 (d, 1H), 4.61 (d, 1H), 3.86 and 3.84 (2 s, 3H), 3.58 and 3.48 (2 s, 3H), 3.21 (dd, 1H), 3.04 (dd, 1H). IR (KBr): 1743, 1655, 1610. MS: 492.2 (M + H). Anal. ($C_{32}H_{29}NO_4 \cdot 0.5H_2O$) C, H, N.

2-(Diphenylacetyl)-5-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (14). This product was prepared from **37** as an amorphous solid in a similar manner to that described in method A for the preparation of **6**. NMR ($CDCl_3$) two amide isomers present: ∂ 7.5–7.0 (m, 17H), 5.72 and 5.55 (2 s, 1H), 5.24 and 5.12 (2 m, 1H), 5.01 (d, 1H), 4.78 (d, 1H), 3.30 (dd, 1H), 3.11 (dd, 1H). MS: 478.0 (M + H). IR (KBr): 1742, 1655, 1610, 1514. Anal. ($C_{31}H_{27}NO_4 \cdot 0.25H_2O$) C, H, N.

Method D. Methyl 2-(Diphenylacetyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (16). Methyl 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, 15 (1.03 g, 4.23 mmol), was dissolved in 100 mL of glyme. Diisopropylethylamine (1.5 mL, 8.4 mmol) was added. After 5 min, diphenylacetyl chloride (1.03 g, 4.47 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was dissolved in dichloromethane, washed with water, dried over $MgSO_4$, and evaporated. The material was chromatographed using 5% methanol in dichloromethane to yield product as a white solid (0.42 g, 1.0 mmol) in 25% yield. NMR ($CDCl_3$) two amide isomers present: ∂ 7.4–7.2 (m, 10H), 6.76 (m, 1H), 6.60 (m, 2H), 5.45 (M, 1H), 5.37 and 5.30 (2 s, 1H), 4.67 (d, 1H), 4.49 (d, 1H), 3.61 and 3.50 (2 s, 3H), 3.17 (dd, 1H), 3.04 (dd, 1H). MS: 402.1 (M + H).

Methyl 2-(Diphenylacetyl)-6-[(trifluoromethyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (17). The above product, 16, was dissolved in 5 mL of pyridine. The solution was cooled in an ice bath. Trifluoromethanesulfonic anhydride (0.34 mL, 2.0 mmol) was added dropwise into the solution. The reaction mixture was stirred at 0 °C for 5 min. It was then warmed to room temperature and stirred overnight. The reaction mixture was poured into 25 mL of water and extracted three times with ether. The combined ether extracts were washed with water, 10% HCl, water, and brine, dried over $MgSO_4$, and evaporated. The triflate was obtained as a white solid (0.49 g, 0.92 mmol) in 90% yield. NMR ($CDCl_3$) two amide isomers present: ∂ 7.4–6.9 (m, 13H), 5.57 and 4.95 (2 m), 5.35 and 5.18 (2 s, 1H), 4.75 (d, 1H), 4.56 (d, 1H), 3.62 and 3.53 (2 s, 3H), 3.30 (dd, 1H), 3.14 and 2.82 (2 dd, 1H). MS: 534.0 (M + H).

Methyl 2-(Diphenylacetyl)-6-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (18). LiCl (0.11 g, 2.6 mmol), phenyltrimethyltin (0.24 g, 1.0 mmol), and 17 were added to 15 mL of dioxane. Tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.095 mmol) was then added. The reaction mixture was heated to reflux for 3 days. The reaction mixture was poured into butyl chloride and was washed twice with water. The butyl chloride was evaporated. The residue was flash chromatographed using 50% ethyl acetate in hexane. Methyl 2-(diphenylacetyl)-6-phenyltetrahydroisoquinoline-3-carboxylate was obtained as a foam (0.19 g, 0.41 mmol) in 45% yield. NMR ($CDCl_3$) two amide isomers: ∂ 7.5–7.0 (m, 18H), 5.57 and 4.98 (2 m, 1H), 5.39 and 5.20 (2 s, 1H), 4.80 (d, 1H), 4.62 (d, 1H), 3.62 and 3.52 (2 s, 3H), 3.4–3.2 (m, 2H). MS: 462.0 (M + H).

2-(Diphenylacetyl)-6-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (19). This was prepared from 18 as an amorphous solid in a similar manner to that described in method A for the preparation of 6. NMR (acetone-d_6) two amide isomers present: δ 7.6–7.1 (m, 17H), 5.75 and 5.63 (2 s, 1H), 5.52 and 5.27 (2 m, 1H), 5.10 and 5.04 (2 d, 1H), 4.78 and 4.55 (2 d, 1H), 3.4–3.2 (m, 2H). Anal. ($C_{30}H_{25}NO_3 \cdot 0.75H_2O$) C, H, N.

Methyl 2-[(*N*,*N*-Diphenylamino)carbonyl]-5-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid. Methyl 5-[(4-methoxyphenyl)methyl]tetrahydroisoquinoline-3-carboxylate (0.95 g, 3.1 mmol) and diisopropylethylamine (0.53 mL, 3.0 mmol) were dissolved in 200 mL of THF. After 5 min, diphenylcarbamoyl chloride (0.72 g, 3.1 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in dichloromethane, washed with water, dried over $MgSO_4$, and evaporated. The product was then flash chromatographed using 0–2% methanol in dichloromethane to yield an amorphous solid (0.57 g, 1.1 mmol) in 36% yield. NMR ($CDCl_3$): δ 7.3–6.8 (m, 17H), 5.00 (bs, 1H), 4.54 (d, 1H), 4.22 (d, 1H), 3.89 (s, 2H), 3.79 (s, 3H), 3.60 (s, 3H), 3.10 (dd, 1H). MS: 507.4 (M + H). IR (KBr): 1742, 1713, 1663, 1609, 1590, 1511. Anal. ($C_{32}H_{30}N_2O_4$) C, H, N.

2-[(*N*,*N*-Diphenylamino)carbonyl]-5-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (31). This was prepared from the methyl ester as an amorpous solid in a similar manner as was described in method A for the preparation of 6. NMR (acetone-d_6): δ 7.3–6.9 (m, 17H), 4.92 (m, 1H), 4.59 (d, 1H), 4.36 (d, 1H), 3.91 (s, 2H), 3.76 (s, 3H), 3.18 (m, 1H), 2.68 (m, 1H). MS: 493.4 (M + H). IR (KBr): 1739, 1663, 1612, 1591, 1510, 1492. Anal. ($C_{31}H_{28}N_2O_4 \cdot 0.5H_2O$) C, H; N: calcd, 5.58; found, 4.90.

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