(Dipropylphenoxy)phenylacetic Acids: A New Generation of Nonpeptide Angiotensin II Receptor Antagonists

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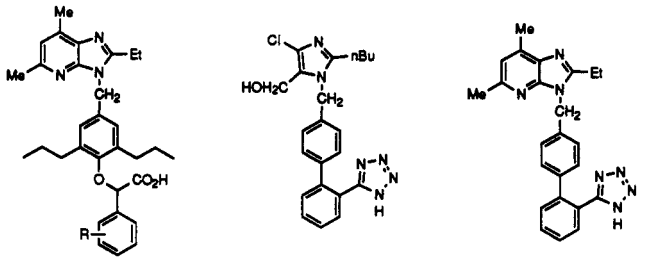
The renin–angiotensin system (RAS) is a major regulator of blood pressure/ and electrolyte and fluid homeostasis.[1-5] The first step in the renin–angiotensin cascade is the production of biologically inactive decapeptide angiotensin I (AI) by cleavage of angiotensinogen by renin. AI is converted to the potent vasoconstrictor octapeptide angiotensin II (AII) by angiotensin-converting enzyme (ACE). Biochemical effects of the active hormone AII, such as vasoconstriction, aldosterone release, and renal reabsorption of sodium are thought to be mediated by actions of membrane-bound receptors present on various tissues and organs such as adrenal cortex, heart, kidney, arterioles, and sympathetic nerve endings.

Inhibition of the RAS[6-8] by renin inhibitors,[9] ACE inhibitors,[10] and AII receptor antagonists[11] continues to be the most active area of drug discovery for the treatment of hypertension and congestive heart failure. Despite the considerable progress made in the design of orally active renin inhibitors, the ultimate goal of discovering renin inhibitors with adequate oral bioavailability remained unachieved until recently.[6,9,12] Designs of orally active renin inhibitors with good oral bioavailability have recently been reported.[12] Although ACE inhibitors are highly effective and widely used antihypertensive agents, they suffer from side effects such as cough and angiodema due to elevated levels of bradykinin and substance P caused by the inhibition of their cleavage by ACE inhibitors.[10,13,14] An alternate and more direct mode of blocking the RAS is by antagonism of the effector hormone AII at the receptor level. This specific approach to inhibit the RAS offers considerable potential for the treatment of hypertension with minimal side effects. Peptidic AII antagonists such as saralasin ([Sar[1],Ala[8]]AII) have been known for sometime, but their use as therapeutic agents is limited by their lack of oral absorption, rapid clearance, and partial agonist activity.[15] The development of nonpeptide AII receptor antagonists has attracted much attention.[6] The first report on the prototype imidazole-based nonpeptide AII antagonists was disclosed by the Takeda group.[16] Structural modifications of the Takeda lead compound by Du Pont led to the discovery of 2-*n*-butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole (**2**, DuP 753, losartan, Figure 1) which is currently undergoing clinical trials.[17] A highly potent, orally-active, and longer-acting AII antagonist 5,7-dimethyl-2-ethyl-3-[[2-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazo[4,5-*b*]pyridine (**3**, L-158,809, Figure 1), in which the imidazole of DuP 753 is replaced with imidazopyridine, has been reported by Merck.[18] A potent series of AII antagonists which incorporates triazoles and imidazotriazoles as replacements for the heterocycles of **2** and **3** has recently been reported.[19] While a number of studies have appeared in which the imidazole of **2** is varied,[20] reports on efficient biphenyl–tetrazole replacements are scarce.[21] In our continuing efforts to discover an efficient bioisostere replacement for biphenyl–tetrazole moiety, we have recently reported two new series of AII receptor antagonists in which N-substituted indoles/dihydroindoles and N-substituted (phenylamino)phenylacetic acids and acylsulfonamides serve as efficient biphenyl–tetrazole replacements.[22,23] We then became interested in developing phenoxyphenylacetic acids as a biphenyl–tetrazole mimic for **3**.[24] Herein, we report the discovery of a new generation of potent and orally active nonpeptide AII receptor antagonists (**1**, Figure 1) derived from (dipropylphenoxy)-phenylacetic acids.



1 **2** (DuP 753, Losartan) **3** (L-158,809)

Figure 1. Angiotensin II receptor antagonists.

Chemistry. Synthesis of (dipropylphenoxy)phenylacetic acids (**22–32**) is illustrated in Scheme I and II. Methyl 4-hydroxybenzoate (**4**) was alkylated with allyl bromide using K_2CO_3 in refluxing acetone to give **5**. Claisen rearrangement of the allyl aryl ether **5** in refluxing 1,2-dichlorobenzene in the presence of a trace amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) gave the rearranged product **6**. Methyl 3-allyl-4-hydroxybenzoate (**6**) was alkylated once again with allyl bromide to give allyl aryl ether **7** which was subjected to Claisen rearrangement conditions (1,2-dichlorobenzene/BHT/reflux) to give **8**. Methyl 3,5-diallyl-4-hydroxybenzoate **8** was silylated with *tert*-butyldimethylsilyl chloride in the presence of triethylamine and DMAP to provide the silyl ether **9** which upon hydrogenation in the presence of 5% Rh/C as a catalyst in ethanol gave the reduced dipropyl derivative **10**. $LiAlH_4$ reduction of **10** in THF afforded the corresponding alcohol **11** as a common intermediate for two different synthetic routes for the production of (dipropylphenoxy)phenylacetic acids (**22–32**). In the first method, **11** was desilylated with *n*-Bu_4NF in THF to give alcohol **12** which was selectively alkylated with various α-bromo esters **16** using cesium carbonate in DMF to give **18** as described in Scheme I. Treatment of various alcohol derivatives **18** with Ph_3P and CBr_4 in CH_2Cl_2 gave the corresponding bromides **19**. Alkylation of 5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (**20**)[18] with aryl bromides **19** yielded the esters **21**. Saponification of esters **21** with aqueous LiOH or NaOH in methanol gave the desired (dipropylphenoxy)phenylacetic acids (**22–32**).

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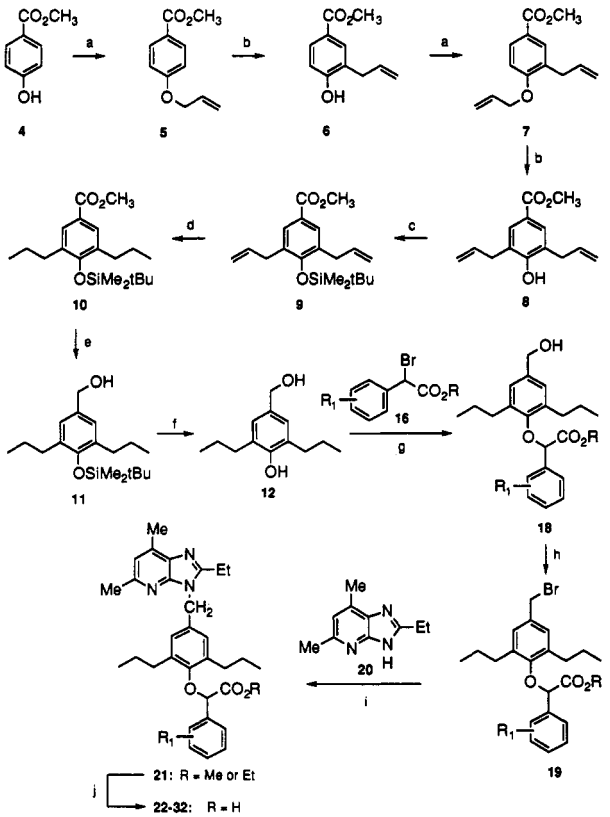
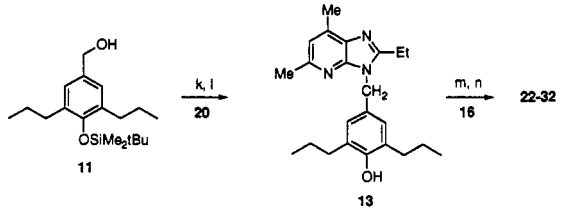
Scheme I[a]



[a] (a) K_2CO_3, $CH_2{=}CHCH_2Br$, acetone, reflux (89%); (b) 1,2-dichlorobenzene, BHT, reflux (90%); (a) **6** to **7** (87%); (b) **7** to **8** (94%); (c) t-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2 (97%); (d) H_2, 5% Rh/C, EtOH (90%); (e) $LiAlH_4$ (1 M in THF), THF, 0 °C to room temperature (92%); (f) *n*-Bu_4NF, THF (88%); (g) Cs_2CO_3, DMF, **16** (52–65%); (h) Ph_3P, CBr_4, CH_2Cl_2 (68–85%); (i) **20**, Cs_2CO_3, DMF (55–72%); (j) 1 N aqueous LiOH/NaOH, MeOH (58–85%).

Scheme II[a]

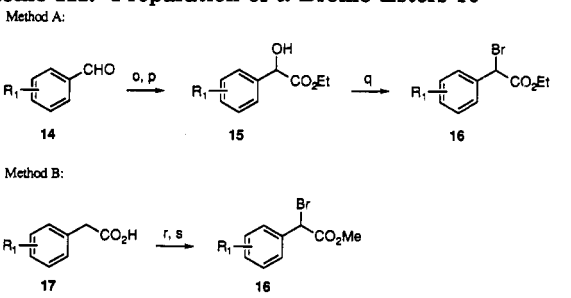


[a] (k) **20**, Ph_3P, DEAD, THF, 0 °C (82%); (l) *n*-Bu_4NF, THF (93%); (m) K_2CO_3, acetone, **16**, reflux (80–96%); (n) 1 N aqueous LiOH/NaOH, MeOH (58–85%).

In an alternate route, the common intermediate **11** was coupled with the imidazopyridine **20** under Mitsunobu conditions[25] (Ph_3P/DEAD/THF), followed by desilylation of the coupled product with *n*-Bu_4NF in THF to give **13** as described in Scheme II. The phenol derivative **13** was then alkylated cleanly with various α-bromo esters **16** by simply refluxing in acetone with K_2CO_3 to produce the corresponding esters **21** which upon saponification yielded the corresponding (dipropylphenoxy)phenylacetic acids (**22–32**).

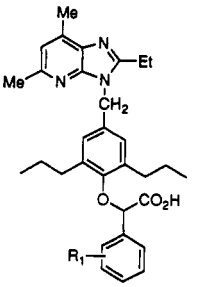
Various α-bromo esters **16** utilized in the synthesis of (**22–32**) were prepared by two methods as described in Scheme III. In method A, substituted aryl aldehydes **14** were treated with Me_3SiCN in CH_2Cl_2 and a trace amount of KCN and 18-crown-6 to give trimethylsilyl ethers of cyanohydrin adducts (not shown) which were hydrolyzed by treatment with gaseous HCl in ethanol to provide the corresponding α-hydroxy esters **15**. These ethyl α-hydroxyphenylacetates **15** were converted to α-bromo esters **16** by treatment with $Ph_3P/CBr_4/CH_2Cl_2$. In method B, various phenylacetic acids **17** were converted to their corresponding esters (not shown) by refluxing in MeOH or EtOH with a catalytic amount of H_2SO_4. These esters were then brominated by refluxing with *N*-bromosuccinimide (NBS) in CCl_4 to give the α-bromo esters **16**.

Scheme III. Preparation of α-Bromo Esters **16**[a]



[a] Method A: (o) Me_3SiCN, KCN, 18-crown-6, CH_2Cl_2 (84–92%); (p) HCl gas, EtOH (82–95%); (q) Ph_3P, CBr_4, CH_2Cl_2, 0 °C to room temp (76–95%). Method B: (r) MeOH, cat. H_2SO_4, reflux (75–96%); (s) NBS, AIBN, CCl_4, reflux (55–72%).

Table I. AT_1 (rabbit aorta) and AT_2 (rat midbrain) Receptor Antagonist Activity of (Dipropylphenoxy)phenylacetic Acids (**22–32**)



compd	R_1	IC_{50}, nM[a] AT_1	AT_2
22	H	0.9	2600
23	2-Me	1.2	7500
24	2-Cl	0.53	3500
25	3-Me	0.74	800
26	3-Cl	0.75	2300
27	3-OPh	0.47	1600
28	3-Ph	6.8	740
29	4-Me	4.0	400
30	4-Cl	2.8	450
31	4-Et	19	240
32	4-OPh	5.2	1900
2[b]		54	>30000
3[b]		0.54	>10000

[a] For racemic mixtures. [b] Data from ref 26.

Biological Results and Discussion. The *in vitro* [^{125}I][Sar^1,Ile^8]AII binding assays of compounds (**22–32**) reported here (Table I) were performed as described by Chang et al. using rabbit aorta and rat midbrain as receptor sources for AT_1 and AT_2 receptors, respectively.[26] The relative potencies of the antagonists are expressed as the inhibitory concentration (IC_{50}) of the test compound required to completely displace 50% of the specifically bound [^{125}I][Sar^1,Ile^8]AII from the receptor. The data shown in Table I for racemic **22–32** demonstrate that (dipropylphenoxy)phenylacetic acid-based AII antagonists in general exhibit high potency at the AT_1 receptor subsite; the parent compound **22** shows a subnanomolar AT_1 activity (0.9 nM). Substitution at the ortho and meta position of the bottom phenyl ring of (dipropylphenoxy)-phenylacetic acids generally gives antagonists with in-

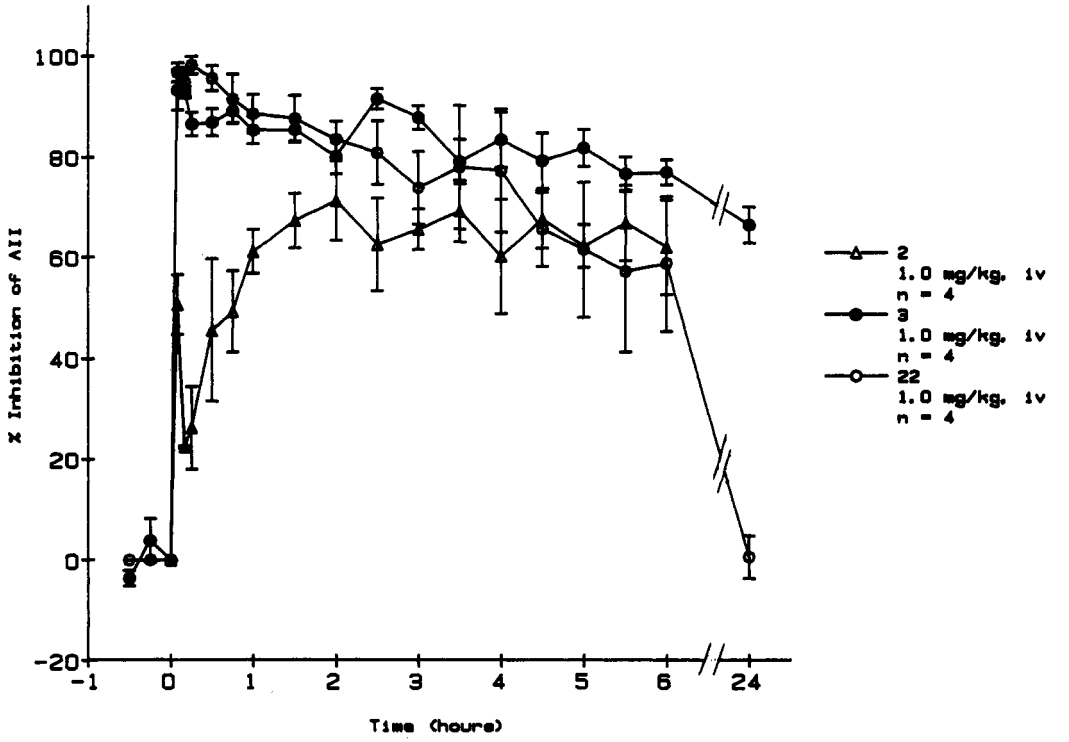


Figure 2. Comparison of *in vivo* activity of **22** with **2** and **3** in conscious normotensive rats. Inhibition of AII-induced (0.1 μg/kg) pressor response after iv administration of **22**, **2**, and **3**. *n* is the number of animals treated.

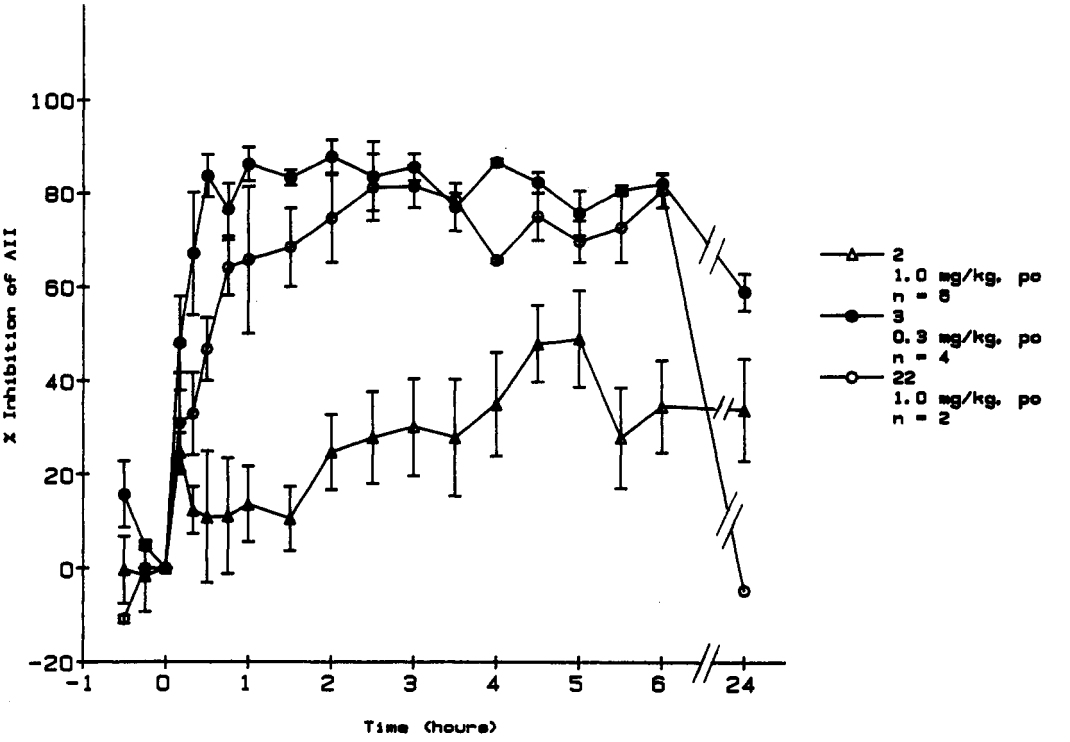


Figure 3. Comparison of *in vivo* activity of **22** with **2** and **3** in conscious normotensive rats. Inhibition of AII-induced (0.1 μg/kg) pressor response after po administration of **22**, **2**, and **3**. *n* is the number of animals treated.

creased binding affinity for the AT_1 receptor. Incorporation of 2-Cl and 3-Cl resulted in subnanomolar AT_1 antagonists **24** (AT_1IC_{50} = 0.53 nM) and **26** (AT_1 IC_{50} = 0.75 nM), respectively. While substitution by 2-methyl gave a nanomolar compound **23**, incorporation of a 3-methyl group produced a subnanomolar antagonist **25**. Further enhancement in the AT_1 potency was realized when a *m*-phenoxy (3-OPh) group was introduced in **27** (IC_{50} = 0.47 nM). Substitution at C-4 (**29–32**) results in a decrease of the AT_1 binding affinity. These SAR suggest that the C-2 and C-3 substituents bind to the hydrophobic region of the AT_1 receptor more effectively than the C-4 substituents. Comparison of the AT_1 binding affinities of the (dipropylphenoxy)phenylacetic acid-based AII antagonists with **2** and **3** shows that several subnanomolar AT_1-selective antagonists (**24–27**) are equipotent to **3** and exhibit higher AT_1 potency than **2**.

The AT_2-receptor binding affinity of these compounds (**22–32**) was increased with substitution at C-3 and C-4 of the bottom phenyl ring while C-2 substitution resulted in

a decrease in potency (Table I). AT_2 binding affinity of **31** (IC_{50} = 0.24 μM) is noteworthy in which incorporation of C-4 Et not only enhances the AT_2 binding affinity but decreases the AT_1 affinity as well. The results presented in Table I suggest that lipophilic groups at C-3 and particularly at C-4 may be binding to the hydrophobic region of the AT_2 receptor binding site.[27] These observations offer considerable potential for development of this new class of compounds into AII receptor antagonists with balanced AT_1/AT_2 activity. Although no definitive physiological role for the AT_2 binding site has, as yet, been established, several possibilities have been proposed.[28] Should a physiologically or pharmacologically important role for this receptor be uncovered, a balanced receptor antagonist may prove to be an important tool for research as well as an important therapeutic agent.

Antagonist **22** was evaluated for *in vivo* activity by determining the inhibition of AII-induced pressor response in conscious normotensive rats.[29] Compound **22** inhibited the AII-induced pressor response with long duration of action (>6 h) when administered at 1.0 mg/kg intravenously (Figure 2) and orally (Figure 3) to conscious normotensive rats. Comparison of the potent AII antagonist **22** with **2** and **3** in Figures 2 and 3 shows that **22** has excellent *in vivo* activity in rats both in iv and po administrations.

In conclusion, the new design of nonpeptide AII antagonists disclosed here, which incorporates a (dipropylphenoxy)phenylacetic acid element, serves as a highly-efficient biphenyl–tetrazole mimic for the potent AII antagonist **3**. Thus, we have discovered a new series of orally-active AII antagonists with high affinity for AT_1 receptor and considerable potential for balanced affinity for the AT_1/AT_2 receptors.

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Supplementary Material Available: Experimental details for the syntheses of all compounds (11 pages). Ordering information is given on any current masthead page.

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