

(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 RAS⁶⁻⁸ by renin inhibitors,⁹ ACE inhibitors,¹⁰ and AII receptor antagonists¹¹ 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 ([Sar¹,Ala⁸]AII) have been known for some time, 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

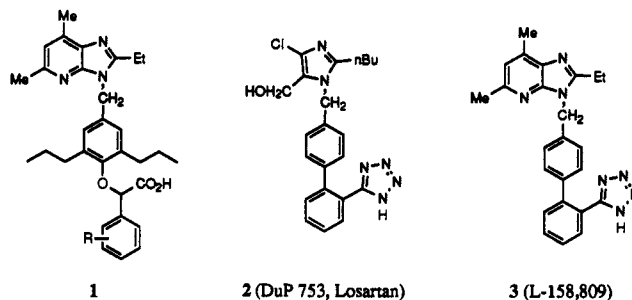


Figure 1. Angiotensin II receptor antagonists.

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 acyl-sulfonamides 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.

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 K₂CO₃ 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. LiAlH₄ 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*-Bu₄NF 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 Ph₃P and CBr₄ in CH₂Cl₂ 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).

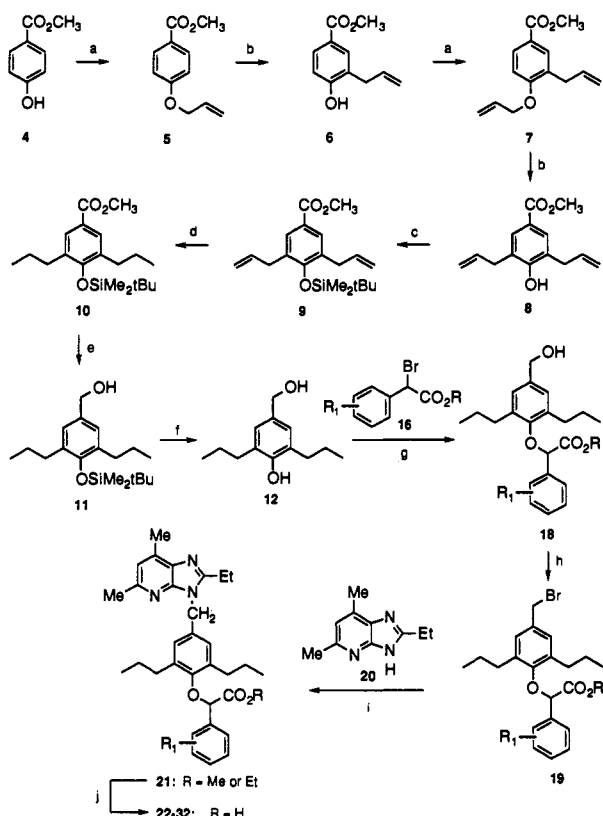
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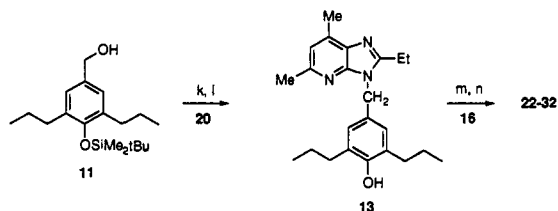
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Scheme I^a

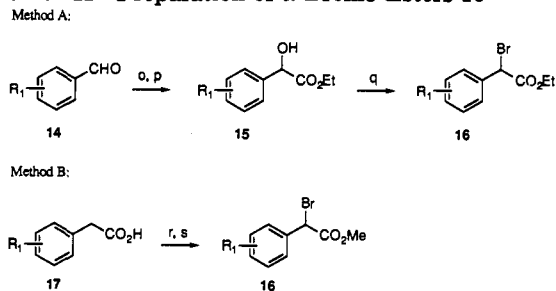
^a (a) K_2CO_3 , $CH_2=CHCH_2Br$, acetone, reflux (89%); (b) 1,2-dichlorobenzene, BHT, reflux (90%); (c) 6 to 7 (87%); (d) 7 to 8 (94%); (e) $t-BuMe_2SiCl$, Et_3N , DMAP, CH_2Cl_2 (97%); (f) H_2 , 5% Rh/C, EtOH (90%); (g) $LiAlH_4$ (1 M in THF), THF, 0 °C to room temperature (92%); (h) $n-Bu_4NF$, THF (88%); (i) Ca_2CO_3 , DMF, 16 (52–65%); (j) Ph_3P , CBR_4 , CH_2Cl_2 (68–85%); (k) 20 , Ca_2CO_3 , DMF (55–72%); (l) 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 conditions²⁵ (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 -hy-

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. AT₁ (rabbit aorta) and AT₂ (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.

droxyphenylacetates **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**.

Biological Results and Discussion. The *in vitro* [¹²⁵I][Sar¹,Ile⁸]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 AT₁ and AT₂ receptors, respectively.²⁶ The relative potencies of the antagonists are expressed as the inhibitory concentration (IC₅₀) of the test compound required to completely displace 50% of the specifically bound [¹²⁵I][Sar¹,Ile⁸]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 AT₁ receptor subsite; the parent compound **22** shows a subnanomolar AT₁ 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-

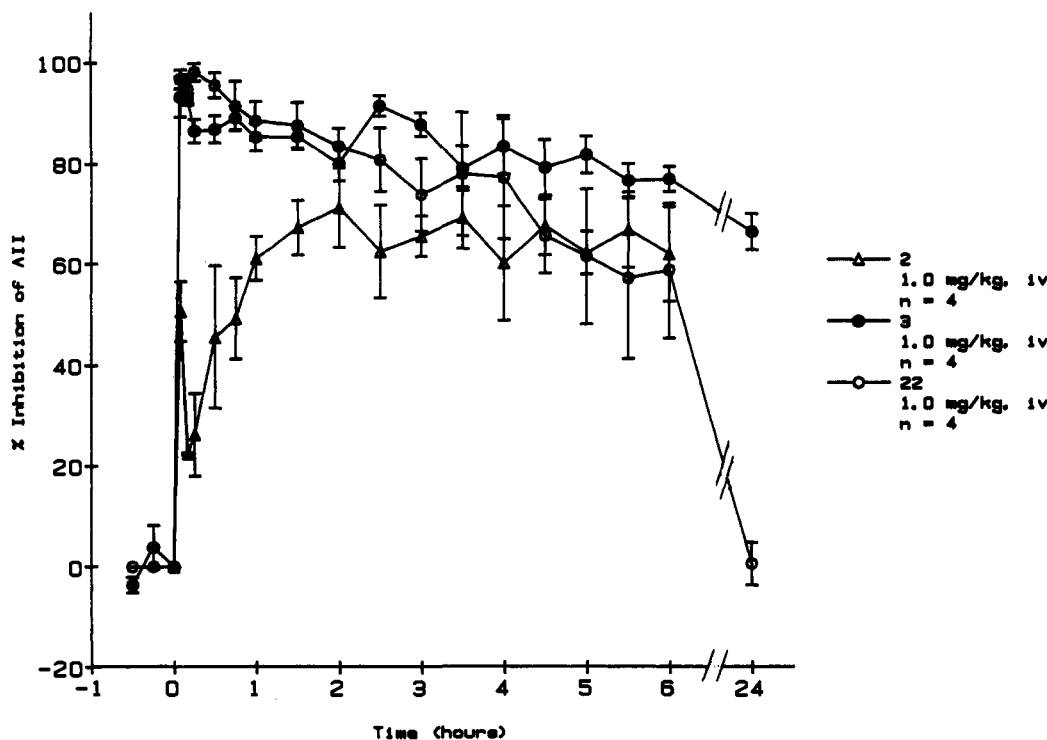


Figure 2. Comparison of *in vivo* activity of 22 with 2 and 3 in conscious normotensive rats. Inhibition of AII-induced ($0.1 \mu\text{g}/\text{kg}$) pressor response after iv administration of 22, 2, and 3. n is the number of animals treated.

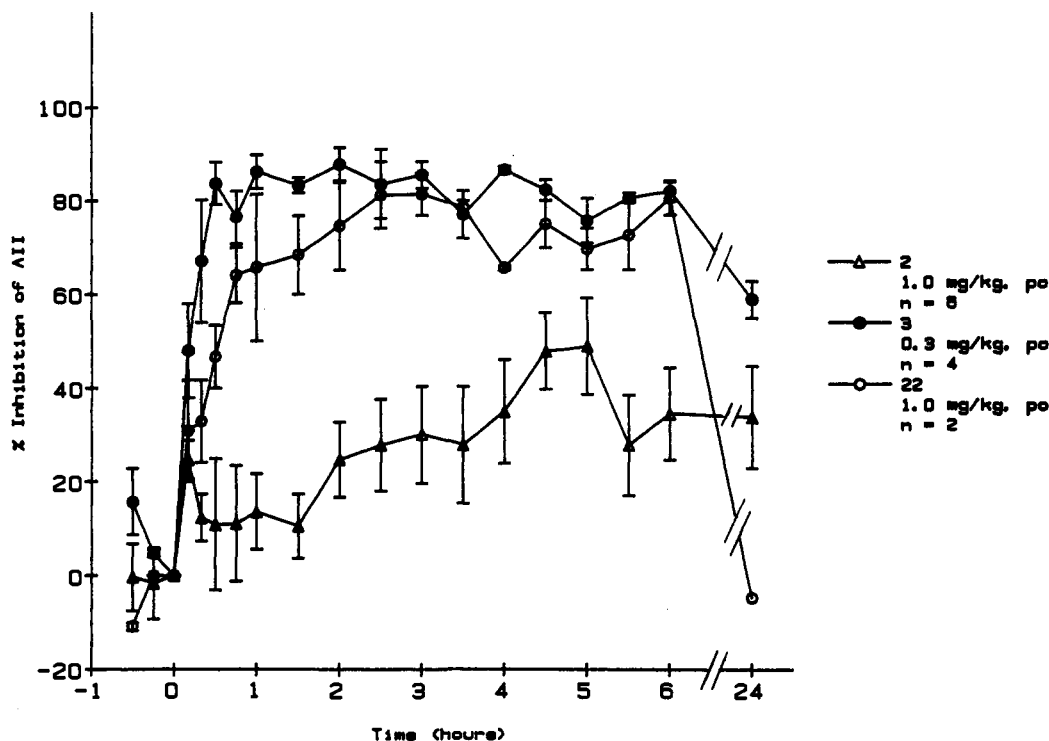


Figure 3. Comparison of *in vivo* activity of 22 with 2 and 3 in conscious normotensive rats. Inhibition of AII-induced ($0.1 \mu\text{g}/\text{kg}$) pressor response after po administration of 22, 2, and 3. n is the number of animals treated.

creased binding affinity for the AT_1 receptor. Incorporation of 2-Cl and 3-Cl resulted in subnanomolar AT_1 antagonists 24 ($\text{AT}_1 \text{IC}_{50} = 0.53 \text{ nM}$) and 26 ($\text{AT}_1 \text{IC}_{50} = 0.75 \text{ nM}$), 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 ($\text{IC}_{50} = 0.47 \text{ nM}$). 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). AT₂ binding affinity of 31 (IC₅₀ = 0.24 μM) is noteworthy in which incorporation of C-4 Et not only enhances the AT₂ binding affinity but decreases the AT₁ 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 AT₂ receptor binding site.²⁷ These observations offer considerable potential for development of this new class of compounds into AII receptor antagonists with balanced AT₁/AT₂ activity. Although no definitive physiological role for the AT₂ 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 AT₁ receptor and considerable potential for balanced affinity for the AT₁/AT₂ 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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