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# α-PHENOXYPHENYLACETIC ACID DERIVED ANGIOTENSIN II ANTAGONISTS WITH LOW NANOMOLAR $AT_1/AT_2$ RECEPTOR SUBTYPE AFFINITY (Part II)[1]

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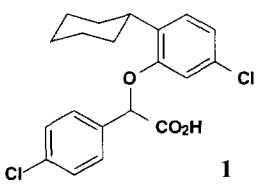
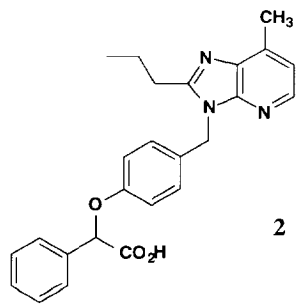
***Abstract:*** Directed synthesis and pharmacological evaluation in a recently described class of α-phenoxyphenylacetic acid bearing angiotensin II (AII) receptor antagonists has afforded further potent $AT_1$-selective AII antagonists. Substitution in the central aromatic ring significantly increases $AT_2$ receptor affinity such that the *n*-propyl derivative **7g** displayed low nanomolar potency at both $AT_1$ and $AT_2$ receptor subtypes.

The vasoconstrictive hormone angiotensin II (AII) produced by the renin-angiotensin system (RAS) is a potent regulator of blood pressure homeostasis, fluid volume and electrolyte balance in mammals.[2] Pharmacological blockade of the RAS cascade with angiotensin converting enzyme (ACE) inhibitors is now firmly established for the management of essential hypertension and the prevention of congestive heart failure.[3] In the last several years new orally active, nonpeptidic AII receptor antagonists such as losartan have emerged as alternative and potentially superior agents for lowering blood pressure in hypertensive patients.[4] We recently described the design of a new series of AII antagonists exemplified by **2** (Figure 1) based upon integrating the α-phenoxyphenylacetic acid element of a weakly active lead (**1**) found through screening with a 2-propyl-6-methylimidazo[4,5-*b*]pyridine heterocyclic element which had previously been reported by these laboratories to enhance the potency for another series of AII antagonists.[5] In this paper we describe efforts to optimize the heterocyclic substituent of the α-phenoxyphenylacetic acid based AII antagonists, as well as further structure-activity relationship (SAR) studies which have afforded highly potent $AT_1$-selective and low-nanomolar $AT_1/AT_2$ balanced AII receptor antagonists.




**1**




**2**

Figure 1.

**Chemistry.** Identification of an effective heterocyclic substituent for α-phenoxyphenylacetic acids was greatly facilitated by the availability of several novel heterocycles which were concurrently under investigation in our laboratories as pharmacophores in other biphenyltetrazole based AII antagonists. Figure 2 illustrates the structures of several of these prototypes (**6-8**)[6] which were prepared from either 2-butylbenzimidazole (**3**),[7] 2-ethyl-5,7-dimethylimidazo[4,5-*b*]pyridine (**4**),[5] or 2-butyl-6-methylquinazolin-4(3H)-one (**5**)[8] and methyl α-(4-bromomethylphenoxy)phenylacetate (**11a**, $R^1$-$R^3$ = H) as previously described.[1] Additionally, the imidazo[1,2-*b*]pyridazine bearing α-phenoxyphenylacetic acid (**10**) was also prepared from phenol **9**[9] as indicated in Scheme I. Examination of the AII receptor binding affinities for the prototype compounds that are summarized in Table 1[10] prompted the selection of the 2-ethyl-5,7-dimethylimidazo[4,5-*b*]pyridine **4** as the preferred substituent for subsequent SAR studies in this series.

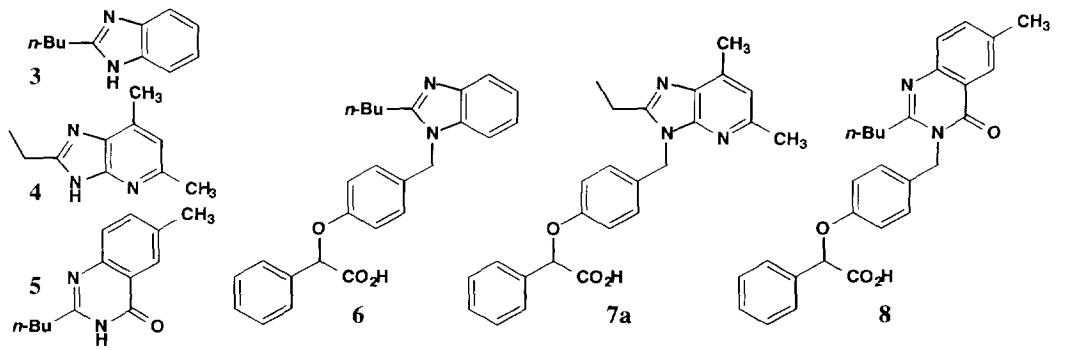
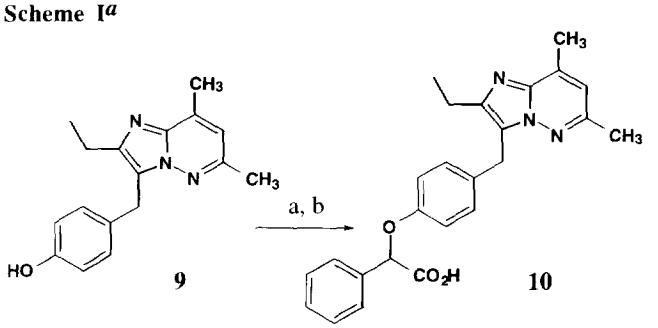



Figure 2.

**Scheme I**[a]



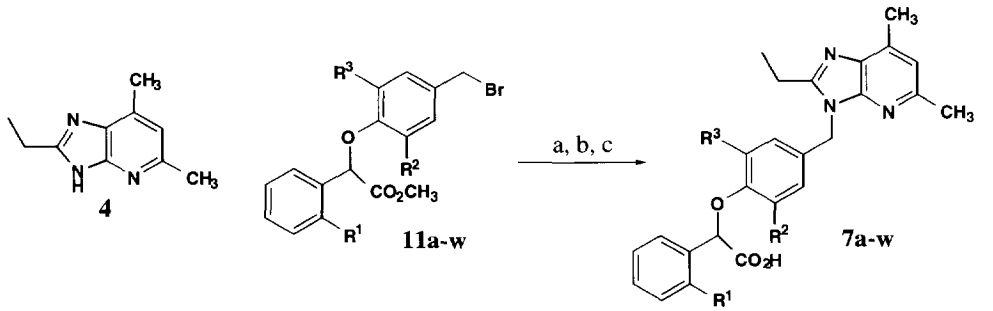

[a]Reagents: (a) methyl α-bromophenylacetate, $K_2CO_3$, acetone, reflux, 2 h; (b) NaOH, MeOH, rt, 3 h.

**Table 1.** $IC_{50}$s (nM) for **2, 6-8, 10**.

| Entry | $AT_1$ (rabbit aorta) | $AT_2$ (rat midbrain) |
|---|---|---|
| **2** | 65 | 3400 |
| **6** | 93 | 2000 |
| **7a** | 29 | 2000 |
| **8** | 260 | 760 |
| **10** | 69 | 3000 |

At the outset of our studies we were intrigued by the hydrophobic cyclohexyl substituent present in the screening lead (**1**) and chose to evaluate the potential contribution of substituents at this position (**7d-7w**) in the middle aromatic ring of this series. We were also aware from our previous studies that *ortho* substitution in the lower aromatic ring could increase the $AT_1$ receptor antagonist potency for these compounds,[1] consequently derivatives bearing one or both of these substitutions were of interest. Table 2 lists the structures and AII receptor binding affinities for the imidazo[4,5-*b*]pyridine substituted α-phenoxyphenylacetic acids (**7a-w**)

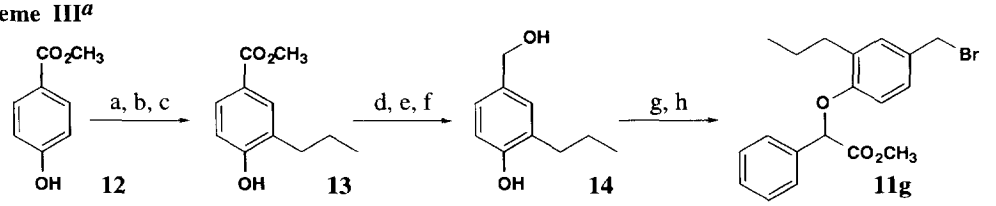
**Scheme II**[a]




[a]Reagents: (a) **4**, NaH, DMF, rt, 30 min; (b) add **11a-w**, DMF, rt, 2 h; (c) NaOH, MeOH, rt, 3 h.

targeted in this investigation. Compounds **7a-w** were prepared using the generalized method illustrated in Scheme II. The requisite methyl α-(4-bromomethylphenoxy)phenylacetates (**11a-w**) were synthesized by alkylation of various readily available phenols with *ortho*-substituted methyl α-bromophenylacetates as previously described.[1] A representative preparation of alkylating agent **11g** bearing the hydrophobic *n*-propyl substituent at position $R^2$ is illustrated in Scheme III.

**Scheme III**[a]




[a]Reagents: (a) allyl bromide, $K_2CO_3$, acetone, 65°C, 2 h; (b) *o*-dichlorobenzene, 190°C, 3 h; (c) $H_2$ (45 psi), 10% Pd/Carbon, EtOH; (d) *t*-BuMe$_2$SiCl, $Et_3N$, DMAP (cat), $CH_2Cl_2$, rt, 1 h; (e) $LiAlH_4$, THF, rt, 1 h; (f) (*n*-Bu)$_4$NF, THF, rt, 3 h; (g) methyl α-bromophenylacetate, $K_2CO_3$, acetone, 65°C; (h) $PBr_3$, $CCl_4$, rt, 30 min.

**Results.** Examination of the $IC_{50}$s obtained for compounds **7a-w** (Table 2) reveals several trends. A single substitution at the $R^1$ position in the lower aromatic ring (**7b-c**) provides $AT_1$-selective compounds with low nanomolar potency consistent with our earlier findings. Alkyl or chloro substituents at the $R^2$ position in the middle aromatic ring (**7d-7k**) are also potency enhancing towards $AT_1$ receptors, but these appear to have an even greater influence at the $AT_2$ subtype. This effect is most striking for the *n*-propyl substituted derivative **7g** which displays a 40-fold improvement in $AT_2$ potency relative to the unsubstituted derivative **7a**, and achieves low nanomolar potency for both receptor subtypes. The contributions of the $R^1$ and $R^2$ substituents are not additive however, as evidenced by the hybrid structures **7q-t** which revert to $AT_1$ selectivity.

We further sought to examine the *in vivo* pharmacological efficacy for one of the imidazo[4,5-*b*]pyridine substituted α-phenoxyphenylacetic acid AII antagonists. The mono-chloro derivative **7d** (L-159,257) was selected for evaluation based upon its good $AT_1$ binding affinity (15 nM), and was used in a standard protocol which assesses a test compounds ability to block the pressor effects induced by exogenous AII challenges (0.1 μg/kg i.v.) in conscious normotensive male Sprague-Dawley rats.[11] Figure 3 illustrates the time course for inhibition of AII-induced pressor responses following intravenous and oral administration of **7d** at 3 mg/kg. As illustrated in Figure 3, **7d** achieved effective initial inhibition of the pressor response following either route

**Table 2.** $IC_{50}$s (nM) for compounds **7a-w**.

| Entry | $R^1$ | $R^2$ | $R^3$ | $AT_1$ | $AT_2$ |
|---|---|---|---|---|---|
| **7a** | | | | 29 | 2000 |
| **7b** | Me | | | 6 | 5200 |
| **7c** | Cl | | | 10 | 15000 |
| **7d** | | Cl | | 15 | 720 |
| **7e** | | Me | | 14 | 940 |
| **7f** | | Et | | 12 | 410 |
| **7g** | | *n*-propyl | | 11 | 47 |
| **7h** | | *n*-butyl | | 12 | 140 |
| **7i** | | allyl | | 20 | 270 |
| **7j** | | *i*-propyl | | 30 | 3300 |
| **7k** | | *t*-butyl | | 50 | 300 |
| **7l** | | benzyl | | 95 | 800 |
| **7m** | | acetyl | | 62 | 610 |
| **7n** | | benzoyl | | 120 | 60 |
| **7o** | | OMe | | 170 | 2900 |
| **7p** | | OEt | | 140 | 1200 |
| **7q** | Cl | *n*-propyl | | 8 | >1000 |
| **7r** | Me | *n*-propyl | | 11 | 2400 |
| **7s** | OMe | *n*-propyl | | 9.5 | 1200 |
| **7t** | Me | Cl | | 3.4 | 1700 |
| **7u** | | allyl | Cl | 2.2 | 760 |
| **7v** | | Cl | Cl | 21 | 9000 |
| **7w** | | Cl | OMe | 16 | 7800 |

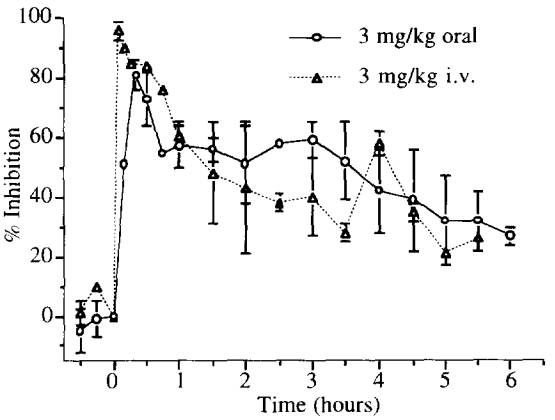



Figure 3. *In vivo* inhibition of pressor response by **7d**.

of administration indicating acceptable oral bioavailability, and it provides sustained functional blockade with a duration of action greater than four hours.

The demonstration of significant improvement in the $AT_2$ receptor potency in the α-phenoxyphenylacetic acid class of AII antagonists may present potential pharmacological advantages for compounds similar to those described here. We continue our interest in this series of compounds and will communicate our further efforts in due course.

**Acknowledgment**. We thank Dr. Lawrence Colwell and Mrs. Amy Bernick for FAB-mass spectrometry analysis.

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10. Binding affinities expressed as $IC_{50}$s for the compounds in Tables 1 and 2 were determined by their ability to displace the specific binding ligand $^{125}$I-Sar$^1$,Ile$^8$-AII from rabbit aortic membrane ($AT_1$) and rat brain membrane in the presence of 5 mM dithiothreitol ($AT_2$) receptors as described in: Chang, R.S.L.; Siegl, P.K.S.; Clineschmidt, B.V.; Mantlo, N.B.; Chakravarty, P.K.; Greenlee, W.J.; Patchett, A.A.; Lotti, V.J. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 133 with the exception that the 0.2% BSA component was ommited.
11. See reference 5, footnote 11.

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