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AT_1 SELECTIVE ANGIOTENSIN II ANTAGONISTS WITH PHENOXYPHENYLACETIC ACID AS A BIPHENYL REPLACEMENT PART I[1]

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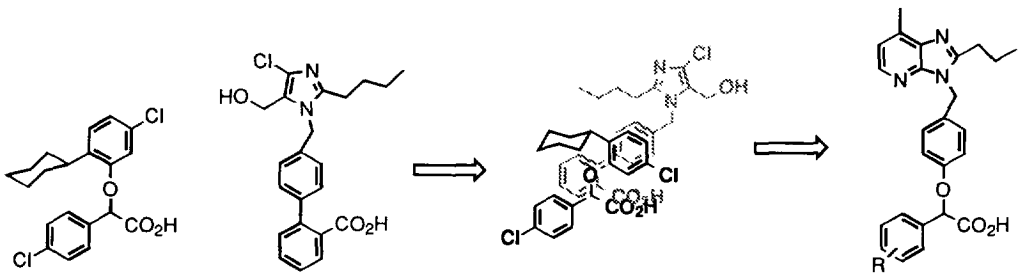
Abstract: A series of nonpeptidic AT_1 selective angiotensin II (AII) antagonists containing a phenoxyphenylacetic acid element as a biphenyl tetrazole replacement have been identified. This series yielded compound **20** which exhibited binding affinities of AT_1 = 16 nM; AT_2 = 22 μM and demonstrated modest *in vivo* duration in blockade of AII pressor response in conscious rats after either i.v. or p.o. administration.

Inhibiting the renin-angiotensin system remains an important target for drug development.[2] Renin inhibitors have demonstrated potent antihypertensive effects, but suffer from low oral bioavailability and short duration.[3] Angiotensin converting enzyme (ACE) inhibitors successfully manage hypertension and treat congestive heart failure. However, ACE inhibitors have side effects, presumably linked to bradykinin, another substrate of ACE.[2,3] Alternatively, specific, non-peptidic, AII receptor antagonists present a potential antihypertensive therapy with minimal side effects.[2]

Recently, highly potent, orally-active, non-peptidic AII receptor antagonists such as losartan[4] (DuP753; MK-954) and L-158,809[5] have been reported. These and most other recently reported AII antagonists contain a biphenyl tetrazole or biphenyl carboxylic acid moiety. From a broad AT_1 receptor antagonists screening program, we discovered the phenoxyphenylacetic acid **1** (Figure 1), a moderately active AT_1 receptor antagonist (IC_{50} = 21 μM). The two phenyl rings and carboxylic acid of **1** were modelled (Figure 1) onto the biphenyl of EXP 7711, the carboxylic acid analog of losartan. This overlay suggested heterocyclic phenoxyphenylacetic acids such as **2** as potential AT_1 antagonists.

Figure 1

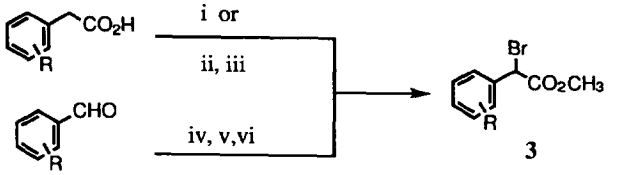


1 EXP 7711 **2**

Chemistry

The phenoxyphenylacetic acid compounds were synthesized by two general methods depending upon the desired substitution pattern and starting material availability. A common alkylating agent (**3**) was prepared via either a Hell-Vollhard-Zelinsky or a Strecker synthesis as shown in Scheme I. Bromoester **3** was then utilized (Scheme II) to prepare benzyl bromides (**5**) for subsequent heterocycle alkylation (Scheme III, step iv), or was utilized to alkylate a heterocyclic phenol (**8**) (Scheme III, step iii).

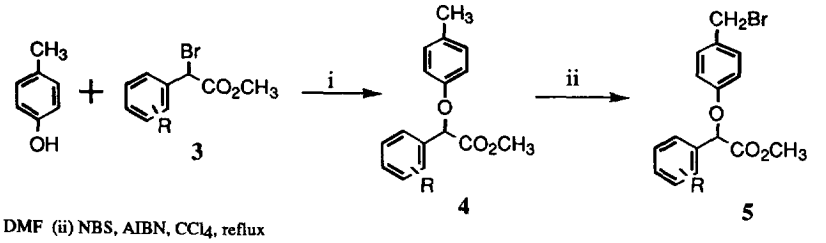
Scheme I



(i) a. $SOCl_2$ / Br_2 reflux b. MeOH[6] (ii) H_2SO_4, MeOH, reflux (iii) NBS, AIBN, CCl_4, reflux (iv) TMSCN, KCN, 18-crown-6, CH_2Cl_2[7](v) HCl, EtOH, 0 °C to RT [8](iv) CBr_4 Ph_3P, CH_2Cl_2

Alkylation (Scheme II) of *para*-cresol with bromoesters (**3**) afforded phenoxyethers (**4**). Subsequent NBS bromination provided the requisite alkylating agents **5**.

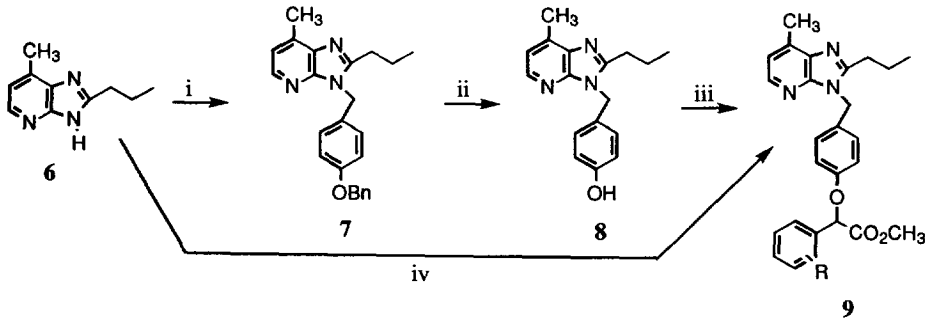
Scheme II



(i) NaH, DMF (ii) NBS, AIBN, CCl_4, reflux

The advanced intermediate (**9**, Scheme III) was prepared by alkylation of (**6**), followed by benzyl ether hydrogenolysis and alkylation with bromoester **3** to afford **9**. Alternatively, **6** was alkylated with **5** to provide **9**.

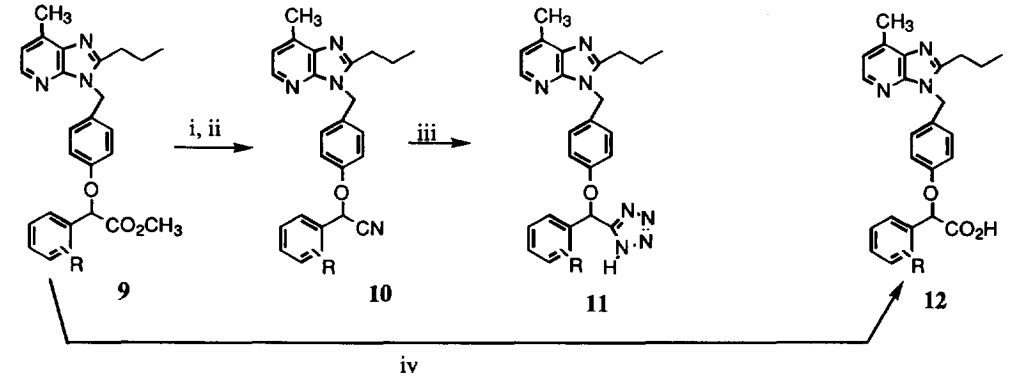
Scheme III



(i) *p*-benzyloxy benzylchloride, NaH, DMF (ii) H_2, Pd/C, EtOH (iii) **3**, NaH, DMF (iv) **5**, NaH, DMF

The key intermediate **9** was treated (Scheme IV) with sodium hydroxide in methanol to afford the carboxylic acid **12**. The ester **9** was also converted (Scheme IV) to a tetrazole **11** by treating **9** with methanolic ammonia followed by phosphorus oxychloride dehydration to yield the nitrile **10**. Subsequent trimethyltin azide cyclization of nitrile **10** provided the tetrazole **11**.

Scheme IV

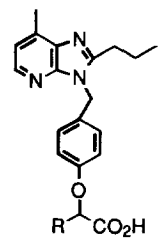


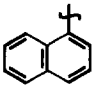
(i) NH_3, MeOH 0°Cto RT (ii) $POCl_3$, Et_3N, 0°C to reflux [9](iii) Me_3SnN_3, toluene reflux (iv) NaOH, MeOH

Results and Discussion

In vitro receptor binding data were obtained using a rabbit aorta binding assay[10] and *in vivo* data were obtained using a conscious rat AII pressor response model.[11] The investigation of phenoxyphenylacetic acid AT_1 selective antagonists (AT_2 binding affinities ranged from 2 μM to >50 μM) began with variations of the lower R group (Table 1), the acidic group (Table 2) and finally ring substitutions where the lower R group was phenyl (Table 3). The results of the lower R group investigation (Table 1) are summarized below.

Table 1

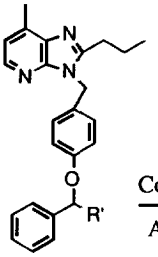


R				
Compound	**13**	**14**	**15**	**16**
AT_1 (nM)	840	325	42	36

Analogs **13** or **14** with a propyl or a cyclohexyl substituent had modest binding affinity, but both aromatic analogs **15** and **16** had improved binding affinity. Thus, subsequent analogs contained a lower phenyl ring.

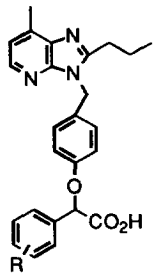
Although losartan is more potent than its carboxylic acid analog EXP 7711[2], a comparison of **15** and its tetrazole analog **17** revealed that a carboxylic acid is preferred in the phenoxyphenylacetic series.

Table 2



R'	CO_2H	
Compound	**15**	**17**
AT_1 (nM)	42	77

Table 3



Compound	R Group	AT_1 (nM)	Compound	R Group	AT_1 (nM)
15	H	42	**22**	2-CO_2H	235
18	4-Cl	530	**23**	2-NO_2	57
19	3-Cl	60	**24**	2-CH_3	5
20	2-Cl	16	**25**	2-OCH_3	38
21	2,6 di-Cl	21	**26**	2-OEt	18
			27	2-O-n-Hexyl	80

Focusing next on the lower phenyl ring (Table 3), it appears that appropriate ortho substitution enhances binding affinity and that the substituent position ranking is ortho > meta >> para based on the chloro analogs. Compound **20**[12] was tested *in vivo* using a conscious rat AII pressor response model.[11] The i.v. and p.o administration of **20** at 1 mg/kg showed 85% and 34% peak inhibition of pressor response respectively with moderate duration of action (~1 hr) in both cases.

Summary

Starting from a micromolar screening lead (**1**), a series of potent AT_1 receptor antagonists was developed. One of these antagonists (**20**) showed inhibition of AII pressor response after both i.v. and p.o. administration to rats. Further work in this series has demonstrated that substitutents in the central phenyl ring yield analogs with improved *in vivo* properties.[13,14]

Acknowledgments:

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12. ^1H NMR (300 MHz, CD_3OD, ppm) δ 0.85-0.95 (t, 3H), 1.55-1.72 (m, 2H), 2.63 (s, 3H), 2.80-2.91 (t, 2H), 5.50 (s, 2H), 6.05 (s, 1H), 6.85-6.95 (d, 2H), 7.04-7.20 (m, 2H), 7.25-7.32 (m, 2H), 7.35-7.43 (m, 1H), 7.55-7.62 (m, 1H), 8.20 (d,1H) FAB-MS: *m/e* 450, 452 (M+1) in a 3:1 ratio.
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