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POTENT DUAL ANTAGONISTS OF ENDOTHELIN AND ANGIOTENSIN II RECEPTORS DERIVED FROM α-PHENOXYPHENYLACETIC ACIDS (Part III)[1]

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Abstract: Screening a collection of α-phenoxyphenylacetic acid derived angiotensin II antagonists identified weak actives in an endothelin receptor binding assay. Synthetic modification of one of these leads has provided L-746,072 (**13**), a highly potent dual antagonist of angiotensin II and endothelin receptors.

The endothelins (ET-1, 2 and 3) constitute a family of homologous 21-amino acid peptides first isolated in 1988 from cultured endothelial cells, which play an important role in the control of vascular smooth muscle tone and blood flow.[2] The ETs exert their biological effects by interacting with at least two specific membrane receptors (ET_A and ET_B) which are differentiated by their relative affinities for these peptides.[3] Stimulation of the ET-1 selective ET_A receptor elicits an intense and prolonged vasoconstriction, while ET_B receptors bind the three ETs with approximately equal affinity and can mediate both vasoconstriction[4] and vasodilatation.[5] In addition to being among the most potent vasoconstrictors known, the endothelins are potent mitogens, bronchoconstrictors, and inducers of the release of other vasoactive substances.[6] The characterization of elevated ET levels in a variety of pathologies has prompted an intense effort to identify potent non-peptide ET antagonists in order to assess the therapeutic potential of blocking the deleterious effects of these peptides. Recently, several laboratories have reported the synthesis and pharmacological characterization of non-peptide ET antagonists.[7]

Our approach to the identification of ET antagonists focused on the recognition of structural and functional similarities between the ET and AII receptors, and the known sensitivities that these two G-protein coupled receptors exhibit toward sequence variations in their respective agonists. In particular, the influence of a C-terminal carboxylic acid and of aromatic amino acid residues at positions 13 and 14 for binding affinity of the ETs was well documented.[8] Thus we were prompted to screen selected compounds from the Merck AII receptor antagonist collection since this afforded a unique assortment of low molecular weight acidic compounds bearing diverse aromatic scaffolds. Among the categories of AII antagonists which were available for scrutiny in the ET receptor binding assay was a class of α-phenoxyphenylacetic acid derived AII antagonists which we had recently developed at Merck.

In previous communications,[9] we showed that elaboration of an α-phenoxyphenylacetic acid with an appropriate heterocyclic element chosen from another series of AII antagonists provided compounds which displayed low nanomolar AT_1 potency, and that further incorporation of an *n*-propyl substituent into the middle

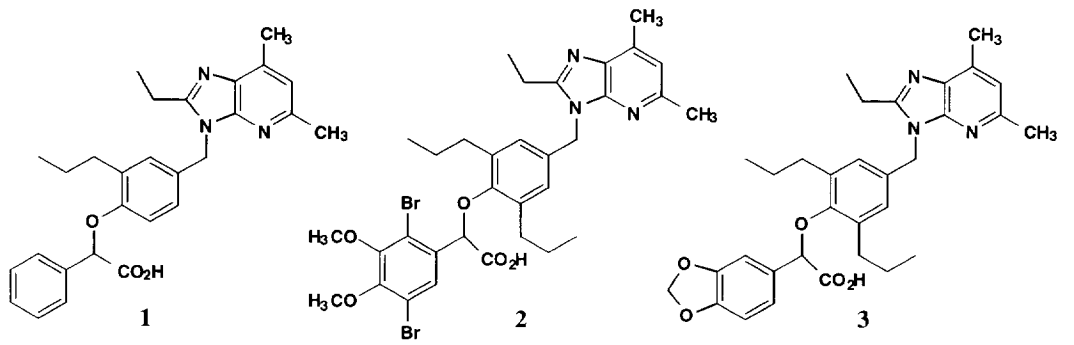
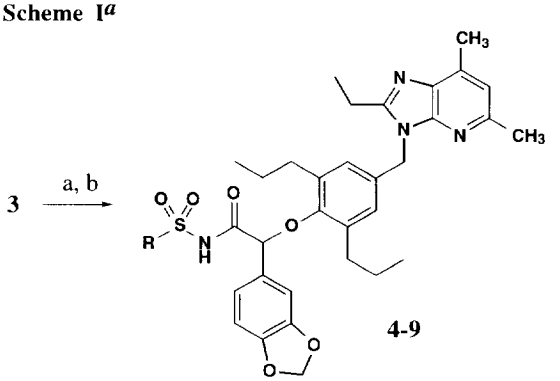


Figure 1.

aromatic ring provided potent compounds such as **1** (Figure 1) having nearly balanced (AT_1 = 11 nM; AT_2 = 47 nM) subtype affinity. Evaluation of compounds from this class of AII antagonists in cell lines expressing ET_A or ET_B receptors provided several weakly active leads such as **2** (ET_A = 11 μM; ET_B = 31 μM) which were used as the starting point for structure-activity relationship (SAR) studies. In this communication we describe new dual antagonists of ET and AII receptors derived from *n*-propyl substituted α-phenoxyphenylacetic acids.

Initial synthetic studies conducted in this series focused on simplification of the substitution pattern on the 2,5-dibromo-3,4-dimethoxyphenyl functionality present in the screening lead **2**. This effort rapidly succeeded in identifying the potency contribution available from a methylenedioxyphenyl group (**3**).[10] We next turned our attention toward the synthesis of acylsulfonamides, arguing that exploration of the SAR related to the acidic moiety might afford improvements in both the *in vitro* ET antagonist potency as well as block potential *O*-acyl glucuronidation sometimes observed for carboxylic acids *in vivo*. Scheme I illustrates the general

Scheme I[a]



[a]Reagents: (a) 1,1'-carbonyldiimidazole, THF, 65°C, 1 h (Ref. 11); (b) RSO_2NH_2, DBU, THF.

Table 1. IC_{50}s (μM) for compounds **4-9**.

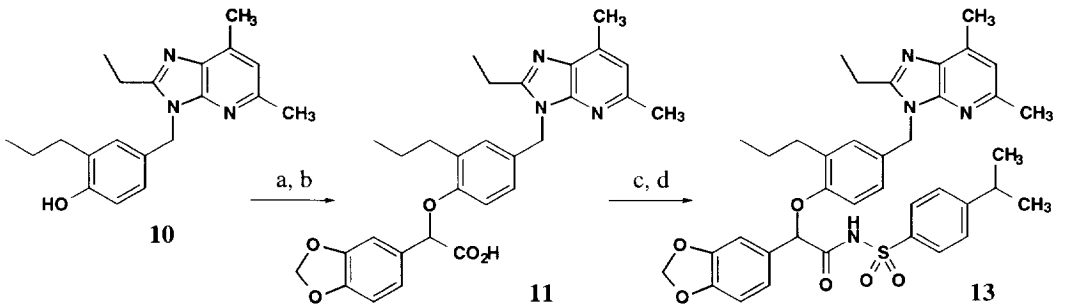
Entry	R	ET_A	ET_B
4	methyl	0.50	1.20
5	*i*-propyl	0.70	1.90
6	phenyl	1.60	0.80
7	thiophene-2-yl	0.82	0.54
8	5-*i*-butylthiophene-2-yl	0.60	0.42
9	4-*i*-propylphenyl	0.33	1.30

procedure for preparation of acylsulfonamides (**4-9**)[12] from carboxylic acid **3** and Table 1 lists the IC_{50}s obtained for **4-9** in cloned human ET receptors stably expressed in Chinese hamster ovary cells.[13]

Examination of the IC_{50}s for compounds **4-9** revealed that the ET binding affinities were significantly poorer than those determined for the parent carboxylic acid (**3**). Nevertheless, we were intrigued by the observations that the more sterically demanding acylsulfonamides **8** and **9** afforded ET_A potencies equivalent to the methylacylsulfonamide **4**, and that the branched alkylsubstituted thiophene (**8**) displayed the best ET_B

potency for the series. Consideration of the relative binding affinities for these antagonists led to the proposal that the dipropylphenoxyphenylacetic acid (**3**) derived its potency in part from beneficial hydrophobic interactions of the *n*-propyl groups with elements of the ET receptor. In this model the arylsulfonyl substituent present in the dipropylacylsulfonamides (**4-9**) is forced to compete with one of the propyl groups for this interaction, and as a consequence acylsulfonamides similar to **8** and **9** prepared from the corresponding mono-propylphenoxyphenylacetic acid (**11**) might provide superior antagonists. Therefore we next turned our attention to the synthesis of the mono-propylacylsulfonamides **12** and **13** derived from 5-*i*-butylthiophene-2-yl-sulfonamide and 4-*i*-propylbenzenesulfonamide respectively. Scheme II illustrates a representative synthesis of

Scheme II[a]



[a]Reagents: (a) Cs_2CO_3, DMF, ethyl α-bromo-3,4-methylenedioxyphenylacetate, rt, 14 h, 82%; (b) NaOH, MeOH, rt, 2 h, 86%; (c) 1,1'-carbonyldiimidazole, THF, 65°C, 20 min; (d) 4-*i*-propylbenzene-sulfonamide, DBU, 65°C, 1.5 h, 42%.

one of these (**13**, L-746,072)[14] starting from the imidazo[4,5-*b*]pyridine substituted *n*-propylphenol **10** which was available in our laboratories.[9]

Table 2 summarizes the IC_{50}s for the three derivatives in each series and the data observed clearly supports the model in which the mono-propylacylsulfonamides **12** and **13** can adopt conformations in which the arylsulfonyl moieties and one *n*-propyl group are accomodated in hydrophobic interactions with the receptor affording binding affinity equivalent or superior to the dipropyl substituted acid (**3**). In cloned human ET_A receptors, **13** had an IC_{50} of 24 nM for functional antagonism of ET-1-stimulated phosphatidyl inositol hydrolysis in good agreement with the binding data. Interestingly, this new class of α-phenoxyphenylacetic acid derived ET antagonists also bears those structural features that we previously reported were important for AII antagonism in this series.[9] In AT_1 and AT_2 radioligand binding assays,[15] **13** displayed IC_{50}s of 13 and 32 nM respectively. These observations suggest the intriguing possibility that a unique pharmacological agent could be identified which might prove useful for the management of hypertension associated with elevated levels of both angiotensin II and the endothelins. Development of further examples of potent and selective endothelin receptor antagonists from α-phenoxyphenylacetic acids is currently under active investigation and will be communicated in due course.

Table 2. IC_{50}s (μM) for compounds **3**, **8**, **9**, and **11-13**.

	mono-propyl series Cpd.		di-propyl series Cpd.	
carboxylic acids	**11**	$ET_A = 0.84$ $ET_B = 1.60$	**3**	$ET_A = 0.038$ $ET_B = 0.230$
5-*i*-butylthiophene acylsulfonamides	**12**	$ET_A = 0.075$ $ET_B = 0.090$	**8**	$ET_A = 0.60$ $ET_B = 0.42$
4-*i*-propylbenzene acylsulfonamides	**13**	$ET_A = 0.024$ $ET_B = 0.060$	**9**	$ET_A = 0.33$ $ET_B = 1.30$

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14. Data for **13**: ^{1}H NMR (400 MHz, CD_3OD, ppm): δ 0.79 (t, *J*=7.60 Hz, 3H), 1.17 (d, *J*=7.20 Hz, 6H), 1.21 (t, *J*=7.60 Hz, 3H), 1.45-1.53 (m, 2H), 2.41-2.49 (m, 1H), 2.53-2.64 (m, 1H), 2.59 (s, 3H), 2.61 (s, 3H), 2.82 (q, *J*=7.60 Hz, 2H), 5.23 (s, 1H), 5.41 (s, 2H), 5.91 (br s, 2H), 6.57 (d, *J*=8.40 Hz, 1H), 6.72-6.76 (m, 2H), 6.91 (d, *J*=2.40 Hz, 1H), 6.59-6.97 (m, 2H), 7.02 (s, 1H), 7.15 (d, *J*=8.20 Hz, 2H), 7.63 (d, *J*=8.20 Hz, 2H). FAB-MS: *m/e* 683 (M+1).
15. Binding affinities expressed as IC_{50}s'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.

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