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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF A NOVEL SERIES OF 5-ARYL BENZIMIDAZOLE ANGIOTENSIN II RECEPTOR ANTAGONISTS

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Abstract: A novel series of benzimidazole angiotensin II (Ang II) receptor antagonists (**4**, **13**, **5**, **17**) were synthesized and compared pharmacologically to the previously described imidazole analogues (**1**, **3a-b**).

Recently, we reported the discovery of a polysubstituted 4-aminoimidazole derivative as a novel nonpeptide antagonist of the angiotensin II (AT_1) receptor (**1**, Figure 1).[1-2] Further structural studies revealed that incorporation of a phenoxyproline side chain via an amide linkage to the carboxyl group produced a set of diastereomeric derivatives (**2a-b**) with enhanced *in vitro* potency. The more active isomer **2a** (*R,S,S*) has a pK_B of 9.1 (pK_B of **2b** = 7.6) as determined by its ability to block Ang II induced contractions of rabbit aorta strips. Additional structure-activity relationship (SAR) studies showed that modification of the phenoxy ring with acidic substituents produced a series of triacid derivatives (exemplified by **3a**) that displayed oral activity in animal models of hypertension.[2]

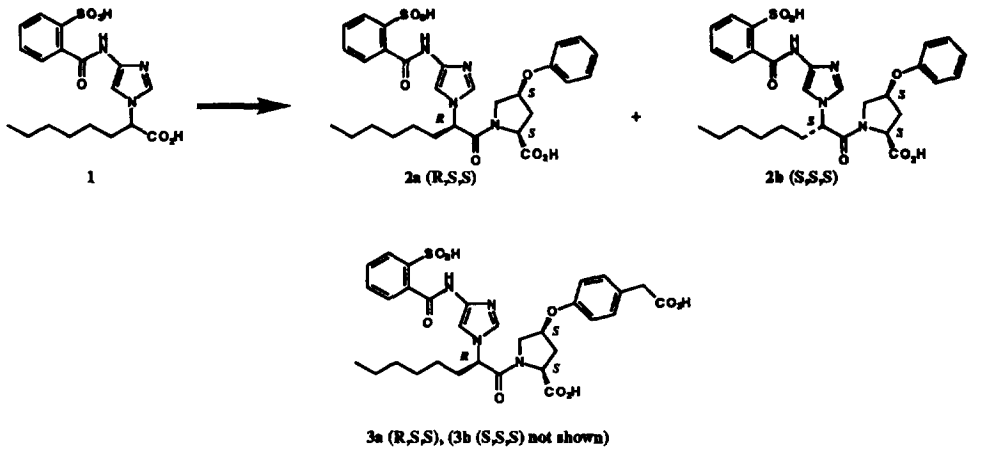


Figure 1

As an elaboration of this work, we replaced the imidazole-4-benzoylamide moiety of **1** with a 5-aryl benzimidazole (**4**, Figure 2) and studied the effect of this modification on biological activity both before and after incorporation of the phenoxyproline side chain. This study was designed to test the hypothesis that incorporation of a biphenyl substructure into **1** would produce a molecule (**4**) with close conformational similarity to the biphenyltetrazole derived Ang II antagonists exemplified by losartan (Figure 3). It was anticipated that this modification would result in a molecule with increased receptor affinity.

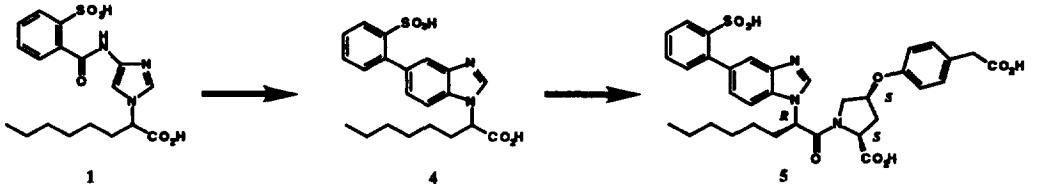


Figure 2

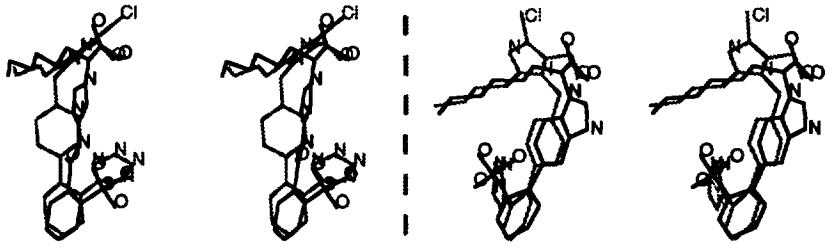
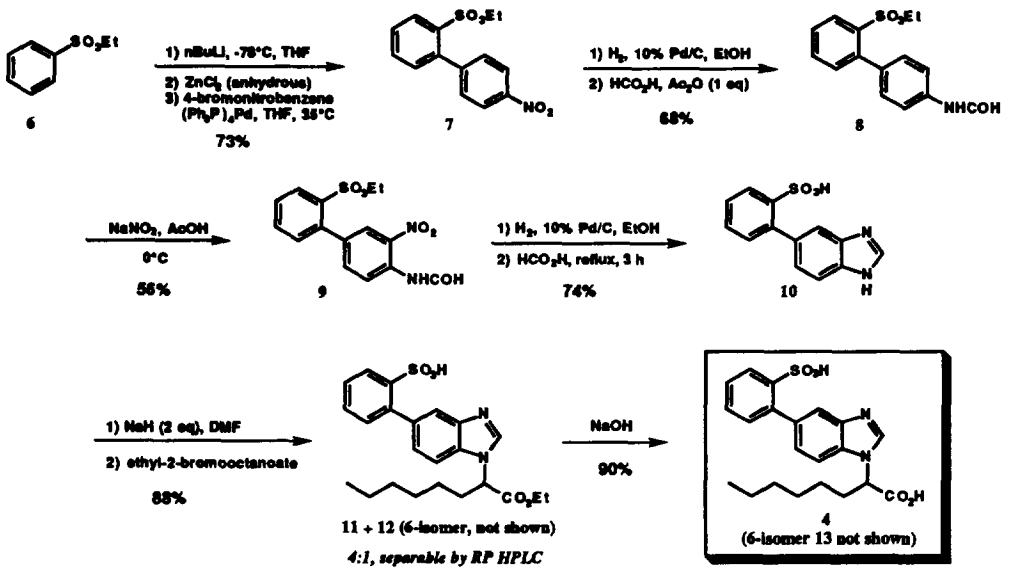


Figure 3. Stereo molecular graphics of the structures from flexibly fitting of (left) **1** (black) and losartan (gray), and (right) the benzimidazole **4** (black) and losartan (gray). Compared to **1**, the benzimidazole is more biphenyl-like in terms of hydrogen-bonding ability, internal rotation possibilities, and lipophilicity characteristics. Molecular modeling was done with the TRIPOS force field in SYBYL (ref. 3) according to the protocol described in ref. 4.

The synthesis of **4** is outlined in Scheme I.[5] *Ortho*-metallation of ethylbenzenesulfonate (**6**) followed by reaction with 4-bromonitrobenzene and catalytic $(Ph_3P)_4Pd$ provided 4'-nitrobiphenyl derivative **7** in 78% yield.[5,6] Reduction of **7** to the biphenylaniline (H_2, 10% Pd/C, EtOH), followed by derivatization with formic acid, gave the formamide **8** in 68% overall yield. This material was converted regioselectiviely to nitro derivative **9** in 56% yield by treatment with $NaNO_2$ in acetic acid. The conversion of **9** to the benzimidazole **10** was thus accomplished by reduction of the nitro group (H_2, 10% Pd/C, EtOH), followed by refluxing in formic acid. In this transformation, the ethyl

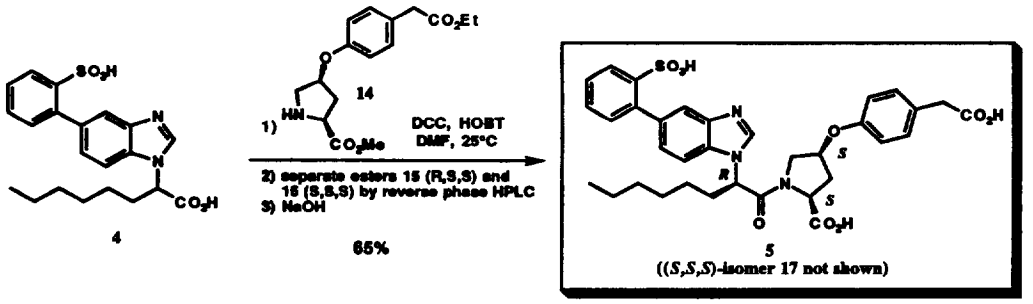
sulfonate was cleaved, and the product was isolated as a solid in 74% overall yield by direct filtration of the reaction mixture. Incorporation of the octanoic acid side chain was achieved by treatment of **10** with 2 eq of NaH in DMF followed by ethyl-2-bromooctanoate. The alkylation produced a 4:1 mixture of regioisomers, with the desired 5-isomer **11** as the major component. The origin of regioselectivity seen in this alkylation may be due to a more favorable separation of charge in the di-anionic substrate that would impart greater reactivity toward the benzimidazole N-1 position (leading to **11**). The regioisomers were readily separated by reverse phase chromatography. The purified ester **11** was then hydrolyzed to give **4** in 35% overall yield. The 6-regioisomer **12** was also converted to the diacid derivative **13** for pharmacological comparison.[7]

Scheme I



The preparation of phenoxyproline analog **5** is summarized in Scheme II. DCC coupling of **4** to 4-phenoxyproline methyl ester **14** produced a 1:1 mixture of diastereomeric amides **15** and **16**. The isomers were separated by reverse phase HPLC and then individually hydrolyzed to give the triacid derivatives **5** and **17** in 90% yield.[7] Stereochemical assignments of **5** and **17** were based on ^{1}H NMR spectroscopic analogy to **3a** and its (*S,S,S*) isomer **3b**, as well as *in vitro* activity profile as described in the next section.

Scheme II



Results: Antagonism of Ang II *in vitro* was determined in isolated rabbit thoracic aorta as described in detail previously.[1] *In vivo*, compounds were studied for their ability to block the pressor response to Ang II in pithed rats following oral administration. Antagonist potency was determined by calculation of K_B using competitive (**1**, **4**, and **13**) or noncompetitive (**3a-b**, **5**, and **17**) kinetics. Table I summarizes the results of our studies.

Table 1. Antagonism of Ang II (*in vitro* and *in vivo*) by **1**, **3a-b**, **4-5**, **13**, and **17**.

compound	*in vitro* (rabbit aorta) $pK_B \pm SE$[a]	*in vivo* (pithed rat) $K_B \pm SE$ (mg/kg, p.o.)[b,c]
1	7.2 ± 0.04 (32)	NA
3a	9.7 ± 0.1 (17)	2.8 ± 0.8 (16)
3b	8.4 ± 0.1 (5)	NA
4	7.7 (2)	NA
13	5.6 ± 0.2 (3)	NT
5	9.0 ± 0.4 (3)	NA
17	7.8 ± 0.3 (3)	NT

[a]Numbers in parentheses represent the number of individual experiments.
[b]NA = not active at the dose (10 mg/kg) and time tested (4 h). [c]NT = not tested.

Replacement of the imidazole amide nucleus of **1** with the benzimidazole system resulted in a modest increase in *in vitro* potency (pK_B of 7.2 vs. 7.7 for **1** and **4**, respectively). The benzimidazole 6-regio-isomer (**13**) was less potent than either **1** or **4**. Neither **1** nor **4** was active orally in the pithed rat model (10 mg/kg, p.o., 4 h). As was observed in the imidazole series, incorporation of the phenoxyproline side chain into **4** led to an increase (20 fold) in *in vitro* potency (**4** vs. **5**). Furthermore,

there was a marked separation in potency between the diastereomeric amides **5** and **17** (pK_B 9.0 and 7.8, respectively). By analogy to **3a-b**, this result is consistent with the stereochemical assignment of **5** and **17** as (*R,S,S*) and (*S,S,S*), respectively.

Although the benzimidazole **5** was nearly as potent as **3a** *in vitro*, there was a marked difference between the compounds in their ability to block Ang II induced pressor responses *in vivo* following oral dosing. Compound **3a** yielded an *in vivo* K_B of 2.8 mg/kg at 4 h following an oral dose of 10 mg/kg. The benzimidazole analog **5** was devoid of oral activity when studied under the same conditions. This result is remarkable in that only minor structural differences distinguish the two compounds. It is possible that electronic differences between the imidazole-benzoylamide and benzimidazole substructures alter the charge distribution of these highly ionized molecules at physiologic pH, thus influencing their relative bioavailability. Further studies are needed to understand the different *in vivo* pharmacological profile of these compounds following oral administration.

In summary, in an extension of earlier work describing a series of imidazole-derived phenoxyproline octanoamides, we prepared representative benzimidazole analogs for pharmacological comparison. While compounds from the two series were equipotent *in vitro*, the benzimidazole **5** was devoid of oral activity, while the imidazole analog **3a** gave an *in vivo* K_B of 2.8 mg/kg at 4 h following oral administration.

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7. Data for **4**: ^{1}H NMR (DMSO-*d6*) δ 9.78 (s, 1H), 8.14 (s, 1H), 7.96-7.91 (m, 2H), 7.66 (d, J = 8.6 Hz, 1H), 7.38-7.32 (m, 2H), 7.16 (dd, J = 6.9, 1.5 Hz, 1H), 5.71 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 2.31-2.27 (m, 2H), 1.34-1.17 (m, 8H), 0.78 (t, J = 6.5 Hz, 3H). FD mass spec: 417. *Anal.* Calcd for $C_{21}H_{24}N_2O_5S \cdot 0.35HCl$: C, 58.76; H, 5.72; N, 6.53. Found: C, 58.73; H, 5.86; N, 5.93.
Data for **13**: ^{1}H NMR (DMSO-*d6*) δ 9.70 (s, 1H), 8.12 (s, 1H), 7.94 (dd, J = 6.9, 1.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.39-7.33 (m, 2H), 7.17 (dd, J = 6.9, 1.5 Hz, 1H), 5.62 (dd, J = 9.5, 5.4 Hz, 1H), 2.35-2.26 (m, 2H), 1.26-1.07 (m,8H), 0.78 (t, J = 6.5 Hz, 3H). FD mass spec: 417. *Anal.* Calcd for $C_{21}H_{24}N_2O_5S \cdot 0.63HCl$: C, 57.40; H, 5.65; N, 6.37. Found: C, 57.43; H, 5.65; N, 5.06.
Data for **5**: ^{1}H NMR (DMSO-*d6*) δ (doubling due to amide rotamers) 9.66 and 9.61 (s, 1H), 8.11 and 8.07 (s, 1H), 7.94-7.58 (m, 3H), 7.39-7.08 (m, 5H), 6.82 and 6.76 (d, J = 8.4 Hz, 2H), 5.77 and 5.64 (dd, $J_1 = J_2 = 7.3$ Hz, 1H), 5.17 and 4.47 (dd, J = 9.2, 2.1 Hz, 1H), 5.14 and 4.94 (m, 1H), 4.16 and 3.75 (dd, J = 11.4 Hz, 4.8 Hz, 1H), 3.97 and 3.48 (masked) (d, J = 11.1 Hz, 1H), 3.44 (s, 2H), 2.55-2.09 (m, 4H), 1.18-0.96 (m, 8H), 0.81 (m, 3H). FD mass spec: 664. *Anal.* Calcd for $C_{34}H_{37}N_3O_9S \cdot 1.25HCl$: C, 57.57; H, 5.44; N, 5.92. Found: C, 57.63; H, 5.35; N, 5.65.
Data for **17**: ^{1}H NMR (DMSO-*d6*) δ (doubling due to amide rotamers) 9.85 and 9.83 (s, 1H), 8.05-7.64 (m, 4H), 7.37-7.31 (m, 2H), 7.18-7.08 (m, 3H), 6.86 and 6.71 (d, J = 8.4 Hz, 2H), 5.81-5.76 (m, 1H), 5.15-5.02 (m, 1H), 4.99 and 4.49 (dd, J = 9.2, 2.1 Hz, 1H), 4.33 and 3.69 (dd, J = 11.4, 4.8 Hz, 1H), 3.85 and 3.52 (d, J = 11.1 Hz, 1H), 3.46 (s, 2H), 2.59-2.14 (m, 4H), 1.46-1.16 (m, 8H), 0.78 (m, 3H). FD mass spec: 664. *Anal.* Calcd for $C_{34}H_{37}N_3O_9S$: C, 61.53; H, 5.62; N, 6.33. Found: C, 61.29; H, 5.62; N, 6.19.

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