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TETRAHYDROISOQUINOLINE DERIVATIVES WITH AT_2-SPECIFIC ANGIOTENSIN II RECEPTOR BINDING INHIBITORY ACTIVITY

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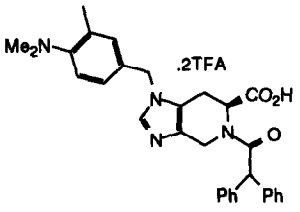
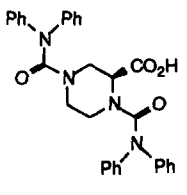
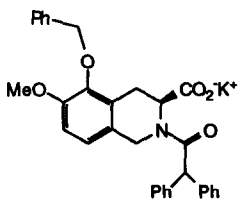
Abstract. Syntheses and structure-activity relationships for a series of substituted tetrahydroisoquinoline-3-carboxylic acid derivatives with AT_2-specific angiotensin II receptor binding inhibitory activity are reported.

Angiotensin receptors are known to exist in two subtypes, AT_1 and AT_2[1], which were discovered using selective binding inhibitors such as DuP 753[2] for AT_1 and CGP 42112A[3] or PD 123319 (and various analogues thereof)[4] for AT_2. The AT_1 receptor has been shown to mediate virtually all of the physiological responses traditionally associated with angiotensin II administration, including vasoconstriction, aldosterone release, and central nervous system control of blood pressure and thirst[5]. Although numerous isolated reports have recently been published[6], the functional roles of the AT_2 receptor have not been widely confirmed and still remain the topic of active current research.

The first nonpeptide AT_2 ligands, PD 123319 and analogues, were described by our laboratories in 1991[7]. Recently, a second, somewhat structurally related class, exemplified by L-159686, was presented by the Merck group[8]. Yet a third chemical class is reported here,[9] typified by the tetrahydroisoquinoline derivative, PD 126055. Our impetus for exploring tetrahydroisoquinoline carboxylic acids (TICs) as AT_2 ligands arose from a

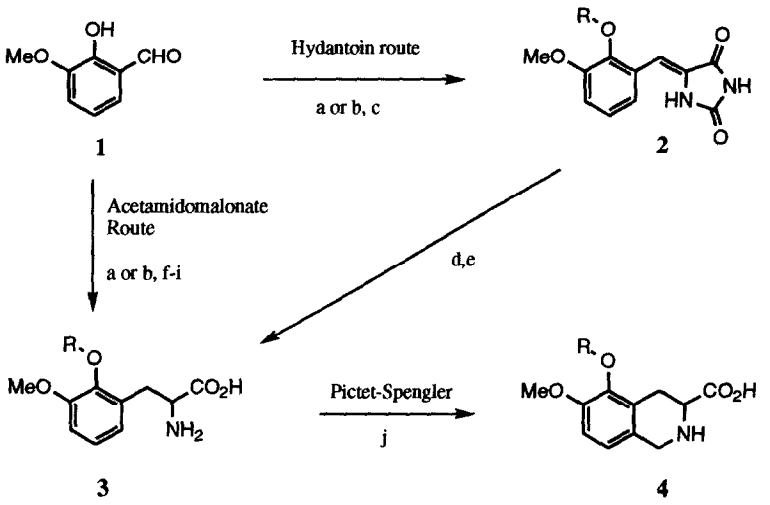
TABLE 1: Comparison of Nonpeptide AT_2 Ligands

	PD 123319	L-159686	PD 126055
			
AT_2 IC_{50} (nM)	6.9 [n=1]	0.89 [n=1]	0.58 [n=1]
AT_1/AT_2	>100,000	>100,000	>100,000

continuation of the study of structure-activity relationships (SAR) associated with PD 123319. We examined a number of imidazole ring replacements and found that a similarly substituted phenyl ring gave molecules with greater AT_2 affinity, while maintaining excellent AT_2/AT_1 selectivity.

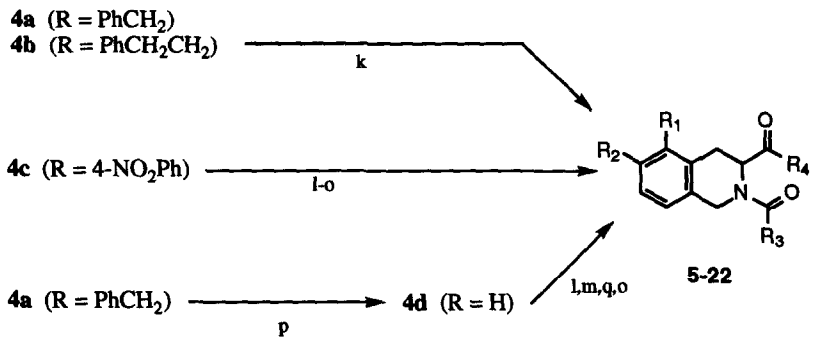
Synthetic routes are summarized in Schemes I and II. Two well known amino acid syntheses, both of which begin with *o*-vanillin (**1**), were used to prepare a suitably substituted phenylalanine derivative (**3**) which was subsequently cyclized under Pictet-Spengler conditions and acylated to afford the desired compounds in racemic form. Usually, acylation of the amino acids **4** under Schotten-Baumann type conditions (Scheme II) offered the most direct route to the desired target compounds, albeit in modest yield when an acid chloride was the acylating agent. In the case of **4c**, the yield was improved by esterifying first, followed by acylation to afford **14**, which was further elaborated to **9** by reduction of the nitro group and ester saponification. Compound **4a** also served as a useful point of synthetic divergence. Removal of the benzyl group was accomplished by heating with conc. HCl to give **4d** which was esterified, N-acylated and O-alkylated before saponification to give additional target analogs. Optical resolution of PD 126055 (**5**) was accomplished through fractional crystallization of its (S)-(-)-α-methylbenzylamine salt to afford **5(+)**.

Scheme I



a) RX (e.g. $PhCH_2Br$), K_2CO_3, EtOH, reflux, 6 hr (84%). b) RX (e.g. 4-F-NO_2Ph or $PhCH_2CH_2Br$), K_2CO_3, DMF reflux, 10 min (71%) and 3 hr (49%) respectively. c) Hydantoin, HOAc, β-Alanine (cat.), reflux, 6 hr (84%). d) Me_4NOH, H_2/RaNi, MeOH. e) NaOH, H_2O, 100°, 24 hr (75%). f) $NaBH_4$, EtOH, 0.5 hr (86%). g) $SOCl_2$, toluene, 25°, 0.5 hr (100%). h) $AcNHCH(CO_2Et)_2$, NaOEt, EtOH, reflux, 6 hr (66%) for R = $PhCH_2$ or NaH, DMSO, NaI (cat.), 25°, 3 days (96%) for R = 4-NO_2Ph. i) NaOH, H_2O, EtOH, reflux, 48 hr (44%) for R = $PhCH_2$ or conc. HCl, EtOH, reflux, 24 hr (67%) for R = 4-NO_2Ph. j) HCHO, 1N HCl, 25°, 24 hr (85%).

Scheme II



k) R_3COCl (e.g. $Ph_2CHCOCl$, or *c*-PentCH(Ph)COCl), 2 eq. 20% NMe_4OH-in-MeOH, CH_2Cl_2, 0°, 5 min., then 25°, 0.5 hr (30-50%); or R'NCO (e.g. 4-FPhNCO or 4-MeOPhNCO), 1 eq. 1 N NaOH, THF, 10°, then 25°, 1 hr. (90%). l) MeOH, HCl, 25°, 24 hr (84%). m) $Ph_2CHCOCl$, NEt_3, MeCN, 25°, 1 hr (100%). n) H_2/5% Pd/C MeOH-THF (100%). o) 1N NaOH, MeOH, reflux, 15 min (60-80%). p) conc. HCl, reflux, 10 min (86%). q) R-X (e.g. 4-MeO_2CPhCH_2Br or 4-MeO-3-$MePhCH_2Cl$), K_2CO_3, DMF, reflux, 5 - 15 min (80 and 29% respectively).

The AT_2 affinities of selected examples from this genus are shown in Table 2. SAR of the tetrahydropyridine ring resemble those described for the PD 123319 series[7]. A free carboxylic acid at the 3-position is optimal for potent receptor affinity. Based on a preliminary comparison of IC_{50} values, the (+) enantiomer appears to be the more active constituent of the racemic mixture. Presumably, **5**(+) is the S-enantiomer, based on the stereochemical preference seen with the other two series of compounds. A hydrophobic amide is required at N(2) with superior affinity seen in acyl groups bearing two lipophilic moieties, one of which is a phenyl ring. Hence compounds bearing diphenylacetyl, cyclopentyl-phenylacetyl, and diphenylcarbamyl radicals at N(2) (e.g. **5**, **18** and **22**) were among the most potent agents. Typically, any aryl substitution on the 2-acyl group detracted from *in vitro* potency. The tetrahydropyridine ring itself is also required for activity since the phenylalanine derivative of **5** shows markedly less AT_2 affinity ($IC_{50} \approx 2 \times 10^{-5}$ M). Insofar as they are required for high affinity, the benzyloxy and phenoxy substituents at the 5-position of the TICs are analogous to the 1-benzyl substituent in PD 123319. Unlike the PD 123319 series, however, that the addition of a *p*-electron donating group did not afford a marked boost in receptor affinity[7]. Such substitution is consistent with AT_2 affinity but affords no enhancement within the TIC series as is shown by the comparison of the IC_{50} values for **5**, **7** and **9**. In this respect, the SAR of the TICs more closely resemble those of Merck's piperazine series, wherein a 4-(diphenyl urea) was more potent than a 4-(4-methoxy-3-methylphenyl urea)[8]. A comparison of PD 123319, L-159686 and PD 126055 assayed side by side under identical conditions[9] is shown in Table 1. These three

TABLE 2: AT_2 Receptor Binding SAR

Compound†	R_1	R_2	R_3	R_4	AT_2 IC_{50}[10] (nM)
5	5-$PhCH_2O$	6-MeO	$CHPh_2$	OH	2.4 ±0.26 [n=5]
5(+)	5-$PhCH_2O$	6-MeO	$CHPh_2$	OH	0.84 [n=2]
6	5-$PhCH_2CH_2O$	6-MeO	$CHPh_2$	OH	4.8 [n=1]
7	5-(3-Me-4-MeOPh)CH_2O	6-MeO	$CHPh_2$	OH	1.9 [n=1]
8	5-(4-CO_2HPh)CH_2O	6-MeO	$CHPh_2$	OH	750 [n=1]
9	5-(4-NH_2Ph)O	6-MeO	$CHPh_2$	OH	40 [n=1]
10	H	H	$CHPh_2$	OH	200 [n=1]
11	OH	6-MeO	N(Me)Ph	OH	na @10^{-6}M [n=1]
12	6-$PhCH_2O$	7-MeO	$CHPh_2$	OH	59 [n=1]
13	5-$PhCH_2O$	6-MeO	$CHPh_2$	OEt	150 [n=1]
14	5-(4-NO_2Ph)O	6-MeO	$CHPh_2$	OMe	370 [n=1]
15	5-(4-NH_2Ph)O	6-MeO	$CHPh_2$	OMe	730 [n=1]
16	5-$PhCH_2O$	6-MeO	$CH(4\text{-}ClPh)_2$	OH	35 [n=1]
17	5-$PhCH_2O$	6-MeO	$CH_2(2,6\text{-}Cl_2Ph)$	OH	70 [n=1]
18	5-$PhCH_2O$	6-MeO	CH(Ph)*c*-Pent.	OH	1.1 [n=1]
19	5-$PhCH_2O$	6-MeO	N(Me)Ph	OH	9.4 [n=1]
20	5-$PhCH_2O$	6-MeO	NH(4-MeOPh)	OH	1100 [n=1]
21	5-$PhCH_2O$	6-MeO	NH(4-FPh)	OH	170 [n=1]
22	5-$PhCH_2O$	6-MeO	NPh_2	OH	5.8 [n=1]

†All compounds are racemates except **5(+)** which is the (+) enantiomer.

molecules are all potent and selective inhibitors of angiotensin II binding at the AT_2 receptor and thus are useful pharmacological probes for the study of its physiological roles.

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10. The authors gratefully acknowledge the the efforts of Gina H. Lu for AT_2 and AT_1 receptor binding assays which were carried out according to the following procedures:

AT_2: Rabbit uterine membranes were prepared freshly by homogenizing tissues in 20 volumes of ice-cold 20 mM sodium phosphate buffer (pH 7.4) using a Brinkmann Polytron at setting 8. The homogenates were centrifuged at 48,000 x g for 20 min at 4°C and the supernatant was discarded. The resulting pellet was washed once in 20 volumes of ice-cold 20 mM sodium phosphate buffer (pH 7.4), centrifuged as above resuspended in 20 mM sodium phosphate buffer and used immediately. The binding was conducted in a final volume of 0.25 mL of 50 mM sodium phosphate buffer (pH 7.4) containing 100 mM NaCl, 10 mM $MgCl_2$, 100 μM EGTA and 100 μM bacitracin with 1 mg of membrane homogenate, 1 mg of wheat germ agglutinin (WGA) coated scintillation proximity (SPA) beads (Amersham, Int.), 50 pM [^{125}I]Ang II, 1 μM DuP 753 and test compound. Samples were placed in a 96 well plate and incubated via continuous mixing at 25°C for 3 hours. Light emitted by the SPA beads was detected by scintillation counting. Nonspecific binding was defined as radioactivity retained on the beads in the presence of 10 μM saralasin and specific binding was defined as total binding minus nonspecific binding. A single determination consists of the average of values from three concurrent experiments.

AT_1: The procedure is identical to that described above except that rat liver membranes were used and DuP 753 was deleted from the assay mixture.

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