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ANGIOTENSIN II RECEPTOR ANTAGONISTS CONTAINING A PHENYLPYRIDINE ELEMENT.

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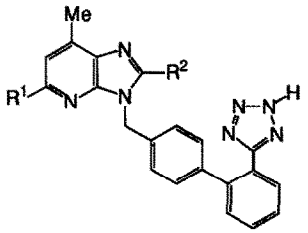
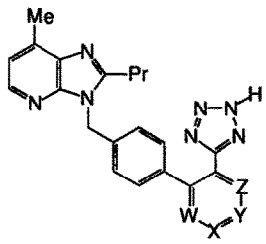
Abstract: Pyridine isomers replacing the tetrazole-bearing phenyl of the angiotensin II antagonist L-158,338 were prepared. The 4-phenyl-3-tetrazolylpyridyl isomer (compound **3**) exhibited low nanomolar binding affinity to the AT_1 receptor. Other isomers prepared were 60 to 100 - fold less active compared to L-158,338. Compound **3** is orally active in rats at 1 mg/kg, but the IV vs. PO activites indicated a somewhat poorer oral bioavailability than that of L-158,338.



L-158,338: R^1 = H; R^2 = Pr
L-158,809: R^1 = Me; R^2 = Et



1: W = N; X = Y = Z = CH
2: X = N; W = Y = Z = CH
3: Y = N; W = X = Z = CH
4: Z = N; W = X = Y = CH

Introduction:

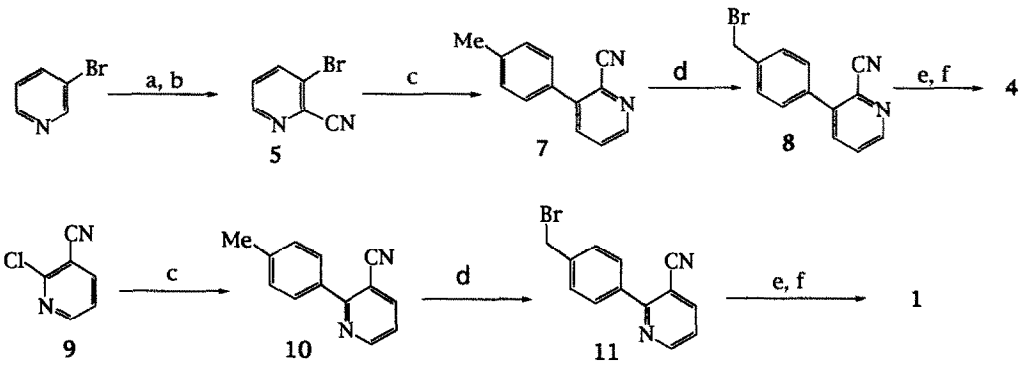
The success achieved by angiotensin converting enzyme inhibitors for the treatment of hypertension and congestive heart failure has generated considerable interest in the development of new pharmacological agents designed to intervene in the renin-angiotensin system at the level of renin inhibition and AII receptor antagonism. A significant advance in the development of potent nonpeptide angiotensin II receptor antagonists was reported in 1988.[1] Since that time many research groups have succeeded in producing potent AII antagonists which have a biphenyl tetrazole moiety as a common feature.[2] During the development of the imidazopyridine class of angiotensin II antagonists exemplified by L-158,338 and L-158,809[3], it became apparent that the structure-activity relationships of the biphenyl fragment had not been fully addressed. Toward this end we examined the effect of replacing the tetrazole-bearing ring of the biphenyl element with a pyridine.[4] This method allowed us to investigate the importance of this relatively hydrophobic portion of the molecule with respect to binding affinity without appreciably altering the overall 3-dimensional structure. In addition it was reasonable to assume that introduction of water solubilizing groups such as a pyridine nitrogen would provide antagonists with distinct pharmacological profiles. The optimal parent structure at the time was

L-158,338, as it exhibited low nanomolar binding affinity to the AT_1 receptor, and was well characterized in animal models.

Synthesis:

The synthetic route used to prepare compounds 1 and 4 is outlined in Scheme I. 3-Bromopyridine was converted to the N-oxide, which in turn was treated with Me_3SiCN under basic conditions to give 5[5] Bromide 5 was coupled with *para*-tolylzinc chloride using nickel catalysis to afford the phenylpyridine 7[6]. Benzylic bromination to give 8, followed by alkylation with 7-methyl-2-propylimidazo[4,5-b]pyridine[3a] and base such as NaH or K_2CO_3, gave the intermediate 3-substituted imidazopyridines (compounds not shown). Subsequent treatment of the nitrile intermediates with Me_3SnN_3 provided the tetrazoles 1, and 4.[7] 2-Chloronicotinonitrile 9 (commercially available through Lancaster Synthesis Inc.) was converted into 1 as described for the conversion of 5 to 4.

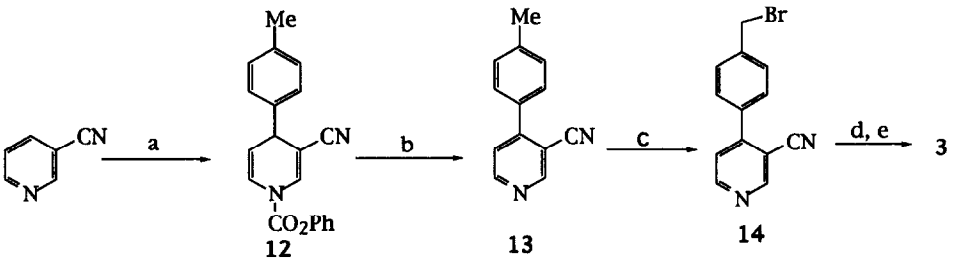
SCHEME I



Reagents: a. m-chloroperbenzoic acid, $CHCl_3$ (87 %); b. trimethylsilyl cyanide, triethylamine, CH_3CN (**5**: 65 %; **6**: 7 %); c. p-tolylmagnesium bromide, $ZnCl_2$, $(Ph_3P)_2NiCl_2$ (70 - 90%); d. N-bromosuccinimide, AIBN, CCl_4 at reflux; e. 7-methyl-2-propylimidazo[4,5-b]pyridine, NaH or K_2CO_3, DMF (40 - 60%); f. Me_3SnN_3, toluene at reflux (70 -90 %).

The preparation of the phenylpyridine isomer 3 is depicted in Scheme II. The biaryl linkage was constructed using the method of Comins,[8] where *para*-tolylmagnesium bromide was reacted with an N-acylpyridinium salt derived from nicotinonitrile and phenyl chloroformate in the presence of catalytic CuI to give dihydropyridine 12. Oxidation of 12 by treatment with hot sulfur afforded 4-(*para*-tolyl)nicotinonitrile 13. Conversion of 13 to the AII antagonist 3 was accomplished by benzylic bromination, followed by alkylation with the sodium salt of 7-methyl-3-propylimidazo[4,5-b]pyridine, and subsequent tetrazole formation by the action of Me_3SnN_3. Due to the unstable nature of these benzyl bromide intermediates, 7, 11 and 14 were used directly or stored as hydrochloride salts.

SCHEME II



Reagents: a. p-tolylmagnesium bromide, 5% CuI, PhOCOCl, THF-DMS (85 %); b. Sulfur, decahydronaphthalene, 190 °C (55 %); c. N-bromosuccinimide, AIBN, CCl_4 at reflux; d. 7-methyl-2-propylimidazo[4,5-b]pyridine, NaH, DMF; e. Me_3SnN_3, toluene at reflux (77 %).

Results and Discussion:

The *in vitro* binding affinities of the compounds in Table I were determined by their ability to displace the specific binding ligand ^{125}I-Sar^1,Ile^8-AII from AT_1 receptors in rabbit aorta membranes or AT_2 receptors in rat midbrain membranes, and are expressed as IC_{50} values.[3b] All of the antagonists were selective for the AT_1 receptor. The most potent pyridine isomer, **3**, showed a modest 4-fold loss in AT_1 binding affinity compared to the parent structure L-158,338. The isomers **1** and **4** exhibited a more dramatic decrease in potency. Pyridine isomer **2** was not prepared due to the lower potency of the other members of this series compared to that of L-158,338.

It is likely that the lower potency observed for compounds **1** and **4** is due to a deleterious interaction of the polar nitrogen, either free or bound to water, with the receptor. It is also arguable that pyridine nitrogen in compound **4** distorts the tetrazolate ion from the bioactive conformation by shared hydrogen bonding with water. The energy barrier for rotation about the phenyl-pyridine C-C bond of compound **1** is 3 kcal lower than rotation about the biphenyl C-C bond of L-158,338.[9,10] However, this entropic factor does not adequately account for the decrease in activity since 1-(2-pyridyl)-2-(5-tetrazolylbenzene) analogs, reported by a research group at G. D. Searle & Co., do not exhibit decreased activity compared to their biphenyl counterparts.[11]

TABLE I Angiotensin II Antagonist Activity of phenylpyridine analogs.

Compound	Structure	AT_1 IC_{50} [a]	AT_2 IC_{50} [a]
L-158,809		0.5 nM	>20 μM
L-158,338		1 nM	>20 μM
1	W = N; X=Y=Z=CH	116 nM	>20 μM
3	Y = N; W=X=Z=CH	4 nM	>20 μM
4	Z = N; W=X=Y=CH	60 nM	>20 μM

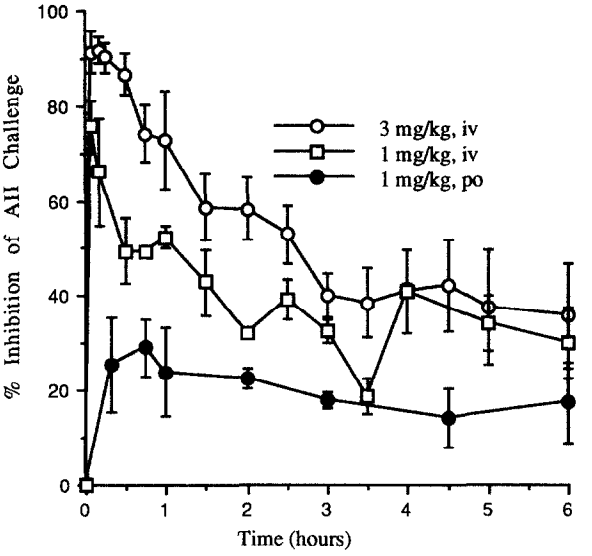
[a]Binding affinities (rabbit aorta and rat mid brain) were performed as described in footnote 3b except that the 0.2 % BSA component was omitted. The standard error, expressed as percent of the mean IC_{50}'s, was determined to be 30 % or less.

In vivo potency of **3** was determined by assessing the inhibition of pressor responses to 0.1 μg/kg i.v. AII in conscious normotensive rats.[3c] Compound **3** produced a dose-related inhibition of the AII pressor response when administered intravenously (Figure 1). An oral dose of 1 mg/kg

produced a minimal response. The specificity of the antihypertensive effect in conscious normotensive rats is evidenced as it does not inhibit the pressor response produced by the α-adrenergic agonist, methoxamine. The iv vs. po activites indicated a somewhat poorer oral bioavailability than that of L-158,338.[12]

In summary, we have demonstrated that the distal phenyl of the biphenyl element found in the angiotensin II antagonist L-158,338 can be replaced only by the 4-pyridine isomer while maintaining low nanomolar potency. Unfortunately, decreasing the lipophilicity in this manner had a deleterious effect on oral potency compared to the parent structure L-158,338.

FIGURE 1. Inhibition of 0.1 μg/kg iv AII by compound 3 in conscious normotensive rats.[13]



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12. *cf.*: L-158,338 exhibited a 70 and 62 % peak inhibition of AII induced pressor response in conscious rats when administered at 0.3 mg/kg by iv and po, respectively.
13. The data represent the mean % inhibition along with the standard error for n = 4.