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DIHYDROPYRIDINES: A NEW CLASS OF ANGIOTENSIN II ANTAGONISTS

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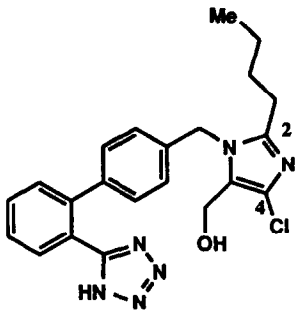
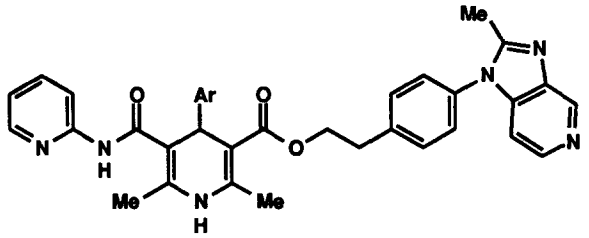
Abstract: The syntheses and biological activities of dihydropyridine angiotensin II (AII) antagonists are described. Compounds such as **12** are examples of a new, structurally distinct class of AT_1-selective agents.

Angiotensin II (AII), an octapeptide derived from the protein angiotensinogen, is a potent vasoconstrictor that has been implicated in maintaining hypertension and contributing to congestive heart failure.[1] Recent clinical evaluations of AII antagonists such as losartan (DuP 753) have shown that blocking the actions of AII at the receptor level can have therapeutic utility.[2a,b] In the past few years, there has been an intense research effort to find other novel AII antagonists. Most of these new compounds are derived from losartan either by replacing the imidazole with a variety of five- or six-membered ring systems or by substituting novel heterocycles for one of the aryl groups in the biphenyl region.[3] A common feature of many AII antagonists is the presence of an acidic functionality such as a tetrazole group which in losartan is attached to the distal phenyl group. We identified UK-77778 with an IC_{50} value of 0.6 uM for the displacement of ^{125}I-Sar^{1}Ile^8-AII from the rat adrenal cortex as an example of a new class of non-acidic AII antagonists.[4] This discovery led to the development of dihydropyridines as potent, AT_1-selective agents.



Losartan



Ar = 2-Cl-Ph-
UK-77778

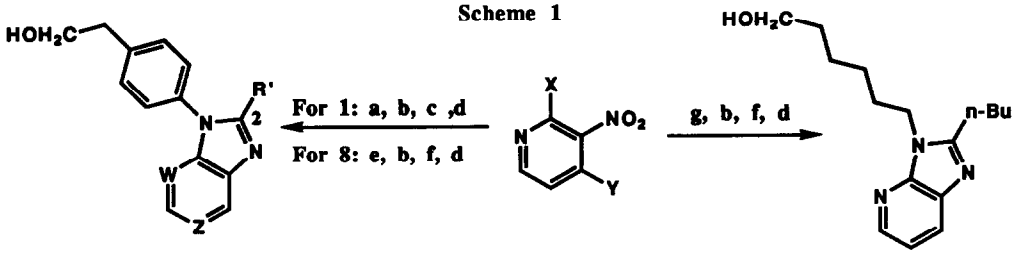
UK-77778 is a platelet activating factor (PAF) antagonist with an IC_{50} value of 20 nM against PAF-induced platelet aggregation.[5a,b] It is also an angiotensin II antagonist with a binding affinity for the receptor (rat adrenal cortex) in the sub-micromolar range (IC_{50} = 0.6 uM).[6] The compound shows functional antagonism in the normotensive rat by shifting the AII pressor response curve to the right when dosed *i.v.* at 3 mg/kg.[7]

Modification of UK-77778 increased both the binding affinity and selectivity for the AII receptor. The assumption was initially made that the N-phenyl imidazo[4,5-c]pyridine moiety in UK-77778 binds in the same pocket of the receptor as does the N-benzyl imidazole group in losartan. The imidazo[4,5-c]pyridine ring was changed to an imidazo[4,5-b]pyridine ring in order to place the pyridine nitrogen atom in the hydrophilic pocket occupied by the 5-hydroxymethyl group in losartan. The imidazo[4,5-b]pyridine ring has since appeared in a number of potent AII antagonists.[8] The C-2 substituent on the imidazo[4,5-b]pyridine was also changed from a methyl group to an *n*-butyl group.

Compound **6**, the 2-*n*-butylimidazo[4,5-b]pyridine analog of UK-77778, was synthesized as shown in Schemes 1 and 2.[9] The 4-(imidazo[4,5-b]pyridyl)phenethyl alcohol **8** was first prepared from 2-chloro-3-nitropyridine **7** in three steps: (i) addition of 2-(4-aminophenyl)ethanol to **7** in refluxing DMF; (ii) reduction of the adduct with Pd/C and H_2; and (iii) condensation of the resulting diamine with acetic anhydride. Coupling of **8** with diketene provided the acetoacetate **3** which was treated with 2-chlorobenzaldehyde to give the Knoevenagel product **4**. A classical Hantzsch reaction of **4** with the enamine **5**[10] in dry acetic acid yielded the desired dihydropyridine (DHP) compound **6**.[11]

The AII binding affinity of compound **6**, IC_{50} = 60 nM, is ten-fold higher than UK-77778. Compound **6** is devoid of PAF activity (PAF IC_{50} > 100 uM), however the compound shows an additional affinity for the nifedipine-sensitive calcium channel (L-channel) with an IC_{50} value of 360 nM for the displacement of nitrendipine.[12] While the combination of AII antagonism and calcium channel blocking (CCB) activity in the same molecule might give a potent anti-hypertensive drug, there was a concern that this additional calcium channel blocking activity might lead to undesirable negative ionotropic activity. The removal of CCB activity was first attempted by resolving the enantiomers of **6** using chiral HPLC;[13] however, both AII and CCB activity lay in the same enantiomer. Since the CCB activity was believed to reside in the dihydropyridine group, modification of this particular subunit was next investigated. We hypothesized that a bulky substituent at the C-2 position in the DHP ring such as an isopropyl or phenyl group would disrupt the critical periplanar orientation of the C-3 carboxyl group with the double bond of the ring, resulting in a torsional change which would reduce calcium channel affinity. In addition, it was believed a large substituent at C-2 on the DHP ring would interfere with the ability of the dihydropyridine ring to act as a critical hydrogen bond donor in the calcium channel. To test these predictions in our series, the C-2 isopropyl analog **9** was synthesized.[14] Compound **9** was a selective AT_1 antagonist (IC_{50} = 120 nM) with no affinity for the nifedipine calcium channels (IC_{50} >100 uM). Compound **12** with a 3-pyridyl amino group at the C-5 position on the dihydropyridine subunit instead of a 2-pyridyl amino group was equally potent (IC_{50} = 130 nM).[15] The 3-pyridyl derivatives such as **12** were preferred for their ease of synthesis.

Scheme 1



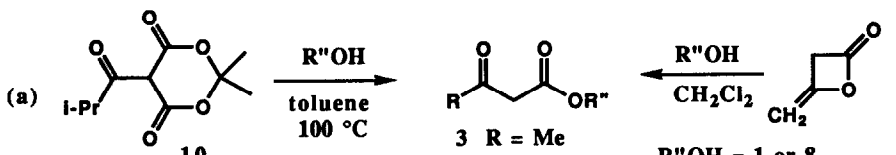
1. W = CH; Z = H; R' = Me
8. W = N; Z = H; R' = n-Bu

2. X = H; Y = Cl
7. X = Cl; Y = H

15

a. 2-(4-aminophenylethanol, EtOH, reflux; b. Pd/C, H_2, EtOH, 35 psi; c. Ac_2O, HOAc; d. NaOH, EtOH; e. 2-(4-aminophenylethanol, KI, $NaHCO_3$, DMF, reflux; f. $(n\text{-}Bu_2CO)_2O$, 170 °C; g. 6-aminohexanol, $NaHCO_3$, DMF, 100 °C

Scheme 2

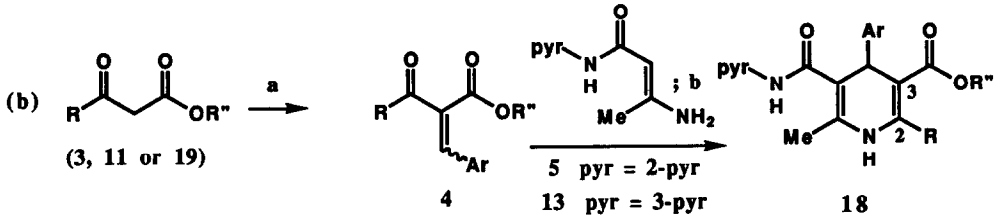


10

R"OH = 8 or 15

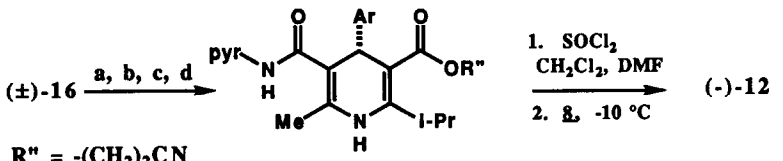
3 R = Me
11 R = i-Pr
19 R = i-Pr; R" = $-(CH_2)_2CN$

R"OH = 1 or 8



a. $2\text{-}ClC_6H_4CHO$, toluene, sieves, pyrrolidinium acetate; b. 2-propanol, 2 days

Scheme 3

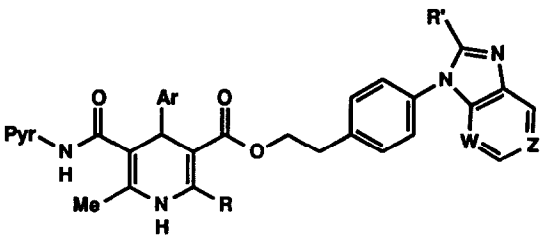


R" = $-(CH_2)_2CN$

(-)-18 R' = $-(CH_2)_2CN$
(-)-21 R" = Na

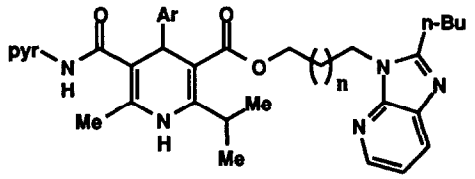
a. S-(+)-1,1-binaphthalene-2,2'-diyl hydrogen phosphate (20), 2-propanol; b. Recrystallization from 2-propanol; c. NaOH, $CHCl_3$; d. NaH, THF, 23 °C

Table 1



Ar = 2-Cl-Ph-

Compound	Pyr	R	R'	W	Z	IC_{50} (nM) AT_1[6]	PAF[5]	CCB[12]
UK-77778	2-pyr	Me	Me	CH	N	600	30	>100,000
6	2-pyr	Me	n-Bu	N	CH	60	>100,000	360
9	2-pyr	i-Pr	n-Bu	N	CH	120	>100,000	>100,000
12	3-pyr	i-Pr	n-Bu	N	CH	140		
(-)-12	3-pyr	i-Pr	n-Bu	N	CH	130		
(+)-12	3-pyr	i-Pr	n-Bu	N	CH	5300		



Ar = 2-Cl-Ph-
pyr = 3-pyridine

14	n = 4	100
16	n = 3	200
17	n = 5	2000

Compound **12** contains two major pharmacophores - the imidazo[4,5-b]pyridine ring and the dihydropyridine moiety - that are separated by a phenethyl group. The phenethyl group appears to be a tether and can be replaced a six-carbon alkyl chain without resulting in a loss of binding affinity (compound **14**[16], IC_{50} = 100 nM). However, increasing or decreasing the length of the tether causes a significant loss of activity (compounds **16** and **17**).

The function of the dihydropyridine pharmacophore in these AII antagonists is unknown. It could bind in some specific pocket in the receptor or it serve as an anchor in the cell membrane, directing binding of the imidazo[4,5-b]pyridine group in proper region of the receptor. To address this issue, the enantiomers of compound **12** were synthesized as shown in Scheme 3. The DHP **18** with a 2-cyanoethyl ester at the C-3 position on the ring was first prepared by the Hantzsch process using **19**, 2-chlorobenzaldehyde and the enamine **13**. Racemic **18** was then treated with S-(+)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate[17] (**S-20**) to give diastereomer salts (±)-**18**·(S)-**20**, one of which precipitated out of 2-propanol. A single recrystallization gave one diastereomer (-)-**18**·(S)-**20** with > 99 %de. Treatment with base yielded the (-)-enantiomer of **18**. The (+)-enantiomer of **18** was prepared by the same route from **R-20**. The 2-cyanoethyl ester in (-)-**18** was cleaved with sodium hydride to give the sodium salt (-)-**21** which upon treatment with thionyl chloride and the alcohol **8** gave optically pure (-)-**12**. The enantiomers of **12** showed markedly different binding affinities with the (-)-isomer having an IC_{50} value of 140 nM while the less active (+)-isomer had an IC_{50} value of 5300 nM. Since the only chiral center in these compounds is in the DHP subunit, the difference in binding affinities between the two enantiomers may be attributed to a difference in the steric environment that surrounds the dihydropyridine moiety at the active site in the receptor, rather than to a non-specific binding of this subunit in the cell membrane.

Based on its *in vitro* potency, compound (-)-**12** was selected for further analysis. The *in vivo* potency was determined in the sodium-depleted normotensive rat by measuring the drop in the animal's blood pressure after oral administration of the compound.[18] Compound (-)-**12** at 60 mg/kg produced a 30 mm/kg decrease in blood pressure that lasted for greater than six hours. This decrease was shown to be dose-dependent.

Conclusion

We have identified a new series of AT_1-selective angiotensin II antagonists. These compounds which consist of a dihydropyridine group connected via a phenethyl spacer to an imidazo[4,5-b]pyridine ring are structurally very different from the prototypical AII antagonist in that they do not contain an acidic functionality. This series of compounds may provide a new pharmacological tool for assessing the blockade of AII at its receptor.

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5. (a) Cooper, K. US Patent No. 4,904,671, **1990**. (b) The synthesis of UK-77778 is shown is Schemes 1 and 2. The 4-(imidazoyl[6,7-b]pyridyl)-phenethyl alcohol **1** was first prepared from 4-chloro-3-nitropyridine **2** in three steps: (i) addition of 2-(4-aminophenyl)ethanol to **2** in refluxing ethanol; (ii) reduction of the adduct with Pd/C and H_2; and (iii) condensation of the resulting diamine with acetic anhydride in acetic acid.

Coupling of the **1** with diketene provided the acetoacetate **3** which was treated with 2-chlorobenzaldehyde and pyrrolidinium acetate in refluxing toluene to give **4**. A classical Hantzsch reaction of **4** with the enamine **5** in dry acetic acid yielded the dihydropyridine UK-77778.

6. The AII antagonists described in this paper were assayed for the ability to displace ^{125}I-Sar^{1}Ile^{8}-AII from rat adrenal cortex membranes. The results are reported as IC_{50} values which represent the concentration of the antagonist necessary to reduce radioligand binding by 50%. See: Chiu, A. T.; Duncia, J. V.; McCall, D. E.; Wong, P. C.; Price, W. A.; Thoolen, M. J.; Carini, D. J.; Johnson, A. L.; Timmermans, P. B. *J. Pharm. Exp. Ther.*, **1989**, *250*, 867-874.

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9. Satisfactory 250 MHz ^{1}H NMR and mass spectral data were obtained for each analog prepared using chromatographically purified samples.

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13. The resolution was performed on a Rainin Rabbit HP unit using a Chiralcel OJ column and a 1:4 mixture of 2-propanol/hexanes.

14. Compound **9** was prepared by the same general methods used to prepare **2** except that in Scheme 2, part a, the alcohol **8** was treated with the malonate **10** (prepared from 2,2-dimethyl-1,3-dioxane-4,6-dione, pyridine and isobutyryl chloride in CH_2Cl_2) to give **11** which was then carried on to the desired product as described in part b.

15. Compound **12** was prepared by the same sequence described for the synthesis of **9** except that the enamine **13** was employed in the Hantzsch reaction.

16. Compound **14** was prepared by the sequence described in Scheme 2 from the malonate **10** and the alcohol **15** (synthesized as described in Scheme 1 from **7** and 6-amino-1-hexanol).

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