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NEW NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS. SYNTHESIS, BIOLOGICAL PROPERTIES AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 3-SUBSTITUTED 2,6-DIALKYL-4-(BIPHENYLYL)METHYLAMINOPYRIDINE DERIVATIVES.

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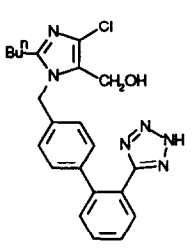
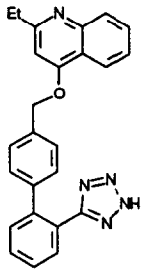
Abstract: The synthesis and biological activities of novel 3-substituted 4-amino-2,6-dialkylpyridine derivatives are described. Compounds from this series have potent *in vitro* and *in vivo* angiotensin II antagonist activity, including good activity when dosed orally in animal models.

Blockade of the renin-angiotensin system (RAS), principally using angiotensin converting enzyme (ACE) inhibitors, is now a well established method of attenuating blood pressure. Alternative points of intervention in the RAS cascade have been investigated in detail; most recently the successful application of nonpeptide angiotensin II antagonists (AII), notably DuP 753[1] (I), now seem to present a viable alternative to ACE inhibitors. We have previously described series of 4-alkoxyquinoline[2] and 4-alkoxypyridine[3] AII antagonists, typified by II and III respectively, in which a biphenyl tetrazole moiety is linked to the 4-position of a quinoline or pyridine ring through a methylenoxy functionality. Work in this area has now been extended in order to attempt to improve *in vivo* activity. It was proposed that analogous compounds linked by methyleneamino functionality would have increased basicity and hence decreased lipophilicity (i.e. log D), compared to the corresponding methyleneoxy quinolines, and that this would give compounds with improved duration of action *in vivo*.



I (DuP 753)



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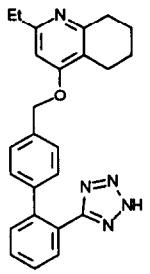
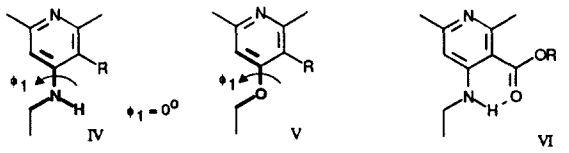


III (Zeneca ZD6888)

Molecular modelling using ENIGMA[4a] and AESOP[4b] confirmed that such compounds would adopt a planar -CH=C-NH-CH_2- conformation IV, analogous to that of the corresponding methyleneoxy linked compounds V[2,3]. It was initially proposed that in compounds with an ester functionality in the 3-position, hydrogen bonding as in VI would reinforce this situation. However, modelling further indicated that even with a sterically demanding non-hydrogen bonding substituent in the 3-position, the interaction between the substituent and the hydrogen atom on the linking nitrogen was insufficient to distort the planar conformation.

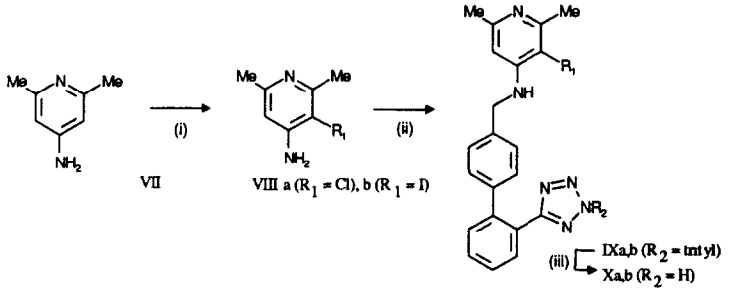


We now wish to report the synthesis of a series of methyleneamino linked pyridines which are potent AII antagonists *in vitro*. Additionally, some of these compounds have shown much improved *in vivo* activity, when dosed both *i.v.* and *p.o.* against an AII challenge in a normotensive rat model.

Chemistry

The compounds described in Table 1 were synthesised as described in Schemes 1-4. The halogenated pyridines VIIIa,b were prepared by chlorination and iodination of 4-amino-2,6-dimethylpyridine[5] VII as described in Scheme 1. Chlorination was carried out by treatment of a sulphuric acid solution of the VII with chlorine, according to the literature precedence[7] for the chorination of 4-amino-3,5-dimethylpyridine, giving the monochlorinated product VIIIa in high yield.

Scheme 1



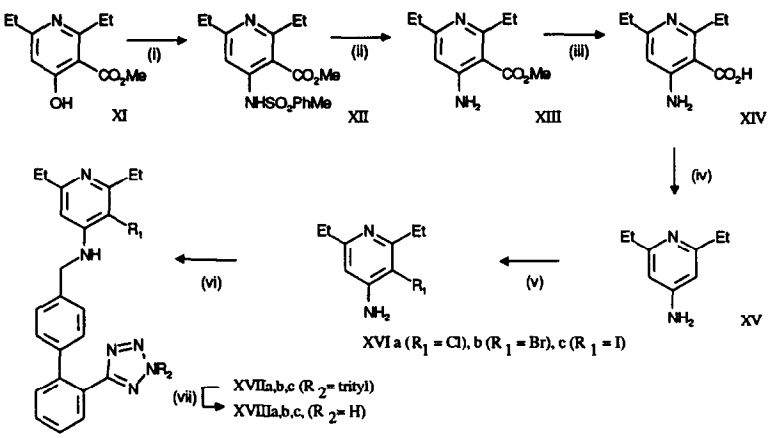
Reagents: (i) VIIIa, Cl_2/H_2SO_4; VIIIb, $(CF_3CO_2)_2IPh/HCl/MeCO_2H$; (ii) KOBu^t/18-CR-6/THF/5-[4'-bromomethylbiphenylyl]-2-triphenyl-2*H*-tetrazole; (iii) $HCl/CH_2Cl_2/MeOH$

Iodination under literature conditions[5] gave 4-amino-2,6-dimethyl-3-iodopyridine VIIIb contaminated with the 3-chloro derivative. However it was subsequently shown that use of bis(trifluoroacetoxy)iodobenzene-iodine[6], under acidic conditions, gave the desired compound VIIIb in high yield. Alkylation of the halopyridines VIII with 5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2*H*-tetrazole[1a] gave the desired compounds with substitution on the exocyclic nitrogen, this being shown by coupling (J = 6.6 Hz) of the benzylic protons to an exchangeable (-NH-) proton in their H^1 NMR spectra. Deprotection of the tetrazole under acidic conditions then gave the final products Xa,b. Preparation of the corresponding diethyl analogues XVIIIa,b,c was accomplished in an analogous manner, starting from 4-amino-2,6-diethylpyridine XV, as described in Scheme 2. The latter compound was most easily prepared by hydrolysis of the amino ester XIII and subsequent decarboxylation of the acid XIV. Though the amino ester XIII could be prepared by classical methodology[8] (see Scheme 3), it was subsequently shown that it was more conveniently prepared from the hydroxy ester XI via a hydroxy-amino transposition utilising 4-toluenesulphonyl isocyanate[9]. This high

yielding process (74% for the two steps XI-XIII) gave an analytically pure product without the need for chromatography and could be operated on a considerable (up to 250 g) scale.

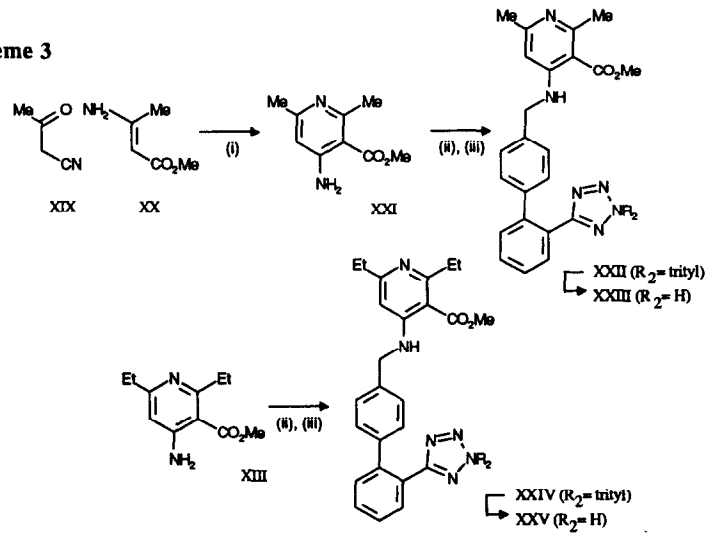
The ester derivatives XXIII and XXV were prepared as described in Scheme 3. The dimethyl precursor XXI was prepared by the literature route[8] starting from the α-cyanoketone XIX and the amino crotonate XX[10] using a stannic chloride catalysed condensation. The corresponding diethyl analogue XIII was prepared as described above (Scheme 2).

Scheme 2



Reagents: (i) (4-MePh)SO_2NCO/MeCN/reflux; (ii) c.H_2SO_4/50°C; (iii) NaOH/MeOH/reflux; (iv) 200°C; (v) XVIa, Cl_2/H_2SO_4; XVIb, NBS/1,4-dioxan; XVIc, $(CF_3CO_2)_2IPh/I_2$/HCl/$MeCO_2H$/reflux; (vi) KOBu^t/18-CR-6/THF/5-[4'-bromomethylbiphenylyl]-2-triphenyl-2*H*-tetrazole; (vii) HCl/CH_2Cl_2/MeOH

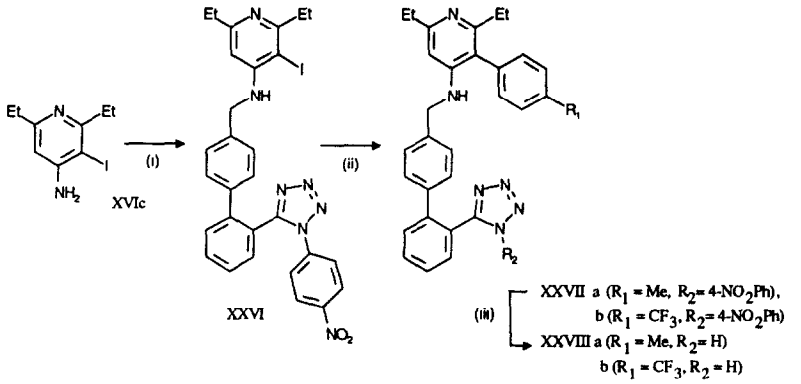
Scheme 3



Reagents: (i) $SnCl_4$/PhMe/reflux; (ii) NaH/DMF/5-[4'-bromomethylbiphenylyl]-2-triphenyl-2H-tetrazole; (iii) HCl/CH_2Cl_2/MeOH

The 3-aryl substituted pyridines XXVIIIa,b were prepared as described in Scheme 4, via the amino iodide XVIc (see Scheme 2). The 3-aryl substituents were introduced using a palladium catalysed coupling to the biphenyl substituted analogue XXVI. This derivative incorporated the nitrophenyl protecting group[11] which is more stable to conditions of the palladium catalysed coupling reaction than the corresponding trityl protected analogue. Thus reaction of the requisite aryl boronic acids with the iodide XXVI gave the protected 3-aryl derivatives XXVIIa,b. The final products XXVIIIa,b were obtained by methoxide promoted removal of the nitrophenyl protecting group.

Scheme 4



Reagents: (i) KOBu^t/18-CR-6/THF/5-(4'-bromomethylbiphenyl-2-yl)-2-(4-nitrophenyl)-1*H*-tetrazole; (ii) XXVIIIa, (4-Me)PhB(OH)$_2$/(Ph$_3$P)$_4$Pd/NaHCO$_3$/H$_2$O/PhMe/reflux; XXVIIIb, (4-CF$_3$)PhB(OH)$_2$/(Ph$_3$P)$_4$Pd/NaHCO$_3$/ H$_2$O/PhMe/reflux; (iii) MeOH/MeONa/reflux

Biological Results

The compounds described in Table 1 were evaluated in a conventional radioligand binding assay, based on displacement of monoiodinated angiotensin II from a membrane preparation prepared from guinea pig adrenal glands. *I.v.* and *p.o.* activity was determined in an AII challenged conscious normotensive rat model. All of these assay procedures have been described in detail elsewhere[2,12]. *In vitro* and *in vivo* (*i.v.*) results are shown in Table 1, together with the corresponding results for compounds I-III.

Discussion

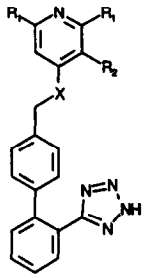
The 3-halo and 3-ester pyridine derivatives described in Table 1 all have nanomolar potency in the *in vitro* binding assay and on the whole these compounds are more potent than there correspondind oxymethylene analogues, for example the iodide XVIIIc is approximateley 5 fold more potent than the oxymethylene analogue XXIX[3a]. In both the dimethyl series and diethyl series the iodides Xb and XVIIIc are marginally more potent than the corresponding chloro derivatives Xa and XVIIIa. The esters XXIII and XXV are also of lower potency, similar to that of the chloro derivatives. Finally the aryl substituted compounds are slightly less potent again. This order is essentially the reverse of that observed for the corresponding methyleneoxy compound[3]. Additionally there is no obvious difference between the potency of the dimethyl compounds Xa,b and XXIII and their corresponding diethyl analogues XVIIIa,c and XXV. Again this is in contrast to

the corresponding methyleneoxy compounds where there was generally a 10 fold improvement in potency in the diethyl analogues compared to the dimethyl analogues[3].

In vivo, on *i.v.* administration, the halo pyridine derivatives Xa,b and XVIIIa,b,c were generally more potent than analogues from the methyleneoxy quinoline[2] or pyridine[3] series. For example the chloro derivative XVIIIa is approximately 16 fold more potent than the quinoline II. This potency was also manifest in extended duration of action on *i.v.* dosing with XVIIIa showing significant inhibition (66%) of the AII challenge remaining 5 hours after dosing at 1.0 mg/kg, whereas the methyleneoxy quinoline II was essentially inactive at this dose. Though some improvement in *i.v.* activity of the methyleneamino linked compounds was undoubtedly due to their more potent *in vitro* activity, there is a greater improvement than would be expected from this alone. This further improvement may be due to their more favourable (hydrophilic) physical properties. Thus the chloro compound XVIIIa has pKb = 8.1 and log D (est.) = 1.7 compared to the quinoline II which has pKb = 7.4 and log D (est.) 2.4.

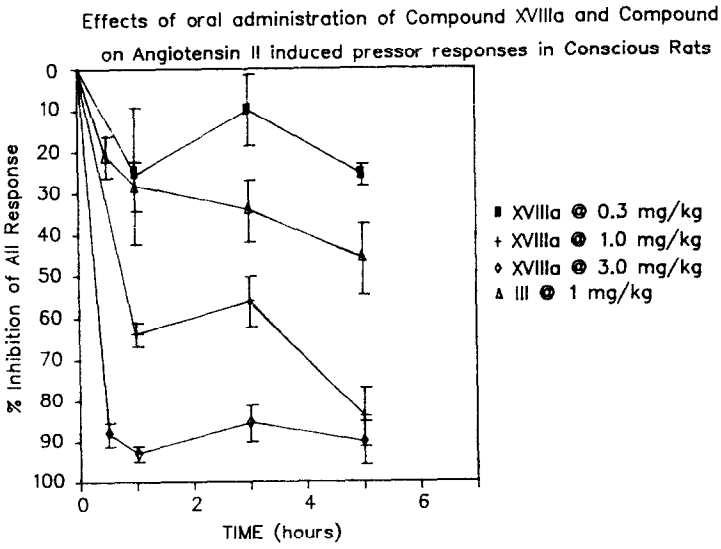
Several of methyleneamino compounds in Table 1 showed good activity on oral administration. The data for compound XVIIIa is presented in Figure 1 and for comparison the effect of the methyleneoxy pyridine III in the same animal model at 1.0 mg/kg is also shown. This demonstrates the improved activity of XVIIIa which may reflect greater oral absorption; however the greater *i.v.* potency of this compound, compared to III, may also be a contributing factor.

Table 1



COMPOUND	R_1	R_2	X	*IN VITRO*[13a] (IC_{50}, nM)	*IN VIVO,I.V.*[13b] (ED_{50}, mg/kg)
Xa	Me	Cl	NH	6.65	0.03
Xb	Me	I	NH	3.48	0.05
XVIIIa	Et	Cl	NH	7.58	0.06
XVIIIb	Et	Br	NH	3.83	0.09
XVIIIc	Et	I	NH	2.64	0.13
XXIII	Me	CO_2Me	NH	8.03	NT
XXV	Et	CO_2Me	NH	6.21	NT
XXVIIIa	Et	(4-CF_3)Ph	NH	26.4	NT
XXVIIIb	Et	(4-Me)Ph	NH	24.9	NT
XXIX[3a]	Et	I	O	14.00	0.44
I	-	-	-	8.0	0.65
II (ZD 8731)	-	-	-	31.0	1.0
III (ZD 6888)	-	-	-	5.0	0.39

Figure 1



References

1. (a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chui, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B. III; Wells, G, J.;Wexler, R. E.; Wong, P. C.; Yoo, S-E; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**,*34*,2525. (b) Duncia, J. V.; Carini, D. J.; Chui, A. T.; Johnson, A. L.; Price, G. J.; Wong, P. C.; Wexler, R. E.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**,*12*,149.
2. Bradbury, R. H.; Allott, C. P.; Dennis, M.; Fisher, E.; Major, J. S.; Masek, B. B.; Oldham, A. A. *J. Med. Chem.* **1992**,*35*,4027.
3. (a) Bradbury, R. H.; Allott, C. P.; Dennis, M.; Girdwood, J. A.; Kenny, P. W.; Major, J. S.; Oldham, A. A.; Ratcliffe, A. H.; Rivett, J.; Roberts, D. A.; Robins, P. J. *J. Med. Chem.* **1993**,*36*,1245. (b) Allott, C. P.; Bradbury, R. H.; Dennis, M.; Fisher. E.; Luke, R. W. A.; Major, J. S.; Oldham, A. A.; Pearce, R. J.; Reid, A. C.; Roberts, D. A.; Rudge, D. A. Russell, S. T. *Bioorg. Med. Chem. Lett.* **1993**,*3*,899.
4. (a) ENIGMA™ is an in-house molecular Graphics programme, ZENECA Inc., Wilmington, DE 19897. (b) AESOP™ is an in house molecular mechanics programme, ZENECA Inc., Wilmington, DE 19897, derived in part from BIGSTRN-3 (QCPE 514), Nachbar, R.; Mislow, K.; *QCPE Bulletein* **1980**,*12*,395.
5. Ochiai, E.; Fujimoto, M.; *Pharm. Bull.* **1954**, *2*, 131.
6. Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synthesis* **1980**,486.
7. *Eur. Pat. Appl.* No. EP 184322.
8. Veronese, A. C.; Callegari, R; Salah, S. A. A.; *Tett. Letters* **1980**,*31*,3485.
9. Wright, R. G. McR.; *Synthesis* **1984**,1058.
10. Hackler, R. E.; Burrow, K. W.; Kaster, S. V. *J. Het. Chem.* **1989**,*26*,1575.
11. *Eur. Pat. Appl.* No. EP 495626.
12. Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A. *J. Med. Chem.* **1992**, *35*,877
13 (a) IC_{50} for inhibition of specific binding of [^{125}I]AII to guinea pig adrenal membrane preparation, (b) ED_{50} following *i.v.* administration to conscious rats for inhibition of AII-induced pressor response.

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