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QUINOLINE, 1,5-NAPHTHYRIDINE AND PYRIDINE DERIVATIVES AS POTENT, NONPEPTIDIC ANGIOTENSIN II RECEPTOR ANTAGONISTS

C. P. Allott, R. H. Bradbury, M. Dennis, E. Fisher, R. W. A. Luke, J. S. Major, A. A. Oldham, R. J. Pearce, A. C. Reid, D. A. Roberts, D. A. Rudge and S. T. Russell
Departments of Chemistry and Bioscience, ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

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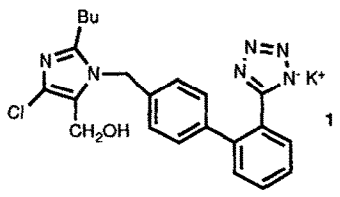
Abstract: Quinoline-, 1,5-naphthyridine- and pyridine-based angiotensin II antagonists are reported. The more potent compounds gave IC_{50} values of ca 0.01 μM in a guinea pig adrenal membrane binding assay and intravenous ED_{50} values in the range 0.1-1.0 mg/kg for inhibition of the AII-induced pressor response in normotensive rats. Several of these compounds, for example **4d** (ICI D6888), showed good oral activity in this animal model.

As a potential treatment for hypertension and congestive heart failure, blockade of the renin-angiotensin system by a receptor antagonist of the endogenous vasoconstrictor octapeptide angiotensin II (AII) has long been recognised as an alternative to suppression of AII biosynthesis by inhibition of angiotensin converting enzyme (ACE).[1] Such an agent would be expected to display a similar therapeutic profile to an ACE inhibitor, but might lack the undesirable side effects thought to be related to potentiation of bradykinin and other biologically significant peptides such as substance P.[2] Until recently, all known potent AII antagonists have been peptide analogues[3] and have consequently suffered from all the problems normally associated with peptides, such as poor oral absorption, short plasma half-life, rapid clearance and partial agonism.[4]

More recently, the first potent, non-peptidic AII receptor antagonists have been described,[5-9] examples of which are shown below (**1** and **2a,b**). Starting from a weakly active lead compound, extensive structure-activity investigations[5] by the Du Pont group led to potent and specific antagonists such as DuP 753 (**1**).[5,10] This compound displays good oral activity in animal models[10b] and has undergone clinical evaluation as an antihypertensive agent.[11] The chloro- and hydroxymethyl-substituents on the imidazole ring of **1** are not essential for in vitro activity and can be replaced by a fused benzene ring (compound **2a**[8]), albeit with some reduction in potency. Introduction of a nitrogen atom at the 4-position of the benzimidazole ring and fine tuning of the heterocycle substituents provided the highly potent antagonist L-158,809 (**2b**),[9] which shows good antihypertensive activity in animal models.



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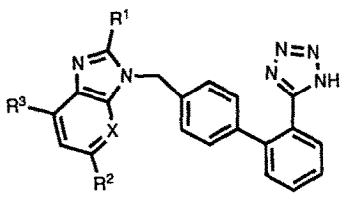


2a, X = CH, R^1 = Bu, R^2 = R^3 = H
2b, X = N, R^1 = Et, R^2 = R^3 = Me

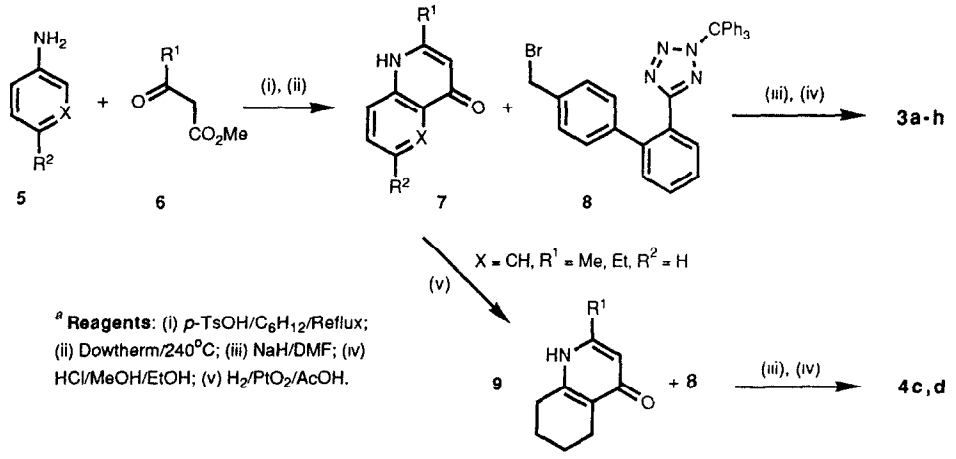
Based on published work,[5,8,9] a number of structural features desirable for optimal biological activity are apparent

in antagonists such as **1** and **2a,b**. Firstly, compounds containing a biphenyltetrazole moiety linked to the heterocycle by a methylene group have the best binding affinities and oral potencies. Secondly, a short alkyl chain at the 2-position of the imidazole or fused imidazole ring is needed for efficient receptor binding. Finally, the imidazole ring itself is required, most probably as an acceptor in a hydrogen bonding interaction with the receptor.

In seeking new nonpeptidic ligands for the AII receptor, we chose to focus on the nature of the putative hydrogen bond acceptor. Obvious candidates include heterocycles such as triazoles and pyrazoles, but these are known to be inferior to imidazole in terms of acceptor ability [12] As an alternative, we considered non-azole acceptors and in particular those derived from 4-pyridones and 4-alkoxypyridines, both of which have comparable acceptor potential to imidazole.[12] We envisaged that these structural types could be available from *N*- or *O*-alkylation of an appropriate 4-pyridone precursor with a protected bromomethylbiphenyltetrazole intermediate.[5a] In this communication we report the synthesis and biological properties of antagonists containing the 4-alkoxypyridine moiety as a nonpeptidic ligand.

Selected compounds **3a-h** and **4a-d** prepared during the course of this work are listed in Tables 1 and 2 and their syntheses are outlined in Scheme 1. 4-Alkoxyquinoline derivatives **3a-e** and analogous 1,5-napthyridines **3f-h** were synthesised by *O*-alkylation of quinolones and naphthyridones **7** with bromomethylbiphenyl compound **8**,[5a] followed by acid-promoted detritylation of the resulting intermediates. In the ^{13}C NMR spectra of **3a-h** the benzylic CH_2 signals at ca ∂ 70 ppm were consistent with *O*- rather than *N*-alkylation [13] In the case of compound **3a**, an X-ray crystal structure determination[14] confirmed the regiochemistry of the alkylation step. Under a variety of basic conditions *N*-alkylation of **7** was not seen The starting quinolones and naphthyridones **7** were prepared from the appropriate aniline or aminopyridine **5** and ß-ketoester **6** using the Conrad-Limpach method.[15] 4-Alkoxypyridine derivatives **4a,b** were obtained similarly by *O*-alkylation of the requisite pyridone precursor.[16] For the preparation of tetrahydroquinoline derivatives **4c,d**, the appropriate quinolones **7** were hydrogenated[17] and the products **9** *O*-alkylated.

Scheme 1[a]



[a] **Reagents**: (i) *p*-TsOH/C_6H_{12}/Reflux; (ii) Dowtherm/240°C; (iii) NaH/DMF; (iv) HCl/MeOH/EtOH; (v) H_2/PtO_2/AcOH.

Compounds **3a-h** and **4a-d** were evaluated as AII antagonists in vitro in a radioligand binding assay involving displacement of [^{125}I]AII from a guinea pig adrenal membrane preparation,[8b] which corresponds to the AT_1 receptor subtype,[18] and in vivo by determining their ED_{50} values for inhibition of the pressor response induced by infusion of

Figure 1. Effects of Oral Administration of Compound **4d** and DuP 753 on Angiotensin II Induced Pressor Responses in Conscious Rats

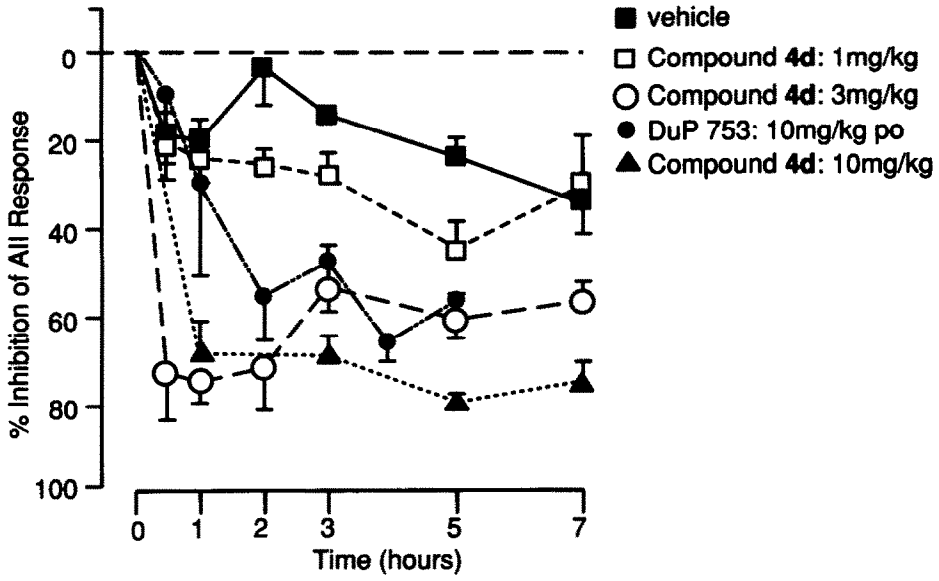
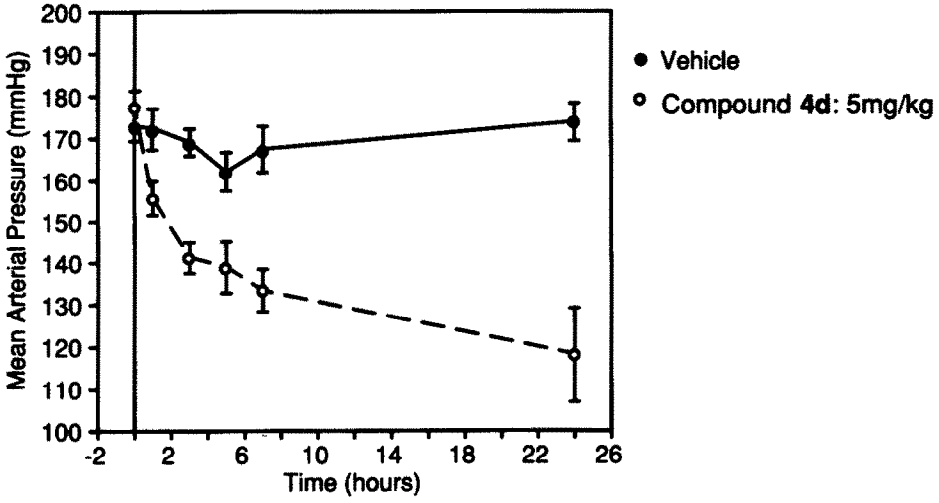


Figure 2. Effects of Oral Administration of Compound **4d** on Mean Arterial Pressure of Renal Hypertensive Rats

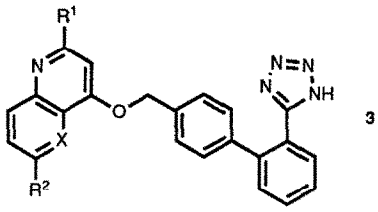


AII in conscious normotensive rats.[8b] The IC_{50} and ED_{50} values for DuP 753 (1) in these tests are included in Table 1 for comparison.

The initial compounds prepared **3a,b** showed comparable in vitro and in vivo potency to DuP 753. Introduction of a longer chain at the quinoline 2-position (**3c**) resulted in a significant fall in potency both in vitro and in vivo. A variety of substituents was introduced at the 5-,6-,7- and 8-positions of the quinoline ring (data not shown), but only substitution at the 6-position by an alkoxy group provided compounds (e.g. **3d,e**) with similar affinity to the parent **3b**. These compounds did, however, show improved in vivo potency relative to **3b**.

In contrast to the significant enhancement in binding affinity reported[9] on going from a benzimidazole-based AII antagonist such as **2a** to an imidazo[4,5-*b*]pyridine-based antagonist such as **2b**, only small changes in potency were seen on introduction of a nitrogen atom at the analogous position in the quinoline ring. 1,5-Naphthyridine derivatives **3f-h** thus showed similar profiles of activity to the corresponding quinolines **3b,e,f**.

Table 1. In Vitro and In Vivo Data for Quinoline and Naphthyridine Derivatives **3a-h**



3

no.	R^1	R^2	X	IC_{50}, μM[a]	iv ED_{50}, mg/kg[b]
1				0.018	0.65 ± 0.21
3a	Me	H	CH	0.016	0.73 ± 0.14
3b	Et	H	CH	0.031	1.0 ± 0.42
3c	Pr	H	CH	0.066	>5
3d	Et	OMe	CH	0.022	0.32 ± 0.06
3e	Et	OPr^i	CH	0.026	0.18 ± 0.02
3f	Et	H	N	0.024	0.86 ± 0.07
3g	Et	OMe	N	0.014	0.81 ± 0.34
3h	Et	OPr^i	N	0.008	0.18 ± 0.03

[a] IC_{50} for inhibition of specific binding of [^{125}I]AII to a guinea pig adrenal membrane preparation (n = 1-3)

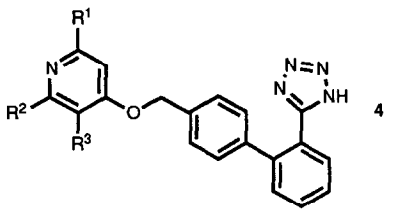
[b] ED_{50} following iv administration to conscious rats for inhibition of AII-induced pressor response (n = 3-10)

Simplification of the quinoline ring, to give the 2,6-dimethyl pyridine derivative **4a**, resulted in a ca 20-fold reduction in binding affinity relative to **2b**. This reduction in affinity could be partially redressed by substitution of a methyl group at the 3-position of the pyridine ring (compound **4b**) and completely redressed by linking the 2,3-dimethyl substituents to give the tetrahydroquinoline derivatives **4c,d**, both of which display good in vivo activity.

The potency and specificity of compound **4d** was also assessed by analysing dose-tension curves to AII in isolated guinea pig ileum. At concentrations of 0.73 nM and 3.65 nM, the compound produced dose-related, parallel-rightward shifts in the AII dose-response curves without depressing maximum responses to the agonist, a pattern of activity consistent with competitive antagonism. Schild analysis gave a pA2 value of 9.7. The slope of the Schild

regression line was not significantly different from minus one, again in accord with competitive antagonism.

Table 2. In Vitro and In Vivo Data for Pyridine Derivatives **4a-d**



4

no.	R^1	R^2	R^3	IC_{50}, μM[a]	iv ED_{50}, mg/kg[b]
4a	Me	Me	H	0.30	*c*
4b	Me	Me	Me	0.13	0.31 ± 0.19
4c	Me	$(CH_2)_4$		0.025	0.48 ± 0.12
4d	Et	$(CH_2)_4$		0.005	0.39 ± 0.07

[a,b] See Table 1.

[c] Compound too insoluble for in vivo testing

Several of the compounds showed good oral activity in an AII-infused, conscious, normotensive rat model. As an example, the data for compound **4d** at doses of 1, 3 and 10 mg/kg are presented in Figure 1, showing a dose-related inhibition of pressor response lasting for the seven hour time course of the experiment at the 3 mg/kg dose. For comparison, the effect of DuP 753 in the same animal model at a dose of 10 mg/kg is also shown.

Compound **4d** also demonstrated good activity in a renal hypertensive rat model.[19] When administered orally at a dose of 5 mg/kg (Figure 2), the compound had a rapid effect in reducing the blood pressure of rats with renal hypertension. The blood pressure of the animals was normalised within two hours of dosing, and the effect was still evident 8 and 24 hours after dosing. In contrast, the effects of **4d** in normotensive, sham operated rats were small (data not shown), consistent with a specific antihypertensive effect in renal hypertensive rats. Based on its pharmacological profile, this compound, designated ICI D6888, has been selected for clinical investigation.

The AII antagonists reported here differ structurally from previously described imidazole-derived antagonists such as DuP 753 both in the nature of the putative hydrogen bond acceptor (quinoline, naphthyridine or pyridine vs imidazole) and the chain linking the biphenyltetrazole moiety and the heterocyclic fragment (methyleneoxy vs methylene). Despite these differences, examination of overlays of certain of their low energy conformations generated by molecular mechanics shows a very good correspondence both of the tetrazole groups and of the N-1 atoms of the quinoline, naphthyridine or pyridine rings with the N-1 atom of the imidazole ring. In addition, good fits of the rings of the biphenyl units and of the alkyl groups at the 2-positions of each series are also observed. Details of these studies, which are consistent with the two types of ligand acting as a common pharmacophore at the AII receptor, will be reported elsewhere.[20]

Acknowledgement

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(19) Male Alderley Park Wistar rats weighing 280-300 g were anaesthetised with Saffan (alphaxalone/alphadolone). The left renal artery was exposed and a platinum clip with an internal diameter of 0 25 mm was placed around it causing a partial occlusion. After 12-14 days, the animals were prepared under Saffan anaesthesia with an indwelling arterial catheter and allowed to recover for 18-24 h. Blood pressure was measured via the arterial catheter before and for up to 24 h following oral dosing with the antagonist.

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