New Nonpeptide Angiotensin II Receptor Antagonists. 3.[1] Synthesis, Biological Properties, and Structure–Activity Relationships of 2-Alkyl-4-(biphenylylmethoxy)pyridine Derivatives

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A novel series of nonpeptide angiotensin II (AII) receptor antagonists is reported, derived from linkage of the biphenylyltetrazole moiety found in previously described antagonists via a methyleneoxy chain to the 4-position of a 3-substituted 2,6-dialkylpyridine. When evaluated in an in vitro binding assay using a guinea pig adrenal membrane preparation, compounds in this series generally gave IC_{50} values in the range 0.005–0.5 μM. A variety of substituents was found to be effective at the 3-position of the pyridine ring. On intravenous administration in a normotensive rat model, the more potent compounds inhibited the AII-induced pressor response with ED_{50} values in the range 0.1–1.0 mg/kg. One of the compounds, 2-ethyl-5,6,7,8-tetrahydro-4-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methoxy}quinoline (26), demonstrated good oral activity in two rat models. At doses in the range 1–10 mg/kg po in AII-infused, conscious, normotensive rats, the compound exhibited a dose-related inhibition of the pressor response with a good duration of action at the higher doses. In a renal hypertensive rat model compound 26 showed a rapid and sustained lowering of blood pressure at a dose of 5 mg/kg po. Based on its profile, this compound, designated ICI D6888, has been selected for evaluation in volunteers.

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 recognized as an alternative to suppression of AII biosynthesis by inhibition of angiotensin converting enzyme (ACE).[2] 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.[3] Until recently, all known potent AII antagonists have been peptide analogues[4] and have consequently suffered from all the problems normally associated with peptides, such as poor oral absorption, short plasma half-life, and rapid clearance.[5] In addition, all have demonstrated partial agonism.[5]

More recently, the first potent, orally active nonpeptide AII antagonists have been described,[6] selected examples of which are shown in Figure 1. Starting from a weakly active lead compound,[7] extensive structure–activity investigations[8,9] by the Du Pont group led to potent and specific antagonists such as DuP 753 (losartan, 1).[8c,9,10] This compound displays good oral activity in animal models[10b] and is currently undergoing clinical evaluation as an antihypertensive agent.[11]

On the basis of published work,[1a,8,12] a number of structural features desirable for optimal biological activity are apparent in antagonists such as 1 and related compounds. Firstly, compounds containing a biphenylyltetrazole moiety linked to a 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 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.
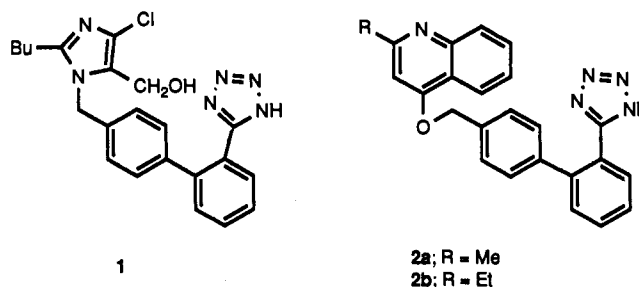

Figure 1. Selected nonpeptide AII antagonists.

We recently described[1b] a novel series of potent, nonpeptide AII antagonists derived from linkage of the biphenylyltetrazole moiety found in previously described antagonists via a methyleneoxy chain to the 4-position of a 2-alkylquinoline. Although these antagonists, for example 2a,b, differ structurally from previous series both in the nature of the putative hydrogen bond acceptor (quinoline vs imidazole) and the linking chain from the biphenylyltetrazole moiety (methyleneoxy vs methylene), examination of overlays of the low-energy conformations of each structural type generated by molecular mechanics showed a very good correspondence of the tetrazole groups and of the respective N-1 and N-3 atoms of the quinoline and imidazole rings.

When administered intravenously in a normotensive rat model, compound 2b (ICI D8731) inhibited the AII-induced pressor response with an ED_{50} value of 1.0 mg/kg. The compound also demonstrated good oral activity in normotensive and renal hypertensive rat models. On the basis of its pharmacological profile,[13] compound 2b was selected for clinical evaluation as an antihypertensive agent. In seeking new series of antagonists with improved in vitro and in vivo activity over 2b, we chose to replace the quinoline ring of the existing series by a pyridine ring, and in this paper we describe the synthesis, biological

Table I. Characterization Data for Pyridone Intermediates 3-11
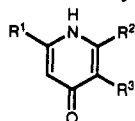
no.	R^1	R^2	R^3	mp, °C	formula^a
3	Me	Me	CHO	>100	C$_8$H$_9$NO$_2$
4a	Me	Me	CO$_2$Me	218–219	C$_9$H$_{11}$NO$_3$·0.1H$_2$O
4b	Me	Et	CO$_2$Me	148–150	C$_{10}$H$_{13}$NO$_3$
4c	Me	Pr	CO$_2$Me	142–144	C$_{11}$H$_{15}$NO$_3$·0.2H$_2$O
5	Me	Me	Ph	231–235	C$_{13}$H$_{13}$NO·0.25H$_2$O
6	Me	Me	4-Pyridyl	>250	C$_{12}$H$_{12}$N$_2$O·0.1H$_2$O
7	Me	Me	CH$_2$Ph	212–215	C$_{14}$H$_{15}$NO
8a	Et	Me	CO$_2$Me	176–180	C$_{10}$H$_{13}$NO$_3$·0.2H$_2$O^b
8b	Pr	Me	CO$_2$Me	132–136	C$_{11}$H$_{15}$NO$_3$
8c	Et	Et	CO$_2$Me	127–130	C$_{11}$H$_{15}$NO$_3$·0.1H$_2$O
8d	Et	Me	COMe	172–174	C$_{10}$H$_{13}$NO$_2$·0.1H$_2$O
8e	Et	Me	COPh	202–204	C$_{15}$H$_{15}$NO$_2$·0.4H$_2$O
9a	Et	(CH$_2$)$_3$		212–214	C$_{10}$H$_{13}$NO·0.1H$_2$O
9b	Et	(CH$_2$)$_5$		196–198	C$_{12}$H$_{17}$NO·H$_2$O
10	Et	(CH$_2$)$_4$		226–227	C$_{11}$H$_{15}$NO·0.1H$_2$O
11	Et	Et	I	225–227	C$_9$H$_{12}$INO

^{a} Analyses for C, H, N were correct within ±0.4% unless otherwise stated. ^{b} C, H; N: calcd, 7.0; found 7.5.

properties, and molecular modeling of this class of compounds.

Chemistry

The compounds 14–27 prepared during the course of this work are listed in Table II. The majority were prepared as illustrated in Scheme I for 19–27 by O-alkylation of 4(1*H*)-pyridones 3–11 with (bromomethyl)biphenyl compound 12^{8c} in DMF using sodium hydride as base, followed by acid-promoted detritylation of the resulting intermediates 13. Compounds 14a–d were obtained similarly from known pyridone precursors.[14-16] Analogously to our previous work,[1b] in the ^{13}C NMR spectra of 14a–d, 19–27 the benzylic CH$_2$ signal at ca. ∂ 70 was consistent with O- rather than N-alkylation of the precursor pyridones. In the case of compound 26, an X-ray crystal structure determination (Figure 2) confirmed the regiochemistry of the alkylation step.

The syntheses of compounds 15–17 involved manipulation of the ester functionality in intermediate 13a as summarized in Scheme II. Reduction of 13a provided alcohol 28, which gave 15 on detritylation. Compound 16 was obtained by methylation of 15 followed by detritylation of 29. For the preparation of 17, intermediate 28 was converted to chloro compound 30a. Reduction to 30b and detritylation then provided 17. Carboxylic acid 18 was prepared by hydrolysis of 20a.

Characterization data for new pyridones 3–11 prepared during the course of this work are given in Table I. The 3-formylpyridone 3 was prepared by formylation of 2,6-dimethyl-4(1*H*)-pyridone using conditions employed previously for 4(1*H*)-quinolone formylation.[17] Pyridone 5 was obtained by reaction of 2,6-dimethyl-3-phenyl-4-pyrone[18] with ammonia. Tetrahydroquinolone 10 was synthesized by catalytic hydrogenation of 2-ethyl-4(1*H*)-quinolone[1b] analogously to a previously described reduction of quinolones.[19] The remaining pyridone precursors were prepared as summarized in Schemes III–VI.

Pyridones 4a–c, 6 were obtained by using diketene chemistry (Scheme III). Heating aminocrotonate esters 31a–c with diketene provided 4a–c directly.[16] An analogous reaction of ketone 32 with diketene gave pyrone 33, which was converted to 6 by reaction with ammonia.

The 3-benzylpyridone derivative 7 was prepared (Scheme IV) by O-benzylation of 2,6-dimethyl-3-iodo-4(1*H*)-pyridone,[15] followed by palladium-catalyzed coupling of the resulting intermediate 34 with benzyl bromide. Debenzylation of 35 then provided 7.

Pyridones 8a–e were synthesized (Scheme V) using acyl Meldrum's acid derivatives 36a,b.[20] Heating 36a,b with aminocrotonate esters 31a,b or aminobutenones 31d,e gave the pyridones directly. An analogous reaction of enamines 37a,b with 36a provided pyrone derivatives 38a,b, which were converted to pyridones 9a,b by reaction with ammonia.

For the preparation of iodopyridone 11 (Scheme VI), pyridone ester 8c was hydrolyzed and decarboxylated, and the resulting symmetrical pyridone 40 was treated with iodine.

In Vitro AII Antagonism

Compounds 14–27 (Table II) were evaluated as antagonists of AII in a radioligand binding assay involving displacement of [^{125}I]AII from a guinea pig adrenal membrane preparation, which corresponds to the AT$_1$ receptor subtype.[21] IC$_{50}$ values in this assay for 1 and 2a,b are included in Table II for comparison.

The simplest compound prepared, the 2,6-dimethylpyridine derivative 14a, showed a ca. 20-fold reduction in binding affinity compared with the corresponding quinoline derivative 2a. This reduction in affinity could be redressed by introduction of a variety of substituents at the 3-position of the pyridine ring. Thus substitution by halo (14b), aryl (21), heteroaryl (22), benzyl (23), and electron-withdrawing groups (14c,d, 20a) all gave compounds with significantly improved affinity. In contrast, introduction of a methyl group (17), a substituted methylene group (15, 16), or a formyl group (19) led to only a modest increase in binding. Compound 18 containing a carboxyl group at the pyridine 3-position showed significantly reduced binding affinity.
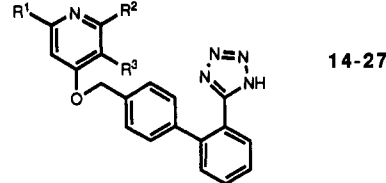
With a methoxycarbonyl group at the pyridine 3-position, a limited range of alkyl substituents at the 2- and 6-positions were explored. Whereas at the 2-position little discrimination was seen between methyl, ethyl, and propyl groups (20a–c), at the 6-position ethyl and propyl substitution (24a–c) gave a 5–10-fold increase in binding affinity over the methyl-substituted compound (20a). With an ethyl group at the 6-position, selected substituents were then introduced at the 3-position to give compounds 24d,e, 27, all of which showed good affinity.

Finally, the 2- and 3-positions of the pyridine ring were joined in a saturated ring by a chain three to give atoms in length. The resulting compounds 25a,b, 26 all demonstrated good receptor antagonism, with the compounds with three- and four-carbon chains displaying the highest affinity.

Introduction of substituents at the pyridine 5-position was not attempted, since in our earlier work[1b] on quinoline-based antagonists such as 2a,b incorporation of a methyl group at the analogous position caused a major reduction in binding affinity.

The potency and specificity of compound 26 was also assessed by analyzing dose–tension curves to AII in isolated guinea pig ileum. At concentrations of 0.73 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

Table II. Characterization, in Vitro AII Antagonism, and in Vivo Activity of Compounds 1, 2a,b, and 14–27

14–27

no.	R¹	R²	R³	mp, °C	formula^a	IC$_{50}$, μM^b	iv ED$_{50}$, mg/kg^c
1						0.018	0.65 ± 0.21
2a						0.016	0.73 ± 0.14
2b						0.031	1.0 ± 0.42
14a	Me	Me	H	223–225	$C_{21}H_{19}N_5O\cdot HCl^d$	0.30	e
14b	Me	Me	I	237–245	$C_{21}H_{18}IN_5O\cdot HCl\cdot H_2O$	0.034	0.49 ± 0.08
14c	Me	Me	COMe	138–141	$C_{23}H_{21}N_5O_2\cdot HCl\cdot 0.17H_2O$	0.030	0.48 ± 0.07
14d	Me	Me	COPh	198–200	$C_{28}H_{23}N_5O_2\cdot HCl\cdot 0.25H_2O$	0.006	0.13 ± 0.03
15	Me	Me	CH$_2$OH	222–224	$C_{22}H_{21}N_5O_2\cdot HCl\cdot 0.5H_2O\cdot 0.1EtOH$	0.12	1.60 ± 0.86
16	Me	Me	CH$_2$OMe	191–193	$C_{23}H_{23}N_5O_2\cdot HCl\cdot 2H_2O^f$	0.086	0.39 ± 0.12
17	Me	Me	Me	210–212	$C_{22}H_{21}N_5O\cdot HCl^g$	0.13	0.31 ± 0.19
18	Me	Me	CO$_2$H	235–237	$C_{22}H_{19}N_5O_3\cdot 0.5H_2O$	1.17	
19	Me	Me	CHO	124–130	$C_{22}H_{19}N_5O_2\cdot HCl\cdot 0.75H_2O$	0.19	4.85 ± 3.43
20a	Me	Me	CO$_2$Me	137–140	$C_{23}H_{21}N_5O_3\cdot HCl\cdot H_2O$	0.050	0.13 ± 0.06
20b	Me	Et	CO$_2$Me	189–190	$C_{24}H_{23}N_5O_3\cdot HCl$	0.023	1.99 ± 1.59
20c	Me	Pr	CO$_2$Me	162–163	$C_{25}H_{25}N_5O_3\cdot HCl$	0.054	0.62 ± 0.29
21	Me	Me	Ph	142–144	$C_{27}H_{23}N_5O\cdot HCl\cdot 0.5H_2O\cdot 0.5Et_2O$	0.006	1.12 ± 0.51
22	Me	Me	4-pyridyl	178–180	$C_{26}H_{22}N_6O\cdot 2HCl\cdot 2.5H_2O\cdot 0.2Et_2O$	0.025	0.21 ± 0.15
23	Me	Me	CH$_2$Ph	211–214	$C_{28}H_{25}N_5O\cdot HCl\cdot 0.25H_2O$	0.014	0.28 ± 0.11
24a	Et	Me	CO$_2$Me	152–154	$C_{24}H_{23}N_5O_3\cdot HCl$	0.005	0.13 ± 0.06
24b	Pr	Me	CO$_2$Me	105–110	$C_{25}H_{25}N_5O_3\cdot HCl\cdot 0.6H_2O$	0.009	1.03 ± 0.12
24c	Et	Et	CO$_2$Me	174–175	$C_{25}H_{25}N_5O_3\cdot HCl$	0.005	0.15 ± 0.05
24d	Et	Me	COMe	140–142	$C_{24}H_{23}N_5O_2\cdot HCl\cdot 0.6H_2O$	0.008	0.08 ± 0.01
24e	Et	Me	COPh	211–213	$C_{29}H_{25}N_5O_2\cdot HCl$	0.004	0.34 ± 0.05
25a	Et	(CH$_2$)$_3$		212–214	$C_{24}H_{23}N_5O\cdot HCl$	0.008	1.05 ± 0.22
26b	Et	(CH$_2$)$_5$		208–211	$C_{26}H_{27}N_5O\cdot HCl$	0.025	0.78 ± 0.36
26	Et	(CH$_2$)$_4$		232–233	$C_{25}H_{25}N_5O\cdot HCl$	0.05	0.39 ± 0.07
27	Et	Et	I	201–205	$C_{23}H_{22}IN_5O\cdot HCl$	0.014	0.44 ± 0.15

^{a} Analyses for C, H, N were correct within ±0.4% unless otherwise stated. ^{b} IC$_{50}$ for inhibition of specific binding of [125I]AH to a guinea pig adrenal membrane preparation (n = 1–3, see ref 1a for description of assay). ^{c} ED$_{50}$ following intravenous administration to conscious rats for inhibition of pressor response induced by infusion of AII. Mean ± SE values are given (n = 3–10, see refs 1a,b for description of assay). ^{d} H, N; C: calcd, 64.2; found 63.7. ^{e} Compound too insoluble for in vivo testing. ^{f} H, N; C: calcd, 58.3; found 58.8. ^{g} N; C: calcd, 64.8; found 64.2; H: calcd, 5.4; found 6.1.

Scheme I^a

3–11   **12**   **13**

19–27
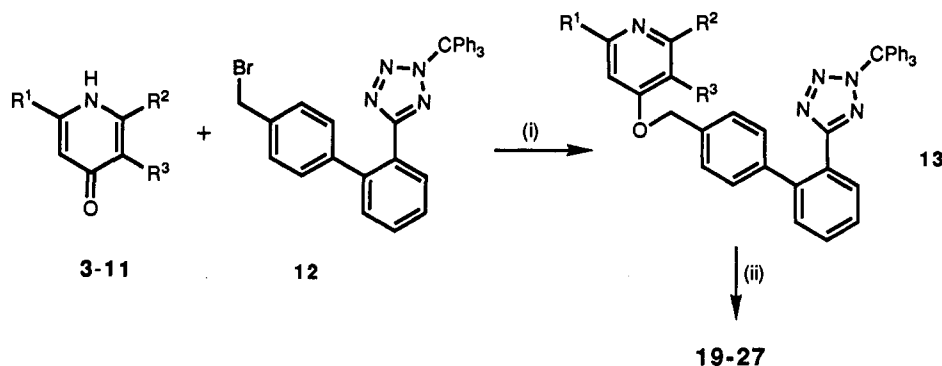
^{a} Reagents: (i) NaH/DMF; (ii) HCl/MeOH/EtOH.

consistent with competitive antagonism. Schild analysis gave a pA_2 value of 9.7. The slope of the Schild regression line was not significantly different from minus one, again in accord with competitive antagonism.

Molecular Modeling Studies

In our previous paper[1b] we described the low-energy conformations of imidazole- and 4-alkoxyquinoline-derived AII antagonists. In these studies the low-energy conformations of the model structural fragments 42 and 44 (Figure 3) were calculated using AESOP 2.3.[22] Of the three conformations identified for each fragment, the helix-1 conformation of 42 and the gauche conformation of 44 were seen to be similar. The low-energy conformations of

structures 2a and 43 (a model structure for 1) were then obtained by combining the low-energy conformations of 42 and 44 with the low-energy conformations of the biphenylyltetrazole moiety 41, also derived from AESOP calculations. When the low-energy conformations of the protonated forms of 2a and 43 were overlaid using ENIGMA,[23] a good correspondence of the tetrazole groups and of the N-1 and N-3 atoms of the quinoline and imidazole rings was seen for the gauche and helix-1 conformations of 2a and 43, respectively.

A similar analysis was performed for the 4-alkoxypyridine derivative 26 as a representative member of the series. As a model for compound 26, structure 45 (Figure 3) was used. Of the three rotatable bonds in the methyleneoxy
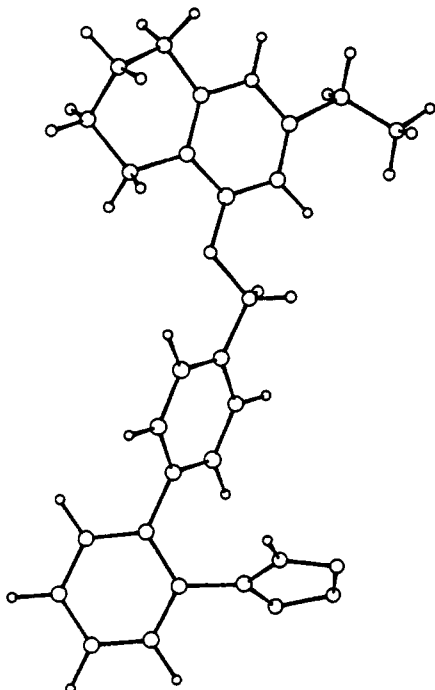
Figure 2. X-ray crystal structure of compound 26.

part of the structure, ϕ_1 is quite rigid. Thus for 45, in close analogy to 44,[1b] a planar conformation with the methylene turned away from the steric repulsion of the peri hydrogen atoms might be expected, with ϕ_2 adopting either the gauche (ca. ±60°) or anti (ca. 180°) conformation. A much wider range of low-energy conformations than seen for 44[1b] was detected by AESOP for 45 due to subtle conformational variations of the methylene groups of the tetrahydroquinoline ring. Among these conformations, with respect to the conformation of the methyleneoxy link, those conformations that are gauche and anti are directly analogous to the conformations reported previously for 44.[1b] The anti conformation of 45 is similar to that observed in the X-ray crystal structure of 26 (Figure 2), even though this conformation is predicted to be slightly higher in energy than the gauche conformation. An analogous correspondence between the anti conformation of 44 and the crystal structure of 2a was seen in our previous work.[1b]

Each of the low-energy conformations of structure 45 can be combined with the two twisted conformations of biphenylyltetrazole moiety 41[1b] to give the low-energy conformations of 26. This results in a total of four biphenyl orientations for each overall conformation of the heterocyclic and linking group moieties. As an example, one of these orientations is shown as a stereopair in Figure 4 for the gauche conformation of 26 in the protonated form. In total, the three conformations of 45 combined with the four biphenyl orientations give 12 low-energy conformations for 26.

The low-energy conformations of the protonated form 26 were overlaid with the low-energy conformations of the protonated form of structure 43[1b] using ENIGMA. As previously,[1b] simple visual examination of the conformations of 42 and 45 highlighted the similarity of the helix-1 and gauche structures. As shown in Figure 5 for one of the biphenylyltetrazole orientations, this similarity carries over to 26 and 43. In this and the overlays with the other biphenyl orientations (not shown), a very good correspondence of the tetrazole groups and of the respective

N-1 and N-3 atoms of the pyridine and imidazole rings can be seen. In addition, good fits of the rings of the biphenyl units and of the alkyl groups at the 2-positions of the pyridine and imidazole rings are also observed. The close overlays of the helix-1 and gauche conformations are consistent with the imidazole-, alkoxyquinoline-, and alkoxypyridine-derived series of antagonists acting as a common pharmacophore at the AII receptor.

Pharmacological Evaluation

The compounds listed in Table II were evaluated for AII antagonism in vivo by determining their intravenous ED_{50} values for inhibition of the pressor response induced by infusion of AII in conscious, normotensive rats as described previously.[1b] The ED_{50} values obtained in this model for 1 and 2a,b are included in Table II as standards.

For compound 14a low solubility precluded in vivo evaluation. For the remaining compounds, potency in vivo broadly follows the relative affinities determined in the in vitro binding assay. The majority of the compounds gave ED_{50} values of less than 1 mg/kg, with the more potent members of the series such as 14d, 20a, 22, 24a,c, and 26 being superior to 1 and 2a,b. Like the earlier quinoline-based antagonists,[1b] these compounds showed no evidence for partial agonism in this model.

Selected compounds were evaluated orally in an AII-infused, conscious, normotensive rat model. The data for compound 26 at doses of 1, 3, and 10 mg/kg are presented in Figure 6, showing a dose-related inhibition of pressor response with a duration of action lasting for the 7-h time course of the experiment at the 3 mg/kg dose. For comparison, the effect of 1 (DuP 753) in the same animal model at a dose of 10 mg/kg po is also shown. Analogs 14d, 20a, 22, 24a,c, which showed comparable ED_{50} values to 26 on intravenous dosing, were also comparable in potency and duration of effect to 26 when dosed orally (data not shown). The pharmacological profile of these compounds in this model thus represents an improvement over the earlier clinical candidate 2b.[1b,13a]

Compound 26 also showed good activity in a renal hypertensive rat model. When administered orally at a dose of 5 mg/kg (Figure 7), the compound had a rapid effect in reducing the blood pressure of rats with renal hypertension. The blood pressure of the animals was normalized within 2 h of dosing, and the effect was still evident 8 and 24 h after dosing. In contrast, the effects of 26 in normotensive, sham-operated rats were small (data not shown), consistent with a specific antihypertensive effect in renal hypertensive rats. Again, the potency of this compound in this model is improved relative to 2b.[1b]

Compound 26, designated ICI D6888, is thus a potent, competitive, and orally active AII antagonist lacking agonist activity. On the basis of its improved profile over the earlier clinical candidate 2b on more detailed pharmacological evaluation, this compound has been selected for clinical investigation as an antihypertensive agent.

Summary

This paper describes a novel series of potent, orally active, nonpeptide AII receptor antagonists derived from linkage of the biphenylyltetrazole moiety found in previously described antagonists, such as 1 (DuP 753) and 2b (ICI D8731), via a methyleneoxy chain to the 4-position of a 3-substituted 2,6-dialkylpyridine. Molecular modeling studies for a representative member of the series identified

Scheme II[a]
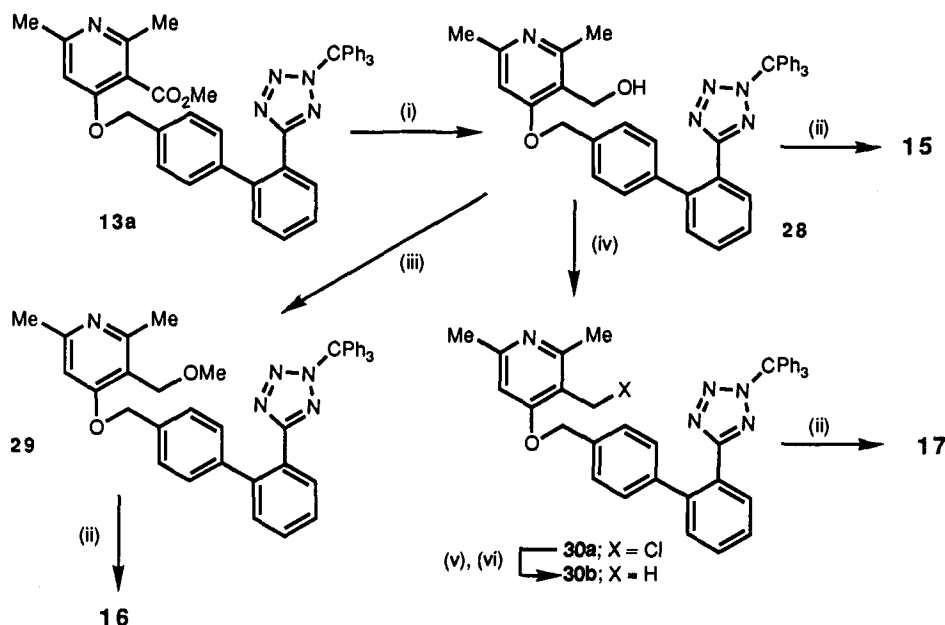
a Reagents: (i) LiBH₄/THF; (ii) HCl/MeOH/EtOH; (iii) NaH/MeI/DMF; (iv) MeSO₂Cl/Et₃N/CH₂Cl₂; (v) NaI/Me₂CO/reflux; (vi) NaBH₃CN/DMF.

a Reagents: (i) LiBH$_4$/THF; (ii) HCl/MeOH/EtOH; (iii) NaH/MeI/DMF; (iv) MeSO$_2$Cl/Et$_3$N/CH$_2$Cl$_2$; (v) NaI/Me$_2$CO/reflux; (vi) NaBH$_3$CN/DMF.

Scheme III[a]

31a; R^2 = Me
31b; R^2 = Et
31c; R^2 = Pr
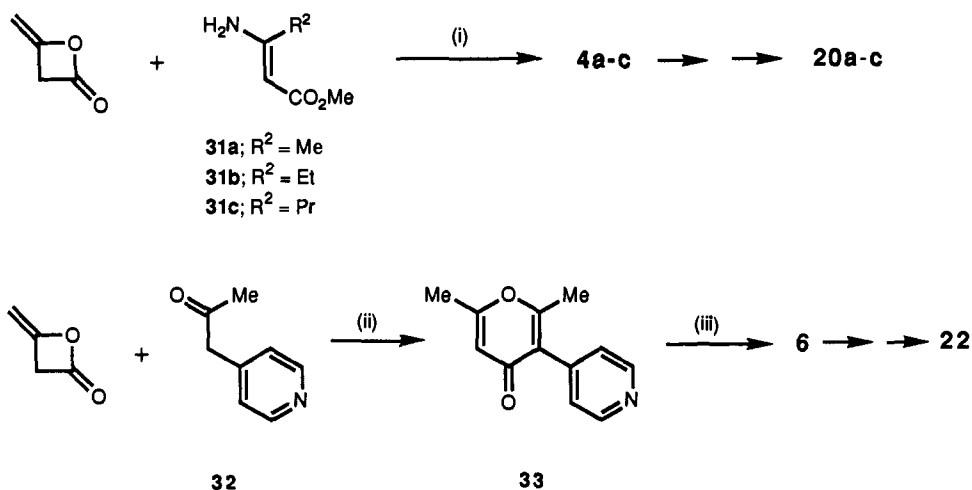
a Reagents: (i) 70 °C; (ii) AcOH/50 °C; NH$_3$/EtOH/120 °C.

Scheme IV[a]
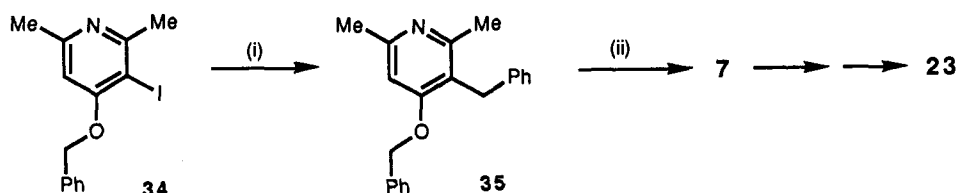
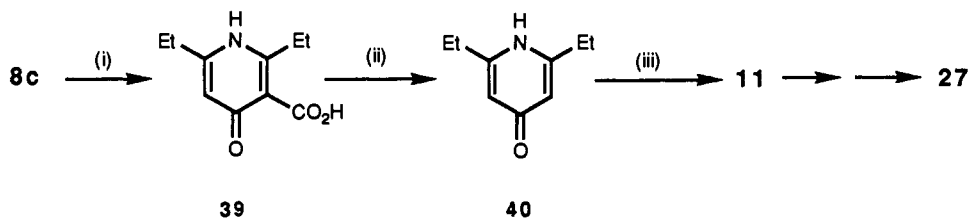*a* Reagents: (i) PhCH$_2$Br/Zn/Pd(Ph$_3$P)$_4$/THF/reflux; (ii) H$_2$/Pd–C/MeOH.

low-energy conformations analogous to those proposed previously for members of the corresponding 4-alkoxy-2-alkylquinoline series of antagonists, such as 2a,b. Certain of these conformations again overlay well with particular conformations of a model analogue of imidazole derivative 1.

When evaluated in an in vitro binding assay using a guinea pig adrenal membrane preparation, compounds in this series generally gave IC$_{50}$ values in the range 0.005–0.5 μM. A variety of substituents was found to be effective at the 3-position of the pyridine ring. On intravenous administration in a conscious, normotensive rat model,

the compounds inhibited the AII-induced pressor response with ED$_{50}$ values generally in the range 0.1–1.0 mg/kg. Potencies broadly reflect the relative affinities determined in the in vitro binding assay. One of the compounds, 26, demonstrated good oral activity in two rat models. At doses in the range 1–10 mg/kg po in AII-infused, normotensive rats, the compound exhibited a dose-related inhibition of the pressor response with a good duration of action at the higher doses. In a renal hypertensive rat model compound 26 showed a rapid and sustained lowering of blood pressure at a dose of 5 mg/kg po. Based on its

Scheme V[a]

36a; R^1 = Et
36b; R^1 = Pr

31a,b
31d; R^2 = Me, R^3 = COMe
31e; R^2 = Me, R^3 = COPh

37a; n = 3
37b; n = 5

38a; n = 3
38b; n = 5
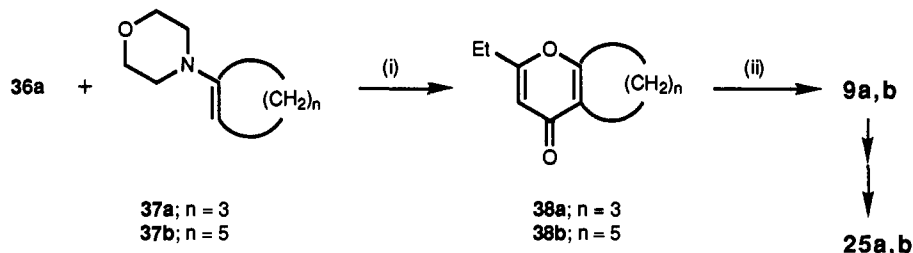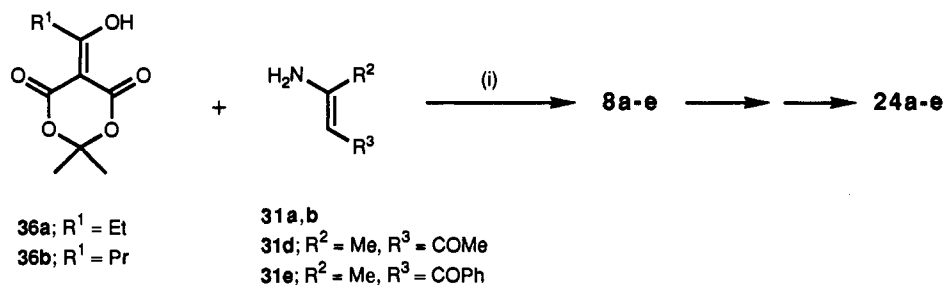
[a] Reagents: (i) 120 °C; (ii) $NH_3/EtOH/120$ °C.

Scheme VI[a]

39

40

[a] Reagents: (i) $NaOH/H_2O/MeOH/reflux$; (ii) 250 °C; (iii) $I_2/NaOH/H_2O$.

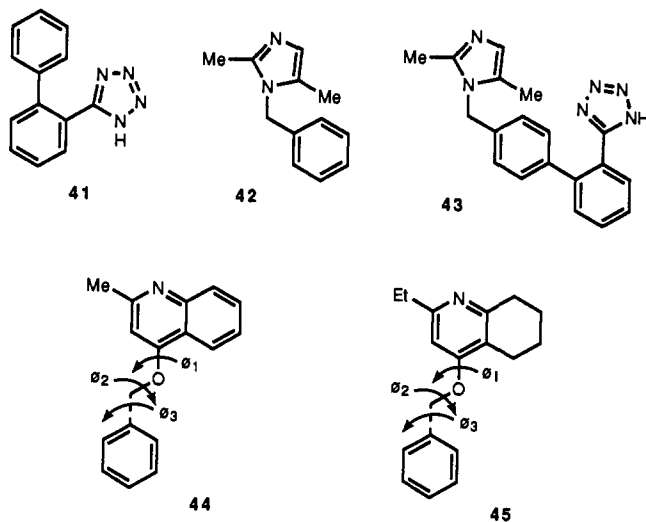**41**   **42**   **43**

44   **45**

Figure 3. Structural fragments 41–45 used in molecular modeling studies.

profile, this compound, designated ICI D6888, has been selected for evaluation in volunteers.

Experimental Section

All operations were carried out at ambient temperature unless otherwise stated. Tetrahydrofuran (THF) was dried by distillation from calcium hydride. All evaporations were carried out at below 50 °C using a rotary evaporator. Flash chromatography was performed on silica (Merck Kieselgel: Art. 9385). Melting points were taken on a Buchi apparatus with use of glass capillary tubes and are uncorrected. ¹H NMR spectra were recorded on Bruker WM200, WM250, or WM400 instruments and are
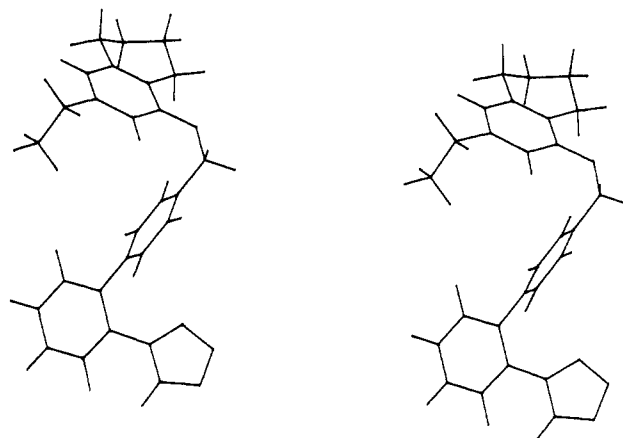

Figure 4. Stereoview of the protonated form of compound **26** in the gauche conformation showing one of the four possible biphenyl orientations.

reported as ∂ values (parts per million) relative to Me_4Si as internal standard. Chemical ionization mass spectra (CIMS) were recorded on a VG 12-12 quadrapole or a VG 70-250 SE spectrometer. Positive or negative fast-atom bombardment mass spectra (FABMS) were determined on a VG ZAB 2-SE or a VG modified AE1/Kratos MS9 spectrometer. The experimental procedures for measuring AII antagonism in vitro in guinea pig adrenal membranes and in vivo in AII-infused, conscious rats or renal hypertensive rats have been described previously.[1]

2,6-Dimethyl-3-formyl-4(1H)-pyridone (3). Chloroform (12 mL, 17.8 g, 0.15 mol) was added in 1-mL portions over a period of 2 h to a refluxing solution of 2,6-dimethyl-4(1H)-pyridone[15] (6.2 g, 0.05 mol) in 6 M NaOH (112 mL). The solution was heated under reflux for 6 h, cooled, and acidified to pH 6 with AcOH. Volatile material was removed by evaporation, and the residue
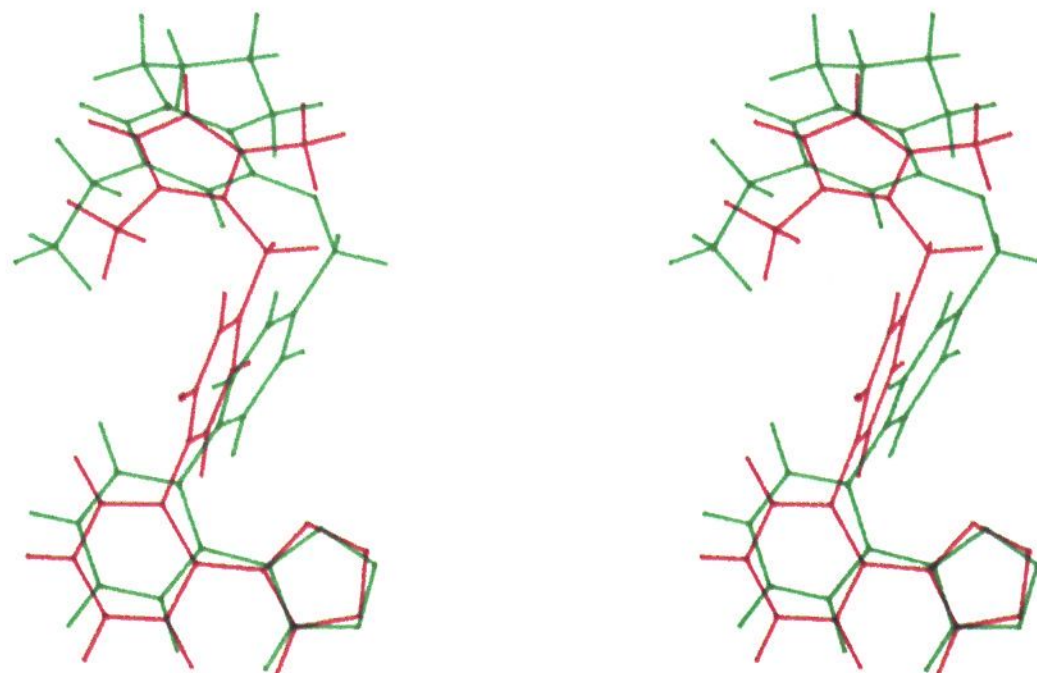
Figure 5. Stereoview of the overlay of the protonated forms of structures **26** (colored green) and **43** (colored red) in the gauche and helix-1 conformations, respectively, showing one of the four possible biphenyl orientations.
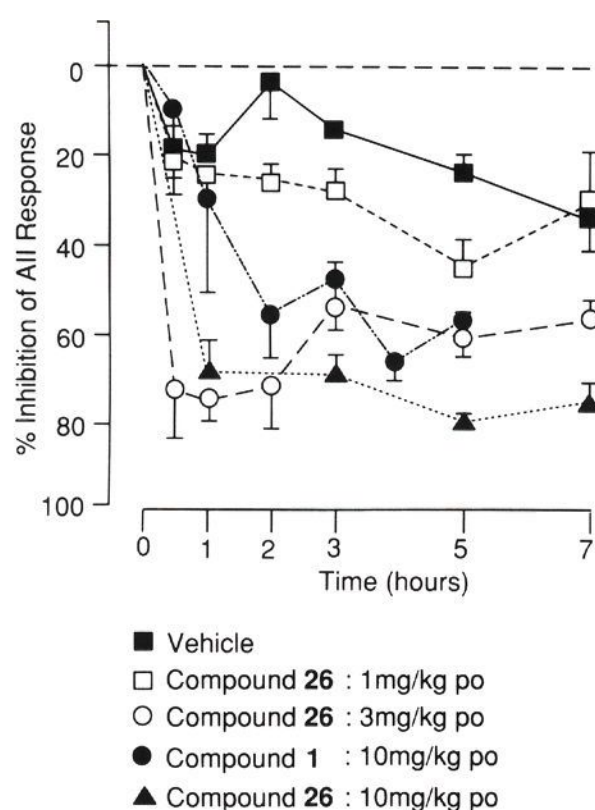

■ Vehicle
□ Compound **26** : 1mg/kg po
○ Compound **26** : 3mg/kg po
● Compound **1** : 10mg/kg po
▲ Compound **26** : 10mg/kg po

Figure 6. Effects of compounds **26** and **1** (DuP 753) after oral dosing to AII-infused, conscious rats. Effects are expressed as a percentage inhibition of the pressor response induced by AII infusion. Mean ± SE values are shown (n = 4–20).

was extracted with MeOH (3 × 100 mL). The extracts were concentrated and the residue was purified by flash chromatography, eluting with MeOH/CH$_2$Cl$_2$ (1:9 v/v), to give **3** (2.1 g, 28%): mp >100 °C dec; ^{1}H NMR (DMSO-d_6) 2.2 (s, 3 H), 2.5 (s, 3 H), 6.1 (s, 1 H), 10.25 (s, 1 H). Anal. (C$_8$H$_9$NO$_2$) C, H, N.

Methyl 1,4-Dihydro-2,6-dimethyl-4-oxopyridine-3-carboxylate (4a). Methyl 3-aminocrotonate (9.0 g, 78.0 mmol) and diketene (6.0 mL, 6.5 g, 78.0 mmol) were heated together at 70 °C for 3 h. The residue was triturated with Et$_2$O to give **4a** (5.7 g, 40%): mp 218–219 °C; ^{1}H NMR (CDCl$_3$) 2.2 (s, 6 H), 3.7 (s, 6 H), 5.9 (s, 1 H), 11.3 (br s, 1 H); CIMS m/e 182 (M + H)$^+$. Anal. (C$_9$H$_{11}$NO$_3$·0.1H$_2$O) C, H, N.

Pyridones **4b,c** were prepared by analogous procedures from the appropriate aminocrotonate precursor.

2,6-Dimethyl-3-(4-pyridyl)-4-pyrone (33). Diketene (27.5 mL, 30.0 g, 0.36 mol) was added dropwise to a stirred solution of 1-(4-pyridyl)-2-propanone (20.2 g, 0.15 mol) in AcOH (100 mL) at 0 °C. The solution was heated at 50 °C for 2 h, and then volatile material was removed by evaporation. The residue was purified by flash chromatography, eluting with MeOH/CH$_2$Cl$_2$ (1:19 v/v), to give **33** (21.6 g, 76%) as a foam: ^{1}H NMR (CDCl$_3$) 2.3 (s, 3 H), 2.35 (s, 3 H), 6.2 (s, 1 H), 7.2 (dd, 2 H), 8.65 (dd, 2 H); CIMS m/e 202 (M + H)$^+$.
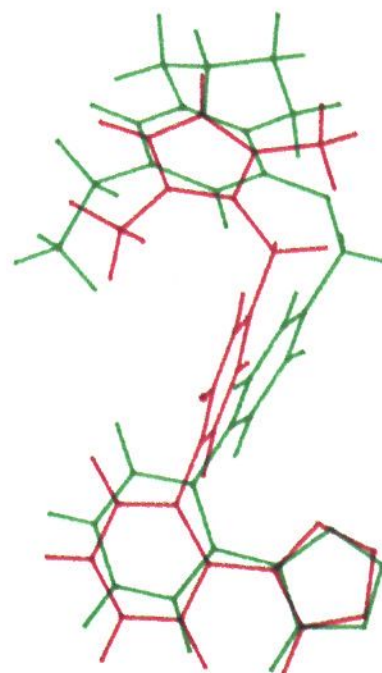

● Vehicle
○ Compound **26** : 5mg/kg po

Figure 7. Effects of compound **26** on mean arterial pressure after oral dosing at 5 mg/kg to renal hypertensive, conscious rats. Mean ± SE values are shown (n = 6–15).

2,6-Dimethyl-3-(4-pyridyl)-4(1*H*)-pyridone (6). A solution of **33** (8.4 g, 44.4 mmol) in saturated ethanolic ammonia (150 mL) was heated at 120 °C in an autoclave for 67 h. Volatile material was removed by evaporation, and the residue was recrystallized from MeOH/EtOAc to give **6** (5.1 g, 61%): mp >250 °C; ^{1}H NMR (DMSO-d_6) 2.1 (s, 3 H), 2.2 (s, 3 H), 6.0 (s, 1 H), 7.2 (d, 1 H), 8.5 (br s, 2 H), 11.2 (br s, 1 H); CIMS m/e 201 (M + H)$^+$. Anal. (C$_{12}$H$_{12}$N$_2$O·0.1H$_2$O) C, H, N.

Pyridone **5** was prepared by an analogous procedure from 2,6-dimethyl-3-phenyl-4-pyrone.[18]

2,6-Dimethyl-3-iodo-4-(phenylmethoxy)pyridine (34). 2,6-Dimethyl-3-iodo-4(1*H*)-pyridone[16] (6.5 g, 26.1 mmol) was added to a stirred suspension of oil-free NaH (0.63 g, 26.1 mmol) in DMF (35 mL). When evolution of hydrogen ceased, benzyl chloride (3.3 g, 26.0 mmol) was added and the mixture was heated at 50 °C for 4 h. The mixture was added to water (150 mL), and the precipitated solid was filtered off and dried under vacuum to give **34** (5.7 g, 65%): mp 68–70 °C; ^{1}H NMR (CDCl$_3$) 2.45 (s, 3 H), 2.75 (s, 3 H), 5.2 (s, 2 H), 6.45 (s, 1 H), 7.35–7.45 (m, 5 H).

2,6-Dimethyl-4-(phenylmethoxy)-3-(phenylmethyl)pyridine (35). A mixture of activated Zn (290 mg, 4.4 mmol) and benzyl bromide (760 mg, 4.4 mmol) in THF (15 mL) was stirred for 1 h. Intermediate **34** (500 mg, 1.47 mmol) was added, followed by tetrakis(triphenylphosphine)palladium (50 mg). The mixture was heated under reflux for 2 h, and then volatile material was removed by evaporation. EDTA (2 g) in water (20 mL) was added to the residue, and the mixture was extracted with EtOAc (3 × 20 mL). The extracts were washed with saturated Na$_2$CO$_3$ (20 mL), water (20 mL), and saturated brine (20 mL) and then dried (MgSO$_4$). The solvent was removed by evaporation, and the

residue was purified by flash chromatography, eluting with EtOAc/hexane (1:1 v/v), to give 35 (197 mg, 44%) as an oil: ^{1}H NMR (CDCl₃) 2.5 (2 × s, 6 H), 4.05 (s, 2 H), 5.1 (s, 2 H), 6.6 (s, 1 H), 7.05–7.4 (m, 10 H).

2,6-Dimethyl-3-(phenylmethyl)-4(1H)-pyridone (7). A solution of 35 (375 mg, 1.24 mmol) in MeOH (5 mL) was catalytically hydrogenated over 10% Pd–C (50 mg). When hydrogen uptake ceased, the catalyst was removed by filtration through Celite. The filtrate was concentrated by evaporation, and the residue was purified by flash chromatography, eluting with EtOAc/hexane (1:9 v/v), to give 7 (191 mg, 72%): mp 212–215 °C; ^{1}H NMR (CDCl₃) 2.2 (2 × s, 6 H), 3.9 (s, 2 H), 6.1 (s, 2 H), 7.0–7.2 (m, 5 H), 12.35 (br s, 1 H). Anal. (C₁₄H₁₅NO) C, H, N.

Methyl 1,4-Dihydro-6-ethyl-2-methyl-4-oxopyridine-3-carboxylate (8a). A mixture of methyl 3-aminocrotonate (5.0 g, 43.5 mmol) and 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione²¹ (36a; 10.0 g, 50.0 mmol) was heated at 120 °C for 1 h. The residue was allowed to cool to ambient temperature, and a mixture of EtOAc and hexane (1:6 v/v, 35 mL) was added. The mixture was left to stand for 18 h, and the solvent was decanted off. The residue was purified by flash chromatography, eluting with MeOH/CH₂Cl₂ (1:9 v/v), to give 8a (1.0 g, 12%): mp 176–180 °C; ^{1}H NMR (CDCl₃) 1.2 (t, 3 H), 2.45 (s, 3 H), 2.65 (q, 2 H), 3.8 (s, 3 H), 6.3 (s, 3 H); CIMS m/e 196 (M + H)⁺. Anal. (C₁₀H₁₃NO₃·0.2H₂O) C, H; N: calcd, 7.0; found 7.5.

Pyridones 8b (from 31a and 36b), 8c (from 31b and 36a), 8d (from 31d and 36a), and 8e (from 31e and 36a) were prepared by analogous procedures.

2-Ethyl-1,5,6,7-tetrahydro-4(1H)-cyclopenta[b]pyridone (9a). A mixture of 36a²¹ (20.0 g, 0.1 mol) and 4-(1-cyclopenten-1-yl)morpholine (37a; 7.7 g, 0.05 mol) was heated at 120 °C for 1 h. The residue was purified by flash chromatography, eluting with MeOH/CH₂Cl₂ (1:19 v/v), to give a mixture of 6,7-dihydro-2-ethyl-4(5H)-cyclopenta[b]pyrone (38a) and 4-(1,3-dioxopentyl)morpholine. The mixture was heated with concentrated ammonia solution (150 mL) at 120 °C in an autoclave for 15 h. Volatile material was removed by evaporation, and the residue was partitioned between Et₂O/EtOAc (1:1 v/v, 300 mL) and 2 M NaOH (200 mL). The aqueous layer was separated, acidified to pH 6 with concentrated HCl, and extracted with EtOAc (3 × 100 mL) and then CHCl₃ (3 × 100 mL). The combined organic extracts were washed with saturated brine (50 mL) and dried (MgSO₄). Volatile material was removed by evaporation, and the residue was purified by flash chromatography, eluting with MeOH/CH₂Cl₂ (1:9 v/v) to give 9a (2.2 g, 27%): mp 212–214 °C dec; ^{1}H NMR (DMSO-d₆) 1.5 (t, 3 H), 1.9–2.05 (m, 2 H), 2.35–2.6 (m, 4 H), 2.8 (t, 2 H), 5.8 (s, 2 H), 11.3 (br s, 1 H); CIMS m/e 164 (M + H)⁺. Anal. (C₁₀H₁₃NO·0.1H₂O) C, H, N.

Pyridone 9b was prepared by an analogous procedure from 36a and 37b.

2-Ethyl-5,6,7,8-tetrahydro-4(1H)-quinolone (10). 2-Ethyl-4(1H)-quinolone[1b] (30.0 g, 0.17 mol) in AcOH (300 mL) was catalytically hydrogenated over PtO₂ (3.0 g) at atmospheric pressure. When hydrogen uptake ceased, the catalyst was removed by filtration through Celite and the filtrate was concentrated. The residual oil was triturated with Et₂O to give 10 (22.6 g, 74%): mp 226–227 °C; ^{1}H NMR (CDCl₃) 1.2 (t, 3 H), 1.65–1.85 (m, 4 H), 2.5–2.7 (m, 6 H), 6.1 (s, 1 H), 12.3 (br s, 1 H). Anal. (C₁₁H₁₅NO·0.1H₂O) C, H, N.

2,6-Diethyl-1,4-dihydro-4-oxopyridine-3-carboxylic Acid (39). NaOH (2 M, 30 mL, 60 mmol) was added to a solution of methyl 2,6-diethyl-1,4-dihydro-4-oxopyridine-3-carboxylate (8c; 2.93 g, 14.0 mmol) in MeOH (60 mL), and the solution was heated under reflux for 48 h. Volatile material was removed by evaporation, and the residue was dissolved in water (50 mL). The solution was washed with EtOAc (50 mL) and acidified to pH 4 with 1 M citric acid solution. The precipitated solid was collected by filtration and dried under high vacuum to give 39 (2.1 g, 77%): mp 238–240 °C dec; ^{1}H NMR (CDCl₃) 1.3 (t, 6 H), 2.7 (q, 2 H), 3.3 (q, 2 H), 6.45 (s, 1 H), 12.1 (br s, 1 H).

2,6-Diethyl-4(1H)-pyridone (40). Carboxylic acid 39 (1.0 g, 5.1 mmol) was heated at 250 °C in a sublimation apparatus. The sublimate was collected and purified by flash chromatography, eluting with MeOH/CH₂Cl₂ (1:9 v/v), to give 40 (0.58 g, 82%):

mp 103–110 °C; ^{1}H NMR (CDCl₃) 1.3 (t, 6 H), 2.7 (q, 4 H), 6.2 (s, 2 H), 12.6 (br s, 1 H).

2,6-Diethyl-3-iodo-4(1H)-pyridone (11). Iodine (720 mg, 2.83 mmol) was added to a solution 40 (430 mg, 2.85 mmol) and NaOH (120 mg, 3.0 mmol) in water (15 mL), and the mixture was stirred for 1 h. The insoluble solid was collected by filtration and purified by flash chromatography, eluting with MeOH/CH₂Cl₂ (1:19 v/v), to give 11 (290 mg, 37%): mp 225–227 °C; ^{1}H NMR (DMSO-d₆) 1.15 (t, 6 H), 2.5 (q, 2 H), 2.8 (q, 2 H), 5.9 (s, 1 H), 11.4 (br s, 1 H). Anal. (C₉H₁₂INO) C, H, N.

2-Ethyl-5,6,7,8-tetrahydro-4-{[2′-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy}quinoline (13; R¹ = Et, R², R³ = (CH₂)₄). NaH (60% dispersion in oil; 140 mg, 3.5 mmol) was added to stirred suspension of 10 (640 mg, 3.6 mmol) in DMF (20 mL). When evolution of hydrogen ceased, 5-[2-[4′-(bromomethyl)biphenylyl]]-2-(triphenylmethyl)-2H-tetrazole[8c] (12; 2.0 g, 3.5 mmol) was added, and the mixture was heated at 40 °C for 1.5 h. Volatile material was removed by evaporation, and the residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was separated, washed with saturated brine (50 mL), and dried (MgSO₄). Evaporation gave a foam, which was purified by flash chromatography, eluting with EtOAc/hexane (1:1 v/v), to give 13 (R¹ = Et, R², R³ = (CH₂)₄; 1.66 g, 71%): mp 111–115 °C; ^{1}H NMR (DMSO-d₆) 1.2 (t, 3 H), 1.6–1.8 (m, 4 H), 2.5–2.8 (m, 6 H), 5.1 (s, 2 H), 6.75 (s, 1 H), 6.8–6.9 (m, 6 H), 7.1 (d, 2 H), 7.25–7.4 (m, 11 H), 7.45–7.7 (m, 3 H), 7.8 (dd, 1 H). Anal. (C₄₄H₃₉N₅O·0.3EtOAc·0.5H₂O) C, H, N.

Intermediates 13 for the preparation of final compounds 14a–d, 19–25, and 27 were prepared from the appropriate pyridone precursor by analogous procedures.

2-Ethyl-5,6,7,8-tetrahydro-4-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methoxy}quinoline Hydrochloride (26). Concentrated hydrochloric acid (1.5 mL) was added to a suspension of 13 (R¹ = Et, R², R³ = (CH₂)₄) in EtOH (6 mL) and MeOH (3 mL), and the mixture was warmed gently until a clear solution was obtained. The mixture was left to stand for 2 h, and the precipitated solid was collected by filtration and washed with Et₂O (3 × 20 mL). Recrystallization from MeOH gave 26 (560 mg, 50%): mp 232–233 °C; ^{1}H NMR (DMSO-d₆) 1.3 (t, 3 H), 1.7–1.9 (m, 4 H), 2.6–2.7 (m, 2 H), 2.9–3.0 (m, 4 H), 5.5 (s, 2 H), 7.2 (d, 2 H), 7.4 (s, 1 H), 7.45 (d, 2 H), 7.55–7.8 (m, 4 H); ^{13}C NMR (benzylic CH₂) 70.8; FABMS m/e 410 (M − H)⁻. Anal. (C₂₅H₂₅N₅O·HCl) C, H, N.

Compounds 14–17, 19–25, and 27 were prepared by analogous procedures.

2,6-Dimethyl-3-(hydroxymethyl)-4-{[2′-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methoxy}pyridine (28). A 1.0 M DIBAL-H solution in toluene (41.9 mL, 41.9 mmol) was added dropwise to a solution of methyl 2,6-dimethyl-4-{[2′-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methoxy}pyridine-3-carboxylate (13a; 12.6 g, 19.2 mmol) in toluene (40 mL) at −78 °C. The solution was kept at −78 °C for 30 min, and then MeOH (5 mL) was added followed by a saturated solution of Rochelle's salt in water (100 mL). The mixture was extracted with CHCl₃ (3 × 100 mL), and the extracts were washed with saturated brine (100 mL) and dried (MgSO₄). Volatile material was removed by evaporation, and the residue was triturated with EtOH (100 mL) to give 28 (10.9 g, 90%): mp 110–112 °C; ^{1}H NMR (DMSO-d₆, CD₃CO₂D) 2.55 (s, 3 H), 2.65 (s, 3 H), 4.7 (s, 2 H), 5.4 (s, 2 H), 6.9–7.0 (m, 6 H), 7.2 (d, 2 H), 7.25–7.45 (m, 12 H), 7.5–7.8 (m, 3 H), 7.9 (dd, 1 H); FABMS m/e 630 (M + H)⁺.

2,6-Dimethyl-3-(methoxymethyl)-4-{[2′-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methoxy}pyridine (29). Oil-free NaH (39 mg, 1.60 mmol) was added to a solution of 28 (1.0 g, 1.59 mmol) in DMF (30 mL), and the mixture was stirred for 10 min. Iodomethane (0.3 mL, 684 mg, 4.82 mmol) was added, and the mixture was left to stand for 18 h. Water (120 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The extracts were washed with saturated brine (50 mL) and then dried (MgSO₄). The solvent was removed by evaporation, and the residue was purified by flash chromatography, eluting with MeOH/CH₂Cl₂ (1:49 v/v, changing on a gradient to 1:19 v/v), to give 29 (740 mg, 72%): mp 132–135 °C; ^{1}H NMR (DMSO-d₆, CD₃CO₂D) 2.55 (s, 6 H), 3.2 (s, 3 H), 4.45 (s, 2 H), 5.25 (s, 2 H), 6.8–7.9 (m, 24 H).

3-(Chloromethyl)-2,6-dimethyl-4-{[2′-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methoxy}pyridine (30a). Triethylamine (2.2 mL, 1.6 g, 16.0 mmol) and methanesulfonyl chloride (1.24 mL, 1.83 g, 16.0 mmol) were added to a solution of **28** (10.0 g, 15.9 mmol) in CH_2Cl_2 (150 mL). The solution was left to stand for 20 h, and then water (150 mL) was added. The organic layer was separated, washed with saturated brine (150 mL), and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was purified by flash chromatography, eluting with $MeOH/CH_2Cl_2$ (1:19 v/v), to give **30a** (8.5 g, 83%): mp 142–143 °C (from EtOAc); ^{1}H NMR (DMSO-d_6, CD_3CO_2D) 2.5 (s, 3 H), 2.65 (s, 3 H), 4.75 (s, 2 H), 5.45 (s, 2 H), 6.9–7.9 (complex m, 24 H); FABMS m/e 648 (M + H)$^+$.

2,3,6-Trimethyl-4-{[2′-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methoxy}pyridine (30b). A solution of **30a** (1.0 g, 1.54 mmol) and NaI (232 mg, 1.55 mmol) in Me_2CO (20 mL) was heated under reflux for 6 h. The solvent was removed by evaporation, and the residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was separated, washed with saturated brine (20 mL), and dried ($MgSO_4$). Volatile material was removed by evaporation, and the residue was dissolved in DMF (25 mL). Sodium cyanoborohydride (221 mg, 3.51 mmol) was added, and the mixture was stirred for 3 h. The solvent was removed by evaporation, and the residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was separated, washed with saturated brine (20 mL), and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was purified by flash chromatography, eluting with $MeOH/CH_2Cl_2$ (1:19 v/v), to give **30b** (650 mg, 69%): mp 136–138 °C; ^{1}H NMR (DMSO-d_6, CD_3CO_2D) 2.1 (s, 3 H), 2.5 (s, 3 H), 2.6 (s, 3 H), 5.3 (s, 2 H), 6.8–7.0 (m, 6 H), 7.2–7.85 (m, 18 H); FABMS m/e 614 (M + H)$^+$.

2,6-Dimethyl-4-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]-methoxy}pyridine-3-carboxylic Acid (18). A solution of compound **20a** (240 mg, 0.53 mmol) in 2 M NaOH (5 mL) was heated under reflux for 2 h. The solution was cooled and acidified to pH 3 with 6 M hydrochloric acid. The precipitated solid was collected by filtration and triturated with hot MeOH (10 mL) to give **3h** (67 mg, 32%): mp 235–237 °C; ^{1}H NMR (DMSO-d_6, CD_3CO_2D) 2.45 (s, 3 H), 2.55 (s, 3 H), 5.3 (s, 2 H), 7.1 (s, 1 H), 7.2 (d, 2 H), 7.4 (d, 2 H), 7.45–7.75 (m, 4 H); FABMS m/e 400 (M − H)$^-$. Anal. ($C_{22}H_{19}N_5O_3 \cdot 0.5H_2O$) C, H, N.

X-ray Crystallographic Analysis of 26. Crystals of **26** were obtained from methanol: $C_{25}H_{25}N_5O \cdot HCl$; monoclinic space group $P\bar{1}$ (No. 2); cell constants a = 12.823(3) Å, b = 11.895(3) Å, c = 9.363(2) Å, α = 112.90(2)°, β = 72.86(2)°, γ = 118.33(2)°, U = 1147.29 Å^3, and D_c = 1.256 g cm^{-3}. Data were recorded using a Philips PW1100 diffractometer with a constant scan width of 0.80° in the θ range 3–23°, using graphite crystal monochromated Mo Kα radiation. A total of 3181 reflections were measured with a θ–2θ scan mode, and no significant change occurred in three reference reflections which were checked every 5 h. Lorenz polarization corrections were applied to the data, and equivalent reflections were merged to give a total of 1837 unique reflections with $I/\sigma(I) > 2.0$. The structure was solved using the direct methods routine of SHELX86, assuming the centrosymmetric space group $P\bar{1}$ (No. 2), which was confirmed by subsequent satisfactory refinement. All non-hydrogen atoms were located, and preliminary refinement showed very high thermal parameters for two of the carbon atoms of the saturated ring and the terminal carbon atom of the ethyl group. It proved possible to resolve the atoms of the ring into two components of equal site population corresponding to a 50:50 disorder of the structure, but the carbon atom of the terminal methyl group was not resolved. A difference-Fourier syntheses with sin θ less than 0.35 revealed the positions of all carbon-bonded hydrogen atoms except those of the ethyl group. For consistency all hydrogen atoms (except that bonded to the tetrazole ring) were included at calculated positions, and all those of the disordered ring were allowed to ride on the atoms to which they were bonded, but those of the terminal carbon atom of the ethyl group and the protonated quinoline nitrogen atom were not used in structure factor calculation. The hydrogen atoms were assigned common isotropic thermal parameters which refined to final values of 0.12 Å^2 (sp^3) and 0.06 Å^2 (sp^2); the hydrogen atom of the tetrazole ring was allowed to refine without constraint (final U 0.07 Å^2). In the final cycles of full-matrix

refinement, with the two components of the disordered ring refining in alternate cycles, anisotropic thermal parameters were assigned to all the non-hydrogen atoms, except the two disordered carbon atoms. Weights were applied to the individual reflections as $1/\sigma^2(F)$ and refinement converged at R 0.0750 and R_w 0.0679, with a total of 286 refined parameters. Neutral scattering factors, corrected for the real and imaginary parts of the anomalous scattering, were used for all atoms and were taken from *International Tables of X-Ray Crystallography, Volume 4.*

Guinea Pig Ileum Preparation. Guinea pigs of either sex were killed by cervical dislocation, and a length of ileum was removed and placed in oxygenated Krebs buffer of the following composition (mM): NaCl 118; KCl 4.75; $CaCl_2$ 2.54; $MgCl_2$ 1.2; $NaHCO_3$ 25; KH_2PO_4 0.93; glucose 11. Segments of 3–4-cm length were mounted for isotonic tension recording in 20-mL organ baths containing Krebs solution at 32 °C and were oxygenated with 95% O_2/5% CO_2. Dose–tension curves to AII were constructed in the absence and the presence of the compound at single concentrations (0.73 or 3.65 nM, n = 4 for each concentration). A pA_2 value was estimated under equilibrium conditions by the method of Arundlakshana and Schild.[24]

Supplementary Material Available: Coordinates for the conformations of **26** and **43** shown in Figure 5 and tables containing bond lengths, bond angles, fractional atomic coordinates, and thermal parameters for **26** (8 pages). Ordering information is given on any current masthead page.

References

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