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

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A novel series of nonpeptidic angiotensin II (AII) receptor antagonists is reported, derived from linkage of the biphenylcarboxylic acid or biphenylyltetrazole moiety found in previously described antagonists via a methyleneoxy chain to the 4-position of a 2-alkyl quinoline. 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 0.01–1 μM. Structure–activity studies showed the quinoline nitrogen atom and a short alkyl chain at the quinoline 2-position to be essential for receptor binding. 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 0.1–2.0 mg/kg. One of the compounds, 2-ethyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methoxy]quinoline (**5g**), demonstrated good oral activity in two rat models. At doses in the range 1–10 mg/kg 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 **5g** showed a rapid and sustained lowering of blood pressure at a dose of 5 mg/kg. On the basis of its profile, this compound, designated ICI D8731, has been selected for clinical evaluation.

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 nonpeptidic AII antagonists have been described, examples of which are shown in Figure 1. Starting from a weakly active lead compound,[6] extensive structure–activity investigations[7,8] by the Du Pont group led to potent and specific antagonists such as EXP7711 (**1a**)[7c,8] and DuP 753 (**1b**).[7c,8,9] The latter compound displays good oral activity in animal models[9b] and is currently undergoing clinical evaluation as an antihypertensive agent.[10] The chloro and hydroxymethyl

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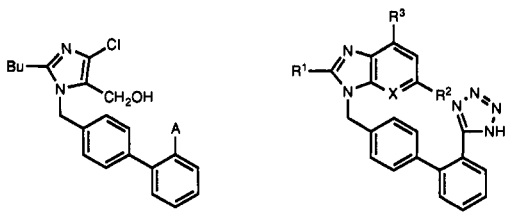

1a, A = CO_2H
1b, A = Tetrazol-5-yl (K^+ salt)

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

Figure 1. Nonpeptidic AII antagonists.

substituents on the imidazole ring of **1a,b** are not essential for in vitro activity and can be replaced by a fused benzene ring (compound **2a**[1,11]), albeit with some reduction in potency. This can be redressed by introduction of a nitrogen atom at the 4-position of the benzimidazole ring to give the imidazo[4,5-*b*]pyridine derivative **2b**.[12] Fine-tuning of the substituents on the heterocyclic ring provided the highly potent antagonist L-158,809 (**2c**),[13] which shows good antihypertensive activity in animal models.

On the basis of published work,[1,7,11a,13] a number of structural features essential for biological activity are apparent in antagonists such as **1a,b** and **2a–c**. 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 series of AII antagonists, we chose to focus on the nature of the putative hydrogen-bond acceptor. Obvious candidates include heterocycles such as triazoles[14] and pyrazoles,[15] but these are known to be inferior to imidazole in terms of acceptor ability.[16] 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 that of imidazole.[16] As outlined in Figure 2, incorporation of the other key features necessary for receptor binding suggested as targets derivatives of a 4-quinolone (generic structure **3**) and a 4-alkoxyquinoline (generic structure **4**). We envisaged that these structural types could be available from N- or O-alkylation of an appropriate 4-quinolone precursor. In this paper we describe the synthesis and biological properties of antagonists of the alkoxyquinoline class, together with details of molecular modeling studies relating to their proposed bioactive conformation.

Chemistry

The compounds **5a–m**, **6**, and **7a–t** prepared during the course of this work are listed in Tables I and III and their syntheses are outlined in Schemes I–IV.

4-Alkoxyquinoline derivatives **5a–d,f,g,i** and **7a–t** were prepared (Scheme I) by O-alkylation of 2-alkyl-4(1*H*)-quinolones **8** with (bromomethyl)biphenyl compounds **9a,b**[7c] in DMF using sodium hydride as base, followed by saponification or acid-promoted detritylation of the resulting intermediates **10**. In the ^{13}C NMR spectra of **10** the benzylic CH_2 signal at ca. δ 70 was consistent with O- rather than N-alkylation.[17] In the case of derivative **5f**, an X-ray crystal-structure determination (Figure 3) confirmed the regiochemistry of the alkylation step. Under a variety of basic conditions N-alkylation of the 2-alkyl quinolones was not seen. The starting quinolones **8** are either known compounds[18] or were prepared from the appropriate aniline and β-keto ester using the Conrad–Limpach method.[19] In the case of meta-substituted anilines, mixtures of 5- and 7-substituted quinolones were obtained, which were either separated by chromatography

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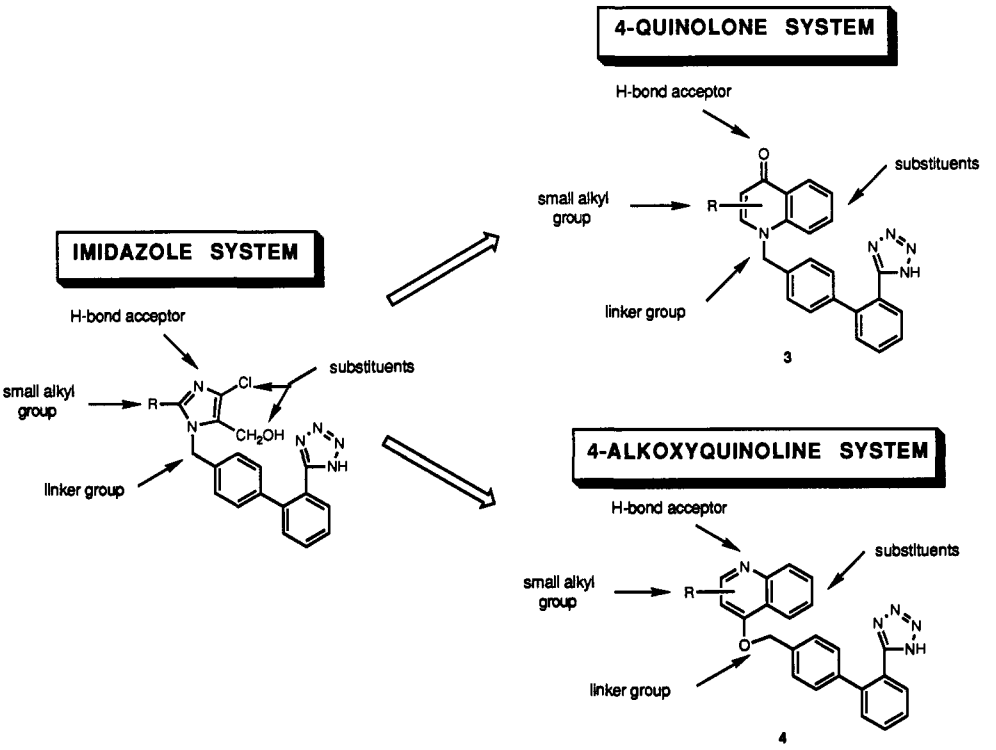
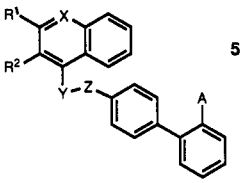


Figure 2. Generation of 4-quinolones and 4-alkoxyquinolines as potential AII antagonists.

Table I. Characterization and in Vitro AII Antagonism of Compounds **1a,b** and **5a–m**



no.	X	R^1	R^2	Y–Z	A	mp, °C	formula[a]	IC_{50}, μM[b]
1a								0.43
1b								0.018
5a	N	Me	H	OCH_2	CO_2H	184–186	$C_{24}H_{19}NO_3$·HCl	0.18
5b	N	Et	H	OCH_2	CO_2H	204–205	$C_{25}H_{21}NO_3$	0.17
5c	N	Pr	H	OCH_2	CO_2H	198–200	$C_{26}H_{23}NO_3$·0.33C_2H_5OH	0.60
5d	N	Bu	H	OCH_2	CO_2H	147–148	$C_{27}H_{25}NO_3$·0.5H_2O	3.1
5e	N	H	H	OCH_2	tetrazol-5-yl	163–164	$C_{23}H_{17}N_5O$·HCl	6.3
5f	N	Me	H	OCH_2	tetrazol-5-yl	188–190	$C_{24}H_{19}N_5O$·HCl·0.5H_2O[c]	0.016
5g	N	Et	H	OCH_2	tetrazol-5-yl	178–181	$C_{25}H_{21}N_5O$·HCl	0.031
5h	CH	Me	H	OCH_2	tetrazol-5-yl	210–213	$C_{25}H_{20}N_4O$	90
5i	N	Me	Me	OCH_2	tetrazol-5-yl	155–156	$C_{25}H_{21}N_5O$·HCl·0.25CH_3OH	4.6
5j	N	Me	H	$OCH(CH_3)$	tetrazol-5-yl	168–169	$C_{25}H_{21}N_5O$·HCl·0.5H_2O	0.040
5k	N	Me	H	SCH_2	tetrazol-5-yl	231–232	$C_{24}H_{19}N_5S$·HCl·0.25H_2O	0.37
5l	N	Me	H	CH=CH[d]	tetrazol-5-yl	283–285	$C_{25}H_{19}N_5$·HCl·H_2O[e]	1.3
5m	N	Me	H	CH_2CH_2	tetrazol-5-yl	145–150	$C_{25}H_{21}N_5$·HCl·1.5H_2O[f]	0.27

[a] Analyses for C, H, N were correct within ±0.4% unless otherwise stated. [b] IC_{50} for inhibition of specific binding of [^{125}I]AII to a guinea pig adrenal membrane preparation (n = 1–3, see ref 1 for description of assay). [c] C, H; N: calcd, 16.0; found, 15.5. [d] 2:1 mixture of *E* and *Z* isomers. [e] C, H; N: calcd, 15.7; found, 15.1. [f] C, H; N: calcd, 15.4; found, 14.8.

or alkylated as mixtures and the products separated. The isomeric 5- and 7-substituted quinolones and their O-alkylated quinoline derivatives were distinguished on the basis of the splitting patterns of the aromatic signals in their ^{1}H NMR spectra. Characterization data for new quinolones **8a–r** prepared during the course of this work are given in Table II.

The alkoxyquinoline derivative **5e** lacking a substituent at the 2-position was prepared (Scheme II) via reaction of 4-chloroquinoline with alcohol **11b**, which was readily obtained from **9b** by conversion to acetate **11a** followed by reductive cleavage. Similarly, compound **5j** was obtained from the secondary alcohol **13b**, derived from **11b** by oxidation to aldehyde **13a** and addition of methyllithium.

Naphthalene derivative **5h** was synthesized via alkylation of 3-methyl-1-naphthol[20] with **9b**.

Compound **5k** containing a thiomethylene link between the quinoline ring and the biphenylyltetrazole moiety was synthesized via S-alkylation of 2-methyl-4(1*H*)-quinolonethione[21] with **9b** followed by detritylation. For the preparation of compounds **5l,m** with vinylene and ethylene

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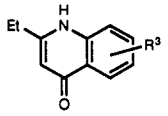
Table II. Characterization Data for Quinolone Intermediates 8a–r



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no.	R^3	mp, °C	formula[a]
8a	H	178–181	$C_{11}H_{11}NO$
8b	5-Me	264–266	$C_{12}H_{13}NO$
8c	5-Cl	236–239	$C_{11}H_{10}ClNO$
8d	5-CN	–	$C_{12}H_{10}N_2O$[b]
8e	6-CN	>250	$C_{12}H_{10}N_2O$[c]
8f	6-CF_3	288–289	$C_{12}H_{10}F_3NO$[d]
8g	6-CO_2Me	>250	$C_{13}H_{13}NO_3$
8h	6-OMe	210–212	$C_{12}H_{13}NO_2$[e]
8i	6-O*i*-Pr	179–181	$C_{14}H_{17}NO_2$
8j	6-OCH_2CH_2F	267–269	$C_{13}H_{14}FNO_2 \cdot 0.2EtOAc$
8k	6-OCH_2CF_3	>250	$C_{13}H_{12}F_3NO_2$
8l	7-Me	242–244	$C_{12}H_{13}NO$
8m	7-Cl	–	$C_{11}H_{10}ClNO$[f]
8n	7-CN	–	$C_{12}H_{10}N_2O$[f]
8o	7-OMe	–	$C_{12}H_{13}NO_2$[f]
8p	8-Cl	184–186	$C_{11}H_{10}ClNO$[g]
8r	8-CF_3	162–163	$C_{12}H_{10}F_3NO$[c]

[a] Analyses for C, H, N were correct within ±0.4% unless otherwise stated. [b] Isolated as a mixture with the corresponding 7-substituted quinolone. [c] Characterized spectroscopically. [d] H, N; C: calcd, 59.7; found, 59.2. [e] H, N; C: calcd, 70.9; found, 70.2. [f] Isolated as a mixture with the corresponding 5-substituted quinolone. [g] H, N; C: calcd, 63.6; found, 63.1.

links (Scheme III), Wittig reaction of the phosphonium salt **15** derived from **9b** with 2-methylquinoline-4-carboxaldehyde[22] gave olefin **16** as a mixture of geometrical isomers. Detritylation provided **5l**, isolated as a 2:1 mixture of *E* and *Z* isomers, and olefin hydrogenation than gave **5m**.

N-Alkylquinolone derivative **6** was obtained (Scheme IV) by alkylation of 3-ethyl-4(1*H*)-quinolone (**18**) with **9a** and subsequent ester hydrolysis. In this instance, the benzylic CH_2 signal at δ 56 in the ^{13}C NMR spectrum of intermediate **19** was consistent with N-alkylation.[17] As in a previously reported 3-alkyl-4-quinolone synthesis,[23] the starting quinolone **18** was prepared by hydrolysis and decarboxylation of quinolone ester **17**.

In Vitro AII Antagonism

Compounds **5a–m** and **7a–t** (Tables I and III) 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.[24] IC_{50} values for **1a,b** in this assay are included in Tables I and III for comparison.

The initial alkoxyquinoline derivatives **5a–d** contained a biphenylcarboxylic acid moiety and a short alkyl chain at the 2-position of the quinoline ring. Compounds **5a,b** with a methyl or ethyl group at the 2-position showed affinity comparable to the prototype imidazole-derived biphenylcarboxylic acid **1a**. The *N*-alkylquinolone derivative **6** (Scheme IV) analogous to **5b** displayed a ca. 8-fold reduction in receptor binding (IC_{50} = 1.4 μM).

As observed in previous series of AII antagonists,[1,7c] replacement of the biphenylcarboxylic acid by a biphenylyltetrazole resulted in a 1 order of magnitude increase of in vitro activity (compounds **5f,g** vs **5a,b**). The importance of the short alkyl chain at the 2-position of the quinoline ring was demonstrated by the dramatic loss of activity seen with the unsubstituted analogue **5e**. Equally significant was the very poor affinity of the naphthalene analogue **5h**, consistent with the nitrogen atom of the quinoline ring playing a key role in a hydrogen-bonding interaction with the receptor. Introduction of an additional methyl group at the quinoline 3-position (**5i**) also caused a major reduction in affinity. As discussed below in the molecular modeling section, this seems likely to reflect an unfavorable effect on the conformation of the oxymethylene chain linking the quinoline ring and the biphenyl moiety. Substitution on the linking chain with a methyl group (**5j**) resulted in similar affinity to the parent. However, compounds with thiomethylene (**5k**), vinylene (**5l**), and ethylene (**5m**) as linking chains all showed significantly lower affinity.

A variety of substituents were introduced at the 5-, 6-, 7-, and 8-positions of the quinoline ring (compounds **7a–t**) in order to probe their effect on in vitro activity. In general, substitution at the 5-, 7-, and 8-positions gave compounds with significantly lower affinity, whereas substitution at the 6-position by an alkoxy group provided compounds **7i–l** with similar affinity to the parent **5g**.

The potency and specificity of compound **5g** was also assessed by analyzing dose–tension curves to AII in isolated rabbit aorta.[1] At concentrations in the range from 0.01 to 1 μM 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 pA_2 value of 8.3. The slope of the Schild regression line was not significantly different from –1, again in accord with competitive antagonism. In a separate experiment, no effect of compound **5g** was seen on responses to noradrenaline in the isolated rabbit aorta, consistent with the compound having a specific effect on AII responses in this model.

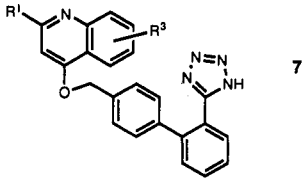
Molecular Modeling Studies

AII antagonists of the alkoxyquinoline class reported in this paper differ structurally from previously described imidazole-derived antagonists such as **1b** both in the nature of the putative hydrogen-bond acceptor (quinoline vs imidazole) and the chain linking the biphenylyltetrazole moiety and the heterocyclic fragment (methyleneoxy vs methylene). The conformations revealed in the X-ray crystal structures of representative members of the two classes, **5f** (Figure 3) and **1a** (Figure 4), could not be overlaid satusfactorily. For example, when the biphenyl moieties were superimposed, little correspondence of the quinoline and imidazole rings was seen. In order to analyze whether the two structural types could act as a common pharmacophore, it was therefore of interest to examine overlays of their low-energy conformations generated by molecular mechanics.

For the purpose of constructing a model pharmacophore, alkoxyquinoline **5f** and imidazole **1b** were used initially.

(21) Rosenhauer, E.; Hoffman, H. Uber eine Synthese von $\alpha(\gamma)$-Chinolylmercaptenen. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 2730–2736.
(22) Giordano, C.; Minisci, F.; Vismara, E.; Levi, S. A General, Selective, and Convenient Procedure of Homolytic Formylation of Heteroaromatic Bases. *J. Org. Chem.* **1986**, *51*, 536–537.
(23) Baker, R. H.; Dodson, R. M. The Synthesis of 3-(3-Cyclohexylpropyl)-4-quinolinol. *J. Am. Chem. Soc.* **1946**, *68*, 1283–1284.
(24) (a) Bumpus, F. M.; Catt, K. J.; Chiu, A. T.; DeGasparo, M.; Goodfriend, T.; Husain, A.; Peach, M. J.; Taylor, D. G. Jr.; Timmermans, P. B. M. W. M. Nomenclature for Angiotensin Receptors. *Hypertension* **1991**, *17*, 720–721. (b) Herblin, W. F.; Chiu, A. T.; McCall, D. E.; Ardecky, R. J.; Carini, D. J.; Duncia, J. V.; Pease, L. J.; Wong, P. C.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. Angiotensin II Receptor Heterogeneity. *Am. J. Hypertens.* **1991**, *4*, 299S–302S.

Table III. Characterization, in Vitro AII Antagonism, and in Vivo Activity of Compounds **1b,5f,g**, and **7a–t**



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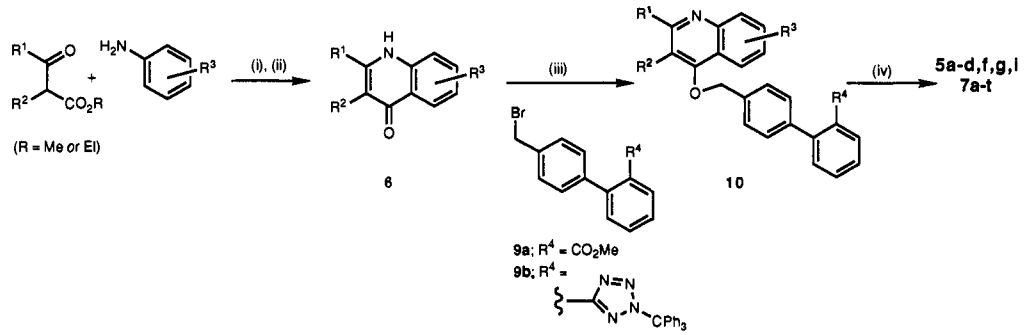
no.	R^1	R^3	mp, °C	formula[a]	IC_{50}, μM[b]	iv ED_{50}, mg/kg[c]
1b					0.018	0.65 ± 0.21
5f[d]	Me	H			0.016	0.73 ± 0.14
5g[d]	Et	H			0.031	1.0 ± 0.42
7a	Et	5-Me	168–169	$C_{26}H_{23}N_5O\cdot HCl\cdot 0.5H_2O\cdot 0.33EtOAc$	0.013	*e*
7b	Et	5-Cl	189–190	$C_{25}H_{20}ClN_5O\cdot HCl$	0.12	>5
7c	Et	5-CN	239–240	$C_{26}H_{20}N_6O\cdot HCl\cdot 0.5H_2O$[f]	0.060	*e*
7d	Me	6-Me	200–202	$C_{25}H_{21}N_5O\cdot HCl\cdot 0.25H_2O$	0.47	>5
7e	Me	6-Cl	197–198	$C_{24}H_{16}ClN_5O\cdot HCl$	1.2	*e*
7f	Et	6-CN	153–155	$C_{26}H_{20}N_6O\cdot HCl$	0.36	>5
7g	Et	6-CF_3	188–190	$C_{26}H_{20}F_3N_5O\cdot HCl$	0.86	>5
7h	Et	6-CO_2Me	202–204	$C_{27}H_{23}N_5O_3\cdot HCl$	0.066	2.1 ± 0.5
7i	Et	6-OMe	213–215	$C_{26}H_{23}N_5O_2\cdot HCl$	0.022	0.32 ± 0.06
7j	Et	6-O-*i*-Pr	178–180	$C_{28}H_{27}N_5O_2\cdot HCl\cdot 0.5H_2O$	0.026	0.18 ± 0.02
7k	Et	6-OCH_2CH_2F	161–163	$C_{27}H_{24}FN_5O_2\cdot HCl\cdot 0.5H_2O$[g]	0.007	0.34 ± 0.06
7l	Et	6-OCH_2CF_3	140–141	$C_{27}H_{22}F_3N_5O_2\cdot HCl\cdot H_2O$	0.026	0.71 ± 0.27
7m	Et	7-Me	213–215	$C_{26}H_{23}N_5O\cdot HCl$	0.14	>5
7n	Et	7-Cl	170–172	$C_{25}H_{20}ClN_5O\cdot HCl\cdot 0.5H_2O$	0.16	>5
7o	Et	7-CN	160–163	$C_{26}H_{20}N_6O\cdot HCl\cdot H_2O\cdot 0.1$dioxane	0.46	>5
7p	Et	7-OMe	172–174	$C_{25}H_{23}N_5O_2\cdot HCl\cdot H_2O$	0.22	>5
7q	Me	8-Me	193–195	$C_{25}H_{21}N_5O\cdot HCl$	0.31	>5
7r	Et	8-Cl	146–148	$C_{25}H_{20}ClN_5O\cdot HCl\cdot H_2O$	0.14	*e*
7s	Et	8-CF_3	110–113	$C_{26}H_{20}F_3N_5O\cdot 0.67$dioxane	2.0	>5
7t	Et	8-OMe	125–127	$C_{26}H_{23}N_5O_2\cdot HCl\cdot 0.5H_2O\cdot 0.5$dioxane	0.96	>5

[a,b] See Table I for explanation of tabulated data. [c] ED_{50} following intravenous administration to conscious rats for inhibition of pressor response induced by infusion of AII (n = 3–10). [d] See Table I for characterization data. [e] Compound too insoluble for in vivo testing. [f] C, H; N: calcd, 17.6; found, 16.6. [g] C, H; N: calcd, 13.6; found, 12.9.

Scheme I [a]



[a] Reagents: (i) *p*-TsOH/C_6H_{12}/reflux; (ii) Dowtherm A/240 °C; (iii) NaH/DMF; (iv) $R^4 = CO_2Me$, NaOH/MeOH/H_2O; R^4 = 2-trityltetrazol-5-yl, HCl/MeOH/EtOH or HCl/Dioxan.

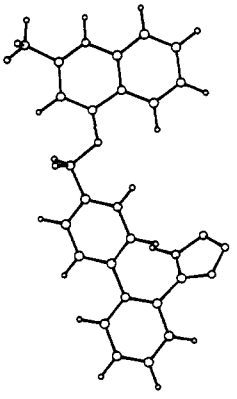
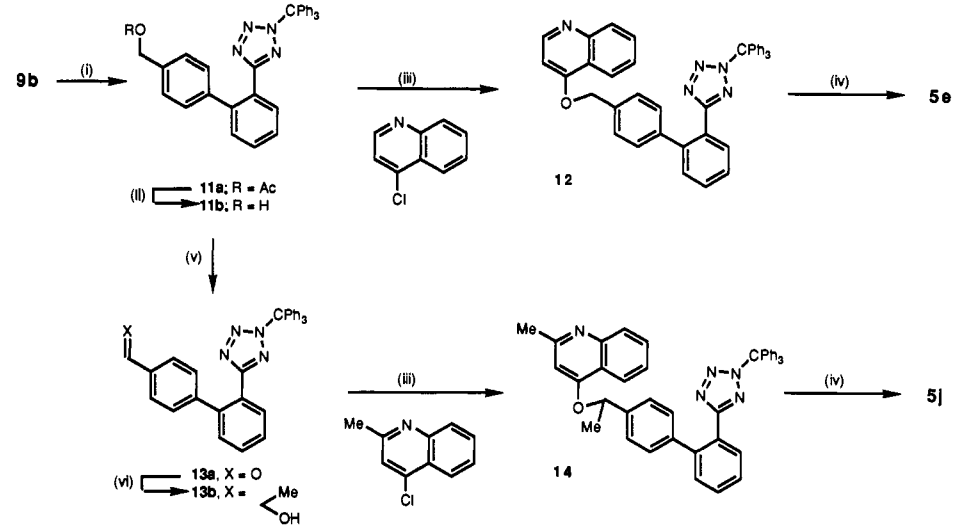


Figure 3. X-ray crystal structure of compound **5f**.

Both the quinoline and imidazole nitrogens were treated as protonated cations so that the N–H vector could be used to indicate the direction along which these nitrogens would form hydrogen bonds, either as acceptors[25] or donors.[26] On the basis of pK_a values,[27] it is most likely the nitrogens are binding in the neutral form and acting as acceptors. Assuming free rotation of all acyclic bonds, initial overlays of **5f** and **1b** using ENIGMA[28] showed that the N–H bonds and tetrazole groups could be superimposed, and thus a common pharmacophore for the two structures is geometrically possible. However, the geometries adopted often contained severe intramolecular contacts. Also, different answers were obtained from different starting conformations. Thus, geometrical constraints alone appear to be insufficient to determine a unique pharmacophore. In order to obtain a unique, energetically reasonable pharmacophore, attention was focused on the energetically reasonable conformations of

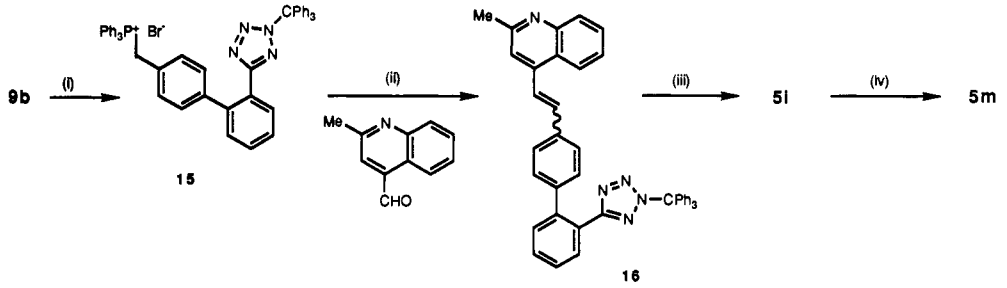
(25) Vedani, A.; Dunitz, J. D. Lone-Pair Directionality in Hydrogen Bond Potential Functions for Molecular Mechanics Calculations: The Inhibition of Human Carbonic Anhydrase II by Sulfonamides. *J. Am. Chem. Soc.* **1985**, *107*, 7653–7658.

Scheme II [a]



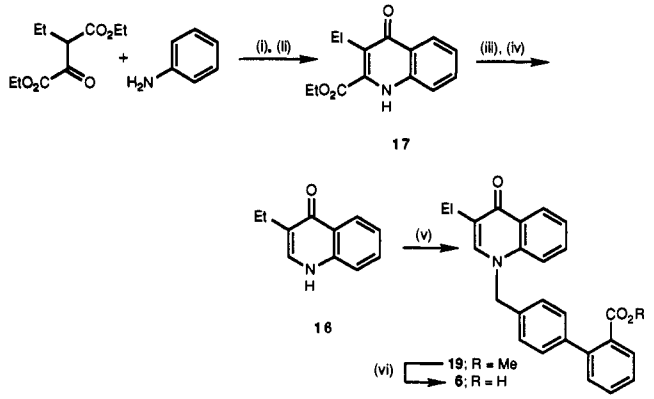
[a] Reagents: (i) KOAc/18-crown-6/DME/reflux; (ii) $LiAlH_4$/THF; (iii) NaH/DMF/40 °C; (iv) HCl/MeOH/EtOH; (v) Py·SO_3/Et_3N/DMSO; (vi) MeLi/THF/Et_2O.

Scheme III [a]



[a] Reagents: (i) PPh_3/$CHCl_3$/reflux; (ii) NaH/THF; (iii) HCl/MeOH/EtOH; (iv) H_2/Pd-C/MeOH.

Scheme IV [a]



[a] Reagents: (i) *p*-TsOH/C_6H_{12}/reflux; (ii) Dodecylbenzene/240 °C; (iii) NaOH/H_2O; (iv) Dodecylbenzene/240 °C; (v) 9a/NaH/DMF; (vi) NaOH/MeOH/H_2O.

5f and **1b** identified by molecular mechanics calculations using AESOP-2.3.[29]

Model structures used in the molecular mechanics calculations are shown in Figure 5. The biphenylyltetrazole moiety **20** is common to both **5f** and **1b**. AESOP calculations indicate two enantiomeric minimum-energy conformations with the planes of the phenyl rings twisted by ±61° and a barrier to planarity of 6.7 kcal/mol. The perpendicular (90°) conformation is found to be a low-energy transition state (0.3 kcal/mol) between the two twisted conformations. These results are in accord with

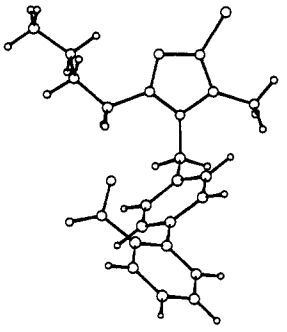


Figure 4. X-ray crystal structure of compound **1a**.

(26) (a) Murray-Rust, P.; Glusker, J. P. Directional Hydrogen Bonding to sp^2- and sp^3-Hybridized Oxygen Atoms and Its Relevance to Ligand-Macromolecule Interactions. *J. Am. Chem. Soc.* **1984**, *106*, 1018–1025. (b) Taylor, R.; Kennard, O. Hydrogen-Bond Geometry in Organic Crystals. *Acc. Chem. Res.* **1984**, *17*, 320–326. (c) Legon, A. C.; Millen, D. J. Angular Geometries and Other Properties of Hydrogen-Bonded Dimers: A Simple Electrostatic Interpretation of the Success of the Electron-Pair Model. *Chem. Soc. Rev.* **1987**, *16*, 467–498. (d) Legon, A. C.; Millen, D. J. Directional Character, Strength, and Nature of the Hydrogen Bond in Gas-Phase Dimers. *Acc. Chem. Res.* **1987**, *20*, 39–46.

(27) Calculations from pK values determined using a log D/pH profile technique (see: Albert, A.; Serjeant, E. P. In *The Determination of Ionisation Constants*, 3rd ed.; Chapman and Hall: London, 1984; pp 103–108) show that **1b** (pK_a = 4.4, pK_b = 3.2) exists almost exclusively in the anionic form at pH 7.4. For the more basic **5f** (pK_a = 4.3, pK_b = 7.4) 52% anion and 48% zwitterion are present at pH 7.4.

(28) ENIGMA is an in-house molecular graphics program, ICI Americas, Wilmington, DE 19897.

(29) AESOP is an in-house molecular mechanics program, ICI Americas, Wilmington, DE 19897, derived in part from BIGSTRN-3 (QCPE 514), Nachbar, R.; Mislow, K. *QCPE Bull.* **1986**, *6*, 96. AESOP employs MM2 force field parameters, see: Allinger, N. L. *QCPE Bull.* **1980**, *12*, 395.

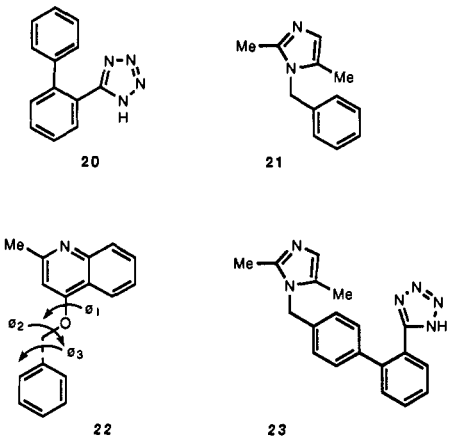


Figure 5. Structural fragments **20–23** used in molecular modeling studies.

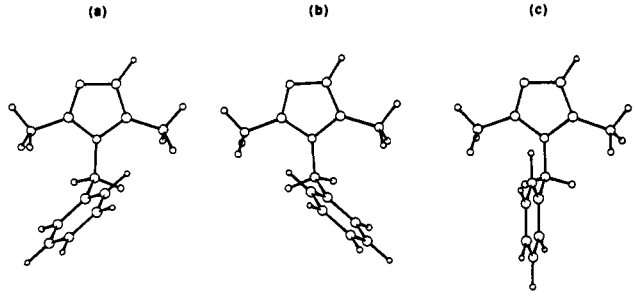


Figure 6. Low-energy conformations of structure **21**: (a) helix-1, relative energy = 0.0 kcal/mol; (b) helix-2, relative energy = 0.1 kcal/mol; (c) perpendicular, relative energy = 0.5 kcal/mol.

the conformational properties of other ortho-substituted biphenyls.[30]

As a model for the biphenyl–imidazole linkage in **1b**, structure **21** was considered as outlined in our earlier paper.[1] The conformational analysis of **21** is analogous to that of diphenylmethane.[31] AESOP calculations on **21** show two helical conformations, of nearly equal energy, as minima (Figure 6a,b). One of these, helix-1, is the conformation observed in the X-ray crystal structure of **1a** (Figure 4), supporting the conclusion that this conformation is energetically reasonable. Between the two helical conformations, a third conformation with the imidazole and phenyl rings perpendicular (Figure 6c) is found with an energy 0.5 kcal/mol above that of helix-1. The alternative gable conformation (not shown), is found to be 1.5 kcal/mol above either helix. Thus, molecular mechanics predicts three low-energy conformations of **21**.

Structure **22** was used as a model for the biphenyl–quinoline linkage in **5f**. Of the three rotatable bonds in **22**, ϕ_1 is quite rigid and a planar conformation with the methylene turned away from the steric repulsion of the peri hydrogen is expected.[32] ϕ_2 might adopt either gauche (ca. ±60°) or anti (ca. 180°) conformations. Three low-energy conformations are detected by AESOP, with the relative energies and dihedral angles given in Figure 7. Of these conformations, the anti conformation (Figure 7b) is

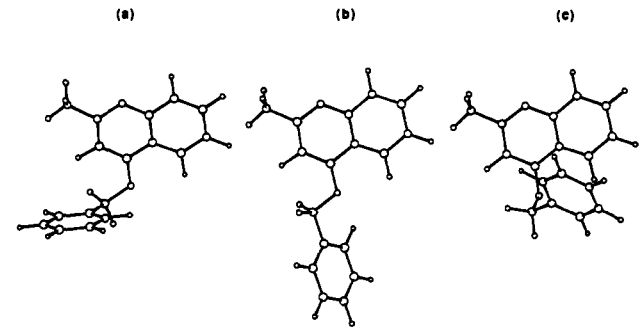


Figure 7. Low-energy conformations of structure **22**: (a) gauche, relative energy = 0.0 kcal/mol; $\phi_1 = -7°$, $\phi_2 = -64°$, $\phi_3 = -32°$; (b) anti, relative energy = 0.7 kcal/mol; $\phi_1 = 0°$, $\phi_2 = 179°$, $\phi_3 = -53°$; (c) relative energy = 1.2 kcal/mol; $\phi_1 = 76°$, $\phi_2 = 63°$, $\phi_3 = 83°$.

similar to that observed in the X-ray crystal structure of **5f** (Figure 3), even though this conformation is predicted to be slightly (0.7 kcal/mol) higher in energy than the gauche conformation (Figure 7a).

Each of the low-energy conformations of structures **21** and **22** can be combined with the two twisted conformations of biphenylyltetrazole **20** to give the low-energy conformations of **23** (a model structure for **1b**) and **5f**, respectively. This results in a total of four biphenyl orientations for each overall conformation of the heterocycle and linking group moieties. As an example, one of these is shown as a stereopair in Figure 8 for the gauche conformation of **5f** in the protonated form. In total, the three conformations of **22** combined with the four biphenyl orientations give 12 low-energy conformations for **5f**. Similarly, 12 low-energy conformations are found for **23**.

The low-energy conformations of the protonated forms of **5f** and **23** were overlaid using ENIGMA. Interestingly, simple visual examination of the conformations of **21** and **22** highlighted the similarity of the helix-1 and gauche structures. As shown in Figure 9 for one of the biphenylyltetrazole orientations, this similarity carries over to **5f** and **23**. In this and the overlays with the other biphenyl orientations (not shown) a very good correspondence both of the tetrazole groups and of the N-1 atoms of the quinoline and imidazole rings can be seen. In addition, good fits of the rings of the biphenyl units and of the methyl groups at the 2-positions of the quinoline and imidazole rings are also observed. Helix-1 and gauche thus represent strong candidates for the bioactive conformations of the imidazole- and alkoxyquinoline-derived series of AII antagonists, respectively. This pharmacophore model cannot, however, discriminate between the four orientations of the biphenylyltetrazole moiety.

As mentioned previously, the helix-1 conformation proposed for imidazole derivative **23** corresponds to that seen by X-ray diffraction for the analogous structure **1a**. In contrast, for quinoline derivative **5f** the proposed bioactive gauche conformation differs from the anti conformation observed in the X-ray crystal structure, the key difference between the two conformations being the orientation about the O–CH_2 bond (ϕ_2). To support the proposal by molecular mechanics that the gauche conformation is energetically feasible, a search of the Cambridge Crystallographic Database[33] was undertaken. The search identified 29 examples of X-ray structures containing an unconstrained Ar–O–CH_2–Ar substructure. Most (27) of the structures are related to the anti conformation, but two structures do correspond to the

(30) Dynes, J. J.; Baudais, F. L.; Boyd, R. K. Inter-ring Dihedrals in Polychlorinated Biphenyls from Photoelectron Spectroscopy. *Can. J. Chem.* **1985**, *63*, 1292–1299.

(31) Barnes, J. C.; Paton, J. D.; Damewood, J. R., Jr.; Mislow, K. Crystal and Molecular Structure of Diphenylmethane. *J. Org. Chem.* **1981**, *46*, 4975–4979.

(32) Chang, M. H.; Masek, B. B.; Dougherty, D. A. DNMR and Molecular Mechanics Studies of the Enantiomerization of Long-Chain (1,5)-Naphthalenophanes. *J. Am. Chem. Soc.* **1985**, *107*, 1124–1133.

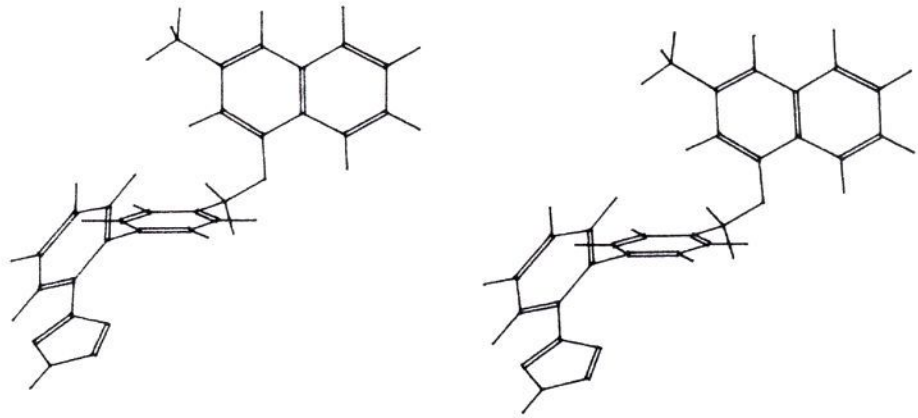


Figure 8. Stereoview of the protonated form of compound **5f** in the gauche conformation showing one of the four possible biphenyl orientations.

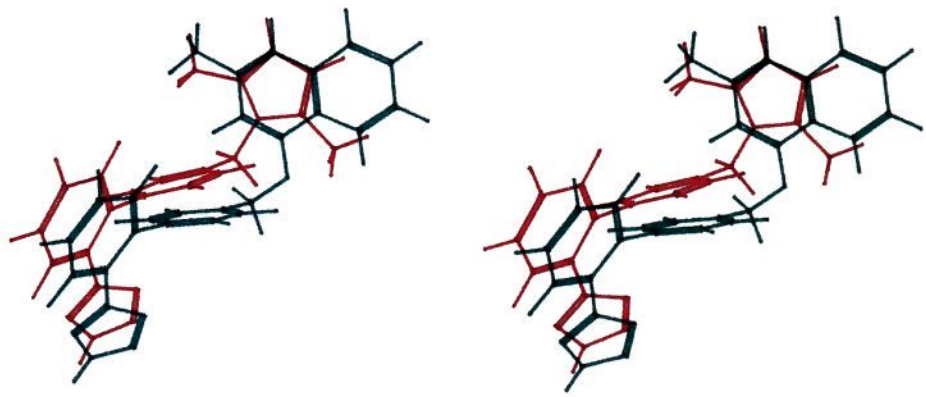


Figure 9. Stereoview of the overlay of the protonated forms of structures **5f** (green) and **23** (red) in the gauche and helix-1 conformations, respectively, showing one of the four possible biphenyl orientations.

gauche conformation.[34] Visual examination of the packing of these two structures did not reveal any unusual crowding or hydrogen-bonding interactions which might be responsible for the conformation. These structures offer experimental verification that the gauche conformation is energetically accessible and is a viable candidate for the bioactive conformation of **5f**. Further support for the proposed conformation is provided by the activity of compound **5j** in which a methyl group is introduced on the biphenyl–quinoline linkage. For this compound, AESOP calculations indicate that the proposed bioactive gauche conformation is now 3 kcal/mol more stable than the anti conformation. In this case, a search of the Cambridge Crystallographic Database revealed seven unconstrained examples of the Ar–O–CH(R)–Ar linkage (R = CH_2R' or CH_3), all of which correspond to the proposed conformation.

A number of active series have been examined to determine their ability to adopt the proposed bioactive conformation. For example, biphenylcarboxylate derivatives **5a–d** easily fit the model, since AESOP calculations indicate that the exchange of carboxylate for tetrazole does not cause any significant changes in the conformation of the biphenyl moiety. Perturbation of the imidazole ring, as in benzimidazole **2a** and imidazo[4,5-*b*]pyridines **2b,c**, retains the helix-1 bioactive conformation according to AESOP calculations. The model also rationalizes aspects of the in vitro SAR around the biphenyl–quinoline linkage. Substitution at the quinoline 3-position ortho to the oxygen (e.g. compound **5i**) would be expected to force the conformation of the quinoline–oxygen bond away from the desired planarity, as would replacement of methylene for oxygen in the linking chain (compound **5m**). Replacement of the oxymethylene link by *trans*-vinylene (*E*-isomer of compound **5l**) would result in adoption of a conformation analogous to the anti conformation of **5f**. As discussed previously, all of these changes lead to a significant decrease in binding affinity.

Pharmacological Evaluation

The compounds listed in Table III 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. The ED_{50} obtained for **1b** in this model is included in Table III as a standard.

For compounds **7a,c,e,r**, low solubility precluded in vivo evaluation. For the remaining compounds, potency in vivo

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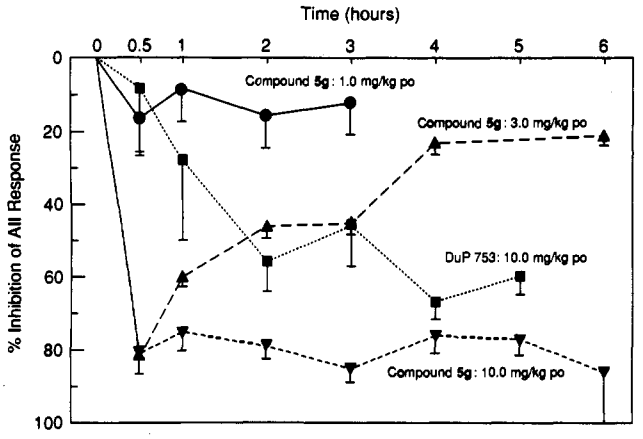

Figure 10. Effects of compounds **5g** and **1b** (DuP 753) after oral dosing to AII-infused, conscious rats. Effects are expressed as a percentage inhibition of the pressor response induced by AII infusion. Mean ± SE values are shown (n = 6–11).

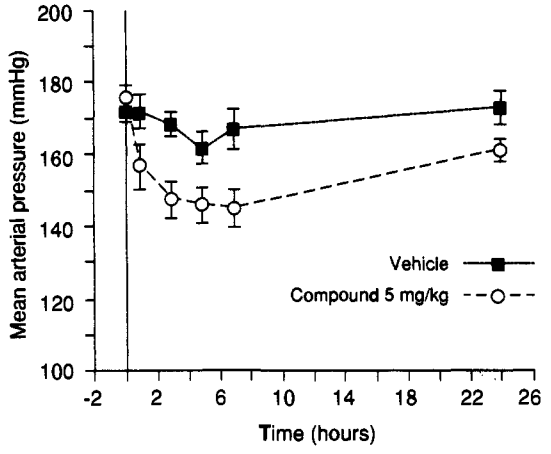

Figure 11. Effects of compound **5g** on mean arterial pressure after oral dosing at 5 mg/kg to renal hypertensive, conscious rats. Mean ± SE values are shown (n = 15).

broadly follows the relative affinities determined in the in vitro binding assay. The most potent compounds, **5f,g** and **7i–l**, gave ED_{50} values of <1 mg/kg, comparable with the activity of **1b**. In contrast to the peptide antagonist saralasin,[35] these compounds showed no evidence for partial agonism in this model.

Compound **5g** was evaluated orally in an AII-infused, conscious, normotensive rat model at doses of 10, 3, and 1 mg/kg. As shown in Figure 10, a dose-related inhibition of pressor response was seen with a duration of action lasting for the 6-h time course of the experiment at the 10 mg/kg dose. For comparison, the effect of **1b** (DuP 753) in the same animal model at a dose of 10 mg/kg is also shown. Analogues **5f** and **7i–l**, which showed comparable ED_{50} values to **5g** on intravenous dosing, were inferior in potency to **5g** when dosed orally (data not shown).

Compound **5g** also showed good activity in a renal hypertensive rat model. When administered orally at a dose of 5 mg/kg (Figure 11), 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 **5g** in normotensive, sham-operated rats were small (data not shown), consistent with a specific antihypertensive effect in renal hypertensive rats.

Compound **5g**, designated ICI D8731, is thus a potent, competitive, and orally active AII antagonist lacking agonist activity. On the basis of this profile, it has undergone more detailed pharmacological evaluation[36] and has been selected for clinical investigation as an antihypertensive agent.

Summary

This paper describes a novel series of potent, nonpeptidic AII receptor antagonists derived from linkage of the biphenylcarboxylic acid or biphenylyltetrazole acidic moieties found in previously described antagonists, such as **1a,b**, via a methyleneoxy chain to the 4-position of a 2-alkylquinoline. Although these antagonists 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 certain of their low-energy conformations of each structural type generated by molecular mechanics shows a very good correspondence both of the tetrazole groups and of the N-1 atoms of the quinoline and imidazole rings.

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 0.01–1 μM. The biphenylyltetrazole derivatives were more potent than the corresponding carboxylic acids. Structure–activity studies showed the quinoline nitrogen atom and a short alkyl chain at the quinoline 2-position to be essential for receptor binding. Oxymethylene was optimal as the linking chain to the biphenylyltetrazole. A variety of substituents was introduced in the quinoline ring, but at best only a small improvement in binding affinity was seen.

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 0.1–2.0 mg/kg. One of the compounds, **5g**, demonstrated good oral activity in two rat models. At doses in the range 1–10 mg/kg 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 **5g** showed a rapid and sustained lowering of blood pressure at a dose of 5 mg/kg. On the basis of its profile, this compound, designated ICI D8731, has been selected for clinical evaluation.

Experimental Section

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

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were recorded on Bruker WM200, WM250, or WM400 instruments and are reported as of 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 the isolated rabbit aorta have been described previously.[1]

2-Ethyl-4(1*H*)-quinolone (8a). A solution of aniline (173 mL, 186 g, 2.0 mol), methyl propionylacetate (251 mL, 260 g, 2.0 mol), and *p*-toluenesulfonic acid (2.75 g) in cyclohexane (700 mL) was heated under reflux in connection with a Dean–Stark water separator for 7 h. On cooling, insoluble material was removed by filtration and the filtrate was concentrated to give the intermediate 3-anilinopentenoate, which was used without purification. A 2-L flask fitted with an air stirrer, distillation head, and dropping funnel was purged with argon. Dowtherm A (500 mL) was added and heated to 240 °C. The crude 3-anilinopentenoate was added over 10 min, while the temperature was maintained in the range 230–240 °C, and the methanol formed was removed by distillation. The mixture was heated at 240 °C for a further 15 min and then allowed to cool. The insoluble solid was filtered off and washed with EtOAc/hexane (1:9 v/v, 3 × 500 mL, then 1:1 v/v, 400 mL) to give **8a** (213 g, 62%): mp 179–181 °C (lit.[37] mp 176–177 °C); ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3 H), 2.6 (q, 2 H), 5.9 (s, 1 H), 7.25 (t, 1 H), 7.45–7.7 (m, 1 H), 8.05 (d, 1 H), 11.5 (br s, 1 H). Anal. ($C_{11}H_{11}NO$) C, H, N.

Quinolone precursors **8b–r** were prepared from methyl propionylacetate and the appropriate substituted aniline using analogous procedures. Using *m*-toluidine, 3-chloroaniline, 3-aminobenzonitrile, and *m*-anisidine, mixtures of 5- and 7-substituted quinolones were obtained, which were either separated by chromatography (**8b**,c,l) or used as mixtures in the next stage (**8d**,**m–o**).

Ethyl 3-Ethyl-1,4-dihydro-4-oxoquinoline-2-carboxylate (17). A solution of aniline (46.5 g, 0.5 mol) and ethyl oxalobutyrate[38] (108 g, 0.5 mol) in dichloromethane (250 mL) was heated under reflux in connection with a water separator for 5 days. The solution was washed with 0.5 M HCl (250 mL), water (250 mL), 0.5 M NaOH (250 mL), and water (250 mL) and then dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was added over 5 min to dodecylbenzene (750 mL) at 240 °C. The temperature was maintained at 240 °C and the ethanol formed was removed by distillation. The solution was allowed to cool and the precipitated solid was filtered off and washed with hexane (3 × 250 mL) to give **17** (108 g, 86%): mp 174–175 °C; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3 H), 1.5 (t, 3 H), 3.05 (q, 2 H), 4.5 (q, 2 H), 7.2–7.4 (m, 2 H), 7.55–7.65 (m, 1 H), 8.35 (d, 1 H), 9.1 (br s, 1 H). Anal. ($C_{14}H_{15}NO_3$) H, N; C: calcd, 68.6; found 68.0.

3-Ethyl-4(1*H*)-quinolone (18). A solution of **17** (35 g, 0.144 mol) in 1.5 M aqueous NaOH (288 mL, 0.432 mol) was heated under reflux for 2 h. The hot solution was treated with charcoal and then acidified with concentrated HCl to precipitate the intermediate carboxylic acid, which was filtered off and dried at 80 °C. The carboxylic acid was added to dodecylbenzene at 240 °C and the mixture was heated for 5 min and then allowed to cool. The insoluble solid was filtered off and washed with hexane (3 × 500 mL) to give **18** (22.9 g, 93%): mp 190–191 °C; ^{1}H NMR (DMSO-d_6) δ 1.1 (t, 3 H), 2.45 (q, 2 H), 7.3 (dt, 1 H), 7.5–7.65 (m, 2 H), 7.8 (d, 1 H), 8.1 (d, 1 H), 11.6 (br s, 1 H). Anal. ($C_{11}H_{11}NO$) C, H, N.

Methyl 4′-[[(2-Ethylquinolin-4-yl)oxy]methyl]biphenyl-2-carboxylate (10; R^1 = Et, R^2 = R^3 = H, R^4 = methoxycarbonyl). A mixture of **8a** (260 mg, 1.50 mmol) and NaH (60% dispersion in mineral oil; 60 mg, 1.50 mmol) in DMF (2.5 mL) was stirred until evolution of hydrogen ceased. A solution of methyl 4′-(bromomethyl)biphenyl-2-carboxylate (**9a**;[7c] 460 mg, 1.51 mmol) in DMF (1 mL) was added and the mixture was stirred for 16 h. Volatile material was removed by evaporation and the residue was partitioned between water (20 mL) and EtOAc (2 × 10 mL). The combined extracts were washed with water (10 mL) and saturated brine (10 mL) and dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with EtOAc/CH_2Cl_2 (1:4 v/v), to give **10** (R^1 = Et, R^2 = R^3 = H, R^4 = methoxycarbonyl; 385 mg, 63%): mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, 3 H), 3.0 (q, 2 H), 3.7 (s, 3 H), 5.3 (s, 2 H), 6.8 (s, 1 H), 7.45–7.7 (complex m, 9 H), 7.9 (dd, 1 H), 8.0 (d, 1 H), 8.3 (dd, 1 H); ^{13}C NMR (benzylic CH_2) δ 69.7; CIMS *m/e* 398 (M + H)$^+$.

4′-[[(2-Ethylquinolin-4-yl)oxy]methyl]biphenyl-2-carboxylic Acid (5b). NaOH (1.25 M, 2.4 mL, 3.0 mol) was added to a solution of **10** (R^1 = Et, R^2 = R^3 = H, R^4 = methoxycarbonyl; 380 mg, 0.94 mmol) in EtOH (5 mL). The solution was heated under reflux for 2 h and then the volatile material was removed by evaporation. The residue was dissolved in water (30 mL) and the solution was acidified to pH 4 with 2 M HCl. The precipitated solid was filtered off and recrystallized from EtOH to give **5b** (254 mg, 65%): mp 204–205 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3 H), 2.9 (q, 2 H), 5.4 (s, 2 H), 7.1 (s, 1 H), 7.4–7.8 (complex m, 10 H), 7.9 (d, 1 H), 8.15 (dd, 1 H), 12.7 (br, 1 H); FABMS *m/e* 382 (M − H)$^-$. Anal. ($C_{25}H_{21}NO_3$) C, H, N.

Compounds **5a**,c,d were prepared using analogous procedures starting from the appropriate quinolone precursor and proceeding via the appropriate intermediate **10**.

Methyl 4′-[(3-Ethyl-1,4-dihydro-4-oxoquinolinyl)methyl]-biphenyl-2-carboxylate (19). Using an analogous procedure to that described above for the preparation of **10** (R^1 = Et, R^2 = R^3 = H, R^4 = methoxycarbonyl) but starting from compound **18**, **19** was obtained in 84% yield as a gum: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.7 (q, 2 H), 3.6 (s, 3 H), 5.4 (s, 2 H), 7.15 (d, 2 H), 7.3–7.55 (m, 8 H), 7.6 (s, 1 H), 7.85 (d, 1 H), 8.55 (d, 1 H); ^{13}C NMR δ (benzylic CH_2) 56.0.

4′-[(3-Ethyl-1,4-dihydro-4-oxoquinolinyl)methyl]biphenyl-2-carboxylic Acid (6). Using an analogous procedure to that described for the preparation of compound **5b**, **6** was obtained in 77% yield: mp 205–209 °C; ^{1}H NMR (DMSO-d_6) δ 1.2 (t, 2 H), 2.5 (q, 2 H), 5.6 (s, 2 H), 7.2–7.7 (m, complex m, 11 H), 8.15 (s, 1 H), 8.25 (d, 1 H); FABMS *m/e* 382 (M − H)$^-$. Anal. ($C_{25}H_{21}NO_3$) C, H, N.

2-Ethyl-4-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methoxy]quinoline [10; R^1 = Et, R^2 = R^3 = H, R^4 = 2-(triphenylmethyl)-2*H*-tetrazol-5-yl]. A mixture of **8a** (346 mg, 2.0 mmol) and NaH (60% dispersion in mineral oil; 80 mg, 2.0 mmol) in DMF (8 mL) was stirred until evolution of hydrogen ceased. A solution of 5-[2-[4′-(bromomethyl)biphenylyl]]-2-(triphenylmethyl)-2*H*-tetrazole (**9b**;[7c] 90% strength; 1.24 g, 2.0 mmol) in DMF (2 mL) was added and the mixture was stirred for 20 h. The volatile material was removed by evaporation and the residue was partitioned between water (20 mL) and EtOAc (2 × 10 mL). The combined extracts were washed with water (10 mL) and saturated brine (10 mL) and dried ($MgSO_4$). The volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with EtOAc/CH_2Cl_2 (1:9 v/v), to give **10** [R^1 = Et, R^2 = R^3 = H, R^4 = 2-(triphenylmethyl)-2*H*-tetrazol-5-yl] (930 mg, 71%): mp 173–174 °C (after trituration with EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.4 (t, 3 H), 3.0 (q, 2 H), 5.2 (s, 2 H), 6.7 (s, 1 H), 6.9–7.0 (m, 6 H), 7.15–7.55 (m, 17 H), 7.7 (dt, 1 H), 7.95–8.05 (m, 2 H), 8.1 (d, 1 H). Anal. ($C_{44}H_{35}N_5O$) C, H, N.

2-Ethyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methoxy]-quinoline Hydrochloride (5g). Concentrated hydrochloric acid (2 mL) was added to a solution of **10** [R^1 = Et, R^2 = R^3 = H, R^4 = 2-(triphenylmethyl)-2*H*-tetrazol-5-yl; 930 mg, 1.43 mmol] in EtOH (10 mL) and MeOH (5 mL). The mixture was stirred for 2 h and then the volatile material was removed by evaporation. EtOH (20 mL) was added and the solution was re-evaporated. The solid residue was triturated with Et_2O (2 × 30 mL) and then recrystallized from EtOH/EtOAc to give **5g** (400 mg, 63%): mp 178–181 °C; ^{1}H NMR (DMSO-d_6) δ 1.5 (t, 3 H), 3.2 (q, 2 H), 5.7

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(s, 2 H), 7.2 (d, 2 H), 7.5–7.8 (m, 7 H), 7.85 (t, 1 H), 8.1 (t, 1 H), 8.3 (t, 2 H); FABMS *m/e* 406 (M – H)⁻. Anal. ($C_{25}H_{21}N_5O$·HCl) C, H, N.

Compounds **5f,h,i,k** and **7a–t** were prepared using analogous procedures starting from the appropriate quinolone precursor.

5-[2-[4′-(Acetoxymethyl)biphenylyl]]-2-(triphenylmethyl)-2*H*-tetrazole (11a). Powdered KOAc (17.6 g, 0.18 mol) was added to a solution of **9a** (50.0 g, 0.09 mol) and 18-crown-6 (100 mg) in DME (600 mL) and the mixture was heated under reflux for 20 h. Insoluble material was removed by filtration and the residue was triturated with EtOAc/hexane (1:4 v/v, 400 mL) to give **11a** (41.8 g, 87%): mp 119–121 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 5.0 (s, 2 H), 6.8–6.95 (complex m, 8 H), 7.2–7.55 (complex m, 14 H), 7.9–8.0 (m, 1 H). Anal. ($C_{35}H_{28}N_4O_2$) C, H, N.

5-[2-[4′-(Hydroxymethyl)biphenylyl]]-2-(triphenylmethyl)-2*H*-tetrazole (11b). A solution of **11a** (41.8 g, 0.078 mol) in THF (200 mL) was added over a period of 40 min to a stirred suspension of $LiBH_4$ (4.1 g, 0.19 mol) in THF at 0 °C under an atmosphere of argon. The mixture was stirred for 20 h and then cooled to 0 °C. Aqueous citric acid (20%, 40 mL) was added and the mixture was diluted with saturated brine (600 mL). The mixture was extracted with EtOAc (2 × 500 mL) and the extracts were washed with water (500 mL) and saturated brine (500 mL). The extracts were dried and the volatile material was removed by evaporation. The residue was purified by flash chromatography, eluting with EtOAc/hexane (2:3 v/v), to give **11b** (17.4 g, 45%): mp 168–169 °C (after recrystallization from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 4.6 (s, 2 H), 6.85–7.0 (m, 6 H), 7.2–7.5 (complex m, 16 H), 7.9–8.0 (m, 1 H). Anal. ($C_{33}H_{26}N_4O$) C, H, N.

5-[2-(4′-Formylbiphenylyl)]-2-(triphenylmethyl)-2*H*-tetrazole (13a). A solution of pyridine–sulfur trioxide complex (2.91 g, 18.3 mmol) in DMSO (20 mL) was added over a period of 10 min to a stirred solution of **11b** (3.0 g, 6.1 mmol) and triethylamine (2.55 mL, 1.87 g, 18.3 mmol) in DMSO (20 mL). The mixture was stirred for 1.5 h and then acidified to pH 5 by addition of 20% aqueous citric acid. Water (250 mL) was added and the precipitated solid was filtered off, washed with water (4 × 100 mL) and hexane (4 × 100 mL), and dried under high vacuum to give **13a** (2.28 g, 77%): mp 154–156 °C (after recrystallization from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 6.8–6.95 (m, 6 H), 7.15–7.45 (complex m, 12 H), 7.5–7.7 (complex m, 4 H), 8.0–8.1 (m, 1 H), 9.9 (s, 1 H). Anal. ($C_{33}H_{24}N_4O$) C, H, N.

5-[2-[4′-(1-Hydroxyethyl)biphenylyl]]-2-(triphenylmethyl)-2*H*-tetrazole (13b). Methyllithium in Et_2O (0.98 M, 3.1 mL, 3.0 mmol) was added to a stirred solution of **13a** (1.50 g, 3.0 mmol) in THF (25 mL) and Et_2O (25 mL) at −50 °C under an atmosphere of argon. The solution was kept at −50 °C for 1 h and then left to stand for 20 h. Water (50 mL) was added and the mixture was extracted with EtOAc (2 × 30 mL). The extracts were washed with water (20 mL) and saturated brine (20 mL) and then dried ($MgSO_4$). The volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with EtOAc/hexane (1:1 v/v), to give **13b** (1.08 g, 71%) as a foam: ^{1}H NMR (DMSO-d_6) δ 1.2 (d, 3 H), 4.6–4.7 (m, 1 H), 5.1 (d, 1 H), 6.75–6.9 (m, 6 H), 7.0 (d, 2 H), 7.2 (d, 2 H), 7.25–7.4 (complex m, 9 H), 7.45–7.7 (complex m, 3 H), 7.8 (dd, 1 H).

2-Methyl-4-[1-[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-biphenyl-4-yl]ethoxy]quinoline (14). A mixture of **13b** (1.05 g, 2.10 mmol) and NaH (60% dispersion in mineral oil; 84 mg, 2.10 mmol) in DMF (15 mL) was stirred until evolution of hydrogen ceased. 4-Chloro-2-methylquinoline (370 mg, 2.1 mmol) in DMF (2 mL) was added and the mixture was heated at 40 °C for 20 h. The volatile material was removed by evaporation and the residue was partitioned between water (40 mL) and EtOAc (2 × 40 mL). The combined extracts were washed with water (40 mL) and saturated brine (40 mL) and dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with EtOAc/hexane (1:1 v/v), to give **14** (400 mg, 29%): mp 160–161 °C (after recrystallization from EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 1.5 (d, 3 H), 2.45 (s, 3 H), 5.8 (q, 1 H), 6.75–6.9 (complex m, 8 H), 7.1 (d, 2 H), 7.25–7.45 (complex m, 11 H), 7.45–7.75 (complex m, 4 H), 7.8–7.9 (m, 2 H), 8.2 (dd, 1 H); FABMS *m/e* 406 (M – triphenylmethyl)⁻. Anal. ($C_{44}H_{35}N_5O$) C, H, N.

2-Methyl-4-[1-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]ethoxy]quinoline Hydrochloride (5j). Using an analogous procedure to that described for the preparation of **5g**, but starting from **14**, **5j** was obtained in 60% yield: mp 168–169 °C; ^{1}H NMR (DMSO-d_6) δ 1.8 (d, 3 H), 2.9 (s, 3 H), 6.2 (q, 1 H), 7.2 (d, 2 H), 7.45 (s, 1 H), 7.5–7.6 (m, 4 H), 7.65–7.7 (m, 2 H), 7.85 (t, 1 H), 8.1 (t, 1 H), 8.2 (d, 1 H), 8.45 (d, 1 H); FABMS *m/e* 406 (M – H)⁻. Anal. ($C_{25}H_{21}N_5O$·HCl·0.5H_2O) C, H, N.

Compound **5e** was prepared via intermediate **12** using an analogous procedure.

Triphenyl[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]phosphonium Bromide (15). A solution of **9a** (5.0 g, 9.0 mmol) and triphenylphosphine (2.4 g, 9.2 mmol) in $CHCl_3$ (50 mL) was heated under reflux for 7 h. The volatile material was removed by evaporation and the residue was triturated with EtOAc to give **15** (5.63 g, 76%): mp 183–185 °C; ^{1}H NMR (DMSO-d_6) 5.15 (d, 2 H), 6.9–7.0 (m, 6 H), 7.3–7.9 (complex m, 32 H).

(*E,Z*)-2-Methyl-4-[2-[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]ethenyl]quinoline (16). A mixture of **15** (2.18 g, 2.66 mmol) and NaH (60% dispersion in mineral oil; 106 mg, 2.66 mmol) in THF (20 mL) was stirred under an atmosphere of argon until evolution of hydrogen ceased. 2-Methylquinoline-4-carboxaldehyde[22] (455 mg, 2.66 mmol) was added and the mixture was stirred for 4 h. The volatile material was removed by evaporation and the residue was partitioned between EtOAc (40 mL) and water (40 mL). The organic phase was separated, washed with water (20 mL) and saturated brine (20 mL), and dried ($MgSO_4$). The volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with EtOAc/hexane (2:3 v/v), to give **16** (1.01 g, 60%): mp >280 °C; ^{1}H NMR (DMSO-d_6 + CD_3CO_2D) δ 2.50, 2.55 (both s, ratio 1:2, total 3 H), 6.85–7.0 (m, 8 H), 7.2–7.4 (m, 8 H), 7.5–7.8 (m, 14 H); FABMS *m/e* 388 (M – triphenylmethyl)⁻.

2-Methyl-4-[2-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]ethenyl]quinoline Hydrochloride (5l). Using an analogous procedure to that described for the preparation of **5g**, but starting from **16**, **5l** was obtained in 69% yield: mp 283–285 °C; ^{1}H NMR (DMSO-d_6 + CD_3CO_2D) δ 2.85, 2.95 (both s, ratio 1:2, total 3 H), 6.9–7.3 (complex m, 3 H), 7.5–8.3 (complex m, 11 H), 8.8 (d, 1 H); FABMS *m/e* 388 (M – H)⁻. Anal. ($C_{25}H_{19}N_5$·HCl·H_2O) C, H; N: calcd, 15.7; found, 15.1.

2-Methyl-4-[2-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]ethyl]quinoline Hydrochloride (5m). Compound **5l** (200 mg, 0.47 mmol) in MeOH (80 mL) was catalytically hydrogenated over 10% Pd-C at 5 atm of pressure. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by flash chromatography, eluting with $MeOH/CH_2Cl_2$ (1:4 v/v), to give **5m** (45 mg, 22%): mp 145–150 °C (after trituration with Et_2O); ^{1}H NMR (DMSO-d_6 + CD_3CO_2D) δ 2.6 (s, 3 H), 3.0–3.1 (m, 2 H), 3.3–3.4 (m, 2 H), 7.05 (d, 2 H), 7.15–7.35 (m, 3 H), 7.5–7.8 (complex m, 6 H), 8.0 (d, 1 H), 8.2 (d, 1 H); FABMS *m/e* 390 (M – H)⁻. Anal. ($C_{25}H_{19}N_5$·HCl·H_2O) C, H; N: calcd, 15.4; found 14.8.

X-ray Crystallographic Analysis of 1a. Crystals of **1a**[7c] were obtained from aqueous ethanol: $C_{22}H_{23}ClN_2O_3$; monoclinic space group $P2_1/c$; cell constants a = 11.004 (2) Å, b = 19.528 (3) Å, c = 9.899 (2) Å, β = 100.78 (2)°, U = 2089.62 Å^3, and D_c = 1.268 g cm^{-3} (Z = 4). Data were recorded using a Philips PW1100 diffractometer with a constant scan width of 0.70° in the θ range 2.5°–21°, using graphite-crystal-monochromated Mo-Kα radiation. A total of 2455 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 and polarization corrections were applied to the data and equivalent reflections were merged to give a total of 679 unique reflections with $I/\sigma(I)$ > 2.0. The positions of all non-hydrogen atoms were located using the direct methods routine of SHELX86. The phenyl rings were treated as rigid hexagonal groups (C–C = 1.395 Å, C–H = 1.08 Å). Successive difference-Fourier syntheses with sin θ less than 0.35 failed to reveal satisfactory positions for all the hydrogen atoms and, in particular, those of the hydroxy and carboxyl groups were not located. In the final stages of full-matrix refinement the chlorine and oxygen atoms were assigned anisotropic thermal parameters. For consistency all the carbon-bonded hydrogen atoms were included in calculated positions, and the thermal

parameters of those on methylene groups were constrained to be equal, as were those of methyl groups (final values 0.06 and 0.09 Å^2, respectively). Weights were applied to the individual reflections as $1/\sigma^2(F)$ and refinement converged at $R = 0.0974$ and $R_w = 0.0829$, with a total of 109 refined parameters. Neutral scattering factors, corrected for the real and anomalous scattering, were used for all atoms and were taken from *International Tables of X-Ray Crystallography, Volume 4.*

X-ray Crystallographic Analysis of 5f. Crystals of **5f** were obtained from aqueous 2-propanol: $C_{24}H_{19}N_5O\cdot HCl\cdot 0.5H_2O$; monoclinic space group $C2/c$ (No. 15); cell constants $a = 22.979$ (5) Å, $b = 9.883$ (2) Å, $c = 19.430$ (4) Å, $\beta = 95.71$ (2)°, $U = 4390.73$ Å^3, and $D_c = 1.328$ g cm^{-3} ($Z = 8$). Data were recorded using a Philips PW1100 diffractometer with a constant scan width of 0.90° in the θ range 3°–23°, using graphite-crystal-monochromated Mo-Kα radiation. A total of 1969 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 and polarization corrections were applied to the data and equivalent reflections were merged to give a total of 1605 unique reflections with $I/\sigma(I) > 3.0$. The structure was solved using the direct methods routine of SHELX86. Initially no solution was achieved in the centrosymmetric space group, but the atoms of two independent molecules were readily located in the non-centrosymmetric space group. On refinement, very high correlation between the parameters was observed. The molecules were shown to be related by a $C2$ axis and refinement was continued in the space group $C2/c$, which was proved correct. A difference-Fourier syntheses with $\sin\theta$ less than 0.35 revealed the positions of all hydrogen atoms except those on the water oxygen. The two best peaks located for hydrogen atoms on the methyl substituent were used to determine the orientation, and the position of the third hydrogen atom was calculated. The carbon-bonded hydrogen atoms were assigned thermal parameters of 0.08 Å^2 and were included in structure factor calculations but were not refined. The hydrogen atoms on the two nitrogen atoms were refined satisfactorily with a common isotropic thermal parameter that gave a final value of 0.083 Å^2. In the final cycles of full-matrix refinement anisotropic thermal parameters were assigned to the chlorine, nitrogen, and oxygen atoms. Weights were applied to the individual reflections as $1/\sigma^2(F)$ and refinement converged at $R = 0.0632$ and $R_w = 0.06399$, with a total of 175 refined parameters. Neutral scattering factors, corrected for the real and anomalous scattering, were used for all atoms and were taken from *International Tables of X-Ray Crystallography, Volume 4.*

Antagonism of Angiotensin II Induced Pressor Responses in Conscious, Normotensive Rats. (a) ED_{50} Determination. Male Alderley Park Wistar rats weighing 200–250 g ($n = 3$–10) were prepared under Saffan (alphaxalone/alphadolone) anesthesia with indwelling arterial and venous catheters. Blood pressure was measured via the arterial catheter while angiotensin II was infused through the venous catheter at a rate of 1.0 μg/kg per min, which produced a rise in mean arterial pressure of approximately 50 mmHg. During the angiotensin II infusion, a cumulative intravenous dose–response curve was constructed to the antagonist and its ED_{50} value determined.

(b) Determination of Duration of Effect. Blood pressure was measured via the arterial catheter in rats prepared as above while angiotensin II was infused through the venous catheter at a rate of 1.0 μg/kg per min for 3–4 min, which produced a rise in mean arterial pressure of approximately 50 mmHg. Single bolus intravenous or oral doses of antagonist were administered and effects on angiotensin II induced pressor responses were measured at various time intervals. Effects of the antagonist on angiotensin responses were expressed as percentage inhibition of the control angiotensin II response.

Effects on Blood Pressure in Renal Hypertensive Rats. Male Alderley Park Wistar rats weighing 280–300 g were anesthetized 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 anesthesia 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 an antagonist.

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Supplementary Material Available: Coordinates for the conformations of **5f** and **23** shown in Figure 9 and tables containing bond lengths, bond angles, fractional atomic coordinates and thermal parameters for **1a** and **5f** (14 pages). Ordering information is given on any current masthead page.