Nonpeptide Angiotensin II Antagonists: *N*-Phenyl-1*H*-pyrrole Derivatives Are Angiotensin II Receptor Antagonists

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A series of 5-[1-[4-[(4,5-disubstituted-1*H*-imidazol-1-yl)methyl]-substituted]-1*H*-pyrrol-2-yl]-1*H*-tetrazoles and 5-[1-[4-[(3,5-dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]-substituted]-1*H*-pyrrol-2-yl]-1*H*-tetrazoles were investigated as novel AT_1-selective angiotensin II receptor antagonists. Computer-assisted modeling techniques were used to evaluate structural parameters in comparison to the related biphenyl system. New synthetic procedures have been developed to prepare the novel compounds. The best antagonists in this series had IC_{50} values (rat uterine membrane receptor binding) in the 10^{-8} M range and corresponding pA_2 in isolated organ assay (rabbit aorta rings). Structure–activity relationships indicate some similarities with the finding in the biphenyl system. Substitution on the pyrrole ring modulates activity. Compound **5** antagonized angiotensin-induced blood pressure increase when administered to conscious rat at 30 mg/kg per os.

Introduction

Angiotensin II (AII) receptor antagonists, renin inhibitors, and angiotensin I converting enzyme (ACE) inhibitors have all been used to demonstrate the involvement of the renin–angiotensin system in essential hypertension.[1] The development during the last decades of orally active ACE inhibitors has lead to a new, increasingly utilized therapy for treating hypertension. Peptidic AII antagonists have been available for over 30 years as a means to block the renin–angiotensin system; however, their therapeutic use has been severely limited by their partial agonist activity, rapid clearance, and lack of oral bioavailability.[2]

Recently, a series of imidazole-based compounds has been identified as antagonists to the angiotensin II receptor.[3,4] In particular, biphenylimidazoles were found to produce potent antihypertensive effects upon oral administration. Bioisosteric replacement of the carboxylic acid by a tetrazole improved both in vitro binding affinity and in vivo oral antihypertensive activity. The general structure–activity relationship of this series of biphenyl compounds has been recently reported.[5] The biphenyl tetrazole known as DUP753 or MK954 (1) is currently under development by Du Pont Merck (phase III clinical trial) for treatment of hypertension. This compound and related analogues have high AII receptor binding affinity, are competitive AII antagonists devoid of agonist activity, and are orally active and antihypertensive in animal models.

This seminal discovery initiated a flurry of activity in pharmaceutical research. Reviews covering this area have recently appeared.[6] By and large, the remarkable pharmacological properties associated with the biphenyl fragment reported by Duncia and Carini focused research efforts on replacement of the azole fragment while preserving the biphenyl moiety.[7]

Relatively few non-biphenyl-containing compounds endowed with AII antagonist activity have been reported aside from the original compounds reported by Takeda[8] and the initial work by Du Pont.[3] Noteworthy is a family of 4-(carboxybenzyl)imidazole-5-acrylic acid[9] and their tetrazolyl equivalents.[10] Typical of this class is SKF 108566 which was developed from the early Takeda lead to enhance affinity by mimicking critical binding elements of the natural peptidic agonist in its binding conformation.[11] More recently, *N*-alkanoic acid derivatives were reported to have antagonist effect as well.[12]

In addition, phenyl-5-benzo[*b*]furan, phenyl-5-benzo[*b*]thiophene, and phenyl-1*H*-indole surrogates[13,14] for the biphenyl have also been recently disclosed for which antagonist activity was claimed. Replacement of the terminal aromatic ring of the biphenyl with a 3-carboxy-2-furanyl moiety reduced binding affinity by a factor of approximately 20. The presence of 2′,6′-dimethoxy substituents on the biphenyl moiety was found to significantly (10-fold) decrease affinity for the receptor with respect to the unsubstituted analogue.[15] A recent report revealed that naphthalene and tetrahydronaphthalene are mediocre substitutes for the biphenyl spacer.[16]

We became interested in the hypothesis that *N*-phenylpyrrole could be a suitable replacement for the biphenyl group. The validity of the hypothesis was evaluated by molecular modeling methods, and several model compounds were prepared by new synthetic procedures. Several combinations of the two recognized pharmacophoric groups (the acidic function and the azole) were attempted. A modeling study was undertaken to estimate how 1-phenylpyrrole spacers (Table I, models III and IV) would compare to the biphenyl spacers (Table I, models I and II) in terms of distances between comparable atoms.

Computational methods have been employed to calculate the potential hypersurfaces of the anionic model structures I–IV at a STO 3G basis with respect to the two rotatable bonds labeled "tor a" and "tor b". The structures were fully optimized (except for tor a and tor b) at each point on the surface. The distances between the para carbon atom of the phenyl ring and the acidic group have

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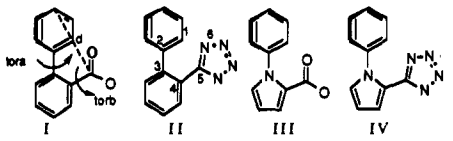
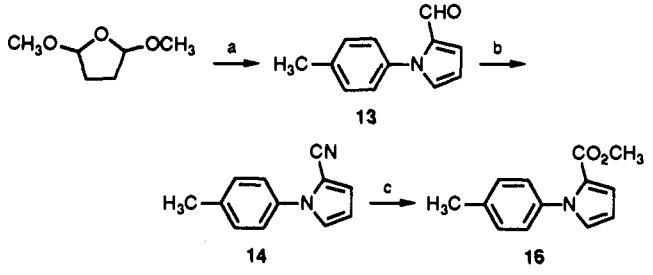
Table I. Comparison of the Carboxylic Acid and Tetrazole Derivatives in the Biphenyl and *N*-Phenylpyrrole Series[a]



	I	II	III	IV
d1[b]	5.40	5.23	5.39	5.34
d2[c]	5.50	5.54	5.49	5.71

[a] The four structures were anions for which the geometry was fully optimized at the STO 3G basis using the ab initio electronic structure code, CADPAC version 4 (R. D. Amos and J. Rice, Cambridge University). [b] Distances expressed in angstroms between the para carbon of the phenyl ring and the carbon of the acidic fragment (independent of conformation due to axial symmetry). [c] Distances expressed in angstroms between the para carbon of the phenyl ring and the center of gravity of the atoms of the acidic fragment (independent of conformation due to axial symmetry).

Scheme I[a]



[a] (a) *p*-Toluidine; acetic acid; DMF, $POCl_3$. (b) NH_2OH; $(AcO)_2O$. (c) KOH, ethylene glycol; MeOH, HCl.

been measured on the models of the optimized structures and fall within a 0.23-Å range. This result indicates that the pyrrole derivatives envisaged for synthesis would allow similar relative spatial positioning of the acidic and azole pharmacophoric groups. In derivatives II and IV, the bulkier tetrazole rings force the biaryl system out of planarity slightly more than the carboxylic group in derivatives I and III. The energy difference between the more stable conformations for the carboxylate and the tetrazole derivative is more pronounced in the biphenyl system than in the *N*-phenylpyrrole system.

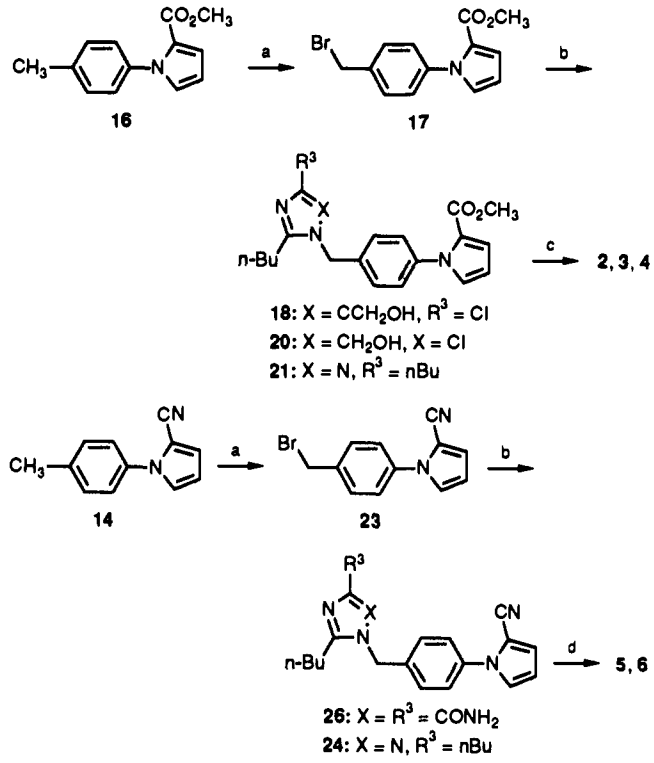
The potential energy surfaces indicate that the carboxylic acid minima correspond to sharp wells 4–6 kcal/mol below a mean valley that extend along the tor a minima and encompasses the entire range of tor b values. On the other hand, the tetrazoles have less well defined minima and can rotate more freely (lower energy increase) around their minimal energy conformations. However, in all fragments, torsional angles of 90° encounter a very high energy barrier. Solvation, although not included in this study, would lead to the same general conclusions as the molecules have similar electronic structures.

Consequently, we felt that, from a structural point of view, the *N*-phenylpyrrole fragment provided an excellent substitute for the biphenyl fragment as a spacer. Thus, we set forth to investigate a family of substituted *N*-tolylpyrroles 2–11 for potential AII antagonist activity.

Chemistry

Scheme I describes a general synthetic pathway to the 1-*p*-tolyl-2-cyano-1*H*-pyrrole derivative (14) based on a described procedure.[17] Treatment of 4-aminotoluidine with 2,5-diethoxytetrahydrofuran in glacial acetic acid at reflux gave good yield of the desired pyrrole. Formylation

Scheme II[a]

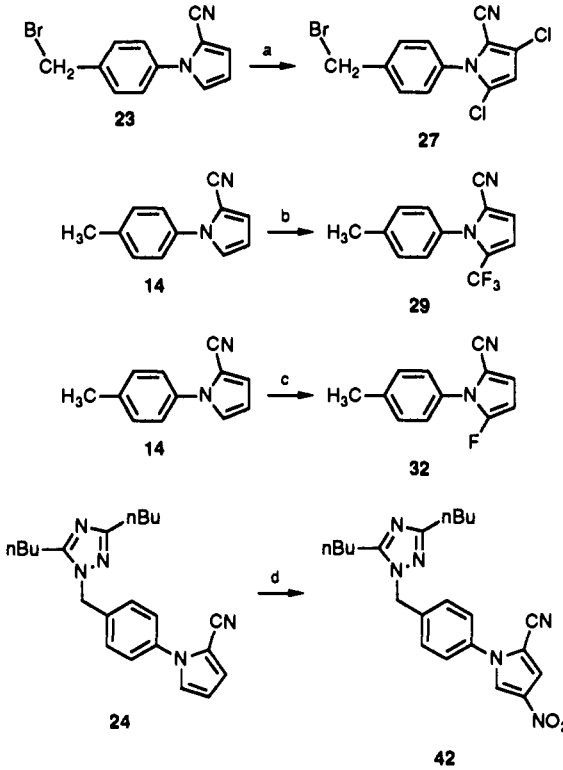


[a] (a) NBS, CCl_4, AIBN. (b) 19, 22, or 25; NaH or tBuOK, DMF. (c) NaOH, H_2O. (d) Me_3SnN_3, HCl(g), EtOH or SiO_2.

of the 1-*p*-tolylpyrrole was carried out according to the Vilsmeyer–Haack reaction. The 1-*p*-tolyl-2-formyl-1*H*-pyrrole (13) derivative was then transformed into the corresponding oxime by treatment with hydroxylamine hydrochloride which furnished the 1-(4-methylphenyl)-2-cyano-1*H*-pyrrole (14) when treated with acetic anhydride. We found that the nitrile 14 provides an easy access to both the carboxylic derivatives 16 and the tetrazole derivatives.

Scheme II describes the sequence of reactions which led to the preparation of the targeted molecules 2–6. We found that radical bromination of the benzylic position of the ester 16 was readily achieved with NBS in carbon tetrachloride in the presence of AIBN or dibenzoyl peroxide. Typically, in this reaction, traces of the α,α-dibromo derivative were generated. Methyl 1-(α-bromotolyl)-1*H*-pyrrole-2-carboxylate (17) was used to alkylate the azoles 19 and 25. The alkylation was performed in dimethylformamide on the azole's anions generated with NaH or tBuOK. In the case of 2-*n*-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole (19), two regioisomers were produced which were separated by silica gel chromatography. Hydrolysis of the ester with dilute aqueous base completed the sequence leading to compounds 2–4. The radical bromination procedure on 1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (14) led to 1-[4-(bromomethyl)-phenyl]-1*H*-pyrrole-2-carbonitrile (23), which was then used to alkylate the anions of azoles 22 and 25 to provide respectively the nitriles 24 and 26. The tetrazole derivatives were obtained by a 1,3-dipolar cycloaddition with trimethyltin azide as described by Sisido et al.[18] The *N*-(trimethylstannyl)tetrazoles can be converted to the free tetrazole by anhydrous hydrogen chloride in an ethereal or alcoholic solution. We have also observed that the passage through a silica gel column was usually an effective procedure to cleave the trimethylstannyl group.

Scheme III[a]



[a] (a) NCS, $MeOH/CH_2Cl_2$. (b) CF_3I, Hg, *hv*. (c) XeF_2, CH_2Cl_2. (d) $(AcO)_2O$, HNO_3 70%, -20 °C.

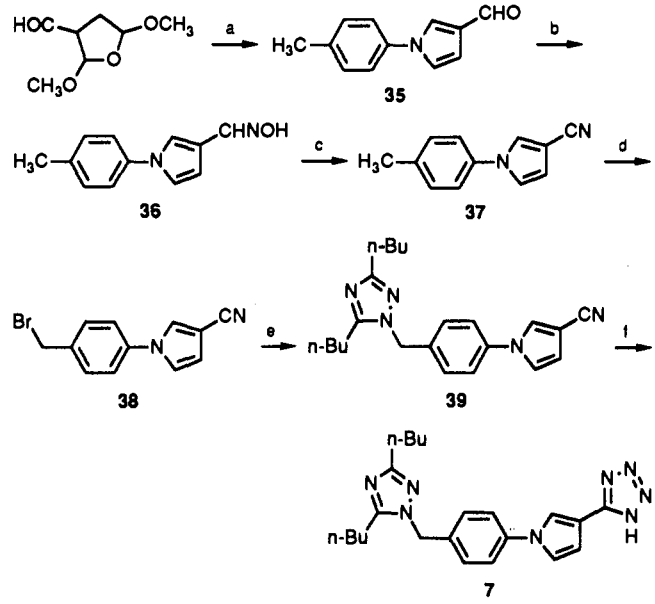
As described in the Discussion, we were interested in introducing electron-withdrawing substituents on the pyrrole ring. These substituents were introduced at various stages of the synthetic scheme. Chlorination in positions 3 and 5 of 1-[4-(bromomethyl)phenyl]-1*H*-pyrrole-2-carbonitrile (**23**) was obtained by treatment with 2 equiv of *N*-chlorosuccinimide (Scheme III). 1-(4-Methylphenyl)-1*H*-pyrrole-2-carbonitrile (**14**) was trifluoromethylated photochemically with trifluoromethyl iodide in the presence of mercury.[19,20] Fluorination of the same nitrile intermediate was achieved in 25% yield by the use of xenon difluoride in dichloromethane.[20] On the other hand, the nitro group on the 3 position of the pyrrole was obtained from direct nitration of the nitrile **24**, in conditions previously described[21] for related compounds. In all cases, the position of the substituents on the pyrrole ring was deduced from the analysis of the proton and/or carbon NMR spectra and from analogy with other cases previously reported in the literature.[22]

Scheme IV describes the synthesis of the 3-tetrazole derivative **7**. The construction of 1-*p*-tolyl-3-formyl-1*H*-pyrrole (**35**) was conducted in one efficient step from *p*-toluidine and 3-formyl-2,5-dimethoxytetrahydrofuran. All subsequent synthetic steps were adapted from the sequence described in Schemes I and II.

Biology

Newly synthesized compounds were evaluated for specific binding to rat uterine AII receptors (IC_{50}) and for antagonism of AII-induced contraction of rabbit aorta rings (pA_2).[23] In the binding assay, the ability of compounds to prevent ^{125}I-angiotensin II binding to a rat uterine membrane preparation[24] was determined, and the calculated IC_{50}s values are listed in Tables II and III. Control experiments indicated an IC_{50} value for AII of 2.2 nM. All

Scheme IV[a]



[a] (a) *p*-Toluidine, AcOH, refl, 2 h. (b) NH_2OH, Na_2CO_3 aq. (c) $(AcO)_2O$, refl, 3 h. (d) NBS, CCl_4, AIBN. (e) tBuOK, **22**, DMF, rt. (f) Me_3SnN_3, HCl(g), EtOH or SiO_2.

new compounds produced a biphasic displacement curve, indicating the presence of high-affinity (80%) and low-affinity (20%) binding sites with IC_{50} values ranging between 30 nM and 2 μM for the high-affinity sites and between 10 and 710 μM for the low-affinity sites. Recent studies using selective AII receptor ligands have revealed that there are two AII receptor subtypes in various target tissues.[25,26] Specifically, peptides[27] and non-peptides[28] have been identified that bind selectively to the high-affinity (AT_1) and to the low-affinity AII receptor population (AT_2). Analysis of the structure–activity relations among these compounds reveals that the AT_1 receptors are involved in vascular contractile activity and blood pressure regulation while the function of AT_2 receptors remains largely unknown.

The binding assay was followed with a functional test for the ability of a compound to antagonize the angiotensin II-induced contraction of isolated rabbit aorta rings.[29] From this assay, pA_2 values were derived and are listed in Tables II and III. In this assay, the compounds tested shifted the AII concentration–response curve to the right in a concentration-dependent and parallel manner. Even in the presence of 0.1 μM of the compounds tested, the maximal response to AII was attainable, indicating the fully reversible and competitive nature of the antagonism. No agonist effect was observed for the compounds tested.

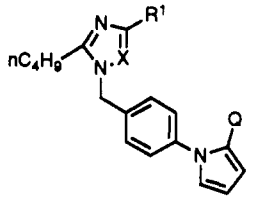
The in vivo activity was determined by assessing the inhibition of the pressor response to a 50 ng/kg per min iv infusion of angiotensin II in conscious rats. Figure 1 displays the dose–response curve for inhibition of AII-induced pressor response of compound **5**. A dose of 30 mg/kg administered id blocked the pressor response for at least 3 h.

Discussion

Figure 2 depicts several key compounds from this work and from the literature to help evaluate the effect of replacement of the terminal phenyl ring of the biphenyl by a pyrrole ring.

In the carboxylic acids series, the introduction of the *N*-phenylpyrrole fragment gave compounds which are

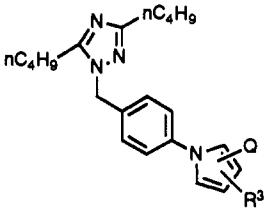
Table II. Comparison of Angiotensin II Antagonist Activity (Measured by Binding Affinities and pA_2) of the New *N*-Toluylpyrrole Derivatives **2–6**, Containing Various Heterocycles and Acidic Functions, to DUP 753, **1**, and the Corresponding Carboxylic Acid **40**



no.[a]	R^1	X	Q	IC_{50}[b,c] (nM) AT_1	IC_{50}[b,c] (nM) AT_2	pA_2[d]	mp, °C
1 (DUP 753)				36[f]	>10000	8.1[f]	183.5–184.5
40 (EXP 7711 (IMI))[g]				170	3300	7.1	168.0–170.0
2	Cl	CCH_2OH	CO_2H	870	59000	5.9	180.0–181.5
3	CH_2OH	CCl	CO_2H	1100	140000	6.1	181.0–182.5
4	*n*-C_4H_9	N	CO_2H	270	159000	6.3	107.5–108.5
5	*n*-C_4H_9	N	CN_4H	33	260000	8.0	125.5–127.0
6	$CONH_2$	$CCONH_2$	CN_4H	290	30000	5.9[e]	216.0–221.0

[a] New compounds were identified by a combination of their spectroscopic data and confirmed by exact mass measurement and/or analysis for C, H, N. [b] Concentration of the test compound inhibiting specific binding of AII by 50% was derived from analysis of plots of the percentage of specific binding vs the log concentration of the compound (at least 10 concentrations ranging over 5 orders of magnitude were used). Data are derived from one experiment performed with doses in triplicate. [c] The IC_{50} values for each receptor subclass separately were obtained by the methodology described in ref 23. [d] pA_2 values were obtained as described in the Experimental Section. [e] The low pA_2 value for this compound may be due to a low solubility in the conditions of this assay. [f] Literature values are 19 nM for the affinity to rat adrenal cortex receptors and 8.48 for rabbit aorta pA_2 (ref 3). [g] See refs 15 and 24.

Table III. Influence of Substitution of the Pyrrole Ring on Angiotensin II Antagonist Activity As Measured by Binding Affinities and pA_2



no.[a]	R^3	Q	IC_{50}[b,c] (nM) AT_1	IC_{50}[b,c] (nM) AT_2	pA_2[d]	mp, °C
5	H	2-CN_4H	33	260000	8.0	125.5–127.0
7	H	3-CN_4H	2000	220000	na[e]	143.5–144.1
8	3,5-Cl	2-CN_4H	52	810000	7.7	164.9–166.4
9	5-CF_3	2-CN_4H	88	450000	7.7	138.0–138.5
10	5-F	2-CN_4H	72	230000	6.4	100.8–101.2
11	4-NO_2	2-CN_4H	480	930000	6.7	167.0–180.0 dec

[a] New compounds were identified by a combination of their spectroscopic data and confirmed by exact mass measurement and/or analysis for C, H, N. [b] Concentration of the test compound inhibiting specific binding of AII by 50% was derived from analysis of plots of the percentage of specific binding vs the log concentration of the compound (at least 10 concentrations ranging over 5 orders of magnitude were used). Data are derived from one experiment performed with doses in triplicate. [c] The IC_{50} values for each receptor subclass separately were obtained by the methodology described in ref 23. [d] pA_2 values were obtained as described in the Experimental Section. [e] No activity detected in this assay.

somewhat less potent than their biphenyl counterpart by about a 5-fold factor (i.e., **2** vs **40** and **4** vs **42**). The pyrrole derivative **2**, however, is about 5 times more potent than the previously described furan derivative **41**. As in the biphenyl series, the regioisomer with respect to the position of the imidazole substituents, **3**, is somewhat less potent. In the compounds examined, replacement of the imidazole ring **19** by the triazole **22** produced an analogue **4** with improved potency. This is similar to the observations reported in the biphenyl series. The SAR of the triazole series has been recently reported.[30,32]

In all cases, introduction of a tetrazole instead of the carboxylic acid function produced compounds with dramatically increased affinity for the receptor. Bioisosteric replacement of the carboxylic acid in **4** by a tetrazole group afforded a compound, **5**, with 1 order of magnitude better affinity for AT_1 receptor. Compound **5** has a potency similar to DUP 753 (**1**). When administered to rats, **5** showed good activity with a shorter half-life than DUP 753.

We have investigated the effect of substitution of the pyrrole ring on the biological activity. In particular, we were interested in the effect of electron-withdrawing groups to test the hypothesis that such substituents may enhance the activity of the pyrrole derivatives. The 3,5-Cl, 5-CF3, 5-F derivatives (**8**, **9**, and **10**) suffered a small drop in affinity. A 4-nitro substituent, **11**, however lowered the binding affinity by 1 order of magnitude. These observations suggest that the pyrrole ring fit a lipophilic pocket which is well defined in size and in which there is insufficient room for the larger nitro group. Similar observations were reported for the biphenyl series.[5] The in vivo activity, however, was weaker with all the substitutions reported than with the unsubstituted compound **5**.

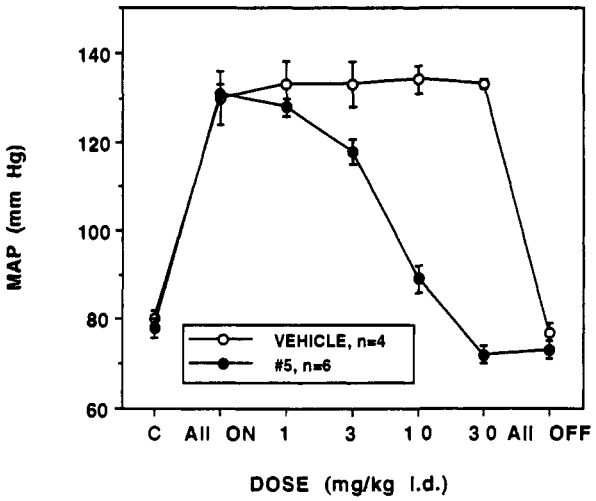


Figure 1. Dose–response curve for the inhibition of AII-induced blood pressure increase upon administration of 50 ng/kg per min of AII to ganglion-blocked, anesthetized rats. The decrease in blood pressure is proportional to the dose of compound **5** administered. Values are reported as the mean ± SEM. The number of animals (n) is shown.

Compound **7**, isomeric to **4** with respect to the position of the tetrazole on the pyrrole ring, is the least active compound in this series. Apparently, in the pyrrole series, the tetrazole group on the 3-position is poorly oriented for good interaction with the receptor. This is in contrast to the observations reported in the biphenyl carboxylic acid series but parallels the biphenyl tetrazole series.[5]

Conclusion

A novel series of nonpeptidic antagonists of AII containing substituted N-phenylpyrroles are described. These compounds are fully reversible competitive antagonists and exhibit no agonistic activity. The results obtained for the new compounds described indicate that they are selective ligands for the type I subclass of AII receptors involved in vascular contractile activity and blood pressure regulation in a manner similar to DUP 753 and its derivatives.[33] The novel N-phenylpyrrole analogues retain the AII antagonist properties of the corresponding biphenyl analogues. A similar decrease of potency (a 5-fold factor) was observed *both* in the carboxylic acid and tetrazole series, which could not be overcome by any of the pyrrole ring structural modifications subsequently investigated. The differences in free energy of binding between phenylpyrrole and biphenyl derivatives (all other structural features being identical) are less than 1 kcal. Subtle modifications in the positions of the pharmacophoric groups can be invoked to justify those differences.

Overall, the N-phenylpyrrole spacer offers an acceptable surrogate to the biphenyl spacer from a receptor-fit perspective. Testing in rats demonstrated in vivo activity of short duration. Substitution of the pyrrole ring was detrimental to both receptor recognition and oral activity.

Experimental Section

The reagents and solvents were commercially available (Aldrich Chemical Co.) and of synthetic grade. 2-n-Butylimidazole-4,5-dicarboxylic acid was purchased from Lancaster and the biphenyl derivatives were obtained via known syntheses.[4,34] Analytical TLC plates and silica gel (230–400 mesh) were purchased from EM Reagents. Melting points were taken using a Mettler FP80/81 apparatus and are uncorrected.

^{1}H NMR spectra were routinely obtained at 300 MHz on a Varian VXR-300 in $CDCl_3$, DMSO-d_6, or CD_3OD. Mass spectra were obtained using a Finnigan MAT 90 or a VG Model 250T spectrometer with either DCI or FAB ionization. Homogeneity of the final polar compounds was assessed by reverse-phase high-performance liquid chromatography on a C_{18} bonded silica gel using a Waters dual 510 pumps system to elute with a linear gradient (5–70% acetonitrile in water over 30 min) containing a constant concentration of trifluoroacetic acid (0.05%). Elemental analysis for C, H, N were obtained from Galbraith Laboratories, Inc. or Searle Analytical Department.

Chemistry. 1-(4-Methylphenyl)-2-formyl-1*H*-pyrrole (13). In 2 L of acetic acid were combined 500 g (4.67 mol) of p-toluidine and 625 g (4.73 mol) of 2,5-dimethoxy-3-tetrahydrofuran. The solution was stirred at reflux for 2 h and concentrated to an oil which solidified upon standing. The pyrrole was distilled under vacuum between 110 and 155 °C, giving 545 g (74%) of the desired material. A solution of 511 g (7 mol) of DMF was cooled in an ice bath and slowly treated with 651 g (7 mol) of phosphorus oxychloride; the mixture was allowed to warm up to 25 °C and stir for 20 min. A solution of the pyrrole in 2.7 L of dry DMF was slowly added. After the addition was complete, the reaction mixture was heated at 110–120 °C for 3 h, cooled, and partitioned between water and ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated in vacuo to give 3.5 mol (100%) of the crude product as an oil.

1-(4-Methylphenyl)-1*H*-pyrrole-2-carbonitrile (14). The crude product from the step above (3.5 mol), was dissolved in 5 L of methanol at reflux. An aqueous solution (2.5 L) of hydroxylamine hydrochloride (250 g, 3.5 mol) and 370 g (3.5 mol) of sodium carbonate was slowly added; the resulting solution was allowed to reflux for an additional 3 h. The reaction mixture was filtered, concentrated in vacuo, and partitioned between water and ethyl acetate. The organic extract was dried with Na_2SO_4 and concentrated to a solid under vacuum. The crude oxime (3.5 mol) was allowed to reflux in 3 L of acetic anhydride for 3 h. The reaction mixture was concentrated and distilled under vacuum to give 498 g (78% from step a) of 1-(4-methylphenyl)-1*H*-pyrrol-2-carbonitrile as an oil which solidified on standing: mp 56–58 °C; bp 175–195 °C (0.5 mm).

1-(4-Methylphenyl)-1*H*-pyrrole-2-carboxylic Acid (15). A 30.6-g sample of the nitrile **14** was stirred for 4 h at 167 °C in a mixture of 250 mL of ethylene glycol and 67 g of KOH. The reaction mixture was poured on crushed ice and the pH adjusted to 4 with concentrated hydrochloric acid. A buff-colored precipitate was collected which was dried and identified as the acid (23 g): mp 182–4 °C.

1-(4-Methylphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (16). The acid **15** was dissolved in 100 mL of thionyl chloride. The resulting dark red solution was stirred at 25 °C for 4 h and then concentrated to an oil. Methanol (100 mL) was slowly added and the reaction mixture stirred for 16 h at 25 °C. The solution was reconcentrated to an oil and purified by filtration through a pad of silica gel (eluant: methylene chloride). Trituration with hexane gave 22 g of ester: mp 74.2–74.7 °C; NMR ($CDCl_3$) δ 7.2 (m, 4 H), 7.05 (d, J = 7 Hz, 1 H), 6.9 (d, J = 7 Hz, 1 H), 6.25 (t, J = 7 Hz, 1 H), 3.7 (s, 3 H), 2.4 (s, 3 H).

1-[4-(Bromomethyl)phenyl]-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (17). To a mixture of 5.0 g (20 mmol) of ester **16** in 80 mL of carbon tetrachloride was added 3.6 g of N-bromosuccinimide followed by 80 mg of AIBN. The reaction was allowed to reflux for 19 h, cooled, and filtered to remove the solids; the resulting solution was concentrated and the oil thus produced dissolved in a small amount of ethyl acetate. Trituration with hexane gave 2.5 g of the desired bromo derivative: NMR ($CDCl_3$) δ 7.4 (m, 4 H), 7.1 (d, J = 7 Hz, 1 H), 6.95 (d, J = 7 Hz, 1 H), 6.25 (t, J = 7 Hz, 1 H), 4.55 (s, 2 H), 3.75 (s, 3 H).

Methyl 1-[4-[[2-*n*-Butyl-4-chloro-5-(hydroxymethyl)imidazolyl]methyl]phenyl]-1*H*-pyrrole-2-carboxylate (18). A solution of 321 mg of 2-n-butyl-4(5)-chloro-5(4)-(hydroxymethyl)-imidazole (**19**)[8] (1.7 mmol) in 6 mL of dry dimethylformamide was placed in a flask under an atmosphere of nitrogen, and 1.7 mL of potassium *tert*-butoxide (1 N solution in hexane) was added. After the resulting solution was stirred at room temperature for 15 min, 500 mg of methyl 1-[4-(bromomethyl)-phenyl]-1*H*-pyrrole-2-carboxylate (**17**) (1.7 mmol) was added at

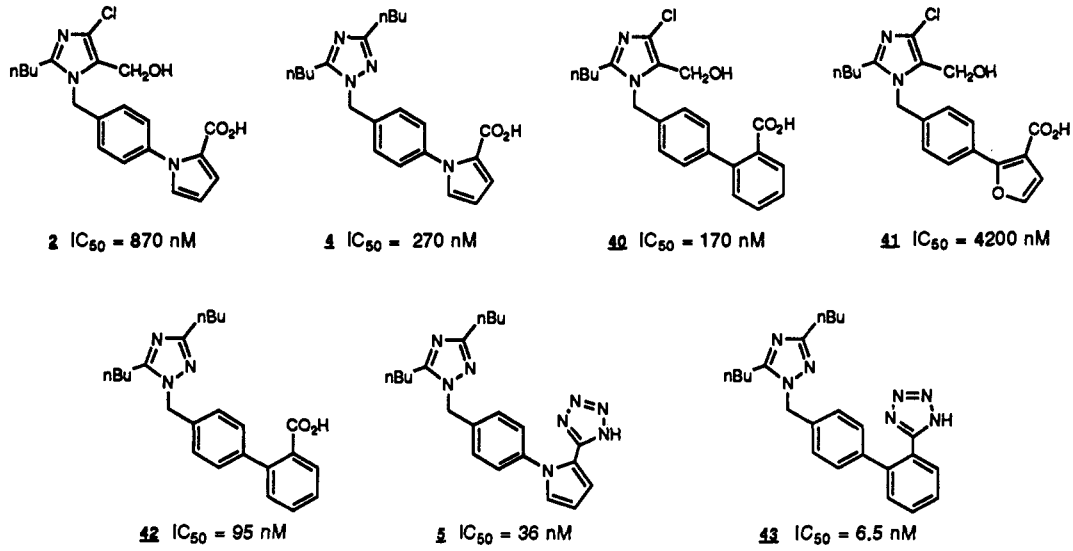


Figure 2. Binding affinities (as IC_{50}) for a series of biphenyl and *N*-phenylpyrrole derivatives from this work and from previous reports as referenced in the text (ref 5, 24, 32, 35).

once. The reaction mixture was stirred for 1 h at room temperature and then concentrated in vacuo as an oil which was partitioned between 0.1 N NaOH and ethyl acetate. The organic extract, dried on $MgSO_4$, and concentrated in vacuo was chromatographed on 50 g of silica gel with 5% ethyl acetate in chloroform as eluant. The first isomer to elute was the methyl [4-[[2-*n*-butyl-4-chloro-5-(hydroxymethyl)imidazolyl)methyl]-phenyl]-1*H*-pyrrole-2-carboxylate: NMR ($CDCl_3$) δ 7.3 (d, J = 6 Hz, 2 H), 7.1 (m, 3 H), 6.9 (d, J = 2.5 Hz, 1 H), 6.25 (t, J = 3 Hz, 1 H), 5.25 (s, 2 H), 4.45 (s, 2 H), 3.75 (s, 3 H), 2.6 (t, J = 7 Hz, 2 H), 1.7–1.6 (m, 2 H), 1.42–1.3 (m, 2 H), 0.9 (t, J = 7 Hz, 3 H).

1-[4-[[2-*n*-Butyl-4-chloro-5-(hydroxymethyl)imidazolyl]-methyl]phenyl]-1*H*-pyrrole-2-carboxylic Acid (2). A solution of 250 mg of methyl ester 18 in 25 mL of methanol and 25 mL of sodium hydroxide in water (10%) was stirred at ambient temperature overnight. The methanol was removed in vacuo and the pH adjusted to 4 with hydrochloric acid which caused the acid to precipitate. The product was collected by filtration: mp 180–181.5 °C; MS(FAB) *m/e* (rel intensity) 388 (90, M + H^+), 370 (20), 200 (100).

Methyl 1-[4-[[2-*n*-Butyl-4-(hydroxymethyl)-5-chloroimidazolyl]methyl]phenyl]-1*H*-pyrrole-2-carboxylate (20). Elution with ethyl acetate of the reaction mixture that afforded 18 provided the isomer methyl 1-[4-[[2-*n*-butyl-4-(hydroxymethyl)-5-chloroimidazolyl]methyl]-phenyl]-1*H*-pyrrole-2-carboxylate: NMR ($CDCl_3$) δ 7.35 (d, J = 6 Hz, 2 H), 7.1 (m, 3 H), 6.9 (d, J = 2.5 Hz, 1 H), 6.25 (t, J = 3 Hz, 1 H), 5.2 (s, 2 H), 4.65 (s, 2 H), 3.75 (s, 3 H), 2.8 (t, J = 7 Hz, 2 H), 1.8–1.65 (m, 2 H), 1.43–1.3 (m, 2 H), 0.9 (t, J = 7 Hz, 3 H).

1-[4-[[2-*n*-Butyl-4-(hydroxymethyl)-5-chloroimidazolyl]-methyl]phenyl]-1*H*-pyrrole-2-carboxylic Acid (3). A solution of 250 mg of methyl ester 19 in 25 mL of methanol and 25 mL of sodium hydroxide in water (10%) was stirred at ambient temperature overnight. The methanol was removed in vacuo and the pH adjusted to 4 with hydrochloric acid which caused the acid to precipitate. The product was collected by filtration: mp 181–182.5 °C; MS(FAB) *m/e* (rel intensity) 388 (80, M + H^+), 370 (10), 200 (100); HRMS calcd for M + H 388.1428, found 388.1496.

Methyl 1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)-methyl]phenyl]-1*H*-pyrrole-2-carboxylate (21). Under a static nitrogen atmosphere, 800 mg (4.42 mmol) of 3,5-dibutyl-1*H*-1,2,4-triazole (**22**)[35] was added in small portions to 6 mmol of sodium hydride in 50 mL of DMF; stirring was continued until hydrogen evolution had ceased. The anion solution was cooled to −10 °C (ice/methanol) and treated with 1.37 g (4 mmol) of methyl 1-[4-(bromomethyl)phenyl]-1*H*-pyrrole-2-carboxylate (**17**). The reaction was allowed to warm to ambient temperature and stir overnight. Methanol (10 mL) was added to destroy any unreacted sodium hydride and the DMF was removed in vacuo. The residue was dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$) to give 1.7 g of crude material upon concentration. Silica gel chromatography (Waters Prep-500A) using 40% ethyl acetate/hexane gave 900 mg (56%) of pure methyl ester as an oil: NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3 H), 0.96 (t, J = 7 Hz, 3 H), 1.30–1.47 (m, 4 H), 1.63–1.79 (m, 4 H), 2.64–2.74 (m, 4 H), 3.71 (s, 3 H), 5.28 (s, 2 H), 6.27–6.31 (m, 1 H), 6.88–6.93 (m, 1 H), 7.07–7.12 (m, 1 H), 7.16–7.23 (m, 2 H), 7.27–7.32 (m, 2 H).

1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]-phenyl]-1*H*-pyrrole-2-carboxylic Acid (4). A solution of 900 mg (2.28 mmol) of methyl ester 21 in 50 mL of methanol and 50 mL of sodium hydroxide (10%) was stirred at ambient temperature overnight. The methanol was removed in vacuo and the pH adjusted to 6 with hydrochloric acid which caused the acid to precipitate. The product was collected and recrystallized from acetonitrile, giving 627 mg (72%) of colorless acid: mp 107.5–108.5 °C; NMR (DMSO-d_6) δ 0.85 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H), 1.23–1.40 (m, 4 H), 1.52–1.67 (m, 4 H), 2.55 (t, J = 7 Hz, 2 H), 2.72 (t, J = 7 Hz, 2 H), 5.35 (s, 2 H), 6.27–6.31 (m, 1 H), 6.88–6.93 (m, 1 H), 7.07–7.12 (m, 1 H), 7.16–7.23 (m, 2 H), 7.27–7.32 (m, 2 H); HRMS (MH^+) calcd for $C_{22}H_{28}N_4O_2$ 381.2291, found 381.2287.

1-[4-(Bromomethyl)phenyl]-1*H*-pyrrole-2-carbonitrile (23). To a mixture of 100 g (0.55 mol) of 1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (**14**) in 2.5 L of carbon tetrachloride was added 98 g (0.55 mol) of *N*-bromosuccinimide followed by 6 g (36 mmol) of AIBN. The reaction mixture was allowed to reflux for 3 h and cool overnight. The succinimide was removed and the filtrate concentrated in vacuo to an oil. Trituration with hexane gave 115 g (80%) of a solid which appears by NMR to be 65% monobromo product: NMR ($CDCl_3$) δ 7.55 (m, 3 H), 7.35 (d, J = 7 Hz, 2 H), 7.05 (m, 1 H), 6.6 (m, 1 H), 4.5 (s, 2 H). Note: Some starting material (singlet at 2.4 ppm) and 4,4′-dibromo compound (singlet at 6.65 ppm) are present as contaminants.

1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]-phenyl]-1*H*-pyrrole-2-carbonitrile (24). Under a static nitrogen atmosphere, 6.20 g (34.2 mmol) of solid 3,5-dibutyl-1*H*-1,2,4-triazole from step g of example 1 was added in small portions to 42 mmol of sodium hydride in 100 mL of DMF; stirring was continued until hydrogen evolution had ceased. The anion solution was cooled to −10 °C (ice/methanol) and treated with 8.96 g (34.3 mmol) of 1-[4-(bromomethyl)phenyl]-1*H*-pyrrole-2-carbonitrile in 50 mL of dry DMF. The reaction was allowed to warm to ambient temperature and stir overnight. Methanol (10 mL) was added to destroy any unreacted sodium hydride, and the DMF was removed in vacuo. The residue was dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Silica gel chromatography (Waters Prep-500A) using 40% ethyl acetate/hexane gave 9.43 g (76%) of pure nitrile as an oil: NMR ($CDCl_3$)

δ 0.90 (t, J = 7 Hz, 3 H), 0.95 (t, J = 7 Hz, 3 H), 1.39–1.47 (m, 4 H), 1.62–1.80 (m, 4 H), 2.66 (t, J = 7 Hz, 2 H), 2.70 (t, J = 7 Hz, 2 H), 5.30 (s, 2 H), 6.33–6.37 (m, 1 H), 6.97–7.02 (m, 1 H), 7.04–7.08 (m, 1 H), 7.23–7.31 (m, 2 H), 7.41–7.48 (m, 2 H).

5-[1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-1*H*-pyrrol-2-yl]-1*H*-tetrazole (5). Under a static nitrogen atmosphere, a solution of 8.75 g (24.2 mmol) of nitrile **24** and 6.0 g (29.2 mmol) of trimethyltin azide in 50 mL of toluene was stirred at reflux for 3 days. The solvent was removed in vacuo; purification of the residue by silica gel chromatography (Waters Prep-500A) using methanol/ethyl acetate (20:80) caused deprotection. Recrystallization from acetonitrile provided 5.35 g (55%) of pure tetrazole: mp 125.5–127 °C; NMR ($CDCl_3$) δ 0.83 (t, J = 7 Hz, 3 H), 0.86 (t, J = 7 Hz, 3 H), 1.23–1.38 (m, 4 H), 1.54–1.71 (m, 4 H), 2.60 (t, J = 7 Hz, 2 H), 2.65 (t, J = 7 Hz, 2 H), 5.22 (s, 2 H), 6.37–6.42 (m, 1 H), 6.91–6.95 (m, 1 H), 6.97–7.02 (m, 1 H), 7.06–7.12 (m, 2 H), 7.15–7.20 (m, 2 H); HRMS (MH^+) calcd for $C_{22}H_{28}N_8$ 405.2515, found 405.2561.

2-*n*-Butylimidazole-4,5-dicarboxamide. In a pressure vessel, a mixture of 20 g of dimethyl 2-*n*-butylimidazole-4,5-dicarboxylate[36] and 200 mL of ammonia was heated at 100 °C for 48 h. The ammonia was vented and the residual solid washed on a fritted glass filter with a saturated solution of sodium bicarbonate. The remaining solid was collected and dried in vacuo (17.7 g): mp 264.7–265.3 °C.

1-[4-[[2-*n*-Butyl-4,5-dicarbamoyl-1*H*-imidazol-1-yl]methyl]phenyl]-1*H*-pyrrole-2-carbonitrile (26). To a solution of the diamide **25** (2 g, 9.6 mmol) in dimethylformamide was added 9.6 mL of a 1 M solution of potassium *tert*-butoxide in tetrahydrofuran. The resulting mixture was stirred at 25 °C for 1 h, and 2.5 g of bromide **23** was added. After 5 h of stirring at 25 °C, the reaction mixture was concentrated in vacuo and the residue partitioned between water and ethyl acetate. The organic phase, upon concentration, gave 1.9 g of a white solid which was used in the next step without further purification.

5-[1-[4-[(2-*n*-Butyl-4,5-dicarbamoyl-1*H*-imidazol-1-yl)methyl]phenyl]-1*H*-pyrrol-2-yl]-1*H*-tetrazole (6). The nitrile **26** (1.9 g, 4.9 mmol) and trimethyltin azide (2.3 g, 1.2 equiv) were combined in a sealed tube with 5 mL of dimethylformamide and heated at 130 °C for 16 h. The crude product was purified by silica gel chromatography (eluant, 5 parts chloroform, 1 part methanol). The resulting product (1.5 g, 61% yield) was reprecipitated from a basic aqueous solution by addition of acid to afford, after drying, 850 mg of a white solid: mp 216–221 °C; NMR ($CDCl_3$) δ 7.95 (s, 1 H), 7.85 (s, 1 H), 7.55 (s, 1 H), 7.25 (m, 3 H), 7.1 (m, 2 H), 6.9 (d, J = 2.5 Hz, 1 H), 6.24 (t, J = 2.5 Hz, 1 H), 5.92 (s, 2 H), 2.68 (t, J = 7 Hz, 2 H), 1.65 (m, 2 H), 1.35 (m, 2 H), 0.9 (t, J = 7 Hz, 3 H); HRMS (MH^+) calcd for $C_{21}H_{23}N_9O_2$ 434.2053, found 434.2080. Anal. $C_{21}H_{23}N_9O_2 \cdot H_2O$: C, H, N.

1-[4-(Bromomethyl)phenyl]-3,5-dichloro-1*H*-pyrrole-2-carbonitrile (27). A 2.6-g (10-mmol) sample of 1-[4-(bromomethyl)phenyl]-1*H*-pyrrole-2-carbonitrile (**23**) was dissolved in a mixture of 50 mL of chloroform and 50 mL of methanol. While the mixture was stirred at 25 °C, 2.7 g (2 mmol) of *N*-chlorosuccinimide was added in one portion and the reaction allowed to stir for an additional 16 h. The solvent was removed, and the resulting solid was dissolved in dichloromethane and extracted three times with 1 M potassium carbonate. After drying ($MgSO_4$), the organic solution was concentrated in vacuum to an orange oil which solidified upon trituration with hexane. The slightly orange solid (1.35 g) was collected by filtration and dried: NMR ($CDCl_3$) δ 7.6 (m, 2 H), 7.35 (m, 2 H), 6.95 (s, 1 H), 4.55 (s, 2 H); FABMS calcd for $C_{12}H_7N_2Cl_2Br$ 328, found 328 (Br/Cl pattern).

1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-3,5-dichloro-1*H*-pyrrole-2-carbonitrile (28). In a flask under nitrogen, 0.71 g (3.9 mmol) of dibutyltriazole **22** was dissolved in 20 mL of dimethylformamide and treated with 3.9 mL of a 1 N solution of potassium *tert*-butoxide in tetrahydrofuran. The mixture was stirred at 25 °C for 15 min and 1.3 g (3.9 mmol) of nitrile **27** was added in one portion. After 4 h of stirring at 25 °C, the solvent was removed under vacuum and the residue partitioned between ethyl acetate and water. The organic phase was concentrated in vacuo to give 1.9 g of a solid: NMR ($CDCl_3$) δ 7.35 (m, 4 H), 6.95 (s, 1 H), 5.35 (s, 2 H), 2.7 (m, 4 H), 1.75 (m, 4 H), 1.35 (m, 4 H), 1.95 (t, J = 7 Hz, 3 H), 1.90 (t, J = 7 Hz, 3 H).

5-[1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-3,5-dichloro-1*H*-pyrrol-2-yl]-1*H*-tetrazole (8). The crude nitrile **28** (1.9 g, 4.4 mmol) was mixed with 115 g (5.8 mmol) of trimethyltin azide in a thick-wall ampula. The mixture was stirred for 16 h in a 110 °C oil bath. The solvent was removed in vacuo and a solid was obtained. The product was dissolved in 20 mL of chloroform and stirred with 5 g silica gel for 1 h. The solvent was removed in vacuo, leaving a free-flowing powder which was applied to a silica gel column and eluted with 5% methanol in chloroform. The fractions containing the desired material (R_f = 0.1) were collected and concentrated to yield 770 mg of a white powder. This material was dissolved in 4 mL of 1 N sodium hydroxide and 10 mL of water. Hydrochloric acid was slowly added to the solution until pH reached 2. The white precipitate was collected by filtration, dried, and recrystallized from boiling ethanol/water. The resulting solid weighed 450 mg: mp 164.9–166.4 °C; NMR ($CDCl_3$) δ 7.25 (m, 4 H), 6.95 (s, 1 H), 5.35 (s, 2 H), 2.65 (m, 4 H), 1.6 (m, 4 H), 1.3 (m, 4 H), 1.9 (t, J = 7 Hz, 3 H), 1.8 (t, 3 H); FABMS calcd for $C_{22}H_{28}N_8C_{12}$ 472.2 (monoisotropic), found 473 (M + H; Cl pattern). Anal. C, H, N.

1-(4-Methylphenyl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carbonitrile (29). A solution of 25 g of 1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (**14**), 5 g of mercury, 10 mL of pyridine, and 250 mL of acetonitrile was chilled under a nitrogen atmosphere to −78 °C while 25 g of trifluoromethyl iodide was added. The reactor was fitted with a quartz immersion well and the reaction mixture was photolyzed 90 h with a Hanovia medium-pressure 450-W mercury lamp at 20 °C. The reaction mixture was concentrated, filtered through Celite, and purified by HPLC on silica gel (5% ethyl acetate in hexane). The first product which eluted was the desired pyrrole (R_f ~0.7 in 10% ethyl acetate in hexane). A total of 9 g (35%) of solid was isolated: mp 77.5 °C; ^1H NMR ($CDCl_3$) δ 7.3 (m, 4 H), 6.95 (d, 1 H, J = 4.2 Hz), 6.85 (d, 1 H, J = 4.2 Hz), 2.47 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.09, 110.80 (q, $^4J_{CF}$ = 2.36 Hz), 111.87, 112.20 (q, $^3J_{CF}$ = 3.6 Hz), 118.50, 119.50 (q, $^1J_{CF}$ = 267.9 Hz), 126.96, 127.80 (q, $^2J_{CF}$ = 39 Hz), 129.84, 132.60, 140.44. Anal. C, H, N.

1-[4-(Bromomethyl)phenyl]-5-(trifluoromethyl)-1*H*-pyrrole-2-carbonitrile (30). To a mixture of 3.5 g (14 mmol) of 1-(4-methylphenyl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carbonitrile (**29**) in 150 mL of carbon tetrachloride was added 2.5 g (14 mmol) of *N*-bromosuccinimide followed by 3.6 mmol of AIBN. The reaction mixture was allowed to reflux for 5 h and cooled to 0 °C. The succinimide was removed by filtration and the filtrate concentrated in vacuo to an oil: NMR ($CDCl_3$) δ 7.55 (m, 3 H), 7.35 (d, 2 H), 7.05 (m, 1 H), 6.6 (m, 1 H), 4.45 (s, 2 H). Note: By NMR, this oil was 60% pure in monobromo nitrile. Some starting material (singlet at 2.4 ppm) and 4,4′-dibromo compound (singlet at 6.65 ppm) are present as contaminants.

1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-5-(trifluoromethyl)-1*H*-pyrrole-2-carbonitrile (31). In a flask under nitrogen, 1.5 g (8.3 mmol) of dibutyltriazole **22** was dissolved in 20 mL of dimethylformamide and treated with 1 equiv of a 1 N solution of potassium *tert*-butoxide in tetrahydrofuran. The mixture was stirred at 25 °C for 15 min and 2.37 g (8.3 mmol) of nitrile **30** added in one portion. After 15 h of stirring at 25 °C, the solvent was removed under vacuum and the residue partitioned between ethyl acetate and water. The organic phase was concentrated in vacuo to a oil which was purified by chromatography on a silica gel column eluted with ethyl acetate/hexane (1:1). The fractions containing the desired material (R_f ~0.5) were concentrated to an oil (1.4 g, 42%): NMR ($CDCl_3$) δ 7.3 (m, 4 H), 6.95 (d, 1 H, J = 4.2 Hz), 6.85 (d, 1 H, J = 4.2 Hz), 5.3 (s, 2 H), 2.65 (m, 4 H), 1.7 (m, 4 H), 1.35 (m, 4 H), 1.95 (t, J = 7 Hz, 3 H), 1.90 (t, J = 7 Hz, 3 H).

5-[1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-5-(trifluoromethyl)-1*H*-pyrrol-2-yl]-1*H*-tetrazole (9). The nitrile (1.4 g, 3.26 mmol) **31** was allowed to reflux with 720 mg (3.5 mmol) of trimethyltin azide in 5 mL of toluene. The mixture was stirred for 16 h at 130 °C and concentrated in vacuo to an oil. Methanol (150 mL) and silica gel (20 g) were added, and the mixture was stirred for 2 h at 25 °C. This mixture was purified by column chromatography (silica gel, methanol 5%–20% in chloroform). The free tetrazole derivative was slowly eluted with a gradient of 5–25% methanol in chloroform. The oil (0.7 g) slowly solidified on standing and was recrystallized from water/

ethanol as shining plates: mp 138.1–138.3 °C; NMR ($CDCl_3$) δ 7.34 (d, J = 7 Hz, 2 H), 7.18 (d, J = 7 Hz, 2 H), 6.96 (d, 1 H, J = 4.02 Hz), 1.95 (t, J = 7 Hz, 3 H), 1.85 (t, J = 7 Hz, 3 H), 6.82 (d, 1 H, J = 4.0 Hz), 5.25 (s, 2 H), 2.7 (m, 4 H), 1.7 (m, 2 H), 1.55 (m, 2 H), 1.4 (m, 2 H), 1.25 (m, 2 H). Anal. C, H, N.

5-Fluoro-1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (32). In a flask were combined 3.6 g (20 mmol) of 1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (14), 5 g (29 mmol) of XeF_2, and 80 mL of dichloromethane. The mixture was stirred for 48 h at 4 °C. After aqueous workup, the mixture was purified by reverse-phase high-pressure chromatography (C18 delta pak, 300 A, eluted with 1:1 mixture of acetonitrile/water containing 0.05% TFA). The first peak to elute was identified as the desired 5-fluoro-1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (1 g, 25%): NMR ($CDCl_3$) δ 7.3 (m, 4 H), 6.82 (dd, J_1 = 5.5 Hz, J_2 = 4 Hz, 1 H), 5.76 (t, J = 4 Hz, 1 H), 2.4 (s, 3 H).

5-Fluoro-1-[4-(bromomethyl)phenyl]-1*H*-pyrrole-2-carbonitrile (33). To a mixture of 700 mg (3.5 mmol) of 5-fluoro-1-(4-methylphenyl)-1*H*-pyrrole-2-carbonitrile (32) in 50 mL of carbon tetrachloride was added 3.2 mmol of *N*-bromosuccinimide followed by 3.2 mmol of AIBN. The reaction mixture was allowed to reflux for 4 h. The solution was cooled, succinimide was removed by filtration, and the filtrate was concentrated in vacuo to an oil which was determined by proton NMR to be a mixture containing about 75% of the desired monobromo derivative (CH_2-Br as a singlet at 4.5 ppm).

1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-5-fluoro-1*H*-pyrrole-2-carbonitrile (34). In a flask under nitrogen, 600 mg (3 mmol) of dibutyltriazole 22 was dissolved in 5 mL of dimethylformamide and treated with 80 mg (3 mmol) of NaH. The mixture was stirred at 25 °C for 15 min and a solution of the crude nitrile 33 in 2 mL of dry DMF was added in one portion. After 15 h of stirring at 25 °C, the solvent was removed under vacuum, and the residue was partitioned between chloroform and water. The organic phase was concentrated in vacuo to a oil which was purified by chromatography on a silica gel column eluted with ethyl acetate/hexane (1:2). The fractions containing the desired material were concentrated to an oil (400 mg): NMR ($CDCl_3$) δ 7.35 (m, 4 H), 6.65 (dd, J_1 = 4 Hz, J_2 = 5.5 Hz, 1 H), 5.75 (t, J = 4 Hz, 1 H), 5.35 (s, 2 H), 2.7 (m, 4 H), 1.65 (m, 4 H), 1.35 (m, 4 H), 1.9 (t, J = 7 Hz, 3 H), 1.85 (t, J = 7 Hz, 3 H); FABMS calcd for $C_{22}H_{26}FN_4$ 379, found 380 (M + H).

5-[1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-5-fluoro-1*H*-pyrrol-2-yl]-1*H*-tetrazole (10). The nitrile 34 (0.4 g, 1.09 mmol) was allowed to reflux with 400 mg (2 mmol) of trimethyltin azide in 10 mL of toluene. The mixture was stirred for 60 h at 100–110 °C. The solvent was removed in vacuo to a brown oil. Methanol (15 mL) and silica gel (2 g) were added, and the mixture was stirred for 2 h at 25 °C. The methanol was removed in vacuo and the resulting material was purified by column chromatography (silica gel, ethyl acetate). The free tetrazole derivative was slowly eluted as an oil (0.2 g) which was solubilized in 20 mL water by addition of 1 mL of 1 N NaOH. Upon acidification with 0.5 N HCl a gummy solid slowly separated. Trituration with ether gave 20 mg of a tan solid: mp 100.8–101.2 °C; NMR ($CDCl_3$) δ 7.35 (m, 4 H), 6.95 (t, J = 4.2 Hz, 1 H), 5.85 (t, J = 4.1 Hz, 1 H), 5.3 (s, 2 H), 3.2 (bs, exch), 2.7 (m, 4 H), 1.65 (m, 4 H), 1.35 (m, 4 H), 1.9 (t, J = 7 Hz, 3 H), 1.85 (t, J = 7 Hz, 3 H); FABMS calcd for $C_{22}H_{26}FN_8$ 422, found 423 (M + H), 242, 214; HRMS calcd for $C_{22}H_{26}FN_8 + H^+$ 423.2419, found 423.2421.

5-[1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-4-nitro-1*H*-pyrrol-2-yl]-1*H*-tetrazole (11). In a flask, under an argon atmosphere was dissolved 1 g (2.77 mmol) of the nitrile 24 in 10 mL of acetic anhydride. The solution was cooled to −20 °C and 0.5 mL (7.8 mmol) of 70% nitric acid was slowly added. The reaction was allowed to stir at −20 °C for 6 h and to come to room temperature over 1 h. Water was added and the resulting solution lyophilized. The residual solid was titurated with diethyl ether to remove any soluble material. The filtered solid 42 (380 mg, 0.93 mmol) was dissolved in 3 mL of toluene and 0.5 mL of DMF containing 1.5 equiv of trimethyltin azide and the solution heated at 120 °C for 16 h. The solvents were removed in vacuo, and the residue was purified by chromatography on a silica gel column [eluant: ethyl acetate/hexane (1:1)], giving 200 mg of an oil which was dissolved in 1 mL of 2.5 N NaOH and 50 mL of water. A solid precipitated upon the addition of HCl (0.5 N) to pH 2.5 which was filtered and dried: mp 167–183 °C with decomposition; FABMS calcd for $C_{22}H_{27}N_9O_2$ 449.2, found 450.2 (M + H^+). Anal. for $C_{22}H_{27}N_9O_2$: C, H, N.

1-(4-Methylphenyl)-3-formyl-1*H*-pyrrole (35). In 200 mL of acetic acid were combined 10.7 g (0.1 mol) of *p*-toluidine and 17.7 g (0.1 mol) of 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde (Aldrich, 90% pure). The mixture was allowed to reflux for 2 h, concentrated in vacuo to an oil, and redissolved in water/acetone; the pH was adjusted to pH 10 with 10% sodium hydroxide. Extraction with ethyl acetate, drying ($MgSO_4$), and concentration provided a brown oil which was filtered through a plug (200 g) of silica gel with chloroform as eluant. The desired material was obtained as a off-white solid (14.8 g, 76%) and used in the next step without further purification.

1-(4-Methylphenyl)-3-(oximinomethyl)-1*H*-pyrrole (36). The crude product 35 (14 g, 0.07 mol) was dissolved in 200 mL of methanol at reflux. An aqueous solution (50 mL) of hydroxylamine hydrochloride (5.3 g, 0.07 mol) and sodium carbonate (8.1 g, 0.07 mol) was slowly added and the resulting solution was allowed to reflux for 3 h after completion of addition. Upon dilution of the reaction mixture with 400 mL of water, a solid precipitated which was collected by filtration, washed with water, and air-dried.

1-(4-Methylphenyl)-1*H*-pyrrole-3-carbonitrile (37). The oxime 36 was allowed to reflux in 250 mL of acetic anhydride for 3 h. The reaction mixture was concentrated to an oil which was partitioned between ethyl acetate and water (pH = 8 with sodium hydroxide). The organic extract was purified by chromatography on silica gel (500 g of SiO_2, chloroform). Upon concentration of the desired fractions, a yellow solid (9.7 g) was obtained: NMR ($CDCl_3$) δ 7.65 (m, 1 H), 7.25 (m, 4 H), 6.95 (m, 1 H), 6.6 (m, 1 H), 2.4 (s, 3 H).

1-[4-(Bromomethyl)phenyl]-1*H*-pyrrole-3-carbonitrile (38). To a mixture of 5 g (27 mmol) of 1-(4-methylphenyl)-1*H*-pyrrole-3-carbonitrile (37) in 250 mL of carbon tetrachloride was added 4.9 g (27 mmol) of *N*-bromosuccinimide followed by 3.6 mmol of AIBN. The reaction mixture was allowed to reflux for 3 h and cooled overnight. The succinimide was removed by filtration and the filtrate concentrated in vacuo to give an oil. Trituration with hexane gave 5.4 g of solid product: NMR ($CDCl_3$) δ 7.55 (m, 3 H), 7.35 (d, J = 7 Hz, 2 H), 7.05 (m, 1 H), 6.6 (m, 1 H), 4.5 (s, 2 H). Note: Some starting material (singlet at 2.4 ppm) and 4,4′-dibromo compound (singlet at 6.65 ppm) were present as contaminants.

1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-1*H*-pyrrole-3-carbonitrile (39). In a flask under nitrogen, 0.7 g (3.9 mmol) of dibutyltriazole 22 was dissolved in 20 mL of dimethylformamide and treated with 4 mL of a 1 N solution of potassium *tert*-butoxide in tetrahydrofuran. The mixture was stirred at 25 °C for 15 min and 1.8 g (5 mmol) of the compound from step d was added in one portion. After 15 h of stirring at 25 °C, the solvent was removed under vacuum, and the residue was partitioned between chloroform and water. The organic phase was concentrated in vacuo to a oil which was purified by chromatography on a silica gel column eluted with chloroform. The fractions containing the desired material were concentrated to a solid (1.3 g, 92%): NMR ($CDCl_3$) δ 7.5 (m, 1 H), 7.3 (m, 4 H), 7.0 (m, 1 H), 6.6 (m, 1 H), 5.25 (s, 2 H), 2.7 (m, 4 H), 1.7 (m, 4 H), 1.37 (m, 4 H), 1.95 (t, J = 7 Hz, 2 H), 1.90 (t, J = 7 Hz, 3 H).

5-[1-[4-[(3,5-Dibutyl-1*H*-1,2,4-triazol-1-yl)methyl]phenyl]-1*H*-pyrrol-3-yl]-1*H*-tetrazole (7). A 1.0-g (2.8-mmol) sample of the nitrile 39 was allowed to reflux with 830 mg (4 mmol) of trimethyltin azide with 10 mL of toluene. The mixture was stirred at reflux temperature for 12 h. The solvent was removed in vacuo to a solid. This solid was dissolved in 20 mL of ethanol and stirred while anhydrous hydrogen chloride was bubbled into the solution. After 1 h, the addition was complete and the reaction mixture allowed to stir for an additional 15 h at room temperature. The solvent was removed in vacuo and the residue partitioned between ethyl acetate and water (pH = 9 with sodium carbonate). The aqueous phase was further extracted with ethyl acetate and acidified to pH 4 with dilute hydrochloric acid. The acid aqueous suspension was extracted with ethyl acetate, dried, and concentrated to a small volume. Trituration with hexane yielded 680

mg of a white solid: mp 143.5–144.1 °C; NMR ($CDCl_3$) δ 8.05 (s, 1 H), 7.7 (d, J = 7 Hz, 2 H), 7.55 (s, 1 H), 7.35 (d, J = 7 Hz, 2 H), 6.8 (s, 1 H), 5.35 (s, 2 H), 2.7 (t, J = 7 Hz, 2 H), 2.55 (t, J = 7 Hz, 2 H), 1.6 (m, 4 H), 1.3 (m, 4 H), 1.90 (t, J = 7 Hz, 3 H), 1.85 (t, J = 7 Hz, 3 H). Anal. for $C_{22}H_{28}N_8$: C, H, N.

Biology. Angiotensin II Receptor Binding. Compounds were tested for binding to angiotensin II receptors by measuring the inhibition of ^{125}I-angiotensin II binding to rat uterine membrane as described previously.

Antagonism of AII-Contracted Rabbit Aorta Rings. The compounds were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2–2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue, and then cut into 3-mm ring segments. For the measurement of antagonistic activity, paired rings from the same rabbits were used; one was exposed to increasing concentrations of AII, (at 30-min intervals), and a second ring was exposed to increasing concentrations of AII in the presence of the test compound which was added 5 min prior to the addition of AII. The concentration–response curves for AII in the presence of the antagonist were evaluated in terms of the percent of the maximal contraction of the control ring exposed only to AII. pD_2 values for AII were calculated from the AII concentration–response curves while pA_2s were determined by Schild analysis.[37]

In Vivo Assay. Male Sprague-Dawley rats weighing 225–300 g were anesthetized with Inactin (100 mg/kg ip), and catheters were implanted into the trachea, femoral artery, femoral vein, and duodenum. Arterial pressure was recorded from the femoral artery catheter on a Gould chart recorder (Gould, Cleveland, OH). The femoral vein catheter was used for injections of mecamylamine and atropine. The tracheal catheter allowed for airway patency and the duodenal catheter was used for intraduodenal (id) administration of test compounds. After surgery, the rats were allowed to equilibrate for 30 min. Mecamylamine (3 mg/kg) and atropine (400 μg/kg) were then given iv to produce ganglion blockade. These compounds were administered every 90 min throughout the test procedure. After 1–2 h of stable base-line recording, the intravenous infusion of angiotensin II (50 ng/kg per min) was given at a rate of 9.6 μL/min. After allowing 1 h for pressure to stabilize, the test compound was administered id. Arterial pressure was monitored for 3 h postdosing. The angiotensin II infusion was then discontinued, and pressure was allowed to reach a stable recovery level.

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