Nonpeptide Angiotensin II Antagonists Derived from 1*H*-Pyrazole-5-carboxylates and 4-Aryl-1*H*-imidazole-5-carboxylates[1]

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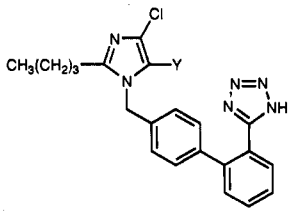
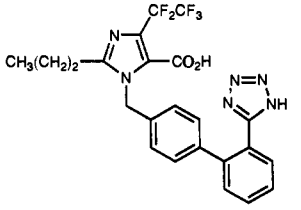
Two series of potential angiotensin II antagonists derived from carboxyl-functionalized "diazole" heterocycles have been prepared and evaluated. Initially, a limited investigation of 4-arylimidazole-5-carboxylates led to 2-*n*-butyl-4-(2-chlorophenyl)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (**12b**), which was found to be a highly potent antagonist of the rabbit aorta AT_1 receptor (IC_{50} 0.55 nM). In conscious, normotensive rats, **12b** at 0.1 mg/kg iv inhibited the pressor response to AII by 88%, with a duration of >6 h. More extensively studied was an isosteric series of 3-alkyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylates bearing aryl, alkyl, or aralkyl substituents at N^1. These compounds were available in highly regioselective fashion via condensation of a substituted hydrazine hydrochloride with a 2-(methoxyimino)-4-oxoalkanoate intermediate. In vitro, the most potent pyrazolecarboxylic acids had *n*-butyl at C^3 and were substituted at N^1 by such groups as 2,6-dichlorophenyl (**19h**), 2-(trifluoromethyl)phenyl (**19k**), benzyl (**19t**), and phenethyl (**19u**), all with IC_{50} values of 0.18–0.24 nM. Although less potent in the receptor assay, 3-*n*-propylpyrazolecarboxylic acids were at least as effective as their butyl counterparts in vivo. Several of the pyrazolecarboxylic acid derivatives demonstrated potent, long-lasting oral activity in rats. At 1 mg/kg po, the 1-benzyl-3-butyl (**19t**), 1-(2,6-dichlorophenyl)-3-propyl (**19v**), 3-propyl-1-(2,2,2-trifluoroethyl) (**19y**), and 1-benzyl-3-propyl (**19z**) analogues all gave ≥75% inhibition of the AII pressor response in the rat model, with duration of action >23 h.

The peptide hormone angiotensin II (AII) is responsible for multiple physiological effects, such as vasoconstriction and stimulation of aldosterone release.[2,3] As such, it is critically involved in homeostatic mechanisms to regulate blood pressure, electrolyte balance, and fluid volume. AII is regarded as a major mediator of hypertensive disorders, including essential hypertension.[4] Consequently, the renin–angiotensin system (RAS) is a prime target for cardiovascular disease therapy. Inhibitors of angiotensin-converting enzyme (ACE), which transforms the decapeptide angiotensin I (AI) to the octapeptide AII, are widely used for the treatment of hypertension and congestive heart failure.[5] Bradykinin and substance P, among other peptides, can also serve as substrates for ACE, and this represents a potential source of side effects for ACE inhibitors.[6] Renin, the enzyme which generates AI from its precursor, angiotensinogen, is highly specific, and potent antihypertensive activity has been demonstrated experimentally for renin inhibitors.[7] Still, the goal of a marketable renin inhibitor drug has not yet been realized. Problems with limited oral absorption and rapid biliary excretion have been difficult to overcome for this class of peptide or peptide-like molecules.[7]

An alternative strategy for blockade of the RAS is antagonism of AII at its receptor site.[8–11] Two receptor subtypes, designated AT_1 and AT_2,[12] have been identified in a variety of human and animal tissues.[13,14] At the present time, the G-protein-linked AT_1 receptor subtype appears to be the site of the major physiological functions of AII.[14] Numerous peptide antagonists of AII have been reported, but these compounds, typified by saralasin, characteristically suffer from lack of oral activity, short duration of action, and partial agonism.[8] Prototype imidazole-based nonpeptide AII antagonists were first discovered by the Takeda group.[15,16] Investigators at Du Pont have developed this lead into a series of potent and selective AII antagonists epitomized by the clinical candidate losartan (DuP 753; MK-954; 1a)[17–19] and its higher-affinity carboxy metabolite, EXP3174 (**1b**).[18,20] Another imidazolecarboxylic acid, DuP 532 (**2**), was reported to be a more active antihypertensive agent than losartan, with a similar or longer duration of action.[21,22] Novel nonpeptide AII antagonist structures have recently been reported by several laboratories.[11,23]



1a, Y = CH_2OH
1b, Y = CO_2H



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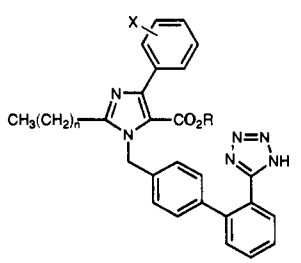

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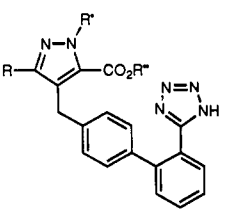

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We had found potent AII antagonist activity in a series of appropriately substituted N^2-aryltriazolin-3-ones.[24] We

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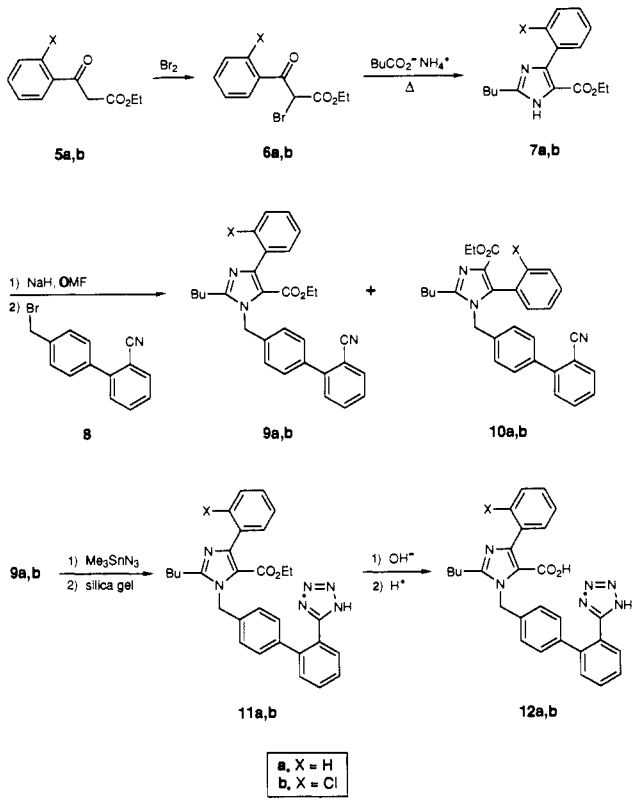
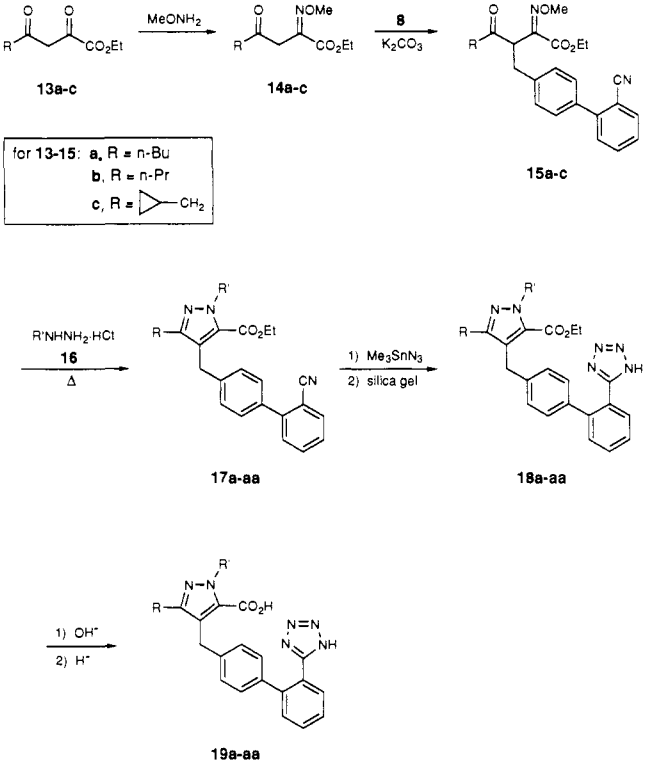
Scheme I



Scheme II



were therefore interested in examining the related 4-arylimidazole-5-carboxylates **3**. A limited investigation into compounds of structure **3** was curtailed after the appearance of a Du Pont patent application[25] that generically covered this class. Consequently, our efforts were redirected toward an isosteric series of 1-substituted 3-alkyl-4-[[2′-(5-tetrazolyl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylates **4**. Independently, studies of some pyrazolecarboxylates of this type have been reported by the Glaxo group.[26] Synthetic routes to **3** and **4**, and their structure–activity relationships with respect to AII antagonism, are described below.

Chemistry

The synthesis of 4-arylimidazole-5-carboxylates corresponding to structure **3** is illustrated in Scheme I. The β-keto ester **5** (commercially available or prepared by the method of Wierenga and Skulnick[27]) was α-brominated under mild conditions[28] to give **6**. Cyclization to the imidazole **7** was accomplished by heating **6** with a large excess of ammonium valerate.[29] This afforded **7a** (X = H) in modest yield (23%). The 2-chlorophenyl analogue **7b**, however, was obtained only in very low yield (5%),[30] demonstrating the unfavorable effect of the *ortho* substituent on the ring closure.

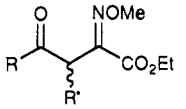
Alkylation of **7** with **8**[18] in the presence of sodium hydride furnished a mixture of two readily separated regioisomers, **9** and **10**. In the phenyl series, the desired product **9a** and its regioisomer **9b** were obtained in a ratio of approximately 4:3. The isomers **9a** and **10a** were assigned unambiguously on the basis of NOE difference spectroscopy. Irradiation of the benzylic methylene protons of **9a** resulted in enhancement only of the signals arising from the flanking biphenyl protons and from the protons on C^1 and C^2 of the butyl side chain. Similar irradiation of **10a** produced enhancement of an additional aromatic signal, presumably from the *ortho* protons of the imidazole phenyl substituent. These results were consistent with alkylation adjacent to the carboxylate in **9a** and adjacent to the phenyl ring in **10a**.

It was hoped that the bulk of the *o*-chloro substituent of **7b** would help direct the alkylation to the desired site adjacent to the carboxylate. Surprisingly, alkylation adjacent to the aromatic ring was the predominant reaction in this case, with **10b** being favored over **9b** by a ratio of about 3:1 on the basis of isolated yields. While the reasons are unclear for this unexpected product ratio, the preferred site of alkylation on the imidazole may reflect a delicate balance of countervailing electronic and steric factors. Although **9b** and **10b** were not studied by NOE spectroscopy, the markedly higher TLC R_f and pronounced downfield shift of the ^{1}H NMR signal for the benzylic methylene group in **9b** relative to **10b** exactly paralleled the results for **9a** and **10a**.

The remainder of the synthetic sequence was straightforward. Transformation of the nitrile in **9a,b** to tetrazole by heating with trimethyltin azide[18,31,32] followed by destannylation with silica gel[33,34] afforded **11a,b**. Finally, saponification of the ethyl ester gave the imidazolecarboxylic acids **12a,b**.

For the synthesis of compounds of type **4** (Scheme II), we adapted our regioselective route to 3-alkyl-1-aryl-1*H*-pyrazole-5-carboxylates.[35] Treatment of the 2,4-diketo ester **13**[36,37] with methoxyamine hydrochloride in the presence of 3-Å molecular sieves[38] selectively yielded the 2-(methoxyimino) product **14**, which was separated from a minor amount of 2,4-bis(methoxyimino) contaminant.[35] Reaction of **14** with the bromomethyl intermediate **8** in DMF in the presence of potassium carbonate gave the C-alkylated product **15**. Intermediates **14** and **15** are listed in Table I. Upon heating **15** with a substituted hydrazine salt (usually the hydrochloride), ring closure to the

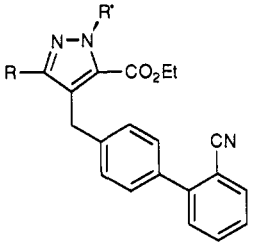
Table I. Physical Properties of 2-(Methoxyimino)-4-oxo Ester Intermediates



no.	R	R′	% yield[a]	mp, °C	formula[b]	FAB-MS, *m/e* (M + H)$^+$
14a	*n*-Bu	H	52[c]	oil[c]	$C_{11}H_{19}NO_4$[c]	230[c]
14b	*n*-Pr	H	37	oil	$C_{10}H_{17}NO_4$[d]	216
14c	c-PrCH$_2$	H	26[e]	oil	$C_{11}H_{17}NO_4 \cdot 0.2CH_2Cl_2$	228
15a	*n*-Bu	2′-CN-biphenyl-4-yl-CH$_2$	56	62–63	$C_{25}H_{28}N_2O_4$	421
15b	*n*-Pr	2′-CN-biphenyl-4-yl-CH$_2$	63	oil	$C_{24}H_{26}N_2O_4 \cdot 0.2CH_2Cl_2$	407
15c	c-PrCH$_2$	2′-CN-biphenyl-4-yl-CH$_2$	63	oil	$C_{25}H_{26}N_2O_4 \cdot 0.2CH_2Cl_2$	419

[a] See the Experimental Section for representative procedures. [b] Analyses for C, H, and N within ±0.4% except as indicated. [c] Data from ref 34. [d] Characterized spectroscopically. [e] The 2,4-diketo ester precursor was prepared by the method of ref 35 from 1-cyclopropyl-2-propanone (Hanack, M.; Ensslin, H. M. Cyclopropane Derivatives. X. Homologation of Cyclopropyl Ketones with Diazomethane. *Liebigs Ann. Chem.* **1966**, *697*, 100–110).

Table II. Physical Properties of Ethyl 1*H*-Pyrazole-5-carboxylate Intermediates



no.	R	R′	% yield[a]	mp, °C	formula[b]	FAB-MS, *m/e* (M + H)$^+$
17a	*n*-Bu	Ph	66	gum	$C_{30}H_{29}N_3O_2$	464
17b	*n*-Bu	Ph(2-Cl)	74	gum	$C_{30}H_{28}ClN_3O_2 \cdot 0.1CH_2Cl_2$	498
17c	*n*-Bu	Ph(3-Cl)	63	oil	$C_{30}H_{28}ClN_3O_2 \cdot CH_2Cl_2$	498
17d	*n*-Bu	Ph(4-Cl)	69	oil	$C_{30}H_{28}ClN_3O_2 \cdot 0.1CH_2Cl_2$	498
17e	*n*-Bu	Ph(2,3-Cl$_2$)	63[c]	oil	$C_{30}H_{27}Cl_2N_3O_2 \cdot 0.25C_6H_{14}$	532
17f	*n*-Bu	Ph(2,4-Cl$_2$)	75	gum	$C_{30}H_{27}Cl_2N_3O_2$	532
17g	*n*-Bu	Ph(2,5-Cl$_2$)	77	oil	$C_{30}H_{27}Cl_2N_3O_2$	532
17h	*n*-Bu	Ph(2,6-Cl$_2$)	74	gum	$C_{30}H_{27}Cl_2N_3O_2$	532
17i	*n*-Bu	Ph(2,4,6-Cl$_3$)	69	oil	$C_{30}H_{26}Cl_3N_3O_2$	566
17j	*n*-Bu	Ph(2-Me)	70	gum	$C_{31}H_{31}N_3O_2$	478
17k	*n*-Bu	Ph(2-CF$_3$)	48	gum	$C_{31}H_{28}F_3N_3O_2$	532
17l	*n*-Bu	Ph(2-NO$_2$)	62	oil	$C_{30}H_{28}N_4O_4$	509
17m	*n*-Bu	Ph(4-OMe)	30	oil	$C_{31}H_{31}N_3O_3$[d]	494
17n	*n*-Bu	Ph(2-NO$_2$-4-OMe)	14	oil	$C_{31}H_{30}N_4O_5$[e]	539
17o	*n*-Bu	biphenyl-2-yl	59	oil	$C_{36}H_{33}N_3O_2 \cdot 0.3CH_2Cl_2$	540
17p	*n*-Bu	2-pyridyl	69	oil	$C_{29}H_{28}N_4O_2 \cdot 0.05CH_2Cl_2$	465
17q	*n*-Bu	H	59	gum	$C_{24}H_{25}N_3O_2$	388
17r	*n*-Bu	Et	40	oil	$C_{26}H_{29}N_3O_2 \cdot 0.1CH_2Cl_2$	416
17s	*n*-Bu	CH$_2$CF$_3$	37	oil	$C_{28}H_{26}F_3N_3O_2$	470
17t	*n*-Bu	CH$_2$Ph	30	oil	$C_{31}H_{31}N_3O_2$[e]	478
17u	*n*-Bu	(CH$_2$)$_2$Ph	27	oil	$C_{32}H_{33}N_3O_2$[e]	492
17v	*n*-Pr	Ph(2,6-Cl$_2$)	67	oil	$C_{29}H_{25}Cl_2N_3O_2 \cdot 0.4CH_2Cl_2$	518
17w	*n*-Pr	Ph(2-CF$_3$)	67	oil	$C_{30}H_{26}F_3N_3O_2 \cdot 0.075CH_2Cl_2$	518
17x	*n*-Pr	H	55	oil	$C_{28}H_{23}N_3O_2$	374
17y	*n*-Pr	CH$_2$CF$_3$	40	oil	$C_{25}H_{24}F_3N_3O_2$	456
17z	*n*-Pr	CH$_2$Ph	27	oil	$C_{30}H_{29}N_3O_2$[e]	464
17aa	c-PrCH$_2$	Ph(2,6-Cl$_2$)	54	oil	$C_{30}H_{25}Cl_2N_3O_2 \cdot 0.3CH_2Cl_2$	530

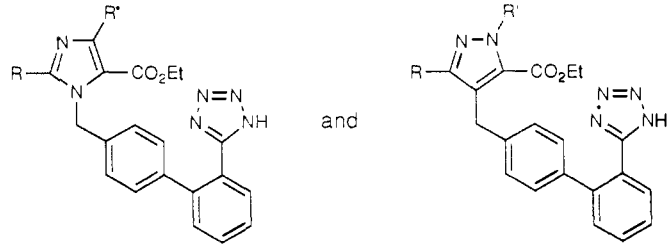
[a] See the Experimental Section for representative procedures. [b] Analyses for C, H, and N within ±0.4% except as indicated. [c] Hexane/EtOAc elution used for column chromatography. [d] N: calcd, 8.51; found, 7.79. [e] Characterized spectroscopically.

pyrazolecarboxylate **17** (Table II) occurred. In each case a single regioisomer was isolated.

Our earlier model study[35] had demonstrated that reaction of **14a** with phenylhydrazine hydrochloride under these conditions favored the 1*H*-pyrazole-5-carboxylate isomer over the 1*H*-pyrazole-3-carboxylate by a ratio of at least 6:1. Structural assignments had been made unambiguously on the basis of NOE difference spectroscopy. Irradiation of the methylene protons of the butyl group adjacent to the pyrazole ring had resulted in a strong aromatic proton signal enhancement in the minor 1*H*-pyrazole-3-carboxylate isomer, whereas no such enhancement was observed for the major isomer. A similar study on **17a** demonstrated no NOE effect, confirming that, in the 4-alkylated series, the favored product was the desired 1*H*-pyrazole-5-carboxylate isomer.

Yields in the cyclization were highest for arylhydrazines, averaging 65% (except for 4-methoxyaryl, in which case the average was 22%). Hydrazine itself gave a yield of 57%, while alkyl- and aralkylhydrazines led to moderate yields, averaging 34%. It is possible that the lower yields for alkyl- and aralkylhydrazines could reflect a change in the isomer ratio, although there was no evidence of this from TLC. The remainder of the sequence to form the tetrazole derivatives **18** (Table III), and subsequent

Table III. Physical Properties and in Vitro AII Antagonist Potencies of Ethyl 1*H*-Imidazole- and 1*H*-Pyrazole-5-carboxylates



11 18

no.	ring[a]	R	R'	% yield[b]	mp, °C	formula[c]	FAB-MS, *m/e* $(M + H)^+$	rabbit aorta AT_1 IC_{50}, nM
1a	Im		(losartan)					40
11a	Im	*n*-Bu	Ph	74	>70 (gradual)	$C_{30}H_{30}N_6O_2$	507.2525[d]	41
11b	Im	*n*-Bu	Ph(2-Cl)	70	glass	$C_{30}H_{29}ClN_6O_2$[e]	541	NT[f]
18a	Py	*n*-Bu	Ph	76	>60 (gradual)	$C_{30}H_{30}N_6O_2$	507	81
18b	Py	*n*-Bu	Ph(2-Cl)	65	>70 (gradual)	$C_{30}H_{29}ClN_6O_2$	541	13
18c	Py	*n*-Bu	Ph(3-Cl)	62	>90 (gradual)	$C_{30}H_{29}ClN_6O_2 \cdot 0.5MeOH$	541	55
18d	Py	*n*-Bu	Ph(4-Cl)	69	>95 (gradual)	$C_{30}H_{29}ClN_6O_2 \cdot 0.75MeOH$[g]	541	100
18e	Py	*n*-Bu	Ph(2,3-Cl_2)	51	>65 (gradual)	$C_{30}H_{28}Cl_2N_6O_2 \cdot MeOH \cdot 0.05CH_2Cl_2$	575	90
18f	Py	*n*-Bu	Ph(2,4-Cl_2)	77	>70 (gradual)	$C_{30}H_{28}Cl_2N_6O_2 \cdot 0.75MeOH$	575	6.7
18g	Py	*n*-Bu	Ph(2,5-Cl_2)	80	>70 (gradual)	$C_{30}H_{28}Cl_2N_6O_2$	575	105
18h	Py	*n*-Bu	Ph(2,6-Cl_2)	51	>80 (gradual)	$C_{30}H_{28}Cl_2N_6O_2$	575	8
18i	Py	*n*-Bu	Ph(2,4,6-Cl_3)	76	>70 (gradual)	$C_{30}H_{27}Cl_3N_6O_2 \cdot 0.8MeOH$	609	37
18j	Py	*n*-Bu	Ph(2-Me)	69	>60 (gradual)	$C_{31}H_{32}N_6O_2 \cdot 0.1CH_2Cl_2$	521	13
18k	Py	*n*-Bu	Ph(2-CF_3)	66	>80 (gradual)	$C_{31}H_{29}F_3N_6O_2$	575	21
18l	Py	*n*-Bu	Ph(2-NO_2)	83	>65 (gradual)	$C_{30}H_{29}N_7O_4 \cdot 0.4CH_2Cl_2$	552	9.5
18m	Py	*n*-Bu	Ph(4-OMe)	66	>65 (gradual)	$C_{31}H_{32}N_6O_3 \cdot 0.4MeOH$	537	20
18n	Py	*n*-Bu	Ph(2-NO_2-4-OMe)	63	oil	$C_{31}H_{31}N_7O_5$[e]	582	NT[f]
18o	Py	*n*-Bu	biphenyl-2-yl	86	>60 (gradual)	$C_{36}H_{34}N_6O_2$	583.2839[h]	23
18p	Py	*n*-Bu	2-pyridyl	51	>65 (gradual)	$C_{29}H_{29}N_7O_2 \cdot 0.6CH_2Cl_2$	508	18
18q	Py	*n*-Bu	H	47	>100 (gradual)	$C_{24}H_{26}N_6O_2 \cdot 0.05H_2O \cdot 0.15CH_2Cl_2$	431	130
18r	Py	*n*-Bu	Et	35	glass	$C_{26}H_{30}N_6O_2$[e]	459	NT[f]
18s	Py	*n*-Bu	CH_2CF_3	65	>45 (gradual)	$C_{26}H_{27}F_3N_6O_2$	513	30
18t	Py	*n*-Bu	CH_2Ph	47	>75 (gradual)	$C_{31}H_{32}N_6O_2 \cdot 0.15CH_2Cl_2$	521	>100
18u	Py	*n*-Bu	$(CH_2)_2Ph$	31	oil	$C_{32}H_{34}N_6O_2$[e]	535	NT[f]
18v	Py	*n*-Pr	Ph(2,6-Cl_2)	85	>70 (gradual)	$C_{29}H_{26}Cl_2N_6O_2 \cdot 0.7H_2O$	561	20
18w	Py	*n*-Pr	Ph(2-CF_3)	58	>85 (gradual)	$C_{30}H_{27}F_3N_6O_2 \cdot 0.1MeOH$	561	56
18x	Py	*n*-Pr	H	62	>85 (gradual)	$C_{23}H_{24}N_6O_2$	416.1990[i]	160
18y	Py	*n*-Pr	CH_2CF_3	50	>125 (gradual)	$C_{25}H_{25}F_3N_6O_2 \cdot 0.2MeOH$	499	76
18z	Py	*n*-Pr	CH_2Ph	44	glass	$C_{30}H_{30}N_6O_2$[e]	507	22
18aa	Py	c-$PrCH_2$	Ph(2,6-Cl_2)	46	>70 (gradual)	$C_{30}H_{28}Cl_2N_6O_2 \cdot 0.7CH_2Cl_2$	573	76

[a] Im = imidazole; Py = pyrazole. [b] See the Experimental Section for representative procedures. [c] Analyses for C, H, and N within ±0.4% except where characterized by high-resolution FAB-MS or otherwise indicated. [d] Calcd for $C_{30}H_{31}N_6O_2$ $(M + H)^+$: 507.2508. [e] Characterized spectroscopically. [f] NT = not tested. [g] N: calcd, 14.87; found, 14.22. [h] Calcd for $C_{36}H_{35}N_6O_2$ $(M + H)^+$: 583.2821. [i] EI-HRMS. Calcd for $C_{23}H_{24}N_6O_2$ (M^+): 416.1961.

hydrolysis of the ester to give the pyrazolecarboxylic acids **19** (Table IV), followed Scheme I.

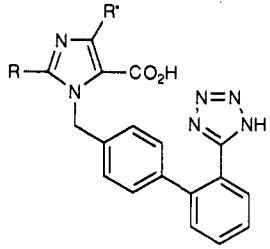
Biological Results and Discussion

In Vitro AII Antagonism. The imidazolecarboxylate and pyrazolecarboxylate esters (**11**, **18**; Table III) and acids (**12**, **19**; Table IV) were evaluated as AII antagonists by displacement of [^{125}I]Sar^{1}Ile^8-AII at the rabbit aorta AT_1 receptor as previously described.[33,39] The 4-phenylimidazole ethyl ester **11a** was comparable to losartan in binding affinity. The corresponding carboxylic acid **12a** was 20-fold more potent, having an IC_{50} value of about 2 nM. This level of potency is similar to that of the reference imidazolecarboxylic acids **1b** and **2**. The 2-chlorophenyl analogue **12b** was still more potent, with IC_{50} 0.55 nM. We had previously observed a strong potency enhancement upon introduction of an *o*-chloro (or similar) substituent on a similarly placed phenyl group in a series of triazolinone AII antagonists.[24] The effect of the chloro substituent is less dramatic here, but this might be expected since the unsubstituted 4-phenylimidazole-5-carboxylic acid **12a** is intrinsically more potent than the corresponding phenyltriazolinone by about 1 order of magnitude.

The structure–activity relationships of the pyrazolecarboxylate esters **18** (Table III) will not be discussed in detail. IC_{50} values were mostly in the 10–100 nM range and to some extent mirrored the activity trends of the more potent acids **19**. A few of the esters were fairly effective AII antagonists in their own right. For example, the 2,4-dichlorophenyl (**18f**), 2,6-dichlorophenyl (**18h**), and 2-nitrophenyl (**18l**) derivatives possessed IC_{50} values ≤10 nM and were therefore superior to losartan in this binding assay.

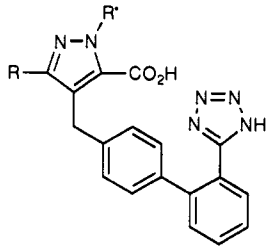
The parent 3-butyl-1-phenylpyrazole-5-carboxylic acid **19a** (Table IV) was similar in potency to the isosteric imidazole **12a**. As in the imidazole series, an *o*-chloro substituent on the phenyl ring boosted potency, in this case by 8-fold to a 0.35 nM IC_{50} for **19b**. Chloro substitution at the meta position (**19c**) had essentially a neutral effect, whereas the *p*-chloro derivative **19d** was about twice as active as **19a**. In our earlier triazolinone work,[24] a similar potency order of *ortho* > *para* > *meta* had been observed for chloro substituents, with *meta* and *para* actually being detrimental in that series. Several di- or trichloro derivatives **19e–i** were evaluated. Except for 2,5-dichloro (**19g**, IC_{50} 3.2 nM), all were subnanomolar

Table IV. Physical Properties and in Vitro AII Antagonist Potencies of 1*H*-Imidazole- and 1*H*-Pyrazole-5-carboxylic Acids



12

and



19

no.	ring[a]	R	R′	% yield[b]	mp, °C	formula[c]	FAB-MS, *m/e* (M + H)$^+$	rabbit aorta AT$_1$ IC$_{50}$, nM
1b	Im		(EXP3174)					2.8
2	Im		(DuP 532)					1.1
12a	Im	*n*-Bu	Ph	66	198–200 dec	$C_{28}H_{26}N_6O_2 \cdot 0.6H_2O$	479	2.1
12b	Im	*n*-Bu	Ph(2-Cl)	93	245–246 dec	$C_{28}H_{25}ClN_6O_2 \cdot 0.25H_2O$	513	0.55
19a	Py	*n*-Bu	Ph	92	>115 (gradual)	$C_{28}H_{26}N_6O_2 \cdot 0.6H_2O$	479	2.9
19b	Py	*n*-Bu	Ph(2-Cl)	96	>125 (gradual)	$C_{28}H_{25}ClN_6O_2 \cdot 0.5H_2O$	513	0.35
19c	Py	*n*-Bu	Ph(3-Cl)	96	>105 (gradual)	$C_{28}H_{25}ClN_6O_2 \cdot H_2O$	513	2.3
19d	Py	*n*-Bu	Ph(4-Cl)	97	>110 (gradual)	$C_{28}H_{25}ClN_6O_2$	513	1.3
19e	Py	*n*-Bu	Ph(2,3-Cl$_2$)	88	>120 (gradual)	$C_{28}H_{24}Cl_2N_6O_2 \cdot 0.8H_2O$	547	0.77
19f	Py	*n*-Bu	Ph(2,4-Cl$_2$)	93	>120 (gradual)	$C_{28}H_{24}Cl_2N_6O_2 \cdot 0.5H_2O$	547	0.6
19g	Py	*n*-Bu	Ph(2,5-Cl$_2$)	88	>105 (gradual)	$C_{28}H_{24}Cl_2N_6O_2 \cdot 1.75H_2O$	547	3.2
19h	Py	*n*-Bu	Ph(2,6-Cl$_2$)	87	>130 (gradual)	$C_{28}H_{24}Cl_2N_6O_2 \cdot 0.4H_2O$	547	0.18
19i	Py	*n*-Bu	Ph(2,4,6-Cl$_3$)	99	>125 (gradual)	$C_{28}H_{23}Cl_3N_6O_2$	581.1010[d]	0.5
19j	Py	*n*-Bu	Ph(2-Me)	91	>125 (gradual)	$C_{29}H_{28}N_6O_2 \cdot 0.6H_2O$	493	0.46
19k	Py	*n*-Bu	Ph(2-CF$_3$)	90	>125 (gradual)	$C_{29}H_{25}F_3N_6O_2$	547	0.24
19l	Py	*n*-Bu	Ph(2-NO$_2$)	82	>115 (gradual)	$C_{28}H_{25}N_7O_4$	524	1.7
19m	Py	*n*-Bu	Ph(4-OMe)	82	>105 (gradual)	$C_{29}H_{26}N_6O_3 \cdot 0.4H_2O$	509	0.8
19n	Py	*n*-Bu	Ph(2-NO$_2$-4-OMe)	67	>80 (gradual)	$C_{29}H_{27}N_7O_5$	554.2159[e]	2.5
19o	Py	*n*-Bu	biphenyl-2-yl	59	>110 (gradual)	$C_{34}H_{30}N_6O_2 \cdot 0.7H_2O$	555	0.64
19p	Py	*n*-Bu	2-pyridyl	85	189–191	$C_{27}H_{25}N_7O_2 \cdot 0.3MeOH$	480	1.7
19q	Py	*n*-Bu	H	93	205.5–207	$C_{22}H_{22}N_6O_2 \cdot 0.95H_2O$	403	2
19r[f]	Py	*n*-Bu	Et	89	>100 (gradual)	$C_{24}H_{28}N_6O_2 \cdot 0.4H_2O$	431	2.7
19s[f]	Py	*n*-Bu	CH_2CF_3	88	>95 (gradual)	$C_{24}H_{23}F_3N_6O_2 \cdot 0.6H_2O$	485	0.52
19t	Py	*n*-Bu	CH_2Ph	85	>95 (gradual)	$C_{29}H_{28}N_6O_2 \cdot 0.8H_2O$	493	0.2
19u	Py	*n*-Bu	$(CH_2)_2Ph$	81	>85 (gradual)	$C_{30}H_{30}N_6O_2 \cdot 0.5MeOH$	507	0.24
19v	Py	*n*-Pr	Ph(2,6-Cl$_2$)	69	>130 (gradual)	$C_{27}H_{22}Cl_2N_6O_2$	533	0.69
19w	Py	*n*-Pr	Ph(2-CF$_3$)	84	>125 (gradual)	$C_{28}H_{28}F_3N_6O_2 \cdot 0.7H_2O$	533	0.67
19x	Py	*n*-Pr	H	93	>135 (gradual)	$C_{21}H_{20}N_6O_2$	389.1716[g]	3.6
19y	Py	*n*-Pr	CH_2CF_3	83	>125 (gradual)	$C_{23}H_{21}F_3N_6O_2 \cdot 0.1H_2O$	471	1.6
19z	Py	*n*-Pr	CH_2Ph	83	>205 (gradual)	$C_{28}H_{26}N_6O_2 \cdot 0.3H_2O$	479	0.42
19aa	Py	c-PrCH$_2$	Ph(2,6-Cl$_2$)	84	>130 (gradual)	$C_{28}H_{22}Cl_2N_6O_2 \cdot H_2O$	545	3.7

[a] Im = imidazole; Py = pyrazole. [b] See the Experimental Section for representative procedures. [c] Analyses for C, H, and N within ±0.4% except where characterized by high-resolution FAB-MS. [d] Calcd for $C_{28}H_{24}Cl_3N_6O_2$ (M + H)$^+$: 581.1026. [e] Calcd for $C_{29}H_{28}N_7O_5$ (M + H)$^+$: 554.2152. [f] This compound has also been reported (without physical properties) in ref 26. [g] Calcd for $C_{21}H_{21}N_6O_2$ (M + H)$^+$: 389.1726.

antagonists, and the 2,6-dichloro derivative **19h** was exceptionally potent (IC$_{50}$ 0.18 nM).

Other small, hydrophobic *ortho* substituents with differing electronic properties, namely, methyl (**19j**) and trifluoromethyl (**19k**), were very effective, the latter being one of the most potent compounds in the series (IC$_{50}$ 0.24 nM). A more polar *ortho* substituent, nitro, alone (**19l**) or in combination with 4-methoxy (**19n**), had a relatively neutral or deleterious effect in comparison with **19a** and **19m**, respectively. This is in contrast to the triazolinone series,[24] where 2-nitro and 4-methoxy-2-nitro derivatives were especially favored. A considerable degree of bulk tolerance at the *ortho* position is evident, judging from the good activity of biphenyl-2-yl at N^1 (**19o**). Replacement of phenyl at the 1-position of the pyrazole by 2-pyridyl (**19p**) had little effect. Surprisingly, pyrazole **19q**, bearing no substituent at N^1, was comparable in potency to the *N*^{1}-phenyl derivative **19a**. This implies that the phenyl moiety at N^1 is not participating in significant binding interactions, except when appropriately substituted. Introduction of an ethyl group at N^1 (**19r**) did not increase potency over **19q**. The more hydrophobic and somewhat larger trifluoroethyl derivative **19s**, however, did show significant benefit. This side chain is analogous to the pentafluoroethyl group in **2**. Aralkyl substituents at N^1 are apparently even more effective in contacting a hydrophobic site on the receptor. Both the benzyl (**19t**) and phenethyl (**19u**) derivatives had IC$_{50}$ values of approximately 0.2 nM, equalling the best of the *N*^{1}-aryl derivatives. These results are consistent with our previous proposals[24,33] for an important hydrophobic receptor interaction at some distance from this region of the heterocycle.

Next, replacements of the butyl side chain at the 3-position of the pyrazole were examined. All members of the 3-propyl series (**19v–z**) were about 2–4-fold less potent in vitro than their butyl counterparts. Nevertheless, subnanomolar potency was still obtained for the 2,6-dichlorophenyl (**19v**), 2-(trifluoromethyl)phenyl (**19w**), and benzyl (**19z**) analogues. One analogue with cyclopropylmethyl at the pyrazole 3-position (**19aa**) had a reduction in potency of about 5-fold compared to propyl (**19v**) and about 20-fold compared to butyl (**19h**).

In Vivo Pharmacology. Many of the imidazole- and pyrazolecarboxylic acid derivatives, as well as a few of the esters, were evaluated as inhibitors of the pressor response to exogenous AII in conscious, normotensive rats (Table

Table V. Inhibition of AII Pressor Resonse by Imidazole and Pyrazole Derivatives in Conscious, Normotensive Rats

no.	dose, mg/kg (route)	peak inhib, % (mean ± SEM)	duration,[a] h (mean ± SEM)	N^b
1a (losartan)	1 (iv)	78 ± 6	>6	4
	0.3 (iv)	52 ± 6	5.5 ± 0.5	4
	3 (po)	94 ± 2	>4.5	4
	0.3 (po)	36 ± 8	>3.5	2
1b (EXP3174)	0.3 (iv)	100 ± 0	>29	2
	0.1 (iv)	63 ± 10	~4	4
	1 (po)	72 ± 10	>7	2
	0.3 (po)	63 ± 4	2.8 ± 2.6	2
12a	3 (iv)	100	>24	1
	0.3 (iv)	84 ± 11	4.0 ± 1	2
12b	0.1 (iv)	88 ± 4	>6	2
	0.3 (po)	50 ± 16	0.4 ± 0.2	2
18b	1 (iv)	43 ± 8	ND[c]	2
	1 (po)	50 ± 5	>2.5	2
18h	1 (iv)	16 ± 1	NA[d]	2
18q	1 (iv)	80 ± 3	>5	2
19a	1 (iv)	96 ± 1	>6	2
19b	1 (iv)	93 ± 4	>6	2
	0.3 (iv)	73 ± 11	~3.8	2
	1 (po)	64 ± 4	>3	2
19h	0.1 (iv)	80 ± 10	>4.5	2
	1 (po)	79 ± 4	>4.5	2
19k	1 (iv)	100 ± 0	5.3 ± 0.8	2
	0.1 (iv)	57 ± 1	3.5 ± 1.5	2
19q	1 (iv)	94 ± 5	>6	2
19t	0.1 (iv)	68 ± 12	>5	4
	1 (po)	100 ± 0	>24	2
	0.3 (po)	75 ± 11	>3	2
19u	1 (iv)	95 ± 3	>24	2
19v	1 (iv)	100 ± 0	>6	2
	0.1 (iv)	60 ± 10	5.4 ± 0.4	2
	1 (po)	87 ± 7	>23	2
	0.3 (po)	56 ± 12	>3	2
19w	1 (iv)	100 ± 0	>6	2
	0.3 (iv)	77 ± 12	~4	2
	1 (po)	71 ± 4	>3.5	2
	0.3 (po)	57 ± 7	>3.5	2
19y	0.3 (iv)	93 ± 8	>24	2
	0.1 (iv)	62 ± 4	~5	2
	1 (po)	75 ± 5	>23	2
	0.3 (po)	66 ± 1	>3	2
	0.1 (po)	54 ± 16	~2	2
19z	0.3 (iv)	95 ± 5	>24	2
	1 (po)	100 ± 0	>23	2
	0.3 (po)	82 ± 1	>4	2

[a] Time from onset of action until significant (i.e., ≥30%) inhibition of pressor response is no longer observed. [b] Number of animals treated. [c] ND = not determined. [d] NA = not active.

V). The imidazolecarboxylic acids **12a,b**, when administered intravenously, were highly effective and long-acting in this system. In terms of peak inhibition and duration of action, **12b** was superior to **1b** at 0.1 mg/kg iv (Figure 1a). By oral administration, however, **12b** was less active than **1b**. Nevertheless, **12b** displayed very respectable oral efficacy at 1 mg/kg. The isosteric pyrazolecarboxylic acids **19a,b** appeared to require somewhat higher doses to achieve the same effects as **12a,b**. Further modification of the *N*-aryl substituent in these pyrazoles led to enhanced efficacy. The excellent in vitro potency of the 2,6-dichlorophenyl analogue **19h** was reflected in its in vivo activity at the low dose of 0.1 mg/kg iv. A 10-fold higher dose orally produced equivalent effects. The 2-(trifluoromethyl)phenyl analogue **19k** was also active at 0.1 mg/kg iv.

Impressive potency and duration were seen for the aralkyl derivatives **19t,u**. In fact, the benzyl analogue **19t** appeared superior to losartan and **1b** at multiple dose levels. Several compounds (**19v,w,y,z**) with propyl in place of butyl at C^3 of the pyrazole had excellent in vivo activity, better than might have been expected from their IC_{50} values. Compounds **19v** and **19y** had good activity at 0.1 mg/kg iv, and all four were effective at 0.3 mg/kg po. The N^1-(trifluoroethyl) compound **19y** showed modest activity even at 0.1 mg/kg orally. In our rat model, the benzyl analogue **19z** at 1 mg/kg po was superior to **1b** at the same dose level and was comparable to losartan (**1a**) at 3 mg/kg po (Figure 1b).

A few pyrazolecarboxylate esters were also tested in vivo on the grounds that they might serve as prodrugs for the carboxylic acids. A comparison of **18b** vs **19b**, **18h** vs **19h**, and **18q** vs **19q** (Table V) reveals that the effectiveness of the ester is very dependent on the nature of the substituent at N^1. Although the intact esters had measurable affinity for the AII receptor (Table III), this did not correlate with antagonism of the AII pressor response. In fact, upon iv administration to the rat, the order of efficacy of the esters (**18q** > **18b** > **18h**) was inversely related to their in vitro potencies (IC_{50} 130 nM for **18q**). Therefore, the in vivo activity of the three esters may be attributable, at least in part, to conversion to the acid metabolite. By the intravenous route, only **18q** (hydrogen at N^1) displayed good activity at 1 mg/kg, approaching that of the acid **19q**. The contrast between **18h** and **19h** is particularly striking, suggesting that the bulky 2,6-dichlorophenyl substituent may render the adjacent ester relatively inert to metabolic cleavage. Although the ester **18b** (2-chlorophenyl) was clearly inferior to the acid **19b** by the intravenous route, it was only modestly less active than **19b** after oral administration. This may reflect better absorption of the monoacidic ester compared to the diacid. Indeed, **18b** was unusual in being at least as effective orally as intravenously.

Conclusions

Two tetrasubstituted 5-membered heterocyclic systems were prepared and evaluated as angiotensin II antagonists in vitro and in vivo. Some 4-aryl-1*H*-imidazole-5-carboxylates were studied initially. Subsequently investigated was a more extensive series of 1-substituted 3-alkyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylates, synthesized by a regioselective route. In both the imidazolecarboxylate and pyrazolecarboxylate series, the ethyl esters were generally at least 1 order of magnitude less potent intrinsically than the corresponding carboxylic acids as AII receptor antagonists. This is in accordance with previous proposals[18,40] that a carboxylic acid at this position on the heterocycle is a key participant in receptor binding through either ionic or hydrogen-bonding interactions. Still, it was shown that certain pyrazolecarboxylate esters are active in vivo and may serve as prodrugs, provided that the adjacent substituent at N^1 is not so bulky as to obstruct the hydrolysis to the acid. In principle, a monoacidic prodrug could represent an expedient approach to improving the oral bioavailability of the diacidic imidazoles **12** and pyrazoles **19**.

The 4-aryl-2-*n*-butyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acids **12a,b** were shown to be potent AII antagonists at the AT_1 AII receptor. When intravenously administered to conscious, normotensive rats, **12a,b** inhibited the AII pressor response at low dose levels (0.1 mg/kg for **12b**) and with a long duration of action. Another utility has been reported previously for compound **12b** (also known as L-158,854); its HPLC

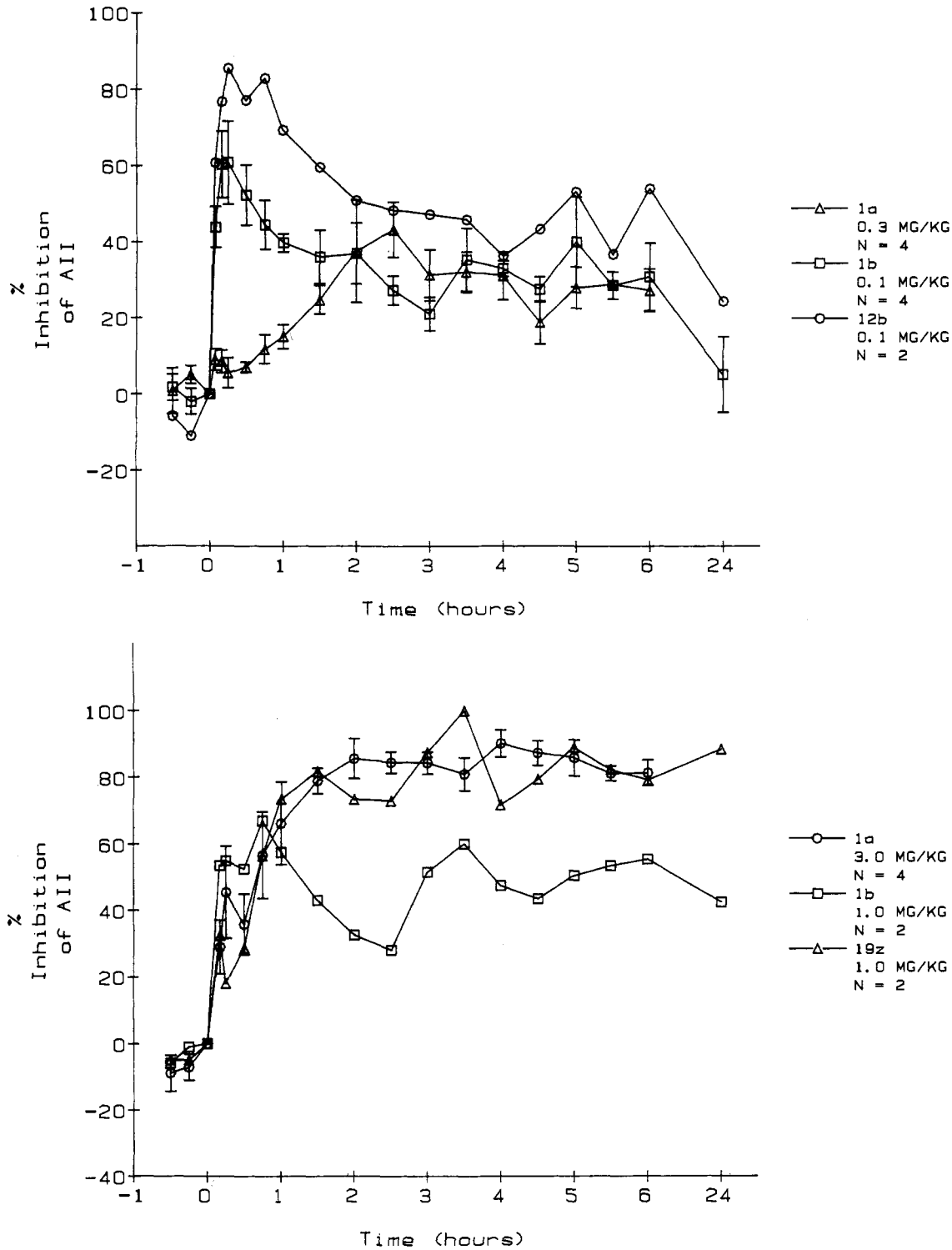


Figure 1. Percent inhibition of AII pressor response in conscious, normotensive rats. (See the Experimental Section for details.) (a, top) Intravenous administration of imidazole **12b** and reference compounds **1a** (losartan) and **1b** (EXP3174). (b, bottom) Oral administration of pyrazole **19z** and reference compounds **1a** (losartan) and **1b** (EXP3174). Mean values were determined from the indicated number of animals (N). Standard error bars are displayed where $N > 2$.

properties led to its selection as the internal standard for the quantitative determination of losartan and its metabolite **1b** in human plasma and urine.[41]

Like the isosteric imidazoles, the pyrazolecarboxylic acids **19** were potent AII receptor antagonists. Because these compounds represent, in effect, a transposition of N^1 and C^4 of the imidazoles, it can be concluded that the imidazole N^1 is not involved in specific binding interactions. Most potent in vitro were those pyrazoles substituted at the 3-position with *n*-butyl and at the 1-position with either (a) phenyl bearing at least one small, hydrophobic *ortho* substituent or (b) aralkyl, such as benzyl or phenethyl. For in vivo activity, especially preferred substituents at N^1 included 2,6-dichorophenyl, benzyl, and 2,2,2-trifluoroethyl. Although pyrazoles with *n*-propyl at C^3 were less potent in vitro, they appeared to be at least as active as their *n*-butyl counterparts in the rat model, with **19z** being an outstanding example. Several of the pyrazolecarboxylic acid derivatives, by oral and intravenous administration, demonstrated powerful and long-

lasting inhibition of the AII pressor response in rats, comparing favorably to the reference compounds losartan and 1b.

Excellent in vivo antihypertensive activity has recently been disclosed by Middlemiss and co-workers[26] for an analogous pyrazolecarboxylic acid with *n*-butyl at C^3 and (cyclopropylmethyl) at N^1. This compound was reported effective at 1 mg/kg po in lowering blood pressure for up to 48 h in renal artery ligated hypertensive rats. Because of the different test systems used, it is not possible to make direct comparisons between the compounds in the present investigation and those in the Glaxo communication. Nevertheless, the studies from both laboratories make it clear that C-linked pyrazolecarboxylic acids represent an important class of potent, orally active AII antagonists with a long duration of action.

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes with a Thomas-Hoover apparatus. ^{1}H NMR spectra were recorded on Varian XL-400, XL-300, or XL-200 spectrometers, using tetramethylsilane as internal standard. Positive ion fast atom bombardment (FAB) or electron-impact (EI) mass spectra (MS) were obtained on Varian MAT 731, JEOL HX110, and Varian MAT 212 instruments. Column chromatography was carried out on EM Science silica gel 60 (70–230 mesh) or grade 62 (60–200 mesh) for gravity columns and silica gel 60 (230–400 mesh) for flash columns. Compounds showed satisfactory purity by TLC on Analtech silica gel GF plates (visualized by UV light at 254 nm and/or I_2) in the indicated solvent systems. Elemental combustion analyses, where indicated only by the elements, were within ±0.4% of theoretical values. Many of the compounds unavoidably analyzed as solvates, owing to their tendency to retain solvent under nondestructive drying conditions. Where solvation is indicated, the presence of solvent in the analytical sample was verified by NMR. Microanalyses were performed by the laboratory of Mrs. Jane T. Wu at Merck or by Robertson Microlit Laboratories, Madison, NJ.

Dry tetrahydrofuran (THF) was obtained by distillation from sodium/benzophenone ketyl under N_2. Dry dimethyl sulfoxide (DMSO) was withdrawn directly from Pierce silylation grade Hypo-vials, or HPLC grade DMSO was dried over 4-Å molecular sieves. Reagent-grade CH_2Cl_2, MeOH, and EtOH were dried over 3-Å molecular sieves. Glassware was oven- or flame-dried for moisture-sensitive reactions. Reactions were routinely conducted under N_2 (bubbler) unless otherwise indicated.

Ethyl 2-Bromo-2-(2-chlorobenzoyl)acetate (6b). A solution of 6.80 g (30 mmol) of ethyl 2-(2-chlorobenzoyl)acetate (**5b**)[27] in 15 mL of CCl_4 was stirred at room temperature as a solution of 1.70 mL (5.28 g, 33 mmol) of bromine in 7.5 mL of CCl_4 was added dropwise over a period of 2 h. After 29 h at room temperature, the mixture was evaporated under a stream of N_2. The residual oil was taken up in Et_2O and washed successively with aqueous 5% $NaHSO_3$, saturated $NaHCO_3$ (2×), H_2O, and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 7.11 g (78%) of a light golden-yellow oil, suitable for use without further purification. By NMR, the material appeared to exist as a mixture of keto (major) and enol (minor) forms: TLC (9:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25, 1.39 (major and minor t, J = 7.1 Hz, total 3 H), 4.26, 4.35 (major and minor q, J = 7.1 Hz, total 2 H), 5.76 (s, <1 H), 7.3–7.6 (m, 4 H); FAB-MS *m/e* 305, 307 $(M + H)^+$.

Ethyl 2-Benzoyl-2-bromoacetate (6a). By the procedure used for **6b**, this material was obtained in 90% yield as a light golden-orange oil: TLC (9:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7 Hz, 3 H), 4.25 (q, J = 7 Hz, 2 H), 5.63 (s, 1H), 7.4–7.65 (m, 3 H), 7.97 (d, J = 8 Hz, 2 H).

Ethyl 2-*n*-Butyl-4-(2-chlorophenyl)-1*H*-imidazole-5-carboxylate (7b). Under a drying tube, a solution of 15.2 mL (14.3 g, 140 mmol) of valeric acid in 90 mL of dry MeOH was stirred in an ice bath as a stream of NH_3 gas was passed through it until the solution was saturated. The solution was then placed in a lukewarm water bath and evaporated under a stream of N_2. By the next day, the residue, which had largely solidified, was treated with 6.94 g (22.7 mmol) of **6b** (washed in with some Et_2O). The mixture was transferred to a lukewarm water bath and stirred as the Et_2O was removed under a stream of N_2. The flask was fitted with a condenser, and the evaporation residue was stirred and heated in an oil bath at 100 °C for 2 h. The mixture was partitioned between EtOAc and a 1:1 mixture of concentrated NH_4OH and H_2O. The organic phase was washed successively with 1:1 concentrated NH_4OH/H_2O, followed by H_2O. Next, the product was extracted three times with 2 N HCl. The combined HCl fractions were cooled and treated gradually with excess concentrated NH_4OH, resulting in separation of an oil, which was extracted with EtOAc. The EtOAc layer was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo at ≤50 °C. The residual oil was chromatographed (gradient elution with 0.3–2% iPrOH in CH_2Cl_2) to yield, after vacuum-drying, 378 mg (5.4%)[30] of a slightly cloudy, light golden-orange gum: TLC in 99:1 CH_2Cl_2/iPrOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H), 1.39 (m, 2 H), 1.75 (m, 2 H), 2.81 (t, J = 7.8 Hz, 2 H), 4.18 (q, J = 7.1 Hz, 2 H), 7.27–7.32 (m, 2 H), 7.40–7.45 (m, 2 H); FAB-MS *m/e* 307 $(M + H)^+$.

Ethyl 2-*n*-Butyl-4-phenyl-1*H*-imidazole-5-carboxylate (7a). Ammonium valerate was prepared in situ and reacted with **6a** as described for **7b**. The crude product was chromatographed twice (gradient elution with 0.5–1% MeOH in CH_2Cl_2) to give a 23% yield of **7a** as a light orange gum: TLC in 98:2 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.5 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 1.40 (m, 2 H), 1.74 (m, 2 H), 2.76 (t, J = 8 Hz, 2 H), 4.29 (q, J = 7 Hz, 2 H), 7.3–7.4 (m, 3 H), 7.87 (d, J = 8 Hz, 2 H), 9.6 (br m, 1 H); FAB-MS *m/e* 273 $(M + H)^+$.

Ethyl 2-*n*-Butyl-4-(2-chlorophenyl)-1-[(2′-cyanobiphenyl-4-yl)methyl]-1*H*-imidazole-5-carboxylate (9b) and Ethyl 2-*n*-Butyl-5-(2-chlorophenyl)-1-[(2′-cyanobiphenyl-4-yl)methyl]-1*H*-imidazole-4-carboxylate (10b). To a suspension of 64 mg (1.6 mmol) of sodium hydride (60% in oil) in 0.9 mL of dry DMF, stirred in an ice–H_2O bath, was added by syringe, over 20 min, a solution of 368 mg (1.2 mmol) of **7b** in 2.4 mL of DMF (**CAUTION**: H_2 evolution). When the addition was complete, the mixture was allowed to warm to room temperature. After 1 h, by which time gas evolution had ceased, 435 mg (1.6 mmol) of 4′-(bromomethyl)-2-biphenylcarbonitrile (**8**)[18] was added, and stirring was continued at room temperature for 1.5 h. Then the mixture was made slightly acidic by careful addition of a few drops of glacial AcOH and then partitioned between Et_2O and H_2O. The Et_2O phase was washed three times with H_2O and dried over $MgSO_4$. The filtered solution was concentrated in vacuo. The residual oil was chromatographed first on a column (gradient elution with 9:1 to 5:1 hexane/EtOAc) and then on six 1000-μm preparative TLC plates (developed in 2:1 hexane/EtOAc). The product bands were isolated, combined, and extracted with EtOAc. Concentration of the extracts followed by vacuum-drying at 100 °C yielded 102 mg (17%) of **9b** as a pale, golden-yellow glass: TLC in 2:1 hexane/EtOAc (R_f 0.6); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88, 0.90 (overlapping t, J = 7.4, 7.1 Hz, each 3 H), 1.37 (m, 2 H), 1.73 (m, 2 H), 2.81 (br m, 2 H), 4.03 (q, J = 7.1 Hz, 2 H), 5.68 (s, 2 H), 7.15 (d, J = 8.1 Hz, 2 H), 7.24–7.30 (m, 2 H), 7.38–7.48 (m, 4 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.62, (m, 1 H), 7.75 (d, J = 7.7 Hz, 1 H); FAB-MS *m/e* 498 $(M + H)^+$.

In another run, the initial column was eluted with a gradient of 0.25–2% MeOH in CH_2Cl_2. The first product eluted was further purified as above to give a 16% yield of **9b**. The second (lower R_f) product to be eluted was isolated and vacuum-dried to give a 52% yield of **10b** as a glass: TLC in 2:1 hexane/EtOAc (R_f 0.2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7.5 Hz, 3 H), 1.12 (t, J = 7 Hz, 3 H), 1.35 (m, 2 H), 1.73 (m, 2 H), 2.70 (t, J = 8 Hz, 2 H), 4.20 (q, J = 7 Hz, 2 H), 4.88 (d, J = 17 Hz, 1 H), 5.06 (d, J = 17 Hz, 1 H), 6.94 (d, J = 8 Hz, 2 H), 7.1–7.5 (m, 8 H), 7.62, (m, 1 H), 7.74 (d, J = 8 Hz, 1 H); FAB-MS *m/e* 498 $(M + H)^+$.

Ethyl 2-*n*-Butyl-1-[(2′-cyanobiphenyl-4-yl)methyl]-4-phenyl-1*H*-imidazole-5-carboxylate (9a) and Ethyl 2-*n*-Butyl-1-[(2′-cyanobiphenyl-4-yl)methyl]-5-phenyl-1*H*-imidazole-4-carboxylate (10a). The alkylation of **7a** with **8** was conducted as described above for **9b/10b**. The crude product was chromatographed twice (first elution with $CHCl_3$ to remove nonpolar

impurities, second elution with a gradient of 9:1 to 1:1 hexane/EtOAc) afforded a 24% yield of **9a** as a nearly colorless gum: TLC in 4:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.5 Hz, 3 H), 1.04 (t, J = 7 Hz, 3 H), 1.37 (m, 2 H), 1.75 (m, 2 H), 2.70 (t, J = 8 Hz, 2 H), 4.09 (q, J = 7 Hz, 2 H), 5.61 (s, 2 H), 7.15 (d, J = 8 Hz, 2 H), 7.3–7.7 (m, 10 H), 7.75 (d, J = 8 Hz, 1 H); FAB-MS m/e 464 $(M + H)^+$.

The second product isolated from the final column amounted to a 17% yield of **10a** as a nearly colorless wax: TLC in 1:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, J = 7.5 Hz, 3 H), 1.18 (t, J = 7 Hz, 3 H), 1.33 (m, 2 H), 1.69 (m, 2 H), 2.62 (t, J = 8 Hz, 2 H), 4.21 (q, J = 7 Hz, 2 H), 5.00 (s, 2 H), 6.93 (d, J = 8 Hz, 2 H), 7.2–7.5 (m, 9 H), 7.62 (m, 1 H), 7.74 (d, J = 8 Hz, 1 H); FAB-MS m/e 464 $(M + H)^+$.

Ethyl 2-*n*-Butyl-4-(2-chlorophenyl)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (11b). A mixture of 97.1 mg (0.195 mmol) of **9b**, 144 mg (0.7 mmol) of trimethyltin azide,[31] and 1 mL of dry toluene was stirred at reflux for 54 h and then concentrated in vacuo. The residual foam was treated with 3 mL of dry MeOH and warmed until a nearly clear solution was achieved. To this was added 1.0 g of silica gel, and the mixture was stirred at room temperature in a stoppered flask for 2 h. After being concentrated (finally under oil pump at 30 °C), the residual dry powder was added as a slurry in CH_2Cl_2 to a column of silica gel. Gradient elution with 1–5% MeOH in CH_2Cl_2 afforded 86 mg (82%) of an off-white, stiff foam: TLC in 9:1 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H), 1.34 (m, 2 H), 1.66 (m, 2 H), 2.43 (br m, 2 H), 3.94 (q, J = 7.1 Hz, 2 H), 5.56 (s, 2 H), 6.87 (d, J = 8.1 Hz, 2 H), 7.0–7.2 (m, 6 H), 7.35–7.40 (m, 2 H), 7.49–7.59 (m, 2 H); FAB-MS m/e 541 $(M + H)^+$.

2-*n*-Butyl-4-(2-chlorophenyl)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (12b). To a solution of 82.4 mg (0.152 mmol) of **11b** in 1.22 mL of MeOH was added 0.61 mL (1.52 mmol) of 2.5 N NaOH (aqueous). The flask was fitted with a condenser, and the mixture was stirred in an oil bath at 60 °C for 3 h. The cooled solution was filtered, diluted with 15 mL of H_2O, and treated gradually with 2 N HCl to bring the pH just below 2. Precipitation occurred during the acidification. After several minutes, the solid was collected on a filter and washed thoroughly with dilute HCl (pH 2). The product was dried under suction overnight and then in vacuo (oil pump) at 100 °C for several hours to give 75.8 mg (97%) of a white powder: mp 251–252 °C dec; TLC in 90:10:1 CH_2Cl_2/MeOH/AcOH; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.80 (t, J = 7.3 Hz, 3H), 1.26 (m, 2 H), 1.54 (m, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 5.64 (s, 2 H), 6.99 (d, J = 8.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 7.3–7.7 (m, 8 H), 12.5 (br m, 1 H); FAB-MS m/e 513 $(M + H)^+$. Anal. ($C_{25}H_{25}ClN_6O_2$) C, H, N.

Ethyl 2-(Methoxyimino)-4-oxoheptanoate (14b). A mixture of 2.11 g (11.3 mmol) of ethyl 2,4-dioxoheptanoate (**13b**),[36] 758 mg (9.07 mmol) of methoxyamine hydrochloride, 9.0 g of 3-Å molecular sieves, and 11 mL of absolute EtOH was stirred at room temperature in a stoppered flask for 22 h. The reaction mixture was filtered through Celite, and the filter cake was washed with additional EtOH. The combined filtrate and washings were concentrated to give a red oil, which was dissolved in Et_2O and shaken with saturated aqueous $NaHCO_3$. The organic phase was washed twice with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residual oil was chromatographed (gradient elution with 3–10% EtOAc in hexane) to yield 723 mg (37%, based on methoxyamine hydrochloride) of a light yellow oil: TLC in 9:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 7.4 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.50 (m, 2 H), 2.35 (t, J = 7.3 Hz, 2 H), 3.58 (s, 2 H), 3.93 (s, 3 H), 4.21 (q, J = 7.1 Hz, 2 H); FAB-MS m/e 216 $(M + H)^+$.

Ethyl 3-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(methoxyimino)-4-oxooctanoate (15a). A mixture of 4.08 g (17.8 mmol) of ethyl 2-(methoxyimino)-4-oxooctanoate (**14a**),[35] 5.70 g (17.8 mmol, based on 85% purity) of 4′-(bromomethyl)-2-biphenylcarbonitrile (**8**),[18] 2.95 g (21.4 mmol) of freshly pulverized, anhydrous K_2CO_3, and 50 mL of dry DMF was stirred vigorously at room temperature for 24 h and then partitioned between EtOAc and 0.2 N HCl. The EtOAc phase was washed three times with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. The viscous residual oil was column chromatographed (gradient elution with 5–10% EtOAc in hexane) to give 4.56 g of a colorless gum, suitable for use without further purification. After prolonged standing at room temperature, the material had partially crystallized and was induced to crystallize fully upon trituration with petroleum ether, affording a 56% yield of white crystals: mp 62–63 °C; TLC in 4:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.3 Hz, 3 H), 1.23 (t, J = 7.1 Hz) overlapping 1.2–1.3 (m, 2 H), 1.53 (m, 2 H), 2.31 (t, J = 7.5 Hz, 2 H), 2.98 (dd, J = 13.9, 9.5 Hz, 1 H), 3.42 (dd, J = 13.9, 5.5 Hz, 1 H), 3.98 (s, 3 H), 4.18–4.29 (m, 3 H), 7.23 (d, J = 7.9 Hz, 2 H), 7.37–7.45 (m, 4 H), 7.60 (m, 1 H), 7.72 (d, J = 7.7 Hz, 1 H); FAB-MS m/e 421 $(M + H)^+$. Anal. ($C_{25}H_{28}N_2O_4$) C, H, N.

Ethyl 3-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(methoxyimino)-4-oxoheptanoate (15b). Alkylation of **14b** with **8** according to the procedure for **15a** gave a 63% yield of **15b** as a colorless oil: TLC in 3:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, J = 7.4 Hz, 3 H), 1.20 (t, J = 7.1 Hz), 1.56 (m, 2 H), 2.27 (t, J = 7.2 Hz, 2 H), 2.96 (dd, J = 13.9, 9.5 Hz, 1 H), 3.41 (dd, J = 13.9, 5.5 Hz, 1 H), 3.94 (s, 3 H), 4.15–4.27 (m, 3 H), 7.20 (d, J = 7.6 Hz, 2 H), 7.34–7.42 (m, 4 H), 7.56 (m, 1 H), 7.68 (d, J = 7.7 Hz, 1 H); FAB-MS m/e 407 $(M + H)^+$. Anal. ($C_{24}H_{28}N_2O_4 \cdot 0.2CH_2Cl_2$) C, H, N.

Ethyl 3-*n*-Butyl-1-(2,6-dichlorophenyl)-4-[(2′-cyanobiphenyl-4-yl)methyl]-1*H*-pyrazole-5-carboxylate (17h). A mixture of 147 mg (0.35 mmol) of **15a**, 224 mg (1.05 mmol) of 2,6-dichlorophenylhydrazine hydrochloride, 2 mL of glacial AcOH, and 1 mL of 2-methoxyethanol was stirred in an oil bath at 105 °C for 45 h. The cooled solution was concentrated in vacuo, and the dark orange residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H_2O and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated. Column chromatography of the residue (elution with 5% and then 7.5% EtOAc in hexane) afforded 137 mg (74%) of a light orange gum: TLC in 4:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, J = 7.3 Hz, 3 H), 1.00 (t, J = 7.1 Hz), 1.31 (m, 2 H), 1.56 (m, 2 H), 2.62 (t, J = 7.7 Hz, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 4.26 (s, 2 H), 7.24–7.50 (m, 9 H), 7.61 (m, 1 H), 7.74 (d, J = 7.6 Hz, 1 H); FAB-MS m/e 532 $(M + H)^+$. Anal. ($C_{30}H_{27}Cl_2N_3O_2$) C, H, N.

Ethyl 4-[(2′-Cyanobiphenyl-4-yl)methyl]-3-*n*-propyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carboxylate (17y). Following the procedure described above for **17h**, **15b** was reacted with 2,2,2-trifluoroethylhydrazine (70% in H_2O; 3 equiv), except that concentrated HCl (3 equiv) was also added. After 24 h at 105 °C, the mixture was worked up as for **17h**. Chromatographic purification (elution with 85:15 hexane/EtOAc) afforded a 40% yield of **17y** as a pale yellow oil: TLC in 3:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3 H), 1.20 (t, J = 7.2 Hz), 1.58 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 4.13 (s, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 5.23 (q, J = 8.3 Hz, 2 H), 7.17 (d, J = 8.1 Hz, 2 H), 7.38–7.48 (m, 4 H), 7.61 (m, 1 H), 7.73 (dd, J = 7.7, 1.5 Hz, 1 H); FAB-MS m/e 456 $(M + H)^+$. Anal. ($C_{25}H_{24}F_3N_3O_2$) C, H, N.

Ethyl 3-*n*-Butyl-1-(2,6-dichlorophenyl)-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylate (18h). The reaction of **17h** with trimethyltin azide was carried out as described for **11b** to provide a 51% yield of **18h** as a very pale yellow-tan, stiff foam: mp >80 °C (gradual); TLC in 9:1 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 7.2 Hz, 3 H), 1.00 (t, J = 7.1 Hz), 1.36 (m, 2 H), 1.63 (m, 2 H), 2.66 (t, J = 7.6 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.28 (s, 2 H), 7.15–7.7 (m, 10 H), 8.26 (d, J = 7.6 Hz, 1 H); FAB-MS m/e 575 $(M + H)^+$. Anal. ($C_{30}H_{28}Cl_2N_6O_2$) C, H, N.

Ethyl 3-*n*-Propyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carboxylate (18y). By the method used for **11b**, **17y** was reacted with trimethyltin azide to give a 50% yield of **18y** as a colorless glass, which could be transformed to a powder upon scraping: mp >125 °C (gradual); TLC in 9:1 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.4 Hz, 3 H), 1.25 (t, J = 7.1 Hz), 1.58 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 4.13 (s, 2 H), 4.31 (q, J = 7.1 Hz, 2 H), 5.21 (q, J = 8.2 Hz, 2 H), 7.14 (m, 4 H), 7.38 (d, J = 7.4, 1.6 Hz, 1 H), 7.54 (m, 2 H), 8.20 (dd, J = 7.7, 1.2 Hz, 1 H); FAB-MS m/e 499 $(M + H)^+$. Anal. ($C_{25}H_{25}F_3N_6O_2 \cdot 0.2MeOH$) C, H, N.

3-n-Butyl-1-(2,6-dichlorophenyl)-4-[[2'-(1H-tetrazol-5-yl-)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic Acid (19h). Saponification of **18h** according to the procedure described for **12b** afforded an 87% yield of **19h** as a white powder: mp >130 °C (gradual, with preliminary softening); TLC in 9:1 CH_2Cl_2/MeOH; ^1H NMR (DMSO-d_6, 400 MHz) δ 0.77 (t, J = 7.3 Hz, 3 H), 1.21 (m, 2 H), 1.41 (m, 2 H), 2.46 (t, J = 7.5 Hz, 2 H), 4.14 (s, 2 H), 7.00 (d, J = 8.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 7.5–7.7 (m, 7 H); FAB-MS m/e 547 $(M + H)^+$. Anal. ($C_{28}H_{24}Cl_2N_6O_2 \cdot 0.4H_2O$) C, H, N.

3-n-Propyl-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylic Acid (19y). Similarly, **18y** was hydrolyzed as described for **12b** to give an 83% yield of **19y** as a white solid: mp >125 °C; TLC in 9:1 CH_2Cl_2/MeOH; ^1H NMR (DMSO-d_6, 400 MHz) δ 0.79 (t, J = 7.3 Hz, 3 H),1.42 (m, 2 H), 2.39 (t, J = 7.5 Hz, 2 H), 4.05 (s, 2 H), 5.37 (q, J = 8.8 Hz, 2 H), 6.97 (d, J = 8.1 Hz, 2 H), 7.02 (d, J = 8.1 Hz, 2 H), 7.49–7.56 (m, 2 H), 7.60–7.67 (m, 2 H); FAB-MS m/e 471 $(M + H)^+$. Anal. ($C_{23}H_{21}F_3N_6O_2 \cdot 0.1H_2O$) C, H, N.

Rabbit Aorta AT_1 Receptor Binding Assay. Methods for the rabbit aorta membrane preparation[39] and binding assay[33,39] have previously been described in detail. Bovine serum albumin (BSA) was omitted from this version of the assay.[33] All binding assays were performed in duplicate tubes. The concentration required to inhibit specific binding of [^{125}I]Sar^{1}Ile^8-AII to the receptor by 50% (IC_{50}) was calculated using nonlinear regression analysis of the displacement curves. Based on the results of several standard compounds having three or more determinations, the standard error (expressed as percent of means) of the IC_{50} measurement in this assay is estimated to be less than 30%. In some cases the reported IC_{50} values represent an average of two or more determinations from separate assays.

Evaluation of AII Antagonists in Conscious, Normotensive Rats. Experimental procedures were as previously described,[33] except that in some instances, PEG 400 was used to solubilize test compounds for oral administration. In brief, male Sprague–Dawley rats (300–400 g) were surgically instrumented with catheters for intravenous administration of compounds and for monitoring arterial blood pressure and heart rate. In the absence of test compound, challenge with AII (0.1 μg/kg iv) typically produced an increase in mean arterial pressure (MAP) of approximately 50 mmHg. The test compound was given intravenously or orally, followed by bolus doses of AII at specified intervals thereafter for as long as the test compound exhibited activity. The percent inhibition of the AII pressor response in the presence of test compound was calculated at each time point. For each compound at a given dose, the peak percent inhibition and duration of action were determined (based on averaged results from at least two rats, unless otherwise indicated). A 30% inhibition of the AII pressor response is considered significant in this assay. The duration of action for a single bolus dose of the test compound is defined as the time from onset of activity until the inhibition of the AII-induced increase in MAP falls below 30% and remains at <30% for two subsequent AII challenges.

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