Diphenylpropionic Acids as New AT_1 Selective Angiotensin II Antagonists

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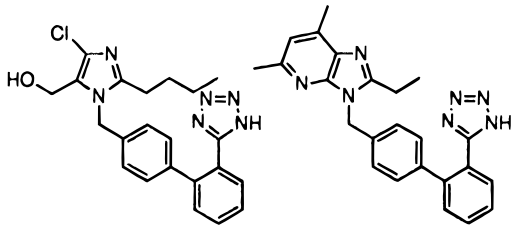
The synthesis and pharmacological evaluation of a new series of potent AT_1 selective diphenylpropionic acid nonpeptide angiotensin II receptor antagonists are reported. The new compounds were evaluated for *in vitro* AT_1 (rat liver) and AT_2 (rat adrenal) binding affinity as well as for *in vivo* inhibition of angiotensin II-induced increase in mean arterial blood pressure in pithed rats. Unsaturation of the diphenylpropionic acids as well as substitution or replacement by alkyl groups of the pendant phenyl ring resulted in a decrease of potency. On the other hand, the presence of small alkyl groups in the α-position to the carboxylic acid was important for activity, with one of the resultant diastereoisomers (*R*,R**) being ca. 10-fold more active than the other (*R*,S**). Oral evaluation of the most active compounds in a furosemide-treated sodium-depleted rat model showed that compound **36g** (UR-7198) reduced blood pressure dose dependently. This compound showed *in vitro* and iv potencies similar to that of the reference compound losartan but faster onset of action and somewhat greater oral activity, presumably due to its improved bioavailability.

The renin−angiotensin system (RAS) plays a key role in the regulation of cardiovascular homeostasis and electrolyte/fluid balance in normotensive and hypertensive subjects.[1] The first step of the cascade is the cleavage of angiotensinogen by renin to give angiotensin I, which is converted to angiotensin II (AII) by the angiotensin-converting enzyme (ACE). Biological responses such as vasoconstriction, aldosterone formation, renal sodium reabsorption, and norepinephrine release are mediated by the interaction of AII with specific receptors located at target organs such as the adrenal cortex, heart, kidney, liver, and arterioles.[2] The success of ACE inhibitors[3] in the treatment of hypertension has increased interest in controlling other targets in the RAS. Substantial effort has gone into finding renin inhibitors, although orally active agents have only recently been reported.[4] Blockade at the receptor level of the effector hormone AII appears to be the most direct way of controlling the RAS. This approach may also be free of the side effects of ACE inhibitors, such as cough and angioedema, which are probably caused by partial inhibition of cleavage of bradykinin and substance P.[5]

The design of AII antagonists began with peptide analogs of the octapeptide AII and led to the development of saralasin as the most active example.[6] Eleven years after, i.e., 1982, Furukawa et al. at Takeda[7] disclosed the first series of nonpeptide AII antagonists, which were the starting point for the discovery of losartan, **1**, at DuPont,[8] the first nonpeptide AII antagonist that reached the market for the treatment of hypertension (1994, Cozaar). These new compounds led to the identification of two major types of AII receptors, the first of which (AT_1) associated with the major physiological functions of AII. The functional role of the second (AT_2) remains uncertain.[9]

Losartan was also the extensively modified lead structure in more than 500 patents and articles, giving rise to a number of AT_1 selective compounds that followed it in clinical trials.[10] Several compounds were generated by replacement of the imidazole group of losartan by a wide variety of cyclic and acyclic substructures, among which the imidazopyridine L-158,809, **2**,[11] showed an outstanding 10-fold increase in potency. However, the duration of effect of **2** showed interspecies variability presumably due in part to glucuronidation of the tetrazole moiety. Replacement of that group by a phenylcarbonylsulfonamide group provided MK-996,[12] currently in phase II clinical trials.

Chart 1. Nonpeptide Angiotensin II Antagonists



Losartan, 1 **L-158,809, 2**

Comparatively less effort has been devoted to finding replacements for the biphenylyltetrazole moiety, with Glaxo's bromobenzofuran GR138950 being the only such non-biphenyl compound in clinical trials.[13] Maintaining the imidazopyridine group of **2**, researchers at Merck have reported several series of N-substituted indoles,[14] N-substituted (phenylamino)phenylacetic acids,[15] and phenoxyphenylacetic acids,[16] which show respectively slightly less, equal, and more *in vivo* potency compared to **1**, although in all three cases the oral effect in rats is shorter.

We became interested in exploring the 3,3-diphenylpropionic moiety as a new surrogate for the biphenylyltetrazole group, since inspection of molecular models showed common features in both structures. Herein we report the structure−activity study which has led to the finding of a new series of potent AT_1 selective AII antagonists.[17]

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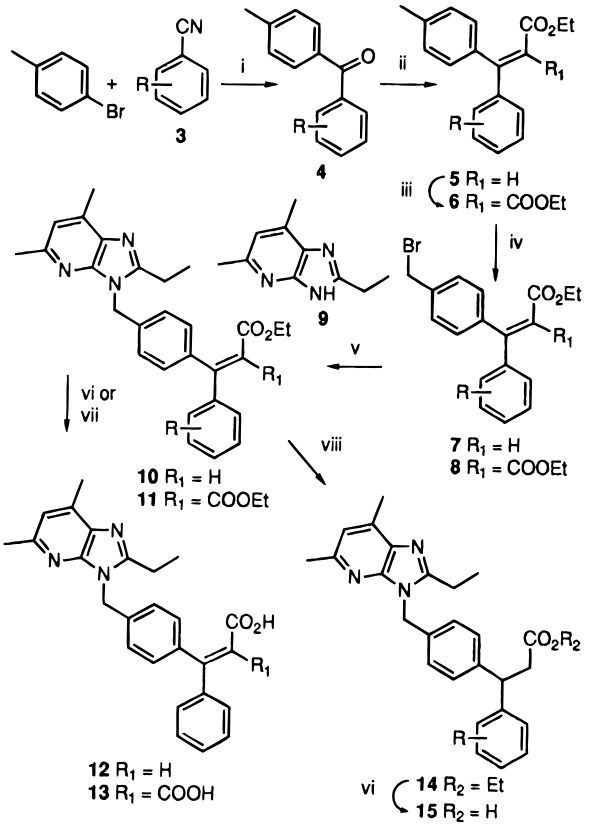
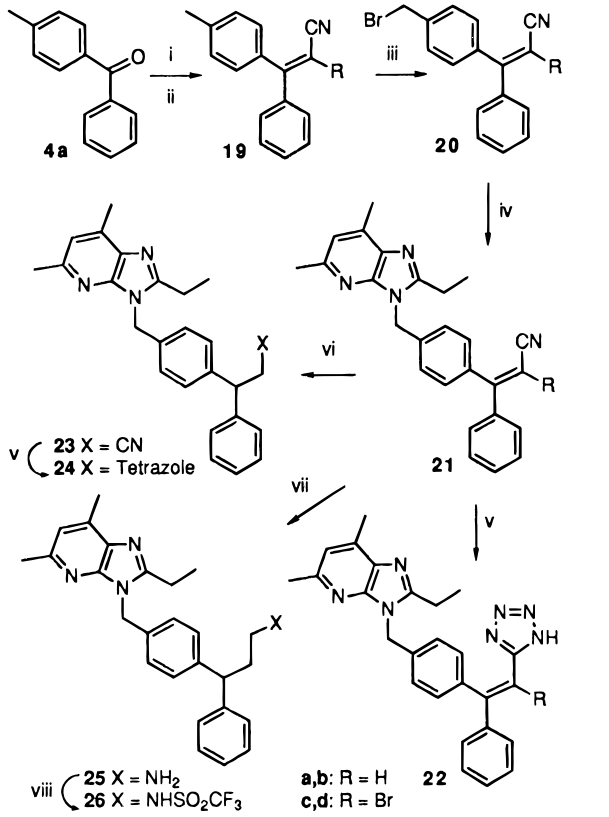
Scheme 1[a]



[a] (i) Mg, Et_2O−THF, 20 °C, 18 h; (ii) NaH, $(EtO)_2POCH_2COOEt$, DME, reflux, 4 days; (iii) LDA, $CO(OEt)_2$, THF, 0 °C, 10 min; (iv) NBS, CCl_4, reflux, 3 h; (v) **9**, NaH, DMF, 20 °C, 18 h; (vi) KOH, EtOH−H_2O, reflux, 2 h; (vii) KOH, 18-crown-6, benzene, 20 °C, 18 h; (viii) H_2, Pd/C, EtOH, 24−48 h.

Scheme 2[a]



[a] (i) CH_3CN, KOH, reflux, 18 h; (ii) **19a**, Br_2, $CHCl_3$, reflux, 1 h; (iii) NBS, CCl_4, $(OCOPh)_2$, reflux, 3−6 h; (iv) **9**, NaH, DMF, 20 °C, 18 h; (v) $ClSnBu_3$, NaN_3, toluene, reflux, 1−4 days; (vi) $NaBH_4$, MeOH−pyridine, reflux, 24 h; (vii) $LiAlH_4$, Et_2O, 20 °C, 2 h; (viii) Tf_2O, NEt_3, CH_2Cl_2, 20 °C, 2 h.

Chemistry

The synthesis of carboxylic acids **12**, **13**, and **15** was effected following the route outlined in Scheme 1. The starting 4-methylbenzophenones **4** were either commercially available or obtained by reacting the Grignard reagent derived from 4-bromotoluene with the corresponding benzonitriles **3**. A Wadsworth−Emmons reaction of **4** with triethyl phosphonoacetate yielded compounds **5**, which were converted to bromides **7** by reaction with NBS. The alkylation of 5,7-dimethyl-2-ethylimidazo[4,5-*b*]pyridine (**9**)[18] with **7** in the presence of NaH in DMF took place regioselectively at the N_3 nitrogen atom as described[11] to give **10**. The same reaction sequence was carried out over diester **6**, which was obtained upon the reaction of the LDA-generated anion[19] of **5a** with diethyl carbonate. Unsaturated esters **10** were hydrolyzed to carboxylic acids **12** with KOH/EtOH, but milder conditions had to be used (KOH, 18-crown-6, benzene) to convert **11** to **13** in order to avoid retroaldol reaction. Compounds **10** were hydrogenated over Pd/C to saturated esters **14**, which were subsequently hydrolyzed to **15**. Acid **15a** (R = H) was converted to sulfonamidocarbonyl derivatives **16** and **17** (Table 1) by reaction with the corresponding sulfonamides in the presence of DCC and DBU,[15] whereas **18** (Table 2) was obtained by treating **15a** with Br_2/P.

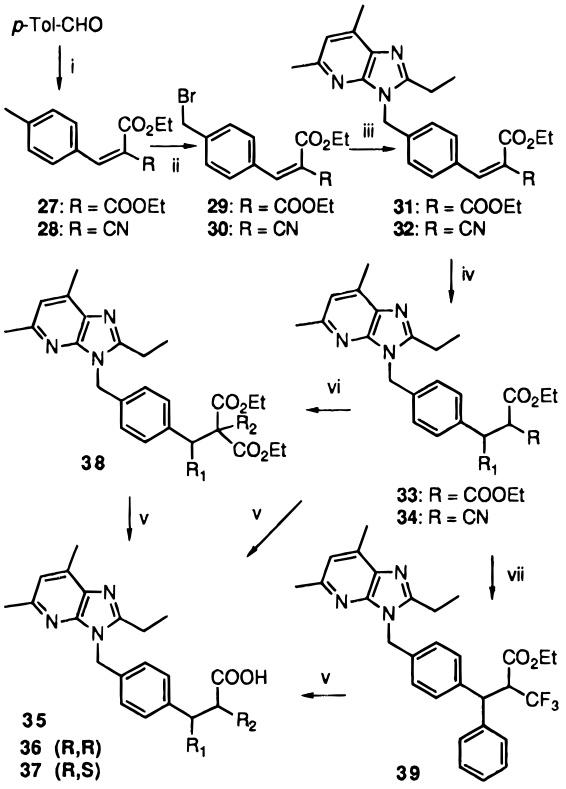
Similar procedures were employed for the synthesis of tetrazoles **22** and **24** (Scheme 2). Reaction of 4-methylbenzophenone (**4a**) with acetonitrile in the presence of KOH afforded the unsubstituted nitrile **19a**, which was converted to bromoolefin **19c** upon reaction with $Br_2/CHCl_3$.[20] Nitriles **19** were then brominated to **20**, alkylated to **21**, and transformed to tetrazoles **22** by treatment with $NaN_3/ClSnBu_3$/toluene.[8]

Compounds **5**, **7**, **10**, **12**, and **19**−**22** consisted of 1:1 mixtures of cis and trans isomers, as determined by ^{1}H-NMR or GC methods, which were separated by flash chromatography in the last step in order to test the activities of each stereoisomer individually (see Table 1).

Selective double-bond reduction of **21a** was effectively accomplished with $NaBH_4$ in pyridine/methanol[21] to give **23**, which was then converted to tetrazole **24**. Exhaustive reduction of **21** with $LiAlH_4$ provided amine **25** which was converted to trifluoromethylsulfonamide **26** on treatment with triflic anhydride in CH_2Cl_2.

α-Substituted saturated acids **35** (Table 2) were prepared according to the method described in Scheme 3. Reaction of *p*-tolualdehyde with diethyl malonate under acidic catalysis[22] gave compound **27**, which was brominated and subsequently alkylated with **9** to yield **31**. Michael addition over the double bond of **31** with the corresponding Grignard reagent (R_1MgBr) in the presence of cuprous bromide[23] afforded diesters **33** in good yield, and these were finally hydrolyzed to diacids **35a**−**e**. Effecting the same process but using ethyl cyanoacetate instead of diethyl malonate, the cyano carboxylic acid derivative **35f** was obtained. Malonic esters **33** were also alkylated (R_2I, NaH, DMF) to afford compounds **38**, which on treatment with KOH/EtOH underwent simultaneous hydrolysis and decarboxylation to give the α-alkylated carboxylic acids **35g**−**j**,**l**−**m**. The trifluoromethyl derivative **35k** was obtained by hydrolysis of **39**, which was prepared by treatment of **33** with

Scheme 3[a]



[a] (i) $CH_2(COOEt)_2$, piperidine (or $CH_2CN(COOEt)$, AcOH, NH_4OAc), benzene, Dean−Stark, reflux, 18 h; (ii) NBS, CCl_4, reflux, 3 h; (iii) **9**, NaH, DMF, 20 °C, 18 h; (iv) R_1Br, Mg, CuBr, benzene, Et_2O, 0 °C, 10 min; (v) KOH, EtOH−H_2O, reflux, 2 h; (vi) R_2I, NaH, DMF, 20 °C, 18 h; (vii) 1. CBr_2F_2, NaH, THF, 20 °C, 7 days, 2. KF, DMSO, 170 °C, 2 h.

dibromodifluoromethane in the presence of sodium hydride followed by simultaneous desethoxycarboxylation and replacement of the bromine atom by fluorine by heating with potassium fluoride in DMSO at 170 °C.[24]

Compounds **35a**−**e** were racemic mixtures, whereas **35f**−**n** consisted of equimolar mixtures of four diastereoisomers. The two pairs of enantiomers of the most active compounds (**35g**−**i**) were separated by flash chromatography to yield a faster (**36g**−**i**) and a slower (**37g**−**i**) eluting component (Table 3). The enantiomers of compounds **36g** and **37g** were obtained in optically pure form by classical resolution, by repeated recrystallization of the salt obtained with α-methylbenzylamine. Their enantiomeric excess was determined to be >95.5% by HPLC using a chiral column (see the Experimental Section).

The relative configuration of the two chiral centers of **36g** was determined by X-ray diffraction of crystals of **(−)-36g**, which unfortunately were not suitable to assess its absolute configuration. As shown in Figure 1, the substituents of the two chiral carbon atoms adopt an anti conformation in which the carboxylic acid group is oriented toward the same side of the distal phenyl ring, indicating an *R*,R** relative configuration. The same configuration was assigned to isomers **36h**,**i** and the opposite (*R*,S**) to isomers **37g**−**i** on the basis of their chromatographic and activity profiles.

The furan analogs of **36g** and **37g**, **40** and **41** (see Table 3), were obtained from 4-methylfurfuraldehyde following the same route outlined in Scheme 3. Dimethylated carboxylic acid **42** (Table 2) was obtained

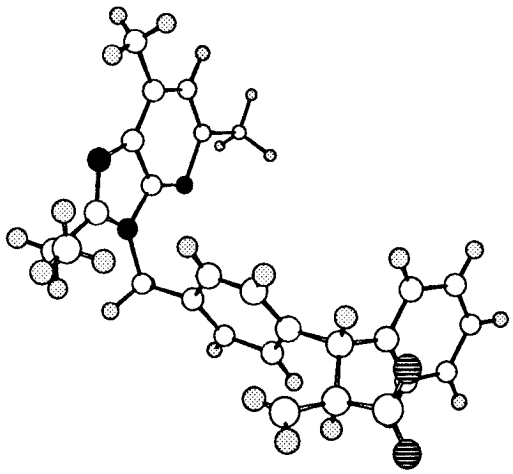


Figure 1. X-ray crystal structure of compound **(−)-36g**. Open circles indicate carbon atoms, dotted circles hydrogen atoms, striped circles oxygen atoms, and black circles nitrogen atoms.

by hydrogenation of **5** followed by dimethylation (MeI, LDA, THF−HMPA) and successive bromination, alkylation with **9**, and hydrolysis.

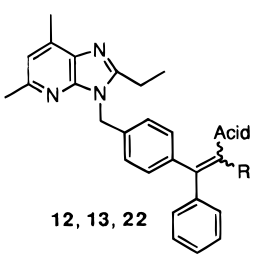
Results and Discussion

The new compounds were tested for their *in vitro* binding affinity to AT_1 (rat liver) and AT_2 (rat adrenal) receptors.[25] The IC_{50} values (concentration for 50% displacement of the specifically bound [^{3}H]AII) were determined in order to compare the relative potencies of the antagonists. *In vivo*, they were evaluated for inhibition of AII-induced increase in mean arterial blood pressure in pithed rats.[26] The percentage of decrease in arterial blood pressure at a submaximal dose of 3 μg/kg AII was calculated for each test compound given at a dose of 3 mg/kg iv (Tables 1−3).

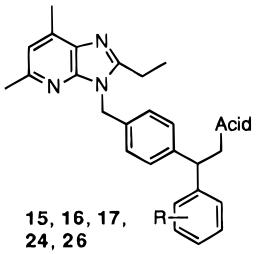
As indicated in Table 1, both isomers of unsaturated acid **12** showed a submicromolar binding affinity and provided only a slight decrease in blood pressure. Diacid **13**, with carboxylic acid groups oriented at both sides of the double bond, showed an increase of *in vivo* potency, whereas replacement of the carboxylic acid group by its bioisostere tetrazole afforded compounds **22a**,**b**, with the most active isomer **22a** being slightly more potent than the parent acid. A study of the substitution at the olefin double bond was undertaken in order to improve the activity of **22a** (results not shown). Introduction of methyl and phenyl groups provided completely inactive compounds, whereas electron-withdrawing substituents (COOEt, SOMe, COOH, CN, and SMe) only maintained potency. The best results were obtained on introduction of a bromine atom, which provided compounds **22c**,**d** (Table 1). Again, a superior activity of the less polar isomer (**22c**) over the more polar one (**22d**) was observed, **22c** showing greater binding affinity than losartan but inferior potency *in vivo*.

Diphenylpropionic acid **15a** maintained binding affinity but exhibited a substantial increase of *in vivo* potency over its unsaturated analog **12**. We decided to focus on the saturated derivatives and began to study the effect of introduction of substituents in the pendant phenyl ring of **15a**. Modification of the 4-position proved to be detrimental for activity (**15b**,**c**,**e**), whereas halogen substituents in the 2-position (**15d**,**f**) maintained potency.

Table 1. Diphenylacrylic (**12**, **13**, **22**) and Diphenylpropionic (**15**−**17**, **24**, **26**) Derivatives



12, 13, 22

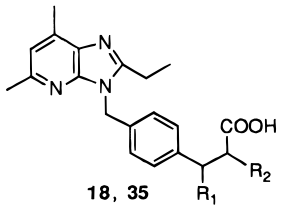


15, 16, 17, 24, 26

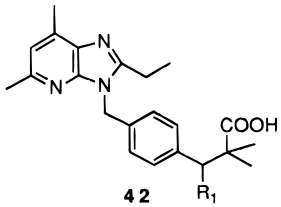
compd no.	acid	R	mp,[a] °C	formula	anal.[b]	AT_1 binding rat liver IC_{50},[c] μM	peak inhibition AII pressor response, pithed rats, % ± SEM[d]
12A[e]	COOH	H	97−101	$C_{26}H_{25}N_3O_2 \cdot 0.75H_2O$	C, H, N	0.12	30.4 ± 5.4
12B[f]	COOH	H	220−223	$C_{26}H_{25}N_3O_2 \cdot 0.75H_2O$	C, H, N	0.17	22.9 ± 3.5
13	COOH	COOH	231	$C_{27}H_{25}N_3O_4 \cdot 0.5H_2O$	C, H, N	0.32	69.2 ± 5.9
15a	COOH	H	208−209	$C_{26}H_{27}N_3O_2$	C, H, N	0.11	68.5 ± 11.1
15b	COOH	4-Pyr	124−128	$C_{25}H_{26}N_4O_2 \cdot 1H_2O$	C, H, N	5.3	NT[g]
15c	COOH	4-OMe	201	$C_{27}H_{29}N_3O_3$	C, H, N	3.7	NT[g]
15d	COOH	2-F	222	$C_{26}H_{26}FN_3O_2$	C, H, N	0.13	68.7 ± 3.2
15e	COOH	2,4-F_2	198	$C_{26}H_{25}F_2N_3O_2$	C, H, N	0.25	40.4 ± 5.4
15f	COOH	2-Cl	97−101	$C_{26}H_{26}ClN_3O_2 \cdot 0.25H_2O$	C, H, N	0.20	69.1 ± 8.7
16	$CONHSO_2Ph$	H	81−86	$C_{32}H_{32}N_4O_3S \cdot 1.5H_2O$	C, H, N	0.36	48.2 ± 6.9
17	$CONHSO_2Me$	H	118−122	$C_{27}H_{30}N_4O_3S$	C, H, N	0.094	72.7 ± 5.3
24	tetrazole	H	173−176	$C_{26}H_{27}N_7$	C, H, N	0.12	55.4 ± 7.4
26	$CH_2NHSO_2CF_3$	H	64−69	$C_{27}H_{29}F_3N_4O_2S \cdot 0.5Et_2O$	C, H, N	>10	NT[g]
22a[e]	tetrazole	H	193−195	$C_{26}H_{25}N_7 \cdot 1H_2O$	C, H, N	0.092	41.0 ± 11.3
22b[f]	tetrazole	H	226	$C_{26}H_{25}N_7 \cdot 0.75H_2O$	C, H, N	0.13	NA[h]
22c[e]	tetrazole	Br	149−151	$C_{26}H_{24}BrN_7 \cdot 1H_2O$	C, H, N	0.044	39.9 ± 6.5
22d[f]	tetrazole	Br	241−243	$C_{26}H_{24}BrN_7 \cdot 0.25H_2O$	C, H, N	0.29	22.8 ± 5.6

[a] Melting points measured directly from chromatographed products. [b] Analyses for the elements indicated were within 0.4% of the theoretical values. [c] Displacement of specifically bound [^{3}H]AII from rat liver AT_1 receptor preparation. [d] Maximum percentage of inhibition ± mean standard error (% ± SEM) of pressor response induced by exogenously administered AII (submaximal dose of 3 μg/kg, iv) in groups of two or more pithed rats, after administration of test compounds (3 mg/kg, iv). [e] Faster running isomer. [f] Slower running isomer. [g] Not tested. [h] Not active (<10% inhibition).

Table 2. α-Substituted Diphenylpropionic Derivatives



18, 35



42

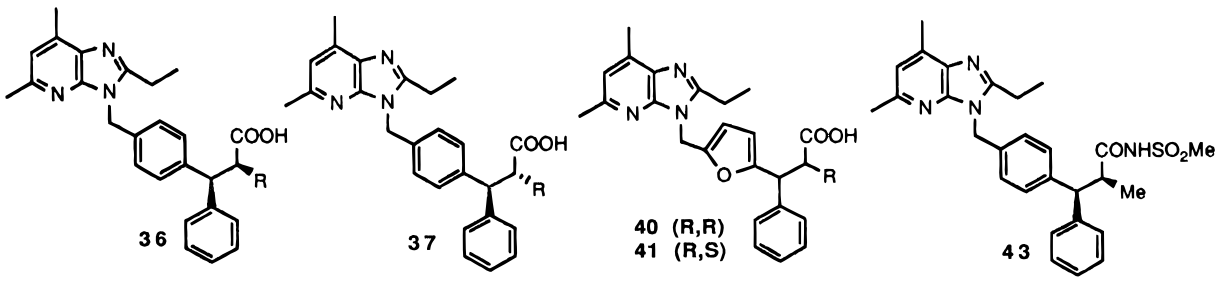
comp no.	R_1	R_2	mp,[a] °C	formula	anal.[b]	AT_1 binding rat liver IC_{50},[c] μM	peak inhibition AII pressor response, pithed rats, % ± SEM[d]
18[e]	Ph	Br		$C_{26}H_{26}BrN_3O_2$	C, H, N	0.17	47.1 ± 10.2
35a[f]	Ph	COOH	130−133	$C_{27}H_{26}KN_3O_4 \cdot 2H_2O$	C, H, N	0.12	79.9 ± 2.4
35b[f]	4-MePh	COOH	140−141	$C_{28}H_{29}N_3O_4 \cdot 2H_2O$	C, H, N	1.1	17.1 ± 6.6
35c[f]	3-MePh	COOH	141−143	$C_{28}H_{29}N_3O_4 \cdot 2H_2O$	C, H, N	0.45	61.7 ± 12.1
35d[f]	2-MePh	COOH	160−161	$C_{28}H_{29}N_3O_4 \cdot 2H_2O$	C, H, N	0.21	62.0 ± 8.4
35e[f]	CH_2Ph	COOH	127−128	$C_{28}H_{29}N_3O_4 \cdot 2H_2O$	C, H, N	>10	NA[g]
35f[e]	Ph	CN		$C_{27}H_{26}N_4O_2 \cdot HCl \cdot H_2O$	C, H, N	0.16	68.7 ± 2.5
35g[e]	Ph	Me		$C_{27}H_{29}N_3O_2 \cdot 0.25H_2O$	C, H, N	0.071	73.7 ± 3.9
35h[e]	Ph	Et		$C_{28}H_{31}N_3O_2 \cdot 0.25H_2O$	C, H, N	0.078	76.2 ± 4.7
35j[e]	Ph	CH_2Ph		$C_{33}H_{33}N_3O_2 \cdot 0.75H_2O$	C, H, N	0.20	31.5 ± 8.7
35k[e]	Ph	CF_3		$C_{27}H_{26}F_3N_3O_2$	C, H, N	8.3	32.3 ± 4.2
35l[e]	Me	Me		$C_{27}H_{27}N_3O_2 \cdot 0.25H_2O$	C, H, N	0.43	46.0 ± 8.0
35m[e]	Et	Me		$C_{23}H_{29}N_3O_2 \cdot 0.75H_2O$	C, H, N	0.33	45.7 ± 5.1
35n[e]	Pr^i	Me		$C_{24}H_{31}N_3O_2 \cdot 0.5H_2O$	C, H, N	0.60	30.4 ± 9.4
42[f]	Ph	Me_2	103−106	$C_{28}H_{31}N_3O_2 \cdot 0.5H_2O$	C, H, N	0.24	50.7 ± 7.8

[a−d] See footnotes a−d of Table 1. [e] Mixture of diastereoisomers. [f] Racemic mixtures. [g] Not active (<10% inhibition).

Among the carboxylic acid surrogates tested (**16**, **17**, **24**, and **26**), only **17** showed some improvement in potency over **15a**. In this case the bioisostere tetrazole **24** showed less potency than the parent acid in both tests, a trend contrary to that observed in the biphenyl series[8] but similar to the results reported with the (phenylamino)phenylacetic acids.[15]

Next, we focused on the introduction of substituents α to the carboxylic acid of **15a** (Table 2). As in the case of the unsaturated analogs (**13** vs **12A**), introduction of an additional carboxylic acid (**35a**) maintained binding affinity and produced some increase of *in vivo* potency. We tried again to improve activity by substitution on the pendant phenyl ring. The activity order 2-Me >

Table 3. α-Substituted Diphenylpropionic Derivatives



compd no.	R	mp,[a] °C	formula	anal.[b]	AT_1 binding rat liver IC_{50},[c] μM	AII ant. rabbit aorta pA_2[d]	peak inhibition AII pressor response, pithed rats, % ± SEM[e] 3 mg/kg, iv	1 mg/kg, iv
36g	Me	218	$C_{27}H_{29}N_3O_2$	C, H, N	0.069	8.69	84.8 ± 1.0	68.5 ± 4.2
(−)-36g	Me	218−219	$C_{27}H_{29}N_3O_2$	C, H, N	0.076		80.3 ± 3.1	
(+)-36g	Me	217−218	$C_{27}H_{29}N_3O_2$	C, H, N	0.071		80.9 ± 4.7	
37g	Me	217−221	$C_{27}H_{29}N_3O_2 \cdot 0.25H_2O$	C, H, N	0.25	7.31	28.2 ± 2.1	
(−)-37g	Me	208−210	$C_{27}H_{29}N_3O_2 \cdot 1.25H_2O$	C, H, N	0.18		22.1 ± 7.8	
(+)-37g	Me	212−214	$C_{27}H_{29}N_3O_2 \cdot 1.25H_2O$	C, H, N	0.44		19.7 ± 3.0	
36h	Et	227−229	$C_{28}H_{31}N_3O_2 \cdot 0.5H_2O$	C, H, N	0.050	8.41	86.1 ± 0.8	73.3 ± 6.1
37h	Et	251	$C_{28}H_{31}N_3O_2 \cdot 0.25H_2O$	C, H, N	0.45		44.9 ± 7.5	
36i	Pr	234−236	$C_{29}H_{33}N_3O_2$	C, H, N	0.083		73.8 ± 7.5	64.0 ± 7.4
37i	Pr	229−231	$C_{29}H_{33}N_3O_2 \cdot 0.25H_2O$	C, H, N	0.59		27.8 + 4.5	
40	Me	191−194	$C_{25}H_{27}N_3O_3$	C, H, N	4.8		NA[f]	
41	Me	196−199	$C_{25}H_{27}N_3O_3$	C, H, N	5.6		NA[f]	
43	Me	117−120	$C_{28}H_{32}N_4O_3S \cdot 0.5H_2O$	C, H, N	0.058		71.3 ± 5.4	55.9 ± 4.5
losartan (1)					0.059	8.53	93.5 ± 1.2	62.5 ± 8.9

[a−c] See footnotes a−c of Table 1. [d] Antagonism of AII-induced contraction of rabbit aortic rings (pA_2). Each value is the average of two or more preparations. [e] See footnote d of Table 1. [f] See footnote h of Table 1.

3-Me > 4-Me, also observed in a related series,[16b] showed again that substituents at the 4-position were not at all tolerated. Analogously, phenyl replacement by a benzyl group (**35e**) resulted in complete loss of activity.

Introduction of a bromine atom (**18**) or a cyano group (**35f**) did not show in this case any improvement in activity as compared to **15a**. However, an α-methyl (**35g**) or ethyl (**35h**) group provided a 2-fold increase in binding affinity and more potency *in vivo*. These two substituents proved to be optimal for activity, since attempts to improve potency by further modification of this position were unfruitful. Lengthening the alkyl chain to propyl (**36i**−**37i**, Table 3) somewhat diminished potency, and introduction of a benzyl group (**35j**) substantially reduced activity. Replacement of methyl by trifluoromethyl (**35k**) produced a binding affinity decrease of 2 orders of magnitude, and finally, introduction of a second methyl group α to the carboxylic acid also yielded a less potent compound, **42** (Table 2).

Maintaining an α-methyl group, the pendant phenyl ring was replaced by alkyl groups, such as methyl (**35l**), ethyl (**35m**), or isopropyl (**35n**), producing in all cases less potent compounds than **35g**. Since phenyl substitution had been previously shown to be detrimental to activity, this position was not further modified. An attempt was made to improve the activity of **35g** by replacement of the central phenyl ring by a smaller spacer, a furan, but this modification was even more detrimental to activity (see **40** and **41**, Table 3). A similar result has been observed in the biphenyl series, where replacement of phenyl by thiophene or furan has produced a substantial decrease in binding affinity, attributed to the relative planar disposition of both rings in contrast to the staggered conformation of the biphenyl moiety.[27]

The activity shown by compounds **35g**−**i** mainly resided in the less polar diastereoisomers **36**, which were substantially more potent in both tests than the most polar **37** (Table 3). Only the different relative configuration of the two chiral centers was shown to be important for activity, since the isolated enantiomers of **36g** and **37g** were equipotent both *in vitro* and *in vivo*.

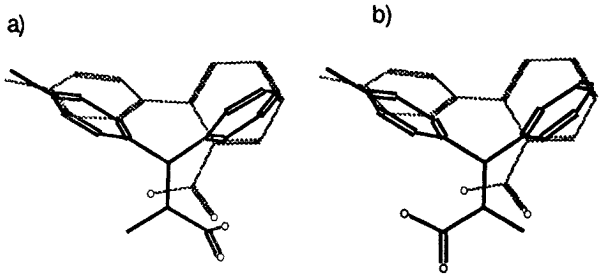


Figure 2. Overlay of 2-methyl-3-(4-methylphenyl)-3-phenylpropionic acid (solid) with 4′-methylbiphenyl-2-carboxylic acid (stippled), performed with CSC Chem3D Plus: (a) most active (*R**,*R**) configuration and (b) less active (*R**,*S**) configuration.

Inspection of molecular models provides a possible explanation for the superior activity of isomers **36** over **37**. In Figure 2 the overlay of the benzyl and pendant phenyl carbons of both diastereoisomers of the α-methyldiphenylpropionic acid (coordinates taken from the X-ray structure of **(−)-37g**) with the benzyl and the carboxyl-bearing phenyl carbon atoms of the parent 4′-methylbiphenyl-2-carboxylic acid (coordinates calculated using the CSC Chem3D Plus force field) is displayed. The carboxylic acid group, which is the key element for activity in both types of fragments, occupies a position that is more similar to the biphenyl carboxylic acid in the case of the *R**,*R** isomer than in the *R**,*S** one. The 2-fold increase of potency of **36g** over the unsubstituted compound **15a** seems to indicate that the α-methyl group acts mainly, but not exclusively, by fixing the preferred conformation, since only small alkyl groups are tolerated at this position.

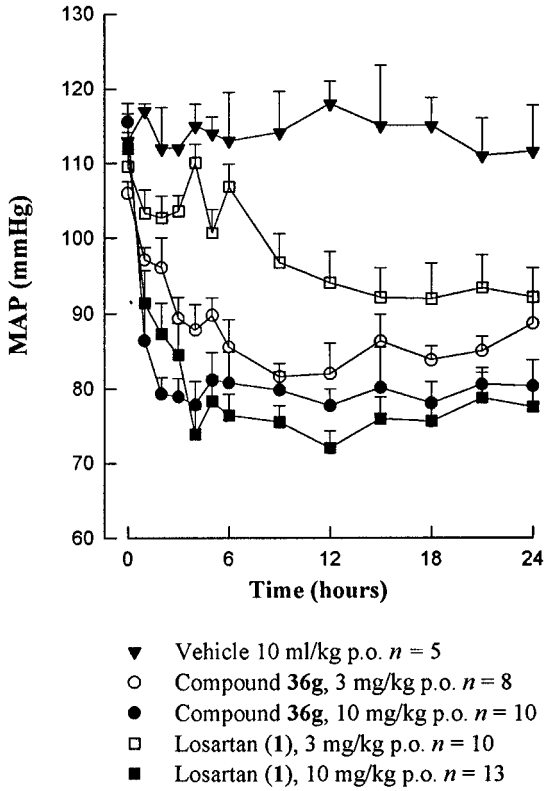


Figure 3. Oral antihypertensive effects of compound **36g** and losartan (**1**) in furosemide-treated sodium-depleted rats. The fall in mean arterial pressure (MAP, mmHg) was monitored using a telemetry device for up to 24 h. SEM are indicated for each point value; *n* is the number of animals treated.

The carboxylic acid group of **36g** was replaced by a methylsulfonamide, the only functionality which had provided an increase of potency among the surrogates tested over the unsubstituted derivative **15a**. However, in this case compound **43** showed less potency *in vivo* than the parent acid.

In vitro, compounds **36g**,**h** showed a binding affinity and a functional antagonism to AII in rabbit aortic rings comparable to losartan, **1**. Compound **36g** behaved as a competitive surmountable antagonist and showed high selectivity for the AT_1 receptor,[28] since the binding affinity for the AT_2 receptor in rat adrenal glands was over 10 μM. In fact, all the compounds reported in this study were evaluated for AT_2 binding affinity, and only **37g**,**i** showed activities in the micromolar range (10 and 5.3 μM, respectively). *In vivo*, by iv route, compounds **36g**,**h** also showed a level of activity that was similar to that of losartan.

The oral antihypertensive activity of the most potent compounds was evaluated in a furosemide-treated sodium-depleted rat model.[29] Whereas compound **35a** was poorly active at 10 mg/kg, **36g** produced a dose dependent decrease in blood pressure, with maximum values of 39 mmHg at 10 mg/kg and 24 mmHg at 3 mg/kg (Figure 3). It showed a rapid onset and good duration of action, in accordance with its good pharmacokinetic profile in rats (91% bioavailability and half-life of 9.1 h[30]). The reference compound losartan (**1**) exhibited a slower onset of action and a potency somewhat inferior to **36g**, a result which may reflect the difference in oral bioavailability of the two compounds (33% bioavailability described for **1** in the same species[31]). Compound **36h** showed an oral activity practically identical with that of **36g** reflecting again the similar profile of both compounds.

In summary, this paper describes a series of potent AT_1 selective nonpeptide AII receptor antagonists derived from substitution of the biphenylyltetrazole moiety present in many AII antagonists by a diphenylpropionic acid. Unsaturation of the diphenylpropionic acids as well as substitution or replacement by alkyl groups of the pendant phenyl ring resulted in a decrease of potency. On the other hand, the presence of small alkyl groups in the α-position to the carboxylic acid was important for activity, with one of the resultant diastereoisomers (*R**,*R**) being ca. 10-fold more active than the other (*R**,*S**). Compound **36g** (UR-7198) showed *in vitro* and iv potencies similar to that of the reference compound losartan but faster onset of action and somewhat greater oral activity, presumably due to its improved bioavailability.

Experimental Section

A. Chemistry. Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^{1}H- (80 MHz) and ^{13}C- (20.1 MHz) NMR spectra were recorded on a Brücker AC 80 spectrometer, and ^{1}H- (500 MHz) NMR spectra were recorded on a VXR-500 spectrometer. They are reported in ppm on the δ scale, from the indicated reference. Combustion analyses were performed with a Carlo Erba 1106 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel Chromagel 60 ACC (230−400 mesh). Analytical thin-layer chromatography (TLC) was performed with Macherey-Nagel 0.25 mm silica gel SIL G-25 plates. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane was distilled from calcium hydride, and chloroform was passed through an alumina column. Compound **1** was kindly provided by the DuPont Merck Pharmaceutical Co.

(4-Methylbenzoyl)pyridine (4b). To a suspension of magnesium turnings (2.30 g, 96 mmol) in Et_2O (57 mL) was added a solution of 4-bromotoluene (16.40 g, 96 mmol) in Et_2O (115 mL) dropwise under an argon atmosphere. After the addition was complete, the resultant mixture was heated at reflux for 30 min. Then, a solution of 4-cyanopyridine (10.00 g, 96 mmol) in anhydrous THF (57 mL) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The resultant mixture was poured into 1 N HCl and extracted several times with EtOAc. The organic phase was dried over $MgSO_4$, and the solvent was removed to afford a crude product that was chromatographed on silica gel (hexane−EtOAc mixtures of increasing polarity) to give **4b** (8.70 g, 46%) as a brown solid which was recrystallized from Et_2O: mp 90−91 °C (lit[32] mp 93−95 °C); ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 2.44 (s, 3H), 7.2−7.8 (m, 6H), 8.82 (m, 2H).

The same procedure was used for the obtention of **4c**−**f**.

Ethyl 3-(4-Methylphenyl)-3-phenyl-2-propenoate (5a). To a solution of 55% NaH (3.33 g, 0.075 mol) in dimethoxyethane (112 mL) was slowly added, at 0 °C under argon, triethyl phosphonoacetate (15.15 mL, 0.075 mol). After the addition was complete, the resultant mixture was stirred at room temperature for 30 min. Then, 4-methylbenzophenone (**4a**) (15.00 g, 0.075 mol) was added, and the mixture was stirred at reflux for 4 days. H_2O was added, and the resultant solution was extracted with Et_2O. The organic phase was dried over $MgSO_4$, and the solvent was removed to yield a crude product that was purified by chromatography on silica gel (hexane−CH_2Cl_2) to provide **5a** as a mixture (1:1) of cis and trans isomers (21.40 g, quantitative): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.08 (t, J = 7 Hz, 0.5 × 3H), 1.13 (t, J = 7 Hz, 0.5 × 3H), 2.32 (s, 0.5 × 3H), 2.37 (s, 0.5 × 3H), 4.03 (q, J = 7 Hz, 0.5 × 2H), 4.05 (q, J = 7 Hz, 0.5 × 2H), 6.31 (s, 0.5 × 1H), 6.34 (s, 0.5 × 1H), 7.24 (m, 9H).

The same procedure was used for the obtention of **5f**−**j**.

Diethyl (4-Methylphenyl)phenylmethylidenemalonate (6). To a solution of diisopropylamine (7.9 mL, 56.13 mmol), in anhydrous THF (100 mL), cooled to −78 °C, was added *n*-BuLi (1.6 M in hexane, 35 mL, 56.13 mmol), and the resultant mixture was stirred for 10 min under an argon atmosphere. Next, **5a** (5.00 g, 18.79 mmol) in THF (50 mL) was added dropwise, and the reaction mixture was stirred for a further 15 min. Finally, the reaction mixture was slowly added to a cold (0 °C) solution of diethyl carbonate (9.1 mL, 74.17 mmol) in Et_2O (100 mL). The resultant mixture was allowed to warm to room temperature, some drops of H_2O were added, and the solvents were removed. The residue was taken up in Et_2O and washed with 1 N HCl. The organic phase was dried over $MgSO_4$, and the solvent was removed to yield a crude product that was chromatographed on silica gel (hexane−EtOAc, 10%) to provide **6** as a white solid which was recrystallized from EtOAc (2.54 g, 40%): mp 86 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.00 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 4.10 (q, J =7.1 Hz, 2H), 7.0−7.5 (m, 9H).

Ethyl 3-[4-(Bromomethyl)phenyl]-3-phenyl-2-propenoate (7a). To a solution of **5a** (10.00 g, 37.6 mmol) in CCl_4 (214 mL), were added *N*-bromosuccinimide (6.80 g, 38.3 mmol) and benzoyl peroxide (0.64 g, 2.6 mmol), and the resultant mixture was stirred at reflux for 3 h. The resultant suspension was allowed to cool, and the imide formed was filtered and washed with CCl_4. The filtrate was evaporated to afford **7a** as a mixture (1:1) of cis and trans isomers (13.00 g, quantitative): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.10 (t, J = 7 Hz, 0.5 × 3H), 1.12 (t, J = 7 Hz, 0.5 × 3H), 4.05 (q, J = 7 Hz, 0.5 × 2H), 4.05 (q, J = 7 Hz, 0.5 × 2H), 4.47 (s, 0.5 × 2H), 4.52 (s, 0.5 × 2H), 6.37 (s, 1H), 7.24 (m, 9H).

5,7-Dimethyl-3-[[4-[2-(ethoxycarbonyl)-1-phenylvinyl]-phenyl]methyl]-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (10a). To a suspension of 50% NaH (2.20 g, 46.4 mmol) in anhydrous DMF (90 mL) at 0 °C was added **9**[18] (5.40 g, 31 mmol), and the mixture was stirred for 15 min under an argon atmosphere. Finally **7a** (13.00 g, 38 mmol) was added, and the reaction mixture was stirred at room temperature overnight. H_2O was added to neutralize the excess hydride, and the solvent was removed. The residue was taken up in EtOAc and washed with brine. The organic phase was dried over $MgSO_4$, and the solvent was removed to yield a crude product which was chromatographed on silica gel (hexane−EtOAc mixtures of increasing polarity) to afford **10a** as a mixture (1:1) of cis and trans isomers (9.40 g, 69%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.08 (t, J = 7 Hz, 3H), 1.32 (t, J = 7 Hz, 0.5 × 3H), 1.33 (t, J = 7 Hz, 0.5 × 3H), 2.57 (s, 0.5 × 3H), 2.59 (s, 0.5 × 3H), 2.62 (s, 3H), 2.79 (q, J = 7 Hz, 2H), 4.03 (q, J = 7 Hz, 2H), 4.43 (s, 0.5 × 2H), 4.49 (s, 0.5 × 2H), 6.31 (s, 1H), 6.88 (s, 1H), 7.24 (m, 9H).

[[4-(2-Carboxy-1-phenylvinyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (12). To a solution of **10a** (9.40 g, 21.4 mmol) in EtOH (470 mL) was added KOH (17.60 g, 270 mmol) dissolved in H_2O (96 mL). The mixture was heated at reflux for 2 h and then allowed to cool to room temperature. The solvent was evaporated, H_2O was added, and the resultant solution was extracted with EtOAc. The aqueous phase was washed with EtOAc, acidified to pH 4, and extracted again with EtOAc. The combined organic phases were dried over $MgSO_4$, and the solvent was removed to yield **12** as a mixture of cis and trans isomers, which were separated by chromatography on silica gel (EtOAc−AcOH) (8.30 g, 85%).

12A: faster running fraction; mp 97−101 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.26 (t, J = 7 Hz, 3H), 2.56 (s, 6H), 2.79 (q, J = 7 Hz, 2H), 5.44 (s, 2H), 6.31 (s, 1H), 6.87 (s, 1H), 7.24 (m, 10H). Anal. ($C_{26}H_{25}N_3O_2$·0.75 H_2O) C, H, N.

12B: slower-running fraction; mp 220−223 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.04 (t, J = 7 Hz, 3H), 2.57 (s, 6H), 2.70 (q, J = 7 Hz, 2H), 5.46 (s, 2H), 6.38 (s, 1H), 6.89 (s, 1H), 7.24 (m, 10H). Anal. ($C_{26}H_{25}N_3O_2$·0.75H_2O) C, H, N.

[[4-(2,2-Dicarboxy-1-phenylvinyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (13). A mixture of **11** (1.80 g, 3.9 mmol), KOH (1.16 g, 0.2 mol), 18-crown-6 (0.41 g), and benzene (18 mL) was stirred at room temperature for 18 h. Then, benzene (63 mL) and 1 N HCl (5 mL) were added, and the layers were separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic phases were dried over $MgSO_4$. The solvent was removed to yield a crude product which was chromatographed on silica gel (EtOAc−MeOH−AcOH mixtures of increasing polarity) to afford **13** as a white solid (0.50 g, 29%): mp 231 °C; ^{1}H-NMR (80 MHz, CD_3OD) δ (TMS) 1.26 (t, J = 7.2 Hz, 3H), 2.59 (s, 3H), 2.61 (s, 3H), 2.81 (m, 2H), 3.65 (broad signal, 2H, 2COOH + MeOH), 5.48 (s, 2H), 6.4−7.4 (m, 10H). Anal. ($C_{27}H_{25}N_3O_4$·0.5H_2O) C, H, N.

[[4-[2-(Ethoxycarbonyl)-1-phenylethyl]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (14a). To a solution of **10a** (0.68 g, 1.55 mmol) in EtOH (10 mL) was added 10% Pd/C (0.070 g), and the mixture was hydrogenated at atmospheric pressure overnight. More 10% Pd/C (0.070 g) was added, and the mixture was hydrogenated for an additional 24 h. The resultant solution was filtered through Celite and washed with EtOH, and the solvent was removed to afford **14a** as an oil (0.60 g, 87%): ^{1}H-NMR (80 MHz, CD_3OD) δ (TMS) 1.08 (t, J = 7.5 Hz, 3H, CH_3), 1.26 (t, J = 7.5 Hz, 3H), 2.57 (s, 3H), 2.61 (s, 3H), 2.75 (q, J = 7.5 Hz, 2H), 2.98 (d, J = 8 Hz, 2H), 4.00 (q, J = 7.5 Hz, 2H), 4.50 (t, J = 8 Hz, 1H), 5.39 (s, 2H), 6.8−7.2 (m, 10H).

5,7-Dimethyl-2-ethyl-3-[[4-[1-phenyl-2-[[(phenylsulfonyl)amino]carbonyl]ethyl]phenyl]methyl]-3*H*-imidazo-[4,5-*b*]pyridine (16). To a solution of **15a** (0.30 g, 0.69 mmol) in THF (13 mL) was added 1,1′-carbonyldiimidazole (0.11 g, 0.69 mmol), and the mixture was heated at reflux for 3 h. Next, it was allowed to cool, and a mixture of benzenesulfonamide (0.13 g, 0.87 mmol) and DBU (1.29 mL, 0.87 mmol) was added. The resultant mixture was heated at 40 °C overnight and then allowed to cool and was concentrated. The residue was taken up in H_2O and acidified with 10% NaH_2PO_4 solution (pH 5). The resultant solution was then extracted with $CHCl_3$ and EtOAc. The combined organic phases were dried over $MgSO_4$, and the solvents were removed to afford a crude product. This was purified by chromatography on silica gel ($CHCl_3$−MeOH, 2%) to give **16** (0.16 g, 42%): mp 81−86 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.21 (t, J = 7.2 Hz, 3H), 2.53 (s, 3H), 2.55 (s, 3H), 2.59 (q, J = 7.2 Hz, 2H), 2.77 (d, J = 7.2 Hz, 2H), 3.4 (broad signal, 1H), 4.37 (t, J = 7.2 Hz, 1H), 5.34 (s, 2H), 7.0−7.2 (m, 15H). Anal. ($C_{32}H_{32}N_4O_3S$·1.5H_2O) C, H, N.

Compound **17** was obtained by the same procedure, using methanesulfonamide instead of benzenesulfonamide.

[[4-(2-Bromo-2-carboxy-1-phenylethyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (18). To a mixture of **15a** (0.30 g, 0.72 mmol) and red phosphorus (0.028 g, 0.92 mmol) was added Br_2 (0.14 mL, 2.7 mmol), and the mixture was heated at 90 °C for 5 h. H_2O (5 mL) was added and the mixture extracted with EtOAc. The aqueous phase was extracted again with EtOAc, and the combined organic phases were dried over $MgSO_4$ and concentrated. The crude product thus obtained was chromatographed on silica gel ($CHCl_3$−MeOH, 2%) to give **18** as a mixture (1:1) of diastereoisomers (0.19 g, 56%): ^{1}H-NMR (80 MHz, CD_3OD) δ (TMS) 1.26 (m, 3H), 2.63 (s, 0.5 × 3H), 2.73 (s, 0.5 × 3H), 2.76 (s, 0.5 × 3H), 2.84 (s, 0.5 × 3H), 2.96 (m, 2H), 3.8 (m, 1H), 4.54 (d, J = 11 Hz, 1H), 4.85 (dd, J = 11 Hz, 1H), 5.46 (s, 0.5 × 2H), 5.46 (s, 0.5 × 2H), 7.0−7.5 (m, 10H). Anal. ($C_{26}H_{26}BrN_3O_2$) C, H, N.

3-(4-Methylphenyl)-3-phenyl-2-propenonitrile (19a). To a solution of KOH (6.50 g, 0.11 mol) in CH_3CN (70 mL) was added dropwise under an argon atmosphere a solution of 4-methylbenzophenone (**4a**) (22.50 g, 0.11 mol) in CH_3CN (45 mL). After the addition was complete, the reaction mixture was heated at reflux overnight. It was then allowed to cool, poured into ice, and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and the solvent was removed. The crude product thus obtained was chromatographed on silica gel (hexane−EtOAc mixtures of increasing polarity) to give **19a** as a mixture (1:1) of cis and trans isomers (19.50 g, 78%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 2.35 (s, 3H), 5.64 (s, 1H), 7.29 (m, 9H).

2-Bromo-3-(4-methylphenyl)-3-phenyl-2-propenonitrile (19c). To a solution of **19a** (3.50 g, 16.1 mmol), in $CHCl_3$ (14 mL) was added Br_2 (0.84 mL, 16.1 mmol), and the

mixture was stirred at reflux for 1 h. After removal of the solvent, **19c** was obtained as a mixture (1:1) of cis and trans isomers (4.47 g, 94%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 2.38 (s, 0.5 × 3H), 2.40 (s, 0.5 × 3H), 7.1−7.5 (m, 9H).

***cis/trans*-[[4-[2-Bromo-1-phenyl-2-(tetrazol-5-yl)vinyl]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]-pyridine (22c,d).** To a solution of **21c** (obtained by bromination of **19c** and alkylation with **9** as described for **10a**; 2.8 g, 5.9 mmol) in toluene (80 mL) were added under an argon atmosphere tributyltin chloride (5.0 mL, 18.6 mmol) and NaN_3 (1.21 g, 18.6 mmol). After heating at reflux for 48 h, it was allowed to cool to room temperature and extracted with 1 N NaOH. The aqueous phase was acidified with 6 N HCl and extracted with EtOAc. The organic phase was dried over $MgSO_4$, and the solvent was removed. The crude product thus obtained consisted of a mixture (1:1) of cis and trans isomers which were separated by chromatography on silica gel (hexane−EtOAc mixtures of increasing polarity).

22c: faster eluting isomer (31%); mp 149−151 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.25 (t, J = 7 Hz, 3H), 2.55 (s, 6H), 2.60 (q, J = 7 Hz, 2H), 5.31 (s, 2H), 6.8−7.3 (m, 11H). Anal. ($C_{26}H_{24}BrN_7 \cdot H_2O$) C, H, N.

22d: slower eluting isomer (27%); mp 241−243 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.25 (t, J = 7 Hz, 3H), 2.55 (s, 6H), 2.60 (q, J = 7 Hz, 2H), 5.31 (s, 2H), 6.8−7.3 (m, 11H). Anal. ($C_{26}H_{24}BrN_7 \cdot 0.25H_2O$) C, H, N.

[[4-(2-Cyano-1-phenylethyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (23). To a solution of **21a** (1.20 g, 3 mmol) in pyridine (6.6 mL) and MeOH (2.2 mL) was slowly added $NaBH_4$ (0.57 g, 15 mmol), and the mixture was heated at reflux for 24 h under an argon atmosphere. The resultant mixture was poured into 10% HCl and extracted with EtOAc. The organic phase was dried over $MgSO_4$, and the solvent was removed to afford a crude product. This was chromatographed on silica gel (hexane−EtOAc mixtures of increasing polarity) to provide **23** as a colorless oil (0.80 g, 68%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.28 (t, J = 7.5 Hz, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 2.75 (q, J = 7.5 Hz, 2H), 2.95 (d, J = 8 Hz, 2H), 4.30 (t, J = 8 Hz, 1H), 5.48 (s, 2H), 6.86 (s, 1H), 7.1−7.4 (m, 9H).

[[4-(3-Amino-1-phenylpropyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (25). To a solution of $LiAlH_4$ (0.20 g, 5.2 mmol) in Et_2O (9 mL) at 0 °C was added dropwise **21a** (0.50 g, 1.3 mmol) in Et_2O (3 mL), and the resultant mixture was stirred under an argon atmosphere at room temperature for 2 h. THF was added until complete dissolution of the paste obtained, and the resultant solution was stirred at room temperature for 3 h. Then, it was cooled (0 °C), and 0.34 mL of H_2O and 0.68 mL of THF were added followed by 0.34 mL of 15% aqueous NaOH and finally 0.9 mL of H_2O. The precipitate formed was filtered and washed with THF. The solvent was removed, and the residue was dissolved in $CHCl_3$. The resultant solution was dried over $MgSO_4$, and the solvent was removed to afford a crude product, which was purified by chromatography on silica gel ($CHCl_3$−MeOH−NH_3 mixtures of increasing polarity) to give **25** (0.20 g, 42%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.27 (t, J = 7.5 Hz, 3H), 1.4 (br s), 2.13 (m, 2H), 2.57 (s, 3H), 2.61 (s, 3H), 2.76 (q, J = 7.5 Hz, 2H), 2.5−2.8 (m, 2H), 3.98 (t, J = 7.7 Hz, 1H), 5.39 (s, 2H), 6.87 (s, 1H), 7.0−7.4 (m, 9H).

5,7-Dimethyl-2-ethyl-3-[[4-[1-phenyl-3-[[(trifluoromethyl)sulfonyl]amino]propyl]phenyl]methyl]-3*H*-imidazo[4,5-*b*]pyridine (26). To a solution of **25** (0.24 g, 0.61 mmol) and triethylamine (0.17 mL, 1.22 mmol) in CH_2Cl_2 (3.4 mL) at 0 °C under an argon atmosphere was added trifluoromethanesulfonic anhydride (0.06 mL, 0.37 mmol). The reaction mixture was stirred at room temperature for 1 h, and another 0.06 mL of trifluoromethanesulfonic anhydride was added. It was stirred at room temperature for 1 h more and then diluted with CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over $MgSO_4$ and concentrated. The crude product thus obtained was chromatographed on silica gel ($CHCl_3$−MeOH−NH_3, 89:10:1) to give **26** (0.10 g, 35%): mp 64−69 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.27 (t, J = 7.2 Hz, 3H), 1.87 (s, 1H), 2.35 (m, 2H), 2.56 (s, 3H), 2.61 (s, 3H), 2.76 (q, J = 7.2 Hz, 2H), 3.24 (t, J = 7.2 Hz, 2H), 3.93 (t, J = 7.2 Hz, 1H), 5.40 (s, 2H), 6.87 (s, 1H), 7.0−7.5 (m, 9H). Anal. ($C_{27}H_{29}F_3N_4O_2S \cdot 0.5Et_2O$) C, H, N.

Diethyl (4-Methylphenyl)methylidenemalonate (27). A mixture of *p*-tolualdehyde (19.6 mL, 166.4 mmol), diethyl malonate (23.8 mL, 158.8 mmol), piperidine (0.5 mL), and benzene (50 mL) was heated at reflux for 18 h using a Dean−Stark water separator. The mixture was allowed to cool to room temperature, and benzene was added. The solution was washed with H_2O, 1 N HCl, and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc; the organic phase was dried over $MgSO_4$, filtered, and evaporated to yield **27** (41.20 g, 99%): mp 49−51 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.24 (t, J = 6.4 Hz, 3H), 1.27 (t, J = 6.4 Hz, 3H), 2.31 (s, 3H), 4.22 (q, J = 6.4 Hz, 2H), 4.28 (q, J = 6.4 Hz, 2H), 7.0−7.3 (m, 4H), 7.88 (s, 1H).

5,7-Dimethyl-3-[[4-[2,2-bis(ethoxycarbonyl)-1-phenylethyl]phenyl]methyl]-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (33a). To a suspension of magnesium turnings (1.40 g, 59.6 mmol) in anhydrous Et_2O (28 mL) was added bromobenzene (6.56 mL, 62 mmol) in Et_2O (56 mL), and the mixture was heated at reflux for 30 min under an argon atmosphere. The resultant solution was cooled to 0 °C and then added to a cooled solution (0 °C) of **31** (mp 104 °C, obtained by bromination of **27** followed by alkylation with **9** following the above-described procedures; 13.00 g, 29.8 mmol) and CuBr (0.21 g) in benzene (42.5 mL). The mixture was stirred at 0 °C for 10 min, 1 N HCl was added; and it was extracted with EtOAc. The organic phase was dried over $MgSO_4$, and the solvent was removed to give a crude product which was chromatographed on silica gel (hexane−EtOAc mixtures of increasing polarity) to afford **33a** as a yellow foam (13.00 g, 85%). A sample was recrystallized from Et_2O to give **33a** as a white solid: mp 105−107 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 0.98 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 6H$_3$), 2.55 (s, 3H), 2.63 (s, 3H), 2.72 (q, J = 7.2 Hz, 2H), 3.97 (q, J = 7.2 Hz, 4H), 4.24 (d, J = 11 Hz, 1H), 4.69 (d, J = 11 Hz, 1H), 5.37 (s, 2H), 6.7−7.2 (m, 10H). Anal. ($C_{31}H_{35}N_3O_4$) C, H, N.

5,7-Dimethyl-3-[[4-[2,2-bis(ethoxycarbonyl)-1-phenylpropyl]phenyl]methyl]-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (38g). To a suspension of 55% NaH (1.40 g, 32.5 mmol) in DMF (103 mL) at 0 °C under argon was added dropwise **33a** (13 g, 25.3 mmol) dissolved in DMF (51 mL) followed by MeI (4.6 mL, 75.9 mmol). After the addition was complete, the reaction mixture was stirred at room temperature overnight. H_2O was added, and the solvent was removed. The residue was taken up in EtOAc and washed with brine. The organic phase was dried over $MgSO_4$, and the solvent was removed to yield a crude product, which was chromatographed on silica gel (EtOAc−hexane mixtures of increasing polarity) to afford **38g** as a white solid (10.20 g, 76%): mp 88−92 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.03 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 6H), 1.54 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 2.74 (q, J = 7.5 Hz, 2H), 4.01 (q, J = 7.5 Hz, 4H), 5.05 (s, 1H), 5.38 (s, 2H), 6.85 (s, 1H), 7.0−7.5 (m, 9H). Anal. ($C_{32}H_{37}N_3O_4$) C, H, N.

3-[[4-(2-Carboxy-1-phenylpropyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (35g). To a solution of **38g** (10.20 g, 19.3 mmol) in EtOH (1.26 L) was added KOH (46.00 g, 0.7 mol) dissolved in H_2O (264 mL). The reaction mixture was heated at reflux for 4 h and then allowed to cool to room temperature. The solvent was evaporated, H_2O was added, and the solution was extracted with EtOAc. The aqueous phase was washed with EtOAc, acidified to pH 4, and extracted again with EtOAc. The combined organic phases were dried over $MgSO_4$, and the solvent was removed to yield 8.70 g of **35g** as a mixture of diastereoisomers, which were separated by chromatography on silica gel (EtOAc−hexane mixtures of increasing polarity).

***rel*-(1*R**,2*R**)-35g, 36g:** faster running fraction, 2.70 g, 33%; mp 218 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 1.11 (t, J = 7.2 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.69 (q, J = 7.5 Hz, 2H), 3.25 (m, 1H), 4.05 (d, J =11 Hz, 1H), 5.35 (s, 2H), 6.0 (broad signal, 1H), 6.85 (s, 1H), 7.0−7.5 (m, 9H). Anal. ($C_{27}H_{29}N_3O_2$) C, H, N.

***rel*-(1*R**,2*S**)-35g, 37g:** slower running fraction, 2.90 g, 35%; mp 218−219 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 0.88 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 2.53 (m, 8H),

3.25 (m, 1H), 4.08 (d, J =11 Hz, 1H), 5.32 (s, 2H), 6.0 (broad signal, 1H), 6.8−7.5 (m, 10H). Anal. ($C_{27}H_{29}N_3O_2 \cdot 0.25H_2O$) C, H, N.

The enantiomers of each of the isomers **36g** and **37g** were separated as follows.

(−)-36g. 36g (3 g, 6.9 mmol) was dissolved in hot EtOAc (30 mL), and to this solution was added L-(−)-α-methylbenzylamine (0.87 mL, 6.9 mmol). The mixture was allowed to crystallize at low temperature overnight, and the solid formed was filtered. This solid was recrystallized from EtOAc−MeOH until a constant α value was obtained in two successive recrystallizations; 0.660 g of the salt was obtained as a white solid: $[\alpha]^{20}_D = -43.9°$ (5, MeOH); ^{1}H-NMR (80 MHz, CD_3OD) δ (TMS) 0.99 (d, J = 7.2 Hz, 3H), 1.17 (t, J = 8 Hz, 3H), 1.54 (d, J = 6.4 Hz, 3H), 2.55 (s, 3H), 2.59 (s, 3H), 2.79 (q, J = 7.5 Hz, 2H), 3.25 (m, 1H), 4.04 (d, J = 11 Hz, 1H), 4.32 (q, J = 8 Hz, 1H), 4.75 (3H), 5.47 (s, 2H), 6.7−7.5 (m, 15H).

The solid was dissolved in a mixture of 1 N NaOH and EtOAc, and the layers were separated. The aqueous phase was acidified with 1 N HCl to pH 6 and then extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed to afford **(−)-36g** (0.340 g). Recrystallization from EtOH gave **(−)-36g** as a white solid: $[\alpha]^{20}_D = -25.2°$ (5, MeOH); mp 219 °C; optical purity >99.5% ee according to HPLC analysis [Chiral AGP (100 × 4), NaH_2PO_4 (pH 7)−THF (99:1), 0.9 mL/min, λ 210 nm]. Anal. ($C_{27}H_{29}N_3O_2$) C, H, N.

(+)-36g. The acid contained in the mother liquor was liberated and treated with D-(+)-α-methylbenzylamine as described above. The salt was obtained as a white solid: $[\alpha]^{20}_D = +43.8°$ (5, MeOH).

Liberation of the acid as described for **(−)-36g** afforded **(+)-36g** (0.065 g) as a white solid: $[\alpha]^{20}_D = +25.2°$ (5, MeOH); mp 217−218 °C; HPLC >99.5% ee. Anal. ($C_{27}H_{29}N_3O_2$) C, H, N.

Following a similar procedure to that described for **36g**, the two enantiomers of **37g** were obtained.

(−)-37g: $[\alpha]^{20}_D = -47.0°$ (5, MeOH); mp 208−210 °C; HPLC >99.5% ee. Anal. ($C_{27}H_{29}N_3O_2 \cdot 1.25H_2O$) C, H, N.

(+)-37g: $[\alpha]^{20}_D = +48.0°$ (5, MeOH); mp 212−214 °C; HPLC >99.5% ee. Anal. ($C_{27}H_{29}N_3O_2 \cdot 1.25H_2O$) C, H, N.

5,7-Dimethyl-3-[[4-[2-(ethoxycarbonyl)-1-phenyl-2-(trifluoromethyl)ethyl]phenyl]methyl]-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (39). To a suspension of NaH (0.05 g, 1.16 mmol) in THF (5 mL) was added **33a** (0.50 g, 0.97 mmol), and the mixture was stirred for 1.5 h under an argon atmosphere. Then dibromodifluoromethane (0.09 mL, 0.97 mmol) was added, and the mixture was stirred for 7 days at room temperature. The solvent was removed, and the residue was dissolved in Et_2O and washed with H_2O. The organic phase was dried over $MgSO_4$ and concentrated to give 5,7-dimethyl-3-[[4-[2,2-bis(ethoxycarbonyl)-2-(bromodifluoromethyl)-1-phenylethyl]phenyl]methyl]-2-ethyl-3*H*-imidazo[4,5-*b*]-pyridine (0.37 g), which was used in the next step without further purification.

To a solution of the previous compound in DMSO (1.5 mL) was added KF (0.11 g, 1.94 mmol), and the mixture was stirred for 2 h at 170 °C under an argon atmosphere. The suspension thus obtained was allowed to cool, H_2O was added, and it was extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated to give a residue which was chromatographed on silica gel to yield **39** (0.11 g, 23%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ (TMS) 0.92 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 2.55 (s, 3H), 2.57 (s, 3H), 2.65 (q, J = 7.1 Hz, 2H), 3.97 (q, J = 7.1 Hz, 2H), 4.24 (d, J = 11 Hz, 1H), 4.72 (d, J = 11 Hz, 1H), 5.36 (s, 2H), 6.8−7.6 (m, 10H).

Crystal data for (−)-36g: $C_{27}H_{29}N_3O_2$; MW = 427.58; monoclinic; $P2_1/n$ (C^22, no. 4); a = 10.156(2) pm; b = 25.827(6) pm; c = 18.910(5) pm; α = 90°; β = 101.35°; γ = 90°; V = 4862.88 × 10^6 pm^3; Z = 8; ρ_x = 1.162 g·cm^{-3}; μ(Cu Kα) = 5.55 cm^{-1}; no. of reflections with $I \geq 3\sigma(I)$ = 6994; no. of refinement parameters 1262; final R values, R = 0.056 and R_w = 0.053.

B. Biological Methods. Angiotensin II Receptor Binding Assay. AII receptors from rat liver microsomes were prepared by modifications of a previously described method.[25] Livers were obtained after cervical dislocation, collected in 50 mM Tris-HCl buffer, pH 7.5, so that the concentration was 20% (w/v), and homogenized at 1000/rpm. The homogenate was centrifuged at 1000g for 10 min and the supernatant further centrifuged at 100000g for 1 h. The resultant membrane pellet was then resuspended in the above buffer at a concentration of 1 g of wet wt/mL; 700 μL aliquots of the membrane suspension were stored frozen at −70 °C until used.

Aliquots containing 15 mg of protein were incubated at 25 °C for 1 h in incubation buffer containing (final concentrations): NaCl (120 mM), $MgCl_2$ (5 mM), 0.006% bovine serum albumin, and Tris (50 mM), adjusted to pH 7.5. Incubation was initiated by the addition of 2 nM [^{3}H]AII. Total incubation volume was 250 μL. Nonspecific binding was measured by incubation in the presence of 0.1 mM Sar^1,Ile^8-AII. Test compounds were studied in the range of concentrations 10^{-10}−10^{-5}M. Binding was terminated by rapid filtration using a Millipore multiscreen device. Filters were washed three times with 250 μL of the corresponding buffer. Dry filters were placed into vials containing 3 mL of scintillation fluid, and the radioactivity was counted in a scintillation counter. The IC_{50} value (concentration for 50% displacement of the specifically bound [^{3}H]AII) was estimated from the linear portion of the displacement curve. Assays were performed in duplicate. Interassay IC_{50} values for a given test compound vary <20%.

Inhibition of Angiotensin II-Induced Pressor Response in Pithed Rats. Male Sprague−Dawley rats (body wt 250 g) were anesthetized with sodium pentobarbital (50 mg/kg, ip). The trachea was cannulated, and the rats were pithed through the orbit with a stainless steel pithing rod. The rats were immediately placed on a rodent ventilator (volume, 1 mL/100 g of body wt; rate, 74 strokes/min). The carotid artery was cannulated and connected to a pressure transducer for arterial pressure measurement. A dose−pressor response curve for AII was obtained administering intravenously and in a cumulative manner doses of AII (0.01−100 mg/kg), with each succesive injection given immediately after the maximal effect of the preceding dose was obtained. The effect of a submaximal dose of AII (3 μg/kg, iv) was calculated in untreated animals. Test compounds (or vehicle) were given to animals 15 min before injection of AII. The inhibition (%) of the effect induced by AII (3 μg/kg, iv) was calculated for each test compound in relation to the one obtained in untreated animals. Experiments were done in quintuplicate.

Angiotensin II Functional Antagonism in Rabbit Aorta.[33] Helical strips of thoracic aorta from male New Zealand White rabbits were kept in an organ bath at 37 °C in a solution containing 154 mM NaCl, 5.4 mM KCl, 1.5 mM $CaCl_2$, 6 mM $NaHCO_3$, and 11 mM glucose, constantly aerated (95% O_2, 5% CO_2). The isometric contraction with a loading tension of 2 g was recorded by a strain gauge transducer connected to a recorder. The strips were left to stabilize during 90 min and then an accumulative dose−response curve with AII was constructed. AII was added to the bath when the maximum contraction induced by a prior concentration was reached. The highest response was considered the maximal response to AII. Then, the strips were washed several times until the base line was recovered. Test compounds were added 30 min before a next concentration−response curve. Responses were expressed as a percentage of the maximal AII concentration. The pA_2 values were determined by the Schild equation.

Oral Activity in Furosemide-Treated Sodium-Depleted Rats.[29] Male Sprague−Dawley rats (250 g) were surgically instrumented with a telemetry device (TA11PA-C40, Data Sciences Inc.) for continuous recording of blood pressure and heart rate. After 1 week, rats were fed a sodium deficient diet (ICN, sodium-deficient diet, rat, modified, 902902, 4% sodium free salt mixture) and given furosemide (5 mg/kg, sc) 48, 24, and 1 h before oral administration of test compounds. Blood pressure and heart rate were monitored for up to 24 h postdose.

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Supporting Information Available: X-ray crystallographic data, including positional parameters, bond distances, bond angles, and anisotropic displacement parameter expressions, for **(−)-36g** (16 pages). Ordering information is given on any current masthead page.

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