Sulfonylureas and Sulfonylcarbamates as New Non-Tetrazole Angiotensin II Receptor Antagonists. Discovery of a Highly Potent Orally Active (Imidazolylbiphenylyl)sulfonylurea (HR 720)

Pierre Deprez,[†] Jacques Guillaume,[†] Reinhard Becker,[‡] Alain Corbier,[†] Stanislas Didierlaurent,[†] Michel Fortin,[†] Daniel Frechet,[†] Gilles Hamon,[†] Bertrand Heckmann,[†] Holger Heitsch,[‡] Heinz-Werner Kleemann,[‡] Jean-Paul Vevert,*[,†] Jean-Claude Vincent,[†] Adalbert Wagner,*[,‡] and Jidong Zhang[†]

Hoechst Roussel PGU Cardiovascular Agents, 65926 Frankfurt am Main, Germany, and 93235 Romainville Cedex, France

Received October 28, 1994[⊗]

The synthesis and pharmacological activity of new potent nonpeptide non-tetrazole angiotensin II (AII) receptor antagonists are described. These compounds are 4-thioimidazole derivatives linked on N_1 to a biphenylsulfonyl fragment by a methylene spacer. Different acidic sulfonamides such as sulfonylureas **12**, sulfonylcarbamates **15**, sulfonylamides **16**, and sulfonylsulfonamides **17** have been investigated as replacements to the known potent tetrazole moiety at the 2′-biphenyl position. Their activity were evaluated by AII receptor binding assay as well as by *in vivo* (iv and po) assays such as inhibition of the AII-induced pressor response in pithed rats. Most of the synthesized sulfonyl derivatives showed nanomolar affinity for the AT_1 receptor subtype. The *N*-propylsulfonylurea **12d** and the ethyl sulfonylcarbamate **15b** as representative members of this series exhibited high oral activity in the pithed rat model with ID_{50} values of 0.38 and 0.4 mg/kg, respectively. Structure–activity relationships on the imidazole ring linked to the methylbiphenyl *N*-propylsulfonylurea fragment demonstrated similar features to those found in the corresponding tetrazole series. For both class of compounds, the linear butyl chain in position 2 and a carboxylic acid in position 5 were important for high *in vitro* and *in vivo* activity. In most cases, replacement of the carboxylic acid was detrimental to *in vivo* activity while maintaining the *in vitro* binding affinity. Introduction of a methylthio group in position 4 was found to enhance oral activity compared to compounds with chloro or other alkylthio, (polyfluoroalkyl)thio, and arylthio groups. 2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (**12d**) as the most promising example of the series was synthesized as its dipotassium salt (**50**, HR 720). This compound **50** inhibited the specific binding of [^{125}I]-AII to rat liver membranes with an IC_{50} value of 0.48 nM. *In vivo*, **50** dose-dependently inhibited the AII-induced pressor response in normotensive pithed rats (ID_{50} = 0.11 mg/kg iv and 0.7 mg/kg po). In addition, this compound produced a marked and long-lasting decrease in blood pressure in high renin animal models and proved to be superior to the corresponding tetrazole **45** as well as to DuP 753 or its active metabolite EXP 3174. Compound **50** has been selected for in-depth investigations and is currently undergoing phase II clinical trials.

Introduction

The renin–angiotensin system (RAS) is known to play an important role in blood pressure regulation and electrolyte homeostasis.[1] Angiotensin II (AII), the biologically active peptide of the RAS, is a potent vasoconstrictor agent which also stimulates aldosterone secretion[2] and is therefore regarded as a major mediator of hypertensive disorders including essential hypertension.[3] Consequently, the RAS has been a prime target for the therapy of cardiovascular diseases.[4] On the basis of the success of the angiotensin converting enzyme inhibitors[5] as antihypertensive drugs, the pharmaceutical industry has devoted considerable effort to discovering nonpeptide renin inhibitors[6] and AII receptor antagonists[7] as alternative means of blocking the RAS in a more specific way.[8,9]

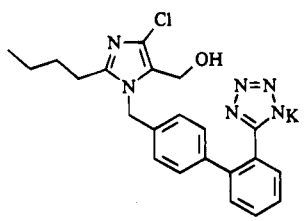
The discovery by Du Pont of the first orally active, nonpeptide, AII antagonist DuP 753 (Losartan, COZAAR),[10–13] opened an exciting new phase of research to investigate AT_1-selective[14] agents for the treatment of hypertension. Since then, many other AII antagonists have been reported.[15] Nearly all of them contain an alkyl-substituted nitrogen heterocycle linked to a biphenylyltetrazole by a methylene spacer. Indeed, it has been demonstrated that an acidic function ortho to the distal phenyl ring is needed for activity. On the basis of Du Pont's findings, replacement of the carboxylic function by the isosteric tetrazole resulted in a greater binding affinity and above all increased oral activity.[11]

However, at that time, tetrazole derivatives were known to display some chemical and metabolic disadvantages. Large-scale synthesis of this moiety could be hazardous[16] due to the use of azide derivatives (sodium azide, tributyltin azide, ...) which are possible precursors of the toxic and extremely explosive hydrazoic acid. In some cases, tin residues are also difficult to remove. Moreover, glucuronidation of the tetrazole moiety had already been observed to be a possible metabolic pathway.[17] In fact, the formation of glucuronide metabolites of DuP 753 in monkeys has been established, resulting in less active compounds.[18] Their rapid elimination

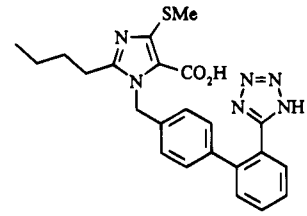
* Author to whom correspondence should be addressed.
[†] Roussel Uclaf, Romainville.
[‡] Hoechst AG, Frankfurt am Main.
[⊗] Abstract published in *Advance ACS Abstracts*, May 15, 1995.

0022-2623/95/1838-2357$09.00/0

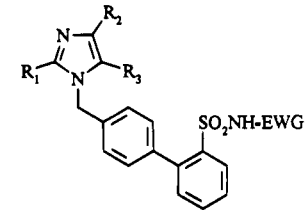
Chart 1



DuP 753
(Losartan)

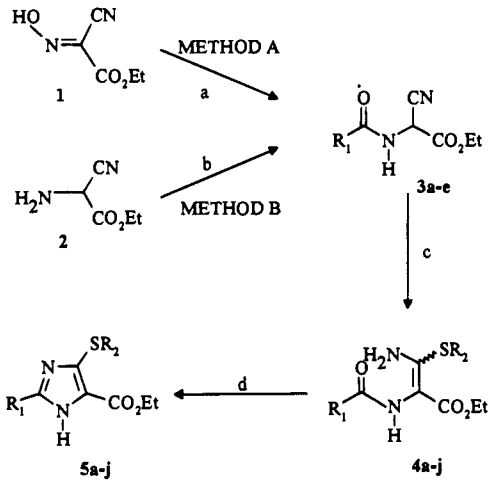


45, RU 56184



Sulfonyl derivatives
EWG = CONHR, CO_2R
COR, SO_2R

Scheme 1[a]



a: R_1 = Me R_2 = Me
b: R_1 = Et R_2 = Me
c: R_1 = *n*-Pr R_2 = Me
d: R_1 = *n*-Bu R_2 = Me
e: R_1 = *c*-Pr R_2 = Me
f: R_1 = *n*-Bu R_2 = $(CH_2)_3OAc$
g: R_1 = *n*-Bu R_2 = $(CH_2)_4OAc$
h: R_1 = *n*-Bu R_2 = CH_2Ph-4-OMe
i: R_1 = *n*-Bu R_2 = Ph
j: R_1 = *n*-Bu R_2 = 2-thienyl

[a] Reagents: (a) H_2/Pt–C, $(R_1CO)_2O$, THF, room temperature; (b) R_1COCl, pyridine, CH_2Cl_2, 0 °C; (c) R_2SH, TEA, EtOH, −10 °C to room temperature, 2–4 d; (d) PCl_5, DMAP, CH_2Cl_2, −78 °C to room temperature, 12 h.

could explain the shorter *in vivo* duration of action of DuP 753 in that species. Glucuronidation being very species-dependent, one could then speculate on whether sufficient plasma concentrations of a tetrazole antagonist could be achieved in humans over a 24 h period to produce consistent reduction in blood pressure.

Today, the synthesis of bulk quantities of tetrazole derivatives no longer seems to be a problem.[19a] In addition, acceptable doses of losartan (50 mg and higher) have, since then, been demonstrated[19b] to display pharmacokinetic characteristics in hypertensive patients sufficient to produce significant blood pressure lowering 24 h after administration. Even so, the trough:peak ratio of the antihypertensive effects of losartan being in the range of 60%,[19b] there is still some need for drugs more effective in achieving a 24 h control of blood pressure. Likewise, drugs showing equipotency of a once *versus* twice daily dose regimen are still awaited.

Therefore, at the onset of this work, these issues on the tetrazole moiety were pending and some of them still are. They led us to seek a tetrazole replacement. Our strategy was to take advantage of a previous structure–activity relationship in the imidazole–biphenylyltetrazole series which had led to the discovery of compound **45** (RU 56184),[20] our most potent orally active tetrazole AII antagonist (IC_{50} = 0.2 nM; ID_{50} = 0.05 mg/kg iv and 0.4 mg/kg po). Therefore, the tetrazole moiety of this compound was extensively replaced by sulfonyl groups (Chart 1). Acidic groups such as tetrazole surrogates only received limited attention. AII antagonists incorporating squaric acid,[21] acidic heterocycles,[22] triflamide,[23] or acidic sulfonamides[24] in place of tetrazole have recently been reported.

The present paper describes the design and the synthesis of sulfonyl derivatives, e.g., sulfonylureas, sulfonylcarbamates, sulfonylamides, and sulfonylsulfonamides as possible acidic isosteres of the tetrazole group in the AII antagonist field. The most potent sulfonyl derivative (*N*-propylsulfonylurea) was then selected and a series of derivatives was synthesized in order to optimize the substitution pattern in positions 2, 4, and 5 of the imidazole ring. This led to the discovery of compound **50**,[25] one of the very few orally active non-tetrazole AII antagonists currently under clinical development.

Chemistry

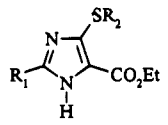
The compounds described in this study are shown in Tables **1**–**7** and their synthetic methods are outlined in Schemes 1–9. All compounds were synthesized through a convergent approach by coupling the requisite imidazole **5** with the [[(bromomethyl)biphenylyl]sulfonyl]amidine **9** as described in Scheme 3.

Suitably substituted imidazoles **5a**–**j** have been synthesized following a three step sequence (Scheme 1) from the oxime **1** *via* Pt-catalyzed hydrogenation in the presence of the desired carboxylic acid anhydride or from ethyl aminocyanoacetate **2** by condensation with the requisite acyl chloride.[26] Addition of the appropriate thiol derivative onto the nitrile and final PCl_5-induced intramolecular cyclization led to imidazoles **5a**–**j** (Table 1).

As outlined in Scheme 2, the biphenyl bromide **9** was obtained from 2-bromobenzenesulfonamide **6**,[27] which was first protected as the amidine derivative **7** with dimethylformamide dimethyl acetal and then subjected to palladium coupling with *p*-tolylboronic acid in the presence of a base under the conditions described by Suzuki[28] in 93% yield. Finally, radical bromination with NBS in chlorobenzene provided [[(bromomethyl)biphenylyl]sulfonyl]amidine **9** in 64% yield after recrystallization.

Coupling of this biphenyl bromide **9** with the requisite ester imidazole **5a**–**j** was performed in DMF in the presence of K_2CO_3. The major product of the reaction was the desired N_1 regioisomer **10a**–**j**, mixed with a

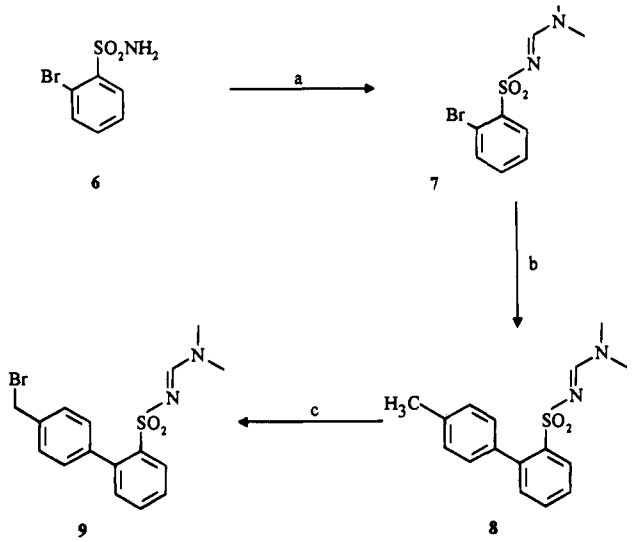
Table 1. Imidazole Compounds **5a–j**



compd	R_1	R_2	mp (°C)	formula[a]	yield (%)
5a	Me	Me	174	$C_8H_{12}N_2O_2S$	48
5b	Et	Me	150	$C_9H_{14}N_2O_2S$	75
5c	*n*-Pr	Me	85	$C_{10}H_{16}N_2O_2S$	67
5d	*n*-Bu	Me	74	$C_{11}H_{16}N_2O_2S$	72
5e	c-Pr	Me	104–108	$C_{10}H_{14}N_2O_2S$	74
5f	*n*-Bu	$(CH_2)_3OAc$	<50	$C_{15}H_{24}N_2O_4S$[b]	81
5g	*n*-Bu	$(CH_2)_4OAc$	55	$C_{16}H_{26}N_2O_4S$[b]	68
5h	*n*-Bu	$CH_2(4\text{-}OCH_3\text{-}C_6H_4)$	105	$C_{18}H_{24}N_2O_3S$[b]	72
5i	*n*-Bu	Ph	74	$C_{16}H_{20}N_2O_2S$	69
5j	*n*-Bu	2-thienyl	*c*	$C_{14}H_{16}N_2O_2S_2$[b]	85

[a] All compounds exhibited NMR consistent with structure and gave satisfactory analyses C, H, N, S (0.4%), except as noted. [b] Analysis not determined. [c] Obtained as a foam.

Scheme 2[a]



[a] Reagents: (a) $(MeO)_2CHNMe_2$, DMF, room temperature, 2 h; (b) $4CH_3PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, Na_2CO_3, toluene, reflux, 4 h; (c) NBS, $(C_6H_5CO)_2O_2$, chlorobenzene, 120 °C, 1 h.

small amount of the N_3 isomer (for example: 91% of N_1 isomer **10d** *vs* 9% of N_3 isomer, Scheme 3). The two isomers[29] could be separated by crystallization or chromatography (the N_1 isomer being less polar). Deprotection of the amidine **10a–j** in ethanolic hydrochloride solution under reflux gave the free sulfonamide **11a–e,i–l** in good yields. In this reaction acetates **10f–g** are also hydrolyzed to the corresponding alcohols **11k,l**. The obtained sulfonamides **11a–e,i–l** were then further converted to the desired sulfonylureas **12a–e,i–l** (Table 2).

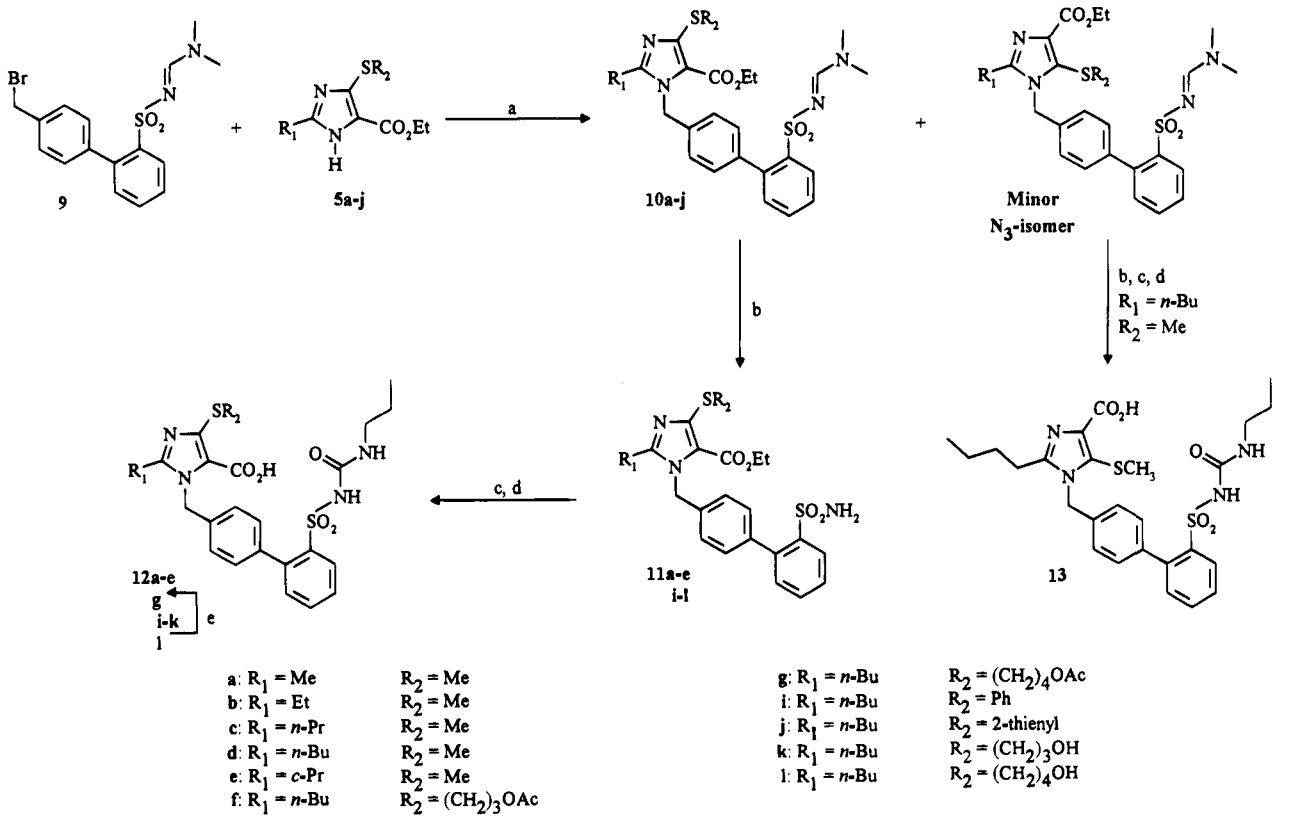
Sulfonylcarbamates **15b–d** were obtained from sulfonamide **11d** by reaction with methyl, ethyl, or 3-methylbut-2-enyl chloroformate, respectively, in refluxing DME in the presence of K_2CO_3 (Scheme 4). In a very similar way, sulfonylureas **12** were prepared from the requisite alkyl isocyanates in refluxing acetone with K_2CO_3. An alternative access to the sulfonylureas **12** involved the reaction of ethyl sulfonylcarbamate **15a** with an amine in refluxing toluene, without affecting the ethyl ester group. Sulfonylthiourea **14** was synthesized as described for sulfonylurea **12d** by using propyl isothiocyanate instead of propyl isocyanate. Sulfonamide **11d** was also treated with benzoyl chloride or phenylacetyl chloride in refluxing toluene in the presence of DMAP to give acylsulfonamide **16b,c**, while refluxing sulfonylurea **12d** in acetic anhydride afforded acetylsulfonamide **16a**. Sulfonylsulfonamide **17a** was obtained by the treatment of **11d** with ethanesulfonyl chloride in refluxing DME in the presence of K_2CO_3. Trifluorosulfonylsulfonamide **17b** was prepared using trifluoromethanesulfonic anhydride and triethylamine in CH_2Cl_2 at room temperature (Scheme 4). The sulfonamide derivatives **12, 14, 15, 16,** and **17** were finally saponified in aqueous ethanolic NaOH or KOH solution at room temperature in order to avoid decarboxylation, to give the free acids or their salts, respectively.

Carbonylurea **43** was prepared in a special manner by coupling imidazole **5d** with the known (bromomethyl)biphenyl *tert*-butyl ester **40**.[11] After acidic cleavage of the *tert*-butyl group, the resulting acid **41** was transformed to the primary amide *via* its acid chloride (using $SOCl_2$ then ammonia) and then converted to carbonylurea **43** with propyl isocyanate followed by saponification using standard procedures (Scheme 9).

All synthesized variations in position 5 of the imidazole ring are outlined in Scheme 5–7. These compounds were synthesized from ester sulfonamide **11d**, except for alcohol **19** (Scheme 5) which was obtained from ester sulfonylamidine **10d** by $LiAlH_4$ reduction ($LiAlH_4$ first reduced the amidine and then the ester). Oxidation of the sulfur atom of compound **11d** was performed using **1** or 2 equiv of MCPBA to give, after reaction with propyl isocyanate and saponification, the sulfoxide **26** or the sulfone **27**, respectively. Amidification or esterification steps are described in Scheme 6. Transesterification of ethyl ester **11d** to benzyl ester **20** was performed with $Ti(O\text{-}i\text{-}Pr)_4$ in benzyl alcohol according to the methodology described by Seebach.[30] Amidification of **11d** with gaseous methylamine dissolved in MeOH was achieved under pressure, affording methylamide **21**. Amide **23** and *tert*-butyl ester **25** were prepared from acid **22** *via* known procedures: *t*-Bu exchange reaction with *N,N'*-diisopropyl-*O-tert*-butylisourea[31] for ester **25** and coupling reaction with Ile-OMe using EDC/DMAP for amide **23** (Scheme 6). However, we adopted a more general pathway for the synthesis of amide derivatives *via* the formation of the acyl chloride of acid **12d** (Scheme 7). This reaction ($SOCl_2$ in toluene) proceeded very cleanly without any interaction with the urea moiety. Treatment of the resulting acyl chloride with aqueous ammonia, methyl ester of glycine, lithium salt of acetamide, or lithium salt of phenylsulfonamide afforded the primary amide **30a**, amino acid amide **30b**, imide **30d** and phenylsulfonamide **30e**, respectively. The ester **28** was transformed to the corresponding free acid **12d** by saponification with 2 N NaOH, followed by acidification. This compound **12d** could be decarboxylated by heating under vacuum to give the 5-H derivative **29** (Scheme 7). On the other hand, saponification of ester **28** with 6 N aqueous KOH in EtOH provided directly the dipotassium salt **50** as a white precipitate.

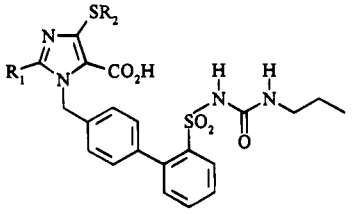
Compounds **37a–d** with a (fluoroalkyl)thio group in position 4 of the imidazole ring were synthesized using the methodology described in Scheme 8. Instead of building the suitably substituted imidazole directly (as in Scheme 1), we first synthesized the corresponding

Scheme 3[a]



[a] Reagents: (a) K_2CO_3, DMF, room temperature; (b) concentrated HCl, EtOH, reflux, 2 h; (c) O=C=NC_3H_7, K_2CO_3, acetone, reflux, 1 h; (d) 2 N NaOH, EtOH, room temperature; (e) Ac_2O, pyridine, room temperature, 1 h.

Table 2. Propylsulfonylureas: Position 2 and 4 Modification of the Imidazole Ring



compd	R1	R2	method	mp (°C)	formula[a]	yield (%)
12a	Me	Me	A	144–150	$C_{23}H_{26}N_4O_5S_2$	73
12b[b]	Et	Me	B	>260	$C_{24}H_{28}K_2N_4O_5S_2$	61
12c	*n*-Pr	Me	A	133–135	$C_{25}H_{30}N_4O_5S_2$	58
12d	*n*-Bu	Me	A	128–130	$C_{26}H_{32}N_4O_5S_2$	80
50[b]	*n*-Bu	Me	B	>260	$C_{26}H_{30}K_2N_4O_5S_2$	89
12e	c-Pr	Me	A	132–138	$C_{25}H_{28}N_4O_5S_2$	53
12f	*n*-Bu	$(CH_2)_4OAc$		150–152	$C_{31}H_{40}N_4O_7S_2$	42
12i	*n*-Bu	Ph	A	142–144	$C_{31}H_{34}N_4O_5S_2$	77
12j	*n*-Bu	2-thienyl	A	175–177	$C_{29}H_{32}N_4O_5S_3$	48
12k	*n*-Bu	$(CH_2)_3OH$	A	*c*	$C_{28}H_{36}N_4O_6S_2$	74
12l	*n*-Bu	$(CH_2)_4OH$	A	*c*	$C_{29}H_{36}N_4O_6S_2$	62

[a] All compounds exhibited NMR consistent with structure and gave satisfactory analyses C, H, N, S (0.4%). [b] As dipotassium salt. [c] Not crystallized.

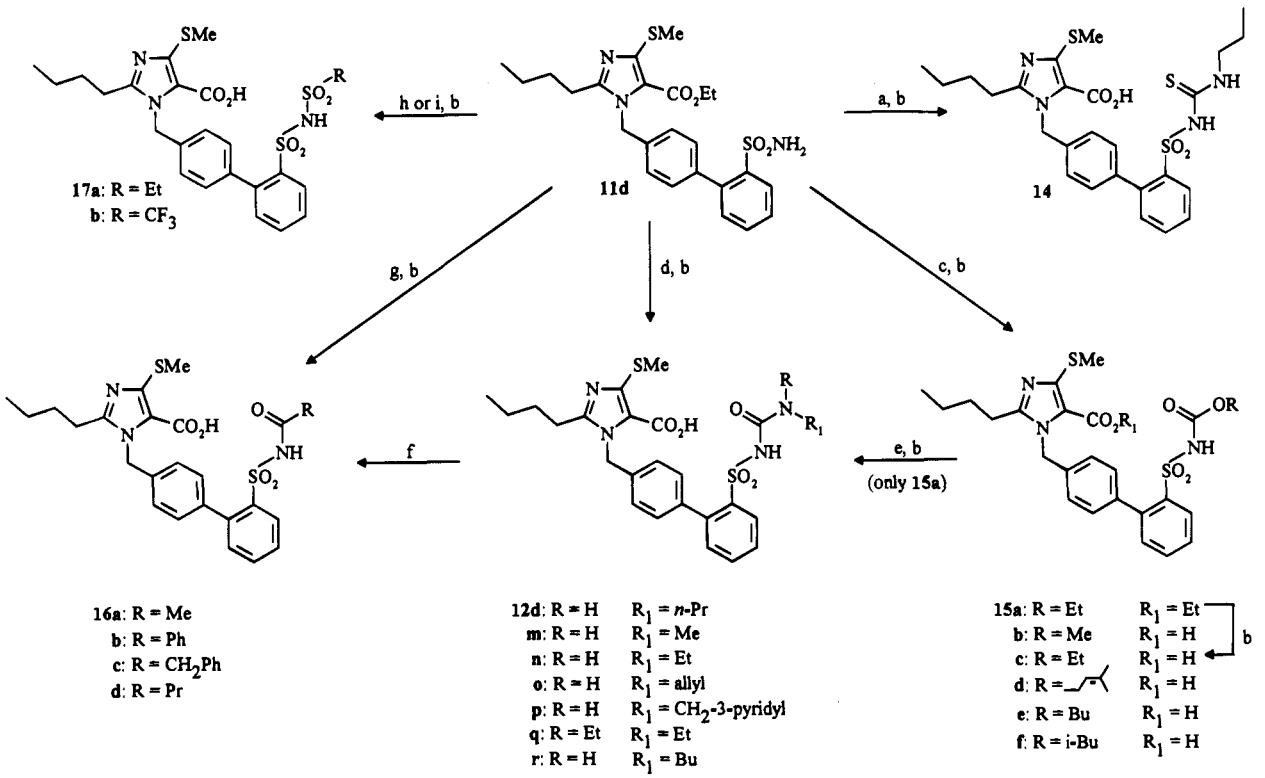
thiol followed by alkylation of the SH function with the requisite electrophile. Starting from the *p*-methoxybenzyl thiol-substituted compound **31** (obtained by coupling the biphenyl fragment **9** with imidazole **5h**), treatment with a 5:1 mixture of trifluoroacetic acid/anisole in the presence of mercuric trifluoroacetate liberated the SH group which was trapped *in situ* as mercuric salt **32**. This salt could be easily purified by column chromatography, providing **32** in 90% yield. The generation of SH occurred quantitatively under mild conditions by bubbling H_2S through an ethyl acetate solution. Filtration on Celite of the black precipitate led to pure thiol **35** which could be stored under nitrogen at −20 °C for several weeks without disulfide formation. Alkylation of this thiol **35** was carried out with various fluorinated alkyl halides in DMF. Conversion to the sodium thiolate with NaH followed by addition of sodium iodide was necessary for alkylation with $ClCH_2CF_3$ (compound **36c**) and $ClCH_2CF_2CF_2CH_2OTBDPS$ (compound **36d**) while use of iodotrifluoromethane for the synthesis of **36a** required *hν* activation. Alkylation of sodium thiolate **35** with $ClCF_2H$ (Freon 22) gave a low (30%) and not reproducible yield of **36b**. Sodium chlorodifluoroacetate (in the presence of NaI) proved to be the reagent of choice for this transformation, leading directly from thiol **35** to the $SCHF_2$ derivative **36b** in 75% yield (*via in situ* decarboxylation). Deprotection of the amidine followed by condensation with propyl isocyanate and saponification afforded the desired fluorinated thio derivatives **37a–d** (Scheme 8). The mercury salt **32** could also be used directly for an electrophilic attack of $ClCH_2SMe$ in presence of NaI to yield very cleanly the SCH_2SCH_3-substituted compound **33**.

The 4-chloro derivative **49** was obtained by coupling chloro aldehyde **46**[11] with the biphenyl moiety **9**, followed by oxidation of the aldehyde to the methyl ester according to Corey's procedure,[32] deprotection of the amidine, reaction with propyl isocyanate, and final saponification (Scheme **10**).

Results and Discussion

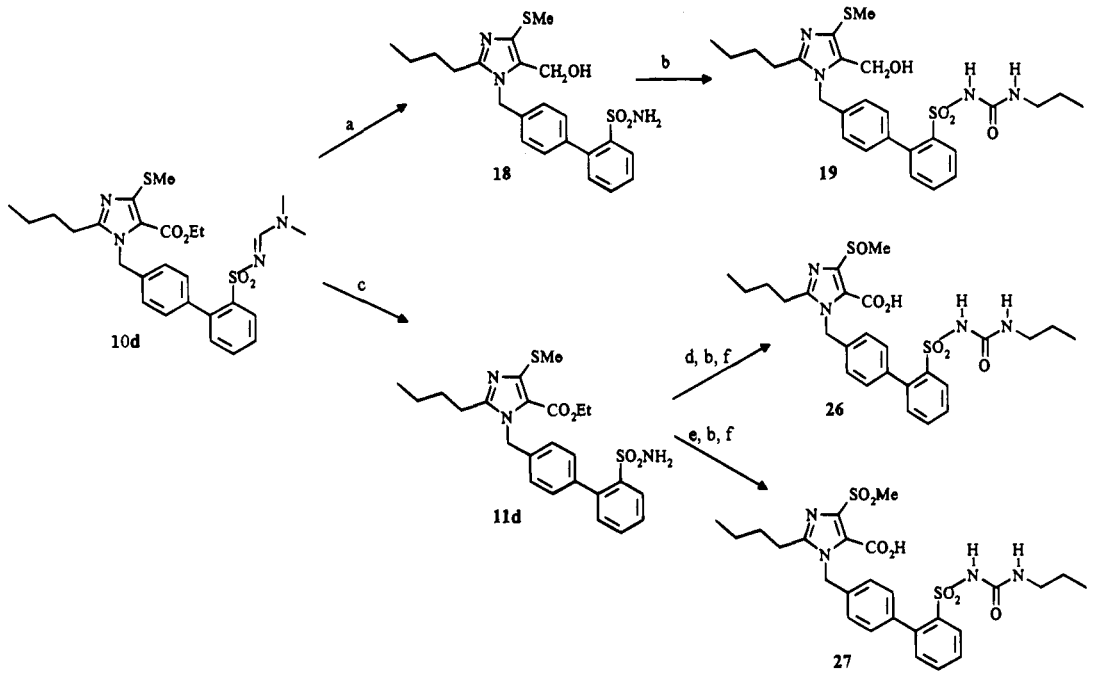
The compounds described in this paper were tested for their affinity for the AT_1 receptor as measured by their ability to displace [^{125}I]AII from its specific binding sites in rat liver membrane preparation. Se-

Scheme 4[a]



[a] Reagents: (a) $CH_3CH_2CH_2N{=}C{=}S$, K_2CO_3, acetone, reflux, 15 h; (b) 2 N NaOH, EtOH, room temperature, 4 d; (c) RCOCl, K_2CO_3, DME, reflux; (d) $R_1N{=}C{=}O$, K_2CO_3, DME, reflux; (e) RR_1NH, toluene, reflux; (f) only on **12d**: Ac_2O, reflux 2 h; (g) RCOCl, DMAP, toluene, 70 °C, 30 min; (h) $EtSO_2Cl$, K_2CO_3, diglyme, reflux 12 h; (i) Tf_2O, TEA, CH_2Cl_2, −60 °C, 1 h.

Scheme 5[a]

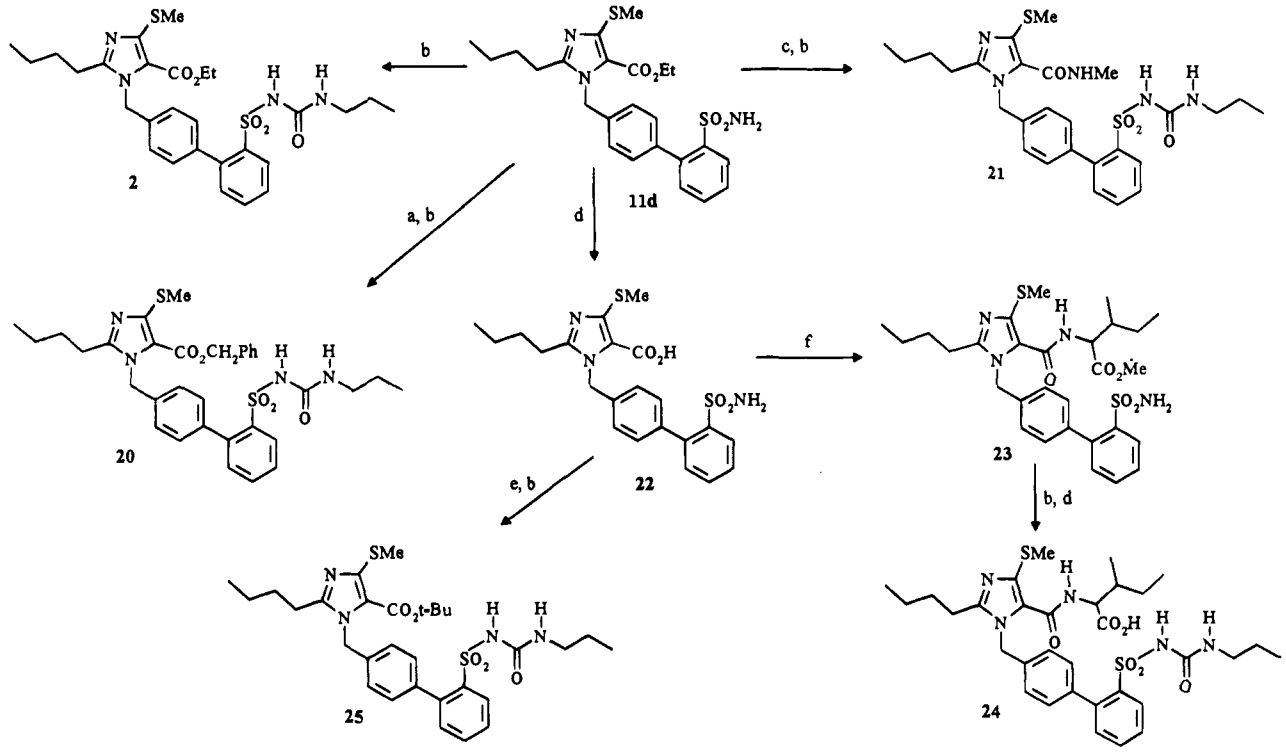


[a] Reagents: (a) $LiAlH_4$, THF, reflux 3 h; (b) $CH_3CH_2CH_2N{=}C{=}O$, K_2CO_3, acetone, reflux, 2 h; (c) concentrated HCl, EtOH, reflux, 2 h; (d) MCPBA (1 mol), CH_2Cl_2, room temperature, 1 h; (e) MCPBA (2.5 mol), CH_2Cl_2; (f) 2 N NaOH, MeOH, room temperature, 24 h.

lected compounds were further evaluated *in vivo* after intravenous as well as oral administration toward the inhibition of the pressor response induced by AII (0.75 μg/kg iv) in normotensive pithed rats.

Acidic Sulfonamides as Tetrazole Isosteres. As mentioned above, the 2′-biphenyl position needs an acidic function, and even if a few compounds in clinical trials still bear a carboxylic acid,[15] in most cases the tetrazole moiety has been found to fulfill this need better with higher binding affinity and enhanced oral absorption.[11] A few years ago, for the reasons explained above, we initiated a search for new non-tetrazolic AII antagonists. Taking into consideration that the pK_a range of arylsulfonylurea (estimated to be 5.5−7.5)[33] is similar to that of aryltetrazole (5−6),[34] it was therefore considered reasonable to investigate sulfonylureas (and by

Scheme 6[a]



[a] Reagents: (a) $PhCH_2OH$, $Ti(O\text{-}i\text{-}Pr)_4$, 140 °C; (b) $CH_3CH_2CH_2N{=}C{=}O$, K_2CO_3, acetone, reflux, 2 h; (c) CH_3NH_2, MeOH, 80 °C, 60 h; (d) 2 N NaOH, MeOH, room temperature, 24 h; (e) $i\text{-}C_3H_7NHC(O\text{-}t\text{-}C_4H_9){=}N\text{-}i\text{-}C_3H_7$, CH_2Cl_2, room temperature, 10 h; (f) L-isoleucine methyl ester hydrochloride, EDC, EtOAc, room temperature, 16 h.

extension other sulfonyl derivatives) as possible tetrazole isosteres. The chemistry of sulfonylureas has been widely investigated for a number of therapeutic targets. For example, the most established potassium channel modulators such as Gibenclamide (in clinic for type II diabetes mellitus) are sulfonylureas.[35] Moreover, replacement of a carboxyl group by a sulfonylurea moiety has already been achieved successfully[36] and led in that case to the discovery of Torasemide,[37] a potent diuretic agent.

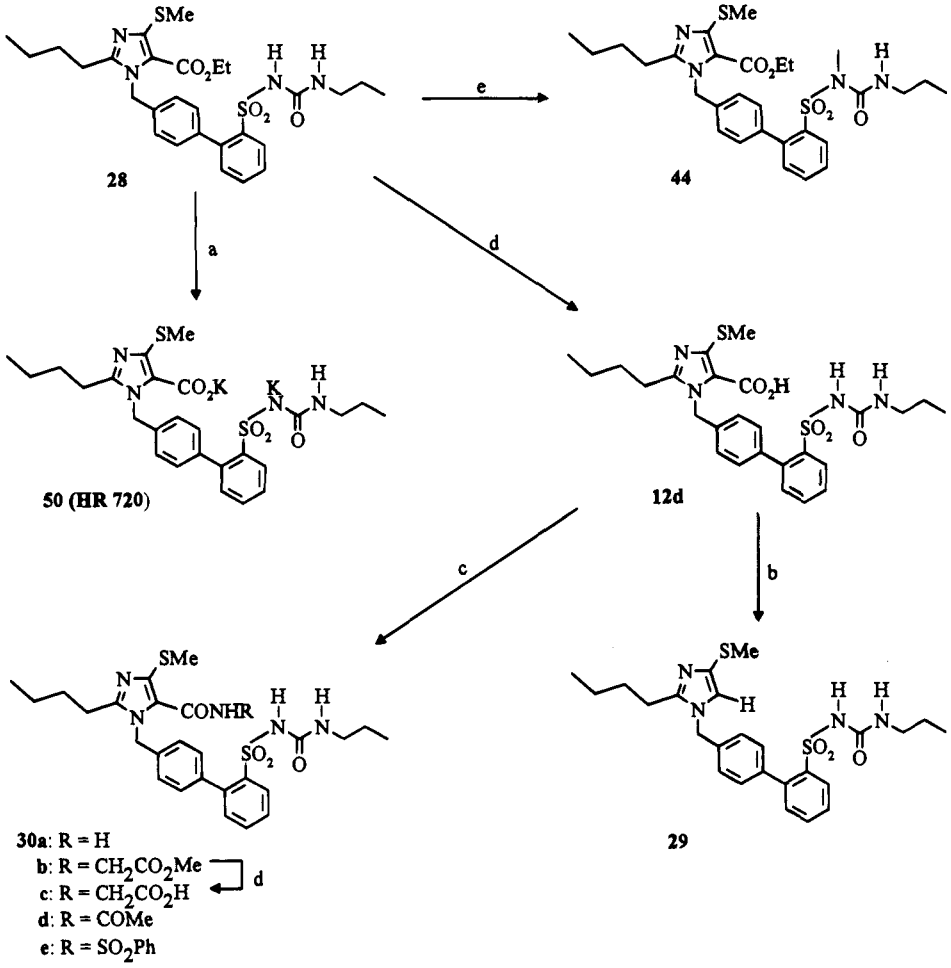
As already noted, imidazole biphenylyltetrazole **45** has proven to be a potent orally active AII antagonist[20] (ID_{50} 0.5 mg/kg po). Replacing the tetrazole in this compound by a sulfonylurea and also by a sulfonylcarbamate, a sulfonylamide, and a sulfonylsulfonamide provided compounds **12**, **15**, **16**, and **17**, respectively. Most of them displayed binding affinity in the nanomolar or subnanomolar range, comparable to the corresponding tetrazole **45** (IC_{50} 0.2 nmol), as shown in Table 3. These data clearly demonstrate that sulfonyl derivatives are suitable surrogates for the tetrazole moiety concerning *in vitro* AII antagonism. Conversely, the parent sulfonamide **11d** (Table 4) is 100-fold less active than the corresponding propylsulfonylurea **12d**, which could be explained by the different pK_a values of the acidic NH functions in **11d** (pK_a = 10.8) and **12d** (pK_a = 7). It is worth noting that the measured pK_a values of our sulfonyl derivatives (between 6 and 7) are comparable to those of the corresponding tetrazole derivatives (between 5 and 6). These data confirm that an acidic group is necessary at this position to make an ionic interaction with a putative basic site on the AT_1 receptor, as it was first suggested by the Du Pont's investigators.[11] The importance of the acidity of NH function in sulfonyl derivatives was clearly demonstrated by N-methylation of sulfonylurea **28** which resulted in the 200-fold less active compound **44** (Table 4). In the same way, replacing the sulfonylurea function of **12d** by the carbonylurea group (**43**) resulted in a more than 200-fold decrease in potency, illustrating again that a less acidic NH function (pK_a = 12.3 for carbonylurea **43** vs pK_a = 7 for sulfonylurea **12d**) is correlated with lower receptor affinity.

From the various sulfonyl derivatives **12**, **15**, **16**, and **17** investigated (Table 3), only the sulfonylsulfonamides **17** behaved quite differently. Although all of them displayed similar affinity to the AT_1 receptor, the sulfonylsulfonamides **17a,b** indeed showed only weak activity (>1 mg/kg) after intravenous administration in inhibiting the AII-induced increase in blood pressure in rats, and consequently, this series was not investigated any further.

Conversely, sulfonylcarbamates **15**, sulfonylureas **12**, and acylsulfonamides **16** (Table 3) displayed iv and oral potency, depending on the length of the side chain substitution. When intravenously administered, these acidic sulfonamides inhibited the AII-induced pressor response in pithed rats at low doses from 0.06 to 0.44 mg/kg for **12d–r**, **15b–f** and **16a–d**. They were further evaluated for oral activity. In the carbamate series, the ethyl side chain was found to be the most effective substitution, the ethyl carbamate **15c** (ID_{50} 0.38 mg/kg) being 4-fold more active po than its methyl analogue **15b**. Increasing the length of the side chain with the *n*-butyl or isobutyl substituent gave rise to the potent carbamates **15e** and **15f**, respectively, albeit slightly less effective po than the ethylcarbamate **15c**.

Sulfonylureas **12** (Table 3) displayed the same kind of oral activity, enhanced with a longer alkyl chain on the urea nitrogen, the propyl and the butyl substituents being optimal among the compounds prepared: butyl

Scheme 7[a]



[a] Reagents: (a) 6 N KOH, EtOH, room temperature; (b) 140 °C (0.06 bar), 1 h; (c) (1) $SOCl_2$, toluene, 50 °C, overnight; (2) for **30a**, NH_4OH, dioxane, room temperature; for **30b**, $H_2NCH_2CO_2CH_3$/HCl, TEA, THF, room temperature; for **30d**, $LiNHCOCH_3$, THF, −60 °C to 0 °C, 1 h; for **30e**, $LiNHSO_2Ph$, THF, −78 °C to room temperature, 2 h; (d) 2 N NaOH, MeOH, room temperature, 24 h; (e) CH_2N_2, CH_2Cl_2.

(**12r**, 0.21 mg/kg) > propyl (**12d**, 0.40 mg/kg) > allyl (**12o**, 0.57 mg/kg) > ethyl (**12n**, 1.12 mg/kg) > methyl (**12m**, 4.94 mg/kg). However, the more lipophilic butyl side chain also significantly increased the binding affinity for the AT_2 receptor subtype of AII (IC_{50} 96 nmol) when compared to its propyl analogue **12d** (IC_{50} 920 nmol). Thus, *N*-propylsulfonylurea **12d** proved to be the best compromise between oral potency and AT_1 selectivity.

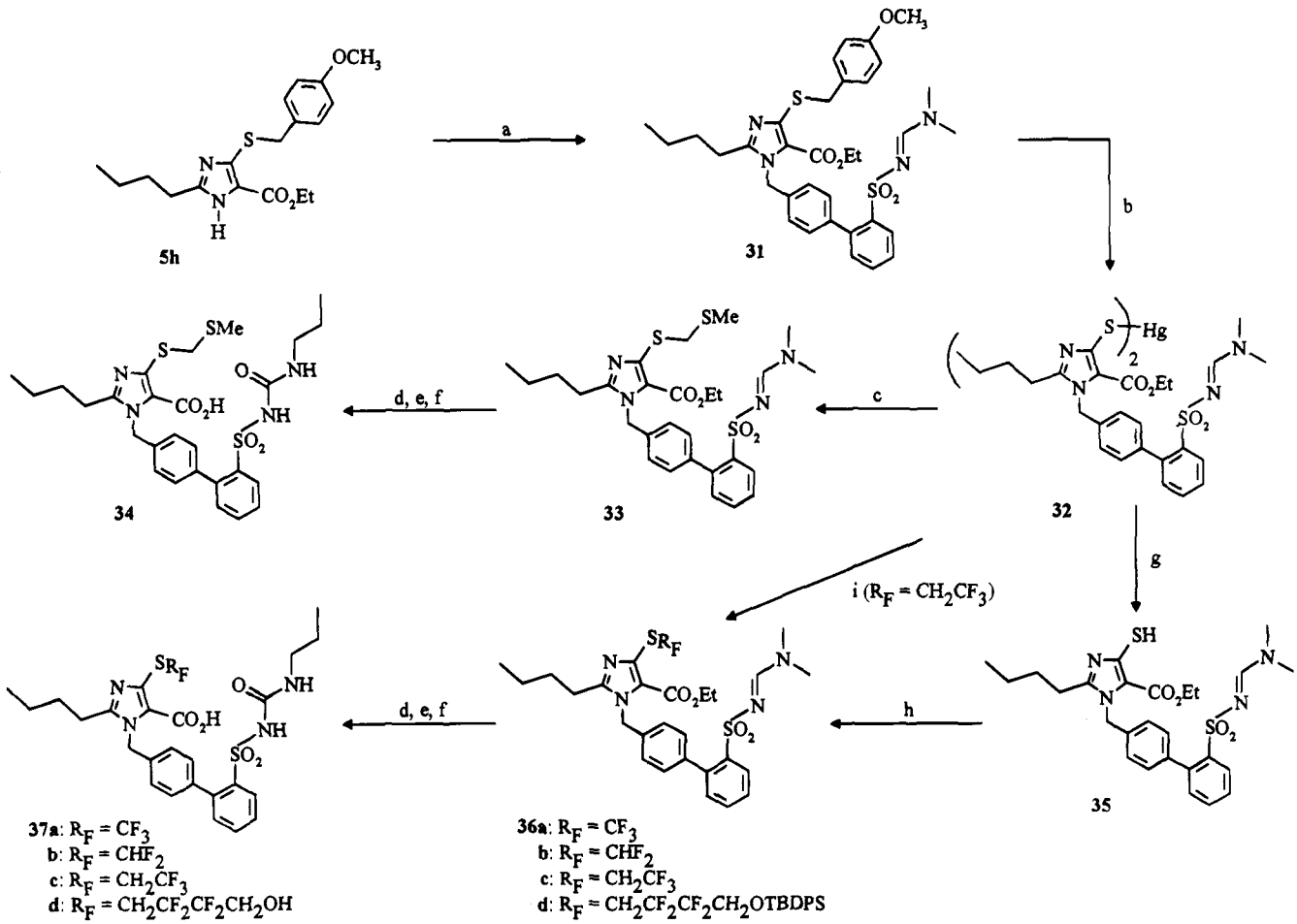
Only little work has been undertaken on acylsulfonamides **16**. Among the four compounds (**16a−d**) synthesized, the propylacylsulfonamide **16d** exhibited the higher oral activity (ID_{50} 0.95 mg/kg) but was still slightly less active when compared to the ethylcarbamate **15c** and the optimized propylsulfonylurea **12d**. The results obtained with compounds **16a−d** did not incite us to focus further on this series, contrary to Merck's investigators.[24d-l]

Therefore, our initial assumption that a sulfonyl derivative could be a promising isosteric surrogate to the tetrazole turned out to be correct both *in vitro* and *in vivo*. In our general screening tests (IC_{50}, ID_{50} iv and po), *N*-propylsulfonylurea **12d** and ethyl sulfonylcarbamate **15c** proved to be as effective as the corresponding tetrazole derivative **45**. In depth *in vivo* evaluation was undertaken in various animal models in order to discriminate these three potent antagonists. *N*-Propylsulfonylurea **12d** and ethyl sulfonylcarbamate **15c** showed a favorable pharmacological profile with in particular a long duration of action in several species (dog, minipig) superior to that of tetrazole **45** (see Figures 3 and 4 for the duration of action of compound **50** in dog, the dipotassium salt of urea **12d**). Among these two sulfonyl compounds with similar *in vivo* profile, *N*-propylurea **12d** was preferred to ethyl carbamate **15c** because of putative higher stability of ureas vs carbamates and also because we feared a lack of specificity of carbamates.[38]

During the course of this work, other companies have discovered independently potent tetrazole isosteres. Glaxo scientists[23] found the acidic triflamide $NHSO_2CF_3$ group to enhance oral absorption in comparison to the tetrazole group, which prompted, after imidazole SAR, the selection of GR 138950 for clinical evaluation. Merck researchers[24] also envisioned the potential of sulfonyl replacements of tetrazole in the AII antagonists field and reported recently the exchange of tetrazole by various acidic sulfonamides (sulfonylureas, sulfonylcarbamates, acylsulfonamides) in their imidazole,[24c,d,j] imidazopyridine,[24a,e,f] and triazolinone series.[24b,i,l]

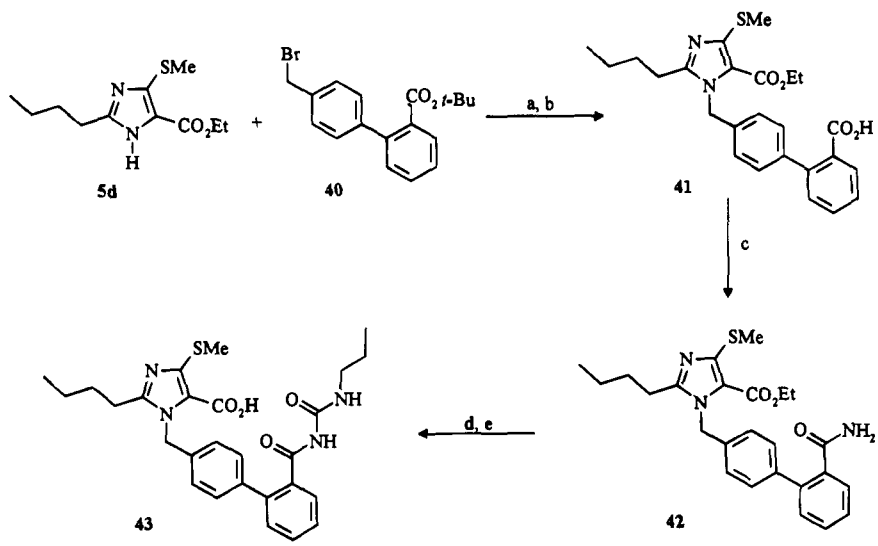
SAR on the Imidazole Ring. After selection of the propyl sulfonylurea as the most effective tetrazole surrogate, we continued our work by optimization of the substituents in remaining positions 2, 4, and 5 on the imidazole ring.

Scheme 8[a]



[a] Reagents: (a) **9**, K_2CO_3, DMF, room temperature; (b) $Hg(CF_3CO_2)_2$, TFA, anisole, 0 °C to room temperature, 20 min; (c) $ClCH_2SCH_3$, NaI, DMF, room temperature, 2 h; (d) concentrated HCl, MeOH, 50 °C, 18 h; (e) $CH_3CH_2CH_2N{=}C{=}O$, K_2CO_3, acetone, reflux; (f) 2 N NaOH, EtOH, room temperature; (g) H_2S, EtOAc, room temperature, 45 min; (h) for **36a**, (1) NaH, DMF, 0 °C; (2) $BrCF_3$, *hv*, 0 °C, 1 h; for **36b**, $ClCHF_2CO_2Na$, NaI, DMF, 87 °C, 45 min; for **36d**, (1) NaH, DMF; (2) $ICH_2CF_2CF_2CH_2OSi(Ph)_2$-*t*-Bu **51**, DMF, 80 °C, 2 h; (i) ICH_2CF_3, NaI, DMF, 50 °C, 2 h.

Scheme 9[a]

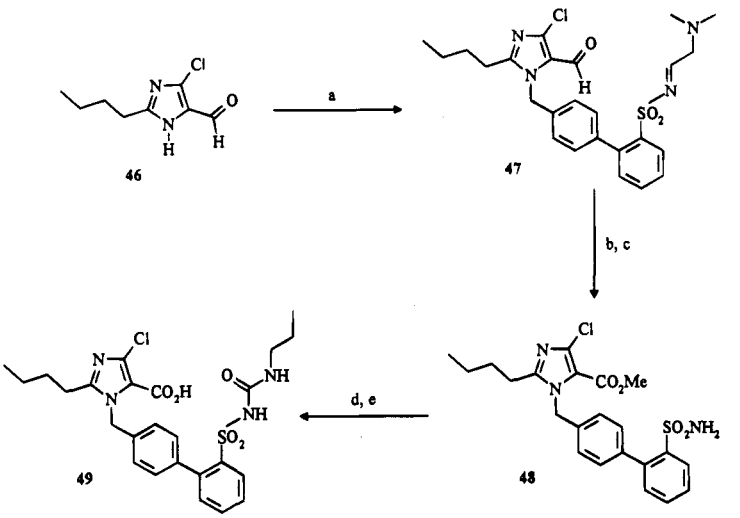


[a] Reagents: (a) K_2CO_3, DMF, room temperature, 16 h; (b) CF_3COOH, CH_2Cl_2, room temperature, 6 h; (c) (1) $SOCl_2$, Δ, 4 h; (2) NH_4OH, room temperature, 30 min; (d) C_3H_7NCO, K_2CO_3, acetone, Δ, 6 h; (e) NaOH, EtOH, room temperature.

***In Vitro* AII Antagonism.** We first turned our attention to the 2-position of the imidazole ring (Table 5). As expected, the activity increased with the length of the unbranched carbon chain from methyl to butyl (**12a–d**), with optimal affinity in the *n*-propyl[39] (**12c**) and *n*-butyl (**12d**) substituted compounds. Substitution of *n*-propyl by cyclopropyl group (**12e**) was correlated with a 35-fold loss of activity.

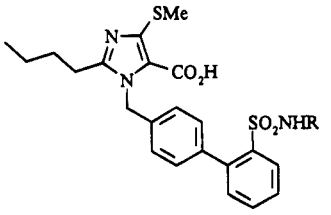
SARs at the 4-position of the imidazole ring are illustrated by the data summarized in Table 6. Most

Scheme 10[a]



[a] Reagents: (a) **9**, K_2CO_3, DMF, room temperature, 16 h; (b) MnO_2, NaCN, AcOH, MeOH; (c) concentrated HCl, EtOH, Δ, 2 h; (d) C_3H_7NCO, acetone, K_2CO_3, Δ, 2 h; (e) NaOH, EtOH, room temperature, 16 h.

Table 3. SAR at the 2'-Biphenyl Position

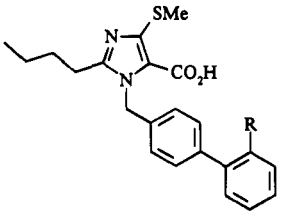


compd	R	IC_{50}[a] (nM)	ID_{50}[b] (mg/kg) iv	ID_{50}[b] (mg/kg) po
12m	CONHMe	1.9	0.27 ± 0.07	4.94 ± 1.95
12n	CONHEt	0.2	0.17 ± 0.03	1.12 ± 0.49
12d	CONHPr	0.3	0.13 ± 0.01	0.40 ± 0.21
12o	CONHallyl	1.1	0.11 ± 0.02	0.57 ± 0.26
12r	CONHBu	0.2	0.09 ± 0.01	0.21 ± 0.10
12p	$CONHCH_2$-3-pyridyl	0.9	NT[c]	NT
12q	$CONEt_2$	4.7	NT	NT
15b	COOMe	0.9	0.10 ± 0.04	1.54 ± 0.47
15c	COOEt	0.9	0.07 ± 0.01	0.38 ± 0.14
15d	$COOCH_2C{=}CMe_2$	1.8	NT	NT
15e	COOBu	0.1	0.10 ± 0.01	0.60 ± 0.13
15f	COO-*i*-Bu	0.2	0.15 ± 0.01	0.43 ± 0.15
16a	COMe	1.0	0.13 ± 0.05	2.02 ± 0.80
16d	COPr	0.2	0.06 ± 0.01	0.95 ± 0.38
16b	COPh	0.09	0.40 ± 0.05	NT
16c	$COCH_2Ph$	0.08	0.44 ± 0.05	1.75 ± 0.64
17a	SO_2Et	1.1	>1[d]	NT
17b	SO_2CF_3	0.8	1.45 ± 0.37	NT

[a] IC_{50} for inhibition of specific binding of [^{125}I]AII to rat liver membrane preparation (n = 1–3). For details, see the Experimental Section. [b] ED_{50} following intravenous (n = 4) or oral (n = 18–28) administration to pithed rats for inhibition of pressor response induced by infusion of AII. [c] NT for not tested compound. [d] Intraduodenally administrated.

of the compounds (**12**, **37**) bearing an arylthio or alkylthio group—with various alkyl chains up to four carbon atoms, substituted or not by fluorine atoms, alkoxy, acetyloxy, or methylthio groups—showed subnanomolar potency toward the AT_1 receptor. This suggests that the receptor accepts bulky substituents at this 4-position, which was consistent with the results obtained in the tetrazole series.[20] Replacement of the methylthio group of imidazole **12d** by a chlorine atom (**49**) led to the imidazole ring of EXP 3174 with a slight decrease in potency *in vitro*. However, introduction at this 4-position of a more polar group such as the methylsulfinyl (**26**) or the methylsulfonyl (**27**) substituent decreased binding affinity by 10-fold when compared to the (methylthio)imidazole **12d**.

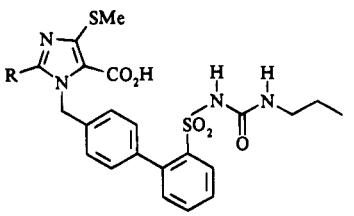
Table 4. SAR at the 2'-Biphenyl Position



compd	R	IC_{50}[a] (nM)	ID_{50}[b] (mg/kg) iv	ID_{50}[b] (mg/kg) po
11d	SO_2NH_2	36	5.60 ± 2.16	>30
12d	$SO_2NHCONHPr$	0.3	0.13 ± 0.01	0.40 ± 0.21
44	$SO_2NMeCONHPr$[d]	78	NT[c]	NT
43	CONHCONHPr	114	NT	NT
14	$SO_2NHCSNHPr$	2.1	1.15 ± 0.32	NT

[a–c] See Table 3 for an explanation of tabulated data. [d] Ethyl ester at the 5-position of imidazole ring.

Table 5. SAR at the Imidazole 2-Position

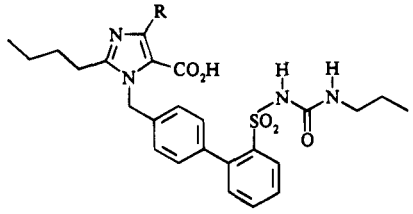


compd	R	IC_{50}[a] (nM)
12a	Me	15
12b	Et	1.3
12c[b]	Pr	0.2
12d	Bu	0.3
12e	c-Pr	7.7
13	N_3 regioisomer of **12d**	103

[a] See Table 3 for an explanation of tabulated data. [b] For *in vivo* evaluation of **12c**, see ref 39.

A great variety of other substituents to the carboxyl group also proved to fulfill the imidazole 5-position requirements (Table 7). Binding affinity was indeed retained when the carboxyl group was replaced by neutral substituents (amides **21** and **30a,b** and esters **20**, **25**, and **28**) as well as by other acidic functions

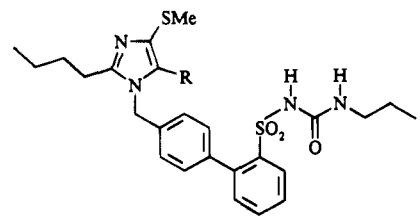
Table 6. SAR at the Imidazole 4-Position



compd	R	IC_{50}[a] (nM)	ID_{50}[b] (mg/kg) iv	ID_{50}[b] (mg/kg) po
12d	SMe	0.3	0.13 ± 0.01	0.40 ± 0.21
12i	SPh	0.3	0.67 ± 0.10	>10
12j	S-2-thienyl	0.2	2.01 ± 0.62	NT[c]
12k	$S(CH_2)_3OH$	0.2	0.11 ± 0.01	5.74 ± 2.20
12l	$S(CH_2)_4OH$	0.4	0.12 ± 0.01	9.81 ± 2.47
12f	$S(CH_2)_4OAc$	0.3	0.60 ± 0.22	>10
37d	$SCH_2CF_2CF_2CH_2OH$	0.3	0.83 ± 0.35	5.30 ± 1.02
34	SCH_2SMe	0.2	NT	2.75 ± 0.16
37a	SCF_3	0.8	0.11 ± 0.01	1.28 ± 0.98
37b	$SCHF_2$	0.5	0.07 ± 0.01	0.73 ± 0.15
37c	SCH_2CF_3	0.6	0.80 ± 0.20	2.28 ± 0.98
26	SOMe	3.1	0.14 ± 0.03	>10
27	SO_2Me	3.2	0.06 ± 0.01	>10
49	Cl	1.0	0.16 ± 0.04	3.10 ± 2.2

[a-c] See Table 3 for an explanation of tabulated data.

Table 7. SAR at the Imidazole 5-Position



compd	R	IC_{50}[a] (nM)	ID_{50}[b] (mg/kg) iv	ID_{50}[b] (mg/kg) po
12d	CO_2H	0.3	0.13 ± 0.01	0.40 ± 0.21
19	CH_2OH	4.5	0.21 ± 0.05	>10
29	H	2.6	0.70 ± 0.10	>10
20	CO_2CH_2Ph	0.1	0.20 ± 0.02	1.73 ± 0.41
25	CO_2-*t*-Bu	0.6	0.10 ± 0.01	NT[c]
28	CO_2Et	0.4	0.08 ± 0.005	1.13 ± 0.29
21	CONHMe	2.1	0.02 ± 0.003	4.86 ± 0.97
24	CONH-IleOH	0.3	0.37 ± 0.03	2.11 ± 0.82
30a	$CONH_2$	1.0	0.06 ± 0.01	2.83 ± 0.79
30b	$CONHCH_2CO_2Me$	0.8	0.05 ± 0.01	2.40 ± 1.85
30c	$CONHCH_2CO_2H$	1.5	0.06 ± 0.005	3.55 ± 1.29
30d	CONHCOMe	1.7	0.09 ± 0.01	3.01 ± 0.65
30e	$CONHSO_2Ph$	0.8	1.15 ± 0.19	NT
50[d]	CO_2K	0.48	0.11 ±0.01	0.70 ± 0.10

[a-c] See Table 3 for an explanation of tabulated data. [d] **50** is the dipotassium salt of **12d**.

(imide **30d** and sulfonamide **30e**). It therefore seems unlikely that the imidazole-5-carboxylic acid of **12d** participates in a full ionic interaction with the receptor, as if this were the case, the above mentioned modifications would lead to more drastic falls in potency. Only decarboxylated 5*H*-imidazole **29** and alcohol **19** displayed lower binding affinity. All these data are consistent with the assumption of a possible hydrogen bond between the receptor and the imidazole 5-substituent.

However, although many substitutions at the 4- and 5-position of the imidazole ring were acceptable, compound **13** (Table 5), the regioisomer of **12d**, was found to be 300-times less active, illustrating the importance of the relative disposition of the different pharmacophores.

***In Vivo* AII Antagonism.** The most active compounds at the receptor level have been chosen for *in vivo* evaluation in order to define precisely the appropriate substitution for oral activity.

In vivo SAR at the 4-position of the imidazole ring are summarized in Table 6. Despite high binding affinity, the arylthio derivatives **12i** and **12j** showed weak activity after intravenous administration while substitution with $S(CH_2)_nOH$ retained the potency iv. Surprisingly,[40] compounds **12k,l** showed poor oral activity and modification of lipophilicity with introduction of an acetate (compound **12f**) or polyfluoroalkyl chain (compound **37d**) failed to enhance significantly the oral antihypertensive activity. This suggests that too long side chains in position 4 are detrimental to oral activity in the biphenylsulfonylurea series. Maximum oral efficacy was observed with the shorter methylthio derivative **12d**. Substitution of the methylthio (**12d**) by more lipophilic $SCHF_2$ (**37b**) or SCF_3 groups (**37a**) also afforded compounds with good oral activity albeit not as potent as **12d**, while increasing the chain length by one carbon resulted in compound **37c** 2-fold less active po (Table 6). It is noteworthy that replacement of the methylthio group by a chlorine atom in **12d** gave compound **49**[41] with comparable *in vitro* affinity and intravenous activity, but with an 8-fold drop in oral potency, thus illustrating the crucial role of the methylthio group for potent oral activity in this sulfonylurea series. Oxidation to methylthio sulfoxide **26** and sulfone **27** resulted in a complete loss of oral activity, while their intravenous activity remained high.

The modifications at the 5-position of the imidazole ring summarized in Table 7 indicate the contribution of the carboxyl group to the *in vivo* activity. Decarboxylated compound **29** and alcohol **19**, in accordance with their weaker binding affinity, exhibited no oral potency. Replacement of the carboxyl group with a neutral primary (**30a**) or secondary amide (**21**) significantly enhanced the inhibitory activity after intravenous administration, but these compounds displayed only limited oral activity. Introduction of a carboxyl function *via* the synthesis of the amino acid amide **24** and **30c** did not improve oral bioavailability, and esterified glycine amide **30b** also suffered from poor oral absorption. The more acidic imide **30d** had similar oral potency, while the sulfonamide **30e** unexpectedly exhibited a 20-fold weaker potency after intravenous administration.

A series of simple ester prodrugs (ethyl **28**, benzyl **20**, and *tert*-butyl **25**) was also investigated (Table 7). These three esters were found to show similar efficacy as the corresponding acid **12d** when evaluated intravenously, and ethyl ester **28** proved to be the most active after oral administration in pithed rats. However, compounds **20**, **25**, and **28** antagonized the pressor response of AII with only a short duration of action when compared to **12d** in conscious normotensive rats (data not shown).

These findings indicate that a carboxyl group in position 5 of the imidazole ring is not needed for high binding affinity but is essential for potent oral activity in this imidazole biphenylsulfonylurea series.

Therefore, imidazole **12d** with a 2-butyl chain, a 4-methylthio group and a 5-carboxylic acid connected to a methylbiphenyl *N*-propylsulfonylurea was selected. The corresponding dipotassium salt **50** was synthesized to improve water solubility (500 mg/mL) and is currently under phase II clinical evaluation under the code name HR 720.[25]

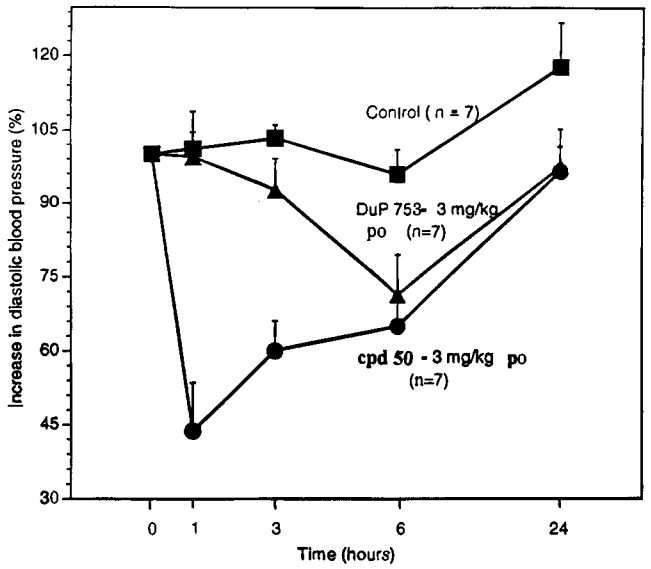


Figure 1. Effects of oral administration of compound **50** and DuP 753 (3 mg/kg po) on angiotensin II response in normotensive conscious rats. Results are shown as mean ± SEM.

Pharmacological Profile of compound 50. Compound **50** is a selective AT_1 receptor antagonist with IC_{50}s of 0.48 and 920 nM for AT_1 (rat liver) and AT_2 (rabbit uterus) membrane preparation, respectively. When administered iv or po prior to a fixed dose of AII (0.75 μg/kg iv) in the normotensive pithed rat, compound **50** induced a dose-dependent inhibition of the pressor response to AII with ID_{50} of 0.11 ± 0.01 mg/kg iv (n = 10) and 0.7 ± 0.1 mg/kg po (n = 27), respectively, compared to 0.39 ± 0.04 mg/kg iv (n = 12) and 3.8 ± 0.3 mg/kg po for DuP 753 (n = 23). Intravenous administration of **50** before pressor response to AII in pithed spontaneously hypertensive rat produced a dose-dependent (from 0.03 to 1 mg/kg) rightward and downward shift of the dose–response curve to AII, indicating an insurmountable antagonism (data not shown). In normotensive conscious rat, **50** antagonized the AII-induced pressor response after oral administration with a maximum reduction in blood pressure observed one hour post dose (Figure 1). This rapid onset of action was also observed in the renal hypertensive rat where compound **50** induced a dose dependent antihypertensive effect which remained stable for more than 24 h (Figure 2).

Inhibition of the pressor effects of AII (0.15 μg/kg iv) was studied in the conscious mongrel dog after oral administration of **50**. The decrease in AII response was dose-dependent and compound **50**, at 1–10 mg/kg po, produced a marked decrease in blood pressure, which reached a plateau after 5 h and lasted for up to 24 h (Figure 3). This long duration of action was also observed in conscious hypertensive dogs where **50**, at 3 mg/kg, proved to be much more potent than EXP 3174, the active metabolite of DuP 753 (Figure 4). The same pharmacological profile with a marked and long-lasting effect was observed in minipigs (data not shown). These data may be correlated with the superior oral bioavailability of **50** (F 30% in dogs)[42] when compared to that of EXP 3174[43] or other diacidic antagonists (F 12–15% in dogs for DUP 532 and DMP 811, Chart 2).[44] Moreover, the longer duration of action of **50** compared to other AII antagonists may be explained by the very slow dissociation constant of the receptor antagonist complex.[45]

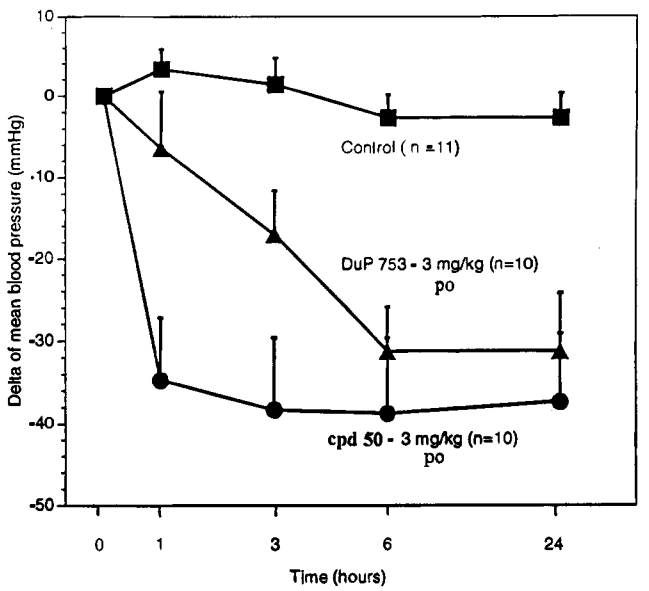


Figure 2. Effects of oral administation of compound **50** and DuP 753 (3 mg/kg po) on mean blood pressure in renal hypertensive conscious rats. Results are shown as mean ± SEM.

Conclusion

The tetrazole moiety of AII receptor antagonists has been successfully replaced by acidic sulfonamide groups. The N-propylsulfonylurea and ethyl sulfonylcarbamate moieties were shown to exhibit high potency both at the receptor level and after *in vivo* evaluation. This clearly demonstrates that acidic sulfonamides could be a promising isosteric surrogates to the tetrazole moiety with an improvement of the pharmacological profile of the antagonist (especially concerning duration of action).

The structure activity relationships around the imidazole ring (connected to the biphenyl N-propylsulfonylurea) led to similar requirements to the corresponding tetrazole series.[20] Both the methylthio and carboxyl group appeared to be the most suitable substitution at the 4- and 5-positions of the imidazole ring, respectively.

This led to the discovery of compound **50** (HR 720, dipotassium salt of **12d**) as a potent, non-tetrazole, AT_1-selective AII receptor antagonist. This orally active compound produces a marked and long lasting decrease in blood pressure in high renin animal models and proved to be superior to the corresponding tetrazole **45** as well as to DuP 753 or its active metabolite EXP 3174. On the basis of this profile, compound **50** has been chosen as a candidate for clinical investigations for treatment of hypertension and congestive heart failure.

Experimental Section

Physical Methods. Melting points are uncorrected and were measured with a Reichert Heizbank Kofler system. Each analytical sample was homogeneous by TLC performed on silica gel (Kieselgel 60 F 254-Merck) plates, which were visualized with UV light or iodine vapor. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). ^1H NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 on Bruker AM 250, AC 300, or AM 400 instruments and are reported as values (ppm) downfield from TMS. IR spectra were recorded on Nicolet FTIR 20 SX or Nicolet FTIR 5 SXB spectrophotometers and were run in $CHCl_3$ or in Nujol. Mass spectra (EI, FAB, SIMS) were recorded on FINNIGAN/4500 (quadrupolar), VG ZAB. HFQ or VG Auto SPEC E mass spectrometers. Elemental analyses were within ±0.4% of theoretical values and were determined in the Analytical Department of Roussel Uclaf and Hoechst AG.

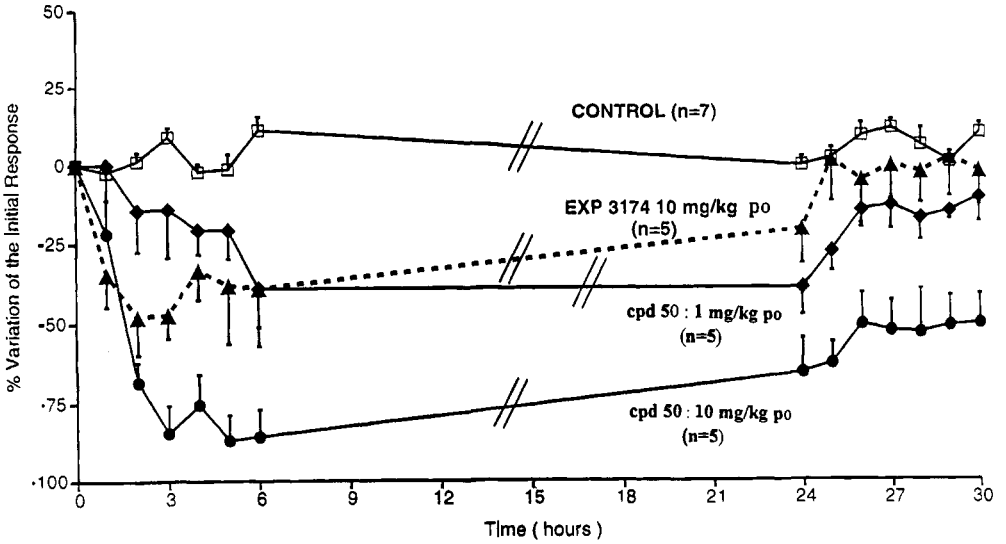


Figure 3. Effects of oral administration of compound **50** (1 and 10 mg/kg po) and EXP 3174 (10 mg/kg po) on angiotensin II induced increase in diastolic blood pressure in conscious dogs. Data show as mean with SE bars. Results are shown as mean ± SEM.

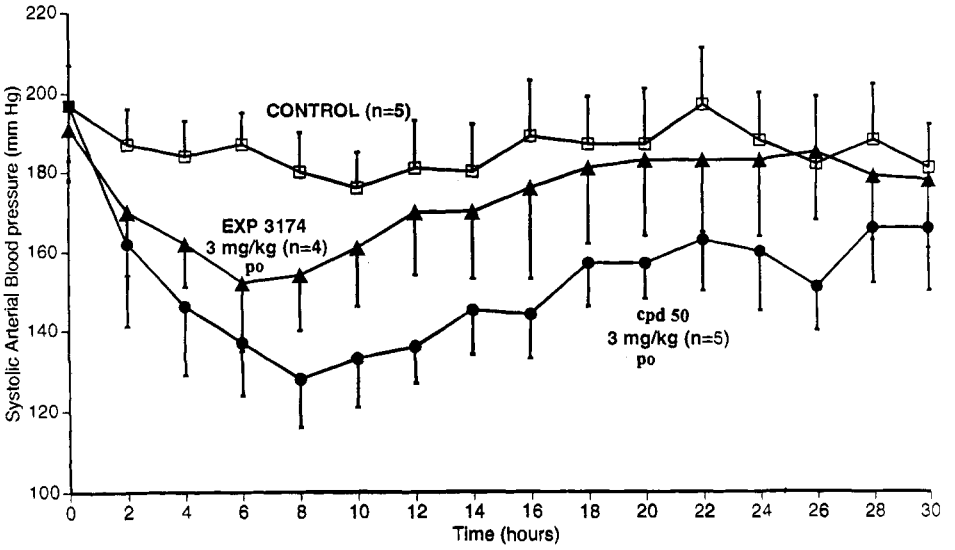
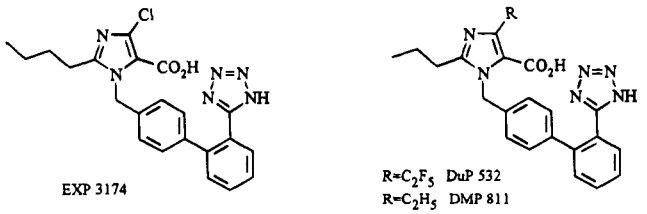


Figure 4. Effect of oral administration of compound **50** and EXP 3174 at 3 mg/kg po on systolic arterial blood pressure in conscious sodium depleted hypertensive dogs. Results are shown as mean ± SEM.

Chart 2



Preparation of Ethyl Cyano[(1-oxoalkyl)amino]acetates. Ethyl Cyano[(1-oxobutyl)amino]acetate (3c). Method A. A mixture of ethyl cyanohydroximinoacetate 1 (5 g, 35 mmol), butyric anhydride (11.12 g, 70 mmol), and 5% platinum on activated carbon with 58.3% moisture (2.5 g) in 40 mL of THF was stirred under H_2 atmosphere at room temperature for 10 h. After filtration the mixture was concentrated under vacuum, and the residue was triturated with petroleum ether (bp 35–60 °C) to afford **3c** (5.73 g, 82% yield) as colorless crystals: mp 110 °C; R_f = 0.4 (CH_2Cl_2/EtOAc, 95:5); IR ($CHCl_3$) 3430, 2245, 1758, 1692 cm^{-1}; ^1H NMR ($CDCl_3$) 0.98 (t, 3H), 1.37 (t, 3H), 1.71 (m, 2H), 2.30 (t, 2H), 4.36 (q, 2H), 5.55 (d, 1H, J = 8 Hz), 6.54 (br d, 1H, J = 8 Hz). Anal. ($C_9H_{14}N_2O_3$) C, H, N.

Compound **3b** was prepared in similar fashion.

Ethyl Cyano[(1-oxopentyl)amino]acetate (3d). Method B. To a cooled (0 °C) solution of ethyl aminocyanoacetate **2**[46] (6.71 g, 52.4 mmol) in CH_2Cl_2 (100 mL) were added pyridine (4.24 mL, 52.4 mmol) and pentanoyl chloride (6.31 mL, 52.4 mmol) dropwise over 30 min. Then the mixture was evaporated to dryness, taken up in CH_2Cl_2, washed with water, and concentrated under vacuum. Trituration with diisopropyl ether gave (8.4 g, 75% yield) a white solid: mp 88 °C; R_f = 0.40 (CH_2Cl_2/EtOAc, 9:1); ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7 Hz), 1.37 (t, 3H, J = 7 Hz), 1.37 (m, 2H), 1.86 (m, 2H), 2.32 (m, 2H), 4.34 (q, 2H), 5.54 (d, 1H, J = 7.5 Hz), 6.36 (br d, 1H, J = 7.5 Hz).

Compounds **3a** and **3e** were similarly prepared.

Ethyl 3-Amino-3-(methylthio)-2-[(1-oxopentyl)amino]-2-propenoate (4d). Through a cooled (−10 °C) solution of **3d** (10.4 g, 49 mmol) and triethylamine (0.68 mL, 4.9 mmol) in ethanol (200 mL) was bubbled methyl mercaptan (5.4 g, 112 mmol). The mixture was stirred at 0 °C for 50 h and then concentrated under vacuum. The residue was triturated with ether, and the resulting solids were filtered to give 11.14 g (87%) of **4d** as a mixture of E and Z isomers (2/3–1/3): colorless crystals; mp 110 °C; R_f = 0.15 (CH_2Cl_2/EtOAc, 8:2); ^1H NMR ($CDCl_3$) δ 0.89 and 0.94 (t, 3H), 1.23 and 1.25 (t, 3H), 1.25–1.70 (m, 4H), 2.12 and 2.27 (t, 2H), 2.34 and 2.35 (s, 3H), 4.12 (m, 2H), 5.96 and 6.15 (s, 1H), 6.75 (br, 2H).

Compounds **4a**, **4b**, **4c**, and **4e** were prepared from **3a**, **3b**, **3c**, and **3e**, respectively, by the same procedure described for the preparation of **4d**.

Compounds **4g–j** were prepared from **3d** by reaction with, respectively, 3-(acetyloxy)propane-1-thiol,[47] 4-(acetyloxy)butane-1-thiol,[47] 4-methoxy-α-toluenethiol,[48] thiophenol, and 2-mercaptothiophene,[48] at room temperature for 2–4 days, using the same procedure described for the preparation of **4d**.

Ethyl 2-Butyl-4-(methylthio)-1*H*-imidazole-5-carboxylate (5d). To a stirred and cooled (−78 °C) mixture of PCl_5 (7.8 g, 37.45 mmol) in CH_2Cl_2 (120 mL) was added a solution of 4-(dimethylamino)pyridine (5 g, 40.9 mmol) in CH_2Cl_2 (35 mL). Stirring was continued for 10 min at −78 °C, and then a solution of **4d** (4.87 g, 18.72 mmol) in CH_2Cl_2 (48 mL) was added over 15 min. The mixture was allowed to warm up to room temperature and was stirred for an additional 12 h. The mixture was then poured onto a saturated aqueous solution of $NaHCO_3$ (300 mL), stirred for 1 h, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography on silica gel (20% EtOAc–CH_2Cl_2) afforded 3.3 g (72%) of **5d** as pale yellow solid: mp 74 °C. Trituration with *n*-hexane gave a white solid: mp 76 °C; R_f = 0.35 (CH_2Cl_2/EtOAc, 8:2); ^{1}H NMR ($CDCl_3$) 0.93 (t, 3H), 1.39 (t, 3H), 1.39 (m, 2H), 1.74 (m, 2H), 2.64 (s, 3H), 2.82 (t, 2H), 4.35 (q, 2H). Anal. ($C_{11}H_{18}N_2O_2S$) C, H, N, S.

Imidazoles **5a–k** were synthesized by the same procedure described for the preparation of **5d**.

2-Bromo-*N*-[(dimethylamino)methylene]benzenesulfonamide (7). To a solution of 2-bromobenzenesulfonamide **6**[27] (59.6 g, 0.25 mol) in dry DMF (160 mL) was added dimethylformamide dimethyl acetal (35.96 g, 0.3 mol). After the mixture was stirred for 2 h, a solution of sodium hydrogen sulfate (5 g) in iced water (500 mL) was added. The precipitate was filtered, carefully washed with water and dried (80 °C, 0.01 bar, 3 h) to afford 71.9 g (98%) of **7**: mp 152 °C; R_f = 0.15 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.20 (s, 3H), 7.38 (m, 2H), 7.65 (dd, 1H, *J* = 8, 1 Hz), 8.25 (dd, 1H, *J* = 8, 1 Hz), 8.30 (s, 1H); MS (EI) *m/e* 291, 293 M^+.

***N*-[(Dimethylamino)methylene]-4′-methyl-(1,1′-biphenyl)-2-sulfonamide (8).** To a suspension of **7** (11.64 g, 39.9 mmol) in toluene (200 mL) were added under N_2 atmosphere a solution of Na_2CO_3 (8.48 g, 80 mmol) in water (40 mL), triphenylphosphine (1.048 g, 3.99 mmol), palladium acetate (0.49 g, 2 mmol), and finally 4-tolylboronic acid (6.4 g, 47 mmol) dissolved in ethanol (100 mL). The mixture was heated under reflux for 4 h and cooled to room temperature, and CH_2Cl_2 (600 mL) was added. The organic layer was separated, washed with water and brine, dried, and concentrated under vacuum. Trituration of the residue with ether at −20 °C afforded 11.2 g (93% yield) of **7**, which was recrystallized from EtOAc as colorless crystals: mp 184–185 °C; R_f = 0.20 (EtOAc/*n*-pentane, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.70 (s, 3H), 2.76 (s, 3H), 7.00 (s, 1H), 7.19 (d, 1H), 7.24 (dd, 1H), 7.29 (d, 1H), 7.50 (m, 2H), 8.30 (dd, 1H). Anal. ($C_{16}H_{18}N_2O_2S$) C, H, N, S.

4′-(Bromomethyl)-*N*-[(dimethylamino)methylene]-(1,1′-biphenyl)-2-sulfonamide (9). To a solution of **8** (4.86 g, 16 mmol) in chlorobenzene (100 mL) were added *N*-bromosuccinimide (2.85 g, 16 mmol) and benzoyl peroxide (4 mg, 0.016 mmol), and the mixture was heated to 120 °C for 1 h. After cooling to 20 °C the mixture was poured into a solution of Na_2SO_3 (10 g) in water (130 mL). The organic layer was separated and washed with a saturated solution of Na_2CO_3 and with brine, dried, and evaporated. The crude product was purified by recrystallization from CH_2Cl_2/EtOAc, 1/3 (100 mL), to afford 3.9 g of **9** (64% yield) as colorless crystals: mp 180–182 °C; R_f = 0.31 (CH_2Cl_2/EtOAc, 92:8); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 2.81 (s, 3H), 4.55 (s, 2H), 7.14 (s, 1H), 7.19 (dd, 1H), 7.40 (m, 4H), 7.52 (m, 2H), 8.31 (dd, 1H). Anal. ($C_{16}H_{17}BrN_2O_2S$) C, H, Br, N, S.

Ethyl 2-butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylate (10d). To a solution of **5d** (15 g, 61.9 mmol) in dry DMF (270 mL) were added **9** (23.6 g, 61.9 mmol) and K_2CO_3 (8.6 g, 61.9 mmol). The mixture was stirred at 20–25 °C for 45 h, and DMF was removed under vacuum. The residue was taken up in water, and the resulting solids were filtered and dried. Trituration at 50 °C with a mixture EtOAc/hexane 60:40 gave 25.2 g (70%) of **10d** as a white solid: mp 149 °C. The filtrate was chromatographed on silica gel (EtOAc/hexane, 60:40) to afford 3.35 g (15%) of **10d** (R_f = 0.25, overall 85% yield) and 2.68 g (8%, R_f = 0.05) of minor N_3 isomer: ^{1}H NMR of **10d** ($CDCl_3$) δ 0.89 (t, 3H), 1.32 (m, 2H), 1.39 (t, 3H), 1.65 (m, 2H), 2.60 (s, 3H), 2.61 (m, 2H), 2.74 (s, 3H), 2.75 (s, 3H), 4.30 (q, 2H), 5.60 (s, 2H), 7.07 (s, 1H), 7.04–7.50 (m, 7H), 8.27 (dd, 1H).

Ethyl 1-[[2′-(Aminosulfonyl)(1,1′-biphenyl)-4-yl]methyl]-2-butyl-4-(methylthio)-1*H*-imidazole-5-carboxylate (11d). A mixture of **10d** (28.55 g), ethanol (500 mL), and concentrated HCl (260 mL) was refluxed for 2 h. After removal of ethanol, the aqueous mixture was made alkaline with 5 N NaOH (400 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined extracts were washed with water, dried over $MgSO_4$, and evaporated. Trituration with 10% EtOH/diisopropyl ether gave 25.65 g (81%) of **11d** as a white solid: mp 130 °C; R_f = 0.40 (CH_2Cl_2/EtOAc, 8:2); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.34 (t, 3H), 1.36 (m, 2H), 1.68 (m, 2H), 2.61 (s, 3H), 2.67 (m, 2H), 4.18 (s, 2H), 4.27 (q, 2H), 5.58 (s, 2H), 7.10 (d, 2H), 7.30–7.59 (m, 5H), 8.14 (dd, 1H).

The compounds **11a–c,e,i–l** were prepared from **5a**, **5b**, **5c**, **5e**, **5i**, **5j**, **5f**, and **5g**, respectively, by the same procedure described for the preparation of **11d**.

General Procedure C: Condensation of Isocyanate. Ethyl 2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylate (28). To a refluxed solution of **11d** (16 g, 32.8 mmol) and K_2CO_3 (9 g, 65 mmol) in dry acetone (112 mL) was added propyl isocyanate (6.2 mL, 65 mmol). After the mixture was refluxed for 2 h, the solvent was removed and the residue was dissolved in CH_2Cl_2, washed with 1 N HCl and water, dried over $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by trituration with EtOAc/diisopropyl ether, 1:1, to afford 16 g (87%) of **28** as colorless crystals: mp 144–146 °C; R_f = 0.45 (CH_2Cl_2/EtOAc, 8:2); ^{1}H NMR ($CDCl_3$) δ 0.77 (t, 3H), 0.91 (t, 3H), 1.35 (m, 4H), 1.35 (t, 3H), 1.69 (m, 2H), 2.61 (s, 3H), 2.70 (t, 2H), 3.02 (q, 2H), 4.25 (q, 2H), 5.54 (s, 2H), 6.09 (t, 1H), 6.38 (br s, 1H), 7.07 (d, 2H), 7.34 (d, 2H), 7.33–7.63 (m, 3H), 8.13 (d, 1H). Anal. ($C_{28}H_{38}N_4O_5S_2$) C, H, N, S.

General Procedure D: Saponification. 2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (12d). A solution of ester **28** (16.5 g, 28 mmol) and 2 N NaOH (56 mL, 112 mmol) in ethanol (330 mL) was stirred at room temperature for 36 h and evaporated in vacuo at 40 °C. The residue was taken up in water and filtered through a Millex GV 0.22 m filter. A 2 N HCl (56 mL) solution was added dropwise to the filtrate, and the resulting white precipitate was collected by filtration, washed with water, and dried (under vacuum and P_2O_5 at room temperature) to provide 14 g (80%) of **12d**: mp 128–130 °C; R_f = 0.30 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 0.76 (t, 3H), 0.84 (t, 3H), 1.31 (m, 4H), 1.57 (m, 2H), 2.46 (s, 3H), 2.63 (t, 2H), 2.86 (q, 2H), 5.63 (s, 2H), 6.13 (t, 1H), 7.07 (d, 2H), 7.26–7.66 (m, 5H), 8.02 (dd, 1H). Anal. ($C_{26}H_{32}N_4O_5S_2$) C, H, N, S.

Compounds **12a–e,i–l** were synthesized from **11a–e,i–l** using the same two step procedure described for the preparation of **12d**: condensation of propyl isocyanate and saponification.

4-[[4-(Acetyloxy)butyl]thio]-2-butyl-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (12g). A solution of **12l** (0.4 g, 0.65 mmol) and acetic anhydride (0.12 mL, 1.3 mmol) in dry pyridine (8 mL) was stirred at room temperature for 1 h. After evaporation the residue was taken up in EtOAc, washed with water, dried, and concentrated. Trituration with ether and recrystallization from acetonitrile gave 0.18 g (42%) of **12g**: mp 150–152 °C; R_f = 0.33 (EtOAc/acetonitrile, 1:1); ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 3H), 0.90 (t, 3H), 1.38 (m, 2H), 1.69 (m, 2H), 1.81 (m, 4H), 2.04 (s, 3H), 2.71 (t, 2H), 3.00 (q, 2H), 3.21 (m, 2H), 4.10 (m, 2H), 5.48 (s, 1H), 6.08 (m, 1H), 7.05 (d, 2H), 7.30 (d, 2H), 7.30–7.61 (m, 3H), 8.11 (d, 1H). Anal. ($C_{31}H_{40}N_4O_7S_2$) C, H, N, S.

2-Butyl-1-[[2′-[[[(methylamino)carbonyl]amino]sulfonyl]-(1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (12m), 2-butyl-1-[[2′-[[[(ethylamino)-carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (12n), and 1-[[2′-[[[(allylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-2-butyl-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (12o). The title compounds were prepared from **11d** by the same procedure described for the preparation of **12d** in two steps by reaction with methyl isocyanate, ethyl isocyanate, or allyl isocyanate, respectively, followed by saponification.

12m: amorphous solid; mp 148 °C dec; 65% yield; $R_f = 0.30$ (EtOAc/MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3H), 1.29 (m, 2H), 1.56 (m, 2H), 2.48 (m, 6H), 2.63 (t, 2H), 5.63 (s, 2H), 6.01 (q, 1H), 7.07 (d, 2H), 7.27 (d, 2H), 7.27–7.66 (m, 3H), 8.03 (dd, 1H), 10.15 (s, 1H). Anal. ($C_{24}H_{28}N_4O_5S_2$) C, H, N, S.

12n: mp 136–140 °C; 74% yield; $R_f = 0.25$ (CH_2Cl_2/MeOH, 9:1); MS (FAB) m/e 531 (M + 1). Anal. ($C_{25}H_{30}N_4O_5S_2$) C, H, N, S.

12o: amorphous solid; 31% yield; $R_f = 0.10$ (EtOAc/MeOH, 10:1); ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 3H, J = 7 Hz), 1.30 (m, 2H), 1.55 (m, 2H), 2.48 (s, 3H), 2.62 (t, 2H, J = 7 Hz), 3.55 (m, 2H), 5.05 (md, 2H, J = 14 Hz), 5.52 (s, 2H), 5.73 (m, 1H), 6.25 (br t, 1H), 7.08 (d, 2H, J = 8 Hz), 7.60 and 7.68 (ddd, 2H, J = 1, 8, 8 Hz), 7.63 (m, 2H), 8.02 (dd, 1H, J = 8, 1 Hz), 10.05 (s, 1H); MS (FAB) m/e 543 (M + 1). Anal. ($C_{26}H_{30}N_4O_5S_2$) C, H, N.

2-Butyl-1-[[2′-[[[(diethylamino)carbonyl]amino]sulfonyl]-(1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (12q). Under argon a mixture of **15a** (300 mg, 0.54 mmol) and diethylamine was refluxed in toluene for 6 h. The mixture was concentrated under vacuum. The residue was suspended in a small amount of EtOAc (5 mL) and filtered to afford 240 mg of an amorphous material, which was dissolved in ethanol (10 mL) and 2 N NaOH (2 mL). After 4 days the solvent was removed under vacuum at 40 °C, and water was added. The solution was adjusted to pH 5 by using 2 N HCl. Filtration of the resulting precipitate gave 130 mg (43%) of **12q** as amorphous solid: $R_f = 0.10$ (EtOAc/MeOH, 10:1); ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 9H), 1.32 (m, 2H), 1.60 (m, 2H), 2.45 (s, 3H), 2.62 (t, 2H), 2.92 (m, 4H), 5.60 (s, 2H), 7.02 (d, 2H), 7.10 (m, 1H), 7.29 (d, 2H), 7.55 (m, 2H), 8.00 (dd, 1H), 10.10 (br s, 1H); MS (FAB) m/e 559 (M + 1). Anal. ($C_{27}H_{34}N_4O_5S_2$) C, H, N.

2-Butyl-4-(methylthio)-1-[[2′-[[[[(3-pyridylmethyl)amino]carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (12p). The title compound was prepared from **15a** by the same procedure described for the preparation of **12q** using 3-(aminomethyl)pyridine: amorphous solid; 39% yield; $R_f = 0.10$ (EtOAc/MeOH, 5:1); ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3H, J = 7 Hz), 1.28 (m, 2H), 1.55 (m, 2H), 2.45 (s, 3H), 2.60 (t, 2H, J = 7 Hz), 4.10 (m, 2H), 5.60 (s, 2H), 6.70 (br s, 1H), 7.00 (d, 2H, J = 8.5 Hz), 7.25 (m, 4H), 7.58 (m, 3H), 8.02 (dd, 1H, J = 8.5, 1 Hz), 8.35 (br s, 1H), 8.42 (m, 1H); MS (FAB) m/e 594 (M +1). Anal. ($C_{29}H_{31}N_5O_5S_2$) C, H, N.

2-Butyl-4-(methylthio)-1-[[2′-[[[(butylamino)carbonyl]-amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (12r). The title compound was prepared from **15a** by the same procedure described for the preparation of **12q** using *n*-butylamine: 70% yield; white solid; mp 125–127 °C; $R_f = 0.30$ (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 7 Hz), 0.90 (t, 3H, J = 7 Hz), 1.17 (m, 2H), 1.34 (m, 4H), 1.67 (m, 2H), 2.60 (s, 3H), 2.73 (t, 2H, J = 7 Hz), 3.03 (q, 2H, J = 7 Hz), 5.48 (s, 2H), 6.03 (br s, 1H), 7.04 (d, 2H, J = 8.5 Hz), 7.30 (m, 3H), 7.56 (m, 2H), 8.12 (dd, 1H, J = 8.5, *1* Hz). Anal. ($C_{27}H_{34}N_4O_5S_2$) C, H, N,S.

2-Butyl-5-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-4-carboxylic Acid (13). The title compound was prepared from the minor N_3 isomer by the same procedure described for the preparation of **12d** (3 steps) and was isolated as a white solid (42% overall yield): ^{1}H NMR (DMSO-d_6) δ 0.75 (t, 3H), 0.84 (t, 3H), 1.29 (m, 4H), 1.57 (m, 2H), 2.29 (s, 3H), 2.62 (t, 2H), 2.82 (m, 2H), 5.40 (s, 2H), 6.00 (m, 1H), 6.99 (d, 2H), 7.34 (d, 2H), 7.19–7.53 (m, 3H), 8.00 (d, 1H). Anal. ($C_{26}H_{32}N_4O_5S_2$) C, H, N, S.

2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)thioxomethyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (14). A mixture of **11d** (6 g, 12.3 mmol), K_2CO_3 (3.5 g, 27 mmol), and propyl isothiocyanate (3 mL, 30 mmol) in acetone (100 mL) was refluxed for 15 h. After cooling, aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. Recrystallization from ether afforded 6.25 g (86%) of the desired ester propylthiourea as a white solid. Saponification using general procedure D afforded **14** (0.22 g, 62%) as a white solid: mp 105–107 °C; $R_f = 0.40$ (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H), 0.91 (t, 3H), 1.39 (m, 2H), 1.50 (m, 2H), 1.69 (m, 2H), 2.61 (s, 3H), 2.71 (t, 2H), 3.39 (dt, 2H), 5.59 (s, 2H), 7.11 (d, 2H), 7.40 (d, 2H), 7.36–7.65 (m, 3H), 7.89 (t, 1H), 8.08 (d, 1H). Anal. ($C_{26}H_{32}N_4O_4S_3$) C, H, N, S.

Ethyl2-Butyl-1-[[2′-[[(ethoxycarbonyl)amino]sulfonyl]-(1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylate (15a). A suspension of **11d** (12.1 g, 25 mmol) and K_2CO_3 (7.8 g, 56 mmol) in dry DME (200 mL) was refluxed, and ethyl chloroformate (4.8 mL, 51 mmol) was added. After 1 h, the mixture was allowed to cool to room temperature, and 50 mL of 10% KH_2PO_4 aqueous solution was added. Extraction with EtOAc, drying over $MgSO_4$, and concentration under vacuum gave a residue which was then chromatographed on silica gel (EtOAc/*n*-heptane, 2:1) to yield 8.4 g (60%) of **15a** as pale yellow foam: $R_f = 0.30$ (EtOAc/*n*-heptane, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 7 Hz), 1.05 (t, 3H, J = 7 Hz), 1.25 (t, 3H, J = 7 Hz), 1.32 (m, 2H), 1.58 (m, 2H), 2.48 (s, 3H), 2.65 (m, 2H), 3.96 (q, 2H, J = 7 Hz), 4.20 (q, 2H, J = 7 Hz), 5.60 (s, 2H), 7.05 (d, 2H, J = 8 Hz), 7.25 (d, 2H, J = 8 Hz), 7.28 (m, 1H), 7.68 (ddd, 2H, J = 8, 8, 1 Hz), 8.05 (dd, 1H, J = 8, 1 Hz), 11.55 (s, 1H). Anal. ($C_{27}H_{33}N_3O_6S_2$) C, H, N.

2-Butyl-1-[[2′-[[(ethoxycarbonyl)amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (15c). Saponification of **15a** (general procedure D) afforded **15c** which was recrystallized from acetonitrile (0.34 g, 60%): colorless crystals; mp 190–192 °C; $R_f = 0.60$ (CH_2Cl_2/ MeOH, 8:2); ^{1}H NMR ($CDCl_3$) 0.91 (t, 3H), 1.12 (t, 3H), 1.38 (m, 2H), 1.68 (m, 2H), 2.62 (s, 3H), 2.72 (m, 2H), 4.03 (q, 2H), 5.57 (s, 2H), 7.05 (d, 2H), 7.25 (d, 2H), 7.27–7.62 (m, 3H), 8.25 (dd, 1H), 9.16 (br s, 1H). Anal. ($C_{25}H_{29}N_3O_6S_2$) C, H, N, S.

2-Butyl-1-[[2′-[[(methoxycarbonyl)amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (15b), 2-Butyl-1-[[2′-[[(3-methylbut-2-enoxycarbonyl)amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (15d), 2-Butyl-1-[[2′-[[(butoxycarbonyl)amino]sulfonyl]-(1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (15e), 2-Butyl-1-[[2′-[[(2-methylpropoxy carbonyl)amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (15f). The title compounds were prepared from **11d** following the same procedure described for the preparation of **15c** in two steps by reaction with methyl chloroformate at room temperature for 72 h, 3-methylbut-2-enyl chloroformate (prepared from 3-methyl-2-buten-1-ol and $COCl_2$ in toluene), isobutylchloroformate, and *n*-butyl chloroformate for 2 h in refluxing DME, respectively.

15b: mp 198–201 °C; 28% yield; $R_f = 0.40$ (EtOAc/MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3H), 1.30 (m, 2H), 1.57 (m, 2H), 2.48 (s, 3H), 2.63 (t, 2H), 3.52 (s, 3H), 5.63 (s, 2H), 7.08 (d, 2H), 7.26 (d, 2H), 7.28–7.70 (m, 3H), 8.06 (br d, 1H), 11.73 (br s, 1H), 12.82 (br s, 1H). Anal. ($C_{24}H_{27}N_3O_6S_2$) C, H, N, S.

15d: amorphous solid; 44% yield; $R_f = 0.10$ (*tert*-butylmethyl ether); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.6 Hz), 1.38 (m, 2H), 1.62 (d, 2H, J = 0.8 Hz), 1.72 (s, 3H), 1.73 (m, 2H), 2.63 (s, 3H), 2.70 (t, 2H, J = 7.8 Hz), 4.45 (d, 2H, J = 8 Hz), 5.12 (m, 1H), 5.55 (s, 2H), 7.03 (d, 2H, J = 8 Hz), 7.27 (d, 2H, J = 8 Hz), 7.29–7.63 (m, 3H), 8.25 (dd, 1H, J = 1, 8 Hz); MS (FAB) m/e 572 (M + 1). Anal. ($C_{28}H_{33}N_3O_6S_2$) C, H, N.

15e: 85% yield; white solid; mp 164 °C; $R_f = 0.30$ (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, J = 7 Hz), 0.92 (t, 3H, J = 7 Hz), 1.17 (m, 2H), 1.41 (m, 4H), 1.71 (m, 2H), 2.62 (s, 3H), 2.70 (t, 2H, J = 7 Hz), 3.97 (t, 2H, J = 7 Hz), 5.55 (s,

2H), 6.87 (br s, 1H), 7.05 (d, 2H, J = 8.5 Hz), 7.30 (m, 3H), 7.56 (m, 2H), 8.25 (dd, 1H, J = 8.5, 1 Hz). Anal. ($C_{27}H_{33}N_3O_6S_2$) C, H, N, S.

15f: 82% yield; white solid; mp 118–120 °C; R_f = 0.30 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.74 (d, 6H, J = 7 Hz), 0.91 (t, 3H, J = 7 Hz), 1.39 (m, 2H), 1.67 (m, 3H), 2.59 (s, 3H), 2.68 (t, 2H, J = 7 Hz), 3.74 (d, 2H, J = 7 Hz), 4.86 (br s, 1H), 5.53 (s, 2H), 7.05 (d, 2H, J = 8.5 Hz), 7.29 (m, 3H), 7.57 (m, 2H), 8.25 (dd, 1H, J = 8.5, J = 1 Hz). Anal. ($C_{27}H_{33}N_3O_6S_2$) C, H, N, S.

1-[[2′-[(Acetylamino)sulfonyl](1,1′-biphenyl)-4-yl]methyl]-2-butyl-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (16a). A solution of **12d** (0.4 g, 0.73 mmol) in acetic anhydride (10 mL) was refluxed for 2 h. After removal of Ac_2O, the residue was taken up in $CHCl_3$/MeOH, 9:1(20 mL), and stirred overnight. The solvent was removed under vacuum, and the residue was dissolved in a saturated solution of $NaHCO_3$ and then filtered off. The filtrate was adjusted to pH 4 using 2 N HCl, and the resulting precipitate was collected to give 0.25 g (70%) of **16a** as a white solid: mp 128–130 °C; R_f = 0.30 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H), 1.29 (m, 2H), 1.54 (s, 3H), 1.55 (m, 2H), 2.44 (s, 3H), 2.58 (t, 2H), 5.71 (s, 2H), 7.01 (m, 2H), 7.13 (d, 1H), 7.33 (m, 2H), 7.48 (m, 2H), 8.00 (dd, 1H); MS (FAB) m/e 502 (M + 1). Anal. ($C_{24}H_{27}N_3O_5S_2$) C, H, N, S.

2-Butyl-4-(methylthio)-1-[[2′-[(benzoylamino)sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (16b). A suspension of 4-(dimethylamino)pyridine (0.16 g, 1.3 mmol), benzoyl chloride (0.13 mL, 1.3 mmol), and **11d** (0.489 g, 1 mmol) in toluene (10 mL) was heated at 70 °C for 30 min. After being cooled, saturated aqueous solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine and concentrated under vacuum. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give 0.293 g of ester which was suspended in MeOH (7 mL). Next, 2 N NaOH (3 mL) was added, and the mixture was stirred for 20 h. MeOH was removed, and water (20 mL) was added. The solution was adjusted to pH 4–5 by using acetic acid, and the precipitate was filtered. Recrystallization from EtOAc afforded 0.204 g (45%) of **16b** as colorless crystals: mp 192–194 °C; R_f = 0.58 (EtOAc/acetic acid, 98:2); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.36 (m, 2H), 1.67 (m, 2H), 2.61 (s, 3H), 2.63 (t, 2H), 5.49 (s, 2H), 6.85–7.65 (m, 12H), 8.38 (m, 1H). Anal. ($C_{29}H_{29}N_3O_5S_2$) C, H, N, S.

2-Butyl-4-(methylthio)-1-[[2′-[[(phenylacetyl)amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (16c). The title compound was prepared from **11d** by the same procedure described for the preparation of **16b** by reaction with phenylacetyl chloride: colorless crystals; mp 172–175 °C; R_f = 0.28 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 0.80 (t, 3H), 1.28 (m, 2H), 1.58 (m, 2H), 2.47 (s, 3H), 2.64 (t, 2H), 3.30 (s, 2H), 5.65 (s, 2H), 7.00–7.40 (m, 10H), 7.58 (dt, 1H), 7.68 (dt, 1H), 8.06 (dd, 1H), 11.86 (s, 1H), 12.52 (s, 1H). Anal. ($C_{30}H_{31}N_3O_5S_2$) C, H, N, S.

Compound **16d** was similarly prepared from **11d** and butyryl chloride.

2-Butyl-1-[[2′-[[(ethylsulfonyl)amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylic Acid (17a). To a solution of **11d** (244 mg, 0.5 mmol) in diglyme (10 mL) was added K_2CO_3 (346 mg, 2.5 mmol) and ethanesulfonyl chloride (47 μL, 0.5 mmol). The mixture was refluxed for 12 h, poured into 50 mL of 5% aqueous $NaHSO_4$, and extracted with EtOAc. After evaporation, chromatography with *tert*-butylmethyl ether/diisopropyl ether (1:1) gave 90 mg (31%) of an amorphous solid which was saponified using 2 N NaOH in EtOH at room temperature to provide 36 mg (41%) of a colorless foam: R_f = 0.10 (EtOAc/MeOH, 1:1); ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 3H, J = 7.3 Hz), 1.08 (t, 3H, J = 7.6 Hz), 1.25–1.35 (m, 2H), 1.50–1.60 (m, 2H), 2.47 (s, 3H), 2.65 (t, 3H, J = 7.6 Hz), 2.82 (q, 2H, J = 7.3 Hz), 5.62 (s, 2H), 6.98 (d, 2H, J = 8.4 Hz), 7.12 (dd, 1H, J = 1.6, 7.2 Hz), 7.42 (td, 1H, J = 1.6, 8 Hz), 7.46 (d, 2H, J = 8 Hz), 7.55–7.65 (m, 1H), 8.03 (dd, 1H, J = 1.6, 8 Hz); MS (FAB) m/e 552 (M + 1).

2-Butyl-4-(methylthio)-1-[[2′-[[[(trifluoromethyl)sulfonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (17b). To a cooled (−60 °C) solution of **11d** (1.5 g, 3.08 mmol) and triethylamine (0.53 mL, 3.80 mmol) in CH_2Cl_2 (30 mL) was slowly added a solution of trifluoromethanesulfonic anhydride (1.3 g, 4.62 mmol) in CH_2Cl_2 (12 mL). After the mixture was stirred at −50 to −60 °C for 1 h, water (10 mL) was added. The mixture was allowed to warm to room temperature, and the organic layer was decanted, washed with water, dried, and evaporated. Purification by chromatography on silica gel with EtOAc as eluent afforded 1.2 g (63%) of ester which was saponified using general procedure D. Recrystallization from EtOH afforded **17b** (492 mg, 46%) as colorless crystals: mp 188–190 °C; R_f = 0.44 (EtOAc/MeOH/H_2O, 80:15:5); ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3H), 1.31 (m, 2H), 1.52 (m, 2H), 2.54 (s, 3H), 2.77 (m, 2H), 5.68 (s, 2H), 7.06 (d, 2H), 7.18–7.50 (m, 5H), 8.03 (dd, 1H); MS (FAB) m/e 592 (M + 1). Anal. ($C_{23}H_{24}F_3N_3O_6S_3$) C, H, F, N, S.

***N*-[4′-[[2-Butyl-5-(hydroxymethyl)-4-(methylthio)-1*H*-imidazol-1-yl]methyl](1,1′-biphenyl)-2-yl]sulfonamide (18).** A mixture of **10d** (313 mg, 0.65 mmol), $LiAlH_4$ (40 mg, 0.98 mmol), and THF (10 mL) was refluxed for 3 h. After usual workup and extraction with EtOAc, the product was purified by chromatography on silica gel ($CHCl_3$/EtOAc, 1:1) to give 147 mg (59%) of **18** as an amorphous solid: R_f = 0.10 ($CHCl_3$/EtOAc, 1:1); ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3H), 1.27 (m, 2H), 1.51 (m, 2H), 2.31 (s, 3H), 2.50 (t, 2H), 4.44 (d, 2H), 5.16 (t, 1H), 5.28 (s, 2H), 7.08 (d, 2H), 7.18 (br s, 2H), 7.26 (dd, 1H), 7.36 (d, 2H), 7.59 (m, 2H), 8.02 (dd, 1H).

***N*-[[4′-[[2-Butyl-5-(hydroxymethyl)-4-(methylthio)-1*H*-imidazol-1-yl]methyl](1,1′-biphenyl)-2-yl]sulfonyl]-*N*′-propylurea (19).** The title compound was prepared using general procedure C from **18** (450 mg, 1 mmol). Column chromatography (EtOAc/CH_2Cl_2, 8:2) followed by trituration with ether afforded 280 mg (52%) of **19** as a colorless amorphous solid: R_f = 0.25 (EtOAc/CH_2Cl_2, 8:2); ^{1}H NMR (DMSO-d_6) δ 0.75 (t, 3H), 0.84 (t, 3H), 1.29 (m, 4H), 1.54 (m, 2H), 2.31 (s, 3H), 2.54 (m, 2H), 2.85 (q, 2H), 4.44 (d, 2H), 5.17 (t, 1H), 5.29 (s, 2H), 6.03 (t, 1H), 7.07 (d, 2H), 7.26–7.67 (m, 5H), 8.02 (d, 1H), 9.33 (s, 1H). Anal. ($C_{26}H_{34}N_4O_4S_2$) C, H, N, S.

Phenylmethyl 2-butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylate (20). A mixture of **11d** (1.8 g, 3.7 mmol), titanium isopropoxide (1.2 mL, 4.03 mmol), and benzyl alcohol (35 mL) was heated at 110 °C for 60 h. Then the solution was reduced to one third of its volume. Benzyl alcohol (10 mL) and titanium isopropoxide (1.2 mL) were added. After the mixture was heated at 140 °C for 4 h, the benzyl alcohol was removed under vacuum and the residue was taken up in water and extracted with CH_2Cl_2. Purification by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) and recrystallization from ether/hexane afforded 1.3 g (62%) of benzyl ester. Then standard procedure C provided 1.1 g (75%) of **20** after recrystallization from CH_2Cl_2/ether: mp 135–140 °C; R_f = 0.50 (heptane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 0.76 (t, 3H), 0.91 (t, 3H), 1.38 (m, 4H), 1.68 (m, 2H), 2.60 (s, 3H), 2.71 (m, 2H), 3.02 (q, 2H), 5.26 (s, 2H), 5.53 (s, 2H), 6.08 (m, 1H), 7.04 (d, 2H), 7.31–7.64 (m, 10H), 8.12 (dd, 1H). Anal. ($C_{33}H_{38}N_4O_5S_2$) C, H, N, S.

2-Butyl-*N*-methyl-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxamide (21). A mixture of **11d** (300 mg, 0.61 mmol), methylamine (5 mL), and MeOH (10 mL) was heated at 80 °C for 60 h in an autoclave and then concentrated. The residue was chromatographed on silica gel (EtOAc) to afford 260 mg (91%) of amide as a white solid (R_f = 0.60, EtOAc) which was treated according to general procedure C to give 188 mg (59%) of **21** as a white solid after recrystallization from ether/CH_2Cl_2: mp 181–182 °C; R_f = 0.50 (EtOAc/hexane, 7:3); ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H), 0.92 (t, 3H), 1.41 (m, 4H), 1.72 (m, 2H), 2.60 (s, 3H), 2.74 (m, 2H), 2.87 (d, 3H), 3.02 (q, 2H), 5.59 (s, 2H), 6.26 (t, 1H), 7.01 (d, 2H), 7.37 (d, 2H), 7.37–7.63 (m, 3H), 7.76 (q, 1H), 8.17 (d, 1H). Anal. ($C_{27}H_{35}N_5O_4S_2$) C, H, N, S.

2-Butyl-4-(methylthio)-1-[[2′-(aminosulfonyl)(1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (22). The title compound was obtained by saponification of **11d** *via* general procedure D and recrystallized from MeOH (62%): colorless crystals; mp 157–160 °C; R_f = 0.27 (EtOAc); ^{1}H NMR

($CDCl_3$) δ 0.83 (t, 3H), 1.29 (m, 2H), 1.54 (m, 2H), 2.46 (s, 3H), 2.63 (t, 2H), 5.62 (s, 2H), 7.04 (d, 2H), 7.13 (s, 2H), 7.35 (d, 2H), 7.30–7.59 (m, 3H), 8.12 (d, 2H). Anal. ($C_{22}H_{35}N_3O_4S_2$) C, H, N, S.

***N*-[[1-[[2′-(Aminosulfonyl)(1,1′-biphenyl)-4-yl]methyl]-2-butyl-4-(methylthio)-1*H*-imidazol-5-yl]carbonyl]isoleucine Methyl Ester (23).** A suspension of **22** (150 mg, 0.32 mmol), L-isoleucine methyl ester hydrochloride (87 mg, 0.48 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (92 mg, 0.48 mmol) in EtOAc (15 mL) was stirred at room temperature for 16 h. The mixture was poured on aqueous NH_4Cl and extracted with EtOAc. The combined extracts were washed with aqueous $NaHCO_3$ and brine and then concentrated. The residue was chromatographed on silica gel (CH_2Cl_2/EtOAc, 1:1) to give 96 mg (51%) of **23** as a white amorphous solid: R_f = 0.44 (CH_2Cl_2/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz), 0.97 (d, 3H, J = 7 Hz), 1.26 (m, 2H), 1.37 (m, 2H), 1.68 (m, 2H), 1.99 (m, 1H), 2.62 (s, 3H), 2.70 (m, 2H), 3.73 (s, 3H), 4.27 (s, 2H), 4.61 (dd, 1H, J = 5, 8.5 Hz), 5.70 (d, 2H, J = 13.5 Hz), 7.10 (d, 2H, J = 8 Hz), 7.30–7.58 (m, 3H), 7.43 (d, 2H, J = 8 Hz), 8.12 (br d, 1H). Anal. ($C_{29}H_{38}N_4O_5S_2$) C, H, N, S.

***N*-[[2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazol-5-yl]carbonyl]isoleucine (24).** A mixture of **23** (870 mg, 1.48 mmol) and K_2CO_3 (409 mg, 2.96 mmol) in DME (9 mL) was stirred at room temperature for 30 min. Propyl isocyanate (0.2 mL, 2.2 mmol) was added, and the mixture was refluxed for 1 h. After being cooled, the reaction mixture was poured in water and the pH was adjusted to 5 with 2 N HCl. The mixture was extracted with CH_2Cl_2 and concentrated. The residue was chromatographed on silica gel (cyclohexane/EtOAc, 1:1) to give 792 mg (80%) of the ester, mp 120 °C, which was saponified with 2 N NaOH (1.2 mL) in EtOH (7.5 mL) at room temperature following general procedure D, to give 694 mg (89%) of **24** as a white solid: mp 103–105 °C; R_f = 0.30 (CH_2Cl_2/MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.73 (t, 3H), 0.93 (t, 3H), 0.95 (t, 3H), 1.05 (d, 3H), 1.20–1.60 (m, 6H), 1.79 (m, 2H), 2.60 (s, 3H), 2.84 (t, 2H), 3.03 (m, 2H), 4.29 (dd, 1H, J = 6, 8 Hz), 5.11 (dd, 1H, J = 15, 5 Hz), 5.91 (dd, 1H, J = 15, 5 Hz), 6.20 (t, 1H), 6.95 (d, 1H), 6.95–7.62 (m, 7H), 8.20 (dd, 1H). Anal. ($C_{32}H_{43}N_5O_6S_2$) C, H, N, S.

1,1-Dimethylethyl 2-butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylate (25). To a suspension of **22** (534 mg, 1.16 mmol) in CH_2Cl_2 (10 mL) was added *N,N′*-diisopropyl-*O*-*tert*-butylisourea[31] (1.2 g, 6 mmol). The resulting solution was stirred at room temperature for 10 h, and the precipitate was removed by filtration. The filtrate was washed with water and brine and concentrated. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 1:2) to afford 509 mg (85%) of *tert*-butyl ester which was treated using general procedure C and purified by recrystallization from CH_2Cl_2/ether to give 250 mg (46%) of **25** as a white solid: mp 158–160 °C; R_f = 0.38 (EtOAc/cyclohexane, 1:1); ^1H NMR ($CDCl_3$) δ 0.77 (t, 3H), 0.90 (t, 3H), 1.37 (m, 4H), 1.46 (m, 2H), 1.52 (s, 9H), 2.60 (s, 3H), 2.67 (m, 2H), 3.03 (q, 2H), 5.34 (s, 2H), 6.00 (br s, 1H), 6.13 (t, 1H), 7.10 (d, 2H), 7.33–7.64 (m, 5H), 8.13 (d, 1H); MS (SIMS) 601 m/e (M + 1).

2-Butyl-4-(methylsulfinyl)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (26). A solution of **11d** (0.5 g, 1.02 mmol) and *m*-chloroperbenzoic acid (0.24 g, 1.4 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and with water, and concentrated. Purification by chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) afforded 420 mg of sulfoxide (R_f = 0.51) which was treated according general procedure C (recrystallization from EtOAc) followed by general procedure D (recrystallization from 2-propanol) to provide 139 mg (53%) of **26** as a white solid: mp 190–192 °C; R_f = 0.18 (EtOAc/EtOH/H_2O, 7:2:1); ^1H NMR (DMSO-d_6) δ 0.76 (t, 3H), 0.85 (t, 3H), 1.31–1.60 (m, 6H), 2.70 (t, 2H), 2.84 (s, 3H), 2.84 (m, 2H), 5.68 (br d, 2H), 6.21 (t, 1H), 7.11 (d, 2H), 7.27 (d, 2H), 7.27–7.62 (m, 3H), 8.03 (dd, 1H). Anal. ($C_{26}H_{32}N_4O_6S_2$) C, H, N, S.

2-Butyl-4-(methylsulfonyl)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (27). The title compound was prepared by the same procedure described for the preparation of **26** using 2.5 equiv of *m*-chloroperbenzoic acid for 1 equiv of **11d** in 51% yield (three steps): mp 193–195 °C (from EtOH/H_2O, 1:1); R_f = 0.45 (EtOAc/EtOH/H_2O, 7:2:1); ^1H NMR (DMSO-d_6) δ 0.76 (t, 3H, J = 7.5 Hz), 0.84 (t, 3H, J = 7.5 Hz), 1.31 (m, 4H), 1.58 (m, 2H), 2.67 (t, 2H, J = 7.5 Hz), 2.86 (q, 2H), 3.30 (s, 3H), 5.59 (s, 2H), 6.12 (t, 1H), 7.14 (d, 2H, J = 8 Hz), 7.29 (d, 2H, J = 8 Hz), 7.27–7.58 (m, 3H), 8.03 (dd, 1H), 9.90 (br s, 1H).

***N*-[[4′-[[2-Butyl-4-(methylthio)-1*H*-imidazol-1-yl]methyl](1,1′-biphenyl)-2-yl]sulfonyl]-*N′*-propylurea (29).** **12d** (793 mg) was heated at 140 °C under vacuum (0.06 bar) for 1 h. The crude mixture was purified by chromatography on silica gel (EtOAc). Recrystallization from EtOAc afforded 380 mg (52%) of **29** as colorless crystals: mp 166–168 °C; R_f = 0.35 (EtOAc); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3H), 0.90 (t, 3H), 1.38 (m, 4H), 1.69 (m, 2H), 2.42 (s, 3H), 2.65 (t, 2H), 3.05 (q, 2H), 5.09 (s, 2H), 6.21 (t, 1H), 6.83 (s, 1H), 7.18 (d, 2H), 7.40 (d, 2H), 7.33 (dd, 1H), 7.55 (td, 1H), 7.66 (td, 1H), 8.12 (dd, 1H). Anal. ($C_{25}H_{32}N_4O_3S_2$) C, H, N, S.

2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxamide (30a). A suspension of acid **12d** (600 mg, 1.1 mmol) and thionyl chloride (600 L) in toluene (15 mL) was stirred at room temperature for 1 h and then at 55 °C overnight. Solvent and excess thionyl chloride were removed under reduced pressure, and the crude mixture was dried under vacuum. Then the resulted acid chloride was suspended in dioxane (15 mL), and 20% NH_4OH (10 drops) was added. The solution was stirred for 1 h, adjusted to pH 4 by using 1 N HCl, and extracted with CH_2Cl_2. Purification by chromatography on silica gel (CH_2Cl_2/EtOAc, 1:1, then CH_2Cl_2 (5%) MeOH/EtOAc, 1:1) gave 350 mg (58%) of **30a** as an amorphous white solid: R_f = 0.45 (EtOAc); ^1H NMR ($CDCl_3$) 0.79 (t, 3H), 0.91 (t, 3H), 1.38 (m, 4H), 1.71 (m, 2H), 2.61 (s, 3H), 2.71 (t, 2H), 2.98 (q, 2H), 5.63 (s, 2H), 6.06 (t, 1H), 7.04 (d, 2H), 7.34–7.61 (m, 5H), 8.15 (d, 1H). Anal. ($C_{26}H_{33}N_5O_4S_2$) C, H, N, S.

***N*-[[2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazol-5-yl]carbonyl]glycine Methyl Ester (30b).** The title compound was prepared from **12d** by the same procedure described for the preparation of **30a** using glycine methyl ester hydrochloride in presence of triethylamine in THF for the amidification step: mp 189–190 °C (from EtOAc), 53% yield; R_f = 0.40 (CH_2Cl_2/EtOAc, 1:1); ^1H NMR (DMSO-d_6) δ 0.76 (t, 3H), 0.82 (t, 2H), 1.30 (m, 4H), 1.54 (m, 2H), 2.50 (s, 3H), 2.60 (t, 2H), 2.85 (q, 2H), 3.64 (s, 3H), 4.05 (d, 2H), 5.58 (br s, 2H), 6.07 (t, 1H), 7.12 (d, 2H), 7.25–7.62 (m, 5H), 8.02 (d, 1H), 8.27 (t, 1H); MS (SIMS) m/e 616 (M + 1). Anal. ($C_{39}H_{37}N_5O_6S_2$) C, H, N, S.

***N*-[[2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazol-5-yl]carbonyl]glycine (30c).** The title compound was prepared from **30b** using general procedure D. The crude precipitate was triturated with acetonitrile/diisopropyl ether to give 470 mg (84%) of **30c** as an amorphous white solid: R_f = 0.50 (CH_2Cl_2/MeOH, 9:1); ^1H NMR ($CDCl_3$) 0.76 (t, 3H), 0.95 (t, 3H), 1.39 (m, 2H), 1.45 (m, 2H), 1.73 (m, 2H), 2.59 (s, 3H), 2.84 (m, 2H), 3.07 (q, 2H), 3.92 (d, 2H), 5.52 (br s, 2H), 6.30 (t, 1H), 7.04 (d, 2H), 7.15 (t, 1H), 7.24 (dd, 1H), 7.33 (d, 2H), 7.51 (dt, 1H), 7.62 (dt, 1H), 8.18 (dd, 1H). Anal. ($C_{28}H_{35}N_5O_6S_2$) C, H, N, S.

***N*-Acetyl-2-butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxamide (30d).** To a cold (0 °C) solution of acetamide (169 mg, 2.87 mmol) in dry THF (10 mL) was added 1.6 M *n*-BuLi in hexane (1.74 mL, 2.79 mmol) under N_2. A white precipitate was formed, and stirring was continued for 30 min. The mixture was cooled to −60 °C, and the acid chloride, prepared from **12d** (450 mg, 0.82 mmol) (see preparation of **30a**) and suspended in dry THF (2 mL) was added. After stirring for 15 min, the mixture was allowed to warm to 0 °C and stirred for 1 h. Aqueous NH_4Cl was added, and the pH was adjusted to 3–4 with 1 N HCl. The mixture

was extracted with CH_2Cl_2, and the combined extracts were washed with water and brine, dried, and concentrated. Purification by flash chromatography (EtOAc then CH_2Cl_2/MeOH, 9:1) gave 329 mg (68%) of **30d** which was recrystallized from ether; colorless crystals: mp 161–162 °C; R_f = 0.50 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.77 (t, 3H), 0.92 (t, 3H), 1.38 (m, 4H), 1.72 (m, 2H), 2.41 (s, 3H), 2.67 (s, 3H), 2.72 (m, 2H), 3.03 (q, 2H), 5.62 (s, 2H), 6.18 (br t, 1H), 7.07 (d, 2H), 7.38 (d, 2H), 7.34–7.64 (m, 3H), 8.14 (dd, 1H), 10.09 (br s, 1H). Anal. ($C_{28}H_{35}N_5O_5S_2$) C, H, N, S.

2-Butyl-4-(methylthio)-*N*-(phenylsulfonyl)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxamide (30e). The title compound was prepared by a procedure analogous to that for **30d** starting from benzene sulfonamide. Chromatographic purification (CH_2Cl_2/MeOH, 95:5) afforded **30e** (57%) as a white solid: mp 208–210 °C; R_f = 0.40 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR (DMSO-d_6) δ 0.78 (t, 3H), 0.83 (t, 3H), 1.30 (m, 4H), 1.51 (m, 2H), 2.31 (s, 3H), 2.54 (t, 3H), 2.85 (q, 2H), 5.79 (s, 2H), 6.39 (s, 1H), 7.01 (d, 2H), 7.37 (d, 2H), 7.21–7.77 (m, 8H), 8.00 (br d, 1H). Anal. ($C_{32}H_{37}N_5O_6S_3$) C, H, N, S.

Ethyl 2-Butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-[[(4-methoxyphenyl)methyl]thio]-1*H*-imidazole-5-carboxylate (31). The title compound was prepared from **5h** by the same procedure described for the preparation of **10d** in 58% yield: amorphous white solid: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.35 (t, 3H, J = 7 Hz), 1.35 (m, 2H), 1.71 (m, 2H), 2.62 (m, 2H), 2.69 (s, 3H), 2.72 (s, 3H), 3.79 (s, 3H), 4.26 (q, 2H, J = 7 Hz), 4.40 (s, 2H), 5.58 (s, 2H), 6.84 (d, 2H), 7.02 (s, 1H), 7.04 (d, 2H), 7.32 (d, 2H), 7.34 (d, 2H), 7.16–7.50 (m, 3H), 8.01 (m, 1H).

Ethyl 2-butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-mercapto-1*H*-imidazole-5-carboxylate, Mercury(II) Salt (32). To a cooled (0 °C) mixture of **31** (5.47 g, 8.44 mmol) and anisole (5.5 mL) were successively added TFA (27.4 mL) and mercury(II) trifluoroacetate (1.8 g, 4.22 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 5 min, and evaporated to dryness under vacuum. Chromatography on silica gel (CH_2Cl_2/EtOAc, 7:3) gave 4.32 g (84%) of **32** as a pale yellow foam: R_f = 0.14 (CH_2Cl_2/EtOAc, 8:2); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, J = 7.5 Hz), 1.30 (m, 2H), 1.41 (s, 3H), 2.48 (t, 2H, J = 7.5 Hz), 2.75 (s, 3H), 2.78 (s, 3H), 4.32 (q, 2H, J = 7 Hz), 5.56 (s, 2H), 7.03 (d, 2H, J = 8 Hz), 7.09 (s, 1H), 7.15 (m, 1H), 7.33 (d, 2H, J = 8 Hz), 7.50 (m, 2H), 8.28 (d, 1H); MS (EI) m/e 1256 M^+.

Ethyl 2-Butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-[[(methylthio)methyl]thio]-1*H*-imidazole-5-carboxylate (33). A mixture of **32** (7.65 g, 6.09 mmol), sodium iodide (3.65 g, 24 mmol), chloromethyl methyl sulfide (1.12 mL, 13.4 mmol), and dry DMF (150 mL) was stirred at room temperature for 2 h. After removal of DMF, the residue was dissolved in EtOAc, washed with water, dried over $MgSO_4$, and concentrated. Recrystallization from EtOH afforded 6.9 g (94%) of **33** as colorless crystals: mp 138–140 °C; R_f = 0.25 (CH_2Cl_2/EtOAc, 9:1); ^{1}H NMR ($CDCl_3$) 0.83 (t, 3H), 1.33 (m, 2H), 1.40 (t, 3H), 1.68 (m, 2H), 2.28 (s, 3H), 2.62 (t, 2H), 2.75 (s, 6H), 4.30 (q, 2H), 4.32 (s, 2H), 5.59 (s, 2H), 7.04 (d, 2H), 7.08 (s, 1H), 7.34 (d, 2H), 7.16–7.50 (m, 3H), 8.28 (d, 1H). Anal. ($C_{28}H_{38}N_4O_4S_3$) C, H, N, S.

2-Butyl-4-[[(methylthio)methyl]thio]-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (34). A mixture of **33** (6.9 g, 11.7 mmol), concentrated HCl (70 mL), and EtOH (140 mL) was heated at 50 °C for 18 h then cooled. The pH was adjusted to 10 with concentrated NaOH, and the mixture was extracted with EtOAc, washed with water, dried, and evaporated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 9:1) to afford 5.7 g (91%) of free sulfonamide which was treated according to general procedure C (trituration with EtOH, 80% yield) followed by saponification *via* general procedure D in 99% yield to afford 5 g of **34** as a white solid: mp 163–164 °C; R_f = 0.45 ($CHCl_3$/MeOH, 8:2). ^{1}H NMR (DMSO-d_6) δ 0.76 (t, 3H), 0.84 (t, 3H), 1.31 (m, 4H), 1.58 (m, 2H), 2.17 (s, 3H), 2.64 (t, 2H), 2.85 (q, 2H), 4.33 (s, 2H), 5.63 (s, 2H), 6.09 (t, 1H), 7.08 (d, 2H), 7.27 (d, 2H), 7.27–7.56 (m, 3H), 9.90 (s, 1H). Anal. ($C_{27}H_{34}N_4O_5S_3$) C, H, N, S.

Ethyl 2-Butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-mercapto-1*H*-imidazole-5-carboxylate (35). Through a suspension of mercury salt **32** (2.2 g, 1.75 mmol) in EtOAc (300 mL) was bubbled H_2S gently for 45 min at room temperature. Then the excess of H_2S was removed under a stream of N_2, the black precipitate was removed by filtration, and the filtrate was concentrated to give 1.85 g (99%) of **35** as a brown foam: R_f = 0.30 (EtOAc/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.35 (m, 2H), 1.40 (t, 3H), 1.66 (m, 2H), 2.63 (m, 2H), 2.77 (s, 3H), 2.78 (s, 3H), 4.33 (q, 2H), 5.60 (s, 2H), 7.03 (d, 2H), 7.16 (s, 1H), 7.17 (dd, 1H), 7.36 (d, 2H), 7.50 (m, 1H), 8.27 (dd, 1H); MS (SIMS) m/e 529 (M + 1).

Ethyl 2-Butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-[(trifluoromethyl)thio]-1*H*-imidazole-5-carboxylate (36a). To a cooled (0 °C) mixture of NaH in 50% dispersion in oil (326 mg, 6.8 mmol) in dry DMF (10 mL) was added dropwise a solution of thiol **35** (3 g, 5.6 mmol) in dry DMF (15 mL). The reaction mixture was stirred at 0 °C for 15 min and then was irradiated with a Heraeus mercury high-pressure lamp TQ150Z3 held in a water-cooled Pyrex sleeve while Freon 13B1 was bubbled through for 15 min. Stirring and irradiation were continued for 1 h. The mixture was warmed to room temperature, diluted with water, extracted with EtOAc, washed, dried, and evaporated. The residue was recrystallized from EtOAc to give 2.7 g (80%) of **36a** as a white solid: mp 124–125 °C; R_f = 0.44 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.27 (m, 2H), 1.39 (t, 3H), 1.68 (m, 2H), 2.65 (t, 2H), 2.76 (s, 3H), 2.77 (s, 3H), 4.33 (q, 2H), 5.61 (s, 2H), 7.02 (d, 2H), 7.36 (d, 2H), 7.16–7.50 (m, 3H), 8.22 (d, 1H); MS (FAB) m/e 597 (M + 1). Anal. ($C_{27}H_{31}F_3N_4O_4S_2$) C, H, F, N, S.

2-Butyl-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-[(trifluoromethyl)thio]-1*H*-imidazole-5-carboxylic Acid (37a). The title compound was prepared in three steps from **36a** by the same procedure as described for the preparation of **34**: mp 118–120 °C; 72% yield; R_f = 0.11 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 0.76 (t, 3H), 0.85 (t, 3H), 1.31 (m, 4H), 1.53 (m, 2H), 2.68 (t, 2H), 2.84 (q, 2H), 5.62 (s, 2H), 6.36 (t, 1H), 7.06 (d, 2H), 7.26 (d, 2H), 7.26–7.70 (m, 3H), 8.03 (d, 1H), 9.95 (s, 1H), 13.70 (br s, 1H). Anal. ($C_{26}H_{29}F_3N_4O_5S_2$) C, H, F, N, S.

Ethyl 2-butyl-4-[(difluoromethyl)thio]-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylate (36b). A solution of thiol **35** (4.1 g, 7.7 mmol) in dry desoxygenated DMF (80 mL) was heated under nitrogen at 87 °C. Sodium chlorodifluoroacetate (Lancaster) (1.85 g, 12.32 mmol) and NaI (1.85 g, 12.32 mmol) were added. Heating was continued for 45 min, and DMF was evaporated. The residue was taken up in aqueous NH_4Cl and extracted with EtOAc. Purification by flash chromatography (CH_2Cl_2/EtOAc, 8:2, then CH_2Cl_2/MeOH, 9:1) afforded 3.3 g (75%) of **36b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.35 (m, 2H), 1.40 (t, 3H), 1.67 (m, 2H), 2.64 (t, 2H), 2.76 (s, 3H), 2.77 (s, 3H), 4.32 (q, 2H), 5.61 (s, 2H), 7.04 (d, 2H), 7.36 (d, 2H), 7.13–7.50 (m, 4H), 7.81 (t, 1H, J = 56 Hz), 8.27 (m, 1H).

2-Butyl-4-[(difluoromethyl)thio]-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (37b). The title compound was prepared in three steps from **36b** by the same procedure as described for the preparation of **34**: mp 95 °C dec; 59% yield; R_f = 0.25 (EtOAc/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.75 (t, 3H), 0.92 (t, 3H), 1.38 (m, 4H), 1.72 (m, 2H), 2.73 (m, 2H), 2.99 (q, 2H), 5.46 (br s, 2H), 6.26 (t, 1H), 7.04 (d, 2H), 7.32–7.63 (m, 5H), 7.72 (t, 1H, J = 56.5 Hz), 8.13 (d, 1H); MS (FAB) m/e 581 (M + 1). Anal. ($C_{26}H_{30}F_2N_4O_5S_2$) C, H, F, N, S.

Ethyl 2-Butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-[(2,2,2-trifluoroethyl)thio]-1*H*-imidazole-5-carboxylate (36c). To a solution of **32** (1.1 g, 0.875 mmol) in DMF (16 mL) were added NaI (525 mg, 3.50 mmol) and 2-iodo-1,1,1-trifluoroethane (0.34 mL, 3.48 mmol) with stirring. Then the mixture was heated at 50 °C for 48 h, poured into water, and extracted with EtOAc. The combined organic extracts were washed with

water and brine, dried, and evaporated. Purification by chromatography (CH_2Cl_2/EtOAc, 9:1) gave 578 mg (54%) of **36c** as a yellow solid: mp 186 °C; R_f = 0.35 (CH_2Cl_2/EtOAc, 9:1); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.40 (m, 4H), 1.65 (m, 2H), 2.60 (t, 2H), 2.77 (s, 3H), 2.80 (s, 3H), 4.00 (m, 2H), 4.35 (m, 2H), 5.60 (s, 2H), 6.90–7.60 (m, 9H).

2-Butyl-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-4-[(2,2,2-trifluoroethyl)thio]-1*H*-imidazole-5-carboxylic Acid (37c). The title compound was prepared in three steps from **36c** by the same procedure as described for the preparation of **34**: mp 105–107 °C; 62% yield; R_f = 0.51 (CH_2Cl_2/MeOH, 8:2); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 0.80 (t, 3H), 0.92 (t, 3H), 1.39 (m, 4H), 1.72 (m, 2H), 2.77 (t, 2H), 2.99 (q, 2H), 4.08 (q, 2H, J = 10 Hz), 5.56 (s, 2H), 5.81 (t, 1H), 7.04 (d, 2H), 7.35 (d, 2H), 7.26–7.59 (m, 3H), 8.22 (dd, 1H). Anal. ($C_{27}H_{31}F_3N_4O_5S_2$) C, H, F, N, S.

Ethyl 2-Butyl-1-[[2′-[[[(dimethylamino)methylene]amino]sulfonyl](1,1′-biphenyl)-4-yl] methyl]-4-[[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,2,3,3-tetrafluorobutyl]thio]-1*H*-imidazole-5-carboxylate (36d). Step 1: Preparation of 1-[(*tert*-Butyldiphenylsilyl)oxy]-4-iodo-2,2,3,3-tetrafluorobutane (51). The title compound was prepared from 2,2,3,3-tetrafluoro-1,4-butanediol (Fluorochem) by protection of one hydroxy with TBDPSCl, TEA, and DMAP in CH_2Cl_2 (55% yield) followed by conversion of the other hydroxy to the corresponding iodide[49] (using PPh_3 3 equiv, I_2 3 equiv and imidazole 3 equiv in refluxing toluene overnight in 91%): oil; ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 3.67 (tt, 2H, J = 1, 17.5 Hz), 4.00 (tt, 2H, J = 1.5, 13 Hz), 7.43 (m, 6H), 7.65 (m, 4H).

Step 2. To a suspension of NaH (50% dispersion in oil) (0.3 g, 6.3 mmol) in dry DMF (21 mL) was added dropwise a solution of **35** (3 g, 5.67 mmol) in DMF (21 mL). Stirring was continued for 15 min at room temperature, and a solution of **50** (4.34 g, 8.5 mmol) in DMF (5 mL) was added dropwise. Then the reaction mixture was heated to 80 °C for 2 h and poured in water, extracted with EtOAc, washed with water, dried, and evaporated. Purification by flash chromatography (CH_2Cl_2/EtOAc, 9:1) gave 3.57 g (69%) of **36d** as a foam: R_f = 0.30 (CH_2Cl_2/EtOAc, 9:1); ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H), 1.07 (s, 9H), 1.30 (m, 2H), 1.41 (t, 3H, J = 7 Hz), 1.64 (m, 2H), 2.57 (t, 2H, J = 7.5 Hz), 2.70 (s, 3H), 2.72 (s, 3H), 4.04 (t, 2H, J = 13.5 Hz), 4.11 (t, 2H, J = 18 Hz), 4.32 (q, 2H, J = 7 Hz), 5.58 (s, 2H), 7.05 (d, 2H, J = 8 Hz), 7.06 (s, 1H), 7.16 (m, 1H), 7.33 (d, 1H, J = 8 Hz), 7.50 (m, 2H), 8.28 (m, 1H).

2-Butyl-4-[(4-hydroxy-2,2,3,3-tetrafluorobutyl)thio]-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (37d). The title compound was prepared in three steps from **36d** by the same procedure as described for the preparation of **34**: mp 172–174 °C; R_f = 0.30 (CH_2Cl_2/MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3H), 0.90 (t, 3H), 1.36 (m, 4H), 1.62 (m, 2H), 2.81 (t, 2H), 3.01 (q, 2H), 3.97–4.03 (m, 4H), 5.55 (s, 2H), 6.18 (t, 1H), 7.05 (d, 2H), 7.20 (dd, 1H), 7.35 (d, 2H), 7.53 (dt, 1H), 7.63 (dt, 1H), 8.12 (dd, 1H). Anal. ($C_{29}H_{34}F_4N_4O_6S_2$) C, H, F, N, S.

Ethyl 2-Butyl-1-[[2′-(hydroxycarbonyl)(1,1′-biphenyl)-4-yl]methyl]-4-(methylthio)-1*H*-imidazole-5-carboxylate (41). The title compound was prepared as **10d** from imidazole **5d** and (bromomethyl)biphenyl **40** in 68% yield, followed by deprotection of *tert*-butyl group with CH_2Cl_2/CF_3COOH (5:1) for 6 h at room temperature (85% yield): oil; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H), 1.29 (t, 3H), 1.34 (m, 2H), 1.60 (m, 2H), 2.66 (t, 2H), 2.57 (s, 3H), 4.25 (q, 2H), 5.56 (s, 2H), 7.00 (d, 2H), 7.27 (d, 2H), 7.32 (dd, 1H), 7.40 (td, 1H), 7.54 (td, 1H), 7.92 (dd, 1H).

Ethyl 1-[[2′-(Aminocarbonyl)(1,1′-biphenyl)-4-yl]methyl]-2-butyl-4-(methylthio)-1*H*-imidazole-5-carboxylate (42). A solution of acid **41** (0.97 g, 2.2 mmol) in thionyl chloride (9 mL) was refluxed for 4 h. The excess of $SOCl_2$ was then removed, and the residue, dissolved in 10 mL of dioxane, was treated with 9 mL of NH_4OH (22%) for 30 min at room temperature. The solution was poured in 50 mL of water and extracted with EtOAc, dried over $MgSO_4$, concentrated, and purified by chromatography (CH_2Cl_2/EtOAc, 1:1) to afford 0.67 g (70%) of amide **41** as a white solid: mp 144 °C; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.37 (m, 2H), 1.34 (t, 3H), 1.67 (m, 2H), 2.61 (s, 3H), 2.65 (m, 2H), 4.28 (q, 2H), 5.24 (br s, 1H), 5.43 (br s, 1H), 5.57 (s, 2H), 7.07 (d, 2H, J = 8 Hz), 7.39 (d, 2H, J = 8 Hz), 7.30–7.53 (m, 3H), 7.75 (dd, 1H).

2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (43). The title compound was prepared from **42** using general procedure C (in DME with 3 equiv C_3H_7NCO and 3 equiv of K_2CO_3 in 50% yield) followed by saponification *via* general procedure D (66% yield after recrystallization in EtOH): mp 201–202 °C; ^1H NMR (DMSO-d_6) δ 0.82 (t, 6H), 1.28 (m, 2H), 1.42 (m, 2H), 1.53 (m, 2H), 2.45 (s, 3H), 2.58 (t, 2H), 3.08 (q, 2H), 5.60 (s, 2H), 7.05 (d, 2H), 7.32 (d, 2H), 7.35–7.60 (m, 4H), 10.60 (br s, 1H), 12.77 (br s, 1H). Anal. ($C_{27}H_{32}N_4O_4S$) C, H, N, S.

Ethyl 2-Butyl-4-(methylthio)-1-[[2′-[[[(*N*-propylamino)carbonyl]methylamino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylate (44). To a solution of urea **28** (0.57 g, 1 mmol) in 10 mL of CH_2Cl_2 was added dropwise a solution of diazomethane in CH_2Cl_2 (1.5 equiv). The solution was stirred for 15 min, and the reaction was quenched with acetic acid (1 mL). The organic layer was washed with water, dried over $MgSO_4$, and concentrated. Purification on column chromatography (EtOAc/hexane, 1:1) afforded 0.45 g (77%) of **44** as a white foam: ^1H NMR ($CDCl_3$) δ 0.77 (t, 3H), 0.91 (t, 3H), 1.35 (m, 4H), 1.35 (t, 3H), 1.68 (m, 2H), 2.31 (q, 2H), 2.65 (m, 2H), 2.60 (s, 3H), 2.68 (s, 3H), 4.28 (q, 2H), 5.56 (s, 2H), 6.48 (br t, 1H), 7.07 (d, 2H), 7.27 (d, 2H), 7.27 (m, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 8.05 (d, 1H); MS (FAB) m/e 587 (M + 1).

4′-[(2-Butyl-4-chloro-5-formyl-1*H*-imidazol-1-yl)methyl]-*N*-[(dimethylamino)methylene](1,1′-biphenyl)-2-sulfonamide (47). The title compound was prepared by coupling imidazole **46** with biphenyl **9** in 78% yield using the procedure described for the preparation of **10d**: mp 90 °C; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.34 (m, 2H), 1.68 (m, 2H), 2.62 (m, 2H), 2.76 (s, 3H), 2.83 (s, 3H), 5.62 (s, 2H), 7.06 (d, 2H), 7.14 (s, 1H), 7.16 (m, 1H), 7.38 (d, 2H), 7.51 (m, 2H), 8.28 (m, 1H), 9.80 (s, 1H); IR ($CHCl_3$) 1665, 1594, 1570, 1518, 1489 cm^{-1}.

Methyl 1-[[2′-(aminosulfonyl)(1,1′-biphenyl)-4-yl]methyl]-2-butyl-4-chloro-1*H*-imidazole-5-carboxylate (48). To a solution of aldehyde **47** (2 g, 4 mmol) in 100 mL of MeOH were added successively NaCN (1 g, 21 mmol), MnO_2 (7.5 g, 66 mmol), and finally CH_3COOH (0.4 mL, 6.4 mmol). The suspension was stirred at room temperature for 36 h and filtered through clarcel, and the filtrate was evaporated to dryness. The brown residue was triturated with water, and the resulting white solids were collected by filtration and dried to afford 1.6 g (77%) of **47** which was treated with EtOH/concentrated HCl according to the procedure described for **11d** to produce **48** in 70% yield: mp 161 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.35 (m, 2H), 1.68 (m, 2H), 2.65 (t, 2H), 3.80 (s, 3H), 4.18 (s, 2H), 5.58 (s, 2H), 7.08 (d, 2H), 7.28 (d, 1H), 7.41 (d, 2H), 7.55 (m, 2H), 8.15 (d, 1H).

2-Butyl-4-chloro-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (49). The title compound was prepared from **48** using general procedure C (72% yield after recrystallization from CH_2Cl_2/Et_2O) followed by saponification by general procedure D (75% yield after recrystallization in CH_3CN) as pink crystals: mp 218 °C; ^1H NMR (DMSO-d_6) δ 0.76 (t, 3H), 0.84 (t, 3H), 1.30 (m, 4H), 1.57 (m, 2H), 2.64 (t, 2H), 2.84 (q, 2H), 5.62 (s, 2H), 6.37 (br t, 1H), 7.05 (d, 2H), 7.24 (d, 2H), 7.25 (m, 1H), 7.58 (dt, 1H), 7.66 (dt, 2H), 8.02 (dd, 1H); IR (Nujol) 1700, 1662, 1614, 1555, 1525, 1513 cm^{-1}. Anal. ($C_{25}H_{29}ClN_4O_5S$) C, H, N, S, Cl.

2-Butyl-4-(methylthio)-1-[[2′-[[[(propylamino)carbonyl]amino]sulfonyl](1,1′-biphenyl)-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid Dipotassium Salt (50, HR 720). To a cold (3–5 °C) suspension of ester **28** (2 g, 3.5 mmol) in ethanol (40 mL) was added dropwise 6 N KOH (2.3 mL, 13.8 mmol). The reaction mixture was allowed to warm at room temperature and was stirred for 72 h. The crude precipitate was filtered and washed with 96% ethanol to afford 1.92 g (89%) of compound **50** as colorless crystals of the dipotassium salt: mp >260 °C; ^1H NMR (D_2O) δ 0.77 (t, 3H), 0.87 (t, 3H), 1.31 (m, 4H), 1.58 (m, 2H), 2.47 (s, 3H), 2.72 (t, 2H), 2.80 (m, 2H), 5.63 (s, 2H), 7.05–7.32 (AA′BB′, 4H), 7.25

(d, 1H), 7.56 (m, 2H), 8.04 (d, 1H); MS (FAB) m/e 621 (M + 1). Anal. ($C_{26}H_{30}K_2N_4O_5S_2$) C, H, N, S.

Angiotensin II Binding Studies on Rat Liver Membranes. The experiments were performed in male Sprague–Dawley rats (Iffa credo) weighing between 150 and 200 g. The preparation was made extemporaneously, and the different steps were carried out at 4 °C in ice. The animals were killed by decapitation, and the liver was removed. The tissue was homogenized in 50 mM Tris-HCl buffer, pH 7.4, by grinding in the Polytron (setting 3; 4 × 10 s) (1 g of tissue to 40 mL of buffer). The homogenate was centrifuged for 15 min at 30000g (Beckman J2-21 ME centrifuge). The resultant pellets were washed twice by resuspension (Dounce A) with 50 mM Tris-HCl buffer, pH 7.4, and centrifuged again under the same conditions. A pellet corresponding to 0.25 g of fresh tissue was taken up (Dounce A) in 125 mL of incubation buffer: Tris (20 mM), NaCl (135 mM), KCl (10 mM), glucose (5 mM), and $MgCl_2{\cdot}6H_2O$ (10 mM). After adjustment to pH 7.4 (2 N HCl), the following were added extemporaneously: PMSF (0.3 mM), Bacitracin (0.1 mM), and Lysozyme (1 g/L).

The assays were performed in most cases in duplicate (n = 1–3) on 1 mL aliquots (glass tubes) in the presence of [^{125}I]-Tyr^4-angiotensin II at a final concentration of about 10^{-11} M and in the absence or presence of seven different concentrations of test compounds (10 μL aliquots). The nonspecific binding was determined in the presence of a high concentration (3×10^{-5} M) of a specific antagonist 4′-[[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl]methyl](1,1′-biphenyl)-2-carboxylic acid (EXP 7711). After incubation for 150 min at 25 °C, the aliquots of homogenate were filtered (Skatron apparatus) on fiberglass filters (Pharmacia Filtermat B) prewashed for 30 min in an aqueous solution of 0.05% polyethyleneimine; the filters were washed rapidly with 50 mM Tris-HCl buffer, pH 7.4 (2 × 2 s), and then dried in a microwave oven (CEM). A Meltilex B/HS sheet (Wallac) was applied to the filter before counting in a Betaplate scintillator (Pharmacia).

Evaluation of AII Antagonists in Pithed Normotensive Rats. Intravenous Administration. Blood pressure was recorded in normotensive Sprague–Dawley pithed rats (n = 4) *via* a catheter introduced in a carotid artery. AII (0.75 μg/kg) was injected to rats *via* a catheter introduced in a jugular vein. Three control responses to AII were obtained. The following injections of AII were preceded (5 min before) by injections of increasing doses of the antagonist under study (dissolved in water for HR 720 and water with 2 equiv of NaOH for the other antagonists). The dose of the compound necessary to block 50% of the initial response to AII (ID_{50}) was determined.

Oral Administration. Normotensive rats (Sprague–Dawley, n = 18–28) were divided in several groups. Each group received by gastric tubing a dose of the antagonist under study (dissolved in water for compound **50** and water with 2 equiv of NaOH for the other antagonists). Another group of rats received the solvent (water) as the control; 50 min later, rats were anaesthetized, pithed, and ventilated. Blood pressure was recorded *via* a catheter introduced in a carotid artery. A catheter was introduced in a jugular vein. One hour after gastric tubing, AII (0.75 μg/kg) was intravenously administered. AII-induced increase in diastolic blood pressure in treated groups was compared to that of observed in the control group. The dose of the compound necessary to block 50% of the AII pressor effect (ID_{50}) was calculated.

Inhibition of AII-Induced Pressor Response in Conscious Normotensive Rats. Blood pressure was recorded from conscious normotensive Sprague–Dawley rats *via* a catheter introduced into a carotid artery. Animals received *via* oral administration either compound **50** or DuP 753 for treated groups or solvent (water) for the control group. They were challenged with AII (0.75 μg/kg)–through a catheter introduced in a jugular vein–before treatment and 1, 3, 6 and 24 h after oral treatment.

Antihypertensive Effect in Conscious Renal Artery-Ligated Hypertensive Rats. Acute renovascular hypertension was induced by a complete left renal artery ligation in male Sprague–Dawley rats (280–300 g). Six days after surgery, blood pressure was recorded from conscious hypertensive animals *via* an arterial catheter. Animals orally received either compound **50** or DuP 753 for treated groups or the solvent (distilled water) for control animals. Blood pressure was recorded before oral dosage and then 1, 3, 6, and 24 h later.

Inhibition of AII-Induced Pressor Response in Conscious Normotensive Dogs. The study was carried out in conscious mongrel dogs of either sex (11–26 kg) fitted with an arterial catheter. After a food restriction of 18 h, a short catheter was introduced into a cephalic vein. Before the administration by gavage of a capsule containing either compound **50** or EXP 3174 at 10 mg/kg, AII was injected at 0.15 μg/kg iv and then at 1 h intervals for 6 h on day 1 and again 6 h on day 2 postdose. The control group received an empty capsule.

Effects on Systolic Arterial Blood Pressure in Conscious Sodium-Depleted Hypertensive Dogs. Experiment was performed in conscious hypertensive dogs (Beagle, 15–21 kg) of either sex. Several months before the experiment and under anaesthesia, the two kidneys of the dogs were wrapped in cellophane (Page's method). A second operation was performed to implant a radiotelemetry device (Data Sciences, Mn) for recording of blood pressure. Furosemide (Hoechst) was administered 17 h before the experiment at a dose of 10 mg/kg by subcutaneous route and 1 h before drug at 10 mg/kg intravenously in order to elevate the plasma renin activity by about seven fold. An empty capsule in the control group or compound **50** or EXP 3174 at 3 mg/kg were administered by gavage. Systolic arterial blood pressure was recorded at 2 h intervals up to 30 h postdose.

Acknowledgment. We thank the physical department of Roussel Uclaf and Hoechst AG for providing spectra and microanalytical data. We also thank all the people involved in this project for their technical assistance. We are also grateful to E. Bricard and J. Weston for the careful reading of the manuscript.

Supplementary Material Available: Physical data (mp, yield, R_f, ^{1}H NMR, MS) of **3a,c,e, 4a–c,e–j, 5a–c,e–j, 11a–c,e,i–l,** and **12a–c,e,j–l** (3 pages). Ordering information is given on any current masthead page.

References

(1) (a) Ferrario, C. M. The Renin-Angiotensin System: Importance in Physiology and Pathology. *J. Cardiovasc. Pharmacol.* **1990**, *15* (Suppl. 3), S1–S5. (b) Vallotton, M. B. The Renin-Angiotensin System. *Trends Pharmacol. Sci.* **1987**, *8*, 69–74.
(2) Johnston, C. I. Biochemistry and Pharmacology of the Renin-Angiotensin System. *Drugs* **1990**, *39* (Suppl. 1), 21–31.
(3) (a) Waeber, B.; Nussberger, J.; Brunner, H. R. The Renin-Angiotensin System: Role in Experimental and Human Hypertension. In *Pathophysiology of Hypertension-Regulatory Mechanisms* (*Handbook of Hypertension*, Vol. 8). (b) Zanchetti, A., Tarazi, R. C., Eds.; Elsevier: Amsterdam, 1986; pp 489–519.
(4) Corvol, P. New Therapeutic Prospects of Renin-Angiotensin System Inhibition. *Clin. Exp. Hypertens., Part A* **1989**, *A11* (Suppl. 2), 463–470.
(5) Wyvratt, M. J.; Patchett, A. A. Recent Developments in the Design of Angiotensin-Converting Enzyme Inhibitors. *Med. Res. Rev.* **1985**, *5*, 483–536.
(6) Greenlee, W. J. Renin Inhibitors. *Med. Res. Rev.* **1990**, *10*, 173–236.
(7) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F.; Benfield, P.; Carini, D. J.; Lee, R. J.; Wexler, R. R.; Saye, J. A. M.; Smith, R. D. Angiotensin II Receptors and Angiotensin II Receptor Antagonists. *Pharm. Rev.* **1993**, *45*, 205–251.
(8) (a) Some of the adverse of ACE inhibitors such as dry cough and angioedema have been attributed to the multisubstrate action of ACE. Coulter, M. D.; Edwards, I. R. Cough Associated with Captopril and Enalapril. *Br. Med. J.* **1987**, *294*, 1521–1523. (b) Erdos, E. G.; Skidgel, R. A. The Unusual Substrate Specificity and the Distribution of Angiotensin I Converting Enzyme. *Hypertension* **1986**, *8* (Suppl. I), I-34–I-37. (c) McEwan, J. R.; Fuller, R. W. Angiotensin Converting Enzyme Inhibitors and Cough. *J. Cardiovasc. Pharmacol.* **1989**, *13* (Suppl. 3), S67–S69. (d) Chin, H. L.; Buchan, D. A. Severe Angioedema after Long-Term Use of an Angiotensin-Converting Enzyme Inhibitor. *Ann. Intern. Med.* **1990**, *112*, 312–313.
(9) (a) AII receptor antagonists could specifically affect the RAS independently of the source of AII. Dzau, V. J. Multiple Pathways of Angiotensin Production in the blood Vessel Wall: Evidence, Possibilities and Hypotheses. *J. Hypertension* **1989**,

7, 933–936. (b) Urata, H.; Kinoshita, A.; Misono, K. S.; Bumpus, F. M.; Husain, A. Identification of a Highly Specific Chymase as the Major Angiotensin II-Forming Enzyme in the Human Heart. *J. Biol. Chem.* **1990**, *265*, 22348–22357.

(10) (a) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A New Class of Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1312–1329. (b) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chui, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: N-[(Benzyloxy)benzyl]imidazoles and Related Compounds as Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1330–1336.

(11) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of a Series of N-(Biphenylmethyl)-imidazoles as Potent, Orally Active Antihypertensives. *J. Med. Chem.* **1991**, *34*, 2525–2547.

(12) (a) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Pierce M. E.; Price, W. A.; Smith R. D.; Wells, G. J.; Wong, P. C.; Wexler R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. DuP 753 Losartan Potassium (MK-954) *Drugs Future* **1992**, *17*, 326–331. (b) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. The Discovery of DuP 753, a Potent, Orally Active Nonpeptide Angiotensin II Antagonist. *Med. Res. Rev.* **1992**, *12*, 149–191.

(13) (a) Wong, P. C.; Hart, S. D.; Duncia, J. V.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists. Studies with DuP 753 and EXP 3174 in Dogs. *Eur. J. Pharmacol.* **1991**, *202*, 323–330. (b) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists. XI. Pharmacology of EXP 3174: An Active Metabolite of DuP 753, an Orally Active Antihypertensive Agent. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 211–217.

(14) Bumpus, F. M.; Catt, K. J.; Chiu, A. T.; DeGasparo, M.; Goodfriend, T.; Husain, A.; Peach, M. J.; Taylor, D. G., Jr.; Timmermans, P. B. M. W. M. Nomenclature for Angiotensin Receptor. *Hypertension* **1991**, *17*, 720–721.

(15) (a) Ashton, W. T. Nonpeptide Angiotensin II Receptor Antagonists. *Exp. Opin. Invest. Drugs* **1994**, *3* (11), 1105–1142. (b) Murray, W. V. Angiotensin II Receptor Antagonists: The Next Step in the Evolution of Antihypertensive Therapy. *Chemtracts—Org.Chem.* **1993**, *6*, 263. (c) Buhlmayer, P. Angiotensin II Antagonists: Patent Activity since the Discovery of Dup 753. *Curr. Opin. Ther. Pat.* **1992**, *2*, 1693–1718. (d) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. Angiotensin II Receptor Binding Inhibitors. *Drugs Future* **1992**, *17* (7), 575–593.

(16) (a) Butler, R. N. Tetrazoles. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 791–838. (b) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908. (c) Luitjen, J. G.; Janssen, M. J.; Van Der Kirk, G. J. M. *Recl. Trav. Chim. Pays-Bas* **1963**, *81*, 286. (d) Thomas, E. W. The Conversion of Secondary Amides to Tetrazoles with Trifluoromethanesulfonic Anhydride and Sodium Azide. *Synthesis* **1993**, 767. (e) Wittenberger, S. J.; Donner, B. G. Dialkyltin oxide Mediated Addition of Trimethylsilyl Azide to Nitriles. A Novel Preparation of 5-Substituted Tetrazoles. *J. Org. Chem.* **1993**, 4139.

(17) (a) Kanai, Y.; Nakai, Y.; Nakajima, N.; Tanayama, S. Metabolic Disposition of 6-Ethyl-3-(1H-tetrazol-5-yl)-chromone, a New Antiallergic Agent, in the Rat, Guinea-Pig, Rabbit, Dog, and Monkey. *Xenobiotica* **1979**, *9*, 33–50. (b) Tateno, M.; Takamatsu, R.; Shibata, M.; Furuta, S.; Nobutoki, M.; Demidzu, K. Metabolism of Traxnox Sodium in Man. *Yakuri To Chiryo* **1988**, *16*, 3251–3257. (c) Huskey, S.-E. W.; Magdalou, J.; Ouzzine, M.; Siest, G.; Chiu, S.-H. L. N-Glucuronidation Reactions. III. Regioselectivity of N-Glucuronidation of Methylbiphenyl Tetrazole, Methylbiphenyl Triazole, and Methylbiphenyl Imidazole Using Human and Rat Recombinant UDP-Glucuronosyltransferases Stably Expressed in V79 Cells. *Drug Metab. Dispos.* **1994**, *22*, 659–662. (d) Huskey, S.-E. W.; Doss, G. A.; Miller, R. R.; Schoen, W. R.; Chiu, S.-H. L. N-Glucuronidation Reactions. II. Relative N-Glucuronidation Reactivity of Methylbiphenyl Tetrazole, Methylbiphenyl Triazole, and Methylbiphenyl Imidazole in Rat, Monkey, and Human Hepatic Microsomes. *Drug Metab. Dispos.* **1994**, *22*, 651–658.

(18) (a) Stearns, R. A.; Doss, G. A.; Miller, R. R.; Chiu, S.-H. L. Synthesis and Identification of a Novel Tetrazole Metabolite of the Angiotensin II Receptor Antagonist DuP 753. *Drug Metab. Dispos.* **1991**, *19*, 1160–1162. (b) Stearns, R. A.; Miller, R. R.; Doss, G. A.; Chakravarty, P. K.; Rosegay, A.; Gatto, G. J.; Chiu, S.-H. L. The Metabolism of DuP 753, a Nonpeptide Angiotensin II Receptor Antagonist, by Rat, Monkey, and Human Liver Slices. *Drug Metab. Dispos.* **1992**, *20*, 281–287. (c) Huskey, S.-E. W.; Randall, R. M.; Chiu, S.-H. L. N-Glucuronidation Reaction. I. Tetrazole N-Glucuronidation of Selected Angiotensin II Receptor Antagonists in Hepatic Microsomes from Rats, Dogs, Monkeys and Humans. *Drug Metab. Dispos.* **1993**, *21*, 792–799.

(19) (a) A new process for the production of Losartan employs 5-phenyltetrazole as a starting material and avoids the use of tin reagents: Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J. Efficient Synthesis of Losartan, a Nonpeptide Angiotensin II Receptor Antagonist. *J. Org. Chem.* **1994**, *59*, 6391–6394. (b) Weber, M. A. Clinical Experience with the Angiotensin II Receptor Antagonist Losartan. *Am. J. Hypertens.* **1992**, *5*, 2475–2515.

(20) (a) Heckmann, B.; Zhang, J.; Caille, J.-C.; Corbier, A.; Deprez, P.; Didierlaurent, S.; Fortin, M.; Frechet, D.; Guillaume, J.; Hamon, G.; Vincent, J.-C.; Vevert, J.-P. Nonpeptide Angiotensin II Receptor Antagonists: Synthesis and Structure Activity Relationships of 4-Thioimidazole Biphenyl Tetrazole Derivatives. Unpublished results. (b) Caille, J. C.; Corbier, A.; Fortin, M.; Jouquey, S.; Vevert, J.-P. New Derivatives of Imidazole. Preparation and Pharmaceutical Composition. Eur. Pat. 0 465 368 A1, 1992; *Chem. Abstr.* **1992**, *116*, 214499g.

(21) Soll, R. M.; Kinney, W. A.; Primeau, J.; Garrick, L.; McCauly, R. J.; Colatsky, T.; Oshiro, G.; Park, C. H.; Hartupee, D.; White, V.; McCallum, J.; Russo, A.; Dinish, J.; Wojdan, A. 3-Hydroxy-3-cyclobutene-1,2-dione: Application of a Novel Carboxylic Acid Bioisostere to an In-Vivo Active Non-Tetrazole Angiotensin II Antagonist. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 757–760.

(22) (a) Kim, D.; Mantlo, N. B.; Chang, R. S. L.; Kivlighn, S. D.; Greenlee, W. J. Evaluation of Heterocyclic Acid Equivalents as Tetrazole Replacements in Imidazopyridine-Based Nonpeptide Angiotensin II Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 41–44. (b) Ferrari, B.; Taillades, J.; Perreaut, P.; Bernhart, C.; Gougat, J.; Guiraudou, P.; Cazaubon, C.; Roccon, A.; Nisato, D.; Le Fur, G.; Brelière, J. C. Development of Tetrazole Bioisosteres in Angiotensin II Antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 45–50.

(23) (a) Dowle, M. D.; Judd, D. B.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Pass, M.; Tranquillini, E.; Jack, T. I.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Drew, G. M.; Robertson, M. J.; Hilditch, A.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Manchee, G. R.; Walker, D. G.; Eddershaw, P. J.; Donnelly, M.; Bayliss, M. K. Benzofuran Based Angiotensin II Antagonists Related to GR 117289: Part III; GR 138950, a Triflamide with High Oral Bioavailability. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2047–2050. (b) Judd, D. B.; Cardwell, K. S.; Panchal, T. A.; Jack, T. I.; Pass, M.; Hubbard, T.; Dean, A. W.; Butt, A. U.; Hobson, J. E.; Heron, N. M.; Watson, S. P.; Currie, G. S.; Middlemiss, D.; Allen, D. G.; Aston, N. M.; Paton, J. M. S.; Drew, G. M.; Hilditch, A.; Gallacher, D.; Bayliss, M. K.; Donnelly, M. C. Benzofuran Based Non-Peptide Antagonists of Angiotensin II Related to GR 117289: Part IV; Imidazopyridinylbenzofurans. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 725–728.

(24) (a) Chakravarty, P. K.; Greenlee, W. J.; Mantlo, N. B.; Patchett, A. A.; Walsh T. F. Substituted Imidazo-Fused 6-Membered Heterocycles as Angiotensin II Antagonists. Eur. Pat. 0 400 974, 1990; *Chem. Abstr.* **1991**, *115*, 29326q. (b) Chang, L. L.; Ashton, W. T.; Maccoss, M.; Chakravarty, P. K.; Greenlee, W. J.; Patchett, A. A.; Walsh T. F. Substituted Triazolinones, Triazolinethiones, and Triazolinimines as Angiotensin II Antagonists. Eur. Pat. 0 412 594, 1991; *Chem. Abstr.* **1991**, *114*, 207268m. (c) Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Walsh, T. F.; Naylor, E. M. Imidazole Angiotensin II Antagonists Incorporating Acidic Fonctional Groups. Eur. Pat. 0 479 479, 1992. (d) Naylor, E. M.; Chakravarty, P. K.; Costello, C. A.; Chang, R. S. L.; Chen, T.-B.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Zingaro, G. J.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. Potent Imidazole Angiotensin II Antagonists: Acyl Sulfamides and Acyl Sulfonamides as Tetrazole Replacements. *Abstracts of Papers*, 205th American Chemical Society National Meeting, March 18–April 2, 1993; MEDI 114. (e) Naylor, E. M.; Chakravarty, P. K.; Chen, A.; Strelitz, R. A.; Chang, R. S. L.; Chen, T.-B.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Zingaro, G. J.; Schorn, T. W.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. Potent Imidazopyridine AII Antagonists: Acyl Sulfonamides as Tetrazole Replacements. *Abstracts of Papers*, 206th American Chemical Society National Meeting, Aug 22–27, 1993; MEDI 76. (f) Mantlo, B. N.; Kim, D.; Ondeyka, D.; Chang, R. S. L.; Kivlighn, S. D.; Siegl, P. K. S.; Greenlee, W. J. Imidazo[4,5-b]Pyridine-Based AT_1/AT_2 Angiotensin II Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 17–22. (g) Chakravarty, P. K.; Strelitz, R. A.; Chen, T.-B.; Chang, R. S. L.; Lotti, V. J.; Zingaro, G. J.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. A New Class of Balanced AT_1/AT_2 Angiotensin II Antagonists: Quinazolinone AII Antagonists with Acylsulfonamide and Sulfonylcarbamate Acidic Functionalities. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 81–86. (h) Glinka, T. W.; de Laszlo, S. E.; Siegl, P. K. S.; Chang, R. S. L.; Kivlighn, S. D.; Schorn, T. S.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Lotti,

V. J.; Greenlee, W. J. Quinazolinone Biphenyl Acylsulfonamides: a Potent New Class of Angiotensin II ReceptorAntagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 75–80. (i) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Bendesky, R. J.; Chen, T.-B.; Faust, K. A.; Kling, P. J.; Schaffer, L. W.; Schorn, T. W.; Zingaro, G. J.; Chang, R. S. L.; Lotti, V. J.; Kivlighn, S. D.; Siegl, P. K. S. Triazolinones as Nonpeptide Angiotensin II Antagonists. 2. Discovery of a Potent and Orally Active TriazolinoneAcylsulfonamide. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 115–120. (j) Naylor, E. M.; Chakravarty, P. K.; Costello, C. A.; Chang, R. S.; Chen, T.-B.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Zingaro, G. J.; Siegl, P. K. S.; Wong, P. C.; Carini, D. J.; Wexler, R. R.; Patchett, A. A.; Greenlee, W. J. Potent Imidazole Angiotensin II Antagonists: Acyl Sulfonamides and Acyl Sulfamides as Tetrazole Replacements. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 69–74. (k) Dhanoa, D. S.; Bagley, S. W.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Kivlighn, S. D.; Zingaro, G. J.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. Non-Peptide Angiotensin II Receptor Antagonists. 2. Design, Synthesis, and Biological Activity of N-Sustituted (Phenylamino)phenylacetic Acids and Acyl Sulfonamides. *J. Med. Chem.* **1993**, *36*, 4239–4249. (l) Ashton, W. T.; Chang, L. L.; Flanagan, K. L.; Hutchins, S. M.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Chen, T.-B.; Faust, K. A.; Chang, R. S. L.; Lotti, V. J.; Zingaro, G. J.; Schorn, T. W.; Siegl, P. K. S.; Kivlighn, S. D. Triazolinone Biphenylsulfonamide Derivatives as Orally Active Angiotensin II Antagonists with Potent AT1 Receptor Affinity and Enhanced AT2 Affinity. *J. Med. Chem.* **1994**, *37*, 2808–2824. (m) Santella, J. B., III; Duncia, J. V.; Ensinger, C. L.; VanAtten, N. K.; Carini, D. J.; Wexler, R. R.; Chiu, A. T.; Wong, P. C.; Timmermans P. B. M. W. M. Balanced Angiotensin II Receptor Antagonists III. The Effects of Substitution at the Imidazole 5-Position. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2235–2240. (n) Quan, M. L.; Olson, R. E.; Carini, D. J.; Ellis, C. D.; Hillyer, G. L., Lalka, G. K.; Liu, J.; VanAtten, M. K.; Chiu, A. T.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. Balanced Angiotensin II Receptor Antagonists I. The Effects of Biphenyl "Ortho"-Substitution on AT_1/AT_2 Affinities. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2011–2016.

(25) Wagner, A.; Englert, H.; Kleemann, H.-W.; Gerhards, H.; Scholkens, B.; Becker, R.; Linz, W.; Caille, J.-C.; Vevert, J.-P. Preparation of N-[(carbamoylaminosulfonyl) biphenylmethyl] Imidazoles as Angiotensin II Receptor Antagonists. Eur. Pat. A 0 503 162, 1992; *Chem. Abstr.* **1993**, *118*, 22235n.

(26) Caille, J. C.; Didierlaurent, S.; Lefrancois, D.; Lelièvre, M. H.; Sury, C.; Aszodi, J. An Expedient Synthesis of Ethyl 4(5)-alkyl-(aryl) thioimidazole-5(4)-carboxylate. Unpublished results.

(27) Sulfonamide **6** was obtained from the corresponding sulfonyl chloride (Lancaster) by aminolyse or from o-aminobenzenesulfonic acid according to Jackson, G. R., Jr.; Martin, S. F. Mercuration of certain Aromatic Compounds. *J. Am. Chem. Soc.* **1955**, *77*, 5625–5628.

(28) Miyaura, N.; Yanagi, T.; Suzuki, A. The Palladium-Catalyzed Cross-Coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **1981**, *11* (7), 513–519.

(29) The structures of the two regioisomers were assigned by analogy with the results obtained in the tetrazole series (see ref 20). A higher chemical shift of NCH_2 for N_1 isomer vs N_3 isomer was observed (see the Experimental Section: **12d** vs **13**)

(30) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. Titanate-Mediated Transesterifications with Functionalized Substrates. *Synthesis*, **1982**, 138.

(31) Schmidt, E.; Moosmüller, F. Zur Kenntnis Aliphatisher Carbodiimide IX. *Justus Liebigs Ann. Chem.* **1955**, *597*, 235.

(32) Corey, E. J.; Gilman, N. W.; Ganem, B. E. New Methods for the Oxidation of Aldehydes to Carboxylic Acids and Esters. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(33) For examples of pK_a, see: Masereel, B.; Renard, P.; Schynts, M.; Pirotte, B.; de Tullio, P.; Delarge, J. Synthesis and Pharmacology of Pyrid-3-yl Sulfonylureas and Thioureas as Astrocytic Na^+ $2Cl^-$ K^+ Cotransporter Inhibitors. *Eur. J. Med. Chem.* **1994**, *29*, 527–535.

(34) The pK_a of 5-alkyl-substituted tetrazole is about 6. Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; John Wiley and Sons: New York, 1980; Vol. 2, pp 301 and 345.

(35) Poyser, R. H.; Hamilton, T. C. Potassium Channel Modulators: Current Situation and Future Expectations. *Drugs Future* **1994**, *19*, 39–47.

(36) (a) Delarge, J. Nouveaux Anti-Inflammatoires Dérivés de la Pyridine. *Ann. Pharm. Franç.* **1973**, *31*, 467–474. (b) Delarge, J.; Lapiere, C. L. *J. Pharm. Bel.* **1973**, *3*, 283. (c) Delarge, J.; Ghys, A. Quelques Dérivés du Gallosemides à Propriétés Diurétiques chez l'Animal. *Ann. Pharm. Franç.* **1981**, *39*, 59–63. (d) Delarge, J.; Lapiere, C. L. Une Nouvelle Classe de Diurétiques "High Ceiling" Dérivés de l'Alkyl-1 ((phenylamino-4 pyridyl-3)-sulfonyl)-3 Urée. *Ann. Pharm. Franç.* **1978**, *36*, 369–380.

(37) Thorpe P. J. Torasemide. *Drugs Future* **1994**, 313.

(38) Carbamates are known to be inhibitors of acetyl choline esterase. For example see: (a) Chen, Y. L.; Liston, D.; Nielsen, J.; Chapin, D.; Dunaiskis, A.; Hedberg, K.; Ives, J.; Johnson, J. Jr.; Jones, S.; Syntheses and Anticholinesterase Activity of Tetrahydrobenzazepine Carbamates. *J. Med. Chem.* **1994**, *37*, 1996–2000. (b) BCPC Monograph No. 43, 1989, Progress and Prospects in Insect Control, K. Naumann, Acetylcholinesterase Inhibitors 21–41.

(39) 2-Propylimidazole **12c** proved to be a slightly more potent AII antagonist than 2-butylimidazole **12d** after iv and po administration (ID_{50} = 0.04 mg/kg iv and 0.15 mg/kg po).

(40) $S(CH_2)_nOH$ substituted imidazole proved to be orally active in the tetrazole series (see ref 20).

(41) Substitution at the 4-position by a chlorine led to the imidazole ring of EXP 3174.

(42) Bonnat, C.; Lenfant, B. Unpublished results.

(43) Wong, P. C.; Hart, S. D.; Duncia, J. V.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Antagonists. Studies with DuP 753 and EXP3174 in Dogs. *Eur. J. Pharmacol.* **1991**, *202*, 323–330.

(44) Carini, D. J.; Ardecky R. J.; Ensinger C. L.; Pruitt, J. R.; Wexler, R. R.; Wong, P. C.; Huang, S.-M.; Aungst, B. J.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: the Discovery of DMP 581 and DMP 811. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 63–68.

(45) Massardier, D.; Hunt, P. Unpublished results.

(46) Sodium dithionite reduction of oxime **1** afforded ethyl aminocyanoacetate **2**. Logemann, F. I.; Shaw, G. Improved Synthesis of Ethyl α-Amino-α-Cyanoacetate and α-Amino-α-Cyanoacetamide. *Chem. Ind.* **1980**, 541.

(47) Harding, J. S.; Owen, L. N. Dithiols. Part 14. The Alkaline Hydrolysis of Acetylated Non Vicinal Hydroxy-Thiols. *J. Chem. Soc.* **1954**, 1536–1545.

(48) Commercialy available.

(49) Lange, G. L.; Gottardo, C. Facile Conversion of Primary and Secondary Alcohols to Alkyl Iodides. *Synth. Commun.* **1990**, 1473.

JM940717V