Biphenylsulfonamide Endothelin Antagonists: Structure−Activity Relationships of a Series of Mono- and Disubstituted Analogues and Pharmacology of the Orally Active Endothelin Antagonist 2′-Amino-*N*-(3,4-dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (BMS-187308)

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Substitution at the ortho position of *N*-(3,4-dimethyl-5-isoxazolyl) benzenesulfonamide led to the identification of the biphenylsulfonamides as a novel series of endothelin-A (ET_A) selective antagonists. Appropriate substitutions on the pendant phenyl ring led to improved binding as well as functional activity. A hydrophobic group such as isobutyl or isopropoxyl was found to be optimal at the 4′-position. Introduction of an amino group at the 2′-position also led to improved analogues. Combination of the optimal 4′-isobutyl substituent with the 2′-amino function afforded an analogue (**20**, BMS-187308) with improved ET_A binding affinity and functional activity. Compound **20** also has good oral activity in inhibiting the pressor effect caused by an ET-1 infusion in rats. Doses of 10 and 30 μmol/kg iv **20** attenuated the pressor responses due to the administration of exogenous ET-1 to conscious monkeys, indicating that the compound inhibits the in vivo activity of endothelin-1 in nonhuman primates.

Introduction

Endothelin-1 (ET-1), originally isolated from cultured porcine endothelial cells, is a potent vasoconstrictor peptide consisting of 21 amino acids.[1] Two additional related isopeptides, ET-2 and ET-3, have subsequently been characterized.[2] It is now known that these peptides are produced by a number of other cell types and that they possess additional important biological activities in addition to potent vasoconstriction.[3] The endothelins elicit their diverse biological effects through at least two distinct G-protein-coupled receptors termed ET_A and ET_B.[4,5] The ET_A subtype, which is selective for ET-1 and ET-2 over ET-3, is found principally in peripheral tissues such as vascular smooth muscle.[6] The ET_A receptor mediates vasoconstriction and vascular smooth muscle proliferation. The ET_B receptor, which is nonselective for all three ET peptides,[7] appears to mediate either vasodilation or vasoconstriction depending on the tissue type.[8] The diversity of physiological effects elicited by the endothelins has implicated these peptides in the pathogenesis of a variety of disease states including restenosis, pulmonary hypertension, renal failure, vasospasm, and congestive heart failure.[3,9] Elevated levels of endothelins have been observed in many of these disease states providing further support for this notion. Therefore, it is widely expected that the discovery of selective or nonselective antagonists would prove to be useful in the treatment of these diseases.[9]

A number of peptidic as well as nonpeptidic endothelin antagonists have been reported in the literature.[9,10] Peptidic antagonists that are selective for the ET_A receptor include the cyclic pentapeptide BQ-123,[11] TAK-044,[12] and the tripeptide FR139317.[13] A nonselective peptide antagonist, PD 142893,[14] as well as the ET_B-selective peptide BQ 788[15] have also been reported. Nonpeptidic ET_A-selective agents include BMS-182874,[16,17] PD 156707,[18] and A-127722;[19] compounds that are nonselective for either receptor include Ro 47-0203 (Bosentan),[20] SB 209670,[21] and L-749,329.[22]

Previously, we described a series of benzenesulfonamides and the subsequent identification of the dansylsulfonamide BMS-182,874 (Chart 1) as a potent and selective ET_A antagonist.[16,17] We subsequently discovered that ortho substitution of the phenyl ring of the benzenesulfonamides leads to improved ET_A antagonist activity. Further development of the structure−activity relationship (SAR) around this position led to the identification of several biphenylsulfonamide analogues with improved binding potency. In the present paper, we report the SAR on this class of compounds and show that certain optimally disubstituted derivatives provide highly potent and selective endothelin antagonists in vitro and in vivo.

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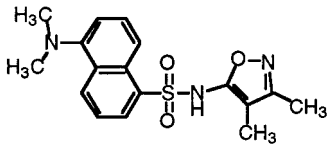
Chart 1



BMS 182,874

Chemistry

The sulfonamides **3a**−**f** and **6** (Table 1) were prepared by condensation of the arylsulfonyl chlorides with the commercially available 3,4-dimethyl-5-isoxazolamine in pyridine. Compounds **3e** and **3f** were prepared from sulfonyl chlorides previously described in the literature (**3e**,[23] **3f**[24]). Hydrogenation of **3c** afforded compound **3b**.

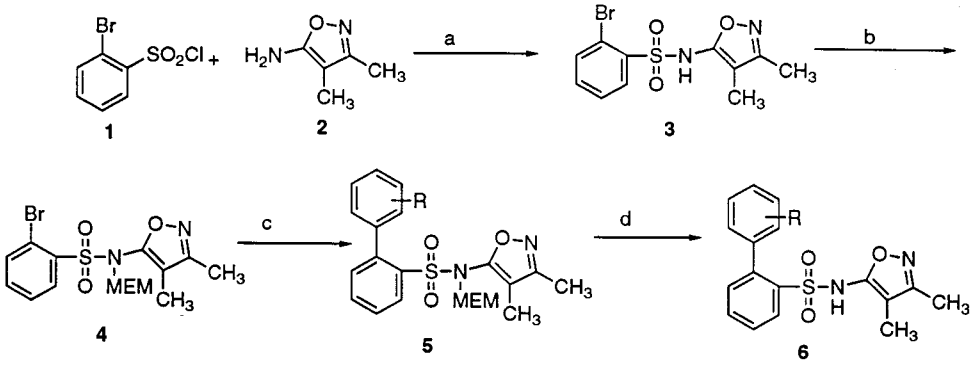
The biphenylsulfonamide analogues listed in Table 2 were prepared using the Suzuki coupling[25,26] as a key reaction as described in Scheme 1. Initial attempts to perform the couplings in the presence of the unprotected sulfonamide **3** were unsuccessful presumably because of the acidic sulfonamide moiety poisoning the Pd(0) catalyst. The sulfonamide **3** was therefore protected using MEM chloride and sodium hydride to provide intermediate **4**. Coupling of **4** with a variety of arylboronic acids under Suzuki conditions followed by deprotection of the MEM group under acidic conditions afforded the biphenylsulfonamide derivatives **6**. The arylboronic acids were either commercially available or readily prepared from the corresponding aryl halides using literature methods. Compounds **6b** and **6f** were prepared by reductive amination of the corresponding 2′- or 3′-amino derivatives (**6a** or **6e**, respectively**)** using formaldehyde and sodium cyanoborohydride. The 4′-carboxylic acid derivative **6i** was prepared via the oxidation of the 4′-aldehyde intermediate, which in turn was prepared via the Suzuki coupling of **4** and the commercially available 4-formylphenylboronic acid.

The 2-heteroarylbenzenesulfonamides **9a**−**c** and **9f** (Table 3) were prepared via a Suzuki coupling reaction between the boronic acid derivative **7** and the corresponding heteroaryl bromide followed by deprotection of the MEM group (Scheme 2). Compounds **9d**, **9e**, and **9g** were prepared using the reaction sequence in Scheme 1.

Exploration of the SAR of the isoxazole moiety was facilitated by the sequence of reactions described in Scheme 3. Suzuki coupling between 4-isobutylbenzeneboronic acid and the sulfonylpyrrole **10** provided the biarylsulfonylpyrrole **11**. Hydrolysis under basic conditions gave the sulfonic acid **12** which was then converted to the sulfonyl chloride derivative **13** using phosphorus pentachloride. Treatment of **13** with a variety of amino heterocylic derivatives then provided compounds **14a**−**h** (Table 4).

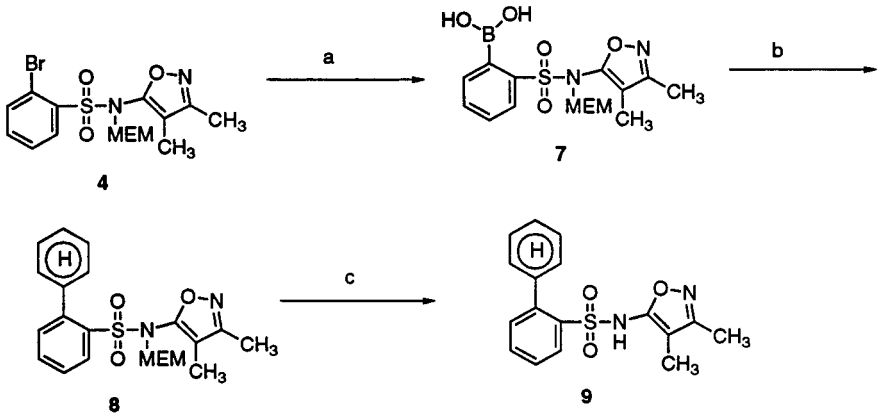
The 2′-amino-4′-isobutylbiphenylsulfonamide derivative **20** was synthesized as shown in Scheme 4. Wittig olefination of *m*-nitrobenzaldehyde using isopropyl triphenylphosphonium iodide followed by hydrogenation using Pt/C afforded the aniline derivative **16**. It was found

Scheme 1[a]



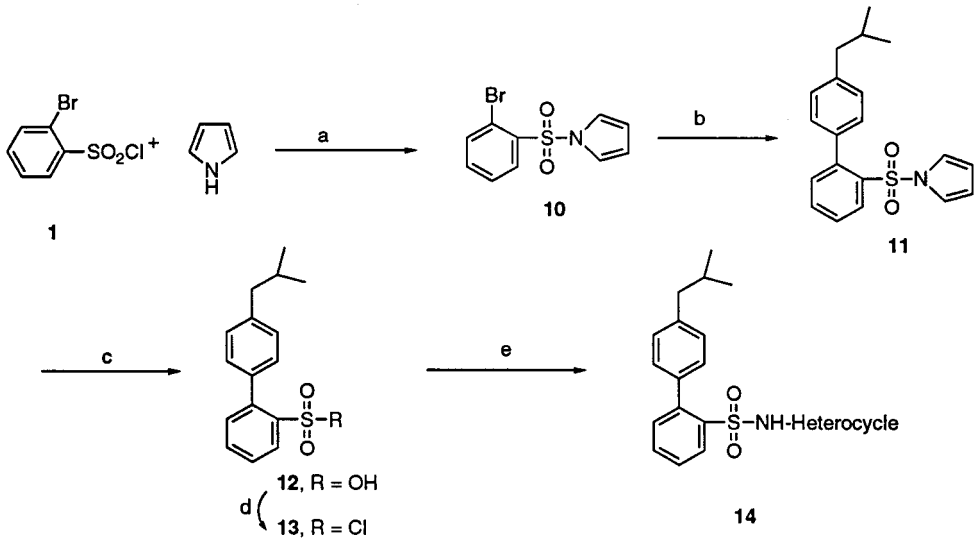
[a] (a) Pyridine, RT; (b) NaH, methoxyethoxymethyl chloride; (c) $ArB(OH)_2$, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (d) 6 N aqueous HCl/EtOH.

Scheme 2[a]



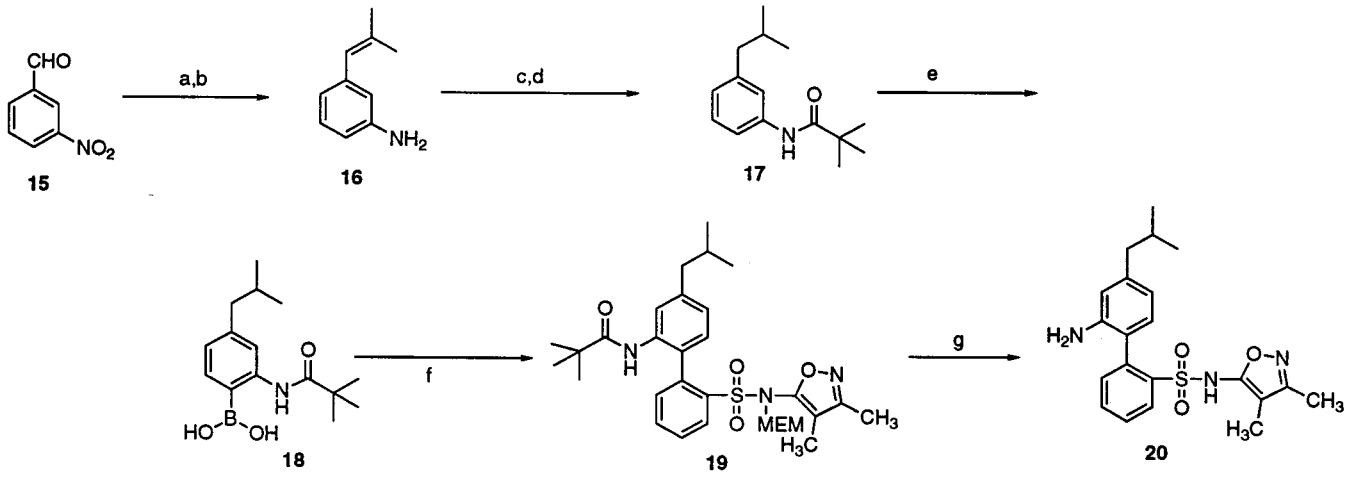
[a] (a) (i) *n*-BuLi, THF, −78 °C, (ii) triisopropyl borate, (iii) HCl; (b) heteroaryl bromide, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (c) 6 N aqueous HCl/EtOH.

Scheme 3[a]



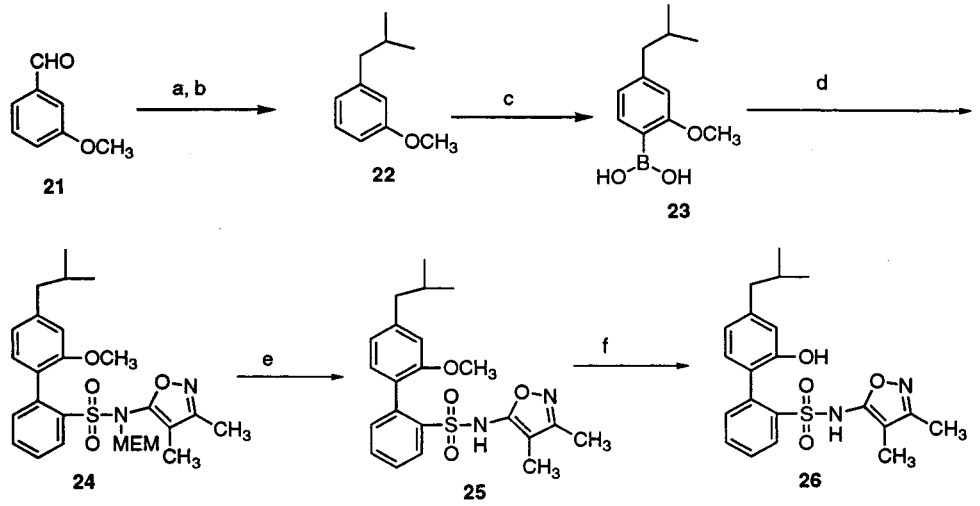
[a] (a) KH, THF; (b) $ArB(OH)_2$, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (c) 5 N NaOH, MeOH; (d) PCl_5; (e) amino heterocycle, Py, DMAP.

Scheme 4[a]



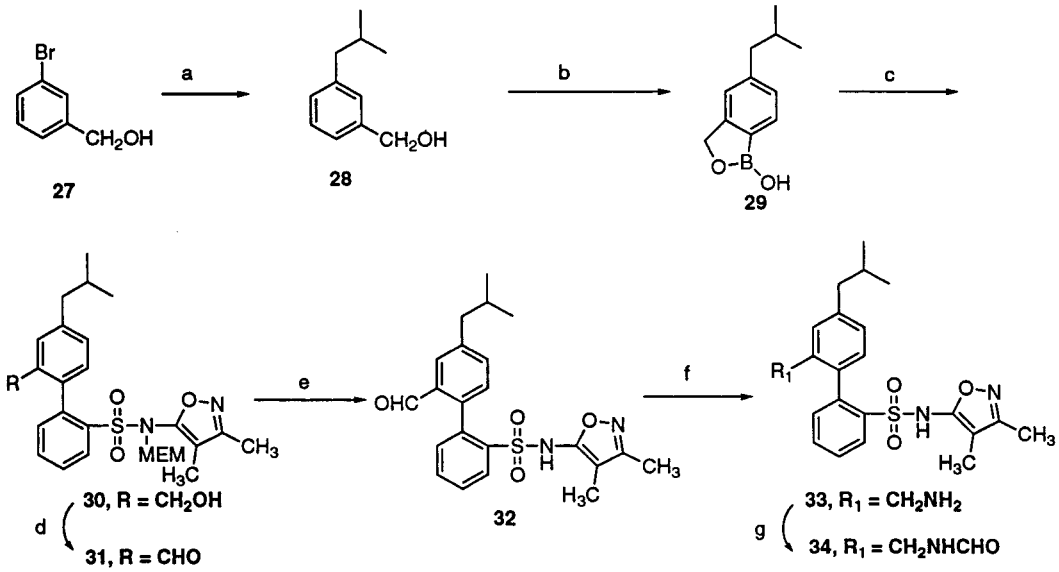
[a] (a) $(CH_3)_2CHP(Ph)_3Br$, *n*-BuLi; (b) H_2/Pt/C, MeOH; (c) $(CH_3)_3CCOCl$, $(Et)_3N$, CH_2Cl_2; (d) H_2/Pd/C, EtOAc; (e) (i) *t*-BuLi, TMEDA, diethyl ether, (ii) $B(OMe)_3$, (iii) HCl; (f) **4**, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (g) (i) DIBAL, (ii) 6 N aqueous HCl.

Scheme 5[a]



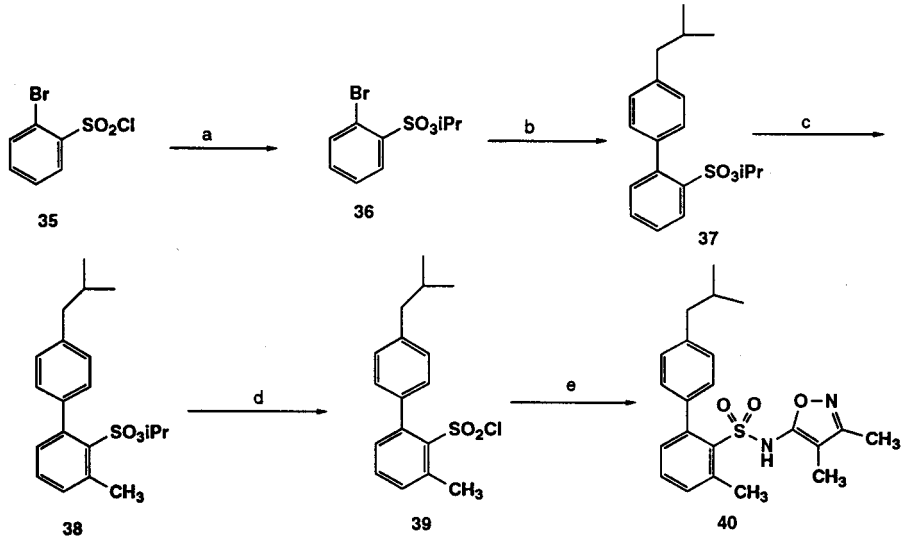
[a] (a) $(CH_3)_2CHP(Ph)_3I$, *n*-BuLi; (b) H_2/Pt/C, MeOH; (c) (i) *t*-BuLi, TMEDA, diethyl ether, (ii) $B(OMe)_3$, (iii) HCl; (d) **4**, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (e) 6 N aqueous HCl/EtOH; (f) BBr_3/CH_2Cl_2.

Scheme 6[a]



[a] (a) Isobutyl-9-BBN, $(Ph_3P)_4Pd$, aqueous NaOH; (b) (i) *t*-BuLi, TMEDA, diethyl ether, (ii) $B(OMe)_3$, (iii) HCl; (c) **4**, $(Ph_3P)_4Pd$ aqueous Na_2CO_3, EtOH/toluene; (d) $COCl_2$/DMSO; (e) 6 N aqueous HCl; (f) ammonium acetate, sodium triacetoxyborohydride, AcOH; (g) acetic formic anhydride, triethylamine, CH_2Cl_2.

Scheme 7[a]



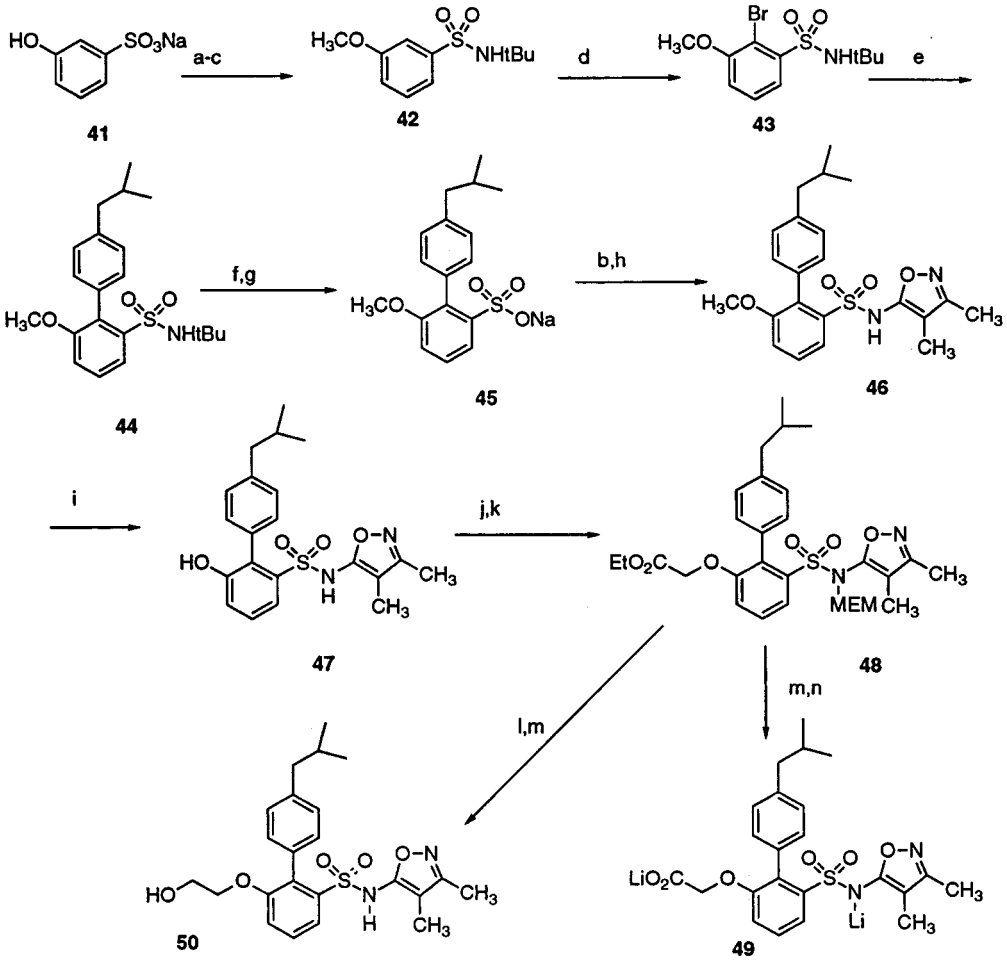
[a] (a) *i*-PrOH/pyridine; (b) 4-isobutylphenylboronic acid, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (c) (i) *n*-BuLi, THF, −78 °C, (ii) MeI; (d) (i) aqueous NaOH, MeOH, (ii) PCl_5; (e) 5-amino-3,4-dimethylisoxazole, pyridine.

that the olefin bond could not be reduced further under these conditions. Amine **16** was then converted to the pivaloyl amide derivative and hydrogenation of this compound using Pd/C then proceeded rapidly to provide **17**. Ortho lithiation of **17** using *t*-BuLi/TMEDA followed by quenching with trimethyl borate and subsequent hydrolysis using dilute hydrochloric acid provided the key boronic acid intermediate **18**. None of the other possible regiomeric product was isolated from this reaction indicating that the ortho lithiation was highly regioselective. Suzuki coupling[26] between **18** and the sulfonamide derivative **4** under standard conditions afforded the biphenylsulfonamide derivative **19**. Direct removal of the pivaloyl group under acidic conditions was found to be problematic. However, deprotection could be carried out by reduction to the hemiaminal using diisobutylaluminum hydride and subsequent treatment with 6 N aqueous hydrochloric acid, which hydrolyzed both the hemiaminal and the MEM groups to provide **20**. The *N*-alkyl derivatives **20a**−**g** were prepared via reductive amination of **20** in the presence of sodium cyanoborohydride or sodium triacetoxyborohydride with the appropriate aldehydes.

Compounds **25** and **26** were prepared as shown in Scheme 5. The boronic acid **23** was prepared from **22** in an analogous manner to the method outlined above. Coupling of **23** with **4** followed by deprotection of the MEM group afforded the 2′-methoxy derivative **25**. Demethylation of **25** using boron tribromide then gave **26**. The fluoro analogue **20j** was prepared starting from 3-fluorobenzaldehyde by an analogous sequence.

The 2′-formylaminomethyl derivative **34** was synthesized as depicted in Scheme 6. Palladium-catalyzed cross-coupling of 3-bromobenzyl alcohol with isobutyl-9-BBN provided 3-isobutylbenzyl alcohol **28**. Ortho lithiation using *t*-BuLi/TMEDA in ether followed by

Scheme 8[a]



[a] (a) Me_2SO_4/aqueous NaOH; (b) PCl_5; (c) *t*-$BuNH_2$, $CHCl_3$; (d) (i) *n*-BuLi, (ii) BrF_2CCF_2Br; (e) 4-isobutylphenylboronic acid, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (f) TFA; (g) (i) NO_2/CCl_4, (ii) aqueous NaOH; (h) 3,4-dimethyl-5-aminoisoxazole, Py, DMAP; (i) BBr_3, CH_2Cl_2; (j) NaH, methoxyethoxymethyl chloride, THF; (k) NaH, ethyl bromoacetate, DMF; (l) $LiBH_4$, MeOH, ether; (m) 6 N aqueous HCl/EtOH; (n) (i) KOH/MeOH, (ii) aqueous LiOH.

sequential treatment with trimethyl borate and dilute HCl provided the cyclic borate ester **29**. Again no regioisomeric product was obtained. Suzuki coupling of **29** with **4** afforded **30.** The 2′-aldehyde analogue **32** was then obtained by Swern oxidation of **30** followed by treatment with 6 N HCl. Reductive amination using ammonium acetate and sodium triacetoxyborohydride provided the aminomethyl derivative **33** which was then converted to **34** by treatment with acetic formic anhydride and triethylamine.

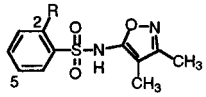
The 3-methyl derivative **40** was prepared starting from the sulfonate ester **36** which can be readily obtained by treatment of the commercially available 2-bromobenzenesulfonyl chloride with 2-propanol in pyridine (Scheme 7). Suzuki coupling of **36** with 4-isobutylphenylboronic acid afforded **37**. Treatment of **37** with *n*-BuLi in THF followed by quenching with MeI provided **38**. The sulfonate ester was then hydrolyzed using aqueous NaOH, and the sulfonic acid thus obtained was converted to the sulfonyl chloride using PCl_5 to afford **39**. Condensation of **39** with 3,4-dimethyl-5-isoxazolamine gave **40**.

The synthesis of the 6-substituted analogues **47**, **49**, and **50** was carried out as shown in Scheme 8. The *tert*-butylsulfonamide **42**, prepared from the sulfonic acid **41**, was regiospecifically brominated via ortho-directed lithiation using butyllithium and subsequent quenching with 1,2-dibromo-1,1,2,2-tetraflouroethane to provide **43**. Submission of **43** to palladium-catalyzed Suzuki coupling conditions with 4-isobutylphenylboronic acid afforded **44**. The *tert*-butyl group in **44** was then removed using TFA, and treatment of the resulting primary sulfonamide with NO_2/CCl_4 afforded the sulfonic acid derivative **45**. Sulfonamide derivative **46** was then prepared from **45** using a sequence similar to that described in Scheme 7. Demethylation of **46** using BBr_3 provided the 6-hydroxy derivative **47**. It was necessary to protect the sulfonamide function in order to alkylate the hydroxy group. Accordingly, the sulfonamide function was first protected using the MEM group and subsequent alkylation with ethyl bromoacetate afforded **48**. Deprotection of the MEM group using 6 N HCl followed by hydrolysis of the ester using aqueous KOH gave the acid derivative **49**. The hydroxyethyl analogue **50** was also derived from **48** first by reducing the ester using lithium borohydride followed by the removal of the MEM group.

Structure−Activity Relationships

In our previous reports from these laboratories,[16,17] we demonstrated that certain para-substituted *N*-isoxazolylbenzenesulfonamides showed moderate affinity for

Table 1. *N*-Isoxazolylbenzenesulfonamide Analogues



compd	R	ET_AK_i, μM[a]	m.p, °C	recrystn solvent
3	2-Br	8.0 ± 1.0	125-126	MeOH / Water
3a	2-F	4.7 ± 2.0	122-124	MeOH / Water
3b	2-NH_2	5.9 ± 2.0	116-118	EtOAc/ Hexanes
3c	2-NO_2	3.5 ± 1.2	91-94	EtOAc/ Hexanes
3d	2-CF_3	0.7 ± 0.3	99-100	CH_2Cl_2/Hexanes
3e	2-i-Pr	0.6 ± 0.18	gum	
3f	2-OPh	2.1 ± 0.3	181-182	Ether
6	2-Ph	0.09 ± 0.02	171-173	EtOAc/ Hexanes

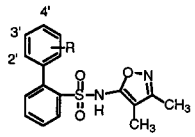
[a] K_i's ± SE were determined from the inhibition of [^{125}I]ET-1 binding to membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) as described in the Experimental Section.

the endothelin receptor. Optimization of this lead series then led to the development of the 5-amino-1-naphthalenesulfonamide derivative BMS-182874, which is a selective ET_A antagonist. We then observed that a number of electronically dissimilar substituents at the ortho position of the benzenesulfonamides (e.g., **3b**, 2-NH_2, and **3c**, 2-NO_2; Table 1) also showed improved receptor binding affinity. This suggested a conformational effect by the 2-substituent resulting in a preferred relative orientation of the phenyl and heterocyclic rings. Following up on this hypothesis, we synthesized a number of analogues by increasing the size of the 2-substituent. The improved binding affinity observed with compounds **3c**−**f** showed the generality of this effect. However, none of these compounds showed significant functional antagonist activity in a tissue-based assay. The biphenylsulfonamide **6** was then synthesized due to the large size of a phenyl substituent and also because the biphenyl moiety is found to be a useful scaffold in a variety of G-protein-coupled receptor ligands. Compound **6** showed improved binding affinity (K_i = 90 nM) and, more importantly, modest functional activity (K_B = 7.6 μM) as well.

Because a 5-dimethylamino substituent contributed dramatically to the activity of the naphthalenesulfonamide series of compounds,[17] we wanted to determine whether analogous substitution on the pendant phenyl ring of the biphenylsulfonamides would provide similar results (Table 2). Substitution at the 2′-, 3′-, or 4′-position of the pendant ring (compounds **6b**, **6f**, or **6h**) with a dimethylamino group did not result in any significant improvement in activity. However, during this exercise, it was found that compound **6a**, incorporating a primary amine substituent at the 2′-position, showed improved binding affinity as well as functional antagonist activity. This suggested that the relatively small amino group at this position may be behaving as an H-bond donor or acceptor. The dimethylamino function may be less active due to its large size, possibly because of a undesirable effect on the dihedral angle between the sulfonamide and the biaryl moieties.

Substitution at the 4′-position with a methyl group (**6j**) also resulted in improved binding and functional

Table 2. *N*-Isoxazolylbiphenylsulfonamide Derivatives



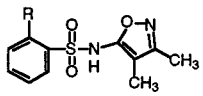
compd	R	ET_A		ET_B
		K_i, μM[a]	K_B or K_{bapp}*, μM[b]	K_i, μM[a]
6	H	0.09 ± 0.02	7.6 ± 1.6	>200
6a	2′-NH_2	0.016 ± 0.004	1.7 ± 0.2	>200
6b	2′-$N(CH_3)_2$	0.103 ± 0.001	10*± 5	>200
6c	2′-NO_2	0.14 ± 0.001	30* ± 10	>200
6d	2′-CH_2OH	0.04 ± 0.002	0.62 ± 0.15	>200
6e	3′-NH_2	0.062 ± 0.002	9.0* ± 3	>200
6f	3′-$N(CH_3)_2$	0.112 ± 0.02	7.9 ± 1.9	>200
6g	3′-$CH_2CH(CH_3)_2$	0.19 ± 0.03	1.0* ± 0.5	5.6 ± 0.5
6h	4′-$N(CH_3)_2$	0.054 ± 0.016	4.9 ± 1.1	6.0± 0.4
6i	4′-COOH	4.4 ± 0.3	ND	>200
6j	4′-CH_3	0.055 ± 0.02	5.9 ± 1.9	23 ± 2
6k	4′-$CH_2CH_2CH_3$	0.028 ± 0.01	1.0 ± 0.3	15 ± 1
6l	4′-$CH_2CH(CH_3)_2$	0.018 ± 0.003	0.21 ± 0.03	1.7 ± 0.1
6m	4′-$CH(CH_3)_2$	0.05 ± 0.004	2.8 ± 1.8	19 ± 1
6n	4′- CH_2CH_2 CH_2CH_3	0.037 ± 0.001	1.2 ± 0.4	1.9 ± 0.1
6o	4′-$C(CH_3)_3$	0.061 ± 0.01	2.0 ± 0.3	15 ± 2
6p	4′-$CH_2C(CH_3)_3$	0.11 ± 0.01	1.6 ± 0.8	4.1 ± 0.2
6q	4′-$CH_2CH_2CH(CH_3)_2$	0.08 ± 0.01	0.53 ± 0.2	30 ± 2
6r	4′-OCH_3	0.033 ± 0.005	2.4 ± 0.3	250 ± 17
6s	4′-$OCH(CH_3)_2$	0.017 ± 0.005	0.32 ± 0.06	1.5 ± 0.1
6t	4′-$OCH_2CH(CH_3)_2$	0.032 ± 0.004	1.3 ± 0.3	2.8 ± 0.2
6u	4′-$OCH_2C_6H_5$	0.19 ± 0.04	1.0* ± 0.2	8.4 ± 1
6v	4′-$NHCH(CH_3)_2$	0.05 ± 0.01	2.6 ± 0.4	17 ± 2
6w	4′-$N(CH_3)CH(CH_3)_2$	0.06 ± 0.01	0.88 ± 0.16	20 ± 3
6x	4′-$SCH(CH_3)_2$	0.039 ± 0.004	0.33 ± 0.05	5.7 ± 0.5
6y	4′-$SO_2CH(CH_3)_2$	0.11 ± 0.002	16* ± 7.6	170 ± 25
6z	4′-$SO_2N(CH_3)_2$	0.56 ± 0.05	ND	>200

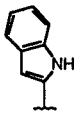
[a] K_i's ± SE were determined using membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) and from rat cerebellum (ET_B) as described in the Experimental Section. [b] K_B's ± SE were determined by assaying for the inhibition of ET-1-induced contractions in rabbit carotid artery rings as described in the Experimental Section. ND, not determined.

antagonist activity. In fact, increasing the chain length of the alkyl substituent at this position increased both binding affinity and functional potency. The 4′-isobutyl analogue **6l** (ET_A K_i = 18 nM, ET_B K_i = 210 nM) was found to be the optimal alkyl substituent, and it showed dramatically improved binding as well as functional activity compared to the unsubstituted biphenylsulfonamide **6**. Because the 3′-isobutyl analogue **6g** suffered a 10-fold loss of binding affinity compared to **6l**, the increased activity of the 4′-alkyl derivatives is likely due to a specific binding interaction of this moiety at the receptor site rather than a general lipophilic effect. Attempts to improve activity by introducing even larger lipophilic groups (e.g., **6m**−**q**) resulted in significant loss of activity suggesting steric limitations at this position. Interestingly, the 4′-alkyl-substituted derivatives also showed improved ET_B affinity although the selectivity for the ET_A receptor was still found to be greater than 100-fold.

Substitution at the 4′-position with alkoxy substituents also resulted in a similar improvement in activity,

Table 3. 2-Heteroarylphenylsulfonamide Derivatives



compd	R	ET_A K_i, μM[a]	ET_B K_i, μM[a]
6	Ph	0.09 ± 0.02	>200
9a		0.82 ± 0.06	>200
9b		0.26 ± 0.05	>200
9c		8.8 ± 2.3	>200
9d		0.95 ± 0.08	>200
9e		0.90 ± 0.02	>200
9f		0.34 ± 0.06	66 ± 12
9g		0.52 ± 0.16	>200

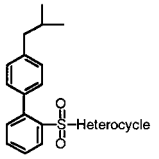
[a] K_i's ± SE were determined using membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) and from rat cerebellum (ET_B) as described in the Experimental Section.

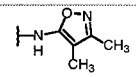
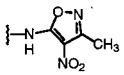
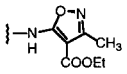
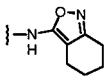
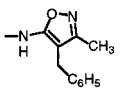
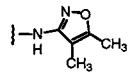
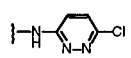
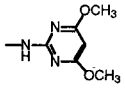
but the functional activity of these analogues was less than that of the corresponding alkyl derivatives. The isopropoxy derivative **6s** was found to be the optimal alkoxy substituent at this position. We also examined several alkylamino, alkylthio, and alkylsulfonyl substitutions (Table 2), but these were generally found to have lower binding affinity than their 4′-alkyl or 4′-alkoxy counterparts. The 4′-carboxyl derivative **6i** showed dramatically lower binding affinity indicating that anionic groups are not tolerated at this position.

Replacement of the pendant phenyl ring with heterocyclic rings was also investigated (Table 3). Substitution with a 2- or 3-pyridinyl (**9a** or **9b**), 2-pyrimidinyl (**9c**), 2- or 3-thienyl (**9d** or **9e**), or 2- or 3-indolyl group (**9f** or **9g**) did not lead to improved binding affinity compared to the unsubstituted biphenylsulfonamide **6**.

Analogues **14a**−**h** were prepared in order to study the structure−activity relationships of the isoxazole region of the molecule in the biphenyl class of compounds (Table 4). This work revealed that the requirements in the isoxazole region are stringent and generally similar to those of the naphthalenesulfonamide class of compounds reported previously.[17] Specifically, replacement of the methyl group at the 3-position with a hydrogen (**14a**) resulted in a large reduction in potency. Introduction of electron-withdrawing groups such as

Table 4. Biological Activity of *N*-Heterocyclic 4′-Isobutylbiphenylsulfonamide Analogues



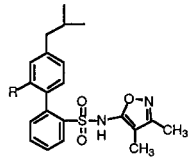
compd	Heterocycle	ET_A K_i, μM[a]	ET_A K_B or K_{bapp}*, μM[b]	ET_B K_i, μM[a]
6l		0.018 ± 0.003	0.21 ± 0.03	1.7 ± 0.1
14a		0.97 ± 0.2	ND	100
14b		2.5 ± 0.3	ND	30 ± 10
14c		7.2 ± 1	ND	42 ± 10
14d		24 ± 2.3	ND	>200
14e		6.4 ± 1	ND	>200
14f		0.013 ± 0.005	0.31 ± 0.06	2.0 ± 0.1
14g		0.4 ± 0.02	1.0* ± 0.5	44 ± 12
14h		3.9 ± 0.5	ND	50 ± 11

[a] K_i's ± SE were determined using membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) and from rat cerebellum (ET_B) as described in the Experimental Section. [b] K_B's ± SE were determined by assaying for the inhibition of ET-1 induced contractions in rabbit carotid artery rings as described in the Experimental Section. ND, not determined.

nitro (**14b**) or ethoxycarbonyl (**14c**) at the 4-position also resulted in loss of binding activity. Constraining the 3- and 4-substituents into a six-membered ring (**14d**) reduced activity as well. Attempts to improve affinity by introducing larger lipophilic groups in place of the 4-methyl (**14e**) indicated that large groups are not tolerated at this position. Replacement of the isoxazole with other heterocyclic rings such as a pyridazine (**14g**) or a substituted pyrimidine (**14h**) also led to a reduction in binding activity. No further optimization was performed on this heterocyclic series. The 3-isoxazole analogue **14f** was equipotent to the corresponding 5-isoxazole analogue **6l**, indicating that the heteroatoms in the isoxazole ring can be interchanged.

The SAR of the monosubstituted biphenylsulfonamides to this point revealed that a 2′-amino substituent or an appropriate 4′-alkyl group such as isobutyl provides analogues with high binding affinity. The improvement in ET_A activity independently seen with the 4′-isobutyl as well as the 2′-amino substituents prompted us to prepare **20**, the analogue incorporating both of these modifications (Table 5). Compound **20** showed an additional 4-fold improvement in ET_A bind-

Table 5. 2′-Substituted Analogues



compd	R	ET_A		ET_B
		K_i, μM[a]	K_B or K_{Bapp}*, μM[b]	K_i, μM[a]
6l	H	0.018 ± 0.0001	0.21 ± 0.03	1.7 ± 0.2
20	NH_2	0.0047 ± 0.001	0.12 ± 0.02	1.7 ± 0.1
20a	$NHCH_3$	0.014 ± 0.006	0.08 ± 0.02	2.2 ± 0.3
20b	$N(CH_3)_2$	0.33 ± 0.008	1.0* ± 0.6	>100
20c	$NHCH_2CH_3$	0.0063 ± 0.001	0.73 ± 0.3	1.4 ± 0.1
20d	$NHCH_2CH_2CH_3$	0.029 ± 0.005	0.28 ± 0.07	3.7 ± 0.3
20e	$NHCH(CH_3)_2$	0.034 ± 0.01	0.38 ± 0.14	2.9 ± 0.5
20f	$NHCH_2CH_2OH$	0.0064 ± 0.004	0.24 ± 0.09	1.6 ± 0.4
20g	$NHCH_2COOH$	0.089 ± 0.01	0.1 ± 0.03	12 ± 2.0
20h	NHCHO	0.017 ± 0.003	0.68 ± 0.19	6.9 ± 2.0
20i	$NHCONHCH_3$	0.043 ± 0.003	0.93 ± 0.31	5.4 ± 1.0
20j	F	0.02 ± 0.006	0.56 ± 0.3	12 ± 2.0
25	OCH_3	0.074 ± 0.04	2.0* ± 0.5	54 ± 11
26	OH	0.008 ± 0.003	0.37 ± 0.16	9.8 ± 1.0
20k	CH_3	0.005 ± 0.001	0.44 ± 0.25	19 ± 2.0
20l	CH_2OH	0.02 ± 0.008	0.24 ± 0.06	1.3 ± 0.04
20m	COOH	1.5 ± 0.03	ND	26 ± 10
20n	$CONH_2$	0.10 ± 0.02	2.4 ± 0.37	12 ± 2.9
33	CH_2NH_2	0.1 ± 0.006	1.9* ± 0.7	9.6 ± 1.4
34	CH_2NHCHO	0.002 ± 0.001	0.11 ± 0.03	1.2 ± 0.03
BQ-123		0.040 ± 0.006	ND	32 ± 1.2
BMS 182874		0.055 ± 0.005	0.520 ± 0.10	>200

[a] K_i's ± SE were determined using membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) and from rat cerebellum (ET_B) as described in the Experimental Section. [b] K_B's ± SE were determined by assaying for the inhibition of ET-1-induced contractions in rabbit carotid artery rings as described in the Experimental Section. ND, not determined.

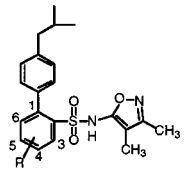
ing activity (ET_A K_i = 4.7 nM, ET_B K_i = 1700 nM) compared to **6l** or **6a**. A 2-fold improvement in functional activity for the ET_A receptor was observed compared to **6l**. The reason for the large differences between the K_i values and the K_B is not understood, but similar differences have been observed with other endothelin antagonists (e.g., FR 139317: K_i = 0.53 nM, K_B = 63 nM).[13] We do not believe it is due to species differences since we have previously shown that the functional potency of several ET receptor agonists and antagonists (e.g., FR 139317 and BQ-123) was similar at both rabbit carotid and rat aorta.[27] We have also previously suggested that the differences in binding affinity and functional potency may reflect differences in cellular versus tissue preparations.[17] While the SAR of this class of compounds was developed primarily based on the binding affinity of the compounds, the functional data was used to understand whether the compound is an agonist or an antagonist and whether the compound is active in a more intact cellular system.

The role of the amino group as a hydrogen bond acceptor or donor was then investigated by preparation of analogues **20a**−**i** (Table 5). Another goal was to gain additional binding interactions by introducing groups on the nitrogen atom. The *N*-methyl analogue **20a** shows 3-fold less potent binding activity compared to **20** but maintained the functional activity. The *N*,*N*-dimethyl analogue **20b** was significantly less active indicating that hydrogen bond donation may be important, although the increased steric requirements of the bulky dimethylamino group may also be detrimental. The *N*-ethyl derivative **20c** was equipotent compared to **20**, and a hydroxyethyl group on the 2′-nitrogen (**20f**) maintained potency as well. However, a carboxymethyl group (**20g**) led to a 20-fold loss of inhibitory potency compared to **20**. Compound **20h** containing a 2′-formamido function was 3-fold less active, and the urea derivative **20i** was also less active. This exercise revealed that secondary amines with small alkyl groups are tolerated at the 2′-position.

Alternative 2′-substitutions in the 4′-isobutyl series were then investigated (Table 5). While the 2′-fluoro analogue **20j** was less potent, the 2′-hydroxy derivative **26** was substantially more potent than the corresponding methoxy derivative **25** indicating that a hydrogen bond donor at the 2′-position leads to improved ET_A activity. However, the 2′-methyl derivative **20h** was equipotent to **20** in its binding affinity to the ET_A receptor suggesting that an effect on the biphenyl conformation may also be important. Nevertheless, its functional potency was 4-fold less than that of **20**. The 2′-carboxyl derivative **20m** as well as the aminomethyl analogue **33** were dramatically less active suggesting that charged groups are not tolerated at this position. Interestingly, removal of the positive charge in **33** by formylating the amine resulted in **34** (ET_A K_i = 2.0 nM, ET_B K_i = 1200 nM), one of the most potent receptor antagonists prepared in this series.

A number of analogues which explore alternative substitution on the core phenyl ring were also prepared (Table 6). All of these derivatives maintained the optimal isobutyl group at the 4′-position of the pendant ring. The 3-methyl derivative **40** was much less potent compared to **6l** suggesting that substitution at this position might force the sulfonamide and the heterocylic groups into a disfavored conformation. Substitutions at each of the 4- and 5-positions with certain large substituents also led to substantial decreases in potency. The poor potency of the analogues **40e**−**h** was particularly dramatic, suggesting that these groups exceed the steric limitations of the receptor binding site. Both the 6-methoxy (**46**)- and 6-hydroxy (**47**)-substituted compounds showed equivalent or better ET_A activity compared to **6l**. The hydroxyethoxy-substituted analogue **50** (ET_A K_i = 2.7 nM, ET_B K_i = 2300 nM) showed more than 6-fold improvement in binding affinity and 4-fold improvement in functional activity compared to **6l** while maintaining ET_A selectivity. However, the glycolic acid derivative **49** was less active indicating that charged groups may not be tolerated. The structure−activity relationships at the C-6 position appeared analogous to those previously determined at C-2′, suggesting that substituents at these two positions may be interacting with similar regions of the receptor.

Table 6. Substitution of the Core Phenyl Ring



compd	R	ET_A		ET_B
		K_i, μM[a]	K_B or K_{Bapp}*, μM[b]	K_i, μM[a]
6l	H	0.018 ± 0.0001	0.21 ± 0.03	1.7 ± 0.2
40	3-CH_3	1.3 ± 0.07	ND	19 ± 0.01
40a	4-OCH_2Ph	>20	ND	>200
40b	4-OH	0.5 ± 0.07	1.0* ± 0.2	24 ± 3.0
40c	5-OCH_3	0.37 ± 0.1	1.0* ± 0.2	6.2 ± 2.0
40d	5-NH_2	0.014 ± 0.001	0.43 ± 0.11	2.1 ± 0.8
40e	5-$NHCOCH_3$	2.8 ± 0.1	ND	9.8 ± 1.0
40f	5-NHCOPh	5.8 ± 1.4	ND	38 ± 15
40g	5-$NHCH_2COOH$	0.55 ± 0.02	2.4 ± 0.37	1.9 ± 0.1
40h	5-$NHCOCH_2NH_2$	1.2 ± 0.3	ND	7.4 ± 1.2
46	6-OCH_3	0.016 ± 0.0	0.14 ± 0.03	2.0 ± 0.2
47	6-OH	0.005 ± 0.001	0.093 ± 0.016	0.94 ± 0.04
49	6-OCH_2COOLi	0.042 ± 0.002	0.74 ± 0.17	4.0 ± 0.13
50	6-OCH_2CH_2OH	0.0027 ± 0.0	0.064 ± 0.01	2.3 ± 0.08

[a] K_i's ± SE were determined using membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) and from rat cerebellum (ET_B) as described in the Experimental Section. [b] K_B's ± SE were determined by assaying for the inhibition of ET-1-induced contractions in rabbit carotid artery rings as described in the Experimental Section. ND, not determined.

On the basis of the above results, compound **20** (BMS-187308) was chosen for further evaluation. Although radioligand binding studies revealed that **20** bound to the ET_B receptor with much less affinity than to the ET_A receptor, functionally the compound was rather nonselective as shown in experiments using isolated blood vessels. Isolated rabbit carotid artery contracts in response to ET-1 primarily via activation of ET_A receptors:[8] compound **20** blocked these contractions in a concentration-dependent fashion (ET_A $K_B = 0.12 \pm 0.02$ μM). The activity of ET_B receptors can be observed in vitro by contracting Wistar rat isolated aorta with phenylephrine and then relaxing that contraction with ET_B-selective peptide sarafotoxin s6c.[28] Compound **20** blocked the relaxations in a concentration dependent manner (ET_B $K_B = 0.64 \pm 0.1$ μM).

Compound **20** was also tested for its ability to inhibit ET-1 (0.1 nmol/kg iv)-induced vasoconstriction in conscious, normotensive rats. After oral administration of 30 μmol/kg, **20** inhibited the pressor response to ET-1 by 56 ± 15%. Essentially the same level of inhibition was still present 3 h after dosing (60 ± 4%) indicating **20** has an acceptable pharmacological duration of effect (Figure 1). Inhibition of the big ET-1 pressor response by **20** ($ED_{25} = 1.2$ μmol/kg iv) was similar to inhibition of the ET-1 pressor response by **20** (Figure 2). Maximum inhibition of the pressor effect of big ET-1 after injection of the iv dose of 3 μmol/kg **20** was 49 ± 5%. We were unable to achieve total inhibition of the pressor effects of ET-1 or big ET-1 after administration of up to 30 μmol/kg compound **20**. Inhibition reached a peak at approximately 50−60%. We reported similar findings of 40% inhibition of the ET-1-induced pressor response after infusion of the ET_A-selective receptor antagonist

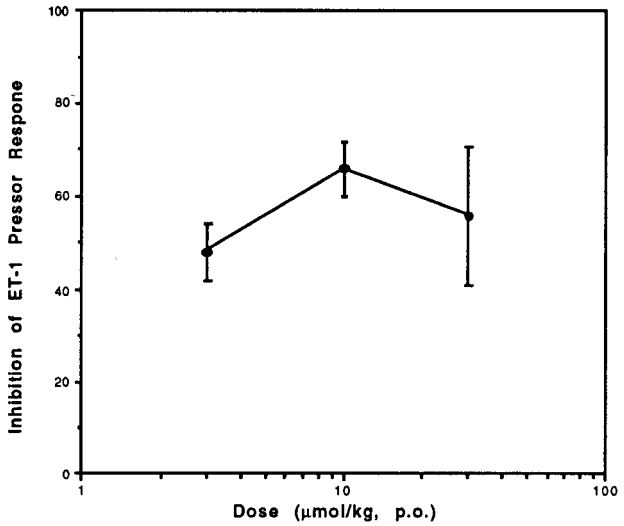


Figure 1. Effects of oral administration of **20** (BMS-187308) on the pressor response to ET-1 (0.1 nmol/kg iv) in conscious, normotensive rats.

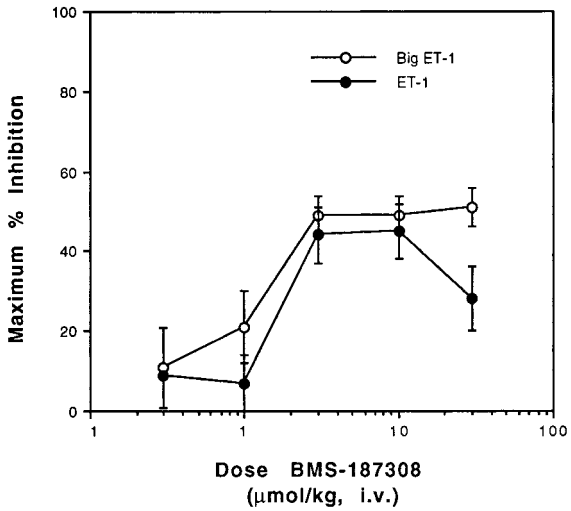


Figure 2. Effects of iv administration of **20** (BMS-187308) on the pressor response to ET-1 (0.1 nmol/kg iv) and big ET-1 (1.0 nmol/kg iv) in conscious, normotensive rats.

BQ-123.[29] Incomplete inhibition of the pressor response to ET-1 was also reported for other ET antagonists.[30] Similar effects were observed in rabbit isolated carotid arteries: compound **20** competitively inhibited ET-1 and big ET-1 contractions with apparent K_B values of 0.16 ± 0.06 and 0.11 ± 0.05 μM, respectively. Maximum inhibition of the pressor effect of big ET-1 after injection of the iv dose of 3 μmol/kg **20** was 49 ± 5%. The pharmacokinetics of **20** was evaluated in rats following a 100 μmol/kg intravenous or oral gavage dose.[31] After oral administration to rats, compound **20** was rapidly absorbed (T_{max} < 30 min), and oral bioavailability was found to be 48%.

Compound **20** was further examined for its ability, after iv administration, to inhibit the increase in mean arterial blood pressure due to the administration of exogenous ET-1 (0.3 μmol/kg iv) to conscious monkeys. After vehicle administration, endothelin-1 increased blood pressure by 30 ± 4 mmHg in the conscious monkeys, while doses of 10 and 30 μmol/kg iv **20** attenuated the pressor responses (Figure 3), indicating

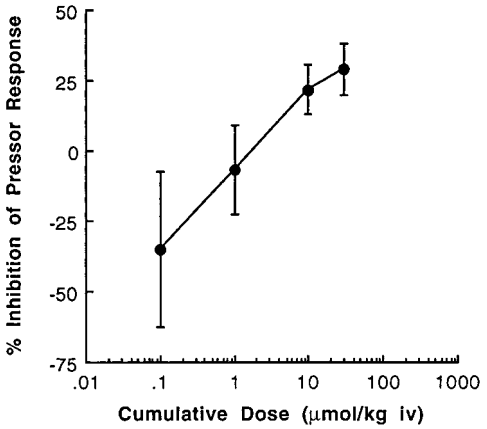


Figure 3. Effects of iv administration of **20** (BMS-187308) on the pressor response to ET-1 (0.3 nmol/kg iv) in conscious monkeys.

that the compound inhibits the in vivo activity of endothelin-1 in nonhuman primates.

Conclusion

In summary, investigation of the SAR of ortho-substituted benzenesulfonamide derivatives resulted in the discovery of the biphenylsulfonamide class of endothelin antagonists. Substitution of the pendant phenyl ring led to the identification of the 2′- and 4′-positions as sites where appropriate substitution led to improved binding affinity. An alkyl or alkoxy group such as isobutyl or isopropoxyl was found to be optimal at the 4′-position. A 2′-primary amino group was found to improve the activity of the parent compound. Combination of the optimal 4′-isobutyl substituent with the 2′-amino function afforded an analogue (**20**, BMS-187308) with potent ET_A binding affinity and functional activity. Compound **20** also had good oral activity in inhibiting the pressor effect caused by an ET-1 infusion in rats. Compound **20** appears to be a suitable tool for investigating the role of endothelin in certain disease models. Further structure−activity relationship studies are in progress and will be the subject of future publications.

Experimental Section

Radioligand Binding Assays. The receptor binding assays were performed using membranes prepared from A10 rat thoracic aorta smooth muscle cells (ET_A) and from rat cerebellum (ET_B) as previously described.[17] Competition binding data were analyzed by iterative curve fitting to a one- or two-site binding model. The inhibition constants (K_i) were calculated from IC_{50} values.

In Vitro Functional Assay. Functional assays (inhibition of ET-1-induced contractions in rabbit carotid artery rings) were performed as previously described.[17] K_B values were obtained from experiments in which at least three different concentrations of test compound were studied. Apparent K_B values were calculated when only one antagonist concentration was used. The ET_B functional assays were performed as previously described.[28]

In Vivo Rat Pressor Studies. This study was performed as previously described.[32] Four iv challenges of ET-1 (0.1 nmol/kg) or big ET-1 (1.0 nmol/kg) were given; 90 min was allowed between challenges to allow blood pressure to return to baseline. The initial challenge was preceded by vehicle administration to establish a control response to the agonist. Three doses of vehicle, compound **20** (0.3, 1, 3, 10, 30 μmol/kg iv), were given prior to the subsequent agonist challenges. Compound **20** was also administered orally at doses of 3, 10, and 30 μmol/kg prior to ET-1 challenges.

In Vivo Monkey Pressor Studies. Conscious male and female cynomolgus monkeys in which chronic arterial and venous catheters had been surgically implanted were seated in restraining chairs. The arterial catheters were connected via Gould-Statham strain gauge transducers to a Beckman recorder for measurement of mean arterial blood pressure (MAP). The pressor responses to 0.3 nmol/kg iv endothelin-1 (dissolved in 0.1 mg/kg saline) were determined after sequential treatment with vehicle (0.1 mL/kg of 5% $NaHCO_3$) and 0.1, 1, 10, and 30 μmol/kg iv compound **20**. MAP was allowed to return to baseline before administration of the next dose of compound **20**. The pressor responses were expressed as percentages of the pressor activity obtained after vehicle treatment. All data are given as mean ± SEM.

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. All chemical experiments were run under a positive pressure of argon. All solvents and reagents were used as obtained. Solutions were dried with magnesium sulfate unless otherwise noted. Proton NMR (^1H NMR) and carbon NMR (^{13}C NMR) spectra were recorded on a JEOL FX-270 or GX-400 spectrometer with tetramethylsilane as an internal standard. Chromatography was performed under flash conditions using EM Science silica gel, 0.040−0.063-mm particle size. Analytical and preparative HPLC were performed on YMC columns (S-5, 120A ODS, 4.6 × 150 mm; S-10, 120A ODS, 30 × 500 mm) with MeOH/water gradients containing 0.1% trifluoroacetic acid. THF was distilled from Na/benzophenone. Solutions were dried with magnesium sulfate unless otherwise noted. The arylboronic or heteroarylboronic acids were either commercially available or easily prepared from the aryl halides using literature methods.[26]

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-bromobenzenesulfonamide (3).** 3,4-Dimethyl-5-isoxazolamine (1.32 g, 11.74 mmol) was added to a solution of 2-bromobenzenesulfonyl chloride (3.0 g, 11.74 mmol) in 10 mL of pyridine, and the mixture was stirred at room temperature overnight. The solution was added to 150 mL of ice water and filtered. The filtrate was acidified to pH 2 using 6 N hydrochloric acid, and the solid was filtered and dried. Crystallization from ethanol/water afforded 3.5 g (90%) of **3** as a white solid: mp 125−126 °C. ^1H NMR ($CDCl_3$ + CD_3OD): δ 1.83 (s, 3H), 2.14 (s, 3H), 7.45 (m, 2H), 7.78 (m, 1H), 8.05 (m, 1H). ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 5.84, 10.25, 106.29, 119.88, 127.51, 131.11, 134.02, 135.14, 138.77, 154.61, 161.60. Anal. ($C_{11}H_{11}BrN_2O_3S·0.32H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-fluorobenzenesulfonamide (3a):** tan solid; mp 122−124 °C. Anal. ($C_{11}H_{11}FN_2O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-aminobenzenesulfonamide (3b).** To a suspension of 135 mg of 10% Pd/C in 20 mL of MeOH under argon was added 0.9 g (3.03 mmol) of **3c** in 20 mL of MeOH, and the mixture was hydrogenated at 1 atm for 90 min. The mixture was then filtered and concentrated to afford 0.9 g of a gum. This material was chromatographed on silica using hexanes/EtOAc (1:1) to provide 0.2 g (24%) of **3b** as a white solid: mp 116−118 °C. Anal. ($C_{11}H_{13}N_3O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-nitrobenzenesulfonamide (3c):** light-yellow solid; mp 91−94 °C. Anal. ($C_{11}H_{11}N_3O_5S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(trifluoromethyl)benzenesulfonamide (3d):** white crystalline needles; mp 99−100 °C. ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H), 2.17 (s, 3H), 7.27−8.07 (m, 4H). Anal. ($C_{12}H_{11}F_3N_2O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-isopropylbenzenesulfonamide (3e).** ^1H NMR ($CDCl_3$): δ 1.29 (d, J = 6.8 Hz, 6H), 1.84 (s, 3H), 2.15 (s, 3H), 3.70 (m, 1H), 7.20−7.80 (m, 4H). Anal. ($C_{14}H_{18}N_2O_3S·0.58H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-phenoxybenzenesulfonamide (3f):** mp 181−182 °C. Anal. ($C_{17}H_{16}N_2O_4S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (6):** mp 171−173 °C. ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 3H), 2.16 (s, 3H), 7.38−8.14 (m, 9H). Anal. ($C_{17}H_{16}N_2O_3S$) C, H, N, S.

2-Bromo-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*′-(methoxyethoxymethyl)benzenesulfonamide (4). To a solution of 1.1 g (3.33 mmol) of **3** in 15 mL of THF at room temperature under argon was added 0.19 g (4.8 mmol) of sodium hydride (60% suspension in mineral oil) in portions, and the mixture was stirred for 10 min. Methoxyethoxymethyl chloride (0.55 g, 4.4 mmol) was added, and the solution was stirred overnight. The mixture was concentrated, diluted with 30 mL of water, and extracted with 3 × 40 mL of EtOAc. The combined organic extracts were washed with brine, dried, and evaporated to provide 1.2 g (87%) of **4** as a brown gum.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′amino[1,1′-biphenyl]-2-sulfonamide (6a).** To a solution of 0.5 g (1.19 mmol) of compound **4** and 0.062 g (0.05 mmol) of tetrakis(triphenylphosphine)palladium(0) in 10 mL of benzene under argon was added 4.0 mL of 2 M aqueous sodium carbonate followed by 0.245 g (1.79 mmol) of 2-aminophenylboronic acid[33] in 5 mL of 95% EtOH. The mixture was refluxed for 10 h, diluted with 50 mL of water, and extracted with 3 × 50 mL of EtOAc. The combined organic extracts were washed once with 50 mL of brine, dried, and evaporated. The residue was chromatographed on 75 g of silica gel using hexanes/EtOAc (2:1) to afford 0.39 g (76%) of 2′-amino-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*′-(methoxyethoxymethyl)[1,1′-biphenyl]-2-sulfonamide (**5**) as a colorless gum. To a solution of 0.35 g (0.81 mmol) of compound **5** in 10 mL of 95% aqueous EtOH was added 10 mL of 6 N aqueous HCl, and the mixture was refluxed for 2 h. The mixture was concentrated and diluted with 10 mL of water. The solution was neutralized using saturated aqueous $NaHCO_3$ and reacidified to pH 4 using glacial AcOH. The mixture was extracted with 3 × 25 mL of EtOAc, and the combined organic extracts were washed once with 50 mL of brine, dried, and evaporated (0.31 g). Chromatography of the residue on 50 g of silica gel using hexanes/EtOAc (1:1) provided 0.087 g (31%) of **6a** as a gum. An analytically pure sample was obtained by repeated crystallizations from EtOAc/MeOH/hexanes: mp 182−183 °C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 1.87 (s, 3H), 2.17 (s, 3H), 6.85−8.00 (m, 8H). ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 6.04, 10.22, 106.39, 116.26, 118.71, 125.72, 128.26, 129.03, 129.41, 130.30, 132.99, 133.39, 137.86, 138.81, 143.05, 155.31, 161.77. Anal. ($C_{17}H_{17}N_3O_3S$) C, H, N, S.

The following compounds were prepared using a procedure similar to the above and substituting with the appropriate arylboronic acids.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-nitro[1,1′-biphenyl]-2-sulfonamide (6c):** mp 128−130 °C. ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 3H), 2.09 (s, 3H), 7.32−8.25 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.48, 10.74, 107.70, 123.05, 124.60, 128.81, 129.04, 129.59, 132.61, 133.44, 135.95, 137.91, 138.86, 140.30, 147.53, 153.89, 162.07. Anal. ($C_{17}H_{15}N_3O_5S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-(hydroxymethyl)-[1,1′-biphenyl]-2-sulfonamide (6d):** mp 70−80 °C. ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H), 2.16 (s, 3H), 4.36 (ABq, J = 12.3 Hz, 2H), 7.27−7.92 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 7.43, 11.55, 63.47, 108.99, 128.00, 129.12, 129.81, 130.19, 130.47, 133.24, 133.82, 138.32, 138.67, 139.56, 140.08, 155.25, 162.78. Anal. ($C_{18}H_{18}N_2O_4S$·0.26H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-3′-amino[1,1′-biphenyl]-2-sulfonamide (6e):** mp 157−160 °C. Anal. ($C_{17}H_{17}N_3O_3S$·0.10cyclohexane) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-3′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (6g):** colorless gum. ^{1}H NMR ($CDCl_3$): δ 1.04 (d, J = 6.4 Hz, 6H), 1.94 (s, 3H), 2.02 (m, 1H), 2.26 (s, 3H), 2.64 (d, J = 7.0 Hz, 2H), 6.66 (br s, 1H), 7.32−8.16 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.25, 10.37, 22.08, 29.96, 45.04, 107.55, 126.87, 127.59, 128.51, 129.06, 130.51, 132.55, 132.90, 137.74, 138.12, 141.18, 141.44, 154.33, 161.74. Anal. ($C_{21}H_{24}N_2O_3S$·0.42H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(dimethylamino)[1,1′-biphenyl]-2-sulfonamide (6h):** mp 135−136 °C. ^{1}H NMR ($CDCl_3$): δ 1.84 (s, 3H), 2.11 (s, 3H), 3.01 (s, 6H), 5.90 (br s, 1H), 6.76−7.98 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 7.11, 11.20, 40.72, 108.82, 112.07, 125.81, 127.54, 128.95, 131.40, 133.44, 133.50, 138.77, 141.88, 150.78, 154.78, 162.24. Anal. ($C_{19}H_{21}N_3O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-methyl[1,1′-biphenyl]-2-sulfonamide (6j):** mp 126−127 °C. ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 3H), 2.12 (s, 3H), 2.42 (s, 3H), 5.79 (br s, 1H), 7.26−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.62, 10.77, 21.28, 108.48, 127.68, 128.69, 128.86, 129.90, 132.72, 133.04, 135.46, 138.05, 138.48, 141.04, 154.03, 161.86. Anal. ($C_{18}H_{18}N_2O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-*n*-propyl[1,1′-biphenyl]-2-sulfonamide (6k):** colorless gum. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 3H), 1.70 (m, 2H), 1.81(s, 3H), 2.10 (s, 3H), 2.63 (t, J = 7.8 Hz, 2H), 6.05 (br s, 1H), 7.24−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.51, 10.63, 13.80, 24.25, 37.66, 108.01, 127.56, 128.08, 128.60,129.76, 132.67, 132.90, 135.64, 138.00, 141.09, 143.02, 154.07, 161.71. Anal. ($C_{20}H_{22}N_2O_3S$) C, H, N, S

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-[1,1′-biphenyl]-2-sulfonamide (6l):** mp 126 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6.4 Hz, 6H), 1.84 (s, 3H), 1.92 (m, 1H), 2.12 (s, 3H), 2.53 (d, J = 7.0 Hz, 2H), 5.83 (br s, 1H), 7.22−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.59, 10.74, 22.40, 30.09, 45.12, 108.24, 127.68, 128.66, 128.86, 129.76, 132.72, 133.01, 135.72, 138.08, 141.10, 142.22, 154.09, 161.86. Anal. ($C_{21}H_{24}N_2O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-isopropyl[1,1′-biphenyl]-2-sulfonamide (6m):** mp 162−163 °C. ^{1}H NMR ($CDCl_3$): δ 1.30 (d, J = 7.0 Hz, 6H), 1.83 (s, 3H), 2.12 (s, 3H), 2.97 (m, 1H), 5.85 (s, 1H), 7.26−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.62, 10.77, 23.90, 33.87, 108.27, 126.25, 127.45, 127.68, 128.72, 129.99, 132.81, 133.04, 135.77, 138.02, 141.13, 149.31, 154.12, 161.87. Anal. ($C_{20}H_{22}N_2O_3S$·0.30H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-*n*-butyl[1,1′-biphenyl]-2-sulfonamide (6n).** ^{1}H NMR (CD_3OD): δ 0.95 (t, J = 7.0 Hz, 3H), 1.40 (m, 2H), 1.64 (m, 2H), 1.84 (s, 3H), 2.12 (s, 3H), 2.67 (t, J = 7.0 Hz, 2H), 5.80 (s, 1H), 7.26−8.00 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.59, 10.74, 13.94, 22.43, 33.40, 35.39, 108.33, 127.65, 128.17, 128.66, 129.90, 132.75, 133.01, 135.60, 138.05, 141.10, 143.46, 154.09, 161.84. Anal. ($C_{21}H_{24}N_2O_3S$·0.07H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-*tert*-butyl[1,1′-biphenyl]-2-sulfonamide (6o):** mp 169−170 °C. ^{1}H NMR (CD_3OD): δ 1.37 (s, 9H), 1.83 (s, 3H), 2.04 (s, 3H), 5.88 (s, 1H), 7.36−8.00 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.56, 10.72, 31.28, 34.69, 108.18, 125.05, 127.62, 128.66, 129.70, 132.78, 133.02, 135.38, 137.98, 141.06, 151.59, 154.10, 161.83. Anal. ($C_{21}H_{24}N_2O_3S$·0.05H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2,2-dimethylpropyl)-[1,1′-biphenyl]-2-sulfonamide (6p):** mp 54−57 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 9H), 1.83 (s, 3H), 2.12 (s, 3H), 2.55 (s, 2H), 5.85 (s, br, 1H), 7.21−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.59, 10.72, 29.41, 31.74, 49.89, 108.15, 127.65, 128.66, 129.24, 130.16, 132.67, 132.99, 135.81, 138.06, 140.25, 141.09, 154.07, 161.83. Anal. ($C_{22}H_{26}N_2O_3S$·0.30H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(3-methylbutyl)[1,1′-biphenyl]-2-sulfonamide (6q):** mp 125−127 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, J = 6 Hz, 6H), 1.56 (m, 3H), 1.84 (s, 3H), 2.12 (s, 3H), 2.67 (m, 2H), 5.83 (s, 1H), 7.26−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.59, 10.72, 22.49, 27.79, 33.50, 40.57, 108.30, 127.62, 128.08, 128.66, 129.90, 132.73, 132.99, 135.58, 138.03, 141.09, 143.66, 154.07, 161.83. Anal. ($C_{22}H_{26}N_2O_3S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-methoxy[1,1′-biphenyl]-2-sulfonamide (6r):** mp 179−181 °C. ^{1}H NMR (CD_3OD): δ 1.85 (s, 3H), 2.12 (s, 3H), 3.86 (s, 3H), 5.79(s, 1H), 6.98−7.99 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.62, 10.75, 55.28, 108.53, 113.57, 127.62, 128.72, 130.42, 131.37, 132.93, 133.07, 138.15, 140.80, 154.01, 159.72, 161.86. Anal. ($C_{18}H_{18}N_2O_4S$·0.04H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(1-methylethoxy)[1,1′-biphenyl]-2-sulfonamide (6s):** mp 49−52 °C. ^{1}H NMR (CD_3OD): δ 1.37 (d, J = 6.0 Hz, 6H), 1.83 (s, 3H), 2.10 (s, 3H), 4.60 (m, 1H), 6.10 (s, 1H), 6.93−7.99 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.54, 10.65, 21.97, 69.80, 108.16, 115.04, 115.33, 127.45, 128.63, 130.02, 131.22, 132.92, 138.08, 140.84, 154.06, 157.98, 161.75. Anal. ($C_{20}H_{22}N_2O_4S\cdot0.10H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropoxy)-[1,1′-biphenyl]-2-sulfonamide (6t):** mp 50−53 °C. ^{1}H NMR (CD_3OD): δ 1.05 (d, J = 6.0 Hz, 6H), 1.84 (s, 3H), 2.10 (s, 3H), 2.13 (m, 1H), 3.76 (d, J = 6.0 Hz, 2H), 6.03 (s, 1H), 6.95−7.99 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.56, 10.69, 19.20, 28.20, 74.35, 108.30, 114.01, 114.30, 127.51, 128.66, 130.13, 130.68, 131.23, 132.93, 138.12, 140.86, 154.07, 159.35, 161.77. Anal. ($C_{21}H_{24}N_2O_4S\cdot0.67H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(phenylmethyloxy)-[1,1′-biphenyl]-2-sulfonamide (6u).** ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.20 (s, 3H), 5.20 (s, 2H), 6.32 (br s, 1H), 7.14−8.11 (m, 13H). ^{13}C NMR ($CDCl_3$): δ 6.48, 10.62, 69.92, 108.01, 114.29, 127.45, 127.97, 128.52, 128.66, 130.68, 131.20, 132.87, 132.92, 136.52, 138.05, 140.73, 154.00, 158.75, 161.72. Anal. ($C_{24}H_{22}N_2O_4S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-((1-methylethyl)amino)-[1,1′-biphenyl]-2-sulfonamide (6v):** mp 62−64 °C. ^{1}H NMR (CD_3OD): δ 1.24 (d, J = 7 Hz, 6H), 1.84 (s, 3H), 2.10 (s, 3H), 3.68 (m, 1H), 6.63−7.97 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.59, 10.72, 22.92, 44.09, 108.30, 112.36, 125.98, 127.07, 128.46, 131.17, 132.93, 133.04, 138.29, 141.41, 147.64, 154.30, 161.74. Anal. ($C_{20}H_{23}N_3O_3S\cdot0.13H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(*N*-methyl-*N*-(1-methylethylamino))[1,1′-biphenyl]-2-sulfonamide (6w):** yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.10 (d, J = 6.4 Hz, 6H), 1.84 (s, 3H), 2.12 (s, 3H), 2.75 (s, 3H), 4.10 (m, 1H), 5.83 (br s, 1H), 7.22−7.99 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.66, 18.75, 19.45, 29.64, 48.39, 188.38, 111.96, 125.83, 127.01, 128.46, 131.05, 132.96, 133.04, 138.32, 141.44, 141.92, 154.36, 161.77. Anal. ($C_{21}H_{25}N_3O_3S\cdot0.22C_6H_{14}$) C, H, N, S.

2′-(*N*,*N*-Dimethylamino)-*N*-(3,4-dimethyl-5-isoxazolyl)-[1,1′-biphenyl]-2-sulfonamide (6b). To a solution of 0.45 g (1.04 mmol) of **5** in 15 mL of MeOH were added glacial AcOH (1 mL) and 37% aqueous formaldehyde (0.25 mL, 3.13 mmol), and the mixture was stirred for 15 min at room temperature. Sodium cyanoborohydride (0.197 g, 3.13 mmol) in 5 mL of MeOH was then added dropwise over 15 min, and the mixture was stirred for 24 h. The mixture was concentrated, added to water (25 mL), and extracted with 2 × 50 mL of EtOAc. The combined organic extracts were dried and evaporated to provide 0.39 g (81%) of a light-brown gum which solidified on standing. To a solution of this material in 10 mL of 95% aqueous EtOH was added 10 mL of 6 N aqueous HCl, and the mixture was refluxed for 2 h. The solution was concentrated in vacuo, 5% aqueous $NaHCO_3$ (10 mL) was added to the residue, and the resulting solution was reacidified to pH 4 using glacial AcOH. The solution was then concentrated to about 5 mL and extracted with 3 × 10 mL of EtOAc. The combined organic extracts were dried and evaporated. The residue was chromatographed on silica gel using 3:1 hexanes/EtOAc followed by crystallization from a mixture of CH_2Cl_2/hexanes to afford 0.14 g (62%) of **6b** as colorless prisms: mp 148−150 °C. ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H), 2.21 (s,3H), 2.62 (s, 6H), 7.15−7.76 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 7.08, 10.88, 43.60, 118.04, 123.82, 128.37, 128.52, 129.24, 132.20, 133.13, 133.53. Anal. ($C_{19}H_{21}N_3O_3S$) C, H, N, S.

3′-(*N*,*N*-Dimethylamino)-*N*-(3,4-dimethyl-5-isoxazolyl)-[1,1′-biphenyl]-2-sulfonamide (6f). To a solution of 0.46 g (1.34 mmol) of **6e** in 15 mL of MeOH were added 37% aqueous formaldehyde (0.44 mL, 5.36 mmol) and glacial acetic acid (0.49 g), and the mixture was stirred at room temperature. Sodium cyanoborohydride (0.34 g, 5.36 mmol) was then added over 10 min, and the solution was stirred overnight. The mixture was then concentrated to about 10 mL, diluted with 40 mL water, and extracted with 3 × 35 mL of EtOAc. The combined organic extracts were washed with brine, dried, and evaporated. The gummy solid thus obtained was chromatographed on silica gel using hexanes/EtOAc (3:1) to afford 0.21 g (42%) of **6f** as an off-white solid: mp 67−70 °C. Anal. ($C_{19}H_{21}N_3O_3S\cdot0.25H_2O$) C, H, N, S.

2′-[[*N*-(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1′-biphenyl]-4-carboxylic Acid (6i). Suzuki coupling of **4** and 4-formylphenylboronic acid as described for **6a** provided 2′-[[*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]-amino]sulfonyl][1,1′-biphenyl]-4-carboxaldehyde in 84% yield. To a solution of this material (1.0 g, 2.25 mmol) and sulfamic acid (437 mg, 4.5 mmol) in 22 mL of THF at 0 °C was added an ice-cooled solution of sodium chlorite (407 mg, 4.5 mmol) in 22 mL of H_2O. The mixture was stirred at 0 °C for 3 min and then diluted with 200 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried, and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH to afford 2′-[[*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]amino]sulfonyl][1,1′-biphenyl]-4-carboxylic acid (950 mg, 92%) as a colorless gum: R_f = 0.20, silica gel, 20:1 CH_2Cl_2/MeOH. Treatment of this material with 6 N aqueous hydrochloric acid as described for **6a** then provided **6i** (30 mg, 12%) as a white solid: mp >180 °C dec. ^{1}H NMR (CD_3OD): δ 1.65 (s, 3H), 2.10 (s, 3H), 7.34−8.13 (m, 8H). ^{13}C NMR (CD_3OD): δ 6.50, 10.56, 105.76, 129.46, 129.80, 130.38, 130.70, 131.73, 133.66, 133.92, 140.20, 142.10, 145.35, 157.51, 163.18, 170.21. Anal. ($C_{18}H_{16}N_2O_5S\cdot0.46H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(1-methylethylthio)-[1,1′-biphenyl]-2-sulfonamide (6x).** This compound was prepared from **7** and 1-bromo-4-(1-methylethylthio)benzene using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **6x** as an amorphous white foam. ^{1}H NMR ($CDCl_3$): δ 1.17 (d, J = 6.4 Hz, 6H), 1.84 (s, 3H), 2.12 (s, 3H), 3.73 (s, 1H), 7.26−7.99 (m, 8H). Anal. ($C_{20}H_{22}N_2O_3S_2$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(1-methylethylsulfonyl)-[1,1′-biphenyl]-2-sulfonamide (6y).** This compound was prepared from **7** and 1-bromo-4-(1-methylethylsulfonyl)benzene using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **6y** as an amorphous white foam. ^{1}H NMR ($CDCl_3$): δ 1.33 (d, J = 7.1 Hz, 6H), 1.88 (s, 3H), 2.12 (s, 3H), 3.28 (s, 1H), 7.27−8.07 (m, 8H). Anal. ($C_{20}H_{22}N_2O_5S_2\cdot0.22H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(*N*,*N*-dimethylsulfonylamido)[1,1′-biphenyl]-2-sulfonamide (6z).** This compound was prepared from **7** and 4-bromo-*N*,*N*-dimethylbenzenesulfonamide using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **6z** as a white solid: mp 175−176 °C. ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 2.12 (s, 3H), 2.77 (s, 6H), 6.39 (br s, 1H), 7.27−8.86 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.68, 10.78, 37.98, 108.68, 127.20, 128.70, 129.48, 130.60, 132.31, 133.26, 135.59, 137.87, 139.58, 143.32, 153.71, 162.04. Anal. ($C_{19}H_{21}N_3O_5S_2$) C, H, N, S.

2-Borono-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*′-(methoxyethoxymethyl)benzenesulfonamide (7). To a solution of **4** (1.69 g, 4.03 mmol) in 40 mL of dry ether and 10 mL of THF at −78 °C was added *n*-BuLi (2 M solution in cyclohexane, 2.52 mL, 5.04 mmol) over 10 min. The resulting solution was stirred at −78 °C for 15 min, and triisopropyl borate (1.52 g, 8.06 mmol) was added. The mixture was slowly warmed to room temperature and stirred overnight. The solution was cooled to 0 °C, 40 mL of 10% aqueous HCl was added, and the mixture was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with 2 × 30 mL of EtOAc. The combined organic layers were washed once with 20 mL of brine, dried, and concentrated to give **7** (600 mg, 39%) as a light-yellow solid. This compound was used in the next step without any further purification.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(2-pyridinyl)benzenesulfonamide (9a).** This compound was prepared from **7** and 2-bromopyridine using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **9a** as white crystals: mp

136−137 °C. ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H), 2.19 (s, 3H), 7.26−8.66 (m, 8H). Anal. ($C_{16}H_{15}N_3O_3S$) C, H, N, S.

The following compounds were prepared similar to the procedure described for **9a**.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(3-pyridinyl)benzenesulfonamide (9b):** mp 147−150 °C. ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 2.12 (s, 3H), 7.19−8.51 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 6.51, 10.72, 105.04, 122.69, 128.34, 128.60, 129.99, 131.92, 132.06, 132.70, 135.61, 136.82, 138.84, 139.56, 146.92, 147.21, 155.69, 161.69. Anal. ($C_{16}H_{15}N_3O_3S\cdot0.25H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(3-pyrimidinyl)-benzenesulfonamide (9c):** mp 160−162 °C. ^{1}H NMR ($CDCl_3$): δ 1.94 (s, 3H), 2.20 (s, 3H), 7.39−8.93 (m, 7H), 10.32 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 6.72, 10.93, 107.65, 116.13, 119.93, 129.34, 130.32, 133.37, 133.60, 136.49, 138.36, 155.87, 157.05, 161.96, 165.04. Anal. ($C_{15}H_{14}N_4O_3S\cdot0.72H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(2-thienyl)benzenesulfonamide (9d):** mp 112−115 °C. ^{1}H NMR ($CDCl_3$): δ 1.83 (s, 3H), 2.11 (s, 3H), 6.30 (s, br, 1H), 7.11−8.03 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.51, 10.69, 108.24, 127.33, 127.79, 128.49, 129.21, 129.81, 132.96, 133.19, 133.97, 138.44, 138.73, 153.84, 161.80. Anal. ($C_{15}H_{14}N_4O_3S_2$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(3-thienyl)benzenesulfonamide (9e):** mp 147−148 °C. ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H), 2.11 (s, 3H), 6.00 (br s, 1H), 7.25−8.01 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 7.86, 12.00, 109.71, 126.99, 127.14, 129.21, 130.16, 131.22, 133.99, 134.33, 137.16, 139.32, 139.43, 155.15, 163.13. Anal. ($C_{15}H_{14}N_4O_3S_2$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(1*H*-indol-2-yl)benzenesulfonamide (9f). a. 2-Iodo-1-(phenylsulfonyl)-indole:** A solution of 1-(phenylsulfonyl)indole (1.35 g; 5.24 mmol) in 10 mL of THF was added dropwise over 10 min to a −78 °C solution of LDA in 15 mL of THF prepared from diisopropylamine (0.86 mL, 5.9 mmol) and 2.5 M *n*-BuLi (2.2 mL; 5.5 mmol). After stirring for 1 h at −78 °C, the mixture was allowed to warm to 0 °C over 1 h. After recooling to −78 °C, iodine (1.78 g, 6.81 mmol) was added in one portion, and the resulting mixture was stirred for 2 h at −78 °C and for 18 h at room temperature. The reaction mixture was partitioned between EtOAc (75 mL) and saturated $NaHCO_3$ solution (50 mL). The organic layer was washed with saturated aqueous $NaHSO_3$ solution (2 × 50 mL) and brine (50 mL). Drying and concentration afforded a ruby-colored oil which was crystallized from ether/hexane to afford 965 mg (48%) of the product as a tan crystalline solid. ^{1}H NMR ($CDCl_3$): δ 6.99 (s, 1H), 7.21 (m, 1H), 7.26 (m, 1H), 7.41 (m, 3H), 7.54 (m, 1H), 7.89 (d, J = 7.5 Hz, 2H), 8.27 (d, J = 7.5 Hz, 1H).

b. *N*-(3,4-Dimethyl-5-isoxazolyl)-2-(1*H*-indol-2-yl)benzenesulfonamide (9f). This compound was prepared from **7** and 2-iodo-1-(phenylsulfonyl)indole using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid and deprotection of the phenylsulfonyl moiety using 1 N aqueous KOH in MeOH at 55 °C to afford **9f** as a yellow powder: mp 172−175 °C. ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 3H), 2.02 (s, 3H), 6.38 (br s, 1H), 6.96 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.26 (m, 1H), 7.49 (m, 2H), 7.68 (m, 2H), 7.73 (d, J = 6.5 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 9.31 (brs, 1H). ^{13}C NMR ($CDCl_3$): δ 6.5, 10.7, 105.9, 108.9, 111.6, 120.7, 121.2, 123.3, 128.2, 128.5, 129.4, 131.8, 133.2, 133.5, 134.1, 136.8, 137.4, 153.4, 161.8. MS (HR): calcd for $C_{19}H_{18}N_3O_3S$, 368.1068; found, 368.0968.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2-(1*H*-indol-3-yl)benzenesulfonamide (9g).** This compound was prepared from **4** and 1-(phenylsulfonyl)indole-3-boronic acid using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid and deprotection of the phenylsulfonyl moiety using 1 N aqueous KOH in MeOH at 55 °C to afford **9g** as a colorless solid: mp 184−186 °C. ^{1}H NMR ($CDCl_3$/CD_3OD, 9:1): δ 1.54 (s, 3H), 2.01 (s, 3H), 7.12 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.45 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.64 (s, 1H), 7.65 (d, J = 9 Hz, 2H), 8.12 (d, J = 7.5 Hz, 1H), 10.09 (br s, 1H). ^{13}C NMR ($CDCl_3$/CD_3OD, 9:1): δ 6.0, 10.6, 105.9, 111.6, 112.1, 119.5, 120.4, 122.5, 126.7, 126.8, 127.2, 129.5, 133.0, 134.5, 134.7, 136.0, 138.7, 155.0, 161.7. Anal. ($C_{19}H_{17}N_3O_3S\cdot0.43H_2O$) C, H, N.

***N*-(2-Bromophenylsulfonyl)pyrrole (10).** Potassium hydride (35% oil dispersion, 5.76 g, 50 mmol; washed three times with hexanes) was covered with dry tetrahydrofuran (200 mL), and the suspension was cooled to 0 °C. Pyrrole (4.16 mL, 60 mmol) in tetrahydrofuran (60 mL) was added dropwise over 20 min. The ice bath was removed, and the solution was stirred at ambient temperature until the gas evolution ceased (20 min), whereupon 2-bromobenzenesulfonyl chloride (10.22 g, 40 mmol) in tetrahydrofuran (60 mL) was added dropwise over 20 min. After stirring for 1 h, the mixture was filtered through Celite, and the filter pad was rinsed with tetrahydrofuran (100 mL). The filtrate was evaporated, and the resulting white solid was recrystallized from methanol to afford 7.47 g (65%) of **10**: mp 85.0−87.0 °C. ^{1}H NMR ($CDCl_3$): δ 6.25 (m, 2H), 7.14 (m, 2H), 7.36 (m, 2H), 7.64 (m, 2H).

***N*-[[4′-(2-Methylpropyl)[1,1′-biphenyl]yl]sulfonyl]-pyrrole (11).** This compond was prepared from **10** and 4-isobutylphenylboronic acid using a Suzuki coupling procedure described for **6a**: yield 86%. ^{1}H NMR ($CDCl_3$): δ 1.11 (m, 6H), 2.07 (m, 1H), 2.67 (m, 2H), 6.20 (m, 2H), 6.72 (m, 2H), 7.20 (m, 4H), 7.43 (d, J = 7.9 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H).

4′-(2-Methylpropyl)[1,1′-biphenyl]-2-sulfonic Acid, Sodium Salt (12). A solution of **11** (3.8 g, 11 mmol) and 5 N aqueous sodium hydroxide (53 mL) in methanol (70 mL) was refluxed for 6.5 h. Evaporation of the solvent afforded a white solid which was collected and dried under vacuum. Recrystallization from water (40 mL) afforded 3.05 g (88%) of **12** as a white solid. ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), 1.90 (m, 1H), 2.49 (m, 2H), 7.11 (d, J = 7.6 Hz, 2H), 7.21 (m, 1H), 7.39 (m, 2H), 7.41 (d, J = 7.6 Hz, 2H), 8.09 (d, J = 7.6 Hz, 1H).

4′-(2-Methylpropyl)[1,1′-biphenyl]-2-sulfonyl Chloride (13). Compound **12** (1.6 g, 5 mmol) and phosphorus pentachloride (3.1 g, 15 mmol) were ground together with a glass rod, and the mixture was heated at 60 °C for 2.5 h. Ice water was added, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated to afford 1.45 g (94%) of **13**. This compound was used in the next step without any furthur purification.

***N*-(4-Methyl-5-isoxazolyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (14a).** Sulfonyl chloride **13** (0.65 g, 2.1 mmol) in pyridine (1.0 mL) was added to a solution of 4-methyl-5-isoxazolamine (0.29 g, 2.9 mmol) and DMAP (58 mg, 0.46 mmol) in 1 mL of pyridine. The solution was stirred at 75 °C for 2.5 h, cooled to room temperature, and diluted with water. The solution was adjusted to pH 3 with 1 N aqueous hydrochloric acid and extracted with ether (2 × 50 mL). The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography using ethyl acetate/methylene chloride to afford 0.12 g (15%) of **14a** as a white solid: mp 153−155 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), 1.57 (m, 1H), 1.93 (s, 3H), 2.54 (m, 2H), 5.76 (s, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.41 (m, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 7.1, 22.4, 30.1, 45.2, 127.7, 128.7, 129.0, 129.8, 132.8, 133.1, 142.4, 153.8. Anal. ($C_{20}H_{22}N_2O_3S\cdot0.39H_2O$) C, H, N, S.

The following compounds were prepared similar to the procedure described for **14a**. The corresponding isoxazolamine starting materials were prepared as described previously.[17]

***N*-(3-Methyl-4-nitro-5-isoxazolyl)-4′-(2-methylpropyl)-[1,1′-biphenyl]-2-sulfonamide (14b):** mp 124−126 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (m, 6H), 1.93 (m, 1H), 2.45 (s, 3H), 2.55 (m, 2H), 7.15 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 8.35 (d, J = 7.6 Hz, 1H), 8.59 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 11.5, 22.4, 30.1, 45.1, 128.2, 128.4, 129.0, 130.3, 133.0, 134.4, 134.8, 136.5, 141.7, 142.6, 143.0, 155.4, 159.2. Anal. ($C_{20}H_{21}N_3O_5S$) C, H, N, S.

***N*-(4,5,6,7-Tetrahydro-2,1-benzisoxazol-3-yl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (14d):** mp 111−114 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), 1.70 (m, 4H), 1.93 (m, 1H), 2.40 (t, J = 6.4 Hz, 2H), 2.54 (m, 2H), 2.60 (t, J = 6.4 Hz, 2H), 5.88 (s, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.38 (m, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.47 (m, 1H), 7.61 (t, J = 7.8 Hz, 1H), 8.02 (t, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 19.0, 22.1, 22.2, 22.4, 30.1, 45.2, 126.4, 127.7, 128.8, 128.9, 129.7, 132.8, 133.1, 135.6, 142.3. Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N, S.

***N*-(3-Methyl-4-(phenylmethyl)-5-isoxazolyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (14e):** mp 137.0−138.5 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), 1.26 (m, 1H), 1.93 (s, 3H), 2.54 (m, 2H), 3.69 (s, 2H), 5.72 (s, 1H), 7.04 (d, J = 7.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 1H), 7.26, (m, 5H), 7.40 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 7.1 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 11.1, 22.4, 27.7, 30.1, 45.2, 126.6, 127.7, 128.3, 128.6, 128.8, 129.0, 129.8, 132.8, 133.1, 135.7, 154.9. Anal. ($C_{27}H_{28}N_2O_3S\cdot 0.86H_2O$) C, H, N, S.

***N*-(4,5-Dimethyl-3-isoxazolyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (14f):** mp 131.5−133.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), 1.64 (s, 3H), 1.91 (m, 1H), 2.19 (s, 3H), 2.52 (m, 2H), 5.94 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.30 (m, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.5, 11.1, 24.7, 29.8, 44.9, 127.8, 128.9, 129.5, 132.5, 132.9, 136.0, 137.3, 140.9, 142.1. Anal. ($C_{21}H_{24}N_2O_3S$) C, H, N, S.

***N*-(4,6-Dimethoxy-2-pyrimidinyl)-4′-(2-methylpropyl)-[1,1′-biphenyl]-2-sulfonamide (14h):** mp 131−134 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 6H), 1.92 (m, 1H), 2.53 (m, 2H), 3.61 (s, 6H), 5.59 (s, 1H), 6.33 (s, 1H), 7.10 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 6.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 6.8 Hz, 1H), 8.35 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.4, 30.2, 45.1, 54.0, 84.7, 127.2, 128.5, 128.8, 130.3, 132.3, 132.6, 135.9, 141.8, 154.7, 171.5. Anal. ($C_{22}H_{25}N_3O_4S$) C, H, N, S.

3-Methyl-5-[[[4′-(2-methylpropyl)[1,1′-biphenyl]-2-yl]-sulfonyl]amino]-4-isoxazolecarboxylic Acid, Ethyl Ester (14c). a. *N*-(1,1-Dimethylethyl)-2-bromobenzenesulfonamide. To a solution of *tert*-butylamine (3.6 mL, 34 mmol) in chloroform (50 mL) at 0 °C was added dropwise a solution of 2-bromobenzenesulfonyl chloride (4.00 g, 15.7 mmol) in chloroform (15 mL). The reaction was allowed to come to room temperature and was stirred for 17 h. The combined filtrates were washed (25 mL of saturated $NaHCO_3$), dried, and concentrated to afford a white solid. ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H), 5.18 (br s, 1H), 7.35−7.49 (m, 2H), 7.71 (dd, J = 8, 1 Hz, 1H), 8.17 (dd, J = 8, 2 Hz, 1H).

b. *N*-(1,1-Dimethylethyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide. Suzuki coupling of the preceding sulfonamide and 4-isobutylbenzeneboronic acid as described in **6a** yielded the product as a white solid. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.17 (dd, J = 8, 1 Hz, 1H), 7.44−7.56 (m, 4H), 7.33 (dd, J = 8, 1 Hz, 1H), 7.24 (d, J = 8 Hz, 2H), 3.52 (br s, 1H), 2.53 (d, J = 7 Hz, 2H), 1.91 (m, 1H), 0.96 (s, 9H), 0.93 (d, J = 6 Hz, 6 H).

c. 4′-(2-Methylpropyl)[1,1′-biphenyl]-2-sulfonamide. The preceding sulfonamide was dissolved in cold trifluoroacetic acid (5 mL). The reaction was brought to room temperature and was stirred for 5 h. The solvent was removed in vacuo, and the residue was passed through a silica plug with ethyl acetate to provide the product as an oil (306 mg, 100%): R_f (silica, 25% ethyl acetate/hexanes) 0.23.

d. 3-Methyl-5-[[[4′-(2-methylpropyl)[1,1′-biphenyl]-2-yl]sulfonyl]amino]-4-isoxazolecarboxylic Acid, Ethyl Ester (14c). The preceding sulfonamide (306 mg, 1.01 mmol), ethyl 5-bromo-3-methyl-4-isoxazolecarboxylate (389 mg), and cesium carbonate (658 mg, 2.02 mmol) were heated at 80 °C in DMF (4 mL) for 2 h. The solvent was removed in vacuo, the residue was diluted with saturated NaCl (10 mL), and the pH was brought to 2 with 1 N HCl. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried, and concentrated. Chromatography (silica, ethyl acetate/hexanes) yielded the product as a yellow-white solid. Recrystallization from ethanol provided 137 mg (31%) of **14c** as fine white needles: mp 133.5−134.0 °C. ^{1}H NMR ($CD_3OD/CDCl_3$): δ 0.94 (d, J = 7 Hz, 6H), 1.22 (t, J = 7 Hz, 3H), 1.90 (m, 1H), 2.27 (s, 3H), 2.50 (d, J = 7 Hz, 2H), 4.01−4.14 (m, 2H), 7.12−7.18 (m, 3H), 7.31−7.78 (m, 4H), 7.78 (m, 1H). ^{13}C NMR ($CD_3OD/CDCl_3$): δ 12.2, 13.8, 22.0, 29.9, 44.9, 126.7, 127.3, 127.9, 128.9, 131.0, 132.4, 137.4, 140.1, 140.5, 141.0, 159.1, 165.9, 170.3. Anal. ($C_{23}H_{26}N_2O_5S\cdot 0.13H_2O$) C, H, N, S

***N*-(6-Chloro-1,2-pyridazinyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (14g).** Treatment of 4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide with 3,6-dichloropyridazine as described for **14c**, step d, provided **14g** as a tan solid: mp 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.2 Hz, 6H), 1.8 (m, 1H), 2.4 (d, J = 7.2 Hz, 2H), 7.0 (d, J = 7.9 Hz, 2H), 7.1 (d, J = 9.5 Hz, 1H), 7.25 (m, 3H), 7.5 (m, 2H), 8.2 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.3, 30.0, 44.9, 127,5, 128.1, 128.3, 129.1, 129.2, 129.3, 132.1, 132.2, 132.3, 132.4, 135.9, 141.2, 141.4, 152.3. Anal. ($C_{20}H_{20}ClN_3O_2S\cdot 0.13H_2O$) C, H, N, S.

3-(2-Methyl-1-propenyl)aniline (16). To isopropyl triphenylphosphonium iodide (74 g, 170 mmol) in 1:1 ether/tetrahydrofuran (850 mL) at −15 °C was added *n*-butyllithium (1.6 M in hexane, 118 mL, 188 mmol) dropwise. The mixture was stirred at room temperature for 3 h and cooled to −50 °C, and a solution of 3-nitrobenzaldehyde (28.4 g, 188 mmol) in tetrahydrofuran (60 mL) was added dropwise. The mixture was stirred at room temperature overnight, cold water and hexane were added, and the mixture was stirred for several minutes and filtered. The organic phase of the filtrate was separated washed three times with water, dried, and concentrated. The residue was chromatographed on silica gel with 50:1 hexanes/ethyl acetate to afford 3-(2-methyl-1-propenyl)-nitrobenzene (23 g, 76%) as a light-yellow liquid. A mixture of this compound (4.0 g, 22 mmol) and 5% Pt/C (400 mg) in methanol (40 mL) was hydrogenated at 45 psi overnight. The mixture was filtered and the filtrate concentrated to provide **16** (3.11 g, 92%). ^{1}H NMR ($CDCl_3$): δ 1.85 (d, J = 1.5 Hz, 3H), 1.87 (d, J = 1.2 Hz, 3H), 3.60 (br s, 2H), 6.18 (br s, 1H), 6.51−7.35 (m, 4H).

***N*-(2,2-Dimethyl-1-oxopropyl)-3-(2-methyl-1-propyl)-aniline (17).** To a mixture of **16** (3.11 g, 21.1 mmol) and trimethylacetyl chloride (3.31 g, 27.5 mmol) in methylene chloride (53 mL) at 0 °C was added triethylamine (4.28 g, 42.2 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature for 15 min and poured into ice water. The aqueous layer was extracted twice with ethyl acetate, and the combined organic phases were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with 25:2 hexanes/ethyl acetate to provide *N*-(2,2-dimethyl-1-oxopropyl)-3-(2-methyl-1-propenyl)aniline (3.81 g, 78%) as a white solid. A mixture of this compound (3.47 g, 15 mmol) and 10% Pd/C (520 mg) in ethyl acetate (35 mL) was hydrogenated at 60 psi for 1 h. The mixture was filtered and the filtrate concentrated to provide **17** (3.41 g, 98%). ^{1}H NMR ($CDCl_3$): δ 1.04 (d, J = 7.0 Hz, 6H), 1.46 (s, 9H), 2.02 (m, 1H), 2.59 (d, J = 7.0 Hz, 2H), 7.02−7.54 (m, 4H).

2-(2,2-Dimethyl-1-oxo-1-propylamino)-4-(2-methyl-1-propyl)phenylboronic Acid (18). To compound **17** (2.86 g, 12.3 mmol) and tetramethylethylenediamine (4.28 g, 36.8 mmol) in ether (25 mL) at −40 °C was added *tert*-butyllithium (1.7 M in pentane, 21.6 mL, 36.8 mmol) dropwise. The solution was stirred at room temperature for 2.5 h and cooled to −20 °C, and trimethyl borate (3.82 g, 36.8 mmol) was added dropwise. The mixture was stirred at −10 to 0 °C for 1 h and at room temperature for 3 h and cooled to 0 °C, and 10% aqueous hydrochloric acid was added. The aqueous layer was extracted three times with methylene chloride, and the combined organic phases were washed with brine, dried, and concentrated. The residue was triturated with ether to afford **18** as a white solid (2.52 g, 74%): mp >250 °C. ^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.5 Hz, 6H), 1.06 (s, 9H), 1.85 (m, 1H),

2.44 (d, J = 7.0 Hz, 2H), 7.0 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.96 (s, 1H), 10.43 (br s, 1H).

2′-(2,2-Dimethyl-1-oxo-1-propylamino)-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (19). To a solution of **4** (6.18 g, 22.30 mmol) and **18** (9.35 g, 22.30 mmol) in 200 mL of toluene and 160 mL of 95% EtOH under argon was added tetrakis(triphenylphosphine)palladium(0) (2.58 g, 2.23 mmol) followed by 120 mL of 2 M aqueous sodium carbonate. The mixture was heated at 75 °C for 3 h, cooled, and diluted with 500 mL of EtOAc. The organic layer was separated, washed with 3 × 150 mL of brine, dried, and concentrated. The residue was chromatographed on silica gel using 4:1 hexane/EtOAc to afford **19** (9.14 g, 72%) as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6.5 Hz, 6H), 1.01 (s, 9H), 1.94 (s, 3H), 1.95 (m, 1H), 2.15 (s, 3H), 2.54 (d, J = 7.0 Hz, 2H), 3.31 (s, 3H), 3.45 (m, 2H), 3.60 (m, 2H), 4.1 (AB_q, J = 11.7, 91.7 Hz, 2H), 7.06−7.99 (m, 7H).

2′-Amino-*N*-(3,4-dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (20). To a solution of **19** (7.55 g, 13.2 mmol) in 75 mL of THF at −78 °C under argon diisobutylaluminum hydride (1 M solution in hexane, 26.2 mL, 26.2 mmol) over 15 min, and the mixture was stirred for 2 h. Additional diisobutylaluminum hydride (5.2 mL, 5.2 mmol) was added, and the mixture was stirred for an additional 3 h. Saturated aqueous ammonium chloride (100 mL) was added slowly to the mixture. The mixture was extracted with 3 × 125 mL of methylene chloride, and the combined organic extracts were washed with brine, dried, and concentrated. The residue thus obtained was dissolved in 150 mL of 95% EtOH and 150 mL of 6 N aqueous hydrochloric acid was added, and the solution was refluxed for 1 h. The solution was concentrated in vacuo to about 100 mL, and the solution was neutralized to pH 7 using saturated aqueous sodium bicarbonate. This solution was then reacidified to pH 5 using glacial acetic acid and extracted with 3 × 200 mL of EtOAc. The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica with 2:1 hexanes/EtOAc to afford **20** (3.0 g, 57%) as a white solid: mp 60−70 °C (amorphous). ^{1}H NMR ($CDCl_3$/CD_3OD, 4:1): δ 0.93 (d, J = 6 Hz, 6H), 1.88 (s, 3H), 2.16 (s, 3H), 2.44 (d, J = 7 Hz, 2H), 3.91 (s, br, 2H), 6.66−7.94 (m, 7H). ^{13}C NMR ($CDCl_3$/CD_3OD, 4:1): δ 6.33, 10.46, 22.20, 22.28, 29.78, 45.01, 107.17, 117.27, 120.24, 123.47, 128.26, 129.01, 130.10, 133.19, 133.39, 137.86, 138.93, 142.22, 143.20, 155.28, 161.83. Anal. ($C_{21}H_{25}N_3O_3S\cdot0.25H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-(methylamino)[1,1′-biphenyl]-2-sulfonamide (20a).** To a suspension of **20** (135 mg, 0.34 mmol), NaOAc (28 mg, 0.34 mmol), and AcOH (41 mg, 0.68 mmol) in 4 mL of MeOH were added H_2CO (37% in H_2O, 0.033 mL, 0.41 mmol) and $NaCNBH_3$ (21 mg, 0.34 mmol). The mixture was stirred at room temperature for 1 h and concentrated. The mixture was diluted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue using silica gel chromatography using hexanes and EtOAc provided **20a** (23 mg, 16%) as a white solid as well as **20b** (30 mg, 20%). **20a:** mp 125−128 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 7 Hz, 6H), 1.93 (m, 4H), 2.17 (s, 3H), 2.50 (d, J = 7 Hz, 2H), 2.76 (s, 3H), 6.61−7.91 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.57, 10.63, 22.35, 29.92, 30.78, 45.56, 107.84, 112.25, 118.93, 122.76, 128.32, 128.95, 129.82, 133.30, 133.42, 137.53, 139.26, 143.67, 145.37, 154.98, 161.78. Anal. ($C_{22}H_{27}N_3O_3S\cdot0.20H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-(*N*,*N*-dimethylamino)[1,1′-biphenyl]-2-sulfonamide (20b):** mp 125−128 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 6 Hz, 6H), 1.90 (m, 1H), 2.00 (s, 3H), 2.20 (s, 3H), 2.53 (d, J = 7 Hz, 2H), 2.61 (s, 6H), 6.94−7.73 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 7.05, 10.83, 22.43, 30.13, 43.63, 45.42, 106.39, 118.77, 124.53, 128.20, 128.49, 131.77, 131.86, 133.04, 133.62, 138.29, 142.91, 156.72, 162.12. Anal. ($C_{23}H_{29}N_3O_3S$) C, H, N, S.

The following compounds were prepared similar to the procedure described for **20a** from **20** using the corresponding aldehyde.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-(ethylamino)[1,1′-biphenyl]-2-sulfonamide (20c).** ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 7 Hz, 6H), 1.11(t, J = 7 Hz, 3H), 1.90 (m, 1H), 1.92 (s, 3H), 2.17 (s, 3H), 2.49 (d, J = 7 Hz, 2H), 3.10 (m, 2H), 6.61−7.90(m, 7H). ^{13}C NMR ($CDCl_3$): δ 7.20, 11.27, 14.81, 22.94, 30.56, 39.45, 46.17, 108.76, 113.52, 119.52, 123.38, 128.95, 129.55, 130.68, 133.85, 134.05, 138.35, 139.97, 144.15, 145.22, 155.66, 162.35. Anal. ($C_{23}H_{29}N_3O_3S\cdot0.20H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-(propylamino)[1,1′-biphenyl]-2-sulfonamide (20d).** ^{1}H NMR ($CDCl_3$): δ 0.86 (t, J = 6 Hz, 3H), 0.95 (d, J = 6 Hz, 6H), 1.50 (m, 2H), 1.92 (s, 3H), 1.93 (m, 1H), 2.17 (s, 3H), 2.49 (d, J = 7 Hz, 2H), 3.02 (t, J = 6 Hz, 2H), 6.61−7.90 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 7.29, 11.36, 12.03, 22.82, 23.08, 30.66, 46.29, 46.87, 108.83, 113.56, 119.38, 123.28, 129.05, 129.65, 130.72, 133.92, 134.15, 138.48, 140.09, 144.25, 145.46, 155.73, 162.45. Anal. ($C_{24}H_{31}N_3O_3S\cdot0.28H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-((1-methylethyl)amino)[1,1′-biphenyl]-2-sulfonamide (20e).** ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6 Hz, 6H), 1.03 (d, J = 6 Hz, 3H), 1.10 (d, J = 6 Hz, 3H), 1.90 (m, 1H), 1.91 (s, 3H), 2.16 (s, 3H), 2.48 (d, J = 7 Hz, 2H), 3.58 (m, 1H), 6.61−7.87 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.70, 10.79, 22.28, 22.43, 22.48, 22.71, 30.11, 44.72, 45.70, 108.59, 113.78, 118.79, 123.08, 128.47, 129.10, 130.42, 133.25, 133.56, 138.03, 139.58, 143.47, 143.56, 155.22, 161.84. Anal. ($C_{24}H_{31}N_3O_3S\cdot0.16H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-((2-hydroxyethyl)amino)[1,1′-biphenyl]-2-sulfonamide (20f).** ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6 Hz, 6H), 1.90 (m, 1H), 1.91 (s, 3H), 2.15 (s, 3H), 2.47 (d, J = 7 Hz, 2H), 3.22−3.81 (m, 4H), 6.58−7.93 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.89, 10.96, 22.64, 22.70, 30.29, 45.89, 46.04, 60.28, 108.86, 112.61, 118.58, 122.36, 128.67, 129.48, 130.17, 133.75, 133.95, 137.87, 139.34, 144.02, 145.08, 154.89, 162.22. Anal. ($C_{23}H_{29}N_3O_4S\cdot0.15H_2O$) C, H, N, S.

[*N*-[2′-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4-(2-methylpropyl)[1,1′-biphenyl]-2-yl]amino]acetic acid (20g): mp 147−150 °C. ^{1}H NMR (1:1 CD_3OD/$CDCl_3$): δ 0.96 (m, 6H), 1.85 (s, 3H), 1.90 (m, 1H), 2.16 (s, 3H), 2.47 (d, J = 7 Hz, 2H), 3.85 (s, 2H), 6.38−7.98 (m, 7H). ^{13}C NMR (1:1 CD_3OD/$CDCl_3$): δ 6.69, 10.78, 22.67, 22.78, 30.77, 45.86, 46.29, 107.26, 112.14, 119.06, 123.36, 129.07, 130.17, 130.95, 134.26, 134.52, 138.76, 140.15, 143.72, 144.42, 162.64, 174.41. Anal. ($C_{23}H_{27}N_3O_5S\cdot0.8H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-2′-formamido[1,1′-biphenyl]-2-sulfonamide (20h).** Treatment of **20** with formic acid in refluxing toluene provided **20h** as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 6H), 1.83 (s, 3H), 1.92 (m, 1H), 2.13 (s, 3H), 2.52 (m, 2H), 7.04−8.37 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 6.55, 10.79, 22.41, 30.06, 45.08, 107.90, 121.92, 124.52, 125.79, 126.34, 127.89, 128.93, 129.05, 129.34, 130.26, 130.58, 132.85, 133.11, 133.72, 134.21, 135.05, 136.58, 136.84, 138.88, 143.67, 144.07, 154.05, 159.77, 162.02, 162.88. Anal. ($C_{22}H_{25}N_3O_4S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[[(methylamino)carbonyl]amino]-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (20i).** Treatment of **20** with methyl isocyanate in methylene chloride afforded **20i** as a white solid: mp 172−174 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6 Hz, 6H), 1.80 (s, 3H), 1.90 (m, 1H), 2.10 (s, 3H), 2.48 (d, J = 7 Hz, 2H), 2.55 (d, J = 4 Hz, 2H), 4.94 (s, br, 1H), 6.30 (s, br, 1H), 6.92−7.98 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.48, 10.72, 22.43, 26.81, 30.04, 45.16, 106.50, 124.77, 125.00, 128.40, 129.18, 130.42, 132.81, 132.99, 135.78, 137.51, 139.39, 143.28, 157.01, 161.80. Anal. ($C_{23}H_{28}N_4O_4S\cdot0.49H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-fluoro-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (20j).** This compound was prepared similar to the procedure described for **25** starting from 3-(fluoroisobutyl)benzene: mp 139−141 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6 Hz, 6H), 1.80 (s, 3H), 1.92 (m, 1H), 2.13 (s, 3H), 2.51 (d, J = 7 Hz, 2H), 6.50 (s, br, 1H), 6.93−7.96 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.91, 11.15, 22.75, 30.39, 45.36, 108.09, 116.29, 116.60, 123.84, 124.82, 128.95, 129.67,

131.11, 133.42, 133.56, 135.44, 138.93, 145.48, 145.59, 154.59, 158.17, 161.80, 162.32. Anal. ($C_{21}H_{23}FN_2O_3S$) C, H, F, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-methyl-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (20k).** Suzuki coupling between **4** and 2-methyl-4-isobutylphenylboronic acid followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid provided **20k** as a white solid: mp 90−92 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6.5 Hz, 6H), 1.87 (s, 3H), 1.94 (m, 1H), 2.09 (s, 3H), 2.16 (s, 3H), 2.49 (d, J = 7.6 Hz, 2H), 5.93 (br s, 1H), 7.05−7.98 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.71, 10.79, 20.38, 22.49, 30.09, 45.12, 108.10, 112.22, 125.89, 127.77, 128.80, 128.87, 130.79, 131.25, 132.38, 133.18, 135.20, 137.42, 138.14, 140.70, 142.43, 154.21, 161.95, 180.15. Anal. ($C_{22}H_{26}N_2O_3S\cdot0.55H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-(hydroxymethyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (20l).** Deprotection of the MEM group in **30** using 6 N aqueous hydrochloric acid provided **20l** as a white solid: mp 60−67 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6 Hz, 6H), 1.86 (s, 3H), 1.92 (m, 1H), 2.14 (s, 3H), 2.51 (d, J = 7 Hz, 2H), 4.35 (s, 2H), 7.10−7.90 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.62, 10.74, 22.37, 30.00, 45.06, 62.69, 108.01, 127.91, 128.11, 128.92, 129.38, 129.96, 132.64, 132.92, 134.80, 138.05, 138.39, 139.49, 142.60, 154.58, 161.92. Anal. ($C_{22}H_{26}N_2O_4S\cdot0.18H_2O$) C, H, N, S.

2′-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4′-(2-methylpropyl)[1,1′-biphenyl]-2-carboxylic Acid (20m). To a solution of **32** and sulfamic acid (48.5 mg, 0.5 mmol) in 2.5 mL of THF at −10 °C was added a solution of sodium chlorite (45.2 mg, 0.5 mmol) in 2.5 mL H_2O and the mixture was stirred for 5 min. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried, and concentrated. The residue was purified by preparative HPLC on a reverse-phase 30 × 500-mm ODS S10 column (68% methanol, 32% water, 0.1% TFA) to afford **20m** (32 mg, 30%) as a white solid: mp >185 °C. ^{1}H NMR (1:1 $CDCl_3$/CD_3OD): δ 0.97 (d, J = 6 Hz, 6H), 1.70 (s, 3H), 1.95 (m, 1H), 2.15 (s, 3H), 2.57 (d, J = 7 Hz, 2H), 6.96−8.00 (m, 7H). ^{13}C NMR (1:1 $CDCl_3$/CD_3OD): δ 5.47, 9.74, 21.51, 29.58, 44.32, 105.00, 126.96, 128.03, 129.50, 130.07, 130.25, 131.23, 131.92, 136.94, 137.34, 141.00, 141.29, 161.40, 168.64. Anal. ($C_{22}H_{24}N_2O_5S\cdot0.50H_2O$) C, H, N, S.

2′-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4′-(2-methylpropyl)[1,1′-biphenyl]-2-carboxamide (20n). Oxidation of **31** using sulfamic acid and sodium chlorite as described for **20m** provided the 2′-carboxy derivative which was converted into the corresponding acid chloride using oxalyl chloride. Treatment of this material with 30% aqueous ammonium hydroxide in THF followed by deprotection of the MEM group using 6 N aqueous HCl provided **20n** as a white solid: mp 85−93 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 6H), 1.87 (s, 3H), 1.90 (m, 1H), 2.17 (s, 3H), 2.53 (d, J = 7 Hz, 2H), 6.26 (s, 2H), 7.24−8.70 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.35, 10.44, 21.98, 22.07, 29.62, 44.56, 107.15, 127.58, 128.04, 128.38, 130.11, 130.23, 131.59, 132.54, 134.12, 134.30, 137.56, 139.29, 141.85, 154.83, 161.55, 172.08. Anal. ($C_{22}H_{25}N_3O_4S$) C, H, N, S.

3-Isobutylanisole (22). To a flask containing 200 mL of ether at 0 °C under argon was added a solution of 2.0 M butyllithium in pentane (56 mL). Isopropyltriphenylphosphonium iodide (48.2 g, 0.11 mol) was then added to the mixture in portions over 15 min, and the mixture was warmed to room temperature and stirred for 3 h. The solution was cooled to −78 °C, and a solution of 3-methoxybenzaldehyde (15.5 g, 0.11 mol) in 100 mL of ether was added dropwise over 30 min. The mixture was slowly warmed to room temperature and stirred for 48 h. The mixture was filtered, and the solid cake was washed with 200 mL of ether. The combined filtrate was washed with 2 × 150 mL of water, dried, and evaporated. The residual liquid was distilled in vacuo to provide 13.1 g of 3-(2-methyl-1-propenyl)anisole as a colorless liquid: bp 95−97 °C (10 mmHg). This compound was then dissolved in 200 mL of ethyl acetate, and the solution was added to a suspension of 10% Pd/C (1 g) in 20 mL of ethyl acetate under argon. The mixture was hydrogenated at 50 psi for 12 h and filtered. The filtrate was evaporated, and the residual liquid was distilled in vacuo to provide 11.1 g (59%) of compound **22** as a colorless liquid: bp 87−88 °C (10 mmHg). ^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.5 Hz, 6H), 1.85 (m, 1H), 2.44 (d, J = 7.0 Hz, 2H), 3.79 (s, 3H), 6.70−7.25 (m, 4H).

4-Isobutyl-2-methoxyphenylboronic Acid (23). To a solution of **22** (4.0 g, 24.3 mmol) in 100 mL of ether under argon at −78 °C was added TMEDA (11.0 mL, 73.0 mmol) followed by *tert*-butyllithium (1.7 M solution in pentane, 43 mL) over 5 min. The mixture was warmed to room temperaure and stirred for 5 h. The solution was cooled to −78 °C, and trimethyl borate (7.59 g) was added in one portion. The mixture was slowly warmed to room temperature, stirred overnight, and cooled to 0 °C; 20% aqueous HCl (250 mL) was added, and the mixture was stirred for 10 min. The solution was extracted with ether (2 × 200 mL), and the combined ether extracts were extracted with 1 M NaOH (3 × 100 mL). A white precipitate was formed which was found to be the sodium salt of **23**. This was filtered and added to the aqueous NaOH extracts. The aqueous extracts were acidified with dilute HCl to pH 2 and extracted with 2 × 200 mL of ether. The combined ether extracts were washed once with water (100 mL), dried, and evaporated to afford 4.3 g of a white solid. Crystallization from hexanes provided 2.13 g (42%) of pure **23** as a white solid in two crops: mp 68−75 °C.

4′-(2-Methylpropyl)-2′-methoxy-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-(methoxyethoxymethyl)[1,1′-biphenyl]-2-sulfonamide (24). This compound was prepared from **4** and **23** using a Suzuki coupling procedure described for **19**: yield 67%.

4′-(2-Methylpropyl)-2′-methoxy-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (25). To a solution of 1.40 g (2.78 mmol) of **24** in 20 mL of 95% EtOH was added 20 mL of 6 N aqueous HCl and the mixture was refluxed for 3 h. The mixture was concentrated to 20 mL, diluted with 50 mL of water, and extracted with 3 × 50 mL of EtOAc. The combined organic extracts were washed once with 100 mL of brine, dried, and evaporated to provide a white foam (1.13 g). Crystallization from hexanes/EtOAc afforded 1.03 g (89%) of **25** as a white crystalline solid: mp 143−144 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 6.5 Hz, 6H), 1.86 (s, 3H), 1.93(m, 1H), 2.15 (s, 3H), 2.52 (d, J = 7.0 Hz, 2H), 3.75 (s, 3H), 6.80 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.59, 10.71, 22.37, 30.06, 45.47, 56.09, 107.26, 112.82, 121.55, 125.81, 127.80, 128.66, 130.19, 132.92, 133.01, 137.93, 138.31, 144.01, 154.87, 156.31. Anal. ($C_{22}H_{26}N_2O_4S\cdot0.38H_2O$) C, H, N, S.

4′-(2-Methylpropyl)-2′-hydroxy-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (26). To a solution of 0.3 g (0.72 mmol) of **25** in 25 mL of dry CH_2Cl_2 at −78 °C under argon was added 1.1 mL of 1M BBr_3 in CH_2Cl_2. The mixture was stirred for 3 h, slowly warmed to room temperature, and stirred overnight. The solution was diluted with 50 mL of CH_2Cl_2, washed with 2 × 100 mL of water, dried, and evaporated. The residue was chromatographed on silica gel using 1% MeOH/CH_2Cl_2 to provide 0.18 g (62%) of **26** as a white foam. Crystallization from hexanes/EtOAc afforded analytically pure **26** as colorless prisms: mp 175 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6.5 Hz, 6H), 1.87 (s, 3H), 1.93(m, 1H), 2.14 (s, 3H), 2.46 (d, J = 7.6 Hz, 2H), 6.71 (br s, 1H), 6.82 (s, 1H), 6.83 (d, J = 7.0 Hz, 1H), 7.22 (t, J = 8.2, 9.4 Hz, 1H), 7.40 (d, J = 7.0 Hz, 1H), 7.47 (t, J = 7.6, 7.0 Hz, 1H), 7.65 (t, J = 7.6, 6.5 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.65, 10.80, 22.43, 29.95, 45.12, 108.45, 118.09, 121.95, 123.77, 128.55, 129.01, 130.50, 133.61, 136.67, 138.83, 144.73, 152.62, 154.29, 162.04. Anal. ($C_{21}H_{24}N_2O_4S\cdot0.46H_2O$) C, H, N, S

3-(2-Methylpropyl)phenylmethanol (28). To a solution of isobutylene (4.4 g, 78 mmol) in 11 mL of tetrahydrofuran at −78 °C was added 9-BBN (0.5 M in tetrahydrofuran, 157 mL, 78 mmol). The mixture was stirred at −78 °C for 3 h, warmed to room temperature, and stirred overnight. In a separate flask containing 3-bromobenzyl alcohol (13.3 g, 71.3 mmol) in 36 mL of tetrahydrofuran were added tetrakis-(triphenylphosphine)palladium(0) (2.47 g, 2.14 mmol) and 60 mL of 3 M sodium hydroxide. The 9-isobutyl-BBN solution

was transferred quickly into the flask under argon, and the mixture was refluxed for 21 h. After cooling with an ice bath, 18 mL of 30% hydrogen peroxide was added slowly; the mixture was stirred for 30 min, concentrated to about 100 mL, and partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel using 9:1 hexanes/ethyl acetate to afford **28** (8.16 g, 70%) as a liquid.

1,3-Dihydro-1-hydroxy-5-(2-methylpropyl)-2,1-benzoxaborole (29). **29** was prepared as a light-yellow solid from **28** as described for **23**: mp 96−100 °C. ^{1}H NMR (DMSO-d_6): δ 0.86 (d, J = 6.4 Hz, 6H), 1.84 (m, 1H), 2.49 (d, J = 7.0 Hz, 2H), 4.95 (s, 2H), 7.13 (s, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 9.09 (br s, 1H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]-2′-(hydroxymethyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (30).** **30** was prepared from **4** and **29** as described for **19**. Chromatography on silica gel using 2.5:1 hexanes/ethyl acetate afforded **30** as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 6.5 Hz, 6H), 1.93 (s, 3H), 1.93-(m, 1H), 2.15 (s, 3H), 2.55 (d, J = 7.1 Hz, 2H), 3.30 (s, 3H), 3.45 (m, 2H), 3.90 (m, 2H), 4.02 (d, J = 11.7 Hz, 1H), 4.35 (m, 3H), 7.09−7.93 (m, 7H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]-2′-formyl-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (31).** To oxalyl chloride (2 M in methylene chloride, 9 mL, 18 mmol) in 26 mL of methylene chloride at −78 °C was added a solution of dimethyl sulfoxide (2.8 g, 36 mmol) in 39 mL of methylene chloride. The solution was stirred for 10 min, **30** (2.4 g, 4.8 mmol) in 40 mL of methylene chloride was added, and the mixture was stirred at −78 °C for 2 h. Triethylamine (6.1 g, 60 mmol) was added, and the mixture was stirred at −78 °C for 5 min and warmed to room temperature over 15 min. The mixture was partitioned between 0.5 N HCl and methylene chloride, the aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried and concentrated. The residue was chromatographed on silica gel using 3.5:1 hexanes/ethyl acetate to afford **31** (1.83 g, 77%) as a gum.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-formyl-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (32).** **32** was prepared from **31** as described for **25**, using 6 N hydrochloric acid and with refluxing for 1.5 h. Chromatography on silica gel using 2.5:1 hexanes/ethyl acetate provided **32** as an amorphous white solid: mp 60−66 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 7.0 Hz, 6H), 1.82 (s, 3H), 1.99 (m, 1H), 2.14 (s, 3H), 2.59 (d, J = 7.6 Hz, 2H), 7.26−8.03 (m, 7H), 9.68 (s, 1H). Anal. ($C_{22}H_{24}N_2O_4S\cdot 0.28H_2O$) C, H, N, S

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-(aminomethyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (33).** A mixture of **32** (480 mg, 1.16 mmol), ammonium acetate (15.44 g, 232 mmol), and 3A molecular sieves in 60 mL of MeOH was stirred overnight. Sodium triacetoxyborohydride (740 mg, 3.49 mmol) was added, and the mixture was stirred for 1 h, concentrated to about 30 mL, diluted with 150 mL CH_2Cl_2, and filtered. The filtrate was washed with 25 mL of H_2O, dried, and concentrated. The residue was chromatographed on silica gel using 100:6 CH_2Cl_2/MeOH to provide **33** (250 mg, 52%) as a white solid: mp >200 °C dec. ^{1}H NMR (DMSO-d_6): δ 0.93 (d, J = 6 Hz, 6H), 1.54 (s, 3H), 1.91 (m, 4H), 2.50 (m, 2H), 3.64 (m, 2H), 6.93−8.00 (m, 10H). ^{13}C NMR (DMSO-d_6): δ 6.51, 10.37, 22.17, 29.34, 44.26, 90.68, 127.45, 127.57, 127.77, 129.15, 129.53, 130.33, 130.59, 131.40, 136.64, 138.60, 140.01, 145.45, 159.10, 165.73. Anal. ($C_{22}H_{27}N_3O_3S\cdot 0.26H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-(formylaminomethyl)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (34).** To a solution of **33** (48 mg, 0.12 mmol) in 0.5 mL of CH_2Cl_2 was added acetic formic anhydride (41 mg, 0.47 mmol) followed by Et_3N (47 mg, 0.47 mmol). The mixture was stirred at room temperature overnight, diluted with 30 mL of CH_2Cl_2, washed with 5 mL of 0.2 N HCl and 0.5 mL H_2O, dried, and concentrated. The residue was chromatographed on silica gel using 100:2.5 CH_2Cl_2/MeOH to afford **34** as a white solid: mp 78−83 °C. ^{1}H NMR ($CDCl_3$): δ 0.92 (m, 6H), 1.86 (m, 1H), 1.89 (s, 3H), 2.16 (s, 3H), 2.49 (d, J = 7 Hz, 2H), 3.76−4.62 (m, 2H), 6.53−8.05 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 8.08, 12.23, 23.77, 23.85, 31.50, 41.19, 46.50, 109.75, 129.19, 129.45, 129.80, 130.61, 130.89, 134.12, 134.79, 136.29, 137.79, 139.29, 140.73, 144.45, 155.55, 162.71, 163.46. Anal. ($C_{23}H_{27}N_3O_4S\cdot 0.36H_2O$) C, H, N, S.

2-Bromobenzenesulfonic Acid, Isopropyl Ester (36). To a solution of 990 mg (16.5 mmol) of 2-propanol and 2.48 g (31.4 mmol) of pyridine cooled to −5 °C was added in one portion 4.00 g (15.7 mmol) of 2-bromobenzenesulfonyl chloride. The mixture became homogeneous after several minutes, and a precipitate formed. The mixture was stirred at 0 °C for 5 h and partitioned between 20 mL of methylene chloride and 20 mL of 1 M aqueous HCl solution. The aqueous layer was separated and extracted with an additional 20 mL of methylene chloride. The combined organic layers were washed with two 15-mL portions of 1 M aqueous HCl solution, dried, and concentrated in vacuo to give 4.10 g (14.7 mmol, 94%) of **36** as a colorless oil which solidified upon cooling in a refrigerator.

4′-(2-Methylpropyl)[1,1′-biphenyl]-2-sulfonic Acid, Isopropyl Ester (37). Suzuki coupling between **36** and 4-isobutylbenzeneboronic acid as described for **19** provided **37** (22%) as a pale-yellow oil.

3-Methyl-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonic Acid, Isopropyl Ester (38). To a solution of 910 mg (2.74 mmol) of **37** in 4 mL of THF cooled to −78 °C was added dropwise 2.0 mL (1.6 M in hexanes, 3.2 mmol) of *n*-butyllithium over 5 min. The yellow anion solution was warmed to −65 °C and stirred for 7 h, and 0.35 mL (5.6 mmol, filtered through basic alumina) of iodomethane was added. The mixture was stirred at −65 °C for 5 min and at 0 °C for 45 min. The resulting solution was quenched by addition of 25 mL of water and extracted with two 20-mL portions of ethyl acetate. The organic extracts were combined, dried (magnesium sulfate), and concentrated in vacuo to a yellow oil. TLC and HPLC analysis indicated the crude material was ∼1:1 starting material/product. The crude oil was purified by flash chromatography (silica, 1:20 ethyl acetate/hexane) to afford 303 mg (0.88 mmol, 32%) of **38** as a colorless oil.

***N*-(3,4-Dimethyl-5-isoxazolyl)-3-methyl-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (40).** A mixture of 298 mg (0.86 mmol) of **38**, 2.5 mL of methanol, 1 mL of THF, and 2.5 mL of 1 M aqueous NaOH solution was stirred at room temperature for 18 h. The mixture was heated to 60 °C for 20 h, cooled to room temperature, added to 25 mL of 6 N aqueous HCl solution, and extracted with two 20-mL portions of methylene chloride. The organic extracts were combined, dried, and concentrated in vacuo to give a dark oil. The oil was solubilized in 20 mL of methylene chloride, washed with two 25-mL portions of 6 N aqueous HCl solution, dried, and concentrated in vacuo to give 241 mg (0.79 mmol, 92%) of crude sulfonic acid as a dark oil. To a solution of 235 mg (0.77 mmol) of the sulfonic acid in 2 mL of anhydrous ether was added at room temperature 31 mg (60% in oil, 0.77 mmol) of sodium hydride dispersion. The mixture was stirred for 10 min and concentrated in vacuo to give the sodium salt as a white solid. To the crude sodium salt was added 482 mg (2.31 mmol) of phosphorus pentachloride. The two solids were mixed with a glass rod, and the mixture turned yellow-brown. After 10 min the mixture was heated to 90° for 1 h during which time the solids melted. The resulting mixture was cooled to room temperature, quenched by the addition of 20 g of ice, and extracted with two 15-mL portions of methylene chloride. The organic extracts were combined, dried (sodium sulfate), and concentrated in vacuo to give crude **39** as a brown-yellow oil. The crude **39** was solubilized in 2 mL of pyridine, and 130 mg (1.16 mmol) of 5-amino-3,4-dimethylisoxazole was added at room temperature. The mixture was heated to 70 °C for 4 h, cooled to room temperature, and concentrated in vacuo and the residue partitioned between 20 mL of 3 N aqueous HCl solution and 20 mL of ethyl acetate. The organic layer was separated, dried, and concentrated in vacuo to give a dark oil.

The crude material was purified by flash chromatography (silica, 1:3 ethyl acetate/hexane) to afford 25 mg (0.063 mmol, 8%) of **40** as an oil. ^{1}H NMR ($CDCl_3$): δ 0.92 (d, J = 6.5 Hz, 6H), 1.78 (s, 3H), 1.93 (m, 1H), 2.13 (s, 3H), 2.51 (d, J = 7.0 Hz, 2H), 2.66 (s, 3H), 7.18−7.41 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.50, 10.74, 22.34, 23.12, 30.06, 45.06, 107.84, 128.83, 129.38, 130.94, 131.54, 132.43, 137.62, 138.77, 141.88, 142.02, 154.40, 161.72. MS (HR): calcd for $C_{22}H_{27}O_3N_2S$, 399.1728; found, 399.1742.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-4-(phenylmethoxy)[1,1′-biphenyl]-2-sulfonamide (40a). a. Sodium 3-(Phenylmethoxy)benzenesulfonate.** A solution of 3-hydroxybenzenesulfonic acid (10.0 g, 57.4 mmol) in water (80 mL) was adjusted to pH 12 with 5 N aqueous NaOH. Benzyl bromide (7.2 mL, 60 mmol) was added dropwise to the vigorously stirred solution. After the mixture stirred for 18 h, ca. 50 mL of the water was removed in vacuo. The residue was chilled to 4 °C, and then the precipitate was collected by filtration, washed with ice water, and dried to provide a white solid (11.2 g, 68%). ^{1}H NMR (CD_3OD): δ 5.11 (s, 2H), 7.04−7.08 (m, 1H), 7.24−7.48 (m, 8H).

b. *N*-(3,4-Dimethyl-5-isoxazolyl)-2-bromo-5-(phenylmethoxy)benzenesulfonamide. A solution of bromine (2.24 g, 14.0 mmol) in water (60 mL) was added dropwise to a stirred solution of sodium 3-(phenylmethoxy)benzenesulfonate (4.00 g, 14.0 mmol) in water (25 mL) and THF (15 mL) at 0 °C. After the mixture stirred for 2 h, the pH of the reaction was brought to 8.5 with 0.5 N aqueous sodium carbonate, excess bromine was discharged with sodium bisulfite, and the reaction was concentrated in vacuo to provide a solid. To this solid was added phosphorus pentachloride (5.82 g, 27.9 mmol). An exotherm ensued and the mixture liquified. After the exotherm subsided, the mixture heated at 50 °C for 1 h and cooled to room temperature. The resultant paste was mixed with crushed ice. After the ice had melted, the mixture diluted with water (25 mL) and was extracted with ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The brownish solid (4 g) thus obtained was dissolved in pyridine (10 mL). Isoxazole **2** (1.6 g, 14 mmol) and DMAP (0.27 g, 2.2 mmol) were added. After 2 h at room temperature the pyridine was removed in vacuo. The residue was partitioned between ether (250 mL) and 0.5 N HCl (250 mL). The aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were washed with 0.5 N HCl (2 × 50 mL). The acid washings and original acid layer were combined, and the whole was extracted with methylene chloride (2 × 100 mL). The methylene chloride and ether extracts were dried and concentrated in vacuo. Chromatography (silica, ethyl acetate/hexanes) provided 361 mg (7%) of the product as a foam. ^{1}H NMR ($CDCl_3$): δ 1.89 (s, 3H), 2.16 (s, 3H), 5.04 (s, 2H), 7.03 (dd, J = 9, 3 Hz, 1H), 7.38−7.40 (m, 5H), 7.61−7.65 (m, 2H).

c. *N*-(3,4-Dimethyl-5-isoxazolyl)-*N*-((2-methoxyethoxy)methyl)-2-bromo-5-(phenylmethoxy)benzenesulfonamide. Treatment of the preceding sulfonamide with sodium hydride in THF followed by treatment with methoxyethoxymethyl chloride as described in **4** yielded 614 mg (79%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 2H), 2.17 (s, 3H), 3.37 (s, 3H), 3.55−3.59 (m, 2H), 3.89−3.92 (m, 2H), 3.89−3.92 (m, 2H), 5.03 (s, 2H), 5.27 (s, 2H), 7.00 (dd, J = 9, 3 Hz, 1H), 7.35−7.39 (m, 5H), 7.58−7.63 (m, 2H).

d. *N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)-4-(phenylmethoxy)[1,1′-biphenyl]-2-sulfonamide (40a). This compound was prepared from the preceding sulfonamide and 4-isobutylphenylboronic acid using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **40a** as a white powder (52%): mp 96.0−101.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 7 Hz, 6H), 1.80−1.95 (m, 1H), 1.83 (s, 3H), 2.13 (s, 3H), 2.52 (d, J = 7 Hz, 2H), 5.09 (s, 2H), 5.77 (br s, 1H), 7.15−7.48 (m, 11H), 7.59 (d, J = 3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.6, 10.8, 22.4, 30.1, 45.1, 70.5, 108.3, 114.5, 119.6, 127.6, 128.3, 128.7, 128.9, 130.2, 133.3, 133.9, 135.4, 136.0, 138.9, 142.1, 154.0, 157.7, 161.9. Anal. ($C_{28}H_{30}N_2O_4S\cdot 0.17H_2O$) C, H, N, S.

4-Hydroxy-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40b). Treatment of the corresponding 4-methoxy derivative (prepared using a similar procedure described for **40a**) with boron tribromide in methylene chloride as described for **26** provided a white foam which was recrystallized from ethyl acetate/hexanes to afford **40b** (86%) as white crystals: mp 159.5−160.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 7 Hz, 6H), 1.73 (s, 3H), 1.85−1.95 (m, 1H), 2.13 (s, 3H), 2.51 (d, J = 7 Hz, 2H), 7.03 (dd, J = 8, 2 Hz, 1H), 7.13−7.17 (m, 3H), 7.27 (d, J = 8 Hz, 2H), 7.49 (d, J = 2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.4, 10.6, 22.4, 30.3, 45.3, 106.2, 115.6, 120.1, 128.5, 130.1, 132.5, 134.4, 136.5, 138.7, 141.3, 156.5, 162.0. Anal. ($C_{21}H_{24}N_2O_4S\cdot 0.62H_2O$) C, H, N, S.

5-Methoxy-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40c). a. *N*-(3,4-Dimethyl-5-isoxazolyl)-2-bromo-4-methoxybenzenesulfonamide. To chlorosulfonic acid (10 mL) held at 0 °C was added, dropwise, 3-bromoanisole (9.3 g, 50 mmol) at such a rate that the internal temperature remained below 5 °C. After stirring at 0 °C for 2 h, the reaction was added to ice. The mixture was extracted with methylene chloride, and the combined organic layers were dried and concentrated in vacuo. The residue (756 mg), a colorless oil, was dissolved in dry pyridine (5 mL) along with 3,4-dimethyl-5-isoxazolamine (386 mg, 3.44 mmol) and 4-(dimethylamino)pyridine (65 mg, 0.53 mmol). The mixture was heated at 70 °C for 2 h. The reaction was then cooled to room temperature and poured into water. The pH of the mixture was adjusted to 8 with saturated aqueous sodium bicarbonate, and the mixture was extracted with ether (2 × 50 mL). The aqueous layer was brought to pH 2 with 6 N HCl and was extracted with ether (3 × 30 mL). The extracts were combined, dried, and concentrated in vacuo to provide a mixture of the title compound and the regiomeric *N*-(3,4-dimethyl-5-isoxazolyl)-4-bromo-2-methoxy sulfonamide as a tan foam. Chromatography (silica, methanol/chloroform) provided pure *N*-(3,4-dimethyl-5-isoxazolyl)-2-bromo-4-methoxybenzenesulfonamide (288 mg, 30%). ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 2.13 (s, 3H), 3.85 (s, 3H), 6.85 (dd, J = 9, 3 Hz, 1H), 7.24 (d, J = 3 Hz, 1H), 7.89 (d, J = 9 Hz, 1H).

b. *N*-(3,4-Dimethyl-5-isoxazolyl)-*N*-(methoxyethoxymethyl)-2-bromo-4-methoxybenzenesulfonamide. Treatment of the preceding sulfonamide with sodium hydride in THF followed by treatment with methoxyethoxymethyl chloride as described in **4** provided the title compound as an oil (88%). ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.16 (s, 3H), 3.38 (s, 3H), 3.56−3.59 (m, 2H), 3.85 (s, 3H), 3.90−3.93 (m, 2H), 5.29 (s, 2H), 6.82 (dd, J = 9, 2 Hz, 1H), 7.24 (d, J = 2 Hz, 1H), 7.86 (d, J = 9 Hz, 1H).

c. 5-Methoxy-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40c). This compound was prepared from the preceding sulfonamide and 4-isobutylphenylboronic acid using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **40c** as a colorless foam (160 mg, 66%). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.88 (d, J = 9 Hz, 1H), 7.46−7.49 (m, 2H), 7.26 (m, 1H), 7.24 (d, J = 3 Hz, 1H), 6.85−6.90 (m, 2H), 5.73 (br s, 1H), 3.86 (s, 3H), 2.53 (d, J = 7 Hz, 2H), 2.13 (s, 3H), 1.85−1.92 (m, 1H), 1.84 (s, 3H), 0.94 (d, J = 7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 162.7, 161.9, 154.4, 143.3, 142.2, 135.7, 131.2, 129.6, 128.8, 118.1, 112.5, 108.0, 55.7, 45.1, 30.1, 22.4, 10.8, 6.6. Anal. ($C_{22}H_{26}N_2O_4S\cdot 0.11H_2O$) C, H, N, S.

5-Amino-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40d). a. 2-Bromo-4-[(1-oxoethyl)amino]-*N*-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide. To 3-bromo-1-(oxoethyl)aniline (6.2 g, 29 mmol) was added chlorosulfonic acid (20 mL). The solution was heated at 57 °C for 3 h, an additional 10 mL of chlorosulfonic acid was added, and the solution was heated at 67 °C for 6 h. The mixture was added dropwise to ice water, and the heterogeneous mixture was extracted with ethyl acetate. The organic extract was washed once with brine, dried, and

evaporated to afford 6.9 g (82%) of the crude sulfonyl chloride as a brown foamy gum. A solution of this material (6.9 g, 22 mmol) was treated with 3,4-dimethyl-5-isoxazolamine (**2**) (3.96 g, 35.3 mmol) and 4-(dimethylamino)pyridine (0.42 g, 3.5 mmol) as described in **40a**, step b, to afford 3.72 g (43%) of the product as a yellow foam.

b. 2-Bromo-4-[(1-oxoethyl)amino]-*N*-(methoxyethoxymethyl)-*N*-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide. Treatment of the preceding sulfonamide with sodium hydride in THF followed by treatment with methoxyethoxymethyl chloride as described in **4** yielded the product as a yellow foamy gum.

c. 5-Amino-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40d). This compound was prepared from the preceding sulfonamide and 4-isobutylphenylboronic acid using a Suzuki coupling procedure described for **6a** followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **40d** as a white foamy solid: mp 69−79 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6.4 Hz, 6H), 1.82 (s, 3H), 1.90 (m, 1H), 2.11 (s, 3H), 2.52 (d, J = 7 Hz, 2H), 4.20 (br s, 2H), 5.82 (s, 1H), 6.53 (m, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.59, 10.74, 22.37, 30.06, 45.09, 107.14, 112.25, 117.83, 126.21, 128.60, 129.47, 131.22, 136.06, 141.88, 143.18, 150.55, 154.69, 161.78. Anal. ($C_{21}H_{25}N_3O_3S\cdot0.16H_2O$) C, H, N, S.

5-Acetamido-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40e). Acetylation of **40d** provided **40e** as a tan solid: mp 150−154 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6.8 Hz, 6H), 1.85 (s, 3H), 1.94 (m, 1H), 2.11 (s, 3H), 2.17 (s, 3H), 2.51 (d, J = 6.8 Hz, 2H), 5.70 (s, 1H), 5.82 (s, 1H), 7.30 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 7.7 Hz, 2H), 7.57 (m, 1H), 7.64 (m, 1H), 7.87 (d, J = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.54, 10.69, 22.33, 25.0, 30.04, 45.04, 117.37, 122.62, 128.45, 128.61, 128.69, 129.49, 130.13, 131.82, 131.96, 135.35, 142.13, 142.18, 155.0, 162.5. Anal. ($C_{23}H_{27}N_3O_4S\cdot0.95H_2O$) C, H, N, S.

5-Benzamido-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40f). Benzoylation of **40d** using benzoyl chloride and triethylamine in THF provided **40e** as a tan solid: mp 207−211 °C. ^{1}H NMR (DMSO-d_6): δ 0.91 (d, J = 6.6 Hz, 6H), 1.60 (s, 3H), 1.90 (m, 1H), 2.08 (s, 3H), 2.50 (d, J = 6.8 Hz, 2H), 7.15−8.0 (m, 12H). ^{13}C NMR (DMSO-d_6): δ 6.36, 10.65, 22.57, 29.99, 44.70, 118.57, 123.73, 128.12, 128.34, 128.46, 128.85, 129.00, 130.36, 132.42, 134.57, 135.93, 137.00, 143.04, 162.18, 165.98. Anal. ($C_{28}H_{29}N_3O_4S\cdot1.15H_2O$) C, H, N, S.

5-[(Carboxymethyl)amino]-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40g): mp 73−78 °C; prepared similar to the procedure described for **20a** from **40d** and glyoxylic acid. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 6.6 Hz, 6H), 1.84 (s, 3H), 1.90 (m, 1H), 2.14 (s, 3H), 2.54 (d, J = 7.2 Hz, 2H), 6.40 (m, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.7 Hz, 1H). Anal. ($C_{23}H_{27}N_3O_5S\cdot0.4C_6H_{14}\cdot0.6AcOH\cdot0.2CHCl_3$) C, H, N.

5-[(Aminoacetyl)amino]-4′-(2-methylpropyl)-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide (40h). This compound was prepared from **40d** by treatment with the acid chloride of BOC-glycine in the presence of triethylamine followed by deprotection of the BOC group using 10% concentrated HCl in formic acid: mp 135−138 °C. ^{1}H NMR (CD_3OD): δ 0.93 (d, J = 6.6 Hz, 6H), 1.67 (s, 3H), 1.85 (m, 1H), 2.10 (s, 3H), 2.53 (d, J = 6.8 Hz, 2H), 3.87 (s, 2H), 7.13−8.06 (m, 7H). Anal. ($C_{23}H_{28}N_4O_4S\cdot1.45H_2O\cdot1.5CF_3COOH$) C, H, N, S.

***N*-(1,1-Dimethylethyl)-3-methoxybenzenesulfonamide (42).** 3-Hydroxybenzenesulfonic acid (10.0 g, 57.4 mmol) was dissolved in water (20 mL) and brought to pH 14 with 5 N sodium hydroxide solution. The mixture was cooled to 0 °C, and dimethyl sulfate (2.9 mL, 30.1 mmol) was added dropwise over a 5-min period. The mixture was brought to room temperature and heated to 85 °C. Additional dimethyl sulfate was added in 2.9-mL portions every 2 h until no starting material remained. The mixture was cooled to room temperature, brought to pH 7, concentrated in vacuo to ca. 20 mL, and cooled to 0 °C. The precipitate was collected by filtration, washed with ice water, and dried in vacuo to provide sodium 3-methoxybenzenesulfonate as an off-white solid (9.50 g, 79%). To this compound was added, portionwise, phosphorus pentachloride (18.9 g, 90.4 mmol). The reaction was exothermic and the mixture liquified. The mixture was stirred at room temperature for 2 h, poured onto crushed ice (200 g), diluted with water (200 mL), and extracted with ether (3 × 150 mL). The combined ether layers were washed with cold water (8 × 50 mL), dried, and concentrated in vacuo to an oil (7.00 g, 75%). This oil was dissolved in chloroform (50 mL) and was added dropwise to a solution of *tert*-butylamine (10.0 mL, 95.2 mmol) in chloroform (50 mL) at 0 °C. The mixture was stirred for 22 h and was filtered through Celite. The pad was rinsed with chloroform (2 × 10 mL), the combined filtrates were concentrated, and the residue was purified on a silica column using hexanes/EtOAc to afford 7.00 g (85%) of **42** as white crystals. ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 9H), 3.85 (s, 3H), 4.96 (br s, 1H), 6.61−6.65 (m, 1H), 6.84 (t, J = 8 Hz, 1H), 7.49−7.53 (m, 1H), 7.58 (t, J = 2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 30.1, 54.7, 55.6, 111.6, 118.5, 119.1, 129.9, 144.6, 159.7.

2-Bromo-*N*-(1,1-dimethylethyl)-3-methoxybenzenesulfonamide (43). To a suspension of **42** (7.00 g, 28.8 mmol) in ether (100 mL) at 0 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 24 mL) so as to keep the internal temperature below 6 °C. The mixture was stirred for 1 h at which time the mixture was homogeneous. 1,2-Dibromo-1,1,2,2-tetraflouroethane (4.13 mL, 34.6 mmol) was added dropwise over a 15-min period. The mixture was stirred at 0 °C for 2 h and was quenched by the addition of 1 N HCl (75 mL). The mixture was diluted with methylene chloride (200 mL) and water (100 mL). The organic phase was washed with water (100 mL), dried, and concentrated in vacuo. The residue was crystallized from ether to provide 2.39 g (80%) of **43**. ^{1}H NMR ($CDCl_3$): δ 1.02 (s, 9H), 3.12 (s, 3H), 6.23 (dd, J = 8, 1 Hz, 1H), 6.79 (t, J = 8 Hz, 1H), 7.90 (dd, J = 8, 1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 29.6, 54.7, 56.7, 105.7, 115.0, 122.2, 128.3, 143.6, 156.7.

***N*-(1,1-Dimethylethyl)-4′-(2-methylpropyl)-6-methoxy[1,1′-biphenyl]-2-sulfonamide (44).** Suzuki coupling between **43** and 4-isobutylbenzeneboronic acid as described for **19** provided **44** (74%). ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 7 Hz, 6H), 1.04 (s, 9H), 1.84−1.99 (m, 1H), 2.53 (d, J = 8 Hz, 2H), 3.31 (br s, 1H), 3.74 (s, 3H), 7.13−7.49 (m, 6H), 7.79 (m, 1H).

4′-(2-Methylpropyl)-6-methoxy[1,1′-biphenyl]-2-sulfonic Acid, Sodium Salt (45). Compound **44** (2.07 g, 5.51 mmol) was dissolved in TFA (15 mL). The mixture was allowed to stand at room temperature for 2 h, concentrated in vacuo, and chromatographed (flash, silica, 80% methylene chloride/hexanes) to provide 4′-(2-methylpropyl)-6-methoxy[1,1′-biphenyl]-2-sulfonamide (1.56 g, 89%). A solution of NO_2 in carbon tetrachloride (6.8 M, 2.2 mL) was diluted with additional carbon tetrachloride (3 mL), and this solution was added dropwise to a solution at −20 °C of the sulfonamide (1.55 g, 4.85 mmol) in acetonitrile over a 20-min period. The mixture was allowed to stir for 30 min, and most of the solvent was removed in vacuo. The brown residue was partitioned between 2 N NaOH (10 mL) and ether (25 mL). The aqueous layer was brought to pH 2 with 1 N HCl and was loaded onto a 10-g acetonitrile-activated, water-equilibrated Waters t-C18 SepPak cartridge. The cartridge was eluted with water (20 mL) and then with acetonitrile (20 mL). The acetonitrile eluent was concentrated in vacuo to provide 1.55 g (93%) of **45** as a solid. ^{1}H NMR (CD_3OD): δ 0.95 (d, J = 8 Hz, 6H), 1.83−1.98 (m, 1H), 2.48 (d, J = 8 Hz, 2H), 3.65 (s, 3H), 7.01−7.30 (m, 5H), 7.31−7.39 (m, 1H), 7.68−7.84 (m, 1H). ^{13}C NMR (CD_3OD) δ 23.0, 31.4, 46.5, 56.6, 114.4, 121.0, 128.7, 131.2, 131.5, 134.9, 140.8, 145.7, 159.3.

***N*-(3,4-Dimethyl-5-isoxazolyl)-6-methoxy-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (46).** Compound **45** (1.63 g, 4.76 mmol) was mixed with phosphorus pentachloride (1.98 g, 9,52 mmol). Once the exotherm had subsided, the

reaction was placed in a 50 °C bath for 2 h. The mixture was cooled to room temperature and diluted with ice (10 g). After the ice had melted, the water was decanted from the organic gum. The gum was further rinsed with water (10 mL) and was dissolved in ether (75 mL). The organic layer was washed with water (6 × 10 mL), and was dried (Na_2SO_4), and concentrated in vacuo. The brown residue was extracted with hot hexanes, and the combined hexanes extracts were concentrated in vacuo to provide 1.34 g of 4′-(2-methylpropyl)-6-methoxy-[1,1′-biphenyl]-2-sulfonyl chloride. 3,4-Dimethyl-5-isoxazolamine (413 mg, 3.68 mmol) and DMAP (75 mg, 0.61 mmol) were sequentially added to a solution of the above compound (1.04 g, 3.07 mmol) in pyridine (8 mL). The mixture was heated at 80 °C for 2 h, cooled, and poured into 0.5 N Na_2CO_3 (150 mL). The mixture was extracted with ether (50 mL). A precipitate formed which was collected by filtration. The aqueous layer of the biphasic filtrate was washed with ether (2 × 50 mL). The combined organic layers were washed with 0.5 N Na_2CO_3 (2 × 15 mL) and discarded. The combined aqueous layers were brought to pH 2 with HCl and were extracted with ether (2 × 50 mL). The precipitate was dissolved in methanol (5 mL), and the solution was poured into 0.01 N HCl (100 mL). The pH was adjusted to 2, and the mixture was extracted with ether (3 × 50 mL). The ether extracts were dried and concentrated in vacuo, and the residue was chromatographed (silica, 25% ethyl acetate/hexanes) to provide **46** as a white solid (648 mg, 51%). Recrystallization from ethanol/water (2:1) provided colorless crystals: mp 175.5−176.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, J = 7 Hz, 6H), 1.70 (s, 3H), 1.89−1.94 (m, 1H), 2.14 (s, 3H), 2.50 (d, J = 7 Hz, 2H), 3.71 (s, 3H), 7.01−7.12 (m, 4H), 7.28 (d, J = 8 Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.66−7.70 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 6.6, 10.7, 22.8, 31.1, 46.1, 56.7, 106.4, 116.7, 121.5, 128.9, 129.6, 130.9, 131.6, 132.4, 141.0, 141.7, 154.5, 159.4, 162.9. Anal. ($C_{22}H_{26}N_2O_4S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-6-hydroxy-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (47).** To a solution at −78 °C of **46** (608 mg, 1.47 mmol) in methylene chloride (15 mL) was added boron tribromide (1 M in methylene chloride, 11.8 mL). The solution was allowed to come to room temperature and was stirred for 17 h. The mixture was poured onto crushed ice (100 g). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with water (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (flash, silica, 3% then 6% ethyl acetate/methylene chloride) provided a white solid which was recrystallized from toluene to provide **47** as a white powder (445 mg, 76%): mp 136.7−137.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 7 Hz, 6H), 1.86 (s, 3H), 1.87−2.14 (m, 1H), 2.15 (s, 3H), 2.55 (d, J = 7 Hz, 2H), 7.23 (dd, J = 8, 1 Hz, 1H), 7.34 (t, J = 8 Hz, 1H), 7.31−7.47 (m, 4H), 7.55 (dd, J = 8, 1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 6.7, 10.8, 22.4, 30.0, 45.2, 108.4, 120.9, 121.0, 125.9, 128.2, 129.0, 130.3, 131.1, 138.7, 143.7, 154.0, 154.5, 162.0. Anal. ($C_{21}H_{24}N_2O_4S\cdot0.28H_2O$) C, H, N, S.

[[6-[((3,4-Dimethyl-5-isoxazolyl)((2-methoxyethoxy)methyl)amino)sulfonyl]-4′-(2-methylpropyl)[1,1′-biphenyl]-2-yl]oxy]acetic Acid, Ethyl Ester (48). To a stirred suspension at 0 °C of sodium hydride (16.5 mg of 80% oil dispersion, 0.55 mmol) in THF (3 mL) was added, dropwise, a solution of **47** (200 mg, 0.500 mmol) in THF (1 mL). After 20 min, MEM-Cl (0.060 mL, 0.525 mmol) was added. The mixture was allowed to come to room temperature, and after 6 h the reaction was poured into water (25 mL). The mixture was brought to pH 2 with 1 N HCl and was extracted with ether (2 × 30 mL). The combined organic layers were dried and concentrated. The resultant oil was chromatographed (silica, 30% ethyl acetate/hexanes) to provide *N*-(3,4-dimethyl-5-isoxazolyl)-*N*-((2-methoxyethoxy)methyl)-6-hydroxy-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (149 mg, 61%). A solution of this compound (108 mg, 0.220 mmol) in dry DMF (1 mL) was added dropwise to a suspension of NaH (8.6 mg of 80% oil dispersion, 0.29 mmol) in DMF (1 mL). After hydrogen evolution ceased (ca. 15 min), ethyl bromoacetate (0.027 mL, 0.24 mmol) was added. The mixture was stirred for 1 h at room temperature and diluted with ether (40 mL), and the mixture was washed with water (5 × 10 mL), dried, and concentrated. The resultant oil (120 mg) was triturated with hexanes (1 mL) to provide **48** as a solid. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6 Hz, 6H), 1.22 (t, J = 7 Hz, 3H), 1.90 (s and m, 3H and 1H), 2.14 (s, 3H), 2.54 (d, J = 7 Hz, 2H), 3.31 (s, 3H), 3.42−3.46 (m, 2H), 3.63−3.66 (m, 2H), 4.04 (s, 2H), 4.17 (q, J = 7 Hz, 2H), 4.49 (s, 2H), 7.07 (dd, J = 8, 1 Hz, 1H), 7.21−7.38 (m, 4H), 7.32 (t, J = 8 Hz, 1H), 7.62 (dd, J = 8, 1 Hz, 1H).

[[6-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4′-(2-methylpropyl)[1,1′-biphenyl]-2-yl]oxy]acetic Acid, Dilithium Salt (49). Deprotection of the MEM group was accomplished by treatment of **48** with 6 N aqueous HCl in EtOH as described for **25**. The ester group was then hydrolyzed using aqueous 2 N KOH in methanol at 70 °C for 4 h. The crude product thus obtained was dissolved in aqueous LiOH, and chromatography of this mixture on HP-20 (gradient elution of water to acetone) provided **49**: mp >250 °C. ^{1}H NMR (CD_3OD): δ 0.94 (d, J = 6 Hz, 6H), 1.59 (s, 3H), 1.85−1.97 (m, 1H), 1.99 (s, 3H), 2.48 (d, J = 7 Hz, 2H), 4.17 (s, 2H), 7.01−7.05 (m, 3H), 7.16−7.19 (m, 2H), 7.28 (t, J = 8 Hz, 1H), 7.79 (dd, J = 8, 1 Hz, 1H). ^{13}C NMR (CD_3OD): δ 6.8, 10.7, 23.0, 31.5, 46.7, 70.6, 93.6, 117.6, 122.6, 128.3, 128.6, 131.7, 132.0, 134.6, 140.7, 146.6, 159.2, 161.7, 167.4, 176.9. Anal. ($C_{23}H_{24}Li_2N_2O_6S\cdot3.8H_2O$) C, H, N.

***N*-(3,4-Dimethyl-5-isoxazolyl)-6-(2-hydroxyethoxy)-4′-(2-methylpropyl)[1,1′-biphenyl]-2-sulfonamide (50).** To a mixture of **48** (57 mg, 0.099 mmol) and lithium borohydride (4.3 mg, 0.20 mmol) in ether (2 mL) was added methanol (0.01 mL). After 2 h, the mixture was diluted with ether (20 mL), washed with water (2 × 5 mL), dried, and concentrated to afford an oil. The oil was dissolved in ethanol (1.5 mL), and concentrated HCl (0.50 mL) was added. The mixture was heated at 70 °C for 38 h. The cooled mixture was diluted with ether (30 mL), washed with water (4 × 10 mL), dried, and concentrated to an oil. Chromatography (silica, ether) provided an oil which was triturated with hexanes to provide **50** as a white solid: mp 94.0−95.5 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 7 Hz, 6H), 1.45 (t, J = 7 Hz, 1H), 1.87−1.95 (m, 1H), 1.87 (s, 3H), 2.15 (s, 3H), 2.54 (d, J = 7 Hz, 2H), 3.66−3.71 (m, 2H), 4.00−4.04 (m, 2H), 5.71 (br s, 1H), 7.20−7.65 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.7, 10.8, 22.4, 30.1, 45.2, 61.0, 70.9, 108.5, 118.4, 121.4, 128.8, 129.0, 130.5, 130.7, 139.6, 142.3, 154.1, 157.2, 161.9. Anal. ($C_{23}H_{28}N_2O_5S$) C, H, N.

References

(1) Yanagisawa, M.; Kurihara, H.; Kimura, H.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. A Novel Potent Vasoconstrictor Peptide Produced by Vascular Endothelial Cells. *Nature* **1988**, *332*, 411−415.

(2) Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Maski, T. The Human Endothelin Family; Three Structurally and Pharmacologically Distinct Isopeptides Predicted by Three Separate Genes. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2863−2867.

(3) Doherty, A. M. Endothelin: A New Challenge. *J. Med. Chem.* **1992**, *35*, 1493−1508.

(4) Sakurai, T.; Yanagisawa, M.; Masaki, T. Molecular Characterization of Endothelin Receptors. *Trends Pharmacol. Sci.* **1992**, *13*, 103−108.

(5) Masaki, T.; Vane, J. R.; Vanhoutte, P. M. V. International Union of Pharmacology. Nomenclature of Endothelin Receptors. *Pharmacol. Rev.* **1994**, *46*, 137−142.

(6) Arai, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanashi, S. Cloning and Expression of a cDNA Encoding an Endothelin Receptor. *Nature* **1990**, *348*, 730−732.

(7) Sakurai, T.; Yanagisawa, M.; Takuwa, Y.; Miyazaki, H.; Kimura, S.; Goto, K.; Masaki, T. Cloning of a cDNA Encoding a Non-Isopeptide-Selective Subtype of the Endothelin Receptor. *Nature* **1990**, *348*, 732−735.

(8) Moreland, S.; McMullen, D. M.; Delaney, C. L.; Lee, V. G.; Hunt, J. T. Venous Smooth Muscle Contains Vasoconstrictor ET_B-Like Receptors. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 100−106.

(9) Webb, M. L.; Meek, T. D. Inhibitors of Endothelin. *Med. Res. Rev.* **1997**, *17*, 17−67.

(10) Lago, M. A.; Luengo, J. A.; Peishoff, C. E.; Elliott, J. D. Endothelin Antagonists. *Annu. Rep. Med. Chem.* **1996**, *31*, 81−90.
(11) Ishikawa, K.; Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niiyama, K.; Mase, T.; Ihara, M.; Yano, M. Cyclic Pentapeptide Endothelin Antagonists with High ET_A Selectivity. Potency- and Solubility-Enhancing Modifications. *J. Med. Chem.* **1992**, *35*, 2139−2142.
(12) Watanabe, T.; Fujino, M. TAK-044- An Endothelin Receptor Antagonist. *Cardiovasc. Drug Rev.* **1996**, *14*, 36−46.
(13) Sogabe, K.; Nirei, H.; Shoubo, M.; Nomoto, A.; Ao, S.; Notsu, Y.; Ono, T. Pharmacological Profile of FR139317, a Novel, Potent Endothelin ET_A Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 1040−1046.
(14) Cody, W. L.; Doherty, A. M.; He, J. X.; DePue, P. L.; Rapundalo, S. T.; Hingorani, G. A.; Major, T. C.; Panek, R. L.; Dudley, D. T.; Haleen, S. J.; LaDouceur, D.; Hill, K. E.; Flynn, M. A.; Reynolds, E. E. Design of a Functional Hexapeptide Antagonist of Endothelin. *J. Med. Chem.* **1992**, *35*, 3301−3303.
(15) Ishikawa, K.; Ihara, M.; Noguchi, K.; Mase, T.; Mino, N.; Saeki, T.; Fukuroda, T.; Fukami, T.; Ozaki, S.; Nagase, T.; Nishikibe, M.; Yano, M. Biochemical and Pharmacological Profile of a Potent and Selective Endothelin-B Receptor Antagonist. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4892−4896.
(16) Stein, P. D.; Hunt, J. T.; Floyd, D. M.; Moreland, S.; Dickenson, K. E. J.; Mitchell, C.; Liu, E. C.-K.; Webb, M. L.; Murugesan, N.; Dickey, J.; McMullen, D.; Zhang, R.; Lee, V. G.; Serafino, R.; Delaney, C.; Schaeffer, T. R.; Kozlowski, M. The Discovery of Sulfonamide Endothelin Antagonists and the Development of the Orally Active ETA Antagonist 5-(Dimethylamino)-*N*-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide (BMS-182874). *J. Med. Chem.* **1994**, *37*, 329−331.
(17) Stein, P. D.; Floyd, D. M.; Bisaha, S.; Dickey, J.; Girotra, R.; Gougoutas, J. Z.; Kozlowski, M.; Lee, V. G.; Liu, E. C.-K.; Malley, M. F.; McMullen, D.; Mitchell, C.; Moreland, S.; Murugesan, N.; Serafino, R.; Webb, M. L.; Zhang, R.; Hunt, J. T. Discovery and Structure−Activity Relationships of Sulfonamide ET_A-selective Antagonists. *J. Med. Chem.* **1995**, *38*, 1344−1354.
(18) Doherty, A. M.; Patt, W. C.; Edmunds, J. J.; Berryman, K.; Reisdorph, B. R.; Plummer, M.; Shahripour, A.; Lee, C.; Cheng, X.-M.; Walker, D. M.; Haleen, S.; Keiser, J. A.; Flynn, M. A.; Welch, K. M.; Hallak, H. O.; Taylor, D. G.; Reynolds, E. E. Discovery of a Novel Series of Orally Active Endothelin-A (ET_A) Receptor-Selective Antagonists. *J. Med. Chem.* **1995**, *38*, 1259−1263.
(19) Winn, M.; Tasker, A. S.; Boyd, S. A.; Jae, H.-S.; Von Geldern, T. N.; Bal, R.; Mantei, R. A.; Wu-Wong, R.; Chiou, W.; Dixon, D.; Opgenorth, T. J. Endothelin Antagonists, S. A. R. of 2,4-Diaryl-3-carboxypyrrolidine-1-acetamides. In 210th National Meeting of the American Chemical Society, Chicago, IL, 1995; Medi 030.
(20) Clozel, M.; Breu, V.; Gray, G. A.; Kalina, B.; Loffler, B. M.; Burri, K.; Cassal, J. M.; Hirth, G.; Muuler, M.; Neidhart, W.; Ramuz, H. Pharmacological Chacterization of Bosentan, a new Potent Orally Active Non-peptide Endothelin Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 228−235.
(21) Elliott, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; DeBrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R. J.; Weinstock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. H. 1,3-Diarylindan-2-carboxylic Acids, Potent and Selective Non-Peptide Endothelin Receptor Antagonists. *J. Med. Chem.* **1994**, *37*, 1553−1557.
(22) Walsh, T. F.; Fitch, K. J.; Chakravarty, K.; Williams, D. L.; Murphy, K. A.; Nolan, N. A.; O'Brien, J. A.; Lis, E. V.; Pettibone, D. J.; Kivlighn, S. D.; Gabel, R. A.; Zingaro, G. J.; Krause, S. M.; Siegl, P. K. S.; Clineschmidt, B. V.; Greenlee, W. J. Discovery of L-749,329, a highly potent, orally active antagonist of endothelin receptors. 208th ACS National Meeting, Washington, D.C., August 1994; Medi 145.
(23) Muth, F. In *Houben-Weyl Methoden der Organischen Chemie*; Muller, E., Ed.; Georg Thieme Verlag: Stutgart, Germany, 1955; Vol. 9, pp 563−585.
(24) Hoffman, R. V., Ed. m-Trifluoromethylbenzenesulfonyl chloride. *Organic Syntheses*; J. Wiley & Sons: New York, 1981; Vol. 60.
(25) 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*, 513−519.
(26) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.
(27) Moreland, S.; McMullen, D. M.; Abboa-Offei, B.; Seymour, A. Evidence for a differential location of vasoconstrictor endothelin receptors in the vasculature. *Br. J. Pharmacol.* **1994**, *112*, 704−708.
(28) Natarajan, S.; Hunt, J. T.; Festin, S.; Serafino, R.; Zhang, R.; Moreland, S. Endothelin analogues which distinguish vasoconstrictor and vasodilator ETB receptors. *Life Sci.* **1995**, *56*, 1251−1256.
(29) Waldron, T. L.; Bird, J. E. Effects of Endothelin A Receptor Antagonist BQ-123 (BQ) on the Pressor and Depressor Responses to Varied Doses of Endothelin (ET)-1 in Rats. *Pharmacology* **1992**, *34*, 160.
(30) Ihara, M.; Noguchi, K.; Saeki, T.; Fukuroda, T.; Tsuchida, S.; Kimura, S.; Fukami, T.; Ishikawa, K.; Nishikibe, M.; Yano, M. Biological studies of Highly Potent Novel Endothelin Antagonists Selective for the ETA Receptor. *Life Sci.* **1992**, *50*, 247.
(31) Unpublished Data.
(32) Bird, J. E.; Moreland, S.; Waldron, T. L.; Powell, J. R. Antihypertensive effects of a novel endothelin-A receptor antagonist in rats. *Hypertension* **1995**, *25*, 1191−1195.
(33) Verbit, L.; Levy, J. S.; Rabitz, H.; Kwalwasser, W. Benzyne Formation from Ortho-aminoboronic acid. *Tetrahedron Lett.* **1966**, *10*, 1053−1055.

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