Biphenylsulfonamide Endothelin Receptor Antagonists. 4. Discovery of *N*-[[2′-[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1′-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide (BMS-207940), A Highly Potent and Orally Active ET_A Selective Antagonist

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We have previously disclosed the selective ET_A receptor antagonist *N*-(3,4-dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (**1**, BMS-193884) as a clinical development candidate. Additional SAR studies at the 2′-position of **1** led to the identification of several analogues with improved binding affinity as well as selectivity for the ET_A receptor. Following the discovery that a 3-amino-isoxazole group displays significantly improved metabolic stability in comparison to its 5-regioisomer, the 3-amino-isoxazole group was combined with the optimal 2′-substituent leading to **16a** (BMS-207940). Compound **16a** is an extremely potent (ET_A K_i = 10 pM) and selective (80000-fold for ET_A vs ET_B) antagonist. It is also 150-fold more potent and >6-fold more selective than **1**. The bioavailability of **16a** was 100% in rats and the systemic clearance and volume of distribution are higher than that of **1**. In rats, intravenous **16a** blocks big ET pressor responses with 30-fold greater potency than **1**. After oral dosing at 3 μmol/kg, **16a** displays enhanced duration relative to **1**.

Introduction

The endothelins (ET-1, ET-2, and ET-3) constitute a family of 21-amino acid vasoconstrictor peptides and are produced by the endothelium of blood vessels and by many other tissues.[1,2] A large number of studies have elucidated that endothelins play many important roles in addition to vasoconstriction, including modulation of vascular tone, cell proliferation, and hormone production.[3−5] The endothelins exert their physiological effects via two specific G-protein coupled receptors termed ET_A and ET_B.[6,7] Both receptor subtypes are found on smooth muscle cells and mediate the vasoconstrictor and pressor actions of endothelin. The ET_B receptor is also found on vascular endothelial cells and cause endothelin-dependent vasodilatation via release of nitric oxide and prostacyclin.[8] Additionally, ET_B receptors in the lung are a major pathway for the clearance of ET-1 from plasma.[9]

A number of selective as well as nonselective endothelin receptor antagonists are being actively developed as new therapeutic agents.[10,11] Extensive preclinical and clinical studies, mainly with ET_A receptor antagonists, have shown excellent therapeutic benefits in disease states such as heart failure, pulmonary hypertension, atherosclerosis, restenosis, systemic hypertension, and chronic renal failure.[12−14] These results indicate endothelin receptor antagonists, especially those selective for the ET_A receptor, may constitute a novel and potentially important class of agents for the treatment of the aforementioned pathological conditions.

Recently we reported a series of biphenylsulfonamides as potent and selective ET_A antagonists.[15−17] In these studies we showed that compounds with a heterocyclic ring such as an oxazole[16] (**1**, Figure 1) or pyrimidine[17] (**2**) at the 4′-position of the biphenyl moiety showed remarkable enhancement in potency and metabolic stability. This work led to the selection of **1** (BMS-193884, ET_A K_i = 1.4 nM; ET_B K_i = 18700 nM) as a clinical development compound. In a Phase I oral ascending single dose tolerance study, **1** was well tolerated up to a dose of 600 mg and showed a dose-dependent increase in plasma concentrations. Evaluation of the effect of intravenous doses of **1** on forearm blood flow after ET-1 infusion indicated that a dose of 50 nmol/min completely abolishes the vasoconstictive response to ET-1. Compound **1** also showed promising hemodynamic effects in a phase II clinical trial for congestive heart failure.[18]

In the present study, we have focused on the optimization of the substituents at the 2′-position of the 4′-oxazolyl biphenylsulfonamides. A wide range of substituents was investigated at this position in combination with selected variations of the isoxazole ring. This paper describes the resulting discovery of a series of second generation analogues with extremely potent ET_A affinity, selectivity, and superior pharmacokinetic properties.

Chemistry

The preparation of a library of 160 2′-acylaminomethyl biphenylsulfonamides of general structure **5** was

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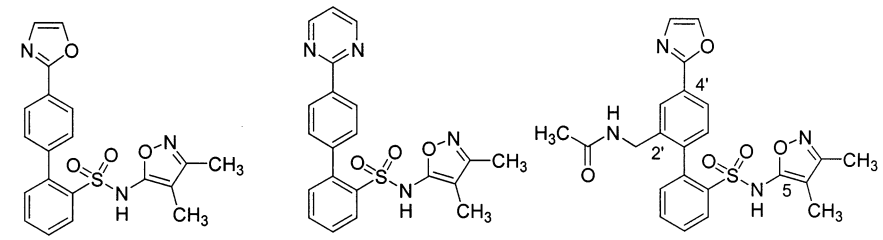


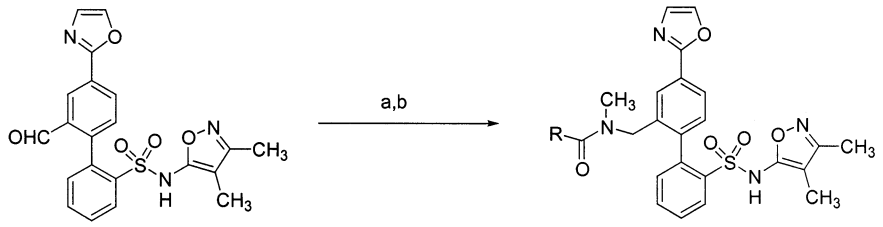
1 (BMS-193884)
ET_A K_i = 1.4 nM
ET_B K_i = 18,700 nM

2
ET_A K_i = 0.9 nM
ET_B K_i = 16,000 nM

3
ET_A K_i = 0.2 nM
ET_B K_i = 4,400 nM

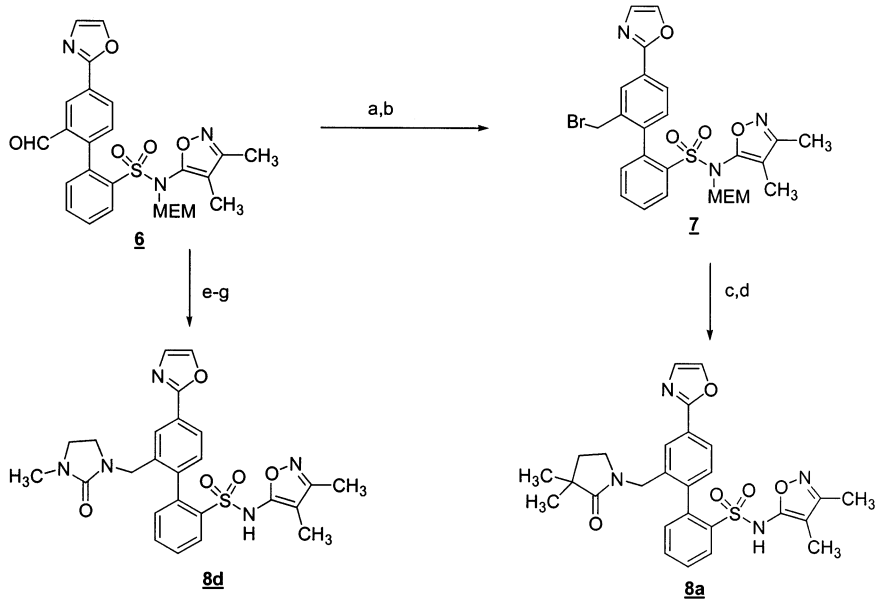
Figure 1.

Scheme 1[a]



[a] (a) Methylamine, sodium triacetoxy borohydride, AcOH; (b) RCOOH, diisopropylcarbodiimide, CH_2Cl_2.

Scheme 2[a]



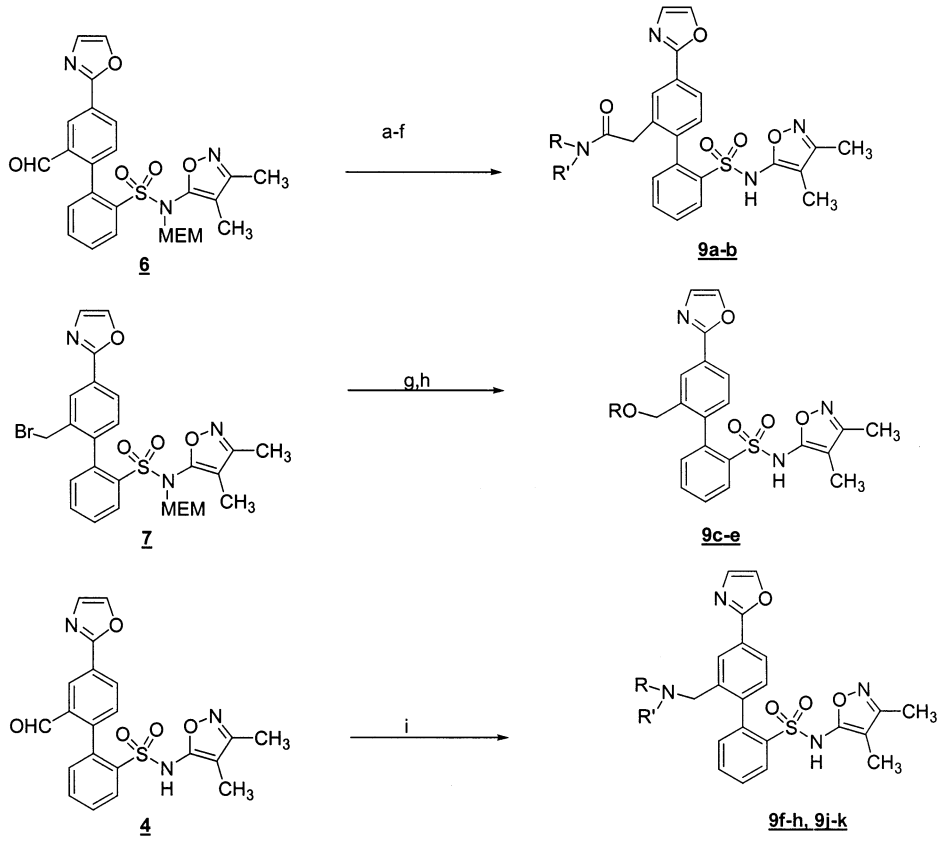
[a] (a) $NaBH_4$, MeOH; (b) CBr_4, PPh_3, DMF; (c) 3,3-dimethyl-2-pyrrolidinone, NaH, DMF; (d) chlorotrimethylsilane, NaI, CH_3CN; (e) $CH_3NHCH_2CH_2NH_2$, sodium triacetoxyborohydride, AcOH; (f) carbonyldiimidazole, CH_2Cl_2; (g) 6 N aq HCl, EtOH.

accomplished using solution-phase parallel synthesis techniques as shown in Scheme 1. The aldehyde group in **4** was converted to the corresponding *N*-methylaminomethyl derivative via reductive amination of **4** in the presence of methylamine, sodium triacetoxyborohydride, and acetic acid. Coupling of this intermediate with a variety of alkyl and aryl carboxylic acids in the presence of 1,3-diisopropylcarbodiimide afforded the library of amide derivatives in yields ranging from 60 to 90%, with purities greater than 90%.

The preparation of the 2′-lactam derivative **8a** and the 2′-cyclic urea derivative **8d** is outlined in Scheme 2. Reduction of the aldehyde group in **6** with sodium borohydride gave the corresponding hydroxymethyl intermediate, which upon treatment with CBr_4 and PPh_3 afforded the bromomethyl derivative **7**. Reaction of **7** with 3,3-dimethyl-2-pyrrolidinone[19] in the presence of sodium hydride followed by deprotection of the MEM group using TMSCl and sodium iodide in acetonitrile provided **8a**. Lactams **8b** and **8c** were prepared by an analogous sequence using either 4,4-dimethyl-2-pyrrolidinone[20] or 3,3-dimethyl-2-piperidinone,[21] respectively. Compound **8d** was prepared from **6** using a three-step sequence: (a) reductive amination using *N*-methyl ethylenediamine, sodium triacetoxyborohydride, and acetic acid, (b) ring closure using carbonyldiimidazole, and (c) deprotection of the MEM group using 6 N aqueous hydrochloric acid in ethanol.

The retroamide derivatives **9a**,**b** were prepared by homologation of the aldehyde group in **4** via Wittig

Scheme 3[a]



[a] (a) (Methoxymethyl)triphenylphosphonium chloride, LDA; (b) p-TSOH, H_2O; (c) sulfamic acid, sodium chlorite, THF/water; (d) oxalyl chloride, CH_2Cl_2; (e) RNHR′; (f) chlorotrimethylsilane, NaI, CH_3CN; (g) ROH, NaH, DMF; (h) 6 N aqueous HCl/EtOH; (i) RNHR′, sodium triacetoxyborohydride, AcOH.

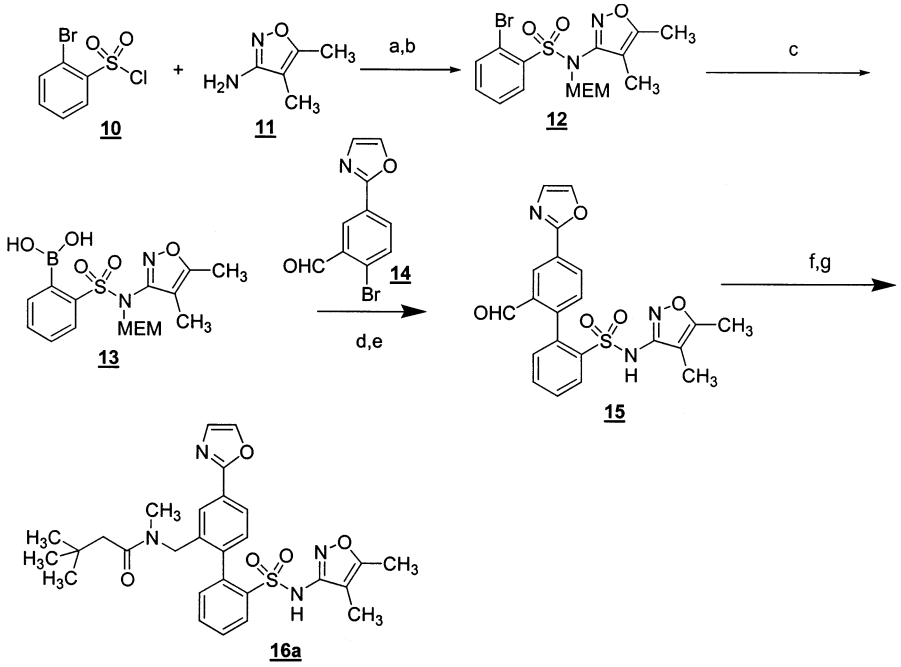
olefination using methoxymethyltriphenylphosphonium chloride followed by treatment with p-TsOH. Oxidation of the resulting aldehyde intermediate to the corresponding carboxylic acid was achieved using sulfamic acid and sodium chlorite in aqueous THF. Conversion of the carboxylic acid moiety to acid chloride followed by coupling with the corresponding alkylamines in the presence of triethylamine and subsequent deprotection of the MEM group provided **9a**,**b** (Scheme 3). The ether derivatives **9c**−**e** were synthesized from **7** by treatment with the corresponding sodium alkoxide derivative followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid in ethanol (Scheme 3). Amines **9f**−**h** and **9j**−**k** were prepared via reductive amination of **4** using the corresponding alkyl or arylamine and sodium triacetoxyborohydide. The olefin derivatives **9l**−**m** were synthesized from **6** via Wittig olefination using benzyltriphenylphosphonium chloride followed by deprotection of the MEM group. The cis and trans isomers were then separated by HPLC. The bisoxazole **9n** was prepared via Suzuki-coupling of 2-[4-bromo-3-(2-oxazolylmethyl)phenyl]oxazole[22] and 2-borono-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]benzenesulfonamide[15] followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid. Analogues **9o**−**q** were prepared from **7** by treatment with the corresponding imidazole or pyrazole heterocycle in the presence of sodium hydride followed by deprotection of the MEM group.

The synthesis of the 3-isoxazolyl biphenylsulfonamide derivative **16a** is outlined in Scheme 4. Coupling of 2-bromobenzenesulfonyl chloride **10** with 3-amino-4,5-dimethyl-isoxazole **11**[23] in pyridine followed by protection of the sulfonamide moiety using sodium hydride as base followed by addition of MEM chloride in DMF at −15 °C provided **12**. The low temperature is required to minimize reaction on the ring nitrogen of the isoxazole. Metalation of **12** with n-BuLi followed by quenching with trimethyl borate and subsequent hydrolysis provided the corresponding boronic acid intermediate **13**. Suzuki coupling of **13** with **14** under standard conditions followed by deprotection of the MEM group provided **15**. Reductive amination of **15** using methylamine and sodium triacetoxy borohydride followed by acylation using *tert*-butylacetyl chloride in the presence of triethylamine afforded the key derivative **16a**. Reductive amination of the aldehyde **15** with 3-carboxy-3-methylbutylammonium chloride gave, after direct cyclization with dicyclohexylcarbodiimide, the lactam derivative **16b**.

Results and Discussion

Compound **1** (BMS-193884) is a selective and competitive ET_A antagonist with 10000-fold greater affinity for the human ET_A receptor than for the ET_B receptor. In our efforts to identify a second generation compound possessing even greater potency and selectivity for the ET_A receptor as well as improved pharmacokinetics relative to **1**, the structure−activity relationships of the pendant phenyl ring was investigated. This led to the discovery that the 2′-acylaminomethyl substituent (**3**, ET_A K_i = 0.2 nM; ET_B K_i = 4,400 nM) improves both

Scheme 4[a]



[a] (a) Pyridine; (b) MEMCl, NaH; (c) (i) n-BuLi, −95 °C, (ii) $B(OMe)_3$, (iii) 3 N aq HCl; (d) compound **14**, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene; (e) 6 N aqueous HCl/EtOH; (f) CH_3NH_2, sodium triacetoxy borohydride, AcOH; (g) $(CH_3)_3CCH_2COCl$, triethylamine.

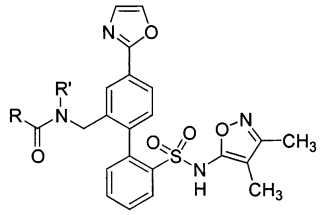
ET_A binding affinity and functional activity 5−10-fold, resulting for the first time in sub-nanomolar biphenylsulfonamide antagonists. However, **3** had poor oral bioavailability in rats (<10%) and showed only modest bioavailability (17%) in cynomologous monkeys. Additional pharmacokinetic studies indicated that poor absorption was the primary contributor to low oral bioavailability. Poor absorption was also suggested by the Caco-2 cell assay results, where **3** had low permeability (P_c = 13 nm/s) compared to **1** (P_c = 213 nm/s). Comparison of the structural and physical properties of **3** to those of **1** suggested that the reduced oral absorption observed might be due to a combination of increased hydrogen bond number, decreased lipophilicity and an overall increase in the desolvation energy. In an effort to optimize the 2′-amide group in an efficient fashion, a library of 160 additional analogues were synthesized by an automated high throughput approach. The activities of some key compounds, **5a**−**p**, from this set are shown in Table 1.

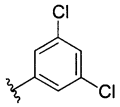
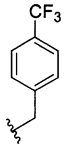
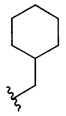
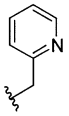
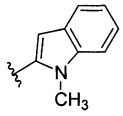
N-Methylation of the amide group of **3** to give **5a** did not improve permeability through Caco-2 cells despite reducing the hydrogen bond number (Table 1). This modification also had little effect on ET_A activity or lipophilicity. The excellent binding affinity for **5a** indicated that a hydrogen bond donor group at 2′ may not be necessary for the enhanced activity of the 2′-substituted analogues. Replacement of the acetyl group in **5a** with larger and more lipophilic alkyl groups such as isopropyl (**5c**) or *tert*-butyl (**5e**) resulted in increases in both ET_A binding affinity and Caco-2 cell permeability. Additional improvements in ET_A selectivity and Caco-2 cell permeability were observed with homologation to the neopentyl group in **5g** (ET_A K_i = 0.02 nM). We also investigated alternative *N*-alkyl groups. A larger, lipophilic *N*-alkyl substituent, such as isopropyl (**5b**) or cyclopropyl (**5d**), was tolerated when combined with a small acyl group but less so for a large acyl group (**5f**). The excellent binding activity of **5g** suggested that the 2′-side chain may be accessing a lipophilic pocket at the receptor. In fact, highly lipophilic *N*-methyl amide side chains such as phenethyl (**5k**), 3,4-dichlorophenyl (**5l**), and p-CF_3-benzyl (**5m**) provided analogues with exceptionally potent ET_A binding affinity (ET_A K_i = 1−9 pM).

Constraining the *tert*-butyl and *N*-methyl groups of **5e** into the lactam **8a** resulted in a substantial increase in ET_A binding affinity (ET_A K_i = 0.005 nM) (Table 2). The 4,4-dimethyl regioisomer **8b** was 10 fold less active than **8a** and the six-membered ring homologue **8c** was 80-fold less potent than **8a**. The cyclic urea analogue **8c** was equipotent to **8a** in its ET_A binding affinity but showed significantly reduced Caco cell permeability.

We also investigated the effect of replacing the 2′ amide group by a variety of amide surrogates (Table 3). Compound **9a**, the retroamide of **5a**, was 5-fold less active than **5a** in its ET_A binding affinity. This result suggested that the position of the carbonyl group may be important for its putative role as a hydrogen bond acceptor or that the retroamide positions the lipophilic alkyl group differently than the amide group does. The related *tert*-butyl retroamide **9b** was also substantially less potent for the ET_A receptor. Replacement of the amide moiety by an ether linker (**9c**−**e**) also resulted in a markedly reduced ET_A activity. In an effort to evaluate the effects of basicity and lipophilicity on ET_A activity and cell permeability, the 2′-amine derivatives **9f**−**k** were prepared. Conversion of the amide in **5c** to the corresponding tertiary amine derivative **9f** resulted in a pronounced drop in ET_A activity suggesting that strongly basic groups are not tolerated at this position. However, 2′-groups incorporating substantially less basic amine derivatives showed improved ET_A activity as well as Caco-2 cell permeability. For example, the *N*-methyl aniline analogue **9g** was a potent ET_A-selective antagonist with significant Caco cell perme-

Table 1. SAR of 2′-Substituted Amide Derivatives



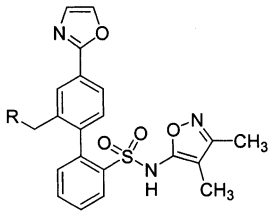
Compd	R	R'	ET_A[a,b] K_i(nM)	ET_A[a,b] K_B(nM)	ET_B K_i (nM)[a]	Caco Pc (nm/s)	cLogP
Bosentan[24]	-	-	8	130	80	ND	ND
1	-	-	1.4	19	18,700	213	2.74
3	CH_3	H	0.2	1.8	4,400	13	1.3
5a	CH_3	CH_3	0.2	0.8	4,000	13	1.57
5b	CH_3	$(CH_3)_2CH$	0.4	4.1*	1,700	23	2.40
5c	$(CH_3)_2CH$	CH_3	0.04	3.2*	790	30	2.40
5d	$CH_3)_2CH$	cyclopropyl	0.05	2.7	550	34	2.76
5e	$(CH_3)_3C$	CH_3	0.03	1.2	640	41	2.80
5f	$(CH_3)_3C$	$(CH_3)_2CH$	6	13	2,300	76	3.60
5g	$(CH_3)_3CCH_2$	CH_3	0.02	4.1	3,360	75	3.42
5h	CF_3CH_2	CH_3	0.05	2.5	380	30	2.85
5i	C_6H_5	CH_3	0.04	1.6	580	28	2.98
5j	$C_6H_5CH_2$	CH_3	0.01	0.38	87	ND	3.13
5k	$C_6H_5CH_2CH_2$	CH_3	0.004	ND	1,200	ND	3.51
5l		CH_3	0.009	2.4*	320	43	4.5
5m		CH_3	0.001	18.7*	1,400	ND	3.99
5n		CH_3	0.44	38*	2,800	59	3.60
5o		CH_3	0.6	7.0*	2,500	<30	1.87
5p		CH_3	0.005	3.0*	310	<20	3.61

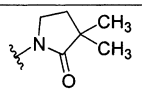
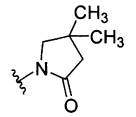
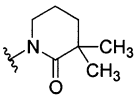
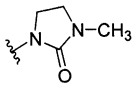
[a] K_i's were determined using human ET_A and ET_B receptors stably expressed in CHO cells. [b] K_B's were determined by assaying for the inhibition of ET-1 induced contractions in rabbit carotid artery rings; K_B* = apparent K_B values; Standard deviations are less than 10% of the mean values for all of the assays; ND = not determined.

ability. The trifluoroethylamine derivative **9h** was also slightly more potent than **1** with good Caco-2 cell permeability. *N*-Methylation (**9i**) resulted in an increase in binding affinity and improved Caco-2 cell permeability but decreased ET_A functional potency in the rabbit carotid tissue assay. The heterocyclic amine derivatives **9j**−**k** were also 10 fold more potent than **1** but **9j** showed reduced functional potency as well as cell permeability.

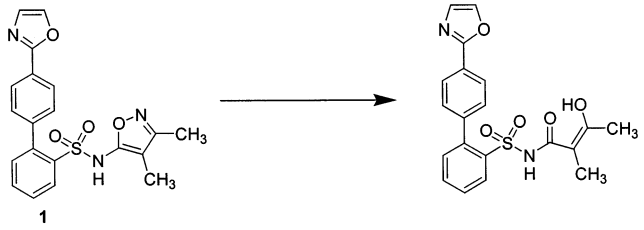
In an attempt to access the putative lipophilic pocket reached by the aryl substituted amide analogues, the styrene derivatives **9l**−**m** were prepared but each displayed reduced binding affinity at ET_A relative to **1**. Heterocyclic groups are also well-known amide surrogates. The bis-oxazole **9n** displayed ET_A activity and Caco cell permeability similar to that observed for **1**. However, the 2′-pyrazole **9o** and 2′-imidazole **9p** showed improved ET_A binding affinity and selectivity compared to **1**. Substitution at the 3-position of the pyrazole ring in **9o** with a lipophilic group such as trifluoromethyl resulted in **9q**, which showed significantly improved ET_A binding affinity and selectivity relative to **1**. Among

Table 2. SAR of 2′-Substituted Lactam Derivatives



Compd	R	ET_A K_i (nM)[a]	ET_A K_B (nM)[b]	ET_B K_i (nM)[a]	Caco Pc (nm/s)	cLogP
8a		0.005	0.75	270	41	2.68
8b		0.045	3.5*	950	ND	2.68
8c		0.39	5.9*	360	86	3.24
8d		0.004	ND	1300	20	2.14

[a] K_i's were determined using human ET_A and ET_B receptors stably expressed in CHO cells. [b] K_B's were determined by assaying for the inhibition of ET-1 induced contractions in rabbit carotid artery rings; K_B* = apparent K_B values. Standard deviations are less than 10% of the mean values for all of the assays; ND = not determined.



1

Figure 2. Metabolism of compound **1** in rats.

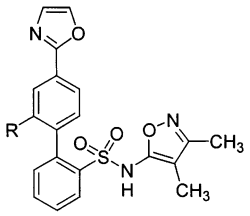
the 2′-heterocyclic substituted analogues studied, **9q** shows the best overall in vitro profile, with substantial ET_A binding affinity, selectivity, and permeability.

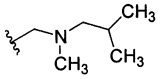
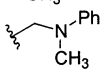
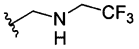
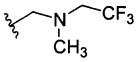
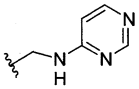
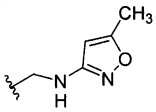
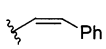
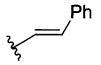
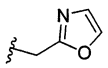
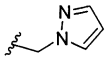
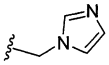
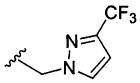
A number of compounds described above were tested in a rat pharmacokinetic model and the amide **5g**, the lactam **8a**, and the pyrazole **9q**, in particular, displayed desirable properties (Table 5). **5g** and **9q** each displayed slightly increased clearance and volume of distribution in comparison to BMS-193884, in addition to a longer plasma elimination half-life and acceptable oral bioavailability. **8a** also showed adequate oral bioavailability and slightly higher volume of distribution and clearance after iv administration in rats. However, at this juncture, it was observed that the modest oral bioavailability for the above analogues may be related to presystemic metabolism resulting from enzymatic cleavage of the 5-isoxazole ring by bacteria in the rat GI tract. A similar metabolic pathway was also observed for **1**, although to a lesser extent possibly due to its rapid absorption from the GI tract (Figure 2). The more potent 2′-substituted analogues were invariably less permeable (based on Caco-2 data) and thus more likely to be exposed to bacteria within the GI tract prior to absorption. It was subsequently determined that analogues containing the 3-aminoisoxazole regioisomer appear resistant to this degradation of the isoxazole ring in vitro.

On the basis of the above analysis, analogous combinations of the 3-aminoisoxazole with the amide and lactam 2′-substituents found in **5g** and **8a**, respectively, were prepared. Analogue **16a**, the 3-aminoisoxazole isomer of **5g**, showed excellent potency and selectivity for the ET_A receptor. (ET_A K_i = 0.01 nM; ET_B K_i = 810 nM; Table 4). These data indicate that **16a** is approximately 80,000-fold selective for human ET_A receptors and displays 140-fold greater ET_A binding affinity and 6-fold greater selectivity for the human ET_A vs ET_B receptors compared to **1**. Lactam **16b**, the 3-aminoisoxazole isomer of **8a**, also shows similarly improved potency and selectivity for the ET_A receptor compared to **1** (ET_A K_i = 0.04 nM; ET_B K_i = 770 nM). Significantly, both analogues displayed enhanced stability to degradation of the isoxazole ring in vitro by rat GI homogenate. Pharmacokinetic studies in rats showed that **16a** has superior (100%) oral bioavailbility (Table 5). In addition, **16a** also showed improved systemic clearance (Cl) and steady-state volume of distribution (V_{ss}) in comparison to **1**. The pharmacokinetic profile of the lactam derivative **16b** in rats was similar to that of **16a**. On the basis of its excellent potency and ET_A selectivity, in addition to its promising pharmacokinetic properties, **16a** (BMS-207940) was selected for additional studies.

Compound **16a** was tested for its ability to inhibit big ET-1 (1 nmol/kg, iv)-induced vasoconstriction in conscious, normotensive rats. This compound blocked the pressor response in a dose-dependent manner when administered orally or intravenously in rats (ED_{25} = 0.004 μmol/kg iv and 0.13 μmol/kg, po). After oral administration at 3 μmol/kg, **16a** inhibited the big ET-1 pressor response 60−70% for the duration of observa-

Table 3. SAR of 2′-Substituted Biphenylsulfonamide Derivatives



Compd	R	ET_A K_i (nM)[a]	ET_A K_B (nM)[b]	ET_B K_i (nM)[a]	Caco Pc (nm/s)
1	H	1.4	19	18,700	213
9a	$-CH_2CON(CH_3)_2$	1	15	7,300	<30
9b	$-CH_2CONHC(CH_3)_3$	0.6	10	1,100	<30
9c	$-CH_2OCH(CH_3)_2$	0.6	>30*	11,000	135
9d	$-CH_2OCH_2CH(CH_3)_2$	0.2	12*	4,800	<30
9e	$-CH_2OPh$	1.0	22*	4,600	ND
9f		8.5	420*	>50,000	ND
9g		0.02	5.5*	150	110
9h		0.8	8	2,700	85
9i		0.15	39	1,900	109
9j		0.15	12.1*	980	<20
9k		0.07	ND	1,050	ND
9l		1.5	6.3	1,900	89
9m		2.5	68	9,100	ND
9n		0.75	13	1,700	148
9o		0.3	6.2*	1,400	46
9p		0.3	11.8	4,300	76
9q		0.02	16	1,500	102

[a] K_i's were determined using human ET_A and ET_B receptors stably expressed in CHO cells. [b] K_B's were determined by assaying for the inhibition of ET-1 induced contractions in rabbit carotid artery rings; K_B* = apparent K_B values; Standard deviations are less than 10% of the mean values for all of the assays; ND = Not determined.

tion, whereas no inhibition was observed for **1** except at the 15-min time point (Figure 3). Thus, **16a** is a more potent ET antagonist as compared with **1** in vivo and has a longer duration of action.

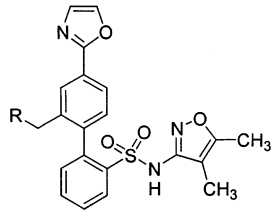
Pharmacokinetic studies in monkeys, in vivo, showed that the systemic clearance and volume of distribution of **16a** are higher than found previously for **1**. In addition, **16a** also showed improved half-life compared to **1** and its oral availability in monkeys averaged 26% (Table 6).

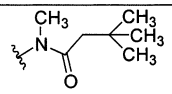
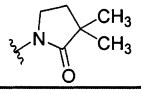
Intravenous injection of ET-1 (0.3 nmol/kg) elicits a transient pressor response in conscious, normotensive cynomolgus monkeys. Oral administration of 10 μmol/kg of **16a** or **1** produced maximal inhibition of the ET-1 pressor response (40 ± 8% and 40 ± 11%) at 15 and 90 min, respectively, after treatment (Figure 4). Significant inhibition of the ET-1 pressor activity was still present 5 h after the compounds were administered. Thus, **16a** blocks the ET pressor response with a magnitude and duration similar to that of **1** in this model.

Conclusion

In summary, introduction of a wide range of functional groups such as an amido, lactam, amines, or heterocyclic rings at the 2′-position of the 4′-oxazolyl biphenylsulfonamides resulted in substantial improvements in both ET_A binding and functional activity compared to the 2′-unsubstituted analogue, **1**. This

Table 4. 2′−Substituted 3-aminoisoxazolyl Biphenylsulfonamides



Compd	R	ET_A K_i (nM)[a]	ET_A K_B (nM)[b]	ET_B K_i (nM)[a]
16a		0.01	1.0	810
16b		0.04	0.62	770

[a] K_i's were determined using human ET_A and ET_B receptors stably expressed in CHO cells. [b] K_B's were determined by assaying for the inhibition of ET-1 induced contractions in rabbit carotid artery rings. Standard deviations are less than 10% of the mean values for all of the assays; ND = not determined.

Table 5. Pharmacokinetic Properties of Select Compounds in Rats[a]

	1	**5g**	**8a**	**9q**	**16a**	**16b**
			Intravenous			
dose (μmol/kg)	10	20	10	20	10	10
Cl (mL/min/kg)	2.6 ± 1.0	13 ± 5.1	28 ± 1.9	34	5.4 ± 0.5	9.3 ± 5.3
V_{ss} (L/kg)	0.08 ± 0.03	0.7 ± 0.3	0.32 ± 0.16	1.5	1.1 ± 0.1	2.3 ± 1.2
$t_{1/2}$ (h)	2.0 ± 0.5	8.2 ± 0.3	1.2 ± 0.2	4	3.4 ± 0.1	4.7 ± 0.2
			Oral			
dose (μmol/kg)	10	20	10	20	20	10
T_{max} (h)	0.4 ± 0.1	0.7 ± 0.3	0.44 ± 0.10	0.5 ± 0.01	0.4 ± 0.1	0.6 ± 0.4
C_{max} (μM)	24 ± 9.8	4.7 ± 1.1	0.28 ± 0.07	3.0 ± 0.5	28 ± 7.8	7.7 ± 2.6
F%	43	27	21	33	100	78

[a] Mean ± SD (n = 3), except **9q** intravenous group (mean only n = 2).

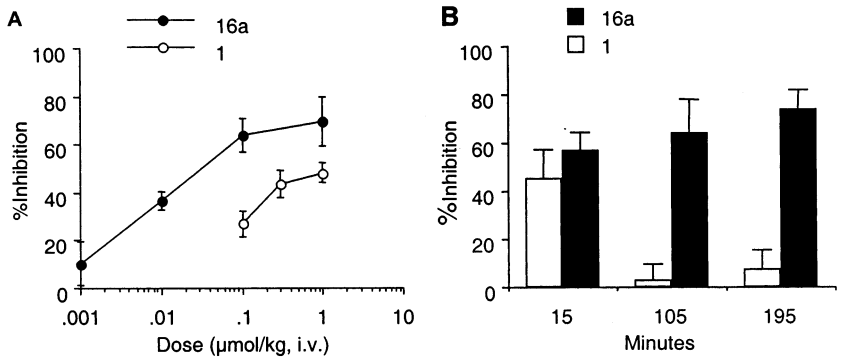


Figure 3. Inhibition of the pressor response to big ET-1 in rats after administration of **16a** and **1**. A. Dose−response curves for the ET antagonists 5 min after iv administration (n = 3−13 rats per dose). B. Time-course of inhibition following oral dosing with antagonist at 3 μmol/kg (n = 3−8 rats per compound).

process resulted in the identification of the 2′-*N*-methyl-*tert*-butylacetamide moiety present in **5g** as one of the optimal groups. Following the discovery that a 3-amino-isoxazole group displays significantly improved metabolic stability in comparison to its 5-regioisomer, the 3-isoxazole group was combined with the optimal 2′-substituent leading to **16a** (BMS-207940). Compound **16a** is an extremely potent (ET_A K_i = 10 pM) and selective (80,000-fold for ET_A vs ET_B) ET_A antagonist and is 150-fold more potent and >6-fold more selective than **1**. Compound **16a** also showed a superior pharmacokinetic profile in rats compared to **1**. The bioavailability was 100% in rats and the systemic clearance and volume of distribution of **16a** are higher than found previously for **1**. In rats, intravenous **16a** blocks big ET pressor responses with 30-fold greater potency than **1**, and after oral dosing at 3 μmol/kg with enhanced duration.

Experimental Section

Radioligand Binding Assays. The receptor binding assays were performed using CHO cells stably expressing human ET_A or ET_B receptors as previously described.[16] 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.[16] K_B values were obtained from experiments in which at least 3 different

Table 6. Comparison of Pharmacokinetic Properties of **16a** ($n = 3$) and **1** ($n = 4$) in Monkeys

		mean ± SD	
parameter	units	**1**	**16a**
	Intravenous		
dose	μmol/kg	50	25
AUC_∞	μM × h	1000 ± 210	161 ± 50
Cl	mL/min/kg	0.86 ± 0.18	2.7 ± 0.73
V_{ss}	L/kg	0.13 ± 0.02	0.25 ± 0.04
$t_{1/2}$	h	8.3 ± 2.6	14 ± 5.0
MRT	h	2.7 ± 0.22	1.6 ± 0.28
	Oral		
dose	μmol/kg	50	25
AUC_∞	μM × hr	704 ± 124	41.5 ± 29
T_{max}	hr	2.4 ± 0.75	1.2 ± 0.29
C_{max}	μM	180 ± 25	16.1 ± 15.9
$t_{1/2}$	hr	8.7 ± 3.9[a]	17 ± 12
bioavailability	%	71 ± 7.0	26[b]

[a] $n = 3$; insufficient data in the terminal phase of one monkey. [b] Individual bioavailability values and SD could not be estimated since different monkeys received the iv and po doses.

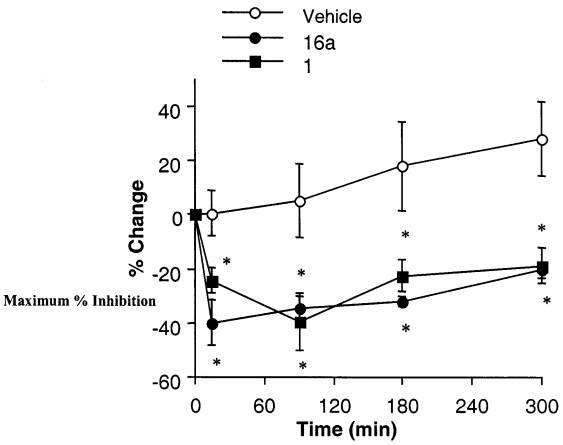


Figure 4. Inhibition of ET-1 pressor responses in monkeys following dosing with **16a** at 10 μmol/kg po, **1**, at 10 μmol/kg po or vehicle ($n = 4$).

concentrations of test compound were studied. Apparent K_B values were calculated when only one antagonist concentration was used.

In Vivo Rat Pressor Studies. This study was performed as previously described.[16] Four iv challenges of ET-1 (0.1 nmol/kg) or big ET-1 (1.0 nmol/kg) were given. Ninety minutes were 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, BMS-207940 (0.3, 1, 3, 10, 30 μmol/kg, iv) were given prior to the subsequent agonist challenges. BMS-207940 was also administered orally at doses of 3, 10, and 30 μmol/kg prior to ET-1 challenges.

Pharmacokinetics and Oral Bioavailability in Rats. Male Sprague−Dawley rats (Harlan Sprague−Dawley, Indianapolis, IN) were surgically prepared with an indwelling jugular vein cannula 1 day prior to drug administration. Rats were fasted overnight prior to dosing and fed 8 h after dosing. They were allowed access to water ad libitum and were conscious and unrestrained during the study. Rats were given a single intravenous dose as a short 10 min infusion or oral dose via gavage. The dosing vehicles were propylene glycol for iv and PEG-400 for PO dose. Serial blood samples were collected at various time points for at least 24 h, and plasma prepared by centrifugation. Drug concentrations were determined by a LC/MS assay with a quantifiable limit of 4 nM, and the pharmacokinetic analysis was performed with the CENTROS (in house) computer program. The bioavailability estimate was based on average AUC values.

Pharmacokinetics and Oral Bioavailability in Monkeys. Single doses of **1 and 16a** were given intravenously (30 min infusion; 5% sodium bicarbonate solution) or orally (gavage; PEG-400 solution) to three to four fasted male cynomolgus monkeys. Serial blood samples were collected at various time points for at least 72 h, and plasma was prepared by centrifugation. Drug concentrations were determined by a LC/MS assay with a quantifiable limit of 4 nM and the pharmacokinetic parameters determined similarly as in rat study.

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 (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were recorded on JEOL FX-270 or GX-400 spectrometers with tetramethylsilane as an internal standard. Chromatography was performed using EM Science silica 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. Solutions were dried with magnesium sulfate unless otherwise noted.

Representative Procedure for Compounds 5a−p. *N*-[[2′-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1′-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide (5g). To a solution of 0.15 g (0.35 mmol) of **4**[17] in 15 mL of dichloromethane, methylamine (33% solution in absolute ethanol, 0.13 mL, 1.06 mmol), glacial acetic acid (0.12 g, 2 mmol), and 1 g of 3 Å molecular sieves were added. The mixture was stirred at room temperature for 1 h. Sodium triacetoxyboro-hydride (0.22 g, 1.06 mmol) was added, and the mixture was stirred overnight. The solution was then filtered, washed once with water, dried, and evaporated to afford 0.15 g of 2′-[(methylamino)methyl]-*N*-(3,4-dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide as a colorless gum. To a solution of this material (32.9 mg, 0.075 mmol) and *tert*-butylacetic acid (0.075 mol) in 0.3 mL of CH_2Cl_2 was added 0.1 mL of DMF followed by a solution of 1,3-diisopropylcarbodiimide in CH_2Cl_2 (0.28N, 0.320 mL, 0.09 mmol). The reaction mixture was vortexed for 3 min and then let stand at room temperature for 24 h. The mixture was then loaded onto 1.5 g of a Strong Anion Exchange (Quaternary Amine) resin and eluted with 20 mL of CH_2Cl_2 followed by 10 mL of 3% TFA in CH_2Cl_2 to give **5g** as a white solid. ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 9H), 1.92 (s, 3H), 2.16 (s, 3H), 2.30 (m, 2H), 3.25 (s, 3H), 4.0−4.6 (m, 2H), 7.25−8.00 (m, 9H). Anal. ($C_{28}H_{32}N_4O_5S$) C, H, N, S.

2′-(Bromomethyl)-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (7). To a solution of **6** (204 mg, 0.4 mmol) in 10 mL of methanol at 0 °C under an argon atmosphere was added sodium borohydride (19 mg, 0.5 mmol). The mixture was stirred at 0 °C for 2.5 h, and 2 mL of a saturated aqueous solution of sodium hydrogen sulfate was added. After stirring for 20 min, 1 N sodium hydroxide (20 mL) was added. The mixture was then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine and dried to afford 195 mg of a colorless oil. To a solution of this material in 4 mL of DMF at 0 °C under an argon atmosphere were added carbon tetrabromide (182 mg, 0.548 mmol) and triphenylphosphine (144 mg, 0.548). The mixture was stirred at 0 °C for 2.5 h, diluted with 20 mL of saturated sodium bicarbonate and extracted with ethyl acetate. The organic extract was washed with aqueous 5% lithium chloride, brine and then dried and evaporated. The crude product was chromatographed on silica gel using 1:1 hexane/ethyl acetate to afford 165 mg (78%) of **7** as a colorless oil, which solidified on standing. This material was used in the next step without any further purification.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (8a).** To a solution of 3,3-dimethyl-2-pyrrolidi-

none (0.035 g, 0.31 mmol) in 2 mL of DMF, NaH (50% suspension in mineral oil, 0.015 g, 0.31 mmol) was added, and the mixture was stirred at room temperature under argon for 30 min. **7** (0.121 g, 0.21 mmol) in 2 mL of DMF was added, and the mixture was stirred overnight. The mixture was then added to water and extracted with EtOAc. The combined organic extracts were washed with water and dried and evaporated. The residue thus obtained was chromatographed on silica gel using 1:1 hexane:EtOAc to afford 0.072 g as a colorless gum. To a solution of this material in 2 mL of acetonitrile were added chlorotrimethylsilane (0.1 g, 0.92 mmol) and sodium iodide (0.138 g, 0.92 mmol), and the mixture was stirred at room temperature for 2 h. Additional portions of chlorotrimethylsilane (0.01 g, 0.092 mmol) and sodium iodide (0.014 g, 0.092 mmol) were added, and the mixture was stirred for an additional 1 h. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were then washed once with water and dried and evaporated. The residue was purified by reverse phase preparative HPLC on a 30 × 500 mm ODS S10 column using 71% solvent B (90% MeOH, 10% H_2O, 0.1% TFA) and 29% solvent A (10% MeOH, 90% H_2O, 0.1% TFA). The appropriate fractions were collected and neutralized with aqueous sodium bicarbonate to pH 7 and concentrated to 10 mL. The solution was then acidified to pH 4 using aqueous sodium bisulfate, and the white solid was filtered and dried to provide 0.019 g (51%) of **8a** as a white solid. mp > 200 °C (dec). ^{1}H NMR ($CDCl_3$): δ 1.13 (d, J = 7.6 Hz, 6H), 1.86 (s, 3H), 1.89 (m, 2H), 2.15 (s, 3H), 3.31 (m, 2H), 4.26 (ABq, J = 16.4, 16.4 Hz, 2H), 7.22−8.00 (m,9H). Anal. ($C_{27}H_{28}N_4O_5S$·0.2 H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(4,4-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (8b).** Compound **8b** was prepared from **7** and 4,4-dimethyl-2-pyrrolidinone in the same manner as **8a**. ^{1}H NMR ($CDCl_3$): δ 1.19(s, 3H), 1.23 (s, 3H), 1.90(s, 3H), 2.17(s, 3H), 2.25(m, 2H), 3.21 (m, 2H), 4.27(m, 2H), 7.25−8.01(m, 9H). HRMS calcd 521.1859 ($C_{27}H_{29}N_4O_5S$), Found 521.1870. Anal. ($C_{27}H_{28}N_4O_5S$·0.3 H_2O) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(3,3-dimethyl-2-oxo-1-piperidinyl)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (8c).** Compound **8c** was prepared from **7** and 3,3-dimethyl-2-piperidone in the same manner as **8a**. ^{1}H NMR ($CDCl_3$): δ 1.09(s, 3H), 1.24 (s, 3H), 1.75 (m, 2H), 1.85−2.10 (m, 2H), 1.93 (s, 3H), 2.17 (s, 3H), 3.48 (m, 2H), 3.94−4.52 (m, 2H), 7.25−8.98 (m, 10H). HRMS calcd 535.2015 ($C_{28}H_{31}N_4O_5S$), Found 535.2026.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-[(2-oxo-3-methyl-1-imidazolidinyl)methyl][1,1′-biphenyl]-2-sulfonamide (8d).** To a solution of 0.3 g (0.586 mmol) of **6** in 15 mL of dichloromethane were added 1 g of 3 Å molecular sieves, 0.074 g (0.997 mmol) of *N*-methyl ethylenediamine, and 0.105 g (1.76 mmol) of acetic acid and stirred under argon for 10 min. Sodium triacetoxyborohydride 0.372 g (1.45 mmol) was then added to the mixture and stirred at room temperature for 12 h. The solution was then filtered through Celite, and the filtrate was washed with of water, dried, and evaporated to afford 0.33 g of a colorless gum. To a solution of this material in 10 mL of dichloromethane was added 0.104 g (0.645 mmol) carbonyldiimidazole. The mixture was stirred at room temperature for 24 h. The mixture was then washed with water, dried, and evaporated to provide 0.26 g of a colorless gum. To a solution of this material in 10 mL of 95% ethanol was added 10 mL of 6 N aqueous hydrochloric acid, and the solution was refluxed for 1 h. The mixture was then diluted with water and extracted with EtOAc. The combined organic extracts were then washed once with water, dried, and evaporated. The residue was purified by reverse phase preparative HPLC to provide 0.039 g (17%) of **8d** as a white solid. mp 105−115 °C (amorphous).

^{1}H NMR ($CDCl_3$): δ 1.91 (s, 3H), 2.17 (s, 3H), 2.73 (s, 3H), 3.39 (m, 4H), 4.18 (s, 3H), 7.25−8.26 (m, 9H). HRMS calcd 508.1674($C_{25}H_{25}N_5O_5S$), Found 508.1655.

2′-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-*N*,*N*-dimethyl-4-(2-oxazolyl)[1,1′-biphenyl]-2-acetamide (9a). To (methoxymethyl)triphenylphosphonium chloride (1.22 g, 3.56 mmol) in 20 mL of THF at −78 °C was added lithium diisopropylamide in THF (1.5 M in cyclohexane, 2.73 mL, 4.09 mmol). The mixture was warmed to 0 °C and stirred for 20 min. The solution was then cooled to −78 °C, and **6** (910 mg, 1.78 mmol) in 5 mL THF was added dropwise. The cold bath was removed, and the reaction was stirred at room temperature for 1 h. The mixture was added to water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using hexane/EtOAc to afford a colorless gum. To a solution of this material (870 mg, 1.61 mmol) in 20 mL of dioxane, a solution of *p*-toluenesulfonic acid (0.3 g) in water was added, and the mixture was refluxed for 4 h. The mixture was cooled and diluted with EtOAc. The organic layer was washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using hexane/EtOAc to afford *N*-(3,4-dimethyl-5-isoxazolyl)-2′-(formylmethyl)-*N*-[(2-methoxyethoxy)methyl]-4′-(2-oxazolyl)-[1,1′-biphenyl]-2-sulfonamide (535 mg, 63%) as a colorless gum. To a solution of this material (300 mg, 0.57 mmol) and sulfamic acid (111 mg, 1.14 mmol) in 15 mL of THF at 0 °C was added an ice-cooled solution of sodium chlorite (103 mg, 1.14 mmol) in 15 mL of water. The mixture was stirred at 0 °C for 2 min and then diluted with dichloromethane. The organic layer was separated, washed with brine, dried, and concentrated. To a solution of this product (90 mg, 0.17 mmol) and 0.01 mL of DMF in 4 mL of dichloromethane was added oxalyl chloride (2 M solution in dichloromethane, 0.21 mL, 0.42 mmol). The mixture was stirred for 1 h and then concentrated. To the residue in 3 mL of THF, 40% aqueous dimethylamine (1 mL) was added. The mixture was stirred at room temperature for 1 h, diluted with EtOAc, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using 1:2 hexane/EtOAc to afford a colorless gum. To a solution of this material (77 mg, 0.135 mmol) in 2 mL of acetonitrile were added chlorotrimethylsilane (74 mg, 0.68 mmol)) and sodium iodide (101 mg, 0.68 mmol). The mixture was stirred at room temperature for 2 h. Additional portions of chlorotrimethylsilane (60 mg, 0.54 mmol) and sodium iodide (82 mg, 0.54 mmol) were added, and the mixture was stirred for an additional 1 h. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were then washed once with water, dried, and evaporated. The residue was purified by reverse phase preparative HPLC to provide **9a** (40 mg, 62%) as a white solid, mp 89−96 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H), 2.17 (s, 3H), 2.85 (s, 3H), 3.02 (s, 3H), 3.66 (m, 2H), 7.26−7.93 (m, 9H). Anal. ($C_{24}H_{24}N_4O_5S$·0.6 H_2O) C, H, N, S.

2′-[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-*N*-*tert*-butyl-4-(2-oxazolyl)[1,1′-biphenyl]-2-acetamide (9b). Compound **9b** was prepared in the same manner as **9a**. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9H), 1.91 (s, 3H), 2.04 (s, 3H), 3.33 (m, 2H), 7.13−7.93 (m, 9H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(1-methylethoxy)-methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9c).** To a solution of 2-propanol (0.104 g, 1.73 mmol) in 2 mL of DMF was added NaH (50% suspension in mineral oil, 0.033 g, 0.69 mmol). The mixture was stirred at room temperature under argon for 10 min. Compound **7** (0.2 g, 0.346 mmol) in 1 mL of DMF was then added, and the mixture was stirred for 12 h. The mixture was then added to water, and the solution was extracted with EtOAc. The combined organic extracts were washed with water, dried, and evaporated. The crude residue was chromatographed on silica gel using 1:1 hexane:EtOAc to afford 0.19 g as a colorless gum. This material was dissolved in 2.5 mL of 95% EtOH and 2.5 mL of 6 N aqueous HCl was added. The solution was refluxed for 1 h. The mixture was then concentrated and diluted with water and extracted with EtOAc. The combined organic extracts were then washed once with water, dried, and evaporated to provide 0.015 g of a colorless gum. The residue was purified by reverse phase preparative HPLC to provide 0.06 g (40%) of **9c**. ^{1}H NMR

($CDCl_3$): δ 1.01 (d, 3H), 1.04 (d, 3H), 1.89 (s, 3H), 2.17 (s, 3H), 3.58 (m, 1H), 4.38 (ABq, J = 16.8, 11.2 Hz, 2H), 7.25−8.17 (m, 9H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-phenoxymethyl)[1,1′-biphenyl]-2-sulfonamide (9e).** Compound **9e** was prepared in the same manner as **9c**. ^{1}H NMR ($CDCl_3$): δ 1.83 (s, 3H), 2.05 (s, 3H), 4.81 (m, 2H), 6.79−8.13 (m, 14H). Anal. ($C_{27}H_{23}N_3O_5S\cdot 0.1\ H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[[methyl(2-methylpropyl)amino]methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9f).** A mixture of **4** (100 mg; 0.24 mmol), isobutylmethylamine (0.087 mL; 0.71 mmol), AcOH (0.08 mL; 1.34 mmol), and 3 Å molecular sieves (670 mg) in 2 mL of dichloromethane was stirred for 1 h at room temperature. Sodium triacetoxyborohydride (150 mg; 0.71 mmol) was then added to the mixture and stirred for 18 h. The reaction mixture was filtered through Celite, and the filtrate was partitioned between EtOAc and saturated aqueous sodium bicarbonate. The organic layer was then washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel using 5% MeOH in CH_2Cl_2 to afford **9f** (88 mg, 83%) as a white powder. mp 90−100 °C. ^{1}H NMR (CD_3OD): δ 0.72 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H), 1.69 (m, 1H), 1.88 (s, 3H), 2.09 (s, 3H), 2.51 (m, 1H), 2.55 (s, 3H), 2.81 (m, 1H), 3.48 (d, J = 13 Hz, 1H), 4.19 (d, J = 12.5 Hz, 1H), 7.12 (d, J = 6.5 Hz, 1H), 7.26 (d, J = 7 Hz, 1H), 7.52 (m, 3H), 7.74 (m, 1H), 8.06 (m, 2H), 8.11 (d, J = 7.5 Hz, 1H). HRMS calcd 494.1988 ($C_{26}H_{30}N_4O_4S$), Found 494.2061.

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

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(methylphenylamino)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9g).** ^{1}H NMR (CD_3OD): δ 1.72 (s, 3H), 2.10 (s, 3H), 3.09 (s, 3H), 4.22 (d, J = 16 Hz, 1H), 4.53 (d, J = 16 Hz, 1H), 6.81 (d, J = 7.5 Hz, 2H), 6.95 (m, 2H), 7.10 (d, J = 8 Hz, 1H), 7.21 (m, 2H), 7.31 (s, 1H), 7.63 (m, 2H), 7.90 (d, 7.5 Hz, 1H), 7.98 (s, 1H), 8.05 (s, 1H), 8.12 (m, 1H). HRMS calcd 514.1675 ($C_{28}H_{26}N_4O_4S$), Found 514.1749.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-[[(2,2,2-trifluoroethyl)amino]methyl][1,1′-biphenyl]-2-sulfonamide (9h).** ^{1}H NMR (CD_3OD): δ 1.73 (s, 3H), 2.13 (s, 3H), 3.95 (q, J = 9 Hz, 2H), 4.11 (d, J = 14 Hz, 1H), 4.29 (d, J = 14 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.40 (s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 8.5 Hz, 1H), 7.81 (t, 7.5 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 8.08 (s, 1H), 8.17 (d, J = 8 Hz, 1H), 8.31 (s, 1H). HRMS calcd 506.1236 ($C_{23}H_{21}F_3N_4O_4S$), Found 506.1230.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′[[methyl(2,2,2-trifluoroethyl)amino]methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9i).** Sodium cyanoborohydride (51 mg; 0.76 mmol) was added to a solution of **9h** (138 mg; 0.254 mmol) and 37% formaldehyde solution (0.21 mL; 2.54 mmol) in 1.2 mL of acetonitrile at room temperature. A vigorous and exothermic evolution of gas was observed. After the reaction cooled back to room temperature, 25 mL of AcOH was added and the reaction mixture was stirred 2 h. After partitioning the reaction mixture between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ solution (30 mL), the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with brine (15 mL), dried, and concentrated. The residue was subjected to preparative HPLC to afford 41 mg (25%) of **9i** as a white powder. mp 49 °C. ^{1}H NMR (CD_3OD): δ 1.71 (s, 3H), 2.15 (s, 3H), 2.29 (s, 3H), 2.92 (m, 1H), 3.05 (m, 1H), 3.47 (d, J = 14 Hz, 1H), 3.54 (d, J = 14 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.63 (t, J = 8 Hz, 1H), 7.70 (t, 7.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 8.02 (s, 1H), 8.10 (d, J = 8 Hz, 1H), 8.24 (s, 1H). HRMS calcd 520.1392 ($C_{24}H_{23}F_3N_4O_4S$), Found 520.1469.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(4-pyrimidinylamino)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9j).** A mixture of 4-aminopyrimidine (20 mg; 0.2 mmol), **4** (42 mg; 0.1 mmol). and $MgSO_4$ (0.1 g) in 2 mL of toluene was heated to reflux for 10 h. After cooling to room temperature, the reaction mixture was filtered and concentrated to ca. 1 mL. After cooling to 0 °C, sodium borohydride (12 mg; 0.3 mmol) was added to the mixture followed by 0.2 mL of MeOH. After stirring for 24 h, the reaction mixture was concentrated and the residue was purified by preparative HPLC to afford 29 mg (54%) of **9j** as a white powder. mp 156−167 °C. ^{1}H NMR (CD_3OD): δ 1.71 (s, 3H), 2.15 (s, 3H), 4.60 (d, J = 15 Hz, 1H), 4.68 (d, J = 15 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.34 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.66 (t, 7.5 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 8.02 (m, 2H), 8.07 (m, 2H), 8.46 (s, 1H). HRMS calcd 502.1423 ($C_{25}H_{22}N_6O_4S$), Found 502.1491.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[[(5-methyl-3-isoxazolyl)amino]methyl]-4′-[2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9k).** Compound **9k** was prepared in the same manner as **9j** using 5-methyl 3-isoxazolamine. ^{1}H NMR (CD_3OD): δ 1.71 (s, 3H), 1.72 (s, 3H), 2.02 (s, 3H), 2.13 (s, 3H), 4.17 (d, J = 15.5 Hz, 1H), 4.25 (d, J = 15.5 Hz, 1H), 7.12 (d, J = 8 Hz, 1H), 7.32 (s, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.70 (t, 7.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 8.00 (s, 1H), 8.10 (s, 1H), 8.11 (d, J = 8 Hz, 1H). HRMS calcd 519.1576 ($C_{26}H_{25}N_5O_5S$), Found 519.1636.

(*Z*)-*N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-(2-phenylethenyl)[1,1′-biphenyl]-2-sulfonamide (9l). To benzyltriphenylphosphonium chloride (300 mg, 0.77 mmol) in 10 mL of THF at −78 °C was added *n*-butyllithium (2 M in pentane, 0.39 mL, 0.78 mmol). The cold bath was removed, and the mixture was stirred at room temperature for 45 min before cooling to −78 °C again. Compound **6** (304 mg, 0.59 mmol) was added at −78 °C, and the reaction mixture was then stirred at room temperature for 2.5 h. Ten milliliters of water and 40 mL of ethyl acetate were added. The organic layer was separated and washed with saturated aqueous ammonium chloride and brine, dried, and concentrated. The residue was dissolved in 6 mL of 95% ethanol and 6 mL of 6 N aqueous hydrochloric acid was added and refluxed for 1 h. The reaction mixture was concentrated and diluted with ethyl acetate. The organic layer was separated, washed with brine, dried, and concentrated. The residue was purified by preparative HPLC to provide **9l** (73 mg, 19% for two steps) as a white solid. mp. 102−109 °C (amorphous): ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H), 2.16 (s, 3H), 6.38−6.51 (m, J = 12.3 Hz, 2H), 6.60−7.98 (m, 15H). HRMS calcd 498.1488 ($C_{28}H_{24}N_3O_4S$), Found 498.1482.

(*E*)-*N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-(2-phenylethenyl)[1,1′-biphenyl]-2-sulfonamide (9m). Subsequent elution of the HPLC column from above provided **9m** (27 mg, 7% for two steps) as a light yellow solid. mp 109−116 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 3H), 2.01(s, 3H), 6.72−7.10 (m, 2H), 7.17−7.98 (m, 15H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-(2-oxazolylmethyl)[1,1′-biphenyl]-2-sulfonamide (9n).** This compound was prepared from 2-[4-bromo-3-(2-oxazolylmethyl)-phenyl]oxazole[22] and 2-borono-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]-benzenesulfonamide using a Suzuki-coupling procedure described previously[16] followed by deprotection of the MEM group using 6 N aqueous hydrochloric acid to provide **9n** as a colorless gum. mp 88−95 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.89 (s, 3H), 2.16 (s, 3H), 4.11 (s, 2H), 7.03−8.30 (m, 12H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-(1*H*-pyrazol-1-ylmethyl)[1,1′-biphenyl]-2-sulfonamide (9o).** A solution of pyrazole (22.3 mg, 0.34 mmol) in 2.5 mL of THF was cooled to 0 °C under an argon atmosphere, and 60% sodium hydride (12 mg, 0.34 mmol) was added. After stirring at 0 °C for 0.5 h, compound **7** (130 mg, 0.225 mmol) in 0.5 mL of DMF was added to the mixture and stirred overnight. The reaction was diluted with water and extracted with ethyl actate. The organic extract was washed with brine, dried, and evaporated. The crude product was purified by column chromatography on silica eluting with methanol/methylene chloride to provide 118 mg of a colorless gum. This material was dissolved in 1.5 mL of ethanol and 1.5 mL of 6 N aqueous HCl, and the mixture was refluxed for 2.5 h. The mixture was concentrated to dryness, dissolved in ethyl acetate, washed with sodium bicarbonate, water, and brine, and dried over sodium sulfate.

The crude product was purified on silica eluting with methanol/methylene chloride yielding 40 mg of **9o** as a colorless solid, mp 140−146 °C. ^{1}H NMR ($CDCl_3$): δ 1.94 (s, 3H), 2.15 (s, 3H), 5.13 (d, J = 16 Hz, 1H), 5.24 (d, J = 16 Hz, 1H), 7.21−7.99 (m, 12H). HRMS calcd 476.1393 ($C_{24}H_{21}N_5O_4S$), Found 476.1382.

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

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-(1*H*-imidazol-1-ylmethyl)-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (9p).** mp 135−145 °C. ^{1}H NMR (CD_3OD): δ 1.73 (s, 3H), 2.15 (s, 3H), 5.32 (d, 2H), 7.22−8.64 (m, 12H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)-2′-[(3-trifluoromethyl-1*H*-pyrazol-1-yl)methyl][1,1′-biphenyl]-2-sulfonamide (9q).** ^{1}H NMR ($CDCl_3$): δ 1.92 (s, 3H), 2.15 (s, 3H), 5.24 (s, 2H), 7.16−8.08 (m, 11H). HRMS calcd 544.1266 ($C_{25}H_{20}F_3N_5O_4S$), Found 544.1246.

2-Bromo-*N*-(4,5-dimethyl-3-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl] benzenesulfonamide (12). To a solution of 4,5-dimethyl-3-isoxazolamine (13.14 g, 117.79 mmol) and 4-(dimethylamino)pyridine (1.44 g, 11.78 mmol) in 80 mL pyridine at 0 °C was added 2-bromobenzenesulfonyl chloride (28.59 g, 111.90 mmol) in portions over 10 min. The mixture was stirred at 40 °C for 6.5 h and concentrated. The residue was dissolved in 3% aqueous sodium bicarbonate, any residual solid was filtered off, and the aqueous filtrate was acidified to pH 1 with 6 N aqueous HCl at 0 °C and extracted with ethyl acetate. The extracts were washed with aqueous 1 N HCl, water, and brine, dried, and concentrated to give 2-bromo-*N*-(4,5-dimethyl-3-isoxazolyl)benzenesulfonamide (34.32 g, 84%). To a solution of this material (32.60 g, 102.78 mmol) in 350 mL of dimethylformamide at −15 °C, NaH (60% in mineral oil, 4.93 g, 123.34 mmol) was added in portions. After stirring at room temperature for 30 min, the mixture was cooled with in ice-salt bath, and 2-methoxyethoxymethyl chloride (16.00 g, 128.48 mmol) was added dropwise over 20 min. The reaction was stirred with an ice-salt bath for 20 min and then at room temperature for 1.5 h. The mixture was diluted with EtOAc, and the organic layer was separated, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using hexane/EtOAc to afford **12** (32.12 g, 75%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H), 2.29 (s, 3H), 3.37 (s, 3H), 3.57 (m, 2H), 3.94 (m, 2H), 5.36 (s, 2H), 7.37−8.03 (m, 4H).

***N*-(4,5-Dimethyl-3-isoxazolyl)-2′-formyl-*N*-[(2-methoxyethoxy)methyl]4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (15).** To a solution of **12** (22.16 g, 52.85 mmol) in 260 mL of THF at −95 °C was added *n*-butyllithium (2 M solution in pentane, 29.07 mL, 58.14 mmol). The mixture was stirred at −95 °C for 10 min, and trimethylborate (6.59 g, 63.42 mmol) was added and stirred at −78 °C for an additional 15 min. The cold bath was removed, and the mixture was slowly warmed to room temperature and stirred for 0.5 h. The mixture was then cooled to 0 °C, and 100 mL of 3 N aqueous HCl was added dropwise. After stirring for 30 min, the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and concentrated to give 2-borono-*N*-(4,5-dimethyl-3-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl]benzenesulfonamide (**13**) as a gum. To a solution of this crude material and **14**[16] (13.32 g, 58.14 mmol) in 260 mL of toluene and 130 mL of 95% ethanol were added 100 mL of 2 M aqueous sodium carbonate and tetrakis-(triphenylphosphine)palladium(0) (6.11 g, 5.29 mmol), and the reaction mixture was heated under argon at 85 °C for 4 h, cooled, and diluted with EtOAc. The organic layer was separated and washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using 1:1 hexane/EtOAc to afford a colorless gum. To a solution of this material (16.95 g, 33.14 mmol) in 400 mL of 95% ethanol was added 400 mL of 6 N aqueous hydrochloric acid and refluxed for 1 h. The mixture was concentrated and diluted with 800 mL of ice water. After standing for 2 h, a white precipitate was formed and was collected by filtration yielding **15** (13.17 g, 92%) as a white solid. ^{1}H NMR ($CDCl_3$/CD_3OD 4:1): δ 1.66 (s, 3H), 2.23 (s, 3H), 7.28−8.62 (m, 9H), 9.58 (s, 1H).

***N*-[[2′-[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1′-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide (16a).** To a solution of **15** (12.91 g, 30.48 mmol) in 300 mL of dichloromethane was added acetic acid (4.58 g, 76.20 mmol) followed by methylamine (8.03 M in EtOH, 13.29 mL, 106.68 mmol). The mixture was stirred for 15 min sodium triacetoxyborohydride (19.38 g, 91.44 mmol) was added, and the mixture was stirred for an additional 2 h. The solution was then filtered, washed with water, and dried, and evaporated to provide *N*-(4,5-dimethyl-3-isoxazolyl)-2′-[(methylamino)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide as a gray white solid. To a solution of this material in 300 mL of CH_2Cl_2 at 0 °C was added triethylamine (6.17 g, 60.96 mmol) and stirred for 5 min. To the mixture was added *tert*-butylacetyl chloride (3.98 g, 29.57 mmol) dropwise over 10 min, and the mixture was then slowly warmed to room temperature and stirred for 1 h. The organic layer was washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using 60:40:1 hexane/EtOAc/AcOH to provide **16a** (13.10 g, 80% for two steps) as a white solid. mp 120−128 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 9H), 1.85 (s, 3H), 2.25 (s, 3H), 2.33 (m, 2H), 3.16 (s, 3H), 4.21−4.61 (m, 2H), 7.25−8.12 (m, 9H). Anal. ($C_{28}H_{32}N_4O_5S$) C, H, N, S.

***N*-(4,5-Dimethyl-3-isoxazolyl)-2′-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (16b).** To a mixture of **15** (2.00 g, 4.72 mmol), 3-carboxy-3-methylbutylammonium chloride (1.58 g, 9.45 mmol), and 3 Å molecular sieves (0.5 g) in 50 mL of dichloromethane was added AcOH (0.85 g, 14.17 mmol) followed by sodium acetate (0.77 g, 9.45 mmol). The mixture was stirred for 10 min, and sodium triacetoxyborohydride (3.00 g, 14.17 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane, and filtered through Celite. The filtrate was washed with water and brine, dried, and concentrated to yield a colorless gum. This material was dissolved in 50 mL of dichloromethane, and 1,3-diisopropylcarbodiimide (775 mg, 6.14 mmol) was added. The mixture was stirred at room temperature for 1 h, diluted with dichloromethane, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using 50:50:1 hexane/EtOAc/AcOH to provide **16b** (1.47 g, 60% for two steps) as a white solid, mp 206−208 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (d, J = 7.6 Hz, 6H), 1.82 (s, 3H), 1.90 (m, 2H), 2.25 (s, 3H), 3.30 (m, 2H), 4.25 (ABq, J = 16.2, 16.2 Hz, 2H), 7.25−8.17 (m, 9H). Anal. ($C_{27}H_{28}N_4O_5S$) C, H, N, S.

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