Biphenylsulfonamide Endothelin Receptor Antagonists. 2. Discovery of 4′-Oxazolyl Biphenylsulfonamides as a New Class of Potent, Highly Selective ET_A Antagonists

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The synthesis and structure−activity relationship (SAR) studies of a series of 4′-oxazolyl-*N*-(3,4-dimethyl-5-isoxazolyl)[1,1′-biphenyl]-2-sulfonamide derivatives as endothelin-A (ET_A) receptor antagonists are described. The data reveal a remarkable improvement in potency and metabolic stability when the 4′-position of the biphenylsulfonamide is substituted with an oxazole ring. Additional 2′-substitution of an acylaminomethyl group further increased the binding activity and provided one of the first subnanomolar ET_A-selective antagonists in the biphenylsulfonamide series (**17**, ET_A K_i = 0.2 nM). Among the compounds described, **3** (*N*-(3,4-dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide; BMS-193884) had the optimum pharmacological profile and was therefore selected as a clinical candidate for studies in congestive heart failure.

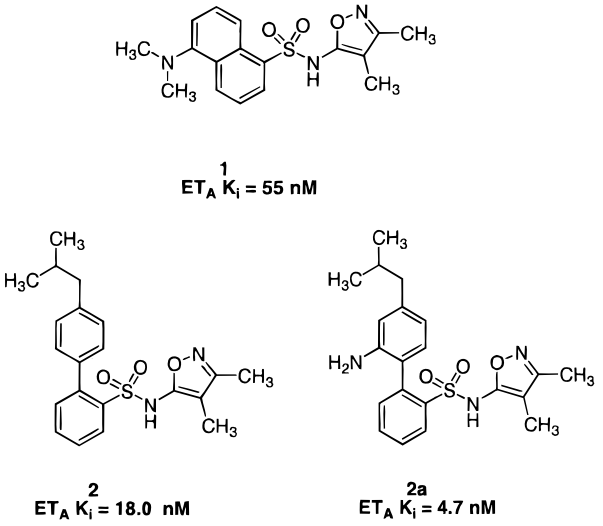
Introduction

Endothelins are a family of closely related 21-amino acid peptides (ET-1, ET-2, and ET-3) with ET-1 being one of the most potent vasoconstrictors identified to date.[1,2] These peptides cause numerous biological effects in addition to vasoconstriction and are the subject of several recent reviews.[3−5] The endothelins have been implicated in a variety of disease states including hypertension,[6] congestive heart failure,[7−9] renal failure,[10,11] pulmonary hypertension,[12] and metastatic prostate cancer.[13] The endothelins exert their physiological activities via two specific G-protein coupled receptors termed ET_A and ET_B.[14,15] The ET_A receptor is selective for ET-1 and is expressed predominately in vascular smooth muscle cells where it mediates vasoconstrictive and proliferative responses. The ET_B receptor is nonselective and binds all three ET isopeptides with equal affinity. The ET_B receptors are mostly found on endothelial cells and mediate ET-1-induced vasodilation possibly through the release of nitric oxide. A small population of ET_B receptors is also found on some smooth muscle cells where their activation leads to vasoconstriction.[16]

A variety of endothelin antagonists with varying degrees of subtype selectivity have been reported in the literature.[5,17,18] A number of these antagonists are currently being investigated to determine the role of endothelin and its receptors in mediating various pathophysiologies.[19,20]

Previously, we described a series of benzene- and naphthalenesulfonamides leading to the identification of **1** (BMS-182874) as a moderately potent and selective ET_A antagonist (ET_A K_i = 55 nM).[21,22] Subsequent structure−activity studies (SAR) led to the identification of biphenylsulfonamide ET_A-selective antagonists with improved binding affinity as well as functional activity. Optimization via substitution off the pendant phenyl ring led initially to the 4′-isobutyl biphenylsulfonamide derivative **2** (ET_A K_i = 18 nM). Additional substitution of **2** with a 2′-amino group led to the identification of the 2′-amino-4′-isobutyl biphenylsulfonamide derivative **2a** (BMS-187308) as one of our key lead compounds (Chart 1).[23] However, subsequent preclinical pharmacokinetic studies indicated that this compound underwent rapid and extensive hydroxylation of the 4′-isobutyl group resulting in inadequate plasma concentrations of **2a** in vivo.[24] We therefore initiated studies focused on identifying metabolically stable replacements for the isobutyl group that maintained or improved the activity of **2a**. This paper describes the resulting dis-

Chart 1



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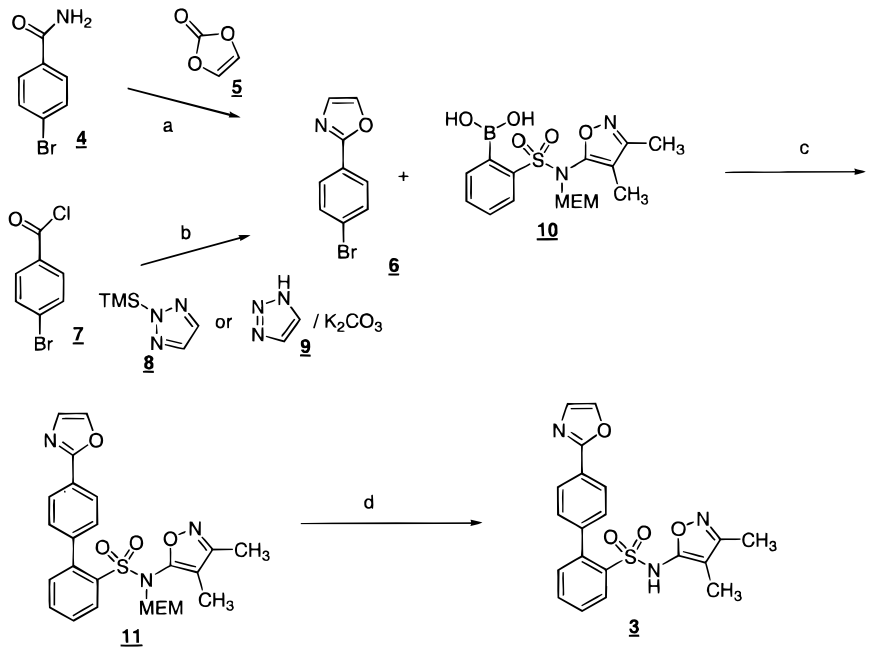
Scheme 1[a]



[a] (a) Polyphosphoric acid, 16 °C; (b) sulfolane, 14 °C; (c) $(Ph_3P)_4Pd$, aq Na_2CO_3, EtOH/toluene; (d) 6 N aq HCl/EtOH.

covery of a 4′-oxazolyl biphenylsulfonamide as a highly potent and ET_A-selective antagonist.

Chemistry

The 4′-oxazolyl biphenylsulfonamide **3** was synthesized as shown in Scheme 1. Reaction of 4-bromophenyl carboxamide **4** with vinylene carbonate **5** and polyphosphoric acid provided the oxazole **6**. Alternatively, **6** may also be prepared by the reaction of the acid chloride **7** with either trimethylsilyl triazole **8** or triazole **9** in the presence of potassium carbonate in sulfolane. Suzuki coupling of the oxazole **6** with our previously reported boronic acid derivative **10**[23] using palladium tetrakis-triphenylphosphine as the catalyst gave the biphenylsulfonamide **11**. Removal of the MEM group was achieved using 6 N aqueous hydrochloric acid in refluxing ethanol to afford compound **3**. Compounds **3a**−**i** were prepared by an analogous sequence to that shown in Scheme 1. The corresponding oxazole intermediates **6a**−**i** were prepared using known methods.

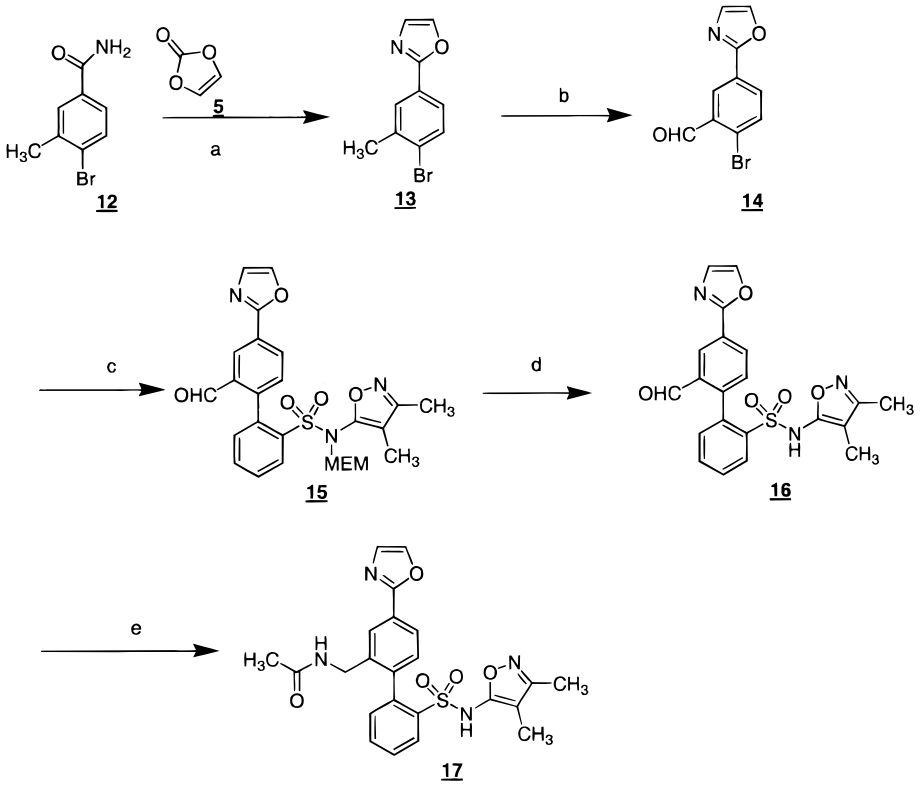
The 2′-acylaminomethyl-4′-oxazolyl biphenylsulfonamide derivative **17** was prepared as depicted in Scheme 2. The 4-bromo-3-methyl carboxamide **12** was prepared from the corresponding, commercially available carboxylic acid. Treatment of **12** with vinylene carbonate **5** and polyphosphoric acid provided the oxazole **13**. The methyl group was then converted to the aldehyde **14** using a two-step sequence. Treatment of **13** with *N*-bromosuccinimide in the presence of benzoyl peroxide gave the corresponding bromomethyl derivative which upon oxidation using anhydrous trimethylamine *N*-oxide in DMSO provided the aldehyde intermediate **14**. Suzuki coupling of **14** with the boronic acid **10** afforded **15** which upon deprotection of the MEM group gave **16**. The aldehyde group in **16** was then converted to the corresponding aminomethyl derivative via reductive amination of **16** in the presence of ammonium acetate, sodium triacetoxyborohydride, and acetic acid. Acylation of this intermediate using acetic anhydride in the presence of triethylamine then afforded the target compound **17**.

Results and Discussion

Primary SAR Evaluation. In our previous report from these laboratories, we described the design and synthesis of a series of biphenylsulfonamides as ET_A-selective antagonists exemplified by the 2′-amino-4′-isobutyl biphenylsulfonamide derivative **2a** (BMS-187,308, ET_A K_i = 5 nM, ET_B K_i = 1700 nM).[23] Compound **2a** also had good oral activity as determined by inhibition of the pressor effect caused by ET-1 infusion in rats. However, subsequent pharmacokinetic studies in rats revealed that the compound was rapidly cleared and the plasma elimination half-life was short (15 min) after intravenous administration. Two major metabolites were detected, both hydroxylated on the isobutyl side chain. Because metabolism of the isobutyl side chain of **2a** probably contributed to the rapid decline of plasma concentration in vivo, we embarked on a program focused on identifying metabolically stable replacements for this group that would also maintain or improve the ET_A activity and ET_A selectivity of **2a**.

Previous SAR of the biphenylsulfonamides suggested steric and conformational limitations at the 4′-position. For example, it was found that introduction of groups larger than isobutyl resulted in significant loss of activity suggesting the need for a substituent with an optimal size and shape.[23] We, therefore, investigated small heteroaromatic rings as potential replacements for the isobutyl group. The 4′-oxazole derivative **3** was one of the first compounds to be synthesized as a part of this effort. Compound **3** was found to be a very potent ET_A receptor antagonist (K_i = 1.4 nM) and displayed weaker binding to the ET_B receptor (K_i = 18 700 nM). These data indicate that **3** is greater than 10 000-fold selective for the ET_A receptor. Therefore, replacement of the isobutyl group in **2** (ET_A K_i = 18 nM, ET_B K_i = 1700 nM) by an oxazole results in greater than 10-fold

Scheme 2[a]



[a] (a) Polyphosphoric acid, 16 °C; (b) (i) *N*-bromosuccinimide/benzoyl peroxide, (ii) trimethylamine *N*-oxide, DMSO; (c) compound **10**, $(Ph_3P)_4Pd$, aq Na_2CO_3, EtOH/toluene; (d) 6 N aq HCl/EtOH; (e) (i) ammonium acetate, sodium triacetoxyborohydride, AcOH, (ii) acetic anhydride, triethylamine.

improvement in ET_A activity and selectivity. Oxazole **3** is also a potent functional antagonist with a K_B value of 19 nM in inhibiting ET-1 induced contraction in rabbit carotid artery rings.

Prompted by the above result, biphenylsulfonamides containing several substituted and unsubstituted oxazole derivatives at the 4′-position were prepared (Table 1). Substitution of the oxazole ring by a methyl group at the 4-position of the oxazole ring (**3a**) did not lead to any improvement in activity, while a methyl substitution at the 5-position (**3b**) was not well tolerated resulting in a 8-fold loss of ET_A binding activity. The 4,5-dimethyloxazole derivative **3c** was also 10-fold less potent than **3**, while the benzoxazole analogue **3d** showed strikingly poor ET_A binding affinity resulting in a 2000-fold loss of activity compared to **3**, thereby reinforcing the size limitations at 4′-position of the molecule. Insertion of a methylene spacer between the pendant phenyl ring and the oxazole (**3e**) again resulted in loss of activity. The isomeric 4-oxazole analogue **3f** was approximately equipotent in both the ET_A binding and functional assays. Substitution of **3f** with methyl groups (**3g**,**h**) resulted in a loss in binding affinity. The 5-oxazole isomer **3i** was slightly less potent than the other two regioisomers.

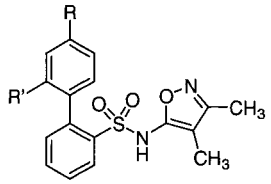
Our prior work in the 4′-isobutyl series had shown that addition of an appropriate 2′-substituent such as an amine, hydroxyl, or acylaminomethyl group resulted in substantial improvement in activity.[23] Among the substituents studied in this series, the acylaminomethyl group was found to be an optimal substituent. Compound **17** incorporating a 4′-oxazole and containing a 2′-acetylaminomethyl group was therefore prepared. The additive effect of a 2′-substituent observed in the isobutyl series was also seen in this case. Compound **17** showed extremely high affinity for the ET_A receptor (ET_A K_i = 0.2 nM) and is the first subnanomolar antagonist discovered in the biphenylsulfonamide series. The ET_A selectivity was also maintained as it was a relatively weak antagonist for the ET_B receptor (ET_B K_i = 1700 nM).

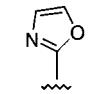
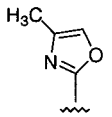
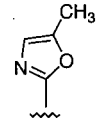
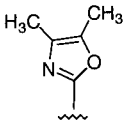
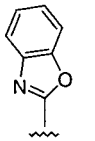
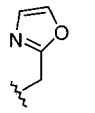
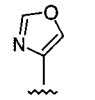
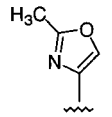
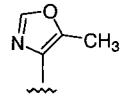
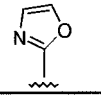
Secondary Evaluations. On the basis of its excellent binding affinity, selectivity, functional potency, and ease of synthesis, **3** (BMS-193884) was chosen for further evaluation. BMS-193884 was tested for its ability to inhibit big ET-1 (1 nmol/kg, iv)-induced vasoconstriction in conscious, normotensive rats. This compound blocked the pressor response in a dose-dependent manner when administered orally or intravenously in rats (ED_{25} = 0.2 μmol/kg, iv and 1.1 μmol/kg, po) (Figure 1).

The high level of tissue ET-1 in DOCA salt hypertensive rats suggested that endothelin might play a role in this model of hypertension. Lowering of blood pressure in this model has been shown with the ET_A-selective antagonists BMS-182874 [25] and EMD-122946.[26] BMS-193884 (30 μmol /kg) had marked depressor effect in this model, lowering mean arterial pressure by 30 mmHg for 6 h (Figure 2).

BMS-193884 has also been reported to show beneficial effects in a pig model of congestive heart failure.[27] In pigs with chronic heart failure induced by pacing, BMS-193884 at 12.5 and 50 mg/kg improved left ventricular fractional shortening, reduced plasma norepinephrine, and also normalized systemic vascular resistance. Basal blood pressure was reduced at the 50 mg dose (from 102

Table 1. Substitution of Biphenylsulfonamides with a 4′-Heterocycle



Compd	R	R'	ET_A K_i (nM)[a]	ET_A K_B (nM)[b]	ET_B K_i (nM)[a]
2a	isobutyl	H	18	210	1,700
3		H	1.4	19	18,700
3a		H	2	18	100,000
3b		H	11	140	12,000
3c		H	16	230	12,000
3d		H	2,000	ND	94,000
3e		H	19	320	34,000
3f		H	0.5	20	20,000
3g		H	70	2,500	110,000
3h		H	4.7	47	94,000
3i		H	3.7	58	78,000
17		$CH_2NHCOCH_3$	0.2	1.8	4,400

[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.

to 84 mmHg), and the endothelin pressor response was reduced by more than 50% at both doses.

Pharmacokinetic studies on BMS-193884, in vivo, showed that it has good oral bioavailability in rats (43%). It also had excellent oral bioavailability (71%) in cynomolgus monkeys. The plasma elimination half-life averaged about 9 h in monkeys, and it also had a slow clearance rate (Cl = 0.86 mL/min/kg). The mean

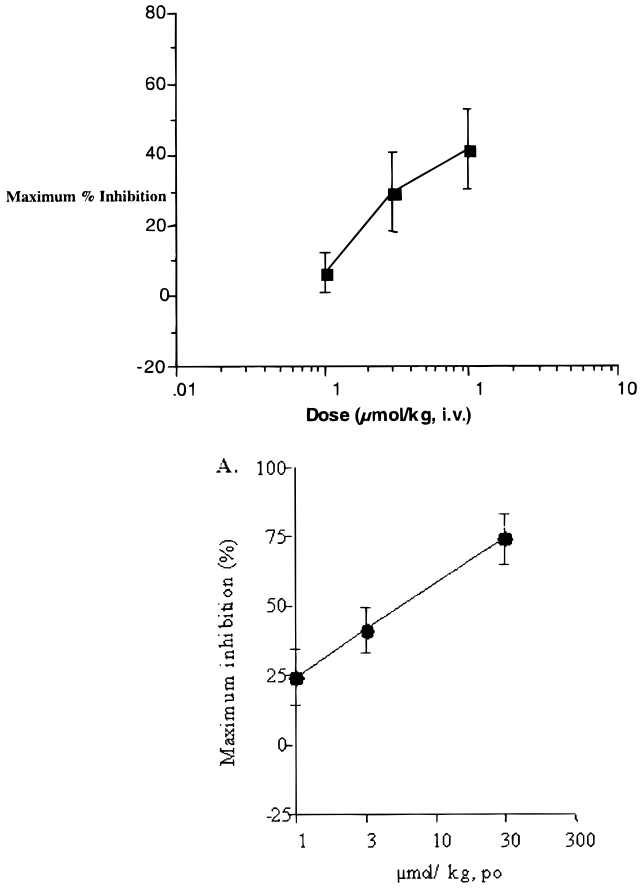


Figure 1. Inhibition of the pressor response to big ET-1 in rats after iv and oral administration of **3** (BMS-193884).

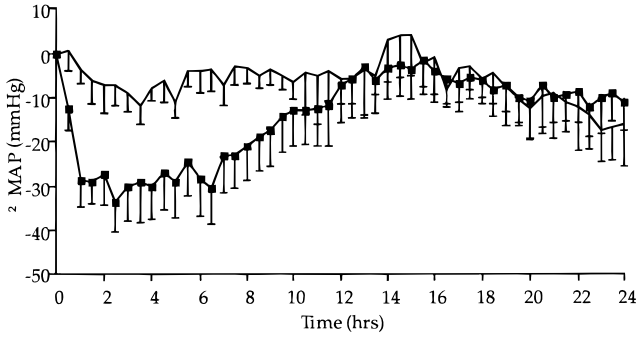


Figure 2. Time course of lowering of mean arterial pressure (MAP) in DOCA salt hypertensive rats following oral administration of vehicle (thin line, no symbol) or 30 μmol/kg **3** (BMS-193884); $n = 7-9$ rats.

residence time was about 2.5 h, and the volume of distribution was 0.13 L/kg, indicating that the extravascular distribution of BMS-193884 is relatively low.[24]

In summary, introduction of an oxazole at the 4′-position of the biphenylsulfonamides resulted in substantial improvements in both ET_A binding and functional activity. The 4′-oxazolyl biphenylsulfonamide BMS-193884 is a potent, selective, and orally active antagonist. Additional 2′-substitution of an acylaminomethyl group further increased the binding activity and provided one of the first subnanomolar ET_A-selective antagonists in this class. On the basis of the in vitro and in vivo profile described above, BMS-193884 was chosen as a clinical candidate for studies in congestive heart failure.

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.[23] 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.[23] K_B values were obtained from experiments in which at least 3 different 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.[25] 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.

General. 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 under flash conditions 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.

2-(4-Bromophenyl)oxazole (6). Method 1.[28] A mixture of 4-bromobenzenecarboxamide (4 g, 20 mmol), vinylene carbonate (1.72 g, 20 mmol) and 10 g of polyphosphoric acid was heated at 170 °C for 3 h. After cooling, the mixture was partitioned between 200 mL of water and 200 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate and the combined organic liquid was washed with water, dried and concentrated. The residue was chromatographed on silica gel using 10:1 hexane/ethyl acetate to afford **6** (2.49 g, 56%) as a white solid.

Method 2.[29] A mixture of 4-bromobenzoyl chloride (0.66 g, 3.0 mmol) and 2-(trimethylsilyl)-1,2,3-triazole (0.47 g, 3.3 mmol) was heated at 140 °C for 3 h. Workup and purification as described above gave 0.55 g (82%) of **6** as a white solid.

Method 3. A mixture of 4-bromobenzoyl chloride (0.72 g, 3.3 mmol), 1*H*-1,2,3-triazole (0.21 g, 3.0 mmol) and potassium carbonate (0.91 g, 6.6 mmol) in 40 mL of sulfolane was heated at 140 °C for 15 h. Workup and purification as described above gave 0.49 g (73%) of **6** as a white solid.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (3).** To a solution of 315 mg (0.82 mmol) of compound **6** and 0.062 g (0.05 mmol) of tetrakis-(triphenylphosphine)palladium(0) in 10 mL of toluene under argon was added 5.0 mL of 2 M aq sodium carbonate followed by 456 mg (2.05 mmol) of 2-borono-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*′-(methoxyethoxymethyl)benzenesulfonamide (**10**)[22] in 6 mL of 95% EtOH. The mixture was refluxed for 2 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 silica gel using hexanes/EtOAc (2:1) to afford 279 mg (70%) of *N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)-methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (**11**) as a colorless gum. To a solution of compound **11** (276 mg, 0.57 mmol) in 10 mL of 95% ethanol was added 10 mL of 6 N aq hydrochloric acid and refluxed for 1 h. The mixture was concentrated and diluted with 10 mL of water. The solution was neutralized using satd aq $NaHCO_3$ and reacidified to pH

4 using glacial AcOH. The mixture was extracted with 3 × 40 mL of EtOAc and the combined organic extracts were washed once with 50 mL of brine, dried and evaporated. Chromatography of the residue on 50 g of silica gel using hexanes/EtOAc (1:1) provided **3** (117 mg, 52%) as a white solid: mp 90−98 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 3H), 2.12 (s, 3H), 7.16−8.70 (m, 11H). ^{13}C NMR ($CDCl_3$): δ 6.59, 10.77, 107.87, 125.67, 126.04, 128.03, 128.20, 129.38, 130.33, 132.46, 132.92, 138.19, 138.48, 140.50, 140.93, 154.55, 161.00, 161.81. Anal. ($C_{20}H_{17}N_3O_4S$) C, H, N, S.

The following compounds were prepared using a Suzuki coupling procedure described for **3** using **10** and the appropriate 4-bromophenyl oxazole derivative[30] followed by the deprotection of the MEM group using 6 N hydrochloric acid.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(4-methyl-2-oxazolyl)-[1,1′-biphenyl]-2-sulfonamide (3a):** mp 85−95 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.78 (s, 3H), 2.09 (s, 3H), 2.19 (s, 3H), 7.35−8.05 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 6.45, 10.69, 11.38, 108.26, 125.63, 126.78, 128.03, 129.12, 130.14, 132.41, 132.93, 134.46, 137.68, 138.06, 140.40, 140.54, 154.24, 160.79, 161.71. Anal. ($C_{21}H_{19}N_3O_4S\cdot0.25H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(5-methyl-2-oxazolyl)-[1,1′-biphenyl]-2-sulfonamide (3b):** mp 90−100 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H), 2.11 (s, 3H), 2.40 (s, 3H), 6.74−9.53 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 7.37, 11.61, 11.78, 108.39, 124.57, 126.01, 126.68, 128.69, 130.22, 131.00, 133.27, 135.62, 139.20, 141.28, 141.48, 149.40, 155.68, 160.43, 162.56. Anal. ($C_{21}H_{19}N_3O_4S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(4,5-dimethyl-2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (3c):** mp 96−102 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.78 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 2.31 (s, 3H), 7.35−8.04 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 6.48, 10.03, 10.72, 11.03, 108.27, 125.28, 127.07, 127.97, 129.12, 130.10, 131.98, 132.47, 132.93, 138.15, 140.02, 140.51, 143.63, 154.30, 158.54, 161.71, 173.14. Anal. ($C_{22}H_{21}N_3O_4S\cdot0.24H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-benzoxazolyl)[1,1′-biphenyl]-2-sulfonamide (3d):** white solid; mp 95−101 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3H), 2.11 (s, 3H), 7.33−8.11 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 6.54, 10.74, 108.48, 110.46, 120.05, 124.77, 125.35, 126.33, 127.05, 128.23, 129.32, 130.39, 132.38, 133.04, 138.14, 140.30, 141.65, 142.05, 150.52, 154.26, 161.86, 162.35. Anal. ($C_{24}H_{19}N_3O_4S\cdot0.9H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-oxazolylmethyl)-[1,1′-biphenyl]-2-sulfonamide (3e):** mp 65−70 °C. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H), 2.11 (s, 3H), 4.16 (s, 2H), 7.04 (s, 1H), 7.27−8.02 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 7.0, 11.2, 34.7, 108.1, 127.5, 128.3, 128.9, 129.5, 130.8, 133.1, 133.4, 135.9, 137.9, 138.5, 139.4, 141.2, 154.7, 162.3, 163.4.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(4-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (3f):** mp 85−93 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.83 (s, 3H), 2.12 (s, 3H), 6.50 (br s, 1H), 7.37−8.04 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 7.23, 11.38, 108.97, 125.81, 128.58, 129.67, 131.11, 131.28, 133.24, 133.70, 134.80, 138.71, 139.03, 141.33, 152.22, 154.67, 162.50 (one aromatic carbon unresolved). Anal. ($C_{20}H_{17}N_3O_4S\cdot0.21H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(2-methyl-4-oxazolyl)-[1,1′-biphenyl]-2-sulfonamide (3g):** mp 90−100 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H), 2.10 (s, 3H), 2.52 (s, 3H), 6.78 (s,1H), 7.36−8.02 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 7.84, 12.09, 15.23, 109.64, 126.31, 129.19, 130.29, 131.61, 132.36, 133.98, 134.33, 134.96, 139.43, 141.33, 142.08, 155.47, 163.11, 163.46. Anal. ($C_{21}H_{19}N_3O_4S$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(5-methyl-4-oxazolyl)-[1,1′-biphenyl]-2-sulfonamide (3h):** mp 86−96 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 1.84 (s, 3H), 2.12 (s, 3H), 2.57 (s, 3H), 6.70 (s, br, 1H), 7.37−8.03 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 6.65, 10.83, 11.98, 108.39, 126.10, 127.92, 129.04, 130.33, 132.03, 132.72, 133.10, 133.39, 137.50, 138.08, 140.82, 144.65, 149.20, 154.12, 161.90. Anal. ($C_{21}H_{19}N_3O_4S\cdot0.16H_2O$) C, H, N, S.

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-(5-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (3i):** mp 189−191 °C. ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H), 2.14 (s, 3H), 7.03−8.13 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 6.56, 10.77, 105.77, 120.68, 123.16, 126.62, 127.97, 129.76, 130.74, 132.61, 132.92, 138.11, 139.17, 140.70, 155.01, 161.81 (two aromatic carbons unresolved). Anal. ($C_{20}H_{17}N_3O_4S\cdot0.28H_2O$) C, H, N, S.

2-(4-Bromo-3-methylphenyl)oxazole (13). A mixture of **12** (12 g, 56 mmol) and vinylene carbonate (6.5 g, 75.5 mmol) in 25 g of polyphosphoric acid was heated at 170 °C for 3 h. The residue was then added to 700 mL of water and extracted with 3 × 250 mL of EtOAc. The combined organic extracts were washed once with water, dried and evaporated. The residue was chromatographed on 200 g of silica gel using CH_2Cl_2 to provide 6.7 g (50%) of **13** as a white solid.

2-Bromo-5-(2-oxazolyl)benzaldehyde (14). A mixture of **13** (6.5 g, 27.3 mmol), *N*-bromosuccinimide (9.72 g, 54.6 mmol) and benzoyl peroxide (250 mg) in 250 mL of carbon tetrachloride was refluxed for 8 h while illuminating the solution with a sun lamp. The mixture was then cooled and filtered. The filtrate was concentrated to provide 10 g of a light yellow solid. To a solution of 7 g of this crude material in 15 mL of anhydrous DMSO under argon was added 5.5 g of anhydrous trimethylamine *N*-oxide and the mixture stirred at 55 °C for 6 h. The mixture was then cooled and added to 150 mL of ice/water and extracted with 3 × 100 mL of EtOAc. The combined organic extracts were washed once with 100 mL of brine, dried and evaporated. The residue was chromatographed on silica gel using hexanes/EtOAc 8:1 to afford 2.2 g (72%) of **14** as a white solid.

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-formyl-4′-(2-oxazolyl)-[1,1′-biphenyl]-2-sulfonamide (16).** This compound was prepared from aldehyde **14** and the boronic acid **10** using a Suzuki coupling procedure described for **3** followed by deprotection of the MEM group using 6 N aq hydrochloric acid to provide **16** as a colorless foam (1.46 g, 90%).

***N*-(3,4-Dimethyl-5-isoxazolyl)-2′-[(acetylamino)methyl]-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide (17).** To a solution of 0.28 g (0.66 mmol) of **16** in 25 mL of MeOH were added 5 g of ammonium acetate and 1 g of 3 Å molecular sieves and stirred at room tempertaure for 1 h. Sodium triacetoxyborohydride (0.42 g, 1.98 mmol) was added and the mixture was stirred for an additional 45 min. The solution was then filtered and concentrated to 10 mL, diluted with 25 mL of water and extracted with 3 × 25 mL of EtOAc. The combined organic extracts were then washed once with water, dried and evaporated. The residue was chromatographed on silica gel using 5% MeOH in CH_2Cl_2 to afford 0.1 g (36%) of *N*-(3,4-dimethyl-5-isoxazolyl)-2′-(aminomethyl)-4′-(2-oxazolyl)[1,1′-biphenyl]-2-sulfonamide as a white solid. To a solution of 0.075 g (0.177 mmol) of this material in 10 mL of CH_2Cl_2 at 0 °C were added 0.019 g (0.19 mmol) of acetic anhydride and 0.019 g triethylamine. The mixture was then slowly warmed to room temperature and stirred for 1 h. The mixture was then diluted with 10 mL of CH_2Cl_2 and washed with 20 mL of 0.1 N aq hydrochloric acid and then with 20 mL of water. The organic layer was then dried and evaporated. The residue was purified by reverse phase preparative HPLC on a 30 × 500 mm ODS S10 column using 58% solvent B (90% MeOH, 10% H_2O, 0.1% TFA) and 42% solvent A (10% MeOH, 90% H_2O, 0.1% TFA). The appropriate fractions were collected and neutralized with aq sodium bicarbonate to pH 7 and concentrated to 10 mL. The solution was then acidified to pH 4 using dilute hydrochloric acid and the white solid was filtered and dried to provide 0.041 g (50%) of **22**: mp 105−107 °C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 1.87 (s, 3H), 1.95 (s, 3H), 2.17 (s, 3H), 4.18 (ABq, J = 14.5, 15.8 Hz, 2H), 7.21−8.00 (m, 9H). ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 7.3, 11.5, 23.4, 42.2, 108.2, 124.9, 125.1, 125.9, 127.8, 128.7, 129.5, 130.2, 131.4, 132.8, 134.0, 138.1, 138.7, 139.1, 139.8, 140.8, 155.7, 171.9, 172.0. Anal. ($C_{23}H_{22}N_4O_5S\cdot0.42H_2O$) C, H, N, S.

Supporting Information Available: Summary of analytical data for compounds **3**, **3a**−**i**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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