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Design and Evaluation of Novel Biphenyl Sulfonamide Derivatives with Potent Histamine H_3 Receptor Inverse Agonist Activity

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Antagonism of the histamine-H_3 receptor is one tactic being explored to increase wakefulness for the treatment of disorders such as excessive daytime sleepiness (EDS) as well as other sleep or cognitive disorders. Phenethyl-*R*-2-methylpyrrolidine containing biphenylsulfonamide compounds were shown to be potent and selective antagonists of the H_3 receptor. Several of these compounds demonstrated *in vivo* activity in a rat model of (*R*)-α-methyl histamine (RAMH) induced dipsogenia, and one compound (**4e**) provided an increase in wakefulness in rats as measured by polysomnographic methods. However, more detailed analysis of the PK/PD relationship suggested the presence of a common active metabolite which may preclude this series of compounds from further development.

Introduction

Histamine is a biogenic amine derived from the enzymatic decarboxylation of the amino acid histidine. Histamine acts through four distinct G-protein coupled receptors (GPCRs,[a] H_1−H_4)[1] to modulate a diverse range of biological functions both in the brain and in the periphery. Among these functions, histamine is involved in the modulation of sleep wake states, as demonstrated by the close relationship between the firing rate of histamine neurons and the sleep−wake cycle.[2] Brain penetrant H_1 receptor antagonists are sedative, suggesting that the sleep-promoting effects of histamine are largely mediated by the H_1 receptor. H_3 receptors are largely expressed in the CNS, and their presynaptic location allows the regulation of histamine synthesis and release through a process of negative feedback. In this way, histamine release and thus H_1 receptor stimulation through inhibition of the H_3 receptor have been shown to alter wakefulness.[3] In addition to the modulation of histamine synthesis and release, the H_3 receptor also acts as a heteroreceptor to influence the release of other neurotransmitters such as noradrenaline, serotonin, dopamine, glutamine, γ-aminobutyric acid (GABA), and acetylcholine.[4a] This additional activity may confer benefits in the treatment of a number of disorders, including narcolepsy, attention-deficit/hyperactivity disorder (ADHD), and other sleep or cognitive impairments.[4] As a result, the H_3 receptor has received significant interest from the pharmaceutical industry as a target for drug discovery.

Our interest in this area was sparked by the natural product Conessine (**1**), which we and others have found to be a moderately potent antagonist of the H_3 receptor.[5] We have previously described our initial foray into this field, exemplified by compounds such as **2** and **3** which contain a 5,5-bicyclic system similar to that found in Conessine but are otherwise greatly simplified compared to the natural product skeleton.[5a,6] While a number of diamino compounds such as **2** were found to be very potent H_3 antagonists, they also had long half-lives, large volumes of distribution, and low clearance, presumably as a direct consequence of their dibasic nature. For a wakefulness-promoting (eugeroic)[7] indication, we sought a drug with a reasonably short half-life ($t_{1/2}$) such that patients could maintain regular sleep patterns as desired.

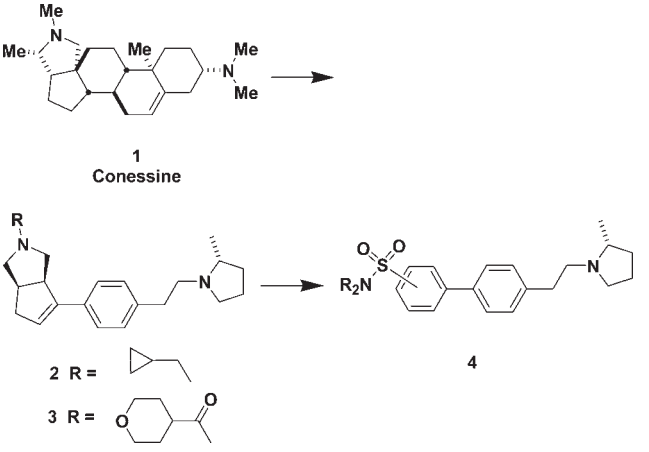

Figure 1. Structures of H_3 antagonists **1**−**4**.

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[a] Abbreviations: H_1−H_4, histamine-1 through histamine-4 receptors; EDS, excessive daytime sleepiness; RAMH, *R*-α-methyl histamine; GPCR, G-protein coupled receptor; PK, pharmacokinetic; PD, pharmacodynamic; CNS, central nervous system; GABA, γ-aminobutyric acid; ADHD, attention-deficit/hyperactivity disorder; $t_{1/2}$, half-life; hERG, human *Ether-à-go-go* related gene; GTPγS, guanosine 5′-*O*-[γ-thio]triphosphate; *F*, bioavailability.

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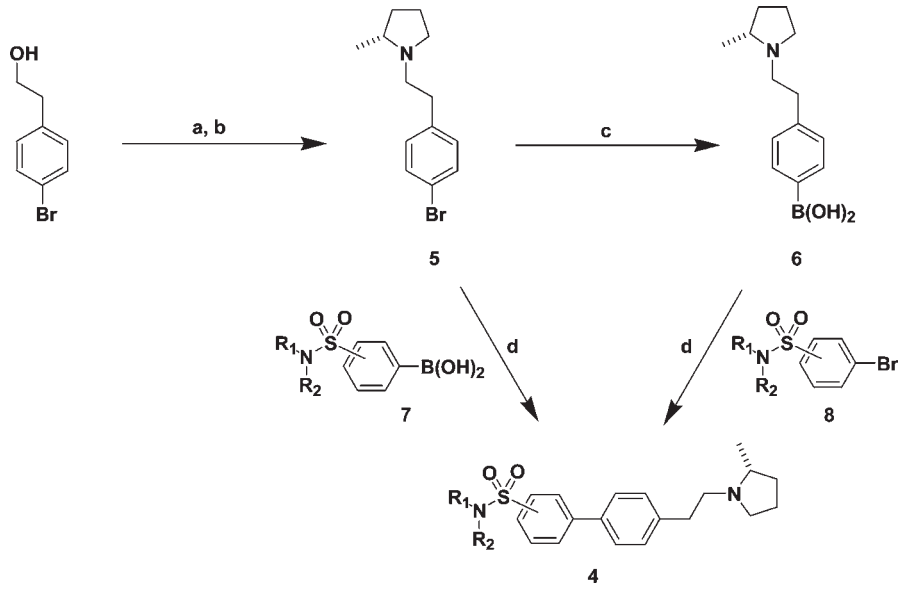
Scheme 1. Synthesis of Biphenyl Sulfonamide Analogues **4**[a]



[a] Conditions: (a) MsCl, DIEA, DCM; (b) (*R*)-2-methylpyrrolidine, Na_2CO_3, CH_3CN, Δ; (c) i. nBuLi, THF, −78 °C; ii. $(iPrO)_3B$, −78 °C to rt; (d) $Pd(PPh_3)_4$, 2 M Na_2CO_3 (aq), benzene/EtOH, Δ.

We found that reducing the basicity of one of the nitrogens (e.g., compound **3**) generally improves the pharmacokinetic (PK) characteristics within this series without significantly sacrificing binding potency or *in vivo* activity.[6] Despite these improvements, compounds such as **3** possess three chiral centers, rendering their large scale synthesis somewhat challenging. In an effort to further simplify our H_3 antagonist series, we examined several core scaffolds as potential replacements for the 5,5-bicyclic system found in compounds **2** and **3**. One of these utilized the phenethyl-*R*-2-methylpyrrolidine functionality[8] found in our earlier antagonists,[5a,6] but the 5,5-bicylic moiety was replaced by a simple phenyl group. The resulting biphenyl scaffold, when appropriately substituted with a functionalized sulfonamide group, served as a highly tractable lead structure enabling the identification of a new series of H_3 antagonists, **4**.[9] Members of this class were readily prepared, showed excellent potency and selectivity for the H_3 receptor, and, in some cases, promising *in vivo* activity in both a functional H_3 pharmacological screen and in assays measuring wakefulness in rats.

Chemistry

Biphenyl sulfonamides of the type described are readily synthesized according to the procedures outlined in Scheme 1. Commercially available 4-bromophenethylalcohol was treated with mesyl chloride and diispropylethylamine to provide the corresponding mesylate in excellent yield. The mesylate was then displaced with (*R*)-2-methylpyrrolidine to give bromophenethylpyrrolidine **5**. The bromide **5** was then subjected to lithium−halogen exchange, and the lithioarene was trapped with triisopropylborate to provide aryl boronic acid **6** in reasonable yield after basic workup. The target compounds **4** were then prepared via Suzuki-Miyaura coupling[10] of compound **5** with commercially available phenyl boronic acids (**7**) or the coupling of boronic acid **6** with readily available bromophenyl sulfonamides (**8**).

Results and Discussion

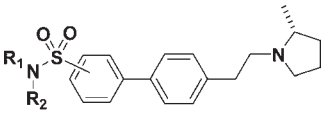
The biphenyl sulfonamides were tested in a rat cortex binding assay and generally bound the H_3 receptor with high affinity. A representative selection shown in Table 1 reveals that while sulfonamides with either a *meta*- or *para*-substitution pattern bound potently to the H_3 receptor, the *para*-substituted analogues maintain consistently higher affinities (compare **4a**−**d** to **4e**−**h**). Among the *para*-substituted analogues, primary, secondary, and tertiary sulfonamides were all highly potent antagonists of the rat H_3 receptor regardless of whether the substituents were aliphatic, aromatic, or heteroaromatic. In addition, both large and small substituents with varying degrees of functionalization were well tolerated.

A common shortcoming for this series was the observation of a significant interaction with the human *Ether-à-go-go* related gene (hERG) channel with several of the tested analogues (Table 1). However, screening in a patch clamp assay at a single concentration of 3 μM showed that more acceptable hERG inhibition values could be obtained for analogues with smaller and more polar sulfonamide substituents (compare **4h** to **4e**, **4i**, and **4r**). This trend is similar to that seen in our earlier series of antagonists and has been noted by others.[11]

The promiscuous nature of the receptor with regard to substitution of the sulfonamide moiety provided the opportunity to modulate other key properties of the molecules without straying from acceptable binding potencies. Thus, our medicinal chemistry efforts quickly became driven by hERG activity, receptor selectivity, and pharmacokinetic data.

Table 2 shows *in vitro* data and pharmacokinetic parameters for four selected analogues, **4e**, **4k**, **4n**, and **4r**, and illustrates some success with regard to our desired compound profile. Screening of compounds **4e**, **4n**, and **4r** against a panel of more than 88 human GPCRs and enzymes, including H_{1-4}, showed that they were highly potent and selective ligands of the human H_3 receptor (< 10% activity at 1 μM for all other receptors). We were also gratified to find that all three compounds displayed potent inverse agonism of the human H_3 receptor in a guanosine 5′-*O*-[γ-thio]triphosphate (GTPγS) functional assay.

Table 1. Binding Affinities (pK_i) of Compounds **4a**−**y** at the Rat H_3 Receptor[a]



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compound	R_1	R_2	substitution pattern	rat H_3[b] (pK_i)	hERG[c] (% Inh., 3 μM)
4a	Et	H	m	7.96 ± 0.06	*d*
4b	^{i}Pr	H	m	8.10 ± 0.13	*d*
4c	Et	Et	m	7.79 ± 0.16	*d*
4d	-$CH_2(CH_2)_3CH_2$-		m	7.90 ± 0.06	*d*
4e	Et	H	p	8.34 ± 0.18	47
4f	^{i}Pr	H	p	8.37 ± 0.13	68
4g	Et	Et	p	8.85 ± 0.21	*d*
4h	-$CH_2(CH_2)_3CH_2$-		p	8.79 ± 0.18	73
4i	H	H	p	8.34 ± 0.18	28
4j	-$C(CH_3)_2CH_2OH$	H	p	8.16 ± 0.20	37
4k	-CH_2CH_2OMe	H	p	8.48 ± 0.24	29
4l	-$CH_2{}^c$Pr	H	p	8.60 ± 0.19	54
4m	-^{c}Bu	H	p	8.64 ± 0.09	79
4n	4-THP	H	p	8.75 ± 0.22	19
4o	Ph	H	p	8.73 ± 0.21	91
4p	-CH_2Ph	H	p	9.53 ± 0.12	84
4q	-CH_2-4-Pyr	H	p	9.74 ± 0.27	27
4r	-$(CH_2)_2O(CH_2)_2$-		p	8.80 ± 0.19	45
4s	-$CH(CH_3)CH_2OCH_2$ $CH(CH_3)$-		p	8.15 ± 0.22	72
4t	-$(CH_2)_2SO_2(CH_2)_2$-		p	9.03 ± 0.28	24
4u	-$(CH_2)_2CH(OMe)(CH_2)_2$-		p	9.19 ± 0.41	59
4v	*e*		p	9.30 ± 0.08	85
4w	-$CH_2CH(OH)(CH_2)_2$-		p	8.61 ± 0.08	30
4x	-$CH(CH_2OMe)(CH_2)_3$-		p	8.29 ± 0.34	61

[a] Displacement of *N*-[^{3}*H*]-methylhistamine from rat cortex membranes. [b] Values are reported as an average of $n \geq 3$ independent measurements for all compounds. Errors are ± log SD. [c] hERG patch clamp assays were performed at Aviva Biosciences, San Diego, CA (http://www.avivabio.com). [d] Not determined. [e] Substituents taken together form an isoindoline ring.

Table 2. *In Vitro* Profiles and Rat Pharmacokinetic Parameters for Compounds Tested *in Vivo*

	4e	**4k**	**4n**	**4r**
	In Vitro Data			
rat H_3 (K_i, nM)	3	3	2	2
human H_3[a] (K_i, nM)	8	*b*	7	3
human GTPγS[a] (K_i, nM)	1	*b*	1	1
selectivity vs $H_{1,2,4}$	> 500	*b*	> 500	> 500
	Pharmacokinetic Parameters[c]			
$t_{1/2}$ (h)	1.8	2.6	2.3	1.2
T_{max} (h)	0.5	0.2	0.8	1.7
F (%)	93	22	62	12
plasma conc.[d] (μg/mL)	1.6	11.2	0.44	0.16
brain conc.[d] (μg/mL)	3.6	8.7	0.14	0.32
brain/plasma ratio[d]	2.3	0.78	0.32	2.0

[a] Human H_3 binding and functional (GTPγS) assays were performed by MDS Pharma Services, Taiwan (http://www.mdsps.com). [b] Not determined. [c] Values represent the mean after a 10 mg/kg p.o. dose, $n = 3$ animals; % *F* calculated relative to a 2 mg/kg i.v. dose. [d] Samples taken at the 0.5 h time point.

Results from pharmacokinetic studies in rats showed that all four analogues exhibited reasonably short half-lives (1.2−2.6 h), consistent with our desire to find a compound with a short duration of action. However, considerably lower bioavailability was observed for compounds **4k** and **4r** (F = 22% and 12%, respectively) compared to analogues **4e** and **4n** (F = 93% and 62%, respectively). Examination of the brain and plasma concentrations of each compound 0.5 h after dosing also demonstrated that compound **4n** (brain-to-plasma ratio = 0.3) had significantly lower brain partitioning compared to compounds **4e**, **4k**, and **4r**, whose brain-to-plasma ratio ranged from 0.77 to 2.3.

In Vivo Pharmacology

Functional *in vivo* H_3 antagonism was demonstrated for compounds **4e**, **4k**, **4n**, and **4r** using a rat dipsogenia model,[12] wherein drinking induced by an H_3 agonist (RAMH) is blocked by prior administration of an H_3 antagonist. The test compounds were administered orally to rats 0.5 h prior to injection of the H_3 agonist (10 mg/kg, SC), with significant inhibition of agonist-induced drinking observed for all compounds at 1 or 3 mg/kg (see Figure 2 and Table 3). These data are similar to those obtained with our earlier series of H_3 antagonists **2** and **3**.[5a,6] The lack of any dramatic differences in efficacy among these compounds suggested that even the relatively low brain concentrations observed for compounds such as **4n** appeared to be sufficient to significantly antagonize H_3 receptor activation in the brain.

In order to examine the potential utility of our compounds to act as wake promoters, compound **4e**, the analogue with the best balance of oral bioavailability, brain partitioning, and *in vivo* antagonist activity, was selected for testing in rats implanted with cortical electrodes, enabling the measurement of sleep and wake states. Specifically, **4e** was administered orally (0.1 and 1 mg/kg) approximately 4 h after lights out (during the animals subjective night), and wake time measured over a 5-h period. At 1 mg/kg, but not 0.1 mg/kg,

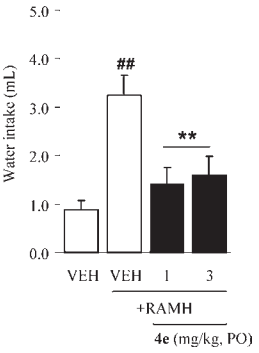

Figure 2. Inhibition of RAMH induced polydipsia by compound **4e** (##, $P < 0.01$ vs vehicle/vehicle; **, $P < 0.01$).

Table 3. Percent Inhibition of RAMH Induced Polydipsia by Compounds **4e**, **4k**, **4n**, and **4r** (**, $P < 0.01$)

compound	dose (mg/kg)	% inhibition (RAMH induced drinking)
4e	1.0	77.6**
	3.0	69.6**
4k	1.0	40.7
	3.0	96.7**
4n	1.0	77.5**
	3.0	85.1**
4r	0.3	34.1
	1.0	99.8**

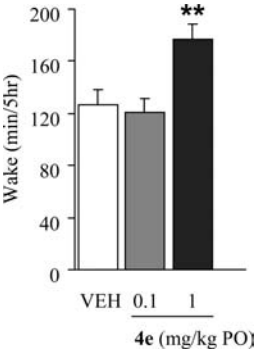

Figure 3. Increase in wakefulness in rats treated with compound **4e** (**, $P < 0.01$).

compound **4e** increased total wake time by 40% (Figure 3). These data are consistent with those obtained in the antagonist studies described above wherein **4e** showed a significant inhibition of RAMH induced polydipsia at the same dose. However, when we examined the data more closely we did not see a clear correlation between duration of action in these two pharmacology models and the PK (brain concentration) data, leading us to further examine the plasma and brain samples from previous experiments.

These efforts resulted in the identification of the primary sulfonamide **4i** as a major metabolite of analogues **4e**, **4k**, and **4n** and a minor metabolite of compound **4r**. It is important to note that in addition to being a potent antagonist of the H_3 receptor, **4i** appears to accumulate in the brain after oral dosing of the parent compound. For example, after a 1 mg/kg oral dose of **4e**, brain concentrations of metabolite **4i** increased approximately 3-fold over a 3.5 h time period, from 79 to 246 ng/mL (Figure 4), whereas the brain concentrations of **4e** decreased with time in accordance with the previously observed PK parameters. In addition, direct (p.o.) dosing of **4i**

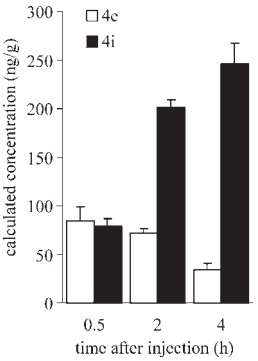

Figure 4. Brain concentrations of **4e** (□) and metabolite **4i** (■) after oral administration of **4e** (1 mg/kg). $N = 3$ animals for each data point.

at 10 mg/kg resulted in peak brain concentrations of approximately 800 ng/g. Compound **4i** also showed efficacy in the RAMH polydypsia test at a dose of 3 mg/kg, which, from the above data, may be expected to result in brain concentrations of around 250 ng/g, which is very close to the level achieved 4 h following the oral administration of compound **4e**. These data suggest that at least some of the *in vivo* effects at and beyond the 4 h time point observed with **4e** may well be as a result of a contribution from its metabolite **4i**.

Unfortunately, efforts to circumvent the problem of active metabolite formation were unsuccessful in this series. We did attempt to design compounds that may reduce the rate of metabolism at this end of the molecule and hence avoid production of the active metabolite **4i**. For example, we tried to incorporate more steric hindrance around the sulfonamide bond (e.g., **4s**) to disfavor hydrolysis, and while this did appear to reduce the level of **4i** generated, we had previously discovered that increasing lipophilicity in this region of the molecule typically led to increased hERG inhibition, and indeed, **4s** did not show an acceptable hERG profile. Additional attempts to include both steric hindrance and the incorporation of an oxygen heteroatom in a side chain, with the aim of simultaneously reducing sulfonamide metabolism and moderating the hERG activity (e.g., **4x**), were not sufficient to achieve either objective. In addition, the increase in lipophilicity led to generally poorer oral bioavailability in those examples tested, and in every case examined, small amounts of the metabolite were always observed *in vivo*. For the present indication, even low levels of a metabolite that may potentially accumulate in the brain would be highly undesirable, and we therefore concluded that the sulfonamide series described would not be suitable for further development.

In summary, a highly practical and versatile biphenyl scaffold was found to serve as a chemistry platform from which many potent and selective sulfonamide-based H_3-receptor ligands were generated. The sulfonamide ligands were initially attractive because of their facile synthesis and favorable *in vitro* properties. Representative examples are presented in which several of the analogues were investigated in established *in vivo* models of H_3 activity. In the rat, oral administration of compounds **4e**, **4k**, **4n**, and **4r** prevented H_3 agonist-induced polydipsia in the 1−3 mg/kg range, and compound **4e** significantly increased wake time after an oral dose of 1 mg/kg. While these results suggest that H_3 antagonists may ultimately be useful in the treatment of human conditions characterized by excessive daytime sleepiness, the identification of active and long-lived metabolites such as **4i** may limit

the utility of compounds from this series in situations where a short duration of action is desirable.

Experimental Section

Chemistry. All reagents were commercially available and used without further purification unless stated otherwise. Microwave irradiations were performed using either Smith Synthesizer or Emrys Optimizer (Biotage). Column chromatography was carried out on prepacked silica gel columns using KP-Sil supplied by Biotage. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance-400 equipped with a Quad Nucleus Probe (QNP) or a Broadband Inverse (BBI) probe and *z*-gradient. Chemical shifts (δ) are given in parts per million (ppm) with the residual solvent signal used as a reference. Coupling constants (*J*) are reported in Hz. NMR abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad.

All target compounds were assessed for purity by analytical high performance liquid chromatography/mass spectrometry (HPLC/MS) conducted on a PE Sciex API 150EX mass spectrometer with an electrospray source, using a Shimadzu Inc. LC-10A VP UV detector monitoring at 214 nm, Analyst 1.2 software, and either (a) a Gilson 215 autosampler and an Alltech Prevail C18 column (5 μm, 250 mm × 4.6 mm), using a gradient of 5% v/v CH_3CN (containing 1% v/v trifluoroacetic acid (TFA)) in H_2O (containing 1% v/v TFA) (t = 0.0 min) gradient to 95% v/v CH_3CN in H_2O (t = 6.0 min), 3.5 mL/min, or (b) a PE 200 autosampler and a Supelco Discovery C18 column (5 μm, 50 mm × 2.1 mm), using a gradient of 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) (t = 0.0 min) gradient to 95% v/v CH_3CN in H_2O (t = 5.0 min), 0.75 mL/min. All target compounds were found to be ≥95% purity except in the cases of **4c** (94%) and **4g** (93%). HPLC/MS purity and retention times for target compounds can be found in Table S1 (Supporting Information).

Preparative HPLC was conducted on a Varian Prostar reverse phase HPLC using either (a) a Phenomenex Luna C18 column (10 μm, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 0.1% v/v TFA) in H_2O (containing 0.1% v/v TFA) gradient to 95% CH_3CN, 20 mL/min, λ = 220 nm, or (b) a Phenomenex Luna C18 column (10 μm, 250 mm × 50 mm), 5% (v/v) CH_3CN (containing 0.1% v/v TFA) in H_2O (containing 0.1% v/v TFA) gradient to 95% CH_3CN, 50 mL/min, λ = 220 nm.

General Procedure A: Suzuki-Miyaura Coupling for the Preparation of Biphenylsulfonamides. Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-3-sulfonic Acid Ethylamide (4a). To a microwave vial was added **5** (0.050 g, 0.19 mmol), 3-(*N*-ethylsulfamoyl)phenylboronic acid (0.064 g, 0.28 mmol), and $Pd(PPh_3)_4$ (6.4 mg, 0.0056 mmol). To this mixture was added benzene (0.74 mL), ethanol (0.21 mL), and aqueous sodium carbonate (2 M, 0.19 mL, 0.37 mmol). The resulting reaction mixture was heated under microwave irradiation at 100 °C for 30 min. The solvents were evaporated, and the mixture was taken up in dimethyl sulfoxide (DMSO), syringe-filtered, and then purified by HPLC. The appropriate fractions were combined and lyophilized to give **4a** as a solid TFA salt (0.11 mg, 12% yield). Exact mass calculated for $C_{21}H_{28}N_2O_2S$: 372.2. Found: HPLC/MS (ES+) m/z = 373.1 $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.09 (t, J = 7.3, 3H), 1.35 (d, J = 6.8, 0.3H), 1.46−1.53 (m, 2.7H), 1.72−1.83 (m, 1H), 2.03−2.24 (m, 2H), 2.33−2.44 (m, 1H), 2.95 (q, J = 7.2, 2H), 3.05−3.24 (m, 2H), 3.25−3.32 (m, 2H), 3.51−3.61 (m, 1H), 3.63−3.73 (m, 1H), 3.75−3.83 (m, 1H), 7.49 (d, J = 8.1, 2H), 7.64−7.74 (m, 3H), 7.82−7.93 (m, 2H), 8.04−8.11 (m, 1H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-3-sulfonic Acid Isopropylamide (4b). Compound **4b** was prepared in a manner similar to that described for **4a**, using **5** (50 mg, 0.19 mmol) and 3-(*N*-isopropylsulfamoyl)phenylboronic acid (68 mg, 0.28 mmol) as starting materials, to give **4b** as a solid TFA salt (6.0 mg, 6%). Exact mass calculated for $C_{22}H_{30}N_2O_2S$: 386.2. Found: HPLC/MS (ES+) m/z = 387.1 $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.03−1.11 (m, 6 H), 1.35 (d, J = 6.8, 0.3H), 1.50 (d, J = 6.6, 2.7H), 1.71−1.84 (m, 1H), 2.03−2.24 (m, 2H), 2.32−2.43 (m, 1H), 3.05−3.24 (m, 2H), 3.25−3.31 (m, 2H), 3.38−3.47 (m, 1H), 3.51−3.61 (m, 1H), 3.63−3.73 (m, 1H), 3.75−3.83 (m, 1H), 7.49 (d, J = 8.3, 2H), 7.63−7.74 (m, 3H), 7.84−7.92 (m, 2H), 8.09−8.14 (m, 1H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-3-sulfonic Acid Diethylamide (4c). Compound **4c** was prepared in a manner similar to that described for **4a**, using **5** (50 mg, 0.19 mmol) and 3-(*N*,*N*-diethylsulfamoyl)phenylboronic acid (72 mg, 0.28 mmol) as starting materials, to give **4c** as a solid TFA salt (9.0 mg, 9%). Exact mass calculated for $C_{23}H_{32}N_2O_2S$: 400.2. Found: HPLC/MS (ES+) m/z = 401.1 $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.05−1.20 (m, 6H), 1.33 (d, J = 6.6, 0.3H), 1.43−1.53 (m, 2.7H), 1.67−1.84 (m, 1H), 2.00−2.26 (m, 2H), 2.30−2.43 (m, 1H), 3.01−3.30 (m, 8H), 3.47−3.60 (m, 1H), 3.60−3.71 (m, 1H), 3.71−3.84 (m, 1H), 7.45−7.53 (m, 2H), 7.61−7.71 (m, 3H), 7.76−7.94 (m, 2H), 7.99 (s, 1H). Purity by reverse-phase HPLC found to be 93.8%.

Preparation of 1-{4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-3-sulfonyl}-piperidine (4d). Compound **4d** was prepared in a manner similar to that described for **4a**, using **5** (50 mg, 0.19 mmol) and 3-(piperidin-1-ylsulfonyl)phenylboronic acid (75 mg, 0.28 mmol) as starting materials, to give **4d** as a solid TFA salt (14 mg, 14%). Exact mass calculated for $C_{24}H_{32}N_2O_2S$: 412.2. Found: HPLC/MS (ES+) m/z = 413.2 $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (d, J = 6.8, 0.3H), 1.42−1.54 (m, 4.7H), 1.62−1.71 (m, 4H), 1.72−1.84 (m, 1H), 2.03−2.25 (m, 2H), 2.33−2.44 (m, 1H), 3.00−3.07 (m, 4H), 3.07−3.25 (m, 2H), 3.25−3.31 (m, 2H), 3.51−3.62 (m, 1H), 3.64−3.73 (m, 1H), 3.74−3.83 (m, 1H), 7.49 (d, J = 8.1, 2H), 7.67−7.80 (m, 4H), 7.92−7.98 (m, 2H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Ethylamide (4e). Compound **4e** was prepared in a manner similar to that described for **4a**, using **5** (50 mg, 0.19 mmol) and 4-(*N*-ethylsulfamoyl)phenylboronic acid (64 mg, 0.28 mmol) as starting materials, to give **4e** as a solid TFA salt (6.0 mg, 6%). Anal. Calcd for $C_{21}H_{28}N_2O_2S...1/2H_2O$: C, 66.11; H, 7.66; N, 7.34. Found: C, 66.36; H, 7.37; N, 7.26. Exact mass calculated for $C_{21}H_{28}N_2O_2S$: 372.2. Found: HPLC/MS (ES+) m/z = 373.2 $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.08 (t, J = 7.2, 3H), 1.33 (d, J = 6.8, 0.3H), 1.48 (d, J = 6.6, 2.7H), 1.70−1.83 (m, 1H), 2.00−2.25 (m, 2H), 2.30−2.42 (m, 1H), 2.93 (q, J = 7.2, 2H), 3.06−3.30 (m, 4H), 3.48−3.59 (m, 1H), 3.59−3.69 (m, 1H), 3.70−3.81 (m, 1H), 7.42−7.51 (m, 2H), 7.67−7.73 (m, 2H), 7.78−7.84 (m, 2H), 7.88−7.94 (m, 2H).

General Procedure B: Suzuki-Miyaura Coupling for the Preparation of Biphenylsulfonamides. Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Isopropylamide (4f). To a microwave vial was added 4-bromo-*N*-isopropylbenzenesulfonamide (151 mg, 0.545 mmol), **6** (127 mg, 0.545 mmol), and $Pd(PPh_3)_4$ (0.019 g, 0.016 mmol). To this mixture was added benzene (3.0 mL), ethanol (1.0 mL), and aqueous sodium carbonate (2M, 0.55 mL, 1.1 mmol). The reaction mixture was heated under microwave irradiation at 100 °C for 60 min. The resulting yellow organic phase was separated, and the clear aqueous layer was extracted twice with ethyl acetate (5 mL each). The solvent was evaporated under reduced pressure. The crude residue was dissolved in a mixture of acetonitrile and acetic acid, and purified by preparative HPLC. The product containing fractions were combined, and the solvents were evaporated under reduced pressure. The resulting aqueous layer was made basic (pH ∼10) with 2 M aqueous sodium carbonate solution (1 mL) and extracted with ethyl acetate (45 mL). The aqueous layer was then saturated

with sodium chloride and extracted twice with ethyl acetate (45 mL each). The ethyl acetate extracts were combined, dried over magnesium sulfate, and filtered. A 1.0 M solution of HCl in diethyl ether (1.5 equiv) was added to the filtrate, and the solvents were evaporated under reduced pressure to give **4f** as a white solid HCl salt (0.17 g, 76%). Exact mass calculated for $C_{22}H_{30}N_2O_2S$: 386.2. Found: HPLC/MS (ES+) $m/z = 387.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.01−1.08 (m, 6H), 1.33 (d, $J = 6.8$, 0.3H), 1.50 (d, $J = 6.3$, 2.7H), 1.71−1.83 (m, 1H), 2.02−2.20 (m, 2H), 2.30−2.40 (m, 1H), 3.07−3.20 (m, 2H), 3.23−3.43 (m, 3H), 3.51−3.69 (m, 2H), 3.72−3.82 (m, 1H), 7.46 (d, $J = 8.1$, 2 H), 7.68 (d, $J = 8.1$, 2H), 7.80 (d, $J = 8.6$, 2H), 7.92 (d, $J = 8.6$, 2H).

General Procedure C: Suzuki-Miyaura Coupling for the Preparation of Biphenylsulfonamides. Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Diethylamide (4g). To a microwave vial was added **5** (200 mg, 0.746 mmol), 4-(*N,N*-diethylsulfamoyl)phenylboronic acid (249 mg, 0.969 mmol), and $Pd(PPh_3)_4$ (0.022 g, 0.019 mmol). To this mixture was added benzene (2.3 mL), ethanol (0.75 mL), and aqueous sodium carbonate (2 M, 0.75 mL, 1.5 mmol). The resulting reaction mixture was heated under microwave irradiation at 100 °C for 30 min. The solvents were evaporated, and the mixture was taken up in DMSO, syringe-filtered, and then purified by HPLC. The appropriate fractions were combined, and the solvent was evaporated. The residue was basified (∼ pH 10) with a 1 M aqueous solution of NaOH and then extracted three times with ethyl acetate. The combined organic phase was washed with brine and dried over sodium sulfate. The solvent was evaporated to give a 0.040 g white solid, which was taken up in MeOH and treated with a 1 M ethereal solution of hydrogen chloride. The solvents were evaporated to give **4g** as a white solid HCl salt (0.039 g, 12%). Exact mass calculated for $C_{23}H_{32}N_2O_2S$: 400.2. Found: HPLC/MS (ES+) $m/z = 401.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.08−1.21 (m, 6H), 1.32 (d, $J = 6.8$, 0.3H), 1.50 (d, $J = 6.3$, 2.7H), 1.71−1.85 (m, 1H), 2.03−2.21 (m, 2H), 2.30−2.41 (m, 1H), 3.07−3.21 (m, 2H), 3.20−3.29 (m, 6H), 3.49−3.59 (m, 1H), 3.59−3.70 (m, 1H), 3.72−3.83 (m, 1H), 7.46 (d, $J = 8.1$, 2H), 7.67 (d, $J = 8.1$, 2H), 7.73−7.83 (m, 2H), 7.84−7.90 (m, 2H). Purity by reverse-phase HPLC found to be 92.7%.

Preparation of 1-{4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine (4h). Compound **4h** was prepared in a manner similar to that described for **4a**, using **5** (0.20 g, 0.75 mmol) and 4-(piperidin-1-ylsulfonyl)phenylboronic acid (0.26 g, 0.97 mmol) as starting materials, to give **4h** as a solid TFA salt (30 mg, 8%). Exact mass calculated for $C_{24}H_{32}N_2O_2S$: 412.2. Found: HPLC/MS (ES+) $m/z = 413.2$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (d, $J = 6.8$, 0.3H), 1.43−1.53 (m, 4.7H), 1.63−1.71 (m, 4H), 1.72−1.83 (m, 1H), 2.04−2.24 (m, 2H), 2.33−2.43 (m, 1H), 3.01−3.05 (m, 4H), 3.06−3.24 (m, 2H), 3.26−3.31 (m, 2H), 3.51−3.61 (m, 1H), 3.64−3.73 (m, 1H), 3.74−3.82 (m, 1H), 7.47−7.51 (m, 2H), 7.71−7.76 (m, 2H), 7.83−7.90 (m, 4H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Amide (4i). Compound **4i** was prepared in a manner similar to that described for **4g**, using **5** (200 mg, 0.746 mmol) and 4-sulfamoylphenylboronic acid (195 mg, 0.969 mmol) as starting materials, to give **4i** as a white solid HCl salt (108 mg, 38%). Exact mass calculated for $C_{19}H_{24}N_2O_2S$: 344.2. Found: HPLC/MS (ES+) $m/z = 345.3$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.48 (d, $J = 5.8$, 3H), 1.7268−1.86 (m, 1H), 2.00−2.22 (m, 2H), 2.297−2.40 (m, 1H), 3.04−3.22 (m, 2H), 3.22−3.30 (m, 2H), 3.47−3.70 (m, 2H), 3.70−3.82 (m, 1H), 7.46 (d, $J = 8.3$, 2H), 7.65−7.71 (m, 2H), 7.74−7.83 (m, 2H), 7.90−8.02 (m, 2H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid (2-Hydroxy-1,1-dimethyl-ethyl)-amide (4j). Compound **4j** was prepared in a manner similar to that described for **4f**, using 4-bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)benzenesulfonamide (0.28 g, 0.90 mmol) and **6** (0.21 g, 0.90 mmol) to give **4j** as an HCl salt (0.19 g, 47%). Exact mass calculated for $C_{23}H_{32}N_2O_3S$: 416.2. Found: HPLC/MS (ES+) $m/z = 417.4$ $[M + H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 1.11−1.15 (m, 6H), 1.32 (d, $J = 6.8$, 1H), 1.48 (d, $J = 6.6$, 3H), 1.70−1.82 (m, 1H), 2.02−2.19 (m, 2H), 2.29−2.40 (m, 1H), 3.06−3.22 (m, 2H), 3.22−3.32 (m, 2H), 3.37−3.40 (m, 2H), 3.50−3.58 (m, 1H), 3.59−3.69 (m, 1H), 3.71−3.80 (m, 1H), 7.45 (d, $J = 8.3$, 2H), 7.68 (d, $J = 8.1$, 2H), 7.76−7.79 (m, 2H), 7.93−7.96 (m, 2H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid (2-Methoxy-ethyl)-amide (4k). Compound **4k** was prepared in a manner similar to that described for **4f**, using **6** (200 mg, 0.858 mmol) and 4-bromo-*N*-(2-methoxyethyl)benzenesulfonamide (252 mg, 0.858 mmol) as starting materials, to give **4k** as a white solid HCl salt (110 mg, 29%). Anal. Calcd for $C_{22}H_{30}N_2O_3S$...HCl: C, 60.19; H, 7.12; N, 6.38. Found: C, 59.89; H, 7.78; N, 6.31. Exact mass calculated for $C_{22}H_{30}N_2O_3S$: 402.2. Found: HPLC/MS (ES+) $m/z = 403.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.23 (d, $J = 6.8$, 0.3H), 1.39 (d, $J = 6.6$, 2.7H), 1.61−1.72 (m, 1H), 1.92−2.11 (m, 2H), 2.21−2.31 (m, 1H), 2.96 (t, $J = 5.6$, 2H), 2.99−3.12 (m, 2H), 3.15 (s, 3H), 3.16−3.19 (m, 2H), 3.29 (t, $J = 5.4$, 2H), 3.39−3.50 (m, 1H), 3.51−3.59 (m, 1H), 3.63−3.71 (m, 1H), 7.37 (d, $J = 8.3$, 2H), 7.59 (d, $J = 8.1$, 2H), 7.69−7.73 (m, 2H), 7.80−7.84 (m, 2H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Cyclopropylmethyl-amide (4l). Compound **4l** was prepared in a manner similar to that described for **4f**, using 4-bromo-*N*-(cyclopropylmethyl)benzenesulfonamide (0.13 g, 0.43 mmol) and **6** (0.10 g, 0.43 mmol), to give **4l** as an HCl salt (0.16 g, 85%). Exact mass calculated for $C_{23}H_{30}N_2O_2S$: 398.2. Found: HPLC/MS (ES+) $m/z = 399.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 0.07−0.13 (m, 2H), 0.39−0.45 (m, 2H), 0.80−0.92 (m, 1H), 1.32 (d, $J = 6.8$, 0.3H), 1.48 (d, $J = 6.3$, 2.7H), 1.70−1.81 (m, 1H), 2.00−2.20 (m, 2H), 2.30−2.39 (m, 1H), 2.76 (d, $J = 6.8$, 2H), 3.05−3.21 (m, 2H), 3.23−3.32 (m, 2H), 3.48−3.59 (m, 1H), 3.60−3.69 (m, 1H), 3.72−3.80 (m, 1H), 7.45 (d, $J = 8.3$, 2H), 7.68 (d, $J = 8.3$, 2H), 7.77−7.82 (m, 2H), 7.87−7.93 (m, 2H).

Preparation of (4′-[2-((*R*)-2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Cyclobutylamide (4m). Compound **4m** was prepared in a manner similar to that described for **4f**, using 4-bromo-*N*-cyclobutylbenzenesulfonamide (0.14 g, 0.49 mmol) and **6** (0.11 g, 0.49 mmol) as starting materials, to give **4m** as a white solid HCl salt (0.14 g, 70%). Exact mass calculated for $C_{23}H_{30}N_2O_2S$: 398.2. Found: HPLC/MS (ES+) $m/z = 399.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.33 (d, $J = 6.8$, 0.3H), 1.50 (d, $J = 5.8$, 2.7H), 1.52−1.63 (m, 2H), 1.72−1.89 (m, 3H), 1.98−2.19 (m, 4H), 2.29−2.41 (m, 1H), 3.06−3.21 (m, 2H), 3.23−3.34 (m, 2H), 3.50−3.70 (m, 2H), 3.70−3.82 (m, 2H), 7.46 (d, $J = 8.1$, 2H), 7.68 (d, $J = 8.1$, 2H), 7.75−7.82 (m, 2H), 7.86−7.93 (m, 2H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid (Tetrahydro-pyran-4-yl)-amide (4n). Compound **4n** was prepared in a manner similar to that described for **4f**, using 4-bromo-*N*-(tetrahydro-2*H*-pyran-4-yl)-benzenesulfonamide (0.14 g, 0.43 mmol) and **6** (0.10 g, 0.43 mmol), to give **4n** as an HCl salt (0.051 g, 24%). Anal. Calcd for $C_{24}H_{32}N_2O_3S$...HCl...H_2O: C, 59.67; H, 7.30; N, 5.80. Found: C, 59.62; H, 7.12; N, 5.85. Exact mass calculated for $C_{24}H_{32}N_2O_3S$: 428.2. Found: HPLC/MS (ES+) $m/z = 429.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 0.89−1.01 (m, 1H), 1.16−1.23 (m, 1H), 1.34 (d, $J = 6.8$, 0.3H), 1.44−1.56 (m, 4.7H), 1.65−1.72 (m, 2H), 1.73−1.85 (m, 1H), 2.04−2.27 (m, 2H), 2.32−2.42 (m, 1H), 3.08−3.24 (m, 2H), 3.26−3.41 (m, 3H), 3.53−3.60 (m, 1H), 3.63−3.72 (m, 1H), 3.74 − 3.88 (m, 3H), 7.49 (d, $J = 8.1$, 2H), 7.72 (d, $J = 8.1$, 2H), 7.83 (d, $J = 8.6$, 2H), 7.96 (d, $J = 8.3$, 2H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Phenylamide (4o). Compound **4o** was

prepared in a manner similar to that described for **4f**, using 4-bromo-*N*-phenylbenzenesulfonamide (0.14 g, 0.43 mmol) and **6** (0.10 g, 0.43 mmol), to give **4o** as an HCl salt (0.18 g, 90%). Exact mass calculated for $C_{25}H_{28}N_2O_2S$: 420.2. Found: HPLC/MS (ES+) $m/z = 421.3$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.34 (d, $J = 6.8$, 0.3H), 1.50 (d, $J = 6.3$, 2.7H), 1.72−1.83 (m, 1H), 2.04−2.24 (m, 2H), 2.31−2.44 (m, 1H), 3.04−3.22 (m, 2H), 3.24−3.31 (m, 2H), 3.49−3.59 (m, 1H), 3.61−3.69 (m, 1H), 3.73−3.81 (m, 1H), 7.04−7.10 (m, 1H), 7.12−7.16 (m, 2H), 7.20−7.27 (m, 2H), 7.45 (d, $J = 8.34$, 2H), 7.65 (d, $J = 8.34$, 2H), 7.71−7.75 (m, 2H), 7.80−7.85 (m, 2H), 7.92 (s, 1H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid Benzylamide (4p). Compound **4p** was prepared in a manner similar to that described for **4f**, using *N*-benzyl-4-bromobenzenesulfonamide (0.14 g, 0.43 mmol) and **6** (0.10 g, 0.43 mmol), to give **4p** as an HCl salt (0.15 g, 74%). Exact mass calculated for $C_{26}H_{30}N_2O_2S$: 434.2. Found: HPLC/MS (ES+) $m/z = 435.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (d, $J = 6.8$, 0.3H), 1.51 (d, $J = 6.6$, 2.7H), 1.73−1.85 (m, 1H), 2.06−2.25 (m, 2H), 2.33−2.43 (m, 1H), 3.08−3.25 (m, 2H), 3.26−3.32 (m, 2H), 3.51−3.61 (m, 1H), 3.62−3.73 (m, 1H), 3.75−3.82 (m, 1H), 4.11 (s, 2H), 7.19−7.27 (m, 5H), 7.49 (d, $J =$ 8.3, 2H), 7.69 (d, $J = 8.3$, 2H), 7.75−7.80 (m, 2H), 7.87−7.93 (m, 3H).

Preparation of 4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic Acid (Pyridin-4-ylmethyl)-amide (4q). Compound **4q** was prepared in a manner similar to that described for **4f**, using 4-bromo-N-(pyridin-4-ylmethyl)benzenesulfonamide (140 mg, 0.429 mmol) and **6** (100 mg, 0.429 mmol) as starting materials, to give **4q** a white solid HCl salt (135 mg, 67%). Exact mass calculated for $C_{25}H_{29}N_3O_2S$: 435.2. Found: HPLC/MS (ES+) $m/z = 436.5$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.33 (d, $J = 6.8$, 0.3H), 1.50 (d, $J = 6.2$, 2.7H), 1.78 (dd, $J = 12.9$, 8.1, 1H), 2.02−2.21 (m, 2H), 2.30−2.41 (m, 1H), 3.11−3.23 (m, 2H), 3.24−3.37 (m, 2H), 3.49−3.71 (m, 2H), 3.72−3.83 (m, 1H), 4.46 (s, 2H), 7.49 (d, $J = 8.1$, 2H), 7.70 (d, $J =$ 8.1, 2H), 7.84 (d, $J = 8.3$, 2H), 7.96 (d, $J = 8.3$, 2H), 8.11 (d, $J =$ 6.3, 2H), 8.80 (d, $J = 6.6$, 2H).

Preparation of 4-{4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-morpholine (4r). Compound **4r** was prepared in a manner similar to that described for **4g**, using **6** (0.20 g, 0.75 mmol) and 4-(morpholinosulfonyl)phenylboronic acid (0.26 g, 0.97 mmol) as starting materials, to give **4r** as a white solid HCl salt (0.040 g, 11%). Anal. Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.18; H, 6.85; N, 6.59. Exact mass calculated for $C_{23}H_{30}N_2O_3S$: 414.2. Found: HPLC/MS (ES+) $m/z = 415.1$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (d, $J = 6.8$, 0.3H), 1.51 (d, $J = 6.3$, 2.7H), 1.73−1.84 (m, 1H), 2.05−2.24 (m, 2H), 2.33−2.43 (m, 1H), 2.99−3.05 (m, 4H), 3.08−3.25 (m, 2H), 3.26−3.32 (m, 2H), 3.53−3.60 (m, 1H), 3.63−3.72 (m, 1H), 3.72−3.76 (m, 4H), 3.76−3.83 (m, 1H), 7.48−7.52 (m, 2H), 7.72−7.77 (m, 2H), 7.84−7.93 (m, 4H).

Preparation of 3,5-Dimethyl-4-{4′-[2-((*R*)-2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-morpholine (4s). Compound **4s** was prepared in a manner similar to that described for **4f**, using 4-(4-bromophenylsulfonyl)-3,5-dimethylmorpholine (0.29 g, 0.87 mmol) and **6** (0.20 g, 0.87 mmol) as starting materials, to give **4s** as the HCl salt (0.30 g, 73%). Exact mass calculated for $C_{25}H_{34}N_2O_3S$: 442.2. Found: HPLC/MS (ES+) $m/z = 443.1$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.12 (t, $J = 6.95$ Hz, 6H), 1.32 (d, $J = 6.8$, 0.3H), 1.49 (d, $J = 6.3$, 2.7H), 1.70−1.82 (m, 1H), 1.90−1.99 (m, 2H), 2.02−2.21 (m, 2H), 2.29−2.40 (m, 1H), 3.06−3.23 (m, 2H), 3.22−3.32 (m, 2H), 3.50−3.72 (m, 6H), 3.72−3.81 (m, 1H), 7.47 (d, $J = 8.3$, 2H), 7.71 (d, $J = 8.3$, 2H), 7.80−7.89 (m, 4H).

Preparation of 4-{4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl4-sulfonyl}-thiomorpholine 1,1-Dioxide (4t). Compound **4t** was prepared in a manner similar to that described for **4f**, using **6** (0.30 g, 1.29 mmol) and 4-(4-bromo-benzenesulfonyl)-thiomorpholine 1,1-dioxide (0.59 g, 1.67 mmol) as starting materials, to give **4t** as a white solid HCl salt (0.052 g, 25%). Exact mass calculated for $C_{23}H_{30}N_2O_4S_2$: 462.2. Found: HPLC/MS (ES+) $m/z = 463.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (d, $J = 6.8$, 0.3H), 1.51 (d, $J = 6.6$, 2.7H), 1.73−1.85 (m, 1H), 2.04−2.21 (m, 2H), 2.33−2.43 (m, 1H), 3.09−3.22 (m, 2H), 3.22−3.27 (m, 4H), 3.27−3.31 (m, 2H), 3.52−3.61 (m, 1H), 3.62−3.71 (m, 5H), 3.75−3.83 (m, 1H), 7.50 (d, $J = 8.1$, 2H), 7.74 (d, $J = 7.8$, 2H), 7.88−7.95 (m, 4H).

Preparation of 4-Methoxy-1-{4′-[2-((*R*)-2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine (4u). Compound **4u** was prepared in a manner similar to that described for **4f**, using 1-(4-bromophenylsulfonyl)-4-methoxypiperidine (156 mg, 0.468 mmol) and **6** (109 mg, 0.468 mmol) as starting materials, to give **4u** as a white solid HCl salt (126 mg, 56%). Exact mass calculated for $C_{25}H_{34}N_2O_3S$: 442.2. Found: HPLC/MS (ES+) $m/z = 443.3$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.33 (d, $J = 6.3$, 0.3H), 1.50 (d, $J = 6.1$, 2.7H), 1.60−1.83 (m, 3H), 1.85−1.95 (m, 2H), 2.11 (s, 2H), 2.35 (s, 1H), 2.89−2.99 (m, 2H), 3.08−3.37 (m, 10H), 3.64 (s, 2H), 3.77 (s, 1H), 7.48 (d, $J =$ 7.8, 2H), 7.70 (d, $J = 7.6$, 2H), 7.84 (m, 4H).

Preparation of 2-{4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-2,3-dihydro-1*H*-isoindole (4v). Compound **4v** was prepared in a manner similar to that described for **4f**, using 2-(4-bromophenylsulfonyl)isoindoline (0.15 g, 0.43 mmol) and **6** (0.10 g, 0.43 mmol), to give **4v** as an HCl salt (0.14 g, 68%). Exact mass calculated for $C_{27}H_{30}N_2O_2S$: 446.2. Found: HPLC/MS (ES+) $m/z = 447.3$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.33 (d, $J = 6.8$, 0.3H), 1.50 (d, $J = 6.6$, 2.7H), 1.71−1.84 (m, 1H), 2.02−2.23 (m, 2H), 2.31−2.43 (m, 1H), 3.06−3.22 (m, 2H), 3.24−3.32 (m, 2H), 3.50−3.60 (m, 1H), 3.59−3.71 (m, 1H), 3.72−3.82 (m, 1H), 4.62−4.68 (m, 4H), 7.23 (s, 4H), 7.46 (d, $J =$ 8.1, 2H), 7.68 (d, $J = 8.1$, 2H), 7.84 (d, $J = 8.6$, 2H), 7.97 (d, $J =$ 8.3, 2H).

Preparation of (*S*)-1-{4′-[2-((*R*)-2-Methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-pyrrolidin-3-ol (4w). Compound **4w** was prepared in a manner similar to that described for **4f**, using (*S*)-1-(4-bromophenylsulfonyl)pyrrolidin-3-ol (0.15 g, 0.48 mmol) and **6** (0.11 g, 0.48 mmol), to give **4w** as an HCl salt (0.16 g, 74%). Exact mass calculated for $C_{23}H_{30}N_2O_3S$: 414.2. Found: HPLC/MS (ES+) $m/z = 415.2$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.32 (d, $J = 6.8$, 0.3H), 1.49 (d, $J = 6.6$, 2.7H), 1.72−1.82 (m, 2H), 1.82−1.94 (m, 1H), 2.01−2.19 (m, 2H), 2.30−2.40 (m, 1H), 3.06−3.22 (m, 3H), 3.23−3.32 (m, 2H), 3.34−3.41 (m, 3H), 3.50−3.58 (m, 1H), 3.60−3.69 (m, 1H), 3.72−3.81 (m, 1H), 4.26−4.32 (m, 1H), 7.46 (d, $J = 8.3$, 2H), 7.68 (d, $J = 8.1$, 2H), 7.81−7.85 (m, 2H), 7.87−7.91 (m, 2H).

Preparation of (*R*)-2-(Methoxymethyl)-1-(4′-(2-((*R*)-2-methyl-pyrrolidin-1-yl)ethyl)biphenyl-4-ylsulfonyl)pyrrolidine (4x). Compound **4x** was prepared in a manner similar to that described for **4f**, using (*R*)-1-(4-bromophenylsulfonyl)-2-(methoxymethyl)pyrrolidine (0.17 g, 0.52 mmol) and **6** (0.12 g, 0.52 mmol), to give **4x** as an HCl salt (0.16 g, 62%). Exact mass calculated for $C_{25}H_{34}N_2O_3S$: 442.2. Found: HPLC/MS (ES+) $m/z = 443.4$ $[M + H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 1.32 (d, $J = 6.8$, 0.3H), 1.48 (d, $J = 6.3$, 2.7H), 1.57 (d, $J = 12.9$, 2H), 1.70−1.90 (m, 3H), 2.01−2.20 (m, 2H), 2.35 (d, $J = 8.1$, 1H), 3.05−3.23 (m, 3H), 3.23−3.31 (m, 2H), 3.36 (s, 3H), 3.37−3.43 (m, 2H), 3.49−3.69 (m, 3H), 3.72−3.80 (m, 2H), 7.46 (d, $J = 8.1$, 2H), 7.70 (d, $J = 8.1$, 2H), 7.83−7.87 (m, 2H), 7.90−7.93 (m, 2H).

(*R*)-1-(4-Bromophenethyl)-2-methylpyrrolidine (5). Step A. A solution of 4-bromophenethyl alcohol (38.9 g, 193 mmol) in dichloromethane (193 mL) was treated with triethylamine (40.4 mL, 290 mmol), and the mixture was cooled in an ice bath. Methanesulfonyl chloride (18.0 mL, 232 mmol) was added dropwise via an addition funnel. The ice bath was removed, and the mixture was stirred for 30 min. The reaction mixture was diluted with 200 mL of DCM, washed twice with an aqueous solution of 1 M HCl (100 mL each), followed by brine, saturated sodium bicarbonate, and brine again. The organic phase was

dried over sodium sulfate and filtered. The solvent was evaporated under reduced pressure to give 4-bromophenethyl methanesulfonate (54.0 g) in quantitative yield. This material was used without further purification.

Step B. A solution of 4-bromophenethyl methanesulfonate (12.2 g, 43.8 mmol) in acetonitrile (88 mL) was treated with sodium carbonate (6.04 g, 57.0 mmol), followed by (*R*)-(−)-2-methylpyrrolidine (4.48 g, 52.6 mmol). The reaction mixture was warmed to 80 °C and stirred overnight. The sodium carbonate was filtered off, and the solvent was evaporated under reduced pressure. The crude residue was dissolved in ethyl acetate (∼200 mL) and extracted with an aqueous solution of 1 M HCl (75 mL). The ethyl acetate was extracted an additional three times with 1 M HCl (30 mL each). The HCl layers were combined and basified (pH ∼10) by the addition of sodium carbonate. The basic aqueous layer was extracted with dichloromethane (100 mL). A 50% sodium hydroxide solution (1 mL) was added to the aqueous layer which was then extracted three times with dichloromethane (50 mL each). The dichloromethane layers were combined, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to give a yellow oil (10.2 g, 87% crude yield). The crude oil was further purified by silica column chromatography eluting with ethyl acetate followed by 0−10% methanol in ethyl acetate to give **5** as a pale yellow oil (8.85 g, 75%). Exact mass calculated for $C_{13}H_{18}BrN$: 267.1. Found: HPLC/MS (ES+) $m/z = 268.0$ $[M + H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 1.15 (d, $J = 6.06$, 3H), 1.37−1.53 (m, 1H), 1.73−1.86 (m, 2H), 1.94−2.07 (m, 1H), 2.21−2.35 (m, 2H), 2.35−2.48 (m, 1H), 2.68−2.91 (m, 2H), 2.98−3.11 (m, 1H), 3.18−3.29 (m, 1H), 7.14−7.20 (m, 2H), 7.38−7.48 (m, 2H).

(*R*)-4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenylboronic Acid (6). Compound **5** (2.16 g, 8.04 mmol) was dissolved in tetrahydrofuran (20 mL) under argon. The reaction mixture was cooled to −78 °C, and *n*-butyllithium (1.6 M in hexanes, 6.53 mL, 10.4 mmol) was added slowly. After 90 min of stirring, triisopropylborate (7.42 mL, 32.1 mmol) was added. The reaction was kept at −78 °C for 2 h. The mixture was allowed to warm to room temperature and stirred for 1.5 h. The cloudy reaction mixture was quenched with an aqueous solution of 1 M HCl (40 mL). The THF was evaporated under reduced pressure. The remaining aqueous solution was basified (pH ∼8) with 50% aqueous sodium hydroxide and extracted twice with ethyl acetate (50 mL each), and then three times with dichloromethane (50 mL each). The combined organics were dried over magnesium sulfate, filtered, and concentrated to give 1.70 g of a yellow foam. The foam was triturated with 20 mL of diethyl ether twice and dried under high vacuum to give **6** as a pale yellow solid (1.19 g, 64%). This material was used without further purification. Exact mass calculated for $C_{13}H_{20}BNO_2$: 233.2. Found: HPLC/MS (ES+) $m/z = 234.2$ $[M + H]^+$.

General Procedure D: Preparation of Bromophenyl Sulfonamides. 4-Bromo-*N*-cyclobutylbenzenesulfonamide (7m). 4-Bromobenzene-1-sulfonyl chloride (1.0 g, 4.0 mmol) was dissolved in THF (16 mL). DIEA (1.4 mL, 7.9 mmol) was added followed by cyclobutanamine (0.41 mL, 4.8 mmol). The reaction mixture was allowed to stir overnight. The reaction mixture was diluted with 100 mL of ethyl acetate and washed first with an aqueous solution of 1 M HCl (20 mL once, 10 mL once) and then brine (10 mL). The organic phase was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give **7m** as a white solid in quantitative yield. This material was used without further purification. Exact mass calculated for $C_{10}H_{12}BrNO_2S$: 289.0. Found: HPLC/MS (ES+) $m/z = 289.9$ $[M + H]^+$, 291.9 $[M + 2 + H]^+$.

Pharmacokinetics. Pharmacokinetic characterizations of compounds **4e**, **4k**, **4n**, and **4r** were conducted in male Sprague−Dawley (SD) rats after a single oral or intravenous administration formulated in 0.9% NaCl at 10 and 2 mg/kg, respectively. Blood samples were collected up to 21 h after administration. CNS distribution of compounds **4e**, **4k**, **4n**, and **4r** were evaluated in male SD rats at 0.5 h after a single oral administration at 10 mg/kg. Plasma samples were obtained by centrifugation of blood samples. Brain samples were homogenized. Plasma and homogenized brain samples were then prepared by protein precipitation with acetonitrile followed by centrifugation. The extract was analyzed for compounds **4e**, **4k**, **4n**, and **4r** using a selective LC-MS/MS method. The LC/MS/MS was operated in multiple reaction monitoring (MRM) mode under optimized conditions for detection of compounds **4e**, **4k**, **4n**, and **4r** and the internal standard using positive ions formed by electrospray ionization. Quantitation was determined using a weighted regression analysis of peak area ratios of analyte and internal standard.

In Vivo Assays

Subjects. Animal studies were performed according to the Guide for the Care and Use of Laboratory Animals published by the National Academy of Sciences (1996) and approved by the Arena Pharmaceuticals Animal Care and Use committee.

Male Sprague−Dawley rats (Harlan, San Diego, CA) were used for all *in vivo* studies. These rats were maintained in a temperature-controlled environment under a 12 h light−dark cycle, and food and water were available *ad-libitum* except during test (see below).

Blockade of RAMH-Induced Drinking. For this assay, rats were housed three per cage, with lights off at 1130 h. At 1030 h on the day of test, rats were individually housed in new cages and food was removed. 2 h later, rats were administered the test article (vehicle or H_3 antagonist). Thirty minutes later, water was removed, and RAMH (vehicle or RAMH 3 mg/kg salt SC) was administered. Ten minutes after the administration of RAMH, water intake was measured over a 20-min period.

Sleep Studies. All rats used in the acute sleep studies were prepared with plastic implants designed to provide continuous EEG and electromyographic (EMG) recordings (Plastics One, Inc., Roanoke, VA). To this end, rats were anesthetized with a ketamine (80 mg/kg)/xylazine(12 mg/kg) cocktail, fitted into a stereotaxic apparatus, and a dorsal midline incision along the top of the head was used to expose the skull. Four stainless steel spring top screws (#000) were implanted so as to penetrate the skull and contact but not disturb the dura. These served as electrodes to which EEG leads were attached. Two of these screws were implanted on the left (β-1.0 mm AP, β −3.0 mm ML; and λ +1.0 mm AP, λ −4.0 mm) and used to record α and δ EEG. The remaining two screws were implanted on the right (β +3.0 mm AP, β +1.0 mm ML; and λ +4.0 mm AP, λ +1.0 mm) and used to record θ waves. Finally, two electrodes for EMG recordings were implanted into dorsal neck muscles and secured with sutures. The plastic connector from which the six recording electrodes emanated was then secured to the skull with cement (3 M Garant), and the scalp was sutured around the implant to allow protrusion of the lead connectors. All animals were treated with buprenex (0.3 mg/kg, intramuscular) for two post operative days. Rats were allowed at least 2 weeks of recovery before experimentation. At test, the rats were housed in plastic testing boxes (Dragonfly, Inc., 34 cm × 24 cm × 50 cm) with free access to food and water. Skull implants were connected to a cable-swivel assembly that allowed the rats to move freely within the cage and transmitted data to a data collection system

(Embla A10; Embla Systems; Broomfield, CO). EEG and EMG recordings were then digitized and analyzed using Somnologica Science Software (Embla Systems; Broomfield, CO).

Supporting Information Available: HPLC/MS purity and retention times for target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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