Novel Terphenyls as Selective Cyclooxygenase-2 Inhibitors and Orally Active Anti-inflammatory Agents

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A novel series of terphenyl methyl sulfones and sulfonamides have been shown to be highly potent and selective cyclooxygenase-2 (COX-2) inhibitors. The sulfonamide analogs **17** and **21** were found to be much more potent COX-2 inhibitors and orally active anti-inflammatory agents than the corresponding methyl sulfone analogs **16** and **20**, respectively, albeit with some decrease in COX-2 selectivity. Structure−activity relationship studies have determined that incorporation of two fluorine atoms in the central phenyl group, as in **20** and **21**, is extremely advantageous for both *in vitro* COX-2 potency and selectivity as well as *in vivo* activity. Several noticeable examples in the 1,2-diaryl-4,5-difluorobenzenesulfonamide series are **21a**−**c**,**k**,**l**,**n** (COX-2, IC_{50} = 0.002−0.004 μM), in which all have *in vitro* COX-1/COX-2 selectivity >1000. In addition, sulfonamides **21a**,**b**,**d**,**g**,**j**,**m**,**n**,**q** were shown to have greatly enhanced oral activity with more than 90% inhibition of prostaglandin E_2 production in the air pouch model of inflammation. Furthermore, sulfonamide **21b** was found to be very active in the rat adjuvant-induced arthritis model (ED_{50} = 0.05 mg/kg) and carrageenan-induced hyperalgesia assay (ED_{50} = 38.7 mg/kg) with no indication of gastrointestinal toxicity in rats at doses as high as 200 mg/kg.

Introduction

Commercially available nonsteroidal anti-inflammatory drugs (NSAIDs) are generally effective and widely used for the treatment of inflammatory conditions.[1−3] However, the disruption of beneficial prostaglandin (PG) production by all currently used NSAIDs results in a mechanism-based toxicity mainly in the gastrointestinal (GI) tract and kidney[4−6] and thus limits their therapeutic usefulness especially when long-term treatment is involved. Recently an inducible cyclooxygenase (COX) isozyme, now commonly known as COX-2, was discovered and found to be expressed primarily in inflamed tissues.[7−10] As a result of this critical finding, a substantial discovery effort has been underway in the pharmaceutical industry to identify selective and orally active COX-2 inhibitors[11,12] because they may provide the desired anti-inflammatory and analgesic profiles without the deleterious side effects commonly associated with the existing NSAIDs. Several distinct classes of selective COX-2 inhibitors, e.g., **1**−**12** (Figure 1), have appeared in the literature,[13−24] and most of these reported examples of selective COX-2 inhibitors demonstrate potent anti-inflammatory activity in the rat adjuvant-induced arthritis model along with exceptional safety profiles in comparison with the current NSAIDs.

The preliminary report[25] that **16a** (Figure 1) was found to be a modestly selective COX-2 inhibitor has prompted us to report our results on terphenyl COX-2 inhibitors. We have successfully identified a novel series of 1,2-diaryl-4,5-difluorobenzenesulfonamides **21** which have greater *in vitro* COX-1/COX-2 enzyme selectivity and vastly superior *in vivo* activity than what was previously observed for **16a**. In this article, we describe the design, synthesis, and structure-activity relationship (SAR) studies of these terphenyl compounds as selective COX-2 inhibitors, which ultimately led to the identification of an anti-inflammatory agent with a greatly improved safety profile.

Chemistry

The general synthetic strategy employed to prepare the terphenyl analogs was based on palladium(0)-catalyzed aryl−aryl-coupling reactions. As shown in Scheme 1, a series of 1,2-diarylbenzenes **16a**−**e** were prepared from 1,2-dibromobenzene (**14**) via sequential Suzuki cross-coupling reactions.[26] Two equivalents of **14** was used in the first coupling step to minimize the formation of symmetrically bis-coupled product. The arylboronic acid starting materials either were commercially available or could be simply prepared in yields of 60−80% from the corresponding aryl bromides in a metal−halogen exchange reaction followed by addition of trimethyl borate and subsequent hydrolysis. Preparation of 1,2-diaryl-4,5-difluorobenzenes **20a**−**o** from commercially available 1,2-dibromo-4,5-difluorobenzene (**18**) was carried out in an analogous manner. Sulfonamide analogs **17a**−**e** and **21a**−**o** were prepared directly from the corresponding methyl sulfone analogs **16a**−**e** and **20a**−**o**, respectively, using the convenient one-pot procedure recently reported by Huang et al.[27]

Due to difficulties in the preparation of pyridylboronic acids, a modified procedure was used for the synthesis of pyridyl analogs **20p**,**q**, as illustrated in Scheme 2. Suzuki cross-coupling reaction of **13** and **18** gave aryl bromide **22**, which was converted to the arylboronic acid **23** via a Grignard intermediate. Subsequent Suzuki cross-coupling reaction of **23** and 2-bromo-5-methylpyridine followed by oxidation with Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) gave pyridyl analog **20p**. For the synthesis of **20q**, the pyridyltin intermediate **25** was

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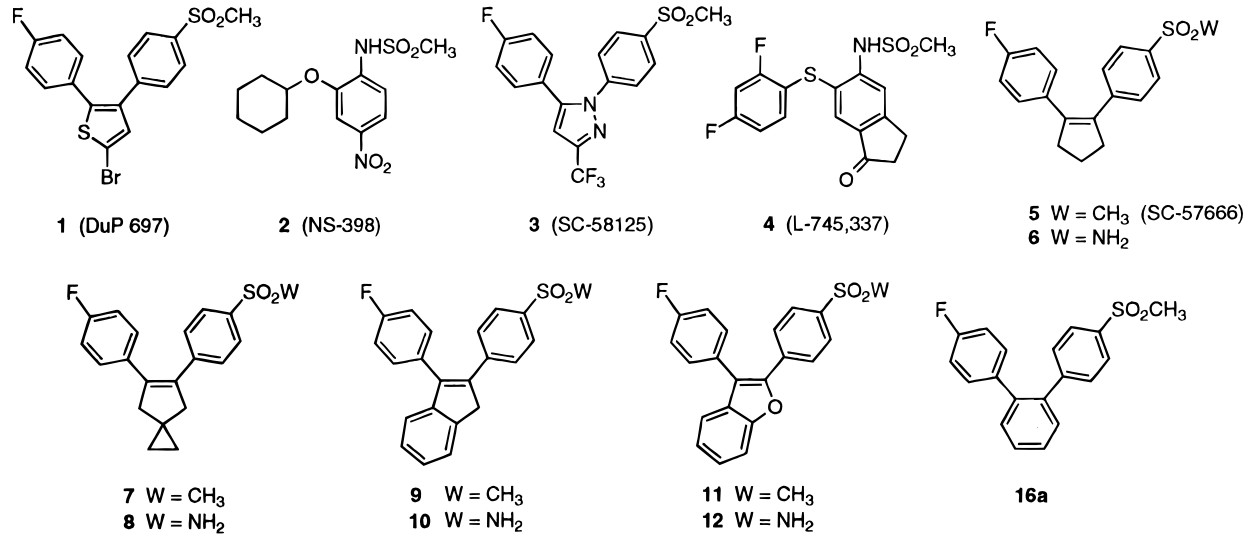
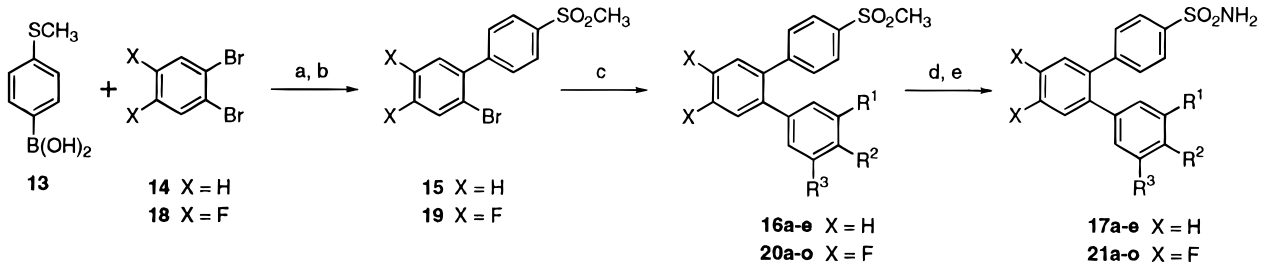


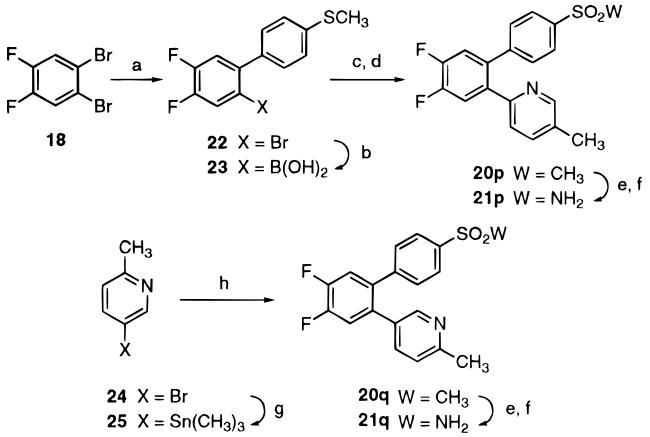
Figure 1. Representative examples of selective COX-2 inhibitors.

Scheme 1[a]



[a] Reagents: (a) 5 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3, ethanol, toluene, reflux; (b) *m*-CPBA; (c) 3-R^1-4-R^2-5-R^3-$C_6H_2B(OH)_2$, 5 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3, ethanol, toluene, reflux; (d) *n*-PrMgCl, 0 °C, BEt_3, 0 °C to reflux; (e) NaOAc, H_2O, H_2NOSO_3H, 0 °C to room temperature.

Scheme 2[a]

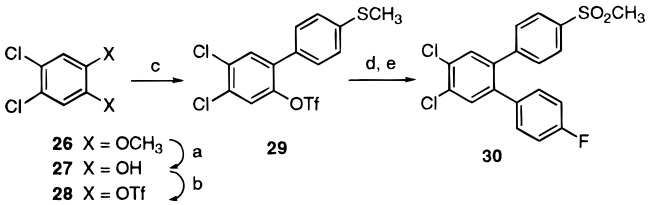


[a] Reagents: (a) **13**, 5 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3, ethanol, toluene, reflux; (b) Mg, reflux, $B(OCH_3)_3$, 0 °C to room temperature, 10% NaOH, (c) 2-bromo-5-methylpyridine, 5 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3, ethanol, toluene, reflux; (d) Oxone; (e) *n*-PrMgCl, 0 °C, BEt_3, 0 °C to reflux; (f) NaOAc, H_2O, H_2NOSO_3H, 0 °C to room temperature; (g) *n*-BuLi, $(CH_3)_3SnCl$, −78 °C to room temperature; (h) **19**, 5 mol % $Pd(PPh_3)_4$, toluene, reflux.

prepared from bromopyridine **24**[28] by treatment with *n*-butyllithium in tetrahydrofuran at −78 °C followed by addition of trimethyltin chloride. Stille cross-coupling reaction[29] of **19** and **25** gave the desired pyridyl analog **20q**.

Preparation of 1,2-diaryl-4,5-dichlorobenzene **30** is shown in Scheme 3. Treatment of dichloroveratrole (**26**)[30] with tribromoborane gave the catechol **27**, which was converted to its ditriflate **28**. A modified Suzuki reaction of **28** with **13** gave **29**; a second modified Suzuki

Scheme 3[a]



[a] Reagents: (a) BBr_3; (b) Tf_2O, pyridine; (c) **13**, 5 mol % $Pd(PPh_3)_4$, K_2CO_3, toluene, reflux; (d) 4-$FC_6H_4B(OH)_2$, 5 mol % $Pd(PPh_3)_4$, K_2CO_3, toluene, reflux; (e) *m*-CPBA.

reaction with (4-fluorophenyl)boronic acid and subsequent *m*-CPBA oxidation produced **30** directly.

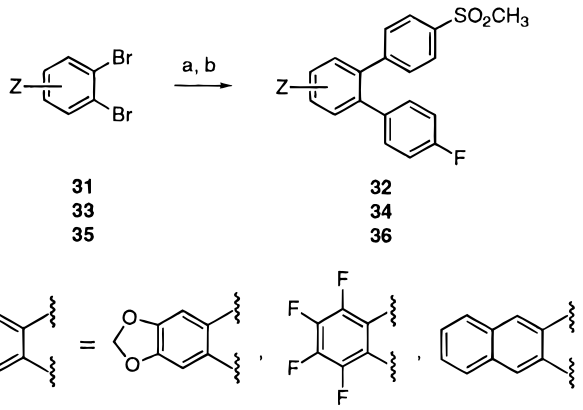
Analogs **32**, **34**, and **36** were prepared by an one-pot reaction procedure using an equal molar ratio of **13**, (4-fluorophenyl)boronic acid, and **31**, **33**, or **35**, respectively, as shown in Scheme 4.[31] Oxidation of the initial mixture followed by purification provided the desired compounds.

Scheme 5 shows the preparation of pyrazine **39**. Nucleophilic aromatic substitution of fluoride in **37** with sodium methanesulfinate gave the (methylsulfonyl)-benzil **38**, which was reacted with ethylenediamine followed by DDQ oxidation to provide pyrazine **39**.

Biological Results and Discussion

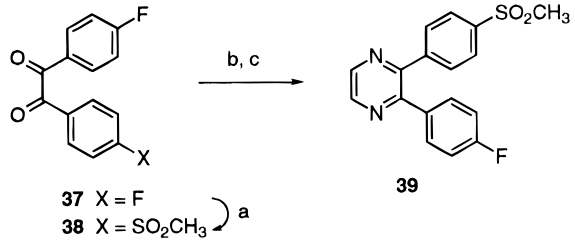
All compounds were initially evaluated for inhibitory activity against both constitutive (COX-1) and inducible (COX-2) forms of the human recombinant enzymes.[14] IC_{50} values were determined, and these values are used in all the following discussion of *in vitro* activity.

Scheme 4[a]



[a] Reagents: (a) **13**, 4-$FC_6H_4B(OH)_2$, 5 mol % $Pd(PPh_3)_4$, 2 M Na_2CO_3, ethanol, toluene, reflux; (b) *m*-CPBA.

Scheme 5[a]

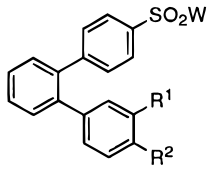


[a] Reagents: (a) CH_3SO_2Na; (b) ethylenediamine; (c) DDQ.

Inhibitors with COX-2 IC_{50} < 0.5 μM and selectivity ratio (IC_{50} of COX-1/IC_{50} of COX-2) of >300 were subsequently measured for their oral activity in an acute inflammation model, the foot-pad air pouch assay.[32] Selected compounds with good activity in this assay were further investigated in a chronic inflammation model, the rat adjuvant-induced arthritis assay,[21,33] and/or an analgesic model, the rat carrageenan-induced hyperalgesia assay.[34] Finally, compounds possessing the desired *in vivo* activity profiles were evaluated for GI toxicity in the rat.[35]

***In Vitro* Activity**. One common feature of many of the previously reported selective COX-2 inhibitors (Figure 1) is 1,2-diaryl substitution to a central ring, e.g., thiophene moiety for **1**, pyrazole for **3**, cyclopentene for **5** and **6**, spiro[2,4]heptene for **7** and **8**, indene for **9** and **10**, and benzofuran for **11** and **12**. It seemed reasonable to us that a phenyl group could serve as the central ring and that it might also provide greater *in vivo* stability relative to the cyclopentene moiety in **5**.[21,23] Thus, a series of simple terphenyls were prepared, and a SAR investigation around the 4-fluorophenyl moiety in **16a** was initiated. Both methyl sulfones **16** and corresponding sulfonamides **17** were evaluated as potential selective COX-2 inhibitors, and their COX-1 and COX-2 IC_{50}s are summarized in Table 1. The methyl sulfones **16a**−**e** were found to be modest (**16c**, COX-2 = 0.14 μM) to weak (**16e**, COX-2 = 11.4 μM) COX-2 inhibitors, whereas the corresponding sulfonamides **17a**−**e** were found to be more potent in both COX-2 and COX-1 inhibition. For example, this trend can be seen from the comparison of sulfone **16b** (COX-2 = 0.36 μM, COX-1 > 100 μM) with sulfonamide **17b** (COX-2 = 0.017 μM, COX-1 = 9.24 μM). This observation is consistent with our earlier findings in the cyclopentene COX-2 inhibitor series.[21,23]

Table 1. *In Vitro* Inhibition of COX-1 and COX-2 Enzyme and *in Vivo* Air Pouch Activity of Sulfones **16**−**e** and Sulfonamides **17a**−**e**



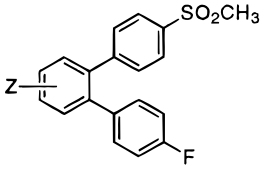
W = CH_3, **16a-e**

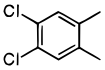
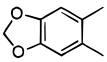
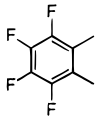
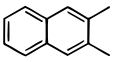
W = NH_2, **17a-e**

compd[a]	R^1	R^2	IC_{50} (μM) COX-2[b]	IC_{50} (μM) COX-1[b]	selectivity[c]	air pouch (2 mg/kg)[a]
16a	H	F	0.26	>100	>380	63
17a	H	F	0.061	19.0	300	68
16b	Cl	F	0.36	>100	>280	ND[d]
17b	Cl	F	0.017	9.2	540	ND[d]
16c	H	Cl	0.14	>100	>710	50
17c	H	Cl	0.006	3.9	650	33
16d	F	CH_3O	>100	>100	ND[d]	ND[d]
17d	F	CH_3O	0.033	13.2	400	34
16e	Cl	CH_3O	11.4	>100	>9	ND[d]
17e	Cl	CH_3O	0.019	8.2	430	45

[a] See the Experimental Section. [b] See Supporting Information and ref 14. [c] Ratio of COX-1/COX-2. [d] Not determined.

Table 2. *In Vitro* Inhibition of COX-1 and COX-2 Enzyme

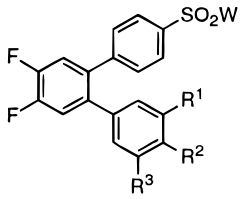


compd[a]	Z	IC_{50} (μM) COX-2[b]	IC_{50} (μM) COX-1[b]
16a		0.26	>100
20a		0.014	>100
30		0.24	>100
32		0.083	>100
34		>100	>100
36		>100	>100
39		>100	>100

[a] See the Experimental Section. [b] See Supporting Information and ref 14.

In order to investigate the SAR of the central phenyl group in **16a**, several 1,2-diaryl-substituted terphenyl analogs (**20a**, **30**, **32**, **34**, **36**, and **39**) were prepared (Scheme 1−5). As shown in Table 2, incorporation of two fluorine atoms to the central phenyl ring gave the 4,5-difluorophenyl analog **20a** (COX-2 = 0.014 μM), which is 18 times more potent than the simple terphenyl **16a** (COX-2 = 0.26 μM). Replacement of two fluorines

Table 3. *In Vitro* Inhibition of COX-1 and COX-2 Enzyme and *in Vivo* Air Pouch Activity of Sulfones **20**−**q** and Sulfonamides **21a**−**q**



W = CH_3, **20a-q**
W = NH_2, **21a-q**

compd[a]	R^1	R^2	R^3	IC$_{50}$ (μM) COX-2[b]	IC$_{50}$ (μM) COX-1[b]	selectivity[c]	air pouch (2 mg/kg)[a]
20a	H	F	H	0.014	>100	>7100	ND[d]
21a	H	F	H	0.004	5.7	1400	99
20b	H	F	Cl	0.010	>100	>10 000	54
21b	H	F	Cl	0.002	5.5	2750	94
20c	H	F	CH_3	0.005	>100	>20 000	44
21c	H	F	CH_3	0.002	3.7	1850	88
20d	H	CH_3O	F	0.021	>100	>4750	37
21d	H	CH_3O	F	0.013	22.5	1700	96
20e	H	CH_3O	Cl	0.019	>100	>5250	28
21e	H	CH_3O	Cl	0.013	18.9	1450	90
20f	Cl	CH_3O	Cl	>100	>100	ND[d]	ND[d]
21f	Cl	CH_3O	Cl	0.021	>100	4750	36
20g	H	CH_3O	CH_3	0.013	>100	>7700	66
21g	H	CH_3O	CH_3	0.005	10.9	2200	98
20h	H	CH_3O	CH_3O	0.34	>100	>300	0
21h	H	CH_3O	CH_3O	0.065	>100	>1500	24
20i	H	OCH_2CH_2O		0.34	>100	>300	0
21i	H	OCH_2CH_2O		0.032	17.9	550	0
20j	H	OCH_2O		0.012	>100	>8300	47
21j	H	OCH_2O		0.004	1.7	400	97
20k	H	CH_3	H	0.007	>100	>14 300	1
21k	H	CH_3	H	0.004	17.0	4250	83
20l	H	CH_3	Cl	0.013	>100	>7700	27
21l	H	CH_3	Cl	0.003	16.5	5500	88
20m	H	CH_3	CH_3	0.023	>100	>4300	51
21m	H	CH_3	CH_3	0.005	14.6	2900	96
20n	H	Cl	CH_3	0.006	>100	>16 600	53
21n	H	Cl	CH_3	0.003	3.9	1300	93
20o	H	$(CH_3)_2N$	Cl	0.008	>100	>12 500	64
21o	H	$(CH_3)_2N$	Cl	0.006	0.59	100	ND[d]
20p	see Scheme 2			52.3	>100	2	2
21p	see Scheme 2			0.33	>100	>300	56
20q	see Scheme 2			0.17	>100	>600	65
21q	see Scheme 2			0.051	265	5200	100
indomethacin[b]				0.9	0.1	0.1	98

[a] See the Experimental Section. [b] See Supporting Information and ref 14. [c] Ratio of COX-1/COX-2. [d] Not determined.

in the central ring in **20a** with chlorine atoms was found to have a deleterious effect on COX-2 potency, as can be seen by comparing 4,5-dichlorophenyl analog **30** (COX-2 = 0.24 μM) with **20a**. Analog **32** (COX-2 = 0.083 μM), in which 1,3-benzodioxole was used as the central ring, proved to be less potent than **20a** but more potent than **30**. Several other phenyl surrogates such as tetrafluorobenzene in **34**, naphthalene in **36**, and pyrazine in **39** were also investigated as possible replacements for the central phenyl group in **16a**; however, all were found to be essentially inactive against COX-2 enzyme (COX-2 > 100 μM). The lack of activity observed for **34** and **39** suggests that the COX-2 binding interactions might be very sensitive to both electronic and steric properties of the positions adjacent to the 1,2-diaryl groups.

On the basis of our investigation with central ring surrogates (*vide supra*), an extensive SAR study was conducted around the 1,2-diaryl-4,5-difluorobenzene sulfones **20a**−**q** and sulfonamides **21a**−**q**. Table 3 summarizes both COX-1 and COX-2 enzyme data; the nonselective COX inhibitor indomethacin is provided as a reference compound. Similar to our previous observation for **20a**, sulfones **20b**−**e** in the 1,2-diaryl-4,5-difluorobenzene series were found to be more potent and more selective COX-2 inhibitors than the corresponding simple terphenyl sulfones **16b**−**e**, respectively. For example, **20b** (COX-2 = 0.010 μM) is 36 times more potent than **16b** (COX-2 = 0.36 μM). Furthermore, sulfonamides **21a**−**e** (Table 3) were found to be more potent COX-2 inhibitors than sulfonamides **17a**−**e** (Table 2). Within the 1,2-diaryl-4,5-difluorobenzene series (Table 3), most of the methyl sulfones **20** were found to be highly (e.g., **20c** COX-2 = 0.005 μM) to modestly potent (e.g., **20h** COX-2 = 0.34 μM) COX-2 inhibitors with IC$_{50}$ values generally ranging from 0.010 to 0.025 μM. On the other hand, COX-1 activity appears to be insensitive to the various 4-fluorophenyl replacements that were investigated, since sulfones **20a**−**q** were all found to be essentially inactive against the COX-1 enzyme (COX-1 > 100 μM). Replacement of the methyl sulfone moiety in **20a**−**q** with a sulfonamide group resulted in a series of even more potent COX-2 inhibitors (**21a**−**q**), which is consistent with our previous observations for cyclopentene COX-2 inhibitors.[21,23] Several noticeable examples were found to have COX-2 potency in the low-nanomolar range, e.g., **21b**,**c** (COX-2 = 0.002 μM), **21l**,**n** (COX-2 = 0.003 μM), and **21a**,**j**,**k**

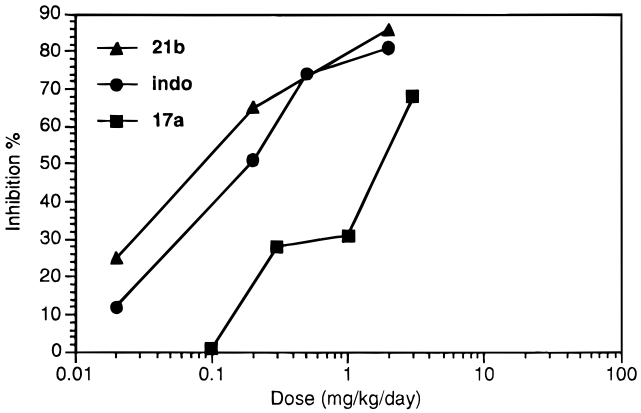


Figure 2. Dose−response curve of adjuvant-induced arthritis assay of **17a**, **21b**, and indomethacin in Lewis rats (see the Experimental Section for assay procedure).

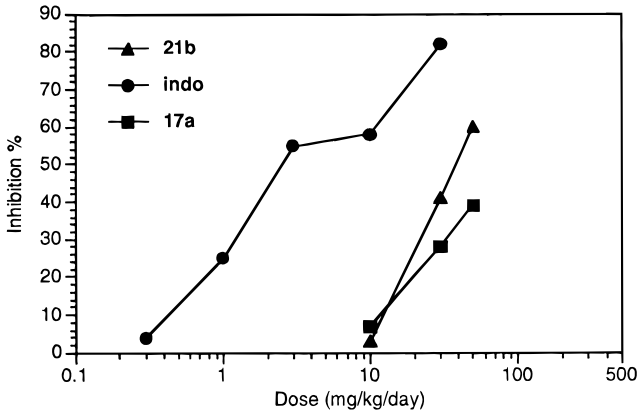


Figure 3. Dose−response curve of carrageenan-induced hyperalgesia assay of **17a**, **21b**, and indomethacin in Sprague−Dawley rats (see the Experimental Section for assay procedure).

(COX-2 = 0.004 μM). The increased COX-1 activity (COX-1 = 3−20 μM) observed for sulfonamides **21a**−**q** caused an overall decrease in COX-1/COX-2 enzyme selectivity relative to methyl sulfones **20a**−**q** (COX-1 > 100 μM), respectively. Nevertheless, sulfonamides **21a**−**q** are very potent and highly selective COX-2 inhibitors with a COX-1/COX-2 enzyme selectivity ratio generally >1000.

***In Vivo* Activity.** To assess the oral activity of terphenyl COX-2 inhibitors, selected methyl sulfones **16** and sulfonamides **17** were evaluated in an acute inflammation model, i.e., the air pouch assay. As shown in Table 1, inhibition values range from 34% to 68% at 2 mg/kg. The most active analog (**17a**) in this assay was further evaluated *in vivo* and found to have modest potency (ED_{50} = 1.5 mg/kg, Figure 2) in the rat adjuvant-induced arthritis assay. However, **17a** was subsequently found to display weak activity (ED_{50} > 50 mg/kg, Figure 3) in the analgesic assay.

Benzodioxole methyl sulfone **32** (Table 2) was similarly evaluated in the air pouch model and found to be inactive (0% inhibition at 2 mg/kg). The corresponding sulfonamide analog of **32** was also tested and found to be weakly active (26% inhibition at 2 mg/kg).

Since simple terphenyls **16** and **17** and benzodioxole **32** were considered to have insufficient oral activity for further development, our attention was focused on the more potent 4,5-difluorobenzene methyl sulfone (**20a**−**q**) and sulfonamide (**21a**−**q**) COX-2 inhibitors. As can be clearly seen from Table 3, the sulfonamides **21a**−**q** were found to be generally superior in oral activity relative to the corresponding methyl sulfones **20a**−**q**. Moreover, 4,5-difluorobenzenesulfonamides **21** are substantially more orally active than the corresponding unsubstituted benzenesulfonamides **17** in the air pouch model, e.g., **21d** inhibits 96%, while **17d** inhibits only 34%. Several noteworthy examples are **21a**,**b**,**d**,**g**,**j**, **m**,**n**,**q** which inhibit more than 90% of the prostaglandin E_2 production in the air pouch model of inflammation, an efficacy comparable to the reference compound indomethacin (Table 3). The exact reason for the superior *in vivo* activity observed for 4,5-difluorobenzenesulfonamides **21** (vs **17**) is not known, although one might speculate that it is a combination of increased *in vitro* binding affinity and metabolic stability.

On the basis of its COX-2 potency (COX-2 = 0.002 μM) and air pouch activity (94% at 2 mg/kg), sulfonamide **21b** was selected for further *in vivo* evaluation. In subsequent testing, **21b** was shown to be slightly more potent than indomethacin in the rat adjuvant-induced arthritis model (ED_{50} = 0.05 vs 0.11 mg/kg), as shown in Figure 2; however, it was found to be less active in the analgesic assay (ED_{50} = 38.7 vs 4.4 mg/kg), as shown in Figure 3. A rat GI toxicity study was conducted to assess the safety of **21b**. When **21b** was administered intragastrically at 200 mg/kg, no gastric lesions were observed after 5 h and no intestinal damage was detected after 72 h. For the purpose of comparison, the nonselective COX inhibitor indomethacin was used in a positive control group, and it caused severe bleeding and/or death at doses as low as 16 mg/kg.

Conclusion

We have discovered a series of novel terphenyl compounds that are selective COX-2 inhibitors and orally active anti-inflammatory agents. Replacement of the methyl sulfone moiety in **16** and **20** with a sulfonamide group as in **17** and **21**, respectively, was found to provide a more potent COX-2 inhibitor with greatly enhanced *in vivo* activity, albeit with some decrease in COX-2 selectivity. SAR studies have indicated that central ring substituents play an important role in COX-2 potency, and only 1,2-diaryl-4,5-disubstituted benzenes, e.g., **16**, **17**, **20**, **21**, **30**, and **32**, were found to be potent COX-2 inhibitors. Other modifications, e.g., at the 3- and 6-positions of the central ring, resulted in a loss of COX-2 activity (COX-2 >100 μM). Incorporation of two fluorine atoms in the central ring of simple terphenylsulfonamides **17** provided 1,2-diaryl-4,5-difluorobenzenesulfonamides **21**, which are very potent (COX-2 = 0.002−0.051 μM) and highly selective (COX-1/COX-2 > 1000) COX-2 inhibitors; of particular significance is the dramatic increase in the oral activity associated with this change. Sulfonamide **21b** was found to be very active in the rat adjuvant-induced arthritis model (ED_{50} = 0.05 mg/kg) and carrageenan-induced hyperalgesia assay (ED_{50} = 38.7 mg/kg). Furthermore, no indication of GI toxicity was observed when **21b** was administered intragastrically at 200 mg/kg. Development of selective and orally active terphenyl COX-2 inhibitors such as sulfonamide **21b** could therefore provide a new generation of NSAIDs with greatly reduced GI toxicity.

Experimental Section

General. Expression and purification of recombinant human COX-1 and COX-2 enzymes,[14] *in vitro* COX-1 and COX-2 enzyme assays,[14] rat adjuvant-induced arthritis,[21,33] rat GI toxicity study,[35] general chemistry method,[21] and preparation of arylboronic acids,[21] preparation of sulfonamides from corresponding methyl sulfones[21,27] have been described previously.

Air Pouch Model of Inflammation.[32] Male Lewis rats (175−200 g; Charles River Laboratories) were used, and the rats were fasted with free access to water at 24 h prior to experiment. Air cavities were produced by subcutaneous injection of 20 mL of sterile air into the intrascapular area of the back at 24 h prior to experiment. Each test compound suspended in 0.5% methyl cellulose, and 0.025% Tween-20 (Sigma) was administered intragastrically at 2 mg/kg in a volume of 5 mL/kg 2 h prior to carrageenan injection. Inflammation was then induced by injecting 2 mL of 1% carrageenan into the rat air pouch with animals sacrificed at 3 h after injection. Pouch exudates were collected, washed, and assayed for PGE_2 by specific ELISAs (Cayman Chemical Co.).

Carrageenan-Induced Hyperalgesia in the Rat.[34] Male Sprague−Dawley rats (195−250 g; Charles River Laboratories) were used, and the rats were fasted with free access to water at least 16 h prior to experiments. The test compound suspended in 1 mL of 0.5% methyl cellulose and 0.025% Tween-20 (Sigma) was dosed orally via an 18-G gavage needle at 2 h prior to induction of inflammation. Inflammation was then induced by injection of 0.1 mL of 1% carrageenan suspension in 0.9% sterile saline via a 27-G needle into the plantar tissue of the right hind foot pad. After 3 h, a radiant heat source was positioned under the paw, and the latency of paw withdraw was measured. The inhibition values were determined on the basis of an average of five Sprague−Dawley rats.

General Procedure A for Preparation of Methyl Sulfone Analogs 16a−e. 2-Chloro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene (**16e**) is described as a typical example.

4-Bromo-2-chloroanisole. Under nitrogen, to a stirred suspension of 10.0 g (48 mmol) of 4-bromo-2-chlorophenol and 5.4 g (38 mmol) of K_2CO_3 powder in 75 mL of acetone was added 7.3 mL (77 mmol) of dimethyl sulfate. The mixture was heated at reflux for 2 h and cooled to ambient temperature. The inorganic salts were removed by filtration, and the organic solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. Concentration *in vacuo* gave 10.2 g (96%) of 4-bromo-2-chloroanisole as a colorless solid: mp 68.5−70.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.80 (d, J = 9 Hz, 1H), 7.33 (dd, J = 2, 9 Hz, 1H), 7.50 (d, J = 2 Hz, 1H).

(3-Chloro-4-methoxyphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 10.2 g (46.2 mmol) of 4-bromo-2-chloroanisole was converted to (3-chloro-4-methoxyphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.57 (s, 2H), 6.83 (d, J = 8 Hz, 1H), 7.64 (dd, J = 2, 8 Hz, 1H), 7.77 (d, J = 2 Hz, 1H).

1-Bromo-2-[4-(methylsulfonyl)phenyl]benzene (15). Under nitrogen, to a stirred solution of 12.0 g (71.4 mmol) of **13**[21] and 17.0 mL (140.9 mmol) of 1,2-dibromobenzene (**14**) in a mixed solvent of 150 mL of toluene, 150 mL of ethanol, and 150 mL of 2 M Na_2CO_3 was added 5 g (4.3 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring for 3 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. Purification by silica gel plug with ethyl acetate/hexane (5:95) gave an oil residue which was dissolved in 200 mL of CH_2Cl_2. To this solution was slowly added 53.0 g (153 mmol) of 3-chloroperoxybenzoic acid (*m*-CPBA, 50%), and the reaction was continued for 30 min at ambient temperature. The excess *m*-CPBA was quenched by adding 7.7 g of Na_2SO_3 at 0 °C, and the mixture was stirred for 10 min at ambient temperature. Most of the solvent was removed *in vacuo*; the residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ twice, and dried over $MgSO_4$. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (3:7) gave 16.2 g (73%) of the title compound **15** as a colorless solid: mp 168.2−169.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.12 (s, 3H), 7.23−7.33 (m, 2H), 7.40 (dt, J = 2, 8 Hz, 1H), 7.61 (d, J = 8 Hz, 2H), 7.70 (dd, J = 2, 8 Hz, 1H), 8.01 (d, J = 9 Hz, 2H).

16e. Under nitrogen, to a stirred solution of 4.0 g (12.8 mmol) of **15** and 2.9 g (15.4 mmol) of (3-chloro-4-methoxyphenyl)boronic acid in a mixed solvent of 35 mL of toluene, 35 mL of ethanol, and 35 mL of 2 M Na_2CO_3 was added 1 g (0.86 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring for 3 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (1:3) gave 3.4 g (70%) of the title compound **16e** as a colorless solid: mp 161.5−162.3 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.88 (s, 3H), 6.75 (d, J = 9 Hz, 1H), 6.87 (dd, J = 2, 9 Hz, 1H), 7.17 (d, J = 2 Hz, 1H), 7.34 (d, J = 9 Hz, 2H), 7.37−7.51 (m, 4H), 7.82 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 372 (100), 243 (24); HRMS calcd for M^+ 372.0587, found 372.0557. Anal. ($C_{20}H_{17}ClO_3S$) C, H, Cl.

1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (16a). Following general procedure A described for **16e**, **15** was reacted with (4-fluorophenyl)boronic acid to give the title compound **16a** as a colorless solid: mp 178.0−179.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 6.93 (t, J = 8 Hz, 2H), 7.03−7.09 (m, 2H), 7.32 (d, J = 8 Hz, 2H), 7.38−7.50 (m, 4H), 7.80 (d, J = 8 Hz, 2H); MS (FAB) m/z 333 $(M + Li)^+$. Anal. ($C_{19}H_{15}FO_2S$) C, H, F.

2-Chloro-1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene (16b). Following general procedure A described for **16e**, **15** was reacted with (3-chloro-4-fluorophenyl)boronic acid to give the title compound **16b** as a colorless solid: mp 179.5−181.1 °C; ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 6.86−6.93 (m, 1H), 6.98 (t, J = 8 Hz, 1H), 7.19 (dd, J = 2, 7 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 7.38−7.53 (m, 4H), 7.84 (d, J = 9 Hz, 2H); MS (FAB) m/z 367 $(M + Li)^+$; HRMS calcd for M^+ 360.0387, found 360.0401. Anal. ($C_{19}H_{14}ClFO_2S$) C, H, F.

1-(4-Chlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (16c). Following general procedure A described for **16e**, **15** was reacted with (4-chlorophenyl)boronic acid to give the title compound **16c** as a colorless solid: mp 180.2−180.6 °C; ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 7.04 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.38−7.51 (m, 4H), 7.81 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 342 (34), 228 (100); HRMS calcd for M^+ 342.0481, found 342.0484. Anal. ($C_{19}H_{15}ClO_2S$) C, H, Cl.

2-Fluoro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene (16d). 3-(Fluoro-4-methoxyphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 4-bromo-2-fluoroanisole was converted to (3-fluoro-4-methoxyphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 6.80 (d, J = 8 Hz, 1H), 7.36−7.48 (m, 2H).

16d. Following general procedure A described for **16e**, **15** was reacted with (3-fluoro-4-methoxyphenyl)boronic acid to give the title compound **16d** as a colorless solid: mp 136.2−136.6 °C; ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 3.87 (s, 3H), 6.72−6.89 (m, 3H), 7.31−7.51 (m, 6H), 7.81 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 356 (100), 262 (28), 246 (22); HRMS calcd for M^+ 356.0882, found 356.0881. Anal. ($C_{20}H_{17}FO_3S$) C, H, F.

4-[2-(4-Fluorophenyl)phenyl]benzenesulfonamide (17a). Following the literature procedure,[21,27] **16a** was converted to the title compound **17a** as a colorless solid: mp 187.3−188.2 °C; ^{1}H NMR ($CDCl_3$) δ 4.83 (s, 2H), 6.92 (t, J = 9 Hz, 2H), 7.02−7.11 (m, 2H), 7.27 (d, J = 9 Hz, 2H), 7.36−7.50 (m, 4H), 7.78 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 327 (75), 245 (100); HRMS calcd for M^+ 327.0729, found 327.0743. Anal. ($C_{18}H_{14}NFO_2S$) C, H, N.

4-[2-(3-Chloro-4-fluorophenyl)phenyl]benzenesulfonamide (17b). Following the literature procedure,[21,27] **16b** was converted to the title compound **17b** as a colorless solid: mp 192.5−193.2 °C; ^{1}H NMR ($CDCl_3$) δ 4.86 (s, 2H), 6.68−6.76 (m, 1H), 6.81 (t, J = 9 Hz, 1H), 7.06 (d, J = 8 Hz, 2H), 7.17−7.32 (m, 5H), 7.63 (d, J = 8 Hz, 2H); MS (FAB) m/z

368 ($M + Li)^+$; HRMS calcd for M^+ 361.0340, found 361.0338. Anal. ($C_{18}H_{13}NClFO_2S$) C, H, N.

4-[2-(4-Chlorophenyl)phenyl]benzenesulfonamide (17c). Following the literature procedure,[21,27] **16c** was converted to the title compound **17c** as a colorless solid: mp 206.2−207.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.77 (s, 2H), 7.04 (d, J = 9 Hz, 2H), 7.16−7.31 (m, 4H), 7.36−7.51 (m, 4H), 7.80 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 343 (100), 262 (21), 228 (82); HRMS calcd for M^+ 343.0434, found 343.0434. Anal. ($C_{18}H_{14}NClO_2S$) C, H, N.

4-[2-(3-Fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide (17d). Following the literature procedure,[21,27] **16d** was converted to the title compound **17d** as a colorless solid: mp >143 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.90 (s, 2H), 6.74−6.90 (m, 3H), 7.29 (d, J = 9 Hz, 2H), 7.35−7.48 (m, 4H), 7.79 (d, J = 9 Hz, 2H); MS (FAB) m/z 364 ($M + Li)^+$; HRMS calcd for M^+ 357.0835, found 357.0809. Anal. ($C_{19}H_{16}FNO_3S \cdot 0.27H_2O$) C, H, N.

4-[2-(3-Chloro-4-methoxyphenyl)phenyl]benzenesulfonamide (17e). Following the literature procedure,[21,27] **16e** was converted to the title compound **17e** as a colorless solid: mp 179.5−180.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 4.76 (s, 2H), 6.75 (d, J = 9 Hz, 1H), 6.86 (dd, J = 2, 9 Hz, 1H), 7.20 (d, J = 3 Hz, 1H), 7.29 (d, J = 9 Hz, 2H), 7.35−7.47 (m, 4H), 7.79 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 373 (100), 243 (29); HRMS calcd for M^+ 373.0539, found 373.0587. Anal. ($C_{19}H_{16}NClO_3S$) C, H, N.

General Procedure B for Preparation of Methyl Sulfone Analogs 20a−o. 1-(3-Chloro-4-methoxyphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (**20e**) is described as a typical example.

1-Bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (19). Under nitrogen, to a stirred solution of 12.3 g (73.2 mmol) of **13**[21] and 40.0 g (147.1 mmol) of 1,2-dibromo-4,5-difluorobenzene (**18**) in a mixed solvent of 160 mL of toluene, 160 mL of ethanol, and 160 mL of 2 M Na_2CO_3 was added 5 g (4.3 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring for 3 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. Purification by silica gel plug with ethyl acetate/hexane (0:100 to 10:90) gave an oil residue which was dissolved in 350 mL of CH_2Cl_2. To this solution was then slowly added 59 g (220 mmol) of *m*-CPBA (64%), and the reaction was continued for 30 min at ambient temperature. The mixture was then diluted with 500 mL of CH_2Cl_2, washed with 5% NaOH, and dried over $MgSO_4$. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (1:4) gave 17.4 g (68%) of **19** as a colorless solid: mp 158.5−159.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.12 (s, 3H), 7.13−7.21 (m, 1H), 7.50−7.60 (m, 3H), 8.02 (d, J = 9 Hz, 2H).

20e. Under nitrogen, to a stirred solution of 4.4 g (12.8 mmol) of **19** and 3.1 g (16.7 mmol) of (3-chloro-4-methoxyphenyl)boronic acid (see **16e**) in a mixed solvent of 37 mL of toluene, 37 mL of ethanol, and 37 mL of 2 M Na_2CO_3 was added 1 g (0.86 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring for 10 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (3:7) gave 4.5 g (95%) of the title compound **20e** as a colorless solid: mp 147.5−148.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.88 (s, 3H), 6.75 (d, J = 9 Hz, 1H), 6.83 (dd, J = 2, 9 Hz, 1H), 7.10 (d, J = 2 Hz, 1H), 7.17−7.32 (m, 4H), 7.83 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 408 (33), 294 (52), 279 (63), 251 (100); HRMS calcd for M^+ 408.0399, found 408.0396. Anal. ($C_{20}H_{15}ClF_2O_3S \cdot 0.27EtOAc$) C, H, F.

1,2-Difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]benzene (20a). Following general procedure B described for **20e**, **19** was reacted with (4-fluorophenyl)boronic acid to give the title compound **20a** as a colorless solid: mp 172.8−173.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 6.94 (t, J = 8 Hz, 2H), 6.98−7.06 (m, 2H), 7.21−7.31 (m, 4H), 7.81 (d, J = 8 Hz, 2H); MS (FAB) m/z 369 ($M + Li)^+$; HRMS calcd for M^+ 362.0588, found 362.0586. Anal. ($C_{19}H_{13}F_3O_2S$) C, H, F.

1-(3-Chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (20b). Following general procedure B described for **20e**, **19** was reacted with (3-chloro-4-fluorophenyl)boronic acid to give the title compound **20b** as a colorless solid: mp 172.2−172.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 6.82−6.89 (m, 1H), 6.99 (t, J = 9 Hz, 1H), 7.14 (dd, J = 2, 8 Hz, 1H), 7.20−7.32 (m, 4H), 7.84 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 396 (22), 282 (100), 262 (25); HRMS calcd for M^+ 396.0199, found 396.0203. Anal. ($C_{19}H_{12}ClF_3O_2S$) C, H, F.

1,2-Difluoro-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (20c). (**4-Fluoro-3-methylphenyl)boronic Acid.** Following the literature procedure described for **13**,[21] 5-bromo-2-fluorotoluene was converted to (4-fluoro-3-methylphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 2.39 (d, J = 2 Hz, 3H), 7.13 (t, J = 9 Hz, 1H), 7.99−8.08 (m, 2H).

20c. Following general procedure B described for **20e**, **19** was reacted with (4-fluoro-3-methylphenyl)boronic acid to give the title compound **20c** as a colorless solid: mp 167.2−167.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 (d, J = 2 Hz, 3H), 3.04 (s, 3H), 6.71−6.78 (m, 1H), 6.84 (t, J = 9 Hz, 1H), 6.92 (dd, J = 2, 8 Hz, 1H), 7.18−7.32 (m, 4H), 7.81 (d, J = 8 Hz, 2H); MS (FAB) m/z 383 ($M + Li)^+$; HRMS calcd for M^+ 376.0745, found 376.0752. Anal. ($C_{20}H_{15}F_3O_2S$) C, H, F.

1,2-Difluoro-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (20d). Following general procedure B described for **20e**, **19** was reacted with (3-fluoro-4-methoxyphenyl)boronic acid (see **16d**) to give the title compound **20d** as a colorless solid: mp 159.2−159.7 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.87 (s, 3H), 6.63−6.85 (m, 3H), 7.16−7.32 (m, 4H), 7.82 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 392 (49), 298 (48), 269 (100), 249 (79); HRMS calcd for M^+ 392.0694, found 392.0683. Anal. ($C_{20}H_{15}F_3O_3S \cdot 0.02$ hexane) C, H.

1-(3,5-Dichloro-4-methoxyphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (20f). 4-Bromo-2,6-dichloroanisole. Following the methylation procedure described for **16e**, 4-bromo-2,6-dichlorophenol was methylated to give 4-bromo-2,6-dichloroanisole as a colorless solid: mp 67.0−68.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.45 (s, 2H).

(3,5-Dichloro-4-methoxyphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 4-bromo-2,6-dichloroanisole was converted to (3,5-dichloro-4-methoxyphenyl)-boronic acid: ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 7.73 (s, 2H).

20f. Following general procedure B described for **20e**, **19** was reacted with (3,5-dichloro-4-methoxyphenyl)boronic acid to give the title compound **20f** as a colorless solid: mp 175.5−175.8 °C; ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 3H), 3.89 (s, 3H), 6.97 (s, 2H), 7.19−7.36 (m, 4H), 7.87 (d, J = 8 Hz, 2H); MS (FAB) m/z 449 ($M + Li)^+$; HRMS calcd for M^+ 442.0009, found 442.0018. Anal. ($C_{20}H_{14}Cl_2F_2O_3S$) C, H.

1,2-Difluoro-4-(3-methyl-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (20g). 4-Bromo-2-methylanisole. Following the methylation procedure described for **16e**, 4-bromo-2-methylphenol was methylated to give 4-bromo-2-methylanisole as a colorless solid: mp 65.0−66.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.80 (s, 3H), 6.67 (d, J = 9 Hz, 1H), 7.22−7.28 (m, 2H).

(3-Methyl-4-methoxyphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 4-bromo-2-methylanisole was converted to (3-methyl-4-methoxyphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.92 (s, 3H), 6.96 (d, J = 8 Hz, 1H), 7.98 (s, 1H), 8.03 (d, J = 8 Hz, 1H).

20g. Following general procedure B described for **20e**, **19** was reacted with (3-methyl-4-methoxyphenyl)boronic acid to give the title compound **20g** as a colorless solid: mp 160.5−161.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 3.04 (s, 3H), 3.79 (s, 3H), 6.63 (d, J = 9 Hz, 1H), 6.74 (dd, J = 2, 9 Hz, 1H), 6.85 (d, J = 2 Hz, 1H), 7.15−7.27 (m, 3H), 7.30 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 2H); MS (FAB) m/z 395 ($M + Li)^+$; HRMS calcd for M^+ 388.0945, found 388.0940. Anal. ($C_{21}H_{18}F_2O_3S$) C, H, F.

1,2-Difluoro-4-(3,4-dimethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (20h). (3,4-Dimethoxyphenyl)-boronic Acid. Following the literature procedure described for **13**,[21] 1-bromo-3,4-dimethoxybenzene was converted to (3,4-

dimethoxyphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 4.02 (s, 3H), 7.02 (d, J = 9 Hz, 1H), 7.69 (s, 1H), 7.86 (d, J = 9 Hz, 1H).

20h. Following general procedure B described for **20e**, **19** was reacted with (3,4-dimethoxyphenyl)boronic acid to give the title compound **20h** as a colorless solid: mp 140.0−141.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 3H), 3.61 (s, 3H), 3.86 (s, 3H), 6.48 (d, J = 2 Hz, 1H), 6.65 (dd, J = 2, 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.17−7.29 (m, 2H), 7.31 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H); MS (FAB) m/z 411 (M + Li)$^+$; HRMS calcd for M$^+$ 404.0894, found 404.0893. Anal. ($C_{21}H_{18}F_2O_4S\cdot 0.24H_2O$) C, H.

1,2-Difluoro-4-[3,4-(ethylenedioxy)phenyl]-5-[4-(methylsulfonyl)phenyl]benzene (20i). [3,4-(Ethylenedioxy)-phenyl]boronic Acid. Following the literature procedure described for **13**,[21] 3,4-(ethylenedioxy)bromobenzene was converted to [3,4-(ethylenedioxy)phenyl]boronic acid: ^{1}H NMR ($CDCl_3$) δ 4.27−4.36 (m, 4H), 6.97 (d, J = 9 Hz, 1H), 7.67−7.72 (m, 2H).

20i. Following general procedure B described for **20e**, **19** was reacted with [3,4-(ethylenedioxy)phenyl]boronic acid to give the title compound **20i** as a colorless solid: mp 82.0−83.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 4.21−4.26 (m, 4H), 6.43 (dd, J = 2, 8 Hz, 1H), 6.61 (d, J = 2 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 7.14−7.24 (m, 2H), 7.31 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H); MS (FAB) m/z 409 (M + Li)$^+$; HRMS calcd for M$^+$ 402.0737, found 402.0749. Anal. ($C_{21}H_{16}F_2O_4S\cdot 0.17$hexane) C, H.

5-[4,5-Difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-1,3-benzodioxole (20j). (1,3-Benzodioxol-5-yl)boronic Acid. Following the literature procedure described for **13**,[21] 5-bromo-1,3-benzodioxole was converted to (1,3-benzodioxol-5-yl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 2H), 6.88 (t, J = 8 Hz, 1H), 7.26−7.41 (m, 2H), 7.80 (br s, 2H).

20j. Following general procedure B described for **20e**, **19** was reacted with (1,3-benzodioxol-5-yl)boronic acid to give the title compound **20j** as a colorless solid: mp 110.0−111.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 5.95 (s, 2H), 6.47−6.52 (m, 2H), 6.67 (d, J = 9 Hz, 1H), 7.16−7.24 (m, 2H), 7.32 (d, J = 9 Hz, 2H), 7.82 (d, J = 9 Hz, 2H); MS (FAB) m/z 395 (M + Li)$^+$; HRMS calcd for M$^+$ 388.0581, found 388.0569. Anal. ($C_{20}H_{14}F_2O_4S$) C, H.

1,2-Difluoro-4-(4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]benzene (20k). Following general procedure B described for **20e**, **19** was reacted with (4-methylphenyl)boronic acid to give the title compound **20k** as a colorless solid: mp 147.0−148.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.05 (s, 3H), 6.92 (d, J = 8 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 7.17−7.32 (m, 4H), 7.79 (d, J = 8 Hz, 2H); MS (FAB) m/z 365 (M + Li)$^+$; HRMS calcd for M$^+$ 358.0839, found 358.0831. Anal. ($C_{20}H_{16}F_2O_2S$) C, H.

1-(3-Chloro-4-methylphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (20l). (3-Chloro-4-methylphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 4-bromo-2-chlorotoluene was converted to (3-chloro-4-methylphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 7.37 (d, J = 8 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 8.08 (s, 1H).

20l. Following general procedure B described for **20e**, **19** was reacted with (3-chloro-4-methylphenyl)boronic acid to give the title compound **20l** as a colorless solid: mp 138.0−139.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.05 (s, 3H), 6.75 (dd, J = 2, 8 Hz, 1H), 7.03−7.10 (m, 2H), 7.18−7.26 (m, 2H), 7.29 (d, J = 8 Hz, 2H), 7.83 (d, J = 8 Hz, 2H); MS (FAB) m/z 399 (M + Li)$^+$; HRMS calcd for M$^+$ 392.0449, found 392.0440. Anal. ($C_{20}H_{15}ClF_2O_2S$) C, H.

1,2-Difluoro-4-(3,4-dimethylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (20m). (3,4-Dimethylphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 4-bromo-*o*-xylene was converted to (3,4-dimethylphenyl)boronic acid: ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 6H), 7.07 (d, J = 8 Hz, 1H), 7.45−7.54 (m, 2H), 7.84 (br s, 2H).

20m. Following general procedure B described for **20e**, **19** was reacted with (3,4-dimethylphenyl)boronic acid to give the title compound **20m** as a colorless solid: mp 125.1−125.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.23 (s, 3H), 3.04 (s, 3H), 6.69 (dd, J = 2, 8 Hz, 1H), 6.86 (s, 1H), 6.95 (d, J = 8 Hz, 1H), 7.16−7.26 (m, 3H), 7.29 (d, J = 9 Hz, 1H), 7.79 (d, J = 9 Hz, 2H); MS (FAB) m/z 379 (M + Li)$^+$; HRMS calcd for M$^+$ 372.0996, found 372.0978. Anal. ($C_{20}H_{18}F_2O_2S$) C, H, F.

1,2-Difluoro-4-(4-chloro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (20n). (4-Chloro-3-methylphenyl)boronic Acid. Following the literature procedure described for **13**,[21] 5-bromo-2-chlorotoluene was converted to (4-chloro-3-methylphenyl)boronic acid: ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H), 7.35 (d, J = 8 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 7.71 (s, 1H), 8.10 (br s, 2H).

20n. Following general procedure B described for **20e**, **19** was reacted with (4-chloro-3-methylphenyl)boronic acid to give the title compound **20n** as a colorless solid: mp 151.5−152.2 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.05 (s, 3H), 6.73 (dd, J = 2, 8 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 7.16 (d, J = 9 Hz, 1H), 7.19−7.32 (m, 4H), 7.82 (d, J = 9 Hz, 2H); MS (FAB) m/z 399 (M + Li)$^+$; HRMS calcd for M$^+$ 392.0449, found 392.0437. Anal. ($C_{20}H_{15}ClF_2O_2S$) C, H, F.

2-Chloro-4-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]-phenyl]-*N*,*N*-dimethylaniline (20o). 4-Bromo-2-chloro-*N*,*N*-dimethylaniline. Under nitrogen, to a stirred solution of 12.8 g (62 mmol) of 4-bromo-2-chloroaniline in 200 mL of DMF were added 42.8 g (310 mmol) of K_2CO_3 powder and 11.6 mL (186 mmol) of CH_3I. After heating at 100 °C with vigorous stirring overnight, most of the DMF was removed *in vacuo*, and the residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with water five times and dried over Na_2SO_4. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (5:95) gave 11.3 g (78%) of 4-bromo-2-chloro-*N*,*N*-dimethylaniline as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.79 (s, 6H), 6.92 (d, J = 9 Hz, 1H), 7.25−7.34 (m, 1H), 7.49 (d, J = 2 Hz, 1H).

[3-Chloro-4-(*N*,*N*-dimethylamino)phenyl]boronic Acid. Following the literature procedure described for **13**,[21] 4-bromo-2-chloro-*N*,*N*-dimethylaniline was converted to [3-chloro-4-(*N*,*N*-dimethylamino)phenyl]boronic acid: ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 6H), 7.12 (d, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 8.12 (s, 1H).

20o. Following general procedure B described for **20e**, **19** was reacted with [3-chloro-4-(*N*,*N*-dimethylamino)phenyl]-boronic acid to give the title compound **20o** as a colorless solid: mp 129.0−130.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.81 (s, 6H), 3.05 (s, 3H), 6.76−6.91 (m, 2H), 7.08 (d, J = 2 Hz, 1H), 7.17−7.26 (m, 2H), 7.31 (d, J = 9 Hz, 2H), 7.83 (d, J = 9 Hz, 2H); MS (FAB) m/z 428 (M + Li)$^+$; HRMS calcd for M$^+$ 421.0715, found 421.0719. Anal. ($C_{21}H_{18}NClF_2O_2S$) C, H, N.

2-[4,5-Difluoro-4′-(methylsulfonyl)-[1,1′-biphenyl]-2-yl]-5-methylpyridine (20p). 1-Bromo-4,5-difluoro-2-[4-(methylthio)phenyl]benzene (22). Following the first step in general procedure B described for **20e**, the reaction was worked up prior to the *m*-CPBA oxidation. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (2:98) gave **22** as a colorless solid: mp 53.5−54.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 7.10−7.19 (m, 1H), 7.29 (s, 4H), 7.45−7.53 (m, 1H).

[4,5-Difluoro-2-[(4-methylthio)phenyl]phenyl]boronic Acid (23). Under nitrogen, to a mixture of 3.87 g (12.3 mmol) of **22** and 300 mg (12.3 mmol) of Mg turnings in 12 mL of anhydrous THF was added 1 mL of dibromoethane. The mixture was heated at reflux for 5 h and cooled to 0 °C followed by the addition of 2.8 mL (24.6 mmol) of trimethyl borate and stirring overnight. After 10 mL of 10% NaOH was added, the solution was stirred for 3 h, acidified to pH 4, extracted with ethyl acetate three times, and dried over $MgSO_4$. Concentration *in vacuo* gave 2.7 g (78%) of **23** as a pale yellow semisolid.

20p. Under nitrogen, to a stirred solution of 2.7 g (9.6 mmol) of **23** and 1.7 g (9.8 mmol) of 2-bromo-5-methylpyridine in a mixed solvent of 25 mL of toluene, 25 mL of ethanol, and 25 mL of 2 M Na_2CO_3 was added 1 g (0.86 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring for 48 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Purification by silica gel plug with ethyl acetate/hexane (15:85) gave a semisolid residue which was then dissolved in a mixed solvent of 15 mL of THF and 15 mL of CH_3OH. To this

mixture was slowly added a solution of 3.5 g (5.7 mmol) of Oxone in 15 mL of H_2O, and the reaction was continued for 3 h at ambient temperature. The excess Oxone was quenched by adding 2 g of Na_2SO_3, and the mixture was stirred for 30 min. Most of the solvent was removed *in vacuo*; the residue was dissolved in ethyl acetate, washed with brine, and dried over Na_2SO_4. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (45:55) gave 1.0 g (29%) of the title compound **20p** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.05 (s, 3H), 6.76 (d, J = 8 Hz, 1H), 7.17−7.36 (m, 4H), 7.53 (t, J = 9 Hz, 1H), 7.82 (d, J = 9 Hz, 2H), 8.42 (s, 1H); MS (FAB) m/z 360 $(M+H)^+$; HRMS calcd for $(M+H)^+$ 360.0870, found 360.0885. Anal. ($C_{19}H_{15}NO_2SF_2$) C, H, N, F.

5-[4,5-Difluoro-4′-(methylsulfonyl)-[1,1′-biphenyl]-2-yl]-2-methylpyridine (20q). 2-Methyl-5-(trimethylstannyl)pyridine (25). Under nitrogen, to a stirred solution of 5.2 g (30 mmol) of **24**[28] in 300 mL of anhydrous THF at −78 °C was added 14 mL (35 mmol) of *n*-BuLi (2.5 M in hexanes). After 10 min, 7.2 g (36 mmol) of trimethyltin chloride in 5 mL of anhydrous THF was added and the solution was allowed to warm to ambient temperature and stirred overnight. Most of the THF was removed *in vacuo*; the residue was dissolved in ethyl acetate, washed with brine, and dried over Na_2SO_4. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (1:3) gave 2.0 g (29%) of **25** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 9H), 2.52 (s, 3H), 7.11 (d, J = 8 Hz, 1H), 7.65 (dd, J = 2, 8 Hz, 1H), 8.49 (s, 1H).

20q.[29] Under nitrogen, to a stirred solution of 200 mg (0.6 mmol) of **19** and 300 mg (1.2 mmol) of **25** in 5 mL of toluene was added 100 mg (0.1 mmol) of $Pd(PPh_3)_4$. After refluxing for 16 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:1) gave 70 mg (32%) of the title compound **20q** as a pale brown solid: mp 141.0−142.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.04 (s, 3H), 7.02 (d, J = 8 Hz, 1H), 7.19−7.32 (m, 5H), 7.82 (d, J = 8 Hz, 2H), 8.24 (s, 1H); MS (FAB) m/z 360 $(M+H)^+$; HRMS calcd for $(M+H)^+$ 360.0870, found 360.0862. Anal. ($C_{19}H_{15}NO_2SF_2 \cdot 0.33H_2O$) C, H, N.

4-[4,5-Difluoro-2-(4-fluorophenyl)phenyl]benzenesulfonamide (21a). Following the literature procedure,[21,27] **20a** was converted to the title compound **21a** as a colorless solid: mp 190.2−191.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.77 (s, 2H), 6.94 (t, J = 8 Hz, 2H), 6.98−7.06 (m, 2H), 7.17−7.28 (m, 4H), 7.79 (d, J = 8 Hz, 2H); MS (FAB) m/z 370 $(M + Li)^+$; HRMS calcd for M^+ 363.0541, found 363.0576. Anal. ($C_{18}H_{12}NF_3O_2S$) C, H, N.

4-[2-(3-Chloro-4-fluorophenyl)-4,5-difluorophenyl]benzenesulfonamide (21b). Following the literature procedure,[21,27] **20b** was converted to the title compound **21b** as a colorless solid: mp 162.5−162.8 °C; ^{1}H NMR ($CDCl_3$) δ 4.80 (s, 2H), 6.81−6.88 (m, 1H), 6.99 (t, J = 9 Hz, 1H), 7.15−7.28 (m, 5H), 7.83 (d, J = 8 Hz, 2H); MS (FAB) m/z 404 $(M + Li)^+$; HRMS calcd for M^+ 397.0151, found 397.0152. Anal. ($C_{18}H_{11}NClF_3O_2S$) C, H, N.

4-[4,5-Difluoro-2-(4-fluoro-3-methylphenyl)phenyl]benzenesulfonamide (21c). Following the literature procedure,[21,27] **20c** was converted to the title compound **21c** as a colorless solid: mp 151.5−152.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (d, J = 2 Hz, 3H), 4.84 (s, 2H), 6.70−6.78 (m, 1H), 6.83 (t, J = 9 Hz, 1H), 6.94 (dd, J = 2, 8 Hz, 1H), 7.15−7.29 (m, 4H), 7.79 (d, J = 8 Hz, 2H); MS (FAB) 384 $(M + Li)^+$; HRMS calcd for M^+ 377.0697, found 377.0720. Anal. ($C_{19}H_{14}NF_3O_2S$) C, H, N.

4-[4,5-Difluoro-2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide (21d). Following the literature procedure,[21,27] **20d** was converted to the title compound **21d** as a colorless solid: mp 132.2−132.8 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 4.85 (s, 2H), 6.71−6.85 (m, 3H), 7.15−7.27 (m, 4H), 7.81 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 393 (32), 298 (21), 282 (25), 269 (100), 249 (46); HRMS calcd for M^+ 393.0646, found 393.0647. Anal. ($C_{19}H_{14}NO_3SF_3$) C, H, N.

4-[2-(3-Chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (21e). Following the literature procedure,[21,27] **20e** was converted to the title compound **21e** as a colorless solid: mp >70 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 4.84 (s, 2H), 6.75 (d, J = 9 Hz, 1H), 6.82 (dd, J = 2, 9 Hz, 1H), 7.14 (d, J = 2 Hz, 1H), 7.16−7.28 (m, 4H), 7.81 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 409 (22), 279 (28), 251 (100), 231 (20); HRMS calcd for M^+ 409.0351, found 409.0340. Anal. ($C_{19}H_{14}ClF_2NO_3S$) C, H, N.

4-[2-(3,5-Dichloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (21f). Following the literature procedure,[21,27] **20f** was converted to the title compound **21f** as a colorless solid: mp 145.5−146.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 4.78 (s, 2H), 6.98 (s, 2H), 7.18−7.29 (m, 4H), 7.85 (d, J = 8 Hz, 2H); MS (FAB) m/z 450 $(M + Li)^+$; HRMS calcd for $(M+H)^+$ 444.0039, found 444.0052. Anal. ($C_{19}H_{13}NCl_2F_2O_3S$) C, H, N.

4-[4,5-Difluoro-2-(3-methyl-4-methoxyphenyl)phenyl]benzenesulfonamide (21g). Following the literature procedure,[21,27] **20g** was converted to the title compound **21g** as a colorless solid: mp 120.0−121.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 3.79 (s, 3H), 4.84 (s, 2H), 6.63 (d, J = 9 Hz, 1H), 6.74 (dd, J = 2, 9 Hz, 1H), 6.88 (d, J = 2 Hz, 1H), 7.13−7.28 (m, 4H), 7.78 (d, J = 8 Hz, 2H); MS (FAB) m/z 396 $(M + Li)^+$; HRMS calcd for M^+ 389.0897, found 389.0921. Anal. ($C_{20}H_{17}NF_2O_3S$) C, H, N.

4-[4,5-Difluoro-2-(3,4-dimethoxyphenyl)phenyl]benzenesulfonamide (21h). Following the literature procedure,[21,27] **20h** was converted to the title compound **21h** as a colorless solid: mp 157.0−158.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H), 3.86 (s, 3H), 4.77 (s, 2H), 6.46 (d, J = 2 Hz, 1H), 6.65 (dd, J = 2, 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.16−7.30 (m, 4H), 7.79 (d, J = 8 Hz, 2H); MS (FAB) m/z 412 $(M + Li)^+$; HRMS calcd for M^+ 405.0846, found 405.0870. Anal. ($C_{20}H_{17}NF_2O_4S \cdot 0.35H_2O$) C, H, N.

4-[4,5-Difluoro-2-[3,4-(ethylenedioxy)phenyl]phenyl]benzenesulfonamide (21i). Following the literature procedure,[21,27] **20i** was converted to the title compound **21i** as a colorless solid: mp 107.0−108.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.22−4.26 (m, 4H), 4.75 (s, 2H), 6.43 (dd, J = 2, 8 Hz, 1H), 6.62 (d, J = 2 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 7.13−7.30 (m, 4H), 7.80 (d, J = 8 Hz, 2H); MS (FAB) m/z 410 $(M + Li)^+$; HRMS calcd for M^+ 403.0690, found 403.0697. Anal. ($C_{20}H_{15}NO_4F_2S$) C, H, N.

4-[2-(1,3-Benzodioxol-5-yl)-4,5-difluorophenyl]benzenesulfonamide (21j). Following the literature procedure,[21,27] **20j** was converted to the title compound **21j** as a colorless solid: mp 142.0−143.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.83 (s, 2H), 5.95 (s, 2H), 6.49−6.54 (m, 2H), 6.69 (d, J = 8 Hz, 1H), 7.15−7.30 (m, 4H), 7.81 (d, J = 8 Hz, 2H); MS (EI) m/z 389 (18), 251 (100), 231 (43); HRMS calcd for M^+ 389.0533, found 389.0517. Anal. ($C_{19}H_{13}NF_2O_4S \cdot 0.19H_2O$) C, H, N.

4-[4,5-Difluoro-2-(4-methylphenyl)phenyl]benzenesulfonamide (21k). Following the literature procedure,[21,27] **20k** was converted to the title compound **21k** as a colorless solid: mp 103.0−104.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 4.81 (s, 2H), 6.93 (d, J = 8 Hz, 2H), 7.04 (d, J = 8 Hz, 2H), 7.16−7.29 (m, 4H), 7.78 (d, J = 9 Hz, 2H); MS (EI) m/z 359 (26), 279 (33), 278 (41), 264 (100), 251 (36), 119 (62), 80 (70), 64 (56); HRMS calcd for M^+ 359.0792, found 359.0777. Anal. ($C_{19}H_{15}NF_2O_2S$) C, H, N.

4-[2-(3-Chloro-4-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide (21l). Following the literature procedure,[21,27] **20l** was converted to the title compound **21l** as a colorless solid: mp 139.0−140.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 4.81 (s, 2H), 6.74 (dd, J = 2, 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 7.12 (d, J = 2 Hz, 1H), 7.17−7.25 (m, 4H), 7.80 (d, J = 8 Hz, 2H); MS (FAB) m/z 400 $(M + Li)^+$; HRMS calcd for M^+ 393.0402, found 393.0400. Anal. ($C_{19}H_{14}NO_2F_2ClS$) C, H, N.

4-[4,5-Difluoro-2-(3,4-dimethylphenyl)phenyl]benzenesulfonamide (21m). Following the literature procedure,[21,27] **20m** was converted to the title compound **21m** as a colorless solid: mp 132.8−133.9 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.22 (s, 3H), 4.83 (s, 2H), 6.68 (dd, J = 2, 8 Hz, 1H), 6.88 (s, 1H), 6.94 (d, J = 8 Hz, 1H), 7.15−7.28 (m, 4H), 7.77 (d, J = 8 Hz, 2H); MS (FAB) m/z 380 $(M + Li)^+$; HRMS for M^+ 373.0948, found 373.0972. Anal. ($C_{20}H_{17}NF_2O_2S$) C, H, N.

4-[2-(4-Chloro-3-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide (21n). Following the literature procedure,[21,27] **20n** was converted to the title compound **21n** as a colorless solid: mp 141.5−142.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 4.89 (s, 2H), 6.73 (dd, J = 2, 8 Hz, 1H), 7.00 (d, J = 2 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.17−7.27 (m, 5H), 7.80 (d, J = 9 Hz, 1H); MS (FAB) m/z 400 (M + Li)$^+$; HRMS for M$^+$ 393.0402, found 393.0416. Anal. ($C_{19}H_{14}NF_2ClO_2S$) C, H, N.

4-[2-[3-Chloro-4-(*N*,*N*-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide (21o). Following the literature procedure,[21,27] **20o** was converted to the title compound **21o** as a colorless solid: mp 193.0−194.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.83 (s, 6H), 4.80 (s, 2H), 6.79 (dd, J = 2, 9 Hz, 1H), 6.87−6.95 (m, 1H), 7.13 (d, J = 2 Hz, 1H), 7.17−7.29 (m, 4H), 7.82 (d, J = 8 Hz, 2H); MS (FAB) m/z 429 (M + Li)$^+$; HRMS for M$^+$ 422.0667, found 422.0667. Anal. ($C_{20}H_{17}N_2ClF_2O_2S\cdot 0.27H_2O$) C, H, N.

4-[4,5-Difluoro-2-(5-methylpyridin-2-yl)phenyl]benzenesulfonamide (21p). Following the literature procedure,[21,27] **20p** was converted to the title compound **21p** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 4.91 (s, 2H), 6.81 (d, J = 8 Hz, 1H), 7.18−7.31 (m, 3H), 7.35 (d, J = 8 Hz, 1H), 7.50−7.59 (m, 1H), 7.82 (d, J = 9 Hz, 2H), 8.47 (s, 1H); MS (FAB) m/z 361 (M+H)$^+$; HRMS calcd for (M + Li)$^+$ 367.0904, found 367.0904. Anal. ($C_{18}H_{14}N_2O_2SF_2\cdot$0.13hexane) C, H, N.

4-[4,5-Difluoro-2-(6-methylpyridin-3-yl)phenyl]benzenesulfonamide (21q). Following the literature procedure,[21,27] **20q** was converted to the title compound **21q** as a colorless solid: mp >96 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.10 (s, 2H), 7.09 (d, J = 8 Hz, 1H), 7.20−7.28 (m, 4H), 7.32 (dd, J = 2, 9 Hz, 1H), 7.81 (d, J = 9 Hz, 2H), 8.21 (d, J = 2 Hz, 1H); MS (FAB) m/z 361 (M+H)$^+$; HRMS calcd for (M+H)$^+$ 361.0822, found 361.0823. Anal. ($C_{18}H_{14}N_2O_2SF_2$) C, H, N, F.

1,2-Dichloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]benzene (30). 1,2-Dichlorocatechol (27). Under nitrogen, to a stirred solution of 5.75 g (27.8 mmol) of dichloroveratrole (**26**)[30] in 200 mL of CH_2Cl_2 was added 83.4 mL (83.4 mmol) of BBr_3 (1.0 M in CH_2Cl_2) at 0 °C, and the reaction was continued for 2 h at ambient temperature. After most of the solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate, washed with brine, and dried over Na_2SO_4. Recrystallization from ethyl acetate/hexane (5:95) gave 5.0 g (96%) of **27** as a gray solid: mp 113.0−114.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.18 (s, 2H), 6.98 (s, 2H).

1,2-Dichloro-4,5-bis[(trifluoromethyl)sulfonyl]benzene (28). Under nitrogen, to a stirred solution of 3.72 g (20.8 mmol) of **27** in 40 mL of CH_2Cl_2 were added 8.4 mL (104 mmol) of pyridine and 9.0 mL (53.5 mmol) of triflic anhydride at 0 °C, and the reaction was continued for 7 days at ambient temperature. The mixture was poured into ice−water and extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. Purification by silica gel plug with ethyl acetate/hexane (5:95) gave 7.9 g (86%) of **28** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 2H).

1,2-Dichloro-4-[4-(methylthio)phenyl]-5-[(trifluoromethyl)sulfonyl]benzene (29). Under nitrogen, to a stirred solution of 7.9 g (17.8 mmol) of **28**, 3.0 g (18 mmol) of **13**,[21] and 7.4 g (54 mmol) of anhydrous K_2CO_3 powder in 90 mL of toluene was added 5 g (4.3 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring for 48 h, the solution was diluted with CH_2Cl_2, washed with water and brine, and dried over $MgSO_4$. Purification by silica gel plug with ethyl acetate/hexane (5:95 to 30:70) gave 4.8 g (56%) of **29** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 7.33 (s, 4H), 7.50 (s, 1H), 7.56 (s, 1H).

30. Under nitrogen, to a stirred solution of 1.64 g (3.93 mmol) of **29**, 1.1 g (7.9 mmol) of (4-fluorophenyl)boronic acid, and 1.6 g (11.6 mmol) of anhydrous K_2CO_3 powder in 20 mL of toluene was added 480 mg (0.42 mmol) of $Pd(PPh_3)_4$. The mixture was heated at reflux with vigorous stirring for 7 days and cooled to ambient temperature. The solution was diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. Purification by silica gel plug with ethyl acetate/hexane (5:95) gave an oil residue which was dissolved in 15 mL of CH_2Cl_2. After cooling down to 0 °C, 1.4 g (11.8 mmol) of *m*-CPBA (70%) was added, and the reaction mixture was stirred overnight at ambient temperature. The excess *m*-CPBA was quenched by adding Na_2SO_3 at 0 °C, and the mixture was stirred for 30 min at ambient temperature. The solution was diluted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 505 mg (33%) of **30** as a colorless solid: mp 143.5−144.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 6.95 (d, J = 9 Hz, 2H), 6.99−7.07 (m, 2H), 7.30 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.83 (d, J = 9 Hz, 2H); MS (CI) m/z 395 (M+H)$^+$; HRMS calcd for (M + Li)$^+$ 401.0157, found 401.0142. Anal. ($C_{19}H_{13}O_2SFCl_2$) C, H, F, Cl.

5-(4-Fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole (32). Under nitrogen, to a stirred solution of 4.0 g (14.3 mmol) of 5,6-dibromo-1,3-benzodioxole (**31**), 2.87 g (17.2 mmol) of **13**,[21] and 2.4 g (17.2 mmol) of (4-fluorophenyl)-boronic acid in a mixed solvent of 70 mL of toluene, 40 mL of ethanol, and 30 mL of 2 M Na_2CO_3 was added 1 g (0.86 mmol) of $Pd(PPh_3)_4$. After refluxing with vigorous stirring overnight, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Purification by silica gel plug with hexane gave a semisolid residue which was dissolved in 30 mL of CH_2Cl_2. To this mixture was then slowly added 12 g (38.2 mmol) of *m*-CPBA (55%) at −10 °C, and the reaction was continued for 30 min at ambient temperature. The excess *m*-CPBA was quenched by adding 4 g of Na_2SO_3 at −10 °C, and the mixture was stirred for 30 min at ambient temperature. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:4) followed by reversed phase chromatography (Waters Delta Prep 3000) with acetonitrile/water/TFA (45:55:0.05) gave 200 mg of the title compound **32** as a colorless solid: mp 173.0−174.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 3H), 6.06 (s, 2H), 6.86−6.92 (m, 4H), 6.96−7.03 (m, 2H), 7.23−7.27 (m, 2H), 7.76 (d, J = 9 Hz, 2H); MS (FAB) m/z 377 (M + Li)$^+$; HRMS calcd for M$^+$ 370.0675, found 370.0680. Anal. ($C_{20}H_{15}FO_4S\cdot 0.25H_2O$) C, H.

1,2,3,4-Tetrafluoro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]benzene (34). Following the procedure described for **32**, **34** was isolated as a colorless solid: mp 134.0−135.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 6.91−7.03 (m, 4H), 7.26 (d, J = 9 Hz, 2H), 7.84 (d, J = 9 Hz, 2H); MS (FAB) m/z 405 (M + Li)$^+$; HRMS calcd for M$^+$ 398.0400, found 398.0393.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]naphthalene (36). Following the procedure described for **32**, **36** was isolated as a colorless solid: mp 147.0−148.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 6.97 (d, J = 9 Hz, 2H), 7.11−7.19 (m, 2H), 7.41 (d, J = 8 Hz, 2H), 7.53−7.60 (m, 2H), 7.84 (d, J = 8 Hz, 2H), 7.87−7.94 (m, 4H); MS (FAB) m/z 383 (M + Li)$^+$; HRMS calcd for M$^+$ 376.0933, found 376.0940.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]pyrazine (39). 4-Fluoro-4′-(methylsulfonyl)benzil (38). Under nitrogen, to a stirred solution of 11.7 g (47.5 mmol) of **37** in 80 mL of DMF was added 4.8 g (47.0 mmol) of CH_3SO_2Na. The mixture was heated at reflux with vigorous stirring for 3 h and then cooled to ambient temperature. The solution was diluted with ethyl acetate, washed with water, and dried over Na_2SO_4. Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (1:4) gave 1.8 g (12%) of **38** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H), 7.18−7.24 (m, 2H), 8.01−8.20 (m, 6H).

39. A stirred solution of 1.8 g (5.9 mmol) of **38** in 5 mL of ethylenediamine was heated at 60 °C for 3 h and then cooled to ambient temperature. Concentration *in vacuo* gave an oil residue which was dissolved in 10 mL of CH_2Cl_2. To this solution was added 3.3 g (14.5 mmol) of DDQ at −10 °C, and the reaction was continued for 5 h at ambient temperature. The excess DDQ was then quenched by adding Na_2SO_3 at 0 °C, and the mixture was stirred for 30 min at ambient temperature. The solution was diluted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. Purification by silica gel chromatography (MPLC) with ethyl acetate/

hexane (3:7) gave 400 mg (23%) of **39** as a pale brown solid: mp 141.0−142.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 7.04 (t, J = 9 Hz, 2H), 7.19−7.25 (m, 2H), 7.67 (d, J = 8 Hz, 2H), 7.91 (d, J = 8 Hz, 2H), 8.66 (dd, J = 1, 8 Hz, 2H); MS (FAB) m/z 329 $(M + H)^+$; HRMS calcd for M^+ 328.0682, found 328.0685.

Supporting Information Available: Summary of *in vitro* and *in vivo* assays (5 pages). Ordering information can be found on any current masthead page.

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