1,2-Diarylcyclopentenes as Selective Cyclooxygenase-2 Inhibitors and Orally Active Anti-inflammatory Agents

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A series of 1,2-diarylcyclopentene methyl sulfones and sulfonamides have been shown to be remarkably potent and selective cyclooxygenase-2 (COX-2) inhibitors. The methyl sulfone analogs **7** showed excellent COX-2 activity, with IC_{50}s ranging from 0.003 (**7f,n**) to 0.87 (**7o**) μM. In addition, most analogs of **7** showed no activity (IC_{50} >100 μM) against the COX-1 enzyme. Replacement of the methyl sulfone moiety with a sulfonamide group gave a slightly more potent (typically 2–5-fold) but less selective COX-2 inhibitor, mainly due to an increase (20–>100-fold) in COX-1 activity. However, *in vitro* COX-1/COX-2 selectivity for the sulfonamides **8** could be increased in many cases by simply incorporating a substituent at the 3-position of the phenyl group. Furthermore, *in vitro* selectivity increased with the size and number of substituents, as demonstrated in the selectivity trend of **8k** (8000) > **8j** (1900) > **8i** (500) > **8h** (100). More importantly, the sulfonamide COX-2 inhibitors showed greatly enhanced oral activity in the rat model of established adjuvant-induced arthritis, with inhibition values of 79.0% (**8a**), 81.5% (**8c**), and 83.0% (**8g**) at 1 mg/kg. On the basis of its overall biological profile, sulfonamide **8c** was evaluated as a potential clinical candidate, displaying an ED_{50} of 22 mpk in the rat carrageenan-induced paw edema model and an ED_{50} of 0.16 mpk in the rat established adjuvant-induced arthritis model with no indication of gastrointestinal toxicity in rats and mice at 200 mpk. In addition, a preparative-scale synthetic route to sulfonamide **8c** has been developed.

Introduction

Currently available nonsteroidal anti-inflammatory drugs (NSAIDs) are effective anti-inflammatory agents and are widely used in the treatment of inflammatory conditions including rheumatoid arthritis. However, gastrointestinal (GI) and renal toxicity associated with common NSAIDs limits their usefulness.[1-3] All NSAIDs are believed to disrupt the biosynthesis of prostaglandins (PGs) by inhibiting the enzyme cyclooxygenase (COX).[3] In the early 1990s, two distinct forms of COX enzyme were distinguished, a constitutive COX-1 enzyme and an inducible form of the enzyme, now commonly known as COX-2. The COX-1 enzyme is expressed in normal tissues and is physiologically important for GI and renal functions, while the previously unidentified COX-2 isoform is found to be located primarily in inflamed tissues.[4-7] It seems reasonable that a selective COX-2 inhibitor could block PG production at the site of inflammation without affecting beneficial PGs in normal tissues such as the stomach and kidney. A selective and orally active COX-2 inhibitor should thus provide the desired therapeutic profile of an anti-inflammatory drug without the deleterious side effects commonly associated with COX-1 inhibition in the GI tract and kidney. Two distinct classes of aryl-containing compounds have been independently reported by workers from DuPont (DuP 697)[8] and Taisho (NS-398)[9] that demonstrate anti-inflammatory activity in the rat established adjuvant-induced arthritis model without concomitant gastric lesions. *In vitro* assays with human recombinant COX-1 and COX-2 enzymes have since confirmed that both Dup 697 and NS-398 are selective COX-2 inhibitors.[10,11] More recently, additional selective COX-2 inhibitors typified by SC-58125 (Searle)[12] and L-745,337 (Merck Frosst)[13] have also been reported to display exceptional safety profiles with regard to currently available NSAIDs such as indomethacin.

We have recently reported some preliminary results on a novel series of carbocyclic COX-2 inhibitors, as illustrated by methyl sulfone **7a** and sulfonamide **8a** (Figure 1), which are highly selective and orally active COX-2 inhibitors.[14,15] As part of continuing efforts in seeking novel COX-2 inhibitors as candidates for safer NSAIDs, we have conducted an extensive inquiry into structure–activity relationships (SARs) in the 1,2-diaryl-substituted cyclopentene series. These compounds were initially evaluated in human recombinant COX enzyme assays, and several potent and selective COX-2 inhibitors were further investigated in rat carrageenan-induced paw edema and/or established adjuvant-induced arthritis models. In this report we describe the details of our findings on the unique characteristics of halophenyl-substituted cyclopentene COX-2 inhibitors and the contribution of the methyl sulfone and sulfonamide groups to overall *in vitro* selectivity and *in vivo* potency. Furthermore, we wish to report our extensive efforts to identify a potential clinical candidate, sulfonamide **8c**, through this novel therapeutic approach.

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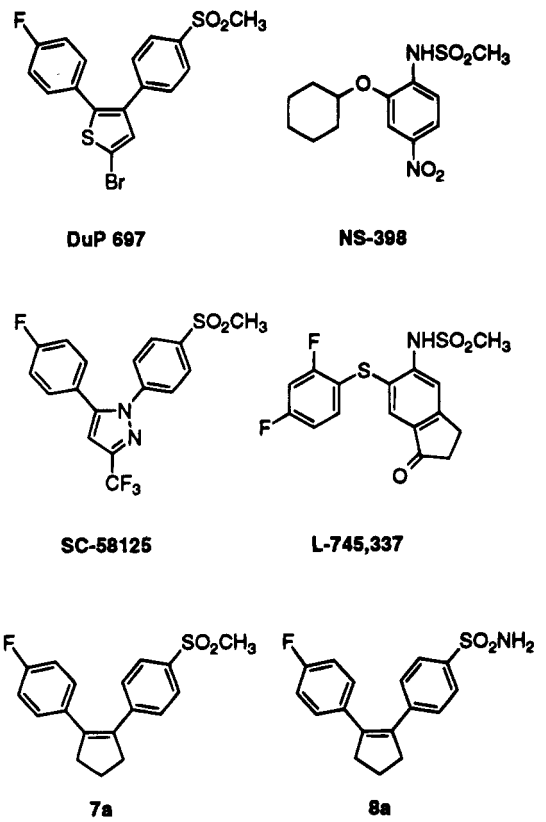


Figure 1. Representative examples of selective COX-2 inhibitors.

Chemistry

The laboratory-scale preparation of 1,2-diarylcyclopentene analogs **7a–p** (Table 1) was conveniently carried out using commercially available 1,2-dibromocyclopentene (**2**) via a sequential Suzuki cross-coupling reaction,[16] as illustrated in Scheme 1. Two equivalents of **2** 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 simply be prepared from the corresponding aryl bromides by treatment with *n*-butyllithium in tetrahydrofuran at −78 °C followed by addition of trimethylborate and base hydrolysis to give the arylboronic acids in yields of 60–80%. Selective conversion of the methyl sulfide to methyl sulfone without oxidation of the cyclopentene double bond was accomplished by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) either with the bis-arylated intermediate **5** described in route A or with the monoarylated intermediate **4** shown in route B. However, we found that methyl sulfone **6** is considerably more stable and easier to purify than its precursor, methyl sulfide **4**, and consequently the synthetic sequence described in route B was the preferred method of synthesis. Finally, sulfonamides **8a–p** (Table 1) were prepared directly from the corresponding methyl sulfone analogs **7** according to a recently reported procedure developed in this laboratory.[17]

The highly promising pharmacological properties of several sulfonamide COX-2 inhibitors in the rat established adjuvant-induced arthritis model made efficient large-scale preparation of these compounds a matter of high priority. A modification of the original synthetic route (Scheme 1) was devised which provided sulfonamide COX-2 inhibitors directly from **2**. As described in Scheme 2, reaction of cyclopentanone with phosphorus pentachloride gave 1-chlorocyclopentene.[18] The latter was brominated *in situ* followed by base-catalyzed elimination of hydrogen chloride, which provided **2** on a kilogram scale with distilled yields of ca. 40%, based on cyclopentanone. The Suzuki cross-coupling reaction of **2** with 3-chloro-4-(fluorophenyl)boronic acid (**9**) gave 1-(2-bromocyclopenten-1-yl)-3-chloro-4-fluorobenzene (**10**), which was readily purified by fractional distillation. Treatment of **10** with *n*-BuLi and quenching with trimethyl borate generated the intermediate vinyl borate *in situ*, which smoothly underwent a second coupling with 4-bromobenzenesulfonamide to give the sulfonamide **8c** directly in 52% yield.

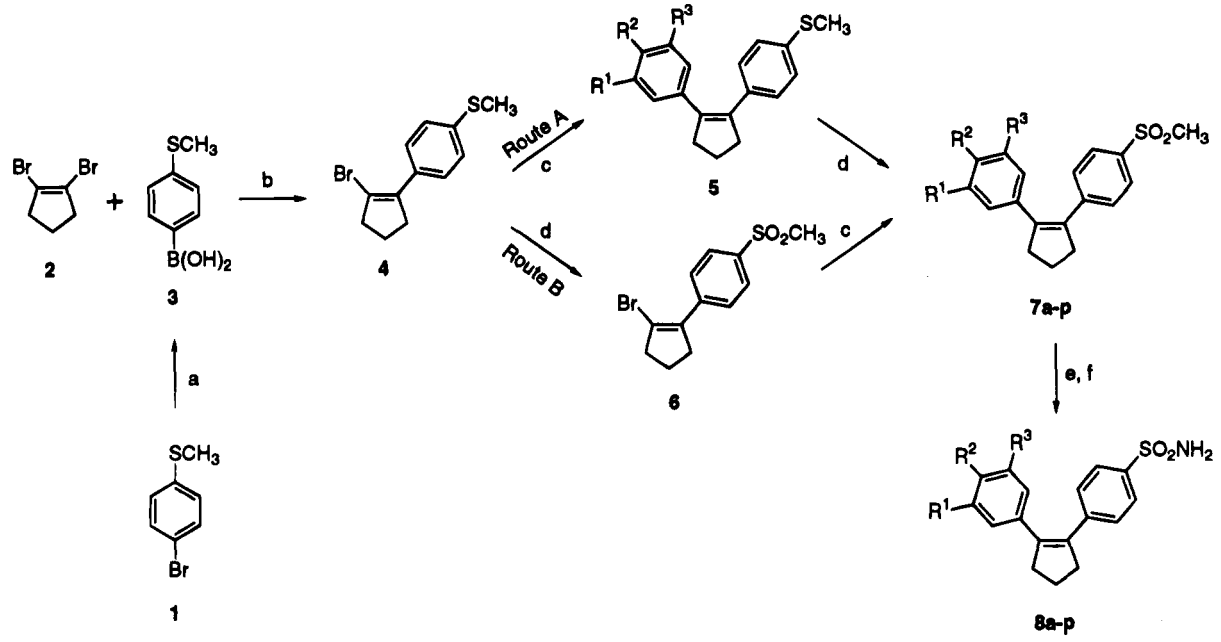
Biological Results and Discussion

As discussed earlier, a more selective and potent COX-2 inhibitor is a desirable target for drug development since it should not display the GI and renal toxicity associated with conventional NSAIDs.[11] In that context, a substantial effort was made to investigate the effects of various phenyl ring substitutions and the interchange of the methyl sulfone with the sulfonamide group on overall *in vitro* potency and/or selectivity. The IC_{50} values of both constitutive (COX-1) and inducible (COX-2) forms of human recombinant COX are summarized in Table 1, and several of our previously published cyclopentene COX-2 inhibitors are included here for the purpose of a clear SAR summary. A few representative selective COX-2 inhibitors (Figure 1) including Dup 697,[11] NS-398,[11] SC-58125,[12] and L-745,-337[13] are also listed as the references, along with the nonselective COX inhibitor indomethacin.[11] As the enzyme data clearly show, replacement of the methyl sulfone moiety (analogs **7**) with a sulfonamide group (analogs **8**) results in a dramatic increase in COX-1 potency (typically 20–>100-fold) along with a modest increase in COX-2 activity (2–5-fold). As illustrated in the 3,4-dichlorophenyl series, the methyl sulfone analog **7g** (COX-2, IC_{50} = 0.01 μM; COX-1, IC_{50} >100 μM) shows an enzyme selectivity of >10 000, whereas the corresponding sulfonamide **8g** (COX-2, IC_{50} = 0.002 μM; COX-1, IC_{50} = 3.8 μM) displays a selectivity of only 1900-fold. In fact, all sulfonamides **8** show a substantial decrease in selectivity as compared with the corresponding methyl sulfones **7**, mainly due to an increase in COX-1 activity.

Several other functional group replacements (Figure 2) were also investigated to determine whether *in vitro* selectivity could be improved relative to the methyl sulfone series. However, replacement of the methyl sulfone moiety with a trifluoromethyl sulfone group as in **11**, methyl sulfoximine group in **12**, methyl ketone group in **13**, carboxylic acid group in **14**, methyl phosphinate group in **15**, and phosphonate group in **16** resulted in a total loss of COX-2 activity (IC_{50} >100 μM). The methyl sulfone or sulfonamide group thus appears to be the preferred component of a pharmacophore possessing good COX-2 activity.

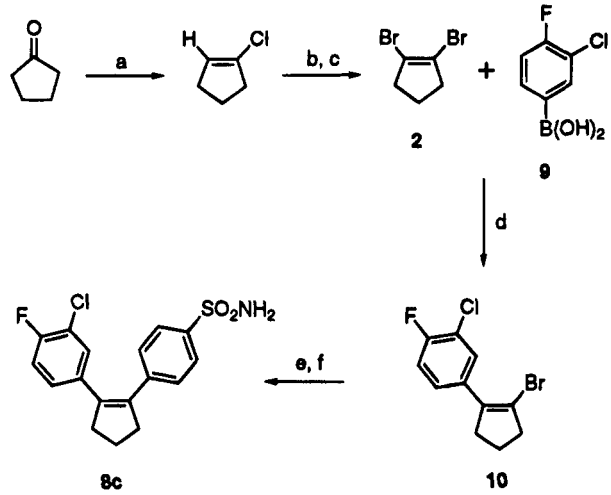
To assess the oral activity of our COX-2 inhibitors, selected analogs in both the methyl sulfone (**7**) and the sulfonamide (**8**) series were subsequently evaluated in two animal models widely used for testing NSAIDs, namely, the rat carrageenan-induced paw edema and established adjuvant-induced arthritis assays. For the

Scheme 1[a]



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

Scheme 2[a]

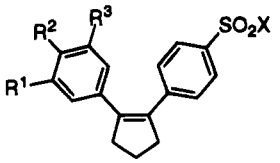


[a] Reagents: (a) PCl_5, toluene; (b) Br_2, toluene; (c) *t*-BuOK, hexane; (d) 5 mol% $Pd(PPh_3)_4$, 2 M Na_2CO_3, ethanol, toluene, reflux; (e) *n*-BuLi, $B(OCH_3)_3$, −55 °C to room temperature; (f) 5 mol% $Pd(PPh_3)_4$, 4-$BrC_6H_4SO_2NH_2$, reflux.

carrageenan-induced paw edema model,[12,19,20] each test compound was dosed orally 2 h prior to induction of inflammation by carrageenan injection, with inhibition measured 3 h after induction. For the established adjuvant-induced arthritis model,[21] arthritis was induced initially by adjuvant injection, which was fully developed in rats in a 14-day period. Each test compound was then administered orally to the arthritic rats twice daily for 11 consecutive days, after which the inhibition was measured. The paw edema assay was employed as a model for acute inflammation, while the established adjuvant-induced arthritis assay was used as a chronic disease condition in order to evaluate the oral potency of our selective COX-2 inhibitors, and the *in vivo* data are summarized in Table 2. When methyl sulfones **7a,c,f,g**, and sulfonamides **8a,c,f,g** were initially examined in the carrageenan-induced edema model, inhibition values generally ranged from 40% to 50% at 30 mpk. However, the most crucial observation was obtained from the results of the chronic arthritis model, in which sulfonamides **8a,c,f,g** were significantly more potent than the corresponding methyl sulfone analogs **7a,c,f,g**. As clearly seen from Table 2, the sulfonamide **8a** displays an inhibition of 79.0%, while methyl sulfone **7a** shows only 29.3% inhibition at 1 mpk. Similarly, sulfonamide **8f** displays an inhibition of 47% even at 0.3 mpk, which is more than 2 times as efficacious as the 21% inhibition from methyl sulfone **7f** at 1 mpk. The exact reason for the superior *in vivo* activity observed for these sulfonamides has not been further investigated at this time, but we suspect it is most likely due to a combination of greater water solubility, absorption, cellular penetration, and metabolic persistence.[22] These results indicate that the sulfonamide moiety provides a more orally active anti-inflammatory agent in the established adjuvant-induced arthritis model as well as a slightly more potent COX-2 inhibitor; unfortunately, it also results in a concomitantly less selective COX-2 inhibitor.

It occurred to us that one reasonable approach to improve the *in vitro* selectivity of these sulfonamide COX-2 inhibitors would be to modify other parts of the molecule while retaining the sulfonamide moiety for better oral activity. An extensive SAR effort was therefore undertaken for the sulfonamide series in an attempt to increase COX-1/COX-2 enzyme selectivity with appropriate substitution at the phenyl group (non-sulfonamide-containing phenyl group). After some experimentation, our attention was focused on the 4-methoxyphenyl series **8h−k** (Table 1). We determined that halogen substitution ortho to the 4-methoxyl moiety, e.g., **8i** (fluoro), **8j** (chloro), and **8k** (dichloro), has the effects of decreasing COX-1 activity while scarcely affecting COX-2 potency, therefore increasing the overall *in vitro* selectivity.[23] In addition, the selectivity was found to increase with the size and number of halogens

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



X = CH_3, **7a-p**

X = NH_2, **8a-p**

compd[a]	R^1	R^2	R^3	IC_{50} (μM) COX-2[b]	IC_{50} (μM) COX-1[b]	selectivity[c]
7a	H	F	H	0.026	>1000	>38 000
8a				0.007	4.2	600
7b	H	F	F	0.051	>100	>2000
8b				0.018	8.1	450
7c	H	F	Cl	0.03	>100	>3300
8c				0.01	5.1	500
7d	H	F	CF_3	>100	>100	
7e	F	F	F	>100	>100	
8e				2.9	>100	
7f	H	Cl	H	0.003	>100	>33 000
8f				0.003	1.3	430
7g	H	Cl	Cl	0.01	>100	>10 000
8g				0.002	3.8	1900
7h	H	CH_3O	H	0.005	9.9	2000
8h				0.002	0.2	100
7i	H	CH_3O	F	0.12	>100	>800
8i				0.016	8.1	500
7j	H	CH_3O	Cl	0.14	>100	>700
8j				0.009	17.3	1900
7k	Cl	CH_3O	Cl	0.017	>100	>5900
8k				0.009	71.6	8000
7l	H	OCH_2O		0.021	>100	>4700
8l				0.002	1.9	950
7m	Cl	$(CH_3)_2N$	H	0.005	37.7	7500
8m				0.002	1.8	900
7n	H	CH_3	H	0.003	>100	>33 000
7o	H	CF_3	H	0.87	>100	>100
8o				0.15	4.0	25
7p	H	CF_3	F	0.76	>100	>130
8p				0.17	14.5	85
Dup697[b]				0.01	0.8	80
NS-398[b]				0.1	>100	>1000
SC-58125[d]				0.05	>100	>2000
L-745,337[e]				0.02	>10	>500
indomethacin[b]				0.9	0.1	0.1

[a] See the Experimental Section. [b] See ref 11. [c] Ratio of COX-1/COX-2. [d] See ref 12. [e] See ref 13.

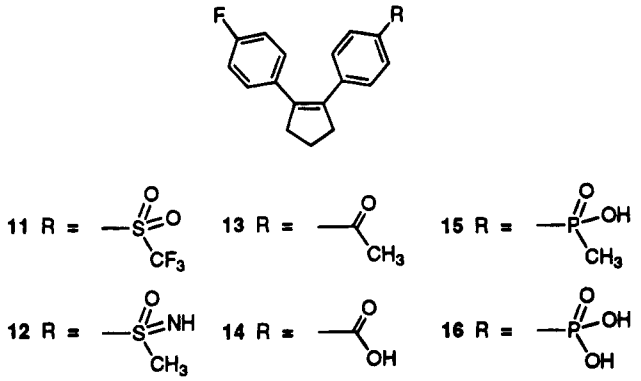


Figure 2. Representative examples of methyl sulfone replacements for **7a**.

adjacent to the 4-methoxyl group, as demonstrated in the selectivity trend of **8k** (8000) > **8j** (1900) > **8i** (500) > **8h** (100). Furthermore, this desired substituent effect was also observed when comparing **8f** with **8g** (selectivity of 430 vs 1900) and **8o** with **8p** (selectivity of 25 vs 85), in which the overall COX-1/COX-2 enzyme selectivity was increased by introducing a chlorine or fluorine atom at the 3-position of the phenyl group. However, such improved enzyme selectivity was not observed in the 3-substituted 4-fluorophenyl analogs **8a** (600), **8b** (450), and **8c** (500). Attempts to increase the selectivity in this series by introducing an even larger substituent at the position adjacent to the 4-fluorine, e.g., 3-trifluoromethyl group in **7d**, resulted in a loss of both COX-2 and COX-1 activity (IC_{50} > 100 μM). The same results were also observed when two fluorine atoms were introduced at the 3,5-positions next to the 4-fluorine moiety, as in analog **7e** or **8e**. Nevertheless, we speculate there might be some generality to this desired substitution effect, and further exploration in other systems is currently under way.

Table 2. *In Vivo* Inhibition in the Carrageenan-Induced Edema and Adjuvant-Induced Arthritis Assays

compd[a]	edema (30 mpk)[a]	arthritis (1 mpk)[a]
7a	45.3	29.3
8a	45.0	79.0
7c	40.0	ND[b]
8c	43.3	81.5
7f	49.0[c]	21.0
8f	49.0	47.0[d]
7g	ND[b]	45.0[e]
8g	31.0	83.0
7h	42.7	0.0[e]
8h	10.0	ND[b]
7i	ND[b]	ND[b]
8i	47.0	25.0[e]
7j	28.0	ND[b]
8j	32.0	25.0

[a] See the Experimental Section. [b] Not determined. [c] Assay performed at 20 mpk. [d] Assay performed at 0.3 mpk. [e] Assay performed at 2 mpk.

Because of their improved COX-1/COX-2 enzyme selectivity, the sulfonamide COX-2 inhibitors **8i,j** were further evaluated *in vivo*. As summarized in Table 2, both **8i,j** showed surprisingly modest activity in the rat established adjuvant-induced arthritis assay with 25% inhibition at 2 and 1 mpk, respectively. Even the sulfonamide **8h** (COX-2, IC_{50} = 0.002 μM), which was one of the most potent *in vitro* COX-2 inhibitors, showed only a marginal oral activity of 10% inhibition in the carrageenan-induced paw edema model, while the sulfone **7h** (COX-2, IC_{50} = 0.005 μM) showed no activity in the rat established adjuvant-induced arthritis model (Table 2). We hypothesize that the diminished *in vivo* activity observed with the sulfone **7h** and sulfonamides **8h–j** might be due to metabolic breakdown of the 4-methoxyphenyl moiety present in these compounds.

On the basis of its overall pharmacological profile, sulfonamide **8c** was selected as a potential clinical candidate for further evaluation. Figures 3 and 4 show the dose–response curve of sulfonamide **8c** (COX-2, IC_{50} = 0.01 μM; COX-1, IC_{50} = 5.1 μM) in the rat carrageenan-induced paw edema and established adjuvant-induced arthritis models, along with the reference compound indomethacin. Sulfonamide **8c** (ED_{50} = 0.16 mpk) showed similar potency to indomethacin (ED_{50} = 0.11 mpk) in the rat established adjuvant-induced arthritis model. However, **8c** (ED_{50} = 22 mpk) was less active than indomethacin (ED_{50} = 1.2 mpk) in the rat carrageenan-induced paw edema model. High-dose toxicology studies have been carried out with **8c** to address the issue of potential GI toxicity that is commonly associated with current NSAIDs. No gastric lesions in the mice were observed after 5 h when **8c** was administered intragastrically at 200 mpk, and similarly, no intestinal bleeding was detected in rats after 72 h

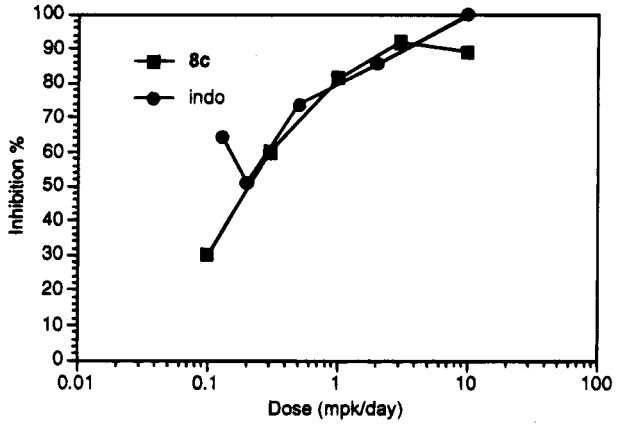


Figure 3. Dose–response curve of established adjuvant-induced arthritis assay of **8c** and indomethacin in Lewis rats. See the Experimental Section for assay procedure.

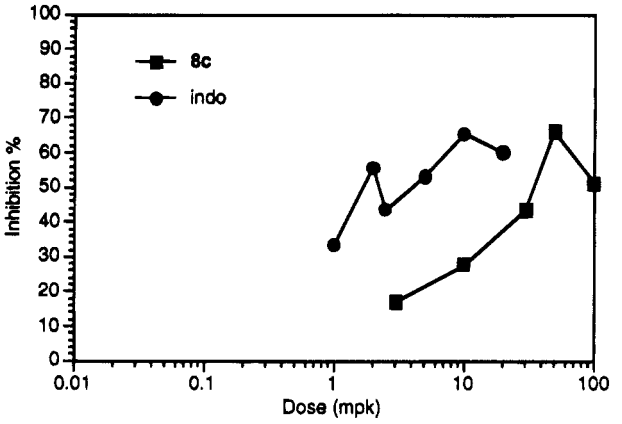


Figure 4. Dose–response curve of carrageenan-induced edema assay of **8c** and indomethacin in Sprague–Dawley rats. See the Experimental Section for assay procedure.

when **8c** was administered intragastrically at 200 mpk. It should be noted that when indomethacin was employed in analogous GI toxicity studies with rats and mice, all test animals experienced severe bleeding or death even at doses as low as 16 mpk. In addition, **8c** was well tolerated in rats when dosed intragastrically at 100 mpk twice daily for an 11-day chronic dosing study. Pharmacokinetic studies in rats indicate that sulfonamide **8c** has an oral bioavailability of 56% and a half-life of 2.1 h (Figure 5).

Conclusion

We have successfully identified an extensive series of 1,2-diarylcyclopentenes that act as potent and selective COX-2 inhibitors. Replacement of the methyl sulfone moiety with a sulfonamide group on the second phenyl ring was found to provide a substantial enhancement of *in vivo* potency, especially in the rat established adjuvant-induced arthritis model, albeit with some decrease in COX-2 selectivity. We have also found that the *in vitro* COX-1/COX-2 selectivity in the sulfonamide series can be increased in many cases by simply incorporating a halogen atom at the 3-position of one of the phenyl rings as represented by the 4-methoxyphenyl compounds **8h–k**. More importantly, the selective COX-2 inhibitor sulfonamide **8c** was shown to be a remarkably orally active anti-inflammatory agent in both the rat carrageenan-induced paw edema and the established adjuvant-induced arthritis models with no

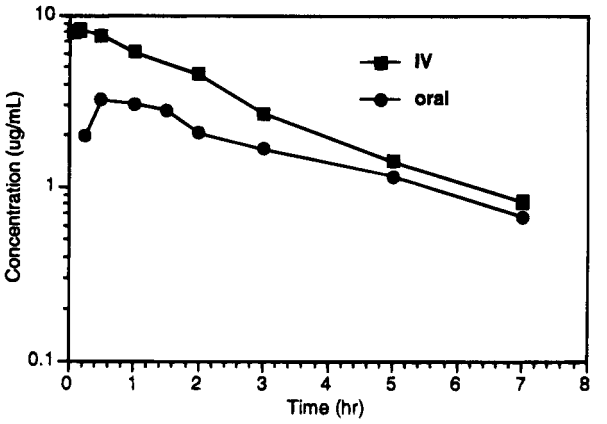


Figure 5. Plasma concentration of **8c** in Sprague–Dawley rats after iv and oral administration at 10 mpk, with 56% bioavailability and 2.1-h plasma half-life.

indication of GI toxicity at 200 mpk. Furthermore, we believe that the development of orally active 1,2-diarylcyclopentene COX-2 inhibitors represents a significant advance for the treatment of acute and chronic inflammatory diseases over conventional NSAIDs.

Experimental Section

Biological Methods. Expression and purification of recombinant human COX-1 and COX-2 enzymes,[11] *in vitro* COX-1 and COX-2 enzyme assays,[11] mouse gastric toxicity study,[24] and rat intestinal toxicity study[24] have been described previously.

Carrageenan-Induced Paw Edema in the Rat.[12,19,20] 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. Edema 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 footpad. Paw volume was measured by a displacement plethysmometer at 3 h after injection of carrageenan, and the mean inhibition values were determined on the basis of an average of five Sprague–Dawley rats.

Adjuvant-Induced Arthritis in the Rat.[21] Adjuvant arthritis was induced in male Lewis rats (150–175 g; Harlan Sprague–Dawley Inc.) by injection of 1 mg of *Mycobacterium butyricum* (Difco Laboratories) in 50 μL of mineral oil (white light, MF; Mallincrodt) into the right hind footpad. The left contralateral footpad volume was measured by water displacement using a plethysmometer at 14 days after injection. Animals with paw volumes 0.37 mL greater than normal paws were then randomized and treated with drug, beginning at 15 days post-adjuvant-injection. Animals were dosed by gavage twice daily at the stated dosages in a volume of 0.1 mL. The drug administration was continued until final assessment on day 25 post-adjuvant-injection, and the mean inhibition values on paw volume were determined on the basis of an average of eight Lewis rats.

Pharmacokinetic Analysis of Sulfonamide 8c. Compound **8c** was administered to male Sprague–Dawley rats by tail-vein injection or gavage in PEG-400/H_2O (2:1), with 4 animals/group. Multiple blood samples were collected from each rat by retro-orbital bleed into heparinized tubes. Bond Elut C-18 solid phase extraction columns (Varian; 100 mg/mL) were used in the extraction, and acetonitrile extracts were concentrated under nitrogen and analyzed on a Beckman System Gold HPLC system which included UV and radioisotope detectors. C-18 columns (Waters Novapak; 3.9 × 150 mm) were eluted isocratically at 1.0 mL/min with 55% acetonitrile and 8.3 mM phosphate buffer with pH at 7.2. Half-life for terminal phase elimination was calculated from plasma concentration versus time data using the CSTRIP computer

program.[25] Area-under-the-curve was calculated using the linear trapezoidal rule.

Chemistry. Proton nuclear magnetic resonance spectra (^{1}H NMR, 300 MHz) were obtained on Varian Unity 300-, VXR 300-, or XL 300-MHz NMR spectrometers, with chemical shifts (δ) reported in parts per million down field from an internal tetramethylsilane or chloroform (7.24 ppm) reference. Fast atom bombardment mass spectra (FABMS) were obtained on a VG40−250 mass spectrometer. Electron impact mass spectra (EIMS) were obtained on a Finnigan 4500 mass spectrometer. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 90 mass spectrometer with FAB or EI ionization. High-performance liquid chromatography (HPLC) separations were performed on a Waters Associates LC 2000 or Prep 500A system with silica gel columns. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. When using air-sensitive reagents, all glassware was oven-dried prior to use and all reactions were performed under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium and benzophenone under a nitrogen atmosphere. All other reagents and solvents were obtained from commercial sources and used without further purification. All new compounds were fully characterized spectrally, and purity was established by being within ±0.4% of the theoretical values in elemental analyses, which were performed by Galbraith Laboratories, Inc.

1,2-Dibromocyclopentene (2).[18] Under nitrogen, to a stirred solution of 1376 g (6.6 mol) of PCl_5 in 3 L of toluene was slowly added 530 mL (6 mol) of cyclopentanone in 40 min. The temperature was kept below 35 °C during the addition, and the nitrogen purge was also used to get rid of excess hydrogen chloride gas. After the solution was cooled down to −20 °C, 255 mL (4.9 mol) of bromine was added in 30 min while the temperature was kept at −20 ± 2 °C during the addition period. Most of the solvent and $POCl_3$ were then removed via a rotary evaporator to give an oil residue which was subsequently dissolved in 1 L of hexane. After cooling down to −25 °C, 694 g (6.2 mol) of *t*-BuOK in 3 L of THF was added in a 30-min period while the temperature was kept below −15 °C. After warming up to ambient temperature, 400 g of Celite, 3 L of H_2O, and 2 L of hexane were added to the solution. The solid residue was removed by passing through a Celite plug. The organic layer was separated and dried over $MgSO_4$. Purification by a silica plug (2−3 kg) with hexane gave a liquid residue. Distillation (38−42 °C, 0.25 mmHg) of this liquid residue gave 542 g (40%) of the title compound **2** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.09 (p, J = 8 Hz, 2H), 2.62 (t, J = 8 Hz, 4H). (Caution: Distillation should be performed with proper safety precautions to guard against exotherms or outgassing, occasionally observed during this process.)

General Procedure A for Preparation of Arylboronic Acids. [4-(Methylthio)phenyl]boronic acid (**3**) is described as a typical example. Under nitrogen, to a stirred solution of 30.0 g (150 mmol) of 4-bromothioanisole (**1**) in 1.5 L of anhydrous THF at −78 °C was added 72 mL (180 mmol, 2.5 M in hexane) of *n*-BuLi. After 30 min, 51 mL (450 mmol) of trimethyl borate was added and the solution was allowed to warm to ambient temperature and stirred overnight; 100 mL of H_2O and 300 mL of 10% NaOH were added, and the stirring was continued vigorously for 1 h. The pH was adjusted to 4−5, most of the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 and reconcentrated *in vacuo*. The solid residue was washed with hexane several times to give 21.0 g (83%) of the title compound **3** as a colorless solid: mp >170 °C; ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H), 7.20 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.96 (br s, 2H).

General Procedure B for Preparation of 1,2-Diarylcyclopentenes (Route A of Scheme 1). 1-[2-(4-Fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (**7a**) is described as an example.

1-(2-Bromocyclopenten-1-yl)-4-(methylthio)benzene (4). Under nitrogen, to a stirred solution of 36.4 g (161 mmol) of 1,2-dibromocyclopentene (**2**) and 18.0 g (107 mmol) of **3** in the mixed solvent of 550 mL of toluene, 365 mL of ethanol, and 235 mL of 2 M Na_2CO_3 was added 6 g (5 mol%) of $Pd(PPh_3)_4$. The reaction mixture was vigorously stirred at reflux overnight and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and reconcentrated *in vacuo*. Purification by silica gel chromatography (Waters Prep 500A) with hexane gave 9.4 g (22%) of the title compound **4** as a colorless solid: mp 52−54 °C; ^{1}H NMR ($CDCl_3$) δ 1.98−2.09 (m, 2H), 2.50 (s, 3H), 2.70−2.78 (m, 2H), 2.80−2.89 (m, 2H), 7.24 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H).

1-[2-(4-Fluorophenyl)cyclopenten-1-yl]-4-(methylthio)-benzene (5, R^1 = R^3 = H, R^2 = F). Under nitrogen, to a stirred solution of 1.5 g (5.6 mmol) of **4** and 1.5 g (11 mmol) of (4-fluorophenyl)boronic acid in the mixed solvent of 30 mL of toluene, 20 mL of ethanol, and 15 mL of 2 M Na_2CO_3 was added 250 mg (5 mol%) of $Pd(PPh_3)_4$. The reaction mixture was vigorously stirred at reflux overnight and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and reconcentrated *in vacuo*. Purification by silica gel plug with hexane gave 1.6 g of the title compound **5** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.97−2.09 (m, 2H), 2.45 (s, 3H), 2.86, (t, J = 7 Hz, 4H), 6.86−6.94 (m, 2H), 7.08 (br s, 4H), 7.10−7.18 (m, 2H).

7a. To a stirred solution of 1.6 g (previous step) of **5** in 46 mL of methanol/THF (1:1) was slowly added 5.2 g (8.4 mmol) of Oxone in 23 mL of H_2O. After stirring for 4 h, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and reconcentrated *in vacuo*. Purification by silica gel chromatography (Waters Prep 500A) with ethyl acetate/hexane (3:7) followed by recrystallization from ethyl acetate/hexane gave 960 mg (54%) of the title compound **7a** as a colorless solid: mp 138−139 °C; ^{1}H NMR ($CDCl_3$) δ 2.03−2.09 (m, 2H), 2.91 (t, J = 7 Hz, 4H), 3.04 (s, 3H), 6.88−6.96 (m, 2H), 7.06−7.14 (m, 2H), 7.32 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 316 (100), 237 (41), 161 (13); HRMS calcd for M^+ 316.0933, found 316.0943. Anal. ($C_{18}H_{17}FO_2S$) C, H, F, S.

General Procedure C for Preparation of 1,2-Diarylcyclopentenes (Route B of Scheme 1). 1-[2-(3-Chloro-4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (**7c**) is described as an example.

1-(2-Bromocyclopenten-1-yl)-4-(methylsulfonyl)benzene (6). Under nitrogen, to a stirred solution of 45.2 g (200 mmol) of **2** and 16.8 g (100 mmol) of **3** in the mixed solvent of 220 mL of toluene, 220 mL of ethanol, and 220 mL of 2 M Na_2CO_3 was added 6 g (5 mol%) of $Pd(PPh_3)_4$. The reaction mixture was vigorously stirred at reflux overnight and concentrated *in vacuo*. The residue was dissolved in Et_2O, filtered through a silica plug with hexane as the eluent, and reconcentrated *in vacuo*. The oil residue was then dissolved in 600 mL of methanol/THF (1:1), cooled to 0 °C, and followed by the addition of 70 g (114 mmol) of Oxone in 300 mL of H_2O. The reaction mixture was allowed to warm to ambient temperature and then stirred for 4 h. After most of the solvent was evaporated, the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and reconcentrated in *vacuo*. Purification by silica gel chromatography (Waters Prep 500A) with ethyl acetate/hexane (3:7) gave 14.5 g (48%) of the title compound **6** as a colorless solid: mp 103.2−103.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.02−2.14 (m, 2H), 2.74−2.83 (m, 2H), 2.86−2.94 (m, 2H), 3.07 (s, 3H), 7.77 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H).

7c. Under nitrogen, to a stirred solution of 3.0 g (9.9 mmol) of **6** and 2.6 g (14.9 mmol) of (3-chloro-4-fluorophenyl)boronic acid in the mixed solvent of 33 mL of toluene, 33 mL of ethanol, and 33 mL of 2 M Na_2CO_3 was added 1 g (5 mol%) of $Pd(PPh_3)_4$. The reaction mixture was vigorously stirred at reflux overnight and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and reconcentrated in *vacuo*. Purification by silica gel chromatography (Waters Prep 500A) with ethyl acetate/hexane (1:4) gave 2.9 g (82%) of the title compound **7c** as a colorless solid: mp 87.5−88.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.03−2.15 (m, 2H), 2.84−2.95 (m, 4H), 3.04 (s, 3H), 6.91−7.02 (m, 2H), 7.19 (dd, J = 8, 2 Hz, 1H), 7.31 (t, J = 9 Hz, 2H), 7.79 (t,

J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 350 (100), 271 (22), 236 (69); HRMS calcd for M^+ 350.0544, found 350.0523. Anal. ($C_{18}H_{16}ClFO_2S$) C, H, F.

1-[2-(3,4-Difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7b). Following the general procedure C described for **7c**, the title compound **7b** was isolated as a colorless solid: mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 2.10 (p, J = 8 Hz, 2H), 2.85–2.96 (m, 4H), 3.05 (s, 3H), 6.79–6.86 (m, 1H), 6.89–7.07 (m, 2H), 7.32 (d, J = 9 Hz, 2H), 7.79 (d, J = 9 Hz, 2H); MS (FAB) m/z 341 (M + Li); HRMS calcd for (M + H) 335.0917, found 335.0925. Anal. ($C_{18}H_{16}F_2O_2S$) C, H, F.

1-[2-[4-Fluoro-3-(trifluoromethyl)phenyl]cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7d). Following the general procedure C described for **7c**, the title compound **7d** was isolated as a colorless solid: mp 81.5–82.8 °C; ^1H NMR ($CDCl_3$) δ 2.12 (p, J = 8 Hz, 2H), 2.92 (t, J = 8 Hz, 4H), 3.03 (s, 3H), 7.03 (t, J = 9 Hz, 1H), 7.21–7.27 (m, 1H), 7.31 (d, J = 9 Hz, 2H), 7.33–7.37 (m, 1H), 7.80 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 384 (25), 177 (80), 141 (43), 128 (100), 115 (75), 91 (55), 63 (42); HRMS calcd for M^+ 384.0807, found 384.0810. Anal. ($C_{19}H_{16}F_4O_2S$) C, H, F.

1-[2-(3,4,5-Trifluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7e). Following the general procedure C described for **7c**, the title compound **7e** was isolated as a colorless solid: mp 144.5–145.5 °C; ^1H NMR ($CDCl_3$) δ 2.09 (p, J = 8 Hz, 2H), 2.83–2.94 (m, 4H), 3.06 (s, 3H), 6.69–6.74 (m, 2H), 7.31 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H); MS (FAB) m/z (rel intensity) 359 (M + Li); HRMS calcd for M^+ 352.0745, found 352.0749. Anal. ($C_{18}H_{15}F_3O_2S$) C, H, F, S.

1-[2-(4-Chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7f). Following the general procedure B described for **7a**, the intermediate **5** (R^1 = R^3 = H, R^2 = Cl) was isolated as a semisolid: mp 72–74 °C; ^1H NMR ($CDCl_3$) δ 1.98–2.10 (m, 2H), 2.46 (s, 3H), 2.86 (t, J = 7 Hz, 4H), 7.07–7.21 (m, 8H).

The title compound **7f**: mp 127.5–128.5 °C; ^1H NMR ($CDCl_3$) δ 2.03–2.15 (m, 2H), 2.91 (t, J = 7 Hz, 4H), 3.04 (s, 3H), 7.06, (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 332 (100), 218 (30); HRMS calcd for M^+ 332.0638, found 332.0628. Anal. ($C_{18}H_{17}ClO_2S$) C, H, Cl, S.

1-[2-(3,4-Dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7g). Following the general procedure C described for **7c**, the title compound **7g** was isolated as a colorless solid: mp 100–101 °C; ^1H NMR ($CDCl_3$) δ 2.10 (p, J = 8 Hz, 2H), 2.85–2.96 (m, 4H), 3.05 (s, 3H), 6.91 (dd, J = 9, 2 Hz, 1H), 7.23–7.28 (m, 2H), 7.32 (d, J = 9 Hz, 2H), 7.79 (d, J = 9 Hz, 2H); MS (FAB) m/z 373 (M + Li); HRMS calcd for M^+ 366.0248, found 366.0269. Anal. ($C_{18}H_{16}Cl_2O_2S$) C, H, Cl, S.

1-[2-(4-Methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7h). Following the general procedure C described for **7c**, the title compound **7h** was isolated as a colorless solid: mp 128.8–129.8 °C; ^1H NMR ($CDCl_3$) δ 2.01–2.14 (m, 2H), 2.90 (t, J = 8 Hz, 4H), 3.04 (s, 3H), 3.79 (s, 3H), 6.78 (t, J = 9 Hz, 2H), 7.08 (t, J = 9 Hz, 2H), 7.36 (t, J = 9 Hz, 2H), 7.75 (t, J = 9 Hz, 2H); MS (FAB) m/z 335 (M + Li); HRMS calcd for M^+ 328.1133, found 328.1125. Anal. ($C_{19}H_{20}O_3S$) C, H, S.

1-[2-(3-Fluoro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7i). Following the general procedure C described for **7c**, the title compound **7i** was isolated as a colorless solid: mp 127.8–128.6 °C; ^1H NMR ($CDCl_3$) δ 2.02–2.14 (m, 2H), 2.84–2.94 (m, 4H), 3.05 (s, 3H), 3.86 (s, 3H), 6.76–6.92 (m, 3H), 7.34 (t, J = 9 Hz, 2H), 7.78 (t, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 346 (100), 267 (10), 191 (10), 139 (12); HRMS calcd for M^+ 346.1039, found 346.1049. Anal. ($C_{19}H_{19}FO_3S$) C, H, F.

1-[2-(3-Chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7j). Following the general procedure C described for **7c**, the title compound **7j** was isolated as a colorless solid: mp 118–120° C; ^1H NMR ($CDCl_3$) δ 2.01–2.14 (m, 2H), 2.83–2.95 (m, 4H), 3.04 (s, 3H), 3.87 (s, 3H), 6.77 (d, J = 9 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.18 (d, J = 2 Hz, 1H), 7.34 (t, J = 9 Hz, 2H), 7.77 (t, J = 9 Hz, 2H); MS (EI) m/z (rel intensity 362 (100), 327 (13), 248 (18); HRMS calcd for M^+ 362.0743, found 362.0727. Anal. ($C_{19}H_{19}ClO_3S$) C, H, Cl.

1-[2-(3,5-Dichloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7k). Following the general procedure C described for **7c**, the title compound **7k** was isolated: ^1H NMR ($CDCl_3$) δ 2.04–2.15 (m, 2H), 2.82–2.95 (m, 4H), 3.05 (s, 3H), 3.88 (s, 3H), 7.03 (s, 2H), 7.34 (d, J = 9 Hz, 2H), 7.82 (t, J = 9 Hz, 2H); MS (FAB) m/z 403 (M + Li); HRMS calcd for M^+ 396.0354, found 396.0366. Anal. ($C_{19}H_{18}Cl_2O_3S \cdot 0.42H_2O$) C, H.

5-[2-[4-(Methylsulfonyl)phenyl]cyclopenten-1-yl]-1,3-benzodioxole (7l). Following the general procedure C described for **7c**, the title compound **7l** was isolated as a colorless solid: mp 140.0–140.7 °C; ^1H NMR ($CDCl_3$) δ 2.06 (p, J = 8 Hz, 2H), 2.82–2.93 (m, 4H), 3.04 (s, 3H), 5.93 (s, 2H), 6.59–6.72 (m, 3H), 7.35 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H); HRMS M^+ 342.0926, found 342.0932. Anal. ($C_{19}H_{18}O_4S$) C, H.

1-[2-[3-Chloro-4-(*N*,*N*-dimethylamino)phenyl]cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7m). Following the general procedure C described for **7c**, the title compound **7m** was isolated as a colorless solid: mp 127–128 °C; ^1H NMR ($CDCl_3$) δ 2.07 (p, J = 7 Hz, 2H), 2.80 (s, 6H), 2.84–2.95 (m, 4H), 3.04 (s, 3H), 6.86–6.93 (m, 2H), 7.16 (d, J = 2 Hz, 1H), 7.36 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H); MS (FAB) m/z 376, 378 (M + H); HRMS calcd for M^+ 375.1060, found 375.1044. Anal. ($C_{20}H_{22}NClO_2S$) C, H, N, Cl, S.

1-[2-(4-Methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7n). Following the general procedure B described for **7a**, the intermediate **5** (R^1 = R^3 = H, R^2 = CH_3) was isolated as a colorless solid: mp 64.5–66.5 °C; ^1H NMR ($CDCl_3$) δ 1.97–2.09 (m, 2H), 2.30 (s, 3H), 2.45 (s, 3H), 2.86 (t, J = 7 Hz, 4H), 6.99–7.15 (m, 8H).

The title compound **7n**: mp 118.0–118.5 °C; ^1H NMR ($CDCl_3$) δ 2.01–2.14 (m, 2H), 2.32 (s, 3H), 2.90 (t, J = 7 Hz, 4H), 3.03 (s, 3H), 6.99–7.08 (m, 4H), 7.34 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H); MS (EI) m/e (rel intensity) 312 (100), 218 (22); HRMS calcd for M^+ 312.1184, found 312.1194. Anal. ($C_{19}H_{20}O_2S$) C, H, S.

1-[2-[4-(Trifluoromethyl)phenyl]cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7o). Following the general procedure B described for **7a**, the intermediate **5** (R^1 = R^3 = H, R^2 = CF_3) was isolated as a colorless solid: mp 60.0–61.5 °C; ^1H NMR ($CDCl_3$) δ 2.00–2.13 (m, 2H), 2.46 (s, 3H), 2.89 (t, J = 7 Hz, 4H), 7.06 (d, J = 6 Hz, 2H), 7.10 (d, J = 6 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H).

The title compound **7o**: mp 134.5–135.0 °C; ^1H NMR ($CDCl_3$) δ 2.07–2.19 (m, 2H), 2.95 (t, J = 7 Hz, 4H), 3.05 (s, 3H), 7.24 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 7.78 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 366 (100), 287 (33); HRMS calcd for M^+ 366.0901, found 366.0913. Anal. ($C_{19}H_{17}F_3O_2S$) C, H, F, S.

1-[2-[3-Fluoro-4-(trifluoromethyl)phenyl]cyclopenten-1-yl]-4-(methylsulfonyl)benzene (7p). Following the general procedure C described for **7c**, the title compound **7p** was isolated as a colorless solid: mp 97–100 °C; ^1H NMR ($CDCl_3$) δ 2.12–2.20 (m, 2H), 2.89–2.99 (m, 4H), 3.02 (s, 3H), 7.16–7.21 (m, 1H), 7.24–7.31 (m, 4H), 7.45 (d, J = 9 Hz, 2H); MS (FAB) m/z 391 (M + Li); HRMS calcd for M^+ 384.0807, found 384.0796. Anal. ($C_{19}H_{16}F_4O_2S$) C, H, S.

General Procedure D for the Conversion of Methyl Sulfone to Sulfonamide.[17] 4-[2-(3-Chloro-4-fluorophenyl)-cyclopenten-1-yl]benzenesulfonamide (**8c**) is described as a typical example. Under nitrogen, to a stirred solution of 2.0 g (5.7 mmol) of **7c** in 6.5 mL of anhydrous THF at 0 °C was added 3.9 mL (6.2 mmol, 1.6 M in Et_2O) of *n*-propylmagnesium chloride. The solution was allowed to warm to ambient temperature and then stirred for 30 min. After cooling down to 0 °C, 8.6 mL (8.6 mmol, 1.0 M in THF) of triethylborane was added, and the reaction mixture was refluxed for 40 h. After cooling down to 0 °C, 4.3 g (53 mmol) of NaOAc, 7.2 mL of H_2O, and 5.2 g (46 mmol) of hydroxyamine-*O*-sulfonic acid were added, and the stirring was continued for 4 h at ambient temperature. Most of the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate, washed with

saturated Na_2CO_3 and brine, dried over $MgSO_4$, and reconcentrated *in vacuo*. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:4) followed by recrystallization from ethyl acetate/hexane gave 1.23 g (61%) of the title compound **8c** as a colorless solid: mp 150.5–151.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.02–2.16 (m, 2H), 2.83–2.96 (m, 4H), 4.78 (s, 2H), 6.90–7.03 (m, 2H), 7.18–7.24 (m, 1H), 7.28 (t, J = 9 Hz, 2H), 7.78 (t, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 351 (100), 316 (16), 271 (40), 236 (28); HRMS calcd for M^+ 351.0496, found 351.0516. Anal. ($C_{17}H_{15}FClNO_2S$) C, H, N.

Large-Scale Preparation of 8c (Scheme 2). 1-(2-Bromocyclopenten-1-yl)-3-chloro-4-fluorobenzene (10). Under nitrogen, to a stirred solution of 90.0 g (398 mmol) of **2** and 34.7 g (200 mmol) of (3-chloro-4-fluorophenyl)boronic acid (**9**) in the mixed solvent of 400 mL of toluene, 400 mL of ethanol, and 430 mL of 2 M Na_2CO_3 was added 11.6 g (10 mmol) of $Pd(PPh_3)_4$. The reaction mixture was vigorously stirred at reflux for 4 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and reconcentrated *in vacuo*. Purification by silica gel plug with hexane as the eluent gave a liquid residue. Distillation (80–90 °C, 0.07 mmHg) of this liquid residue gave 22 g (40%) of **10** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.04 (p, J = 8 Hz, 2H), 2.67–2.77 (m, 2H), 2.81–2.91 (m, 2H), 7.12 (t, J = 9 Hz, 1H), 7.45–7.54 (m, 1H), 7.65 (dd, J = 2, 8 Hz, 1H).

8c. Under nitrogen, to a stirred solution of 77.6 g (282 mmol) of **10** in 2.5 L of anhydrous THF at −55 °C was added 113 mL (283 mmol) of *n*-BuLi (2.5 M in hexanes). After stirring for 15 min at −45 °C, 64 mL (564 mmol) of trimethyl borate was added in 10 min, and the solution was allowed to warm to ambient temperature. To the solution were added 63.2 g (268 mmol) of 4-bromobenzenesulfonamide, 19.6 g (28 mmol) of $PdCl_2(PPh_3)_2$, and 900 mL of 2 M Na_2CO_3 solution, and the resulting solution was heated to reflux for 4 h. Most of the solvent was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and reconcentrated *in vacuo*. Recrystallization in toluene/ethyl acetate/hexane (95:2.5:2.5) gave 52 g (52%) of the title compound **8c** as a colorless solid.

4-[2-(4-Fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (8a). Following the general procedure D described for **8c**, the title compound **8a** was isolated as a colorless solid: mp 173–174 °C; ^{1}H NMR ($CDCl_3$) δ 2.02–2.15 (m, 2H), 2.92 (t, J = 7 Hz, 4H), 4.73 (br s, 2H), 6.93 (t, J = 10 Hz, 2H), 7.06–7.15 (m, 2H), 7.28 (d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 317 (100), 237 (40), 221 (30), 109 (55); HRMS calcd for M^+ 317.0886, found 317.0916. Anal. ($C_{17}H_{16}FNO_2S$) C, H, N.

4-[2-(3,4-Difluorophenyl)cyclopenten-1-yl]benzenesulfonamide (8b). Following the general procedure D described for **8c**, the title compound **8b** was isolated as a colorless solid: mp 147–147.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (p, J = 9 Hz, 2H), 2.84–2.95 (m, 4H), 4.76 (s, 2H), 6.80–6.86 (m, 1H), 6.90–7.07 (m, 2H), 7.27 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H); MS (FAB) m/z 342 (M + Li); HRMS calcd for (M + H) 336.0870, found 336.0856. Anal. ($C_{17}H_{15}F_2NO_2S$) C, H, N.

4-[2-(3,4,5-Trifluorophenyl)cyclopenten-1-yl]benzenesulfonamide (8e). Following the general procedure D described for **8c**, the title compound **8e** was isolated as a colorless solid: mp 175.5–177 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (p, J = 8 Hz, 2H), 2.83–2.93 (m, 4H), 4.88 (s, 2H), 6.73 (t, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H); MS (FAB) m/z 354 (M + H); HRMS calcd for M^+ 353.0697, found 353.0707. Anal. ($C_{17}H_{14}NF_3O_2S$) C, H, N, S.

4-[2-(4-Chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (8f). Following the general procedure D described for **8c**, the title compound **8f** was isolated as a colorless solid: mp 177–178 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (p, J = 8 Hz, 2H), 2.90 (t, J = 8 Hz, 4H), 4.78 (s, 2H), 7.06 (d, J = 9 Hz, 2H), 7.20 (d, J = 9 Hz, 2H), 7.27 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 335 (57), 333 (100), 253 (24), 218 (70), 217 (47), 202 (36), 125 (29), 115 (36), 91 (24); HRMS calcd for M^+ 333.0590, found 333.0587. Anal. ($C_{17}H_{16}ClNO_2S$) C, H, N, Cl, S.

4-[2-(3,4-Dichlorophenyl)cyclopenten-1-yl]benzenesulfonamide (8g). Following the general procedure D described for **8c**, the title compound **8g** was isolated as a colorless solid: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (p, J = 8 Hz, 2H), 2.84–2.95 (m, 4H), 4.76 (s, 2H), 6.91 (dd, J = 9, 2 Hz, 1H), 7.23–7.30 (m, 4H), 7.78 (d, J = 9 Hz, 2H); MS (FAB) m/z 372, 370, 368 (M + H). Anal. ($C_{17}H_{15}Cl_2NO_2S$) C, H, N.

4-[2-(4-Methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (8h). Following the general procedure D described for **8c**, the title compound **8h** was isolated as a colorless solid: mp 171–175 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.00–2.12 (m, 2H), 2.89 (t, J = 8 Hz, 4H), 3.79 (s, 3H), 4.74 (s, 2H), 6.77 (t, J = 9 Hz, 2H), 7.08 (t, J = 9 Hz, 2H), 7.30 (t, J = 9 Hz, 2H), 7.73 (t, J = 9 Hz, 2H); MS (FAB) m/z 330 (M + H); HRMS calcd for M^+ 329.1086, found 329.1112. Anal. ($C_{18}H_{19}NO_3S$) C, H, N.

4-[2-(3-Fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (8i). Following the general procedure D described for **8c**, the title compound **8i** was isolated as a colorless solid: mp 170.0–170.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.01–2.13 (m, 2H), 2.83–2.93 (m, 4H), 3.87 (s, 3H), 4.75 (s, 2H), 6.76–6.92 (m, 3H), 7.30 (t, J = 9 Hz, 2H), 7.76 (t, J = 2H); MS (EI) m/z (rel intensity) 347 (100), 316 (12), 267 (12), 252 (19), 236 (20), 191 (16); HRMS calcd M^+ 347.0991, found 347.0955. Anal. ($C_{18}H_{18}FNO_3S$) C, H, N.

4-[2-(3-Chloro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (8j). Following the general procedure D described for **8c**, the title compound **8j** was isolated as a colorless solid: mp 178.8–180.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.01–2.13 (m, 2H), 2.83–2.93 (m, 4H), 3.87 (s, 3H), 4.75 (s, 2H), 6.76 (d, J = 9 Hz, 1H), 6.94 (dd, J = 9, 2 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 7.30 (t, J = 8 Hz, 2H), 7.76 (t, J = 8 Hz, 2H); MS (EI) m/z (rel intensity) 363 (100), 328 (14), 268 (16), 233 (17); HRMS calcd for M^+ 363.0696, found 363.0701. Anal. ($C_{18}H_{18}ClNO_3S$) C, H, N.

4-[2-(3,5-Dichloro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (8k). Following the general procedure D described for **8c**, the title compound **8k** was isolated as a colorless solid: mp 121–121.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (p, J = 8 Hz, 2H), 2.82–2.94 (m, 4H), 3.90 (s, 3H), 4.76 (s, 2H), 7.05 (s, 2H), 7.30 (d, J = 9 Hz, 2H), 7.80 (d, J = 9 Hz, 2H); MS (FAB) m/z 404 (M + Li); HRMS calcd for M^+ 397.0306, found 397.0292. Anal. ($C_{18}H_{17}Cl_2NO_3S$) C, H, N.

4-[2-[3,4-(Methylenedioxy)phenyl]cyclopenten-1-yl]benzenesulfonamide (8l). Following the general procedure D described for **8c**, the title compound **8l** was isolated as a colorless solid: mp 151–152.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.06 (p, J = 8 Hz, 2H), 2.82 (t, J = 8 Hz, 4H), 4.82 (s, 2H), 5.93 (s, 2H), 6.58–6.72 (m, 3H), 7.31 (d, J = 9 Hz, 2H), 7.74 (d, J = 9 Hz, 2H); MS (FAB) m/z 344 (M + H); HRMS calcd for M^+ 343.0878, found 343.0875. Anal. ($C_{18}H_{17}NO_4S \cdot 0.32H_2O$) C, H, N.

4-[2-[3-Chloro-4-(*N*,*N*-dimethylamino)phenyl]cyclopenten-1-yl]benzenesulfonamide (8m). Following the general procedure D described for **8c**, the title compound **8m** was isolated as a colorless solid: mp 133–134.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.06 (p, J = 7 Hz, 2H), 2.81 (s, 6H), 2.88 (t, J = 7 Hz, 4H), 4.80 (s, 2H), 6.92 (s, 2H), 7.18 (s, 1H), 7.31 (d, J = 7 Hz, 2H), 7.77 (d, J = 7 Hz, 2H); MS (FAB) m/z 383 (M + Li); HRMS calcd for M^+ 376.1012, found 376.1012. Anal. ($C_{19}H_{21}N_2ClO_2S$) C, H, N, Cl, S.

4-[2-[4-(Trifluoromethyl)phenyl]cyclopenten-1-yl]benzenesulfonamide (8o). Following the general procedure D described for **8c**, the title compound **8o** was isolated as a colorless solid: mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 2.05–2.18 (m, 2H), 2.93 (t, J = 8 Hz, 4H), 4.75 (s, 2H), 7.20–7.30 (m, 4H), 7.48 (t, J = 8 Hz, 2H), 7.66 (t, J = 8 Hz, 2H); MS (FAB) m/z 374 (M + Li); HRMS calcd for M^+ 367.0854, found 367.0832. Anal. ($C_{18}H_{16}F_3NO_2S$) C, H, N.

4-[2-[3-Fluoro-4-(trifluoromethyl)phenyl]cyclopenten-1-yl]benzenesulfonamide (8p). Following the general procedure D described for **8c**, the title compound **8p** was isolated as a colorless solid: mp 184.0–185.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.09–2.19 (p, J = 8 Hz, 2H), 2.89–2.98 (m, 4H), 4.85 (s, 2H), 7.16–7.30 (m, 5H), 7.72–7.75 (d, J = 9 Hz, 2H); MS (EI) m/z (rel intensity) 385 (47), 305 (89), 177 (52), 128 (100), 115 (63),

91 (47), 69 (47); HRMS calcd for M^+ 385.0760, found 385.0778. Anal. ($C_{18}H_{15}NF_4O_2S$), C, H, N.

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