2,3-Diarylcyclopentenones as Orally Active, Highly Selective Cyclooxygenase-2 Inhibitors

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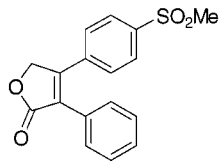
Cyclopentenones containing a 4-(methylsulfonyl)phenyl group in the 3-position and a phenyl ring in the 2-position are selective inhibitors of cyclooxygenase-2 (COX-2). The selectivity for COX-2 over COX-1 is dramatically improved by substituting the 2-phenyl group with halogens in the meta position or by replacing the phenyl ring with a 2- or 3-pyridyl ring. Thus the 3,5-difluorophenyl derivative **7** (L-776,967) and the 3-pyridyl derivative **13** (L-784,506) are particularly interesting as potential antiinflammatory agents with reduced side-effect profiles. Both exhibit good oral bioavailability and are potent in standard models of pain, fever, and inflammation yet have a much reduced effect on the GI integrity of rats compared to standard nonsteroidal antiflammatory drugs.

Introduction

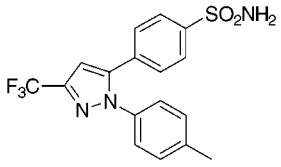
The conversion of arachadonic acid to prostaglandins is mediated by the two-step action of prostaglandin H synthase (PGHS). The first committed step in this process is the oxidative cyclization of arachidonic acid to PGG_2, which is followed by peroxide reduction to PGH_2 at a second distinct binding site. PGHS, commonly known as cyclooxygenase or COX, is known to be the principal target of nonsteroidal antiinflammatory drugs (NSAIDs). Recently, it has been found that there are two isoforms of COX, each with a distinct physiological role.[1] One isoform, COX-1, is constitutively produced in a variety of tissues and appears to be important in the maintenance of normal physiological functions including gastric cytoprotection. The second isoform, COX-2, is induced by a wide variety of inflammatory stimuli and appears to be largely responsible for the high-level production of prostaglandins that results in inflammation.[2] It has been proposed that a selective COX-2 inhibitor could have useful antiinflammatory activity without the ulcerogenic side effects associated with currently available NSAIDs, all of which inhibit both COX-1 and COX-2.[3] Indeed, evidence supporting this hypothesis is now beginning to appear.[4]

Phenyl sulfone-containing tricyclic molecules have proved to be a fertile area for the discovery of selective inhibitors of COX-2. A number of central ring templates have been successfully developed by ourselves[5] and others.[6] Among these are the γ-lactone of MK-0966 (**1**, rofecoxib, Vioxx)[7] and the (trifluoromethyl)diazole of SC-58635 (**2**, celecoxib, Celebrex).[8]

We wish to report here that 2,3-disubstituted cyclopentenones also provide a useful template for the design of COX-2-selective inhibitors. Two compounds in this series, the 3,5-difluorophenyl derivative **7** (L-776,967) and the 3-pyridyl derivative **13** (L-784,506), were found to be particularly interesting, and their pharmacological profiles will be discussed.



MK-0966 (**1**)



SC-58635 (**2**)

Chemistry

The majority of the compounds listed in Table 1 were prepared from a common intermediate, sulfone **28**. This intermediate was most efficiently prepared as outlined in Scheme 1. 3-Ethoxycyclopentenone was treated with bromine followed by triethylamine-mediated dehydrobromination to give **27** in 91% yield. 4-Bromothioanisole was lithiated with nBuLi at −78 °C and then was treated with **27** to give the 1,2 addition product, which was converted to the unsaturated ketone on acidic workup. Tungsten-catalyzed oxidation[9] of the sulfide then provided **28** in 71% yield for the two steps.

Substituted phenyl analogues **3**−**12** were prepared from the appropriate boronic acids via palladium-catalyzed Suzuki couplings with intermediate **28.** The base sensitivity of the cyclopentenone group prevented the use of normal bases (e.g., Na_2CO_3) in these coupling reactions. However, using 2 equiv of diethylamine in refluxing 3:1:1 toluene/nPrOH/water generally provided the product in good yield. In the case of the 3-pyridyl analogue **13**, the isolation of the required pyridine-3-boronic acid was found to be problematic. As a result, it was found that the Suzuki coupling could be carried out very efficiently using the crude trialkylboronate. Thus 3-bromopyridine was lithiated (nBuLi, ether, −78 °C) and then quenched with triisopropylborate (Scheme

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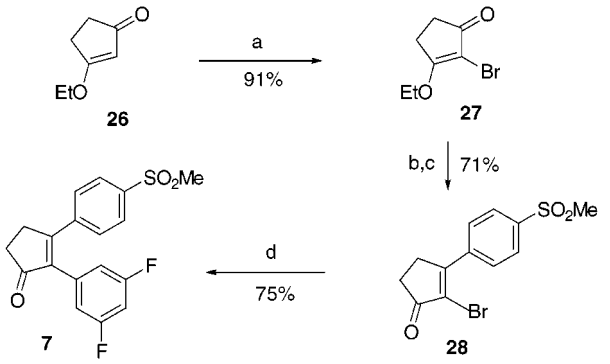
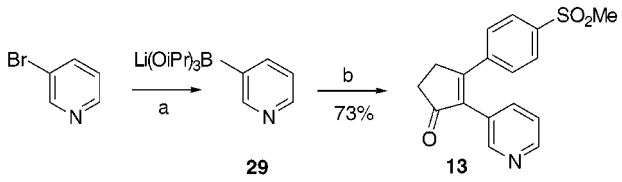
Scheme 1[a]



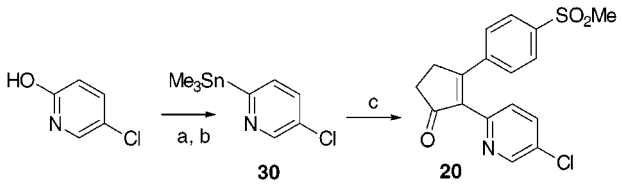
[a] (a) Br_2, Et_3N, $CHCl_3$; (b) 4-bromothioanisole, nBuLi, THF, then **27**, 6 N HCl; (c) $Na_2WO_4 \cdot 2H_2O$, H_2O_2, Aliquat 336, EtOAc/CH_2Cl_2; (d) 3,5-difluorophenylboronic acid, $Pd_2(dba)_3$, PPh_3, Et_2NH, $PhCH_3$/nPrOH/H_2O.

Scheme 2[a]



[a] (a) nBuLi, ether, −78 °C, $(iPrO)_3B$; (b) **28**, $Pd_2(dba)_3$, PPh_3, $PhCH_3$/nPrOH/H_2O.

Scheme 3[a]



[a] (a) Tf_2O, iPr_2NEt, CH_2Cl_2; (b) $(Me_3Sn)_2$, $Pd_2(dba)_3$, PPh_3, LiCl, $PhCH_3$; (c) **28**, $Pd_2(dba)_3$, $AsPh_3$, NMP.

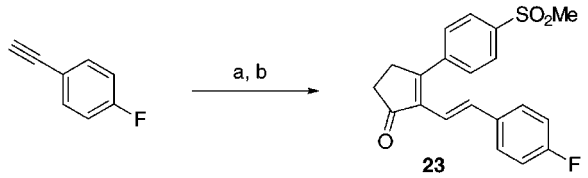
2). Removal of solvent provided the lithium trialkylboronate **29** which was used directly in the Suzuki coupling without the use of additional base. This method obviated the problem of isolating the water-soluble pyridineboronic acid. Similar couplings with the pyridine trialkylboronates were used to provide analogues **15** and **17**.

For analogues **14**, **16**, and **18**−**20**, where the required boronic acids were deemed to be inaccessible, the corresponding trimethylstannanes were prepared. These were generally derived from the hydroxypyridine via the triflate which was coupled with hexamethylditin as illustrated for 4-chloro-2-pyridyl(trimethyl)stannane (**30**), which was then coupled under Stille conditions ($Pd_2(dba)_3$, Ph_3As, NMP, 100 °C) to provide analogue **20** (Scheme 3).

Styryl analogue **23** was prepared from (4-fluorophenyl)acetylene by treatment with disiamylborane and then coupling the resulting crude vinylborane with **28** under Suzuki conditions as described above (Scheme 4). Acetylenic derivatives **24** and **25** were prepared directly by Heck coupling of **28** with phenylacetylene and *tert*-butylacetylene, respectively ($Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 60 °C).

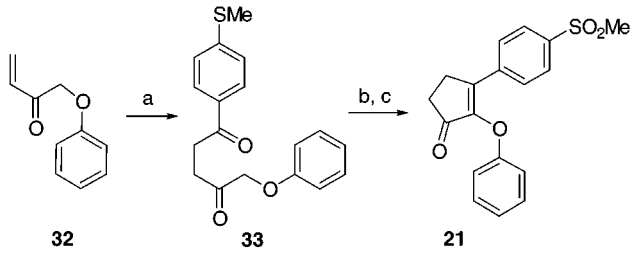
Oxygen-linked compounds **21** and **22** could not be prepared from intermediate **28**. Instead, the cyclopentenone ring was synthesized by the intramolecular aldol condensation of an appropriately substituted diketone (Scheme 5). The lithium salt of phenoxyacetic acid was treated with freshly prepared vinylmagnesium bromide to give the vinyl ketone **32**.[10] A thiazolium salt-catalyzed addition[11] of (thiomethyl)benzaldehyde to **32** provided diketone **33**, which could be cyclized in the presence of DBU to provide the desired 2-phenoxycyclopentenone **21**.

Scheme 4[a]



[a] (a) Sia_2BH, THF; (b) **28**, $Pd_2(dba)_3$, PPh_3, $PhCH_3$/nPrOH/H_2O.

Scheme 5[a]



[a] (a) 4-(Methylthio)benzaldehyde, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N, dioxane; (b) DBU, MeOH; (c) Oxone, acetone/H_2O.

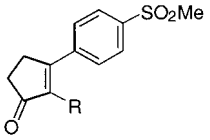
Results and Discussion

Compounds were tested in initial screens for potency against hCOX-2 in transfected CHO cells[12] and against hCOX-1 in U937 microsomes at low (100 nM) arachidonic acid concentration.[13] Selected compounds were subsequently tested in the human whole blood assay against both COX-2 and COX-1.[14] In vivo efficacy was evaluated using a carageenen-induced rat paw edema model.[15]

The first compound synthesized in this series, **3**, containing a 4-fluorophenyl group in the 2-postition, was characterized by its high potency in COX-2 assays as well as its efficacy in the rat paw edema model (ED_{50} = 3.0 mg/kg) (Table 1). However, its potency against COX-1 (3.7 μM in the COX-1 whole blood assay) was determined to be too great to provide an adequate safety margin in our standard toxicology models at 100 mg/kg (vide infra). Placing methyl substituents in either the 4- or 5-position of the cyclopentenone ring was not productive: the former case led to a decrease in activity,[16] while the latter substantially increased the COX-1 potency.[17] We thus turned to modifications of the 2-aryl moiety to achieve an acceptable level of potency and selectivity.

Previous experience in other series has shown that substitutions in the para position of this lower ring increased potency against both COX-1 and COX-2, while substitutions in the meta position increased the selectivity of COX-2 inhibition.[6d,7a] As can be seen in Table 1, this trend generally held true in the cyclopentenone series. Thus, in the highly sensitive U937 microsome assay, the COX-1 potency decreases by 10-fold when the

Table 1. In Vitro and Rat Paw Edema Data for Diarylcyclopentenones



entry		COX-2 (IC_{50}, μM)		COX-1 (IC_{50}, μM)		rat paw edema (ED_{50}, mg/kg)[d]
		CHO cells[a]	human whole blood[b]	U937 microsomes[c]	human whole blood[b]	
1	MK-0966	0.02	0.5	1.7	19	1.7
2	SC-58635	0.002	1.0	0.05	6.3	3.2
3	4-fluorophenyl	0.019	0.08	0.5	3.7	3.0
4	phenyl	0.011	0.19	3.1	4.1	10
5	3-fluorophenyl	0.014	0.34	6.6		6.4
6	3,4-difluorophenyl	0.014	0.21	1.7	3.2	
7	3,5-difluorophenyl	0.015	0.62	11	61	2.6
8	3,5-dichlorophenyl	0.014	0.28	9.2	>100	>10
9	3-chloro-4-fluorophenyl	0.009	0.09	0.3		
10	3-fluoro-4-chlorophenyl	0.015	0.15	0.7	0.1	
11	3,4,5-trichlorophenyl	0.006	0.93	2.5		
12	2-benzothiophenyl	0.014	0.08	0.1		
13	3-pyridyl	0.17	0.64	34	73	1.7
14	5-chloro-3-pyridyl	0.087	1.5	>100	>100	1.3
15	5-bromo-3-pyridyl	0.30	1.7	>100		
16	4-methyl-3-pyridyl	0.44	0.45	5.5	4.1	
17	4-methoxy-3-pyridyl	0.15	0.09	0.06		
18	2-pyridyl	1.53	9.8	>10		
19	4-bromo-2-pyridyl	0.63	0.47	18		
20	4-chloro-2-pyridyl	0.19	0.52	27	34	2.5
21	phenoxy	0.011	0.98	11		
22	3,5-difluorophenoxy	0.017	1.1	2.7	94	6.6
23	4-fluorostyryl	0.175	0.5		27	>10
24	phenylacetylenyl	0.006	0.64	0.71		
25	*tert*-butylacetylenyl	0.15	5.2	>100		

[a] Average of at least two independent determinations, each run in triplicate. [b] Average of at least three determinations. [c] Average of at least two independent determinations. [d] ED_{50} values were determined using a minimum of four dose points, 5 animals/goup.

fluorine is moved from the para position (**3**) to the meta position (**5**). When fluorine atoms are placed in both meta positions (**7**), a further loss of COX-1 potency is achieved. The intrinsic COX-2 potency as measured by the CHO cell assay is not greatly affected by these substituents, and while the COX-2 whole blood potency is also decreased, it is still comparable to that of Vioxx (**1**).

Several heterocycles were also examined. It was noted that the 3-pyridyl moiety (**13**) provided a substantial improvement in COX-2 selectivity. The potency against COX-2 in the CHO cell assay was significantly reduced relative to **7**, but the potency in the human whole blood assay was similar, and the compound was efficacious in the rat paw edema model (ED_{50} = 1.7 mg/kg). Halogen substituents on the pyridine ring reduced the potency against both COX-1 and COX-2. It is interesting to note the effect of the 4-methoxy substituent on COX-1 potency (**17**). The IC_{50} of 60 nM for compound **17** in U937 microsomes is the most potent COX-1 inhibition observed in this series and shows the dramatic effect of a para substituent on COX selectivity.

The 2-pyridyl moiety (**18**) showed relatively poor activity against both enzymes, but the addition of a *p*-chloro substituent (**20**) gave a dramatic improvement in COX-2 potency and provided a compound with good rat paw edema efficacy (ED_{50} = 2.5 mg/kg). Phenoxy (**21**), styryl (**23**), and acetylenyl (**24**) substituents provide an interesting measure of the flexibility possible in this position of the molecule but did not provide the required level of selectivity for COX-2.

As a result of their characteristics of COX-2 potency, selectivity, and rat paw edema efficacy, compounds **7** and **13** were chosen for further examination. It was of immediate interest that while the whole blood COX-2 potencies of **13**, **7**, and MK-0966 were comparable (0.64, 0.62, and 0.5 μM, respectively), the intrinsic potency of **13** was nearly 10-fold less as measured in the CHO cell assay (170 nM vs 26 nM and 20 nM). We originally speculated that **13** might be a dual inhibitor, with activity against another proinflammatory enzyme such as p38 kinase, but screening in relevant assays did not support this hypothesis.[18] Further, no effect was seen on COX-2 expression, TNF-α or IL-1β production in human mononuclear cells.[19] A more likely cause for the discrepancy was a differential shift in potency by protein present in the human whole blood assay. Indeed, when MK-0966 was tested in a human blood mononuclear cell assay in the presence of 10% human serum, it showed an IC_{50} of 0.04 μM, 16-fold more potent than observed in the protein-rich whole blood assay and comparable to the value obtained in the CHO cell assay. In contrast, compound **13** showed an IC_{50} of 0.62 μM in the human blood mononuclear cell assay, not significantly different from the 0.64 μM value obtained in the human whole blood assay. In a separate protein-binding experiment, **13** was found to be 55% protein-bound in human plasma, while MK-0966 was found to be 85% protein-bound. Thus the favorable, low protein-binding characteristics of **13** appear to compensate for its lower intrinsic potency, thus giving an *effective* potency in blood comparable to that of MK-0966.

Detailed kinetic studies were carried out on compound **7** to determine the mechanism of inhibition of COX-2. These studies indicated that **7** is a time-dependent, reversible inhibitor of COX-2 that forms a noncovalent enzyme−inhibitor complex similar to other COX-2-selective inhibitors which have been studied.[20]

Compounds **7** and **13** had substantially different pharmacokinetics in the rat (Figure 1). Compound **7**

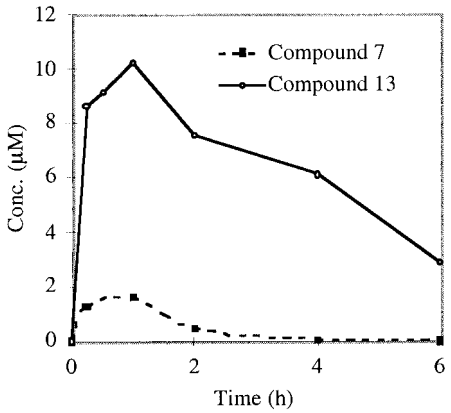


Figure 1. Rat plasma levels, 3 mg/kg po.

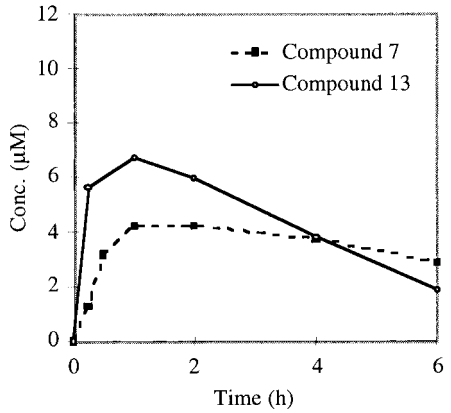


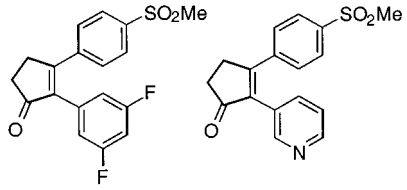
Figure 2. Dog plasma levels, 3 mg/kg po.

showed 55% bioavailability in male rats and gave a 1.6 μM C_{max} when dosed orally at 3 mg/kg. In contrast, compound **13** gave 100% bioavailability with a 10 μM C_{max} when dosed under the same conditions. Additionally, the observed half-life in rats based on intravenous dosing was considerably longer for **13**: 3 h vs 1 h for compound **7**. When dosed in male beagle dogs, the pharmacokinetic differences between the two compounds were much less apparent (Figure 2). Both **7** and **13** showed excellent oral bioavailability (90% and 84%, respectively). In this species, compound **7** was found to have the longer intravenous half-life: 4 h compared to 2 h for compound **13**.

Both compounds were pursued in other in vivo models of efficacy and tolerability that were at our disposal (Table 2). Both **7** and **13** were efficacious in standard rat models of inflammation, pyresis, and hyperalgesia,[15] with **13** being slightly superior in all three models. In the case of the rat adjuvant arthritis model,[21] a chronic inflammation model with b.i.d. dosing over 21 days, compound **13** showed marked superiority, but these data must be interpreted in light of the differing pharmacokinetics between the two compounds. With only a 1-h half-life in rats, compound **7** would not be expected to provide protection against chronic inflammation at doses that are efficacious in acute efficacy models.

To evaluate the initial toxicology of these two compounds, male and female rats were treated with either **7** or **13** at 100 mg/kg for 4 days and then examined for changes in liver weight. Both compounds were well-tolerated, with only minor liver weight increases being

Table 2. In Vivo Profiles



7 **13**

	7	**13**
efficacy:		
rat paw edema (ED_{50}, mg/kg)[a]	2.7	1.7
rat pyresis (ED_{50}, mg/kg)[a]	0.8	0.7
rat hyperalgesia (ID_{50}, mg/kg)[a]	3.0	0.7
adjuvant arthritis, 21 day (ID_{50}, mg/kg)[a]	4.0	0.6
safety:		
% change in rat liver weight, chronic dosing (M/F, 4 days at 100 mg/kg/day)[c]	+7/+9	+12/+15
rat GI tolerance, ^{51}Cr leakage (10 days at 100 mg/kg/day)	12/12 clean	11/12 clean (1 death)

[a] ED_{50} values were determined using a minimum of four dose points, 5 animals/goup. [b] ID_{50} values were determined using a minimum of four dose points, 10 animals/goup. [c] Mean change relative to control using 4 animals/group.

observed (7−15%). Finally, to test the hypothesis that a selective COX-2 inhibitor would not be associated with increased levels of gastrotoxicity, rats were treated with either **7** or **13** at 100 mg/kg for 10 days and then given an intravenous dose of ^{51}Cr to test for any increased gastric permeability.[15] The amount of ^{51}Cr in the feces was determined to be indistinguishable from control for all 12 rats treated with **7**, indicating a high level of GI tolerance. In contrast, a single dose of a nonselective inhibitor such as diclofenac or indomethacin at 10 mg/kg caused a significant increase in ^{51}Cr excretion. Eleven out of 12 of the rats treated with **13** were also found to have an insignificant level of ^{51}Cr excretion; however one rat died during the course of the study due to acute peritonitis. This appears to indicate that compound **13** at high dosages is still associated with some gastric toxicity. As the mean plasma concentration of **13** observed in the surviving rats 1 h postdose was 185 μM, it is possible that COX-1 inhibition is a factor at these high dosages.

These studies have shown that a COX-2-selective inhibitor can be a potent antiinflammatory, analgesic, and antipyretic drug with a much reduced risk of GI toxicity compared to conventional NSAIDs. Further, the 2,3-diarylcyclopentenone moiety has been shown to be a useful template for the construction of such COX-2-selective inhibitors. As a result of these studies, it was decided to take compound **7** forward for evaluation in preclinical safety assessment.

Experimental Section

Chemistry. ^1H NMR spectra were determined on Bruker AM300, AMX300, or AMX400 spectrometers, and proton chemical shifts are relative to tetramethylsilane as internal standard. Elemental analyses were performed by Oneida Research Services, Whitesboro, NY, or by the Université de Montreal, Department of Chemistry.

Preparation of Intermediate 28. 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one. Step 1. 2-Bromo-3-ethoxy-2-cyclopenten-1-one (27). To a −15 °C solution of 3-ethoxy-2-cyclopenten-1-one (**26**) (165 g, 1.30 mol) in 1.8 L of

$CHCl_3$ was added a solution of bromine (219 g, 1.37 mol) in $CHCl_3$ (200 mL) via dropping funnel over 1.5 h to give a thick yellow slurry. After 30 min of additional stirring, a solution of Et_3N (210 mL, 1.5 mol) in $CHCl_3$ (300 mL) was added via dropping funnel over 30 min. The resulting mixture was concentrated, suspended in EtOAc, and filtered through a pad of 2-cm Celite over 1-cm silica gel. The filtrate was concentrated and the resulting material recrystallized from 4:1 ether/hexanes to provide 245 g of the title compound: ^{1}H NMR (CD_3COCD_3) δ 4.43 (2H, q), 2.95 (2H, m), 2.47 (2H, m), 1.39 (1H, t).

Step 2. 2-Bromo-3-(4-(methylthio)phenyl)-2-cyclopenten-1-one. To a −78 °C solution of 4-bromothioanisole (253 g, 1.25 mol) in THF (5 L) was added nBuLi (2.5 M in hexanes, 500 mL, 1.25 mol) over 20 min to give a thick slurry which was stirred 2 h at −78 °C. A solution of 2-bromo-3-ethoxy-2-cyclopenten-1-one (**27**) (242 g, 1.18 mol) in THF (1 L) was then added via cannula, and the mixture was allowed to warm to −10 °C; 6 N HCl (430 mL) was then added, and the resulting mixture stirred 20 min. EtOAc (3 L) was added, and the aqueous phase was separated. The organic layer was concentrated. The residue was suspended in ether and filtered to give 287 g of the title compound: ^{1}H NMR (CD_3COCD_3) δ 8.12 (4H, m), 3.22 (2H, m), 3.20 (3H, s), 2.69 (2H, m).

Step 3. 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (28). To a solution of $Na_2WO_4 \cdot 2H_2O$ (6.7 g, 20.3 mmol) in water (70 mL) was added a few drops of concentrated H_2SO_4 to give a solution of pH 6. This solution was added to a room temperature suspension of 2-bromo-3-(4-(methylthio)-phenyl)-2-cyclopenten-1-one (304.9 g, 1.07 mol) in EtOAc (3 L) and dichloromethane (300 mL). Aliquat 336 (22 g, 54.4 mmol) was added, and the mixture was warmed to 40 °C. Hydrogen peroxide (30%, 350 mL, 3.1 mol) was added dropwise to maintain an internal reaction temperature of approximately 50 °C (external cooling with a water bath was used). After the addition was complete, stirring was continued for 3 h at 50 °C; then the aqueous phase was removed by cannula. Two portions of warm water were added, stirred, and removed by cannula. The organic phase was then concentrated to approximately 1 L, and the crystalline product was filtered to provide 290.6 g (86%) of the title compound: ^{1}H NMR (CD_3COCD_3) δ 8.12 (4H, m), 3.22 (2H, m), 3.20 (3H, s), 2.69 (2H, m).

3,5-Difluorophenylboronic Acid. To a −78 °C solution of 1-bromo-3,5-difluorobenzene (50 g, 0.26 mol) in ether (860 mL) was added nBuLi (2.4 M in hexanes, 108 mL, 0.26 mol) dropwise over 20 min. The resulting solution was stirred for 10 min and then treated with triisopropylborate (61 mL, 0.27 mol). The reaction mixture was warmed to 0 °C for 30 min and then quenched with 1 M HCl. After stirring 30 min, the mixture was partitioned between ethyl acetate and water. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The resulting product was dried under high vacuum overnight to give 38 g of the title compound: ^{1}H NMR (CD_3COCD_3) δ 7.50 (2H, br s), 7.40 (2H, m), 7.04 (1H, m).

Representative Procedure for Suzuki Coupling with Phenylboronic Acids: 2-(3,5-Difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (7). A mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (**28**)-(52.2 g, 166 mmol), 3,5-difluorophenylboronic acid (31.9 g, 202 mmol), tris(dibenzylideneacetone)dipalladium(0) (3.3 g, 3.6 mmol), and triphenylphosphine (1.89 g, 7.2 mmol) were dissolved in toluene (800 mL) and nPrOH (250 mL) and degassed. After the mixture stirred for 10 min, diethylamine (21 mL, 203 mmol) and water (250 mL) were added. The mixture was degassed again, heated to reflux for 1 h, then cooled, and poured into EtOAc (2 L). The aqueous layer was separated, and the organic layer was washed with 0.2 N NaOH (500 mL), 0.5 N HCl (500 mL), and brine. The organic phase was then dried over $MgSO_4$, filtered through Celite, and evaporated. The resulting light-brown solid was slurried with hot EtOAc (250 mL), cooled, and filtered to give 45.8 g (75%) of the title compound: mp 174−175 °C; ^{1}H NMR (CD_3COCD_3) δ 7.95 (2H, m), 7.66 (2H, m), 6.98 (1H, m), 6.80 (2H, m), 3.17 (2H, m), 3.12 (3H, s), 2.68 (2H, m). Anal. ($C_{18}H_{14}F_2O_3S$) C,H,N.

2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (3): ^{1}H NMR (CD_3COCD_3) δ 7.93 (2H, m), 7.63 (2H, m), 7.23 (2H, m), 7.07 (2H, m), 3.16 (2H, m), 3.14 (3H, s), 2.67 (2H, m). Anal. ($C_{18}H_{15}FO_3S$) C,H,N.

2-Phenyl-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (4): ^{1}H NMR (CD_3COCD_3) δ 7.90 (2H, m), 7.62 (2H, m), 7.31 (3H, m), 7.15 (2H, m), 3.14 (2H, m), 3.12 (3H, s), 2.65 (2H, m). Anal. ($C_{18}H_{16}O_3S$) C,H,N.

2-(3-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (5): ^{1}H NMR (CD_3COCD_3) δ 7.93 (2H, m), 7.65 (2H, m), 7.34 (1H, m), 7.10 (1H, m), 6.95 (2H, m), 3.16 (2H, m), 3.13 (3H, s), 2.68 (2H, m); HRMS calcd for $C_{18}H_{16}FO_3S$ 331.08042, found 331.08034. Anal. ($C_{18}H_{15}FO_3S \cdot {}^1/_2H_2O$) C,H,N.

2-(3,4-Difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (6): ^{1}H NMR (CD_3COCD_3) δ 7.95 (2H, m), 7.65 (2H, m), 7.25 (2H, m), 6.95 (1H, m), 3.16 (2H, m), 3.12 (3H, s), 2.67 (2H, m); HRMS calcd for $C_{18}H_{14}F_2O_3S$ 349.07099, found 349.07115.

2-(3,5-Dichlorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (8): ^{1}H NMR (CD_3COCD_3) δ 7.95 (2H, m), 7.68 (2H, m), 7.44 (1H, t), 7.18 (2H, d), 3.18 (2H, m), 3.12 (3H, s), 2.68 (2H, m); HRMS calcd for $C_{18}H_{15}Cl_2O_3S$ 381.01190, found 381.01187. Anal. ($C_{18}H_{14}Cl_2O_3S \cdot {}^1/_4H_2O$) C,H,N.

2-(3-Chloro-4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (9): ^{1}H NMR (CD_3COCD_3) δ 7.95 (2H, m), 7.67 (2H, m), 7.38 (1H, dd), 7.25 (1H,t), 7.12 (1H, m), 3.17 (2H, m), 3.13 (3H, s), 2.18 (2H, m). Anal. ($C_{18}H_{14}ClFO_3S$) C,H,N.

2-(4-Chloro-3-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (10): ^{1}H NMR (CD_3COCD_3) δ 7.95 (2H, m), 7.65 (2H, m), 7.45 (1H, t), 7.18 (1H, dd), 6.98 (1H, dd), 3.15 (2H, m), 3.12 (3H, s), 2.69 (2H, m). Anal. ($C_{18}H_{14}ClFO_3S$) C,H,N.

2-(3,4,5-Trichlorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (11): ^{1}H NMR (CD_3COCD_3) δ 7.97 (2H, m), 7.80 (4H, m), 7.68 (1H, s), 7.32 (2H, m), 3.19 (3H, s), 3.15 (2H, m), 2.72 (2H, m). Anal. ($C_{18}H_{13}Cl_3O_3S$) C,H,N.

2-(2-Benzothiophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (12): ^{1}H NMR (CD_3COCD_3) δ 8.05 (2H, m), 7.72 (2H, m), 7.35 (2H, s), 3.19 (2H, m), 3.14 (3H, s), 2.69 (2H, m); MS (CI, CH_4) *m/z* 369 (M + 1, 100). Anal. ($C_{20}H_{16}O_3S_2 \cdot {}^1/_2H_2O$) C,H,N.

Representative Procedure for Suzuki Coupling with Pyridyltrialkylboronates: 3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one (13). Step 1. Lithium 3-Pyridinyltriisopropylboronate (29). To a −73 °C solution of 3-bromopyridine (960 g, 6.08 mol) in diethyl ether (20 L) was added *n*-butyllithium (2.5 M in hexanes, 2.43 L, 6.08 mol) over 4.5 h, maintaining an internal temperature below −70 °C. To the resulting thick yellow slurry was added triisopropylborate (1165 g, 6.19 mol) over 2 h, again maintaining the internal temperature below −70 °C. The resulting solution was warmed to room temperature and concentrated until the product began to separate (~10 L). Hexane (6 L) was added with stirring to give a gum. The remaining solvent was removed and the residue placed under vacuum for 3 days to give 1.7 kg of the crude salt as a light-brown solid. This material was used in the next step without further purification: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.50 (1H, m), 8.15 (1H, m), 7.85 (1H, m), 7.15 (1H, m), 1.15 (21H, s). (Alternatively, the salt could be purified by evaporating twice from EtOH and swishing in ether/hexanes to give lithium 3-pyridinyltriethylboronate as a white, hygroscopic crystalline solid.)

Step 2. 3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one (13). A mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (**28**) (120 g, 381 mmol), lithium 3-pyridinyltriisopropylboronate (**29**) (122 g, 447 mmol), and PPh_3 (3.99 g, 15.2 mmol) was suspended in 3:1:1 toluene: *n*-propanol:water (2.5 L). The mixture was degassed, and $Pd_2(dba)_3$ (6.95 g, 7.59 mmol) was added. The mixture was heated to reflux for 3 h, then cooled, and diluted with EtOAc (1.5 L).

The layers were separated, and the organic phase was washed with water (1 L). The aqueous layers were back-extracted with EtOAc, and the combined organic layers were washed with water, dilute aqueous $NaHCO_3$, and brine. The organic phases were then filtered through Celite and concentrated to give 148 g of a black oil. Purification by flash chromatography (100% EtOAc) followed by swishing in EtOAc gave 87.6 g (73%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 8.55 (1H, m), 8.34 (1H, m), 7.40 (2H, m), 7.65 (1H, m), 7.49 (2H, m), 7.33 (1H, m), 3.12 (2H, m), 3.05 (3H, s), 2.80 (2H, m); MS (CI, CH_4) *m*/*z* 314 (M + 1, 100).

The hydrochloride salt could be prepared: 40 g of the title compound was dissolved in 2:1 CH_2Cl_2:hexanes (700 mL), and a stream of HCl gas was bubbled through the solution, giving an oil which separated. Excess HCl was flushed with a stream of nitrogen. The oil solidified on standing, and the solvent was decanted. The salt was crystallized from hot EtOH/iPrOH to give 37.1 g of the hydrochloride salt: ^{1}H NMR (DMSO-d_6) δ 8.79 (1H, m), 8.61 (1H, m), 8.06 (1H, m), 7.93 (2H, m), 7.88 (1H, m), 7.65 (2H, m), 3.24 (3H, s), 3.17 (2H, m), 2.74 (2H, m). Anal. ($C_{17}H_{15}NO_3S\cdot HCl\cdot H_2O$) C,H,N.

2-(5-Bromo-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (15): ^{1}H NMR (CD_3COCD_3) δ 8.59 (1H, m), 8.24 (1H, m), 7.98 (2H, m), 7.86 (1H, m), 7.68 (2H, m), 3.23 (2H, m), 3.14 (3H, m), 2.70 (2H, m); MS (CI, CH_4) *m*/*z* 394 (90), 392 (M + 1, 100), 314 (8), 237 (5). Anal. ($C_{17}H_{14}BrNO_3S\cdot{}^1/_2H_2O$) C,H,N.

2-(4-Methoxy-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (17): ^{1}H NMR (CD_3COCD_3) δ 7.98 (3H, m), 7.67 (2H, m), 7.45 (1H, dd), 6.72 (1H, d), 3.86 (3H, s), 3.14 (5H, m), 2.65 (2H, m). Anal. ($C_{18}H_{17}NO_4S$) C,H,N.

Representative Procedure for (Trimethylstannyl)-pyridine Formation: 2-(Trimethylstannyl)-5-chloropyridine (30). Step 1. Trifluoromethanesulfonic Acid 5-Chloro-2-pyridinyl Ester. To a −78 °C solution of 5-chloro-2-hydroxypyridine (1.0 g, 7.72 mmol) and diisopropylethylamine (1.88 mL, 10.81 mmol) in CH_2Cl_2 (35 mL) was added trifluoromethanesulfonic anhydride (1.56 mL, 9.26 mmol), and the reaction mixture was allowed to warm to room temperature. After 30 min, the mixture was washed with water and brine, filtered through cotton, and concentrated to dryness. The residue was purified by flash chromatography (8% EtOAc/hexanes) to give 1.0 g of the title compound: ^{1}H NMR (CD_3COCD_3) δ 8.50 (1H, d), 8.23 (1H, dd), 7.58 (1H, d).

Step 2. 2-(Trimethylstannyl)-5-chloropyridine (30). To a degassed room temperature mixture of trifluoromethanesulfonic acid 5-chloro-3-pyridinyl ester (0.510 g, 2.06 mmol), hexamethylditin (0.443 mL, 2.16 mmol), lithium chloride (0.262 g, 6.18 mmol), and a few crystals of butylated hydroxytoluene in dioxane (20 mL) was added a freshly prepared solution of 0.1 M solution of $Pd(PPh_3)_4$ in toluene (0.807 mL, 0.081 mmol). The resulting mixture was heated to reflux for 1.5 h before it was cooled to room temperature, diluted with EtOAc, washed with 10% NH_4OH and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was used in step 3 without further purification.

Representative Procedure for Stille Coupling with (Trimethylstannyl)pyridines: 2-(4-Chloro-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (20). To a degassed room temperature solution of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (**28**) (0.630 g, 2.0 mmol), $Pd_2(dba)_3$ (0.036 g, 0.04 mmol), and $AsPh_3$ (0.098 g, 0.32 mmol) in NMP (5 mL) was added a degassed NMP solution (8 mL) of 2-(trimethylstannyl)-5-chloropyridine (**30**) (~4.0 mmol). The resulting mixture was heated to 60 °C for 16 h and then to 100 °C for a further 2 h. The mixture was then cooled to room temperature, diluted with EtOAc, washed two times with 10% NH_4OH and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by flash chromatography (70% EtOAc/hexanes) followed by a CH_2Cl_2/Et_2O swish to provide 130 mg of the title compound: ^{1}H NMR (CD_3SOCD_3) δ 8.54 (1H, d), 8.00 (1H, dd), 7.89 (2H, m), 7.55 (2H, m), 7.45 (1H, d), 3.23 (3H, s), 3.13 (2H, m), 2.69 (2H, m); MS (CI, CH_4) *m*/*z* 350 (30), 348 (M + 1, 100), 237 (20). Anal. ($C_{17}H_{14}ClNO_3S$) C,H,N.

2-(5-Chloro-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (14): ^{1}H NMR (CD_3COCD_3) δ 8.50 (1H, d), 8.20 (1H, d), 7.95 (2H, m), 7.22, (1H, dd), 7.18 (2H, m), 3.22 (2H, m), 3.16 (3H, s), 2.71 (2H, m); MS (CI, CH_4) *m*/*z* 350 (38), 348 (M + 1, 100), 312 (5). Anal. ($C_{17}H_{14}ClNO_3S\cdot{}^1/_2H_2O$) C,H,N.

2-(4-Methyl-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (16): ^{1}H NMR (CD_3COCD_3) δ 8.20 (1H, d), 7.94 (2H, m), 7.65 (2H, m), 7.47 (1H, dd), 7.20 (1H, d), 3.18 (2H, m), 3.14 (3H, s), 2.69 (2H, m); HRMS calcd for $C_{18}H_{18}NO_3S$ 328.10074, found 328.10062.

2-(2-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (18): ^{1}H NMR (CD_3COCD_3) δ 8.46 (1H, m), 7.88 (2H, m), 7.80 (1H, m), 7.62 (2H, m), 7.45 (1H, m), 7.30 (1H, m), 3.21 (2H, m), 3.12 (2H, m), 2.71 (2H, m); MS (CI, CH_4) *m*/*z* 314 (M + 1, 100), 100 (10).

2-(4-Bromo-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (19): ^{1}H NMR ($CDCl_3$) δ 8.58 (1H, d), 7.90 (3H, m), 7.49 (2H, m), 7.39 (1H, d), 3.10 (2H, m), 3.04 (3H, s), 2.79 (2H, m). Anal. ($C_{17}H_{14}BrNO_3S\cdot{}^1/_2H_2O$) C,H,N.

2-((*E*)-2-(4-Fluorophenyl)ethenyl)-3-(4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one (23). To a 0 °C solution of freshly prepared disiamylborane (from 2.5 mmol of $BH_3\cdot$DMS) in THF (4 mL) was added (4-fluorophenyl)acetylene (0.30 mL, 2.6 mmol). The solution was stirred for 1 h, then warmed to room temperature, stirred for 1 h, and concentrated in vacuo. The residue was then placed under high vacuum to romove traces of DMS. 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (**28**) (467 mg, 1.48 mmol), tris(dibenzylideneacetone)dipalladium(0) (86 mg, 0.094 mmol), and triphenylphosphine (98 mg, 0.37 mmol) were dissolved in toluene (15 mL), nPrOH (10 mL), and water (8 mL). The freshly prepared vinylborane was added as a solution in toluene (10 mL), and the mixture was degassed. After the mixture stirred for 15 min, diethylamine (0.53 mL, 5.1 mmol) was added, and the mixture was heated to reflux for 1.5 h. The mixture was then cooled and partitioned between EtOAc and water. The organic phase was washed with 1 M HCl and brine and dried over $MgSO_4$. Purification by flash chromatography (60% EtOAc/hexanes), followed by crystallization from CH_2Cl_2/ether/hexanes, provided 253 mg of the title compound: ^{1}H NMR (CD_3COCD_3) δ 8.09 (2H, m), 7.92 (1H, d, J = 15 Hz), 7.87 (2H, m), 7.54 (2H, m), 7.10 (2H, m), 6.88 (1H, d, J = 15 Hz), 3.18 (3H, s), 3.05 (2H, m), 2.62 (2H, m). Anal. ($C_{20}H_{17}FO_3S$) C,H,N.

Representative Procedure for Preparation of 2-Phenoxy Derivatives: 3-(4-(Methylsulfonyl)phenyl)-2-phenoxy-2-cyclopenten-1-one (21). Step 1. 1-(4-(Methylthio)-phenyl)-5-phenoxy-1,4-pentadione (33). A mixture of phenoxymethyl vinyl ketone (**32**)[10] (1.00 g, 6.17 mmol), 4-(methylthio)benzaldehyde (0.62 g, 4.1 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (0.11 g, 0.41 mmol), and triethylamine (0.34 mL, 2.44 mmol) in dioxane (20 mL) was heated to 70 °C for 5 h and then to 100 °C for 18 h. The reaction mixture was poured into water and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated. Purification by flash chromatography provided 140 mg of the desired diketone.

Step 2. 3-(4-(Methylthio)phenyl)-2-phenoxy-2-cyclopenten-1-one. To a solution of diketone **33** (70 mg, 0.22 mmol) in MeOH (40 mL) was added 14 drops of DBU, and the solution was stirred at 60 °C for 18 h. The reaction mixture was poured into aqueous ammonium chloride and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated. Purification by flash chromatography (20% EtOAc/hexanes) provided 60 mg of the desired cyclopentenone.

Step 3. 3-(4-(Methylsulfonyl)phenyl)-2-phenoxy-2-cyclopenten-1-one (21). To a solution of phenoxy-3-(4-(thiomethyl)phenyl)-2-cyclopenten-1-one (60 mg, 0.20 mmol) in acetone was added a solution of Oxone (0.45 g, 0.73 mmol) in 1.6 mL water. After stirring 1 h at room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated. Purification by flash chromatography provided

50 mg of the title compound: ^{1}H NMR (CD_3COCD_3) δ 8.10 (4H, m), 7.20 (5H, m), 3.20 (2H, m), 3.15 (3H, s), 2.60 (2H, m); HRMS calcd for $C_{18}H_{17}O_4S$ 329.0847, found 329.0847.

2-(3,5-Difluorophenoxy)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (22): ^{1}H NMR (CD_3COCD_3) δ 8.10 (4H, m), 6.70 (3H, m), 3.20 (2H, m), 3.15 (3H, s), 2.80 (2H, m); HRMS calcd for $C_{18}H_{15}F_2O_4S$ 365.0659, found 329.0657. Anal. ($C_{18}H_{14}F_2O_4S$) Calcd: C, 59.33; H, 3.87. Found: C, 58.86; H, 3.79.

Representative Procedure for Heck Coupling with Acetylenes: 2-(2-Phenylethynyl)-3-(4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one (24). To a suspension of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (**28**) (500 mg, 1.58 mmol) and dichloropalladium(II) bistriphenylphosphine (56 mg, 0.08 mmol) in triethylamine (13 mL) and DMF (5 mL) was added phenylacetylene (0.26 mL, 2.4 mmol), and the mixture was degassed. The reaction was heated to 60 °C for 90 min, giving an orange solution. This solution was cooled and partitioned between 1 M HCl and dichloromethane. The aqueous layer was washed with 1 M HCl, water, and brine, filtered through cotton, and concentrated. Purification by flash chromatography (60% EtOAc/hexanes) provided 36 mg of the title compound: ^{1}H NMR (CD_3COCD_3) δ 8.48 (2H, m), 8.13 (2H, m), 7.60 (2H, m), 7.42 (3H, m), 3.28 (2H, m), 3.20 (3H, s), 2.68 (2H, m); HRMS calcd for $C_{20}H_{17}O_3S$ 337.08984, found 337.08973. Anal. ($C_{20}H_{16}O_3S\cdot{}^1/_2H_2O$) C,H,N.

2-(3,3-Dimethyl-1-butynyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (25): ^{1}H NMR (CD_3COCD_3) δ 8.43 (2H, m), 8.06 (2H, m), 3.17 (5H, m), 2.57 (2H, m), 1.34 (9H, s); HRMS calcd for $C_{18}H_{21}O_3S$ 317.12114, found 317.12124. Anal. ($C_{18}H_{20}O_3S$) C,H,N.

Biological Methods. The hCOX-2 transfected CHO cell assay,[12] the U937 microsome assay,[13] and the COX-1 and COX-2 human whole blood assays[14] have been described previously.

Rat Paw Edema Assay.[15] Male Sprague−Dawley rats (150−200 g) were fasted overnight and were given, po, either vehicle (1% methocel or 5% Tween 80) or a test compound. After 1 h, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_0) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected subplantarly with 50 μL of 1% carrageenan solution in saline (FMC Corp., Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e., 500 μg of carrageenan/paw); 3 h later, the paw volume (V_3) was measured, and the increases in paw volume ($V_3 - V_0$) were calculated. The animals were sacrificed by CO_2 asphyxiation, and the absence or presence of stomach lesions was scored. Data were compared with the vehicle-control values, and percent inhibition was calculated. All treatment groups were coded to eliminate observer bias.

Rat Pyresis Assay.[15] Male Sprague−Dawley rats (150−200 g) were fasted overnight, and the baseline rectal temperature was recorded using a flexible temperature probe (YSI series 400) connected to a digital thermometer (model 08502, Cole Parmer). At time 0, the rats were injected interperitoneally with either saline or LPS (0.36 mg/kg), and the rectal temperature was measured 5, 6, and 7 h following LPS injection. After the measurement at 5 h, when the increase in rectal temperature had reached a plateau, the LPS-injected rats were given orally either the vehicle or a test compound to determine whether the rise in temperature could be reversed. Percent reversal (antipyretic activity) was calculated using the rectal temperature obtained at 7 h, taking this value in the vehicle-control group as zero reversal.

Rat Hyperalgesia Assay.[15] Hyperalgesia to mechanical compression of the hind paw of male Sprague−Dawley rats (90−110 g) was induced by intraplantar injection of carrageenan (4.5 mg/paw) 3 h previously. A test compound was given orally 2 h after carrageenan. The vocalization response to compression of the carrageenan-injected paw was measured 1 h later by an algesiometer (Ugo-Basile, Italy).

Rat Adjuvant-Induced Arthritis Assay.[21] Seventy 7-week-old female Lewis rats (144−172 g) were used. Adjuvant-induced arthritis (AIA) was induced in 6 groups of 10 rats each by an intradermal injection of 0.5 mg of *Mycobacterium butyricum* in light mineral oil in the left hind foot pad. Ten rats were not injected and served as nonadjuvant controls. Body weights, radiographs, and foot volumes of the noninjected (secondary) paws were determined on various days (0, 14, and 21). Test compound (0.1, 0.3, 1.0, and 3.0 mg/kg/day po b.i.d.), indomethacin (1 mg/kg/day po b.i.d.), and appropriate vehicles were started on day 0 and continued thoughout the experiment. Rats were euthanized by carbon dioxide inhalation on day 21. Two-factor ('treatment' and 'time') analysis of variance with repeated measures on 'time' was applied to the percent changes for body weight and foot volumes and to the rank-transformed radiographic total scores. A post hoc Dunnett's test was conducted to compare the effect of treatments to vehicle.

Preliminary Hepatotoxicity Study in Rats. Four male and four female rats (100−200 g) were used for each of three groups: a vehicle control group (0.5% methylcellulose at 5 mL/kg, used as the vehicle for all other dosage groups), a positive control group (phenobarbitol/bezafibrate at 50/50 mg/kg/day), and the test compound (100 mg/kg/day). All animals were dosed by gavage once a day for 4 days, then were weighed, and euthanized by carbon dioxide inhalation on the fifth day, approximately 24 h after the final dose. The livers were harvested and weighed. The weights as a fraction of total body weight were then compared to those of the vehicle-control group.

^{51}Cr Fecal Excretion Assay in Rats.[15] Male Sprague−Dawley rats (150−200 g) were administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats were injected via a tail vein with 0.5 mL of ^{51}Cr-labeled red blood cells from a donor rat. The animals were placed individually in metabolism cages with food and water ad lib. Feces were collected for a 48-h period, and ^{51}Cr fecal excretion was calculated as a percent of total injected dose. ^{51}Cr-labeled red blood cells were prepared using the following procedures: 10 mL of blood was collected in heparinized tubes via the vena cava from a donor rat. Plasma was removed by centrifugation and replenished with equal volume of HBSS. The red blood cells were incubated with 400 Ci of sodium chromate-51 for 30 min at 37 °C. At the end of the incubation, the red blood cells were washed twice with 20 mL of HBSS to remove free sodium chromate-51. The red blood cells were finally reconstituted in 10 mL of HBSS, and 0.5 mL of the solution (about 20 Ci) was injected per rat.

Measurement of Plasma Levels in Rats. For po studies, the drug was suspended in 1% methocel by mixing with a plantary micromill (Fritsch Pulverizette 7) for 10 min. Rats were dosed by gavage at 3 mg/kg with a dose volume of 10 mL/kg. Blood samples (1 mL) were taken at 0, 0.25, 0.5, 1, 2, 4, and 6 h after dosing. For iv studies, the drug was dissolved in 60% PEG-200 and injected intravenously into the jugular vein at a dose of 3 mg/kg with a dose volume of 1 mL/kg. Blood samples (1 mL) were taken at 0, 0.08, 0.5, 1, 2, 4, and 6 h after dosing. The blood was centrifuged and the plasma collected. To 150 μL of each plasma sample was added an equal volume of acetonitrile to precipitate the protein. The sample was centrifuged, and a 100-μL aliquot of the supernatant was analyzed by reverse-phase HPLC on a NovaPak C18 column (3.9 × 150 mm). The solvent system used for compound **7** was 33% CH_3CN in aqueous NH_4OAc (1 g/L) at a flow rate of 1 mL/min with UV detection at 270 nM. The solvent system used for compound **13** was 20% CH_3CN in aqueous NH_4OAc (1 g/L) at a flow rate of 1 mL/min with UV detection at 275 nM. The area of the resulting peak was quantified by comparison to a standard (plasma sample at time 0 spiked with the parent compound corresponding to a plasma concentration of 6.7 μg/mL).

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