Articles

In Vitro Structure−Activity Relationship and in Vivo Studies for a Novel Class of Cyclooxygenase-2 Inhibitors: 5-Aryl-2,2-dialkyl-4-phenyl-3(2*H*)furanone Derivatives

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Received December 3, 2002

5-Aryl-2,2-dialkyl-4-phenyl-3(2*H*)furanone derivatives were studied as a novel class of selective cyclooxygenase-2 inhibitors with regard to synthesis, in vitro SAR, antiinflammatory activities, pharmacokinetic considerations, and gastric safety. **1f**, a representative compound for methyl sulfone derivatives, showed a COX-2 IC_{50} comparable to that of rofecoxib. In case of **20b**, a representative compound for sulfonamide derivatives, a potent antiinflammatory ED_{50} of 0.1 mg kg^{-1} day^{-1} was observed against adjuvant-induced arthritis by a preventive model, positioning **20b** as one of the most potent COX-2 inhibitors ever reported. Furthermore, **20b** showed strong analgesic activity as indicated by its ED_{50} of 0.25 mg/kg against carrageenan-induced thermal hyperalgesia in the Sprague−Dawley rat. 3(2*H*)Furanone derivatives showed due gastric safety profiles as selective COX-2 inhibitors upon 7-day repeat dosing. A highly potent COX-2 inhibitor of the 3(2*H*)furanone scaffold could be considered suitable for a future generation COX-2 selective arthritis medication with improved safety profiles.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) have been widely used over 100 years to alleviate symptoms of arthritis, arthritis-associated disorders, fever, postoperative pain, migraine, and so on.[1] Despite their widespread use and desirable therapeutic efficacy for the treatment of inflammation and inflammation-associated disorders, NSAIDs are generally regarded to have life-threatening toxicity in the gastrointestinal (GI) tract. Severity of the GI toxicity is well illustrated by a report that 16 500 patients on NSAIDs therapy died due to the GI toxicity in the year of 1994 alone in the US.[2] Frequently, the gastric toxicity of perforation, ulceration, and bleeding (PUB) is not noticed by patients before hospitalization, leading to such a high mortality rate upon chronic use of NSAIDs.

Despite the huge amount of efforts directed to reduce the GI toxicity of NSAIDs, it was only about a decade ago that the origin of the GI toxicity began to be understood through the discovery of an inducible isoform of cyclooxygenases.[3] There are at least two kinds of cyclooxygenases, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively expressed in various tissues including the GI tract, the kidneys, and the platelets. COX-1 is known to be responsible for bodily homeostasis such as the gastrointestinal integrity, vascular dilatation, renal functions, and so on. Overt inhibition of COX-1 can, therefore, elicit undesirable side effects such as gastric PUB and blood thinning.[4] In the meantime, COX-2 is induced upon inflammatory stimuli and is known to be responsible for progression of inflammation. Traditional NSAIDs, such as aspirin, naproxen, piroxicam, ibuprofen, diclofenac, etc., inhibit both COX-1 and COX-2, which accounts for NSAIDs' antiinflammatory effects as well as their notorious side effects of GI toxicity and blood thinning. Thus, selective inhibition of COX-2 over COX-1 should be useful for treatment of inflammation without incurring the side effects associated with inhibition of COX-1.

A study with COX-2 knockout mice suggests that complete inhibition of COX-2 could lead to peritonitis secondary to intestinal toxicity.[5] Animal safety data for COX-2 inhibitors indicated that the intestinal toxicity was the dose-limiting toxicity in the dog and the rat.[6] However, primates seem to possess robust intestinal tolerance to selective inhibition of COX-2.[6c] Indeed, COX-2 inhibitors are regarded to have better gastrointestinal safety profiles than traditional NSAIDs.[7]

Long term use of traditional NSAIDs has been known to elicit cardiorenal toxicity such as edema and worsening blood pressure. There have been some attempts to assess cardiorenal safety of COX-2 inhibitors;[8] however, more clinical data are needed to estimate the cardiorenal safety of COX-2 inhibitors. Considering that COX-2 inhibitors are supposed to be chronically taken mostly

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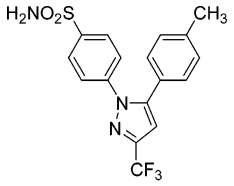
10.1021/jm020545z CCC: $27.50
Published on Web 01/14/2004

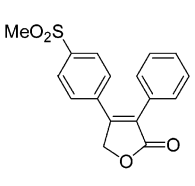
by elderly arthritis patients, the importance of the long-term cardiorenal safety can never be overemphasized. COX-2 is constitutively expressed in the glomerular region and the small blood vessels of the kidneys in primates including the human,[8d] suggesting that the smaller inhibition of renal COX-2 could lead to smaller renal and consequently cardiovascular adverse effects. Given that only protein-unbound drug molecules are subject to glomerular filtration, a drug with higher plasma protein binding is expected to exert a smaller renal effect for a given lipophilicity or hydrophilicity of drug.

There are already several COX-2 inhibitors being prescribed for chronic indications, and they mostly maintain a tricyclic structure as in rofecoxib,[9a] celecoxib,[9b] valdecoxib,[9c] and etoricoxib.[9d,9e] As more clinical data accumulate, it may become possible to differentiate profiles of COX-2 inhibitors based on efficacy and safety. There have been some, but not conclusive, attempts to differentiate profiles of COX-2 inhibitors, though.[10,11]

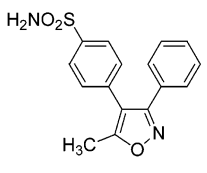
Previously, we reported 2,2-dimethyl-4,5-diaryl-3(2*H*)-furanone (**1**) derivatives as orally active COX-2 inhibitors. In case of **1f** (see Table 1 for the chemical structure), the observed adjuvant-induced arthritis ED_{50} was 0.03 mpk/day by the therapeutic model.[12] Such a pronounced oral activity in the adjuvant arthritis is one of the most potent among the reported COX-2 inhibitors. The 3(2*H*)furanone derivatives are structurally similar to celecoxib and rofecoxib, in that they have a scaffold or pharmacophore of *cis*-1,2-diaryl-alkene type.[13] The scaffold of COX-2 inhibitors not only is important for COX-2 selectivity but also can be critical to their in vivo profiles. For example, the major primary metabolic pathway for celecoxib in humans involves cytochrome P450 isozymes.[14a] On the other hand, rofecoxib is metabolized mainly by unidentified cytosolic reductases.[14b] Some COX-2 inhibitors with a scaffold of *cis*-1,2-diaryl-alkene type failed to show pharmacological profiles acceptable for clinical development. For example, a metabolite of **DuP 697** from Dupont Merck was reported to accumulate in the body.[15] **SC-236** from G. D. Searle has been reported to show an unacceptably long plasma half-life.[9b] In this article will be presented the synthesis, structure−activity relationship, and pharmacological properties of 4,5-diaryl-3(2*H*)furanone derivatives as a novel class of highly potent selective COX-2 inhibitors.



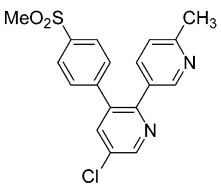
Celecoxib



Rofecoxib

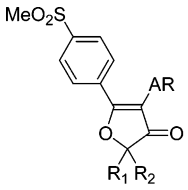


Valdecoxib



Etoricoxib

Table 1. In Vitro COX-1/COX-2 Inhibitory Activities by the Mouse Peritoneal Macrophage Method for 2,2-Dialkyl-4-aryl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)-furanone Derivatives **1**∼ **3**



1: R_1, R_2 = Methyl
2: R_1 = Methyl, R_2 = Ethyl
3: R_1, R_2 = Ethyl

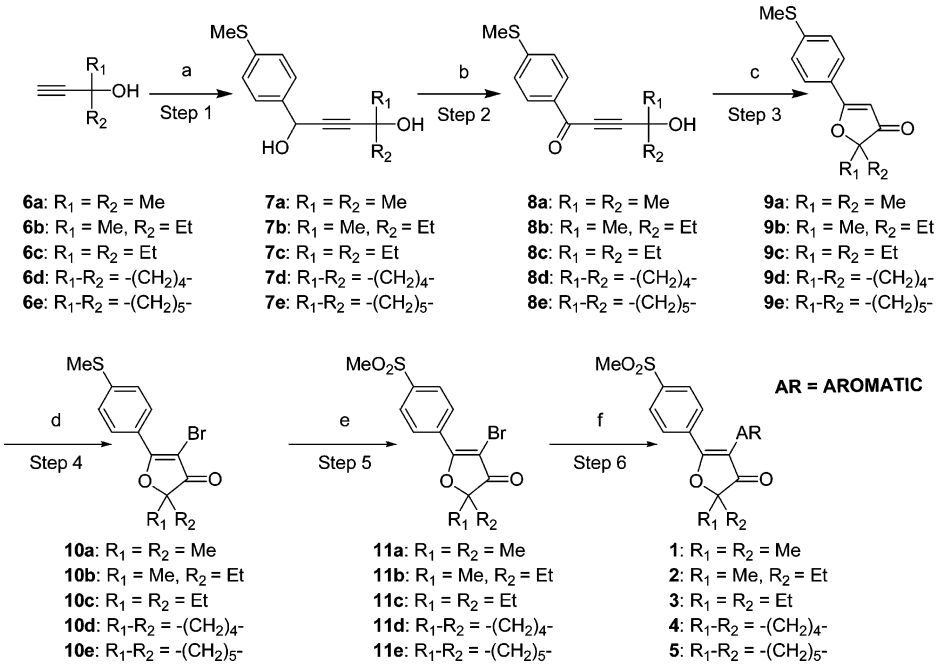
AR = Aromatic Group

entry	AR	IC_{50}, μg/mL COX-2	IC_{50}, μg/mL COX-1	COX-2 selectivity
1a	phenyl	0.05	3	60
1b	3-fluorophenyl	0.02	5	250
1c	3-chlorophenyl	0.01	2	200
1d	4-bromophenyl	0.03	0.03	1
1e	3-chloro-4-fluorophenyl	0.3	3	10
1f	3,5-difluorophenyl	0.05	20	400
1g	3,5-dichlorophenyl	0.03	3	100
1h	3-(trifluoromethyl)-phenyl	0.05	3	60
1i	3-*iso*propylphenyl	0.03	30	1000
1j	4-*iso*propylphenyl	0.03	3	100
1k	4-*n*-butylphenyl	0.002	5	2500
1l	3-acetylphenyl	0.05	50	1000
1m	4-acetylphenyl	0.3	50	167
1n	3-methoxyphenyl	0.1	30	300
1o	2-furanyl	0.2	30	150
1p	3-pyridyl	0.5	10	20
1q	3-thienyl	0.2	30	150
1r	4-(1-*N*-methyl-pyrazolyl)	0.5	30	60
2a	phenyl	0.2	20	100
2b	2-fluorophenyl	0.3	30	100
2c	3-chlorophenyl	0.03	5	167
2d	3,5-dichlorophenyl	0.03	20	666
2e	3-(trifluoromethyl)-phenyl	0.05	10	400
2f	3-methoxyphenyl	0.3	30	100
3a	phenyl	5	30	6
3b	4-(trifluoromethyl)-phenyl	0.03	3	100
3c	3-methylphenyl	0.5	10	20
3d	4-methylphenyl	0.03	3	100
celecoxib		0.02	1.86	93
rofecoxib		0.06	>100	>1667

Synthesis

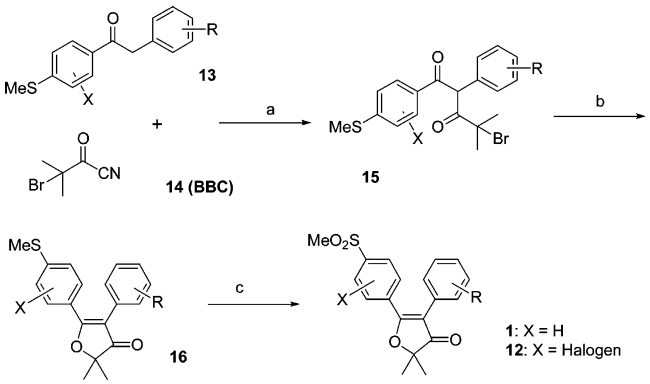
2,2-Dialkyl-4,5-diaryl-3(2*H*)furanone derivatives (**1** ∼ **5**) with methylsulfonyl group were prepared as outlined in Scheme 1. We previously reported synthesis of 2,2-dimethyl-4,5-diphenyl-3(2*H*)furanone derivatives by the same reaction sequence as Scheme 1.[12] 4-(Methylthio)-benzaldehyde was coupled with the in situ-generated lithium acetylenide of **6** to afford diol **7**. The benzylic hydroxyl group of **7** was then oxidized to the corresponding ketone **8** by reaction either with MnO_2 or with pyridinium dichromate (PDC). Often MnO_2 allowed smoother conversion of **7** to **8** than PDC. The acyclic ketone **8** was then cyclized to give 2,2-dialkyl-5-(4-methylthiophenyl)-3(2*H*)furanone **9** in the presence of diethylamine as described in the literature.[16] The methylthio group of furanone **9** was smoothly converted to the methylsulfonyl group of 3(2*H*)furanone **10** by reaction with OXONE. 3(2*H*)furanone **10** was then subjected to bromination with bromine in acetic acid to afford the corresponding bromide compound **11**. Suzuki coupling[17] of **11** with an appropriate arylboronic acid

Scheme 1[a]



[a] Reagents and conditions: (a) *n*-BuLi, 4-(methylthio)benzaldehyde, THF, −78 °C; (b) CrO_3/acetone, PDC/CH_2Cl_2, or MnO_2/CH_2Cl_2; (c) $(Et)_2NH/CH_3OH$; (d) $Br_2/Ac_2O/CCl_4$; (e) oxone/THF/CH_3OH/H_2O; (f) arylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$/toluene/EtOH, Δ.

Scheme 2[a]

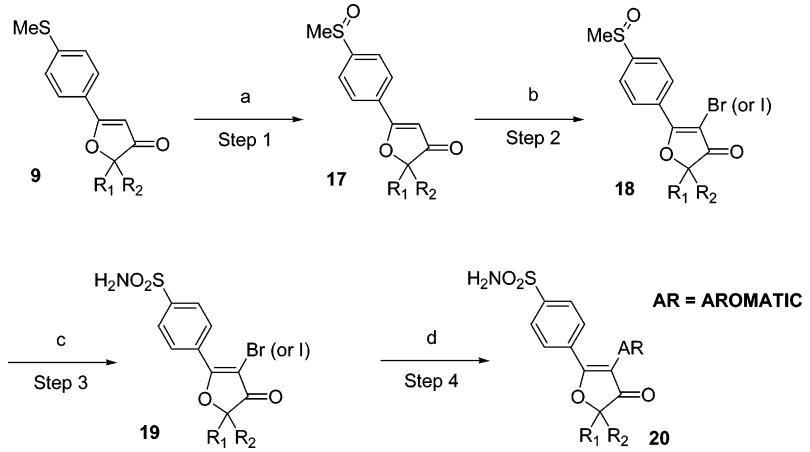


[a] Reagents and conditions: (a) NaHMDS, THF; (b) NaH, THF; (c) OXONE, THF/CH_3OH/H_2O.

was employed to generate structural diversity for 3(2*H*)-furanone derivatives **1** ∼ **5**. In some cases, the reaction sequence of Scheme 1 was modified to obtain desired target compounds. For example, the sequence of the OXONE and the bromination reactions were reverted to yield target molecules **1** ∼ **5**.

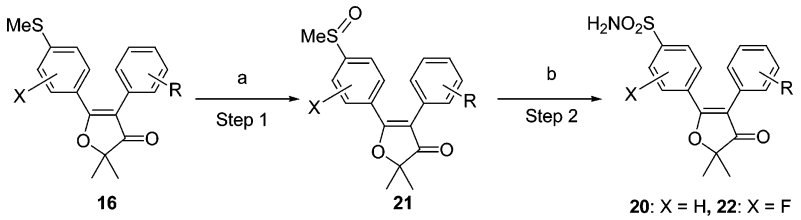
Alternatively, 2,2-dimethyl-4,5-diphenyl-3(2*H*)furanone derivatives (**1** and **12**) with methylsulfonyl group were prepared according to Scheme 2. The enolate of 1-(4-methylthiophenyl)-2-phenyl-ethan-1-one (**13**) was reacted with 2-bromo-isobutyryl-cyanide (**14**: BBC)[18] to effect the desired *C-acylation* against the *O-acylation*. BBC worked very effectively as a soft electrophile for this specific case to resolve the classical issue of "*C- vs O-acylation*". The acyclic C-acylation product **15** could be isolated; however, use of excess base allowed **15** to be cyclized to 3(2*H*)furanone derivatives **16** in one pot. The effectiveness of the one-pot cyclization reaction was discussed recently in detail with regard to its potential application to a GMP-compatible scale-up process of 2,2-

Scheme 3[a]



[a] Reagents and conditions: (a) *m*-CPBA/THF, 0 °C; (b) $Br_2/Ac_2O/CH_2Cl_2$ or cat. BTI/I_2/CCl_4; (c) (i) TFAA, 0 °C; (ii) TEA/CH_3OH; (iii) Cl_2/AcOH; and (iv) aq NH_4OH/THF; (d) arylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$/tolene/EtOH, Δ.

Scheme 4[a]



16 **21** **20**: X = H, **22**: X = F

[a] Reagents and conditions: (a) *m*-CPBA, THF, 0 °C; (b) (i) TFAA, 0 °C; (ii) TEA, CH_3OH; (iii) Cl_2, AcOH; (iv) aq NH_4OH, THF.

dimethyl-4,5-diaryl-3(2*H*)furanone derivatives.[19] The methyl sulfide group of **16** was then converted to the corresponding methyl sulfone group of **1** and **12** by reacting with OXONE.

3(2*H*)Furanone derivatives **20** with a sulfonamide moiety were prepared as described in Scheme 3. First, the methylthio group of 2,2-dialkyl-5-(4-methylthiophenyl)-3(2*H*)furanone **9** was subjected to partial oxidation with *m*-CPBA to give the corresponding sulfoxide **17**. Then, the sulfoxide **17** was halogenated either with bromine in acetic acid, or with iodine in the presence of a catalytic amount of BTI [{bis(trifluoroacetoxy)iodo}-benzene] to yield the corresponding halide **18**. Sulfoxide **18** was converted to the corresponding sulfonamide **19** by a series of reactions with (1) trifluoroacetic anhydride, (2) triethylamine in methanol, (3) chlorine in acetic acid, and then (4) ammonia water according to the literature.[20] Finally, Suzuki coupling of **19** with appropriate arylboronic acids afforded the desired 3(2*H*)-furanone derivative **20** for evaluation of COX-1/COX-2 inhibition.

Sulfonamide-containing 3(2*H*)furanone derivatives could also be prepared by modifying Scheme 3. In Scheme 4, 2,2-dimethyl-5-(4-methylthiophenyl)-4-phenyl-3(2*H*)furanone derivatives were used as starting materials to prepare sulfonamide-containing COX-2 inhibitors **20** or **22**. Step 1 is basically partial oxidation of methylthio group to the sulfoxide moiety similar to the step 1 of Scheme 3. The step 2 of Scheme 2 refers to a series of reactions for the step 3 of Scheme 3. Schemes 3 and 4 are essentially the same. However, the former scheme may be better suited to generate structural diversity, and the latter could be more appropriate for a scale-up synthesis due to facile availability of starting material **16** in large quantity.

Detailed analytical and physical data of 3(2*H*)furanone COX-2 inhibitors are summarized in Experimental Section along with actual synthetic examples for representative compounds according to the aforementioned synthetic schemes.

Results and Discussion

In Vitro COX-1 and COX-2 Activities. Compounds in this article were evaluated against COX-1 and COX-2 mostly by using freshly harvested mouse peritoneal macrophages.[21] Some compounds were evaluated by the human whole blood method as reported in the literature,[22] to assess their inhibitory activities against human COX-1 and COX-2.[23]

In Table 1, in vitro COX-1/COX-2 inhibitory activities are summarized for 2,2-dimethyl-4-aryl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone derivatives (**1**) along with COX-2 inhibitors celecoxib and rofecoxib. By the assay method employing mouse peritoneal macrophages, celecoxib and rofecoxib showed about 100-fold and over 1500-fold COX-2 selectivity over COX-1, respectively. It is interesting that the two blockbusters showed comparable COX-2 IC_{50}'s by this cell-based assay, though. The 3(2*H*)furanone derivatives in Table 1 showed a wide range of COX-2 selectivity. For example, compounds **1d** and **1e** showed COX-2 selectivity too marginal to be classified as a selective COX-2 inhibitor. Compounds such as **1b**, **1c**, **1f**, and **1h** showed in vitro profiles comparable to celecoxib in terms of COX-2 selectivity and COX-2 IC_{50}. A very high COX-2 selectivity was achieved with **1k**, reaching the level of the rofecoxib's COX-2 selectivity. It is often the case that relatively better COX-2 selectivity was observed by having a substituent at the 3-position of the 4-phenyl group of **1**. Structural flexibility of the *n*-butyl moiety of **1k** seems to allow itself to maneuver into the ideal space for COX-2 selectivity near the 3-position of the 4-phenyl group.

Heterocycle-containing compounds **1o** ∼ **1r** showed relatively poor in vitro COX-2 activities when compared with 4-phenyl-3(2*H*)furanone derivatives as well as the blockbuster drugs. Their COX-2 selectivity was not far off from that of celecoxib, though.

In case of 2-ethyl-2-methyl-5-{4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)-furanone derivatives (**2**) and 2,2-diethyl-5-{4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)-furanone derivatives (**3**), there was not much noticeable improvement of in vitro COX-2 inhibitory potency and COX-2 selectivity when compared with 2,2-dimethyl-4-aryl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone derivatives (**1**). There was some improvement in COX-2 selectivity for **2d** and **2e** when compared to the corresponding gem-dimethyl furanone analogues **1g** and **1h**, respectively. However, there are cases of decreased COX-2 selectivity such as with **2f**, when compared with the corresponding gem-dimethyl analogue **1n**.

Figure 1 shows an energy-minimized structure of **1k** bound to the active site of COX-2, where the 3-dimensional structure for the COX-2 active site was constructed from the reported crystallographic structure.[24] According to Figure 1, the dimethyl moiety on the 3(2*H*)-furanone scaffold occupies the vacancy near the entrance of the active site of COX-2. The hydroxyl group of the Tyr355 residue of COX-2 is close to the enol ether moiety enough to potentially form a hydrogen bond with the enolic oxygen of the 3(2*H*)furanone scaffold. Previously, the role of Tyr355 was implicated as a building block for a hydrophobic pocket in the reported complex structure for **SC-558**.[24] Whatever the underlying microscopic binding interactions, it is interesting that **1k** showed a COX-2 IC_{50} reaching down to 2 ng/mL.

In the case of spirocyclopentyl moiety containing derivatives **4**, COX-2 activities are better than the

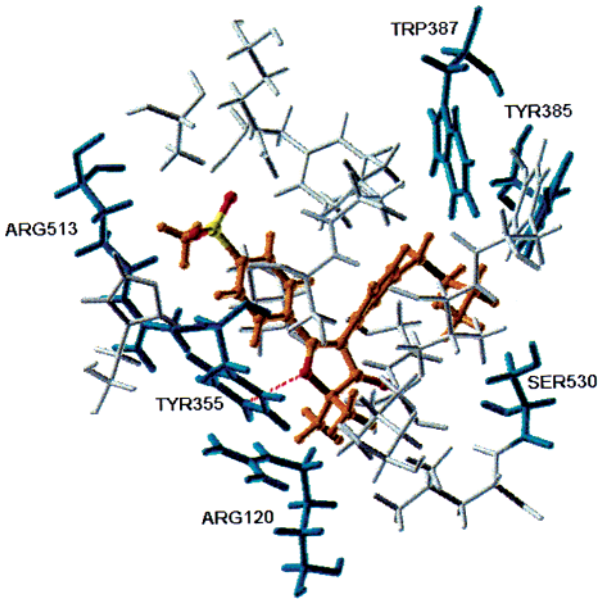
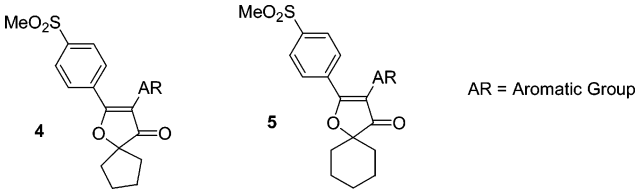


Figure 1. A docking structure for 3(2*H*)furanone derivative **1k** (orange balls and sticks) in the active site of human COX-2 (green blue and gray capped sticks). In this docking structure, the cavity near the entrance of the active site is visually present around Arg120. The enolic oxygen of the 3(2*H*)-furanone scaffold is close to the hydroxyl group of Tyr355 with a distance of 2.66 Å, and the potential hydrogen bonding between the enolic oxygen and the phenolic hydrogen of Tyr355 is highlighted by a red dashed line.

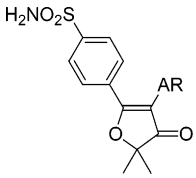
Table 2. In Vitro COX-1/COX-2 Inhibitory Activities against the Mouse Peritoneal Macrophage Method for Spirocyclic Compounds **4** and **5**



entry	AR	IC50, μg/mL COX-2	IC50, μg/mL COX-1	COX-2 selectivity
4a	phenyl	0.03	5	167
4b	3-fluorophenyl	3	3	1
4c	3-methylphenyl	0.03	3	100
4d	4-isopropylphenyl	0.05	10	200
5a	phenyl	2	10	5
5b	3-methylphenyl	0.5	3	6

corresponding 2,2-diethyl-3(2*H*)furanone derivatives **3** (see Table 2): compare the COX-2 inhibitory potencies of **3a** and **3c** with those of **4a** and **4c**, respectively. The spirocyclopentyl moiety of **4** occupies a smaller space than the diethyl moiety of **3**, which may have to do with the improved the COX-2 inhibitory potency of **4** when compared to that of **3**. Upon the basis of the reported crystal structure of COX-2,[24] there should be a cavity of limited size available to the 2,2-dialkyl moiety of 3(2*H*)furanone COX-2 inhibitors. Spirocyclohexyl moiety containing derivatives **5** showed quite poor in vitro COX-2 inhibitory activities, again supporting the rationale for "the cavity of limited size near the entrance of the COX-2 active site". For now, the gem-dimethyl moiety appears to be the optimal size for the cavity near the entrance of the COX-2 active site. Previously, scientists of G. D. Searle investigated the effect of the

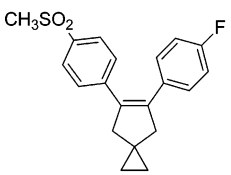
Table 3. In Vitro COX-1/COX-2 Inhibitory Activities against the Mouse Peritoneal Macrophage Method for 2,2-Dimethyl-5-{4-(aminosulfonyl)phenyl}-4-aryl-3(2*H*)-furanone Derivatives **20**



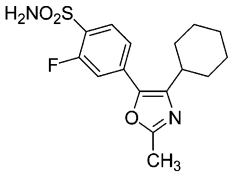
20 AR = Aromatic Group

entry	AR	IC50, μg/mL COX-2	IC50, μg/mL COX-1	COX-2 selectivity
20a	phenyl	0.008	0.061	77
20b	3-fluorophenyl	0.003	0.3	100
20c	3-chlorophenyl	0.014	3.8	270
20d	3,4-difluorophenyl	0.007	1.9	290
20e	3-(trifluoromethyl)-phenyl	0.011	0.82	74
20f	4-acetylphenyl	0.013	0.26	20
20g	2-furanyl	0.057	>10	>175
20h	3-thienyl	0.12	4.8	93
20i	4-(1-*N*-methylpyrazolyl)	0.03	100	3333

3,3-spiro group on the cyclopentene moiety on the in vitro COX-2 inhibitory activity and COX-2 selectivity for 1,2-diaryl cyclopentene derivatives.[25] According to their reports, the spirocyclopropyl moiety as represented by **SC-58451** appeared to be optimal for the in vitro COX-2 inhibitory activity for their COX-2 inhibitors of the 1,2-diarylcyclopentane scaffold. Thus, the SAR with respect to the aliphatic substitution at the 2-position of the 3(2*H*)furanone scaffold seems to correlate well with the prior observations made with the cyclopentene scaffold. For the sake of completeness in the SAR, it would have been nicer to study 3(2*H*)furanone derivatives without aliphatic substituents at the 2-position of the 3(2*H*)furanone scaffold. Unfortunately, synthetic attempts were hampered by unexpected problems relating to the stability and tautomerization of the key intermediate 2,2-dihydro-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone leading to 3(2*H*)furanone derivatives without aliphatic substituents at the 2-position of the 3(2*H*)furanone scaffold.[26]



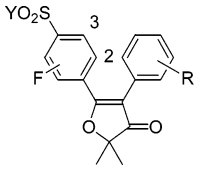
SC-58451



JTE-522

The sulfonamide moiety has been reported to be a reasonable replacement for the methyl sulfone moiety for selective binding to COX-2.[13] When the methyl sulfone group of 3(2*H*)furanone derivatives **1** was replaced with the sulfonamide group, two major changes were observed as previously reported by scientists of G. D. Searle:[25a] COX-2 selectivity decreased; however, in vitro COX-2 inhibitory potency improved considerably (Table 3). For example, the COX-2 IC_{50} of **20b** is better than the corresponding methylsulfonyl compound **1b** by ~7-fold. Many sulfonamide analogues of the 3(2*H*)-furanone scaffold showed COX-2 IC_{50}'s reaching a few ng/mL. However, many of the sulfonamide derivatives **20** showed reduced COX-2 selectivity, when compared

Table 4. In Vitro COX-1/COX-2 Inhibitory Activities against the Mouse Peritoneal Macrophage Method for 2,2-Dimethyl-5-{Fluoro-4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)furanone Derivatives **12** and 2,2-Dimethyl-5-{Fluoro-4-(aminosulfonyl)-phenyl}-4-phenyl-3(2*H*)furanone Derivatives **22**



12: Y = CH_3
22: Y = NH_2

entry	fluoride position	R	IC_{50}, μg/mL COX-2	IC_{50}, μg/mL COX-1	COX-2 selectivity
12a	2	H	0.03	20	667
12b		3-F	0.03	10	333
12c		3-Cl	0.02	3	150
12d		3-F, 5-F	0.03	20	667
12e	3	H	0.03	20	667
12f		3-F	0.03	200	6667
12g		3-Cl	0.05	30	600
12h		3-F, 5-F	0.03	200	6667
22a	2	H	0.03	20	667
22b		3-F	0.003	10	3333
22c		3-F, 5-F	0.003	3	1000
22d	3	H	0.03	20	667
22e		3-F	0.03	5	167
22f		3-F, 5-F	0.02	100	5000

to the corresponding methyl sulfone derivatives **1**. Improved COX-2 activity was traded off with reduced COX-2 selectivity by having sulfonamide in place of methyl sulfone. It should be nice if a COX-2 inhibitor retained the potency level of sulfonamide compounds **20** while maintaining the selectivity level of the corresponding methyl sulfone compounds **1**.

Previously, scientists of Japan Tobacco Company devised an innovative approach to improve COX-2 selectivity of their COX-2 inhibitors with 2-methyloxazole scaffold. Substitution with a halide next to the aminosulfonyl group improved COX-2 selectivity from the corresponding compound without the halide substituent, as exemplified by **JTE-522**.[27] To improve the COX-2 selectivity of sulfonamide derivatives **20**, a halide moiety was introduced to the phenyl ring substituted with sulfonamide group. According to Table 4, the trend observed by the Japan Tobacco scientists appears to be maintained to a large extent in COX-2 inhibitors of the 3(2*H*)furanone scaffold. Many of sulfonamide derivatives **20** have only modest COX-2 selectivity. The sulfonamide compounds **22** in Table 4 showed COX-2 selectivity well over 100-fold and frequently over several 1000-fold. When the same approach was applied to methyl sulfone derivatives as in **12** (Table 4), the same trend was observed: COX-2 selectivity improved while maintaining in vitro COX-2 inhibitory potency. Thus, fluoride substitution at the 5-phenyl ring should be a valid option to improve COX-2 selectivity while maintaining in vitro COX-2 inhibitory potency for COX-2 inhibitors of the 3(2*H*)furanone scaffold.[28]

Acute in Vivo Antiinflammatory Activity. Carrageenan-induced rat foot edema (CFE)[29a] can be regarded to be an animal model for acute inflammation, and the data obtained therefrom would not be appropriate to be extrapolated to chronic inflammatory situations such as oesteoarthritis and rheumatoid arthritis. However, CFE could still serve as an efficient animal model to test the antiinflammtory efficacy of a drug by oral route, in that it takes only several hours to evaluate a drug by CFE. Oral antiinflammatory potencies of COX-2 inhibitors of the 3(2*H*)furanone scaffold against CFE are summarized in Table 5. Celecoxib showed 34% inhibition when orally administered at 3 mg/kg, and most of the COX-2 inhibitors of Table 5 showed 30 ∼ 35% CFE inhibition at 3 mg/kg. Traditional NSAID indomethacin was the most potent among the compounds of Table 5 at the 3 mg/kg dose level. Considering that COX-2 induction is not fully responsible for this acute inflammatory animal model, most of the COX-2 inhibitors in Table 5 could be regarded to possess due and reasonable oral antiinflammatory potency as COX-2 inhibitors. Thus, the 3(2*H*)furanone scaffold turned out to be a good choice for oral bioavailability.

Table 5. Oral Antiinflammatory Activity of COX-2 Inhibitors and Traditional NSAID Indomethacin against CFE in the Sprague−Dawley Rat[a]

entry	% inhibition ± SD	entry	% inhibition ± SD
1b	36 ± 22	**1c**	16 ± 26
1e	31 ± 7	**1f**	34 ± 8
1h	31 ± 12	**1k**	8 ± 12
1l	22 ± 12	**1r**	36 ± 11
2c	23 ± 7	**4c**	26 ± 15
12g	28 ± 5	**20b**	47 ± 9
20c	39 ± 13	**20f**	26 ± 17
20i	29 ± 12	**22c**	32 ± 11
22e	27 ± 5	**22f**	31 ± 11
celecoxib	34 ± 4	**indomethacin**	45 ± 4

[a] Antiinflammatory activities were measured using at least 5 animals/group at 3 mg/kg of body weight.

Subchronic in Vivo Antiinflammatory Activity. Adjuvant-induced arthritis (AA) is a reasonable animal model to simulate the chronic inflammatory situation of arthritis, in that what is monitored for an antiinflammatory drug is suppression of the secondary hyperimmunological response developing over 10 ∼ 22 days or so after induction of arthritis by inoculation with *Mycobacterium butyricum* in the Freund's adjuvant. There have been two methods to evaluate the antiinflammatory effect of a drug by AA, *preventive* and *therapeutic model*. In the preventive model, drug treatment is commenced 1 day before the induction of arthritis, and is continued usually up to day 21 or so on a daily basis.[29b] In the therapeutic model, however, drug is usually administered on a daily basis from day 14 to day 21 or so after induction of arthritis.[25b] In the preventive model, the uninflammed foot is taken as the reference foot for evaluation of AA activity. In the meantime, the inflamed foot is used as the reference in the therapeutic model. Usually, an antiinflammatory drug tends to show nominally stronger potency by the therapeutic model than by the preventive model. In-house experiences indicated that a 5-fold difference in ED_{50} between the two models was not uncommon when male SD rats were used for the therapeutic model.[30a] Antiinflammatory effects of COX-2 inhibitors against AA are summarized along with that of positive comparator indomethacin in Table 6.

According to Table 6, COX-2 inhibitors of the 3(2*H*)-furanone scaffold are highly potent against AA. Some of them are significantly more potent than currently marketed COX-2 inhibitors rofecoxib and etoricoxib.[30] Especially the antiinflammatory potency of compound **20b** against AA is impressively high. Its ED_{50} of 0.1

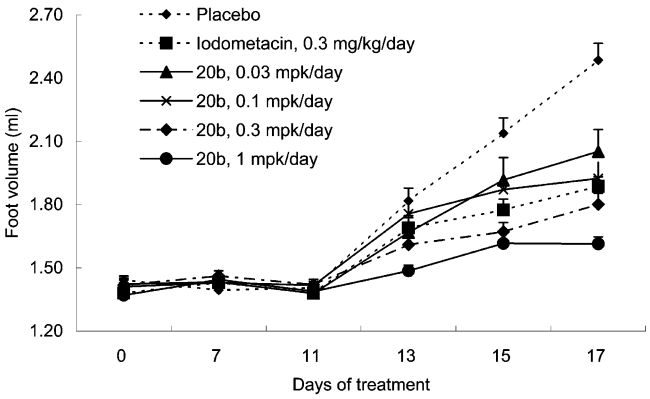


Figure 2. Inhibition of contralateral foot swelling by **20b** and indomethacin as positive control against adjuvant-induced arthritis in male Lewis rats. The mode of administration was by oral gavage, BID, and 10 animals per group. The observed % inhibitions on day 17 were (40 ± 10), (51 ± 9), (63 ± 9), and (77 ± 4)%, for 0.03, 0.1, 0.3, and 1.0 mg kg^{-1} day^{-1} **20b**, respectively. The positive comparator indomethacin showed (51 ± 4)% inhibition at 0.3 mg kg^{-1} day^{-1}. The errors are by standard error.

Table 6. Oral Antiinflammatory Potency of COX-2 Inhibitors and Indomethacin against Adjuvant-Induced Arthritis

	AA ED_{50}, mg kg^{-1} day^{-1} (QD or BID)[a]	
compound	preventive[b]	therapeutic[c]
1b	0.2 ~ 0.3, BID	0.07, QD
1f		0.03, QD
1h		0.06, QD
1m	0.1 ~ 0.2, BID	
1r		~0.3, QD
12h		>0.1, QD
20b	0.1, BID	0.02, QD; 0.01, BID
20c		0.03, QD
celecoxib		0.37, BID in Lewis rats;[d] 0.2, QD in SD rats
rofecoxib[d]	0.74, BID	
meloxicam[d]	0.28, QD	
etoricoxib[d]	0.7, BID	
valdecoxib[d]		0.032, BID in Lewis rats
indomethacin	0.2 ~ 0.3, BID	

[a] QD = once daily, BID = twice daily (dosing regimen). [b] Performed using Lewis rats, 10 animals per group. [c] Performed using SD rats unless noted otherwise, 5 ~ 8 animals per group. [d] Literature data. See ref 30 for the relevant literature.

mpk/day by the preventive model could be regarded as one of the most potent among the COX-2 inhibitors ever reported. It is notable that **20b** is more potent than indomethacin. Figure 2 illustrates a dose−response diagram for AA by the preventive model, from which the AA ED_{50} of 0.1 mg kg^{-1} day^{-1} was read for **20b**. A similar dose response curve by the therapeutic model was reported for compound **1f** previously.[12]

Pharmacokinetics. Sometimes AA ED_{50} values can be misleading, if a drug molecule is not cleared from the body fast enough. If a drug molecule accumulates upon repeated dosing due to slow elimination of drug, its apparent antiinflammatory potency is likely to be overestimated. Such a situation is more pronounced especially when multiple and long-term dosing is required as in AA. Pharmacokinetic studies have been conducted for many COX-2 inhibitors of the 3(2*H*)-furanone scaffold, which indicated that the antiinflammatory potencies presented in Table 6 should not be an artifact from slow drug elimination. For example,

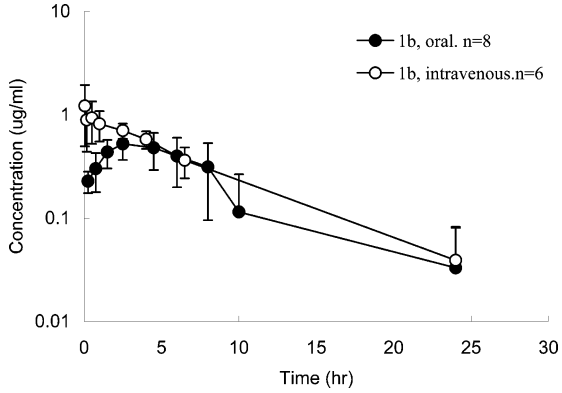


Figure 3. Pharmacokinetic diagrams for intravenous and oral administration of **1b** at 10 mg/kg in male SD rats. For the intravenous route, AUC_{0-24h} was (7.75 ± 1.86) μg/mL × h. with an apparent plasma half-life of 3.78 ± 1.01 h. The oral route yielded C_{max} = 0.57 μg/mL, T_{max} = 3.17 h, and AUC_{0-24h} = (5.01 ± 2.70) μg/mL × h.

Table 7. Gastric Ulcerogenicity Data for 3(2*H*)furanone COX-2 Inhibitors and Indomethacin (male SD rats)[a,b]

compound	oral daily dose	ulcerogenicity score ± SD
placebo	QD	1.8 ± 1.0
1b	30 mg/kg, QD	1.8 ± 0.7
1f	30 mg/kg, QD	1.8 ± 1.0
20b[c]	5 mg/kg, BID	1.5 ± 1.0
indomethacin[d]	5 mg/kg, QD	3.5 ± 0.7

[a] Ulcerogenicity was scored according to the following scales. score 1: apparently normal stomach; score 2: ulcers of pinpoint size only; score 3: one or two erosion(s); score 4: erosions more than two; and score 5: erosions with hemorrhage, in which erosion is defined as ulcerative lesion of diameter larger than 1 mm. [b] Eight animals were used for each group and the treatment schedule throughout one week was QD, i.e., daily once, except for the case of **20b**. [c] Ten animals. [d] 6/8 animals died from peritonitis during the one-week treatment. The ulcerogenicity was scored only for the two animals that survived.

compound **1b** was appropriately cleared from the plasma with an apparent plasma half-life of 3.8 h after oral administration at 10 mg/kg in male SD rats.[31] Figure 3 shows pharmacokinetic data for compound **1b** at 10 mg/kg in male SD rats, where the intravenous decay diagram overlays well with the oral counterpart.

Gastric Safety. Selective COX-2 inhibitors are expected to show reduced gastric toxicity of PUB, when compared with traditional NSAIDs. To substantiate that the COX-2 inhibitors of the 3(2*H*)furanone scaffold meet the expectation of selective COX-2 inhibition in vivo, some of the 3(2*H*)furanone COX-2 inhibitors were evaluated for gastric safety according to the literature.[32] Gastric safety data for representative compounds are provided in Table 7. In the case of indomethacin, repeat dosing for 7 days at 5 mg kg^{-1} day^{-1} resulted in substantial toxicity. Six out of eight SD rats died from the GI toxicity and peritonitis during the one-week treatment, which could be explained by overt inhibition of COX-1. When gastric ulcerogenicity of indomethacin was scored for the two surviving animals, a significantly high level of gastric ulcerogenicity was observed. Considering that indomethacin is a nonselective COX inhibitor, such a high level of gastric toxicity is not surprising. In the case of 3(2*H*)furanone COX-2 inhibitors **1b** and **1f**, their ulcerogenicity level was essentially the same as the placebo level at 30 mg kg^{-1} day^{-1} for 7

days. Considering their strong antiinflammatory potencies in AA by the therapeutic model, the dose level of 30 mg kg^{-1} day^{-1} is considered huge for treatment of human arthritis with **1b** and **1f**. Thus, the in vitro COX-2 selectivity of the 3(2*H*)furanone derivatives was further substantiated by the in vivo animal model for gastric safety. Reflecting its moderate COX-2 selectivity, the gastric ulcerogenicity of **20b** was evaluated at a relatively small daily dose, that is, 5 mg kg^{-1} day^{-1}, BID.

Analgesic Activity. Traditionally, the analgesic activity of NSAIDs has been assessed by several animal models, including carrageenan-induced hyperalgesia[33] and the mouse writhing test.[34] However, it may not be appropriate to evaluate the analgesic activity of COX-2 inhibitors by the mouse writhing test. It is unlikely that a significant level of COX-2 is induced during such a short time frame of the analgesia induction by a noxious chemical stimulus in the mouse writhing test. In the meantime, COX-2 inhibitors have been reported responsive to the carrageenan-induced hyperalgesia.[30b] When **20b** was evaluated against the carrageenan-induced thermal hyperalgesia in the SD rat, an ED_{50} of 0.25 mg/kg was observed. Under the same measurement conditions, indomethacin inhibited the thermal hyperalgesia by 47% at 1 mg/kg.[35a] Rofecoxib has been reported to show an ED_{50} of 1.03 mg/kg by the Randall-Selitto method, a variation of the carrageenan-induced hyperalgesia, where the positive comparator indomethacin's ED_{50} has been reported to be 1.5 mg/kg.[30b] It is difficult to make a direct comparison of analgesic potency between **20b** and rofecoxib, due to differences in the experimental conditions employed for the two COX-2 inhibitors. Considering that similar analgesic activities were observed with indomethacin in the two separate experiments, however, the analgesic potency of 3(2*H*)-furanone derivative **20b** may be regarded comparable to that of rofecoxib.[35b] Thus, **20b** should be regarded as one of the most potent COX-2 inhibitors in terms of analgesic as well as chronic antiinflammatory activity.

Conclusion

The COX-2 inhibitors of the 3(2*H*)furanone scaffold manifested strong in vitro COX-2 inhibitory activity with moderate to high COX-2 selectivity, strong oral antiinflammatory, and analgesic activity. Also COX-2 inhibitors of this class were observed to meet the due gastric safety profile as COX-2 inhibitors. Some of the COX-2 inhibitors, such as **1f** and **20b**, showed highly potent oral antiinflammatory activities by adjuvant-induced arthritis, positioning those COX-2 inhibitors as the most potent COX-2 inhibitors. Obviously, the smaller therapeutic dose is expected to elicit the smaller renal and hepatic burden upon long-term use, at least, through non-COX-2 dependent pathways. Also a small therapeutic dose may be useful in reducing the intestinal burden during gastrointestinal drug influx after oral intake, through use of a fast absorption formulation.[36] The shorter absorptive influx through the intestinal mucosa may lead to a smaller chance of COX-associated toxicity at a given COX-2 selectivity in the intestinal tract. Therefore, the importance of a small therapeutic dose needs to be addressed with regard to clinical safety of COX-2 inhibitors. Finally, a small therapeutic dose would facilitate development of an injectable formulation without resorting to a prodrug approach or an invasive vehicle for injection.

Experimental Section

Biological and Pharmacological Studies. Biological and pharmacological profiles of compounds in this article were evaluated according to the methods described as follows. The reagents used for the following biological and pharmacological studies were purchased mostly from Sigma. The ELISA kits used for the in vitro COX-1/COX-2 assays were purchased from Cayman Chemical.

In Vitro Assay for COX-1 Inhibition (Human Whole Blood Method). Venous blood was sampled from healthy young adults using acid citrate dextrose (170 mM trisodium citrate, 142 nM citric acid, and 222 nM dextrose) as an anticoagulant. A total of 140 μL of blood was added to each well of a 96-well plate, which was previously treated with 1.5 μL of an inhibitor dissolved in DMSO. After a 10-min incubation at 37 °C, 10 μL of PBS solution of 150 μM calcium ionophore A23187 was added to each well and the plate was incubated for another 10 min. The COX-1 reaction was terminated by adding to each well 50 μL of 50 μg/mL indomethacin in 0.1% BSA buffer. Then the 96-well plate was spun for 10 min at 1000 rpm, and the resulting TXB_2 level in the supernatant was measured by ELISA according to the manufacturer's instructions (Cayman cat. no. 419030).

In Vitro Assay for COX-2 Inhibition (Human Whole Blood Method). To 140 μL of human whole blood in each well of a 96-well plate which was pretreated with 1.5 μL of DMSO stock solution of an inhibitor was added 10 μL of 1.5 mg/mL LPS in PBS. To the reaction mixture was added 50 μL of 50 μg/mL indomethacin in 0.1% BSA buffer after 18 h incubation at 37 °C to terminate the reaction. Then the 96-well plate was spun for 10 min at 1000 rpm and the resulting PGE_2 level in the supernatant was measured by ELISA according to the manufacturer's instructions (Cayman cat. no. 414010).

In Vitro Assay for COX-1/COX-2 Inhibition (Mouse Peritoneal Macrophage Method). The mouse peritoneal macrophage method employed for this article is basically the same as the above-described human whole blood method, except for the source of the enzymes. In this murine method mouse peritoneal macrophages which were freshly harvested according to the literature[21] were used as the enzyme source. For the COX-2 assay, however, the COX-1 activity of the macrophages was knocked out prior to the induction of COX-2 with LPS stimulation by incubation with 50 μM aspirin for 2 h, which was followed by washing two times with PBS to remove the residual aspirin.

Carrageenan-Induced Rat Paw Edema. Acute inflammation was induced by subplantar injection of 0.05 mL of 1% carrageenan saline solution to the right hindpaw of male SD rats (160 ~ 190 g) fasted overnight. A designated amount of an inhibitor was suspended in 1% methylcellulose and administered by oral gavage to the rats 1 h prior to the injection of carrageenan. The antiinflammatory effect by the inhibitor was determined by % inhibition of the paw swelling measured 4 h after the administration by using a plethysmometer (Ugobasil 7240, Comerio, Italy) according to the literature.[33]

Adjuvant-Induced Arthritis (Preventive Model). Arthritis was induced on day 0 by subplantar injection of 0.1 mL of a 1% suspension of heat-killed *M. butyricum* mixed in the incomplete Freund's adjuvant into right hindpaw of male Lewis rats (200 ~ 210 g). Designated daily doses of an inhibitor were administered to the randomized rats with arthritis by oral gavage from day −1 to day 16 after the injection of the adjuvant. The left hindpaw volumes of the control and the treatment groups on day 17 were measured using a plethysmometer and averaged to determine % inhibitions of adjuvant arthritis at the designated doses of the inhibitor according to the literature.[29b]

Adjuvant-Induced Arthritis (Therapeutic Model). Arthritis was induced by subplantar injection of 0.1 mL of 1% suspension of heat-killed *M. butyricum* mixed in the incom-

plete Freund's adjuvant into the right hindpaw of male SD rats (160 ~ 190 g) on day 0. On day 14, arthritis-induced rats with foot volume increase (swelling) of the left hind paw over 0.37 mL were selected and randomized for grouping. The arthritis-induced rats were subjected to daily drug treatment from day 14 to day 22. The foot volumes on day 22 were used for assessment of % inhibitions of adjuvant arthritis at designated daily dose of the inhibitor.

Carrageenan-Induced Thermal Hyperalgesia. Male SD rats (140 ~ 160 g) were subjected to overnight fasting and were adapted to polypropylene test cage (210 × 210 × 210 mm) for 10 min before experiment. A total of 100 μL of 1% carrageenan saline solution was intradermally injected to the left footpad except for the vehicle control group, where saline was injected instead. After 2 h, designated doses of an inhibitor were administered to the rats by oral gavage. At 3 h after the carrageenan injection, focused heat radiation (Model 336 Analgesia Meter, IITC INC/Life Science Instruments) was applied to the left footpad and subsequent withdrawal latency was measured. Withdrawal latency for the control and the treatment groups was averaged to determine % inhibitions of carrageenan-induced thermal hyperalgesia by the inhibitor according to the literature.[30b]

Gastric Ulcerogenicity. Male SD rats (130 ~ 140 g) were administered by oral gavage for 7 days at a designated daily dose of an inhibitor suspended in 1% methylcellulose. The animals were fasted overnight before necropsy examination. Four hours after the last administration, the rats were sacrificed and the stomachs were scored for ulceration. Ulcerogenicity of the inhibitor was scored according to the scales as defined in the footnote of Table 7.

Pharmacokinetics. Male SD rats (250 ~ 280 g) were fasted overnight prior to dosing and until approximately 4 h after drug administration either by oral gavage or intravenously through the tail vein. Blood samples were collected from the retro-orbital sinus at various time points over the following 24 h. Immediately after each collection, the plasma was separated from the blood by centrifugation and stored at 4 °C until analysis. The plasma samples were analyzed using a reverse phase HPLC method with an appropriate internal standard.

Molecular Modeling. The basic modeling methodology leading to the energy-minimized complex was performed using the Tripos force field implemented in Sybyl 6.8 Dock module (Tripos Associates, Inc.) with a cutoff to compute the nonbonded interactions. A human COX-2 structure complexed with **SC-558**, determined by X-ray diffraction (Brookhaven PDB entries 1CX2), was utilized.[24] The conformations of the ligand were optimized using the Tripos force field including the electrostatic term calculated from Gasteiger and Huckel atomic charges. The method of conjugated gradients was used for energy minimization until the gradient value was smaller than 0.05 kcal/mol. The lowest energy conformation obtained in this way was superimposed onto the original position of **SC-558** in the active site channel using the Sybyl 6.8 Dock module, after which **SC-558** was deleted. Energy minimization of the inhibitor-enzyme complex was performed with 8 Å cutoff to compute the nonbonded interactions by the conjugate gradients method until the gradient value was smaller than 0.05 kcal/mol.

Materials and Methods for Chemical Synthesis. Reagents and solvents were obtained from commercial suppliers and used as received, unless noted otherwise. Dry solvents used for this study were purchased from Aldrich (Aldrich Sure/Seal) and used without further drying manipulation. Column chromatography was performed on silica gel 60 (Merck Catalog no. 1.09385). ^{1}H NMR spectra were recorded on a Varian 300 MHz NMR spectrometer (Varian Gemini2000) with TMS as an internal standard. Melting points were measured on a capillary melting point apparatus (Thomas Scientific) and were reported as uncorrected. Mass spectral analyses were carried out either at National Center for Inter-University Research Facilities, Seoul, or at Korea Basic Science Support Center, Taejon, South Korea. Elemental analyses were performed at National Center for Inter-University Research Facilities, Seoul. Detailed experimental procedures for synthesis of compounds in this article are provided as follows.

2,2-Dimethyl-5-{4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)-furanone (1a). 1a was prepared according to the following six-step procedure (also see Scheme 1).

Step 1: Preparation of 1-{4-(Methylthio)phenyl}-4-hydroxy-4-methyl-2-pentyn-1-ol (7a). To a stirred solution of 2-methyl-3-butyn-2-ol (416 mg) and dry THF (30 mL) under argon and at −78 °C was added 1.6 M butyllithium in hexane (5 mL) dropwise over 10 min. A total of 20 min later, 0.5 mL of *p*-methylthiobenzaldehyde was added dropwise to the reaction solution. Then, the reaction solution was allowed to warm to the ambient temperature by removing the cold bath. After the reaction mixture was stirred for another 2 h, the reaction solvent was removed in vacuo, which was followed by neutralization with dilute aqueous HCl. The reaction mixture was then extracted with dichloromethane (50 mL × 3), and the organic layer was washed with water (50 mL × 1). The organic layer was concentrated in vacuo and the resulting residue was subjected to column chromatographic separation (hexane/ethyl acetate = 1:1) to yield 724 mg of 1-{4-(methylthio)phenyl}-4-hydroxy-4-methyl-2-pentyn-1-ol. NMR: δ 1.54 (s, 6H), 2.36 (s, 1H), 2.48 (s, 3H), 2.62 (d, 1H), 5.43 (d, J = 5.4 Hz, 1H), 7.25 (d, J = 6.9 Hz, 2H), 7.43 (d, J = 6.9 Hz, 2H).

Step 2: Preparation of 1-{(4-Methylthio)phenyl}-4-hydroxy-4-methyl-2-pentyn-1-one (8a). To a stirred solution of 724 mg of **7a** in 30 mL of acetone was added dropwise 451 mg of chromium trioxide dissolved in 10 mL of water and 0.25 mL of concentrated sulfuric acid. After being overnight at the ambient temperature, the reaction solution was concentrated in vacuo. The resulting residue was extracted with 50 mL of water and dichloromethane (50 mL × 3). The organic layer was concentrated in vacuo and subjected to column chromatographic separation (hexane/ethyl acetate = 1:1) to yield 200 mg of **8a** as a solid. mp: 102−103 °C. NMR: δ 1.67 (s, 6H), 2.41 (s, 1H), 2.54 (s, 3H), 7.28 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 8.7 Hz, 2H). IR (cm^{-1}): 3404, 1613, 1176, 747. Alternatively, **8a** was prepared by using PDC (pyridinium dichromate) in place of chromium trioxide as follows. To a stirred suspension of **7a** (20 g) and Celite (30 g) in 500 mL of dichloromethane was added PDC (40 g) portion-wise over 10 min. The reaction mixture was stirred for 12 h at room temperature. The suspension was then filtered through a Florisil pad (150 g) and the Florisil pad was washed with 500 mL of methylene chloride. The filtrate was washed with dilute aqueous HCl (200 mL × 1) and the organic layer was concentrated in vacuo. The resulting residue was chromatographed as above to afford 12.3 g of **8a**. Another variation of oxidation reaction to prepare **8a** from **7a** was performed as follows: A suspension of **7a** (150 g) and activated manganese dioxide (200 g) in methylene chloride (2 L) was stirred using an overhead stirrer for 20 h at room temperature. Then the suspension was filtered through Celite (300 g) and the filtrate was concentrated under reduced pressure. The resulting crude solid was recrystallized from ethyl acetate/hexane to afford 120 g of **8a**.

Step 3: Preparation of 2,2-Dimethyl-5-{4-(methylthio)-phenyl}-3(2*H*)-furanone (9a). To a stirred solution of **8a** (120 mg) in 20 mL of ethanol was added dropwise diethylamine (0.08 mL) diluted in 7 mL of ethanol over 5 min at room temperature. The reaction solution was stirred for another 1 h and then the solvent was removed in vacuo. The resulting residue was diluted with 50 mL of water and then extracted with dicloromethane (30 mL × 3). The organic layer was concentrated in vacuo and subjected to column chromatographic separation (hexane/ethyl acetate = 4:1) to give 90 mg of **9a** as a solid. mp: 107−109 °C. NMR: δ 1.48 (s, 6H), 2.54 (s, 3H), 5.91 (s, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H). IR (cm^{-1}): 1676, 1579, 1485, 1376, 1174, 1095, 1050, 809.

Step 4: Preparation of 4-Bromo-2,2-dimethyl-5-{4-(methylthio)phenyl}-3(2*H*)-furanone (10a). To a stirred solution of **9a** (58 mg) in 20 mL of carbon tetrachloride were added 0.5 mL of acetic acid and 0.1 mL of bromine. The

reaction solution was stirred at room temperature for 1 h. Then the reaction was quenched with 20 mL of saturated aq sodium thiosulfate. Removal of the carbon tetrachloride in vacuo was followed by extraction with dichloromethane (50 mL × 3). Then, the organic layer was washed with water (50 mL × 1), concentrated in vacuo, and then subjected to chromatographic separation (hexane/ethyl acetate = 2:1) to yield 69 mg of **10a** as a solid. NMR: δ 1.52 (s, 6H), 2.55 (s, 3H), 7.33 (d, J = 9.3 Hz, 2H), 8.15 (d, J = 9.0 Hz, 2H); IR (cm^{-1}): 1704, 1594, 1574, 1486, 1348, 1184, 1069.

Step 5: Preparation of 4-Bromo-2,2-dimethyl-5-{(4-methylsulfonyl)-phenyl}-3(2*H*)furanone (11a). A total of 42 mg of **10a** was dissolved in 15 mL of THF and 15 mL of ethanol, to which was added 178 mg of OXONE. The mixture was stirred overnight at room temperature. Then the solvent was removed in vacuo. The resulting residue was extracted with 50 mL of water and methylene chloride (50 mL × 3). The organic layer was concentrated under reduced pressure and subjected to column chromatography (hexane/ethyl acetate = 2:1) to afford 45 mg of desired **11a** as a solid. mp: 196−196.5 °C. NMR: δ 1.57 (s, 6H), 3.11 (s, 3H), 8.11 (d, J = 8.7 Hz, 2H), 8.40 (d, J = 8.7 Hz, 2H). IR (cm^{-1}): 2928, 1703, 1559, 1270, 1148, 1076, 847. MS (EI): 346 (*m*).

Step 6: Preparation of 2,2-Dimethyl-5-{4-(methylsulfonyl)phenyl}-4-(phenyl)-3(2*H*)furanone (1a). To a stirred solution of **11a** (380 mg) and tetrakis(triphenylphosphine)-palladium(0) (40 mg) in 50 mL of toluene/15 mL of ethanol were added 2 M aq sodium carbonate (15 mL) and benzeneboronic acid (200 mg). The reaction solution was stirred at 90 °C for 12 h. Then the solvent was evaporated off under reduced pressure. The resulting residue was extracted with 50 mL of water and dichloromethane (30 mL × 3). Then the organic layer was concentrated in vacuo and separated by column chromatography (hexane/ethyl acetate = 2:1) to give 200 mg of **1a** as a solid. mp: 192−193 °C. NMR: δ 1.58 (s, 6H), 3.07 (s, 3H), 7.27 (m, 2H), 7.36 (m, 3H), 7.84 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H). IR (cm^{-1}): 1697, 1503, 1404, 1245, 1148, 959, 770. HRMS (EI) calcd for $C_{19}H_{18}O_4S$ 342.0926 (M^+), found 342.0936.

Compounds **1b** ∼ **1r** were prepared similarly as the case of compound **1a** by reacting bromide compound **11a** with appropriate arylboronic acids. The analytical and physical data for compounds **1b** ∼ **1r** may be found in Supporting Information.

2-Ethyl-2-methyl-5-{4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)furanone (2a). To a stirred solution of 4-bromo-2-ethyl-2-methyl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone (**11b**, 200 mg; see Supporting Information for details) in 15 mL of toluene were added 40 mg of tetrakis-(triphenylphosphine)palladium(0), 5 mL of 2 M aq sodium carbonate, and 100 mg of benzeneboronic acid. The reaction solution was stirred at reflux for 12 h. Then the reaction solvent was evaporated under reduced pressure. The resulting residue was extracted with water and dichloromethane (30 mL × 3). The organic layer was concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate = 2:1) to give 60 mg of **2a** as a solid. mp: 115−117 °C. NMR: δ 0.96 (t, J = 7.5 Hz, 3H), 1.55 (s, 3H), 1.97 (q, J = 7.5 Hz, 2H), 3.07 (s, 3H), 7.37 (m, 5H), 7.85 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H). IR (cm^{-1}): 2928, 1697, 1620, 1403, 1318, 1149, 959, 769, 552. HRMS (EI) calcd for $C_{20}H_{20}O_4S$ 356.1082 (M^+), found 356.1068.

Compounds **2b** ∼ **2f** were prepared by reacting bromide **11b** with appropriate arylboronic acids by Suzuki coupling as similarly as described for compound **2a**. The analytical and physical data for compounds **2b** ∼ **2f** may be found in Supporting Information.

2,2-Diethyl-5-{4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)furanone (3a). To a stirred solution of 4-bromo-2,2-diethyl-2−5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone (**11c**, 300 mg; see Supporting Information for details) in 25 mL of toluene and 10 mL of ethanol were added 40 mg of tetrakis-(triphenylphosphine)palladium(0), 10 mL of aqueous 2 M sodium carbonate, and 140 mg of benzeneboronic acid. Then the reaction solution was stirred at 95 °C for 12 h. The reaction solvent was evaporated off in vacuo, and the resulting residue was extracted with 50 mL of water and dichloromethane (30 mL × 3). The organic layer was concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate) to give 130 mg of **3a** as a solid. mp: 139−140 °C. NMR: δ 0.93 (t, J = 7.5 Hz, 6H), 1.99 (q, J = 7.5 Hz, 4H), 3.07 (s, 3H), 7.24 (m, 2H), 7.37 (m, 3H), 7.86 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H). IR (cm^{-1}): 2972, 1695, 1621, 1403, 1318, 1149. HRMS (EI) calcd. for $C_{21}H_{22}O_4S$ 370.1239 (M^+), found 370.1243.

Compounds **3b** ∼ **3d** were prepared by reacting bromide **11c** with appropriate arylboronic acids by Suzuki coupling as similarly as described for compound **3a**. The analytical and physical data for compounds **3b** ∼ **3d** may be found in Supporting Information.

2-{4-(Methylsulfonyl)phenyl}-3-phenyl-1-oxa-spiro[4,4]-non-2-en-4-one (4a). To a stirred solution of 3-bromo-2-(4-(methylsulfonyl)phenyl)-1-oxa-spiro[4,4]non-2-en-4-one (**11d**, 77 mg; see Supporting Information for details) in 5 mL of toluene and 15 mL of ethanol were added 15 mg of tetrakis-(triphenylphosphine)palladium(0), 5 mL of 2 M aqueous sodium carbonate, and 27 mg of benzeneboronic acid. Then the reaction solution was stirred at 90 °C for 12 h. The reaction solvent was evaporated off under reduced pressure and the resulting residue was extracted with 20 mL of water and dichloromethane (30 mL × 1). The organic layer was concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate) to obtain 57 mg of **4a** as a solid. mp: 184−185 °C. NMR: δ 2.09 (m, 6H), 2.17 (m, 2H), 3.06 (s, 3H), 7.26 (m, 2H), 7.35 (m, 3H), 7.81 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H). IR (cm^{-1}): 2925, 1695, 1591, 1403, 1150, 771. HRMS (EI) calcd for $C_{21}H_{20}O_4S$ 368.1082 (M^+), found 368.1092.

Compounds **4b** ∼ **4d** were prepared by reacting bromide **11d** with appropriate arylboronic acids by Suzuki coupling as similarly as described for compound **4a**. The analytical and physical data for compounds **4b** ∼ **4d** may be found in Supporting Information.

2-{4-(Methylsulfonyl)phenyl}-3-phenyl-1-oxa-spiro[4,5]-dec-2-en-4-one (5a). To 102 mg of 3-bromo-2-{4-(methylsulfonyl)phenyl}-1-oxa-spiro[4,5]dec-2-en-4-one (**11e**; see Supporting Information for details) dissolved in 3 mL of toluene and 15 mL of ethanol were added 16 mg of tetrakis-(triphenylphosphin)palladium(0), 3 mL of 2 M aqueous sodium carbonate, and 35 mg of benzeneboronic acid. The reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was then purified by a procedure similar to that for **4a** to afford 50 mg of **5a** as a solid. mp: 126−127 °C. NMR: δ 1.77−1.85 (m, 10H), 3.06 (s, 3H), 7.27 (m, 2H), 7.35 (m, 3H), 7.83 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H). IR (cm^{-1}): 2936, 1693, 1621, 1404, 1318, 1147, 1129, 730. HRMS (EI) calcd for $C_{22}H_{22}O_4S$ 382.1239 (M^+), found 382.1229.

5b was prepared by reacting bromide **11e** with 3-methylphenylboronic acid by Suzuki coupling as similarly as described for compound **5a**. Analytical and physical data for **5b** may be found in Supporting Information.

2,2-Dimethyl-5-{2-fluoro-4-(methylthio)phenyl}-4-phenyl-3(2*H*)furanone (16a). 1-{2-Fluoro-4-(methylthio)phenyl}-2-phenyl-ethan-1-one (675 mg) was dissolved in 50 mL of dry THF at 0 °C, which was followed by portionwise addition of sodium hydride (120 mg). The reaction mixture was stirred for an hour at 0 °C, which was followed by dropwise addition of 0.35 mL of α-bromoisobutyryl cyanide diluted in 20 mL of dry THF. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction solvent was removed in vacuo and the resulting residue was extracted with 50 mL of water and dichloromethane (30 mL × 3). The organic layer was concentrated under reduced pressure and purified by column chromatography (hexane/ethyl acetate = 6:1) to yield 353 mg of **16a**. NMR: δ 1.54 (s, 6H), 2.49 (s, 3H), 6.90 (dd, J = 10.8, 1.8 Hz, 1H), 7.00 (dd, J = 8.4, 1.8 Hz, 1H), 7.22−7.29 (m, 5H), 7.40 (dd, J = 8.4, 7.2 Hz, 1H). IR (cm^{-1}): 1699, 1610, 1388, 1175, 1049.

2,2-Dimethyl-5-{2-fluoro-4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)furanone (12a). A total of 305 mg of **16a** was dissolved in 30 mL of methanol, 20 mL of THF, and 20 mL of

water, to which was added 1.4 g of OXONE. The reaction mixture was stirred overnight at room temperature. Then the solvent was removed in vacuo and the resulting residue was extracted with 50 mL of water and dichloromethane (30 mL × 3). The organic layer was concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate = 3:2) to obtain 70 mg of **12a** as a solid. mp: 175−176 °C. NMR: δ 1.57 (s, 6H), 3.10 (s, 3H), 7.22 (m, 2H), 7.28 (m, 3H), 7.75 (dd, J = 8.7, 1.8 Hz, 1H), 7.77 (m, 2H). IR (cm^{-1}): 1702, 1408, 1321, 1147. MS (FAB): 361 (MH^+). HRMS (EI) calcd for $C_{19}H_{17}FO_4S$ 360.0832 (M^+), found 360.0833.

Methyl sulfone compounds **12b** ∼ **12h** were prepared from a suitable 1-{4-(methylthio)phenyl}-2-phenyl-ethan-1-one derivative (**13**), as similarly as the procedure employed for preparation of **12a**. For the analytical and physical data of compounds **12b** ∼ **12h**, see Supporting Information.

5-{4-(Aminosulfonyl)phenyl}-2,2-dimethyl-4-phenyl-3(2*H*)furanone (20a). 20a was prepared according to the following four-step synthetic procedure (also refer to Scheme 3).

Step 1: Preparation of 2,2-Dimethyl-5-{4-(methylsulfinyl)phenyl}-3(2*H*)furanone (17a). To a stirred solution of 2,2-dimethyl-5-{4-(methylthio)phenyl}-3(2*H*)furanone (**9a**: 10 g) in 200 mL of dichloromethane at 0 °C was added dropwise 4.8 g of *m*-chloroperoxybenzoic acid dissolved in 50 mL of dichloromethane. The reaction mixture was stirred at 0 °C for another 2 h and then concentrated in vacuo. The resulting residue was extracted with water and dichloromethane (50 mL × 3), followed by washing of the organic layer with aqueous sodium carbonate. The organic layer was then subjected to column chromatography (hexane/ethyl acetate) to give 7.5 g of sulfoxide **17a** as a solid. mp: 108−109 °C. NMR: δ 1.51 (s, 6H), 2.78 (s, 3H), 6.06 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H). IR (cm^{-1}): 2925, 1697, 1603, 1558, 1173, 1087, 1049.

Step 2: Preparation of 2,2-Dimethyl-4-iodo-5-{4-(methylsulfinyl)phenyl}-3(2*H*)-furanone (18). To a stirred solution of 6 g of **17a** in 200 mL of carbon tetrachloride and 100 mL of chloroform were added at room temperature 5.15 g of [bis(trifluoroacetoxy)iodo]benzene and 6.5 g of iodine. The reaction was quenched after 4 h by adding saturated aqueous sodium thiosulfate until the characteristic color of iodine disappeared. The quenched solution was extracted with water and dichloromethane (100 mL × 3). The organic layer was concentrated in vacuo and the resulting crude product was recrystallized from hexane/ethyl acetate to yield 4.5 g of **18**. NMR: δ 1.53 (s, 6H), 2.79 (s, 3H), 7.81 (d, J = 8.1 Hz, 2H), 8.38 (d, J = 8.1 Hz, 2H). IR (cm^{-1}): 2975, 2929, 1699, 1595, 1404, 1319, 1150, 969, 766, 552.

Step 3: Preparation of 5-{4-(Aminosulfonyl)phenyl}-2,2-dimethyl-4-iodo-3(2*H*)furanone (19). A total of 1.11 g of **18** was reacted with 30 mL of trifluoroacetic anhydride for 2 h at 0 °C. After removal of the volatile solvent in vacuo, the resulting residue was dissolved in 50 mL of 1:1 methanol/triethylamine. The solvent was removed again in vacuo. Then the resulting residue was dissolved in 30 mL of carbon tetrachloride, to which was added slowly 40 mL of acetic acid saturated with chlorine at 0 °C. After the reaction solution was stirred at 0 °C for 20 min, the reaction solvent and the unreacted chlorine were removed under reduced pressure. The resulting residue was dissolved in 30 mL of toluene and the toluene was removed again under reduced pressure. Then the residue was the reacted with 3 mL of ammonia water in 40 mL of THF at 0 °C for 30 min. The reaction solution was concentrated in vacuo and the resulting residue was diluted with 30 mL of water. The aqueous solution was then extracted with dichloromethane (30 mL × 3). The organic layer was concentrated in vacuo and was purified by column chromatography (hexane/ethyl acetate = 3:2) to obtain 450 mg of **19** as a solid. mp: 179−180 °C. NMR: δ 1.50 (s, 6H), 5.63 (br. s, 2H), 8.05 (dd, J = 9.0, 1.5 Hz, 2H), 8.29 (dd, J = 9.0, 5.7 Hz, 2H). IR (cm^{-1}): 3367, 3261, 2985, 1684, 1582, 1405, 1188, 913. MS (FAB): 393 (MH^+).

Step 4: Preparation of 5-{4-(Aminosulfonyl)phenyl}-2,2-dimethyl-4-phenyl-3(2*H*)furanone (20a). To stirred solution of 150 mg of **19** dissolved in 15 mL of toluene and 5 mL of ethanol were added 25 mg of tetrakis(triphenylphosphine)palladium(0), 5 mL of 2 M aq sodium carbonate, and 70 mg of benzeneboronic acid. The reaction solution was stirred at 95 °C for 24 h, followed by removal of the solvent in vacuo. Then the residue was extracted with 30 mL of water and dichloromethane (30 mL × 3). The organic layer was concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate = 1:1) to give 20 mg of sulfonamide **20a** as a solid. mp: 180−182 °C. NMR: δ 1.58 (s, 6H), 4.91 (br s, 2H), 7.30 (m, 5H), 7.78 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H). IR (cm^{-1}): 3375, 3245, 1697, 1617, 1559, 1395, 1241, 1161, 899, 752. HRMS (EI) calcd for $C_{18}H_{17}NO_4S$ 343.0878 (M^+), found 343.0891.

Sunfonamide derivatives **20b** ∼ **20i** were prepared by Suzuki coupling of iodide **19** with appropriate arylboronic acids, as similarly as employed for sulfonamide **20a**. The physical and analytical data sulfonamides **20b** ∼ **20i** may be found in Supporting Information.

5-{4-(Aminosulfonyl)-2-fluorophenyl}-2,2-dimethyl-4-phenyl-3(2*H*)furanone (22a). A total of 154 mg of 2,2-dimethyl-5-{2-fluoro-4-(methylsulfinyl)phenyl}-4-phenyl-3(2*H*)-furanone (**21a**; see Supporting Information for details) was stirred in 30 mL of trifluoroacetic anhydride at 0 °C for 2 h. Then the volatile material was removed in vacuo, to which was added 50 mL of 1:1 methanol and triethylamine. The solution was stirred for 20 min at 0 °C and the solvent was removed in vacuo. The resulting residue was dissolved in 40 mL of dichloromethane, which was followed by dropwise addition of 15 mL of acetic acid saturated with chlorine. The reaction solution was stirred for 20 min at 0 °C. Then the solvent and unreacted chlorine were removed in vacuo. The resulting residue was dissolved in 30 mL of toluene and the toluene was evaporated off under reduced pressure. The resulting residue was stirred overnight in 40 mL of THF and reacted with 5 mL of ammonia water. The solvent was removed in vacuo and the resulting residue was extracted with 30 mL of water and dichloromethane (30 mL × 3). The organic layer was concentrated in vacuo and then purified by column chromatography (hexane/ethyl acetate = 3:2) to give 42 mg of sulfonamide **22a** as a solid. mp: 79−81 °C. NMR: δ 1.58 (s, 6H), 5.01 (br s, 2), 7.20−7.31 (m, 5H), 7.69−7.76 (m, 3H). IR (cm^{-1}): 3340, 3274, 1591, 1526, 1328. MS (FAB): 362 (MH^+). HRMS (EI) calcd for $C_{18}H_{16}FNO_4S$ 361.0784 (M^+), found 361.0781.

Sulfonamides **22b** ∼ **22f** were prepared from appropriate 2,2-dimethyl-5-{4-(methylsulfinyl)-fluoro-phenyl}-4-phenyl-3(2*H*)furanone derivatives (**21**), by a procedure similar to that employed for preparation of **22a**.

Acknowledgment. First of all, we would like to thank Dr. Woo Young Lee of Pacific Pharmaceuticals for in-depth discussions and understanding with regard to the COX-2 inhibitors program in general. Also technical support by The National Center for Inter-University Research Facilities located in Seoul National University is acknowledged for mass spectral analysis.

Supporting Information Available: Analytical and physical data for compounds **1b** ∼ **1r**, **2b** ∼ **2f**, **3b** ∼ **3d**, **4b** ∼ **4d**, **5b**, **12b** ∼ **12h**, **20b** ∼ **20i**, and **22b** ∼ **22f**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Posting

Incorrect units for IC_{50} in Tables 1−3 were included in the manuscript posted January 14, 2004. The correct units are μg/mL. The manuscript was reposted January 20, 2004.

References

(1) (a) Roth, S. H. Nonsteroidal Anti-inflammatory Drugs: Gastropathy, Deaths, and Medical Practice. *Ann. Intern. Med.* **1988**, *109*, 353−354. (b) Jones, R. Nonsteroidal Anti-inflammatory Drug Prescribing: Past, Present, and Future. *Am. J. Med.* **2001**, *110*, 4S−7S.

(2) (a) Singh, G. Recent Considerations in Nonsteroidal Anti-inflammatory Drug Gastropathy. *Am. J. Med.* **1988**, *105*, 31S−38S. (b) Wolfe, M. M.; Lichtenstein, D. R.; Singh, G. Gastrointestinal Toxicity of Nonsteroidal Anti-inflammatory Drugs. *N. Engl. J. Med.* **1999**, *340*, 1888−1899.

(3) (a) Fu, J.-Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. The Induction and Suppression of Prostaglandin H_2 Synthase (Cyclooxygenase) in Human Monocytes. *J. Biol. Chem.* **1990**, *265*, 16737−16740. (b) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. Expression of a Mitogen-responsive Gene Encoding Prostaglandin Synthase is Regulated by mRNA Splicing. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692−2696.

(4) (a) Smith, W. L.; DeWitt, D. L. Prostaglandin Endoperoxidase H Synthase-1 and -2. *Adv. Immunol.* **1996**, *62*, 167−215. (b) Pariet, M.; Churchill, L.; Engelhardt, G. In *New Targets in Inflammation: Inhibitors of COX-2 or Adhesion Molecules*; Bazan, N.; Botting, J.; Vane, J., Eds.; Kluwer Academic: London, 1996; pp 23−38.

(5) Morham, S. G.; Langenbach, R.; Loftin, C. D.; Tiano, H. F.; Vouloumanos, N.; Jennette, J. C.; Mahler, J. F.; Kluckman, K. D.; Ledford, A.; Lee, C. A.; Smithies, D. Prostaglandin Synthase-2 Gene Disruption Causes Severe Renal Pathology in the Mouse. *Cell* **1995**, *83*, 473−482.

(6) For animal safety data of COX-2 inhibitors, see the FDA NDA reports as follows: (a) Celecoxib: Pharmacology Review, Application Number 20−998. (b) Rofecoxib: Pharmacology Review, Application Number 21,042. (c) Valdecoxib: Pharmacology Review, Application Number 21−341.

(7) (a) Bombardier, C.; Laine, L.; Reicin, A.; Shapiro, D.; Burgos-Vargas, R.; Davis, B.; Day, R.; Ferraz, M. B.; Hawkey, C. J.; Hochberg, M. C.; Kevin, T. K.; Schnitzer, T. J. The VIGOR Study Group. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Reumatoid Arthritis. *N. Engl. J. Med.* **2000**, *343*, 1520−1528. (b) Silverstein, F. E.; Faich, G.; Goldstein, J. L.; Simon, L. S.; Pincus, T.; Whelton, A.; Makuch, R.; Eisen, G.; Agrawal, N. M.; Stenson, W. F.; Burr, A. M.; Zhao, W. W.; Kent, J. D.; Lefkowith, J. B.; Verburg, K. M.; Geis, G. S. Gastrointestinal Toxicity with Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: A Randomized Controlled Trial. *JAMA* **2000**, *284*, 1247−1255. (c) Distel, M.; Mueller, C.; Bluhmki, E.; Fries, J. Safety of Meloxicam: A Global Analysis of Clinical Trials. *Br. J. Rheumatol.* **1996**, *35* (Suppl. 1), 68−77.

(8) (a) Mukherjee, D.; Nissen, S. E.; Topol, E. J. Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors. *JAMA* **2001**, *286*, 954−959. (b) Barkin, R. L.; Sable, K. S. Caution Recommended for Prescribing and Administering COX1/COX2 and COX2 Specific NSAIDs. *P&T* **2000**, *25*, 196−202. (c) Cheng, Y.; Austin, S. C.; Rocca, B.; Koller. B. H.; Coffman, T. M.; Grosser, T.; Lawson, J. A.; FitzGerald, G. A. Role of Prostacyclin in the Cardiovascular Response to Thromboxane A_2. *Science* **2002**, *296*, 539−541. (d) Khan, K. N. M.; Paulson, S. K.; Verburg, K. M.; Lefkowith, J. B.; Maziasz, T. J. Pharmacology of Cyclooxygenase-2 Inhibition in the Kidney. *Kidney Int.* **2002**, *61*, 1210−1219.

(9) (a) Prasit, P.; Wang, Z.; Briedeau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Legar, S.; Mancini, J.; O'Neill, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vikers, P.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupiniak, N.; Forrest, M.; Visco, D.; Patrick, D. The Discovery of Rofecoxib, [MK966, VIOXX, 4-(4′-Methylsulfonylphenyl)-3-phenyl-2(5*H*)-furanone], an Orally Active Cyclooxygenase-2 Inhibitor. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773−1778. (b) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Gogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K. Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzene Sulfonamide (**SC-58635**, Celecoxib). *J. Med. Chem.* **1997**, *40*, 1347−1365. (c) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, Valdecoxib: A Potent and Selective Inhibitor of COX-2. *J. Med. Chem.* **2000**, *43*, 775−777. (d) Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y. Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, L. J.; Young, R. N. 2-Pyridnyl-3-(4-methylsulfonyl)phenylpyridines: Selective and Orally Active Cyclooxygenase-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2777−2782. (e) Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Paluki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J. A Practical Synthesis of a COX-2 Specific Inhibitor. *J. Org. Chem.* **2000**, *65*, 8415−8420.

(10) Geba, G. P.; Weaver, A. L.; Polis, A. B.; Dixon, M. E.; Schnitzer, T. J. Efficacy of Rofecoxib, Celecoxib, and Acetaminophen in Osteoarthritis of the Knee: a Randomized Trial. *JAMA* **2002**, *287*, 64−71.

(11) Whelton, A.; Fort, J. G.; Puma, J. A.; Normandin, D.; Bello, A. E.; Verburg, K. M.Cyclooxygenase-2-Specific Inhibitors and Cardiorenal Function: A Randomized, Controlled Trial of Celecoxib and Rofecoxib in Older Hypertensive Osteoarthritis Patients. *Am. J. Ther.* **2001**, *8*, 85−95.

(12) Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J.-Y.; Kim, J. K.; Lee, C. H.; Chung, S. 2,2-Dimethyl-4,5-diaryl-3(2*H*)furanone Derivatives as Selective Cyclooxygenase-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 165−168.

(13) (a) Prasit, P.; Riendeau, D. Selective Cyclooxygenase-2 Inhibitors. *Ann. Rep. Med. Chem.* **1997**, *32*, 211−220. (b) Leval, X. D.; Julémont, F.; Delarge, J.; Sanna, V.; Pirotte, B.; Dogné, J.-M. Advances in the Field of COX-2 Inhibition. *Expert Opin. Ther. Patents* **2002**, *12*, 969−989.

(14) (a) Tang, C.; Shou, M.; Rushmore, T. H.; Mei, Q.; Sandhu, P.; Woolf, E. J.; Rose, M. J.; Gelmann, A.; Greenberg, H. E.; De Lepeleire, I.; Hecken, A. V.; De Schepper, P. J.; Ebel, D. L.; Schwartz, J. I.; Rodrigues, A. D. *In-vitro* Metabolism of Celecoxib, a Cyclooxygenase-2 Inhibitor, by Allelic Variant Forms of Human Liver Microsomal Cytochrome P450 2C9: Correlation with CYP2C9 Genotype and in-vivo Pharmacokinetics**.** *Pharmacogenetics* **2001**, *11*, 223−235. (b) Nicoll-Griffith, D. A.; Yergey, J. A.; Trimble, L. A.; Silva, J. M.; Li, C.; Chauret, N.; Gauthier, J. Y.; Grimm, E.; Léger, S.; Roy, P.; Thérien, M.; Wang, Z.; Prasit, P.; Zamboni, R.; Young, R. N.; Brideau, C.; Chan, C.-C.; Mancini, J.; Riendeau, D. Synthesis, Characterization, and Activity of Metabolites Derived from the Cyclooxygenase-2 Inhibitor Rofecoxib (**MK-0966**, Vioxx). *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2683−2686.

(15) Joshi, A. S.; Raghavan, N.; Williams, R. M.; Takahashi, K.; Shingu, H.; King, S.-Y. P. Simultaneous Quantification of an Antiinflammatory Compound (**DuP 697**) and a Potential Metabolite (**X6882**) in Human Plasma and Urine by High-Performance Liquid Chromatography. *J. Chromatogr. B: Biomed. Sci. Appl.* **1994**, *660*, 143−150.

(16) Parker, W.; Raphael, R. A.; Wilkinson, D. I. The Structure and Synthesis of Bullatenone. *J. Chem. Soc.* **1958**, 3871−3875.

(17) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. The Palladium-catalyzed Cross-coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **1981**, *11*, 513−517. (b) Hoshino, Y.; Miyaura, N.; Suzuki. A. Novel Synthesis of Isoflavones by the Palladium-catalyzed Cross-coupling Reaction of 3-Bromochromones with Arylboronic Acids of Its Esters. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008−3010.

(18) Herrmann, K.; Simchen, G. Synthese von Acylcyaniden (α-Oxonitrilen) mit Cyanotrimethylsilan. *Synthesis* **1979**, 204−205.

(19) Lee, K.-W.; Choi, Y. H.; Joo, Y. H.; Kim, J. K.; Shin, S. S.; Byun, Y. J.; Kim, Y.; Chung, S. A Facile One-Pot Synthesis of 4,5-Diaryl-2,2-dimethyl-3(2*H*)-furanones**.** *Bioorg. Med. Chem.* **2002**, *10*, 1137−1142.

(20) (a) Kharasch, N.; Bruice, T. C. Derivatives of Sulfenic Acids. V. 1-Fluorenone Sulfur Compounds. *J. Am. Chem. Soc.* **1951**, *73*, 3240−3244. (b) Vleeschauwer, M. D.; Gauthier, J. Y. Remarkably Mild and Simple Preparations of Sulfinates, Sulfonyl Chlorides and Sulfonamides from Thioanisoles. *Synlett* **1997**, 375−377.

(21) Mitchell, J. A.; Akarasereenont, P.; Thiemermann, C.; Flower, R. J.; Vane, J. R. Selectivity of Nonsteroidal Antiinflammatory Drugs as Inhibitors of Constitutive and Inducible Cyclooxygenase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 11693−11697.

(22) Brideau, C.; Kargman, S.; Liu, S.; Dallob, A. L.; Ehrich, E. W.; Rodger, I. W.; Chan, C.-C. A Human Whole Blood Assay for Clinical Evaluation of Biochemical Efficacy of Cyclooxygenase Inhibitors. *Inflammation Res.* **1996**, *45*, 68−74.

(23) The following COX-1/COX-2 IC_{50}'s were observed by the human whole blood method: (a) for **1b**, COX-1 $IC_{50} = 0.26$ μg/mL and COX-2 $IC_{50} = 0.005$ μg/mL; (b) for **1f**, COX-1 $IC_{50} = 0.72$ μg/mL and COX-2 $IC_{50} = 0.005$ μg/mL; (c) for **22f**, COX-1 $IC_{50} = 12$ μg/mL and COX-2 $IC_{50} = 1.5$ μg/mL.

(24) Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; Mcdonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildhaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K. Isakson, P. C.; Stallings, W. C. Structual Basis for Selective Inhibition of Cyclooxygenase-2 by Anti-inflammatory Agent. *Nature* **1996**, *384*, 644−648

(25) Li, J. J.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H.-C.; Isakson, P. C.; Koboldt, C. M.; Logusch, E. W.; Norton, M. B.; Perkins, W. E.; Reinhard, E. J.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y.; Reitz, D. B. 1,2-Diarylcyclopentenes as Selective Cyclooxygenase-2 Inhibitors and Orally Active Anti-inflammatory Agents. *J. Med. Chem.* **1995**, *38*, 4570−4578. (b) Huang, H.-C.; Li, J. J.;

Garland, D. J.; Chamberlain, T. S.; Reinhard, E. J.; Manning, R. E.; Seibert, K.; Koboldt, C. M.; Gregory, S. A.; Anderson, G. D.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E.; Burton, E. G.; Cogburn, J. N.; Isakson, P. C.; Reitz, D. B. Diaryl-sprio[2,4]-heptenes as Orally Active, Highly Selective Cyclooxygenase-2 Inhibitors: Synthesis and Struture−activity Relationships. *J. Med. Chem.* **1996**, *39*, 253−266. (c) Reitz, D. B.; Huang, H.-C.; Li, J. J.; Garland, D. J.; Manning, R. E.; Anderson, G. D.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. Selective Cyclooxygeanse-2 Inhibitors: Novel 4-Spiro 1,2-Diarylcyclopentenes Are Potent and Orally Active COX-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 867−872.

(26) {4-(Methylsulfonyl)phenyl}-3(2*H*)furanone was actually prepared and identified by ^{1}H NMR after chromatographic separation. Unfortunately, the key intermediate spontaneously decomposed upon standing for a few days at ambient temperature. Furthermore, the 3(2*H*)furanone intermediate appeared to be in equilibrium with its tautomer 3-hydroxy-5-{4-(methylsulfonyl)-phenyl}-furane in a 1:4 ratio in the NMR solvent ($CDCl_3$) by careful analysis of the initial ^{1}H NMR spectrum. The furan form was the major tautomer.

(27) (a) Matsushita, M.; Masaki, M.; Yagi, Y.; Tanaka, T.; Wakitani, K. Pharmacological Profile of JTE−522, a Novel Prostaglandin H Synthase-2 Inhibitor, in Rats. *Inflammation Res.* **1997**, *46*, 461−466. (b) **JTE−522**. *Drugs of the Future* **1998**, *23*, 598−601. (c) Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. 4-(4-Cycloalkyl/aryl-oxazol-5-yl)-benzenesulfonamides as Selective Cyclooxygenase-2 Inhibitors: Enhancement of the Selectivity by Introduction of a Fluorine Atom and Identification of a Potent, Highly Selective, and Orally Active COX-2 Inhibitor JTE-522. *J. Med. Chem.* **2002**, *45*, 1511−1517.

(28) Even though only derivatives substituted with fluorine were described in Table 4 due to space limitation, derivatives substituted with a halogen other than fluorine may be found in the following patent. The trend observed in Table 4 was grossly maintained also with the derivatives substituted with chlorine and bromine. Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. K.; Lim, K. M.; Kim, J. Y.; Choi, Y. H.; Ha, J.-Y.; Lee, K.-W.; Moh, J. H.; Jeong, Y. S.; Chung, S.; Joo, Y. H.; Lee, C. H.; Kang, S. H.; Park, Y.-H.; Yi, J. B. 4,5-Diaryl-3(2*H*)furanone Derivatives as Cyclooxygenase-2 Inhibitors. U.S. Patent 6,492,-416, 2002.

(29) (a) Lombardino, J. G. Nonsteroidal Antiinflammatory Drugs. In *Chemistry and Pharmacology of Drugs*; Lednicer, D. Ed.; John Wiley & Sons: New York, 1985; pp 116−129. (b) Lombardino, J. G. Nonsteroidal Antiinflammatory Drugs. In *Chemistry and Pharmacology of Drugs*; Lednicer, D. Ed.; John Wiley & Sons: New York, 1985; pp 150−154.

(30) (a) There are not much data available to directly compare AA ED_{50}'s assessed by the therapeutic model using Lewis rats with those by the preventive model. (b) For the AA data for rofecoxib, refer to Chan, C. C.; Boyce, S.; Brideau, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.; Ford-Hutchinson, A. W.; Forrest, M. J.; Gauthier, J. Y.; Gordon, R.; Gresser, M.; Guay, J.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neill, G. P.; Ouellet, M.; Patrick, D.; Percival, M. D.; Perrier, H.; Prasit, P.; Rodger, I.; Tagari, P.; Therien, M.; Vickers, P.; Visco, D.; Wang, Z.; Webb, J.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R. Riendeau, D. Rofecoxib [Vioxx, **MK-0966**; 4-(4′-Methylsulfonylphenyl)-3-phenyl-2-(5*H*)-furanone]: A Potent and Orally Active Cyclooxygenase-2 Inhibitor. Pharmacological and Biochemical Profiles. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 551−560. (c) For the AA data for celecoxib, see ref 9b. (d) For the AA data for meloxicam, refer to Pairet, M.; Ryn, J. v.; Schierok, H.; Mauz, A.; Trummlitz, G.; Engelhardt, G. Differential Inhibition of Cyclooxygenases-1 and -2 by Meloxicam and Its 4′-Isomer. *Inflammation Res.* **1998**, *47*, 270−276. (e) For the AA data for etoricoxib, see *Drugs of the Future* **2001**, *26*, 346−353. (f) For the AA data for valdecoxib, refer to *Drugs of the Future* **2001**, *26*, 133−140.

(31) Toxicokinetic studies also suggested no indication of drug accumulation upon repeat dose in male SD rats for compounds **1b**, **1f**, and **20b**.

(32) Lombardino, J. G. Nonsteroidal Antiinflammatory Drugs. In *Chemistry and Pharmacology of Drugs*; Lednicer, D., Ed.; John Wiley & Sons: New York, 1985; pp 219−230.

(33) Riendeau, D.; Percival, M. D.; Boyce, S.; Brideau, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, E. J.; Falgueyret, J.-P.; Ford-Hutchinson, A. W.; Gordon, R.; Greig, G.; Gresser, M.; Guay, J.; Kargman, S.; Léger, S.; Mancini, J. A.; O'Neil, G.; Ouellet, M.; Rodger, I. W.; Thérien, M.; Wang, Z.; Webb, J. K.; Wong, E.; Xu, L.; Young, R. N.; Zamboni, R.; Prasit, P.; Chan, C.-C. Biochemical and Pharmacological Profile of a Tetrasubstituted Furanone as a Highly Selective COX-2 Inhibitor. *Brit. J. Pharmacol.* **1997**, *121*, 105−117.

(34) Futaki, N.; Yoshikawa, K.; Hamasaka, Y.; Arai, I.; Higuchi, S.; Iizuka, H.; Otomo, S. NS-398, a Novel Non-steroidal Anti-inflammatory Drug with Potent Analgesic and Antipyretic Effects, which Causes Minimal Stomach Lesions. *Gen. Pharmacol.* **1993**, *24*, 105−110.

(35) (a) The observed % inhibitions against carrageenan-induced thermal hyperalgesia were (26 ± 10), (59 ± 21), and (118 ± 30) % for 0.1, 0.3, and 1.0 mg/kg **20b** in the male SD rat by oral gavage, respectively. In case of indomethacin as the positive control, the observed % inhibitions were (18 ± 13) and (47 ± 30)% for 0.3 and 1.0 mg/kg, respectively. $N = 8$ per group. (b) The oral analgesic activity of **20b** was not directly compared with that of rofecoxib. Considering that rofecoxib has comparable lipophilicity to **20b** as judged by calculated logP values (1.83 for rofecoxib and 2.38 for **20b** by the Crippen's method on CS ChemDraw Ultra version 5.0), rofecoxib is a reasonable COX-2 inhibitor for comparison of analgesic activity with **20b**, though.

(36) Chung, S.; et al. *Bioorg. Med. Chem. Lett.*, submitted. When sulfoxide analogue **21** (X = H, R = 3,5-difluoro; see Scheme 4 for structure) was orally administered to rats, the sulfoxide analogue was absorbed fast and subsequently in vivo transformed into methyl sulfone compound **1f** according to pharmacokinetic studies. Repeat dose oral safety studies for both **21** and **1f** indicated that rats were significantly more tolerant to **21** than to **1f** at comparable systemic exposure level of **1f**, suggesting that there should be a notable level of local gastrointestinal toxicity occurring during the drug absorption in the gastrointestinal tract. Thus, minimization of the time needed for GI drug influx could be important for further improvement of GI safety of COX-2 inhibitor of a given COX-2 selectivity.

JM020545Z