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[1]

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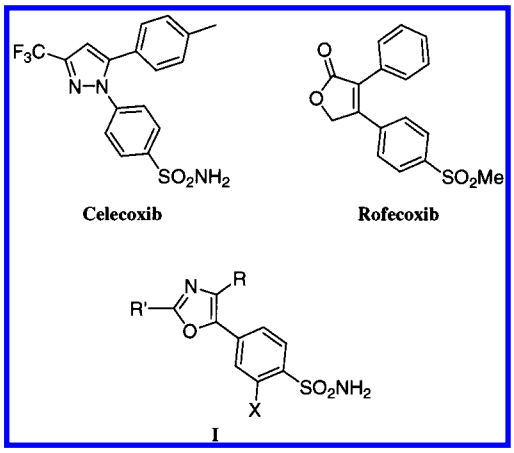
A series of 4-(4-cycloalkyl/aryl-oxazol-5-yl)benzenesulfonamide derivatives were synthesized and evaluated for their abilities to inhibit cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1) enzymes. In this series, substituent effects at the ortho position to the sulfonamide group on the phenyl ring were examined. Most substituents reduced or lost both COX-2 and COX-1 activities. In contrast, introduction of a fluorine atom preserved COX-2 potency and notably increased COX1/COX-2 selectivity. This work led to the identification of a potent, highly selective, and orally active COX-2 inhibitor JTE-522 [**9d**, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide], which is currently in phase II clinical trials for the treatment of rheumatoid arthritis, osteoarthritis, and acute pain.

Introduction

Since the discovery of two cyclooxygenase (COX) isoforms in the early 1990s,[2−4] a scenario that selective COX-2 inhibitors may offer a new generation of nonsteroidal antiinflammatory drugs (NSAIDs) without unfavorable side effects such as gastrointestinal (GI) damage has been well recognized.[5,6] The following facts undergird this scenario. Traditional NSAIDs such as aspirin and indomethacin inhibit both COX-1 and COX-2. COX-1 is constitutively expressed and produces physiologically important prostaglandins which contribute to mucosal cytoprotection for example. On the other hand, COX-2 is induced significantly under inflammatory conditions.[2−6] From these facts, the side effects of traditional NSAIDs are believed to be due to the inhibition of COX-1.

A large number of research studies aimed at finding selective COX-2 inhibitors have been performed.[7−10] From these efforts, two compounds, celecoxib[11] and rofecoxib,[12] are now on the market. It seems that these selective COX-2 inhibitors are as effective as traditional NSAIDs. The COX-2 inhibitors are promising for antiinflammatory activity with reduced GI side effects,[13] but their safety profiles are still not perfect.[14] Several new clinical uses of COX-2 inhibitor are being investigated.[10] These indications include certain types of cancer and Alzheimer's disease. Clinical trials are now underway, and the therapeutic possibilities of COX-2 inhibitors for these diseases will be clearer soon. There remains a medical need for a more specific and effective COX-2 inhibitor with improved safety profile.

Many selective COX-2 inhibitors have been reported since the mid-1990s.[7−10] They fit in several structural classes.[10] Vicinal diaryl heterocycles are the most investigated and important class and include cerecoxib and rofecoxib. We and another group have independently reported oxazole derivatives of this class.[15−18] The structural requirement of this class of compounds is that one phenyl ring attached to a central heterocyclic ring must have a methylsulfonyl or a sulfonamide substituent at the para position.[10,19] This is very critical for COX-2 inhibition. It is generally seen that sulfonamides have less COX-1/COX-2 selectivity compared to methyl sulfones. But, in vivo, sulfonamides are superior to the corresponding methyl sulfones.[11,19] Therefore, it is important to improve the COX-2 selectivity of the sulfonamide compound to produce a more specific inhibitor with good oral activity. Many sulfonamide COX-2 inhibitors have been reported, but there is no example in which a second substituent on the phenyl ring bearing sulfonamide group is introduced. We decided to investigate the possibility that introduction of a substituent at the ortho position to the sulfonamide group on the phenyl ring could improve the COX-2 selectivity and potency. In this article, we report the synthesis and structure−activity relationship studies of a series of 4-(4-cycloalkyl/aryl-oxazol-5-yl)benzenesulfonamide derivatives **I** as selective COX-2 inhibitors. This study led to the identification of highly selective



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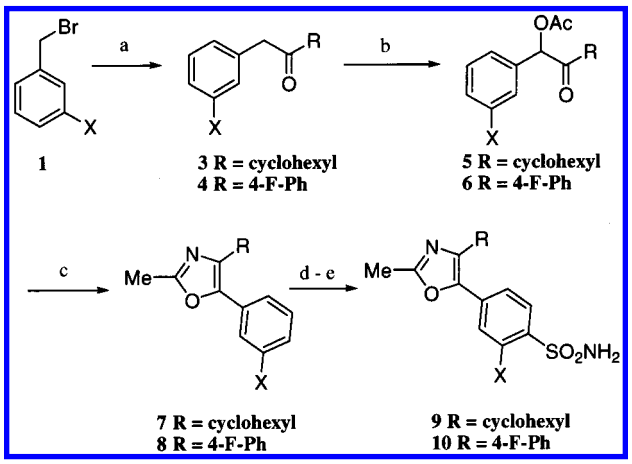
Scheme 1[a]



[a] Reagents: (a) Zn, $Pd(PPh_3)_4$ (10 mol %), RCOCl (**2**), DME, 0 °C to rt; (b) $Pb(OAc)_4$, AcOH reflux; (c) NH_4OAc, AcOH reflux; (d) $ClSO_3H$, $CHCl_3$ reflux; (e) 28% aq NH_3, THF, rt.

and orally active COX-2 inhibitor **9d** (JTE-522) which is currently in phase II clinical trials for the treatment of rheumatoid arthritis osteoarthritis and acute pain.

Chemistry

A series of 4-(4-cyclohexyl-2-methyloxazol-5-yl)benzenesulfonamide derivatives **9** and 4-[2-methyl-(4-fluorophenyl)oxazol-5-yl]benzenesulfonamide derivatives **10** were synthesized from benzylbromide **1** in five steps as shown in Scheme 1. Benzylbromides **1** were coupled with an appropriate acid chloride **2** in the presence of zinc powder and a catalytic amount of tetrakis(triphenylphosphin)palladium(0) in 1,2-dimethoxyethane to give benzyl ketones **3** or **4**.[20] The ketones **3** and **4** were converted to α-acetoxy ketones **5** and **6**, respectively, by the reaction with lead tetraacetate in refluxing acetic acid (AcOH).[21] Heating the α-acetoxy ketone **5** and **6** in refluxing AcOH in the presence of NH_4OAc afforded oxazoles **7** and **8**, respectively.[22] The oxazoles **7** and **8** were reacted with chlorosulfonic acid in refluxing $CHCl_3$ followed by the treatment with 28% aqueous ammonia in THF to give sulfonamides **9** and **10**, respectively.

Compounds **12**, **13**, and **15** were prepared from **9d** as shown in Scheme 2. Compound **9d** was reacted with benzyl alcohol in the presence of sodium hydride in DMF at 80 °C to give compound **11**. The benzyl group of **11** was removed by treating with 33% HBr−AcOH in AcOH at 80 °C to give a phenol **12**. Methylation of the phenol **12** by the reaction with methyl iodide and K_2CO_3 in refluxing acetone gave compound **13**. Compound **9d** was converted to compound **14** by the reaction with benzylamine in the presence of K_2CO_3 in DMF at 150 °C. Compound **14** was hydrogenated in the presence of 20% palladium hydroxide on charcoal in methanol to give **15**.

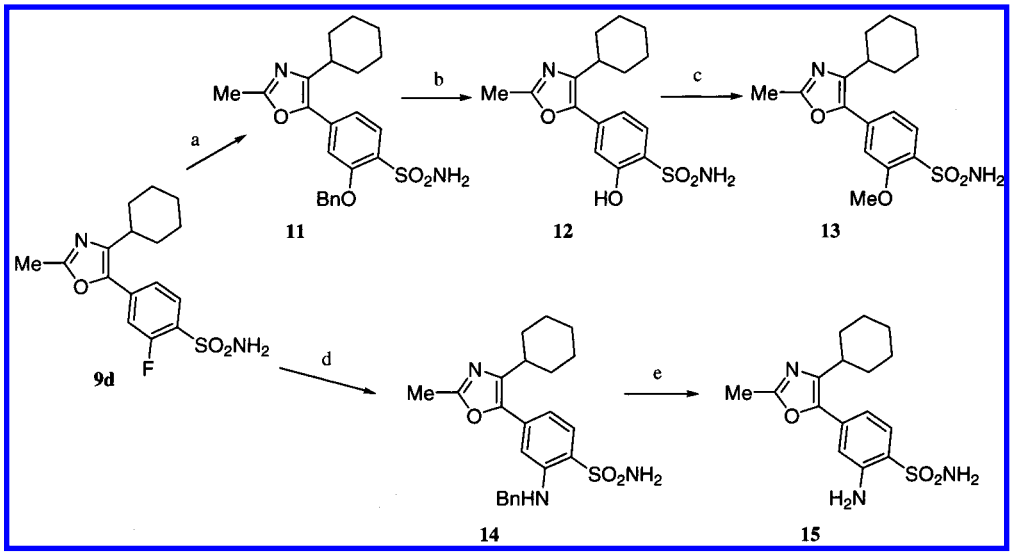
The 4-thienyl oxazoles **18** were synthesized from 4-(*N*-*tert*-butyl-aminosulfonyl)benzylbromides **16** (prepared from *p*-toluenesulfonyl chloride; see Experimental Section) as shown in Scheme 3. The bromides **16** were converted to the oxazoles **17** in three steps by using the procedure described for the prerartion of **7** and **8** in Scheme 1. The *N*-*tert*-butyl group of **17** was removed by treating with trifluoroacetic acid to give 4-thienyl oxazoles **18**.

Oxazoles **21** were prepared from benzyl ketone **3d** as shown in Scheme 4. Compound **3d** was reacted with Br_2 in toluene−$CHCl_3$ and then with the corresponding carboxylic acid potassium salt in refluxing EtOH to give α-acyloxy ketones **19**. Compounds **19** were converted to oxazoles **21** in three steps by using the procedure described in Scheme 1.

Results and Discussion

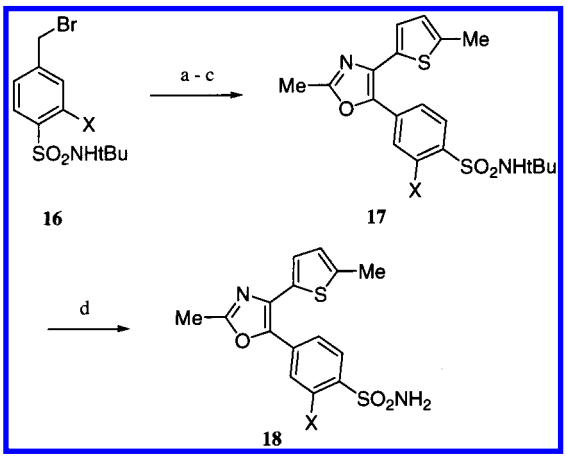
The compounds synthesized in this study were evaluated for their abilities to inhibit human COX-2 and COX-1 enzyme activities in vitro. The results of 4-(2-methyloxazol-5-yl)benzenesulfonamide derivatives are summarized in Table 1. We chose compound **9a** as a parent compound. This compound was reported previously to be a potent and selective COX-2 inhibitor (IC_{50}: COX-2 = 0.07 μM, COX-1 = 47.5 μM).[17] The ratio of COX-1/COX-2 IC_{50} values is 679. Compound **9a** is considered to possess relatively high selectivity for COX-2. Changing the cyclohexyl ring of compound **9a** to 4-fluorophenyl (**10a**) or 5-methylthienyl ring (**18a**)

Scheme 2[a]



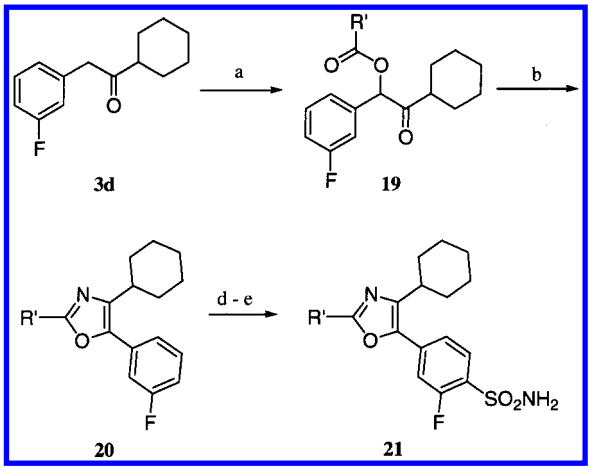
[a] Reagents: (a) BnOH, NaH, DMF, 80 °C; (b) 33% HBr/AcOH, AcOH, 80 °C; (c) K_2CO_3, MeI, acetone reflux; (d) $BnNH_2$, K_2CO_3, DMF, 150 °C; (e) 20% $Pd(OH)_2/C$, H_2, MeOH, rt.

Scheme 3[a]



[a] Reagents: (a) Zn, $Pd(PPh_3)_4$ (10 mol %), RCOCl (**2**), DME, 0 °C to rt; (b) $Pb(OAc)_4$, AcOH reflux; (c) NH_4OAc, AcOH reflux; (d) CF_3COOH, 50 °C.

Scheme 4[a]



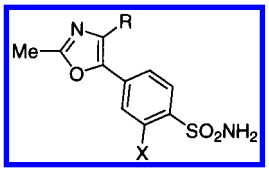
[a] Reagents: (a) Br_2, toluene−$CHCl_3$, rt; (b) R′COOK, EtOH reflux; (c) NH_4OAc, AcOH reflux; (d) $ClSO_3H$, $CHCl_3$ reflux; (e) 28% aq NH_3, THF, rt.

increased the potencies for COX-2 (**10a**, $IC_{50} = 0.02\ \mu M$; **18a**, $IC_{50} = 0.012\ \mu M$), but the activities for COX-1 were also increased nearly 10 times or more (**10a**, $IC_{50} = 5\ \mu M$; **18a**, $IC_{50} = 1.8\ \mu M$). Consequently the COX-1/COX-2 ratios are decreased in both cases. The bulky and lipophilic cyclohexyl ring is more selective than aromatic rings in this case, although the potency for COX-2 is slightly weak. These sulfonamides are selective COX-2 inhibitors, but the selectivities are not high enough.

Next, we introduced a substituent ortho to the sulfonamide group on the phenyl ring of compound **9a** to examine whether the substituent affects the activity and selectivity. As seen in Table 1, introduction of a chlorine (**9b**) or a methoxy group (**13**) decreased the COX-2 activity markedly. These compounds are not inhibitors for both COX-2 and COX-1. Introduction of hydroxy group (**12**) showed a weak inhibition of COX-2 ($IC_{50} = 19.7\ \mu M$) and no inhibition of COX-1. In the case of the methyl (**9c**) and amino (**15**) group, the COX-2 activities were weakened more than 10-fold (**9c**, $IC_{50} = 2\ \mu M$; **15**, $IC_{50} = 0.93\ \mu M$), although they are selective COX-2 inhibitors.

All the substituents mentioned above diminished or lost the COX-2 activities, but we found a exception: the

Table 1. In Vitro Human COX-2[a] and COX-1[b] Enzyme Inhibitory Concentrations of 4-(2-Methyloxazol-5-yl)benzenesulfonamide Derivatives



compd	R	X	COX-2 IC_{50} (μM)[c]	COX-1 IC_{50} (μM)[c]	selectivity COX-1/COX-2
9a	cyclohexyl	H	0.07	47.5	679
9b	cyclohexyl	Cl	>10	>100	
9c	cyclohexyl	Me	2.0	>100	>50
9d	cyclohexyl	F	0.085	>100	>1176
12	cyclohexyl	OH	19.7	>100	>5
13	cyclohexyl	OMe	>100	>100	
15	cyclohexyl	NH_2	0.93	>100	>108
10a	4-F-phenyl	H	0.02	5	250
10d	4-F-phenyl	F	0.04	40	1000
18a	5-Me-2-thienyl	H	0.012	1.8	150
18d	5-Me-2-thienyl	F	0.026	25	962
indomethacin			2.38	0.15	0.063
celecoxib			0.23	27	117
rofecoxib			0.34[d]	26[d]	76[e]

[a] Human recombinant COX-2 enzyme. [b] Human COX-1 enzyme from human platelets. [c] Values are means of at least three experiments. [d] Data taken from the literature (ref 23). [e] Calculated from the data in ref 23.

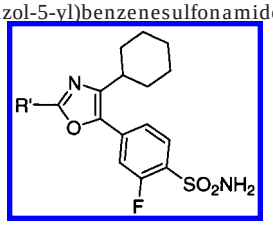
fluorine atom of compound **9d**. The COX-2 activity of **9d** was essentially the same as that of the parent compound **9a** (**9d**, $IC_{50} = 0.085\ \mu M$; **9a**, $IC_{50} = 0.07\ \mu M$). A marked phenomenon is the increase in COX-2 selectivity. Compound **9d** did not inhibit COX-1 up to 100 μM (17% inhibition at 100 μM). The COX-1/COX-2 ratio was increased from 679 (**9a**) to >1176 (**9d**).

To examine the generality of this phenomenon, we synthesized and tested compounds **10d** and **18d**, in which the cycloalkyl ring is replaced by phenyl or thienyl, respectively. Comparison of **10d** or **18d** with the corresponding parent compounds (**10a** or **18a**) showed that the COX-1 activities are decreased more than 10 times by introduction of a fluorine atom, whereas the COX-2 activities are virtually preserved.

The reason why the fluorine atom did not much affect the COX-2 activity but did increase the selectivity is not clear at present. Both hydrophobic (Me) and hydrophilic (OH and NH_2) groups diminished the activities, whereas only the smallest substituent, fluorine atom, is allowed in the case of COX-2 but not COX-1. It seems that the size of the substituent is important, although electronic effects of the substituent may also be influential. Basically, COX-2 and COX-1 do not exhibit a preference for a substituent group at this position, except for a fluorine atom in COX-2. COX-2 is considered to have a little more room at the site where the sulfonamide moiety binds. It is not known if the same effect of the fluorine atom can be seen in other vicinal diaryl heterocycles.

Next, we examined the effect of the substituent at the 2-position of the oxazole ring. The results are shown in Table 2. Instead of the methyl group of compound **9d**, an ethyl (**21a**) and an isopropyl (**21b**) group were introduced. As seen in Table 2, the COX-2 activities are decreased gradually in proportion to the size of the substituent. But interestingly, the COX-1 activities are enhanced as the substituent becomes bulkier. Conse-

Table 2. In Vitro Human COX-2[a] and COX-1[b] Enzyme Inhibitory Concentrations of 4-(4-Cyclohexyloxazol-5-yl)benzenesulfonamide Derivatives



compd	R	COX-2 IC_{50} (μM)[c]	COX-1 IC_{50} (μM)[c]	selectivity COX-1/COX-2
9d	Me	0.085	>100	>1176
21a	Et	0.12	47	392
21b	*i*-Pr	0.60	29.7	50

[a] Human recombinant COX-2 enzyme. [b] Human COX-1 enzyme from human platelets. [c] Values are means of at least three experiments.

Table 3. In Vivo Pharmacological Properties of 4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide **9d**

	9d	indomethacin	celecoxib
rat carrageenan paw edema[a] ED_{30} (mg/kg, po)	4.7	1.6	2.8
rat adjuvant-induced arthritis[b] ED_{50} (mg/kg, po)	1.8	0.13	0.37[f]
rat hyperthermia[c] ED_{50} (mg/kg, po)	3.9	1.4	
rat hyperalgesia[d] ED_{50} (mg/kg, po)	4.4	3.1	
rat gastric ulcerogenic activity[e] UD_{50} (mg/kg, po)	>300	3.4	>200[f]

[a] See ref 24. [b] See ref 25. [c] Rat yeast-induced hyperthermia model, see ref 24. [d] Rat yeast-induced hyperalgesia model using Randall−Selitto method, see ref 24. [e] See ref 24. [f] Data taken from the literature (ref 11).

quently, a methyl group is best for both COX-2 potency and selectivity.

As the best compound in this study, we chose compound **9d** for further evaluation. The in vivo pharmacological activities of **9d** were reported previously[24,25] and are summarized in Table 3. Compound **9d** showed good oral activities for several inflammation models such as rat carrageenan paw edema model (acute model) and rat adjuvant arthritis model (chronic model), and showed no acute ulcerogenic toxicity in rats at doses up to 300 mg/kg, po.

Conclusion

We have synthesized a series of 4-(4-cycloalkyl/aryloxazol-5-yl)benzenesulfonamide derivatives and evaluated for their COX-2 and COX-1 inhibitory activities. First, the cyclohexyl ring was found to be more selective than the aromatic rings at the 4-position of the oxazole ring. Second, a study of the substituent effect at the *ortho* position to the sulfonamide group on the phenyl ring showed most substituents diminished or lost both COX-2 and COX-1 activities. However, the introduction of a fluorine atom at this position was found to preserve the COX-2 activity and thus enhance the COX-2 selectivity. Third, both COX-2 potency and selectivity are found to be higher, as the size of the substituent at the 2-position of the oxazole ring decreases. This study has led to the identification of the best compound **9d**, which showed a good potency for COX-2 with very high COX-2 selectivity (COX-1/COX-2 > 1176) in vitro and good oral antiinflammatory activities with low GI toxicity. Compound **9d** is currently in phase II clinical trials for the treatment of rheumatoid arthritis, osteoarthritis, and acute pain.

Experimental Section

Biological Methods. Expression and purification of human COX-1 and recombinant human COX-2 enzymes as well as in vitro COX-2 and COX-1 enzyme assays have been described previously.[26] The in vivo pharmacological effects and rat ulcerogenic toxicity study of compound **9d** were published previously. [24,25]

Chemistry. Melting points were determined using a Yanagimoto micro melting point apparatus or a Mettler-Toledo FP62 melting point instrument and are uncorrected. Proton nuclear magnetic resonance specrta (^{1}H NMR) were recorded on a JEOL JNM-A300W or Bruker AMX-300 spectrometers in the solvent indicated. Chemical shifts (δ) are reported in parts per million relative to internal standard tetramethylsilane. Elemental analysis was performed with a Perkin-Elmer 2400 Series II CHNS/O analyzer, and all values were within $\pm$0.4% of the calculated values.

4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide (9d). Step 1: Preparation of Cyclohexyl 3-Fluorobenzyl Ketone (3d). To a suspension of zinc powder (17.98 g, 275.0 mmol) and tetrakis(triphenylphosphin)palladium(0) (2.00 g, 1.73 mmol) in 1,2-dimethoxyethane (DME, 50 mL) was added a solution of cychohexanecarbonyl chloride (**2d**, 20.00 g, 136.4 mmol) in DME (50 mL) at room temperature under nitrogen atmosphere. To this mixture was added a solution of 3-fluorobenzybromide (**1d**, 26.00 g, 137.5 mmol) in DME (100 mL) dropwise in 2 h with cooling by an ice−water bath. The reaction mixture was stirred for 2 h with cooling and then for 2 h at room temperature. The insoluble material was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in AcOEt (200 mL). The solution was washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine and was dried over Na_2SO_4. Filtration and evaporation of the solvent gave **3d** (29.30 g) as a crude oil: ^{1}H NMR ($CDCl_3$) δ 1.2−1.4 (m, 5H), 1.6−1.8 (m, 5H), 2.43 (m, 1H), 3.72 (s, 2H), 6.88−6.97 (m, 3H), 7.28 (dt, J = 6.1, 7.7 Hz, 1H).

Step 2: Preparation of 2-Cyclohexyl-1-(3-fluorophenyl)-2-oxoethyl Acetate (5d). To a solution of **3d** (29.20 g) obtained above in AcOH (300 mL) was added lead tetraacetate (75.00 g, 152.2 mmol). The solution was heated at reflux temperature for 1.5 h. The solvent was removed by evaporation in vacuo. The residue was diluted with AcOEt, washed with water, saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 9/1) gave 18.30 g (47% from **2d**) of **5d** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.1−1.4 (m, 5H), 1.6−1.8 (m, 4H), 1.97 (m, 1H), 2.17 (s, 3H), 2.44 (m, 1H), 6.06 (s, 1H), 7.06−7.13 (m, 2H), 7.19 (d, J = 6 Hz, 1H), 7.37 (dt, J = 6.1, 7.7 Hz, 1H).

Step 3: Preparation of 4-Cyclohexyl-5-(3-fluorophenyl)-2-methyloxazole (7d). A solution of **5d** (18.00 g) and NH_4OAc (15.00 g, 194.6 mmol) in AcOH (100 mL) was heated at reflux temperature for 5 h. The solvent was removed by evaporation in vacuo. The residue was diluted with AcOEt, washed with water, saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. Filtration and concentration in vacuo gave 17.20 g of **7d** as a crude oil: ^{1}H NMR ($CDCl_3$) δ 1.2−1.4 (m, 4H), 1.6−1.9 (m, 6H), 2.45 (s, 3H), 2.79 (tt, J = 3.6, 11.4 Hz, 1H), 6.99 (ddt, J = 1, 2.6, 8.4 Hz, 1H), 7.24 (ddd, J = 1, 3, 10 Hz, 1H), 7.31 (dt, J = 8.1, 1.2 Hz, 1H), 7.39 (dt, J = 5.7, 8.1 Hz, 1H).

Steps 4 and 5: Preparation of 4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide (9d). To a solution of **7d** (17.00 g) obtained above in $CHCl_3$ (80 mL) was added chlorosulfonic acid (27 mL, 406 mmol) dropwise with cooling by an ice−water bath. The solution was heated at

reflux temperature for 3 h and poured in ice. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo gave 20.31 g (87%) of the sulfonyl chloride as a crude solid: ^{1}H NMR ($CDCl_3$) δ 1.4 (m, 3H), 1.7−1.9 (m, 7H), 2.62 (s, 3H), 2.84 (tt, J = 3.6, 11.4 Hz, 1H), 7.46 (m, 2H), 8.02 (dd, J = 6, 7 Hz, 1H).

To a solution of the sulfonyl chloride (10.00 g) obtained above in THF (40 mL) was added 28% aqueous NH_3 at room temperature. The solution was stirred for 1 h and concentrated in vacuo. The residue was dissolved in AcOEt, washed with water and brine, and dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 6/1) gave 5.74 g (61%) of **9d** as a white solid: mp 166−167 °C; ^{1}H NMR ($CDCl_3$) δ 1.3−1.5 (m, 3H), 1.6−1.9 (m, 7H), 2.51 (s, 3H), 2.79 (tt, J = 3.7, 11.3 Hz, 1H), 5.11 (s, 2H), 7.36−44 (m, 2H), 7.94 (t, J = 7.9 Hz, 1H). Anal. ($C_{16}H_{19}FN_2O_3S$) C, H, N.

The following compounds were prepared by using the general procedure described above.

4-(4-Cyclohexyl-2-methyloxazol-5-yl)benzenesulfonamide (9a): mp 184.5−186.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.2−1.5 (m, 3H), 1.55−2.0 (m, 7H), 2.51 (s, 3H), 2.80 (m, 1H), 4.94 (broad s, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 8.6 Hz, 2H). Anal. ($C_{16}H_{20}N_2O_3S$) C, H, N.

4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-chlorobenzenesulfonamide (9b): mp 200−201 °C; ^{1}H NMR ($CDCl_3$) δ 1.28−1.44 (m, 4H), 1.62−1.92 (m, 6H), 2.51 (s, 3H), 2.78 (m, 1H), 5.18 (s, 2H), 7.53 (dd, J = 1.6, 8.4 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H). Anal. ($C_{16}H_{19}ClN_2O_3S$) C, H, N.

4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-methylbenzenesulfonamide (9c): mp 183−184 °C; ^{1}H NMR ($CDCl_3$) δ 1.3−1.5 (m, 3H), 1.7−1.9 (m, 7H), 2.50 (s, 3H), 2.73 (m, 1H), 4.92 (s, 2H), 7.43−7.49 (m, 2H), 8.05 (d, J = 8.3 Hz, 1H). Anal. ($C_{17}H_{22}N_2O_3S$) C, H, N.

4-[4-(4-Fluorophenyl)-2-methyloxazol-5-yl]benzenesulfonamide (10a): mp 207−208 °C; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 4.83 (s, 2H), 7.10 (t, J = 8.7 Hz, 2H), 7.58 (dd, J = 5.4, 8.8 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.7 Hz, 2H). Anal. ($C_{16}H_{13}FN_2O_3S$) C, H, N.

4-[4-(4-Fluorophenyl)-2-methyloxazol-5-yl]-2-fluorobenzenesulfonamide (10d): mp 208 °C; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 5.07 (s, 2H), 7.14 (t, J = 8.8 Hz, 1H), 7.36 (dd, J = 1.5, 11.0 Hz, 2H), 7.47 (dd, J = 1.8, 7.7 Hz, 1H), 7.59 (dd, J = 5.5, 8.8 Hz, 2H), 7.88 (t, J = 7.7 Hz, 1H). Anal. ($C_{16}H_{12}F_2N_2O_3S$) C, H, N.

2-Benzyloxy-4-(4-cyclohexyl-2-methyloxazol-5-yl)benzenesulfonamide (11). To a suspension of NaH (355 mg, 60%, 8.88 mmol) in DMF (5 mL) was added a solution of benzyl alcohol in DMF (2 mL) dropwise with cooling by an ice−water bath. The solution was stirred for 15 min, followed by the addition of **9d** in DMF (5 mL). The solution was heated at 80 °C for 3 h. After cooling, the solution was poured into water and extracted with AcOEt. The AcOEt layer was separated, washed with 1 N aqueous HCl and saturated aqueous $NaHCO_3$, and was dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 3/2) gave 632 mg (50%) of **11** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.2−1.4 (m, 3H), 1.5−1.8 (m, 7H), 2.42 (s, 3H), 2.68 (m, 1H), 5.47 (s, 2H), 7.13−7.21 (m, 4H), 7.30 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 7.8 Hz, 1H).

4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-hydroxybenzenesulfonamide (12). To a suspension of **11** (618 mg, 1.45 mmol) in AcOH (2 mL) was added 33% HBr/AcOH (0.5 mL). The solution was heated at 80 °C for 1 h. After cooling to the ambient temperature, 10 mL of ether was added to give a precipitate. The mixture was stirred for 30 min, and the precipitate was collected by filtration to give a crude solid (538 mg). The solid was crystallized from EtOH−ether and collected by filtration to give 463 mg (95%) of **12** as a white crystal: mp 208−209 °C; ^{1}H NMR (DMSO-d_6) δ 1.2−1.5 (m, 3H), 1.5−1.8 (m, 7H), 2.44 (s, 3H), 2.80 (m, 1H), 6.98 (s, 2H), 7.07 (dd, J = 1.6, 8.2 Hz, 1H), 7.17 (d, J = 1.6 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 10.87 (s, 1H). Anal. ($C_{16}H_{20}N_2O_4S$) C, H, N.

4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-methoxybenzenesulfonamide (13). To a suspension of **12** (197 mg, 0.586 mmol) in acetone (5 mL) was added K_2CO_3 (89 mg, 0.64 mmol) and MeI (80 μL, 1.3 mmol). The mixture was heated at reflux temperature for 2 h. The reaction solution was diluted with AcOEt, washed with water, 1 N aqueous HCl, and saturated aqueous $NaHCO_3$, and was dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 2/3) gave a solid, which was triturated in ether and collected by filtration to give 98 mg (48%) of **13** as a white solid: mp 198−199 °C; ^{1}H NMR (DMSO-d_6) δ 1.1−1.4 (m, 3H), 1.5−1.8 (m, 7H), 2.46 (s, 3H), 2.80 (m, 1H), 3.97 (s, 3H), 7.14−7.20 (m, 4H), 7.81 (d, J = 8.3 Hz, 1H). Anal. ($C_{17}H_{22}N_2O_4S$) C, H, N.

2-Amino-4-(4-cyclohexyl-2-methyloxazol-5-yl)benzenesulfonamide (15). To a solution of **9d** (1.05 g, 3.12 mmol) in DMF (10 mL) was added K_2CO_3 (474 mg, 3.43 mmol) and benzylamine (1.74 mL, 15.9 mmol). The mixture was heated at 150 °C for 4 h. The reaction mixture was diluted with AcOEt and washed with water, 10% aqueous citric acid and brine, and was dried over Na_2SO_4. Filtration, concentration in vacuo, and separation by silica gel flash chromatography (*n*-hexane/AcOEt = 1/1) gave 744 mg of a mixture of **9d** and **14** (2:1 by ^{1}H NMR) as a white solid.

A solution of the mixture obtained above (732 mg) in methanol (5 mL) was stirred under H_2 (atmospheric pressure) in the presence of 20% $Pd(OH)_2$/C (50 mg) at room temperature for 3 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel flash chromatography (*n*-hexane/AcOEt = 1/1) to give a solid (269 mg). The solid was crystallized from ether−hexane and collected by filtration to give 130 mg (13% from **9d**) of **15** as a white solid: mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 1.3−1.4 (m, 3H), 1.6−1.9 (m, 7H), 2.49 (s, 3H), 2.79 (tt, J = 3.8, 11.4 Hz, 1H), 4.94 (s, 4H), 6.96 (d, J = 1.5 Hz, 1H), 6.99 (dd, J = 1.5, 8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H). Anal. ($C_{16}H_{21}N_3O_3S$) C, H, N.

***N-tert*-Butyl-4-bromomethyl-2-benzenesulfonamide (16a).** To a solution of *tert*-butylamine (15.00 g, 205.1 mmol) and pyridine (30 mL, 371 mmol) in $CHCl_3$ (100 mL) was added a solution of *p*-toluenesulfonyl chloride (39.00 g, 204.6 mmol) in $CHCl_3$ (50 mL) dropwise with cooling by an ice−water bath. The solution was stirred overnight at room temperature. The solution was concentrated in vacuo, and the residue was dissolved in AcOEt. The solution was washed with water, 2 N aqueous HCl, and brine and was dried over Na_2SO_4. Filtration and concentration in vacuo gave a crude solid, which was triturated in ether. The precipitate was collected by filtration to give 20.05 g (43%) of *N*-*tert*-butyl-*p*-toluenesulfonamide.

To a suspension of the sulfonamide obtained above (5.00 g, 22.0 mmol) in CCl_4 (50 mL) was added *N*-bromosuccinimide (3.13 g, 17.6 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 100 mg, 0.619 mmol). The solution was heated at reflux temperature for 3 h. After cooling, the insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give a crude solid, which was purified by silica gel flash chromatography (*n*-hexane/AcOEt = 4/1) to give 4.17 g (62%) of **16a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 4.49 (s, 2H), 4.64 (s, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.3 Hz, 1H). Anal. ($C_{11}H_{16}BrNO_2S$) C, H, N.

***N-tert*-Butyl-4-bromomethyl-2-fluorobenzenesulfonamide (16d).** To a solution of *N*-*tert*-butyl-*p*-toluenesulfonamide prepared above (20.00 g, 87.98 mmol) in THF (120 mL) was added a solution of *n*-butyllithium in *n*-hexane (1.6 M, 121 mL, 194 mmol) dropwise at −40 to −30 °C. After completion of the addition, the solution was stirred for 2 h, followed by the addition of a solution of *N*-fluorobenzenesulfonimide (33.30 g, 105.6 mmol) in THF (70 mL). The solution was stirred for 3 h, and saturated aqueous NH_4Cl was added. The solution was extracted with AcOEt, washed with water and brine, and dried over Na_2SO_4. Filtration, concentra-

tion in vacuo, and separation by silica gel flash chromatography (*n*-hexane/AcOEt = 4/1) gave 16.06 g (74%) of *N*-*tert*-butyl-2-fluoro-4-methylbenzenesulfonamide as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 2.42 (s, 3H), 4.68 (s, 1H), 6.99 (d, J = 11 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H).

To a suspension of the sulfonamide obtained above (15.00 g, 61.15 mmol) in CCl_4 (150 mL) was added *N*-bromosuccinimide (10.00 g, 56.18 mmol) and AIBN (0.50 g, 3.04 mmol). The solution was heated at reflux temperature for 3 h. After cooling, the insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give a crude solid, which was purified by silica gel flash chromatography (*n*-hexane/AcOEt = 4/1) to give 11.14 g (59%) of **16d** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 4.45 (s, 2H), 4.72 (s, 1H), 7.22−7.28 (m, 2H), 7.88 (d, J = 7.8 Hz, 1H). Anal. ($C_{11}H_{15}BrFNO_2S$) C, H, N.

***N*-*tert*-Butyl-4-[2-methyl-4-(5-methylthien-2-yl)-oxazol-5-yl]benzenesulfonamide (17a).** Compound **17a** was prepared from **16a** using the procedure described above for **9d** (steps 1−3) in 11% yield: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 4.45 (s, 2H), 4.72 (s, 1H), 7.22−7.28 (m, 2H), 7.88 (d, J = 7.8 Hz, 1H).

***N*-*tert*-Butyl-2-fluoro-4-[2-methyl-4-(5-methylthien-2-yl)-oxazol-5-yl]benzenesulfonamide (17d).** Compound **17d** was prepared from **16d** using the procedure described above for **9d** (steps 1−3) in 20% yield: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 2.53 (S, 3H), 2.55 (S, 3H), 4.73 (s, 1H), 6.74 (d, J = 3 Hz, 1H), 7.16 (d, J = 3 Hz, 1H), 7.55 (d, J = 11.7 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.89 (t, J = 8.4 Hz, 1H).

2-Fluoro-4-[2-methyl-4-(5-methylthien-2-yl)-oxazol-5-yl]benzenesulfonamide (18d). A solution of **17d** (500 mg, 1.22 mmol) in CF_3COOH was heated at 50 °C for 4 h. The solution was concentrated in vacuo, and the residue was dissolved in AcOEt. The solution was washed with saturated aqueous $NaHCO_3$ and brine and was dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 2/1) gave 385 mg (90%) of **18d** as a white solid: mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (d, J = 1.2 Hz, 3H), 2.55 (S, 3H), 5.08 (s, 2H), 6.73 (m, 1H), 7.16 (d, J = 3 Hz, 1H), 7.58 (dd, J = 1.5, 11 Hz, 1H), 7.63 (dd, J = 1.5, 8.4 Hz, 1H), 7.89 (dd, J = 7.2, 8.4 Hz, 1H). Anal. ($C_{15}H_{13}FN_2O_3S_2$) C, H, N.

4-[2-Methyl-4-(5-methylthien-2-yl)-oxazol-5-yl]benzenesulfonamide (18a). Compound **18a** was prepared from **17a** using the procedure described for **18d** in 85% yield: mp 164−165 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (d, J = 1.1 Hz, 3H), 2.55 (S, 3H), 4.86 (s, 2H), 6.71 (m, 1H), 7.14 (d, J = 3.7 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H). Anal. ($C_{15}H_{14}N_2O_3S_2$) C, H, N.

4-(4-Cyclohexyl-2-ethyloxazol-5-yl)-2-fluorobenzenesulfonamide (21a). Step 1: Preparation of 2-Cyclohexyl-1-(3-fluorophenyl)-2-oxoethyl Propionate (19a). To a solution of **3d** (5.00 g, 22.7 mmol) in toluene (30 mL) was added a solution of Br_2 (3.6 g, 22.5 mmol) in $CHCl_3$ (5 mL) dropwise at room temperature. The solution was stirred for 30 min and poured in saturated aqueous $NaHCO_3$. AcOEt was added to the solution, and the organic layer was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ again and brine and was dried over Na_2SO_4. Evaporation of the solvent in vacuo gave 6.95 g of α-bromoketone as a crude oil. The α-bromoketone was dissolved in EtOH (60 mL). A total of 3.82 g (34.1 mmol) of propionic acid potassium salt was added to the solution. The solution was heated at reflux temperature for 2 h. The solution was concentrated in vacuo, and the residue was dissolved in AcOEt. The solution was washed with water and brine and was dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 9/1) gave 1.88 g (28%) of **19a** as an colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.5 Hz, 3H), 1.1−1.4 (m, 5H), 1.6−1.8 (m, 4H), 2.0 (m, 1H), 2.3−2.4 (m, 1H), 2.45 (q, J = 7.5 Hz, 2H), 6.06 (s, 1H), 7.05−7.15 (m, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.37 (dt, J = 6.1, 7.7 Hz, 1H).

Step 2: Preparation of 4-Cyclohexyl-5-(3-fluorophenyl)-2-ethyloxazole (20a). Compound 20a was prepared from **19a** using the procedure described for **9d** (step 3) in 84% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.2−1.4 (m, 4H), 1.36 (t, J = 7.6 Hz), 1.6−1.9 (m, 6H), 2.8 (m, 1H), 2.82 (q, J = 7.6 Hz, 1H), 6.99 (dt, J = 2.2, 8.3 Hz, 1H), 7.22−7.41 (m, 3H).

Steps 3 and 4: Preparation of 4-(4-Cyclohexyl-2-ethyloxazol-5-yl)-2-fluorobenzenesulfonamide (21a). Compound **21a** was prepared from **20a** using the procedure described for **9d** (steps 4 and 5) in 51% yield: mp 154−155 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.8 Hz, 3H), 1.3−1.4 (m, 3H), 1.6−1.9 (m, 7H), 2.8 (m, 1H), 2.84 (q, J = 8.7 Hz, 3H), 5.10 (s, 2H), 7.37−44 (m, 2H), 7.94 (t, J = 7.8 Hz, 1H). Anal. ($C_{17}H_{21}FN_2O_3S$) C, H, N.

4-(4-Cyclohexyl-2-isopropyloxazol-5-yl)-2-fluorobenzenesulfonamide (21b). Compound **21b** was prepared from **3d** using the procedure described for **21a** in 15% yield. In this case, 2-methylpropionic acid potassium salt was used instead of propionic acid potassium salt in step 1: mp 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 6.9 Hz, 6H), 1.3−1.4 (m, 3H), 1.7−1.9 (m, 7H), 2.79 (m, 1H), 3.13 (heptad, J = 6.9 Hz, 1H), 5.08 (s, 2H), 7.36−44 (m, 2H), 7.94 (t, J = 7.8 Hz, 1H). Anal. ($C_{18}H_{23}FN_2O_3S$) C, H, N.

References

(1) A part of this work was presented earlier: Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. Potent and Selective COX-2 Inhibitors. The 214th National Meeting of the American Chemical Society, Las Vegas, NV, September 1997; MEDI 90.

(2) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. Expression of a Mitogen-response Gene Encoding Prostaglandin Synthesis is Regulated by mRNA Splicing. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692−2696.

(3) Kujubu, D. A.; Fletcher, B. S.; Varnum, B. C.; Lim, R. W.; Herschman, H. R. TIS10, a Phorbol Ester Tumor Promotor-inducible mRNA from Swiss 3T3 Cells, Encodes a Novel Prostaglandin Synthase/ Cyclooxygenase Homologue. *J. Biol. Chem.* **1991**, *266*, 12866−12872.

(4) Hla, T.; Neilson, K. Human Cyclooxygenase-2 cDNA. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7384−7388.

(5) Vane, J. Towards a better aspirin. *Nature* **1994**, *367*, 215−216.

(6) Masferrer, J. L.; Zweifel, B. S.; Manning, P. T.; Hauser, S. D.; Leahy, K. M.; Smith, W. G.; Isakson, P. C.; Seibert, K. Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3228−3232.

(7) For a review, see: Reitz, D. B.; Seibert, K. Selective Cyclooxygenase Inhibitors. *Annu. Rep. Med. Chem.* **1995**, *30*, 179−188.

(8) For a review, see: Prasit, P.; Riendeau, D. Selective Cyclooxygenase-2 Inhibitors. *Annu. Rep. Med. Chem.* **1997**, *32*, 211−220.

(9) Tally, J. J. Selective Inhibitors of COX-2. In *Progress in Medicinal Chemistry 36*; King, F. D., Oxford, A., Eds.; Elsevier: Amsterdam, 1999; pp 201−234.

(10) For a review, see: Dannhardt, G.; Kiefer, W. Cyclooxygenase inhibitors − Current status and future prospects. *Eur. J. Med. Chem.* **2001**, *36*, 109−126.

(11) Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, 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.; Cogburn, 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]benzenesulfonamide (SC-58635, Celecoxib). *J. Med. Chem.* **1997**, *40*, 1347.

(12) Prasit, P.; Wang, Z.; Brideau, 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.; Leger, 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.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. The discovery of rofecoxib, [MK 966, Vioxx, 4-(4′-methylsulfonylphenyl)-3-phenyl-2 (*5H*)-furanone], an orally active cyclooxygenase-2 inhibitor. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.

(13) Jackson, L. M.; Hawkey, C. J. Gastrointestinal effects of COX-2 Inhibitors. *Expert Opin. Invest. Drugs* **1999**, *8*, 963−971.

(14) *Scrip* **2000**, *2554*, 20.

(15) Haruta, J.; Hashimoto, H.; Matsushita, M. Patent JP-8325249, 1996.

(16) Haruta, J.; Hashimoto, H.; Matsushita, M. Patent WO9619463, 1996.

(17) Hashimoto, H.; Maeda, K.; Ozawa, K.; Haruta, J.; Wakitani, K. 4-Aryl/Cycloalkyl-5-Phenyloxazole Derivatives as Selective COX-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 65−68.
(18) Norman, B. H.; Lee, L. F.; Masferrer, J. L.; Talley, J. J. Patent WO9427980, 1994.
(19) 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.
(20) Sato, T.; Naruse, K.; Enokiya, M.; Fujisawa, T. Facile Synthesis of Benzyl Ketones by the Reductive Coupling of Benzyl Bromide and Acyl Chorides in the Presence of a Palladium Catalyst and Zinc Powder. *Chem. Lett.* **1981**, 1135−1138.
(21) Mee, A.; Robertson, A.; Whalley, W. B. The Chemistry of the "Insoluble Red" Woods. VIII. The Synthesis of Analogous Anhydro-7-hydroxybenzopyranols and a Note on the Oxidation of Deoxybenzoins. *J. Chem. Soc.* **1957**, 3093.
(22) Davidson, D.; Weiss, M.; Jelling, M. The Action of Ammonia on Benzoin. *J. Org. Chem.* **1937**, *2*, 328−334.
(23) 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-(*5H*)-furanone]: A potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and biochemical profiles. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 551−560.
(24) Matsushita, M.; Masaki, M.; Yagi, Y.; Tanaka, T.; Wakitani, K. Pharmacological profile of JTE-522, a novel prostaglandin H synthase-2 inhibitor, in rats. *Inflamm. Res.* **1997**, *46*, 461−466.
(25) Masaki, M.; Matsushita, M.; Wakitani, K. Inhibitory effects of JTE-522, a novel prostaglandin H synthase-2 inhibitor, on adjuvant-induced arthrits and bone changes in rats. *Inflamm. Res.* **1998**, *47*, 187−192.
(26) Wakitani, K.; Nanayama, T.; Masaki, M.; Matsushita, M. Profile of JTE-522 as a Human Cyclooxygenase-2 Inhibitor. *Jpn. J. Pharmacol.* **1998**, *78*, 365−371.

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