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2,2-Dimethyl-4,5-diaryl-3(2*H*)furanone Derivatives as Selective Cyclo-oxygenase-2 Inhibitors

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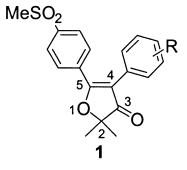
Abstract—A series of 2,2-dimethyl-5-{4-(methylsulfonyl)phenyl}-4-phenyl-3(2*H*)furanones was prepared and evaluated for their ability to inhibit cyclo-oxygenase-2 (COX-2)

Introduction

There are at least two kinds of cyclo-oxygenases.[1] Cyclo-oxygenase-1 (COX-1) is constitutively expressed in the gastro-intestinal tract and the kidney. COX-1 is known to be responsible for the maintenance of physiological homeostasis, such as gastrointestinal integrity and renal function. Interruption of COX-1 activity can lead to life-threatening gastro-intestinal toxicity of perforation, ulceration and bleeding. In the meantime, cyclooxygenase-2 (COX-2) is induced upon inflammatory stimuli and is responsible for progression of inflammation. Thus, selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastro-intestinal toxicities when compared with traditional non-steroidal antiinflammatory drugs (NSAIDs).[2]



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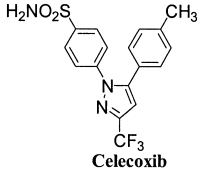
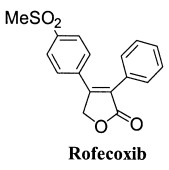


Celecoxib



Rofecoxib

Even though blockbuster COX-2 inhibitors such as celecoxib[3] and rofecoxib[4] are considered to have resolved the gastro-intestinal toxicities of traditional NSAIDs to a large extent, there are still strong demands for a COX-2 inhibitor with improved efficacy and safety profiles. For example, a high daily dosing level of celecoxib would be a metabolic burden for the elderly, who are often metabolically insufficient. Recently, rofecoxib experienced negative comment regarding its cardiovascular adverse effects.[5]

Phenyl sulfone-containing *cis*-1,2-diaryl-alkenes or their structural equivalents are known to be a pharmacophore for achieving selective COX-2 inhibition over COX-1.[6] In this paper will be presented a novel class of 2,2-dimethyl-4,5-diaryl-3(2*H*)furanones (**1**), which are orally active, highly potent and selective COX-2 inhibitors.

Synthesis

A synthetic route for 4,5-diaryl-3(2*H*)furanones (**1**) is outlined in Scheme 1. 4-(Methylthio)benzaldehyde was coupled with the in situ generated lithium acetylenide of **2** to afford diol **3**. The benzylic hydroxyl group of **3** was then smoothly oxidized to the corresponding ketone **4** with manganese dioxide (MnO_2).[7] The acyclic ketone **4** was cyclized to give 5-aryl-2,2-dimethyl-3(2*H*)-furanone **5** by using diethylamine as a catalyst in methanol as described previously.[8] The oxidation of **5** by OXONE was followed by a halogenation reaction either with bromine in acetic acid or with iodine, in the presence of a catalytic amount of BTI ({bis(trifluoroacetoxy)iodo}benzene),[9] to afford the corresponding bromide or iodide compound **6**, respectively. The halide **6** was finally subjected to Suzuki coupling reaction with an appropriate arylboronic acid to give diaryl compound **1**.[10] Synthetic details for Scheme 1 can be found in ref 11.

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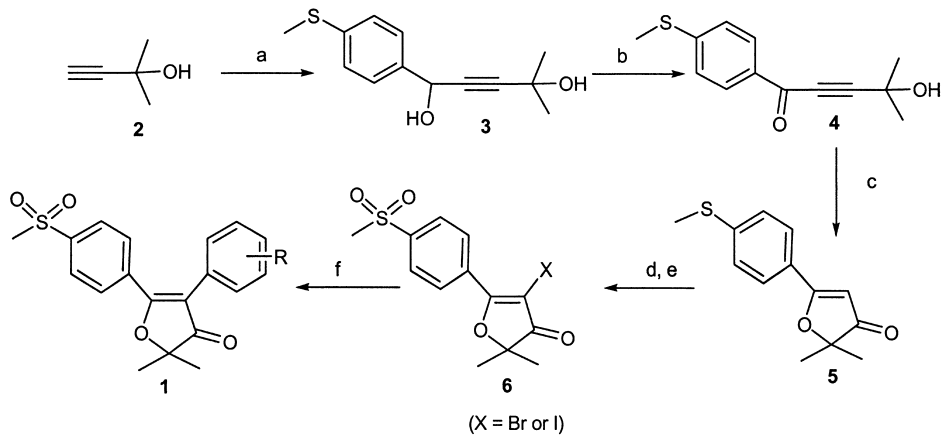

Scheme 1. Reaction conditions: (a) (i) *n*-BuLi (2.2 equiv)/THF, −78°C; (ii) 4-(methylthio)benzaldehyde, 81%; (b) MnO_2/CH_2Cl_2, 81%; (c) $(Et_2)NH/CH_3OH$, 75%; (d) Oxone®/$THF/CH_3OH/H_2O$; (e) $Br_2/AcOH/CH_2Cl_2$, 86% two steps or cat. $BTI/I_2/CCl_4$, 82% two steps; (f) arylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$/toluene–EtOH (3:1), Δ.

Results and Discussion

Compounds of this study were evaluated for their ability to inhibit COX-2 and COX-1 by using freshly harvested mouse peritoneal macrophages as described in the literature.[12] The results of inhibition are summarized in Table 1. As shown in Table 1, 4,5-diaryl-3(2*H*)furanone derivatives inhibit COX-2 selectively over COX-1 and most of the compounds possess COX-2/COX-1 selectivity over 100-fold.

The in vivo oral antiinflammatory activities of 3(2*H*)-furanone derivatives were evaluated by the inhibition of carrageenan-induced rat paw edema according to the literature.[13] Table 2 indicates that 3(2*H*)furanone derivatives of this study are orally active with antiinflammatory potency comparable to celecoxib.

When 3(2*H*)furanone derivatives were evaluated by adjuvant arthritis test,[14] impressively strong oral activities were observed for some of the furanones, far exceeding that of celecoxib (Table 3 and Fig. 1). Since adjuvant arthritis is a more realistic animal model for human arthritis than carrageenan-induced rat paw edema, the pronounced activities of 3(2*H*)furanones in adjuvant arthritis need to be addressed.[15]

When rats were orally administered once daily with either **1h** or **1o** at 10 mg/kg/day for 4 weeks, there was no detectable evidence of gastric toxicity upon autopsy examinations of the stomach.[16] Thus, the 3(2*H*)furanone derivatives could be drug candidates without gastric adverse effects, which are frequently encountered with traditional NSAIDs.

Table 1. Inhibitory effects of 4,5-diaryl-2,2-dimethyl-3(2*H*)furanone (**1**) derivatives on COX-1 and COX-2 (mouse macrophage method)

Compound	R	IC_{50} (μg/mL)[a]		
		COX-2	COX-1	COX-2 selectivity over COX-1
1a	H	0.05	3	60
1b	2-CH_3	0.3	20	67
1c	2-OCH3	0.1	50	500
1d	2-Cl	0.3	50	167
1e	3-*iso*-Pr	0.03	30	1000
1f	3-Cl	0.01	2	200
1g	3-CF_3	0.05	3	60
1h	3-F	0.02	5	250
1i	3-$COCH_3$	0.05	50	1000
1j	4-*iso*-Pr	0.03	3	100
1k	4-*n*-Pr	0.02	3	150
1l	3-Cl, 5-Cl	0.03	3	100
1m	2-F, 5-F	0.03	20	667
1n	3-F, 4-F	0.05	5	100
1o	3-F, 5-F	0.03	20	667
1p	4-{$CH(OH)CH_3$}	0.3	50	167
Celecoxib		0.02	1.86	93
Rofecoxib		0.06	>100	>1667

[a]Each result is the average of at least two determinations.

Summary

A novel class of 2,2-dimethyl-4,5-diaryl-3(2*H*)furanone derivatives was synthesized and evaluated to be highly selective and potent COX-2 inhibitors. The pronounced oral antiinflammatory potency in adjuvant arthritis

Table 2. Inhibition data of 3(2*H*)furanones for carrageenan-induced paw edema in Sprague–Darley rats

Compound	% Inhibition[a]
1f	32
1g	32
1h	36
1o	34
Celecoxib	31

[a]Percent of inhibition at 3 mg/kg body weight by oral administration and inhibition values were determined using five animals/group.

Table 3. Therapeutic effects of the 3(2*H*)furanones on adjuvant arthritis in Sprague–Darley rats

Compound	Adjuvant arthritis ED_{50}[a] (mg/kg/day)
1g	0.06
1h	0.08
1o	0.03
Celecoxib	0.2

[a]ED_{50} values were determined using 7–8 animals/group per dose.

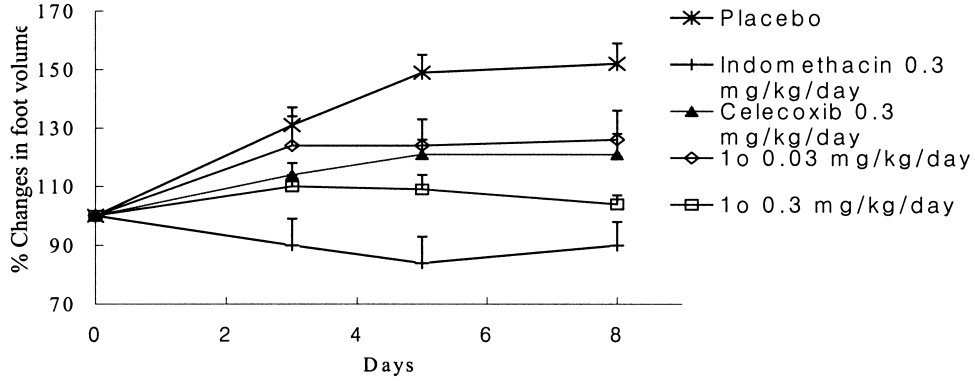

Figure 1. Dose-dependent inhibition of adjuvant arthritis (therapeutic model).

would place 2,2-dimethyl-4,5-diaryl-3(2*H*)furanones in a highly promising position for development of the next generation anti-arthritic medications.

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11. Compounds of Scheme 1 were prepared as follows.
4-Bromo-2,2-dimethyl-5-{4-(methylthio)phenyl}-3(2*H*)furanone. To a stirred solution of 2,2-dimethyl-5-{4-(methylthio)-phenyl}-3(2*H*)furanone (**5**, 58 mg) in 20 mL carbon tetrachloride, were added acetic acid (0.5 mL) and bromine (0.1 mL). The reaction solution was stirred at rt for 1 h. Then the reaction was quenched by adding 20 mL of saturated aqueous sodium thiosulfate solution. After removing the carbon tetrachloride in vacuo, the resulting residue was extracted with CH_2Cl_2, dried over $MgSO_4$ and then concentrated in vacuo. The resulting residue was chromatographed (SiO_2, hexane/ethyl-acetate, 2:1) to yield 69 mg (89%) of 4-bromo-2,2-dimethyl-5-{4-(methylthio)phenyl}-3(2*H*)furanone as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): 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.
4-Bromo-2,2-dimethyl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone (**6**). 4-Bromo-2,2-dimethyl-5-{4-(methylthio)phenyl}-3-(2*H*)furanone (42 mg) and 178 mg of Oxone were dissolved in 15 mL THF/15 mL ethanol/10 mL H_2O and stirred overnight at rt. Then the solvent was removed in vacuo. The resulting residue was extracted and then dried over $MgSO_4$. The organic layer was concentrated under reduced pressure and the resulting residue was subjected to column chromatographic separation (SiO_2, hexane/ethyl acetate, 2:1) to afford 45 mg (97%) of desired 4-bromo-2,2-dimethyl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone. Mp, 196–196.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 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*).
A typical Suzuki coupling reaction is described as follows to prepare 3(2*H*)furanone derivatives (**1**).
2,2-Dimethyl-4-(3-fluorophenyl)-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone (**1h**). To a stirred solution of 4-bromo-2,2-dimethyl-5-{4-(methylsulfonyl)phenyl}-3(2*H*)furanone (**6**, 170 mg) in 30 mL toluene and 10 mL ethanol, were added 25 mg of tetrakis(triphenylphosphine)palladium(0), 10 mL of saturated aqueous sodium bicarbonate, and 100 mg of 3-fluorobenzeneboronic acid. The reaction solution was stirred at 90 °C for 12 h. Then the solvent was removed under reduced pressure. The resulting residue was extracted with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. Then the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 120 mg (68%) of 2,2-dimethyl-4-(3-fluorophenyl)-5-{4-(methylsulfonyl)-phenyl}-3(2*H*)furanone (**1h**). Mp, 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 6H), 3.08 (s, 3H), 7.05 (m, 3H), 7.33 (m, 1H), 7.83 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H). IR (cm^{-1}): 3020, 1697, 1620, 1403, 1318, 1149, 958, 768. MS (FAB): 361 (m + 1).
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15. Even though the human daily dose for arthritic indications for a COX-2 inhibitor can be determined through human clinical trials, a certain degree of correlation is available between the human daily dose for arthritis and adjuvant arthritis ED_{50} of COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib, meloxicam, and so on. Adjuvant arthritis ED_{50} may serve as a measure for the human daily dose for arthritis. Since 3(2*H*)furanone derivatives **1g**, **1h** and **1o** possess appreciably higher activities of adjuvant arthritis than celecoxib, **1g**, **1h** and **1o** are likely to have daily arthritis doses far lower than celecoxib, which could be translated into a reduced metabolic burden to the elderly.

16. When **1h** and **1o** were orally administered to Sprague–Darley rats at 10 mg/kg, quaque die for 13 weeks, there was no observed evidence of renal anomalies. The renal functions appeared normal as indicated by serum biochemistry (BUN and creatinine) as well as histologic examinations of the kidneys. Considering renal safety of **1h** and **1o** in Sprague–Darley rats, **1h** and **1o** are not likely to have cardiovascular problems arising at least from renal malfunctions.