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A NEW STRUCTURAL VARIATION ON THE METHANESULFONYLPHENYL CLASS OF SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

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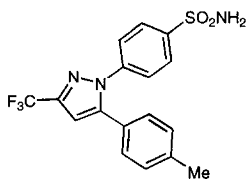
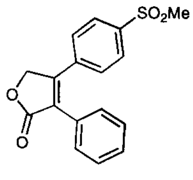
Abstract: By inserting an oxygen link between the 3-fluorophenyl and the lactone ring of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methanesulfonylphenyl)-2(5H)-furanone **1** (DFU), analogs with enhanced *in vitro* COX-2 inhibitory potency as well as *in vivo* potency in models of inflammation were obtained.

Introduction

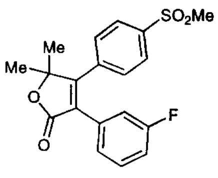
Selective cyclooxygenase-2 (COX-2) inhibitors[1] hold promise as a new generation of anti-inflammatory drugs with reduced side effects, particularly gastrointestinal toxicity, compared to current non-steroidal anti-inflammatory drugs (NSAIDs). This recognition is based on the observation that current NSAIDs inhibit both the constitutive cyclooxgenase-1 (COX-1) and the inducible cyclooxygenase-2 (COX-2). COX-1 is responsible for normal physiological functions, such as platelet aggregation, cytoprotection in the stomach, and maintenance of normal kidney function and COX-2 is associated with inflammatory conditions.[2] Recently, two compounds from this new class of anti-inflammatory drugs, celecoxib (Celebrex)[3] and rofecoxib (Vioxx)[4], have been approved by FDA. As part of our continuing efforts in exploring structural diversity of COX-2 inhibitors, we have discovered a related analog of rofecoxib, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methanesulfonylphenyl)-2(5H)-furanone **1** (DFU),[5] as a very potent and selective inhibitor. We now found that spacer units could be inserted between the 3-fluorophenyl and the lactone ring of **1** without significant loss of the *in vitro* COX-2 inhibitory potency. Herein we report our results on the identification of the oxygen atom as the optimal linking unit and the structure activity relationship (SAR) of this series.



Celecoxib (Celebrex)



Rofecoxib (Vioxx)



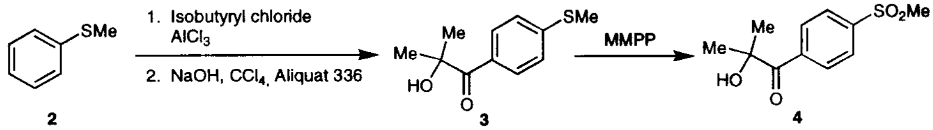
DFU (1)

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00559-4

Chemistry

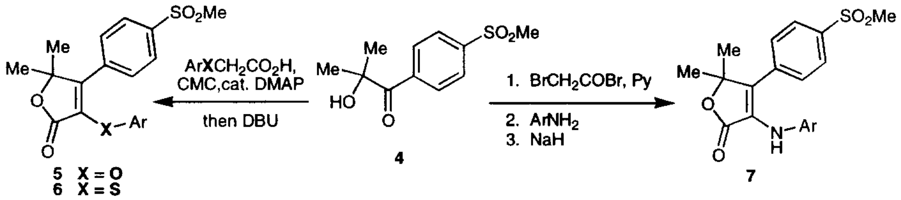
The methanesulfonylphenyl component was derived from the methyl sulfide intermediate **3**, which was prepared from the Friedel-Crafts reaction of thioanisole with isobutryl chloride, followed by α-hydroxylation;[6] or from the methyl sulfone intermediate **4**, which was obtained from the oxidation of sulfide **3** with magnesium monoperoxyphthalate (MMPP) (Scheme 1).

Scheme 1



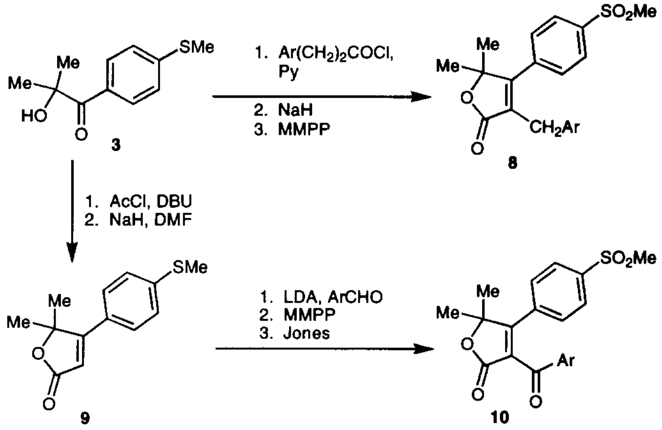
Syntheses of the various linker analogs were carried out as shown in Scheme 2 and Scheme 3. The oxygen-linked analog **5**, the sulfur-linked analog **6** and the nitrogen-linked analog **7** were prepared from the coupling of the sulfone intermediate **4** with appropriate carboxylic acids. The ester intermediates for the oxygen-linked and the sulfur-linked compounds were cyclized *in situ* with DBU at room temperature or under refluxing condition (Scheme 2). For the nitrogen-linked analog **7**, the ester intermediate was isolated and treated with sodium hydride in DMF to effect the cyclization and dehydration reactions (Scheme 2). The carbon-linked analog **8** was prepared from the sulfide intermediate **3** and the methyl sulfide group was then converted to the methyl sulfone by oxidation with MMPP (Scheme 3). In the case of the carbonyl-linked analog **10**, the C-3 anion derived from the treatment of lactone **9** with LDA was reacted with an aldehyde, followed by oxidation of the sulfide to sulfone and Jones oxidation of the hydroxyl intermediate to ketone **10** (Scheme 3).

Scheme 2



CMC = 1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate

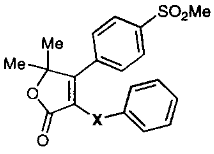
Scheme 3



Results and Discussion

Table 1 shows the *in vitro* potency of various linker analogs in stably transfected chinese hamster ovary (CHO) cell expressing human COX-2 and COX-1 whole cell assays,[7] as well as the human whole blood (HWB) COX-2 and COX-1 assays.[8] In terms of COX-2 inhibitory potency, the oxygen linker **5a** was clearly superior to the other linkers in the HWB COX-2 assay. Compound **5a** also showed a superior selectivity ratio in the HWB assay (HWB COX-1/HWB COX-2 = 115) relative to conventional NSAIDs such as indomethacin (HWB COX-1/HWB COX-2 = 0.4).

Table 1

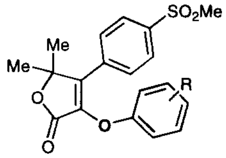


Compound	X	CHO COX-2 (IC_{50} μM)	CHO COX-1 (IC_{50} μM)	HWB COX-2 (IC_{50} μM)	HWB COX-1 (IC_{50} μM)
Indomethacin		0.026	0.018	0.5	0.2
5a	O	0.02	> 50	0.04	4.6
6a	S	0.07	> 50	1.5	58
7a	NH	0.5	n.d.	4.5	n.d.
8a	CH_2	0.3	n.d.	2.6	> 90
10a	CO	0.6	> 50	0.8	> 90

n.d. = not determined

More oxygen-linked analogs were then prepared to assess the potential of the series. Since many test compounds showed an $IC_{50} > 50$ μM in the CHO COX-1 assay and some encountered interference in the assay at high concentrations, a more sensitive U-937 microsomal COX-1 assay[9] at a low concentration of arachidonic acid was used to determine the potency of the test compounds against COX-1. Usually, compounds having an $IC_{50} > 1$ μM in the U-937 COX-1 assay were further studied in the HWB COX-1 assay. The results of these oxygen-linked analogs in the *in vitro* assays are summarized in Table 2.

Table 2



Compound	R	CHO COX-2 (IC_{50} μM)	U-937 COX-1 (IC_{50} μM)	HWB COX-2 (IC_{50} μM)	HWB COX-1 (IC_{50} μM)
Indomethacin		0.03	0.02	0.5	0.2
Celecoxib		0.002	0.05	1.0	6.3
Rofecoxib		0.02	2.0	0.5	19
1 (DFU)		0.04	14	0.3	> 70
5a	H	0.02	1 - 3	0.04	4.6
5b	3-F	0.02	1 - 3	0.07	23.1
5c	3,4-di F	0.01	1.0	0.06	7.9
5d	2,4-di F	0.02	< 0.3	0.04	<1.2
5e	4-F	0.02	< 0.7	0.05	3.6
5f	3,5-di F	0.04	1 - 5	0.18	10.0
5g	4-Cl	0.01	0.3 - 1	0.02	1.8
5h	4-Me	0.02	< 0.3	0.04	n.d.
5i	3-Me	0.02	0.3 - 1	0.28	3.2
5j	2-Me	0.02	< 0.3	0.10	n.d.

n.d. = not determined

All the compounds shown were very potent in the CHO COX-2 cell assay and that was only slightly shifted in the HWB COX-2 assay. They were also less potent against COX-1 in either the U-937 or the HWB COX-1 assays than the conventional NSAID indomethacin, but were more potent against COX-1 than the selective COX-2 inhibitor **1** (DFU) and rofecoxib. Monosubstitution with a halogen (**5b, 5e** and **5g**) or a methyl group (**5h**, **5i** and **5j**) on the 2-, 3-, or 4-position of the phenyl ring had no significant effect on the COX-2 inhibitory potency in either the CHO cell or the HWB assays. Disubstitution with fluorine on the 2,4-, (**5d**); 3,4-, (**5c**); and 3,5-, (**5f**) positions was also tolerated. On the other hand, positions of the substitutents had an important effect on both the selectivity and the pharmacokinetic properties of the compounds. Substitution on the 3-position of the phenyl ring seemed to provide enhanced selectivity in both the mono (**5b** vs **5e**; **5i** vs **5h** and **5j**) and disubstituted compounds (**5c** and **5f** vs **5d**). In terms of pharmacokinetics, analogs with a fluorine substitutent on the 4-position had superior plasma levels in the rats. For example, when dosed orally at 20 mg/kg in the rats, the 4-fluoro-substituted compound **5e** showed a C_{max} = 44 μM at 4h with 77% bioavailability and translated into good activity in the rat paw edema assay[10] with an ED_{50} = 0.5 mg/kg. The 3-fluoro-substituted compound **5b** only showed a C_{max} = 0.8 μM at 0.5h with 14% bioavailability, and therefore might be partly responsible for the poorer potency in the rat paw edema assay with an ED_{50} = 2.4 mg/kg. Addition of a 4-fluoro-substitutent to **5b** provided the 3,4-difluoro-substituted compound **5c** and significantly enchanced the bioavailability to 77% with a C_{max} = 26 μM at 2h. Compound **5c** has an excellent activity in the rat paw edema assay with an ED_{50} = 0.1 mg/kg. All of the methyl analogs had very poor bioavailability in the rats. Overall, the 3,4-difluoro-substituted analog **5c** was found to possess the most promising profile and was evaluated further in other *in vivo* models.

Compound **5c** was extremely potent in the *in vivo* efficacy animal models such as the rat paw edema assay (ED_{50} = 0.1 mg/kg), the rat pyresis assay[10] (ED_{50} = 0.5 mg/kg), the rat hyperalgesia assay[10] (ID_{50} = 1.3 mg/kg) and the rat adjuvant arthritis assay[11] (ED_{50} = 0.2 mg/kg). This compound was studied in the rat ^{51}Cr assay for GI toxicity and showed no loss of GI integrity at 100 mg/kg bid for 5 days.[10]

In summary, we have identified **5c** as a potent and selective COX-2 inhibitor with very good *in vitro* and *in vivo* activities. The linking oxygen atom between the 5,5-dimethyl-furan-2-one ring and the 3-substituent is well tolerated and provides compounds with excellent potency in the *in vitro* COX-2 assays, but the selectivity of these oxygen-linked phenyl analogs is somewhat inferior to the very selective COX-2 inhibitor **1** (DFU). Further investigations to improve the selectivity of these oxygen-linked analogs will be reported in the following paper.

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