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SAR IN THE ALKOXY LACTONE SERIES: THE DISCOVERY OF DFP, A POTENT AND ORALLY ACTIVE COX-2 INHIBITOR

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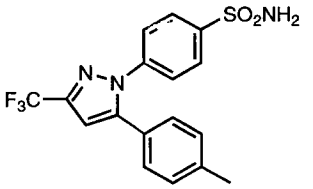
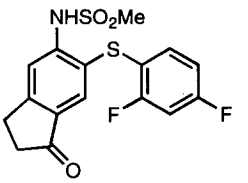
Abstract: Extensive SAR has been established in the alkoxy lactone series and this has lead to the discovery of DFP (5,5-dimethyl-3-(2-propoxy)-4-methanesulfonylphenyl)-2(5H)-furanone), a potent COX-2 inhibitor exhibiting in vivo efficacy in all models studied.

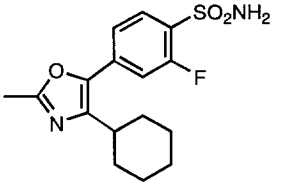
Cyclooxygenase is known to exist in two distinct isoforms, namely COX-1 and COX-2.[1] The constitutive isoform COX-1 is present in a variety of tissues, and is thought to be important in maintaining normal physiological functions such as gastric cytoprotection. COX-2 is the inducible isoform, which appears to play a major role in the inflammation cascade through the production of inflammatory prostaglandins.[2] It is well accepted that a selective COX-2 inhibitor will have the therapeutic effect of NSAIDS without the side effects



Celecoxib



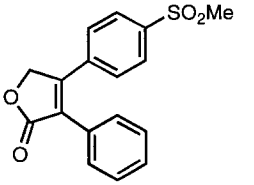
L-745,337



JTE-522

associated with nonselective COX inhibitors. Since the discovery that cyclooxygenase exists in two isoforms, several research groups have reported COX-2 selective inhibitors such as celecoxib,[3] L-745,337,[4] and JTE-522.[5]

In a previous paper we disclosed rofecoxib[6] as a potent COX-2 inhibitor that is equipotent to indomethacin in the COX-2 human whole blood assay (HWB).[7] In the COX-1 HWB assay, rofecoxib is nearly 100 times less potent than indomethacin. This compound shows good efficacy in animal models of inflammation and clinical efficacy in both dental pain and osteoarthritis studies.[8]



Rofecoxib

After the clinical trials started with rofecoxib, our group directed its attention to the search for a backup that was structurally different, yet had optimum selectivity and potency. This work lead to the discovery of DFU (**1**),[9] (see Scheme 1) a compound that is equipotent to rofecoxib against COX-2 but is ten times more selective based on HWB assays. More recently, it has been observed that when an oxygen atom is inserted between the

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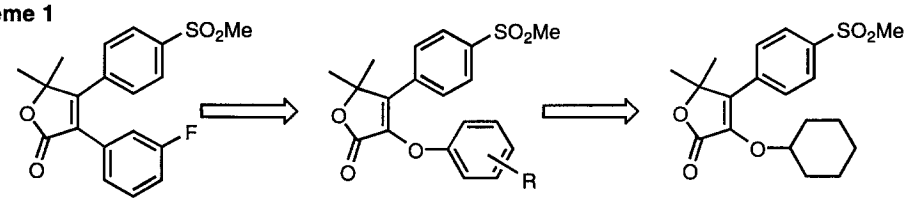
phenyl group and the lactone moiety (**2**), the activity is enhanced even further.[10] Therefore, we felt that exploring the alkoxy series as typified by the cyclohexyl analog **3** should also lead to selective inhibitors of COX-2. This paper describes our synthetic effort in the alkoxy lactone series as well as the SAR that lead to the identification of DFP.

Scheme 1

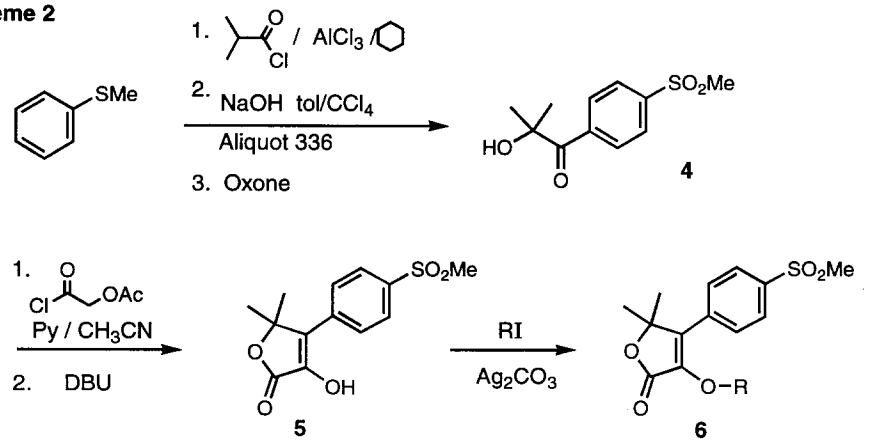


1 DFU **2** **3**

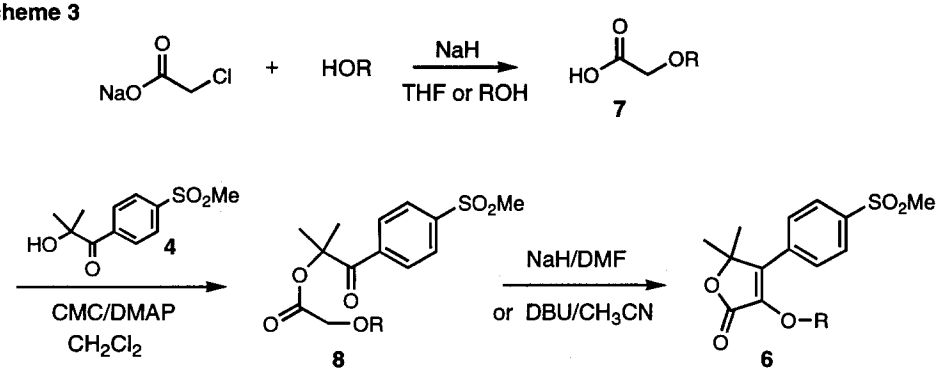
Chemistry

The oxygen link compounds were initially prepared as described in Scheme 2. Thioanisole was acylated with 2-methylpropionyl chloride, and the resulting tertiary centre was hydroxylated under phase transfer conditions. Treatment with Oxone® then afforded sulfone tertiary alcohol **4**. This alcohol was coupled with acetoxyacetyl chloride, followed by in situ cyclization with DBU to give hydroxy lactone **5**. Alkylation was then effected either by treatment with Ag_2CO_3/alkyl iodide in benzene, or with NaH/alkyl iodide in DMF to give the desired alkoxy lactone **6**. This approach was very substrate dependent, however, and gave poor yields in some cases. A more versatile approach is shown in Scheme 3. Alcohols were condensed with sodium chloroacetate to provide the 5-alkoxy acetic acid **7.** The acid was coupled with tertiary alcohol **4** with a carbodiimide to give ester **8** which was then treated with NaH in DMF or with DBU in CH_3CN to provide the corresponding lactone **6**. This method worked for primary, secondary, and tertiary alkyl groups.

Scheme 2



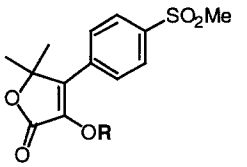
Scheme 3



Results

Table 1 shows the HWB data for representative examples from the alkoxy lactone series. The cyclohexyl analog **3** was found to be very potent against COX-2 (IC_{50} < 40 nM in COX-2 HWB assay). However, unlike the O-phenoxy series (**2**), this compound was found to be extremely selective (IC_{50} > 58 μM in COX-1 HWB assay). As expected, compound **3** was highly metabolized as are the cyclopentyl and cyclobutyl analogs **9** and **10**. To our surprise the cyclopropyl compound **11** was a relatively poor inhibitor of the COX-2 enzyme with an IC_{50} of 5.2 μM. This observation suggested that the SAR in that series is relatively tight. Subsequently, it was decided to explore acyclic analogs. The 2-butoxy and the 3-pentoxy analogs **12** and **13** were found to be very potent against COX-2. In addition, good COX-2 selectivity was preserved as exemplified by compound **12**. However, as observed in the cycloalkoxy series, these two analogs are still highly metabolized. In order to minimize the number of sites susceptible to metabolism, the methoxy **14** and ethoxy **15** analogs were prepared. These compounds with small alkoxy groups were found to be inactive against the COX-2 enzyme as was the cyclopropyloxy analog **11**. The variation in the IC_{50} from the active compounds **12** and **13** to the inactive **14** and **15** suggested that the isopropoxy compound **16** might be active. Indeed, the isopropoxy analog **16** was not only found to be active against COX-2 with an IC_{50} of 300 nM in the HWB assay, but was also very selective with an IC_{50} > 100 μM against COX-1. To complete the SAR in that series the methylene cyclopropyl and ethylene cyclopropyl analogs **17** and **18** were also prepared and were potent against COX-2, with selectivity comparable to the isopropoxy compound **16**. However, given the high concentrations required to measure the COX-1 IC_{50}'s for these compounds, it is possible that we are exceeding the limit of solubility in the assay system. In order to differentiate between selective compounds, a new assay was developed involving the use of U937 microsomes with a low arachidonic acid concentration of 100 nM.[9] This highly sensitive assay permits us to better determine the rank order of COX-1 activity for very selective compounds (see Table 2). From these data we can see that although entries **16**, **17**, and **18** appear to have similar activity in the COX-1 HWB assay, **16** was the least active in the U937 COX-1 assay. Of the compounds studied in this series, **16** was chosen as having the best overall in

Table 1. In Vitro Data of Representative Cyclooxygenase-2 Inhibitors



Entry (R)	Human Whole Blood Cox-2 IC_{50} (μM)	Human Whole Blood Cox-1 IC_{50} (μM)
3 	0.04	>58
9 	<0.4	>100
10 	<0.4	30
11 	5.2	ND
12 	0.04	10
13 	<0.4	39
14 Me	33	ND
15 Et	23	ND
16 DFP 	0.3	>100
17 	0.14	>100
18 	0.08	36
Indomethacin	0.4	0.2
Celecoxib	1.0	6.3
Rofecoxib	0.5	19

vitro and in vivo profile. 5,5-Dimethyl-3-(2-propoxy)-4-(4-methanesulfonylphenyl)-2(5*H*)-furanone **16** (DFP) has excellent pharmacokinetic properties in a variety of species as shown in Table 3. In addition DFP shows good dose proportionality in several species. The in vitro data and the pharmacokinetic properties confer to DFP an excellent profile in pain and inflammatory models. (See Table 4) The efficacy is, in general, better than that of indomethacin.

As with rofecoxib, DFP shows no gastrointestinal side effects as demonstrated by the ^{51}Cr assay[4c] to probe the intestinal permeability. No chromium leakage was observed with DFP at a daily dose of 100 mg /kg bid for 10

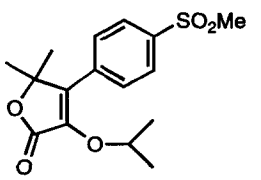
days in rats and 5 days in monkeys. In contrast, a single 10 mg/kg dose of indomethacin in rats gives a ten fold increase in chromium leakage.

Table 2. Data for U937 Microsome COX-1 Assay

Entry R	U937 Microsome COX-1 IC_{50} (μM)	Human Whole Blood COX-1 IC_{50} (μM)
16 DFP 	32 % inhib. at 30 μM	>100
17 	25	>100
18 	6.5	36

Table 3. Pharmacokinetics of DFP in Various Species

Species (dose mg/kg)	Half Life (h)	Cmax (μM)
Rat (10)	7.1	15
Squirrel monkey (5)	1.4	5.5
Rhesus monkey (5)	2.0	3.0
Dog (5)	4.8	12



DFP

Table 4. Comparison of DFP and Indomethacin in Various in vivo Assays

Assay	DFP ED_{50}(mg/kg)	Indomethacin ED_{50}(mg/kg)
Rat Paw Edema[4c]	0.8	2.0
Rat Pyresis[4c]	0.3	1.1
Rat Hyperalgesia[4c]	0.8	1.5
Rat Adjuvant Arthritis[11]	0.15 (bid)	0.2

In conclusion, DFP is one of the most selective COX-2 inhibitors reported to date. The high selectivity makes this compound potentially very useful in chronic dosing situations.

References and Notes

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