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Discovery of a Potent and Selective COX-2 Inhibitor in the Alkoxy Lactone Series with Optimized Metabolic Profile

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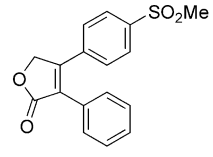
Abstract—The COX-2 inhibitor DFP [5,5-dimethyl-3-(2-propoxy)-4-methanesulfonylphenyl)-2(5H)-furanone] was found to have a long half-life in humans. Analogues have been characterized in order to optimize pharmacokinetics. This has lead to the discovery of 5(*S*)-(5-ethyl-5-methyl-3-(2-propoxy)-4-methanesulfonylphenyl)-2(5H)-furanone analogue **11** a potent and selective COX-2 inhibitor which is metabolized to a greater extent than DFP upon incubation with rat and human hepatocytes, suggesting a shorter half-life in humans.

Since the discovery that the cyclooxygenase exists in two isoforms[1] it has been demonstrated that selective cyclooxygenase-2 (COX-2) inhibitors have the desirable therapeutic effects of nonsteroidal antiinflammatory drugs (NSAIDS) with less gastrointestinal side effects associated with dual COX-1/2 inhibitors.[2–4]

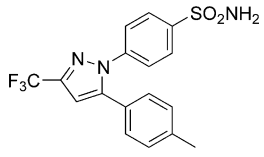
Heretofore, several groups have reported COX-2 selective inhibitors such as rofecoxib,[5] celecoxib,[6] etoricoxib,[7] valdecoxib,[8] and others.[9,10]

Following the discovery of rofecoxib (VIOXX), several efforts were made to identify other selective COX-2 inhibitors in the lactone series. This work lead to the discovery of DFU(**1**)[11] DFP(**2**).[12] DFP was found to be a potent and highly selective COX-2 inhibitor with excellent pharmacokinetic properties in a variety of species. In addition, pre-clinical data showed that DFP possesses anti-inflammatory activity in animals.[13] This COX-2 inhibitor was shown to be potent and selective in human ex vivo assays.[14] However, the human half-life of DFP was found to be long, with a value of 64 h.[14]

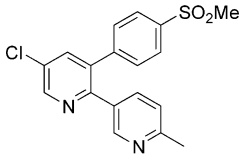
It has been well documented that metabolic processes play an important role in the excretion of COX-2 inhibitors.[15–17] In vivo and in vitro studies with DFP in



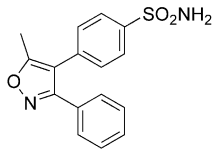
Rofecoxib



Celecoxib



Etoricoxib



Valdecoxib

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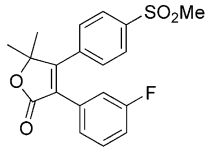
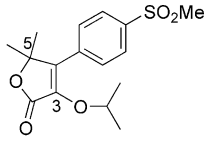
animal models showed that metabolism, at the alkoxy side chain, is the key determinant in its clearance.[18] DFP has a very low turn over in human in vitro metabolism experiments[19] thus correlating with the long human half-life. Therefore, modifications made to the structure of DFP, introducing sites for increased metabolism would be expected to provide COX-2 inhibitors with reduced half-life in humans.

With the goal of increasing the metabolism of DFP, modifications at the 3- and 5-positions on the molecule

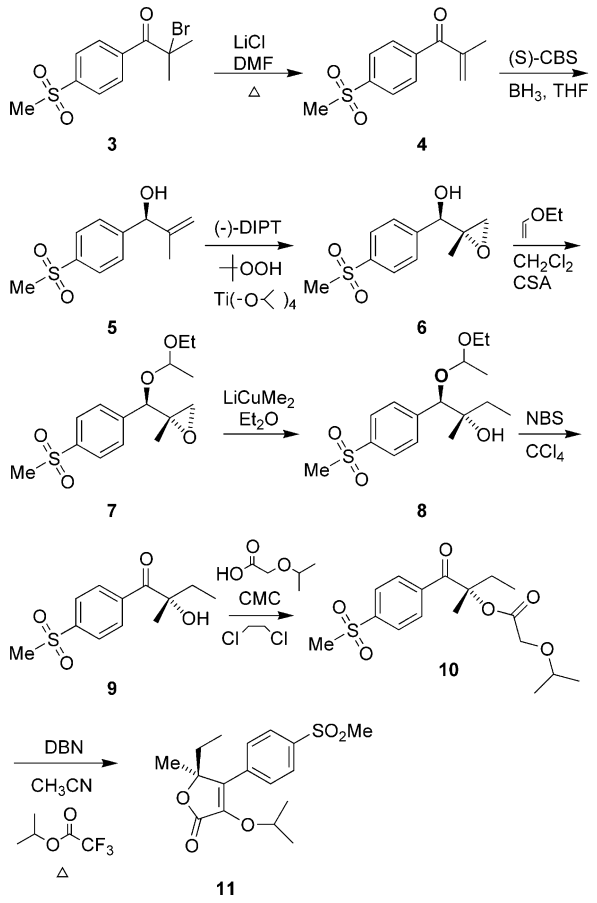


1 DFU



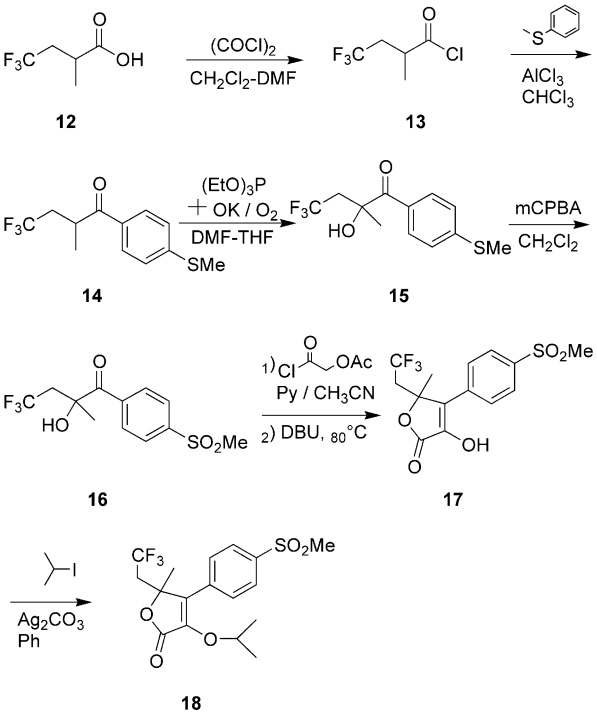
2 DFP

were considered. As already reported in our previous paper,[12] several 3-alkoxy analogues were prepared. Longer alkoxy groups at the 3-position gave analogues with more metabolism, that correlated with increased clearance in pre-clinical species (data not shown). However, the isopropoxy substituent at the 3-position was found to be the ultimate group for COX-2 inhibitory potency, selectivity and pharmacokinetics in different species. The second approach was to keep the isopropoxy group and modify the substitution at the C-5 position of the lactone ring. It is known from study of several analogues in this series, that the gem-dimethyl groups at the C-5 position are metabolically inert.[18,20] Thus, trifluoroethyl and ethyl analogues were prepared to provide potential sites for metabolic oxidation. The biological and metabolic profiles of these analogues are described herein.



Scheme 1.

The analogue **11** was prepared as described in Scheme 1. The α-bromoketone **3**[21] was heated in DMF in the presence of LiCl at 100 °C for 7 h to provide the vinyl ketone compound **4** in 84% yield. Treatment of ketone **4** with (*S*)-CBS and borane afforded the alcohol **5** in 86% yield with an enantiomeric excess of 88%. The absolute stereochemistry of the alcohol **5** was proven by X-ray crytallographic analysis. The allylic alcohol **5** was then epoxidized using Sharpless conditions to give the epoxy alcohol **6** in 77% yield. After protection of the alcohol as its 1-ethoxyethyl ether, the epoxide **7** was treated with $LiCuMe_2$ to provide compound **8**. The α-hydroxy ketone **9** was obtained by treatment of **8** with NBS in CCl_4. The chiral alcohol **9** was then condensed on isopropoxyacetic acid[21] in the presence of CMC to give the ester **10**. In turn, the ester **10** was heated in CH_3CN in the presence of DBU and isopropyl trifluoroacetate to provide compound **11** in 59% yield. The trifluoroethyl analogue **18** was prepared from 2-methyl-4,4,4-triflurobutyric acid **12** (Scheme 2). The acid was transformed to the acyl chloride **13** followed by a Friedel–Crafts reaction with thiomethylanisole to provide ketone **14**. The ketone was hydroxylated with $(EtO)_3P$/potassium *tert*-butoxide/O_2[22] to give **15** in 50% yield. After oxidation with mCPBA, the alcohol **16** was condensed on acetoxyacetyl chloride followed by DBU



Scheme 2.

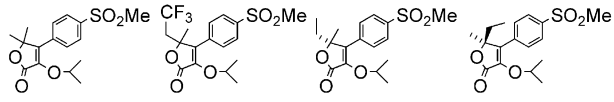
treatment to provide **17**. The isopropyl moeity was then introduced by treatment with 2-iodopropane in the presence of Ag_2CO_3 to give the final compound **18**.

The racemate trifluoroethyl analogue **18** was found to be four times less potent than DFP in the COX-2 human whole blood assay (COX-2 HWB), as shown in Table 1. In addition, poor in vivo activity was observed with compound **18** in the rat paw edema assay (ED_{50} 7.8 mg/kg). The ethyl methyl analogue was found to have comparable activity to DFP. The *R*-(**19**) and *S*-(**11**) enantiomers have similar potency in the COX-2 HWB assay with IC_{50}'s of 0.5 and 0.4 μM, respectively. Both enantiomers were found to be very selective with IC_{50}'s of >100 μM for the *R*-enantiomer and 86 μM for the *S*-enantiomer **11** in the COX-1 HWB assay. However, the pharmacokinetics and the in vivo profile in rats of the *S*-enantiomer **11** were found to be superior compared to the *R*-enantiomer(**19**) as described in Tables 2 and 3. As observed with rofecoxib, no gastrointestinal side effects were observed in rats with analogue **11** as demonstrated by the ^{51}Cr assay to probe the intestinal permeability.[9c] No chromium leakage was observed with compound **11** at a daily dose of 100 mg/kg bid for 10 days.

Studies were performed to evaluate the overall metabolic profile of **11**. In standard incubations with rat hepatocytes (10^6 cells, 50 μM substrate, 2 h),[20] the analogue **11** was highly metabolized (25–35%) as opposed to DFP (~2%). These results are in accordance with the shorter half-life of **11**, 2 h versus 7 h for DFP.[12] LC/MS studies using APCI-MS[18] and ^1H NMR experiments on a purified sample of the most significant metabolite indicated that the major metabolic pathway for **11** was now occurring on the ethyl side chain at the methylene position, yielding both possible hydroxy diastereomers (data not shown). In order to predict whether the half-life of analogue **11** would also be shorter than DFP in humans, human hepatocyte incubations were performed with both **11** and DFP. As observed for rat hepatocyte incubations, **11** was significantly more metabolized than DFP[19] (~18% for **11** vs <2% for DFP). The turn-over of **11** in human hepatocytes was faster than that obtained for etoricoxib (~8%),[23] a once-a-day COX-2 drug with an apparent terminal half life of 22 h.[24]

In conclusion, it has been possible to modulate the degree of metabolism and therefore the pharmacokinetics of this inhibitor class by adding metabolic soft sites to DFP, while maintaining the biological properties essential for a COX-2 inhibitor. The in vitro and in vivo data of analogue **11** are comparable to DFP. The incubation with human hepatocytes suggests that the human half-life of compound **11** should be shorter than that for DFP.

Table 1. In vitro potency and selectivity data of DFP(**2**), **18**, **19** and **11**



	DFP **2**	**18**	R-enantiomer **19**	S-enantiomer **11**
	IC_{50} (μM)			
COX-2 HWB	0.3	1.3	0.5	0.4
COX-1 HWB	>100	n/a	>100	>86

Table 2. Pharmacokinetic data of **11** in rats (DFP in parentheses)

Dose (mg/kg)	Half-life (DFP)	C_{max} (DFP)	Bioavailability
10	2 h (7.1 h)	1.7 μM (15 μM)	100%

The rat half life of the *R*-enantiomer **19** is <2 h.

Table 3. Comparison of rofecoxib, DFP (**2**), (**11**), *R*-enantiomer (**19**) and Indomethacin in various in vivo assays [ED_{50} (mg/kg)]

Assay	Rofecoxib	DFP (**2**)	**11**	**19**	Indomethacin
Rat paw edema	1.5	0.8	1.2	4.5	2.0
Ray pyresis	0.2	0.3	0.7	4.9	1.0
Rat hyperalgesia	1.0	0.8	0.7	nd	1.4
Rat adjuvant arthritis	0.8	0.3	3.3	nd	0.2

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