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SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-HETEROARYLOXY-4-PHENYL-2(5H)-FURANONES AS SELECTIVE COX-2 INHIBITORS

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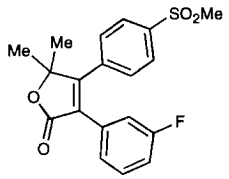
Abstract: A series of 3-heteroaryloxy-4-phenyl-2-(5H)-furanones were prepared and evaluated for their potency and selectivity as COX-2 inhibitors. This led to the identification of L-778,736 as a potent, orally active and selective inhibitor of the COX-2 enzyme.

Introduction

It has been demonstrated recently that selective cyclooxygenase-2 (COX-2) inhibitors retain the antiinflammatory effect but with markedly reduced GI toxicity compared to current NSAIDs which are non selective COX inhibitors.[1,2] This has lead to intense efforts in the search for potent and selective COX-2 inhibitors as the next generation of antiinflammatory drugs. Recently, our laboratory has reported that 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methanesulfonyl)-2-(5H)-furanone **1** (DFU) is a potent and selective COX-2 inhibitor.[3] In the preceeding papers, we described the modification of this template and discovered that an oxygen atom spacer can be inserted between the 3-phenyl substituent and the lactone ring of **1** (e.g. compound **2**) resulting in increased potency. As a further diversification of the furanone template, we have also studied the substitution of various oxygen-linked heterocycles at the 3-position (**3**). Herein we present the results of these efforts leading to the identification of L-778,736 as a potent, orally active and selective COX-2 inhibitor with no sign of GI ulceration at >100 times the dose required for antiinflammmatory, analgesic and antipyretic activities.



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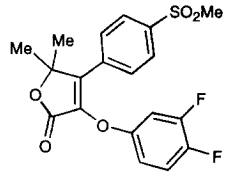

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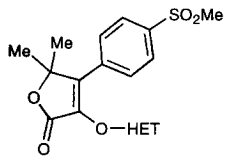

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Synthesis

With the exception of compound **3p**, all the 3-heteroaryloxy-4-(4-methylsulfonyl)phenyl-2(5H)-furanones were prepared from the tertiary alcohol **4**, the preparation of which has been described in the preceeding paper. Coupling of compound **4** with chloroacetyl chloride gave compound **5**. Treatment of compound **5** with DBU gave epoxide **6**.

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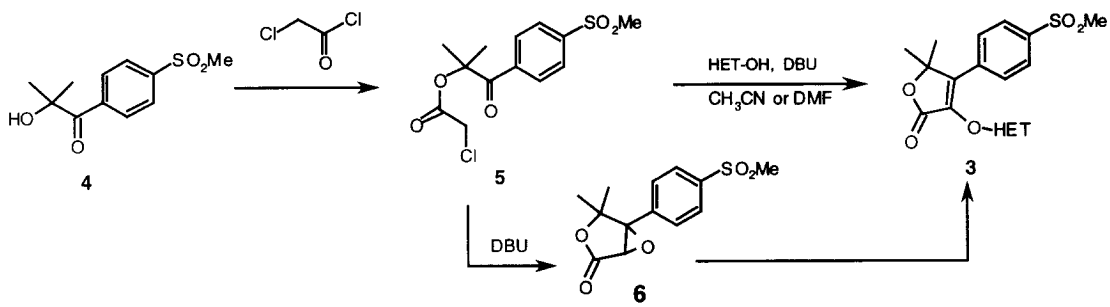
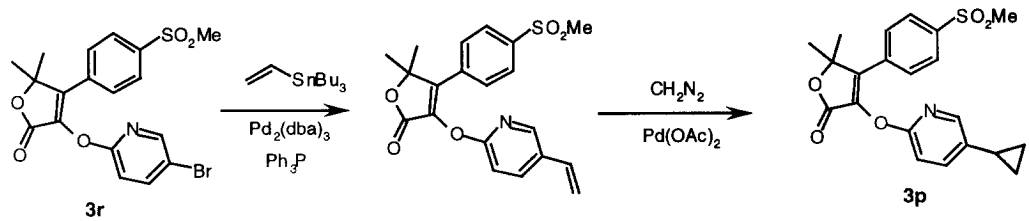
Displacement of the chloride **5** or the epoxide **6** with the appropriate hydroxy-heteroaryls followed by *in situ* cyclization and dehydration in the presence of DBU in acetonitrile or DMF gave the lactone **3** (Scheme 1).

Scheme 1



Compound **3p** was prepared from compound **3r.** Palladium-catalyzed coupling of **3r** with tributylvinylstannane followed by palladium-catalyzed cyclopropanation of the resulting vinyl intermediate with diazomethane gave **3p** in good yield.

Scheme 2



Discussion

A diverse array of oxygen-linked heteroaryls were prepared and tested for their potency as inhibitors of PGE_2 production in transfected Chinese hamster ovarian (CHO) cells expressing human COX-2[4] and in the human whole blood (HWB COX-2) assay.[5] Their selectivities against COX-1 were determined in a sensitive assay with U-937 cell microsomes at a low arachidonic acid concentration (0.1 μM).[6] Results of selected representatives of this class of compounds are summarized in Table 1.

It is interesting to note that a wide variety of heterocycles were tolerated without dramatic loss in potency. However, some compounds such as the benzothiophene derivative (**3a**) was potent (IC_{50} = 0.08 μM in the HWB COX-2 assay) but showed poor selectivity (COX-1, IC_{50} < 0.3 μM). The indole (**3b**), quinoline (**3c**) or isoquinoline derivatives (**3d**) that are potent (IC_{50} = 0.24, 0.66 and 0.26 μM against HWB COX-2) and selective (3-10 μM against COX-1) have

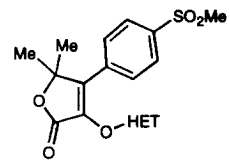
poor oral bioavailability. Compounds like **3e** and **3f** that are not active against COX-1 (IC_{50} >10 μM against COX-1) are also only moderately potent in the COX-2 HWB assay (IC_{50} =1.7, 3.8 μM respectively). Compounds **3g** and **3h** have reasonable potency in the HWB COX-2 assay (IC_{50} = 0.86, and 1 μM), are selective for COX-2 over COX-1, and they both have very high peak plasma levels. Since compound **3h** appeared to be more selective than the other compounds, the other pyridine positional isomers **3i** and **3j** were prepared and characterized. Compound **3j** is significantly more potent than **3h** and **3i** with an IC_{50} = 0.12 μM in the HWB COX-2 assay. Derivatives of **3j** were prepared and evaluated, the results are summarized in Table 2.

The 5-chloropyridine (**3k**) is significantly more potent (IC_{50} = 0.03 μM in the HWB COX-2 assay) than the unsubstituted pyridine (**3j**). The compound has good oral bioavailability (C_{max} =16 μM at 20 mg/kg p.o.) and slow clearance (CL = 4.8). It is active in the rat paw edema assay[7] with an ED_{50} = 0.75 mg/kg. The 6-chloro-pyridine (**3l**) is significantly less potent *in vitro* while the 3-chloro-substituted pyridine (**3m**) is less selective and has poor pharmacokinetics. The 3,5-dichloro analog (**3n**) is potent in the COX-2 assay (IC_{50} = 0.04 μM in the HWB COX-2 assay) but is relatively potent against COX-1. Alkyl substituted pyridines **3o** and **3p** have poor pharmacokinetics. Replacing the 5-chloro substituent with the 5-fluoro (**3q**) or the 5-bromo subtituent (**3r**) maintains the potency in COX-2 (IC_{50} = 0.08 and 0.03 μM in the HWB COX-2 assay) with slight improvement in selectivity (IC_{50} for COX-1 = 4.6 and 5.6 μM respectively) . Both compounds have good pharmacokinetics which translate to good *in vivo* potency. Both **3q** and **3r** are active in the rat paw edema assay with an ED_{50} = 0.32 and 0.86 mg/kg respectively.

Overall, compound **3r** (L-778,736) has an excellent *in vitro* and *in vivo* profile and was chosen for further evaluation. The compound was tested in other *in vivo* models. It has an ED_{50} = 0.86 mg/kg in the rat paw edema assay, it is also very potent in the rat pyrexia,[7] rat hyperalgesia[7] and rat adjuvant arthritis[8] assays with ED_{50}s = 0.3, 0.6 and 0.2 mg/kg respectively. In the ^{51}Cr fecal excretion model for GI integrity in rats,[7] chronic dosing of compound **3r** at 100 mg/kg bid for 7 days has no effect on fecal ^{51}Cr excretion. In contrast, acute dosing of indomethacin at 10 mg/kg caused a significant increase in fecal ^{51}Cr excretion in a 48 h period.

In conclusion, this study has identified compound **3r** (L-778,736) as a potent, orally active and selective COX-2 inhibitor that is devoid of ulcerogenic effect at >100 times the dose for antiinflammatory, analgesic and antipyretic effects.

Table 1



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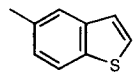
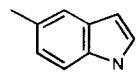
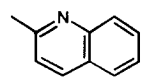
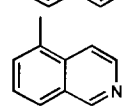
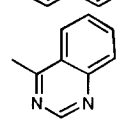
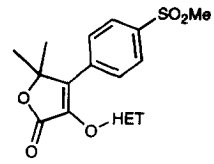
Compound	HET	COX-2 (IC_{50}, μM) CHO	COX-2 (IC_{50}, μM) HWB	COX-1 (IC_{50}, μM) U-937
3a		0.02	0.08	< 0.3
3b		0.03	0.24	1-3
3c		0.33	0.66	3-10
3d		0.67	0.26	3
3e		2.9	1.7	>10
3f		0.55	3.8	>10
3g		0.62	0.86	>10
3h		0.27	1	>100
3i		0.26	0.52	>30
3j		0.12	0.12	>10
Celecoxib		0.002	1.0	0.05
Rofecoxib		0.02	0.5	2.0
Indomethacin		0.026	0.5	0.02

Table 2



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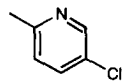
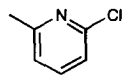
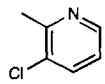
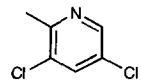
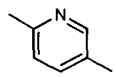
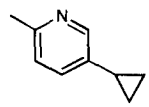
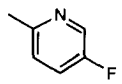
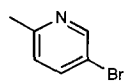
Compound	HET	COX-2 (IC_{50}, μM) CHO	COX-2 (IC_{50}, μM) HWB	COX-1 (IC_{50}, μM) U-937	Paw Edema (ED50 , mg/kg)
3j		0.12	0.12	>10	>10
3k		0.02	<0.01	3	0.75
3l		0.35	3.60	>10	
3m		0.09	<0.4	1-3	
3n		0.04	0.04	0.3-1	
3o		0.15.	0.38	3-10	
3p		0.03	< 0.4	3-10	
3q		0.04	0.08	4.6	0.32
3r		0.02	0.03	5.6	0.86
Celecoxib		0.002	1.0	0.05	
Rofecoxib		0.02	0.5	2.0	1.5

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