Articles

Synthesis of Celecoxib Analogues Possessing a *N*-Difluoromethyl-1,2-dihydropyrid-2-one 5-Lipoxygenase Pharmacophore: Biological Evaluation as Dual Inhibitors of Cyclooxygenases and 5-Lipoxygenase with Anti-Inflammatory Activity

Morshed A. Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Dipankar Das, Mavanur R. Suresh, and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, T6G 2N8, Canada

Received December 2, 2008

A novel class of 1-(4-methanesulfonylphenyl and 4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole hybrid cyclooxygenase-2 (COX-2)/5-lipoxygenase (5-LOX) inhibitory anti-inflammatory agents was designed. Replacement of the tolyl ring present in celecoxib by the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety provided compounds showing dual selective COX-2/5-LOX inhibitory activities. 1-(4-Aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole exhibited good anti-inflammatory (AI) activity (ED_{50} = 27.7 mg/kg po) that compares favorably with the reference drugs celecoxib (ED_{50} = 10.8 mg/kg po) and ibuprofen (ED_{50} = 67.4 mg/kg po). The *N*-difluoromethyl-1,2-dihydropyridin-2-one moiety provides a novel 5-LOX pharmacophore for the design of cyclic hydroxamic mimetics for exploitation in the development of COX-2/5-LOX inhibitory AI drugs.

Introduction

Arachidonic acid (AA[a]), the most abundant polyunsaturated fatty acid present in cell membranes, is metabolized after its release by the cyclooxygenase (COX-1, -2, -3) and lipoxygenase (5-LOX, 8-, 12-, -15) enzyme families. Proinflammatory prostaglandins (PGs) produced via the COX pathway, and leukotrienes (LTs) produced via the LOX pathway, are implicated in physiological processes such as inflammation, fever, arthritis, and bronchospasm.[1,2] PGs that cause contraindicated inflammation, fever, and pain are formed via the inducible COX-2 isozyme, whereas PGs that regulate beneficial gastrointestinal cytoprotection and renal effects are produced via the constitutive COX-1 isozyme.[1−3] Alternatively, 5-LOX is associated with the production of LTs that cause inflammatory, bronchoconstrictor, hypersensitivity, anaphylactic, and asthmatic actions. On the other hand, 15-LOX is implicated in atherosclerosis because it catalyzes the oxidation of lipoproteins (LDL, HDL) to atherogenic forms.[4,5]

There is a general belief that a dual inhibitor of the LOX/COX enzymatic pathways[6] constitutes a rational approach for the design of more effective anti-inflammatory agents with a superior safety profile relative to ulcerogenic nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors that increase the incidence of adverse cardiovascular thrombotic effects.[7,8] It has been pointed out that inhibition of only one of the COX/LOX pathways could shift the metabolism of AA toward the other pathway, thereby inducing potential side effects.[9] One of the more successful strategies to develop 5-LOX inhibitors utilized hydroxamic acids and related *N*-hydroxyureas that act by chelation of iron present in the 5-LOX enzyme.[10] Two representative examples of iron chelating 5-LOX inhibitors include zileuton (**1**)[11] and tepoxalin (**2**)[10] (see structures in Figure 1). A potent hybrid COX-2/5-LOX inhibitor (**3**) in which the C-3 trifluoromethyl substituent present in the COX-2 inhibitor celecoxib (**4**) was replaced by a nonredox competitive 4-(3-fluoro-5-oxymethyl)phenyl-4-methoxytetrahydropyran 5-LOX pharmacophore was reported by Henichart et al.[2] In a recent study we described a novel class of dual COX/5-LOX inhibitor

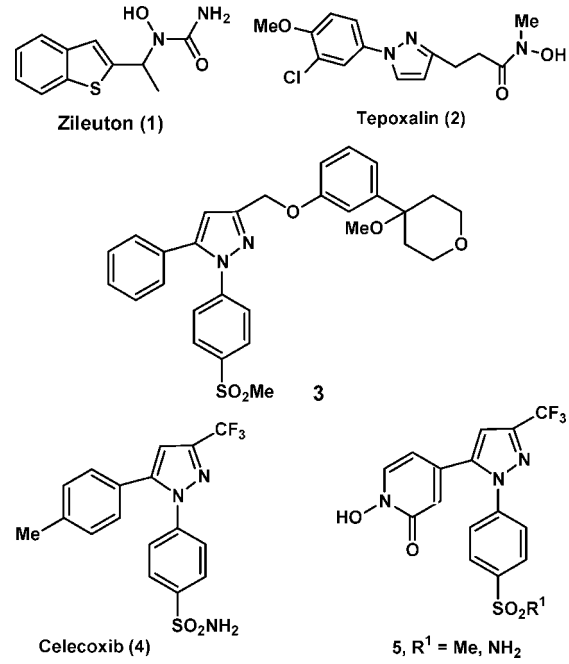


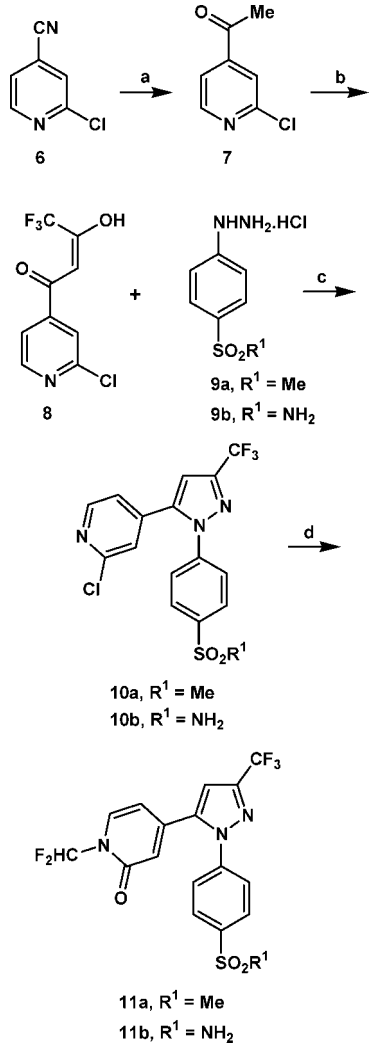
Figure 1. Chemical structures of some representative iron-chelating 5-LOX inhibitors (**1**, **2**), a COX-2/5-LOX inhibitor (**3**), the selective COX-2 inhibitor celecoxib (**4**), and the COX/5-LOX inhibitors (**5**).

* To whom correspondence should be addressed. Phone: (780) 492-5993. Fax: (780) 492-1217. E-mail: eknaus@pharmacy.ualberta.ca.

[a] Abbreviations: AA, arachidonic acid; AI, anti-inflammatory; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; HDL, high density lipoprotein; LTs, leukotrienes; LDL, low density lipoprotein; 5-LOX, 5-lipoxygenase; PGs, prostaglandins; NSAIDs, nonsteroidal anti-inflammatory drugs.

10.1021/jm8015188 CCC: $40.75
Published on Web 02/18/2009

Scheme 1[a]



[a] Reagents and conditions: (a) MeMgI, Et_2O, 25 °C, 20 h; (b) NaOMe, CF_3CO_2Et, Et_2O, −5 to 0 °C, 2 h; (c) ethanol (95%), reflux, 20 h; (d) FSO_2CF_2COOH, $NaHCO_3$, reflux, overnight.

celecoxib analogues (**5**) that possess a *N*-hydroxy-1,2-dihydropyrid-2-one 5-LOX pharmacophore.[12] Accordingly, it was anticipated that replacement of the tolyl ring present in the selective COX-2 inhibitor celecoxib (**4**)[13] by a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety may provide a hitherto unknown class of dual 5-LOX/COX-2 inhibitory anti-inflammatory agents. Accordingly, we now describe the synthesis of a novel class of celecoxib analogues that possess a potentially novel *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety that may represent a new 5-LOX pharmacophore (**11a**,**b**), their in vitro evaluation as COX-1/COX-2, 5-LOX inhibitors, and in vivo assessment as AI agents.

Chemistry

The target 1-(4-methanesulfonylphenyl and 4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazoles (**11a**,**b**) were prepared using the reaction sequence illustrated in Scheme 1. Accordingly, reaction of 2-chloroisonicotinonitrile (**6**) with methylmagnesium iodide, using a literature method for elaboration of cyano to acetyl, furnished 1-(2-chloropyridin-4-yl)ethanone (**7**, 81%).[14] The base catalyzed condensation of the acetyl compound **7** with ethyl trifluoroacetate afforded 4,4,4-trifluoro-3-hydroxy-1-(2-chloropyridin-4-yl)but-2-en-1-one (**8**, 91%).[15] The subsequent condensation of **8** with either 4-(methylsulfonylphenyl)hydrazine-HCl (**9a**) or 4-(aminosulfonylphenyl)hydrazine-HCl (**9b**) afforded the respective 1,5-diarylpyrazole **10a** (40%) or **10b** (28%). Reaction of **10a** or **10b** with 2,2-difluoro-2-(fluorosulfonyl)acetic acid (FSO_2CF_2COOH)[16] afforded the target 1-difluoromethyl-1,2-dihydropyrid-2-one products (**11a**,**b**) in 46−52% yields (Scheme 1).

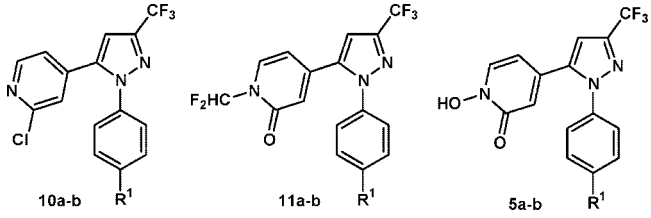
Results and Discussion

The rational for the design of the 1-(4-methanesulfonylphenyl and 4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazoles (**11a**,**b**) was based on the expectation that replacement of a tolyl moiety in celecoxib (**4**) or replacement of the *N*-hydroxy-1,2-dihydropyridin-2-one moiety present in the hybrid compounds **5** would furnish a novel class of compounds with dual COX-2/5-LOX inhibitory activities. The $CONCHF_2$ fragment of the *N*-difluoromethyl-1,2-dihydropyrid-2-one ring present in **11a**,**b** can be viewed as a cyclic hydroxamic acid mimetic. These *N*-difluoromethyl-1,2-dihydropyrid-2-ones **11a**,**b** could inhibit the 5-LOX enzyme by two possible mechanisms. In this regard **11a**,**b**, like acyclic hydroxamic acids, may act as effective iron chelators to exhibit 5-LOX inhibitory activity. It has been reported that there is a substantial buildup of negative potential around the two fluorine atoms of a CHF_2 group.[17] Despite this high electron density, an aliphatic fluorine seldom acts as a hydrogen-bond acceptor, presumably because of its high electronegativity and low polarizability.[18,19] Therefore, it is also plausible that the CHF_2 group may interact with a positively charged region on the enzyme that may contribute to enhanced affinity and competitive reversible inhibition of the COX and/or 5-LOX enzymes.[20] In addition, these cyclic *N*-difluoromethyl-1,2-dihydropyrid-2-ones, unlike acyclic hydroxamic acids that undergo facile biotransformation to the acids, are expected to have a greater metabolic stability with increased oral efficacy. Although there is some distortion from planarity at the N^1-nitrogen atom of the *N*-difluoromethyl-1,2-dihydropyrid-2-one ring system, the relatively flat diene portion of this quasi-planar ring system has the potential to serve as a suitable replacement for the tolyl group present in celecoxib (**4**), resulting in retention of selective COX-2 inhibitory activity.

In vitro COX-1 and COX-2 enzyme inhibition studies showed that the celecoxib analogues (**10a**,**b**) having a respective SO_2Me and SO_2NH_2 COX-2 pharmacophore in conjunction with a 2-chloropyridyl ring substituent exhibited potent and selective COX-2 inhibitory activity (COX-1 $IC_{50} = 8.3-258\ \mu M$; COX-2 $IC_{50} = 0.19-0.73\ \mu M$) that compared favorably to the reference drug celecoxib (COX-1 $IC_{50} = 7.7\ \mu M$; COX-2 $IC_{50} = 0.07\ \mu M$). In addition, the 2-chloropyridyl compounds **10a**,**b** also exhibited unexpected potent 5-LOX inhibition ($IC_{50} = 0.39-0.47\ \mu M$) that was 9- to 10-fold more potent than that of the reference drug caffeic acid ($IC_{50} = 4.0\ \mu M$) (see data in Table 1). Elaboration of the 2-chloropyridyl ring in **10a**,**b** to a 1-difluoromethyl-1,2-dihydropyrid-2-one moiety (**11a**,**b**) resulted in a 9-fold reduction in COX-2 inhibition for the SO_2Me compound **11a** ($IC_{50} = 1.82\ \mu M$). In contrast, the SO_2NH_2 compound **11b** ($IC_{50} = 0.69\ \mu M$) was equipotent with the 2-chloropyridyl compound **10b** ($IC_{50} = 0.73\ \mu M$). The equipotent 1-difluoromethyl-1,2-dihydropyrid-2-ones **11a**,**b** exhibited comparable 5-LOX inhibitory activity ($IC_{50} = 4.4-5.0\ \mu M$) to the reference drug caffeic acid.

The oral AI activities (ED_{50} values) exhibited by the 2-chloropyridyl compounds **10a**,**b** and the 1-difluoromethyl-1,2-

Table 1. In Vitro COX-1, COX-2, 5-LOX Enzyme Inhibition and in Vivo Anti-Inflammatory Activity Data for Celecoxib Analogues Having a 2-Chloropyridyl (**10a**,**b**), 1-Difluoromethyl-1,2-dihydropyrid-2-one (**11a**,**b**), or *N*-Hydroxy-1,2-dihydropyrid-2-one (**5a-b**) Moiety



compd	R^1	COX-1 IC_{50} (μM)[a]	COX-2 IC_{50} (μM)[a]	5-LOX IC_{50} (μM)[b]	AI activity[c] ED_{50} (mg/kg)
10a	SO_2Me	258	0.19	0.47	<150[d]
10b	SO_2NH_2	8.3	0.73	0.39	<150[e]
11a	SO_2Me	7.8	1.82	4.4	42.9
11b	SO_2NH_2	13.1	0.69	5.0	27.7
5a[f]	SO_2Me	13.2	7.5[g]	0.35	66.9
5b[f]	SO_2NH_2	10.2	7.5[g]	4.90	99.8
celecoxib		7.7	0.12		10.8
ibuprofen		2.9	1.1[g]		67.4
caffeic acid				4.0	

[a] The in vitro test compound concentration required to produce 50% inhibition of ovine COX-1 or human recombinant COX-2. The result (IC_{50}, μM) is the mean of two determinations acquired using the enzyme immunoassay kit (catalog no. 560131, Cayman Chemicals Inc., Ann Arbor, MI), and the deviation from the mean is <10% of the mean value. [b] The in vitro test compound concentration required to produce 50% inhibition of potato 5-LOX (Cayman Chemicals Inc. catalog no. 60401). The result (IC_{50}, μM) is the mean of two determinations acquired using a LOX assay kit (catalog no. 760700, Cayman Chemicals Inc., Ann Arbor, MI), and the deviation from the mean is <10% of the mean value. [c] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the ED_{50} value (mg/kg) at 3 h after oral administration of the test compound. [d] 43.1% reduction in inflammation at a 150 mg/kg po dose. [e] 33.3% reduction in inflammation at a 150 mg/kg po dose. [f] Data taken from the literature.[12] [g] Data acquired using ovine COX-2 (catalog no. 560101, Cayman Chemicals Inc.).

dihydropyrid-2-ones **11a**,**b** were determined using a carrageenan-induced rat foot paw edema model (see data in Table 1). In spite of the fact that the 2-chloropyridyl compounds **10a**,**b** are more potent in vitro inhibitors of the 5-LOX enzyme than the 1-difluoromethyl-1,2-dihydropyrid-2-ones **11a**,**b**, the in vivo AI structure−activity data acquired showed that **11a** (SO_2Me, AI ED_{50} = 42.9 mg/kg po) and **11b** (SO_2NH_2, AI ED_{50} = 27.7 mg/kg po) are more potent AI agents than the 2-chloropyridyl compounds **10a** and **10b** which showed a respective 43.1% and 33.3% reduction in inflammation for a 150 mg/kg po dose. This superior AI activity exhibited by the 1-difluoromethyl-1,2-dihydropyrid-2-ones **11a**,**b** could be due to a number of factors that include oral bioavailability, biodistribution, and/or metabolic stability. A comparison of the AI activities for the 1-difluoromethyl-1,2-dihydropyrid-2-ones **11a**,**b** to the previously reported *N*-hydroxy-1,2-dihydropyrid-2-one compounds **5a**,**b**[12] shows that compounds **11a**,**b** exhibit greater oral AI activity than compounds **5a**,**b**. The more potent AI activity exhibited by **11a**,**b**, relative to **5a**,**b**, could be due to their superior adsorption, distribution, metabolism, and/or excretion (ADME) properties. These AI data suggest that the 1-difluoromethyl-1,2-dihydropyrid-2-one moiety may be a superior 5-LOX pharmacophore relative to the *N*-hydroxy-1,2-dihydropyrid-2-one group for the design of hybrid COX-2/5-LOX inhibitory AI drugs. The most potent compound 1-(4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole (**11b**) exhibited good AI activity (ED_{50} = 27.7 mg/kg po) that compares favorably with the reference drugs celecoxib (ED_{50} = 10.8 mg/kg po) and ibuprofen (ED_{50} = 67.4 mg/kg po).

Conclusions

A hitherto unknown class of 1-(4-methanesulfonylphenyl and 4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazoles (**11a**,**b**) was designed for evaluation as dual 5-LOX and COX-1/COX-2 isozyme inhibitors of inflammation. The structure−activity data acquired indicate that (i) compounds **11a**,**b** exhibit acceptable in vitro COX-2 isozyme inhibitory potency and selectivity in conjunction with potent inhibition of the 5-LOX enzyme, (ii) the relative AI potency order with respect to the COX-2 pharmacophore is SO_2NH_2 > SO_2Me, (iii) the 1-difluoromethyl-1,2-dihydropyrid-2-one moiety provides a novel 5-LOX pharmacophore for the design of cyclic hydroxamic mimetics, and (iv) the dual acting compounds **11a**,**b** exhibit AI activity that is dependent upon inhibition of proinflammatory prostaglandin and leukotriene biosyntheses in the respective cyclooxygenase and lipoxygenase pathways.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Unless otherwise noted, infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer. Microanalyses (MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta) of compounds **11a**,**b** were performed for C, H, and N and were within ±0.4% of theoretical values for all elements listed. Compounds **10a**,**b** showed a single spot on Macherey−Nagel Polygram Sil G/UV_{254} silica gel plates (0.2 mm) using a low, medium, and highly polar solvent system, and no residue remained after combustion, indicating a purity of >95%. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70−230 mesh). 4-(Methylsulfonylphenyl)hydrazine-HCl (**9a**) was synthesized in 53% yield starting from 1-chloro-4-methanesulfonylbenzene,[21] which was prepared by the Fridel−Crafts reaction of methanesulfonyl chloride with chlorobenzene.[22] 4-(Aminosulfonylphenyl)hydrazine-HCl (**9b**) was synthesized in 84% yield starting from sulfanilamide.[23] All other reagents, purchased from the Aldrich Chemical Co. (Milwaukee, WI), were used without further purification. The in vivo anti-inflammatory assay was carried out using a protocol approved by the Health Sciences Animal Welfare Committee at the University of Alberta.

General Procedure for the Synthesis of 1-(4-Methanesulfonylphenyl or 4-aminosulfonylphenyl)-5-(2-chloropyridin-4-yl)-3-trifluoromethyl-1*H*-pyrazoles (10a,b). A solution of 4-(methylsulfonylphenyl)hydrazine-HCl (**9a**) or 4-(aminosulfonylphenyl)hydrazine-HCl (**9b**) (20 mmol) and 4,4,4-trifluoro-3-hydroxy-1-(2-chloropyridin-4-yl)but-2-en-1-one (**8**, 4.58 g, 18.20 mmol) in 95% ethanol (225 mL) was heated at reflux with stirring for 20 h. After cooling to 25 °C, the reaction mixture was concentrated in vacuo to give a crude solid which was purified by silica gel column chromatography using hexanes−acetone (2:1, v/v) as eluent to furnish the respective title compound **10a** or **10b**. Some physical and spectroscopic data for **10a** and **10b** are listed below.

1-(4-Methanesulfonylphenyl)-5-(2-chloropyridin-4-yl)-3-trifluoromethyl-1*H*-pyrazole (10a). This compound was obtained as a pale-yellow solid in 40% yield, mp 220−222 °C; IR 1299, 1155 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 3H, SO_2*Me*), 7.28 (s, 1H, pyrazole H-4), 7.66 (dd, J = 5.5, 1.2 Hz, 1H, pyridyl H-5), 7.80 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.82 (dd, J = 6.7, 1.8 Hz, 2H, phenyl H-2, H-6), 8.15 (dd, J = 6.7, 1.8 Hz, 2H, phenyl H-3, H-5), 8.49 (d, J = 5.5 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 44.5, 108.1, 118.8, 119.2, 120.6, 126.0, 128.8, 134.8, 141.4, 141.5, 142.8, 148.9, 150.4, 152.5.

1-(4-Aminosulfonylphenyl)-5-(2-chloropyridin-4-yl)-3-trifluoromethyl-1*H*-pyrazole (10b). This compound was obtained as a white solid in 28% yield, mp 235−237 °C; IR 3365, 3272 (NH_2), 1330, 1162 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 6.89 (s, 2H, SO_2NH_2 that exchanges with D_2O), 6.91 (s, 1H, pyrazole H-4), 6.94 (dd, J = 5.5, 1.2 Hz, 1H, pyridyl H-5), 7.25 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.38 (dd, J = 8.5, 1.8 Hz, 2H, phenyl H-2, H-6), 7.94 (dd, J = 8.5, 1.8 Hz, 2H, phenyl H-3, H-5), 8.31 (d, 1H, J = 5.5 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 107.4, 120.3, 121.2, 122.8, 125.0, 126.9, 138.5, 140.0, 140.3, 143.2, 144.2, 149.7, 151.4.

General Procedure for the Synthesis of 1-(4-Methanesulfonylphenyl or 4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole (11a,b). To a stirred solution of 1-(4-methanesulfonylphenyl or 4-aminosulfonylphenyl)-5-(2-chloropyridin-4-yl)-3-trifluoromethyl-1*H*-pyrazole (**10a** or **10b**) (6 mmol) in dry acetonitrile (45 mL) was added FSO_2CF_2COOH (3.28 g, 18 mmol) and $NaHCO_3$ (0.51 g, 6 mmol), and the mixture was heated at reflux overnight under argon. After cooling to 25 °C, the reaction mixture was concentrated in vacuo and a solution of saturated $NaHCO_3$ (50 mL) was added. This mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were concentrated to about 25 mL and washed with 10 N hydrochloric acid (1 × 25 mL) to remove unreacted starting material **10a** or **10b**. The organic phase was washed successively with water and brine and dried ($MgSO_4$). Filtration and then removal of the solvent in vacuo from the organic fraction afforded the impure product which was purified by silica gel column chromatography. Elution with hexanes−acetone (2:1, v/v) furnished the respective 1-(4-methanesulfonylphenyl or 4-aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole **(11a** or **11b)**. The spectral and microanalytical data for compounds **11a** and **11b** are listed below.

1-(4-Methanesulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole (11a). This compound was obtained as a pale-yellow solid in 46% yield, mp 200−202 °C; IR 1678 (CO), 1327, 1152 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (s, 3H, SO_2Me), 6.02 (dd, J = 7.5, 1.8 Hz, 1H, pyridone H-5), 6.56 (d, J = 1.8 Hz, 1H, pyridone H-3), 6.93 (s, 1H, pyrazole H-4), 7.46 (d, J = 7.5 Hz, 1H, pyridone H-6), 7.64 (dd, J = 6.7, 1.8 Hz, 2H, phenyl H-2, H-6), 7.65 (t, $^2J_{HCF}$ = 60 Hz, 1H, C*H*F_2), 8.07 (dd, J = 6.7, 1.8 Hz, 2H, phenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 44.4, 106.5, 107.2, 108.2, 120.4, 120.9, 125.6, 129.1, 130.5, 140.7, 141.0, 141.1, 142.5, 144.8, 159.9. Anal. ($C_{17}H_{12}F_5N_3O_3S$) C, H, N.

1-(4-Aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1*H*-pyrazole (11b). This compound was obtained as a white solid in 52% yield, mp 190−192 °C; IR 3260 (broad NH_2), 1680 (CO), 1347, 1169 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 6.03 (dd, J = 7.5, 1.8 Hz, 1H, pyridone H-5), 6.42 (s, 1H, pyridone H-3), 6.92 (s, 1H, pyrazole H-4), 7.08 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.45 (d, J = 7.5 Hz, 1H, pyridone H-6), 7.47 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.57 (t, $^2J_{HCF}$ = 60 Hz, 1H, C*H*F_2), 7.97 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 106.0, 106.6, 107.1, 119.7, 119.9, 124.5, 126.8, 129.7, 139.9, 140.3, 143.1, 143.9, 159.1. Anal. ($C_{16}H_{11}F_5N_4O_3S$) C, H, N.

Cyclooxygenase Inhibition Assays. The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and human recombinant COX-2 (IC_{50} value, μM) was determined using an enzyme immunoassay (EIA) kit (catalog no. 560131, Cayman Chemical, Ann Arbor, MI) according to our previously reported method.[24]

5-Lipoxygenase Inhibition Assay. The ability of the test compounds listed in Table 1 to inhibit potato 5-LOX (catalog no. 60401, Cayman Chemical, Ann Arbor, MI) (IC_{50} values, μM) were determined using an enzyme immunoassay (EIA) kit (catalog no. 760700, Cayman Chemical, Ann Arbor, MI) according to our previously reported method.[12]

Anti-Inflammatory Assay. The test compounds **10a**,**b** and **11a**,**b** and the reference drugs celecoxib, ibuprofen, and aspirin were evaluated using the in vivo carrageenan-induced rat foot paw edema model reported previously.[25]

Acknowledgment. We are grateful to the Canadian Institutes of Health Research (Grant No. MOP-14712) for financial support of this research. We also thank Dr. M. Rahman for recording rat paw volumes acquired in the anti-inflammatory assays.

Supporting Information Available: Table of combustion data for compounds **11a** and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Charlier, C.; Michaux, C. Dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) as a new strategy to provide safer non-steroidal anti-inflammatory drugs. *Eur. J. Med. Chem.* **2003**, *38*, 645–659.

(2) Barbey, S.; Goossens, L.; Taverne, T.; Cornet, J.; Choesmel, V.; Rouaud, C.; Gimeno, G.; Yannic-Arnoult, S.; Michaux, C.; Charlier, C.; Houssin, R.; Henichart, J.-P. Synthesis and activity of a new methoxytetrahydropyran derivative as dual cyclooxygenase-2/5-lipoxygenase inhibitor. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 779–782.

(3) Dannhardt, G.; Laufer, S. Structural approaches to explain the selectivity of COX-2 inhibitors: Is there a common pharmacophore? *Curr. Med. Chem.* **2000**, *7*, 1101–1112.

(4) Vila, L. Cyclooxygenase and 5-lipoxygenase pathways in the vessel wall: role in atherosclerosis. *Med. Res. Rev.* **2004**, *24*, 399–424.

(5) Zhao, L.; Funk, C. D. Lipoxygenase pathways in atherogenesis. *Trends Cardiovasc. Med.* **2004**, *14*, 191–195.

(6) Praveen Rao, P. N.; Chen, Q.-H.; Knaus, E. E. Synthesis and structure−activity relationship studies of 1,3-diarylprop-2-yn-1-ones: dual inhibitors of cyclooxygenases and lipoxygenases. *J. Med. Chem.* **2006**, *49*, 1668–1683.

(7) Scheen, A. J. Withdrawal of rofecoxib (Vioxx): What about cardiovascular safety of selective COX-2 selective non-steroidal anti-inflammatory drugs? *Rev. Med. Liege* **2004**, *59*, 565–569.

(8) Dogné, J.-M.; Supuran, C. T.; Pratico, D. Adverse cardiovascular effects of the coxibs. *J. Med. Chem.* **2005**, *48*, 2251–2257.

(9) Asako, H.; Kubes, P.; Wallace, J.; Gaginella, T.; Wolf, R. E.; Granger, N. Indomethacin-induced leukocyte adhesion in mesenteric venules: role of lipoxygenase products. *Am. J. Physiol.: Gastrointest. Liver Physiol.* **1992**, *262*, G903–G908.

(10) Muri, E. M. F.; Nieto, M. J.; Sindelar, R. D.; Williamson, J. S. Hydroxamic acids as pharmacological agents. *Curr. Med. Chem.* **2002**, *9*, 1631–1653.

(11) Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R.; Bell, R. L.; Summers, J. B.; Brooks, D. W. Hydroxamic acids as pharmacological agents. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 929–937.

(12) Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. Synthesis of celecoxib analogs that possess a *N*-hydroxypyrid-2(1*H*)one 5-lipoxygenase pharmacophore: biological evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6138–6141.

(13) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). *J. Med. Chem.* **1997**, *40*, 1347–1365.

(14) LaMattina, J. L. The synthesis of 2-amino-4-(4-imidazolyl)pyridines. *J. Heterocycl. Chem.* **1983**, *20*, 533–538.

(15) Schallner, O.; Linker, K.-H.; Dollinger, M.; Erdelen, C.; Wachendorff-Neumann, U. Preparation of Pyridylpyrazoles As Herbicides, Insecticides and Acaricides. Ger. Offen. DE 19721031, 1998.

(16) Ando, M.; Wada, T.; Sato, N. Facile one-pot synthesis of *N*-difluoromethyl-2-pyridone derivatives. *Org. Lett.* **2006**, *8*, 3805–3808.

(17) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. A designed P_1 cysteine mimetic for covalent and non-covalent inhibitors of HCV NS3 protease. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701–704, and references cited therein.

(18) Dunitz, J. D.; Taylor, R. Organic fluorine hardly ever accepts hydrogen bonds. *Chem.−Eur. J.* **1997**, *3*, 89–98.

(19) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. How good

is fluorine as a hydrogen bond acceptor? *Tetrahedron* **1996**, *52*, 12613–126122.

(20) Chavatte, P.; Yous, S.; Marot, C.; Baurin, N.; Lesieur, D. Three-dimensional quantitative structure−activity relationships of cyclooxygenase-2 (COX-2) inhibitors: a comparative molecular field analysis. *J. Med. Chem.* **2001**, *44*, 3223–3230.

(21) Pommery, N.; Taverne, T.; Telliez, A.; Goossens, L.; Charlier, C.; Pommery, J.; Goossens, J.-F.; Houssin, R.; Durant, F.; Henichart, J.-P. New COX-2/5-LOX inhibitors: apoptosis-inducing agents potentially useful in prostate cancer chemotherapy. *J. Med. Chem.* **2004**, *47*, 6195–6206.

(22) Truce, W. E.; Vriesen, C. W. Friedel−Crafts reactions of methanesulfonyl chloride with benzene and certain substituted benzenes. *J. Am. Chem. Soc.* **1953**, *75*, 5032–5036.

(23) Soliman, R. Preparation and antidiabetic activity of some sulfonylurea derivatives of 3,5-disubstituted pyrazoles. *J. Med. Chem.* **1979**, *22*, 321–325.

(24) Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A.; Knaus, E. E. Design, synthesis, and biological evaluation of 6-substituted-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-ones: a novel class of diarylheterocyclic selective cyclooxygenase-2 inhibitors. *J. Med. Chem.* **2003**, *46*, 4872–4882.

(25) Winter, C. A.; Risley, E. A.; Nuss, G. W. Carrageenan-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544–552.

JM8015188