

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

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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 pathways⁶ 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

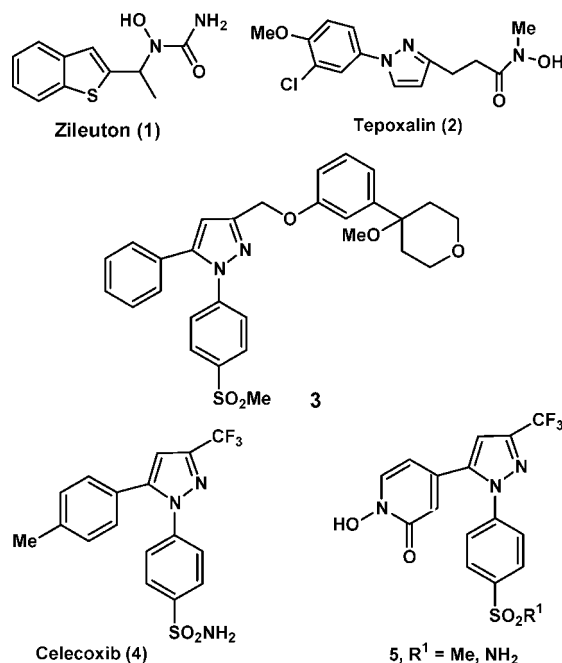
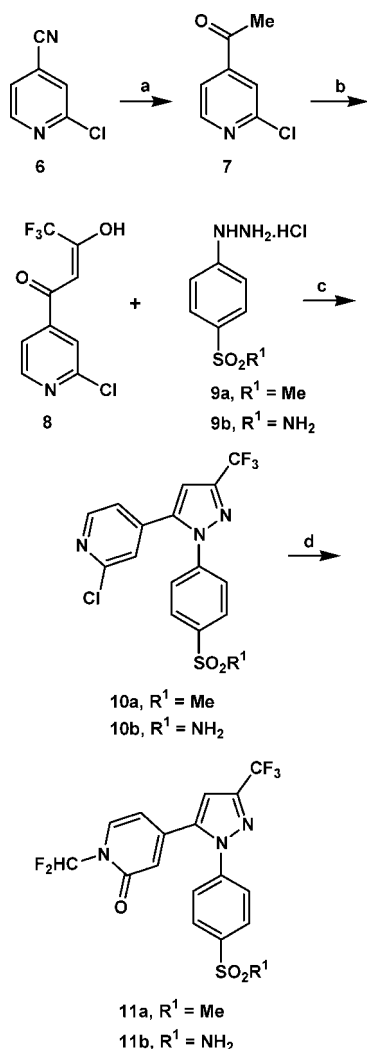


Figure 1. Chemical structures of some representative iron-chelating 5-LOX inhibitors (1, 2), a COX-2/5-LOX inhibitor (3), the selective COX-2 inhibitor celecoxib (4), and the COX/5-LOX inhibitors (5).

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

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^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.

Scheme 1^a

^a Reagents and conditions: (a) MeMgI, Et₂O, 25 °C, 20 h; (b) NaOMe, CF₃CO₂Et, Et₂O, -5 to 0 °C, 2 h; (c) ethanol (95%), reflux, 20 h; (d) FSO₂CF₂COOH, NaHCO₃, 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-chloro-

pyridin-4-yl)but-2-en-1-one (**8**, 91%).¹⁵ The subsequent condensation of **8** with either 4-(methanesulfonylphenyl)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 (FSO₂CF₂COOH)¹⁶ afforded the target 1-difluoromethyl-1,2-dihydropyrid-2-one products (**11a,b**) in 46–52% yields (Scheme 1).

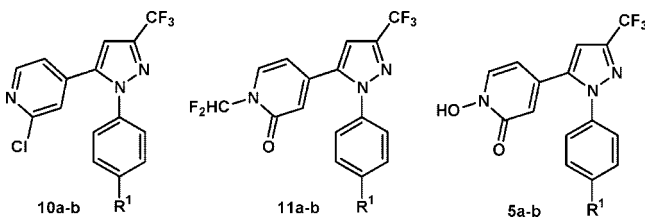
Results and Discussion

The rationale 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 CONCHF₂ 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 CHF₂ 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 CHF₂ 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 N¹-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 SO₂Me and SO₂NH₂ COX-2 pharmacophore in conjunction with a 2-chloropyridyl ring substituent exhibited potent and selective COX-2 inhibitory activity (COX-1 IC₅₀ = 8.3–258 μM; COX-2 IC₅₀ = 0.19–0.73 μM) that compared favorably to the reference drug celecoxib (COX-1 IC₅₀ = 7.7 μM; COX-2 IC₅₀ = 0.07 μM). In addition, the 2-chloropyridyl compounds **10a,b** also exhibited unexpected potent 5-LOX inhibition (IC₅₀ = 0.39–0.47 μM) that was 9- to 10-fold more potent than that of the reference drug caffeic acid (IC₅₀ = 4.0 μM) (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 SO₂Me compound **11a** (IC₅₀ = 1.82 μM). In contrast, the SO₂NH₂ compound **11b** (IC₅₀ = 0.69 μM) was equipotent with the 2-chloropyridyl compound **10b** (IC₅₀ = 0.73 μM). The equipotent 1-difluoromethyl-1,2-dihydropyrid-2-ones **11a,b** exhibited comparable 5-LOX inhibitory activity (IC₅₀ = 4.4–5.0 μM) to the reference drug caffeic acid.

The oral AI activities (ED₅₀ 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 ₂ Me	258	0.19	0.47	<150 ^d
10b	SO ₂ NH ₂	8.3	0.73	0.39	<150 ^e
11a	SO ₂ Me	7.8	1.82	4.4	42.9
11b	SO ₂ NH ₂	13.1	0.69	5.0	27.7
5a ^f	SO ₂ Me	13.2	7.5 ^g	0.35	66.9
5b ^f	SO ₂ NH 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 (IC₅₀, 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 (IC₅₀, 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 ED₅₀ 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** (SO₂Me, AI ED₅₀ = 42.9 mg/kg po) and **11b** (SO₂NH₂, AI ED₅₀ = 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 (ED₅₀ = 27.7 mg/kg po) that compares favorably with the reference

drugs celecoxib (ED₅₀ = 10.8 mg/kg po) and ibuprofen (ED₅₀ = 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 SO₂NH₂ > SO₂Me, (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. ¹H NMR and ¹³C 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/UV₂₅₄ 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 (SO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 3.15 (s, 3H, SO₂Me), 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); ¹³C NMR (CDCl₃) 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-1H-pyrazole (10b). This compound was obtained as a white solid in 28% yield, mp 235–237 °C; IR 3365, 3272 (NH₂), 1330, 1162 (SO₂) cm⁻¹; ¹H NMR (CDCl₃ + DMSO-*d*₆) δ 6.89 (s, 2H, SO₂NH₂ that exchanges with D₂O), 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); ¹³C NMR (CDCl₃ + 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-1H-pyrazole (11a,b). To a stirred solution of 1-(4-methanesulfonylphenyl or 4-aminosulfonylphenyl)-5-(2-chloropyridin-4-yl)-3-trifluoromethyl-1H-pyrazole (**10a** or **10b**) (6 mmol) in dry acetonitrile (45 mL) was added FSO₂CF₂COOH (3.28 g, 18 mmol) and NaHCO₃ (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 NaHCO₃ (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 (MgSO₄). 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-1H-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-1H-pyrazole (11a). This compound was obtained as a pale-yellow solid in 46% yield, mp 200–202 °C; IR 1678 (CO), 1327, 1152 (SO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 3.12 (s, 3H, SO₂Me), 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, ²*J*_{HCF} = 60 Hz, 1H, CHF₂), 8.07 (dd, *J* = 6.7, 1.8 Hz, 2H, phenyl H-3, H-5); ¹³C NMR (CDCl₃): 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. (C₁₇H₁₂F₅N₃O₃S) C, H, N.

1-(4-Aminosulfonylphenyl)-5-[4-(1-difluoromethyl-1,2-dihydropyrid-2-one)]-3-trifluoromethyl-1H-pyrazole (11b). This compound was obtained as a white solid in 52% yield, mp 190–192 °C; IR 3260 (broad NH₂), 1680 (CO), 1347, 1169 (SO₂) cm⁻¹; ¹H NMR (CDCl₃ + 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, SO₂NH₂ that exchanges with D₂O), 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, ²*J*_{HCF} = 60 Hz, 1H, CHF₂), 7.97 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); ¹³C NMR (CDCl₃ + 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. (C₁₆H₁₁F₅N₃O₃S) 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 (IC₅₀ 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) (IC₅₀ 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

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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>.

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