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Synthesis and biological evaluation of salicylic acid and *N*-acetyl-2-carboxybenzenesulfonamide regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore: Dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity

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ABSTRACT

A novel class of salicylic acid and *N*-acetyl-2-carboxybenzenesulfonamide regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore attached to its C-4 or C-5 position was designed for evaluation as anti-inflammatory (AI) agents. Replacement of the 2,4-difluorophenyl ring in diflunisal by the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety provided compounds showing dual selective cyclooxygenase-2 (COX-2)/5-lipoxygenase (5-LOX) inhibitory activities. AI structure–activity studies showed that the C-4 (**14a**) and C-5 (**14b**) salicylate regioisomers were 1.4- and 1.6-fold more potent than aspirin, and the C-5 *N*-acetyl-2-carboxybenzenesulfonamide regioisomer (**22b**) was 1.3- and 2.8-fold more potent than ibuprofen and aspirin, respectively. In vivo ulcer index (UI) studies showed that the 4- and 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acids (**14a** and **14b**) were completely non-ulcerogenic since no gastric lesions were present (UI = 0) relative to aspirin (UI = 57) at an equivalent μmol/kg oral dose. 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 dual COX-2/5-LOX inhibitory AI drugs.

Salicylic acid derivatives are widely used for treatment of various diseases. For example, acetylsalicylic acid (aspirin, **1**) is one of the most extensively used nonsteroidal anti-inflammatory drugs (NSAIDs) (see structure in Fig. 1). The complex biological actions exhibited by the simple salicylate class of compounds have attracted ongoing attention for more than a century. In this context, the moderately active anti-inflammatory (AI) and non-narcotic analgesic agent acetylsalicylic acid (**1**) continues to be a frequent first choice drug in the treatment of some arthritic disorders. However, these beneficial actions of aspirin may also be accompanied by adverse effects that include tinnitus, hypersensitization, and contraindicated gastrointestinal irritation, bleeding and/or ulceration.[1] The ability of aspirin to inhibit blood platelet aggregation is now viewed as a clinically useful prophylactic action that can reduce the incidence of thrombus formation in individuals with cardiovascular disease. The search for a clinical replacement for aspirin resulted in the development of the nonacetylating salicylic acid derivative diflunisal (**2**) that is a more potent AI and analgesic agent with a longer duration of action and is less ulcerogenic than aspirin.[2] The subsequent discovery[3,4] of two cyclooxygenase isozymes COX-1 and COX-2 provided the basis for the drug design concept that selective COX-2 inhibitors such as celecoxib[5] elicit effective AI activity devoid of the ulcerogenic effect associated with the use of NSAIDs such as aspirin that inhibit both COX-1 and COX-2. Some of aspirin's beneficial therapeutic effects arise from acetylation of COX-2, whereas its antithrombotic and ulcerogenic effects result from acetylation of COX-1. These observations were exploited in the design of the aspirin analog *o*-(acetoxyphenyl)hept-2-ynyl sulfide (APHS, **3**) that is a selective COX-2 inhibitor.[6–8] On the other hand, dual inhibitors of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) represent an attractive safer alternative to selective COX-2 inhibitors. This view is based on a potentially greater AI efficacy due to their ability to synergistically block both metabolic pathways of the arachidonic acid (AA) cascade.[9] 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.[10,11] 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

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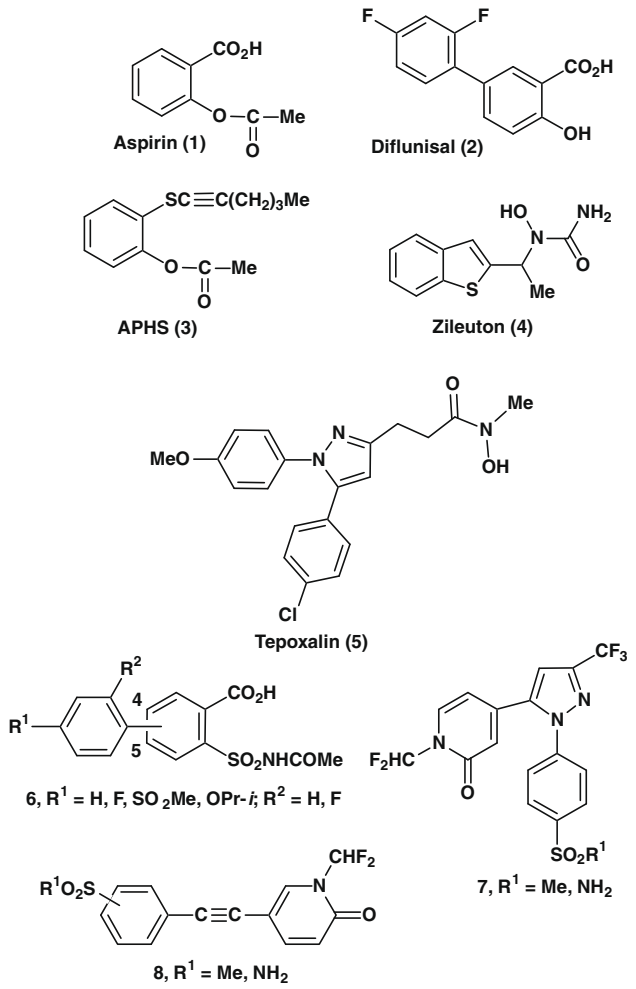


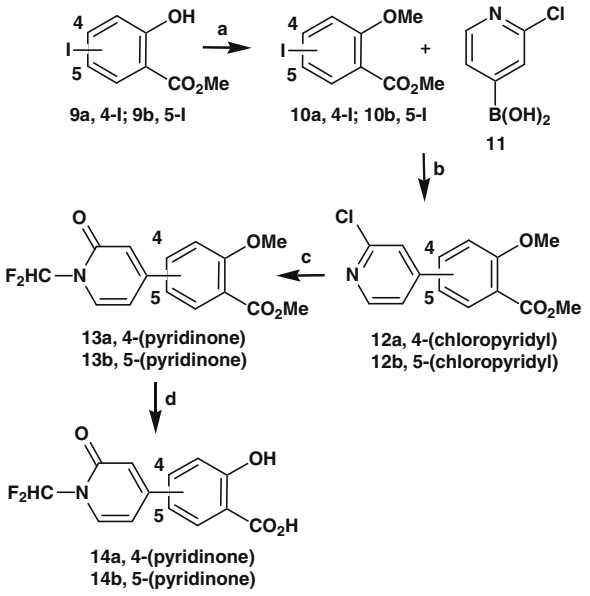
Figure 1. Chemical structures of some representative cyclooxygenase (COX) inhibitors (**1**–**3**), iron-chelating 5-LOX inhibitors (**4**–**5**), COX inhibitors (**6**), and the COX/5-LOX inhibitors (**7**–**8**).

the constitutive COX-1 isozyme.[10–12] 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.[13,14] There is a general belief that a dual inhibitor of the LOX/COX enzymatic pathways[15] constitutes a rational approach for the design of more effective AI agents with a superior safety profile relative to ulcerogenic NSAIDs, and selective COX-2 inhibitors that increase the incidence of adverse cardiovascular thrombotic effects.[16,17] It has been pointed out that inhibition of only one of the COX/LOX pathways could shift the metabolism of AA towards the other pathway, thereby inducing potential side effects.[18] 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.[19] Two representative examples of iron-chelating 5-LOX inhibitors include zileuton (**4**)[20] and tepoxalin (**5**)[19] (see structures in Fig. 1). Previously, we showed that the $SO_2NHCOMe$ pharmacophore present in *N*-acetyl-2-carboxybenzenesulfonamides (**6**) is a suitable bioisostere for the acetoxy (OCOMe) group in aspirin (**1**).[21] In recent studies, we described a novel class of dual COX/5-LOX inhibitors of celecoxib[22] analogs (**7**)[23] and 1,2-diarylacetylene regioisomers (**8**)[24] that possess a *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-LOX pharmacophore.

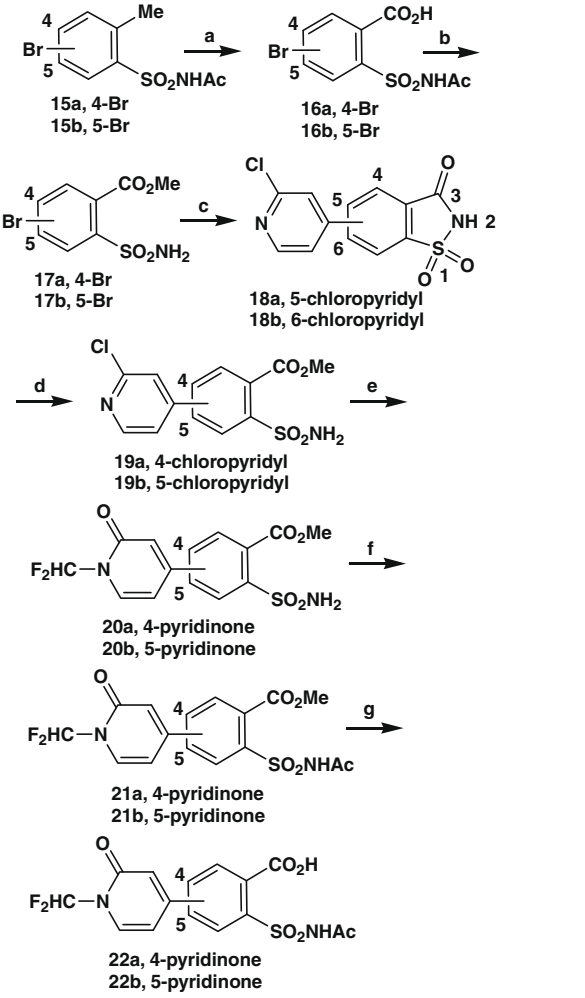
It is known that the $SO_2NHCOCH_3$ moiety is a 10^5–10^6 more reactive acetylating agent of enzyme serine hydroxyls than simple amides.[25] In an earlier study, it was shown that the incorporation of a *para*-*N*-acetylsulfonamido substituent on the C-3 phenyl ring of a rofecoxib regioisomer provided a highly potent and selective COX-2 inhibitor that has the potential to acetylate the COX-2 isozyme.[26] After acetylation of the COX-2 Ser^{530} OH by a *N*-acetylsulfonamido compound, a free SO_2NH_2 compound would be released that could also exhibit COX-2 inhibitory activity. This rationale is based on the observation that the water soluble non-narcotic analgesic agent parecoxib sodium[27] is a prodrug to the selective COX-2 inhibitor valdecoxib.[28] Accordingly, the $SO_2NHCOCH_3$ pharmacophore could serve the dual role of acetylating agent and prodrug.

It was anticipated that replacement of the 2,4-difluorophenyl moiety in the salicylic acid derivative diflunisal (**2**) by a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety may provide a hitherto unknown class of dual COX-2/5-LOX inhibitory anti-inflammatory agents. As part of our ongoing research program to design dual COX/5-LOX inhibitors, we describe herein the synthesis of a new class of salicylic acid analogs (**14a–b**) and *N*-acetyl-2-carboxybenzenesulfonamides (**22a–b**) possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety attached to its C-4 or C-5 position that may represent a new 5-LOX-inhibiting pharmacophore, their in vitro evaluation as COX-1/COX-2, 5-LOX inhibitors, in vivo assessment as AI agents, and results from ulcerogenicity studies for the two salicylic acid regioisomers (**14a–b**).

A Suzuki–Miyaura cross-coupling reaction[29,30] was used to synthesize the biaryl compounds **12a** and **18a**, and their respective regioisomers **12b** and **18b**. Reaction of methyl 4- or 5-iodo-2-methoxybenzoate (**10a** or **10b**) with 2-chloropyridine-4-boronic acid (**11**) in the presence of tetrakis(triphenylphosphine)palladium(0) catalyst and 2 M aqueous Na_2CO_3 in THF afforded methyl 4- or 5-(2-chloropyridin-4-yl)-2-methoxybenzoate (**12a**, **12b**) in 71% and 85% yield, respectively. In contrast, the Suzuki cross-coupling reaction of 4- or 5-bromo-2-methoxycarbonylbenzenesulfonamide (**17a** or **17b**) with **11** afforded 5- or 6-(2-chloropyridin-4-yl)-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (**18a** or **18b**) in 65–90% yields. The saccharin ring system present in the bicyclic compounds (**18a–b**) arises via an intramolecular cyclization involving the CO_2Me and SO_2NH_2 substituent present in **17a–b**. Treatment of **18a** or **18b** with methanolic-HCl opened the saccharin ring[31] to furnish the desired 4-(2-chloropyridin-4-yl)-2-methoxycarbonylbenzenesulfonamide (**19a**, 81%) or its regioisomer **19b** (80%). Subsequent transformation of the 2-chloropyridin-4-yl compound **12a–b** or **19a–b** to the target 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acid (**14a** or **14b**) or *N*-acetyl-4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-carboxybenzenesulfonamide (**22a** or **22b**) were carried out using the synthetic strategies shown in Schemes 1 and 2. Reaction of **12a–b**, or **19a–b**, with 2,2-difluoro-2-(fluorosulfonyl)acetic acid (FSO_2CF_2COOH)[32] afforded methyl 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxybenzoates (**13a–b**) in 54–61% yield or 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamides (**20a–b**) in 35–38% yield. Treatment of **13a–b** with BBr_3 in dichloromethane[33] at −78 °C resulted in simultaneous deprotection of the OMe and CO_2Me substitutents to afford the target 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acid regioisomers (**14a** or **14b**) in quantitative yield. On the other hand, N-acetylation of **20a** and **20b** using silica–sulfuric acid (SiO_2–OSO_2H) and acetyl chloride in chloroform–acetonitrile[34] furnished the respective regioisomer **21a** and **21b** in 13% and 57% yields, respectively. Deprotection of the CO_2Me group in **21a** and **21b** with aqueous 2 M lithium hydroxide in methanol-tetrahydrofuran[33] furnished the target *N*-acetyl-4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-



Scheme 1. Reagents and conditions: (a) MeI, K_2CO_3, DMF, 2 h, 25 °C; (b) $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux, 16 h; (c) FSO_2CF_2COOH, $NaHCO_3$, reflux, 16 h; (d) BBr_3, CH_2Cl_2, −78 °C for 1 h, and then 25 °C for 16 h.



Scheme 2. Reagents and conditions: (a) $KMnO_4$, 0.5 N NaOH, 60 °C, 16 h; (b) MeOH, concd H_2SO_4, reflux, 16 h; (c) 2-chloropyridin-4-boronic acid (**11**), $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux, 16 h; (d) methanolic-HCl, −5 °C, 1 h, reflux, 1 h; (e) $FSO_2CF_2CO_2H$, $NaHCO_3$, reflux, 16 h; (f) SiO_2–OSO_3H, THF–MeCN, CH_3COCl, reflux, 16 h; (g) LiOH, THF–MeOH–H_2O, reflux, 1 h.

one-4-yl)-2-carboxybenzenesulfonamide regioisomers (**22a** and **22b**) in 72% and 79% yields, respectively.

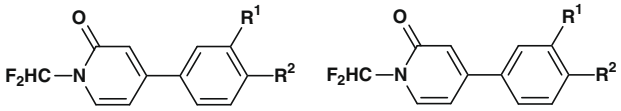
The rational for the design of the 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acids (**14a**–**b**) and *N*-acetyl-4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-carboxybenzenesulfonamides (**22a–b**) was based on the expectation that replacement of a 2,4-difluorophenyl ring in the salicylic acid derivative (diflunisal, **2**) by a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety may provide a hitherto unknown 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 **14a–b** and **22a–b** can be viewed as a cyclic hydroxamic acid mimetic. These *N*-difluoromethyl-1,2-dihydropyrid-2-ones **14a–b** and **22a–b** could inhibit the 5-LOX enzyme by two possible mechanisms. In this regard **14a**–**b** and **22a–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 build-up of negative potential around the two fluorine atoms of a CHF_2 group.[35] Despite this high electron-density, an aliphatic fluorine seldom acts as a hydrogen-bond acceptor, presumably due to its high electronegativity and low polarizability.[36,37] 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.[38] In addition, these cyclic *N*-difluoromethyl-1,2-dihydropyrid-2-ones, unlike acyclic hydroxamic acids which 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 2,4-difluorophenyl group present in diflunisal (**2**) resulting in retention of selective COX-2 inhibitory activity.

In vitro COX-1 and COX-2 enzyme inhibition studies (see data in Table 1) showed that the salicylic acid regioisomers (**14a–b**) exhibited a more potent inhibition, and hence selectively, for the COX-2 isozyme (COX-1 IC_{50} = 15.4 to >100 μM range; COX-2 IC_{50} = 0.98–4.4 μM range). In this regard, the C-4 regioisomer was a less potent, and the C-5 regioisomer was a more potent, COX-2 inhibitor than the reference drugs ibuprofen and aspirin. These COX-1/COX-2 isozyme inhibition data indicate that attachment of a *N*-difluoromethyl-1,2-dhydropyrid-2-one moiety to salicylic acid confers COX-2 selectivity relative to the COX-1 selective aspirin (see data in Table 1). The *N*-acetylbenzenesulfonamide regioisomers (**22a–b**) did not inhibit COX-1 (IC_{50} >100 μM). In comparison, the C-4 regioisomer (**22a**) was a weaker COX-2 inhibitor (IC_{50} = 17.6 μM) than the C-5 regioisomer (IC_{50} = 2.6 μM) that exhibited an inhibitory potency approaching that of the reference drugs aspirin (IC_{50} = 2.4 μM) and ibuprofen (IC_{50} = 1.1 μM).

In vitro 5-LOX inhibition studies showed that the point of attachment of the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety was a determinant of activity where the C-5 regioisomer was more potent than the corresponding C-4 regioisomer (**14b** > **14a**; **22b** ⩾ **22a**). In this regard, the 5-LOX inhibition potency of the less potent salicylic acid regioisomer (**14a**) (IC_{50} = 4.7 μM) compared favorably to the reference drug caffeic acid (IC_{50} = 4.0 μM) whereas the more potent C-5 regioisomers **14b** and **22b** with respective 5-LOX IC_{50} values of 0.37 and 0.28 μM were 11- and 14-fold more potent than the reference drug caffeic acid.

The oral AI activities (ED_{50} values) exhibited by the *N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl derivatives of the salicylic

Table 1
In vitro COX-1, COX-2, 5-LOX enzyme inhibition, and in vivo anti-inflammatory activity, data for salicylic acid (**14a**–**b**), and *N*-acetyl-2-carboxybenzenesulfonamide (**22a**–**b**), regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety



Compd	R^1	R^2	IC_{50}[a] (μM)		COX-2 S.I.[b]	5-LOX IC_{50}[c] (μM)	AI activity[d] ED_{50} (μmol/kg)
			COX-1	COX-2			
14a	OH	CO_2H	>100	4.4	>22	4.7	497
14b	CO_2H	OH	15.4	0.98	>15	0.37	434
22a	CO_2H	SO_2NHAc	>100	17.6	>5	0.32	Inactive
22b	SO_2NHAc	CO_2H	>100	2.6	>38	0.28	258
Ibuprofen	—	—	2.9	1.1[e]	>2	—	327
Aspirin	—	—	0.35	2.4[e]	0.15	—	716
Diflunisal	—	—	—	—	—	—	68
Caffeic acid[f]	—	—	—	—	—	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] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).
[c] 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.
[d] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the ED_{50} value (μmol/kg) at 3 h after oral administration of the test compound.
[e] Data acquired using ovine COX-2 (Catalog No. 560101, Cayman Chemicals Inc.).
[f] Caffeic acid: 3,4-dihydroxycinnamic acid.

acids (**14a**–**b**), and the *N*-acetyl-2-carboxybenzenesulfonamides (**22a–b**), were determined using a carrageenan-induced rat foot paw edema model (see data in Table 1). AI structure–activity data acquired showed that the salicylic acid regioisomers **14a** (AI ED_{50} = 497 μmol/kg po) and **14b** (AI ED_{50} = 434 μmol/kg po) are more potent AI agents than the reference drug aspirin (AI ED_{50} = 716 μmol/kg po). The C-5 2-carboxybenzenesulfonamide regioisomer **22b** (AI ED_{50} = 258 μmol/kg po), unlike the inactive C-4 regioisomer (**22a**) that is an extremely weak inhibitor of COX-2, is a more potent AI agent than the reference drugs ibuprofen (AI ED_{50} = 327 μmol/kg po) and aspirin. This superior AI activity exhibited by the *N*-difluoromethyl-1,2-dihydropyrid-2-ones **14a–b** relative to aspirin, and **22b** relative to both aspirin and ibuprofen, could be due to a number of factors which include oral bioavailability, biodistribution, and/or metabolic stability. Compounds **14a–b**, **22b** bearing a *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-LOX pharmacophore were less potent AI agents than diflunisal **2** (AI ED_{50} = 68 μmol/kg po) having a 2,4-difluorophenyl moiety.

The most common side effects associated with the long-term administration of NSAIDs are gastric erosions, ulcer formation, and sometimes severe bleeding. Therefore, the potential of the salicylates **14a** and **14b** to induce adverse gastric ulcerogenicity was determined in comparison to the reference NSAID aspirin (Table 2). It is significant that the two salicylate regioisomers (**14a–b**) were completely devoid of any gastric ulcerogenicity [ulcer index (UI) = 0] relative to aspirin (UI = 57) at equivalent 1.38 mmol/kg oral doses.

In conclusion, a hitherto unknown class of 4- and 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acids (**14a**–**b**), and *N*-acetyl 4- and 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)carboxybenzenesulfonamides (**22a**–**b**), was synthesized[40] for evaluation as dual 5-LOX[41] and COX-1/COX-2[42] isozyme inhibitors of inflammation. The structure–activity data acquired indicate that (i) compounds **14a–b** and **22a–b** exhibit weak to moderate in vitro COX-2 isozyme inhibitory potency and good COX-2 selectivity in conjunction with potent inhibition of the 5-LOX enzyme, (ii) the relative AI potency order[43] with respect to the point of attachment of the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety is C-5 > C-4 regioisomer, (iii) the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety provides a novel 5-LOX-inhibiting pharmacophore for the design of cyclic hydroxamic mimetics, and (iv) the non-ulcerogenic[44] dual acting compounds **14a–b**, **22b** exhibit AI activity that is dependent upon inhibition of proinflammatory prostaglandin and leukotriene biosyntheses in the respective cyclooxygenase and lipoxygenase pathways.

Table 2
Ulcer index assay data for the salicylates **14a** and **14b**

Compound	Dose (mmol/kg)	Ulcer index[a]
14a	1.38	0
14b	1.38	0
Aspirin (**1**)	1.38	57.4 ± 3.1[b]
Control group[b,c]	—	0

[a] Calculated by adding the total length (in mm) of individual lesion (ulceration) in each stomach and averaging over the number of animals (n = 4) in each group. Data are presented as mean total length ± SEM at 6 h after oral administration of the test compound.
[b] Data taken from the literature.[39]
[c] 1.0% Methyl cellulose solution.

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40. Experimental procedures and spectral data for compounds **10**, **12–14**, **17–22**. *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) were performed for C, H and N and were within ±0.4% of theoretical values for all elements listed. Compounds **12a–b**, **13a–b**, **18a–b**, **19a–b**, **20a–b** and **21a–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. Silica gel column chromatography was performed using Merck Silica Gel 60 ASTM (70–230 mesh). Methyl 5-iodosalicylate (**9b**) was synthesized in 81% yield by esterification of 5-iodosalicylic acid with MeOH in the presence of concd H_2SO_4. 2-Chloropyridine-4-boronic acid (**11**) was purchased from Combi-Blocks, Inc. (San Diego, CA). *N*-Acetyl-4- or 5-bromo-2-methylbenzenesulfonamide (**15a** or **15b**) were prepared according to a previously reported procedure.[21] Silica–sulfuric acid (SiO_2–OSO_2H) was readily prepared by mixing silica gel with chlorosulfonic acid.[45] All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. The in vivo anti-inflammatory and ulcerogenesis assays were carried out using protocols approved by the Health Sciences Animal Welfare Committee at the University of Alberta.

General procedure for the synthesis of methyl 4- or 5-iodo-2-methoxybenzoates (**10a–b**): A solution of methyl 4- or 5-iodosalicylate (**9a** or **9b**) (3 g, 10.79 mmol), methyl iodide (3.06 g, 21.58 mmol) and potassium carbonate (5.97 g, 43.16 mmol) in *N,N′*-dimethylformamide (75 mL) was stirred at 25 °C for 2 h.[33] Water (200 mL) was added, the mixture was extracted with ethyl acetate (3 × 75 mL), the combined organic extracts were washed successively with 5% HCl (2 × 75 mL), water and brine, and the organic fraction was dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the product (**10a** or **10b**). The spectral data for compounds **10a** and **10b** are listed below.

Methyl 4-iodo-2-methoxybenzoate (**10a**): This compound was obtained as a pale brown liquid in 100% yield; IR 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 7.31 (d, J = 1.8 Hz, 1H, phenyl H-3), 7.34 (dd, J = 7.9, 1.8 Hz, 1H, phenyl H-5), 7.50 (d, J = 7.9 Hz, 1H, phenyl H-6).

Methyl 5-iodo-2-methoxybenzoate (**10b**): This compound was obtained as a white solid in 97% yield; mp 56–58 °C (lit.[46] 57 °C); IR 1731 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 6H, 2 × OCH_3), 6.76 (d, J = 9.1 Hz, 1H, phenyl H-3), 7.73 (dd, J = 9.1, 2.4 Hz, 1H, phenyl H-4), 8.07 (d, J = 2.4 Hz, 1H, phenyl H-6).

General procedure for the synthesis of N-acetyl-4- or 5-bromo-2-carboxybenzenesulfonamide (**16a–b**): $KMnO_4$ (6.5 g, 41.1 mmol) was added to a solution of *N*-acetyl-4- or 5-bromo-2-methylbenzenesulfonamide (**15a** or **15b**) (2.0 g, 6.85 mmol) in aqueous 0.5 N NaOH (82 mL), and the reaction was allowed to proceed at 60 °C with stirring for 6 h prior to quenching with acetone. The insoluble material was removed by filtration, and the filtrate was diluted with H_2O (300 mL) prior to acidification to pH 3 using 5% HCl. This mixture was extracted with EtOAc (3 × 150 mL) and the combined organic phases were washed successively with water and brine, and dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the product (**16a** or **16b**). The spectral data for compounds **16a** and **16b** are listed below.

N-Acetyl-4-bromo-2-carboxybenzenesulfonamide (**16a**): This compound was obtained as a white solid in 76% yield; mp 170–172 °C; IR 1722 (CO), 1368, 1166 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.95 (s, 3H, $SO_2NHCOCH_3$), 6.75 (br s, 1H, $SO_2NHCOCH_3$ that exchanges with D_2O), 7.65 (dd, J = 8.5, 1.8 Hz, 1H, phenyl H-5), 7.74 (d, J = 1.8 Hz, 1H, phenyl H-3), 8.00 (d, J = 8.5 Hz, 1H, phenyl H-6), 11.38 (br s, 1H, COO*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 23.0, 127.4, 131.8, 132.4, 132.5, 134.4, 135.2, 166.4, 168.6.

N-Acetyl-5-bromo-2-carboxybenzenesulfonamide (**16b**): This compound was obtained as a white solid in 66% yield; mp 195–197 °C; IR 3270 (NH), 1715 (CO), 1373, 1166 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.96 (s, 3H, $SO_2NHCOCH_3$), 6.87 (br s, 1H, $SO_2NHCOCH_3$ that exchanges with D_2O), 7.53 (d, J = 7.9 Hz, 1H, phenyl H-3), 7.71 (dd, J = 7.9, 1.8 Hz, 1H, phenyl H-4), 8.24 (d, J = 1.8 Hz, 1H, phenyl H-6), 11.48 (br s, 1H, COO*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 23.0, 124.5, 129.7, 133.3, 134.3, 135.5, 143.1, 166.7, 168.6.

General procedure for the synthesis of 4- or 5-bromo-2-methoxycarbonylbenzenesulfonamide (**17a–b**): Concentrated H_2SO_4 (2 mL) was added to a solution of *N*-acetyl-4- or 5-bromo-2-carboxybenzenesulfonamide (**16a** or **16b**) (1.42 g, 4.41 mmol) in MeOH (30 mL) and the mixture was refluxed for 16 h. The mixture was then concentrated in vacuo to remove excess MeOH, and a saturated solution of aqueous Na_2CO_3 (25 mL) was added. After extraction with EtOAc (3 × 30 mL), the combined organic extracts were successively washed with water and brine, and dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the product (**17a** or **17b**). The spectral data for compounds **17a** and **17b** are listed below.

4-Bromo-2-methoxycarbonylbenzenesulfonamide (**17a**): This compound was obtained as a white solid in 53% yield; mp 130–132 °C; IR 3339, 3257 (NH_2), 1715 (CO), 1346, 1167 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H, OCH_3), 5.75 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.78 (dd, J = 8.5, 1.8 Hz, 1H, phenyl H-5), 7.99 (d, J = 1.8 Hz, 1H, phenyl H-3), 8.00 (d, J = 8.5 Hz, 1H, phenyl H-6); ^{13}C NMR ($CDCl_3$) δ 53.7, 127.0, 129.9, 131.3, 133.7, 135.0, 140.5, 166.6.

5-Bromo-2-methoxycarbonylbenzenesulfonamide (**17b**): This compound was obtained as a white solid in 93% yield; mp 185–187 °C; IR 3346, 3255 (NH_2), 1704 (CO), 1348, 1167 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.98 (s, 3H, OCH_3), 6.66 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.70–7.80 (m, 2H, phenyl H-3, H-4), 8.28 (d, J = 1.2 Hz, 1H, phenyl H-6); ^{13}C NMR ($CDCl_3$) δ 53.1, 126.0, 128.1, 131.0, 131.8, 134.6, 143.4, 166.7.

*General procedure for the synthesis of methyl 4- or 5-(2-chloropyridin-4-yl)-2-methoxybenzoate (**12a–b**) and 5- or 6-(2-chloropyridin-4-yl)-1,2-benzisothiazol-3(2H)-one-1,1-dioxide* (**18a–b**): 2-Chloropyridine-4-boronic acid (**11**) (0.47 g, 3 mmol) and an aryl halide (**10a**, **10b**, **17a** or **17b**, 2.0 mmol) were dissolved in THF (30 mL). Aqueous 2 M Na_2CO_3 (3.0 mL) and then tetrakis(triphenylphosphine)palladium (70 mg, 0.06 mmol) were added. The reaction was allowed to proceed at reflux for 16 h, cooled to 25 °C, water (150 mL) was added, the mixture was acidified to pH 3 using 5% w/v HCl, and this mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were successively washed with water (3 × 50 mL) and brine, and the organic fraction was dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the crude product. The product **12a** or **12b** was purified by silica gel column chromatography using hexanes–acetone (2:1, v/v) as eluent. On the other hand, 5- or 6-(2-chloropyridin-4-yl)-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (**18a** or **18b**) were purified by washing the respective crude solid with Et_2O. Some physical and spectroscopic data for **12a–b** and **18a–b** are listed below.

Methyl 4-(2-chloropyridin-4-yl)-2-methoxybenzoate (**12a**): This compound was obtained as a pale yellow solid in 71% yield; mp 111–113 °C; IR 1727 (CO)

cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.15 (d, J = 1.8 Hz, 1H, phenyl H-3), 7.22 (dd, J = 7.9, 1.8 Hz, 1H, phenyl H-5), 7.44 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.56 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.92 (d, J = 7.9 Hz, 1H, phenyl H-6), 8.48 (d, J = 4.9 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 52.3, 56.3, 110.6, 118.9, 120.6, 121.1, 122.3, 132.6, 141.9, 150.1, 150.6, 152.3, 159.6, 166.0.

Methyl 5-(2-chloropyridin-4-yl)-2-methoxybenzoate (**12b**): This compound was obtained as a pale yellow solid in 85% yield; mp 93–95 °C; IR 1731 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.11 (d, J = 9.2 Hz, 1H, phenyl H-3), 7.44 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.54 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.76 (dd, J = 9.2, 2.4 Hz, 1H, phenyl H-4), 8.10 (d, J = 2.4 Hz, 1H, phenyl H-6), 8.43 (d, J = 4.9 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 52.3, 56.3, 112.8, 119.8, 120.8, 121.4, 128.5, 130.4, 131.8, 149.9, 150.0, 152.2, 160.2, 166.0.

5-(2-Chloropyridin-4-yl)-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (**18a**): This compound was obtained as a white solid in 90% yield; mp 260–262 °C; IR 3306 (NH), 1736 (CO), 1322, 1113 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.47 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.57 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.97 (d, J = 7.9 Hz, 1H, saccharinyl H-7), 8.05 (dd, J = 7.9, 1.8 Hz, 1H, saccharinyl H-6), 8.14 (d, J = 1.8 Hz, 1H, saccharinyl H-4), 8.45 (d, J = 4.9 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 120.5, 121.4, 121.9, 126.8, 129.1, 133.2, 139.9, 142.0, 148.0, 150.0, 151.6, 160.1.

6-(2-Chloropyridin-4-yl)-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (**18b**): This compound was obtained as a white solid in 65% yield; mp >360 °C; IR 1739 (CO) 1317, 1122 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.69 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.81 (d, J = 1.2 Hz, 1H, pyridyl H-3), 8.05 (d, J = 7.9 Hz, 1H, saccharinyl H-4), 8.17 (dd, J = 7.9, 1.8 Hz, 1H, saccharinyl H-5), 8.42 (d, J = 1.8 Hz, 1H, saccharinyl H-7), 8.46 (d, J = 4.9 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 119.6, 120.6, 122.0, 125.2, 128.0, 132.7, 140.4, 142.8, 147.7, 150.0, 151.6, 159.7.

General procedure for the synthesis of 4- or 5-(2-chloropyridin-4-yl)-2-methoxycarbonylbenzenesulfonamide (**19a–b**): Hydrogen chloride gas was passed into a suspension of the saccharin derivative (**18a** or **18b**) (1.16 g, 3.94 mmol) in MeOH (100 mL) at −5 °C for 1 h. The mixture was then heated at reflux for 1 h, the mixture was cooled to 25 °C and the excess MeOH was removed in vacuo. A saturated solution of aqueous $NaHCO_3$ (25 mL) was added to the residue and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were successively washed with water (50 mL) and brine, and the organic fraction was dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the crude product which was purified by silica gel column chromatography using hexanes–ethyl acetate (1:3, v/v) as eluent to furnish the respective title compound **19a** or **19b**. Some physical and spectroscopic data for **19a–b** are listed below.

4-(2-Chloropyridin-4-yl)-2-methoxycarbonylbenzenesulfonamide (**19a**): This compound was obtained as a white solid in 80% yield; mp 138–140 °C; IR 3359, 3273 (NH_2), 1724 (CO), 1349, 1169 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (s, 3H, OCH_3), 5.81 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.47 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.59 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.89 (dd, J = 8.0, 1.9 Hz, 1H, phenyl H-5), 8.09 (d, J = 1.9 Hz, 1H, phenyl H-3), 8.30 (d, J = 8.0 Hz, 1H, phenyl H-6), 8.54 (d, J = 4.9 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 53.3, 120.1, 121.8, 129.0, 129.1, 129.9, 130.5, 140.5, 142.0, 148.1, 150.1, 152.2, 166.8.

4-(2-Chloropyridin-4-yl)-2-methoxycarbonylbenzenesulfonamide (**19a**): This compound was obtained as a white solid in 80% yield; mp 138–140 °C; IR 3359, 3273 (NH_2), 1724 (CO), 1349, 1169 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (s, 3H, OCH_3), 5.81 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.47 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.59 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.89 (dd, J = 8.0, 1.9 Hz, 1H, phenyl H-5), 8.09 (d, J = 1.9 Hz, 1H, phenyl H-3), 8.30 (d, J = 8.0 Hz, 1H, phenyl H-6), 8.54 (d, J = 4.9 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 53.3, 120.1, 121.8, 129.0, 129.1, 129.9, 130.5, 140.5, 142.0, 148.1, 150.1, 152.2, 166.8.

5-(2-Chloropyridin-4-yl)-2-methoxycarbonylbenzenesulfonamide (**19b**): This compound was obtained as a white solid in 81% yield; mp 180–182 °C; IR 1716 (CO), 1363, 1122 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.91 (s, 3H, OCH_3), 6.94 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.50 (dd, J = 5.5, 1.2 Hz, 1H, pyridyl H-5), 7.59 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.80–7.90 (m, 2H, phenyl H-3, H-4), 8.28 (s, 1H, phenyl H-6), 8.43 (d, J = 5.5 Hz, 1H, pyridyl H-6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 52.8, 120.3, 121.6, 126.2, 129.9, 130.0 130.8, 138.8, 142.6, 148.3, 150.1, 151.6, 167.0.

*General procedure for the synthesis of methyl 4- or 5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxybenzoates (**13a–b**), or 4- or 5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamides* (**20a–b**): $FSO_2CF_2CO_2H$ (1.92 g, 10.84 mmol), and then $NaHCO_3$ (0.30 g, 3.60 mmol), was added to a solution of a methyl 4- or 5-(2-chloropyridin-4-yl)-2-methoxybenzoate (**12a** or **12b**) (1.0 g, 3.60 mmol), or 4- or 5-(2-chloropyridin-4-yl)-2-methoxycarbonylbenzenesulfonamide (**19a** or **19b**) (1.18 g, 3.60 mmol) in acetonitrile (25 mL). The mixture was then heated at reflux under argon for 16 h, cooled to 25 °C, a saturated solution of aqueous $NaHCO_3$ (25 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were successively washed with 10 N HCl (30 mL) to remove some unreacted starting material, water (50 mL) and brine, and the organic fraction was dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the respective title product (**13a–b**, **20a–b**). Some physical and spectroscopic data for **13a–b** and **20a–b** are listed below.

Methyl 4-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxybenzoate (**13a**): This compound was obtained as a pale yellow solid in 54% yield; mp 75–77 °C; IR 1729, 1678 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.57 (dd, J = 7.3, 1.2 Hz, 1H, pyridone H-5), 6.77 (d, J = 1.2 Hz, 1H, pyridone H-3), 7.12 (d, J = 1.8 Hz, 1H, phenyl H-3), 7.22 (dd, J = 7.9, 1.8 Hz, 1H, phenyl H-5), 7.55 (d, J = 7.3 Hz, 1H, pyridone H-6), 7.73 (t, J = 60 Hz, 1H, CHF_2), 7.89 (d, J = 7.9 Hz, 1H, phenyl H-6); ^{13}C NMR ($CDCl_3$) δ 52.2, 56.2, 106.9, 107.4, 110.3, 118.3, 118.5, 121.5, 129.6, 132.4, 141.6, 152.3, 159.4, 161.0, 165.9.

Methyl 5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxybenzoate (**13b**): This compound was obtained as a pale yellow solid in 61% yield; mp 125–127 °C; IR 1732, 1675 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.59 (dd, J = 7.3, 1.2 Hz, 1H, pyridone H-5), 6.74 (d, J = 1.2 Hz, 1H, pyridone H-3), 7.09 (d, J = 9.2 Hz, 1H, phenyl H-3), 7.52 (d, J = 7.3 Hz, 1H, pyridone H-6), 7.72 (t, J = 60 Hz, 1H, CHF_2), 7.73 (dd, J = 9.2, 2.4 Hz, 1H, phenyl H-4), 8.07 (d, J = 2.4 Hz, 1H, phenyl H-6); ^{13}C NMR ($CDCl_3$) δ 52.3, 56.3, 106.5, 107.5, 112.7, 116.5, 120.6, 128.1, 129.3, 130.3, 131.7, 151.5, 160.6, 161.2, 165.8.

4-(N-Difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamide (**20a**): This compound was obtained as a pale yellow solid in 38% yield; mp 215–217 °C; IR 3338 (NH_2), 1725, 1674 (CO) 1348, 1166 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.90 (s, 3H, OCH_3), 6.67 (d, J = 7.4 Hz, 1H, pyridone H-5), 6.76 (s, 1H, pyridone H-3), 7.11 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.69 (d, J = 7.4 Hz, 1H, pyridone H-6), 7.70 (t, J = 60 Hz, 1H, CHF_2), 7.89 (d, J = 8.5 Hz, 1H, phenyl H-5); 7.91 (s, 1H, phenyl H-3), 8.10 (d, J = 8.5 Hz, 1H, phenyl H-6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 52.9, 105.9, 107.5, 117.9, 127.7, 128.5, 129.3, 130.1, 130.8, 139.3, 142.6, 149.9, 160.0, 166.8.

5-(N-Difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamide (**20b**): This compound was obtained as a pale yellow solid in 35% yield; mp 205–207 °C; IR 3371, 3262 (NH_2), 1734, 1675 (CO) 1340, 1140 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.90 (s, 3H, OCH_3), 6.65 (d, J = 7.4 Hz, 1H, pyridone H-5), 6.77 (s, 1H, pyridone H-3), 7.06 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.67 (d, J = 7.4 Hz, 1H, pyridone H-6), 7.68 (t, J = 60 Hz, 1H, CHF_2), 7.78 (d, J = 8.0 Hz, 1H, phenyl H-3); 7.85 (d, J = 8.0 Hz, 1H, phenyl H-4), 8.25 (s, 1H, phenyl H-6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 52.7, 105.6, 107.4, 117.7, 125.8, 129.5, 129.9, 131.1, 131.5, 138.5, 142.5, 149.9, 160.0, 166.8.

General procedure for the synthesis of 4- or 5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acid (**14a–b**): A solution of BBr_3 (5.24 mL of a 1 M solution in CH_2Cl_2, 5.24 mmol) was added to a solution of a methyl 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxybenzoate (**13a–b**) (0.81 g, 2.62 mmol) in CH_2Cl_2 (15 mL) at −78 °C with stirring for 1 h under argon. The mixture was then warmed to 25 °C, the mixture was stirred for another 16 h, quenched with water (50 mL), and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 extracts were successively washed with water (50 mL) and brine, and the organic fraction was dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the respective product **14a** or **14b**. The spectral and microanalytical data for compounds **14a** and **14b** are listed below.

4-(N-Difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acid (**14a**): This compound was obtained as a white solid in 100% yield; mp 255–257 °C; IR 1679 (CO) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 6.54 (dd, J = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.65 (d, J = 1.8 Hz, 1H, pyridone H-3), 7.01 (dd, J = 8.5, 1.8 Hz, 1H, phenyl H-5), 7.07 (d, J = 1.8 Hz, 1H, phenyl H-3), 7.52 (d, J = 7.3 Hz, 1H, pyridone H-6), 7.63 (t, J = 60 Hz, 1H, CHF_2), 7.87 (d, J = 8.5 Hz, 1H, phenyl H-6), 11.32 (br s, 1H, COO*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$) δ 106.0, 106.8, 113.4, 114.6, 116.4, 117.3, 128.9, 130.5, 142.2, 151.2, 160.1, 161.2, 171.2. Anal. Calcd for $C_{13}H_9F_2NO_4$: C, 55.52; H, 3.23; N, 4.98. Found: C, 55.83; H, 3.44; N, 4.89.

5-(N-Difluoromethyl-1,2-dihydropyrid-2-one-4-yl)salicylic acid (**14b**): This compound was obtained as a white solid in 100% yield; mp 258–260 °C; IR 1677 (CO) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 6.55 (dd, J = 7.9, 1.8 Hz, 1H, pyridone H-5), 6.61 (d, J = 1.8 Hz, 1H, pyridone H-3), 6.97 (d, J = 9.2 Hz, 1H, phenyl H-3), 7.48 (d, J = 7.9 Hz, 1H, pyridone H-6), 7.63 (t, J = 60 Hz, 1H, CHF_2), 7.64 (dd, J = 9.2, 2.4 Hz, 1H, phenyl H-4), 8.07 (d, J = 2.4 Hz, 1H, phenyl H-6), 11.50 (br s, 1H, COO*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$) δ 104.9, 106.3, 112.1, 114.1, 116.9, 125.4, 127.6, 128.3, 132.1, 150.2, 159.4, 161.9, 170.5. Anal. Calcd for $C_{13}H_9F_2NO_4$: C, 55.52; H, 3.23; N, 4.98. Found: C, 55.53; H, 3.34; N, 4.87.

General procedure for the synthesis of N-acetyl-4- or 5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamide (**21a–b**): Acetyl chloride (0.14 mL, 2 mmol), and then SiO_2–OSO_3H (8 mg), was added to a solution of a 4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamide (**20a** or **20b**, 0.36 g, 1 mmol) in $CHCl_3$ (10 mL) and CH_3CN (3 mL). The reaction was allowed to proceed at reflux for 16 h under argon. The mixture was filtered and the solvent was removed in vacuo. The crude residue was purified by silica gel column chromatography using hexanes–ethyl acetate (1:2, v/v), and then ethyl acetate, as eluent to furnish the respective title product **21a** or **21b**. Some physical and spectroscopic data for **21a–b** are listed below.

N-Acetyl-4-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamide (**21a**): This compound was obtained as a pale yellow solid in 13% yield; mp 218–220 °C; IR 1715, 1670 (CO) 1362, 1166 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.15 (s, 3H, $COCH_3$), 4.00 (s, 3H, OCH_3), 6.56 (dd, J = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.82 (d, J = 1.8 Hz, 1H, pyridone H-3), 7.60 (d, J = 7.3 Hz, 1H, pyridone H-6), 7.72 (t, J = 60 Hz, 1H, CHF_2), 7.85 (dd, J = 8.6, 1.8 Hz, 1H, phenyl H-5); 7.98 (d, J = 1.8 Hz, 1H, phenyl H-3), 8.42 (d, J = 8.6 Hz, 1H, phenyl H-6), 9.00 (br s, 1H, N*H* that exchanges with D_2O); ^{13}C NMR (DMSO-d_6) δ 23.2, 53.3, 105.8, 107.5, 117.8, 128.9, 129.8, 131.4, 132.1, 133.0, 137.0, 137.8, 149.8, 160.0, 166.3, 169.0.

N-Acetyl-5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonyl benzenesulfonamide (**21b**): This compound was obtained as a pale yellow solid in 57% yield; mp 225–227 °C; IR 1715, 1670 (CO) 1362, 1166 (SO_2) cm^{-1}; ^1H

NMR ($CDCl_3$ + DMSO-d_6) δ 1.96 (s, 3H, $COCH_3$), 3.90 (s, 3H, OCH_3), 6.58 (dd, J = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.73 (d, J = 1.8 Hz, 1H, pyridone H-3), 7.55 (d, J = 7.3 Hz, 1H, pyridone H-6), 7.63 (t, J = 60 Hz, 1H, CHF_2), 7.68 (d, J = 8.0 Hz, 1H, phenyl H-3); 7.80 (dd, J = 8.0, 1.8 Hz, 1H, phenyl H-4), 8.40 (d, J = 1.8 Hz, 1H, phenyl H-6), 11.70 (br s, 1H, N*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 22.9, 52.7, 105.8, 107.5, 117.9, 129.5, 129.8, 130.9, 132.6, 137.3, 138.0, 149.8, 159.9, 165.9, 168.5.

General procedure for the synthesis of N-acetyl-4- or 5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-carboxybenzenesulfonamide (**22a**–**b**): Aqueous LiOH (2 M, 5 mL) was added to a solution of *N*-acetyl-4- or 5-(*N*-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-methoxycarbonylbenzenesulfonamide (**21a** or **21b**, 0.30 g, 0.75 mmol) in MeOH (5 mL) and THF (5 mL), and the reaction was allowed to proceed at reflux for 1 h. The mixture was cooled to 25 °C, and acidified to pH 3 using 5% HCl prior to extraction with EtOAc (3 × 25 mL). The combined organic extracts were successively washed with water (50 mL) and brine, and the organic fraction was dried ($MgSO_4$). Filtration and then removal of the solvent from the organic fraction in vacuo afforded the respective product **22a** or **22b**. The spectral and microanalytical data for compounds **22a** and **22b** are listed below.

N-Acetyl-4-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-carboxybenzenesulfonamide (**22a**): This compound was obtained as a white solid in 72% yield; mp 210–212 °C; IR 1723, 1672 (CO), 1350, 1169 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (s, 3H, $COCH_3$), 6.55 (dd, J = 7.9, 1.8 Hz, 1H, pyridone H-5), 6.69 (d, J = 1.8 Hz, 1H, pyridone H-3), 7.57 (d, J = 7.9 Hz, 1H, pyridone H-6), 7.64 (t, J = 60 Hz, 1H, CHF_2), 7.73 (dd, J = 8.0, 1.9 Hz, 1H, phenyl H-5); 7.82 (d, J = 1.9 Hz, 1H, phenyl H-3), 8.24 (d, J = 8.0 Hz, 1H, phenyl H-6), 11.60 (br s, 1H, COO*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 22.8, 105.6, 106.7, 118.0, 127.0, 127.4, 129.5, 131.4, 133.8, 137.2, 140.3, 149.8, 159.8, 166.9, 168.5. Anal. Calcd for $C_{15}H_{12}F_2N_2O_6S{\cdot}3/7H_2O$: C, 45.72; H, 3.29; N, 7.11. Found: C, 46.09; H, 3.67; N, 6.55.

N-Acetyl-5-(N-difluoromethyl-1,2-dihydropyrid-2-one-4-yl)-2-carboxybenzenesulfonamide (**22b**): This compound was obtained as a white solid in 79% yield; mp 230–233 °C; IR 1723, 1675 (CO), 1352, 1152 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 1.94 (s, 3H, $COCH_3$), 6.61 (d, J = 7.3 Hz, 1H, pyridone H-5), 6.72 (s, 1H, pyridone H-3), 7.61 (d, J = 7.3 Hz, 1H, pyridone H-6), 7.65 (t, J = 60 Hz, 1H, CHF_2), 7.72 (d, J = 8.5 Hz, 1H, phenyl H-3); 7.84 (d, J = 8.5 Hz, 1H, phenyl H-4), 8.33 (s, 1H, phenyl H-6), 11.70 (br s, 1H, COO*H* that exchanges with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 22.4, 105.3, 106.5, 117.2, 128.6, 128.9, 129.2, 130.1, 133.7, 136.5, 136.9, 149.5, 159.5, 166.5, 168.1. Anal. Calcd for $C_{15}H_{12}F_2N_2O_6S{\cdot}1/18H_2O$: C, 46.51; H, 3.16; N, 7.23. Found: C, 46.85; H, 3.44; N, 6.84.

41. *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, USA) (IC_{50} values, μM) were determined using an enzyme immuno assay (EIA) kit (Catalog No. 760700, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[47]
42. *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) were determined using an enzyme immuno assay (EIA) kit (Catalog No. 560131, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[48]
43. *Anti-inflammatory assay*: The test compounds **14a–b**, **22a–b**, and the reference drugs ibuprofen, aspirin and diflunisal were evaluated using the in vivo carrageenan-induced rat foot paw edema model reported previously.[49]
44. *Acute ulcerogenesis assay*: The ability of the test compounds **14a–b** to produce gastric damage (lesions) was evaluated according to reported procedures.[50–53] Ulcerogenic activity was evaluated after oral administration of **14a** or **14b** (1.38 mmol/kg) at an equimolar to that used for the reference drug aspirin (1.38 mmol/kg). All drugs were suspended and administered in a 1% methylcellulose solution. Food, but not water, was removed 24 h before administration of test compounds. Six hours after oral administration of the drug, rats were euthanized in a CO_2 chamber, and their stomachs were removed, cut out along the greater curvature of the stomach, gently rinsed with water, and placed on ice. The number and the length of ulcers observed in each stomach were determined by using magnifier lenses. In this assay, the severity of each gastric lesion is measured along its greatest length (1 mm, rating of 1; 1–2 mm, rating of 2; and >2 mm, rating according to their length in millimeter). The UI for each test compound is calculated by adding the total length (L, in mm) of individual gastric lesions in each stomach and averaging over the number of animals in each group (n = 4): UI = ($L1$ + $L2$ + $L3$ + $L4$)/4.
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