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Phenylacetic acid regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore: Evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity

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ABSTRACT

A novel class of phenylacetic acid regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore attached to its C-2, C-3 or C-4 position was designed for evaluation as anti-inflammatory (AI) agents. A number of compounds exhibited a combination of potent in vitro cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) inhibitory activities. 2-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9a**) exerted the most potent AI activity among this group of compounds. Molecular modeling studies showed that the *N*-difluoromethyl-1,2-dihydropyridin-2-one moiety present in **9a** inserts into the secondary pocket present in COX-2 to confer COX-2 selectivity, and that the *N*-difluoromethyl-1,2-dihydropyrid-2-one group (**9a**) binds close to the region of the 15-LOX enzyme containing catalytic iron (His361, His366). Accordingly, the *N*-difluoromethyl-1,2-dihyrdopyrid-2-one moiety possesses properties that make it an attractive pharmacophore suitable for the design of dual COX-2/5-LOX inhibitory AI drugs.

The design of agents to relieve pain and inflammation associated with inflammatory diseases has undergone continual evolution targeted toward the development of more efficacious classes of drugs that exhibit fewer adverse side effects. In this regard, non-steroidal anti-inflammatory drugs (NSAIDs) belonging to the aryl(heteroaryl)acetic acid class became invaluable agents for the treatment of arthritis and osteoarthritis. Inhibition of the cyclooxygenase (COX) enzyme, that catalyzes the biotransformation of arachidonic acid (AA) to inflammatory prostaglandins and thromboxanes in the COX pathway, became a hallmark feature of virtually all marketed NSAIDs. However, NSAIDs such as indomethacin (**1**), and many arylacetic acids, frequently cause mechanism based side effects that include gastrointestinal bleeding and/or ulceration (see structure in Fig. 1).[1] It was subsequently discovered that there are two isoforms of COX, each with a distinct physiological role.[2,3] The COX-1 isozyme is constitutively produced in a variety of tissues, and appears to be important to the maintenance of normal physiological functions including gastric cytoprotection. A second inducible isozyme, COX-2 is largely responsible for the production of prostaglandins that cause inflammation.[4,5] Accordingly, it was proposed that a selective COX-2 inhibitor would have useful anti-inflammatory (AI) activity without the ulcerogenic side effects associated with the use of NSAIDs that inhibit both COX-1 and COX-2.[6] This concept was validated with the clinical introduction of the selective COX-2 inhibitor celecoxib (**2**, Celebrex®) that is devoid of adverse ulcerogenic effects.[7] Alternatively, AA is also metabolized by the lipoxygenase (5-LOX, 8-, 12-, 15-) enzyme family to produce proinflammatory leukotrienes (LTs) that are associated with the production of inflammatory, bronchoconstrictor, hypersensitivity, anaphylactic, and asthmatic actions.[8]

There is credence for the concept that a dual inhibitor of the LOX/COX enzymatic pathways[9] constitutes a logical approach for the design of more efficacious AI agents with a superior safety profile relative to non-selective COX inhibitory NSAIDs, and selective COX-2 inhibitors that increase the incidence of adverse thrombotic events.[10,11] This supposition is based on the premise that inhibiting only one of the COX/LOX pathways may shift the metabolism of AA to the other uninhibited pathway that may culminate in undesirable side effects.[12] In a recent study, the tolyl ring in celecoxib (**2**) was replaced by a *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-LOX pharmacophore[13] to provide a novel class of dual COX/5-

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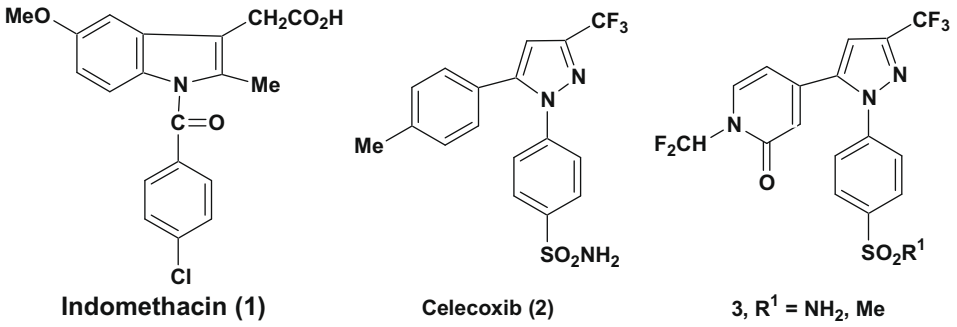


Figure 1. Some representative examples of a highly ulcerogenic non-selective COX-1/COX-2 inhibitor indomethacin (**1**), the selective COX-2 inhibitor celecoxib (**2**), and dual COX/5-LOX inhibitors having a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore (**3**).

LOX inhibitors (**3**) that exhibited effective AI activity.[14] It was anticipated that attachment of this *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-LOX pharmacophore to a classical arylacetic acid NSAID template would furnish a hitherto unknown group of dual 5-LOX/COX inhibitory AI agents. Accordingly, we now describe the synthesis of a novel class of arylacetic acid regioisomers having a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety (**9a–f**), their in vitro evaluation as COX-1/COX-2, 5-LOX inhibitors, some molecular modeling studies, and their in vivo assessment as AI agents.

The methyl 2-, 3- and 4-iodophenylacetates (**5a–c**) were prepared from the corresponding acid (**4a–c**) using a previously reported procedure.[15] Subsequent treatment of the acetates (**5a–c**) with lithium diisopropylamide (LDA), followed by alkylation using methyl iodide at −78 °C,[16] afforded the respective methyl 2-(2-, 3-, and 4-iodophenyl)propanoates (**5d–f**). A Suzuki–Miyaura[17,18] cross-coupling reaction was used to synthesize the biaryl compounds **7a–f**. Thus, reaction of an aryl iodide **5a–f** with 2-chloropyridine-4-boronic acid (**6**) in the presence of tetrakis(triphenylphosphine)palladium (0) catalyst and 2 M aqueous Na_2CO_3 in THF afforded the respective diaryl product **7a–f** in moderate yield (45–55%).[19] Transformation of the 2-chloropyridyl compounds (**7a–c** or **7d–f**) to the target methyl 2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetates (**8a–c**) and methyl 2-[2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoates (**8d–f**) were carried out using the synthetic strategies shown in Scheme 1. In this regard, reaction of a 2-chloropyridyl compound (**7a–f**) with 2,2-difluoro-2-(fluorosulfonyl)acetic acid (FSO_2CF_2COOH)[20] in the presence of $NaHCO_3$ in CH_3CN gave the respective 1-difluoromethyl-2-oxo-1,2-dihydropyridine product **8a–f** in moderate to good yields (40–83%). Hydrolysis of the 2-, 3-, and 4-(*N*-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl) esters **8a–f** using aqueous 2 N NaOH at 80–85 °C[21] afforded the target 2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acids (**9a–c**) and 2-[2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acids (**9d–f**) in moderate to excellent yield (51–90%).

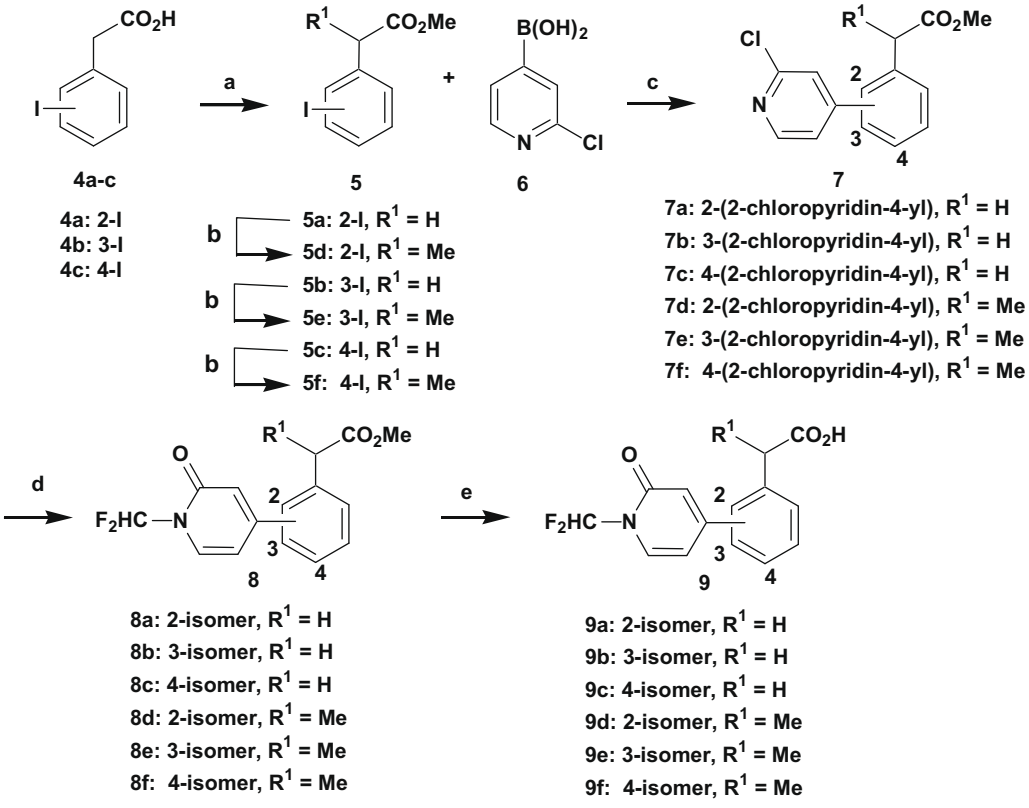
Non-steroidal AI arylacetic acid derivatives possess several common structural features that include a carboxyl group separated by one-carbon atom from a flat aromatic nucleus, and one or more large lipophilic groups attached to the aromatic nucleus that is two, three or four carbon atoms removed from the point of attachment of the acetic acid side chain.[22] The rational for the design of the 2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acids (**9a–c**) and 2-[2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acids (**9d–f**) was based on the expectation that attachment of a lipophilic *N*-difluoromethyl-2-oxo-1,2-dihydropyridyl moiety to a phenylacetic acid template 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 **9a–f** can be viewed as a cyclic hydroxamic acid mimetic. These *N*-difluoromethyl-1,2-dihydropyrid-2-ones **9a–f** could inhibit the 5-LOX enzyme by two possible mechanisms. In this regard **9a–f**, like acyclic hydroxamic acids, may act as effective iron chelators to exhibit 5-LOX inhibitory activity. There is a substantial build-up of negative potential around the two fluorine atoms of a CHF_2 group.[23] Even with this high electron-density, an aliphatic fluorine rarely acts as a hydrogen-bond acceptor, most likely due to its high electronegativity and low polarizability.[24,25] Consequently, it is also possible that the CHF_2 group could interact with a positively charged region on the enzyme that may provide enhanced affinity and competitive reversible inhibition of the COX and/or 5-LOX enzymes.[26]

In vitro COX-1 and COX-2 enzyme inhibition studies (see data in Table 1) showed that the *N*-difluoromethyl-1,2-dihydropyrid-2-one regioisomers **9a–f** exhibited a more potent inhibition, and hence selectively, for the COX-2 isozyme (COX-1 IC_{50} = 5.5 to >100 μM range; COX-2 IC_{50} = 0.86–11.1 μM range). The point of attachment of the *N*-difluoromethyl-1,2-dihydropyrid-2-one ring system to the phenylacetic acid moiety was not, with the exception of **9b**, a determinant of COX-2 inhibitory activity since the potencies of **9a**, **9c** and **9d–f** were similar to each other and to that of the reference drug ibuprofen (IC_{50} = 1.1 μM). The COX-2 inhibitory activity of the phenylacetic acids **9a** and **9c** (R^1 = H) was marginally more potent than that of the phenylpropionic acids **9d–f** (R^1 = Me).

In vitro 5-LOX inhibition studies showed that attachment of the *N*-difluoromethyl-1,2-dhydropyrid-2-one ring system to a phenylacetic acid moiety confers 5-LOX inhibitory activity that is absent in traditional NSAIDs. This group of compounds **9a–f** exhibited more potent 5-LOX inhibitory activity (IC_{50} = 0.20–3.47 μM range) than the reference drug caffeic acid (IC_{50} = 4.0 μM). The point of attachment of the *N*-difluoromethyl-1,2-dhydropyrid-2-one moiety was a determinant of activity where the C-2 and C-3 regioisomers were more potent than the corresponding C-4 regioisomer (**9a–b** > **9c**; **9d–e** > **9f**). The R^1 substituent was a determinant of 5-LOX inhibitory potency for the C-2 regioisomers (**9a**, R^1 = H, IC_{50} = 0.20 μM; **9d**, R^1 = Me, IC_{50} = 2.0 μM), but not the C-3 and C-4 regioisomers (**9b–c**, R^1 = H equipotent to **9e–f**, R^1 = Me).

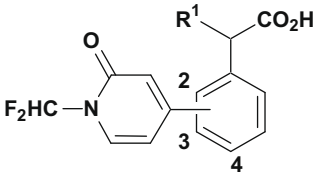
Some physicochemical comparisons indicate that the phenylacetic acids **9a–c** (R^1 = H) are less lipophilic (calculated Log *P* = 1.07–1.37 range) and smaller in size (calculated volume of 228 Å^3) than the corresponding phenylpropionic acids **9d–f** (R^1 = Me; calculated Log *P* = 1.38–1.68 range; calculated volume of 244 Å^3; see data in Table 1).

Molecular modeling (docking) studies were carried out to investigate binding interactions between a phenylacetic acid derivative possessing the novel *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore and the mammalian COX-2 and 15-LOX enzymes. In this regard, the binding interaction of the most potent 2-(1-



Scheme 1. Reagents and conditions: (a) MeOH, concd H_2SO_4, reflux, 3 h; (b) LDA, MeI, THF, −78 °C for 30 min, and then 0 °C for 1 h; (c) $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, reflux, 16 h; (d) FSO_2CF_2COOH, $NaHCO_3$, reflux, 12 h; (e) aqueous 2 N NaOH, 80–85 °C, 4 h.

Table 1
In vitro COX-1, COX-2 and 5-LOX enzyme inhibition data for 2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acids (**9a–c**) and 2-[2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acids (**9d–f**)



Compound	R^1	COX-1 IC_{50}[a] (μM)	COX-2 IC_{50}[a] (μM)	5-LOX IC_{50}[b] (μM)	Log P[c]	Volume[d] (Å^3)
9a	H	5.5	0.86	0.20	1.07	228.2
9b	H	>100	11.1	0.37	1.37	228.9
9c	H	9.6	0.89	3.47	1.37	228.9
9d	Me	>100	2.6	2.0	1.38	244.9
9e	Me	13.9	1.2	0.37	1.68	244.8
9f	Me	15.3	2.4	3.0	1.68	244.7
Ibuprofen		2.9	1.1[e]	—	3.68	211.8
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 immuno assay kit (Catalog No. 560131, Cayman Chemicals Inc., Ann Arbor, MI, USA) 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, USA) and the deviation from the mean is <10% of the mean value.
[c] The log P value was calculated using the ChemDraw Ultra program, Version 6.0, CambridgeSoft company.
[d] The volume of the molecule, after minimization using the MM3 force field, was calculated using the Alchemy 2000 program, Tripos Inc.
[e] Data acquired using ovine COX-2 (Catalog No. 560101, Cayman Chemicals Inc.).
[f] Caffeic acid: 3,4-dihydroxycinnamic acid.

difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9a**, COX-2 IC_{50} = 0.86 μM) within the COX-2 binding site is illustrated in Figure 2. The most stable enzyme–ligand complex shows that the *N*-difluoromethyl-1,2-dihydropyrid-2-one group is buried deep inside the secondary pocket of COX-2 suggesting that the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety is a potential

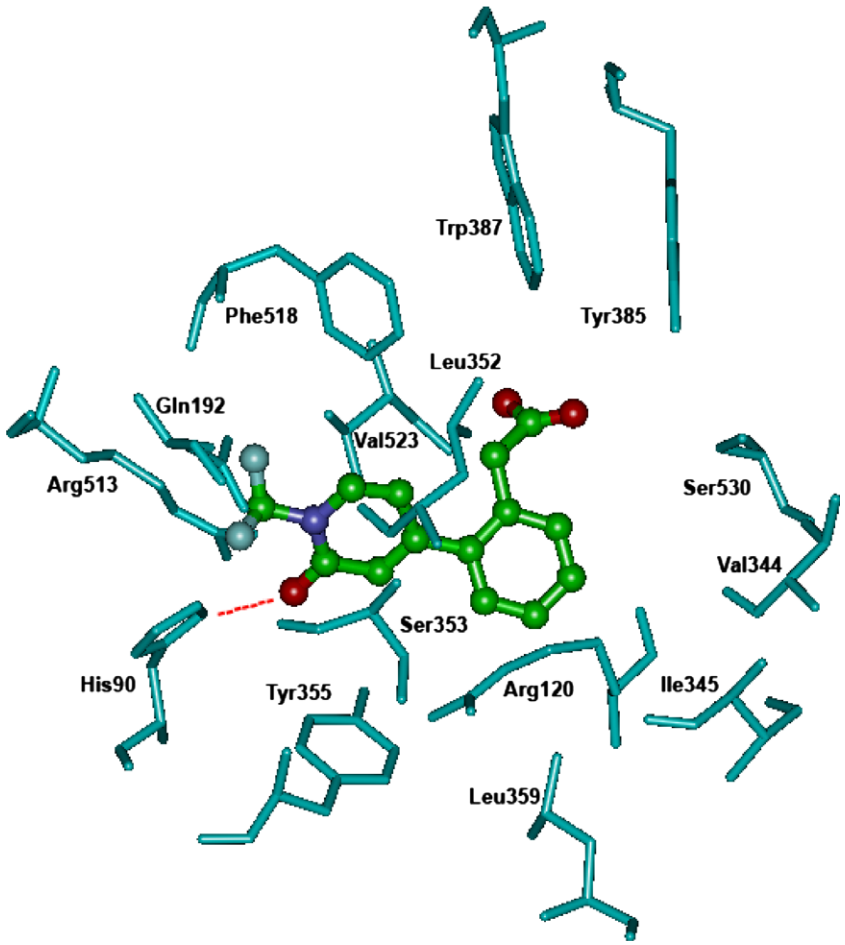


Figure 2. Docking 2-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9a**) (ball-and-stick) in the active site of mammalian COX-2 ($E_{intermolecular}$ = −22.46 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

COX-2 pharmacophore. The 1,2-dihydropyrid-2-one ring is surrounded by His90, Gln192, Arg513, Phe518 and Val523 (distance <5 Å). The C═*O* (dihydropyrid-2-one) undergoes a favorable hydrogen bonding interaction with the N*H* of His90 (distance = 2.17 Å). The $NCHF_2$ (part of 1,2-dihydropyrid-2-one ring) is positioned in the vicinity of polar amino acids such as His90, Gln192 and Arg513 (distance <4.50 Å). The fluorine atoms (CHF_2) are located about 1.99 Å and 3.83 Å from the N*H* of His90, and the guanidino NH_2 of Arg513, respectively. This data confirms the preferential interaction of the highly electronegative CHF_2 substituent with a polar electropositive environment. The phenylacetic acid ($PhCH_2COOH$) ring is oriented in the vicinity of Trp387, Tyr385, Ser530, Leu359, Leu352, Ile345 and Val344 (distance <5 Å). Furthermore, the distance between C═*O* of CH_2COOH and O*H* of Tyr385 at the apex of the COX-2 binding site is about 4.59 Å. This observation is consistent with crystal structure data for the NSAID diclofenac [*ortho*-(2,6-dichloroanilino)phenylacetic acid] bound to the COX-2 enzyme where the carboxylate is oriented in the region of Tyr385 and Ser530.[27]

The mammalian lipoxygenase isozymes (5, 12 and 15-LOX) are closely related since they share 35–80% sequence identity. X-ray data for mammalian 15-LOX has been reported,[28] but is not available for the 5-LOX isozyme. Therefore, 15-LOX x-ray data was used as a model to investigate the binding interactions of 2-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9a**, 5-LOX IC_{50} = 0.20 μM) within a LOX binding site (see Fig. 3). This docking study indicated that **9a** is oriented such that the phenylacetic acid ($PhCH_2COOH$) moiety is oriented toward the hydrophobic base of the 15-LOX active site in the vicinity of Ile414, Phe415, Met419 and Ile593 (distance <5 Å). The CH_2COOH substituent appears in a region comprised of Gln548, Val594 and Leu597 (distance <5 Å). A favorable hydrogen bonding interaction was observed between the C═*O* (CH_2COOH) and NH_2 of Gln548 (distance = 1.98 Å). The *N*-difluoromethyl-1,2-dihydropyrid-2-one LOX pharmacophore is oriented close to the region containing the catalytic iron (His361 and His366). Furthermore, the distance between the fluorine atoms (CHF_2) and N*H*s of His361 and His366 is about 4.61 Å and 4.67 Å, respectively. In addition, the C═*O* (dihydropyrid-2-one) is located about 3.85 Å from the C═*O* of Glu357. The distance between the CHF_2 and NH_2 (guanidine) group of Arg403 that is closer to the mouth of the 15-LOX binding site is about 10.78 Å. This molecular modeling data provides credence for our hypothesis that the $CONCHF_2$ fragment present in the *N*-difluoromethyl-1,2-dihydropyrid-2-one ring can be viewed as a cyclic hydroxamic acid mimetic.

The acetic acid (**9a**, **9b**), and propionic acid (**9e**) compounds, based on in vitro enzyme inhibition data, were selected for in vivo pharmacological evaluation to determine their anti-inflammatory (AI) activities. In a carrageenan-induced rat paw edema assay model, the acetic acid 2-regioisomer **9a** exhibited weak AI activity (19.9 ± 0.9% inhibition) for a 150 mg/kg oral (po) dose at 3 h post-drug administration relative to the non-selective COX-1/COX-2 inhibitor (ibuprofen, ED_{50} = 67.4 mg/kg po dose), 5-LOX inhibitor (caffeic acid, 8.2% inhibition for a 30 mg/kg po dose), and the 15-LOX inhibitor (nordihydroguaiaretic acid, NDGA, 15.1% inhibition for a 30 mg/kg po dose, ED_{50} = 205 mg/kg) refer-

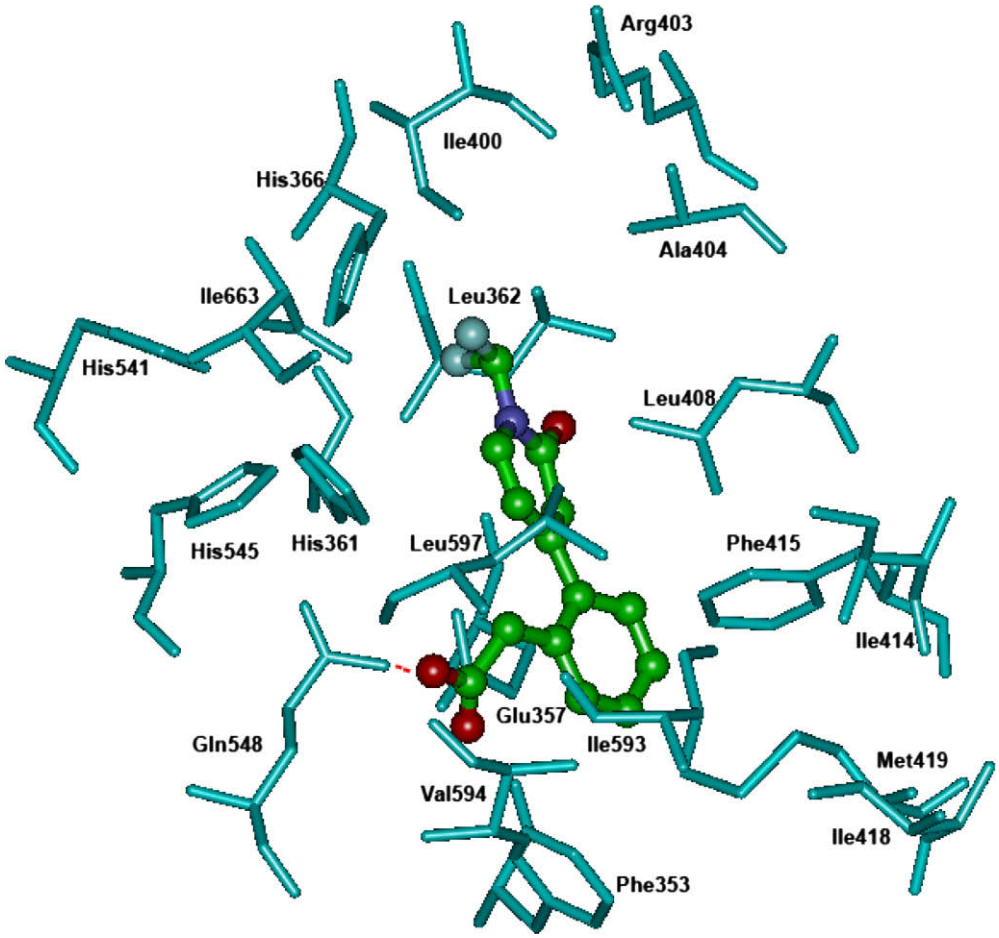


Figure 3. Docking 2-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9a**) (ball-and-stick) in the active site of mammalian 15-LOX ($E_{intermolecular}$ = −46.26 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

ence drugs. The related acetic acid 3-regioisomer **9b** was also a weak AI agent (11.2 ± 4.2% inhibition for a 100 mg/kg po dose). In contrast, the propionic acid 3-regioisomer **9e** was an inactive AI agent at a 100 mg/kg po dose. The route of administration was not a determinant of AI activity for **9a** since a 150 mg/kg intraperitoneal (ip) dose provided similar AI activity (18.5 ± 3.9% inhibition) to that determined for the same oral dose. The in vivo AI potency exhibited by compounds **9a**, **9b** and **9e** was weaker than expected based on their excellent in vitro inhibition of the COX-2 and/or 5-LOX enzymes. One possible explanation is that the acetic acid moiety in **9a** is oriented toward the apex of the COX binding site as indicated in the molecular modeling study (see Fig. 2) in comparison to traditional arylacetic NSAIDs where the carboxyl group generally interacts with Arg120 at the mouth of the COX binding site.

In conclusion, a new class of 2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acids (**9a–c**) and 2-[2-, 3-, and 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acids (**9d–f**) was synthesized[29] for evaluation as dual 5-LOX[30] and COX-1/COX-2[31] isozyme inhibitors of inflammation. Biological data acquired indicate that compounds **9a–b** and **9e** exhibit the best combination of in vitro COX-2 and 5-LOX inhibitory potency. Among this group of compounds **9a–f**, the C-2 phenylacetic acid regioisomer (**9a**) exhibited the most potent AI activity.[32] Molecular modeling (docking) studies[33] showed that the *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety present in **9a** inserts into the secondary pocket present in COX-2 similar to the sulfonamide (SO_2NH_2) COX-2 pharmacophore present in celecoxib (**2**) to confer selectivity for the COX-2 isozyme, and that the *N*-difluoromethyl-1,2-dihydropyrid-2-one group (**9a**) is oriented close to the region of the 15-LOX enzyme containing the catalytic iron (His361, His366). Accordingly, the *N*-difluoromethyl-1,2-dihyrdopyrid-2-one moiety possesses properties suitable for the design of dual COX-2/5-LOX inhibitory AI drugs.

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29. Experimental procedures and spectral data for compounds **5**, **7–9**. *General.* Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. Microanalyses were performed for C, H, N (Micro Analytical Service Laboratory, Department of Chemistry, University of Alberta) and were within ±0.4% of theoretical values. Compounds **5a–f**, **7a–f**, and **8a–f** 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, indicative of high purity. Silica gel column chromatography was performed using Merck Silica Gel 60 ASTM (70–230 mesh). All reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), with the exception of 2-chloropyridine-4-boronic acid which was purchased from Combi-Blocks Inc., 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 methyl 2-, 3-, and 4-iodophenylacetates (**5a–c**): Concentrated sulfuric acid (97–98%, 1.10 mL) was added to a solution of an iodophenylacetic acid (**4a–c**, 2.0 g, 7.6 mmol) in MeOH (5 mL), and the reaction mixture was heated at reflux for 3 h. After cooling to 25 °C, the MeOH was removed in vacuo, H_2O (80 mL) was added to the residue, and this mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water and then brine. The organic fraction was dried (Na_2SO_4) and the solvent was removed in vacuo to furnish the respective methyl ester product (**5a–c**) as a pale yellow oil that was sufficiently pure for use in subsequent reactions. ^{1}H NMR spectral data for **5a–c** are listed below.

Methyl 2-iodophenylacetate (**5a**): Yield, 95%; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H, O*Me*), 3.84 (s, 2H, CH_2), 6.97–7.03 (m, 1H, H-4), 7.29–7.36 (m, 2H, H-5, H-6), 7.88 (d, J = 7.9 Hz, H-3).

Methyl 3-iodophenylacetate (**5b**): Yield, 99%; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H, O*Me*), 3.73 (s, 2H, CH_2), 7.09 (dd, J = 7.9, 7.9 Hz, 1H, H-5), 7.28 (d, J = 7.9 Hz, 1H, H-6), 7.64 (d, J = 7.9 Hz, 1H, H-4), 7.68 (s, 1H, H-2).

Methyl 4-iodophenylacetate (**5c**): Yield, 98%; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3H, O*Me*), 3.69 (s, 2H, CH_2), 7.03 (d, J = 8.5 Hz, 2H, H-2, H-6), 7.65 (d, J = 8.5 Hz, 2H, H-3, H-5).

General procedure for the synthesis of methyl 2-(2-, 3-, and 4-iodophenyl)propanoates (**5d–f**): *n*-Butyllithium (1.52 M in hexane, 2.4 mL) was added to a solution of diisopropylamine (0.83 mL, 6.0 mmol) in THF (6 mL) at −78 °C under argon, and the mixture was stirred for 30 min. A solution of a methyl iodophenylacetate (**5a–c**, 1.38 g, 5.0 mmol) in THF (10 mL) was added dropwise, the mixture was stirred for 30 min, iodomethane (0.60 mL, 9.6 mmol) was added dropwise, the reaction was allowed to proceed with stirring at −78 °C for 30 min prior to raising the temperature to 0 °C and quenching the reaction with saturated aqueous NH_4Cl (30 mL). The aqueous layer was washed with EtOAc (2 × 50 mL), the combined organic phases were washed with brine, and the organic fraction was dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue that was purified by silica gel column chromatography (EtOAc/hexanes, 1:16, v/v) to give the respective product (**5d–f**) as a yellow oil. ^{1}H NMR spectral data for **5d–f** are listed below.

Methyl 2-(2-iodophenyl)propanoate (**5d**): Yield, 72%; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 6.7 Hz, 3H, CH*Me*), 3.69 (s, 3H, O*Me*), 4.12 (q, J = 6.7 Hz, 1H, C*H*Me), 6.92–6.98 (m, 1H, H-4), 7.26–7.35 (m, 2H, H-5, H-6), 7.85 (d, J = 7.9 Hz, H-3).

Methyl 2-(3-iodophenyl)propanoate (**5e**): Yield, 49%; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 6.7 Hz, 3H, CH*Me*), 3.68 (s, 3H, O*Me*), 4.12 (q, J = 6.7 Hz, 1H, C*H*Me), 7.07 (dd, J = 7.9, 7.9 Hz, 1H, H-5), 7.29 (d, J = 7.9, Hz, 1H, H-6), 7.61 (d, J = 7.9 Hz, 1H, H-4), 7.66 (d, J = 1.8 Hz, 1H, H-2).

Methyl 2-(4-iodophenyl)propanoate (**5f**): Yield, 98%; ^{1}H NMR ($CDCl_3$) δ 1.48 (d, J = 6.7 Hz, 3H, CH*Me*), 3.66 (s, 3H, O*Me*), 4.06 (q, J = 6.7 Hz, 1H, C*H*Me), 7.03 (dd, J = 7.9, 1.8 Hz, 2H, H-2, H-6), 7.65 (dd, J = 7.9, 1.8 Hz, 2H, H-3, H-5).

General procedure for the synthesis of methyl 2-, 3-, or 4-(2-chloropyridin-4-yl)phenylacetates (**7a–c**) *and methyl 2-[2-, 3-, or 4-(2-chloropyridin-4-yl)phenyl]propanoates* (**7d–f**): A methyl 2-, 3-, or 4-iodophenylacetate (**5a–c**) (828 mg, 3.0 mmol), or a methyl 2-(2-, 3-, or 4-iodophenyl)propanoate **(5d–f)** (870 mg, 3.0 mmol), and 2-chloropyridine-4-boronic acid (306 mg, 3.9 mmol) were dissolved in THF (40 mL). Aqueous 2 M Na_2CO_3 (4.5 mL) and then $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) were added. The reaction was allowed to proceed at reflux under argon 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 the mixture was extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with water (3 × 50 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo. The dark brown residue obtained was purified by silica gel column chromatography using hexanes/EtOAc (3:1, v/v) as eluent to afford the respective product **7a–f**. Spectroscopic data for **7a–f** are listed below.

Methyl 2-(2-chloropyridin-4-yl)phenylacetate (**7a**): Yield, 50%; pale yellow solid, mp 63–64 °C; IR (film): 2919, 1735, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H, O*Me*), 3.67 (s, 2H, CH_2), 7.22–7.25 (m, 2H, phenyl H-5, H-6), 7.33 (s, 1H, pyridyl H-3), 7.35–7.40 (m, 3H, phenyl H-3, H-4 and pyridyl H-5), 8.44 (d, J = 4.7 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 38.5, 52.2, 123.0, 124.7, 127.6, 129.1, 129.5, 130.8, 131.3, 138.4, 149.4, 151.6, 152.1, 171.6.

Methyl 3-(2-chloropyridin-4-yl)phenylacetate (**7b**): Yield, 52%; yellow oil; IR (film): 2920, 1736, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H, O*Me*), 3.73 (s, 2H, CH_2), 7.39–7.55 (overlapping multiplets, 6H total, pyridyl H-3, H-5, phenyl H-2, H-4, H-5, H-6), 8.44 (d, J = 5.5 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 41.0, 52.2, 120.5, 122.1, 125.8, 128.0 129.5, 130.6, 135.1, 137.2, 150.0, 151.2, 152.2, 171.5.

Methyl 4-(2-chloropyridin-4-yl)phenylacetate (**7c**): Yield, 54%; pale yellow solid, mp 92–94 °C; IR (film): 2918, 1734, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, O*Me*), 3.72 (s, 2H, CH_2), 7.41 (dd, J = 4.9, 1.8 Hz, 1H, pyridyl H-5), 7.43 (dd, J = 6.7, 1.8 Hz, 2H, phenyl H-2, H-6), 7.54 (s, 1H, pyridyl H-3), 7.59 (dd, J = 6.7 Hz, 1.8 Hz, 2H, phenyl H-3, H-5), 8.43 (d, J = 4.9 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 40.8, 52.2, 120.2, 121.9, 127.2, 130.2, 135.6, 135.7, 149.9, 151.1, 152.2, 171.5.

Methyl 2-[2-(2-chloropyridin-4-yl)phenyl]propanoate (**7d**): Yield, 50%; pale yellow solid, mp 63–64 °C; IR (film): 2919, 1736, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 6.7 Hz, 3H, CH*Me*), 3.68 (s, 3H, O*Me*), 3.78 (q, J = 6.7 Hz, 1H, C*H*Me), 7.20–7.51 (overlapping multiplets, 6H total, pyridyl H-3, H-5, phenyl H-3, H-4, H-5, H-6), 8.48 (d, J = 4.9 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 19.1, 41.0, 52.2, 123.3, 124.9, 127.2, 127.3, 129.3, 129.4, 137.5, 138.1, 149.4, 151.6, 152.2, 174.5.

Methyl 2-[3-(2-chloropyridin-4-yl)phenyl]propanoate (**7e**): Yield, 45%; yellow oil; IR (film): 2945, 1736, 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (d, J = 6.7 Hz, 3H, CH*Me*), 3.69 (s, 3H, O*Me*), 3.81 (q, J = 6.7 Hz, 1H, C*H*Me), 7.38–7.56 (overlapping multiplets, 6H total, pyridyl H-3, H-5, phenyl H-2, H-4, H-5, H-6), 8.44 (d, J = 4.9 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 18.7, 45.4, 52.2, 120.5, 122.1, 125.9, 126.2 128.8, 129.5, 137.3, 141.7, 150.0, 151.3, 152.2, 174.5.

Methyl 2-[4-(2-chloropyridin-4-yl)phenyl]propanoate (**7f**): Yield, 55%; yellow oil; IR (film): 2918, 1734, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 6.7 Hz, CH*Me*), 3.70 (s, 3H, O*Me*), 3.80 (q, J = 6.7 Hz, 1H, C*H*Me), 7.41 (dd, J = 4.9, 1.2 Hz, 1H, pyridyl H-5), 7.43 (dd, J = 8.5, 1.8 Hz, 2H, phenyl H-2, H-6), 7.54 (d, J = 1.2 Hz, 1H, pyridyl H-3), 7.59 (dd, J = 8.5, 1.8 Hz, 2H, phenyl H-3, H-5), 8.43 (d, J = 4.9 Hz, pyridyl H-6); ^{13}C NMR ($CDCl_3$) δ 18.5, 45.1, 52.2, 120.3, 121.9, 127.3, 128.4, 135.7, 142.2, 150.0, 151.1, 152.2, 174.5.

General procedure for the synthesis of methyl 2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetates (**8a–c**) *and methyl 2-[2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoates* (**8d–f**): To a solution of a methyl 2-, 3-, or 4-(2-chloropyridin-4-yl)phenylacetate **(7a–c)** (261 mg, 1.0 mmol), or methyl 2-[2-, 3-, or 4-(2-chloropyridin-4-yl)phenyl]propanoate **(7d–f)** (275 mg, 1.0 mmol), in acetonitrile (15 mL) was added $FSO_2CF_2CO_2H$ (310 mL, 3.0 mmol) followed by $NaHCO_3$ (93 mg, 1.1 mmol). This mixture was then heated at reflux under argon for 12 h, cooled to 25 °C, a saturated solution of aqueous $NaHCO_3$ (25 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were successively washed with 10 N HCl (2 × 20 mL) to remove unreacted starting material, the organic fraction was washed with water (50 mL) and brine, and the organic fraction was dried (Na_2SO_4). Removal of the solvent from the organic fraction in vacuo afforded the respective title product **8a–f**. The physical and spectral data for **8a–f** are listed below.

Methyl 2-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetate (**8a**): Yield, 40%; pale yellow solid, mp 63–64 °C; IR (film): 1734, 1676, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H, O*Me*), 3.72 (s, 2H, CH_2), 6.58 (dd, J = 7.9, 1.8 Hz, 1H, pyridone H-5), 6.76 (s, 1H, pyridone H-3), 7.38–7.50 (m, 4H, phenyl H-3, H-4, H-5, H-6), 7.49 (d, J = 7.9 Hz, 1H, pyridone H-6), 7.73 (t, J = 60.4 Hz, 1H, C*H*F$_2$); ^{13}C NMR ($CDCl_3$) δ 41.0, 52.2, 107.1, 107.5 (t, J = 255 Hz), 117.6, 125.6, 127.7, 129.3 (t, J = 4 Hz), 129.4, 131.1, 135.0, 136.9, 153.0, 161.3, 171.5.

Methyl 3-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetate (**8b**):

Yield, 73%; pale yellow oil; IR (film): 1735, 1681, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 3H, O*Me*), 3.67 (s, 2H, CH_2), 6.40 (dd, *J* = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.53 (s, 1H, pyridone H-3), 7.23 (d, *J* = 7.3 Hz, phenyl H-6), 7.33–7.43 (m, 1H, phenyl H-5), 7.36 (s, 1H, phenyl H-2), 7.39 (d, *J* = 7.3 Hz, 1H, phenyl H-4), 7.50 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.74 (t, *J* = 60.4 Hz, 1H, CHF_2); ^{13}C NMR ($CDCl_3$) δ 38.3, 52.1, 107.4 (t, *J* = 255 Hz), 109.5, 120.6, 127.6, 128.5, 128.9 (t, *J* = 4 Hz), 129.3, 131.0, 138.2, 154.4, 160.7, 171.5, 173.5.

Methyl 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetate (**8c**): Yield, 80%; pale yellow solid, mp 65–67 °C; IR (film): 1734, 1675, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H, O*Me*), 3.73 (s, 2H, CH_2), 6.58 (dd, *J* = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.76 (d, *J* = 1.8 Hz, 1H, pyridone H-3), 7.40 (d, *J* = 7.9 Hz, 2H, phenyl H-2, H-6), 7.52 (d, *J* = 7.9 Hz, 1H, pyridone H-6), 7.56 (d, *J* = 7.9 Hz, 2H, phenyl H-3, H-5), 7.73 (t, *J* = 60.4 Hz, 1H, CHF_2); ^{13}C NMR ($CDCl_3$) δ 40.8, 52.2, 107.0, 107.5 (t, *J* = 255 Hz), 117.3, 127.0, 129.2, 130.3, 135.4, 136.3, 152.7, 161.2, 171.4.

Methyl 2-[2-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoate (**8d**): Yield, 48%; pale yellow oil; IR (film): 1735, 1683, 1057 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (d, *J* = 6.7 Hz, 3H, CH*Me*), 3.67 (s, 3H, O*Me*), 3.87 (q, *J* = 6.7 Hz, 1H, C*H*Me), 6.38 (dd, *J* = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.55 (s, 1H, pyridone H-3), 7.20 (d, *J* = 7.9 Hz, 1H, phenyl H-6), 7.31–7.45 (m, 3H, phenyl H-3, H-4, H-5), 7.51 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.76 (t, *J* = 60.4 Hz, 1H, CHF_2); ^{13}C NMR ($CDCl_3$) δ 19.3, 41.2, 52.2, 107.5 (t, *J* = 255 Hz), 109.7, 121.0, 127.3, 127.4, 128.6 (t, *J* = 4 Hz), 128.7, 129.6, 137.5, 137.9, 154.5, 160.8, 174.5.

Methyl 2-[3-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoate (**8e**): Yield, 83%; pale yellow solid, mp 94–96 °C; IR (film): 1735, 1678, 1072 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (d, *J* = 6.7 Hz, 3H, CH*Me*), 3.69 (s, 3H, O*Me*), 3.80 (q, *J* = 6.7 Hz, 1H, C*H*Me), 6.58 (dd, *J* = 7.3 Hz, 1.8 Hz, 1H, pyridone H-5), 6.76 (s, 1H, pyridone H-3), 7.43 (dd, *J* = 7.9, 2.4 Hz, 1H, phenyl H-6), 7.45 (d, *J* = 2.4 Hz, 1H, phenyl H-2), 7.47 (t, *J* = 2.4 Hz, 1H, phenyl H-5), 7.50 (dd, *J* = 7.9, 2.4 Hz, 1H, phenyl H-4), 7.52 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.73 (t, *J* = 60.4 Hz, 1H, CHF_2); ^{13}C NMR ($CDCl_3$) δ 18.6, 45.3, 52.2, 107.1, 107.5 (t, *J* = 255 Hz), 117.6, 125.6, 126.0, 129.2, 129.3 (t, *J* = 4 Hz), 129.6, 137.0, 141.6, 153.0, 161.2, 174.5.

Methyl 2-[4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoate (**8f**): Yield, 70%; pale yellow oil; IR (film): 1735, 1677, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (d, *J* = 6.7 Hz, 3H, CH*Me*), 3.69 (s, 3H, O*Me*), 3.79 (q, *J* = 6.7 Hz, 1H, C*H*Me), 6.57 (dd, *J* = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.74 (s, 1H, pyridone H-3), 7.42 (dd, *J* = 7.9, 1.8 Hz, 2H, phenyl H-2, H-6), 7.55 (dd, *J* = 7.9, 1.8 Hz, 2H, phenyl H-3, H-5), 7.56 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.76 (t, *J* = 60.4 Hz, 1H, CHF_2); ^{13}C NMR ($CDCl_3$) δ 18.5, 45.2, 52.2, 106.9, 107.5 (t, *J* = 255 Hz), 117.3, 127.0, 128.3, 129.2 (t, *J* = 4 Hz), 135.4, 142.8, 152.7, 161.2, 174.4.

General procedure for the synthesis of 2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acids (**9a–c**) *and 2-[2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acids* (**9d–f**): A mixture of a methyl 2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetate (**8a–c**) (221 mg, 0.75 mmol), or a methyl 2-[2-, 3-, or 4-(1-difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoate (**8d–f**) (230 mg, 0.75 mmol), and aqueous 2 N sodium hydroxide (5 mL) was stirred at 80–85 °C for 4 h. The reaction mixture was cooled to 25 °C and acidified to pH 3 by addition of 3 N hydrochloric acid prior to extraction with EtOAc (3 × 50 mL). The combined EtOAc extracts were washed with water, brine, the organic fractions was dried (Na_2SO_4) and the solvent was removed in vacuo. The impure product was purified by silica gel column chromatography using hexanes/EtOAc (2:1, v/v) as eluent to give the title product **9a–c**. The physical and spectral data for 9a–c are listed below.

2-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9a**): Yield, 63%; pale yellow solid, mp 136–138 °C; IR (film): 3033, 1724, 1682, 1071 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 2H, CH_2), 6.37 (dd, *J* = 7.3, 1.8 Hz, 1H, pyridone H-5), 6.61 (s, 1H, pyridone H-3), 7.23 (dd, *J* = 7.3, 1.2 Hz, 1H, phenyl H-6), 7.34–7.40 (m, 3H, phenyl H-3, H-4, H-5), 7.51 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.74 (t, *J* = 59.8 Hz, 1H, CHF_2), 10.22 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 38.3, 107.4 (t, *J* = 255 Hz), 109.9, 120.7, 127.8, 128.6, 128.9, 129.2, 129.5 (t, *J* = 4 Hz), 131.1, 138.3, 154.6, 161.1, 175.8. Anal. Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; N, 5.02. Found: C, 60.13; H, 4.30; N, 4.91.

3-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9b**): Yield, 70%; pale yellow solid, mp 160–161 °C; IR (film): 3453, 1733, 1675, 1027 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 3.61 (s, 2H, CH_2), 6.54 (dd, *J* = 7.9, 1.8 Hz, 1H, pyridone H-5), 6.68 (s, 1H, pyridone H-3), 7.35–7.46 (m, 4H, phenyl H2, H-4, H-5, H-6), 7.46 (d, *J* = 7.9 Hz, 1H, pyridone H-6), 7.66 (t, *J* = 60.4 Hz, 1H, CHF_2), 10.40 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$ + DMSO) δ 40.1, 107.1, 107.4 (t, *J* = 255 Hz), 117.3, 125.2, 127.7, 129.0 (t, *J* = 4 Hz), 129.3, 131.0, 135.5, 136.5, 153.0, 161.1, 173.1. Anal. Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; N, 5.02. Found: C, 59.94; H, 4.01; N, 4.99.

4-(1-Difluoromethyl- 2-oxo-1,2-dihydropyridin-4-yl)phenylacetic acid (**9c**): Yield, 90%; pale yellow solid, mp 133–134 °C; IR (film): 3080, 1734, 1653, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 2H, CH_2), 6.59 (dd, *J* = 7.3, 1.8 Hz, pyridone H-5), 6.77 (d, *J* = 1.2 Hz, 1H, pyridone H-3), 7.42 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.55 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 7.56 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.73 (t, *J* = 60.4 Hz, 1H, CHF_2), 10.63 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 40.9, 107.0, 107.4 (t, *J* = 255 Hz), 117.1, 126.8, 129.1, 130.2, 135.0, 136.8, 152.9, 161.3, 173.3. Anal. Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; N, 5.02. Found: C, 60.20; H, 4.01; N, 5.03.

2-[2-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acid (**9d**): Yield, 51%; pale yellow solid, mp 147–149 °C; IR (film): 2981, 1735, 1662, 1067 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (d, *J* = 6.7 Hz, 3H, CH*Me*), 3.88 (q, *J* = 7.3 Hz, 1H, C*H*Me), 6.46 (d, *J* = 6.7 Hz, pyridone H-5), 6.63 (s, 1H, pyridone H-3), 7.20 (d, *J* = 7.3 Hz, 1H, phenyl H-6), 7.33 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, phenyl H-4), 7.43 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H, phenyl H-5), 7.48 (dd, *J* = 7.3, 1.2 Hz, 1H, phenyl H-3), 7.51 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.76 (t, *J* = 60.4 Hz, 1H, CHF_2), 11.2 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 18.9, 41.1, 107.4 (t, *J* = 255 Hz), 110.1, 120.9, 127.4 (t, *J* = 4 Hz), 127.5, 128.5, 128.7, 129.6, 137.5, 137.6, 154.8, 161.1, 178.9. Anal. Calcd for $C_{15}H_{13}F_2NO_3$: C, 61.43; H, 4.47; N, 4.78. Found: C, 61.47; H, 4.55; N, 4.58.

2-[3-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acid (**9e**): Yield, 63%; pale yellow solid, mp 133–134 °C; IR (film): 2929, 1724, 1672, 1067 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (d, *J* = 6.7 Hz, 3H, CH*Me*), 3.80 (q, *J* = 6.7 Hz, 1H, C*H*Me), 6.58 (dd, *J* = 7.3, 1.2 Hz, pyridone H-5), 6.77 (s, 1H, pyridone H-3), 7.43–7.53 (m, 4H, phenyl H-3, H-4, H-5, H-6), 7.51 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.72 (t, *J* = 60.4 Hz, 1H, CHF_2), 8.96 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 18.2, 45.3, 107.3, 107.4 (t, *J* = 255 Hz), 125.8, 126.1, 127.5, 129.2, 129.4 (t, *J* = 4 Hz), 129.6, 136.9, 141.0, 153.1, 161.4, 179.0. Anal. Calcd for $C_{15}H_{13}F_2NO_3$: C, 61.43; H, 4.47; N, 4.78. Found: C, 61.59; H, 4.40; N, 4.67.

2-[4-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl]propanoic acid (**9f**): Yield, 70%; pale yellow solid, mp 106–108 °C; IR (film): 2909, 1734, 1675, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (d, *J* = 7.3 Hz, 3H, CH*Me*), 3.85 (q, *J* = 7.3 Hz, 1H, C*H*Me), 6.61 (dd, *J* = 7.3, 1.8 Hz, pyridone H-5), 6.79 (s, 1H, pyridone H-3), 7.48 (dd, *J* = 7.9 Hz, 1.8 Hz, 2H, phenyl H-2, H-6), 7.55 (d, *J* = 7.3 Hz, 1H, pyridone H-6), 7.58 (dd, *J* = 7.9, 1.8 Hz, 2H, phenyl H-3, H-5), 7.76 (t, *J* = 60.4 Hz, 1H, CHF_2), 10.10 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 18.1, 45.1, 107.2, 107.5 (t, *J* = 255 Hz), 117.2, 127.1, 128.5, 129.3, 135.4, 142.4, 152.9, 161.5, 178.9. Anal. Calcd for $C_{15}H_{13}F_2NO_3$: C, 61.43; H, 4.47; N, 4.78. Found: C, 61.33; H, 4.60; N, 4.72.

30. *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.[34]
31. *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.[35]
32. *Anti-inflammatory assay*: The test compounds **9a–b**, **9e**, and the reference drugs ibuprofen, caffeic acid and nordihydroguaiaretic acid (NDGA) were evaluated using the in vivo carrageenan-induced rat foot paw edema model reported previously.[36]
33. *Molecular modeling (docking) studies*: Docking experiments were performed using Discovery Studio Client v2.5.0.9164 (2005-09), Accelrys Software Inc. running on a HP xw4600 workstation (Processor x86 family 6 model 23 stepping 10 GenuineIntel 2999 ~ MHz). The coordinates for the X-ray crystal structure of the enzyme COX-2 and 15-LOX were obtained from the RCSB Protein Data Bank and hydrogens were added. The ligand molecules were constructed using the Build Fragment tool and energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The docking experiment on COX-2 was carried out by superimposing the energy minimized ligand on SC-558 in the PDB file 1cx2 after which SC-558 was deleted. The coordinates for 15-LOX was obtained from PDB file1lox and the energy minimized ligand was superimposed on the inhibitor RS75091 after which RS75091 was deleted. In all these experiments the resulting ligand–enzyme complex was subjected to docking using the Libdock command in the receptor–ligand interactions protocol of Discovery Studio after defining subsets of the enzyme within 10 Å sphere radius of the ligand. The force field, Chemistry at HARvard Macromolecular Mechanics (CHARMM) was employed for all docking purposes. The ligand–enzyme assembly was then subjected to a molecular dynamics (MD) simulation using Simulation protocol at a constant temperature of 300 K with a 100 step equilibration for over 1000 iterations and a time step of 1 fs using a distance dependent dielectric constant 4*r*. The optimal binding orientation of the ligand–enzyme assembly obtained after docking was further minimized for 1000 iterations using the conjugate gradient method until a convergence of 0.001 kcal/mol Å was reached after which $E_{\text{intermolecular}}$ (kcal/mol) of the ligand–enzyme assembly was evaluated.

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