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Synthesis and biological evaluation of *N*-difluoromethyl-1,2-dihydropyrid-2-one acetic acid regioisomers: Dual Inhibitors of cyclooxygenases and 5-lipoxygenase

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ABSTRACT

A new group of acetic acid (**7a**–**c**, R^1 = H), and propionic acid (**7d**–**f**, R^1 = Me), regioisomers wherein a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety is attached via its C-3, C-4, and C-5 position was synthesized. This group of compounds exhibited a more potent inhibition, and hence selectivity, for the cyclooxygenase-2 (COX-2) relative to the COX-1 isozyme. Attachment of the *N*-difluoromethyl-1,2-dihydropyrid-2-one ring system to an acetic acid, or propionic acid, moiety confers potent 5-LOX inhibitory activity, that is, absent in traditional arylacetic acid NSAIDs. 2-(1-Difluoromethyl-2-oxo-1,2-dihydropyridin-5-yl)acetic acid (**7c**) exhibited the best combination of dual COX-2 and 5-LOX inhibitory activities. Molecular modeling (docking) studies showed that the highly electronegative CHF_2 substituent present in **7c**, that showed a modest selectivity for the COX-2 isozyme, is oriented within the secondary pocket (Val523) present in COX-2 similar to the sulfonamide (SO_2NH_2) COX-2 pharmacophore present in celecoxib, and that the *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore is oriented close to the region containing the LOX enzyme catalytic iron (His361, His366, and His545). Accordingly, the *N*-difluoromethyl-1,2-dihyrdopyrid-2-one moiety possesses properties suitable for the design of dual COX-2/5-LOX inhibitory drugs.

The eicosanoid family of inflammatory mediators arise from the biotransformation of arachidonic acid (AA) via the cyclooxygenase (COX) and lipoxygenase (LOX) pathways.[1] In this regard, the prostanoids (prostaglandins, prostacyclin, and thromboxanes) and leukotrienes (LTs) are produced via their respective COX and LOX pathways. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory effect by inhibition of the *constitutive* COX-1 and *inducible* COX-2 isozymes.[2] Adverse side effects, in particular gastrointestinal (GI) irritation, ulcerogenicity and renal toxicity attributed to inhibition of the cytoprotective COX-1 isozyme, are frequent deterrents to the chronic use of NSAIDs.[3] Alternatively, LTs produced via the 5-LOX enzyme catalyzed pathway are known to play a role in the pathogenesis of inflammatory and allergic disorders.[1] The related isozyme 15-LOX is linked to cardiovascular complications since it is known to participate in oxidative modification of low-density lipoproteins (LDL) leading to the development of atherosclerosis.[4] In addition, the 5-LOX pathway is up-regulated during COX blockade that may be due to a shift in the metabolism of AA to the uninhibited LOX pathway. Accordingly, increased levels of LTs may induce undesirable adverse effects such as bronchial constriction. Therefore, dual inhibitors of COXs and LOXs represent an attractive safer clinical alternative to COX inhibitors in view of their potentially greater anti-inflammatory efficacy due to a synergistic block of both the COX and LOX metabolic pathways in the AA cascade.[5]

In an earlier study, we reported that replacement of the tolyl ring in celecoxib (**1**) by a *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-LOX pharmacophore[6] furnished a novel class of dual COX/5-LOX inhibitors (**2**) which exhibited effective AI activity.[7] It was subsequently discovered that phenylacetic acid regioisomers (**3**) possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety attached to its C-2, C-3, or C-4 position also exhibited dual COX/5-LOX inhibitory activities (see structures in Fig. 1).[8] It was anticipated that replacement of the aryl ring in a classical arylacetic acid NSAID template by a *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-LOX pharmacophore would similarly provide dual 5-LOX/COX inhibitors. Accordingly, we now describe the synthesis of a novel class of acetic acid regioisomers having a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety (**7a**–**f**), their in vitro evaluation as

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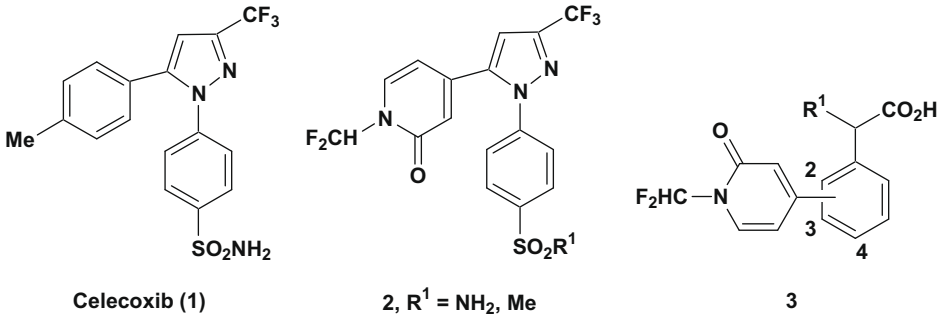
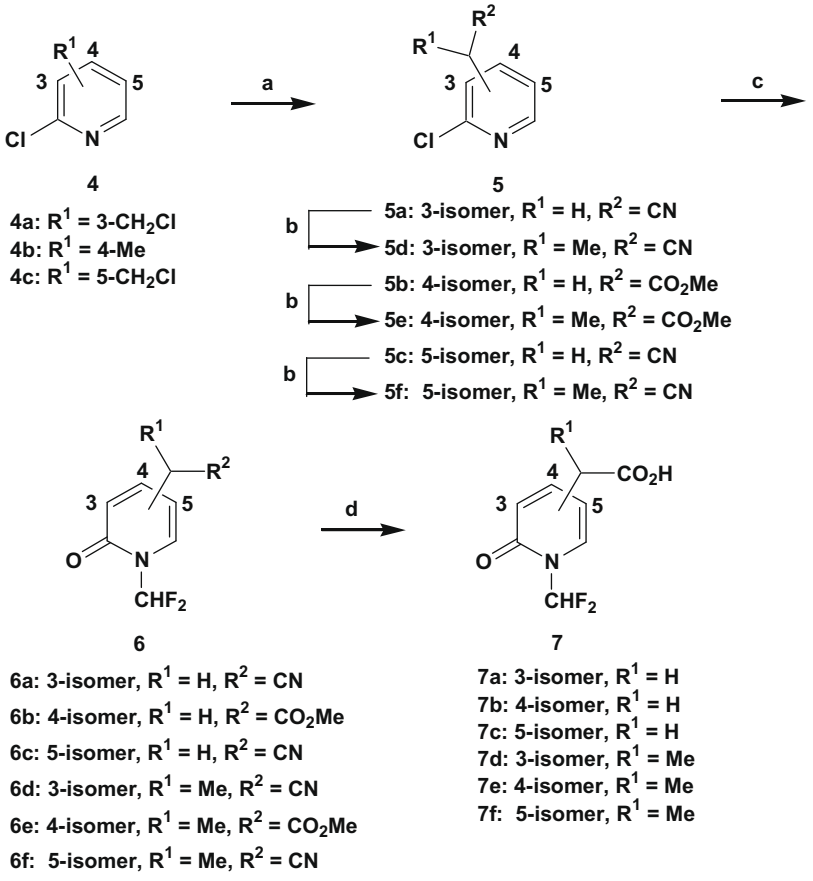


Figure 1. Some representative examples of the selective COX-2 inhibitor celecoxib (**1**), and dual COX/5-LOX inhibitors having a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore (**2**–**3**).

COX-1/COX-2, 5-LOX inhibitors, and some molecular modeling studies.

A group of acetic acid (**7a**–**c**, R^1 = H), and propionic acid (**7d**–**f**, R^1 = Me), regioisomers in which a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety was attached via its C-3, C-4, and C-5 position was synthesized as illustrated in Scheme 1. Reaction of the chloromethylpyridines (**4a**, **4c**) with NaCN furnished the respective cyanomethylpyridines (**5a**, 85%; **5c**, 70%).[9,10] 2-Chloro-4-methylpyridine (**4b**) was elaborated to methyl 2-chloroisonicotinate (**5b**, 53% yield) upon reaction with lithium diisopropylamide (LDA) and methyl chloroformate.[11] The subsequent methylation of **5a**–**c** using iodomethane in the presence of LDA at low temperature under argon afforded the respective products (**5d**–**f**) in 75–83% yields.[12,13] Reaction of the 2-chloropyridyl compounds **5a**–**f** in acetonitrile with 2,2-difluoro-2-(fluorosulfonyl)acetic acid ($FSO_2CF_2CO_2H$)[7,14] in the presence of $NaHCO_3$ under an argon atmosphere at reflux temperature afforded the respective *N*-difluoromethyl-1,2-dihydropyrid-2-one product (**6a**–**f**) in 39–65% yields. Acid hydrolysis of the cyano substituent present in the acetonitrile compounds (**6a**, **6c**–**d**, **6f**) using 30% HCl in 1,4-dioxane at 80 °C afforded the respective carboxylic acid target products **7a**, **7c**–**d**, or **7f** in 57–79% yield. Alkaline hydrolysis of the methyl ester moiety present in compounds **6b** and **6e** using aqueous 2 N NaOH in MeOH at reflux furnished the respective target acetic acid (**7b**, 75%), and propionic acid (**7e**, 74%), product.[15]

Traditional arylacetic acid NSAIDs share a number of similar structural features that include a carboxyl group separated by one-carbon atom from a flat aromatic nucleus, and one or more



Scheme 1. Reagents and conditions: (a) NaCN, $EtOH/H_2O$, reflux, 12 h for **5a**, **5c**; LDA, $ClCO_2Me$, THF, −78 °C, 1 h; then 0 °C, 30 min for **5b**; (b) LDA, MeI, THF, −78 °C, 30 min; then 0 °C, 30 min; (c) $FSO_2CF_2CO_2H$, $NaHCO_3$, MeCN, argon atmosphere, reflux, 6 h; (d) 30% HCl, 1,4-dioxane, reflux, 8 h for **7a**, **7c**–**d**, **7f**; aqueous 2 N NaOH, MeOH, reflux, 3 h for **7b**, **7e**.