Bioorganic & Medicinal Chemistry Letters 18 (2008) 6138–6141

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of celecoxib analogs that possess a *N*-hydroxypyrid-2(1*H*)one 5-lipoxygenase pharmacophore: Biological evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity

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

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

ARTICLE INFO

Article history:
Received 18 September 2008
Revised 1 October 2008
Accepted 2 October 2008
Available online 7 October 2008

Keywords:
Celecoxib analogs
N-Hydroxypyridin-2(1*H*)ones
Cyclooxygenase-1, cyclooxygenase-2 and 5-lipoxygenase inhibition
Anti-inflammatory activity

ABSTRACT

A hitherto unknown class of celecoxib analogs was designed for evaluation as dual inhibitors of the 5-lipoxygenase/cyclooxygenase-2 (5-LOX/COX-2) enzymes. These compounds possess a SO_2Me (**11a**), or SO_2NH_2 (**11b**) COX-2 pharmacophore at the *para*-position of the N^1-phenyl ring in conjunction with a 5-LOX *N*-hydroxypyrid-2(1*H*)one iron-chelating moiety in place of the celecoxib C-5 tolyl group. The title compounds **11a–b** are weak inhibitors of the COX-1 and COX-2 isozymes (IC_{50} = 7.5–13.2 μM range). In contrast, the SO_2Me (**11a**, IC_{50} = 0.35 μM), and SO_2NH_2 (**11b**, IC_{50} = 4.9 μM), compounds are potent inhibitors of the 5-LOX enzyme comparing favorably with the reference drug caffeic acid (5-LOX IC_{50} = 3.47 μM). The SO_2Me (**11a**, ED_{50} = 66.9 mg/kg po), and SO_2NH_2 (**11b**, ED_{50} = 99.8 mg/kg po) compounds exhibited excellent oral anti-inflammatory (AI) activities being more potent than the non-selective COX-1/COX-2 inhibitor drug aspirin (ED_{50} = 128.9 mg/kg po) and less potent than the selective COX-2 inhibitor celecoxib (ED_{50} = 10.8 mg/kg po). The *N*-hydroxypyridin-2(1*H*)one moiety constitutes a novel pharmacophore for the design of cyclic hydroxamic mimetics capable of chelating 5-LOX iron for exploitation in the design of 5-LOX inhibitory AI drugs.

Arachidonic acid (AA) is metabolized by two major enzyme families that include the lipoxygenases (5-, 8-, 12- and 15-LOX) and the cyclooxygenases (COX-1, -2 and -3). Proinflammatory leukotrienes (LTs) produced via the LOX pathway, and prostaglandins (PGs) produced via the COX pathway, are associated with adverse physiologic processes such as inflammation, fever, arthritis, bronchospasm[1] and the etiology of cancer.[2] Two of the three major isoforms (5-, 12- and 15-LOX) observed in humans cause undesirable physiological effects. In this regard, 5-LOX is implicated in the production of LTs that are associated with inflammatory, bronchoconstrictor, hypersensitivity, anaphylactic and asthmatic actions.[1,3] In contrast, 15-LOX is implicated in atherosclerosis since it catalyzes the oxidation of lipoproteins (LDL, HDL) to atherogenic forms.[4] Alternatively, PGs that induce undesirable inflammation, fever and pain are produced via the inducible COX-2 isozyme whereas PGs that regulate desirable gastrointestinal cytoprotective and renal functions are produced via the constitutive COX-1 isozyme.[1,5]

It is generally agreed that a dual inhibitor of the LOX/COX enzymatic pathways[6] constitutes a rational concept for the design of more efficacious anti-inflammatory agents with an improved safety profile relative to ulcerogenic non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors that increase the incidence of adverse cardiovascular thrombotic effects.[7,8] Henichart et al.[1] described a potent hybrid COX-2/5-LOX inhibitor in which the C-3 trifluoromethyl substituent present in COX-2 inhibitor celecoxib was replaced by a non-redox competitive 4-(3-fluoro-5-oxymethyl)phenyl-4-methoxytetrahydropyran 5-LOX pharmacophore.[1] Hydroxamic acids and related *N*-hydroxyureas that act by chelation of iron present in the 5-LOX enzyme have provided one of the most successful strategies to develop 5-LOX inhibitors.[9] Some representative examples of iron-chelating 5-LOX inhibitors such as zileuton (**1**)[10] and tepoxalin (**2**)[9] are shown in Figure 1. In a recent study, we described a novel class of acyclic 1-(benzenesulfonamido)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]-acetylene regioisomeric 5-LOX inhibitors (**3**).[11] Accordingly, it was anticipated that replacement of the tolyl ring present in the selective COX-2 inhibitor celecoxib (**4**)[12] by a *N*-hydroxypyridin-2(1*H*)one moiety, that has the potential to chelate iron, may provide a hitherto unknown class of dual 5-LOX/COX-2 inhibitory anti-inflammatory agents. Accordingly, we now describe the synthesis of a novel class of celecoxib analogs that possess a *N*-hydroxypyrid-2(1*H*)one 5-lipoxygenase pharmacophore (**11a–b**), their in vitro evaluation as 5-LOX, COX-1/COX-2 inhibitors, and in vivo assessment as anti-inflammatory (AI) agents.

* Corresponding author. Tel.: +1 780 492 5993; fax: +1 780 492 1217.
E-mail address: eknaus@pharmacy.ualberta.ca (E.E. Knaus).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.10.009

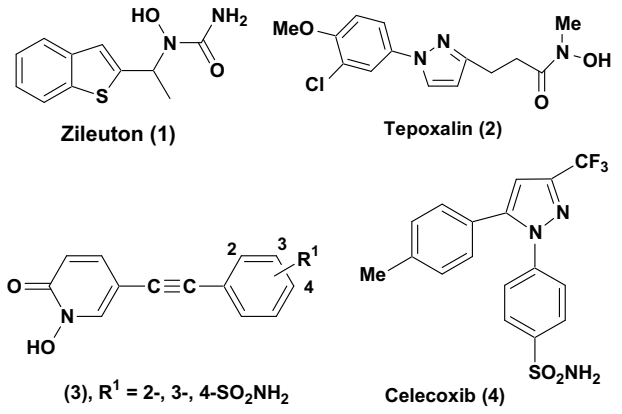


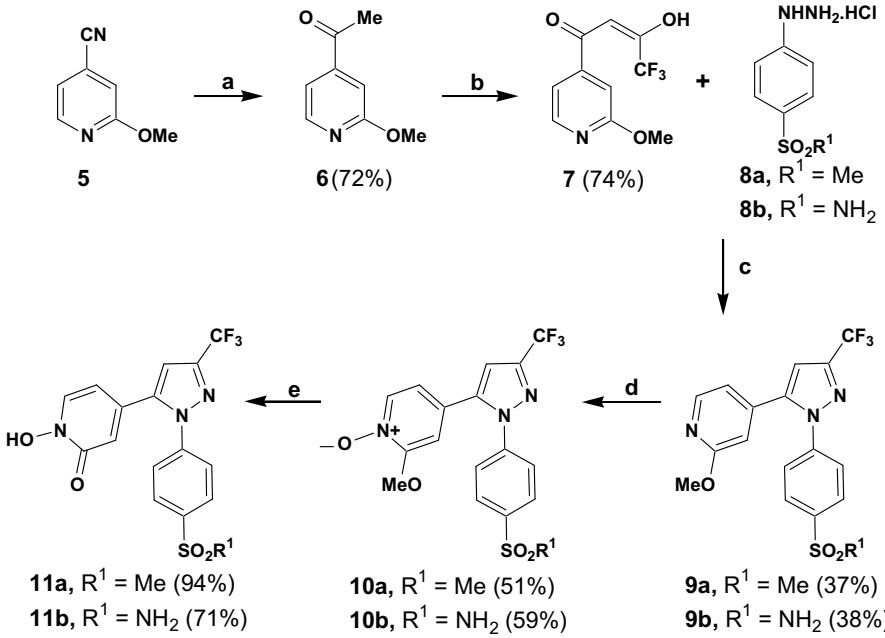
Figure 1. Some representative iron-chelating 5-LOX inhibitors (**1**–**3**) and the selective COX-2 inhibitor celecoxib (**4**).

The target 1-[4-methyl(or amino)sulfonylphenyl]-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1*H*-pyrazoles (**11a–b**) were prepared using the reaction sequence illustrated in Scheme 1. Accordingly, reaction of 2-methoxyisonicotinonitrile (**5**) with methyllithium, using a literature method for elaboration of cyano to acetyl,[13] furnished 1-(2-methoxypyridin-4-yl)ethanone (**6**, 72%). The base catalyzed condensation[14] of the acetyl compound **6** with ethyl trifluoroacetate afforded 4,4,4-trifluoro-3-hydroxy-1-(2-methoxypyridin-4-yl)-but-2-en-1-one (**7**, 74%). The subsequent condensation of **7** with either 4-(methylsulfonylphenyl)hydrazine-HCl (**8a**), or 4-(aminosulfonylphenyl)hydrazine-HCl (**8b**), afforded the respective 1,5-diarylpyrazole **9a** (37%), or **9b** (38%). Oxidation of the 2-methoxypyridine moiety present in compounds **9a–b** using *meta*-chloroperbenzoic acid in dichloromethane[15] afforded the respective 1-oxido-2-methoxypyridine derivative **10a** (51%) or **10b** (59%). Finally, reaction of the 1-oxido-2-methoxypyridyl compounds **10a–b** with acetyl chloride at reflux, followed by methanolysis in place of hydrolysis,[15] furnished the target 1-[4-methyl(or amino)sulfonylphenyl]-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1*H*-pyrazole **11a** (94%), or **11b** (71%).

The rational for the design of the 1-[4-methyl(or amino)sulfonylphenyl]-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1*H*-pyrazoles (**11a–b**) was based on the expectation that replacement of the tolyl substituent in celecoxib (**4**) by a *N*-hydroxypyridin-2(1*H*)one moiety would furnish a novel class of compounds with dual 5-LOX/COX-2 inhibitory activities. The CON-OH part of the *N*-hydroxypyrid-2(1*H*)-one ring present in **11a–b** can be viewed as a cyclic hydroxamic acid mimetic. These *N*-hydroxypyridin-2(1*H*)-ones, like acyclic hydroxamic acids, are expected to serve as effective iron chelators to exhibit 5-LOX inhibitory activity. However, these cyclic *N*-hydroxypyridin-2(1*H*)-ones, unlike acyclic hydroxamic acids which undergo facile biotransformation to the acids, are expected to have a greater metabolic stability with improved oral efficacy. Although, there is some distortion from planarity at the N^1-nitrogen atom of the *N*-hydroxypyridin-2(1*H*)-one ring system, the relatively flat diene portion of this quasi-planar ring system has the potential to serve as a suitable replacement for the tolyl group in celecoxib resulting in retention of selective COX-2 inhibitory activity.

In vitro COX-1 and COX-2 enzyme inhibition studies showed that the *N*-hydroxypyridin-2(1*H*)-ones (**11a–b**) were much weaker inhibitors (COX-1 IC_{50} = 10.2–3.2 μM range; COX-2 IC_{50} = 7.5 μM) than the selective COX-2 inhibitor celecoxib (COX-1 IC_{50} = 7.7 μM; COX-2 IC_{50} = 0.07 μM). The SO_2Me (**11a**) and SO_2NH_2 (**11b**) compounds exhibited similar COX-1/COX-2 inhibitory activity (see data in Table 1). In contrast, the SO_2Me compound (**11a**) was a much more potent in vitro inhibitor of the potato 5-LOX enzyme (5-LOX IC_{50} = 0.35 μM) than the SO_2NH_2 compound (**11b**, 5-LOX IC_{50} = 4.9 μM). In comparison, the SO_2Me compound (**11a**) was about 10-fold more potent, and the SO_2NH_2 compound (**11b**) was a slightly less potent, 5-LOX inhibitor than the reference drug caffeic acid (5-LOX IC_{50} = 3.47 μM).

The oral AI activities (ED_{50} values) exhibited by the cyclic *N*-hydroxypyridin-2(1*H*)-ones **11a–b** were determined using a carrageenan-induced rat foot paw edema model (see data in Table 1). The AI structure–activity data acquired showed that the SO_2Me



Scheme 1. Reagents and conditions: (a) i—MeLi, THF, −78 °C → 25 °C, 2.5 h; ii—3 N HCl; iii—Na_2CO_3; (b) i—NaOMe, CF_3CO_2Et, reflux, 6 h; ii—CH_3CO_2H; (c) ethanol (95%), reflux, 20 h; (d) *meta*-chloroperbenzoic acid, CH_2Cl_2, 25 °C, 12 h; (e) i—acetyl chloride, reflux, 1 h, ii—MeOH, 25 °C, 12 h.

Table 1
In vitro COX-1, COX-2, 5-LOX enzyme inhibition, and in vivo anti-inflammatory activity, data for the 1-[4-methyl(or amino)sulfonylphenyl]-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1*H*-pyrazoles (**11a–b**)

Compound	COX-1 IC_{50} (μM)[a]	COX-2 IC_{50} (μM)[a]	5-LOX IC_{50} (μM)[b]	AI activity[c] ED_{50} (mg/kg)
11a	13.2	7.5	0.35	66.9
11b	10.2	7.5	4.90	99.8
Celecoxib	7.7	0.07	>10	10.8
Aspirin	0.35	2.4	—	128.7
Caffeic acid	—	—	3.47	—

[a] The in vitro test compound concentration required to produce 50% inhibition of COX-1 or COX-2. The result (IC_{50}, μM) is the mean of two determinations acquired using an ovine COX-1/COX-2 assay kit (Catalog No. 560101, 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] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the ED_{50} value (mg/kg) at 3 h after oral administration of the test compound.

(**11a**, ED_{50} = 66.9 mg/kg po) and SO_2NH_2 (**11b**, ED_{50} = 99.8 mg/kg po), compounds exhibited AI activities between that of the reference drugs celecoxib (ED_{50} = 10.8 mg/kg po) and aspirin (ED_{50} = 128.7 mg/kg po). The in vitro and in vivo structure–activity data acquired suggest that the *N*-hydroxypyridin-2(1*H*)-ones **11a–b**, that are very weak inhibitors of the COX-1 and COX-2 isozymes, exhibit their AI activity primarily by preventing the biosynthesis of proinflammatory leukotrienes (LTs) produced via the LOX pathway.

In conclusion, a hitherto unknown class of 1-[4-methyl(or amino)sulfonylphenyl]-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1*H*-pyrazoles (**11a–b**)[16] was designed for evaluation as dual 5-LOX[17] and COX-1/COX-2 isozyme[18] inhibitors of inflammation. The structure–activity data acquired indicate that (i) the SO_2Me compound (**11a**) is a 14-fold more potent inhibitor of 5-LOX than the SO_2NH_2 compound (**11b**), (ii) the *N*-hydroxypyrid-2(1*H*)-one moiety provides a novel 5-LOX pharmacophore for the design of cyclic hydroxamic mimetics and (iii) the title compounds 11a–**b**, that are very weak inhibitors of the COX-1/COX-2 isozymes, exhibit anti-inflammatory activity[19] predominately via inhibition of proinflammatory leukotriene biosynthesis in the lipoxygenase pathway.

Acknowledgments

We are grateful to the Canadian Institutes of Health Research (CIHR) (MOP-14712) for financial support of this research.

References and notes

1. (a) Charlier, C.; Michaux, C. *Eur. J. Med. Chem.* **2003**, *38*, 645; (b) Barbey, S.; Goossens, L.; Taverne, T.; Cornet, J.; Choesmel, V.; Rouaud, C.; Gimeno, G.; Yannic-Arnoult, S.; Michaux, C.; Charlier, C.; Houssin, R.; Henichart, J.-P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 779.
2. Pommery, N.; Taverne, T.; Telliez, A.; Goossens, L.; Charlier, C.; Pommery, J.; Goossens, J.-F.; Houssin, R.; Durant, F.; Henichart, J.-P. *J. Med. Chem.* **2004**, *47*, 6195. and reference cited therein.
3. (a) McMillan, R. M.; Walker, E. R. H. *Trends Pharmacol. Sci.* **1992**, *13*, 323; (b) Ford-Hutchinson, A. W.; Gresser, M.; Young, R. N. *Annu. Rev. Biochem.* **1994**, *63*, 383; (c) Young, R. N. *Eur. J. Med. Chem.* **1999**, *34*, 671.
4. (a) Vila, L. *Med. Res. Rev.* **2004**, *24*, 399; (b) Zhao, L.; Funk, C. D. *Trends Cardiovasc. Med.* **2004**, *14*, 191.
5. Dannhardt, G.; Laufer, S. *Curr. Med. Chem.* **2000**, *7*, 1101.
6. Praveen Rao, P. N.; Chen, Q.-H.; Knaus, E. E. *J. Med. Chem.* **2006**, *49*, 1668. and references cited therein.
7. Scheen, A. J. *Rev. Med. Liege* **2004**, *59*, 565.
8. Dogné, J.-M.; Supuran, C. T.; Pratico, D. *J. Med. Chem.* **2005**, *48*, 2251.
9. Muri, E. M. F.; Nieto, M. J.; Sindelar, R. D.; Williamson, J. S. *Curr. Med. Chem.* **2002**, *9*, 1631.
10. Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R.; Bell, R. L.; Summers, J. B.; Brooks, D. W. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 929.
11. Chowdhury, M. A.; Chen, H.; Abdellatif, K. R.; Dong, Y.; Petruk, K. C.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4195.
12. Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
13. Huang, H.-C.; Li, J. J.; Garland, D. J.; Chamberlain, T. S.; Reinhard, E. J.; Manning, R. E.; Seibert, K.; Koboldt, C. M.; Gregory, S. A.; Anderson, G. D.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E.; Burton, E. G.; Cogburn, J. N.; Isakson, P. C.; Reitz, D. B. *J. Med. Chem.* **1996**, *39*, 253.
14. Levine, R.; Sneed, J. K. *J. Am. Chem. Soc.* **1951**, *73*, 4478.
15. Choi, H.-Y.; Yoon, S.-H. *Bull. Korean Chem. Soc.* **1999**, *20*, 857.
16. Experimental procedures and spectral data for compounds **6–7, 9–11**.
*1-(2-Methoxypyridin-4-yl)ethanone (**6**):* Methyllithium (8.75 mL of 1.6 M in Et_2O, 14 mmol) was added to a stirred solution of 2-methoxyisonicotinonitrile (**5**, 1.5 g, 11.19 mmol) in THF (20 mL) under nitrogen at −78 °C with stirring. Compound **5** was prepared in 91% yield from 2-chloroisonicotinonitrile (Peters, R.; Althaus, M.; Diolez, C.; Rolland, A.; Manginot, E.; Veyrat, M. *J. Org. Chem.* **2006**, *71*, 7583). The resulting solution was warmed to 25 °C and stirring was continued for 2.5 h. The reaction mixture was quenched with 3 N HCl and the mixture as stirred for 1 h at 25 °C. After washing with EtOAc, the aqueous fraction was neutralized with Na_2CO_3 and extracted with EtOAc (3× 25 mL). The combined organic fractions were washed successively with water and brine, and dried ($MgSO_4$). After filtration, the solvent from the organic fraction was removed in vacuo to give **6** as a brown syrup in 72% yield; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H, CO*Me*), 3.98 (s, 3H, O*Me*), 7.18 (d, *J* = 1.2 Hz, 1H, pyridyl H-3), 7.31 (dd, *J* = 5.5, 1.2 Hz, 1H, pyridyl H-5), 8.31 (d, *J* = 5.5 Hz, 1H, pyridyl H-6).
*4,4,4-Trifluoro-3-hydroxy-1-(2-methoxypyridin-4-yl)-but-2-en-1-one (**7**):* A mixture of 1-(2-methoxypyridin-4-yl)ethanone (**6**, 1.21 g, 8.01 mmol), sodium methoxide (1.73 mL of a 25% w/v solution in MeOH, 8.01 mmol) and ethyl trifluoroacetate (0.95 mL, 8.01 mmol) was refluxed for 6 h. The reaction mixture was cooled to 25 °C and glacial acetic acid (0.46 mL, 8.01 mmol) was added. Water (15 mL) was added, the reaction mixture was extracted with $CHCl_3$ (3× 25 mL), the organic phase was washed successively with water and then brine, and the organic fraction was dried ($MgSO_4$). After filtration, the solvent from the organic fraction was removed in vacuo to give product **7** as a brown syrup in 74% yield; ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H, O*Me*), 6.55 [s, 1H, $CF_3C(OH)$=*CH*CO−], 7.21 (d, *J* = 1.2 Hz, 1H, pyridyl H-3), 7.29 (dd, *J* = 5.5, 1.2 Hz, 1H, pyridyl H-5), 8.34 (d, *J* = 5.5 Hz, 1H, pyridyl H-6), 14.25 (br s, 1H, O*H*).
*General procedure for the synthesis of 1-[4-methyl(amino)sulfonylphenyl]-3-trifluoromethyl-5-(2-methoxypyridin-4-yl)-1H-pyrazoles (**9a–b**):* A solution of the hydrazine hydrochloride **8a** or **8b** (6.46 mmol) and the ketone **7** (1.45 g, 5.87 mmol) in 95% ethanol (75 mL) was heated at reflux for 20 h. Compound **8a** was synthesized in 53% yield starting from 1-chloro-4-methanesulfonylbenzene[2] which was prepared by the Fridel–Crafts reaction of methanesulfonyl chloride with chlorobenzene (Truce, W. E.; Vriesen, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 5032), and compound **8b** was synthesized in 84% yield starting from sulfanilamide (Soliman, R. *J. Med. Chem.* **1979**, *22*, 321). After cooling to 25 °C, the reaction mixture was concentrated in vacuo to yield a gummy mass. The crude product **9a**, or **9b**, was purified by silica gel column chromatography using acetone-hexane (1:2, v/v) as eluent to furnish the respective product **9a** or **9b**. Some physical and spectroscopic data for **9a–b** are listed below.
*1-(4-Methylsulfonylphenyl)-3-trifluoromethyl-5-(2-methoxypyridin-4-yl)-1H-pyrazole (**9a**):* Product **9a** was obtained as dark brown syrup in 37% yield; IR (neat) 1380, 1160 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2*Me*), 3.95 (s, 3H, O*Me*), 6.61–6.68 (m, 2H, pyridyl H-3, H-5), 6.87 (s, 1H, pyrazol H-4), 7.57 (d, *J* = 9.0 Hz, 2H, phenyl H-2, H-6), 8.00 (d, *J* = 9.0 Hz, 2H, phenyl H-3, H-5), 8.17 (d, *J* = 6.0 Hz, 1H, pyridyl H-6). Anal. Calcd for $C_{17}H_{14}F_3N_3O_3S$: C, 51.38; H, 3.55. Found: C, 51.46; H, 3.94.
*1-(4-Aminosulfonylphenyl)-3-trifluoromethyl-5-(2-methoxypyridin-4-yl)-1H-pyrazole (**9b**):* Product **9b** was obtained as a white solid in 38% yield, mp 175–177 °C; IR (film) 3350, 3280 (NH_2), 1325, 1165 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H, O*Me*), 6.79–6.91 (m, 2H, pyridyl H-3, H-5), 7.45 (s, 1H, pyrazol H-4), 7.57 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.62 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.91 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 8.19 (d, 1H, *J* = 6.1 Hz, pyridyl H-6). Anal. Calcd for $C_{16}H_{13}F_3N_4O_3S$: C, 48.24; H, 3.29. Found: C, 47.93; H, 3.43.
*General procedure for the synthesis of 1-[4-methyl(amino)sulfonylphenyl]-3-trifuoromethyl-5-(1-oxido-2-methoxypyridin-4-yl)-1H-pyrazoles (**10a–b**):* *meta*-Chloroperoxybenzoic acid (77% max) (6 mmol) was added to a stirred solution of either **9a** or **9b** (2 mmol) in dry CH_2Cl_2 (25 mL), and the reaction was allowed to proceed with stirring at 25 °C overnight. The solvent (CH_2Cl_2) was removed in vacuo to give a residue which was purified by silica gel column chromatography using methanol–EtOAc (1:3, v/v) as eluent to afford the respective product **10a** or **10b**. Some physical and spectroscopic data for **10a–b** are listed below.
*1-(4-Methylsulfonylphenyl)-3-trifuoromethyl-5-(1-oxido-2-methoxypyridin-4-yl)-1H-pyrazole (**10a**):* Product **10a** was obtained as a white solid in 51% yield, mp 165–167 °C; IR (film) 1350, 1125 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.28 (s,

3H, SO_2Me), 3.85 (s, 3H, O*Me*), 6.82 (dd, *J* = 6.7, 2.4 Hz, 1H, pyridyl H-5), 7.21 (d, *J* = 2.4 Hz, 1H, pyridyl H-3), 7.48 (s, 1H, pyrazol H-4), 7.72 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 8.05 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 8.21 (d, 1H, *J* = 6.7 Hz, pyridyl H-6). Anal. Calcd for $C_{17}H_{14}F_3N_3O_4S$ 1/2H_2O: C, 48.34; H, 3.58. Found: C, 48.37; H, 3.53.

*1-(4-Aminosulfonylphenyl)-3-trifuoromethyl-5-(1-oxido-2-methoxypyridin-4-yl)-1H-pyrazole (**10b**):* Product **10b** was obtained as white solid in 59% yield, mp 220–222 °C; IR (film) 3400–3000 broad (NH_2), 1280, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.86 (s, 3H, O*Me*), 6.83 (dd, *J* = 6.7, 2.4 Hz, 1H, pyridyl H-5), 7.18 (d, *J* = 2.4 Hz, 1H, pyridyl H-3), 7.48 (s, 1H, pyrazol H-4), 7.54 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.66 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.93 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 8.23 (d, 1H, *J* = 6.7 Hz, pyridyl H-6). Anal. Calcd for $C_{16}H_{13}F_3N_4O_4S$: C, 46.38; H, 3.16. Found: C, 46.07; H, 3.42.

*General procedure for the synthesis of 1-[4-methyl(amino)sulfonylphenyl]-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1H-pyrazoles (**11a–b**):* Acetyl chloride (6 mL) was added to either **10a**, or **10b** (2 mmol), and the reaction mixture was allowed to proceed at reflux for 1 h. The reaction mixture was cooled to 25 °C, and excess acetyl chloride was removed in vacuo. The residue was dissolved in methanol prior to stirring at 25 °C overnight. Methanol was removed in vacuo to give a solid product which was then mixed with Et_2O (10 mL) to form a slurry. Finally, the solid product was filtered out and dried under vacuum to give the respective product **11a** or **11b**. Some physical and spectroscopic data for **11a–b** are listed below.

*1-(4-Methylsulfonylphenyl)-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1H-pyrazole (**11a**):* Product **11a** was obtained as a brown solid in 94% yield, mp 188–190 °C; IR (film) 3105 broad (OH), 1657 (C=O), 1325, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (s, 3H, SO_2Me), 6.08 (dd, *J* = 7.3, 2.4 Hz, 1H, dihydropyridyl H-5), 6.71 (d, *J* = 2.4 Hz, 1H, dihydropyridyl H-3), 6.90 (s, 1H, pyrazol H-4), 7.62 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.82 (d, *J* = 6.7 Hz, 1H, dihydropyridyl H-6), 8.05 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 43.3, 104.0, 107.6, 119.0, 121.0, 126.2, 128.4, 136.4, 137.3, 141.0, 142.0, 142.2, 142.4, 156.9; MS $(M+1)^+$ 399.98.

*1-(4-Aminosulfonylphenyl)-3-trifluoromethyl-5-[4-(1-hydroxy-1,2-dihydropyrid-2-one]-1H-pyrazole (**11b**):* Product **11b** was obtained as brown solid in 71% yield, mp 235–237 °C; IR (film) 3400–3000 broad (OH, NH_2), 1655 (C=O), 1280, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.04 (dd, *J* = 7.3, 2.4 Hz, 1H, dihydropyridyl H-5), 6.53 (d, *J* = 2.4 Hz, 1H, dihydropyridyl H-3), 7.41 (s, 1H, pyrazol H-4), 7.57 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.67 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.94 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 7.96 (d, *J* = 7.3 Hz, 1H, dihydropyridyl H-6), 11.90 (br s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 103.9, 107.6, 118.9, 121.0, 126.0, 128.9, 136.3, 137.2, 139.4, 142.0, 142.1, 142.3, 156.9; MS $(M+1)^+$ 400.94.

17. *5-Lipoxygenase inhibition assay:* The ability of the test compounds **11a** and **11b** to inhibit potato 5-LOX (Catalog No. 60401, Cayman Chemical, Ann Arbor, MI, USA) (IC_{50} values, μM) was determined using an enzyme immuno assay (EIA) kit (Catalog No. 760700, Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions. The Cayman Chemical lipoxygenase inhibitor screening assay detects and measures the hydroperoxides produced in the lipoxygenation reaction using a purified lipoxygenase. Stock solutions of test compounds were dissolved in a minimum volume of DMSO and were diluted using the supplied buffer solution (0.1 M, Tris–HCl, pH 7.4). To a 90 μl solution of 5-LOX enzyme in 0.1 M, Tris–HCl, pH 7.4 buffer, 10 μl of various concentrations of test drug solutions (0.01, 0.1, 1 and 10 μM in a final volume of 210 μl) were added and the lipoxygenase reaction was initiated by the addition of 10 μl (100 μM) of linoleic acid (LA). After maintaining the 96-well plate on a shaker for 5 min, 100 μl of chromogen was added and the plate was retained on a shaker for 5 min. The lipoxygenase activity was determined after measuring absorbance at a wavelength of 500 nm. Percent inhibition was calculated by the comparison of compound-treated to various control incubations. The concentration of the test compound causing 50% inhibition (IC_{50}, μM) was calculated from the concentration–inhibition response curve (duplicate determinations).
18. *Cyclooxygenase inhibition assays:* The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using an enzyme immuno assay (EIA) kit (Catalog No. 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method. Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A.; Knaus, E. E. *J. Med. Chem.* **2003**, *46*, 4872.
19. *In vivo anti-inflammatory assay:* The test compounds **11a** and **11b** and the reference drugs celecoxib and aspirin were evaluated using the in vivo carrageenan-induced rat foot paw edema model reported previously. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.