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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 14 (2004) 2195–2198

2,3-Diarylpyran-4-ones: a new series of selective cyclooxygenase-2 inhibitors

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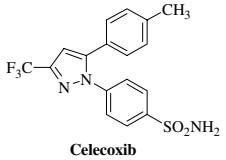
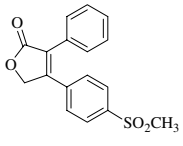
Received 24 November 2003; revised 5 February 2004; accepted 5 February 2004

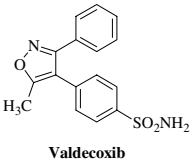
Abstract—A new series of cyclooxygenase-2 (COX-2) inhibitors with γ-pyrone as central scaffold unit has been synthesized and their biological activities were evaluated against cyclooxygenase inhibitory activity. The changes of physical properties of the molecules were performed according to the medicinal chemistry principles and moderate oral anti-inflammatory activity was obtained with this series of inhibitors.

1. Introduction

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Even though NSAIDs are effective in the management of inflammation and pain, chronic use of NSAIDs has been associated with unwanted adverse effects including gastrointestinal PUB (perforation, ulceration, and bleeding), and renal toxicity. Inhibition of constitutively expressed COX-1 interrupts bodily homeostasis and is known to contribute much to such adverse effects.[1] On the other hand, the anti-inflammatory effect of NSAIDs appears to be originating from inhibition of COX-2, being induced upon inflammatory stimuli. Therefore, selective inhibition of COX-2 could be suitable to treat inflammation and inflammation-associated disorders without incurring adverse effects from inhibition of COX-1, which had been the main theme for development of blockbuster selective COX-2 inhibitors such as celecoxib and rofecoxib.

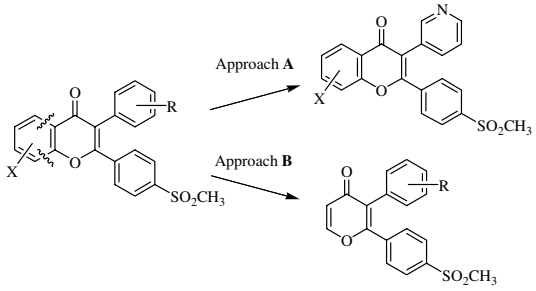

Celecoxib


Rofecoxib


Valdecoxib

Even though selective COX-2 inhibitors are regarded to have reduced the notorious GI toxicity of traditional NSAIDs to a large extent, there appears to be some room for improvement especially in renal and cardiovascular safety. Next generation selective COX-2 inhibitors are expected to address in more detail issues relating to the cardio-renal safety.[2]

Previously, we reported that naturally occurring flavone scaffold could be useful to achieve selective inhibition of COX-2 over COX-1. COX-2 inhibitors with the benzopyran scaffold in Scheme 1 showed poor oral anti-inflammatory activity despite their strong COX-2 inhibitory potency, though. The poor oral anti-inflammatory activity was ascribed to the poor oral bioavailability due to the hydrophobic nature of the tricyclic COX-2 inhibitors.[3] In this article, will be discussed



Scheme 1. Approaches to improve oral bioavailability of 2,3-diphenylbenzopyran derivatives.

Keywords: Pyrone; Cyclooxygenase-2; Benzopyran.
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doi:10.1016/j.bmcl.2004.02.028

efforts to improve in vivo activity profiles of COX-2 inhibitors by truncating the benzopyran scaffold.

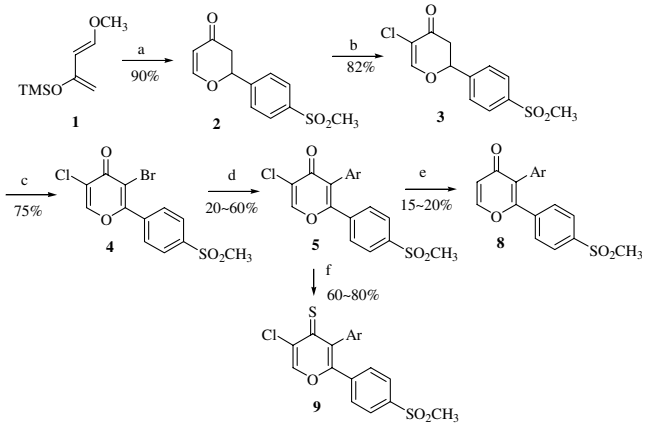
We reported that oral bioavailability of COX-2 inhibitors with the benzopyran scaffold could be improved by switching the phenyl moiety to 3-pyridyl group on the 3-position of the benzopyran scaffold (Approach A of Scheme 1). Given that the hydrophobic character of the benzopyran scaffold contributes much to the poor oral bioavailability,[4] truncation of the benzopyran moiety could lead to reduced hydrophobicity and subsequently to improved bioavailability. In this regard, γ-pyrone was conceived as a replacement for the benzopyran scaffold to improve oral bioavailability of COX-2 inhibitors (Approach B of Scheme 1).

2. Synthesis

2,3-Diarylpyran-4-one derivatives were synthesized as outlined in Scheme 2. First, hetero-Diels–Alder reaction of 4-(methylsulfonyl)benzaldehyde with Danishefsky's diene (**1**) in the presence of zinc chloride gave dihydropyran-4-one **2**, which was followed by α-chlorination with *N*-chlorosuccinimide (NCS) to afford dihydropyran-4-one **3**. Chloride compound **3** was subjected to bromination using bromine/pyridine to obtain bromide **4**, which was then transformed into desired 2,3-diarylpyran-4-one **5**[5] by Suzuki coupling[6] with appropriate aryl boronic acid. Reductive dechlorination of **5** was effected by reaction with Zn/KI to give **8**. Thione compound **9** was prepared by reacting **5** with Lawesson's reagent in toluene at reflux.[7]

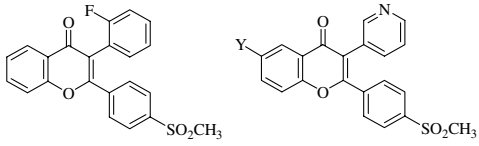
3. In vitro activities

The diarylpyran-4-one analogs of this article were tested for their ability to inhibit COX-2 and COX-1 by using freshly harvested mouse peritoneal macrophages as described in the literature.[8] The in vitro inhibitory activities against COX-2 and COX-1 are summarized in Table 1.



Scheme 2. Reagents and conditions: (a) 4-(Methylsulfonyl)benzaldehyde, $ZnCl_2$, benzene; (b) NCS, pyridine; (c) Br_2, pyridine; (d) $ArB(OH)_2$ (**6**) or $ArB^-(OCH_3)_3Li^+$ (**7**), $Pd(PPh_3)_4$, 2 M Na_2CO_3, EtOH–H_2O–Toluene; (e) KI, Zn, MeOH; (f) Lawesson's reagent, toluene; Ar = substituted or unsubstituted aryl, heteroaryl.

Most 2,3-diarylpyran-4-one **5** and 2,3-diarylpyran-4-thione **9** showed modest COX-2 inhibitory activities, which were considerably weaker than that of celecoxib. Even though COX-1 IC_{50}'s were not quantified, most of the pyrone COX-2 inhibitors in Table 1 did not show notable inhibition at 10 μg/mL. In case of biphenyl compounds **5j** and **5p**, were observed COX-1 inhibition over 50% at 10 μg/mL. However, these biphenyl compounds showed COX-2 IC_{50}'s of 0.04 μg/mL, yielding COX-2 selectivity over COX-1 approaching 100-fold. When compared to previously reported benzopyran derivatives,[3] many of compounds **5** and **9** showed somewhat reduced COX-2 inhibitory activity.



Compound **5b** and **8b** showed similar COX-2 inhibitory activities, suggesting that lack of the chloride on the 5-position of the pyrone scaffold does not seem to show

Table 1. In Vitro mCOX-2 and mCOX-1 enzyme inhibitory activities of diarylpyran-4-one derivatives **5**, **8**, and **9**

Compd	Ar	mCOX-2 (IC_{50}, μg/mL)[a]	mCOX-1 (% inhibition @ 10 μg/mL)[a]
5a	Phenyl	0.39	<5
5b	4-Fluorophenyl	0.56	<5
5c	2-Fluorophenyl	2.39	19
5d	3-Fluorophenyl	0.54	<5
5e	4-Chlorophenyl	0.37	<5
5f	3-Chlorophenyl	0.56	<5
5g	2,4-Difluorophenyl	0.55	6
5h	3,4-Difluorophenyl	0.49	20
5i	3,5-Difluorophenyl	0.93	<5
5j	4-Biphenyl	0.04	68
5k	4-Ethylphenyl	0.28	14
5l	4-Methoxyphenyl	2.68	<5
5m	3-Thienyl	0.27	<5
5n	2-Thienyl	9%[b]	<5
5o	4-Methylphenyl	0.66	<5
5p	(3-Fluoro-4-phenyl)-phenyl	0.04	70
5q	4-Hydroxyphenyl	Na[b]	17
5r	(3-Phenyl)phenyl	Na[b]	<5
5s	4-Benzyloxyphenyl	Na[b]	<5
5t	3-Pyridyl	2.55	<5
8b	4-Fluorophenyl	0.77	<5
9b	4-Fluorophenyl	0.33	<5
10[c]		0.03	<5
11[c]		0.5	13
12[c]		0.5	12
	Celecoxib	0.01	79

[a] Values are means of at least two measurements.
[b] Inhibition (%) @ 10 μg/mL (Na = not active).
[c] See Ref. 3.

much effect on the COX-2 inhibitory activity. COX-2 inhibitory activity was quite insensitive to substitution in the phenyl group on the 3-position of the γ-pyrone compared to that of benzopyran series, even though presence of biphenyl moiety on the 3-position of the γ-pyrone appeared to improve in vitro COX-2 activity significantly (**5j** and **5p**). It is interesting to note that the COX-2 inhibitors with biphenyl group on the 3-position of γ-pyrone showed COX-2 inhibitory activities not far off that of celecoxib. Compound **5t** containing 3-pyridyl group showed COX-2 inhibitory activity significantly reduced from those of compounds containing phenyl group on the 3-position of γ-pyrone, paralleling a prior observation made with COX-2 inhibitors of the benzopyran scaffold.[3] Also thiocarbonyl compound **9** failed to show notable improvement in COX-2 inhibitory activity.

4. In vivo anti-inflammatory activities

The oral anti-inflammatory activities for compounds of this article were assessed by carrageenan-induced rat paw edema[9] using male SD rats. Reflecting their modest COX-2 inhibitory activities, the anti-inflammatory activities of γ-pyrone COX-2 inhibitors were moderate. Compound **5b** and **5h** were the most potent of the pyrone analogs despite their modest COX-2 inhibitory activities (see Tables 1 and 2). In the meantime, biphenyl containing COX-2 inhibitor **5j** showed a relatively poor oral anti-inflammatory activity for its COX-2 inhibitory potency, suggesting a poor pharmacokinetic profile for **5j**. It is notable that **5h** showed an oral anti-inflammatory activity close to that of celecoxib in the rat paw edema.

Previously, benzopyran COX-2 inhibitors **11** and **12** were designed to overcome the poor oral bioavailability of COX-2 inhibitors with the benzopyran scaffold. Even though a short plasma half-life of 0.5 h was observed for **11** in male SD rats, consideration on the metabolic stability of the benzopyran analogs yielded **12** as a benzopyran COX-2 inhibitor with good oral absorption and extended plasma half-life.[3] The pyridine moiety of **11** and **12** was the key functionality for improvement in oral bioavailability. Flavonoid **11**,**12**, and pyrone **5h** were quite similar with regards to COX-2 inhibitory activity and lipophilicity. These compounds showed COX-2 inhibitory activities around 0.5 μg/mL. Calculated log P's of 1.98, 2.14, and 2.24 were obtained for **11**,**12**, and **5h**, respectively.[10] When **5h** was orally administered to male SD rats at 10 mg/kg, a plasma half-life ($T_{1/2}$) of 3.7 h was observed along with $T_{max} = 4.0$ h, $C_{max} = 5.1$ μg/mL. The plasma half-life of **5h** was extended than that of flavonoid **11**, and the anti-inflammatory activity of pyrone **5h** was improved from the activity of flavonoid **11** and **12**.

In conclusion, we prepared a new series of COX-2 inhibitors containing the γ-pyrone scaffold, which was evolved from the hydrophobic benzopyran scaffold through rational modification to improve oral bioavailability. The physico-chemical factors such as lipophilicity, molecular size, and metabolic stability were appropriately modulated by truncating the benzopyran structure. Pyrone **5h** was obtained as an orally active COX-2 inhibitor and selected as a lead compound for further modifications.

Table 2. Inhibition effect of diarylpyran-4-one derivatives **5** on carrageenan-induced rat paw edema

Compounds	Dose (mg/kg, po)	Swelling (%) inhibition[a]
Indomethacin	3	42
Celecoxib	3	29
Celecoxib	10	42
11[b]	10	25
11[b]	30	41
12[b]	3	20
12[b]	10	26
12[b]	30	41
5b	3	20
5b	10	33
5g	3	20
5h	3	10
5h	10	37
5j	10	21
5k	10	4
5m	10	13

[a] Inhibition values were determined using five animals/group.
[b] See Ref. 3.

References and notes

1. (a) Fu, J.-Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. *J. Biol. Chem.* **1990**, *265*, 16737; (b) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 2692; (c) DeWitt, D. L. *Mol. Pharmacol.* **1999**, *55*, 625.
2. (a) Mukherjee, D.; Nissen, S. E.; Topol, E. J. *JAMA* **2001**, *286*, 954; (b) Chiolero, A.; Maillard, M.; Burnier, M. *Expert Opin. Drug Saf.* **2002**, *1*, 45.
3. Joo, Y. H.; Kim, J. K.; Kang, S.; Noh, M.; Ha, J.; Choi, J. K.; Lim, K. M.; Lee, C. J.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413.
4. Possibility of tight crystal packing due to the fused aromatic ring of benzopyran cannot be excluded for poor oral bioavailability of 2,3-diarylbenzopyran analogs.
5. Selected compounds were prepared as follows. *2-{4-(Methylsulfonyl)-phenyl}-2,3-dihydro-(4H)-pyran-4-one* (**2**): To a mixture of 4-(methylsulfonyl) benzaldehyde (1.7 g, 9.2 mmol) and anhydrous $ZnCl_2$ (0.6 g, 4.4 mmol) in anhydrous benzene (50 mL) was added *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**1**) (1.6 g, 9.34 mmol) and the mixture stirred at room temperature for 24 h under the argon atmosphere. The reaction mixture was washed with 0.1 N aqueous HCl and the brine. The resulting organic layer was dried and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, ethyl acetate/hexanes, 3:1) to yield the title compound as a pale yellow solid (2.08 g, 90%). Mp; 154 ~ 155 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) 8.03 ~ 8.00 (m, 2H), 7.64 ~ 7.61 (m, 2H), 7.50 (d, 1H, $J = 6.0$ Hz), 5.59 ~ 5.51 (m, 2H), 3.08 (s, 3H), 2.91–2.68 (m, 2H): IR(Neat); 3007, 2926, 1677, 1593, 1275, 1149, 750.

5-Chloro-2-{4-(methylsulfonyl)-phenyl}-2,3-dihydro-(4H)-pyran-4-one (**3**): To a solution of 2-{4-(methylsulfonyl)-phenyl}-2,3-dihydro-(4*H*)-pyran-4-one (**2**) (0.17 g, 0.67 mmol) and pyridine (0.06 g, 0.74 mmol) in $CHCl_3$ (15 mL) was added NCS (0.1 g, 0.74 mmol) and the mixture was refluxed for 12 h. The solution was cooled and washed with 1 N aqueous HCl, saturated $NaHCO_3$, and brine. The resulting organic layer was dried and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexane/ethyl acetate, 1:1) to yield the title compound as a pale yellow solid (0.157 g, 82%). Mp; 227 ~ 229 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 ~ 8.01 (m, 2H), 7.75 (s, 1H), 7.63 ~ 7.60 (m, 2H), 5.62 (dd, 1H, J = 5.1, 12.9 Hz), 3.08 (s, 3H), 3.00 ~ 2.91 (m, 2H): IR(Neat); 3007, 2926, 1688, 1591, 1300, 1150, 1107 cm^{-1}.

3-Bromo-5-chloro-2-{4-(methylsulfonyl)-phenyl}-(4H)-pyran-4-one (**4**): To a solution of 5-chloro-2-{4-(methylsulfonyl)-phenyl}-2,3-dihydro-(4*H*)-pyran-4-one (**3**) (0.064 g, 0.22 mmol) in pyridine (2 mL) was added bromine (0.78 g, 0.5 mmol) and the mixture was stirred at 50 ~ 60 °C for 2 h. After cooling to room temperature, the reaction mixture was washed with aqueous $Na_2S_2O_3$ solution, 1 N aqueous HCl, satd $NaHCO_3$, and brine. The resulting organic layer was dried and concentrated under reduced pressure to yield the title compound as a pale yellow solid (0.06 g, 75%). Mp; 205 ~ 207 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (s, 1H), 8.13 ~ 8.10 (m, 2H), 7.99 ~ 7.96 (m, 2H), 7.27 (s, 1H), 3.16 (s, 3H): IR(KBr); 3007, 1651, 1276, 1152, 750 cm^{-1}.

Chloro-3-(4-fluorophenyl)-2-{4-(methylsulfonyl)-phenyl}-(4H)-pyran-4-one (**5b**): To a solution of 3-bromo-5-chloro-2-{4-(methylsulfonyl)-phenyl}-(4*H*)-pyran-4-one (**4**) (0.04 g, 0.11 mmol), 4-fluorophenylboronic acid (0.018 g, 0.64 mmol) in toluene (2 mL) and ethanol (2 mL) was added 2 M aqueous sodium carbonate (0.2 mL), tetrakis (triphenylphosphine)palladium (0.004 g, 3 mol%) and the mixture was stirred at 100 °C for 2 h. After being concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL), washed with water, and brine. The organic layer was dried and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate, 10:1) to yield the title compound as a pale yellow solid (0.01 g, 25%). Mp; 196 ~ 197 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 7.87 ~ 7.85 (m, 2H), 7.48 ~ 7.45 (m, 2H), 7.17 ~ 7.12 (m, 2H), 7.06 ~ 7.00 (m, 2H), 3.05 (s, 3H): IR(KBr); 3076, 2927, 1647, 1510, 1315, 1163, 998, 837 cm^{-1}: MS(EI); 378 (M^+): HRMS(EI); calcd for $C_{18}H_{12}O_4$ FSCl 378.0129, found: 378.0122.

6. (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513; (b) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008; (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.
7. Michael, P.; Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
8. Mtchell, J. A.; Akarasereenont, P.; Thiemermann, C.; Flower, R. J.; Vane, J. R. *Proc. Natl. Acad. Sci. USA* **1994**, *90*, 11693.
9. Futaki, N.; Yoshikawa, K.; Hamasaka, Y.; Arai, I.; Higuchi, S.; Iizuka, H.; Otomo, S. *Gen. Pharmacol.* **1993**, *24*, 105.
10. Calculated *n*-octanol/water partition coefficients; C logP was calculated by Crippen's fragmentation method[11] using Chemdraw Ultra 5.0 CambridgeSoft.
11. Ghose, A. K.; Crippen, G. M. *J. Chem. Inf. Comput. Sci.* **1987**, *27*, 21.