Available online at www.sciencedirect.com

Bioorganic & Medicinal Chemistry Letters 14 (2004) 1757–1760

Bioorganic & Medicinal Chemistry Letters

A prodrug approach to COX-2 inhibitors with methylsulfone

Joo Hyun Moh, Young Hoon Choi, Kyoung Min Lim, Ki-Wha Lee, Song Seok Shin, Jin Kyu Choi, Hyun Joo Koh and Shin Chung*

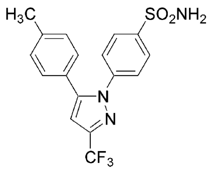
Drug Discovery, AmorePacific R&D Center, 314-1 Bora-ri, Giheung-eup, Yongin, Gyeonggi-do 449-729, Republic of Korea

Received 13 November 2003; accepted 15 January 2004

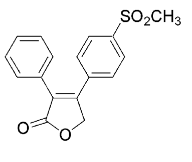
Abstract—2,2-Dimethyl-4-phenyl-5-{4-(methylsulfinyl)phenyl}-3(*2H*)furanone derivatives, **3** and **6**, were shown to be effectively transformed in vivo into the corresponding methylsulfone derivatives **1** and **4**, when orally administered to rats. Pharmacological implications for use of sulfoxide analogues **3** and **6** are discussed as prodrugs to potent selective COX-2 inhibitors **1** and **4**.

1. Introduction

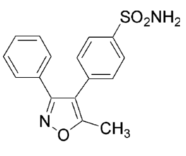
Commercial success of selective cyclooxygenase-2 (COX-2) inhibitors has relied much on their improved gastrointestinal safety when compared to traditional non-steroidal anti-inflammatory drugs (NSAIDs).[1] Many currently available selective COX-2 inhibitors possess a tricyclic pharmacophore of *cis*-1,2-diaryl alkene type with either sulfonamide or methylsulfone moiety, as exemplified by celecoxib, rofecoxib, valdecoxib, and etoricoxib.[2] According to our experiences, such tricyclic COX-2 inhibitors with a methylsulfone moiety often show poor oral bioavailability[3] possibly from slow dissolution speed due to the hydrophobic character of this class of tricyclic compounds. Considering that even selective COX-2 inhibitors appear to have a limited safety margin with regards to gastrointestinal safety, a large extent of inter-subject variation in oral bioavailability may not be desirable in humans. In this article, we will discuss a prodrug approach by which poor bioavailability could be resolved for a specific case of highly lipophilic tricyclic selective COX-2 inhibitors with a methylsulfone moiety.



Celecoxib



Rofecoxib



Valdecoxib

Previously we reported 2,2-dimethyl-4-phenyl-5-{4-(methylsulfonyl)phenyl}-3(*2H*)furanone derivatives as a novel class of potent selective COX-2 inhibitors.[4] COX-2 inhibitors of the 3(*2H*)furanone scaffold showed very strong anti-inflammatory potencies by adjuvant-induced arthritis. For example, compound **1** showed an adjuvant-induced arthritis ED_{50} of 0.03 mg/kg/day, QD (therapeutic model, SD rats), which could be regarded as one of the most potent among the reported COX-2 selective inhibitors.[4] Despite its strong anti-inflammatory potency, compound **1** showed poor bioavailability in dogs,[5] which would pose a technical issue relating to oral intake by humans.

The sulfoxide moiety is known to be an efficient functionality to facilitate *trans*-dermal penetration.[6a] In the meantime, the sulfoxide moiety is often transformed in vivo into the corresponding sulfone by oxidative enzymes.[6b] There is a reported case that intravenous administration of a selective p38 MAP kinase inhibitor with a sulfoxide moiety effectively led to transformation of the sulfoxide to the corresponding sulfone compound in rats.[7] Thus, a sulfoxide analogue could be a good choice of prodrug for improvement in bioavailability of the corresponding sulfone analogue with poor oral bioavailability (Scheme 1).

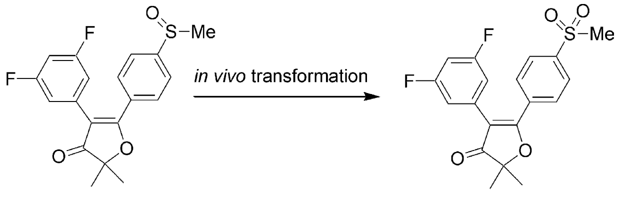
2. Synthesis

Compounds in this article were prepared as outlined in Scheme 2. Methylsulfones **1** and **4** were prepared by oxidation of sulfides **2** and **5**, respectively, with OXONE® in 1:1:1 THF/MeOH/H_2O in quantitative yield as reported previously.[4] Sulfoxide **3**[8a] was

---

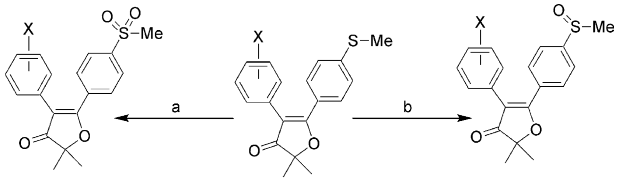
* Corresponding author. Tel.: +82-31-280-5910; fax: +82-31-281-8391; e-mail: schung@amorepacific.com

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.01.048



3 1

Scheme 1. In vivo transformation of a sulfoxide prodrug into parent sulfone drug in COX-2 inhibitors with a 3(*2H*)furanone scaffold.



1 (X = 3-F, 5-F)
4 (X = 3-Cl)
2 (X = 3-F, 5-F)
5 (X = 3-Cl)
3 (X = 3-F, 5-F)
6 (X = 3-Cl)

Scheme 2. Reagents and conditions: (a) Oxone, MeOH/THF/water, room temperature, overnight; (b) *m*-CPBA, methylene chloride, 0 °C, 1 h.

prepared by partial oxidation of the corresponding methylsulfide **2**, using *m*-CPBA. Methyl sulfide **2**[9] was subjected to reaction with 1 equiv *m*-CPBA at 0 °C in methylene chloride for 1 h to afford sulfoxide **3** in 91% yield. Sulfoxide **6**[8b] was similarly prepared from the corresponding sulfide **5**.[9]

3. Pharmacokinetic studies

Oral administration of **3** to male SD rats resulted in fast absorption through the gastrointestinal tract, followed by rapid in vivo transformation into the parent drug molecule **1** (Fig. 1). Intravenous administration of **3** yielded a pharmacokinetic pattern similar to the oral counter part, indicating that absorption of the prodrug in the gastrointestinal tract was very rapid. The following pharmacokinetic data was obtained for the parent drug **1** after oral administration of the prodrug: $T_{\max} = 2$ h, $C_{\max} = 2.6$ μg/mL, and $AUC_{0\text{–}24\ \mathrm{h}} = 23.1$ h×μg/mL (10 mg/kg, $n = 3$). In the meantime, oral administration of parent drug **1** resulted in a notably reduced systemic exposure of **1** by about 3.5-fold as indicated by its pharmacokinetic parameters:[10] $T_{\max} = 4.3$ h, $C_{\max} = 0.64$ μg/mL, and $AUC_{0\text{–}24\ \mathrm{h}} = 6.6$ h×μg/mL (10 mg/kg, $n = 2$).

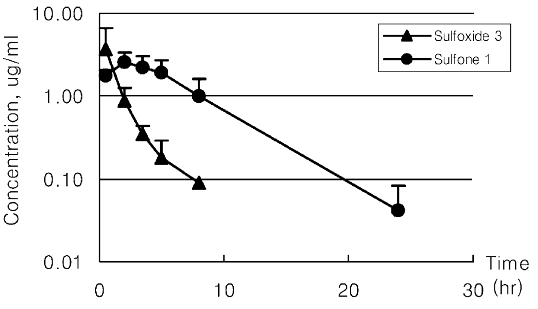


Figure 1. Pharmacokinetic decay diagrams for sulfone parent drug **1** and sulfoxide prodrug **3** following oral administration of prodrug **3** at 10 mg/kg in male SD rats. Error bar is by standard deviation ($n = 3$).

Table 1 summarizes pharmacokinetic data for **1** obtained after oral administration of its prodrug **3** at various doses. Even when the oral dose of **3** was increased up to 100 mg/kg, its oral bioavailability did not appear to decrease as demonstrated by its pseudo-linear increase of $C_{\max}$ with dose escalation.

The generality of the prodrug approach was further substantiated for COX-2 inhibitors of the 3(*2H*)furanone scaffold by evaluating a set of sulfone **4** and its sulfoxide prodrug **6**. When **6** was orally administered to male SD rats, **6** was rapidly absorbed into the blood stream and transformed in vivo into **4**.[11]

4. Therapeutic activity

Even though the sulfoxide prodrugs were transformed in vivo into the parent sulfone drugs, pharmacokinetic studies were carried out at dose levels too high for therapeutic relevance. Therapeutic activity was assessed for prodrug **3** by adjuvant-induced arthritis (AA) in male Lewis rats (preventive model) at therapeutically relevant dose levels, which yielded an ED_{50} of ~0.2 mg/kg/day, BID, po.[12] Previously parent drug **1** was reported to show an AA ED_{50} of 0.03 mg/kg/day, QD, po in SD rats (therapeutic model).[4] According to in-house experiences, AA potency by the therapeutic model tends to be nominally stronger than the potency by the preventive model. Since 5- to 10-fold differences in the potency were not uncommon between the two models, prodrug **3** may be regarded to have anti-inflammatory activity as strong as expected for parent drug **1** at therapeutically relevant dose levels. Thus, prodrug **3** is effectively transformed in vivo into parent drug **1** at doses ranging from therapeutically relevant low doses to very high doses.

5. In vitro activities

COX-1/COX-2 inhibitory activities were assessed for the sulfoxide compounds against COX-1 and COX-2 expressed in mouse peritoneal macrophage as reported previously.[4] The COX-2 inhibitory activities of sulfoxides **3** and **6** were weaker by 50-fold and 30-fold than those of the corresponding sulfone parent drugs **1** and **4**,

Table 1. Pharmacokinetic data for parent drug **1** obtained after oral administration of prodrug **3** to male SD rats

Dose, mg/kg	$C_{\max}$, μg/mL	$T_{\max}$, h	$AUC_{0\text{–}24\ \mathrm{h}}$, h×μg/mL	n
10	2.58	2.0	23.1	3
50	11.7	4.3	359	3
100	24.9	5.0	487	3

Table 2. In vitro inhibitory activities against COX-2 and COX-1 in mouse peritoneal macrophages

Compd	IC_{50}, μg/mL	
	COX-2	COX-1
1	0.02	5
3	1	10
4	0.01	2
6	0.3	5

respectively. COX-1 inhibitory activities were also lower for the sulfoxide prodrugs. However, COX-1 inhibitory activities did not decrease much when compared to the COX-2 inhibitory activities (Table 2).

6. Pharmacological implications

For a drug with a limited safety margin, including COX-2 inhibitors, an overdose could result in unwanted side effect(s). Poor oral bioavailability could lead to a large extent of inter-subject variation in the systemic exposure of drug, leading to poor safety outcomes for a drug intrinsically with a limited safety margin. The sulfoxide approach is an attractive option for COX-2 inhibitors containing a sulfone moiety to reduce inter-subject variation in the systemic exposure of the parent drug.

Even though COX-2 inhibitors are regarded to have resolved the life-threatening GI toxicity of traditional NSAIDs to a large extent, COX-2 inhibitors still seem to show a certain degree of the gastrointestinal (GI) toxicity upon long term administration. There could be two factors contributing to the GI toxicity: One is from systemic redistribution of drug to the GI tract, and the other is from drug influx through the GI tract after oral intake of drug. The relative contribution of the two factors could vary depending on the nature of drug and formulation. During the local influx of drug, the GI tract is exposed to the drug at much higher concentration than the plasma concentration. Theoretically, the smaller contribution from the drug influx through the GI tract should lead to a smaller GI burden for a drug of oral formulation. The faster a drug is absorbed through the GI tract, the less GI damage is expected from the drug influx. In this regard, a COX-2 inhibitor with fast absorption may be preferred.[13]

Since the sulfoxide compounds showed weaker COX-1/COX-2 inhibitory potencies than the corresponding parent sulfone COX-2 inhibitors, the sulfoxide prodrugs may provide a suitable approach to reduce GI burden of COX-2 inhibitors with a methylsulfone at least in terms of the mechanism-associated pathway.

Acknowledgements

We would like to thank Ms. K. M. Joo of the Analysis Research Team for mass spectral analysis.

References and notes

1. (a) Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Kellog, M. S.; Koboldt, C. M.; Yuan, J.; Zhang, Y. Y.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 1661. (b) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkin, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775. (c) Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. *J. Med. Chem.* **2002**, *45*, 1511.
2. Leval, X. D.; Julémont, F.; Delarge, J.; Sanna, V.; Pirotte, B.; Dogné, J.-M. *Exp. Opin. Ther. Patents* **2002**, *12*, 969.
3. Joo, Y. H.; Kim, J. K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413.
4. Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J.-Y.; Kim, J. K.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 165.
5. A C_{max} of 0.13 μg/mL was observed, when **1** was orally administered to a male beagle dog at 10 mg/kg. The C_{max} value is smaller than a quarter of the corresponding C_{max} value for the administration of **1** in male SD rats at 10 mg/kg.
6. (a) Büyüktimkin, N.; Büyüktimkin, S.; Rytting, J. H. In *Transdermal and Topical Drug Delivery Systems*; Ghosh, T. K., Pfister, W. R., Eds.; Interpharm Press: Buffalo Grove, 1997; p 357–475 (b) Williams, D. A. In *Principles of Medicinal Chemistry*; Foye, W. O., Lemke, T. L., Williams, D. A., Eds.; Williams & Wilkins: Media, 1995; p 83–140.
7. de Laszlo, S. E.; Visco, D.; Agarwal, L.; Chang, L.; Chin, J.; Croft, G.; Forsyth, A.; Fletcher, D.; Frantz, B.; Hacker, C.; Hanlon, W.; Harper, C.; Kostura, M.; Li, B.; Luell, S.; MacCoss, M.; Mantlo, N.; O'Neill, E. A.; Orevillo, C.; Pang, M.; Parsons, J.; Ronaldo, A.; Sahly, Y.; Sidler, K.; Widmer, W. R.; O'Keefe, S. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2689.
8. Compound **3** was prepared as follows: To a stirred solution of 4-{3,5-(difluoro)phenyl}-2,2-dimethyl-5-{4-(methylthio)-phenyl}-3(*2H*)furanone (**2**)[9] (4.00 g, 11.5 mmol) in 200 mL CH_2Cl_2, was added dropwise at 0 °C 70% *m*-CPBA (2.83 g, 11.5 mmol, 1 equiv) dissolved in 200 mL CH_2Cl_2. The reaction mixture was stirred for 1 h at 0 °C. Then the reaction solvent was removed under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (50 mL×2) and H_2O (100 mL). The organic layer was dried over $MgSO_4$ and then concentrated in vacuo. Flash column chromatography of the residue over silica gel eluting hexane/ethyl acetate (1:1) afforded 4-{3,5-(difluoro)-phenyl}-2,2-dimethyl-5-{4-(methyl-sulfinyl)phenyl}-3(*2H*)furanone (**3**) (3.80 g, 10.5 mmol, yield 91%). (a) Analytical data for **3**: mp 143–144 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 6H), 2.76 (s, 3H), 7.26–7.08 (m, 3H), 7.30–7.38 (m, 1H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.80 (d, $J = 8.2$ Hz, 2H). IR (cm^{-1}, neat): 1697 (C=O), 1624, 1390, 1054 (S=O). MS (ESI) 363 (MH^+). (b) Analytical data for **6**: mp 109–110 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.57 (s, 6H), 2.75 (s, 3H), 7.14–7.18 (m, 1H), 7.30–7.32 (m, 2H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.80 (d, $J = 8.7$ Hz, 2H). IR (cm^{-1}): 1697 (C=O), 1615, 1383, 1052 (S=O). MS (ESI) 363 (MH^+).
9. Lee, K.-W.; Choi, Y. H.; Joo, Y. H.; Kim, J. K.; Shin, S. S.; Byun, Y. J.; Kim, Y.; Chung, S. *Bioorg. Med. Chem.* **2002**, *10*, 1137.
10. Oral bioavailability of **1** varied batch to batch, suggesting crystal polymorphism or variation in particle size distribution.

11. Oral administration of **6** at 10 mg/kg yielded pharmacokinetic data as follows ($n = 3$): (a) for **4**, $T_{max} = 1.50$ h, $C_{max} = 1.39$ μg/mL, and $AUC_{0–24\ h} = 12.68$ h×μg/mL. (b) for **6**, $T_{max} = 0.50$ h, $C_{max} = 0.46$ μg/mL, and $AUC_{0–24\ h} = 3.61$ h×μg/mL.
12. The observed % inhibitions of AA by the preventive model were as follows: 76 ± 7% for 0.3 mg/kg/day sulfoxide **3** and 60 ± 6% for 0.3 mg/kg/day positive comparator indomethacin; 40 ± 7% for 0.1 mg/kg/day sulfoxide **3** and 61 ± 5% for 0.3 mg/kg/day indomethacin. Deviations are by standard error mean. BID and $n = 10$ per group.
13. When sulfone **1** was orally administered to male SD rats for 4 weeks at 5 mg/kg/day, QD, there were two unscheduled deaths out of ten from peritonitis secondary to the intestinal toxicity upon necropsy examination. There were no gastric findings, suggesting that the observed toxicity was likely to be from inhibition of COX-2. In case of sulfoxide prodrug **3**, all 10 male SD rats survived to the end of the 4 week repeat dose study at 5 mg/kg/day, QD.