Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 1195–1198

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

3,4-Diaryl-5-hydroxyfuranones: Highly Selective Inhibitors of Cyclooxygenase-2 with Aqueous Solubility

W. Cameron Black,* Christine Brideau, Chi-Chung Chan, Stella Charleson, Wanda Cromlish, Robert Gordon, Erich L. Grimm, Gregory Hughes, Serge Leger, Chun-Sing Li, Denis Riendeau, Michel Thérien, Zhaoyin Wang, Li-Jing Xu and Petpiboon Prasit

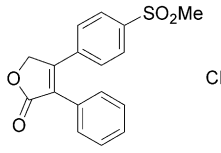
Merck Frosst Centre for Therapeutic Research, PO Box 1005, Pointe-Claire-Dorval, Quebec, Canada H9R 4P8

Received 26 September 2002; accepted 26 November 2002

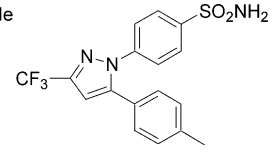
Abstract—The introduction of a hydroxyl group into the 5-position of the diaryl furanone system provides highly selective inhibitors of cyclooxygenase-2. These molecules can be converted into their sodium salts which are water soluble, facilitating intravenous formulation. These salts show excellent potency in rat models of pain, fever and inflammation.

Selective inhibitors of cyclooxygenase-2 (COX-2) have been demonstrated to be clinically effective anti-inflammatory and analgesic drugs with reduced gastrointestinal toxicity as compared to NSAIDs.[1] This improved safety profile is attributable to the lack of inhibition of COX-1, which plays a role in cytoprotection of the GI tract. There is currently interest in the identification of a COX-2 inhibitor suitable for parenteral administration. One such molecule is parecoxib, a prodrug which requires metabolic activation to give the active drug, valdecoxib.[2] There could be an advantage to a COX-2 inhibitor with intrinsic water-solubility that could be administered orally or intravenously without having to resort to a prodrug approach. The 5-hydroxyfuranones described here have the potential to fulfil such a role.

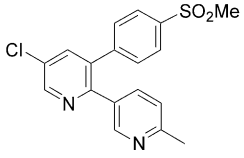
Phenylsulfone- and phenylsulfonamide-containing tricyclic molecules have proved to be a fertile area for the discovery of selective inhibitors of COX-2. A number of central ring templates have been successfully developed.[3] Among these are the furanone of rofecoxib,[4] the trifluoromethyldiazole of celecoxib,[5] the chloropyridine of etoricoxib,[6] and the isoxazole ring of valdecoxib.[7]



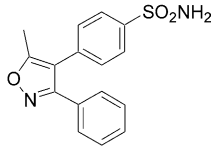
rofecoxib



celecoxib



etoricoxib



valdecoxib

Extensive exploration of the furanone template has revealed that the introduction of alkyl substituents at the 5-position of the ring provides enhanced selectivity over COX-1.[8] Furthermore, the 2-phenyl substituent can be replaced with a wide variety of groups, in many cases improving both potency and selectivity of the resulting inhibitors.[9]

We wish to report that the introduction of a hydroxyl group into the 5-position of the furanone ring provides compounds with beneficial biological and physical properties. Alkoxy substituents in this position provide potent and highly selective inhibitors of COX-2. Hydroxyl-substituted furanones, while being somewhat

*Corresponding author. Fax: +1-514-428-4939; e-mail: blackc@merck.com

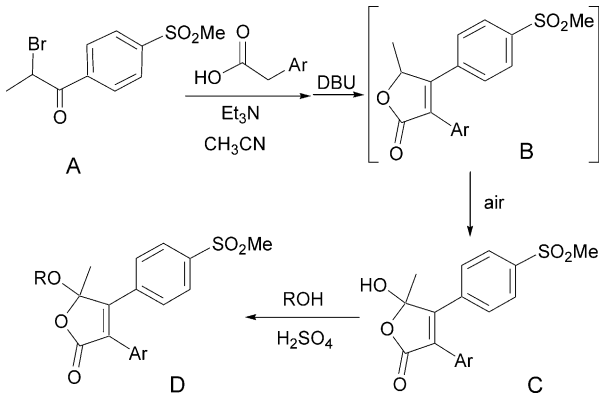
0960-894X/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0960-894X(03)00046-5

less potent than their alkoxy analogues, are also highly selective for COX-2. Furthermore these compounds can be readily converted into water-soluble salts.

The majority of the compounds listed in Table 1 were prepared using the route outlined in Scheme 1. α-Bromo ketone **A** was prepared by known methods.[10] The bromide was displaced by the triethylammonium salt of an arylacetic acid to provide the corresponding ester, which underwent an intramolecular aldol condensation in the presence of DBU. If oxygen was rigourously excluded, the intermediate 5-methyl furanone **B** could be isolated. However, exposure to air in the presence of the base led to rapid oxidation of the ring, providing the desired hydroxyfuranone **C**.[11] In practice, the cyclization and oxidation were accomplished in one step by treating the ester with DBU followed by passing a stream of air through the dark solution using a gas diffusion tube. Alkyl ethers **D** were formed by heating a solution of the hydroxyfuranone with the appropriate alcohol in the presence of sulfuric acid.

The initial 5-hydroxy-5-methylfuranone **3** (Table 1) was found to have only modest activity in the COX-2 CHO cell assay.[12] However, its complete lack of activity against COX-1 in the sensitive U937 microsome assay[13] justified further study. It was found that the potency of **3** in the COX-2 whole blood assay[14] was relatively good, implying a small protein shift in this protein-rich assay. Pharmacokinetics in rats showed high drug exposure (60 μM C_{max} following a 20 mg/kg oral dose) and a low clearance (2.6 mL/min). This prompted us to evaluate the compound in our standard model of in vivo anti-inflammatory activity, the rat paw edema assay[15] where it proved to be equally efficacious to rofecoxib.

Since the chemical behaviour of this hydroxyfuranone was reminiscent of a weak acid (vide infra), it was treated with diazomethane, leading to the methyl ether **4**. This derivative was found to be 5-fold more potent than **3** in the CHO assay, and nearly 15-fold more potent in the COX-2 whole blood assay. While the undesired COX-1 activity of **4** was greater than that of **3**, its selectivity profile was markedly superior to that of rofecoxib and celecoxib, particularly in the critical whole blood assays. Pharmacokinetic evaluation showed modest plasma concentrations of **4**, but also a large amount of a circulating metabolite, which was subsequently identified to be the demethylated material **3**.



Scheme 1.

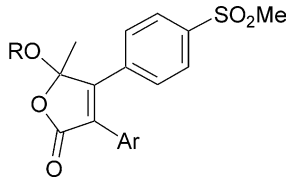
In an attempt to limit this route of metabolism, several alkyl ether substituents on the furanone ring were evaluated (Table 1). Increasing the size of the alkyl group gave a gradual reduction in the COX-2 activity. Pharmacokinetic evaluation showed that although the larger alkyl groups were successful at reducing the amount of the circulating metabolite **3**, the overall oral bioavailability decreased dramatically. The trifluoroethyl derivative **7** provided an exception to this trend. It exhibited reasonable COX-2 activity and an oral bioavailability in rats of 35%. However, it gave only modest efficacy in the rat paw edema assay and was not pursued further.

The 5-hydroxyfuranone template was chosen for further study and the nature of the aryl group at the 3-position of the furanone ring was evaluated. Previous experience in other series had shown that aryl groups with para substituents increase potency against COX-1 while meta substituents decrease COX-1 potency.[4] In the hydroxyfuranone series, this trend was difficult to ascertain, since little or no inhibition was observed in the COX-1 assays for most compounds. However, the 4-thiomethoxy substituent **11** did result in a significant increase in COX-1 activity. Other lipophilic substituents in the 4-position of the phenyl were well-tolerated. The 4-chlorophenyl derivative **9** was found to have the best overall profile of COX-2 potency and antiinflammatory activity. The more polar hydroxyphenyl derivative **13** was inactive in the COX-2 assays, consistent with the requirement for a lipophilic group in this position of the inhibitor. Halogen substituents in the *ortho* or *meta* positions of this ring led to reduced potency in the COX-2 assays (**14**–**16**, **19**), with the exception of a *meta* chloro substituent, which appeared particularly well-tolerated (**17** and **18**). Several heterocyclic groups were explored as phenyl replacements, without success (**21**–**23**).

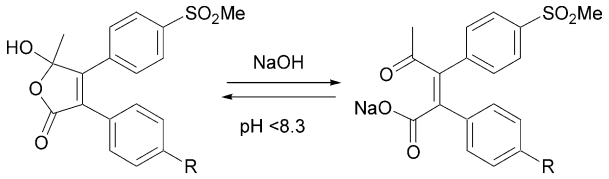
Previous studies in the 5,5-dimethylfuranone series had found that oxygen and sulfur substituents in the 3-position were well-tolerated and provided potent and selective inhibitors of COX-2.[9] In the case of the hydroxyfuranones, it was surprising to see that such substitution gave inactive compounds (**24** and **25**).

These hydroxyfuranones have several distinctive characteristics compared to other furanone derivatives we have encountered in the COX-2 program. Their lack of potency against COX-1 is remarkable, with undetectable activity under our assay conditions in many cases. While most furanone derivatives have limited aqueous solubility, the hydroxyfuranones are freely soluble in aqueous base. This can be explained by the formation of the salt of an open chain isomer under basic conditions (Scheme 2). This salt can be isolated as an amorphous solid which contains none of the corresponding cyclic alkoxide by ^{1}H NMR analysis. At neutral or acidic pH, the molecule exists exclusively in the cyclic form as evidenced by ^{1}H NMR and IR analysis. The aqueous solubilities of **26** and **27** are >100 mg/mL, but decrease rapidly as the solution is acidified below pH 8.3.[16] A

Table 1. In vitro and rat paw edema data for diarylalkoxy- and diarylhydroxyfuranones



Entry	R	Ar	COX-2		COX-1		
			CHO cells (IC_{50}, μM)	Human whole blood (IC_{50}, μM)	U937 microsomes (IC_{50}, μM)	Human whole blood (IC_{50}, μM)	Rat paw edema (ED_{50}, mg/kg)
1		Rofecoxib	0.02	0.5	1.7	19	1.5
2		Celecoxib	0.002	1.0	0.05	6.3	3.2
3	H	4-F-Ph	0.38	1.8	>100		1.8
4	Me	4-F-Ph	0.069	0.1	14	57	2.8
5	Et	4-F-Ph		0.5	10		
6	*i*Pr	4-F-Ph		0.8	3		
7	CF_3CH_2–	4-F-Ph	0.32	0.4	>10		6.4
8	H	Ph	0.16	1.2	>100	>90	1.5
9	H	4-Cl-Ph	0.11	1.7	105		1.4
10	H	4-Br-Ph	0.14	1.7	101	>100	1.6
11	H	4-MeS-Ph	0.31	1.7	7	38	
12	H	4-*i*Pr-Ph	0.41	4.3	>300	>100	
13	H	4-HO-Ph	>5	>33	>10		
14	H	3-F-Ph	0.25	12.8	>100		>10
15	H	3,4-F_2-Ph	0.20	6.3	>300		>10
16	H	3,5-F_2-Ph	0.55	13.4	>100	>90	
17	H	3-Cl-4-F-Ph	0.11	2.2	81		
18	H	3,4-Cl_2-Ph	0.07	0.85	35	75	1.9
19	H	2,4-Cl_2-Ph	1.2	7.5	>100		
20	H	2-Np	0.45	3.2	30		>10
21	H	2-Thienyl	1.9	>33	>100		
22	H	3-Thienyl	0.11	24	>100		
23	H	2-Benzothiophene	0.65	3.2	>100		
24	H	SPh	>5	>10	>10		
25	H	O-(3,4-F_2-Ph)	>5	>33	>10		



8 R = H
9 R = Cl

26 R = H
27 R = Cl

Scheme 2.

100 mg/mL solution of **26** in water was allowed to stand at room temperature for 8 weeks without evidence of decomposition.

The use of the sodium salt of these molecules for oral dosing provided equivalent efficacy to the neutral, cyclic form in animal models. Compound **27** was found to be highly efficacious in rat paw edema (ED_{50} = 1.8 mg/kg), rat pyresis[15] (ED_{50} = 0.7 mg/kg), rat hyperalgesia[15] (ID_{50} = 0.8 mg/kg) and rat adjuvent arthritis[17] (ID_{50} = 0.6 mg/kg). This compound was studied in the rat ^{51}Cr assay for GI toxicity[18] and showed no loss of GI integrity after dosing for 10 days at 100 mg/kg.

In conclusion, a highly-selective, orally-active inhibitor of COX-2 has been identified in the tricyclic sulfone class of cyclooxygenase-2 inhibitors. Furthermore, compound **9** shows aqueous solubility due to the formation of an open-chain salt. This solubility allows for the preparation of stable aqueous solutions that may be suitable for intravenous formulation.

References and Notes

1. Bombardier, C. *Am. J. Cardiol.* **2002**, *89* (Suppl.), 3D.
2. Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Kellogg, M. S.; Koboldt, C. M.; Yuan, J.; Zhang, Y. Y.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 1661.
3. (a) Gauthier, J. Y.; Leblanc, Y.; Black, W. C.; Chan, C.-C.; Cromlish, W.; Gordon, R.; Kennedy, B. P.; Lau, C. K.; Léger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 87. (b) Puig, C.; Crespo, M. I.; Godessart, N.; Feixas, J.; Ibarzo, J.; Jiménez, J.-M.; Soca, L.; Cardelús, I.; Heredia, A.; Miralpeix, M.; Puig, J.; Beleta, J.; Huerta, J. M.; López, M.; Segarra, V.; Ryder, H.; Palacios, J. *J. Med. Chem.* **2000**, *43*, 214. (c) 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.
4. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Léger, S.; Mancini, J.; O'Neil, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Thérien, M.; Vickers, P.;

Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1773.
5. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, 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. M.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem*. **1997**, *40*, 1347.
6. Friesen, R. W.; Brideau, C.; Chan, C.-C.; Charleson, S.; Deschenes, D.; Dube, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, L. J.; Young, R. N. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2777.
7. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem*. **2000**, *43*, 775.
8. Riendeau, D.; Percival, M. D.; Boyce, S.; Brideau, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.; Falgueyret, J.-P.; Ford-Hutchinson, A. W.; Gordon, R.; Greig, G.; Gresser, M.; Guay, J.; Kargman, S.; Léger, S.; Mancini, J. A.; O'Neill, G.; Ouellet, M.; Rodger, I. W.; Thérien, M.; Wang, Z.; Webb, J. K.; Wong, E.; Xu, L.; Young, R. N.; Zamboni, R.; Prasit, P.; Chan, C.-C. *Br. J. Pharmacol*. **1997**, *121*, 105.
9. Li, C.-S.; Black, W. C.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W. A.; Claveau, D.; Gauthier, J. Y.; Gordon, R.; Greig, G.; Grimm, E.; Guay, J.; Lau, C. K.; Riendeau, D.; Therien, M.; Visco, D. M.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 3181.
10. Bosch, J.; Roca, T.; Catena, J.-L.; Llorens, O.; Pérez, J.-J.; Lagunas, C.; Fernandez, A. G.; Miquel, I.; Fernandez-Serrat, A.; Farrerons, C. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1745.
11. Mechanistic studies on this oxidation will be reported separately (Z. Wang and J. Wong unpublished results).
12. Kargman, S.; Wong, E.; Greig, G.; Falgueyret, J.-P.; Cromlish, W.; Ethier, D.; Yergey, J.; Riendeau, D.; Evan, J.; Kennedy, B.; Tagari, P.; Francis, D.; O'Neill, G. P. *Biochem. Pharmacol*. **1996**, *52*, 1113.
13. Riendeau, D.; Charleson, S.; Cromlish, W.; Mancini, J. A.; Wong, E.; Guay, J. *Can. J. Physiol. Pharmacol*. **1997**, *75*, 1088.
14. Brideau, C.; Kargman, S.; Liu, S.; Dallob, A. L.; Ehrich, E. W.; Rodger, I. W.; Chan, C.-C. *Inflamm. Res*. **1996**, *45*, 68.
15. Chan, C.-C.; Boyce, S.; Brideau, C.; Ford-Hutchinson, A. W.; Gordon, R.; Guay, D.; Hill, R.; Li, C.-S.; Mancini, J.; Penneton, M.; Prasit, P.; Rasori, R.; Riendeau, D.; Roy, P.; Targari, P.; Vickers, P.; Wong, E.; Rodger, I. W. *J. Pharmacol. Exp. Ther*. **1995**, *274*, 1531.
16. Compound **9** has a pK_a of 7.5 as measured by GLpK_a: S.-D. Clas and K. Khougaz, Merck Frosst Centre for Therapeutic Research, unpublished results.
17. Fletcher, D. S.; Widmer, W. R.; Luell, S.; Christen, A. J.; Orevillo, C.; Shah, C.; Visco, D. M. *J. Pharmacol. Exp. Ther*. **2001**, *284*, 714.
18. Riendeau, D.; Percival, M. D.; Brideau, C.; Charleson, S.; Dubé, D.; Ethier, D.; Falgueyret, J.-P.; Friesen, R. W.; Gordon, R.; Greig, G.; Guay, J.; Mancini, J.; Ouellet, M.; Wong, E.; Xu, L.; Boyce, S.; Visco, D.; Girard, Y.; Prasit, P.; Zamboni, R.; Rodger, I. W.; Gresser, M.; Ford-Hutchinson, A. W.; Young, R. N.; Chan, C.-C. *J. Pharmacol. Exp. Ther*. **2001**, *296*, 563.