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Racemic and chiral sulfoxides as potential prodrugs of 4-pyrone COX-2 inhibitors

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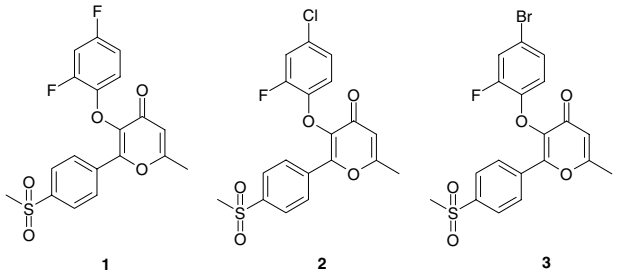
Abstract—The preparation of the sulfoxide analogues **7**, **8**, and **9** and their enantiomerically pure forms is discussed as well as their ability to act as prodrugs of the potent and selective sulfone-containing COX-2 inhibitors **1**, **2**, and **3**. Sulfoxide derivatives **7** and **9** were shown to be rapidly transformed in vivo into the corresponding sulfone derivatives **1** and **3**, after oral administration to rats.

In spite of recent reports of side effects, the commercial utilization of selective COX-2 inhibitors in the treatment of pain and inflammatory disorders is well established and such compounds may also have potential in other therapeutic areas.[1] We have been interested in the design of novel COX-2 inhibitors in our laboratories for some time.[2] During the course of these investigations we have discovered the potential of certain arylsulfoxides to act as both COX-2 inhibitors in their own right but also potential prodrugs to the prototypical sulfones found in many COX-2 inhibitors described in the literature. In addition, we have found that such sulfoxides often offer distinct advantages in terms of solubility and pharmacokinetic profiles over the parent sulfones.

Given the interesting biological profiles presented by the racemic sulfoxides synthesized, we decided to undertake the enantioselective synthesis and biological profiling of several chiral sulfoxides as potential prodrugs of COX-2 inhibitors. We selected three preclinical candidates (1–3) originating from our own laboratories, shown below, in order to further explore these findings.



The medicinal use of sulfoxide-containing active agents is fairly common. For example, such a moiety is found in the H^+/K^+ ATPase inhibitor omeprazole (Losec®) or its single enantiomer form esomeprazole (Nexium®), in certain p38 kinase inhibitors,[3] or in investigational drugs such as RP52891 (aprikalim). However, the ability of sulfoxides to act as prodrugs of sulfones in vivo is not well documented and we are aware of only one other recent report, also in the area of COX-2 inhibitors where this concept has been described.[4] In this paper, we report our investigations into the biological activities and ADME profiles of sulfoxides as potential prodrugs of sulfones.

The synthetic strategy employed to prepare the sulfoxide derivatives was based on the racemic or enantioselective oxidation of the corresponding thioethers.[5] In the case of pyran-4-one derivatives, the thioether intermediates

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were synthesized following a protocol previously described by our laboratories[2c] in which a series of 2-(4-methanesulfanylphenyl)pyran-4-one derivatives **4**–**6** were prepared from the corresponding phenacyl derivatives **10**–**12** by heating in a mixture of PPA in Ac_2O at 100 °C. The racemic sulfoxides **7**–**9** were subsequently obtained by oxidation of the corresponding thioethers with $NaIO_4$ in MeOH–water (ratio 2:1) in moderate to good yields (43–77%) (Scheme 1).

Several asymmetric oxidation methods were attempted to gain access to the enantiomerically enriched sulfoxides (*R*)- or (*S*)-**7**–**9**. Utilizing methodologies described by Kagan[6] or Bolm[7] provided compounds with only slight enantiomeric excesses. However, excellent results were obtained utilizing the Modena catalytic system[8] using $Ti(O^iPr)_4$ and either (*R*,*R*)- or (*S*,*S*)-DET (1:4) and *t*-BuOOH at −20 °C in 1,2-dichloroethane, as depicted in Scheme 2.

The enantiomeric excesses were determined using capillary electrophoresis (Table 1) and were in accordance with those determined by ^1H NMR using Pirkle's alcohol[9] as a shift reagent.

The absolute configuration at the sulfur center was assigned in each case following precedents described in the literature.[10] Thus, the (*R*)-sulfoxides were obtained using (*R*,*R*)-DET as a chiral source, while the use of (*S*,*S*)-DET provided the (*S*)-sulfoxides. An X-ray crystal structure of compound (*S*)-**7** (CCDC deposition number: 601850) confirmed the stereochemical assignment (Fig. 1). It was subsequently assumed that this rule would hold for the other sulfoxides synthesized.

Table 1. Enantiomeric excesses of pyrones **7**–**9** obtained via assymetric oxidation

Substrate	R	Product	(*R*)-Enantiomer ee (%)	(*S*)-Enantiomer ee (%)
4	F	**7**	100	88.4
5	Cl	**8**	100	98.4
6	Br	**9**	98.8	98.2

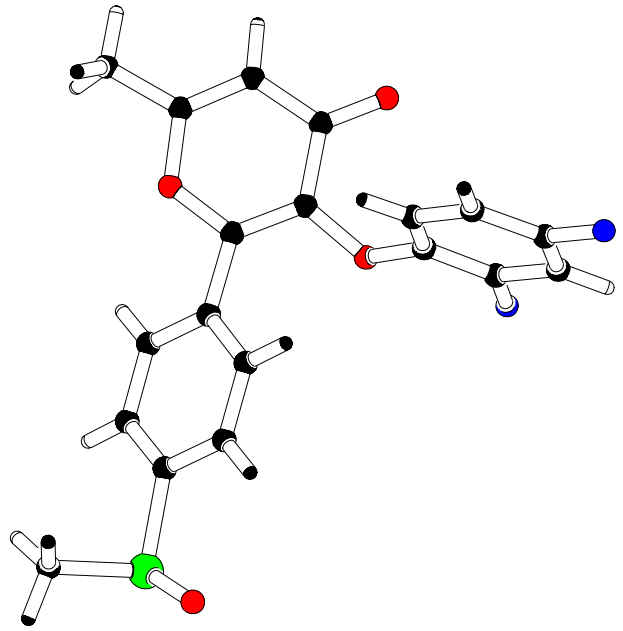
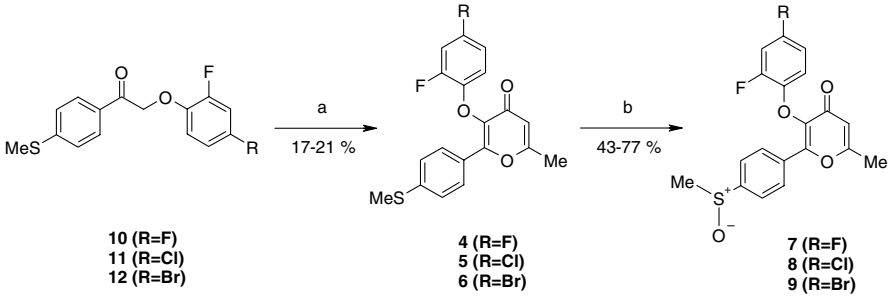
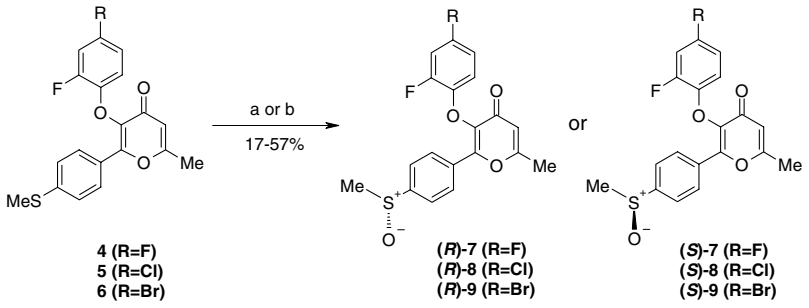


Figure 1. X-ray structure of sulfoxide (*S*)-**7**.



Scheme 1. Reagents and conditions: (a) PPA, Ac_2O, 100 °C; (b) $NaIO_4$, MeOH–H_2O (2:1).



Scheme 2. Reagents and conditions: (a) $Ti(O^iPr)_4$/(*R*,*R*)-DET (1:4), *tert*-BuOOH, 1,2-DCE, −20 °C; (b) $Ti(O^iPr)_4$/(*S*,*S*)-DET (1:4), *t*-BuOOH, 1,2-DCE, −20 °C.

All compounds described herein were tested for their ability to inhibit human COX-1 and COX-2 using the whole blood assay described by Patrignani et al.[11] The sulfoxides were found to be highly potent versus COX-2. The COX-1/COX-2 selectivity of the sulfoxides was similar to the corresponding sulfones of the 4-pyrones and comparable to that of an included standard, Etoricoxib (Merck). For the enantiomerically pure sulfoxides, the *S*-forms were more potent for COX-2 and showed higher COX-1/COX-2 selectivity than the corresponding *R*-forms (Table 2).

In vitro studies using pooled microsomes from rat and human livers showed that all the sulfoxides assayed were significantly metabolized. In rat microsomes, the extent of metabolism of the sulfoxides was greater than in human microsomes (Table 3). Parallel studies carried out after incubation of the sulfoxides with human hepatic microsomes showed that the corresponding sulfone was the main metabolite formed in all cases (data not shown).

In addition, all sulfoxides were assayed in human whole blood and were found to be stable (data not shown).

Table 2. In vitro inhibitory activities against COX-2 and selectivity COX-1/COX-2 in human whole blood

Compound	COX-2 [IC_{50}] (μM)	Selectivity ratio COX-1/COX-2
1	0.08	279
2	0.20	94
3	0.15	91
7	0.92	78
(*R*)-**7**	2.10	24
(*S*)-**7**	0.27	320
8	0.67	121
(*R*)-**8**	2.47	30
(*S*)-**8**	0.25	400
9	0.57	135
(*R*)-**9**	1.58	20
(*S*)-**9**	0.20	430
Rofecoxib	0.76	15
Etoricoxib	0.81	122

Table 3. In vitro metabolism and thermodynamic solubility of sulfoxide prodrugs (**7**–**9**) and parent drugs (**1**–**3**)

Compound	Microsome metabolism[a] (%)		Thermodynamic solubility[b] (μg/mL)	
	Human	Rat	SGF[c] (pH 1.8)	PBS[d] (pH 7.2)
1	2	26	9	7
2	6	27	18	5
3	12	34	4	1
7	24	54	527	150
(*R*)-**7**	20	55	—	—
(*S*)-**7**	17	38	—	—
8	57	86	70	37
(*R*)-**8**	48	87	—	—
(*S*)-**8**	41	67	—	—
9	64	77	31	15
(*R*)-**9**	62	93	—	—
(*S*)-**9**	42	80	—	—

[a] Assay conditions: metabolism (1 mg/mL microsomal protein, 5 μM compound, 30 min and 37 °C incubation).
[b] Thermodynamic solubility for crystalline compound (Target concentration: 1 mg/mL, 24 h and 37 °C incubation).
[c] SGF, simulated gastric fluid.
[d] PBS, phosphate buffer saline.

Table 4. Therapeutic activity

Compound	Adjuvant arthritis EC_{50} or % inhibition (dose) (mg/kg)	Pyresis ED_{50} (mg/kg)
1	68% (0.1)	0.7
2	63% (0.1)	0.8
3	60% (0.01)	3.2
7	59% (0.1)	1.3
8	56% (0.1)	2.3
9	58% (0.01)	2.8
Etoricoxib	0.440	1.0
Rofecoxib	0.300	0.9

Data are indicated as ED_{50} (mg/kg) using four doses (six to eight animals per group) or percentage of inhibition with dose (mg/kg) in parentheses. Since SEM values never exceeded 15% of the media, they have been omitted.

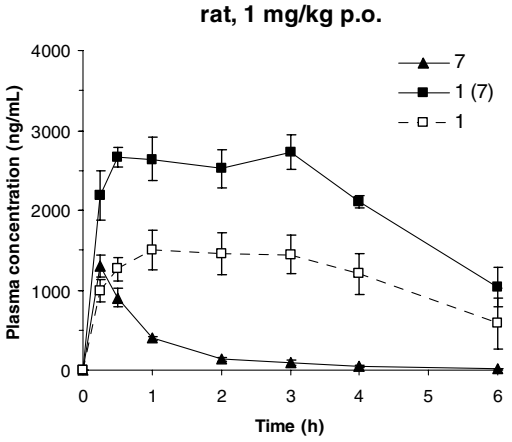


Figure 2. Plasma concentrations of sulfoxide **7** (prodrug) and sulfone **1** (drug) after oral administration of prodrug or drug at 1 mg/kg to male Wistar rats as a suspension of 0.5% methylcellulose and 0.1% Tween 80. Each data point represents the means ± SD of three values.

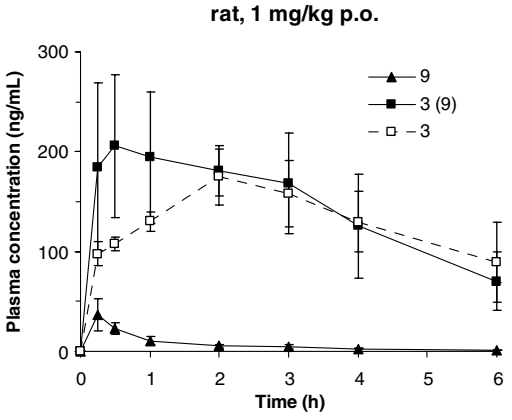


Figure 3. Plasma concentrations of sulfoxide **9** (prodrug) and sulfone **3** (drug) after oral administration of prodrug or drug at 1 mg/kg to male Wistar rats as a suspension of 0.5% methylcellulose and 0.1% Tween 80. Each data point represents the means ± SD of three values.

Table 5. Pharmacokinetic parameters following sulfoxide (**7** and **9**) and sulfone (**1** and **3**) administration to male Wistar rats

Parameter	7		1	9		3
	7	1		9	3	
C_{max} (ng/mL)	1309 (195)	2959 (171)	1507 (245)	37 (23)	243 (26)	177 (31)
t_{max} (h)	0.3 (0.1)	2.3 (1.2)	1.0 (0.0)	0.3 (0.0)	1.5 (1.3)	2.2 (0.2)
AUC (ng.h/mL)	1314 (174)	18646 (5255)	9216 (3423)	43 (19)	1125 (280)	1268 (445)

Results expressed as means ($n = 3$) and SD (in parentheses). Assay conditions: pharmacokinetic parameters of prodrug or parent drugs following single oral administration of 1 mg/kg to male Wistar rats as a suspension of 0.5% methylcellulose and 0.1% Tween 80.

In general, the metabolism tended to be slightly lower for the *S*-forms compared to the *R*-forms both in rat and human microsomes (Table 3). These data suggest that the *R*-form of sulfoxide **9** could be the best prodrug in humans, based on its metabolism in human microsomes (Tables 2 and 3).

Regardless of the pH, the solubility of a given sulfoxide was always higher than that of the corresponding sulfone. The greatest difference was found for the sulfoxide **7** at the acidic pH, with a solubility almost 60 times higher than that of the sulfone **1** (Table 3).

Therapeutic activities were assessed for all racemic sulfoxides and the corresponding sulfones in the yeast-induced pyresis model and the adjuvant-induced arthritis model. The yeast-induced pyresis in a therapeutic protocol is an acute model. In this model, temperature measurements were taken at 1 h intervals from 1 to 5 h after single oral administration of the compounds. As a chronic model of inflammation, the compounds were tested in the adjuvant-induced arthritis in male Wistar rats in a therapeutic protocol. The test compounds were administered orally once daily for 7 days starting from day 14 after arthritis induction and paw edema was measured 24 h after the last administration. The results showed that the sulfoxides demonstrated good oral efficacy at comparable doses to the sulfones, and higher efficacy than that of both Etoricoxib and Rofecoxib in the adjuvant arthritis model (Table 4).

The pharmacokinetic profiles were evaluated for the sulfoxides **7** and **9**, and compared to those of the corresponding sulfones **1** and **3**. Oral administration of **7** and **9** to male Wistar rats (1 mg/kg) resulted in rapid absorption followed by quick in vivo conversion of the sulfoxides into the corresponding sulfones **1** and **3** (Figs. 2 and 3). The sulfone-to-sulfoxide AUC ratios were 14 and 28 for **1** and **3**, respectively. In each case, plasma concentrations of the sulfone, derived from prodrug administration of the sulfoxide, at the earliest measured time point (0.25 h) were approximately two-fold higher than those obtained after direct administration of the sulfone itself. Similar increases were noted in the C_{max} and AUC parameters for sulfone **1**. For sulfone **3**, a tendency to higher C_{max} and similar AUC was observed (Table 5).

However, although the pharmacokinetic properties of sulfone **1** improved after prodrug administration, no significant improvement in its pharmacodynamics was found.

In conclusion, the present study shows that the sulfoxides of 4-pyrones have COX-2 activity and good COX-1/COX-2 selectivity. After oral administration of the sulfoxides and the corresponding sulfones in the rat, higher levels of the sulfone were achieved from sulfoxide prodrug than the sulfone itself. These results show that such sulfoxides may be of use as prodrugs of the corresponding 4-pyrone sulfones. Studies on potential sulfoxide prodrugs of the sulfone-containing products Etoricoxib and Rofecoxib will be reported in due course.

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