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Racemic and chiral sulfoxides as potential prodrugs of the COX-2 inhibitors Vioxx® and Arcoxia®

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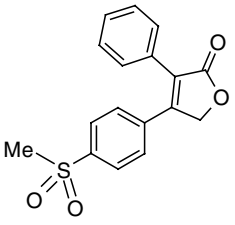
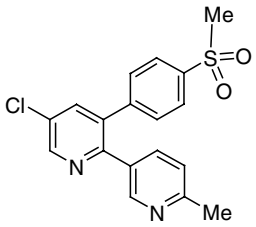
Abstract—The preparation of the sulfoxide analogues **2** and **4**, and their enantiomeric pure forms is discussed as well as their potential to act as prodrugs to the potent and selective sulfone-containing COX-2 inhibitors rofecoxib and etoricoxib. Sulfoxides **2** and **4** were shown to be effectively transformed in vivo into rofecoxib and etoricoxib, respectively, after oral administration in rats. In the case of sulfoxide **2**, both a slightly improved pharmacokinetic profile and a better pharmacological activity in an arthritis model were seen when compared with rofecoxib.

In a previous publication we disclosed the potential advantages in the use of arylsulfoxides as prodrugs of arylsulfones.[1] Continuing our efforts in the design of arylsulfoxides as potential prodrugs for the prototypical sulfones found in the field of COX-2 inhibitors, we selected the widely known drugs rofecoxib (Vioxx®) and etoricoxib (Arcoxia®) in order to explore the properties of the corresponding racemic and enantiomerically pure sulfoxides.



Rofecoxib



Etoricoxib

The synthetic strategy employed to prepare the sulfoxide derivatives was based on the racemic or enantioselective oxidation of the corresponding thioethers.[2] Thus, in the case of rofecoxib, the potential sulfoxide prodrug 4-[4-(methylsulfinyl)phenyl]-3-phenylfuran-2(5*H*)-one (**2**) was prepared according to Scheme 1. The thioether **1** was synthesized by condensation of phenylacetic acid with the bromoacetophenone **5**. Using protocols previously described in these laboratories,[1] the thioether **1** was oxidized in racemic fashion with $NaIO_4$ (81%) or in an enantioselective manner with (*R*,*R*)- or (*S*,*S*)-DET. Based upon evidence accumulated from a previous publication,[1] it was assumed in this study that the (*R*)-sulfoxide was obtained when (*R*,*R*)-DET was used as chiral source, while the use of (*S*,*S*)-DET provided the (*S*)-sulfoxide. The enantiomeric excesses, as determined by capillary electrophoresis (CE), were found to be 100% for the (*R*)-sulfoxide and 93.4% for the (*S*)-sulfoxide.

In a similar fashion, the synthesis of the potential sulfoxide prodrug of etoricoxib, 2-pyridinyl-3-(4-methylsulfinyl)phenylpyridine (**4**), was successfully accomplished as outlined in Scheme 2. The key synthetic step in the preparation of **4** was the selective palladium-catalyzed cross-coupling reaction of the dichloropyridine **7** (prepared from the known intermediate **6**[3]) employing the pyridinyl stannane **8**[3] as the organometallic partner.

The thioether **3** was chemoselectively oxidized to the racemic sulfoxide using $NaIO_4$ (70%) (Scheme 2) or in an enantioselective manner with (*R*,*R*)- or (*S*,*S*)-DET (Scheme 3), obtaining in both cases the exclusive oxidation of the sulfur atom according to the ^{1}H NMR data.

Keywords: COX-2; Sulfoxides; Prodrugs.
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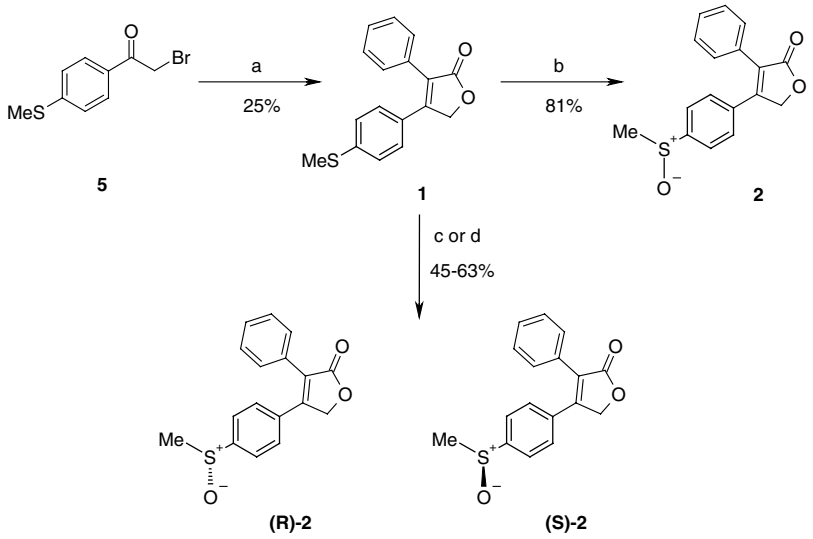
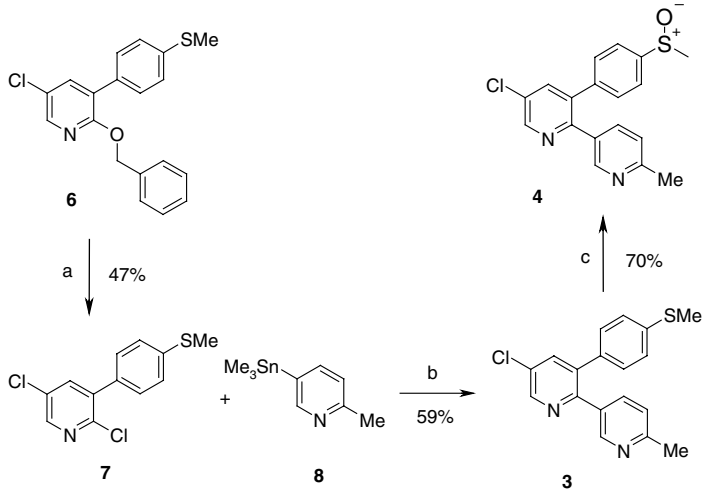
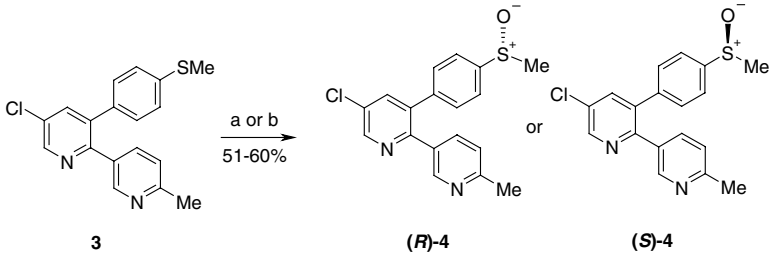


Scheme 1. Reagents and conditions: (a) Phenylacetic acid, K_2CO_3, 18-crown-6, CH_3CN; (b) $NaIO_4$, MeOH–H_2O (2:1); (c) Ti(O^{i}Pr)$_4$/(*R*,*R*)-DET (1:4), *t*-BuOOH, 1,2-DCE, −20 °C; (d) Ti(O^{i}Pr)$_4$/(*S*,*S*)-DET (1:4), *t*-BuOOH, 1,2-DCE, −20 °C.



Scheme 2. Reagents: (a) i—TFA, ii—$POCl_3$; (b) $Pd(PPh_3)_4$, NMP; (c) $NaIO_4$, MeOH–H_2O (2:1).



Scheme 3. Reagents and conditions: (a) Ti(O^{i}Pr)$_4$/(*R*,*R*)-DET (1:4), *t*-BuOOH, 1,2-DCE, −20 °C; (b) Ti(O^{i}Pr)$_4$/(*S*,*S*)-DET (1:4), *t*-BuOOH, 1,2-DCE, −20 °C.

The enantiomeric excesses, as determined by CE, were found to be 100% for both the (*R*)-4 and the (*S*)-4 sulfoxides.

All final 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.[4] All the sulfoxides except the (*R*)-**4** enantiomer of etoricoxib showed COX-2 activity in their own right. The selectivity ratio COX-1/COX-2 of all the sulfoxide prodrugs tested was similar (Table 1).

Metabolic stability was found to be higher in human than in rat microsomes for all the sulfoxides tested.

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

Compound	COX-2 IC_{50} or % inhibition (concentration (μM))	Selectivity ratio COX-1/COX-2
2	4.93	7
(*R*)-**2**	4.22	8
(*S*)-**2**	2.10	18
Rofecoxib	0.76	15
4	3.70	12
(*R*)-**4**	24.4 (10)	<2
(*S*)-**4**	3.50	22
Etoricoxib	0.81	122

These results suggest that the metabolism of these compounds is mediated by an isoenzyme with species-dependent activity. In each case, no significant differences in the extent of metabolism were found between the *R*- and *S*-enantiomers and the corresponding racemic sulfoxide (Table 2). Data obtained from pooled human liver microsomes showed that the sulfoxides studied were converted mainly into the corresponding sulfones (rofecoxib and etoricoxib) (data not shown).

A comparison of the racemic sulfoxide **2** with the corresponding sulfone (rofecoxib) shows that at both acidic and neutral pH a marked increase in solubility is attained going from sulfone to sulfoxide. Likewise, at neutral pH the solubility of sulfoxide **4** was higher than that of the corresponding sulfone (etoricoxib), while at acidic pH both sulfoxide **4** and sulfone showed similarly good solubility (Table 2).

Therapeutic activities were assessed for the 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 rofecoxib prodrug produced better effects than rofecoxib in both models (Table 3).

Table 2. In vitro metabolism and thermodynamic solubility of sulfoxides (**2** and **4**) and the corresponding sulfones (etoricoxib and rofecoxib)

Compound	Microsome metabolism[a] (%)		Thermodynamic solubility[b] (μg/ml)	
	Human	Rat	SGF[c] (pH 1.8)	PBS[d] (pH 7.2)
2	5	35	717	537
(*R*)-**2**	1	49	—	—
(*S*)-**2**	4	40	—	—
Rofecoxib	—	38	16	15
4	6	21	>1000	>1000
(*R*)-**4**	5	26	—	—
(*S*)-**4**	2	17	—	—
Etoricoxib	4	6	>1000	104

[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-buffered saline.

Table 3. Therapeutic activity

Compound	Adjuvant arthritis % inhibition (dose) (mg/kg)	Pyresis % inhibition (dose (mg/kg))
2	72% (0.3)	56% (1)
Rofecoxib	41% (0.3)	48% (1)
4	67% (1)	49% (3)
Etoricoxib	60% (1)	81% (3)

Data are indicated as percentage of inhibition with dose (mg/kg) in parentheses. Since SEM values never exceeded 15% of the media, they have been omitted.

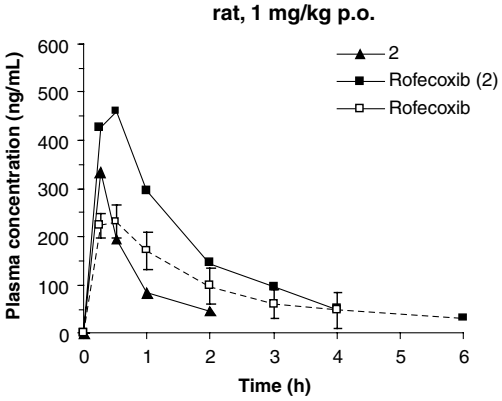


Figure 1. Plasma concentrations of sulfoxide 2 (prodrug) and sulfone rofecoxib (drug) after oral administration of prodrug or drug at 1 mg/kg to male Wistar rats as a suspension of 0.5% methylcellulose and 0.1% Tween 80. Each data point represents the mean ± SD of two to three values.

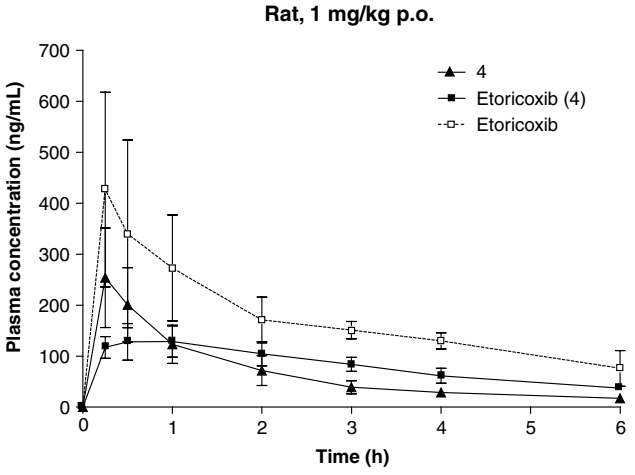


Figure 2. Plasma concentrations of sulfoxide 4 (prodrug) and sulfone etoricoxib (drug) after oral administration of prodrug or drug at 1 mg/kg to male Wistar rats as a suspension of 0.5% methylcellulose and 0.1% Tween 80. Each data point represents the mean ± SD of three values.

Table 4. Pharmacokinetic parameters following prodrug (**2**, **4**) and parent drug (etoricoxib, rofecoxib) administration to male Wistar rats

Parameter	**2**		Rofecoxib	**4**		Etoricoxib
	2	Rofecoxib		**4**	Etoricoxib	
C_{max} (ng/ml)	334	468	237 (34)	133 (33)	254 (98)	427 (191)
t_{max} (h)	0.3	0.4	0.4 (0.1)	0.6 (0.4)	0.3 (0.0)	0.3 (0.0)
AUC0-t (ng h/ml)	318	979	531 (234)	578 (96)	803 (117)	1656 (497)

Results expressed as means ($n = 2$–3) and SD (between brackets). 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.

Following oral administration of 1 mg/kg to male Wistar rats, the sulfoxides were well absorbed and rapidly converted into their sulfones (Figs. 1 and 2). The sulfone-to-sulfoxide AUC ratio was greater for the rofecoxib prodrug than for the etoricoxib prodrug (3.1 vs 1.4 for prodrugs **2** and **4**, respectively) (Table 4). Thus, after rofecoxib prodrug administration (i.e., sulfoxide **2**), both the C_{max} and AUC of rofecoxib were greater than those observed after direct administration of rofecoxib itself, while the opposite was observed in the case of etoricoxib (Table 4, Figs. 1 and 2).

In conclusion, the sulfoxide-based rofecoxib prodrug **2**, when compared with rofecoxib itself, led to improved pharmacokinetic levels of circulating rofecoxib after oral administration. As such, the rofecoxib prodrug gave a better pharmacological response in in vivo models. These effects are likely due to a marked increase in solubility of the sulfoxide over the sulfone. On the other hand, the observed increase in solubility of the sulfoxide-based etoricoxib prodrug **4** did not translate into an improvement of the pharmacokinetic and the pharmacodynamic properties of etoricoxib itself.

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