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(2*RS*,5*SR*,6*SR*)-Methyl 4-{*cis*-2-[3-fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxymethyl]-6-hydroxy-3-phenylmorpholino}-benzenesulfinate

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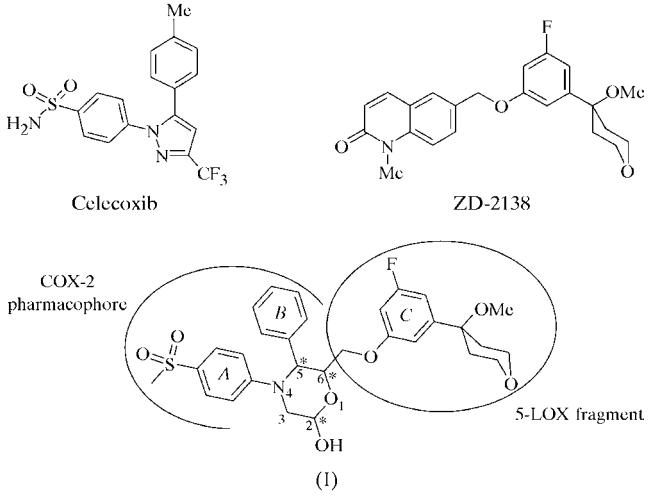
The title compound, $C_{30}H_{34}FNO_7S$, is a key intermediate in the design of dual 5-LOX (5-lipoxygenase)/COX-2 (cyclooxygenase-2) inhibitors. The compound crystallizes as a racemate. Linear hydrogen-bonded chains are aligned along the [201] direction, and stacked π–π interactions and C—H···O contacts stabilize the crystal structure.

Comment

A promising new strategy in cancer chemoprevention is being developed based on the design of inhibitors of the two major arachidonic acid metabolizing enzymes, namely type-2 cyclooxygenase (COX-2) and 5-lipoxygenase (5-LOX). These enzymes are indeed up-regulated in many tumours and some of their inhibitors exhibit marked proapoptotic and/or antiangiogenic activities (Zha *et al.*, 2004; Hoque *et al.*, 2005). For the development of new therapeutic treatments, therefore, it is of interest to design dual COX-2/5-LOX inhibitors (Charlier *et al.*, 2003; Romano *et al.*, 2003; Ye *et al.*, 2005; Li *et al.*, 2005). Taking into account the key pharmacophoric elements of celecoxib, a COX-2 selective inhibitor known for its highly potent antitumour activity (Kismet *et al.*, 2004), and those of ZD-2138, a referenced competitive 5-LOX inhibitor (Crawley *et al.*, 1992), a series of novel compounds has been explored (Barbey *et al.*, 2002; Pommery *et al.*, 2004; Charlier *et al.*, 2004). As part of this continuing project, the importance of the central pyrazole ring of celecoxib on antiproliferative activity has been investigated by replacement with diverse saturated rings. The present paper reports the structure of the title compound, (I), a key intermediate hydroxymorpholine.

Briefly, compound (I) was synthesized by reduction of the corresponding morpholinedione using a borane–dimethyl sulfide complex in tetrahydrofuran. The morpholinedione itself resulted from the cyclization of the aminoalcohol with oxalyl chloride. The NMR spectrum of (I) does not allow us to determine the position of the hydroxyl group on the morpholine. However, in order to delineate relevant structure–activity relationships, it is essential to determine the position of this hydrophilic moiety. It might very likely influence the binding of the compound to COX-2 as well as 5-LOX, through the formation of hydrogen bonds within the active sites. Thus, in order to elucidate the structure of (I), we carried out the present X-ray crystal structure analysis.



(I)

Compound (I) crystallizes in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit. Its molecular structure and conformation are shown in Fig. 1. The substituents of the morpholine ring are in an all-*cis* orientation. The morpholine and tetrahydropyran rings both adopt chair conformations. The 5-LOX fragment and the hydroxyl group are positioned equatorially, whereas the unsubstituted phenyl ring (ring *B*) lies in an axial position. Compound (I) crystallizes as a racemate: both 2*R*,5*S*,6*S* and 2*S*,5*R*,6*R* enantiomers are present in the unit cell.

In the crystal packing of (I), hydrogen bonds (weak and strong) and π–π interactions exist between symmetry-related molecules. In particular, a strong hydrogen bond occurs between hydroxyl atom H7 and sulfonyl atom O15, forming infinite chains running along the [201] direction (Fig. 2 and

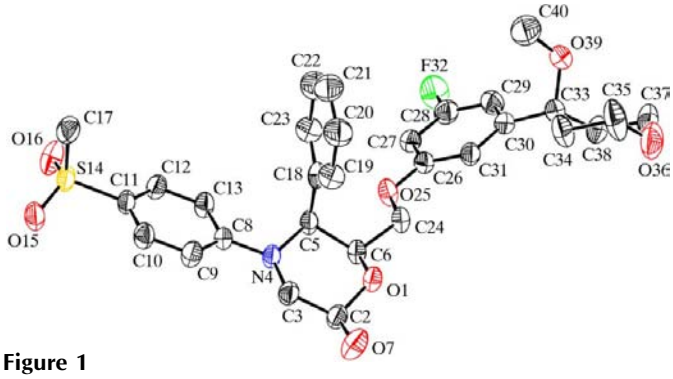


Figure 1
A view of compound (I) (2*R*,5*S*,6*S* enantiomer), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

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Table 1). Stacked π–π interactions between benzene rings *A* and *C* reinforce the cohesion between the chains (Fig. 2). The stacking geometry is such that rings *A* and *C* of one molecule are superimposed on rings *C* and *A* of two symmetry-related molecules at $(x, \frac{1}{2}-y, -\frac{1}{2}+z)$ and $(x, \frac{1}{2}-y, \frac{1}{2}+z)$, respectively. The distance between the centroids of rings *A* and *C* is 3.834 (2) Å and the dihedral angle between the planes is 18.9°. Several weak C—H···O and C—H···F contacts (Desiraju *et al.*, 1999) further stabilize the packing of (I) (Table 1), yielding a three-dimensional assembly. A weak intramolecular hydrogen bond, involving benzene atom H12 and sulfonyl atom O16, influences the conformation of the sulfonyl moiety with respect to the benzene ring (Table 1).

In order to assess the influence of stereochemistry on COX-2 binding, a preliminary docking study was performed. Both enantiomers were manually docked inside the COX-2 active site and compared with the conformation of SC-558, a tricyclic sulfonamide parent to celecoxib, cocrystallized with murine COX-2 (PDB code 6COX; Kurumbail *et al.*, 1996). The two vicinal aromatic rings (rings *A* and *B*) and the morpholine N atom were correctly aligned with their counterparts in SC-558. As illustrated in Fig. 3, the COX-2 pharmacophore in both enantiomers is able to bind the COX-2 active site in a manner similar to that of SC-558. This suggests that phenyl ring *B* could occupy the upper part of the channel, while sulfonylphenyl ring *A* could accommodate the hydrophilic side pocket in the COX-2 active site and thus form π–π interactions with Tyr355 and hydrogen bonds with polar residues such as Arg513 and His90. In both enantiomers, the 5-LOX pharmacophoric group could be oriented to point towards the upper part of the channel and could fit a small lipophilic cavity present in the N/E region of the active site and bordered by, among other residues, Phe209, Val228 and Leu534. In the 2*R*,5*S*,6*S* enantiomer, the hydroxyl moiety on the morpholine ring points in the direction of hydrophobic residues at the bottom of the cavity, such as Val349 and Leu359. In contrast, in the 2*S*,5*R*,6*R* enantiomer, the hydroxyl moiety is oriented towards Arg120 and could realise a strong hydrogen bond with this residue, stabilizing the complex.

This preliminary study suggests an influence of the stereochemistry on COX-2 affinity. The crystal structure reported here will be the starting point for further binding-mode studies into the COX-2 active site by means of automated docking algorithms.

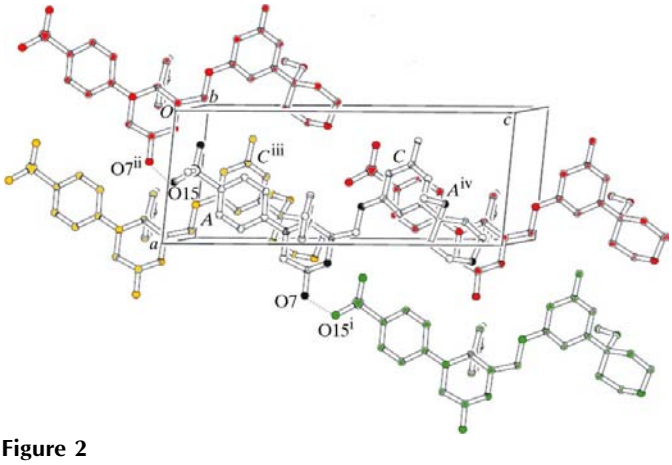

Figure 2
A packing diagram for (I), illustrating the π–π interactions between rings *A* and *C* and the strong hydrogen-bonding network (dashed grey lines) forming infinite chains along the [201] direction. [Symmetry codes: (i) $x+1, \frac{1}{2}-y, \frac{1}{2}+z$; (ii) $x-1, \frac{1}{2}-y, z-\frac{1}{2}$; (iii) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (vi) $x, \frac{1}{2}-y, z+\frac{1}{2}$.]

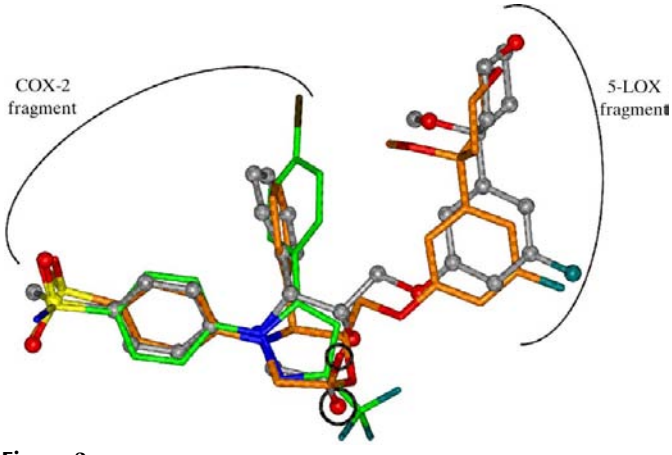

Figure 3
A superimposition of compound (I) (2*R*,5*S*,6*S* enantiomer drawn as sticks and 2*S*,5*R*,6*R* enantiomer as balls and sticks) on to the cocrystallized conformation of SC-558 (as sticks). H atoms have been omitted for clarity and the O atom of the hydroxyl group of both enantiomers has been circled.

Experimental

Crystals of (I) suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution in a mixture of diethyl ether and methanol (1:1 *v*/*v*).

Crystal data

$C_{30}H_{34}FNO_7S$
$M_r = 571.64$
Monoclinic, $P2_1/c$
$a = 7.151$ (3) Å
$b = 21.430$ (4) Å
$c = 18.274$ (3) Å
$\beta = 95.479$ (10)°
$V = 2787.6$ (14) Å^3
$Z = 4$
$D_x = 1.362$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 21 reflections
$\theta = 20.0$–29.9°
$\mu = 1.51$ mm^{-1}
$T = 293$ (2) K
Needle, colourless
0.40 × 0.08 × 0.06 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
$T_{min} = 0.584$, $T_{max} = 0.915$
6196 measured reflections
5730 independent reflections
4215 reflections with $I > 2\sigma(I)$
$R_{int} = 0.037$
$\theta_{max} = 75.2°$
$h = -8 \rightarrow 0$
$k = -26 \rightarrow 0$
$l = -22 \rightarrow 22$
3 standard reflections every 200 reflections
intensity decay: 4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.061$
$wR(F^2) = 0.176$
$S = 1.03$
5730 reflections
351 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0848P)^2 + 2.272P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 1.00$ e Å^{-3}
$\Delta\rho_{min} = -0.45$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O7—H7···O15^{i}	0.82	1.96	2.736 (3)	157
C5—H5···O7^{ii}	0.98	2.38	3.358 (4)	177
C12—H12···O16	0.93	2.55	2.922 (4)	105
C13—H13···O7^{ii}	0.93	2.37	3.283 (3)	168
C17—H17A···O39^{iii}	0.96	2.46	3.406 (3)	167
C17—H17C···O36^{iv}	0.96	2.44	3.326 (4)	152
C34—H34A···F32^{v}	0.97	2.52	3.470 (4)	166

Symmetry codes: (i) $x+1, -y+\frac{1}{2}, z+\frac{1}{2}$; (ii) $x-1, y, z$; (iii) $-x+1, -y, -z+1$; (iv) $x-1, y, z-1$; (v) $x+1, y, z$.

All H atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms. For the methyl and hydroxyl groups, the C—H and O—H distances were fixed at 0.96 and 0.82 Å, respectively, with U_{iso}(H) = 1.5U_{eq}(C,O). Aromatic and aliphatic C—H distances were fixed at 0.93 Å, with U_{iso}(H) = 1.2U_{eq}(C). It should be noted that hydroxyl atom H7 was initially located in a difference Fourier map and was then treated as a riding atom.

Data collection: *CAD-4 MACH3* (Nonius, 2000); cell refinement: *CAD-4 MACH3*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *enCIFer* (Allen *et al.*, 2004).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF1022). Services for accessing these data are described at the back of the journal.

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