

## Valdecoxib, a non-steroidal anti-inflammatory drug

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## Key indicators

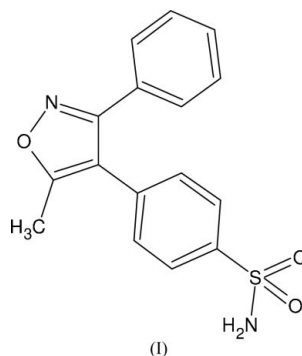
Single-crystal X-ray study  
 $T = 293\text{ K}$   
Mean  $\sigma(\text{C}-\text{C}) = 0.005\text{ \AA}$   
 $R$  factor = 0.055  
 $wR$  factor = 0.179  
Data-to-parameter ratio = 20.6

For details of how these key indicators were  
automatically derived from the article, see  
<http://journals.iucr.org/e>.

Valdecoxib [systematic name: 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide],  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ , a diaryl-substituted isoxazole, is a non-steroidal anti-inflammatory drug (NSAID) that is used for the treatment of rheumatoid arthritis, osteoarthritis and dysmenorrhea pain. The planar isoxazole ring is oriented at angles of  $22.2(1)$  and  $54.3(1)^\circ$  with respect to the phenyl and benzenesulfonamide groups, respectively.  $\text{N}-\text{H}\cdots\text{O}$  and  $\text{C}-\text{H}\cdots\text{O}$  hydrogen bonds and  $\text{N}-\text{H}\cdots\pi$ ,  $\text{C}-\text{H}\cdots\pi$  and  $\pi-\pi$  interactions stabilize the crystal packing.

## Comment

Valdecoxib, whose brand name is Bextra, is a nonsteroidal anti-inflammatory drug (NSAID) that is used for the treatment of osteoarthritis or rheumatoid arthritis and for the treatment of primary dysmenorrhea (Scheen & Malaise, 2004). Valdecoxib is a potent and specific inhibitor of cyclo-oxygenase-2 (COX-2), an isoform of *cyclo*-oxygenase which is the key enzyme catalysing the inversion of arachidonic acid into prostaglandins and thromboxane (Coats *et al.*, 2004). COX-2 is an inducible enzyme that is primarily found in inflammatory cells and tissues and so the inhibition of this enzyme by valdecoxib does not affect the normal cells (Gierse *et al.*, 1996). Valdecoxib is a diaryl-substituted isoxazole that exhibits analgesic and antipyretic properties in addition to anti-inflammatory properties in animal models. These COX-2-selective diarylheterocyclic inhibitors have been reported to be a reversible competitive inhibitor of COX-1 while demonstrating time-dependent irreversible inhibition of COX-2, which accounts for the potency and selectivity

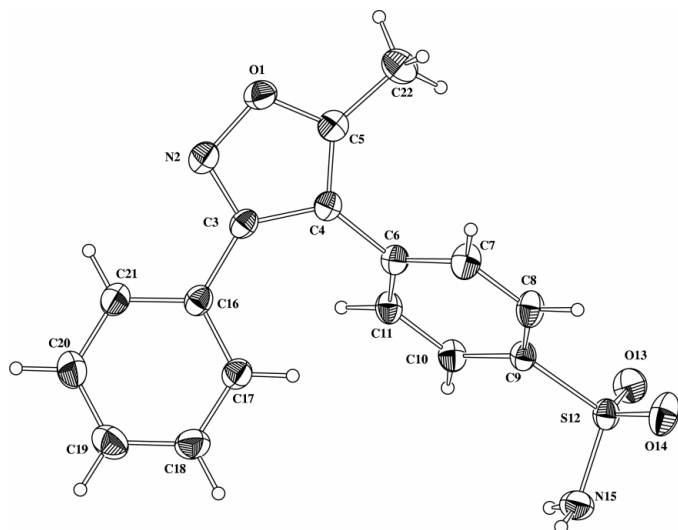


demonstrated by members of this structural class (Walkeri *et al.*, 2001). The phenylsulfonamide moiety of the diaryl-heterocycles associate within a side pocket present in the active site of COX-2, and this pocket is more accessible in COX-2 than in COX-1, which is the result of the substitution of valine for isoleucine at position 523 in COX-1 (Kurumbail *et al.*, 1996).

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**Figure 1**  
ORTEP-3 (Farrugia, 1997) plot of the title compound, showing 30% probability displacement ellipsoids and the atom-numbering scheme.

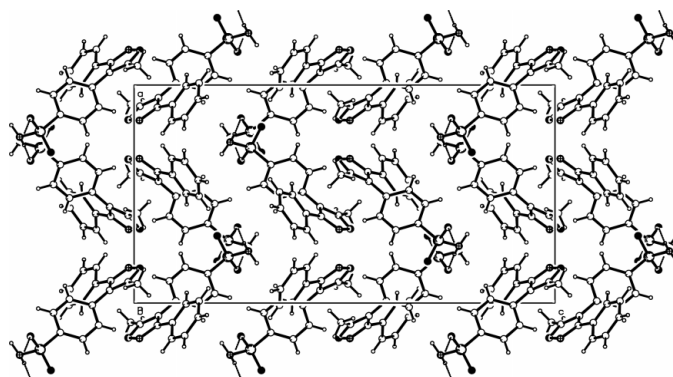
In the title molecule, (I) (Fig. 1), the isoxazole ring (*A*) is planar and forms dihedral angles of 54.3 (1) and 22.2 (1)° with the planes through the *B* (C6–C11) and *C* (C16–C21) benzene rings, respectively. The S atom in the sulphonamide group has  $sp^3$  hybridization. Atom N15 forms an N–H···O hydrogen bond with atom O13<sup>i</sup> [symmetry code: (i)  $\frac{3}{2} - x, \frac{1}{2} + y, z$ ], forming chains along the *b* axis (Fig. 2). An N–H··· $\pi$  interaction between atom N15 and ring *C* of the symmetry-related molecule at  $(2 - x, y - \frac{1}{2}, \frac{1}{2} - z)$  occurs, with an N···centroid (*Cg*) distance of 3.429 (4) Å. The isoxazole rings of the inversion-related molecules at  $(x, y, z)$  and  $(2 - x, 1 - y, 1 - z)$  interact *via* face-to-face  $\pi$ – $\pi$  interaction, the *Cg*···*Cg* distance being 3.606 (2) Å (Fig. 3). In addition to the above interactions, the molecular packing in the crystal structure is further stabilized by a number of weak C–H···O and C–H··· $\pi$  interactions (Table 1; *Cg*1, *Cg*2 and *Cg*3 denote the centroids of rings *A*, *B* and *C*, respectively).

## Experimental

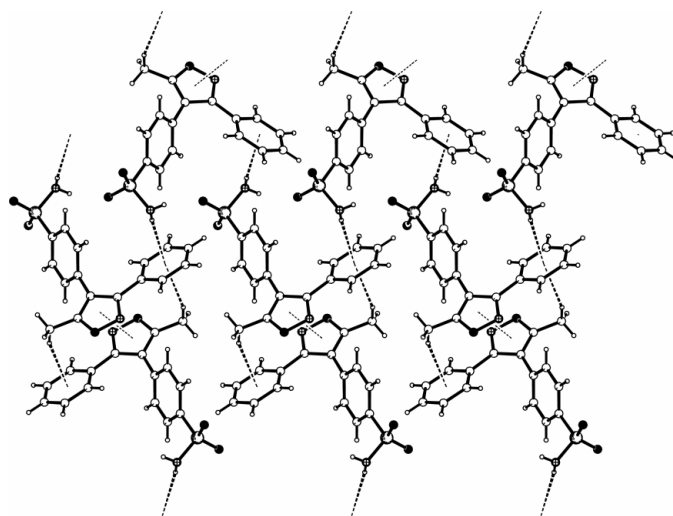
Deoxybenzoin (0.01 *M*) was treated with hydroxylamine hydrochloride (0.01 *M*) in the presence of sodium acetate to produce the corresponding oxime. When the oxime was deprotonated using *n*-butyllithium (2 equivalents) and condensed with ethyl acetate (25 ml) the corresponding isoxazoline was produced. Chlorosulfonic acid (0.01 *M*) treatment followed by addition of sulfonyl chloride (0.01 *M*) with aqueous ammonia to the isoxazoline yielded valdecoxib.

### Crystal data

$C_{16}H_{14}N_2O_3S$	$D_x = 1.412 \text{ Mg m}^{-3}$
$M_r = 314.35$	Mo $K\alpha$ radiation
Orthorhombic, <i>Pbca</i>	Cell parameters from 25 reflections
$a = 12.872$ (2) Å	$\theta = 8\text{--}15^\circ$
$b = 9.282$ (3) Å	$\mu = 0.23 \text{ mm}^{-1}$
$c = 24.761$ (7) Å	$T = 293$ (2) K
$V = 2958.4$ (14) Å <sup>3</sup>	Rectangular block, colourless
$Z = 8$	$0.35 \times 0.30 \times 0.20 \text{ mm}$



**Figure 2**  
Packing diagram of the molecules, viewed down the *b* axis. Dotted lines indicate the N–H···O hydrogen bond between atoms N15 and O13.



**Figure 3**  
A view, down the *a* axis, of the N–H··· $\pi$ , C–H··· $\pi$  and  $\pi$ ··· $\pi$  interactions (dashed lines).

### Data collection

Enraf–Nonius CAD-4 diffractometer	$h = 0 \rightarrow 18$
Non-profiled $\omega/2\theta$ scans	$k = 0 \rightarrow 13$
4295 measured reflections	$l = -34 \rightarrow 0$
4295 independent reflections	3 standard reflections every 120 min
2167 reflections with $I > 2\sigma(I)$	intensity decay: none
$\theta_{\max} = 30.0^\circ$	

### Refinement

Refinement on $F^2$	$w = 1/[\sigma^2(F_o^2) + (0.0714P)^2 + 1.6196P]$
$R[F^2 > 2\sigma(F^2)] = 0.055$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.179$	$(\Delta/\sigma)_{\max} = 0.002$
$S = 1.03$	$\Delta\rho_{\max} = 0.32 \text{ e Å}^{-3}$
4295 reflections	$\Delta\rho_{\min} = -0.35 \text{ e Å}^{-3}$
208 parameters	
H atoms treated by a mixture of independent and constrained refinement	

**Table 1**

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N15—H15A $\cdots$ O13 <sup>i</sup>	0.90 (1)	2.12 (3)	3.010 (4)	168 (2)
N15—H15B $\cdots$ Cg3 <sup>ii</sup>	0.90 (1)	2.59 (3)	3.429 (4)	156 (2)
C7—H7 $\cdots$ N2 <sup>iii</sup>	0.93	2.82	3.429 (5)	124
C8—H8 $\cdots$ O1 <sup>iv</sup>	0.93	2.82	3.529 (4)	134
C11—H11 $\cdots$ O13 <sup>v</sup>	0.93	2.65	3.383 (4)	136
C17—H17 $\cdots$ O14 <sup>i</sup>	0.93	2.61	3.273 (4)	128
C18—H18 $\cdots$ O14 <sup>i</sup>	0.93	2.84	3.387 (5)	119
C18—H18 $\cdots$ O13 <sup>vi</sup>	0.93	2.61	3.389 (5)	142
C19—H19 $\cdots$ Cg2 <sup>vi</sup>	0.93	3.10	3.708 (4)	125
C21—H21 $\cdots$ Cg1 <sup>vii</sup>	0.93	2.88	3.631 (4)	138
C22—H22A $\cdots$ Cg3 <sup>iii</sup>	0.96	2.74	3.637 (4)	157

Symmetry codes: (i)  $-x + \frac{3}{2}, y + \frac{1}{2}, z$ ; (ii)  $-x + 2, y - \frac{1}{2}, -z + \frac{1}{2}$ ; (iii)  $-x + 2, -y + 1, -z + 1$ ; (iv)  $x - \frac{1}{2}, -y + \frac{1}{2}, -z + 1$ ; (v)  $-x + 2, y + \frac{1}{2}, -z + \frac{1}{2}$ ; (vi)  $x, y + 1, z$ ; (vii)  $-x + \frac{5}{2}, y + \frac{1}{2}, z$ . Cg1, Cg2 and Cg3 denote the centroids of rings A, B and C, respectively.

Amine H atoms were located in a difference Fourier map and were refined isotropically, with an N—H distance restraint of 0.90 (1) Å. The remaining H atoms were placed in idealized positions (C—H<sub>aromatic</sub> = 0.93 Å and C—H<sub>methyl</sub> = 0.96 Å) and allowed to ride on their parent atoms, with  $U_{iso}(H) = 1.2U_{eq}(C)$  or  $1.5U_{eq}(C_{methyl})$ .

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97*

(Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003) and *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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