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Valdecoxib, a non-steroidal anti-inflammatory drug

S. M. Malathy Sony,[a] P. Charles,[a] M. N. Ponnuswamy[a]* and H. S. Yathirajan[b]

[a]Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai 600 025, India, and [b]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India

Correspondence e-mail: mnpsy2004@yahoo.com

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
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.

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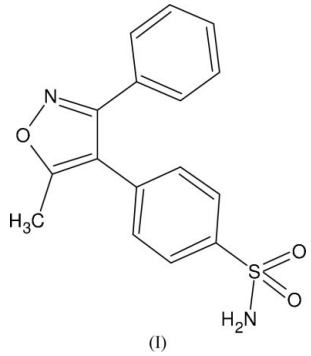
Valdecoxib [systematic name: 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide], $C_{16}H_{14}N_2O_3S$, a diaryl-substituted isoxazole, is a non-steroidal anti-inflammatory drug (NSAID) that is used for the treatment of rheumatoid arthritis, osteoarthritis and dysmenorrhea pain. The planar isoxazole ring is oriented at angles of 22.2 (1) and 54.3 (1)° with respect to the phenyl and benzenesulfonamide groups, respectively. N—H···O and C—H···O hydrogen bonds and N—H···π, C—H···π and π–π 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



(I)

demonstrated by members of this structural class (Walkeri *et al.*, 2001). The phenylsulphonamide 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).

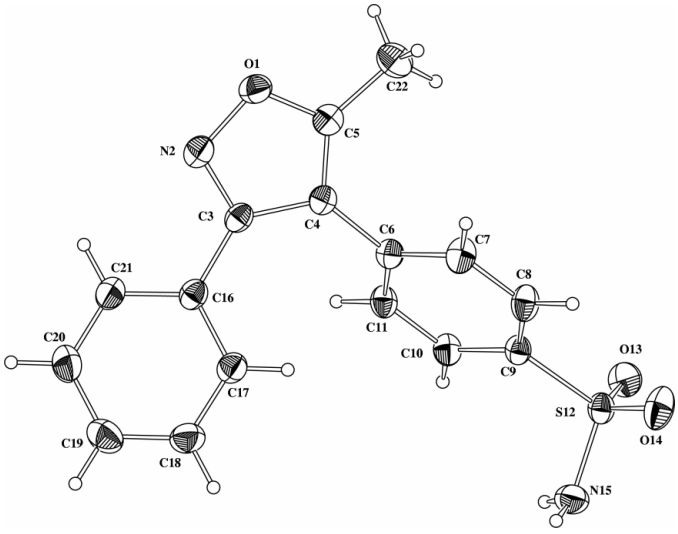


Figure 1
ORTEP-3 (Farrugia, 1997) plot of the title compound, showing 30% probability displacement ellipsoids and the atom-numbering scheme.

In the title molecule, (I) (Fig. 1), the isoxzaole 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^{i} [symmetry code: (i) $\frac{3}{2} - x$, $\frac{1}{2} + y$, z], forming chains along the *b* axis (Fig. 2). An N—H···π 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 π–π 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···π interactions (Table 1; *Cg*1, *Cg*2 and *Cg*3 denote the centroids of rings *A*, *B* and *C*, respectively).

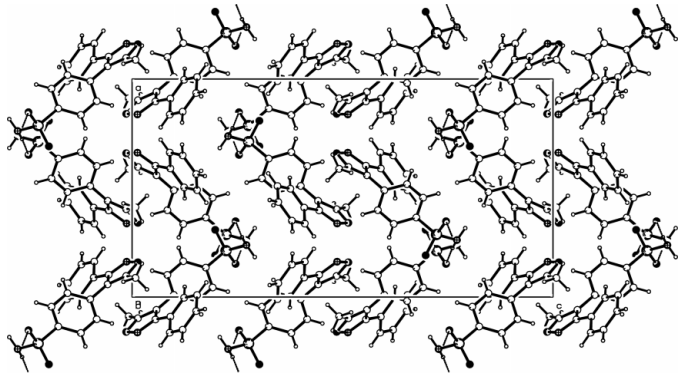


Figure 2
Packing diagram of the molecules, viewed down the *b* axis. Dotted lines indicate the N—H···O hydrogen bond between atoms N15 and O13.

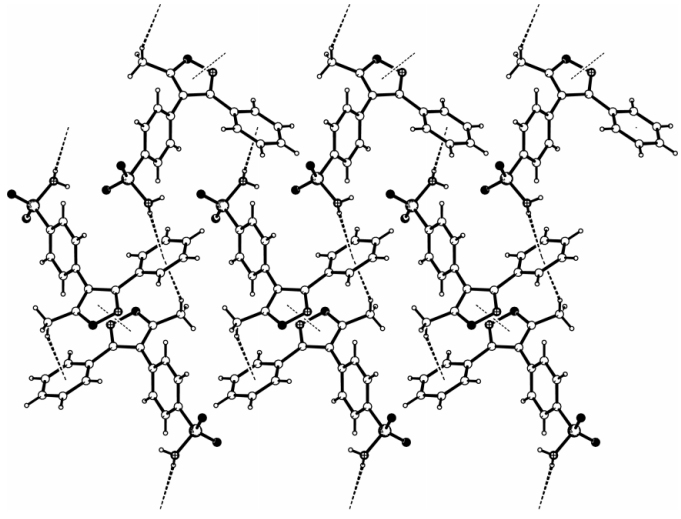


Figure 3
A view, down the *a* axis, of the N—H···π, C—H···π and π···π interactions (dashed lines).

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

$C_{16}H_{14}N_2O_3S$
M_r = 314.35
Orthorhombic, *Pbca*
a = 12.872 (2) Å
b = 9.282 (3) Å
c = 24.761 (7) Å
V = 2958.4 (14) Å^3
Z = 8
D_x = 1.412 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 8–15°
μ = 0.23 mm^{-1}
T = 293 (2) K
Rectangular block, colourless
0.35 × 0.30 × 0.20 mm

Data collection

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

Refinement

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

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

D—H···A	D—H	H···A	D···A	D—H···A
N15—H15A···O13^{i}	0.90 (1)	2.12 (3)	3.010 (4)	168 (2)
N15—H15B···$Cg3^{ii}$	0.90 (1)	2.59 (3)	3.429 (4)	156 (2)
C7—H7···N2^{iii}	0.93	2.82	3.429 (5)	124
C8—H8···O1^{iv}	0.93	2.82	3.529 (4)	134
C11—H11···O13^{v}	0.93	2.65	3.383 (4)	136
C17—H17···O14^{i}	0.93	2.61	3.273 (4)	128
C18—H18···O14^{i}	0.93	2.84	3.387 (5)	119
C18—H18···O13^{vi}	0.93	2.61	3.389 (5)	142
C19—H19···$Cg2^{vi}$	0.93	3.10	3.708 (4)	125
C21—H21···$Cg1^{vii}$	0.93	2.88	3.631 (4)	138
C22—H22A···$Cg3^{iii}$	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—$H_{aromatic}$ = 0.93 Å and C—H_{methyl} = 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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