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Ezetimibe monohydrate

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Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.004 Å
R factor = 0.041
wR factor = 0.090
Data-to-parameter ratio = 7.5

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

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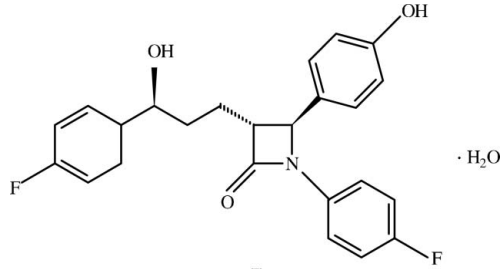
Ezetimibe monohydrate or 1-(4-fluorophenyl)-3(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-azetidin-2-one monohydrate, $C_{24}H_{21}F_2NO_3\cdot H_2O$, belongs to a class of agents that inhibit cholesterol absorption in the intestine. The solvent water molecule present in the structure is involved in several hydrogen bonds.

Comment

Ezetimibe (SCH 58235) is a drug discovered by Schering–Plough, USA (Rosenblum *et al.*, 1998), used for the treatment of elevated blood cholesterol levels. Ezetimibe lowers blood cholesterol by blocking the absorption of cholesterol, including dietary cholesterol, from the intestine (Van Heek *et al.*, 2000). It has a favourable pharmacokinetic profile, which allows it to be administered daily and to be given in conjunction with statins. Moreover, coadministration of ezetimibe with a statin (simvastatin, atorvastatin, lovistatin or pravastatin) has been shown to be more effective than statin monotherapy in lowering LDL cholesterol and improving other lipid parameters (Davidson, 2003). Ezetimibe was approved by the US Food and Drug Administration (FDA) in October 2002. In continuation of our ongoing programmes on the structural elucidation of drug molecules and to gain further insights into structure–activity relationships, the crystal structure determination of the title compound, (I), was undertaken and the results are presented here.



(I)

In all essential details, the geometry of (I), in terms of interatomic distances and angles (Fig. 1 and Table 1), is in good agreement with that of similar structures (Mousser *et al.*, 1996; Kabak *et al.*, 1999). The bonds between the sp^3 hybridized C atoms have the following conformations. The azetidinone ring is antiperiplanar to C12 [C9—C10—C11—C12 −167.1 (3)°] and the fluorophenyl ring is antiperiplanar to C10 [C13—C12—C11—C10 167.8 (2)°], whereas the hydroxyl group O3 is anticlinal to C10 [O3—C12—C11—C10 −68.9 (3)°].

Atom N1 is 0.101 (2) Å above the plane of its three attached atoms. The sum of the bond angles about N1 is

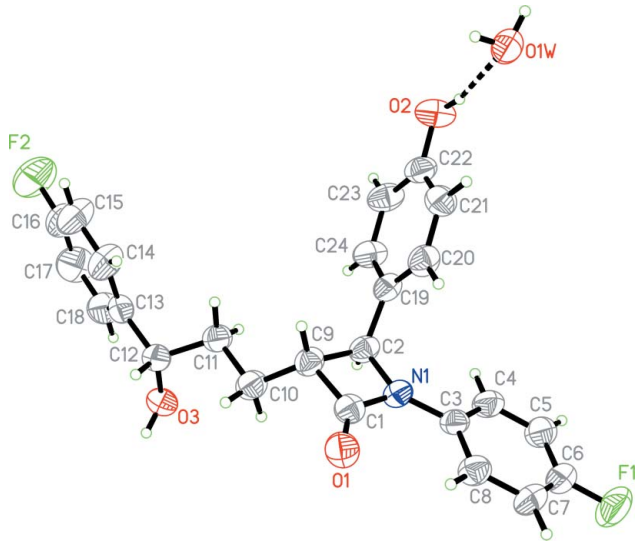


Figure 1
A view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The hydrogen bond is shown as a dashed line.

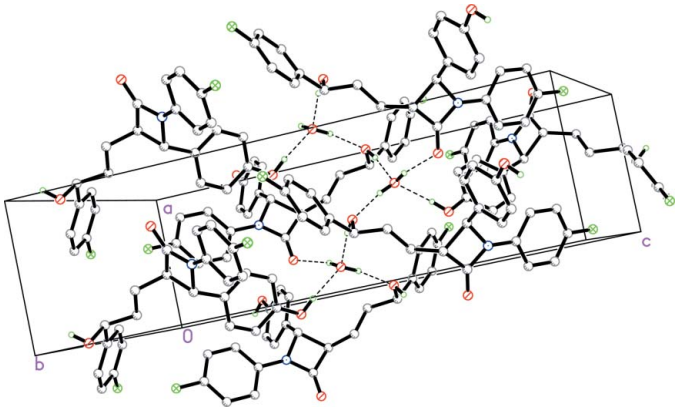


Figure 2
Part of the unit-cell packing of (I), showing the hydrogen-bond networks (dashed lines) involving the water molecules as bridging units. For the sake of clarity, H atoms bonded to C atoms have been omitted.

358.4°. The azetidinone ring is coplanar with the fluorophenyl ring at N1 [dihedral angle 9.3 (1)°], while it is inclined with respect to the other fluorophenyl ring [69.6 (1)°] and the hydroxyphenyl ring [75.1 (1)°].

The two fluorophenyl rings are inclined to one another, with a dihedral angle of 62.2 (1)°. Interestingly, the hydroxyphenyl ring is nearly perpendicular to the fluorophenyl ring at N1 [dihedral angle 84.2 (1)°], while the corresponding angle with the other fluorophenyl ring is 42.7 (1)°.

In the structure of (I), the water molecule acts as both donor and acceptor in strong hydrogen bonds; it links azetidinone atom O1 with hydroxyl atoms O3 and O2 of neighbouring molecules (Fig. 2). Thus, a chain of hydrogen bonds is formed in the crystal packing, involving water molecules as the bridging unit. In addition, C—H···O, C—H···F and C—H···π interactions are also seen in the crystal packing.

It is noteworthy that the two F atoms occupying the two terminal positions of the ezetimibe molecule are separated by a distance of 15.687 (3) Å. Furthermore, the hydroxyl group O2 is almost equidistant from the two F atoms [F1···O2 9.740 (3) Å and F2···O2 9.836 (4) Å]. Considering the molecular structure from the point of view of a structure–activity model, it may be speculated that the binding site accommodates a 'T' shape, with the two arm ends occupied by the two fluorophenyl rings and the tail end by the hydroxyphenyl ring, while the azetidinone ring is located at the junction (Fig. 3).

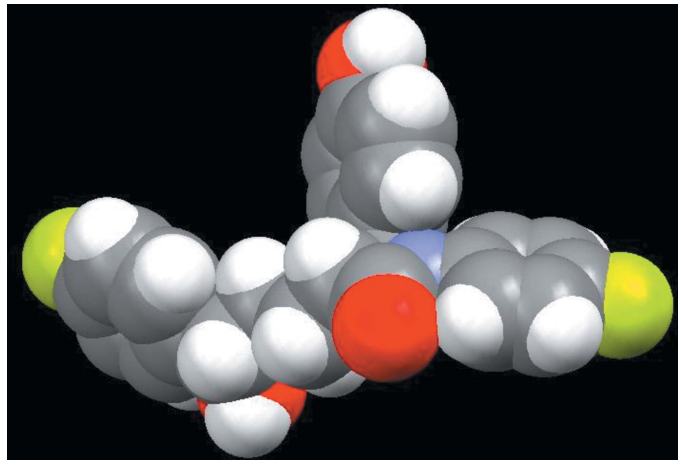


Figure 3
A CPK model of (I).

Experimental

To obtain crystals suitable for X-ray studies, ezetimibe (procured from the Pharmacology Department, IICT, Hyderabad) was dissolved in a mixture of methanol and water (90:10) and the solution was allowed to evaporate slowly.

Crystal data

$C_{24}H_{21}F_2NO_3\cdot H_2O$
M_r = 427.43
Orthorhombic, $P2_12_12_1$
a = 6.2396 (4) Å
b = 15.4657 (10) Å
c = 22.3320 (14) Å
V = 2155.0 (2) Å^3
Z = 4
D_x = 1.317 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4486 reflections
θ = 2.3–21.9°
μ = 0.10 mm^{-1}
T = 273 (2) K
Block, colourless
0.25 × 0.11 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
15753 measured reflections
2215 independent reflections
2036 reflections with $I > 2\sigma(I)$
R_{int} = 0.032
θ_{max} = 25.0°
$h = -7 \rightarrow 7$
$k = -18 \rightarrow 18$
$l = -26 \rightarrow 26$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.090
S = 1.17
2215 reflections
296 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0342P)^2 + 0.4556P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

F1—C6	1.358 (3)	C2—C9	1.562 (4)
F2—C16	1.359 (4)	C9—C10	1.516 (4)
O1—C1	1.220 (3)	C10—C11	1.519 (4)
O2—C22	1.358 (3)	C11—C12	1.516 (4)
C1—C9	1.504 (4)	C12—C13	1.509 (4)
C1—N1—C3	131.9 (2)	C1—C9—C2	85.85 (19)
C1—N1—C2	94.8 (2)	O3—C12—C11	108.7 (2)
C3—N1—C2	131.7 (2)	C13—C12—C11	112.3 (2)
N1—C2—C19	117.4 (2)	O2—C22—C23	117.4 (3)
C19—C2—C9	117.3 (2)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2O···O1*W*	0.87 (4)	1.95 (4)	2.801 (4)	166 (3)
O3—H30···O1*W*^{i}	0.84 (4)	1.88 (4)	2.708 (3)	169 (3)
O1*W*—H1*W*···O1^{ii}	0.82 (3)	1.91 (3)	2.698 (3)	161 (3)
O1*W*—H2*W*···O3^{iii}	0.89 (5)	1.85 (5)	2.737 (3)	171 (5)
C2—H2···O1^{iv}	0.98	2.60	3.521 (3)	157
C5—H5···F2^{v}	0.93	2.51	3.123 (4)	124
C23—H23···*Cg*2^{vi}	0.93	2.95	3.613	129

Symmetry codes: (i) $-x+\frac{1}{2}, -y+1, z-\frac{1}{2}$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$; (iv) $x-1, y, z$; (v) $-x-\frac{1}{2}, -y+1, z+\frac{1}{2}$; (vi) $x+\frac{5}{2}, -y-\frac{1}{2}, -z$. *Cg*2 is the centroid of the C3—C8 ring.

The H atoms of the water molecule and the hydroxyl O atoms were located in a difference density map and refined freely. All other H atoms were positioned geometrically and treated as riding, with C—H distances in the range 0.93–0.98 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration of the procured material was known in advance.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL*/*PC* (Sheldrick, 1990); software used to prepare material for publication: *SHELXL97*.

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