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Ezetimibe anhydrate, determined from laboratory powder diffraction data

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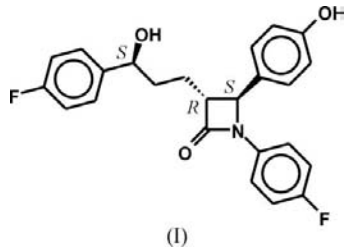
Ezetimibe {systematic name: (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one}, $C_{24}H_{21}F_2NO_3$, is used to lower cholesterol levels by inhibiting cholesterol resorption in the human intestine. The crystal structure of ezetimibe anhydrate was solved from laboratory powder diffraction data by means of real-space methods using the program *DASH* [David *et al.* (2006). *J. Appl. Cryst.* **39**, 910–915]. Subsequent Rietveld refinement with *TOPAS Academic* [Coelho (2007). *TOPAS Academic User Manual*. Version 4.1. Coelho Software, Brisbane, Australia] led to a final R_{wp} value of 8.19% at 1.75 Å resolution. The compound crystallizes in the space group $P2_12_12_1$ with one molecule in the asymmetric unit. The molecules are closely packed and two intermolecular hydrogen bonds form an extended hydrogen-bond architecture.

Comment

Ezetimibe {systematic name: (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-azetidin-2-one}, (I) (Fig. 1), is a drug that is used to lower intestinal resorption of cholesterols and related phytosterols by inhibiting the brush border of the microvilli in the small intestine. The compound belongs to the class of azetidin-2-ones and was first described in 1995 (Rosenblum *et al.*, 1995, 1998) as an active pharmaceutical ingredient. Ezetimibe is traded under the brand name Ezetrol (MSD Sharp & Dohme). However, as ezetimibe is less effective than, for example, statins, it is mainly marketed as a fixed-combination drug together with statins, *e.g.* Inegy (MSD Sharp & Dohme), leading to potent drugs that lower LDL (lowest density lipoprotein) cholesterol levels in blood, improve other lipid parameters and reduce the risk of, for example, atherosclerosis. For ezetimibe, a monohydrate, an anhydrate and an amorphous form have been described (Parthasaradhi *et al.*, 2005; Stimac *et al.*, 2008).

The crystal structure of the monohydrate of (I) is known from single-crystal structure analysis [Cambridge Structural Database (CSD; Allen, 2002) refcode QATNEF; Ravikumar & Sridhar, 2005]. In order to search for other polymorphic forms, a polymorph screening of (I) was performed using different solvents and solvent mixtures. Since the solubility of (I) is quite high, (I) was recrystallized in order to obtain either suitable single crystals or at least a powder of improved crystallinity of other phases. Different crystallization methods were used: (i) recrystallization from solvents and solvent mixtures; (ii) diffusion by overlaying a solution of compound (I) with an anti-solvent; (iii) diffusion of an anti-solvent *via* the gas phase into a solution of the investigated compound. Various solvents were used, *e.g. N*-methylpyrrolidone, dimethyl sulfoxide, alcohols, ethers and esters, acetone, chloroform, water, acids and bases. The solvents were not dried before use. Technical grade ezetimibe, which consisted of a mixture of the anhydrous and monohydrate forms in a 12 (1):88 (1) ratio (determined from quantitative Rietveld analysis), was used as starting material. Single crystals could be obtained only for the monohydrate form.



(I)

Thermal analysis, *i.e.* differential thermal analysis (DTA) and thermal gravimetry (TG), experiments were carried out to determine the temperature at which the monohydrate transforms to the anhydrate. The DTA–TG measurements were performed on a TGA 92 (SETARAM) device. About 10–15 mg of the samples were loaded into corundum crucibles and heated from room temperature to 473 K at a rate of 3 K min^{-1} under a nitrogen atmosphere. The DTA–TG

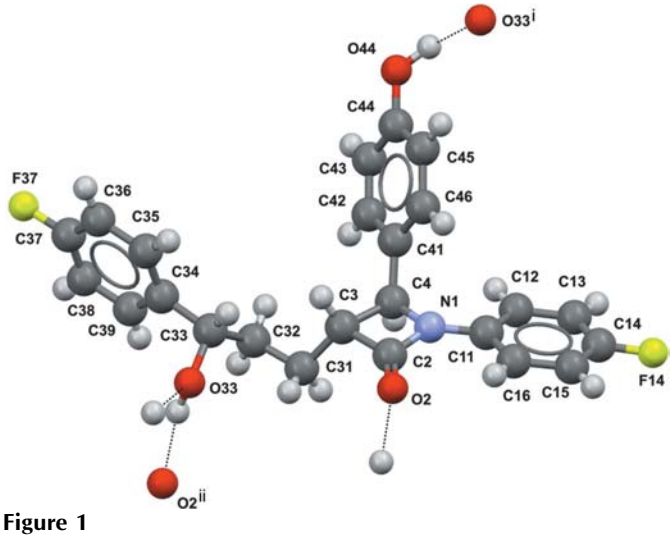


Figure 1
The molecular structure of compound (I). Hydrogen bonds are shown as dotted lines. [Symmetry codes: (i) $-x+\frac{3}{2}, -y+2, z-\frac{1}{2}$; (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+2$.]

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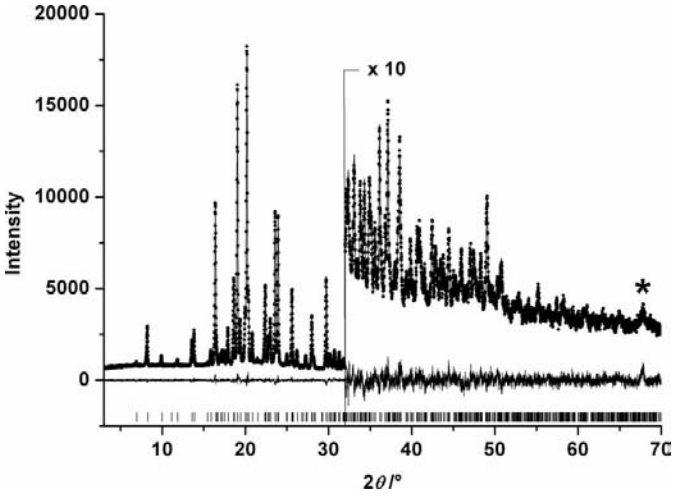

Figure 2
Final Rietveld plot: observed (points), calculated (line) and difference [$(y_{obs} - y_{calc})$] profiles for the Rietveld refinement of the title compound. Change of scale at 32° in 2θ is a factor of 10 and the increment for the whole pattern in 2θ is 0.01°. Tick marks are shown as vertical lines. The star indicates an instrumental artefact.

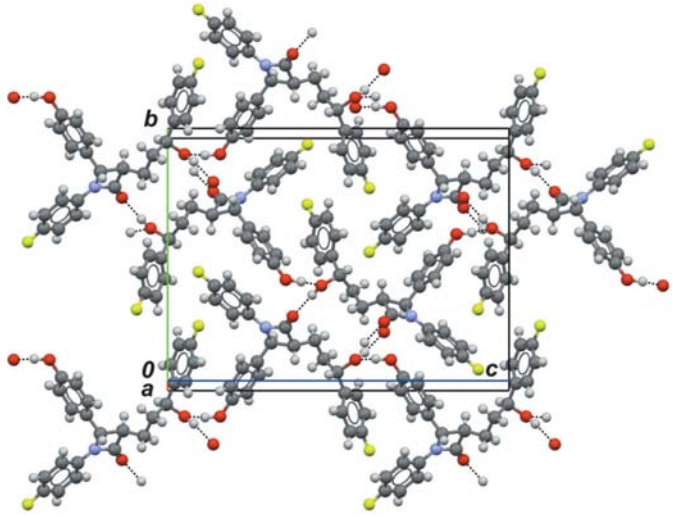

Figure 3
The crystal packing of (I), viewed in the [100] direction. Hydrogen bonds are shown as dashed lines.

analysis shows that the monohydrate releases water continuously between 311 and 353 K.

The anhydrous form was obtained by drying the raw material of (I) at 393 K (see *Experimental*). The resulting white powder was of good crystallinity and corresponded to the known anhydrate phase as ascertained by X-ray powder diffraction (XRPD). Subsequently, the crystal structure of (I) was determined from its XRPD pattern.

For the determination of the crystal structure of (I) *DASH* software (David *et al.*, 2006) was used. Initially, the XRPD pattern of (I) was truncated to a real-space resolution of 3.0765 Å, which corresponds to the range 3.5–29° in 2θ. The background was subtracted with a Bayesian high-pass filter (David & Sivia, 2001). The indexing was performed with the program *DICVOL91* (Boultif & Louër, 1991), as implemented in *DASH* (David *et al.*, 2006). Accurate peak positions for the indexing were obtained by fitting about 20 manually selected peaks with an asymmetry-corrected Voigt function. The indexing yielded an orthorhombic cell. The cell volume was verified by calculating the expected cell volume from volume increments (Hofmann, 2002). The expected cell volume of 2031 Å^3 is similar to the value found in the indexing (2013.63 Å^3) and suggested four molecules per unit cell ($Z = 4$).

Pawley refinement was used to extract integrated intensities and their correlations. The Pawley fit converged with a Pawley χ^2 value of 3.02. From the Pawley refinement, the space group was determined to be $P2_12_12_1$ using Bayesian statistical analysis (Markvardsen *et al.*, 2001).

The crystal structure was solved from the powder pattern in direct space using simulated annealing (SA). The starting molecular geometry was taken from the single-crystal structure of the monohydrate by excluding the water molecule. The background subtraction, peak fitting, Pawley refinement, space-group determination and SA algorithms were used as implemented in *DASH*; only the number of SA runs was increased from 10 to 50 to get better statistics regarding reproducibility. The molecule of (I) has six flexible torsions which were left free during the SA (the orientation of the OH groups was not refined during structure solution). Together with the three rotational and three translational degrees of freedom, this results in a total number of 12 degrees of freedom. In 50 SA runs, the crystal structure was found 16 times. The obtained lowest profile χ^2 of 6.91 is less than twice the Pawley χ^2 value; this is a strong indication that the crystal structure is the correct one. The good reproducibility is an indication, too, that the global minimum (within this model) has been found. The 16 structure solutions with the lowest profile χ^2 are superimposable, and hence the structures are the same.

For the Rietveld refinement, the program *TOPAS Academic* (Coelho, 2007) was used. The refinement converged quickly and smoothly and yielded acceptable *R* values (R_{exp} = 3.356%, R'_{exp} = 7.052%, R_p = 2.964%, R'_p = 7.927%, R_{wp} = 3.946%, R'_{wp} = 8.19%; the values marked with a prime are background subtracted, all others are artificially low and should not be used to indicate the correctness of the crystal structure). The H atoms of the OH groups were in senseless positions and so these H atoms were set to the correct positions according to assumed hydrogen bonds (*Mercury*; Macrae *et al.*, 2008) and the structure was rerefined. The H-atom coordinates did not change significantly after this refinement. Fig. 2 displays the final fit.

A *Mogul* (Bruno *et al.*, 2004) geometry check of the crystal structure of (I) shows that all bond lengths and angles are within the expected range of the corresponding values found in the CSD (Allen, 2002).

The molecules of (I) show a central four-membered ring (azetidinone) with three different fragments: the 4-fluorophenyl group is linked to N1, the 4-fluorophenyl-3-hydroxypropyl group to C3 and the 4-hydroxyphenyl group to C4. The N1 atom is 0.164 (2) Å above the plane formed by atoms C2,

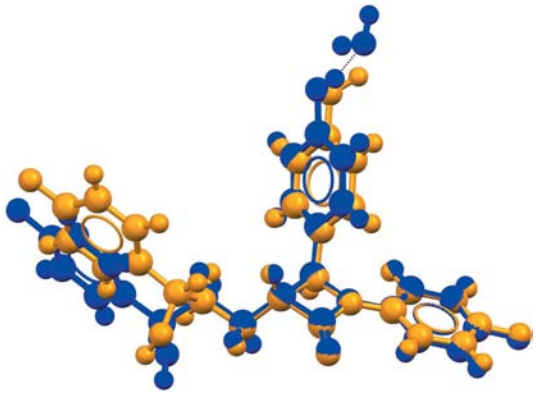

Figure 4
Structural overlay of ezetimibe anhydrate, (I) (light shading; yellow in the electronic version of the paper), and ezetimibe monohydrate (blue).

C3 and C4 of the azetidinone ring. There is further discussion on azetidinone rings in earlier published work (Mousser *et al.*, 1996; Kabak *et al.*, 1999; Ravikumar & Sridhar, 2005). The 4-fluorophenyl fragment linked to atom N1 is almost coplanar to the azetidinone ring [inclination only 3.8 (6)°]. The angle between the plane of the 4-fluorophenyl group and the hydroxyphenyl group is 67.89 (2)°. Since the two F atoms are in *para* positions, their intramolecular distance is 15.744 (6) Å, but the shortest intermolecular F···F distance is only 4.014 (6) Å. The intramolecular distance between O44 and F14 is 9.339 (6) Å, and the distance between O44 and F37 is 9.630 (5) Å, showing that these distances are almost equal.

The molecules are densely packed with reasonable van der Waals interactions. The crystal structure is stabilized by a hydrogen-bond architecture constructed from two symmetry-independent intermolecular hydrogen bonds (Fig. 3), one involves the two distinct hydroxy groups and the second one is between a hydroxy group and the carbonyl group of the azetidinone (Table 1). Hence, there is an O44—H44···O33^{i} hydrogen bond [symmetry code: (i) $-x+\frac{3}{2}, -y+2, z-\frac{1}{2}$] between the 4-hydroxyphenyl group and the 3-hydroxypropyl group of an adjacent molecule, which links the molecules into extended zigzag chains along the [001] direction that can be described by a graph-set motif $C(12)$ (Etter, 1990; Bernstein *et al.*, 1995). In addition, there is an O33—H33*B*···O2^{ii} hydrogen bond [symmetry code: (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+2$] between the 3-hydroxypropyl group and the carbonyl group of a different adjacent molecule, which links the molecules into extended zigzag chains along the [100] direction that can be described by the graph-set motif $C(8)$. The combination of these interactions links the molecules into a three-dimensional framework, as shown in Fig. 3.

Comparing the crystal structures of anhydrate (I) and the monohydrate shows that the major difference is the conformation of the 3-(4-fluorophenyl)-3-hydroxypropyl fragment (see Fig. 4). The torsion angle C3—C31—C32—C33 of −86.6 (4)° in (I) is considerably larger than the corresponding angle in the monohydrate [−167.1 (3)°]. Also the torsion angle between the propyl group and the phenyl ring (C32—C33—C34—C35) differs considerably [−128.2 (4)° in (I) and −63.3 (4)° in the monohydrate]. The other torsion angles differ much less (Table 2). Structural solution trials on the anhydrate by SA with a fixed C3—C31—C32—C33 torsion angle of 180° yielded unfavourable profile χ^2 values, indicating that this conformation is not the correct one.

In summary, the anhydrate structure reported here is quite similar to the monohydrate structure, but shows a different conformation of the propyl group and a different hydrogen-bond architecture caused by fewer donor and acceptor atoms.

Experimental

The powder used for the structure determination of (I) was obtained by drying the technical grade powder of (I) (which consisted of a mixture of the monohydrate and the anhydrate) at 393 K for 1 d in an oven.

Crystal data

$C_{24}H_{21}F_2NO_3$
M_r = 409.42
Orthorhombic, $P2_12_12_1$
a = 5.94606 (19) Å
b = 15.8898 (5) Å
c = 21.3765 (6) Å
V = 2019.69 (11) Å^3
Z = 4
Cu $K\alpha_1$ radiation, λ = 1.5406 Å
μ = 0.84 mm^{-1}
T = 293 K
cylinder, 10 × 0.7 mm

Data collection

Stoe Stadi-P diffractometer with linear position-sensitive detector
Specimen mounting: glass capillary
Data collection mode: transmission
Scan method: step
$2\theta_{min}$ = 3°, $2\theta_{max}$ = 69.99°, $2\theta_{step}$ = 0.01°

Refinement

R_p = 0.079
R_{wp} = 0.082
R_{exp} = 0.071
R_{Bragg} = 1.094
χ^2 = 1.161
6700 data points
196 parameters
208 restraints
All H-atom parameters refined

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

D—H···A	D—H	H···A	D···A	D—H···A
O44—H44···O33^{i}	0.99 (1)	1.99 (3)	2.842 (6)	143 (2)
O33—H33*B*···O2^{ii}	0.97 (1)	1.82 (1)	2.715 (7)	152 (1)

Symmetry codes: (i) $-x+\frac{3}{2}, -y+2, z-\frac{1}{2}$; (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+2$.

Table 2
Comparison of selected torsion angles (°) of (I) and (I)·H_2O.

	(I)	(I)·H_2O
C3—C31—C32—C33	−86.6 (4)	−167.1 (3)
C34—C33—C32—C31	172.2 (3)	167.8 (2)
C35—C34—C33—C32	−128.2 (4)	−63.3 (4)
O33—C33—C32—C31	−65.2 (4)	−68.9 (3)
N1—C4—C41—C46	−11.8 (5)	−23.9 (4)
C31—C3—C4—C41	123.6 (4)	120.4 (3)
C4—N1—C11—C12	3.8 (6)	6.4 (4)

The whole-powder pattern out to 1.75 Å resolution was used for the Rietveld refinement. Suitable restraints were taken from *Mogul* (Bruno *et al.*, 2004) for bond lengths, bond angles and planarity. Atomic coordinates and lattice parameters were refined together

with anisotropic peak broadening, the zero-point error, a scale parameter and the background. An overall isotropic displacement parameter for non-H and H atoms, and another for the F atoms were employed in the model and also refined. Compound (I) showed no significant preferred orientation, and hence a preferred-orientation correction was not necessary.

Data collection: *WINX*^{POW} (Stoe & Cie, 2004); cell refinement: *TOPAS Academic* (Coelho, 2007); data reduction: *DASH* (David *et al.*, 2006); program(s) used to solve structure: *DASH*; program(s) used to refine structure: *TOPAS Academic*; molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2010).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GT3018). Services for accessing these data are described at the back of the journal.

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