

Solvates of zafirlukast

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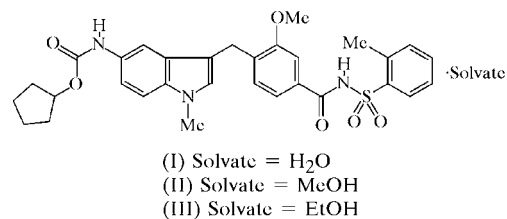
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The crystal structures of three solvates of zafirlukast [systematic name: cyclopentyl *N*-{1-methyl-3-[2-methyl-4-(*o*-tolylsulfonylamino)carbonyl]benzyl]-1*H*-indol-5-yl}carbamate], *viz.* the monohydrate, C₃₁H₃₃N₃O₆S·H₂O, (I), the methanol solvate, C₃₁H₃₃N₃O₆S·CH₃OH, (II), and the ethanol solvate, C₃₁H₃₃N₃O₆S·C₂H₅OH, (III), have been determined by single-crystal X-ray diffraction analysis. All three compounds crystallize in the monoclinic crystal system. Zafirlukast adopts a similar Z-shaped conformation in all three solvates. The methanol and ethanol solvates are isostructural. The packing of the zafirlukast molecules in all three crystal structures is similar and is expressed by hydrogen-bonded molecules that are related by translation, along (101) in (I) and along the *b* axis in (II) and (III). The methanol and ethanol solvent molecules are hydrogen bonded to two molecules of zafirlukast. The water molecule, on the other hand, acts as a connector *via* hydrogen bonds between three molecules of zafirlukast. The solvent molecules are not released at temperatures below the melting points of the solvates.

Comment

Zafirlukast is an effective and safe prophylactic treatment for asthma, its effect remaining evident up to 12 h after drug take-up. Certain different phases and derivatives of zafirlukast have been found to possess useful medical and biological activities (Adkins & Brogden, 1998). Zafirlukast can be prepared according to methods described by Matassa *et al.* (1990). The patent (Timko *et al.*, 1992) discloses three forms of zafirlukast, differing with respect to their physical properties, stability, spectroscopic data and method of preparation; these are designated forms *A*, *B* and *X*. Form *X* is a stable crystalline form of zafirlukast, but has relatively poor bioavailability. Form *B* is an unstable crystalline form of zafirlukast hydrate. The method disclosed in the patent for the preparation of form *B* is by precipitation with water from acetone. Because of

its unstable nature, this hydrate is difficult to prepare and maintain in a form having a constant and reproducible water content, and is particularly difficult to handle during formulation. Form *A* is an amorphous form of zafirlukast, pre-



pared by dehydration of form *B* in a vacuum oven for up to 24 h at 393 K; typically, the pressure is about 20 mbar (1 bar = 100 000 Pa). Form *A* has relatively good bioavailability. However, under conditions of high relative humidity and elevated temperatures, conversion of form *A* into form *B* has been found to occur. Accordingly, it may, in certain circumstances, be desirable to store pharmaceutical formulations of form *A* in the presence of a suitable desiccant, such as silica gel. It may also be desirable to keep them in an airtight container, such as a blister pack.

The crystal structure of zafirlukast itself is not known. We have crystallized three different solvates of zafirlukast, namely the monohydrate, (I) (US Patent 5 993 859; Timko *et al.* 1992), the methanol solvate, (II), and the ethanol solvate, (III), in order to examine the possibility of introducing new drugs and as useful intermediate products for fabrication processes. The three solvates crystallize in the monoclinic crystal system, with (I) in space group *P*2₁/*n*, and (II) and (III) in space group *C**c*. The molecular structure of zafirlukast in the monohydrate form, with the atomic labelling, is shown in Fig. 1.

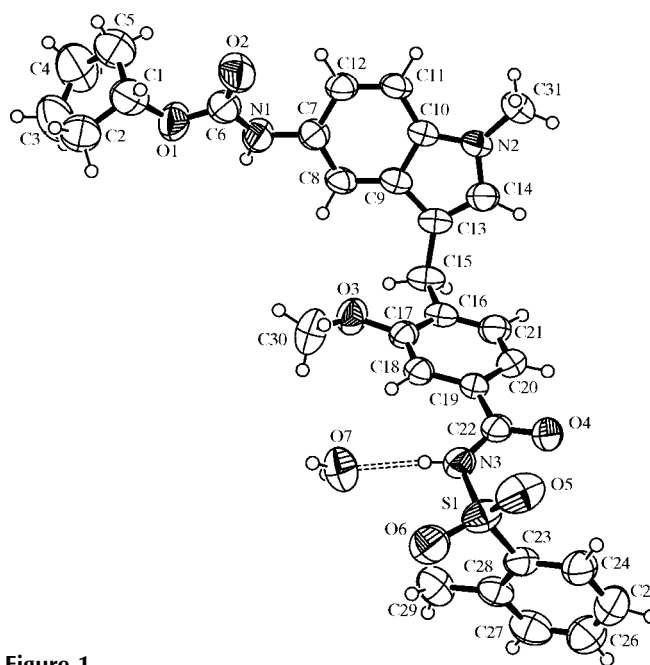


Figure 1

The molecular structure of the monohydrate of zafirlukast, (I), showing 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 dashed lines indicate the hydrogen bond.

Zafirlukast adopts a Z-shaped conformation in the three crystal structures. Selected torsion angles for the three solvates and for the calculated structure of zafirlukast itself (MM+; Allinger & Yuh, 1982) are given in Table 1. The conformation of the pentyloxycarbonylamino phenyl moiety in the three solvates may be compared with that of 3-(4-bromobenzoyloxy)cyclopentyl *N*-phenylcarbamate [Vigne *et al.*, 1991; refcode PACGIJ in the Cambridge Structural Database (CSD; Allen, 2002)] and (–)-[1*R*,3*S*,2(1*E*)]-3-*N*-(4-bromophenylcarbamoyloxy)-2-(1-*N,N*-diisopropylcarbamoyloxymethylidene)cyclopentyl *N,N*-diisopropylcarbamate (Gralla *et al.*, 2002; CSD refcode PUZBOB]. The conformation may be expressed by the angles between the mean planes formed by the atoms C1/C2/C5 (*P*1), O1/O2/N1/C6 (*P*2) and C7–C12 (*P*3). The angles between planes *P*1 and *P*2 are in the range 72.0–86.8° in the solvates of zafirlukast, and 74.3 and 60.6° in PACGIJ and PUZBOB, respectively. The angles between planes *P*2 and *P*3 are in the range 31.3–33.3° in the solvates, and 27.8 and 13.5° in PACGIJ and PUZBOB, respectively. Finally, the angles between the mean planes *P*1 and *P*3 are in the range 39.7–75.5° in the solvates, and 81.5 and 67.5° in PACGIJ and PUZBOB, respectively. It is also important to note the difference in the O1–C1 bond length. This bond was found to be 1.441 Å in PUZBOB, as well as in many other cyclopentyl carbamates, while it is significantly longer in PACGIJ (1.522 Å) and in the present solvates of zafirlukast [1.521 (5), 1.521 (11) and 1.517 (15) Å in (I)–(III), respec-

tively]. The reason for the lengthening of this bond is not known. As a result of the large atomic displacement parameters of the terminal groups [cyclopentane in all three compounds and a benzene ring in compound (III)], some bond lengths are too short.

The methanol, (II), and ethanol, (III), solvates are isostructural. The solvent molecules are connected to two zafirlukast molecules through N–H···O–H and C=O···H–O hydrogen bonds (Table 2). The water molecule in the monohydrate, (I), takes part in three hydrogen bonds, thus serving as a connector between three molecules of zafirlukast. These hydrogen bonds are H₂O···H–N, HOH···O=C and HOH···O=S (Table 2). Although the role of the water molecules in (I) differs from that of methanol or ethanol in (II) or (III), the packing of zafirlukast is very similar (Fig. 2). All three structures contain layers of zafirlukast molecules that are exactly comparable. In (I), these lie in the *ac* plane, while in (II) and (III), they lie in the *ab* plane. The solvate molecules lie in positions adjacent to these layers, hydrogen bonded to the C=O groups (Table 2). The differences between the structures lie in how the layers are stacked.

In (I), the water molecule has its second O–H bond projecting approximately perpendicular to the plane of the layer. This forms a hydrogen bond to one S=O group in an adjacent layer. Adjacent layers are 'flipped' in order to form this hydrogen bond. Stacked along the *b* direction, the water molecules appear to be 'sandwiched' in hydrophilic regions between two layers of zafirlukast molecules. These sandwiches then meet in hydrophobic regions. The flipping of the layer to form the hydrophilic sandwich introduces a centre of symmetry and gives rise to the centrosymmetric space group.

In (II) and (III), a methyl or ethyl group projects perpendicular to the plane of the layer, forming a hydrophobic interface, and the layers stack one on top of the other (along the *c* direction) without flipping. This gives the polar space group.

From differential scanning calorimeter (DSC) thermographs, it was seen that the solvent release in each of the compounds is either close to or at the melting temperatures of the solid materials, which are above the boiling points of the pure solvents. This high-temperature release is an indication that the solvents are involved in strong hydrogen bonding. Since the solvent release is so close to the melting temperature it was not possible to measure the enthalpy of release. The measured enthalpies of fusion are 77.96 (6), 80.22 (6), and 55.96 (6) kJ mol^{–1} for (I), (II), and (III), respectively.

Experimental

All chemicals were of analytical grade and the water used was filtered through a Milli-Q water purification system prior to use. Zafirlukast monohydrate, (I), was recrystallized from a mixture of water and acetone, which are the solvents used in the original patent. Zafirlukast ethanol solvate, (II), was prepared according to a previously reported procedure (Gutman *et al.*, 2002). Zafirlukast methanol solvate, (III), was prepared as follows. Zafirlukast ethanol solvate (2 g, 3.2 mmol) was dissolved in CH₂Cl₂ (150 ml) and the resulting solution was washed with water (3 × 300 ml). The organic layer was separated, dried over anhydrous sodium sulfate and filtered. The

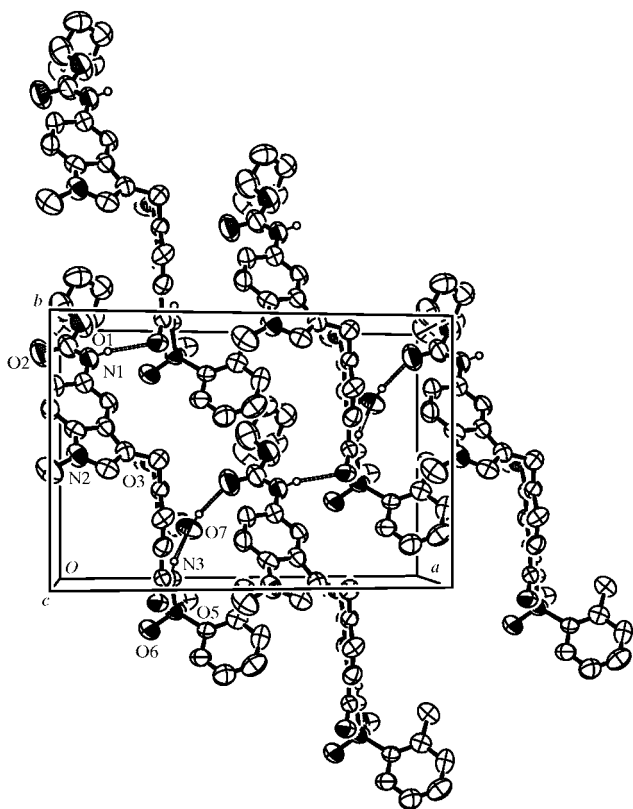


Figure 2

The typical packing of molecules of zafirlukast in (II) connected by hydrogen bonds (dashed lines). Displacement ellipsoids are drawn at the 50% probability level. H atoms not involved in the hydrogen bonding have been omitted for clarity.

filtrate was heated to reflux, methanol (200 ml) was added to the solution, and dichloromethane was distilled off from the stirred mixture until a solid was precipitated. This solid was filtered off, washed on the filter with methanol (2 × 30 ml) and dried under reduced pressure at 333 K. Differential scanning calorimetry (DSC) was employed to characterize the thermal behaviour of the zafirlukast solvates. A Mettler DSC 30 system was used, under a nitrogen atmosphere, at a heating rate of 5 K min⁻¹.

Compound (I)

Crystal data

C₃₁H₃₃N₃O₆S·H₂O
M_r = 593.68
 Monoclinic, *P*2₁/*n*
a = 9.983 (2) Å
b = 31.580 (6) Å
c = 10.192 (2) Å
 β = 111.55 (3)°
V = 2988.6 (12) Å³
Z = 4

D_x = 1.320 Mg m⁻³
 Mo *K*α radiation
 Cell parameters from 16 987 reflections
 θ = 2.2–25.1°
 μ = 0.16 mm⁻¹
T = 293 (2) K
 Prism, colourless
 0.34 × 0.26 × 0.16 mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ scans
 16 987 measured reflections
 5087 independent reflections
 2909 reflections with *I* > 2σ(*I*)

*R*_{int} = 0.080
 θ_{\max} = 25.1°
h = 0 → 11
k = -37 → 37
l = -12 → 11

Refinement

Refinement on *F*²
R [*F*² > 2σ(*F*²)] = 0.060
wR (*F*²) = 0.192
S = 1.03
 5087 reflections
 391 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1097P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 (Δ/σ)_{max} = 0.001
 $\Delta\rho_{\max} = 0.42 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.41 \text{ e } \text{Å}^{-3}$
 Extinction correction: *SHELXL97* (Sheldrick, 1997)
 Extinction coefficient: 0.047 (5)

Compound (II)

Crystal data

C₃₁H₃₃N₃O₆S·CH₄O
M_r = 607.71
 Monoclinic, *Cc*
a = 17.002 (3) Å
b = 11.111 (2) Å
c = 17.129 (3) Å
 β = 105.94 (2)°
V = 3111.4 (10) Å³
Z = 4

D_x = 1.297 Mg m⁻³
 Mo *K*α radiation
 Cell parameters from 13 868 reflections
 θ = 2.2–17.1°
 μ = 0.16 mm⁻¹
T = 293 (2) K
 Plate, colourless
 0.39 × 0.33 × 0.03 mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ scans
 2839 measured reflections
 2839 independent reflections

1811 reflections with *I* > 2σ(*I*)
 θ_{\max} = 25.4°
h = 0 → 20
k = 0 → 13
l = -20 → 19

Refinement

Refinement on *F*²
R [*F*² > 2σ(*F*²)] = 0.048
wR (*F*²) = 0.138
S = 1.01
 2839 reflections
 396 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0792P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 (Δ/σ)_{max} = 0.001
 $\Delta\rho_{\max} = 0.29 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.17 \text{ e } \text{Å}^{-3}$
 Extinction correction: *SHELXL97* (Sheldrick, 1997)
 Extinction coefficient: 0.0052 (10)

Table 1

Selected torsion angles (°) in the solvates of zafirlukast, (I)–(III).

The torsion angles for (II) are taken from a mirror-symmetry-related molecule for comparison reasons.

	(I)	(II)	(III)	Calculated
C14–C13–C15–C16	66.2 (4)	65.3 (7)	68.7 (10)	67.8
C13–C15–C16–C21	-81.3 (4)	-85.9 (6)	-84.1 (9)	-83.4
C22–N3–S1–C23	-61.8 (3)	-63.7 (4)	-65.4 (6)	-58.7
N3–S1–C23–C28	-66.4 (3)	-71.2 (5)	-67.7 (7)	-64.1
O2–C6–O1–C1	-5.4 (6)	0.8 (13)	3.4 (18)	3.9
C1–C2–C3–C4	-16.9 (6)	-14.6 (11)	-1.0 (18)	-21.0
C2–C3–C4–C5	-0.8 (7)	-6.0 (9)	14.3 (19)	-2.8
C3–C4–C5–C1	18.9 (6)	22.3 (8)	23.7 (18)	25.6
C4–C5–C1–C2	-28.9 (5)	-32.1 (10)	-24 (2)	-38.5
C5–C1–C2–C3	28.5 (5)	28.6 (12)	14.7 (17)	36.8

Compound (III)

Crystal data

C₃₁H₃₃N₃O₆S·C₂H₆O
M_r = 621.73
 Monoclinic, *Cc*
a = 17.216 (3) Å
b = 11.033 (2) Å
c = 18.258 (4) Å
 β = 109.47 (3)°
V = 3269.7 (11) Å³
Z = 4

D_x = 1.263 Mg m⁻³
 Mo *K*α radiation
 Cell parameters from 9728 reflections
 θ = 2.2–27.8°
 μ = 0.15 mm⁻¹
T = 293 (2) K
 Prism, colourless
 0.40 × 0.30 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ scans
 9728 measured reflections
 2726 independent reflections
 1030 reflections with *I* > 2σ(*I*)

*R*_{int} = 0.076
 θ_{\max} = 25.1°
h = 0 → 20
k = 0 → 13
l = -21 → 19

Refinement

Refinement on *F*²
R [*F*² > 2σ(*F*²)] = 0.050
wR (*F*²) = 0.114
S = 0.81
 2724 reflections
 405 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.05P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 (Δ/σ)_{max} = 0.046
 $\Delta\rho_{\max} = 0.17 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.11 \text{ e } \text{Å}^{-3}$
 Extinction correction: *SHELXL97* (Sheldrick, 1997)
 Extinction coefficient: 0.0027 (5)

Table 2

Comparison of hydrogen-bonding geometry (Å, °) in the solvates of zafirlukast, (I)–(III).

<i>D</i> –H... <i>A</i>	<i>D</i> –H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> –H... <i>A</i>	Symmetry code
(I)					
N1–H41...O4	0.86	2.133	2.984 (4)	170	<i>x</i> – 1, <i>y</i> , <i>z</i> – 1
N3–H42...O7	0.86	1.992	2.828 (4)	164	
O7–H7A...O2	0.90 (4)	1.904 (4)	2.792 (4)	170 (4)	<i>x</i> + 1, <i>y</i> , <i>z</i>
O7–H7B...O6	0.88 (5)	2.042 (5)	2.904 (4)	168 (5)	2 – <i>x</i> , – <i>y</i> , 2 – <i>z</i>
(II)					
N1–H41...O4	0.86	2.163	3.008 (7)	168	<i>x</i> , <i>y</i> + 1, <i>z</i>
N3–H42...O7	0.86	1.992	2.829 (8)	164	
O7–H43...O2	0.805 (9)	1.94 (9)	2.731 (8)	169 (9)	<i>x</i> + $\frac{1}{2}$, <i>y</i> – $\frac{1}{2}$, <i>z</i>
(III)					
N1–H41...O4	0.86	2.190	3.03 (1)	167	<i>x</i> , <i>y</i> – 1, <i>z</i>
N3–H42...O7	0.86	1.977	2.81 (1)	166	<i>x</i> – $\frac{1}{2}$, <i>y</i> + $\frac{1}{2}$, <i>z</i>
O7–H43...O2	0.821 (9)	1.92 (9)	2.74 (1)	177 (8)	

For the ethanol and methanol solvates, the uncertainties on the Flack (1983) parameters were too high [0.14 (10) and 0 (1), respectively] and the data were merged before the final refinement. In all three solvates, the H atoms were located in difference Fourier maps. The coordinates of the H atoms in the OH groups of water, methanol and ethanol were freely refined in the first two solvates and refined with bond-distance restraints in the third. The remaining H atoms were constrained riding on their parent atoms, with C—H = 0.93–0.98 Å and N—H = 0.86 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

For all three solvates, data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1199). Services for accessing these data are described at the back of the journal.

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