Acta Cryst E CRYSTALLOGRAPHIC COMMUNICATIONS

ISSN 2056-9890

Crystal structure of an apremilast ethanol hemisolvate hemihydrate solvatomorph

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Received 18 April 2017
Accepted 3 May 2017

Edited by M. Weil, Vienna University of Technology, Austria

Keywords: apremilast; PDE4; psoriatic arthritis; crystal structure; hydrogen bonding; solvatomorph.

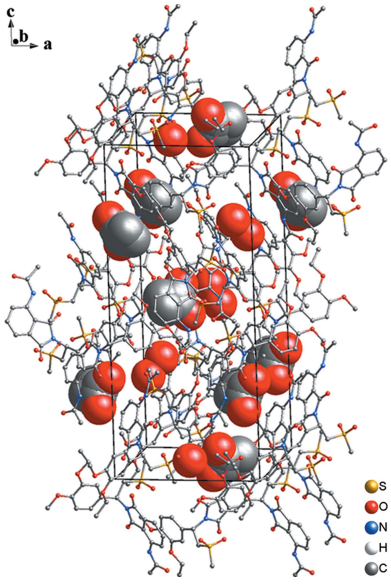
CCDC reference: 1504229

Supporting information: this article has supporting information at journals.iucr.org/e

The title compound, $C_{22}H_{24}N_2O_7S\cdot0.5C_2H_5OH\cdot0.5H_2O$ {systematic name: (*S*)-4-acetamido-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione ethanol hemisolvate hemihydrate}, is a novel solvatomorph of apremilast (AP), which is an inhibitor of phosphodiesterase 4 (PDE4) and is indicated for the treatment of adult patients with active psoriatic arthritis. The asymmetric unit contains one molecule of AP and disordered molecules of ethanol and water, both with half occupancy. The dihedral angle between the planes of the phenyl ring and the isoindole ring is 67.9 (2)°. Extensive intra- and intermolecular hydrogen bonds help to stabilize the molecular conformation and sustain the crystal packing.

1. Chemical context

Analogues of thalidomide have been reported to possibly enhance tumor necrosis factor alpha (TNFα) inhibitory activity (Corral *et al.*, 1996; Muller *et al.*, 1996) and phosphodiesterase type 4 (PD4) inhibition (Muller *et al.*, 1998), hence showing potential for the treatment of inflammatory diseases (de Brito *et al.*, 1997). Among these substances are phenethylsulfones substituted in the α position to the phenyl group with a 1-oxoisoindoline or 1,3-dioxoisoindoline group that can reduce the levels of TNFα in a mammal. Typical embodiments are (*S*)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)-ethyl]-4-acetamidoisoindoline-1,3-dione] with the generic name apremilast (AP), which is an inhibitor of phosphodiesterase 4 (PDE4) and is indicated for the treatment of adult patients with active psoriatic arthritis (Gottlieb *et al.*, 2008; Man *et al.*, 2009; Duplantier *et al.*, 1996). In our previous studies, we reported three solvatomorphs of AP with ethyl acetate, toluene and dichloromethane, respectively (Wu *et al.*, 2017). However, these three solvates exhibit toxicity, in particular the solvates of toluene and dichloromethane, which clearly limits the possibility of these compounds being developed into drugs. In a continuation of our work, a novel solvatomorph of AP with ethanol and water solvents in the molar ratio 1:0.5:0.5 was prepared and its crystal structure determined. This solvatomorph of AP appears to be suitable for development into a powerful drug, showing much lower toxicity than the solvatomorphs of ethyl acetate, toluene and dichloromethane.



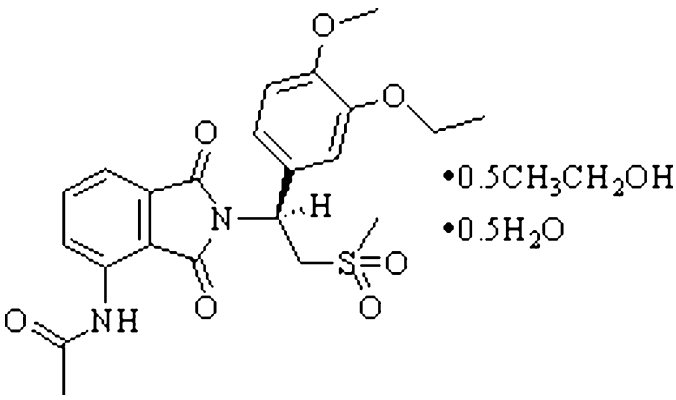


Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O3	0.86	2.31	2.986 (7)	136
O8—H8A···O9	0.92	2.30	3.20 (3)	166
O9—H9B···O1	0.89	2.54	2.994 (17)	112
C8—H8···O4	0.93	2.30	2.894 (9)	121
C1—H1A···O5	0.97	2.45	3.068 (8)	121
C1—H1A···O5^{i}	0.97	2.32	3.172 (8)	147
C1—H1B···O4^{ii}	0.97	2.56	3.524 (9)	172
C14—H14···O5^{i}	0.93	2.49	3.415 (8)	178
C19—H19C···O4^{iii}	0.96	2.61	3.567 (10)	173
C20—H20···O2^{ii}	0.93	2.46	3.370 (9)	166
C22—H22C···O3^{iv}	0.96	2.44	3.088 (9)	124
C22—H22C···O9	0.96	2.61	3.36 (2)	136

Symmetry codes: (i) $y, x, -z+1$; (ii) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+\frac{3}{4}$; (iii) $-y+\frac{5}{2}, x+\frac{1}{2}, z+\frac{1}{4}$; (iv) $-y+\frac{3}{2}, x-\frac{1}{2}, z+\frac{1}{4}$.

2. Structural commentary

The title solvatomorph (I) crystallizes in the same space group ($P4_12_12$) as the other three structurally characterized solvatomorphs of ethyl acetate, toluene and dichloromethane (Wu *et al.*, 2017). The structures of the molecular components of (I) are shown in Fig. 1. The asymmetric unit comprises one molecule of AP and one solvent molecule each of ethanol and water, both being disordered about a twofold rotation axis (occupancy for both solvent molecules = 0.5). A space-filling drawing of the structure is given in Fig. 2, emphasizing the positions of the solvent molecules in the crystal structure. The bond lengths and angles in the AP molecule are in normal ranges and very similar to those in the previous three solvatomorphs (Wu *et al.*, 2017). The same applies to the dihedral

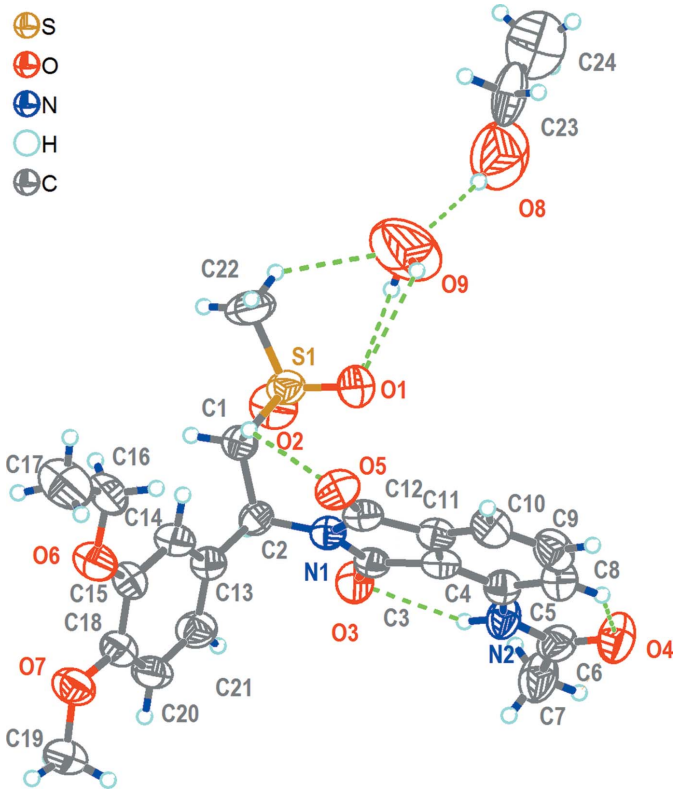


Figure 1
The structures of the molecular components in (I). Displacement ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as dashed lines.

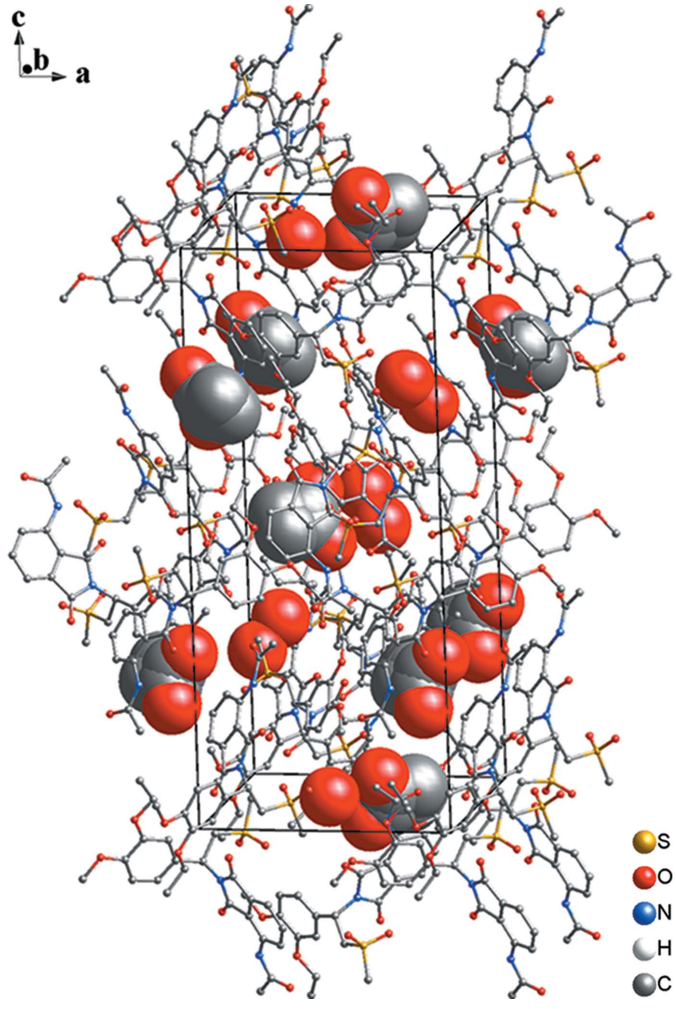


Figure 2
The unit cell of (I), with the solvent molecules shown in space-filling mode. [See Table 1 for symmetry codes.]

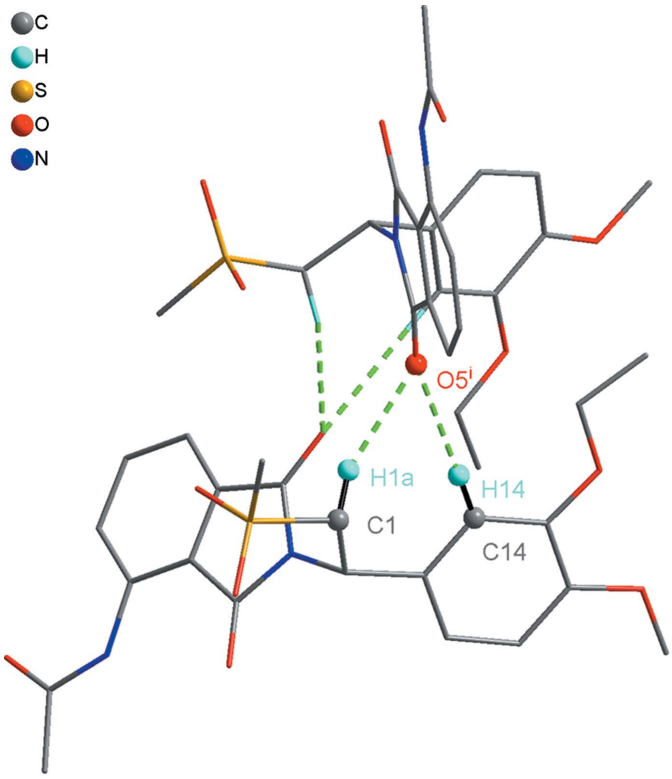


Figure 3
$(AP)_2$ dimers with an $R_2^1(7)$ motif formed by C—H···O hydrogen bonds. [See Table 1 for symmetry code.]

angle between the phenyl (C13–C20) and isoindole (C3–C5/C8–C12/N1) rings, which is 67.9 (2)° in the title structure. The conformation of the AP molecule is stabilized by several intramolecular hydrogen bonds of types N—H···O and C—H···O (Table 1).

3. Supramolecular features

An extensive network of intermolecular hydrogen-bonding interactions exists in the crystal structure (Figs. 1, 2–4; Table 1). The water molecule (O9) is hydrogen-bonded to the AP molecule by C22—H22*C*···O9 and O9—H9*B*···O1 interactions and likewise is bonded by an O8—H8*A*···O9 interaction to the ethanol solvent molecule. As well as these hydrogen bonds involving the solvent molecules, there are interactions between AP molecules. Two AP molecules are arranged into a dimer with an $R_2^1(7)$ motif (Fig. 3) by C—H···O hydrogen bonds, and a zipper-like chain including $R_2^2(18)$ motifs (Fig. 4) is formed parallel to the *a* axis by additional C—H··O hydrogen bonds.

4. Synthesis and crystallization

AP was prepared according to a literature protocol (Muller *et al.*, 2006, 2008*a*,*b*). A 100 ml round-bottomed flask equipped with a magnetic stirring bar was charged with a solution of (*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethanamine *N*-acetyl leucine salt (5.0 g, 11.2 mmol, 1.0 eq) and 3-acetamidophthalic anhydride (2.42 g, 11.8 mmol, 1.05 eq) to which glacial acetic acid (50 ml) was added. The mixture was refluxed for 16 h and then cooled to room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water (2 × 50 ml), saturated aqueous sodium bicarbonate (2 × 50 ml), brine (2 × 50 ml), and dried over anhydrous sodium sulfate. The solvents were evaporated *in vacuo*, and the obtained AP recrystallized from an ethanol/acetone mixture (2:1, *v*/*v*). Single crystals of (I) were obtained by slow evaporation of an AP-saturated solution from an *N*,*N*-dimethylformamide/ethanol/water mixture (1:10:2, *v*/*v*/*v*), at room temperature over 90 days.

5. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. Hydrogen atoms bound to nitrogen or carbon atoms were placed in calculated positions (N—H = 0.87, C—H = 0.93–0.98 Å) and constrained to ride on their carrier atoms [U_{iso}(H) = 1.2U_{eq}(C,N) or 1.5U_{eq}(C_{methyl})].

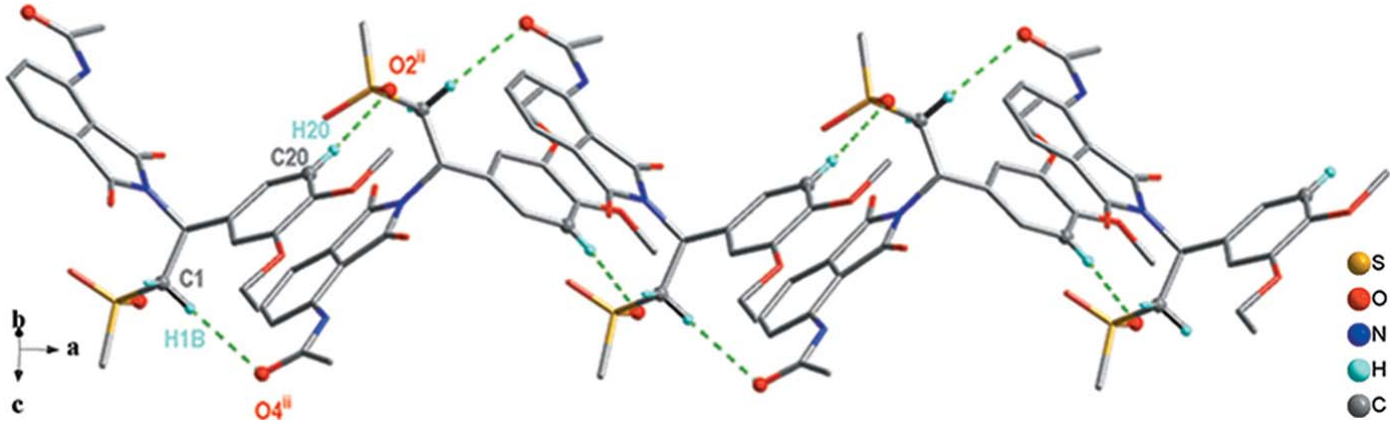


Figure 4
C1—H1*B*···O4^{ii} and C20—H20···O2^{ii} hydrogen bonds incorporating $R_2^2(18)$ motifs expand the structure parallel to the *a*-axis direction. [See Table 1 for symmetry codes.]

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{22}H_{24}N_2O_7S{\cdot}0.5C_2H_6O{\cdot}0.5H_2O$
M_r	492.53
Crystal system, space group	Tetragonal, $P4_12_12$
Temperature (K)	298
a, c (Å)	12.9905 (18), 29.942 (6)
V (Å^3)	5052.8 (17)
Z	8
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.18
Crystal size (mm)	0.3 × 0.3 × 0.2
Data collection	
Diffractometer	Bruker P4
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	9575, 4390, 2811
R_{int}	0.079
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.592
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.066, 0.183, 1.05
No. of reflections	4390
No. of parameters	329
No. of restraints	30
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.62, −0.30
Absolute structure	Flack x determined using 833 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter	0.15 (8)

Computer programs: *APEX2* and *SAINT* (Bruker, 2009), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2014* (Sheldrick, 2015*b*) and *OLEX2* (Dolomanov *et al.*, 2009).

Hydrogen atoms bound to oxygen atoms were deduced from difference-Fourier maps and their positions relative to donor and possible acceptor atoms. They were refined with $U_{iso}(H) = 1.5U_{eq}(O)$. The solvent ethanol and water molecules are disordered about a twofold rotation axis and were refined with an occupancy of 0.5. To get reasonable shape and displacement parameters for both molecules, they were treated with DFIX, RIGU and ISOR restraints in *SHELXL2014* (Sheldrick, 2015*b*).

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supporting information

Acta Cryst. (2017). E**73**, 821-824 [https://doi.org/10.1107/S2056989017006661]

Crystal structure of an apremilast ethanol hemisolvate hemihydrate solvatomorph

Yun-Deng Wu, Xiao-Hong Liu, Jian Xu, Si-Han Zhang, Kun Shen, Ling Sun, Yong-Mei He, Yan Ma and Ai-Hua Zhang

Computing details

Data collection: *APEX2* (Bruker, 2009); cell refinement: *SAINT* (Bruker, 2009); data reduction: *SAINT* (Bruker, 2009); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015b); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *OLEX2* (Dolomanov *et al.*, 2009).

(*S*)-4-Acetamido-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione ethanol hemisolvate hemihydrate

Crystal data

$C_{22}H_{24}N_2O_7S{\cdot}0.5C_2H_6O{\cdot}0.5H_2O$
M_r = 492.53
Tetragonal, $P4_12_12$
a = 12.9905 (18) Å
c = 29.942 (6) Å
V = 5052.8 (17) Å^3
Z = 8
$F(000)$ = 2080
D_x = 1.295 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 2016 reflections
θ = 2–20°
μ = 0.18 mm^{-1}
T = 298 K
Block, colourless
0.3 × 0.3 × 0.2 mm

Data collection

Bruker P4 diffractometer
ω scans
9575 measured reflections
4390 independent reflections
2811 reflections with $I > 2\sigma(I)$
R_{int} = 0.079
θ_{max} = 24.9°, θ_{min} = 1.7°
h = 0→15
k = 0→15
l = −35→35
1 standard reflections every 60 reflections
intensity decay: 1%

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.066
$wR(F^2)$ = 0.183
S = 1.05
4390 reflections
329 parameters
30 restraints
Hydrogen site location: mixed
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0992P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.62 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}

Absolute structure: Flack *x* determined using 833 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter: 0.15 (8)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
S1	0.89768 (15)	0.65667 (14)	0.46183 (6)	0.0537 (5)	
O3	0.9782 (4)	0.7422 (4)	0.33313 (15)	0.0565 (12)	
O6	1.2492 (4)	1.0317 (4)	0.51740 (15)	0.0650 (15)	
O5	0.8948 (4)	0.9600 (4)	0.44709 (16)	0.0618 (14)	
O1	0.8059 (4)	0.7045 (4)	0.44502 (17)	0.0690 (14)	
O2	0.9386 (4)	0.5729 (4)	0.43657 (18)	0.0728 (16)	
O4	0.6990 (5)	0.8281 (4)	0.21258 (18)	0.0774 (16)	
O7	1.3846 (4)	1.0504 (4)	0.45344 (16)	0.0660 (14)	
N1	0.9578 (4)	0.8403 (4)	0.39684 (16)	0.0425 (12)	
N2	0.8221 (4)	0.8054 (5)	0.26522 (17)	0.0544 (15)	
H2	0.8764	0.7699	0.2710	0.065*	
C3	0.9329 (5)	0.8089 (5)	0.3537 (2)	0.0418 (14)	
C2	1.0379 (5)	0.7928 (5)	0.4242 (2)	0.0441 (15)	
H2A	1.0637	0.7333	0.4075	0.053*	
C12	0.8912 (5)	0.9175 (5)	0.4107 (2)	0.0487 (16)	
C11	0.8173 (5)	0.9376 (5)	0.3739 (2)	0.0452 (15)	
C13	1.1290 (5)	0.8638 (5)	0.4319 (2)	0.0455 (16)	
C14	1.1440 (5)	0.9163 (5)	0.4720 (2)	0.0512 (17)	
H14	1.0952	0.9100	0.4945	0.061*	
C4	0.8437 (5)	0.8713 (5)	0.3392 (2)	0.0451 (16)	
C8	0.7059 (5)	0.9390 (5)	0.2964 (3)	0.0572 (18)	
H8	0.6670	0.9408	0.2703	0.069*	
C5	0.7893 (5)	0.8709 (5)	0.2996 (2)	0.0477 (16)	
C1	0.9941 (5)	0.7515 (5)	0.4684 (2)	0.0467 (15)	
H1A	0.9657	0.8086	0.4853	0.056*	
H1B	1.0501	0.7225	0.4858	0.056*	
C20	1.2874 (5)	0.9370 (6)	0.4048 (2)	0.0575 (18)	
H20	1.3353	0.9435	0.3819	0.069*	
C6	0.7810 (7)	0.7888 (6)	0.2243 (2)	0.0599 (19)	
C18	1.3020 (5)	0.9885 (5)	0.4443 (3)	0.0533 (18)	
C15	1.2291 (5)	0.9771 (5)	0.4791 (2)	0.0504 (17)	
C21	1.2011 (6)	0.8752 (5)	0.3988 (2)	0.0571 (19)	
H21	1.1921	0.8409	0.3718	0.069*	
C10	0.7368 (5)	1.0042 (6)	0.3713 (3)	0.0585 (18)	
H10	0.7199	1.0481	0.3947	0.070*	

C16	1.1741 (5)	1.0248 (6)	0.5523 (2)	0.065 (2)	
H16A	1.1668	0.9539	0.5619	0.078*	
H16B	1.1078	1.0488	0.5417	0.078*	
C9	0.6809 (6)	1.0032 (6)	0.3313 (3)	0.067 (2)	
H9	0.6249	1.0473	0.3282	0.081*	
C7	0.8411 (6)	0.7188 (7)	0.1951 (2)	0.076 (2)	
H7A	0.9067	0.7050	0.2086	0.114*	
H7B	0.8513	0.7508	0.1665	0.114*	
H7C	0.8043	0.6553	0.1912	0.114*	
C22	0.8740 (7)	0.6177 (7)	0.5166 (2)	0.083 (3)	
H22A	0.8596	0.6769	0.5347	0.124*	
H22B	0.9334	0.5827	0.5281	0.124*	
H22C	0.8159	0.5720	0.5171	0.124*	
C19	1.4549 (6)	1.0668 (8)	0.4174 (3)	0.086 (3)	
H19A	1.4204	1.1022	0.3936	0.128*	
H19B	1.4798	1.0017	0.4068	0.128*	
H19C	1.5118	1.1076	0.4277	0.128*	
C17	1.2096 (8)	1.0901 (9)	0.5904 (3)	0.104 (4)	
H17A	1.2163	1.1602	0.5807	0.157*	
H17B	1.2750	1.0656	0.6009	0.157*	
H17C	1.1602	1.0866	0.6142	0.157*	
O8	0.4584 (16)	0.3998 (17)	0.4571 (7)	0.177 (8)	0.5
H8A	0.5022	0.4544	0.4613	0.265*	0.5
C23	0.3896 (19)	0.3736 (17)	0.4889 (8)	0.108 (7)	0.5
H23A	0.3470	0.4341	0.4933	0.130*	0.5
H23B	0.4291	0.3653	0.5161	0.130*	0.5
C24	0.319 (3)	0.287 (3)	0.4878 (12)	0.164 (13)	0.5
H24A	0.3262	0.2506	0.4601	0.247*	0.5
H24B	0.2492	0.3117	0.4904	0.247*	0.5
H24C	0.3334	0.2412	0.5122	0.247*	0.5
O9	0.6400 (13)	0.5606 (12)	0.4753 (9)	0.192 (11)	0.5
H9A	0.6367	0.6301	0.4706	0.289*	0.5
H9B	0.7011	0.5451	0.4635	0.289*	0.5

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0592 (11)	0.0558 (11)	0.0461 (9)	−0.0131 (9)	−0.0010 (8)	0.0016 (8)
O3	0.057 (3)	0.067 (3)	0.045 (3)	0.013 (2)	0.002 (2)	−0.015 (2)
O6	0.060 (3)	0.082 (4)	0.053 (3)	−0.023 (3)	0.007 (2)	−0.021 (3)
O5	0.081 (3)	0.062 (3)	0.043 (3)	0.003 (3)	0.006 (2)	−0.014 (2)
O1	0.058 (3)	0.083 (4)	0.066 (3)	−0.008 (3)	−0.010 (3)	0.005 (3)
O2	0.085 (4)	0.058 (3)	0.076 (4)	−0.012 (3)	0.002 (3)	−0.017 (3)
O4	0.079 (4)	0.092 (4)	0.062 (3)	0.015 (3)	−0.021 (3)	−0.006 (3)
O7	0.054 (3)	0.080 (4)	0.064 (3)	−0.019 (3)	0.007 (3)	−0.004 (3)
N1	0.049 (3)	0.043 (3)	0.036 (3)	0.000 (3)	0.004 (2)	−0.007 (2)
N2	0.057 (4)	0.064 (4)	0.043 (3)	0.015 (3)	−0.006 (3)	−0.008 (3)
C3	0.042 (3)	0.046 (4)	0.037 (3)	−0.003 (3)	0.009 (3)	−0.002 (3)

C2	0.049 (4)	0.048 (4)	0.035 (3)	0.000 (3)	0.000 (3)	−0.005 (3)
C12	0.059 (4)	0.045 (4)	0.041 (4)	−0.010 (3)	0.008 (3)	−0.003 (3)
C11	0.048 (4)	0.043 (4)	0.044 (4)	−0.002 (3)	0.008 (3)	−0.006 (3)
C13	0.047 (4)	0.045 (4)	0.044 (4)	0.000 (3)	0.003 (3)	0.000 (3)
C14	0.051 (4)	0.052 (4)	0.051 (4)	−0.008 (3)	0.013 (3)	−0.004 (3)
C4	0.051 (4)	0.042 (4)	0.042 (4)	−0.006 (3)	0.011 (3)	−0.001 (3)
C8	0.054 (4)	0.054 (4)	0.063 (5)	0.003 (4)	−0.005 (4)	−0.003 (4)
C5	0.050 (4)	0.046 (4)	0.048 (4)	−0.001 (3)	0.003 (3)	0.001 (3)
C1	0.049 (4)	0.050 (4)	0.040 (3)	−0.007 (3)	−0.001 (3)	−0.004 (3)
C20	0.051 (4)	0.069 (5)	0.053 (4)	−0.007 (4)	0.013 (4)	0.006 (4)
C6	0.070 (5)	0.068 (5)	0.042 (4)	−0.008 (4)	−0.001 (4)	0.002 (4)
C18	0.046 (4)	0.055 (4)	0.059 (4)	−0.005 (4)	0.002 (3)	0.003 (3)
C15	0.041 (4)	0.055 (4)	0.055 (4)	−0.003 (3)	−0.001 (3)	−0.003 (3)
C21	0.063 (5)	0.065 (5)	0.043 (4)	−0.006 (4)	0.005 (3)	−0.006 (3)
C10	0.059 (5)	0.053 (4)	0.063 (5)	0.010 (4)	0.009 (4)	−0.010 (4)
C16	0.044 (4)	0.090 (6)	0.062 (5)	−0.006 (4)	0.004 (3)	−0.021 (4)
C9	0.053 (5)	0.059 (5)	0.090 (6)	0.011 (4)	0.007 (4)	−0.001 (4)
C7	0.079 (5)	0.098 (6)	0.051 (4)	0.024 (5)	−0.009 (4)	−0.017 (4)
C22	0.102 (7)	0.096 (7)	0.050 (5)	−0.029 (5)	0.010 (4)	0.017 (4)
C19	0.062 (5)	0.123 (8)	0.072 (6)	−0.027 (5)	0.004 (4)	0.023 (5)
C17	0.086 (7)	0.148 (9)	0.079 (7)	−0.024 (7)	0.014 (5)	−0.052 (6)
O8	0.161 (12)	0.190 (14)	0.180 (14)	0.097 (10)	−0.023 (11)	0.023 (12)
C23	0.110 (11)	0.086 (10)	0.129 (13)	0.061 (8)	−0.053 (9)	0.002 (10)
C24	0.179 (19)	0.150 (17)	0.16 (2)	0.014 (15)	−0.043 (16)	−0.010 (15)
O9	0.126 (14)	0.125 (14)	0.33 (3)	−0.030 (11)	0.032 (16)	0.084 (16)

Geometric parameters (Å, º)

S1—O1	1.436 (5)	C20—H20	0.9300
S1—O2	1.428 (6)	C20—C18	1.372 (10)
S1—C1	1.768 (6)	C20—C21	1.390 (10)
S1—C22	1.744 (7)	C6—C7	1.485 (10)
O3—C3	1.214 (7)	C18—C15	1.417 (10)
O6—C15	1.373 (8)	C21—H21	0.9300
O6—C16	1.433 (8)	C10—H10	0.9300
O5—C12	1.221 (7)	C10—C9	1.400 (11)
O4—C6	1.232 (9)	C16—H16A	0.9700
O7—C18	1.368 (8)	C16—H16B	0.9700
O7—C19	1.430 (9)	C16—C17	1.495 (11)
N1—C3	1.394 (8)	C9—H9	0.9300
N1—C2	1.461 (8)	C7—H7A	0.9601
N1—C12	1.388 (8)	C7—H7B	0.9599
N2—H2	0.8600	C7—H7C	0.9602
N2—C5	1.401 (8)	C22—H22A	0.9600
N2—C6	1.353 (9)	C22—H22B	0.9600
C3—C4	1.478 (9)	C22—H22C	0.9600
C2—H2A	0.9800	C19—H19A	0.9600
C2—C13	1.518 (9)	C19—H19B	0.9600

C2—C1	1.539 (8)	C19—H19C	0.9600
C12—C11	1.485 (9)	C17—H17A	0.9600
C11—C4	1.392 (8)	C17—H17B	0.9600
C11—C10	1.360 (9)	C17—H17C	0.9600
C13—C14	1.394 (9)	O8—H8A	0.9182
C13—C21	1.372 (9)	O8—C23	1.35 (2)
C14—H14	0.9300	C23—H23A	0.9700
C14—C15	1.375 (9)	C23—H23B	0.9700
C4—C5	1.381 (9)	C23—C24	1.46 (2)
C8—H8	0.9300	C24—H24A	0.9600
C8—C5	1.401 (9)	C24—H24B	0.9600
C8—C9	1.377 (10)	C24—H24C	0.9600
C1—H1A	0.9700	O9—H9A	0.9150
C1—H1B	0.9700	O9—H9B	0.8918

O1—S1—C1	109.0 (3)	C20—C18—C15	119.4 (6)
O1—S1—C22	108.0 (4)	O6—C15—C14	125.3 (6)
O2—S1—O1	117.0 (3)	O6—C15—C18	115.7 (6)
O2—S1—C1	109.1 (3)	C14—C15—C18	118.9 (6)
O2—S1—C22	110.0 (4)	C13—C21—C20	121.3 (6)
C22—S1—C1	102.8 (4)	C13—C21—H21	119.3
C15—O6—C16	116.6 (5)	C20—C21—H21	119.3
C18—O7—C19	115.9 (6)	C11—C10—H10	121.9
C3—N1—C2	124.2 (5)	C11—C10—C9	116.3 (6)
C12—N1—C3	110.2 (5)	C9—C10—H10	121.9
C12—N1—C2	125.5 (5)	O6—C16—H16A	110.1
C5—N2—H2	115.3	O6—C16—H16B	110.1
C6—N2—H2	114.8	O6—C16—C17	108.2 (6)
C6—N2—C5	129.9 (6)	H16A—C16—H16B	108.4
O3—C3—N1	124.4 (6)	C17—C16—H16A	110.1
O3—C3—C4	128.5 (6)	C17—C16—H16B	110.1
N1—C3—C4	107.0 (5)	C8—C9—C10	122.2 (7)
N1—C2—H2A	106.9	C8—C9—H9	118.9
N1—C2—C13	112.7 (5)	C10—C9—H9	118.9
N1—C2—C1	111.5 (5)	C6—C7—H7A	109.4
C13—C2—H2A	106.9	C6—C7—H7B	109.4
C13—C2—C1	111.6 (5)	C6—C7—H7C	109.6
C1—C2—H2A	106.9	H7A—C7—H7B	109.5
O5—C12—N1	124.8 (6)	H7A—C7—H7C	109.5
O5—C12—C11	127.4 (6)	H7B—C7—H7C	109.4
N1—C12—C11	107.9 (5)	S1—C22—H22A	109.5
C4—C11—C12	106.6 (6)	S1—C22—H22B	109.5
C10—C11—C12	130.7 (6)	S1—C22—H22C	109.5
C10—C11—C4	122.7 (6)	H22A—C22—H22B	109.5
C14—C13—C2	122.5 (5)	H22A—C22—H22C	109.5
C21—C13—C2	119.2 (6)	H22B—C22—H22C	109.5
C21—C13—C14	118.3 (6)	O7—C19—H19A	109.5
C13—C14—H14	119.1	O7—C19—H19B	109.5

C15—C14—C13	121.8 (6)	O7—C19—H19C	109.5
C15—C14—H14	119.1	H19A—C19—H19B	109.5
C11—C4—C3	108.3 (6)	H19A—C19—H19C	109.5
C5—C4—C3	130.6 (6)	H19B—C19—H19C	109.5
C5—C4—C11	121.1 (6)	C16—C17—H17A	109.5
C5—C8—H8	119.6	C16—C17—H17B	109.5
C9—C8—H8	119.6	C16—C17—H17C	109.5
C9—C8—C5	120.8 (7)	H17A—C17—H17B	109.5
N2—C5—C8	124.6 (6)	H17A—C17—H17C	109.5
C4—C5—N2	118.5 (6)	H17B—C17—H17C	109.5
C4—C5—C8	116.9 (6)	C23—O8—H8A	120.7
S1—C1—H1A	108.7	O8—C23—H23A	105.6
S1—C1—H1B	108.7	O8—C23—H23B	105.6
C2—C1—S1	114.1 (4)	O8—C23—C24	127 (3)
C2—C1—H1A	108.7	H23A—C23—H23B	106.1
C2—C1—H1B	108.7	C24—C23—H23A	105.6
H1A—C1—H1B	107.6	C24—C23—H23B	105.6
C18—C20—H20	119.8	C23—C24—H24A	109.5
C18—C20—C21	120.3 (6)	C23—C24—H24B	109.5
C21—C20—H20	119.8	C23—C24—H24C	109.5
O4—C6—N2	122.3 (7)	H24A—C24—H24B	109.5
O4—C6—C7	122.7 (7)	H24A—C24—H24C	109.5
N2—C6—C7	115.1 (7)	H24B—C24—H24C	109.5
O7—C18—C20	124.7 (6)	H9A—O9—H9B	101.7
O7—C18—C15	116.0 (6)		

O3—C3—C4—C11	179.6 (6)	C12—C11—C10—C9	−179.1 (7)
O3—C3—C4—C5	−0.2 (11)	C11—C4—C5—N2	177.4 (6)
O5—C12—C11—C4	179.6 (6)	C11—C4—C5—C8	−1.0 (10)
O5—C12—C11—C10	−1.3 (12)	C11—C10—C9—C8	−0.4 (11)
O1—S1—C1—C2	−71.1 (6)	C13—C2—C1—S1	−173.0 (4)
O2—S1—C1—C2	57.7 (6)	C13—C14—C15—O6	179.5 (7)
O7—C18—C15—O6	1.6 (9)	C13—C14—C15—C18	1.6 (10)
O7—C18—C15—C14	179.7 (6)	C14—C13—C21—C20	0.2 (10)
N1—C3—C4—C11	−0.2 (7)	C4—C11—C10—C9	−0.2 (10)
N1—C3—C4—C5	180.0 (6)	C5—N2—C6—O4	−5.0 (12)
N1—C2—C13—C14	102.5 (7)	C5—N2—C6—C7	175.8 (7)
N1—C2—C13—C21	−79.2 (7)	C5—C8—C9—C10	0.3 (12)
N1—C2—C1—S1	60.1 (6)	C1—C2—C13—C14	−23.8 (9)
N1—C12—C11—C4	−0.3 (7)	C1—C2—C13—C21	154.5 (6)
N1—C12—C11—C10	178.8 (7)	C20—C18—C15—O6	−179.6 (6)
C3—N1—C2—C13	111.8 (6)	C20—C18—C15—C14	−1.5 (10)
C3—N1—C2—C1	−121.8 (6)	C6—N2—C5—C4	177.9 (7)
C3—N1—C12—O5	−179.8 (6)	C6—N2—C5—C8	−3.9 (12)
C3—N1—C12—C11	0.1 (7)	C18—C20—C21—C13	−0.1 (11)
C3—C4—C5—N2	−2.9 (11)	C15—O6—C16—C17	−179.4 (7)
C3—C4—C5—C8	178.7 (6)	C21—C13—C14—C15	−1.0 (10)
C2—N1—C3—O3	−3.8 (9)	C21—C20—C18—O7	179.5 (7)

C2—N1—C3—C4	176.1 (5)	C21—C20—C18—C15	0.8 (11)
C2—N1—C12—O5	4.3 (10)	C10—C11—C4—C3	−178.9 (6)
C2—N1—C12—C11	−175.8 (5)	C10—C11—C4—C5	0.9 (10)
C2—C13—C14—C15	177.3 (6)	C16—O6—C15—C14	−0.5 (10)
C2—C13—C21—C20	−178.2 (6)	C16—O6—C15—C18	177.4 (6)
C12—N1—C3—O3	−179.8 (6)	C9—C8—C5—N2	−177.9 (7)
C12—N1—C3—C4	0.1 (6)	C9—C8—C5—C4	0.4 (10)
C12—N1—C2—C13	−72.8 (7)	C22—S1—C1—C2	174.5 (5)
C12—N1—C2—C1	53.6 (8)	C19—O7—C18—C20	4.8 (10)
C12—C11—C4—C3	0.3 (7)	C19—O7—C18—C15	−176.4 (7)
C12—C11—C4—C5	−179.9 (6)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O3	0.86	2.31	2.986 (7)	136
O8—H8*A*···O9	0.92	2.30	3.20 (3)	166
O9—H9*B*···O1	0.89	2.54	2.994 (17)	112
C8—H8···O4	0.93	2.30	2.894 (9)	121
C1—H1*A*···O5	0.97	2.45	3.068 (8)	121
C1—H1*A*···O5^{i}	0.97	2.32	3.172 (8)	147
C1—H1*B*···O4^{ii}	0.97	2.56	3.524 (9)	172
C14—H14···O5^{i}	0.93	2.49	3.415 (8)	178
C19—H19*C*···O4^{iii}	0.96	2.61	3.567 (10)	173
C20—H20···O2^{ii}	0.93	2.46	3.370 (9)	166
C22—H22*C*···O3^{iv}	0.96	2.44	3.088 (9)	124
C22—H22*C*···O9	0.96	2.61	3.36 (2)	136

Symmetry codes: (i) *y*, *x*, −*z*+1; (ii) *x*+1/2, −*y*+3/2, −*z*+3/4; (iii) −*y*+5/2, *x*+1/2, *z*+1/4; (iv) −*y*+3/2, *x*−1/2, *z*+1/4.