



Febuxostat ethanol monosolvate

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Received 20 February 2020

Accepted 4 May 2020

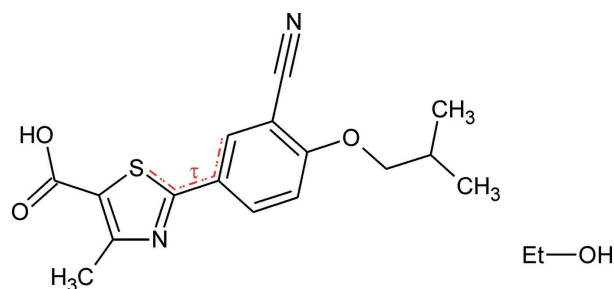
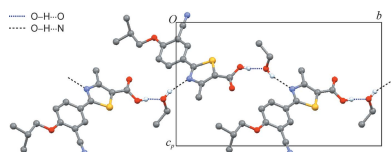
Edited by L. Fabian, University of East Anglia, England

Keywords: crystal structure; solvate; pharmaceuticals; hydrogen bonding; isostructural.**CCDC reference:** 2000973**Supporting information:** this article has supporting information at journals.iucr.org/e

The title compound, 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid ethanol monosolvate, C₁₆H₁₆N₂O₃S·C₂H₆O, (I), displays intermolecular O—H···O and O—H···N bonds in which the carboxyl group of the febuxostat molecule and the hydroxyl group of the ethanol molecule serve as hydrogen-bond donor sites. These interactions result in a helical hydrogen-bonded chain structure. The title structure is isostructural with a previously reported methanol analogue.

1. Chemical context

Febuxostat is a novel, small-molecule, non-purine-selective inhibitor of xanthine oxidase developed for the treatment of chronic gout and hyperuricemia, *via* oral administration (Pascual *et al.*, 2009; Gray & Walters-Smith, 2011; Kataoka *et al.*, 2015). This drug is currently marketed by Takeda Pharmaceuticals Inc. under the trade name Uloric. Matsumoto *et al.* (1999) disclosed the existence of five solid forms of febuxostat, *i.e.* of the anhydrous forms *A*, *B* and *C*, a methanol solvate *D* and a hemihydrate *G*. The crystal structures of two polymorphs were reported by Maddileti *et al.* (2013) and Yadav *et al.* (2017). Additionally, solvate structures containing the febuxostat molecule and methanol (Jiang *et al.*, 2011), acetic acid (Wu *et al.*, 2015) or pyridine (Zhu *et al.*, 2009) have been described.



The current study was carried out as part of an investigation with the aim of establishing a modified synthetic route for febuxostat (Lutra *et al.*, 2012), avoiding harsh conditions, toxic reagents to form the thioamide and the highly toxic cyanides. One of the key aspects of the novel route of synthesis was the introduction of a modified version of the Duff reaction (Duff & Bills, 1932, 1934) in the first step, which finally resulted in improved overall yields compared to the original synthesis by Hasegawa (1998).

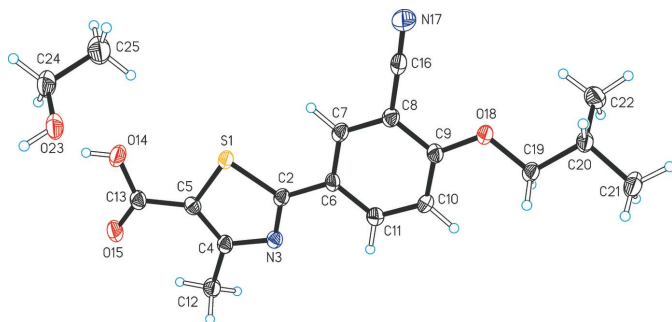


Figure 1
Asymmetric unit of (I) with displacement ellipsoids drawn at the 50% probability level and hydrogen atoms drawn as spheres of arbitrary size.

2. Structural commentary

The febusostat molecule (Fig. 1) is essentially planar. This is illustrated by the fact that the mean plane defined by all its non-H atoms, except for C22 of the isobutyl group, results in a root-mean-square deviation for the 21 fitted atoms of only 0.0890 Å. Atom C22 is located at a distance of 1.498 (3) Å from this mean plane. All bond lengths and angles are in good agreement with the geometrical characteristics of previously determined febusostat structures (see below). The relative mutual orientation of the CN substituent at the phenyl ring and the Me group at the thiazole ring is characterized by the torsion angle S1–C2–C6–C7 of -6.5 (3)°. This torsion is also defined as τ in the Scheme. The isobutoxy group adopts the expected extended chain geometry with C9–O18–C19–C20 = 175.3 (2)° and O18–C19–C20–C21 = 170.7 (2)°.

3. Supramolecular features

The carboxyl group of the febusostat molecule is linked to the OH group of an EtOH molecule *via* an O23–H23···N3($-x + 1, y + \frac{1}{2}, -z + 1$) interaction. The hydroxy group of the solvent additionally serves as a hydrogen-bond donor group for an O14–H14···O23($x - 1, y, z$) bond to a second febusostat molecule (see Table 1). Together, these two interactions result in a hydrogen-bonded chain composed of alternating febusostat and ethanol molecules that displays a 2_1 symmetry and propagates parallel to the b axis (Fig. 2). The same hydrogen-bonded structure is also present in the

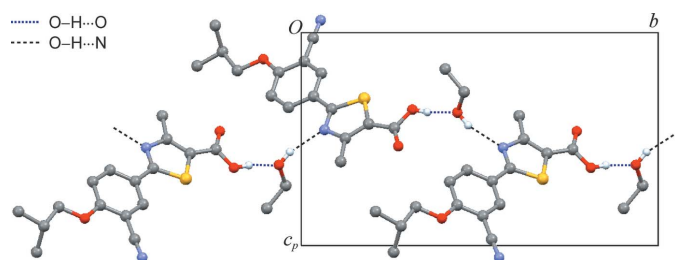


Figure 2
Hydrogen-bonded layer structure of (I), viewed along the a axis.

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O23–H23···N3 ⁱ	0.83 (2)	2.07 (2)	2.878 (3)	162 (4)
O14–H14···O23 ⁱⁱ	0.84 (2)	1.80 (2)	2.631 (3)	170 (4)

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

analogous MeOH solvate of febusostat, first reported (at 296 K) by Jiang *et al.* (2011) and redetermined by us at 173 K as part of this study (Gelbrich *et al.*, 2020a). Indeed, a comparison with the program *XPac* (Gelbrich & Hursthouse, 2005) reveals that the EtOH and MeOH solvates are isostructural. The comparison of corresponding geometrical parameters generated from the complete set of 22 non-H atomic positions in the febusostat molecule resulted in a dissimilarity index (Gelbrich *et al.*, 2012) of $x = 3.3$, which indicates a high agreement of the febusostat packing in the EtOH and MeOH solvates.

4. Database survey

Table 2 displays those entries in the Cambridge Structural Database (version 5.41, November 2019; Groom *et al.*, 2016) that relate to crystal structures containing the febusostat molecule. The febusostat geometries in most of these structures are in good agreement with the parameters of (I), *i.e.* the torsion τ (see Scheme) typically adopts a value close to 0°. However, an opposite geometry with τ values close to 180° has been reported for the polymorphs Q and H1, a co-crystal with 4-aminobenzoic acid and a 2-(pyridin-2-ylamino)pyridinium salt.

5. Synthesis and crystallization

5.1. Synthesis

The preparation of febusostat was carried out according to the scheme in Fig. 3 in a modified procedure based on the original synthesis by Hasegawa (1998).

5.1.1. Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate (3). Ethyl 2-(4-hydroxyphenyl)-4-methyl-5-thiazole carboxylate (**2**, 10.0 g) and hexamethylenetetramine (5.86 g) were added to trifluoroacetic acid (100 ml). The reaction mixture was heated to reflux under stirring for 40 h,

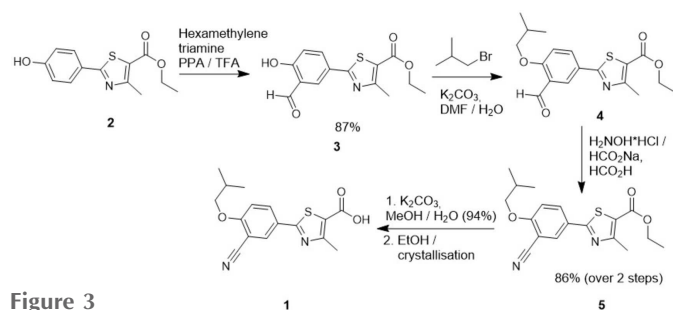


Figure 3
Synthetic scheme for the preparation of febusostat (1).

Table 2

Conformation of febuxostat molecules in polymorphs and multi-component structures, indicated by the torsion angle τ .

Form	CSD	τ (°)	Ref.
Polymorph Q	HIQQAB	-174.1	Maddileti <i>et al.</i> (2013)
Polymorph H1	HIQQAB02	177.9	Yadav <i>et al.</i> (2017)
		-1.2	
MeOH solvate (173 K)	CCDC 1981184	5.6	Gelbrich <i>et al.</i> (2020a)
MeOH solvate (296 K)	UREQOY	5.0	Jiang <i>et al.</i> (2011)
EtOH solvate (I)	-	4.5	This study
Acetic acid solvate (173 K)	CCDC 1981185	-2.8	Gelbrich <i>et al.</i> (2020b)
Acetic acid solvate (296 K)	XULRUT	-3.2	Wu <i>et al.</i> (2015)
Pyridine solvate	PUHGUV	2.7	Zhu <i>et al.</i> (2009)
Acetamide co-crystal	HIQQEF	-6.9	Maddileti <i>et al.</i> (2013)
Nicotinamide co-crystal	HIQQIJ	0.7	Maddileti <i>et al.</i> (2013)
4-Aminobenzoic acid co-crystal	HIQQOP	-176.9	Maddileti <i>et al.</i> (2013)
Urea co-crystal	HIQQUV	4.4	Maddileti <i>et al.</i> (2013)
Isonicotinamide co-crystal	OYADAV	-3.8	Kang <i>et al.</i> (2017)
2-Methyl-1 <i>H</i> -imidazole salt	FAMQIW	-19.4	Zhang & Zhang (2017)
		13.4	
Imidazole salt monohydrate	KIPMAA	-5.7	Gao <i>et al.</i> (2019)
2-(Pyridin-2-ylamino)pyridinium salt	FAMQOC	-174.5	Zhang & Zhang (2017)

and trifluoroacetic acid was distilled out. The obtained residue was cooled to 298 K, water (200 ml) was added slowly, and the slurry was stirred for 4 h. After filtration, the product was washed and dried under vacuum to give 9.60 g of **3**.

5.1.2. Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate (4). Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate (**3**, 350 g), potassium carbonate (332 g) and isobutyl bromide (330 g) were added to DMF (1.75 l). The reaction mixture was heated to 383±3 K and stirred for 4 h. The reaction mixture was cooled to 298 K, and water (0.50 l) was added slowly. The slurry was stirred for 2 h. After filtration, the product was washed and dried under vacuum to give 389 g of **4**. ¹H NMR (CDCl₃), 400 MHz): δ = 1.079–1.101 (*d*, 6H), 1.366–1.413 (*t*, 3H), 2.185–2.230 (*m*, 1H), 2.769 (*s*, 3H), 3.914–3.935 (*d*, 2H), 4.316–4.387 (*q*, 2H), 7.045–7.074 (*d*, 1H), 8.188–8.225 (*dd*, 1H), 8.353–8.361 (*d*, 1H).

5.1.3. Ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate (5). Ethyl 2-(3-formyl-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate (**4**, 350 g), sodium formate (123 g) and hydroxylamine hydrochloride (84 g) were successively added to formic acid (1.4 l). The reaction mixture was heated to reflux and stirred for 5 h to complete the reaction. The reaction solution was cooled to 298 K, and water (2.8 l) was slowly added. After stirring for approximately 1 h, the slurry was filtered, the product was washed with water and dried under vacuum to give 321 g of **5**. ¹H NMR (CDCl₃), 400 MHz): δ = 1.053–1.104 (*d*, 6H), 1.368–1.463 (*t*, 3H), 2.164–2.225 (*m*, 1H), 2.768 (*s*, 3H), 3.890–3.911 (*d*, 2H), 4.324–4.395 (*q*, 2H), 6.998–7.027 (*d*, 1H), 8.188–8.225 (*dd*, 1H), 8.353–8.361 (*d*, 1H).

5.1.4. 2-(3-Cyano-4-isobutoxyphenyl)-4-methyl-5-thiazole carboxylic acid (1). Ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate (**5**, 250 g) and potassium carbonate (200 g) were successively added to a mixture of MeOH (7.5 l) and water (250 ml). To complete the reaction, the solution was heated to reflux for 3 h under stirring. The clear solution was cooled, and vacuum was applied to distil out the solvent below 313 K. Water (5 l) was added to the residue.

After stirring, EtOAc (2.5 l) was added. The solution was stirred, and the layers were separated. The pH of the aqueous solution was adjusted to 2.5±0.2 by adding diluted hydrochloric acid solution at 313 K. After stirring for 1 h, the slurry was filtered, and the product was washed with water and dried under vacuum to give 215 g of **1**.

5.2. Crystallization

Febuxostat (1 g) was dissolved in ethanol (10 ml), which yielded a clear solution upon heating to 338 K. After filtration, the solution was allowed to cool to room temperature, and the subsequent crystallization resulted in febuxostat ethanol solvate.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. All H atoms were identified in difference maps. Methyl H atoms were idealized and included as rigid groups allowed to rotate but not tip (C–H = 0.98 Å), and their U_{iso} parameters were set to 1.5 U_{eq} (C) of the parent carbon atom. H atoms bonded to secondary CH₂ (C–H = 0.99 Å) or tertiary CH (C–H = 0.99 Å) carbon atoms and H atoms bonded to C atoms in aromatic rings (C–H = 0.95 Å) were positioned geometrically and refined with U_{iso} set to 1.2 U_{eq} (C) of the parent carbon atom. H atoms in OH groups were identified in difference maps, refined with a distance restraint [O–H = 0.84 (2) Å] and a free U_{iso} parameter. Two outliers ($\bar{4}74$) and ($\bar{2}, \bar{1}6, 2$) were omitted in the final cycles of refinement.

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Table 3
Experimental details.

Crystal data	
Chemical formula	C ₁₆ H ₁₆ N ₂ O ₃ S·C ₂ H ₆ O
<i>M</i> _r	362.43
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	173
<i>a</i> , <i>b</i> , <i>c</i> (Å)	4.7274 (2), 17.7820 (5), 10.7340 (4)
β (°)	98.994 (4)
<i>V</i> (Å ³)	891.23 (6)
<i>Z</i>	2
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.21
Crystal size (mm)	0.40 × 0.40 × 0.36
Data collection	
Diffractometer	Rigaku Oxford Diffraction Xcalibur, Ruby, Gemini ultra
Absorption correction	Multi-scan (<i>CrysAlis PRO</i> ; Rigaku OD, 2015)
<i>T</i> _{min} , <i>T</i> _{max}	0.760, 1.000
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	6054, 3070, 2917
<i>R</i> _{int}	0.028
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.641
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.030, 0.077, 1.04
No. of reflections	3070
No. of parameters	238
No. of restraints	3
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.26, -0.17
Absolute structure	Flack <i>x</i> determined using 1046 quotients [(<i>I</i> ^h)-(<i>I</i> ^l)]/[(<i>I</i> ^h)+(<i>I</i> ^l)] (Parsons <i>et al.</i> , 2013).
Absolute structure parameter	-0.02 (4)

Computer programs: *CrysAlis PRO* (Rigaku OD, 2015), *SHELXT* (Sheldrick, 2015a), *SHELXL2014/6* (Sheldrick, 2015b), *XP* in *SHELXTL* (Sheldrick, 2008), *Mercury* (Macrae *et al.*, 2020), *PLATON* (Spek, 2020) and *publCIF* (Westrip, 2010).

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supporting information

Acta Cryst. (2020). E76, 816-819 [https://doi.org/10.1107/S2056989020006076]

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Computing details

Data collection: *CrysAlis PRO* (Rigaku OD, 2015); cell refinement: *CrysAlis PRO* (Rigaku OD, 2015); data reduction: *CrysAlis PRO* (Rigaku OD, 2015); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: SHELXL2014/6 (Sheldrick, 2015b); molecular graphics: XP in SHELXTL (Sheldrick, 2008) and Mercury (Macrae *et al.*, 2020); software used to prepare material for publication: PLATON (Spek, 2020) and publCIF (Westrip, 2010).

2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid ethanol monosolvate

Crystal data

$C_{16}H_{16}N_2O_3S \cdot C_2H_6O$

$M_r = 362.43$

Monoclinic, $P2_1$

$a = 4.7274$ (2) Å

$b = 17.7820$ (5) Å

$c = 10.7340$ (4) Å

$\beta = 98.994$ (4)°

$V = 891.23$ (6) Å³

$Z = 2$

$F(000) = 384$

$D_x = 1.351$ Mg m⁻³

Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å

Cell parameters from 2681 reflections

$\theta = 2.3$ – 28.6 °

$\mu = 0.21$ mm⁻¹

$T = 173$ K

Prism, colourless

$0.40 \times 0.40 \times 0.36$ mm

Data collection

Rigaku Oxford Diffraction Xcalibur, Ruby,

Gemini ultra

diffractometer

Radiation source: fine-focus sealed X-ray tube,

Enhance (Mo) X-ray Source

Graphite monochromator

Detector resolution: 10.3575 pixels mm⁻¹

ω scans

Absorption correction: multi-scan

CrysAlisPro (Rigaku OD, 2015)

$T_{\min} = 0.760$, $T_{\max} = 1.000$

6054 measured reflections

3070 independent reflections

2917 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.028$

$\theta_{\max} = 27.1$ °, $\theta_{\min} = 1.9$ °

$h = -5$ → 6

$k = -17$ → 22

$l = -12$ → 13

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.030$

$wR(F^2) = 0.077$

$S = 1.04$

3070 reflections

238 parameters

3 restraints

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0439P)^2 + 0.0696P]$

where $P = (F_o^2 + 2F_c^2)/3$

$$(\Delta/\sigma)_{\max} < 0.001$$

$$\Delta\rho_{\max} = 0.26 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.17 \text{ e } \text{\AA}^{-3}$$

Absolute structure: Flack x determined using
1046 quotients $[(F^+)-(F)]/[(F^+)+(F)]$ (Parsons *et al.*, 2013).

Absolute structure parameter: -0.02 (4)

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 (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
S1	0.32087 (12)	0.17683 (3)	0.31163 (5)	0.02221 (15)
C2	0.3894 (5)	0.08540 (14)	0.3610 (2)	0.0195 (5)
N3	0.2673 (4)	0.06576 (12)	0.45794 (18)	0.0199 (4)
C4	0.1127 (5)	0.12385 (14)	0.4979 (2)	0.0210 (5)
C5	0.1165 (5)	0.18918 (14)	0.4308 (2)	0.0209 (5)
C6	0.5737 (5)	0.03525 (14)	0.3007 (2)	0.0188 (5)
C7	0.6801 (5)	0.05673 (15)	0.1922 (2)	0.0211 (5)
H7	0.6309	0.1045	0.1555	0.025*
C8	0.8571 (5)	0.00904 (14)	0.1371 (2)	0.0208 (5)
C9	0.9280 (5)	-0.06253 (15)	0.1882 (2)	0.0207 (5)
C10	0.8252 (5)	-0.08344 (15)	0.2980 (2)	0.0231 (5)
H10	0.8757	-0.1309	0.3357	0.028*
C11	0.6499 (5)	-0.03524 (14)	0.3523 (2)	0.0225 (5)
H11	0.5797	-0.0505	0.4266	0.027*
C12	-0.0406 (5)	0.11107 (16)	0.6073 (2)	0.0269 (6)
H12A	0.0985	0.1093	0.6852	0.040*
H12B	-0.1448	0.0633	0.5962	0.040*
H12C	-0.1761	0.1522	0.6125	0.040*
C13	-0.0224 (5)	0.26111 (15)	0.4499 (2)	0.0234 (5)
O14	0.0142 (5)	0.31184 (12)	0.36340 (19)	0.0339 (5)
H14	-0.062 (8)	0.3537 (16)	0.375 (4)	0.072 (13)*
O15	-0.1558 (4)	0.27251 (11)	0.53494 (18)	0.0345 (5)
C16	0.9755 (6)	0.03373 (15)	0.0278 (2)	0.0259 (6)
N17	1.0707 (5)	0.05481 (15)	-0.0569 (2)	0.0387 (6)
O18	1.0943 (4)	-0.10584 (10)	0.12590 (16)	0.0248 (4)
C19	1.1767 (5)	-0.17866 (15)	0.1797 (2)	0.0227 (5)
H19A	1.0042	-0.2076	0.1919	0.027*
H19B	1.2988	-0.1724	0.2627	0.027*
C20	1.3396 (5)	-0.22023 (14)	0.0906 (2)	0.0236 (5)
H20	1.4987	-0.1875	0.0709	0.028*
C21	1.4684 (6)	-0.29130 (17)	0.1579 (3)	0.0327 (6)
H21A	1.5817	-0.2775	0.2390	0.049*
H21B	1.5919	-0.3164	0.1054	0.049*
H21C	1.3139	-0.3254	0.1722	0.049*
C22	1.1480 (7)	-0.24066 (17)	-0.0320 (3)	0.0336 (6)

H22A	1.0040	-0.2773	-0.0148	0.050*
H22B	1.2643	-0.2625	-0.0907	0.050*
H22C	1.0519	-0.1953	-0.0694	0.050*
O23	0.7299 (4)	0.43799 (11)	0.37730 (18)	0.0347 (5)
H23	0.741 (8)	0.4681 (18)	0.437 (3)	0.053 (11)*
C24	0.4973 (6)	0.45692 (16)	0.2805 (3)	0.0347 (7)
H24A	0.5205	0.5091	0.2515	0.042*
H24B	0.3143	0.4538	0.3142	0.042*
C25	0.4914 (7)	0.40395 (19)	0.1727 (3)	0.0440 (8)
H25A	0.4835	0.3521	0.2031	0.066*
H25B	0.6647	0.4107	0.1343	0.066*
H25C	0.3222	0.4141	0.1097	0.066*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0281 (3)	0.0153 (3)	0.0243 (3)	0.0024 (3)	0.0077 (2)	0.0010 (3)
C2	0.0205 (11)	0.0154 (12)	0.0214 (11)	-0.0005 (9)	-0.0003 (10)	-0.0001 (10)
N3	0.0210 (10)	0.0168 (11)	0.0219 (10)	-0.0017 (8)	0.0028 (8)	-0.0008 (8)
C4	0.0212 (12)	0.0173 (12)	0.0234 (12)	-0.0013 (10)	-0.0002 (10)	-0.0031 (10)
C5	0.0207 (11)	0.0209 (14)	0.0211 (11)	-0.0028 (10)	0.0034 (9)	-0.0034 (10)
C6	0.0199 (11)	0.0149 (12)	0.0211 (11)	0.0003 (10)	0.0014 (9)	-0.0033 (9)
C7	0.0237 (12)	0.0146 (12)	0.0244 (12)	-0.0014 (10)	0.0018 (10)	0.0006 (10)
C8	0.0231 (12)	0.0164 (12)	0.0225 (12)	-0.0018 (10)	0.0025 (10)	-0.0008 (10)
C9	0.0233 (12)	0.0167 (12)	0.0223 (12)	-0.0004 (10)	0.0040 (10)	-0.0033 (10)
C10	0.0303 (14)	0.0151 (13)	0.0240 (12)	0.0027 (10)	0.0046 (10)	0.0029 (10)
C11	0.0259 (13)	0.0200 (13)	0.0219 (12)	0.0001 (11)	0.0045 (10)	-0.0006 (10)
C12	0.0309 (14)	0.0218 (14)	0.0296 (13)	0.0002 (11)	0.0095 (11)	-0.0001 (11)
C13	0.0255 (12)	0.0192 (13)	0.0245 (13)	-0.0024 (11)	0.0006 (11)	-0.0046 (10)
O14	0.0474 (12)	0.0196 (10)	0.0387 (11)	0.0099 (9)	0.0189 (9)	0.0045 (9)
O15	0.0518 (12)	0.0232 (10)	0.0327 (10)	0.0046 (9)	0.0191 (9)	-0.0043 (8)
C16	0.0314 (13)	0.0166 (13)	0.0305 (14)	0.0045 (11)	0.0072 (12)	-0.0009 (11)
N17	0.0512 (15)	0.0318 (15)	0.0377 (13)	0.0033 (12)	0.0210 (12)	0.0081 (12)
O18	0.0328 (9)	0.0175 (9)	0.0260 (9)	0.0062 (8)	0.0105 (8)	0.0031 (7)
C19	0.0267 (13)	0.0162 (13)	0.0259 (12)	0.0018 (10)	0.0068 (10)	0.0024 (10)
C20	0.0264 (12)	0.0172 (13)	0.0292 (13)	0.0025 (10)	0.0108 (11)	0.0018 (10)
C21	0.0333 (14)	0.0225 (14)	0.0452 (16)	0.0077 (12)	0.0146 (13)	0.0072 (13)
C22	0.0447 (16)	0.0284 (16)	0.0290 (14)	-0.0006 (13)	0.0099 (12)	-0.0043 (12)
O23	0.0465 (12)	0.0218 (10)	0.0345 (11)	0.0092 (9)	0.0025 (9)	-0.0071 (9)
C24	0.0395 (16)	0.0237 (15)	0.0416 (16)	0.0086 (13)	0.0078 (13)	-0.0036 (12)
C25	0.0536 (19)	0.0343 (18)	0.0424 (17)	0.0044 (15)	0.0020 (15)	-0.0067 (14)

Geometric parameters (Å, °)

S1—C2	1.725 (3)	O14—H14	0.84 (2)
S1—C5	1.733 (2)	C16—N17	1.139 (3)
C2—N3	1.313 (3)	O18—C19	1.446 (3)
C2—C6	1.466 (3)	C19—C20	1.511 (3)

N3—C4	1.372 (3)	C19—H19A	0.9900
C4—C5	1.369 (4)	C19—H19B	0.9900
C4—C12	1.491 (3)	C20—C22	1.520 (4)
C5—C13	1.467 (4)	C20—C21	1.534 (4)
C6—C7	1.393 (3)	C20—H20	1.0000
C6—C11	1.395 (3)	C21—H21A	0.9800
C7—C8	1.387 (3)	C21—H21B	0.9800
C7—H7	0.9500	C21—H21C	0.9800
C8—C9	1.406 (4)	C22—H22A	0.9800
C8—C16	1.444 (4)	C22—H22B	0.9800
C9—O18	1.350 (3)	C22—H22C	0.9800
C9—C10	1.394 (3)	O23—C24	1.430 (4)
C10—C11	1.383 (4)	O23—H23	0.83 (2)
C10—H10	0.9500	C24—C25	1.489 (4)
C11—H11	0.9500	C24—H24A	0.9900
C12—H12A	0.9800	C24—H24B	0.9900
C12—H12B	0.9800	C25—H25A	0.9800
C12—H12C	0.9800	C25—H25B	0.9800
C13—O15	1.205 (3)	C25—H25C	0.9800
C13—O14	1.325 (3)		
C2—S1—C5	89.55 (12)	N17—C16—C8	178.3 (3)
N3—C2—C6	123.6 (2)	C9—O18—C19	117.03 (18)
N3—C2—S1	114.17 (18)	O18—C19—C20	108.51 (19)
C6—C2—S1	122.25 (18)	O18—C19—H19A	110.0
C2—N3—C4	111.7 (2)	C20—C19—H19A	110.0
C5—C4—N3	115.0 (2)	O18—C19—H19B	110.0
C5—C4—C12	126.3 (2)	C20—C19—H19B	110.0
N3—C4—C12	118.7 (2)	H19A—C19—H19B	108.4
C4—C5—C13	128.6 (2)	C19—C20—C22	111.8 (2)
C4—C5—S1	109.62 (19)	C19—C20—C21	108.0 (2)
C13—C5—S1	121.80 (19)	C22—C20—C21	110.5 (2)
C7—C6—C11	118.3 (2)	C19—C20—H20	108.9
C7—C6—C2	121.3 (2)	C22—C20—H20	108.9
C11—C6—C2	120.4 (2)	C21—C20—H20	108.9
C8—C7—C6	120.7 (2)	C20—C21—H21A	109.5
C8—C7—H7	119.7	C20—C21—H21B	109.5
C6—C7—H7	119.7	H21A—C21—H21B	109.5
C7—C8—C9	120.6 (2)	C20—C21—H21C	109.5
C7—C8—C16	119.8 (2)	H21A—C21—H21C	109.5
C9—C8—C16	119.6 (2)	H21B—C21—H21C	109.5
O18—C9—C10	125.0 (2)	C20—C22—H22A	109.5
O18—C9—C8	116.4 (2)	C20—C22—H22B	109.5
C10—C9—C8	118.6 (2)	H22A—C22—H22B	109.5
C11—C10—C9	120.1 (2)	C20—C22—H22C	109.5
C11—C10—H10	119.9	H22A—C22—H22C	109.5
C9—C10—H10	119.9	H22B—C22—H22C	109.5
C10—C11—C6	121.6 (2)	C24—O23—H23	111 (3)

C10—C11—H11	119.2	O23—C24—C25	109.5 (2)
C6—C11—H11	119.2	O23—C24—H24A	109.8
C4—C12—H12A	109.5	C25—C24—H24A	109.8
C4—C12—H12B	109.5	O23—C24—H24B	109.8
H12A—C12—H12B	109.5	C25—C24—H24B	109.8
C4—C12—H12C	109.5	H24A—C24—H24B	108.2
H12A—C12—H12C	109.5	C24—C25—H25A	109.5
H12B—C12—H12C	109.5	C24—C25—H25B	109.5
O15—C13—O14	123.9 (2)	H25A—C25—H25B	109.5
O15—C13—C5	123.5 (2)	C24—C25—H25C	109.5
O14—C13—C5	112.7 (2)	H25A—C25—H25C	109.5
C13—O14—H14	113 (3)	H25B—C25—H25C	109.5

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
O23—H23 \cdots N3 ⁱ	0.83 (2)	2.07 (2)	2.878 (3)	162 (4)
O14—H14 \cdots O23 ⁱⁱ	0.84 (2)	1.80 (2)	2.631 (3)	170 (4)

Symmetry codes: (i) $-x+1, y+1/2, -z+1$; (ii) $x-1, y, z$.