

Crystal structure of tebipenem pivoxil

Chao Tang,^a Li Cai,^{b*} Shuai Liu,^a Zhiwei Zheng,^a Gen Li,^a Jianli Chen^a and Qiang Sui^{a‡}^aChina State Institute of Pharmaceutical Industry, 285 Gebaini Rd, Shanghai 201203, People's Republic of China, and^bUniversity of South Carolina Lancaster, 476 Hubbard Drive, Lancaster, SC 29720, USA. *Correspondence e-mail: CAILI@mailbox.sc.edu

Received 29 June 2018

Accepted 25 July 2018

Edited by J. Ellena, Universidade de São Paulo, Brazil

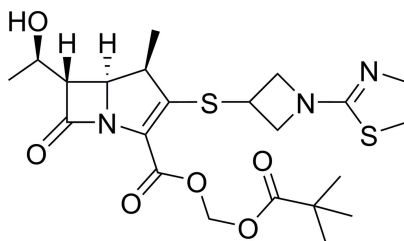
‡ Additional correspondence author, e-mail: Chem_sq@163.com.

Keywords: crystal structure; carbapenem; antibiotics; tebipenem; prodrug; hydrogen bonding.**CCDC reference:** 1816052**Supporting information:** this article has supporting information at journals.iucr.org/e

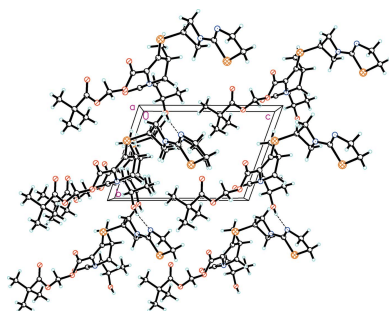
The molecular structure of the first orally active carbapenem antibacterial agent, tebipenem pivoxil (systematic name: (2,2-dimethylpropanoyloxy)methyl (4*R*,5*S*,6*S*)-3-[[1-(4,5-dihydro-1,3-thiazol-2-yl)azetidin-3-yl]sulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate), C₂₂H₃₁N₃O₆S₂, has been determined and the configurations of the four chiral centers validated. The title compound crystallizes in the triclinic space group *P*1 with one molecule in the unit cell. Three out of the four rings adopt planar conformations while the thiazolanyl ring adopts an enveloped conformation. In the crystal, O—H···N hydrogen bonds link the molecules into chains along [1 $\bar{1}$ 0].

1. Chemical context

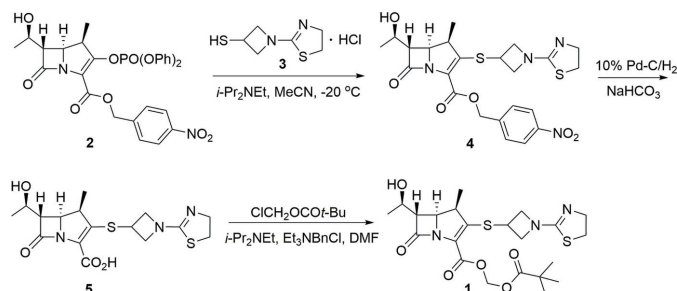
Carbapenem antibiotics, like all β -lactam antibacterials that bind to and inhibit the peptidoglycan cross-linking transpeptidases, have attracted increasing attention recently because of their broader spectrum activities and stronger bactericidal actions compared to cephalosporins and penicillins. Since the first carbapenem structure thienamycin, a natural product derived from *Streptomyces cattleya*, was isolated in 1976 (Johnston *et al.*, 1978), a handful of subsequent parenteral carbapenem agents, such as imipenem, panipenem, meropenem, biapenem, have been developed based on this parent compound and used clinically for the treatment of severe bacterial infections.



Tebipenem pivoxil (see scheme), as a novel oral carbapenem agent, was approved by the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) on Apr 22, 2009. It was developed and marketed as Orapenem[®] by Meiji Seika in Japan (as of 05/16/2016, the only approved country/area for its usage was Japan for treating children, as these oral antibiotics are often better tolerated than infusions) (Kijima *et al.*, 2009). It is a prodrug that is quickly hydrolysed to the active antimicrobial agent LJC11,036 (**5**, reaction scheme) because the absorption rate of the pivaloyloxymethyl ester is higher than that of other prodrug-type β -lactam antibiotics (Kato *et al.*, 2010). The active metabolite **5** shows potent and well-



balanced antibacterial activity and also shows higher stability to human renal dehydropeptidase-I than meropenem (Isoda *et al.*, 2006a; Kobayashi *et al.*, 2005). Research has also revealed that the tebipenem acyl- β -lactamase covalent complex remains very stable for longer than 90 min, partly explaining its resistance towards hydrolysis (Papp-Wallace *et al.*, 2011).



Tebipenem pivoxil has a complex structure with four chiral centers and a 1-(1,3-thiazolin-2-yl)azetidion-3-ylthio side chain at the C-2 position. We hope the structural elucidation will facilitate future mechanistic studies of this molecule and of its interactions with enzymes that are responsible for bacterial resistance.

2. Structural commentary

Tebipenem pivoxil (Fig. 1) crystallizes in the triclinic space group *P1* with one molecule in the unit cell. The present crystal structure determination allowed the configurations of the four chiral centers to be validated as: C2*S*, C3*S*, C4*R*, C7*R*. Rings I (N1/C1–C3), II (N1/C3–C6) and III (N2/C11–C13) adopt planar conformations (with r.m.s. deviations of 0.0251, 0.0838, and 0.0967 Å, respectively) while ring IV (N3/S2/C14–C16) adopts an envelope conformation with atom C16 as the flap. The dihedral angles between rings I and II, II and III, and III and IV are 46.7 (2), 85.7 (2), and 11.9 (4)°, respectively. Atoms C9 (methyl) and C7 are located above and below the planes of rings I and II because of steric hindrance.

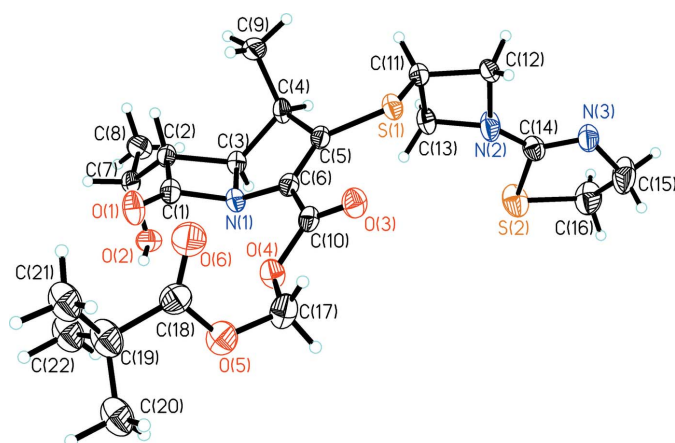


Figure 1
The molecular structure of the title compound, showing the atom labelling and 30% probability displacement ellipsoids.

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

<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>
O2—H2A···N3 ⁱ	0.82	2.01	2.816 (6)	169
C11—H11A···O2 ⁱⁱ	0.98	2.43	3.366 (6)	160

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

3. Supramolecular features

In the crystal, O—H···N hydrogen bonds (Table 1) link the molecules into chains along [1 $\bar{1}$ 0]. C—H···O hydrogen bonds are also observed. The packing viewed along the *a* axis is shown in Fig. 2.

4. Database survey

The tebipenem pivoxil we obtained was well characterized spectroscopically and carefully compared with reference values (Isoda *et al.*, 2006a). To the best of our knowledge, including a search of the Cambridge Structural Database (CSD Version 5.39; Groom *et al.*, 2016), no single crystal structure determination has previously been reported for this drug.

5. Synthesis and crystallization

As shown in the reaction scheme (also see Supporting Information), 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine hydrochloride (3) was first synthesized according to a method previously reported (Isoda *et al.*, 2006b) with minor optimizations. The side chain 3 was then coupled with the commercially available carbapenem core (2), followed by hydrogenation/deprotection and S_N2 esterification to afford the desired tebipenem pivoxil 1 (Isoda *et al.*, 2006a,b).

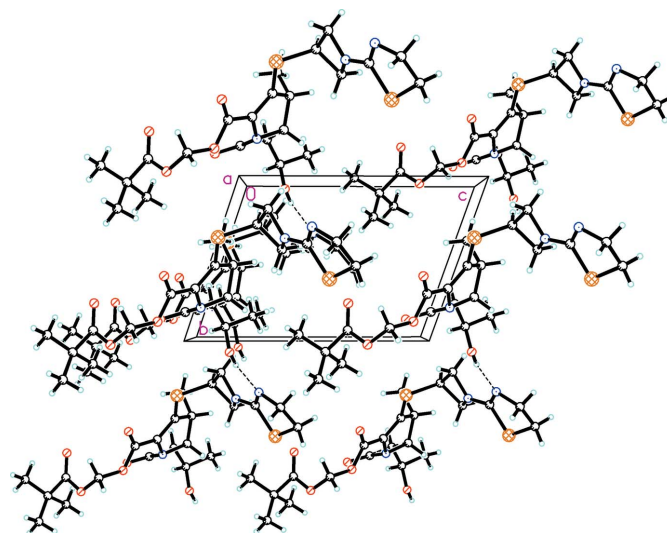


Figure 2
The crystal packing viewed along the crystallographic *a* axis showing the O—H···N hydrogen bonds (Table 1) as dashed lines.

Table 2
Experimental details.

Crystal data	
Chemical formula	C ₂₂ H ₃₁ N ₃ O ₆ S ₂
<i>M_r</i>	497.62
Crystal system, space group	Triclinic, <i>P</i> 1
Temperature (K)	296
<i>a</i> , <i>b</i> , <i>c</i> (Å)	7.7292 (10), 7.9892 (9), 11.2035 (13)
α , β , γ (°)	108.300 (7), 92.553 (7), 101.499 (8)
<i>V</i> (Å ³)	639.36 (14)
<i>Z</i>	1
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	2.23
Crystal size (mm)	0.17 × 0.12 × 0.10
Data collection	
Diffractometer	Bruker APEXII CCD
Absorption correction	Multi-scan (<i>SADABS</i> ; Bruker, 2014)
<i>T_{min}</i> , <i>T_{max}</i>	0.703, 0.808
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	3454, 2483, 2389
<i>R_{int}</i> ($\sin \theta/\lambda$) _{max} (Å ⁻¹)	0.019 0.592
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.042, 0.115, 1.04
No. of reflections	2483
No. of parameters	298
No. of restraints	3
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.33, -0.21
Absolute structure	Flack <i>x</i> determined using 531 quotients [(<i>I</i> ⁺) - (<i>I</i> ⁻)] / [(<i>I</i> ⁺) + (<i>I</i> ⁻)] (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	0.140 (12)

Computer programs: *APEX2* and *SAINT* (Bruker, 2014), *SHELXS2018/3* and *SHELXTL* (Sheldrick, 2008) and *SHELXL2018/3* (Sheldrick, 2015).

of using column chromatography, we successfully obtained pure tebipenem pivoxil on a relatively large scale through recrystallization from ethyl acetate, yielding colourless block-shaped crystals. The HPLC spectrum of the final product showed a single peak with less than 0.1% of impurities. $[\alpha]_{\text{D}}^{25} = +9.6^\circ$, m.p. = 407–409 K. Elemental analysis calculated for C₂₂H₃₁N₃O₆S₂: C, 53.10; H, 6.28; N, 8.44; S, 12.89; Found: C, 53.13; H, 6.32; N, 8.45; S, 12.94. HRESI-MS calculated for C₂₂H₃₂N₃O₆S₂ ([*M* + *H*)⁺): 498.1727, found: 498.1867. The

structure has also been characterized with ¹H NMR, ¹³C NMR, and IR spectroscopy. ¹H NMR, ¹³C NMR, and IR spectra of tebipenem pivoxil **1** are included in the supporting information and compared with reference values, including the assignment of NMR chemical shifts and IR absorption bands (Isoda *et al.*, 2006a).

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. In the refinement, all H atoms were positioned geometrically and refined as riding: C–H = 0.96–0.98 Å with *U*_{iso}(H) = 1.2*U*_{eq}(C) or 1.5*U*_{eq}(C-methyl).

Acknowledgements

The authors thank Dr Jialiang Zhong at the China State Institute of Pharmaceutical Industry for helpful discussion.

References

- Bruker (2014). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison Wisconsin, USA.
- Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* **B72**, 171–179.
- Isoda, T., Ushirogouchi, H., Satoh, K., Takasaki, T., Yamamura, I., Sato, C., Mihira, A., Abe, T., Tamai, S., Yamamoto, S., Kumagai, T. & Nagao, Y. (2006a). *J. Antibiot.* **59**, 241–247.
- Isoda, T., Yamamura, I., Tamai, S., Kumagai, T. & Nagao, Y. (2006b). *Chem. Pharm. Bull.* **54**, 1408–1411.
- Johnston, D. B. R., Schmitt, S. M., Bouffard, F. A. & Christensen, B. G. (1978). *J. Am. Chem. Soc.* **100**, 313–315.
- Kato, K., Shirasaka, Y., Kuraoka, E., Kikuchi, A., Iguchi, M., Suzuki, H., Shibasaki, S., Kurosawa, T. & Tamai, I. (2010). *Mol. Pharm.* **7**, 1747–1756.
- Kijima, K., Morita, J., Suzuki, K., Aoki, M., Kato, K., Hayashi, H., Shibasaki, S. & Kurosawa, T. (2009). *Jpn. J. Antibiot.* **62**, 214–240.
- Kobayashi, R., Konomi, M., Hasegawa, K., Morozumi, M., Sunakawa, K. & Ubukata, K. (2005). *Antimicrob. Agents Chemother.* **49**, 889–894.
- Papp-Wallace, K. M., Endimiani, A., Taracila, M. A. & Bonomo, R. A. (2011). *Antimicrob. Agents Chemother.* **55**, 4943–4960.
- Parsons, S., Flack, H. D. & Wagner, T. (2013). *Acta Cryst.* **B69**, 249–259.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Sheldrick, G. M. (2015). *Acta Cryst.* **C71**, 3–8.

supporting information

Acta Cryst. (2018). E74, 1215-1217 [https://doi.org/10.1107/S2056989018010770]

Crystal structure of tebipenem pivoxil

Chao Tang, Li Cai, Shuai Liu, Zhiwei Zheng, Gen Li, Jianli Chen and Qiang Sui

Computing details

Data collection: *APEX2* (Bruker, 2014); cell refinement: *SAINTE* (Bruker, 2014); data reduction: *SAINTE* (Bruker, 2014); program(s) used to solve structure: *SHELXS2018/3* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2018/3* (Sheldrick, 2015); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

\ (2,2-Dimethylpropanoyloxy)methyl (4*R*,5*S*,6*S*)-3-[[1-(4,5-dihydro-1,3-thiazol-2-yl)azetidin-3-yl]sulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

Crystal data

$C_{22}H_{31}N_3O_6S_2$

$M_r = 497.62$

Triclinic, *P1*

$a = 7.7292$ (10) Å

$b = 7.9892$ (9) Å

$c = 11.2035$ (13) Å

$\alpha = 108.300$ (7)°

$\beta = 92.553$ (7)°

$\gamma = 101.499$ (8)°

$V = 639.36$ (14) Å³

$Z = 1$

$F(000) = 264$

$D_x = 1.292$ Mg m⁻³

Cu *K* α radiation, $\lambda = 1.54178$ Å

Cell parameters from 2598 reflections

$\theta = 4.2\text{--}65.6^\circ$

$\mu = 2.23$ mm⁻¹

$T = 296$ K

Block, colorless

$0.17 \times 0.12 \times 0.10$ mm

Data collection

Bruker APEXII CCD
diffractometer

φ and ω scans

Absorption correction: multi-scan
(SADABS; Bruker, 2014)

$T_{\min} = 0.703$, $T_{\max} = 0.808$

3454 measured reflections

2483 independent reflections

2389 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.019$

$\theta_{\max} = 65.9^\circ$, $\theta_{\min} = 4.2^\circ$

$h = -7 \rightarrow 9$

$k = -9 \rightarrow 9$

$l = -13 \rightarrow 12$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.042$

$wR(F^2) = 0.115$

$S = 1.04$

2483 reflections

298 parameters

3 restraints

Hydrogen site location: inferred from
neighbouring sites

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0826P)^2 + 0.0878P]$

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

$(\Delta/\sigma)_{\max} = 0.015$

$\Delta\rho_{\max} = 0.33$ e Å⁻³

$\Delta\rho_{\min} = -0.21$ e Å⁻³

Absolute structure: Flack x determined using

531 quotients $[(I^-)-(I)]/[(I^+)+(I)]$ (Parsons *et al.*,
2013)

Absolute structure parameter: 0.140 (12)

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)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
S1	0.33764 (12)	0.37913 (11)	0.01567 (9)	0.0531 (3)
S2	0.6657 (3)	0.6243 (2)	0.50488 (14)	0.0889 (5)
O1	-0.0384 (5)	0.8665 (5)	-0.1269 (3)	0.0695 (9)
O2	-0.0964 (4)	1.0714 (4)	0.1973 (3)	0.0601 (8)
H2A	-0.139807	1.152553	0.240566	0.090*
O3	0.4728 (4)	0.6066 (5)	-0.1353 (3)	0.0626 (8)
O4	0.3985 (4)	0.8733 (4)	-0.1081 (3)	0.0589 (8)
O5	0.4493 (5)	1.0081 (6)	-0.2577 (4)	0.0781 (11)
O6	0.2673 (7)	0.7659 (6)	-0.3881 (6)	0.1060 (16)
N1	0.1226 (4)	0.7928 (4)	0.0285 (3)	0.0447 (7)
N2	0.5213 (7)	0.3896 (6)	0.2801 (4)	0.0737 (12)
N3	0.7629 (6)	0.3330 (6)	0.3725 (4)	0.0679 (11)
C1	-0.0250 (6)	0.8214 (6)	-0.0352 (4)	0.0486 (9)
C2	-0.1483 (5)	0.7724 (5)	0.0574 (4)	0.0455 (8)
H2B	-0.238265	0.661201	0.014328	0.055*
C3	0.0144 (5)	0.7296 (5)	0.1179 (4)	0.0442 (8)
H3B	0.050788	0.808606	0.205772	0.053*
C4	0.0397 (6)	0.5350 (6)	0.0968 (4)	0.0498 (9)
H4A	0.058878	0.516830	0.178516	0.060*
C5	0.2114 (5)	0.5408 (5)	0.0341 (4)	0.0437 (8)
C6	0.2416 (5)	0.6785 (5)	-0.0123 (4)	0.0436 (8)
C7	-0.2320 (5)	0.9153 (5)	0.1391 (4)	0.0483 (9)
H7A	-0.316888	0.944012	0.085209	0.058*
C8	-0.3299 (7)	0.8508 (7)	0.2361 (5)	0.0651 (12)
H8A	-0.421147	0.744567	0.193571	0.098*
H8B	-0.247930	0.822482	0.289674	0.098*
H8C	-0.382809	0.944259	0.286473	0.098*
C9	-0.1081 (6)	0.3822 (7)	0.0108 (7)	0.0762 (16)
H9A	-0.215396	0.379378	0.050815	0.114*
H9B	-0.127753	0.402322	-0.068287	0.114*
H9C	-0.073970	0.268830	-0.004165	0.114*
C10	0.3811 (5)	0.7099 (6)	-0.0923 (4)	0.0472 (9)
C11	0.2935 (6)	0.3012 (6)	0.1482 (5)	0.0535 (10)
H11A	0.175564	0.222769	0.139734	0.064*
C12	0.4501 (6)	0.2200 (5)	0.1758 (5)	0.0532 (10)
H12A	0.415244	0.115292	0.202918	0.064*
H12B	0.525236	0.196247	0.108146	0.064*
C13	0.3520 (6)	0.4482 (6)	0.2791 (5)	0.0581 (11)
H13A	0.364717	0.570857	0.277752	0.070*

H13B	0.280849	0.428426	0.344663	0.070*
C14	0.6465 (6)	0.4232 (6)	0.3738 (4)	0.0559 (11)
C15	0.8971 (11)	0.4207 (12)	0.4850 (8)	0.116 (3)
H15A	1.004355	0.482093	0.461013	0.140*
H15B	0.927124	0.329086	0.516839	0.140*
C16	0.8293 (11)	0.5528 (11)	0.5860 (6)	0.098 (2)
H16A	0.924735	0.655012	0.632517	0.118*
H16B	0.775573	0.496738	0.644719	0.118*
C17	0.5186 (7)	0.9092 (9)	-0.1956 (6)	0.0739 (14)
H17A	0.634318	0.976545	-0.150543	0.089*
H17B	0.532612	0.796482	-0.255647	0.089*
C18	0.3224 (8)	0.9266 (8)	-0.3535 (5)	0.0724 (14)
C19	0.2625 (11)	1.0577 (9)	-0.4111 (5)	0.0854 (18)
C20	0.406 (2)	1.2163 (17)	-0.4024 (14)	0.181 (6)
H20A	0.455241	1.276802	-0.315584	0.271*
H20B	0.497695	1.176572	-0.451723	0.271*
H20C	0.358495	1.298285	-0.434103	0.271*
C21	0.179 (2)	0.9556 (19)	-0.5419 (9)	0.183 (6)
H21A	0.087040	0.855032	-0.541445	0.274*
H21B	0.127395	1.033571	-0.575774	0.274*
H21C	0.266596	0.911858	-0.593394	0.274*
C22	0.1304 (18)	1.1339 (17)	-0.3284 (9)	0.142 (4)
H22A	0.188241	1.199331	-0.244299	0.213*
H22B	0.082558	1.214142	-0.361897	0.213*
H22C	0.035952	1.036984	-0.326218	0.213*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0556 (6)	0.0528 (5)	0.0564 (6)	0.0265 (4)	0.0067 (4)	0.0168 (4)
S2	0.1153 (13)	0.0862 (10)	0.0592 (7)	0.0530 (9)	0.0044 (7)	-0.0025 (7)
O1	0.078 (2)	0.096 (3)	0.0542 (19)	0.0412 (19)	0.0077 (16)	0.0382 (18)
O2	0.0553 (17)	0.0497 (16)	0.070 (2)	0.0134 (14)	0.0171 (15)	0.0107 (15)
O3	0.0572 (18)	0.0701 (19)	0.067 (2)	0.0282 (17)	0.0193 (15)	0.0220 (16)
O4	0.0610 (18)	0.0706 (18)	0.0592 (18)	0.0253 (15)	0.0183 (14)	0.0332 (16)
O5	0.081 (2)	0.102 (3)	0.0598 (19)	0.014 (2)	0.0054 (17)	0.042 (2)
O6	0.099 (3)	0.077 (3)	0.126 (4)	0.020 (2)	-0.015 (3)	0.014 (3)
N1	0.0461 (17)	0.0475 (17)	0.0448 (17)	0.0201 (14)	0.0055 (14)	0.0155 (14)
N2	0.072 (3)	0.076 (3)	0.068 (3)	0.045 (2)	-0.005 (2)	0.002 (2)
N3	0.064 (2)	0.065 (2)	0.064 (2)	0.029 (2)	-0.0105 (19)	0.001 (2)
C1	0.050 (2)	0.052 (2)	0.041 (2)	0.0208 (18)	0.0003 (16)	0.0081 (18)
C2	0.0405 (19)	0.048 (2)	0.046 (2)	0.0151 (16)	-0.0009 (16)	0.0099 (17)
C3	0.043 (2)	0.052 (2)	0.0400 (18)	0.0173 (16)	0.0043 (15)	0.0141 (17)
C4	0.044 (2)	0.058 (2)	0.058 (2)	0.0244 (18)	0.0084 (17)	0.026 (2)
C5	0.0399 (18)	0.0476 (19)	0.0424 (19)	0.0142 (16)	-0.0011 (15)	0.0112 (17)
C6	0.0399 (19)	0.047 (2)	0.0416 (18)	0.0131 (16)	0.0002 (14)	0.0097 (16)
C7	0.0414 (19)	0.048 (2)	0.058 (2)	0.0179 (17)	0.0050 (17)	0.0158 (18)
C8	0.062 (3)	0.061 (3)	0.079 (3)	0.019 (2)	0.024 (2)	0.026 (2)

C9	0.045 (2)	0.053 (3)	0.129 (5)	0.008 (2)	0.004 (3)	0.031 (3)
C10	0.0422 (19)	0.057 (2)	0.043 (2)	0.0152 (19)	-0.0019 (16)	0.0155 (18)
C11	0.045 (2)	0.051 (2)	0.070 (3)	0.0151 (18)	0.0032 (19)	0.026 (2)
C12	0.057 (2)	0.043 (2)	0.062 (2)	0.0210 (18)	0.001 (2)	0.0162 (18)
C13	0.059 (3)	0.066 (3)	0.063 (3)	0.035 (2)	0.016 (2)	0.026 (2)
C14	0.063 (3)	0.057 (2)	0.049 (2)	0.025 (2)	0.008 (2)	0.013 (2)
C15	0.098 (5)	0.119 (6)	0.102 (5)	0.055 (5)	-0.043 (5)	-0.016 (5)
C16	0.101 (5)	0.115 (5)	0.067 (4)	0.036 (4)	-0.014 (3)	0.010 (4)
C17	0.056 (3)	0.113 (4)	0.070 (3)	0.024 (3)	0.019 (2)	0.051 (3)
C18	0.069 (3)	0.072 (3)	0.069 (3)	0.012 (3)	0.008 (3)	0.016 (3)
C19	0.128 (5)	0.087 (4)	0.048 (3)	0.037 (4)	0.001 (3)	0.025 (3)
C20	0.247 (16)	0.137 (9)	0.167 (11)	0.007 (9)	-0.005 (11)	0.089 (8)
C21	0.267 (18)	0.196 (12)	0.070 (5)	0.079 (12)	-0.037 (7)	0.014 (6)
C22	0.190 (11)	0.185 (10)	0.095 (6)	0.122 (9)	0.017 (6)	0.057 (6)

Geometric parameters (Å, °)

S1—C5	1.737 (4)	C8—H8A	0.9600
S1—C11	1.802 (4)	C8—H8B	0.9600
S2—C14	1.778 (5)	C8—H8C	0.9600
S2—C16	1.807 (7)	C9—H9A	0.9600
O1—C1	1.197 (5)	C9—H9B	0.9600
O2—C7	1.409 (5)	C9—H9C	0.9600
O2—H2A	0.8200	C11—C13	1.544 (7)
O3—C10	1.196 (5)	C11—C12	1.546 (6)
O4—C10	1.354 (5)	C11—H11A	0.9800
O4—C17	1.433 (6)	C12—H12A	0.9700
O5—C18	1.323 (7)	C12—H12B	0.9700
O5—C17	1.370 (7)	C13—H13A	0.9700
O6—C18	1.198 (7)	C13—H13B	0.9700
N1—C1	1.413 (5)	C15—C16	1.480 (11)
N1—C6	1.414 (6)	C15—H15A	0.9700
N1—C3	1.477 (5)	C15—H15B	0.9700
N2—C14	1.319 (6)	C16—H16A	0.9700
N2—C12	1.468 (6)	C16—H16B	0.9700
N2—C13	1.476 (6)	C17—H17A	0.9700
N3—C14	1.258 (6)	C17—H17B	0.9700
N3—C15	1.481 (7)	C18—C19	1.523 (8)
C1—C2	1.527 (6)	C19—C21	1.479 (10)
C2—C7	1.500 (6)	C19—C20	1.483 (15)
C2—C3	1.549 (5)	C19—C22	1.499 (13)
C2—H2B	0.9800	C20—H20A	0.9600
C3—C4	1.551 (6)	C20—H20B	0.9600
C3—H3B	0.9800	C20—H20C	0.9600
C4—C9	1.527 (7)	C21—H21A	0.9600
C4—C5	1.528 (6)	C21—H21B	0.9600
C4—H4A	0.9800	C21—H21C	0.9600
C5—C6	1.342 (6)	C22—H22A	0.9600

C6—C10	1.466 (6)	C22—H22B	0.9600
C7—C8	1.512 (6)	C22—H22C	0.9600
C7—H7A	0.9800		
C5—S1—C11	102.76 (19)	C13—C11—H11A	114.7
C14—S2—C16	88.8 (3)	C12—C11—H11A	114.7
C7—O2—H2A	109.5	S1—C11—H11A	114.7
C10—O4—C17	116.1 (4)	N2—C12—C11	88.2 (3)
C18—O5—C17	120.2 (5)	N2—C12—H12A	114.0
C1—N1—C6	132.4 (3)	C11—C12—H12A	114.0
C1—N1—C3	93.1 (3)	N2—C12—H12B	114.0
C6—N1—C3	108.6 (3)	C11—C12—H12B	114.0
C14—N2—C12	128.7 (4)	H12A—C12—H12B	111.2
C14—N2—C13	130.5 (5)	N2—C13—C11	88.0 (4)
C12—N2—C13	92.8 (4)	N2—C13—H13A	114.0
C14—N3—C15	111.1 (5)	C11—C13—H13A	114.0
O1—C1—N1	131.4 (4)	N2—C13—H13B	114.0
O1—C1—C2	136.6 (4)	C11—C13—H13B	114.0
N1—C1—C2	91.9 (3)	H13A—C13—H13B	111.2
C7—C2—C1	118.6 (3)	N3—C14—N2	124.9 (5)
C7—C2—C3	117.9 (3)	N3—C14—S2	117.5 (4)
C1—C2—C3	86.1 (3)	N2—C14—S2	117.3 (4)
C7—C2—H2B	110.7	N3—C15—C16	111.0 (6)
C1—C2—H2B	110.7	N3—C15—H15A	109.4
C3—C2—H2B	110.7	C16—C15—H15A	109.4
N1—C3—C2	88.6 (3)	N3—C15—H15B	109.4
N1—C3—C4	104.6 (3)	C16—C15—H15B	109.4
C2—C3—C4	123.7 (3)	H15A—C15—H15B	108.0
N1—C3—H3B	112.2	C15—C16—S2	105.3 (5)
C2—C3—H3B	112.2	C15—C16—H16A	110.7
C4—C3—H3B	112.2	S2—C16—H16A	110.7
C9—C4—C5	109.9 (4)	C15—C16—H16B	110.7
C9—C4—C3	115.8 (4)	S2—C16—H16B	110.7
C5—C4—C3	100.8 (3)	H16A—C16—H16B	108.8
C9—C4—H4A	110.0	O5—C17—O4	108.0 (4)
C5—C4—H4A	110.0	O5—C17—H17A	110.1
C3—C4—H4A	110.0	O4—C17—H17A	110.1
C6—C5—C4	110.6 (4)	O5—C17—H17B	110.1
C6—C5—S1	125.5 (3)	O4—C17—H17B	110.1
C4—C5—S1	123.7 (3)	H17A—C17—H17B	108.4
C5—C6—N1	110.9 (3)	O6—C18—O5	120.9 (6)
C5—C6—C10	125.1 (4)	O6—C18—C19	126.3 (6)
N1—C6—C10	124.0 (3)	O5—C18—C19	112.8 (5)
O2—C7—C2	107.8 (3)	C21—C19—C20	113.4 (9)
O2—C7—C8	111.5 (4)	C21—C19—C22	111.2 (10)
C2—C7—C8	111.3 (4)	C20—C19—C22	105.0 (9)
O2—C7—H7A	108.7	C21—C19—C18	108.6 (7)
C2—C7—H7A	108.7	C20—C19—C18	113.3 (8)

C8—C7—H7A	108.7	C22—C19—C18	105.0 (6)
C7—C8—H8A	109.5	C19—C20—H20A	109.5
C7—C8—H8B	109.5	C19—C20—H20B	109.5
H8A—C8—H8B	109.5	H20A—C20—H20B	109.5
C7—C8—H8C	109.5	C19—C20—H20C	109.5
H8A—C8—H8C	109.5	H20A—C20—H20C	109.5
H8B—C8—H8C	109.5	H20B—C20—H20C	109.5
C4—C9—H9A	109.5	C19—C21—H21A	109.5
C4—C9—H9B	109.5	C19—C21—H21B	109.5
H9A—C9—H9B	109.5	H21A—C21—H21B	109.5
C4—C9—H9C	109.5	C19—C21—H21C	109.5
H9A—C9—H9C	109.5	H21A—C21—H21C	109.5
H9B—C9—H9C	109.5	H21B—C21—H21C	109.5
O3—C10—O4	123.8 (4)	C19—C22—H22A	109.5
O3—C10—C6	124.3 (4)	C19—C22—H22B	109.5
O4—C10—C6	111.9 (4)	H22A—C22—H22B	109.5
C13—C11—C12	87.3 (3)	C19—C22—H22C	109.5
C13—C11—S1	114.7 (3)	H22A—C22—H22C	109.5
C12—C11—S1	107.7 (3)	H22B—C22—H22C	109.5
C6—N1—C1—O1	-56.9 (7)	C17—O4—C10—O3	8.5 (6)
C3—N1—C1—O1	-175.8 (5)	C17—O4—C10—C6	-173.7 (4)
C6—N1—C1—C2	122.9 (4)	C5—C6—C10—O3	7.5 (6)
C3—N1—C1—C2	4.0 (3)	N1—C6—C10—O3	-173.8 (4)
O1—C1—C2—C7	-64.2 (7)	C5—C6—C10—O4	-170.2 (4)
N1—C1—C2—C7	116.0 (4)	N1—C6—C10—O4	8.4 (5)
O1—C1—C2—C3	176.0 (6)	C5—S1—C11—C13	-61.7 (3)
N1—C1—C2—C3	-3.8 (3)	C5—S1—C11—C12	-156.9 (3)
C1—N1—C3—C2	-3.9 (3)	C14—N2—C12—C11	165.7 (6)
C6—N1—C3—C2	-140.9 (3)	C13—N2—C12—C11	15.0 (4)
C1—N1—C3—C4	120.6 (3)	C13—C11—C12—N2	-14.4 (4)
C6—N1—C3—C4	-16.3 (4)	S1—C11—C12—N2	100.7 (4)
C7—C2—C3—N1	-116.8 (4)	C14—N2—C13—C11	-164.9 (6)
C1—C2—C3—N1	3.7 (3)	C12—N2—C13—C11	-15.1 (4)
C7—C2—C3—C4	136.5 (4)	C12—C11—C13—N2	14.3 (4)
C1—C2—C3—C4	-103.1 (4)	S1—C11—C13—N2	-93.9 (4)
N1—C3—C4—C9	-98.4 (5)	C15—N3—C14—N2	172.4 (7)
C2—C3—C4—C9	-0.1 (6)	C15—N3—C14—S2	-0.9 (7)
N1—C3—C4—C5	20.2 (4)	C12—N2—C14—N3	21.4 (9)
C2—C3—C4—C5	118.5 (4)	C13—N2—C14—N3	161.4 (5)
C9—C4—C5—C6	104.1 (4)	C12—N2—C14—S2	-165.3 (4)
C3—C4—C5—C6	-18.6 (4)	C13—N2—C14—S2	-25.3 (8)
C9—C4—C5—S1	-71.2 (5)	C16—S2—C14—N3	-12.7 (5)
C3—C4—C5—S1	166.1 (3)	C16—S2—C14—N2	173.4 (5)
C11—S1—C5—C6	156.3 (3)	C14—N3—C15—C16	18.3 (10)
C11—S1—C5—C4	-29.1 (4)	N3—C15—C16—S2	-26.1 (10)
C4—C5—C6—N1	9.5 (4)	C14—S2—C16—C15	21.0 (7)
S1—C5—C6—N1	-175.3 (3)	C18—O5—C17—O4	-80.2 (6)

C4—C5—C6—C10	-171.7 (4)	C10—O4—C17—O5	143.8 (4)
S1—C5—C6—C10	3.5 (5)	C17—O5—C18—O6	-0.7 (9)
C1—N1—C6—C5	-108.0 (4)	C17—O5—C18—C19	-179.7 (5)
C3—N1—C6—C5	4.8 (4)	O6—C18—C19—C21	-21.0 (12)
C1—N1—C6—C10	73.2 (5)	O5—C18—C19—C21	158.0 (9)
C3—N1—C6—C10	-174.1 (3)	O6—C18—C19—C20	-148.0 (9)
C1—C2—C7—O2	-50.0 (5)	O5—C18—C19—C20	31.0 (10)
C3—C2—C7—O2	51.5 (5)	O6—C18—C19—C22	98.0 (9)
C1—C2—C7—C8	-172.6 (4)	O5—C18—C19—C22	-83.0 (8)
C3—C2—C7—C8	-71.1 (5)		

Hydrogen-bond geometry (Å, °)

<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>
O2—H2 <i>A</i> ...N3 ⁱ	0.82	2.01	2.816 (6)	169
C11—H11 <i>A</i> ...O2 ⁱⁱ	0.98	2.43	3.366 (6)	160

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