Crystal structures of anhydrous and hydrated ceftibuten

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Ceftibuten, C_{15}H_{14}N_{4}O_{6}S_{2}, with the systematic name (6R,7R)-7-[(Z)-2-(2-amino-1,3-thiazol-4-yl)-4-carboxybut-2-enoyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, is a third generation, orally administered cephalosporin antibiotic with broad antimicrobial activity and stability against extended spectrum β-lactamases. Ceftibuten can exist in various hydration states and to better understand the location of the water molecules of crystallization and their effect on the structure, the crystal structures of anhydrous (I) and hydrated (II) ceftibuten were determined and both occur as zwitterions with proton transfer from the carboxylate group adjacent to the β-lactam ring to the N atom of the thiazole ring. The β-lactam ring in (I) is almost planar but the equivalent grouping in (II) is slightly buckled. In the extended structure of (I), O—H···O and N—H···O hydrogen bonds link the molecules into a three-dimensional network. In (II), O—H···O, N—H···O, O—H···O, N—H···O, and O—H···O (c = ceftibuten, w = water) hydrogen bonds link the components into a three-dimensional network. A large void space is present within the anhydrous crystal structure that can accommodate between two and three molecules of water.

1. Chemical context

Ceftibuten, originally marketed under the tradename Cedax in the USA, is a third-generation cephalosporin antibiotic with activity against a variety of bacterial strains and resistance to extended spectrum β-lactamases (Wiseman & Balfour, 1994; Hamashima et al., 1990). Oral administration of ceftibuten is effective for treating urinary tract or respiratory tract infections, including many caused by β-lactamase-expressing bacterial strains (Owens et al., 1997). Despite its withdrawal from the US market, because of its effectiveness and stability against β-lactamases, renewed interest in ceftibuten for multidrug-resistant urinary tract infections (UTIs) has emerged, and studies are underway investigating oral administration of ceftibuten co-administered with a β-lactamase inhibitor as an alternative to hospitalization for complicated UTIs (Veeraraghavan et al., 2021; Chatwin et al., 2021).

Despite its long-time commercial availability, to our knowledge no crystal structures of ceftibuten have been previously reported. The structures of anhydrous ceftibuten (I) and hydrated ceftibuten (II) are reported herein.
2. Structural commentary

The anhydrous compound (I) (Fig. 1) has the formula C_{15}H_{14}N_{4}O_{6}S_{2} and crystallizes in the orthorhombic space group P_{2}1_{2}1_{2}1. The asymmetric unit of (I) contains one molecule of ceftibuten: the chiral C8 and C12 centers both have an absolute configuration of \( \text{R} \). This is reflected in the N13—C12—C8—S7 torsion angle of 5.0 (10°). The C24—C25—O26—O27 atoms were treated as disordered over two adjacent sets of sites with a population ratio of 0.841 (11): 0.159 (11). The \( \beta \)-lactam ring is almost planar with the C8/C12/C10/N9 atoms in the ring having a calculated r.m.s. deviation of 0.032 Å. Based on the refined bond distances of C3—O1 = 1.258 (9) Å and C3—O2 = 1.254 (9) Å, we have assigned the O1—O2—C3 group as a carboxylate and the N22 atom of the thiazole ring as protonated based on peaks in the residual electron-density map, i.e., the molecule exists as a zwitterion in the solid state.

The hydrated compound (II) (Fig. 2) has the formula C_{15}H_{14}N_{4}O_{6}S_{2}·2.7H_{2}O and crystallizes in the orthorhombic space group P_{2}1_{2}1_{2}1 with similar unit-cell parameters to (I). The asymmetric unit of (II) includes one ceftibuten molecule, one fully occupied O31 water molecule, and two partially occupied O32 and O33 water molecules, which were independently refined to occupancies of 0.828 (10) and 0.824 (12), respectively. The chiral C8 and C12 centers both have an absolute configuration of \( \text{R} \) and N13—C12—C8—S7 = 17.2 (4°). The \( \beta \)-lactam ring is slightly buckled in (II) compared to (I), with the atoms in the ring having a calculated r.m.s. deviation of 0.078 Å. As in (I), we have assigned the O1—C3—O2 group as a carboxylate anion based on bond distances of C3—O1 = 1.252 (4) Å and C3—O2 = 1.256 (4) Å and the N22 atom as protonated based on peaks in the residual electron-density map.

3. Supramolecular features

The extended structure of (I) displays a three-dimensional hydrogen-bonding network with O—H···O and N—H···O hydrogen bonds linking adjacent ceftibuten molecules (Table 1). The structure of (I) contains four void spaces per

| D—H···A | D—H | H···A | D···A | D—H···A |
|---------|-----|------|-------|---------|
| N13—H13···O15\(^i\) | 0.90 (3) | 1.91 (3) | 2.807 (9) | 177 (7) |
| N21—H21A···O2\(^ii\) | 0.87 (3) | 2.02 (5) | 2.824 (8) | 153 (8) |
| N21—H21B···O2\(^ii\) | 0.88 (3) | 1.96 (4) | 2.816 (9) | 164 (8) |
| N22—H22···O1\(^iii\) | 0.89 (3) | 1.75 (3) | 2.637 (9) | 172 (9) |
| O27A—H27A···O26A\(^iv\) | 0.84 | 1.85 | 2.683 (9) | 170 |
| O27B—H27B···O26B\(^iv\) | 0.84 | 1.84 | 2.62 (6) | 154 |
| C12—H12···O11\(^v\) | 1.00 | 2.27 | 3.172 (10) | 150 |
| C23—H23···O11\(^v\) | 0.95 | 2.35 | 3.237 (9) | 156 |

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

Figure 1
Molecular structure of (I). Ellipsoids of non-H elements are drawn at 50% probability.

Figure 2
Molecular structure of (II). Ellipsoids of non-H elements are drawn at 50% probability.
unit cell of about 42 Å³ each (total void volume = 167.3 Å³), which account for 9.2% of the unit-cell volume, as calculated in PLATON (Spek, 2020). The void spaces form channels propagating along the [100] direction (Fig. 3). The layers of ceftibuten molecules are linked along the a-axis direction by N—H / C1 / C1 / C1 O hydrogen bonds. Two weak C—H / C1 / C1 / C1 O interactions are also present.

Compound (II) displays a three-dimensional hydrogen-bonding network composed of O—H···O and N—H···O hydrogen bonds between ceftibuten and the free water molecules, and O—H···O hydrogen bonds between the free water molecules (Table 2). Four weak C—H···O bonds occur. The O32 and O33 water molecules occupy the channel void space that is present in (I) (Fig. 4).

4. Database survey

A Cambridge Structural Database search for compounds containing a β-lactam ring resulted in 1381 hits [CSD version 5.42 (December 2020), ConQuest version 2020.3.0; Groom et al., 2016]. Atoms in the β-lactam rings in these compounds have an average r.m.s. deviation of 0.024 Å, with the r.m.s. deviations of atoms in the β-lactam rings in (I) and (II) falling in the 69th and 98th percentiles of the distribution, respectively.

A previous study examined the structures of 32 known water-containing β-lactams (Hickey et al., 2007). Following the system of Gillon et al. (2003), the authors describe three distinct hydrogen-bonding motifs in hydrated β-lactam compounds based on the donor/acceptor roles of the water molecules in hydrogen bonds. The O31 water molecule in (II) acts as a donor in two hydrogen bonds and acceptor in two hydrogen bonds, meaning that the hydrogen-bonding behavior of the O31 water molecule in (II) can be classified as ‘environment C’. In contrast, the O32 and O33 water molecules can be assigned environment B based on their participation as donors in two hydrogen bonds and as acceptors in one hydrogen bond.

5. Synthesis and crystallization

Ceftibuten hydrate was purchased from ACS Dobfar (Tribiano, Italy). Dehydration occurs following exposure to an atmosphere below 30% relative humidity at 298 K, and the material was confirmed to be anhydrous following receipt at the University of South Florida X-Ray Facility. A crystal in the

| Table 2 | Hydrogen-bond geometry (Å, °) for (II). |
|--------|---------------------------------------|
| D—H···A | D—H | H···A | D···A | D—H···A |
| N13—H13···O15i | 0.85 (2) | 2.01 (3) | 2.799 (4) | 154 (4) |
| N21—H21A···O31i | 0.86 (5) | 2.05 (5) | 2.838 (4) | 153 (4) |
| N21—H21B···O2ii | 0.85 (4) | 1.97 (5) | 2.811 (4) | 173 (4) |
| N22—H22···O1iii | 0.87 (5) | 1.78 (5) | 2.654 (4) | 178 (5) |
| O26—H26···O27iv | 0.87 (5) | 1.80 (5) | 2.647 (4) | 164 (4) |
| O31—H31A···O2iv | 0.85 (2) | 2.29 (3) | 3.071 (4) | 155 (4) |
| O31—H31B···O2 | 0.86 (3) | 1.91 (3) | 2.756 (4) | 167 (6) |
| O32—H32A···O33i | 0.88 (3) | 2.02 (3) | 2.874 (6) | 164 (8) |
| O32—H32B···O31i | 0.87 (3) | 2.46 (3) | 3.305 (5) | 167 (6) |
| O33—H33A···O15ii | 0.87 (8) | 2.40 (8) | 3.226 (5) | 159 (6) |
| O33—H33B···O32 | 0.88 (8) | 1.97 (8) | 2.857 (6) | 165 (6) |
| C12—H12···O11iv | 1.00 | 2.39 | 3.349 (4) | 161 |
| C23—H23···O1iv | 0.95 | 2.41 | 3.281 (4) | 152 |
| C24—H24B···O26i | 0.99 | 2.54 | 3.387 (5) | 143 |

Symmetry codes: (i) x−1, y, z; (ii) x+1, y, z; (iii) −x+1, −y+1, −z; (iv) x−1, −y+1, z; (v) x+1, y, z; (vi) x, y, z.
form of a colorless needle was selected directly from the bulk sample (I) and deemed suitable for analysis.

For rehydration, ceftibuten powder was placed in an uncapped scintillation vial within a container of pure water. The sealed container was stored at room temperature for four weeks, and a sufficiently large crystal (a colorless needle) was selected for analysis.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. The N—H and O—H hydrogen positions were assigned from residual electron density peaks and refined with distances constrained. All remaining hydrogen atoms were assigned with a riding model. The C24—C25—O26—O27 atoms in (I) were treated as disordered with a population ratio of approximately 80:20 and refined with restrained interatomic distances. The occupancies of the O32 and O33 water molecules in (II) were freely refined.

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Table 3

| Experimental details | (I) | (II) |
|----------------------|-----------------|-----------------|
| **Crystal data**     | C₁₅H₁₄N₄O₆S₂   | C₁₅H₁₄N₄O₆S₂·2·652H₂O |
| Chemical formula     | 410.42          | 458.21          |
| M                    | Orthorhombic, P2₁2₁2₁ | Orthorhombic, P2₁2₁2₁ |
| Temperature (K)      | 100             | 100             |
| a, b, c (Å)          | 4.7727 (2), 17.5228 (8), 21.8526 (9) | 4.6690 (1), 17.8029 (4), 23.1486 (5) |
| V (Å³)               | 1827.56 (14)    | 1924.15 (7)     |
| Z                    | 4               | 4               |
| Radiation type       | Cu Ko           | Cu Ko           |
| µ (mm⁻¹)             | 3.02            | 3.04            |
| Crystal size (mm)    | 0.04 × 0.01 × 0.01 | 0.1 × 0.02 × 0.02 |

Computor programs: SAINT (Bruker, 2016), SHELXT (Sheldrick, 2015a), SHELXL (Sheldrick, 2015b), and OLEX2 (Dolomanov et al., 2009).
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Computing details

For both structures, data collection: SAINT (Bruker, 2016); cell refinement: SAINT (Bruker, 2016); data reduction: SAINT (Bruker, 2016); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: SHELXL (Sheldrick, 2015b); molecular graphics: OLEX2 (Dolomanov et al., 2009); software used to prepare material for publication: OLEX2 (Dolomanov et al., 2009).

Crystal data

C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>  
Mr = 410.42
Orthorhombic, P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>  
a = 4.7727 (2) Å  
b = 17.5228 (8) Å  
c = 21.8526 (9) Å  
V = 1827.56 (14) Å<sup>3</sup>  
Z = 4

\( F(000) = 848 \)

Data collection

Bruker D8 Venture Photon-II CPAD diffractometer  
\( \omega \) scans  
Absorption correction: multi-scan (SADABS; Bruker, 2016)

\( T_{\text{min}} = 0.790, T_{\text{max}} = 1.000 \)
14411 measured reflections
3215 independent reflections
1954 reflections with \( I > 2\sigma(I) \)
\( R_{\text{int}} = 0.128 \)
\( \theta_{\text{max}} = 68.3^\circ, \theta_{\text{min}} = 3.2^\circ \)
\( h = -5 \rightarrow 5 \)
\( k = -20 \rightarrow 20 \)
\( l = -25 \rightarrow 25 \)

Refinement

Refinement on \( F^2 \)
Least-squares matrix: full
\( R[F^2 > 2\sigma(F^2)] = 0.060 \)
\( wR(F^2) = 0.146 \)
\( S = 1.02 \)
3215 reflections
297 parameters
127 restraints
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement

\( w = 1/[\sigma^2(F_o^2) + (0.0594P)^2 + 0.1157P] \)

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

\( \Delta\sigma/\sigma < 0.001 \)
\( \Delta \rho_{\text{max}} = 0.25 \text{ e Å}^{-3} \)
\( \Delta \rho_{\text{min}} = -0.30 \text{ e Å}^{-3} \)

Absolute structure: Flack \( x \) determined using 544 quotients \([I^-]/[I^+]\) (Parsons et al., 2013)
Absolute structure parameter: 0.02 (3)
**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(eq) | Occ. (<1) |
|-------|-------|-------|-------|-------|-----------|
| O1    | 0.1910 (13) | 0.4734 (3) | 0.5240 (2) | 0.0496 (15) |            |
| O2    | 0.3613 (13) | 0.3637 (3) | 0.4870 (2) | 0.0478 (15) |            |
| C3    | 0.3498 (19) | 0.4351 (5) | 0.4898 (3) | 0.046 (2) |            |
| C4    | 0.5398 (18) | 0.4812 (4) | 0.4497 (3) | 0.0386 (19) |            |
| C5    | 0.577 (2) | 0.5565 (4) | 0.4568 (3) | 0.048 (2) |            |
| H5    | 0.477736 | 0.579712 | 0.489583 | 0.057* |            |
| C6    | 0.756 (2) | 0.6079 (5) | 0.4189 (3) | 0.053 (2) |            |
| H6A   | 0.943643 | 0.611709 | 0.437976 | 0.064* |            |
| H6B   | 0.672455 | 0.659595 | 0.418555 | 0.064* |            |
| S7    | 0.7947 (5) | 0.57482 (13) | 0.34071 (8) | 0.0534 (6) |            |
| C8    | 0.9042 (19) | 0.4805 (4) | 0.3648 (3) | 0.043 (2) |            |
| H8    | 1.093338 | 0.480121 | 0.384487 | 0.052* |            |
| N9    | 0.6880 (14) | 0.4440 (3) | 0.4024 (2) | 0.0381 (16) |            |
| C10   | 0.626 (2) | 0.3886 (4) | 0.3593 (3) | 0.043 (2) |            |
| O11   | 0.4465 (13) | 0.3410 (3) | 0.3547 (2) | 0.0452 (14) |            |
| C12   | 0.8659 (17) | 0.4161 (4) | 0.3178 (3) | 0.041 (2) |            |
| C13   | 0.907561 | 0.379824 | 0.317186 | 0.049* |            |
| N13   | 0.7684 (15) | 0.4356 (4) | 0.2567 (2) | 0.0389 (16) |            |
| H13   | 0.587 (7) | 0.442 (4) | 0.247 (3) | 0.047* |            |
| C14   | 0.955 (2) | 0.4546 (4) | 0.2131 (3) | 0.0386 (19) |            |
| O15   | 1.2075 (14) | 0.4538 (3) | 0.2209 (2) | 0.0522 (16) |            |
| C16   | 0.8241 (17) | 0.4785 (4) | 0.1533 (3) | 0.0360 (18) |            |
| C17   | 0.8370 (17) | 0.5608 (4) | 0.1416 (3) | 0.0373 (19) |            |
| C18   | 1.0011 (19) | 0.6113 (4) | 0.1705 (3) | 0.047 (2) |            |
| H18   | 1.132680 | 0.598209 | 0.201402 | 0.057* |            |
| S19   | 0.9437 (5) | 0.70346 (12) | 0.14471 (9) | 0.0518 (6) |            |
| C20   | 0.6983 (19) | 0.6708 (4) | 0.0931 (3) | 0.045 (2) |            |
| N21   | 0.5589 (17) | 0.7123 (4) | 0.0538 (3) | 0.0439 (17) |            |
| H21A  | 0.586 (19) | 0.7617 (17) | 0.054 (4) | 0.06 (3)* |            |
| H21B  | 0.448 (15) | 0.690 (4) | 0.027 (3) | 0.07 (3)* |            |
| N22   | 0.6717 (15) | 0.5942 (4) | 0.0971 (2) | 0.0402 (17) |            |
| H22   | 0.548 (16) | 0.568 (4) | 0.075 (4) | 0.09 (4)* |            |
| C23   | 0.6960 (18) | 0.4289 (4) | 0.1170 (3) | 0.0421 (19) |            |
| H23   | 0.609951 | 0.447977 | 0.080944 | 0.051* | 0.841 (11) |
| H23A  | 0.641091 | 0.447275 | 0.077935 | 0.051* | 0.159 (11) |
| C24A  | 0.677 (4) | 0.3432 (5) | 0.1291 (4) | 0.044 (4) | 0.841 (11) |
| H24A  | 0.792881 | 0.329912 | 0.165094 | 0.053* | 0.841 (11) |
| H24B  | 0.480167 | 0.329273 | 0.138372 | 0.053* | 0.841 (11) |
| C25A  | 0.773 (3) | 0.3002 (6) | 0.0761 (4) | 0.042 (3) | 0.841 (11) |
### Atomic displacement parameters (Å²)

| Atom | $U_11$   | $U_{22}$   | $U_{33}$   | $U_{12}$   | $U_{13}$   | $U_{23}$   |
|------|----------|------------|------------|------------|------------|------------|
| O26A | 0.066 (4) | 0.048 (3)  | 0.035 (3)  | 0.004 (3)  | 0.013 (3)  | 0.003 (2)  |
| O27A | 0.068 (4) | 0.042 (3)  | 0.034 (3)  | 0.006 (3)  | 0.004 (3)  | 0.002 (2)  |
| C24B | 0.059 (6) | 0.054 (6)  | 0.023 (4)  | 0.003 (5)  | 0.000 (4)  | 0.000 (4)  |
| C25B | 0.048 (6) | 0.047 (5)  | 0.021 (3)  | 0.004 (4)  | 0.000 (4)  | 0.000 (4)  |
| C26B | 0.062 (6) | 0.050 (5)  | 0.031 (4)  | 0.001 (5)  | 0.000 (4)  | 0.000 (4)  |
| C27B | 0.067 (7) | 0.046 (5)  | 0.046 (4)  | 0.001 (5)  | 0.000 (5)  | 0.000 (5)  |
| S7   | 0.05756 (17) | 0.0481 (12) | 0.0365 (10) | 0.0027 (12) | 0.00074 (11) | 0.00017 (9) |
| C8   | 0.054 (6) | 0.046 (5)  | 0.029 (4)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| N9   | 0.050 (4) | 0.042 (4)  | 0.022 (3)  | 0.000 (3)  | 0.000 (3)  | 0.000 (3)  |
| C10  | 0.063 (7) | 0.040 (5)  | 0.025 (4)  | 0.008 (5)  | 0.000 (4)  | 0.000 (4)  |
| O11  | 0.065 (4) | 0.046 (3)  | 0.025 (2)  | 0.000 (3)  | 0.000 (3)  | 0.000 (3)  |
| C12  | 0.048 (6) | 0.050 (5)  | 0.025 (4)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| N13  | 0.050 (5) | 0.050 (4)  | 0.017 (3)  | 0.003 (4)  | 0.000 (3)  | 0.000 (3)  |
| C14  | 0.046 (6) | 0.039 (4)  | 0.031 (4)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| O15  | 0.040 (4) | 0.080 (4)  | 0.037 (3)  | 0.000 (3)  | 0.000 (3)  | 0.000 (3)  |
| C16  | 0.044 (5) | 0.044 (4)  | 0.020 (3)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| C17  | 0.051 (5) | 0.042 (5)  | 0.019 (3)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| C18  | 0.063 (7) | 0.046 (5)  | 0.033 (4)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| S19  | 0.0628 (15) | 0.0459 (12) | 0.0466 (11) | 0.0040 (12) | 0.0005 (11) | 0.0002 (10) |
| C20  | 0.069 (7) | 0.041 (5)  | 0.025 (4)  | 0.000 (5)  | 0.000 (4)  | 0.000 (3)  |
| N21  | 0.068 (5) | 0.035 (4)  | 0.029 (3)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| N22  | 0.051 (5) | 0.044 (5)  | 0.025 (3)  | 0.000 (4)  | 0.000 (3)  | 0.000 (3)  |
| C23  | 0.060 (5) | 0.045 (5)  | 0.021 (3)  | 0.000 (4)  | 0.000 (4)  | 0.000 (4)  |
| C24A | 0.063 (10) | 0.041 (6)  | 0.029 (6)  | 0.001 (6)  | 0.000 (6)  | 0.000 (6)  |
| C25A | 0.059 (8) | 0.037 (6)  | 0.029 (5)  | 0.003 (6)  | 0.002 (5)  | 0.008 (4)  |
| O26A | 0.074 (7) | 0.083 (6)  | 0.034 (4)  | 0.013 (5)  | 0.004 (4)  | 0.018 (4)  |
| O27A | 0.072 (6) | 0.065 (5)  | 0.036 (4)  | 0.010 (5)  | 0.000 (4)  | 0.013 (3)  |
| C24B | 0.07 (3)  | 0.05 (3)   | 0.03 (2)   | 0.00 (2)   | 0.01 (2)   | 0.00 (2)   |
| C25B | 0.09 (2)  | 0.06 (2)   | 0.043 (19) | 0.01 (2)   | 0.001 (18) | 0.015 (17) |
| O26B | 0.15 (3)  | 0.12 (4)   | 0.11 (3)   | 0.01 (3)   | 0.07 (3)   | 0.02 (3)   |
| O27B | 0.14 (4)  | 0.09 (3)   | 0.13 (4)   | 0.02 (3)   | 0.01 (3)   | 0.05 (3)   |
### Geometric parameters (Å, °)

| Bond/Distance/Angle | Value     | Bond/Distance/Angle | Value     |
|---------------------|-----------|---------------------|-----------|
| O1—C3               | 1.258 (9) | C17—N22             | 1.382 (9) |
| O2—C3               | 1.254 (9) | C18—H18             | 0.9500    |
| C3—C4               | 1.497 (11)| C18—S19             | 1.732 (8) |
| C4—C5               | 1.340 (10)| S19—C20             | 1.724 (8) |
| C4—N9               | 1.412 (9) | C20—N21             | 1.307 (10)|
| C5—H5               | 0.9500    | C20—N22             | 1.351 (10)|
| C5—C6               | 1.493 (11)| N21—H21A            | 0.87 (3)  |
| C6—H6A              | 0.9900    | N21—H21B            | 0.88 (3)  |
| C6—H6B              | 0.9900    | N22—H22             | 0.89 (3)  |
| C6—S7               | 1.814 (8) | C23—H23             | 0.9500    |
| S7—C8               | 1.812 (8) | C23—H23A            | 0.9500    |
| C8—H8               | 1.0000    | C23—C24A            | 1.527 (11)|
| C8—N9               | 1.467 (10)| C23—C24B            | 1.527 (16)|
| C8—C12              | 1.536 (10)| C24A—H24A           | 0.9900    |
| N9—C10              | 1.384 (9) | C24A—H24B           | 0.9900    |
| C10—O11             | 1.202 (9) | C24A—C25A           | 1.456 (14)|
| C10—C12             | 1.536 (11)| C25A—O26A           | 1.226 (12)|
| C12—H12             | 1.0000    | C25A—O27A           | 1.315 (12)|
| C12—N13             | 1.455 (8) | O27A—H27A           | 0.8400    |
| N13—H13             | 0.90 (3)  | C24B—H24C           | 0.9900    |
| N13—C14             | 1.345 (10)| C24B—H24D           | 0.9900    |
| C14—O15             | 1.220 (9) | C24B—C25B           | 1.460 (18)|
| C14—C16             | 1.506 (10)| C25B—O26B           | 1.21 (2)  |
| C16—C17             | 1.466 (10)| C25B—O27B           | 1.31 (2)  |
| C16—C23             | 1.327 (10)| O27B—H27B           | 0.8400    |
| C17—C18             | 1.340 (10)|                     |           |
N9—C8—C12 88.3 (5)  C16—C23—C24B 128 (2)
C12—C8—S7 116.2 (5)  C24A—C23—H23 117.6
C12—C8—H8 113.0  C24B—C23—H23A 116.2
C4—N9—C8 124.2 (6)  C23—C24A—H24A 109.5
C10—N9—C4 135.7 (7)  C23—C24A—H24B 109.5
C10—N9—C8 94.2 (5)  H24A—C24A—H24B 108.1
N9—C10—C12 91.4 (6)  C25A—C24A—C23 110.6 (8)
O11—C10—N9 134.1 (7)  C25A—C24A—H24A 109.5
O11—C10—C12 134.1 (7)  C25A—C24A—H24B 109.5
C8—C12—H12 112.6  O26A—C25A—C24A 125.0 (14)
C10—C12—C8 85.7 (5)  O26A—C25A—O27A 121.4 (9)
C10—C12—H12 112.6  O27A—C25A—C24A 113.6 (12)
N13—C12—C8 118.6 (6)  C25A—O27A—H27A 109.5
N13—C12—C10 112.2 (7)  C23—C24B—H24C 109.5
N13—C12—H12 112.6  C23—C24B—H24D 109.5
C12—N13—C14—C16 88.2 (9)  O27B—C25B—C24B 114 (4)
O15—C14—C16 123.5 (7)  C16—C23—C24B—C25B −159 (3)
O15—C14—C16 122.3 (7)  C16—C23—C24A—C25A −127.6 (12)
C17—C16—C14 114.1 (6)  C16—C23—C24A—C25A −178.7 (6)
C23—C16—C14 121.7 (7)  C16—C23—C24B—C25B −159 (3)
C23—C16—C17 124.1 (6)  C16—C23—C24B—C25A −127.6 (12)

O1—C3—C4—C5 11.5 (11)  C12—C8—N9—C10 −5.2 (6)
O1—C3—C4—N9 −168.8 (7)  C12—N13—C14—O15 2.8 (11)
O2—C3—C4—C5 −168.4 (8)  C12—N13—C14—C16 −176.1 (6)
O2—C3—C4—N9 11.4 (11)  N13—C14—C16—C23 −70.5 (10)
C3—C4—C5—C6 −178.8 (8)  N13—C14—C16—C17 105.8 (8)
C3—C4—C5—S7 28.5 (12)  C14—C16—C17—C18 15.9 (11)
C3—C4—C5—C6 −178.8 (8)  C14—C16—C17—N22 −164.4 (7)
C3—C4—N9—C8 −172.5 (7)  C14—C16—C23—C24A −3.0 (15)
C3—C4—N9—C10 42.2 (11)  C14—C16—C23—C24B 8 (5)
C4—C5—C6—S7 11.5 (11)  C14—C16—C23—C24B 8 (5)
C4—C5—C6—C7 −19.3 (14)  C15—C14—C16—C23 110.6 (10)
C4—N9—C10—O11 157.0 (8)  C15—C14—C16—C17 −73.1 (9)
C4—N9—C10—C12 7.2 (11)  O15—C14—C16—C17 −73.1 (9)
C5—C4—N9—C8 7.2 (11)  O15—C14—C16—C23 110.6 (10)
C5—C4—N9—C10 −138.0 (8)  C16—C17—C18—S19 −178.0 (6)
C5—C6—S7—C8 28.5 (12)  C16—C17—C18—S19 −178.0 (6)
C5—C6—S7—C8 −138.0 (8)  C16—C17—N22—C20 177.7 (7)
C6—S7—C8—N9 59.2 (6)  C16—C17—N22—C20 177.7 (7)
C6—S7—C8—C12 158.0 (7)  C16—C23—C24A—C25A −127.6 (12)
S7—C8—N9—C4 44.1 (8)  C16—C23—C24B—C25B −159 (3)
S7—C8—N9—C10 112.3 (5)  C17—C16—C23—C24A −179.0 (11)
S7—C8—C12—C10 −107.9 (6)  C17—C16—C23—C24B −168 (5)
S7—C8—C12—N13 5.0 (10)  C17—C18—S19—C20 −1.1 (6)
C8—N9—C10—O11 −171.1 (9)  C18—C17—N22—C20 −2.5 (9)
C8—N9—C10—C12 5.2 (6)  C18—S19—C20—N21 −178.7 (8)
C8—C12—N13—C14 88.2 (9)  C18—S19—C20—N22 −0.3 (6)
N9—C4—C5—C6 1.4 (13)  S19—C20—N22—C17 1.6 (8)
N9—C4—C5—C6
N9—C8—C12—C10 4.7 (5) N22—C17—C18—S19 2.2 (9)
N9—C8—C12—N13 117.6 (7) C23—C16—C17—C18 −167.9 (8)
N9—C10—C12—C8 −4.9 (6) C23—C16—C17—N22 11.9 (12)
N9—C10—C12—N13 −124.1 (6) C23—C24A—C25A—O26A 73.7 (15)
C10—C12—N13—C14 −174.4 (6) C23—C24B—C25B—O26B −61 (7)
O11—C10—C12—C8 171.3 (9) C23—C24B—C25B—O27B 119 (7)
O11—C10—C12—N13 52.2 (12) C12—C8—N9—C4 −161.7 (7)

Hydrogen-bond geometry (Å, º)

| D—H···A  | D—H | H···A | D···A | D—H···A |
|----------|------|-------|-------|---------|
| N13—H13···O15i | 0.90 (3) | 1.91 (3) | 2.807 (9) | 177 (7) |
| N21—H21A···O2ii | 0.87 (3) | 2.02 (5) | 2.824 (8) | 153 (8) |
| N21—H21B···O2iii | 0.88 (3) | 1.96 (4) | 2.816 (9) | 164 (8) |
| N22—H22···O1iii | 0.89 (3) | 1.75 (3) | 2.637 (9) | 172 (9) |
| O27A—H27A···O26Aiv | 0.84 | 1.85 | 2.683 (9) | 170 |
| O27B—H27B···O26Biv | 0.84 | 1.84 | 2.62 (6) | 154 |
| C12—H12···O11v | 1.00 | 2.27 | 3.172 (10) | 150 |
| C23—H23···O1iii | 0.95 | 2.35 | 3.237 (9) | 156 |

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

(6R,7R)-7-[(Z)-2-(2-Amino-1,3-thiazol-4-yl)-4-carboxybut-2-enoyl]amino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 2.652-hydrate (II)

Crystal data

C₁₅H₁₄N₄O₆S₂·2.652H₂O  
Mr = 458.21  
Orthorhombic, P2₁2₁2₁  
a = 4.6690 (1) Å  
b = 17.8029 (4) Å  
c = 23.1486 (5) Å  
V = 1924.15 (7) Å³  
Z = 4  
F(000) = 954

Data collection

Bruker D8 Venture Photon-II CPAD  
ediffactometer  
Radiation source: INCOATEC Imus micro-focus source  
θ = 3.1–77.2°  
μ = 3.04 mm⁻¹  
θ = 3.1–77.2°  
F(000) = 954

Refinement

Refinement on F²  
wR(F²) = 0.085  
Least-squares matrix: full  
S = 1.04  
R[F² > 2σ(F²)] = 0.038

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### Supporting Information

317 parameters  
7 restraints  
Hydrogen site location: mixed  
H atoms treated by a mixture of independent and constrained refinement  

\[ w = \frac{1}{\sigma^2(F_o^2) + (0.0405P)^2 + 0.5445P} \]

\[ \text{where } P = \frac{(F_o^2 + 2F_c^2)}{3} \]

\[ (\Delta/\sigma)_{\text{max}} < 0.001 \]
\[ \Delta \rho_{\text{max}} = 0.30 \text{ e Å}^{-3} \]
\[ \Delta \rho_{\text{min}} = -0.23 \text{ e Å}^{-3} \]

Absolute structure: Flack \( x \) determined using 1302 quotients \([I^+]-[I^-])/([I^+]+[I^-])\) (Parsons et al., 2013)  
Absolute structure parameter: 0.029 (11)

### 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          | Uiso*/Ueq | Occ. (<1) |
|----|------------|------------|------------|-----------|-----------|
| O1 | 0.2135 (6) | 0.50647 (13)| 0.50496 (10)| 0.0213 (6) |           |
| O2 | 0.5160 (6) | 0.59068 (13)| 0.54303 (10)| 0.0232 (6) |           |
| C3 | 0.4020 (8) | 0.52690 (19)| 0.54008 (14)| 0.0180 (7) |           |
| C4 | 0.5001 (8) | 0.46858 (18)| 0.58327 (14)| 0.0160 (7) |           |
| C5 | 0.4378 (8) | 0.39600 (19)| 0.57856 (14)| 0.0192 (7) |           |
| H5 | 0.329092   | 0.381498   | 0.545704   | 0.023*    |           |
| C6 | 0.5210 (10)| 0.3343 (2) | 0.61975 (15)| 0.0273 (9) |           |
| H6A| 0.687457   | 0.307006   | 0.603607   | 0.033*    |           |
| H6B| 0.360269   | 0.298288   | 0.622794   | 0.033*    |           |
| S7 | 0.6123 (2) | 0.36755 (5) | 0.69200 (4) | 0.0228 (2) |           |
| C8 | 0.8320 (8) | 0.4455 (2) | 0.66878 (15)| 0.0186 (7) |           |
| H8 | 1.025171   | 0.430505   | 0.654104   | 0.022*    |           |
| N9 | 0.6706 (6) | 0.49483 (15)| 0.62916 (12)| 0.0163 (6) |           |
| C10| 0.6178 (8) | 0.54808 (19)| 0.67132 (14)| 0.0167 (7) |           |
| O11| 0.4464 (5) | 0.59867 (13)| 0.67441 (10)| 0.0198 (5) |           |
| C12| 0.8375 (8) | 0.5122 (2) | 0.71215 (14)| 0.0172 (7) |           |
| H12| 1.024780   | 0.539335   | 0.710828   | 0.021*    |           |
| N13| 0.7457 (7) | 0.50003 (17)| 0.77034 (13)| 0.0172 (6) |           |
| H13| 0.572 (6)  | 0.491 (2)  | 0.7776 (16) | 0.016 (10)*|           |
| C14| 0.9261 (7) | 0.50079 (17)| 0.81555 (14)| 0.0146 (7) |           |
| O15| 1.1831 (5) | 0.51428 (16)| 0.81065 (11)| 0.0261 (6) |           |
| C16| 0.7879 (7) | 0.48572 (18)| 0.87346 (14)| 0.0140 (7) |           |
| C17| 0.6484 (8) | 0.41288 (19)| 0.87863 (14)| 0.0160 (7) |           |
| C18| 0.6852 (8) | 0.35256 (18)| 0.84425 (15)| 0.0179 (7) |           |
| H18| 0.811218   | 0.351654   | 0.812040   | 0.021*    |           |
| S19| 0.4772 (2) | 0.27702 (4) | 0.86532 (4) | 0.0196 (2) |           |
| C20| 0.3429 (8) | 0.32934 (19)| 0.92227 (15)| 0.0176 (7) |           |
| N21| 0.1548 (7) | 0.30362 (18)| 0.95965 (14)| 0.0199 (7) |           |
| H21A| 0.081 (10)| 0.260 (3)  | 0.9539 (18) | 0.029 (12)*|           |
| H21B| 0.089 (10)| 0.333 (2)  | 0.9849 (18) | 0.023 (11)*|           |
| N22| 0.4532 (6) | 0.39822 (15)| 0.92347 (12)| 0.0149 (6) |           |
| H22| 0.398 (13) | 0.430 (3)  | 0.949 (2)   | 0.056 (16)*|           |
| Atomic displacement parameters (Å²) |
|-----------------------------------|
| $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
| O1 0.0269 (14) | 0.0204 (12) | 0.0167 (12) | −0.0034 (11) | −0.0091 (11) | 0.0025 (10) |
| O2 0.0267 (14) | 0.0194 (12) | 0.0236 (12) | −0.0047 (11) | −0.0078 (12) | 0.0047 (10) |
| C3 0.0193 (18) | 0.0208 (17) | 0.0138 (16) | 0.0021 (14) | 0.0040 (15) | −0.0003 (13) |
| C4 0.0169 (17) | 0.0201 (16) | 0.0110 (14) | 0.0023 (14) | 0.0027 (14) | 0.0002 (12) |
| C5 0.0237 (19) | 0.0213 (16) | 0.0127 (15) | 0.0040 (15) | −0.0025 (15) | −0.0010 (13) |
| C6 0.044 (2) | 0.0194 (16) | 0.0190 (17) | 0.0040 (18) | −0.0067 (18) | −0.0022 (14) |
| S7 0.0331 (5) | 0.0195 (4) | 0.0158 (4) | 0.0004 (4) | −0.0037 (4) | 0.0026 (3) |
| C8 0.0152 (18) | 0.0262 (18) | 0.0142 (17) | 0.0053 (14) | 0.0007 (14) | 0.0026 (14) |
| N9 0.0169 (15) | 0.0166 (14) | 0.0154 (14) | 0.0009 (11) | −0.0001 (12) | 0.0037 (11) |
| C10 0.0159 (16) | 0.0187 (16) | 0.0154 (16) | −0.0044 (15) | 0.0031 (15) | 0.0027 (13) |
| O11 0.0207 (13) | 0.0197 (12) | 0.0190 (11) | −0.0004 (10) | 0.0030 (10) | 0.0007 (10) |
| C12 0.0137 (17) | 0.0257 (18) | 0.0121 (15) | −0.0035 (14) | 0.0020 (14) | 0.0014 (13) |
| N13 0.0127 (14) | 0.0256 (16) | 0.0132 (14) | −0.0059 (13) | 0.0011 (12) | 0.0004 (12) |
| C14 0.0157 (16) | 0.0144 (15) | 0.0139 (15) | 0.0006 (13) | −0.0001 (13) | −0.0024 (12) |
| O15 0.0165 (13) | 0.0451 (16) | 0.0166 (12) | 0.0002 (11) | −0.0004 (11) | −0.0013 (12) |
| C16 0.0146 (16) | 0.0150 (15) | 0.0125 (16) | 0.0024 (13) | 0.0005 (13) | 0.0007 (13) |
| C17 0.0177 (17) | 0.0183 (16) | 0.0122 (15) | 0.0017 (14) | −0.0005 (14) | 0.0006 (13) |
| C18 0.0236 (19) | 0.0139 (16) | 0.0161 (16) | −0.0004 (13) | 0.0006 (15) | 0.0008 (13) |
| S19 0.0289 (5) | 0.0134 (4) | 0.0165 (4) | −0.0009 (4) | 0.0025 (4) | −0.0031 (3) |
| C20 0.0233 (18) | 0.0174 (16) | 0.0122 (15) | 0.0005 (15) | −0.0039 (15) | −0.0001 (13) |
| N21 0.0277 (18) | 0.0135 (15) | 0.0186 (16) | −0.0040 (13) | 0.0039 (14) | −0.0020 (12) |
| N22 0.0164 (15) | 0.0145 (13) | 0.0139 (13) | 0.0005 (12) | 0.0010 (12) | −0.0011 (11) |
| C23 0.0190 (19) | 0.0172 (16) | 0.0146 (16) | 0.0012 (14) | 0.0011 (14) | 0.0008 (13) |
| C24 0.0216 (19) | 0.0198 (16) | 0.0180 (16) | −0.0033 (15) | 0.0003 (15) | −0.0044 (13) |
| C25 0.0219 (19) | 0.0186 (17) | 0.0162 (16) | −0.0038 (15) | −0.0035 (15) | 0.0014 (13) |
| O26 0.0243 (14) | 0.0187 (12) | 0.0317 (14) | −0.0015 (11) | 0.0046 (12) | −0.0078 (11) |
|    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|
| O27 | 0.0301 (15) | 0.0207 (13) | 0.0301 (14) | -0.0055 (12) | 0.0043 (12) | -0.0073 (11) |
| O31 | 0.0174 (14) | 0.0176 (12) | 0.0390 (16) | 0.0012 (12) | -0.0020 (13) | -0.0008 (11) |
| O32 | 0.038 (3) | 0.039 (2) | 0.046 (3) | 0.0030 (19) | -0.010 (2) | -0.0041 (18) |
| O33 | 0.040 (2) | 0.030 (2) | 0.038 (2) | 0.0079 (18) | -0.003 (2) | -0.0082 (16) |

**Geometric parameters (Å, °)**

|    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|
| O1—C3 | 1.252 (4) | C17—C18 | 1.348 (5) |
| O2—C3 | 1.256 (4) | C17—N22 | 1.406 (4) |
| C3—C4 | 1.512 (5) | C18—H18 | 0.9500 |
| C4—C5 | 1.329 (5) | C18—S19 | 1.729 (4) |
| C4—N9 | 1.407 (4) | S19—C20 | 1.732 (4) |
| C5—H5 | 0.9500 | C20—N21 | 1.315 (5) |
| C5—C6 | 1.505 (5) | C20—N22 | 1.330 (4) |
| C6—H6A | 0.9900 | N21—H21A | 0.86 (5) |
| C6—H6B | 0.9900 | N21—H21B | 0.85 (4) |
| C6—S7 | 1.824 (4) | N22—H22 | 0.87 (5) |
| S7—C8 | 1.807 (4) | C23—H23 | 0.9500 |
| C8—H8 | 1.0000 | C23—C24 | 1.494 (5) |
| C8—N9 | 1.477 (4) | C24—H24A | 0.9900 |
| C8—C12 | 1.555 (5) | C24—H24B | 0.9900 |
| N9—C10 | 1.383 (4) | C24—C25 | 1.498 (5) |
| C10—O11 | 1.207 (4) | C25—O26 | 1.312 (5) |
| C10—C12 | 1.534 (5) | C25—O27 | 1.215 (4) |
| C12—H12 | 1.0000 | O26—H26 | 0.87 (5) |
| C12—N13 | 1.430 (4) | O31—H31A | 0.85 (2) |
| N13—C14 | 0.85 (2) | O31—H31B | 0.86 (3) |
| N13—C14 | 1.343 (5) | O32—H32A | 0.88 (3) |
| C14—O15 | 1.229 (4) | O32—H32B | 0.87 (3) |
| C14—C16 | 1.512 (5) | O33—H33A | 0.87 (8) |
| C16—C17 | 1.456 (5) | O33—H33B | 0.88 (8) |
| C16—C23 | 1.336 (5) | |

**Supplementary Material**

|    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|
| O1—C3—O2 | 126.6 (3) | O15—C14—N13 | 122.8 (3) |
| O1—C3—C4 | 116.3 (3) | O15—C14—C16 | 122.2 (3) |
| O2—C3—C4 | 117.2 (3) | C17—C16—C14 | 115.0 (3) |
| C5—C4—C3 | 123.2 (3) | C23—C16—C14 | 119.7 (3) |
| C5—C4—N9 | 120.6 (3) | C23—C16—C17 | 125.3 (3) |
| N9—C4—C3 | 116.2 (3) | C18—C17—C16 | 127.2 (3) |
| C4—C5—H5 | 116.5 | C18—C17—N22 | 111.8 (3) |
| C4—C5—C6 | 126.9 (3) | N22—C17—C16 | 121.1 (3) |
| C6—C5—H5 | 116.5 | C17—C18—H18 | 123.8 |
| C5—C6—H6A | 108.8 | C17—C18—S19 | 112.4 (3) |
| C5—C6—H6B | 108.8 | S19—C18—H18 | 123.8 |
| C5—C6—S7 | 113.9 (2) | C18—S19—C20 | 89.99 (17) |
| H6A—C6—H6B | 107.7 | N21—C20—S19 | 123.7 (3) |
| S7—C6—H6A | 108.8 | N21—C20—N22 | 124.5 (3) |
| S7—C6—H6B | 108.8 | N22—C20—S19 | 111.8 (3) |
### C8—S7—C6
- C8—S7—C6: 96.25 (17)°

### S7—C8—H8
- S7—C8—H8: 114.1°

### N9—C8—S7
- N9—C8—S7: 110.6 (2)°

### N9—C8—H8
- N9—C8—H8: 114.1°

### C12—C8—S7
- C12—C8—S7: 113.8 (2)°

### C12—C8—H8
- C12—C8—H8: 114.1°

### C4—N9—C8
- C4—N9—C8: 124.0 (3)°

### C10—N9—C4
- C10—N9—C4: 131.3 (3)°

### C8—C12—H12
- C8—C12—H12: 111.3°

### C10—C12—C8
- C10—C12—C8: 84.8 (2)°

### N9—C10—N9
- N9—C10—N9: 132.2 (3)°

### O11—C10—N9
- O11—C10—N9: 132.2 (3)°

### C8—C10—C12
- C8—C10—C12: 135.9 (3)°

### C12—C10—C12
- C12—C10—C12: 111.3°

### C12—C10—C12
- C12—C10—C12: 111.3°

### C13—C12—C8
- C13—C12—C8: 119.2 (3)°

### C12—C13—C12
- C12—C13—C12: 116.3 (3)°

### C12—C13—H13
- C12—C13—H13: 120 (3)°

### O11—C13—C12
- O11—C13—C12: 132.2 (3)°

### N13—C12—C10
- N13—C12—C10: 116.3 (3)°

### N13—C12—C10
- N13—C12—C10: 116.3 (3)°

### C8—N9—C10
- C8—N9—C10: 93.5 (3)°

### C8—N9—C10
- C8—N9—C10: 93.5 (3)°

### C12—N13—C14
- C12—N13—C14: 2.3 (5)°

### C14—C12—C10
- C14—C12—C10: 116.3 (3)°

### C12—C14—C16
- C12—C14—C16: 114.9 (3)°

### O1—C3—C4—C5
- O1—C3—C4—C5: 12.9 (5)°

### O1—C3—C4—N9
- O1—C3—C4—N9: -168.6 (3)°

### O2—C3—C4—C5
- O2—C3—C4—C5: -167.3 (4)°

### O2—C3—C4—N9
- O2—C3—C4—N9: 11.2 (5)°

### C3—C4—C5—C6
- C3—C4—C5—C6: -178.8 (4)°

### C3—C4—N9—C8
- C3—C4—N9—C8: -167.6 (3)°

### C3—C4—N9—C10
- C3—C4—N9—C10: 58.7 (5)°

### C4—C5—C6—S7
- C4—C5—C6—S7: 20.6 (5)°

### C4—N9—C10—O11
- C4—N9—C10—O11: -19.3 (6)°

### C4—N9—C10—C12
- C4—N9—C10—C12: 155.7 (3)°

### C5—C4—N9—C8
- C5—C4—N9—C8: 10.9 (5)°

### C5—C4—N9—C10
- C5—C4—N9—C10: -122.7 (4)°

### C5—C6—S7—C8
- C5—C6—S7—C8: 44.7 (3)°

### C6—S7—C8—N9
- C6—S7—C8—N9: 55.0 (3)°

### C6—S7—C8—N9
- C6—S7—C8—N9: 151.5 (3)°

### S7—C8—N9—C4
- S7—C8—N9—C4: -45.0 (4)°

### S7—C8—N9—C10
- S7—C8—N9—C10: 102.0 (3)°

### S7—C8—C12—C10
- S7—C8—C12—C10: -100.1 (3)°

### S7—C8—C12—N13
- S7—C8—C12—N13: 17.2 (4)°

### C8—N9—C10—O11
- C8—N9—C10—O11: -162.4 (4)°

### C8—N9—C10—C12
- C8—N9—C10—C12: 12.7 (3)°

### C8—C12—N13—C14
- C8—C12—N13—C14: 110.4 (4)°

### N9—C4—C5—C6
- N9—C4—C5—C6: 2.7 (6)°

### N9—C8—C12—C10
- N9—C8—C12—C10: 11.3 (2)°

### O11—C10—C12—C8
- O11—C10—C12—C8: 162.7 (4)°

### O11—C10—C12—N13
- O11—C10—C12—N13: 162.7 (4)°

### C12—C8—N9—C4
- C12—C8—N9—C4: -159.5 (3)°

### C12—C8—N9—C10
- C12—C8—N9—C10: 12.5 (3)°

### C12—N13—C14—C16
- C12—N13—C14—C16: 61.6 (4)°

### H24A—C24—H24B
- H24A—C24—H24B: 107.4°

### C14—C16—C17—C18
- C14—C16—C17—C18: 16.9 (5)°

### H31A—O31—H31B
- H31A—O31—H31B: 109 (4)°

### H32A—O32—H32B
- H32A—O32—H32B: 107 (5)°

### H33A—O33—H33B
- H33A—O33—H33B: 110 (6)°
### Supporting Information

N9—C8—C12—N13 128.6 (3)
N9—C10—C12—C8 −12.0 (2)
N9—C10—C12—N13 −132.2 (3)
C10—C12—N13—C14 −150.3 (3)

C23—C16—C17—N22 17.0 (5)
C23—C24—C25—O26 −12.3 (5)
C23—C24—C25—O27 168.2 (3)

### Hydrogen-bond geometry (Å, °)

| D—H···A  | D—H | H···A | D···A | D—H···A |
|----------|------|-------|-------|---------|
| N13—H13···O15i | 0.85 (2) | 2.01 (3) | 2.799 (4) | 154 (4) |
| N21—H21A···O31ii | 0.86 (5) | 2.05 (5) | 2.838 (4) | 153 (4) |
| N21—H21B···O2iii | 0.85 (4) | 1.97 (5) | 2.811 (4) | 173 (4) |
| N22—H22···O1iii | 0.87 (5) | 1.78 (5) | 2.654 (4) | 178 (5) |
| O26—H26···O27iv | 0.87 (5) | 1.80 (5) | 2.647 (4) | 164 (4) |
| O31—H31A···O2v | 0.85 (2) | 2.29 (3) | 3.071 (4) | 154 (5) |
| O31—H31B···O2 | 0.86 (3) | 1.91 (3) | 2.756 (4) | 167 (6) |
| O32—H32···O33v | 0.88 (3) | 2.02 (3) | 2.874 (6) | 164 (8) |
| O32—H32B···O31i | 0.87 (3) | 2.46 (3) | 3.305 (5) | 167 (6) |
| O33—H33A···O15iv | 0.87 (8) | 2.40 (8) | 3.226 (5) | 159 (6) |
| O33—H33B···O32 | 0.88 (8) | 1.97 (8) | 2.837 (6) | 165 (6) |
| C12—H12···O11v | 1.00 | 2.39 | 3.349 (4) | 161 |
| C23—H23···O1iii | 0.95 | 2.41 | 3.281 (4) | 152 |
| C24—H24B···O26v | 0.99 | 2.54 | 3.387 (5) | 143 |

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