Crystal structure of nafamostat dimesylate

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Nafamostat dimesylate [systematic name: [amino([6-[(4-[[amino(iminiumyl)-methyl][amino][phenyl]carbonyloxy]naphthalen-2-yl)methylidene]azanium bis-(methanesulfonate)], C$_{19}$H$_{19}$N$_5$O$_2$\/C$_1$2CH$_3$O$_3$S\/C$_0$, is a broad-spectrum serine protease inhibitor and has been applied clinically as an anticoagulant agent during hemodialysis and for treatment of severe acute pancreatitis (SAP). Since nafamostat contains flexible moieties, it is necessary to determine the conformation to understand the structure–activity relationships. The divalent cation has a screw-like motif. The guanidinium group is approximately perpendicular to the naphthyl ring system, subtending a dihedral angle of 84.30 (14)$^\circ$. In the crystal, the nafamostat molecules form columnar structures surrounded by a hydrophilic region.

1. Chemical context

Nafamostat mesylate (I) is the bismethanesulfonic salt of 6-amidino-2-naphthyl-4-guanidinobenzoate. It shows broad-spectrum serine protease inhibition effect, and is also a reversible competitive inhibitor as camostat mesylate (II) (Tamura et al., 1977; Fujii & Hitomi, 1981; Matsumoto et al., 1989). Although nafamostat mesylate has been applied clinically with success as an effective anticoagulant and anti-inflammatory agent during hemodialysis and for treatment of severe acute pancreatitis (Takeda et al., 1989), the crystal structure has not previously been reported.

In addition, nafamostat has attracted attention as an inhibitor for the activity of transmembrane protease serine 2 (TMPRSS2), a host cell serine protease that mediates viral cell incursion for influenza virus and coronavirus, thereby inhibiting viral infection and replication (Yamamoto et al., 2016, 2020; Hoffmann et al., 2020). Since nafamostat contains flex-
ible moieties, it is necessary to determine the conformation to understand the structure–activity relationships. The crystal structure of nafamostat mesylate (I) is reported herein. From the crystallographic study, the phenylguanidine groups in nafamostat and camostat are essentially similar except for the direction of residual groups.

2. Structural commentary

The nafamostat moiety in the title compound (Fig. 1) shows a divalent cation with a screw-like motif, which consists of four planar parts: the amidino group, the naphthyl group (rings A and B), phenyl ring C and the guanidinium group (shown in Fig. 1). The dihedral angles between the amidino and naphthyl groups, the naphthyl group and ring C, and ring C and guanidinium group are 11.35 (13), 44.66 (10) and 51.11 (15)°, respectively. The guanidinium group is approximately perpendicular to the naphthyl group, subtending a dihedral angle of 84.30 (14)°.

The C14—N15 and C14—N22 bond distances [1.319 (3) and 1.311 (3) Å, respectively] indicate a resonance structure in the protonated amidinium group (Table 1). On the other hand, the bond distances C24—N23 = 1.357 (3), C24—N25 = 1.302 (4) and C24—N26 = 1.325 (3) Å indicate a localized electron on the C24—N25 bond in the protonated guanidinium group.

The overlay of nafamostat (green) and camostat (red) is presented in Fig. 2, in which the r.m.s. deviation is 0.027 Å for phenylguanidino acylation of Ser441 in the active site. Very recently, the crystal structure of human TMPRSS2 in a covalent complex with nafamostat has been solved (Fraser et al., 2021). The nafamostat in the complex is hydrolysed, and results in phenylguanidino acylation of Ser441 (yellow) in the active site. It was considered that the nafamostat moiety may be easily nucleophilic-attacked, approaching from the O13 atom side without steric hindrance.

3. Supramolecular features

In the crystal, the naphthyl groups of nafamostat form hydrophobic columnar structures, shown in Fig. 3. The naph-
The crystal structures of serine protease inhibitors have been reported for benzamidine (TEKTUY: Barker et al., 1996), benzamidine HCl (DOHHAJ: Thailambal et al., 1986) and camostat mesylate (JAMREU: Matsumoto et al., 1989). Moreover, a search of the Cambridge Structural Database (CSD version 5.42, last updated May 2021; Groom et al., 2016) yielded another comparable structure, 4-guainidinobenzoic acid HCl dihydrate (NIQCEW: Light et al., 2007). Another database search (PDB: Berman et al., 2000) yielded the crystal structure of human TMPRSS2 in a covalent complex with nafamostat (PDB7MEQ: Fraser et al., 2021).

5. Synthesis and crystallization
Nafamostat mesylate (CAS No. 82956-11-4) was purchased from Tokyo Chemical Industry Co. Ltd (TCI). A small portion (ca 10 mg) was dissolved in a small volume of hot water (ca 100 μL), and acetone (ca 900 μL) was added slowly until it became cloudy white. On slow cooling to ambient temperature, colourless octahedral crystals suitable for X-ray measurements were obtained.

6. Refinement
Crystal data, data collection and structure refinement details at a low temperature (95 K) are summarized in Table 3. All the H atoms were located in difference-Fourier maps. In the NH and NH₂ groups, H atoms were freely refined. The C-bound H atoms were included in calculated positions and treated as riding atoms: C–H = 0.95–0.98 Å with U(eq)(H) = 1.2–1.5Ueq(C).

Acknowledgements
The author thanks Tokai University for a research grant, which partially supported this work.

Table 2
Hydrogen-bond geometry (Å, °).

| D—H···A | D—H | H···A | D···A | D···H |
|---------|------|-------|-------|-------|
| C18—H18···O31² | 0.95 | 2.64 | 3.419 (3) | 140 |
| C30—H30A···O36i | 0.98 | 2.36 | 3.314 (3) | 165 |
| N15—H15A···O33ii | 0.93 (4) | 1.97 (4) | 2.884 (3) | 159 (3) |
| N15—H15A···O34ii | 0.93 (4) | 2.63 (4) | 3.327 (3) | 132 (3) |
| N15—H15A···S32ii | 0.93 (4) | 2.75 (4) | 3.612 (2) | 154 (3) |
| N15—H15B···O34iv | 0.85 (4) | 2.00 (4) | 2.830 (3) | 164 (4) |
| N22—H22A···O31iv | 0.83 (3) | 2.12 (3) | 2.928 (3) | 162 (3) |
| N22—H22B···O33iv | 0.83 (3) | 2.31 (3) | 3.018 (3) | 144 (3) |
| N23—H23···O36 | 0.99 (4) | 1.88 (5) | 2.836 (3) | 163 (4) |
| N23—H23···S32 | 0.99 (4) | 2.72 (4) | 3.683 (2) | 166 (3) |
| N25—H25A···O28 | 0.87 (4) | 2.00 (4) | 2.827 (3) | 159 (3) |
| N25—H25A···S27 | 0.87 (4) | 2.86 (4) | 3.558 (2) | 139 (3) |
| N25—H25B···O29iv | 0.83 (3) | 2.12 (3) | 2.951 (3) | 167 (3) |
| N26—H26A···O31iv | 0.85 (4) | 2.10 (4) | 2.916 (3) | 163 (4) |
| N26—H26A···S27iv | 0.85 (4) | 3.01 (4) | 3.799 (2) | 156 (3) |
| N26—H26B···O29iv | 0.89 (4) | 2.46 (4) | 2.925 (3) | 113 (3) |
| N26—H26B···O36 | 0.89 (4) | 2.45 (4) | 3.174 (3) | 139 (3) |
| C30—H30B···Cg(C)iv | 0.98 | 2.96 (4) | 3.405 (3) | 109 |

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

4. Database survey
The crystal structures of serine protease inhibitors have been reported for benzamidine (TEKTUY: Barker et al., 1996), benzamidine HCl (DOHHAJ: Thailambal et al., 1986) and camostat mesylate (JAMREU: Matsumoto et al., 1989). Moreover, a search of the Cambridge Structural Database (CSD version 5.42, last updated May 2021; Groom et al., 2016) yielded another comparable structure, 4-guainidinobenzoic acid HCl dihydrate (NIQCEW: Light et al., 2007). Another database search (PDB: Berman et al., 2000) yielded the crystal structure of human TMPRSS2 in a covalent complex with nafamostat (PDB7MEQ: Fraser et al., 2021).

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Acknowledgements
The author thanks Tokai University for a research grant, which partially supported this work.

Table 3
Experimental details.

| Crystal data | Chemical formula | C₁₉H₁₉N₅O₂₂⁻·2CH₃O₃S²⁻ | Mᵣ | 539.58 | Monoclinic, P₂₁/c |
| Temperature (K) | a, b, c (Å) | 11.0631 (1), 9.7215 (1), 21.9271 (3) |
| β (°) | V (Å³) | 96.746 (1) |
| Z | Cu Kα | 2341.93 (5) |
| μ (mm⁻¹) | | 2.59 |
| Crystal size (mm) | | 0.4 × 0.3 × 0.3 |

Data collection
Diffractometer | A Rigaku XtaLAB P200 |
Absorption correction | Multi-scan (CrysAlis PRO; Rigaku, 2015) |
| | |
| T_min, T_max | 0.46, 1 |

No. of measured, independent and observed | 4675, 4675, 4457 |
I > 2σ(I) reflections | 0.058 |
(sin θ/λ) max (Å⁻¹) | 0.623 |

Refinement
R[F² > 2σ(F²)], wR(F²), S | 0.055, 0.126, 1.07 |
No. of reflections | 4675 |
No. of parameters | 363 |
H-atom treatment | H atoms treated by a mixture of independent and constrained refinement |
Δρ_max, Δρ_min (e Å⁻³) | 0.64, −0.52 |

Computer programs: CrysAlis PRO (Rigaku, 2015), SORTAV (Blessing, 1995), SHELXT (Sheldrick, 2015a), SHELXL (Sheldrick, 2015b), ORTEP-3 for Windows and WinGX (Farrugia, 2012), Mercury (Macrae et al., 2020), PLATON (Spek, 2020) and publICIF (Westrip, 2010).
References

Barker, J., Phillips, P. R., Wallbridge, M. G. H. & Powell, H. R. (1996). Acta Cryst. C52, 2617–2619.

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N. & Bourne, P. E. (2000). Nucleic Acids Res. 28, 235–242.

Blessing, R. H. (1995). Acta Cryst. A51, 33–38.

Farrugia, L. J. (2012). J. Appl. Cryst. 45, 849–854.

Fraser, B., Beldar, S., Hutchinson, A., Li, Y., Seitova, A., Edwards, A. M., Benard, F., Arrowsmith, C. H. & Halabelian, L. (2021). doi: 10.2210/pdb7MEQ/pdb.

Fujii, S. & Hitomi, Y. (1981). Biochim. Biophys. Acta Enzymology, 661, 342–345.

Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). Acta Cryst. B72, 171–179.

Hoffmann, M., Schroeder, S., Kleine-Weber, H., Müller, M. A., Drosten, C. & Pöhlmann, S. (2020). Antimicrob. Agents Chemother. 64, e00754–20.

Light, M. E., Martinez, J. C. & Gale, P. A. (2007). CSD Communication (refcode NIQCEW). CCDC, Cambridge, England. https://doi.org/10.5517/cerp2ht3

Macrae, C. F., Sovago, I., Cottrell, S. J., Galek, P. T. A., McCabe, P., Pitcock, E., Platings, M., Shields, G. P., Stevens, J. S., Towler, M. & Wood, P. A. (2020). J. Appl. Cryst. 53, 226–235.

Matsumoto, O., Taga, T. & Machida, K. (1989). Acta Cryst. C45, 913–915.

Rigaku (2015). CrysAlis PRO. Rigaku, The Woodlands, Texas, USA.

Sheldrick, G. M. (2015a). Acta Cryst. A71, 3–8.

Sheldrick, G. M. (2015b). Acta Cryst. C71, 3–8.

Spek, A. L. (2020). Acta Cryst. E76, 1–11.

Takeda, K., Kikutani, Y., Kobari, M. & Matsuno, S. (1989). Gastroenterol. Jpn. 24, 340.

Tamura, Y., Hirado, M., Okamura, K., Minato, Y. & Fujii, S. (1977). Biochim. Biophys. Acta Enzymology, 484, 417–422.

Thailambal, V. G., Pattabhi, V. & Guru Row, T. N. (1986). Acta Cryst. C42, 587–589.

Westrip, S. P. (2010). J. Appl. Cryst. 43, 920–925.

Yamamoto, M., Kiso, M., Sakai-Tagawa, Y., Iwatsuki-Horimoto, K., Imai, M., Takeda, M., Kinoshita, N., Ohmagari, N., Gohda, J., Semba, K., Matsuda, Z., Kawaguchi, Y., Kawaoka, Y. & Inoue, J. (2020). Virus. 12, 629–638.

Yamamoto, M., Matsuyama, S., Li, X., Takeda, M., Kawaguchi, Y., Inoue, J. & Matsuda, Z. (2016). Antimicrob. Agents Chemother. 60, 6532–6539.
supporting information

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Computing details

Data collection: CrysAlis PRO (Rigaku, 2015); cell refinement: CrysAlis PRO (Rigaku, 2015); data reduction: SORTAV (Blessing, 1993); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: SHELXL (Sheldrick, 2015b); molecular graphics: ORTEP-3 for Windows (Farrugia, 2012), Mercury (Macrae et al., 2020); software used to prepare material for publication: PLATON (Spek, 2020), WinGX (Farrugia, 2012) and publCIF (Westrip, 2010).

[Amino([6-[[4-[[amino(iminiumyl)methyl]amino]phenyl]carbonyloxy]naphthalen-2-yl])methylidene]azanium bis(methanesulfonate)

Crystal data

\[\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}_2\text{S}^2\cdot2\text{CH}_3\text{O}_3\text{S}^-\]

\[M_r = 539.58\]

Monoclinic, \(P2_1/c\)

Hall symbol: -P 2ybc

\(a = 11.0631 (1)\) Å

\(b = 9.7215 (1)\) Å

\(c = 21.9271 (3)\) Å

\(\beta = 96.746 (1)^\circ\)

\(V = 2341.93 (5)\) Å\(^3\)

\(Z = 4\)

\(F(000) = 1128\)

\(D_{\text{x}} = 1.53\) Mg m\(^{-3}\)

\(\text{Cu} K\alpha\) radiation, \(\lambda = 1.54184\) Å

Cell parameters from 17552 reflections

\(\theta = 5.0–73.5^\circ\)

\(\mu = 2.59\) mm\(^{-1}\)

\(T = 95\) K

Octahedron, clear light colourless

\(0.4 \times 0.3 \times 0.3\) mm

Data collection

A Rigaku XtaLAB P200 diffractometer

Radiation source: fine-focus sealed X-ray tube

Graphite monochromator

\(\phi\) or \(\omega\) oscillation scans

Absorption correction: multi-scan (CrysAlis PRO; Rigaku, 2015)

\(T_{\text{min}} = 0.46, T_{\text{max}} = 1\)

4675 measured reflections

4675 independent reflections

4457 reflections with \(I > 2\sigma(I)\)

\(R_{\text{int}} = 0.058\)

\(\theta_{\text{max}} = 73.8^\circ, \theta_{\text{min}} = 4.0^\circ\)

\(h = -13\rightarrow13\)

\(k = 0\rightarrow11\)

\(l = 0\rightarrow27\)

Refinement

Refinement on \(F^2\)

Least-squares matrix: full

\(R[F^2 > 2\sigma(F^2)] = 0.055\)

\(wR(F^2) = 0.126\)

\(S = 1.07\)

4675 reflections

363 parameters

0 restraints

0 constraints

Primary atom site location: dual

Secondary atom site location: dual

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

\(w = 1/[\sigma^2(F_c^2) + (0.0324P)^2 + 4.9921P]\)

where \(P = (F_c^2 + 2F_s^2)/3\)
(Δ/σ)_{max} = 0.001
Δρ_{max} = 0.64 \text{ e Å}^{-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_{iso}*/U_{eq} |
|--------|-------|-------|-------|-----------------|
| C1     | 0.1422(2) | 0.5583(3) | 0.56523(13) | 0.0225(5) |
| C2     | 0.0580(2) | 0.5892(3) | 0.60620(13) | 0.0237(5) |
| H2     | 0.061778 | 0.544066 | 0.644799 | 0.028* |
| C3     | −0.0304(2) | 0.6865(3) | 0.58945(12) | 0.0234(5) |
| H3     | −0.086637 | 0.710328 | 0.617287 | 0.028* |
| C4     | −0.0384(2) | 0.7505(3) | 0.53201(12) | 0.0225(5) |
| C5     | −0.1241(2) | 0.8550(3) | 0.51578(12) | 0.0229(5) |
| H5     | −0.177017 | 0.883065 | 0.544597 | 0.027* |
| C6     | −0.1333(2) | 0.9184(3) | 0.45831(13) | 0.0229(5) |
| C7     | −0.0545(2) | 0.8762(3) | 0.41562(12) | 0.0237(5) |
| H7     | −0.060246 | 0.917718 | 0.376162 | 0.028* |
| C8     | 0.0302(2) | 0.7756(3) | 0.43105(12) | 0.0228(5) |
| H8     | 0.081746 | 0.747936 | 0.401556 | 0.027* |
| C9     | 0.0437(2) | 0.7116(3) | 0.48926(12) | 0.0221(5) |
| C10    | 0.1352(2) | 0.6151(3) | 0.50758(12) | 0.0224(5) |
| H10    | 0.191808 | 0.589251 | 0.480271 | 0.027* |
| C12    | 0.3080(2) | 0.4764(3) | 0.63457(12) | 0.0205(5) |
| C14    | −0.2214(2) | 1.0326(3) | 0.44424(12) | 0.0203(5) |
| C16    | 0.4005(2) | 0.3658(3) | 0.64313(12) | 0.0206(5) |
| C17    | 0.4753(2) | 0.3600(3) | 0.69882(12) | 0.0223(5) |
| H17    | 0.466534 | 0.426978 | 0.729554 | 0.027* |
| C18    | 0.5632(2) | 0.2563(3) | 0.70998(12) | 0.0222(5) |
| H18    | 0.61345 | 0.252049 | 0.748167 | 0.027* |
| C19    | 0.5758(2) | 0.1599(3) | 0.66434(12) | 0.0217(5) |
| C20    | 0.5019(2) | 0.1658(3) | 0.60820(12) | 0.0237(5) |
| H20    | 0.51147 | 0.100093 | 0.577062 | 0.028* |
| C21    | 0.4145(2) | 0.2678(3) | 0.59814(12) | 0.0229(5) |
| H21    | 0.363537 | 0.271047 | 0.560152 | 0.027* |
| C24    | 0.7756(2) | 0.0499(3) | 0.69864(12) | 0.0212(5) |
| C30    | 0.7107(2) | 0.5832(3) | 0.76962(13) | 0.0245(6) |
| H30A   | 0.661242 | 0.637008 | 0.738122 | 0.037* |
| H30B   | 0.734263 | 0.641357 | 0.805571 | 0.037* |
| H30C   | 0.663287 | 0.504665 | 0.781635 | 0.037* |
| C35    | 0.6293(2) | −0.4167(3) | 0.57039(13) | 0.0262(6) |
| H35A   | 0.717501 | −0.403331 | 0.578279 | 0.039* |
| H35B   | 0.607172 | −0.441466 | 0.527188 | 0.039* |
| H35C   | 0.604676 | −0.490755 | 0.596665 | 0.039* |
### Atomic displacement parameters (Å²)

|   | $U^{11}$  | $U^{22}$  | $U^{33}$  | $U^{12}$  | $U^{13}$  | $U^{23}$  |
|---|-----------|-----------|-----------|-----------|-----------|-----------|
| C1 | 0.0136 (11) | 0.0182 (13) | 0.0341 (14) | 0.0017 (9) | −0.0030 (10) | −0.0012 (10) |
| C2 | 0.0163 (12) | 0.0241 (14) | 0.0307 (14) | −0.0010 (10) | 0.0023 (10) | 0.0018 (11) |
| C3 | 0.0134 (11) | 0.0253 (14) | 0.0324 (14) | 0.0000 (10) | 0.0060 (10) | −0.0028 (11) |
| C4 | 0.0129 (11) | 0.0224 (13) | 0.0319 (14) | −0.0016 (10) | 0.0021 (10) | −0.0035 (11) |
| C5 | 0.0141 (11) | 0.0245 (14) | 0.0306 (13) | −0.0018 (10) | 0.0047 (10) | −0.0030 (11) |
| C6 | 0.0126 (11) | 0.0194 (13) | 0.0359 (14) | −0.0009 (9) | 0.0002 (10) | −0.0011 (11) |
| C7 | 0.0184 (12) | 0.0250 (14) | 0.0271 (13) | −0.0014 (10) | 0.0005 (10) | 0.0011 (10) |
| C8 | 0.0160 (12) | 0.0217 (13) | 0.0301 (13) | 0.0023 (10) | 0.0008 (10) | −0.0031 (10) |
| C9 | 0.0156 (11) | 0.0249 (14) | 0.0256 (13) | −0.0039 (10) | 0.0015 (10) | −0.0012 (10) |
| C10| 0.0177 (12) | 0.0224 (14) | 0.0277 (13) | −0.0004 (10) | 0.0051 (10) | −0.0012 (10) |
| C12| 0.0138 (11) | 0.0196 (13) | 0.0286 (13) | −0.0014 (9) | 0.0050 (10) | −0.0004 (10) |
| C14| 0.0114 (11) | 0.0187 (13) | 0.0303 (13) | −0.0028 (9) | 0.0000 (9) | −0.0012 (10) |
| C16| 0.0126 (11) | 0.0201 (13) | 0.0293 (13) | −0.0013 (9) | 0.0033 (9) | 0.0019 (10) |
| C17| 0.0170 (12) | 0.0255 (14) | 0.0244 (12) | −0.0037 (10) | 0.0018 (10) | 0.0002 (10) |
| C18| 0.0182 (12) | 0.0219 (13) | 0.0259 (13) | −0.0015 (10) | 0.0000 (10) | −0.0001 (10) |
| C19| 0.0144 (11) | 0.0218 (13) | 0.0290 (13) | −0.0016 (10) | 0.0029 (10) | 0.0020 (10) |
| C20| 0.0166 (12) | 0.0250 (14) | 0.0290 (13) | 0.0003 (10) | 0.0010 (10) | 0.0008 (11) |
| C21| 0.0209 (12) | 0.0217 (13) | 0.0270 (13) | −0.0021 (10) | 0.0069 (10) | 0.0000 (10) |
| C24| 0.0142 (11) | 0.0256 (14) | 0.0247 (12) | 0.0026 (10) | 0.0057 (9)  | 0.0020 (10) |
| C30| 0.0151 (12) | 0.0286 (15) | 0.0301 (14) | 0.0051 (10) | 0.0035 (10) | 0.0020 (11) |
|    |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|
| C35| 0.0194 (12) | 0.0225 (14) | 0.0359 (15) | 0.0023 (10) | 0.0004 (11) | 0.0014 (11) |
| N15| 0.0169 (10) | 0.0226 (12) | 0.0324 (12) | 0.0037 (9)  | 0.0054 (9)  | 0.0062 (10)  |
| N22| 0.0149 (10) | 0.0217 (12) | 0.0280 (12) | 0.0019 (9)  | 0.0037 (9)  | 0.0004 (9)   |
| N23| 0.0137 (10) | 0.0245 (12) | 0.0334 (12) | 0.0027 (9)  | −0.0012 (9) | −0.0001 (10) |
| N25| 0.0160 (11) | 0.0187 (12) | 0.0378 (13) | 0.0028 (9)  | 0.0037 (10) | 0.0035 (10)  |
| N26| 0.0146 (11) | 0.0202 (12) | 0.0409 (14) | 0.0014 (9)  | 0.0034 (9)  | 0.0005 (10)  |
| O1  | 0.0142 (8)  | 0.0238 (10) | 0.0267 (9)  | 0.0021 (7)  | 0.0002 (7)  | −0.0028 (7)  |
| O13 | 0.0184 (9)  | 0.0270 (10) | 0.0310 (10) | 0.0029 (7)  | 0.0019 (7)  | −0.0023 (8)  |
| O28 | 0.0234 (9)  | 0.0202 (9)  | 0.0264 (9)  | 0.0013 (7)  | 0.0021 (7)  | −0.0010 (7)  |
| O29 | 0.0202 (9)  | 0.0200 (10) | 0.0358 (10) | −0.0005 (7) | 0.0059 (8)  | 0.0036 (8)   |
| O31 | 0.0136 (8)  | 0.0236 (10) | 0.0288 (9)  | 0.0045 (7)  | 0.0012 (7)  | 0.0060 (7)   |
| O33 | 0.0126 (9)  | 0.0248 (10) | 0.0547 (13) | 0.0006 (7)  | 0.0027 (8)  | 0.0066 (9)   |
| O34 | 0.0288 (10) | 0.0214 (10) | 0.0358 (11) | 0.0005 (8)  | 0.0102 (8)  | 0.0067 (8)   |
| O36 | 0.0398 (11) | 0.0225 (10) | 0.0282 (10) | 0.0011 (8)  | −0.0038 (8) | 0.0013 (8)   |
| S27 | 0.0124 (3)  | 0.0184 (3)  | 0.0264 (3)  | 0.0017 (2)  | 0.0034 (2)  | 0.0019 (2)   |
| S32 | 0.0117 (3)  | 0.0167 (3)  | 0.0281 (3)  | 0.0007 (2)  | 0.0021 (2)  | 0.0025 (2)   |

**Geometric parameters (Å, °)**

|     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|
| C1—O11 | 1.391 (3) | C35—S32 | 1.762 (3) |
| C1—C2  | 1.401 (4) | C35—H35C | 0.98 |
| C1—C10 | 1.373 (4) | C35—H35B | 0.98 |
| C10—H10 | 0.95 | C35—H35A | 0.98 |
| C12—O13 | 1.204 (3) | C4—C9 | 1.430 (4) |
| C12—O11 | 1.377 (3) | C4—C5 | 1.407 (4) |
| C12—C16 | 1.481 (3) | C5—H5 | 0.95 |
| C14—N22 | 1.311 (3) | C5—C6 | 1.396 (4) |
| C14—N15 | 1.319 (3) | C6—C7 | 1.413 (4) |
| C16—C21 | 1.393 (4) | C6—C14 | 1.486 (3) |
| C16—C17 | 1.393 (4) | C7—H7 | 0.95 |
| C17—H17 | 0.95 | C7—C8 | 1.369 (4) |
| C17—C18 | 1.402 (4) | C8—H8 | 0.95 |
| C18—H18 | 0.95 | C8—C9 | 1.412 (4) |
| C18—C19 | 1.390 (4) | C9—C10 | 1.403 (4) |
| C19—N23 | 1.417 (3) | N15—H15B | 0.85 (4) |
| C19—C20 | 1.397 (4) | N15—H15A | 0.93 (4) |
| C2—H2  | 0.95 | N22—H22B | 0.83 (3) |
| C2—C3  | 1.379 (4) | N22—H22A | 0.83 (3) |
| C20—H20 | 0.95 | N23—H23 | 0.99 (4) |
| C20—C21 | 1.384 (4) | N25—H25B | 0.83 (3) |
| C21—H21 | 0.95 | N25—H25A | 0.87 (4) |
| C24—N26 | 1.325 (3) | N26—H26B | 0.89 (4) |
| C24—N25 | 1.302 (4) | N26—H26A | 0.85 (4) |
| C24—N23 | 1.357 (3) | O28—S27 | 1.4515 (19) |
| C3—H3  | 0.95 | O29—S27 | 1.4570 (19) |
| C3—C4  | 1.398 (4) | O31—S27 | 1.4700 (18) |
| C30—S27 | 1.764 (3) | O33—S32 | 1.4545 (18) |
| C30—H30C | 0.98 | O34—S32 | 1.4553 (19) |
C30—H30B 0.98  O36—S32 1.448 (2)
C30—H30A 0.98

C10—C1—O11 116.5 (2)  C21—C20—H20 120.2
C10—C1—C2 122.3 (2)  C19—C20—H20 120.2
O11—C1—C2 121.2 (2)  C20—C21—C16 120.7 (3)
C3—C2—C1 118.7 (2)  C20—C21—H21 119.6
C3—C2—H2 120.6  C16—C21—H21 119.6
C1—C2—H2 120.6  N25—C24—N26 121.0 (2)
C2—C3—C4 120.8 (2)  N25—C24—N23 123.3 (2)
C2—C3—H3 119.6  N26—C24—N23 115.7 (2)
C4—C3—H3 119.6  S27—C30—H30A 109.5
C3—C4—C5 121.2 (2)  S27—C30—H30B 109.5
C3—C4—C9 119.7 (2)  H30A—C30—H30B 109.5
C5—C4—C9 119.1 (2)  S27—C30—H30C 109.5
C6—C5—C4 121.5 (2)  H30A—C30—H30C 109.5
C6—C5—H5 119.3  H30B—C30—H30C 109.5
C3—C5—H5 119.3  S32—C35—H35A 109.5
C5—C6—C7 119.0 (2)  S32—C35—H35B 109.5
C5—C6—C14 119.6 (2)  H35A—C35—H35B 109.5
C7—C6—C14 121.3 (2)  S32—C35—H35C 109.5
C8—C7—C6 120.1 (2)  H35A—C35—H35C 109.5
C8—C7—H7 120  H35B—C35—H35C 109.5
C6—C7—H7 120  C14—N15—H15A 116 (2)
C7—C8—C9 122.3 (2)  C14—N15—H15B 120 (3)
C7—C8—H8 118.8  H15A—N15—H15B 121 (3)
C9—C8—H8 118.8  C14—N22—H22A 123 (2)
C10—C9—C8 123.3 (2)  C14—N22—H22B 121 (2)
C10—C9—C4 118.7 (2)  H22A—N22—H22B 116 (3)
C8—C9—C4 117.9 (2)  C24—N23—C19 127.7 (2)
C1—C10—C9 119.6 (2)  C24—N23—H23 115 (2)
C1—C10—H10 120.2  C19—N23—H23 117 (2)
C9—C10—H10 120.2  C24—N25—H25B 121 (2)
O13—C12—O11 122.9 (2)  C24—N25—H25A 122 (2)
O13—C12—C16 125.5 (2)  H25B—N25—H25A 116 (3)
O11—C12—C16 111.6 (2)  C24—N26—H26B 122 (2)
N22—C14—N15 119.1 (2)  C24—N26—H26A 120 (3)
N22—C14—C6 121.9 (2)  H26B—N26—H26A 117 (4)
N15—C14—C6 119.0 (2)  C12—O11—C1 118.4 (2)
C17—C16—C21 119.3 (2)  O28—S27—O29 113.51 (11)
C17—C16—C12 118.1 (2)  O28—S27—O31 112.04 (11)
C21—C16—C12 122.6 (2)  O29—S27—O31 111.41 (11)
C16—C17—C18 120.7 (2)  O28—S27—C30 106.72 (12)
C16—C17—H17 119.7  O29—S27—C30 106.21 (12)
C18—C17—H17 119.7  O31—S27—C30 106.39 (12)
C19—C18—C17 119.0 (2)  O36—S32—O33 113.48 (13)
C19—C18—H18 120.5  O36—S32—O34 111.82 (12)
C17—C18—H18 120.5  O33—S32—O34 110.96 (12)
C18—C19—C20  &  120.6 (2)  &  O36—S32—C35  &  106.84 (13)  
C18—C19—N23  &  122.1 (2)  &  O33—S32—C35  &  105.73 (12)  
C20—C19—N23  &  117.2 (2)  &  O34—S32—C35  &  107.57 (12)  
C21—C20—C19  &  119.7 (3)  

Hydrogen-bond geometry (Å, °)

$Cg(C)$ is the center of gravity of phenyl ring C.

| D—H···A         | D—H | H···A | D···A  | D—H···A |
|----------------|------|-------|--------|---------|
| C18—H18···O13i | 0.95 | 2.64  | 3.419 (3) | 140     |
| C30—H30A···O36i | 0.98 | 2.36  | 3.314 (3) | 165     |
| N15—H15A···O33iii | 0.93 (4) | 1.97 (4) | 2.854 (3) | 159 (3) |
| N15—H15A···O34iii | 0.93 (4) | 2.63 (4) | 3.327 (3) | 132 (3) |
| N15—H15A···S32iii | 0.93 (4) | 2.75 (4) | 3.612 (2) | 154 (3) |
| N15—H15A···O34iii | 0.85 (4) | 2.00 (4) | 2.830 (3) | 164 (4) |
| N22—H22A···O31v | 0.83 (3) | 2.12 (3) | 2.928 (3) | 162 (3) |
| N22—H22B···O33iii | 0.83 (3) | 2.31 (3) | 3.018 (3) | 144 (3) |
| N23—H23···O36  | 0.99 (4) | 1.88 (5) | 2.836 (3) | 163 (4) |
| N23—H23···S32  | 0.99 (4) | 2.72 (4) | 3.683 (2) | 166 (3) |
| N25—H25A···O28  | 0.87 (4) | 2.00 (4) | 2.827 (3) | 159 (3) |
| N25—H25A···S27v | 0.87 (4) | 2.86 (4) | 3.558 (2) | 139 (3) |
| N25—H25B···O29vi | 0.83 (3) | 2.12 (3) | 2.931 (3) | 167 (3) |
| N26—H26A···O31vi | 0.85 (4) | 2.10 (4) | 2.916 (3) | 163 (4) |
| N26—H26A···S27vi | 0.85 (4) | 3.01 (4) | 3.799 (2) | 156 (3) |
| N26—H26B···O29vi | 0.89 (4) | 2.46 (4) | 2.925 (3) | 113 (3) |
| N26—H26B···O36 | 0.89 (4) | 2.45 (4) | 3.174 (3) | 139 (3) |
| C30—H30B···Cg(C)iii | 0.98 | 2.96  | 3.405 (3) | 109     |

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