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Paliperidone: 3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-9-hydroxy-2-methyl-1,6,7,8,9,9a-hexahydroxyprido[1,2-a]pyrimidin-4-one

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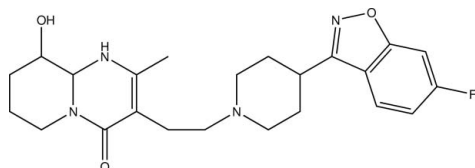
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Key indicators: single-crystal X-ray study; $T = 200$ K; mean $\sigma(\text{C}-\text{C}) = 0.002$ Å; disorder in main residue; R factor = 0.045; wR factor = 0.130; data-to-parameter ratio = 17.7.

The title compound (also known as 9-hydroxyrisperidone), $\text{C}_{23}\text{H}_{27}\text{FN}_4\text{O}_3$, is a heterocyclic compound with manifold pharmacological properties. The hydroxy group shows disorder over two positions, with site-occupancy factors of 0.856 (2) and 0.144 (2). The piperidine ring adopts a chair conformation, while the annulated ring bearing the hydroxy group is present in a half-chair conformation. Classical $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds as well as $\text{C}-\text{H}\cdots\text{N}$ contacts connect the molecules into undulating sheets lying perpendicular to the crystallographic b axis. The shortest centroid-centroid distance between two centers of gravity is 3.5867 (8) Å and is apparent between the benzoxazole moiety and the six-membered ring bearing the keto substituent.

Related literature

For pharmacological background, see: de Leon *et al.* (2010); Spina & Crupi (2011). For related structures, see: Peeters *et al.* (1993); Ravikumar *et al.* (2005); Sun & Zhang (2009); Wang & Pan (2006). For graph-set analysis of hydrogen bonds, see: Etter *et al.* (1990); Bernstein *et al.* (1995). For puckering analysis, see: Cremer & Pople (1975).



Experimental

Crystal data

$\text{C}_{23}\text{H}_{27}\text{FN}_4\text{O}_3$
 $M_r = 426.49$
Monoclinic, $P2_1/c$
 $a = 6.8537$ (1) Å
 $b = 21.5613$ (5) Å
 $c = 15.3472$ (3) Å
 $\beta = 113.857$ (1)°
 $V = 2074.15$ (7) Å³
 $Z = 4$
Mo $K\alpha$ radiation
 $\mu = 0.10$ mm⁻¹
 $T = 200$ K
 $0.52 \times 0.37 \times 0.23$ mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (SADABS; Bruker, 2008)
 $T_{\min} = 0.944$, $T_{\max} = 1.000$
19267 measured reflections
5138 independent reflections
4130 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.015$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.045$
 $wR(F^2) = 0.130$
 $S = 1.07$
5138 reflections
291 parameters
3 restraints
H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.39$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.30$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
$\text{O1}-\text{H1}\cdots\text{O2}^i$	0.84	1.86	2.6945 (16)	174
$\text{O1B}-\text{H1B}\cdots\text{O2}^i$	0.84	2.39	3.153 (8)	152
$\text{C4}-\text{H4A}\cdots\text{N4}^{ii}$	0.99	2.55	3.4830 (19)	157

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

Data collection: APEX2 (Bruker, 2010); cell refinement: SAINT (Bruker, 2010); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: ORTEP-3 (Farrugia, 1997) and Mercury (Macrae *et al.*, 2008); software used to prepare material for publication: SHELXL97 and PLATON (Spek, 2009).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: ZL2406).

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supplementary materials

Acta Cryst. (2011). E67, o2945–o2946 [doi:10.1107/S160053681104164X]

Paliperidone: 3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-9-hydroxy-2-methyl-1,6,7,8,9,9a-hexahydropyrido[1,2-*a*]pyrimidin-4-one

R. Betz, T. Gerber, E. Hosten, A. S. Dayananda, H. S. Yathirajan and S. Thomas

Comment

Paliperidone, or 9-hydroxyrisperidone, is one of the most recently available atypical antipsychotics (Spina & Crupi, 2011). It is a benzisoxazole derivative and the major active metabolite of risperidone, a widely used atypical antipsychotic approved for the treatment of schizophrenia and other psychiatric disorders. The pharmacokinetics of paliperidone *versus* risperidone have been published (de Leon *et al.*, 2010). Related crystal structures, *viz.* 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl}-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one [risperidone] (Peeters *et al.*, 1993), risperidone *N*-oxide hydrogen peroxide methanol solvate (Ravikumar *et al.*, 2005), risperidone chloride 2.5 hydrate (Wang & Pan, 2006), 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidinium nitrate (Sun & Zhang, 2009) have been reported. In view of the importance of the title compound we herein report its molecular and crystal structure.

The hydroxy group as well as the hydrogen atoms of the methyl group show disorder. While the hydroxy group is disordered over two defined positions with site occupancy factors of 0.856 (2) and 0.144 (2), rotational disorder is observed for the hydrogen atoms of the methyl group (occupancy ratio 0.68 (2) to 0.32 (2)). The low puckering amplitude of the six-membered ring bearing the keto group precludes a conformational analysis (Cremer & Pople, 1975). The piperidine ring is present in a 1C_4 conformation (${}^{N^3}C_{C23}$) and the hydroxy-tetrahydropyrido ring annulated on the pyrimidin-4-one ring adopts a 5H_4 conformation (${}^{C^4}H_{C3}$) (Fig. 1). Proton NMR spectra of dissolved crystals of the title compound do not indicate the presence of the two stereoisomers as became apparent upon modelling the disorder for the hydroxy group in an axial-equatorial configuration.

In the crystal, classical hydrogen bonds of the O–H \cdots O type as well as C–H \cdots N contacts whose range falls by 0.2 Å below the sum of van-der-Waals radii can be observed. While the classical hydrogen bonds are apparent between the hydroxy group as donor and the keto group as acceptor, the C–H \cdots N contacts appear between one of the methylene groups of the central aza-cyclohexane moiety and the nitrogen atom of the oxazol subunit. In terms of graph-set analysis (Etter *et al.*, 1990; Bernstein *et al.*, 1995), the descriptor for the classical hydrogen bonds is $C^1_1(7)$ whereas the C–H \cdots N contacts necessitate a $C^1_1(14)$ descriptor on the same level. In total, the molecules are connected to undulated sheets perpendicular to the crystallographic *b* axis. The shortest intercentroid distance between two centers of gravity was found at 3.5871 (8) Å and is observed between the oxazol subunit and the six-membered heterocycle bearing the keto-group (Fig. 2). Furthermore, a F \cdots C_g contact ($d_{F\cdots C_g}$: 3.2038 (12) Å) is observed between the fluorine atom and the six-membered ring bearing the keto group.

The packing of the title compound is shown in Figure 3.

Experimental

The title compound was obtained as a gift sample from Jubilant Life Sciences Ltd., Noida, India. Paliperidone was recrystallized from *N,N*-dimethylformamide by slow evaporation at room temperature.

Refinement

Four reflections, 1 0 4, -1 3 1, 0 4 4 and 0 1 1 were found to be obstructed by the beam stop and were omitted from the refinement. Carbon-bound H atoms were placed in calculated positions (C—H = 0.95 Å for aromatic carbon atoms and C—H = 0.99 Å for methylene groups) and were included in the refinement in the riding model approximation, with $U(\text{H})$ set to $1.2U_{\text{eq}}(\text{C})$. The H atoms of the methyl groups were refined as rotationally disordered over two positions (orientations separated by 60° rotation of the H atoms) and allowed to rotate with a fixed angle around the C—C bond to best fit the experimental electron density and to account for rotational disorder (HFIX 127 in the *SHELX* program suite (Sheldrick, 2008)), with $U(\text{H})$ set to $1.5U_{\text{eq}}(\text{C})$. Occupancies refined to 0.68 (2) and 0.32 (2). The H atom of the hydroxy group was allowed to rotate with a fixed angle around the C—O bond to best fit the experimental electron density (HFIX 147 in the *SHELX* program suite (Sheldrick, 2008)), with $U(\text{H})$ set to $1.5U_{\text{eq}}(\text{O})$. The disorder of the hydroxy group was handled with a disorder model over two positions and site occupancy factors of 0.856 (2) and 0.144 (2). The anisotropic displacement parameters of the two oxygen atoms and of the two carbon atoms of the disordered group were each constrained to be identical. Equivalent bond distances in the disordered sections (C2—O1 and C2b—O1b, C1—C2 and C1—C2b, and C2—C3 and C2b—C3) were restrained to be the same within a standard deviation of 0.02 Å. Some minor residual electron density – that could not be resolved in any chemically meaningful way – remained.

Figures

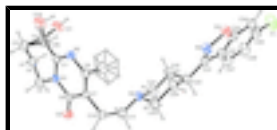


Fig. 1. The molecular structure of the title compound, with atom labels and anisotropic displacement ellipsoids (drawn at 50% probability level).

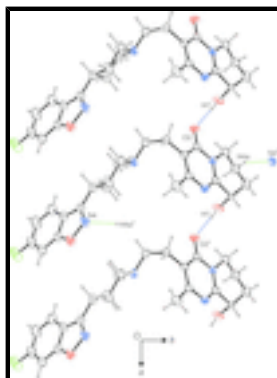


Fig. 2. Selected intermolecular contacts, viewed along [0 0 -1]. For clarity, only the main components of the disordered parts of the molecule are depicted. Blue dashed lines indicate classical hydrogen bonds of the O—H \cdots O type, green dashed lines indicate C—H \cdots N contacts. Symmetry operators: ⁱ $x - 1, y, z$; ⁱⁱ $x - 1, -y + 1/2, z - 1/2$; ⁱⁱⁱ $x + 1, -y + 1/2, z + 1/2$; ^{iv} $x + 1, y, z$.

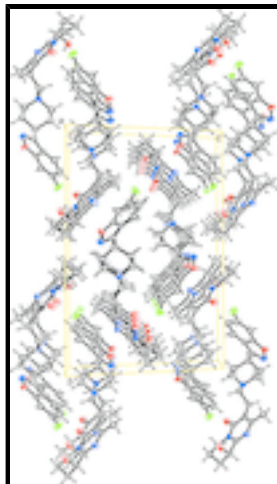


Fig. 3. Molecular packing of the title compound, viewed along $[-1\ 0\ 0]$ (anisotropic displacement ellipsoids drawn at 50% probability level). For clarity, only the main components of the disordered part of the molecule are depicted.

3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-9-hydroxy-2-methyl-1,6,7,8,9,9a-hexahydro-*pyrido*[1,2-*a*]pyrimidin-4-one

Crystal data

$C_{23}H_{27}FN_4O_3$

$M_r = 426.49$

Monoclinic, $P2_1/c$

Hall symbol: $-P\ 2ybc$

$a = 6.8537\ (1)\ \text{\AA}$

$b = 21.5613\ (5)\ \text{\AA}$

$c = 15.3472\ (3)\ \text{\AA}$

$\beta = 113.857\ (1)^\circ$

$V = 2074.15\ (7)\ \text{\AA}^3$

$Z = 4$

$F(000) = 904$

$D_x = 1.366\ \text{Mg m}^{-3}$

Melting point = 431–433 K

Mo $K\alpha$ radiation, $\lambda = 0.71073\ \text{\AA}$

Cell parameters from 8433 reflections

$\theta = 2.4\text{--}28.3^\circ$

$\mu = 0.10\ \text{mm}^{-1}$

$T = 200\ \text{K}$

Platelet, colourless

$0.52 \times 0.37 \times 0.23\ \text{mm}$

Data collection

Bruker APEXII CCD
diffractometer

Radiation source: fine-focus sealed tube
graphite

φ and ω scans

Absorption correction: multi-scan
(*SADABS*; Bruker, 2008)

$T_{\min} = 0.944$, $T_{\max} = 1.000$

19267 measured reflections

5138 independent reflections

4130 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.015$

$\theta_{\max} = 28.3^\circ$, $\theta_{\min} = 1.9^\circ$

$h = -9 \rightarrow 5$

$k = -28 \rightarrow 28$

$l = -19 \rightarrow 20$

Refinement

Refinement on F^2

Least-squares matrix: full

Primary atom site location: structure-invariant direct
methods

Secondary atom site location: difference Fourier map

supplementary materials

$$R[F^2 > 2\sigma(F^2)] = 0.045$$

$$wR(F^2) = 0.130$$

$$S = 1.07$$

5138 reflections

291 parameters

3 restraints

Hydrogen site location: inferred from neighbouring sites

H-atom parameters constrained

$$w = 1/[\sigma^2(F_o^2) + (0.0609P)^2 + 0.7502P]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

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

$$\Delta\rho_{\max} = 0.39 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.30 \text{ e } \text{\AA}^{-3}$$

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 (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$	Occ. (<1)
F1	0.9472 (2)	-0.23734 (5)	0.06766 (8)	0.0637 (3)	
C1	0.3065 (2)	0.34124 (6)	0.10562 (9)	0.0263 (3)	
C2	0.4057 (3)	0.38777 (13)	0.0575 (3)	0.0303 (5)	0.856 (2)
H2	0.5363	0.4076	0.1061	0.036*	0.856 (2)
O1	0.4566 (2)	0.35414 (7)	-0.00902 (10)	0.0441 (4)	0.856 (2)
H1	0.5676	0.3332	0.0197	0.066*	0.856 (2)
C2B	0.371 (2)	0.3800 (9)	0.0602 (19)	0.0303 (5)	0.144 (2)
H2B	0.3836	0.3531	0.0096	0.036*	0.144 (2)
O1B	0.5863 (13)	0.4016 (4)	0.1090 (6)	0.0441 (4)	0.144 (2)
H1B	0.6707	0.3714	0.1204	0.066*	0.144 (2)
O2	-0.19649 (16)	0.28148 (5)	0.07163 (8)	0.0385 (3)	
O3	0.98743 (17)	-0.07016 (5)	0.27657 (8)	0.0355 (2)	
N1	0.09124 (17)	0.33395 (5)	0.07005 (8)	0.0243 (2)	
N2	0.43993 (18)	0.30815 (6)	0.17546 (9)	0.0304 (3)	
N3	0.19463 (19)	0.10440 (5)	0.16460 (8)	0.0297 (3)	
N4	0.8250 (2)	-0.02973 (6)	0.27986 (10)	0.0358 (3)	
C3	0.2461 (2)	0.43659 (7)	0.00112 (11)	0.0352 (3)	
H3A	0.2185	0.4652	0.0453	0.042*	
H3B	0.3052	0.4611	-0.0371	0.042*	
C4	0.0400 (2)	0.40636 (7)	-0.06404 (10)	0.0343 (3)	
H4A	-0.0587	0.4382	-0.1050	0.041*	
H4B	0.0687	0.3760	-0.1058	0.041*	
C5	-0.0608 (2)	0.37407 (7)	-0.00587 (10)	0.0310 (3)	
H5A	-0.1195	0.4056	0.0238	0.037*	
H5B	-0.1811	0.3484	-0.0486	0.037*	
C6	-0.0004 (2)	0.28750 (6)	0.10498 (10)	0.0257 (3)	
C7	0.1457 (2)	0.24916 (6)	0.17907 (10)	0.0256 (3)	
C8	0.3594 (2)	0.26122 (6)	0.21256 (10)	0.0283 (3)	

C9	0.5251 (2)	0.22464 (8)	0.29070 (12)	0.0410 (4)	
H9A	0.6444	0.2519	0.3278	0.061*	0.68 (2)
H9B	0.5769	0.1909	0.2629	0.061*	0.68 (2)
H9C	0.4623	0.2073	0.3325	0.061*	0.68 (2)
H9D	0.4780	0.1815	0.2877	0.061*	0.32 (2)
H9E	0.5455	0.2425	0.3525	0.061*	0.32 (2)
H9F	0.6601	0.2261	0.2830	0.061*	0.32 (2)
C10	0.0456 (2)	0.19768 (6)	0.21276 (11)	0.0321 (3)	
H10A	-0.0903	0.2126	0.2135	0.038*	
H10B	0.1416	0.1864	0.2788	0.038*	
C11	0.0019 (2)	0.13990 (7)	0.14944 (12)	0.0365 (3)	
H11A	-0.1000	0.1128	0.1624	0.044*	
H11B	-0.0659	0.1528	0.0818	0.044*	
C21	0.1578 (3)	0.06087 (7)	0.08649 (12)	0.0398 (4)	
H21A	0.1067	0.0839	0.0255	0.048*	
H21B	0.0453	0.0310	0.0833	0.048*	
C22	0.3598 (3)	0.02553 (7)	0.09942 (11)	0.0370 (3)	
H22A	0.4695	0.0550	0.0983	0.044*	
H22B	0.3286	-0.0040	0.0461	0.044*	
C23	0.4457 (2)	-0.01007 (7)	0.19418 (11)	0.0325 (3)	
H23	0.3353	-0.0411	0.1920	0.039*	
C24	0.4728 (3)	0.03595 (7)	0.27396 (11)	0.0370 (3)	
H24A	0.5180	0.0134	0.3352	0.044*	
H24B	0.5860	0.0662	0.2794	0.044*	
C25	0.2667 (3)	0.07031 (7)	0.25493 (11)	0.0371 (3)	
H25A	0.1553	0.0403	0.2526	0.044*	
H25B	0.2889	0.0997	0.3076	0.044*	
C31	0.6466 (2)	-0.04472 (6)	0.20962 (10)	0.0299 (3)	
C32	0.6772 (2)	-0.09575 (6)	0.15598 (10)	0.0300 (3)	
C33	0.8930 (2)	-0.10890 (6)	0.20159 (10)	0.0296 (3)	
C34	0.9956 (3)	-0.15634 (7)	0.17502 (11)	0.0346 (3)	
H34	1.1440	-0.1646	0.2068	0.041*	
C35	0.8610 (3)	-0.19004 (7)	0.09821 (12)	0.0415 (4)	
C36	0.6432 (3)	-0.17991 (8)	0.04974 (12)	0.0480 (4)	
H36	0.5604	-0.2055	-0.0026	0.058*	
C37	0.5487 (3)	-0.13217 (7)	0.07852 (12)	0.0414 (4)	
H37	0.4001	-0.1242	0.0465	0.050*	

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1	0.0769 (8)	0.0536 (7)	0.0580 (7)	0.0184 (6)	0.0246 (6)	-0.0218 (5)
C1	0.0285 (7)	0.0250 (6)	0.0276 (6)	0.0007 (5)	0.0135 (5)	-0.0010 (5)
C2	0.0238 (10)	0.0304 (11)	0.0399 (8)	-0.0053 (8)	0.0161 (9)	0.0069 (7)
O1	0.0381 (7)	0.0552 (8)	0.0450 (8)	0.0164 (6)	0.0231 (6)	0.0159 (6)
C2B	0.0238 (10)	0.0304 (11)	0.0399 (8)	-0.0053 (8)	0.0161 (9)	0.0069 (7)
O1B	0.0381 (7)	0.0552 (8)	0.0450 (8)	0.0164 (6)	0.0231 (6)	0.0159 (6)
O2	0.0243 (5)	0.0380 (6)	0.0518 (7)	0.0046 (4)	0.0138 (5)	0.0109 (5)

supplementary materials

O3	0.0336 (5)	0.0306 (5)	0.0390 (6)	0.0009 (4)	0.0111 (4)	-0.0088 (4)
N1	0.0258 (5)	0.0229 (5)	0.0244 (5)	0.0036 (4)	0.0105 (4)	0.0017 (4)
N2	0.0257 (6)	0.0310 (6)	0.0342 (6)	0.0010 (5)	0.0118 (5)	0.0038 (5)
N3	0.0293 (6)	0.0254 (5)	0.0320 (6)	0.0026 (4)	0.0099 (5)	0.0025 (5)
N4	0.0368 (7)	0.0295 (6)	0.0396 (7)	0.0040 (5)	0.0137 (6)	-0.0069 (5)
C3	0.0407 (8)	0.0291 (7)	0.0355 (8)	-0.0008 (6)	0.0153 (6)	0.0053 (6)
C4	0.0366 (8)	0.0336 (7)	0.0306 (7)	0.0041 (6)	0.0114 (6)	0.0057 (6)
C5	0.0289 (7)	0.0325 (7)	0.0286 (7)	0.0055 (5)	0.0085 (5)	0.0061 (5)
C6	0.0260 (6)	0.0237 (6)	0.0305 (6)	0.0032 (5)	0.0146 (5)	0.0000 (5)
C7	0.0275 (6)	0.0229 (6)	0.0297 (6)	0.0043 (5)	0.0151 (5)	0.0021 (5)
C8	0.0280 (7)	0.0271 (6)	0.0300 (7)	0.0037 (5)	0.0118 (5)	0.0020 (5)
C9	0.0302 (8)	0.0421 (9)	0.0441 (9)	0.0054 (6)	0.0082 (7)	0.0151 (7)
C10	0.0314 (7)	0.0280 (7)	0.0419 (8)	0.0047 (5)	0.0201 (6)	0.0080 (6)
C11	0.0264 (7)	0.0284 (7)	0.0512 (9)	-0.0004 (5)	0.0120 (6)	0.0038 (6)
C21	0.0369 (8)	0.0350 (8)	0.0362 (8)	0.0028 (6)	0.0031 (6)	-0.0050 (6)
C22	0.0392 (8)	0.0373 (8)	0.0293 (7)	0.0052 (6)	0.0086 (6)	-0.0032 (6)
C23	0.0336 (7)	0.0256 (6)	0.0385 (8)	0.0021 (5)	0.0148 (6)	0.0002 (5)
C24	0.0460 (9)	0.0348 (8)	0.0297 (7)	0.0147 (6)	0.0149 (6)	0.0054 (6)
C25	0.0453 (9)	0.0310 (7)	0.0407 (8)	0.0096 (6)	0.0233 (7)	0.0089 (6)
C31	0.0349 (7)	0.0238 (6)	0.0316 (7)	-0.0001 (5)	0.0141 (6)	0.0001 (5)
C32	0.0352 (7)	0.0249 (6)	0.0294 (7)	-0.0002 (5)	0.0125 (6)	-0.0011 (5)
C33	0.0367 (7)	0.0237 (6)	0.0292 (7)	-0.0020 (5)	0.0144 (6)	-0.0012 (5)
C34	0.0396 (8)	0.0301 (7)	0.0367 (8)	0.0040 (6)	0.0182 (6)	0.0000 (6)
C35	0.0566 (10)	0.0321 (8)	0.0377 (8)	0.0082 (7)	0.0211 (7)	-0.0054 (6)
C36	0.0575 (11)	0.0385 (9)	0.0383 (9)	0.0000 (8)	0.0093 (8)	-0.0139 (7)
C37	0.0396 (8)	0.0360 (8)	0.0385 (8)	-0.0001 (6)	0.0055 (7)	-0.0071 (6)

Geometric parameters (Å, °)

F1—C35	1.3537 (18)	C9—H9A	0.9800
C1—C2B	1.277 (18)	C9—H9B	0.9800
C1—N2	1.3042 (18)	C9—H9C	0.9800
C1—N1	1.3596 (17)	C9—H9D	0.9800
C1—C2	1.556 (2)	C9—H9E	0.9800
C2—O1	1.406 (4)	C9—H9F	0.9800
C2—C3	1.512 (3)	C10—C11	1.533 (2)
C2—H2	1.0000	C10—H10A	0.9900
O1—H1	0.8400	C10—H10B	0.9900
C2B—O1B	1.434 (16)	C11—H11A	0.9900
C2B—C3	1.555 (15)	C11—H11B	0.9900
C2B—H2B	1.0000	C21—C22	1.521 (2)
O1B—H1B	0.8400	C21—H21A	0.9900
O2—C6	1.2363 (16)	C21—H21B	0.9900
O3—C33	1.3559 (16)	C22—C23	1.536 (2)
O3—N4	1.4309 (16)	C22—H22A	0.9900
N1—C6	1.3990 (17)	C22—H22B	0.9900
N1—C5	1.4865 (16)	C23—C31	1.499 (2)
N2—C8	1.3811 (18)	C23—C24	1.528 (2)
N3—C11	1.4615 (18)	C23—H23	1.0000

N3—C21	1.4619 (19)	C24—C25	1.515 (2)
N3—C25	1.4671 (18)	C24—H24A	0.9900
N4—C31	1.3019 (19)	C24—H24B	0.9900
C3—C4	1.509 (2)	C25—H25A	0.9900
C3—H3A	0.9900	C25—H25B	0.9900
C3—H3B	0.9900	C31—C32	1.4392 (19)
C4—C5	1.503 (2)	C32—C33	1.386 (2)
C4—H4A	0.9900	C32—C37	1.399 (2)
C4—H4B	0.9900	C33—C34	1.392 (2)
C5—H5A	0.9900	C34—C35	1.374 (2)
C5—H5B	0.9900	C34—H34	0.9500
C6—C7	1.4344 (18)	C35—C36	1.390 (3)
C7—C8	1.3667 (19)	C36—C37	1.381 (2)
C7—C10	1.5023 (19)	C36—H36	0.9500
C8—C9	1.4994 (19)	C37—H37	0.9500
C2B—C1—N2	121.6 (7)	H9D—C9—H9E	109.5
C2B—C1—N1	114.6 (7)	C8—C9—H9F	109.5
N2—C1—N1	123.57 (12)	H9A—C9—H9F	56.3
N2—C1—C2	116.57 (14)	H9B—C9—H9F	56.3
N1—C1—C2	119.70 (13)	H9C—C9—H9F	141.1
O1—C2—C3	106.2 (2)	H9D—C9—H9F	109.5
O1—C2—C1	107.2 (2)	H9E—C9—H9F	109.5
C3—C2—C1	111.50 (15)	C7—C10—C11	112.43 (12)
O1—C2—H2	110.6	C7—C10—H10A	109.1
C3—C2—H2	110.6	C11—C10—H10A	109.1
C1—C2—H2	110.6	C7—C10—H10B	109.1
C1—C2B—O1B	116.0 (15)	C11—C10—H10B	109.1
C1—C2B—C3	126.9 (14)	H10A—C10—H10B	107.9
O1B—C2B—C3	104.9 (11)	N3—C11—C10	113.10 (12)
C1—C2B—H2B	101.6	N3—C11—H11A	109.0
O1B—C2B—H2B	101.6	C10—C11—H11A	109.0
C3—C2B—H2B	101.6	N3—C11—H11B	109.0
C2B—O1B—H1B	109.5	C10—C11—H11B	109.0
C33—O3—N4	107.11 (10)	H11A—C11—H11B	107.8
C1—N1—C6	120.76 (11)	N3—C21—C22	111.62 (12)
C1—N1—C5	123.39 (11)	N3—C21—H21A	109.3
C6—N1—C5	115.84 (11)	C22—C21—H21A	109.3
C1—N2—C8	118.38 (12)	N3—C21—H21B	109.3
C11—N3—C21	111.13 (12)	C22—C21—H21B	109.3
C11—N3—C25	110.49 (12)	H21A—C21—H21B	108.0
C21—N3—C25	109.50 (12)	C21—C22—C23	110.76 (13)
C31—N4—O3	107.63 (11)	C21—C22—H22A	109.5
C4—C3—C2	110.17 (15)	C23—C22—H22A	109.5
C4—C3—C2B	101.3 (7)	C21—C22—H22B	109.5
C4—C3—H3A	109.6	C23—C22—H22B	109.5
C2—C3—H3A	109.6	H22A—C22—H22B	108.1
C2B—C3—H3A	107.6	C31—C23—C24	113.02 (12)
C4—C3—H3B	109.6	C31—C23—C22	112.03 (12)
C2—C3—H3B	109.6	C24—C23—C22	108.06 (12)

supplementary materials

C2B—C3—H3B	120.2	C31—C23—H23	107.8
H3A—C3—H3B	108.1	C24—C23—H23	107.8
C5—C4—C3	109.78 (12)	C22—C23—H23	107.8
C5—C4—H4A	109.7	C25—C24—C23	111.19 (13)
C3—C4—H4A	109.7	C25—C24—H24A	109.4
C5—C4—H4B	109.7	C23—C24—H24A	109.4
C3—C4—H4B	109.7	C25—C24—H24B	109.4
H4A—C4—H4B	108.2	C23—C24—H24B	109.4
N1—C5—C4	112.96 (12)	H24A—C24—H24B	108.0
N1—C5—H5A	109.0	N3—C25—C24	111.00 (12)
C4—C5—H5A	109.0	N3—C25—H25A	109.4
N1—C5—H5B	109.0	C24—C25—H25A	109.4
C4—C5—H5B	109.0	N3—C25—H25B	109.4
H5A—C5—H5B	107.8	C24—C25—H25B	109.4
O2—C6—N1	119.85 (12)	H25A—C25—H25B	108.0
O2—C6—C7	124.13 (12)	N4—C31—C32	111.00 (13)
N1—C6—C7	116.02 (11)	N4—C31—C23	120.13 (13)
C8—C7—C6	119.12 (12)	C32—C31—C23	128.87 (13)
C8—C7—C10	125.46 (12)	C33—C32—C37	119.37 (13)
C6—C7—C10	115.42 (12)	C33—C32—C31	103.89 (12)
C7—C8—N2	122.05 (12)	C37—C32—C31	136.70 (14)
C7—C8—C9	123.40 (13)	O3—C33—C32	110.37 (12)
N2—C8—C9	114.54 (12)	O3—C33—C34	125.22 (13)
C8—C9—H9A	109.5	C32—C33—C34	124.39 (13)
C8—C9—H9B	109.5	C35—C34—C33	113.34 (14)
H9A—C9—H9B	109.5	C35—C34—H34	123.3
C8—C9—H9C	109.5	C33—C34—H34	123.3
H9A—C9—H9C	109.5	F1—C35—C34	117.38 (15)
H9B—C9—H9C	109.5	F1—C35—C36	117.24 (15)
C8—C9—H9D	109.5	C34—C35—C36	125.38 (14)
H9A—C9—H9D	141.1	C37—C36—C35	119.17 (15)
H9B—C9—H9D	56.3	C37—C36—H36	120.4
H9C—C9—H9D	56.3	C35—C36—H36	120.4
C8—C9—H9E	109.5	C36—C37—C32	118.34 (15)
H9A—C9—H9E	56.3	C36—C37—H37	120.8
H9B—C9—H9E	141.1	C32—C37—H37	120.8
H9C—C9—H9E	56.3		
C2B—C1—C2—O1	-86 (16)	C6—C7—C8—C9	179.06 (14)
N2—C1—C2—O1	82.2 (2)	C10—C7—C8—C9	-1.5 (2)
N1—C1—C2—O1	-93.42 (18)	C1—N2—C8—C7	-0.7 (2)
C2B—C1—C2—C3	30 (16)	C1—N2—C8—C9	178.41 (13)
N2—C1—C2—C3	-161.95 (19)	C8—C7—C10—C11	-95.84 (17)
N1—C1—C2—C3	22.4 (3)	C6—C7—C10—C11	83.63 (15)
N2—C1—C2B—O1B	-22 (3)	C21—N3—C11—C10	-164.00 (13)
N1—C1—C2B—O1B	163.6 (13)	C25—N3—C11—C10	74.24 (15)
C2—C1—C2B—O1B	-9 (14)	C7—C10—C11—N3	75.21 (16)
N2—C1—C2B—C3	-158.1 (15)	C11—N3—C21—C22	177.66 (13)
N1—C1—C2B—C3	27 (3)	C25—N3—C21—C22	-60.00 (17)
C2—C1—C2B—C3	-146 (18)	N3—C21—C22—C23	58.12 (17)

C2B—C1—N1—C6	171.9 (15)	C21—C22—C23—C31	-179.23 (12)
N2—C1—N1—C6	-2.7 (2)	C21—C22—C23—C24	-54.09 (17)
C2—C1—N1—C6	172.62 (19)	C31—C23—C24—C25	179.45 (12)
C2B—C1—N1—C5	-9.0 (15)	C22—C23—C24—C25	54.90 (17)
N2—C1—N1—C5	176.46 (13)	C11—N3—C25—C24	-177.07 (12)
C2—C1—N1—C5	-8.2 (2)	C21—N3—C25—C24	60.21 (17)
C2B—C1—N2—C8	-171.1 (16)	C23—C24—C25—N3	-59.11 (17)
N1—C1—N2—C8	3.1 (2)	O3—N4—C31—C32	0.47 (16)
C2—C1—N2—C8	-172.37 (19)	O3—N4—C31—C23	-179.79 (12)
C33—O3—N4—C31	-0.26 (15)	C24—C23—C31—N4	-7.0 (2)
O1—C2—C3—C4	66.51 (17)	C22—C23—C31—N4	115.40 (16)
C1—C2—C3—C4	-50.0 (3)	C24—C23—C31—C32	172.73 (14)
O1—C2—C3—C2B	106 (7)	C22—C23—C31—C32	-64.91 (19)
C1—C2—C3—C2B	-11 (6)	N4—C31—C32—C33	-0.51 (16)
C1—C2B—C3—C4	-53 (3)	C23—C31—C32—C33	179.79 (14)
O1B—C2B—C3—C4	167.3 (14)	N4—C31—C32—C37	176.94 (18)
C1—C2B—C3—C2	165 (9)	C23—C31—C32—C37	-2.8 (3)
O1B—C2B—C3—C2	25 (5)	N4—O3—C33—C32	-0.07 (15)
C2—C3—C4—C5	64.6 (2)	N4—O3—C33—C34	-178.55 (13)
C2B—C3—C4—C5	57.3 (11)	C37—C32—C33—O3	-177.66 (13)
C1—N1—C5—C4	21.57 (18)	C31—C32—C33—O3	0.33 (16)
C6—N1—C5—C4	-159.23 (12)	C37—C32—C33—C34	0.8 (2)
C3—C4—C5—N1	-48.73 (16)	C31—C32—C33—C34	178.83 (13)
C1—N1—C6—O2	-179.85 (12)	O3—C33—C34—C35	177.88 (14)
C5—N1—C6—O2	0.92 (18)	C32—C33—C34—C35	-0.4 (2)
C1—N1—C6—C7	-0.04 (17)	C33—C34—C35—F1	-179.75 (14)
C5—N1—C6—C7	-179.26 (11)	C33—C34—C35—C36	-0.3 (2)
O2—C6—C7—C8	-178.03 (13)	F1—C35—C36—C37	179.98 (16)
N1—C6—C7—C8	2.17 (18)	C34—C35—C36—C37	0.5 (3)
O2—C6—C7—C10	2.5 (2)	C35—C36—C37—C32	-0.1 (3)
N1—C6—C7—C10	-177.33 (11)	C33—C32—C37—C36	-0.6 (2)
C6—C7—C8—N2	-1.9 (2)	C31—C32—C37—C36	-177.72 (17)
C10—C7—C8—N2	177.58 (13)		

Hydrogen-bond geometry (\AA , $^\circ$)

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O1—H1 \cdots O2 ⁱ	0.84	1.86	2.6945 (16)	174.
O1B—H1B \cdots O2 ⁱ	0.84	2.39	3.153 (8)	152.
C4—H4A \cdots N4 ⁱⁱ	0.99	2.55	3.4830 (19)	157.

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

Fig. 1

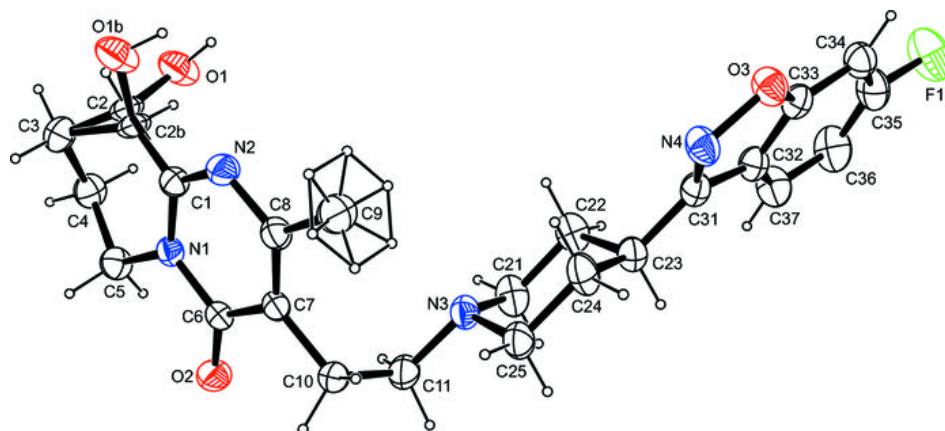


Fig. 2

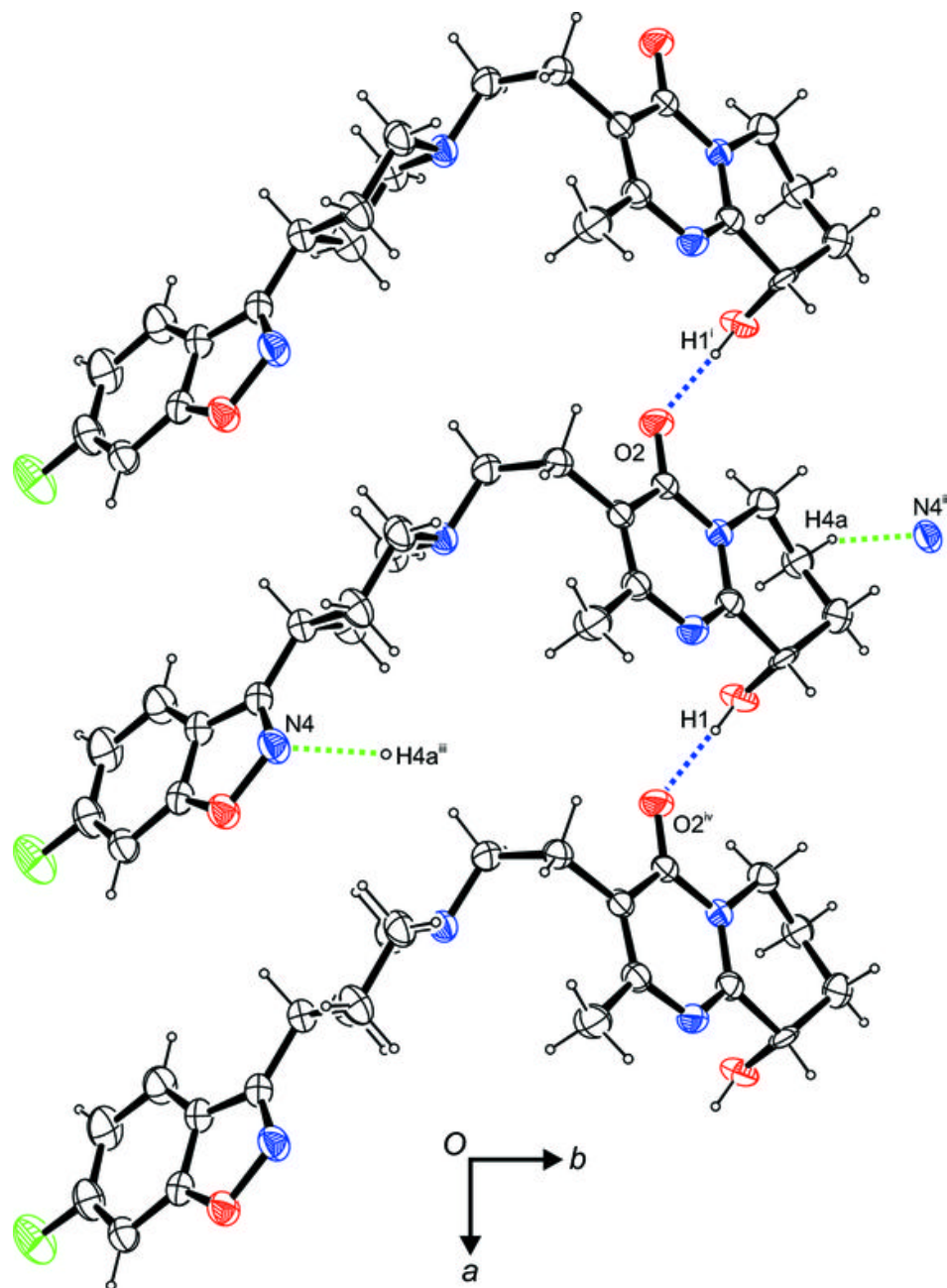


Fig. 3

