Solid-state tautomeric structure and invariom refinement of a novel and potent HIV integrase inhibitor

John Bacsa,^{a*} Maurice Okello,^b Pankaj Singh^b and Vasu Nair^b

^aDepartment of Chemistry, Emory University, Atlanta, GA 30322, USA, and ^bCenter for Drug Discovery and the College of Pharmacy, University of Georgia, Athens, GA 30602, USA

Correspondence e-mail: jbacsa@emory.edu

Received 17 January 2013

Accepted 7 February 2013

Online 14 February 2013

The conformation and tautomeric structure of (Z)-4-[5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl]-4-hydroxy-2-oxo-N-(2-oxopyrrolidin-1-yl)but-3-enamide, C₂₇H₂₂F₃N₃O₅, in the solid state has been resolved by single-crystal X-ray crystallography. The electron distribution in the molecule was evaluated by refinements with invarioms, aspherical scattering factors by the method of Dittrich *et al.* [*Acta Cryst.* (2005), **A61**, 314–320] that are based on the Hansen–Coppens multipole model [Hansen & Coppens (1978). *Acta Cryst.* **A34**, 909–921]. The β -diketo portion of the molecule exists in the enol form. The enol –OH hydrogen forms a strong asymmetric hydrogen bond with the carbonyl O atom on the β -C atom of the chain. Weak intramolecular hydrogen bonds exist between the weakly acidic α -CH hydrogen of the keto–enol group and the pyridinone carbonyl O atom, and also between the hydrazine N–H group and the carbonyl group in the β -position from the hydrazine N–H group. The electrostatic properties of the molecule were derived from the molecular charge density. The molecule is in a lengthened conformation and the rings of the two benzyl groups are nearly orthogonal. Results from a high-field ¹H and ¹³C NMR correlation spectroscopy study confirm that the same tautomer exists in solution as in the solid state.

Comment

The retroviral enzyme HIV-1 integrase is essential for HIV replication and is a significant target for the discovery and development of anti-HIV therapeutic agents (Moir *et al.*, 2011; Frankel & Young, 1998; Nair & Chi, 2007; Pommier *et al.*, 2005). Research efforts on anti-HIV integrase inhibitors for the treatment of acquired immunodeficiency syndrome (AIDS) have resulted in several anti-HIV agents, two of which, raltegravir and elvitegravir, have been approved by the US Food and Drug Administration for the clinical treatment

of HIV–AIDS (Nair *et al.*, 2006; Summa *et al.*, 2008; Min *et al.*, 2010; Shimura & Kodama, 2009; Taktakishvili *et al.*, 2000). The crystallographic structures of some HIV integrase inhibitors have been reported [see, for example, Rhodes *et al.* (2011) and Newton *et al.* (2005)]. As resistance, toxicity and drug–drug interactions are recurring issues with all classes of anti-HIV drugs, the discovery of new anti-HIV active integrase inhibitors remains a significant scientific challenge. The compound (Z)-4-[5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl]-4-hydroxy-2-oxo-N-(2-oxopyrrolidin-1-yl)but-3-enamide, (1), discovered in our laboratory, is an integrase inhibitor which possesses potent (low nM) anti-HIV activity against a diverse set of HIV-1 isolates and also against HIV-2 and SIV. However, this compound can exist in three possible forms (I, II and III) with respect to the β -diketo functionality (see Scheme 1). In order to determine which tautomeric form is dominant in the solid state, the single-crystal X-ray structure of integrase inhibitor (1) was undertaken. An invariom refinement (Dittrich *et al.*, 2005; Hansen & Coppens, 1978) was performed to examine the electrostatic properties of the molecule in further detail.

Scheme 1

The molecular structure of (1) contains a variety of distinct groups, including a central pyridinone ring, fluorobenzene rings, a keto–enol group and a 2-oxopyrrolidin-1-yl group (Fig. 1 and Table 1). The scattering factors of some fragments were not yet present in the invariom database (Dittrich *et al.*, 2006) and so were calculated here using quantum mechanics. This method of refinement led to C–H distances somewhat

Figure 1

The molecular structure of the dominant tautomeric form of (1) present in the crystalline state. Displacement ellipsoids are drawn at the 50% probability level. Dashed lines indicate intramolecular hydrogen bonds.

longer [1.013 (15)–1.107 (12) Å] than ordinarily expected from an X-ray determination but closer to distances determined from neutron diffraction (Allen *et al.*, 2006).

The refined position of the H atom in the strong intramolecular O—H...O hydrogen bond indicated that it is not symmetrically located between the two O-atom centers but rather favors atom O14 over O11, *i.e.* form I is the dominant form in the solid. This is reflected by the longer C—O bond for O14 [1.3033 (12) Å, compared with 1.2678 (11) Å for O11]. However, this is not a completely localized H atom and there is some residual disorder. This was seen in the residual electron-density map about atom O11, with a maximum peak height of 0.24 e Å⁻³ between atoms O11 and H14 (Fig. 2). A deformation electron-density map (with contour step values of ±0.05 e Å⁻³) is shown in Fig. 3. The hydrogen bond is not

Figure 2

A residual electron-density map in the plane of the atoms of the keto-enol group. Contours are drawn at 0.05 e Å⁻³ intervals. Solid lines represent positive contours and dashed lines negative contours.

Figure 3

A deformation electron-density map in the plane of the atoms of the keto-enol group. Contours are drawn at 0.05 e Å⁻³ intervals. Solid lines represent positive contours and dashed lines negative contours.

linear; the O14—H14...O11 angle is 155.5 (16)° (Table 2). The H atom on atom N6 donates an intermolecular hydrogen bond to atom O9ⁱ (N6—H6...O9ⁱ; Table 2), forming a centrosymmetric dimer. The slightly acidic α-C—H hydrogen of the keto-enol group donates a weak intramolecular hydrogen bond to carbonyl atom O21 (C12—H12...O21; Table 2).

Since a complete static electron-density distribution is available from the invariom model scattering factors, various properties like the dipole moment and electrostatic potential [V(*r*)] can be derived from the electron density. They were calculated using the program XDPROP in XD2006 (Volkov *et al.*, 2006). The results could provide information on the capacity of this molecule to interact with a protein-binding site. The dipole moment (*p*) for the molecule calculated from the multipole populations is 12.06 D. The electrostatic field is

Figure 4

Positive (0.2 e Å⁻³) and negative (-0.06 e Å⁻³) electrostatic potential isosurfaces of (1) shown in light and dark grey, respectively.

the force that a hypothetical proton would be subjected to if it were present. The electrostatic potential (a scalar quantity) at a given point can be defined as the amount of work that is needed to bring a unit of charge from infinity to that point. A composite of the positive ($0.2 \text{ e } \text{\AA}^{-3}$) and negative ($-0.06 \text{ e } \text{\AA}^{-3}$) electrostatic potential isosurfaces plotted with the program *Molekel* (Molekel, 2009) is shown in Fig. 4. Regions of strong positive potential are shown in lighter grey and negative potential in dark grey. Atom H14, involved in a strong intramolecular hydrogen bond, shows a strong positive potential, while adjacent atom O11 shows a strong negative potential.

The results of a high-field ^1H and ^{13}C NMR correlation spectroscopy study (COSY, HSQC, HMQC, HMBC and NOESY) are consistent with the structure observed in the solid state.

Experimental

The integrase inhibitor was prepared from the coupling of the corresponding diketo acid (Seo *et al.*, 2011) and 1-amino-2-pyrrolidinone *p*-toluenesulfonate. Compound (1) crystallized from dichloromethane as yellow prisms (yield 78%; m.p. 448–449 K). UV (CH_3OH , λ , nm): 401 (ϵ 9, 139), 318 (ϵ 6, 225). HRMS calculated for $\text{C}_{27}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_5$: $[M + \text{H}]^+$ 526.1590; found: 526.1589.

Crystal data

$\text{C}_{27}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_5$	$\gamma = 106.435 (2)^\circ$
$M_r = 525.48$	$V = 1188.3 (2) \text{ \AA}^3$
Triclinic, $P\bar{1}$	$Z = 2$
$a = 8.8182 (10) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 11.5986 (13) \text{ \AA}$	$\mu = 0.12 \text{ mm}^{-1}$
$c = 12.2741 (14) \text{ \AA}$	$T = 173 \text{ K}$
$\alpha = 98.594 (2)^\circ$	$0.75 \times 0.65 \times 0.35 \text{ mm}$
$\beta = 90.904 (2)^\circ$	

Data collection

Bruker APEXII area-detector diffractometer	22962 measured reflections
Absorption correction: empirical (using intensity measurements) (<i>SADABS</i> ; Sheldrick, 2008b)	5447 independent reflections
$T_{\min} = 0.841$, $T_{\max} = 1.000$	5175 reflections with $I > 3\sigma(I)$
	$R_{\text{int}} = 0.029$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$	431 parameters
$wR(F^2) = 0.067$	All H-atom parameters refined
$S = 2.00$	$\Delta\rho_{\text{max}} = 0.24 \text{ e } \text{\AA}^{-3}$
5175 reflections	$\Delta\rho_{\text{min}} = -0.19 \text{ e } \text{\AA}^{-3}$

The program *InvariomTool* (Hübschle *et al.*, 2007) was used to prepare master and input files for an invariom refinement with the *XDLSM* program of the *XD2006* suite (Volkov *et al.*, 2006). The program assigns invarioms to all atoms in a given crystal structure by examining the connectivity in terms of nearest or next-nearest neighbors. Nonspherical valence scattering contributions for atoms in an environment of single bonds were obtained from theoretical calculations on model compounds that included nearest-neighbour atoms, whereas for H atoms and atoms in a delocalized chemical environment the model compounds also included the next-nearest neighbor atoms. Several fragments were not present in the invariom database. Therefore, new scattering factors for these fragments,

Table 1

Selected geometric parameters ($\text{\AA}$, $^\circ$).

F36—C24	1.3484 (12)	N6—C7	1.3531 (13)
F37—C31	1.3467 (13)	C7—C10	1.5271 (14)
F38—C35	1.3444 (13)	C10—C12	1.3986 (14)
O8—C7	1.2102 (11)	C12—C13	1.3979 (14)
O9—C5	1.2178 (12)	C12—H12	1.038 (12)
O11—C10	1.2678 (11)	C13—C15	1.4682 (14)
O14—C13	1.3033 (12)	C15—C16	1.4553 (13)
O21—C16	1.2245 (11)	C15—C20	1.3784 (13)
N1—N6	1.3802 (11)	C18—C19	1.3676 (14)
N1—C2	1.4605 (13)	C19—C20	1.4078 (14)
N1—C5	1.3608 (12)		
O11—C10—C7	117.89 (9)	C13—C12—H12	120.1 (7)
O11—C10—C12	125.07 (9)	O14—C13—C12	120.11 (9)
C7—C10—C12	117.02 (9)	O14—C13—C15	116.09 (9)
C10—C12—C13	119.72 (9)	C12—C13—C15	123.79 (9)
C10—C12—H12	120.1 (7)		

Table 2

Hydrogen-bond geometry ($\text{\AA}$, $^\circ$).

$D\cdots H\cdots A$	$D\cdots H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N6—H6 $\cdots$ O9 ⁱ	1.000 (14)	1.924 (14)	2.8014 (12)	144.8 (10)
O14—H14 $\cdots$ O11	1.092 (18)	1.492 (18)	2.5270 (11)	155.5 (16)
C12—H12 $\cdots$ O21	1.038 (13)	2.135 (12)	2.8346 (13)	122.7 (9)

Symmetry code: (i) $-x + 2, -y, -z - 1$.

including the keto–enol group, were calculated from geometry optimizations at the B3LYP/D95++(3df,3pd) level of theory and included in the invariom database to increase its coverage of chemical environments. These calculations were performed using *GAUSSIAN09* (Frisch *et al.*, 2009). Full-matrix least-squares refinements on F^2 using complete multipole expansions were carried out with the program *XDLSM* using statistical weights. Only reflections with intensities $I > 3\sigma(I)$ were included in the refinement. Initially, bond lengths involving H atoms were set to the $X\cdots H$ distances obtained from model compounds that included the next-nearest neighbors of the H atom of interest. However, in the final cycles, these atom positions were refined freely. Positional and displacement (anisotropic for non-H atoms) parameters, but not multipoles, were refined. However, a hexadecapolar level of the multipole expansion was used for all atoms. A molecular electroneutrality constraint was applied. The introduction of invarioms improved $R(F)$ from 0.0511 to 0.0349 while using the same weighting scheme $\{w = 1/[\sigma^2(F_o^2)]\}$ as the spherical-atom refinement, and improved the goodness-of-fit value from 2.832 to 2.001.

Data collection: *APEX2* (Bruker, 2011); cell refinement: *SAINT* (Bruker, 2009); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008a); program(s) used to refine structure: *XD2006* (Volkov *et al.*, 2006); molecular graphics: *XD2006*, *Molekel* (Molekel, 2009) and *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *XD2006*.

Support of this research by the US National Institutes of Health (grant Nos. R01 AI 43181 and NCR R01-RR025444) is gratefully acknowledged. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. VN also acknowledges research support from the Terry Endowed Chair in Drug Discovery and from the Georgia Research Alliance Eminent

Scholar Award. JB gratefully acknowledges assistance from Birger Dittrich with using *XD2006* and the invariom refinements. The authors acknowledge an NSF MRI-R2 grant (No. CHE-0958205) and the use of the resources of the Cherry L. Emerson Center for Scientific Computation.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FN3128). Services for accessing these data are described at the back of the journal.

References

- Allen, F. H., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (2006). *Typical interatomic distances: organic compounds*, in *International Tables for Crystallography*, Vol. C, edited by E. Prince, pp. 790–811. Dordrecht: Kluwer Academic Publishers.
- Bruker (2009). *SAINT-Plus*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2011). *APEX2*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Dittrich, B., Hübschle, C. B., Luger, P. & Spackman, M. A. (2006). *Acta Cryst. D* **62**, 1325–1335.
- Dittrich, B., Hübschle, C. B., Messerschmidt, M., Kalinowski, R., Girnt, D. & Luger, P. (2005). *Acta Cryst. A* **61**, 314–320.
- Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.
- Frankel, A. D. & Young, J. A. T. (1998). *Annu. Rev. Biochem.* **67**, 1–25.
- Frisch, M. J., *et al.* (2009). *GAUSSIAN09*. Gaussian Inc., Wallingford, CT, USA.
- Hansen, N. K. & Coppens, P. (1978). *Acta Cryst. A* **34**, 909–921.
- Hübschle, C. B., Luger, P. & Dittrich, B. (2007). *J. Appl. Cryst.* **40**, 623–627.
- Min, S., Song, I., Borland, J., Chen, S., Lou, Y., Fujiwara, T. & Piscitelli, S. C. (2010). *Antimicrob. Agents Chemother.* **54**, 254–258.
- Moir, S., Chun, T. & Fauci, A. (2011). *Annu. Rev. Pathol. Mech. Dis.* **6**, 223–248.
- Molekel (2009). *Molekel. Multiplatform Molecular Visualization*, <http://cscs.ch/molekel>.
- Nair, V. & Chi, G. (2007). *Rev. Med. Virol.* **17**, 277–295.
- Nair, V., Chi, G., Ptak, R. & Neamati, N. (2006). *J. Med. Chem.* **49**, 445–447.
- Newton, M. G., Campana, C. F., Chi, G.-C., Lee, D., Liu, Z.-J., Nair, V., Phillips, J., Rose, J. P. & Wang, B.-C. (2005). *Acta Cryst. C* **61**, o518–o520.
- Pommier, Y., Johnson, A. A. & Marchand, C. (2005). *Nat. Rev. Drug Discov.* **3**, 236–248.
- Rhodes, D. I., Peat, T. S., Vandegraaff, N., Jeevarajah, D., Newman, J., Martyn, J., Coates, J. A. V., Ede, N. J., Rea, P. & Deadman, J. J. (2011). *ChemBioChem*, **12**, 2311–2315.
- Seo, B. I., Uchil, V. R., Okello, M., Mishra, S., Ma, X., Nishonov, M., Shu, Q., Chi, G. & Nair, V. (2011). *ACS Med. Chem. Lett.* **2**, 877–881.
- Sheldrick, G. M. (2008a). *Acta Cryst. A* **64**, 112–122.
- Sheldrick, G. M. (2008b). *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Shimura, K. & Kodama, E. N. (2009). *Antivir. Chem. Chemother.* **20**, 79–85.
- Summa, V. *et al.* (2008). *J. Med. Chem.* **51**, 5843–5855.
- Taktakishvili, M., Neamati, N., Pommier, Y., Pal, S. & Nair, V. (2000). *J. Am. Chem. Soc.* **122**, 5671–5677.
- Volkov, A., Macchi, P., Farrugia, L. J., Gatti, C., Mallinson, P., Richter, T. & Koritsanszky, T. (2006). *XD2006*. Middle Tennessee State University, USA, Università di Milano and CNR-ISTM Milano, Italy, University of Glasgow, Scotland, State University of New York at Buffalo, USA, and Freie Universität Berlin, Germany.

supplementary materials

Acta Cryst. (2013). C69, 285–288 [doi:10.1107/S0108270113003806]

Solid-state tautomeric structure and invariom refinement of a novel and potent HIV integrase inhibitor

John Bacsa, Maurice Okello, Pankaj Singh and Vasu Nair

(*Z*)-4-[5-(2,6-Difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl]-4-hydroxy-2-oxo-*N*-(2-oxopyrrolidin-1-yl)but-3-enamide

Crystal data

C₂₇H₂₂F₃N₃O₅

M_r = 525.48

Triclinic, *P* $\bar{1}$

Hall symbol: -P 1

a = 8.8182 (10) Å

b = 11.5986 (13) Å

c = 12.2741 (14) Å

α = 98.594 (2)°

β = 90.904 (2)°

γ = 106.435 (2)°

V = 1188.3 (2) Å³

Z = 2

F(000) = 544

D_x = 1.469 Mg m⁻³

Mo *K*α radiation, λ = 0.71073 Å

Cell parameters from 7934 reflections

θ = 2.3–30.8°

μ = 0.12 mm⁻¹

T = 173 K

Prism, yellow

0.75 × 0.65 × 0.35 mm

Data collection

Bruker APEXII area-detector
diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

Detector resolution: 512 pixels mm⁻¹

ω scans with a narrow frame width

Absorption correction: empirical (using
intensity measurements)

(*SADABS*; Sheldrick, 2008b)

T_{min} = 0.841, *T_{max}* = 1.000

22962 measured reflections

5447 independent reflections

5175 reflections with *I* > 3σ(*I*)

R_{int} = 0.029

$\theta_{\max}$ = 29.6°, $\theta_{\min}$ = 1.7°

h = −11→11

k = −15→15

l = −15→15

Refinement

Refinement on *F*²

Least-squares matrix: full

R [*F*² > 2σ(*F*²)] = 0.035

wR(*F*²) = 0.067

S = 2.00

5175 reflections

431 parameters

0 restraints

0 constraints

Primary atom site location: structure-invariant
direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: difference Fourier map

All H-atom parameters refined

*w*2 = 1/[σ²(*F_o*²)]

(Δ/σ)_{max} = 0.001

Δρ_{max} = 0.24 e Å⁻³

Δρ_{min} = −0.19 e Å⁻³

Special details

Experimental. Absorption correction: SADABS-2008/1 (Sheldrick, 2008b) was used for absorption correction. R(int) was 0.0701 before and 0.0457 after correction. The ratio of minimum to maximum transmission is 0.8414. The $\lambda/2$ correction factor is 0.0015.

Refinement. An invariom refinement was performed (Dittrich, Acta Cryst. A62, 217). This improves the positional and thermal parameters compared to an independent-atom refinement. Using non-spherical scattering factors improves the standard uncertainties of H-atom coordinates.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
F36	0.43508 (7)	0.48237 (5)	0.20138 (5)	0.040
F37	1.10909 (8)	0.35495 (6)	0.30948 (6)	0.056
F38	0.69726 (8)	0.51711 (6)	0.41718 (7)	0.056
O8	0.61975 (9)	0.03150 (7)	−0.37267 (6)	0.040
O9	0.89472 (8)	0.07428 (6)	−0.55828 (6)	0.030
O11	0.92594 (8)	0.00319 (7)	−0.20485 (6)	0.032
O14	0.89726 (8)	0.08095 (7)	−0.00493 (6)	0.031
O21	0.44806 (8)	0.13856 (6)	−0.05132 (6)	0.032
N1	0.74444 (9)	−0.10877 (7)	−0.51980 (7)	0.026
N6	0.78886 (10)	−0.08321 (8)	−0.40847 (7)	0.027
N17	0.47097 (9)	0.22606 (7)	0.12787 (7)	0.026
C2	0.59985 (13)	−0.20406 (10)	−0.56282 (9)	0.030
C3	0.60702 (14)	−0.20228 (11)	−0.68715 (10)	0.034
C4	0.70382 (13)	−0.07230 (10)	−0.69638 (9)	0.031
C5	0.79433 (11)	−0.02298 (9)	−0.58611 (8)	0.025
C7	0.72582 (12)	−0.00616 (9)	−0.34317 (8)	0.026
C10	0.79722 (11)	0.02670 (9)	−0.22452 (8)	0.025
C12	0.71226 (12)	0.07741 (9)	−0.14522 (8)	0.027
C13	0.76709 (11)	0.10337 (9)	−0.03424 (8)	0.025
C15	0.68748 (11)	0.15791 (8)	0.05478 (8)	0.023
C16	0.53049 (11)	0.17108 (8)	0.03520 (8)	0.025
C18	0.55138 (13)	0.26522 (9)	0.22759 (9)	0.027
C19	0.69925 (12)	0.25366 (9)	0.24642 (8)	0.026
C20	0.76563 (12)	0.19723 (9)	0.15766 (8)	0.025
C22	0.30840 (12)	0.23427 (10)	0.11434 (10)	0.028
C23	0.29157 (11)	0.33550 (9)	0.05620 (8)	0.027
C24	0.34957 (12)	0.45652 (9)	0.10419 (9)	0.030
C25	0.32205 (15)	0.55113 (11)	0.05877 (10)	0.039
C26	0.23228 (15)	0.52338 (12)	−0.04004 (11)	0.045
C27	0.17407 (15)	0.40330 (12)	−0.09244 (11)	0.044
C28	0.20515 (13)	0.31053 (11)	−0.04469 (9)	0.035
C29	0.78772 (14)	0.30277 (10)	0.35756 (9)	0.030
C30	0.89726 (12)	0.42953 (9)	0.36200 (8)	0.029
C31	1.05463 (14)	0.45206 (10)	0.33765 (9)	0.037
C32	1.15813 (17)	0.56781 (12)	0.34235 (10)	0.045
C33	1.10320 (17)	0.66716 (12)	0.37361 (10)	0.045
C34	0.94689 (17)	0.65072 (11)	0.39929 (10)	0.044
C35	0.84898 (13)	0.53338 (10)	0.39215 (9)	0.036
H14	0.936 (2)	0.0436 (16)	−0.0830 (15)	0.053 (5)

H6	0.8968 (15)	−0.0894 (11)	−0.3899 (10)	0.036 (3)
H2A	0.5006 (14)	−0.1793 (10)	−0.5299 (9)	0.038 (3)
H2B	0.6042 (13)	−0.2869 (11)	−0.5403 (9)	0.041 (3)
H3A	0.4934 (16)	−0.2245 (11)	−0.7261 (11)	0.054 (4)
H3B	0.6686 (15)	−0.2627 (12)	−0.7202 (11)	0.050 (4)
H4A	0.7850 (15)	−0.0637 (11)	−0.7592 (11)	0.054 (4)
H4B	0.6282 (15)	−0.0147 (12)	−0.7042 (11)	0.055 (4)
H12	0.6069 (14)	0.0930 (10)	−0.1683 (10)	0.039 (3)
H18	0.4929 (13)	0.3053 (11)	0.2901 (10)	0.039 (3)
H20	0.8849 (14)	0.1866 (10)	0.1697 (10)	0.038 (3)
H22A	0.2669 (14)	0.2444 (10)	0.1953 (11)	0.039 (3)
H22B	0.2365 (14)	0.1492 (12)	0.0699 (10)	0.037 (3)
H25	0.3690 (16)	0.6390 (13)	0.0960 (12)	0.058 (4)
H26	0.2090 (15)	0.5964 (13)	−0.0762 (12)	0.059 (4)
H27	0.1059 (17)	0.3832 (13)	−0.1684 (13)	0.067 (5)
H28	0.1608 (14)	0.2165 (12)	−0.0843 (11)	0.047 (4)
H29A	0.7030 (14)	0.3050 (10)	0.4217 (10)	0.013 (3)
H29B	0.8555 (13)	0.2408 (11)	0.3777 (9)	0.012 (3)
H32	1.2722 (16)	0.5736 (12)	0.3248 (12)	0.058 (4)
H33	1.1802 (16)	0.7552 (13)	0.3791 (11)	0.060 (4)
H34	0.9033 (16)	0.7221 (14)	0.4222 (12)	0.064 (5)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F36	0.0471 (4)	0.0312 (4)	0.0363 (4)	0.0096 (3)	−0.0060 (3)	−0.0037 (3)
F37	0.0528 (4)	0.0452 (4)	0.0686 (5)	0.0202 (4)	0.0188 (4)	−0.0092 (4)
F38	0.0463 (4)	0.0451 (4)	0.0762 (6)	0.0249 (3)	−0.0070 (4)	−0.0091 (4)
O8	0.0446 (5)	0.0544 (5)	0.0282 (4)	0.0321 (4)	−0.0023 (3)	−0.0024 (4)
O9	0.0286 (4)	0.0259 (4)	0.0354 (4)	0.0079 (3)	0.0004 (3)	0.0014 (3)
O11	0.0268 (4)	0.0433 (4)	0.0259 (4)	0.0141 (3)	0.0019 (3)	−0.0003 (3)
O14	0.0270 (4)	0.0352 (4)	0.0283 (4)	0.0103 (3)	−0.0016 (3)	−0.0021 (3)
O21	0.0284 (4)	0.0382 (4)	0.0270 (4)	0.0114 (3)	−0.0034 (3)	−0.0075 (3)
N1	0.0255 (4)	0.0284 (5)	0.0239 (4)	0.0084 (4)	0.0012 (3)	0.0000 (4)
N6	0.0282 (5)	0.0314 (5)	0.0232 (5)	0.0126 (4)	0.0005 (4)	−0.0001 (4)
N17	0.0286 (4)	0.0227 (4)	0.0250 (5)	0.0082 (4)	0.0032 (4)	0.0005 (4)
C2	0.0290 (6)	0.0268 (6)	0.0322 (6)	0.0064 (5)	−0.0010 (5)	0.0006 (5)
C3	0.0362 (6)	0.0333 (6)	0.0305 (6)	0.0099 (5)	−0.0038 (5)	−0.0038 (5)
C4	0.0285 (6)	0.0372 (6)	0.0253 (6)	0.0085 (5)	0.0000 (4)	0.0015 (5)
C5	0.0235 (5)	0.0273 (5)	0.0248 (5)	0.0106 (4)	0.0010 (4)	0.0007 (4)
C7	0.0289 (5)	0.0291 (5)	0.0222 (5)	0.0122 (4)	0.0009 (4)	0.0011 (4)
C10	0.0276 (5)	0.0275 (5)	0.0210 (5)	0.0098 (4)	0.0014 (4)	0.0008 (4)
C12	0.0302 (5)	0.0302 (6)	0.0222 (5)	0.0134 (4)	0.0010 (4)	−0.0003 (4)
C13	0.0272 (5)	0.0232 (5)	0.0230 (5)	0.0070 (4)	0.0023 (4)	−0.0012 (4)
C15	0.0266 (5)	0.0216 (5)	0.0213 (5)	0.0082 (4)	0.0007 (4)	−0.0012 (4)
C16	0.0262 (5)	0.0227 (5)	0.0239 (5)	0.0068 (4)	0.0009 (4)	−0.0013 (4)
C18	0.0352 (6)	0.0248 (5)	0.0226 (5)	0.0113 (4)	0.0038 (5)	0.0014 (4)
C19	0.0349 (6)	0.0241 (5)	0.0200 (5)	0.0108 (4)	−0.0002 (4)	0.0004 (4)
C20	0.0317 (5)	0.0227 (5)	0.0218 (5)	0.0092 (4)	−0.0004 (4)	0.0003 (4)
C22	0.0285 (5)	0.0242 (6)	0.0317 (6)	0.0076 (4)	0.0063 (5)	0.0036 (5)

C23	0.0270 (5)	0.0235 (5)	0.0285 (6)	0.0076 (4)	0.0038 (4)	0.0015 (4)
C24	0.0335 (5)	0.0243 (6)	0.0304 (6)	0.0082 (4)	0.0043 (4)	0.0014 (5)
C25	0.0525 (7)	0.0244 (6)	0.0381 (7)	0.0095 (5)	0.0021 (6)	0.0045 (5)
C26	0.0594 (8)	0.0355 (7)	0.0442 (8)	0.0146 (6)	0.0002 (6)	0.0146 (6)
C27	0.0535 (8)	0.0422 (8)	0.0355 (7)	0.0110 (6)	−0.0064 (6)	0.0087 (6)
C28	0.0396 (6)	0.0302 (6)	0.0308 (6)	0.0060 (5)	−0.0018 (5)	0.0013 (5)
C29	0.0425 (6)	0.0277 (6)	0.0208 (6)	0.0122 (5)	−0.0015 (5)	0.0012 (4)
C30	0.0403 (6)	0.0263 (5)	0.0206 (5)	0.0130 (5)	−0.0026 (4)	−0.0015 (4)
C31	0.0448 (7)	0.0346 (6)	0.0292 (6)	0.0111 (5)	0.0057 (5)	−0.0033 (5)
C32	0.0493 (8)	0.0425 (8)	0.0358 (7)	0.0032 (6)	0.0076 (6)	−0.0012 (6)
C33	0.0635 (9)	0.0314 (7)	0.0318 (6)	0.0031 (6)	−0.0076 (6)	0.0027 (5)
C34	0.0631 (9)	0.0278 (7)	0.0400 (7)	0.0179 (6)	−0.0166 (6)	−0.0039 (5)
C35	0.0462 (7)	0.0292 (6)	0.0342 (6)	0.0168 (5)	−0.0090 (5)	−0.0033 (5)

Geometric parameters (Å, °)

F36—C24	1.3484 (12)	C18—C19	1.3676 (14)
F37—C31	1.3467 (13)	C18—H18	1.055 (13)
F38—C35	1.3444 (13)	C19—C20	1.4078 (14)
O8—C7	1.2102 (11)	C19—C29	1.5088 (14)
O9—C5	1.2178 (12)	C20—H20	1.104 (12)
O11—C10	1.2678 (11)	C22—C23	1.5017 (14)
O14—C13	1.3033 (12)	C22—H22A	1.066 (13)
O21—C16	1.2245 (11)	C22—H22B	1.072 (13)
N1—N6	1.3802 (11)	C23—C24	1.3842 (14)
N1—C2	1.4605 (13)	C23—C28	1.3915 (15)
N1—C5	1.3608 (12)	C24—C25	1.3795 (15)
N6—C7	1.3531 (13)	C25—C26	1.3820 (17)
N6—H6	1.000 (12)	C25—H25	1.017 (14)
N17—C16	1.4026 (12)	C26—C27	1.3908 (18)
N17—C18	1.3533 (13)	C26—H26	1.079 (14)
C2—C3	1.5313 (16)	C27—C28	1.3881 (16)
C2—H2A	1.063 (12)	C27—H27	1.059 (15)
C2—H2B	1.050 (12)	C28—H28	1.083 (13)
C3—C4	1.5297 (16)	C29—C30	1.5061 (15)
C3—H3A	1.049 (13)	C29—H29A	1.097 (13)
C3—H3B	1.043 (14)	C29—H29B	1.107 (12)
C4—C5	1.5074 (14)	C30—C31	1.3838 (15)
C4—H4A	1.057 (14)	C30—C35	1.3895 (15)
C4—H4B	1.082 (14)	C31—C32	1.3858 (16)
C7—C10	1.5271 (14)	C32—C33	1.3782 (19)
C10—C12	1.3986 (14)	C32—H32	1.018 (14)
C12—C13	1.3979 (14)	C33—C34	1.3851 (19)
C12—H12	1.038 (12)	C33—H33	1.046 (14)
C13—C15	1.4682 (14)	C34—C35	1.3793 (16)
C15—C16	1.4553 (13)	C34—H34	1.013 (15)
C15—C20	1.3784 (13)		
N6—N1—C2	121.04 (8)	C18—C19—C29	120.67 (10)
N6—N1—C5	120.87 (8)	C20—C19—C29	121.98 (9)

C2—N1—C5	113.84 (8)	C15—C20—C19	121.74 (9)
N1—N6—C7	118.08 (8)	C15—C20—H20	118.8 (6)
N1—N6—H6	114.6 (7)	C19—C20—H20	119.4 (6)
C7—N6—H6	120.9 (7)	C23—C22—H22A	110.3 (6)
C16—N17—C18	123.69 (9)	C23—C22—H22B	109.0 (6)
N1—C2—C3	101.58 (8)	H22A—C22—H22B	107.5 (9)
N1—C2—H2A	109.0 (6)	C22—C23—C24	121.77 (10)
N1—C2—H2B	109.4 (6)	C22—C23—C28	120.88 (10)
C3—C2—H2A	112.5 (6)	C24—C23—C28	117.14 (10)
C3—C2—H2B	113.5 (7)	F36—C24—C23	117.88 (9)
H2A—C2—H2B	110.4 (8)	F36—C24—C25	118.66 (10)
C2—C3—C4	104.61 (9)	C23—C24—C25	123.45 (10)
C2—C3—H3A	111.5 (7)	C24—C25—C26	118.15 (11)
C2—C3—H3B	108.3 (7)	C24—C25—H25	120.8 (8)
C4—C3—H3A	111.7 (7)	C26—C25—H25	121.0 (8)
C4—C3—H3B	109.2 (7)	C25—C26—C27	120.47 (11)
H3A—C3—H3B	111.3 (10)	C25—C26—H26	118.9 (7)
C3—C4—C5	105.07 (9)	C27—C26—H26	120.6 (7)
C3—C4—H4A	115.9 (7)	C26—C27—C28	119.79 (12)
C3—C4—H4B	111.4 (7)	C26—C27—H27	119.8 (8)
C5—C4—H4A	108.8 (7)	C28—C27—H27	120.4 (8)
C5—C4—H4B	105.5 (7)	C23—C28—C27	120.97 (11)
H4A—C4—H4B	109.5 (10)	C23—C28—H28	118.2 (7)
O9—C5—N1	124.55 (9)	C27—C28—H28	120.8 (7)
O9—C5—C4	128.21 (9)	C19—C29—C30	112.22 (8)
N1—C5—C4	107.24 (9)	C19—C29—H29A	109.6 (6)
O8—C7—N6	124.60 (10)	C19—C29—H29B	109.8 (6)
O8—C7—C10	121.88 (9)	C30—C29—H29A	108.4 (6)
N6—C7—C10	113.48 (8)	C30—C29—H29B	110.0 (6)
O11—C10—C7	117.89 (9)	H29A—C29—H29B	106.6 (8)
O11—C10—C12	125.07 (9)	C29—C30—C31	122.72 (10)
C7—C10—C12	117.02 (9)	C29—C30—C35	122.73 (10)
C10—C12—C13	119.72 (9)	C31—C30—C35	114.55 (10)
C10—C12—H12	120.1 (7)	F37—C31—C30	117.32 (10)
C13—C12—H12	120.1 (7)	F37—C31—C32	118.89 (11)
O14—C13—C12	120.11 (9)	C30—C31—C32	123.78 (11)
O14—C13—C15	116.09 (9)	C31—C32—C33	118.85 (13)
C12—C13—C15	123.79 (9)	C31—C32—H32	117.1 (8)
C13—C15—C16	121.08 (9)	C33—C32—H32	124.1 (8)
C13—C15—C20	118.32 (9)	C32—C33—C34	120.18 (12)
C16—C15—C20	120.60 (9)	C32—C33—H33	119.9 (8)
O21—C16—N17	118.61 (9)	C34—C33—H33	119.9 (8)
O21—C16—C15	127.00 (9)	C33—C34—C35	118.40 (12)
N17—C16—C15	114.39 (9)	C33—C34—H34	121.8 (8)
N17—C18—C19	122.22 (10)	C35—C34—H34	119.8 (8)
N17—C18—H18	115.8 (6)	F38—C35—C30	117.21 (10)
C19—C18—H18	122.0 (6)	F38—C35—C34	118.54 (10)
C18—C19—C20	117.33 (10)	C30—C35—C34	124.24 (12)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
N6—H6 $\cdots$ O9 ⁱ	1.00 (1)	1.92 (1)	2.8014 (12)	145 (1)
O14—H14 $\cdots$ O11	1.09 (2)	1.49 (2)	2.5270 (11)	156 (2)
C4—H4A $\cdots$ O11 ⁱ	1.06 (1)	2.51 (1)	3.4214 (14)	144 (1)
C4—H4B $\cdots$ O8 ⁱⁱ	1.08 (1)	2.36 (1)	3.1312 (15)	127 (1)
C12—H12 $\cdots$ O21	1.04 (1)	2.13 (1)	2.8346 (13)	123 (1)
C22—H22A $\cdots$ F37 ⁱⁱⁱ	1.07 (1)	2.47 (1)	3.3627 (14)	141 (1)
C22—H22B $\cdots$ O14 ^{iv}	1.07 (1)	2.59 (1)	3.6281 (14)	163 (1)
C29—H29B $\cdots$ O9 ^v	1.11 (1)	2.30 (1)	3.3441 (14)	156 (1)
C32—H32 $\cdots$ F36 ^{vi}	1.02 (2)	2.44 (2)	3.3062 (16)	143 (1)

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