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Crystal structure of 4-amino-5-fluoro-2-oxo-2,3-dihydropyrimidin-1-ium 3-hydroxypyridine-2-carboxylate

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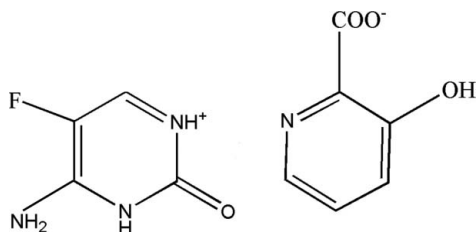
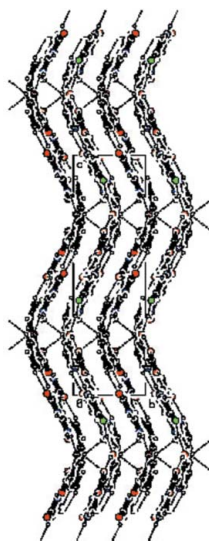
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The asymmetric unit of the title salt, $C_4H_5FN_3O^+ \cdot C_6H_4NO_3^-$, contains one 4-amino-5-fluoro-2-oxo-2,3-dihydropyrimidin-1-ium (5-fluorocytosinium, 5FC) cation and a 3-hydroxypicolinate (3HAP) anion. The 4-amino-5-fluoro-2-oxo-2,3-dihydropyrimidine molecule is protonated at one of the pyrimidine N atoms. The typical intramolecular N—H...F and O—H...O *S*(5) and *S*(6) hydrogen-bond ring motifs are observed in the cations and anions. The protonated N atom and 2-amine group of the 5FC cation interact with the 3HAP anion through a pair of nearly parallel N—H...O hydrogen bonds, forming a robust $R_2^2(8)$ ring motif. The ions are further linked by N—H...N, O—H...O, N—H...O and C—H...O hydrogen bonds, generating $R_2^2(7)$, $R_3^3(12)$ and $R_6^5(18)$ ring motifs, respectively, leading to supramolecular wave-like sheets parallel to (010). The crystal structure is further stabilized by C—H... π interactions, generating a three-dimensional architecture.

1. Chemical context

Fluorinated pyrimidine and purine derivatives have received much interest because of their wide range of biological applications (Giner-Sorolla & Bendich, 1958). 5-Fluorocytosine is a fluorinated pyrimidine derivative anti-metabolite drug and is also extensively used as an anti-fungal agent for the treatment of *Candida* and *Cryptococcus* (Vermes *et al.*, 2000). 5-Fluorocytosine is a versatile molecule that plays essential roles in many biological applications, such as anti-tumour, potential gene therapy and gene-directed prodrug therapy (GDEPT) in the treatment of cancer (Kohila *et al.*, 2012). The crystal structures of 5-fluorocytosine monohydrate, 5-fluorocytosine co-crystals and salts have also been reported (Louis *et al.*, 1982; Tutughamiarso *et al.*, 2012; Perumalla & Sun, 2014; Prabakaran *et al.*, 2001). The crystal structures of various salts and complexes of 3-hydroxypicolinic acid have also been reported (Quintal *et al.*, 2000; Soares-Santos *et al.*, 2003; Betz and Gerber, 2011; Nirmalram *et al.*, 2011).



We report herein the molecular structure of the title salt, formed from the reaction of 5-fluorocytosine with 3-hy-

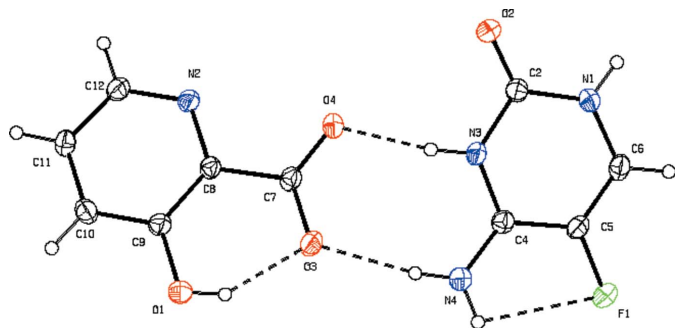


Figure 1
The asymmetric unit of the title compound, showing 30% probability displacement ellipsoids. Dashed lines represent hydrogen bonds.

droxypicolinic acid, namely 5-fluorocytosinium 3-hydroxypicolinate.

2. Structural commentary

The asymmetric unit contains a 5-fluorocytosinium cation and a 3-hydroxypicolinate anion (Fig. 1). The 5-fluorocytosine molecule is protonated at N3, as is evident from the increase in the internal angle at N3 from 120.8 (5) in neutral 5-fluorocytosine (Louis *et al.*, 1982) to 124.85 (15)°. There is an intramolecular N—H···F hydrogen bond with an *S*(5) ring motif between the N4 amino group and the F atom of the 5-fluorocytosinium cation. These hydrogen-bonding parameters are similar to those observed in 5-fluorocytosinium salicylate (Prabakaran *et al.*, 2001). An intramolecular O—H···O interaction forms an *S*(6) motif between the phenolic OH and carboxylate group, which is also observed in 3-hydroxypyridinium-2-carboxylate (Betz & Gerber, 2011).

3. Supramolecular features

In the crystal structure, the carboxylate group of the 3-hydroxypicolinate anion (O3 and O4) interacts with the protonated N3 atom and the 4-amino group of the 5-fluorocytosinium moiety through a pair of N—H···O hydrogen bonds, forming a robust *R*₂²(8) motif (Etter, 1990; Bernstein *et al.*, 1995).

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

Cg is the centroid of the N2/C8–C12 ring.

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···N2 ⁱ	0.86	2.04	2.873 (2)	163
N3—H3···O4	0.86	1.85	2.6665 (18)	158
N4—H4A···O3	0.86	1.98	2.830 (2)	169
N4—H4B···O1 ⁱⁱ	0.86	2.26	3.076 (2)	159
N4—H4B···F1	0.86	2.43	2.7312 (18)	101
O1—H1A···O3	0.82	1.83	2.5542 (18)	146
C6—H6···O2 ⁱ	0.93	2.29	3.127 (2)	150
C10—H10···O3 ⁱⁱⁱ	0.93	2.54	3.272 (2)	136
C12—H12···O2 ^{iv}	0.93	2.39	3.129 (2)	137
C11—H11···Cg1 ^v	0.93	2.88	3.426 (2)	119

Symmetry codes: (i) $x - \frac{1}{2}, -y + \frac{3}{2}, -z + 1$; (ii) $x - \frac{1}{2}, y, -z + \frac{1}{2}$; (iii) $-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$; (iv) $x + \frac{1}{2}, -y + \frac{3}{2}, -z + 1$; (v) $-x + \frac{3}{2}, y - \frac{1}{2}, z$.

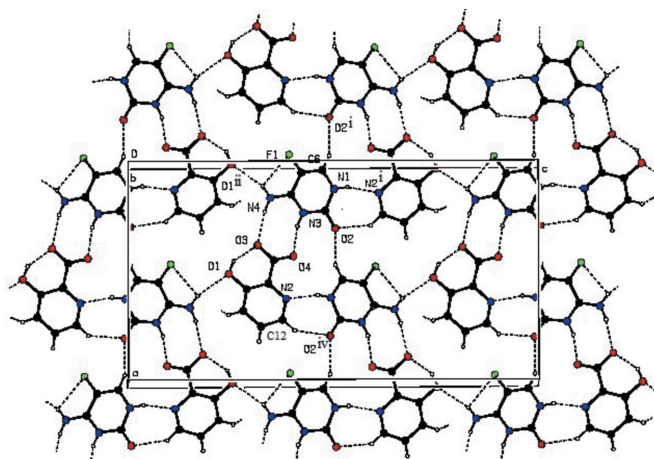


Figure 2
A view of the supramolecular wavy sheet-like structure formed by N—H···F, O—H···O, N—H···O, N—H···N and C—H···O hydrogen bonds. Symmetry codes are given in Table 1. Dashed lines represent hydrogen bonds.

The 3-hydroxypicolinate (N2 and C12) atoms interact with the N1 atom and the exocyclic oxygen O2 atom of the 5-fluorocytosinium moiety through a pair of N—H···N and C—H···O hydrogen bonds, forming an *R*₂²(7) motif. This type of motif rarely occurs in cytosinium carboxylate interactions (Benali-Cherif *et al.*, 2009). The motif is further

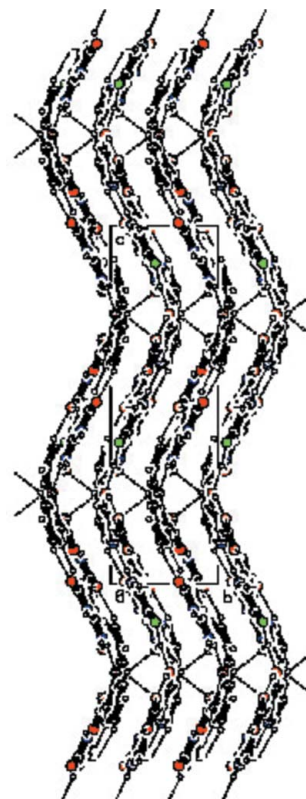


Figure 3
The wavy sheets interlinked by C—H···O hydrogen bonds. Dashed lines represent hydrogen bonds (see Table 1 for details).

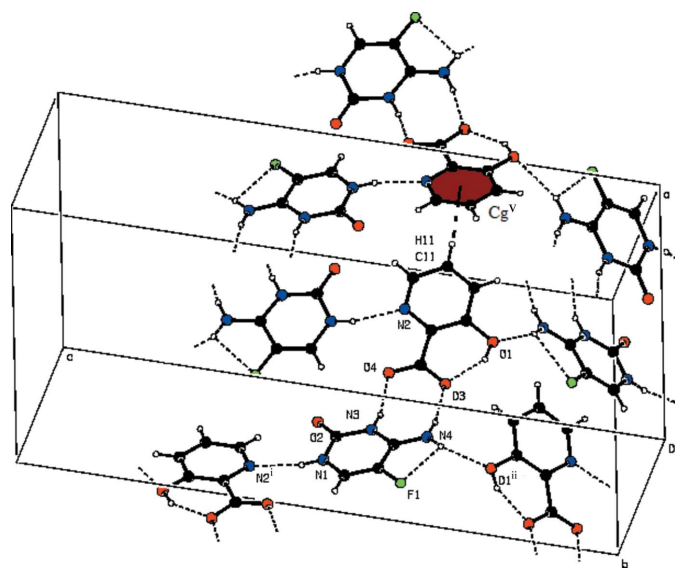


Figure 4
A view of the C—H... π interactions shown as dashed lines. Symmetry codes are given in Table 1.

connected on the other side by $R_3^3(12)$ and $R_5^6(18)$ motifs formed (Bernstein *et al.*, 1995) through C—H...O and N—H...O hydrogen bonds involving the O2 and N4 atoms of the 5-fluorocytosinium cation and the symmetry-related C6 atom of the another cytosinium cation and O1 atoms of 3-hydroxypicolinate anions, generating a wavy sheet-like structure parallel to (010) (Fig. 2). These wavy sheets are interconnected via C10—H10...O2 hydrogen bonds (Fig. 3). The crystal structure is further stabilized by C—H... π interactions between 3-hydroxypicolinate anions, Table 1.

4. Synthesis and crystallization

Hot aqueous solutions of 5-fluorocytosine (32 mg, Alfa Aesar) and 3-hydroxypicolinic acid (37 mg, Alfa Aesar) were mixed in a 1:1 molar ratio. The resulting solution was warmed over a water bath for half an hour and then kept at room temperature for crystallization. After a week, colourless prismatic crystals were obtained.

5. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. All H atoms were initially located in difference Fourier maps and were subsequently treated as riding atoms in geometrically idealized positions, with C—H = 0.93, N—H = 0.86 and O—H = 0.83 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C,N})$ and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$.

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Table 2
Experimental details.

Crystal data	
Chemical formula	$\text{C}_4\text{H}_5\text{FN}_3\text{O}^+ \cdot \text{C}_6\text{H}_4\text{NO}_3^-$
M_r	268.21
Crystal system, space group	Orthorhombic, <i>Pbca</i>
Temperature (K)	293
a, b, c (Å)	12.6487 (4), 7.0786 (2), 23.7200 (6)
V (Å ³)	2123.77 (10)
Z	8
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.14
Crystal size (mm)	0.15 × 0.05 × 0.05
Data collection	
Diffractometer	Agilent SuperNova (Dual, Cu at zero, Atlas)
Absorption correction	Multi-scan (<i>CrysAlis PRO</i> ; Agilent, 2011)
$T_{\text{min}}, T_{\text{max}}$	0.979, 0.993
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	8914, 2437, 1955
R_{int}	0.027
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.042, 0.111, 1.08
No. of reflections	2437
No. of parameters	173
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.24, -0.19

Computer programs: *CrysAlis PRO* (Agilent, 2011), *SHELXS97* and *SHELXL97* (Sheldrick, 2008) and *PLATON* (Spek, 2009).

1000 Ljubljana, Slovenia, for use of the SuperNova diffractometer.

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Crystal structure of 4-amino-5-fluoro-2-oxo-2,3-dihydropyrimidin-1-ium 3-hydroxypyridine-2-carboxylate

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Computing details

Data collection: *CrysAlis PRO* (Agilent, 2011); cell refinement: *CrysAlis PRO* (Agilent, 2011); data reduction: *CrysAlis PRO* (Agilent, 2011); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *PLATON* (Spek, 2009).

4-Amino-5-fluoro-2-oxo-2,3-dihydropyrimidin-1-ium 3-hydroxypicolinate

Crystal data

$C_4H_5FN_3O^+ \cdot C_6H_4NO_3^-$
 $M_r = 268.21$
 Orthorhombic, *Pbca*
 Hall symbol: -P 2ac 2ab
 $a = 12.6487$ (4) Å
 $b = 7.0786$ (2) Å
 $c = 23.7200$ (6) Å
 $V = 2123.77$ (10) Å³
 $Z = 8$

$F(000) = 1104$
 $D_x = 1.678$ Mg m⁻³
 Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
 Cell parameters from 3551 reflections
 $\theta = 3.7$ – 29.7°
 $\mu = 0.14$ mm⁻¹
 $T = 293$ K
 Needle, colourless
 0.15 × 0.05 × 0.05 mm

Data collection

Agilent SuperNova (Dual, Cu at zero, Atlas) diffractometer
 Radiation source: SuperNova (Mo) X-ray Source
 Mirror monochromator
 Detector resolution: 10.4933 pixels mm⁻¹
 ω scans
 Absorption correction: multi-scan (*CrysAlis PRO*; Agilent, 2011)

$T_{\min} = 0.979$, $T_{\max} = 0.993$
 8914 measured reflections
 2437 independent reflections
 1955 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.027$
 $\theta_{\max} = 27.5^\circ$, $\theta_{\min} = 3.2^\circ$
 $h = -16 \rightarrow 11$
 $k = -9 \rightarrow 6$
 $l = -30 \rightarrow 30$

Refinement

Refinement on F^2
 Least-squares matrix: full
 $R[F^2 > 2\sigma(F^2)] = 0.042$
 $wR(F^2) = 0.111$
 $S = 1.08$
 2437 reflections
 173 parameters
 0 restraints

Primary atom site location: structure-invariant direct methods
 Secondary atom site location: difference Fourier map
 Hydrogen site location: inferred from neighbouring sites
 H-atom parameters constrained

$$w = 1/[\sigma^2(F_o^2) + (0.0458P)^2 + 0.8599P]$$

where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$

$$\Delta\rho_{\max} = 0.24 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.19 \text{ e } \text{\AA}^{-3}$$

Special details

Experimental. 185 frames in 5 runs of ω scans. Crystal-detector distance = 55.0 mm.

Geometry. All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R -factor wR and goodness of fit S are based on F^2 , conventional R -factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R -factors(gt) etc. and is not relevant to the choice of reflections for refinement. R -factors based on F^2 are statistically about twice as large as those based on F , and R -factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
F1	-0.04979 (8)	0.58078 (18)	0.39473 (5)	0.0483 (3)
N1	0.10109 (11)	0.8014 (2)	0.50442 (6)	0.0335 (3)
H1	0.0909	0.8491	0.5373	0.040*
N3	0.21136 (11)	0.7249 (2)	0.42943 (6)	0.0312 (3)
H3	0.2733	0.7239	0.4145	0.037*
N4	0.14821 (12)	0.5828 (2)	0.34880 (6)	0.0392 (4)
H4A	0.2108	0.5846	0.3347	0.047*
H4B	0.0966	0.5360	0.3298	0.047*
O2	0.27785 (10)	0.8667 (2)	0.50714 (5)	0.0446 (4)
C2	0.20128 (14)	0.8021 (3)	0.48270 (7)	0.0317 (4)
C4	0.13147 (14)	0.6513 (2)	0.39922 (7)	0.0296 (4)
C5	0.03071 (13)	0.6548 (3)	0.42474 (7)	0.0332 (4)
C6	0.01722 (14)	0.7286 (3)	0.47624 (7)	0.0346 (4)
H6	-0.0496	0.7299	0.4926	0.041*
O1	0.49981 (11)	0.4529 (2)	0.24635 (5)	0.0430 (4)
H1A	0.4410	0.4833	0.2578	0.064*
O3	0.36400 (10)	0.5738 (2)	0.31741 (5)	0.0408 (3)
O4	0.41321 (10)	0.6570 (2)	0.40413 (5)	0.0416 (3)
N2	0.61308 (11)	0.5297 (2)	0.38561 (6)	0.0296 (3)
C7	0.43231 (13)	0.5915 (3)	0.35634 (7)	0.0301 (4)
C8	0.54219 (13)	0.5251 (2)	0.34318 (7)	0.0274 (4)
C9	0.56959 (14)	0.4572 (3)	0.28970 (7)	0.0306 (4)
C10	0.67182 (14)	0.3927 (3)	0.28059 (7)	0.0347 (4)
H10	0.6918	0.3464	0.2455	0.042*
C11	0.74279 (14)	0.3982 (3)	0.32407 (7)	0.0339 (4)
H11	0.8118	0.3565	0.3189	0.041*
C12	0.71035 (14)	0.4669 (3)	0.37608 (7)	0.0332 (4)
H12	0.7589	0.4690	0.4055	0.040*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1	0.0265 (6)	0.0690 (8)	0.0494 (7)	-0.0079 (5)	-0.0027 (5)	-0.0139 (6)
N1	0.0293 (8)	0.0439 (9)	0.0272 (7)	0.0025 (7)	0.0027 (6)	-0.0036 (6)
N3	0.0221 (7)	0.0427 (8)	0.0288 (7)	-0.0005 (6)	0.0025 (5)	-0.0008 (6)
N4	0.0295 (8)	0.0552 (10)	0.0330 (8)	-0.0036 (8)	0.0024 (6)	-0.0086 (7)
O2	0.0291 (7)	0.0668 (9)	0.0379 (7)	-0.0048 (7)	-0.0022 (5)	-0.0131 (7)
C2	0.0278 (9)	0.0392 (9)	0.0280 (8)	0.0024 (8)	0.0003 (7)	0.0009 (7)
C4	0.0278 (9)	0.0330 (9)	0.0280 (8)	0.0017 (7)	-0.0008 (6)	0.0039 (7)
C5	0.0238 (8)	0.0406 (10)	0.0351 (9)	-0.0010 (8)	-0.0034 (7)	-0.0001 (8)
C6	0.0249 (8)	0.0426 (10)	0.0362 (9)	0.0019 (8)	0.0043 (7)	0.0038 (8)
O1	0.0331 (7)	0.0677 (9)	0.0280 (6)	0.0063 (7)	-0.0043 (5)	-0.0070 (6)
O3	0.0251 (6)	0.0644 (9)	0.0329 (7)	0.0030 (6)	-0.0020 (5)	0.0009 (6)
O4	0.0275 (7)	0.0623 (9)	0.0349 (7)	0.0053 (6)	0.0032 (5)	-0.0091 (6)
N2	0.0244 (7)	0.0380 (8)	0.0265 (7)	-0.0016 (6)	0.0002 (5)	0.0011 (6)
C7	0.0247 (8)	0.0361 (9)	0.0294 (8)	-0.0013 (7)	0.0015 (7)	0.0045 (7)
C8	0.0238 (8)	0.0326 (9)	0.0258 (8)	-0.0020 (7)	0.0014 (6)	0.0024 (7)
C9	0.0292 (9)	0.0367 (9)	0.0258 (8)	-0.0007 (8)	-0.0012 (6)	0.0007 (7)
C10	0.0357 (10)	0.0394 (10)	0.0290 (8)	0.0047 (8)	0.0048 (7)	-0.0026 (7)
C11	0.0257 (9)	0.0375 (9)	0.0386 (9)	0.0058 (8)	0.0028 (7)	0.0011 (8)
C12	0.0267 (9)	0.0411 (10)	0.0319 (9)	0.0005 (8)	-0.0030 (7)	0.0012 (8)

Geometric parameters (Å, °)

F1—C5	1.348 (2)	O1—C9	1.355 (2)
N1—C6	1.356 (2)	O1—H1A	0.8200
N1—C2	1.368 (2)	O3—C7	1.271 (2)
N1—H1	0.8600	O4—C7	1.248 (2)
N3—C4	1.344 (2)	N2—C12	1.328 (2)
N3—C2	1.383 (2)	N2—C8	1.348 (2)
N3—H3	0.8600	C7—C8	1.500 (2)
N4—C4	1.308 (2)	C8—C9	1.400 (2)
N4—H4A	0.8600	C9—C10	1.388 (2)
N4—H4B	0.8600	C10—C11	1.368 (2)
O2—C2	1.218 (2)	C10—H10	0.9300
C4—C5	1.411 (2)	C11—C12	1.388 (2)
C5—C6	1.340 (2)	C11—H11	0.9300
C6—H6	0.9300	C12—H12	0.9300
C6—N1—C2	122.73 (15)	C9—O1—H1A	109.5
C6—N1—H1	118.6	C12—N2—C8	118.75 (14)
C2—N1—H1	118.6	O4—C7—O3	124.40 (16)
C4—N3—C2	124.84 (15)	O4—C7—C8	118.99 (15)
C4—N3—H3	117.6	O3—C7—C8	116.60 (15)
C2—N3—H3	117.6	N2—C8—C9	121.32 (15)
C4—N4—H4A	120.0	N2—C8—C7	116.96 (14)
C4—N4—H4B	120.0	C9—C8—C7	121.70 (15)

H4A—N4—H4B	120.0	O1—C9—C10	118.77 (15)
O2—C2—N1	123.98 (16)	O1—C9—C8	122.25 (16)
O2—C2—N3	120.68 (16)	C10—C9—C8	118.98 (15)
N1—C2—N3	115.34 (15)	C11—C10—C9	118.99 (16)
N4—C4—N3	120.63 (16)	C11—C10—H10	120.5
N4—C4—C5	123.02 (16)	C9—C10—H10	120.5
N3—C4—C5	116.34 (15)	C10—C11—C12	119.08 (16)
C6—C5—F1	122.47 (16)	C10—C11—H11	120.5
C6—C5—C4	120.85 (16)	C12—C11—H11	120.5
F1—C5—C4	116.68 (15)	N2—C12—C11	122.87 (16)
C5—C6—N1	119.89 (16)	N2—C12—H12	118.6
C5—C6—H6	120.1	C11—C12—H12	118.6
N1—C6—H6	120.1		
C6—N1—C2—O2	179.95 (18)	C12—N2—C8—C7	178.04 (16)
C6—N1—C2—N3	0.7 (3)	O4—C7—C8—N2	4.0 (2)
C4—N3—C2—O2	-179.68 (17)	O3—C7—C8—N2	-174.95 (16)
C4—N3—C2—N1	-0.4 (3)	O4—C7—C8—C9	-177.49 (17)
C2—N3—C4—N4	179.33 (17)	O3—C7—C8—C9	3.6 (3)
C2—N3—C4—C5	0.0 (3)	N2—C8—C9—O1	-179.39 (16)
N4—C4—C5—C6	-179.16 (18)	C7—C8—C9—O1	2.2 (3)
N3—C4—C5—C6	0.2 (3)	N2—C8—C9—C10	0.3 (3)
N4—C4—C5—F1	0.8 (3)	C7—C8—C9—C10	-178.17 (16)
N3—C4—C5—F1	-179.85 (15)	O1—C9—C10—C11	179.43 (17)
F1—C5—C6—N1	-179.86 (16)	C8—C9—C10—C11	-0.3 (3)
C4—C5—C6—N1	0.1 (3)	C9—C10—C11—C12	0.4 (3)
C2—N1—C6—C5	-0.5 (3)	C8—N2—C12—C11	0.7 (3)
C12—N2—C8—C9	-0.5 (3)	C10—C11—C12—N2	-0.7 (3)

Hydrogen-bond geometry (Å, °)

C_g is the centroid of the N2/C8—C12 ring.

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1...N2 ⁱ	0.86	2.04	2.873 (2)	163
N3—H3...O4	0.86	1.85	2.6665 (18)	158
N4—H4A...O3	0.86	1.98	2.830 (2)	169
N4—H4B...O1 ⁱⁱ	0.86	2.26	3.076 (2)	159
N4—H4B...F1	0.86	2.43	2.7312 (18)	101
O1—H1A...O3	0.82	1.83	2.5542 (18)	146
C6—H6...O2 ⁱ	0.93	2.29	3.127 (2)	150
C10—H10...O3 ⁱⁱⁱ	0.93	2.54	3.272 (2)	136
C12—H12...O2 ^{iv}	0.93	2.39	3.129 (2)	137
C11—H11...C _g 1 ^v	0.93	2.88	3.426 (2)	119

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