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5-Fluoro-1-[(4*S*,5*R*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-pyrimidine-2,4(1*H*,3*H*)-dione

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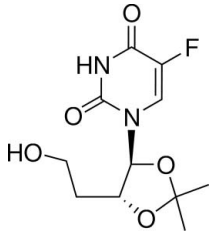
Key indicators: single-crystal X-ray study; T = 298 K; mean σ(C–C) = 0.003 Å; R factor = 0.027; wR factor = 0.071; data-to-parameter ratio = 9.9.

In the title compound, $C_{11}H_{15}FN_2O_5$, the five-membered ring has an envelope conformation, while the six-membered ring is essentially planar, with a maximum deviation of 0.032 (2) Å from the mean plane. The crystal packing is stabilized by intermolecular N—H···O and O—H···O hydrogen bonds, generating a layer structure parallel to (001).

Related literature

For applications of modified nucleosides in medical chemistry, see: Huryn & Okabe (1992); Minuk *et al.* (1992); Luscombe *et al.* (1996); Korba & Boyd (1996). For the synthesis, see: Valdivia *et al.* (2005); Xie *et al.* (1996). For ring conformation analysis, see: Cremer & Pople (1975).



Experimental

Crystal data

$C_{11}H_{15}FN_2O_5$
M_r = 274.25
Monoclinic, $C2$
a = 20.8905 (8) Å
b = 5.5751 (1) Å
c = 13.5639 (5) Å
β = 126.297 (6)°
V = 1273.21 (12) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 1.06 mm^{-1}
T = 298 K
0.40 × 0.12 × 0.08 mm

Data collection

Oxford Diffraction Gemini Atlas CCD diffractometer
Absorption correction: analytical (*CrysAlis RED*; Oxford Diffraction, 2009)
T_{min} = 0.885, T_{max} = 0.964
4606 measured reflections
1786 independent reflections
1732 reflections with $I > 2\sigma(I)$
R_{int} = 0.013

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.071
S = 1.04
1786 reflections
181 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Absolute structure: Flack (1983), 498 Friedel pairs
Flack parameter: 0.0 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H1N···O5^{i}	0.83 (2)	2.01 (2)	2.828 (2)	167 (3)
O5—H1O···O2^{ii}	0.75 (3)	2.16 (3)	2.876 (2)	160 (3)

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

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2009); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2009); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: IS2543).

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supplementary materials

Acta Cryst. (2010). E**66**, o1317 [**doi:10.1107/S1600536810016065**]

5-Fluoro-1-[(4*S*,5*R*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrimidine-2,4(1*H*,3*H*)-dione

A. Mendoza, M. Sosa-Rivadeneyra, F. Sartillo-Piscil, L. Quintero and M. Flores-Alamo

Comment

For many years, design of modified nucleosides has been a focal point of research in medicinal chemistry (Huryn & Okabe, 1992). Modified nucleosides have acquired an important role as therapeutic agents for the treatment of patients with devastating infections with viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and herpes viruses. A class of nucleoside analogues for antiviral chemotherapy is that where cyclic carbohydrate moiety is replaced with open-chain "acyclic" sugar moieties. Among purine acyclic nucleosides, are Acyclovir, Ganciclovir and Penciclovir (Minuk *et al.*, 1992; Luscombe *et al.*, 1996; Korba & Boyd, 1996).

In this context and as result of our continuing investigations on the synthesis of nucleoside analogues, we report a new compound **1** (Scheme 1). This new analogue might present a similarity with a number of acyclic nucleosides, which showed remarkable antiviral properties.

In the present paper, we report the structure of title compound **1**. In the [(1'*S*, 2'*R*)-(1', 2'-*O*-isopropylidene-4'-hydroxy-1-butyl)], the five member ring (C5/C6/O3/O4/C9) shows an envelope conformation on atom C6 with puckering parameters (Cremer & Pople, 1975) q_2 = 0.238 (2) Å and φ_2 = 69.8 (6)°. For the six member ring uracil, shows a planar configuration with torsion angle (N1—C4—N2—C3) of 4.8 (3)°, and C1—C2 = 1.325 (3) Å and N2—C4 = 1.384 (2) Å (double bond). The crystal packing is stabilized by two intermolecular hydrogen bonds [O5···O2 = 2.828 (2) Å and N2···O5 = 2.876 (2) Å], generating a layer parallel to the (001) plane.

Experimental

Deshomologation of previos nucleoside analogue, 1-[(1'*S*,2'*R*,4'*S*)-(1',2'-*O*-isopropylidene-4',5'-dihydroxy-1'-pentyl)]-5-fluorouracil, was achieved following non-aqueous protocol (Valdivia *et al.*, 2005; Xie *et al.*, 1996). Reaction was carried out by two steps: a) periodic acid/ethyl acetate, 30 min, b) EtOH/H2O/ NaBH4, 20 min, rt. Final purification of compound **1** was achieved by crystallization from hexane. Yield 80%, white solid, m.p. 184 °C; $[\alpha]_D$ -18.51 (c 1.0, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) 1.53 (s, 3H), 1.57 (s, 3H), 1.95 (m, 1H), 2.11 (m, 1H), 3.80 (m, 2H), 4.21 (m, 1H), 5.90 (d, 1H, J = 5.1 Hz), 7.3 (s, 1H). ^{13}C MNR (75 MHz, $CDCl_3$/TMS) 26.9, 27.9, 34.9, 55.8, 58.9, 79.4, 86.8, 111.6, 142.2, 149.5, 157.5.

Refinement

H atoms bonded to N2 and O5 atoms were located in a difference Fourier map and refined with free coordinates and isotropic *U* parameters. H atoms linked to C atoms were placed in geometrical idealized positions and refined as riding on their parent atoms, with C—H = 0.93–0.98 Å, and with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C) for methyl groups.

Figures

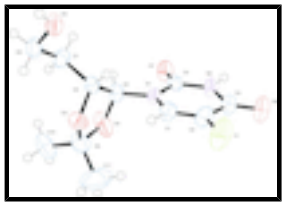

Fig. 1. The molecular structure of compound **1**, with atom labels and 50% probability displacement ellipsoids for non-H atoms.

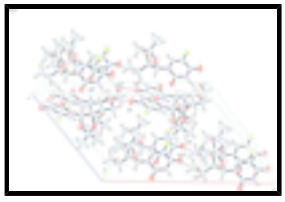

Fig. 2. The packing of compound **1**, viewed down the *b* axis, showing one layer of molecules connected by O5—H···O2 and N2—H···O5 hydrogen bonds (dashed lines).

5-Fluoro-1-[(4*S*,5*R*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3- dioxolan-4-yl]pyrimidine-2,4(1*H*,3*H*)-dione

Crystal data

$C_{11}H_{15}FN_2O_5$	$F(000) = 576$
$M_r = 274.25$	$D_x = 1.431$ Mg m^{-3}
Monoclinic, *C*2	Cu *K*α radiation, λ = 1.54184 Å
Hall symbol: C 2y	Cell parameters from 4215 reflections
$a = 20.8905$ (8) Å	θ = 4.0–68.0°
$b = 5.5751$ (1) Å	μ = 1.06 mm^{-1}
$c = 13.5639$ (5) Å	$T = 298$ K
β = 126.297 (6)°	Prism, colorless
$V = 1273.21$ (12) Å^3	0.40 × 0.12 × 0.08 mm
$Z = 4$	

Data collection

Oxford Diffraction Gemini Atlas CCD diffractometer	1786 independent reflections
Radiation source: fine-focus sealed tube	1732 reflections with $I > 2\sigma(I)$
graphite	$R_{int} = 0.013$
Detector resolution: 10.4685 pixels mm^{-1}	$\theta_{max} = 68.1°$, $\theta_{min} = 4.0°$
ω scans	$h = -22 \rightarrow 24$
Absorption correction: analytical (*CrysAlis RED*; Oxford Diffraction, 2009)	$k = -4 \rightarrow 6$
$T_{min} = 0.885$, $T_{max} = 0.964$	$l = -16 \rightarrow 16$
4606 measured reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites

Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.027$	$w = 1/[\sigma^2(F_o^2) + (0.038P)^2 + 0.4768P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.071$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.04$	$\Delta\rho_{max} = 0.23$ e Å^{-3}
1786 reflections	$\Delta\rho_{min} = -0.19$ e Å^{-3}
181 parameters	Extinction correction: *SHELXL97* (Sheldrick, 2008), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
1 restraint	Extinction coefficient: 0.0075 (4)
Primary atom site location: structure-invariant direct methods	Absolute structure: Flack (1983), 498 Friedel pairs
Secondary atom site location: difference Fourier map	Flack parameter: 0.0 (2)

Special details

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 (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.69200 (8)	0.0051 (3)	0.95722 (12)	0.0519 (4)
N1	0.66380 (8)	0.2920 (3)	0.81679 (12)	0.0339 (3)
O4	0.72382 (7)	0.3751 (3)	0.65042 (11)	0.0438 (3)
F1	0.52029 (9)	0.7673 (3)	0.69645 (15)	0.0816 (5)
O5	0.90402 (9)	0.7069 (3)	0.88915 (13)	0.0478 (4)
O2	0.49424 (9)	0.5250 (3)	0.84757 (15)	0.0627 (5)
C5	0.72230 (11)	0.1894 (4)	0.80156 (17)	0.0403 (4)
H5	0.7609	0.0950	0.8745	0.048*
N2	0.59707 (9)	0.2801 (4)	0.90550 (15)	0.0434 (4)
C1	0.61955 (10)	0.4901 (4)	0.75175 (16)	0.0418 (4)
H1	0.6291	0.5673	0.7009	0.050*
O3	0.68552 (11)	0.0402 (3)	0.69943 (16)	0.0681 (5)
C4	0.65428 (10)	0.1784 (4)	0.89752 (15)	0.0362 (4)
C6	0.76688 (9)	0.3754 (4)	0.78102 (14)	0.0350 (4)
H6	0.7625	0.5332	0.8084	0.042*
C2	0.56349 (11)	0.5732 (4)	0.76007 (18)	0.0466 (5)
C3	0.54650 (10)	0.4653 (4)	0.83818 (17)	0.0435 (5)
C8	0.89973 (11)	0.4915 (4)	0.83002 (18)	0.0469 (5)
H8A	0.9528	0.4318	0.8649	0.056*

H8B	0.8733	0.5206	0.7435	0.056*
C7	0.85368 (10)	0.3099 (4)	0.84748 (17)	0.0437 (5)
H7A	0.8779	0.2948	0.9342	0.052*
H7B	0.8572	0.1551	0.8184	0.052*
C9	0.68429 (13)	0.1521 (4)	0.60232 (19)	0.0533 (6)
C10	0.72705 (17)	−0.0147 (5)	0.5721 (2)	0.0689 (7)
H10A	0.6979	−0.1621	0.5400	0.103*
H10B	0.7793	−0.0473	0.6448	0.103*
H10C	0.7313	0.0588	0.5121	0.103*
C11	0.60061 (17)	0.2034 (8)	0.4934 (3)	0.1094 (13)
H11A	0.5725	0.0550	0.4592	0.164*
H11B	0.6016	0.2893	0.4330	0.164*
H11C	0.5743	0.2986	0.5185	0.164*
H1N	0.5950 (12)	0.236 (5)	0.9622 (19)	0.048 (6)*
H1O	0.9348 (15)	0.789 (6)	0.896 (2)	0.072 (9)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0606 (7)	0.0506 (9)	0.0586 (7)	0.0216 (7)	0.0430 (7)	0.0239 (8)
N1	0.0336 (6)	0.0365 (9)	0.0345 (7)	0.0036 (7)	0.0218 (6)	0.0044 (6)
O4	0.0520 (7)	0.0397 (8)	0.0390 (6)	−0.0028 (6)	0.0265 (5)	0.0009 (6)
F1	0.0799 (8)	0.0748 (11)	0.1109 (11)	0.0463 (8)	0.0678 (8)	0.0532 (10)
O5	0.0529 (8)	0.0445 (10)	0.0622 (8)	−0.0061 (7)	0.0430 (7)	−0.0071 (7)
O2	0.0621 (8)	0.0584 (11)	0.0954 (11)	0.0167 (8)	0.0619 (8)	0.0137 (10)
C5	0.0465 (9)	0.0352 (11)	0.0509 (9)	0.0048 (9)	0.0353 (8)	0.0038 (9)
N2	0.0502 (8)	0.0455 (10)	0.0498 (8)	0.0083 (8)	0.0381 (7)	0.0092 (8)
C1	0.0410 (8)	0.0437 (12)	0.0447 (9)	0.0064 (9)	0.0275 (7)	0.0138 (9)
O3	0.1087 (12)	0.0487 (10)	0.0938 (11)	−0.0334 (9)	0.0857 (10)	−0.0292 (9)
C4	0.0368 (8)	0.0390 (11)	0.0359 (8)	0.0011 (8)	0.0232 (7)	0.0018 (8)
C6	0.0397 (8)	0.0320 (10)	0.0388 (8)	0.0022 (8)	0.0263 (7)	0.0006 (8)
C2	0.0444 (9)	0.0382 (12)	0.0563 (11)	0.0122 (9)	0.0294 (9)	0.0139 (9)
C3	0.0417 (8)	0.0401 (12)	0.0557 (10)	0.0025 (9)	0.0326 (8)	0.0013 (9)
C8	0.0430 (9)	0.0492 (13)	0.0608 (11)	0.0008 (10)	0.0374 (9)	−0.0079 (11)
C7	0.0400 (9)	0.0402 (12)	0.0531 (10)	0.0056 (9)	0.0288 (8)	0.0001 (9)
C9	0.0641 (12)	0.0483 (14)	0.0551 (11)	−0.0145 (11)	0.0394 (10)	−0.0142 (10)
C10	0.1132 (18)	0.0523 (16)	0.0761 (14)	−0.0072 (15)	0.0752 (15)	−0.0113 (13)
C11	0.0695 (16)	0.110 (3)	0.086 (2)	−0.0123 (19)	0.0121 (15)	−0.043 (2)

Geometric parameters (Å, °)

O1—C4	1.206 (2)	O3—C9	1.444 (3)
N1—C1	1.373 (3)	C6—C7	1.516 (2)
N1—C4	1.378 (2)	C6—H6	0.9800
N1—C5	1.471 (2)	C2—C3	1.434 (3)
O4—C9	1.419 (3)	C8—C7	1.509 (3)
O4—C6	1.435 (2)	C8—H8A	0.9700
F1—C2	1.345 (2)	C8—H8B	0.9700
O5—C8	1.417 (3)	C7—H7A	0.9700

O5—H1O	0.75 (3)	C7—H7B	0.9700
O2—C3	1.218 (2)	C9—C11	1.504 (4)
C5—O3	1.393 (3)	C9—C10	1.505 (3)
C5—C6	1.526 (3)	C10—H10A	0.9600
C5—H5	0.9800	C10—H10B	0.9600
N2—C3	1.369 (3)	C10—H10C	0.9600
N2—C4	1.384 (2)	C11—H11A	0.9600
N2—H1N	0.83 (2)	C11—H11B	0.9600
C1—C2	1.325 (3)	C11—H11C	0.9600
C1—H1	0.9300		
C1—N1—C4	121.43 (14)	N2—C3—C2	112.25 (16)
C1—N1—C5	121.47 (14)	O5—C8—C7	108.20 (15)
C4—N1—C5	117.10 (15)	O5—C8—H8A	110.1
C9—O4—C6	109.72 (14)	C7—C8—H8A	110.1
C8—O5—H1O	110 (2)	O5—C8—H8B	110.1
O3—C5—N1	110.92 (16)	C7—C8—H8B	110.1
O3—C5—C6	105.14 (14)	H8A—C8—H8B	108.4
N1—C5—C6	114.14 (16)	C8—C7—C6	113.23 (17)
O3—C5—H5	108.8	C8—C7—H7A	108.9
N1—C5—H5	108.8	C6—C7—H7A	108.9
C6—C5—H5	108.8	C8—C7—H7B	108.9
C3—N2—C4	128.17 (16)	C6—C7—H7B	108.9
C3—N2—H1N	113.4 (16)	H7A—C7—H7B	107.7
C4—N2—H1N	118.1 (16)	O4—C9—O3	105.54 (16)
C2—C1—N1	121.28 (17)	O4—C9—C11	107.9 (2)
C2—C1—H1	119.4	O3—C9—C11	111.2 (2)
N1—C1—H1	119.4	O4—C9—C10	112.88 (19)
C5—O3—C9	110.51 (16)	O3—C9—C10	106.8 (2)
O1—C4—N1	123.91 (16)	C11—C9—C10	112.5 (2)
O1—C4—N2	121.80 (16)	C9—C10—H10A	109.5
N1—C4—N2	114.29 (16)	C9—C10—H10B	109.5
O4—C6—C7	112.88 (14)	H10A—C10—H10B	109.5
O4—C6—C5	102.72 (13)	C9—C10—H10C	109.5
C7—C6—C5	111.86 (15)	H10A—C10—H10C	109.5
O4—C6—H6	109.7	H10B—C10—H10C	109.5
C7—C6—H6	109.7	C9—C11—H11A	109.5
C5—C6—H6	109.7	C9—C11—H11B	109.5
C1—C2—F1	121.20 (18)	H11A—C11—H11B	109.5
C1—C2—C3	122.28 (19)	C9—C11—H11C	109.5
F1—C2—C3	116.51 (17)	H11A—C11—H11C	109.5
O2—C3—N2	121.46 (18)	H11B—C11—H11C	109.5
O2—C3—C2	126.3 (2)		
C1—N1—C5—O3	−82.0 (2)	N1—C5—C6—C7	141.06 (16)
C4—N1—C5—O3	96.83 (19)	N1—C1—C2—F1	179.91 (19)
C1—N1—C5—C6	36.5 (2)	N1—C1—C2—C3	1.0 (3)
C4—N1—C5—C6	−144.63 (16)	C4—N2—C3—O2	173.9 (2)
C4—N1—C1—C2	−3.0 (3)	C4—N2—C3—C2	−6.5 (3)
C5—N1—C1—C2	175.8 (2)	C1—C2—C3—O2	−177.1 (2)

N1—C5—O3—C9	107.78 (18)	F1—C2—C3—O2	4.0 (3)
C6—C5—O3—C9	−16.1 (2)	C1—C2—C3—N2	3.3 (3)
C1—N1—C4—O1	−179.53 (18)	F1—C2—C3—N2	−175.64 (18)
C5—N1—C4—O1	1.6 (3)	O5—C8—C7—C6	67.2 (2)
C1—N1—C4—N2	0.4 (3)	O4—C6—C7—C8	65.3 (2)
C5—N1—C4—N2	−178.50 (15)	C5—C6—C7—C8	−179.47 (16)
C3—N2—C4—O1	−175.3 (2)	C6—O4—C9—O3	15.2 (2)
C3—N2—C4—N1	4.8 (3)	C6—O4—C9—C11	134.1 (2)
C9—O4—C6—C7	96.42 (19)	C6—O4—C9—C10	−101.1 (2)
C9—O4—C6—C5	−24.21 (19)	C5—O3—C9—O4	1.4 (2)
O3—C5—C6—O4	24.16 (19)	C5—O3—C9—C11	−115.3 (2)
N1—C5—C6—O4	−97.61 (16)	C5—O3—C9—C10	121.8 (2)
O3—C5—C6—C7	−97.17 (18)		

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H1N···O5^{i}	0.83 (2)	2.01 (2)	2.828 (2)	167 (3)
O5—H1O···O2^{ii}	0.75 (3)	2.16 (3)	2.876 (2)	160 (3)

Symmetry codes: (i) −*x*+3/2, *y*−1/2, −*z*+2; (ii) *x*+1/2, *y*+1/2, *z*.

Fig. 1

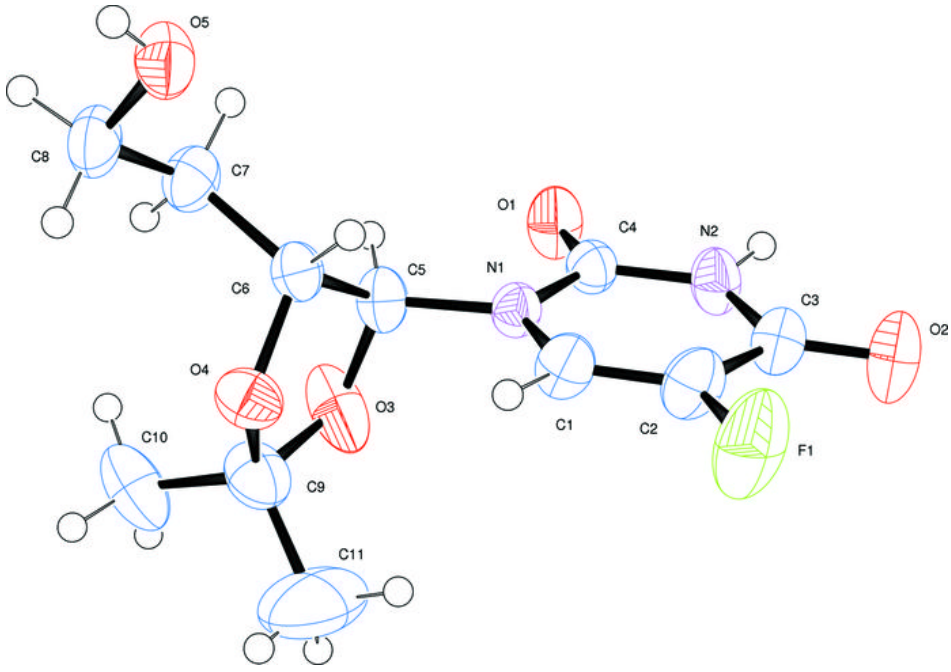

Fig. 2