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6-Amino-3-(β-D-2-deoxy-*erythro*-furanosyl)-2-fluoropyridine: a nucleoside analogue

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Key indicators

Single-crystal X-ray study
T = 193 K
Mean σ(C–C) = 0.002 Å
R factor = 0.033
wR factor = 0.082
Data-to-parameter ratio = 10.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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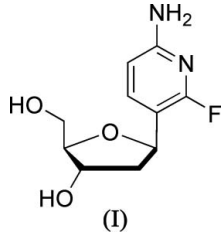
The title compound [systematic name: (2*R*,3*R*,5*R*)-5-(6-amino-2-fluoropyridin-3-yl)-2-(hydroxymethyl)-2,3,4,5-tetrahydrofuran-3-ol], $C_{10}H_{13}FN_2O_3$, is a C-nucleoside with fluorine replacing the O2 carbonyl of deoxycytidine (dC). The furanose ring adopts a C2′-*endo* conformation, while the orientation of the pyridine ring with respect to the sugar group is *anti*. The C-glycosidic bond torsion angle χ is *anti* [−121.32 (13)°]. The C—C glycosidic bond is 1.4952 (17) Å in length, while the C—F bond length is 1.3463 (16) Å.

Comment

Modified nucleobases, nucleosides and nucleotides are important in processes of regulation and are used broadly in chemistry, biochemistry and pharmacology as probes of biological mechanisms (Dyson *et al.*, 1970; Meisel *et al.*, 1990). Two classes of DNA analogues that have been described recently include those in which specific functional groups have been deleted from the pyrimidine residues (Hsieh & McLaughlin, 1995; Lan & McLaughlin, 2001; Fraley *et al.*, 2003) and those in which hydrophobic isosteres having the desired molecular shape (with F replacing the carbonyls and CH_3 replacing the exocyclic amino groups) are used to replace the nucleobase (Dzantiev *et al.*, 2001; Moran *et al.*, 1997; Matray & Kool, 1998). Here we describe a hybrid version of these classes of analogues, a series of pyrimidine-like analogues that maintain bidentate Watson–Crick hydrogen bonding faces, but use isosteric fluorine to replace the minor groove carbonyls. The unique structural features and interesting biological activities of C-nucleosides have rendered them attractive as targets for structural analyses. The title compound, (I) (an analogue of deoxycytidine, dC), was prepared for incorporation into DNA, as well as for pharmaceutical analyses. We report here its crystal structure.



(I)

We were able to crystallize (I) as colorless needles from a water–methanol mixture at 253 K. A perspective view of (I) with the atom-labeling scheme is shown in Fig. 1, and selected bond lengths and angles are summarized in Table 1. The orientation of the nucleobase relative to the sugar group (*syn*/

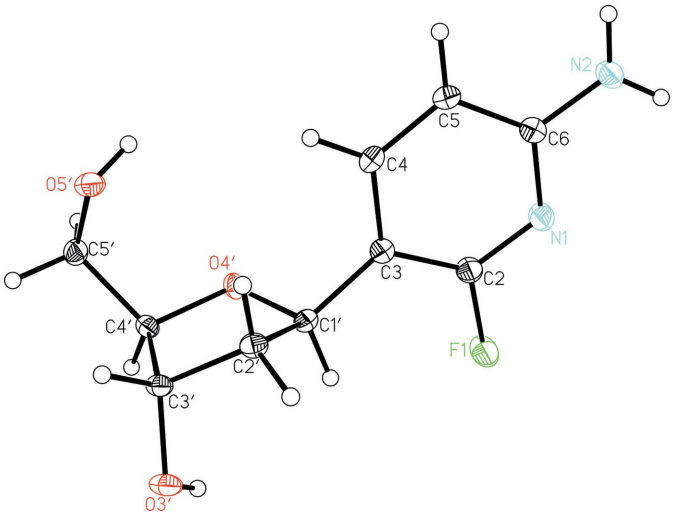


Figure 1
A perspective view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

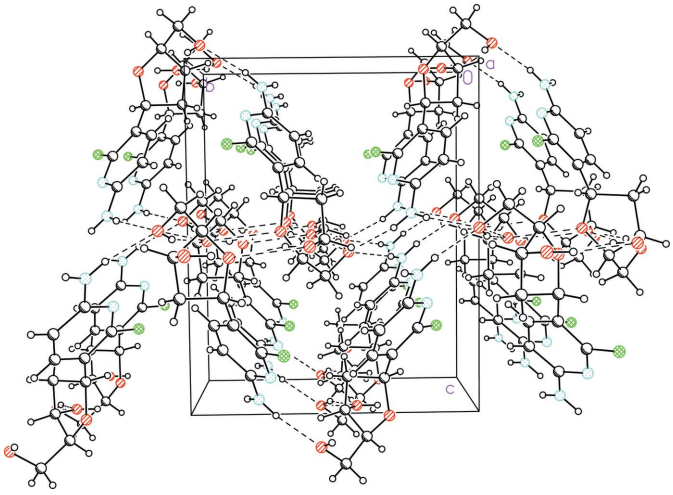


Figure 2
The intermolecular hydrogen-bond (dashed lines) network and crystal packing.

anti) is defined by analogy to the natural pyrimidine nucleoside by the torsion angle χ, O4′—C1′—C3—C2 (O4′—C1′—N1—C2 in the pyrimidine; IUPAC–IUB, 1983). In the crystalline state of (I), the glycosidic bond (C1′—C3) is 1.4952 (17) Å in length, which compares favorably with the 1.472 Å and 1.499 Å lengths reported for the C1′—N1 bond of dC (Young & Wilson, 1975). The C2—F bond length of 1.3463 (16) Å is slightly longer than the C2—O2 double bond in dC (1.239 and 1.243 Å) but compares favorably with the 1.328 Å length typical for aromatic C—F bonds (Weast, 1976). The glycosidic bond torsion angle is in the *anti* range [χ = −121.32 (13)°]. The sugar ring in (I) is puckered, as shown by the C3′—C4′—O4′—C1′ [6.54 (12)°] and C4′—O4′—C1′—C2′ [−28.24 (13)°] torsion angles. The puckering amplitude τ_m = 35.9°, which is a little smaller than the average value of 38.6 (3)° (Saenger, 1984), and the pseudorotation phase angle (*P*) of 162.3° indicate an S-type sugar conformation (2′-*endo*-3′-*exo*, $^2T_3$) preferred by most 2′-deoxy-β-D-ribofuranosyl nucleosides. The torsion angle γ [O5′—C5′—C4′—C3′ = 55.87 (15)°] describing the orientation of the 5′-hydroxy group relative to the sugar ring shows that the C4′—C5′ bond is in a *gauche*+*syn* (+*sc*) orientation (Saenger, 1984). Thus, atom O5′ is oriented towards the sugar ring. The base group of (I) is nearly planar.

Intermolecular hydrogen bonds generate a three-dimensional network and provide additional crystal structure stabilization (Fig. 2 and Table 2). The crystal packing results in the formation of a multiple-layer network of nucleosides (I). The molecules of (I) are interconnected with one another by four strong hydrogen bonds, as listed in Table 2, *viz*. two N—H···O and two O—H···O interactions.

Experimental

Compound (I) was synthesized from 6-amino-2-fluoro-3-iodopyridine and 1,4-anhydrodeoxy-3-*O*-(*tert*-butyldiphenylsilyl)-D-*erythro*-1-enitol according to the Heck type coupling reaction (Sun *et al.*, 2006). Compound (I) was crystallized slowly from methanol and water (9:1) at 253 K.

Crystal data

$C_{10}H_{13}FN_2O_3$
M_r = 228.22
Orthorhombic, $P2_12_12_1$
a = 6.3295 (16) Å
b = 11.365 (3) Å
c = 13.908 (3) Å
V = 1000.5 (4) Å^3
Z = 4
D_x = 1.515 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3580 reflections
θ = 2.3–28.4°
μ = 0.12 mm^{-1}
T = 193 (2) K
Chunk, colorless
0.2 × 0.1 × 0.1 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: none
7552 measured reflections
1469 independent reflections
1365 reflections with $I > 2\sigma(I)$
R_{int} = 0.042
θ_{max} = 28.4°
$h = -6 \rightarrow 8$
$k = -13 \rightarrow 15$
$l = -18 \rightarrow 12$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.082
S = 1.13
1469 reflections
147 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0513P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

F1—C2	1.3463 (16)	C3—C1′	1.4952 (17)
C3′—C2′—C1′	102.70 (10)	O4′—C1′—C3	110.13 (10)
C2′—C3′—C4′	103.31 (10)	O4′—C1′—C2′	103.39 (9)
C1′—C2′—C3′—C4′	−34.23 (12)	C4′—O4′—C1′—C2′	−28.24 (13)
O4′—C4′—C3′—C2′	17.80 (12)	C4—C3—C1′—O4′	61.36 (15)

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

D—H···A	D—H	H···A	D···A	D—H···A
O5′—H5B···O3′^{i}	0.84	1.95	2.762 (1)	161
O3′—H3···O4′^{ii}	0.84	1.98	2.805 (2)	167
N2—H2A···O5′^{iii}	0.88	2.14	3.002 (2)	165
N2—H2B···O5′^{iv}	0.88	2.22	3.069 (2)	162

Symmetry codes: (i) $x+1, y, z$; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iii) $-x+2, y-\frac{1}{2}, -z+\frac{3}{2}$; (iv) $-x+\frac{5}{2}, -y+1, z+\frac{1}{2}$.

All H atoms were placed in calculated positions and refined using a riding model; C—H = 0.95–1.00 Å, N—H = 0.88 Å, O—H = 0.84 Å, and U_{iso}(H) = 1.2U_{eq}(C,N) or 1.5U_{eq}(O).

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1998); software used to prepare material for publication: *SHELXTL*.

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