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2′-Deoxy-5-fluorotubercidin

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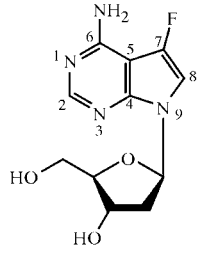
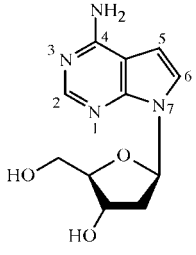
In the title compound, 4-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine, $C_{11}H_{13}FN_4O_3$, the conformation of the glycosyl bond lies between *anti* and high *anti* [$\chi = -101.1\ (3)^\circ$]. The furanose moiety adopts the S-type sugar pucker ($^2T_3$), with $P = 164.7\ (3)^\circ$ and $\tau = 40.1\ (2)^\circ$. The extended structure is a three-dimensional hydrogen-bond network involving a C—H···F, two N—H···O and two O—H···O hydrogen bonds.

Comment

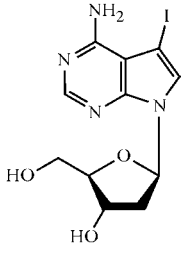
Fluorine-substituted analogues of nucleic acid components have become established as antiviral, antitumour and antifungal agents. Nucleosides with fluorine in the sugar moiety, usually at the 2′- and 3′-positions, have attracted considerable attention in the last few decades. There are some promising compounds, such as D-FMAU (Fanucchi, *et al.* 1983) and 3′-deoxy-3′-fluorothymidine (Etzold *et al.*, 1971). One of the most successful cases is 5-fluorouracil, with the F atom in the base moiety. Accordingly, it was conceivable to introduce an F atom at the 7-position of the 7-deazapurine system, which is considered to be a matching position for the 5-position in pyrimidines (Gourlain *et al.*, 2001). (Purine numbering is used throughout this discussion.) Recently, Wang *et al.* (2004) reported that the 5-fluoro analogue of tubercidin exhibits reduced cytotoxicity compared with the parent nucleoside. In continuation of our efforts to correlate nucleoside structure with biological activity, we have synthesized 5-fluoro-2′-deoxytubercidin, (I), and incorporated it into oligonucleotides. We report here the single-crystal X-ray structure of compound (I).



(I)
purine numbering



(II)
systematic numbering



(III)

Canonical purine 2′-deoxyribonucleosides tend to adopt the *anti* conformation. The orientation of the base relative to the sugar moiety (*syn*/*anti*) of purine nucleosides is defined by the torsion angle χ (O4′—C1′—N9—C4; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). In the crystal structure of compound (I), the torsion angle of the glycosylic bond is between the *anti* and high *anti* range, with $\chi = -101.1\ (3)^\circ$ (Fig. 1 and Table 1). This conformation is close to that of the parent compound, (II) (see scheme), which has no substituent at the 7-position, with $\chi = -104.4\ (3)^\circ$ (Zabel *et al.*, 1987). The iodo derivative, (III), has a much larger torsion angle χ of $-147.1\ (8)^\circ$ (Seela *et al.*, 1996), showing an *anti* conformation. The glycosyl bond length (N9—C1′) in (I) is 1.444 (4) Å, which is almost identical to those in (II) [1.449 (2) Å] and (III) [1.453 (5) Å].

The most frequently observed ring conformations of nucleosides are C2′-*endo* and C3′-*endo* (Arnott & Hukins, 1972). The pseudorotation phase angle P and the puckering amplitude angle τ (Rao *et al.*, 1981) show that the sugar ring of (I) adopts an S conformation, with an unsymmetrical twist of C2′-*endo*–C3′-*exo* ($^2T_3$), a P value of $164.7\ (3)^\circ$ and a τ value of $40.1\ (2)^\circ$. This is consistent with the conformation in solution, where nucleoside (I) shows a predominantly S population (70%; Seela, Chittepu *et al.*, 2005). In the case of (II), the sugar ring conformation is $_3T^2$, with $P = 186.6\ (2)^\circ$. Compound (III) has a $_3E$ sugar conformation ($P = 197^\circ$). The conformation about the C4′—C5′ bond of (I) is −*ap* (*gauche*, *trans*),

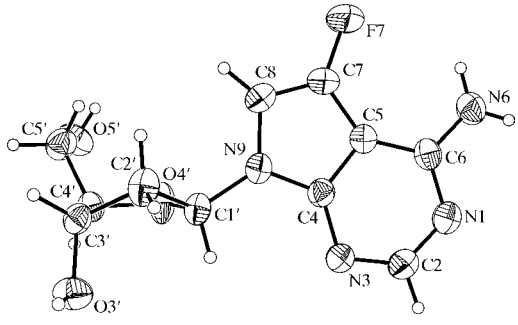


Figure 1
A perspective view of the nucleoside moiety of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

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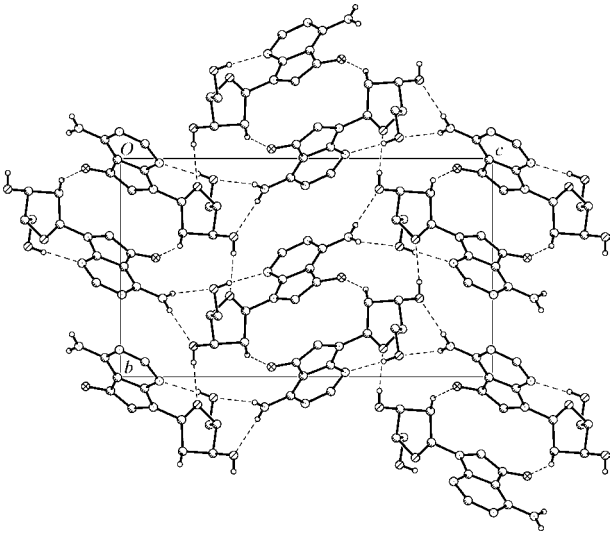

Figure 2
The crystal packing of (I), showing the intermolecular hydrogen-bonding network in a [100] projection.

with $\gamma = -179.7\ (2)^\circ$, whereas in (II), the C4′—C5′ bond shows an *ap* (*gauche*, *trans*) conformation, with $\gamma = 179.6\ (2)^\circ$.

In the three-dimensional network of (I), both nucleobases and sugar residues are stacked. The bases are arranged head-to-head and separated by 6.878 (4) Å (N3···N3; Fig. 2). This distance is longer than observed for related nucleosides (Seela, Shaikh & Eickmeier, 2005), which results from steric hindrance by the sugar moiety. The structure is stabilized by several hydrogen bonds (Table 2 and Fig. 2). All four H atoms bonded to heteroatoms take part in the formation of the three-dimensional network (O3′—H3′···O4′, O5′—H5′···N3, N6—H6*A*···O3′ and N6—H6*B*···O5′). Additionally, the 2′α H atom forms a hydrogen bond with the F atom of an adjacent molecule (C2′—H2′···F). The contact distance is 2.33 Å (Table 2), which is significantly shorter than the sum of the van der Waals radii (2.67 Å; Bondi, 1964). This is unusual, not only for nucleoside crystal structures but also for other organic fluorinated compounds. Statistical analysis of crystal structures taken from the Cambridge Structural Database (Version 5.09, April 1995 release; Allen, 2002) and the Brookhaven Protein Data Bank (ceased operation 30 June 1999; October 1994 release; Bernstein *et al.*, 1977) shows that covalently bonded fluorine hardly ever acts as a hydrogen-bond acceptor (Dunitz & Taylor, 1997). Recently, Haufe *et al.* (2002) reported C—F···H—C contacts in the X-ray crystal structures of monofluorinated cyclopropanes, with corresponding distances in the range 2.17–2.41 Å.

Experimental

Nucleoside (I) was synthesized as described by Seela, Chittepu *et al.* (2005). The nucleoside was dissolved in a small volume of methanol at 323 K and then half of this volume of dichloromethane was added. Crystals of (I) (m.p. 438 K) were grown by storing the solution overnight at room temperature.

Crystal data

$C_{11}H_{13}FN_4O_3$
$M_r = 268.25$
Orthorhombic, $P2_12_12_1$
$a = 6.8780\ (18)$ Å
$b = 10.144\ (2)$ Å
$c = 17.283\ (2)$ Å
$V = 1205.8\ (4)$ Å^3
$Z = 4$
$D_x = 1.478$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 37 reflections
$\theta = 5.1$–12.4°
$\mu = 0.12$ mm^{-1}
$T = 293\ (2)$ K
Prism, colourless
0.6 × 0.4 × 0.3 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2482 measured reflections
1858 independent reflections
1355 reflections with $I > 2\sigma(I)$
$R_{int} = 0.030$
$\theta_{max} = 29.0^\circ$
$h = -9 \rightarrow 1$
$k = -1 \rightarrow 13$
$l = -1 \rightarrow 23$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.045$
$wR(F^2) = 0.120$
$S = 1.03$
1858 reflections
175 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0526P)^2 + 0.1524P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997*b*)
Extinction coefficient: 0.010 (3)

Table 1
Selected geometric parameters (Å, °).

C5—C7	1.415 (4)	C7—F7	1.351 (4)
C7—C8	1.346 (4)	N9—C1′	1.444 (4)
C8—C7—F7	125.9 (3)	F7—C7—C5	124.0 (3)
C8—C7—C5	110.1 (3)		
C2—N1—C6—N6	178.5 (3)	F7—C7—C8—N9	−178.9 (3)
C4—C5—C6—N6	−179.1 (3)	C4—N9—C1′—O4′	−101.1 (3)
C7—C5—C6—N6	2.1 (6)	C8—N9—C1′—O4′	67.6 (4)
C4—C5—C7—F7	179.7 (3)	O4′—C4′—C5′—O5′	62.7 (3)
C6—C5—C7—F7	−1.4 (6)	C3′—C4′—C5′—O5′	−179.8 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6*A*···O3′^{i}	0.86	2.13	2.948 (3)	158
N6—H6*B*···O5′^{ii}	0.86	2.23	3.018 (3)	152
O3′—H3′···O4′^{iii}	0.82	1.98	2.752 (3)	156
O5′—H5′···N3^{iv}	0.82	1.97	2.789 (3)	175
C2′—H2′2···F7^{v}	0.97	2.33	3.205 (4)	150

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

In the absence of suitable anomalous scattering, Friedel equivalents could not be used to determine the absolute structure. Therefore, Friedel equivalents were merged before the final refinement. The known configuration of the parent molecule was used to define the enantiomer of the final model. All H atoms were initially found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, the H atoms were then placed in geometrically idealized positions (C—H = 0.93–0.98 Å, O—H = 0.82 Å and N—H = 0.86 Å) and constrained to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$, $1.2U_{eq}(N)$ or $1.5U_{eq}(O)$.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997*a*); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997*b*); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997*b*); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1715). Services for accessing these data are described at the back of the journal.

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