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4-Amino-7-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine: a bis-fluorinated analogue of 2′-deoxytubercidin

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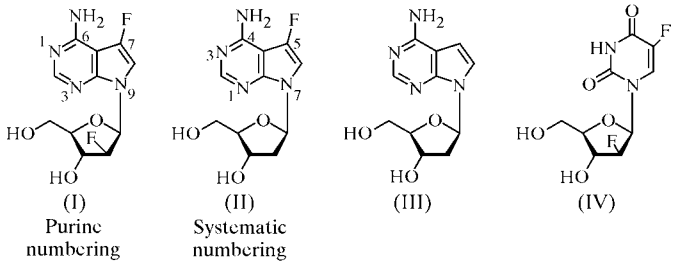
The title compound, $C_{11}H_{12}F_2N_4O_3$, exhibits an *anti* glycosylic bond conformation, with a torsion angle $\chi = -117.8\ (2)^\circ$. The sugar pucker is N-type (C4′-*exo*, between ${}^3T_4$ and E_4, with $P = 45.3^\circ$ and $\tau_m = 41.3^\circ$). The conformation around the exocyclic C—C bond is −*ap* (*trans*), with a torsion angle $\gamma = -177.46\ (15)^\circ$. The nucleobases are stacked head-to-head. The crystal structure is characterized by a three-dimensional hydrogen-bond network involving N—H···O, O—H···O and O—H···N hydrogen bonds.

Comment

7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine) nucleosides are a class of compounds with significant biological activity. Among them are the nucleoside antibiotics tubercidin, toyocamycin and sangivamycin, which all show antitumour activity (Rao & Renn, 1963; Tolman *et al.*, 1969). A series of 7-substituted tubercidin analogues (purine numbering is used throughout the discussion) exhibit antiviral activity against various RNA and DNA viruses, including herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) (Bergstrom *et al.*, 1984; De Clercq *et al.*, 1986). The extraordinary activity of pyrrolo[2,3-*d*]-pyrimidine nucleosides against the hepatitis C virus is a subject of current investigation (Eldrup *et al.*, 2004). Among the base- and sugar-modified nucleosides, those with an F atom in the 2′-up (*arabino*) configuration make purine nucleosides stable towards acids (Marquez *et al.*, 1990, 1987) and more resistant towards hydrolysis by adenosine deaminase (ADA) or purine nucleoside phosphorylase (PNP) (Hitchcock *et al.*, 1990). Recently, the synthesis and properties of the 7-fluoro analogue of tubercidin, which exhibits less cytotoxicity than the parent tubercidin, have been reported (Wang *et al.*, 2004). In an effort to correlate the structural characteristics with biological activity, we have synthesized the bis-fluorinated 2′-deoxytubercidin analogue, (I), and subjected it to single-crystal X-ray analysis.

The orientation of the nucleobase 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). The natural 2′-deoxyribonucleosides usually adopt an *anti* conformation. From the crystal structure of (I), the glycosylic bond torsion angle was determined to be in the *anti* range, with a χ value of $-117.8\ (2)^\circ$ (Fig. 1 and Table 1). The conformation of the nucleoside (II), lacking the 2′-fluoro substituent, falls into the range between the *anti* and high-*anti* conformations [$\chi = -101.1\ (3)^\circ$; Seela, Xu & Eickmeier, 2005], which is similar to the situation in natural 2′-deoxytubercidin, (III) [$\chi = -104.(4)^\circ$; Zabel *et al.*, 1987]. The related pyrimidine nucleoside (IV) exhibits an *anti* orientation [$\chi = -158.6\ (3)^\circ$; Hempel *et al.*, 1999].



The sugar moiety of nucleoside (I) shows an N conformation (C4′-*exo*; ${}^3T_4/E_4$), with a pseudorotation phase angle, P (Rao *et al.*, 1981), of 45.3° and an amplitude, τ_m, of 41.3°, while compound (II) exhibits an S conformation [C2′-*endo*; ${}^2E$; $P = 164.7\ (3)^\circ$ and $\tau_m = 40.1\ (2)^\circ$]. An S conformation was observed for the non-fluorinated 2′-deoxytubercidin (III) [C3′-*exo*; ${}^2T_3$; $P = 186.6\ (2)^\circ$]. The fluorinated pyrimidine nucleoside (IV), with the same sugar moiety as (I), adopts an S conformation (${}^0T_1$), with $P = 101.6\ (2)^\circ$ and $\tau_m = 43.2\ (1)^\circ$.

The conformation around the C4′—C5′ bond, which is defined by the torsion angle γ (O5′—C5′—C4′—C3′), is $-177.46\ (15)^\circ$ for (I), representing an antiperiplanar (*trans*) conformation. The length of the N9—C1′ glycosylic bond is

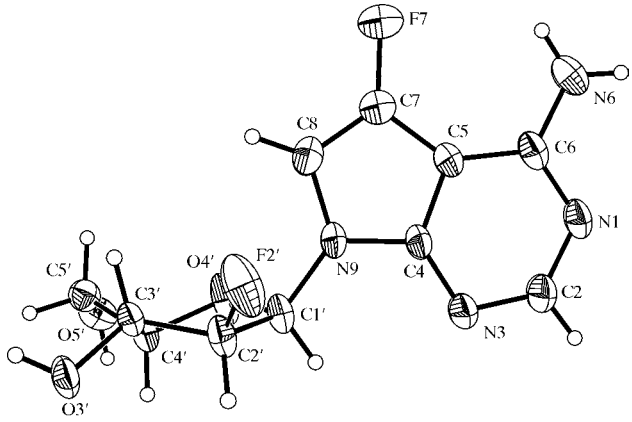


Figure 1
A perspective view of nucleoside (I). Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

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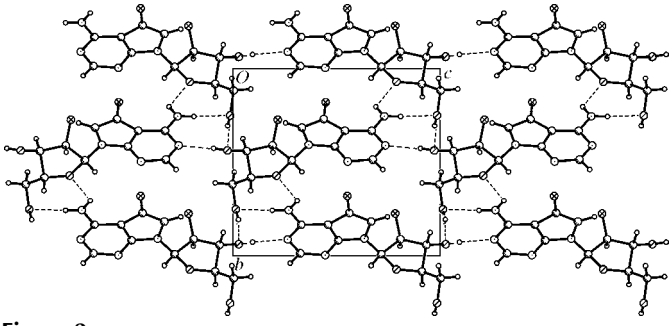

Figure 2
The crystal packing of (I), showing the intermolecular hydrogen-bonding network (projection parallel to the *a* axis).

1.436 (3) Å, which is close to that in (II) [1.444 (4) Å]. The F2′—C2′ distance is 1.379 (3) Å, similar to C—F bonds found in other 2′-fluoroarabino nucleosides (Birnbaum *et al.*, 1982) and also in 2′-fluoro ribonucleosides (Suck *et al.*, 1974; Hakoshima *et al.*, 1981).

The sugar conformations of the 7-deazapurine nucleosides have been also determined in D_2O solution. The conformational analysis of nucleoside (I) was determined on the basis of $^3J_{H,H}$ and $^3J_{H,F}$ coupling constants obtained from ^{1}H NMR spectra measured in D_2O by applying *PSEUDOROT6.3* (Van Wijk *et al.*, 1999). Compound (I) has two populations (67% S and 33% N). The sugar pucker is similar to that of related 2′-deoxyribonucleosides (II) (70% S) and (III) (69% S).

In the close-packed network of (I), both the nucleobases and the sugar residues are stacked. The bases are arranged head-to-head. The structure is stabilized by several hydrogen bonds (Fig. 2 and Table 2). Three hydrogen bonds combine to form highly corrugated layers with an overall position parallel to the *xy* plane. A fourth hydrogen bond (O5′—H5′···O3′^{iii}; Table 2) connects the layers. An intramolecular hydrogen bond is also observed (N6—H6*B*···F7); it forms one component of a three-centre system at H6*B*.

Experimental

Compound (I) was prepared according to the method described by Seela, Chittepu *et al.* (2005) and was crystallized from methanol as colourless needles (m.p. 470–473 K).

Crystal data

$C_{11}H_{12}F_2N_4O_3$
M_r = 286.25
Monoclinic, $P2_1$
a = 5.7355 (6) Å
b = 9.8374 (13) Å
c = 10.9428 (13) Å
β = 97.856 (9)°
V = 611.62 (13) Å^3
Z = 2
D_x = 1.554 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 54 reflections
θ = 5.5–12.5°
μ = 0.14 mm^{-1}
T = 293 (2) K
Needle, colourless
0.5 × 0.3 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2846 measured reflections
2056 independent reflections
1809 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 31.0°
$h = -8 \rightarrow 1$
$k = -14 \rightarrow 1$
$l = -15 \rightarrow 15$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.102
S = 1.05
2056 reflections
188 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0515P)^2 + 0.0481P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N3—C4	1.338 (3)	N9—C1′	1.436 (3)
C4—C5	1.394 (3)	C1′—O4′	1.440 (3)
C5—C6	1.412 (2)	C2′—F2′	1.379 (3)
C7—F7	1.346 (3)	C4′—O4′	1.442 (2)
F7—C7—C8	126.3 (2)	O4′—C1′—C2′	105.46 (14)
F7—C7—C5	124.21 (19)	F2′—C2′—C3′	112.28 (18)
C4—N9—C1′	123.65 (17)	F2′—C2′—C1′	112.44 (16)
C8—N9—C1′	127.29 (16)	C3′—C2′—C1′	104.93 (15)
C6—C5—C7—F7	−2.7 (5)	F2′—C2′—C3′—C4′	150.92 (17)
F7—C7—C8—N9	−179.4 (2)	C2′—C3′—C4′—O4′	−40.19 (18)
C4—N9—C1′—O4′	−117.8 (2)	N9—C1′—O4′—C4′	−142.98 (18)
C8—N9—C1′—O4′	55.9 (3)	C2′—C1′—O4′—C4′	−19.1 (2)
N9—C1′—C2′—F2′	−10.0 (3)	C5′—C4′—O4′—C1′	158.90 (18)
O4′—C1′—C2′—F2′	−129.45 (19)	C3′—C4′—O4′—C1′	37.6 (2)
N9—C1′—C2′—C3′	112.27 (19)	O4′—C4′—C5′—O5′	68.0 (2)
F2′—C2′—C3′—O3′	−87.7 (2)	C3′—C4′—C5′—O5′	−177.46 (15)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6*A*···O5′^{i}	0.86	2.23	3.009 (3)	151
N6—H6*B*···O4′^{i}	0.86	2.42	2.968 (3)	122
O3′—H3′···N1^{ii}	0.82	1.88	2.683 (2)	165
O5′—H5′···O3′^{iii}	0.82	1.95	2.760 (2)	171
N6—H6*B*···F7	0.86	2.64	3.225 (3)	126

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

In the absence of suitable anomalous scattering, refinement of the Flack (1983) parameter led to inconclusive values (Flack & Bernardinelli, 2000); Friedel equivalents were therefore merged before the final refinement. The known configuration of the parent molecule was used to define the enantiomer employed in the refined model. All H atoms were found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, C- and N-bound H atoms were placed in geometrically idealized positions (C—H = 0.93–0.98 Å and N—H = 0.86 Å; AFIX 93) and constrained to ride on their parent atoms with U_{iso}(H) values of $1.2U_{eq}$(C,N). The OH groups were refined as rigid groups allowed to rotate but not tip (AFIX 147), with O—H distances of 0.82 Å and U_{iso}(H) values of $1.5U_{eq}$(O).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997); program(s) used to solve structure: *SHELXTL*; program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3003). Services for accessing these data are described at the back of the journal.

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