Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

2′-Deoxy-2-fluorotubercidin

Frank Seela,[a]* Xiaohua Peng,[a] Henning Eickmeier[b] and Hans Reuter[b]

[a]Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, 49069 Osnabrück, Germany, and [b]Anorganische Chemie II, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, 49069 Osnabrück, Germany
Correspondence e-mail: frank.seela@uni-osnabrueck.de

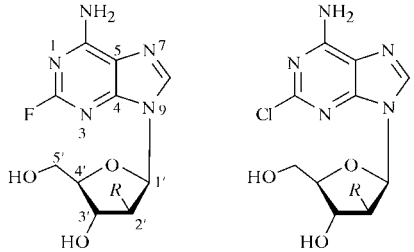
Received 13 October 2006
Accepted 11 December 2006
Online 13 January 2007

In the title compound [systematic name: 7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine], $C_{11}H_{13}FN_4O_3$, the conformation of the N-glycosylic bond is between *anti* and high-*anti* [$\chi = -110.2\ (3)^\circ$]. The 2′-deoxyribofuranosyl unit adopts the *N*-type sugar pucker ($_4T^3$), with $P = 40.3^\circ$ and $\tau_m = 39.2^\circ$. The orientation of the exocyclic C4′—C5′ bond is *−ap* (*trans*), with a torsion angle $\gamma = -168.39\ (18)^\circ$. The nucleobases are arranged head-to-head. The crystal structure is stabilized by four intermolecular hydrogen bonds of types N—H···N, N—H···O and O—H···O.

Comment

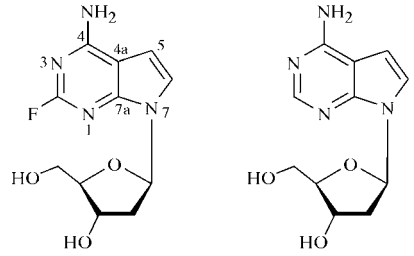
Halogen-substituted analogues of nucleic acid components have become established as antiviral, antitumour and antifungal agents (Pankiewicz, 2000). An interesting family of this class of compounds is the haloadenine nucleosides, *e.g.* fludarabine, (I*a*), cladribine (2-chloro-2′-deoxyadenosine), (II*a*), clofarabine, (II*b*), and 2′-deoxy-2-fluoroadenosine, (I*b*) (Montgomery & Hewson, 1969; Montgomery, 1982; Bryson & Sorkin, 1993; Hassan *et al.*, 2000). They are resistant to adenosine deaminase and effective in the treatment of indolent lymphoid malignancies, including chronic lymphocytic leukemia, hairy-cell leukemia, low-grade non-Hodgkin's lymphoma and acute myeloid leukaemia. Fludarabine and cladribine are used for the treatment of chronic lymphocytic leukaemia. However, the dose limitation of such drugs is imposed by cleavage resulting from rapid dephosphorylation, leading to a toxic 2-haloadenine with no anticancer activity (Struck *et al.*, 1982). The introduction of fluorine at the 2′-position, as in (II*b*), confers resistance to phosphorolytic cleavage, which leads to lower toxicity (Montgomery *et al.*, 1992).

As 7-deazapurine (pyrrolo[2,3-*d*]pyrimidine) nucleosides show resistance to the deamination caused by adenosine deaminase and cleavage by mammalian purine nucleoside phosphorylase, we became interested in 7-deaza-2-fluoroadenine nucleosides (purine numbering is used throughout the manuscript; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). Thus, 2′-deoxy-2-fluorotubercidin, (III), was prepared and its activity and base-pairing properties were studied (Peng *et al.*, 2006). Similar to 2-haloadenine nucleosides (Montgomery & Hewson, 1970; Ramzaeva & Seela, 1994), (III) is a convertible nucleoside, allowing the attachment of functional groups to DNA for structural studies (Peng *et al.*, 2006). The single-crystal X-ray analysis of compound (III) is described here.



(I*a*) *R*=OH (I*b*) *R*=H (II*a*) *R*=H (II*b*) *R*=F

Purine numbering



(III) (IV)

Systematic numbering

The three-dimensional structure of (III) is shown in Fig. 1 and selected geometric parameters are summarized in Table 1. The space group ($P2_12_12_1$) is identical to that of the parent compound 2′-deoxytubercidin, (IV) (Zabel *et al.*, 1987), and the related compound (II*a*) (Koellner *et al.*, 1998).

The orientation of the base relative to the sugar (*syn*/*anti*) of purine nucleosides is defined by the torsion angle χ (O4′—C1′—N9—C4). For the 'purine' 2′-deoxyribonucleosides, the preferred conformation around the N-glycosyl bond is usually in the *anti* range (Saenger, 1989; Sato, 1984). In the crystalline state of (III), the torsion angle of the glycosyl bond is between *anti* and high-*anti*, with $\chi = -110.2\ (3)^\circ$. This conformation is

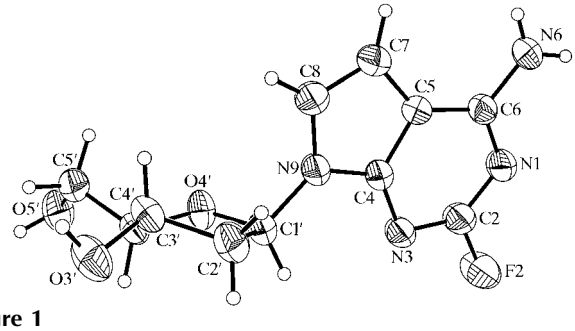


Figure 1
Perspective view of (III), showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary size.

  DOI: 10.1107/S0108270106053704

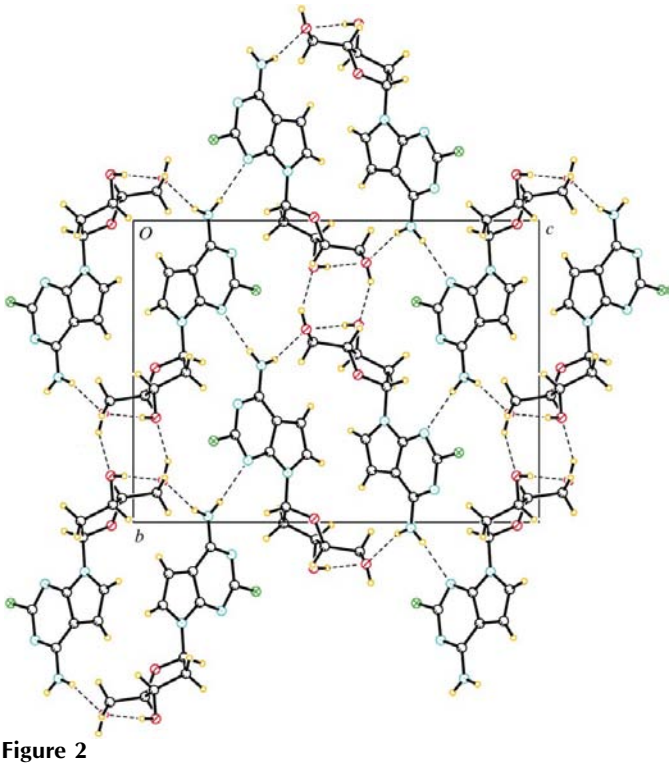


Figure 2
The packing of (III), showing the intermolecular hydrogen-bonding network (projection parallel to the *a* axis).

close to that of (IV) (χ = −104.4°; Zabel *et al.*, 1987), but different from that of (II*a*), which shows a *syn* conformation of the N-glycosylic bond [χ = 72.9 (3)°; Koellner *et al.*, 1998]. The glycosyl bond length (N9—C1′) in (III) is 1.451 (3) Å, which is almost identical to those in (IV) [1.449 (2) Å] and (II*a*) [1.458 (3) Å].

For (III), the phase angle of pseudorotation (*P*) is 40.3° and the maximum amplitude of puckering (τ_m) is 39.2°. This indicates that the sugar ring of (III) adopts an *N* conformation, with an unsymmetrical twist C3′-*endo*-C4′-*exo* ($_4T^3$) (Saenger, 1989). In the cases of (IV) and (II*a*), the sugar ring conformation is *S*, with *P* = 186.6 (2)° ($_3T^2$) for (IV) (Zabel *et al.*, 1987) and 178.3° for (II*a*) (Koellner *et al.*, 1998). The conformation around the C4′—C5′ bond of (III) is −*ap* (*gauche*, *trans*), with a torsion angle γ (C3′—C4′—C5′—O5′) of −168.39 (18)°, whereas in (IV) and (II*a*), the C4′—C5′ bond shows a +*ap* (*gauche*, *trans*) conformation, with γ equal to 179.6 (2)° for (IV) and 178.0 (2)° for (II*a*).

The base unit of compound (III) is essentially planar. The N3—C2 [1.305 (3) Å] and C2—N1 [1.315 (3) Å] bond lengths in (III) are shorter than those in (IV) (N3—C2 = 1.335 Å and C2—N1 = 1.333 Å). This might be caused by the strong electron-withdrawing effect of the 2-fluoro atom (pK_a < 1.5; Peng *et al.*, 2006).

The structure of (III) is stabilized by hydrogen bonds, leading to a three-dimensional network (Fig. 2 and Table 2). All four H atoms bonded to heteroatoms take part in the formation of the three-dimensional network (Table 2). The nucleobases are arranged head-to-head in a staircase-like fashion, in a pattern propagated by the *a* axis of the unit cell. Successive bases are nearly parallel with an interplanar spacing of approximately 3.894 Å, and are slipped in such a way that the C—F bond of the base at (*x*, *y*, *z*) projects on to the five-membered ring of the base at (1 + *x*, *y*, *z*). Thus, the average base-pair distance is in the range of that of B-DNA (3.5 Å).

Experimental

Compound (III) was synthesized as described by Peng *et al.* (2006) and crystallized from methanol (m.p. 476 K). For the diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{11}H_{13}FN_4O_3$
M_r = 268.25
Orthorhombic, $P2_12_12_1$
a = 5.5515 (8) Å
b = 12.6547 (12) Å
c = 17.0171 (19) Å
V = 1195.5 (2) Å^3
Z = 4
D_x = 1.490 Mg m^{-3}
Mo *K*α radiation
μ = 0.12 mm^{-1}
T = 293 (2) K
Plate, colourless
0.5 × 0.3 × 0.3 mm

Data collection

Bruker *P*4 diffractometer
2θ/ω scans
2481 measured reflections
1846 independent reflections
1586 reflections with $I > 2\sigma(I)$
R_{int} = 0.032
θ_{max} = 29.0°
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.115
S = 1.04
1846 reflections
175 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.061P)^2 + 0.1652P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.016 (3)

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.315 (3)	C2—F2	1.362 (3)
N1—C6	1.345 (3)	N3—C4	1.355 (3)
C2—N3	1.305 (3)	N9—C1′	1.451 (3)
N3—C2—F2	112.8 (2)	N6—C6—C5	123.4 (2)
N1—C2—F2	113.5 (2)	C4—N9—C1′	125.5 (2)
N6—C6—N1	117.1 (2)	C8—N9—C1′	126.6 (2)
C6—N1—C2—F2	180.0 (2)	O3′—C3′—C4′—C5′	80.9 (2)
F2—C2—N3—C4	−178.4 (2)	O4′—C4′—C5′—O5′	74.4 (2)
C4—N9—C1′—O4′	−110.2 (3)	C3′—C4′—C5′—O5′	−168.39 (18)
C8—N9—C1′—O4′	74.2 (3)	C5′—C4′—O4′—C1′	157.37 (18)
C1′—C2′—C3′—C4′	29.2 (2)	C3′—C4′—O4′—C1′	34.0 (2)
C2′—C3′—C4′—O4′	−38.8 (2)	C2′—C1′—O4′—C4′	−14.8 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6*A*···N3^{i}	0.86	2.29	3.144 (3)	172
N6—H6*B*···O5′^{ii}	0.86	2.23	3.061 (3)	162
O3′—H3′···O5′^{iii}	0.82	2.05	2.864 (3)	169
O5′—H5′···O3′^{iv}	0.82	2.10	2.809 (3)	145

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

In the absence of suitable anomalous scattering, Friedel equivalents could not be used to determine the absolute structure. Refinement of the Flack (1983) parameter led to an inconclusive value (Flack & Bernardinelli, 2000) [0.1 (13)]. Therefore, Friedel equivalents (440) were 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, H atoms were placed in geometrically idealized positions [with C—H distances of 0.93–0.98 Å and N—H distances of 0.86 Å (AFIX 93)] and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C,N)]. The OH groups were refined as rigid groups allowed to rotate but not tip [AFIX 147; O—H distances of 0.82 Å and U_{iso}(H) = 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, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3053). Services for accessing these data are described at the back of the journal.

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