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7-Fluorotubercidin: a halogenated derivative of a naturally occurring nucleoside antimetabolite

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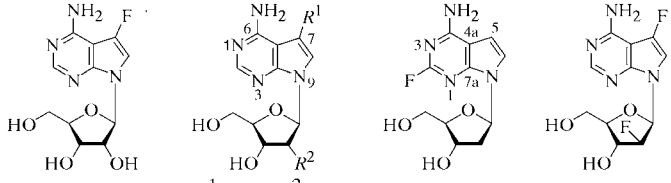
The title compound [systematic name: 4-amino-5-fluoro-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine], $C_{11}H_{13}FN_4O_4$, exhibits an *anti* glycosylic bond conformation, with a χ torsion angle of −124.7 (3)°. The furanose moiety shows a twisted C2′-*endo* sugar pucker (*S*-type), with P = 169.8 (3)° and τ_m = 38.7 (2)°. The orientation of the exocyclic C4′—C5′ bond is +*sc* (*gauche, gauche*), with a γ torsion angle of 59.3 (3)°. The nucleobases are stacked head-to-head. The extended crystal structure is a three-dimensional hydrogen-bond network involving O—H···O, O—H···N and N—H···O hydrogen bonds. The crystal structure of the title nucleoside demonstrates that the C—C bonds nearest the F atom of the pyrrole system are significantly shortened by the electronegative halogen atom.

Comment

The naturally occurring nucleoside antibiotic tubercidin is a close structural analogue of adenosine and shows significant biological activities (Suhadolnik, 1970, and references therein). 50 years ago, tubercidin was isolated from *Streptomyces tubercidicus* (Anzai *et al.*, 1957), while its crystal structure was reported by Stroud and Abola & Sundaralingam in 1973 (Stroud, 1973; Abola & Sundaralingam, 1973). A series of 7-substituted tubercidin derivatives (purine numbering is used throughout this 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). Moreover, 2′-*C*-methyltubercidin, as well as its 7-fluoro derivative, are potent and selective inhibitors of hepatitis C virus (HCV) RNA replication (Olsen *et al.*, 2004; Eldrup *et al.*, 2004).

The introduction of an F atom as a substituent of the sugar residue or of the heterocyclic ring moiety of nucleosides has a positive effect on the biological activity. A number of fluorine-substituted analogues of nucleic acid components were established as antiviral, anticancer and antifungal agents (Pankiewicz, 2000). Recently, Wang *et al.* (2004) reported the synthesis and characteristics of 7-fluorotubercidin, (I), which exhibits reduced cytotoxicity compared with its parent derivative tubercidin.



Due to the favorable biological activity of 7-fluorotubercidin, (I), we became interested in performing a single-crystal X-ray analysis of (I) and comparing the solid-state structure with closely related nucleosides. The parent tubercidin, (II*a*) (Stroud, 1973; Abola & Sundaralingam, 1973), 2′-deoxytubercidin, (II*b*) (Zabel *et al.*, 1987), 7-fluoro-2′-deoxytubercidin, (II*c*) (Seela *et al.*, 2005), 2′-deoxy-2-fluorotubercidin, (III) (Seela *et al.*, 2007), as well as the difluorinated tubercidin analogue (IV) (Seela *et al.*, 2006), were selected for comparison.

Compound (I) was synthesized according to the 'one-pot' Vorbrüggen glycosylation protocol reported by Wang *et al.* (2004) and was crystallized from methanol as colorless needles. The three-dimensional structure of (I) is shown in Fig. 1 and selected geometric parameters are listed in Table 1.

From the crystal structure of (I), the orientation of the nucleobase relative to the sugar moiety was determined to be in the *anti* range, with χ (O4′—C1′–N9—C4) = −124.7 (3)° (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). The glycosylic bond conformation of the parent

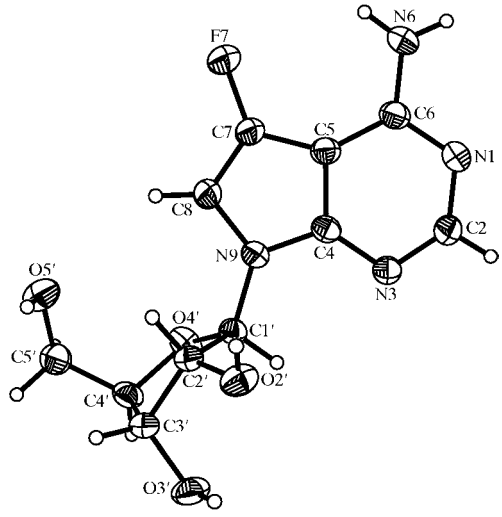


Figure 1
A perspective view of nucleoside (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

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unsubstituted compound, (II*a*), as well as that of the difluorinated nucleoside (IV), adopt χ values within the same *anti* range, with χ values of −112.8 (4)° for (II*a*) (Abola & Sundaralingam, 1973) and −117.8 (2)° for (IV) (Seela *et al.*, 2006). For comparison, the conformations of the 2′-deoxyribonucleoside analogues (II*b*), (II*c*) and (III) fall into the range between *anti* and high-*anti* [χ values of −104.4 (2)° for (II*b*) (Zabel *et al.*, 1987), −101.1 (3)° for (II*c*) (Seela *et al.*, 2005) and −110.2 (3)° for (III) (Seela *et al.*, 2007)]. The glycosylic bond length (N9—C1′) in (I) is 1.444 (3) Å, which is identical to that in (II*c*) [1.444 (4) Å; Seela *et al.*, 2005].

The most frequently observed sugar ring conformations of nucleosides are C2′-*endo* ('south' or *S*) and C3′-*endo* ('north' or *N*) (Arnott & Hukins, 1972). The sugar moiety of nucleoside (I) shows an *S* conformation with an unsymmetrical twist of C2′-*endo*–C3′-*exo* ($^2T_3$), a pseudorotation phase angle, *P* (Rao *et al.*, 1981), of 169.8 (3)° and a maximum amplitude of pucker, τ_m, of 38.7 (2)°. This is very similar to compound (II*c*), which also has a $^2T_3$ sugar conformation [*P* = 164.7 (3)°; Seela *et al.*, 2005]. In the case of parent unsubstituted compound (II*a*) and closely related (II*b*), the sugar ring conformation is C2′-*endo*–C1′-*exo* ($^2T_1$; *S* conformation), with *P* values of 149.3 and 186.6 (2)°, respectively (Abola & Sundaralingam, 1973; Zabel *et al.*, 1987). In contrast, an *N* conformation was observed for difluorinated compound (IV) (C4′-*exo*, between $^3T_4$ and E_4, with *P* = 45.3°; Seela *et al.*, 2006) and nucleoside (III) (C3′-*endo*–C4′-*exo*, $_4T^3$, with *P* = 40.3°; Seela *et al.*, 2007). From the examples mentioned above, it can be seen that the sugar conformations obtained for nucleosides in the solid state do not reflect the sugar conformations found in DNA or RNA. The *S* conformation of the sugar moiety of ribonucleoside (I) is in contrast to the *N* sugar conformation of RNA.

The sugar conformation of nucleoside (I) was also determined in solution and compared with the conformation of the parent tubercidin (II*a*). In solution, both compounds show a predominantly *S* conformation [85% *S* for (I) and 88% *S* for (II*a*)], which is consistent with their sugar conformation in the solid state. The conformation analysis was performed on the basis of the vicinal $^3J_{HH}$ coupling constants of ^{1}H NMR spectra measured in D_2O, applying the program *PSEUROT6.3* (Van Wijk *et al.*, 1999).

The conformation about the exocyclic C4′—C5′ bond, which is defined by the torsion angle γ (O5′—C5′—C4′—C3′), is 59.3 (3)° for (I), representing a *+sc* (*gauche, gauche*) conformation, whereas in the parent (II*a*) and in (II*b*), the C4′—C5′ bond shows an *ap* (*gauche*, *trans*) conformation [(II*a*): γ = −178.3 (4)°; (II*b*): γ = −179.6 (2)°] (Abola & Sundaralingam, 1973; Zabel *et al.*, 1987).

The 7-deazapurine ring system is nearly planar. The r.m.s. deviation of the ring atoms from their calculated least-squares planes is 0.0103 Å, with a maximum deviation of 0.0159 (2) Å for atom C6. The F7 substituent of (I) lies −0.0142 (8) Å below and atom N6 of the amino group lies 0.0379 (3) Å above this plane. The C5—C7 [1.409 (4) Å] and C7—C8 [1.349 (4) Å] bond lengths in (I) are shorter than those in parent (II*a*) [C5—C7 = 1.433 (4) Å and C7—C8 = 1.359 (5) Å; Abola & Sundaralingam, 1973]. This might be caused by the strong electron-withdrawing effect of the 7-fluoro substituent.

In the close-packed network of (I), both the nucleobases and sugar residues are stacked. The bases are arranged head-to-head. The structure is stabilized by several hydrogen bonds, leading to a three-dimensional layered network (Fig. 2 and Table 2). In the solid-state structure of nucleoside (I), the distance of each atom between neighboring sheets is 3.264 Å, which is less than the average base-pair stacking distance in B-DNA (3.5 Å). Hydrogen bonds are mainly formed between adjacent nucleobases and sugar moieties. N6—H6*A*···O2′ and O3′—H3′···N1 hydrogen bonds are formed within each sheet, while N6—H6*B*···O5′, O2′—H2′···N3 and O5′—H5′*A*···O4′ hydrogen bonds connect neighboring sheets. Contrary to what is seen for nucleoside (II*c*), the 7-fluoro substituent does not take part in hydrogen-bond formation (Seela *et al.*, 2005).

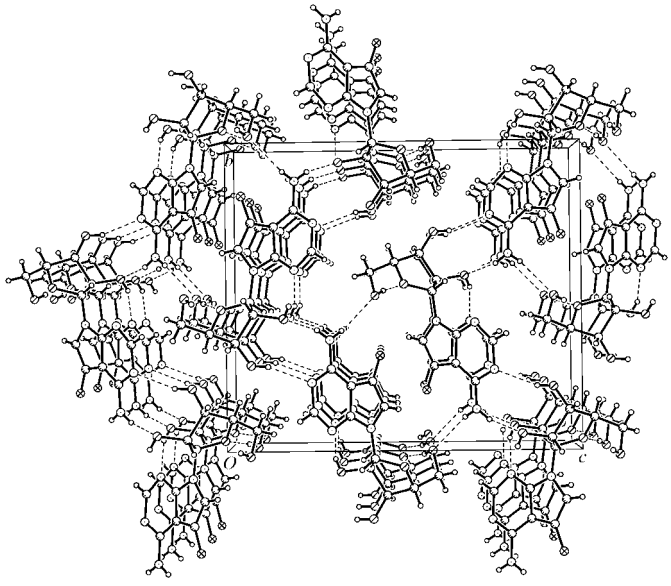

Figure 2
The crystal packing of (I), showing the intermolecular hydrogen-bonding network. The projection is parallel to the *a* axis.

Experimental

Compound (I) was synthesized according to the 'one-pot' Vorbrüggen glycosylation protocol reported by Wang *et al.* (2004) and was crystallized from methanol as colorless needles (m.p. 494–495 K). For the diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{11}H_{13}FN_4O_4$
M_r = 284.25
Orthorhombic, $P2_12_12_1$
a = 4.9394 (13) Å
b = 14.6718 (19) Å
c = 16.8181 (16) Å
V = 1218.8 (4) Å^3
Z = 4
Mo *K*α radiation
μ = 0.13 mm^{-1}
T = 293 (2) K
0.5 × 0.3 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
2181 measured reflections
1580 independent reflections
1438 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
$wR(F^2) = 0.107$	$\Delta\rho_{min} = -0.20$ e Å^{-3}
$S = 1.09$	Absolute structure: established by known chemical absolute configuration
1580 reflections	
185 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

C5—C7	1.409 (4)	C7—F7	1.360 (3)
C7—C8	1.349 (4)	N9—C1′	1.444 (3)
C8—C7—F7	125.7 (2)	F7—C7—C5	124.3 (2)
C8—C7—C5	110.0 (2)		
C2—N1—C6—N6	−178.8 (3)	F7—C7—C8—N9	179.0 (3)
C4—C5—C6—N6	178.9 (3)	C4—N9—C1′—O4′	−124.7 (3)
C7—C5—C6—N6	−1.6 (6)	C8—N9—C1′—O4′	64.2 (4)
C6—C5—C7—F7	0.7 (6)	O4′—C4′—C5′—O5′	−60.5 (3)
C4—C5—C7—F7	−179.8 (3)	C3′—C4′—C5′—O5′	59.3 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N6—H6A···O2′^{i}	0.86	2.15	2.982 (3)	161
N6—H6B···O5′^{ii}	0.86	2.26	3.026 (3)	149
O2′—H2′···N3^{iii}	0.82	1.95	2.726 (3)	158
O3′—H3′···N1^{iv}	0.82	2.10	2.841 (3)	149
O5′—H5′···O4′^{iii}	0.82	2.03	2.846 (3)	172

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

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 refinements. 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 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 [U_{iso}(H) = 1.2U_{eq}(C,N) and 1.5U_{eq}(O)].

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 2008); 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: HJ3068). Services for accessing these data are described at the back of the journal.

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