

6-Amino-3-bromo-1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one–acetone–water (1/1/1): a fluorinated 2'-deoxyguanosine analogue with the sugar conformation of a ribonucleoside

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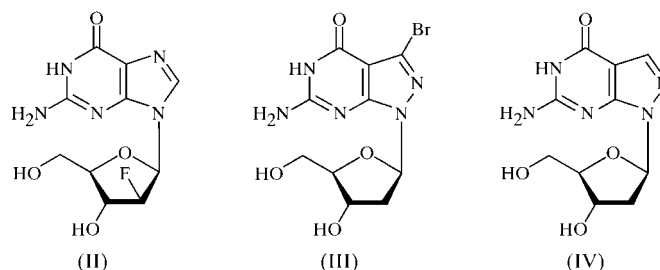
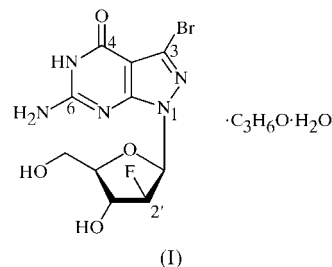
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In the title compound, $C_{10}H_{11}BrFN_5O_4 \cdot C_3H_6O \cdot H_2O$, the N-glycosylic bond torsion angle, χ , is *anti* [$-108.0(4)^\circ$]. The sugar pucker is *N*-type [$C2'$ -*exo*, ${}_2E$ with $P = 346.5(4)^\circ$ and $\tau_m = 34.5(2)^\circ$], and the conformation around the C–C bond linking the CH_2 group and the furan ring is $-sc$ [torsion angle $\gamma = -70.0(4)^\circ$].

Comment

The introduction of an F atom into nucleoside molecules leads to compounds with antiviral or anticancer activity (Pankiewicz, 2000). More than 75% of the fluorinated nucleosides synthesized to date contain F atoms at the $C2'$ -position of the sugar moiety. This modification causes only minor changes to the size of the molecule but strongly influences its physical and biological properties. Thus, the 2'-fluoroarabino nucleoside FMAU (2'-fluoro-5-methyl- β -D-arabinofuranosyluracil) is an antivirally active compound (Watanabe *et al.*, 1979), while the 2',2'-difluorocytidine gemcitabine (Hertel *et al.*, 1988) shows anticancer activity. The 2'-fluoro substituent can also stabilize the glycosylic bond, thereby increasing the life span of the nucleoside *in vivo* (Marquez *et al.*, 1990; Singhal *et al.*, 1997). Moreover, the fluorine substituent shifts the conformational equilibrium of the sugar moiety of a nucleoside, depending on its configuration (Guschlbauer & Jankowski, 1980; Berger *et al.*, 1998; Ikeda *et al.*, 1998; Thibaudeau *et al.*, 1998). Oligonucleotide duplexes incorporating 2'-fluoroarabino sugars become susceptible to RNase H cleavage, which makes them useful for antisense therapeutics (Damha *et al.*, 1998; Ikeda *et al.*, 1998; Yazbeck *et al.*, 2002).

The title compound, (I), has been synthesized (He & Seela, 2003) and its sugar conformation in aqueous solution has been determined as 98% *N*-type (Van Wijk *et al.*, 1999; He *et al.*, 2003). This behaviour differs from that of most other nucleosides with a fluoro substituent at the 2'-up position; for example, the 2'-deoxy-2'-fluoroarabinoguanosine (II) shows only a 55% *N*-conformer population in solution (Tennilä *et al.*, 2000). The conformation of (I) also differs from that of the non-fluorinated compounds (III) and (IV), which show a preferred *S* conformation [61% *S* for (III) and 64% *S* for (IV); Seela *et al.*, 1999] that is typical for 2'-deoxy ribonucleosides (Rosemeyer *et al.*, 1997). The unusual conformational properties of (I) in solution prompted us to study its solid-state structure.



The orientation of the nucleobase relative to the sugar moiety (*syn/anti*) of purine nucleosides is defined by the $O4' - C1' - N1 - C7a$ torsion angle, χ (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). In the crystalline state of (I), the glycosylic bond torsion angle is in the *anti* range, with χ equal to $-108.0(4)^\circ$ (Fig. 1 and Table 1).

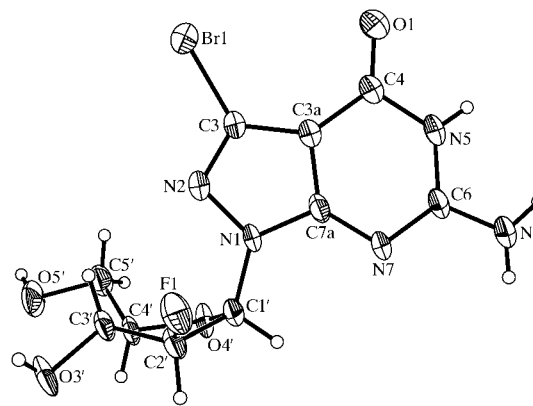


Figure 1

A perspective view of the nucleoside moiety of (I). Displacement ellipsoids for non-H atoms have been drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

Compound (III), in which the 2'-fluoro substituent is missing, is closer to the high-*anti* conformation [$\chi = -93.2$ (6) $^\circ$; Seela *et al.*, 1999]. The more pronounced *anti* conformation of (I) compared with (III) reflects an intramolecular repulsion between the 2'-fluoro 'up'-substituent and the ring N atom next to the glycosylation position (N2).

The sugar moiety of (I) shows a pseudorotation phase angle, P , of 346.5 (4) $^\circ$ and an amplitude, τ_m , of 34.5 (2) $^\circ$ (Rao *et al.*, 1981), which indicate the *N*-conformation. The sugar puckering is ${}_2E$, with atom C2' located in the *exo* position, while atom C3' is close to the C1'–O4'–C4' plane, as indicated by the C1'–O4'–C4'–C3' and C2'–C3'–C4'–O4' torsion angles (Table 1). Although both (I) and (III) show an *N*-type sugar pucker, the conformation of (I) is closer to envelope, while (III) shows a twist conformation (3T_2). The O5'–C5'–C4'–C3' torsion angle, defined as γ , is also different for these two nucleosides. For (I), angle γ [-70.0 (4) $^\circ$] represents a *-sc* (*gauche*) conformation, while an *ap* conformation is observed for (III) [$\gamma = -169.2$ (6) $^\circ$].

The bond lengths in the sugar moiety are affected only slightly by the 2'-fluoro substituent. The C1'–O4' distance in (I) is about 0.03 Å shorter than the C4'–O4' distance. This difference is more pronounced than that in (III) (0.01 Å). The bond angles around the sugar ring vary unevenly compared with those in (III) (Table 1). The length of the N1–C1' glycosylic bond is 1.445 (4) Å, which is close to that in (III) [1.443 (7) Å]. The F2'–C2' distance is similar to C–F bonds found in other 2'-fluoroarabino nucleosides (Birnbaum *et al.*, 1982) and 2'-fluoro ribonucleosides (Suck *et al.*, 1974; Hakoshima *et al.*, 1981). The atoms of the pyrazolo[3,4-*d*]pyrimidine ring system of (I) are coplanar; the least-squares deviations of the ring atoms range from -0.021 (3) to 0.027 (4) Å, with an r.m.s. deviation of 0.017 Å. The bromo

substituent and 6-NH₂ group deviate from this plane by 0.026 (5) and 0.054 (6) Å, respectively.

Compound (I) was crystallized from aqueous acetone, and one acetone molecule and one water molecule are found in the asymmetric unit. An intermolecular three-dimensional hydrogen-bonded framework is observed, which involves the nucleoside molecules and the solvent molecules (Fig. 2 and Table 2). One water molecule donates two H atoms, *viz.* one to the 4-oxo group of (I) and one to the oxo group of an acetone molecule, and accepts another two hydrogen bonds, *viz.* one each from the 3'-OH and 5'-OH groups of the sugar moieties of two neighbouring nucleoside molecules. The nucleoside molecules are linked by three intermolecular hydrogen bonds; the 6-NH₂ and 5-NH groups interact with the 3'-OH and 5'-OH groups, respectively, of the same neighbouring nucleoside molecule, and the 6-NH₂ group has a second intermolecular interaction involving the 5'-OH group of a different neighbouring molecule. The F atom of the sugar moiety of one nucleoside molecule is within the van der Waals contact distance of the bromo substituent of a second molecule [3.115 (4) Å].

Although (I) can be considered as a derivative of 2'-deoxyguanosine, (I) shows the sugar conformation of a ribonucleoside. This conformation is not just observed in the solid state; an *N*-conformer population of nearly 100% is also found in solution, which is uncommon for nucleosides with a 2'-up fluoro substituent (He *et al.*, 2003). This unusual *N*-conformation is probably due to the counteractive influence of the *gauche* effect of the 2'-fluoro atom and the anomeric effect of the nucleobase with the N atom next to the glycosylation side (Plavec *et al.*, 1996). We have therefore looked for other compounds showing the same properties and found that the 2'-fluoroarabino derivative of 6-aza-2'-deoxyuridine exhibits such behaviour (He & Seela, 2003).

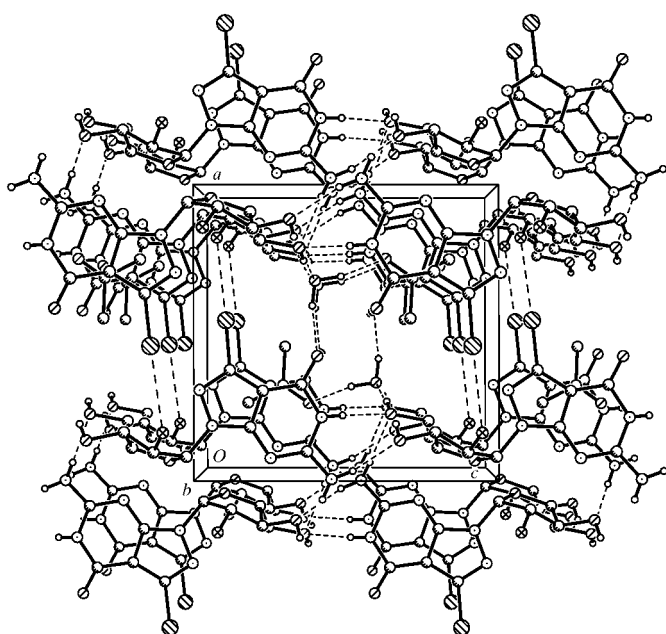


Figure 2
The crystal packing of (I), viewed along the b axis, showing the intermolecular hydrogen-bonding network.

Experimental

Compound (I) was prepared as described by He *et al.* (2003). Light-yellow crystals (m.p. 535 K) were grown from aqueous acetone. For the diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

C₁₀H₁₁BrFN₅O₄·C₃H₆O·H₂O
 $M_r = 440.24$
 Monoclinic, $P2_1$
 $a = 10.8449$ (10) Å
 $b = 7.3649$ (9) Å
 $c = 11.1537$ (17) Å
 $\beta = 90.182$ (8) $^\circ$
 $V = 890.86$ (19) Å³
 $Z = 2$

$D_x = 1.641$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 39 reflections
 $\theta = 5.0$ – 14.0 $^\circ$
 $\mu = 2.36$ mm⁻¹
 $T = 293$ (2) K
 Transparent plate, light yellow
 $0.54 \times 0.34 \times 0.26$ mm

Data collection

Bruker P4 diffractometer
 $2\theta/\omega$ scans
 Absorption correction: ψ scan
 (SHELXTL; Sheldrick, 1997)
 $T_{\min} = 0.193$, $T_{\max} = 0.456$
 3029 measured reflections
 2639 independent reflections
 2466 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.017$
 $\theta_{\text{max}} = 28.0$ $^\circ$
 $h = -14 \rightarrow 1$
 $k = -9 \rightarrow 1$
 $l = -14 \rightarrow 14$
 3 standard reflections
 every 97 reflections
 intensity decay: none

Refinement

Refinement on F^2	$(\Delta/\sigma)_{\max} < 0.001$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$\Delta\rho_{\max} = 0.83 \text{ e } \text{\AA}^{-3}$
$wR(F^2) = 0.124$	$\Delta\rho_{\min} = -0.88 \text{ e } \text{\AA}^{-3}$
$S = 1.16$	Extinction correction: <i>SHELXL97</i>
2639 reflections	Extinction coefficient: 0.152 (9)
251 parameters	Absolute structure: Flack &
H atoms treated by a mixture of independent and constrained refinement	Bernardinelli (2000); 328 Friedel pairs
$w = 1/[\sigma^2(F_o^2) + (0.0927P)^2]$	Flack parameter = 0.009 (11)
where $P = (F_o^2 + 2F_c^2)/3$	

Table 1

Selected geometric parameters (\AA , $^\circ$).

Br1—C3	1.867 (3)	C1'—O4'	1.415 (5)
F1—C2'	1.391 (5)	O4'—C4'	1.448 (3)
N1—C1'	1.445 (4)		
N2—C3—Br1	119.7 (3)	F1—C2'—C3'	112.5 (3)
C7a—C3a—C3	103.7 (3)	F1—C2'—C1'	112.9 (3)
O4'—C1'—C2'	103.8 (3)	C3'—C2'—C1'	104.9 (3)
C7a—N1—N2—C3	−0.5 (5)	F1—C2'—C3'—O3'	−85.2 (4)
N1—N2—C3—Br1	179.7 (3)	N1—C1'—O4'—C4'	−104.7 (3)
Br1—C3—C3a—C7a	−179.4 (3)	C2'—C1'—O4'—C4'	18.1 (3)
C7a—N1—C1'—O4'	−108.0 (4)	C1'—O4'—C4'—C5'	127.1 (3)
N2—N1—C1'—O4'	62.4 (4)	C1'—O4'—C4'—C3'	2.9 (4)
O4'—C1'—C2'—F1	−155.0 (3)	C2'—C3'—C4'—O4'	−22.5 (3)
N1—C1'—C2'—F1	−33.9 (4)	C2'—C3'—C4'—C5'	−143.1 (3)
O4'—C1'—C2'—C3'	−32.2 (3)	O4'—C4'—C5'—O5'	170.6 (3)
N1—C1'—C2'—C3'	88.9 (4)	C3'—C4'—C5'—O5'	−70.0 (4)

Table 2

Hydrogen-bonding geometry (\AA , $^\circ$).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N5—H5A \cdots O5 ⁱ	0.86 (2)	2.23 (2)	3.087 (5)	170 (6)
N6—H6A \cdots O5 ⁱⁱ	0.86 (5)	2.25 (5)	3.117 (6)	178 (6)
N6—H6B \cdots O3 ⁱ	0.84 (4)	2.11 (2)	2.932 (4)	167 (6)
O3'—H3'B \cdots O21 ⁱⁱⁱ	0.81 (6)	1.94 (6)	2.749 (5)	172 (7)
O5'—H5'A \cdots O21 ^{iv}	0.81 (6)	1.98 (3)	2.779 (6)	167 (7)
O21—H211 \cdots O1	0.97	1.87	2.760 (4)	151
O21—H212 \cdots O11 ^v	0.96	1.78	2.702 (5)	158

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

Methyl H atoms were constrained to have an ideal geometry [C—H = 0.96 \AA and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$] but were allowed to rotate freely about the C—C bonds. The positions of the amine and hydroxy H atoms were refined freely, with $U_{\text{iso}}(\text{H})$ values of 1.2 $U_{\text{eq}}(\text{N})$ and 1.5 $U_{\text{eq}}(\text{O})$, respectively. Water H atoms were placed in positions determined from a difference Fourier map and were constrained to ride on their parent atoms, with $U_{\text{iso}}(\text{H})$ values of 1.5 $U_{\text{eq}}(\text{O})$. All remaining H atoms were placed in idealized positions (C—H = 0.97–0.98 \AA) and were constrained to ride on their parent atoms, with $U_{\text{iso}}(\text{H})$ values of 1.2 $U_{\text{eq}}(\text{C})$. The absolute configuration was determined conclusively by this experiment and was found to agree with that expected for a D-nucleoside.

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: LN1167). Services for accessing these data are described at the back of the journal.

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