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2′-Deoxyimmunosine: a thiazolo-[4,5-*d*]pyrimidine nucleoside adopting the *syn* conformation

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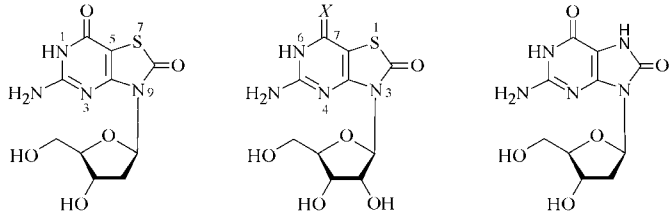
The title compound [systematic name: 5-amino-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)thiazolo[4,5-*d*]pyrimidine-2,7-(3*H*,6*H*)-dione], $C_{10}H_{12}N_4O_5S$, exhibits a *syn* glycosylic bond conformation, with a torsion angle χ of 61.0 (3)°. The furanose moiety adopts the *N*-type sugar pucker ($^3T_4$), with P = 33.0 (5)° and τ_m = 15.1 (1)°. The conformation at the exocyclic C4′—C5′ bond is +*ap* (*trans*), with the torsion angle γ = 176.71 (14)°. The extended structure is a three-dimensional hydrogen-bond network involving O—H···O and N—H···O hydrogen bonds.

Comment

The development of clinically useful agents that restore and enhance the ability of the human immune system to ward off infection or other invasion challenges has become a major objective of current pharmaceutical research efforts. The AIDS epidemic and the need for adjuvant therapy to boost the immune system of the elderly and cancer patients has brought this area of immunopotentiation into sharp focus (Hadden, 1987, 1993; St Georgiev, 1990; Failli & Caggiano, 1992; Werner, 1990). Many different types of compounds have been demonstrated to possess immunostimulatory properties. Among them, the nucleoside-based guanosine derivatives are very promising (Reitz *et al.*, 1994). In this context, 7-deazaguanosine and 7-allyl-8-oxoguanosine (loxoribine) have been extensively studied (Smee *et al.*, 1995; Reitz *et al.*, 1994) (purine numbering is used throughout this paper). Another guanosine analogue, 8-oxo-7-thiaguanosine [(II*b*); immunosine, isatoribine, TOG] has been investigated in great detail and shown to possess excellent *in vivo* activity against a variety of DNA and RNA viruses (Nagahara *et al.*, 1990; Smee *et al.*, 1989; Smee, Alaghamandan, Bartlett & Robins, 1990; Smee, Alaghamandan, Cottam *et al.*, 1990). Immunosine exhibits a stimulatory effect on both cellular and humoral components of the immune response. The observed antiviral effect has been attributed primarily to the induction of α-interferon (Smee, Alaghamandan, Bartlett & Robins, 1990; Smee, Alaghamandan, Cottam *et al.*, 1990). Recently, it was found that immunosine and other guanosine analogues activate immune cells *via* the Toll-like receptor 7 (TLR7; Lee *et al.*, 2003). Immunosine has also been reported to be effective at reducing the plasma virus concentration in patients with chronic hepatitis C virus (HCV) infections, with minimal side effects (Horsmans *et al.*, 2005).



(I) Purine numbering

(II*a*) X=S
(II*b*) X=O
Systematic numbering

(III)

While immunosine can be readily prepared by glycosylation of the immunosine base, the synthesis of the corresponding title 2′-deoxyribonucleoside analogue, (I), encountered difficulties (Seela & Ming, 2007). We have developed a stereoselective synthesis for compound (I) and have incorporated this compound into oligonucleotides. The replacement of two dG residues by 2′-deoxyimmunosine within a DNA duplex resulted in the same stability as observed for the unmodified parent duplex (T_m = 323 K; Seela & Ming, 2007). This shows that 2′-deoxyimmunosine forms a stable base pair with 2′-deoxycytidine (Seela & Ming, 2007). However, compound (I) does not show the base pairing ambiguity observed for 2′-deoxy-8-oxoguanosine, (III) (Oka & Greenberg, 2005). From this context, we became interested in undertaking a single-crystal X-ray analysis of compound (I). Slow crystallization from ethanol afforded the compound as colourless crystals. The three-dimensional structure of (I) is shown in Fig. 1 and selected geometric parameters are listed in Table 1.

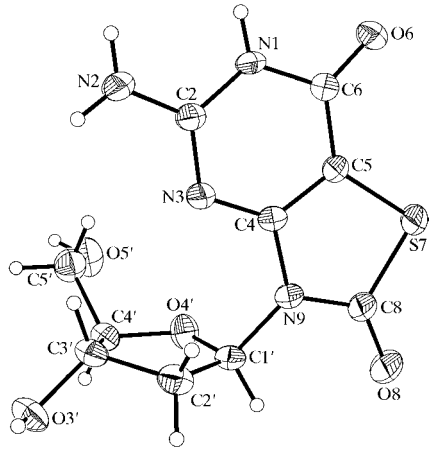


Figure 1
A perspective view of nucleoside (I), showing the purine numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary size.

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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. In contrast, from the crystal structure of (I), the glycosylic bond torsion angle is determined to be in the *syn* range, with a χ value of 61.0 (3)°. It is generally observed that the introduction of bulky substitutents at position-8 of the purine moiety switches the preference of the glycosylic torsion angle from *anti* to *syn* (Uesugi & Ikehara, 1977; Lipscomb *et al.*, 1995). This conversion arises from steric repulsion between the 8-substituent and the 2′-deoxyribose. For related compound (II*a*) (see scheme), a *syn* conformation of the glycosylic bond has also been reported [O4′—C1′—N9—C8 = −120.0 (2)°; Nagahara *et al.*, 1990]. In contrast, in the crystal structure of a DNA duplex, the glycosylic bond torsion angle of compound (III) is in the *anti* conformation, with χ = −53.0°, when paired with 2′-deoxycytidine (Lipscomb *et al.*, 1995). The length of the N9—C1′ glycosidic bond of (I) is 1.477 (2) Å, which is longer than that of compound (II*a*) [1.458 (3) Å; Nagahara *et al.*, 1990].

The sugar moiety of nucleoside (I) shows a pseudorotation phase angle P of 33.0 (5)° and a maximum amplitude of puckering τ_m of 15.1 (1)°, which indicates a north (*N*) conformation (3′-*endo*–4′-*exo*, $^3T_4$; Rao *et al.*, 1981). In contrast, the sugar moiety of related compound (II*a*) adopts a south (*S*) conformation (2′-*endo*–1′-*exo*, $^2T_1$) (Nagahara *et al.*, 1990). The torsion angle γ (O5′—C5′—C4′—C3′) characterizes the orientation of the exocyclic 5′-hydroxyl group relative to the 2′-deoxyribose ring. In the crystal structure of compound (I), the value of γ is 176.71 (14)°. This shows that the C4′—C5′ bond is in an antiperiplanar (+*ap*, *trans*) orientation. For compound (II*a*), the exocyclic C4′—C5′ bond adopts a synclinal (+*gauche*) orientation, with γ = 53.7 (2)°.

The thiazolopyrimidine system of (I) is nearly planar; the r.m.s. deviation of the ring atoms from their calculated least-squares planes is 0.033 Å, with a maximum deviation of −0.051 (2) Å for atom C8. The exocyclic amino and oxo groups are almost coplanar with the heterocyclic ring system. Atom C1′ of the sugar moiety deviates from the plane by 0.358 (3) Å. The S7—C8 and S7—C5 bond lengths are 1.765 (2) Å and 1.743 (2) Å, which are very similar to the corresponding bond lengths in related compound (II*a*) [S7—C8 = 1.764 (3) Å and S7—C5 = 1.737 (3) Å; Nagahara *et al.*, 1990].

The structure of nucleoside (I) is stabilized by several intermolecular hydrogen bonds, leading to the formation of layered sheets (Table 2 and Fig. 2). Within the three-dimensional network, the nucleobases are arranged head-to-head and are stacked. Hydrogen bonds are mainly formed between adjacent nucleobases and sugar moieties (N1—H1···O3′, N2—H2*A*···O5′, O3′—H3′*B*···O6 and O5′—H5′*C*···O6). One further hydrogen bond is formed between neighbouring nucleobases (N2—H2*B*···O8). The hydrogen bonds N1—H1···O3′ and N2—H2*B*···O8 are formed within each sheet, while the other three hydrogen bonds (N2—H2*A*···O5′, O3′—H3′*B*···O6 and O5′—H5′*C*···O6) connect neighbouring sheets. In contrast with other compounds showing a *syn* conformation of the glycosylic bond, such as (II*a*) (Nagahara *et al.*, 1990), no intramolecular O5′—H5′···N3 hydrogen bond was found for the crystal structure of (I).

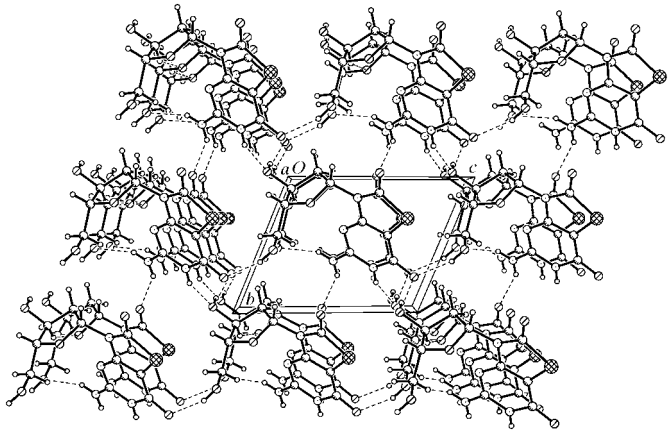

Figure 2
The crystal packing of (I), viewed down the *a* axis, showing the intermolecular hydrogen-bonding network.

Experimental

Compound (I) was synthesized by the stereoselective glycosylation of the protected immunosine base with the 2′-deoxyribose halide and was crystallized from ethanol as colourless needles (m.p. 451 K; decomposition). For the X-ray diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{10}H_{12}N_4O_5S$
M_r = 300.30
Triclinic, $P1$
a = 5.2347 (10) Å
b = 7.1855 (13) Å
c = 8.9972 (16) Å
α = 110.756 (12)°
β = 96.827 (13)°
γ = 99.511 (19)°
V = 306.28 (10) Å^3
Z = 1
Mo $K\alpha$ radiation
μ = 0.29 mm^{-1}
T = 293 (2) K
0.4 × 0.2 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
2042 measured reflections
2042 independent reflections
2029 reflections with $I > 2\sigma(I)$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.073
S = 1.07
2042 reflections
184 parameters
3 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Absolute structure: Flack (1983), with 427 Friedel pairs
Flack parameter: 0.04 (6)

The absolute configuration of (I) results from the Flack (1983) parameter, but also from the defined configuration of the sugar halide used in the glycosylation reaction. All H atoms were found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, the H atoms were placed in geometrically idealized positions, with C—H = 0.93–0.98 Å and N—H = 0.86 Å (AFIX 93 for N2 and AFIX 43 for N1 in *SHELXTL*; Sheldrick, 1997), and constrained to

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.379 (2)	C5—S7	1.743 (2)
N1—C6	1.381 (2)	C6—O6	1.256 (2)
C2—N3	1.323 (2)	S7—C8	1.765 (2)
C2—N2	1.325 (3)	C8—O8	1.213 (3)
N3—C4	1.330 (2)	C8—N9	1.389 (3)
C4—N9	1.381 (2)	N9—C1′	1.477 (2)
C4—C5	1.390 (2)	C1′—O4′	1.413 (2)
C5—C6	1.402 (3)	C4′—O4′	1.436 (2)
C2—N1—C6	123.23 (15)	O8—C8—S7	124.10 (18)
N3—C2—N2	119.79 (17)	N9—C8—S7	110.73 (14)
C4—C5—S7	112.27 (14)	C4—N9—C8	114.14 (15)
C6—C5—S7	128.76 (14)	C4—N9—C1′	124.67 (15)
O6—C6—N1	118.83 (16)	C8—N9—C1′	119.31 (16)
C5—S7—C8	90.16 (10)	O4′—C1′—N9	106.88 (14)
O8—C8—N9	125.17 (19)		
N3—C4—C5—S7	−179.34 (16)	C8—N9—C1′—O4′	−102.4 (2)
N9—C4—C5—S7	−0.7 (2)	O4′—C1′—C2′—C3′	−5.75 (19)
C4—C5—C6—O6	−174.06 (18)	N9—C1′—C2′—C3′	114.07 (16)
S7—C5—C6—N1	178.30 (14)	C2′—C3′—C4′—O4′	−14.93 (18)
C5—S7—C8—O8	177.7 (2)	N9—C1′—O4′—C4′	−129.23 (16)
C5—S7—C8—N9	−2.09 (16)	C2′—C1′—O4′—C4′	−3.9 (2)
O8—C8—N9—C4	−177.7 (2)	C5′—C4′—O4′—C1′	134.39 (17)
S7—C8—N9—C4	2.2 (2)	C3′—C4′—O4′—C1′	12.09 (19)
O8—C8—N9—C1′	−12.6 (4)	O4′—C4′—C5′—O5′	57.4 (2)
S7—C8—N9—C1′	167.28 (14)	C3′—C4′—C5′—O5′	176.71 (14)
C4—N9—C1′—O4′	61.0 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3′^{i}	0.86	2.11	2.911 (2)	155
N2—H2*A*···O5′^{ii}	0.86	2.21	3.009 (2)	154
N2—H2*B*···O8^{iii}	0.86	2.05	2.794 (3)	145
O3′—H3′*B*···O6^{iv}	0.82	1.99	2.795 (2)	166
O5′—H5′*C*···O6^{v}	0.82	2.01	2.778 (2)	156

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

ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C) = 1.2U_{eq}(N)$. The OH groups were refined as rigid groups allowed to rotate but not tip (AFIX 147), with O—H = 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: JZ3073). Services for accessing these data are described at the back of the journal.

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