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A toyocamycin analogue with the sugar moiety in a *syn* conformation

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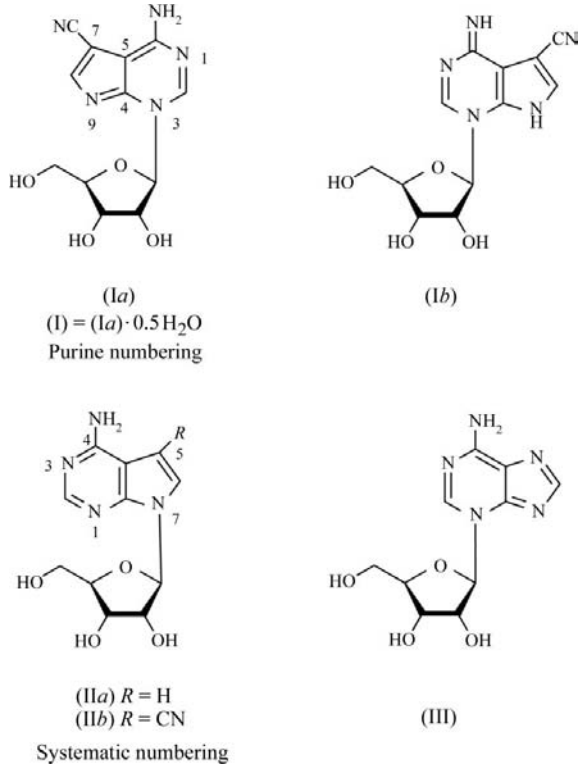
The title compound [systematic name: 4-amino-5-cyano-1-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine hemihydrate], $C_{12}H_{13}N_5O_4\cdot0.5H_2O$, is a regioisomer of toyocamycin with the ribofuranosyl residue attached to the pyrimidine moiety of the heterocycle. This analogue exhibits a *syn* glycosylic bond conformation with a χ torsion angle of 57.51 (17)°. The ribofuranose moiety shows an envelope C2′-*endo* (^2E) sugar conformation (*S*-type), with P = 161.6 (2)° and τ_m = 41.3 (1)°. The conformation at the exocyclic C4′—C5′ bond is +*sc* (*gauche*, *gauche*), with a γ torsion angle of 54.4 (2)°. The crystal packing is stabilized by intermolecular O—H···O, N—H···N and O—H···N hydrogen bonds; water molecules, located on crystallographic twofold axes, participate in interactions. An intramolecular O—H···N hydrogen bond stabilizes the *syn* conformation of the nucleoside.

Comment

Toyocamycin is a naturally occurring 7-deazapurine ribonucleoside produced by *Streptomyces toyocaensis* or other *Streptomyces* strains (purine numbering is used throughout this discussion) (Nishimura *et al.*, 1956; Ohkuma, 1961). The chemical synthesis of the antibiotic toyocamycin was described by different laboratories (Tolman *et al.*, 1968, 1969; Sharma *et al.*, 1993; Porcari & Townsend, 1999). Moreover, the crystal structure of toyocamycin was reported by Prusiner & Sundaralingam (1978). Recently, the N-3 regioisomer of toyocamycin was synthesized (Leonard *et al.*, 2009). Generally, purine N-3 nucleosides are relatively labile molecules. They are formed as intermediates during convergent nucleoside synthesis under kinetically controlled conditions and are rearranged to the thermodynamically more stable N-9 isomers (Vorbrüggen *et al.*, 1981). In the case of the toyocamycin analogue (I), the glycosylic bond is more stable owing to the electronic properties of the 7-deazapurine moiety, a fact which was already reported for other 7-deazapurine nucleosides (Seela & Peng, 2006).



As relatively few X-ray analyses of N-3 nucleosides are known (Kumar *et al.*, 1988, 1989), a single-crystal X-ray analysis of compound (I) was performed. The conformation and hydrogen-bonding pattern in the crystalline state is now studied and compared with the closely related structures of toyocamycin, (II*b*) (Prusiner & Sundaralingam, 1978), tubercidin, (II*a*) (Stroud, 1973; Abola & Sundaralingam, 1973), and

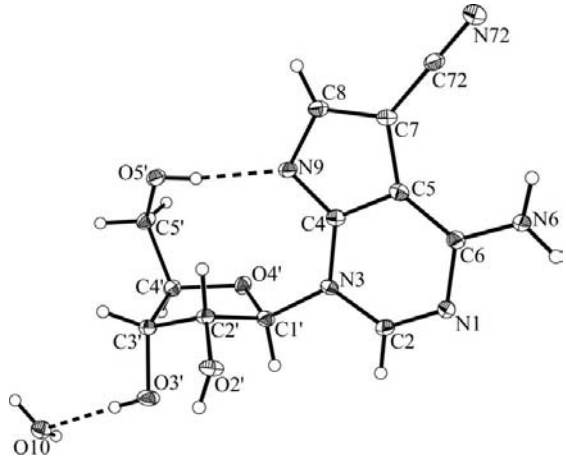


Figure 1
A perspective view of nucleoside (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size. Hydrogen bonds are shown as dashed lines.

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3-isoadenosine, (III) (Kumar *et al.*, 1988). The three-dimensional structure of (I) is shown in Fig. 1 and selected geometric parameters are listed in Table 1.

The title compound can form two main tautomers, namely (I*a*) and (I*b*), as shown in the scheme. Tautomer (I*a*) bears an amine group and no H atom at the pyrrole N atom, while tautomer (I*b*) carries a pyrrole H atom and an imino group on the pyrimidine ring. These tautomers differ in bond length. The tautomeric structure (I*a*) with two H atoms at N6 is evidenced by X-ray analysis in the solid state and in solution by ^{1}H NMR spectroscopy. For related compounds, it was observed that the rotation around the H_2N-C bond of the amine group is restricted, causing two distinct signals in the ^{1}H NMR spectrum due to the different environments encountered by this group (Seela & Bussmann, 1984). This is also found for compound (I). The bond lengths between atoms C6 and N6 of the amine substituent are similar in (I) and (II*b*). On the other hand, in (I), the C2—N1 bond is significantly shorter [1.306 (2) Å] than the C4—N3 bond [1.385 (2) Å], while in toyocamycin these bonds are of almost equal length (C2—N1 = 1.3471 Å and C4—N3 = 1.3470 Å; Prusiner & Sundaralingam, 1978). The same effect was observed in the crystal structure of 3-isoadenosine (Kumar *et al.*, 1988). Altogether, this confirms that tautomer (I*a*) exists in the solid state and in dimethyl sulfoxide solution.

For the common purine nucleosides, the preferred conformation at the N-glycosylic bond is usually *anti* (Saenger, 1984). 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) (purine numbering; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). For the N-3 nucleoside (I), a different notation has to be used in analogy to the already reported definition for the N-3 nucleoside (III). The torsion angle χ is defined by O4′—C1′—N3—C4 (Kumar *et al.*, 1988).

Contrary to the crystal structure of (III), the glycosylic bond torsion angle of (I) is in the *syn* range, with a χ value of 57.51 (17)°. This conformation differs from that in toyocamycin [N-9 isomer, (II*b*)], which adopts an *anti* conformation at the glycosylic bond (χ = −121.88°; Prusiner & Sundaralingam, 1978). The glycosylic bond conformations of (II*a*) and N-3 nucleoside (III) show torsion angle values in the *anti* range, with χ values of −112.8 (4)° for (II*a*) (Abola & Sundaralingam, 1973) and −161.5° for (III) (Kumar *et al.*, 1988). In the tautomeric form (I*b*) with an H atom at the pyrrole N atom, a *syn* conformation of the glycosylic bond cannot be stabilized by the 5′-OH group acting as H-atom donor. Apparently, this pyrrole N atom is a better H-atom acceptor than that of the imidazole unit in (III). The glycosylic bond length of (I) is 1.472 (2) Å. Toyocamycin (1.4490 Å; Prusiner & Sundaralingam, 1978), tubercidin [1.428 (8) Å (Stroud, 1973); 1.438 (4) Å (Abola & Sundaralingam, 1973)] and 3-isoadenosine [1.488 (5) Å; Kumar *et al.*, 1988] exhibit longer glycosylic bond lengths.

The most frequently observed sugar ring conformation of purine 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 almost envelope C2′-*endo* (^2E) sugar pucker. The phase angle of pseudorotation (*P*) and maximum puckering amplitude (τ_m) (Altona & Sundaralingam, 1972) are 161.6 (2) and 41.3 (1)°, respectively. In the case of (II*b*), the sugar ring conformation is C2′-*endo*–C3′-*exo* ($^2T_3$, *S* conformation), with *P* = 165.7° and τ_m = 42.5° (Prusiner & Sundaralingam, 1978), and for compound (II*a*), C2′-*endo*–C1′-*exo* ($^2T_1$, *S* conformation), with *P* = 149.3° and τ_m = −43.8° (Abola & Sundaralingam, 1973).

The conformation about the exocyclic C4′—C5′ bond, which is defined by the torsion angle γ (O5′—C5′—C4′—C3′), is 54.4 (2)° for (I), representing a +*sc* (*gauche*, *gauche*) conformation. This is similar to the parent compound (II*b*), which has the torsion angle γ = 57.10° (+*sc*; *gauche*, *gauche*; Prusiner & Sundaralingam, 1978), whereas in compound (II*a*), the C4′—C5′ bond adopts an *ap* (*gauche*, *trans*) conformation [γ = −178.3 (4)°; Abola & Sundaralingam, 1973].

The 7-deazapurine ring system of (I) is nearly planar (for details see the supporting information). The cyano group of (I) is slightly inclined by 2.2 (3)° with respect to the aromatic ring of the molecule. The amine group is also out of plane; both lie on the same side of the heterocycle [deviations: −0.055 (2) Å for C72, −0.136 (2) Å for N72 and −0.1221 (18) Å for N6].

Within the three-dimensional network of (I), both the nucleobases and the sugar residues are stacked (Fig. 2). The

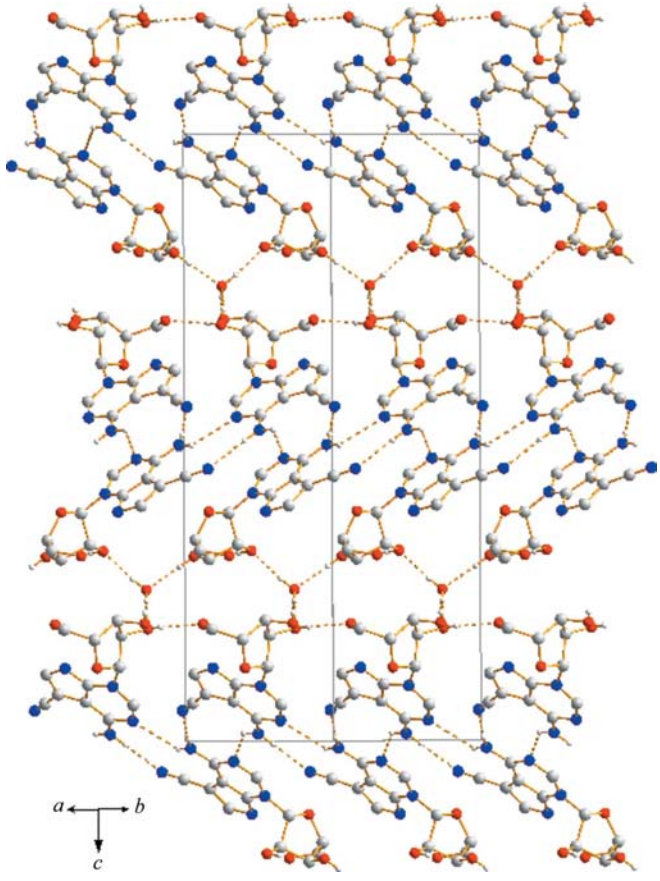

Figure 2
The crystal packing of (I) (projection parallel to the [110] direction), showing the intermolecular hydrogen-bonding network.

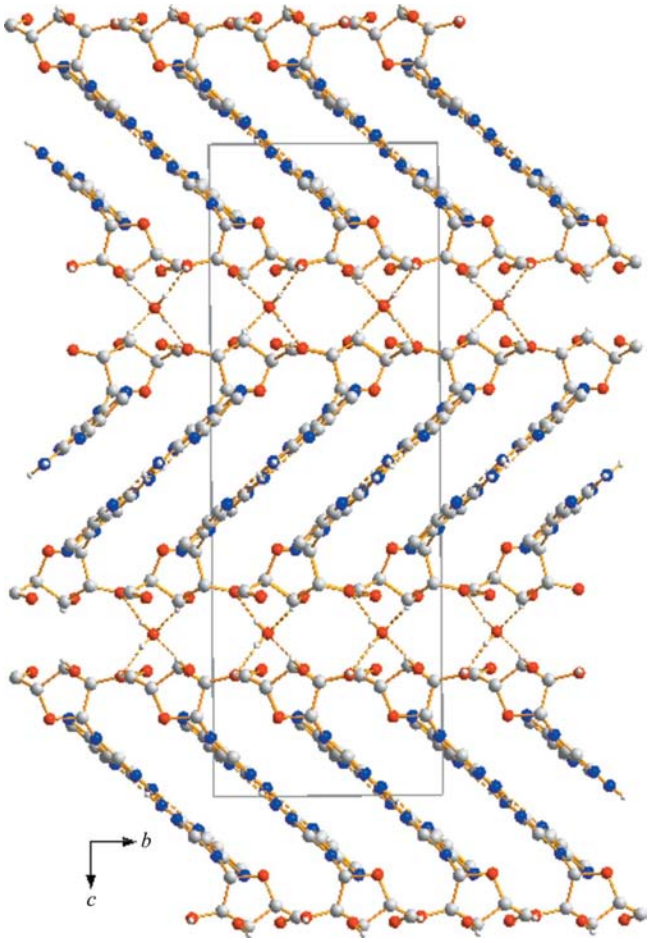

Figure 3
The crystal packing of (I) (projection parallel to the *a* axis), showing the zigzag arrangement of the molecules and the participation of the water molecules in hydrogen bonding.

crystal structure of (I) is further stabilized by several intermolecular and one intramolecular hydrogen bond (O5′—H5′···N9). The intramolecular bond stabilizes the *syn* conformation of the glycosylic bond. Hydrogen bonds are formed between neighboring nucleobases with the amine group as H-atom donor (N6—H6*A*···N72^{iv} and N6—H6*B*···N1^{iii}; see Table 2 for symmetry codes and geometry). The N atom of the cyano group of (I) takes part in hydrogen bonding as an H-atom acceptor, which is different to the crystal structure of toyocamycin (II*b*), in which the cyano group is not involved in any hydrogen bonding (Prusiner & Sundaralingam, 1978). Interbase hydrogen bonding is found in the crystal of (I) but not in that of (II*b*). Moreover, adjacent sugar residues form hydrogen bonds (O2′—H2′*B*···O5′^{ii}). The water molecule participates in the hydrogen-bonding pattern shown in Fig. 3. It acts as a donor (O10—H10···O2′^{i}) as well as an acceptor (O3′—H3′···O10) between two nucleoside molecules. In total, each water molecule participates in four hydrogen bonds, as shown in Fig. 3.

A search of the Cambridge Structural Database (Allen, 2002) for crystallographic nucleoside structures with a constrained *syn* orientation of the base about the glycosyl bond, caused by an intramolecular hydrogen bond, revealed that the large majority of compounds adopt close conformations, including the *S* conformation of the sugar moiety, the γ^+ conformation of the C4′—C5′ bond and a *syn* conformation with χ = 50–90° (Seela *et al.*, 1998). Although the glycosylation position and the H-atom acceptor site are different, these properties are also valid for (I).

Experimental

Compound (I) was synthesized as described by Leonard *et al.* (2009) and crystallized from aqueous methanol. The crystals decompose above 463 K. For the diffraction experiment, a single crystal was mounted on a MiTeGen MicroMesh fiber in a thin smear of oil.

Crystal data

$C_{12}H_{13}N_5O_4{\cdot}0.5H_2O$
M_r = 300.28
Orthorhombic, $C222_1$
a = 9.5382 (7) Å
b = 9.9155 (6) Å
c = 28.2197 (19) Å
V = 2668.9 (3) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.12 mm^{-1}
T = 296 K
0.30 × 0.10 × 0.10 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2008)
T_{min} = 0.966, T_{max} = 0.988
41187 measured reflections
1790 independent reflections
1646 reflections with $I > 2\sigma(I)$
R_{int} = 0.039

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.075
S = 1.08
1790 reflections
199 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.306 (2)	C7—C72	1.414 (3)
N3—C4	1.385 (2)	C72—N72	1.153 (3)
N3—C1′	1.472 (2)	C8—N9	1.362 (3)
C4—N9	1.341 (2)		
C2—N1—C6—N6	175.38 (16)	C2—N3—C1′—O4′	−130.59 (17)
C4—C5—C6—N6	−175.27 (17)	C4—N3—C1′—O4′	57.5 (2)
C6—C5—C7—C72	−1.7 (3)	C3′—C4′—C5′—O5′	54.4 (2)
C72—C7—C8—N9	−176.12 (18)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O10—H10···O2′^{i}	0.82	1.88	2.6971 (17)	174
O5′—H5′···N9	0.82	1.92	2.728 (2)	171
O3′—H3′···O10	0.82	1.90	2.7153 (17)	179
O2′—H2′*B*···O5′^{ii}	0.82	2.03	2.7594 (18)	148
N6—H6*B*···N1^{iii}	0.86	2.53	3.171 (2)	132
N6—H6*A*···N72^{iv}	0.86	2.17	3.024 (2)	175

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

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 inconclusive values (Flack

& Bernardinelli, 2000) [−0.2 (8)]. Therefore, 1339 Friedel equivalents 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. 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) 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 [O—H = 0.82 Å and U_{iso}(H) = $1.5U_{eq}$(O)]. The H atom of the water molecule was also treated as riding but in this case the U_{iso}(H) parameter was refined.

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* and *DIAMOND* (Brandenburg & Putz, 2004); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3204). Services for accessing these data are described at the back of the journal.

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