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Synthesis and Antiviral Evaluation of 4'-C-Azidomethyl- β -D-Ribofuranosyl Purine

and Pyrimidine Nucleosides

Jean-François Griffon^a, Audrey Dumas^a, Richard Storer^{a b}, Jean-Pierre Sommadossi^c & Gilles Gosselin^a

^a Idenix Pharmaceuticals, Medicinal Chemistry Laboratory, Montpellier, France

^b Summit PLC, Abingdon, Oxfordshire, United Kingdom

^c Idenix Pharmaceuticals, Cambridge, Massachusets, USA Published online: 29 Jul 2009.

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SYNTHESIS AND ANTIVIRAL EVALUATION OF 4'-C-AZIDOMETHYL- β -D-RIBOFURANOSYL PURINE AND PYRIMIDINE NUCLEOSIDES

Jean-François Griffon,¹ Audrey Dumas,¹ Richard Storer,^{1,2} Jean-Pierre Sommadossi,³ and Gilles Gosselin¹

¹Idenix Pharmaceuticals, Medicinal Chemistry Laboratory, Montpellier, France ²Summit PLC, Abingdon, Oxfordshire, United Kingdom (Current address) ³Idenix Pharmaceuticals, Cambridge, Massachusets, USA

□ In the search for inhibitors of the replication of RNA viruses, including hepatitis C virus (HCV), the hitherto unknown 4 -C-azidomethyl-β-D-ribofuranosyl nucleosides of the five naturally occurring nucleic acid bases have been synthesized and their antiviral properties examined. These 4 -C-branched nucleosides were stereospecifically prepared by glycosylation of purine and pyrimidine aglycons with a suitable peracylated 4-C-azidomethyl-D-pentofuranose sugar, followed by removal of the protecting groups. The prepared compounds were tested for their activity against several viruses, but they did not show an antiviral effect.

Keywords 4'-C-Azidomethyl-β-D-ribofuranosyl nucleosides; RNA viruses; HCV

INTRODUCTION

RNA viruses of the family *Flaviviridae* are the agents of numerous widespread and often severe diseases. Among these viruses, we can mention the members of the genus *Flavivirus*, including yellow fever virus (YFV) which is still a leading cause of hemorrhagic fever and related mortality (up to 50%) worldwide, the dengue virus (DEN) which is increasing in prevalence in the tropical and subtropical areas of the world, and the West Nile virus (WNV) emerging in North America.^[1] Infections resulting

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In honor of and in celebration of Morris J. Robins' 70th birthday.

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Address correspondence to Gilles Gosselin and Jean-François Griffon, Laboratoires Idenix Sarl, Cap Gamma, 1682 rue de la Valsiere, B.P. 50001, 34189, Montpellier, Cedex 4, France. E-mail: gosselin.gilles@idenix.com; griffon.j-f@idenix.com

from these viruses are important examples of emerging diseases. We can also mention a member of the genus Hepacivirus, namely hepatitis C virus (HCV) which is a causative agent of chronic liver disease, estimated to affect over 170 million people worldwide.^[2] Currently, no specific antiviral drugs are available for the prevention or the treatment of infections caused by the majority of RNA viruses. Perhaps the only exception is represented by HCV; current therapy for chronic hepatitis C consists of pegylated interferon- α and the nucleoside analogue ribavirin. However, such standard therapy is poorly tolerated and has limited efficacy, with no more than 45% and 52% response rates among patients infected with the most prevalent HCV genotypes 1 and 4.^[3] Therefore, there is an urgent need for more efficient and better tolerated anti-HCV agents, as well as for specific and selective treatments against a higher number of RNA virus infections. The unique RNA-dependant RNA polymerase (RDRP) is essential for replication of RNA viruses, and recent progress have been made in the development of inhibitors of the HCV RDPR.^[4] In this regard, we had investigated sugar-modified ribonucleoside analogues and discovered that compounds possessing a β -methyl substituent at the 2'-position of the D-ribose moiety are potent and broad-spectrum anti-RNA virus agents.^[5] Among them, and although no longer in development, valopicitabine,^[6] an orally bioavailable prodrug of 2'-C-methylcytidine (Figure 1) was the first HCV nucleoside polymerase inhibitor to demonstrate proof-of-concept in the clinic by achieving reduction in plasma HCV RNA.^[7] More recently, orally biovailable prodrugs (R7128^[8] and R1626^[9]) of two other branched nucleoside analogues inhibiting HCV replication, namely 2'-deoxy-2'fluoro-2'-C-methylcytidine (PSI-6130)^[10] and 4'-azidocytidine (R1479)^[11] (Figure 1), have been evaluated in clinical studies for the treatment of chronic hepatitis C.

In continuation of our interest in 4'-*C*-branched nucleoside derivatives,^[12] here we focused on the synthesis and antiviral evaluation studies of the hitherto unknown 4'-*C*-azidomethyl- β -D-ribofuranosyl nucleosides bearing the five naturally occurring nucleic acid bases and two modified purines (Figure 1).

RESULTS AND DISCUSSION

Chemistry

It was anticipated that the title β (trans-1',2') 4'-C-azidomethyl-Dribofuranosyl nucleoside compounds could be synthesized by condensation of a suitably protected 4-C-azidomethyl-D-ribofuranose with the purine and pyrimidine bases. In accord with the Baker's rule,^[13] a 2-Oacyl-4-C-azidomethyl-D-ribofuranose was required for preferential or exclusive formation of the β nucleoside anomers. As starting sugar, we



FIGURE 1 Examples of nucleoside analogues with anti-HCV activity and structures of 4'-C-azidomethyl- β -D-ribofuranosyl nucleosides.

decided to use the syrupy 1,2,3-tri-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl- α/β -D-ribofuranose (**5**), hitherto unknown and specially prepared for our present purpose. In this regard, 5-*O*-benzoyl-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-1-*O*-methyl- β -D-ribofuranose (**1**)^[14] was synthesized first in 6 steps from D-ribose by implementing at each step convenient published procedures.^[14,15] Introduction of the azido function at the 6-position of **1** was performed *via* the displacement of a 6-*O*-*p*-toluenesulfonyl function (intermediate **2**) by sodium azide to afford **3** in 68% yield (Scheme 1).



SCHEME 1 Reagents and conditions: (a) *p*-toluenesulfonyl chloride, pyridine, 25° C; (b) sodium azide, DMF, 150° C; (c) 85% acetic acid, 110° C; (d) acetic anhydride, 4-dimethylaminopyridine, pyridine, 25° C; (e) acetic acid, acetic anhydride, conc. sulfuric acid, 25° C.

Cleavage of the 2,3-*O*-isopropylidene protecting group of **3** with 85% acetic acid at 110°C, followed by acetylation with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine led to a mixture of the expected 1,2,3-tri-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl- α/β -D-ribofuranose (**4**) and of the corresponding methyl- β -D-ribofuranoside **5**, the latter resulting from the single cleavage of the 2,3-acetonide during the acidic treatment. After separation of **4** from **5**, the methyl- β -D-ribofuranoside **5** was subjected to an acetolysis which allowed to obtain **4** with an 80% overall yield from **3**.



SCHEME 2 Reagents and conditions: (a) silvlated uracil, thymine or N^4 -benzoylcytosine, TMSOTf; 1,2-dichloroethane, 25°C; (b) methanolic ammonia, 25°C.

Glycosylations were carried out by various procedures which, except for the cytosine nucleoside, did not require prior protection of the heterocyclic bases. Thus, in the pyrimidine series, condensation of **4** respectively with silylated uracil, thymine and N^{4} -benzoylcytosine was performed in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) under Vorbrüggen conditions^[16] to afford the corresponding fully acylated 4'-*C*-azidomethyl- β -D-ribofuranosyl nucleosides **6–8** in yields around 50% (Scheme 2).

Compounds **6–8** were deprotected with saturated methanolic ammonia to give the target pyrimidine 4'-*C*-azidomethyl- β -D-ribofuranosyl nucleosides **9–11**.

In the purine series (Scheme 3), **4** was condensed with: i) adenine in the presence of tin(IV) chloride in acetonitrile at room temperature following the Saneyoshi procedure^[17] to afford **12** in 50% yield; ii) 6-chloropurine in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and TMSOTf in acetonitrile at 60°C, affording the crude intermediate **14**, which directly was treated with methylamine in water to give **15** in an overall 76% yield; iii) silylated 2-amino-6-chloropurine under Vorbrüggen condition^[16] to afford **16** in 42% yield.

4'-Azidomethyladenosine (13) was obtained in a near quantitative yield by stirring 12 with saturated methanolic ammonia at room temperature overnight. 4'-Azidomethylguanosine (17) was obtained in 31% yield by refluxing the 2-amino-6-chloropurine nucleoside 16 with 2-mercaptoethanol and sodium methoxide in methanol, as described in oxaselenolane nucleoside series.^[18] Finally, treatment of 16, successively with saturated methanolic ammonia at 25°C and with cyclopropylamine in ethanol at reflux, afforded the 4'-C-azidomethyl-2-amino-6-cyclopropylaminopurine β -D-ribofuranonucleoside 18 in 64% yield.

Structural assignments for all the hitherto unknown 4'-*C*-azidomethyl- β -D-ribofuranosyl nucleosides **9–11**, **13**, **15**, **17**, and **18** are based on elemental analysis, mass spectra and on their physical properties.

Antiviral Evaluations

The 4'-C-azidomethyl- β -D-ribofuranosyl nucleosides 9–11, 13, 15, 17, and 18 were evaluated in cell-based assays (following methods described



SCHEME 3 Reagents and conditions: (a) adenine, tin(IV) chloride, acetonitrile, 25°C; (b) methanolic ammonia, 25°C; (c) 6-chloropurine, DBU, TMSOTf, acetonitrile, 60°C; (d) 40% methylamine in water, 25°C; (e) silylated 2-amino-6-chloropurine, TMSOTf, toluene, 110°C; (f) 2-mercaptoethanol, sodium methoxide, methanol, 65°C; (g) methanolic ammonia, 25°C; (h) cyclopropylamine, ethanol, reflux.

in^[5c]) against viruses representative of three genera of the ssRNA⁺ Flaviviridae, that is, Pestivirus (bovine virus diarrhoea virus), Flavivirus (Yellow Fever, Dengue and West Nile viruses) and Hepacivirus (HCV). They were also tested against a virus representative of another ssRNA⁺ family, Retroviridae (HIV-1), against a virus representative of a ssRNA⁻ families, Paramyxoviridae (RSV), and finally against a virus representative of DNA families, that is, Hepadnaviridae (HBV). Unfortunately, all the compounds showed neither antiviral activity nor cytotoxicity at the highest concentration tested (generally 100 μ M).

CONCLUSION

A series of hitherto unknown 4'-C-azidomethyl- β -D-ribofuranosyl nucleosides were synthesized and evaluated against a broad range of RNA viruses (including HCV) and against a DNA virus (HBV). All compounds were found inactive and non cytotoxic in all antiviral assays. Several factors could be responsible for their inactivity. Their inability to enter cells or to serve as substrates for intracellular enzymes catalyzing phosphorylation, as well as a lack of inhibition of viral polymerases by their triphosphate forms, would account for their lack of antiviral activity.

EXPERIMENTAL

All reactions were performed with reagent-grade materials and solvents under an atmosphere of nitrogen. Evaporation of the solvent was carried out in a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Büchi B-545 apparatus and are uncorrected. The UV absorption spectra were recorded on an Uvikon XS spectrophotometer (99-9089). ¹H-NMR spectra were run at room temperature in DMSO- d_6 or CDCl₃ with a Bruker AC 200, 250, or 400 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual peak (DMSO- d_6) set at $\delta_{\rm H}$ 2.49 or (CDCl₃) set at $\delta_{\rm H}$ 7.26 ppm. Deuterium exchange, decoupling experiments or 2D-COSY spectra were performed in order to confirm proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), m (multiplet), p (pseudo). All J-values are in Hz. FAB mass spectra were recorded in the positive- (FAB > 0) or negative- (FAB < 0) ion mode on a [EOL JMS DX 300 mass spectrometer; the matrix was a mixture (50:50, v/v) of glycerol and thioglycerol (GT). IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR. Elemental analyses were carried out by the "Service de Microanalyses du CNRS, Division de Vernaison" (France) or by the "Laboratoire de Mesures Physiques, Université Montpellier 2" (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F₂₅₄ (Merck, Art. 5554), visualization of products being accomplished by UV absorbency or by charring after immersion in a solution of $(NH_4)_2SO_4$ (150 g) in EtOH-H₂SO₄-water (300:30:450 mL) with heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385) or LiChroprep RP-18 (40-63 μ m, Merck Art. 1.13900.0250) at atmospheric pressure.

4-*C*-Azidomethyl-5-*O*-benzoyl-2,3-*O*-isopropylidene-1-*O*-methyl- β -D-ribofuranose (3)

To a solution of $1^{[14]}$ (18.8 g, 55.5 mmol) in anhydrous pyridine (280 mL) under argon was added *p*-toluenesulfonyl chloride (21.3 g, 111.7 mmol). The reaction mixture was stirred overnight at room temperature. Ice-cold water was added (20 mL) and the reaction was diluted with methylene chloride (400 mL). The organic layer was washed with aqueous

hydrochloric acid (1N, 250 mL), with water (250 mL) and then dried over sodium sulfate and evaporated under reduced pressure to give the crude tosylate **2** which was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (10–20%) in petroleum ether] to give **2** (25.1g, 92%) as a pale yellow solid. To a solution of **2** (25.1 g, 551.0 mmol) in dry DMF (360 mL) was added sodium azide (16.6 g, 254.8 mmol). The reaction mixture was refluxed for 2 days, cooled to room temperature, diluted with ice-cold water (300 mL) and extracted with methylene chloride (3 × 200 mL). The combined organic layers were washed with a saturated aqueous sodium hydrogen carbonate solution (200 mL), with water (5 × 200 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (0–10%) in petroleum ether] to afford pure **3** (12.7 g, 68%) as a yellow oil.

¹H-NMR (DMSO-*d*₆): δ 8.1–7.5 (m, 5H, C₆H₅CO), 5.04 (s, 1H, H-1), 5.46 (dd, 2H, H-2 and H-3, J = 17 Hz, J = 6.0 Hz); 4.34 (dd, 2H, H-5, H-5', J = 20.0 Hz, J = 11.5 Hz), 3.69 (pt, 2H, H-6', H-6'), 3.27 (s, 3H, OCH₃), 1.49 (s, 3H CH₃), 1.32 (s, 3H CH₃); (matrix GT): FAB > 0 *m*/*z* 363 (M+H)⁺, 332 (M-OCH₃)⁺, 105 (C₆H₅CO)⁺ FAB < 0 *m*/*z* 121 (C₆H₅CO₂)⁻; IR (neat) 2106 cm⁻¹ (N₃).

1,2,3-Tri-O-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl- α/β -D-ribofuranose (4)

Compound 3 (12,4 g, 34.12 mmol) was suspended in a 85% aqueous acetic acid solution (170 ml). The solution was heated at 110°C for 6 hours. The solvents were removed under vacuum and the residue was successively coevaporated with toluene, absolute ethanol, and pyridine. The oily residue was dissolved in pyridine (190 ml) and acetic anhydride (54.4 ml, 575 mmol) and a catalytic amount of 4-dimethylaminopyridine were added. The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was dissolved with methylene chloride (600 mL) and successively washed with a saturated aqueous sodium hydrogen carbonate solution (300 mL), a 1M hydrochloric acid (300 mL) and water (2×500 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (30-40%) in petroleum ether] to give 2,3,di-O-acetyl-5-O-benzoyl-4-C-azidomethyl-1-O-methyl- β -Dribofuranose 5 (10.76 g, 77%) and 4 (2.08 g, 14%) as a pale yellow syrup. Compound 5 was further converted to 4 by acetolysis. Thus, to a solution of 5 (10.76 g, 26.44 mmol) in acetic acid (132 mL) and acetic anhydride (13.2 ml) was added conc.H₂SO₄ (0.79 mL). The reaction mixture was stirred overnight at room temperature, cooled to 0°C, neutralized with

solid sodium hydrogen carbonate and extracted with methylene chloride $(3 \times 250 \text{ mL})$. The combined organic layers were washed with water (500 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel chromatography [eluent: stepwise gradient of diethyl ether (30–40%) in petroleum ether] to give **4** (9.86 g, 66%). A small fraction of **4** (overall yield, 80%) was repurified on silica gel chromatography [eluent: stepwise gradient of diethyl ether (30–40%) in petroleum ether] to give **4** (9.86 g, 66%). A small fraction of **4** (overall yield, 80%) was repurified on silica gel chromatography [eluent: stepwise gradient of diethyl ether (30–40%) in petroleum ether] in order separate the α and the β anomer.

α anomer: ¹H-NMR (DMSO-*d*₆): δ 8.1–7.5 (m, 5H, C₆H₅CO), 6.41 (d, 1H, H-1, J_{1,2} = 4.6 Hz), 5.61 (d, 1H, H-3, J₂₋₃ = 6.5 HZ), 5.52 (dd, 1H, H-2, J₂₋₃ = 6.5 Hz, J_{1,2} = 4.7 Hz), 4.5–4.4 (dd, 2H, H-5, H-5', J = 14.9 Hz, J = 11.7 Hz); 3.9–3.5 (dd, 2H, H-6, H-6', J = 64.5 Hz, J = 13.3 Hz), 2.16 (s, 3H, CH₃CO₂), 2.14 (s, 3H, CH₃CO₂), 2.07 (s, 3H, CH₃CO₂); MS (matrix GT): FAB > 0 *m*/*z* 376 (M-CH₃CO₂⁻)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 *m*/*z* 121 (C₆H₅CO₂)⁻, 59 (CH₃CO₂)⁻.

β anomer: ¹H-NMR (DMSO- d_6): δ 8.0–7.5 (m, 5H, C₆H₅CO), 6.09 (s, 1H, H-1), 5.63 (d, 1H, H-3, J = 5.4 Hz), 5.35 (d, 1H, H-2, J = 6.0 Hz), 4.6–4.3 (dd, 2H, H-5, H-5', J = 33.0 Hz, J = 11.8 Hz); 3.8–3.5 (dd, 2H, H-6, H-6', J = 44.0 Hz, J = 11.4 Hz), 2.12 (s, 3H, CH₃CO₂), 2.06 (s, 3H, CH₃CO₂), 1.87 (s, 3H, CH₃CO₂); MS (matrix GT): FAB > 0 m/z 376 (M-CH₃CO₂⁻)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 m/z 121 (C₆H₅CO)⁻, 59 (CH₃CO₂)⁻.

1-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)uracil (6)

A suspension of uracil (0.388 g, 3.46 mmol) was treated during 17 hours under reflux with hexamethyldisilazane (HMDS, 18 mL) and a catalytic amount of ammonium sulfate. After cooling to room temperature, the mixture was evaporated under reduced pressure, and the residue, obtained as a colorless oil, was diluted with anhydrous 1,2-dichloroethane (7 mL). To the resulting solution was added **4** (1.05 g, 2.41 mmol) in anhydrous 1,2-dichloroethane (13 mL), followed by addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.93 mL, 4.82 mmol). The solution was stirred for 22 hours at room temperature under argon atmosphere, then diluted with chloroform (150 mL), washed with a saturated aqueous sodium hydrogen carbonate solution (150 mL), and with water (2×100 mL). The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (10–30%) in methylene chloride] to afford pure **9** (620 mg, 53%) as a pale yellow foam.

¹H-NMR (DMSO- d_6): δ 11.52 (s, 1H, NH), 8.0–7.4 (m, 6H, C₆H₅CO, H-6), 6.01 (d, 1H, H-1', J_{1'-2'} = 4.9 Hz), 5.72 (d, 1H, H-3', J_{2'-3'} = 6.9 Hz), 5.59 (m, 2H, H-5, H-3'), 4.45 (dd, 2H, H-6', H-6'', J = 36.8 Hz, J = 11.5 Hz), 3.9–3.5 (dd, 2H, H-5, H-5', J = 17.0 Hz, J = 117.9 Hz), 2.06 (s, 3H, CH₃CO₂),

2.03 (s, 3H, CH₃CO₂); MS (matrix GT): FAB > 0 m/z 975 (2M+H)⁺, 488 (M+H)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 m/z 486 (M-H)⁻, 121 (C₆H₅CO₂)⁻, 111 (B)⁻, 59 (CH₃CO₂)⁻.

1-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)thymine (7)

Thymine was condensed with 4 (1.05 g, 2.41 mmol) under the same conditions as described for 6 to give 7 (517 mg) in 45% yield.

¹H-NMR (DMSO-*d*₆): δ 11.52 (s, 1H, NH), 8.0–7.3 (m, 6H, C₆H₅CO, H-6), 5.99 (d, 1H, H-1', J_{1'-2'} = 5.4 Hz), 5.65 (d, 1H, H-3', J_{2'-3'} = 6.8 Hz), 5.50 (pt, 1H, H-2', J_{2'-3'} = 6.7, = J_{1'-2'} = 5.5 Hz), 4.40 (dd, 2H, H-6', H-6'', J = 52.2 Hz, J = 11.5 Hz), 3.9–3.5 (dd, 2H, H-5, H-5', J = 17.0 Hz, J = 121.9 Hz), 2.00 (s, 3H, CH₃CO₂), 1.98 (s, 3H, CH₃CO₂), 1.51 (s, 3H, CH₃); MS (matrix GT): FAB > 0 *m*/*z* 1003 (2M+H)⁺, 502 (M+H)⁺, 376 (S)⁺, 127 (BH₂)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 *m*/*z* 500 (M-H)⁻, 125 (B)⁻, 121 (C₆H₅CO₂)⁻, 59 (CH₃CO₂)⁻.

1-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl- β -D-ribofuranosyl)- N^4 -benzoylcytosine (8)

 N^4 -Benzoylcytosine was condensed with **4** (1.04 g, 2.39 mmol) under the same conditions as described for **6** to give **8** (670 mg) in 47% yield.

¹H-NMR (DMSO-*d*₆): δ 11.37 (brs, 1H, NH), 8.19 (d, 1H, H-6, J₅₋₆ = 7.4 Hz), 7.7–7.4 (m, 10H, 2C₆H₅CO), 7.33 (d, 1H, H-5, J₅₋₆ = 7.4 Hz), 6.06 (d, 1H, H-1', J_{1'-2'} = 3.7 Hz), 5.84 (d, 1H, H-3', J_{2'-3'} = 7.1 Hz), 5.70 (dd, 1H, H-2', J_{2'-3'} = 7.0, = J_{1'-2'} = 3.7 Hz), 4.51 (dd, 2H, H-6', H-6'', J = 23.0 Hz, J = 11.5 Hz), 4.0–3.6 (dd, 2H, H-5, H-5', J = 13.5 Hz, J = 74.8 Hz), 2.08 (s, 6H, 2CH₃CO₂); MS (matrix GT): FAB > 0 *m*/*z* 591 (M+H)⁺, 376 (S)⁺, 216 (BH₂)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 *m*/*z* 589 (M-H)⁻, 214 (B)⁻, 121 (C₆H₅CO₂)⁻, 59 (CH₃CO₂)⁻.

1-(4-C-Azidomethyl-β-D-ribofuranosyl)uracil (9)

A solution of **6** (620 mg, 1.27 mmol) in methanolic ammonia (previously saturated at -10° C) (32 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (60 ml) and water (60 ml). The aqueous layer was washed with ethyl acetate (2 × 60 mL) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: methanol (10%) in methylene chloride] to give pure **9** (330 mg, 87%) which was crystallized from absolute ethanol to afford white crystals.

m.p.: 202–203°C (dec.); UV (EtOH): $\lambda_{max} = 260 \text{ nm} (\varepsilon = 11700), \lambda_{min} = 229 \text{ nm} (\varepsilon = 3000); {}^{1}\text{H-NMR} (DMSO-d_6): \delta 11.35 (s, 1H, NH), 8.06 (d, 1H, NH)$

H-6, $J_{6-5} = 8.3 \text{ Hz}$), 5.90 (d, 1H, H-1', $J_{1'-2'} = 7.7 \text{ Hz}$), 5.69 (d, 1H, H-5, $J_{5-6} = 8.1 \text{ Hz}$), 5.45 (d, 1H, OH-2', $J_{2'\text{OH}} = 6.4 \text{ Hz}$), 5.40 (d, 1H, OH-3', $J_{3'\text{OH}} = 4.7 \text{ Hz}$), 5.29 (t,1, OH-5', $J_{5'\text{OH}} = J_{5''\text{OH}} = 5.1 \text{ Hz}$), 4.23 (m, 1H, H-2'), 4.04 (pt, 1H, H-3', J = 4.6 Hz, J = 5.0 Hz), 3.56–3.50 (m, 2H, H-5', H-5''), 3.47–3.31 (m, 2H, H-6', H-6''); MS (matrix GT): FAB > 0 *m*/*z* 300 (M+H)⁺, 113 (BH₂)⁺, FAB < 0 *m*/*z* 298 (M-H)⁻, 111 (B⁻); Anal. Calcd (C₁₀H₁₃N₅O₆): C 40.14, H 4.38, N 23.40. Found: C 39.77, H 4.40, N 23.20.

1-(4-C-Azidomethyl- β -D-ribofuranosyl)thymine (10)

Compound 7 (494 mg, 0.985 mmol) was treated with methanolic ammonia under the same conditions as described for the preparation of **9**. After the usual work-up, the residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (5%-7%) in methylene chloride] to give pure **10** (286 mg, 93%) which was crystallized from a methylene chloride/methanol mixture as white crystals.

m.p.: 184–185°C (dec.); UV (EtOH): $\lambda_{max} = 265$ nm ($\varepsilon = 7700$), $\lambda_{min} = 232$ nm ($\varepsilon = 2000$); ¹H-NMR (DMSO- d_6): δ 11.35 (s, 1H, NH), 7.89 (s, 1H, H-6), 5.89 (d, 1H, H-1', J_{1'-2'} = 7.8 Hz), 5.40 (d, 1H, OH-2', J_{2'-OH} = 6.5 Hz), 5.34 (d, 1H, OH-3', J_{3'-OH} = 4.6 Hz), 5.29 (t,1, OH-5', J_{5'-OH} = J_{5''-OH} = 5.2 Hz), 4.26 (m, 1H, H-2'), 4.04 (pt, 1H, H-3', J = 4.6 Hz, J = 5.0 Hz), 3.57–3.48 (m, 2H, H-5', H-5''), 3.39–3.34 (m, 2H, H-6', H-6''), 1.79 (s, 1H, CH₃); MS (matrix GT): FAB > 0 *m*/*z* 627 (2M+H)⁺, 314 (M+H)⁺, 127 (BH₂)⁺, FAB < 0 *m*/*z* 625 (2M+H)+, 312 (M-H)⁻, 125 (B⁻); Anal. Calcd (C₁₁H₁₅N₅O₆): C 42.17, H 4.83, N 22.36. Found: C 42.31, H 4.88, N 21.96.

1-(4-*C*-Azidomethyl- β -D-ribofuranosyl)cytosine, hydrochloride form (11)

Compound 8 (670 mg, 1.13 mmole mmol) was treated with methanolic ammonia (previously saturated at -10° C), (23 mL) at 100°C in a stainlesssteel bomb for 3 hours, then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride (40 ml) and water (40 mL). The aqueous layer was washed with methylene chloride (2 × 40 mL) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: methylene chloride/methanol/ammonium hydroxide solution 75:20:5, v/v)]. The collected fractions were concentrated and diluted with absolute ethanol (6.3 mL). To the solution was added a 2N hydrochloric acid solution (1.5 mL) and the mixture was repeated twice to allow 11 (217 mg, 57%) to crystallize as a white solid from absolute ethanol. m.p.: 213–215°C (dec.); UV (EtOH): $\lambda_{max} = 277$ nm ($\varepsilon = 11900$), $\lambda_{min} = 229$ nm ($\varepsilon = 5300$); ¹H-NMR (DMSO- d_6): δ 9.80 (s, 1H, NH₂), 8.70 (s, 1H, NH₂), 8.21 (1H, H-6, J₆₋₅ = 7.8 Hz), 6.20 (1H, H-5, J₆₋₅ = 7.8 Hz), 5.89 (d, 1H, H-1', J_{1'-2'} = 7.8 Hz), 5.8–5.0 (brs, 3H, OH-2', OH-3', OH-5'), 4.23 (pt, 1H, H-2', J = 5.6 Hz, J = 6.2 Hz), 4.10 (d, 1H, H-3', J = 5.1 Hz), 3.64–3.48 (m, 4H, H-5', H-5'', H-6', H-6''); MS (matrix GT): FAB > 0 *m/z* 627 (2M+H)⁺, 314 (M+H)⁺, 127 (BH₂)⁺, FAB < 0 *m/z* 625 (2M+H)+, 312 (M-H)⁻, 125 (B⁻); Anal. Calcd (C₁₀H₁₅ClN₆O₅): C 35.88, H 4.52, N 25.11, Cl 10.59. Found: C 36.04, H 4.65, N 24.88, Cl 10.66.

9-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)adenine (12)

A solution of **4** (1.00 g, 2.30 mmol) in anhydrous acetonitrile (46 ml) was treated with adenine (379 mg, 2.80 mmol) and tin(IV) chloride (SnCl₄, 540 μ l, 4.60 mmol) and stirred at room temperature overnight. The solution was concentrated under reduced pressure, diluted with chloroform (100 ml) and treated with a cold saturated aqueous solution of NaHCO₃ (100 ml). The mixture was filtered on celite, and the precipitate was washed with hot chloroform. The combined filtrates were washed with water (100 ml) and brine (100 ml), dried (Na₂SO₄), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (2–4%) in dichloromethane] to afford **12** (581 mg, 50%), which was crystallized from absolute ethanol to afford white crystals.

m.p.: 120–122°C (dec.); ¹H-NMR (DMSO- d_6): δ 8.31 (s, 1H, H-2), 8.1–7.3 (m, 6H, C₆H₅CO, H-8), 7.36 (brs, 2H, NH₂), 6.37 (d, 1H, H-1', J_{1'-2'} = 5.8 Hz), 6.27 (t, 1H, H-2', J_{1'-2'} = J_{2'-3'} = 6.0 Hz), 5.98 (d, 1H, H-3', J_{2'-3'} = 6.2 Hz), 4.67 (d, 1H, H-5', J = 11.8 Hz), 4.45 (d, 1H, H-5'', J = 11.8 Hz), 3.94 (d, 1H, H-6', J = 13.4 Hz), 3.67 (d, 1H, H-6'', J = 13.4 Hz), 2.14 (s, 3H, CH₃CO₂), 2.02 (s, 3H, CH₃CO₂); MS (matrix GT): FAB > 0 *m*/z 1021 (2M+H)⁺, 511 (M+H)⁺, 136 (BH₂)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 *m*/z 509 (M-H)⁻, 134 (B)⁻, 121 (C₆H₅CO₂)⁻, 59 (CH₃CO₂)⁻.

9-(4-C-Azidomethyl- β -D-ribofuranosyl)adenine (13)

Compound 12 (575 mg, 1.13 mmol) was treated with methanolic ammonia and purified under the same conditions as described for 9 to give pure 13 (350 mg, 96%) which was crystallized from absolute ethanol to give white crystals.

m.p.: 120–122°C (dec.); UV (ethanol): $\lambda_{max} = 258 \text{ nm}$ ($\varepsilon = 15600$), $\lambda_{min} = 226 \text{ nm}$ ($\varepsilon = 1800$); ¹H-NMR (DMSO- d_6): δ 8.42 (s, 1H, H-2), 8.21 (s, 1H, H-8), 7.42 (s, 2H, NH₂), 5.98 (d, 1H, H-1', $J_{1'-2'} = 7.8 \text{ Hz}$), 5.67 (pt, 1H, OH-5', J = 4.7 Hz, J = 6.7 Hz), 5.56 (d, 1H, OH-2', J = 6.7 Hz), 5.51 (d, 1H,

OH-3', J = 4.3 Hz), 4.99 (dd, 1H, H-2', J = 6.8 Hz, J = 12.3 Hz), 4.23 (dd, 1H, H-3', J = 4.3 Hz, J = 4.7 Hz), 3.74–3.62 (m, 2H, H-5', H-5"); MS (matrix GT): FAB > 0 m/z 645 (2M+H)⁺, 323 (M+H)⁺, 136 (B+2H)⁺, FAB < 0 m/z 321 (M-H)⁻, 134 (B)⁻; Anal. Calcd (C₁₁H₁₄N₈O₄.0.5 H₂O): C 39.88, H 4.56, N 33.82. Found: C 39.48, H 4.46, N 33.38.

9-(4-C-Azidomethyl- β -D-ribofuranosyl)-6-methylaminopurine (15)

To a solution of 4 (600 mg, 1.38 mmol) and 6-chloropurine (234 mg, 1.52 mmol) in dry acetonitrile (5.5 ml) was added at 0° C under argon DBU (0.62 ml, 4.15 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSTf, 1.06 mL, 5.48 mmol). The solution was stirred for 2 hrs at 60°C under argon atmosphere, then diluted with methylene chloride (100 mL), washed with a saturated aqueous sodium hydrogen carbonate solution (100 mL) and with water (100 mL). The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude material 14 was treated with 40% methylamine in water (27.6 ml) and stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride (50 ml) and water (50 ml). The aqueous layer was washed with methylene chloride (2 \times 50 mL), and concentrated under reduced pressure. The residue was purified by chromatography on LiChroprep RP-18, using a stepwise gradient of acetonitrile (2-12%) in water and lyophilized to give 15 (355 mg, 76%, 2 steps) as a white powder.

¹H-NMR (DMSO-*d*₆): δ 8.35 (s, 1H, H-2), 8.24 (s, 1H, H-8), 7.84 (brs, 1H, NH), 5.92 (d, 1H, H-1', $J_{1'-2'} = 7.8$ Hz), 5.61 (brs, 1H, OH-5'), 5.49 (brs, 2H, OH-2', OH-3'), 4.93 (dd, 1H, H-2', J = 5.0 Hz, J = 7.7 Hz), 4.18 (d, 1H, H-3', J = 4.9 Hz), 3.67–4.46 (m, 4H, 4H, H-5', H-5'', H-6', H-6''), 2.96 (brs, 1H, CH₃); MS (matrix GT): FAB > 0 *m*/*z* 337 (M+H)⁺, 150 (B+2H)⁺, FAB < 0 *m*/*z* 671 (2M-H)⁻, 335 (M-H)⁻, 1148 (B)⁻.

9-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)-2-amino-6-chloropurine (16)

A suspension of 2-amino-6-chloropurine (1.52 g, 8.96 mmol) was treated with HMDS (45 mL) and a catalytic amount of ammonium sulfate during 17 hours under reflux. After cooling to room temperature, the mixture was evaporated under reduced pressure, and the residue, obtained as a yellow solid, was diluted with dry toluene (15 mL). To the resulting solution was added **4** (3.0 g, 6.89 mmol) in dry toluene (15 mL), followed by addition of TMSOTf (2.26 mL, 11.7 mmol). The solution was refluxed for 1 hours under argon atmosphere, then diluted with ethyl acetate (200 mL), washed with a saturated aqueous sodium hydrogen carbonate solution (100 mL), and with water (2 × 100 mL). The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of ethyl acetate (15–20%) in methylene chloride] to afford pure **16** (1.56 g, 42%) as a beige foam.

¹H-NMR (DMSO-*d*₆): δ 8.36 (s, 1H, H-8), 8.0–7.4 (m, 5H, C₆H₅CO), 7.04 (brs, 2H, NH₂), 6.30 (d, 1H, H-1', J_{1'-2'} = 6.0 Hz), 6.10 (t, 1H, H-2', J_{1'-2'} = J_{2'-3'} = 6.1 Hz), 6.02 (d, 1H, H-3', J_{2'-3'} = 6.2 Hz), 4.63 dd (2H, H-5', H-5'', J = 11.6 Hz, J = 46, 4 Hz), 3.82 (dd, 2H, H-6', H-6'', J = 61.5 Hz), 2.18 (s, 3H, CH₃CO₂), 2.05 (s, 3H, CH₃CO₂); MS (matrix GT): FAB > 0 *m*/*z* 545 (M+H)⁺, 376 (S)⁺, 170 (BH₂)⁺, 105 (C₆H₅CO)⁺, 43 (CH₃CO)⁺ FAB < 0 *m*/*z* 543 (M-H)⁻, 168 (B)⁻, 121 (C₆H₅CO₂)⁻, 59 (CH₃CO₂)⁻.

9-(4-C-Azidomethyl- β -D-ribofuranosyl)guanine (17)

To a solution of **16** (810 mg, 1.49 mmol) in dry methanol (30 mL) was added 2-mercaptoethanol (0.418 mL, 5.96 mmol) and sodium methoxide (322 mg, 5.96 mmol). The reaction mixture was stirred at reflux overnight under argon atmosphere, neutralized with Dowex 50 W × 2 resin (H⁺ form) and concentrated under reduced pressure. The residue was partitioned between methylene chloride (70 mL) and water (50 mL). The aqueous layer was washed with methylene chloride (50 mL), with ethyl acetate (50 mL), filtered and evaporated to dryness. The crude residue was purified by chromatography on LiChroprep RP-18 [eluent: stepwise gradient of acetonitrile (0–7%) in water] to afford pure **17** (155 mg, 31%). Crystallization from water gave **17** as a crystalline solid.

m.p.: 242–243°C (dec.); UV (ethanol): $\lambda_{max} = 252 \text{ nm}$ ($\varepsilon = 14600$), $\lambda_{shoulder} = 268 \text{ nm}$ ($\varepsilon = 10200$), $\lambda_{min} = 221 \text{ nm}$ ($\varepsilon = 3000$); ¹H-NMR (DMSO- d_6): δ 10.64 (s, 1H, NH), 8.22 (s, 1H, H-8), 6.47 (sl, 2H, NH₂), 5.75 (d, 1H, H-1', $J_{1'-2'} = 7.9 \text{ Hz}$), 5.47 (d, 1H, OH, OH-2', $J_{OH-2'} = 6.7 \text{ Hz}$), 5.37 (d, 1H, OH-3', $J_{OH-3'} = 4.3 \text{ Hz}$), 5.23 (t, 1H, OH, OH-5', $J_{OH-5'} = J_{OH-5''} = 5.4 \text{ Hz}$), 4.69 (dd, 1H, H-2', J = 7.1 Hz, J = 12.3 Hz), 4.12 (t, 1H, H-3', $J_{3'-2'} = J_{3'-OH'} = 4.5 \text{ Hz}$), 3.58–3.50 (m, 4H, H-5', H-5'', H-6', H-6''); MS (matrix GT): FAB > 0 m/z 677 (2M+H)⁺, 339 (M+H)⁺, 152 (BH₂)⁺, FAB < 0 m/z 337 (M-H)⁻, 150 (B)⁻; Anal. Calcd (C₁₁H₁₄N₈O₅.1.5 H₂O): C 36.16, H 4.69, N 30.68. Found: C 36.87, H 5.20, N 30.66.

9-(4-*C*-Azidomethyl- β -D-ribofuranosyl)-2-amino-6-cyclopropylaminopurine (18)

A solution of **16** (750 mg, 1.37 mmol) in methanolic ammonia (previously saturated at -10° C) (28 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (5–6%) in dichloromethane] to afford the intermediate 9-(4-*C*-azidomethyl- β -D-ribofuranosyl)2-amino-6-chloropurine as a white solid (355 mg, 0.995 mmol). This intermediate was treated with cyclopropylamine (0.482 ml, 6.97 mmol) in dry ethanol (20 ml) at reflux overnight. The solvents were evaporated under reduced pressure and the residue was purified by chromatography on LiChroprep RP-18, using a stepwise gradient of acetonitrile (0–15%) in water and lyophilized to give **18** (330 mg, 64%, 2 steps) as a white powder.

¹H-NMR (DMSO-*d*₆): δ 8.57 (s, 1H, H-8), 8.19 (s, 1H, NH), 5.82 (sl, 2H, NH₂), 5.77 (d, 1H, H-1', J_{1'-2'} = 7.9 Hz), 5.62 (brs, 1H, OH-5'), 5.43 (brs, 1H, OH-2'), 5.37 (brs, 1H, OH-3'), 4.79 (dd, 1H, H-2', J = 5.0 Hz, J = 7.7 Hz), 4.12 (d, 1H, H-3', J = 4.9 Hz), 3.61–3.33 (m, 4H, H-5', H-5'', H-6', H-6''), 3.05 (brs, 1H, CH), 0.69–0.57 (m, 2H, CH₂-CH₂); MS (matrix GT): FAB > 0 *m/z* 755 (2M+H)⁺, 378 (M+H)⁺, 191 (BH₂)⁺, FAB < 0 *m/z* 753 (2M-H)^{-,} 376 (M-H)^{-,} 189 (B)⁻.

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