Azido/Tetrazole Tautomerism in 2-Azidoadenine β-D-Pentofuranonucleoside Derivatives

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The β-D-ribofuranoside derivative of 2-azidoadenine and its 2′-deoxy-, 2′,3′-dideoxy- and 2′,3′-dideoxy-2′,3′-didehydro counterparts have been synthesized. All these compounds were obtained through the preparation of their 2-chloro precursors. These were converted into their 2-hydrazino derivatives, which upon treatment with sodium nitrate in acid medium gave the target nucleosides. The azido/tetrazole tautomerism observed in such nucleoside analogues was studied in detail. The compounds were also tested for their activity against HIV and HBV, but did not show significant antiviral effects.

Introduction

Some adenosine analogues substituted at the 2-position show interesting biological properties.[1] 2-Chloroadenosine derivatives, for instance, exhibit potent antitumor and antiviral activities, as demonstrated by 2-chloro-2′-deoxyadenosine (Cladribine),[2] 2-chloro-2′,3′-dideoxyadenosine,[3] and 2-chloro-2′,3′-dideoxy-2′,3′-didehydroadenosine.[3] In efforts to discover new nucleoside derivatives endowed with antiviral activity, modifications of the base and/or sugar moiety of natural nucleosides can be attempted. According to the literature, little attention has been paid to structural modifications containing a pseudohalogen such as an azido group[4] at the 2-position of the base adenine. As a part of our ongoing research program on this topic, we have synthesized various β-D-pentofuranonucleoside derivatives bearing 2-azidoadenine as the base. The first synthesis of 2-azidoadenosine (**6**) was reported in 1958,[5] while the synthesis of 2-azido-2′-deoxyadenosine (**7**) was described during the course of our studies,[6] although no antiviral evaluation was reported. We thus decided to undertake the synthesis of the β-D-ribofuranoside derivative of 2-azidoadenine and its 2′-deoxy-, 2′,3′-dideoxy- and 2′,3′-dideoxy-2′,3′-didehydro counterparts in order to perform the antiviral evaluation of the whole series. We have also observed azido/tetrazole tautomerism in 2-azidoadenine nucleoside derivatives and present here a more thorough investigation on such tautomerism. In particular, the structures of the observed tautomers were fully established from ^{1}H and ^{13}C NMR spectra.

Results and Discussion

Syntheses of 2-azidoadenosine (**6**)[7] and 2-azido-2′-deoxyadenosine (**7**),[6] starting from a 2-amino-6-chloropurine riboside derivative or 2′-deoxyguanosine by treatment with trimethylsilyl azide in the presence of isoamyl or butyl nitrite, respectively, have been reported previously. For our purposes, we chose to synthesize the 2-azidoadenine nucleoside derivatives from their 2-chloro counterparts (Scheme 1). The synthesis of 2-azidoadenosine (**6**) was carried out by a modification of Schaeffer's procedure.[5] In brief, a glycosylation reaction between 2,6-dichloropurine and commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (**1**) with stannic chloride[8] as a catalyst gave the corresponding protected nucleoside, which upon treatment with methanolic ammonia afforded 2-chloroadenosine (**2**). This was converted into the 2-hydrazino derivative, which on treatment with sodium nitrite in an acid medium gave the first target molecule, **6**. 2-Chloroadenosine (**2**) was converted into its 2′-deoxynucleoside counterpart through simultaneous protection of the 3′- and 5′-hydroxy groups with dichlorotetraisopropyldisiloxane[9] (TIPDSCl$_2$). A Barton−McCombie-type radical reductive process[10] and deprotection of the intermediate with ammonium fluoride provided 2-chloro-2′-deoxyadenosine (**3**).[11] Compound **3** was selectively converted into the 5′-*O*-TBDMS derivative, which was subjected to a second radical reductive process. Finally, deprotection with ammonium fluoride gave 2-chloro-2′,3′-dideoxyadenosine (**4**).[3,12] Additionally, the 2-chloro-2′,3′-unsaturated nucleoside **5** was also obtained

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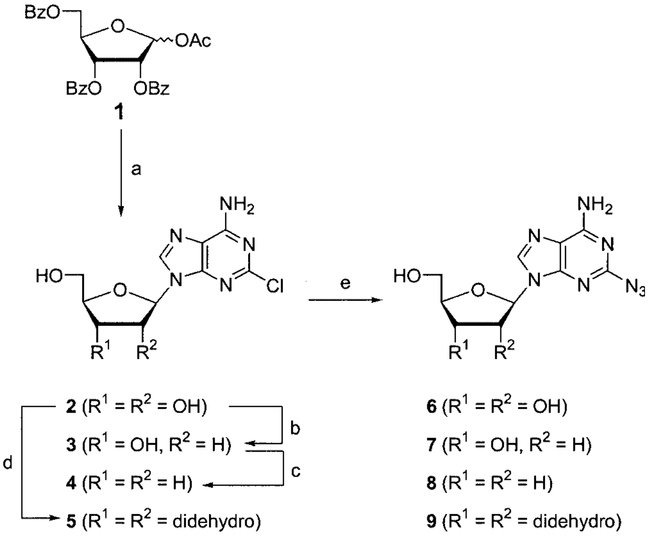

Scheme 1. a) i) 2,6-Dichloropurine, $SnCl_4$, CH_3CN, room temp., ii) $MeOH/NH_3$, room temp.; b) i) TIPSCl, pyridine, room temp., ii) DMAP, PhO(C=S)Cl, CH_3CN, room temp., iii) $(Me_3Si_3)SiH$, AIBN, dioxane, reflux, iv) NH_4F, MeOH, reflux; c) i) TBDMSCl, imidazole, pyridine, room temp., ii) DMAP, PhO(C=S)Cl, CH_3CN, room temp., iii) $(Me_3Si_3)SiH$, AIBN, dioxane, reflux, iv) NH_4F, MeOH, reflux; d) i) TBDMSCl, imidazole, pyridine, room temp., ii) 1,1′-thiocarbonyldiimidazole, CH_3CN, room temp., iii) 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine, THF, room temp., iv) TBAF on silica gel, THF, room temp.; e) i) H_2NNH_2, H_2O, room temp., ii) aq. AcOH, $NaNO_2$, 0 °C

from 2-chloroadenosine. After selective 5′-*O*-TBDMS protection and treatment with 1,1′-thiocarbonyldiimidazole, the resultant 2′,3′-thiocarbonate was subject to a Corey−Winter-type reaction to afford the protected unsaturated derivative, which upon treatment with TBAF on silica gel gave the target compound **5**.[3] Finally, compounds **3−5** were converted into their 2-hydrazino derivatives, which gave the target molecules **7−9** on treatment with sodium nitrite in an acid medium.

The physicochemical properties of the β-D-pentofuranonucleoside derivatives **6−9** of 2-azidoadenine were examined in detail. The infrared spectra in pressed potassium bromide and DMSO exhibit azido absorption bands between 2120 and 2150 cm^{-1}. The UV spectra are in accordance with those previously reported for compound **6** and elemental analyses are consistent with the proposed structures. However, the ^1H and ^{13}C NMR spectra in each case show the presence of two compounds, implying the existence of tautomeric forms of the 2-azidoadenine nucleoside derivatives. It is noteworthy that the existence of such tautomeric forms has also been mentioned in the cases of the previously reported compounds **6**[7] and **7**.[6]

Indeed, azido-substituted π-deficient nitrogen heterocycles with an azido group attached to a carbon atom adjacent to an annular nitrogen atom may spontaneously cyclize to give a fused tetrazole ring, or at least an equilibrium mixture of both forms.[13] The equilibrium is dependent on the presence of electron-withdrawing substituents or electron-donating groups on the ring. As a general rule, electron-withdrawing substituents promote the azido form, while electron-donating groups enhance ring closure and stabilize the tetrazole form. The bigger this capacity, the stronger is the N−N bond and the more stable is the tetrazole form. The equilibrium is also dependent on the temperature. Cleavage of the tetrazole ring is generally an endothermic process, which explains why high temperatures favor the azido form at the expense of the tetrazole form. Finally, the tautomerism is also determined by the physical state the substance is in and by the solvent. In polar solvents the equilibrium is in general displaced towards the tetrazole form, and in non-polar solvent towards the azido species. Such azido/tetrazole tautomerism has previously been reported for the base 2-azidoadenine.[14] This base has been shown to exist in DMSO solution in the form of 6-amino-2-azidopurine (A form) in balance with the tetrazole forms 8-aminotetrazolo[1,5-*a*]purine (T*a* form) and 5-aminotetrazolo[5,1-*b*]purine (T*b* form) in the proportions of 43, 41 and 16%, respectively. Tautomeric assignments were based upon the chemical shifts of the protons of the imidazole ring and exocyclic amine. With regard to the azido/tetrazole tautomerism of 2-azidoadenine nucleoside derivatives, three forms can be expected (A, T*a*, and T*b*) (Figure 1). Such an observation has previously been reported in the case of nucleotide derivatives of 2-azidoadenosine.[15,16] In our case, according to the physicochemical properties of the β-D-pentofuranonucleoside derivatives of 2-azidoadenine (**6−9**), two forms were observed (A and either T*a* or T*b*). For our determination of which tetrazole form was present, we based our judgement on ^1H NMR studies of nucleosides **6−9** and mainly on the chemical shifts of protons of the imidazole ring and exocyclic amine. The ^1H NMR spectroscopic data are shown in Table 1. Two sets of signals are found: one at high field and another at low field. The high-field set is assigned to the azido form, the low-field to the tetrazole form. This difference is due to a shield-

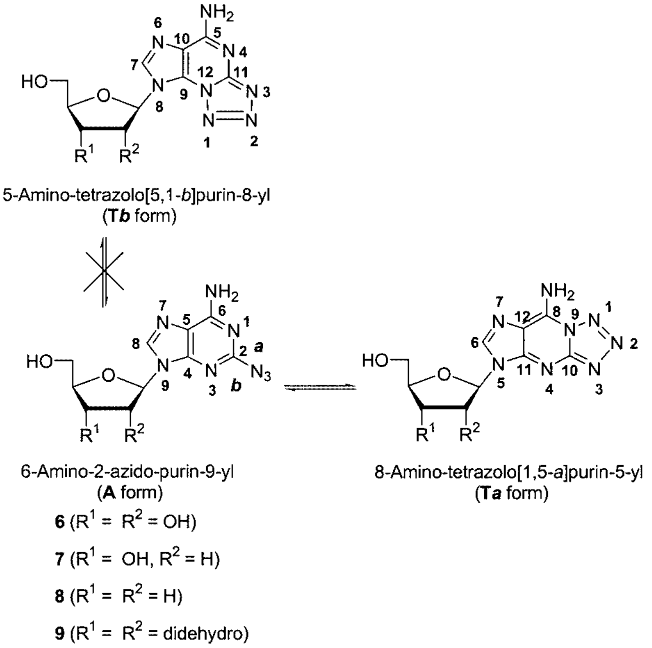

Figure 1. Numbering according to IUPAC nomenclature

Table 1. ^{1}H NMR chemicals shifts (δ, ppm) of protons of the imidazole ring and exocyclic amine (numbering according to IUPAC nomenclatur) for the A and T*a* tautomeric forms of compounds **6−9** at 298 K

	Compound **6**		Compound **7**		Compound **8**		Compound **9**	
Form A	8-H, 8.28	6-NH_2, 7.67	8-H, 8.25	6-NH_2, 7.60	8-H, 8.29	6-NH_2, 7.60	8-H, 8.08	6-NH_2, 7.58
Form T*a*	6-H, 8.56	8-NH_2, 9.46	6-H, 8.53	8-NH_2, 9.40	6-H, 8.59	8-NH_2, 9.40	6-H, 8.35	8-NH_2, 9.39
Δδ[a] (ppm)	0.28	1.79	0.28	1.80	0.30	1.80	0.27	1.81
Ratio[b] A/T*a*	67:33		65:35		67:33		66:34	

[a] Δδ (ppm) show the chemical shift difference between 6-H/8-H and 8-NH_2/6-NH_2. [b] Ratio determined by integration of 8-H and 6-H protons.

ing effect of the electron-donating azido group, while the electron-withdrawing tetrazole group produces a deshielding effect. Interestingly, the chemical shift differences (Δδ) between the protons of exocyclic amine group of both forms, as well as the protons of the imidazole ring, exhibit similar values of $\delta \approx 0.3$ and 1.8 ppm, respectively. A larger deshielding effect of the tetrazole ring occurs on the exocyclic amine group, as shown with $\Delta\delta \approx 1.8$ ppm, if the form is the T*a* one resulting from a cyclisation on the *a* face and in position 1 of the purine. Similar observations have been made in the case of the base 2-azidoadenine in order to discriminate between the A, T*a*, and T*b* forms.[14] At ambient temperature, the ratio determined by integration of the imidazole protons 8-H and 6-H has been shown to be around 2:3:1:3 in favor of the azido species for compounds **6−9**. Further evidence in favor of the presence of the T*a* form was also obtained from ^{13}C NMR spectroscopic data. Indeed, the azido/tetrazole tautomerism in aromatic nitrogen heterocycles produces characteristic changes in the ^{13}C NMR chemical shifts,[17,18] which can be used for tautomeric determinations. While the chemical shifts of C-2, C-4, C-5, C-6, and C-8 for the A forms of compounds **6−9** do not differ much from those of adenine, striking differences are observed for the T*a* forms. In particular, C-11 and C-12 (IUPAC nomenclature, corresponding to C-4 and C-5 in the purine ring) exhibit downfield chemical shift differences of around 9 and 5 ppm, respectively. The presence of a T*b* form should have provided chemical shifts similar to C-4 and C-5 of the purine ring for C-9 and C-10 (IUPAC nomenclature).

We have also examined the solvent effect on the equilibrium between the azido A form and tetrazole T*a* form by ^{1}H NMR spectroscopy. As a model, we chose 2-azidoadenosine (**6**). DMSO and MeOH were used as solvents on account of solubility problems with compound **6**. As the polarity of the solvent decreases, the percentage of the azido form increases strongly, as demonstrated by the A/T*a* ratio (92:8) observed in MeOH (with a dielectric constant $\varepsilon = 32.7$) in contrast with the A/T*a* ratio (67:33) seen in DMSO ($\varepsilon = 47$). This effect is probably due to the contribution of the enthalpy of solvation, which reflects the preferential stabilization of the tetrazole form, the species with the larger dipole moment. Thus, in water ($\varepsilon = 78$) a larger proportion of the tetrazole T*a* form could be expected at the expense of the azido A form. Additionally, we also examined the temperature effect on the equilibrium by means of ^{1}H NMR spectra, using the integration of the imidazole protons 8-H and 6-H. Clearly, it appears that, when the temperature is increased gradually from 25 to 100 °C, the azido form (Table 2) becomes the prominent compound, suggesting that cleavage of the tetrazole ring is an endothermic process and that high temperatures favor the azido species. Determination of the thermodynamic parameters in the equilibrium between the tetrazole T*a* form and the azido A form of compound **6** were carried out by ^{1}H NMR spectroscopy. By plotting $\ln(K_{eq}) = f(10^3/T)$ (Figure 2), the thermodynamic parameters $\Delta H°$ and $\Delta S°$ were calculated to be 4.7 kcal·mol^{-1} and 1.70 10^{-2} kcal·K^{-1}·mol^{-1}, respectively. At 298° K, $\Delta G°$ was found to be −0.38 kcal·mol^{-1}.

Table 2. Temperature effect on the equilibrium A/T*a* for compound **6** in [D$_6$]DMSO

T [K]	Compound **6** (ratio[a] A/T*a*)	K_{eq}[b]
298	67:33	2.03
323	77:23	3.35
348	85:15	5.67
373	91:9	10.11

[a] Ratio determined by means of the integration of 8-H and 6-H protons. [b] K_{eq} = A/T*a*.

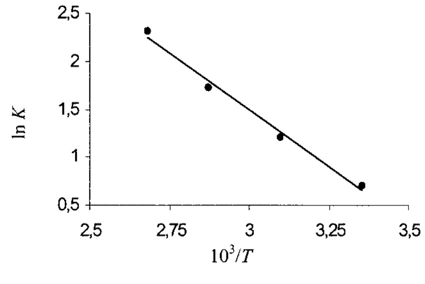

Figure 2. Plotting of $\ln K_{eq} = -\Delta H°/(RT^{-1}) + \Delta S°/R$; *T* [K], R = 1.986 cal·mol^{-1}·K^{-1}

All the nucleosides **6−9** were tested for their in vitro inhibitory effects on the replication of HIV-1 in MT-4 cells. However, none of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (generally 100 μM). When evaluated in anti-HBV assays in HepG2 cells, none of the tested compounds showed significant antiviral effect (up to a concentration of 10 μM) nor cytotoxicity (up to the same concentration of 10 μM).

Conclusion

The syntheses of the β-D-ribofuranoside derivative of 2-azidoadenine and its 2′-deoxy-, 2′,3′-dideoxy- and 2′,3′-dideoxy-2′,3′-didehydro counterparts were undertaken with the hope of discovering new nucleoside derivatives endowed with antiviral effects. The azido/tetrazole tautomerism observed in such nucleoside analogues was studied in detail. However, none of the target compounds exhibited significant antiviral activity. Several factors could be responsible for the inactivity of these nucleoside derivatives. 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, could all account for their antiviral inactivity.

Experimental Section

General Remarks: Evaporation of solvents was carried out in a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes with a Gallenkamp MFB-595-010 M apparatus and are uncorrected. UV spectra were recorded with a Uvikon 931 (Kontron) spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, in $(CD_3)_2SO$ at ambient temperature with a Bruker DRX 400. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak, $(CD_3)(CD_2H)SO$ being set at $\delta_H = 2.49$ ppm and $\delta_C = 39.5$ ppm relative to tetramethylsilane (TMS). Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in Hz. 2D ^{1}H-^{13}C heteronuclear COSY data were recorded for the attribution of ^{13}C signals. FAB mass spectra were recorded in the positive-ion or negative-ion modes with a JEOL SX 102. The matrix was a mixture (50:50, v/v) of glycerol and thioglycerol (G-T) or 3-nitrobenzyl alcohol (NBA). IR spectra were recorded with a Perkin−Elmer FT-IR spectrometer paragon 1000. Specific rotations were measured with a Perkin−Elmer Model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} deg·cm^2·g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbency followed by charring with 5% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385). All moisture-sensitive reactions were carried out under rigorous anhydrous conditions under argon using oven-dried glassware. Solvents were dried and distilled prior to use and solids were dried with P_2O_5 under reduced pressure.

2-Chloro-9-(β-D-ribofuranosyl)adenine (2):[5] M.p. (from ethanol) 145−147 °C (ref.[5] 142 °C). $[\alpha]_D^{20} = -52.1$ (*c* = 1.17 in DMSO). UV (95% EtOH): λ_{max} (ε) = 263 nm (16400). ^{1}H NMR: δ = 3.64−3.53 (m, 2 H, 5′-H and 5"-H), 3.92 (m, 1 H, 4′-H), 4.10 (t, *J* = 3.8 Hz, 1 H, 3′-H), 4.50 (m, 1 H, 2′-H), 5.05 (dd, *J* = 5.7, 5.3 Hz, 1 H, 5′-OH), 5.19 (d, *J* = 4.8 Hz, 1 H, 3′-OH), 5.47 (d, *J* = 6.1 Hz, 1 H, 2′-OH), 5.80 (d, *J* = 5.9 Hz, 1 H, 1′-H), 7.84 (s, 2 H, 6-NH$_2$), 8.37 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 62.2 (C-5′), 71.2 (C-3′), 74.4 (C-2′), 86.5 (C-4′), 88.2 (C-1′), 119.0 (C-5), 140.9 (C-8), 151.2 (C-4), 153.8 (C-2), 157.7 (C-6) ppm. MS (FAB): *m*/*z* = 302 [M + H]$^+$, 300 [M − H]$^-$. $C_{10}H_{12}ClN_5O_4 \cdot 3/4\ H_2O$ (315.20): calcd. C 38.11, H 4.32, Cl 11.25, N 22.22; found C 38.25, H 4.36, Cl 10.95, N 22.10.

2-Chloro-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)adenine (3):[11] M.p. (from ethanol) 208−210 °C (ref.[11] 210−215 °C). $[\alpha]_D^{20} = -23.5$ (*c* = 1.15, DMSO). UV (95% EtOH): λ_{max} (ε) = 263 nm (19900). ^{1}H NMR: δ = 2.27 (m, 1 H, 2"-H), 2.63 (m, 1 H, 2′-H), 3.54 (m, 2 H, 5′-H and 5"-H), 3.84 (m, 1 H, 4′-H), 4.37 (m, 1 H, 3′-H), 4.95 (dd, *J* = 5.7, 5.5 Hz, 1 H, 5′-OH), 5.29 (d, *J* = 4.1 Hz, 1 H, 3′-OH), 6.25 (dd, *J* = 7.2, 6.4 Hz, 1 H, 1′-H), 7.80 (s, 2 H, 6-NH$_2$), 8.34 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 40.6 (C-2′), 62.5 (C-5′), 71.6 (C-3′), 84.4 (C-1′), 88.8 (C-4′), 119.0 (C-5), 140.7 (C-8), 150.9 (C-4), 153.8 (C-2), 157.6 (C-6) ppm. MS (FAB): *m*/*z* = 286 [M + H]$^+$, 284 [M − H]$^-$. $C_{10}H_{12}ClN_5O_3 \cdot 1/6H_2O$ (288.67): calcd. C 41.62, H 4.30, Cl 12.29, N 24.27; found C 41.92, H 4.44, Cl 12.12, N 23.92.

2-Chloro-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)adenine (4):[3] M.p. (from ethanol) 228−230 °C (ref.[3] 240 °C). $[\alpha]_D^{20} = -33.3$ (*c* = 1.02, DMSO). UV (95% EtOH): λ_{max} (ε) = 263 nm (15500). ^{1}H NMR: δ = 2.02 (m, 2 H, 3′-H and 3"-H), 2.37 (m, 2 H, 2′-H and 2"-H), 3.58 (m, 2 H, 5′-H and 5"-H), 4.09 (m, 1 H, 4′-H), 4.92 (dd, *J* = 4.5, 5.3 Hz, 1 H, 5′-OH), 6.13 (m, 1 H, 1′-H), 7.76 (s, 2 H, 6-NH$_2$), 8.36 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 26.3 (C-3′), 32.6 (C-2′), 63.5 (C-5′), 82.8 (C-4′), 85.2 (C-1′), 118.9 (C-5), 140.3 (C-8), 150.7 (C-4), 153.7 (C-2), 157.6 (C-6) ppm. MS (FAB): *m*/*z* = 270 [M + H]$^+$, 268 [M − H]$^-$. $C_{10}H_{12}ClN_5O_2$ (269.06): calcd. C 44.54, H 4.48, Cl 13.15 N 25.97; found C 44.47, H 4.46, Cl 13.04, N 25.61.

2-Chloro-9-(2,3-dideoxy-β-D-*glycero*-pent-2-ene-furanosyl)adenine (5):[3] M.p. (from methanol/dichloromethane) 198−200 °C (ref.[3] 200−205 °C). $[\alpha]_D^{20} = -27.7$ (*c* = 1.01, DMSO). UV (95% EtOH): λ_{max} (ε) = 263 nm (15800). ^{1}H NMR: δ = 3.56 (m, 2 H, 5′-H and 5"-H), 4.87 (m, 1 H, 4′-H), 4.91 (t, *J* = 5.2 Hz, 1 H, 5′-OH), 6.12 (dd, *J* = 1.5, 4.3 Hz, 1 H, 3′-H), 6.47 (dd, *J* = 1.4, 5.9 Hz, 1 H, 2′-H), 6.84 (d, *J* = 1.0 Hz, 1 H, 1′-H), 7.79 (s, 2 H, 6-NH$_2$), 8.15 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 63.5 (C-5′), 88.8 (C-1′), 89.1 (C-4′), 118.7 (C-5), 126.0 (C-3′), 135.5 (C-2′), 140.5 (C-8), 151.1 (C-4), 154.0 (C-2), 157.7 (C-6) ppm. MS (FAB): *m*/*z* = 268 [M + H]$^+$, 266 [M − H]$^-$. $C_{10}H_{10}ClN_5O_2 \cdot 1/5H_2O$ (271.28): calcd. C 44.28, H 3.86, Cl 13.07, N 25.82; found C 44.29, H 3.92, Cl 13.07, N 25.74.

2-Azido-9-(β-D-ribofuranosyl)adenine (6):[5] Compound **2** (0.296 g, 0.98 mmol) was added to a solution of hydrazine monohydrate (5 mL). The reaction mixture was stirred at room temperature for 16 h. The solution was diluted with 2-propanol and the solvents were evaporated to dryness. The residue was dissolved in a 5% aqueous acetic acid solution (12 mL) and cooled in an ice bath, and sodium nitrite (0.097 g, 1.47 mmol) was then added. The reaction mixture was stirred for 1 h. The white precipitate was collected by filtration, washed with water, and dried with P_2O_5 at 80 °C for 24 h to give **6** (0.184 g, 61%), m.p. 166−168 °C (ref.[5] 158−160 °C). $[\alpha]_D^{20} = -30.5$ (*c* = 1.02, DMSO). UV (95% EtOH): λ_{max} (ε) = 268 nm (20700). IR (KBr): $\tilde{\nu}$ = 2144 cm^{-1}; (DMSO): $\tilde{\nu}$ = 2126 cm^{-1}. MS (FAB): *m*/*z* = 309 [M + H]$^+$, 307 [M − H]$^-$. $C_{10}H_{12}N_8O_4 \cdot 8/5H_2O$ (337.08): calcd. C 35.63, H 4.55, N 33.24; found C 35.83, H 3.99, N 32.82. **Azido Tautomer:** ^{1}H NMR: δ = 3.91−3.62 (m, 2 H, 5′-H and 5"-H), 3.91 (m, 1 H, 4′-H), 4.11 (t, *J* = 3.5 Hz, 1 H, 3′-H), 4.54 (m, 1 H, 2′-H), 5.05 (t, *J* = 5.4 Hz, 1 H, 5′-OH), 5.17 (d, *J* = 4.5 Hz, 1 H, 3′-OH), 5.43 (d, *J* = 6.0 Hz, 1 H, 2′-OH), 5.78 (d, *J* = 5.9 Hz, 1 H, 1′-H), 7.67 (s, 2 H, 6-NH$_2$), 8.28 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 62.4 (C-5′), 71.3 (C-3′), 74.2 (C-2′), 86.5 (C-4′), 88.2 (C-1′), 117.8 (C-5), 140.4 (C-8), 151.4

(C-4), 156.4 (C-2), 157.5 (C-6) ppm. **Tetrazole Tautomer:** ^{1}H NMR: δ = 3.91−3.62 (m, 2 H, 5′-H and 5"-H), 3.96 (m, 1 H, 4′-H), 4.17 (t, J = 4.2 Hz, 1 H, 3′-H), 4.54 (m, 1 H, 2′-H), 5.12 (t, J = 5.1 Hz, 1 H, 5′-OH), 5.21 (d, J = 4.8 Hz, 1 H, 3′-OH), 5.51 (d, J = 5.9 Hz, 1 H, 2′-OH), 5.95 (d, J = 5.3 Hz, 1 H, 1′-H), 8.56 (s, 1 H, 6-H), 9.42 (s, 1 H, 8-NH$_2$) ppm. ^{13}C NMR: δ = 62.0 (C-5′), 71.0 (C-3′), 74.4 (C-2′), 86.3 (C-4′), 88.3 (C-1′), 112.3 (C-12), 141.9 (C-11), 143.6 (C-6), 153.0 (C-10), 154.6 (C-8) ppm.

2-Azido-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)adenine (7): Compound **3** (0.205 g, 0.72 mmol) was added to a solution of hydrazine monohydrate (10 mL). The reaction mixture was kept at room temperature for 16 h. The solution was concentrated to dryness and co-evaporated with 2-propanol (3 × 20 mL) until a white gum was obtained. The residue was dissolved in a 10% aqueous acetic acid solution (10 mL) and then cooled in an ice bath. Sodium nitrite (0.075 g, 1.1 mmol) was added, and the reaction mixture was stirred for 1 h. The solid was collected by filtration, washed with water, and dried with P$_2$O$_5$ at 80 °C to give compound **7** (0.192 g, 91%), m.p. 181−182 °C. $[\alpha]_D^{20}$ = −25.6 (c = 0.78, DMSO). UV (95% EtOH): λ_{max} (ε) = 268 nm (18800). IR (KBr): $\tilde{\nu}$ = 2146 cm^{-1}; (DMSO): $\tilde{\nu}$ = 2124 cm^{-1}. MS (FAB): m/z = 293 [M + H]$^+$, = 291 [M − H]$^-$. $C_{10}H_{12}N_8O_3 \cdot 2/5H_2O$ (299.46): calcd. C 40.11, H 4.31, N 37.42; found C 40.50, H 4.24, N 37.10. **Azido Tautomer:** ^{1}H NMR: δ = 2.27 (m, 1 H, 2"-H), 2.65 (m, 1 H, 2′-H), 3.56 (m, 2 H, 5′-H and 5"-H), 3.83 (m, 1 H, 4′-H), 4.36 (m, 1 H, 3′-H), 4.95 (t, J = 5.6 Hz, 1 H, 5′-OH), 5.29 (d, J = 4.1 Hz, 1 H, 3′-OH), 6.22 (dd, J = 7.3, 6.5 Hz, 1 H, 1′-H), 7.60 (s, 2 H, 6-NH$_2$), 8.25 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 39.9 (C-2′), 62.6 (C-5′), 71.7 (C-3′), 84.3 (C-1′), 88.7 (C-4′), 117.7 (C-5), 140.1 (C-8), 151.1 (C-4), 156.3 (C-2), 157.5 (C-6) ppm. **Tetrazole Tautomer:** ^{1}H NMR: δ = 2.27 (m, 1 H, 2"-H), 2.65 (m, 1 H, 2′-H), 3.56 (m, 2 H, 5′-H and 5"-H), 3.88 (m, 1 H, 4′-H), 4.42 (m, 1 H, 3′-H), 5.00 (t, J = 5.5 Hz, 1 H, 5′-OH), 5.33 (d, J = 4.1 Hz, 1 H, 3′-OH), 6.38 (t, J = 6.8 Hz, 1 H, 1′-H), 8.53 (s, 1 H, 6-H), 9.40 (s, 2 H, 8-NH$_2$) ppm. ^{13}C NMR: δ = 39.7 (C-2′), 62.4 (C-5′), 71.5 (C-3′), 84.3 (C-1′), 88.7 (C-4′), 112.3 (C-12), 141.8 (C-11), 153.5 (C-6), 156.3 (C-2), 157.5 (C-6) ppm.

2-Azido-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)adenine (8): Compound **4** (0.269 g, 1 mmol) was added to a solution of hydrazine monohydrate (14 mL). The reaction mixture was stirred at room temperature for 16 h. The solution was concentrated to dryness and co-evaporated with 2-propanol (3 × 30 mL) until a white gum was obtained. The residue was dissolved in a 5% acetic acid solution (15 mL) and then cooled in an ice bath. Sodium nitrite (0.108 g, 1.5 mmol) was added, and the reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with methanol/dichloromethane (1:9) as eluent to afford compound **8** (0.205 g, 74%), which was crystallized from water, m.p. 198−200 °C. $[\alpha]_D^{20}$ = −20.5 (c = 1.27, DMSO). UV (95% EtOH): λ_{max} (ε) = 268 nm (16200). MS (FAB): m/z = 277 [M + H]$^+$, 275 [M − H]$^-$. IR (KBr): $\tilde{\nu}$ = 2142 cm^{-1}; (DMSO): $\tilde{\nu}$ = 2128 cm^{-1}. $C_{10}H_{12}N_8O_2$ (276.11): calcd. C 43.48, H 4.38, N 40.56; found C 43.54, H 4.53, N 40.36. **Azido Tautomer:** ^{1}H NMR: δ = 2.06 (m, 2 H, 3′-H and 3"-H), 2.39 (m, 2 H, 2′-H and 2"-H), 3.56 (m, 2 H, 5′-H and 5"-H), 4.10 (m, 1 H, 4′-H), 4.94 (m, 1 H, 5′-OH), 6.13 (m, 1 H, 1′-H), 7.60 (s, 2 H, 6-NH$_2$), 8.29 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 26.6 (C-3′), 32.4 (C-2′), 63.7 (C-5′), 82.6 (C-4′), 85.0 (C-1′), 117.6 (C-5), 139.8 (C-8), 150.8 (C-4), 154.8 (C-2), 157.4 (C-6) ppm. **Tetrazole Tautomer:** ^{1}H NMR: δ = 2.06 (m, 2 H, 3′-H and 3"-H), 2.39 (m, 2 H, 2′-H and 2"-H), 3.56 (m, 2 H, 5′-H and 5"-H), 4.10 (m, 1 H, 4′-H), 5.02 (m, 1 H, 5′-OH), 6.30 (m, 1 H, 1′-H), 8.59 (s, 1 H, 6-H), 9.40 (s, 2 H, 8-NH$_2$), ^{13}C NMR: δ = 26.2 (C-3′), 32.6 (C-2′), 63.4 (C-5′), 82.7 (C-4′), 85.2 (C-1′), 112.5 (C-12), 142.4 (C-6), 142.5 (C-11), 152.0 (C-10), 157.2 (C-8) ppm.

2-Azido-9-(2,3-dideoxy-β-D-*glycero*-pent-2-ene-furanosyl)adenine (9): Compound **5** (0.350 g, 1.3 mmol) was added to a solution of hydrazine monohydrate (16 mL). The reaction mixture was stirred at room temperature for 16 h. The solution was concentrated to dryness and co-evaporated with 2-propanol (3 × 30 mL) until a white gum was obtained. The residue was dissolved in a 2% acetic acid solution (15 mL) and then cooled in an ice bath. Sodium nitrite (0.300 g, 4.3 mmol) was added, and the reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography with a stepwise gradient of methanol (0−6%) in dichloromethane to afford compound **9** (0.205 g, 75%), which was crystallized from methanol, m.p. 182−184 °C. $[\alpha]_D^{20}$ = −39.1 (c = 0.64, DMSO). UV (95% EtOH): λ_{max} (ε) = 268 nm (16200). MS (FAB): m/z = 275 [M + H]$^+$, 273 [M − H]$^-$. IR (KBr): $\tilde{\nu}$ = 2144 cm^{-1}; (DMSO): $\tilde{\nu}$ = 2128 cm^{-1}. $C_{10}H_{10}N_8O_2 \cdot 1/7H_2O$ (276.94): calcd. C 43.37, H 3.75, N 40.46; found C 43.80, H 3.93, N 40.05. **Azido Tautomer:** ^{1}H NMR: δ = 3.55 (m, 2 H, 5′-H and 5"-H), 4.86 (m, 1 H, 4′-H), 4.91 (t, J = 5.3 Hz, 1 H, 5′-OH), 6.11 (d, J = 5.9 Hz, 1 H, 3′-H), 6.45 (d, J = 5.9 Hz, 1 H, 2′-H), 6.81 (s, 1 H, 1′-H), 7.58 (s, 2 H, 6-NH$_2$), 8.08 (s, 1 H, 8-H) ppm. ^{13}C NMR: δ = 63.6 (C-5′), 88.6 (C-1′), 88.9 (C-4′), 117.3 (C-5), 126.1 (C-3′), 135.3 (C-2′), 139.8 (C-8), 151.3 (C-4), 156.4 (C-2), 157.5 (C-6) ppm. **Tetrazole Tautomer:** ^{1}H NMR: δ = 3.59 (m, 2 H, 5′-H and 5"-H), 4.86 (m, 1 H, 4′-H), 4.96 (t, J = 5.4 Hz, 1 H, 5′-OH), 6.16 (d, J = 5.9 Hz, 1 H, 3′-H), 6.50 (d, J = 5.9 Hz, 1 H, 2′-H), 7.00 (s, 1 H, 1′-H), 8.35 (s, 1 H, 6-H), 9.39 (s, 2 H, 8-NH$_2$) ppm. ^{13}C NMR: δ = 63.4 (C-5′), 88.5 (C-1′), 89.0 (C-4′), 112.0 (C-12), 126.1 (C-3′), 135.6 (C-2′), 141.8 (C-11), 143.5 (C-6), 152.9 (C-10), 154.7 (C-8) ppm.

Biological Evaluation: The anti-HIV and anti-HBV assays on cell culture were performed by previously established procedures.[19]

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