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Synthesis and biological evaluation of 6-substituted purine and 9-β-D-ribofuranosyl purine analogues

Jun-Feng Wang, Liang-Ren Zhang, Zhen-Jun Yang and Li-He Zhang*

National Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, China

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Abstract—6-Substituted purine and 9-β-D-ribofuranosyl purine analogues were synthesized and their biological activities were evaluated. CD Spectra and thermal melting studies showed that compounds **8**, **9**, **10** could interact with RNA and DNA in solution. Compound **8** and **10** may bind with RNA single strand and interfere the formation of RNA duplex. Among of these compounds, compound **8** showed middle inhibition on the growth of HeLa cells (70.21%) and HL-60 cells (70.85%) at 10 μM. Comparing to the structures of these synthetic compounds, it may indicate that the sugar moiety and the 6-amino side chain of nucleoside **8** play an important role in the biological activities.

1. Introduction

Aminoglycoside antibiotics have long been used as very efficient drugs against Gram-positive and Gram-negative bacteria, and against mycobacterial infections. These molecules are multiply charged compounds of high flexibility. The positive charges are attracted to the negatively charged RNA backbone. The flexibility of the aminoglycosides facilitates accommodation into a binding pocket within internal loops of RNA helices or into ribozyme cores for making specific contacts. On the basis of the study of RNA in the presence of aminoglycosides and other small molecules, the interactions of RNA with small molecules are affected by the distribution of charged, aromatic, and H-bonding groups of a relatively rigid scaffold.[1–5] Furthermore, the structure of RNA is dynamic, and the conformational change can be induced by a small molecule. Nucleoside analogues play an important role in the antiviral and anticancer chemotherapy. Most of these nucleosides act as inhibitors of varied enzymes by disrupting the synthesis of nucleic acids.[6] It would be interesting to study whether the modified nucleosides could be used as a site-directing moiety towards RNA. Some aminoglycosyl-nucleosides and peptide-conjugated nucleosides have been synthesized in our laboratory and showed the high affinity of interaction with RNA.[7–9] In our previous works, all of the modifications focus on the sugar moiety of nucleosides. Here, we reported the synthesis and biological evaluation of 6-substituted purine and 9-β-D-ribofuranosyl purine analogues. CD Spectra and thermal melting studies showed that compounds **8**, **9**, **10** could interact with RNA and DNA in solution. Among of these compounds, 6-(2′-aminoethyl)-9-β-D-ribofuranosyl purine **8** showed the interesting growth inhibition to HeLa cells and HL-60 cells in vitro.

2. Results and discussion

6-(2′-Aminoethyl)-9H-purine **3** and 6-(2′-butylaminoethyl)-9H-purine **4b** were synthesized starting from 6-chloropurine.[10] For the substitution at 6- position, 6-chloropurine was protected by benzyl group first, but the reaction gave a mixture of N-7 and N-9 benzyl protected 6-chloropurine. After the further reaction, the *N*-benzyl group was very difficult to remove. However, the 6-chloropurine was selectively protected by DHP, the N-9 protected 6-chloropurine was in 89% yield and the tetrahydropyran-2-yl group can be deprotected smoothly after reaction. Therefore, the protected 6-chloropurine **1** was vinylated via a Pd (II)-catalyzed Stille-coupling

Abbreviations: CD, circular dichroism spectrum; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; DHP, 3,4-dihydro-2H-pyran; HMPT, hexamethylphosphorous triamide; DMF, dimethylformamide; NMR, nuclear magnetic resonance; DMSO, dimethyl sulfoxide; CSA, D(+)-10-Camphorsulfonic acid; EDTA, ethylenediaminetetraacetic acid.

* Corresponding author. E-mail: zdszlh@bjmu.edu.cn

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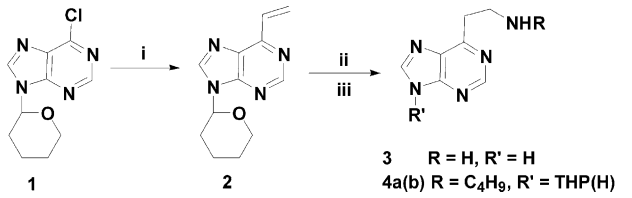


Scheme 1. Regents and conditions: (i) $(PhP_3)_2PdCl_2$, tributylvinyltin, DCE, reflux; (ii) NH_3/CH_3OH or n-butylamine/DCM, rt; (iii) DCM/CH_3OH, 1M HCl, rt.

reaction and 6-vinyl-9-(tetrahydropyran-2-yl)-purine **2** was obtained in 84% yield.[11] Nucleophilic addition to the terminal olefin of 6-vinyl purine **2** with ammonia or n-butylamine and followed deprotection gave **3** (78%) and **4b** (70%) respectively (Scheme 1). For the synthesis of 6-substituted 9-β-D-ribofuranosyl purine analogues, inosine was reacted with Ac_2O in pyridine, then 2′,3′,5′-tri-*O*-acetyl-inosine **5** was treated with CCl_4, HMPT in CH_3CN at reflux and 6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purine **6** was obtained in 60% yields.[12] Similar reaction as described in the synthesis of compound **2**, 6-vinyl 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purine **7** was obtained from compound **6** in 85% yield by treatment with $(Ph_3P)_3PdCl_2$, tributylvinyltin in DMF at 100 °C.[13] Nucleophilic addition to 6-vinylpurine nucleoside **7** with ammonia or aniline or sodium methoxide in methanol and then deprotection gave 6-(2′-aminoethyl)-9-β-D-ribofuranosylpurine **8** (79%), 6-(2′-anilinoethyl)-9-β-D-ribofuranosyl purine **9** (66%) and 6-(2′-methoxyethyl)-9-β-D-ribofuranosylpurine **10** (54%) respectively.[14] (Scheme 2).

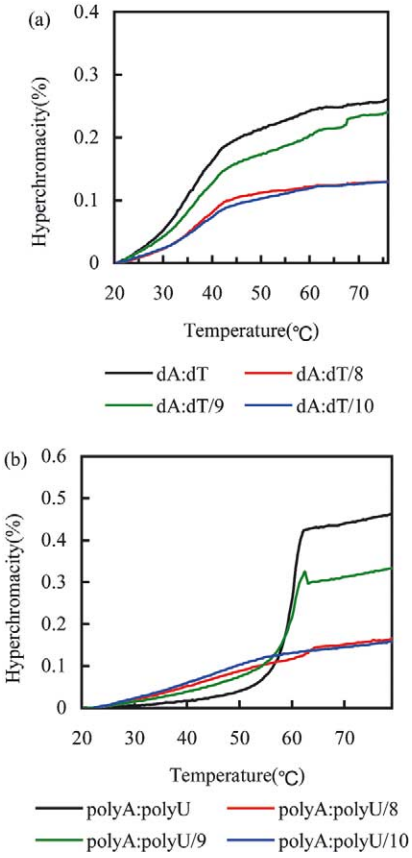
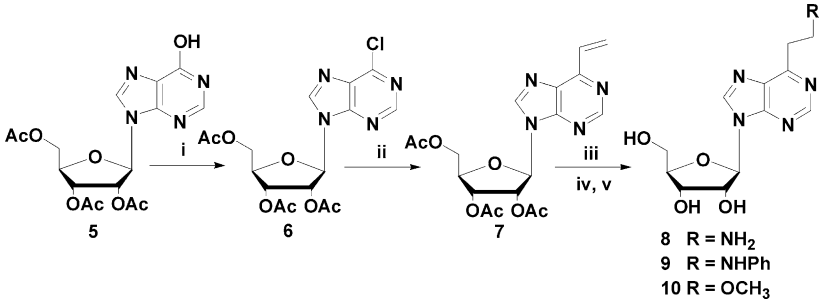


Figure 1. (a) and (b). Thermal melting curves of dA_{14}/dT_{14} (a) and polyA/polyU (b) in the absence or presence of synthetic 6-Substituted 9-β-D-ribofuranosyl purine analogues.

It has been demonstrated that the total number of amino groups and aromatic substitutions in the aminoglycoside are correlated with the activities of RNA binding and modify gene expression.[15,16] In order to explore the biological properties of compounds **8**, **9**, **10**, the interaction of 6-modified nucleoside analogues with dA_{14}/dT_{14} duplex and polyA/polyU duplex were studied by thermal denaturation and CD spectra (Figs 1 and 2). The stability of RNA (DNA) duplex was affected by the integrated effects of hydrogen bonding, stacking and electrostatic interactions between RNA (DNA) and small molecule.[17–20] It was found that compounds **8**, **9**, **10** effected significantly the stabilities of duplex both of DNA and RNA. Melting curves showed that compounds **8**, **9**, **10** resulted in an increase of melting temperature of DNA duplex with an extent of 2.5 to 6.0 °C, it indicated that the binding of those compounds could enhance the duplex stabilities (Fig. 1a, Table 1). The decreases of hyperchromicity were also observed in all cases. CD Spectra showed that the 6-substituted 9-β-D-ribofuranosyl purine analogues did not make obvious effect to the configuration of DNA duplex (Fig. 2a). Melting curves showed that compound **9** resulted in no change of melting temperature of RNA (Table 1). By contrast with the results in the case of DNA, no obvious melting behavior of RNA duplexes was observed in the presence of compounds **8** and **10** (Fig. 1b). It implied that the stable complex of RNA single strand with compound **8** or **10** was formed in this condition, which hindered the formation of stable RNA duplex. However, the melting curve and temperature of RNA in the presence of compound **9** showed the existence of duplex



Scheme 2. Regents and conditions: (i) CCl_4, HMPT, ACN, 70 °C; (ii) $(Ph_3P)_2PdCl_2$, tributylvinyltin, DMF, 100 °C; (iii) for compd **8**, NH_3/CH_3OH, rt; (iv) for compd **9**, a. CSA, Aniline, DCM, rt; b. $NaOCH_3/CH_3OH$, rt; (v) for compd **10**, CSA, $NaOCH_3/CH_3OH$, rt.

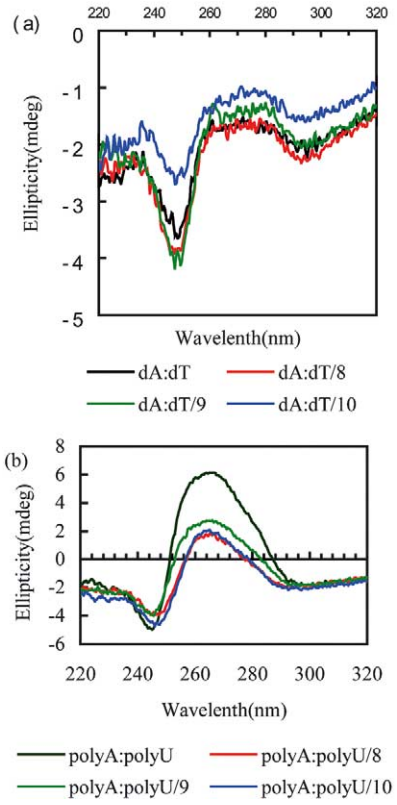


Figure 2. (a) and (b). CD spectra of dA_{14}/dT_{14} (a) and polyA/polyU (b) in the absence or presence of synthetic 6-substituted 9-β-D-ribofuranosyl purine analogues.

(Fig. 1b, Table 1). The anilino group in compound **9** may contribute the aromatic interaction with RNA duplex. CD Spectra showed the significant changes of intensity in all of these compounds (Fig. 2b), the rearrangement in the configuration of RNA duplex may occur in the presence of compounds **8**, **9**, **10**.[21] The synthetic compounds **3**, **4b**, **8**, **9**, **10** were screened by culture of tumor cells (Table 2),[22,23] only compound **8** exhibited inhibition effects on the growth of HeLa cells (70.21%) and HL-60 cells (70.85%) at 10 μM. Comparing to the structures of compounds **3**, **8** and **10**, it may indicate that the sugar moiety and the 6-amino side chain of nucleoside **8** play an important role in the biological activity.

In summary, 6-substituted purine and 9-β-D-ribofuranosyl purine derivatives were synthesized and the interaction of 6-substituted 9-β-D-ribofuranosyl purine derivatives with polyA/polyU duplex and dA_{14}/dT_{14} duplex were studied by thermal denaturation and CD spectra. It was found that compounds **8**, **9**, **10** could enhance the duplex stability of DNA, but compounds **8** and **10** may bind with RNA single strand and interfere the formation of RNA duplex. Among of these compounds, compound **8** showed the middle inhibition on the growth of HeLa cells (70.21%) and HL-60 cellc (70.85%) at 10 μM. Comparing to the structures of these synthetic compounds, it may indicate that the sugar moiety and the 6-amino side chain of nucleoside **8** play an important role in the biological activities.

Table 2. Inhibition on the growth of various tumor cells by compound **8**

	Tumor cell line	conc (μM)	Inhibition rate
1	HeLa(SRB)	1	–8.76%
		10	70.21%
		100	83.49%
2	HL-60 (MTT)	1	–6.91%
		10	70.85%
		100	79.62%
3	BGC-823 (SRB)	1	–8.94%
		10	0.64%
		100	35.49%
4	Bel-7420 (SRB)	1	–23.79%
		10	7.29%
		100	59.76%

3. Experimental

Thin-layer chromatography was performed by using silica gel GF-254 (Qing Dao Chemical Company, China) plates with detection by UV. NMR spectra were recorded on Varian-300 or Varian INOVA-500 instrument with TMS as an internal standard. The structural positions of the synthetic compounds are numbered as described in Notes.[24] PE SCLEX QSTAR and Autospec-Ultima ETOF spectrometers were used for mass spectra. Melting points were determined on an XT-4Amelting point apparatus and are uncorrected.

3.1. 6-(2′-Aminoethyl)-9H-purine (3)

Compound **2** (373 mg, 1.6 mmol) was dissolved in 50 mL of saturated NH_3/CH_3OH solution and stirred at room temperature for 21 h. The solvent was evaporated and CH_2Cl_2/CH_3OH (3 mL:30 mL) was added to the residue. 1M HCl was added to the resulting solution and stirring was continued overnight. A solution of 2N $NaOH/H_2O$ was added to adjust the solution to PH = 12 and the solvent was evaporated to dryness. The residue was dissolved with MeOH and the undissolved salt was filtered. The filtrate was evaporated and

Table 1. Melting temperatures of polyA/polyU duplex and dA_{14}/dT_{14} duplex in the absence or presence of synthetic 6-substituted 9-β-D-ribofuranosyl purine analogues

PolyA/polyU/compd	T_m (°C)	ΔT_m (x°C)	dA_{14}/dT_{14}/compd	T_m (°C)	ΔT_m (x°C)
PolyA/polyU	60.97		dA_{14}/dT_{14}	35.00	
PolyA/polyU/**8**	—	—	dA_{14}/dT_{14}/**8**	40.99	5.99
PolyA/polyU/**9**	60.97	0	dA_{14}/dT_{14}/**9**	37.51	2.51
PolyA/polyU/**10**	—	—	dA_{14}/dT_{14}/**10**	41.01	6.01

separated with silica gel column. 215 mg (78%) of **3** was obtained as a white solid. Mp 240 °C (dec). HRMS (TOF) calcd for $C_7H_{10}N_5$ (MH^+): 164.0930; found: 164.0932. ^{1}H NMR(DMSO) δ: 3.36 (t, 1H, $H_{2'}$), 3.46 (t, 1H, $J_{1',2'}$ = 7.5 Hz, $H_{1'}$), 8.56 (s, 1H, H_2), 8.80 (s, 1H, H_8) ; ^{13}C NMR (DMSO) δ: 30.74 ($C_{2'}$), 38.35 ($C_{1'}$), 130.73 (C_5), 146.55 (C_8), 153.23 (C_4), 154.95 (C_2), 156.50 (C_6).

3.2. 6-(2′-Butylaminoethyl)-9-(tetrahydro-pyran-2-yl)-purine (4a)

Compound **2** (707 mg, 3.1 mmol) was dissolved in 30 mL of dry CH_2Cl_2, and *n*-butylamine (3.04 mL, 30.8 mmol) was added under stirring. After stirring at ambient temperature for 25 h, the solution was evaporated and the residue was separated with a silica gel column. Compound **4a** (830 mg, 89%) was collected as a light yellow oil. EI: 303. ^{1}H NMR(DMSO) δ: 0.94 (t, 3H, butyl), 1.42–1.92 (m, 4H, butyl), 1.42–1.92 (m, 6H, THP), 3.11 (t, 2H, butyl), 3.59 (t, 1H, $H_{2'}$), 3.82 (t, 1H, $J_{1',2'}$ = 6.6 Hz, $H_{1'}$), 4.18 (d, 2H, THP), 5.79 (d, 1H, THP), 8.39 (s, 1H, H_2), 8.84 (s, 1H, H_8); ^{13}CNMR (DMSO) δ: 13.27 (butyl), 19.72, 22.39, 24.50, 28.39, 31.37 (butyl and THP), 45.11 (butyl), 47.50 ($C_{2'}$), 49.88 ($C_{1'}$), 81.91 (THP), 131.78 (C_5), 142.43 (C_8), 149.80 (C_4), 151.85 (C_2), 157.44 (C_6).

3.2.1. 6-(2′-Butylaminoethyl)-9H-purine (4b). Compound **3** (810 mg, 2.6 mmol) was dissolved in a solution of CH_2Cl_2/CH_3OH (3 mL/30 mL), and 1M HCl (7 mL) was added. After stirred at ambient temperature for 3 h, the solution was neutralized with saturated $NaHCO_3$/H_2O and evaporated. The residue was purified by a silica gel column, which gave compound **4b** (426 mg, 72%) as a white solid. Mp 145–147 °C. HRMS (TOF) calcd for $C_{11}H_{18}N_5$ (MH^+): 220.1556; found: 220.1543. ^{1}H NMR (DMSO) δ: 0.87 (t, 3H, butyl), 1.32 (m, 2H, butyl), 1.62 (m, 2H, butyl), 2.94 (t, 2H, butyl), 3.55 (m, 1H, $H_{2'}$), 3.70 (t, 1H, $J_{1',2'}$ = 7.5 Hz, $H_{1'}$), 8.45 (s, 1H, H_2), 8.77 (s, 1H, H_8), 9.33 (br, 1H, Base –NH–); ^{13}C NMR (DMSO) δ: 13.50 (butyl), 19.34, 27.44 (butyl), 41.36 (butyl), 44.06 ($C_{2'}$), 46.43 ($C_{1'}$), 131.88 (C_5), 144.18 (C_8), 150.68 (C_4), 151.65 (C_2), 156.32 (C_6).

3.3. 6-Vinyl-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranosyl)—purine (7)

A solution of compound **6** (0.84 g, 2.1 mmol) and (PhP_3) $PdCl_2$ (99 mg, 0.14 mmol) in 30 mL of DMF was treated with tributylvinyltin (1.15 mL, 3.94 mmol) under argon, and stirring was continued for 2.5 h at 100 °C. The solution was evaporated and separated with a silica gel column. Compound **7** (700 mg, 85%) was collected as a light yellow oil. ^{1}H NMR($CDCl_3$) δ : 2.03 (s, 3H, –OAc), 2.08 (s, 3H, –OAc), 2.11 (s, 3H, –OAc), 4.36–4.51 (m, 3H, $H_{4''}$, $H_{5''}$), 5.61 (t, 1H, $J_{3'',4''}$ = 4.8 Hz, $H_{3''}$), 5.89 (t, 1H, $J_{2'',3''}$ = 5.4 Hz, $H_{2''}$), 6.05 (d, 1H, $J_{1'',2'a}$ = 10.5 Hz, $H_{2'a}$), 6.23 (d, 1H, $J_{1'',2''}$ = 5.4 Hz, $H_{1''}$), 7.14 (d, 1H, $J_{1',2'b}$ = 17.4 Hz, $H_{2'b}$), 7.31 (dd, 1H, $H_{1'}$), 8.28 (s, 1H, H_2), 8.91 (s, 1H, H_8); ^{13}CNMR($CDCl_3$) δ: 62.90 ($C_{5''}$), 70.48 ($C_{3''}$), 73.10 ($C_{2''}$), 80.48 ($C_{4''}$), 86.39 ($C_{1''}$), 129.65 ($C_{2'}$), 130.06 ($C_{1'}$), 131.23 (C_5), 143.75 (C_8), 151.08 (C_4), 151.98 (C_2), 152.70 (C_6), 169.31 (CO), 169.51 (CO), 170.18 (CO).

3.4. 6-(2′-Aminoethyl)-9-β-D-ribofuranosyl-purine (8)

Compound **7** (90 mg, 0.2 mmol) was dissolved in 25 mL of saturated NH_3/CH_3OH solution. After stirred at ambient temperature in a sealed vessel for 22 h, the mixture was evaporated and purified by a silica gel column. Compound **8** (54 mg, 79%) was obtained as a white solid. Mp 182–184 °C. HRMS (TOF) calcd for $C_{12}H_{18}N_5O_4$ (MH^+): 296.1353; found: 296.1368. ^{1}H NMR ($CDCl_3$) δ: 3.51 (br, 4H, $H_{1',2'}$), 3.51 (br, 2H, –NH_2), 3.76 (dd, 1H, $H_{5''}$), 3.90 (dd, 1H, $H_{5''}$), 4.18 (d, 1H, $J_{4'',5''}$ = 2.5 Hz, $H_{4''}$), 4.33 (dd, 1H, $J_{3'',4''}$ = 2.5 Hz, $H_{3''}$), 4.75 (t, 1H, $J_{2'',3''}$ = 5.0 Hz, $H_{2''}$), 5.96 (d, 1H, $J_{1'',2''}$ = 6.5 Hz, $H_{1''}$), 8.19 (s, 1H, H_2), 8.20 (s, 1H, H_8) ; ^{13}C NMR($CDCl_3$) δ: 39.02 ($C_{2'}$, $_{1'}$), 63.51 ($C_{5''}$), 72.68 ($C_{3''}$), 75.22 ($C_{2''}$), 88.12 ($C_{4''}$), 91.20 ($C_{1''}$), 121.98 (C_5), 140.17 (C_8), 150.65 (C_4), 152.65 (C_2), 156.23 (C_6).

3.5. 6-(2′-Anilinoethyl)-9-β-D-ribofuranosylpurine (9)

Compound **7** (295 mg, 0.75 mmol) was dissolved in 15 mL of CH_2Cl_2 and CSA (173 mg, 0.75 mmol), aniline (0.12 mL, 1.21 mmol) were added to the solution under stirring. After stirred at room temperature for 2 h, the solution was evaporated and the residue was dissolved in 15 mL of CH_3OH. Catalytic amount of $NaOCH_3$/CH_3OH solution (5.4 mol/L) was added and stirring was continued at room temperature for 3 h. The mixture was evaporated and separated with a silica gel column. Compound **9** (185 mg, 66%) was obtained as a slight yellow solid. HRMS (TOF) calcd for $C_{18}H_{22}N_5O_4$ (MH^+): 372.1666; found: 372.1666. ^{1}H NMR($CDCl_3$) δ: 3.38 (t, 2H, $J_{1',2'}$ = 7.2 Hz, $H_{1'}$), 3.59 (t, 2H, $J_{1',2'}$ = 7.2 Hz, $H_{2'}$), 3.72 (dd, 1H, $H_{5''b}$), 3.85 (dd, 1H, $H_{5''a}$), 4.11 (d, 1H, $H_{4''}$), 4.32 (t, 1H, $J_{3'',4''}$ = 3.6 Hz, $H_{3''}$), 4.67 (t, 1H, $J_{2'',3''}$ = 5.1 Hz, $H_{2''}$), 6.06 (d, 1H, $J_{1'',2''}$ = 5.4 Hz, $H_{1''}$), 8.67 (s, 1H, H_2), 8.77 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$) δ: 32.61 ($C_{2'}$), 41.44 ($C_{1'}$), 61.37 ($C_{5''}$), 70.43 ($C_{3''}$), 73.72 ($C_{2''}$), 85.79 ($C_{4''}$), 87.68 ($C_{1''}$), 112.18 (2C, PH), 115.91 (PH), 129.03 (2C, PH), 132.98 (C_5), 144.35 (C_8), 148.54 (PH), 150.40 (C_4), 151.91 (C_2), 159.72 (C_6).

3.6. 6-(2′-Methoxyethyl)-9-β-D-ribofuranosylpurine (10)

Compound **7** (166 mg, 0.48 mmol) was dissolved in 20 mL of CH_2Cl_2 and CSA (100 mg, 0.42 mmol) was added. The solution was stirred at room temperature for 10 min and a solution of $NaOCH_3$/CH_3OH (15.4 mmol/2.8 mL) was added. After stirred at room temperature overnight, the mixture was evaporated and purified with a silica gel column. Compound **10** (80 mg, 54%) was collected. HRMS (TOF) calcd for $C_{13}H_{19}N_4O_5$ (MH^+): 311.1349; found: 311.1346. ^{1}H NMR ($CDCl_3$) δ: 3.31 (s, 3H, $-OCH_3$), 3.33 (t, 2H, $J_{1',2'}$ = 6.6 Hz, $H_{1'}$), 3.89 (t, 2H, $J_{1',2'}$ = 6.6 Hz, $H_{2''}$), 3.56 (m, 1H, $H_{5''b}$), 3.68 (dd, 1H, $H_{5'a}$), 4.17 (d, 1H, $J_{4'',5''}$ = 4.2 Hz, $H_{4''}$), 4.64 (dd, 1H, $J_{3'',4''}$ = 5.7 Hz, $H_{3''}$), 5.12 (t, 1H, $J_{2'',3''}$ = 5.1 Hz, $H_{2''}$), 6.01 (d, 1H, $J_{1'',2''}$ = 6.0 Hz, $H_{1''}$), 8.77 (s, 1H, H_2), 8.84 (s, 1H, H_8) ; ^{13}C NMR ($CDCl_3$) δ: 42.30 ($C_{1'}$),

61.40 ($C_{5''}$), 57.82 ($C_{2'}$), 69.82 (–OCH_3), 70.46 ($C_{3''}$), 73.70 ($C_{2''}$), 85.82 ($C_{4''}$), 87.66 ($C_{1''}$), 133.15 (C_5), 144.33 (C_8), 150.37 (C_4), 151.81 (C_2), 159.29 (C_6).

3.7. Circular dichroism and thermal melting measurements

CD spectra were recorded by JASCO J-720 spectropolarimeter at 4 °C in thermostatically controlled 1-cm cuvette. Thermal denaturation studies of polyA/polyU and dA_{14}/dT_{14} were conducted on Varian Cray 300. CD spectra and T_m values in the absence and presence of synthetic nucleoside were determined in buffer containing 10 mM Na_2HPO_4. 0.14 M NaCl, 1.0 mM EDTA (PH 7.2). The solution containing synthetic nucleoside was mixed with equimolar per nucleotide amount of polyA and polyU (or dA and dT). The concentration of synthetic compound was 10 and 20 μM in the case of CD and thermal melting measurements, respectively.

3.8. Assays for the inhibition on the growth of various tumor cells

Growth inhibition of the synthetic compounds to various tumor cells were determined by MTT and SRB assays.[22,23] Briefly, tumor cells ($1–2.5\times10^4$ cells·mL^{-1}) were inoculated in 96-well culture plates (180 μL/well). After 24 h culture, 20 μL of culture medium containing synthetic compound of various concentrations were added to the wells, and RPMI-1640 medium in control cells, then the cells were incubated for 48 h. The growth inhibition of HL-60 cells were determined by MTT method, and the other cell lines were assayed by SRB method. The absorbance of each well was measured using a microculture plate reader at 570 nm (MTT) and 540 nm (SRB).

Acknowledgements

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24. In this paper, the structural positions of 6-substituted purine and 9-β-D-ribofuranosyl purine analogues are numbered as follows: for the 6-substituted purine, a single prime numbering scheme is used for the position of 6-side chain of purine; for the 6-substituted 9-β-D-ribofuranosyl purine, a single prime numbering scheme is used for the position of 6-side chain of purine and a double prime numbering scheme is used for the position of the N-9 ribosyl moiety.