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Synthesis and Binding Affinity of Homologated Adenosine Analogues as A_3 Adenosine Receptor Ligands

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Homologated analogues **3a** and **3b** of potent and selective A_3 adenosine receptor ligands, IB-MECA and dimethyl-IB-MECA were synthesized from commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**) *via* $Co_2(CO)_8$-catalyzed siloxymethylation as a key step. Unfortunately, homologated analogues **3a** and **3b** did not show significant binding affinities at three subtypes of adenosine receptors, indicating that free rotation, resulting from homologation, induced unfavorable interactions in the binding site of the receptor maybe due to the presence of many conformations.

Key Words : $Co_2(CO)_8$-catalyzed siloxymethylation, A_3 adenosine receptor, Homologation

Introduction

Adenosine receptors (ARs) consisting of four subtypes, A_1, A_{2A}, A_{2B}, and A_3 play an important roles in regulating many physiological functions through binding with an endogenous adenosine.[1] Thus, A_3AR has been promising targets for the developments of new therapeutic agents against cancer, ischemia, inflammation, asthma, and glaucoma related to the signal transduction of cell.[2]

On the basis of the structure of adenosine, a number of adenosine analogues have been synthesized as AR ligands.[2] Among these, IB-MECA (**1**, N^6-(3-iodobenzyl)-5'-*N*-methylcarboxamidoadenosine)[3] has been known as one of the representative A_3AR agonists. This compound showed high binding affinity (K_i = 1.0 nM) at the human A_3AR with high selectivity to other subtypes. Compound **1** exhibited potent anticancer activity by inhibiting Wnt signaling pathway.[4]

Molecular modeling study indicates that NH of the 5'-uronamide served as a key hydrogen bonding donor in the binding site of A_3AR, which was essential for the conformational change of the binding site required for receptor activation.[5] Thus, the addition of methyl group on the 5'-uronamide of A_3AR agonist **1**, resulting in the formation of **2** (Dimethyl-Cl-IB-MECA) converted A_3AR agonist **1** into potent and selective A_3AR antagonist (K_i = 15.5 nM) because of the removal of a hydrogen bonding donor essential for the receptor activation.[6]

Introduction of the single bond between the purine base and the sugar makes the molecule adopt many conformations by free rotation, which can give a good chance to induce maximum favorable interactions in the binding site of the receptor.[7] Thus, on the basis of potent binding affinity of compounds **1** and **2** at the A_3AR, we designed and synthesized the homologated analogues **3a** and **3b** of compounds **1** and **2**, using $Co_2(CO)_8$-catalyzed siloxymethylation[8] as a key step. Herein, we report the synthesis of the homologated adenosine analogues **3a** and **3b** and their binding affinity at the A_3AR.

Results and Discussion

Our synthetic strategy was to synthesize the homologated glycosyl donor and then to condense with 6-chloropurine. The homologated glycosyl donor **6** was synthesized from

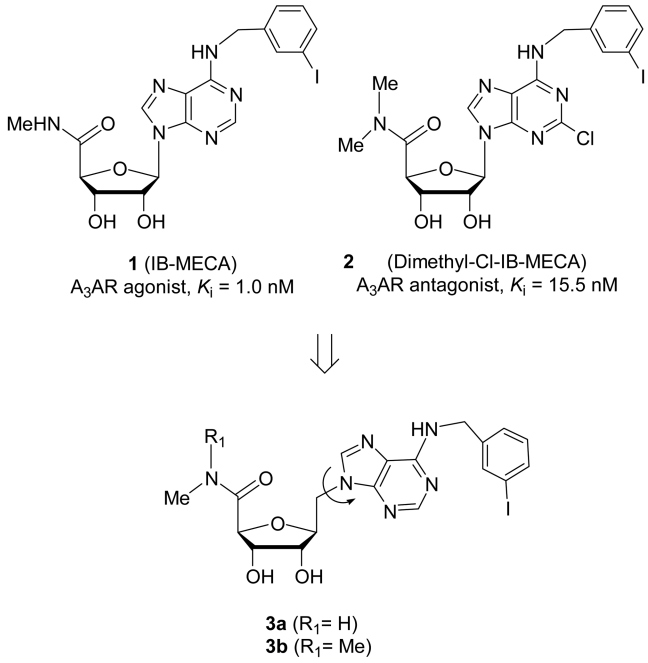
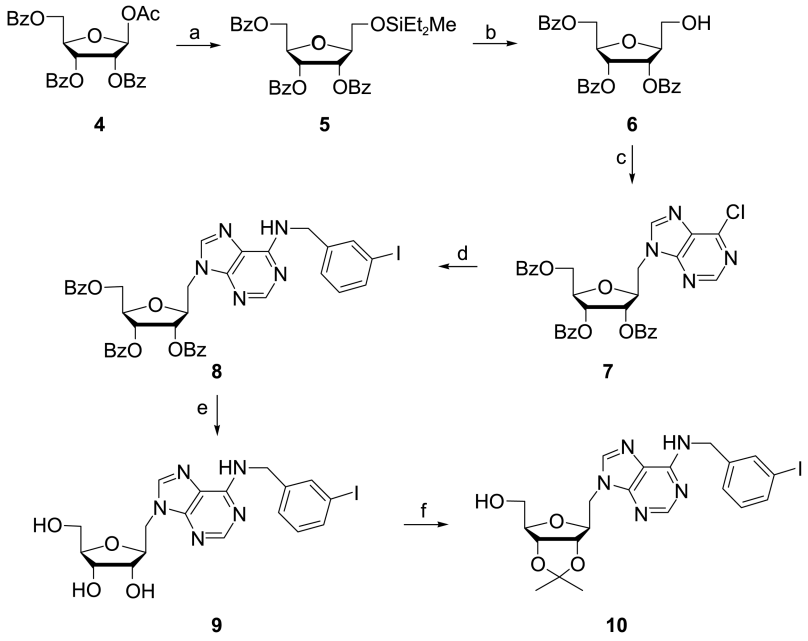


Figure 1. The rationale for the design of homologated A_3AR ligands **3a** and **3b**.



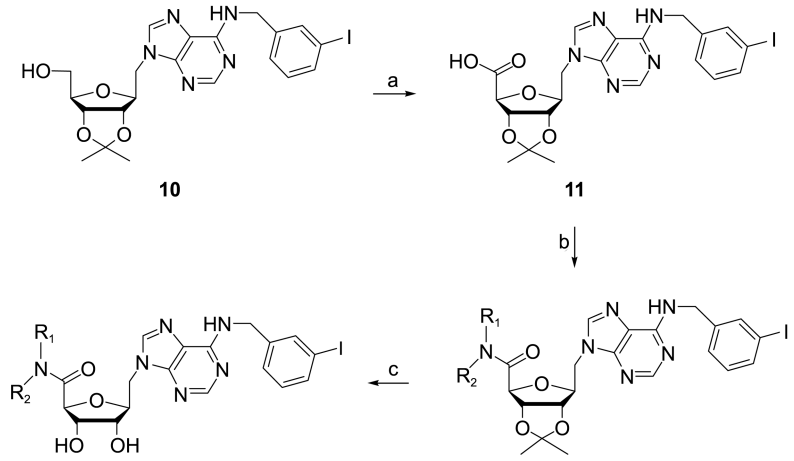
[a]Reagents & Conditions: a) $HSiEt_2Me$, CO, $Co_2(CO)_8$, CH_2Cl_2, 30 °C, 15 h, 58%; b) TBAF, THF, rt, 1 h, 84%; c) TPP, 6-chloropurine, DIAD, THF, rt, 12 h, 68%; d) 3-iodobenzylamine, Et_3N, EtOH, rt, 24 h, 82%; e) NaOMe, MeOH, rt, 1 h, 93%; f) 2,2-dimethoxypropane, *p*-TsOH, acetone, rt, 89%.

Scheme 1[a]

commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**), as shown in Scheme 1.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**) was treated with carbon monoxide and a hydrosilane ($HSiEt_2Me$) in the presence of catalytic amounts of $Co_2(CO)_8$ to give the siloxymethylated compound **5**.[8] Treatment of **5** with tetra-*n*-butylammonium fluoride (TBAF) afforded glycosyl donor **6** which is ready for the Mitsunobu condensation. Condensation of **6** with 6-chloropurine under the Mitsunobu conditions produced 6-chloropurine derivative **7**. Treatment of **7** with 3-iodobenzyl amine afforded the N^6-(3-iodobenzyl)-amine derivative **8**, which was treated with sodium methoxide to give triol **9**. Compound **9** was treated with 2,2-dimethoxypropane under acidic conditions to give acetonide **10**.

Scheme 2 illustrates the conversion of 4'-hydroxymethyl moiety into amide. Treatment of **10** with PDC in DMF afforded acid **11**, which was coupled with methylamine and dimethylamine in the presence of HOBt and EDC to give the methylamido derivative **12** and dimethylamido derivative **13**, respectively.[9] Removal of the isopropylidene moiety in **12** and **13** under acidic conditions produced the final nucleo-



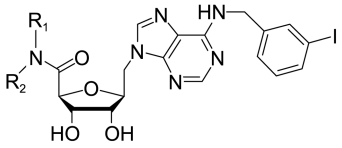
3a (R_1 = Me, R_2 = H, 92%)
3b (R_1 = R_2 = Me, 90%)

12 (R_1 = Me, R_2 = H, 64%)
13 (R_1 = R_2 = Me, 72%)

[a]Reagents and Conditions: a) PDC, DMF, rt, 20 h, 83%; b) $MeNH_2$-HCl or Me_2NH-HCl, HOBt, EDC, DIPEA, CH_2Cl_2, rt; c) 2*N* HCl, THF, rt, 12 h

Scheme 2[a]

Table 1. Binding affinities of homologated adenosine derivatives **3a** and **3b** at three subtypes of ARs



Compounds	K_i (hA_1AR)[a]	K_i ($hA_{2A}AR$)[a]	K_i (hA_3AR)[a]
	nM or % displ. at 10 μM	nM or % displ. at 10 μM	nM or % displ. at 10 μM
3a (R_1 = H, R_2 = Me)	0.3 ± 0.3%	14.0 ± 5.6%	8.7 ± 6.0%
3b (R_1 = R_2 = Me)	3.3 ± 3.3%	13.0 ± 8.2%	8.9 ± 1.8%
IB-MECA (**1**)	1620 ± 760	2910 ± 580	1.8 ± 0.7
Dimethyl-Cl-IB-MECA (**2**)	5870 ± 930	> 10,000	29.0 ± 4.9

[a]All AR experiments were performed using adherent CHO cells stably transfected with cDNA encoding the human ARs. Binding was carried out using radioligand [^{3}H]CCPA at the human A_1AR, [^{3}H]CGS 21680 at the human A_{2A}AR, or [^{125}I]I-AB-MECA at the human A_3AR. Values from the present study are expressed as mean ± s.e.m., n = 3-5.

sides **3a** and **3b**, respectively.

Radioligand binding assay was performed using adherent mammalian CHO (Chinese hamster ovary) cells stably transfected with cDNA encoding the appropriate human ARs (A_1 AR and A_3 AR in CHO cells and A_{2A} AR in HEK-293 cells), using 1 nM [^{3}H]CCPA (2-chloro-N^6-cyclopentyladenosine) for A_1AR, 10 nM [^{3}H]CGS21680 {2-[*p*-(2-carboxyethyl)-phenylethylamino]-5'-*N*-ethylcarboxamido-adenosine} for A_{2A}AR, or 0.5 nM [^{125}I]I-AB-MECA [N^6-(4-amino-3-iodobenzyl)-5'-*N*-methylcarboxamidoadenosine] for A_3AR as radioligands, respectively.[9] Values are expressed as mean ± sem, n = 3-4 (outliers eliminated), and normalized against a non-specific binder, 5'-*N*-ethylcarboxamidoadenosine (NECA, 10 μM). Percentage value indicates the percent inhibition at a fixed concentration of 10 μM.

As shown in Table 1, homologated compounds **3a** and **3b** exhibited very low binding affinities at all three subtypes of human ARs, when compared with those of IB-MECA (**1**) and dimethyl-IB-MECA (**2**), which showed potent and selective binding affinity at the human A_3AR. This result indicates that the homologation disrupted favorable binding interactions of the compound at the ARs despite free rotation. Loss of binding affinities may be attributed to many conformations caused by free rotation, some of which induced unfavorable interactions at the AR binding sites.

In summary, we have accomplished the synthesis of homologated adenosine analogues **3a** and **3b** of potent A_3AR ligands, IB-MECA and dimethyl-IB-MECA. Homologation was achieved using $Co_2(CO)_8$-catalyzed siloxymethylation. Despite their poor binding affinities at the AR, the result obtained from this study may be utilized for the identification of the binding mode of ARs.

Experimental Section

^{1}H NMR spectra ($CDCl_3$, CD_3OD, or DMSO-d_6) were recorded on Varian Unity Inova 400 MHz. Chemical shifts were reported in ppm units with TMS as the internal standard. ^{13}C NMR spectra ($CDCl_3$, CD_3OD, or DMSO-d_6) were recorded on Varian Unity Inova 100 MHz. Optical rotations were determined on Jasco in methanol or DMSO. UV spectra were recorded on U-3000 made by Hitachi in methanol or DMSO. Elemental analyses were measured on EA1110. The crude products were purified using a silica gel 60 (230-400 mesh, Merck). Reagents were purchased from Sigma Aldrich Company. All the anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to the reaction.

1-Diethylmethylsilyloxymethyl-2,3,5-tribenzoyl-β-D-ribofuranose (5). To the 250 mL of round bottomed flask flashed with CO (1atm from a stock balloon), $Co_2(CO)_8$ (752.3 mg, 1.98 mmol) and $HSiEt_2Me$ (17.2 mL, 118.8 mmol) were added at room temperature. After the reaction mixture was stirred for 10 min, a solution of **4** (20.0 g, 39.6 mmol) in anhydrous CH_2Cl_2 (80 mL) was added, and the reaction mixture was stirred at 30 °C for 15 h under CO (1atm). After the removal of the solvent, the residue was purified by silica gel column chromatography to give **5** (13.2 g, 58%) as a colorless syrup: $[\alpha]_D^{25}$ +166.9° (*c* 8.30, MeOH); HR-MS (ESI): *m/z* calcd for $C_{32}H_{37}O_8Si$ $[M+H]^+$: 577.2258; Found: 577.2230; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.62 (m, 4H), 0.96 (m, 6H), 3.88 (d, 2H, J = 3.6 Hz), 4.39 (q, 1H, J = 3.6 Hz), 4.56 (dd, 1H, J = 5.6, 11.4 Hz), 4.62 (m, 1H), 4.67 (dd, 1H, J = 3.6, 9.2 Hz), 5.69 (m, 2H), 7.31-8.08 (m, 15H); ^{13}C NMR ($CDCl_3$) δ −4.89, 6.23, 6.87, 62.93, 64.91, 73.14, 73.32, 79.02, 83.63, 128.50, 128.56, 129.36, 129.62, 129.84, 129.86, 1239.91, 133.22, 133.43, 133.46, 165.49, 165.69, 166.41; Anal. Calcd for $C_{32}H_{36}O_8Si$: C, 66.64; H, 6.29. Found: C, 66.71; H, 6.31.

1-Hydroxymethyl-2,3,5-tribenzoyl-β-D-ribofuranose (6). To a solution of **5** (12.0 g, 20.8 mmol) in anhydrous THF (100 mL) was added TBAF (25.0 mL, 25.0 mmol, 1.0 M in THF) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography to give **6** (8.35 g, 84%) as a colorless syrup: $[\alpha]_D^{25}$ +70.92° (*c* 6.50, MeOH); HR-MS (ESI): *m/z* calcd for $C_{27}H_{25}O_8$ $[M+H]^+$: 477.1549; Found: 477.1521; ^{1}H NMR ($CDCl_3$) δ 2.48 (br s, 1H), 3.82 (m, 1H), 3.94 (m, 1H), 4.38 (m, 1H), 4.59-4.72 (m, 3H), 5.69 (m, 2H), 7.36-7.96 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 61.93, 64.33, 72.18, 73.04, 80.18, 82.73, 128.60, 128.69, 129.28, 129.34, 129.74, 129.80, 129.88, 129.89, 129.92, 133.33, 133.46, 133.62, 165.61, 165.79, 166.67; Anal. Calcd for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 68.11; H, 5.06.

6-Chloro-(2,3,5-tribenzoyl-β-D-ribofuranosyl-9-ylmethyl)purine (7). To a solution of 6-chloropurine (1.77 g, 11.4 mmol) and Ph_3P (4.13 g, 15.74 mmol) in anhydrous THF (50 mL) was added DIAD (3.10 mL, 15.74 mmol) at 0 °C under N_2, and the reaction mixture was stirred for 30 min. To this mixture was added a solution of **3** (5.0 g, 10.5 mmol) in anhydrous THF (20 mL), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture

was evaporated, and the residue was purified by silica gel column chromatography to give **7** (4.39 g, 68%) as a white foam: UV (MeOH) λ_{max} 265.0 (pH 7); $[\alpha]_D^{25}$ −35.2° (*c* 14.0, MeOH); HR-MS (ESI): *m/z* calcd for $C_{32}H_{26}ClN_4O_7$ $[M+H]^+$: 613.1490; Found: 613.1460; ^{1}H NMR ($CDCl_3$) δ 4.47 (dd, 1H, *J* = 4.0, 12.0 Hz), 4.55-4.76 (m, 5H), 5.34 (dd, 1H, *J* = 6.0, 7.6 Hz), 5.60 (dd, 1H, *J* = 3.2, 5.8 Hz), 7.36-7.91 (m, 15H), 8.22 (s, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.02, 64.05, 72.33, 72.84, 78.68, 81.45, 128.73, 128.85, 129.07, 129.26, 129.74, 129.93, 131.30, 133.72, 133.86, 133.91, 146.33, 151.26, 152.20, 152.25, 165.53, 165.58, 166.17; Anal. Calcd for $C_{32}H_{25}ClN_4O_7$: C, 62.70; H, 4.11; N, 9.14. Found: C, 62.83; H, 4.16; N, 9.18.

N^6-(3-Iodobenzylamino)-(2,3,5-tribenzoyl-β-D-ribofuranosyl-9-ylmethyl)adenine (8). To a solution of 6-chloropurine derivative **7** (4.1 g, 6.68 mmol) and 3-iodobenzylamine (1.34 mL, 10.03 mmol) in EtOH (50 mL) was added Et_3N (2.79 mL, 20.04 mmol), and the reaction mixture was stirred overnight at room temperature. After evaporating the solvent, the residue was purified by silica gel column chromatography to give **8** (4.45 g, 82%) as a white foam: UV (MeOH) λ_{max} 268.5 nm (pH 7); $[\alpha]_D^{25}$ −60.46° (*c* 6.50, MeOH); HR-MS (ESI): *m/z* calcd for $C_{39}H_{33}IN_5O_7$ $[M+H]^+$: 810.1425; Found: 810.1393; ^{1}H NMR ($CDCl_3$) δ 4.48-4.80 (m, 8 H), 5.35 (dd, 1H, *J* = 5.6, 7.4 Hz), 5.59 (dd, 1H, *J* = 3.6, 5.8 Hz), 6.03 (t, 1H, *J* = 6.0 Hz), 7.04 (t, 1H, *J* = 7.6 Hz), 7.29-7.42 (m, 7 H), 7.51-7.60 (m, 4H), 7.70 (brs, 1H), 7.82 (s, 1H), 7.90-7.99 (m, 6H), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 44.54, 64.27, 72.55, 72.91, 78.85, 81.26, 127.11, 128.61, 128.66, 128.74, 129.05, 129.16, 129.50, 129.86, 129.91, 129.96, 130.54, 133.42, 133.68, 133.74, 136.69, 136.78, 141.17, 153.41, 154.57, 165.50, 165.57, 166.25; Anal. Calcd for $C_{39}H_{32}IN_5O_7$: C, 57.86; H, 3.98; N, 8.65. Found: C, 57.82; H, 4.01; N, 8.70.

N^6-(3-Iodobenzylamino)-(β-D-ribofuranosyl-9-ylmethyl)adenine (9). To a solution of **8** (4.0 g, 4.94 mmol) in MeOH (40 mL) was added NaOMe (0.934 mg, 17.29 mmol) at room temperature, and the reaction mixture was stirred for 1 h, neutralized with glacial AcOH, and evaporated. The residue was purified by silica gel column chromatography to give **9** (2.29 g, 93%) as a white solid: UV (MeOH) λ_{max} 271.1 nm (pH 7); $[\alpha]_D^{25}$ −171.0° (*c* 1.0, MeOH); mp 174-178 °C (dec); HR-MS (ESI): *m/z* calcd for $C_{18}H_{21}IN_5O_4$ $[M+H]^+$: 498.0638; Found: 498.0615; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 3.54 (dd, 1H, *J* = 3.6, 12.2 Hz), 3.66 (dd, 1H, *J* = 3.2, 12.4 Hz), 3.84 (m, 2H), 3.87 (t, 1H, *J* = 5.6 Hz), 4.11 (m, 1H), 4.30 (dd, 1H, *J* = 8.4, 14.4 Hz), 4.46 (dd, 1H, *J* = 2.8, 3.2 Hz), 4.76 (brs, 2H), 7.06 (t, 1H, *J* = 7.6 Hz), 7.37 (d, 1H, *J* = 7.6 Hz), 7.57 (d, 1H, *J* = 7.6 Hz), 7.74 (s, 1H), 8.10 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (CD_3OD + $CDCl_3$) δ 44.27, 46.91, 62.42, 72.14, 73.97, 82.89, 85.87, 94.93, 119.92, 127.68, 131.17, 137.21, 137.36, 142.51, 142.74, 153.53, 155.68; Anal. Calcd for $C_{18}H_{20}IN_5O_4$: C, 43.47; H, 4.05; N, 14.08. Found: C, 43.50; H, 4.02; N, 14.13.

N^6-(3-Iodobenzylamino)-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl-9-ylmethyl)adenine (10). To a stirred suspension of **9** (2.1 g, 4.22 mmol) and catalytic amounts of $TsOH{\cdot}H_2O$ (160 mg, 0.8 mmol) in anhydrous acetone (20 mL) was added 2,2-dimethoxypropane (0.62 mL, 5.06 mmol) at 0 °C, and the suspension was stirred at room temperature until a clean solution was achieved. The reaction mixture was treated with $NaHCO_3$ (1.42 g, 16.88 mmol) and stirred at room temperature for additional 30 min. The solid was filtered, and the filtrate was dried and purified by silica gel column chromatography to give **10** (2.03 g, 89%) as a white foam: UV (MeOH) λ_{max} 266.5 nm (pH 7); $[\alpha]_D^{25}$ −27.47° (*c* 10.7, MeOH); HR-MS (ESI): *m/z* calcd for $C_{21}H_{25}IN_5O_4$ $[M+H]^+$: 538.0951; Found: 538.0923; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.52 (s, 3H), 3.62 (dd, 1H, *J* = 2.0, 12.8 Hz), 3.71 (dd, 1H, *J* = 2.4, 12.8 Hz), 4.15 (m, 1H), 4.19 (dd, 1H, *J* = 3.2, 14.0 Hz), 4.52 (m, 1H), 4.60 (dd, 1H, *J* = 2.4, 6.2 Hz), 4.82 (brs, 2H), 4.92 (dd, 1H, *J* = 2.8, 6.4 Hz), 4.92 (dd, 1H, *J* = 2.8, 6.4 Hz), 6.07 (brs, 1H), 6.32 (brs, 1H), 7.05 (t, 1H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 7.6 Hz), 7.60 (d, 1H, *J* = 7.6 Hz), 7.72 (s, 1H), 7.76 (s, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.58, 27.30, 44.01, 46.67, 62.33, 82.83, 83.56, 85.11, 88.12, 94.79, 113.66, 127.10, 130.61, 136.78, 136.82, 139.91, 141.03, 153.07, 155.02; Anal. Calcd for $C_{21}H_{24}IN_5O_4$: C, 46.94; H, 4.50; N, 13.03. Found: C, 46.98; H, 4.52; N, 13.06.

N^6-(3-Iodobenzylamino)-(2',3'-*O*-isopropylidene-5'-*N*-methylcarboxamide-β-D-ribofuranosyl-9-ylmethyl)adenine (12). To a solution of **10** (2.0 g, 3.72 mmol) in anhydrous DMF (30 mL) was added pyridinium dichromate (14.0 g, 37.2 mmol), and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was poured into water (200 mL) and stirred at room temperature for 1 h. The precipitate was filtered, and the filter cake was washed with water (50 mL) and dried under high vacuum to give brownish solid **11** (1.70 g, 83%), which was used in the next step without further purification.

To a solution of **11** (1.0 g, 1.81 mmol), EDC (551 mg, 2.72 mmol), HOBt (367 mg, 2.72 mmol), and methylamine·HCl (183.7 mg, 2.72 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (0.946 mL, 5.43 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was evaporated, and the residue was purified by a silica gel column chromatography (hexane/EtOAc = 2:1-1:1) to give **12** (641.6 mg, 64%) as a white foam: UV (MeOH) λ_{max} 265.5 nm (pH 7); $[\alpha]_D^{25}$ −49.88° (*c* 8.20, MeOH); HR-MS (ESI): *m/z* calcd for $C_{22}H_{26}IN_6O_4$ $[M+H]^+$: 565.1060; Found: 565.1034; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.52 (s, 3H), 2.84 (d, 3H, *J* = 4.8 Hz), 4.28-4.36 (m, 3H), 4.47 (m, 1H), 4.52 (d, 1H, *J* = 2.4 Hz), 4.80 (brs, 2H), 4.94 (dd, 1H, *J* = 2.4, 6.2 Hz), 6.85 (brs, 1H), 7.00 (t, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.68 (brs, 2H), 8.36 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 25.46, 25.92, 27.44, 43.74, 46.73, 81.27, 84.18, 84.50, 86.10, 94.69, 114.75, 119.79, 126.94, 130.47, 136.60, 140.01, 141.17, 149.86, 153.24, 154.99, 170.20; Anal. Calcd for $C_{22}H_{25}IN_6O_4$: C, 46.82; H, 4.46; N, 14.89. Found: C, 46.88; H, 4.50; N, 14.92.

N^6-(3-Iodobenzylamino)-(2',3'-*O*-isopropylidene-5'-*N*,*N*-dimethylcarboxamide-β-D-ribofuranosyl-9-ylmethyl)adenine (13). Compound **13** (756.9 mg, 72%) was synthesized from **11** (1.0 g, 1.81 mmol) using dimethylamine·HCl (221.7 mg,

2.72 mmol) according to the procedure used in the preparation of compound **12**.

UV (MeOH) λ_{max} 267.0 nm (pH 7); $[\alpha]_D^{25}$ −44.67° (*c* 10.7, MeOH); HR-MS (ESI): *m/z* calcd for $C_{23}H_{28}IN_6O_4$ $[M+H]^+$: 579.1217; Found: 579.1191; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.48 (s, 3H), 2.97 (s, 3H), 3.04 (s, 3H), 4.32 (dd, 1H, *J* = 9.2, 14.2 Hz), 4.40 (dd, 1H, *J* = 4.0, 14.0 Hz), 4.56 (m, 1H), 4.69 (dd, 1H, *J* = 2.4, 6.2 Hz), 4.80 (brs, 2H), 4.83 (d, 2H, *J* = 2.0 Hz), 6.59 (t, 1H, *J* = 6.0 Hz), 7.00 (t, 1H, *J* = 8.0), 7.30 (d, 1H, *J* = 7.2 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.68 (s, 1H), 7.86 (s, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.41, 27.07, 35.95, 37.27, 43.95, 45.72, 82.63, 83.32, 83.71, 84.97, 94.68, 113.89, 119.58, 126.96, 130.44, 136.52, 136.62, 141.42, 149.56, 153.17, 154.67, 169.85; Anal. Calcd for $C_{23}H_{27}IN_6O_4$: C, 47.76; H, 4.71; N, 14.53. Found: C, 46.80; H, 4.70; N, 14.59.

***N*^{6}-(3-Iodobenzylamino)-(5'-*N*-methylcarboxamide-β-D-ribofuranosyl)-9-ylmethyl-adenine (3a).** To a solution of **12** (500 mg, 0.886 mmol) in THF (20 mL) was added 2 *N* HCl (5 mL), and the mixture was stirred at room temperature for 12 h. The mixture was neutralized with NH_4OH and evaporated. The residue was purified by a silica gel column chromatography (CH_2Cl_2:EtOAc:MeOH = 10:10:1) to give **3a** (427.3 mg, 92%) as white solid: UV (DMSO) λ_{max} 280.0 nm (pH 7); $[\alpha]_D^{25}$ −60.30° (*c* 6.60, DMSO); mp 192-194 °C; HR-MS (ESI): *m/z* calcd for $C_{19}H_{22}IN_6O_4$ $[M+H]^+$: 525.0747; Found: 525.0725; ^{1}H NMR (DMSO-d_6) δ 2.65 (d, 3H, *J* = 4.8), 3.71 (m, 1H), 4.01 (m, 3H), 4.26 (dd, 1H, *J* = 8.8, 14.4 Hz), 4.47 (dd, 1H, *J* = 2.8, 14.4 Hz), 4.66 (brs, 2H), 5.20 (brs, 2H), 7.10 (t, 1H, *J* = 7.6 Hz), 7.37 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 7.6), 7.72 (s, 1H), 8.17 (q, 1H, *J* = 4.4 Hz), 8.26 (s, 1H), 8.44 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 25.33, 42.32, 45.94, 72.68, 74.10, 80.80, 83.88, 94.69, 126.66, 130.45, 135.36, 135.72, 141.47, 142.82, 152.20, 154.17, 170.30; Anal. Calcd for $C_{19}H_{21}IN_6O_4$: C, 43.52; H, 4.04; N, 16.03. Found: C, 43.56; H, 4.08; N, 16.09.

***N*^{6}-(3-Iodobenzylamino)-(5'-*N*,*N*-dimethylcarboxamide-β-D-ribofuranosyl-9-ylmethyl)adenine (3b).** Compound **3b** (520.15 mg, 90%) was synthesized from **13** (620 mg, 1.07 mmol) according to the procedure used in the preparation of compound **3a**.

UV (DMSO) λ_{max} 277.0 nm (pH 7); $[\alpha]_D^{25}$ −20.56° (*c* 5.40, DMSO); mp 184-187 °C; HR-MS (ESI): *m/z* calcd for $C_{20}H_{24}IN_6O_4$ $[M+H]^+$: 539.0904; Found: 539.0896; ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3H), 2.98 (s, 3H), 3.82 (m, 1H), 4.08 (m, 2H), 4.24 (dd, 1H, *J* = 7.2, 14.0 Hz), 4.40 (dd, 1H, *J* = 4.0, 14.0 Hz), 4.56 (d, 1H, *J* = 3.6 Hz), 4.65 (br s, 2H), 5.10 (d, 1H, *J* = 6.0 Hz), 5.19 (d, 1H, *J* = 5.2 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 7.6 Hz), 7.72 (s, 1H), 8.11 (s, 1H), 8.20 (s, 1H), 8.32 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 35.10, 36.47, 42.26, 45.19, 72.70, 73.36, 80.08, 81.00, 94.67, 126.63, 130.42, 135.28, 135.71, 141.62, 142.99, 152.23, 154.16, 169.16; Anal. Calcd for $C_{20}H_{23}IN_6O_4$: C, 44.62; H, 4.31; N, 15.61. Found: C, 44.58; H, 4.29; N, 15.63.

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