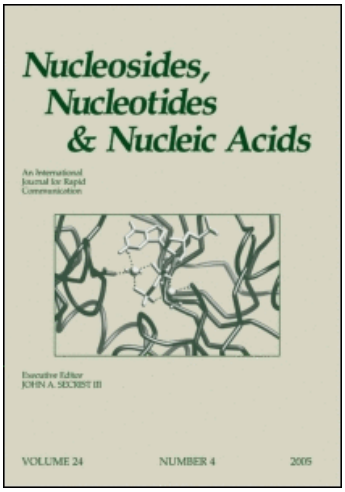

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Synthesis and Anti-HIV Activity of 2-Substituted 2'-Deoxy-2'-fluoroadenosines

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SYNTHESIS AND ANTI-HIV ACTIVITY OF 2-SUBSTITUTED 2'-DEOXY-2'-FLUOROADENOSINES[1)]

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ABSTRACT

2-Iodo-6-methoxypurine 2'-deoxy-2'-fluororiboside **8** was prepared from 2-iodo-6-methoxypurine riboside **1** in 8 steps. Reaction of **8** with ammonia in methanol gave the 2-iodoadenosine derivative **9** in 69% yield. Treatment of **9** with various nucleophiles gave 2-substituted analogues of 2'-deoxy-2'-fluoroadenosine **10-12**. 2'-Deoxy-2,2'-difluoroadenosine **14** was also prepared by the treatment of the quaternary salt **13** with fluoride ion, but similar reactions of **13** with chloride or bromide ion gave the corresponding piperidine congeners **15a,b**.

INTRODUCTION

In the search for analogues with antiviral and antitumor activity, 2-substituted adenosines have attracted much attention. For example, 2-fluoro- and 2-chloro-adenosines are potent inhibitors of the growth of a number of experimental tumors.[2)] In addition, 2-chloro- and 2-methylthioadenosines exhibit interesting activities to the circulatory organ.[3)] This background prompted us to prepare the sugar-modified analogues of 2-substituted adenosine. This paper reports a general methodology for the synthesis of 2-substituted 2'-deoxy-2'-fluoroadenosine. Also reported here is their anti-HIV activity.

This paper is dedicated to Dr. Morio Ikehara, Emeritus Professor of Osaka University, in cerebration of 70th birthday.

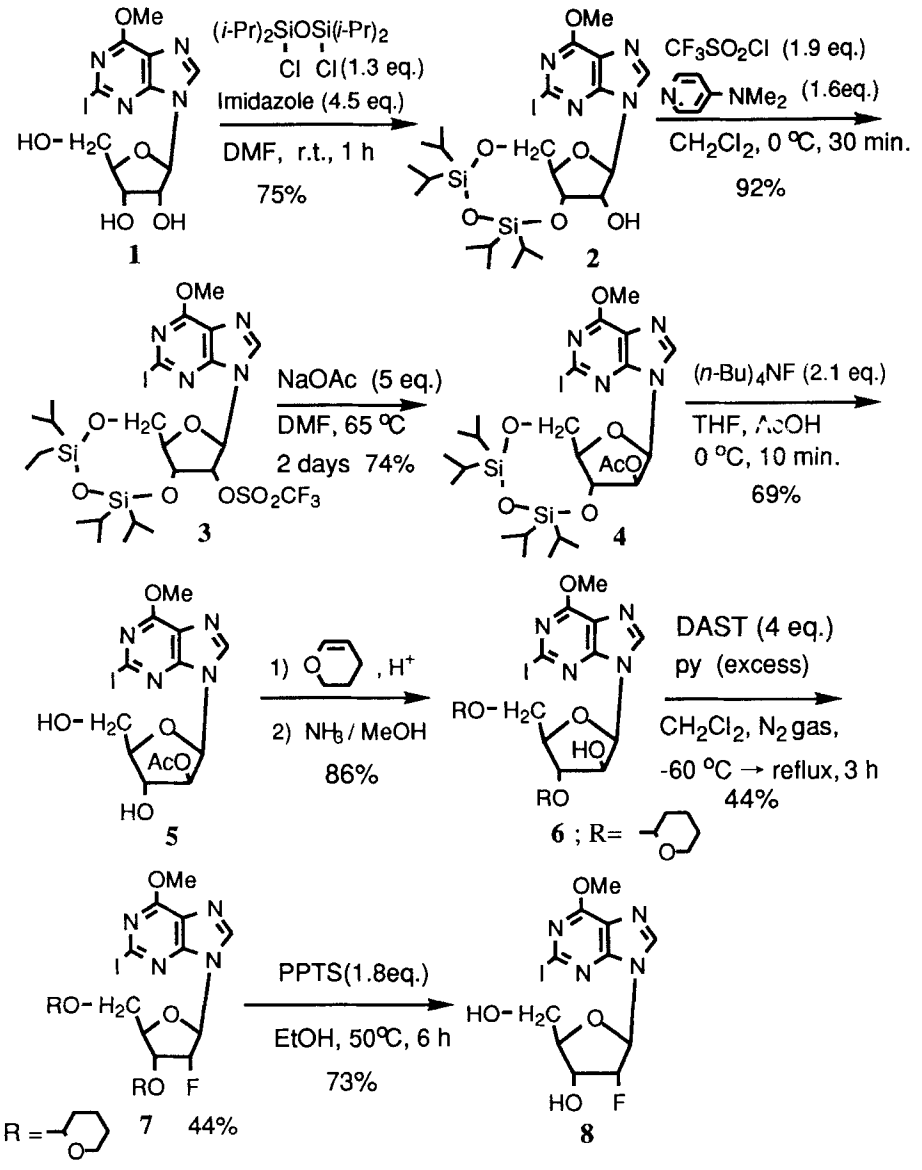

Chart 1

RESULT

Introduction of the fluorine atom at 2'-carbon of 2-iodo-6-methoxypurine riboside **1** was achieved according to the method of the earlier report.[4] Starting material **1**[5] was reacted with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane and subsequently treated with trifluoromethanesulfonyl chloride in the presence of 4-dimethylaminopyridine to give the 2'-*O*-triflate **3**. The product **3** was subjected to SN2 displacement with acetate anion to give the 2'(*S*)(ara)-*O*-acetate **4**. Conversion of **4** to its 3',5'-di-*O*-(tetrahydro-2-pyranyl) derivative followed by the hydrolysis with ammonia in methanol gave the arabinoside **6**. Compound **6** was reacted with DAST in CH_2Cl_2 in the presence of pyridine at reflux for 3 h to give **7** in 44% yield and a 32% yield of recovered **6**. Deprotection of **7** with pyridinium *p*-toluenesulfonate (PPTS) in ethanol gave the 2'-deoxy-2'-fluororiboside **8**. The structure of **8** was confirmed by its ^{1}H-NMR spectrum in which the signal attributable to the 2'-proton appeared at lowfield (5.39 ppm) and showed a large H2'-C-F geminal coupling (52.4Hz). When **8** was treated with ammonia in methanol at 70 °C overnight, a sole spot was observed on TLC. After evaporation of the solution, **9** was obtained as white crystals. The ^{1}H-NMR spectrum of **9** showed the disappearance of the 6-methoxy group and a partial structure of the base moiety has been identified as 2-iodoadenine from the UV absorption spectrum. Combined with elementary analysis, the structure of **9** was determined as 2'-deoxy-2'-fluoro-2-iodo-adenosine, a key intermediate for the synthesis of 2-substituted analogues of 2'-deoxy-2'-fluoroadenosine. The Pullmans already described the high localizing energy (β) of the 2 carbon of various purines in nucleophilic reaction.[5] This calculation explains the relative susceptibility of the 6-methoxy group of **8** in comparison with the 2-iodo group. Reaction of **9** with various nucleophiles under drastic conditions afforded the 2-substituted derivatives. For example, a 2-methoxy analogue **12** was obtained by the treatment of **9** with 1 M NaOMe under reflux overnight. Similar reactions of **9** with dimethylamine or sodium thiomethoxide gave the corresponding 2-substituted analogues **10, 11**. But a trial to obtain the 2-fluoro analogue with a similar reaction using fluoride ion as a nucleophile was unsuccessful. We have explored alternative routes for the preparation of 2,2'-difluoro derivative.

Kiburis and Lister[7] succeeded in synthesizing 6-fluoropurine nucleosides employing fluoride displacement on 6-purinyl-trimethylammonium salt in 30%. We adopted this method for the synthesis of 2'-deoxy-2,2'-difluoroadenosine **14**. The quaternary salt **13**

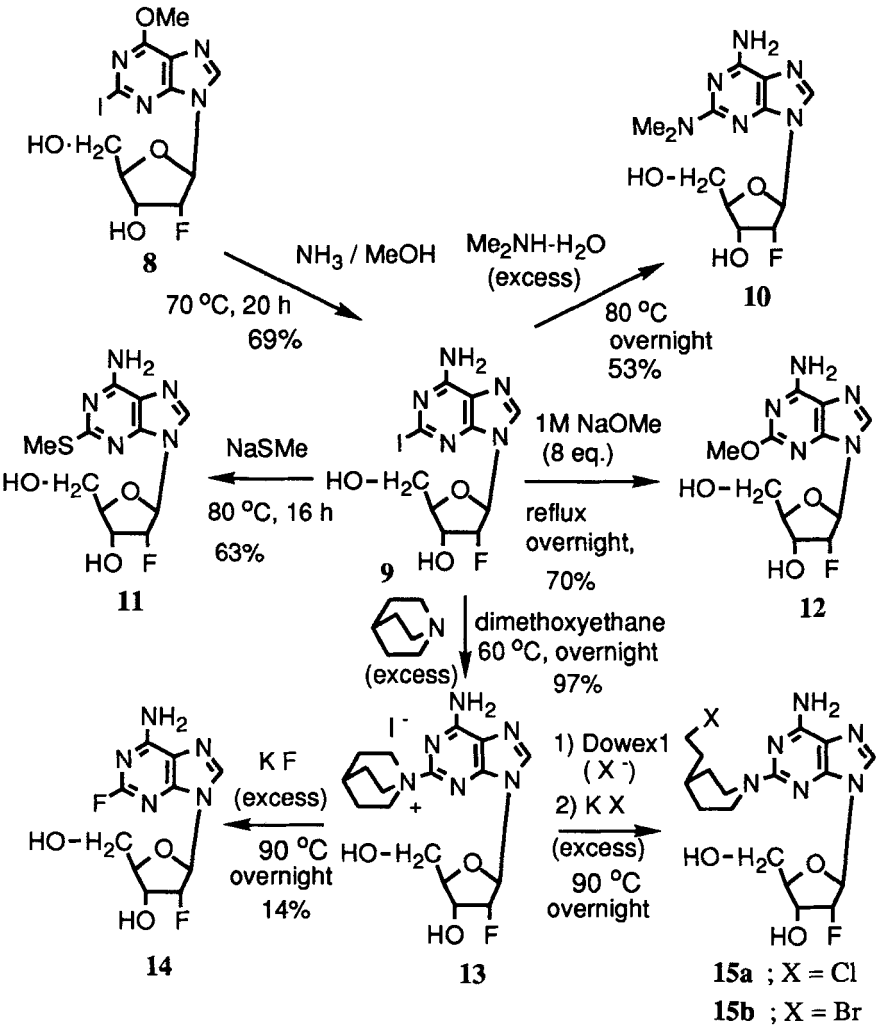

Chart 2

was obtained by the treatment of **9** with quinuclidine in 1,2-dimethoxyethane. In consideration of the weak susceptibility of the 2-carbon of **9** to nucleophilic attack, quinuclidine was chosen as the tertiary amine. Reaction of **13** with potassium fluoride in HMPA gave 2'-deoxy-2,2'-difluoroadenosine **14** in 14% yield. This approach would be a general method to introduce a fluorine at 2-position of adenine ring. But a similar reaction of **13** with chloride or bromide ion gave the corresponding piperidine compounds **15a** or **15b**.

BIOLOGICAL ACTIVITY

The antiviral activities of **8-12** were assayed by HIV plaque reduction in CD4-expressing HeLa cell monolayers as previously described (Table I).[8] Compounds **8-12** showed no activity against HIV-1. This result indicates that the introduction of a substituent at the 2-position of the adenine ring diminishes the antiviral effect of 2'-deoxy-2'-fluoroadnosine. Reduced affinity to cellular nucleoside kinase or weak activity against HIV DNA polymerase of the test componds would explain these results. In addition, compound **12** was quite toxic to proliferating CD4 expressing HeLa cell at 10 μM.

EXPERIMENTAL

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low resolution mass spectra were obtained on a Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. High resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and silica gel 60 (Merck 7734, 60 - 200 mesh) was employed for column chromatography.

2-Iodo-6-methoxy-9-(3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl)purine (2). 2-Iodo-6-methoxy-9-(β-D-ribofuranosyl)purine (**1**) (16.6 g, 40.69 mmol) and imidazole (12.5 g, 4.5 eq.) were dissolved in DMF 130 (m*l*), and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (14.37 m*l*, 1.3 eq.) was added to the solution and the mixture was stirred at room temperature for 1 h. The residue obtained after work-up of the solution was chromatographed over a column of silica gel G (5.3× 26cm) using 0 - 33% AcOEt in *n*-hexane (2 *l*) and the residue thus obtained was crystallized from *n*-hexane to give white crystals (19.85g , 75%). *Anal.* Calcd for $C_{23}H_{39}IN_4O_6Si_2$: C, 42.46; H, 6.04; N, 8.61. Found C, 42.21; H, 6.09; N, 8.79. Ms *m/z* 650 (M^+). mp 59-62 °C. UV: λ max (0.05 N HCl) 262 nm, λ max (MeOH) 262 nm, λ max (0.05 N NaOH) 262 nm. ^{1}H-NMR ($CDCl_3$) δ: 7.97 (1 H, s, H8), 5.95 (1 H, s, H1'),

Table 1. Plaque assay results of compounds **8-12**.

Compd. No	Concentration (μM)	Average	Reduction
8	10	251	16
	1.0	300	0
	none	299	
9	10	258	14
	1.0	314	0
10	10	109	6
	1.0	119	0
11	10	272	9
	1.0	280	6
12	10	Very Toxic	
	1.0	255	15
	0.1	260	13
AZT	10	9	97
	1.0	48	84
	0.1	134	55
	0.01	235	21
	0.001	286	4

The assay was performed by plaque inhibition assay in CD4 expressing HeLa cells using the LAV-1(HIV-1BRU) virus.

4.95 (1 H, t, H2', J = 5.5 Hz), 4.56 (1 H, d, H3', J = 5.5 Hz), 4.15 (3 H, s, 6-OCH_3), 4.04-4.11 (3 H, m, H4', H5'), 3.23 (1 H, d, 2'-OH), 1.1 (28 H, -$CH(CH_3)_2$×4).

2-Iodo-6-methoxy-9-(2-*O*-triflyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl)purine (3). Compound **2** (1.95 g, 3.00 mmol) and 4-dimethylaminopyridine (600 mg, 1.6 eq.) were dissolved in a mixture of triethylamine (0.74 m*l*) and CH_2Cl_2 (30 m*l*), then ice-cooled. Trifluoromethanesulfonyl chloride (0.61 m*l*, 1.9 eq.) was added to the solution and the mixture was stirred at 0 °C for 30 min. The usual

workup of the resulting solution gave a caramel (2.15 g, 92%). UV:λ max (0.05 N HCl) 262 nm, λ max (MeOH), 262 nm, λ max (0.05 N NaOH) 262 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.03 (1 H, s, H8), 6.15 (1 H, s, H1'), 5.57 (1 H, d, H2', *J* = 4.7 Hz), 4.93 (1 H, dd, H3', *J* = 9.0, 4.7 Hz), 4.15 (3 H, s, 6-OCH_3), 4.00-4.25 (3 H, m, H4' and H5'), 1.1 (28 H, -$C\underline{H}(C\underline{H}_3)_2\times 4$).

2-Iodo-6-methoxy-9-(2-*O*-acetyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl)purine (4). A solution of **3** (1.98 g, 2.53 mmol) and NaOAc (1.08 g, 5 eq.) in DMF (10 m*l*) was stirred at 65 °C for 2 days and filtered to remove insoluble materials. The usual workup of the filtrate and crystallization from MeOH gave white crystals (1.30 g, 74%). *Anal.* Calcd for $C_{25}H_{41}IN_4O_7Si_2$: C, 43.35; H, 5.97; N, 8.09. Found: C,: 43.17; H, 6.02; N, 8.33. mp 135-137 °C. UV: λ max (0.05 N HCl) 261 nm, λ max (MeOH) 261 nm, λ max (0.05 N NaOH) 261 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.09 (1 H, s, H8), 6.39 (1 H, d, H1', *J* = 6.5 Hz), 4.57 (1 H, dd, H2', *J* = 8.5, 6.5 Hz), 4.79 (1 H, t, H3', *J* = 8.5 Hz), 4.15 (3 H, s, 6-OCH_3), 4.13 (2 H, m, H5'), 3.94 (1 H, m, H4'), 1.75 (3 H, s, 2'-$OCOCH_3$), 1.1 (28 H, -$C\underline{H}(C\underline{H}_3)_2\times 4$)

2-Iodo-6-methoxy-9-(2-*O*-acetyl-β-D-arabinofuranosyl)purine (5). To an ice-cooled solution of **4** (1.20 g, 1.73 mmol) in THF (10 m*l*) and acetic acid (0.22 m*l*) was added dropwise 1.0 M tetrabutylammonium fluoride solution in THF (3.74 m*l*, 2.1 eq.) and stirred at 0 °C for 10 min. The solution was concentrated to a small volume and subjected to a column of silica gel G (3.0×18 cm) using a 0 - 10% EtOH in $CHCl_3$ (1.5 *l*) as an eluent. The fraction was collected and the solution was evaporated to give a syrup, which was crystallized from EtOH to afford white crystals (541 mg, 69%). *Anal.* Calcd for $C_{13}H_{15}IN_4O_6$: C, 34.68; H, 3.36; N, 12.45. Found: C, 34.89; H, 3.45; N, 12.07. mp 198-200 °C. UV: λ max (0.05 N HCl) 261 nm, λ max (MeOH) 261 nm, λ max (0.05 N NaOH) 261 nm. ^{1}H-NMR (DMSO-d_6) δ: 8.41 (1 H, s, H8), 6.44 (1 H, d, H1', *J* = 5.8 Hz), 5.86 (1 H, d, 3'-OH, *J* = 5.3 Hz), 5.33 (1 H, t, H2', *J* = 5.8 Hz), 5.25 (1 H, t, H4'), 5.09 (1 H, t, 5'-OH), 4.32 (1 H, m, H3'), 4.00 (3 H, s, 6-OCH_3), 3.83 (1 H, m, H4'), 3.65 (2 H, m, H5'), 1.63 (3 H, s, 2'-$OCOCH_3$).

2-Iodo-6-methoxy-9-(3,5-di-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)purine (6). To a solution of **5** (1.00 g, 2.22 mmol) in DMF (10 m*l*) and 3,4-dihydro-2*H*-pyran (6.53 m*l*) was added *p*-toluenesulfonic acid (1.1 g) and the solution was stirred at 0 °C for 3 h. After neutralization with triethylamine (1.1 m*l*), the solution was subjected to

the usual workup and silica gel chromatography to give the 2'-*O*-acetate as a caramel (1.31 g, 96%). Ms *m/z* 618 (M^+). UV: λ max (0.05 N HCl) 261 nm, λ max (MeOH) 261 nm, λ max (0.05 N NaOH) 261 nm .

The 2'-*O*-acetate (1.19 g, 1.92 mmol) was dissolved in methanol (5 m*l*) saturated with ammonia and kept at 0 °C for 4 h in a sealed tube. After evaporation of the solution, the residue was dissolved in $CHCl_3$ (100 m*l*) and the organic layer was washed with water (50 m*l*) twice, dried over $MgSO_4$ and evaporated to give a caramel (998 mg, 90%). UV: λ max (MeOH) 264 nm, 250 nm (sh). Ms *m/z* 576 (M^+).

2-Iodo-6-methoxy-9-(2-deoxy-2-fluoro-3,5-di-*O*-(tetrahydro-2-pyranyl)-β-D-ribofuranosyl)purine (7). To a cooled solution (-60 °C) of **6** (730 mg, 1.27 mmol) in a mixture of CH_2Cl_2 (10 m*l*) and pyridine (1.3 m*l*) was added DAST (0.68 m*l*, 4 eq.) dropwise under N_2 atmosphere. The solution was heated under reflux for 3 h, then cooled. The solution was poured into the stirred solution of 10% $NaHCO_3$ (40 m*l*) and diluted with CH_2Cl_2 (10 m*l*). The organic layer was washed with water (20 m*l* × 2), dried over $MgSO_4$ and evaporated to a small volume. The solution was chromatographed over a column of silica gel G (2.0×34 cm) with 0 - 2% EtOH in $CHCl_3$ (2 *l*). From the first fraction **7** was obtained as a caramel (323 mg, 44%). UV: λ max (MeOH) 262 nm.

2-Iodo-6-methoxy-9-(2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (8). A solution of **7** (323 mg, 0.40 mmol) in EtOH (8 m*l*) was stirred in the presence of pyridinium *p*-toluenesulfonate (200 mg) at 50 °C for 6 h and the solution was concentrated to 3 m*l*. The solution was chromatographed over a column of silica gel G (2.0 × 34 cm) with 0 - 4.8% EtOH in $CHCl_3$ (1.2 *l*) to give a caramel, which was crystallized from EtOH to afford white crystals (170 mg, 73%). *Anal.* Calcd for $C_{11}H_{12}FIN_4O_4 \cdot 1/2H_2O$: C, 31.52; H, 3.13; N, 13.37. Found: C, 31.30; H, 2.88; N, 13.10. Ms *m/z* 410 (M^+). mp 168-170 °C. UV: λ max (0.1 N HCl) 262 nm (ε 13700), λ max (H_2O) 262 nm (ε 13800), λ max (0.1 N NaOH) 261 nm (ε 14100). ^{1}H-NMR (DMSO-d_6) δ: 8.55 (1 H, s, H8), 6.26 (1 H, dd, H1', J = 16.9, 2.2 Hz), 5.75 (1 H, d, 3'-OH, J = 5.9 Hz), 5.39 (1 H, ddd, H2', J = 52.4, 4.4, 2.2 Hz), 5.59 (1 H, brs, 5'-OH), 4.45 (1 H, m, H3', J = 20.6 Hz), 4.08 (3 H, s, 6-OCH_3), 3.99 (1 H, m, H4'), 3.61, 3.77 (each 1 H, m, H5')

2-Iodo-2'-deoxy-2'-fluoroadenosine (9). A solution of **8** (850 mg, 2.07 mmol) in methanol (20 m*l*) was saturated with ammonia at 0 °C and heated in a sealed tube (100

m*l*) at 70 °C for 20 h. After cooling in a ice-bath, the solution was evaporated and the residue was dissolved in water (30 m*l*). The aqueous layer was washed with $CHCl_3$ (5 m*l*) and concentrated to a small volume to give white crystals (564 mg, 69%). *Anal.* Calcd for $C_{10}H_{11}FIN_5O_3$: C, 30.40; H, 2.81; N, 17.72. Found: C, 30.23; H, 2.83; N, 17.59. mp 221 - 223 °C. UV: λ max (0.1 N HCl) 265 nm (ε 15100), λ max (H_2O) 266 nm (ε 14800), λ max (0.1 N NaOH) 266.5 nm (ε 15100). ^{1}H-NMR (DMSO-d_6) δ: 8.26 (1 H, s, H8), 7.74 (2 H, brs, 6-NH_2), 6.13 (1 H, dd, H1', *J* = 11.0, 2.3 Hz), 5.69 (1 H, d, 3'-OH, *J* = 5.0 Hz), 5.34 (1 H, ddd, H2', *J* = 53.1, 5.8, 2.3 Hz), 5.08 (1 H, brs, 5'-OH), 4.40 (1 H, m, H3', *J* = 18.5 Hz), 3.94 (1 H, m, H4'), 3.55, 3.72 (each 1 H, m, H5').

2-Dimethylamino-2'-deoxy-2'-fluoroadenosine (10). A solution of **9** (70 mg, 0.177 mmol) in 50% dimethylamine (3 m*l*) was stirred at 80 °C overnight. The solution was evaporated and the residue was crystallized from EtOH to give white crystals (29 mg, 53%). *Anal.* Calcd for $C_{12}H_{17}FN_6O_3 \cdot 0.7H_2O$: C, 44.35; H, 5.71; N, 25.87. Found: C, 44.74; H, 5.50; N, 25.97. Ms *m/z* 312 (M^+), 313(M^++1). mp 193-195 °C. UV: λ max (0.1 N HCl) 260 nm (ε 17300), 305 (ε 8500), λ max (H_2O) 262 nm (ε 13600), 294 (ε 7700), λ max (0.1 N NaOH) 262 nm (ε 13400), 294 nm (ε 8300). ^{1}H-NMR (DMSO-d_6) δ: 7.92 (1 H, s, H8), 6.83 (2 H, brs, 6-NH_2), 6.06 (1 H, dd, H1', *J* = 19.0, 2.5 Hz), 5.66 (1 H, d, 3'-OH, *J* = 5.0 Hz), 5.46 (1 H, ddd, H2', *J* = 53.2, 4.5, 2.5 Hz), 4.96 (1 H, t, 5'-OH, *J* = 5.5 Hz), 4.52 (1 H, m, H3', *J* = 18.0 Hz), 3.88 (1 H, m, H4'), 3.53, 3.70 (each 1 H, m, H5'), 3.05 (6 H, s, 2-$N(CH_3)_2$).

2-Methylmercapto-2'-deoxy-2'-fluoroadenosine (11). A solution of **9** (70 mg, 0.177 mmol) in 15% sodium thiomethoxide (3 m*l*) was stirred at 80 °C for 16 h. After removal of the volatile by N_2 gas, the solution was evaporated and the residue was chromatographed over a column of silica gel G (1.9×15cm) with 0 - 20% EtOH in $CHCl_3$ (0.6 *l*) to give a caramel (35 mg, 63%). *Anal.* Calcd for $C_{11}H_{14}FN_5O_3S$: C, 41.90; H, 4.47; N, 22.21. Found: C, 41.88; H, 4.63; N, 21.90. Ms *m/z* 315 (M^+). mp 201-203 °C. UV: λ max (0.1 N HCl) 269 nm (ε 17200), 283 (sh, ε 13100), λ max (H_2O) 274 nm (ε 15100), λ max (0.1 N NaOH) 275 nm (ε 15200). ^{1}H-NMR (DMSO-d_6) δ: 8.23 (1 H, s, H8), 7.40 (2 H, brs, 6-NH_2), 6.17 (1 H, m, H1', *J* = 18.1 Hz), 5.47 (1 H, m, H2', *J* = 53.8 Hz), 4.52 (1 H, m, H3', *J* = 18.1 Hz), 3.95 (1 H, m, H4'), 3.72, 3.57 (each 1 H, m, H5'), 2.46 (3 H, s, 2-SCH_3).

2-Methoxy-2'-deoxy-2'-fluoroadenosine (12). Compound **9** (70 mg, 0.177 mmol) was dissolved in 1M NaOMe (1.4 m*l*, 8 eq.) and the solution was heated under reflux overnight, then neutralized with acetic acid to give white crystals (37 mg, 70%). *Anal.* Calcd for $C_{11}H_{14}FN_5O_4 \cdot 4/5H_2O$: C, 42.12; H, 5.01; N, 22.33. Found: C, 42.14; H, 4.83 ; N, 21.86. Ms *m/z* 299 (M^+). mp 170-172 °C. UV: λ max (0.1 N HCl) 274.5 nm (ε 11700), 246 (ε 8900), λ max (H_2O) 266.5 nm (ε 11800), 255 (sh, ε 9500), λ max (0.1 N NaOH) 267 nm (ε 12300), 255 nm (sh, ε 9600). ^{1}H-NMR (DMSO-d_6) δ: 8.15 (1 H, s, H8), 7.35 (2 H, brs, 6-NH_2), 6.11 (1 H, dd, H1', *J* = 12.6, 2.6 Hz), 5.41 (1 H, ddd, H2', *J* = 52.6, 4.7, 2.6 Hz), 4.40 (1 H, m, H3', *J* = 19.0 Hz), 3.91 (1 H, m, H4'), 3.80 (3 H, s, 2-OCH_3), 3.71, 3.55 (each 1 H, m, H5').

N-(9-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)adenin-2-yl)quinuclidinium iodide (13). A solution of **9** (400 mg, 1 mmol) quinuclidine (2.0 g, 18 mmol) in 1,2-dimethoxyethane (15 m*l*) was heated at 60°C overnight. The resulting crystals were collected by the filtration and washed with ether to give **13** (498 mg, 97%). *Anal.* Calcd for $C_{17}H_{24}FIN_6O_3$: C, 40.33; H, 4.78; N, 16.60. Found: C, 40.80; H, 4.93; N, 15.97. mp 213-215 °C. UV: λ max (0.05 N HCl) 257 nm, λ max (MeOH) 260 nm, λ max (0.05 N NaOH) 260 nm .

2'-Deoxy-2,2'-difluoroadenosine (14). A solution of **13** (448 mg, 0.89 mmol) and KF (2.00 g) in HMPA (15 m*l*) was stirred at 90 °C overnight, then cooled. After dilution with $CHCl_3$ (150 m*l*), the organic layer was washed with water (100 m*l*) twice. The aqueous layer was evaporated to dryness and dissolved in ethanol (5 m*l*). The solution was chromatographed over a column of silica gel G (3.2 × 22 cm) with 0 - 20% EtOH in $CHCl_3$ (1.2 *l*) to give white crystals (36 mg, 14%). mp 227 - 231°C. MS: *m/z* 287(M^+). UV: λ max (0.05 N HCl) 261, 268 nm (sh), λ max (MeOH) 261, 268 nm (sh), λ max (0.05 N NaOH) 261, 268 nm (sh). ^{1}H-NMR ($CDCl_3$) δ: 8.30 (1 H, dd, H8), 7.87 (2 H, m, NH_2), 6.1 (1 H, dd, H1'), 5.68 (1 H, dd, 2'-OH), 5.3 (1 H, m, H2'), 5.08 (1 H, m, 3'-OH), 4.4 (1 H, m, H3'), 3.9 (1 H, m, H4'), 3.6 (2 H, m, H5').

N-(9-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)adenin-2-yl)-4-(2-chloroethyl)-piperidine (15a). A solution of **13** (200 mg, 0.4 mmol) was passed through the column of Dowex 1 (Cl^-, 10 m*l*) and the solvent of eluate and the washings (100 m*l*) was evaporated to dryness to give the solid. The product and KCl (290 mg, 3.9 mmol) was suspended in DMF (10 m*l*) and the solution was stirred at 90 °C overnight, then cooled. The solution was evaporated and the residue was dissolved in a small amount of

ethanol. The solution was chromatographed over a column of silica gel G (2.0 × 20 cm) with 0 - 25% EtOH in $CHCl_3$ (500 m*l*) to give a caramel (57 mg, 35%). MS *m/z* 414, 416 (ca. 3:1, M^+). UV: λ max (0.05 N HCl) 262, 305 nm, λ max (MeOH) 264, 290 nm, λ max (0.05 N NaOH) 263, 290 nm. ^{1}H-NMR ($CDCl_3$) δ: 7.54 (1 H, s, H8), 5.98 (1 H, dd, H1', J = 14.0, 5.9), 5.88 (1 H, dt, J = 53.9, 5.9 Hz), 5.39 (2 H, br s, NH_2), 4.5 - 4.7 (3 H, m, 3'-OH, 5'-OH, H3'), 4.20 (1 H, m, H4'), 3.93 (1 H, d, H5'a, J = 11.9 Hz), 3.74 (1 H, d, H5'b, J = 11.9 Hz), 3.59 (2 H, t, -$CH_2C\underline{H}_2Cl$, J = 6.5 Hz), 2.83 (2 H, m, -$C\underline{H}_2CH_2Cl$), 1.0 - 1.9 (piperidine protons).

N-(9-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)adenin-2-yl)-4-(2-bromoethyl)-piperidine (15b). The anion of compound **13** (200 mg, 0.4 mmol) was exchanged to Br^- using Dowex 1 (Br^-, 10 m*l*). The product and NaBr (401 mg, 3.9 mmol) was suspended in DMF (10 m*l*) and stirred at 90 °C overnight. A similar work-up of the solution as mentioned above gave a caramel (45 mg, 25%). MS *m/z* 458, 460 (ca. 1:1, M^+). UV: λ max (0.05 N HCl) 262, 305.5 nm, λ max (MeOH) 265, 291 nm, λ max (0.05 N NaOH) 264, 290 nm. ^{1}H-NMR ($CDCl_3$) δ: 7.53 (1 H, s, H8), 5.97 (1 H, dd, H1', J = 16.4, 5.5 Hz), 5.89 (1 H, dt, J = 54.6, H2', 5.5 Hz), 5.37 (2 H, br s, NH_2), 4.5 - 4.8 (3 H, m, 3'-OH, 5'-OH, H3'), 4.20 (1 H, m, H4'), 3.93 (1 H, d, H5'a, J = 12.4 Hz), 3.74 (1 H, d, H5'b, J = 12.5 Hz), 3.44 (2 H, t, -$CH_2C\underline{H}_2Br$, J = 6.9 Hz), 2.82 (2 H, m, -$C\underline{H}_2CH_2Br$), 1.0 - 1.9 (piperidine protons).

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