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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'-FLUOROADENOSINES¹⁾**

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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-chloroadenosines 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 celebration of 70th birthday.

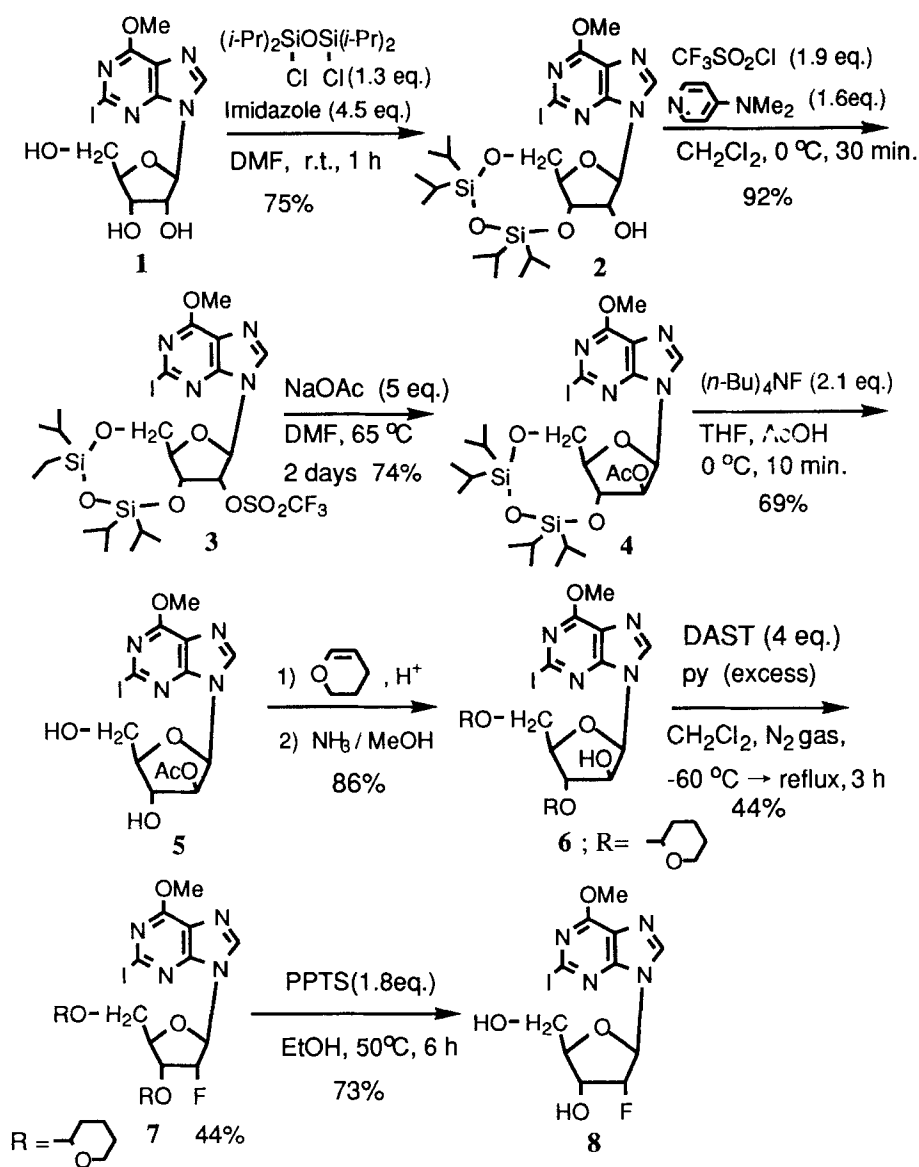


Chart 1

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-tetraisopropylidisiloxane 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 CH₂Cl₂ 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 ¹H-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 ¹H-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-iodoadenosine, 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 Lister⁷⁾ 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**

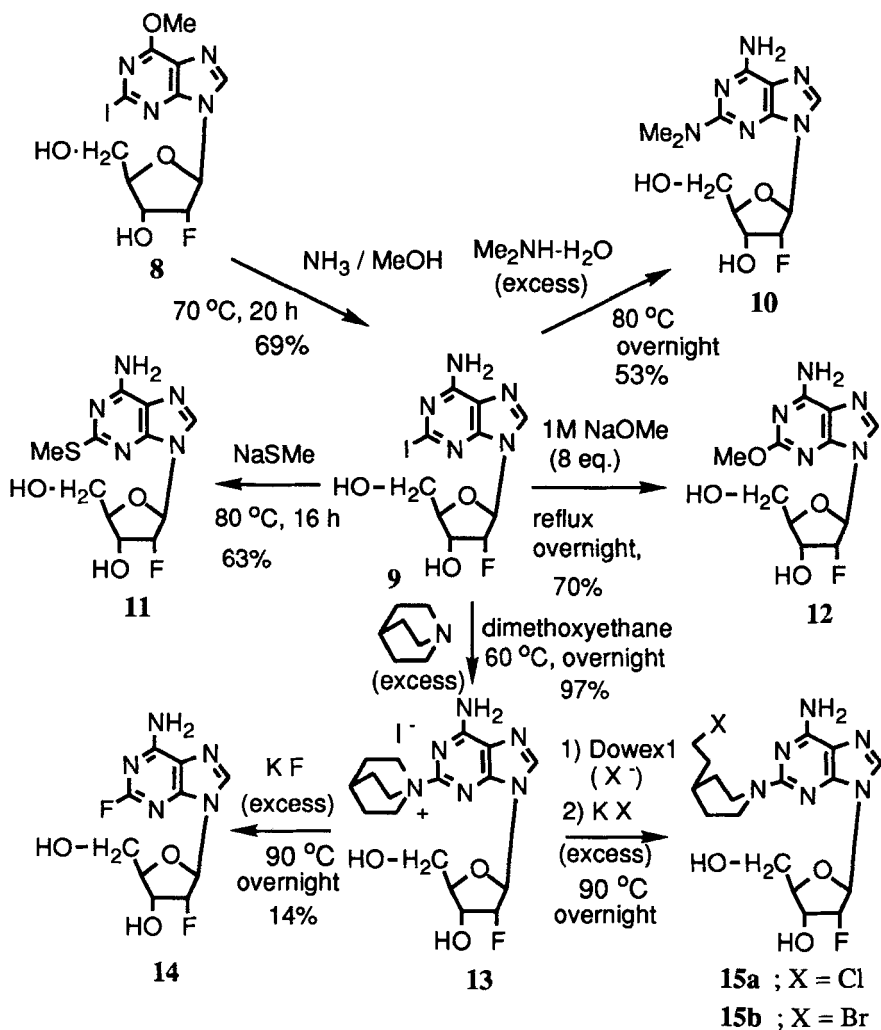


Chart 2

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'-fluoroadenosine. Reduced affinity to cellular nucleoside kinase or weak activity against HIV DNA polymerase of the test compounds would explain these results. In addition, compound **12** was quite toxic to proliferating CD4 expressing HeLa cell at 10 μ M.

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. ¹H-NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in CDCl₃ (or dimethyl sulfoxide (DMSO)-*d*₆) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F₂₅₄ 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*-(tetraisopropylidisiloxane-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 (ml), and 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (14.37 ml, 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 \times 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 C₂₃H₃₉IN₄O₆Si₂: 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. ¹H-NMR (CDCl₃) 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 (μ M)	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-OCH₃), 4.04-4.11 (3 H, m, H4', H5'), 3.23 (1 H, d, 2'-OH), 1.1 (28 H, -CH(CH₃)₂ \times 4).

2-Iodo-6-methoxy-9-(2-*O*-triflyl-3,5-*O*-(tetraisopropylidisiloxane-1,3-diyl)- β -D-ribofuranosyl)purine (3). Compound **2** (1.95 g, 3.00 mmol) and 4-dimethylamino-pyridine (600 mg, 1.6 eq.) were dissolved in a mixture of triethylamine (0.74 ml) and CH₂Cl₂ (30 ml), then ice-cooled. Trifluoromethanesulfonyl chloride (0.61 ml, 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. $^1\text{H-NMR}$ (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-OCH₃), 4.00-4.25 (3 H, m, H4' and H5'), 1.1 (28 H, -CH(CH₃)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 ml) 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 C₂₅H₄₁IN₄O₇Si₂: 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. $^1\text{H-NMR}$ (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-OCH₃), 4.13 (2 H, m, H5'), 3.94 (1 H, m, H4'), 1.75 (3 H, s, 2'-OCOCH₃), 1.1 (28 H, -CH(CH₃)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 ml) and acetic acid (0.22 ml) was added dropwise 1.0 M tetrabutylammonium fluoride solution in THF (3.74 ml, 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 \times 18 cm) using a 0 - 10% EtOH in CHCl₃ (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 C₁₃H₁₅IN₄O₆: 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. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) 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-OCH₃), 3.83 (1 H, m, H4'), 3.65 (2 H, m, H5'), 1.63 (3 H, s, 2'-OCOCH₃).

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 ml) and 3,4-dihydro-2H-pyran (6.53 ml) 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 ml), 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 ml) 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 ml) and the organic layer was washed with water (50 ml) 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-pyran-1-yl)- 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 ml) and pyridine (1.3 ml) was added DAST (0.68 ml, 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 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with water (20 ml \times 2), dried over MgSO_4 and evaporated to a small volume. The solution was chromatographed over a column of silica gel G (2.0 \times 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 ml) was stirred in the presence of pyridinium *p*-toluenesulfonate (200 mg) at 50 °C for 6 h and the solution was concentrated to 3 ml. The solution was chromatographed over a column of silica gel G (2.0 \times 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 $\text{C}_{11}\text{H}_{12}\text{FIN}_4\text{O}_4 \cdot 1/2\text{H}_2\text{O}$: 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). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) 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-OCH₃), 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 ml) was saturated with ammonia at 0 °C and heated in a sealed tube (100

ml) at 70 °C for 20 h. After cooling in a ice-bath, the solution was evaporated and the residue was dissolved in water (30 ml). The aqueous layer was washed with CHCl_3 (5 ml) and concentrated to a small volume to give white crystals (564 mg, 69%). *Anal.* Calcd for $\text{C}_{10}\text{H}_{11}\text{FIN}_5\text{O}_3$: 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). ^1H -NMR ($\text{DMSO}-d_6$) 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 ml) 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 $\text{C}_{12}\text{H}_{17}\text{FN}_6\text{O}_3 \cdot 0.7\text{H}_2\text{O}$: 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). ^1H -NMR ($\text{DMSO}-d_6$) 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- $\text{N}(\text{CH}_3)_2$).

2-Methylmercapto-2'-deoxy-2'-fluoroadenosine (11). A solution of **9** (70 mg, 0.177 mmol) in 15% sodium thiomethoxide (3 ml) 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 ($1.9 \times 15\text{cm}$) with 0 - 20% EtOH in CHCl_3 (0.6 l) to give a caramel (35 mg, 63%). *Anal.* Calcd for $\text{C}_{11}\text{H}_{14}\text{FN}_5\text{O}_3\text{S}$: 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). ^1H -NMR ($\text{DMSO}-d_6$) 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 mL, 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). 1H -NMR ($DMSO-d_6$) δ : 8.15 (1 H, s, H8), 7.35 (2 H, brs, 6-NH₂), 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-OCH₃), 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 mL) 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 mL) was stirred at 90 °C overnight, then cooled. After dilution with $CHCl_3$ (150 mL), the organic layer was washed with water (100 mL) twice. The aqueous layer was evaporated to dryness and dissolved in ethanol (5 mL). The solution was chromatographed over a column of silica gel G (3.2 \times 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). 1H -NMR ($CDCl_3$) δ : 8.30 (1 H, dd, H8), 7.87 (2 H, m, NH₂), 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 mL) and the solvent of eluate and the washings (100 mL) was evaporated to dryness to give the solid. The product and KCl (290 mg, 3.9 mmol) was suspended in DMF (10 mL) 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 CHCl₃ (500 ml) 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. ¹H-NMR (CDCl₃) 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, NH₂), 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, -CH₂CH₂Cl, *J* = 6.5 Hz), 2.83 (2 H, m, -CH₂CH₂Cl), 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 ml). The product and NaBr (401 mg, 3.9 mmol) was suspended in DMF (10 ml) 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. ¹H-NMR (CDCl₃) 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, NH₂), 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, -CH₂CH₂Br, *J* = 6.9 Hz), 2.82 (2 H, m, -CH₂CH₂Br), 1.0 - 1.9 (piperidine protons).

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