Synthesis and Hypnotic and Anti-Human Immunodeficiency Virus-1 Activities of N^3-Substituted 2′-Deoxy-2′-fluorouridines

Yoshiko SATO,[a] Kunihiko UTSUMI,[a] Tokumi MARUYAMA,*[,a] Toshiyuki KIMURA,[b] Ikuo YAMAMOTO,[b] and Douglas D. RICHMAN[c]

Department of Pharmaceutical Sciences, Tokushima Bunri University,[a] Yamashiro-cho, Tokushima 770, Japan, Department of Hygienic Chemistry, Faculty of Pharmaceutical Sciences, Hokuriku University,[b] Kanazawa 920–11, Japan, and Departments of Pathology and Medicine, University of California,[c] San Diego, La Jolla, California 92093–0679, U.S.A. Received September 16, 1993; accepted October 29, 1993

Reaction of 9-[3,5-di-*O*-(tetrahydropyran-2-yl)-β-D-arabinofuranosyl]uracil (2) with diethylaminosulfur trifluoride in the presence of pyridine afforded 2′-deoxy-2′-fluororiboside 3a, from which 2′-deoxy-2′-fluorocytidine (4b) has been synthesized in good yield. Compound 3a was deprotected and subsequently treated with various benzyl halides or 2-chloro-4-fluoroacetophenone to give corresponding N^3-substituted 2′-deoxy-2′-fluorouridines 5a—c and 6. Compounds 5a—c, as well as 6, showed weak hypnotic activity in mice. Compound 4b showed moderate antiviral activity against human immunodeficiency virus-1 but 3b, 5a—c, and 6 were virtually inactive.

Keywords 2′-deoxy-2′-fluorouridine; hypnotic activity; central nervous system-depressant; anti-human immunodeficiency virus activity

It is of considerable interest to investigate the role of the 2′-OH group in ribonucleosides which differentiate RNA from DNA. In this connection, 2′-deoxy-2′-fluoro analogues of nucleosides, oligonucleotides and polynucleotides have been synthesized.[1,2] In studies of the physico-chemical and biological properties, 2′-deoxy-2′-fluoronucleosides have been shown to adopt the 3′-endo conformation and the corresponding polynucleotides behave like polyribonucleotides.[3] Recently, uridine was identified as a sleep-promoting substances[4] and some N^3-substituted uridine, 6-azauridine and thymidine were found to have central nervous system (CNS)-depressant effects.[5] But no report concerning N^3-substituted uridines that contain unusual sugars has appeared. In this paper, we wish to report the synthesis and CNS-depressant effect of N^3-benzyl-2′-deoxy-2′-fluorouridine **5a—c** or the N^3-phenacyl derivative **6**, as well as the anti-HIV-1 activity of 2′-deoxy-2′-fluorouridines **3b**, **5a—c**, **6** in addition to the cytidine congener **4b**.

Chemical Synthesis 2′-Deoxy-2′-fluorouridine (**3b**) was prepared by a modification of Hayakawa's method[6] using the tetrahydropyran-2-yl group[7] for 3′- and 5′-hydroxyl protection. Thus, 3′,5′-di-*O*-protection of 2,2′-*O*-cyclouridine (**1a**)[8] with 3,4-dihydro-2*H*-pyran and subsequent alkaline treatment afforded the arabinoside **2**. Compound **2** was reacted with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 in the presence of pyridine to give an intermediate **3a** in 57% yield. Deprotection of **3a** with pyridinium *p*-toluenesulfonate (PPTS)[9] in EtOH gave 2′-deoxy-2′-fluorouridine **3b**.[6,10] By using the procedure of

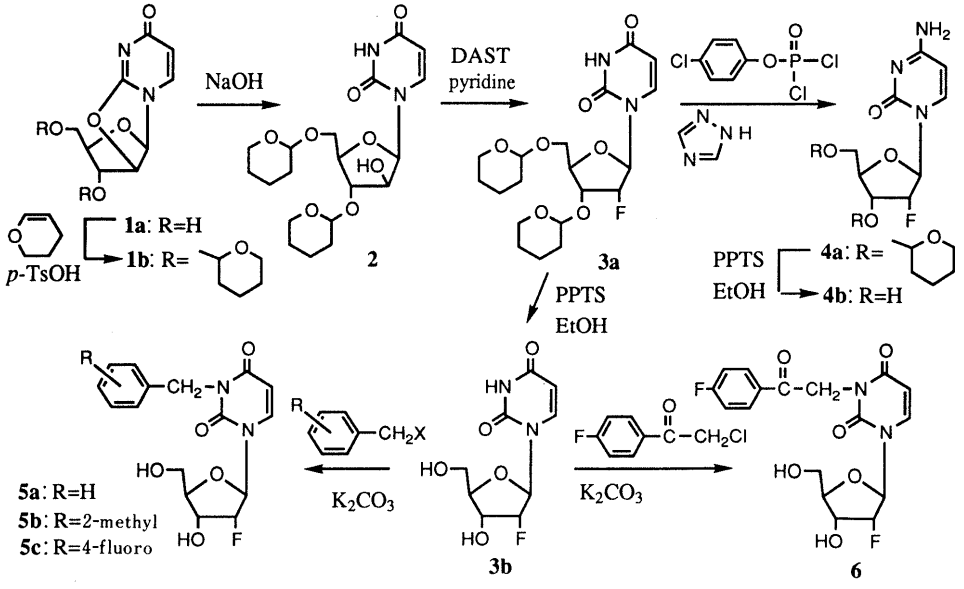

Chart 1

This paper is dedicated to Prof. Leroy B. Townsend on the occasion of his 60th birthday.

TABLE I. Reaction Conditions of N^3-Substituted 2′-Deoxy-2′-fluorouridines

Compound No.	**3b** (mmol)	R–X	(mmol)	K_2CO_3 (mmol)	Temp. (°C)	Time (h)	Yield (%)
5a	0.5	$C_6H_5CH_2Br$	0.82	0.85	50	2	Quantitative
5b	0.5	o-CH_3–$C_6H_5CH_2Cl$	0.75	0.85	50	8	Quantitative
5c	0.5	p-F–$C_6H_5CH_2Cl$	0.83	0.85	50	4	Quantitative
6	0.5	p-F–$C_6H_5COCH_2Cl$	1.13	0.85	50	4	90.4

All reactions were carried out in a mixture of DMF and acetone.

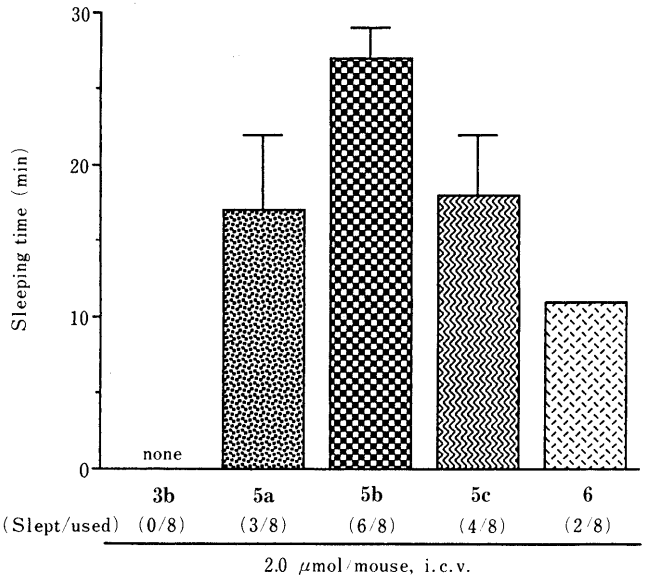

Fig. 1. Hypnotic Activities of N^3-Substituted 2′-Deoxy-2′-fluorouridines

Mice were administered an N^3-substituted 2′-deoxy-2′-fluorouridine by i.c.v. injection. The hypnotic activity was expressed as the mean sleeping time of mice (min)±S.E.

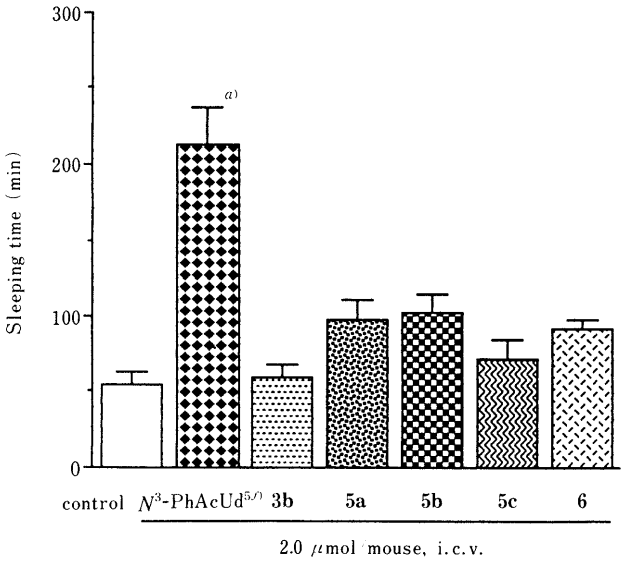

Fig. 2. Effects of N^3-Substituted 2′-Deoxy-2′-fluorouridine on Pentobarbital-Induced Sleep

Mice were pretreated with N^3-phenacyluridine[5f] and N^3-substituted 2′-deoxy-2′-fluorouridine (2.0 μmol/mouse) i.c.v. before challenge with sodium pentobarbital (40 mg/kg, i.p.). Pentobarbital-induced sleep was expressed as the mean sleeping time of mice (min)±S.E. *a*) Significant difference from the control by Bonferroni test, $p<0.01$.

Divakar and Reese,[11] **3a** was also successively treated with 4-chlorophenyl phosphorodichloridate in the presence of 1,2,4-triazole and concentrated ammonium hydroxide to give the cytidine congener **4b**.[12] When **3b** was treated with benzyl halides or 2-chloro-4-fluoroacetophenone in the presence of K_2CO_3,[13] N^3-substituted 2′-deoxy-2′-fluorouridines **5a**—**c** and **6** were obtained in good yield.

Pharmacological Results

Hypnotic Activity of N^3-Substituted 2′-Deoxy-2′-fluorouridines The hypnotic activity of the 2′-desoxy-2′-fluorouridine and its N^3-substituted derivatives were assayed according to previously established procedures[5] and the results are presented in Fig. 1. In accordance with the result for uridine,[5b] 2′-deoxy-2′-fluorouridine itself showed no hypnotic activity. But the N^3-benzyl derivative **5a** exhibited hypnotic activity (17 min) when administered by intracerebroventricular (i.c.v.) injection at 2 μM to mice. This is the first demonstration that N^3-benzyluridine with an unusual sugar has CNS-depressant activity. N^3-Benzyluridine showed strong hypnotic acitivity (36 min) in this system.[5b] It appeared that the conversion of the 2′-OH to a fluorine atom reduced the CNS-depressant effect by about 50 percent. To explore the effect of substituents on the benzene ring, the hypnotic activity of **5b**, **c** was also examined. The 4-fluorobenzyl derivative **5c** showed equal activity to **5a** but the 2-methylbenzyl derivative **5b** was demonstrated to be more effective than **5a**. The N^3-(4-fluorophenacyl) derivative **6** showed the weakest hypnotic activity among the N^3-substituted derivatives.

TABLE II. Plaque Assay Results of Compounds **3b**, **4b**, **5a**—**c**, and **6**

Compound No.	Concentration (μM)	Average	Reduction (%)
4b	10	64	43
	1.0	94	16
	None	112	
3b	10	109	3
5a	10	110	2
5b	10	111	1
5c	10	124	0
6	10	101	10
AZT	3.16	3	97
	1.0	4	96
	0.316	15	87
	0.1	23	79
	0.00316	36	68

The assay was performed by plaque inhibition assay in CD4 expressing HeLa cells using the HIV-1_{LAI} virus.

Effects of N^3-Substituted 2′-Deoxy-2′-fluorouridine on Pentobarbital-Induced Sleep The effects of the 2′-deoxy-2′-fluorouridine (**3b**) and its N^3-substituted derivatives **5a**—**c** are presented in Fig. 2. Here again the N^3-benzyl derivative showed a short prolongation of pentobarbital-induced sleep while 2′-deoxy-2′-fluorouridine itself had no effect. The effect of substituents on the benzene ring was not clear in this sytem.

Anti-Human Immunodeficiency Virus (HIV)-1 Activity The antiviral activity of **3b**, **4b**, **5a**—**c**, and **6** were assayed by HIV plaque reduction in CD4 expressing HeLa cell monolayers as previously described[14] (Tabel II). In this series, compound **4b** displayed indications of activity (43% reduction) against HIV-1 at 10 μM. In contrast, the uridine congener **3b** as well as the N^3-benzyl analogues **5a**—**c** and N^3-phenacyl analog **6** proved inactive against HIV-1.

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. ^{1}H-NMR spectra were recorded on a Varian UNITY 200 (200 MHz) or 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.

3′,5′-Di-*O*-(tetrahydropyran-2-yl)-2,2′-*O*-cyclouridine (1b) *p*-Toluenesulfonic acid (30 g) was added to an ice-cooled solution of **1a** (37.0 g, 0.16 mol) in *N*,*N*-dimethylformamide (DMF) (700 ml) and 3,4-dihydro-2*H*-pyran (380 ml), and the solution was kept at 0 °C for 2.5 h. After neutralization with triethylamine (30 ml), the solution was subjected to the usual work-up and silca gel chromatography to give a caramel (56.3 g, 87%). UV λ_{max}^{MeOH} nm (ε): 250 (7800), $\lambda_{max}^{0.05\ N\ HCl}$ nm (ε): 251 (7700); $\lambda_{max}^{0.05\ N\ HCl}$ nm (ε): 250 (8100). MS *m/z*: 394 (M^+). *Anal.* Calcd for $C_{19}H_{16}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.84; H, 6.74; N, 7.00.

9-[3,5-Di-*O*-(tetrahydropyran-2-yl)-β-D-arabinofuranosyl]uracil (2) A solution of **1b** (56.0 g, 0.14 mol) in methanol (300 ml) was treated with 1 N NaOH (180 ml) and the solution was stirred at room temperature for 1.5 h, then neutralized with acetic acid (12 ml). The solution was subjected to the usual work-up to give white crystals (25.1 g), mp 187—191 °C. UV λ_{max}^{MeOH} nm (ε): 262 (11000); $\lambda_{max}^{0.05\ N\ HCl}$ nm (ε): 262 (11300); $\lambda_{max}^{0.05\ N\ NaOH}$ nm (ε): 260 (11600). MS *m/z*: 328 ($M^+ - C_5H_8O$). *Anal.* Calcd for $C_{19}H_{28}N_2O_8$: C, 55.33; H, 6.84; N, 6.79. Found: C, 55.13; H, 6.88; N, 6.68. Evaporation of the mother liquor afforded further product as a caramel (31.1 g).

9-[2-Deoxy-2-fluoro-3,5-di-*O*-(tetrahydropyran-2-yl)-β-D-ribofuranosyl]uracil (3a) DAST (16 ml, 4 eq) was added dropwise to a cooled solution (−60 °C) of **2** (30.0 g, 73 mmol) in a mixture of CH_2Cl_2 (370 ml) and pyridine (25 ml) under an N_2 atmosphere. After heating at reflux for 3 h, the solution was subjected to the usual work-up and silica gel chromatography to give a caramel (17.2 g, 57%). UV λ_{max}^{MeOH} nm: 262; $\lambda_{max}^{0.05\ N\ HCl}$ nm: 262; $\lambda_{max}^{0.05\ N\ NaOH}$ nm: 262. MS *m/z*: 414 (M^+).

2′-Deoxy-2′-fluorouridine (3b) A solution of **3a** (3.81 g, 9.2 mmol) in EtOH (100 ml) was stirred in the presence of PPTS (1.5 g) at 50 °C for 1 d. After concentration to 3 ml, the solution was chromatographed over a column of Silica gel G (4.2 × 28 cm) with 0—20% EtOH in $CHCl_3$ (2.4 l) to give a caramel (1.48 g, 66%). UV λ_{max}^{MeOH} nm: 260; $\lambda_{max}^{0.05\ N\ HCl}$ nm: 260; $\lambda_{max}^{0.05\ N\ NaOH}$ nm: 259. ^{1}H-NMR (DMSO-d_6) δ: 11.39 (1H, br s, N^3-H), 7.88 (1H, d, J=7.5 Hz, H6), 5.87 (1H, d, J=17.2 Hz, H1′), 5.58 (2H, m, H5, 3′-OH), 5.2 (1H, br s, 5′-OH), 5.0 (1H, d-like, J=54.7 Hz, H2′), 4.12 (1H, m, H3′), 3.4—3.9 (3H, m, H4′, H5′). MS *m/z*: 246 (M^+).

9-[2-Deoxy-2-fluoro-3,5-di-*O*-(tetrahydropyran-2-yl)-β-D-ribofuranosyl]cytosine (4a) 4-Chlorophenyl phosphorodichloridate (9.2 ml) was added dropwise to an ice-cooled solution of **3a** (5.34 g, 12.9 mmol) and 1,2,4-triazole (11 g) in pyridine (70 ml), and the solution was stirred at room temperature for 2 d. Usual work-up of the solution gave the triazolidate as a syrup. The product was dissolved in dioxane (100 ml) and concentrated ammonium hydroxide (33 ml) was added to the solution. After stirring at room temperature for 1 d, the solution was subjected to usual work-up and silica gel chromatography to give **4a** as a syrup (5.02 g, 94%). UV λ_{max}^{MeOH} nm: 271; $\lambda_{max}^{0.05\ N\ HCl}$ nm: 281; $\lambda_{max}^{0.05\ N\ NaOH}$ nm: 270. MS *m/z*: 413 (M^+).

2′-Deoxy-2′-fluorocytidine (4b) A solution of **4a** (5.02 g, 12 mmol) and PPTS (2.0 g, 8 mmol) in EtOH (150 ml) was refluxed for 1 d. After evaporation of the solution, the residue thus obtained was dissolved in water (200 ml) and the aqueous layer was passed through a column of Dowex 1 (OAc^- form, 50 ml). The combined aqueous eluate and washing (500 ml) was concentrated to a small volume to give white crystals (1.96 g, 66%). UV λ_{max}^{MeOH} nm: 270; $\lambda_{max}^{0.05\ N\ HCl}$ nm: 281; $\lambda_{NaOH}^{0.05\ N\ HCl}$ nm: 270.5. mp 115—120 °C.

Typical Procedure for the Synthesis of N^3-Substituted 2′-Deoxy-2′-fluorouridines Benzyl bromide (0.1 ml, 0.82 mmol) was added to a solution of **3b** (123 mg, 0.50 mmol) and K_2CO_3 (118 mg, 0.85 mmol) in DMF (2 ml) and acetone (2 ml), and the solution was stirred at 50 °C for 2 h, then cooled. After evaporation of the solution, the residue was dissolved in a small amount of $CHCl_3$ and chromatographed over a column of Silica gel G (2.2 × 15 cm) with 0—10% EtOH in $CHCl_3$ (400 ml) to give N^3-benzyl-2′-deoxy-2′-fluorouridine (**5a**) as a caramel (172 mg, quantitative). UV λ_{max}^{MeOH} nm (ε): 261 (11200); $\lambda_{max}^{0.05\ N\ HCl}$ nm (ε): 261 (11500); $\lambda_{max}^{0.05\ N\ NaOH}$ nm (ε): 263 (11600). ^{1}H-NMR ($CDCl_3$) δ: 7.55 (1H, d, J=8.6 Hz, H6), 7.23—7.50 (5H, m, $C_6\underline{H}_5CH_2$–), 5.81 (1H, d, J=8.6 Hz, H5), 5.75—5.85 (1H, m, H1′), 5.2 (1H, ddd, J=53.9, 4.9, 3.2 Hz, H2′), 5.10 (2H, d, $C_6H_5C\underline{H}_2$–), 4.52 (1H, m, H3′), 3.98—4.12 (2H, m, 3′-OH, 5′-OH), 3.85 (1H, m, H4′), 2.52 (1H, dd, J=7.0, 3.2 Hz, H5′a), 2.38 (1H, dd, J=7.0, 3.8 Hz, H5′b). MS *m/z*: 336 (M^+). *Anal.* Calcd for $C_{16}H_{17}FN_2O_5 \cdot 1.5H_2O$: C, 52.89; H, 5.55; N, 7.71. Found: C, 52.98; H, 4.85; N, 7.57.

The reaction conditions of analogous reactions are illustrated in Table I.

N^3-(2-Methyl)benzyl-2′-deoxy-2′-fluorouridine (5b) UV λ_{max}^{MeOH} nm (ε): 261 (13700); $\lambda_{max}^{0.05\ N\ HCl}$ nm (ε): 261 (14100); $\lambda_{NaOH}^{0.05\ N\ HCl}$ nm (ε): 263 (14200). ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, d, J=8.1 Hz, H6), 6.93—7.28 (5H, m, $C_6\underline{H}_5CH_2$–), 5.84 (1H, d, J=8.1 Hz, H5), 5.82 (1H, dd, J=18.2, 3.5 Hz, H1′), 5.20 (1H, ddd, J=53.1, 4.8, 1.8 Hz, H2′), 5.10 (2H, d, J=2.5 Hz, $C_6H_5C\underline{H}_2$–), 4.5 (1H, m, H3′), 3.98—4.12 (2H, m, 3′-O$\underline{H}$, 5′-O$\underline{H}$), 3.85 (1H, m, H4′), 2.48 (1H, dd, J=7.1, 3.5 Hz, H5′a), 2.35 (1H, dd, J=7.1, 3.3 Hz, H5′b), 2.42 (3H, s, $-CH_3$). MS *m/z*: 350 (M^+). *Anal.* Calcd for $C_{17}H_{19}FN_2O_5 \cdot 0.5H_2O$: C, 56.82; H, 5.61; N, 7.80. Found: C, 56.15; H, 5.49; N, 7.57.

N^3-(4-Fluoro)benzyl-2′-deoxy-2′-fluorouridine (5c) UV λ_{max}^{MeOH} nm (ε): 260 (13700); $\lambda_{max}^{0.05\ N\ HCl}$ nm (ε): 261 (12600); $\lambda_{max}^{0.05\ N\ NaOH}$ nm (ε): 262 (13400). ^{1}H-NMR ($CDCl_3$) δ: 7.55 (1H, d, J=6.7 Hz, H6), 6.90—7.50 (5H, m, $C_6\underline{H}_5CH_2$–), 5.81 (1H, d, J=6.7 Hz, H5), 5.80 (1H, dd, J=3.4, 19.0 Hz, H1′), 5.20 (1H, ddd, J=4.9, 53.7 Hz, H2′), 5.05 (2H, d, $C_6H_5C\underline{H}_2$–), 4.53 (1H, m, H3′), 3.98—4.12 (2H, m, 3′-O$\underline{H}$, 5′-O$\underline{H}$), 3.85 (1H, m, H4′), 2.42 (1H, dd, J=5.5, 2.9 Hz, H5′a), 2.28 (1H, dd, J=5.5, 3.1 Hz, H5′b). MS *m/z*: 354 (M^+). *Anal.* Calcd for $C_{16}H_{16}F_2N_2O_5 \cdot H_2O$: C, 51.61; H, 4.87; N, 7.52. Found: C, 51.91; H, 4.71; N, 7.45.

N^3-(4-Fluorophenacyl)-2′-deoxy-2′-fluorouridine (6) UV λ_{max}^{MeOH} nm: 248; $\lambda_{max}^{0.05\ N\ HCl}$ nm: 249; $\lambda_{max}^{0.05\ N\ NaOH}$ nm: 250. ^{1}H-NMR ($CDCl_3$) δ: 7.73 (1H, d, J=6.9 Hz, H6), 7.10—8.08 (5H, m, $C_6\underline{H}_5CH_2$–), 5.85 (1H, d, J=6.9 Hz, H5), 5.82 (1H, dd, J=14.9, 2.4 Hz, H1′), 5.20 (1H, ddd, J=43.2, 4.2, 2.3 Hz, H2′), 5.33 (2H, s, $C_6H_5C\underline{H}_2$–), 4.5 (1H, m, H3′), 3.98—4.12 (2H, m, 3′-O$\underline{H}$, 5′-O$\underline{H}$), 3.82 (1H, m, H4′), 2.6 (1H, dd, J=5.7, 3.2 Hz, H5′a), 2.48 (1H, dd, J=5.7, 2.8 Hz, H5′b). MS *m/z*: 382 (M^+). *Anal.* Calcd for $C_{17}H_{16}F_2N_2O_6 \cdot H_2O$: C, 51.00; H, 4.53; N, 7.00. Found: C, 51.21; H, 4.12; N, 6.92.

Hypnotic Activity The compounds tested were suspended in 1% Tween 80-saline solution because of their insolubility in saline. The compounds were given by i.c.v. and this method is able to evaluate the real CNS activity without the influence of hepatic metabolism. The sleeping time produced by compounds tested in mice was measured as the time between the loss and recovery of righting reflex.

Effects of Uridine Derivatives on Pentobarbital-Induced Sleep The compound tested was injected, i.c.v., to mice 15 min before pentobarbital challenge. Sodium pentobarbital was administered intraperitoneally (i.p.) to mice at a dose of 40 mg/kg. Pentobarbital-induced sleeping time in mice was measured as the time between the loss and recovery of the righting reflex. The sleeping time modified by uridine derivatives was

compared with that of the vehicle control group.

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