Synthesis and γ-Radiolysis of 2′-Deoxy-5-fluorouridine and 5-Fluorouridine Derivatives

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Seventeen compounds having a variety of substituents at the 3- and 5′-positions of 2′-deoxy-5-fluorouridine (5-FUdR) and 5-fluorouridine (5-FUR) were synthesized, and their γ-radiolysis in aqueous solutions were studied. The compounds having thioureido (RNHCSNH, R = H, $PhCH_2$, acyl) and thiocarbonylamino (XCSNH, X = $PhCH_2S$, PhO) groups at the 3-position of 5-FUdR were efficiently cleaved to give 5-FUdR with high G values upon γ-irradiation of their aqueous solutions. The active species for these cleavage reactions were hydrated electron (e^-_{aq}), H· and HO·. However, the compounds having a dimethylsulfoxyimino group at 3-position of 5-FUdR and 5-FUR afforded 5-FUdR and 5-FUR only under the radiolysis conditions where e^-_{aq} becomes a principal active species. The compound having a 2-benzoylthiazoylthiocarbonylamino group at the 3-position of 5-FUdR showed the highest reactivity toward HO·. The mechanisms of these γ-radiolysis reactions are discussed. The examination of anticellular activities of γ-irradiated compounds having a thiocarbonylamino group at the 3-position of 5-FUdR toward murine Sarcoma 180 cells revealed that these compounds may be utilized as a candidate for a radiation-induced drug (RID).

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Introduction.

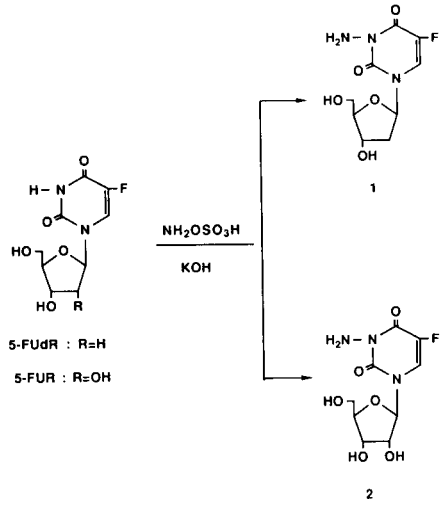
Recently, we have proposed the concept of "Radiation-Induced drug (RID)" as a new type of drug, especially for cancer therapy [1]. This drug is a sort of prodrug in which an active drug is protected by an appropriate functional group that can be removed by γ-radiolysis to regenerate the active drug [1]. On the basis of this concept, we have studied the γ-radiolysis of a variety of 1-substituted 5-fluorouracils in aqueous solutions and found that 1-sulfonyl- and 1-thioureido-5-fluorouracils efficiently generate 5-fluorouracils (5-FU) which is an active drug for cancer therapy. However, 5-fluorodeoxyuridine (5-FUdR) and 5-fluorouridine (5-FUR) have been reported to exhibit a much stronger cytotoxic activity than 5-FU [2]. For this reason, we have chosen their derivatives as candidates for RID and studied the γ-radiolysis of these compounds in aqueous solutions. We now report the synthesis of 3- and 5′-*O*-substituted 5-FUdR and 5-FUR derivatives and their γ-radiolysis in aqueous solutions.

Results and Discussion.

Preparation of Materials.

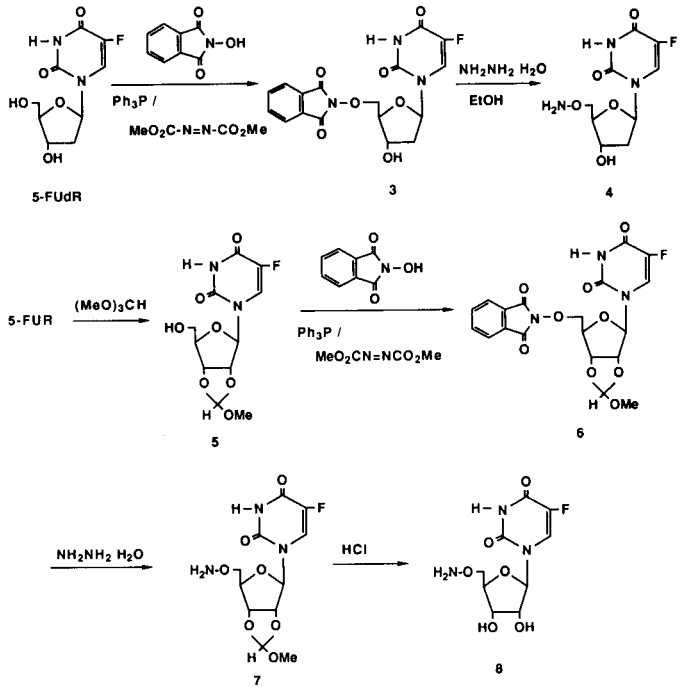
The materials tested for the γ-radiolysis are listed in Table 1. They were synthesized mostly from 5-FUdR *via* its 3-amino and 5′-aminooxy derivatives. One compound was synthesized from 5-FUR *via* its 3-amino derivative. These amino and aminooxy derivatives were prepared *via* the routes shown in Schemes 1 and 2.

Scheme 1

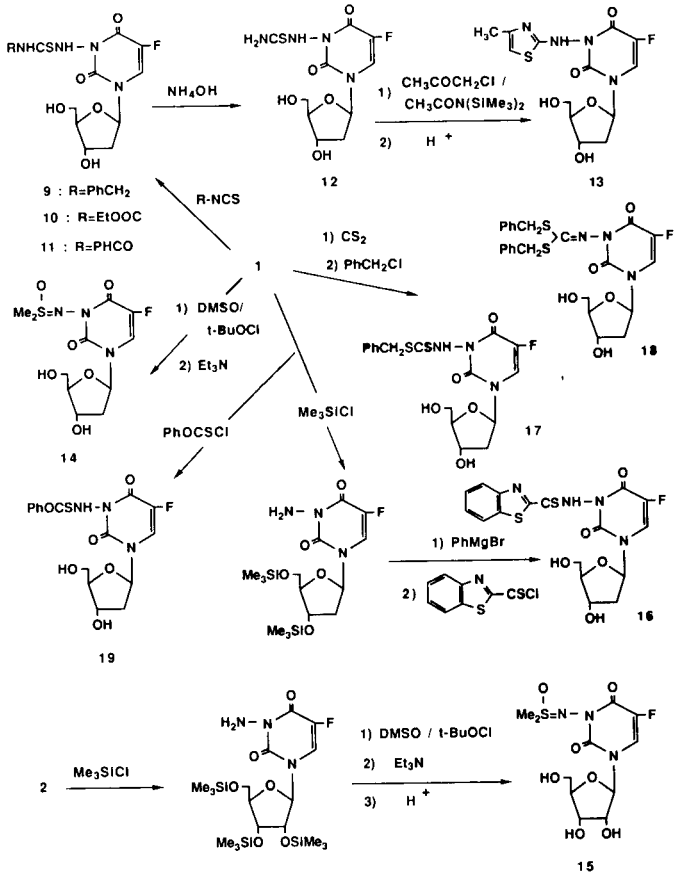


The reaction of 5-FUdR and 5-FUR with hydroxylamine-*O*-sulfonic acid in the presence of potassium hydroxide in *N*,*N*-dimethylformamide (DMF) gave 3-amino-5-FUdR (**1**) and 3-amino-5-FUR (**2**), respectively. In preparation of 5′-aminooxy-5-FUdR (**4**), 5-FUdR was first converted to 5′-phthalimidoxy derivative **3** by the reaction with *N*-hydroxyphthalimide using triphenylphosphine and dimethyl azodicarboxylate as a condensation agent. No protection of the hydroxy group on C-3′ of 5-FUdR was needed in this condensation. The hydrazonolysis of **3** with

Scheme 2

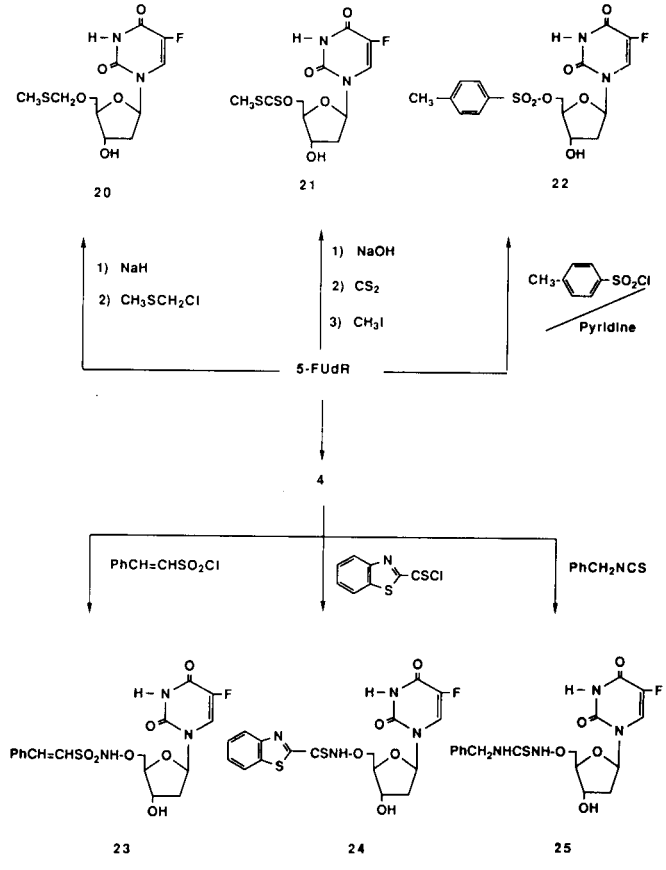


Scheme 3



hydrazine hydrate in ethanol gave **4**. The 5′-aminooxy derivative **8** of 5-FUR could be synthesized *via* this route. In this case, however, the hydroxy groups on C-2′ and C-3′ of 5-FUR had to be protected by transforming them into the 1,3-dioxorane derivative **5** (Scheme 2).

Scheme 4



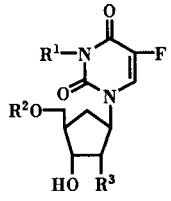
Schemes 3 and 4 show the synthetic routes of compounds which were subjected to the γ-radiolysis. The reaction of **1** with three isothiocyanate compounds (RNCS, R = $PhCH_2$, EtO_2C, PhCO) in DMF gave 3-(*N*-substituted thioureido)-5-FUdR derivatives **9**, **10**, and **11**. The ammonolysis of **11** with ammonium hydroxide yielded 3-(thioureido)-5-FUdR (**12**). Treatment of **12** with chloroacetone in the presence of bis(*N*-trimethylsilyl)acetamide, followed by acid hydrolysis with *p*-toluenesulfonic acid, gave 3-[(4-methylthiazol-2-yl)amino]-5-FUdR (**13**). The reaction of **1** with dimethyloxosulfonium cation, which was generated *in situ* from dimethyl sulfoxide (DMSO) and *t*-butyl hypochlorite in dichloromethane and then treatment with triethylamine afforded 3-dimethylsulfoxyimidyl-5-FUdR (**14**). By applying this methodology, 3-dimethylsulfoxyimidyl-5-FUR (**15**) was synthesized from **2**. In this synthesis, three hydroxy groups on C-2′, C-3′ and C-5′ of **2** were first protected by the trimethylsilyl group. The reaction of

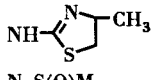
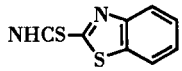
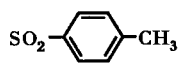
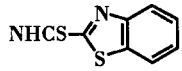
2′,3′,5′-*O*-tris(trimethylsilyl)-5-FUR with the dimethyloxosulfonium cation and triethyl amine, followed by acid hydrolysis, gave **15**. In the synthesis of 3-(benzothiazol-2-yl)-thiocarbonylamino-5-FUdR (**16**), **1** was first transfered into 3-amino-3′,5′-*O*-bis(trimethylsilyl)-5-FUdR by treating with chlorotrimethylsilane. This compound was converted into the amide ion by treating with phenylmagnesium bromide in THF. The reaction of the amide ion with 2-chlorothiocarbonylbenzothiazole, followed by hydrolysis, afforded **16**. Treatment of **1** with carbon disulfide and then with benzyl chloride gave 3-[(benzylthio)thiocarbonyl]amino-5-FUdR (**17**). However, a similar treatment of **1** with carbon disulfide and benzyl chloride in the presence of triethylamine afforded 3-[bis(benzylthio)methylene]imino-5-FUdR (**18**). On the other hand, the reaction of **1** with phenoxythiocarbonyl chloride in the presence of 4-dimethylaminopyridine in DMF yielded 3-(phenyoxythiocarbonyl)amino-5-FUdR (**19**).

Compounds **20**, **21** and **22** were derived directly from 5-FUdR. Treatment of 5-FUdR with sodium hydride, followed by reaction with (methylthio)methyl chloride in THF gave 5′-*O*-(methylthiomethyl)-5-FUdR (**20**). 5′-*O*-[(Methylthio)thiocarbonyl]-5-FUdR (**21**) was obtained by the reaction of 5-FUdR with carbon disulfide in the presence of sodium hydroxide and the subsequent treatment of the dithiocarboxylate with methyl iodide. The reaction of 5-FUdR with *p*-toluenesulfonyl chloride in pyridine gave 5′-*O*-[(4-methylphenyl)sulfonyl]-5-FUdR (**22**). Compounds **23** and **24** were, respectively, synthesized from **4** by the reactions with 2-phenylethenesulfonyl chloride and

Table 1

G Values for the Formation of 5-FUdR or 5-FUR upon γ-Irradiation of Aqueous Solutions of 5-FUdR or 5-FUR Derivatives



Compound No	R^1	R^2	R^3	G(5-FUdR) or G(5-FUR) e_{aq}^- [a]	$H^\bullet$ [b]	$^\bullet OH$ [c]
9	$NHCSNHCH_2Ph$	H	H	0.40	0.60	0.27
10	$NHCSNHCO_2Et$	H	H	0.73	0.71	0.24
11	NHCSNHCOPh	H	H	0.64	0.10	0.24
12	$NHCSNH_2$	H	H	0.29	0.69	0.35
13		H	H	0.41	–	0.22
14	$N{=}S(O)Me_2$	H	H	0.42	trace	trace
15	$N{=}S(O)Me_2$	H	OH	0.65	trace	trace
16		H	H	trace	trace	trace
17	$NHCS_2CH_2Ph$	H	H	0.31	0.27	0.32
18	$N{=}C(SCH_2Ph)_2$	H	H	trace	trace	trace
19	NHCSOPh	H	H	0.35	0.37	0.25
20	CH_2SCH_3	H	H	trace	0.14	0.17
21	H	CS_2Me	H	–	trace	0.46
22	H		H	0.11	0.08	0.07
23	H	$NHSO_2CH{=}CHPh$	H	0.50	0.28	0.40
24	H		H		hydrolysis	
25	H	$NHCSNHCH_2Ph$	H		hydrolysis	

[a] γ-Irradiation was carried out in aqueous 1% (v/v) methanol solution. [b] γ-Irradiation was carried out in aqueous 0.05 *M* sulfuric acid solution containing 1% (v/v) methanol. [c] γ-Irradiation was carried out in aqueous 1% (v/v) acetonitrile solution saturated with nitrous oxide gas.

2-(chlorothiocarbonyl)benzothiazole in the presence of triethylamine. Treatment of **4** with benzyl isothiocyanate in dimethylacetamide gave **25**.

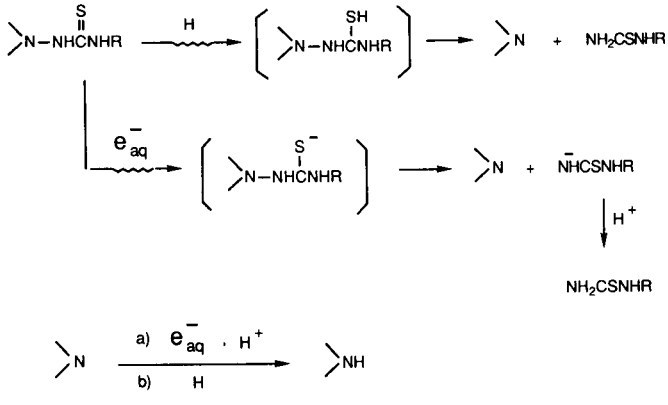
Radiolysis.

γ-Irradiation of aqueous solutions usually results in generation of a variety of transient species such as an hydrated electron (e^-_{aq}), an hydroxyl radical (HO·) and an hydrogen atom (H·) that act as active species of successive chemical reactions. Such active species are generated by the γ-radiolysis of water. However, we have previously demonstrated that types of active species can be practically controlled by adding chemical substances into reaction systems. For example, if the γ-radiolysis is conducted in an aqueous 1% (v/v) methanol solution, e^-_{aq} becomes a principal active species. However, if the γ-radiolysis is conducted in an aqueous 1% (v/v) acetonitrile solution saturated with nitrous oxide, HO· becomes a principal active species. The γ-radiolysis in an aqueous 0.05 *M* sulfuric acid solution containing 1% (v/v) methanol produces H· as a principal active species.

The γ-radiolysis of **9-25** was carried out under three different conditions where e^-_{aq}, HO· and H· are, respectively, generated as a principal active species. After irradiation of γ-ray of 100 Gy from a ^{137}Cs source, the amounts of 5-FUdR and 5-FUR produced by the γ-radiolysis were analyzed and the G values for the formation of these compounds were calculated. The results are given in Table 1. The efficiency of the γ-radiolysis to give 5-FUdR and 5-FUR depended on the substituents attached at the 3- and 5'-positions of 5-FUdR and 5-FUR and also on the nature of active species involved.

The results shown in Table 1 revealed that the compounds having a thioureido function at the 3-position of 5-FUdR such as **9-12** are efficiently cleaved to produce 5-FUdR upon γ-irradiation of their aqueous solutions. Furthermore, this cleavage reaction is promoted mainly by the reductive species e^-_{aq} and H· and to a lesser extent by the oxidative species HO·. Similar reactivity features of the thioureido group was also found in the γ-radiolysis of 5-FU derivatives [1]. A mechanistic explanation for this reactivity feature is shown in Scheme 5 in which N represents nitrogen at 3-position of 5-FUdR.

Scheme 5



The thioureido group has both a high electron-accepting ability and a high hydrogen atom-accepting ability. In addition, the radical anion and the free radical, which are generated respectively by electron capture and hydrogen atom abstraction, undergo N-N bond cleavage ultimately to form 5-FUdR and thiourea derivatives.

The compounds having NHCSX (X = SR, OR) function such as **17** and **19** would react with the same active species in a similar manner and undergo the N-N bond cleavage upon γ-irradiation of their aqueous solutions.

Table 2

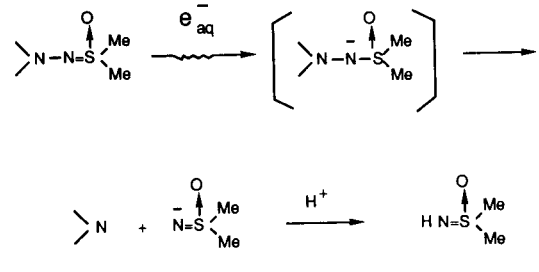
Effect of Reaction Conditions on G (5-FUR) Values in the γ-Radiolysis of Aqueous Solutions of **15**

Conditions	G (5-FUR) [a]
(A) Aqueous solution saturated with nitrogen	0.65
(B) Aqueous solution saturated with oxygen	0.16
(C) Aqueous 1% (v/v) methanol solution saturated with nitrogen	1.08
(D) Aqueous 1% (v/v) methanol solution saturated with oxygen	0.33

[a] G values for the formation of 5-FUR.

The other interesting feature of the γ-radiolysis is that the compounds having a dimethyl sulfoxyimino function such as **14** and **15** react preferentially with e^-_{aq}. This reactivity feature was further confirmed by examining the γ-radiolysis of **15** under a variety of conditions. The results are shown in Table 2. The G (5-FUR) value was largest in the γ-radiolysis under the conditions (Conditions C) where the maximal generation of e^-_{aq} can be attained. The G (5-FUR) value was decreased by the addition of oxygen, suggesting that a principal active species in the γ-radiolysis of **15** is e^-_{aq}. The results also suggest that **14** and **15** are cleaved *via* the route shown in Scheme 6.

Scheme 6



It may also be important to note that HO· becomes a principal active in the γ-radiolysis of **21**, although the mechanism of the cleavage reaction of this compound is not clear at present.

Biological Activity.

In order to test the effectiveness of the compounds prepared in this investigation as RID, anticellular activities of **9**, **10** and **11** toward murine Sarcoma 180 cells *in vitro* were studied. Sample solutions to be tested were prepared by irradiating physiological salt solutions of these compounds with γ-rays from a ^{137}Cs source. These sample solutions were added to a RPMI 1640 culture medium containing murine Sarcoma 180 cells (1 x 10^4 cells/ml). The anticellular activities of the γ-irradiated samples were assayed by counting the number of cells after culturing the cells at 37° for 72 hours in the culture media containing the sample solutions. The anticellular activity was defined as follows:

$$\text{Anticellular activity (\%)} = \frac{\text{Number of cells after culturing the cells in the medium containing a (γ-irradiated) sample to be tested for the anticellular activity under definite conditions}}{\text{Number of cells after culturing the cells in the same media in the absence of the sample under the same conditions}} \times 100$$

The results are shown in Figure 1. The anticellular activities of the γ-irradiated solutions of **9**, **10** and **11** were potentiated as compared with non-irradiated samples. In addition, we found that the anticellular activity of **9** increased with increasing irradiated γ-ray doses (Figure 2).

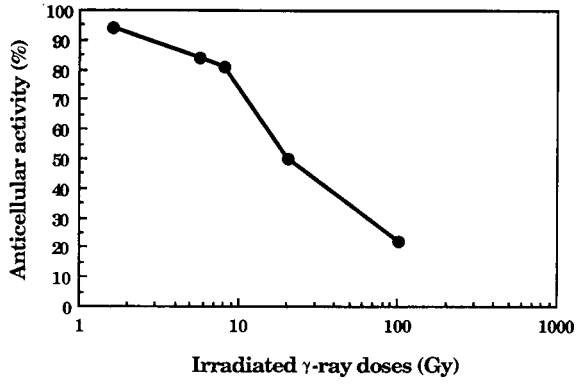


Figure 2. Dependence of the anticellular activity of 9 toward murine P388 cells on irradiated γ-ray doses

These results strongly suggest that FUdR is indeed generated by the γ-radiolysis of **9**, **10** and **11** even under physiological conditions, and indicate that these compounds cound be utilized as a candidate for RID.

EXPERIMENTAL

Melting points were determined with a Buchi 510 capillary melting point apparatus and are uncorrected. The ^1H nmr spectra were recorded on a JEOL JNM-GX270 FT NMR spectrometer using TMS as the internal standard. Infrared spectra were obtained on a Shimadzu IR-4000 instrument. Column chromatog-

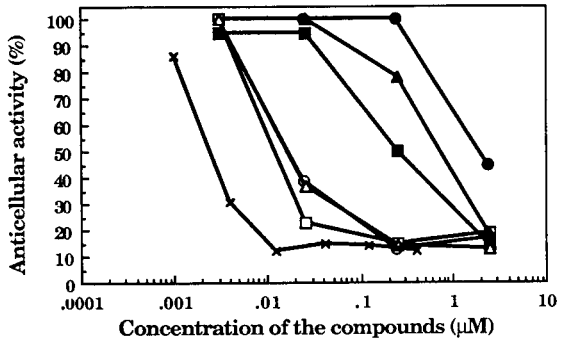


Figure 1. Anticellular activities of γ-irradiated (246 Gy) and non-irradiated samples of 9, 10 and 11 toward murine Sarcoma 180 : the anticellular activities were plotted against concentrations of the samples (for the definition of the anticellular activity, see text). —●— , non-irradiated 9 ; —○— , irradiated 9 ; —■— , non-irradiated 10 ; —□— , irradiated 10 ; —▲— , non-irradiated 11 ; —△— , irradiated 11 ; —×— FUdR non-irradiated

raphy was carried out on silica gel (Silica gel 60, Merck). The purity of compounds was checked by tlc on silica gel plates (Silica gel 60, F 254, Merck). Elementary analyses were performed by a Yanagimoto CHN Corder MT-3, and the errors were within 0.4% of the calculated values. γ-Irradiations were carried out by use of a ^{137}Cs source at the National Institute of Genetics. The hplc was performed on a Shimadzu LC-3A, using a 25 cm x 4 mm i.d. stainless steel column packed with a RP-18 chemically bonded silica gel (Lichrosorb, 10 μm, Merck).

3-Amino-2'-deoxy-5-fluorouridine (**1**).

A solution of hydroxylamine-*O*-sulfonic acid (9.2 g, 78.6 mmoles) in DMF (60 ml) was added to a suspension of 2'-deoxy-5-fluorouridine (5-FUdR, 10.0 g, 42.7 mmoles) and potassium hydroxide (9.2 g, 164.3 mmoles) in DMF (300 ml) over 1.5 hours under ice-bath cooling. The mixture was stirred at room temperature for 20 hours and concentrated. The solid residue was recrystallized from 2-propanol (500 ml) to give 7.24 g (68%) of **1** mp 144.5-145.0°; tlc (chloroform-methanol, 4:1) Rf 0.30; ir (potassium bromide): 1715, 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.13-2.18 (2H, m), 3.53-3.70 (2H, m), 3.89-3.95 (1H, m), 4.20-4.30 (1H, m), 5.19 (1H, t, J = 4.9 Hz), 5.29 (1H, d, J = 4.4 Hz), 5.50-5.52 (1H, bs), 6.19 (1H, dd, J = 6.4 Hz, 20 Hz), 8.29 (1H, d, J = 6.8 Hz), 11.80 (1H, bs); ms: (m/z) 261 (M^+).

Anal. Calcd. for $C_9H_{12}N_3O_5F$: C, 41.39; H, 4.63; N, 16.09. Found: C, 41.21; H, 4.49; N, 15.88.

3-Amino-5-fluorouridine (**2**).

Hydroxylamine-*O*-sulfonic acid (8.60 g, 73.5 mmoles) in DMF (140 ml) was added slowly over 1 hour to a cooled solution of 5-FUR (10.0 g, 40 mmoles) and potassium hydroxide (11.3 g, 202 mmoles) in DMF (300 ml) at 0°, and stirred at the same temperature for 1 hour and at room temperature for 15 hours. The resulting mixture was diluted with water (250 ml), adjusted to *p*H 7.2 with 1*M* hydrochloric acid and concentrated. The solid residue was recrystallized from 2-propanol to give white crystals 8.84 g (84%) of **2**, mp 105-107°; ir (potassium bromide): 1720, 1650 cm^{-1}; ^1H nmr (DMSO-d_6) δ = 3.60 (1H, dd, J = 12.2 Hz, 2.4 Hz), 3.71 (1H, dd, J = 12.2 Hz, 2.4 Hz), 3.83-3.96 (1H, m), 3.96-4.08 (2H, m), 5.22-6.08 (5H, m), 5.78-5.84 (1H, m), 8.41 (1H, d, J = 7.3 Hz); ms: (m/z) 277 (M^+).

Anal. Calcd. for $C_9H_{12}N_3O_6F$: C, 39.00; H, 4.36; N, 15.16. Found: C, 38.63; H, 4.21; N, 14.88.

2'-Deoxy-5-fluoro-5'-*O*-(*N*-phthalimidyl)uridine (**3**).

Dimethyl azodicarboxylate (196 mg, 1.13 mmoles) was added slowly to a suspension of 5-FUdR (247 mg, 1.06 mmoles), triphenylphosphine (263 mg, 1.00 mmole) and *N*-hydroxyphthalimide (163 mg, 1.00 mmole) in anhydrous THF (5 ml). The mixture was stirred at room temperature for 17.5 hours and concentrated. The residue was extracted with aqueous ethyl acetate and the organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (30:1) to give 100 mg (26%) of **3**, mp 218.5-219.5°; tlc (chloroform-methanol, 4:1) Rf 0.58; ir (potassium bromide): 1780, 1720, 1685, 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.06-2.30 (2H, m), 4.02-4.16 (1H, m), 4.27-4.47 (3H, m), 5.48 (1H, d, J = 4.4 Hz), 6.17 (1H, dd, J = 6.4 Hz, 1.5 Hz), 7.81-7.94 (4H, m), 8.01 (1H, d, J = 7.3 Hz), 11.82 (1H, bs); ms: (m/z) 391 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_3O_7F$: C, 52.18; H, 3.61; N, 10.74. Found: C, 52.42; H, 3.67; N, 10.59.

5'-*O*-Amino-2'-deoxy-5-fluorouridine (**4**).

A mixture of **3** (1.00 g) and hydrazine hydrate (0.13 ml) in anhydrous ethanol (80 ml) was refluxed for 1 hour and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (4:1) to give 330 mg (49%) of **4**, mp 182.0-183.0°; tlc (chloroform-methanol, 4:1) Rf 0.28; ir (potassium bromide): 3300, 3240, 1693 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.02-2.20 (2H, m), 3.67 (1H, dd, J = 11.2 Hz, 5.4 Hz), 3.75 (1H, dd, J = 11.2 Hz, 3.9 Hz), 3.88-3.98 (1H, m), 4.14-4.24 (1H, m), 5.32 (1H, bs), 6.12 (1H, dd, J = 6.4 Hz, 2.0 Hz), 5.8-6.5 (2H, bs), 7.94 (1H, d, J = 6.8 Hz), 11.80 (1H, bs); ms: (m/z) 261 (M^+).

Anal. Calcd. for $C_9H_{12}N_3O_5F$: C, 41.39; H, 4.63; N, 16.09. Found: C, 41.19; H, 4.45; N, 16.30.

2',3'-Bis(*O*-methoxymethylene)-5-fluorouridine (**5**).

A mixture of 5-FUR (10.0 g, 40 mmoles), trimethoxymethane (6.89 g, 93 mmoles) and *p*-toluenesulfonic acid (730 mg, 4.2 mmoles) in acetonitrile (400 ml) was stirred at room temperature for 6 hours, and then potassium methoxide (387 mg, 5.5 mmoles) in methanol (60 ml) was added. The mixture was stirred for 1.5 hours and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (20:1) to give 9.13 g (79%) of **5**, mp 131.0-133.0°; ir (potassium bromide): 1725, 1685 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.21 (3H, s), 3.57-3.70 (2H, m), 4.08-4.12 and 4.16-4.23 (1H, m), 4.79 and 4.85 (1H, dd, J = 3.6 Hz, 7.6 Hz), 4.96-5.03 (1H, m), 5.14-5.28 (1H, m), 5.79-5.83 and 5.94-5.99 (1H, m), 6.01 and 6.10 (1H, s), 8.17 (1H, d, J = 6.8 Hz), 11.90 (1H, bs); ms: (m/z) 304 (M^+).

Anal. Cacld. for $C_{11}H_{13}N_2O_7F$: C, 43.42; H, 4.28; N, 9.21. Found: C, 43.53; H, 4.33; N, 9.46.

2',3'-Bis(*O*-methoxymethylene)-5-fluoro-5'-*O*-(*N*-phthalimidyl)uridine (**6**).

Diethyl azodicarboxylate (20.1 g, 116 mmoles) in THF (15 ml) was added slowly into a suspension of **5** (9.13 g, 29 mmoles), *N*-hydroxyphthalimide (17.1 g, 105 mmoles) and triphenylphosphine (27.5 g, 105 mmoles) in THF (300 ml) at room temperature over 1 hour, stirred at the same temperature for 18 hours and then concentrated. The residue was chromatographed on silica gel with chloroform-acetone (9:1) to give 9.26 g (69%) of **6**, mp 199.0-201.0°; tlc (chloroform-methanol, 4:1) to Rf 0.72; ir (potassium bromide): 1780, 1720, 1690 cm^{-1}; ^1H nmr (DMSO-d_6) δ = 3.21 and 3.30 (3H, s), 3.75-3.89 (2H, m), 4.29-4.35 and 4.40-4.46 (1H, m), 4.75 and 4.85 (1H, dd, J = 7.4 Hz, 4.4 Hz and 6.3 Hz, 4.0 Hz), 5.02-5.07 (1H, m), 5.75-5.79 and 5.90-5.95 (1H, m), 6.02 and 6.10 (1H, s) 7.83-7.92 (4H, m), 8.15 (1H, d, J = 6.5 Hz), 11.86 (1H, bs); ms: (m/z) 449 (M^+).

Anal. Calcd. for $C_{19}H_{16}N_3O_9F$: C, 50.79; H, 3.59; N, 9.35. Found: C, 50.94; H, 3.78; N, 9.54.

5'-*O*-Amino-2',3'-bis(*O*-methoxymethylene)-5-fluorouridine (**7**).

A mixture of **6** (9.26 g, 20.6 mmoles) and hydrazine hydrate (1.2 ml) in ethanol (650 ml) was refluxed for 12 hours and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (9:1) to give 2.97 g (45%) of **7**, mp 130-134°; tlc (chloroform-methanol, 20:1) Rf 0.45; ir (potassium bromide): 1690

cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.21 and 3.31 (3H, s), 3.68-3.32 (2H, m), 4.21-4.29 and 4.32-4.41 (1H, m), 4.75 and 4.85 (1H, dd, J = 7.3 Hz, 4.4 Hz and 6.4 Hz, 3.9 Hz), 5.00-5.08 (1H, m), 5.74-5.77 and 5.86-5.92 (1H, m), 6.01 and 6.10 (1H, s), 8.06 and 8.11 (1H, d, J = 6.8 Hz), 11.86 (1H, bs); ms: (m/z) 319 (M^+).

Anal. Calcd. for $C_{11}H_{14}N_3O_7F$: C, 41.39; H, 4.42; N, 13.16. Found: C, 41.62; H, 4.31; N, 13.02.

5'-*O*-Amino-5-fluorouridine (**8**).

To a solution of **7** (2.97 g, 9.3 mmoles) in methanol (100 ml) was added 1 *M* hydrochloric acid (18.6 ml). The mixture was stirred at room temperature for 7 hours and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (4:1) to give 3.08 g (95%) of **8**, mp 124-126°; tlc (chloroform-methanol, 2:1) Rf 0.32; ir (potassium bromide): 1710, 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.97-4.08 (3H, m), 4.17-4.28 (2H, m), 5.73 (1H, dd, J = 4.9 Hz, 1.5 Hz), 7.90 (1H, d, J = 6.8 Hz), 10.89 (1H, bs), 11.91 (1H, d, J = 4.9 Hz); ms: (m/z) 277 (M^+).

Anal. Calcd. for $C_9H_{12}N_3O_6F$: C, 39.00; H, 4.36; N, 15.16. Found: C, 39.21; H, 4.20; N, 15.38.

2'-Deoxy-5-fluoro-3-(*N'*-Benzylthioureido)uridine (**9**).

A solution of **1** (500 mg, 1.9 mmoles) and benzyl isothiocyanate (353 mg, 2.4 mmoles) in DMF (25 ml) was stirred at room temperature for 20 hours and then concentrated. The residue was extracted with aqueous ethyl acetate, and the organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-acetone (4:1) to give 610 mg (74%) of **9**, mp 169-170°; tlc (ethyl acetate) Rf 0.20; ir (potassium bromide): 1725, 1675, 1545, 1180 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.05-2.28 (2H, m), 3.50-3.75 (2H, m), 3.85-3.90 (1H, m), 4.16-4.33 (1H, bs), 4.71 (2H, bs), 5.24 (1H, bs), 5.31 (1H, bs), 6.08-6.25 (1H, m), 7.10-7.50 (5H, m), 8.30-8.50 (1H, m), 8.85 (1H, bs), 9.88 (1H, bs); ms: (m/z) 410 (M^+).

Anal. Calcd. for $C_{17}H_{19}N_4O_5FS$: C, 49.75; H, 4.67; N, 13.65. Found: C, 49.82; H, 4.61; N, 13.59.

2'-Deoxy-5-fluoro-3-(*N'*-ethoxycarbonylthioureido)uridine (**10**).

Compound **10** was obtained in 73% yield from **1** (500 mg, 1.9 mmoles) and ethoxycarbonyl isothiocyanate (314 mg, 2.4 mmoles) in a similar manner to that for the synthesis of **9**, mp 126-128°; tlc (ethyl acetate) Rf 0.38; ir (potassium bromide): 1730, 1690, 1525, 1200 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.27 (3H, t, J = 7.1 Hz), 2.15-2.28 (2H, m), 3.53-3.73 (2H, m), 3.78-3.86 (1H, m), 4.08-4.42 (1H, m), 4.23 (2H, q, J = 7.2 Hz), 5.24 (1H, dd, J = 10.3 Hz, 4.8 Hz), 5.32 (1H, d, J = 4.4 Hz), 6.12 (1H, dd, J = 1.1 Hz, 6.1 Hz), 8.46 (1H, d, J = 6.8 Hz), 11.39 (1H, bs), 11.73 (1H, bs); ms: (m/z) 392 (M^+).

Anal. Calcd. for $C_{13}H_{17}N_4O_7FS$: C, 39.79; H, 4.37; N, 14.28. Found: C, 39.91; H, 4.17; N, 14.39.

2'-Deoxy-5-fluoro-3-(*N'*-benzoylthioureido)uridine (**11**).

Benzoyl isothiocyanate (200 mg, 1.27 mmoles) was added to a solution of **1** (300 mg, 1.15 mmoles) in DMF (10 ml). After stirring at room temperature for 1 hour, the mixture was concentrated and extracted with aqueous ethyl acetate. The ethyl acetate layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (9:1) to give 290 mg (75%) of **11**, mp 115° dec; tlc (chloroform-methanol H, 4:1) Rf 0.60; ir (potassium bromide): 3430, 1740, 1690, 1525, 1195 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.12-2.19 (2H, m), 3.52-3.75 (2H, m), 3.80-3.90 (1H, m), 4.19-4.37 (1H, m), 5.24 (1H, bs), 5.32 (1H, d, J = 4.3 Hz), 6.20 (1H, dd, J = 6.6 Hz, 6.6 Hz), 7.41-7.60 (2H, m), 7.62-7.78 (1H, m), 7.82-8.12 (2H, m), 8.48 (1H, d, J = 8.3 Hz), 12.07 (1H, s), 12.23 (1H, s); ms: (m/z) 424 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_4O_6FS$: C, 48.11; H, 4.04; N, 13.20. Found: C, 48.00; H, 3.98; N, 13.31.

2'-Deoxy-5-fluoro-3-(thioureido)uridine (**12**).

To a solution of **11** (170 mg, 0.40 mmole) in ethanol (10 ml) was added concentrated ammonium hydroxide (10 ml). The mixture was stirred at room temperature for 20 hours and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (4:1) to give 70 mg (55%) of **12**, mp 130-132°; tlc (chloroform-methanol, 4:1) Rf 0.15; ir (potassium bromide): 3400, 1735, 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.20-2.28 (2H, m), 3.55-3.77 (2H, m), 3.78-3.92 (1H, m), 4.17-4.37 (1H, m), 5.10-5.29 (1H, m), 5.29-5.37 (1H, m), 6.03-6.25 (1H, m), 7.88 and 7.97 (1H, bs), 8.11 and 8.16 (1H, bs), 8.30-8.48 (1H, m), 9.73 (1H, bs); ms: (m/z) 320 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_4O_5FS$: C, 37.50; H, 4.09; N, 17.49. Found: C, 37.78; H, 4.27; N, 17.62.

2'-Deoxyl-5-fluoro-3-[(4-methylthiazol-2-yl)amino]uridine (**13**).

A mixture of **12** (300 mg, 0.94 mmole), chloroacetone (0.375 ml) and bis(*N*-trimethylsilyl)acetamide (1.16 ml) in dioxane (10 ml) was stirred at 80-90° for 8 hours, and concentrated. The residue was dissolved in ethanol (10 ml), and the solution was stirred at room temperature for 1 hour in the presence of *p*-toluenesulfonic acid (100 mg) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (6:1) to give 60 mg (18%) of **13**, mp 166-167°; tlc (chloroform-methanol, 4:1) Rf 0.50; ir (potassium bromide): 1720, 1680, 1480 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.09 (3H, s), 2.13-2.28 (2H, m), 3.52-3.73 (2H, m), 3.74-3.88 (1H, m), 4.20-4.32 (1H, m), 5.23 (1H, t, J = 4.9 Hz), 5.31 (1H, d, J = 4.4 Hz), 6.10-6.23 (1H, m), 6.43 (1H, s), 8.43 (1H, d, J = 7.3 Hz), 10.28 (1H, bs); ms: (m/z) 358 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_4O_5FS$: C, 43.58; H, 4.22; N, 15.64. Found: C, 43.52; H, 4.11; N, 15.58.

2'-Deoxy-3-(dimethylsulfoxyimidyl)-5-fluorouridine (**14**).

A mixture of DMSO (100 mg, 1.28 mmoles) and dichloromethane (1 ml) was added into a dichloromethane solution (2 ml) containing a few drops of *t*-butyl hypochlorite at −60° and stirred at the same temperature for 1 hour. Compound **1** (100 mg, 0.38 mmole) was then added to the above mixture. The resulting mixture was kept at −50° for 4 hours, then triethylamine (0.2 ml) was added and stirred at room temperature overnight. The reaction mixture was concentrated and the residue was chromatographed on silica gel with chloroform-methanol (9:1) to give 30 mg (23%) of **14**, mp 115°; tlc (chloroform-methanol, 9:1) Rf 0.40; ir (potassium bromide): 1715, 1665, 1460, 1275, 1225, 1200, 1110 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.11-2.22 (2H, m), 3.22 (6H, s), 3.54-3.71 (2H, m), 3.80-3.85 (1H, m), 4.22-4.31 (1H, m), 5.19 (1H, t, J = 5.9 Hz), 5.27 (1H, d, J = 4.4 Hz), 6.15 (1H, dd, J = 6.4 Hz, 6.4 Hz), 8.24 (1H, d, J = 7.3 Hz); ms: (m/z) 337 (M^+).

Anal. Calcd. for $C_{11}H_{16}N_3O_6FS$: C, 39.17; H, 4.78; N, 12.46. Found: C, 39.02; H, 4.71; N, 12.51.

3-Dimethylsulfoxyimidyl-5-fluorouridine (**15**).

A solution of DMSO (1.12 g, 14.3 mmoles) in dichloromethane (5 ml) was added to a solution of *t*-butyl hypochlorite (470 mg, 4.33 mmoles) in dichloromethane (12 ml) at −65° over 10 minutes and the mixture was stirred at the same temperature for 1 hour. A solution of 5-fluoro-2′,3′,5′-*O*-tris(trimethylsilyl)uridine (3.38 mmoles) in dichloromethane (5 ml) was added. The resulting mixture was stirred at −45° for 4 hours, and then triethylamine (1.2 ml) in dichloromethane (5 ml) was added and stirred at room temperature for 17 hours. The reaction mixture was concentrated and treated with an hydrogen chloride saturated ethanol (50 ml)-methanol (0.5 ml) solution at room temperature for 30 minutes. The resulting mixture was stirred with phenyl isothiocyanate (523 mg, 3.87 mmoles) at room temperature for 4 hours, and then extracted with aqueous ethyl acetate. The aqueous layer was concentrated and chromatographed on silica gel with chloroform-methanol (4:1) to give 150 mg (11%) of **15**, mp 72-78°; tlc (chloroform-methanol, 2:1) Rf 0.32; ir (potassium bromide): 1660, 1210, 1050 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.22 (6H, s), 3.58-3.72 (2H, m), 3.84-3.91 (1H, m), 3.98-4.09 (2H, m), 5.09 (1H, d, J = 5.4 Hz), 5.31 (1H, t, J = 4.6 Hz), 5.46 (1H, d, J = 4.9 Hz), 5.77 (1H, dd, J = 3.7 Hz, 1.7 Hz), 8.34 (1H, dd, J = 7.1 Hz, 1.7 Hz); ms: (m/z) 353 (M^+).

Anal. Calcd. for $C_{11}H_{16}N_3O_7FS$: C, 37.40; H, 4.56; N, 11.89. Found: C, 37.11; H, 4.40; N, 11.76.

3-(Benzothiazol-2-yl)thiocarbonylamino-2′-deoxy-5-fluorouridine (**16**).

A solution of phenylmagnesium bromide (4.0 mmoles) in anhydrous THF (10 ml) was added to a solution of 3-amino-3′,5′-*O*-bis(trimethylsilyl)-2′-deoxy-5-fluorouridine (630 mg, 1.68 mmoles) in anhydrous THF (20 ml) and the mixture was stirred for 1 hour at room temperature. 2-Chlorothiocarbonyl-1,3-benzothiazole (700 mg, 3.28 mmoles) was added. The resulting mixture was stirred at −30° for 40 minutes and at room temperature for 2 days, and then concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with ethyl acetate-hexane (1:2) to give 200 mg (29%) of **16**, mp 152-153°; tlc (chloroform-methane, 4:1) Rf 0.15; ir (potassium bromide): 1680, 1480 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.15-2.22 (2H, m), 3.56-3.73 (2H, m), 3.80-3.88 (1H, m), 4.21-4.35 (1H, m), 5.23 (1H, d, J = 4.4 Hz), 5.32 (1H, t, J = 4.4 Hz), 6.14-6.24 (1H, m), 7.44-7.66 (2H, m), 8.13 (2H, m), 8.39 (1H, d, J = 6.8 Hz), 10.23 (1H, br); ms: (m/z) 438 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_4O_5FS_2$: C, 46.58; H, 3.42; N, 12.79. Found: C, 46.47; H, 3.51; N, 12.29.

3-[(Benzylthio)thiocarbonyl]amino-2′-deoxy-5-fluorouridine (**17**).

A mixture of **1** (313 mg, 1.20 mmoles) and carbon disulfide (280 mg, 3.68 mmoles) in DMF (15 ml) was stirred at room temperature for 1.5 hours. Benzyl chloride (462 mg, 3.65 mmoles) was then added and the mixture was stirred at room temperature for 24 hours. The resulting mixture was filtered and the filtrate was concentrated. The residue was extracted with aqueous ethyl acetate and the ethyl acetate layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (4:1) to give 70 mg (14%) of **17**, mp 107-109°; tlc (ethyl acetate) Rf 0.38; ir (potassium bromide): 1740, 1685, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.08-2.30 (2H, m), 3.53-3.76 (2H, bs), 3.78-3.87 (1H, m), 4.20-4.30 (1H, m), 4.46 and 4.55 (2H, s), 5.25 (1H, bs), 5.31 (1H, bs), 6.10-6.22 (1H, m), 7.20-7.50 (5H, m), 8.25-8.52 (1H, m), 12.12 and 12.48 (1H, bs); ms: (m/z) 427 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_3O_5FS_2$: C, 47.76; H, 4.24; N, 9.83. Found: C, 47.69; H, 4.25; N, 9.91.

3-[Bis(benzylthio)methylene]imino-2′-deoxy-5-fluorouridine (**18**).

A mixture of triethylamine (490 mg, 4.85 mmoles) and carbon disulfide (370 mg, 4.87 mmoles) was dissolved in a solution of **1** (520 mg, 1.99 mmoles) in DMF (10 ml) and the solution was stirred at room temperature for 3.5 hours. Benzyl chloride (610 mg, 4.82 mmoles) was then added, and the resulting mixture was stirred at room temperature for 1.5 hours, concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with ethyl acetate-hexane (4:1) to give 230 mg (33%) of **18**, mp 74-75°; ir (potassium bromide): 1720, 1655, 1495, 1455 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.08-2.28 (2H, m), 3.52-3.71 (2H, m), 3.77-3.89 (1H, m), 4.18-4.30 (1H, m), 4.36 (2H, s), 4.53 (2H, s), 5.21 (1H, bs), 5.30 (1H, d, J = 3.9 Hz), 6.12-6.24 (1H, m), 7.20-7.46 (8H, m), 7.48-7.60 (2H, m), 8.36 (1H, d, J = 6.8 Hz); ms: (m/z) 517 (M^+).

Anal. Calcd. for $C_{24}H_{24}N_3O_5FS_2$: C, 55.69; H, 4.67; N, 8.12. Found: C, 55.53; H, 4.62; N, 8.38.

2′-Deoxy-5-fluoro-3-(phenoxythiocarbonyl)aminouridine (**19**).

To a solution of **1** (260 mg, 1.0 mmole) in DMF (10 ml) were added phenoxythiocarbonyl chloride (180 mg, 1.04 mmoles) and 4-dimethylaminopyridine (130 mg, 1.07 mmoles). The mixture was stirred at room temperature for 20 minutes, concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (9:1) to give 170 mg (57%) of **19**, mp 176-177°; tlc (chloroform-methanol, 4:1) Rf 0.46; ir (potassium bromide): 3420, 1740, 1690, 1490 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.14-2.24 (2H, m), 3.62-3.70 (2H, m), 3.73-3.87 (1H, m), 4.28 (1H, bs), 5.23 (1H, t, J = 4.4 Hz), 5.31 (1H, bs), 6.20 (1H, dd, J = 6.8 Hz, 6.8 Hz), 6.96-7.48 (5H, m), 8.48 and 8.49 (1H, d, J = 7.3 Hz), 12.05 and 12.40 (1H, bs); ms: (m/z) 397 (M^+).

Anal. Calcd. for $C_{16}H_{16}N_3O_6FS$: C, 48.36; H, 4.06; N, 10.57. Found: C, 48.20; H, 4.22; N, 10.71.

2′-Deoxy-5-fluoro-5′-*O*-(methylthiomethyl)uridine (**20**).

A powdered sodium hydride (50 mg, 2.08 mmoles) was added to a suspension of 5-FUdR (250 mg, 1.07 mmoles) in THF (10 ml) and the mixture was stirred at room temperature for 30 minutes. Then, methylthiomethyl chloride (150 mg, 1.55 mmoles) and a small amount of sodium iodide were added, and the resulting mixture was stirred at room temperature overnight, concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with ethyl acetate-hexane (9:1) to give 100 mg (33%) of **20**, 94-95°; tlc (ethyl acetate) Rf 0.32; ir (potassium bromide): 1715, 1655 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.20 (3H, s), 2.10-2.28 (2H, m), 3.52-3.72 (2H, m), 3.78-3.86 (1H, m), 4.20-4.31 (1H, m), 4.89-4.91 (2H, m), 5.19 (1H, t, J = 4.9 Hz), 5.27 (1H, d, J = 4.4 Hz), 6.18 (1H, dd, J = 6.4 Hz, 6.4 Hz), 8.35 (1H, d, J = 7.3 Hz); ms: (m/z) 306 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_2O_5FS$: C, 43.13; H, 4.94; N, 9.15. Found: C, 43.27; H, 4.91; N, 9.04.

2'-Deoxy-5-fluoro-5'-*O*-[(methylthio)thiocarbonyl]uridine (**21**).

A solution of 5-FUdR (374 mg, 1.60 mmoles) in DMF (4.0 ml) was added to a mixture of aqueous 5*M* sodium hydroxide solution (4.0 ml) and carbon disulfide (0.7 ml). After stirring for 10 minutes at room temperature, methyl iodide (250 mg, 1.76 mmoles) was added, and the resulting mixture was stirred at room temperature for 18 hours, concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (15:1) to give 110 mg (22%) of **21**, mp 156.5-157°; tlc (chloroform-methanol, 4:1) Rf 0.50; ir (potassium bromide): 1690, 1265, 1205 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.10-2.30 (2H, m), 2.58 (3H, s), 4.07 (1H, bs), 4.29 (1H, bs), 4.65-4.86 (2H, m), 5.50 (1H, bs), 6.10-6.25 (1H, m), 7.89 (1H, d, J = 6.8 Hz), 11.86 (1H, bs); ms: (m/z) 336 (M^+).

Anal. Calcd. for $C_{11}H_{13}N_2O_5FS_2$: C, 39.27; H, 3.90; N, 8.33. Found: C, 39.31; H, 3.78; N, 8.29.

2'-Deoxy-5-fluoro-5'-*O*-[(4-methylphenyl)sulfonyl]uridine (**22**).

To a solution of 5-FUdR (200 mg, 0.85 mmole) in pyridine (10 ml) was added *p*-toluenesulfonyl chloride (460 mg, 2.41 mmoles). The mixture was stirred at room temperature for 17 hours, concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-acetone (4:1) to give 140 mg (43%) of **22**, mp 154°; tlc (ethyl acetate) Rf 0.45; ir (potassium bromide): 1720, 1680, 1135 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.02-2.24 (2H, m), 2.29 (3H, s), 3.82-3.97 (2H, m), 4.08-4.29 (2H, m), 5.43 (1H, bs), 6.12 (1H, dd, J = 12.7 Hz, 6.5 Hz), 7.43 and 7.63 (4H, ABq, J = 7.8 Hz), 7.90 (1H, d, J = 7.8 Hz), 11.86 (1H, t, J = 4.2 Hz); ms: (m/z) 400 (M^+).

Anal. Calcd. for $C_{16}H_{17}N_2O_7FS$: C, 48.00; H, 4.28; N, 7.00. Found: C, 48.21; H, 4.10; N, 7.14.

2'-Deoxy-5-fluoro-5'-*O*-[(2-phenylethenesulfonyl)amino]uridine (**23**).

To a solution of **3** (90.1 mg, 0.35 mmole) in DMF (3 ml) were added triethylamine (69 mg, 0.68 mmole) and 2-phenylethenesulfonyl chloride (69 mg, 0.35 mmole). The mixture was stirred at room temperature for 30 minutes, concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (12:1) to give 70 mg (48%) of **23**, mp 177-179°; tlc (chloroform-methanol, 4:1) Rf 0.49; ir (potassium bromide): 3400, 1700, 1335, 1260, 1150 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.02-2.21 (2H, m), 3.93-4.20 (4H, m), 5.40 (1H, d, J = 3.9 Hz), 6.08-6.17 (1H, m), 7.17 (1H, d, J = 15.6 Hz), 7.38-7.49 (3H, m), 7.51 (1H, d, J = 15.6 Hz), 7.68-7.79 (2H, m), 7.87 (1H, d, J = 7.3 Hz), 10.42 (1H, bs), 11.82 (1H, bs); ms: (m/z) 427 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_3O_7FS$: C, 47.77; H, 4.25; N, 9.83. Found: C, 47.61; H, 4.19; N, 9.94.

5'-*O*-[(Benzothiazol-2-ylthiocarbonyl)amino]-2'-deoxy-5-fluorouridine (**24**).

A mixture of **3** (200 mg, 0.99 mmole), 2-(chlorothiocarbonyl)-benzothiazole (548 mg, 2.57 mmoles) and triethylamine (0.2 ml) in DMF (10 ml) was stirred at room temperature for 20 hours. The reaction mixture was concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (4:1) to give 50 mg (18%) of **24**, mp 156-157°; tlc (chloroform-methanol, 4:1) Rf 0.38; ir (potassium bromide): 1710 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.08-2.15 (2H, m), 3.90-4.06 (1H, m), 4.20-4.34 (1H, m), 4.37-4.57 (1H, m), 4.52-4.70 (2H, m), 6.18 (1H, bs), 7.44-7.66 (2H, m), 8.13 (2H, m), 8.50 (1H, bs), 11.22 (1H, bs), 11.83 (1H, bs); ms: (m/z) 438 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_4O_5FS_2$: C, 46.56; H, 3.45; N, 12.78. Found: C, 46.38; H, 3.30; N, 12.93.

5'-*O*-(*N*-benzylthioureido)-2'-deoxy-5-fluorouridine (**25**).

A solution of **3** (90.6 mg, 0.35 mmole) and benzyl isothiocyanate (104 mg, 0.70 mmole) in *N,N*-dimethylacetamide (3 ml) was stirred at room temperature for 18 hours. The resulting mixture was concentrated and chromatographed on silica gel with chloroform-methanol (12:1) to give 120 mg (84%) of **25**, mp 208-210°; tlc (chloroform-methanol, 4:1) Rf 0.47; ir (potassium bromide): 1700, 1550 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.01-2.28 (2H, m), 3.86-4.08 (3H, m), 4.19-4.31 (1H, m), 4.62-4.82 (2H, m), 5.39 (1H, d, J = 5.4 Hz), 6.04-6.17 (1H, m), 7.15-7.39 (5H, m), 7.92 (1H, d, J = 7.3 Hz), 8.54 (1H, t, F = 6.1 Hz), 10.79 (1H, bs), 11.82 (1H, bs); ms: (m/z) 410 (M^+).

Anal. Calcd. for $C_{17}H_{19}N_4O_5FS$: C, 49.74; H, 4.67; N, 13.65. Found: C, 49.53; H, 4.72; N, 13.89.

General Procedure for γ-Radiolyses of 5-FUR and 5-FUdR Derivatives.

Three kinds of sample solutions were prepared for all of 5-FUR and 5-FUdR derivatives by dissolving the samples into the following three deaerated solvents in concentration of 50 μg/ml; (a) deaerated aqueous 1% (v/v) methanol, (b) deaerated aqueous 0.1 *M* sulfuric acid containing 1% (v/v) methanol (c) deaerated aqueous 1% (v/v) acetonitrile saturated with nitrous oxide gas. The sample solution (2 ml) was placed into a 5 mmϕ Pyrex glass tube and irradiated with γ-ray of 100 Gy at a rate of 3.15 Gy/minute from a ^{137}Cs source at room temperature (20°). After irradiation, the amount of 5-FUR or 5-FUdR produced by the radiolysis was analyzed by hplc. The conditions of the hplc analyses were as follows: Column; Lichrosorb RP-18. Mobile phase; aqueous 8% (v/v) methanol solution. Detection; uv, 270 nm. Retention time; 5.4 minutes for 5-FUR, 9.4 minutes for 5-FUdR.

Anticellular Activities.

Sample solutions were prepared by dissolving compounds to be tested in a physiological salt solution in various concentrations. These sample solutions were irradiated with γ-ray of 246 Gy from a ^{137}Cs source at a rate of 3.15 Gy/minute. The γ-irradiated sample solution (50 μl) was added to murine Sarcoma 180 cells (1 x 10^4 cells/ml) which had been suspended in a RPMI 1640 culture medium containing 10% (v/v) fetal bovine serum and 2-hydroxyethanethiol (50 μM). After the cells were cultured at 37° for 72 hours in this medium, the number of cells was countered by a microcell counter (Toa Medical Electronics Co. Ltd., Type CC-110). A control experiment was carried out by culturing the cells in the same medium under the same conditions as above, without adding any of the sample solutions, but with adding a

physiological salt solution (50 μl). The anticellular activities of the samples were determined by taking the ratio of the number of the cells obtained by the above two experiments (see text).

The dependence of irradiated γ-ray doses on the anticellular activity of **9** was measured as follows: The sample solution of **9** in a physiological salt solution ($2.4 \times 10^{-4}M$) was irradiated with varing doses of γ-ray at a rate of 3.15 Gy/minute at room temperature. The anticellular activities of the γ-irradiated solutions of **9** were determined toward P-388 cells in the same manner as above.

REFERENCES AND NOTES

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