γ-Radiolysis of 2′-Deoxy-5-fluorouridine Derivatives with Sulfur-containing Substituents

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2′-Deoxy-5-fluorouridine (5-FUdR) derivatives having various types of sulfur-containing substituents at the 5′-*O*-position were synthesized and their γ-radiolyses were studied in aqueous solutions. The γ-radiolysis of compounds having 1,3-dithiol-2-yl and 1,3-dithian-2-yl substituents at the 5′-*O*-position efficiently gave 5-FUdR, specifically *via* the attack of hydroxyl radical. On the other hand, the γ-radiolysis of a compound having a sulfonylmethyl substituent at the 5′-*O*-position gave less efficiently 5-FUdR, specifically *via* the attack of the hydrated electron. The mechanistic features of these reactions are discussed.

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Introduction.

2′-Deoxy-5-fluorouridine (5-FUdR) has a strong cytotoxic activity and has been widely used as a useful anticancer agent [1-3]. Therefore, if there is a compound that generates 5-FUdR upon γ-irradiation, such a compound would become a radiation-induced drug (RID) for cancer therapy [4,5]. From this standpoint, we previously studied the γ-radiolysis of a variety of 3-substituted 5-FUdR derivatives and demonstrated that the 3-thioureido and 3-thiocarbonylamino derivatives were efficiently cleaved to give 5-FUdR upon γ-irradiation of their aqueous solutions. The active species for the cleavage reaction depended on the nature of substituents; for example, the active species is principally an hydrated electron and an hydrogen atom, and to a small extent an hydroxyl radical, for 3-thioureido derivatives.

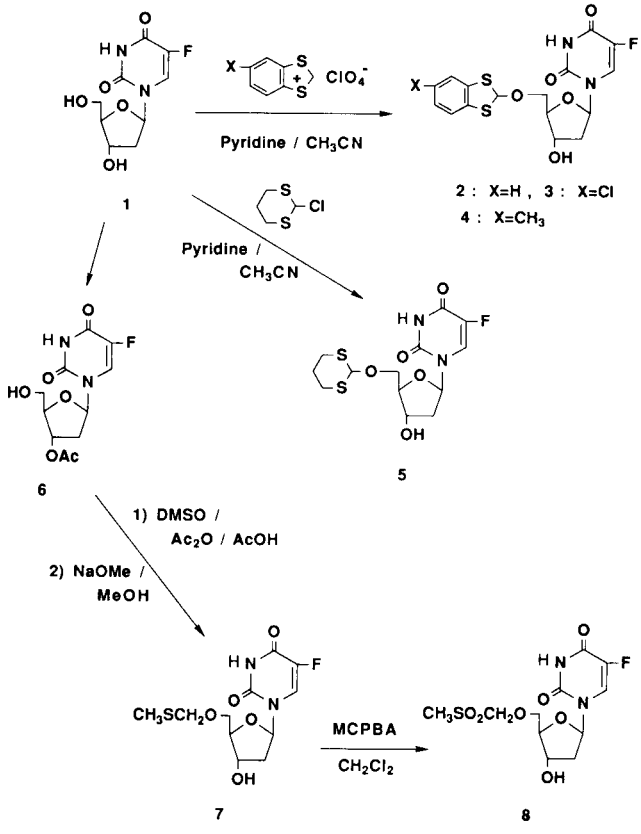
However, we have recently found that 5-FUdR derivatives having 1,3-dithian-2-yl and benzo[1,3]dithiol-2-yl substituents at the 5′-*O*-position undergo efficiently γ-radiolysis to give 5-FUdR and the principal reactive species for this reaction is an hydroxyl radical. This paper describes the synthesis of these and related compounds and their reactivity features of γ-radiolysis.

Results and Discussion.

Preparation of Materials.

The materials tested for γ-radiolysis were prepared from 5-FUdR (**1**) *via* routes shown in Scheme 1. The reactions of **1** with benzo[1,3]dithiol-2-ylium perchlorate and its 5-chloro and 5-methyl derivatives [6] in acetonitrile in the presence of pyridine gave 5′-*O*-(benzo[1,3]dithio-2-yl)-5-FUdR derivatives **2**, **3** and **4**. 5′-*O*-(1,3-Dithian-2-yl) derivative **5** was prepared by the reaction of **1** with 2-chloro-1,3-dithiane, which was obtained *in situ* from 1,3-dithiane and *N*-chlorosuccinimide [7]. In the preparation of 5′-*O*-methylthiomethyl derivatives **7**, the 3′-hydroxyl group of 5-FUdR had first to be protected. Thus, the reaction of 3′-*O*-acetyl-5-FUdR (**6**) with dimethyl sulfoxide (DMSO) in acetic anhydride-acetic acid, followed by hydrolysis gave **7**. The oxidation of **7** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane gave the methyl sulfonylmethyl derivative **8**.

Scheme 1



γ-Radiolysis.

It has been pointed out that in γ-radiolysis of aqueous solutions, a variety of chemically reactive species such as an hydrated electron (e^-_{aq}), an hydrogen atom (H·) and an hydroxyl radical (HO·) are generated as a result of the γ-radiolysis of water. We previously demonstrated that the principal active species can practically be controlled by adding appropriate chemical substances into the reaction systems. In this study, the γ-radiolysis was carried out under the conditions where e^-_{aq} and HO· are, respectively, generated as a principal active species (see footnotes in Table 1).

The γ-radiolysis of aqueous solutions of **2-5** and **7-8** gave 5-FUdR. The G values for the formation of 5-FUdR, G (5-FUdR), were calculated from the amounts of 5-FUdR produced by γ-irradiation of γ-ray 50 Gy from a ^{137}Cs source at a rate of 3.15 Gy/minute at room temperature. In these experiments, the amounts of 5-FUdR generated were measured after allowing the irradiated samples to stand at 4° for 24 hours. The results are given in Table 1. The striking features of these γ-radiolyses are that 1) **2-5** and **7** are radiolyzed to give 5-FUdR by HO·, but not by e^-_{aq}, and 2) **8**, which has an electron-attractive SO_2 group, is radiolyzed only by a reducing species, e^-_{aq}.

Table 1

G Values for the Formation of 5-FUdR from 5'-*o*-Substituted 5-FUdR Derivatives

Compound	G(5-FUdR) [a]	
	e^-_{aq} [b]	•OH [c]
2	trace	1.32
3	trace	0.51
4	trace	0.67
5	trace	0.37
7	trace	0.31
8	0.41	trace

[a] The sample solutions were stored for 24 hours at 4° in a refrigerator after γ-irradiation of 50 Gy at a rate of 3.15 Gy/minute and then the amounts of 5-FUdR produced were measured by means of hplc and converted to G values. [b] γ-Irradiation was carried out in aqueous 1% (v/v) methanol, where a principal active species is e^-_{aq} [4]. [c] γ-Irradiation was carried out in aqueous 1% (v/v) acetonitrile saturated with nitrous oxide, where a principal active species is HO•.

During the course of this study, we found that in the γ-radiolysis of **2-5** in aqueous 1% methanol (v/v) where the principal active species is HO·, the amounts of 5-FUdR produced gradually increase with increasing standing time of the sample solutions after cessation of γ-irradiation. We also found that **2-5** are slowly hydrolyzed to give 5-FUdR under the reaction conditions even when γ-ray irradiation did not occur. The time course for the formation of 5-FUdR from **2** is shown in Figure 1.

The results in Figure 1 indicate that in the case of **2**, the rate for the formation of 5-FUdR from the γ-irradiated sample was significantly faster than that from the unirradiated sample under the same reaction conditions. Similar results were obtained for **3-5**. However, such a phenomenon was not observed for **7** and **8**. For these compounds, the amounts of 5-FUdR never increased after cessation of γ-irradiation (Table 2).

Table 2

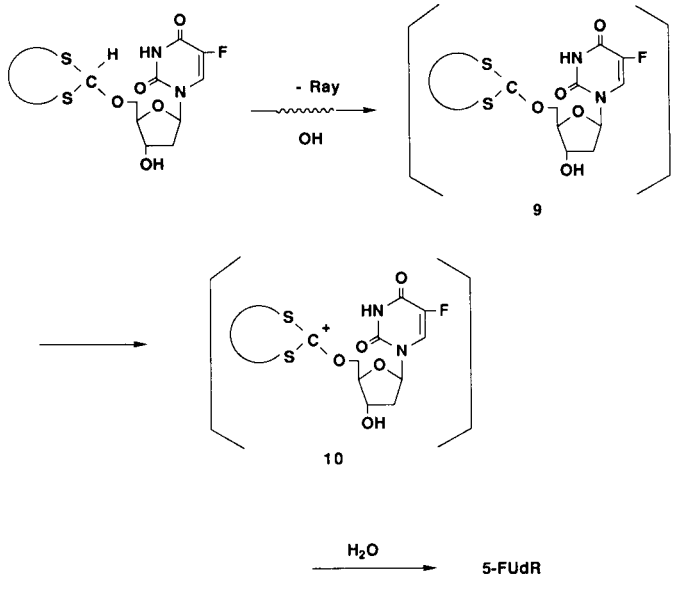
Variation of the Amounts of 5-FUdR Produced from **3-5** and **7** with Standing Time after Cessation of γ-Irradiation [a]

Compound	Amount of 5-FUdR /nmol	
	Standing for 3.5 hours	Standing for 24 hours
3	trace	2.6
4	0.65	1.9
5	1.2	3.4
7	1.7	1.6

[a] γ-Ray of 50 Gy was irradiated to the sample solution containing the substrate (230 nmol) under the same conditions as described in Figure 1, and then the samples were allowed to stand at 5°.

These results strongly suggest that the γ-radiolysis of the compounds having cyclic sulfur-containing substituents, such as **2-5**, proceed *via* metastable intermediates. A proposed pathway for the γ-radiolysis for such compounds is shown in Scheme 2. The hydroxyl radical generated by the γ-radiolysis of water picks up a hydrogen from the substrates. The resulting radicals **9** may be stabilized by inter-

Scheme 2



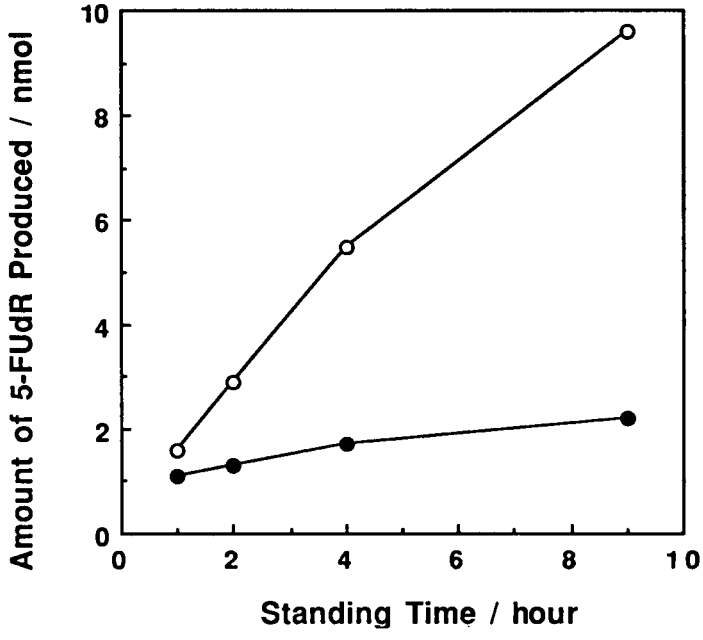


Figure 1 Variation of the amounts of 5-FUdR produced from aqueous 1% (v/v) CH_3CN solutions saturated N_2O containing 2 (230 nmol) with standing time. —○— ; the γ - irradiated sample, for which γ - ray of 50 Gy was irradiated at room temperature at a rate of 3.15 Gy / minute, and the sample solution was allowed to stand at 5°, —●— ; the unirradiated sample, for which the sample solution was allowed to stand at 5° without γ -irradiation.

action with two adjacent sulfur atoms. Such a radical stabilization has been proposed for the hydrogen abstraction reaction from heteroatom-substituted carbon compounds with an oxygen radical such as *t*-BuO·; in this reaction, the hydrogen atom is abstracted at a remarkably high rate especially from compounds having two or more sulfur substituents to give stable radicals [8,9]. Therefore, it seems reasonable to assume that the radicals **9** are able to exist as metastable intermediates. The detailed mechanism of the conversion of **9** to 5-FUdR is unclear at present. However, a plausible pathway is a hydrolysis *via* the carbocations **10** that can be produced by the oxidation of **9**; note that an oxidizing agent such as nitrous oxide is present in the reaction system. The rates of decomposition of **2-5** through this pathway would be much faster than the rates of a direct hydrolysis of the same compounds to give 5-FUdR under the reaction conditions. This mechanism accounts for the relatively high G values and also for the chemical behavior of **2-5** in their γ-radiolyses. For **7**, the intermediary carbon radical would not be appreciably stabilized. Therefore, **7** decomposes spontaneously to 5-FUdR *via* an unstable intermediate upon γ-irradiation, but with a lower G value, as compared with **2-5**. It is noteworthy that **8** is radiolyzed only by e^-_{aq}. This implies that the mechanism of the γ-radiolysis of this compound is quite different from that of the other compounds.

Although we do not have detailed biological data at present, the results of this investigation imply that the compounds having cyclic sulfur-containing substituents at 5'-*O*-position of 5-FUdR, such as **2-5**, would serve as a good candidate for RID [5].

EXPERIMENTAL

The ^1H nmr spectra were recorded on a JEOL JNM-GX270 FT NMR spectometer using TMS as the internal standard. Infrared spectra were recorded on a Shimadzu IR-4000 instrument. The purity of compounds was checked by tlc on silica-gel plates (Silica gel 60, F254, Merck). Elemental analyses were performed with a Yanagimoto CHN Corder MT-3, and the errors were within ±0.4% of calculated values. γ-Irradiations were carried out with a ^{137}Cs source at the National Institute of Genetics. The hplc analyses were 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).

2'-Deoxyl-5-fluoro-5'-*O*-(benzo[1,3]dithiol-2-yl)uridine (**2**).

Benzo[1,3]dithiol-2-ylium perchlorate [6] (400 mg, 1.58 mmoles) and pyridine (0.5 ml) were added into a suspension of 2'-deoxy-5-fluorouridine (5-FUdR, 300 mg, 1.22 mmoles) in acetonitrile (15 ml), and the mixture was stirred at room temperature for 18 hours and concentrated. The residue was extracted with aqueous ethyl acetate and the organic layer was washed with an aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with chloroform-acetone (9:1) to give 240 mg (0.6 mmole, 50%) of **2**, mp 122-125°; tlc (ethyl acetate) Rf 0.50; ir (potassium bromide): 1720, 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.98-2.10 (2H, m), 3.59 (1H, dd, J = 10.3 Hz, 4.4 Hz), 3.67 (1H, dd, J = 10.7 Hz, 3.4 Hz), 3.82-3.90 (1H, m), 4.08-4.17 (1H, m), 5.37 (1H, d, J = 4.4 Hz), 6.09 (1H, dd, J = 3.0 Hz, 3.0 Hz), 7.13-7.22 (2H, m), 7.07 (1H, s), 7.43-7.55 (2H, m), 7.83 (1H, d, J = 6.8 Hz), 11.85 (1H, bs); ms: (m/z) 398 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_2O_5FS_2$: C, 48.23; H, 3.79; N, 7.03. Found: C, 47.96; H, 3.61; N, 7.20.

2'-Deoxy-5-fluoro-5'-*O*-(5-chlorobenzo[1,3]dithiol-2-yl)uridine (**3**).

This compound was prepared from 5-chlorobenzo[1,3]dithiol-2-ylium perchlorate [6] (640 mg, 2.22 mmoles) and 5-FUdR (500 mg, 2.03 mmoles) in a similar manner as above, yielding **3** in 49% yield, mp 132-134°; tlc (ethyl acetate) Rf 0.42; ir (potassium bromide): 1720, 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.04-2.20 (2H, m), 3.52-3.78 (2H, m), 3.78-3.95 (1H, m), 4.06-4.31 (1H, m), 5.15-5.31 (1H, m), 5.37 (1H, d, J = 3.9 Hz), 6.11 (1H, dd, J = 6.6 Hz, 6.6 Hz), 7.13 (1H, s), 7.15-7.72 (3H, m), 7.85 and 8.35 (1H, d, J = 6.9 Hz, 6.3 Hz), 8.74 and 11.85 (1H, d, J = 3.9 Hz, 4.9 Hz); ms: (m/z) 433 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_2O_5ClFS_2$: C, 44.39; H, 3.26; N, 6.47. Found: C, 44.13; H, 3.14; N, 6.27.

2'-Deoxy-5-fluoro-5'-*O*-(5-methylbenzo[1,3]dithiol-2-yl)uridine (**4**).

This compound was prepared from 5-methylbenzo[1,3]dithiol-2-ylium perchlorate [6] (650 mg, 2.43 mmoles) and 5-FUdR (300 mg, 1.22 mmoles) in a similar manner as above, yielding **4** in a 38% yield, mp 128-130°; tlc (ethyl acetate-hexane, 4:1) Rf 0.30; ir (potassium bromide): 1730, 1690 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.97-2.15 (2H, m), 2.27 (3H, s), 3.64 (1H, dd, J = 10.7 Hz, 3.2 Hz), 3.57 (1H, dd, J = 10.8 Hz, 4.4 Hz), 3.80-3.90 (1H, m), 4.01-4.13 (1H, m), 5.34 (1H, d, J = 2.9 Hz), 6.09 (1H, dd, J = 6.8 Hz, 6.8 Hz), 6.98 (1H, d, J = 8.3 Hz), 7.07 (1H, s), 7.30 (1H, s), 7.35 (1H, dd, J = 7.8 Hz, 1.4 Hz), 7.83 (1H, d, J = 6.9 Hz), 11.84 (1H, d, J = 4.9 Hz); ms: (m/z) 412 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_2O_5FS_2$: C, 49.50; H, 4.15; N, 6.79. Found: C, 49.78; H, 4.23; N, 6.63.

2'-Deoxy-5-fluoro-5'-*O*-(1,3-dithian-2-yl)uridine (**5**).

N-Chlorosuccinimide (440 mg, 3.30 mmoles) was added into a solution of 1,3-dithiane (360 mg, 3.0 mmoles) in anhydrous benzene (5 ml) over 20 minutes. The mixture was stirred at room temperature for 20 minutes and filtered. The filtrate was allowed to react with stirring with a solution of 5-FUdR (400 mg, 1.63 mmoles) in acetonitrile (20 ml) containing pyridine (2 ml) at room temperature for 20 hours. The resulting mixture was concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with an aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with ethyl acetate-hexane (4:1) to give 250 mg (42%) of **5**, mp 61.5-62.5°; tlc (ethyl acetate) Rf 0.52; ir (potassium bromide): 1720, 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.83-2.01 (2H, m), 2.05-2.20 (2H, m), 2.60-2.71 (2H, m), 3.03-3.21 (2H, m), 3.75 (2H, d, J = 2.9 Hz), 3.98 (1H, dd, J = 2.9 Hz, 2.9 Hz), 4.24-4.35 (1H, m), 5.41 (1H, d, J = 3.9 Hz), 5.57 (1H, s), 6.19 (1H, dd, J = 4.9 Hz, 6.8 Hz), 8.06 (1H, d, J = 6.8 Hz), 11.86 (1H, bs); ms: (m/z) 365 (M^+).

Anal. Calcd. for $C_{13}H_{17}N_2O_5FS_2$: C, 42.85; H, 4.70; N, 7.69. Found: C, 42.61; H, 4.52; N, 7.48.

2'-Deoxy-5-fluoro-3'-*O*-acetyluridine (**6**).

A mixture of bis(4-methoxyphenyl)chlorophenylmethane (4.14 g, 12.2 mmoles) and triethylamine (1.24 g, 12.3 mmoles) containing a small amount (50 mg) of 4-dimethylaminopyridine was added to a solution of 5-FUdR (2.0 g, 0.81 mmole) in DMF (40 ml). The resulting mixture was stirred at room temperature for 1 hour and filtered. The filtrate was concentrated. The residue was extracted with aqueous ethyl acetate and the organic layer was washed with an aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residual solid was chromatographed on silica gel with chloroform-acetone (4:1) to give 3.5 g (79%) of 2'-deoxy-5-fluoro-5'-*O*-[bis(4-methoxyphenyl)phenylmethyl]uridine; tlc (ethyl acetate) Rf 0.64; ms: (m/z) 548 (M^+). This compound (3.0 g, 0.55 mmole) was dissolved in pyridine (50 ml), and then the solution was allowed to react with acetic anhydride (5 ml), with stirring at room temperature for 4 hours. The resulting mixture was concentrated and extracted with aqueous ethyl acetate. The organic layer was washed with an aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. A solution of the residue in an 80% aqueous acetic acid (300 ml) was stirred at room temperature for 3 hours. The mixture was concentrated and the residue was chromatographed on silica gel with chloroform-acetone (4:1) to give 1.50 g (95%) of **6**, mp 194-195°; tlc (chloroform-acetone, 4:1) Rf 0.15; ir (potassium bromide): 1715, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.06 (3H, s), 2.20-2.38 (2H, m), 3.59-3.78 (2H, m), 3.99-4.05 (1H, m), 5.18-5.25 (1H, m), 5.35 (1H, t, J = 4.9 Hz), 6.16 (1H, m), 8.22 (1H, d, J = 6.8 Hz), 11.90 (1H, d, J = 4.9 Hz); ms: (m/z) 288 (M^+).

Anal. Calcd. for $C_{11}H_{13}N_2O_6F$: C, 45.84; H, 4.55; N, 9.72. Found: C, 45.99; H, 4.71; N, 9.58.

2'-Deoxy-5-fluoro-5'-*O*-(methylthiomethyl)uridine (**7**).

To a solution of **6** (0.40 g, 1.39 mmoles) in DMSO (4 ml) were added acetic anhydride (2.5 ml) and acetic acid (0.5 ml). The mixture was stirred overnight at room temperature, neutralized with a saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with an aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was chromatographed on silica gel with ethyl acetate-hexane (1:1) to give 130 mg (27%) of 3'-*O*-acetyl compound of **7**; ^1H nmr (deuteriochloroform): δ = 2.02-2.35 (2H, m), 2.12 (3H, s), 2.18 (3H, s), 3.79 and 3.86 (2H, ABq, d, J = 10.7 Hz, 2.4 Hz), 4.20-4.30 (1H, m), 4.73 and 4.74 (2H, ABq, J = 12.0 Hz), 5.22-5.33 (1H, m), 6.34-6.67 (1H, m), 7.95 (1H, d, J = 6.4 Hz), 9.55 (1H, bs); ms: (m/z) 348 (M^+). Sodium methoxide (100 mg) was then added to a solution of the above *O*-acetyl compound in methanol (8 ml). The mixture was stirred for 1.2 hours, concentrated and extracted with aqueous ethyl acetate at *p*H 4.5. The organic layer was washed with an aqueous sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was triturated with ether to give 90 mg (21%) of **7**, mp 144.5-145.5°; tlc (chloroform-methanol, 4:1) Rf 0.42; ir (potassium bromide): 1720, 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.10 (3H, s), 2.10-2.18 (2H, m), 3.60

(1H, dd, J = 10.8 Hz, 4.2 Hz), 3.72 (1H, dd, J = 10.7 Hz, 3.4 Hz), 3.90-3.99 (1H, m), 4.16-4.28 (1H, m), 4.72 (2H, s), 5.36 (1H, d, J = 3.4 Hz), 6.14 (1H, dd, J = 6.8 Hz, 6.5 Hz), 7.95 (1H, d, J = 6.8 Hz), 11.83 (1H, bs); 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, 43.38; H, 4.85; N, 9.34.

2'-Deoxy-5-fluoro-5'-*O*-(methylsulfonylmethyl)uridine (**8**).

m-Chloroperbenzoic acid (120 mg, 69.6 mmoles) was added into a suspension of **7** (100 mg, 32.7 mmoles) in dichloromethane (20 ml) and stirred at room temperature for 15 minutes. The resulting mixture was concentrated and chromatographed on silica gel with chloroform-methanol, (4:1) Rf 0.42; ir (potassium bromide): 1720, 1680, 1350 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.02-2.30 (2H, m), 2.95 (3H, s), 3.83-4.10 (3H, m), 4.20-4.30 (1H, m), 4.69 and 4.72 (2H, ABq, J = 3.2 Hz), 5.40 (1H, bs), 6.15 (1H, t, J = 6.6 Hz), 7.88 (1H, d, J = 6.8 Hz), 11.86 (1H, bs); ms: (m/z) 338 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_2O_7FS$: C, 39.05; H, 4.47; N, 8.28. Found: C, 39.25; H, 4.59; N, 8.03.

General Procedure for γ-Radiolysis.

For each of synthesized compounds, two kinds of sample solutions were prepared by dissolving the compound into the following two solvents in concentration of 50 μg/ml; (a) deaerated aqueous 1% (v/v) methanol, and (b) deaerated aqueous 1% (v/v) acetonitrile saturated with nitrous oxide gas. An approximately 2 ml of the sample solution was placed into a 5 mmϕ Pyrex glass tube, and γ-ray of 50 Gy from a ^{137}Cs source was irradiated at a rate of 3.15 Gy/minute to the sample at room temperature (*ca* 20°). After irradiation, the amount of 5-FUdR produced was analyzed by hplc. The analysis conditions were as follows: Column, Lichrosorb RP-18; Mobile phase, aqueous 8% (v/v) methanol solution; Detection, uv 270 nm; Retention time, 9.4 minutes.

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