γ-Radiolysis of 5-Fluorouracil and 5-Fluorouridine Derivatives Having Sulfur-Containing Substituents

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γ-Radiolysis reactions of eight 5-fluorouracil (5-FU) derivatives having sulfonyl group-containing substituents at the 1-position and five 5-fluorouridine (5-FUR) derivatives having thioureido group-containing substituents were studied under the conditions where hydrated electron (e_{aq}^-) and hydroxyl radical (HO•) become the principal reactive species. The 5-FU and 5-FUR derivatives were radiolyzed to give 5-FU and 5-FUR, respectively. The efficiency of the reactions depended upon the nature of reactive species and also upon the nature of substituents. The reactivity features of the γ-radiolysis reactions are discussed.

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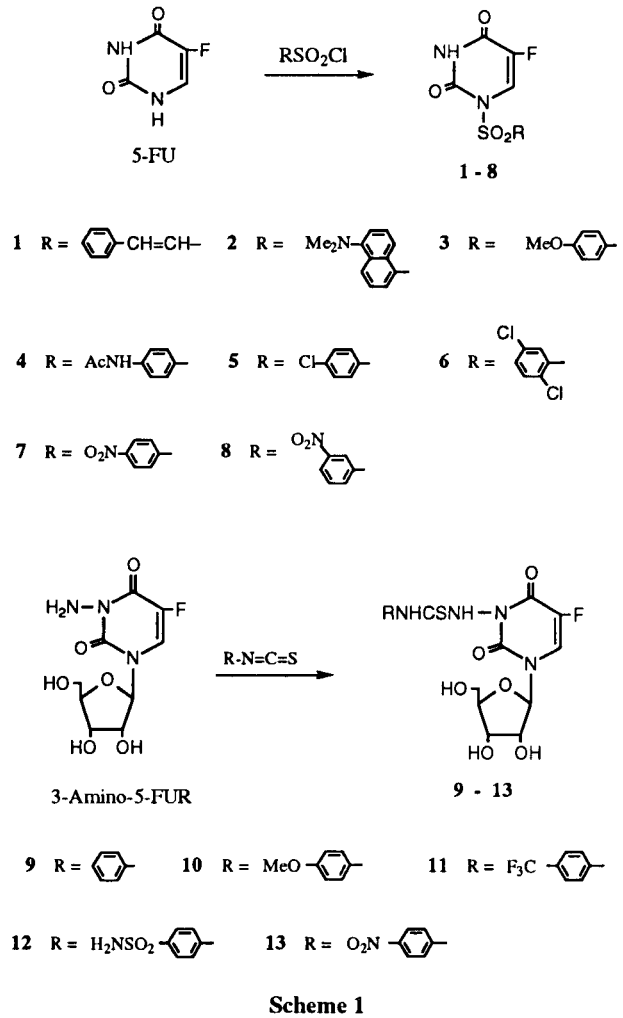
Introduction

In the course of our studies directed toward the development of radiation-induced drugs (RID's) for cancer therapy, we have found that certain 1-substituted 5-fluorouracil and 3-substituted 5-fluorouridine derivatives afford 5-fluorouracil (5-FU) and 5-fluorouridine (5-FUR), respectively, upon γ-irradiation in aqueous solutions [1,2]. Since 5-FU and 5-FUR are known to exhibit a cytotoxic activity, these results imply that such compounds may serve as a candidate for a RID toward cancer therapy [1,2]. Our previous studies have also indicated that 1) the efficiency of the γ-radiolysis reactions strongly depends upon the nature of substituents and also upon the reaction conditions, and 2) sulfonyl functionality at 1-position of 5-FU derivatives and thioureido functionality at 3-position of 5-FUR derivatives can be relatively easily cleaved by γ-radiolysis [1,2]. However, the reactivity features of these reactions remained obscure. We now report γ-radiolysis reactions of 5-FU derivatives bearing a variety of sulfonyl group-containing substituents and 5-FUR derivatives bearing a variety of thioureido group-containing substituents. The reactions were carried out under the conditions where hyrdated electron (e^-_{aq}) and hydroxyl radical (HO•) become the principal reactive species [1]. The reactivity features of the compounds toward these reactive species are compared.

Results and Discussion.

Synthesis of materials.

Synthetic routes of compounds examined in this investigation are shown in Scheme 1. Eight 5-FU derivatives **1-8** were synthesized by the reaction of 5-FU with aryl- and arylalkenylsulfonyl chlorides. Five 5-FUR derivatives **9-13** were synthesized from 3-amino-5-fluorouridine [1] and arylisothiocyanates. All the reactions proceeded satisfactorily and the compounds could be purified by chromatography.



Scheme 1

γ-Radiolysis.

In a previous paper, we demonstrated that the nature of chemically reactive species generated by γ-radiolysis in aqueous solutions could be controlled by adding chemical substances into reaction systems [1]. For example, if the γ-radiolysis is carried out in an aqueous 1% (v/v) methanol, e^-_{aq} becomes a principal reactive species. However, if the γ-radiolysis is conducted in an aqueous 1% (v/v) acetonitrile saturated with nitrous oxide gas, HO• becomes a principal reactive species.

γ-Radiolysis reactions of 5-FU derivatives **1-8** and 5-FUR derivatives **9-13** were carried out under the above two conditions. After irradiation of γ-ray of 100 Gy from a ^{137}Cs source, amounts of 5-FU and 5-FUR produced by the γ-radiolysis were analyzed by hplc and the G values for the formation of 5-FU and 5-FUR, G(5-FU) and G(5-FUR), were determined. The results are given in Tables 1 and 2. All the compounds, except **13**, were radiolyzed by both e^-_{aq} and HO• to give 5-FU or 5-FUR. However, the efficiency of the γ-radiolysis depended upon the nature of substiuents and also upon the reactive species involved.

Table 1

G Values for the Formation of 5-FU upon γ-Irradiation of 1-Substituted 5-FU Derivatives and their Reduction Potentials

Compound	G-(5-FU) e^-_{aq}	G-(5-FU) HO•	$E_{1/2}$/V [a]
1	0.82	0.69	-0.73
2	0.52	0.89	-0.89
3	0.52	0.59	-1.42
4	0.30	0.34	-1.21
5	0.69	0.28	-1.27
6	0.32	0.05	-0.99
7	0.52	0.14	-1.41 (-0.28) [b]
8	0.11	0.07	-1.35 (-0.31) [b]

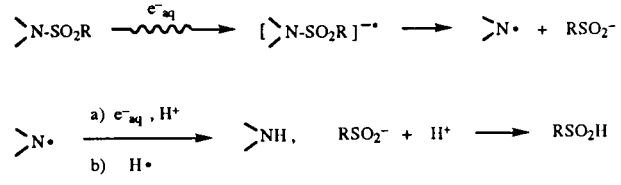
[a] Polarographic half-wave reduction potentials *vs* S.C.E. in 0.05 *M* AcONa-0.05 *M* NaH_2PO_4-10% (v/v) methanol. [b] The values in parenthesis are half-wave reduction potentials associated with the reduction of nitro groups.

Table 2

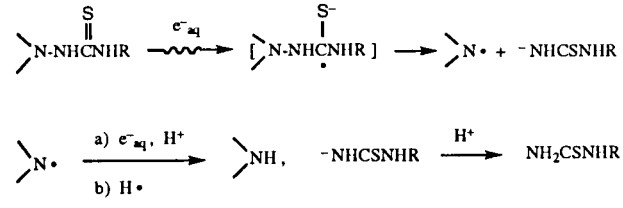
G Values for the Formation of 5-FUR upon γ-Irradiation of 3-substituted 5-FUR Derivatives

Compound	G (5-FUR) e^-_{aq}	G (5-FUR) HO•
9	0.56	0.25
10	0.46	0.31
11	0.51	0.21
12	0.57	0.15
13	0	0

We now discuss the reactivity features of the γ-radiolysis reactions of 5-FU and 5-FUR derivatives, separately. Our previous study has indicated that the γ-radiolysis of **1** with e^-_{aq} proceeds most probably *via* the pathway shown in Scheme 2 in which >N represents the nitrogen at 1-position of 5-FU [1]. THe electron-capturing ability of **1** to form the radical anion is large and comparable to that of nitrobenzene [3]. Furthermore, this process proceeds very rapidly and cannot be the rate-determining step; the rate constant for the formation of the radical anion of **1** was estimated to be *ca.* 5 x 10^{10} dm^3 mol^{-1} s^{-1} [3]. It is, therefore, reasonable to assume that the reactivity of compounds **1-8** in the γ-radiolysis is determined by the facility of the N-S bond cleavage reaction from their radical anions $[>NSO_2R]^{-\cdot}$. Figure 1 shows a plot of log G(5-FU) values for the reaction with e^-_{aq} against polarographic half-wave reduction potentials ($E_{1/2}$), for the sulfonyl groups of the compounds, which were determined experimentally and given in Table 1: the polarographic half-wave reduction potentials of the compounds were assigned by the reference to polarographic and cyclic voltammetric studies of the redox behavior of *N*-alkyl arenesulfonylanilides [4,5]. A fairly good correlation was obtained between these two quantities, except for **3**, **5** and **7**. This implies that the reactivity of the N-S bond cleavage reaction decreases with increasing the stability of the radical anions. The deviation from the linear correlation for **3**, **5** and **7** suggests that under the reaction conditions, **3** may undergo a Birch-type reduction of 4-methoxyphenyl ring [6], and **5** may undergo a reductive dechlorination by the reaction with e^-_{aq} [7] before the N-S bond cleavage reaction occurs. These side reactions appear to facilitate the N-S bond cleavage by decreasing the stability of the radical anions. There is also the possibility that the very stable radical anion of **7** undergoes an unexpected reaction.



Scheme 2



Scheme 3

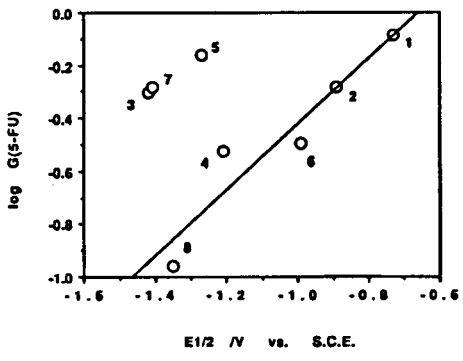


Figure 1. Plot of log G(5-FU) values *vs* polarographic half-wave reduction potentials ($E_{1/2}$ for 5-FU derivatives. Numbers in the figure correspond to the numbers of compounds (see Table 1).

The mechanistic pathway for the N-S bond cleavage reaction by HO• is not clear at present. A plausible pathway may be an attack of HO• on the sulfonyl group. However, an anomalous high reactivity of **2**, **3** and **4**, which have electron-donating substituents, suggests that HO• attacks the aromatic rings of these compounds.

We now turn to a discussion about the reactivity features of 5-FUR derivatives in their γ-radiolysis. Table 2 indicates that the N-N bond cleavage reaction occurs mainly by e^-_{aq}, but to a lesser extent by HO•. We have shown that in the γ-radiolysis of 5-fluorophenylthioureidouracil (**14**) with e^-_{aq}, the thioureido function has a high electron-capturing ability [1]; the rate constant for the formation of the radical anion of **14** by the reaction with e^-_{aq} is *ca.* 1.3-1.5 x 10^{10} dm^{-3} mol^{-1} s^{-1} and about one third of that for **1** [3]. The most probable pathway for the N-N bond cleavage reaction of **9-13** by e^-_{aq} to form 5-FUR is shown in Scheme 3, in which >N represents the nitrogen at 3-position of 5-FUR. The reactivity of this reaction will also be determined by the facility of the N-N bond cleavage process from the radical anions $[>N\text{-}NHCSNHR]^{-\cdot}$. Noteworthy is that 4-nitrophenylthioureido compound **13** is unreactive toward both e^-_{aq} and HO•. Anormalous reactions are supposed to occur in this compound.

EXPERIMENTAL

The ^1H nmr spectra were recorded on a JEOL JNM-GX 270 FT NMR Spectrometer using TMS as an internal standard. Infrared spectra were obtained on a Shimadzu IR-4000 instrument. Column chromatography was carried out on silica gel (Silica gel 60, Merck). The purity of compounds was checked by tlc on a silica gel plate (Silica gel 60, F 254, Merck). Elementary analyses were performed by a Yanagimoto CHN Corder MT-3. Half-wave redox potentials of compounds were measured by a differential pulse polarography, using a PAR model 174 polarographic analyser. 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).

General Procedure for the Synthesis of 5-Fluorouracil Derivatives.

A mixture of 5-FU (200 mg, 1.54 mmoles), an appropriate sulfonyl chloride (2.31 mmoles) and triethylamine (2 ml) in dimethylacetamide (2 ml) was stirred at room temperature for several hours. Water (8 ml) and 1*M* hydrochloric acid (2 ml) were added and then the mixture was extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and concentrated. Chromatography of the residue on silica gel gave the product.

5-Fluoro-1-(2-phenylethenesulfonyl)uracil (**1**).

This compound was prepared from 5-FU and 2-phenylethenesulfonyl chloride in 59% yield and purified by chromatography on silica gel with chloroform-acetone (30:1), mp 180-182°; ir (potassium bromide): 1700, 1670, 1330, 1170 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 7.26-8.08 (7H, m), 8.19 (1H, d, J = 6.6 Hz), 12.24 (1H, bs); ms: (m/z) 296 (M^+).

Anal. Calcd. for $C_{12}H_9N_2O_4FS$: C, 48.65; H, 3.06; N, 9.46. Found: C, 48.48; H, 3.11; N, 9.51.

1-(5-Dimethylaminonaphtyl-1-yl)sulfonyl-5-fluorouracil (**2**).

This compound was prepared from 5-FU and 5-dimethylamino-1-naphthylsulfonyl chloride in 57% yield and purified by chromatography on silica gel with *n*-hexane-ethyl acetate (2:1), mp 217.0-218.5°; ir (potassium bromide): 1735, 1705, 1665, 1565, 1360, 1320, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.86 (6H, s), 7.12-8.88 (7H, m), 12.18 (1H, bs) ; ms: (m/z) 363 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_3O_4FS$: C, 52.89; H, 3.88; N, 11.56. Found: C, 52.71; H, 3.75; N, 11.80.

5-Fluoro-1-(4-methoxyphenylsulfonyl)uracil (**3**).

This compound was prepared from 5-FU and 4-methoxyphenylsulfonyl chloride in 65% yield and purified by chromatography on silica gel with *n*-hexane-ethyl acetate (2:1), mp 209.0-210.5°; ir (potassium bromide): 1760, 1700, 1665, 1590, 1370, 1315, 1162 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.90 (3H, s), 7.06-8.00 (4H, ABq, J = 9.0 Hz), 8.18 (1H, d, J = 5.6 Hz); ms: (m/z) 300 (M^+).

Anal. Calcd. for $C_{11}H_9N_2O_5FS$: C, 44.00; H, 3.02; N, 9.33. Found: C, 44.24; H, 2.93; N, 9.57.

1-(4-Acetylaminophenylsulfonyl)-5-fluorouracil (**4**).

This compound was prepared from 5-FU and 4-acetylaminophenylsulfonyl chloride in 38% yield and purified by chromatography on silica gel with ethyl acetate, mp 229.5-230.0°; ir (potassium bromide): 1720, 1705, 1670, 1610, 1585, 1530, 1375, 1325, 1165 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.10 (3H, s), 7.90 & 7.98 (4H, ABq, J = 9.4 Hz), 8.40 (1H, d, J = 6.8 Hz), 10.54 (1H, bs), 12.24 (1H, bs); ms: (m/z) 327 (M^+).

Anal. Calcd for $C_{12}H_{10}N_3O_5FS$: C, 44.04; H, 3.08; N, 12.84. Found: C, 43.79; H, 3.23; N, 12.69.

1-(4-Chlorophenylsulfonyl)-5-fluorouracil (**5**).

This compound was prepared from 5-FU and 4-chlorophenyl-

sulfonyl chloride in 30% yield and purified by chromatography on silica gel with *n*-hexane-ethyl acetate (2:1), mp 254.0-255.5°; ir (potassium bromide): 1720, 1590, 1390, 1330, 1180 cm^{-1}; ^1H nmr (DMSO-$_6$): δ = 7.82 & 8.14 (4H, ABq, J = 8.8 Hz), 8.44 (1H, d, J = 7.2 Hz), 12.34 (1H, bs); ms: (m/z) 326 (M^+).

Anal. Calcd. for $C_{10}H_6N_2O_4ClFS$: C, 39.42; H, 1.99; N, 9.19. Found: C, 39.20; H, 2.11; N, 9.00.

1-(2,5-Dichlorophenylsulfonyl)-5-fluorouracil (**6**).

This compound was compared from 5-FU and 2,5-dichlorophenylsulfonyl chloride in 71% yield and purified by chromatography on silica gel with chloroform-acetone (15:1), mp 248.0-251.0°; ir (potassium bromide): 1735, 1705, 1680, 1385, 1322, 1182 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 7.70-8.34 (3H, m), 8.46 (1H, d, J = 6.4 Hz), 12.44 (1H, bs); ms: (m/z) 338 (M^+).

Anal. Calcd. for $C_{10}H_5N_2O_4Cl_2FS$: C,35.42; H, 1.49; N,8.26. Found: C, 35.29; H, 1.53; N, 8.41.

5-Fluoro-1-(4-nitrophenylsulfonyl)uracil (**7**).

This compound was prepared from 5-FU and 4-nitrophenylsulfonyl chloride in 39% yield and purified by chromatography on silica gel with *n*-hexane-ethyl acetate (2:1), mp 234.5-235.5°; ir (potassium bromide): 1720, 1665, 1600, 1530, 1380, 1360, 1320, 1180 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 7.88-8.70 (5H, m), 12.54 (1H, bs); ms: (m/z) 315 (M^+).

Anal. Calcd. for $C_{10}H_6N_3O_6FS$: C, 38.10; H, 1.92; N, 13.33. Found: C, 38.31; H, 2.11; N, 13.18.

5-Fluoro-1-(3-nitrophenylsulfonyl)uracil (**8**).

This compound was prepared from 5-FU and 3-nitrophenylsulfonyl chloride in 37% yield and purified by chromatography on silica gel with *n*-hexane-ethyl acetate (2:1), mp 208.0-210.0°; ir (potassium bromide): 1720, 1665, 1600, 1525, 1380, 1355, 1320, 1180 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 7.84-8.96 (5H, m), 12.36 (1H, bs); ms: (m/z) 315 (M^+).

Anal. Calcd. for $C_{10}H_6N_3O_6FS$: C, 38.10; H, 1.92; N, 13.33. Found: C, 38.25; H, 1.80; N, 13.45.

General Procedure for the Synthesis of 5-Fluorouridine Derivatives.

A mixture of 3-amino-5-fluorouridine (AFUR 801 mg, 2.89 mmoles) and an arylisothiocyanate (3.48 mmoles) in dimethylformamide (25 ml) was stirred at room temperature for 12 hours. The mixture was concentrated and extracted with water-ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried over sodium sulfate and concentrated. Chromatography of the residue on silica gel with chloroform-methanol (9:1) gave the product.

5-Fluoro-3-(*N'*-phenylthioureido)uridine (**9**).

This compound was prepared from AFUR and phenylisothiocyanate in 78% yield, mp 87.5-89.0°; ir (potassium bromide): 1680, 1530 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.57-3.88 (2H, m), 3.88-3.98 (1H, bs), 3.98-4.11 (2H, m), 5.10-5.20 (1H, m), 5.30-5.42 (1H, m), 5.42-5.48 (1H, m), 5.73 & 5.82 (1H, s, dd, J = 4.4 Hz, 1.5 Hz), 7.12-7.60 (5H, m), 8.48 & 8.60 (1H, d, J = 7.3 Hz), 9.80-10.50 (2H, m); ms: (m/z) 412 (M^+).

Anal. Calcd. for $C_{16}H_{17}N_4O_6FS$: C, 46.60; H, 4.16; N, 13.59. Found: C, 46.57; H, 4.11; N, 13.52.

5-Fluoro-3-{*N'*-(4-methoxyphenyl)thioureido}uridine (**10**).

This compound was prepared from AFUR and 4-methoxyphenylisothiocyanate in 82% yield, mp 92-94°; ir (potassium bromide): 1680, 1520 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.62-3.72 (2H, m), 3.75 (3H, s), 3.92 (1H, bs), 3.99-4.06 (2H, m), 5.17 & 5.15 (1H, d, J = 4.9Hz), 5.40 & 5.35 (1H, bs, d, J = 4.4 Hz), 5.56 & 5.51 (1H, d, bs, J = 5.4 Hz), 5.81 & 5.72 (1H, dd, bs, J = 4.4 Hz, 1.5 Hz), 6.84-6.98 (2H, m), 7.05-7.50 (2H, m), 8.61 & 8.48 (1H, d, J = 6.8 Hz), 9.75, 10.00 & 10.25 (2H, bs); ms: (m/z) 442 (M^+).

Anal. Calcd. for $C_{17}H_{19}N_4O_7FS$: C, 46.15; H, 4.33; N, 12.66. Found: C, 46.20; H, 4.19; N, 12.85.

5-Fluoro-3-{*N'*-(4-trifluoromethyl)thioureido}uridine (**11**).

This compound was prepared from AFUR and 4-trifluoromethylisothiocyanate in 76% yield, mp 77.0-79.0°; ir (potassium bromide): 1680, 1530 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.60-3.76 (2H, m), 3.92 (1H, bs), 3.99-4.08 (2H, m), 5.17 & 5.19 (1H, d, J = 4.4 Hz, 4.9 Hz), 5.36 (1H, t, J = 4.6 Hz), 5.51 & 5.56 (1H, bs, d, J = 5.4 Hz), 5.74 & 5.82 (1H, bs, dd, J = 4.4 Hz, 1.5 Hz), 7.65-7.83 (4H, m), 8.52 & 8.64 (1H, d, bs, J = 7.3 Hz) 10.09, 10.18, 10.36 & 10.77 (2H, bs); ms: (m/z) 480 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_4O_6F_4S$: C, 42.50; H, 3.36; N, 11.66. Found: C, 42.62; H, 3.23; N, 11.48.

3-{*N'*-(4-Aminosulfonylphenyl)thioureido}-5-fluorouridine (**12**).

This compound was prepared from AFUR and 4-aminosulfonylphenylisothiocyanate in 75% yield, mp 115-117°; ir (potassium bromide): 1685, 1525, 1320, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.60-3.73 (2H, m), 3.92 (1H, bs), 4.01-4.08 (2H, m), 5.17 (1H, d, J = 5.9 Hz), 5.36 (1H, bs), 5.53 (1H, bs), 5.74 & 5.82 (1H, dd, bs, J = 4.4 Hz, 1.5 Hz), 7.33 (2H, bs), 7.46-7.90 (4H, m), 8.51 & 8.61 (1H, bs), 10.13, 10.35 & 10.75 (2H, bs); ms: (m/z) 491 (M^+).

Anal. Calcd. for $C_{16}H_{18}N_5O_8FS_2$: C, 39.10; H, 3.69; N, 14.25. Found: C, 39.00; H, 3.45; N, 14.08.

5-Fluoro-3-{*N'*-(4-nitrophenyl)thioureido}uridine (**13**).

This compound was prepared from AFUR and 4-nitrophenylisothiocyanate in 57% yield, mp 122.0-124.0°; ir (potassium bromide): 1680, 1510, 1340 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.59-3.74 (2H, m), 3.96 (1H, bs), 4.01-4.56 (2H, m), 5.18 & 5.19 (1H, d, J = 5.9 Hz, 4.9 Hz), 5.36 (1H, t, J = 4.2 Hz), 5.51 & 5.56 (1H, bs, d, J = 4.9 Hz), 5.75 & 5.82 (1H, bs, dd, J = 4.4 Hz, 1.5 Hz), 7.44-8.26 (4H, m), 8.53 & 8.63 (1H, d, bs, J = 7.3 Hz), 10.21, 10.28, 10.55 & 11.02 (1H, bs); ms: (m/z) 457 (M^+).

Anal. Calcd. for $C_{16}H_{16}N_5O_8FS$: C, 42.01; H, 3.53; N, 15.31. Found: C, 42.23; H, 3.37; N, 15.56.

Polarographic Measurements.

Polarographic data were obtained under the following conditions: Electrode, Hg, Pt-SCE; Substrate concentration, *ca.* 0.2 m*M*; Supporting electrolyte, 0.05 *M* sodium acetate-0.05 *M* sodium dihydrogen phosphate-10% (v/v) methanol; Pulse interval, 1 second/drop; Scanning rate, 5 mV/second; Scanning potentials, +0.2 V to -1.8 V. Test solutions were deoxygenated by bubbling with nitrogen gas in a H-type electrode cell and polarograms were recorded at 25 ± 0.1°. Half-wave potentials ($E_{1/2}$) were measured against a saturated calomel electrode.

General Procedure for γ-Radiolysis.

Two kinds of sample solutions of 5-fluorouracil and 5-fluorouridine derivatives were prepared by dissolving the compounds 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 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-FU or 5-FUR produced by γ-radiolysis was analyzed by hplc. The conditions of the hplc analyses were as follows: Column; Lichrosorb RP-18, Mobile phase; 0.02 *M* potassium dihydrogen phosphate-0.02 *M* dipotassium hydrogen phosphate -2% (v/v) acetonitrile for 5-FU, aqueous 8% (v/v) methanol for 5-FUR. Detection; UV, 270 nm.

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