γ-Radiolysis of 1-Substituted 5-Fluorouracil Derivatives

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A new concept, "Radiation-Induced Drug (RID)", was proposed as a novel type of drugs for cancer therapy. To test the usefulness of this concept, 5-fluorouracil (5-FU) derivatives having various types of substituents at the 1-position were prepared and the γ-radiolyses of their aqueous solutions were studied. The compounds having sulfonyl and thioureido groups as the substituents produced efficiently 5-FU with high *G* values upon γ-irradiation. The medium effects on the radiolyses revealed that the above two substituents were removed mainly with HO· and hydrated electrons e^-_{eq}.

It has long been recognized that a serious problem in cancer chemotherapy is the lack of site-selectivity in drug action for tumor cells.[1-3] The drugs usually manifest severe side effects on normal cells.[1-3] In the radiotherapy, tumor cells often resist against γ-radiation, and also most of solid tumors are known to have a low sensitivity to γ-radiation.[3-6] However, there is the possibility that these defects in the cancer therapies may be removed by developing a novel type of drugs which we call "Radiation-Induced Drug (RID)". We define the RID as that the drug itself is pharmaceutically inactive both for cancer and normal cells, but it produces an active drug specifically for cancer cells upon γ-irradiation. Since γ-ray can be irradiated selectively on cancer cells, the RID is supposed to become an anticancer drug with minimal toxicity for normal cells. We have thought that the RID may be prepared by the chemical modification of a drug which is known to be active for cancer cells. This approach consists in the conversion of the active drug to its functionalized derivative from which the functional group can be removed by γ-radiolysis to reproduce the active drug.

The previous work has shown that the chemically active species in the radiotherapy are the species generated by the γ-radiolysis of water.[7] Such species are shown in Eq. 1 with the *G* values of their formation.

$$\underset{\text{G value}}{H_2O} \xrightarrow{\gamma\text{-ray}} \underset{2.6}{e^-_{aq}}, \quad \underset{2.6}{HO\cdot}, \quad \underset{0.7}{H\cdot}, \quad \underset{0.65}{H_2O_2}, \quad \underset{0.4}{H_2} \qquad (1)$$

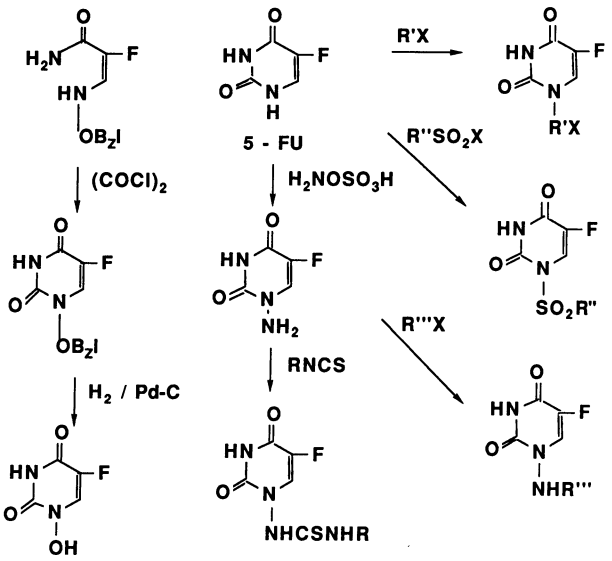
With this background we have initiated to search candidate compounds for the RID. In this investigation, we chose 5-fluorouracil (5-FU, 5-fluoro-2,4(1*H*, 3*H*)-pyrimidinedione) as a base active drug of the RID and synthesized its derivatives having various substituents at the 1-position. We then studied the γ-radiolysis of aqueous solutions of these compounds. A special attention was focused on what kinds of the reactive species play an important role in the γ-ray radiolysis of the aqueous solutions of the RID candidate compounds. The results are described in this paper.

Results and Discussion

Synthesis of 5-FU Derivatives. Twenty-five 5-FU derivatives (Table 1) which have various substituents at the 1-position were synthesized according to the routes outlined in Scheme 1. The detailed synthetic procedures and the structure confirmation of the compounds are described in the Experimental section.

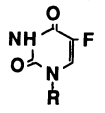
Chemically Reactive Species Generated by the γ-Radiolysis of Water. The reactive species generated by the γ-radiolyses of water (Eq. 1) may be classified into two types: the reductive species such as hydrated electron (e^-_{aq}), H· and H_2, and the oxidative species such as HO· and H_2O_2. In this investigation, we confined our attention specifically to the reactivities of three reactive species, e^-_{aq}, HO· and H·, toward the RID candidate compounds because of the large *G* values of the formation of these reactive species. We then attempted to examine the way to discriminate the predominant reactive species from other species.

The rate constants for the reactions of these reactive species with molecules closely related to this investiga-



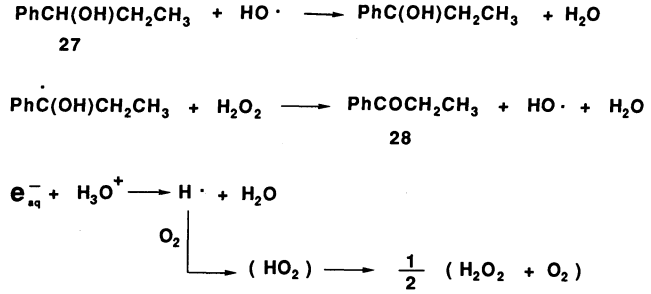
Scheme 1.

Table 1. *G* Values for the Formation of 5-FU upon γ-Irradiations of Aqueous Solutions of 1-Substituted 5-FU Derivatives

	Compound	*G*(5-FU)		
		e^-_{aq} [a]	H· [b]	HO· [c]
1	R = -$SO_2N(CH_3)_2$	0.75	0.02	0.14
2	R = -$SO_2CH{=}CHPh$	0.82	0.22	0.69
3	R = -$CO_2CH_2CCl_3$		Hydrolysis	
4	R = -CO_2CH_2- 	0.05	0.10	0.11
5	R = -$COSCH_2$- 	Trace	Trace	Trace
6	R = -NH_2· HCl	—	—	—
7	R = -N 	0.35	0.11	Trace
8	R = -$N(COCH_3)_2$	0.34	Trace	Trace
9	R = -$N(COPh)_2$	0.60	Trace	Trace
10	R = -N 	Trace	Trace	Trace
11	R = -$NHSO_2$- 	0.41	Trace	0.15
12	R = -$NHCO_2CH_2CCl_3$	0.11	0.05	0.04
13	R = -$NHCSNHCO_2Et$	1.00	1.14	0.40
14	R = -NHCSNHPh	0.59	0.89	0.15
15	R = -$NHCSNHBu^t$	0.40	1.11	0.20
16	R = -$NHCSNHCH_2Ph$	0.49	0.82	0.17
17	R = -NHCONHPh	Trace	Trace	Trace
18	R = -$NHCONHBu^t$	Trace	Trace	Trace
19	R = -$NHSO_2N(CH_3)_2$	0.07 (>NH) 0.64 (>N-NH_2)	Trace	Trace
20	R = -$CH(CH_3)$- 	—	—	—
21	R = -CH(-  $)_2$	Trace	Trace	Trace
22	R = -$C(CH_3)_2$-		Hydrolysis	
23	R = -OH	—	—	—
24	R = -OCH_2Ph	0.48	Trace	Trace
25	R = -OSO_2-	0.24	Trace	Trace
26	R = -OCO- 	0.31	Trace	Trace

a) γ-Irradiations were carried out in 1 vol% methanol-water solutions. b) γ-Irradiations were carried out in 1 vol% methanol-water solutions containing 0.05 M H_2SO_4. c) γ-Irradiations were carried out in 1 vol% acetonitrile-water solutions saturated with N_2O gas.

tion have already been reported. The typical data are shown in Eqs. 2—7.[7,8] The other data have shown that the rate constants for the reactions of e^-_{aq} and HO· with organic compounds lie in the region of 10^8—10^{11}.[9-12]



Scheme 2.

$$k(CH_3OH + HO\cdot \longrightarrow \dot{C}H_2OH + H_2O) = 4.8\times10^8 \quad (2)$$

$$k(CH_3OH + e^-_{aq}) < 10^4 \quad (3)$$

$$k(CH_3CN + HO\cdot \longrightarrow \cdot CH_2CN + H_2O) = 5.5\times10^6 \quad (4)$$

$$k(CH_3CN + e^-_{aq}) = 2.5\times10^7 \quad (5)$$

$$k(e^-_{aq} + H_3O^+ \longrightarrow H\cdot + H_2O) = 2.4\times10^{10} \quad (6)$$

$$k(e^-_{aq} + N_2O \longrightarrow HO\cdot + HO^- + N_2) = 8.7\times10^9 \quad (7)$$

These data indicate that methanol reacts with HO· much faster than with e^-_{aq}. Therefore, it is reasonable to assume that in the γ-radiolysis of an aqueous solution, the HO· species can be quenched effectively by adding methanol to the reaction mixture. On the other hand, acetonitrile reacts rather slowly and at comparable rates with both HO· and e^-_{aq}. Hence, even if acetonitrile is added to the reaction mixture, no selective quenching of both the reactive species can be expected. This presumption was confirmed by the following experiments.

Previously, Yamamoto et al. have reported that the γ-ray radiolysis of an aqueous solution of 1-phenyl-1-propanol (**27**) gives 1-phenyl-1-propanone (**28**) via the pathways shown in Scheme 2.[13]

By examining the solvent effects on this reaction, we found that the *G* value for the formation of **28** was affected to a small extent by adding acetonitrile, but to a great extent by adding methanol to the reaction system. The results are shown in Fig. 1. The addition of 1 vol% methanol caused the significant decrease in the *G* value for the formation of **28**; the *G* value decreased from 1.17 to 0.24. However, the addition of 1 vol% of acetonitrile caused no appreciable change in the *G* value; the *G* value changed from 1.17 to 1.14. These results strongly suggest that the reactive species would be quenched in accord with the pathways indicated in Eqs. 2—7.

From these quenching experiments, we made the following assumption about the reactive species in the γ-radiolysis: (1) e^-_{aq} is the principal reactive species in the reactions in 1 vol% methanol aqueous solution, (2) H· is that in the reaction in 0.05 M (M=mol dm^{-3}) H_2SO_4 solution in 1 vol% methanol aqueous solution,

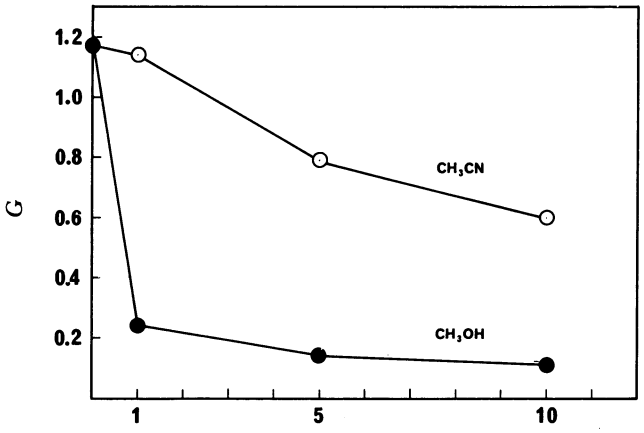
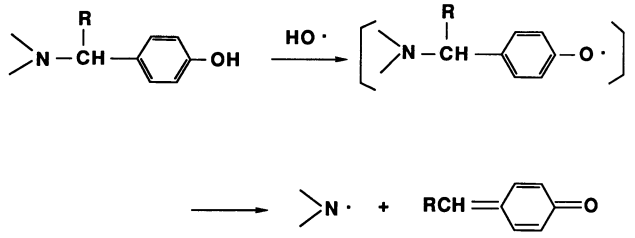


Fig. 1. Effects of added organic solvents on the *G* values for the formation of **28** in the γ-radiolysis of the aqueous solution of **27**.



Scheme 3.

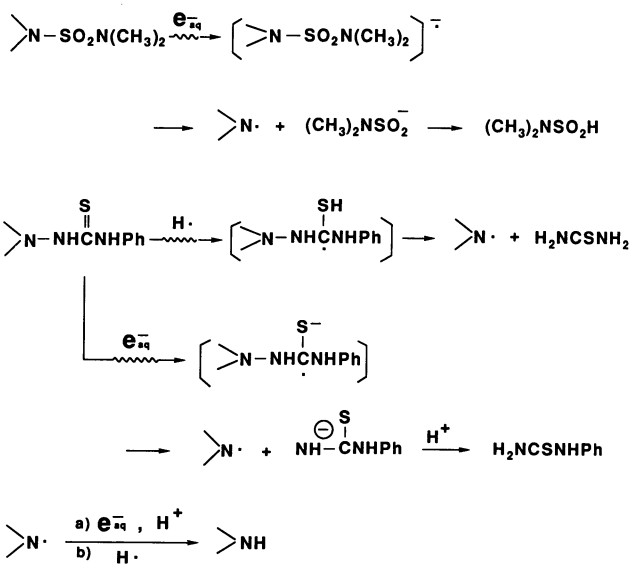
(3) HO· is that in the reaction in N_2O saturated 1 vol% acetonitrile aqueous solution.

γ-Radiolyses of 5-FU Derivatives. The γ-radiolyses of 5-FU derivatives were carried out under the conditions described in the preceding section and the *G* values for the formation of 5-FU were measured. The results are summarized in Table 1. The efficiency of the γ-radiolyses of the compounds are discussed separately according to types of bonds that are cleaved.

(1) N-C Bond Cleavage: We expected at the outset of this study that **20** and **21** may be cleaved to 5-FU via the routes shown in Scheme 3 (N represents the nitrogen at the 1-position of 5-FU). But, this type of the reaction was found not to occur appreciably. We also found that **22**, which has no hydrogen at the α carbon of the substituent, was unstable under the reaction conditions and gave 5-FU along with 2-(4-hydroxyphenyl)-2-propanol by sponthaneous hydrolysis.

For the γ-radiolysis of compound **3**, we expected that the reaction with e^-_{aq} may occur to produce 5-FU. However, this compound was also unstable under the reaction conditions and gave 5-FU by spontaneous hydrolysis.

(2) N-O Bond Cleavage: Compounds **24**, **25**, and **26** produced 5-FU mainly by the reaction with e^-_{aq} upon γ-irradiation, but the efficiency of this reaction was low.



Scheme 4.

(3) N-S Bond Cleavage: The *N*-sulfonyl compounds, **1** and **2**, were cleaved efficiently to produce 5-FU upon γ-irradiation. The medium effects on this reaction showed that the radiolysis was promoted mainly with e^-_{aq} and partly with HO··.

(4) N-N Bond Cleavage: The *N*-imido compounds, **7** and *N*-diacylamino compounds **8**, **9** were cleaved relatively efficiently to produce 5-FU mainly with e^-_{aq} upon γ-irradiation. However, we found that among all the compounds examined, the compounds having thioureido substituents such as **13—16** were efficiently cleaved to produce 5-FU upon γ-irradiation, although ureido substituents were insensitive to the γ-radiolysis. The high sensitivity of the thioureido substituents to the γ-radiolysis is due to the fact that these substituents are highly reactive toward two reductive species e^-_{aq} and H· as well as the oxidative species HO··. It should be pointed out here that the results for compounds **1** and **19** show that the N-S bond is much more sensitive than the N-N bond to the γ-radiolysis.

Mechanistic Implication. The results so far obtained indicate that 5-FU derivatives having sulfonyl or thioureido groups at the 1-position efficiently produce 5-FU upon γ-irradiation of their aqueous solutions, and they would become good candidates for the RID. The results also indicate that the sulfonyl and thioureido substituents of 5-FU derivatives are eliminated mainly with reductive species such as e^-_{aq} and H··. The plausible mechanisms for the γ-radiolysis of these sulfur-containing compounds are presented in Scheme 4.

The sulfonyl and thioureido groups have a relatively high electron-accepting ability. In addition, the radical anions of these group produced by electron

transfer become good leaving groups as their anions, and hence these groups are cleaved efficiently upon γ-irradiation.

The usefulness of the concept of RID and the mechanistic details of their γ-radiolysis are now under investigation, and will be reported in subsequent papers.

Experimental

Melting points were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer using Me_4Si as an internal standard. IR spectra were obtained on a Shimadzu IR-400 spectrometer. Mass spectra were recorded on a JEOL JMS-D300 mass spectrometer. Column chromatography was performed 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 an Yanagimoto CHN Corder MT-3, and the errors were within ±0.4% of calculated values. γ-Irradiations were carried out by ^{137}Cs source at the National Institute of Genetics. HPLC analyses were performed on a Shimadzu LC-3A, using a 25 cm×4 mm i.d. stainless steel column packed with RP-18 chemically bonded silica gel (Lichrosorb, 10 μm, Merck).

Preparation of Materials. 1-(Dimethylaminosulfonyl)-5-fluorouracil (1). To a solution of 5-FU (200 mg, 1.54 mmol) in 2 cm^3 of *N,N*-dimethylacetamide were added *N,N*-dimethylsulfamoyl chloride (342 mg, 2.38 mmol) and triethylamine (0.5 cm^3). The mixture was stirred at room temperature for 6 h, acidified to pH 3.0 with 1 M HCl, and filtered. The filtrate was concentrated, and the residue was chromatographed on silica gel with $CHCl_3$–acetone (15:1) to give 280 mg (77%) of **1**; mp 211—212 °C. IR (KBr) 1700, 1670, 1330, 1170 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.16 (6H, s), 8.42 (1H, d, *J*=6.0 Hz), 12.46 (1H, bs); MS *m/z* 237 (M$^+$). Found: C, 30.61; H, 3.35; N, 17.49%. Calcd for $C_6H_8N_3O_4FS$: C, 30.38; H, 3.40; N, 17.72%.

5-Fluoro-1-(2-phenylethenesulfonyl)uracil (2). A mixture of 5-FU (200 mg, 1.54 mmol), 2-phenylethenesulfonyl chloride (467 mg, 2.31 mmol) and triethylamine (2 cm^3) in *N,N*-dimethylacetamide (2 cm^3) was stirred at room temperature for 2.5 h. Water (8 cm^3) and 1 M HCl (2 cm^3) were added and then the mixture was extracted three times with 20 cm^3 portions of $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (30:1) to give **2** (270 mg, 59%) as colorless crystals; mp 180—182 °C. IR (KBr) 1700, 1670, 1330, 1170 cm^{-1}; ^{1}H 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$^+$). Found: C, 48.48; H, 3.11; N, 9.51%. Calcd for $C_{12}H_9N_2O_4FS$: C, 48.65; H, 3.06; N, 9.46%.

5-Fluoro-1-(2,2,2-trichloroethoxycarbonyl)uracil (3). To a solution of 5-FU (156 mg, 1.20 mmol) in 2.2 cm^3 of DMF were added 1,1,1-trichloroethoxycarbonyl chloride (386 mg, 1.82 mmol) and triethylamine (170 mg, 1.68 mmol). The mixture was stirred under ice-cooling for 1.5 h and filtered. The filtrate was concentrated. The residue was dissolved in a small amount of DMF and poured into water to give **3** (176 mg, 48%) as white crystals; mp 164—166 °C. IR (KBr) 1800 and 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=5.14 (2H, s), 8.22 (1H, d, *J*=7.2 Hz), 11.22 (1H, bs); MS *m/z* 304 (M$^+$). Found: C, 27.37; H, 1.39; N, 9.34%. Calcd for $C_7H_4N_2O_4Cl_3F$: C, 27.52; H, 1.32; N, 9.17%.

5-Fluoro-1-(4-methoxybenzyloxycarbonyl)uracil (4). A mixture of trichloromethyl chloroformate (0.3 cm^3) and active carbon (200 mg) in $ClCH_2CH_2Cl$ (10 cm^3) was stirred at room temperature for 30 min, and cooled to 5 °C. A solution of 4-methoxybenzyl alcohol (350 mg, 4 mmol) and triethylamine (610 mg, 6 mmol) in 2 cm^3 of $ClCH_2CH_2Cl$ was then added dropwise, and stirred at room temperature for 3.5 h. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in a small amount of DMF, and then 5-FU (260 mg, 2 mmol) and triethylamine (0.4 cm^3) were added to this solution. After stirring for 6 h, the mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated to give crystals, which were recrystallized from $CHCl_3$–hexane to afford pure **4** (120 mg, 20%); mp 162.5—163.5 °C. IR (KBr) 1700, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.76 (3H, s), 4.76 (2H, s), 6.94—7.34 (4H, m), 8.18 (1H, d, *J*=6.8 Hz), 11.84 (1H, bs); MS *m/z* 294 (M$^+$). Found: C, 52.83; H, 3.91; N, 9.47%. Calcd for $C_{13}H_{11}N_2O_5F$: C, 53.07; H, 3.77; N, 9.52%.

5-Fluoro-1-[(4-methoxybenzylthio)carbonyl]uracil (5). A mixture of trichloromethyl chloroformate (0.3 cm^3) and active carbon (200 mg) in dioxane (12 cm^3) was stirred at room temperature for 30 min and cooled to 5 °C. A solution of 4-methoxyphenylmethanethiol (460 mg, 3 mmol) and triethylamine (610 mg, 6 mmol) in dioxane (2 cm^3) was added dropwise and stirred at room temperature for 3 h. The precipitate was filtered off and the filtrate was evaporated. The residue was dissolved in a small amount of DMF and then 5-FU (260 mg, 2 mmol) and triethylamine (0.4 cm^3) were added. After stirring for 1.75 h, the mixture was poured into water. The deposited solid was recrystallized from AcOEt–acetone to give **5** (430 mg, 74%); mp 197—198 °C. IR (KBr) 1735, 1700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.68 (3H, s), 4.12 (2H, s), 6.86—7.30 (4H, m), 8.36 (1H, d, *J*=7.2 Hz), 12.30 (1H, bs); MS *m/z* 310 (M$^+$). Found: C, 50.20; H, 3.44; N, 9.26%. Calcd for $C_{13}H_{11}N_2O_4FS$; C, 50.32; H, 3.57; N, 9.03%.

1-(Benzylideneamino)-5-fluorouracil. To a solution of 5-FU (50 g, 0.38 mol) and KOH (112 g, 1.71 mol) in water (600 cm^3) was added an aqueous solution (200 cm^3) containing hydroxylamine-*O*-sulfonic acid (6.44 g, 1.16 mol) below 10 °C. The mixture was stirred for 4 h at room temperature and acidified to pH 3 with 5 M HCl. A solution of benzaldehyde (40 g, 0.38 mol) in ether (300 cm^3) was then added, and the resulting mixture was stirred at room temperature for 4 h. The precipitated solid was filtered, washed with water and dried to give 74.7 g of crude product which was then stirred in 750 cm^3 of dioxane at 60 °C for 30 min and cooled. The precipated white crystals were filtered to give 47.5 g (64%) of 1-(benzylideneamino)-5-fluorouracil; mp 229—231 °C. TLC (AcOEt) R_f 0.60; IR (KBr) 1722, 1650, 1605, 1565 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=7.39—8.04 (6H, m), 8.67 (1H, s), 11.31 (1H, bs).

1-Amino-5-fluorouracil Hydrochloride (6). Hydrogen gas was bubbled into a solution of 1-benzylideneamino-5-fluorouracil (20 g, 0.086 mol) in CH_3OH (200 cm^3) containing 0.5 M HCl (200 cm^3) and 10% Pd-C (2.0 g) with stirring at room temperature for 9 h. The mixture was filtered, and the filtrate was concentrated to dryness and triturated with

ether to give amorphous **6** (15.1 g, 97%). IR (KBr) 1735, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.47 (2H, bs), 7.76 (1H, d, J=5.6 Hz); MS m/z 181 (M^+). Found: C, 26.21; H, 2.71; N, 23.02%. Calcd for $C_4H_5N_3O_2ClF$: C, 26.46; H, 2.78; N, 23.15%.

5-Fluoro-1-succinimidouracil (7). To a solution of **6** (1.0 g, 5.5 mmol) in 20 cm^3 of DMF were added succinyl dichloride (0.67 cm^3, 6.1 mmol) and triethylamine (3.1 cm^3, 22 mmol) under ice-cooling. The mixture was stirred at room temperature for 15 h, and filtered. The filtrate was concentrated, poured into water, and extracted with AcOEt. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give **7** (500 mg, 42.5%); mp 204—206.5 °C. IR (KBr) 1755, 1735, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.97 (4H, s), 7.40 (1H, d, J=5.4 Hz), 11.44 (1H, bs); MS m/z 227 (M^+). Found: C, 42.48; H, 2.69; N, 18.73%. Calcd for $C_8H_6N_3O_4F$: C, 42.30; H, 2.66; N, 18.50%.

1-(Diacetylamino)-5-fluorouracil (8). Acetyl chloride (1.73 g, 22 mmol) was added to a solution of **6** (1.0 g, 5.5 mmol) in DMF (10 cm^3) and pyridine (20 cm^3) under ice-bath cooling. The mixture was stirred at room temperature for 3 h and filtered. The filtrate was concentrated, poured into water (40 cm^3) and then extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was recrystallized from AcOEt to give **8** (420 mg, 33%); mp 154.5—156.0 °C. TLC (AcOEt) R_f 0.58; IR (KBr) 1760, 1745, 1700, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.29 (6H, s), 8.06 (1H, d, J=6.2 Hz), 11.33 (1H, bs); MS m/z 229 (M^+). Found: C, 41.79; H, 3.65; N, 18.46%. Calcd for $C_8H_8N_3O_4F$: C, 41.93; H, 3.52; N, 18.34%.

1-(Dibenzoylamino)-5-fluorouracil (9). Benzoyl chloride (1.15 g, 8.22 mmol) was added to a solution of **6** (500 mg, 2.75 mmol) in 10 cm^3 of pyridine under ice-cooling. The mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated, poured into water (200 cm^3), and extracted with AcOEt. The extracts was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give **9** (535 mg, 55%); mp 168.5—170 °C. TLC (AcOEt–hexane (1:2) R_f 0.35; IR (KBr) 1760, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.79—7.85 (11H, m), 9.24 (1H, bs); MS m/z 353 (M^+). Found: C, 60.92; H, 3.38; N, 11.63%. Calcd for $C_{18}H_{12}N_3O_4F$; C, 61.19; H, 3.42; N, 11.89%.

5-Fluoro-1-phthalimidouracil (10). Phthaloyl dichloride (1.40 g, 6.9 mmol) was added to a solution of **6** (1.0 g, 5.5 mmol) in *N,N*-dimethylacetamide (20 cm^3) and pyridine (20 cm^3) under ice-bath cooling. The mixture was stirred at room temperature for 1 h, concentrated to dryness, poured into water (50 cm^3), and then extracted with AcOEt. The extracts was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (20:1). Recrystallization of the crude product from AcOEt–hexane gave pure **10** (300 mg, 20%) as white crystals; mp 248.0—249.5 °C. TLC (AcOEt) R_f 0.65; IR (KBr) 1760, 1740, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ=7.79—8.36 (4H, m), 8.23 (1H, d, J=6.0 Hz), 10.57 (1H, bs); MS m/z 275 (M^+). Found: C, 52.51; H, 2.28; N, 15.34%. Calcd for $C_{12}H_6N_3O_4F$: C, 52.37; H, 2.20; N, 15.27%.

1-(4-Chlorobenzenesulfonamide)-5-fluorouracil (11). To a solution of **6** (2.0 g, 11.0 mmol) in 20 cm^3 of pyridine and 40 cm^3 of *N,N*-dimethylacetamide was added 4-chlorobenzenesulfonyl chloride (2.79 g, 13.2 mmol). The mixture was stirred at room temperature for 3.5 h, concentrated to dryness, poured into water (50 cm^3), and then extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (9:1) to give **11** (1.31 g, 37%); mp 254—255.5 °C. TLC (AcOEt) R_f 0.57; IR (KBr) 1745, 1700, 1680, 1370, 1170 cm^{-1}; ^1H NMR (DMSO-d_6) δ=7.55—8.25 (5H, m), 11.02 (1H, br), 11.81 (1H, br); MS m/z 319 (M^+). Found: C, 37.39; H, 2.10; N, 13.36%. Calcd for $C_{10}H_7N_3O_4ClFS$: C, 37.57; H, 2.21; N, 13.14%.

5-Fluoro-1-(2,2,2-trichloroethoxycarbonylamino)uracil (12). 2,2,2-Trichloroethyl chloroformate (2.90 g, 13.7 mmol) was added to a solution of **6** (1.0 g, 5.5 mmol) in *N,N*-dimethylacetamide (20 cm^3) and pyridine (20 cm^3) under ice-bath cooling. The mixture was stirred at room temperature overnight, concentrated to dryness, poured into water (50 cm^3), and then extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (20:1) to give **12** (1.06 g, 60.3%); mp 226.5—227.0 °C. TLC (AcOEt) R_f 0.80; IR (KBr) 1735, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.73—5.02 (2H, m), 7.73—8.13 (1H, m), 9.39 (2H, bs); MS m/z 319 (M^+). Found: C, 26.51; H, 1.58; N, 13.27%. Calcd for $C_7H_5N_3O_4Cl_3F$: C, 26.24; H, 1.57; N, 13.11%.

1-[*N'*-(Ethoxycarbonyl)thioureido]-5-fluorouracil (13). To a solution of **6** (500 mg, 2.75 mmol) in 20 cm^3 of pyridine was added ethoxycarbonyl isothiocyanate (397 mg, 3.03 mmol). The mixture was stirred at room temperature for 4 h, concentrated, poured into water (50 cm^3) and then extracted with AcOEt. The extract was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated to give **13** (547 mg, 72%) as white crystals; mp 188—189 °C. IR (KBr) 1735, 1695, 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.25 (3H, t, J=7.3 Hz), 4.21 (2H, q, J=7.2 Hz), 7.90 (1H, d, J=5.8 Hz), 11.31 (3H, bs); MS m/z 276 (M^+). Found: C, 34.51; H, 3.02; N, 20.49%. Calcd for $C_8H_9N_4O_4FS$: C, 34.78; H, 3.28; N, 20.28%.

5-Fluoro-1-[*N'*-(phenyl)thioureido]uracil (14). From **6** (2.75 mmol) and phenyl isothiocyanate (3.03 mmol), **14** was obtained in a 98% yield in a similar manner as described for **13**; mp 188—189 °C. TLC ($CHCl_3$–MeOH (4:1)) R_f 0.50; IR (KBr) 1740, 1690, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ=7.02—7.66 (5H, m), 7.89 (1H, d, J=5.2 Hz), 10.12 (2H, br), 11.12 (1H, bs); MS m/z 280 (M^+). Found: C, 47.29; H, 3.08; N, 20.24%. Calcd for $C_{11}H_9N_4O_2FS$: C, 47.14; H, 3.24; N, 19.99%.

1-[*N'*-(*t*-Butyl)thioureido]-5-fluorouracil (15). From **6** (2.75 mmol) and *t*-butyl isothiocyanate (3.03 mmol), **15** was obtained in a 79% yield in a similar manner as described for **13**; mp 201—202 °C. TLC ($CHCl_3$–MeOH (4:1)) R_f 0.52; IR (KBr) 1720, 1680, 1525 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.44 (9H, s), 7.79 (1H, bs), 7.84 (1H, d, J=5.8 Hz), 9.14 (1H, bs), 11.06 (1H, bs). MS m/z 260 (M^+). Found: C, 41.70; H, 5.31; N, 21.38%. Calcd for $C_9H_{13}N_4O_2FS$: C, 41.53; H, 5.03; N, 21.53%.

1-[*N'*-(Benzyl)thioureido]-5-fluorouracil (16). From **6** (2.75 mmol) and benzyl isothiocyanate (3.03 mmol), **16** was obtained in a 84% yield in a similar manner as above; mp 163—165 °C. TLC ($CHCl_3$–MeOH (4:1)) R_f 0.48; IR (KBr) 1740, 1680, 1555 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.68 (2H, d, J=5.4 Hz), 7.00—7.42 (3H, m), 7.82 (1H, d, J=5.2 Hz), 8.72

(1H, t, J=5.7 Hz), 9.69 (1H, bs); MS m/z 294 (M^+). Found: C, 49.18; H, 3.93; N, 19.17%. Calcd for $C_{12}H_{11}N_4O_2FS$: C, 48.97; H, 3.77; N, 19.04%.

5-Fluoro-1-(*N'*-phenylureido)uracil (17). From **6** (2.75 mmol) and phenyl isocyanate (3.02 mmol), **17** was obtained in a 22% yield; mp 258—260 °C. IR (KBr) 1740, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.78—7.63 (5H, m), 7.90 (1H, d, J=5.8 Hz), 8.62 (1H, bs), 9.12 (1H, bs), 11.27 (1H, bs); MS m/z 264 (M^+). Found: C, 49.79; H, 3.21; N, 21.13%. Calcd for $C_{11}H_9N_4O_3F$: C, 50.00; H, 3.43; N, 21.21%.

1-(*N'-t*-Butylureido)-5-fluorouracil (18). To a solution of **6** (1.0 g, 5.51 mmol) in pyridine (40 cm^3) was added *t*-butyl isocyanate (600 mg, 6.06 mmol) and the mixture was stirred at room temperature for 10 h. Work-up of the reaction mixture in the similar manner as above gave **18** in a 45% yield as white crystals; mp 238 °C. TLC (AcOEt) R_f 0.20; IR (KBr) 1740, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.25 (9H, s), 6.33 (1H, bs), 7.71 and 7.80 (1H, d, J=6.0 Hz, 5.2 Hz), 7.96 (1H, bs), 11.09 (1H, bs); MS m/z 244 (M^+). Found: C, 44.44; H, 5.48; N, 22.84%. Calcd for $C_9H_{13}N_4O_3F$: C, 44.26; H, 5.37; N, 22.94%.

1-(*N,N*-Dimethylsulfamoylamino)-5-fluorouracil (19). To a solution of **6** (1.0 g, 5.51 mmol) and triethylamine (5 cm^3) in DMF (25 cm^3) was added *N,N*-dimethylsulfamoyl chloride (1.22 g, 8.50 mmol). The mixture was stirred at room temperature for 5 h, and filtered. The filtrate was concentrated, poured into water and extracted with AcOEt. The extract was washed with aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residue was recrystallized from acetone to give **19** (690 mg, 50%); mp 187—189 °C. TLC (AcOEt) R_f 0.60; IR (KBr) 1710, 1680, 1380, 1180 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.40 (6H, s), 8.00 (1H, d, J=6.0 Hz), 11.01 (1H, br), 11.47 (1H, br); MS m/z 252 (M^+). Found: C, 28.35; H, 3.57; N, 21.93%. Calcd for $C_6H_9N_4O_4FS$: C, 28.57; H, 3.60; N, 22.21%.

1-[4-(Tetrahydropyranyloxy)phenyl]ethanol. A mixture of *p*-hydroxylbenzaldehyde (2.4 g), 3,4-dihydro-2*H*-pyran (20 cm^3) and pyridine *p*-toluenesulfonate (0.7 g) was stirred at room temperature for 15 h, concentrated and poured into water (200 cm^3), and then extracted with $CHCl_3$. The chloroform layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (40:1) to give 2.2 g (54.3%) of 4-(tetrahydro-2-pyranyloxy)benzaldehyde; TLC ($CHCl_3$–acetone (20:1)) R_f 0.80. The protected aldehyde thus obtained was dissolved into ether (10 cm^3), and the ether solution was added to a solution of CH_3Li (2.12 mmol) in ether over 5 min. The resulting mixture was refluxed for 1 h, cooled, and poured into water (100 cm^3). The ether layer was separated, washed with an aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (40:1) to give 1.28 g (54%) of 1-[4-(tetrahydropyranyloxy)phenyl]ethanol. IR (KBr) 3410, 2950, 1620, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.39 (3H, d, J=6.4 Hz), 1.10—2.24 (6H, m), 2.71 (1H, bs), 3.26—4.15 (2H, m), 4.74 (1H, q, J=6.4 Hz), 5.22—5.46 (1H, m), 6.94 and 7.18 (4H, ABq, J=8.8 Hz).

5-Fluoro-1-[1-(4-hydroxyphenyl)ethyl]uracil (20). To a solution of 1-[4-(tetrahydropyranyloxy)phenyl]ethanol (435 mg) in $ClCH_2CH_2Cl$ (30 cm^3) was added thionyl chloride (1 cm^3). The mixture was stirred at room temperature for 30 min and concentrated. The residue was dissolved into acetonitrile (10 cm^3), and 2,4-*O*-bis(trimethylsilyl)-5-fluorouracil (1.5 g) and $SnCl_4$ (0.06 cm^3) was then added to the solution. The mixture was stirred at room temperature for 1 h, and 5% aqueous $NaHCO_3$ solution (20 cm^3) was added and the reacting mixture was extracted with AcOEt. The organic layer was washed with an aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (30:1) to give 330 mg (67%) of amorphous **20**. TLC ($CHCl_3$–acetone (4:1)) R_f 0.20; IR (KBr) 1700, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.61 (3H, d, J=7.0 Hz), 5.68 (1H, q, J=7.5 Hz), 6.76—7.18 (4H, m), 7.88 (1H, d, J=6.1 Hz), 9.46 (1H, bs), 11.78 (1H, bs); MS m/z 250 (M^+). Found: C, 57.43; H, 4.29; N, 11.02%. Calcd for $C_{12}H_{11}N_2O_3F$: C, 57.60; H, 4.43; N, 11.20%.

Bis(4-acetoxyphenyl)methyl Bromide. Acetic anhydride (6 cm^3) was added to a solution of bis(4-hydroxyphenyl)methanol (1.0 g, 5 mmol) in pyridine (20 cm^3) and stirred at room temperature for 15 h. The mixture was concentrated, poured into water, and extracted with AcOEt. The organic layer was washed successively with 5% aqueous $NaHCO_3$ and aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (20:1) to give 1.22 g (26%) of bis(4-acetoxyphenyl)-methane; mp 66—68 °C. IR (KBr) 1745, 1200 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.19 (6H, s), 3.88 (2H, s), 6.94 and 7.16 (8H, ABq, J=8.4 Hz). To a solution of bis(4-acetoxyphenyl)-methane (90 mg, 3.16 mmol) in CCl_4 (30 cm^3) was added *N*-bromosuccinimide (0.63 g) and catalytic amount of AIBN. After refluxing for 1 h, the reaction mixture was concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (40:1) to give 0.73 g (64%) of bis(4-acetoxyphenyl)methyl bromide. TLC ($CHCl_3$–actone (20:1)) R_f 0.7; ^1H NMR ($CDCl_3$) δ=2.27 (6H, s), 5.36 (1H, s), 7.06 and 7.35 (8H, ABq, J=8.8 Hz).

1-[Bis(4-hydroxyphenyl)methyl]-5-fluorouracil (21). To a solution of bis(4-acetoxyphenyl)methyl bromide (0.63 g, 1.74 mmol) and 2,4-*O*-bis(trimethylsilyl)-5-fluorouracil (0.98 g) in acetonitrile (20 cm^3) was added $SnCl_4$ (0.2 cm^3) and the mixture was stirred for 1.2 h. After adding 5% aqueous $NaHCO_3$ solution (20 cm^3), the reaction mixture was extracted with AcOEt. The AcOEt layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (30:1) to give 0.5 g of 1-[bis(4-acetoxyphenyl)methyl]-5-fluorouracil. IR (KBr) 1760, 1705, 1670, 1380, 1245, 1205 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.25 (6H, s), 6.92 (1H, bs), 7.16 and 7.25 (4H, ABq, J=9.0 Hz), 7.63 (1H, d, J=6.8 Hz), 11.93 (1H, bs). 1-[Bis(4-acetoxyphenyl)methyl]-5-fluorouracil (0.32 g, 0.78 mmol) in ethanol was dissolved in aqueous 1 M NaOH solution. The solution was acidified to pH 3.8 with dil HCl and extracted with AcOEt. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4), and concentrated to give solids. The solids was triturated with ether to afford 250 mg (68%) of amorphous **23**. TLC ($CHCl_3$–acetone (4:1)) R_f 0.10; IR (KBr) 1700, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.53—7.20 (9H, m), 7.45 (1H, d, J=6.8 Hz), 9.68 (2H, bs), 11.69 (1H, bs); MS m/z 328 (M^+). Found: C, 62.45; H, 4.18; N, 8.38%. Calcd for $C_{17}H_{13}N_2O_4F$: C, 62.20; H, 3.99; N, 8.53%.

2-[4-(Tetrahydropyranyloxy)phenyl]-2-propanol. Pyridine *p*-toluenesulfonate (10.7 g) was added to a solution of methyl *p*-hydroxybenzoate (2.13 g) and 3,4-dihydro-2*H*-pyran (20 cm^3) in acetone (20 cm^3). The mixture was stirred

at room temperature for 15 h, concentrated, poured into water, and then extracted with $CHCl_3$. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with hexane–AcOEt (15:1) to give 3.34 g (100%) of methyl 4-(tetrahydropyranyloxy)benzoate, which was dissolved in ether (30 cm^3). To this ether solution was added CH_3Li (60 mmol) in ether over 10 min. The reaction mixture was refluxed for 1 h, diluted with water (10 cm^3) and then extracted with AcOEt. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated to afford 2.64 g of 2-[4-(tetrahydropyranyloxy)phenyl]-2-propanol. TLC ($CHCl_3$–acetone (4:1)) R_f 0.80; ^1H NMR ($CDCl_3+D_2O$) δ=1.50 (6H, s), 1.16—2.10 (6H, m), 3.27—4.08 (2H, m), 5.24—5.43 (1H, m), 6.92 and 7.31 (4H, ABq, J= 8.7 Hz).

5-Fluoro-1-[1-(4-hydroxyphenyl)-1-methylethyl]uracil (22). To a solution of 2-[4-(tetrahydropyranyloxy)phenyl]-2-propanol (2.1 g) and 2,4-*O*-bis(trimethylsilyl)-5-fluorouracil (10.0 g) in acetonitrile (50 cm^3) was added $SnCl_4$ (1 cm^3) at −20 °C. The mixture was stirred at the same temperature for 30 min, and then 5% aqueous $NaHCO_3$ (20 cm^3) was added and was extracted with AcOEt. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–acetone (30:1) to give 330 mg (14%) of **22**; mp 270—272 °C. TLC ($CHCl_3$–acetone (4:1) R_f 0.12; IR (KBr) 1710, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.74 (6H, s), 6.67—7.03 (4H, m), 8.07 (1H, d, J=8.4 Hz), 9.23 (1H, bs), 11.43 (1H, d, J=5.0 Hz); MS m/z 264 (M^+). Found: C, 58.88; H, 4.86; N, 10.83%. Calcd for $C_{13}H_{13}N_2O_3F$: C, 59.09; H, 4.96; N, 10.60%.

5-Fluoro-1-hydroxyuracil (23). Hydrogen gas was introduced at room temperature into a solution of **24** (500 mg, 2.1 mmol) in ethanol–water (8:2) containing 10% Pd–C (50 mg) for 1.3 h and the catalyst was filtered off. The filtrate was concentrated and the residue was triturated with ether to give 220 mg (72%) of **23**; mp 208 °C (decomp). TLC ($CHCl_3$–MeOH–AcOH (40:5:1)) R_f 0.22; IR (KBr) 3450, 1710, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ=8.33 (1H, d, J=7.0 Hz), 11.28 (2H, bs); MS m/z 146 (M^+). Found: C, 32.61; H, 2.21; N, 18.93%. Calcd for $C_4H_3N_2O_3F$: C, 32.85; H, 2.07; N, 19.15%.

1-Benzyloxy-5-fluorouracil (24). A mixture of 3-benzyloxyamino-2-fluoroacrylamide (5.3 g, 25 mmol) and oxalyl dichloride (7.2 g, 57 mmol) in CH_2Cl_2 (220 cm^3) was refluxed for 27 h and then concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (100:1) to give 1.55 g (26%) of **24**; mp 184—185 °C. IR (KBr) 1725, 1695 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.10 (2H, s), 6.98—7.79 (6H, m), 11.91 (1H, bs); MS m/z 236 (M^+). Found: C, 55.77; H, 3.60; N, 11.72%. Calcd for $C_{11}H_9N_2O_3F$: C, 55.94; H, 3.84; N, 11.86%.

1-(4-Chlorophenylsulfonyloxy)-5-fluorouracil (25). To a solution of **23** (300 mg, 2.05 mmol) in pyridine (5 cm^3) was added 4-chlorobenzenesulfonyl chloride. The mixture was stirred at room temperature for 15 min, concentrated, diluted with water, and then extracted with AcOEt. The organic layer was successively washed with 0.1 M NaOH and aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (4:1) to give 220 mg (33%) of **25**; mp>300 °C. TLC ($CHCl_3$–MeOH (4:1)) R_f 0.63; IR (KBr) 1720, 1640 cm^{-1}, ^1H NMR (DMSO-d_6) δ=7.72—7.98 (4H, m), 8.47 (1H, d, J=6.0 Hz), 11.07 (1H, bs); MS m/z 320 (M^+). Found: C, 37.63; H, 1.71; N, 8.53%. Calcd for $C_{10}H_6N_2O_5ClFS$: C, 37.45; H, 1.89; N, 8.74%.

1-(4-Chlorobenzyloxy)-5-fluorouracil (26). To a solution of **23** (500 mg, 3.42 mmol) in pyridine (10 cm^3) was added 4-chlorobenzoyl chloride (0.46 cm^3, 3.60 mmol). The mixture was stirred at room temperature for 30 min, concentrated, diluted with water (70 cm^3) and then extracted with AcOEt. The organic layer was washed with aqueous NaCl solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (4:1). The crude product obtained by evaporation of the solvent was diluted with tetrahydrofuran, and then the insoluble matter was filtered off. The filtrate was concentrated and the residue was triturated with ether to give 350 mg (36%) of **26**; mp 201—203 °C. TLC ($CHCl_3$–MeOH (4:1)) R_f 0.68; IR (KBr) 1780, 1710 cm^{-1}; ^1H NMR (DMSO-d_6) δ=7.69—8.09 (4H, m), 8.67 (1H, d, J=6.0 Hz), 10.68 (1H, bs); MS m/z 284 (M^+). Found: C, 46.27; H, 2.30; N, 9.89%. Calcd for $C_{11}H_6N_2O_4ClF$: C, 46.42; H, 2.12; N, 9.84%.

γ-Radiolysis of 1-Phenyl-1-propanol (27). Stock solutions of **27** were prepared by dissolving it in deionized distilled water or in 1%, 5%, and 10% (v/v) aqueous acetonitrile or methanol in concentration of 200 μg cm^{-3}. The each solution was deaerated with N_2 bubbling for 20 min. An approximately 2 cm^3 of the solution was put into a 5 mmϕ Pyrex glass tube under N_2 and irradiated for 100 Gy (3.15 Gy min^{-1}) with the γ-ray of ^{137}Cs at room temperature (ca. 20 °C). The irradiated mixture was subjected to HPLC to analyze **28**. The conditions of the HPLC analyses were as follows: Column; Lichrosorb RP-18, Mobile phase; aqueous 30% (v/v) methanol solution, Detection; UV, 254 nm.

General Procedure for γ-Radiolysis of 5-Fluorouracil Derivatives. Three kinds of sample solutions of 5-fluorouracil derivatives were prepared by dissolving them in the following three deaerated solvents in concentration of 50 μg cm^{-3}; (a) deaerated aqueous 1% methanol (v/v) solution, (b) 0.1 M H_2SO_4 deaerated solution in aqueous 1% methanol (v/v), (c) deaerated aqueous 1% acetonitrile (v/v) solution saturated with N_2O gas.

Each sample solution was irradiated with γ-ray in the same manner as the γ-radiolysis of **27**. After irradiation, the amount of 5-FU produced by the radiolysis was analyzed by HPLC. The conditions of the HPLC were as follows: Column; Lichrosorb RP-18, Mobile phase; 0.02 M KH_2PO_4–0.02 M K_2HPO_4–2% CH_3CN, Detection; UV, 270 nm.

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