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Studies on Antitumor Agents. VII.[1] Antitumor Activities of *O*-Alkoxyalkyl Derivatives of 2′-Deoxy-5-trifluoromethyluridine

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Various *O*-alkoxyalkyl derivatives of 2′-deoxy-5-trifluoromethyluridine (F_3Thd) were synthesized, and the antitumor activities of the compounds against sarcoma 180 were examined by oral administration to mice. Among the formal-type derivatives, 3′,5′-di-*O*-ethoxymethyl (**3**), 3′,5′-di-*O*-benzyloxymethyl (**12**), 5′-*O*-benzyloxymethyl (**13**) and 3′-*O*-benzyloxymethyl (**14**) compounds showed high activities, which were six-fold higher than that of F_3Thd itself. Since acetal-type derivatives were unstable under acidic conditions, antitumor testing of the compounds was also carried out with co-administration of sodium bicarbonate. 5′-*O*-(1-Ethoxypropyl)-F_3Thd (**25**) and 5′-*O*-(1-benzyloxypropyl)-F_3Thd (**37**) showed the highest activities among the acetal-type derivatives, but the ED_{50} values of the compounds were not lower than those of effective formal-type compounds.

These *O*-alkoxyalkyl derivatives of F_3Thd are resistant to degradation by thymidine phosphorylase and are activated by microsomal drug-metabolizing enzymes after absorption.

Keywords——2′-deoxy-5-trifluoromethyluridine; protecting group; benzyloxymethylation; antitumor activity; drug-metabolizing enzyme

2′-Deoxy-5-trifluoromethyluridine (F_3Thd) was first synthesized by Heidelberger and his coworkers in 1962.[2] A metabolite of F_3Thd, 2′-deoxy-5-trifluoromethyluridine 5′-monophosphate (F_3TMP) has been reported to inhibit the enzyme (thymidylate synthetase).[3] It has also been reported that deoxyribonucleic acid (DNA) chain elongation and joining were inhibited by incorporation of another metabolite of F_3Thd, 2′-deoxy-5-trifluoromethyluridine 5′-triphosphate, into DNA.[4] As a result of these actions of the metabolites of F_3Thd, F_3Thd is a potent antiviral and antitumor agent in some systems.[5–7] However, F_3Thd is unsatisfactory for practical medicinal use in cancer chemotherapy, because of its short half-life in plasma.[8] Rapid metabolic degradation by thymidine phosphorylase has been reported to be responsible for this.[8,9] Therefore, depot forms of F_3Thd which resist degradation by the enzyme would be expected to maintain higher concentrations of F_3Thd in plasma and to show improved antitumor activity *in vivo*.

Recently, we have reported syntheses and antitumor activities of acyl derivatives of F_3Thd.[1] Acylation was effective in elevating the antitumor activity of F_3Thd, but the derivatives were rather easily saponified to F_3Thd by intestinal homogenate.

It has been reported that tetrahydrofuryl groups of 3′,5′-di-*O*-(tetrahydro-2-furyl)-thymidine can be removed by microsomal drug-metabolizing enzymes.[10] Alkoxyalkyl substituents on 5-fluorouracil have also been reported to be removed by the enzyme in the same way as the tetrahydrofuryl group of 1-(tetrahydro-2-furyl)-5-fluorouracil (tegafur, which is widely used clinically).[11] These observations suggest that *O*-alkoxyalkyl derivatives

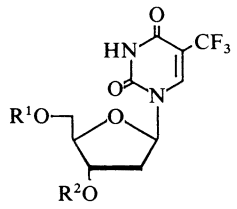
of F_3Thd would resist degradation by thymidine phosphorylase and be activated slowly after absorption, possibly giving a high therapeutic index.

Therefore, various *O*-alkoxyalkyl derivatives of F_3Thd were synthesized and their antitumor activities on oral administration were evaluated to find candidate compounds for clinical use, especially for maintenance therapy after surgical treatment like other depot forms of 5-fluorouracil. This paper describes the synthesis of such derivatives of F_3Thd and the antitumor activities of the compounds against sarcoma 180.

Results and Discussion

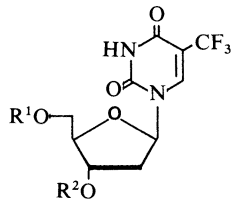
The structures and antitumor activities of *O*-(tetrahydro-2-furyl) (**1**) and *O*-(tetrahydro-2-pyranyl) (**2**) compounds and formal-type derivatives of F_3Thd are shown in Table I. Compound **1** was obtained by the reaction of F_3Thd and 2,3-dihydrofuran, with *p*-toluenesulfonic acid (TsOH) as a catalyst, in dioxane. Treatment of F_3Thd with an excess of 2-methoxytetrahydropyran and a small amount of TsOH in dioxane under heating gave a mixture of 5′-*O*- (**2**), 3′-*O*- and 3′,5′-di-*O*-(tetrahydro-2-pyranyl)-F_3Thd. The products were purified by silica gel column chromatography. Compounds **3**—**14** were similarly synthesized by the reaction of F_3Thd and dialkoxymethane using TsOH. The dialkoxymethanes were obtained by treatment of methylene chloride with an excess of sodium hydroxide and alcohol

TABLE I. Antitumor Effects of Formal-Type Compounds of F_3Thd



Compd.	R^1	R^2	ED_{50} (mg/kg/d)
1		R^1	42
2		H	46
3	$CH_2OC_2H_5$	R^1	12
4	$CH_2OC_2H_5$	H	23
5	CH_2OCH_3	H	36
6	CH_2SCH_3	H	>40
7	$CH_2O(CH_2)_3CH_3$	H	23
8	$CH_2OCH_2CH_2SCH_3$	H	>80
9	H	$CH_2OCH_2CH_2SCH_3$	>80
10	CH_2OCH_2 	H	46
11	H	CH_2OCH_2	>80
12	CH_2OCH_2 	R^1	12
13	CH_2OCH_2 	H	10
14	H	CH_2OCH_2	11
F_3Thd			63

TABLE II. Antitumor Effects of Acetal-Type Compounds of F_3Thd



Compd.	R^1	R^2	ED_{50} (mg/kg/d)
15	$CH(CH_3)CH_2CH(CH_3)_2$	H	>40
16	$CH(CH_3)O$-Ph	H	>40
17	$CH(CH_3)OCH_2$-Ph	R^1	>40
18	$CH(CH_3)OCH_2$-Ph	H	>40
19	H	$CH(CH_3)OCH_2$-Ph	>40
20	$CH(CH_3)O(CH_2)_5CH_3$	H	34
21	H	$CH(CH_3)O(CH_2)_5CH_3$	>40
22	$CH(CH_3)O(CH_2)_9CH_3$	H	>40
23	$CH(CH_3)OCH_2$-Fu	H	>40
F_3Thd			63

at 140 °C in a sealed stainless steel tube.

Acetals were synthesized by the reaction of aldehyde and alcohol in the presence of calcium chloride at room temperature. Treatment of F_3Thd in dioxane with acetals under the same reaction conditions as used for alkoxymethylation gave compounds **15**—**43**.

The structures and antitumor activities of those componds are shown in Tables II, III and V.

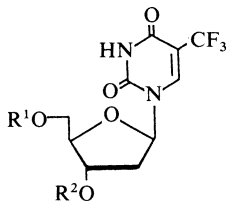
Biological Activity

Compounds **1** and **2** were slightly more effective than F_3Thd, and some of the formal-type derivatives showed high activities. The ED_{50} values of the 3′,5′-di-*O*-ethoxymethyl (**3**), 3′,5′-di-*O*-benzyloxymethyl (**12**), 5′-*O*-benzyloxymethyl (**13**) and 3′-*O*-benzyloxymethyl (**14**) compounds were 12, 12, 10 and 11 mg/kg/d, respectively. These results show that the antitumor activity of F_3Thd can be elevated by *O*-ethoxymethylation or *O*-benzyloxymethylation to 6 times that of F_3Thd itself.

Compounds **6**, **8** and **9** with chains containing a methylthio group showed no activity at the same dose as that of F_3Thd. These compounds are presumably not activated by microsomal drug-metabolizing enzymes.

Three metabolic pathways can be assumed for the activation of formal-type derivatives of F_3Thd (Chart 1). One is the oxidative route which results in release of benzaldehyde and formaldehyde. Oxidation of another carbon would release benzyl alcohol and formyl ester,

TABLE III. Antitumor Effects of Acetal-Type Compounds of F_3Thd

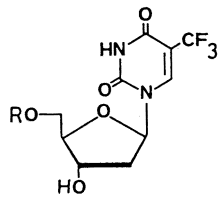


Compd.	R^1	R^2	ED_{50} (mg/kg/d)
24	$CH(CH_3)OC_2H_5$	H	51
25	$CH(CH_2CH_3)OC_2H_5$	H	29
26	$CH(C_6H_5)OC_2H_5$	H	—
27	$CH(CH_2C_6H_5)OC_2H_5$	H	>40
28	$CH(CH_2CH_2C_6H_5)OC_2H_5$	H	>37
29	$CH(C(CH_3)_3)OC_2H_5$	H	40
30	$CH(CH_3)OCH_2C_6H_5$	R^1	26
31	$CH(CH_3)OCH_2C_6H_5$	H	25
32	H	$CH(CH_3)OCH_2C_6H_5$	31
33	$CH(CH_3)OCH_2C_6H_4$-C_4H_9	R^1	>40
34	$CH(CH_3)OCH_2C_6H_4$-C_4H_9	H	27
35	H	$CH(CH_3)OCH_2C_6H_4$-C_4H_9	>40
36	$CH_2OCH_2CH_2C_6H_5$	H	32
37	$CH(CH_2CH_3)OCH_2C_6H_5$	H	22
38	$CH(CH(CH_3)_2)OCH_2C_6H_5$	H	36
39	H	$CH(CH(CH_3)_2)OCH_2C_6H_5$	>20
40	$CH(C(CH_3)_3)OCH_2C_6H_5$	H	>40
41	H	$CH(C(CH_3)_3)OCH_2C_6H_5$	>40
F_3Thd			63

TABLE IV. Antitumor Effects of F_3Thd Derivatives with Co-administration of Sodium Bicarbonate

Compd.	ED_{50} (mg/kg/d)		Compd.	ED_{50} (mg/kg/d)	
	Alone	$NaHCO_3$ added		Alone	$NaHCO_3$ added
4	23	19	**28**	37	31
13	12	12	**29**	>40	20
18	>40	>20	**31**	25	17
20	34	>20	**34**	27	>20
22	>40	>20	**37**	22	30
23	>40	>20	**38**	36	35
24	51	40	**40**	>40	24
25	29	19	**43**	>40	>20
27	>40	38			

TABLE V. Antitumor Effects of 1-Phenethyloxy Compounds of F_3Thd



Compd.	R	ED_{50} (mg/kg/d)	
		Alone	$NaHCO_3$ added
13	CH_2OCH_2-Ph	10	12
31	CH_3 CHOCH$_2$-Ph	25	17
42	CH_3 CH_2OCH-Ph	25	—
43	CH_3 CH_3 CHOCH-Ph	40	20
36	$CH_2OCH_2CH_2$-Ph	32	—

which would eventually give F_3Thd. The third route would be direct hydrolysis, giving benzyl alcohol, formaldehyde and F_3Thd. The role of these metabolites in the toxicity of F_3Thd derivatives is not clear. Therefore, various acetal-type derivatives of F_3Thd were synthesized with the aim of obtaining more effective compounds with ED_{50} values of 10 mg/kg/d or less.

Since there is expected to be a parallel relation between antitumor activity and F_3Thd-releasing capability by the drug-metabolizing enzymes, F_3Thd derivatives which have a lipophilic activated site were synthesized and tested on S 180 (Table II). The ED_{50} values of most of the compounds were equal to that of F_3Thd or higher.

Various ethoxyalkyl and benzyloxyalkyl derivatives were next synthesized, in view of the high activities of the ethyl- and benzyl-formal-type compounds (Table III). Among the ethoxyalkyl-type compounds (**24**—**29**), *O*-(1-ethoxypropyl)-F_3Thd (**25**) showed the highest activity. Among the benzyloxy-type compounds (**30**—**41**), *O*-(1-benzyloxypropyl)-F_3Thd (**37**) was expected to show the highest activity because of the similarity of the structure, and this was indeed the case. Nevertheless, the ED_{50} values of both compounds (**25** and **37**) were

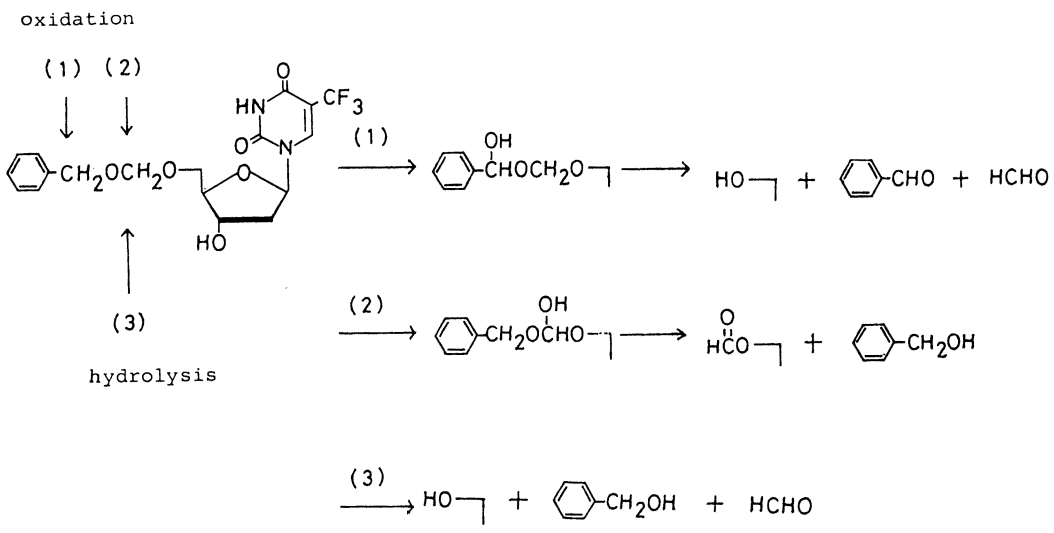


Chart 1

rather high (29 and 22 mg/kg/d, respectively) compared with those of the effective formal-type derivatives.

Since these alkoxyalkyl derivatives of F_3Thd are generally unstable under acidic conditions, some of the compounds would be hydrolyzed to F_3Thd in the gastro-intestinal tract before absorption, resulting in rather lower antitumor activities. Therefore, various F_3Thd derivatives were next examined with co-administration of sodium bicarbonate to prevent acidic hydrolysis. The results are summarized in Table IV.

Compounds **4** and **13** were not affected by co-administration of sodium bicarbonate, because those compounds were reasonably stable under acidic conditions. The antitumor activities of compounds **18**, **20**, **22** and **23** were also not elevated by sodium bicarbonate. These compounds may not be activated well by the microsomal drug-metabolizing enzymes. In contrast, co-administration of sodium bicarbonate decreased the ED_{50} values of compounds **24**, **25**, **27**, **28** and **29** by about 10 mg/kg/d. The antitumor activities of compounds **31** and **40**, among the compounds having a benzyloxy group, were also elevated by the co-administration. However, among the acetal-type compounds, none showing ED_{50} values in the region of 10 mg/kg/d could be obtained.

5′-*O*-(1-Phenethyloxy)methyl-F_3Thd (**42**) and 5′-*O*-1-(1-phenethyloxy)ethyl-F_3Thd (**43**) were next synthesized and compared with compounds **13**, **31** and **36** to elucidate the oxidation site at the first step of the metabolic pathway. As shown in Table V, the introduction of a methyl group into either formalic methylene or benzylic methylene decreased the antitumor activities. The ED_{50} value of compound **43** with two methyl groups was the highest among the compounds.

These results suggest that oxidative activation of the F_3Thd derivatives by the enzyme occurs at both the formalic and benzylic positions, and is retarded by the introduction of a methyl group.

Experimental

Chemicals——Melting points were determined with a Yanagimoto MP-3 micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a JEOL LMN-FX 100 spectrometer (using tetramethylsilane as an internal standard). Formals and acetals were purchased or synthesized by

TABLE VI. Physical Constants and Analytical Data of Alkoxyalkyl Derivatives of F_3Thd

Compd.	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
1	155—159	EtOH	67	$C_{18}H_{23}F_3N_2O_7$	49.54 (49.57)	5.31 5.47	6.42 6.46)
2	Foam		18	$C_{15}H_{19}F_3N_2O_6$	47.37 (47.18)	5.04 5.12	7.37 7.27)
3	Oil		19	$C_{16}H_{23}F_3N_2O_7$	46.60 (46.64)	5.62 5.69	6.79 6.91)
4	185—187	$CHCl_3$	17	$C_{13}H_{17}F_3N_2O_6$	44.07 (44.12)	4.84 4.92	7.91 8.00)
5	179—182	EtOH	19	$C_{12}H_{15}F_3N_2O_6$	42.36 (42.39)	4.44 4.51	8.23 8.35)
6	180.5—182.5	EtOH	15	$C_{12}H_{15}F_3N_2O_5S$	40.45 (40.17)	4.24 4.20	7.86 7.73)
7	187.5—188.5	EtOH	19	$C_{15}H_{21}F_3N_2O_6$	47.12 (46.89)	5.54 5.52	7.33 7.26)
8	160.5—161.5	EtOH	13	$C_{14}H_{19}F_3N_2O_6S$	42.00 (41.72)	4.78 4.76	7.00 6.96)
9	Oil		9	$C_{14}H_{19}F_3N_2O_6S$	42.00 (41.78)	4.78 4.68	7.00 6.88)
10	155—156	$CHCl_3$–EtOH	18	$C_{16}H_{21}F_3N_2O_7$	46.83 (46.69)	5.16 5.11	6.83 6.69)
11	Oil		14	$C_{16}H_{21}F_3N_2O_7$	46.83 (46.66)	5.16 5.10	6.83 6.65)
12	Oil		15	$C_{26}H_{27}F_3N_2O_7$	58.21 (57.98)	5.07 5.02	5.22 5.11)
13	184.5—186	EtOH	24	$C_{18}H_{19}F_3N_2O_6$	51.93 (51.84)	4.60 4.54	6.73 6.71)
14	Oil		23	$C_{18}H_{19}F_3N_2O_6$	51.93 (51.88)	4.60 4.61	6.73 6.69)
15	Foam		20	$C_{15}H_{19}F_3N_2O_6$	47.37 (47.20)	5.03 4.96	7.37 7.27)
16	Foam		23	$C_{18}H_{25}F_3N_2O_6$	51.18 (51.00)	5.97 5.88	6.42 6.22)
17	Oil		16	$C_{28}H_{43}F_3N_2O_7$	58.32 (58.00)	6.24 6.08	6.42 6.36)
18	163—165	EtOH	22	$C_{19}H_{27}F_3N_2O_6$	52.29 (52.33)	6.24 6.11	6.42 6.40)
19	Oil		12	$C_{19}H_{27}F_3N_2O_6$	52.29 (52.22)	6.24 6.13	6.42 6.40)
20	Foam		34	$C_{18}H_{27}F_3N_2O_6$	50.94 (50.64)	6.41 6.30	6.60 6.28)
21	Foam		17	$C_{18}H_{27}F_3N_2O_6$	50.94 (50.41)	6.41 6.40	6.60 6.33)
22	152—153	EtOH	18	$C_{22}H_{35}F_3N_2O_6$	54.99 (54.88)	7.34 7.31	5.83 5.78)
23	179.5—181	EtOH	22	$C_{23}H_{31}F_3N_2O_6$	56.55 (56.80)	6.40 6.56	5.73 5.82)
24	163—165	EtOH	24	$C_{14}H_{19}F_3N_2O_6$	45.66 (45.36)	5.20 5.28	7.61 7.63)
25	161—164.5	EtOH	33	$C_{15}H_{21}F_3N_2O_6$	47.12 (46.89)	5.53 5.65	7.33 7.40)
26	Foam		12	$C_{19}H_{21}F_3N_2O_6$	53.02 (52.85)	4.91 4.91	6.51 6.56)

TABLE VI. (continued)

Compd.	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
27	127 (dec.)	EtOH–pet. ether	32	$C_{20}H_{23}F_3N_2O_6$	54.05	5.22	6.30
					(54.23	5.34	6.33)
28	121—123	EtOH–pet. ether	36	$C_{21}H_{25}F_3N_2O_6$	55.02	5.50	6.11
					(55.14	5.61	6.16)
29	149—153	$CHCl_3$–pet. ether	22	$C_{17}H_{25}F_3N_2O_6$	49.75	6.14	6.83
					(49.76	6.11	6.77)
30	Oil		20	$C_{28}H_{31}F_3N_2O_7$	59.57	5.53	4.96
					(59.73	5.61	4.80)
31	163.5—166	EtOH	27	$C_{19}H_{21}F_3N_2O_6$	53.03	4.92	6.51
					(52.94	5.08	6.55)
32	Foam		22	$C_{19}H_{21}F_3N_2O_6$	53.03	4.92	6.51
					(53.10	5.02	6.49)
33	Oil		12	$C_{36}H_{47}F_3N_2O_7$	63.89	7.00	4.14
					(64.00	7.14	4.12)
34	147—149	Benzene–EtOH	18	$C_{23}H_{29}F_3N_2O_6 \cdot 1/2\,H_2O$	55.75	6.10	5.65
					(55.67	6.03	5.95)
35	Foam		13	$C_{23}H_{29}F_3N_2O_6$	56.79	6.01	5.76
					(56.68	6.08	5.63)
36	164	EtOH–pet. ether	26	$C_{19}H_{21}F_3N_2O_6$	53.03	4.92	6.51
					(52.79	5.12	6.74)
37	145—148	EtOH	12	$C_{20}H_{23}F_3N_2O_6$	54.05	5.22	6.30
					(53.78	5.13	6.42)
38	Foam		17	$C_{21}H_{25}F_3N_2O_6 \cdot 1/4\,H_2O$	54.48	5.55	6.05
					(54.65	5.58	6.06)
39	Foam		15	$C_{21}H_{25}F_3N_2O_6$	55.02	5.50	6.11
					(54.80	5.56	5.88)
40	135.5—137	Benzene–$CHCl_3$	22	$C_{22}H_{27}F_3N_2O_6$	55.93	5.76	5.93
					(55.95	5.92	5.93)
41	Foam		17	$C_{22}H_{27}F_3N_2O_6$	55.93	5.76	5.93
					(55.83	5.81	5.78)
42	148—151	EtOH–pet. ether	12	$C_{19}H_{21}F_3N_2O_6$	53.02	4.92	6.51
					(52.74	5.21	6.74)
43	Foam		11	$C_{20}H_{23}F_3N_2O_6$	54.05	5.22	6.30
					(53.78	5.24	6.10)

the methods cited.

2′-Deoxy-3′,5′-di-*O*-(tetrahydro-2-furyl)-5-trifluoromethyluridine (1)——*p*-Toluenesulfonic acid (80 mg) was added to a suspension of F_3Thd (20 g, 0.067 mol) and 2,3-dihydrofuran (16.8 g, 0.24 mol) in dioxane (160 ml), and the mixture was stirred for 0.5 h at room temperature. The mixture was neutralized with 0.1 N C_2H_5ONa and concentrated. The residue was extracted with $CHCl_3$, then the extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was crystallized from EtOH, giving 19.6 g of **1** in 67% yield. NMR (DMSO-d_6): 11.90 (1H, s, N^3-H), 8.12 (1H, s, H-6), 5.95 (1H, t, H-1′), 5.16 (2H, d, H-2 of tetrahydrofuryl group), 4.16 (2H, m, H-3′, 4′), 3.86 (6H, br, H-5′ and H-5 of tetrahydrofuryl group), 2.30 (2H, t, H-2′).

2′-Deoxy-5′-*O*-(tetrahydro-2-pyranyl)-5-trifluoromethyluridine (2)——*p*-Toluenesulfonic acid (60 mg) was added to a suspension of F_3Thd (2 g, 6.7 mmol) and 2-methoxytetrahydropyran (2.4 g, 20.4 mmol), and the mixture was stirred for 4 h at 60 °C, then neutralized with 0.1 N C_2H_5ONa and concentrated. The residue was extracted with $CHCl_3$, then the extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 10 : 1, v/v) and the eluate was concentrated to dryness to afford **2** (0.46 g, 18%) as a foam. NMR (DMSO-d_6): 11.90 (1H, s, N^3-H), 8.14 (1H, d, H-6), 6.06 (1H, t, H-1′), 5.35 (1H, d, HO-3′), 4.60 (1H, s, H-2 of tetrahydropyranyl group), 4.24 (1H, m, H-3′), 4.04 (1H, m, H-4′), 2.21 (2H, t, H-2′).

5′-*O*-Benzyloxymethyl-2′-deoxy-5-trifluoromethyluridine (13)——*p*-Toluenesulfonic acid (120 mg) was added to a suspension of F_3Thd (2 g, 6.7 mmol) and dibenzyloxymethane (6.2 g, 27.2 mmol), and the mixture was stirred for 3 h

at 60 °C, then neutralized with 0.1 N C_2H_5Na and concentrated. The residue was extracted with $CHCl_3$. The extract was washed with water and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 10 : 1, v/v) and the product was crystallized from EtOH, giving 680 mg of **13** in 24% yield. NMR (DMSO-d_6): 11.88 (1H, s, N^3-H), 8.40 (1H, s, H-6), 6.09 (1H, t, H-1′), 5.40 (1H, d, HO-3′), 4.76 (2H, s, formalic methylene), 4.54 (2H, s, benzylic methylene), 4.26 (1H, m, H-3′), 3.97 (1H, q, H-4′), 2.31 (2H, t, H-2′). Other fractions of the eluate gave 560 mg (15%) of **12** and 655 mg (23%) of **14**.

Compounds **3**—**11** and **15**—**43** were synthesized similarly. The structures of these compounds were confirmed by the elemental analyses as well as by ^{1}H-NMR measurements (Table VI).

Antitumor Activity Test——Five-week-old male ICR mice (Japan Clea Inc., Tokyo, Japan) were inoculated subcutaneously in the axillary region with 5×10^6 sarcoma 180 cells, and test compounds were given orally once a day for 7 consecutive days beginning 24 h after inoculation of the tumor cells. Groups of seven mice were used for each dose and the test compounds were suspended in 0.5% carboxymethylcellulose (CMC) solution containing 0.1% Tween 80. On day 10, the tumors were excised and weighed. The inhibitory effects of test compounds were calculated from the ratio of the tumor weight in the test group to that in the control group.

Inhibitory effects of F_3Thd derivatives on the growth of solid tumor S 180 are shown in terms of the ED_{50} values in Tables I—V.

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