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Studies on Antitumor Agents. IV.[1] Syntheses and Antitumor Activities of Compounds related to 1-(Tetrahydro-2-furanyl)-5-fluorouracil Metabolites

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A hydroxylated metabolite of 1-(tetrahydro-2-furanyl)-5-fluorouracil (FT), 1-(*trans*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil (*trans*-3′-OH-FT, VIII) and its isomer, 1-(*cis*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil (*cis*-3′-OH-FT, VI), were synthesized and isolated at high purity. As compounds related to FT metabolites, 2,3′-anhydro-1-(*cis*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil (2,3′-anhydro-FT, V), 1-(2,5-dihydro-2-furanyl)-5-fluorouracil (3′,4′-dehydro-FT, XII) and 1-(5-acetoxytetrahydro-2-furanyl)-5-fluorouracil (5′-AcO-FT, XI) were also synthesized.

The antitumor activities of these compounds against sarcoma 180 and L 1210 were examined. The activities of *cis*-3′-OH-FT (VI) and 2,3′-anhydro-FT (V) were found to be lower than that of FT. The activity of 5′-AcO-FT (XI) was the same as that of FT. 3′,4′-Dehydro-FT (XII) showed much greater activity than FT.

Keywords——1-(tetrahydro-2-furanyl)-5-fluorouracil; 1-(*trans*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil; 1-(*cis*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil; antitumor activities; NMR shift reagent

1-(Tetrahydro-2-furanyl)-5-fluorouracil (FT), first synthesized by Hiller *et al.*[2] is used clinically as an antitumor agent with low toxicity. FT is a masked form of 5-fluorouracil (5-FU),[3] and is converted *in vivo* to the active substance, 5-FU. Various 5-FU derivatives, such as 1-hexylcarbamoyl-5-fluorouracil,[4] 5′-deoxy-5-fluorouridine,[5] and 1,3-bis(tetrahydro-2-furanyl)-5-fluorouracil (FD-1),[6] have been synthesized and examined for antitumor activities in order to obtain antitumor agents with an even higher therapeutic index than 5-FU or FT.

As part of an attempt to develop such antitumor agents, we synthesized compounds related to FT metabolites. FT is metabolized to 1-(*trans*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil (*trans*-3′-OH-FT, VIII), 1-(*cis*-4-hydroxytetrahydro-2-furanyl)-5-fluorouracil (*cis*-4′-OH-FT), 1-(dihydro-2-furanyl)-5-fluorouracil (dehydro-FT), and some other compounds in addition to 5-FU.[7–9] It has been reported that the antitumor activities of these hydroxylated FT metabolites are lower than that of FT.[10] However the antitumor activities of their isomers, *cis*-3′-OH-FT (VI) and *trans*-4′-OH-FT are not known.

Therefore, we undertook the synthesis of VI, the isomer of the natural metabolites, by an unambiguous route. 1-(5-Hydroxytetrahydro-2-furanyl)-5-fluorouracil (5′-OH-FT) has not been isolated as a hydroxylated FT methabolite because of its lability.[7] Therefore the synthesis of 1-(5-acetoxytetrahydro-2-furanyl)-5-fluorouracil (5′-AcO-FT, XI) was also attempted. Although 1-(2,5-dihydro-2-furanyl)-5-fluorouracil (3′,4′-dehydro-FT, XII) has been synthesized,[11] its antitumor activity has not been reported. Since 3′-OH-FT and 4′-OH-FT might be converted to XII *in vivo*, the antitumor activity of this compound was also compared with those of the hydroxylated derivatives.

Synthesis

Although syntheses of VI and VIII have been reported,[10] the procedure required the separation of a mixture of 1-(*trans*-3-acetoxytetrahydro-2-furanyl)-5-fluorouracil (*trans*-3′-AcO-FT, IX) and *cis*-3′-AcO-FT (VII) by silica gel column chromatography, which was not

satisfactory. We therefore synthesized VI and VIII in high purity *via* 2,3′-anhydro-1-(*cis*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil (2,3′-anhydro-FT, V).

Treatment of 2,4-bis(trimethylsilyl)-5-fluorouracil (I) with 2,3-dihalogenotetrahydrofuran (II) in dichloromethane under catalysis with stannic chloride at room temperature yielded a mixture of 1-(3-halogenotetrahydro-2-furanyl)-5-fluorouracils (III and IV). The ratio of the *cis* and *trans* isomers was *ca.* 1:1, as judged from the nuclear magnetic resonance (NMR) data. Treatment of the halogeno compounds (III and IV) with 0.2 N NaOH at room temperature for 15 h, followed by removal of the unreacted 1-(*cis*-3-halogenotetrahydro-2-furanyl)-5-fluorouracil (III), yielded V. Compound V exhibits absorption maxima at 226 and 252 nm in the ultraviolet (UV) spectrum, which is consistent with the maxima due to the 2,2′-anhydro structure of nucleosides.[12b]

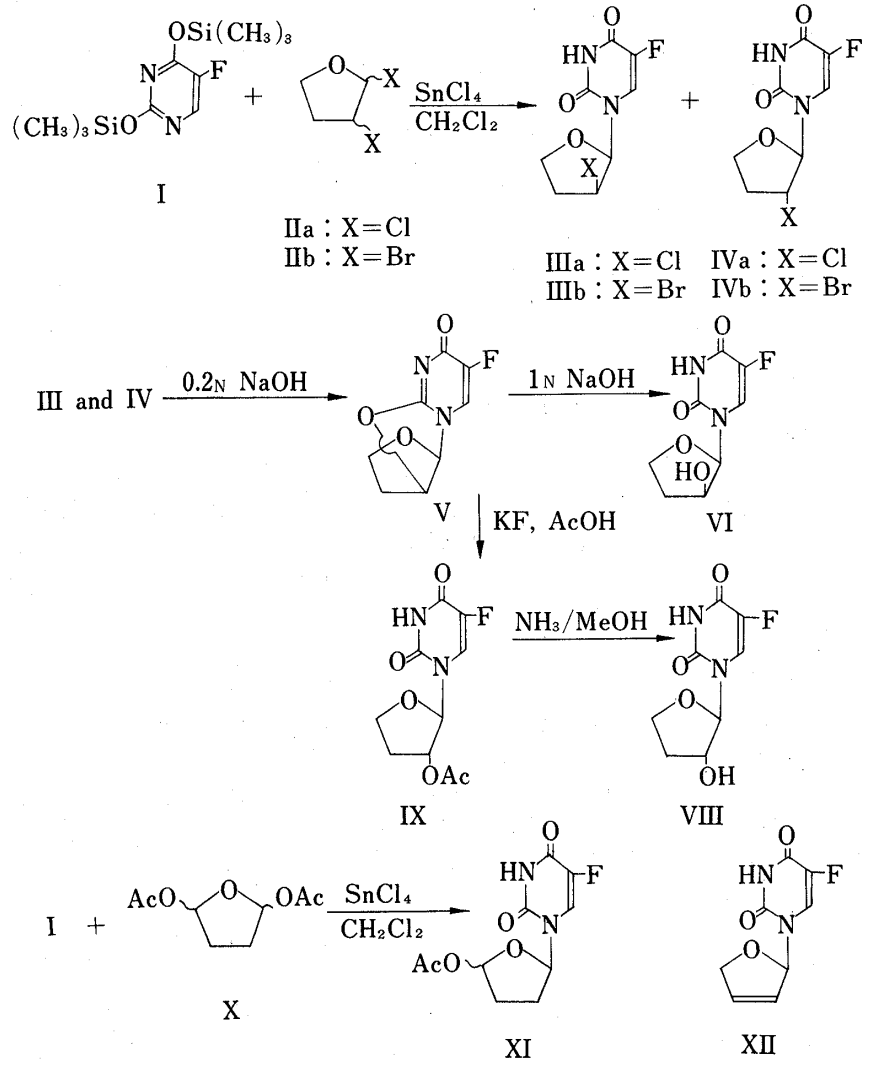

Chart 1

Treatment of V with 1 N NaOH at room temperature gave VI in high yield.[12a] In the NMR spectrum, C-2′-H of VI appears as doublets (δ 5.85, $J_{2',3'}$=3.7 Hz and $J_{2',F}$=1.8 Hz) indicating coupling with C-3′-H and a long-range coupling with C-5-F. A similar long-range coupling between the anomeric proton and a fluorine of 5-fluoro-2′-deoxyuridine has been reported.[13] The 3′-acetylated derivative (VII) of VI exhibited a doublet at δ 5.49 (C-2′-H, $J_{2',3'}$=4.2 Hz).

Treatment of V with acetic acid and KF in acetonylacetone at 180—190°C afforded IX.[15] In the NMR spectrum, the C-2′-H signal of IX appears as a doublet (δ 5.60, J=1.2 Hz).

Deacetylation of IX with NH_3/CH_3OH yielded VIII. In the NMR spectrum, C-2′-H of VIII appears as a doublet (δ 5.49, J=1.2 Hz).

It is reported that the coupling constant of vicinal *cis* protons is larger than that of *trans* protons in acylated pentofuranose derivatives.[15] It is also known that a pentofuranosyl nucleoside with 2′-OH *trans* to the base shows an anomeric proton signal at higher field than the corresponding nucleoside with the 2′-OH *cis* to the base.[15] Therefore, from the NMR data of VI—IX, the structure of VI (and VII) can be assigned as the *cis* form and that of VIII (and IX) as the *trans* form. The ^{13}C-NMR data of the compounds prepared in this work are consistent with the structures summarized in Table I.

Table I. ^{13}C-NMR Spectral Data in DMSO-d_6[a]

Compound	δ_{C-2}	δ_{C-4}	δ_{C-5}	δ_{C-6}	$\delta_{C-2'}$	$\delta_{C-3'}$	$\delta_{C-4'}$	$\delta_{C-5'}$	J_{C_1-F}	J_{C_2-F}	J_{C_3-F}
2,3′-Anhydro-FT (V)	157.9	163.6	145.5	121.3	91.1	84.6	32.2	66.1	16.5	249.6	37.4
cis-3′-OH–FT (VI)	140.9	157.1	139.0	126.4	87.2	69.3	33.3	67.7	26.9	228.3	34.2
trans-3′-OH–FT (VIII)	148.8	157.1	140.0	124.6	92.2	74.0	31.7	68.7	26.3	230.1	34.2
5′-AcO–FT (XI)[b]	149.2 148.3	156.9 157.0	140.1 140.1	124.0 124.0	86.7 86.1	27.1 28.1	31.1 29.4	97.8 98.3	26.2 26.3	232.0 232.0	34.1 34.1

a) δ, ppm from TMS; J_{C-F}, Hertz.
b) $\underline{C}H_3CO_2$=20.9 ppm, $CH_3\underline{C}O_2$=169.2 ppm.
$\underline{C}H_3CO_2$=20.9 ppm, $CH_3\underline{C}O_2$=169.5 ppm.

The reported melting point of VI was 154—156°C[10] but VI synthesized by us showed a sharp mp at 191—192°C. It is clear that our synthetic method yields VI and VIII in high purity and excellent yield.

We have previously reported that chiral shift reagents can be used to distinguish enantiomeric isomers of FT and FD-1.[1] Figure 1 shows the NMR spectra of VII with and without tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium [Eu(TFC)$_3$]. The results

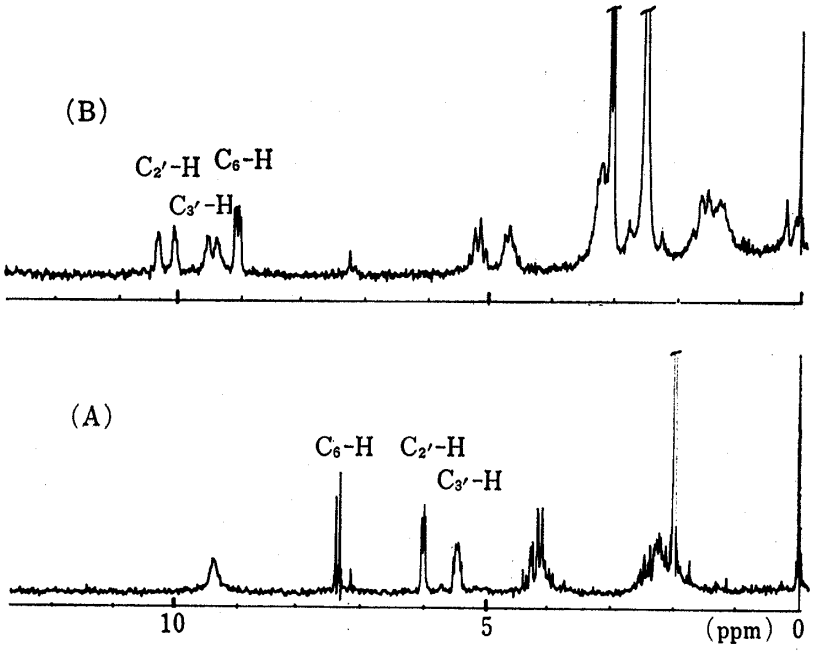

Fig. 1. ^1H-NMR Spectra of *cis*-3′-AcO-FT (VII) in $CDCl_3$ at 35°C
A: with out Eu(TFC)$_3$, B: with Eu(TFC)$_3$ at a molar ratio of 0.5 with respect to VII.

clearly indicate the presence of (*R*)- and (*S*)-isomers in VII. A similar result was obtained in the measurement of IX.

Benvenuto and Lin *et al.* suggested that 5′-OH-FT might be produced in addition to 3′-OH-FT and 4′-OH-FT as an FT metabolite.[7,10] If 5′-OH-FT is unstable and decomposes to 5-FU, it would be an interesting masked form of 5-FU and would be expected to have antitumor activity. Therefore we tried to synthesize the 5′-acetoxy derivative. Treatment of I with 2,5-diacetoxytetrahydrofuran (X) in dichloromethane under catalysis with stannic chloride gave XI. Treatment of XI with acid or alkali afforded 5-FU rapidly. Compound XI obtained here is a mixture *cis*- and *trans*-isomer at the 5′-position as judged from the NMR

Table II. Inhibitory Effects of *cis*-3′-OH-FT (VI) and Related Compounds on Sarcoma 180 (*s.c.–p.o.*)[a]

	Dose (mg/kg/d)	Body wt. change g, day 10—day 0)	Tumor weight (g, mean±S.D.)	Inhibition (%)
Control	—	+7.5	1.19±0.36	—
2,3′-Anhydro-	200	+6.9	1.10±0.22	8
FT (V)	100	+7.1	0.88±0.26	26
	50	+7.6	1.10±0.24	8
cis-3′-OH-FT	200	+6.8	0.86±0.21	28
(VI)	100	+6.6	1.02±0.24	14
	50	+7.0	1.21±0.26	−4
3′,4′-Dehydro-	100	−1.3	0.27±0.10[b]	77
FT (XII)	50	+5.4	0.68±0.14[c]	43
	25	+6.9	0.92±0.19	23
5′-AcO-FT	200	+5.7	0.46±0.16[b]	61
(XI)	100	+5.9	0.66±0.12[c]	45
	50	+7.1	0.78±0.27[d]	34
FT	200	+5.1	0.38±0.14[b]	68
	100	+5.7	0.63±0.22[c]	47
	50	+7.0	0.85±0.13[d]	29

a) See Experimental.
b) $p<0.001$. *c*) $p<0.01$. *d*) $p<0.05$.

Table III. Effects of *cis*-3′-OH-FT (VI) and Related Compounds on L 1210 (*i.p.–p.o.*)[a]

	Dose (mg/kg/d)	Survival time (d, mean±S.D.)	ILS[b] (%)
Control	—	8.33±0.52	—
2,3′-Anhydro-	200	8.57±0.53	3
FT (V)	100	8.43±0.53	1
	50	8.57±0.53	3
cis-3′-OH-FT	200	8.29±0.49	0
(VI)	100	9.00±1.15	8
	50	8.57±0.79	3
3′,4′-Dehydro-	200	10.43±1.81[c]	25
FT (XII)	100	11.14±1.46[d]	34
	50	13.00±1.00[d]	56
5′-AcO-FT (XI)	200	12.86±1.21[d]	54
	100	11.00±1.00[d]	32
	50	9.43±0.79[c]	13
FT	200	12.71±0.75[d]	53
	100	10.43±0.98[d]	25
	50	9.00±0.82	8

a) See Experimental. *b*) Increase of life span. *c*) $p<0.05$. *d*) $p<0.001$.

spectrum. Its spectrum exhibits signals of C-6-H at δ 7.82 and 7.66, C-5-H at δ 6.40 and 6.13, and acetoxy groups at δ 2.00 and 1.95.

Antitumor Activities

The antitumor activities of compounds prepared in the present work toward sarcoma 180 and L 1210 are shown in Tables II and III, respectively. Antitumor activities of VI, which is the isomer of the natural metabolite (VIII), and V are lower than those of FT. Against sarcoma 180, the activity of XII at a dose of 100 mg/kg is even greater than that of FT. Against L 1210, the activity of XII at a dose of 50 mg/kg is greater than that of FT, but at higher doses (100—200 mg/kg) XII was less effective due to its toxicity . The antitumor activity of XI is almost equal to that of FT. In order to determine whether XI and XII are more useful antitumor drugs than FT, it will be necessary to examine the antitumor activity spectrum of these compounds. The result of such studies will be reported separately.

Experimental

$SnCl_4$ was a product of Wako Chemical Co. Ltd. (Osaka, Japan). Tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium, [Eu(TFC)$_3$] was a product of Merck Co. (Germany). ^{1}H-NMR spectra were recorded on a Hitachi R-22 spectrometer using tetramethylsilane as an internal standard. ^{13}C-NMR spectra were recorded on a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a JEOL JMS-01G-2 spectrometer and UV spectra were recorded on a Hitachi 124 spectrometer. Elemental analyses were carried out with a Yanagimoto CHN Corder MT-2 analyzer. Melting points were determined with a Yanagimoto micro melting point apparatus and are reported as uncorrected values.

1-(3-Chlorotetrahydro-2-furanyl)-5-fluorouracil (IIIa and IVa)——$SnCl_4$ (0.03 ml, 0.00026 mol) and 2,3-dichlorotetrahydrofuran (IIa, 4.2 g, 0.03 mol) were added to a solution of 2,4-bis(trimethylsilyl)-5-fluorouracil (I, 8.2 g, 0.03 mol) in dichloromethane (50 ml), and the mixture was stirred at room temperature for 12 h. Then dichloromethane (100 ml) and water (50 ml) were added to the reaction mixture and the resulting mixture was shaken thoroughly. The dichloromethane layer was separated, dried over Na_2SO_4, and evaporated to dryness. Crystallization of the residue from EtOH gave 6.2 g (88.1%) of a mixture of IIIa and IVa, mp 167—169°C. Fractional crystallization of the mixture of IIIa and IVa gave 3.6 g (51.2%) of 1-(*trans*-3-chlorotetrahydro-2-furanyl)-5-fluorouracil (IVa): mp 189—190°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 265 (8300). ^{1}H-NMR (DMSO-d_6) δ: 5.77 (1H, d, J=1.2 Hz, $C_{2'}$–H), 7.74 (1H, d, J=7.0 Hz, C_6–H). *Anal.* Calcd for $C_8H_8ClFN_2O_3$: C, 40.96; H, 3.44; N, 11.94. Found: C, 40.85; H, 3 53; N, 11.92.

Concentration of the mother liquor gave a solid, which was crystallized from EtOH to give 1.6 g (22.7%) of 1-(*cis*-3-chlorotetrahydro-2-furanyl)-5-fluorouracil (IIIa): mp 203—205°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 267 (8800). ^{1}H-NMR (DMSO-d_6) δ: 5.98 (1H, d, d, J=4.2, 2.0 Hz, $C_{2'}$–H), 7.84 (1H, d, J=7.0 Hz, C_6–H). *Anal.* Calcd for $C_8H_8ClFN_2O_3$: C, 40.96; H, 3.44; N, 11.94. Found: C, 40.90; H, 3.35; N, 12.02. MS *m/e*: 234 (M^+).

1-(3-Bromotetrahydro-2-furanyl)-5-fluorouracil (IIIb and IVb)——1-(3-Bromotetrahydro-2-furanyl)-5-fluorouracil (IIIb and IVb) was synthesized from 2,4-bis(trimethylsilyl)-5-fluorouracil (I, 8.2 g, 0.03 mol) and 2,3-dibromotetrahydrofuran (IIb, 9.0 g, 0.039 mol) by the same method as described for the synthesis of IIIa and IVa. It was recrystallized from EtOH giving 6.9 g (82.4%) of a mixture of IIIb and IVb, mp 165—166°C.[17] Fractional crystallization of the mixture of IIIb and IVb from EtOH gave 4.3 g (51.4%) of 1-(*trans*-3-bromotetrahydro-2-furanyl)-5-fluorouracil (IVb): mp 187—189°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 267 (8300). ^{1}H-NMR (DMSO-d_6) δ: 5.84 (1H, d, J=1.2 Hz, $C_{2'}$–H), 7.70 (1H, d, J=7.0 Hz, C_6–H). *Anal.* Calcd for $C_8H_8BrFN_2O_3$: C, 34.43; H, 2.89; N, 10.04. Found: C, 34.34; H, 2.90; N, 9.88. MS *m/e*: 280 $[M+1]^+$, 278 $[M-1]^+$.

Concentration of the mother liquor gave a solid, which was crystallized from EtOH to give 1.8 g (21.5%) of 1-(*cis*-3-bromotetrahydro-2-furanyl)-5-fluorouracil (IIIb): mp 200—201°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 268 (8900). ^{1}H-NMR (DMSO-d_6) δ: 5.86 (1H, d, d, J=4.2, 2.0 Hz, $C_{2'}$–H), 7.82 (1H, d, J=7.0 Hz, C_6–H). *Anal.* Calcd for $C_8H_8BrFN_2O_3$: C, 34.43; H, 2.89; N, 10.04. Found: C, 34.38; H, 2.92; N, 9.85. MS *m/e*: 280 $[M+1]^+$, 278 $[M-1]^+$.

2,3′-Anhydro-1-(*cis*-3-hydroxytetrahydro-2-furanyl)-5-fluorouracil (V)——A mixture of IIIa and IVa (8.0 g, 0.0342 mol) or IVa alone (4.0 g, 0.0171 mol) in 0.2 N NaOH (140 ml) was stirred at room temperature for 15 h. The solution was adjusted to pH 5—6 with 1 N HCl and the insoluble material IIIa was filtered off. The filtrate was extracted three times with 200 ml portions of chloroform. The chloroform extracts were combined, dried over Na_2SO_4 and evaporated to dryness, yielding a white powder that was recrystallized from acetone–benzene (1: 1) to give 3.4 g (50.2%) of V from the mixture of IIIa and IVa, or 3.2 g (94.5%) of V from IVa, mp 182—183°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 226 (7300) and 252 (8500). ^{1}H-NMR (DMSO-d_6) δ:

5.33 (1H, t, J=5.2 Hz, $C_{3'}$–H), 6.17 (1H, d, J=5.2 Hz, $C_{2'}$–H), 8.12 (1H, d, J=4.6 Hz, C_6–H). *Anal.* Calcd for $C_8H_7FN_2O_3$: C, 48.49; H, 3.56; N, 14.14. Found: C, 48.36; H, 3.33; N, 14.14. MS *m/e*: 198 (M^+).

V was synthesized from a mixture of IIIb and IVb, or IVb alone by a similar procedure.

1-(*cis*-3-Hydroxytetrahydro-2-furanyl)-5-fluorouracil (VI)——Compound V (1.98 g, 0.01 mol) was stirred in 1 N NaOH (50 ml) at room temperature for 20 min. This solution was adjusted to pH 5—6 with acetic acid and cooled. The precipitated VI was collected on a filter. Recrystallization from EtOH gave 2.03 g (94.0%) of VI: mp 191—192°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 269 (8300). ^{1}H-NMR (DMSO-d_6) δ: 5.85 (1H, d, d, J=3.7, 1.8 Hz, $C_{2'}$–H), 6.35 (1H, bs, D_2O-exchangeable, $C_{3'}$–OH), 7.63 (1H, d, J=7.0 Hz, C_6–H). *Anal.* Calcd for $C_8H_9FN_2O_4$: C, 44.45; H, 4.20; N, 12.96. Found: C, 44.55; H, 4.35; N, 12.83. MS *m/e*: 216 (M^+).

1-(*cis*-3-Acetoxytetrahydro-2-furanyl)-5-fluorouracil (VII)——Compound VI (1.0 g, 0.00436 mol) in Ac_2O (10 ml) with pyridine (2 drops) was left at room temperature for 12 h. The reaction mixture was concentrated and water (50 ml) was added to the residue. The mixture was extracted with chloroform (100 ml). The chloroform layer was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give 1.0 g (83.7%) of VII: mp 169—171°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 268 (8300). ^{1}H-NMR (DMSO-d_6) δ: 5.94 (1H, d, d, J=4.2, 2.0 Hz, $C_{2'}$–H), 7.74 (1H, d, J=7.0 Hz, C_6–H), 1.89 (3H, s, –$OCOCH_3$). *Anal.* Calcd for $C_{10}H_{11}FN_2O_5$: C, 46.52; H, 4.29; N, 10.85. Found: C, 46.45; H, 4.32; N, 10.82. MS *m/e*: 258 (M^+).

1-(*trans*-3-Acetoxytetrahydro-2-furanyl)-5-fluorouracil (IX)——A mixture of compound V (1.0 g, 0.00505 mol), KF (2.52 g, 0.0434 mol) and acetic acid (3.3 ml) in acetonylacetone (150 ml) was stirred at 190°C for 90 min. The reaction mixture was concentrated and the oily residue was chromatographed on a silica gel column [silica gel 100 g, chloroform–EtOH (4: 1)] to provide IX, which was recrystallized from EtOH. The yield was 0.81 g (62.2%); mp 182—183°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 267 (8600). ^{1}H-NMR (DMSO-d_6) δ: 5.60 (1H, d, J=1.2 Hz, $C_{2'}$–H), 7.79 (1H, d, J=7.0 Hz, C_6–H), 1.98 (3H, s, –$OCOCH_3$). *Anal.* Calcd for $C_{10}H_{11}FN_2O_5$: C, 46.52; H, 4.29; N, 10.85. Found: C, 46.44; H, 4.25; N, 10.82. MS *m/e*: 258 (M^+).

1-(*trans*-3-Hydroxytetrahydro-2-furanyl)-5-fluorouracil (VIII)——Compound IX (1.0 g, 0.00388 mol) was dissolved in NH_3-saturated MeOH (50 ml) and kept at 5°C overnight. The solvent was then evaporated off and the residue was recrystallized from acetone–benzene (1: 1) to give 0.79 g (94.3%) of VIII; mp 210—211°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 269 (8000). ^{1}H-NMR (DMSO-d_6) δ: 5.49 (1H, d, J=1.2 Hz, $C_{2'}$–H), 7.71 (1H, d, J=7.0 Hz, C_6–H), 5.43 (1H, b, D_2O-exchangeable, $C_{3'}$–OH). *Anal.* Calcd for $C_8H_9FN_2O_4$: C, 44.45; H, 4.20; N, 12.96. Found: C, 44.50; H, 4.32; N, 12.84. MS *m/e*: 216 (M^+).

1-(2,5-Dihydro-2-furanyl)-5-fluorouracil (XII)——Compound IIIa (10 g, 0.00426 mol) was dissolved in a solution of *tert*-C_4H_9OK in *tert*-C_4H_9OH, prepared from K (8.0 g, 0.205 mol) in *tert*-C_4H_9OH (400 ml), and the mixture was stirred at room temperature for 4 h. Water (1 l) was then added and the pH was adjusted to 5—6 with 1 N HCl. The solution was extracted with chloroform (1 l). The chloroform layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was recrystallized from MeOH to give 7.0 g (83.0%) of XII: mp 260°C<. UV $\lambda_{max}^{95\%\ EtOH}$ nm: 266.5. ^{1}H-NMR DMSO-d_6) δ: 4.51 (1H, m, $C_{5'}$–H), 4.84 (1H, m, $C_{5'}$–H), 5.80 (1H, m, $C_{3'}$–H), 6.48 (1H, m, $C_{2'}$–H), 6.73 (1H, m, $C_{4'}$–H), 7.47 (1H, d, J=6.6 Hz, C_6–H). *Anal.* Calcd for $C_8H_7FN_2O_3$: C, 48.49; H, 3.56; N, 14.14. Found: C, 48.47; H, 3.58; N, 14.15. MS *m/e*: 198 (M^+).

1-(5-Acetoxytetrahydro-2-furanyl)-5-fluorouracil (XI)——$SnCl_4$ (0.23 ml, 0.002 mol) and 2,5-diacetoxytetrahydrofuran (X, 18.18 g, 0.1 mol) were added to a solution of 2,4-bis(trimethylsilyl)-5-fluorouracil (I, 27.4 g, 0.1 mol) in dichloromethane (200 ml), and the mixture was stirred at room temperature for 4 h. Next, a saturated $NaHCO_3$ solution (50 ml) was added. The mixture was extracted with dichloromethane (200 ml). The dichloromethane layer was dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from acetone–benzene (1: 1) to give 16.8 g (65.1%) of XI: mp 171—172°C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 267 (8200). ^{1}H-NMR (DMSO-d_6) δ: 6.13, 6.40 ($C_{5'}$–H), 7.66, 7.82 (d, J=7.0 Hz, C_6–H), 1.95, 2.00 (s, –$OCOCH_3$). *Anal.* Calcd for $C_{10}H_{11}FN_2O_5$: C, 46.52; H, 4.29; N, 10.85. Found: C, 46.61; H, 4.25; N, 10.80. MS *m/e*: 258 (M^+).

Measurements of ^{1}H-NMR in the Presence of Eu(TFC)$_3$——Calculated amounts of $Eu(TFC)_3$ were added to a solution of 10 mg of *cis*-3′-AcO-FT or *trans*-3′-AcO-FT in 0.3 ml of $CDCl_3$ and the ^{1}H-NMR spectra were measured at 35°C.

Antitumor Activity——Male ICR/JCL mice (Japan Clea Inc., Tokyo) and hybrid BDF_1 mice (Shizuoka Agr. Co-op., Shizuoka) weighing 22—25 g were used. The compounds were dissolved or suspended in 5% acacia solution and administered in a volume of 10 ml/kg. Each group consisted of 10 animals.

For studies on tumor inhibition (Sarcoma 180), 1×10^6 tumor cells were inoculated *s.c.* into the right axilla of ICR/JCL mice on day 0. The compounds were administered orally once a day for 7 consecutive days (days 1 to 7 after tumor implantation). The control group was given 5% acacia solution only in the same way. The percentage inhibition of tumor growth was calculated from the mean tumor weight of the treated group compared with that of the control group on day 10.

For testing survival with L 1210, BDF_1 mice were injected *i.p.* with ascites cells (5×10^5 cells) on day 0 and treated with compounds orally once a day for 7 consecutive days (days 1 to 7). The percentage increase

in life span (ILS %) was calculated from the mean survival period of the treated group compared with that of the control group.

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