5-Fluorouracil Derivatives. XVII.[1] Synthesis and Antitumor Activity of 5′-*O*-Acyl-5-fluorouridines

Shoichiro OZAKI,*,[a] Takahiko AKIYAMA,[a] Yoshimasa IKE,[b] Haruki MORI,[b] and Akio HOSHI[c]

Faculty of Engineering, Ehime University,[a] Bunkyo-cho, Matsuyama 790, Japan, Research Center, Mitsui Toatsu Chemicals,[b] Kasama-cho, Sakae-ku, Yokohama 247, Japan, and National Cancer Center Research Institute,[c] 5-1-1 Tsukiji, Chuo-ku 104, Japan. *Received June 13, 1989*

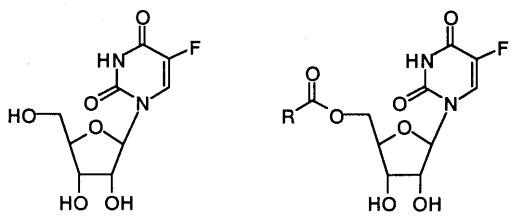
With the aim of diminishing the toxicity of 5-fluorouridine (1) and obtaining biologically active derivatives of 1, various kinds of 5′-*O*-acyl-5-fluorouridines 2 were synthesized. The antitumor activity of the compounds against L-1210 leukemia in mice was examined. The 5′-*O*-heptanoyl derivative 2h showed the highest antitumor activity.

Keywords 5′-*O*-acyl-5-fluorouridine; 5-fluorouracil; antitumor activity; 5-fluorouridine

5-Fluorouridine (FUR) (**1**) was first synthesized by Heidelberger and his co-workers in 1957 as one of the 5-fluorouracil (5-FU) derivatives having antitumor activity.[2] As it showed considerable biological activity and a different metabolic pathway from 5-FU, clinical utility was expected.[3] The antitumor activity of **1** in a preclinical study was excellent,[4] and **1** was superior to 5-FU and 5-fluoro-2′-deoxyuridine (FUDR), particularly in mice with methotrexate-resistant leukemia.[3] However, FUR showed leukopenia and thrombopenia with slight gastrointestinal toxicity as side effects. On account of these side effects, FUR is not in clinical use. Thus, FUR derivatives with excellent antitumor activity and low toxicity were sought, and a modified FUR derivative, 5′-*O*-(L-valyl)-5-fluorouridines, has been reported.[5]

In our laboratory, with the aim of finding antitumor agents with high antitumor activity and low toxicity, we have synthesized various kinds of 5-FU derivatives, such as 1-carbamoyl-,[6] 1-acyloxyalkyl-,[7] and 1-alkylthiocarbamoyl-5-fluorouracils.[8]

This time we prepared 5′-*O*-acyl derivatives of 5-fluorouridine **2** as masked 5-FU compounds with the expectation of improving the pharmacological properties.[9] Twelve kinds of aliphatic acyl groups with carbon numbers of 1—27 were introduced at the 5′-*O*-position of FUR (Chart 1, **2a**—**l**). They showed high antitumor activity compared to FUR itself. This paper describes the synthesis of 5′-*O*-acyl-5-fluorouridines and the intraperitoneal antitumor activity



FUR **1** **2a**—**l**

a: R=H, **b**: R=CH_3, **c**: R=C_3H_7,
d: R=iso-C_3H_7, **e**: R=C_4H_9, **f**: R=*tert*-C_4H_9,
g: R=C_5H_{11}, **h**: R=C_7H_{15}, **i**: R=C_9H_{19},
j: R=$C_{13}H_{27}$, **k**: R=$C_{15}H_{31}$, **l**: R=$C_{17}H_{35}$

Chart 1

TABLE I. 2′,3′-*O*-Isopropylidene-5′-*O*-acyl-5-fluorouridines **4**

Run	Comp. No.	R	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Found (Calcd) C	H	F	N	^{1}H-NMR (DMSO-d_6)
1	**4d**	iso-C_3H_7	79	143—145	$C_{16}H_{21}FN_2O_7$	51.50 (51.61)	5.93 (5.68)	5.18 (5.10)	7.48 (7.52)	1.15 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.35 (3H, d, J=7 Hz, $(CH_3)_2$), 1.59 (3H, d, J=7 Hz, $(CH_3)_2$), 2.60 (1H, m, $(CH_3)_2$H), 4.35 (3H, m, H2′,3′,4′), 4.8 (2H, m, H5′), 5.75 (1H, m, H1′), 7.50 (1H, d, J=7 Hz, H6), 9.70 (1H, br s, NH)
2	**4e**	C_4H_9	75	102—103	$C_{17}H_{23}FN_2O_7$	52.58 (52.85)	5.71 (6.00)	4.72 (4.72)	6.90 (6.90)	0.94 (3H, t, J=7 Hz, CH_3), 1.2—1.8 (4H, m, $(CH_2)_2$), 1.49 (3H, s, CH_3), 1.60 (3H, s, CH_3), 2.37 (2H, t, J=6 Hz, CH_2CO), 4.3—4.4 (3H, m, H2′,3′,4′), 4.8 (2H, m, m, H5′), 5.76 (1H, m, H1′), 7.48 (1H, J=7 Hz, H6), 10.0 (1H, br s, NH)
3	**4f**	*tert*-C_4H_9	40	Oil	$C_{17}H_{23}FN_2O_7$	52.65 (52.85)	6.12 (6.00)	4.92 (4.72)	6.85 (6.90)	1.22 (9H, s, $(CH_3)_3$), 1.35 (3H, s, CH_3), 1.68 (3H, s, CH_3), 4.3—4.4 (3H, m, H2′,3′,4′), 4.8 (2H, m, H5′), 5.75 (1H, m, H1′), 7.45 (1H, d, J=7 Hz), 9.5 (1H, br s, NH)
4	**4h**	C_7H_{15}	79	Oil	$C_{20}H_{29}FN_2O_7$	56.25 (56.06)	6.75 (6.82)	4.35 (4.43)	6.41 (6.54)	0.88 (3H, t, J=7 Hz, CH_3), 1.1—1.8 (10H, m, $(CH_2)_5$), 1.35 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.1—2.5 (2H, m, CH_2CO), 4.3—4.4 (3H, m, H2′,3′,4′), 4.8 (2H, m, H5′), 5.75 (1H, d, J=3 Hz, H1′), 7.46 (1H, d, J=7 Hz), 9.5 (1H, br s, NH)
5	**4i**	C_9H_{19}	48	84—86	$C_{22}H_{33}FN_2O_7$	58.00 (57.88)	7.12 (7.29)	4.09 (4.16)	5.94 (6.14)	0.88 (3H, t, J=7 Hz, CH_3), 1.0—1.8 (14H, m, $(CH_2)_7$), 1.38 (3H, s, CH_3), 1.59 (3H, s, CH_3), 2.3 (2H, m, CH_2CO), 4.32 (3H, m, H2′,3′,4′), 4.8 (2H, m, H5′), 5.75 (1H, m, H1′), 7.45 (1H, d, J=7 Hz), 9.8 (1H, br s, NH)

a) Recrystallized from 2-propanol.

TABLE II. 5′-*O*-Acyl-5-fluorouridines **2**

Run	Comp. No.	Synthetic method	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Found (Calcd) C	H	F	N	^{1}H-NMR (DMSO-d_6)
1	**2a**	C	60	Oil	$C_{10}H_{11}FN_2O_7$	41.42 (41.39)	3.88 (3.82)	6.71 (6.55)	9.35 (9.65)	4.32 (2H, s, H5′), 2.8—3.0 (2H, br s, OH), 4.35—4.8 (3H, m, H2′,3′,4′), 5.8—6.0 (1H, m, H1′), 7.90 (1H, d, J=7 Hz, H6), 8.30 (1H, s, CHO), 11.7 (1H, br s, NH)
2	**2b**	A	30	160	$C_{11}H_{13}FN_2O_7$	43.72 (43.42)	4.61 (4.31)	5.90 (6.25)	8.89 (9.20)	2.1 (3H, s, CH_3), 2.9—3.0 (2H, br s, OH), 3.6—3.8 (3H, m, H2′,3′,4′), 4.2 (2H, m, H5′), 5.7 (1H, m, H1′), 7.8 (1H, d, J=7 Hz, H6), 11.8 (1H, br s, NH)
3	**2c**	A	52	116—118	$C_{13}H_{17}FN_2O_7$	46.56 (46.99)	5.27 (5.16)	5.97 (5.71)	8.43 (8.43)	0.92 (3H, t, J=7 Hz, CH_3), 1.64 (2H, m, $CH_3C\underline{H}_2$–), 2.38 (2H, m, $COCH_2$), 3.0—3.1 (2H, br s, OH), 4.0—5.0 (5H, m, H2′,3′,4′), 5.82 (1H, m, H1′), 7.83 (1H, d, J=7 Hz, H6), 10.45 (1H, br s, NH)
4	**2d**	B	67	117—118	$C_{13}H_{17}FN_2O_7$	46.70 (46.99)	5.01 (5.16)	5.98 (5.71)	8.71 (8.43)	1.10 (3H, d, J=7 Hz, CH_3), 1.22 (3H, d, J=7 Hz, CH_3) 2.5 (1H, m, CH), 2.9—3.0 (2H, br s, OH), 4.0 (3H, m, H2′,3′,4′), 4.23 (2H, m, H5′), 5.7 (1H, m, H1′), 8.22 (1H, d, J=7 Hz, H6), 11.8 (1H, br s, NH)
5	**2e**	A	54	110—113	$C_{14}H_{19}FN_2O_7$	48.72 (48.56)	5.85 (5.53)	5.78 (5.49)	8.36 (8.09)	0.89 (3H, t, J=7 Hz, CH_3), 1.1—1.8 (4H, m, $(CH_2)_2$), 2.3—2.4 (2H, m, $COCH_2$), 2.9—3.0 (2H, br s, OH), 4.0 (3H, m, H2′,3′,4′), 4.2 (2H, m, H5′), 5.7 (1H, m, H1′), 7.88 (1H, d, J=7 Hz, H6), 11.75 (1H, br s, NH)
6	**2f**	A	75	129—131	$C_{14}H_{19}FN_2O_7$	48.37 (48.56)	5.44 (5.53)	5.19 (5.49)	8.23 (8.09)	1.18 (9H, s, $(CH_3)_3$, 2.8—2.9 (2H, br s, OH), 3.9—4.0 (3H, m, H2′,3′,4′), 4.20 (2H, s, H5′), 5.6—5.8 (1H, m, H1′), 7.80 (1H, d, J=7 Hz, H6), 11.75 (1H, br s, NH)
7	***2g***	A	65	113—114	$C_{15}H_{21}FN_2O_7$	49.90 (50.00)	5.96 (5.87)	5.03 (5.27)	7.76 (7.77)	0.86 (3H, t, J=7 Hz, CH_3), 1.3—1.4 (6H, m, $(CH_2)_3$), 2.3—2.4 (2H, m, CH_2CO), 2.9—3.0 (2H, br s, OH), 3.7—3.9 (3H, m, H2′,3′,4′), 4.2 (2H, m, H5′), 5.75 (1H, m, H1′), 7.90 (1H, d, J=7 Hz, H6), 11.80 (1H, br s, NH)
8	**2h**	A	31	111—113	$C_{17}H_{25}FN_2O_7$	52.87 (52.57)	6.19 (6.49)	5.16 (4.89)	7.49 (7.21)	0.88 (3H, t, J=7 Hz, CH_3), 1.2—1.3 (10H, m, $(CH_2)_5$), 2.22 (2H, t, J=7 Hz, CH_2CO), 2.9—3.0 (2H, br s, OH), 3.9—4.0 (3H, m, H2′,3′,4′), 4.2 (2H, m, H5′), 5.72 (1H, m, H1′), 7.89 (1H, d, J=7 Hz, H6), 11.85 (1H, br s, NH)
9	**2i**	A	49	119—120	$C_{19}H_{29}FN_2O_7$	54.53 (54.80)	6.78 (7.02)	4.33 (4.56)	7.01 (6.73)	0.85 (3H, t, J=7 Hz, CH_3), 1.2—1.6 (14H, m, $(CH_2)_7$), 2.1—2.2 (2H, m, CH_2CO), 2.8—3.0 (2H, br s, OH), 3.7—3.9 (3H, m, H2′,3′,4′), 4.2 (2H, m, H5′), 5.80 (1H, m, H1′), 7.35 (1H, d, J=7 Hz, H6), 10.80 (1H, br s, NH)
10	**2j**	B	49	83—85	$C_{23}H_{37}FN_2O_7$	58.16 (58.46)	8.21 (7.89)	3.63 (4.02)	5.77 (5.93)	0.90 (3H, t, J=7 Hz, CH_3), 1.2—1.3 (22H, m, $(CH_2)_{11}$), 2.3—2.4 (2H, m, CH_2CO), 2.9—3.0 (2H, br s, OH), 3.6—4.2 (3H, m, H2′,3′,4′), 4.8 (2H, m, H5′), 5.75 (1H, m, H1′), 7.4 (1H, d, J=7 Hz, H6), 12.05 (1H, br s NH)
11	**2k**	B	26	165—166	$C_{25}H_{41}FN_2O_7$	59.77 (59.98)	8.46 (8.25)	3.59 (3.80)	5.66 (5.60)	0.85 (3H, t, J=7 Hz, CH_3), 1.2—1.3 (26H, m, $(CH_2)_{13}$), 2.36 (2H, m, CH_2CO), 3.0—3.1 (2H, br s, OH), 3.62 (3H, m, H2′,3′,4′), 4.1 (2H, m, H5′), 5.9 (1H, m, H1′), 7.3 (1H, d, J=7 Hz, H6), 10.8 (1H, br s, NH)
12	**21**	A	52	120—122	$C_{27}H_{45}FN_2O_7$	61.04 (61.34)	8.88 (8.58)	3.29 (3.59)	5.32 (5.30)	0.8—1.0 (3H, m, CH_3), 1.25—1.3 (30H, m, $(CH_2)_{15}$), 2.2—2.5 (2H, m, CH_2CO), 2.9—3.0 (2H, br s, OH), 3.95 (3H, m, H2′, 3′,4′), 4.20 (2H, m, H5′), 5.70 (1H, m, H1′), 7.90 (1H, d, J=7 Hz, H6), 11.80 (1H, br s, NH)

a) Recrystallized from 2-propanol.

of these compounds against leukemia 1210 in mice.

Various kinds of acyl groups were introduced into the 5′-*O*-position of FUR according to one of the following methods.

Method A FUR (**1**) was treated with *p*-toluenesulfonic acid and 2,2-dimethoxypropane in acetone at room temperature overnight to afford 2′,3′-*O*-isopropylidene-5-fluorouridine[10] (**3**) in good yield, followed by treatment with acyl chloride in pyridine at room temperature to afford 5′-*O*-acyl-2′,3′-*O*-isopropylidene-5-fluorouridine (**4**) as shown in Table I. The isopropylidene moiety was removed by hydrolysis with aqueous acetic acid at 120 °C for 2 h for the preparation of **2b**, **c**, **f**, **g**, **l** or with aqueous trifluoroacetic acid at room temperature for **2e**, **h**, **i**.

Method B Direct acylation of **1** by the use of acyl chloride in pyridine gave the 5′-*O*-monoacylated compound **2** as a major product. The 2′,5′- or 3′,5′-bis-*O*-acylated product (**5**) was obtained as a by-product. The position of the acylation has not been clarified.

5′-*O*-Formyl-5-fluorouridine (**2a**) was prepared by method C.

Method C Compound **1** was allowed to react with formic acid, sodium formate and sulfuric acid to obtain 5′-*O*-formyl-5-fluorouridine (**2a**).

The structures of the 5′-*O*-acyl-5-fluorouridines (**2**) were confirmed by elemental analysis, nuclear magnetic resonance (NMR), and infrared (IR) spectral analyses.

The antitumor activity of these compounds **2** was tested against L-1210 leukemia by intraperitoneal administration in mice, and the *ILS* (increase in life span) value and *TR*

TABLE III. Antitumor Activity of 5′-*O*-Acyl-5-fluorouridines **2**

Compound	R	*ILS*[a] Dose (mg/kg/d) 0.1	0.3	1	3	10	30	ILS_{30}[a]	ILS_{max}[a]	*TR*[a]
2a	H			29	59	69	29	1	10	10
2b	CH_3				29	59	14	3	10	3.3
2c	C_3H_7		22	42	60	60	−16	0.5	10	20
2d	iso-C_3H_7			19	42	93	0	1.7	10	5.9
2e	C_4H_9	13	30	38	63	103	10	0.3	10	33
2f	*tert*-C_4H_9		14	38	56	65	18	0.7	10	14
2g	C_5H_{11}	6	35	54	96	81	−22	0.25	3	12
2h	C_7H_{15}		35	50	63	96	21	0.2	10	50
2i	C_9H_{19}		8	52	57	81	18	0.74	10	13
2j	$C_{13}H_{27}$		13	33	66	73	35	0.85	10	12
2k	$C_{15}H_{31}$		11	34	50	65	21	0.8	10	12
2l	$C_{17}H_{35}$			27	44	65	81	2.4	30	12
5-FU					38	73	60	2.3	10	4
FUR			46	62	91	33		0.1	3	30

a) See Experimental.

(therapeutic ratio) value are shown in Table III. The compounds showed moderate to good *ILS* values, and high *TR* values. The pentanoyl (**2e**) and octanoyl (**2h**) derivatives showed higher antitumor activity than FUR. The *TR* values of **2e** and **2h** were 33 and 50, respectively, which were superior to that of FUR. Although no correlation between carbon number of the acyl group and antitumor activity was observed in this screening system, it is noteworthy that masked FUR derivatives with high antitumor activity were synthesized. As they are more lipophilic than FUR itself, different pharmacological properties are expected. Further biological tests are in progress in our laboratories.

Experimental

The melting points were recorded on a Büchi melting-point apparatus. The ^{1}H-NMR spectra were recorded in $CDCl_3$ or dimethyl sulfoxide-d_6 (DMSO-d_6) on JEOL 60HL and JEOL JNM-FX 100S apparatus with tetramethylsilane as an internal standard. The IR spectra were obtained on a JASCO IR-A-1 apparatus.

General Procedure of Method A; 5′-*O*-Pentanoyl-2′,3′-*O*-isopropylidene-5-fluorouridine (4e) Pentanoyl chloride (2.4 g, 0.02 mol) was added to a solution of 2′,3′-*O*-isopropylidene-5-fluorouridine (**3**) (5.0 g, 16.5 mmol) in pyridine (20 ml) at room temperature and the mixture was stirred for 1.5 h. After evacuation of pyridine *in vacuo*, CH_2Cl_2 (250 ml) was added to the mixture. The organic layer was washed successively with 1 M aqueous HCl and water, dried over anhydrous $MgSO_4$, and concentrated to give an oil, which was subjected to column chromatography (SiO_2, CH_2Cl_2–MeOH, 100:2) to afford **4e** (4.8 g, 75%) as crystals.

a) Deprotection by Use of Trifluoroacetic Acid; 5′-*O*-Pentanoyl-5-fluorouridine (2e) An ethanol (5 ml) solution of **4e** (4.5 g, 11.6 mmol) was added to a mixture of H_2O (20 ml) and trifluoroacetic acid (10 ml) at room temperature. The mixture was stirred at that temperature for 2.5 h, then concentrated to leave an oil, which was dissolved in CH_2Cl_2 (300 ml). The solution was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated to leave an oil. The residue was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 100:3—100:8) to afford **2e** as colorless crystals (54%).

b) Deprotection by Use of Acetic Acid; 5′-*O*-Pivaloyl-5-fluorouridine (2f) A solution of **4f** (2.5 g, 0.006 mol) in AcOH (8 ml) and H_2O (30 ml) was heated at 120 °C for 2 h, and concentrated *in vacuo* to give an oil, which was purified by SiO_2 (CH_2Cl_2–MeOH, 100:3) to afford **2f** as colorless crystals (1.67 g, 75%).

General Procedure of Method B; 5′-*O*-Tetradecanoyl-5-fluorouridine (2j) Tetradecanoyl chloride (5.4 g, 22 mmol) was added to a solution of FUR (4.0 g, 0.015 mol) in pyridine (20 ml) at room temperature, and the mixture was stirred overnight. After addition of ice water, the mixture was stirred for an additional 0.5 h, and concentrated. The residue was dissolved in CH_2Cl_2 (300 ml) and washed with 1 M aqueous HCl solution. The organic layer was concentrated *in vacuo* to leave an oil, which was purified by column chromatography (SiO_2, CH_2Cl_2). Compound **2j** was obtained as colorless crystals (3.5 g, 49%).

2′,5′- or 3′,5′-*O*-Bis-tetradecanoyl-5-fluorouridine (**5j**) was also obtained as colorless crystals (0.3 g, 2.7%); mp 83—85 °C (recrystallized from 2-propanol). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H×2, t, J=4.5 Hz, CH_3), 1.26 (44H, m, $(CH_2)_{11}$×2), 2.32 (2H×2, t, J=7.5 Hz, CH_2CO), 2.6 (1H, br s, OH), 3.88 (3H, br s, 2′,3′,4′-CH), 4.20 (2H, br s, 5′-CH_2), 5.85 (1H, br s, 1′-CH), 8.05 (1H, d, J=6 Hz, 6-CH), 10.40 (1H, br s, NH). IR (KBr): 3450, 3200, 3100, 2950, 2850, 1740, 1680, 1480, 1420, 1270, 1195, 1120, 1100 cm^{-1}. *Anal.* Calcd for $C_{37}H_{63}FN_2O_8$: C, 65.07; H, 9.30; F, 2.78; N, 4.10. Found: C, 64.28; H, 9.07; F, 2.84; N, 5.19.

Compounds **5d** and **5k** were obtained by a method similar to that described above as minor products.

5d: (27% yield) amorphous. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (6H, d, J=6 Hz, $(CH_3)_2C$), 1.28 (6H, d, J=6 Hz, $(CH_3)_2C$), 2.3—2.9 (3H, m, OH and CH), 4.38 (3H, br s, 2′,3′,4′-CH), 4.8—5.6 (2H, m, 5′-CH_2), 5.90 (1H, br s, 1′-CH), 7.70 (1H, d, J=6 Hz, 6-CH), 10.10 (1H, br s, NH). IR (neat): 3450, 3210, 3100, 3000, 1740, 1720, 1680, 1480, 1400, 1270, 1200, 1160, 1120 cm^{-1}.

5k: (12% yield) mp 103 °C (ethanol). ^{1}H-NMR (acetone-d_6) δ: 0.87 (6H, t, J=5 Hz, (CH_3)×2), 1.30 (52H, m, CH_2), 2.39 (4H, m, $COCH_2$), 2.8 (1H, br s, OH), 4.3—4.6 (3H, m, CH), 5.1—5.5 (2H, m, 5′-CH_2), 5.90 (1H, m, 1′-CH), 7.58 (1H, d, J=6 Hz, C_6-H), 10.10 (1H, br s, NH). *Anal.* Calcd for $C_{41}H_{71}FN_2O_8$: C, 66.36; H, 9.55; F, 2.57; N, 3.27. Found: C, 66.63; H, 9.68; F, 2.21; N, 3.29.

5′-Formyl-5-fluorouridine (2a) (Method C) Sodium formate (3.5 g) and concentrated H_2SO_4 (2.0 g) were added successively to a solution of FUR (1.31 g, 5 mmol) in formic acid (15 ml) at 0 °C. After stirring at room temperature overnight, MeOH (100 ml) was added. The precipitate thus formed was filtered off and the filtrate was concentrated in a rotary evaporator to give an oil, which was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 100:5). Compound **5a** was obtained as a hygroscopic solid (0.87 g, 60%). IR (KBr): 3420, 1720, 1270, 1120 cm^{-1}.

Animals and Tumor System Male BDF_1 mice weighing 20±2 g were used. Six mice in each group, either test or control, were implanted intraperitoneally with 1×10^5 L-1210 leukemia cells. The compound to be tested was injected intraperitoneally once daily for 5 d, starting 24 h after tumor implantation.

Evaluation of Antitumor Activity The *ILS* and the therapeutic index were calculated by using the following formulae:

$$ILS\ (\%) = (T-C)/C \times 100$$

where T is the average number of days before death in the test group and C is the average number of days before death in the control group.[11]

$$TR = ILS_{max}/ILS_{30}$$

ILS_{max} = dose amount which shows highest *ILS*

ILS_{30} = dose amount which shows 30% *ILS*

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