5-Fluorouracil Derivatives. XXII.[1] Synthesis and Antitumor Activities of 1-Carbamoyl-5-fluorouracils

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Fifty-four 1-carbamoyl-5-fluorouracils were synthesized from 5-fluorouracil and isocyanate or amine. Antitumor activity was tested in the L-1210 tumor system, and 11 compounds gave better values of therapeutic ratio than HCFU (1-hexylcarbamoyl-5-fluorouracil). 1-(4-Methoxycyclohexylcarbamoyl)-5-fluorouracil gave the best result.

Key words 1-carbamoyl-5-fluorouracil; 5-fluorouracil; 1-(4-methoxycyclohexyl)-5-fluorouracil; 1-(3-methylcyclohexyl)-5-fluorouracil; antitumor agent

5-Fluorouracil (**1**, 5-FU) is an effective antitumor agent,[2,3] but it has a strong toxicity and poor tumor affinity. Chemical modification of **1** by introducing lipophilic substituents has therefore been tried. Syntheses of tetrahydrofuryl,[4] alkyl,[5] 2,3-dihydroxypropyl,[6] sulfonyl,[7] carbamoyl,[8] acetoxymethyl,[9] alkoxymethyl,[10] alkylthiocarbonyl,[11] alkylthiomethyl[12]-5-fluorouracils have been reported and a review article[13] has appeared. 1-Carbamoyl-5-fluorouracils are the best derivatives for oral administration, because they are stable to acid in the stomach and decompose gradually in the tissues. Among the carbamoyl compounds, 1-hexylcarbamoyl-5-fluorouracil (HCFU) was the most effective[14]; it has been in clinical use[15] in Japan since 1981, and has recently been approved in Korea and Finland. This compound has a therapeutic ratio (TR) of 4.5 in the L-1210 leukemia system. We are trying to find compounds having higher TR, and have synthesized many 1-carbamoyl-5-fluorouracils. Eleven compounds had TR values higher than 4.5, and 1-(4-methoxycyclohexylcarbamoyl)-5-fluorouracil (**22**) had a TR of 17.6.

1-Carbamoyl-5-fluorouracil (**2**) can be obtained by two different methods.[8] Method A. The reaction of **1** with isocyanates is carried out in pyridine by heating at 90 °C for 2 h. Isocyanates can be obtained commercially or derived from amines and phosgene[16] or carboxylic acids and diphenylphosphoryl azide,[17] while alicyclic amines can be obtained commercially or by catalytic reduction of aromatic amines with hydrogen over ruthenium oxide.[18] Method B. The reaction of **1** with phosgene at low temperature gives 1-chloroformyl-5-fluorouracil (**3**), which is treated with alicyclic amines in pyridine at lower temperature to afford **2**.

The antitumor activity of the synthesized compounds was tested against L-1210 leukemia by oral administration in male BDF_1 mice, and the ILS (increase in life span) value, ILS_{30} (dose giving 30% ILS, mg/kg/d), ILS_{max} (dose giving the highest ILS, mg/kg/d) and TR were obtained. The synthesis and the antitumor activity of these compounds are shown in Table 1.

1-*n*-Hexylcarbamoyl-5-FU HCFU (ILS_{30} 44, ILS_{max} 200, TR 4.5)[14b] was the best compound among *n*-alkylcarbamoyl-5-FU, and 1-cyclohexylcarbamoyl-5-FU has similar antitumor activities (ILS_{30} 60, ILS_{max} 200, TR 3.3).[14b] In both cases, toxicity appeared at the dose level of 300 mg/kg/d, and ILS_{max} was 200 mg/kg/d. When a methyl group was introduced on the cyclohexyl group, toxicity decreased to give ILS_{max} 300. 1-(3-Methylcyclohexylcarbamoyl)-5-FU (**7**) showed strong antitumor activity (ILS_{30} 20) and low toxicity (ILS_{max} 300) and as a result, the TR was as high as 15. When a butyl group (**8**) was introduced, the activity decreased. Two methyl groups at the 2,3-(**9**, TR 6.0), 2,6-(**12**, TR 10.0) and 3,5-(**14**, TR 6.9) positions, afforded compounds with high TR, but two or three methyl groups at other positions, 2,4-(**10**), 2,5-(**11**), 3,4-(**13**), 2,4,6-(**15**), 3,3,5-(**16**), gave similar results to that obtained with the unsubstituted compound. Cyclopentyl and cyclohexenyl carbamoyl-5-FU gave similar results. When a methoxy group was introduced at the 4-position of the cyclohexyl group, the highest TR compound (**22**, ILS_{30} 17, ILS_{max} 300, TR 17.6) was obtained. 4-Methoxybenzyl carbamoyl)-5-FU (**57**) also gave a high TR of 11.5. Introduction of two or three methoxy groups on the cyclohexyl group reduced the effectiveness (**24**—**31**). Cyclohexylmethyl-(**32**), 1-cyclohexylethyl-(**33**), and 1-cyclohexylpropyl (**34**) carbamoyl-5-FU showed moderate activities. Introduction of one methyl group at the

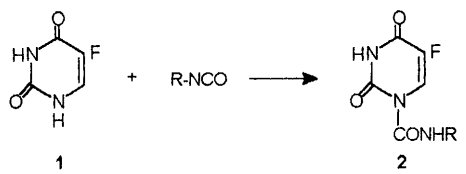

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Chart 1

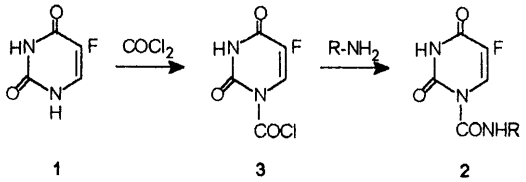

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Chart 1

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Table 1. Synthesis and Antitumor Activity of Carbamoyl-5-fluorouracils

Compd. No.	R	Method	Yield (%)	mp (°C)	Formula	Analysis (%) Found (Calcd)			ILS (%) Dose (mg/kg/d)				ILS_{30} (mg/kg/d)	ILS_{max} (mg/kg/d)	TR
						C	H	N	10	30	100	300			
4	4-*trans*-Methylcyclohexyl	A	31	128—129	$C_{12}H_{16}FN_3O_3$	53.48 (53.52	5.75 5.99	15.67 15.61)		20	35	46	60	300	3.3
5	4-*cis*-Methylcyclohexyl	A	25	127	$C_{12}H_{16}FN_3O_3$	53.39 (53.52	5.76 5.99	15.48 15.61)			0	43	150	300	2.0
6	2-Methylcyclohexyl	A	55	138—140	$C_{12}H_{16}FN_3O_3$	53.39 (53.52	6.12 5.99	15.68 15.61)		16	38		59	10	1.9
7	3-Methylcyclohexyl	B	52	129	$C_{12}H_{16}FN_3O_3$	53.65 (53.52	6.05 5.99	15.83 15.61)	24	38	39	40	20	300	15
8	4-Butylcyclohexyl	A	33	129—130	$C_{15}H_{22}FN_3O_3$	58.02 (57.86	7.07 7.12	13.39 13.50)		10	25	43	115	300	2.6
9	2,3-Dimethylcyclohexyl	A	63	163—164	$C_{13}H_{18}FN_3O_3$	55.15 (55.11	6.55 6.40	14.97 14.84)	13	39	41	41	50	300	6.0
10	2,4-Dimethylcyclohexyl	A	72	130—131	$C_{13}H_{18}FN_3O_3$	55.32 (55.11	6.35 6.40	14.69 14.84)			6	69	150	300	2.0
11	2,5-Dimethylcyclohexyl	A	55	154—155	$C_{13}H_{18}FN_3O_3$	55.15 (55.11	6.52 6.40	14.77 14.84)		19	48	50	150	300	2.6
12	2,6-Dimethylcyclohexyl	A	36	130	$C_{13}H_{18}FN_3O_3$	55.33 (55.11	6.55 6.40	14.98 14.84)		29	45	51	30	300	10
13	3,4-Dimethylcyclohexyl	A	55	127—128	$C_{13}H_{18}FN_3O_3$	55.08 (55.11	6.55 6.40	14.98 14.84)		29	65	37	30	100	3.3
14	3,5-Dimethylcyclohexyl	A	57	154	$C_{13}H_{18}FN_3O_3$	54.98 (55.11	6.32 6.40	14.90 14.84)		25	39	49	45	300	6.7
15	2,4,6-Trimethyl cyclohexyl	B	19	148	$C_{14}H_{20}FN_3O_3$	56.39 (56.55	6.59 6.78	14.10 14.14)		17	36	54	68	300	4.4
16	3,3,5-Trimethyl cyclohexyl	B	36	153	$C_{14}H_{20}FN_3O_3$	56.50 (56.55	6.78 6.78	14.19 14.14)		23	41	35	50	100	2.0
17	Cyclopentyl	A	58	136—138	$C_{10}H_{12}FN_3O_3$	49.77 (49.79	5.21 5.01	17.55 17.42)		13	44	25	55	100	1.8
18	2-Methyl-5-isopropylcyclohexyl	A	66	93—96	$C_{16}H_{22}FN_3O_3$	57.59 (57.86	7.02 7.12	13.35 13.50)		0	20				
19	3-Cyclohexenyl	A	15	140—141	$C_{11}H_{12}FN_3O_3$	52.65 (52.77	4.68 4.78	16.48 16.60)		4	21	65	115	300	2.6
20	2-Methoxycyclohexyl	A	19.5	163—165	$C_{13}H_{16}FN_3O_4$	50.20 (50.53	5.78 5.65	14.65 14.73)			25				
21	3-Methoxycyclohexyl	B	51	138—140	$C_{12}H_{16}FN_3O_4$	50.46 (50.53	5.72 5.65	14.78 14.73)			27				
22	4-Methoxycyclohexyl	B	78	151—152	$C_{12}H_{16}FN_3O_4$	50.50 (50.53	5.84 5.65	14.62 14.73)	18	44	50	66	17	300	17.6
23	4-Ethoxycyclohexyl	A	31	132—133	$C_{13}H_{18}FN_3O_4$	52.40 (52.16	6.12 6.06	14.19 14.04)		13	48	48	50	300	6.0
24	2,3-Dimethoxy cyclohexyl	A	39	164	$C_{13}H_{18}FN_3O_5$	49.35 (49.52	5.55 5.75	13.01 13.32)		9	30	17	100	100	1.0
25	2,4-Dimethoxy cyclohexyl	B	35	123	$C_{13}H_{18}FN_3O_5$	49.45 (49.52	5.45 5.75	13.13 13.32)		3	35	50	107	300	2.8
26	2,5-Dimethoxy cyclohexyl	B	28	171	$C_{13}H_{18}FN_3O_5$	49.35 (49.52	5.62 5.75	13.46 13.32)		−1	31	11	100	100	1.0
27	3,4-Dimethoxy cyclohexyl	B	19	166	$C_{13}H_{18}FN_3O_5$	49.71 (49.52	5.55 5.75	13.11 13.32)		9	39	14	45	100	2.2
28	2-Methoxy-4 methylcyclohexyl	A	38	163	$C_{13}H_{18}FN_3O_4$	52.36 (52.16	6.16 6.06	14.12 14.04)		29	41	38	36	100	3.3
29	2,3,4-Trimethoxy cyclohexyl	A	48	140	$C_{14}H_{20}FN_3O_6$	48.75 (48.69	5.96 5.90	12.27 12.17)			8	33	270	300	1.1
30	2,4,5-Trimethoxy cyclohexyl	A	18	150—152	$C_{14}H_{20}FN_3O_6$	48.55 (48.69	5.16 5.90	12.10 12.17)			21				
31	3,4,5-Trimethoxy cyclohexyl	A	22	149—151	$C_{14}H_{20}FN_3O_6$	48.39 (48.69	5.88 5.90	12.15 12.17)		13	25	40	136	300	2.2
32	Cyclohexylmethyl	A	71	171—172	$C_{12}H_{16}FN_3O_3$	53.29 (53.52	5.12 5.99	15.81 15.61)			17	41	187	300	1.6
33	1-Cyclohexylethyl	A	55	118—119	$C_{13}H_{18}FN_3O_3$	55.01 (55.11	6.28 6.40	14.65 14.84)		6	46	18	45	100	2.2
34	1-Cyclohexylpropyl	B	31	117—118	$C_{14}H_{20}FN_3O_3$	56.35 (56.35	6.72 6.78	14.06 14.14)		6	23	48	120	300	2.5
35	4-Methyl cyclohexylmethyl	A	62	156	$C_{13}H_{18}FN_3O_3$	55.39 (55.11	6.65 6.40	14.87 14.84)	13	36	44	23	17.8	100	5.6
36	2,4-Dimethyl cyclohexylmethyl	A	66	155	$C_{14}H_{20}FN_3O_3$	56.32 (56.55	6.60 6.78	14.35 14.11)		4	28	54	115	300	2.6

Table 1. (continued)

Compd. No.	R	Method	Yield (%)	mp (°C)	Formula	Analysis (%) Found (Calcd) C	H	N	ILS (%) Dose (mg/kg/d) 10	30	100	300	ILS_{30} (mg/kg/d)	ILS_{max} (mg/kg/d)	TR
37	2-Methoxy cyclohexylmethyl	A	42	144	$C_{13}H_{18}FN_3O_4$	52.40 (52.16)	6.16 (6.06)	14.12 (14.12)		3					
38	3-Methoxy cyclohexylmethyl	A	36	109	$C_{13}H_{18}FN_3O_4$	52.01 (00.00)	6.09 (0.00)	14.04 (00.00)			9				
39	4-Methoxy cyclohexylmethyl	A	52	137	$C_{13}H_{18}FN_3O_4$	51.96 (52.16)	5.95 (6.06)	13.87 (14.04)			28	35	250	300	1.2
40	4-*cis*-Ethoxy cyclohexylmethyl	A	30	115	$C_{14}H_{20}FN_3O$	53.46 (53.46)	6.25 (6.43)	13.29 (13.41)		8	33	43	85	300	3.5
41	4-*trans*-Ethoxy cyclohexylmethyl	A	25	138	$C_{14}H_{20}FN_3O_6$	53.50 (53.66)	6.37 (6.43)	13.46 (13.41)		10	48		64	100	1.6
42	2,3-Dimethoxy cyclohexylmethyl	A	8	100	$C_{14}H_{20}FN_3O_5$	52.06 (51.01)	6.19 (6.12)	12.86 (12.76)		16	36	11	30	170	1.0
43	2,4-Dimethoxy cyclohexylmethyl	B	12	132	$C_{14}H_{20}FN_3O_5$	51.20 (51.0)	6.12 (6.12)	12.76 (12.76)		0	55	13	50	100	2.0
44	2,5-Dimethoxy cyclohexylmethyl	A	27	127	$C_{14}H_{20}FN_3O_5$	50.98 (51.01)	6.08 (6.12)	12.55 (12.76)		−3	37		83	100	1.2
45	3,4-Dimethoxy cyclohexylmethyl	A	56	102	$C_{14}H_{20}FN_3O_3$	50.95 (51.01)	6.07 (6.12)	12.55 (12.76)		6	29	45	100	300	3.3
46	4-Ethoxy-3-methoxy cyclohexylmethyl	A	60	41	$C_{15}H_{22}FN_3O_5$	52.36 (52.47)	3.29 (3.52)	12.20 (12.24)			0	14			
47	3,4,5-Trimethoxy cyclohexylmethyl	A	49	275	$C_{15}H_{22}FN_3O_6$	50.38 (51.41)	6.15 (6.21)	11.85 (11.76)			10	48	22	100	4.5
48	4-Ethoxycarbonyl cyclohexylmethyl	A	30	273	$C_{15}H_{20}FN_3O_5$	52.58 (52.78)	5.88 (5.91)	12.40 (12.31)			22	50	136	300	2.4
49	Cyclohexylethyl	A	74	139	$C_{13}H_{18}FN_3O_3$	55.19 (55.11)	6.60 (6.40)	14.90 (14.84)		6	30		100	100	1.0
50	2-Methoxy-cyclohexylmethyl	A	58	130	$C_{14}H_{20}FN_3O_4$	53.88 (53.66)	6.52 (6.43)	13.62 (13.41)		15	47		36	100	1.8
51	4-*trans*-Methoxy-cyclohexylethyl	A	37	134	$C_{14}H_{20}FN_3O_4$	53.68 (53.66)	6.38 (6.43)	13.49 (13.41)		17	33		90	100	1.1
52	4-*cis*-Methoxy-cyclohexylethyl	A	29	127	$C_{14}H_{20}FN_3O_5$	53.77 (53.66)	6.55 (6.43)	13.33 (13.41)		9	11				
53	3,4-Dimethoxy-cyclohexylethyl	A	58	130	$C_{15}H_{22}FN_3O_5$	52.48 (52.78)	5.78 (5.7)	12.09 (12.31)		36	41		20	100	5.0
54	2,3,4-Tridimethoxy-cyclohexylethyl	A	41	126	$C_{16}H_{24}FN_3O_6$	51.41 (51.46)	6.4 (6.48)	11.22 (11.26)	0	30	48	60	30	300	10
55	2-Cyclohexylpropyl	A	77	133	$C_{14}H_{20}FN_3O_3$	56.71 (56.55)	6.55 (6.78)	14.03 (14.14)		13	38	48	61	300	4.9
56	4-Methoxy-eyclohexylpropyl	A	35	167	$C_{15}H_{22}FN_3O_4$	55.18 (55.09)	6.57 (6.77)	12.54 (12.84)		0	23				
57	4-Methoxybenzyl	A	48	152—153	$C_{13}H_{12}FN_3O_4$	53.02 (53.24)	4.37 (4.12)	14.11 (14.33)	6	32	38	52	26	300	11.5

4-position of cyclohexylmethyl was favorable (**35**, TR 5.6). The introduction of a methyl, methoxy or ethoxy group at other positions (**36**—**40**) or two or three methoxy at various positions (**42**—**46**) gave moderately active compounds. 3,4-Dimethoxycyclohexylpropyl-(**53**, TR 5.0), 2-cyclohexylpropyl (**55**, TR 4.9) and 2,3,4-trimethoxy-cyclohexylethylcarbamoyl-5-FU (**54**, TR 10.0) were active compounds.

1-(4-Methoxycyclohexylcarbamoyl)-5FU (**22**, TR 17.6) was the best compound, followed by 1-(3-methylcyclohexylcarbamoyl)-5FU (**7**, TR 15.0). When we compare their TR values with these of HCFU (TR, 4.5), Tegafur (1.0) and 5FU (1.6), compounds **22** and **7** seem to be promising candidates for clinical use.

Experimental

Melting points were determined on a Yamato melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM FX-100S with tetramethylsilane as an internal standard.

Method A: 1-(4-Methoxycyclohexylcarbamoyl)-5-fluorouracil (22) 4-Methoxycyclohexyl isocyanate (15.1 g, 0.0973 mol) and **1** (11.5 g, 0.0884 mol) were heated in 35 ml of pyridine at 90 °C for 2 h. The reaction mixture was kept at room temperature overnight. The crystals that deposited were collected by filteration and recrystallized from ethanol to give **22** (6.1 g, 24%). Filtrates of the reaction mixture and the recrystallization solution were combined and evaporated at 45 °C under reduced pressure, and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with dilute HCl aqueous solution and water, then dried (Na_2SO_4) and evaporated to afford **22** (13.7 g, 54%). Total yield was 78%. mp 151—152 °C. ^{1}H-NMR δ: 1.15—2.1 (8H, m, CH_2), 3.1 (3H, s, CH_3O), 3.28 (1H, br, CHN) 3.45—3.9 (1H, br, OCH), 8.30 (1H, d, C_6H), 8.75 (1H, d, NHCO).

Method B: 1-(3-Methoxycyclohexylcarbamoyl)-5-fluorouracil (21) Phosgene (13.3g, 0.134 mol) was bubbled over a 1 h period into a cold (5 °C) solution of **1** (8.74 g, 0.0672 mol) in 200 ml of pyridine. Nitrogen gas was passed through the mixture to expel the excess phosgene. 3-Methylcyclohexylamine (7.22 g, 0.064 mol) and triethylamine (6.46 g, 0.064 mol) were added, and the mixture was stirred for 1 h. The resulting triethylamine hydrochloride was filtered off and the reaction mixture was evaporated to dryness. The residue was taken up in CH_2Cl_2 (100 ml)

and the solution was washed with diluted HCl solution. The CH_2Cl_2 solution was then dried (Na_2SO_4) and evaporated, and the residue was recrystallized from EtOH to afford **21** (5.0 g, 45%). mp 114—116 °C. ^{1}H-NMR δ: 1.2—2.2 (8H, br, CH_2), 3.3 (3H, s, CH_3O), 3.33 (1H, br, CHN), 3.3—3.8 (1H, br, CHOC), 8.38 (1H, d, C_6-H), 7.2 (1H, d, NHCO).

The antitumor activity tests were carried out using the same method as described in our previous publications.[10,14]

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