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Antitumor Activity of 1-Alkylcarbamoyl Derivatives of 5-Fluorouracil in a Variety of Mouse Tumors

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Summary. *The antitumor properties of 1-alkylcarbamoyl derivatives of 5-fluorouracil were examined in various mouse tumor systems to select promising compounds for clinical use. Almost all alkylcarbamoyl derivatives were active against various tumors when given by oral administration. Among them, 1-methyl, 1-ethyl, 1-isopropyl, 1-hexyl and 1-octyl carbamoyl derivatives of 5-fluorouracil were moderately or markedly active in six mouse tumor systems tested. However, 1-methyl, 1-ethyl, and 1-isopropyl carbamoyl derivatives were toxic to mice, though not lethal. As a result, 1-hexyl and 1-octyl carbamoyl derivatives were selected as the best candidates for antitumor agents in further study.*

Introduction

5-Fluorouracil, which is one of the antitumor antimetabolites, has been used clinically for carcinoma of breast and gastrointestinal tract by parenteral administration [1]. However, this compound is rather toxic when given by oral administration in an effective dose, causing severe gastrointestinal disorders [5]. Recently, 1-(2-tetrahydrofuryl)-5-fluorouracil, the masked form of 5-fluorouracil, was used orally for maintenance therapy after surgical treatment [11], and this compound shows minimal gastrointestinal toxicity [3]. However, it is only slightly active against mouse tumors [2] and is not activated to 5-fluorouracil in tumor cells [13]. These findings prompted us to attempt the rational design of 'masked-form' 5-fluorouracil as an internal medicine that would be more easily activated in tumor cells, with less toxicity to the host when given by oral administration, than 1-(2-tetrahydrofuryl)-5-fluorouracil. Among the tested masked-form derivatives of 5-fluorouracil, 1-alkylcarbamoyl-5-fluorouracils fulfilled the above concept in the L1210 leukemia system [8, 9]. To evaluate the scope of antitumor activity of a series of compounds, the tumor spectrum study was performed as the secondary screening system, in addition to an efficacy test in one tumor screening [6]. In this way, the antitumor activity of oral 1-alkylcarbamoyl-5-fluorouracils was examined in a variety of mouse tumors.

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Materials and Methods

Animals and Tumors

Male BDF_1 mice weighing 20–23 g were used for C1498 leukemia and adenocarcinoma 755. Female ddN mice weighing 20–23 g were used for ascites sarcoma 180, Ehrlich ascites carcinoma, and Nakahara-Fukuoka sarcoma. Groups of six mice, either test or control, were implanted with one of the tumors. With leukemia, 1×10^6 cells of C1498 leukemia were implanted intraperitoneally. With ascites tumors, 1×10^7 cells of ascites sarcoma 180 or Ehrlich ascites carcinoma were implanted intraperitoneally. With solid tumors, 40 or 20 mg tumor fragments of adenocarcinoma 755 or Nakahara-Fukuoka sarcoma was implanted subcutaneously in the interscapular region of the mouse.

Compounds

Test compounds were supplied by Mitsui Parmaceuticals Inc., Tokyo, Japan. Fourteen 1-alkylcarbamoyl-5-fluorouracil derivatives [12] were tested, and their chemical structures are shown in Table 1. 5-Fluorouracil (I) and 1-(2-tetrahydrofuryl)-5-fluorouracil (II) were used as reference compounds. The compounds were homogenized with 0.5% carboxymethyl cellulose in physiological saline and administered orally in a volume of 0.01 ml/g body weight.

Evaluation of Antitumor Activity

The compound to be tested was administered orally once daily for 5 days, starting 24 h after implantation. Antitumor activity of the compounds against the tumors was evaluated by the increase in life-span over controls (ILS = T/C% -100) in leukemia, by the total packed cell volume (TPCV) ratio (T/C%) on day 7 in ascites tumors,

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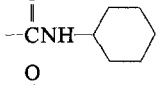
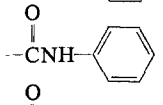
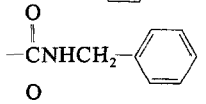
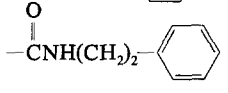
Table 1. Chemical structures of 5-fluorouracil derivatives

Compound no.	R
I	$-H$
II	
III	$-\overset{O}{\overset{\|}{C}}NHCH_3$
IV	$-\overset{O}{\overset{\|}{C}}NHCH_2CH_3$
V	$-\overset{O}{\overset{\|}{C}}NH(CH_2)_2CH_3$
VI	$-\overset{O}{\overset{\|}{C}}NH(CH_2)_3CH_3$
VII	$-\overset{O}{\overset{\|}{C}}NH(CH_2)_4CH_3$
VIII	$-\overset{O}{\overset{\|}{C}}NH(CH_2)_5CH_3$
IX	$-\overset{O}{\overset{\|}{C}}NH(CH_2)_6CH_3$
X	$-\overset{O}{\overset{\|}{C}}NH(CH_2)_7CH_3$
XI	$-\overset{O}{\overset{\|}{C}}NHCH(CH_3)_2$
XII	$-\overset{O}{\overset{\|}{C}}NHC(CH_3)_3$
XIII	
XIV	
XV	
XVI	

or by the tumor weight ratio (T/C%) on the day 10 or 12 in the solid tumors.

The degree of antitumor activity was graded according to the following scheme: – (inactive), 0~9; + (slightly active), 10~19; ++ (moderately active), 20~29; +++ (markedly active), 30 or more of ILS% in leukemias; –, 100~66; +, 65~41; ++, 40~11; +++, 10~0 of T/C% in ascites tumors; –, 100~71; +, 70~51; ++, 50~21; +++, 20~0 of T/C% in solid tumors.

Results

Antitumor Activity of Compounds against C1498 Leukemia

Table 2 shows the effect of structural modification of the alkylcarbamoyl group at position 1 of 5-fluorouracil on antitumor activity against C1498. All of the derivatives were markedly active by oral administration. The most active compound against the tumor was 1-methylcarbamoyl-5-fluorouracil (III) and it was more active than 5-fluorouracil (I) and 1-(2-tetrahydrofuryl)-5-fluorouracil (II).

Antitumor Activity of Compounds against Ascites Sarcoma 180

As shown in Table 3, 5-fluorouracil (I) and 1-(2-tetrahydrofuryl)-5-fluorouracil (II) were weak and inactive against the tumor, respectively. On the other hand, III, IV, VIII, XI, and XVI were moderately active. Methyl (III), ethyl (IV), isopropyl (XI), and phenethyl (XVI) carbamoyl derivatives were markedly active on growth inhibition of sarcoma 180.

Antitumor Activity of Compounds against Ehrlich Ascites Carcinoma

As shown in Table 4, III and IV were markedly active against the tumor and V, VI, VIII, IX, and XI were moderately active against the carcinoma, at the optimal doses. 5-Fluorouracil was moderately active and 1-(2-tetrahydrofuryl)-5-fluorouracil was slightly active.

Antitumor Activity of Compounds against Nakahara-Fukuoka Sarcoma

As shown in Table 5, all the 1-alkylcarbamoyl-5-fluorouracil derivatives except XI, XIII, and XIV were markedly active against the tumor, to a similar extent to the reference compounds. Among them, 1-hexylcarbamoyl-5-fluorouracil (VIII) was the most active.

Antitumor Activity of Compounds against Adenocarcinoma 755

As shown in Table 6, III, IV, VI, VII, XI, XIII, XV, and XVI were markedly active against the carcinoma at the optimal doses. 5-Fluorouracil and 1-(2-tetrahydrofuryl)-5-fluorouracil were nonactive and moderately active, respectively.

Table 2. Effect of compounds on the growth of leukemia C1498

Compound no.	Dose (mg/kg/day)	ILS (%)[a]	Antitumor activity[b]
I	10	19	+
	20	37	+++
	30	43	+++
	50	49	+++
	70	13	+
II	70	9	−
	100	27	++
	200	40	+++
	300	53	+++
	500	13	+
III	10	30	+++
	30	32	+++
	100	75	+++
	200	6	−
IV	10	22	++
	30	46	+++
	70	63	+++
	100	−11	Toxic[c]
V	50	18	+
	100	46	+++
	300	72	+++
	400	24	++
VI	50	31	+++
	100	58	+++
	200	17	+
VII	200	52	+++
VIII	50	15	+
	70	34	+++
	100	43	+++
	200	59	+++
	300	48	+++
	500	24	++
IX	200	36	+++
	300	6	−
X	300	42	+++
	500	0	−
XI	70	52	+++
	100	52	+++
XII	50	48	+++
	100	− 3	Toxic
XIII	100	15	+
	200	57	+++
	300	9	−
XIV	50	53	+++
XV	100	61	+++
	200	19	+
XVI	100	48	+++
	200	19	+

[a] Mean survival time of untreated controls was 9.3 days

[b] Antitumor activity was graded as: −, 0 ~ 9; +, 10 ~ 19; ++, 20 ~ 29; and +++, 30 or more of increase in lifespan (ILS%) over control

[c] Mean survival time in treated group was shorter than that in control group

Table 3. Effect of compounds on the growth of ascites sarcoma 180

Compound no.	Dose (mg/kg/day)	Growth ratio[a] (T/C %)	Mortality (died/used)	Antitumor activity[b]
I	30	70	0/6	−
	50	63	0/6	+
	70	53	0/6	+
	100	−	3/6	Toxic
II	100	100	0/6	−
	200	106	0/6	−
	300	68	0/6	−
	400	−	1/6	Toxic
III	1	41	0/6	+
	3	19	0/6	++
	10	12	0/6	++
	30	7	0/6	+++
	100	0	0/6	+++
	200	0	0/6	+++
	300	−	6/6	Toxic
IV	10	52	0/6	+
	30	29	0/6	++
	70	7	0/6	+++
	100	0	0/6	+++
	200	−	2/6	Toxic
V	30	81	0/6	−
	100	84	0/6	−
	200	69	0/6	−
	300	−	1/6	Toxic
VI	100	64	0/6	+
	200	65	0/6	+
	300	−	2/6	Toxic
VII	100	81	0/6	−
	200	31	0/6	++
	300	19	0/6	++
	400	−	4/6	Toxic
VIII	50	96	0/6	−
	100	54	0/6	+
	200	17	0/6	++
	300	9	0/6	+++
	400	−	2/6	Toxic
IX	100	80	0/6	−
	200	40	0/6	++
	300	26	0/6	++
	400	−	1/6	Toxic
X	500	12	0/6	++
XI	100	80	0/6	−
	200	20	0/6	++
	300	0	0/6	+++
XII	200	27	0/6	++
XIII	100	84	0/6	−
	200	43	0/6	+
	300	26	0/6	++
XIV	100	50	0/6	+
XV	100	38	0/6	++
	300	−	2/6	Toxic
XVI	200	10	0/6	+++
	300	0	0/6	+++

[a] Growth ratio (T/C %) was determined on day 7 after implantation of 10^7 ascites cells

[b] Antitumor activity was graded as: +++, 0 ~ 10; ++, 11 ~ 40; +, 41 ~ 65; and −, 66 or more of growth ratio (T/C %)

Table 4. Effect of compounds on the growth of Ehrlich ascites carcinoma

Compound no.	Dose (mg/kg/day)	Growth ratio (T/C %)	Mortality (died/used)	Antitumor activity[a]
I	50	54	0/6	+
	70	28	0/6	++
	100	–	3/6	Toxic
II	100	85	0/6	–
	200	51	0/6	+
	300	–	2/6	Toxic
III	30	54	0/6	+
	100	1	0/6	+++
	200	–	2/6	Toxic
IV	100	10	0/6	+++
	200	0	0/6	+++
	300	–	3/6	Toxic
V	50	59	0/6	+
	100	20	0/6	++
	200	–	2/6	Toxic
VI	100	55	0/6	+
	200	36	0/6	++
	300	–	1/6	Toxic
VII	100	99	0/6	–
	200	63	0/6	+
	300	–	4/6	Toxic
VIII	70	80	0/6	–
	100	57	0/6	+
	200	13	0/6	++
	300	–	1/6	Toxic
IX	300	40	0/6	++
X	500	36	0/6	++
XI	100	92	0/6	–
	300	12	0/6	++
XII	100	87	0/6	–
	300	–	6/6	Toxic
XIII	100	51	0/6	+
XIV	50	63	0/6	+
XV	100	44	0/6	+
XVI	100	97	0/6	–
	200	42	0/6	+

[a] Criteria are the same as in Table 3

Table 5. Effect of compounds on the growth of Nakahara-Fukuoka sarcoma

Compound no.	Dose (mg/kg/day)	Growth ratio[a]	Mortality (died/used)	Antitumor activity[b]
I	30	78	0/6	–
	50	20	0/6	+++
	70	10	0/6	+++
	100	–	3/6	Toxic
II	200	52	0/6	+
	300	10	0/6	+++
	400	–	1/6	Toxic
III	30	17	0/6	+++
	50	6	0/6	+++
	100	–	2/6	Toxic
IV	100	11	0/6	+++
	200	–	2/6	Toxic
V	100	10	0/6	+++
	200	–	1/6	Toxic
VI	100	11	0/6	+++
	200	11	0/6	+++
	300	–	4/6	Toxic
VII	100	91	0/6	–
	200	13	0/6	+++
VIII	30	85	0/6	–
	50	50	0/6	++
	100	14	0/6	+++
	300	0	0/6	+++
	400	–	2/6	Toxic
IX	300	10	0/6	+++
X	500	6	0/6	+++
XI	100	33	0/6	++
XII	100	8	0/6	+++
	200	–	2/6	Toxic
XIII	100	50	0/6	++
	200	39	0/6	++
	300	–	2/6	Toxic
XIV	100	40	0/6	++
XV	100	11	0/6	+++
	200	–	2/6	Toxic
XVI	100	19	0/6	+++
	200	–	3/6	Toxic

[a] Growth ratio (T/C %) was determined on day 12 after implantation of 20 mg tumor fragments

[b] Antitumor activity was graded as: –, 71 ~ 100; +, 51 ~ 70; ++, 21 ~ 50; +++, 0 ~ 20 of T/C %

The maximum effects with the optimal doses of alkylcarbamoyl-5-fluorouracil derivatives in a variety of tumors are summarized in Table 7. All the derivatives were markedly or moderately active against the two leukemias and Nakahara-Fukuoka sarcoma. However, effects of these derivatives varied in the two ascites tumors and adenocarcinoma 755. Five (III, IV, VIII, X, XI) of the 14 tested derivatives were moderately or markedly active against these three tumors, whereas 5-fluorouracil and 1-(2-tetrahydrofuryl)-5-fluorouracil were inactive or only slightly active against those tumors.

As a result, the active derivatives showing marked or moderate activity against the six tumors tested, are five compounds, namely the methyl (III), ethyl (IV), isopropyl (XI), hexyl (VIII), and octyl (X) carbamoyl derivatives of 5-fluorouracil. Two reference compounds, 5-fluorouracil and 1-(2-tetrahydrofuryl)-5-fluorouracil, were markedly or moderately active against only four out of six tumors.

Discussion

5-Fluorouracil shows a broad, strong antitumor activity against various tumors in mice when given by intrave-

Table 6. Effect of compounds on the growth of adenocarcinoma 755

Compound no.	Dose (mg/kg/day)	Growth ratio[a] (T/C %)	Mortality (died/used)	Antitumor activity[b]
I	30	73	0/6	–
	50	–	2/6	Toxic
II	200	44	0/6	++
	300	–	3/6	Toxic
III	30	63	0/6	+
	50	4	0/6	+++
	100	–	3/6	Toxic
IV	30	8	0/6	+++
	50	0	0/6	+++
	100	–	2/6	Toxic
V	50	55	0/6	+
	100	–	1/6	Toxic
VI	200	4	0/6	+++
	300	–	4/6	Toxic
VII	100	67	0/6	+
	200	3	0/6	+++
VIII	30	89	0/6	–
	100	44	0/6	++
	200	5	0/6	+++
	300	–	1/6	Toxic
IX	300	42	0/6	++
X	300	32	0/6	++
	500	–	3/6	Toxic
XI	100	13	0/6	+++
XII	50	50	0/6	++
	100	–	6/6	Toxic
XIII	100	21	0/6	++
	300	0	0/6	+++
XIV	50	70	0/6	+
	100	–	2/6	Toxic
XV	70	0	0/6	+++
	100	–	1/6	Toxic
XVI	100	10	0/6	+++
	200	–	6/6	Toxic

[a] Growth ratio (T/C %) was determined on day 14 after implantation of 40 mg tumor fragments

[b] Criteria were the same as in Table 5

Table 7. Maximum effect of 5-fluorouracil derivatives by oral administration

Compound no.	Tumor[a]					
	NFS	Ca755	S180	EAC	C1498	L1210[b]
I	+++	–	+	++	+++	+++
II	+++	++	–	+	+++	+++
III	+++	+++	+++	+++	+++	+++
IV	+++	+++	+++	+++	+++	+++
V	+++	+	+	++	+++	+++
VI	+++	+++	+	++	+++	+++
VII	+++	+++	++	+	+++	+++
VIII	+++	+++	+++	++	+++	+++
IX	+++	++	++	+	+++	+++
X	+++	++	++	++	+++	+++
XI	++	+++	+++	++	+++	+++
XII	+++	++	++	–	+++	+++
XIII	++	+++	++	+	+++	+++
XIV	++	+	+	+	+++	+++
XV	+++	+++	++	+	+++	+++
XVI	+++	+++	+++	+	+++	+++

[a] NFS: Nakahara-Fukuoka sarcoma; Ca755: adenocarcinoma 755; S180: ascites sarcoma 180; EAC: Ehrlich ascites carcinoma; C1498: leukemia C1498; L1210: leukemia L1210

[b] This result has been reported previously [9]

nous or intraperitoneal injection, but shows limited activity following oral administration. In the past few years, many 5-fluorouracil derivatives have been studied for antitumor activity [7]. Recently, 1-(2-tetrahydrofuryl)-5-fluorouracil given by mouth was found to be active against stomach cancer and breast cancer with lower gastrointestinal toxicity [3]. But this antitumor activity is not so strong. We went on to search for 5-fluorouracil derivatives that are more active than 1-(2-tetrahydrofuryl)-5-fluorouracil and less toxic than 5-fluorouracil.

As previously reported [9], 1-alkylcarbamoyl-5-fluorouracils showed marked antitumor activity against L1210 when given by oral administration. Leukemia L1210 is used as a primary screen, because of the suggestive evidence of predictive value for clinical activity [14]. According to the report by Gellhorn and Hirschberg in 1955 [4], suitable screening systems for antitumor agents at that time were the following three mouse tumors: leukemia L1210, sarcoma 180, and adenocarcinoma 755. Through several years of experience with these systems, the number of tumor systems at the National Cancer Institute of the USA was increased yearly [10]. At the National Cancer Center Research Institute of Japan, leukemia L1210, ascites sarcoma 180, Ehrlich ascites carcinoma, Nakahara-Fukuoka sarcoma, adenocarcinoma 755, and leukemia C1498 are used for detailed evaluation of drugs [6]. In this paper, antitumor activity of 1-alkylcarbamoyl-5-fluorouracils against various mouse tumors was examined.

In the C1498 system, many alkylcarbamoyl-5-fluorouracils were effective. Among them, 1-methylcarbamoyl-5-fluorouracil (III) showed the highest increase in lifespan. In the L1210 system, 1-ethyl (IV) (maximum ILS over controls at optimal dose: 62%), 1-propyl (V) (60%), 1-butyl (VI) (54%), 1-hexyl (VIII) (53%), 1-isopropyl (XI) (56%), 1-tert-butyl (XII) (54 %), and 1-cyclohexyl (XIII) (59%) carbamoyl derivatives were markedly active, as reported previously [9]. In this system, 5-fluorouracil (I) (56%) and 1-(2-tetrahydrofuryl)-5-fluorouracil (II) (31%) were markedly active [9]. In the ascites sarcoma 180 and Ehrlich ascites carcinoma systems, 5-fluorouracil was slightly active, but 1-methyl (III), 1-ethyl (IV), 1-hexyl (VIII), and 1-isopropyl (XI) carbamoyl derivatives were markedly active. 1-Phenethylcarbamoyl-5-fluorouracil (XVI) showed complete

inhibition in the ascites sarcoma 180 system but slight activity in the Ehrlich ascites carcinoma system.

In solid tumor systems, many alkyl carbamoyl derivatives of 5-fluorouracil were markedly active against Nakahara-Fukuoka sarcoma. In particular, 1-hexylcarbamoyl-5-fluorouracil (VIII) was the only compound showing complete inhibition. In the adenocarcinoma 755 system, 5-fluorouracil (I) was inactive, but 1-(2-tetrahydrofuryl)-5-fluorouracil (II) was moderately active. Many carbamoyl derivatives were markedly active.

In the tumor spectrum study, 1-methyl and 1-ethyl carbamoyl derivatives showed marked antitumor activity in six mouse tumor systems, followed by 1-hexyl, 1-isopropyl and 1-octyl carbamoyl derivatives (Table 7). However, the two most active compounds, 1-methyl and 1-ethyl carbamoyl derivatives, are toxic to mice, though not lethal. The behavior of mice treated with those compounds is not normal. Their motor activity was increased, and the change was irreversible. The 1-isopropyl carbamoyl derivative is also toxic. In conclusion, the compounds showing higher activity in a variety of tumors with lower toxicity to the host animals are 1-hexyl and 1-octyl carbamoyl derivatives. These two derivatives were selected as the best candidates for further evaluation.

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