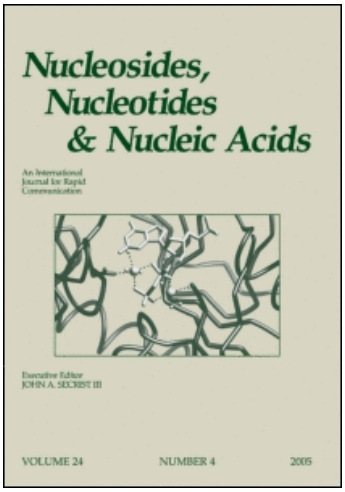

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Synthesis and Antitumor Activities of 5-Fluorouracil Derivatives

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SYNTHESIS AND ANTITUMOR ACTIVITIES OF 5-FLUOROURACIL DERIVATIVES

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Abstract - 1-Carbonyl 5-fluorouracil derivatives, 5'-acyl-5-fluorouridines, and 5-fluorouridilic acid esters were synthesized and their antitumor activities were tested.

INTRODUCTION

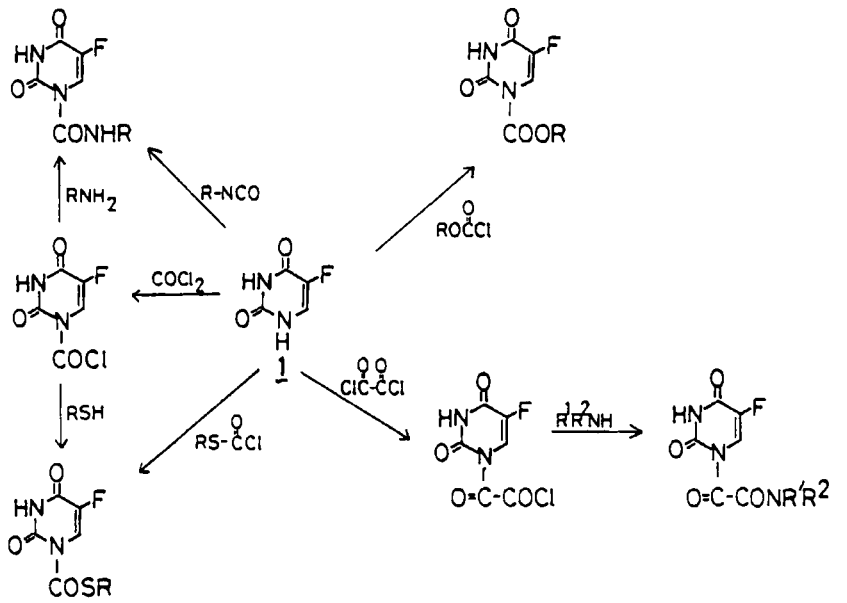
5-Fluorouracil (1) is well known to have strong antitumor activity but its toxicity limits the use of 1 as a practical antitumor agent for the human beings. With the aim of diminishing the toxicity of 1 and obtaining biologically active derivatives, suitable for oral administration, we have prepared various modified 5-fluorouracil derivatives, such as 1-carbamoyl-[1)], 1-acyloxyalkyl-[2)], 1-alkylthiocarbamoyl-[3)] and α-alkoxyalkyl-[4)] 5-fluorouracils and so on, and have tested their antitumor activities. During these examination, 1-hexylcarbamoyl-5-fluorouracil (HCFU) showed very good results (HCFU is now in clinical use named by Mifurol[R]). After the dicovery of HCFU, we are continuing the study to obtain much better compound than HCFU. In this report, we wish to mention, at first the preparation of 1-carbamoyl- and other 1-carbonyl-5-fluorouracil derivatives and their antitumor activities in the case of oral administration. Secondary, we describe the preparation of 5-fluorouridine, 5-fluorouridilic acid and their derivatives in large quantity and their antitumor activities against L-1210 leukemia.

The first two compounds have strong toxicity, so that have not been in clinical use.

RESULTS AND DISCUSSION

1-carbonyl-5-fluorouracil derivatives such as 1-carbamoyl-, 1-alkylthiocarbonyl-, 1-alkoxycarbonyl-, 1-amidoxalyl-5-fluorouracils could be prepared by the reaction of the corresponding chlorides as decribe in Scheme 1. 1-chlorocarbonyl-5-fluorouracil was also the very important intermediate to prepare 1-carbamoyl, 1-alkylthiocarbonyl and 1-alkoxycarbonyl derivatives.

HCFU, one of the carbamoyl-type derivative, has marked antitumor activity against leukemia L-1210 and C-1498, ascites sarcoma 180, Nakahara-Fukuoka sarcoma and adenocarcinoma 755 and shows a greater antitumor activity and a wider antitumor spectrum against many mouse tumor than 5-FU and Tegafur[5]. Response rate of HCFU in human gastric, colorectal and breast cancers were 18.5, 46.2 and 33.3%,



Scheme 1

respectively[6]. Only weak point of HCFU is such side effect as hot sensation and pollakiuria. We are now trying to obtain such compounds that have the same antitumor activity as HCFU and no side effects.

When we look at the antitumor activity, toxicity and stability of masked 5-FU compounds and the parent 5-FU, we find that 5-FU is the most active but the most toxic material. Oxalyl, acyl and alkoxycarbonyl compounds were so unstable that their behavior were almost the same as that

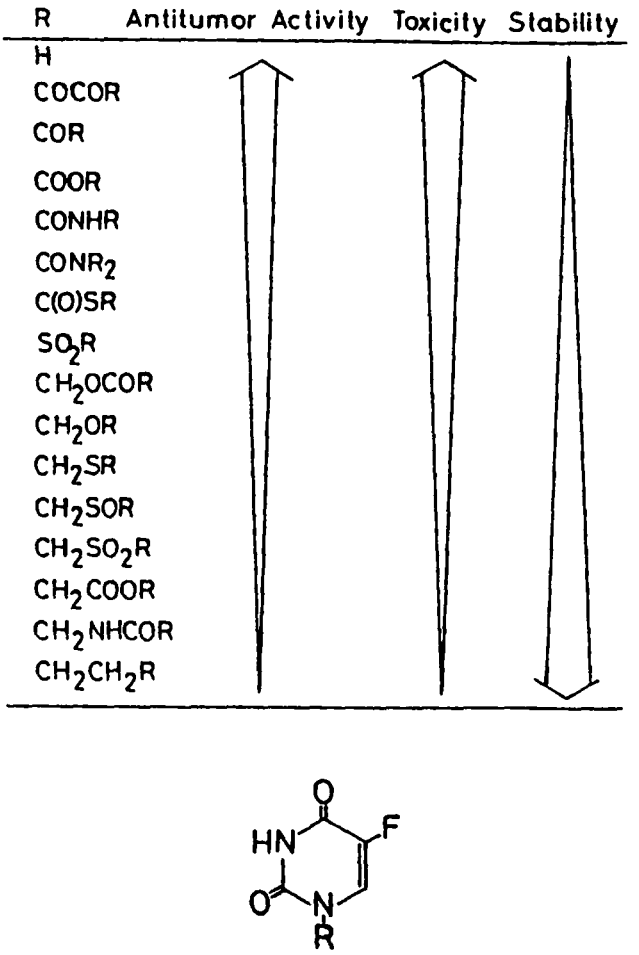
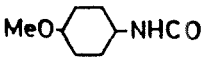
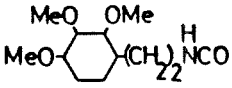
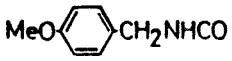
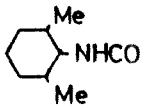
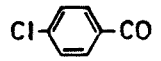
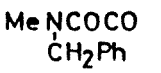


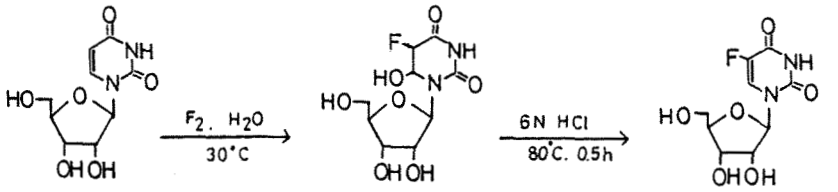
Fig. 1

Table 1

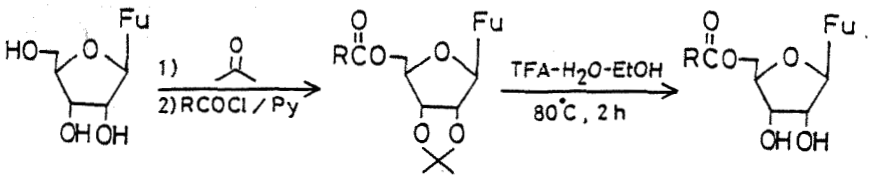
Antitumor Activity of 1-Carbonyl-5FU against L-1210

X	ILS (%) Dose mg/Kg; po 30	100	300	ILS_{30}	TR
	44	50	66	17	18
	30	48	60	30	10
	32	38	52	27	11
	29	45	51	31	9.6
$C_6H_{13}NHCO$	21	50	23	44	4.5
$C_8H_{17}SCO$	27	44	67	38	8.1
$C_8H_{17}OCO$	13	29	47	107	2.7
	12	36	-14	77	1.3
	14	30		100	1
	0	31	13	100	1
5-FU	30	Tox.	Tox.	26	1.9

of 5-FU, because when administered orally, they soon decomposed in the stomach, that is, under acidic conditions. Carboxymethyl, sulfonylmethyl derivatives were so stable that they did not decompose, therefore they were inactive and not toxic. Carbamoyl and alkylthiocarbonyl compounds had moderate and optimal properties between two extreme



Scheme 2



Scheme 3

classes, so that they were balanced well in their antitumor activity and toxicity (Fig. 1). To compare the many kinds of 1-carbonyl-5-fluorouracils, the most typical compounds of each group are listed in Table 1.

As mentioned in introduction, 5-fluorouridine and 5-fluorouridilic acid have strong toxicity. So in order to diminish these toxicity we transfered these two compounds to 5'-acyl-5-fluorouridine and 5-fluorouridilic acid ester, respectively.

Uridine was reacted with fluorine gas in water at 30° C and the resultant fluorohydrin was treated with 6N HCl to afford 5-fluorouridine (Scheme 2). This was converted to 5'-acyl-5-fluorouridine as described in Scheme 3. 5-Fluorouridine was acetonized and then acylated in pyridine. Acetonide was then hydrolysed with heating in trifluoroacetic acid, water and ethanol at 80°C for two hour.

5'-Acyl-5-fluorouridines showed very high antitumor activity against L-1210. When R=C_4H_9 , ILS_{30} was 0.3 and therapeutic ratio was 33 (Table 2). According to these

Table 2

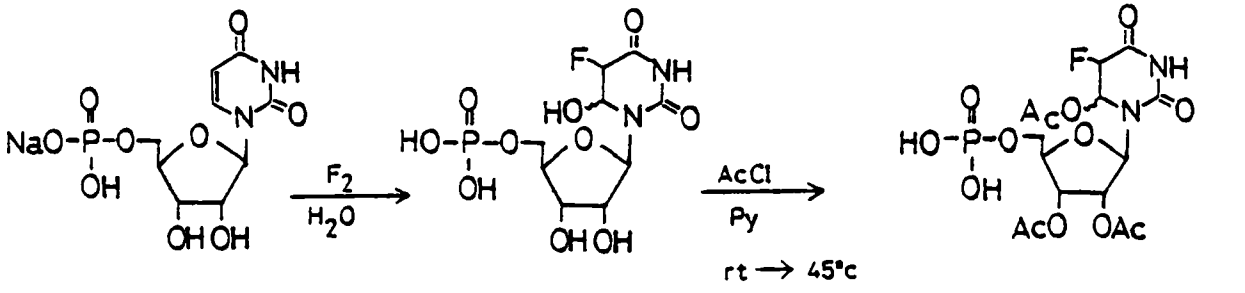
Antitumor Activity of 5'-Acyl-5-fluorouridines against L-1210

R	ILS (%) Dose (mg/Kg); ip						ILS_{30}	TR
	0.1	0.3	1	3	10	30		
H			29	59	69	29	1	10
CH_3				29	59	14	3	3.3
C_3H_7		22	42	60	60	-16	0.5	20
i-C_3H_7			19	42	93	0	1.7	5.9
C_4H_9	13	35	38	63	103	10	0.3	33
t-C_4H_9		2	38	5	65	18	0.78	12.8
C_5H_{11}	6	35	54	96	81	-22	0.25	12
FUR		46	62	91	33		0.1	30

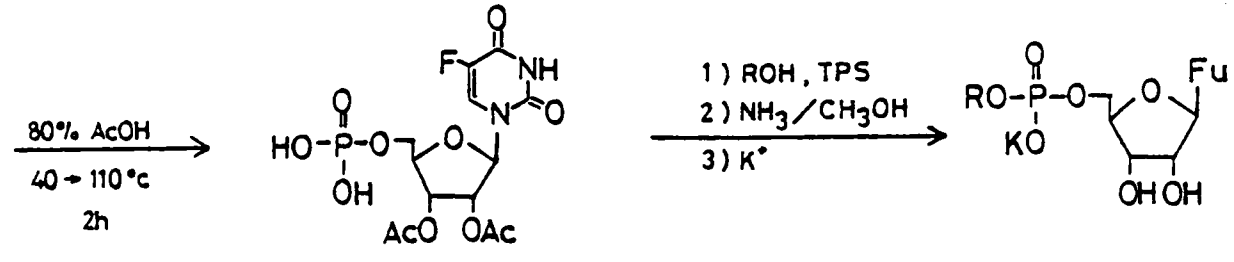
results, toxicity of FUR was slightly improved by the esterification of 5'-hydroxyl group.

The preparation of 5-fluorouridilic acid esters is detailed in Scheme 4. Monosodium salt of uridilic acid was fluorinated in water. The resulted fluorohydrin was acylated to triacetate, which was heated at 40 to 110°C in 80% acetic acid to afford diacetyl-5-fluorouridilic acid. This acid was esterified with various alcohols in the presence of TPS-chloride, and then acetyl group was cleaved by ammonia. The esters were isolated as potassium salts. According to these procedures large amount of 5-fluorouridilic acid esters could be easily prepared.

Antitumor activity of FURP-esters was tested against L-1210. The results are summarized in Table 3. FURP (R=H) showed very strong activity and TR was as high as 45.



(cis / trans = 47/53)



Scheme 4

Table 3

Antitumor Activity of FURP-esters against L-1210

R	ILS (%)						ILS_{30}	TR
	Dose (mg/Kg); ip							
	0.1	0.3	1	3	10	30		
H	8	35	44	75	100	6	0.22	45
CH_3		13	47	71	46	28	0.55	9
C_2H_5					65	6		
C_3H_7					55	81		
C_4H_9			9	44	54	103	1.9	19.8
C_6H_{13}				24	66	14	3.6	2.8
C_9H_{19}				33	69	96	2.7	3.7

Ester of FURP showed improvement in toxicity. When R=C_4H_9, the ester did not show any toxicity at 30 mg/kg dosage, and TR of it was 19.8. Other esters did not show such high TR.

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