

CHEMOTHERAPEUTIC POLYMERS

XII. SYNTHESIS AND ANTITUMOR ACTIVITY OF
POLYAMIDES CONTAINING 5-FLUOROURACILS
AS PENDANT GROUP

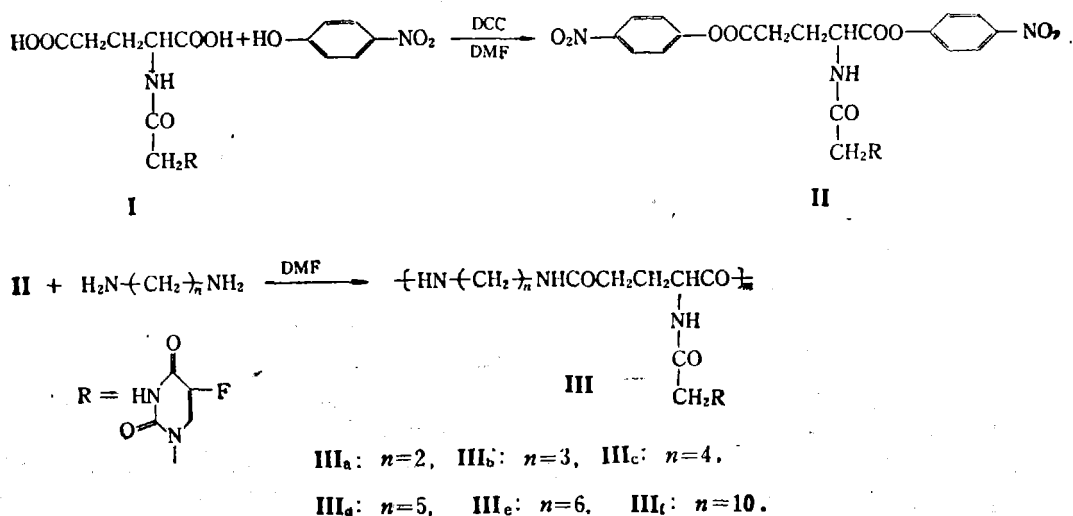
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ABSTRACT

Six polyamides with pendant 5-fluorouracil group were synthesized by the polycondensation of di-*p*-nitrophenyl *N*-(5-fluorouracil-1-acetyl)glutamate with a series of polymethylene diamines. All of the new polyamides obtained are soluble in water. Their chemical structures were confirmed by ^1H NMR, UV and IR spectra as well as elemental analyses. The antitumor activity of some of these polyamides were tested against Ehrlich Ascites Carcinoma in mice, III_a showed an inhibition rate of 43%.

In the previous paper we reported the synthesis of polyamides containing 5-fluorouracil in the main chain^[1]. The present work reports on the preparation, characterization and anti-tumor activity of water-soluble polyamides with pendant 5-fluorouracil group. These new polyamides have been prepared by the polycondensation of di-*p*-nitrophenyl *N*-(5-fluorouracil-1-acetyl)glutamate with a series of polymethylene diamines in *N,N*-dimethylformamide (DMF):



EXPERIMENTAL

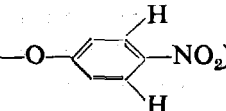
Materials: N,N-Dimethylformamide (DMF) was dried over potassium hydroxide and distilled. Analytical reagent grade α,ω -polymethylene diamines were used. N-(5-fluorouracil-1-acetyl)glutamic acid was prepared as described earlier^[2]. N,N'-dicyclohexylcarbodiimide (DCC) was reagent grade without further purification.

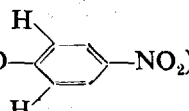
Measurements: IR spectra were recorded on a Nicolet 170 SX spectrophotometer. ¹H NMR spectra were determined with a EM-360L apparatus. UV spectra were measured on a UV-240 spectrophotometer. Elemental analyses were performed using a 240 Belemental analyzer.

Monomer: Di-p-nitrophenyl N-(5-fluorouracil-1-acetyl)glutamate (II)

A mixture of N-(5-fluorouracil-1-acetyl)glutamic acid (3.2g, 0.02mol), p-nitrophenol (2.78g, 0.02mol) and N,N'-dicyclohexylcarbodiimide (4.1g, 0.02mol) in DMF (40ml) was stirred at 0°C for 4h, and then at room temperature for 72h. The precipitate was filtered off, and the filtrate was concentrated at 90°C under reduced pressure. The residue was triturated and washed several times with ether, and recrystallized from acetone, white crystals, m.p. 152°C, yield: 5.2g (93%).

IR(KBr): 3080 (s, C=C), 1706, 1657 (s, C=O), 1615, 1512 (s, )
1246 (m, C—F), 1385, 1340 (m, —CH₂CH₂—)

¹H NMR(TFA): δ =8.30 (d; 4H, )

7.30 (m; 4H, )

7.82 (m; 2H, C⁵-H and CONH), 2.10—3.00 (m; 4H, —CH₂CH₂—)
4.80 (m; 3H, COCH₂N and C ^{α} -H of glutamic acid)

UV (ethanol): $\lambda_{\max}$ 276nm (ϵ 1548)

C₂₃H₁₈N₅O₁₁F (559.48)

Calcd.: C 49.37 H 3.24 N 12.52

Found: C 49.23 H 3.49 N 12.68

Polymers: Poly[polymethylene α -(5-fluorouracil-1-acetyl-amino)glutaramide] (III_{a-f})

Di-p-nitrophenyl N-(5-fluorouracilacetyl)glutamate (2.79g, 0.005mol) was added to a solution of α,ω -polymethylene diamine (0.005mol) in DMF (30ml). The reaction mixture was stirred at 0°C for 5h, then at room temperature for 48h, and poured into acetone (100ml). The precipitated polymer was washed several times with acetone, dried in vacuo to give white polymer. Yield, physical constant, molecular weight and elemental analyses of polymers (III_{a-f}) are listed in Table 1.

Table 1 Yield, physical constant, elemental analyses and IR data of the polymer

Polymer	$\bar{M}_n^*$	Yield (%)	Elemental analyses Found (calcd.)**			IR (cm ⁻¹)			
			C	H	N	C—F	C=O	CONH	(CH ₂) _n
III _a	8500	81.0	43.45 (44.46)	5.04 (5.29)	19.20 (18.70)	1246	3080	3350 1650 1549	2900 2850 1370
III _b	8500	84.3	45.51 (45.04)	5.65 (5.36)	17.51 (18.72)	1245	3078	3400 1649 1536	2939 2864 1384
III _c	10600	85.1	45.55 (46.50)	5.80 (5.68)	17.42 (18.09)	1243	3068	3320 1648 1540	2997 2841 1380
III _d	9300	79.5	45.83 (46.80)	6.28 (6.22)	16.70 (16.48)	1249	3069	3296 1662 1549	2939 2864 1381
III _e	8600	85.6	49.65 (49.10)	6.64 (6.27)	16.34 (16.87)	1237	3071	3289 1667 1540	2958 2840 1375
III _f	8700	80.1	53.81 (53.52)	7.35 (7.27)	14.70 (14.86)	1244	3065	3289 1663 1548	2926 2855 1360

* $\bar{M}_n$ were determined by dynamic osmometry (DMF, 30°C).

** Calculation for polymers was upon the repeating unit plus one equivalent of water.

RESULTS AND DISCUSSION

The preparation of 5-fluorouracil containing di-*p*-nitrophenyl glutamate and its condensation with polymethylene diamines to give polyamides afforded good yields. As shown in Tab. 1, these resulting polyamides had average molecular weight between 8500 and 10600. All of the obtained polyamides are easily soluble in water and acetic acid, slightly soluble in ethanol and insoluble in acetone.

Fig. 1 shows the ¹H NMR spectrum of di-*p*-nitrophenyl N-(5-fluorouracil-1-acetyl)-glutamate. In combination with IR and UV spectra as well as elemental analyses, the chemical structure of the monomer (II) was further confirmed.

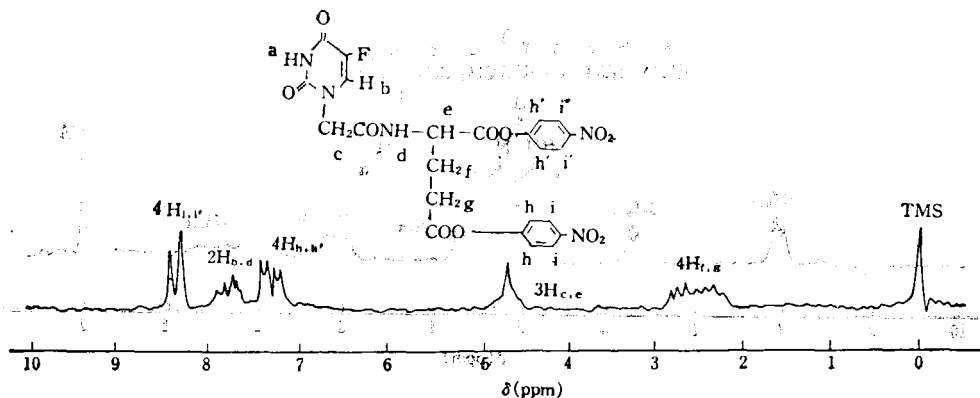


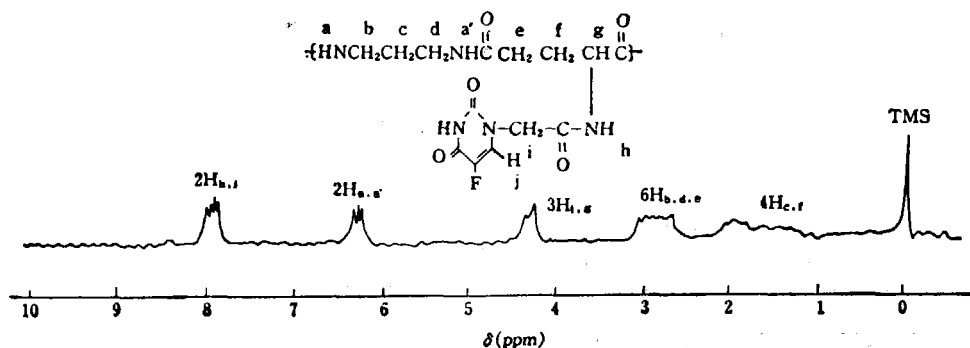
Fig. 1 ¹H NMR spectrum of di-*p*-nitrophenyl N-(5-fluorouracil-1-acetyl)glutamate (II).

Table 2 ^1H NMR and UV Data of the polymer

Polymer	^1H NMR (ppm) Solvent: CF_3COOH			UV (water)	
	CONH and $\text{C}^\alpha\text{-H}$	NCH_2CO and NCHCO	$(\text{CH}_2)_n$ and $-\text{CH}_2\text{CH}_2-$	λ_{max} (nm)	$\epsilon \times 10^{-3}$
III _a	8.10—8.51 (m, 2H) 7.61—7.92 (m, 2H)	4.70—5.01 (m, 3H)	3.51—4.02 (m, 4H) 2.21—3.90 (m, 4H)	272.5	15.7
III _b	7.80—8.20 (m, 2H) 6.00—6.40 (m, 2H)	4.10—4.30 (m, 3H)	2.74—3.22 (m, 6H) 1.00—2.51 (m, 4H)	269.5	12.1
III _c	7.90—8.30 (m, 2H) 7.00—7.50 (m, 2H)	4.40—4.65 (m, 3H)	2.60—3.30 (m, 6H) 1.20—2.30 (m, 6H)	272.5	13.4
III _d	8.00—8.50 (m, 2H) 7.50—7.80 (m, 2H)	4.50—4.80 (m, 3H)	3.05—3.51 (m, 4H) 2.00—2.81 (m, 4H) 1.21—1.81 (m, 6H)	271.0	17.8
III _e	7.50—8.00 (m, 2H) 6.65—6.95 (m, 2H)	4.50—4.80 (m, 3H)	3.00—3.51 (m, 4H) 2.00—2.42 (m, 4H) 0.92—1.51 (m, 8H)	273.5	25.0
III _f	7.60—8.24 (m, 4H)	4.80—5.15 (m, 3H)	3.21—3.82 (m, 4H) 2.20—2.97 (m, 4H) 1.00—1.80 (m, 16H)	271.5	11.0

Internal standard: tetramethylsilane.

Fig. 2 shows the ^1H NMR spectrum of polymer III_b. The appearance of new polyamide groups exhibit a signal at $\delta=6.6$ (2H), and both the proton signals of nitrobenzene ring and amino group due to the monomers disappeared. Moreover, from Tab. 2 it can be seen that all of the polyamides obtained (III_{a-f}) had analogous ^1H NMR data, but it shows an increase of the number of protons at $\delta=1.00$ —2.00 with an increase of the methylene group in the polymer backbone. The IR Spectral data of polymer III_b (Tab. 1) show absorption at 3080 cm^{-1} of 5-fluorouracil ring. The absorption band at 1246 cm^{-1} due to C—F. The characteristic absorption at 2939 cm^{-1} , 2864 cm^{-1} and 1384 cm^{-1} due to polymethylene group and at

Fig. 2 ^1H NMR spectrum of poly[propylene α -(5-fluorouracil-1-acetylaminoglutaramide)] (III_b)

3320 cm^{-1} , 1630 cm^{-1} and 1549 cm^{-1} due to amide groups. The IR spectra also show loss of absorption bands corresponding to amino group.

The preliminary screening (performed by the Department of Pharmacology, Wuhan Tongji Medical University, Wuhan) has indicated that polymer **III_b** is active against EAC in mice, it showed an inhibition rate of 43%.

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REFERENCES

- [1] Liu Zhenhua, Chen Qusheng, Liu Gaowei, Wang Xuan and Zhuo Renxi, Preprints of Symposium on Functional and Specialty Polymers, p. 55 (Guilin, China, 1984).
- [2] Zhuo Renxi, Fan Changlie and Zhao Rulin, *Chemical Journal of Chinese Universities*, 1986, 7, 503.