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Synthesis of Polyphosphonates Containing 5-Flouro-N^1-furanyl-N^3-glyceroalkyl-uracil and Formyl Groups

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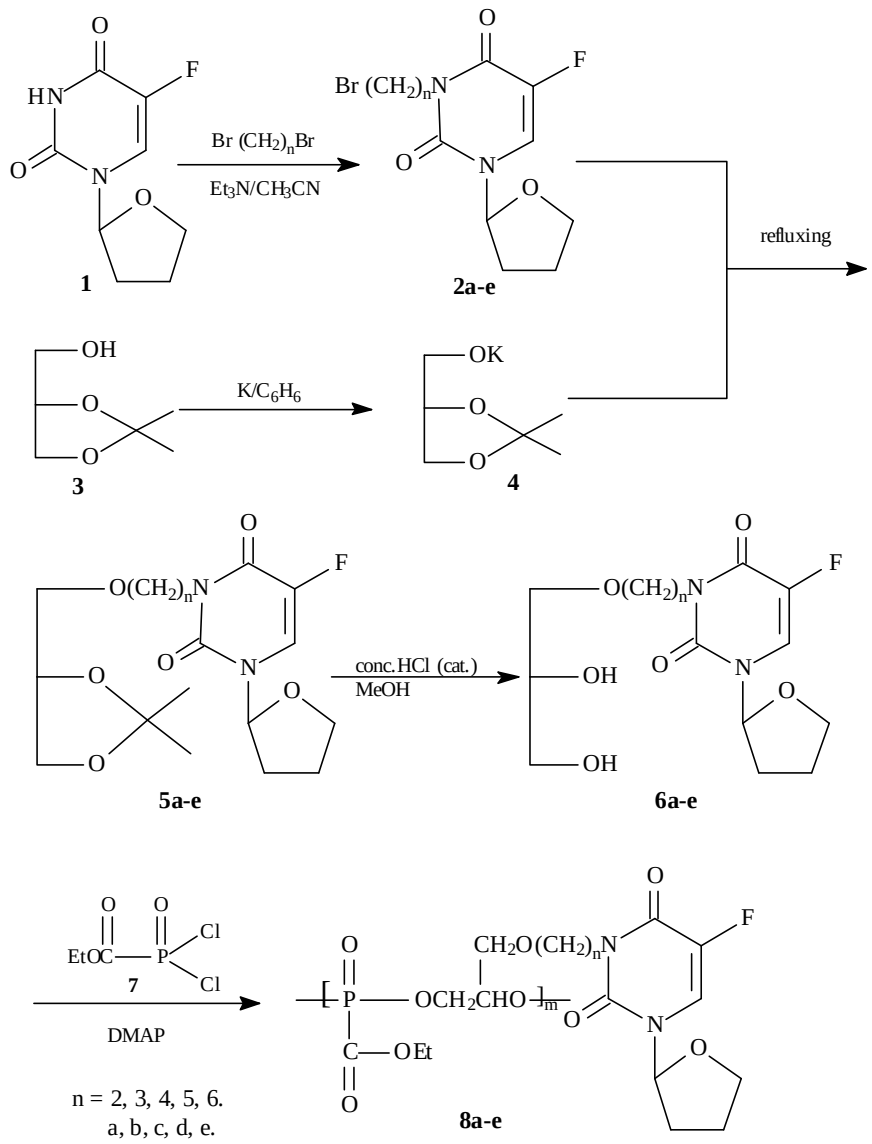
Abstract: A series of novel polyphosphonates containing 5-flouro- N^1-furanyl-N^3-glyceroalkyl-uracil and formyl groups was synthesized by the condensation of 3-(ω-(1′-furanyl-5-flourouracil-3-yl) alkoxy)-1, 2-dihydroxy propane with phosphonyl dichloride. The products were characterized by IR, ^{1}H NMR, ^{31}P NMR, $\overline{M}$, and elemental analysis. The results of bioassay show that compound **8a** possesses potential anticancer activity.

Keywords: Polyphosphates, furanyl,glyceryl, 5-flourouracil, formyl.

In the past twenty years, it has been shown that polyphosphonates are a class of biodegradable polymer and have been widely used in the investigation of polymer drugs or the vehicle for biologically active substance[1-6]. As the mimics of biological membrane, various glycerophosphonates have also been synthesized and studied in the field of biology, and medicinal chemistry, *etc.*[7]. Recently, we developed a kind of potential anticancer glycerophosphonate[8-9]. On the other hand, it is known that phosphonoformic acid (PFA) can inhibit the DNA polymerase of several herps and AIDS viruses[10]. But its clinical applications were restricted due to its poor penetration into cells[11]. In an attempt to search for new polyphosphonate drugs with high activity and low toxicity, we designed and synthesized a series of novel polyphosphonates containing groups of 5-flouro-N^1-furanyl-N^3-glyceroalkyl-uracil and formyl groups. The synthetic route is shown in **Scheme 1**.

The intermediate **2** was obtained in 74-93% yield by refluxing the mixture of N^1-furanyl-5-flourouracil and α, ω-dibromoalkane in CH_3CN in the presence of triethyl amine. Glycerol protected with propylene **3** was treated with potassium in anhydrous benzene to produce potassium glyceroxide **4**, without isolation to which was added compound **2** in benzene and refluxed for 5 hours to give the intermediates **5** in yields of 61-77%. Monomers **6** were obtained from compounds **5** by deprotection in weak acidic methanol in 89-96% yields, and another monomer **7** was synthesized according to the literature method[12]. Both monomers **6** and **7** were condensed to produce the title polymers **8** in yields of 76-88%. Some of the experimental results were listed in the **Table 1**. The structures of title compounds **8a-e** were characterized by ^{1}H NMR, ^{31}P NMR, $\overline{M}$, elemental analysis, and IR[13].

Scheme 1



1 **2a-e** **3** **4** **5a-e** **6a-e** **7** **8a-e**

In order to obtain polyphosponates of higher molecular weight, some polymeriza-tion conditions have been investigated, such as the basic catalysts, solvents, and temperatures. It has been found that the method for solution condensation, with the aid of both 4-DMAP (4-N, N-dimethylpyridine) and K_2CO_3 as catalysts, appears to be the most efficient in obtaining higher molecular weights.

The properties of title polymers also have been studied. The following results are

identified:

1. A good solubility in DMSO and alcohol, but not in chloroform, dichloromethane, ethyl acetate, acetone, and DMF.

2. Good film forming properties.

3. In the accelerated degradation test, polymer **8c** lost to less than 8% of its weight in two weeks in pH=7.4 phosphate buffer at 37°C, and completely decomposed in less than one week in a solution of 0.1mol/L NaOH at 37°C.

So their hydrolysis mechanism could be considered as basic catalysis.

The tests of preliminary biological activity for title compounds indicate that polymer **8a** has potential inhibitory activities on HL-60 (human leukemia-60) cell (Inhibition rate: 87%, $c = 10^{-6}$M).

Table 1 Experimental Data of Polymer **8a-e**

Polymers	n	State	$\overline{M}$ *	Yields
8a	2	White Solid	8035	76
8b	3	White Solid	18441	81
8c	4	White Solid	7203	85
8d	5	White Solid	7847	88
8e	6	White Solid	6890	84

* GPC Method

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References and Notes

1. J. Brosse, L. Fontaine, D. Derouet, S. Charatanathvorn, *Makromol. Chem.*, **1989**, *190*, 2329.
2. J. Pretula and St. Penczek, *Makromol. Chem.*, **1990**, *191*, 671.
3. R. Tzevi, P. Novakov, K. Troev, and D. M. Roundhill, *J. Polymer Science: Party A: Polymer Chemistry*, **1997**, *35*, 625.
4. C. L. Fan, B. Li, Z. H. Liu, R. X. Zuo, *Chem. J. Chinese Universities*, **1996**, *17*(11), 1788.
5. N. E. Zhou, Q. S. Chen, R. X. Zhuo, *Acta. Polymerica Sinica*, **1987**, (6), 417.
6. C. L. Fan, C. S. Mai, J. J. Xu, R. X. Zhuo, *Polymer Communications*, **1985**, (1), 77.
7. M. G. Low, A. R. Saltiel, *Science*, **1988**, *239*, 257.
8. R. Y. Chen, C. X. Zhang, C. C. Tang *Chem. J. Chinese Universities*, **1997**, *18*(11), 1809.
9. Chen Ru-Yu, Zhang Ming *Science in China, Series B*, **1994**, *24*, 113.
10. B. Oberg, *Pharmacol Ther.*, **1989**, *40* (2), 213.
11. M. A. Wainberg, O. Kendall, N. Gilmore, *Can. Med. Assoc. J.*, **1988**, *138*, 797.
12. M. M. Veghefi, P. A. Mckernan, and R. K. Robins, *J. Med. Chem.*, **1986**, *29*, 1389.
13. Selected spectroscopic data for polymer **8a**:
^{1}H NMR (DMSO, δ ppm): 1.64 (m, 3H), 1.89-2.45 (m, 4H), 3.95-4.51 (m, 13H), 5.92 (t, 1H, J=6.8Hz), 7.42 (d, 1H, J=7.5Hz). ^{31}P NMR (DMSO, δ ppm): -2.15, -1.83. EA: Calcd. C (42.49), H (4.90), N (6.19), Found: C (42.53), H (4.82), N (6.26). IR (KBr, cm^{-1}): 3371, 3024, 2937, 2886, 1676, 1552, 1379, 1222, 1186, 1012, 936, 764.

Selected spectroscopic data for polymer **8c**:
^{1}H NMR (DMSO, δ ppm): 1.65 (m, 3H), 2.11 (m, 7H), 2.32 (m, 1H), 3.50-3.64 (m, 8H), 3.96 (m, 4H), 4.26 (m, 1H), 5.94 (t, 1H, J=6.2Hz), 7.32 (d, 1H, J=7.5Hz). ^{31}P NMR (DMSO, δ ppm): -4.69, -5.40. EA: Calcd. C (46.55), H (5.64), N (6.03), Found: C (46.71), H (5.36), N (6.22). IR (KBr, cm^{-1}): 3280, 3052, 2940, 2837, 1690, 1550, 1384, 1225, 1180, 1024, 955.

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