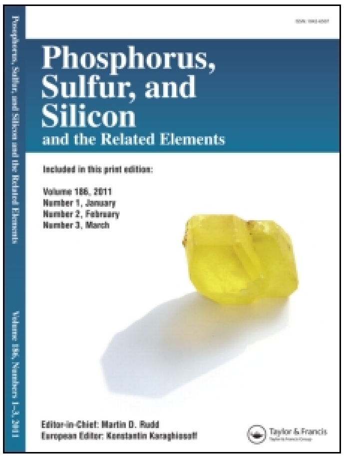

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Synthesis of Novel Phosphoramide-Tegafur Derivatives Containing Aminopropylsilatrane

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A series of novel phosphoramide-tegafur derivatives containing γ-aminopropyl silatrane were synthesized via the condensation reactions of phosphoryl dichloride with N^1*-(2-furanidyl)-*N^3*-(hydroxyethyl)-5-fluorouracil, followed by condensation with γ-aminopropyl silatrane. The structures of the products were confirmed by* ^1H *NMR,* ^{31}P *NMR, IR, MS, and elemental analysis. The results of preliminary bioassay showed that the new compounds had an inhibition effect against HCT-8 and Bel-7402 cell lines.*

Keywords Anti-tumor activity; γ-aminopropyl silatrane; phosphoramide; tegafur

INTRODUCTION

N^1-(2-furanidyl)-5-fluorouracil **1** (tegafur) is a potent inhibitor of mammalian cell growth in clinical use. However, the undesirable side effects such as hot sensations, pollakiuria syndrome,[1] and low selectivity between the normal cells and cancer cells has attracted the interests of many medical and chemistry scientists to develop better, new anticancer drugs. There are many reports on synthesizing uracil derivatives containing α-hydroxy phosphonates, phosphonopeptides, glycerophospholipids, phosphoramides, and cyclic thiophosphonates.[2–6] 1-substituted silatrane compounds continue to attract considerable

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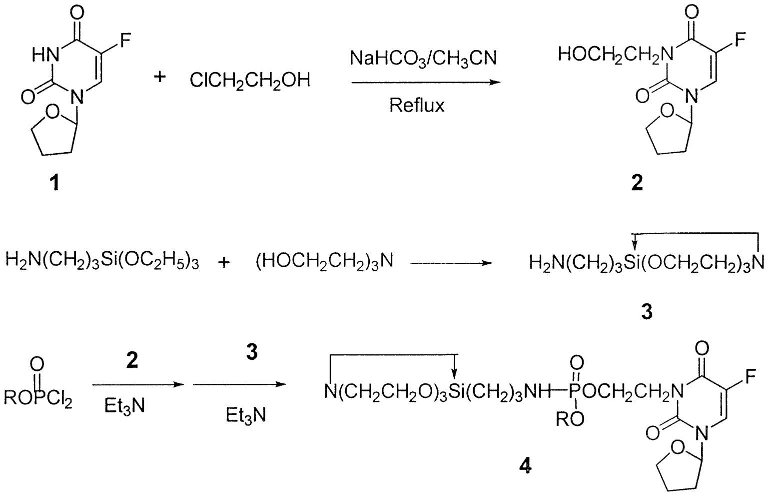
attention due to their wide biological activities such as antitumor activity and special structures.[7–9] In order to improve its antitumor activity and lower its toxicity, we introduced γ-aminopropylsilatrane into tegafur, utilizing a phosphorylation reaction designed to synthesize a number of phosphoramide-tegafur derivatives **4** containing γ-aminopropyl silatrane. The synthetic route is shown in Scheme 1.



SCHEME 1

The results of preliminary biological tests show that some of these new compounds have certain selective anti-tumor activities.

RESULTS AND DISCUSSION

Preparation of the Title Compounds 4

The title compounds **4** were synthesized by the multi-step route outlined in Scheme 1. Most of phosphoramides were usually synthesized by a *one-pot* method, but we found that this was not suitable to synthesize this type of compounds because γ-aminopropyl silatrane is unstable and decomposes to acyclic compounds in acidic media (HCl was formed when phosphoryl dichloride reacted with N^1-(2-furanidyl)-N^3-(hydroxyethyl)-5-fluorouracil). However, the reaction went smoothly when γ-aminopropyl silatrane was added dropwise and slowly to the reaction mixtures with triethyl amine as a catalyst. Moreover, the reaction was remarkably affected by the solvents used. When chloroform and ethyl acetate were used, the yields of products were very low. On the other hand, *N*,*N*-dimethyl formamide resulted in decomposing the

γ-aminopropyl silatrane. Finally, toluene was a suitable solvent for the reaction; the reaction proceeded smoothly and the target compounds **4** were obtained in moderate yields without any byproducts being detected by TLC.

The Structures of the Title Compounds 4

All the products **4** were purified by recrystalization or flash column chromatography on silica gel with a mixture of ethyl acetate and petroleum ether as the eluent. The structure of compounds **4** was confirmed by ^{1}H NMR, ^{31}P NMR, IR spectra, MS, and elemental analysis.

For ^{1}H NMR spectra, because of the formation of the nitrogen- and silicon-coordinated bond and the shielded effects, the hydrogens of carbon nearest to the silicon atom appear upfield with the chemical shifts at 0.4 in contrast of the corresponding protons of γ-aminopropyl[triethoxy]silane at 0.65; moreover, the protons of methylene linking with nitrogen in silatrane appear as triple peaks downfield with the chemical shifts at 2.8 relative to the protons of trihydroxyethylamine at 2.5. Because of coupling with the fluorine atom, the uracil proton exhibited a set of doublet peaks with a coupling constant of 7.6 ppm. 5-position protons of furanyl cycle (5′-H) appears as two sets of multiple peaks. It is probably due to the two protons lying in different chemical environments. For ^{31}P NMR spectra, the phosphorus atom of all compounds displayed one set of a single peak with the chemical shifts in the range of 5–10 ppm.

The IR spectra of all compounds showed normal stretching absorption bands indicating the existence of the N-H (~3285 cm^{-1}), C=O (1680–1710 cm^{-1}), P=O (~1260 cm^{-1}), Si←O (~1052 cm^{-1}, 760 cm^{-1}), P—O—C (~1000 cm^{-1}), and Si←N (~585 cm^{-1}) moiety. The EI mass spectra of compound **4** revealed the existence of the weak molecular ion peaks, but the fragmentation peaks were in accordance with the given structures of products **4**.

Biological Activities

The cell toxicity experiments indicated that the title compounds had some inhibition effect against HCT-8 and Bel7402 cell lines. For example, the ratios of the inhibition against HC7-8 cell lines of compounds **4d** and **4c** were, respectively, 29.33% and 12.36% at a mass concentration of 5.0×10^{-6}, and the inhibitory ratio of Bel7402 cell lines of compounds **4d** was 20.26% at the same concentration. The cell toxicity experiments show that the title compounds have little inhibition against A-549 cell lines.

EXPERIMENTAL

^{1}H NMR and ^{31}P NMR spectra were recorded with a VARIAN MERCURY-PLUS400 spectrometer with TMS and 85% H_3PO_4 as the internal and external reference, respectively, and $CDCl_3$ as the solvent. Mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. IR spectra were measured by a NICOLET NEXUS470 spectrometer. Elemental analysis was performed with an ELEMENTAR Vario ELIIICHNSO elementary analyzer. Melting points were determined with a WRS-1B digital melting point apparatus and were uncorrected.

The reagents and solvents were commercially available and purified according to conventional methods before use. Tegafur was purchased from the Qilu medical factory in Sandong province, and γ-aminopropyl[triethoxy]silane was purchased from the chemical factory in Wuhan University and redistillated before use. Phosphoryl dichlorides were synthesized according to the literatures.[10,11] N^1-(2-furanidyl)-N^3-(hydroxyethyl)-5-fluorouracil **2** was prepared by the reaction of Tegafur with chloroethanol according to literature.[12]

Synthesis of γ-Aminopropyl Silatrane

0.1 mol γ-aminopropyl[triethoxy]silane and 0.1 mol trihydroxyethyl amine were added to 100 mL in a three-necked flask. The resulting mixture was stirred under reflux, and the formed ethanol was distilled during the reaction until no ethanol was produced. The reaction mixture was cooled in a refrigerator and filtered, and a light yellow product was obtained in 86% yield. (m.p. 87–88°C,[13] m.p. 87.2–87.9°C).

General Procedure for the Synthesis of Phosphoramide-Tegafur Derivatives Containing Aminopropyl Silatrane

5 mmol alkoxy(substituted phenoxy)phosphoryl dichloride and 10 mL anhydrous toluene were added to a 50 mL three-necked reaction flask. A solution of 5 mmol N^1-(2-furanidyl)-N^3-(hydroxyethyl)-5-fluorouracil and 6 mmol triethylamine dissolved in 15 mL toluene was added dropwise with cooling in an ice bath. After the addition, the mixture was then stirred at 0°C for 1 h, and continued to stir at room temperature for another 2 h. After removing the triethylammonium chloride, the solution of phosphoryl chloride was added dropwise to the solution of 5 mmol γ-aminopropyl silatrane and 6 mmol triethylamine in 10 mL anhydrous toluene at room temperature. After the addition, the mixtures were allowed to stir at room temperature for 2 h and 50°C for 1 h;

the mixtures were cooled to room temperature, the solid was filtered, and washed with water, and the crude product was recrystallized by anhydrous ethanol or purified by silica gel-flash column chromatography (petroleuom ether/ethyl acetate 1:2 as eluant) to give compounds **4a–h**, yield: 41–67%.

4a ($R{=}CH_3$): colorless crystal, m.p. 166–167°C, yield 41.2%; ^{1}H NMR ($CDCl_3$) δ 0.40 (t, 2H, CH_2Si), 1.60 (m, 2H, $\underline{CH_2}CH_2Si$), 1.79–2.60 (m, 4H, 3′, 4′-H of furanyl), 2.78 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.90 (m, 2H, $PNH\underline{CH_2}$), 3.45 (s, 1H, NH), 3.75 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.80–4.00 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.18–4.38 (m, 5H, $POCH_3$, $POCH_2$), 5.95 (d, br, 1H, 2′-H of furanyl), 7.42(d, 1H, 6-H of uracil, $^3J_{H-F} = 7.2$ Hz); IR (KBr) (υ_{max}/cm^{-1}) 3285 (N-H), 1717 and 1679 (C=O), 1263 (P=O), 1089 and 990 (P—O—C), 1065 and 760 (Si—O), 585(Si←N); MS, m/e (%) 552 (M^+, 1.07), 174 (100), 156 (60.5), 130 (35.2), 71 (20.6), 58 (25.3); Anal. Calcd. For $C_{20}H_{34}O_9N_4FPSi$ (552): C, 43.48; H, 6.16; N, 10.14. Found: C, 43.35; H, 6.20; N, 9.95.

4b ($R{=}C_2H_5$): white solid, m.p. 160–162°C, yield 51.3%; ^{1}H NMR ($CDCl_3$) δ 0.41 (t, 2H, CH_2Si), 1.30 (t, 3H, CH_3), 1.61 (m, 2H, $\underline{CH_2}CH_2Si$), 1.79–2.01 (m, 4H, 3′, 4′-H of furanyl), 2.80 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.92 (m, 2H, $PNH\underline{CH_2}$), 3.50 (s, 1H, NH), 3.78 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.83–4.05 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.20–4.35 (m, 4H, $PO\underline{CH_2}CH_3$, $POCH_2$), 5.94 (d, br, 1H, 2′-H of furanyl), 7.44(d, 1H, 6-H of uracil, $^3J_{H-F} = 7.6$ Hz); ^{31}P NMR ($CDCl_3$) $\delta = 5.78$; IR (KBr) (υ_{max}/cm^{-1}) 3280 (N-H), 1710 and 1680(C=O), 1270(P=O), 1090 and 980 (P—O—C), 1050 and 760 (Si—O), 591(Si←N); MS, m/e (%) 567 (M + 1, 1.31), 174 (100), 156 (97), 130 (41), 71 (22), 58 (31.3); Anal. Calcd. for $C_{21}H_{36}O_9N_4FPSi$ (566): C, 44.52; H, 6.36; N, 9.89. Found: C, 44.61; H, 6.21; N, 10.24.

4c (R=n-Pr): white solid, m.p. 156–157° C, yield 48.7%; ^{1}H NMR ($CDCl_3$) δ 0.35 (t, 2H, CH_2Si), 0.96 (t, 3H, CH_3), 1.32 (m, 2H, $\underline{CH_2}CH_3$), 1.58 (m, 2H, $\underline{CH_2}CH_2Si$), 1.80–1.98 (m, 4H, 3′, 4′-H of furanyl), 2.80 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.90 (m, 2H, $PNH\underline{CH_2}$), 3.48 (s, 1H, NH), 3.75 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.80–3.95 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.20–4.37 (m, 4H, $PO\underline{CH_2}CH_2CH_3$, $POCH_2$), 5.96 (d, br, 1H, 2′-H of furanyl), 7.50 (d, 1H, 6-H of uracil, $^3J_{H-F} = 7.4$ Hz); IR (KBr) (υ_{max}/cm^{-1}) 3280 (N-H), 1710 and 1675(C=O), 1265(P=O), 1085 and 988 (P—O—C), 1050 and 760 (Si—O), 583(Si ← N); MS, m/e (%) 580 (M^+, 1.16), 174 (100), 156 (54.2), 130 (40.6), 71 (34.6), 58 (23.4); Anal. Calcd. for $C_{22}H_{38}O_9N_4FPSi$ (580): C, 45.52; H, 6.55; N, 9.66. Found: C, 45.83; H, 6.69; N, 9.57.

4d (R=i-Pr): white solid, m.p. 152–154°C, yield 47.5%; ^{1}H NMR ($CDCl_3$) δ 0.40 (t, 2H, CH_2Si), 1.18 (d, 6H, $2CH_3$), 1.60 (m, 2H, $\underline{CH_2}CH_2Si$), 1.78–2.00 (m, 4H, 3′, 4′-H of furanyl), 2.78 (t, 6H,

$Si(OCH_2\underline{CH_2})_3$ N), 2.90 (m, 2H, $PNH\underline{CH_2}$), 3.50 (s, 1H, NH), 3.78 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.80–4.05 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.22–4.40 (m, 3H, $PO\underline{CH}(CH_3)_2$, $POCH_2$), 6.02 (d, br, 1H, 2′-H of furanyl), 7.42 (d, 1H, 6-H of uracil, $^3J_{H-F} = 7.6$ Hz); IR (KBr) (υ_{max}/cm^{-1}) 3278 (N—H), 1715 and 1680 (C=O), 1265(P=O), 1087 and 990 (P—O—C), 1049 and 760 (Si—O), 585(Si ← N); MS, m/e (%) 580 (M^+, 1.21), 174 (100), 156 (50.2), 130 (20.2), 71 (40.35), 58 (28.3); Anal. Calcd. for $C_{22}H_{38}O_9N_4FPSi$ (580): C, 45.52; H, 6.55; N, 9.66. Found: C, 45.66; H, 6.25; N, 9.61.

4e (R=Ph): white solid, m.p. 147–149°C, yield 50.1%; ^1H NMR ($CDCl_3$) δ 0.42 (t, 2H, CH_2Si), 1.58 (m, 2H, $\underline{CH_2}CH_2Si$), 1.80–2.00 (m, 4H, 3′, 4′-H of furanyl), 2.80 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.90 (m, 2H, $PNH\underline{CH_2}$), 3.50 (s, 1H, NH), 3.75 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.80–4.00 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.20–4.30 (m, 2H, $POCH_2$), 5.96 (d, br, 1H, 2′-H of furanyl), 7.22–7.50 (m, 6H, C_6H_5, 6-H of uracil); ^{31}P NMR ($CDCl_3$) $\delta = 10.38$; IR (KBr) (υ_{max}/cm^{-1}) 3282 (N—H), 1710 and 1670 (C=O), 1280(P=O), 1110 and 995 (P—O—C), 1050 and 760 (Si—O), 583(Si ← N); MS, m/e (%) 614 (M^+, 0.05), 174 (100), 156 (57.3), 130 (10.5), 71 (14), 58 (20.1); Anal. Calcd. for $C_{25}H_{36}O_9N_4FPSi$ (614): C, 48.86; H, 5.86; N, 9.12. Found: C, 48.96; H, 5.92; N, 9.25.

4f (R=4-ClPh): colorless crystal, m.p. 144–145°C, yield 67.4%; ^1H NMR ($CDCl_3$) δ 0.38 (t, 2H, CH_2Si), 1.60 (m, 2H, $\underline{CH_2}CH_2Si$), 1.85–2.10 (m, 4H, 3′, 4′-H of furanyl), 2.86 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.91 (m, 2H, $PNH\underline{CH_2}$), 3.56 (s, 1H, NH), 3.75 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.86–4.12 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.21–4.28 (m, 2H, $POCH_2$), 5.93 (d, br, 1H, 2′-H of furanyl), 7.12–7.56 (m, 5H, C_6H_4, 6-H of uracil); IR (KBr) (υ_{max}/cm^{-1}) 3285 (N—H), 1710 and 1680 (C=O), 1280(P=O), 1050 and 990 (P—O—C), 1040 and 760 (Si—O), 585 (Si ← N); MS, m/e (%) 648 (M^+, 0.1), 174 (100), 156 (34), 130 (27.5), 71 (46), 58 (12); Anal. Calcd. for $C_{25}H_{35}O_9N_4ClFPSi$ (648.5): C, 46.26; H, 5.40; N, 8.64. Found: C, 46.14; H, 5.25; N, 8.97.

4g (R = 2, 4-Cl_2Ph): white solid, m.p. 152–153°C, yield 56.5%; ^1H NMR ($CDCl_3$) δ 0.40 (t, 2H, CH_2Si), 1.58 (m, 2H, $\underline{CH_2}CH_2Si$), 1.80–2.05 (m, 4H, 3′, 4′-H of furanyl), 2.78 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.90 (m, 2H, $PNH\underline{CH_2}$), 3.50 (s, 1H, NH), 3.75 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.82–4.10 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.20–4.28 (m, 2H, $POCH_2$), 6.02 (d, br, 1H, 2′-H of furanyl), 7.30–7.85 (m, 4H, C_6H_3, 6-H of uracil); IR (KBr) (υ_{max}/cm^{-1}) 3290 (N—H), 1705 and 1670 (C=O), 1280 (P=O), 1115 and 996 (P—O—C), 1050 and 760 (Si—O), 580(Si ← N); MS, m/e (%) 683 (M^+, weak), 174 (100), 156 (15), 130 (34), 71 (78), 58 (23); Anal. Calcd. for $C_{25}H_{34}O_9N_4Cl_2FPSi$ (683): C, 43.92; H, 4.98; N, 8.20. Found: C, 44.07; H, 5.20; N, 7.96.

4h (R = 3, 4-Cl_2Ph): white solid, m.p. 163–165°C, yield 45.7%; ^1H NMR ($CDCl_3$) δ 0.35 (t, 2H, CH_2Si), 1.50 (m, 2H, $\underline{CH_2}CH_2Si$), 1.82–2.10 (m, 4H, 3′, 4′-H of furanyl), 2.84 (t, 6H, $Si(OCH_2\underline{CH_2})_3$ N), 2.95 (m, 2H, $PNH\underline{CH_2}$), 3.45 (s, 1H, NH), 3.85 (t, 6H, $Si(O\underline{CH_2}CH_2)_3$ N), 3.80–4.15 (m, 4H, $N\underline{CH_2}CH_2OP$, 5′-H of furanyl), 4.20–4.30 (m, 2H, $POCH_2$), 6.00 (d, br, 1H, 2′-H of furanyl), 7.35–7.88 (m, 4H, C_6H_3, 6-H of uracil); IR (KBr) (υ_{max}/cm^{-1}) 3280 (N—H), 1700 and 1670 (C=O), 1277(P=O), 1110 and 990 (P—O—C), 1050 and 760 (Si—O), 560 (Si ← N); MS, m/e (%) 683 (M^+, 0.1), 174 (100), 156 (64), 130 (45), 71 (28), 58 (39.5); Anal. Calcd. for $C_{25}H_{34}O_9N_4Cl_2FPSi$ (683): C, 43.92; H, 4.98; N, 8.20. Found: C, 43.79; H, 5.11; N, 8.43.

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