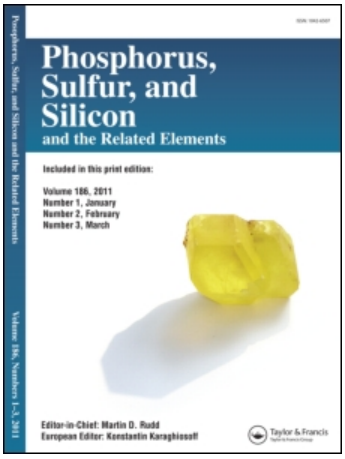

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Synthesis of Novel Phosphonotripeptides Containing Uracil or Thymine Group

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SYNTHESIS OF NOVEL PHOSPHONOTRIPEPTIDES CONTAINING URACIL OR THYMINE GROUP

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In order to search for highly active anticancer and antiviral agent, a new type of novel phosphonotripeptides containing a uracil or thymine group was synthesized by means of two-step peptide coupling reaction with DCC as the dehydrating agent and N-hydroxysuccinimide as the activating agent of the carboxyl group. All products were characterized by ^{1}H NMR, ^{31}P NMR, IR spectra, and elemental analyses. The results of bioassay show that compound 8 g possesses potential anticancer activity.

Keywords: Anticancer; coupling reaction; phosphonopeptide

INTRODUCTION

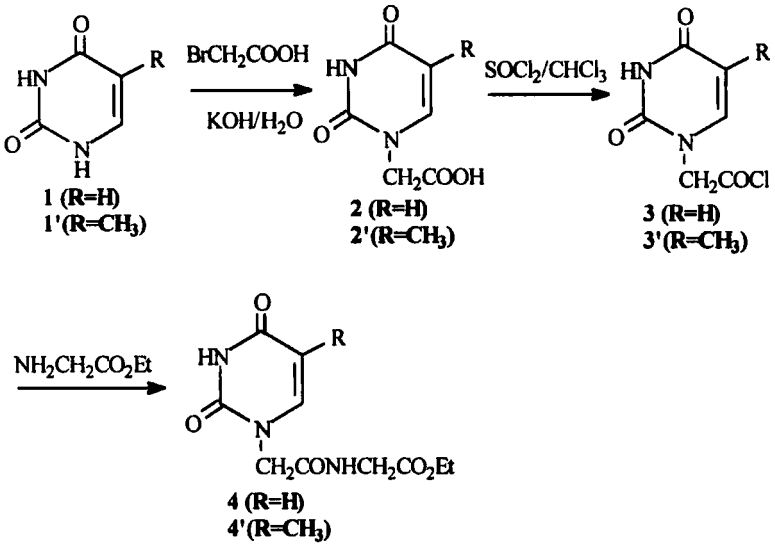
The introduction of a peptide backbone into some biologically active molecules is very attractive to organic chemists. For example, Peptide Nucleic Acids (PNAs),[1] used as potential antisense therapeutic and diagnostic tools,[2–5] were synthesized by introducing a peptide group into the nucleoside structure. As mimics of amino acids and peptides, α-aminophosphonic acids and phosphonopeptides exhibit various interesting biological activities.[6–9] Some of them have been used as anticancer, antibacterial, and antibiotic agents.[10–12]

Various uracil and thymine derivatives have been synthesized and tested as anticancer or antiviral drugs.[13–17] Pyrimidin-1-yl or purin-9-yl phosphonic acids also were found to be a new class of antiviral agents with a broad spectrum of activities against retroviruses and DNA virus for inhibiting DNA polymerase.[18,19]

As part of our research program[20,21] and interest in the development of new biologically active phosphonopeptide compounds, we designed and synthesized a number of novel phosphonotripeptides containing a uracil or thymine group.

RESULT AND DISCUSSION

The key intermediates (**4** and **4'**) were synthesized by the route shown in Scheme 1. The tymin-1-ylacetic acid **2** or uracil-1-ylacetic acid **2'** was

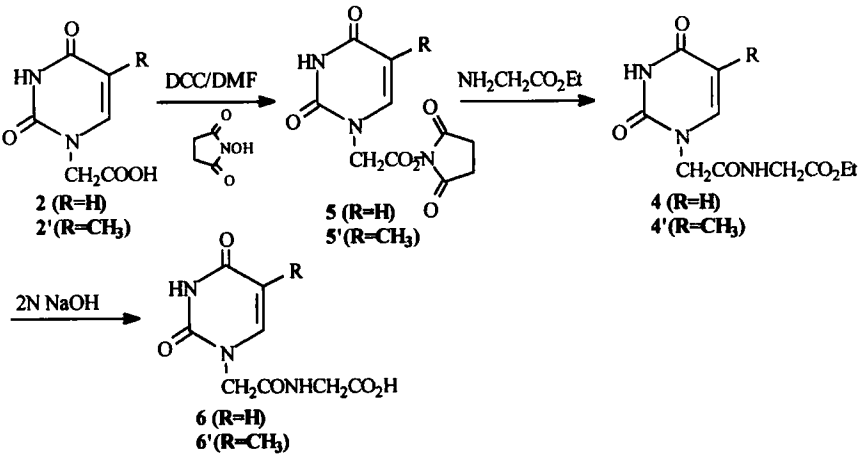


SCHEME 1

obtained by the reaction of bromoacetic acid with thymine **1** (or uracil **1'**) in the water at 40°C in the presence of potassium hydroxide.[22] The compounds **2** and **2'** were converted into the acetyl chlorides **3** and **3'** by the addition of $SOCl_2$ to the solution of the acetic acids **2** and **2'** in $CHCl_3$ at 0°C. The glycine ethyl ester was then added to the acetyl chloride **3** (or **3'**) to afford the intermediates **4** and **4'** in poor yields (48% and 53%).

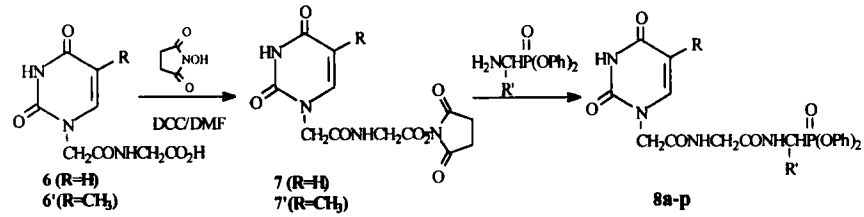
In order to improve the yields of the products, the route shown in Scheme 2 was selected. DCC and N-hydroxysuccinimide were used as the dehydrating agent and the activating reagent of the carboxyl group, respectively. Thus, the acetic acids **2** and **2'** formed the intermediates **5** and **5'** by the action of DCC/N-hydroxysuccinimide, then glycine ethyl esters were added to the crude intermediates **5** and **5'** to produce compounds **4** and **4'** smoothly and in good yields (82% and 85%). The compounds **4** and **4'** were hydrolyzed in 2N NaOH to give the acids **6** and **6'** in the yield of 96% and 98%, respectively.

Using the same general procedure as above, the title compounds (**8a-p**) were obtained by the reaction of the acids **6** and **6'** with



SCHEME 2

α-aminophosphonic acid esters[23,24] in presence of DCC as dehydrating agent and N-hydroxysuccinimide as the activating agent of the carboxyl group (Scheme 3).



8a. R=CH_3, R'=C_6H_5; **8b.** R=CH_3, R'=C_6H_4-Cl-4; **8c.** R=CH_3, R'=C_6H_4-OMe-2; **8d.** R=CH_3, R'=C_6H_4-NO_2-4; **8e.** R=CH_3, R'=C_6H_4-OMe-4; **8f.** R=CH_3, R'=C_6H_3-OCH_2O-3, 4; **8g.** R=CH_3, R'=C_6H_4-NO_2-3; **8h.** R=CH_3, R'=C_6H_4-Me-4; **8i.** R=H, R'=C_6H_5; **8j.** R=H, R'=C_6H_4-Cl-4; **8k.** R=H, R'=C_6H_4-OMe-2; **8l.** R=H, R'=C_6H_4-NO_2-4; **8m.** R=H, R'=C_6H_4-OMe-4; **8n.** R=H, R'=C_6H_3-OCH_2O-3, 4; **8o.** R=H, R'=C_6H_4-NO_2-3; **8p.** R=H, R'=C_6H_4-Me-4

SCHEME 3

It was found that two main factors affected the conversion of **6** to **8**. One is the apparent steric hindrance of an α-aryl group having a bulky substituent at the ortho-position. Another is the electronic effect of the substituent of the α-aryl groups. The electron-withdrawing groups

decrease the nucleophilicity of the amino group. The yields of all products containing the nitro group were lower than those of other products. In fact, the desired products containing a nitro group at the ortho-position were not obtained. All the products (**8a-p**) were purified by flash column chromatography on silica-gel.

The molecular structures of the compounds (**8a-p**) were confirmed by **^{1}H NMR, ^{31}P NMR, IR** spectroscopy, and elemental analyses. The experimental data for **8a-p** are listed in Tables I and II.

In the **^{1}H NMR** spectra of compounds **8**, the methylene protons of the resonances of the acetyl group and the glycine group appear as a characteristic singlet peaks at δ 4.34–4.36 ppm and a doublet peaks at δ 3.82–3.90 ppm . It is noteworthy that the protons of the CH group linking with the phosphorus atom exhibit doublet of doublet peaks at δ 5.84–6.35 ppm ($^2J_{H-C-P}$ = 21–27Hz) due to the splitting and coupling of both the phosphorus atom and the hydrogen atom of the amino group. The **^{1}H NMR** spectrum also reveals a two sets of peaks at δ 1.72–1.73 ppm (singlet signals), δ 11.24–11.32 ppm (singlet signal) and δ 5.54–5.58 ppm (doublet signal), δ 11.18–11.30 ppm (singlet signal) supporting the thymine and uracil structure, respectively. The hydrogen at position 6 of thymine and uracil appear in the range of the peaks of the hydrogens of the aryl groups. The **^{31}P NMR** spectrum of all products exhibit chemical shifts at δ 18.25–20.06 ppm. The **IR** spectra of compounds **6** show normal stretching absorption bands to indicate the existence of the groups NH (3324 ~ 3453 cm^{-1}), C=O (1631 ~ 1673 cm^{-1}), P=O (1204 ~ 1252 cm^{-1}), P—O—C (1158 ~ 1186 cm^{-1}).

BIOLOGICAL ACTIVITY

The preliminary biological activities were determined for compounds **8a-p**. The anticancer activities given in TABLE III indicate that compound **8 g** has potential inhibitory activities on HL-60 (human leukemia-60) cell.

EXPERIMENTAL

Elemental analyses were performed with a CHNCORDERD MT-3 elementary analyzer. NMR spectra were recorded with a BRUKER AC-P200 spectrometer with TMS and 85% H_3PO_4 as internal and external references, respectively, and DMSO as the solvent. An SHIMADZU-435 instrument was used to measure IR spectra. Melting points

TABLE I Experimental Data of Compounds **8a–p**

No	IR (v, cm^{-1}) (NH),	(C=O),	(P=O),	(P-O-C)	Yield (%)	State	m.p. (°C)	Element analyses C, H, N (calculation)
8a	3413	1670	1210	1170	75	Solid	245(dec.)	59.65, 4.97, 9.86(59.77, 4.84, 9.96)
8b	3324	1668	1214	1178	72	Solid	254(dec.)	56.00, 4.27, 9.32(56.33, 4.39, 9.38)
8c	3324	1664	1219	1186	68	Solid	231(dec.)	58.52, 5.01, 9.47(58.78, 4.39, 9.46)
8d	3412	1671	1204	1166	57	Solid	251(dec.)	55.02, 4.18, 11.74(55.36, 4.31, 11.53)
8e	3437	1665	1219	1185	77	Solid	239(dec.)	58.45, 5.16,9.27(58.78, 4.93, 9.46)
8f	3378	1669	1255	1163	73	Solid	242(dec.)	57.85, 4.78, 9.39(57.43, 4.49, 9.24)
8g	3316	1665	1208	1186	55	Solid	249(dec.)	55.26, 4.35, 11.27(55.36, 4.31, 11.53)
8h	3423	1664	1213	1176	79	Solid	254(dec.)	60.20, 5.04, 9.91(60.42, 5.07, 9.72)
8i	3340	1670	1212	1172	74	Solid	235(dec.)	58.77, 4.68, 10.49(59.12, 4.59, 10.21)
8j	3422	1673	1211	1186	73	Solid	246(dec.)	55.36,4.10, 9.57(55.63, 4.15, 9.61)
8k	3427	1631	1207	1184	68	Solid	236(dec.)	58.23, 4.54, 9.32(58.23, 4.92, 9.70)
8l	3416	1672	1252	1172	56	Solid	258(dec.)	54.35, 4.03, 11.70(54.60, 4.08, 11.80)
8m	3453	1671	1209	1158	76	Solid	238(dec.)	57.92, 4.58, 9.61(58.24, 4.54, 9.70)
8n	3341	1668	1214	1163	71	Solid	226(dec.)	56.54, 4.45, 9.08(56.76, 4.25, 9.46)
8o	3415	1671	1209	1158	54	Solid	223(dec.)	54.76, 4.19, 11.51(54.64, 4.08, 11.80)
8p	3444	1670	1212	1171	78	Solid	252(dec.)	59.95, 4.92, 9.85(59.78, 4.84, 9.96)

TABLE II ^{1}H NMR (DMSO, δ, ppm) and ^{31}P NMR (DMSO, δ, ppm) of Compounds **8a–p**

No	^{31}P NMR	^{1}H NMR
8a	19.80	1.72(s, 3H, =CC**H**$_3$) 3.89(d, 2H, $^3J_{HCNH}$ = 5.8 Hz, NHC**H**$_2$) 4.34(s, 2H, C**H**$_2$CO) 5.85(dd., 1H, PC**H**, $^2J_{PCH}$ = 21.6 Hz, $^3J_{HCNH}$ = 10.0 Hz) 7.41-6.90(m, 16H, 3 × C$_6$**H**$_5$ + C=C**H**N) 8.47(t, 1H, $^3J_{HCNH}$ = 5.8 Hz, N**H**CH$_2$) 9.36(d, 1H, $^3J_{HCNH}$ = 10.0 Hz, N**H**CHP) 11.28(s, br, 1H, (CO)$_2$N**H**)
8b	19.05	1.72(s, 3H, =CC**H**$_3$) 3.82(d, 2H, $^3J_{HCNH}$ = 5.9 Hz, NHC**H**$_2$) 4.34(s, 2H, C**H**$_2$CO) 5.92(dd., 1H, $^2J_{PCH}$ = 21.8 Hz, $^3J_{HCNH}$ = 9.0 Hz, PC**H**) 7.60-6.96(m, 15H, 2×C$_6$**H**$_5$ + 4-ClC$_6$**H**$_4$ + C=C**H**N) 8.42(t, 1H, $^3J_{HCNH}$ = 5.9 Hz, N**H**CH$_2$) 9.31(d, 1H, $^3J_{HCNH}$ = 9.0 Hz, N**H**CHP) 11.28(s, br, 1H, (CO)$_2$N**H**)
8c	20.04	1.72(s, 3H, =CC**H**$_3$) 3.76(s, 3H, C**H**$_3$OC$_6$H$_4$) 3.85(d, 2H, $^3J_{HCNH}$ = 4.8 Hz, NHC**H**$_2$) 4.33(s, 2H, C**H**$_2$CO) 6.35(dd., 1H, $^2J_{PCH}$ = 22.0 Hz, $^3J_{HCNH}$ = 9.3 Hz, PC**H**) 7.70-6.83(m, 15H, 2 × C$_6$**H**$_5$ + 2-MeOC$_6$**H**$_4$ + C=C**H**N) 8.45(t, 1H, $^3J_{HCNH}$ = 4.8 Hz, N**H**CH$_2$) 9.10(d, 1H, $^3J_{HCNH}$ = 9.3 Hz, N**H**CHP) 11.24(s, br, 1H, (CO)$_2$N**H**)
8d	18.25	1.72(s, 3H, =CC**H**$_3$) 3.88(d, 2H, $^3J_{HCNH}$ = 5.6 Hz, NHC**H**$_2$) 4.34(s, 2H, C**H**$_2$CO) 6.35(dd., 1H, $^2J_{PCH}$ = 22.7 Hz, $^3J_{HCNH}$ = 9.9 Hz, PC**H**) 8.26-7.04(m, 15H, 2 × C$_6$**H**$_5$ + 4-NO$_2$C$_6$**H**$_4$ + C=C**H**N) 8.51(t, 1H, $^3J_{HCNH}$ = 5.6 Hz, N**H**CH$_2$) 9.94(d, 1H, $^3J_{HCNH}$ = 9.9 Hz, N**H**CHP) 11.32(s, br, 1H, (CO)$_2$N**H**)
8e	20.06	1.73(s, 3H, =CC**H**$_3$) 3.75(s, 3H, C**H**$_3$OC$_6$H$_4$) 3.87(d, 2H, $^3J_{HCNH}$ = 5.5 Hz, NHC**H**$_2$) 4.34(q, 2H, C**H**$_2$CO) 5.85(dd., 1H, $^2J_{PCH}$ = 23.7 Hz, $^3J_{HCNH}$ = 9.8, PC**H**) 7.52-6.92(m, 15H, 2 × C$_6$**H**$_5$ + 4-MeOC$_6$**H**$_4$ + C=C**H**N) 8.49(t, 1H, $^3J_{HCNH}$ = 5.5 Hz, N**H**CH$_2$) 9.28(d, 1H, $^3J_{HCNH}$ = 9.8 Hz, N**H**CHP) 11.26(s, br, 1H, (CO)$_2$N**H**)
8f	19.46	1.73(s, 3H, =CC**H**$_3$) 3.88(d, 2H, $^3J_{HCNH}$ = 5.6 Hz, NHC**H**$_2$) 4.34(s, 2H, C**H**$_2$CO) 5.86(dd., 1H, PC**H**, $^2J_{PCH}$ = 23.1 Hz, $^3J_{HCNH}$ = 9.7 Hz) 6.02(s, 2H, OC**H**$_2$O) 7.41-6.94(m, 14H, 2 × C$_6$**H**$_5$ + 3,4-OCH$_2$OC$_6$**H**$_3$ + C=C**H**N) 8.42(t, 1H, $^3J_{HCNH}$ = 5.6 Hz, NHC**H**$_2$) 9.31(d, 1H, $^3J_{HCNH}$ = 9.7 Hz, N**H**CHP) 11.24(s, br, 1H, (CO)$_2$N**H**)
8g	18.52	1.72(s, 3H, =CC**H**$_3$) 3.90(d, 2H, $^3J_{HCNH}$ = 5.4 Hz, NHC**H**$_2$) 4.33(s, 2H, C**H**$_2$CO) 6.21(dd., 1H, $^2J_{PCH}$ = 22.6 Hz, $^3J_{HCNH}$ = 9.2 Hz, PC**H**) 8.61-6.99(m, 16H, 2 × C$_6$**H**$_5$ + 3-NO$_2$C$_6$**H**$_4$ + C=C**H**N + N**H**CH$_2$) 9.56(d, 2H, $^3J_{HCNH}$ = 9.2 Hz, N**H**CHP) 11.30(s, br, 1H, (CO)$_2$N**H**)
8h	19.74	1.72(s, 3H, =CC**H**$_3$) 2.29(s, 3H, C**H**$_3$C$_6$H$_4$) 3.82(d, 2H, $^3J_{HCNH}$ = 5.7 Hz, NHC**H**$_2$) 4.33(s, 2H, C**H**$_2$CO) 5.88(dd., 1H, $^2J_{PCH}$ = 23.3 Hz, $^3J_{HCNH}$ = 9.9 Hz, PC**H**) 7.44-6.92(m, 15H, 2 × C$_6$**H**$_5$ + 4-MeC$_6$**H**$_4$ + C=C**H**N) 8.46(t, 1H, $^3J_{HCNH}$ = 5.7 Hz, N**H**CH$_2$) 9.30(d, 1H, $^3J_{HCNH}$ = 9.9 Hz, N**H**CHP) 11.18(s, br, 1H, (CO)$_2$N**H**)
8i	19.60	3.88(d, 2H, $^3J_{HCNH}$ = 5.8 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.56(d, 1H, $^3J_{HCCH}$ = 7.7 Hz, C**H**=CN) 5.89(dd., H, $^2J_{PCH}$ = 23.8 Hz, $^3J_{HCNH}$ = 8.6 Hz, PC**H**) 7.67-6.97(m, 16H, 3 × C$_6$**H**$_5$ + C=C**H**N) 8.46(t, 1H, $^3J_{HCNH}$ = 5.8 Hz, N**H**CH$_2$) 9.68(d, 1H, $^3J_{HCNH}$ = 8.6 Hz, N**H**CHP) 11.27(s, br, 1H, (CO)$_2$N**H**)

TABLE II ^{1}H NMR (DMSO, δ, ppm) and ^{31}P NMR (DMSO, δ, ppm) of Compounds **8a–p** (*Continued*)

No	^{31}P NMR	^{1}H NMR
8j	19.90	3.84(d, 2H, $^{3}J_{HCNH}$ = 5.8 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.54(d, 1H, $^{3}J_{HCCH}$ = 7.5 Hz, C**H**=CN) 5.90(dd., 1H, $^{2}J_{PCH}$ = 23.2 Hz, $^{3}J_{HCNH}$ = 7.5 Hz, PC**H**) 7.62-6.82(m, 15H, 2 × C$_6$**H**$_5$ + 4-ClC$_6$**H**$_4$ + C=C**H**N) 8.46(t, 1H, $^{3}J_{HCNH}$ = 5.8 Hz, N**H**CH$_2$) 9.78(d, 1H, $^{3}J_{HCNH}$ = 7.5 Hz, N**H**CHP) 11.24(s, br, 1H, (CO)$_2$N**H**)
8k	19.89	3.76(s, 3H, C**H**$_3$OC$_6$H$_4$) 3.87(d, 2H, $^{3}J_{HCNH}$ = 5.6 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.58(d, 1H, $^{3}J_{HCCH}$ = 7.8 Hz, C**H**=CN) 6.29(dd., 1H, $^{2}J_{PCH}$ = 23.3 Hz, $^{3}J_{HCNH}$ = 9.3 Hz, PC**H**) 7.60-6.85(m, 15H, 2 × C$_6$**H**$_5$ + 2-MeOC$_6$**H**$_4$ + C=C**H**N) 8.52(t, 1H, $^{3}J_{HCNH}$ = 5.6 Hz, N**H**CH$_2$) 9.52(d, 1H, $^{3}J_{HCNH}$ = 9.3 Hz, N**H**CHP) 11.28(s, br, 1H, (CO)$_2$N**H**)
8l	18.33	3.86(d, 2H, $^{3}J_{HCNH}$ = 5.9 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.56(d, 1H, $^{3}J_{HCCH}$ = 7.7 Hz, C**H**=CN) 6.35(dd., 1H, $^{2}J_{PCH}$ = 23.1 Hz, $^{3}J_{HCNH}$ = 9.1 Hz, PC**H**) 7.65-6.84(m, 15H, 2 × C$_6$**H**$_5$ + 4-NO$_2$C$_6$**H**$_4$ + C=C**H**N) 8.52(t, 1H, $^{3}J_{HCNH}$ = 5.9 Hz, N**H**CH$_2$) 9.46(d, 1H, $^{3}J_{HCNH}$ = 9.1 Hz, N**H**CHP) 11.24(s, br, 1H, (CO)$_2$N**H**)
8m	19.96	3.76(s, 3H, C**H**$_3$OC$_6$H$_4$) 3.88(d, 2H, $^{3}J_{HCNH}$ = 5.7 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.58(d, 1H, $^{3}J_{HCCH}$ = 7.7 Hz, C**H**=CN) 5.84(dd., 1H, $^{2}J_{PCH}$ = 23.4 Hz, $^{3}J_{HCNH}$ = 9.9 Hz, PC**H**) 7.54-6.90(m, 15H, 2 × C$_6$**H**$_5$ + 4-MeOC$_6$**H**$_4$ + C=C**H**N) 8.50(t, 1H, $^{3}J_{HCNH}$ = 5.7 Hz, N**H**CH$_2$) 9.28(d, 1H, $^{3}J_{HCNH}$ = 9.9 Hz, N**H**CHP) 11.24(s, br, 1H, (CO)$_2$N**H**)
8n	19.68	3.88(d, 2H, $^{3}J_{HCNH}$ = 5.5 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.58(d, 1H, $^{3}J_{HCCH}$ = 7.7 Hz, C**H**=CN) 5.89(dd., 1H $^{2}J_{PCH}$ = 22.9 Hz, $^{3}J_{HCNH}$ = 9.1 Hz, PC**H**,) 6.02(s, 2H, OC**H**$_2$O) 7.41-6.90(m, 14H, 2 × C$_6$**H**$_5$ + 3,4-OCH$_2$OC$_6$**H**$_3$ + C=C**H**N) 8.46(t, 1H, $^{3}J_{HCNH}$ = 5.5 Hz, N**H**CH$_2$) 9.31(d, 1H, $^{3}J_{HCNH}$ = 9.1 Hz, N**H**CHP), 11.20(s, br, 1H, (CO)$_2$N**H**)
8o	18.65	3.90(d, 2H, $^{3}J_{HCNH}$ = 5.6 Hz, NHC**H**$_2$) 4.36(q, 2H, C**H**$_2$CO) 5.56(d, 1H, $^{3}J_{HCCH}$ = 7.7 Hz, C**H**=CN) 6.21(dd., 1H, $^{2}J_{PCH}$ = 27.7 Hz, $^{3}J_{HCNH}$ = 9.2 Hz, PC**H**) 8.55-7.01(m, 16H, 2 × C$_6$**H**$_5$ + 3-NO$_2$C$_6$**H**$_4$ + C=C**H**N+N**H**CH$_2$) 9.76(d, 1H, $^{3}J_{HCNH}$ = 9.2 Hz, N**H**CHP) 11.26(s, br, 1H, (CO)$_2$N**H**)
8p	19.90	2.31(s, 3H, C**H**$_3$C$_6$H$_4$) 3.81(d, 2H, $^{3}J_{HCNH}$ = 5.8 Hz, NHC**H**$_2$) 4.36(s, 2H, C**H**$_2$CO) 5.55(d, 1H, $^{3}J_{HCCH}$ = 7.4 Hz, C**H**=CN) 5.86(dd., 1H, $^{2}J_{PCH}$ = 23.5 Hz, $^{3}J_{HCNH}$ = 9.4 Hz, PC**H**) 7.50-6.93(m, 15H, 2 × C$_6$**H**$_5$ + 4-MeC$_6$**H**$_4$ + C=C**H**N) 8.48(t, 1H, $^{3}J_{HCNH}$ = 5.8 Hz, N**H**CH$_2$) 9.31(d, 1H, $^{3}J_{HCNH}$ = 9.4 Hz, N**H**CHP) 11.30(s, br, 1H, (CO)$_2$N**H**)

TABLE III Inhibitory Effects of **8a–p** (10^{-5} M) on cell line (HL-60)

Compds	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**	**8i**	**8j**	**8k**	**8l**	**8m**	**8n**	**8o**	**8p**
Inhibition rate (HL-60) %	57	69	79	53	48	59	86	63	45	51	56	44	41	46	67	54

were determined with a Thomas-Hoover melting point apparatus and the thermometer was uncorrected. Column chromatography was performed on silica gel GF_{254} (Qingdao Haiyang Chemical Group Co. of China).

Synthesis of Thymin-1-yl Acetic Acid 2 or Uracil-1-yl Acetic acid 2′

Thymine or uracil (30 mmol) was dissolved in a solution of potassium hydroxide (6.45 g, 115 mmol) in 20 ml of water. While this solution was warmed in a 45°C water bath, a solution of bromacetic acid (6.25 g, 45 mmol) in 10 ml of water was added over 30 min. The reaction mixture was stirred for another 4 h at this temperature. It was allowed to cool to room temperature and the pH was adjusted to 5.5 with concentrated HCl. The solution was then cooled in a refrigerator for 2 h. Any precipitate (unreacted thymine or uracil) formed was removed by filtration. The solution was then adjusted to pH = 2 with cocn. HCl and placed in a freezer for 2 h. The white precipitates were collected by filtration and dried in a vacuum oven at 40°C for 6 h. The yields were 86% and 91% of theoretical, based on thymine and uracil, respectively. **2**: m.p. > 270°, ^{1}H NMR 4.40(s, 2H) 5.57(d, 1H, $^3J_{HCCH} = 7.9$Hz) 7.59(d, 1H, $^3J_{HCCH} = 7.9$Hz) 11.33(s, 1H); **2′**: m.p. > 270°, ^{1}H NMR 1.74(s, 3H) 4.34(s, 2H) 7.47(s, 1H) 11.31(s, 1H).

Synthesis of [(Uracil-1-yl or Thymin-1-yl)methylformyl] aminomethylformic Acid Ethyl Esters (4 or 4′)

The thymin-1-yl acetic acid **2** or uracil-1-yl acetic acid **2′** (10 mmol) and N-hydroxysuccinimide (1.15 g, 10 mmol) were dissolved in 25 ml of DMF. While this solution was cooled in an ice bath, a solution of DCC (2.27 g, 11 mmol) in DMF (15 ml) was added dropwise over 40 min at 0°C under N_2. The mixture was allowed to warm to room temperature and stirred for 2 h; the glycine acid ethyl ester was added to the reaction mixture and stirring was continued for 18 h. The precipitate was filtrated off. The solvent was removed under reduced pressure from the filtrate and the residue was then purified by flash chromatography on silica gel ($CHCl_3$: CH_3OH = 15:1) to give **4** and **4′**. **4**: yield of 82%, m.p. 211–212°C; ^{1}H NMR (DMSO) 1.18(t, 3H, $^3J_{HCCH} = 6.9$Hz) 3.86(d, 2H, $^3J_{HNCH} = 5.9$Hz) 4.08(q, 2H, $^3J_{HCCH} = 6.9$Hz) 4.39(s, 2H) 5.55(d, 1H, $^3J_{HCCH} = 8.0$Hz) 7.54(d, 1H, $^3J_{HCCH} = 8.0$Hz) 8.61(d, 1H, $^3J_{HNCH} = 5.9$Hz) 11.24(s, br, 1H). **4′**: yield of 85%; m.p. 225–226°C; ^{1}H NMR(DMSO) 1.18(t, 3H, $^3J_{HCCH} = 7.2$Hz) 1.73(s, 3H) 3.85(d, 2H, $^3J_{HNCH} = 5.8$Hz) 4.08(q, 2H, $^3J_{HCCH} = 7.2$Hz) 4.34(s, 2H) 7.42(s, ^{1}H) 8.58(d, 1H, $^3J_{HNCH} = 5.8$Hz) 11.25(s, br, 1H).

Synthesis of [(Uracil-1-yl or Thymin-1-yl)methylformyl] aminomethylformic Acids (6 or 6′)

The compounds **4** or **4′** (10 mmol) was dissolved in 20 ml of 2N NaOH. The mixture was stirred at room temperature for 4 h. This was then acidified to pH 2 with conc. HCl and put in a freezer for 3 h. The precipitates were collected by filtration and dried in a vacuum oven at 50°C for 24 h to give **6** and **6′**. **6**: yield of 96%, m.p. > 270°C; ^{1}H NMR (DMSO) 3.81(d, 2H, $^3J_{HNCH} = 5.8$Hz) 4.36(s, 2H) 5.56(d, 1H, $^3J_{HCCH} = 7.7$Hz) 7.52(d, 1H, $^3J_{HCCH} = 7.7$Hz) 8.51(d, 1H, $^3J_{HNCH} = 5.8$Hz) 11.24 (s, br, 1H); **6′**: yield of 98%; m.p. > 270°C; ^{1}H NMR(DMSO) 1.74(s, 3H) 3.79(d, 2H, $^3J_{HNCH} = 5.9$Hz) 4.33(s, 2H) 7.42(s, 1H) 8.48(d, 1H, $^3J_{HNCH} = 5.9$Hz) 11.25(s, br, 1H).

Synthesis of α-{[(Uracil-1-yl or Thymin-1-yl)methylformyl] aminomethylformyl}amino-α-arylmethyl-O,O-diphenyl Phosphonates (8a–p): General Procedure

The acid **6** or acid **6′** (1 mmol) and N-hydroxysuccinimide (0.12 g, 1 mmol) were dissolved in 15 ml of DMF. While this solution was cooled in an ice bath, a solution of DCC (0.25 g, 1.2 mmol) in DMF (10 ml) was added dropwise over 40 min at 0°C under N_2. The mixture was allowed to warm to room temperature and stirred for 2 h; the α-aminophosphonate[23,24] was added to the reaction mixture and stirring was continued for 24 h. The precipitate was filtrated off. The solvent was removed under reduced pressure from the filtrate and the residue was then purified by flash chromatography on silica gel ($CHCl_3$: CH_3OH = 10:1) to give the title compounds **8a–p**. The appropriate experimental data are listed in Tables I and II.

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