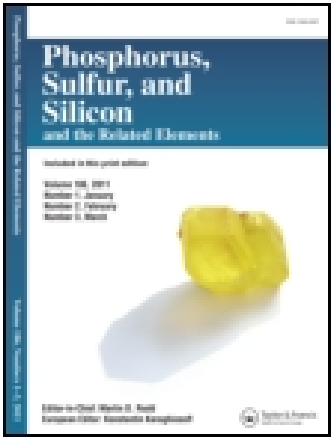

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5-Fluorouracil Derivatives Containing α-Hydroxy Phosphonates

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5-Fluorouracil Derivatives Containing α-Hydroxy Phosphonates

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In order to find high acitivity and low toxicity antitumor drug-lead compounds, 13 novel N^1*-(2-furanidyl)-*N^3*-(*O,O*-dialkylphosphonyl aryl (alkyl)methoxycarbonylmethyl)-5-fluorouracils were synthesized via phase-transferred catalytic reactions of chloroacetyloxyalkyl phosphonates* **2** *with* N^1*-(2-furanidyl)-5-fluorouracil. The structures of the products were confirmed by* ^{1}*H NMR,* ^{31}*P NMR, IR, and MS spectra and elemental analyses. The results of preliminary bioassay showed that the new compounds possess some extent of inhibitory effect against HCT-8 and Bel-7402 cell lines and good fungicidal activities.*

Keywords α-hydroxy phosphonates; fungicidal activities; N^1-(2-furanidyl)-5-fluorouracil

INTRODUCTION

N^1-(2-furanidyl)-5-fluorouracil (Tegafur) is a potent inhibitor of mammalian cell growth in clinical use. However, undesirable side effects such as hot sensation and pollakiuria syndrome[1] and low selectivity between normal cells and cancer cells has attracted interests of many medical and chemical scientists to develop better, new antitumor drugs. There are many reports on synthesizing

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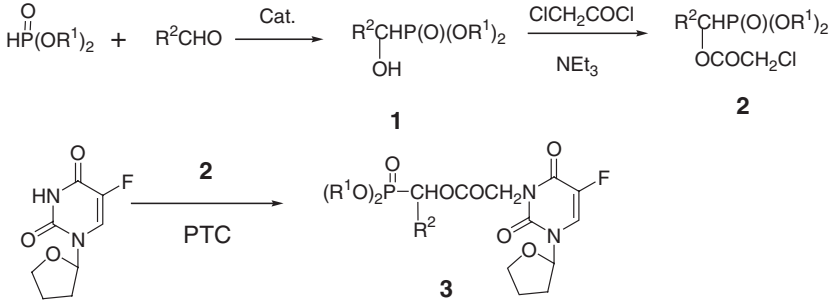

R^1=CH_3; R^2=CH_3, Ph, 2-ClPh, 2-CH_3OPh, 4-ClPh, 4-CH_3OPh, 3, 4-Cl_2Ph
R^1=C_2H_5; R^2= Ph, 4-ClPh, 4-CH_3OPh, 2-furyl, 2, 4-Cl_2Ph, 3, 4-Cl_2Ph

SCHEME 1

5-fluorouracil derivatives containing α-hydroxy phosphonates, phosphonopeptides, and cyclic thiophosphonates.[2–5] As a mimic of α-hydroxy acids, α-hydroxy phosphonates and their derivatives represent an important class of organophosphorus compounds that continue to attract considerable attention due to their wide biological activities and extensive applications in organic and medical chemistry. In an attempt to search for novel high activities and low-toxicity anti-tumor drug-lead compounds, we designed and synthesized a type of N^1-(2-furanidyl)-5-fluorouracil derivatives containing α-hydroxy phosphonates **3**. The synthetic route is shown in Scheme 1.

The results of preliminary biological bioassay show that some of these new compounds have certain selective anti-tumor activities and good fungicidal activities.

RESULTS AND DISCUSSION

Synthesis and Structure of the Title Compounds

The title compounds **3** were synthesized by the multistep route outlined in Scheme 1. For converting aldehydes to α-hydroxy alkyl(aryl)methylphosphonates **1**, both a solid base (1:1 KF/Al_2O_3) and an organic base (such as triethylamine) were used as the catalyst. When KF/Al_2O_3 was used, compounds **1** were given in better yields than triethylamine. Moreover, the addition reaction was affected by the inductive effect of the carbonyl compounds as well as the stereohindered effect. For example, aromatic aldehydes gave a better yield than aliphatic aldehydes. In the same substituent, the yields decreased according to the order of *para*, *meta*, and *ortho* one. Moreover, the yields

were better using *O,O*–dimethyl phosphite as the starting material than *O,O*–diethyl phosphite.

We tried to prepare the target compounds **3** in a homogeneous reaction condition (KOH/DMF, 50–55°C), but the yield of the product was very low. However, improving the reaction temperature led to cleavage of the furanyl ring from N^1-(2-furanidyl)-5-fluorouracil. It is noteworthy that the reaction took place smoothly under the two-phase catalytic system of chloroform and water using tetrabutyl ammonium bromide as the phase-transferred catalyst, and the target compounds **3** were obtained in better yields without byproducts being detected by TLC.

All the products **3** were purified by flash column chromatography on silica gel with a mixture of ethyl acetate and petroleum ether as the eluent. The structures of compounds **3** were confirmed by ^{1}H NMR, ^{31}P NMR, IR, and MS spectra and elemental analyses.

In ^{1}H NMR spectra, the uracil ring proton exhibited a doublet due to coupling with the fluorine atom. 5-position furanyl protons (5′-H) appeared multiplet because of their different magnetic surroundings. It is noteworthy that the methylene proton adjacent to the phosphonyl group displayed a doublet because of coupling with the phosphorus atom with the coupling constant of 13 Hz. Moreover, the methylene proton appeared in downfield when linking with an aromatic group relative to an aliphatic one. In ^{31}P NMR spectra, the phosphorus atom of all compounds displayed a singlet with the chemical shifts in 14–17. IR spectra of all compounds showed normal stretching absorption bands indicating the existence of the P=O (∼1260 cm^{-1}), C=O (1680∼1710 cm^{-1}), and P–O–C (∼1000 cm^{-1}) moiety. EI mass spectra of compound **3** revealed that the existence of molecular ion peaks and fragmentation peaks were in accordance with the given structures of products **3**.

Biological Activities

The cell toxicity experiments (in vitro) indicated that some of the title compounds had some extent of inhibitory effect against HCT-8 and Bel-7402 cell lines. For example, the inhibitory ratios against HCT-8 cell lines of compounds **3b** and **3e** were, respectively, 38.0% and 40.1% at the concentration of 5.0×10^{-6}; the inhibitory ratios of Bel-7402 cell lines of compounds **3f** and **3g** were 39.8% and 54.4% at the same concentration, respectively. However, cell toxicity experiments showed that the title compounds had little inhibitory effect against A-549 cell lines.

Moreover, the preliminary fungicidal activities of title compounds **3** were evaluated against *Fusarium oxysporium, Gibberella zeae, Botryosphaeria berengeriana, Rhizoctonia solani,* and *Cercospora beticola* by the classic plate method[6] at a the concentration of 0.005%. The

results indicated that most of compounds **3** had significant inhibitory activities against the five fungi. The relative inhibitory ratios against the five fungi were in the range 60–100%; for example, compound **3j** had 100% relative ratios of the inhibition against these five fungi.

EXPERIMENTAL

Instruments

^{1}H NMR and ^{31}P NMR spectra were recorded with VARIAN MERCURY-PLUS400 400 MHz spectrometer with TMS and 85% H_3PO_4 as the internal and external reference, respectively, and $CDCl_3$ as the solvent, while mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. IR spectra were measured by a NICOLET NEXUS470 spectrometer. Elemental analyses was performed with an ELEMENTAR Vario EL III CHNSO elementary analyzer. Melting points were determined with a WRS-1B digital melting point apparatus, and the thermometer was uncorrected.

Reagents and solvents were available commercially and purified according to conventional methods before use. α-hydroxy alkyl(aryl)methylphosphonates **1** were synthesized by addition reactions of aldehydes with dialkyl phosphites according to the literature.[7,8] Chloroacetyloxyalkyl phosphonates **2** were prepared by condensation reactions of chloroacetyl chloride with α-hydroxy alkyl(aryl)methylphosphonates in the presence of triethylamine according to the literature.[9]

General Procedure for the Synthesis of *N*^{1}-(2-furanidyl)-*N*^{3}-(*O,O*-dialkylphosphonyl Aryl (Alkyl)methoxy-carbonylmethyl)-5-fluorouracil

Ten milliliter of water, 15 mL chloroform, 0.97 g (3 mmol) tetrabutyl ammonium bromide, and 10 mmol compounds **2** were added into a 100-mL three-necked flask; 2.0 g (10 mmol) N^1-(2-furanidyl)-5-fluorouracil (Tegafur) dissolved in 15 mL 0.8mol/L of sodium hydroxide solution was added dropwise at r.t. After the addition was complete, the mixture was stirred vigorously at 50∼55°C for about 10 h until the reaction was complete (monitored by TLC). The workup involved phase separation, washing with aqueous sodium hydroxide (removal of excess N^1-(2-furanidyl)-5-fluorouracil) and drying over anhydrous magnesium sulphate, filtration, and evaporation. The crude product was purified by flash column chromatography on silica gel using petroleuom ether and acetone (1:1 v/v) as an eluant, giving compounds **3a–m**, yield: 48–77%.

3a ($R^1 = CH_3$, $R^2 = CH_3$): light yellow solid, m.p. 74–76°C, yield 70%; ^{1}H NMR $\delta = 1.45$ (q, 3H, CH-$\underline{CH_3}$), 1.82–2.50 (m, 4H, 3′, 4′-H), 3.82 (2d,$^3J_{P\text{-}H} = 10.6$ Hz, 6H, $2OCH_3$), 3.90–4.05 (m, 1H, 5′-H), 4.20–4.30 (m, 1H, 5′-H), 4.78 (s, 2H, $NCH_2C{=}O$), 5.28–5.40 (m, 1H, PCH), 6.00 (d, br, 1H, 2′-H), 7.55 (d, $^3J_{H\text{-}F} = 6.2$ Hz, 1H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1761, 1716 and 1683 (C=O), 1261 (P=O), 1050(P–O–C); EI-MS, m/z (%) 395 (M+1, 52), 324 (92), 171 (78), 142 (90), 109 (87), 71 (100); anal. calcd. for $C_{14}H_{20}O_8N_2FP$ (394): C, 42.64; H, 5.08; N, 7.11. Found: C, 42.35; H, 4.86; N, 6.75.

3b ($R^1 = C_2H_5$, $R^2 = Ph$): colorless crystal, m.p. 93–94°C, yield 67%; ^{1}H NMR $\delta = 1.20$ (2t, 6H, $2OCH_2\underline{CH_3}$), 1.80–2.45 (m, 4H, 3′, 4′-H), 3.90–4.25 (m, 6H, $2O\underline{CH_2}CH_3$, 5′-H), 4.78 (s, 2H, $NCH_2C{=}O$), 5.95 (d, br, 1H, 2′-H), 6.16 (d, $^2J_{H\text{-}P} = 12.6$ Hz, 1H, PCH), 7.30–7.52 (m, 6H, C_6H_5, FC=CH); IR (KBr) (υmax/cm^{-1}) 1763, 1720 and 1655 (C=O), 1254 (P=O), 1044 (P–O–C); EI-MS, m/z (%) 484 (M^+, 15.5), 171 (46), 143 (76), 109 (27), 71 (100); anal. calcd. for $C_{21}H_{26}O_8N_2FP$ (484): C, 52.07; H, 5.37; N, 5.79. Found: C, 52.05; H, 5.50; N, 5.44.

3c ($R^1 = C_2H_5$, $R^2 = 2,4\text{-}Cl_2Ph$): light yellow syrup, yield: 75%; ^{1}H NMR $\delta = 1.26$ (2t, 6H, $2OCH_2\underline{CH_3}$), 1.92–2.40 (m, 4H, 3′, 4′-H), 3.85–4.20 (m, 6H, $2O\underline{CH_2}CH_3$, 5′-H), 4.81 (s, 2H, $NCH_2C{=}O$), 5.87 (d, br, 1H, 2′-H), 6.21 (d, $^2J_{H\text{-}P} = 13.0$ Hz, 1H, PCH), 7.35–7.80 (m, 4H, $C_6H_3Cl_2$, FC=CH); IR (KBr) (υmax/cm^{-1}) 1764, 1720 and 1650 (C=O), 1260 (P=O), 1047(P–O–C); EI-MS, m/z (%) 553 (M^+, 11), 556 (4), 483 (5), 449 (24), 314 (36), 244 (26), 138 (51), 71 (100); anal. calcd. for $C_{21}H_{24}O_8N_2Cl_2FP$ (553): C, 45.57; H, 4.34; N, 5.06. Found: C, 45.45; H, 4.30; N, 4.98.

3d ($R^1 = C_2H_5$, $R^2 = 4\text{-}CH_3OPh$): colorless solid, m.p. 96–98°C, yield 52%; ^{1}H NMR $\delta = 1.23$ (2t, 6H, $2OCH_2\underline{CH_3}$), 1.84–2.44 (m, 4H, 3′, 4′-H), 3.80 (s, 3H, $ArOCH_3$), 3.84–4.26 (m, 6H, $2O\underline{CH_2}CH_3$, 5′-H), 4.82 (s, 2H, $NCH_2C{=}O$), 5.95 (d, br, 1H, 2′-H), 6.09 (d, $^2J_{H\text{-}P} = 12.8$ Hz, 1H, PCH), 6.88 (d, $^3J_{H-H} = 8.1$ Hz, 2H, Ar-H), 7.40–7.46(m, 3H, Ar-H, FC=CH); ^{31}P NMR $\delta = 16.69$; IR (KBr) (υmax/cm^{-1}) 1755, 1719 and 1659 (C=O), 1258 (P=O), 1026 (P–O–C); EI-MS, m/z (%) 514 (M^+, 17), 444 (32), 257 (100), 229 (30), 171 (65), 142 (28), 109 (25), 71 (100); anal. calcd. for $C_{22}H_{28}O_9N_2FP$ (514): C, 51.36; H, 5.45; N, 5.45. Found: C, 51.20; H, 5.66; N, 5.38.

3e ($R^1 = C_2H_5$, $R^2 = 2\text{-furyl}$): yellow crystal, m.p. 101–102°C, yield 48%; ^{1}H NMR $\delta = 1.28$ (2t, 6H, $2OCH_2\underline{CH_3}$), 1.82–2.45 (m, 4H, 3′, 4′-H), 3.92–4.30 (m, 6H, $2O\underline{CH_2}CH_3$, 5′-H), 4.80 (s, 2H, $NCH_2C{=}O$), 5.98 (d, br, 1H, 2′-H), 6.28 (d, $^2J_{H\text{-}P} = 14.8$ Hz, 1H, PCH), 6.40 (s, 1H, Fu-H), 6.64(s, 1H, Fu-H), 7.40–7.50(m, 2H, Fu-H, FC=CH); ^{31}P NMR $\delta = 14.04$; IR (KBr) (υmax/cm^{-1}) 1764, 1720 and 1656 (C=O), 1265 (P=O), 1023 (P–O–C); EI-MS, m/z(%) 475 (M+1, 26), 404 (43), 233 (42), 217 (100),

189 (47), 171 (52), 143 (33), 71 (95); anal. calcd. for $C_{19}H_{24}O_9N_2FP$ (474): C, 48.10; H, 5.06; N, 5.91. Found: C, 47.99; H, 5.13; N, 5.08.

3f ($R^1 = C_2H_5$, $R^2 = 3,4\text{-}Cl_2Ph$): white syrup, yield 61%; ^{1}H NMR $\delta = 1.28$ (2t, 6H, $2OCH_2\underline{CH_3}$), 1.82–2.40 (m, 4H, 3′, 4′-H), 3.90–4.25 (m, 6H, $2O\underline{CH_2}CH_3$, 5′-H), 4.80 (s, 2H, $NCH_2C{=}O$), 5.97 (d, br, 1H, 2′-H), 6.20 (d, $^2J_{H\text{-}P} = 13$ Hz, 1H, PCH), 7.35–7.90 (m, 4H, $C_6H_3Cl_2$, FC=CH); IR (KBr) (υmax/cm^{-1}) 1761, 1722 and 1683 (C=O), 1261 (P=O), 1026 (P–O–C); EI-MS, m/z (%) 553 (M^+, 31), 555 (M+2, 20.5), 557 (M+4, 5), 483 (22.33), 485 (14.1), 487 (2.7), 295 (36.8), 297 (24.7), 299 (4.78), 251 (19.2), 171 (51.78), 138 (58.26), 114 (46.2), 109 (19.8), 71 (100); anal. calcd. for $C_{21}H_{24}O_8N_2Cl_2FP$ (553): C, 45.57; H, 4.34; N, 5.06. Found: C, 45.86; H, 4.42; N, 5.27.

3g ($R^1 = CH_3$, $R^2 = 2\text{-}ClPh$): yellow syrup, yield 53%; ^{1}H NMR $\delta = 1.82$–2.45 (m, 4H, 3′, 4′-H), 3.72 (2d, $^3J_{P\text{-}H} = 10.8$ Hz, 6H, $2OCH_3$), 3.92–4.05 (m, 1H, 5′-H), 4.20–4.30 (m, 1H, 5′-H), 4.80 (s, 2H, $NCH_2C{=}O$), 5.92 (d, br, 1H, 2′-H), 6.67 (d, $^2J_{H\text{-}P} = 13.2$ Hz, 1H, PCH), 7.23–7.50 (m, 4H, Ar-H), 7.65 (d, $^3J_{H-F} = 7.6$ Hz, 1H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1770, 1716 and 1652 (C=O), 1261 (P=O), 1061 (P–O–C); EI-MS, m/z (%) 491(M^+, 4), 421 (20), 385 (43), 233 (43), 171 (55), 143 (58), 114 (57), 109 (44), 71 (100); anal. calcd. for $C_{19}H_{21}O_8N_2ClFP$ (490.5): C, 46.48; H, 4.28; N, 5.71. Found: C, 46.56; H, 4.09; N, 5.96.

3h ($R^1 = CH_3$, $R^2 = Ph$): light yellow crystal, m.p. 152–153°C, yield 58%; ^{1}H NMR $\delta = 1.82$–2.40 (m, 4H, 3′, 4′-H), 3.70 (2d, $^3J_{P\text{-}H} = 10.8$ Hz, 6H, $2OCH_3$), 3.99–4.03 (m, 1H, 5′-H), 4.22–4.24 (m, 1H, 5′-H), 4.83 (s, 2H, $NCH_2C{=}O$), 5.96 (d, br, 1H, 2′-H), 6.19 (d, $^2J_{H\text{-}P} = 13.2$ Hz, 1H, PCH), 7.32–7.49 (m, 6H, Ar-H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1770, 1723 and 1658 (C=O), 1259 (P=O), 1065 (P–O–C); EI-MS, m/z (%) 457(M+1, 3), 386 (56), 215 (18), 171 (45), 143 (61), 109 (48), 77 (38), 71 (100); anal. calcd. for $C_{19}H_{22}O_8N_2FP$ (456): C, 50.00; H, 4.82; N, 6.14. Found: C, 49.87; H, 4.47; N, 6.30.

3i ($R^1 = CH_3$, $R^2 = 4\text{-}CH_3OPh$): colorless solid, m.p. 138–140°C, yield 70%; ^{1}H NMR $\delta = 1.90$–2.40 (m, 4H, 3′, 4′-H), 3.66–3.78 (m, 9H, $ArOCH_3$, $2OCH_3$), 3.99–4.01 (m, 1H, 5′-H), 4.23–4.24 (m, 1H, 5′-H), 4.82 (s, 2H, $NCH_2C{=}O$), 5.95 (d, br, 1H, 2′-H), 6.13 (d, $^2J_{H\text{-}P} = 13.6$ Hz, 1H, PCH), 7.35–7.48 (m, 5H, Ar-H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1774, 1721 and 1655 (C=O), 1253 (P=O), 1061 (P–O–C); EI-MS, m/z (%) 486 (M^+, 25), 215 (7), 171 (85), 109 (37), 77 (55), 71 (100); anal. calcd. for $C_{20}H_{24}O_9N_2FP$ (486): C, 49.38; H, 4.94; N, 5.76. Found: C, 49.74; H, 5.06; N, 5.49.

3j ($R^1 = CH_3$, $R^2 = 2\text{-}CH_3OPh$): yellow syrup, yield 54%; ^{1}H NMR $\delta = 1.93$–2.44 (m, 4H, 3′, 4′-H), 3.74 (2d, $^3J_{P\text{-}H} = 11.0$ Hz, 6H, $2OCH_3$), 3.88 (s, 3H, CH_3OAr), 3.98–4.00 (m, 1H, 5′-H), 4.22–4.28 (m, 1H, 5′-H),

4.79 (s, 2H, $NCH_2C{=}O$), 5.95 (d, br, 1H, 2′-H), 6.76 (d, $^2J_{H\text{-}P} = 12.8$ Hz, 1H, PCH), 6.88–7.00 (m, 2H, Ar-H), 7.28–7.46 (m, 2H, Ar-H), 7.54 (d, $^3J_{H\text{-}F} = 7.6$ Hz, 1H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1762, 1723 and 1671 (C=O), 1265 (P=O), 1033 (P–O–C); EI-MS, m/z(%) 486 (M^+, 7), 215 (59), 171 (77), 109 (43), 77 (89), 71 (100); anal. calcd. for $C_{20}H_{24}O_9N_2FP$ (486): C, 49.38; H, 4.94; N, 5.76. Found: C, 49.29; H, 4.97; N, 5.62.

3k ($R^1 = CH_3$, $R^2 = 4$-ClPh): white wax, yield 69%; ^{1}H NMR $\delta = 1.91$–2.40 (m, 4H, 3′, 4′-H), 3.71 (2d, $^3J_{P\text{-}H} = 10.8$ Hz, 6H, $2OCH_3$), 3.98–4.00 (m, 1H, 5′-H), 4.21–4.24 (m, 1H, 5′-H), 4.81 (s, 2H, $NCH_2C{=}O$), 5.95 (d, br, 1H, 2′-H), 6.13 (d, $^2J_{H\text{-}P} = 13.2$ Hz, 1H, PCH), 7.35–7.43 (m, 4H, Ar-H), 7.47 (d, $^3J_{H\text{-}F} = 6.0$ Hz, 1H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1762, 1719 and 1656 (C=O), 1252 (P=O), 1029 (P–O–C); EI-MS, m/z (%) 491 (M^+, 26), 422 (33), 385 (43), 233 (69), 171 (75), 143 (67), 138 (57), 109 (52), 71 (100); anal. calcd. for $C_{19}H_{21}O_8N_2ClFP$ (490.5): C, 46.48; H, 4.28; N, 5.71. Found: C, 46.60; H, 4.46; N, 5.83.

3l ($R^1 = C_2H_5$, $R^2 = 4$-ClPh): yellow solid, m.p. 133–135°C yield 77%; ^{1}H NMR $\delta = 1.30$ (2t, 6H, $2OCH_2\underline{CH_3}$), 1.85–2.40 (m, 4H, 3′, 4′-H), 3.80–4.20 (m, 6H, $2O\underline{CH_2}CH_3$, 5′-H), 4.80 (s, 2H, $NCH_2C{=}O$), 5.81 (d, br, 1H, 2′-H), 6.34 (d, $^2J_{H\text{-}P} = 13.6$ Hz, 1H, PCH), 7.40–7.55 (m, 6H, C_6H_5, FC=CH); IR (KBr) (υmax/cm^{-1}) 1764, 1721 and 1656 (C=O), 1265 (P=O), 1031(P–O–C); EI-MS, m/z (%) 519 (M^+, 8), 448 (41), 277 (55), 233 (60), 171 (65), 142 (28), 109 (25), 71 (100); anal. calcd. for $C_{21}H_{25}O_8N_2ClFP$ (518.5): C, 48.60; H, 4.82; N, 5.40. Found: C, 48.26; H, 4.90; N, 5.72.

3m ($R^1 = CH_3$, $R^2 = 3,4$-Cl_2Ph): colorless syrup, yield 55%; ^{1}H NMR $\delta = 1.82$–2.40 (m, 4H, 3′, 4′-H), 3.60–3.80 (2d, $^3J_{P\text{-}H} = 10.8$ Hz, 6H, $2OCH_3$), 3.82–3.90 (m, 1H, 5′-H), 3.96–4.00 (m, 1H, 5′-H), 4.40 (s, 2H, $NCH_2C{=}O$), 5.87 (d, br, 1H, 2′-H), 6.46 (d, $^2J_{H\text{-}P} = 13.4$ Hz, 1H, PCH), 7.40–7.55 (m, 4H, Ar-H, FC=CH); IR (KBr) (υmax/cm^{-1}) 1761, 1721 and 1683 (C=O), 1261 (P=O), 1026 (P–O–C); EI-MS, m/z (%) 529, 527, 525 (M^+, 18), 171 (48), 143 (34), 114 (62), 109 (88), 71 (100); anal. calcd. for $C_{19}H_{20}O_8N_2Cl_2FP$ (525): C, 43.43; H, 3.81; N, 5.33. Found: C, 43.53; H, 3.92; N, 5.27.

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