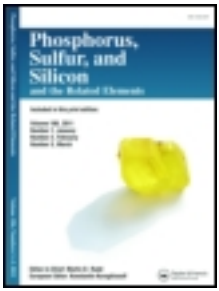

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

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Published online: 03 Nov 2009.

To cite this article: Jinwei Yuan , Xiaolan Chen , Lingbo Qu , Shouren Zhang , Jiansha Lu & Yufen Zhao (2009): A Convenient Synthesis of Novel Phosphoramide Mustard Analogues of 2-Arylquinolone, Phosphorus, Sulfur, and Silicon and the Related Elements, 184:11, 2936-2944

To link to this article: http://dx.doi.org/10.1080/10426500802625529

Phosphorus, Sulfur, and Silicon, 184:2936–2944, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802625529

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A Convenient Synthesis of Novel Phosphoramide Mustard Analogues of 2-Arylquinolone

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A series of novel phosphoramide mustard analogues of 2-arylquinolones are synthesized through a convenient and facile phosphorylated reaction, and their structures are elucidated by NMR, IR, and HR MS. The amino acid esters and phosphoryl nitrogen mustard are linked to 2-arylquinolone to improve their undesirable physicochemical and biological properties.

Keywords Amino acid ester; 2-arylquinolone; phosphoramide mustard

INTRODUCTION

2-Arylquinolones are a class of molecules used as aza analogues of flavones (Figure 1). Over the last 10 years, 2-arylquinolones and related compounds have been the subject of extensive studies as potent cytotoxic antimitotic agents,[1,2] antibacterial agents, anti-platelet agents, and as cardiovascular protectors.[3,4,5] Moreover, 2-arylquinolones have been the subject of investigations as a new class of antitumor agents. With the goal of enhancing their pharmacological and biological activity, several 2-arylquinolone derivatives have been synthesized previously, and their biological activities have also been studied.[6,7,8,9]

Glyciphosphoramide, *N*,*N*-bis(chloroethyl)-*N*′,*N*′′-bis-(carbethoxymethyl)phosphoric triamide (Figure 2 is a synthetic anticancer agent

Received 12 September 2008; accepted 13 November 2008.

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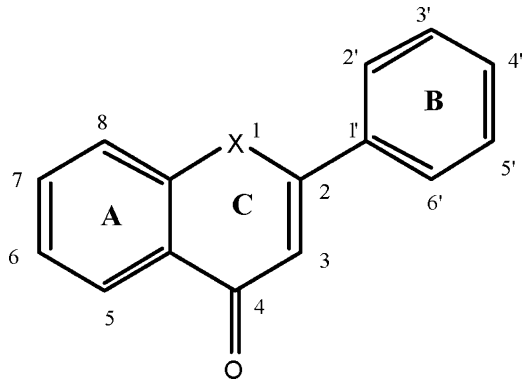


FIGURE 1 X = O: flavone; X = N: 2-phenyl-4-quinolone.

used against a broad spectrum of tumor in animal tests and has been undergoing evaluation in China for some time. Glyciphosphoramide is activated in the presence of plasma or serum. This unique property of glyciphosphoramide makes the compound a useful agent for topical use in the treatment of cancerous ulceration and malignant tumors.[10–12] Within the pharmaceutical industry, several candidates belonging to this structural class have been synthesized as potential antitumor agents.[13,14] In the hope of increasing the biological specificity of these compounds, the phosphoramide mustard group has been linked to various carrier molecules such as carbohydrates.[15,16]

Our interest was in synthesizing a series of amino acid esters and phosphoryl nitrogen mustard linked 2-arylquinolone derivatives to improve their undesirable physicochemical and biological properties as potential antitumor agents. In the work described in this article, novel phosphoramide mustard analogues of 2-arylquinolone **4a–g** are synthesized through a convenient and facile phosphorylated reaction (Scheme 1). The structures of compounds **4a–g** have been elucidated by NMR, IR, and HR MS for the first time.

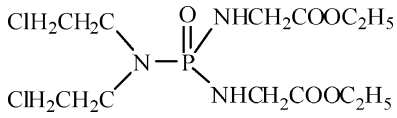
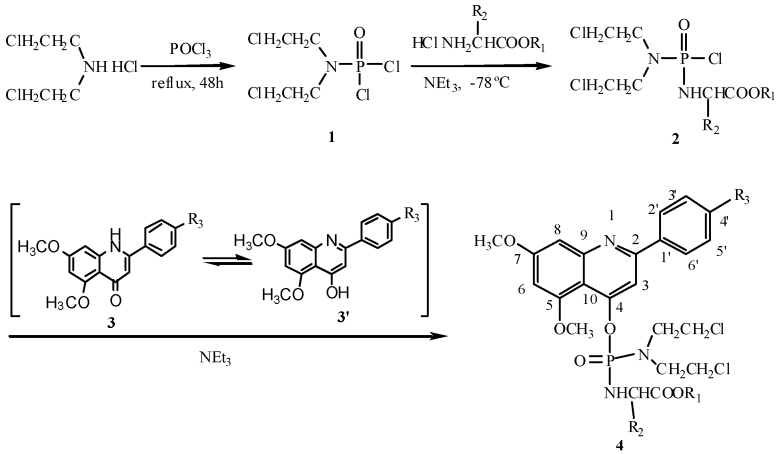


FIGURE 2 Glyciphosphoramide.



a: $R_1 = CH_3$, $R_2 = H$, $R_3 = H$; b: $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$;

c: $R_1 = C_2H_5$, $R_2 = CH_3$, $R_3 = H$; d: $R_1 = CH_3$, $R_2 = H$, $R_3 = Cl$;

e: $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$; f: $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$;

g: $R_1 = C_2H_5$, $R_2 = H$, $R_3 = CH_3$

SCHEME 1 Synthesis of phosphoramide mustard analogues of 2-arylquinolone **4a–g**.

RESULTS AND DISCUSSION

In the synthesis of phosphoramide mustard analogues of 2-arylquinolone (**4**) (Scheme 1), bis-(β-chloroethyl)-amine hydrochloride was first reacted with phosphorus oxychloride at reflux temperature to give di-(2-chloroethyl)-phosphoramidic dichloride **(1)**. Then it was coupled with different *L*-amino acid esters hydrochloride salts at low temperature to achieve *N*,*N*-bis(2-chloroethyl) phosphonamidic chlorides **(2)**, which were not purified further by the chromatography. 2-Arylquinolone (**3**) was reacted with *N*,*N*-bis(2-chloroethyl) phosphonamidic chloride **(2)** in THF by a convenient and facile phosphorylation reaction to form phosphoramide mustard analogues of 2-arylquinolone **(4)** in the presence of triethylamine at low temperatures. The yields of the final purified compounds were in the range 30–49%. The structures of all the newly synthesized 2-arylquinolone derivatives were confirmed by NMR, IR, and HR MS.

2-Arylquinolones can be synthesized by several pathways.[2,3] The degree of unsaturation in the C-ring causes it to exist in tautomeric equilibriums, 2-arylquinolone and 2-aryl-4-hydroquinoline isomer. 2-Arylquinolones are found to exist exclusively in solution phase and solid state.[17] The experimental results show that the final product is compound **(4)**. This conclusion was confirmed by ^{13}C NMR. For example, ^{13}C NMR of compound **4a** showed 3-C at δ 109.01($^{3}J_{\text{P-C}}$ = 2.83 Hz), 4-C at δ 154.82($^{2}J_{\text{P-C}}$ = 7.38 Hz), and 10-C at δ 108.57($^{3}J_{\text{P-C}}$ = 5.00 Hz) were split into doublet, respectively. The reason is because the phosphorus atom makes the surrounding carbon atoms split. We speculate that 2-arylquinolone **(3)** first undergoes a tautomeric change to become 2-aryl-4-hydroquinoline **(3′)**, and then reacts with *N*, *N*-bis(2-chloroethyl) phosphonamidic chloride **(2)** to obtain the final product **(4)**.

NMR spectra of **4a**, **4d**, **4e**, **4f**, and **4g** show only a group of signals because these compounds are formed by a pair of enantiomers, respectively. However, two groups of signals could be found from NMR spectra of **4b** and **4c**. The reason is due to the chirality at the phosphorus center and *L*-amino acid esters. Each of compound **4b** and **4c** includes two isomers (Sp and Rp), and the confirmation of the presence of two isomers is shown by ^{31}P NMR. Separation of the diastereoisomers by column chromatography has been difficult and problematic. By using ^{31}P NMR, we were able to approximately determine the ratios of each isomer. It is interesting to note that in the case of the *L*-alanine methylester isomer (**4b** and **4c**), a ratio of approximately 20% of isomer **|** and 80% isomer **||** can be obtained. This indicates that the approach of 2-arylquinolone in the final segment of the synthesis is affected by the configuration at the amino acid terminal of the phosphorochloridate.

In summary, novel phosphoramide mustard analogues of 2-arylquinolone **4a–g** have been synthesized through a versatile method. Work is in progress in our laboratory to further evaluate the biological activity of these analogues as potential antitumor prodrugs.

EXPERIMENTAL

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions. The solvents were dried by appropriate methods.[18] IR spectra were recorded on a Shimadazu IR-408. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance DPX spectrometer operating at 400.13, 100.61, and 161.98 MHz, respectively, with ^{13}C and ^{31}P spectra being recorded as proton-decoupled. All NMR spectra were recorded in $CDCl_3$ at room temperature (20°C ± 3°C). ^{1}H

and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. ^{31}P chemical shifts are quoted in parts per million relative to an external 85% H_3PO_4 standard. *J* values refer to coupling constants, and signal splitting patterns are described as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), multiplet (m), or combinations thereof. TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200–300 mesh). TOF MS were recorded on Q-Tof Micro.

Di-(2-chloroethyl)-phosphoramidic Dichloride (1)

A suspension of bis-(*β*-chloroethyl)-amine hydrochloride (40 g, 0.23 mol) in distilled phosphorus oxychloride (174 mL, 1.78 mol, b.p. 105.5–107.5°C) was refluxed for 24 h until complete solution resulted. The excess phosphorus oxychloride was removed by distillation, and the residue was crystallized from acetone-petroleum ether, yielding the desired product, mp 55–57°C.[19]

General Procedure to Prepare *N*,*N*-Bis(2-chloroethyl) Phosphonamidic Chloride (2a–g)

Di-(2-chloroethyl)-phosphoramidic dichloride (5 g, 19.5 mmol) and the appropriate *L*-amino acid ester hydrochloric salt (19.5 mmol) were suspended in anhydrous dichloromethane. Anhydrous triethylamine (2.7 mL, 19.5 mmol) was added dropwise at –78°C, and after 2 h, the reaction was left to warm to room temperature. The formation of *N*,*N*-bis(2-chloroethyl) phosphonamidic chloride was monitored by ^{31}P NMR. After 6–15 h, the solvent was removed under reduced pressure, and the solid obtained was washed with anhydrous ether (2 × 20 mL), filtered, and the filtrate was concentrated to dryness to give the crude products **(2)**, which were used without further purification.

General Procedure to Prepare Phosphoramide Mustard Analogues of 2-Arylquinolone (4a–g)

A solution of 2-arylquinolone (1.8 mmol) and the appropriate *N*, *N*-bis(2-chloroethyl) phosphonamidic chloride **(2)** (2.0–3.0 mol) in anhydrous tetrahydrofuran was stirred at –40°C for 30 min, and anhydrous triethylamine (0.3 mL, 2.0 mmol) was added dropwise to the solution over a period of 30 min. After 1 h, the reaction was left to warm to room temperature and stirred for a further 10–24 h. The solution was filtered, and the filtrate was evaporated to dryness to give the residues

as yellow oils. The residues were purified by column chromatography on silica gel (cyclohexane:ethyl acetate, 3:1).

Compound 4a ($C_{24}H_{28}Cl_2N_3O_6P$)

Mp: 165–166°C, Yield: 49%. HR MS 556.1170 $[M + H]^+$ (calculated for $C_{24}H_{28}Cl_2N_3O_6PH$ 556.1171); IR(KBr) $\nu(cm^{-1})$: 3408 (N-H), 2926, 2854 (-CH_3, -CH_2), 1748 (C = O), 1619 (heterocycle), 1584 (C = N), 1374 (P = O), 1212 (P-O-Ar), 772 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.77 (d, 1H, $^4J_{P\text{-}H}$ = 1.68 Hz, 3-H), 6.59 (d, 1H, $^4J_{H\text{-}H}$ = 2.24 Hz, 6-H), 7.16 (d, 1H, $^4J_{H\text{-}H}$ = 2.08 Hz, 8-H), 8.12 (d, 2H, $^3J_{H\text{-}H}$ = 8.12 Hz, 2′6′-H), 7.47 (m, 3H, 3′4′5′-H), 4.08 (s, 3H, 5-OCH_3), 4.03 (s, 3H, 7-OCH_3), 3.73 (m, 8H, NCH_2CH_2Cl), 3.70 (s, 3H, $OOCH_3$); ^{13}C NMR($CDCl_3$) δ: 158.94 (2-C), 109.01 (d, $^3J_{P\text{-}C}$ = 2.83 Hz, 3-C), 154.82 (d, $^2J_{P\text{-}C}$ = 7.38 Hz, 4-C), 155.73 (5-C), 99.70 (6-C), 161.19 (7-C), 101.38 (8-C), 153.52 (9-C), 108.57 (d, $^3J_{P\text{-}C}$ = 5.00 Hz, 10-C), 138.64 (C-1′), 128.73 (2′6′-C), 127.55 (3′5′-C), 129.64 (4′-C), 55.68 (5-OCH_3), 56.28 (7-OCH_3), 49.21 (d, $^2J_{P\text{-}C}$ = 4.57 Hz, NCH_2), 42.24 (CH_2Cl), 42.06 (d, $^2J_{P\text{-}C}$ = 3.42 Hz, -CH_2), 171.37 (d, $^3J_{P\text{-}C}$ = 9.40 Hz, C = O), 52.43 ($OOCH_3$); ^{31}P NMR($CDCl_3$) δ: 11.00.

Compound 4b ($C_{25}H_{30}Cl_2N_3O_6P$)

Mp: 155–157°C, Yield: 36%. HR MS 570.1320 $[M + H]^+$ (calculated for $C_{25}H_{30}Cl_2N_3O_6PH$ 570.1328); IR(KBr) $\nu(cm^{-1})$: 2929, 2851 (-CH_3, -CH_2), 1743 (C = O) 1636(heterocycle), 1609 (C = N), 1374 (P = O), 1213 (P-O-Ar), 772 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.81, 7.79 (d, 1H, $^4J_{P\text{-}H}$ = 1.56 Hz, 3-H), 6.60, 6.59 (d, 1H, $^4J_{H\text{-}H}$ = 2.24Hz, 6-H), 7.17, 7.16 (d, 1H, $^4J_{H\text{-}H}$ = 2.04 Hz, 8-H), 8.14, 8.11 (d, 2H, $^3J_{H\text{-}H}$ = 8.36 Hz, 2′6′-H), 7.47, 7.47 (m, 3H, 3′4′5′-H), 4.07, 4.03 (s, 3H, 5-OCH_3), 3.96, 3.96 (s, 3H, 7-OCH_3), 3.68, 3.52 (m, 8H, NCH_2CH_2Cl), 4.10, 4.10 (m, 1H, -CH), 1.44, 1.26 (d, 3H, $^4J_{P\text{-}H}$ = 6.72 Hz, -CH_3), 3.74, 3.60 (s, 3H, $OOCH_3$); ^{13}C NMR($CDCl_3$) δ: 158.94, 158.86 (2-C), 108.65, 108.57 (d, $^3J_{P\text{-}C}$ = 2.78 Hz, 3-C), 154.92, 154.85 (d, $^2J_{P\text{-}C}$ = 6.91 Hz, 4-C), 155.93, 155.73 (5-C), 99.68, 99.60 (6-C), 161.22, 161.19 (7-C), 101.38, 101.26 (8-C), 153.49, 153.49 (9-C), 109.17, 109.14 (d, $^3J_{P\text{-}C}$ = 3.03 Hz, 10-C), 138.67, 138.63 (C-1′), 128.75, 128.75 (2′6′-C), 127.54, 127.54 (3′5′-C), 129.66, 129.63 (4′-C), 56.33, 56.15 (5-OCH_3), 55.71, 55.68 (7-OCH_3), 49.49, 49.17 (d, $^2J_{P\text{-}C}$ = 4.56 Hz, NCH_2), 42.20, 42.20 (CH_2Cl), 49.74, 49.71 (d, $^2J_{P\text{-}C}$ = 3.20 Hz, -CH), 21.57, 20.83 (d, $^3J_{P\text{-}C}$ = 3.72 Hz, -CH_3), 174.49, 174.05 (d, $^3J_{P\text{-}C}$ = 8.58 Hz, C = O), 52.57, 52.48 ($OO\underline{C}H_3$); ^{31}P NMR($CDCl_3$) δ: 9.76, 9.56.

Compound 4c ($C_{26}H_{32}Cl_2N_3O_6P$)

Mp: 167–169°C, Yield: 40%. HR MS 584.1480 $[M + H]^+$ (calculated for $C_{26}H_{32}Cl_2N_3O_6PH$ 584.1484); IR(KBr) $\nu(cm^{-1})$: 3399 (N-H), 2930,

2852 (-CH_3, -CH_2), 1740 (C = O), 1626 (heterocycle), 1285 (P = O), 1213 (P-O-Ar), 776 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.82, 7.79 (d, 1H, $^4J_{P\text{-}H}$ = 1.48 Hz, 3-H), 6.60, 6.58 (d, 1H, J = 2.16Hz, 6-H), 7.17, 7.16 (d, 1H, $^4J_{H\text{-}H}$ = 1.96 Hz, 8-H), 8.14, 8.12 (d, 2H, $^4J_{H\text{-}H}$ = 8.00 Hz, 2′6′-H), 7.47, 7.47 (m, 3H, 3′4′5′-H), 4.07, 4.03 (s, 3H, 5-OCH_3), 3.96, 3.96 (s, 3H, 7-OCH_3), 3.60, 3.60 (m, 8H, NCH_2CH_2Cl), 4.05, 4.05 (m, 1H, -CH), 1.44, 1.28 (d, 3H, $^3J_{H\text{-}H}$ = 6.88 Hz, -CH_3), 4.18, 4.18 (q, 2H, $^3J_{H\text{-}H}$ = 7.36 Hz, $OOCH_2$), 1.26, 1.15 (t, 3H, $^3J_{H\text{-}H}$ = 7.16 Hz, $OOCCH_3$); ^{13}C NMR($CDCl_3$) δ: 158.94, 158.87 (2-C), 108.68, 108.64 (d, $^3J_{P\text{-}C}$ = 3.56 Hz, 3-C), 154.94, 154.87 (d, $^2J_{P\text{-}C}$ = 7.13 Hz, 4-C), 155.93, 155.76 (5-C), 99.66, 99.58 (6-C), 161.21, 161.18 (7-C), 101.37, 101.25 (8-C), 153.50, 153.50 (9-C), 109.17, 109.13 (d, $^3J_{P\text{-}C}$ = 3.09 Hz, 10-C), 138.67, 138.65 (C-1′), 128.75, 128.75 (2′6′-C), 127.54, 127.54 (3′5′-C), 129.65, 129.61 (4′-C), 56.34, 56.14(5-OCH_3), 55.71, 55.68 (7-OCH_3), 49.51, 49.20 (d, $^2J_{P\text{-}C}$ = 4.49 Hz, NCH_2), 42.21, 42.21 (CH_2Cl), 49.77, 49.74 (d, $^2J_{P\text{-}C}$ = 3.32 Hz, -CH), 21.63, 20.88 (d, $^3J_{P\text{-}C}$ = 3.52 Hz, -CH_3), 174.03, 173.57 (d, $^3J_{P\text{-}C}$ = 8.84 Hz, C = O), 61.65, 61.57 ($OO\underline{C}H_2$), 14.16, 14.00 ($OOC\underline{C}H_3$); ^{31}P NMR($CDCl_3$) δ: 9.81, 9.58.

Compound 4d ($C_{24}H_{27}Cl_3N_3O_6P$)

Mp: 80–81°C, Yield: 30%. HR MS 590.0780 $[M + H]^+$ (calculated for $C_{24}H_{27}Cl_3N_3O_6PH$ 590.0781); IR(KBr) ν(cm^{-1}): 3411 (N-H), 2954, 2926, 2854 (-CH_3, -CH_2), 1748 (C = O), 1619 (heterocycle), 1577 (C = N), 1279 (P = O), 1211 (P-O-Ar), 752 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.74 (d, 1H, $^4J_{P\text{-}H}$ = 1.52 Hz, 3-H), 6.60 (d, 1H, $^4J_{H\text{-}H}$ = 2.24Hz, 6-H), 7.13 (d, 1H, $^4J_{H\text{-}H}$ = 2.20 Hz, 8-H), 8.08 (d, 2H, $^3J_{H\text{-}H}$ = 8.68 Hz, 2′6′-H), 7.44 (d, 2H, $^3J_{H\text{-}H}$ = 8.60 Hz, 3′5′-H), 4.08 (s, 3H, 5-OCH_3), 3.96 (s, 3H, 7-OCH_3), 3.71 (m, 8H, NCH_2CH_2Cl), 3.52 (m, 2H, -CH_2), 3.71 (s, 3H, $OOCH_3$); ^{13}C NMR($CDCl_3$) δ: 157.60 (2-C), 108.63 (d, $^3J_{P\text{-}C}$ = 2.88 Hz, 3-C), 155.00 (d, $^2J_{P\text{-}C}$ = 7.11 Hz, 4-C), 155.74 (5-C), 99.91 (6-C), 161.35 (7-C), 101.34 (8-C), 153.52 (9-C), 108.72 (d, $^3J_{P\text{-}C}$ = 3.62 Hz, 10-C), 137.08 (C-1′), 128.84 (2′6′-C), 128.92 (3′5′-C), 135.85 (4′-C), 55.72 (5-OCH_3), 56.34 (7-OCH_3), 49.20 (d, $^2J_{P\text{-}C}$ = 4.59 Hz, NCH_2), 42.23 (CH_2Cl), 42.05 (d, $^2J_{P\text{-}C}$ = 3.44 Hz, -CH_2), 171.38 (d, $^3J_{P\text{-}C}$ = 9.40 Hz, C = O), 52.48 ($OO\underline{C}H_3$); ^{31}P NMR($CDCl_3$) δ: 11.05.

Compound 4e ($C_{25}H_{30}Cl_2N_3O_7P$)

Mp: 105–106°C, Yield: 39%. HR MS 586.1272 $[M + H]^+$ (calculated for $C_{25}H_{30}Cl_2N_3O_7PH$ 586.1277); IR(KBr) ν(cm^{-1}): 3422 (N-H), 2958, 2926, 2853 (-CH_3, -CH_2), 1747 (C = O), 1616 (heterocycle), 1375 (P = O), 1212 (P-O-Ar), 832 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.72 (d, 1H, $^4J_{P\text{-}H}$ = 1.52 Hz, 3-H), 6.56 (d, 1H, $^4J_{H\text{-}H}$ = 2.20Hz, 6-H), 7.13 (d, 1H, $^4J_{H\text{-}H}$ =

2.08 Hz, 8-H), 8.10 (d, 2H, $^3J_{H\text{-}H}$ = 8.84 Hz, 2′6′-H), 7.00 (d, 2H, $^3J_{H\text{-}H}$ = 8.88 Hz, 3′5′-H), 4.05 (s, 3H, 5-OCH_3), 3.95 (s, 3H, 7-OCH_3), 3.87(s, 3H, 4′-OCH_3), 3.72(m, 8H, NCH_2CH_2Cl), 3.51(m, 2H, -CH_2), 3.72(s, 3H, $OOCH_3$); ^{13}C NMR($CDCl_3$) δ: 158.49 (2-C), 108.45 (d, $^3J_{P\text{-}C}$ = 2.78 Hz, 3-C), 154.70 (d, $^2J_{P\text{-}C}$ = 7.35 Hz, 4-C), 155.74 (5-C), 99.37 (6-C), 161.16 (7-C), 101.24 (8-C), 153.50 (9-C), 108.22 (d, $^3J_{P\text{-}C}$ = 4.87 Hz, 10-C), 128.84 (C-1′), 128.95 (2′6′-C), 114.09 (3′5′-C), 161.07 (4′-C), 55.39 (5-OCH_3), 56.27 (7-OCH_3), 55.68 (4′-OCH_3), 49.22 (d, $^2J_{P\text{-}C}$ = 4.56 Hz, NCH_2), 42.25 (CH_2Cl), 42.07 (d, $^2J_{P\text{-}C}$ = 3.35 Hz, -CH_2), 171.40 (d, $^3J_{P\text{-}C}$ = 9.28 Hz, C = O), 52.44 ($OOCH_3$); ^{31}P NMR($CDCl_3$) δ: 11.00.

Compound 4f ($C_{25}H_{30}Cl_2N_3O_6P$)

Mp: 77–78°C, Yield: 36%. HR MS 570.1322 $[M + H]^+$ (calculated for $C_{25}H_{30}Cl_2N_3O_6PH$ 570.1328); IR(KBr) ν(cm^{-1}): 3442 (N-H), 2927, 2856 (-CH_3, -CH_2), 1744 (C = O), 1634 (heterocycle), 1374 (P = O), 1212 (P-O-Ar), 771 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.73 (d, 1H, $^4J_{P\text{-}H}$ = 1.68 Hz, 3-H), 6.58 (d, 1H, $^4J_{H\text{-}H}$ = 2.28Hz, 6-H), 7.13 (d, 1H, $^4J_{H\text{-}H}$ = 2.28 Hz, 8-H), 8.01 (d, 2H, $^3J_{H\text{-}H}$ = 8.20 Hz, 2′6′-H), 7.27 (d, 2H, $^3J_{H\text{-}H}$ = 8.00 Hz, 3′5′-H), 4.06 (s, 3H, 5-OCH_3), 3.96 (s, 3H, 7-OCH_3), 2.41 (s, 3H, 4′-CH_3), 3.75 (m, 8H, NCH_2CH_2Cl), 3.51 (m, 2H, -CH_2), 3.75 (s, 3H, $OOCH_3$); ^{13}C NMR($CDCl_3$) δ: 158.96 (2-C), 108.79 (d, $^3J_{P\text{-}C}$ = 2.90 Hz, 3-C), 154.67 (d, $^2J_{P\text{-}C}$ = 8.18 Hz, 4-C), 155.71 (5-C), 99.54 (6-C), 161.13 (7-C), 101.41 (8-C), 153.58 (9-C), 108.45 (d, $^3J_{P\text{-}C}$ = 4.97 Hz, 10-C), 135.83 (C-1′), 127.40 (2′6′-C), 129.46 (3′5′-C), 139.79 (4′-C), 55.69 (5-OCH_3), 56.28 (7-OCH_3), 21.36 (4′-CH_3), 49.24 (d, $^2J_{P\text{-}C}$ = 4.50 Hz, NCH_2), 42.24 (CH_2Cl), 42.07 (d, $^2J_{P\text{-}C}$ = 3.33 Hz, -CH_2), 171.39 (d, $^3J_{P\text{-}C}$ = 9.28 Hz, C = O), 52.45 ($OOCH_3$); ^{31}P NMR($CDCl_3$) δ: 10.93.

Compound 4g ($C_{26}H_{32}Cl_2N_3O_6P$)

Mp: 85–86°C, Yield: 32%. HR MS 584.1485 $[M + H]^+$ (calculated for $C_{26}H_{32}Cl_2N_3O_6PH$ 584.1484); IR(KBr) ν(cm^{-1}): 3402 (N-H), 2925, 2848 (-CH_3, -CH_2), 1744 (C = O), 1619 (heterocycle), 1591 (C = N), 1350 (P = O), 1210 (P-O-Ar), 829 (C-Cl); ^{1}H NMR($CDCl_3$) δ: 7.75 (d, 1H, $^4J_{P\text{-}H}$ = 1.52 Hz, 3-H), 6.58 (d, 1H, $^4J_{H\text{-}H}$ = 2.16Hz, 6-H), 7.14 (d, 1H, $^4J_{H\text{-}H}$ = 2.16 Hz, 8-H), 8.02 (d, 2H, $^3J_{H\text{-}H}$ = 8.16 Hz, 2′6′-H), 7.28 (d, 2H, $^3J_{H\text{-}H}$ = 8.16 Hz, 3′5′-H), 4.06 (s, 3H, 5-OCH_3), 3.96 (s, 3H, 7-OCH_3), 2.41 (s, 3H, 4′-CH_3), 3.71 (m, 8H, NCH_2CH_2Cl), 3.51 (m, 2H, -CH_2), 4.18 (q, 2H, $^3J_{H\text{-}H}$ = 2.12 Hz, $OOCH_2$), 1.25 (t, 3H, $^3J_{H\text{-}H}$ = 2.36 Hz, -$OOCCH_3$); ^{13}C NMR($CDCl_3$) δ: 158.96 (2-C), 108.82 (d, $^3J_{P\text{-}C}$ = 3.02 Hz, 3-C), 154.73 (d, $^2J_{P\text{-}C}$ = 7.35 Hz, 4-C), 155.74 (5-C), 99.52 (6-C), 161.12 (7-C), 101.39 (8-C), 153.58 (9-C), 108.48 (d, $^3J_{P\text{-}C}$ = 5.07 Hz, 10-C), 135.87 (C-1′), 127.42 (2′6′-C), 129.46 (3′5′-C), 139.77 (4′-C), 55.69 (5-OCH_3), 56.29 (7-OCH_3),

49.28 (d, $^2J_{P\text{-}C} = 4.75$ Hz, NCH_2), 42.27 (CH_2Cl), 42.21 (d, $^2J_{P\text{-}C} = 3.05$ Hz, -CH_2), 170.96 (d, $^3J_{P\text{-}C} = 9.69$ Hz, C = O), 61.65 ($OO\underline{C}H_2$), 14.14 (-$OOC\underline{C}H_3$); ^{31}P NMR($CDCl_3$) δ: 10.97.

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