Synthesis and antibacterial activities of α-hydroxyphosphonates and α-acetyloxyphosphonates derived from 2-chloroquinoline-3-carbaldehyde

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Abstract

α-Hydroxyphosphonates **2a-g** derived from 2-chloroquinolin-3-carbaldehyde **1a-g** by modified Abramov reaction using chloro(trimethyl)silane (TMSCl) and subsequent α-hydroxyphosphonate produced were acetylated using acetic anhydride in the presence of 1,8-Diazabicyclo-undec-7-ene (DBU) to afford the α-acetyloxyphosphonate **3a-g** in high yields. The synthesized α-hydroxyphosphonate and α-acetyloxyphosphonate compounds were screened for antibacterial activities. The compound no. 2d, 2e and 3e, 3f has shown comparative activity against their standard Streptomycin.

Keywords: 2-Chloroquinoline-3-carbaldehyde, Abramov reaction, α-hydroxyphosphonate, α-acetyloxyphosphonate, TMSCl, DBU

Introduction

Quinolines[1-3] are an important class of heterocyclic compounds. Several compounds of this class have been screened for biological activities such as bactericidal,[4] antitumor,[5] anti-inflammatory,[6] antimalerial[7] etc. Among quinolines, 2-choloroquinolin-3-carbaldehydes occupy a prominent position, as the latter are key intermediates for further annelation of a wide variety of ring and for various functional group interconversions.[8-9]

Phosphates are a class of important organic compounds. Similar to pesticides, they have potent insecticidal activities having wide field of application.[10] Recently, some new vinyl phosphates have been reported as potent mechanism based inhibitors of phosphatase[11-13] or phosphodiesterase.[14-15] There are only few reports about synthesis and bioactivity of their

analogues with C-P bond, which have been found to have insecticidal[16] and antifungal[17] activities.

Phosphonates,[18] α-substituted phosphonate and α-hydroxyphosphonates[19] in particular are the quinquavalent organophosphorus compounds of wide applicability in terms of biological activities. α-acetyloxyphosphonates are considered as an important and valuable phosphorus compounds for the synthesis of optically active α-hydroxyphosphonates. Enzymatic systems have been introduced for the enantioselective hydrolysis of racemic α-hydroxyphosphonates.[20-21] Chiral and non-racemic α-hydroxyphosphonates are useful precursors for a variety of α-substituted phosphonate especially for α-aminophosphonic acids, which have received considerable attention in medical, bioorganic and organic chemistry owing to their potential activities as analogues of α-amino acids.[22-25]

We have studied combination of highly bioactive quinoline compounds with phosphonate for antibacterial activities so as to find new antibacterial bioactive compounds and enrich the quinoline and phosphorus chemistry.

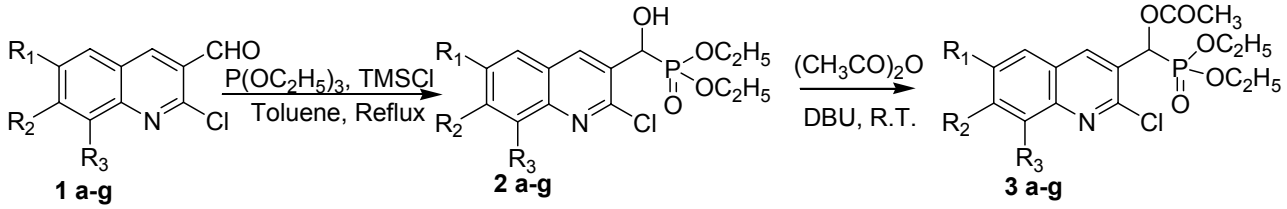
Results and Discussion

The original work of Abramov reaction involved the heating of an aldehyde or a ketone with trialkylphosphite at 70-100^{0}C for several hours in sealed tube[26]. Under these stringent conditions dialky-α-alkoxyalkylphosphonates could be isolated in various yields.

To overcome these difficulties in attempting Abramov reaction silyl halide can be used along with the carbonyl compounds and the phosphorous reagent[27]. Removal of the residual silyl ester linkages at the phosphonate centre is accomplished with water or alcohol under mild conditions[28]. Hence the Abramov reaction with such modification is referred as "Modified Abramov Reaction".

α-hydroxyphosphonates may serve as precursors for the synthesis of alpha amino phosphonates which are analogs of alpha amino acid[29]. Hence a search for new biological active compound has stimulated recent studies on the synthesis of α-substituted phosphonates.

In continuation of our work on phosphorus chemistry, [30, 31] herein several examples of modified Abramov reaction on 2-chloroquinolin-3-carbaldehydes **(1a-g)** are presented to afford α-hydroxyphosphonates **(2a-g)** compounds. The α-acetyloxyphosphonate **(3a-g)** compounds were obtained on further treatment on α-hydroxyphosphonates compounds with acetic anhydride in the presence of DBU catalyst. α-hydroxy as well as α-acetyloxy phosphonate compounds are screened for antibacterial (Gram positive: Staphylococai, Bacillus megtesium-I and Gram negative: Escherichia coli, Salmonella typhi, Proteus vulgaris) activities. Almost all tested compounds exhibited moderate activities against all species of bacteria used in this study. Table-2 indicates that the α-hydroxyphosphonates **(2a-g)** showed more prominent results than the Table-1 parent quinolines (**1a-g**) and Table-3 α-acetyloxyphosphonates **(3a-g)**.



Scheme 1

Table 1. Antibacterial activities of 2-chloroquinolin-3-carbaldehyde

Entry	Antibacterial (zone of inhibition in cm)														
	Gram positive						Gram negative								
	Staphylococci			B. megtesium-I			Escherichia Coli			Salmonella Typhi			Proteus vulgaris		
	Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)		
	40	80	160	40	80	160	40	80	160	40	80	160	40	80	160
1a.	1.4	1.6	1.6	0.9	1.0	1.2	1.2	1.6	1.7	1.3	1.3	1.4	1.2	1.4	1.4
1b.	1.3	1.4	1.6	1.6	1.8	1.8	1.2	1.3	1.5	1.4	1.5	1.5	1.2	1.2	1.6
1c.	1.2	1.4	1.5	1.0	1.3	1.5	1.3	1.5	1.5	1.5	1.5	1.6	1.0	1.3	1.3
1d.	1.0	1.2	1.2	1.3	1.6	1.6	1.5	1.6	1.6	1.2	1.4	1.4	1.1	1.4	1.5
1e.	1.5	1.6	1.7	1.5	1.6	1.8	1.4	1.4	1.6	1.0	1.2	1.3	1.3	1.5	1.5
1f.	1.3	1.4	1.5	1.1	1.3	1.8	1.4	1.7	1.7	1.5	1.5	1.5	1.4	1.6	1.7
1g.	1.2	1.4	1.4	1.3	1.5	1.6	1.6	1.8	1.8	1.4	1.6	1.6	1.3	1.5	1.8
Strep.	1.8	1.8	2.0	1.2	1.2	1.2	1.5	1.6	1.8	1.7	1.8	2.0	1.4	1.6	2.0

Antibacterial activity

All the compounds were screened for antibacterial activities. Antibacterial activities were screened against Gram positive Staphylococai, Bacillus megtesium-I and Gram negative *Escherichia coli*, *Salmonella typhi*, and *Proteus vulgaris*. While screening antibacterial activities, Streptomycin (Strep.) was used as a standard.

Petri dishes and necessary glasswares were autoclaved (121^0, 15 Ib, 30 min). The nutrient agar plates were prepared by pour plate method. The sensitivity of the compounds was tested by disc diffusion method (paper disc method). All the bacterial cells were cultured in nutrient agar plates and the compounds to be tested were dissolved in *N,N*-Dimethylformamide and were soaked on paper disc. The discs were placed into the plates and incubated at 37 ^{0}C for 24 hrs. The diameter (cm) of the zone of inhibition around each disc was measured and results were recorded.

Table 2. Antibacterial activities of diethyl (2-chloro-quinolin-3-yl) hydroxymethylphosphonate:

Entry	Antibacterial (zone of inhibition in cm)														
	Gram positive						Gram negative								
	Staphylococci			B. megtesium-I			Escherichia Coli			Salmonella Typhi			Proteus vulgaris		
	Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)		
	40	80	160	40	80	160	40	80	160	40	80	160	40	80	160
2a.	1.3	1.4	1.4	1.2	1.2	1.3	1.2	1.3	1.4	1.2	1.3	1.3	1.1	1.2	1.2
2b.	1.5	1.6	1.6	2.0	2.0	2.0	1.3	1.5	1.7	1.0	1.2	1.6	1.0	1.0	1.7
2c.	1.1	1.2	2.0	1.2	1.3	2.0	1.4	1.5	1.7	1.0	1.3	1.3	0.9	1.0	1.2
2d.	1.6	1.6	1.7	1.3	1.5	1.5	1.6	1.6	1.8	1.5	1.6	1.6	1.5	1.8	1.8
2e.	1.4	1.5	1.8	1.2	1.2	1.6	1.6	1.9	1.9	2.0	2.1	2.1	1.6	2.0	2.0
2f.	1.5	1.7	1.7	1.6	1.8	1.8	1.5	1.6	1.6	1.5	1.5	1.6	1.4	1.5	1.8
2g.	1.2	1.3	1.5	1.6	1.8	1.8	1.6	1.6	1.8	1.0	1.0	1.3	2.0	2.0	2.0
Strep.	1.8	1.8	2.0	1.2	1.2	1.2	1.5	1.6	1.8	1.7	1.8	2.0	1.4	1.6	2.0

Table 3. Antibacterial activities of diethyl acetoxy (2-chloro-quinolin-3-yl) methylphosphonate

Entry	Antibacterial (zone of inhibition in cm)														
	Gram + ve						Gram – ve								
	Staphylococci			B. megtesium-I			Escherichia Coli			Salmonella Typhi			Proteus vulgaris		
	Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)			Conc. (mg/mL)		
	40	80	160	40	80	160	40	80	160	40	80	160	40	80	160
3a.	0.9	1.0	1.2	1.5	1.5	1.6	1.1	1.2	1.2	1.2	1.3	1.3	1.0	1.2	1.2
3b.	1.1	1.2	1.2	1.2	1.2	1.4	1.0	1.2	1.2	1.1	1.2	1.3	1.0	1.0	1.3
3c.	1.0	1.1	1.2	1.0	1.2	1.2	1.0	1.0	1.1	1.0	1.3	1.6	1.2	1.2	1.2
3d.	1.2	1.2	1.5	1.2	1.2	1.2	1.5	1.5	1.8	1.0	1.0	1.0	1.3	1.3	1.4
3e.	0.8	0.8	1.0	1.2	1.2	1.5	1.6	1.6	1.6	1.0	1.0	1.2	1.2	1.2	1.6
3f.	0.9	1.3	1.3	1.0	1.0	1.0	1.4	1.4	1.4	1.0	1.0	1.2	2.0	2.0	2.0
3g.	1.0	1.2	1.2	1.1	1.2	1.5	1.1	1.1	1.2	0.8	1.1	1.2	1.6	1.7	1.7
Strep.	1.8	1.8	2.0	1.2	1.2	1.2	1.5	1.6	1.8	1.7	1.8	2.0	1.4	1.6	1.8

Conclusions

We have developed a convenient procedure for the preparation of α-hydroxyphosphonates **2a-g** derived from 2-chloroquinolin-3-carbaldehyde **1a-g** by modified Abramov reaction using TMSCl. The α-hydroxyphosphonate **2a-g** was acetylated using acetic anhydride in the presence

of DBU to afford the α-acetyloxyphosphonate **3a-g** in high yields. Standard preparative procedures with simple purification techniques were used. All the reactions were performed in mild reaction conditions. The procedures developed may be suitable for combinatorial use. Synthesized α-hydroxyphosphonate and α-acetyloxyphosphonate compounds were screened for antibacterial activities. The compound no.2d, 2e and 3e, 3f showed comparative activity against their standard Streptomycin. Alpha hydroxy phosphonates are more active than parent aldehyde see table-1 &2 for comparison.

Experimental section

General Procedures. 2-Chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported method.[32] 1, 8-Diazabicyclo-undec-7-ene (DBU), triethylphosphite, chloro(trimethyl)silane were procured from Lancaster. Toluene, dichloromethane, methanol and hexane were procured from S. D. Fine-chem.

All melting points were determined in open capillaries on Kumar's melting point apparatus. The products were characterized by their spectral data. ^{1}H NMR spectra were recorded on Varian Gemini 2000 in $CDCl_3$ at 200 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quatrro-II using electrospray Ionisation technique, showing (m+1) peak as a base peak. The test for the purity of products and the progress of the reactions were accomplished by TLC on Merck silica gel plates.

General procedure. Diethyl (2 –chloro-quinolin-3-yl) (hydroxy) methylphosphonate (2a). A mixture of 2-chloroquinoline-3-carbaldehyde (0.95 gm, 5 mmol) and triethylphosphite (1.66 gm, 10 mmol) in 10 ml toluene was refluxed in an oil-bath and chloro(trimethyl)silane (1.08 gm, 10 mmol) was added to the refluxing solution. Progress of reaction was monitored on TLC. After completion of reaction (20 min.), the mixture was concentrated on rotary-evaporator under reduced pressure, to obtain an oily residue. The oily residue was dissolved in methanol for the removal of excess TMSCl. This methanolic solution was concentrated, dissolved in dichloromethane and reprecipitated with hexane. Thus obtained solid was filtered, washed with hexane and dried in oven at 40 ^{0}C (1.38 gm, yield 76.4 %, m.p. 124-126 ^{0}C).

IR (KBr), cm^{-1}: 3246 (- OH); 1218 (- P=O); 1033 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-C$\underline{H}_3$); 1.3 (t, 3H, O-CH_2-C$\underline{H}_3$); 2.0 (s, 1H, -CH-O$\underline{H}$); 4.0 (m, 4H, O-C$\underline{H}_2$-CH_3 and O-C$\underline{H}_2$-CH_3); 5.6 (d, 1H, -C$\underline{H}$-P=O); 7.5 (t, 1H, Ar-$\underline{H}$, C_6); 7.7 (t, 1H, Ar-$\underline{H}$, C_7); 7.8 (d,1H, Ar-$\underline{H}$, C_5); 8.0 (d, 1H, Ar-$\underline{H}$, C_8); 8.6 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 330 (m+1) base peak and 331.9 (m+3).

Elemental analysis: $C_{14}H_{17}ClNO_4P$ Calcd.: C: 51.00 %, H: 5.20 %, N: 4.25 %; Found: C: 51.027 %, H: 5.393 %, N: 4.353 %.

Diethyl (2-chloro-6-methylquinolin-3-yl)(hydroxy)methylphosphonate (2b). Yield 80.8 %, m.p. 145-147 ^{0}C. IR (KBr), cm^{-1}: 3278 (-OH); 1218 (-P=O); 1037 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ

ppm: 1.2 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.3 (t, 3H , O-CH_2-$C\underline{H}_3$); 2.4 (s, 1H, -CH-O$\underline{H}$); 2.5 (s, 3H , Ar-$C\underline{H}_3$); 4.1 (q, 2H , O-CH_2-$C\underline{H}_3$); 4.2 (q, 2H , O-$C\underline{H}_2$-CH_3); 5.6 (d, 1H , C$\underline{H}$-P=O); 7.5 (s, 1H , Ar-$\underline{H}$, C_5); 7.6 (d, 1H , Ar-$\underline{H}$, C_7); 7.9 (d, 1H , Ar-$\underline{H}$, C_8); 8.5 (s, 1H , Ar-$\underline{H}$, C_4). ES-MS: m/z 344 (m+1) base peak and 345.9 (m+3). Elemental analysis: $C_{15}H_{19}ClNO_4P$ Calcd.: C: 52.41 %, H: 5.57 %, N: 4.07 %; Found: C: 52.50 %, H: 5.67 %, N: 4.17 %.

Diethyl (2-chloro-8-methylquinolin-3-yl)(hydroxy)methylphosphonate (2c). Yield 80.8 %, m.p. 141-143 ^{0}C. IR (KBr) cm^{-1}: 3240 (-OH); 1215 (-P=O); 1037 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.3 (t, 3H, O-CH_2-$C\underline{H}_3$); 2.4 (s,1H, -CH-O$\underline{H}$); 2.7 (s, 3H, Ar-$C\underline{H}_3$); 4.2 (q, 2H, O-$C\underline{H}_2$-CH_3); 4.3 (q, 2H, O-$C\underline{H}_2$-CH_3); 5.6 (d,1H, C$\underline{H}$-P=O); 7.4 (t, 1H, Ar-$\underline{H}$, C_6); 7.6 (d, 1H, Ar-$\underline{H}$, C_5); 7.7 (d, 1H, Ar-$\underline{H}$, C_7); 8.5 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 344 (m+1) base peak and 346 (m+3). Elemental analysis: $C_{15}H_{19}ClNO_4P$ Calcd.: C: 52.41 %, H: 5.57 %, N: 4.07 %; Found: C: 52.61 %, H: 5.63 %, N: 4.18 %.

Diethyl (2-chloro-6-methoxyquinolin-3-yl)(hydroxy)methylphosphonate (2d). Yield 83.3 %, m.p. 170-172 ^{0}C. IR (KBr) cm^{-1}: 3269 (-OH); 1218 (-P=O); 1033 (-P-O-C).**),** δ ppm^{1}H NMR ($CDCl_3$: 1.2 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.3 (t, 3H, O-CH_2-$C\underline{H}_3$); 2.6 (s, 1H, -CH-O$\underline{H}$); 3.8 (s, 3H, Ar-O-$C\underline{H}_3$); 4.1 (q, 2H, O-$C\underline{H}_2$-CH_3); 4.2 (q, 2H, O-$C\underline{H}_2$-CH_3); 5.6 (d, 1H, C$\underline{H}$-P=O); 7.0 (s, 1H, Ar-$\underline{H}$, C_5); 7.4 (d, 1H, Ar-$\underline{H}$, C_7); 7.9 (d, 1H, Ar-$\underline{H}$, C_8); 8.5 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 360 (m+1) base peak and 362 (m+3).

Elemental analysis: $C_{15}H_{19}ClNO_5P$ Calcd.: C: 50.08 %, H: 5.32 %, N: 3.89 %; Found: C: 50.20 %, H: 5.39 %, N: 3.93 %.

Diethyl (2-chloro-7-methoxyquinolin-3-yl)(hydroxy)methylphosphonate (2e). Yield 80.3 %, m.p. 154-156 ^{0}C. IR (KBr) cm^{-1}: 3269 (-OH); 1218 (-P=O); 1033 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.3 (t, 3H, O-CH_2-$C\underline{H}_3$); 2.7 (s, 1H, -CH-O$\underline{H}$); 3.9 (s, 3H, Ar-O-$C\underline{H}_3$); 4.1 (q, 2H, O-$C\underline{H}_2$-CH_3); 4.2 (q, 2H, O-$C\underline{H}_2$-CH_3); 5.6 (d, 1H, C$\underline{H}$-P=O); 7.2 (d, 1H, Ar-$\underline{H}$, C_6); 7.3 (s, 1H, Ar-$\underline{H}$, C_8), 7.7 (d, 1H, Ar-$\underline{H}$, C_5); 8.5 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 343.9 (m+1) base peak and 346 (m+3).

Elemental analysis: $C_{15}H_{19}ClNO_5P$ Calcd.: C: 50.08 %, H: 5.32 %, N: 3.89 %; Found: C: 50.157 %, H: 5.52 %, N: 4.10 %.

Diethyl (2-chloro-6-ethoxyquinolin-3-yl)(hydroxy)methylphosphonate (2f). Yield 79.2 %, m.p. 168-170 ^{0}C. IR (KBr) cm^{-1}: 3255 (-OH); 1234 (-P=O); 1049 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.3 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.4 (t, 3H, Ar-O-CH_2-$C\underline{H}_3$); 3.4 (bs, 1H, -CH-O$\underline{H}$); 4.1 (q, 2H, O-$C\underline{H}_2$-CH_3); 4.2 (q, 2H, O-$C\underline{H}_2$-CH_3); 4.3 (q, 2H,, O-$C\underline{H}_2$-CH_3); 5.6 (d, 1H, C$\underline{H}$-P=O); 7.0 (s, 1H, Ar-$\underline{H}$,C_5); 7.4 (d, 1H, Ar-$\underline{H}$, C_7); 7.9 (d, 1H, Ar-$\underline{H}$, C_8); 8.4 (s, 1H, Ar-$\underline{H}$, C_4). **ES-MS:** m/z 374 (m+1) base peak and 376 (m+3). Elemental analysis: $C_{16}H_{21}ClNO_5P$ Calcd.: C: 51.41 %, H: 5.66 %, N: 3.75 %; Found: C: 51.527 %, H: 5.793 %, N: 3.85 %.

Diethyl (2-chloro-8-ethylquinolin-3-yl)(hydroxyl)methylphosphonate (2g). Yield 77.1 %, m.p. 145-147 ^{0}C. IR (KBr) cm^{-1}: 3252 (-OH); 1223 (-P=O); 1041 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-$C\underline{H}_3$); 1.35 (m, 6H, O-CH_2-$C\underline{H}_3$ and Ar-CH_2-$C\underline{H}_3$); 2.3 (s, 1H, -CH-O$\underline{H}$);3.25 (q, 2H, Ar-$C\underline{H}_2$-CH_3); 4.2 (m, 4H, O-$C\underline{H}_2$-CH_3 and O-$C\underline{H}_2$-CH_3); 5.6 (d, 1H, C$\underline{H}$-P=O); 7.5 (t, 1H, Ar-$\underline{H}$, C_6); 7.6 (d, 1H, Ar-$\underline{H}$, C_7); 7.7 (d, 1H, Ar-$\underline{H}$, C_5); 8.5 (s,1H, Ar-$\underline{H}$, C_4).

ES-MS: m/z 358 (m+1) base peak and 360 (m+3). Elemental analysis: $C_{16}H_{21}ClNO_4P$ Calcd.: C: 53.71 %, H: 5.92 %, N: 3.92 %; Found: C: 53.82 %, H: 5.99 %, N: 4.05 %.

Diethyl acetoxy(2-chloro-quinolin-3-yl)methylphosphonate (3a). To the stirring mixture of diethyl (2-chloro-quinolin-3-yl) (hydroxy) methylphosphonate (0.49 gm, 1.5 mmol) and acetic anhydride (0.46 gm, 4.5 mmol), DBU (0.25 gm, 1.64 mmol) catalyst was added at room temperature. The reaction mixture was stirred at room temperature. Progress of reaction was monitored on TLC. After completion of reaction (10 min.), reaction mixture was poured on crushed ice and stirred to get a solid product. The obtained solid was filtered and washed with water, dried in oven at 40 ^{0}C (0.52 gm, yield 96.2 %, m.p. 85-87 ^{0}C). IR (KBr) cm^{-1}: 1757 cm^{-1} (-O-CO-CH3); 1218 cm^{-1} (-P=O); 1027 cm^{-1}(-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-C$\underline{H}_3$); 1.3 (t, 3H, O-CH_2-C$\underline{H}_3$); 2.2 (s, 3H, O-CO-C$\underline{H}_3$); 4.0 (q, 2H, O-C$\underline{H}_2$-CH_3); 4.2 (q, 2H, O-C$\underline{H}_2$-CH_3); 6.6 (d,1H, -C$\underline{H}$-P=O); 7.6 (t, 1H, Ar-$\underline{H}$, C_6); 7.7 (t, 1H, Ar-$\underline{H}$, C_7); 7.8 (d, 1H, Ar-$\underline{H}$, C_5); 8.0 (d, 1H, Ar-$\underline{H}$, C_8); 8.4 (s,1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 372 (m+1) base peak and 374 (m+3). Elemental analysis: $C_{16}H_{19}ClNO_5P$ Calcd.: C: 51.69 %, H: 5.15 %, N: 3.77 %; Found: C: 51.82 %, H: 5.25 %, N: 3.85 %.

Diethyl acetoxy(2-chloro-6-methylquinolin-3-yl)methylphosphonate (3b). Yield 94.6 %, m.p. 86-88 ^{0}C. IR (KBr) cm^{-1}: 1759 (-O-CO-CH3); 1217 (-P=O); 1020.3 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-C$\underline{H}_3$); 1.3 (t, 3H, O-CH_2-C$\underline{H}_3$); 2.2 (s, 3H, O-CO-C$\underline{H}_3$); 2.5 (s, 3H, Ar-C$\underline{H}_3$); 4.2 (q, 2H, O-C$\underline{H}_2$-CH_3); 4.2 (q, 2H, O-C$\underline{H}_2$-CH_3); 6.6 (d, 1H, -C$\underline{H}$-P=O); 7.5 (d, 1H, Ar-$\underline{H}$, C_7); 7.6 (s, 1H, Ar-$\underline{H}$, C_5); 7.9 (d, 1H, Ar-$\underline{H}$, C_8); 8.4 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 386 (m+1) base peak and 388 (m+3). Elemental analysis: $C_{17}H_{21}ClNO_5P$ Calcd.: C: 52.93 %, H: 5.49 %, N: 3.63 %; Found: C: 53.027 %, H: 5.59 %, N: 3.75 %.

Diethyl acetoxy(2-chloro-8-methylquinolin-3yl)methylphosphonate (3c). Yield 92.8 %, m.p. 98-100 ^{0}C. IR (KBr) cm^{-1}: 1751.2 (-O-CO-CH3); 1218.9 (-P=O); 1041.5 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-C$\underline{H}_3$); 1.3 (t, 3H, O-CH_2-C$\underline{H}_3$); 2.2 (s, 3H, O-CO-C$\underline{H}_3$); 2.7 (s, 3H, Ar-C$\underline{H}_3$); 4.0 (q, 2H, O-C$\underline{H}_2$-CH_3); 4.2 (q, 2H, O-C$\underline{H}_2$-CH_3); 6.6 (d, 1H, -C$\underline{H}$-P=O); 7.4 (t, 1H, Ar-$\underline{H}$, C_6); 7.6 (d, 1H, Ar-$\underline{H}$, C_7); 7.7 (d, 1H, Ar-$\underline{H}$, C_5); 8.4 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 386 (m+1) base peak and 388.1 (m+3). Elemental analysis: $C_{17}H_{21}ClNO_5P$ Calcd.: C: 52.93 %, H: 5.49 %, N: 3.63 %; Found: C: 52.98 %, H: 5.65 %, N: 3.80 %.

Diethyl acetoxy(2-chloro-6-methoxyquinolin-3-yl)methylphosphonate (3d). Yield 96.2 %, m.p. 96-98 ^{0}C. IR (KBr) cm^{-1}: 1747.4 (-O-CO-CH3); 1224.7 (-P=O); 1047.3 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-C$\underline{H}_3$); 1.3 (t, 3H, O-CH_2-C$\underline{H}_3$); 2.2 (s, 3H, O-CO-C$\underline{H}_3$); 3.9 (s, 3H, Ar-O-C$\underline{H}_3$); 4.0 (q, 2H, O-C$\underline{H}_2$-CH_3); 4.2 (q, 2H, O-C$\underline{H}_2$-CH_3); 6.6 (d, 1H, -C$\underline{H}$-P=O); 7.1 (s, 1H, Ar-$\underline{H}$, C_5), 7.4 (d, 1H, Ar-$\underline{H}$, C_7); 7.9 (d, 1H, Ar-$\underline{H}$, C_8); 8.4 (s, 1H, Ar-$\underline{H}$, C_4). ES-MS: m/z 401.9 (m+1) base peak and 404 (m+3). Elemental analysis: $C_{17}H_{21}ClNO_6P$ Calcd.: C: 50.82 %, H: 5.27 %, N: 3.49 %; Found: C: 51.00 %, H: 5.39 %, N: 3.65 %.

Diethyl acetoxy(2-chloro-7-methoxyquinolin-3-yl)methylphosphonate (3e). Yield 94.6 %, m.p. 98-100 ^{0}C. IR (KBr) cm^{-1}: 1751.2 (-O-CO-CH3); 1211.2 (-P=O); 1031.8 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-C$\underline{H}_3$); 1.3 (t, 3H, O-CH_2-C$\underline{H}_3$); 2.2 (s, 3H, O-CO-C$\underline{H}_3$); 3.9 (s, 3H, Ar-O-C$\underline{H}_3$); 4.0 (q, 2H, O-C$\underline{H}_2$-CH_3); 4.2 (q, 2H, O-C$\underline{H}_2$-CH_3); 6.6 (d, 1H, -C$\underline{H}$-P=O);

7.2 (d, 1H, Ar-H, C_6); 7.4 (s, 1H, Ar-H, C_8); 7.7 (d,1H, Ar-H, C_5); 8.4 (s, 1H, Ar-H, C_4). ES-MS: m/z 402 (m+1) base peak and 403.9 (m+3). Elemental analysis: $C_{17}H_{21}ClNO_6P$ Calcd.: C: 50.82 %, H: 5.27 %, N: 3.49 %; Found: C: 50.927 %, H: 5.46 %, N: 3.59 %.

Diethyl acetoxy(2-chloro-6-ethoxyquinolin-3-yl)methylphosphonate (3f). Yield 94.6 %, m.p. 113-115 ^{0}C. IR (KBr) cm^{-1}: 1763 (-O-CO-CH3); 1223 (-P=O); 1029 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (m, 6H, O-CH_2-CH_3 and Ar-O-CH_2- CH_3); 2.2 (s, 3H, O-CO-CH_3); 3.2 (q, 2H, Ar-O-CH_2-CH_3); 4.0 (q, 2H, O-CH_2-CH_3); 4.2 (q, 2H, O-CH_2-CH_3); 6.6 (d, 1H, -CH-P=O); 7.4 (t, 1H, Ar-H, C_6); 7.6 (d, 1H, Ar-H, C_7); 7.7 (d, 1H, Ar-H, C_5); 8.4 (s, 1H, Ar-H,C_4). ES-MS: m/z 416 (m+1) base peak and 418.1 (m+3). Elemental analysis: $C_{18}H_{23}ClNO_6P$ Calcd.: C: 51.99 %, H: 5.58 %, N: 3.37 %; Found: C: 52.12 %, H: 5.69 %, N: 3.45 %.

Diethyl acetoxy (2-chloro-8-ethylquinolin-3-yl) methylphosphonate (3g). Yield 96.4 %, m.p. 85-87 ^{0}C. IR (KBr) cm^{-1}: 1751.2 (-O-CO-CH3); 1234.4 (-P=O); 1041.5 (-P-O-C). ^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (m, 6H, O-CH_2-CH_3 and Ar-CH_2- CH_3); 2.2 (s, 3H, O-CO-CH_3); 3.2 (q, 2H, Ar-CH_2-CH_3); 4.0 (q, 2H, O-CH_2-CH_3); 4.2 (q, 2H, O-CH_2-CH_3); 6.6 (d, 1H, -CH-P=O); 7.4 (t, 1H, Ar-H, C_6); 7.6 (d, 1H, Ar-H, C_7); 7.7 (d, 1H, Ar-H, C_5); 8.4 (s, 1H, Ar-H, C_4). **ES-MS:** m/z 400.1 (m+1) base peak and 402 (m+3). Elemental analysis: $C_{18}H_{23}ClNO_5P$ Calcd.: C: 54.07 %, H: 5.80 %, N: 3.50 %; Found: C: 54.12 %, H: 5.95 %, N: 3.60 %.

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