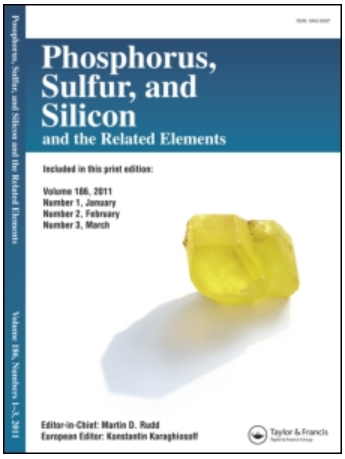

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Simple and High Yielding Synthesis of New α-Aminophosphonates from Imines

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A simple and high yielding method was developed for the synthesis of novel α-aminophosphonates from imines, obtained from 2-chloroquinoline-3-carbaldehyde, by using triethylphosphite in the presence of chlorotrimethylsilane (TMSCl). This method developed for the synthesis of α-aminophosphonates gave excellent yields.

Keywords 2-Chloroquinoline-3-carbaldehyde; α-aminophosphonate; imines; TMSCl; triethylphosphite

INTRODUCTION

Quinolines[1] are an important class of heterocyclic compounds and have been screened for biological activities such as bactericidal,[2] antitumor,[3] anti-inflammatory,[4] antimalarial[5] activities. Quinolines such as 2-chloroquinoline-3-carbaldehyde occupy a prominent position as they are key intermediates for further annelation and for various functional group interconversions.[6] It is also reported that organophosphates are potent pesticides, which have wide variety of application.[7]Recently, some new vinyl phosphates have been reported as potent inhibitors of phosphatase[8] and phosphodiesterase.[9] There are only few reports on the synthesis and bioactivity of their analogues which have been found to have insecticidal[10] and antifungal[11] activities. Also, phosphonates[12] and α-aminophosphonates are important biologically active compounds[13]due to their structural analogy to amino acids,

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and has been the subject of considerable current interest. They act as peptide mimics,[14] enzyme inhibitors,[15]antibiotics and pharmacological agents.[16]

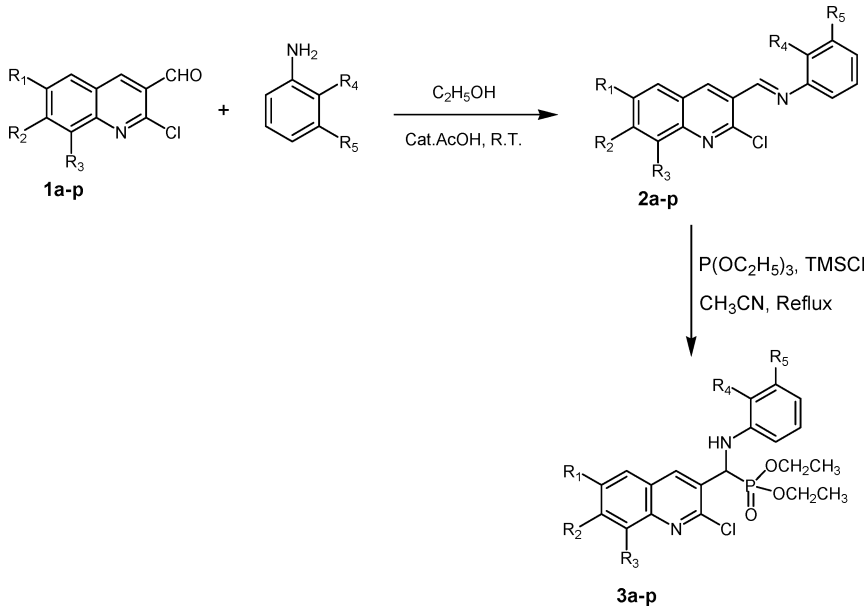
Generally, α-aminophosphonates are prepared in the presence of Lewis acids or bases by the addition of phosphorous nucleophiles to the imines. Lewis acids such as $SnCl_4$, $SnCl_2$, $ZrCl_4$, $ZnCl_2$ and $MgBr_2$ have been used as catalysts for such reactions.[17] Recently, Lewis and Bronsted acids such as $LiClO_4$,[18] $InCl_3$,[19] lanthanide triflates,[20] $TaCl_5$-SiO_2,[21]montmorillonite clay-MW,[22]Al_2O_3-MW,[23] CF_3COOH[24] were found to be effective in the preparation of α-aminophosphonates. However, many of these procedures require expensive reagents, long reaction times and suffer from poor yields. These reactions cannot be carried out in one-step by the reaction between a carbonyl compounds, an amine and dialkylphosphite because the amine and water present during imine formation can decompose or deactivate the Lewis acid.[25]

RESULTS AND DISCUSSION

In continuation of our work related to phosphorus chemistry,[26] we were interested in the synthesis of α-aminophosphonates. We have synthesized for the first time α-aminophosphonates containing highly bioactive quinoline moiety in two steps. In the first step, imines of

TABLE I Synthesis of Imines of 2-Chloroquinoline-3-carbaldehydes

Entry	R_1	R_2	R_3	R_4	R_5	Reaction time (min.)	Yield (%)	m.p. (^{0}C).
2a	H	H	H	H	F	20	95.7	108–110
2b	CH_3	H	H	H	F	30	96.2	117–119
2c	H	CH_3	H	H	F	24	96.0	115–117
2d	H	H	CH_3	H	F	25	95.2	106–108
2e	OCH_3	H	H	H	F	30	94.8	200–202
2f	H	OCH_3	H	H	F	25	96.2	148–150
2g	OC_2H_5	H	H	H	F	25	94.6	157–159
2h	H	H	C_2H_5	H	F	30	96.2	91–93
2i	H	H	H	CH_3	H	22	95.8	133–135
2j	CH_3	H	H	CH_3	H	25	94.6	130–132
2k	H	CH_3	H	CH_3	H	30	95.5	125–127
2l	H	H	CH_3	CH_3	H	25	96.0	142–144
2m	OCH_3	H	H	CH_3	H	25	95.4	172–174
2n	H	OCH_3	H	CH_3	H	20	96.2	132–134
2o	OC_2H_5	H	H	CH_3	H	30	94.8	161–163
2p	H	H	C_2H_5	CH_3	H	25	96.0	106–108



SCHEME 1 Synthesis of α-aminophosphonates from Imines of 2-Chloroquinoline-3-carbaldehyde.

2-chloroquinoline-3-carbaldehyde were synthesized and converted to α-aminophosphonates using TMSCl and triethylphosphite in the next step.

Imines (**2a–p**) (Scheme 1, Table I) were prepared at room temperature from derivatives of 2-chloroquinoline-3-carbaldehyde and 3-fluoroaniline or 2-methylaniline in ethanol using catalytic amount of acetic acid in excellent yields and were characterized by mass spectra. α-aminophosphonates (**3a–p**) (Scheme 1, Table II) were then prepared in excellent yields by reacting imines (**2a–p**) with triethylphosphite in the presence of TMSCl under reflux using acetonitrile as the solvent. After completion of the reaction, the excess TMSCl was removed using methanol. Sixteen new compounds were synthesized using this methodology in excellent yields. All the compounds synthesized were unequivocally characterized based on analytical data.[27]

CONCLUSION

In conclusion, a new methodology was developed for the synthesis of new α-aminophosphonate derivatives from imines of 2-chloroquinoline-3-carbaldehydes for first time using TMSCl. All the reactions were

TABLE II TMSCl Facilitated Synthesis of α-Aminophosphonates

Entry	R_1	R_2	R_3	R_4	R_5	Reaction time (min.)	Yield (%)	m.p. (^{0}C).
3a	H	H	H	H	F	60	92.1	146–148
3b	CH_3	H	H	H	F	55	90.1	136–138
3c	H	CH_3	H	H	F	60	92.5	163–165
3d	H	H	CH_3	H	F	60	89.2	113–115
3e	OCH_3	H	H	H	F	50	91.0	153–155
3f	H	OCH_3	H	H	F	60	93.3	155–157
3g	OC_2H_5	H	H	H	F	60	91.0	160–162
3h	H	H	C_2H_5	H	F	70	92.2	159–161
3i	H	H	H	CH_3	H	50	90.0	139–141
3j	CH_3	H	H	CH_3	H	60	89.5	104–106
3k	H	CH_3	H	CH_3	H	55	92.0	143–145
3l	H	H	CH_3	CH_3	H	60	92.0	160–162
3m	OCH_3	H	H	CH_3	H	65	90.0	98–100
3n	H	OCH_3	H	CH_3	H	60	92.0	126–128
3o	OC_2H_5	H	H	CH_3	H	50	90.5	146–148
3p	H	H	C_2H_5	CH_3	H	60	91.2	133–135

performed under mild reaction conditions, shorter reaction time and in quantitative yields (Table II). The methodology developed will be of much use to combinatorial chemist.

EXPERIMENTAL

2-Chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported procedure[28]and were purified by column chromatography over silica gel (60–120 mesh). 3-fluoroaniline, 2-methylaniline, triethylphosphite, TMSCl were procured from Lancaster. Acetonitrile, *N*, *N*-Dimethylformamide (DMF), absolute ethanol, acetic acid, methanol and hexane were procured from S.D.Fine-chem. All melting points were determined in open capillaries on Kumar's melting point apparatus. ^{1}H NMR spectra were recorded on Mercury Plus Varian in $CDCl_3$at 400 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 Ionization 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: (2a) *N*-((2-chloroquinolin-3-yl) methylene)-3-fluorobenzenamine

To the stirred solution of 2-chloroquinoline-3-carbaldehyde (0.95 g, 5 mmol) in 10 ml absolute ethanol was added 3-fluoroaniline (0.68 g, 6 mmol) and 4 to 5 drops of acetic acid. The progress of reaction was monitored on TLC (solvent system-Hexane: Ethyl acetate). After the completion of the reaction (20 min), 20 ml of water was added and the solid obtained was filtered and washed with water, dried in oven at 50°C for 5.0 h (1.35 g, yield 95.7 %). **ES-MS:** m/z 285 (m+1) and 287 (m+3)

3a) Diethyl (3-fluorophenylamino)(2-chloroquinolin-3-yl)methylphosphonate:

To a mixture of *N*-((2-chloroquinolin-3-yl-methylene)-3-fluorobenze namine (1.12 g, 4 mmol) and triethylphosphite (1.66 g, 10 mmol) in 10 ml acetonitrile under reflux was added TMSCl (1.08 g, 10 mmol). The progress of the reaction was monitored on TLC using Hexane: Ethyl acetate (8:2) as the solvent system. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain an oily residue. The oily residue was dissolved in methanol and was concentrated, and triturated with hexane. The solid obtained was filtered, washed with hexane. The solid was further recrystallized from DMF and water mixture, dried in oven at 50°C for 8.0 h (dry wt. = 1.53 g, yield 92.1%).

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[27] Spectral data for the all the compounds are as given as follows. **3a) Diethyl (3-fluorophenylamino)(2-chloroquinolin-3-yl)methylphosphonate: IR (KBr):** 3311 cm^{-1} (-NH) ; 1234 cm^{-1} (—P═O) ; 1032 cm^{-1}(—P—O—C) ^{1}**H NMR (CDCl$_3$,** δ **ppm):** 1.05 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.35 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.9 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.2 (m, 2H, O—C$\underline{H}_2$—CH_3); 5.4 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.3–6.5 (m, 3H, Ph-$\underline{H}$, C_2, C_4, C_6); 7.0 (dd, 1H, Ph—$\underline{H}$, C_5, J = 8 Hz); 7.5 (t, 1H, Quinolin-$\underline{H}$, C_5, J = 8 Hz); 7.69 (t, 1H, Quinolin-$\underline{H}$, C_6, J = 8 Hz); 7.75 (d,1H, Quinolin-$\underline{H}$, C_7, J = 8 Hz); 7.99 (d, 1H, Quinolin-$\underline{H}$, C_8, J = 8 Hz); 8.34 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 8 Hz). **ES-MS:** m/z 423.1 (m+1) and 425.1 (m+3). **Elemental analysis:** $C_{20}H_{21}ClFN_2O_3P$ Calcd.: C: 56.81%, H: 5.01%, N: 6.63%; Found: C: 56.72%, H: 4.95%, N: 6.65%. **3b) Diethyl (3-fluorophenylamino)(2-chloro-6-methylquinolin-3-yl)methylphosphonate: IR (KBr):** 3305 cm^{-1} (—NH) ; 1230 cm^{-1} (═P═O) ; 1022 cm^{-1}(—P—O—C) ^{1}**H NMR (CDCl$_3$,** δ **ppm):** 1.05 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.38 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.48 (s, 3H, Quinolin-C$\underline{H}_3$); 3.68 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.88 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.22 (m, 2H, O—C$\underline{H}_2$—CH_3); 5.16 (s, 1H, —CH—N$\underline{H}$—Ph); 5.35

(d, 1H, —NH—CH—P═O, J = 24 Hz); 6.28–6.42 (m, 3H, Ph—H, C_2, C_4, C_6); 7.02 (dd, 1H, Ph—H, C_5, J = 8 Hz); 7.5 (d, 1H, Quinolin-H, C_7, J = 8 Hz); 7.6 (s, 1H, Quinolin-H, C_5); 7.9 (d,1H, Quinolin-H, C_8, J = 8 Hz); 8.3 (d, 1H, Quinolin-H, C_4, J = 8 Hz). **ES-MS:** m/z 437.1 (m+1) and 439.2 (m+3). **Elemental analysis:** $C_{21}H_{23}ClFN_2O_3P$ Calcd.: C: 57.74%, H: 5.31%, N: 6.41%; Found: C: 57.62%, H: 5.21%, N: 6.35%. **3c) Diethyl (3-fluorophenylamino)(2-chloro-7-methylquinolin-3-yl)methylphosphonate: IR (KBr):** 3296 cm^{-1} (—NH) ; 1230 cm^{-1} (—P═O) ; 1033 cm^{-1}(—P—O—C) **^{1}H NMR ($CDCl_3$, δ ppm):** 1.03 (t, 3H, O—CH_2—CH, J = 8 Hz); 1.36 (t, 3H, O—CH_2—CH, J = 8 Hz); 2.54 (s, 3H, Quinolin-CH_3); 3.66 (m, 1H, O—CH_2—CH_3); 3.89 (m, 1H, O—CH_2-CH_3); 4.22 (m, 2H, O—CH_2—CH_3); 5.15 (s, 1H, —CH—NH—Ph); 5.35 (d, 1H, —NH—CH—P═O, J = 24 Hz); 6.28–6.5 (m, 3H, Ph—H, C_2, C_4, C_6); 7.0 (dd, 1H, Ph—H, C_5, J = 8 Hz); 7.34 (d, 1H, Quinolin-H, C_6, J = 4 Hz); 7.65 (d, 1H, Quinolin-H, C_5, J = 8 Hz); 7.77 (s, 1H, Quinolin-H, C_8); 8.27 (d, 1H, Quinolin-H, C_4, J = 8 Hz). **ES-MS:** m/z 437.0 (m+1) and 439.1 (m+3). **Elemental analysis:** $C_{21}H_{23}ClFN_2O_3P$ Calcd.: C: 57.74%, H: 5.31%, N: 6.41%; Found: C: 57.50%, H: 5.15%, N: 6.30%. **3d) Diethyl (3-fluorophenylamino)(2-chloro-8-methylquinolin-3-yl) methylphosphonate: IR (KBr):** 3296 cm^{-1} (—NH) ; 1235 cm^{-1} (—P═O) ; 1028 cm^{-1}(—P—O—C) **^{1}H NMR ($CDCl_3$, δ ppm):** 1.05 (t, 3H, O—CH_2—CH, J = 8 Hz); 1.36 (t, 3H, O—CH_2—CH, J = 8 Hz); 2.5 (s, 3H, Quinolin—CH_3); 3.68 (m, 1H, O—CH_2—CH_3); 4.22 (m, 2H, O—CH_2—CH_3); 5.18 (s, 1H, —CH—NH—Ph); 5.35 (d, 1H, —NH—CH—P═O, J = 24 Hz); 6.2–6.5 (m, 3H, Ph—H, C_2, C_4, C_6); 7.0 (dd, 1H, Ph—H, C_5, J = 8 Hz); 7.33 (t, 1H, Quinolin-H, C_6, J = 8 Hz); 7.5 (d, 1H, Quinolin-H, C_7, J = 4 Hz); 7.6 (d, 1H, Quinolin-H, C_5, J = 8 Hz); 8.22 (s, 1H, Quinolin-H, C_4, J = 8 Hz). **ES-MS:** m/z 437.2 (m+1) and 439.1 (m+3). **Elemental analysis:** $C_{21}H_{23}ClFN_2O_3P$ Calcd.: C: 57.74%, H: 5.31%, N: 6.41%; Found: C: 57.65%, H: 5.25%, N: 6.40%. **3e) Diethyl (3-fluorophenylamino)(2-chloro-6-methoxyquinolin-3-yl) methylphosphonate: IR (KBr):** 3305 cm^{-1} (— NH); 1224 cm^{-1} (— P═O); 1033 cm^{-1}(—P—O—C) **^{1}H NMR ($CDCl_3$, δ ppm):** 1.05 (t, 3H, O—CH_2—CH, J = 8 Hz); 1.35 (t, 3H, O—CH_2—CH, J = 8 Hz); 3.68 (m, 1H, O—CH_2-CH_3); 3.88 (s, 3H, Quinolin—O—CH_3); 3.9 (m, 1H, O—CH_2—CH_3); 4.22 (m, 2H, O—CH_2—CH_3); 5.16 (s, 1H, —CH—NH—Ph); 5.35 (d, 1H, —NH—CH—P═O, J = 24 Hz); 6.28–6.5 (m, 3H, Ph-H, C_2, C_4, C_6);; 6.9 (s, 1H, Quinolin-H, C_5); 7.0 (dd, 1H, Ph-H, C_5, J = 8 Hz); 7.33 (d, 1H, Quinolin-H, C_7, J = 8 Hz); 7.88 (d, 1H, Quinolin-H, C_8, J = 8 Hz); 8.22 (d, 1H, Quinolin-H, C_4, J = 8 Hz).**ES-MS:** m/z 453.1 (m+1) and 455.1 (m+3).**Elemental analysis:** $C_{21}H_{23}ClFN_2O_4P$ Calcd.: C: 55.70%, H: 5.12%, N: 6.19%; Found: C: 55.52%, H: 4.90%, N: 6.05%. **3f) Diethyl (3-fluorophenylamino)(2-chloro-7-methoxyquinolin-3-yl) methylphosphonate: IR (KBr):** 3296 cm^{-1} (— NH) ; 1230 cm^{-1} (— P═O) ; 1024 cm^{-1}(—P—O—C) **^{1}H NMR ($CDCl_3$, δ ppm):** 1.05 (t, 3H, O—CH_2—CH, J = 8 Hz); 1.33 (t, 3H, O—CH_2—CH, J = 8 Hz); 3.68 (m, 1H, O—CH_2—CH_3); 3.86 (s, 3H, Quinolin—O—CH_3); 3.9 (m, 1H, O-CH_2—CH_3); 4.22 (m, 2H, O—CH_2—CH_3); 5.16 (s, 1H, -CH-NH-Ph); 5.32 (d, 1H, —NH—CH—P═O, J = 24 Hz); 6.3–6.5 (m, 3H, Ph-H, C_2, C_4, C_6); 7.0 (dd, 1H, Ph—H, C_5, J = 8 Hz); 7.2 (d, 1H, Quinolin-H, C_6, J = 8 Hz); 7.3 (s, 1H, Quinolin-H, C_8); 7.62 (d,1H, Quinolin-H, C_5, J = 8 Hz); 8.22 (d, 1H, Quinolin-H, C_4, J = 8 Hz). **ES-MS:** m/z 453.1 (m+1) and 455.0 (m+3). **Elemental analysis:** $C_{21}H_{23}ClFN_2O_4P$ Calcd.: C: 55.70%, H: 5.12%, N: 6.19%; Found: C: 55.62%, H: 5.02%, N: 6.10%. **3g) Diethyl (3-fluorophenylamino) (2-chloro-6-ethoxyquinolin-3-yl) methylphosphonate: IR (KBr):** 3302 cm^{-1} (— NH) ; 1232 cm^{-1} (— P═O) ; 1035 cm^{-1}(—P—O—C) **^{1}H NMR ($CDCl_3$, δ ppm):** 1.03 (t, 3H, O—CH_2—CH, J = 8 Hz); 1.35 (t, 3H,

O—CH_2-C$\underline{H}_3$, J = 8 Hz); 1.45 (t, 3H, Quinolin—O—CH_2—C$\underline{H}_3$, J = 4 Hz); 3.66 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.89 (m, 1H, O—C$\underline{H}_2$-CH_3); 4.06 (m, 2H, Quinolin—O—C$\underline{H}_2$—CH_3); 4.22 (m, 2H, O—C$\underline{H}_2$-CH_3); 5.34 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.28–6.5 (m, 3H, Ph-$\underline{H}$, C_2, C_4, C_6); 6.99 (d,1H, Quinolin-$\underline{H}$, C_5, J = 8 Hz); 7.02 (dd, 1H, Ph-$\underline{H}$, C_5, J = 8 Hz); 7.32 (d, 1H, Quinolin-$\underline{H}$, C_7, J = 4 Hz); 7.87 (d,1H, Quinolin-$\underline{H}$, C_8, J = 8 Hz); 8.2 (s, 1H, Quinolin-$\underline{H}$, C_4, J = 4 Hz).**ES-MS:** m/z 467.2 (m+1) and 469.2 (m+3). **Elemental analysis:** $C_{22}H_{25}ClFN_2O_4P$ Calcd.: C: 56.60%, H: 5.40%, N: 6.00%; Found: C: 56.72%, H: 5.30%, N: 6.02%. **3h) Diethyl (3-fluorophenylamino) (2-chloro-8-ethylquinolin-3-yl) methylphosphonate: IR (KBr):** 3297 cm^{-1} (— NH); 1237 cm^{-1} (—P═O); 1028 cm^{-1}(—P—O—C) ^{1}**H NMR (CDCl$_3$, δ ppm):** 1.04 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.35 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 7 Hz); 1.38 (t, 3H, Quinolin—CH_2—C$\underline{H}_3$, J = 8 Hz); 3.22 (m, 2H, Quinolin —C$\underline{H}_2$—CH_3); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.9 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.2 (m, 2H, O—C$\underline{H}_2$—CH_3); 5.37 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.28–6.40 (m, 3H, Ph—$\underline{H}$, C_2, C_4, C_6); 7.02 (dd, 1H, Ph—$\underline{H}$, C_5, J = 8 Hz); 7.42 (t, 1H, Quinolin-$\underline{H}$, C_6, J = 8 Hz); 7.54 (d, 1H, Quinolin-$\underline{H}$, C_7, J = 8 Hz; 7.59 (d,1H, Quinolin-$\underline{H}$, C_5, J = 8 Hz); 8.28 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 4 Hz).**ES-MS:** m/z 451.3 (m+1) and 453.2 (m+3). **Elemental analysis:** $C_{22}H_{25}ClFN_2O_3P$ Calcd.: C: 58.61%, H: 5.59%, N: 6.21%; Found: C: 58.52%, H: 5.46%, N: 6.12%. **3i) Diethyl (*o*-tolylamino) (2-chloroquinolin-3-yl) methylphosphonate: IR (KBr**): 3395 cm^{-1} (— NH); 1236 cm^{-1} (— P═O); 1024 cm^{-1}(—P—O—C) ^{1}**H NMR (CDCl$_3$, δ ppm):** 1.0 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.3 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.3 (s, 3H, Ph—C$\underline{H}_3$,); 3.7 (m, 1H, O—C$\underline{H}_2$-CH_3); 3.9 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.2 (m, 2H, O—C$\underline{H}_2$-CH_3); 4.9 (s, 1H, —CH—N$\underline{H}$—Ph); 5.4 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.4 (d, 1H, Ph—$\underline{H}$, C_6); 6.6 (t, 1H, Ph—$\underline{H}$, C_4); 6.9 (t, 1H, Ph—$\underline{H}$, C_5, J = 8 Hz); 7.0 (d, 1H, Ph—$\underline{H}$, C_3, J = 8 Hz); 7.5 (t, 1H, Quinolin—$\underline{H}$, C_6, J = 8 Hz); 7.7 (t, 1H, Quinolin-$\underline{H}$, C_7, J = 8 Hz); 7.8 (d,1H, Quinolin-$\underline{H}$, C_5); 8.0 (d, 1H, Quinolin-$\underline{H}$, C_8, J = 8 Hz); 8.3 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 8 Hz).**ES-MS:** m/z 419.1 (m+1) and 421.1 (m+3).**Elemental analysis:** $C_{21}H_{24}ClN_2O_3P$ Calcd.: C: 60.22%, H: 5.78%, N: 6.69%; Found: C: 60.12%, H: 5.65%, N: 6.61%. **3j) Diethyl (*o*-tolylamino) (2-chloro-6-methylquinolin-3-yl) methylphosphonate: IR (KBr):** 3392 cm^{-1} (—NH); 1232 cm^{-1} (—P═O); 1033 cm^{-1} (—P—O—C) ^{1}**H NMR (CDCl$_3$, δ ppm):** 1.1 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.3 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.3 (s, 3H, Ph—C$\underline{H}_3$,); 2.5 (s, 3H, Quinolin—C$\underline{H}_3$,); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.9 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.2 (m, 2H, O—C$\underline{H}_2$—CH_3); 4.88 (s, 1H, —CH—N$\underline{H}$—Ph); 5.38 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.4 (d, 1H, Ph—$\underline{H}$, C_6, J = 8 Hz); 6.6 (t, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.9 (t, 1H, Ph—$\underline{H}$, C_5); 7.0 (d, 1H, Ph—$\underline{H}$, C_3); 7.5 (d, 1H, Quinolin-$\underline{H}$, C_7, J = 8 Hz); 7.55 (s, 1H, Quinolin-$\underline{H}$, C_5); 7.9 (d,1H, Quinolin-$\underline{H}$, C_8, J = 8 Hz); 8.3 (s, 1H, Quinolin-$\underline{H}$, C_4).**ES-MS:** m/z 433.2 (m+1) and 435.1 (m+3). **Elemental analysis:** $C_{22}H_{26}ClN_2O_3P$ Calcd.: C: 61.04%, H: 6.05%, N: 6.47%; Found: C: 60.92%, H: 5.94%, N: 6.35%. **3k) Diethyl (*o*-tolylamino) (2-chloro-7-methylquinolin-3-yl) methylphosphonate: IR (KBr):** 3354 cm^{-1}(—NH); 1235 cm^{-1} (—P═O); 1035 cm^{-1} (—P—O—C) ^{1}**H NMR (CDCl$_3$, δ ppm):** 1.05 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.35 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.33 (s, 3H, Ph—C$\underline{H}_3$,); 2.52 (s, 3H, Quinolin-C$\underline{H}_3$,); 3.73 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.94 (m, 1H, O—C$\underline{H}_2$-CH_3); 4.26 (m, 2H, O—C$\underline{H}_2$—CH_3); 4.92 (s, 1H, —CH—N$\underline{H}$-Ph); 5.49 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.36 (d, 1H, Ph—$\underline{H}$, C_6, J = 8 Hz); 6.63 (t, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.94 (t, 1H, Ph—$\underline{H}$, C_5, J = 8 Hz); 7.04 (d, 1H, Ph—$\underline{H}$, C_3, J = 8 Hz); 7.33 (d, 1H, Quinolin-$\underline{H}$, C_6, J = 8 Hz); 7.64 (d, 1H, Quinolin-$\underline{H}$, C_5, J = 8 Hz); 7.76 (s,1H, Quinolin-$\underline{H}$, C_8); 8.26 (s, 1H, Quinolin-$\underline{H}$, C_4).**ES-MS:** m/z 433.3 (m+1) and 435.2 (m+3). **Elemental analysis:** $C_{22}H_{26}ClN_2O_3P$ Calcd.: C: 61.04%, H: 6.05%, N: 6.47%; Found: C: 60.86%,

H: 5.90%, N: 6.30%. **3l) Diethyl (*o*-tolylamino) (2-chloro-8-methylquinolin-3-yl) methylphosphonate: IR (KBr):** 3418 cm^{-1} (—NH); 1238 cm^{-1} (—P═O); 1024 cm^{-1} (—P—O—C) ^{1}**H NMR (CDCl$_3$,δ ppm):** 1.0 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.3 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.3 (s, 3H, Ph—C$\underline{H}_3$,); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.9 (m, 1H, O—C$\underline{H}_2$-CH_3); 4.2 (m, 2H, O—C$\underline{H}_2$—CH_3); 4.88 (s, 1H, —CH—N$\underline{H}$-Ph); 5.3 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.4 (d, 1H, Ph-$\underline{H}$, C_6, J = 8 Hz); 6.6 (d, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.9 (t, 1H, Ph—$\underline{H}$, C_5); 7.0 (d, 1H, Ph—$\underline{H}$, C_3, J = 8 Hz); 7.3 (t, 1H, Quinolin-$\underline{H}$, C_6); 7.4 (d, 1H, Quinolin-$\underline{H}$, C_7); 7.6 (d,1H, Quinolin-$\underline{H}$, C_5); 8.22 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 8 Hz). **ES-MS:** m/z 433.3 (m+1) and 435.2 (m+3).**Elemental analysis:** $C_{22}H_{26}ClN_2O_3P$ Calcd.: C: 61.04%, H: 6.05%, N: 6.47%; Found: C: 60.96%, H: 5.99%, N: 6.40%. **3m) Diethyl (*o*-tolylamino) (2-chloro-6-methoxyquinolin-3-yl) methylphosphonate: IR (KBr):** 3341 cm^{-1} (-NH); 1237 cm^{-1} (—P═O); 1032 cm^{-1} (—P—O—C) ^{1}**H NMR (CDCl$_3$,δ ppm):** 1.05 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.35 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.34 (s, 3H, Ph—C$\underline{H}_3$,); 3.69 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.87 (s, 3H, Quinolin—O —C$\underline{H}_3$); 4.0 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.22 (m, 2H, O—C$\underline{H}_2$—CH_3); 5.4 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.35 (d, 1H, Ph—$\underline{H}$, C_6, J = 8 Hz); 6.63 (t, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.94 (t, 1H, Ph—$\underline{H}$, C_5, J = 8 Hz); 7.0 (s, 1H, Quinolin—$\underline{H}$, C_5, J = 4 Hz); 7.05 (d, 1H, Ph—$\underline{H}$, C_3, J = 8 Hz); 7.31 (d, 1H, Quinolin-$\underline{H}$, C_7, J = 4 Hz); 7.87 (d,1H, Quinolin-$\underline{H}$, C_8, J = 8 Hz); 8.21 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 4 Hz).**ES-MS:** m/z 449.2 (m+1) and 451.1 (m+3). **Elemental analysis:** $C_{22}H_{26}ClN_2O_4P$ Calcd.: C: 58.86%, H: 5.84%, N: 6.24%; Found: C: 58.72%, H: 5.72%, N: 6.15%. **3n) Diethyl (*o*-tolylamino)(2-chloro-7-methoxyquinolin-3-yl) methylphosphonate: IR (KBr):** 3386 cm-1 (—NH); 1236 cm-1 (—P═O); 1026 cm-1 (—P—O—C) ^{1}**H NMR (CDCl3,δ ppm):** 1.06 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.33 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.3 (s, 3H, Ph—C$\underline{H}_3$,); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.85 (s, 3H, Quinolin—O —C$\underline{H}_3$); 3.92 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.22 (m, 2H, O—C$\underline{H}_2$—CH_3); 4.88 (s, 1H, —CH—N$\underline{H}$—Ph); 5.38 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.4 (d, 1H, Ph—$\underline{H}$, C_6, J = 8 Hz); 6.6 (t, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.9 (t, 1H, Ph—$\underline{H}$, C_5, J = 4 Hz); 7.0 (d, 1H, Ph—$\underline{H}$, C_3, J = 8 Hz); 7.2 (d, 1H, Quinolin—$\underline{H}$, C_6, J = 8 Hz);7.3 (s, 1H, Quinolin-$\underline{H}$, C_8); 7.6 (d,1H, Quinolin-$\underline{H}$, C_5); 8.2 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 8 Hz).**ES-MS:** m/z 449.0 (m+1) and 451.1 (m+3). **Elemental analysis:** $C_{22}H_{26}ClN_2O_4P$ Calcd.: C: 58.86%, H: 5.84%, N: 6.24%; Found: C: 58.79%, H: 5.76%, N: 6.10%. **3o) Diethyl (*o*-tolylamino) (2-chloro-6-ethoxyquinolin-3-yl) methylphosphonate: IR (KBr):** 3341 cm-1 (—NH); 1237 cm-1 (—P═O); 1032 cm-1 (—P—O—C) ^{1}**H NMR (CDCl3,δ ppm):** 1.05 (t, 3H, O—CH_2-C$\underline{H}_3$, J = 8 Hz); 1.35 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.44 (t, 3H, Quinolin—O—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.33 (s, 3H, Ph—C$\underline{H}_3$,); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.9 (m, 1H, O-C$\underline{H}_2$—CH_3); 4.05 (q, 2H, Quinolin—O—C$\underline{H}_2$—CH_3); 4.22 (m, 2H, O—C$\underline{H}_2$—CH_3); 5.39 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.36 (d, 1H, Ph—$\underline{H}$, C_6, J = 8 Hz); 6.63 (t, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.94 (t, 1H, Ph—$\underline{H}$, C_5, J = 8 Hz); 6.96 (d, 1H, Quinolin-$\underline{H}$, C_5, J = 4 Hz); 7.05 (d, 1H, Ph—$\underline{H}$, C_3, J = 8 Hz); 7.33 (d, 1H, Quinolin—$\underline{H}$, C_7, J = 8 Hz); 7.86 (d,1H, Quinolin-$\underline{H}$, C_8, J = 8 Hz); 8.2 (d, 1H, Quinolin-$\underline{H}$, C_4, J = 8 Hz).**ES-MS:** m/z 463.3 (m+1) and 465.3 (m+3). **Elemental analysis:** $C_{23}H_{28}ClN_2O_4P$ Calcd.: C: 59.68%, H: 6.10%, N: 6.05%; Found: C: 59.72%, H: 5.96%, N: 6.00%. **3p) Diethyl (*o*-tolylamino) (2-chloro-8-ethylquinolin-3-yl) methylphosphonate: IR (KBr):** 3323 cm^{-1} (— NH) ; 1238 cm^{-1} (—P═O) ; 1030 cm^{-1}(—P—O—C) ^{1}**H NMR (CDCl$_3$,δ ppm):** 1.06 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.32 (t, 3H, O—CH_2—C$\underline{H}_3$, J = 8 Hz); 1.4 (t, 3H, Quinolin—CH_2—C$\underline{H}_3$, J = 8 Hz); 2.34 (s, 3H, Ph—C$\underline{H}_3$,); 3.2 (q, 2H, Quinolin -C$\underline{H}_2$-CH_3); 3.7 (m, 1H, O—C$\underline{H}_2$—CH_3); 3.9 (m, 1H, O—C$\underline{H}_2$—CH_3); 4.2 (m, 2H, O—C$\underline{H}_2$—CH_3); 4.9 (s, 1H, —CH—N$\underline{H}$-Ph); 5.36 (d, 1H, —NH—C$\underline{H}$—P═O, J = 24 Hz); 6.4 (d, 1H, Ph-$\underline{H}$, C_6, J = 8 Hz); 6.6 (t, 1H, Ph—$\underline{H}$, C_4, J = 8 Hz); 6.9 (t, 1H,

Ph—H, C_5, J = 4 Hz); 7.04 (d, 1H, Ph—H, C_3, J = 8 Hz); 7.42 (t,1H, Quinolin-H, C_6, J = 8 Hz); 7.5 (d, 1H, Quinolin-H, C_7, J = 8 Hz); 7.67 (d, 1H, Quinolin-H, C_5, J = 8 Hz); 8.3 (d, 1H, Quinolin-H, C_4, J = 8 Hz).**ES-MS:** m/z 447.1 (m+1) and 449.2 (m+3). **Elemental analysis:** $C_{23}H_{28}ClN_2O_3P$ Calcd.: C: 61.81%, H: 6.32%, N: 6.27%; Found: C: 61.70%, H: 6.21%, N: 6.18%.

[28] O. Meth-Cohn, B. Narine, and B Tarnowski,. *J. Chem. Soc., Perkin Trans-1,* 1520 (1981).