RSC Advances

This article can be cited before page numbers have been issued, to do this please use: M. Pita, J. Kdzia, A. Janecka, D. K. Pomorska, M. Rozalski, U. Krajewska and T. Janecki, *RSC Adv.*, 2015, DOI: 10.1039/C5RA16673J.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

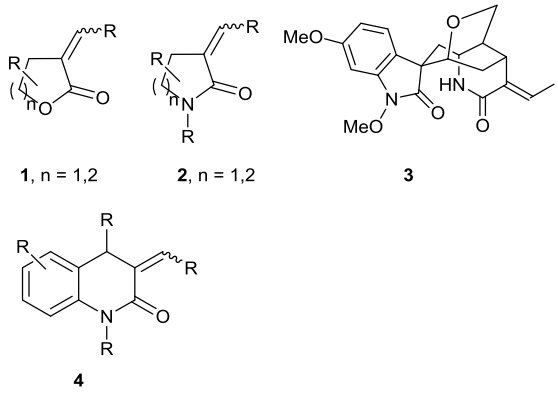
Novel synthesis and cytotoxic activity of 1,4-disubstituted 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones[f]

M. Pięta,[a] J. Kędzia,[a] A. Janecka,[b] D. K. Pomorska, [b] M. Różalski,[c] U. Krajewska,[c] T. Janecki*[a]

Novel, efficient synthesis of 1,4-disubstituted 3-methylidene-3,4-dihydrodihydroquinolin-2(1*H*)-ones was accomplished via a three step reaction sequence comprising of N-alkylation of 3-diethoxyphosphorylquinolin-2(1*H*)-one, Michael addition of various Grignard reagents to N-alkylated 3-diethoxyphosphorylquinolin-2(1*H*)-ones and Horner-Wadsworth-Emmons reaction of the obtained adducts with formaldehyde. Effective synthesis of starting 3-diethoxyphosphorylquinolin-2(1H)-one was also developed. Furthermore, obtained 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones were evaluated for their cytotoxic activity.

Introduction

α-Alkylidene-γ or δ-lactones **1** and corresponding α-alkylidene-γ and δ-lactams **2** are a big class of natural as well as synthetic compounds that display a broad spectrum of biological properties.[1,2] It is generally believed that the conjugated α-alkylidene moiety incorporated onto the lactone or lactam ring is crucial for their biological activities.[3] Undoubtedly, α-alkylidene-γ-lactones constitute the biggest and the best known group within this class. On the other hand, α-alkylidene-δ-lactams are much less recognized and only recently the first natural humantenine-type alkaloid containing this moiety, gelegamine B **3**, was isolated from Gelsemium elegan, a liane growing in Southeast Asia.[4] On the other hand, many synthetic α-alkylidene-δ-lactams are known, however, their biological activity is hardly recognized.[2] In our search for new, biologically active heterocycles we turned our attention to 3-alkylidene-3,4-dihydroquinolin-2(1*H*)-ones **4**, containing α-alkylidene-δ-lactam moiety.



1, n = 1,2 **2**, n = 1,2 **3**

4

Fig. 1 Structures of α-alkylidene-γ and δ-lactons and lactams

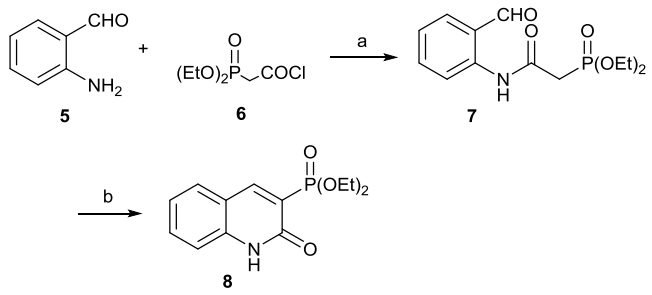
[a] *Institute of Organic Chemistry, Lodz University of Technology, Żeromskiego 116, 90-924 Łódź, Poland, E-mail: tomasz.janecki@p.lodz.pl, tel. (48)426313220, Fax: (+48)426365530*
[b] *Department of Biomolecular Chemistry, Medical University of Łódź, Mazowiecka 6/8, 92-215 Łódź, Poland*
[c] *Department of Pharmaceutical Biochemistry, Medical University of Łódź, Muszyńskiego 1, 90-151 Łódź, Poland*
[f] Electronic Supplementary Information (ESI) available:

A literature survey revealed that 3-alkylidene-3,4-dihydroquinolin-2(1*H*)-ones **4** were usually synthesized using Baylis-Hillman derivatives as starting material. When Baylis-Hillman acetates were subjected to nucleophilic substitution using anilines, followed by PPA-mediated Claisen rearrangement and lactamization of the obtained products, 3-arylmethylidenedihydroquilolin-2(1*H*)-ones were formed in good to moderate yields.[5] In an interesting variation of this method, TFA was used as a promoter of the Claisen rearrangement instead of PPA.[6] Another approach starts with Baylis-Hillman acids which are transformed into corresponding amides followed by a H_2SO_4-catalyzed intramolecular Friedel-Crafts reaction. This method gives 4-substituted 3-methylidenedihydroquinolin-2-ones in moderate yields.[7] Other synthetic approaches to specific 3-methylidenedihydroquinolin-2-ones were also reported. 4-(1-Nitroethyl)-3-methylidene-3,4-dihydroquinolin-2(1*H*)-one and its 5-chloro analogue were prepared from the corresponding 3-aryl-2-methylidene-4-nitroalkanoates.[8] 6-Benzoil- and 6-metoxycarbonyl-1-methyl-3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones were synthesized from methacrylanilides by photochemical electrocyclic ring closure followed by the elimination of the allylic leaving group.[9] Finally, unsubstituted 3-methylidene-3,4-dihydroquinolin-2(1*H*)-one was prepared applying one pot reduction-lactamization sequence to 2-(2-nitrobenzyl)acrylate. [10] Surprisingly, to the best of our knowledge, there are no reports on the biological activity of 3-alkylidene-3,4-dihydroquinolin-2(1*H*)-ones **4**.

In this report we describe novel synthesis of 1,4-disubstituted 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones **20** based on the Horner-Wadsworth-Emmons approach to α-alkylidenelactons and lactams, well recognized in our laboratory.[11] Furthermore, we tested the obtained methylidenequinolinones **20** for their cytotoxic activity against two human leukemia cell lines HL-60 and NALM-6 as well as the MCF-6 breast cancer cell line.

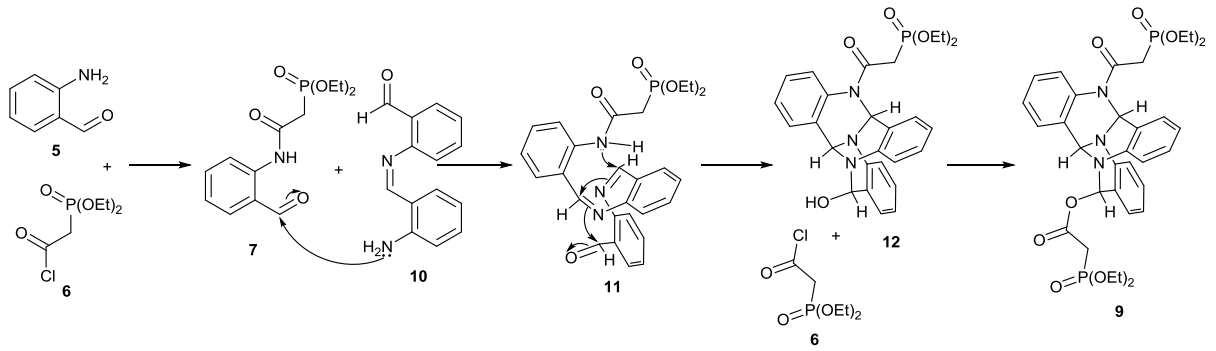
Results and discussion

We started our synthesis with the preparation of 3-diethoxyphosphorylquinolin-2(1*H*)-one **8** as a crucial intermediate. This compound was unknown so far, but the synthesis of 7-substituted 3-diethoxyphosphorylquinolin-2-ones, from 4-substituted 2-aminobenzaldehydes and diethoxyphosphorylacetyl chloride, was described in the literature.[12] Applying the literature conditions (toluene as solvent, 1.2 mol equivalent of pyridine, rt, 45 min.) we performed the reaction of 2-aminobenzaldehyde **5** with diethoxyphosphorylacetyl chloride **6**. Dissapointingly, the intermediate amide **7** was formed in very low, 15% yield. However, further cyclization of the amide **7** to **8** occurred in excellent, 89% yield (Scheme 1).



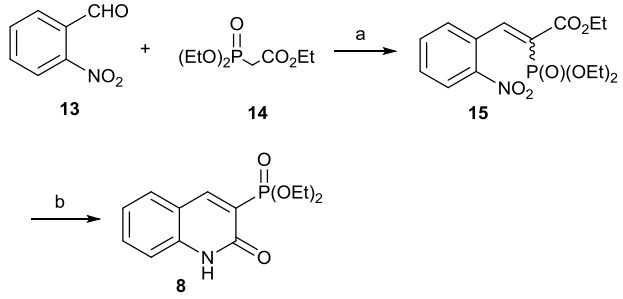
Scheme 1 Reagents and conditions: (a) 2,6-lutidine, toluene, 0^{O}C, 45 min.; (b) piperidine, toluene, reflux, 8h.

To obtain the amide **7** in a reasonable yield we performed an optimization of its synthesis changing solvents, bases and temperature. However, even in the optimized conditions (toluene, 1.2 mol equivalent of 2,6-lutidine, 0°C, 45 min.) the yield of **7** did not exceed 49%. Interestingly, during the optimization we noticed the formation of a considerable amount of a side product, which became the main product when the reaction was performed at room temperature and for a prolonged period of time (2.5 h). Chromatographic isolation and careful analysis of NMR spectra as well as MS data of this side product enabled us to determine its structure as a complex diphosphonate **9**. The formation of **9**, although puzzling at first, can be rationalized assuming a multicomponent reaction between three molecules of 2-aminobenzaldehyde **5** and two molecules of diethoxyphosphorylacetyl chloride **6**. The likely mechanism of this reaction is shown in Scheme 2. The initially formed amide **7** can react with **10**, which is the autocondesation product of two molecules of 2-aminobenzaldehyde, to give imine **11**. Next, intramolecular cyclization yields tricyclic alcohol **12**, which is finally acylated by a second molecule of chloride **6** to give diphosphonate **9**. Similar reactions furnishing the core tricyclic structure present in **12**, by trimerization of 2-aminobenzaldehyde **5**, are described in the literature.[13]



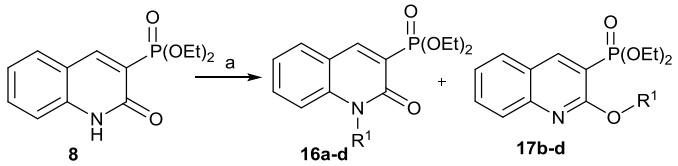
Scheme 2 Proposed mechanism for the formation of diphosphonate **9**

Low efficiency of the synthesis of our crucial intermediate - 3-diethoxyphosphorylquinolin-2(1*H*)-one **8** (44% overall yield, starting from **5**), prompted us to search for new, more effective method. As we had hoped, Knoevenagel condensation of *o*-nitrobenzaldehyde **13** with ethyl diethoxyphosphorylacetate **14** gave ethyl 2-diethoxyphosphoryl-3-(2-nitrophenyl)acrylate **15** in 92% yield, as a mixture of *E* and *Z* isomers, in a 88:12 ratio (Scheme 3). The reduction of the nitro group and the subsequent intramolecular cyclization furnished the expected 3-diethoxyphosphorylquinolin-2-one **8** in 85% yield (78% overall yield, starting from **13**).



Scheme 3 Reagents and conditions: (a) $TiCl_4$, *N*-methylmorpholine, CCl_4, THF, 0°C to rt, 5h; (b) Fe dust, AcOH, 6h.

With the efficient synthesis of **8** in hand we started a three step synthesis of 3-methylidenedihydroquinolin-2-ones **20**. Treatment of **8** with various alkyl iodides or bromides in the presence of NaH lead to the mixtures of N- and O-alkylation products **16** and **17**, respectively (Scheme 4). The ratios of N- to O-alkylation products are given in Table 1. Pleasingly, the mixtures were easily separated using column chromatography and pure N-alkylated quinolin-2-ones **16a-d** were obtained in reasonable yields (Table 1). We also were able to purify and characterize three O-alkylation products **17b-d**. Other bases, such as K_2CO_3, $CsCO_3$ or DIPEA were also tested but performing the reaction in the presence of NaH led to the best ratio of N- to O-alkylated products.



Scheme 4 Reagents and conditions: (a) alkyl halide, NaH, DMF, rt, 6-24h.

Table 1 Synthesis of 1-alkyl-3-diethoxyphosphorylquinolin-2-ones **16a-d** and 2-alkoxy-3-diethoxyphosphorylquinolines **17b-d**.

Compound	Alkyl halide	**16/17** Ratio[a]	**16**[b] Yield [%]	**17**[b] Yield [%]
a	MeI	>95:5	66	-
b	EtI	85:15	61	14
c	*n*-BuI	80:20	59	13
d	BnBr	85:15	70	10

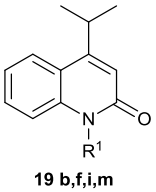
[a] Taken from the ^{31}P NMR spectrum of the crude product.

[b] Yield of isolated, purified product, based on **8**.

In the next step N-alkylated quinolin-2-ones **16a-d** were used as Michael acceptors in reactions with various Grignard reagents (Scheme 5). The additions proceeded smoothly in THF at room temperature yielding 1,4-disubstituted 3-diethoxyphosphoryl-3,4-dihydroquinolin-2(1*H*)-ones **18a-o**, as a single *trans* isomers or as a mixture of *trans* and *cis* isomers (Table 2). However, after the purification of the crude products by column chromatography only *trans*-**18a-o** were isolated and characterized (Table2). Configurational assignments were made on the bases of diagnostic $^3J_{H3H4}$ coupling constants which fell in the range between 1.0 Hz and 1.4 Hz for all *trans* isomers. Similar coupling constants, characteristic for *trans* diaxial arrangement of diethoxyphosphoryl group and substituent in position 4 were observed in *trans*-4-substituted-3-diethoxyphosphorylchroman-2-ones.[14] Furthermore, from the ^{1}H NMR spectrum of the mixture of *trans*- and *cis*-**18d** it was possible to determine $^3J_{H3H4}$ = 4.8 Hz for *cis*-**18d** what confirmed the correctness of assignments. It is noteworthy, that additions of phenylmagnesium chloride proceeded more effectively in the presence of a catalytic amount of Cu_2I_2 (see Table 2). Surprisingly, additions performed with isopropylmagnesium chloride gave considerable amount (19-41%) of dephosphorylated side products **19b**,**f**,**i**,**m**. These products were also separated and purified. One can speculate that the driving force for the elimination of diethoxyphosphoryl moiety from quinolinones **18b**,**f**,**i**,**m** might be the release in steric repulsion between diethoxyphosphoryl and vicinal isopropyl groups. However,

View Article Online
DOI: 10.1039/C5RA16673J

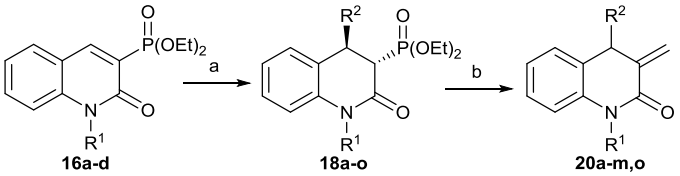
the mechanism of the formation of dephosphorylated quinolin-2-ones **19** is unclear and its explanation needs further investigation.



19 b,f,i,m

Fig. 2 General structure of the dephosphorylated side products **19b,f,i,m**

Finally, the 3-diethoxyphosphoryl-3,4-dihydroquinolin-2(1*H*)-ones **18a-o** were used in the Horner–Wadsworth–Emmons olefination of formaldehyde. Thus, the treatment of **18** with NaH and then with paraformaldehyde gave, after purification by column chromatography, 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones **20a-m,o**, in very good yields (Table 2) and their structures were unequivocally confirmed by spectroscopic methods. Only the olefination of 3-diethoxyphosphoryl-4-vinyl-3,4-dihydroquinolin-2(1*H*)-one **18n** was inefficient and gave a mixture of products difficult to separate and purify. However, ^{1}H NMR spectrum of partially purified reaction mixture revealed signals which could be attributed to 1-benzyl-3-methyl-4-vinyl-1,2-dihydroquinolni-2(1*H*)-one, apparently originated from the isomerization of the initially formed 3-methylidene-3,4-dihydroquinolin-2(1*H*)-one **20n**.



Scheme 5 Reagents and conditions: (a) Grignard reagent, THF, rt, 2h; (b) paraformaldehyde, NaH, THF, rt, 4h.

Table 2 Synthesis of 3-diethoxyphosphorylquinolin-2(1*H*)-ones **18a-o** and 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones **20a-m,o**

Compound	R^1	R^2	**18** *trans*/*cis* ratio[a]	*trans*-**18**[b] Yield [%]	**20**[b] Yield [%]
a	Me	Et	>95 : 5	73	82
b	Me	*i-Pr*	93 : 7	43	87
c	Me	Ph	>95 : 5	52/75[c]	90[d]
d	Et	Me	75 : 25	56	80
e	Et	Et	>95 : 5	88	92
f	Et	*i-Pr*	>95 : 5	50	89
g	Et	Ph	>95 : 5	45/65[c]	73
h	*n*-Bu	Et	>95 : 5	85	92
i	*n*-Bu	*i*-Pr	>95 : 5	41	91
j	*n*-Bu	Ph	>95 : 5	57/91[c]	94
k	Bn	Me	80 : 20	54	94

View Article Online
DOI: 10.1039/C5RA16673J

l	Bn	Et	>95 : 5	58	96
m	Bn	*i*-Pr	92 : 8	65	91
n	Bn	vinyl	>95 : 5	21	-
o	Bn	Ph	>95 : 5	58/79[c]	83

[a] Taken from the ^{31}P NMR spectrum of the crude product.

[b] Yield of isolated, purified product, based on **16** or **18**, respectively.

[c] In the presence of 0.1 eq of Cu_2I_2.

[d] Compound **20c** is known (ref. 7).

Evaluation of cytotoxicity

The obtained 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones **20a-m,o** were tested *in vitro* against three human cancer cell lines: leukemia NALM-6 and HL-60 as well as breast cancer MCF-7 and the results are shown in Table3. Carboplatin was used as a reference compound.[15] In general, cytotoxicities of all these compounds are moderate or low, with IC_{50} values ranging from 40.2 μM (**25b**, against MCF-7 cells) to 405 μM (**25l**, against HL-60 cells) and no significant differences between cell lines were observed. However, the activity of the specific compound depends significantly on the nature of substituents in positions 1 and 4. Moderate activity, with IC_{50} values below 100 μM against all three cell lines display compounds **20h-n** with n-butyl or benzyl substituent in position 1. The only exception is quinolinone **20l** which has low cytotoxicity against all three cell lines. On the other hand phenyl is definitely the best substituent in position 4. All four 4-phenylquinolinones **20c,g,j,n** are among the most active compounds and have IC_{50} values in the range between 40 μM and 100 μM against all three cancer cell lines tested.

Table 3 *In vitro* cytotoxic activity of 3-methylidene-3,4-dihydroquinolin-2(1*H*)-ones **20a-m,o**

Compound **20**	R^1	R^2	IC_{50}[a] (μM)		
			HL-60	NALM-6	MCF-7
a	Me	Et	228±19	238±15	216±18
b	Me	*i-Pr*	183±12	331±22	40.2±3.1
c	Me	Ph	69.9±3.2	61.0±3.9	100±6.4
d	Et	Me	304±15	289±33	156±22
e	Et	Et	114±16	166±19	233±29
f	Et	*i-Pr*	128±13	96.7±4.2	70.3±5.8
g	Et	Ph	61.5±3.5	54.0±5.4	60.2±4.8
h	*n*-Bu	Et	60.3±7.2	72.7±5.8	88.3±7.7
i	*n*-Bu	*i*-Pr	75.9±7.4	58.7±3.6	65.3±4.7
j	*n*-Bu	Ph	55.4±2.6	47.2±5.8	70.3±5.7
k	Bn	Me	66.4±4.5	61.5±6.6	72.9±4.4
l	Bn	Et	405±33	96.6±4.2	200±17
m	Bn	*i*-Pr	61.3±5.4	54.4±5.6	101±15
o	Bn	Ph	48.0±4.9	43.6±4.1	74.3±6.9
Carboplatin	-	-	2.9±0.1	0.7±0.3	3.8±0.45

[a] Compound concentration required to inhibit tumor cell proliferation by 50%. Data are expressed as the mean ± SD from the concentration-response curves of at least three experiments.

Conclusions

We have developed simple, general and efficient method for the synthesis of biologically important 3-methylidenedihydroquinolin-2-ones **20** with various substituents in positions 1 and 4. Contrary to the reported so far methods, which are based on Baylis-Hillman derivatives, our synthesis starts with easily available 3-diethoxyphosphorylquinolin-2-one **8**, which is N-alkylated and next subjected to Michael addition of Grignard reagents to give 1,4-disubstituted 3-diethoxyphosphorylquinolin-2-ones **18**. In the last step, final 3-methylidenedihydroquinolin-2-ones **20** are synthesized using Horner-Wadsworth-Emmons methodology. During the search for the efficient synthesis of starting 3-diethoxyphosphorylquinolin-2-one **8**, we elaborated the structure of the complex diphosphonate **9** which was formed as a side product in the reaction of 2-aminobenzaldehyde **5** with diethoxyphosphorylacetyl chloride **6**. Eventually, we developed simple and effective synthesis of **8** from *o*-nitrobenzaldehyde **13** and ethyl diethoxyphosphorylacetate **14**. Furthermore, cytotoxic activity of the final 3-methylidenedihydroquinolin-2-ones **20** was tested *in vitro* against three human cancer cell lines and compounds with n-butyl or benzyl substituent in position 1 and phenyl substituent in position 4 were found to possess the best cytotoxicity, with IC_{50} values in the range of 40 to 100 μM. It is worth to stress that cytotoxicity of 3-methylidenedihydroquinolin-2-ones haven't been so far evaluated.

Experimental section

General

NMR spectra were recorded on a Bruker DPX 250 or Bruker Avance II instrument at 250.13 MHz or 700 MHz for ^{1}H, 62.9 MHz or 176 MHz for ^{13}C, and 101.3 MHz for ^{31}P NMR using tetramethylsilane as internal and 85% H_3PO_4 as external standard. ^{31}P NMR spectra were recorded using broadband proton decoupling. IR spectra were recorded on a Bruker Alpha ATR spectrophotometer. Melting points were determined in open capillaries and are uncorrected. Column chromatography was performed on Aldrich® silica gel 60 (230-400 mesh). Thin-layer chromatography was performed with precoated TLC sheets of silica gel 60 F_{254} (Aldrich®). The purity of tested compounds was determined by combustion elemental analyses (CHN, elemental analyzer EuroVector 3018, Elementar Analysen systeme GmbH). MS spectra were performed on combined Waters 2695-Waters ZQ 2000 LC/MS apparatus. Reagents and starting materials were purchased from commercial vendors and used without further purification. All organic solvents were dried over appropriate drying agents and distilled prior to use. Standard syringe techniques were used for transferring dry solvents.

1. Synthesis of 3-diethoxyphosphorylquinolin-2(1*H*)-one 8

1.1. Synthesis of 3-diethoxyphosphorylquinolin-2(1*H*)-one 8 from *o*-aminobenzaldehyde (5)

1.1.1 Synthesis of diethyl [(2-formylphenyl)carbamoyl]methylphosphonate (7)

To a solution of 2-aminobenzaldehyde **5** (0.434 g, 4.00 mmol) and 2,6-lutidine (0.428 g, 4.00 mmol) in toluene (5 ml) under nitrogen atmosphere a solution of diethyl 2-chloro-2-oxoethylphosphonate **6** (0.858 g, 4.00 mmol) in toluene (5 ml) was added dropwise maintaining the temperature below 0 °C. When the addition was completed, the mixture was stirred at room temperature for 45 min. The mixture was washed with H_2O (10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was

removed in vacuo to yield a crude product which was purified by column chromatography (eluent: toluene/EtOAc 4/1). Yellow oil was obtained (0.587 g, 49%). Rf: 0.2 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3259, 2982, 1667, 1609, 1587, 1526, 1247, 1046. ^{31}P NMR (101 MHz, $CDCl_3$) δ 20.82 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.30 (s, 1H), 9.91 (d, *J* = 0.7 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.24 (dt, *J* = 7.6, 1.0 Hz, 1H), 4.28 – 4.12 (m, 4H), 3.08 (d, *J* = 21.6 Hz, 2H), 1.33 (td, *J* = 7.0, 0.5 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.12, 162.75 (d, *J* = 6.1 Hz), 139.35, 135.05, 134.89, 122.34, 120.87, 119.06, 61.82 (d, *J* = 6.4 Hz), 37.29 (d, *J* = 131.4 Hz), 15.32 (d, *J* = 6.0 Hz). Anal. Calcd for $C_{13}H_{18}NO_5P$: C, 52.18; H, 6.06; N, 4.68. Found: C, 52.30; H, 6.08; N, 4.66.

Along with diethyl [(2-formylphenyl)carbamoyl]methylphosphonate (**7**) also diphosphonate **9** was isolated by column chromatography.

(8,16,24)-9-[2-(diethoxyphosphoryl)acetyl]-1,9,17-triazahexacyclo[14.8.0.0^{2,7}.0^{8,17}.0^{10,15}.0^{18,23}]tetracosa-2(7),3,5,10(15),11,13,18(23),19,21-nonaen-24-yl 2-(diethoxyphosphoryl)acetate (9): Off-white solid mp 116-118 °C. Rf: 0.3 (UV active, CH_2Cl_2 : EtOAc = 1:2). IR (neat) *v* (cm^{-1}): 2982, 2926, 1740, 1667, 1482, 1371, 1228, 1112, 1017, 966. ^{31}P NMR (101 MHz, $CDCl_3$) δ 19.87, 21.11 ppm. ^{1}H NMR (250MHz MHz, DMSO-d_6, 333K) δ 1.08 – 1.25 (m, 12H), 3.24 (dd, *J* = 21.5, 2.4 Hz, 1H), 3.33 (dd, *J* = 21.2, 14.6 Hz, 1H), 3.59 (d, *J* = 21.6 Hz, 2H), 3.90 – 4.18 (m, 8H), 5.45 (s, 1H), 6.47 (s, 1H), 6.52 (s, 1H), 6.87 (ddd, *J* = 7.6, 5.9, 2.6 Hz, 1H), 6.99 – 7.23 (m, 8H), 7.32 (m, 2H), 7.49 (ddd, *J* = 10.0, 8.0, 1.4 Hz, 2H). ^{13}C NMR (63MHz MHz, $CDCl_3$) δ 16.37, 16.46, 16.54, 34.32 (d, *J* = 136.3 Hz), 34.98 (d, *J* = 132.6 Hz), 62.76, 63.03, 63.13, 63.23, 65.27, 67.91, 85.10, 123.48, 124.19, 124.43, 125.05, 125.63, 125.71, 127.22, 128.15, 128.95, 129.31, 129.65, 130.23, 136.28, 141.91, 144.34, 165.09 (d, *J* = 6.7 Hz), 165.39. ESI-MS [M+H]+ = 684; [M-H]- = 682. Anal. Calcd for $C_{13}H_{16}NO_4P$: C, 57.98; H, 5.75; N, 6.15. Found: C, 57.77; H, 5.76; N, 6.12.

1.1.2 Synthesis of ethyl (2-oxo-1,2-dihydroquinolin-3-yl)phosphonate (8)

Diethyl [(2-formylphenyl)carbamoyl]methylphosphonate **7** (1.20 g, 4.00 mmol) was dissolved in dry toluene (12 mL) in argon atmosphere and then piperidine (0.029 g, 0.40 mmol) was added. The mixture was stirred in Dean-Stark apparatus for 8 hours at reflux. Than it was condensed in vacuo and the residue was triturated with Et_2O to give off-white solid (1.00 g, 89 %) mp 170-172 °C. Rf: 0.3 (UV active, CH_2Cl_2 : EtOAc = 1:2). IR (neat) *v* (cm^{-1}): 3165, 2984, 1648, 1474, 1054, 1222, 1022, 968. ^{31}P NMR (101 MHz, $CDCl_3$) δ 14.52 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.63 (s, 1H), 8.59 (d, *J* = 17.6 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.61 – 7.52 (m, 1H), 7.50 – 7.42 (m, 1H), 7.28 – 7.18 (m, 1H), 4.43 – 4.19 (m, 4H), 1.38 (td, *J* = 7.1, 0.6 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.51 (d, *J* = 11.6 Hz), 150.52 (d, *J* = 6.7 Hz), 140.47, 132.86, 129.17, 122.95, 121.17 (d, *J* = 194.9 Hz), 118.73 (d, *J* = 15.8 Hz), 116.21, 62.90 (d, *J* = 5.8 Hz), 16.46 (d, *J* = 6.5 Hz). ESI-MS [M+H]+ = 282; [M-H]- = 280. Anal. Calcd for $C_{13}H_{16}NO_4P$: C, 55.52; H, 5.73; N, 4.98. Found: C, 55.46; H, 5.77; N, 4.96.

1.2. Synthesis of 3-diethoxyphosphorylquinolin-2(1*H*)-one 8 from *o*-nitrobenzaldehyde (13)

1.2.1 Synthesis of ethyl 2-(diethoxyphosphoryl)-3-(2-nitrophenyl)prop-2-enoate (15):

To dry THF (60 mL) in argon atmosphere at 0 °C the solution of $TiCl_4$ (5.04 mL, 45.65 mmol) in CCl_4 (15 mL) was added dropwise followed by the ethyl diethoxyphosphorylacetate (5.16 g, 22.83 mmol) and N-methylmorpholine (9.54 g, 94.30 mmol). It was stirred for 30 min at 0 °C and then the solution of 2-nitrobenzaldehyde **13** (3.0 g, 19.85 mmol) in THF (15 mL) was added portionwise. The reaction

View Article Online
DOI: 10.1039/C5RA16673J

mixture was slowly warmed to rt and stirred for 4 h. Then water was added (100 mL) and the mixture was extracted with Et_2O (2*80 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure, affording the crude product that was purified by column chromatography (eluent: CH_2Cl_2/EtOAc 5/1). Yellow oil was obtained (6.02g, 92%) as the mixture of *E* and *Z* isomers. Analytical data for ethyl (*E*)-2-(diethoxyphosphoryl)-3-(2-nitrophenyl)prop-2-enoate (**15**): Rf: 0.7 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3467, 2983, 1719, 1602, 1523, 1369, 1250, 1014, 971. ^{31}P NMR (101 MHz, $CDCl_3$) δ 12.91 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.1, 1.5, 1H), 8.19 (d, *J* = 21.4 Hz, 1H), 7.65 (ddd, *J* = 7.5, 7.4, 1.5, 1H), 7.55 (ddd, *J* = 8.1, 7.5, 1.1, 1H), 7.35 (dd, *J* = 7.4, 1.1, 1H), 4.26 (m, 4H), 4.03 (q, *J* = 7.1 Hz, 2H), 1.39 (td, *J* = 7.1, 0.7 Hz, 6H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.05 (d, *J* = 13.6 Hz), 149.21 (d, *J* = 8.0 Hz), 146.39, 133.60, 131.63 (d, *J* = 20.3 Hz), 129.73, 129.63 (d, *J* = 2.4 Hz), 126.67 (d, *J* = 180.5 Hz), 124.55, 62.94 (d, *J* = 5.5 Hz), 61.25, 16.11 (d, *J* = 6.4 Hz), 13.49. ESI-MS [M+H]+ = 358; [M+Na]+ = 380. Anal. Calcd for $C_{15}H_{20}NO_7P$: C, 50.42; H, 5.64; N, 3.92. Found: C, 50.60; H, 5.64; N, 3.83.

1.2.2. Synthesis of ethyl (2-oxo-1,2-dihydroquinolin-3-yl)phosphonate (8)

Ethyl 2-(diethoxyphosphoryl)-3-(2-nitrophenyl)prop-2-enoate **15** (1.43 g, 4.00 mmol) was dissolved in acetic acid (15 mL) and then to the intensively stirred solution reduced iron powder (1.34 g, 24.00 mmol) was added. The mixture was warmed to 80 ^{o}C and stirred for 6 hours. Then it was filtered through celite cake and the solid residue was washed with acetic acid (15 mL) and EtOAc (15 mL). The filtrate was evaporated. The dark residue was dissolved in EtOAc (15 mL) and washed with 5% $NaHCO_3$ (2*15mL), then with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. Obtained brown solid was purified by column chromatography on silica gel (eluent: EtOAc/CH_2Cl_2 1/1) to give 3-diethoxyphosphorylquinolin-2-one **8** (0.956 g, 85%).

2. General procedure for the synthesis of 1-alkyl-3-diethoxyphosphorylquinolin-2-ones 16a-d:

To the solution of 3-diethoxyphosphorylquinolin-2-one **8** (1.41 g, 5.0 mmol) in DMF (15 mL) under argon atmosphere, provided with water bath, 80% sodium hydride (0.165 g, 5.5 mmol) was added portionwise. The reaction mixture was stirred for 10 min. Then the alkyl halide (6.0 mmol) was added in one portion and the reaction mixture was stirred at rt overnight (for **16 d**) or for 8h (for **16c**) or for 6 h (for **16a-b**). Then solvent was removed under reduced pressure and the residue was separated between ethyl acetate (25 mL) and water (25 mL). The water layer was extracted with the second portion of ethyl acetate (25 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure, affording the crude product that was purified by column chromatography (eluent: CH_2Cl_2/EtOAc). For 1-alkyl-3-diethoxyphosphorylquinolin-2-ones **17b-d** also O-alkylation products were isolated and characterized.

Diethyl (1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)phosphonate (16a). White solid (0.974 g, 66 %) mp 50-52^{o}C. Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.4 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3042, 2980, 2906, 1729, 1638, 1588, 1474, 1418, 1162, 1049, 1019, 966. ^{31}P NMR (101 MHz, $CDCl_3$) δ 14.55 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.47 (d, *J* = 17.6 Hz, 1H), 7.65 (m, 2H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.26 (m, 1H), 4.41 – 4.14 (m, 4H), 3.71 (s, 3H), 1.48 – 1.29 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.84 (d, *J* = 12.0 Hz), 148.20 (d, *J* = 6.5 Hz), 141.16, 132.79, 130.01, 122.22, 121.03 (d, *J* = 196.9 Hz), 118.86 (d, *J* = 16.5 Hz), 113.97, 62.62 (d, *J* = 6.0 Hz), 29.17, 16.18 (d, *J* = 6.2 Hz). ESI-MS [M+H]+ =

View Article Online
DOI: 10.1039/C5RA16673J

296; [M+Na]+ = 318. Anal. Calcd for $C_{14}H_{18}NO_4P$: C, 56.95; H, 6.14; N, 4.74. Found: C, 57.05; H, 6.15; N, 4.73.

Diethyl (1-ethyl-2-oxo-1,2-dihydroquinolin-3-yl)phosphonate (16b). Yellow oil (0.943 g, 61 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.4 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2979, 1638, 1616, 1562, 1449, 1242, 1219, 1049, 1019. ^{31}P NMR (101 MHz, $CDCl_3$) δ 14.67 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.45 (d, *J* = 17.5 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.29 – 7.21 (m, 1H), 4.41 – 4.19 (m, 6H), 1.37 (td, *J* = 7.1, 0.4 Hz, 6H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.59 (d, *J* = 12.2 Hz), 148.34 (d, *J* = 6.5 Hz), 140.40, 132.90, 130.46, 122.18, 121.16 (d, *J* = 197.4 Hz), 119.37 (d, *J* = 16.5 Hz), 113.96, 62.86 (d, *J* = 6.1 Hz), 37.39, 16.33 (d, *J* = 6.2 Hz), 12.47. ESI-MS [M+H]+ = 310; [M+Na]+ = 332. Anal. Calcd for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53. Found: C, 58.33; H, 6.54; N, 4.51.

Diethyl (2-ethoxyquinolin-3-yl)phosphonate (17b). Yellow oil (0.216 g, 14 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2980, 2931, 2905, 1618, 1592, 1416, 1338, 1252, 1074, 1019. ^{31}P NMR (101 MHz, $CDCl_3$) δ 15.16 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 16.2, 0.7 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.69 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 4.62 (q, *J* = 7.1 Hz, 2H), 4.33 – 4.07 (m, 4H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.36 (td, *J* = 7.0, 0.6 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.57 (d, *J* = 5.3 Hz), 148.32, 147.42 (d, *J* = 7.0 Hz), 131.75, 128.50, 126.97, 124.53, 123.80 (d, *J* = 12.3 Hz), 113.23 (d, *J* = 190.0 Hz), 62.55 (d, *J* = 5.6 Hz), 62.29, 16.37 (d, *J* = 6.3 Hz), 14.44. ESI-MS [M+H]+ = 310, [M+Na]+ = 332. Anal. Calcd for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53. Found: C, 58.10; H, 6.54; N, 4.51.

Diethyl (1-butyl-2-oxo-1,2-dihydroquinolin-3-yl)phosphonate (16c). White solid (0.995 g, 59 %) mp 89-90 °C. Chromatography (CH_2Cl_2/EtOAc 8/1). Rf: 0.5 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2961, 1630, 1586, 1562, 1451, 1237, 1057, 1026, 940. ^{31}P NMR (101 MHz, $CDCl_3$) δ 14.77 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.45 (d, *J* = 17.6, 1H), 7.64 (m, 2H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.20 (m, 1H), 4.40 – 4.15 (m, 6H), 1.78-1.65 (m, 2H), 1.55 – 1.42 (m, 2H), 1.36 (td, *J* = 7.1, 0.6 6H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.84 (d, *J* = 11.7 Hz), 148.50, 140.77, 132.86, 130.50, 122.19, 121.39 (d, *J* = 196.3 Hz), 119.46 (d, *J* = 16.5 Hz), 114.17, 62.89 (d, *J* = 6.1 Hz), 42.31, 29.36, 20.21, 16.42 (d, *J* = 6.2 Hz), 13.76. ESI-MS [M+H]+ = 338; [M+Na]+ = 360. Anal. Calcd for $C_{17}H_{24}NO_4P$: C, 60.53; H, 7.17; N, 4.15. Found: C, 60.39; H, 7.20; N, 4.13.

Diethyl (2-butoxyquiolin-3-yl)phosphonate (17c). Colourless oil (0.219 g, 13 %). Chromatography (CH_2Cl_2/EtOAc 8/1). Rf: 0.7 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2959, 2933, 2872, 1618, 1592, 1415, 1341, 1251, 1074, 1020, 957. ^{31}P NMR (101 MHz, $CDCl_3$) δ 15.46 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 16.3, 0.7 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.69 (ddd, *J* = 8.5, 6.9, 1.6, 1H), 7.40 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.56-4.51 (m, 2H), 4.32 – 4.05 (m, 4H), 1.94 – 1.75 (m, 2H), 1.65 – 1.48 (m, 2H), 1.38 – 1.28 (m, 6H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.84 (d, *J* = 5.2 Hz), 148.44, 147.67 (d, *J* = 7.3 Hz), 131.83, 128.59, 127.00, 124.56, 123.85 (d, *J* = 12.5 Hz), 113.14 (d, *J* = 190.0 Hz), 66.26, 62.50 (d, *J* = 5.6 Hz), 31.01, 19.23, 16.39 (d, *J* = 6.4 Hz), 13.85. ESI-MS [M+H]+ = 338, [M+Na]+ = 360. Anal. Calcd for $C_{17}H_{24}NO_4P$: C, 60.53; H, 7.17; N, 4.15. Found: C, 60.52; H, 7.20; N, 4.16.

Diethyl (1-benzyl-2-oxo-1,2-dihydroquinolin-3-yl)phosphonate (16d). Colourless oil (1.30 g, 70 %). Chromatography (CH_2Cl_2/EtOAc 8/1). Rf: 0.5 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2981,

2931, 2905, 1641, 1563, 1450, 1241, 1223, 1049, 1020, 959. ^{31}P NMR (101 MHz, $CDCl_3$) δ 14.18 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.53 (d, *J* = 17.5 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.35 – 7.17 (m, 7H), 5.55 (s, 2H), 4.44 – 4.19 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.71 (d, *J* = 12.3 Hz), 148.28, 140.28, 135.38, 132.45, 129.82, 128.13, 126.74, 126.08, 122.04, 120.90 (d, *J* = 196.3 Hz), 118.81 (d, *J* = 16.5 Hz), 114.50 , 62.42 (d, *J* = 5.9 Hz), 45.23, 15.93 (d, *J* = 6.0 Hz).ESI-MS [M+H]+ = 372. Anal. Calcd for $C_{20}H_{22}NO_4P$: C, 64.68; H, 5.97; N, 4.15. Found: C, 64.58; H, 5.99; N, 4.13.

Diethyl (2-benzyloxyquiolin-3-yl)phosphonate (17d). Colourless oil (0.186 g, 10 %). Chromatography (CH_2Cl_2/EtOAc 8/1). Rf: 0.7 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3033, 2981, 2930, 2905, 1617, 1592, 1411, 1341, 1249, 1075, 1018, 964. ^{31}P NMR (101 MHz, $CDCl_3$) δ 15.05 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 16.2, 0.7 Hz, 1H), 7.75 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.69 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.35 – 7.14 (m, 4H), 5.53 (s, 2H), 4.17 – 3.87 (m, 4H), 1.16 (td, *J* = 7.0, 0.6 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.26 (d, *J* = 5.0 Hz), 148.22, 147.73 (d, *J* = 7.2 Hz), 137.03, 131.92, 128.60, 128.31, 127.80, 127.70, 127.09, 124.81, 124.06 (d, *J* = 12.4 Hz), 113.33 (d, *J* = 190.3 Hz), 67.91, 62.62 (d, *J* = 5.8 Hz), 16.33 (d, *J* = 6.6 Hz). ESI-MS [M+H]+ = 372. Anal. Calcd for $C_{20}H_{22}NO_4P$: C, 64.68; H, 5.97; N, 3.77. Found: C, 64.54; H, 5.98; N, 3.85.

3. General procedure for the synthesis of 1,4-alkyl or aryl 3-diethoxyphosphorylquinolin-2-ones 18a-o:

To a solution of 1-alkyl-3-diethoxyphosphorylquinolin-2-one **16** (1.0 mmol) in THF (5 mL) under argon atmosphere Grignard reagent (3.0 mmol as 2.0 M THF solution) was added dropwise at rt. The reaction mixture was stirred at ambient temperature overnight. Next the saturated ammonium chloride solution in water (10 mL) was added to the reaction mixture and it was extracted with ethyl acetate (2*10 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure, affording the crude product which was purified by column chromatography (eluent CH_2Cl_2/EtOAc). For 1,4-alkyl or aryl 3-diethoxyphosphorylquinolin-2-ones **18b**,**f**,**I**,**m** also dephosphorylated side products **19b**,**f**,**I**,**m** were isolated and characterized.

Diethyl (4-ethyl-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18a). Light yellow oil (237 mg, 73 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2967, 2930, 1664, 1601, 1472, 1367, 1245, 1017, 962. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.64 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 7.17 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.03 (ddd, *J* = 7.5, 7.4, 1.1 Hz 1H), 6.97 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.08 (dq, *J* = 8.0, 7.1 Hz, 2H), 3.72 (m, 1H), 3.47-3.34 (m, 4H),3.31-3.12 (m, 2H), 1.57 (p, *J* = 7.4 Hz, 2H), 1.29 (td, *J* = 7.1, 0.6 Hz, 3H), 0.96 – 0.79 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.06 (d, *J* = 5.1 Hz), 138.75, 128.35, 127.25, 126.51, 122.47, 114.24, 61.98 (d, *J* = 6.6 Hz), 61.65 (d, *J* = 6.8 Hz), 46.56 (d, *J* = 127.8 Hz), 38.94 (d, *J* = 4.3 Hz), 29.29 , 28.24 (d, *J* = 19.3 Hz), 15.72 (d, *J* = 6.2 Hz), 15.45 (d, *J* = 6.2 Hz), 10.80. ESI-MS [M+H]+ = 326, [M+Na]+ = 348. Anal. Calcd for $C_{16}H_{24}NO_4P$: C, 59.07; H, 7.44; N, 4.31. Found: C, 59.19; H, 7.46; N, 4.29.

Diethyl (1-methyl-2-oxo-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18b). Light yellow oil (146 mg, 43 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2962, 2932, 2907, 2873, 1664, 1600, 1498, 1363, 1247, 1017, 965. ^{31}P NMR (101 MHz, $CDCl_3$) δ 23.28 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H), 7.17

View Article Online
DOI: 10.1039/C5RA16673J

(dd, *J* = 7.4, 1.7 Hz, 1H), 7.03 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.97 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.07 (dd, *J* = 8.0, 7.1 Hz, 2H), 3.72 (m, 1H), 3.49 – 3.27 (m, 5H), 3.03 (dd, *J* = 14.9, 7.3 Hz, 1H), 1.79 (sp, *J* = 6.9 Hz, 1H), 1.28 (td, *J* = 7.1, 0.6 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.83 (td, *J* = 7.1, 0.6 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.87 (d, *J* = 5.2 Hz), 139.66, 129.68, 127.59, 125.86, 122.64, 114.44, 62.35 (d, *J* = 6.7 Hz), 62.04 (d, *J* = 6.8 Hz), 45.84, 43.86 (d, *J* = 5.3 Hz), 32.76 (d, *J* = 17.7 Hz), 29.64, 19.80, 19.38, 16.05 (d, *J* = 6.2 Hz), 15.80 (d, *J* = 6.2 Hz). ESI-MS [M+H]+ = 340. Anal. Calcd for $C_{17}H_{26}NO_4P$: C, 60.17; H, 7.72; N, 4.13. Found: C, 60.03; H, 7.75; N, 4.14.

1-Methyl-4-(propan-2-yl)-1,2-dihydroquinolin-2-one (19b). Yellow solid (42 mg, 21 %) mp 38-39 °C. Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3036, 2959, 2870, 1639, 1594, 1459, 1226, 1040. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 3H), 7.33 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.21 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H), 3.75 (s, 3H), 3.31 (spd, *J* = 6.9, 0.9 Hz, 1H), 1.27 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.11, 139.79, 138.70, 132.24, 129.31, 128.16, 121.88, 120.73, 113.73, 29.71, 28.21, 21.86. ESI-MS [M+H]+ = 202. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.68; H, 7.53; N, 6.94.

Diethyl (1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18c). Light yellow oil (280 mg, 75 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.7 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2979, 1665, 1600, 1496, 1471, 1364, 1246, 1014, 965. ^{31}P NMR (101 MHz, $CDCl_3$) δ 21.99 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40 – 7.13 (m, 6H), 7.15 – 6.98 (m, 4H), 4.70 (d, *J* = 14.6 Hz, 1H), 4.23 – 4.03 (m, 2H), 3.80 (m, 1H), 3.57-3.44 (m, 1H), 3.55 (dd, *J* = 25.3, 1.2 Hz, 1H), 3.41 (s, 3H), 1.31 (td, *J* = 7.1, 0.6 Hz, 3H), 0.93 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.65 (d, *J* = 5.0 Hz), 141.50 (d, *J* = 18.8 Hz), 139.76, 128.91, 128.54, 128.03, 126.77, 126.35, 125.22, 123.24, 114.59, 62.41 (d, *J* = 6.5 Hz), 62.09 (d, *J* = 5.7 Hz), 48.94 (d, *J* = 125.2 Hz), 42.24, 29.59 (d, *J* = 3.2 Hz), 15.88 (d, *J* = 6.2 Hz), 15.65 (d, *J* = 6.3 Hz). ESI-MS [M+H]+ = 374, [M-H]- = 372. Anal. Calcd for $C_{20}H_{24}NO_4P$: C, 64.34; H, 6.48; N, 3.75. Found: C, 64.25; H, 6.51; N, 3.76.

Diethyl (1-ethyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18d). Light yellow oil (182 mg, 56 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2: EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2977, 2930, 2870, 1662, 1600, 1496, 1462, 1379, 1248, 1019, 963. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.49 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 7.05 – 6.97 (m, 2H), 4.23 – 3.87 (m, 4H), 3.73 (m, 1H), 3.55 – 3.32 (m, 2H), 3.13 (dd, *J* = 24.8, 1.2 Hz, 1H), 1.33 – 1.21 (m, 9H), 0.86 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.74 (d, *J* = 5.5 Hz), 137.67, 128.86, 128.02, 127.60, 123.19, 114.47, 62.51 (d, *J* = 6.6 Hz), 62.10 (d, *J* = 6.8 Hz), 48.55 (d, *J* = 127.5 Hz), 37.42, 32.91 (d, *J* = 4.2 Hz), 22.39 (d, *J* = 20.6 Hz), 16.12 (d, *J* = 6.2 Hz), 15.81 (d, *J* = 6.4 Hz), 12.25. ESI-MS [M+H]+ = 326, [M+Na]+ = 348. Anal. Calcd for $C_{16}H_{24}NO_4P$: C, 59.07; H, 7.44; N, 4.31. Found: C, 58.90; H, 7.48; N, 4.31.

Diethyl (1,4-diethyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18e). Light yellow oil (299 mg, 88 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2973, 2932, 2874, 1663, 1600, 1495, 1460, 1377, 1244, 1018, 962. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.80 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (ddd, *J* = 8.7, 7.5, 1.7 Hz, 1H), 7.17 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.04-6.98 (m, 2H), 4.16-3.86 (m, 4 H), 3.80-3.56 (m, 1H), 3.47-3.31 (m, 1H), 3.23 (dd, *J* = 25.4, 1.1 Hz, 1H), 3.22-3.10 (m, 1H), 1.56 (p, *J* = 7.4 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.59 (d, *J* = 5.4 Hz), 137.64, 128.79, 127.35, 126.85, 122.41, 114.14, 62.10 (d, *J* = 6.7 Hz), 61.71 (d, *J* = 6.7 Hz), 46.69 (d, *J* = 127.8

View Article Online
DOI: 10.1039/C5RA16673J

Hz), 39.12 (d, *J* = 4.4 Hz), 37.04, 28.30 (d, *J* = 19.5 Hz), 15.81 (d, *J* = 6.3 Hz), 15.51 (d, *J* = 6.3 Hz), 11.89, 10.88. ESI-MS [M+H]+ = 340, [M+Na]+ = 362. Anal. Calcd for $C_{17}H_{26}NO_4P$: C, 60.17; H, 7.72; N, 4.13. Found: C, 60.06; H, 7.77; N, 4.14.

Diethyl [1-ethyl-2-oxo-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-3-yl]phosphonate (18f). Light yellow oil (177 mg, 50 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2972, 2933, 1662, 1600, 1496, 1460, 1381, 1247, 1019, 965. ^{31}P NMR (101 MHz, $CDCl_3$) δ 23.47 ppm. ^1H NMR (250 MHz, $CHCl_3$) δ 7.25 (ddd, *J* = 8.1, 7.5, 1.9 Hz, 1H), 7.17 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.04 - 6.98 (m, 2H), 4.19 – 3.87 (m, 4H), 3.80-3.65 (m, 1H), 3.49 – 3.37 (m, 1H), 3.37 (dd, *J* = 26.2, 1.0 Hz, 1H), 3.02 (ddd, *J* = 15.2, 7.2, 1.0 Hz, 1H), 1.77 (p, *J* = 7.2 Hz, 1H), 1.28 (td, *J* = 7.0, 0.6 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (td, *J* = 7.0, 0.6 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.55 (d, *J* = 5.4 Hz), 138.71, 130.32, 127.81, 126.36, 122.70, 114.49, 62.67 (d, *J* = 6.7 Hz), 62.30 (d, *J* = 6.9 Hz), 44.66 (d, *J* = 128.0 Hz), 44.21 (d, *J* = 4.4 Hz), 37.46, 33.12 (d, *J* = 18.0 Hz), 20.11, 19.65, 16.30 (d, *J* = 6.2 Hz), 16.01 (d, *J* = 6.3 Hz), 12.30. ESI-MS [M+H]+ = 354. Anal. Calcd for $C_{18}H_{28}NO_4P$: C, 61.18; H, 7.99; N, 3.96. Found: C, 61.05; H, 8.03; N, 3.94.

1-Ethyl-4-(propan-2-yl)-1,2-dihydroquinolin-2-one (19f). Colourless oil (82 mg, 38 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2960, 2932, 2870, 1638, 1595, 1580, 1456, 1069. ^1H NMR (250 MHz, $CDCl_3$) δ 7.55-7.44 (m, 3H), 7.36 – 7.31 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.18 (ddd, *J* = 7.7, 7.2, 1.1 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.31 (spd, *J* = 6.9, 1.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.62, 139.95, 137.78, 132.28, 129.33, 128.49, 121.70, 121.13, 113.68, 37.67, 28.10, 21.96, 12.83. ESI-MS [M+H]+ = 216. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.18; H, 7.98; N, 6.46.

Diethyl (1-ethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18g). Light yellow oil (248 mg, 64 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2978, 2934, 2908, 1664, 1601, 1462, 1380, 1246, 1016, 964. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.02 ppm. ^1H NMR (700 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.28 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.24-7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 7.09 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.08 – 7.01 (m, 3H), 4.68 (d, *J* = 14.7 Hz, 1H), 4.18 – 4.04 (m, 3H), 4.00 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.84-3.78 (m, 1H), 3.55-3.49 (m, 1H), 3.51 (dd, *J* = 25.0, 1.1 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.55 (d, *J* = 5.1 Hz), 141.88 (d, *J* = 19.0 Hz), 139.03, 129.79, 128.85, 128.36, 127.13, 126.90, 125.85, 123.48, 114.74, 62.88 (d, *J* = 6.7 Hz), 62.44 (d, *J* = 6.8 Hz), 49.38 (d, *J* = 124.9 Hz), 42.69 (d, *J* = 3.5 Hz), 37.53, 16.27 (d, *J* = 6.3 Hz), 15.99 (d, *J* = 6.3 Hz), 12.28. ESI-MS [M+H]+ = 388, [M+Na]+ = 410. Anal. Calcd for $C_{21}H_{26}NO_4P$: C, 65.11; H, 6.76; N, 3.62. Found: C, 65.02; H, 6.78; N, 3.59.

Diethyl (1-butyl-4-ethyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18h). Light yellow oil (312 mg, 85 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.7 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2960, 2931, 2873, 1663, 1600, 1460, 1378, 1247, 1020, 963. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.68 ppm. ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 8.0, 7.7, 1.7 Hz, 1H), 7.16 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.00 (ddd, *J* = 7.7, 7.5, 1.1 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.07 (dq, *J* = 8.1, 7.1 Hz, 2H), 3.93 (t, *J* = 7.7 Hz, 2H), 3.79-3,64 (m, 1H), 3.37 (qdd, *J* = 10.0, 8.6, 7.0 Hz, 1H), 3.22 (dd, *J* = 25.2, 1.1 Hz, 2H), 1.72-1.46 (m, 4H), 1.45 – 1.28 (m, 2H), 1.28 (td, *J* = 7.0, 0.5 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.89 (d, *J* = 7.6 Hz, 3H), 0.85 (td, *J* = 7.1, 0.5 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.85 (d, *J* = 5.3 Hz), 137.89, 128.84, 127.34, 126.92, 122.43, 114.33, 62.13 (d, *J* = 6.4 Hz), 61.74 (d, *J* = 6.9 Hz), 46.76

View Article Online
DOI: 10.1039/C5RA16673J

(d, *J* = 127.9 Hz), 41.83, 39.21 (d, *J* = 4.4 Hz), 28.66, 28.43 (d, *J* = 19.7 Hz), 19.80, 15.85 (d, *J* = 6.2 Hz), 15.56 (d, *J* = 6.3 Hz), 13.42, 10.96. ESI-MS [M+H]+ = 368, [M-H]- = 366.Anal. Calcd for $C_{19}H_{30}NO_4P$: C, 62.11; H, 8.23; N, 3.81. Found: C, 62.25; H, 8.25; N, 3.77.

Diethyl [1-butyl-2-oxo-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-3-yl]phosphonate (18i). Light yellow oil (156 mg, 41 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2958, 2932, 2872, 1662, 1600, 1460, 1382, 1249, 1020, 962. ^{31}P NMR (101 MHz, $CDCl_3$) δ 23.32 ppm. ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 7.15 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.00 (ddd, *J* = 7.4, 7.3, 1.0 Hz, 1H), 6.96 (dd, *J* = 8.2, 1.0 Hz, 1H),, 4.12-4.00 (m, 2H), 3.91 (t, *J* = 7.8 Hz, 2H), 3.83 – 3.60 (m, 1H), 3.45 – 3.32 (m, 1H), 3.35 (dd, *J* = 26.1, 1.1 Hz, 1H), 3.00 (dd, *J* = 15.1, 7.3 Hz, 1H), 1.85 – 1.70 (m, 1H), 1.69-1.49 (m, 2H), 1.48 – 1.30 (m, 2H), 1.27 (td, *J* = 7.1, 0.6 Hz, 3H), 0.98 – 0.81 (m, 12H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.54 (d, *J* = 5.4 Hz), 138.82, 130.15, 127.64, 126.23, 122.52, 114.48, 62.49 (d, *J* = 6.7 Hz), 62.13 (d, *J* = 7.0 Hz), 46.02, 44.16 (d, J = 4.4 Hz), 43.99, 42.25, 32.88 (d, *J* = 17.8 Hz), 28.90, 20.10 (d, *J* = 8.5 Hz), 19.54 , 16.15 (d, *J* = 6.2 Hz), 15.88 (d, *J* = 6.2 Hz), 13.72. ESI-MS [M+H]+ = 382. Anal. Calcd for $C_{20}H_{32}NO_4P$: C, 62.97; H, 8.46; N, 3.65. Found: C, 63.11; H, 8.48; N, 3.66.

1-Butyl-4-(propan-2-yl)-1,2-dihydroquinolin-2-one (19i). Yellow oil (114 mg, 47 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2957, 2930, 2869, 1640, 1625, 1595, 1455, 1207. ^1H NMR (250 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 3H), 7.32 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.19 (ddd, *J* = 7.7, 7.2, 1.1 Hz, 1H), 4.35 – 4.26 (m, 2H), 3.31 (spd, *J* = 6.8, 0.9 Hz, 1H), 1.81 – 1.64 (m, 2H), 1.58 – 1.40 (m, 2H), 1.27 (s, 3H), 1.25-1.17 (m, 2H), 1.24 (s, 3H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.72, 139.73, 137.90, 132.16, 129.17, 128.35, 121.58, 120.97, 113.71, 42.46, 29.59, 28.07, 21.83, 20.34, 13.84. ESI-MS [M+H]+ = 244. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.09; H, 8.75; N, 5.77.

Diethyl (1-butyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18j). Light yellow oil (378 mg, 91 %). Chromatography (CH_2Cl_2 : EtOAc = 6:1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2958, 2931, 2871, 1663, 1600, 1461, 1372, 1245, 1049, 1016. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.09 ppm. ^1H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5H), 7.10 – 7.00 (m, 4H), 4.68 (d, *J* = 15.1. 1H), 4.20 – 4.05 (m, 2H), 3.96 (m, 2H), 3.80 (m, 1H), 3.59 – 4.42 (m, 1H), 3.51 (dd, *J* = 25.2, 1.2 Hz, 2H), 1.72 – 1.49 (m, 2H), 1.42- 1.25 (m, 2H), 1.31 (td, *J* = 7.1, 0.6 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.92 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.58 (d, *J* = 5.1 Hz), 141.68 (d, *J* = 19.1 Hz), 139.07, 129.62, 128.67, 128.23, 126.98, 126.75, 125.65, 123.31, 114.77, 62.72 (d, *J* = 6.5 Hz), 62.33 (d, *J* = 6.9 Hz), 49.20 (d, *J* = 125.3 Hz), 42.48 (d, *J* = 3.5 Hz), 42.17, 28.88, 20.04, 16.12 (d, *J* = 6.3 Hz), 15.86 (d, *J* = 6.4 Hz), 13.66. ESI-MS [M+H]+ = 416, [M+Na]+ = 438. Anal. Calcd for $C_{23}H_{30}NO_4P$: C, 66.49; H, 7.28; N, 3.37. Found: C, 66.35; H, 7.31; N, 3.36.

Diethyl (1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18k). Light yellow oil (209 mg, 54 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2980, 2928, 1664, 1601, 1496, 1378, 1251, 1052, 1019, 961. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.28 ppm. ^1H NMR (250 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 7.20 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 6.99 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H),, 5.62 (d, *J* = 16.3 Hz, 1H), 4.80 (d, *J* = 16.3 Hz, 1H), 4.13 (dq, *J* = 8.1, 7.1 Hz, 2H), 3.89 – 3.71 (m, 1H), 3.56 (m, 1H), 3.46 – 3.34 (m, 1H), 3.27 (dd, *J* = 25.1, 1.1 Hz, 1H), 1.34 – 1.27 (m, 6H), 0.83 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.58 (d, *J* = 5.0 Hz), 137.48, 135.88, 127.78, 127.56, 126.79, 126.61,

View Article Online
DOI: 10.1039/C5RA16673J

126.04, 125.39, 122.51, 114.59, 61.67 (d, *J* = 6.4 Hz), 61.31 (d, *J* = 6.9 Hz), 47.70 (d, *J* = 127.6 Hz), 45.86, 32.02 (d, *J* = 4.4 Hz), 21.77 (d, *J* = 20.2 Hz), 15.22 (d, *J* = 6.2 Hz), 14.85 (d, *J* = 6.3 Hz). ESI-MS [M+H]+ = 388, [M-H]- = 386. Anal. Calcd for $C_{21}H_{26}NO_4P$: C, 65.11; H, 6.76; N, 3.62. Found: C, 64.99; H, 6.79; N, 3.60.

Diethyl (1-benzyl-4-ethyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18l). Light yellow solid (261 mg, 65 %) mp 84-85 °C. Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2962, 2932, 1664, 1602, 1495, 1458, 1382, 1242, 1181, 1017, 955. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.72 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32-7.23 (m, 5H), 7.18 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 6.99 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.62 (d, *J* = 16.3 Hz, 1H), 4.74 (d, *J* = 16.3 Hz, 1H), 4.23 – 4.03 (m, 2H), 3.79 (m, 1H), 3.44-3.19 (m, 3H), 1.63 (p, *J* = 7.6 Hz, 2H), 1.31 (td, *J* = 7.1, 0.5 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.83 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.79, 138.76, 136.87, 128.87, 128.52, 127.62, 127.09, 126.98, 126.30, 123.05, 115.55, 62.59 (d, *J* = 6.4 Hz), 62.24 (d, *J* = 6.8 Hz), 47.05 (d, *J* = 128.7 Hz), 46.89, 39.50 (d, *J* = 4.2 Hz), 28.90 (d, *J* = 19.4 Hz), 16.20 (d, *J* = 6.2 Hz), 15.84 (d, *J* = 6.3 Hz), 11.32. ESI-MS [M+H]+ = 402, [M+Na]+ = 324. Anal. Calcd for $C_{22}H_{28}NO_4P$: C, 65.82; H, 7.03; N, 3.49. Found: C, 65.96; H, 7.01; N, 3.52.

Diethyl [1-benzyl-2-oxo-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-3-yl]phosphonate (18m). White solid (241 mg, 58 %) mp 85-87. Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2996, 2966, 2931, 2876, 1664, 1601, 1457, 1369, 1241, 1049, 1020, 967. ^{31}P NMR (101 MHz, $CDCl_3$) δ 23.37 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 7.17 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H), 6.98 (dd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.64 (d, *J* = 16.3 Hz, 1H), 4.66 (d, *J* = 16.3 Hz, 1H), 4.21 – 4.05 (m, 2H), 3.89 – 3.71 (m, 1H), 3.49 (dd, *J* = 26.5, 1.1 Hz, 1H), 3.34 (m, 1H), 3.11 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.85 (sp, *J* = 6.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.87-0.82 (m, 6H). ^{13}C NMR (176 MHz, $CHCl_3$) δ 165.25 (d, *J* = 5.4 Hz), 139.56, 137.02, 129.90, 128.57, 127.71, 127.04, 126.43, 126.17, 122.91, 115.52, 62.66 (d, *J* = 6.7 Hz), 62.35 (d, *J* = 6.6 Hz), 47.12 , 45.20 (d, *J* = 127.8 Hz), 44.22 (d, *J* = 4.3 Hz), 33.12 (d, *J* = 17.7 Hz), 20.07, 19.68, 16.26 (d, *J* = 6.2 Hz), 15.92 (d, *J* = 6.2 Hz). ESI-MS [M+H]+ = 416, [M-H]- = 414. Anal. Calcd for $C_{23}H_{30}NO_4P$: C, 66.49; H, 7.28; N, 3.37. Found: C, 66.70; H, 7.31; N, 3.37.

1-Benzyl-4-(propan-2-yl)-1,2-dihydroquinolin-2-one (19m). Yellow oil (53 mg, 19 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3061, 3031, 2959, 2870, 1640, 1593, 1495, 1453, 1226, 1207, 1069, 971. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.58 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.39 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.28 – 7.24 (m, 4H), 7.19 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 5.62 (s, 2H), 3.42 (spd, *J* = 6.9, 0.9 Hz, 1H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 162.34, 139.98, 138.34, 136.83, 132.87, 129.42, 128.83, 128.37, 127.24, 126.76, 122.07, 121.12, 114.72, 46.40, 28.30, 22.02. ESI-MS [M+H]+ = 278. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.40; H, 6.92; N, 5.06.

Diethyl (1-benzyl-4-ethenyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18n). Light yellow solid (84 mg, 21 %) mp 69-71 °C. Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.6 (UV active, CH_2Cl_2: EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2980, 1666, 1601, 1495, 1461, 1378, 1250, 1172, 1049, 1017, 966. ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.07 ppm. ^{1}H NMR (250 MHz, $CHCl_3$) δ 7.31-7.20 (m, 5H), 7.21 (dd, *J* =7.4, 1.8 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.6, 1.8 Hz, 1H), 7.01 (ddd, *J* = 7.6, 7.4, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.91 (ddd, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.50 (d, *J* = 16.3 Hz, 1H), 5.08 (ddd, *J* = 10.2, 1.6, 0.8 Hz,

View Article Online
DOI: 10.1039/C5RA16673J

1H), 4.88 (ddd, *J* = 17.0, 1.8, 0.9 Hz, 2H), 4.82 (d, *J* = 16.4 Hz, 0H), 4.21 – 4.08 (m, 3H), 3.81 (m, 1H), 3.46 (dd, *J* = 25.0, 1.4 Hz, 1H), 3.48-3.34 (m, 1H), 1.32 (td, *J* = 7.1, 0.6 Hz, 3H), 0.86 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.38 (d, *J* = 5.3 Hz), 139.02, 137.94 (d, *J* = 20.6 Hz), 136.71, 128.75, 128.47, 128.03, 126.99, 126.38, 125.00, 123.48, 115.83, 115.64, 62.79 (d, *J* = 6.4 Hz), 62.39 (d, *J* = 6.7 Hz), 47.57 (d, *J* = 128.0 Hz), 46.56, 41.09 (d, *J* = 3.1 Hz), 16.19 (d, *J* = 6.1 Hz), 15.83 (d, *J* = 6.3 Hz). ESI-MS [M+H]+ = 400, [M-H]- = 398. Anal. Calcd for $C_{22}H_{26}NO_4P$: C, 59.07; H, 7.44; N, 4.31. Found: C, 59.15; H, 7.49; N, 4.29.

Diethyl (1-benzyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)phosphonate (18o). Light yellow oil (355 mg, 79 %). Chromatography (CH_2Cl_2/EtOAc 6/1). Rf: 0.7 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 3062, 3029, 2981, 2931, 2907, 1666, 1601, 1495, 1462, 1379, 1248, 1167, 1017, 965. ^{31}P NMR (101 MHz, $CDCl_3$) δ 21.53 ppm. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 8H), 7.25-7.20 (m, 2H), 7.12 – 7.04 (m, 3H), 7.04-6.99 (m, 1H), 5.55 (d, *J* = 16.2 Hz, 1H), 4.96 (d, *J* = 16.2 Hz, 1H), 4.82 (d, *J* = 14.7 Hz, 1H), 4.33 – 4.12 (m, 2H), 3.93 (m, 1H), 3.72 (dd, *J* = 25.3, 1.1 Hz, 1H), 3.64 – 3.45 (m, 1H), 1.38 (td, *J* = 7.1, 0.6 Hz, 3H), 0.95 (td, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.42 (d, *J* = 4.1 Hz), 141.89, 141.59, 139.71, 136.78, 129.50, 128.97, 128.63, 128.36, 127.24, 127.04, 126.76, 125.80, 123.81, 115.87, 62.97 (d, *J* = 6.7 Hz), 62.70 (d, *J* = 6.8 Hz), 49.44 (d, *J* = 125.5 Hz), 46.90, 42.65, 16.35 (d, *J* = 7.5 Hz), 15.97 (d, *J* = 7.5 Hz). ESI-MS [M+H]+ = 450, [M-H]- = 448. Anal. Calcd for $C_{26}H_{28}NO_4P$: C, 69.48; H, 6.28; N, 3.12. Found: C, 69.67; H, 6.31; N, 3.12.

4. General procedure for the synthesis of 1,4-alkil or aryl 3-methylidene-1,2,3,4-tetrahydroquinolin-2-ones 20a-o:

To the solution of 1,4-alkyl or aryl 3-diethoxyphosphorylquinolin-2-one **18** (0.5 mmol) in THF (2 mL) under argon atmosphere, sodium hydride (16.5 mg, 0.55 mmol) was added in one portion. The reaction mixture was stirred at ambient temperature for 5 min. Then formaldehyde (75.1 mg, 2.5 mmol) was added. After 4 hours water was added (3 mL) and the mixture was extracted with dichloromethane (2*5 mL) Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure, affording the crude product which was purified by column chromatography (CH_2Cl_2).

4-Ethyl-1-methyl-3-methylidene-1,2,3,4-tetrahydroquinolin-2-one (20a). Colourless oil (82 mg, 82 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2963, 2930, 2873, 1666, 1628, 1597, 1497, 1459, 1351, 1112, 1050. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 1H), 7.14 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.03 (ddd, *J* = 7.4, 7.3, 1.1 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.17 (d, *J* = 1.6 Hz, 1H), 5.43 (dd, *J* = 1.6, 0.8 Hz, 1H), 3.40 (s, 3H), 1.71 – 1.49 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.65, 140.22, 138.81, 128.84, 127.92, 127.49, 123.41, 122.90, 114.70, 47.10, 30.03, 29.71, 11.17. ESI-MS [M+H]+ = 202. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.72; H, 7.55; N, 6.96.

1-Methyl-3-methylidene-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one (20b). White solid (94 mg, 87 %) mp 43-44 °C. Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2977, 2964, 2909, 2867, 1666, 1636, 1596, 1471, 1350, 1120, 1049. ^{1}H NMR (250 MHz, $CDCl_3$)δ 7.26 (ddd, *J* = 8.1, 7.6, 1.7 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.02 (ddd, *J* = 7.6, 7.3, 1.2 Hz, 1H), 6.96 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.17 (d, *J* = 1.7 Hz, 1H), 5.38 (dd, *J* = 1.7, 0.8 Hz, 1H), 3.37 (s, 3H), 3.19 (d, *J* = 7.3 Hz, 1H), 1.79 (dqd, *J* = 6.9, 6.8 Hz, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ

View Article Online
DOI: 10.1039/C5RA16673J

165.30, 139.50, 139.38, 128.99, 127.86, 127.58, 124.28, 122.62, 114.66, 52.28, 33.64, 29.74, 20.31, 19.34. ESI-MS [M+H]+ = 216. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.22; H, 7.94; N, 6.55.

1-Methyl-3-methylidene-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (20c).[16] White solid (112 mg, 90 %) mp 38-39 °C. Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 3052, 3021, 2922, 2849, 1671, 1633, 1597, 1454, 1352, 1110, 945. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35 (ddd, *J* = 7.8, 7.6, 1.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.26-7.24 (m, 1H), 7.19 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.17 – 7.13 (m, 2H), 7.11 – 7.05 (m, 2H), 6.31 (t, *J* = 1.1 Hz, 1H), 5.57 (d, *J* = 1.3 Hz, 1H), 4.91 (s, 1H), 3.43 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.40, 140.90, 140.34, 139.58, 128.77, 128.75, 128.14, 127.67, 127.14, 127.10, 124.20, 123.14, 114.93, 49.48, 29.91. ESI-MS [M+H]+ = 250.2. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.83; H, 6.06; N, 5.62. Found: C, 81.99; H, 6.08; N, 5.59.

1-Ethyl-4-methyl-3-methylidene-1,2,3,4-tetrahydroquinolin-2-one (20d). White solid (80 mg, 80 %) mp 84-85 °C. Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2958, 1664, 1624, 1575, 1368, 1258, 1127. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 8.0, 7.6, 1.8 Hz, 1H), 7.17 (ddd, *J* = 7.6, 1.6, 0.8 Hz, 1H), 7.02 (m, 2H), 6.09 (m, 1H), 5.44 (dd, *J* = 1.3 Hz, 1.4 Hz, 1H), 4.09 (m, 1H), 4.02 (m, 1H), 3.71 – 3.67 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.12, 142.35, 137.60, 130.13, 127.53, 127.10, 123.05, 121.53, 114.78, 39.26, 37.50, 22.63, 12.64. ESI-MS [M+H]+ = 202. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.70; H, 7.53; N, 6.93.

1,4-Diethyl-3-methylidene-1,2,3,4-tetrahydroquinolin-2-one (20e). Colourless oil (99 mg, 92 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}) : 2968, 2933, 2874, 1665, 1622, 1590, 1495, 1457, 1371, 1252. ^{1}H NMR (250 MHz $CDCl_3$) δ 7.24 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.13 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.14 (d, *J* = 1.6 Hz, 1H), 5.40 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.13-3.95 (m, 2H), 3.45 – 3.31 (m, 1H), 1.69 – 1.47 (m, 2H), 1.29 (t, *J* = 7.1, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.02, 140.53, 137.62, 129.12, 128.26, 127.50, 123.01, 122.75, 114.72, 47.15, 37.30, 30.18, 12.56, 11.08. ESI-MS [M+H]+ = 216. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.27; H, 7.98; N, 6.50.

1-Ethyl-3-methylidene-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one (20f). Colourless oil (102 mg, 89 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 1:1). IR (neat) *v* (cm^{-1}): 2959, 2934, 1665, 1630, 1599, 1495, 1461, 1372, 1256, 1123. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (ddd, *J* = 8.2, 7.6, 1.8 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.16 (d, *J* = 1.7 Hz, 1H), 5.36 (dd, *J* = 1.7, 0.8 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.20 (d, *J* = 6.9 Hz, 1H), 1.85 – 1.70 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.64, 139.67, 138.18, 129.31, 128.09, 127.57, 123.95, 122.44, 114.66, 52.19, 37.18, 34.04, 20.18, 19.16, 12.53. ESI-MS [M+H]+ = 230. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.71; H, 8.39; N, 6.11.

1-Ethyl-3-methylidene-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (20g). Colourless oil (96 mg, 73 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 3057, 3026, 2973, 2931, 1665, 1627, 1597, 1493, 1459, 1371, 1256, 1114. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 8.8, 7.5, 1.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.17 (m, 1H), 7.12 (m, 3H), 7.07 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 1H), 6.26 (t, *J* = 1.0 Hz, 1H), 5.55 (t, *J* = 1.3 Hz, 1H), 4.88 (s, 1H), 4.06 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.85, 141.07, 140.72, 138.48, 129.14, 128.77, 128.18, 127.67,

View Article Online
DOI: 10.1039/C5RA16673J

127.45, 127.13, 123.76, 123.07, 115.06, 49.67, 37.52, 12.57. ESI-MS [M+H]+ = 264. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.01; H, 6.58; N, 5.27.

1-Butyl-4-ethyl-3-methylidene-1,2,3,4-tetrahydroquinolin-2-one (20h). Colourless oil (112 mg, 92 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2959, 2930, 2872, 1666, 1630, 1598, 1495, 1460, 1368, 1119, 935. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 1H), 7.16 – 7.10 (m, 1H), 7.05 – 6.96 (m, 2H), 6.13 (d, *J* = 1.6 Hz, 1H), 5.40 (dd, *J* = 1.5, 0.7 Hz, 1H), 4.13 – 3.82 (m, 2H), 3.38 (dd, *J* = 8.1, 6.6 Hz, 1H), 1.81 – 1.50 (m, 4H), 1.50 – 1.34 (m, 2H), 1.01 – 0.93 (t, *J* = 7.4 Hz, 3H), 0.93 – 0.84 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.24, 140.55, 137.74, 129.13, 128.25, 127.45, 122.96, 122.72, 114.86, 47.20, 41.88, 30.21, 29.16, 20.35, 13.88, 11.12. ESI-MS [M+H]+ = 244. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.74; N, 5.76. Found: C, 79.10; H, 8.70; N, 5.74.

1-Butyl-3-methylidene-4-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one (20i). Colourless oil (117 g, 91 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2957, 2930, 2871, 1666, 1631, 1598, 1494, 1457, 1366, 1205, 1140. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 7.17 – 7.05 (m, 1H), 7.07 – 6.92 (m, 2H), 6.15 (d, *J* = 1.7 Hz, 1H), 5.36 (dd, *J* = 1.7, 0.8 Hz, 1H), 4.04 (m, 1H), 3.85 (m, 1H), 3.19 (d, *J* = 7.1 Hz, 1H), 1.85 – 1.71 (m, 1H), 1.71 – 1.51 (m, 1H), 1.50 – 1.34 (m, 2H), 0.97 (t, *J* =7.2 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.73 , 139.68, 138.27, 129.23, 128.00, 127.47, 123.75, 122.33, 114.68, 52.19, 41.88, 33.86, 29.09, 20.38, 20.16, 19.15, 13.85. ESI-MS [M+H]+ = 258. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.45; H, 9.07; N, 5.45.

1-Butyl-3-methylidene-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (20j). White solid (137 mg, 94 %) mp 51-53 °C. Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2952, 2928, 2868, 1626, 1599, 1456, 1375, 1321, 1112. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (ddd, *J* = 8.5, 7.5, 1.6 Hz, 1H), 7.32-7.30 (m, 2H), 7.26 – 7.24 (m, 1H), 7.23 – 7.22 (dd, *J* = 7.3, 1.7 Hz,1H), 7.16 – 7.14 (m, 2H), 7.12 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.10 (ddd, *J* = 7.4, 7.3, 1.1 Hz, 1H), 6.28 (d, *J* = 1.0 Hz, 1H), 5.58 (d, *J* = 1.2 Hz, 1H), 4.90 (s, 1H), 4.17-4.12 (m, 1H), 3.93 -3.89 (m, 1H), 1.74-1.67 (m, 1H), 1.65 – 1.58 (m, 1H), 1.39 – 1.25 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.17, 140.99, 140.76, 138.58, 129.16, 128.71, 128.13, 127.64, 127.54, 127.11, 123.67, 123.02, 115.25, 49.63, 41.90, 29.11, 20.17, 13.87. ESI-MS [M+H]+ = 292. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.66; H, 7.30; N, 4.80.

1-Benzyl-4-methyl-3-methylidene-1,2,3,4-tetrahydroquinolin-2-one (20k). Colourless oil (124 mg, 94 %). Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 3062, 3031, 2963, 2924, 1666, 1630, 1597, 1367, 1318, 1186. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 – 7.16 (m, 6H), 7.11 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.01 (ddd, *J* = 7.4, 6.5, 1.3 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.22 (d, *J* = 1.1 Hz, 1H), 5.56 (d, *J* = 1.3 Hz, 1H), 5.37 (d, *J* = 16.2 Hz, 1H), 5.19 (d, *J* = 16.2 Hz, 1H), 3.81 (q, *J* = 7.3 Hz, 1H), 1.44 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.83, 141.95, 137.75, 136.80, 129.78, 128.75, 127.41, 127.07, 126.88, 126.44, 123.27, 122.32, 115.70, 46.32, 39.17, 22.74. ESI-MS [M+H]+ = 264. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.23; H, 6.52; N, 5.29.

1-Benzyl-4-ethyl-3-methylidene-1,2,3,4-tetrahydroquinolin-2-one (20l). White solid (133 mg, 96 %) mp 115-117 °C. Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 2963, 2922, 1668, 1634, 1597, 1494, 1451, 1370, 1187, 1017. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 5H), 7.15 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.09 (dd, *J* = 8.0, 7.6, 1.8 Hz, 1H), 6.99 (ddd, *J* = 7.6, 7.4, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.2

View Article Online
DOI: 10.1039/C5RA16673J

Hz, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 5.51 (dd, *J* = 1.6, 0.8 Hz, 1H), 5.42 (d, *J* = 16.2 Hz, 1H), 5.09 (d, *J* = 16.2 Hz, 1H), 3.48 (t, *J* = 7.4 Hz, 1H), 1.74 – 1.61 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.84, 140.21, 137.93, 136.89, 128.91, 128.78, 128.10, 127.46, 127.10, 126.50, 123.87, 123.03, 115.74, 47.22, 46.37, 30.33, 11.20. ESI-MS [M+H]+ = 278. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.19; H, 6.94; N, 5.03.

1-Benzyl-3-methylidene-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one (20m). White solid (132 mg, 91 %) mp 79-81ºC. Rf: 0.9 (UV active, CH_2Cl_2 : EtOAc = 3:2). IR (neat) *v* (cm^{-1}): 3033, 2968, 2950, 2901, 1665, 1629, 1597, 1494, 1453, 1369, 1186, 1016. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 – 7.31 (m, 5H), 7.27 – 7.18 (m, 2H), 7.14 – 7.06 (m, 1H), 6.98 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 5.59 (dd, *J* = 1.7, 0.8 Hz, 1H), 5.56 (d, *J* = 16.2 Hz, 1H), 5.09 (d, *J* = 16.2 Hz, 1H), 3.40 (d, *J* = 7.1 Hz, 1H), 1.98 (qd, *J* = 6.9, 6.8 Hz, 2H), 1.03 (d, *J* = 2.1 Hz, 3H), 1.01 (d, *J* = 2.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.48, 139.45, 138.64, 137.00, 129.15, 128.83, 127.90, 127.56, 127.16, 126.62, 124.74, 122.73, 115.68, 52.32, 46.66, 33.97, 20.31, 19.33. ESI-MS [M+H]+ = 292. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.61; H, 7,29; N, 4.77.

1-Benzyl-3-methylidene-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (20o). Colourless oil (135 mg, 83 %). Rf: 0.8 (UV active, CH_2Cl_2 : EtOAc = 2:1). IR (neat) *v* (cm^{-1}): 3064, 3025, 1665, 1638, 1597, 1493, 1459, 1370, 1187, 941. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 8H), 7.19 – 7.09 (m, 4H), 7.06 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.38 (s, 1H), 5.69 (s, 1H), 5.36 (d, *J* = 16.2 Hz, 1H), 5.16 (d, *J* = 16.2 Hz, 1H), 4.97 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.78, 140.69, 140.40, 138.57, 136.61, 129.00, 128.78, 128.71, 128.12, 127.75, 127.34, 127.22, 127.13, 126.68, 124.46, 123.29, 116.11, 49.55, 46.07. ESI-MS [M+H]+ = 326. Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.77; H, 5.92; N, 4.34.

Cytotoxicity Assay by MTT

Cytotoxicity of the compounds was assessed by the mitochondrial reduction assay on two leukemia cell lines, promyelocytic HL-60 and lymphoblastic NALM-6 and on one solid tumor-derived cell line, breast cancer MCF-7 adenocarcinomas. Cells were purchased from the European Collection of Cell Cultures (ECACC). Leukemia cells were cultured in RPMI 1640 medium, while MCF-7 cells in DMEM (Dulbecco's Modified Eagle Medium), both supplemented with 10% heat-inactivated fetal bovine serum (Invitrogen, Paisley, UK) and antibiotics (100 µg/mL streptomycin and 100 U/ml penicillin). Normal human umbilical vein endothelial cells (HUVECs) and all reagents for cell culture were purchased from Cascade Biologics (Portland, Oregon, USA). The HUVECs were cultured according to the manufacturer`s instructions and the cells underwent 3-8 passages. Cells were grown in 37 ºC in a humidified atmosphere of 5% CO_2 in air. Exponentially growing cells were seeded at 8×10^3/well on 96-well plates (Nunc, Roskilde, Denmark). After 24 h, the tested compounds (freshly prepared in DMSO and diluted with complete culture medium to obtain the concentration range from 10^{-7} to 10^{-3} M) were added and the plates were incubated for 48 h. Afterwards, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 5 mg/mL in PBS) was added and

View Article Online
DOI: 10.1039/C5RA16673J

incubation was continued for 2h. The metabolically active cells reduced MTT to blue formazan crystals. Then, the MTT-containing medium was carefully aspirated and 100 µL DMSO was added to dissolve the crystals. After shaking 10 min in the dark absorbance was read at 560 nm on an ELISA–plate reader (ELX 800, Bio-Tek, USA) and compared with control (untreated cells). The IC_{50} values were calculated from concentration-response curves.

Acknowledgements

This work was financially supported by the National Science Centre of Poland (project DEC-2012/07/B/ST5/02006).

Notes and references

1. Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K.; *Angew. Chem. Int. Ed.* **2009**, *48*, 9426-9452.

2. Albrecht, A.; Albrecht, Ł.; Janecki, T.; *Eur. J. Org. Chem.* **2011**, *15*, 2747-2766.

3. (a) Zhang, S.; Won, Y.-K.; Ong, C.-N.; Shen, H.-M.; *Curr. Med. Chem.: Anti-Cancer Agents* **2005**, *5,* 239-249; (b) Janecka, A.; Wyrębska, A.; Gach, K.; Fichna, J.; Janecki, T.; *Drug Disc. Today* **2012**, *17*, 561-572.

4. Zhang, Z.; Di, Y.-T.; Wang, Y.-H.; Zhang, Z.; Mu, S.-Z.; Fang, X.; Zhang, Y.; Tan, C.-J.; Zhang, Q.; Yan, X.-H.; Guo, J.; Li, C.-S.; Hao, X.-J.; *Tetrahedron* **2009**, *65*, 4551–4556.

5. Lee, Ch. G.; Lee, K.Y.; Lee, S.; Kim, J.N.; *Tetrahedron* **2005**, *61*, 1493-1499.

6. Pathak, R.; Madapa, S.; Batra, S.; *Tetrahedron* **2007**, *63*, 451-460.

7. Kim, K. H.; Lee, H.S.; Kim. J.N.; *Tetrahedron Lett.* **2009**, *50*, 1249-1251.

8. Singh, V.; Kanojiya, S.; Batra, S.; *Tetrahedron* **2006**, *62*, 10100-10110.

9. Jia, J.; Sarker, M.; Steinmetz, M.G.; Shukla, R.; Rathore, R.; *J. Org. Chem.* **2008**, *73*, 8867-8879.

10. Ramachary, D. B.; Venkaiah, C.; Reddy, Y.V.; *Org. Biomol. Chem.* **2014**, *12*, 5400-5406.

11. (a) Janecki, T.; *Targets in Heterocyclic Systems* (Eds.: Attanasi, O. A.; Spinelli, D.), Italian Society of Chemistry, Rome, **2006**, *10*, 301–320; (b) Modranka, J.; Jakubowski, R.; Janecki, T.; *Synlett* **2014**, *25*, 105-109; (c) Modranka, J.; Jakubowski, R.; Różalski, M.; Krajewska, U.; Janecka, A.; Gach, K.; Pomorska, D.; Janecki, T.; *Eur. J. Med. Chem.* **2015**, *92*, 565-574.

12. Cordi, A.A.; Desos, P.; Ruano, E.; Al-Badri, H.; Fugier, C.; Chapman, A.G.; Meldrum, B.S.; Thomas, J-Y.; Roger, A.; Lestage. P.; *Il Farmaco* **2002**, *57*, 787-802.

13. (a) Skuratowicz, J. S.; Madden, I. L.; Busch, D. H.; *Inorg. Chem.* **1977**, *16*, 1721-1725; (b) Sridharan, V.; Ribelles, P.; Ramos, T.; Mendez, J. C. *J. Org. Chem.* **2009**, *74*, 5715-5718.

14. (a) Modranka, J; Albrecht, A.; Jakubowski, R.; Krawczyk, H.; Różalski, M.; Krajewska, U; Janecka, A.; Wyrębska , A.; Różalska, B.; Janecki, T. *Bioorg. Med. Chem*. **2012**, *20*, 5017-5026; (b) Janecki, T.; Wąsek, T. *Tetrahedron* **2004**, *60*, 1049-1055.

15. Wong, E.; Giandomenico, C. M. *Chem. Rev*. **1999**, *99*, 2451-2466.

16. Compound **20c** has been reported in ref. 7.