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A Simple Synthesis of 3-Phosphonyl-4-Aminoquinolines from β-Enaminophosphonates

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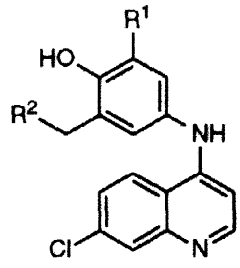
Abstract: An easy and efficient synthesis of 4-aminoquinolines substituted with a phosphorylated group or a phosphine oxide group in the 3-position is described. The key step is a regioselective addition of lithiated β-enamino phosphonates to isocyanates to give functionalized amides. Subsequent cyclization of these compounds with triphenylphosphine and hexachloroethane in the presence of triethylamine afforded substituted 4-aminoquinolines. The deprotection of *N*-PMP substituted 4-amino-quinolines with CAN in acetonitrile gave primary 4-aminoquinolines.

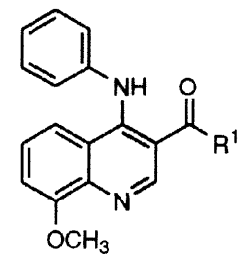
Keywords: 4-aminoquinolines, enamines, phosphonates, phosphine oxides.

4-Aminoquinoline ring systems represent an important class of compounds[1] and have attracted a great deal of attention in recent years because these compounds have interesting pharmacological properties and are widely used in medicinal chemistry. 4-Arylaminoquinolines such as *Amodiaquine*[2] **Ia** or the significantly more active *Tebuquine*[3] **Ib** display antimalarial activity, while *SK&F 96067* **IIa** has been recently applied to the treatment of ulcers and related gastric disorders[4a,b] and *CP-113,411* **IIb** has been used as a potent inhibitor of bone resorption[4c] (Scheme 1). Likewise, *N*-substituted 4-aminoquinolines containing an aryl or heteroaryl group in the 2-position **III** have been used as potent immunostimulants[5a] and as non-nucleoside HIV-1 inhibitors.[5b] In some of these types of 4-aminoquinolines the presence of a carbonyl (see compounds **II**, Scheme 1) or an ester group in the 3-position seems to play a key role in establishing the orientation of the arylamino group and therefore in the biological activity of these compounds.[4b]



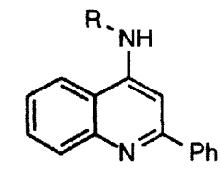
Ia R^1=H, R^2=Et_2N

Ib R^1=*p*Cl-C_6H_4, R^2=^{t}BuNH



IIa R^1=C_3H_7

IIb R^1=$OCH_2CH_2CO_2Et$



III

Scheme 1

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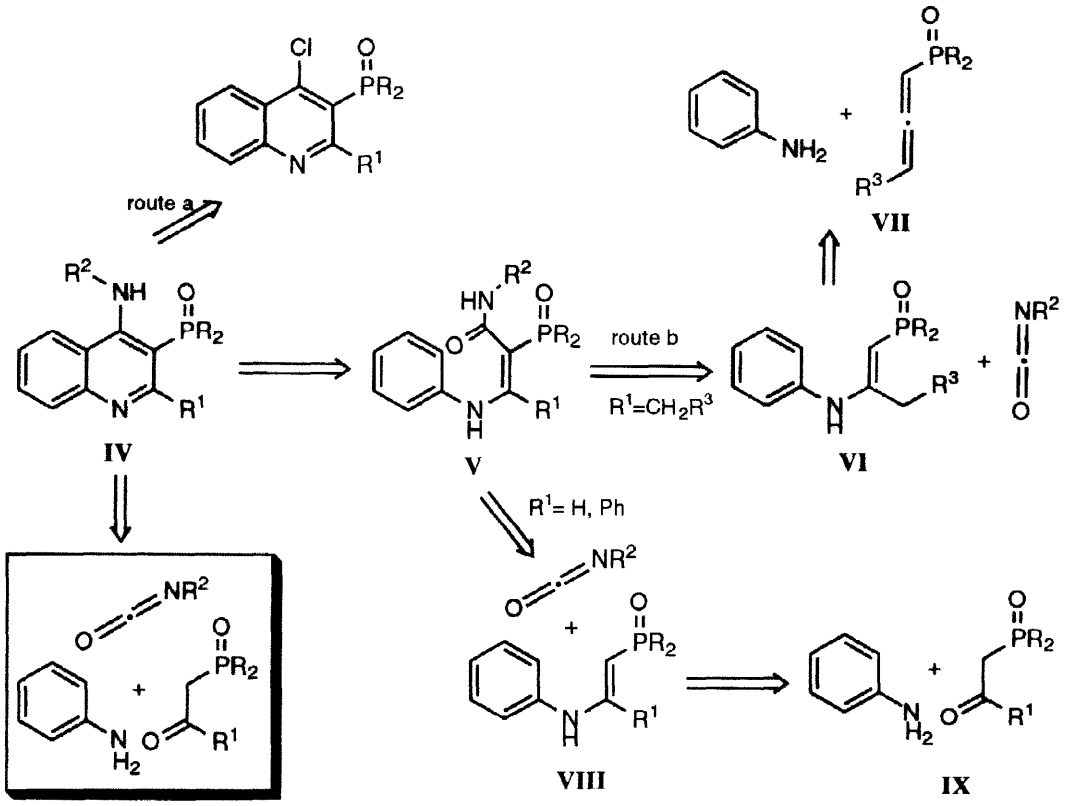
We are interested in the design of new aminoquinoline derivatives (**IV**, R = H, Ar, Scheme 2) substituted with a phosphonate group in the 3-position of the heterocyclic system. The phosphonyl group, might be responsible for fixing the conformation of the 4-arylamino moiety and this substituent could regulate important biological functions and increase the biological activity of these type of compounds, in a similar way to that reported for other pharmaceuticals.[6]

Synthetic routes to 4-aminoquinolines are relatively few and most of them involve nucleophilic displacement of the chlorine atom of 4-chloroquinoline[1,3,7] (Scheme 2, route a). Likewise, 4-aminoquinolines can alternatively be prepared by tandem reactions that simultaneously involve both the construction of the quinoline ring and the introduction of the amino group in the 4-position, when cyanoaryl-enamines[8a] or amido-enamines[8b] (see Scheme 2, route b) have been used.



Scheme 2

In connection with our interest in the synthesis of five[9] and six[8,10] membered phosphorylated nitrogen heterocycles we have used β-functionalized enamines derived from phosphazenes, phosphonium salts, phosphine oxides and phosphonates as synthetic intermediates in the synthesis of acyclic derivatives such as oximes,[11a] allylamines,[11b] hydrazones[11c] and β-aminofunctionalized compounds[11d] as well as pyridines[12a] and phosphorus containing heterocycles.[13b-c] We have recently described the synthesis of *N*-unsubstituted-4-aminoquinolines[8a] and *N*-aryl-4-aminoquinolines[8b] (see Scheme 2, route b) derived from phosphine oxides, and easily prepared from β-amido-*N*-arylenamines **V** obtained from arylamines, allenes **VII** and isocyanates. However, the use of allenes **VII** leads to the formation of 4-aminoquinolines **IV** ($R^1 = CH_2R^3$) and does not allow the preparation of 4-aminoquinolines **IV** without substitution in the 2-position (R^1 = H) or substitututed with aryl groups (R^1 = Ph). Here we aim to extend the synthetic use of phosphorylated

enamines **VIII** (R = OEt, Ph) in the preparation of substituted 4-aminoquinolines **IV** containing phosphonate and phosphine oxide groups in the 3-position. Retrosynthetically, we envisaged obtaining quinolines **IV** by insertion of both a carbon atom and the amino group between the *ortho*-position of the aryl group and the enaminic carbon atom of functionalized compound **V** (Scheme 2) by condensation of β-carbonyl phosphonates **IX** (R^1 = H, Ph) with arylamines followed by isocyanate addition and subsequent cyclization of amido-enamines **V**. Enamines **VIII** (R^1= H, Ph) are used, in order to avoid the above restrictions of the substituents of the allenes **VII** ($R^1 = CH_2R^3$).

RESULTS AND DISCUSSION

Synthesis of β-functionalized enamines 2 and 8

The preparation of enamines derived from phosphonates without substituents in the position a **2** was accomplished very easily and in very high yields by means of a simple condensation reaction of arylamines with 2-phosphonylacetaldehyde **1** using $MgSO_4$ at room temperature (see Table 1, entries 1-3) or at 0 °C, (see Table 1, entry 4). Compounds **2** were characterized by their spectroscopic data, which indicate that they are isolated as a mixture of *Z*- and *E*-β-enamino compounds **2**, although for our purposes the separation of both enamines is not necessary for subsequent reactions. Thus, the ^{31}P-NMR spectrum for crude compound *E*-**2a** showed two different absorptions at δ_P = 24.2 and 25.7 ppm in an approximate isomer ratio of 40:60, as evidenced by the relative peak areas for each compound, in which the high-field and the low-field chemical shift corresponds to the *Z*-isomer and the *E*-isomer respectively. In the ^{1}H-NMR spectrum of **2a**, the vinylic proton in the α position of the enamine resonates at δ_H = 7.41 ppm as a well resolved double quartet with coupling constants of $^3J_{PH}$ = 15.1, $^3J_{HH}$ = 14.4, and $^3J_{HH}$ = 12.3 Hz, while the β enaminic proton appears at δ_H = 4.66 ppm as a triplet with coupling constants of $^2J_{PH}$= 14.4, and $^3J_{HH}$= 14.4, Hz. Conversely, for **2a** the *Z*-isomer showed clearly different absorptions, namely a double quartet at δ_H = 7.30 ppm with coupling constants of $^3J_{PH}$ = 44.8, $^3J_{HH}$ = 10.5, and $^3J_{HH}$ = 12.8 Hz, while the β enaminic proton appears at δ_H = 4.10 ppm as a triplet with coupling constants of $^2J_{PH}$ = 13.2, and $^3J_{HH}$ = 10.2 Hz. In a similar way, the condensation reaction of aniline and 2-diphenylphosphinoyl-acetaldehyde **7** led to the formation of the enamine derived from phosphine oxide **8**, isolated in this case only as the *E* isomer (see Table 1, entry 5).

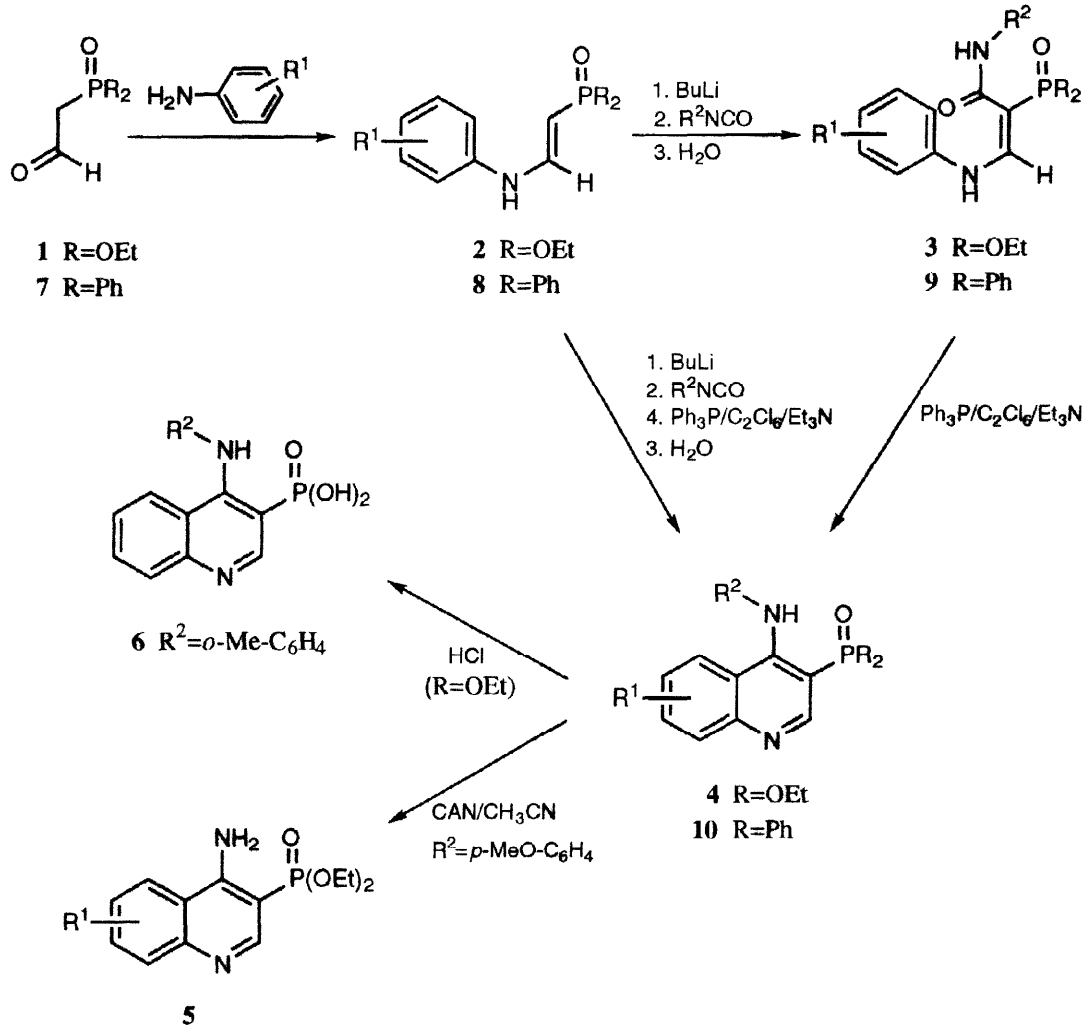
Table 1. Enamines derived from phosphonates **2** and phosphine oxides **8** prepared.

Entry	Compound	R	R^1	Z/E[a]	Yield (%)[d]	m.p. (°C)
1	**2a**	OEt	3-Cl	40/60[b]	93	oil[e]
2	**2b**	OEt	3-CF_3	65/35[b]	94	102-103
3	**2c**	OEt	H	35/65[b]	96	oil[e]
4	**2d**	OEt	3,4-$(MeO)_2$	50/50[c]	95	oil[e]
5	**8**	Ph	H	0/100[b]	92	184-185

[a] Ratio of isomers *Z/E* asigned on the basis of ^{31}P-NMR. [b] Ratio of isomers *Z/E*- asigned on the basis of ^{31}P-NMR, method A. [c] Ratio of isomers *Z-/E*- asigned on the basis of ^{31}P-NMR, method B. [d] Yield of isolated products **2** and **8**. [e] Oil purified by flash chromatography.

Reaction of metallated enamines derived from phosphonate **2** and phosphine oxide **8** with isocyanates.

Enamines **2** (R = OEt), were treated with butyllithium in tetrahydrofuran followed by addition of aryl and alkyl isocyanates (TLC monitoring) and aqueous work-up, giving polyfunctionalized phosphonates **3** in high yield (see Table 2, entries 1-8). Compounds **3** were characterized on the basis of their spectroscopic data, which indicate that they are isolated as the *E*-enamino tautomer **3**. Mass spectrometry of **3a** showed the molecular ion peak (m/z, 438, 48%), and the ^{31}P-NMR spectrum of **3a** showed absorption at δ_P = 23.1 ppm, while in the ^{1}H-NMR spectrum of this derivative **3a**, the vinylic proton gave a triplet at δ_H = 7.75 ppm with coupling contants of $^{3}J_{PH}$ = 12.6 and $^{3}J_{HH}$ = 12.6 Hz. Likewise, the coupling constant $^{3}J_{PH}$ = 12.6 observed for the vinylic proton can be taken as a firm indication for the *E*-configuration[13] around the enaminic moiety of functionalized β-enaminophosphonates **3**. Similarly, the enamine derived from phosphine oxide **8** reacted with phenyl isocyanate and gave *E*-β-functionalized phosphine oxides **9** in very high yield (see Table 2, entries 9 and 10).



1 R=OEt
7 R=Ph

2 R=OEt
8 R=Ph

3 R=OEt
9 R=Ph

6 R^2=*o*-Me-C_6H_4

4 R=OEt
10 R=Ph

5

Scheme 3

Table 2. Functionalized phosphonates **3** and phosphine oxides **9** obtained.

Entry	Compound	R	R^1	R^2	Yield (%)[a]	m.p. (°C)
1	**3a**	OEt	3-Cl	*p*-$MeOC_6H_4$	88	269-270
2	**3b**	OEt	3-Cl	Octadecyl	43	oil[b]
3	**3c**	OEt	H	Ph	89	278-279
4	**3d**	OEt	H	Pr	72	oil[b]
5	**3e**	OEt	H	*o*-MeC_6H_4	93	253-254
6	**3f**	OEt	H	*p*-$MeOC_6H_4$	96	261-262
7	**3g**	OEt	3-CF_3	Ph	91	245-246
8	**3h**	OEt	3,4-$(MeO)_2$	*p*-$MeOC_6H_4$	94	246-247
9	**9a**	Ph	H	Ph	84	265-266
10	**9b**	Ph	H	Pr	76	194-195

[a]Yield of isolated products **3** and **9**. [b]Oil purified by flash chromatography.

Preparation of 4-aminoquinolines **4-6** and **10** from phosphonate **3** and phosphine oxide derivatives **9**.

Treatment of functionalized enamines **3** with dichlorotriphenylphosphorane, generated *"in situ"* from triphenylphosphine and hexachloroethane,[14] in the presence of triethylamine led to the formation of *N*-aryl and *N*-alkyl substituted 4-aminoquinolinylphosphonates **4** (Scheme 3) in excellent yield (see Table 3, entries 1-7). Spectroscopic data were in agreement with the assigned structure. Mass spectrometry of **4a** showed the molecular ion peak (m/z, 420, 52%). The scope of this reaction was not limited to phosphonate derivatives **3**, since the enamine derived from phosphine oxide **9** also reacted with dichlorotriphenylphosphorane in the presence of triethylamine and gave, in excellent yield, the 4-aminoquinoline containing a phosphine oxide group in 3 position **10** (see Table 3, entries 8-9). From a preparative point of view it is noteworthy that the synthesis of phosphorylated 4-aminoquinolines **4** and **10** does not require the isolation and purification of functionalized phosphonate **3** and phosphine oxides **9** , which can be obtained in *"one pot"* reaction from the enamines derived from phosphonate **2** and phosphine oxides **8** when these compounds are directly metallated with butyllithium in THF with subsequent addition of isocyanates, triphenylphosphine with hexachloroethane, triethylamine and aqueous work-up.

These results prompted us to extend this process and to explore whether 4-unsubstituted aminoquinolines derived from phosphonates **5** could also be prepared, in order to enhance the scope and the synthetic use of this reaction. Some 4-aminoquinolines such as *Anquisin* display hypotensive activity,[15a] while *Dequalinium* analogues are potent and selective K^+ channel blockers.[15b] With this aim, the deprotection of *N*-aryl 4-aminoquinolines containing easily removable groups such as *p*-methoxyphenyl[16] (PMP) was performed. The *N*-PMP protecting group of the 4-aminoquinolines **4a**, **e**, **g** was then selectively cleaved by treatment with cerium (IV) amonium nitrate (CAN) in acetonitrile, furnishing the primary 4-aminoquinoline **5** (see Table 3, entries 10-12) in a similar way to that previously reported for the synthesis of allylamines.[17] On the other hand, and taking into account the interest in aminophosphonic acid

derivatives,[6,18,19] the ester cleavage of phosphonates is explored. Phosphorylated 4-aminoquinoline **4d** underwent ester cleavage with 20% HCl [17a] to give heterocycle **6**.

Table 3. 4-Aminoquinolines **4-6**, and **10** obtained.

Entry	Compound	R	R^1	R^2	Yield (%)[a]	m.p. (°C)
1	**4a**	OEt	7-Cl	*p*-$MeOC_6H_4$	68	oil[c]
2	**4b**	OEt	H	Ph	70	275-276
3	**4c**	OEt	H	Pr	58	oil[c]
4	**4d**	OEt	H	*o*-MeC_6H_4	81	oil[c]
5	**4e**	OEt	H	*p*-$MeOC_6H_4$	77 (64)[b]	oil[c]
6	**4f**	OEt	7-CF_3	Ph	53	oil[c]
7	**4g**	OEt	6,7-$(MeO)_2$	*p*-$MeOC_6H_4$	72	oil[c]
8	**10a**	Ph	H	Ph	85 (81)[b]	223-224
9	**10b**	Ph	H	Pr	61	76-77
10	**5a**	OEt	H	H	91	196-197
11	**5b**	OEt	6,7-$(MeO)_2$	H	72	oil[c]
12	**5c**	OEt	7-Cl	H	73	101-102
13	**6**	OH	H	*o*-MeC_6H_4	83	115 (dec)

[a]Yield of isolated products **4-6**, and **10**. [b] Yield of isolated product in "*one pot*" reaction from **2/8**. [c] Oil purified by flash chromatography.

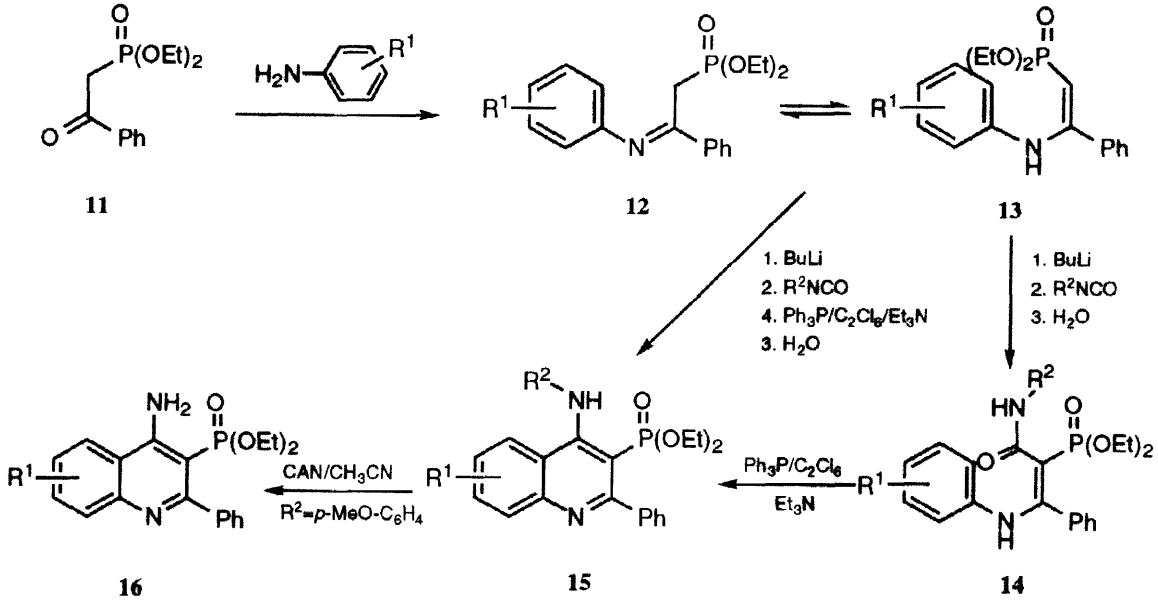
Synthesis of 2-aryl substituted 4-aminoquinolines derived from phosphonates **14**.

This methodology used for the preparation of aminoquinolines **4** and **9** can also be applied to the synthesis of 2-aryl substituted 4-aminoquinolines derived from phosphonates **15** when β-phosphonylacetophenone **11** is used instead of β-phosphonylacetaldehyde **1**. The preparation of the required enamines derived from phosphonates **13** was accomplished very easily and in very high yields by a condensation reaction of arylamines with 2-phosphonylacetophenone **11** in refluxing toluene (see Table 4, entries 1-3). The spectroscopic data indicate that they are isolated as a mixture of the imino- **12** and *Z*-β-enamino compounds **13**, although for our purposes the separation of the imine and the enamines is not necessary for subsequent reactions. Thus, the ^{31}P-NMR spectrum for crude compound **12/13a** showed two different absorptions at δ_P = 21.6 and 23.7 ppm in an approximate isomer ratio of 35:65 as evidenced by the relative peak areas for each compound, in which the high-field and the low-field chemical shift corresponds to the imino-isomer **12a** and the *Z*-enamino compound **13a** respectively. In the ^{1}H-NMR spectrum of **12a**, methylene protons resonate at δ_H = 3.39 ppm as a well resolved doublet with coupling constant of $^2J_{PH}$ = 23.3 Hz. Conversely, in the ^{1}H-NMR spectrum of **13a**, the *Z*-isomer showed clearly different absorptions, namely a doublet at δ_H = 4.37 ppm with a coupling constant of $^2J_{PH}$ = 12.2 Hz for the enaminic proton, while the ^{13}C-NMR spectrum of **13a** showed absorptions at δ_C = 83.3 ppm ($^1J_{PC}$ = 187.3 Hz) for the carbon bonded to phosphorus as well a doublet at δ_C = 137.1 ppm ($^3J_{PC}$ = 19.6 Hz) assignable to the *ipso* aromatic carbon of the *Z*-enamino configuration.[9a,11c, 20]

Table 4. Acyclic and heterocyclic phosphonate derivatives **12-16** obtained

Entry	Compound	R^1	R^2	Imine/Enamine[a]	Yield (%)[c]	m.p. (°C)
1	**12/13a**	H	-	35/65[b]	97	oil[e]
2	**12/13b**	4-Cl	-	40/60[b]	95	oil[e]
3	**12/13c**	3-CF_3	-	40/60[b]	96	oil[e]
4	**14a**	3-CF_3	Ph	0/100	92	227-228
5	**14b**	H	Ph	0/100	95	257-258
6	**14c**	4-Cl	*p*-$MeOC_6H_4$	0/100	93	240-241
7	**14d**	H	Pr	0/100	80	oil[e]
8	**15a**	7-CF_3	Ph	-	63	oil[e]
9	**15b**	H	Ph	-	82 (68)[d]	132-133
10	**15c**	6-Cl	*p*-$MeOC_6H_4$	-	76	126-127
11	**15d**	H	Pr	-	64	116-117
12	**16**	6-Cl	H	-	67	135-136

[a] Ratio of tautomers imine/enamine asigned on the basis of ^{31}P-NMR. [b] Only *Z* enamines were isolated. [c] Yield of isolated products **12-16**. [d] Yield of isolated product in "*one pot*" reaction from **12/13**. [e] Oil purified by flash chromatography.



Scheme 4

Metallation of β-imino and β-enamino phosphonates **12/13** with butyllithium in tetrahydrofuran followed by addition of isothiocyanates (TLC monitoring) and aqueous work-up afforded the functionalized amides **14** (see Table 4, entries 4-7). The structure of adducts **14** is supported by the spectroscopic data. Mass spectrometry of **14a** showed the molecular ion peak (m/z, 450, 14%) and in the ^{13}C-NMR spectrum of compound **14a**, the coupling constant observed in the *ipso* aromatic carbon ($^3J_{PC}$ = 4.0 Hz) can be taken as a firm indication for the inversion of the *Z*-configuration[9a,11c,20] around the enaminic moiety of

functionalized primary β-enaminophosphonates **14** related to the starting enamine **13**. Treatment of amides **14** with triphenylphosphine and hexachloroethane in the presense of triethylamine (Scheme 4) gave 2-aryl-3-phosphonyl-4-aminoquinolines **15** (see Table 4, entries 8-11). From a preparative point of view it is noteworthy that 4-aminoquinolines **15** can be obtained in a *"one pot"* reaction when enamines **12/13** are directly metallated with butyllithium in THF with subsequent addition of isocyanates, triphenylphosphine with hexachloroethane, triethylamine and aqueous work-up. The deprotection of *N*-aryl 4-aminoquinolines containing easily removable groups such as *p*-methoxyphenyl[18] (PMP) was then selectively achieved by treatment with cerium (IV) amonium nitrate (CAN) in acetonitrile, leading to the formation of the primary 4-aminoquinoline **16** (see Table 4, entry 12).

In conclusion, we describe an easy and efficient method for the synthesis of 4-aminoquinolines substituted with a phosphonate **4-6**, **15**, **16** and a phosphine oxide group **10** in the 3-position from readily available starting materials such as aldehydes and ketones derived from phosphonates or phosphine oxides, arylamines, and isocyanates (see Scheme 2), and under mild reaction conditions. 4-Aminoquinolines are useful compounds in medicinal chemistry since these products display a broad range of biological activities and have been widely used as pharmaceuticals.[1-5]

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SPM-20 apparatus and are uncorrected. Analytical TLC was performed on 0.25mm silica gel plates (Merck). Visualization was accomplished by UV light and iodine. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: CH_2Cl_2 (P_2O_5); *n*-hexane and diethyl ether (sodium benzophenone ketyl); ethyl acetate (K_2CO_3). All solvents used in reactions were freshly distilled from appropriate drying agents before use: acetonitrile (P_2O_5); THF (sodium benzophenone ketyl), toluene (sodium). All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was carried out on silica gel (Merck, 70-230 mesh). Mass spectra were obtained on a Hewlett Packard 5890 spectrometer. Infrared spectra were taken on a Nicolet IRFT Magna 550 spectrometer. ^{1}H-NMR spectra were recorded on a Varian 300 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ or DMSO solutions. ^{13}C-NMR spectra were recorded at 75 MHz with chloroform (77.0 ppm) as an internal reference in $CDCl_3$ or DMSO solutions. ^{31}P-NMR spectra were recorded at 120 MHz with 85% phosphoric acid as an external reference. ^{19}F-NMR spectra were recorded at 280 MHz with $CFCl_3$ as an external reference. R_f values are taken using ethyl acetate as an eluting system. Elemental analyses were performed in a Leco CHNS-932 instrument. Chemical shifts are given in ppm (d); multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet), q (quartet) or m (multiplet). Coupling constants, J, are reported in Hertz. Infrared spectra (IR) were obtained as neat liquids, or as solids in KBr. Peaks are reported in cm^{-1}. Mass spectra (EI) were obtained with a ionization voltage of 70 eV. Data are reported in the form

m/z (intensity relative to base = 100). Functionalized phosphonates **1** and **11** and 2-(diphenylphosphinoyl) acetaldehyde **7** were synthesized as described in the literature with minor modification.[21-23]

Preparation of β-functionalized enamines. 2 and 8 Diethyl *E*- and *Z*-2-(*N*-3-chlorophenylamino)ethenylphosphonate (2a)

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 5 mmol of 2-(diethylphosphonyl)acetaldehyde[21] **1**, 5 mmol of arylamine, 1g of $MgSO_4$ and 40 mL of THF. The mixture was stirred at room temperature until TLC indicated the disappearance of the arylamine. The crude product was purified by flash chromatography (50% n-hexane/ethyl acetate) to give the title compound **2a** (1350 mg, 93%) as a yellow oil. Rf: 0.32; *^{1}H-NMR* (300 MHz): 1.21 (m, 6H, CH_3, *E* and *Z*), 3.95 (m, 4H, OCH_2, *E* and *Z*), 4.10 (dd, 1H, $^2J_{PH}$= 13.2 Hz, $^3J_{HH}$= 10.2 Hz, CH, *Z*), 4.66 (t, 1H, $^2J_{PH}$= 14.4 Hz, $^3J_{HH}$= 14.4 Hz, CH, *E*), 6.56-7.07 (m, 4H, arom), 7.31 (dq, 1H, $^3J_{PH}$= 44.8 Hz, $^3J_{HH}$= 10.2 Hz, $^3J_{HH}$= 12.6 Hz, CH, *Z*), 7.43 (dq, 1H, $^3J_{PH}$=15.1 Hz, $^3J_{HH}$= 14.4 Hz, $^3J_{HH}$= 12.3 Hz, CH, *E*), 8.79 (d, 1H, $^3J_{HH}$= 12.3 Hz, NH, *E*), 9.21 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH, *Z*). *^{13}C-NMR* (75 MHz): 16.1 (CH_3 *E* and *Z*), 61.3 (OCH_2 *E* and *Z*), 78.9 (d,$^1J_{PC}$= 186.8 Hz, CH, *Z*), 82.8 (d,$^1J_{PC}$= 209.1 Hz, CH, *E*), 112.7-144.8 (C-arom). *^{31}P-NMR* (120 MHz). 24.3 (*Z*) and 25.7 (*E*); *IR* (*KBr*) 3308, 1235 cm^{-1}; *MS* (EI) 289 (M^+, 61). Anal. Calcd for $C_{12}H_{17}ClNO_3P$: C, 49.82; H, 5.88; N, 4.84. Found: C, 49.66; H, 5.97; N, 4.75.

Diethyl *E*- and *Z*-2-(*N*-3-trifluoromethylphenylamino)ethenylphosphonate (2b). (1520 mg, 94%) as a white solid, mp 102-103; *^{1}H-NMR* (300 MHz): 1.12 (m, 6H, CH_3, *E* and *Z*), 3.97 (m, 4H, OCH_2, *E* and *Z*), 4.16 (dd, 1H, $^2J_{PH}$= 13.2 Hz, $^3J_{HH}$= 10.2 Hz, CH, *Z*), 4.71 (dd, 1H, $^2J_{PH}$= 13.3 Hz, $^3J_{HH}$= 14.4 Hz, CH, *E*), 6.93-7.33 (m, 4H, arom), 7.43 (dq, 1H, $^3J_{PH}$= 44.7 Hz, $^3J_{HH}$= 10.2 Hz, $^3J_{HH}$= 12.6 Hz, CH, *Z*), 7.50 (dq, 1H, $^3J_{PH}$=15.1 Hz, $^3J_{HH}$= 14.4 Hz, $^3J_{HH}$= 12.3 Hz, CH, *E*), 8.47 (d, 1H, $^3J_{HH}$= 12.3 Hz, NH, *E*), 9.38 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH, *Z*). *^{3}C-NMR* (75 MHz): 16.3 (CH_3 *E* and *Z*), 61.4 (OCH_2 *E* and *Z*), 82.7 (d,$^1J_{PC}$= 191.8 Hz, CH, *Z*), 85.4 (d,$^1J_{PC}$= 210.1 Hz, CH, *E*), 114.8-140.8 (C-arom). *^{31}P-NMR* (120 MHz). 24.1 (*Z*) and 25.2 (*E*). *^{19}F-NMR* (280 MHz). - 114 (*E* and *Z*); *IR* (*KBr*) 3341, 1240, 1136 cm^{-1}; *MS* (EI) 323 (M^+, 54). Anal. Calcd for $C_{13}H_{17}F_3NO_3P$: C, 48.29; H, 5.26; N, 4.33. Found: C, 48.34; H, 5.29; N, 4.25.

Diethyl *E*- and *Z*-2-(*N*-phenylamino)ethenylphosphonate (2c). (1220 mg, 96%) as a yellow oil. Rf: 0.35; *^{1}H-NMR* (300 MHz): 1.30 (m, 6H, CH_3, *E* and *Z*), 4.00 (m, 5H, OCH_2, *E* and *Z*, and CH *Z*), 4.69 (dd, 1H, $^2J_{PH}$= 13.8 Hz, $^3J_{HH}$= 14.4 Hz, CH, *E*), 6.67-7.28 (m, 5H, arom), 7.45 (dq, 1H, $^3J_{PH}$= 44.9 Hz, $^3J_{HH}$= 10.2 Hz, $^3J_{HH}$= 12.9 Hz, CH, *Z*), 7.57 (dq, 1H, $^3J_{PH}$=15.5 Hz, $^3J_{HH}$= 14.4 Hz, $^3J_{HH}$= 12.6 Hz, CH, *E*), 8.13 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH, *E*), 9.25 (d, 1H, $^3J_{HH}$= 12.9 Hz, NH, *Z*). *^{13}C-NMR* (75 MHz): 16.2 (CH_3 *E* and *Z*), 61.1 (OCH_2 *E* and *Z*), 79.0 (d,$^1J_{PC}$= 186.6 Hz, CH, *Z*), 82.8 (d,$^1J_{PC}$= 209.0 Hz, CH, *E*), 114.8-140.8 (C-arom), 145.3 (d,$^2J_{PC}$= 17.6 Hz, CH-N, *E*). *^{31}P-NMR* (120 MHz). 25.0 (*Z*) and 26.1 (*E*); *IR* (*KBr*) 3326, 1211 cm^{-1}; *MS* (EI) 255 (M^+, 31). Anal. Calcd for $C_{12}H_{18}NO_3P$: C, 56.47; H, 7.06; N, 5.49. Found: C, 56.30; H, 7.32; N, 5.24.

Diethyl *E*- and *Z*-2-(*N*-3,4-dimethoxyphenylamino)ethenylphosphonate (2d).

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 5 mmol of 2-(diethylphosphonyl)acetaldehyde[21] **1**, 5 mmol of 3,4-dimethoxyaniline, 1g of $MgSO_4$ and 40 mL of THF. The mixture was stirred at 0 °C until TLC indicated the disappearance of the arylamine, to give the title compound **2d** (1500 mg, 95%) as a brown oil. Rf: 0.29; *^{1}H-NMR* (300 MHz): 1.35 (m, 6H, CH_3, *E* and *Z*), 3.83 (s, 3H, OCH_3, *E* and *Z*), 3.86 (s, 3H, OCH_3, *E* and *Z*), 4.09 (m, 5H, OCH_2, *E* and *Z*, and CH *Z*), 4.52 (dd, 1H, $^2J_{PH}$= 12.6 Hz, $^3J_{HH}$= 14.4 Hz, CH, *E*), 6.21-6.77 (m, 5H, arom, CH *E* and NH *E*), 7.37 (dq, 1H, $^3J_{PH}$= 43.0 Hz, $^3J_{HH}$= 10.2 Hz, $^3J_{HH}$= 12.9 Hz, CH, *Z*), 9.11 (d, 1H, $^3J_{HH}$= 12.9 Hz, NH, *Z*). *^{13}C-NMR* (75 MHz): 15.6 (CH_3 *E* and *Z*), 55.0 (OCH_3 *E* and *Z*), 55.5 (OCH_3 *E* and *Z*), 60.6 (OCH_2 *E* and *Z*), 75.3 (d,$^1J_{PC}$= 188.3 Hz, CH, *Z*), 78.9 (d,$^1J_{PC}$= 210.5 Hz, CH, *E*), 100.1-145.9 (C-arom). *^{31}P-NMR* (120 MHz). 25.5 (*Z*) and 27.1 (*E*); *IR* (*KBr*) 3307, 1214 cm^{-1}; *MS* (EI) 315 (M^+, 11). Anal. Calcd for $C_{14}H_{22}NO_5P$: C, 53.33; H, 6.98; N, 4.44. Found: C, 53.94; H, 6.69; N, 4.05.

***E*-2-(*N*-Phenylamino)ethenyl diphenylphosphine oxide (8).**

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 5 mmol of 2-diphenylphosphinoyl)acetaldehyde[23] **7**, 5 mmol of arylamine, 1g of $MgSO_4$ and 40 mL of THF. The mixture was stirred at room temperature until TLC indicated the disappearance of the arylamine. The crude product was purified by flash chromatography (50% n-hexane/ethyl acetate) gave the title compound **2a** (1470 mg, 92%) as a white solid, mp 184-185; *^{1}H-NMR* (300 MHz): 5.19 (dd, 1H, $^2J_{PH}$= 18.3 Hz, $^3J_{HH}$= 14.7 Hz, CH), 6.81-7.80 (m, 15H, arom), 7.25 (m, 1H, $^3J_{PH}$= 14.3 Hz, $^3J_{HH}$= 14.3 Hz, $^3J_{HH}$= 12.3 Hz, CH), 9.21 (d, 1H, $^3J_{HH}$= 12.3 Hz, NH). *^{13}C-NMR* (75 MHz): 87.6 (d,$^1J_{PC}$= 121.4 Hz, CH), 113.8-141.6 (C-arom), 142.7 (d,$^2J_{PC}$= 12.1 Hz, CH-N). *^{31}P-NMR* (120 MHz). 24.2; *IR* (*KBr*) 3272, 1174 cm^{-1}; *MS* (EI) 319 (M^+, 100). Anal. Calcd for $C_{20}H_{18}NOP$: C, 75.23; H, 5.64; N, 4.38. Found: C, 75.31; H, 5.59; N, 4.35.

Reaction of enamino carbanions derived from phosphonates 2 and phosphine oxide 8 with isocyanates

***E*-3-(*N*-3-Chlorophenylamino)-2-(diethylphosphonyl)-*N*-(*p*-methoxyphenyl)prop-2-enamide (3a).**

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 5 mmol of β-enamino phosphonates **2** and 25 mL of THF. The temperature was reduced to 0 °C and a solution (5.5 mmol) of butyllithium in THF was then added. The mixture was allowed to stir for 1 hour. A solution (5 mmol) of isocyanate in 10 mL of THF was added at this temperature. The temperature was allowed to rise to room temperature. The mixture was stirred at room temperature until TLC indicated the disappearance of the enamine (~5 hours). The mixture was washed with water and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization from diethyl ether or by flash chromatography (50% n-hexane/ethyl acetate)gave the title compound **3a** (1930 mg 88%) as a white solid, mp 269-270 °C; *^{1}H-NMR* (300 MHz): 1.32 (m, 6H, CH_3), 3.73 (s, 3H, OCH_3), 4.09 (m, 4H, OCH_2), 6.81-7.42 (m, 8H, arom), 7.75 (t, 1H, $^3J_{PH}$= 12.8 Hz, $^3J_{HH}$= 12.8 Hz, CH), 9.63 (s, 1H, NH), 11.86 (d, 1H, $^3J_{HH}$= 12.8 Hz, NH). *^{13}C-NMR* (75 MHz): 16.3 (CH_3), 55.4 (OCH_3), 62.3 (OCH_2), 88.0 (d,$^1J_{PC}$= 192.4 Hz, C=), 114.0-130.7 (C-arom), 133.5 (C-ipso arom), 140.7 (C-ipso arom), 150.4 (d,$^2J_{PC}$= 15.6 Hz, HC-N), 156.3 (C-ipso arom), 159.8 (C-ipso arom), 166.5 (d,$^2J_{PC}$= 16.1 Hz, C=O). *^{31}P-NMR* (120 MHz). 23.1; *IR* (*KBr*) 3288, 3105, 1690, 1222 cm^{-1}; *MS* (EI) 438 (M^+, 48). Anal. Calcd for $C_{20}H_{24}ClN_2O_5P$: C, 54.79; H, 5.48; N, 6.39. Found: C, 54.72; H, 5.52; N, 6.36.

***E*-3-(*N*-3-Chlorophenylamino)-2-(diethylphosphonyl)-*N*-octadecylprop-2-enamide (3b).** (1250 mg, 43%) as a white oil. Rf: 0.91; *^{1}H-NMR* (300 MHz): 0.86 (m, 3H, CH_3), 1.23 (m, 38H, CH_3 and CH_2), 3.28 (m, 2H, NCH_2), 4.09 (m, 4H, OCH_2), 6.47-7.21 (m, 4H, arom), 7.42 (s, 1H, NH), 7.78 (dd, 1H, $^3J_{PH}$= 14.4 Hz, $^3J_{HH}$= 12.6 Hz, CH), 11.86 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH). *^{13}C-NMR* (75 MHz): 14.0 (CH_3), 16.1 (CH_3), 22.5 (CH_2), 29.6 (CH_2), 31.8 (CH_2), 39.2 (NCH_2), 62.1 (OCH_2), 87.7 (d,$^1J_{PC}$= 193.3 Hz, C=), 113.0-130.6 (C-arom and C-ipso arom), 150.1 (d,$^2J_{PC}$= 16.6 Hz, HC-N), 167.9 (d,$^2J_{PC}$= 15.6 Hz, C=O). *^{31}P-NMR* (120 MHz). 23.3; *IR* (*KBr*) 3343, 3290, 1635, 1252 cm^{-1}; *MS* (EI) 584 (M^+, 22). Anal. Calcd for $C_{31}H_{54}ClN_2O_4P$: C, 63.70; H, 9.25; N, 4.79. Found: C, 63.81; H, 9.47; N, 4.86.

***E*-2-(Diethylphosphonyl)-*N*-phenyl-3-(*N*-phenylamino)prop-2-enamide (3c).** (1660 mg, 89%) as a white solid, mp 278-279 °C; *^{1}H-NMR* (300 MHz): 1.38 (t, 6H, $^3J_{HH}$= 7.2 Hz, CH_3),4.17 (m, 4H, OCH_2), 7.09-7.59 (m, 10H, arom), 7.88 (t, 1H, $^3J_{PH}$= 13.2 Hz, $^3J_{HH}$= 12.9 Hz, CH), 9.90 (s, 1H, NH), 11.90 (d, 1H, $^3J_{HH}$= 12.9 Hz, NH). *^{13}C-NMR* (75 MHz): 16.3 (CH_3), 62.1 (OCH_2), 86.6 (d,$^1J_{PC}$= 192.9 Hz, C=), 116.7-133.5 (C-arom), 138.2 (C-ipso arom), 139.4 (C-ipso arom), 148.6 (C=O), 151.2 (d,$^2J_{PC}$= 15.1 Hz, HC-N). *^{31}P-NMR* (120 MHz). 23.8; *IR* (*KBr*) 3314, 3242, 1696, 1251 cm^{-1}; *MS* (EI) 374 (M^+, 31). Anal. Calcd for $C_{19}H_{23}N_2O_4P$: C, 60.96; H, 6.15; N, 7.49. Found: C, 60.87; H, 6.06; N, 7.58.

***E*-2-(Diethylphosphonyl)-3-(*N*-phenylamino)-*N*-propylprop-2-enamide (3d).** (1220 mg, 72%) as a yellow oil. Rf: 0.69; *^{1}H-NMR* (300 MHz): 1.09 (m, 6H, CH_3), 1.52 (m, 3H, CH_3), 1.81 (m, 2H, CH_2), 3.99 (m, 2H, NCH_2), 4.26 (m, 4H, OCH_2), 7.20-7.48 (m, 5H, arom), 7.72 (s, 1H, NH), 8.00 (t, 1H, $^3J_{PH}$= 12.8 Hz, $^3J_{HH}$= 12.8 Hz, CH), 12.02 (d, 1H, $^3J_{HH}$= 12.8 Hz, NH). *^{13}C-NMR* (75 MHz): 11.0 (CH_3), 16.1 (CH_3),

21.0 (CH_2), 44.3 (NCH_2), 61.8 (OCH_2), 86.4 (d,$^1J_{PC}$= 193.9 Hz, C=), 116.3-129.6 (C-arom), 139.6 (C-ipso arom), 151.2 (d,$^2J_{PC}$= 16.6 Hz, HC-N), 168.3 (d,$^2J_{PC}$= 15.6 Hz, C=O). *^{31}P-NMR* (120 MHz). 24.1; *IR* (*KBr*) 3326, 3168, 1712, 1235 cm^{-1}; *MS* (EI) 340 (M^+, 34). Anal. Calcd for $C_{16}H_{25}N_2O_4P$: C, 56.47; H, 7.35; N, 8.23. Found: C, 56.12; H, 7.44; N, 8.41.

***E*-2-(Diethylphosphonyl)-3-(*N*-phenylamino)-*N*-*o*-tolylprop-2-enamide (3e).** (1800 mg, 93%) as a yellow solid, mp 253-254 °C; *^{1}H-NMR* (300 MHz): 1.31 (m, 6H, CH_3), 2.27 (s, 3H, CH_3), 4.10 (m, 4H, OCH_2), 6.95-7.18 (m, 9H, arom), 7.87 (t, 1H, $^3J_{PH}$= 12.8Hz, $^3J_{HH}$= 12.6 Hz, CH), 9.44 (s, 1H, NH), 11.82 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 18.2 (CH_3), 62.1 (OCH_2), 86.8 (d,$^1J_{PC}$= 193.9 Hz, C=), 116.6-129.7 (C-arom), 131.1 (C-ipso arom), 136.3 (C-ipso arom), 139.5 (C-ipso arom), 151.3 (d,$^2J_{PC}$= 16.1 Hz, HC-N), 167.0 (d,$^2J_{PC}$= 6.6 Hz, C=O). *^{31}P-NMR* (120 MHz). 24.0; *IR* (*KBr*) 3304, 3142, 1665, 1248 cm^{-1}; *MS* (EI) 388 (M^+, 19). Anal. Calcd for $C_{20}H_{25}N_2O_4P$: C, 61.85; H, 6.44; N, 7.22. Found: C, 61.99; H, 6.38; N, 7.14.

***E*-2-(Diethylphosphonyl)-*N*-(p-methoxyphenyl)-3-(*N*-phenylamino)prop-2-enamide (3f).** (1940 mg, 96%) as a yellow solid, mp 261-262 °C; *^{1}H-NMR* (300 MHz): 1.38 (m, 6H, CH_3), 3.80 (s, 3H, OCH_3), 4.17 (m, 4H, OCH_2), 6.86-7.47 (m, 9H, arom), 7.87 (dd, 1H, $^3J_{PH}$= 14.1 Hz, $^3J_{HH}$= 12.6 Hz, CH), 9.71 (s, 1H, NH), 11.90 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 55.5 (OCH_3), 62.2 (OCH_2), 86.7 (d,$^1J_{PC}$= 193.9 Hz, C=), 114.1-129.8 (C-arom), 131.3 (C-ipso arom), 139.6 (C-ipso arom), 151.0 (d,$^2J_{PC}$= 15.6 Hz, HC-N), 156.2 (C-ipso arom), 166.8 (d,$^2J_{PC}$= 16.7 Hz, C=O). *^{31}P-NMR* (120 MHz). 23.9; *IR* (*KBr*) 3298, 3087, 1716, 1247 cm^{-1}; *MS* (EI) 404 (M^+, 53). Anal. Calcd for $C_{20}H_{25}N_2O_5P$: C, 59.40; H, 6.19; N, 6.93. Found: C, 59.35; H, 6.32; N, 7.06.

***E*-2-(Diethylphosphonyl)-*N*-phenyl-3-(*N*-trifluoromethylphenylamino)prop-2-enamide (3g).** (2010 mg, 91%) as a yellow solid, mp 245-246 °C; *^{1}H-NMR* (300 MHz): 1.39 (m, 6H, CH_3), 4.19 (m, 4H, OCH_2), 7.25-7.58 (m, 9H, arom), 7.88 (dd, 1H, $^3J_{PH}$= 14.1 Hz, $^3J_{HH}$= 12.6 Hz, CH), 9.85 (s, 1H, NH), 12.10 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 62.4 (OCH_2), 88.9 (d,$^1J_{PC}$= 192.3 Hz, C=), 113.3-130.4 (C-arom), 133.6 (C-ipso arom), 138.0 (C-ipso arom), 140.1 (C-ipso arom), 150.6 (d,$^2J_{PC}$= 15.6 Hz, HC-N), 166.7 (d,$^2J_{PC}$= 15.5 Hz, C=O). *^{31}P-NMR* (120 MHz): 23.0. *^{19}F-NMR* (280 MHz): - 63.0; *IR* (*KBr*) 3250, 3069, 1705, 1247, 1027 cm^{-1}; *MS* (EI) 442 (M^+, 8). Anal. Calcd for $C_{20}H_{22}F_3N_2O_4P$: C, 54.30; H, 4.98; N, 6.33. Found: C, 54.19; H, 5.20; N, 6.26.

***E*-2-(Diethylphosphonyl)-3-(*N*-3,4-dimetoxyphenylamino)-*N*-(p-methoxyphenyl)prop-2-enamide (3h).** (2180 mg, 94%) as a yellow solid, mp 245-246 °C; *^{1}H-NMR* (300 MHz): 1.33 (m, 6H, CH_3), 3.74 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.12 (m, 4H, OCH_2), 6.57-7.42 (m, 7H, arom), 7.76 (t, 1H, $^3J_{PH}$= 12.9 Hz, $^3J_{HH}$= 12.9 Hz, CH), 9.52 (s, 1H, NH), 11.80 (d, 1H, $^3J_{HH}$= 12.9 Hz, NH). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 55.3 (OCH_3), 55.9 (OCH_3), 56.1 (OCH_3), 62.1 (OCH_2), 85.2 (d,$^1J_{PC}$= 194.9 Hz, C=), 113.9-129.3 (C-arom), 131.1 (C-ipso arom), 133.3 (C-ipso arom), 146.2 (C-ipso arom), 149.8 (C-ipso arom), 151.6 (d,$^2J_{PC}$= 16.1 Hz, HC-N), 156.1 (C-ipso arom), 166.9 (d,$^2J_{PC}$= 16.1 Hz, C=O). *^{31}P-NMR* (120 MHz). 24.3; *IR* (*KBr*) 3389, 3049, 1709, 1214 cm^{-1}; *MS* (EI) 464 (M^+, 34). Anal. Calcd for $C_{22}H_{29}N_2O_7P$: C, 56.90; H, 6.25; N, 6.03. Found: C, 56.99; H, 6.12; N, 6.17.

***E*-2-(Diethylphosphinoyl)-*N*-phenyl-3-(*N*-phenylamino)prop-2-enamide (9a).**

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 5 mmol of β-enamino phosphine oxide **8** and 25 mL of THF. The temperature was reduced to 0 °C and a solution (5.5 mmol) of butyllithium in THF was then added. The mixture was allowed to stir for 1 hour. A solution (5 mmol) of isocyanate in 10 mL of THF was added at this temperature. The temperature was allowed to rise to room temperature. The mixture was stirred at room temperature until TLC indicated the disappearance of the enamine (~5 hours). The mixture was washed with water and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization from diethyl ether or by flash chromatography (50% n-hexane/ethyl acetate) gave the title compound **9a** (1840 mg (84%) as a white solid, mp 265-266 °C; *^{1}H-NMR* (300 MHz): 6.85-7.94 (m, 21H, arom and CH), 10.71 (s,

1H, NH), 11.76 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH). *^{13}C-NMR* (75 MHz): 81.6 (d,$^1J_{PC}$= 111.8 Hz, C=), 114.7-132.3 (C-arom and C-ipso arom), 138.2 (C-ipso arom), 139.6 (C-ipso arom), 149.7 (d,$^2J_{PC}$= 21.1 Hz, HC-N), 167.7 (d,$^2J_{PC}$= 10.1 Hz, C=O). *^{31}P-NMR* (120 MHz). 36.0; *IR (KBr)* 3221, 3150, 1690, 1159 cm^{-1}; *MS* (EI) 438 (M^+, 68). Anal. Calcd for $C_{27}H_{23}N_2O_2P$: C, 73.97; H, 5.25; N, 6.39. Found: C, 73.88; H, 5.34; N, 6.29.

***E*-2-(Diethylphosphinoyl)-*N*-propyl-3-(*N*-phenylamino)prop-2-enamide (9b)**. (1530 mg, 76%) as a white solid, mp 194-195 °C; *^{1}H-NMR* (300 MHz): 0.70 (t, 3H, $^3J_{HH}$= 7.2 Hz, CH_3), 1.37 (m, 2H, CH_2), 3.14 (m, 2H, NCH_2), 6.61-7.69 (m, 15H, arom), 6.84 (dd, 1H, $^3J_{PH}$= 14.4 Hz, $^3J_{HH}$= 12.6 Hz, CH), 8.13 (s, 1H, NH), 11.51 (d, 1H, $^3J_{HH}$= 12.6 Hz, NH). *^{13}C-NMR* (75 MHz): 11.2 (CH_3), 22.6 (CH_2), 40.8 (NCH_2), 91.5 (d,$^1J_{PC}$= 113.8 Hz, C=), 115.8-132.1 (C-arom and C-ipso arom), 139.8 (C-ipso arom), 148.8 (d,$^2J_{PC}$= 21.6 Hz, HC-N), 169.1 (d,$^2J_{PC}$= 10.1 Hz, C=O). *^{31}P-NMR* (120 MHz). 35.3; *IR (KBr)* 3250, 3179, 1644, 1174 cm^{-1}; *MS* (EI) 404 (M^+, 50). Anal. Calcd for $C_{24}H_{25}N_2O_2P$: C, 71.29; H, 6.19; N, 6.93. Found: C, 71.21; H, 6.26; N, 7.02.

Preparation of 4-Aminoquinolines 4/10. Diethyl 7-chloro-4-*p*-methoxyphenylaminoquinoline-3-phosphonate (4a).

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 6 mmol of Ph_3P, 6 mmol of C_2Cl_6 and 30 ml of toluene. A solution of 5 mmol of amide **3** in 20 mL of toluene was added over 10 minutes. The mixture was stirred at room temperature during 15 minutes, and then was added 15 mmol of Et_3N. The mixture was stirred and refluxed until TLC indicated the disappearance of the compounds **3** (~ 20 hours). The mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The CH_2Cl_2 layers were washed with water (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 1/1). Quinolines can also be obtained in a *"one pot"* reaction: A solution of β-enamino phosphonate **3** was treated with butyllithium in THF, at 0 °C, and 1 hour later was added a solution of isocyanate. The mixture was stirred at room temperature (~ 4 hours). The solvent was eliminated under an inert atmosphere of dry N_2, and was added a solution of Ph_3P, C_2Cl_6 and Et_3N in toluene. The mixture was stirred and refluxed (~ 20 hours). Quinolines **4** were purified as described above to give the title compound **4a** (1430 mg, 68%) as a yellow oil. Rf: 0.58; *^{1}H-NMR* (300 MHz): 1.28 (t, 6H, $^3J_{HH}$= 7.1 Hz, CH_3), 3.74 (s, 3H, OCH_3), 4.07 (m, 4H, OCH_2), 6.75-6.89 (m, 4H, arom), 7.03 (d, 1H, $^3J_{HH}$= 9.0 Hz, H_6), 7.47 (d, 1H, $^3J_{HH}$= 9.0 Hz, H_5), 7.87 (s, 1H, H_8), 8.65 (d, 1H, $^3J_{PH}$= 6.9 Hz, H_2), 9.38 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 16.1 (CH_3), 55.4 (OCH_3), 62.6 (OCH_2), 103.5 (d,$^1J_{PC}$= 184.3 Hz, C=), 114.6-128.6 (C-arom), 135.9 (C-ipso arom), 136.9 (C-ipso arom), 151.9 (C-ipso arom), 153.0 (d,$^2J_{PC}$= 9.6 Hz, HC-N), 154.7 (d,$^2J_{PC}$= 8.5 Hz, =C-N), 156.8 (C-ipso arom). *^{31}P-NMR* (120 MHz): 20.3; *IR (KBr)* 3259, 1581, 1236 cm^{-1}; *MS* (EI) 420 (M^+, 52). Anal. Calcd for $C_{20}H_{22}ClN_2O_4P$: C, 57.14; H, 5.23; N, 6.66. Found: C, 57.06; H, 5.16; N, 6.78.

Diethyl 4-phenylaminoquinoline-3-phosphonate (4b). (1310 mg, 70%) as a white solid, mp 275-276 °C; *^{1}H-NMR* (300 MHz): 1.23 (t, 6H, $^3J_{HH}$= 7.2 Hz, CH_3), 4.03 (m, 4H, OCH_2), 6.86-7.94 (m, 9H, arom), 8.75 (d, 1H, $^3J_{PH}$= 6.3 Hz, CH), 9.25 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 16.1 (CH_3), 62.5 (OCH_2), 105.7 (d,$^1J_{PC}$= 183.3 Hz, C=), 120.1-143.4 (C-arom and C-ipso arom), 151.8 (d,$^2J_{PC}$= 9.6 Hz, HC-N), 153.9 (d,$^2J_{PC}$= 7.6 Hz, =C-N). *^{31}P-NMR* (120 MHz): 19.6; *IR (KBr)* 3321, 1563, 1234 cm^{-1}; *MS* (EI) 356 (M^+, 100). Anal. Calcd for $C_{19}H_{21}N_2O_3P$: C, 64.05; H, 5.90; N, 7.86. Found: C, 64.11; H, 6.03; N, 7.77.

Diethyl 4-propylaminoquinoline-3-phosphonate (4c). (930 mg, 58%) as a brown oil. Rf: 0.53; *^{1}H-NMR* (300 MHz): 0.94 (m, 3H, CH_3), 1.32 (m, 6H, CH_3), 1.68 (m, 2H, CH_2), 3.85 (m, 2H, NCH_2), 4.12 (m, 4H, OCH_2), 6.95-8.02 (m, 4H, arom), 8.82 (d, 1H, $^3J_{PH}$= 6.3 Hz, CH), 9.32 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 11.0 (CH_3), 16.2 (CH_3), 21.1 (CH_2), 44.4 (NCH_2), 62.6 (OCH_2), 115.8 (d,$^1J_{PC}$= 181.4 Hz, C=), 120.8-132.7 (C-arom), 143.5 (C-ipso arom), 151.1 (C-ipso arom), 151.9 (d,$^2J_{PC}$= 9.6 Hz, HC-N), 154.0 (d,$^2J_{PC}$= 7.6 Hz, =C-N). *^{31}P-NMR* (120 MHz): 20.0; *IR (KBr)* 3257, 1601, 1222 cm^{-1}; *MS* (EI) 322 (M^+, 32). Anal. Calcd for $C_{16}H_{23}N_2O_3P$: C, 59.63; H, 7.14; N, 8.69. Found: C, 59.44; H, 7.29; N, 8.86.

Diethyl 4-*o*-tolylaminoquinoline-3-phosphonate (4d). (1500 mg, 81%) as a yellow oil. Rf: 0.61; *^{1}H-NMR* (300 MHz): 1.33 (m, 6H, CH_3), 2.42 (s, 3H, CH_3), 4.16 (m, 4H, OCH_2), 6.71-8.00 (m, 8H, arom), 8.82 (d, 1H, $^3J_{PH}$= 6.6 Hz, CH), 9.22 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 16.1 (CH_3), 18.0 (CH_3), 62.4 (OCH_2), 106.1 (d,$^1J_{PC}$= 183.7 Hz, C=), 121.1-132.0 (C-arom), 141.7 (C-ipso arom), 151.0 (C-ipso arom), 151.8 (d,$^2J_{PC}$= 9.6 Hz, HC-N), 154.5 (d,$^2J_{PC}$= 8.1 Hz, =C-N). *^{31}P-NMR* (120 MHz): 20.3; *IR (KBr)* 3378, 1567, 1226 cm^{-1}; *MS* (EI) 370 (M^+, 52). Anal. Calcd for $C_{20}H_{23}N_2O_3P$: C, 64.86; H, 6.22; N, 7.57. Found: C, 64.81; H, 6.13; N, 7.69.

Diethyl 4-*p*-methoxyphenylaminoquinoline-3-phosphonate (4e). (1490 mg, 77%) as a yellow oil. Rf: 0.52; *^{1}H-NMR* (300 MHz): 1.34 (m, 6H, CH_3), 3.79 (s, 3H, OCH_3), 4.13 (m, 4H, OCH_2), 6.81-7.98 (m, 8H, arom), 8.76 (d, 1H, $^3J_{PH}$= 6.6 Hz, CH), 9.37 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 16.0 (CH_3), 55.4 (OCH_3), 62.4 (OCH_2), 103.7 (d,$^1J_{PC}$= 183.8 Hz, C=), 114.5-132.1 (C-arom), 136.4 (C-ipso arom), 151.1 (C-ipso arom), 151.8 (d,$^2J_{PC}$= 9.6 Hz, HC-N), 154.7 (d,$^2J_{PC}$= 8.1 Hz, =C-N). *^{31}P-NMR* (120 MHz): 20.7; *IR (KBr)* 3383, 1569, 1243 cm^{-1}; *MS* (EI) 386 (M^+, 100). Anal. Calcd for $C_{20}H_{23}N_2O_4P$: C, 62.17; H, 5.96; N, 7.25. Found: C, 62.11; H, 6.02; N, 7.33.

Diethyl 7-trifluoromethyl-4-phenylaminoquinoline-3-phosphonate (4f). (1120 mg, 53%) as a yellow oil. Rf: 0.43; *^{1}H-NMR* (300 MHz): 1.35 (m, 6H, CH_3), 4.37 (m, 4H, OCH_2), 6.63 (s, 1H, NH), 7.23-8.05 (m, 9H, arom). *^{13}C-NMR* (75 MHz): 16.5 (CH_3), 62.8 (OCH_2), 100.9 (d,$^1J_{PC}$= 182.4 Hz, C=), 119.0-132.1 (C-arom), 138.1 (C-ipso arom), 143.1 (C-ipso arom), 147.3 (d,$^2J_{PC}$= 9.6 Hz, HC-N), 149.1 (d,$^2J_{PC}$= 7.4 Hz, =C-N). *^{31}P-NMR* (120 MHz): 16.3. *^{19}F-NMR* (280 MHz): - 63.1; *IR (KBr)* 3164, 1592, 1250, 1057 cm^{-1}; *MS* (EI) 424 (M^+, 37). Anal. Calcd for $C_{20}H_{20}F_3N_2O_3P$: C, 56.61; H, 4.72; N, 6.60. Found: C, 56.76; H, 4.59; N, 6.87.

Diethyl 6,7-dimethoxy-4-*p*-methoxyphenylaminoquinoline-3-phosphonate (4g). (1600 mg, 72%) as a yellow oil. Rf: 0.47; *^{1}H-NMR* (300 MHz): 1.30 (m, 6H, CH_3), 3.38 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.07 (m, 4H, OCH_2), 6.79-7.66 (m, 6H, arom), 8.57 (d, 1H, $^3J_{PH}$= 7.5 Hz, CH), 9.23 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 55.2 (OCH_3), 55.5 (OCH_3), 56.1 (OCH_3), 62.6 (OCH_2), 101.7 (d,$^1J_{PC}$= 185.9 Hz, C=), 104.9-132.1 (C-arom), 136.1 (C-ipso arom), 147.7 (C-ipso arom), 149.6 (d,$^2J_{PC}$= 10.1 Hz, HC-N), 153.2 (d,$^2J_{PC}$= 7.5 Hz, =C-N), 156.5 (C-ipso arom), 174.5 (C-ipso arom). *^{31}P-NMR* (120 MHz): 20.9; *IR (KBr)* 3101, 1592, 1250 cm^{-1}; *MS* (EI) 446 (M^+, 61). Anal. Calcd for $C_{22}H_{27}N_2O_6P$: C, 59.19; H, 6.05; N, 6.28. Found: C, 59.35; H, 5.97; N, 6.33.

4-Phenylaminoquinoline-3-Diphenylphosphine oxide (10a).

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 6 mmol of Ph_3P, 6 mmol of C_2Cl_6 and 30 ml of toluene. A solution of 5 mmol of amide **9** in 20 mL of toluene was added over 10 minutes. The mixture was stirred at room temperature during 15 minutes, and then was added 15 mmol of Et_3N. The mixture was stirred and refluxed until TLC indicated the disappearance of the compounds **9** (~ 20 hours). The mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The CH_2Cl_2 layers were washed with water (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 1/1). Quinolines can also be obtained in a *"one pot"* reaction: A solution of β-enamino phosphine oxide **9** was treated with butyllithium in THF, at 0 °C, and 1 hour later was added a solution of isocyanate. The mixture was stirred at room temperature (~ 4 hours). The solvent was eliminated under an inert atmosphere of dry N_2, and was added a solution of Ph_3P, C_2Cl_6 and Et_3N in toluene. The mixture was stirred and refluxed (~ 20 hours). Quinolines **10** were purified as described above to give the title compound **10a** (1790 mg, 85%) as a white solid, mp 223-224 °C; *^{1}H-NMR* (300 MHz): 6.84-7.98 (m, 19H, arom), 8.25 (d, 1H, $^3J_{PH}$= 6.9 Hz, CH), 9.78 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 109.4 (d,$^1J_{PC}$= 102.7 Hz, C=), 120.6-132.4 (C-arom), 143.1 (C-ipso arom), 150.9 (C-ipso arom), 151.7 (d,$^2J_{PC}$= 14.1 Hz, HC-N), 155.3 (=C-N). *^{31}P-NMR* (120 MHz): 34.5; *IR (KBr)* 3201, 1562, 1162 cm^{-1}; *MS* (EI) 420 (M^+, 24). Anal. Calcd for $C_{27}H_{21}N_2OP$: C, 77.14; H, 5.00; N, 6.66. Found: C, 77.02; H, 5.11; N, 6.60.

4-Propylaminoquinoline-3-Diphenylphosphine oxide (10b). (1180 mg, 61%) as a white solid, mp 78-79°C; *^{1}H-NMR* (300 MHz): 0.78 (m, 3H, CH_3), 1.75 (m, 2H, CH_2), 3.61 (m, 2H, NCH_2), 6.44-8.19 (m, 16H, arom and NH). *^{13}C-NMR* (75 MHz): 11.8 (CH_3), 22.9 (CH_2), 52.1 (NCH_2), 108.7 (d,$^1J_{PC}$= 99.2 Hz, C=), 122.8-154.9 (C-arom, C-ipso arom, HC-N and =C-N). *^{31}P-NMR* (120 MHz): 28.8; *IR (KBr)* 3200, 1568, 1122 cm^{-1}; *MS* (EI) 386 (M^+, 33). Anal. Calcd for $C_{24}H_{23}N_2OP$: C, 74.61; H, 5.96; N, 7.25. Found: C, 74.73; H, 5.88; N, 7.32.

Preparation of Primary 4-Aminoquinolines 5. Diethyl 4-aminoquinoline-3-phosphonate (5a).
A dry flask, 100-mL, 2-necked, fitted with a dropping funnel and magnetic stirrer, was charged with 5 mmol of 4-aminoquinoline **4a**, **4e** or **4g** (*N-p*-methoxyphenyl substituted) and 40 mL of acetonitrile. The temperature was allowed to descend to 0 °C and a solution of 15 mmol of ceric ammonium nitrate (CAN) in 75 mL of water was then added. The mixture was stirred at this temperature during 30 minutes and diluted with 300 mL of water. The mixture was extracted with ethyl acetate (3 x 200mL). The organic extracts were washed with 20% sodium sulfite (aqueous solution, 3 x 100 mL), potassium bicarbonate (aqueous saturated solution, 2 x 100mL), NaCl (aqueous saturated solution) and water. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization from diethyl ether or by flash chromatography (50% n-hexane/ethyl acetate) to give the title compound **5a** (1270 mg, 91%) as a yellow solid, mp 196-197 °C; *^{1}H-NMR* (300 MHz): 1.34 (t, 6H, $^3J_{HH}$= 7.1 Hz, CH_3), 4.19 (m, 4H, OCH_2), 6.82-7.97 (m, 4H, arom), 8.72 (d, 1H, $^3J_{PH}$= 6.9 Hz, CH), 9.37 (s, 2H, NH_2). *^{13}C-NMR* (75 MHz): 16.1 (CH_3), 62.7 (OCH_2), 102.6 (d,$^1J_{PC}$= 185.2 Hz, C=), 116.4-132.1 (C-arom), 150.6 (C-ipso arom), 151.5 (d,$^2J_{PC}$= 10.1 Hz, HC-N), 154.9 (C-ipso arom), 155.4 (d,$^2J_{PC}$= 8.1 Hz, =C-N). *^{31}P-NMR* (120 MHz): 20.8; *IR (KBr)* 3246, 3165, 1548, 1230 cm^{-1}; *MS* (EI) 280 (M^+, 21). Anal. Calcd for $C_{13}H_{17}N_2O_3P$: C, 55.71; H, 6.07; N, 10.00. Found: C, 56.06; H, 5.62; N, 9.54.

Diethyl 4-amino-6,7-dimethoxyquinoline-3-phosphonate (5b). (1220 mg, 72%) as a yellow oil. R_f: 0.34; *^{1}H-NMR* (300 MHz): 1.31 (t, 6H, $^3J_{HH}$= 7.0 Hz, CH_3), 3.36 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.17 (m, 4H, OCH_2), 7.41-7.67 (m, 2H, arom), 8.54 (d, 1H, $^3J_{PH}$= 7.5 Hz, CH), 9.23 (s, 2H, NH_2). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 55.3 (OCH_3), 56.1 (OCH_3), 62.5 (OCH_2), 106.7 (d,$^1J_{PC}$= 183.7 Hz, C=), 116.3-155.7 (C-arom, C-ipso arom, HC-N and =C-N). *^{31}P-NMR* (120 MHz): 21.2; *IR (KBr)* 3238, 3146, 1572, 1223 cm^{-1}; *MS* (EI) 340 (M^+, 7). Anal. Calcd for $C_{15}H_{21}N_2O_5P$: C, 52.94; H, 6.17; N, 8.23. Found: C, 53.11; H, 6.06; N, 8.17.

Diethyl 4-amino-7-chloroquinoline-3-phosphonate (5c). (1150 mg, 73%) as a brown solid, mp 101-102 °C; *^{1}H-NMR* (300 MHz): 1.25 (t, 6H, $^3J_{HH}$= 7.2 Hz, CH_3), 4.08 (m, 4H, OCH_2), 6.56 (s, 2H, NH_2), 7.62 (d, 1H, $^3J_{HH}$= 8.2 Hz, H_6), 7.66 (s, 1H, H_8), 8.01 (d, 1H, $^3J_{HH}$= 8.2 Hz, H_5), 9.12 (d, 1H, $^3J_{PH}$= 5.7 Hz, H_2). *^{13}C-NMR* (75 MHz): 16.2 (CH_3), 62.7 (OCH_2), 108.6 (d,$^1J_{PC}$= 181.7 Hz, C=), 129.5-133.9 (C-arom and C-ipso arom), 152.5 (d,$^2J_{PC}$= 10.5 Hz, HC-N), 153.3 (d,$^2J_{PC}$= 10.7 Hz, =C-N), 158.9 (C-ipso arom). *^{31}P-NMR* (120 MHz): 14.2; *IR (KBr)* 3249, 3134, 1533, 1211 cm^{-1}; *MS* (EI) 314 (M^+, 3). Anal. Calcd for $C_{13}H_{16}ClN_2O_3P$: C, 49.68; H, 5.09; N, 8.92. Found: C, 49.83; H, 5.14; N, 8.85.

Synthesis of 4-*o*-tolylaminoquinoline-3-phosphonic acid 6
A 20% aqueous solution of HCl (20 mL) was added to **4d** (1850 mg, 5 mmol). The mixture was stirred and refluxed until TLC indicated the disappearance of the compound **4d** (4 hours). The mixture was concentrated and the crude product was triturated with diethyl ether to afford 1300 mg (83%) of **6** as a yellow solid, mp 115 °C (dec); *^{1}H-NMR* (300 MHz): 1.96 (s, 3H, CH_3), 6.02-8.04 (m, 8H, arom), 7.85 (d, 1H, $^3J_{PH}$= 6.6 Hz, CH). *^{13}C-NMR* (75 MHz): 35.5 (CH_3), 80.6 (d,$^1J_{PC}$= 193.3 Hz, C=), 118.5-174.9 (C-arom, C-ipso arom, HC-N and =C-N). *^{31}P-NMR* (120 MHz): 6.9; *IR (KBr)* 3190, 1544, 1220 cm^{-1}; *MS* (EI) 314 (M^+, 4). Anal. Calcd for $C_{16}H_{15}N_2O_3P$: C, 61.15; H, 4.78; N, 8.92. Found: C, 60.93; H, 4.53; N, 9.19.

Preparation of β-imino and β-enamino phosphonates 12/13. Diethyl 2-phenyl-2-(*N*-phenylimino)ethylphosphonate (12a) and Diethyl *Z*-2-phenyl-2-(*N*-phenylamino)ethenylphosphonate (13a).

A dry flask, 100-mL, 2-necked, fitted with a dropping funnel, a Dean-Stark trap and magnetic stirrer, was charged with 5 mmol of 2-(diethylphosphonyl)acetophenone[22] **11**, 5 mmol of arylamine and 40 mL of toluene. The mixture was refluxed until the formation of 5 mmol of water (~ 15 hours). The crude product was purified by flash chromatography (50% n-hexane/ethyl acetate) to give the title compound **12/13a** (1600 mg, 97%) as a yellow oil. Rf: 0.62; *^{1}H-NMR* (300 MHz) **12a**: 1.11 (m, 6H, CH_3), 3.39 (d, 2H, $^2J_{PH}$= 23.3 Hz), 3.82 (m, 4H, OCH_2), 6.56-7.41 (m, 10H, arom). **13a**: 1.34 (m, 6H, CH_3), 4.12 (m, 4H, OCH_2), 4.37 (d, 1H, $^2J_{PH}$= 12.2 Hz), 6.56-7.41 (m, 10H, arom), 9.28 (s, 1H, NH).*^{13}C-NMR* (75 MHz) **12a**: 16.0 (CH_3), 29.8 (d,$^1J_{PC}$= 133.9 Hz, CH_2), 61.9 (OCH_2), 119.2-141.2 (C-arom). **13a**: 16.2 (CH_3), 61.3 (OCH_2), 84.2 (d,$^1J_{PC}$= 187.3 Hz, CH), 119.2-141.2 (C-arom), 137.1 (d,$^3J_{PC}$= 19.6 Hz, C-ipso arom). *^{31}P-NMR* (120 MHz) **12a**: 21.6 and **13a**: 23.7; *IR* (*KBr*) 3350, 1250 cm^{-1}; *MS* (EI) 331 (M^+, 32). Anal. Calcd for $C_{18}H_{22}NO_3P$: C, 65.26; H, 6.64; N, 4.23. Found: C, 64.87; H, 6.92; N, 4.28.

Diethyl 2-(*N*-4-Chlorophenylimino)-2-phenylethylphosphonate (12b) and Diethyl *Z*-2-(*N*-4-chlorophenylamino)-2-phenylethenylphosphonate (13b). (1730 mg, 95%) of **12/13b** as a yellow oil. Rf: 0.56; *^{1}H-NMR* (300 MHz) **12b**: 1.18 (m, 6H, CH_3), 3.42 (d, 2H, $^2J_{PH}$= 23.4 Hz), 3.88 (m, 4H, OCH_2), 6.56-7.53 (m, 9H, arom). **13b**: 1.40 (m, 6H, CH_3), 4.17 (m, 4H, OCH_2), 4.49 (d, 1H, $^2J_{PH}$= 12.0 Hz), 6.56-7.53 (m, 9H, arom), 9.39 (s, 1H, NH).*^{13}C-NMR* (75 MHz) **12b**: 15.9 (CH_3), 29.5 (d,$^1J_{PC}$= 133.9 Hz, CH_2), 62.0 (OCH_2), 115.9-139.8 (C-arom). **13b**: 16.1 (CH_3), 61.3 (OCH_2), 84.6 (d,$^1J_{PC}$= 187.7 Hz, CH), 115.9-139.8 (C-arom), 136.6 (d,$^3J_{PC}$= 19.7 Hz, C-ipso arom). *^{31}P-NMR* (120 MHz) **12b**: 21.3 and **13b**: 23.3; *IR* (*KBr*) 3349, 1250 cm^{-1}; *MS* (EI) 365 (M^+, 43). Anal. Calcd for $C_{18}H_{21}ClNO_3P$: C, 59.17; H, 5.75; N, 3.83. Found: C, 59.47; H, 5.89; N, 3.38.

Diethyl 2-phenyl-2-(*N*-3-trifluoromethylphenylimino)ethylphosphonate (12c) and Diethyl *Z*-2-phenyl-2-(*N*-3-trifluoromethylphenylamino)ethenylphosphonate (13c). (1910 mg, 96%) of **12/13c** as a yellow oil. Rf: 0.67; *^{1}H-NMR* (300 MHz) **12c**: 1.12 (m, 6H, CH_3), 3.35 (d, 2H, $^2J_{PH}$= 23.4 Hz), 3.93 (m, 4H, OCH_2), 6.82-7.46 (m, 9H, arom). **13c**: 1.35 (m, 6H, CH_3), 4.12 (m, 4H, OCH_2), 4.50 (d, 1H, $^2J_{PH}$= 11.7 Hz), 6.82-7.46 (m, 9H, arom), 9.51 (s, 1H, NH).*^{13}C-NMR* (75 MHz) **12c**: 15.8 (CH_3), 29.5 (d,$^1J_{PC}$= 133.9 Hz, CH_2), 62.1 (OCH_2), 110.9-141.7 (C-arom). **13c**: 16.1 (CH_3), 61.5 (OCH_2), 86.2 (d,$^1J_{PC}$= 186.3 Hz, CH), 110.9-141.7 (C-arom), 136.3 (d,$^3J_{PC}$= 19.1 Hz, C-ipso arom). *^{31}P-NMR* (120 MHz) **12c**: 21.0 and **13c**: 22.8. *^{19}F-NMR* (280 MHz) **12/13c**: - 107; *IR* (*KBr*) 3338, 1241, 1178 cm^{-1}; *MS* (EI) 399 (M^+, 28). Anal. Calcd for $C_{19}H_{21}F_3NO_3P$: C, 57.14; H, 5.26; N, 3.51. Found: C, 57.47; H, 4.89; N, 3.39.

Reaction of enamino carbanions derived from phosphonates 12/13 with isocyanates. *E*-2-(Diethylphosphinoyl)-3, *N*-diphenyl-3-(*N*-3-trifluoromethylphenylamino)prop-2-enamide (14a).

Functionalized amides **14** have been obtained as described above for preparation of compounds **3** and **9**, using β-enamino/imino phosphonates **12/13** as starting materials to give the title compound **14a** (2380 mg, 92%) as a yellow solid, mp 227-228 °C; *^{1}H-NMR* (300 MHz): 1.11 (m, 3H, CH_3), 1.28 (m, 3H, CH_3), 3.83 (m, 2H, OCH_2), 4.12 (m, 2H, OCH_2), 6.77-7.61 (m, 14H, arom), 11.47 (s, 1H, NH), 14.15 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 14.5 (CH_3), 15.7 (CH_3), 61.4 (OCH_2), 61.6 (OCH_2), 86.3 (d,$^1J_{PC}$= 197.4 Hz, C=), 118.6-129.7 (C-arom and C-ipso arom), 133.4 (d, $^3J_{PC}$= 4.1 Hz, C-ipso arom), 138.6 (C-ipso arom), 139.4 (C-ipso arom), 168.4 (d, $^2J_{PC}$= 16.1 Hz, CN), 169.2 (d,$^2J_{PC}$= 18.6 Hz, C=O). *^{31}P-NMR* (120 MHz): 24.2. *^{19}F-NMR* (280 MHz): - 62.2; *IR* (*KBr*) 3334, 3104, 1711, 1231, 1084 cm^{-1}; *MS* (EI) 518 (M^+, 11). Anal. Calcd for $C_{26}H_{26}F_3N_2O_4P$: C, 60.23; H, 5.02; N, 5.41. Found: C, 60.31; H, 5.11; N, 5.33.

***E*-2-(Diethylphosphinoyl)-3, *N*-diphenyl-3-(*N*-phenylamino)prop-2-enamide (14b).** (2140 mg, 95%) as a white solid, mp 256-257 °C; *^{1}H-NMR* (300 MHz): 1.12 (m, 6H, CH_3), 3.82 (m, 4H, OCH_2), 6.65-7.62 (m, 15H, arom), 11.50 (s, 1H, NH), 13.98 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 15.8 (CH_3), 61.3 (OCH_2), 84.6 (d,$^1J_{PC}$= 198.4 Hz, C=), 120.7-129.5 (C-arom), 133.8 (d, $^3J_{PC}$= 4.0 Hz, C-ipso arom), 138.6 (C-ipso arom), 138.8 (C-ipso arom), 168.9 (d,$^2J_{PC}$= 16.1 Hz, CN), 169.5 (d,$^2J_{PC}$= 18.6 Hz, C=O). *^{31}P-NMR* (120 MHz):

25.1; *IR* (*KBr*) 3103, 3032, 1640, 1264 cm^{-1}; *MS* (EI) 450 (M^+, 14). Anal. Calcd for $C_{25}H_{27}N_2O_4P$: C, 66.66; H, 6.00; N, 6.22. Found: C, 66.59; H, 6.08; N, 6.35.

***E*-3-(*N*-*p*-Chlorophenylamino)-2-(Diethylphosphinoyl)-*N*-(*p*-methoxyphenyl)-3-phenylprop-2-enamide (14c).** (2390 mg, 93%) as a yellow solid, mp 240-241 °C; *^{1}H-NMR* (300 MHz): 1.11 (m, 6H, CH_3), 3.80 (m, 7H, OCH_2 and OCH_3), 6.85-7.50 (m, 13H, arom), 11.33 (s, 1H, NH), 14.00 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 15.9 (CH_3), 55.4 (OCH_3), 61.4 (OCH_2), 85.3 (d,$^1J_{PC}$= 198.4 Hz, C=), 113.9-129.4 (C-arom), 133.6 (C-ipso arom), 137.4 (C-ipso arom), 149.1 (C-ipso arom), 156.0 (C-ipso arom), 159.8 (C-ipso arom), 168.3 (d,$^2J_{PC}$= 16.1 Hz, CN), 169.2 (d,$^2J_{PC}$= 18.6 Hz, C=O). *^{31}P-NMR* (120 MHz): 24.6; *IR* (*KBr*) 3177, 3055, 1640, 1237 cm^{-1}; *MS* (EI) 515 (M^+, 7). Anal. Calcd for $C_{26}H_{29}ClN_2O_5P$: C, 60.58; H, 5.63; N, 5.44. Found: C, 60.44; H, 5.72; N, 5.30.

***E*-2-(Diethylphosphinoyl)-3-phenyl-3-(*N*-phenylamino)-*N*-propylprop-2-enamide (14d).** (1660 mg, 80%) as a yellow oil. Rf: 0.89; *^{1}H-NMR* (300 MHz): 0.88 (m, 3H, CH_3), 1.04 (m, 6H, CH_3), 1.57 (m, 2H, CH_2), 3.24 (m, 2H, NCH_2), 3.73 (m, 4H, OCH_2), 6.55-7.29 (m, 10H, arom), 9.19 (s, 1H, NH), 13.96 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 11.4 (CH_3), 15.6 (CH_3), 22.4 (CH_2), 41.0 (NCH_2), 60.8 (OCH_2), 84.2 (d,$^1J_{PC}$= 199.9 Hz, C=), 114.7-130.5 (C-arom), 133.8 (d, $^3J_{PC}$= 4.0 Hz, C-ipso arom), 138.7 (C-ipso arom), 167.4 (d,$^2J_{PC}$= 16.6 Hz, CN), 170.6 (d,$^2J_{PC}$= 19.1 Hz, C=O). *^{31}P-NMR* (120 MHz). 25.1; *IR* (*KBr*) 3378, 3102, 1691, 1264 cm^{-1}; *MS* (EI) 416 (M^+, 16). Anal. Calcd for $C_{22}H_{29}N_2O_4P$: C, 63.46; H, 6.97; N, 6.73. Found: C, 63.21; H, 6.74; N, 6.98.

Preparation of 4-Aminoquinolines 15. Diethyl 2-phenyl-4-phenylamino-7-trifluoromethylquinoline-3-phosphonate (15a)

Quinolines **15** have been obtained as described above for preparation of compounds **4** and **10**, using amides **14** as starting materials to give the title compound **15a** (1580 mg, 63%) as a yellow oil. Rf: 0.90; *^{1}H-NMR* (300 MHz): 1.11 (t, 6H, $^3J_{HH}$= 7.2 Hz, CH_3), 3.90 (m, 4H, OCH_2), 6.98-8.37 (m, 13H, arom), 10.60 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 15.8 (CH_3), 62.4 (OCH_2), 106.4 (d,$^1J_{PC}$= 181.8 Hz, C=), 120.8-129.4 (C-arom), 142.0 (C-ipso arom), 143.7 (C-ipso arom), 148.8 (C-ipso arom), 156.1 (d,$^2J_{PC}$= 9.0 Hz, *C(4)*), 163.3 (d,$^2J_{PC}$= 9.1 Hz, *C(2)*). *^{31}P-NMR* (120 MHz): 19.5. *^{19}F-NMR* (280 MHz): - 63.6; *IR* (*KBr*) 3238, 1563, 1205, 1088 cm^{-1}; *MS* (EI) 500 (M^+, 100). Anal. Calcd for $C_{26}H_{24}F_3N_2O_3P$: C, 62.40; H, 4.80; N, 5.60. Found: C, 62.19; H, 4.71; N, 5.88.

Diethyl 2-phenyl-4-phenylaminoquinoline-3-phosphonate (15b). (1770 mg, 82%) as a white solid, mp 131-132 °C; *^{1}H-NMR* (300 MHz): 1.10 (t, 6H, $^3J_{HH}$= 7.2 Hz, CH_3), 3.86 (m, 4H, OCH_2), 6.95-8.04 (m, 14H, arom), 10.39 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 15.7 (CH_3), 62.0 (OCH_2), 105.2 (d,$^1J_{PC}$= 182.8 Hz, C=), 120.2-131.4 (C-arom), 142.3 (C-ipso arom), 144.2 (C-ipso arom), 149.3 (C-ipso arom), 156.0 (d,$^2J_{PC}$= 8.6 Hz, *C(4)*), 161.8 (d,$^2J_{PC}$= 9.6 Hz, *C(2)*). *^{31}P-NMR* (120 MHz): 20.2; *IR* (*KBr*) 3223, 1550, 1213 cm^{-1}; *MS* (EI) 432 (M^+, 87). Anal. Calcd for $C_{25}H_{25}N_2O_3P$: C, 69.44; H, 5.79; N, 6.48. Found: C, 69.39; H, 5.85; N, 6.47.

Diethyl 6-chloro-2-phenyl-4-*p*-methoxyphenylaminoquinoline-3-phosphonate (15c). (1880 mg, 76%) as a yellow solid, mp 126-127 °C; *^{1}H-NMR* (300 MHz): 1.08 (t, 6H, $^3J_{HH}$= 7.0 Hz, CH_3), 3.74 (s, 3H, OCH_3), 3.85 (m, 4H, OCH_2), 6.78-7.88 (m, 12H, arom), 10.41 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 15.8 (CH_3), 55.4 (OCH_3), 62.0 (OCH_2), 103.8 (d,$^1J_{PC}$= 182.8 Hz, C=), 114.6-131.9 (C-arom), 136.7 (C-ipso arom), 142.2 (C-ipso arom), 147.9 (C-ipso arom), 155.9 (d,$^2J_{PC}$= 9.6 Hz, *C(4)*), 156.3 (C-ipso arom), 162.1 (d,$^2J_{PC}$= 9.6 Hz, *C(2)*). *^{31}P-NMR* (120 MHz): 20.4; *IR* (*KBr*) 3233, 1510, 1240 cm^{-1}; *MS* (EI) 496 (M^+, 84). Anal. Calcd for $C_{26}H_{26}ClN_2O_4P$: C, 62.91; H, 5.24; N, 5.64. Found: C, 62.84; H, 5.29; N, 5.71.

Diethyl 2-phenyl-4-propylaminoquinoline-3-phosphonate (15d). (1270 mg, 64%) as a white solid, mp 116-117 °C; *^{1}H-NMR* (300 MHz): 0.99 (m, 3H, CH_3), 1.07 (m, 6H, CH_3), 1.71 (m, 2H, CH_2), 3.65 (m, 2H, NCH_2), 3.79 (m, 4H, OCH_2), 7.20-7.36 (m, 6H, arom), 7.59 (t, 1H, $^3J_{HH}$= 8.4 Hz, $^3J_{HH}$= 8.4 Hz, H7), 7.88 (d, 1H, $^3J_{HH}$= 8.1 Hz, H5), 8.10 (d, 1H, $^3J_{HH}$= 8.4 Hz, H8), 8.94 (s, 1H, NH). *^{13}C-NMR* (75 MHz): 11.5

(CH_3), 15.8 (CH_3), 24.5 (CH_2), 52.3 (NCH_2), 61.5 (OCH_2), 98.6 (d,$^1J_{PC}$= 185.4 Hz, C=), 123.7-131.1 (C-arom), 142.7 (C-ipso arom), 149.8 (C-ipso arom), 161.5 (d,$^2J_{PC}$= 10.6 Hz, C(4)), 162.0 (d,$^2J_{PC}$= 10.0 Hz, C(2)). *^{31}P-NMR* (120 MHz): 22.1; *IR (KBr)* 3298, 1568, 1217 cm^{-1}; *MS* (EI) 398 (M^+, 94). Anal. Calcd for $C_{22}H_{27}N_2O_3P$: C, 66.33; H, 6.78; N, 7.04. Found: C, 66.27; H, 6.84; N, 7.11.

Diethyl 4-Amino-6-chloro-2-phenylquinoline-3-phosphonate 16.
Quinoline **16** has been obtained as described above for preparation of primary 4-aminoquinolines **5**, using the 4-aminoquinoline **15c** (*N-p*-methoxyphenyl substituted) as starting material, to give the title conpound **16** (1310 mg, 67%) as a yellow solid, mp 135-136 °C; *^{1}H-NMR* (300 MHz): 1.14 (t, 6H, $^3J_{HH}$= 7.2 Hz, CH_3), 3.81 (m, 4H, OCH_2), 6.63 (s, 2H, NH_2), 7.37-7.70 (m, 8H, arom), 8.01 (d, 1H, $^3J_{PH}$= 9.0 Hz, CH). *^{13}C-NMR* (75 MHz): 15.9 (CH_3), 62.1 (OCH_2), 108.3 (d,$^1J_{PC}$= 187.1 Hz, C=), 118.4-134.3 (C-arom), 142.1 (C-ipso arom), 146.3 (C-ipso arom), 158.6 (d,$^2J_{PC}$= 6.0 Hz, C(4)), 159.3 (C-ipso arom), 161.7 (d,$^2J_{PC}$= 10.1 Hz, C(2)), 186.8 (C-ipso arom). *^{31}P-NMR* (120 MHz): 13.5; *IR (KBr)* 3290, 3146, 1567, 1238 cm^{-1}; *MS* (EI) 390 (M^+, 14). Anal. Calcd for $C_{19}H_{20}ClN_2O_3P$: C, 58.46; H, 5.13; N, 7.18. Found: C, 58.63; H, 5.16; N, 7.09.

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