Article

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An Eco-friendly Three Component Manifold for the Synthesis of α-Aminophosphonates under Catalyst and Solvent-free Conditions, X-ray Characterization and Their Evaluation as Anticancer Agents

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A series of α-aminophosphonates were synthesized through one-pot condensation of aryl aldehydes, aryl amines and diethyl phosphite in the absence of any catalyst and organic solvents. All the synthesized α-aminophosphonates were characterized by spectral and elemental analysis and in the case of compound **4j** by X-ray crystallography. Some of these new α-aminophosphonate derivatives were found to have cytotoxic activity on the cancer cell line DU145 in vitro by the MTT method.

Keywords: Anticancer activity; Catalyst free; Solvent free; α-Aminophosphonates; X-ray analysis.

INTRODUCTION

α-aminophosphonates which are structural analogs of α-amino acid esters are of interest as potential anticancer drugs,[1,2] enzymes inhibitors,[3,4] haptens of catalytic antibodies,[5-7] pharmacologic agents,[6,7] antifungal activity,[8] insecticides,[9] plant growth regulators,[10] and anti-HIV agents.[11] Several multi-step synthetic approaches for the synthesis of α-aminophosphonates have been reported in the literature including alkylation of nucleophilic Schiff bases, Hofmann rearrangement of substituted phosphonoacetic esters and conversion of 1-hydroxyphosphonates to the corresponding α-aminophosphonates.[12]

An alternative synthesis of α-aminophosphonates involves nucleophilic addition of phosphite to imine.[13-19] However, since many imines are hygroscopic and are not sufficiently stable for isolation, this method has certain limitations. The most simple and straightforward synthetic method for the synthesis of α-aminophosphonates is the Kabachnik–Fields reaction which involves a one-pot three-component coupling of an aldehyde, amine and phosphite ester. In this regard, numerous protocols for the synthesis of these compounds have been developed using various Lewis and Brønsted acid catalysts such as sulfonic catalyst,[20] molecular iodine,[21] Xanthan Sulfuric Acid,[22] DTP/SiO_2,[23] succinic acid,[24] Phenylphosphonic acid,[25] $SnCl_2$,[26] SiO_2-$AlCl_3$,[27] $InCl_3$,[28] $Mg(ClO_4)_2$,[29] $M(OTf)_3$,[30] $CeCl_3.7H_2O$,[31] $FeCl_3$,[1] TiO_2,[32] $NaHSO_4$-SiO_2,[33] Nano Fe_3O_4,[34] γ-Fe_2O_3@SiO_2-PA,[35] DHAA-Fe_3O_4,[36] IRMOF-3 nano,[37] Fe/SWCNTs,[38] $ZrOCl_2.8H_2O$,[39] $TiCl_4$,[40] VCl_3,[41] and ethyl ammonium nitrate.[42] However, most of these methods have drawbacks, have drawbacks, because they use toxic and/or expensive catalysts and polluting organic solvents, have unsatisfactory yields or involve difficult preparations, prolonged reaction times and harsh reaction conditions, therefore researchers have been developed various eco-friendly method for their synthesis.[43-49]

As part of our continuous efforts to develop a green, ecofriendly, general and cost effective protocol for synthesis α-aminophosphonates, we have been reported an efficient and eco-friendly green one-pot multi-component protocol for the synthesis of α-aminophosphonate derivatives in excellent yields via a one-pot three component condensation of various aldehydes, amines and diethyl phosphite under catalyst and solvent-free conditions. The cytotoxic activity of the newly synthesized α-aminophosphonates (**4a–p**) on the cancer cell line DU145 was also studied using the MTT method and as the result compounds **4b** & **4d** proved to be potential cancer cytotoxic agents.

RESULTS AND DISCUSSION

We previously reported a catalyst-free method for the three-component Mannich reaction.[48] Now we have ex-

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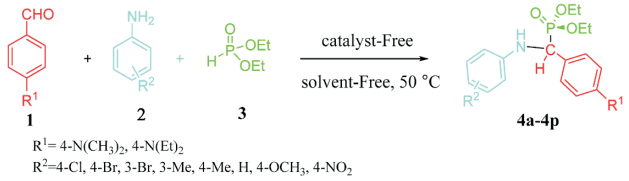
panded our interest in multi-component reactions through synthesis of α-aminophosphonates under catalyst and solvent-free conditions (Scheme 1). In order to optimize the reaction condition, a model reaction was chosen between 4-chloroaniline, 4-diethylaminobenzaldehyde and diethyl phosphite in the absence of any catalyst at room temperature. We used freshly distilled materials in these reactions to minimize the chances of any impurity catalysis. 4-diethylaminobenzaldehyde was washed carefully with sodium bicarbonate solution to remove any acidic impurity. The reaction produced the desired product after 5 h. Next, the temperature was optimized in order to minimize the reaction time. At 50-60 °C the highest yield of the α-aminophosphonate was obtained.

Scheme 1 Catalyst-free and solvent-free coupling of benzaldehydes and anilines with diethyl phosphite for synthesis α-aminophosphonate[a]

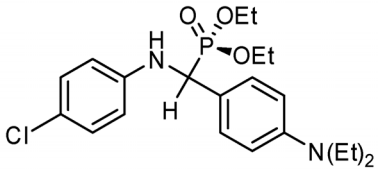
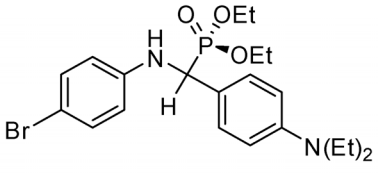
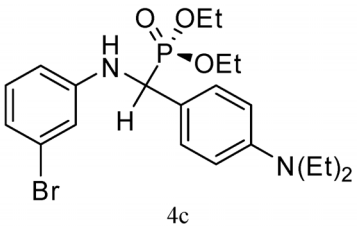


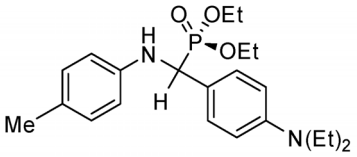
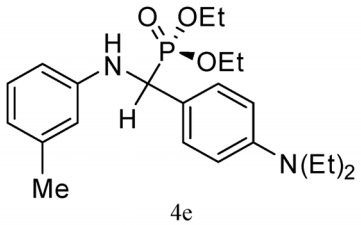
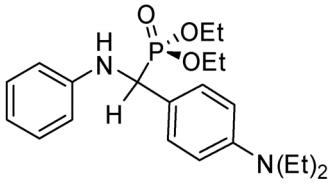
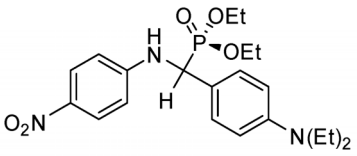
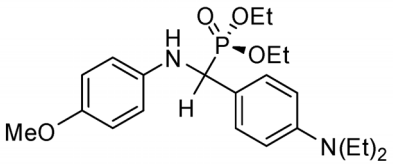
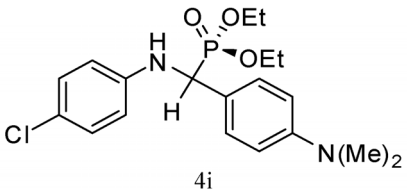
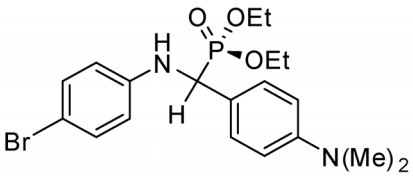
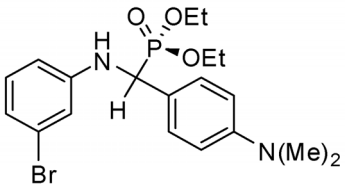
R^1= 4-N$(CH_3)_2$, 4-N$(Et)_2$
R^2=4-Cl, 4-Br, 3-Br, 3-Me, 4-Me, H, 4-OCH_3, 4-NO_2

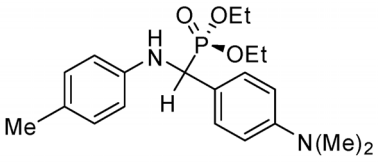
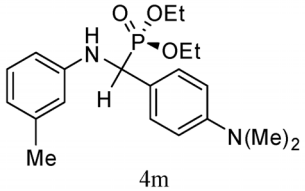
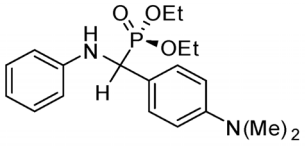
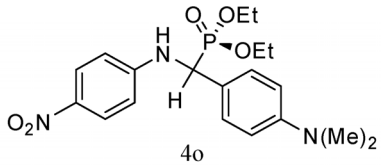
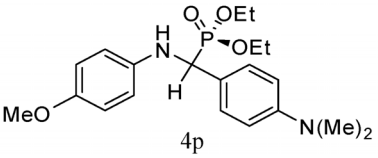
Based on these observations, we decide to synthesis novel α-aminophosphonate derivatives in solvent-free and catalyst-free condition, and to study their biological properties, so we used p-dimethylaminobenzaldehyde and p-diethylaminobenzaldehyde to compare biological properties. It was considered worthwhile to study the generality of this method by employing several other carbonyl compounds and amines. The reactions of 4-diethylaminobenzaldehyde and diethyl phosphite with different amines under catalyst-free and solvent-free conditions were investigated. The results of this study are shown in (Table 1, entry 1-8). The treatment of *4-(dimethylamino)benzaldehyde* with several substituted aromatic amines under catalyst and solvent-free conditions was also studied (Table 1, entry 9-16). It is clear that there is no significant electronic effect on the progress of three-component couplings using different substituted aromatic amines. *p*-methoxyaniline as a reactive amine (Table 1, entry 8, 16) and *p*-nitroaniline as a deactivated substrate (Table 1, entry 7, 15) were equally efficient substrates.

In order to comprehensively understand the complete structural features of compounds **4a-4p**, the X-ray structure of the *diethyl (((4-bromophenyl) amino) (4-(dimethylamino) phenyl) methyl) phosphonate* **4j** as an example was

Table 1. Catalyst-free and solvent-free coupling of benzaldehydes and anilines with diethyl phosphite for synthesis α-aminophosphonate[a]

Entry	Aldehyde	Amine	α-aminophosphonate	Time (min)	Yield[b] (%)
1	4-N$(Et)_2$	4-Cl	 4a	60	96
2	4-N$(Et)_2$	4-Br	 4b	90	95
3	4-N$(Et)_2$	3-Br	 4c	100	90

4	4-N(Et)$_2$	4-Me		45	92
			4d		
5	4-N(Et)$_2$	3-Me		30	90
			4e		
6	4-N(Et)$_2$	H		60	90
			4f		
7	4-N(Et)$_2$	4-NO$_2$		120	85
			4g		
8	4-N(Et)$_2$	4-OCH$_3$		60	95
			4h		
9	4-N(Me)$_2$	4-Cl		60	95
			4i		
10	4-N(Me)$_2$	4-Br		30	96
			4j		
11	4-N(Me)$_2$	3-Br		50	92
			4k		

12	4-N(Me)$_2$	4-Me	 4l	60	92
13	4-N(Me)$_2$	3-Me	 4m	90	95
14	4-N(Me)$_2$	H	 4n	45	90
15	4-N(Me)$_2$	4-NO$_2$	 4o	120	85
16	4-N(Me)$_2$	4-OCH$_3$	 4p	60	95

a) Reaction conditions: aldehyde (10 mmol), amine (10 mmol), diethylphosphite (10 mmol) under catalyst-free at 50-60 °C.
b) Isolated yields after recrystallization characterised by ^{1}H NMR.

obtained (Figure 1). The crystal structure of **4j** is triclinic system with the space group P-1. As seen from (Figure 1), the P atom has tetrahedral geometry involving two O-ethyl groups, one C_α atom, and a double bond with O atom. Location of the N-H group is in the opposite direction to the C-H. The C-P and P=O bond lengths are almost comparable with similar structures.[50] There is an intermolecular hydrogen bond which is N(1)–H(1)···O(1) (symmetry code, $-x + 1, -y, -z + 1$), with N(1)–H(1) = 0.83 Å, H(1)···O(1) = 2.23, N(1)···O(1) = 3.038 Å, and N(1)–H(1)···O(1) = 167°. (Figure 2).

Crystallographic data

CCDC 1001926 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, *www.ccdc.cam.ac.uk/data-request/cif*.

On the basis of kinetic studies, there are two plausible mechanisms depending on the nature of the reactants (Scheme 2).[49-51] According to one of the suggested mechanisms, at the first stage H-bond is formed between the P=*O* function of the phosphite and the *NH* unit of the electron with-drawing aniline to follow the imine formation, then diethylphosphite added to the C=N bond of imine **A**, to give α-aminophosphonate **4**, the other stage diethylphosphite was activated by forming a weak H-bond between the N atom of electron-donating aniline and P–H function which leads to the formation of α-hydroxyphosphite **B**, Finally, the reaction of α-hydroxyphosphite moiety **B** between aniline resulted in dehydration to form the target compound **4**.

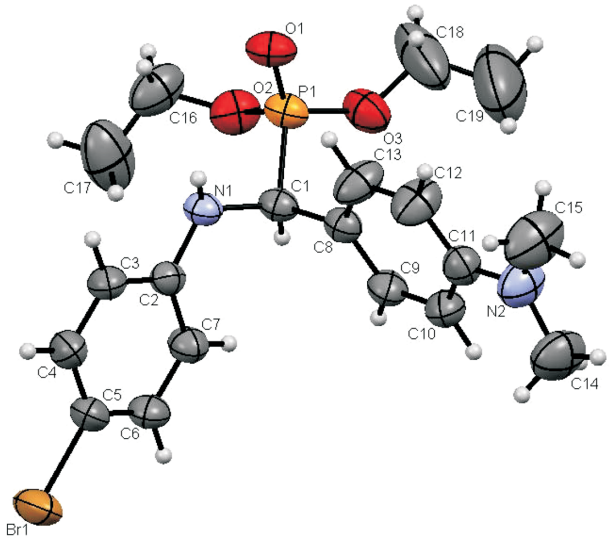


Fig. 1. ORTEP view of the molecular geometry of compound **4j** Ellipsoids have been drawn at the 30% probability level.

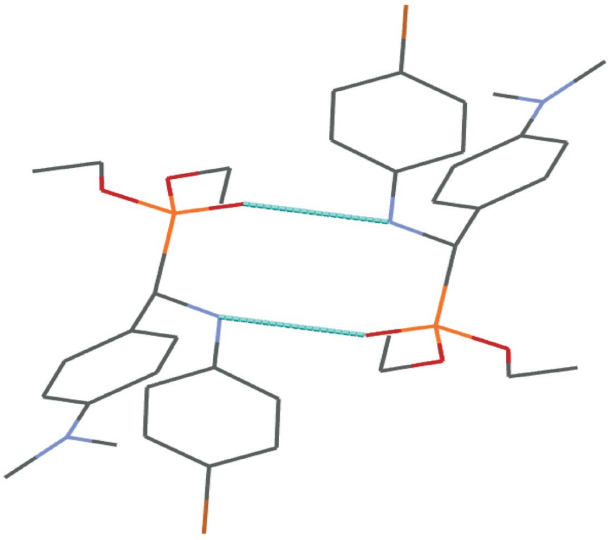


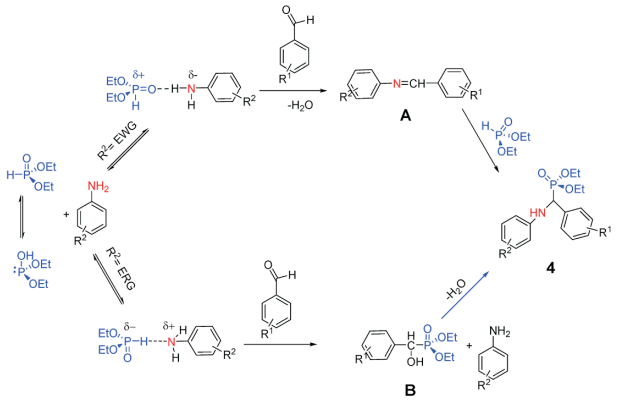
Fig. 2. A pair of hydrogen bonds in a Centro symmetric dimer of **4j**.

Biological activity

The *in vitro* cytotoxicity of these compounds *was* evaluated against DU145 prostate cancer cells by the MTT method[52] The percentage of cell viability was plotted versus the log of the concentrations, and nonlinear regression with a variable slope sigmoidal dose-response curve was generated along with IC_{50} using Graph Pad Prism V.3 software.

The results summarized in Table 2 indicate that changes of substituents could affect the cytotoxicity of the

Scheme 2 Plausible mechanism for the synthesis of α-aminophosphonates **4a–p**.



compound. The MTT studies showed that the most cytotoxic compounds were **4b** which has 4-Br, and 4-diethylamino moieties in its structure, with IC_{50} = 44 μM and **4d** which has 4-Me, and 4-diethyl amino moieties in its structure, with IC_{50} = 42 (μM) on **DU145** (Table 2). However, the replacement of the 4-diethylamino group in the benzaldehyde derived moiety of compounds **4b** and **4d** with *a* 4-dimethylamino group, resulted in the compounds **4j** and **4l** with complete loss of activity, and the other compounds didn't show significant inhibitory activity. Currently do-

Table 2. Comparative cytotoxic effects of compounds 4a-4p on DU145 prostate Cancer cells after 24, 48, 72 as assessed by MTT method

Compound	IC_{50} (μg)[a]		
	24h	48h	72h
4a	230 ± 2.4	235 ± 2.3	232 ± 4.8
4b	50 ± 4.4	46.5 ± 4.3	48 ± 4.6
4c	200 ± 2.3	201 ± 4.5	204 ± 4.8
4d	49 ± 4.4	45 ± 4.2	42 ± 4.4
4e	140 ± 0.75	145 ± 4.2	142 ± 4.3
4f	NA[b]	NA[b]	NA[b]
4g	200 ± 4.3	NA[b]	NA[b]
4h	NA[b]	NA[b]	NA[b]
4i	210 ± 2.5	212 ± 4.4	215 ± 4.2
4j	180 ± 2.3	182 ± 2.7	191 ± 4.9
4k	246 ± 4.5	240 ± 2.4	239 ± 4.7
4l	NA[b]	NA[b]	NA[b]
4m	≥ 250	246 ± 2.4	≥ 250
4n	NA[b]	NA[b]	NA[b]
4o	≥ 250	245 ± 1.2	NA[b]
4p	NA[b]	NA[b]	NA[b]
docetaxel	44 ± 4.5	40 ± 4.4	30 ± 4.3

[a] Arithmetic mean ± standard deviation of at least 3 independent experiments.
[b] NA: Not active up to significant concentration.

cetaxel (taxotere), a member of taxane family, is widely used in chemotherapy to treat advanced stages of prostate cancer.[53] In this study, the cytotoxic effects of docetaxel were evaluated on **DU145** cells and the data are shown in (Table 2). Its IC_{50} values were 44, 40 and 30 μM after 24, 48 and 72 h, respectively (Figure 3). According to these data, compound **4d** has the most cytotoxic effects, similar to docetaxel.

Biological assays

Materials

DU145 cells were obtained from the Pasteur Institute (Tehran, Iran) and were grown in RPMI 1640 medium, supplemented with 10% fetal bovine serum (FBS, Gibco, Scotland). Cells were incubated at 37 °C in a humidified atmosphere of 10% CO_2 in air for 2–3 days before experimental use. In order to subculture DU145 cells, they were washed with phosphate buffered saline (PBS) and incubated with 0.25% trypsin/1 mM EDTA for 3–5 min. Then detached cells were resuspended in fresh serum-containing medium to inactivate the trypsin, and transferred to new labeled flasks as required.

Preparation of various concentrations of the selected product

To prepare different concentrations of **4a-4p** (6.25, 12.5, 25, 50, 100, 250 μM), 2 mmol of each powder was dissolved in 100 μl dimethylsulfoxide (DMSO, Merck, Germany) and diluted with complete culture medium before experiments.

In order to exclude the background cytotoxic effects of the solvent, control treatments were also run with DMSO only. These controls included 0.25%, DMSO, equivalent to the DMSO content of their **4a-4p** solutions.

In vitro cytotoxicity assay

The reduction of tetrazolium dye, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, by living cells is used in a rapid drug-screening assay. Briefly, cells were seeded at a density of 8×10^3 cells/well in 96-well tissue culture plates (organic scientific, France, USA). To identify the half maximal inhibitory concentration (IC_{50}) values of 4a-4p, DU145 cells were then incubated with increasing concentrations of 4a-4p (6.25, 12.5, 25, 50, 100, 250 μM) for 24, 48 and 72 h, respectively. Docetaxel (Darou Pakhsh Holding, Iran) was used at the, 6.25, 12.5, 25, 50, 100 and 250 μM concentrations as a positive control. 5 mg MTT dye (Sigma, Germany) was dissolved in 1 ml (PBS), filtered and used freshly before each experiment. 20 μl MTT solution was then added to each well and plates were incubated for 4 h at 37 °C. After this period, the purple insoluble formazan, produced from yellow MTT by living cells, was dissolved in DMSO (150 μl/well) during 2–3 min. The optical density[18] of each well was then measured spectrophotometrically at 540 nm using an ELISA plate reader (Awareness, USA). All tests were performed in triplicates. Since the formation of formazan is correlated with

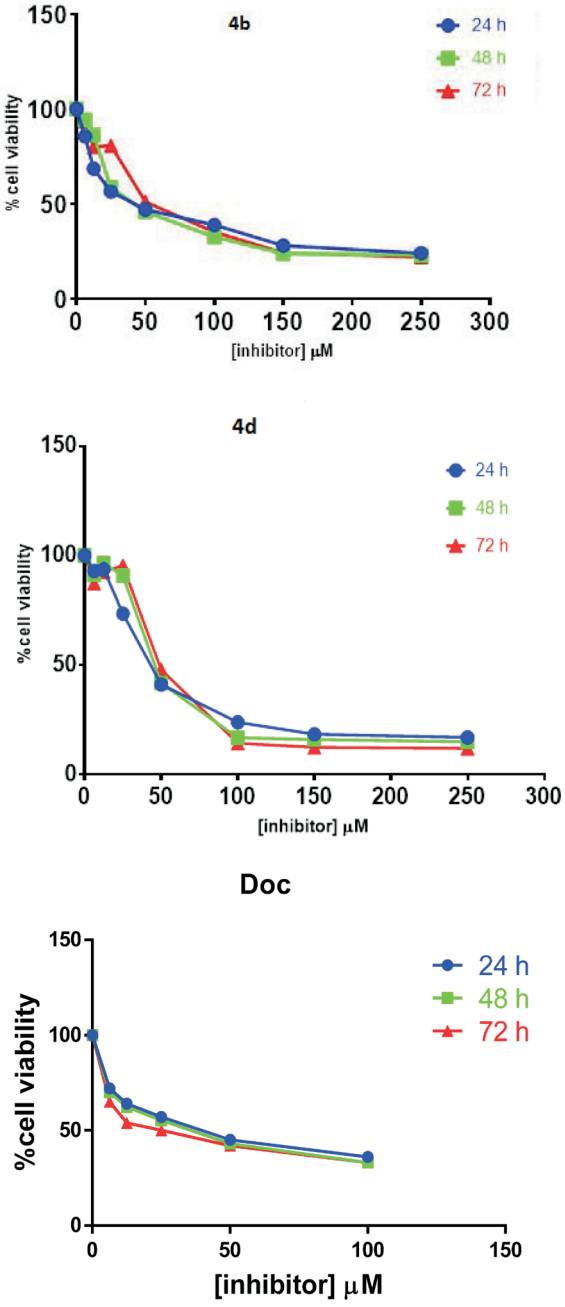


Fig. 3. Time-based dose response curves of DU445 prostate cancer cells to (**4b**), (**4d**) and docetaxel (Doc) during 24, 48 and 72 h.

the number of living cells, the OD read-outs from the treated wells were converted to the percentage of living cells against controls. This was calculated by dividing the absorbance of treated cells in each well to the mean absorbance of controls multiply by 100. The average background absorbance from control wells (DMSO without added MTT) was subtracted from MTT-treated samples and data were plotted as a percentage using Prism v.3 software.

EXPERIMENTAL

All solvents and reagents were purchased from Fluka or Merck Chemical Companies. FT-IR spectra were recorded using KBr disks on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. NMR spectra were recorded on a Bruker Avance DPX 400 and 100 instrument at 400 and 100 for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 162 MHz for ^{31}P NMR in $CDCl_3$ solution, using TMS as an internal standard. Melting points were recorded on an electrothermal type 9100. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. The mass spectra were recorded on a 5973 Network Mass Selective Detector.

General procedure for the synthesis of α-aminophosphonates 4a-4p: A mixture of aldehyde (5 mmol), amine (5 mmol), and diethylphosphite (5 mmol) was stirred in a 10 ml round bottom flask at 50-60 °C for the appropriate reaction time (Table 1). The completion of the reaction was monitored by TLC. After the completion of the reaction, resulting crude material was recrystallized from EtOAC/n-Hexane (1:4) to afford the pure α-aminophosphonates.

Spectral data of the prepared compounds

Diethyl(((4-chlorophenyl) amino) (4-(diethylamino) phenyl)methyl) phosphonate (4a): Yield 96%; m.p = 120-121 °C; IR (KBr, cm^{-1}) υ: 3297 (NH), 3048, 2978, 1613, 1598, 1521, 1492, 1232 (P=O), 1050 (P-OEt), 578; ^{1}H NMR (100 MHz, $CDCl_3$) δ: 1.00-1.40 (m, 6H, $OCH_2\underline{CH_3}$, 6H, $NCH_2\underline{CH_3}$), 3.33 (q, J = 8.0 Hz, 4H, $N\underline{CH_2}CH_3$), 3.78-4.07 (m, 4H, $O\underline{CH_2}CH_3$), 4.60 (dd, $^{1}J_{PH}$ = 24.2 Hz, $^{2}J_{PH}$ = 7.1 Hz, 1H, CHP), 4.70 (br, 1H, NH), 6.40-6.70 (m, 4H, Ar-H), 7.00-7.30 (m, 4H, Ar-H), ^{31}P (162.03 MHz, $CDCl_3$): δ 20.88. *m/z* (ESI) 424 [75%, M^+], 426 [25%, M^++2]. Anal. Calc. for $C_{21}H_{30}ClN_2O_3P$: C, 59.36; H, 7.12; N, 6.59. Found: C, 59.30; H, 7.10; N, 6.56.

Diethyl (((4-bromophenyl)amino) (4-(diethylamino) phenyl) methyl) phosphonate (4b): Yield 95%; m.p = 123-124 °C; IR (KBr, cm^{-1}) υ: 3294 (NH), 3018, 2972, 1613, 1592, 1524, 1497, 1232 (P=O), 1047 (P-OEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (t, J = 7.2 Hz, 6H, $NCH_2\underline{CH_3}$), 1.16 (t, J = 8.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.31 (t, J = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 3.33 (q, J = 7.0 Hz, 4H, $N\underline{CH_2}CH_3$), 3.66-4.73 (m, 1H, $O\underline{CH_2}CH_3$), 3.91-3.98 (m, 1H, $O\underline{CH_2}CH_3$), 4.07-4.17 (m, 2H, $O\underline{CH_2}CH_3$), 4.60 (dd, $^{1}J_{PH}$ = 23.0 Hz, $^{2}J_{PH}$ = 7.2 Hz, 1H, CHP), 4.78 (br, 1H, NH), 6.52 (d, J = 8.8 Hz, 2H, Ar-H), 6.63 (d, J = 7.2 Hz, 2H, Ar-H), 7.20 (d, J = 8.8 Hz, 2H, Ar-H), 7.27 (d, J = 7.2 Hz, 2H, Ar-H), ^{13}CNMR (100.64 MHz, $CDCl_3$): δ 12.5, 16.2 (d, $^{3}J_{PC}$ = 5.6 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.6 Hz), 44.2, 55.3 (d, $^{1}J_{PC}$ = 152.9 Hz), 63.0 (d, $^{2}J_{PC}$ = 7.0 Hz), 63.3 (d, $^{2}J_{PC}$ = 6.9 Hz), 109.8, 111.8, 115.5, 120.9, 128.7, 131.8, (d, $^{2}J_{PC}$ = 5.0 Hz), 145.6 (d, $^{3}J_{PC}$ = 14.0 Hz),147.6. ^{31}P (162.03 MHz, $CDCl_3$): δ 23.11. *m/z* (ESI) 470 (68 %, [M^+]. 472 [68%, M^++2]. Anal. Calc. for $C_{21}H_{30}BrN_2O_3P$: C, 53.74; H, 6.44; N, 5.97. Found: C, 53.50; H, 6.28; N, 5.74.

Diethyl (((3-bromophenyl)amino) (4-(diethylamino) phenyl) methyl) phosphonate (4c): Yield 90%; m.p = 130-131 °C; IR (KBr, cm^{-1}) υ: 3294 (NH), 3018, 2974, 1612, 1594, 1523, 1479, 1235 (P=O), 1057 (P-OEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13-1.16 (m, 3H, $OCH_2\underline{CH_3}$, 6H, $NCH_2\underline{CH_3}$), 1.30 (t, J = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 3.34 (q, J = 7.0 Hz, 4H, $N\underline{CH_2}CH_3$), 3.63-3.72 (m, 1H, $O\underline{CH_2}CH_3$), 3.90-3.99 (m, 1H, $O\underline{CH_2}CH_3$), 4.07-4.18 (m, 2H, $O\underline{CH_2}CH_3$), 4.60 (dd, $^{1}J_{PH}$ = 23.5 Hz, $^{2}J_{PH}$ = 8.4 Hz, 1H, CHP), 4.78 (t, J = 8.4 Hz, 1H, NH), 6.55 (dd, ^{1}J = 8.0 Hz, ^{2}J = 2.4 Hz, 1H, Ar-H), 6.63 (d, J = 8.8 Hz, 2H, Ar-H), 6.70 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H, Ar-H), 6.95 (t, J = 8.2 Hz, 1H, Ar-H), 7.26 (dd, ^{1}J = 8.8 Hz, ^{2}J = 2.4 Hz, 2H, Ar-H), ^{13}CNMR (100.64 MHz, $CDCl_3$): δ 12.5, 16.2 (d, $^{3}J_{PC}$ = 5.6 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.6 Hz), 44.2, 55.3 (d, $^{1}J_{PC}$ = 153.4 Hz), 63.0 (d, $^{2}J_{PC}$ = 7.0 Hz), 63.3 (d, $^{2}J_{PC}$ = 6.9 Hz), 111.8, 112.4, 116.5, 120.8, 120.9, 123.0, 128.7 (d, $^{2}J_{PC}$ = 5.2 Hz), 130.3, 147.6, 148.0 (d, $^{3}J_{PC}$ = 14.3 Hz). ^{31}P (162.03 MHz, $CDCl_3$): δ 22.97, *m/z* (ESI) 470 [20%, M^+], 472 [5%, M^++2]. Anal. Calc. for $C_{21}H_{30}BrN_2O_3P$: C, 53.74; H, 6.44; N, 5.97. Found: C, 53.68; H, 6.36; N, 5.65.

Diethyl (((4-(diethylamino)phenyl) (4-tolylamino) methyl) phosphonate (4d): Yield 92%; m.p = 100-101 °C; IR (KBr, cm^{-1}) υ: 3295 (NH), 3018, 2982, 1611, 1603, 1524, 1497, 1237 (P=O), 1060 (P-OEt); ^{1}H NMR (100 MHz, $CDCl_3$): δ, 1.10-1.19 (m, 6H, $OCH_2\underline{CH_3}$, m, 6H, $NCH_2\underline{CH_3}$), 2.18 (s, 3H, CH_3Ar), 3.30 (q, J = 8.0 Hz, 4H, $N\underline{CH_2}CH_3$), 3.50-4.20 (m, 4H, $O\underline{CH_2}CH_3$), 4.50 (d, J = 22.0 Hz, 1H, CHP), 4.55 (br, 1H, NH), 6.50-7.30 (m, 8H Ar-H). ^{31}P (162.03 MHz, $CDCl_3$): = 21.36. *m/z* (ESI) 404 [70%, M^+]. Anal. Calc. for $C_{22}H_{33}N_2O_3P$: C, 65.33; H, 8.22; N, 6.93. Found: C, 65.25; H, 8.15; N, 6.88.

Diethyl (((4-(diethylamino)phenyl) (3-tolylamino) methyl) phosphonate (4e): Yield 90%; m.p = 140-141 °C; (KBr, cm^{-1}) υ: 3295 NH, 3018, 2982, 1611, 1603, 1524, 1497, 1237 (P=O), 1060 (P-OEt) cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$): 1.13-1.18 (m, 3H, $OCH_2\underline{CH_3}$, 6H, $NCH_2\underline{CH_3}$), 1.30 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.25 (s, 3H, CH_3Ar), 3.33 (q, J = 8.0 Hz, 4H,

N$\underline{CH_2}CH_3$), 3.69–3.77 (m, 1H, O$\underline{CH_2}CH_3$), 3.93-4.02 (m, 1H, O$\underline{CH_2}CH_3$), 4.08-4.20 (m, 2H, O$\underline{CH_2}CH_3$), 4.66 (d, J_{PH} = 23.3 Hz, 1H, CHP), 4.67 (br, 1H, NH), 6.45 (d, J = 8.0 Hz, 1H, Ar-H), 6.51 (s, 1H), 6.53 (t, J = 7.2 Hz, 1H, Ar-H), 6.65 (d, J = 8.0 Hz, 2H, Ar-H), 7.02 (t, J = 7.6 Hz, 1H, Ar-H), 7.30 (d, J = 7.2 Hz, 2H, Ar-H). ^{13}CNMR (100.64 MHz, $CDCl_3$): δ 12.5, 16.3 (d, $^3J_{PC}$ = 6.0 Hz), 16.5 (d, $^3J_{PC}$ = 6.0 Hz), 21.6, 44.3, 55.2 (d, $^1J_{PC}$ = 153.5 Hz), 63.0 (d, $^2J_{PC}$ = 17.2 Hz), 63.1, 110.0, 111.8, 114.8, 119.0, 121.8, 128.0 (d, $^2J_{PC}$ = 6.1 Hz), 129.0, 138.8, 146.7 (d, $^3J_{PC}$ = 16.2 Hz), 147.5. ^{31}P (162.03 MHz, $CDCl_3$): δ 23.58, *m/z* (ESI) 404 [45%, M^+]. Anal. Calc. for $C_{22}H_{33}N_2O_3P$: C, 65.33; H, 8.22; N, 6.93. Found: C, 65.02; H, 8.10; N, 6.82.

Diethyl ((4-(diethylamino)phenyl) (phenylamino) methyl) phosphonate (4f): Yield 90%; m.p = 101-102 °C; IR (KBr, cm^{-1}) υ: 3301 (NH), 3022, 2973, 1611, 1603, 1524, 1497, 1232 (P=O), 1061 (P-OEt); ^{1}H NMR (100 MHz,$CDCl_3$): δ 1.01-1.40 (m, 6H, OCH$_2\underline{CH_3}$, 6H, NCH$_2\underline{CH_3}$), 3.23 (q, J = 8.0 Hz, 4H, N$\underline{CH_2}CH_3$), 3.71-4.01 (m, 4H, O$\underline{CH_2}CH_3$), 4.30 (dd, $^1J_{PH}$ = 23.0 Hz, $^2J_{PH}$ = 7.2 Hz, 1H, CHP), 4.50 (br, 1H, NH), 6.60-7.30 (m, 9H, Ar-H). *m/z* (ESI) 390 [55%, M^+]. Anal. Calc. for $C_{21}H_{31}N_2O_3P$: C, 64.60; H, 8.00; N, 7.17. Found: C, 64.20; H, 7.74; N, 7.10.

Diethyl ((4-(diethylamino)phenyl)((4-nitrophenyl) amino) methyl) phosphonate (4g): Yield 85%; m.p = 140-141 °C; IR (KBr, cm^{-1}) υ: 3269 (NH), 3040, 2972, 1597, 1520, 1505, 1481, 1231 (P=O), 1051 (P-OEt), 574; ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.00-1.40 (m, 6H, OCH$_2\underline{CH_3}$, 6H, NCH$_2\underline{CH_3}$), 3.43 (q, J = 8.1 Hz, 4H, N$\underline{CH_2}CH_3$), 3.50-4.20 (m, 4H, O$\underline{CH_2}CH_3$), 4.70 (dd, $^1J_{PH}$ = 24.0 Hz, $^2J_{PH}$ = 7.5 Hz, 1H, CHP), 5.75 (br, 1H, NH), 6.60 (d, J = 8.0 Hz, 2H, Ar-H), 7.10-7.30 (m, 4H, Ar-H), 8.01 (d, J = 8.0 Hz, 2H, Ar-H); *m/z* (ESI) 435 [45%, M^+]. Anal. Calc. for $C_{21}H_{30}N_3O_5P$: C, 57.92; H, 6.94; N, 9.65. Found: C, 57.24; H, 6.75; N, 9.42.

Diethyl ((4-(diethylamino)phenyl) ((4-methoxyphenyl) amino) methyl) phosphonate (4h): Yield 95%; m.p = 120–121 °C; IR(KBr, cm^{-1}): 3299 (NH), 3018, 2971, 1611, 1520, 1510, 1234 (P=O), 1031 (P-OEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.30 (m, 6H, OCH$_2\underline{CH_3}$, 6H, NCH$_2\underline{CH_3}$), 3.31 (q, J = 8.0 Hz, 4H, N$\underline{CH_2}CH_3$), 3.69 (s, 3H, OCH_3), 3.65-3.80 (m, 1H, O$\underline{CH_2}CH_3$), 3.93-3.97 (m, 1H, O$\underline{CH_2}CH_3$), 4.08-4.14 (m, 2H, O$\underline{CH_2}CH_3$), 4.36 (b, 1H, NH), 4.57 (dd, $^1J_{PH}$ = 23.0 Hz, $^2J_{PH}$ = 7.2 Hz, 1H, CHP), 6.57-6.70 (m, 6H, Ar-H), 7.24-7.26 (m, 2H, Ar-H), ^{13}CNMR (100.62, $CDCl_3$): δ 12.5, 16.2 (d, $^3J_{PC}$ = 6.0 Hz), 16.5 (d, $^3J_{PC}$ = 6.0 Hz), 44.3, 55.6, 56.2 (d, $^1J_{PC}$ = 152.5 Hz), 63.0, 63.1, 111.8, 114.7, 115.3, 121.9, 128.8 (d, $^2J_{PC}$ = 5.0 Hz), 140.9 (d, $^3J_{PC}$ = 1.5 Hz), 147.5, 152.5. ^{31}P (161.99 MHz, $CDCl_3$): δ 23.99 ppm,. *m/z* (ESI) 420 [30%, M^+]. Anal. Calc. for $C_{22}H_{33}N_2O_4P$: C, 62.84; H, 7.91; N, 6.66. Found: C, 62.43; H, 7.68; N, 6.60.

Diethyl (((4-chlorophenyl)amino) (4-(dimethylamino) phenyl) methyl) phosphon (4i): Yield 95%; m.p = 130-131 °C;[45] IR (KBr, cm^{-1}) υ: 3293 (NH), 2982, 1612, 1597, 1525, 1492, 1230 (P=O), 1062 (P-OEt); ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.15 (t, J = 7.8 Hz, 3H, OCH$_2\underline{CH_3}$), 1.31 (t, J = 7.8 Hz, 3H, OCH$_2\underline{CH_3}$), 2.92 (s, 6H, NCH_3), 3.50-4.20 (m, 4H, O$\underline{CH_2}CH_3$), 4.60 (dd, $^1J_{PH}$ = 24.0 Hz, $^2J_{PH}$ = 7.1 Hz, 1H, CHP), 4.7 (br, 1H, NH), 6.55 (d, J = 8.4 Hz, 2H, Ar-H), 6.70 (d, J = 8.2 Hz, 2H, Ar-H), 7.05 (d, J = 8.4 Hz, 2H, Ar-H), 7.30 (d, J = 8.2 Hz, 2H, Ar-H); *m/z* (ESI) 396 [15%, M^+], 398 [10%, M^++2]. Anal. Calc. for $C_{19}H_{26}ClN_2O_3P$: C, 57.50; H, 6.60; N, 7.06. Found: C, 57.01; H, 6.25; N, 6.78.

Diethyl (((4-bromophenyl) amino) (4-(dimethylamino) phenyl)methyl)phosphonate (4j): Yield 96%; m.p = 135-136 °C; IR (KBr, cm^{-1}): 3294 (NH), 2982, 1613, 1592, 1522, 1488, 1231 (P=O), 1063 (P-OEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 3H, OCH$_2\underline{CH_3}$), 1.31 (t, J = 7.2 Hz, 3H, OCH$_2\underline{CH_3}$), 2.94 (s, 6H, NCH_3), 3.65–3.73 (m, 1H, O$\underline{CH_2}CH_3$), 3.90-4.01 (m, 1H, O$\underline{CH_2}CH_3$), 4.07-4.18 (m, 2H, O$\underline{CH_2}CH_3$), 4.62 (d, J_{PH} = 22.4 Hz, 1H, CHP), 4.81 (br, 1H, NH), 6.50 (dd, ^1J = 8.8 Hz, ^2J = 2.2 Hz, 2H, Ar-H), 6.70 (d, J = 8.4 Hz, 2H, Ar-H), 7.18 (d, J = 8.8 Hz, 2H, Ar-H), 7.30 (d, ^1J = 8.4 Hz, ^2J = 2.4 Hz, 2H, Ar-H); ^{13}CNMR (100.64, $CDCl_3$): δ 16.3 (d, $^3J_{PC}$ =6.3 Hz), 16.5 (d, $^3J_{PC}$= 6.2 Hz), 40.5, 55.3 (d, $^1J_{PC}$ = 152.1 Hz), 63.1 (d, $^2J_{PC}$ = 7.0 Hz), 63.4 (d, $^2J_{PC}$ = 7.0 Hz), 109.9, 112.5, 115.5, 122.3, 128.6 (d, $^2J_{PC}$ = 5.0 Hz), 131.8, 145.6 (d, $^3J_{PC}$ = 15.2 Hz), 150.25. ^{31}P (162.03 MHz, $CDCl_3$): δ 23.01. *m/z* (ESI) 440 [40%, M^+], 442 [35%, M^++2]. Anal. Calc. for $C_{19}H_{26}BrN_2O_3P$: C, 51.71; H, 5.94; N, 6.35. Found: C, 51.50; H, 5.80; N, 6.6.21.

Diethyl (((3-bromophenyl) amino) (4-(dimethylamino) phenyl) methyl)phosphonatee (4k): Yield 92%; m.p = 110-111 °C; IR (KBr, cm^{-1}): 3294 (NH), 3018, 2974, 1612, 1594, 1523, 1479, 1235 (P=O), 1057 (P-OEt); ^{1}H NMR (100 MHz,$CDCl_3$): δ 1.15-1.30 (m, 6H OCH$_2\underline{CH_3}$), 2.88 (s, 6H, NCH_3), 3.60-4.21 (m, 4H, O$\underline{CH_2}CH_3$), 4.32 (dd, $^1J_{PH}$ = 23.0 Hz, $^2J_{PH}$ = 7.0 Hz, 1H, CHP), 4.7 (br, 1H, NH), 6.5-7.30 (m, 8H, Ar-H). ^{31}P (162.03 MHz, $CDCl_3$): δ 23.70. *m/z* (ESI) 440 [30%, M^+], 442 [28%, M^++2]. Anal. Calc. for $C_{19}H_{26}BrN_2O_3P$: C, 51.71; H, 5.94; N, 6.35. Found: C, 51.50; H, 5.90; N, 6.24.

Diethyl ((4-tolylamino)(4-(dimethylamino) phenyl) methyl) phosphonate (4l): Yield 92%; m.p = 102-103 °C;[2] IR (KBr, cm^{-1}) υ: 3295 (NH), 3018, 2982, 1611, 1603, 1524, 1497, 1237 (P=O), 1060 (P-OEt), ^{1}H NMR (100 MHz, $CDCl_3$) δ: 1.13-1.45 (m, 6H, OCH$_2\underline{CH_3}$), 2.20 (s, 3H, CH_3Ar), 2.70 (s, 6H, N$\underline{CH_3}$), 3.60-4.22 (m, 4H, O$\underline{CH_2}CH_3$), 4.50-4.65 (m, 1H, CHP), 4.75 (br, 1H, NH), 6.58-7.53 (m, 8H, Ar); MS (*m/z*) 376 [20%, M^+]. Anal. Calc. for $C_{20}H_{29}N_2O_3P$: C, 63.81; H, 7.77; N, 7.44. Found: C, 63.75; H, 7.70; N, 7.26.

Diethyl ((3-tolylamino)(4-(dimethylamino) phenyl) methyl) phosphonate (4m): Yield 95%; m.p = 120-121 °C; IR (KBr, cm^{-1}): 3300 (NH), 3035, 2981, 1607, 1600, 1524, 1489, 1236 (P=O), 1052 (P-OEt); ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.10-1.30 (m, 6H, $OCH_2\underline{CH_3}$), 2.28 (s, 3H, CH_3Ar), 2.91 (s, 6H, $N\underline{CH_3}$), 3.56-4.30 (m, 4H, $O\underline{CH_2}CH_3$), 4.50 (d, J = 21.4, 1H, CHP), 4.60 (br, 1H, NH), 6.42-7.48 (m, 8H, Ar). ^{31}P (162.03 MHz, $CDCl_3$): δ 23.36. *m/z* (ESI) 376 [45%, M^+]. Anal. Calc. for $C_{20}H_{29}N_2O_3P$: C, 63.81; H, 7.77; N, 7.44. Found: C, 63.68; H, 7.36; N, 7.14.

Diethyl ((4-(dimethylamino) phenyl) (phenylamino) methyl) phosphonate (4n): Yield 90%; m.p = 112-113 °C;[54] IR (KBr, cm^{-1}) υ: 3293 (NH), 3031, 2982, 1602, 1525, 1497, 1236 (P=O), 1052 (P-OEt); ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.1-1.4 (m, 6H, $OCH_2\underline{CH_3}$), 2.85 (s, 6H, NCH_3), 3.60-4.20 (m, 4H, $O\underline{CH_2}CH_3$), 4.30 (d, J_{PH} = 23.0 Hz, 1H, CHP), 4.54 (br, 1H, NH), 6.60-7.40 (m, 9H, Ar-H). *m/z* (ESI) 362 [80%, M^+] Anal. Calc. for $C_{19}H_{27}N_2O_3P$: C, 62.97; H, 7.51; N, 7.73. Found: C, 62.21; H, 7.45; N, 7.63.

Diethyl ((4-(dimethylamino)phenyl) ((4-nitrophenyl) amino) methyl) phosphonate (4o): Yield 85%; m.p = 140-141 °C; (KBr, cm^{-1}): 3274 (NH), 3060, 2958, 1618, 1594, 1529, 1479, 1232 (P=O), 1047 (P-OEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 6.8 Hz, 3H, $OCH_2\underline{CH_3}$), 1.26 (t, J = 6.8 Hz, 3H, $OCH_2\underline{CH_3}$), 2.92 (s, 6H, NCH_3), 3.65–3.71 (m, 1H, $O\underline{CH_2}CH_3$), 3.89-3.95 (m, 1H, $O\underline{CH_2}CH_3$), 4.04-4.11 (m, 2H, $O\underline{CH_2}CH_3$), 4.53 (d, J_{PH} = 23.0 Hz, 1H, CHP), 5.70 (br, 1H, NH), 6.43 (d, J = 8.2 Hz, 2H, Ar-H), 6.70 (d, J = 8.4, 2H, Ar-H), 7.21 (d, J = 8.2, 2H, Ar-H), 8.01 (d, J = 8.4, 2H, Ar-H); ^{13}CNMR (100.64, $CDCl_3$): δ 16.3 (d, $^3J_{PC}$ = 7.0 Hz), 16.5 (d, $^3J_{PC}$ = 7.0 Hz), 40.4, 55.5 (d, $^1J_{PC}$ = 155.0 Hz), 63.3 (d, $^2J_{PC}$ = 7.0 Hz), 63.4 (d, $^2J_{PC}$ = 7.0 Hz), 118.8, 120.7, 122.2, 126.8, 129.0 (d, $^2J_{PC}$ = 6.0 Hz), 131.2 (d, $^3J_{PC}$ = 10.1 Hz), 149.9, 150.41 (d, $^3J_{PC}$ = 15.0 Hz). ^{31}P (162.03 MHz, $CDCl_3$): δ 23.14. *m/z* (ESI) 407 [70%, M+]. Anal. Calc. for $C_{19}H_{26}N_3O_5P$: C, 56.02; H, 6.43; N, 10.31. Found: C, 55.92; H, 6.39; N, 9.97.

Diethyl ((4-(dimethylamino) phenyl) ((4-methoxyphenyl) amino)methyl) phosphonate (4p): Yield 95%; m.p = 115-116 °C; IR (KBr, cm^{-1}) υ: 3299 (NH), 3018, 2971, 1613, 1511, 1425, 1238 (P=O), 1024 (P-OEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.30 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 3.60–3.75 (m, 1H, $O\underline{CH_2}CH_3$), 2.90 (s, 6H, NCH_3), 3.78 (s, 3H, OCH_3), 3.90-4.00 (m, 1H, $O\underline{CH_2}CH_3$), 4.06-4.20 (m, 2H, $O\underline{CH_2}CH_3$), 4.67 (dd, $^1J_{PH}$ = 22.4, $^2J_{PH}$ = 7.6 Hz, 1H, CHP), 4.92 (br, 1H, NH), 6.53 (d, J = 8.4 Hz, 2H, Ar-H), 6.70 (d, J = 8.4 Hz, 2H, Ar-H), 7.05 (d, J = 8.4 Hz, 2H, Ar-H), 7.38 (d, J = 7.2 Hz, 2H, Ar-H); ^{13}CNMR (100.64 ,$CDCl_3$): δ 16.3 (d, $^3J_{PC}$ =6.0 Hz), 16.5 (d, $^3J_{PC}$ = 6.0 Hz), 40.5, 55.3 (d, $^1J_{PC}$ = 152.0 Hz), 63.0 (d, $^2J_{PC}$ = 7.0 Hz), 63.3 (d, $^2J_{PC}$ = 7.0 Hz), 114.1 (d, $^2J_{PC}$ = 3.0 Hz), 115.0, 122.9, 127.2 (d, $^2J_{PC}$ = 3.0 Hz), 128.9, 144.9, 145.8, 159.4 (d, $^3J_{PC}$ = 15.3 Hz) ppm. ^{31}P (162.5 MHz, $CDCl_3$): δ 23.01 *m/z* (ESI) 393 [90%, M^+]. Anal. Calc. for $C_{20}H_{29}N_2O_4P$ C, 61.21; H, 7.45; N, 7.14. found: C, 60.85; H, 7.10; N, 7.05.

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