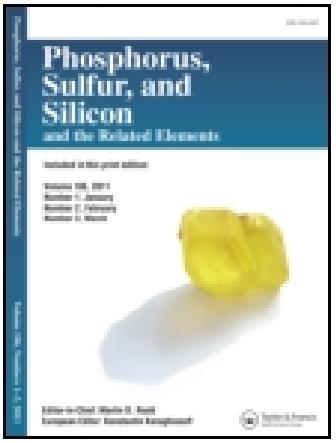

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Ultrasonic Promoted Synthesis and Antibacterial Screening of Some Novel Piperidine Incorporated α-Aminophosphonates

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ULTRASONIC PROMOTED SYNTHESIS AND ANTIBACTERIAL SCREENING OF SOME NOVEL PIPERIDINE INCORPORATED α-AMINOPHOSPHONATES

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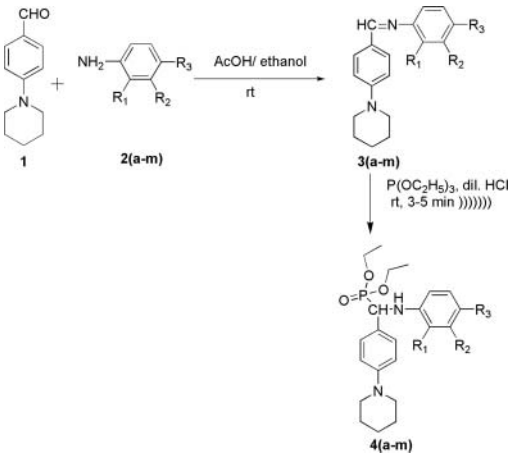
GRAPHICAL ABSTRACT



Abstract *A simple and high-yielding method was developed for the synthesis of novel α-aminophosphonates from imines, obtained from 4-(piperidine-1-yl)benzaldehyde, by using triethylphosphite in the presence of dilute HCl under ultrasound irradiation. This method, which was developed for the synthesis of α-aminophosphonates, gave excellent yields.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords α-Aminophosphonate; dilute HCl; imines; piperidine; triethylphosphite; ultrasonication

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INTRODUCTION

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[2–4] Among α-functional phosphonic acids, α-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. α-Amino phosphonates are biologically and industrially important compounds. They possess anticancer,[5a] anti-HIV,[5b] antithrombotic,[5c] and antibacterial properties.[5d] They are also employed as enzyme inhibitors[6] and peptidemimics.[7] Additionally, they are utilized as insecticides,[8a] herbicides,[8b] and fungicides.[8c] They are also applied as fire retardants for cotton.[9]

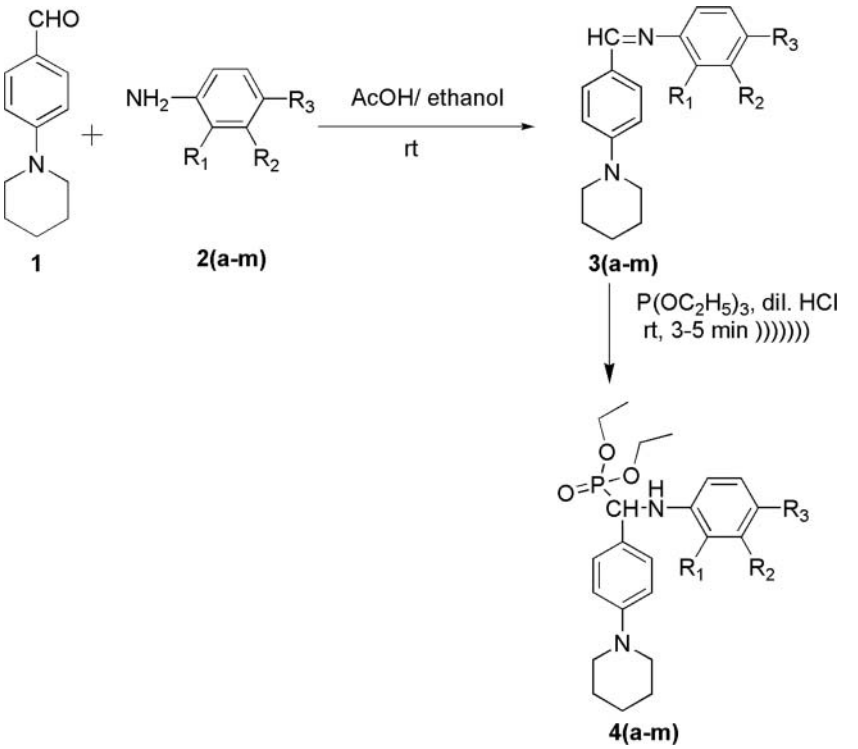
Piperidine and its derivatives are ubiquitous building blocks in the synthesis of pharmaceuticals and fine chemicals. The piperidine scaffold is a structural feature of many alkaloids and drug candidates, and there have been thousands of piperidine compounds mentioned in clinical and preclinical studies.[10] The piperidine ring system is one of the most common structural subunits in natural compounds. Along with this, interest in piperidine-containing structures stems from their widespread occurrence in molecules that exhibited significant biological activities. Several substituted piperidines display important biological properties such as antiviral activity,[11] antidepressant effects,[12] cytotoxic activity,[13] and antimalarial activity.[14]

Ultrasound-accelerated chemical reactions are well known and proceed via the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating.[15] Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities.[16] Therefore ultrasound irradiation has been established as an important technique in organic synthesis. Shorter reaction time, simple experimental procedure, very high yields, increased selectivities, and clean reaction of many ultrasound-induced organic transformations offer additional convenience in the field of synthetic organic chemistry.[17]

In general, α-amino phosphonates are prepared from amines and carbonyl compounds or directly from the imines. However, expensive reagents, long reaction times, high temperatures, and poor yields are the problems in many of these methods. These reactions cannot be carried out in one step by the reaction between a carbonyl compound, an amine, and dialkylphosphite because the amine and water present during imine formation can decompose or deactivate the acid.[18]

RESULTS AND DISCUSSION

In continuation of our work[19] on the development of useful synthesis methodologies, we have synthesized, for the first time, α-aminophosphonates containing highly bioactive piperdine moiety in two steps. In the first step, imine formation of 4-(piperidine-1-yl)benzaldehyde takes place, whereas in the second step this imine is further converted into α-amino phosphonates using triethylphosphite and dilute HCl under ultrasound irradiation. Imines **3a–m** (Scheme 1, Table 1) were prepared at room temperature from 4-(piperidine-1-yl)benzaldehyde and substituted anilines in ethanol using a catalytic amount of acetic acid in excellent yields and were characterized by mass spectra. α-Aminophosphonates



Scheme 1 Synthesis of α-aminophosphonates from imines of 4-(piperidine-1-yl)benzaldehyde.

4a–m (Scheme 1, Table 2) were then prepared in excellent yields by reacting imines **3a–m** with triethylphosphite in the presence of dil. HCl under ultrasound irradiation. Thirteen new compounds were synthesized using this methodology in excellent yields. All the compounds synthesized were unambiguously characterized based on analytical data.

Table 1 Synthesis of imines of 4-(piperidine-1-yl)benzaldehyde

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	Mp (°C)
3a	H	H	H	20	79	130–133
3b	F	H	H	25	81	127–129
3c	H	F	H	25	80	124–126
3d	H	H	F	20	84	119–121
3e	F	F	H	30	88	134–136
3f	F	F	F	25	73	131–133
3g	H	H	CH_3	35	81	132–135
3h	H	OCH_3	H	25	74	163–167
3i	H	H	OCH_3	25	85	155–157
3j	H	H	OC_2H_5	20	82	113–115
3k	H	H	Cl	30	76	135–137
3l	H	NO_2	H	35	80	181–185
3m	H	H	NO_2	25	84	115–118

Table 2 Ultrasound-assisted synthesis of α-amino phosphonates

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	Mp (°C)
4a	H	H	H	5	79	97–99
4b	F	H	H	4	75	184–186
4c	H	F	H	4	80	187–189
4d	H	H	F	3	84	199–201
4e	F	F	H	3	88	215–217
4f	F	F	F	3	73	197–199
4g	H	H	CH_3	5	81	113–115
4h	H	OCH_3	H	4	74	100–103
4i	H	H	OCH_3	5	85	131–134
4j	H	H	OC_2H_5	5	82	89–91
4k	H	H	Cl	3	76	149–151
4l	H	NO_2	H	7	81	221–223
4m	H	H	NO_2	8	78	157–159

CONCLUSION

In conclusion, a new methodology was developed for the synthesis of new α-aminophosphonate derivatives from imines of 4-(piperidine-1-yl)benzaldehyde for first time using dil HCl under ultrasound irradiation. All the reactions were performed under mild reaction conditions and had shorter reaction times and quantitative yields (Table 2). The methodology developed will be of much use to combinatorial chemists. The synthesized α-aminophosphonates show excellent antibacterial activity against Gram-positive and Gram-negative bacteria (see the Supplemental Materials, Table S1, available online).

EXPERIMENTAL

4-(Piperidine-1-yl)benzaldehyde was prepared in the laboratory by the reaction of 4-fluorobenzaldehyde and piperidine in DMF at reflux temperature and was purified by recrystallization in aqueous ethanol. Anilines and triethylphosphite were procured from Dodal Chemical, Aurangabad, India. Acetonitrile, N,N-dimethylformamide (DMF), absolute ethanol, acetic acid, and HCl were procured from S.D. Fine-chem. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. A Bandelin Sonorex (35 kHz) ultrasonic bath was used for ultrasonic irradiation. ^{1}H NMR spectra were recorded on a Mercury Plus Varian in $CDCl_3$/DMSO-d6 at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. Mass spectra were recorded on a Micromass Quattro II using electrospray ionization technique, showing (m+1) peak as a base peak. The test for the purity of products and the progress of the reactions were accomplished by TLC on Merck silica gel plates.

General Procedure: *N*-(4-(Piperidin-1-yl)benzylidene)benzenamine (3a–m)

To a stirred solution of 4-(piperidine-1-yl)benzaldehyde (0.95 g, 5 mmol) in absolute ethanol (10 mL), aniline (0.68 g, 6 mmol) and acetic acid (4 to 5 drops) were added. The progress of the reaction was monitored on TLC (solvent system—hexane:ethyl acetate). After completion of the reaction (20 min), water (20 mL) was added, and the solid thus

obtained was filtered and washed with water, dried in an oven at 50 °C for 5.0 h (1.35 g, yield 79%). ES-MS: m/z 264.9 (m+1).

***N*-(4-(Piperidin-1-yl)benzylidene)benzenamine (3a).** IR (KBr, cm^{-1}): 1609 (C=N), 845 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.57 (s, 2H,$-CH_2$), 1.71 (s, 4H, $-CH_2$), 3.09 (s, 4H, $-CH_2$), 6.92 (d, 2H, Ar-H, J = 8.4 Hz), 7.34 (m, 5H, Ar-H), 7.75 (d, 2H, Ar-H, J = 8.1 Hz), 8.31 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.2, 29.3, 54.2, 116.4, 126.3, 127.3, 127.2, 129.3, 132.2, 152.9, 154.7, 161.2. ES-MS: m/z 264. Elemental analysis: $C_{18}H_{20}N_2$ Calc.: C: 81.78%, H: 7.63%, N: 10.60%; Found: C: 81.23%, H: 7.91%, N: 10.86%.

***N*-(4-(Piperidin-1-yl)benzylidene)-2-fluorobenzenamine (3b).** IR (KBr, cm^{-1}): 1600 (C=N), 1053 (C−F), 820 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.55 (s, 2H, $-CH_2$), 1.75 (s, 4H, $-CH_2$), 3.05 (s, 4H, $-CH_2$), 6.90 (d, 2H, Ar-H, J = 8.1 Hz), 7.13 (dd, 1H, Ar-H, J = 8 Hz, J = 2.2 Hz), 7.15 (m, 1H, Ar-H), 7.25 (dd, 1H, Ar-H, J = 8.1 Hz, J = 2.3 Hz), 7.31 (m, 1H, Ar-H), 7.61 (d, 2H, Ar-H, J = 8.5 Hz), 8.35 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.5, 29.8, 54.1, 115.3, 117.9, 124.5, 125.7, 127.8, 130.4, 132.1, 142.3, 153.5, 156.8, 163.9. ES-MS: m/z 282. Elemental analysis: $C_{18}H_{19}FN_2$ Calc.: C: 76.57%, H: 6.78%, N: 9.92%; Found: C: 76.21%, H: 6.84%, N: 10.01%.

***N*-(4-(Piperidin-1-yl)benzylidene)-3-fluorobenzenamine (3c).** IR (KBr, cm^{-1}): 1615 (C=N), 1051 (C−F), 811 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.53 (s, 2H, $-CH_2$), 1.78 (s, 4H, $-CH_2$), 3.06 (s, 4H, $-CH_2$), 6.52 (d, 2H, Ar-H, J = 8.7 Hz), 7.11 (s, 1H, Ar-H), 7.13 (m, 2H, Ar-H), 7.26 (t, 1H, Ar-H, J = 8.1 Hz), 7.67 (d, 2H, Ar-H, J = 8.3 Hz), 8.34 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.1, 29.7, 54.8, 111.4, 115.8, 116.1, 119.3, 125.1, 131.4, 133.9, 152.1, 156.5, 161.3, 165.4. ES-MS: m/z 282. Elemental analysis: $C_{18}H_{19}FN_2$ Calc.: C: 76.57%, H: 6.78%, N: 9.92%; Found: C: 76.24%, H: 6.94%, N: 10.14%.

***N*-(4-(Piperidin-1-yl)benzylidene)-4-fluorobenzenamine (3d).** IR (KBr, cm^{-1}): 1620 (C=N), 1056 (C−F), 780 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.54 (s, 2H,$-CH_2$), 1.77 (s, 4H, $-CH_2$), 3.11 (s, 4H, $-CH_2$), 6.64 (d, 2H, Ar-H, J = 8.3 Hz), 7.17 (d, 2H, Ar-H, J = 8 Hz), 7.34 (d, 2H, Ar-H, J = 8.6 Hz), 7.67 (d, 2H, Ar-H, J = 8.4 Hz), 8.31 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.3, 29.1, 54.5, 115.4, 118.8, 124.1, 125.9, 132.4, 149.2, 135.4, 162.6, 164.7. ES-MS: m/z 282. Elemental analysis: $C_{18}H_{19}FN_2$ Calc.: C: 76.57%, H: 6.78%, N: 9.92%; Found: C: 76.33%, H: 6.81%, N: 9.98%.

***N*-(4-(Piperidin-1-yl)benzylidene)-2,3-difluorobenzenamine (3e).** IR (KBr, cm^{-1}): 1618 (C=N), 1040 (C−F), 840 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.51 (s, 2H,$-CH_2$), 1.73 (s, 4H, $-CH_2$), 3.14 (s, 4H, $-CH_2$), 6.92 (d, 2H, Ar-H, J = 8.1 Hz), 7.09 (dd, 1H, Ar-H, J = 8.4 Hz, J = 2.3 Hz), 7.14 (dd, 1H, Ar-H, J = 8.2 Hz, J = 2.4 Hz), 7.21 (t, 1H, Ar-H, J = 8.7 Hz), 7.64 (d, 2H, Ar-H, J = 8.5 Hz), 8.33 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.1, 29.9, 54.1, 115.4, 116.6, 121.3, 124.6, 128.7, 132.1, 143.3, 144.5, 151.9, 153.4, 162.3. ES-MS: m/z 300. Elemental analysis: $C_{18}H_{18}F_2N_2$ Calc.: C: 71.98%, H: 6.04%, N: 9.33%; Found: C: 71.45%, H: 6.21%, N: 9.47%.

***N*-(4-(Piperidin-1-yl)benzylidene)-2,3,4-trifluorobenzenamine (3f).** IR (KBr, cm^{-1}): 1650 (C=N), 1045 (C−F), 815 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.55 (s, 2H,$-CH_2$), 1.78 (s, 4H, $-CH_2$), 3.09 (s, 4H, $-CH_2$), 6.52 (d, 2H, Ar-H, J = 8.5 Hz), 6.84 (d, 1H, Ar-H, J = 8.2 Hz), 7.07 (d, 1H, Ar-H, J = 8.6 Hz), 7.66 (d, 2H, Ar-H, J = 7.8 Hz), 8.31 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.4, 29.5, 54.3, 115.6, 116.4, 122.5, 125.9, 131.8, 138.1, 142.4, 145.3, 151.8, 156.9, 160.3. ES-MS: m/z

318. Elemental analysis: $C_{18}H_{17}F_3N_2$ Calc.: C: 67.91%, H: 5.38%, N: 8.80%; Found: C: 67.74%, H: 5.43%, N: 8.93%.

***N*-(4-(Piperidin-1-yl)benzylidene)-4-methylbenzenamine (3g).** IR (KBr, cm^{-1}): 1610 (C=N), 801 (Ar-H). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.51 (s, 2H,$-CH_2$), 1.79 (s, 4H, $-CH_2$), 2.54 (s, 3H, CH_3), 3.02 (s, 4H, $-CH_2$), 6.51 (d, 2H, Ar-H, J = 8.3 Hz), 7.21 (d, 2H, Ar-H, J = 8.1 Hz), 7.24 (d, 2H, Ar-H, J = 8.3 Hz), 7.61 (d, 2H, Ar-H, J = 8.2 Hz), 8.31 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 25.4, 26.6, 29.8, 54.1, 116.1, 123.4, 124.2, 131.8, 132.7, 138.9, 151.7, 153.6, 161.5. ES-MS: m/z 278. Elemental analysis: $C_{19}H_{22}N_2$ Calc.: C: 81.97%, H: 7.97%, N: 10.06%; Found: C: 81.62%, H: 8.14%, N: 10.24%.

***N*-(4-(Piperidin-1-yl)benzylidene)-3-methoxybenzenamine (3h).** IR (KBr, cm^{-1}): 2810 ($O-CH_3$), 1617 (C=N), 745 (Ar-H). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.53 (s, 2H,$-CH_2$), 1.77 (s, 4H, $-CH_2$), 3.07 (s, 4H, $-CH_2$), 3.94 (s, 3H, $-OCH_3$), 6.63 (d, 2H, Ar-H, J = 8.6 Hz), 6.91 (s, 1H, Ar-H), 6.95 (dd, 2H, Ar-H, J = 8.1 Hz, J = 2.2 Hz), 7.32 (t, 1H, Ar-H, J = 8.5 Hz) 7.69 (d, 2H, Ar-H, J = 8.1 Hz), 8.34 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.8, 29.9, 54.5, 57.6, 111.3, 114.2, 115.6, 116.7, 124.4, 131.9, 133.5, 152.5, 155.6, 161.7, 163.8. ES-MS: m/z 294. Elemental analysis: $C_{19}H_{22}N_2O$ Calc.: C: 77.52%, H: 7.53%, N: 9.52%; Found: C: 77.23%, H: 7.61%, N: 9.63%.

***N*-(4-(Piperidin-1-yl)benzylidene)-4-methoxybenzenamine (3i).** IR (KBr, cm^{-1}): 2840 ($O-CH_3$), 1607 (C=N), 790 (Ar-H). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.59 (s, 2H,$-CH_2$), 1.79 (s, 4H, $-CH_2$), 3.01 (s, 4H, $-CH_2$), 3.94 (s, 3H, $-OCH_3$), 6.63 (d, 2H, Ar-H, J = 8.6 Hz), 6.91 (d, 2H, Ar-H, J = 8.7 Hz), 7.41 (d, 2H, Ar-H, J = 8.7 Hz) 7.61 (d, 2H, Ar-H, J = 8.1 Hz), 8.33 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.9, 29.1, 54.6, 57.6, 111.3, 114.3, 115.6, 116.7, 124.4, 131.9, 133.5, 152.5, 155.6, 161.7, 163.8. ES-MS: m/z 294. Elemental analysis: $C_{19}H_{22}N_2O$ Calc.: C: 77.52%, H: 7.53%, N: 9.52%; Found: C: 77.19%, H: 7.71%, N: 9.61%.

***N*-(4-(Piperidin-1-yl)benzylidene)-4-ethoxybenzenamine (3j).** IR (KBr, cm^{-1}): 1604 (C=N), 825 (Ar-H). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.41 (t, 3H, $-CH_3$), 1.62 (s, 2H,$-CH_2$), 1.81 (s, 4H, CH_2), 3.91 (s, 4H, $-CH_2$), 4.01 (q, 2H, $-OCH_2$), 6.91 (d, 2H, Ar-H, J = 8.3 Hz), 6.93 (d, 2H, Ar-H, J = 7.9 Hz), 7.41 (d, 2H, Ar-H, J = 8.1 Hz), 7.92 (d, 2H, Ar-H, J = 8.1 Hz), 8.48 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.4, 26.8, 29.7, 54.8, 65.7, 115.4, 116.3, 123.8, 124.7, 133.4, 143.3, 147.1, 159.2, 162.8. ES-MS: m/z 308. Elemental analysis: $C_{20}H_{24}N_2O$ Calc.: C: 77.89%, H: 7.84%, N: 9.08%; Found: C: 77.64%, H: 7.97%, N: 9.23%.

***N*-(4-(Piperidin-1-yl)benzylidene)-4-chlorobenzenamine (3k).** IR (KBr, cm^{-1}): 1620 (C=N), 810 (Ar-H), 728 (C−Cl). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.67 (s,2H, CH_2),1.83 (s, 4H, CH_2), 3.33 (s, 4H, $-CH_2$), 6.92 (d, 2H, Ar-H, J = 8.4 Hz), 7.12 (d, 2H, Ar-H, J = 8.7 Hz), 7.31 (d, 2H, Ar-H, J = 7.3 Hz), 7.75 (d, 2H, Ar-H, J = 8.1 Hz), 8.28 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.1, 29.2, 54.4, 116.4, 124.5, 125.5, 131.1, 133.5, 134.7, 152.8, 154.5, 163.8. ES-MS: m/z 298.5. Elemental analysis: $C_{18}H_{19}ClN_2$ Calc.: C: 72.35%, H: 6.41%, N: 9.37%; Found: C: 72.63%, H: 6.55%, N: 9.45%.

***N*-(4-(Piperidin-1-yl)benzylidene)-3-nitrobenzenamine (3l).** IR (KBr, cm^{-1}): 1618 (C=N), 1345 ($C-NO_2$), 830 (Ar-H). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.59 (s, 2H,$-CH_2$), 1.88 (s, 4H, $-CH_2$), 3.91 (s, 4H, $-CH_2$), 6.57 (d, 2H, Ar-H, J = 8.1 Hz), 7.54 (d, 2H, Ar-H, J = 8.3 Hz), 7.62 (t, 1H, Ar-H, J = 8.7 Hz), 7.91 (dd, 1H, Ar-H, J = 8.4 Hz, J = 2.3 Hz), 8.27 (s, 1H, Ar-H), 8.31 (dd, 1H, Ar-H, J = 8.2 Hz, J = 2.5 Hz), 8.30 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.2, 29.3, 54.5, 115.4, 118.9,

121.7, 124.3, 129.3, 131.4, 133.1, 151.9, 153.2, 156.7, 163.4. ES-MS: m/z 309. Elemental analysis: $C_{18}H_{19}N_3O_2$ Calc.: C: 69.88%, H: 6.19%, N: 13.58%; Found: C: 69.56%, H: 6.25%, N: 13.75%.

***N*-(4-(piperidin-1-yl)benzylidene)-4-nitrobenzenamine: (3m).** IR (KBr, cm^{-1}): 1610 (C=N), 1333 (C−NO_2), 770 (Ar-H). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.72 (s, 2H,−CH_2), 1.82 (s, 4H, −CH_2), 3.95 (s, 4H, −CH_2), 6.61 (d, 2H, Ar-H, J = 8.0 Hz), 7.56 (d, 2H, Ar-H, J = 7.9 Hz), 7.61 (d, 2H, Ar-H, J = 8.4 Hz), 8.31 (d, 2H, Ar-H, J = 8.4 Hz, J = 2.5 Hz), 8.41 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 26.5, 29.4, 54.7, 116.3, 123.4, 124.3, 125.9, 132.7, 148.6, 153.7, 161.5, 163.6. ES-MS: m/z 309. Elemental analysis: $C_{18}H_{19}N_3O_2$ Calc.: C: 69.88%, H: 6.19%, N: 13.58%; Found: C: 69.61%, H: 6.27%, N: 13.64%.

Diethyl(phenylamino)(4-(piperidin-1-yl)phenyl)methylphosphonate (4a–m)

To a mixture of *N*-(4-(piperidin-1-yl)benzylidene)benzenamine (0.001 mol) and triethylphosphite (0.0035 mol), a catalytic amount of dilute hydrochloric acid (5 mol%) was added. Then the reaction mixture was irradiated under ultrasound waves. The progress of the reaction was monitored on TLC using hexane:ethyl acetate (8:2) as the solvent system. After the completion of reaction, ice cold water was added to it, and the mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Then the solvent was evaporated under reduced vacuum pressure.

4a: IR (KBr, cm^{-1}): 1245 (P=O), 1045 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.17 (t, 3H, −CH_3), 1.28 (t, 3H, −CH_3), 1.58 (s, 2H,−CH_2), 1.78 (s, 4H, −CH_2), 3.18 (s, 4H, −CH_2), 3.67 (d, 1H, NH−C<u>H</u>−P=O), 3.97 (m, 2H, O−CH_2), 4.15 (m, 2H, O−CH_2), 5.01 (d, 1H,CH−N<u>H</u>−Ph), 6.57 (d, 2H, Ar-H), 6.65 (t, 1H, Ar-H), 6.97 (s, 2H, Ar-H), 7.14 (t, 2H, Ar-H), 7.36 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 14.8, 25.5, 25.9, 52.4, 56.5, 62.3, 113.5, 114.3, 117.6, 125.9, 127.6, 129.5, 148.2. ES-MS: m/z 402. Elemental analysis: $C_{22}H_{31}N_2O_3P$ Calc.: C: 65.65%, H: 7.76%, N: 6.96%; Found: C: 65.72%, H: 7.93%, N: 7.04%.

4b: IR (KBr, cm^{-1}): 1234 (P=O), 1032 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.15 (t, 3H, −CH_3), 1.25 (t, 3H, −CH_3), 1.54 (s, 2H,−CH_2), 1.76 (s, 4H, −CH_2), 3.11 (s, 4H, −CH_2), 3.76 (d, 1H, NH−C<u>H</u>−P=O), 4.17 (m, 2H, O−C<u>H</u>$_2$−CH_3), 4.22 (m, 2H, O−C<u>H</u>$_2$−CH_3), 5.03 (d, 1H,CH−N<u>H</u>−Ph), 6.61 (d, 2H, Ar-H), 6.92 (dd, 1H, Ar-H), 7.01 (dd, 1H, Ar-H), 7.11 (d, 2H, Ar-H), 7.33 (dd, 1H, Ar-H), 7.41 (m, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 13.6, 25.4, 26.3, 54.2, 55.6, 63.2, 115.3, 117.2, 120.1, 122.3, 129.2, 130.1, 133.9, 136.1, 149.3, 157.8. ES-MS: m/z 420. Elemental analysis: $C_{22}H_{30}FN_2O_3P$ Calc.: C: 62.84%, H: 7.19%, N: 6.66%; Found: C: 62.92%, H: 7.27%, N: 6.68%.

4c: IR (KBr, cm^{-1}): 1230 (P=O), 1022 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.17 (t, 3H, −CH_3), 1.27 (t, 3H, −CH_3), 1.51 (s, 2H,−CH_2), 1.78 (s, 4H, −CH_2), 3.09 (s, 4H, −CH_2), 3.91 (d, 1H, NH−C<u>H</u>−P=O), 4.13 (m, 2H, O−C<u>H</u>$_2$−CH_3), 4.21 (m, 2H, O−C<u>H</u>$_2$−CH_3), 5.01 (d, 1H,CH−N<u>H</u>−Ph), 6.70 (d, 2H, Ar-H), 6.79 (s, 1H, Ar-H), 6.91 (dd, 1H, Ar-H), 6.96 (d, 1H, Ar-H), 7.04 (d, 2H, Ar-H), 7.15 (dd, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.3, 26.2, 27.1, 54.2, 58.6, 63.1, 105.1, 106.3, 116.3, 123.4, 128.7, 129.7, 134.2, 149.6, 151.2, 165.3. ES-MS: m/z 420. Elemental analysis: $C_{22}H_{30}FN_2O_3P$ Calc.: C: 62.84%, H: 7.19%, N: 6.66%; Found: C: 62.88%, H: 7.25%, N: 6.69%.

4d: IR (KBr, cm^{-1}): 1224 (P=O), 1033 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.16 (t, 3H, $-CH_3$), 1.20 (t, 3H, $-CH_3$), 1.53 (s, 2H,$-CH_2$), 1.81 (s, 4H, $-CH_2$), 3.21 (s, 4H, $-CH_2$), 4.03 (d, 1H, NH−CH−P=O), 3.98 (m, 2H, O−CH_2−CH_3), 4.13 (m, 2H, O−CH_2−CH_3), 4.98 (d, 1H,CH−NH−Ph), 6.67 (d, 2H, Ar-H), 7.01 (d, 2H, Ar-H), 7.16 (d, 2H, Ar-H), 7.24 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.4, 27.2, 29.5, 54.2, 59.5, 65.3, 116.3, 121.1, 125.3, 135.7, 137.9, 145.3, 151.4, 154.8. ES-MS: m/z 420. Elemental analysis: $C_{22}H_{30}FN_2O_3P$ Calc.: C: 62.84%, H: 7.19%, N: 6.66%; Found: C: 62.89%, H: 7.21%, N: 6.71%.

4e: IR (KBr, cm^{-1}): 1232 (P=O), 1035 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.15 (t, 3H, $-CH_3$), 1.27 (t, 3H, $-CH_3$), 1.61 (s, 2H,$-CH_2$), 1.77 (s, 4H, $-CH_2$), 3.13 (s, 4H, $-CH_2$), 4.11 (d, 1H, NH−CH−P=O), 4.23 (m, 2H, O−CH_2−CH_3), 4.27 (m, 2H, O−CH_2−CH_3), 5.07 (d, 1H,CH−NH−Ph), 6.56 (dd, 1H, Ar-H), 6.78 (dd, 1H, Ar-H), 6.91 (d, 2H, Ar-H), 7.08 (dd, 1H, Ar-H), 7.23 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.7, 26.3, 30.9, 53.1, 61.2, 63.5, 108.5, 116.3, 118.2, 127.5, 128.6, 129.7, 142.1, 146.2, 151.3, 154.8. ES-MS: m/z 438. Elemental analysis: $C_{22}H_{29}F_2N_2O_3P$ Calc.: C: 60.27%, H: 6.67%, N: 6.39%; Found: C: 60.31%, H: 6.74%, N: 6.41%.

4f: IR (KBr, cm^{-1}): 1227 (P=O), 1031 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.13 (t, 3H, $-CH_3$), 1.25 (t, 3H, $-CH_3$), 1.59 (s, 2H,$-CH_2$), 1.71 (s, 4H, $-CH_2$), 3.07 (s, 4H, $-CH_2$), 4.11 (d, 1H, NH−CH−P=O), 4.27 (m, 2H, O−CH_2−CH_3), 4.31 (m, 2H, O−CH_2−CH_3), 5.09 (d, 1H,CH−NH−Ph), 6.46 (d, 1H, Ar-H), 6.79 (d, 2H, Ar-H), 6.89 (d, 1H, Ar-H), 7.27 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.3, 27.4, 31.5, 52.6, 62.2, 64.8, 115.3, 116.5, 118.2, 127.3, 128.5, 130.4, 141.6, 143.7, 147.3, 151.9. ES-MS: m/z 456. Elemental analysis: $C_{22}H_{28}F_3N_2O_3P$ Calc.: C: 57.89%, H: 6.18%, N: 6.14%; Found: C: 57.91%, H: 6.21%, N: 6.18%.

4g: IR (KBr, cm^{-1}): 1237 (P=O), 1028 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.12 (t, 3H, $-CH_3$), 1.26 (t, 3H, $-CH_3$), 1.57 (s, 2H,$-CH_2$), 1.73 (s, 4H, $-CH_2$), 2.78 (s, 3H, CH_3), 3.12 (s, 4H, $-CH_2$), 4.17 (d, 1H, NH−CH−P=O), 4.24 (m, 2H, O−CH_2−CH_3), 4.31 (m, 2H, O−CH_2−CH_3), 5.03 (d, 1H,CH−NH−Ph), 6.44 (d, 2H, Ar-H), 6.78 (d, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 7.31 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.5, 25.2, 27.9, 29.3, 54.1, 59.9, 60.4, 115.3, 116.2, 127.4, 128.7, 130.9, 132.1, 146.3, 149.2. ES-MS: m/z 416. Elemental analysis: $C_{23}H_{33}N_2O_3P$ Calc.: C: 66.33%, H: 7.99%, N: 6.73%; Found: C: 66.37%, H: 8.03%, N: 6.77%.

4h: IR (KBr, cm^{-1}): 1235 (P=O), 1035 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.13 (t, 3H, $-CH_3$), 1.21 (t, 3H, $-CH_3$), 1.61 (s, 2H,$-CH_2$), 1.82 (s, 4H, $-CH_2$), 3.09 (s, 4H, $-CH_2$), 3.73 (s, 3H, $-OCH_3$), 3.98 (d, 1H, NH−CH−P=O), 4.08 (m, 2H, O−CH_2−CH_3), 4.12 (m, 2H, O−CH_2−CH_3), 5.03 (d, 1H,CH−NH−Ph), 6.31 (s, 1H, Ar-H), 6.43 (dd, 1H, Ar-H, J = 8.1 Hz, J = 2.3 Hz), 6.51 (dd, 1H, Ar-H, J = 8.4 Hz, J = 2.1 Hz), 6.96 (d, 2H, Ar-H, J = 7.9 Hz), 7.13 (d, 2H, Ar-H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.4, 23.3, 27.5, 30.3, 53.2, 57.9, 59.3, 65.5, 101.6, 105.1, 109.2, 117.4, 127.5, 129.6, 133.4, 149.3, 151.1, 163.6. ES-MS: m/z 432. Elemental analysis: $C_{23}H_{33}N_2O_4P$ Calc.: C: 63.87%, H: 7.69%, N: 6.48%; Found: C: 63.92%, H: 7.73%, N: 6.51%.

4i: IR (KBr, cm^{-1}): 1237 (P=O), 1028 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.17 (t, 3H, $-CH_3$), 1.26 (t, 3H, $-CH_3$), 1.56 (s, 2H,$-CH_2$), 1.79 (s, 4H, $-CH_2$), 3.11 (s, 4H, $-CH_2$), 3.92 (s, 3H, $-OCH_3$), 4.01 (d, 1H, NH−CH−P=O), 4.16 (m, 2H, O−CH_2−CH_3), 4.21 (m, 2H, O−CH_2−CH_3), 5.01 (d, 1H,CH−NH−Ph), 6.49 (d, 2H, Ar-H), 6.64 (d, 2H, Ar-H), 6.89 (d, 2H, Ar-H), 7.14 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.6, 24.7, 27.9, 54.2, 57.1, 58.3, 64.6, 116.9, 117.1, 118.8, 127.1, 129.4,

141.5, 149.2, 151.7. ES-MS: m/z 432. ES-MS: m/z 432. Elemental analysis: $C_{23}H_{33}N_2O_4P$ Calc.: C: 63.87%, H: 7.69%, N: 6.48%; Found: C: 63.89%, H: 7.71%, N: 6.50%.

4j: IR (KBr, cm^{-1}): 1241 (P=O), 1032 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.13 (t, 3H, $-CH_3$), 1.21 (t, 3H, $-CH_3$), 1.29 (t, 3H, $-CH_3$), 1.51 (s, 2H,$-CH_2$), 1.77 (s, 4H, $-CH_2$), 3.17 (s, 4H, $-CH_2$), 3.99 (d, 1H, NH−CH−P=O), 4.13 (m, 2H, O−CH_2−CH_3), 4.28 (m, 2H, O−CH_2−CH_3), 5.04 (d, 1H,CH−NH−Ph), 6.44 (d, 2H, Ar-H, J=8.2 Hz), 6.59 (d, 2H, Ar-H, J = 7.8 Hz), 6.97 (d, 2H, Ar-H, J = 8.1 Hz), 7.11 (d, 2H, Ar-H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.2, 25.5, 27.8, 54.3, 59.3, 64.6, 67.8, 115.4, 115.5, 118.3, 127.3, 130.4, 141.6, 147.7, 149.2. ES-MS: m/z 446. Elemental analysis: $C_{24}H_{35}N_2O_4P$ Calc.: C: 64.56%, H: 7.90%, N: 6.27%; Found: C: 65.72%, H: 7.93%, N: 7.04%.

4k: IR (KBr, cm^{-1}): 1245 (P=O), 1025 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.16 (t, 3H, $-CH_3$), 1.23 (t, 3H, $-CH_3$), 1.58 (s, 2H,$-CH_2$), 1.74 (s, 4H, $-CH_2$), 3.13 (s, 4H, $-CH_2$), 4.05 (d, 1H, NH−CH−P=O), 4.14 (m, 2H, O−CH_2−CH_3), 4.21 (m, 2H, O−CH_2−CH_3), 5.07 (d, 1H,CH−NH−Ph), 6.49 (d, 2H, Ar-H), 6.63 (d, 2H, Ar-H), 7.09 (d, 2H, Ar-H), 7.23 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.7, 26.4, 27.3, 53.4, 57.3, 63.7, 115.7, 116.3, 124.1, 127.8, 129.9, 131.2, 147.3, 151.5. ES-MS: m/z 436.5. Elemental analysis: $C_{22}H_{30}ClN_2O_3P$ Calc.: C: 60.48%, H: 6.92%, N: 6.41%; Found: C: 60.54%, H: 6.98%, N: 6.47%.

4l: IR (KBr, cm^{-1}): IR (KBr, cm^{-1}): 1245 (P=O), 1045 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.17 (t, 3H, $-CH_3$), 1.23 (t, 3H, $-CH_3$), 1.57(s, 2H,$-CH_2$), 1.77 (s, 4H, $-CH_2$), 3.17 (s, 4H, $-CH_2$), 3.93 (d, 1H, NH−CH−P=O), 4.07 (m, 2H, O−CH_2−CH_3), 4.14 (m, 2H, O−CH_2−CH_3), 5.01 (d, 1H,CH−NH−Ph), 6.59 (d, 2H, Ar-H), 6.99 (dd, 1H, Ar-H), 7.10 (d, 2H, Ar-H), 7.35 (dd, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 8.05 (dd, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.4, 26.6, 27.9, 54.3, 58.7, 63.5, 110.3, 115.3, 116.1, 121.5, 127.9, 129.2, 132.5, 143.5, 149.6, 151.2. ES-MS: m/z 447. Elemental analysis: $C_{22}H_{30}N_3O_5P$ Calc.: C: 59.05%, H: 6.76%, N: 9.39%; Found: C: 59.09%, H: 6.79%, N: 9.41%.

4m: 1247 (P=O), 1031 (P−O−C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.14 (t, 3H, $-CH_3$), 1.21 (t, 3H, $-CH_3$), 1.55 (s, 2H,$-CH_2$), 1.71 (s, 4H, $-CH_2$), 3.15 (s, 4H, $-CH_2$), 3.96 (d, 1H, NH−CH−P=O), 4.14 (m, 2H, O−CH_2−CH_3), 4.23 (m, 2H, O−CH_2−CH_3), 5.06 (d, 1H,CH−NH−Ph), 6.58 (d, 2H, Ar-H), 6.96 (d, 2H, Ar-H), 7.11 (d, 2H, Ar-H), 8.23 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 15.7, 26.3, 27.8, 54.9, 56.8, 63.2, 115.3, 116.7, 124.5, 127.9, 129.1, 139.7, 151.4, 156.3. ES-MS: m/z 447. Elemental analysis: $C_{22}H_{30}N_3O_5P$ Calc.: C: 59.05%, H: 6.76%, N: 9.39%; Found: C: 59.11%, H: 6.82%, N: 9.44%.

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