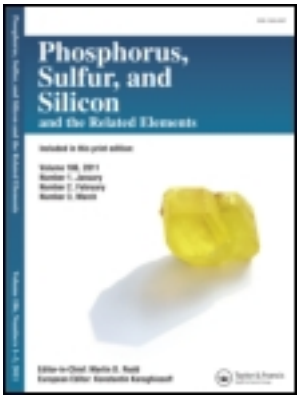

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Synthesis and Application of N-Tosyl Piperidinyl-Containing α-Aminophosphonates

Zhifu Jiang [a], Jian Zhao [a], Beibei Gao [a], Shuo Chen [a], Wenyan Qu [a], Xiangdong Mei [a], Changhui Rui [a], Jun Ning [a] & Dongmei She [a]
[a] Key Laboratory of Pesticide Chemistry and Application, MOA, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing, China
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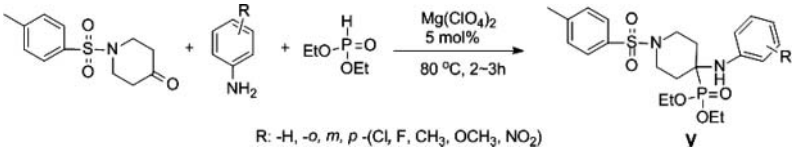
SYNTHESIS AND APPLICATION OF *N*-TOSYL PIPERIDINYL-CONTAINING α-AMINOPHOSPHONATES

Zhifu Jiang, Jian Zhao, Beibei Gao, Shuo Chen, Wenyan Qu, Xiangdong Mei, Changhui Rui, Jun Ning, and Dongmei She

Key Laboratory of Pesticide Chemistry and Application, MOA, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing, China

GRAPHICAL ABSTRACT



Abstract *A series of novel (4′-tosyl) piperidin-4-yl containing α-aminophosphonates were synthesized by a one-pot reaction, efficiently catalyzed by magnesium perchlorate, under solvent-free conditions from 1-tosylpiperidin-4-one, substituted aromatic amines, and diethyl phosphite (DEP). The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and HRMS spectroscopy. A single-crystal X-ray structure of diethyl 4-(2-chlorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**2a**) was obtained, and some of the title compounds displayed insecticidal activities against Plutella xylostella.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files*: Additional figures and tables.

Keywords Tosyl; piperidine; magnesium perchlorate; α-aminophosphonates; synthesis; crystal structure

INTRODUCTION

Due to their diverse and interesting biological and biochemical properties, aminophosphonates are of considerable current interest. This class of compounds is mainly applied as plant growth regulators, herbicides, fungicidal, antiplant virus, enzyme inhibitors, and anticancer agents.[1] Such an impressive array of applications has recently stimulated a growing amount of research on the synthesis of α-aminophosphonates and rendered the

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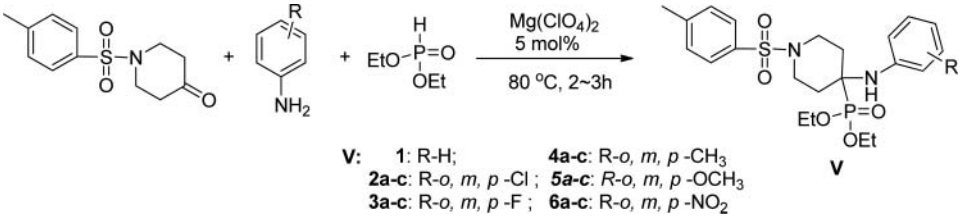
Address correspondence to Dongmei She, Key Laboratory of Pesticide Chemistry and Application, MOA, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Yuanmingyuan West Road 2, Beijing 100193, China. E-mail: dmshe2000@yahoo.com.cn

α-aminophosphonate moiety the status of a novel pharmacophore in the context of drug design.[1,2]

The *N*-substitutent piperidine moiety is a key ingredient, as it appears in the structure of many alkaloid natural products and drugs.[3] In addition, cyclic or heterocyclic rings introduced into the molecular skeleton increase their rigidity and modify electronic effects.[4] Therefore, many cyclic α-amino-phosphonates or -phosphonic acids have been prepared, such as derivatives of α-amino(4-piperidine)phosphonic acid, as well as their 4-pyran, 4-thiopyran, 3-piperidine,[4] and cycloalkyl analogues.[5] However, very few examples of *N*-substitutent piperidine α-aminophosphonic acids or the corresponding phosphonates have been reported in the literature; only *N*-Me, -Boc, -allyl, -Bn, and -Cbz piperidine α-aminophosphonates are described.[4,6] In the synthetic approach to the *N*-Boc example, the Kabachnick-Fields reaction was used from *N*-Boc piperidone, benzylamine and diethyl phosphite (DEP), to provide α-aminophosphonate with 99% yield, but the metal tetra(*tert*-butyl)phthalocyanine complex ^{t}PcAlCl as catalyst is not easily accessible.

N-tosyl piperidinyl-containing heterocycles are subunits of many biologically active pharmaceuticals and reported to exhibit a wide range of bioactivities, including nervous system agents, cardiovascular agents, antitumor, anti-infective, and anti-inflammatory activities.[7]

Magnesium perchlorate has been shown to be very active in promoting a variety of reactions.[8] In 2007, it was reported as an extremely efficient catalyst for the formation of α-aminophosphonate by a one-pot, three-component reaction under solvent-free conditions.[9] In this paper, magnesium perchlorate is explored as catalyst and the reaction involving 1-tosylpiperidine-4-one, aromatic amines with an electron-donating or –withdrawing substituent, and DEP are carried out under solvent-free conditions. Thus, compounds **1–6** were synthesized and a single crystal structure of compound **2a** was obtained. All the novel compounds were analyzed by IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and HRMS spectroscopy. Preliminary tests showed that some of these compounds, to some extent, have insecticidal activities against *Plutella xylostella*. The synthetic route of novel compounds is shown in Scheme 1.



Scheme 1

RESULTS AND DISCUSSION

To determine the best operative experimental conditions, the reaction of 1-tosylpiperidine-4-one (**A**), 4-nitroaniline (**B**) as an electron-deficient amine, DEP was considered as the model (Table 1). The best reaction conditions required the use of a 5% mol $Mg(ClO_4)_2$ and a 2 equivalent of DEP at 80 °C to obtain a good conversion in the desired product without any traces of byproducts. For the same substituent, the yield is not obviously dependent on the position on the benzene ring of the aromatic

Table 1 Reaction of **A**, **B**, and DEP under various conditions[a]

Entry	Catalyst	Solvent	T(°C)	Time(h)	Yield[b,c] (%)
1		neat	rt	4	nil[d]
2		neat	80	2	nil[d]
3	$Mg(ClO_4)_2$	neat	rt	4	nil[d]
4	$Mg(ClO_4)_2$	neat	80	2	77

[a]**A** (2.5 mmol) was treated with **B** (2.5 mmol) and DEP (5.0 mmol) in the presence of the catalyst (5 mol%) (except for entries 1 and 2) under solvent-free conditions. [b]Yield of the isolated and purified **6c**. [c]The product was characterized by the IR, ^{1}H, ^{13}C and ^{31}P NMR, and HRMS. [d]The unreacted starting materials remained unchanged (TLC) and **A** was still solid (except for entry 2).

amine. But it is affected by the electronic effect of the substituent, and the presence of an electron-withdrawing substituent decreases nucleophilicity, then leading to lower reactivity and yield (Supplemental Materials). We tried to extend the procedure to 2,4-dinitroaniline ($pK_a = -4.30$), but unfortunately the corresponding aminophosphonate was not obtained.

The IR spectra of **1–6** contained absorption bands at 3400–3250 cm^{-1} assigned to the N–H group, at 1240–1220 cm^{-1} corresponding to the P=O group and at 1170–1160 cm^{-1} attributed to the S=O group.

The structural parameters of compound **2a** are presented in Table 2. The molecular structure of the title compound **2a** is shown in Figure 1. The conformation with the *N*-tosyl group being equatorial dominates. Selected bond lengths (Å) and torsional angles (°) are

Table 2 Crystal structure and data refinement parameters for **2a**

Compound	**2a**
Empirical formula	$C_{22}H_{30}ClN_2O_5PS$
Formula weight	500.96
Crystal system/Space group	Monoclinic/P2(1)/*n*
a / Å	14.011(3)
b / Å	11.191(2)
c / Å	17.736(4)
α / °	90
β / °	111.07(3)
γ / °	90
V / Å^3	2595.2(9)
Z	4
D_{calc} (g cm^{-3})	1.282×10^{-9}
μ (mm^{-1})	0.323
Crystal size (mm)	0.40 × 0.40 × 0.20
Color/Shape	Colorless
Temp (K)	293(2)
Theta range for collection	2.20° to 27.24°
Reflections collected	5709
Independent reflections	5709 [R(int) = 0.0502]
Data/restraints/parameters	5709/0/293
Goodness of fit on F^2	1.024
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0637, wR2 = 0.1701
R indices (all data)	R1 = 0.0922, wR2 = 0.1886
Largest difference peak/hole	0.685 and –0.514 e. Å^{-3}

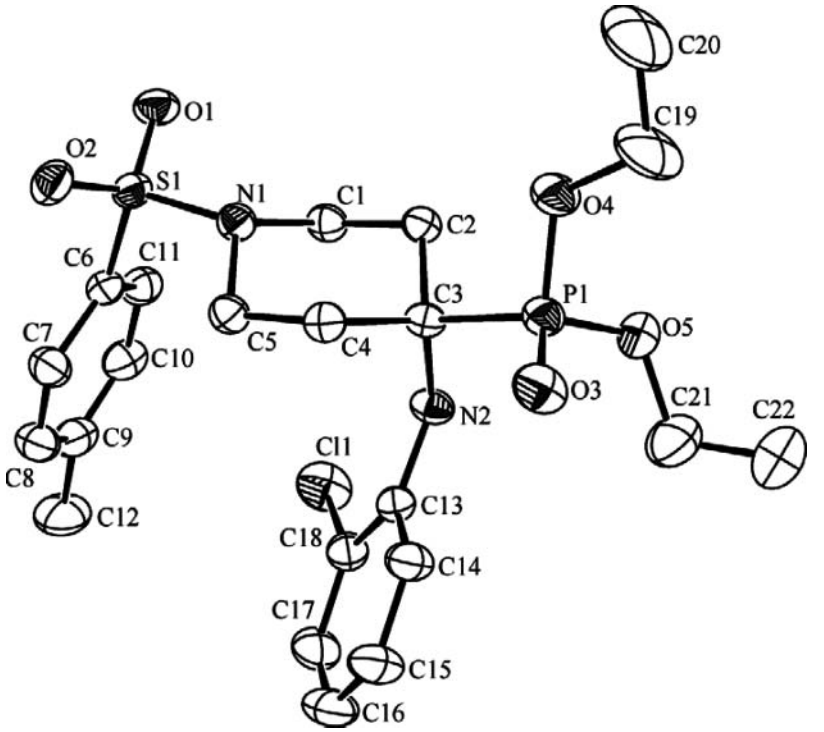


Figure 1 X-ray diffraction analysis of compound **2a**.

P1–C3 1.875(3), C1–N1 1.498(3), C5–N1 1.487(3), N1–S1 1.669(2), and C1 C2 C3 P1 –174.94(18), C2 C1 N1 S1 164.28(17), while in a similar structure in the literature these are P–C3 1.816(2), N–C1 1.436(3), N–C5 1.455(3), N–S 1.621(2), P C3 C4 C5 –95.0, and S N C5 C4 148.5.[10]

The ^{1}H NMR spectra of **1–6** show signals for chemically nonequivalent piperidine ring. The signals for the methylene protons at C_2 and C_6 position appear at δ 2.64–2.72 (m) and 3.61 (br d); the complex multiplets for the methylene protons at C_3 and C_5 position appear at δ 2.15–2.22. A broad singlet at δ 2.50–4.00 corresponds to the amino group.

The ^{13}C NMR spectra of **1–6** show signals at δ 29–31 ($^{2}J_{PC}$ = 1–3 Hz), 40–42 ($^{3}J_{PC}$ = 10–13 Hz), 54–56 ($^{1}J_{PC}$ = 155–175 Hz) for the piperidine ring at C_3 or C_5, C_2 or C_6, and C_4, respectively. Signals for the nonisochronous ethoxy groups appear as two doublets at δ 16 ($^{3}J_{PC}$ = 5–6 Hz, CH_3) and doublets at δ 62–63 ($^{2}J_{PC}$ = 7–8 Hz, OCH_2). The other signals in the ^{1}H and ^{13}C NMR spectra of α-aminophosphonates are consistent with the carbon framework structures of the starting ketones. The ^{31}P NMR spectra of **1–6** exhibit signals at 23.75–28.27 relating to the diethyl phosphonate group.

As indicated in Supplemental Materials, some of the title compounds displayed insecticidal activities against *Plutella xylostella*. But the activities of these compounds were much lower than Fipronil. Thus, different substituents in each series did not have great impact on the activity. The main reason was probably due to the weak interaction with three binding subsites in the GABA receptor: a hydrophobic site, a hydrogen binding site, and a pi bonding site.[11]

CONCLUSIONS

In conclusion, a novel series of *N*-tosyl piperidine-containing α-aminophosphonates were synthesized in high yields by solvent-free Kabachnik-Fields reaction catalyzed by magnesium perchlorate. The catalyst is commercially available, and the reaction conditions are mild. The insecticidal activities against *Plutella xylostella* were evaluated. The results indicated some of the compounds showed certain levels of insecticidal activity.

EXPERIMENTAL

Infrared spectra (ν_{max}, cm^{-1}) were recorded in potassium bromide disks on a Thermo Nicolet 6700 FTIR spectrophotometer; the ^{1}H NMR, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker DPX 300 MHz NMR spectrometer; chemical shifts values are given in ppm relative to TMS in $CDCl_3$; chemical shifts of ^{31}P NMR (121.5 MHz) were referenced to 85% H_3PO_4; HRMS was performed on a Bruker Apex IV FTMS; melting points were measured on a Yu Hua X-4 microscopic melting point apparatus which was uncorrected. All reagents were commercial products of analytical grade and were used directly without additional purification.

Procedure for the Synthesis of 1-tosylpiperidin-4-one

To a slurry of K_2CO_3 (8.9 g, 64 mmol) and 4-piperidone monohydrate hydrochloride (3.8 g, 25 mmol) in H_2O (30 mL)/$CHCl_3$ (30 mL), was added 4-tolylsulfonyl chloride (7.4 g, 39 mmol). The reaction mixture was then stirred at room temperature for 10 h, and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × Vol). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (Petroleum ether/EtOAc:2/3) or recrystallization (Petroleum ether/EtOAc:15/1) afforded 1-tosylpiperidin-4-one (6.0 g, 95%) as a white solid.[12]

Procedure for the Synthesis of *N*-Tosyl Piperidinyl-Containing α-Amino-phosphonates

A mixture of 1-tosylpiperidin-4-one (1.27 g, 5 mmol), $Mg(ClO_4)_2$ (56 mg, 5 mol%), aniline (0.46 g, 5 mmol), and DEP (1.40 g, 10 mmol) was stirred at 80 °C for 2 h. The reaction mixture was dissolved in EtOAc and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was washed with ethyl ether and then purified by a column of silica gel (Petroleum ether/EtOAc:3/2) to give the title compound **1**.

X-Ray Crystallographic Studies of 2a

A single crystal of **2a** was obtained as colorless crystals from a petroleum ether and EtOAc (1:15, v/v). Data collection was performed at 20 °C on a Rigaku RAXIS RAPID IP diffractometer, using graphite-monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). The determination of crystal class and unit cell parameters was carried out by the Rapid-AUTO (Rigaku 2000) program package. The raw frame data were processed using crystal structure (Rigaku/MSC 2000) to yield the reflection data file. The structure was solved by use of SHELXTL program. Refinement was performed on F^2 anisotropically for all the

nonhydrogen atoms by the full-matrix least-squares method. The hydrogen atoms were placed at the calculated positions and were included in the structure calculation without further refinement of the parameters. CCDC 857571 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, B2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Chemical Data

Diethyl 4-phenylamino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**1**): 1.94 g (83%), a pale yellow solid: mp 159°C–160°C. $R_f = 0.30$ (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3338, 2980, 2853, 1600, 1498, 1341, 1224 (P=O), 1170 (S=O), 1067, 1045, 1027 (P−O), 972, 934, 727 (C−S), 596, 549 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.17 (t, $J = 7.1$ Hz, 6H, CH_3−CH_2O), 2.15–2.21 (m, $4H_{cyclc}$), 2.43 (s, 3H, CH_3−C_6H_4), 2.64–2.72 (m, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 3.15 (br s, 1H, NH), 3.61 (br d, $J = 11.2$ Hz, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 3.84–4.04 (m, 4H, CH_2OP), 6.81–6.86 (m, 3H, C_6H_5−NH), 7.08–7.13 (m, 2H, C_6H_5−NH), 7.27–7.31 (m, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.59–7.62 (m, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC} = 5.6$ Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 30.0 (d, $^2J_{PC} = 2.2$ Hz, C_3 or C_5), 40.5 (d, $^3J_{PC} = 11.4$ Hz, C_2 or C_6), 54.8 (d, $^1J_{PC} = 161.6$ Hz, C_4), 62.2 (d, $^2J_{PC} = 7.8$ Hz, CH_2OP), [12 arom C: 119.8 (d, $J = 1.1$ Hz, 2C), 120.7 (1C), 127.5 (2C), 128.7 (2C, C_6H_5−NH), 129.6 (2C), 133.0 (1C), 143.5 (1C, tosyl), 144.9 (1C)]. ^{31}P NMR (CH_3OH, 121.5 MHz) δ: 27.95. HRMS (ESI, *m/z*): calcd mass for $C_{22}H_{31}N_2NaO_5PS$, $[M+Na]^+$: 489.15835. Found: 489.15881.

Diethyl 4-(2-chlorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**2a**): 1.85 g (74%), a white solid: mp 124°C–125°C. $R_f = 0.60$ (Petroleum ether/EtOAc:1/4) IR (KBr) ν: 3367, 2980, 1595, 1470, 1344, 1327, 1227 (P=O), 1170 (S=O), 1066, 1040, 1025 (P-O), 965, 922, 727 (C−S), 650 (C−Cl), 597, 550 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.29 (t, $J = 7.0$ Hz, 6H, CH_3−CH_2O), 2.19–2.40 (m, $6H_{cyclc}$, $4H_{cyclc}$ and 1H−C_2 and 1H−C_6), 2.44 (s, 3H, CH_3−C_6H_4), 3.56 (br d, $J = 11.7$ Hz, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 3.69 (br d, $J = 7.9$ Hz, 1H, NH), 4.04–4.17 (m, 4H, CH_2OP), 6.68–6.74 (m, 1H, C_6H_4−NH), 7.07–7.12 (m, 2H, C_6H_4−NH), 7.27–7.31 (m, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.54–7.57 (m, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$), 7.66–7.69 (m, 1H, C_6H_4−NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.4 (d, $^3J_{PC} = 5.4$ Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 29.0 (d, $^2J_{PC} = 1.7$ Hz, C_3 or C_5), 40.2 (d, $^3J_{PC} = 11.7$ Hz, C_2 or C_6), 54.2 (d, $^1J_{PC} = 172.1$ Hz, C_4), 62.8 (d, $^2J_{PC} = 7.6$ Hz, CH_2OP), [12 arom C: 119.2 (d, $J = 1.7$ Hz, 1C), 120.1 (1C), 122.2 (d, $J = 2.0$ Hz, 1C), 127.4 (1C, C_6H_5−NH), 127.6 (2C), 128.8 (1C, C_6H_5−NH), 129.5 (2C), 132.2 (1C), 139.8 (1C), 143.5 (1C, tosyl)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 24.94. HRMS (ESI, *m/z*): calcd mass for $C_{22}H_{30}ClN_2NaO_5PS$, $[M+Na]^+$: 523.11938. Found: 523.11989.

Diethyl 4-(3-chlorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**2b**): 2.00 g (80%), a white solid: mp 171°C–172°C. $R_f = 0.50$ (Petroleum ether/EtOAc:1/4) IR (KBr) ν: 3299, 2983, 1595, 1483, 1351, 1327, 1223 (P=O), 1168 (S=O), 1066, 1041, 1019 (P-O), 967, 935, 720 (C−S), 649 (C−Cl), 600, 549 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.22 (t, $J = 7.0$ Hz, 6H, CH_3−CH_2O), 2.18 (br d, $J = 4.2$ Hz, $4H_{cyclc}$), 2.43 (s, 3H, CH_3−C_6H_4), 2.52–2.60 (m, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 2.82–3.39 (**br**, 1H, NH), 3.59 (br d, $J = 11.6$ Hz, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 3.92–4.10 (m, 4H, CH_2OP), 6.76–6.78 (m, 3H, C_6H_4−NH), 7.01 (t, $J = 8.3$ Hz, 1H, C_6H_4−NH), 7.28–7.32

(m, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.60 (d, J = 8.2 Hz, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC}$ = 5.6 Hz, CH_3−CH_2O), 21.5 (CH_3−C_6H_4), 29.7 (d, $^2J_{PC}$ = 2.1 Hz, C_3 or C_5), 40.3 (d, $^3J_{PC}$ = 11.3 Hz, C_2 or C_6), 54.5 (d, $^1J_{PC}$ = 164.1 Hz, C_4), 62.5 (d, $^2J_{PC}$ = 7.9 Hz, CH_2OP), [12 arom C: 117.2 (d, J = 1.3 Hz, 2C), 118.8 (d, J = 1.7 Hz, 1C), 120.2 (1C), 127.6 (2C), 129.7 (d, J = 5.7 Hz,2C), 132.8 (1C, tosyl), 134.3 (1C), 143.7 (1C, tosyl), 146.1 (1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 26.95. HRMS (ESI, m/z): calcd mass for $C_{22}H_{30}ClN_2NaO_5PS$, $[M+Na]^+$: 523.11938. Found: 523.11986.

Diethyl 4-(4-chlorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**2c**): 1.99 g (80%), a white solid: mp 157°C–159°C. R_f = 0.50 (Petroleum ether/EtOAc:1/4) IR (KBr) ν: 3302, 2983, 1597, 1492, 1346, 1327, 1229 (P=O), 1170 (S=O), 1065, 1043, 1019 (P−O), 970, 917, 820, 727 (C−S), 650 (C−Cl), 602, 551 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (t, J = 7.1 Hz, 6H, CH_3−CH_2O), 2.16 (br t, J = 3.7 Hz, 4H$_{cyclc}$), 2.43 (s, 3H, CH_3−C_6H_4), 2.58–2.62 (m, 2H$_{cyclc}$, 1H−C_2 and 1H−C_6), 3.60 (br d, J = 11.3 Hz, 2H$_{cyclc}$, 1H−C_2 and 1H−C_6), 3.89–4.05 (m, 4H, CH_2OP), 4.2–4.9 (**br**, 1H, NH), 6.77 (dd, J_1 = 2.1 Hz, J_2 = 4.6 Hz, 1H−$C_{2'}$ and 1H−$C_{6'}$), 7.04 (dd, J_1 = 2.2 Hz, J_2 = 4.5 Hz, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.28–7.32 (m, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.60 (dd, J_1 = 1.6 Hz, J_2 = 5.0 Hz, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC}$ = 5.5 Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 29.7 (d, $^2J_{PC}$ = 2.0 Hz, C_3 or C_5), 40.4 (d, $^3J_{PC}$ = 11.4 Hz, C_2 or C_6), 54.7 (d, $^1J_{PC}$ = 163.0 Hz, C_4), 62.6 (d, $^2J_{PC}$ = 7.9 Hz, CH_2OP), [12 arom C: 120.6 (2C), 125.5 (1C), 127.5 (2C), 128.6 (2C, C_6H_5−NH), 129.6 (2C), 132.9 (1C), 143.3 (1C, tosyl), 143.6 (1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 26.50. HRMS (ESI, m/z): calcd mass for $C_{22}H_{31}ClN_2O_5PS$, $[M+H]^+$: 501.13743. Found: 501.13784.

Diethyl 4-(2-fluorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**3a**): 1.70 g (70%), a white solid: mp 141°C–142°C. R_f = 0.50 (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3354, 2979, 1614, 1491, 1344, 1227 (P=O), 1171 (S=O), 1098 (C−F), 1066, 1047, 1025 (P−O), 962, 918, 757, 724 (C−S), 650, 599, 550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (t, J = 7.1 Hz, 6H, CH_3−CH_2O), 2.18–2.23 (m, 4H$_{cyclc}$), 2.44−2.51 (m, 5H, 3CH_3−C_6H_4 and 1H−C_2 and 1H−C_6), 3.10–3.82 (br, 1H, NH), 3.57 (br d, J = 11.5 Hz, 2H$_{cyclc}$, 1H−C_2 and 1H−C_6), 4.00–4.13 (m, 4H, CH_2OP), 6.72–6.87 (m, 2H, C_6H_4−NH), 6.94 (t, J = 7.6 Hz, 1H, C_6H_4−NH), 7.30 (d, J = 8.5 Hz, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.41 (t, J = 8.5 Hz, 1H, C_6H_4−NH), 7.58 (d, J = 8.2 Hz, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.4 (d, $^3J_{PC}$ = 5.5 Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 29.4 (d, $^2J_{PC}$ = 2.0 Hz, C_3 or C_5), 40.3 (d, $^3J_{PC}$ = 11.5 Hz, C_2 or C_6), 54.6 (d, $^1J_{PC}$ = 168.5 Hz, C_4), 62.7 (d, $^2J_{PC}$ = 7.7 Hz, CH_2OP), [12 arom C: 114.3 (d, $^2J_{CF}$ = 20.2 Hz, 1C), 120.1 (d, $^3J_{CF}$ = 7.5 Hz, 1C, C_6H_5−NH), 120.3 (1C, C_6H_5−NH), 124.1 (d, $^4J_{CF}$ = 3.8 Hz, 1C, C_6H_5−NH), 127.5 (2C), 129.5 (2C), 132.5 (d, $^2J_{CF}$ = 10.3 Hz, 1C, C_6H_5−NH), 132.6 (1C), 143.6 (1C, tosyl), 153.3 (d, $^1J_{CF}$ = 238.7 Hz, 1C, C_6H_5−NH)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.19. HRMS (ESI, m/z): calcd mass for $C_{22}H_{30}FN_2NaO_5PS$, $[M+Na]^+$: 507.14893. Found: 507.14917.

Diethyl 4-(3-fluorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**3b**): 2.03 g (84%), a brown solid: mp 156°C–157°C. R_f = 0.30 (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3342, 2986, 1615, 1495, 1339, 1224 (P=O), 1169 (S=O), 1095 (C−F), 1068, 1043, 1025 (P−O), 966, 943, 913, 760, 726 (C−S), 650, 594, 549 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.22 (t, J = 7.1 Hz, 6H, CH_3−CH_2O), 2.14–2.21 (m, 4H$_{cyclc}$), 2.43 (s, 3H, CH_3−C_6H_4), 2.57 (t, J = 11.0 Hz, 2H, 1H−C_2 and 1H−C_6), 3.60 (br d, J = 11.3 Hz, 2H$_{cyclc}$, 1H−C_2 and 1H−C_6), 3.91–4.08 (m, 4H, CH_2OP), 4.22–5.01 (br, 1H, NH),

6.46–6.59 (m, 3H, C_6H_4—NH), 6.98–7.06 (m, 1H, C_6H_4—NH), 7.28–32 (m, 2H, 1H—C_3 and 1H—$C_{5'}$), 7.60 (d, $J = 8.4$ Hz, 2H, 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC} = 5.5$ Hz, CH_3—CH_2O), 21.4 (CH_3—C_6H_4), 29.7 (d, $^2J_{PC} = 1.9$ Hz, C_3 or C_5), 40.3 (d, $^3J_{PC} = 11.4$ Hz, C_2 or C_6), 54.6 (d, $^1J_{PC} = 163.7$ Hz, C_4), 62.6 (d, $^2J_{PC} = 7.9$ Hz, CH_2OP), [12 arom C: 105.8 (d, $^2J_{CF} = 25.4$ Hz, 1C), 106.8 (d, $^2J_{CF} = 21.4$ Hz, 1C), 114.6 (1C), 127.6 (2C), 129.6 (2C), 129.8 (d, $^3J_{CF} = 10.0$ Hz, 1C, C_6H_5—NH), 132.8 (1C, tosyl), 143.7 (1C, tosyl), 146.6 (d, $^3J_{CF} = 10.4$ Hz, 1C, C_6H_5—NH), 163.2 (d, $^1J_{CF} = 243.8$ Hz, 1C, C_6H_5—NH)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.51. HRMS (ESI, m/z): calcd mass for $C_{22}H_{30}FN_2NaO_5PS$, $[M+Na]^+$: 507.14893. Found: 507.14910.

Diethyl 4-(4-fluorophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**3c**): 1.82 g (75%), a white solid: mp 153°C–154°C. $R_f = 0.30$ (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3308, 2982, 1596, 1508, 1345, 1229 (P=O), 1170 (S=O), 1095 (C—F), 1065, 1043, 1019 (P—O), 966, 920, 821, 781, 724 (C—S), 650, 602, 550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.18 (t, $J = 7.0$ Hz, 6H, CH_3—CH_2O), 2.04–2.21 (m, $4H_{cyclc}$), 2.44 (s, 3H, CH_3—C_6H_4), 2.68 (t, $J = 9.6$ Hz, 2H, 1H—C_2 and 1H—C_6), 3.60 (br d, $J = 11.4$ Hz, $2H_{cyclc}$, 1H—C_2 and 1H—C_6), 3.87–4.02 (m, 4H, CH_2OP), 4.18–5.16 (br, 1H, NH), 6.81 (d, $J = 6.6$ Hz, 4H, C_6H_4—NH), 7.30 (t, $J = 7.5$ Hz, 2H, 1H—$C_{3'}$ and 1H—$C_{5'}$), 7.62 (d, $J = 8.1$ Hz, 2H, 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC} = 5.5$ Hz, CH_3—CH_2O), 21.4 (CH_3—C_6H_4), 29.8 (d, $^2J_{PC} = 2.4$ Hz, C_3 or C_5), 40.5 (d, $^3J_{PC} = 11.2$ Hz, C_2 or C_6), 55.1 (d, $^1J_{PC} = 160.2$ Hz, C_4), 62.4 (d, $^2J_{PC} = 7.9$ Hz, CH_2OP), [12 arom C: 115.2 (d, $^2J_{CF} = 22.2$ Hz, 2C), 122.2 (d, $^3J_{CF} = 6.5$ Hz, 2C), 127.6 (2C), 129.6 (2C), 132.2 (1C), 140.7 (d, $^4J_{CF} = 2.2$ Hz, 1C, C_6H_5—NH), 143.6 (1C, tosyl), 158.0 (d, $^1J_{CF} = 240.2$ Hz, 1C, C_6H_5—NH)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.82. HRMS (ESI, m/z): calcd mass for $C_{22}H_{30}FN_2NaO_5PS$, $[M+Na]^+$: 507.14893. Found: 507.14907.

Diethyl 4-(2-methylphenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**4a**): 2.05 g (85%), a white solid: mp 156°C–158°C. $R_f = 0.50$ (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3367, 2979, 1602, 1481, 1345, 1234 (P=O), 1170 (S=O), 1064, 1044, 1026 (P—O), 968, 923, 753, 725 (C-S), 600, 545 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.22 (t, $J = 7.1$ Hz, 6H, CH_3—CH_2O), 1.84 (s, 3H, CH_3—C_6H_4—NH), 2.16–2.33 (m, $4H_{cyclc}$), 2.43—2.52 (m, 5H, CH_3—C_6H_4, 1H—C_2 and 1H—C_6), 2.88 (**d**, $J = 3.8$ Hz, 1H, NH), 3.57 (br d, $J = 11.3$ Hz, $2H_{cyclc}$, 1H—C_2 and 1H—C_6), 3.92–4.09 (m, 4H, CH_2OP), 6.71 (t, $J = 7.2$ Hz, 1H, C_6H_4—NH), 6.94 (d, $J = 7.3$ Hz, 1H, C_6H_4—NH), 7.01–7.07 (m, 1H, C_6H_4—NH), 7.27–7.32 (m, 3H, C_6H_4—NH, 1H—$C_{3'}$ and 1H—$C_{5'}$),7.58 (d, $J = 8.2$ Hz, 2H, 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC} = 5.5$ Hz, CH_3—CH_2O), 17.5 (CH_3—C_6H_4—NH), 21.4 (CH_3—C_6H_4), 29.7 (d, $^2J_{PC} = 2.6$ Hz, C_3 or C_5), 40.4 (d, $^3J_{PC} = 11.2$ Hz, C_2 or C_6), 55.4 (d, $^1J_{PC} = 165.2$ Hz, C_4), 62.5 (d, $^2J_{PC} = 7.7$ Hz, CH_2OP), [12 arom C: 117.7 (d, $J = 1.7$ Hz, 1C), 119.6 (1C), 125.1 (d, $J = 1.4$ Hz, 1C), 126.6 (1C), 127.6 (2C), 129.6 (d, $J = 5.7$ Hz, 2C), 130.3 (1C), 132.4 (1C), 142.2 (1C), 143.6 (1C, tosyl)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 27.42. HRMS (ESI, m/z): calcd mass for $C_{23}H_{33}N_2NaO_5PS$, $[M+Na]^+$: 503.17400. Found: 503.17405.

Diethyl 4-(3-methylphenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**4b**): 1.89 g (79%), a yellow solid: mp 155°C–157°C. $R_f = 0.50$ (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3311, 2928, 1592, 1485, 1234 (P=O), 1169 (S=O), 1063, 1045, 1016 (P—O), 966, 910, 794, 723 (C—S), 600, 550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.18 (t, $J = 7.1$ Hz, 6H, CH_3—CH_2O), 2.16–2.18 (m, $4H_{cyclc}$), 2.20 (s, 3H, CH_3—C_6H_4—NH), 2.43 (s, 3H, CH_3—C_6H_4), 2.60–2.68 (m, 2H, 1H—C_2 and 1H—C_6), 3.10 (br s, 1H, NH), 3.59 (br d, $J = 11.3$ Hz, $2H_{cyclc}$, 1H—C_2 and 1H—C_6), 3.86–4.05 (m, 4H,

CH_2OP), 6.63–6.67 (m, 3H, C_6H_4—NH), 6.99 (d, $J = 7.7$ Hz, 1H, C_6H_4—NH), 7.27–7.31 (m, 2H, 1H—$C_{3'}$ and 1H—$C_{5'}$), 7.61 (d, $J = 8.3$ Hz, 2H, 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC} = 5.7$ Hz, CH_3—CH_2O), 21.3 (CH_3—C_6H_4—NH), 21.4 (CH_3—C_6H_4), 30.0 (d, $^2J_{PC} = 2.2$ Hz, C_3 or C_5), 40.5 (d, $^3J_{PC} = 12.7$ Hz, C_2 or C_6), 54.7 (d, $^1J_{PC} = 162.6$ Hz, C_4), 62.2 (d, $^2J_{PC} = 7.9$ Hz, CH_2OP), [12 arom C: 116.9 (1C), 120.5 (1C), 127.6 (2C), 128.6 (1C), 129.6 (2C), 133.0 (1C), 138.5 (1C), 143.5 (1C, tosyl), 144.7 (1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.96. HRMS (ESI, *m*/*z*): calcd mass for $C_{23}H_{33}N_2NaO_5PS$, $[M+Na]^+$: 503.17400. Found: 503.17530.

Diethyl 4-(4-methylphenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**4c**): 1.73 g (72%), a pale yellow solid: mp 151°C–153°C. $R_f = 0.40$ (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3301, 2978, 1616, 1512, 1350, 1228 (P=O), 1170 (S=O), 1066, 1038, 1019 (P—O), 974, 934, 815, 721 (C—S), 599, 561 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.17 (t, $J = 7.1$ Hz, 6H, CH_3—CH_2O), 2.12–2.16 (m, $4H_{cyclc}$), 2.22 (s, 3H, CH_3–C_6H_4—NH), 2.43 (s, 3H, CH_3—C_6H_4), 2.65–2.74 (m, 2H, 1H—C_2 and 1H—C_6), 2.91 (br s, 1H, NH), 3.59 (br d, $J = 11.1$ Hz, $2H_{cyclc}$, 1H—C_2 and 1H—C_6), 3.84–4.10 (m, 4H, CH_2OP), 6.71–6.75 (m, 2H, C_6H_4—NH), 6.91 (d, $J = 8.0$ Hz, 2H, C_6H_4—NH), 7.28–7.31 (m, 2H, 1H—$C_{3'}$ and 1H—$C_{5'}$), 7.59–7.63 (m, 2H, 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC} = 5.6$ Hz, CH_3—CH_2O), 20.4 (CH_3—C_6H_4—NH), 21.4 (CH_3—C_6H_4), 30.0 (d, $^2J_{PC} = 2.6$ Hz, C_3 or C_5), 40.6 (d, $^3J_{PC} = 11.2$ Hz, C_2 or C_6), 54.9 (d, $^1J_{PC} = 160.6$ Hz, C_4), 62.2 (d, $^2J_{PC} = 7.8$ Hz, CH_2OP), [12 arom C: 120.4 (d, $J = 1.4$ Hz, 1C), 127.6 (2C), 129.2 (1C), 129.6 (1C), 130.4 (1C), 133.1 (1C), 142.2 (1C), 143.5 (1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 27.51. HRMS (ESI, *m*/*z*): calcd mass for $C_{23}H_{34}N_2O_5PS$, $[M+H]^+$: 481.19206. Found: 481.19240.

Diethyl 4-(2-methoxyphenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**5a**): 1.99 g (80%), a white solid: mp 154°C–156°C. $R_f = 0.50$ (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3387, 2986, 2932, 1598, 1516, 1345, 1225 (P=O), 1167 (S=O), 1066, 1041, 1024 (P—O), 963, 925, 729 (C—S), 598, 550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.27 (t, $J = 7.1$ Hz, 6H, CH_3—CH_2O), 2.15–2.39 (m, 6H, $4H_{cyclc}$ and 1H—C_2 and 1H—C_6), 2.42 (s, 3H, CH_3—C_6H_4), 3.43 (s, 3H, CH_3O—C_6H_4), 3.54 (br d, $J = 11.6$ Hz, $2H_{cyclc}$, 1H—C_2 and 1H-C_6), 3.78 (br d, $J = 9.8$ Hz, 1H, NH), 4.02–4.16 (m, 4H, CH_2OP), 6.60–6.63 (m, 1H, C_6H_4—NH), 6.71–6.83 (m, 2H, C_6H_4—NH), 7.27–7.30 (m, 2H, 1H—$C_{3'}$ and 1H—$C_{5'}$), 7.49 (dd, $J_1 = 1.4$ Hz, $J_2 = 6.4$ Hz, 1H, C_6H_4—NH), 7.57 (dd, $J_1 = 1.7$ Hz, $J_2 = 4.9$ Hz, 2H, 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.4 (d, $^3J_{PC} = 5.5$ Hz, CH_3-CH_2O), 21.4 (CH_3—C_6H_4), 29.1 (d, $^2J_{PC} = 1.9$ Hz, C_3 or C_5), 40.3 (d, $^3J_{PC} = 11.9$ Hz, C_2 or C_6), 53.9 (d, $^1J_{PC} = 172.4$ Hz, C_4), 55.2 (OCH_3), 62.7 (d, $^2J_{PC} = 7.6$ Hz, CH_2OP), [12 arom C: 109.5 (1C), 118.5 (d, $J = 1.8$ Hz, 1C), 119.5 (1C), 120.9 (1C), 127.7 (2C), 129.4 (2C), 133.0 (1C, tosyl), 133.6 (1C), 143.3 (1C), 148.5 (d, $J = 0.9$ Hz, 1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.59. HRMS (ESI, *m*/*z*): calcd mass for $C_{23}H_{33}N_2NaO_6PS$, $[M+Na]^+$: 519.16892. Found: 519.16789.

Diethyl 4-(3-methoxyphenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**5b**): 1.78 g (72%), a white solid: mp 154°C–156°C. $R_f = 0.30$ (Petroleum ether/EtOAc:3/1.5) IR (KBr) ν: 3311, 2984, 2866, 1601, 1498, 1350, 1233, 1168 (S=O), 1036 (P—O), 966, 943, 718 (C—S), 695, 600, 549 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (t, $J = 7.1$ Hz, 6H, CH_3—CH_2O), 2.15–2.22 (m, $4H_{cyclc}$), 2.43 (s, 3H, CH_3—C_6H_4), 2.61–2.64 (m, 2H, 1H—C_2 and 1H—C_6), 3.15 (br d, $J = 3.9$ Hz, 1H, NH), 3.60 (br d, $J = 11.2$ Hz, $2H_{cyclc}$, 1H—C_2 and 1H—C_6), 3.72 (s, 3H, CH_3O—C_6H_4), 3.89–4.07 (m, 4H, CH_2OP), 6.36–6.41 (m, 2H, C_6H_4—NH), 6.48 (t, $J = 2.3$ Hz, 1H, C_6H_4—NH), 6.99 (t, $J = 8.1$ Hz, 1H, C_6H_4—NH), 7.27–7.31 (m, 2H, 1H—$C_{3'}$ and 1H—$C_{5'}$), 7.58–7.62 (m,

2H, 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.4 (d, $^3J_{PC}$ = 5.6 Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 30.0 (d, $^2J_{PC}$ = 2.2 Hz, C_3 or C_5), 40.5 (d, $^3J_{PC}$ = 11.3 Hz, C_2 or C_6), 54.7 (d, $^1J_{PC}$ = 163.2 Hz, C_4), 55.1 (OCH_3), 62.3 (d, $^2J_{PC}$ = 7.8 Hz, CH_2OP), [12 arom C: 105.5 (1C), 105.9 (1C), 112.1 (2C), 127.6 (2C), 129.5 (d, J = 14.9 Hz, 2C), 132.9 (1C), 143.6 (1C), 146.1 (1C), 160.2 (1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.84. HRMS (ESI, *m*/*z*): calcd mass for $C_{23}H_{34}N_2O_6PS$, $[M+H]^+$: 497.18697. Found: 497.18759.

Diethyl 4-(4-methoxyphenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**5c**): 1.87 g (75%), a brown solid: mp 132°C–134°C. R_f = 0.30 (Petroleum ether/EtOAc:3/2) IR (KBr) ν: 3302, 3065, 2982, 1509, 1250, 1236 (P=O), 1169 (S=O), 1066, 1043, 1020 (P−O), 972, 935, 721 (C−S), 600, 561 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.16 (t, J = 7.1 Hz, 6H, CH_3−CH_2O), 2.04–2.16 (m, $4H_{cyclc}$), 2.43 (s, 3H, CH_3−C_6H_4), 2.75 (t, J = 10.7 Hz, 2H, 1H−C_2 and 1H−C_6), 2.98 (br s, 1H, NH), 3.58 (br d, J = 11.2 Hz, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 3.73 (s, 3H, CH_3O−C_6H_4), 3.84–4.03 (m, 4H, CH_2OP), 6.68 (dd, J_1 = 2.3 Hz, J_2 = 4.3 Hz, 2H, C_6H_4−NH), 6.80 (dd, J_1 = 2.3 Hz, J_2 = 4.3 Hz, 2H, C_6H_4−NH), 7.28–7.32 (m, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.61–7.64 (m, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.3 (d, $^3J_{PC}$ = 5.6 Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 29.9 (d, $^2J_{PC}$ = 2.5 Hz, C_3 or C_5), 40.6 (d, $^3J_{PC}$ = 11.2 Hz, C_2 or C_6), 55.2 (d, $^1J_{PC}$ = 158.6 Hz, C_4), 55.4 (OCH_3), 62.1 (d, $^2J_{PC}$ = 7.9 Hz, CH_2OP), [12 arom C: 114.02 (2C), 123.0 (d, J = 1.7 Hz, 2C), 127.6 (2C), 129.6 (2C), 133.0 (1C), 137.8 (1C), 143.5 (1C), 154.9 (1C)]. ^{31}P NMR (CH_3OH, 121.5 MHz) δ: 28.27. HRMS (ESI, *m*/*z*): calcd mass for $C_{23}H_{34}N_2O_6PS$, $[M+H]^+$: 497.18697. Found: 497.18735.

Diethyl 4-(2-nitrophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**6a**): 1.41 g (55%), a yellow solid: mp 161°C–162°C. R_f = 0.60 (Petroleum ether/EtOAc:1/4) IR (KBr) ν: 3414, 2980, 1612, 1505, 1347 (N=O), 1239 (P=O), 1171 (S=O), 1063, 1037, 1021 (P−O), 963, 923, 718 (C−S), 604, 565 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.29 (t, J = 7.1 Hz, 6H, CH_3−CH_2O), 2.23–2.40 (m, 6H, $4H_{cyclc}$ and 1H−C_2 and 1H−C_6), 2.44 (s, 3H, CH_3−C_6H_4), 3.61 (br d, J = 6.5 Hz, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 4.06–4.17 (m, 4H, CH_2OP), 6.75 (t, J = 7.5 Hz, 1H, NH), 7.27 (d, J = 8.3 Hz, 2H, 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.39–7.45 (m, 1H, C_6H_4−NH), 7.52 (d, J = 8.2 Hz, 2H, 1H−$C_{2'}$ and 1H−$C_{6'}$), 7.63 (d, J = 6.2 Hz, 1H, C_6H_4−NH), 7.82 (d, J = 8.7 Hz, 1H, C_6H_4−NH), 8.04 (dd, J_1 = 1.6 Hz, J_2 = 7.0 Hz, 1H, C_6H_4−NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.4 (d, $^3J_{PC}$ = 5.4 Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 29.4 (s, C_3 or C_5), 40.1 (d, $^3J_{PC}$ = 11.1 Hz, C_2 or C_6), 54.6 (d, $^1J_{PC}$ = 168.3 Hz, C_4), 63.1 (d, $^2J_{PC}$ = 7.6 Hz, CH_2OP), [12 arom C: 117.8 (1C), 119.4 (d, J = 2.0 Hz, 1C), 126.5 (1C), 127.4 (2C), 129.6 (2C), 131.8 (1C, C_6H_5−NH), 134.2 (1C, tosyl), 135.7 (1C, C_6H_5−NH), 142.6 (1C, tosyl), 144.1 (1C, C_6H_5−NH)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 23.75. HRMS (ESI, *m*/*z*): calcd mass for $C_{22}H_{30}N_3NaO_7PS$, $[M+Na]^+$: 534.14343. Found: 534.14359.

Diethyl 4-(3-nitrophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**6b**): 1.41 g (55%), a luminous yellow solid: mp 173°C–175°C. R_f = 0.20 (Petroleum ether/EtOAc:2/3) IR (KBr) ν: 3420, 2984, 1623,1527, 1382 (N=O), 1223 (P=O), 1167 (S=O), 1066, 1040, 1017 (P−O), 971, 937, 822, 716 (C−S), 650, 603, 549 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (t, J = 7.1 Hz, 6H, CH_3−CH_2O), 2.18–2.24 (m, $4H_{cyclc}$), 2.42 (s, 3H, CH_3−C_6H_4), 2.55 (t, J = 10.8 Hz, 2H, 1H−C_2 and 1H−C_6), 3.61 (br d, J = 11.7 Hz, $2H_{cyclc}$, 1H−C_2 and 1H−C_6), 3.95−4.12 (m, 5H, $4CH_2OP$ and 1NH), 7.19–7.29 (m, 4H, 2 C_6H_4−NH and 1H−$C_{3'}$ and 1H−$C_{5'}$), 7.57–7.61 (m, 4H, 2 C_6H_4−NH and 1H−$C_{2'}$ and 1H−$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.4 (d, $^3J_{PC}$ = 5.4 Hz, CH_3−CH_2O), 21.4 (CH_3−C_6H_4), 29.5 (d, $^2J_{PC}$ = 1.9 Hz, C_3 or C_5), 40.2 (d, $^3J_{PC}$ = 11.2 Hz, C_2 or C_6),

54.5 (d, $^1J_{PC}$ = 165.3 Hz, C_4), 62.8 (d, $^2J_{PC}$ = 7.8 Hz, CH_2OP), [12 arom C: 112.1 (1C), 114.2 (1C), 123.7 (d, J = 1.1 Hz, 1C), 127.5 (2C), 129.4 (1C, C_6H_5—NH), 129.6 (2C, tosyl), 132.8 (1C), 143.8 (1C, tosyl), 145.9 (1C, C_6H_5—NH), 148.7 (1C, C_6H_5—NH)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 25.14. HRMS (ESI, m/z): calcd mass for $C_{22}H_{30}N_3NaO_7PS$, $[M+Na]^+$: 534.14343. Found: 534.14322.

Diethyl 4-(4-nitrophenyl) amino-1-(4′-methylbezenesulfonyl) piperidin-4-yl-phosphonate (**6c**): 1.97 g (77%), a pale yellow solid: mp 219°C–220°C. R_f = 0.60 (Petroleum ether/EtOAc:1/4) IR (KBr) ν: 3309, 2987, 1598, 1505, 1320 (N=O), 1222 (P=O), 1169 (S=O), 1067, 1041, 1019 (P—O), 971, 936, 718 (C—S), 596, 548 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (t, J = 7.1 Hz, 6H, CH_3—CH_2O), 2.22–2.30 (m, $4H_{cyclc}$), 2.43 (s, 3H, CH_3—C_6H_4), 2.50 (t, J = 11.1 Hz, 2H, 1H—C_2 and 1H—C_6), 3.64 (br d, J = 11.7 Hz, $2H_{cyclc}$, 1H—C_2 and 1H—C_6), 3.99–4.13 (m, 5H, $4CH_2OP$ and 1NH), 7.19–7.29 (m, 4H, 2 C_6H_4—NH and 1H—$C_{3'}$ and 1H—$C_{5'}$), 7.57–7.61 (m, 4H, 2 C_6H_4—NH and 1H—$C_{2'}$ and 1H—$C_{6'}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 16.5 (d, $^3J_{PC}$ = 5.4 Hz, CH_3—CH_2O), 21.5 (CH_3—C_6H_4), 29.9 (C_3 or C_5), 40.2 (d, $^3J_{PC}$ = 10.9 Hz, C_2 or C_6), 54.6 (d, $^1J_{PC}$ = 165.9 Hz, C_4), 62.9 (d, $^2J_{PC}$ = 7.7 Hz, CH_2OP), [12 arom C: 115.7 (2C), 125.5 (2C), 127.6 (2C), 129.8 (2C), 133.0 (1C), 139.8 (1C), 143.9 (1C, tosyl), 150.8 (1C)]. ^{31}P NMR ($CHCl_3$, 121.5 MHz) δ: 24.33. HRMS (ESI, m/z): calcd mass for $C_{22}H_{30}N_3NaO_7PS$, $[M+Na]^+$: 534.14343. Found: 534.14348.

REFERENCES

1. (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon* **1991**, 63, 193–215; (b) Peyman, A.; Buidt, K.-H.; Spanig, J.; Ruppert, D. *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1720–1722; (c) Chen, R.-Y.; Dai, Q. *Sci. China, Ser.B* **1995**, 25, 591–595 (in Chinese); (d) Wang, H.-L.; Zhou, J.; Qiu, Y.-G.; Feng, K.-S.; Chen, R.-Y. *Phosphorus, Sulfur Silicon* **1995**, 104, 135–141; (e) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, Wiley: Chichester, NY, **2000**; (f) Liu, X.-J.; Chen, R.-Y.; Yang, Y.-Y. *Chem. J. Chin. Univ.* **2002**, 23, 1299–1293 (in Chinese); (g) Lang, S.-Y.; Yue, F.; Cao, L.-H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, 187, 461–467.
2. (a) Dhawan, B.; Redmore, D. *Phosphorous Sulfur* **1987**, 32, 119–144; (b) Kukhar, V.P.; Soloshonok, V.A.; Solodenko, V.A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, 92, 239–264; (c) Bennani, Y.L.; Hanessian, S. *Chem. Rev.* **1997**, 97, 3161–3196; (d) Kolodiazhnyi, O.I. *Tetrahedron: Asymmetry* **1998**, 9, 1279–1332; (e) Mikolajczyk, M. *J. Organomet. Chem.* **2005**, 690, 2488–2496; (f) Ma, J.A. *Chem. Soc. Rev.* **2006**, 35, 630–636; (g) Zhang, J.-F.; Cui, Z.-W.; Miao, Z.-W.; Chen, R.-Y. *Chin. J. Org. Chem.* **2008**, 28, 956–953 (in Chinese); (h) Bhagat, S.; Chakraborti, A.K. *J. Org. Chem.* **2008**, 73, 6029–6032; (i) Lang, S.-Y.; Yue, F.; Cao, L.-H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, 187, 461–467; (j) Sundar, C.S.; Srinivasulu, D.; Nayak, S.K.; Reddy, C.S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, 187, 523–534.
3. (a) Bailey, P.D.; Millwood, P.A.; Smith, P.D. *Chem. Commun.* **1998**, 633–640; (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813; (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892; (d) Weintraub, P.M.; Sabol, J.S.; Kane, J.M.; Borcherding, D.R. *Tetrahedron* **2003**, 59, 2953–2989; (e) Maxime, G.P. B. *Tetrahedron* **2004**, 60, 1701–1729.
4. Rabasso, N.; Louaisil, N.; Fadel, A. *Tetrahedron* **2006**, 62, 7445–7454.
5. (a) Guéguen, C.; About-Jaude, E.; Collignon, N.; Savignac, P. *Synth. Commun.* **1996**, 26, 4131–4143; (b) Stoikov, I.I.; Repejkov, S.A.; Antipin, I.S.; Konovalov, A.I. *Heteroat. Chem* **2000**, 11, 518–527; (c) Wieczorek, J.S.; Gancarz, R.; Bielecki, K.; Grzyś, E.; Sarapuk, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, 166, 111–123; (d) Wieczorek, J.S.; Gancarz, R.; Bielecki, K.; Grzyś, E.; Sarapuk, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, 174, 119–128;

(e) Yadav, J.S.; Subba Reddy, B.V.; Madan, C. *Synlett* **2001**, 2001, 1131–1133; (f) Ranu, B.C.; Hajra, A. *Green Chem.* **2002**, 4, 551–554.

6. (a) Dzhiembaev, B.Z.; Abiyurov, B.D.; Zaporozhskaya, N.I.; Minbaev, B.U. *Zh. Obshch. Khim.* **1989**, 59, 77–80; (b) Gancarz, R.; Latajka, R.; Halama, A.; Kafarski, P. *Magn. Reson. Chem.* **2000**, 38, 867–871; (c) Matveeva, E.; Podrugina, T.; Prisyajnoy, M.; Zefirov, N. *Russ. Chem. Bull.* **2006**, 55, 1209–1214; (d) Louaisil, N.; Rabasso, N.; Fadel, A. *Tetrahedron* **2009**, 65, 8587–8595.
7. (a) Barton, P.J.; Jewsbury, P.J.; Pease, J.E. *WO2004033427A1*, **2004**; (b) León, L.G.; Carballo, R.M.; Vega-Hernández, M.C.; Martín, V.S.; Padrón, J.I.; Padrón, J.M. *Bioorg. Med. Chem. Lett.* **2007**, 17, 2681–2684; (c) Matsumura, A.; Mikamiyama, H.; Tsuno, N.; Kyle, D.J.; Shao, B.; Yao, J. *WO2008008398A2*, **2008**; (d) Shah, U.; Boyle, C.D.; Chackalamannil, S. *WO2009023180A1*, **2009**; (e) Wilckens, T.; Weber, L. *EP2243494A1*, **2010**.
8. (a) Chakraborti, A.K.; Sharma, L.; Gulhane, R.; Shivani *Tetrahedron* **2003**, 59, 7661–7668; (b) Chakraborti, A.K.; Bhagat, S.; Rudrawar, S. *Tetrahedron Lett.* **2004**, 45, 7641–7644; (c) Bartoli, G.; Babiuch, K.; Bosco, M.; Carlone, A.; Galzerano, P.; Melchiorre, P.; Sambri, L. *Synlett* **2007**, 2897–2901; (d) Bartoli, G.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Eur. J. Org. Chem.* **2007**, 2037–2049; (e) Khatik, G.L.; Kumar, R.; Chakraborti, A.K. *Synthesis* **2007**, 541–546; (f) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Galzerano, P.; Melchiorre, P.; Sambri, L. *Tetrahedron Lett.* **2008**, 49, 2555–2557.
9. Bhagat, S.; Chakraborti, A.K. *J. Org. Chem.* **2007**, 72, 1263–1270.
10. Haase, M.; Günther, W.; Görls, H.; Anders, E. *Synthesis* **1999**, 1999, 2071–2081.
11. Sammelson, R.E.; Caboni, P.; Durkin, K.A.; Casida, J.E. *Bioorg. Med. Chem.* **2004**, 12, 3345–3355.
12. Engler, T.A.; Wanner, J. *J. Org. Chem.* **2000**, 65, 2444–2457.