AGRICULTURAL AND FOOD CHEMISTRY

Synthesis and Biological Activity Evaluation of Novel α -Amino Phosphonate Derivatives Containing a Pyrimidinyl Moiety as Potential Herbicidal Agents

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Supporting Information

ABSTRACT: To find novel high-activity and low-toxicity herbicide lead compounds with novel herbicidal mode of action, series of novel α -amino phosphonate derivatives containing a pyrimidinyl moiety, I, II, III, and IV, were designed and synthesized by Lewis acid (magnesium perchlorate) catalyzed Mannich-type reaction of aldehydes, amines, and phosphites. Their structures were clearly identified by spectroscopy data (IR, ¹H NMR, ³¹P NMR, EI-MS) and elemental analyses. The bioassay [in vitro, in vivo (GH1 and GH2)] showed that most compounds I exhibited good herbicidal activities; for example, the activities of compounds Ib, Ic, Ig, Ii, Ik, and Im were as good as the positive control herbicides (acetochlor, atrazine, mesotrione, and glyphosate). However, their structural isomers II and III and analogues IV did not display any herbicidal activities in vivo, although some of them possessed selective inhibitory activity against *Arabidopsis thaliana* in vitro. Interestingly, it was found that compounds IVs, IVt, and IVI showed selective insecticidal activities against *Aphis* species or *Plutella xylostella*, respectively. Their preliminary herbicidal mode of action and structure–activity relationships were also studied.

KEYWORDS: pyrimidine, α -amino phosphonate, herbicidal activity, insecticidal activity

INTRODUCTION

Phosphorus-containing compounds have received continuous attention due to their versatile biological activities and are widely used as pharmaceuticals and agrochemicals such as insecticides, fungicides, or plant growth regulators.¹⁻³ Moreover, some phosphorus-containing compounds act as highefficiency ligands in transition metal-catalyzed asymmetric reactions.^{4,5} Phosphonates possess more lipophilic nature and cell permeability along with physiological stability because the phosphorus-carbon bond is not susceptible to enzymatic degradation by phosphatases.^{6,7} α -Amino phosphonic acid and its ester derivatives are the bioisosteres of natural amino acid. When the carboxylic group is replaced by a phosphonic moiety, they resemble the tetrahedral transition state of several enzymatic reactions, particularly amide bond formation and hydrolysis; however, they are significant differences such as molecular dimension, group shape (flat CO₂H vs tetrahedral PO₃H₂), and acidity between amino acids and phosphonic counterparts. Therefore, several enzymes are unable to discriminate between carboxylic and phosphonic function with regard to binding to active sites. The structural antagonism between amino acids and the phosphonic counterparts results in inhibition of enzyme activity.^{8,9} Therefore, α -amino phosphonic acid and its ester derivatives play a vital role in medicinal chemistry and pesticidal science.¹⁰⁻¹⁵ For example, glyphosate (Figure 1), structurally similar to a naturally occurring glutamate analogue, phosphinothricin (PPT, Figure 1), as a synthetic inhibitor of the shikimate pathway enzyme 5-enolpyruvyl-shikimate-3-phosphate (EPSP) synthase (EC 2.5.1.19), is used worldwide as a broad-spectrum herbicide.^{16–18} Moreover,

O,O'-diethyl N-(4-methylbenzothiazol-2-yl) 1-amino-1-(2fluorophenyl)methylphosphonate (Dufulin, Figure 1) is a commercial plant anti-TMV (tobacco mosaic virus) agent.^{19,20} It should be mentioned that some aminomethylenebisphosphonic acid derivatives were evaluated as potential inhibitors of plant δ^1 -pyrroline-5-carboxylate reductase (EC 1.5.1.2), which catalyzes the last step in proline biosynthesis and can probably be functionalized as a novel potential herbicide target enzyme.^{21,22} On the other hand, since the late 1990s, pyrimidinyl carboxylic acid derivatives with notable herbicidal activities, known as inhibitors of branched-chain amino acids (ALS or AHAS) synthase, have attracted increasing attention of pesticide scientists.^{23–27} To date, several pyrimidyl carboxylic acid derivatives such as bispyribac-sodium and pyriminobacmethyl have been commercialized as herbicides (Figure 1). Furthermore, one of the pyrimidyl benzylamine derivatives, Pyribambenz propyl, has also been commercialized recently.²⁸⁻³⁰ Bioisosterism is an effective approach for developing and optimizing bioactive lead compounds, and nitenpyram, acetamiprid, and thiacloprid are some successful cases.³¹ The preliminary herbicidal evaluation of a series of α -amino alkyl phosphonates containing a pyrimidinyl moiety was reported recently by our group;³² to evaluate further their herbicidal activity and study their structure-activity relationship as well as the mode of action, we designed and synthesized

Received:	May 12, 2015
Revised:	July 18, 2015
Accepted:	July 29, 2015

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Figure 1. Structures of commercial α -amino phosphonic acid and pyrimidine pesticides.

four series of novel α -amino alkyl phosphonate derivatives containing a pyrimidinyl moiety via a Lewis acid (magnesium perchlorate) catalyzed Mannich-type reaction of aldehydes, amines, and phosphites (Schemes 1 and 2). The target

Scheme 1. Molecular Design of Title Compounds I-IV



compounds were evaluated for herbicidal activities in vitro and in vivo, and their preliminary herbicidal mode of action and structure—activity relationship were also studied.

MATERIALS AND METHODS

Instruments. ¹H and ³¹P NMR spectra were performed on a Varian Mercury-PLUS400 (400 MHz) or Varian Mercury Plus-600 (600 MHz) spectrometer at room temperature in CDCl₃ with TMS and 85% H₃PO₄ as the internal and external standards, respectively; chemical shift values (δ) are given in parts per million. Elemental analyses were taken on a Vario EL III elemental analysis instrument. Mass spectra were measured on a Finnigan TraceMS 2000 spectrometer at 70 eV using EI method or an Applied Biosystems API 2000 LC/MS/MS (ESI-MS) spectrometer. The IR spectra were recorded on a Nicolet NEXUS470 spectrometer as KBr pellets with absorption given in cm⁻¹. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. Yields were not optimized. Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were dried and redistilled before use.

General Procedure for the Preparation of *O*,*O*'-Dialkyl (Diphenyl) N-Substituted Phenyl-1-amino-[2 or 3 or 4-(4,6dimethoxypyrimidin-2-yloxy)phenyl]methyl Phosphonates I–III. The mixture of aldehyde 1a–1c (3 mmol), dialkyl phosphite, or diphenyl phosphite (3 mmol), substituted aniline (3.3 mmol), and anhydrous Mg(ClO₄)₂ (0.033 g, 0.15 mmol) in anhydrous acetonitrile (5 mL) was stirred at 50–60 °C until the reaction finished (monitored by TLC). The solid was filtered off, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using a mixture of petroleum ether and acetone (v/v, 2:1) as eluent to give the target compounds I, II, and III as a white solid or light yellow oil. The detailed procedures and spectral data for intermediates 1a–1c and 2a–2b and the target compounds I–IV are available in the Supporting Information. Ia–Ir are known compounds, and their spectra data can also be found in the literature.³²

Data for compound Is (R = Et, Ar = 4-FC₆H₄): white solid; yield, 71%; mp, 125.3–126.5 °C; IR (KBr) ν 3316 (NH), 2981 (Ar—H), 1600, 1572, 1502, 1468 (Ar), 1362 (P=O), 1216, 1193 (P=O-C), 1066, 1025 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.06 (t, *J* = 7.8 Hz, 3H, CH₃), 1.30 (t, *J* = 7.2 Hz, 3H, CH₃), 3.70–3.74 (m, 1H, CH₂), 3.79 (s, 6H, 2CH₃O), 3.88–3.94 (m, 1H, CH₂), 4.17–4.22 (m, 2H, CH₂), 4.65 (t, *J* = 8.4 Hz, 1H, NH), 5.15 (dd, *J* = 8.4 Hz, *J* = 24.0 Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.49–6.51 (m, 2H, ArH), 6.71 (t, *J* = 8.4 Hz, 2H, ArH), 7.20 (d, *J* = 7.2 Hz, 2H, ArH), 7.28 (t, *J* = 7.8 Hz, 1H, ArH), 7.63 (d, *J* = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.90; EI-MS (70 eV) *m/z* (%) 491.4 (M⁺, 2.7), 355 (23.7), 354 (100), 214 (12.8). Anal. Calcd for C₂₃H₂₇FN₃O₆P: C, 56.21; H, 5.54; N, 8.55. Found: C, 56.07; H, 5.39; N, 8.31.

Data for compound It (R = Me, Ar = 4-FC₆H₄): white solid; yield, 66%; mp, 159.4–160.7 °C; IR (KBr) ν 3319 (NH), 2983 (Ar—H), 1605, 1571, 1507, 1470 (Ar), 1358 (P=O), 1219, 1187 (P—O—C), 1065, 1022 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 3.46 (d, *J* = 10.8 Hz, 3H, OCH₃), 3.80 (s, 6H, 2CH₃O), 3.88 (d, *J* = 10.8 Hz, 3H, OCH₃), 4.64 (br s, 1H, NH), 5.19 (dd, *J* = 7.8 Hz, *J* = 24.0 Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.50–6.53 (m, 2H, ArH), 6.72 (t, *J* = 7.8 Hz, 2H, ArH), 7.22 (t, *J* = 7.8 Hz, 2H, ArH), 7.31 (t, *J* = 7.8 Hz, 1H, ArH), 7.62 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 24.20; EI-MS (70 eV) *m*/*z* (%) 463.4 (M⁺, 2.9), 355 (22.0), 354 (100), 322 (5.1), 214 (14.4). Anal. Calcd for C₂₁H₂₃FN₃O₆P: C, 54.43; H, 5.00; N, 9.07. Found: C, 54.62; H, 5.15; N, 9.26.

Data for compound **Iu** (R = Ph, Ar = 4-FC₆H₄): white solid; yield, 75%; mp, 173.4–174.3 °C; IR (KBr) ν 3311 (NH), 2980 (Ar—H), 1608, 1577, 1502, 1475 (Ar), 1361 (P=O), 1216, 1182 (P—O—C), 1062, 1028 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 3.71 (s, 6H, 2CH₃O), 4.74 (br s, 1H, NH), 5.62 (dd, *J* = 9.0 Hz, *J* = 24.6 Hz, 1H, PCH), 5.72 (s, 1H, pyrimidine-H), 6.56–6.58 (m, 2H, ArH), 6.73–6.78 (m, 4H, ArH), 7.06–7.09 (m, 3H, ArH), 7.12–7.18 (m, 3H, ArH), 7.21–7.25 (m, 4H, ArH), 7.33 (t, *J* = 7.8 Hz, 1H, ArH), 7.70 (d, *J* = 8.4 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 14.60; EI-MS (70 eV) *m*/*z* (%) 587.5 (M⁺, 1.7), 355 (21.0), 354 (100), 353 (39.3), 338 (5.9), 258 (6.8). 234 (18.0), 214 (47.5). Anal. Calcd for C₃₁H₂₇FN₃O₆P: C, 63.37; H, 4.63; N, 7.15. Found: C, 63.16; H, 4.58; N, 7.22. Scheme 2. Synthetic Route of Title Compounds I-III

H ₃ (осн ₃ сно N + ₂ сн ₃			OCH3 OCH3 O O O O O O O O O O O O O	H ₃ CO OCH ₃ N or	OCH ₃	0
I	1a or 1b + HPO(OR) + I	or 1c Mg(ClO 2 or HP(OPh)2 2 OF H2 2 OF H2 2 OF H2 CH3C		OCH N O POR NHAr Ia~Ix	H ₃ or N N O N N O N N O N N O N O N O N O N	H ₃ CO ICH ₃ N OR or IR	OCH3 N Illa~Illj	O P_OR P_OR NHAr
Compd.	R	Ar	Compd.	R	Ar	Compd.	R	Ar
Ia	Me	C_6H_5	Ib	Et	C_6H_5	Ic	Et	$4-NO_2-C_6H_4$
Id	Me	$4-NO_2-C_6H_4$	Ie	Me	$4-Br-C_6H_4$	If	Et	$4\text{-}Br\text{-}C_6H_4$
Ig	Me	$4\text{-}CH_3O\text{-}C_6H_4$	Ih	Et	$4\text{-}CH_3O\text{-}C_6H_4$	Ii	Me	$2-Cl-C_6H_4$
Ij	Et	$2-Cl-C_6H_4$	Ik	Me	$3-Br-C_6H_4$	I	Et	$3-Br-C_6H_4$
Im	Me	$4-Cl-C_6H_4$	In	Et	$4-Cl-C_6H_4$	Io	Me	$4-CF_3-C_6H_4$
Ip	Et	$4-CF_3-C_6H_4$	Iq	Ph	$4-CF_3-C_6H_4$	Ir	<i>n</i> -Bu	$4-CF_3-C_6H_4$
Is	Et	$4-F-C_6H_4$	It	Me	$4-F-C_6H_4$	Iu	Ph	$4-F-C_6H_4$
Iv	Et	$2\text{-Br-}C_6H_4$	Iw	Et	4-CN-C ₆ H ₄	Ix	Et	$4\text{-}EtOCO\text{-}C_6H_4$
IIa	Et	$4-F-C_6H_4$	IIb	Et	$2-Br-C_6H_4$	IIIa	Et	$4-F-C_6H_4$
IIIb	Et	$2\text{-Br-}C_6H_4$	IIIc	Et	$4-Cl-C_6H_4$	IIId	Et	$4-CH_3-C_6H_4$
IIIe	Et	$4-NO_2-C_6H_4$	IIIf	Et	$4-Br-C_6H_4$	IIIg	Et	C_6H_5
IIIh	Et	2,4-Cl ₂ -C ₆ H ₃	IIIi	Me	$4-Cl-C_6H_4$	IIIj	Et	2-F-C ₆ H ₄

Data for compound Iv (R = Et, Ar = 2-BrC₆H₄): white solid; yield, 64%; mp, 113.2–114.6 °C; IR (KBr) ν 3309 (NH), 2976 (Ar—H), 1598, 1563, 1500, 1472 (Ar), 1359 (P=O), 1218, 1194 (P—O—C), 1062, 1028 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.11 (t, *J* = 7.2 Hz, 3H, CH₃), 1.29 (t, *J* = 7.2 Hz, 3H, CH₃), 3.65–3.68 (m, 1H, CH₂), 3.81 (s, 6H, 2CH₃O), 3.96–3.99 (m, 1H, CH₂), 4.18–4.20 (m, 2H, CH₂), 5.24 (d, *J* = 24.0 Hz, 1H, PCH), 5.41 (br s, 1H, NH), 5.77 (s, 1H, pyrimidine-H), 6.48–6.51 (m, 2H, ArH), 6.89–6.90 (m, 1H, ArH), 7.21–7.23 (m, 2H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 7.35 (d, *J* = 7.2 Hz, 1H, ArH), 7.61–7.63 (m, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.15; EI-MS (70 eV) *m*/*z* (%) 553.4 (5.1), 551.4 (M⁺, 3.5), 417 (21.5), 416 (94.3), 415 (23.8), 414 (100), 334 (8.3), 229 (6.3), 196 (5.8). Anal. Calcd for C₂₃H₂₇BrN₃O₆P: C, 50.01; H, 4.93; N, 7.61. Found: C, 50.15; H, 4.97; N, 7.43.

Data for compound Iw (R = Et, Ar = 4-CNC₆H₄): white solid; yield, 59%; mp, 142.3–143.6 °C; IR (KBr) ν 3315 (NH), 2982 (Ar—H), 2245 (CN), 1563, 1556, 1485, 1461 (Ar), 1365 (P=O), 1215, 1185 (P=O=C), 1060, 1024 (C=O=C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.06 (t, *J* = 7.2 Hz, 3H, CH₃), 1.28 (t, *J* = 7.2 Hz, 3H, CH₃), 3.68–3.72 (m, 1H, CH₂), 3.81 (s, 6H, 2CH₃O), 3.90–3.94 (m, 1H, CH₂), 4.15–4.20 (m, 2H, CH₂), 5.20 (d, *J* = 7.8 Hz, *J* = 24.0 Hz, 1H, PCH), 5.33 (br s, 1H, NH), 5.80 (s, 1H, pyrimidine-H), 6.57(d, *J* = 9.0 Hz, 2H, ArH), 7.20–7.24 (m, 2H, ArH), 7.27–7.29 (m, 2H, ArH), 7.33 (t, *J* = 7.8 Hz, 1H, ArH), 7.59 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.96; EI-MS (70 eV) *m/z* (%) 498.4 (M⁺, 5.8), 362 (24.4), 361 (100), 329 (2.2), 246 (2.4), 244 (3.1), 229 (4.2). Anal. Calcd for C₂₄H₂₇N₄O₆P: C, 57.83; H, 5.46; N, 11.24. Found: C, 57.70; H, 5.33; N, 11.31.

Data for compound Ix (R = Et, Ar = 4-EtOCOC₆H₄): white solid; yield, 66%; mp, 160.2–161.3 °C; IR (KBr) ν 3316 (NH), 2975 (Ar—H),

1738 (C=O), 1561, 1554, 1481, 1459 (Ar), 1362 (P=O), 1218, 1183 (P=O-C), 1057, 1028 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.07 (t, *J* = 7.2 Hz, 3H, CH₃), 1.28 (t, *J* = 7.2 Hz, 3H, CH₃), 1.33 (t, *J* = 7.8 Hz, 3H, CH₃), 3.71–3.74 (m, 1H, CH₂), 3.80 (s, 6H, 2CH₃O), 3.92–3.95 (m, 1H, CH₂), 4.20 (q, *J* = 7.2 Hz, 2H, CH₂), 4.28 (q, *J* = 7.2 Hz, 2H, CH₂), 5.21 (br s, 1H, NH), 5.28 (d, *J* = 7.8 Hz, 1H, PCH), 5.78 (s, 1H, pyrimidine-H), 6.54 (t, *J* = 6.0 Hz, 2H, ArH), 7.20–7.23 (m, 2H, ArH), 7.28–7.31 (m, 1H, ArH), 7.62 (d, *J* = 6.6 Hz, 1H, ArH), 7.71 (t, *J* = 6.0 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.31; EI-MS (70 eV) *m/z* (%) 545.5 (M⁺, 2.5), 410 (4.0), 409 (26.9), 408 (100), 362 (3.6). Anal. Calcd for C₂₆H₃₂N₃O₈P: C, 57.24; H, 5.91; N, 7.70. Found: C, 57.06; H, 5.97; N, 7.63.

Data for compound **IIa** (R = Et, Ar = 4-FC₆H₄): white solid; yield, 65%; mp, 135.2–136.3 °C; IR (KBr) ν 3310 (NH), 2985 (Ar—H), 1561, 1548, 1482, 1459 (Ar), 1358 (P=O), 1219, 1176 (P—O—C), 1057, 1025 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.12 (t, *J* = 7.8 Hz, 3H, CH₃), 1.29 (t, *J* = 7.8 Hz, 3H, CH₃), 3.70 (s, 6H, 2CH₃O), 3.71–3.74 (m, 1H, CH₂), 3.93–3.97 (m, 1H, CH₂), 4.10–4.14 (m, 2H, CH₂), 4.67 (dd, *J* = 7.2 Hz, *J* = 24.0 Hz, 1H, PCH), 4.73 (br s, 1H, NH), 5.76 (s, 1H, pyrimidine-H), 6.50–6.52(m, 2H, ArH), 6.78–6.80 (m, 2H, ArH), 7.14 (t, *J* = 6.6 Hz, 1H, ArH), 7.32 (d, *J* = 7.2 Hz, 2H, ArH), 7.37 (t, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.43; EI-MS (70 eV) *m/z* (%) 491.5 (M⁺, 6.0), 355 (19.2), 354 (100), 353 (7.1), 198 (2.6), 122 (2.9). Anal. Calcd for C₂₃H₂₇FN₃O₆P: C, 56.21; H, 5.54; N, 8.55. Found: C, 56.03; H, 5.77; N, 8.39.

Data for compound **IIb** (R = Et, Ar = 2-BrC₆H₄): white solid; yield, 72%; mp, 108.2–109.8 °C; IR (KBr) ν 3302 (NH), 2988 (Ar—H), 1567, 1542, 1479, 1452 (Ar), 1367 (P=O), 1211, 1170 (P=O-C),

1068, 1024 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.19 (t, *J* = 7.8 Hz, 3H, CH₃), 1.28 (t, *J* = 7.2 Hz, 3H, CH₃), 3.73 (s, 6H, 2CH₃O), 3.82–3.86 (m, 1H, CH₂), 4.00–4.14 (m, 3H, CH₂), 4.76 (dd, *J* = 6.6 Hz, *J* = 24.6 Hz, 1H, PCH), 5.45 (br s, 1H, NH), 5.76 (s, 1H, pyrimidine-H), 6.43 (d, *J* = 7.8 Hz, 1H, ArH), 6.59 (d, *J* = 6.0 Hz, 1H, ArH), 6.99 (t, *J* = 7.2 Hz, 1H, ArH), 7.14 (d, *J* = 7.8 Hz, 1H, ArH), 7.35–7.39 (m, 3H, ArH), 7.42 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.55; EI-MS (70 eV) *m*/*z* (%) 553.4 (4.1), 551 (M⁺, 4.6), 417 (22.6), 416 (99.7), 415 (24.3), 414 (100), 208 (5.3). Anal. Calcd for C₂₃H₂₇BrN₃O₆P: C, 50.01; H, 4.93; N, 7.61. Found: C, 49.93; H, 4.74; N, 7.82.

Data for compound IIIa (R = Et, Ar = 4-FC₆H₄): white solid; yield, 75%; mp, 138.5–139.6 °C; IR (KBr) ν 3319 (NH), 2983 (Ar—H), 1604, 1569, 1506 (Ar), 1364 (P=O), 1217, 1196 (P=O-C), 1065, 1024 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.13 (t, *J* = 7.8 Hz, 3H, CH₃), 1.30 (t, *J* = 7.2 Hz, 3H, CH₃), 3.69–3.74 (m, 1H, CH₂), 3.77 (s, 6H, 2CH₃O), 3.94–3.98 (m, 1H, CH₂), 4.10–4.16 (m, 2H, CH₂), 4.70 (dd, *J* = 7.8 Hz, *J* = 26.4 Hz, 1H, PCH), 4.73 (br s, 1H, NH), 5.77 (s, 1H, pyrimidine-H), 6.53 (dd, *J* = 4.2 Hz, *J* = 7.8 Hz, 2H, ArH), 6.80 (t, *J* = 8.4 Hz, 2H, ArH), 7.19 (d, *J* = 8.4 Hz, 2H, ArH), 7.47 (dd, *J* = 1.8 Hz, *J* = 8.4 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.74; EI-MS (70 eV) *m/z* (%) 491.4 (M⁺, 2.2), 355 (17.8), 354 (100), 353 (8.7), 197 (2.8), 111 (2.4). Anal. Calcd for C₂₃H₂₇FN₃O₆P: C, 56.21; H, 5.54; N, 8.55. Found: C, 56.43; H, 5.37; N, 8.62.

Data for compound IIIb (R = Et, Ar = 2-BrC₆H₄): white solid; yield, 70%; mp, 100.4–101.3 °C; IR (KBr) ν 3395 (NH), 2982 (Ar—H), 1592, 1573, 1505 (Ar), 1367 (P=O), 1224 (P—O—C), 1164, 1020 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.19 (t, J = 7.2 Hz, 3H, CH₃), 1.28 (t, J = 7.8 Hz, 3H, CH₃), 3.76 (s, 6H, 2CH₃O), 3.81– 3.85 (m, 1H, CH₂), 4.00–4.16 (m, 3H, CH₂), 4.80 (dd, J = 7.2 Hz, J = 24.6 Hz, 1H, PCH), 5.45 (t, J = 7.8 Hz, 1H, NH), 5.77 (s, 1H, pyrimidine-H), 6.44 (d, J = 7.8 Hz, 1H, ArH), 6.58 (t, J = 7.2 Hz, 1H, ArH), 7.01 (t, J = 7.8 Hz, 1H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.43 (d, J = 8.4 Hz, 1H, ArH), 7.48 (d, J = 8.4 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.85; EI-MS (70 eV) *m*/*z* (%) 553.4 (M⁺, 1.5), 417 (19.0), 416 (100), 415 (23.6), 414 (94.8), 259 (3.3). Anal. Calcd for C₂₃H₂₇BrN₃O₆P: C, 50.01; H, 4.93; N, 7.61. Found: C, 49.85; H, 4.80; N, 7.44.

Data for compound IIIc (R = Et, Ar = 4-ClC₆H₄): white solid; yield, 78%; mp, 142.3–143.9 °C; IR (KBr) ν 3367 (NH), 2987 (Ar— H), 1582, 1574, 1501 (Ar), 1364 (P=O), 1228 (P–O–C), 1161, 1026 (C–O–C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 1.30 (t, *J* = 7.2 Hz, 3H, CH₃), 3.65–3.72 (m, 1H, CH₂), 3.78 (s, 6H, 2CH₃O), 3.93–3.97 (m, 1H, CH₂), 4.10–4.15 (m, 2H, CH₂), 4.72 (d, *J* = 24.0 Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.52 (d, *J* = 7.8 Hz, 2H, ArH), 7.03 (d, *J* = 8.4 Hz, 2H, ArH), 7.18 (d, *J* = 8.4 Hz, 2H, ArH), 7.45 (d, *J* = 8.4 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 243 MHz) δ , 21.80. Anal. Calcd for C₂₃H₂₇ClN₃O₆P: C, 54.39; H, 5.36; N, 8.27. Found: C, 54.53; H, 5.22; N, 8.39.

Data for compound IIId (R = Et, Ar = $4 \cdot CH_3C_6H_4$): white solid; yield, 72%; mp, 133.3–134.5 °C; IR (KBr) ν 3351 (NH), 2990 (Ar—H), 1575, 1568, 1506 (Ar), 1360 (P=O), 1232 (P—O—C), 1159, 1027 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3H, CH₃), 1.29 (t, *J* = 7.2 Hz, 3H, CH₃), 2.19 (s, 3H, CH₃), 3.71–3.74 (m, 1H, CH₂), 3.78 (s, 6H, 2CH₃O), 3.93–3.99 (m, 1H, CH₂), 4.06– 4.17 (m, 2H, CH₂), 4.75 (dd, *J* = 6.0 Hz, *J* = 24.0 Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.52 (d, *J* = 7.8 Hz, 2H, ArH), 6.91 (d, *J* = 7.8 Hz, 2H, ArH), 7.17 (d, *J* = 7.8 Hz, 2H, ArH), 7.48 (d, *J* = 7.2 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 243 MHz) δ 21.58. Anal. Calcd for C₂₄H₃₀N₃O₆P: C, 59.13; H, 6.20; N, 8.62. Found: C, 59.01; H, 6.08; N, 8.51.

Data for compound **IIIe** (R = Et, Ar = 4-NO₂C₆H₄): white solid; yield, 79%; mp, 195.3–196.3 °C; IR (KBr) ν 3334 (NH), 2993 (Ar—H), 1579, 1562, 1507 (Ar), 1354 (P=O), 1229 (P—O—C), 1164, 1033 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3H, CH₃), 1.31 (t, *J* = 7.2 Hz, 3H, CH₃), 3.65–3.71 (m, 1H, CH₂), 3.79 (s, 6H, 2CH₃O), 3.93–3.98 (m, 1H, CH₂), 4.11–4.18 (m, 2H, CH₂), 4.85 (dd, *J* = 7.8 Hz, *J* = 24.0 Hz, 1H, PCH), 5.78 (s, 1H, pyrimidine-H), 5.91 (t, *J* = 8.4 Hz, 1H, NH), 6.61 (d, *J* = 9.0 Hz, 2H, ArH), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 7.48 (d, *J* = 8.4 Hz, 2H, ArH), 8.02 (d, *J* = 9.0 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 243 MHz) δ 20.49. Anal. Calcd for $C_{23}H_{27}N_4O_8P$: C, 53.28; H, 5.25; N, 10.81. Found: C, 53.12; H, 5.40; N, 10.87.

Data for compound IIIf (R = Et, Ar = 4-BrC₆H₄): white solid; yield, 81%; mp, 136.5–137.3 °C; IR (KBr) ν 3361 (NH), 2985 (Ar—H), 1579, 1572, 1499 (Ar), 1360 (P=O), 1226 (P—O—C), 1158, 1025 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 1.29 (t, *J* = 7.2 Hz, 3H, CH₃), 3.65–3.72 (m, 1H, CH₂), 3.77 (s, 6H, 2CH₃O), 3.92–3.98 (m, 1H, CH₂), 4.08–4.16 (m, 2H, CH₂), 4.72 (dd, *J* = 6.0 Hz, *J* = 24.0 Hz, 1H, PCH), 4.93 (br s, 1H, NH), 5.76 (s, 1H, pyrimidine-H), 6.47 (d, *J* = 9.0 Hz, 2H, ArH), 7.16 (d, *J* = 8.4 Hz, 2H, ArH), 7.18 (d, *J* = 8.4 Hz, 2H, ArH), 7.46 (d, *J* = 8.4 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 243 MHz) δ 21.47. Anal. Calcd for C₂₃H₂₇BrN₃O₆P: C, 50.01; H, 4.93; N, 7.61. Found: C, 49.87; H, 4.74; N, 7.80.

Data for compound **IIIg** (R = Et, Ar = C₆H₅): white solid; yield, 74%; mp, 131.7–133.1 °C; IR (KBr) ν 3345 (NH), 2980 (Ar—H), 1582, 1570, 1486 (Ar), 1359 (P=O), 1223 (P—O—C), 1153, 1027 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.13 (t, *J* = 10.8 Hz, 3H, CH₃), 1.29 (t, *J* = 10.8 Hz, 3H, CH₃), 3.66–3.74 (m, 1H, CH₂), 3.78 (s, 6H, 2CH₃O), 3.93–3.99 (m, 1H, CH₂), 4.08–4.17 (m, 2H, CH₂), 4.78 (d, *J* = 24.0 Hz, 1H, PCH), 4.82 (br s, 1H, NH), 5.76 (s, 1H, pyrimidine-H), 6.60 (d, *J* = 12 Hz, 2H, ArH), 6.70 (t, *J* = 10.8 Hz, 1H, ArH), 7.10 (t, *J* = 12.0 Hz, 2H, ArH), 7.18 (d, *J* = 12.0 Hz, 2H, ArH), 7.49 (d, *J* = 12.0 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 243 MHz) δ 21.76. Anal. Calcd for C₂₃H₂₈N₃O₆P: C, 58.35; H, 5.96; N, 8.88. Found: C, 58.51; H, 6.03; N, 8.74.

Data for compound **IIIh** (R = Et, Ar = 2,4-Cl₂C₆H₃): white solid; yield, 73%; mp, 147.5–148.7 °C; IR (KBr) ν 3364 (NH), 2982 (Ar—H), 1577, 1570, 1500 (Ar), 1360 (P=O), 1223 (P—O—C), 1159, 1022 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.18 (t, *J* = 10.8 Hz, 3H, CH₃), 1.28 (t, *J* = 10.8 Hz, 3H, CH₃), 3.79 (s, 6H, 2CH₃O), 3.80–3.83 (m, 1H, CH₂), 3.98–4.17 (m, 3H, CH₂), 4.74 (dd, *J* = 10.8 Hz, *J* = 36.0 Hz, 1H, PCH), 5.39 (dd, *J* = 10.8 Hz, *J* = 15.6 Hz, 1H, NH), 5.77 (s, 1H, pyrimidine-H), 6.38 (d, *J* = 13.2 Hz, 1H, ArH), 6.93 (d, *J* = 13.2 Hz, 1H, ArH), 7.20 (d, *J* = 12.6 Hz, 2H, ArH), 7.27 (s, 1H, ArH), 7.44 (dd, *J* = 3.6 Hz, *J* = 13.2 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 243 MHz) δ 19.98. Anal. Calcd for C₂₃H₂₆Cl₂N₃O₆P: C, 50.94; H, 4.83; N, 7.75. Found: C, 50.81; H, 4.88; N, 7.91.

Data for compound IIIi (R = Me, Ar = 4-ClC₆H₄): white solid; yield, 87%; mp, 145.0–146.4 °C; IR (KBr) ν 3351 (NH), 2980 (Ar—H), 1577, 1571, 1496 (Ar), 1353 (P=O), 1231 (P—O—C), 1159, 1022 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.48 (d, *J* = 10.4 Hz, 3H, OCH₃), 3.77 (s, 6H, 2CH₃O), 3.79 (d, *J* = 10.4 Hz, 3H, OCH₃), 4.76 (d, *J* = 25.6 Hz, 1H, PCH), 4.87 (br s, 1H, NH), 5.77 (s, 1H, pyrimidine-H), 6.52 (d, *J* = 8.8 Hz, 2H, ArH), 7.04 (d, *J* = 8.8 Hz, 2H, ArH), 7.20 (d, *J* = 8.4 Hz, 2H, ArH), 7.47 (dd, *J* = 2.4 Hz, *J* = 8.8 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 23.49. Anal. Calcd for C₂₁H₂₃ClN₃O₆P: C, 52.56; H, 4.83; N, 8.76. Found: C, 54.72; H, 4.97; N, 8.94.

Data for compound IIIj (R = Et, Ar = $2 \cdot FC_6H_4$): white solid; yield, 73%; mp, 133.6–135.1 °C; IR (KBr) ν 3318 (NH), 2991 (Ar—H), 1559, 1561, 1477, 1463 (Ar), 1366 (P=O), 1227, 1170 (P—O—C), 1052, 1028 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H, CH₃), 1.28 (t, *J* = 7.2 Hz, 3H, CH₃), 3.77 (s, 6H, 2CH₃O), 3.80–3.84 (m, 1H, CH₂), 3.95–4.03 (m, 1H, CH₂), 4.05–4.16 (m, 2H, CH₂), 4.77 (d, *J* = 22.8 Hz, 1H, PCH), 4.98 (br s, 1H, NH), 5.77 (s, 1H, pyrimidine-H), 6.51(t, *J* = 8.4 Hz, 1H, ArH), 6.63(q, *J* = 7.6 Hz, 1H, ArH), 6.83 (t, *J* = 7.6 Hz, 1H, ArH), 6.97 (t, *J* = 9.6 Hz, 1H, ArH), 7.19 (d, *J* = 8.4 Hz, 2H, ArH), 7.48 (dd, *J* = 2.4 Hz, *J* = 8.8 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.73. Anal. Calcd for C₂₃H₂₇FN₃O₆P: C, 56.21; H, 5.54; N, 8.55. Found: C, 56.31; H, 5.39; N, 8.42.

General Procedure for the Preparation of O,O'-Dialkyl (Diphenyl) N-[2-(4,6-Dimethoxypyrimidin-2-yloxy or thio phenyl]-1-amino (Substituted Phenyl) Methyl Phosphonates IV. The mixture of amine 2 (3 mmol), dialkyl phosphite or diphenyl phosphite (3 mmol), substituted benzaldehyde (3.3 mmol), and

Scheme	3.	Syntl	netic	Route	of	Title	Compound	s :	I	7
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H ₃		H ₃ +	$\begin{array}{c} H_3CO \\ H_3CO \\ NH_2 \\ K_2CO_3 \\ XH \\ THF or DMF \\ H_2 \\ 2a (X=O), 2b (N) \end{array}$.OCH3 ArCHO + HI o X=S)	PO(OR)2 Mg(r HP(OPh)2 C	H_3CO H_3CN	$N \rightarrow N$ $X \rightarrow OR$ $N \rightarrow OR$ $N \rightarrow OR$ $N \rightarrow O'OR$ $Va \rightarrow IVv$ $(X = 0, S)$
Compd.	R	Х	Ar	Compd.	R	Х	Ar
IVa	Et	S	C_6H_5	IVb	Et	S	$4-CH_3-C_6H_4$
IVc	Et	S	$4-CH_3O-C_6H_4$	IVd	Et	S	$4-F-C_6H_4$
IVe	Et	S	2-F-C ₆ H ₄	IVf	Et	S	$2-Cl-C_6H_4$
IVg	Et	S	$4-Cl-C_6H_4$	IVh	Me	S	$4-Cl-C_6H_4$
IVi	Ph	S	$4-Cl-C_6H_4$	IVj	Et	S	$4-Br-C_6H_4$
IVk	Et	S	$3-NO_2-C_6H_4$	IVI	Et	S	$4-NO_2-C_6H_4$
IVm	Et	S	2,4-(CH ₃ O) ₂ -C ₆ H ₃	IVn	Et	S	2,4-Cl ₂ -C ₆ H ₃
IVo	Et	S	$4-HO-C_6H_4$	IVp	Et	Ο	C_6H_5
IVq	Et	Ο	$2-Cl-C_6H_4$	IVr	Et	Ο	2-F-C ₆ H ₄
IVs	Et	Ο	$4-F-C_6H_4$	IVt	Et	Ο	$4-Cl-C_6H_4$
IVu	Et	0	$4-CH_3-C_6H_4$	IVv	Et	0	$4-NO_2-C_6H_4$

anhydrous Mg(ClO₄)₂ (0.033 g, 0.15 mmol) in anhydrous acetonitrile (5 mL) was stirred at 50–60 °C until the reaction completed (monitored by TLC). The solid was filtered off, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using a mixture of petroleum ether and acetone (v/v, 2:1) as eluent to yield the target compound **IV** (Scheme 3) as white solid or light yellow oil.

Data for compound IVa (R = Et, X = S, Ar = C₆H₅): white solid; yield, 68%; mp, 120.3–122.2 °C; IR (KBr) ν 3345 (NH), 2985 (Ar—H), 1586, 1552, 1504 (Ar), 1370 (P=O), 1278, 1190 (P=O–C), 1042, 1015 (C=O–C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.10 (t, *J* = 7.2 Hz, 3H, CH₃), 1.18 (t, *J* = 7.2 Hz, 3H, CH₃), 3.64 (s, 6H, 2CH₃O), 3.70–3.74 (m, 1H, CH₂), 3.89–3.95 (m, 2H, CH₂), 3.99–4.02 (m, 1H, CH₂), 4.78 (dd, *J* = 7.8 Hz, *J* = 24.0 Hz, 1H, PCH), 5.72 (s, 1H, pyrimidine-H), 5.91 (t, *J* = 8.4 Hz, 1H, NH), 6.48 (d, *J* = 8.4 Hz, 1H, ArH), 6.68 (t, *J* = 7.2 Hz, 1H, ArH), 7.15 (t, *J* = 7.8 Hz, 1H, ArH), 7.23–7.28 (m, 3H, ArH), 7.35 (d, *J* = 7.8 Hz, 2H, ArH), 7.46 (d, *J* = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.96; EI-MS (70 eV) *m*/*z* (%) 489.4 (M⁺, 5.0), 354 (7.0), 353 (22.9), 352 (100), 212 (14.8), 180 (6.1), 136 (3.5), 109 (4.9). Anal. Cacld for C₂₃H₂₈N₃O₅PS: C, 56.43; H, 5.77; N, 8.58. Found: C, 56.65; H, 5.58; N, 8.70.

Data for compound **IVb** (R = Et, X = S, Ar = 4-CH₃C₆H₄): white solid; yield, 72%; mp, 109.1–110.3 °C; IR (KBr) ν 3347 (NH), 2988 (Ar—H), 1581, 1558, 1501 (Ar), 1366 (P=O), 1275, 1182 (P=O-C), 1041, 1021 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 1.19 (t, *J* = 7.2 Hz, 3H, CH₃), 2.30 (s, 3H, CH₃), 3.64 (s, 6H, 2CH₃O), 3.72–3.76 (m, 1H, CH₂), 3.90–3.95 (m, 2H, CH₂), 3.99–4.03 (m, 1H, CH₂), 4.74 (dd, *J* = 7.8 Hz, *J* = 24.6 Hz, 1H, PCH), 5.72 (s, 1H, pyrimidine-H), 5.86 (t, *J* = 9.0 Hz, 1H, NH), 6.50 (d, *J* = 8.4 Hz, 1H, ArH), 6.68 (t, *J* = 7.2 Hz, 1H, ArH), 7.06 (d, *J* = 7.8 Hz, 2H, ArH), 7.15 (t, *J* = 7.2 Hz, 1H, ArH), 7.06 (d, *J* = 7.8 Hz, 2H, ArH), 7.45 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.16; EI-MS (70 eV) *m/z* (%) 503.3 (M⁺, 4.7), 368 (7.5), 367 (23.7), 366 (100), 274 (7.0), 226 (18.2), 194 (6.8). Anal. Calcd for C₂₄H₃₀N₃O₃PS: C, 57.24; H, 6.00; N, 8.34. Found: C, 57.11; H, 6.13; N, 8.24.

Data for compound IVc (R = Et, X = S, Ar = 4-CH₃OC₆H₄): white solid; yield, 66%; mp, 169.7–170.9 °C; IR (KBr) ν 3342 (NH), 2984 (Ar—H), 1583, 1549, 1508 (Ar), 1371 (P=O), 1260, 1193 (P—O—C), 1054, 1014 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 1.18 (t, *J* = 7.2 Hz, 3H, CH₃), 3.64 (s, 6H, 2CH₃O), 3.71–3.75 (m, 1H, CH₂), 3.77 (s, 3H, OCH₃), 3.88–3.95 (m, 2H, CH₂), 3.97–4.03 (m, 1H, CH₂), 4.73 (dd, *J* = 6.0 Hz, *J* = 24.0 Hz, 1H, PCH), 5.72 (s, 1H, pyrimidine-H), 5.84 (t, *J* = 7.8 Hz, 1H, NH), 6.50 (d, *J* = 8.4 Hz, 1H, ArH), 6.68 (t, *J* = 7.8 Hz, 1H, ArH), 6.80 (d, *J* = 8.4 Hz, 2H, ArH), 7.16 (t, *J* = 8.4 Hz, 1H, ArH), 7.25 (d, *J* = 7.8 Hz, 2H, ArH), 7.45 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.23; EI-MS (70 eV) *m*/*z* (%) 519.3 (M⁺, 3.9), 384 (7.8), 383 (23.7), 382 (100), 274 (11.8), 247 (3.4), 243 (3.6), 242 (21.9), 210 (4.5). Anal. Calcd for C₂₄H₃₀N₃O₆PS: C, 55.48; H, 5.82; N, 8.09. Found: C, 57.63; H, 5.73; N, 7.97.

Data for compound **IVd** (R = Et, X = S, Ar = 4-FC₆H₄): white solid; yield, 69%; mp, 164.6–165.9 °C; IR (KBr) ν 3348 (NH), 2984 (Ar—H), 1586, 1550, 1503 (Ar), 1372 (P=O), 1293, 1194 (P—O—C), 1045, 1014 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3H, CH₃), 1.18 (t, *J* = 7.2 Hz, 3H, CH₃), 3.65 (s, 6H, 2CH₃O), 3.76–3.79 (m, 1H, CH₂), 3.91–3.96 (m, 2H, CH₂), 4.00–4.02 (m, 1H, CH₂), 4.76 (dd, *J* = 5.4 Hz, *J* = 24.6 Hz, 1H, PCH), 5.73 (s, 1H, pyrimidine-H), 5.86 (br s, 1H, NH), 6.44 (d, *J* = 7.8 Hz, 1H, ArH), 6.70 (t, *J* = 7.8 Hz, 1H, ArH), 6.97 (t, *J* = 9.0 Hz, 2H, ArH), 7.16 (t, *J* = 7.8 Hz, 1H, ArH), 7.33 (t, *J* = 6.0 Hz, 2H, ArH), 7.47 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.40; EI-MS (70 eV) *m*/*z* (%) 507.3 (M⁺, 5.2), 372 (6.3), 371 (21.8), 370 (100), 274 (5.0), 230 (16.5), 198 (7.6), 136 (4.4), 109 (9.6). Anal. Calcd for C₂₃H₂₇FN₃O₅PS: C, 54.43; H, 5.36; N, 8.28. Found: C, 54.55; H, 5.51; N, 8.40.

Data for compound IVe (R = Et, X = S, Ar = 2-FC₆H₄): white solid; yield, 72%; mp, 138.6–139.5 °C; IR (KBr) ν 3345 (NH), 2987 (Ar—H), 1582, 1551 (Ar), 1370 (P=O), 1289, 1191 (P—O—C), 1048, 1016 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.10 (t, *J* = 6.6 Hz, 3H, CH₃), 1.23 (t, *J* = 7.2 Hz, 3H, CH₃), 3.60 (s, 6H, 2CH₃O), 3.78–3.81 (m, 1H, CH₂), 3.93–3.97 (m, 1H, CH₂), 4.05–4.12 (m, 2H, CH₂), 5.22 (dd, *J* = 8.4 Hz, *J* = 24.6 Hz, 1H, PCH), 5.70 (s, 1H, pyrimidine-H), 5.90 (t, *J* = 6.0 Hz, 1H, NH), 6.59 (d, *J* = 8.4 Hz, 1H,

ArH), 6.70 (t, J = 7.2 Hz, 1H, ArH), 6.99 (t, J = 7.8 Hz, 1H, ArH), 7.04 (t, J = 9.0 Hz, 1H, ArH), 7.18–7.24 (m, 2H, ArH), 7.27 (t, J =7.2 Hz, 1H, ArH), 7.45 (dd, J = 1.2 Hz, J = 8.4 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.33; EI-MS (70 eV) m/z (%) 507.3 (M⁺, 6.0), 372 (6.6), 371 (22.0), 370 (100), 274 (3.9), 247 (2.8), 230 (16.2), 198 (5.6), 139 (4.2), 136 (4.2), 109 (6.5). Anal. Calcd for C₂₃H₂₇FN₃O₅PS: C, 54.43; H, 5.36; N, 8.28. Found: C, 54.37; H, 5.17; N, 8.33.

Data for compound **IVf** (R = Et, X = S, Ar = $2\text{-ClC}_{6}H_{4}$): white solid; yield, 75%; mp, 140.7–141.4 °C; IR (KBr) ν 3356 (NH), 2982 (Ar—H), 1587, 1550 (Ar), 1373 (P=O), 1289, 1191 (P—O—C), 1050, 1027 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.07 (t, *J* = 7.2 Hz, 3H, CH₃), 1.24 (t, *J* = 7.2 Hz, 3H, CH₃), 3.60 (s, 6H, 2CH₃O), 3.66–3.73 (m, 1H, CH₂), 3.87–3.94 (m, 1H, CH₂), 4.04–4.13 (m, 2H, CH₂), 5.40 (dd, *J* = 8.4 Hz, *J* = 24.6 Hz, 1H, PCH), 5.71 (s, 1H, pyrimidine-H), 6.03 (t, *J* = 9.0 Hz, 1H, NH), 6.52 (d, *J* = 8.4 Hz, 1H, ArH), 7.18 (d, *J* = 7.2 Hz, 2H, ArH), 7.10 (t, *J* = 7.8 Hz, 1H, ArH), 7.36 (d, *J* = 7.8 Hz, 1H, ArH), 7.44 (d, *J* = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.52; EI-MS (70 eV) *m/z* (%) 523.3 (M⁺, 0.39), 489 (4.6), 488 (18.4), 389 (8.4), 388 (42.9), 387 (20.5), 386 (100). Anal. Calcd for C₂₃H₂₇ ClN₃O₅PS: C, 52.72; H, 5.19; N, 8.02. Found: C, 52.51; H, 5.07; N, 8.14.

Data for compound IVg (R = Et, X = S, Ar = 4-ClC₆H₄): white solid; yield, 78%; mp, 143.2-144.4 °C; IR (KBr) v 3359 (NH), 2980 (Ar-H), 1584, 1553 (Ar), 1370 (P=O), 1285, 1193 (P-O-C), 1049, 1024 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.14 (t, J = 7.2 Hz, 3H, CH₃), 1.18 (t, J = 7.2 Hz, 3H, CH₃), 3.66 (s, 6H, 2CH₃O), 3.78-3.84 (m, 1H, CH₂), 3.91-3.98 (m, 2H, CH₂), 4.00-4.04 (m, 1H, CH₂), 4.75 (dd, J = 7.2 Hz, J = 24.6 Hz, 1H, PCH), 5.74 (s, 1H, pyrimidine-H), 5.86 (t, J = 7.8 Hz, 1H, NH), 6.42 (d, J = 8.4 Hz, 1H, ArH), 6.71 (t, J = 7.2 Hz, 1H, ArH), 7.16 (t, J = 7.8 Hz, 1H, ArH), 7.25 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 6.6 Hz, 2H, ArH), 7.47 (d, J = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.62; EI-MS (70 eV) m/z (%) 523.3 (M⁺, 5.6), 389 (6.6), 388 (34.0), 387 (22.5), 386 (100), 248 (8.2), 247 (7.4), 246 (18.8), 214 (5.2), 140 (4.8), 139 (6.8), 136 (5.7), 109 (9.7). Anal. Calcd for C23H27ClN3O5PS: C, 52.72; H, 5.19; N, 8.02. Found: C, 52.83; H, 5.35; N, 8.09.

Data for compound **IVh** (R = Me, X = S, Ar = 4-ClC₆H₄): white solid; yield, 69%; mp, 157.8–158.4 °C; IR (KBr) ν 3368 (NH), 2985 (Ar—H), 1577, 1550 (Ar), 1377 (P=O), 1281, 1196 (P=O–C), 1054, 1027 (C=O–C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 3.52 (d, *J* = 10.2 Hz, 3H, OCH₃), 3.64 (d, *J* = 10.8 Hz, 3H, OCH₃), 3.66 (s, 6H, 2CH₃O), 4.78 (dd, *J* = 7.2 Hz, *J* = 24.0 Hz, 1H, PCH), 5.73 (s, 1H, pyrimidine-H), 5.81 (t, *J* = 7.2 Hz, 1H, NH), 6.45 (d, *J* = 8.4 Hz, 1H, ArH), 6.72 (t, *J* = 7.8 Hz, 1H, ArH), 7.17 (t, *J* = 7.8 Hz, 1H, ArH), 7.25 (d, *J* = 7.8 Hz, 2H, ArH), 7.32 (d, *J* = 7.2 Hz, 2H, ArH), 7.47 (d, *J* = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 22.83; EI-MS (70 eV) *m*/*z* (%) 495.2 (10.7), 493.8 (M⁺, 100), 213 (10.2), 212 (95.2), 202 (27.0), 81 (6.6). Anal. Calcd for C₂₁H₂₃ClN₃O₅PS: C, 50.86; H, 4.67; N, 8.47. Found: C, 50.66; H, 4.80; N, 8.29.

Data for compound IVi (R = Ph, X = S, Ar = 4-ClC₆H₄): white solid; yield, 67%; mp, 129.6–130.8 °C; IR (KBr) ν 3372 (NH), 2987 (Ar—H), 1571, 1553 (Ar), 1374 (P=O), 1275, 1190 (P—O—C), 1057, 1025 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 3.63 (s, 6H, 2CH₃O), 5.11 (dd, *J* = 7.8 Hz, *J* = 25.2 Hz, 1H, PCH), 5.68 (s, 1H, pyrimidine-H), 6.09 (t, *J* = 7.8 Hz, 1H, NH), 6.50 (d, *J* = 8.4 Hz, 1H, ArH), 6.76 (t, *J* = 7.2 Hz, 1H, ArH), 6.91 (d, *J* = 8.4 Hz, 2H, ArH), 6.94 (d, *J* = 8.4 Hz, 2H, ArH), 7.11 (t, *J* = 7.8 Hz, 2H, ArH), 7.18–7.25 (m, 7H, ArH), 7.37 (d, *J* = 9.0 Hz, 2H, ArH), 7.51 (d, *J* = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 12.99; EI-MS (70 eV) *m*/*z* (%) 619.4 (9.3), 618.7 (M⁺, 16.2), 617 (15.1), 608 (22.3), 607 (16.9), 556 (13.8), 504 (11.9), 415 (11.0), 254 (57.8), 253 (73.2), 200 (100). Anal. Calcd for C₃₁H₂₂ClN₃O₅PS: C, 60.05; H, 4.39; N, 6.78. Found: C, 59.87; H, 4.44; N, 6.97.

Data for compound **IV**j (R = Et, X = S, Ar = 4-BrC₆H₄): white solid; yield, 64%; mp, 135.6–136.5 °C; IR (KBr) ν 3363 (NH), 2982 (Ar—H), 1580, 1557 (Ar), 1366 (P=O), 1289, 1190 (P=O=C), 1057, 1028 (C=O=C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.14

(t, *J* = 7.2 Hz, 3H, CH₃), 1.18 (t, *J* = 7.2 Hz, 3H, CH₃), 3.66 (s, 6H, 2CH₃O), 3.78–3.85 (m, 1H, CH₂), 3.91–4.04 (m, 3H, CH₂), 4.73 (dd, *J* = 7.2 Hz, *J* = 24.6 Hz, 1H, PCH), 5.74 (s, 1H, pyrimidine-H), 5.85 (t, *J* = 9.0 Hz, 1H, NH), 6.42 (d, *J* = 8.4 Hz, 1H, ArH), 6.71 (t, *J* = 7.2 Hz, 1H, ArH), 7.16 (t, *J* = 7.2 Hz, 1H, ArH), 7.24 (d, *J* = 8.4 Hz, 2H, ArH), 7.40 (d, *J* = 8.4 Hz, 2H, ArH), 7.47 (d, *J* = 7.2 Hz, 1H, ArH), 6.42 (m, 20.85; EI-MS (70 eV) m/z (%) 569.2 (6.0), 567.2 (M⁺, 6.4), 433 (20.1), 432 (100), 431 (21.6), 430 (95.5), 292 (15.9), 290 (13.5), 247 (5.6), 211 (6.8), 140 (7.2), 139 (7.4), 136 (9.7), 109 (8.8). Anal. Calcd for C₂₃H₂₇BrN₃O₅PS: C, 48.60; H, 4.79; N, 7.39. Found: C, 48.71; H, 4.55; N, 7.17.

Data for compound **IVk** (R = Et, X = S, Ar = $3 \cdot NO_2C_6H_4$): light yellow solid; yield, 69%; mp, 173.2–174.3 °C; IR (KBr) ν 3352 (NH), 2979 (Ar—H), 1587, 1551 (Ar), 1362 (P=O), 1292, 1186 (P—O–C), 1053, 1025 (C–O–C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H, CH₃), 1.20 (t, *J* = 7.2 Hz, 3H, CH₃), 3.66 (s, 6H, 2CH₃O), 3.86–3.93 (m, 1H, CH₂), 3.95–4.09 (m, 2H, CH₂), 4.13–4.20 (m, 1H, CH₂), 4.88 (dd, *J* = 7.2 Hz, *J* = 25.2 Hz, 1H, PCH), 5.75 (s, 1H, pyrimidine-H), 5.95 (t, *J* = 8.4 Hz, 1H, NH), 6.41 (d, *J* = 8.4 Hz, 1H, ArH), 6.75 (t, *J* = 7.2 Hz, 1H, ArH), 7.17 (t, *J* = 7.8 Hz, 1H, ArH), 7.73 (d, *J* = 7.8 Hz, 1H, ArH), 8.13 (d, *J* = 7.8 Hz, 1H, ArH), 8.25 (s, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 19.35; EI-MS (70 eV) *m*/*z* (%) 534.3 (M⁺, 5.5), 399 (7.9), 398 (23.4), 397 (100), 212 (4.3), 140 (5.4), 136 (8.4). Anal. Calcd for C₂₃H₂₇N₄O₇PS: C, 51.68; H, 5.09; N, 10.48. Found: C, 51.87; H, 5.23; N, 10.61.

Data for compound IV1 (R = Et, X = S, Ar = 4-NO₂C₆H₄): light yellow solid; yield, 74%; mp, 180.2–181.5 °C; IR (KBr) ν 3340 (NH), 2959 (Ar—H), 1574, 1544 (Ar), 1359 (P=O), 1285, 1180 (P—O—C), 1049, 1027 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.17 (t, *J* = 7.2 Hz, 3H, CH₃), 1.19 (t, *J* = 7.2 Hz, 3H, CH₃), 3.69 (s, 6H, 2CH₃O), 3.86–3.92 (m, 1H, CH₂), 3.93–3.97 (m, 1H, CH₂), 3.99–4.07 (m, 2H, CH₂), 4.89 (dd, *J* = 6.0 Hz, *J* = 25.2 Hz, 1H, PCH), 5.76 (s, 1H, pyrimidine-H), 5.92 (t, *J* = 7.2 Hz, 1H, NH), 6.35 (d, *J* = 7.8 Hz, 1H, ArH), 6.74 (t, *J* = 7.2 Hz, 1H, ArH), 7.16 (t, *J* = 7.8 Hz, 1H, ArH), 7.50 (d, *J* = 7.2 Hz, 1H, ArH), 7.58 (d, *J* = 7.2 Hz, 2H, ArH), 8.15 (d, *J* = 8.4 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 19.14; EI-MS (70 eV) *m*/*z* (%) 534.3 (M⁺, 6.7), 399 (7.1), 398 (21.0), 397 (100), 211 (4.0), 140 (5.3), 136 (6.7). Anal. Calcd for C₂₃H₂₇N₄O₇PS: C, 51.68; H, 5.09; N, 10.48. Found: C, 51.52; H, 5.05; N, 10.39.

Data for compound IVm (R = Et, X = S, Ar = $2,4-(MeO)_2C_6H_3$): white solid; yield, 69%; mp, 110.9-112.1 °C; IR (KBr) v 3345 (NH), 2951 (Ar-H), 1578, 1541 (Ar), 1350 (P=O), 1283, 1184 (P-O-C), 1055, 1028 (C-O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.08 (t, J = 7.2 Hz, 3H, CH₃), 1.22 (t, J = 7.2 Hz, 3H, CH₃), 3.59 (s, 6H, 2CH₃O), 3.69-3.73 (m, 1H, CH₂), 3.75 (s, 3H, CH₃O), 3.88 (s, 3H, CH₃O), 3.89-3.92 (m, 1H, CH₂), 4.00-4.10 (m, 2H, CH₂), 5.30 (dd, J = 9.0 Hz, J = 24.6 Hz, 1H, PCH), 5.69 (s, 1H, pyrimidine-H), 5.87 (t, J = 9.0 Hz, 1H, NH), 6.32 (d, J = 8.4 Hz, 1H, ArH), 6.42 (s, 1H, ArH), 6.59 (d, J = 8.4 Hz, 1H, ArH), 6.65 (t, J = 7.2 Hz, 1H, ArH), 7.09 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H, ArH), 7.17 (t, J = 7.2 Hz, 1H, ArH), 7.41 (d, J = 7.8 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 22.09; EI-MS (70 eV) m/z (%) 549.3 (M⁺, 0.7), 414 (6.9), 413 (24.6), 412 (100), 274 (9.1), 273 (6.8), 272 (38.2). Anal. Calcd for C₂₅H₃₂N₃O₇PS: C, 54.64; H, 5.87; N, 7.65. Found: C, 54.70; H, 5.93: N. 7.47.

Data for compound **IVn** (R = Et, X = S, Ar = 2,4-Cl₂C₆H₃): white solid; yield, 74%; mp, 190.2–191.3 °C; IR (KBr) ν 3348 (NH), 2955 (Ar—H), 1584, 1546 (Ar), 1352 (P=O), 1287, 1178 (P=O-C), 1051, 1033 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 1.24 (t, *J* = 7.2 Hz, 3H, CH₃), 3.63 (s, 6H, 2CH₃O), 3.76–3.82 (m, 1H, CH₂), 3.91–3.97 (m, 1H, CH₂), 4.04–4.13 (m, 2H, CH₂), 5.33 (dd, *J* = 8.4 Hz, *J* = 24.6 Hz, 1H, PCH), 5.73 (s, 1H, pyrimidine-H), 5.97 (t, *J* = 9.0 Hz, 1H, NH), 6.47 (d, *J* = 7.8 Hz, 1H, ArH), 6.72 (t, *J* = 7.2 Hz, 1H, ArH), 7.09 (d, *J* = 8.4 Hz, 1H, ArH), 7.39 (s, 1H, ArH), 7.45 (d, *J* = 9.0 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.69; EI-MS (70 eV) *m/z* (%) 557.3 (M⁺, 0.5), 524 (6.1), 523 (5.4), 522 (14.8), 424 (14.2), 423 (14.6),

Table 1.	Herbicide	Activity o	f Some (Compounds	I–III (i	n Vitro.	Plate Method	Inhibition	Percent)	a
Table 1.	Tierbicide	Activity 0	I Some C	Joinpounds	ı) m–ı (ı	n viuo,	Flate Methou	, minutuon	reicent)	

compd	Arabidops	is thaliana (10 mg/L)	Poa a	annua (32 m	ng/L)	compd	Arabidops	is thaliana (10 mg/L)	Poa a	nnua (32 m	ng/L)
Is	99	99	99	99	99	99	IIIb	99	99	99	0	0	0
It	99	99	99	99	99	99	IIIc	99	99	99	0	0	0
Iu	0	0	0	99	99	99	IIId	99	99	99	0	0	0
Iv	99	99	99	99	99	99	IIIe	99	99	99	0	0	0
Iw	99	99	99	99	99	99	IIIf	99	99	99	0	0	0
Ix	99	99	99	99	99	99	IIIg	99	99	99	0	0	0
IIa	99	99	99	99	0	49	IIIh	99	99	99	0	0	0
IIb	0	0	0	0	0	0	IIIi	99	99	99	0	0	0
IIIa	99	99	99	0	0	0	IIIj	99	99	99	0	0	0
^a Each samp	ole was test	ed against	each plant	three tim	es.								

Table 2. Herbicide	Activity of Some Comp	ounds I–IV (in Vivo,	Glass House Screen,	GH1) ^{a,b}
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			posteme	rgence			pre-eme	rgence			
compd	dopse (g/ha)	Amaranthus retroflexus	Lolium perenne	Stellaria media	Digitaria sanguinalis	Amaranthus retroflexus	Lolium perenne	Stellaria media	Digitaria sanguinalis	sympto	omology
Ib	1000	100	80	80	80	80	80	60	70	ST	NC
Ic	1000	100	80	80	70	70	70	80	60	NC	ST
If	1000	70	60	40	40	30	20	0	0	NC	ST
Ig	1000	100	80	80	60	80	90	50	70	ST	NC
Ii	1000	100	70	70	60	70	50	10	20	NC	ST
Ik	1000	90	60	60	60	70	40	40	30	NC	CL
In	1000	90	70	60	70	70	70	60	20	NC	CL
Ip	1000	70	30	40	20	70	0	0	0	ST	MR
Iq	1000	0	0	0	0	0	0	0	0		
Is	1000	100	100	70	80	80	80	40	50	NC	BL
It	1000	90	100	80	80	70	80	70	90	NC	ST
Iu	1000	90	60	40	50	70	60	30	30	ST	CL
Iv	1000	100	20	50	0	70	20	40	0	NC	ST
Iw	1000	70	20	20	0	20	0	0	0	CL	NC
Ix	1000	70	20	20	40	60	60	40	60	BL	ST
IIIa	1000	30	0	0	0	0	0	0	0	MR	DG
acetochlor	750	40	70	90	70	100	100	90	100	GI	ST
atrazine	1000	100	100	90	80	100	100	100	50	NC	GI
glyphosate	1000	100	100	90	100	40	100	90	10	NC	ST
mesotrione	250	100	80	100	100	100	70	100	100	BL	NC

^aScores are given as percent phytotoxicity score. The higher the score (% phytotoxicity), the greater the efficacy of the compound. Herbicide symptomologies are given as a phytotoxicity type: NC, necrosis; ST, stunting; GI, germination inhibition; CL, chlorosis; DG, darker green; BL, bleaching. ^bCompounds **II–IV** displayed no herbicidal activity in the GH1 bioassay screening.

422 (70.4), 421 (21.6), 420 (100), 384 (5.8). Anal. Calcd for $C_{23}H_{26}Cl_2N_3O_5PS:$ C, 49.47; H, 4.69; N, 7.52. Found: C, 49.33; H, 4.40; N, 7.73.

Data for compound **IVo** (R = Et, X = S, Ar = 4-HOC₆H₄): white solid; yield, 75%; mp, 201.3–202.5 °C; IR (KBr) ν 3365 (NH), 2987 (Ar—H), 1573, 1559 (Ar), 1361 (P=O), 1284, 1183 (P=O-C), 1056, 1034 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.15 (t, *J* = 7.2 Hz, 3H, CH₃), 1.18 (t, *J* = 7.2 Hz, 3H, CH₃), 3.63 (s, 6H, 2CH₃O), 3.71–3.74 (m, 1H, CH₂), 3.78–3.83 (m, 1H, CH₂), 3.89–4.03 (m, 2H, CH₂), 4.71 (dd, *J* = 7.8 Hz, *J* = 24.0 Hz, 1H, PCH), 5.70 (s, 1H, pyrimidine-H), 5.78 (t, *J* = 8.4 Hz, 1H, NH), 6.50 (d, *J* = 8.4 Hz, 1H, ArH), 6.56 (d, *J* = 8.4 Hz, 2H, ArH), 6.69 (t, *J* = 7.2 Hz, 1H, ArH), 7.45 (d, *J* = 7.8 Hz, 1H, ArH), 7.06 (br s, 1H, OH); ³¹P NMR (CDCl₃, 162 MHz) δ 22.79; EI-MS (70 eV) *m/z* (%) 505.3 (M⁺, 5.0), 370 (9.1), 369 (22.5), 368 (100), 274 (10.9), 263 (6.1), 230 (15.3), 228 (23.4), 196 (5.7). Anal. Calcd for C₂₃H₂₈N₃O₆PS: C, 54.65; H, 5.58; N, 8.31. Found: C, 54.50; H, 5.74; N, 8.57.

Data for compound **IVp** (R = Et, X = O, Ar = C_6H_5): light yellow oil; yield, 68%; IR (KBr) ν 3371 (NH), 2984 (Ar—H), 1570, 1552 (Ar), 1357 (P=O), 1280, 1175 (P=O-C), 1046, 1023 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.09 (t, *J* = 7.2 Hz, 3H, CH₃),

1.18 (t, *J* = 7.2 Hz, 3H, CH₃), 3.66–3.74 (m, 1H, CH₂), 3.80 (s, 6H, 2CH₃O), 3.88–4.06 (m, 3H, CH₂), 4.77 (d, *J* = 24.0 Hz, 1H, PCH), 5.04 (br s, 1H, NH), 5.79 (s, 1H, pyrimidine-H), 6.54 (d, *J* = 8.0 Hz, 1H, ArH), 6.69 (t, *J* = 7.6 Hz, 1H, ArH), 6.95 (t, *J* = 7.6 Hz, 1H, ArH), 7.05 (d, *J* = 8.0 Hz, 1H, ArH), 7.24–7.30 (m, 3H, ArH), 7.40 (d, *J* = 7.6 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.03. Anal. Calcd for C₂₃H₂₈N₃O₆P: C, 58.35; H, 5.96; N, 8.88. Found: C, 58.51; H, 6.07; N, 9.00.

Data for compound **IVq** (R = Et, X = O, Ar = $2\text{-ClC}_{6}H_4$): white solid; yield, 85%; mp, 90.5–91.3 °C; IR (KBr) ν 3353 (NH), 2981 (Ar—H), 1563, 1547 (Ar), 1351 (P=O), 1277, 1169 (P=O-C), 1042, 1021 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.06 (t, *J* = 7.2 Hz, 3H, CH₃), 1.24 (t, *J* = 7.2 Hz, 3H, CH₃), 3.64–3.71 (m, 1H, CH₂), 3.79 (s, 6H, 2CH₃O), 3.86–3.92 (m, 1H, CH₂), 4.05–4.14 (m, 2H, CH₂), 5.19 (t, *J* = 9.0 Hz, 1H, NH), 5.39 (dd, *J* = 9.0 Hz, *J* = 24.6 Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.56 (d, *J* = 8.4 Hz, 1H, ArH), 6.69 (t, *J* = 7.8 Hz, 1H, ArH), 6.98 (t, *J* = 7.8 Hz, 1H, ArH), 7.04 (d, *J* = 7.8 Hz, 1H, ArH), 7.17 (q, *J* = 7.2 Hz, 2H, ArH), 7.36 (d, *J* = 7.2 Hz, 1H, ArH), 7.45 (d, *J* = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.78; EI-MS (70 eV) *m*/*z* (%) 507.5 (M⁺, 4.8), 370.5 (100), 336 (4.0), 232 (5.9), 136 (6.7). Anal. Calcd for

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C₂₃H₂₇ClN₃O₆P: C, 54.39; H, 5.36; N, 8.27. Found: C, 54.41; H, 5.50; N, 8.08.

Data for compound IVr (R = Et, X = O, Ar = 2-FC₆H₄): light yellow oil; yield, 73%; IR (KBr) ν 3364 (NH), 2988 (Ar—H), 1560, 1542 (Ar), 1357 (P=O), 1270, 1173 (P—O—C), 1048, 1026 (C— O—C) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.09 (t, *J* = 6.8 Hz, 3H, CH₃), 1.23 (t, *J* = 6.8 Hz, 3H, CH₃), 3.65–3.72 (m, 1H, CH₂), 3.78 (s, 6H, 2CH₃O), 3.87–3.97 (m, 1H, CH₂), 4.04–4.13 (m, 2H, CH₂), 5.07 (t, *J* = 6.8 Hz, 1H, NH), 5.20 (dd, *J* = 8.0 Hz, *J* = 24.4 Hz, 1H, PCH), 5.78 (s, 1H, pyrimidine-H), 6.63 (d, *J* = 8.0 Hz, 1H, ArH), 6.71 (t, *J* = 7.6 Hz, 1H, ArH), 6.80 (d, *J* = 7.6 Hz, 1H, ArH), 6.91 (d, *J* = 7.6 Hz, 1H, ArH), 7.04 (q, *J* = 7.2 Hz, 2H, ArH), 7.22 (d, *J* = 7.2 Hz, 1H, ArH), 7.40 (t, *J* = 7.2 Hz, 1H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.34. Anal. Calcd for C₂₃H₂₇FN₃O₆P: C, 56.21; H, 5.54; N, 8.55. Found: C, 56.37; H, 5.34; N, 8.31.

Data for compound **IVs** (R = Et, X = O, Ar = 4-FC₆H₄): light yellow oil; yield, 75%; IR (KBr) ν 3353 (NH), 2972 (Ar—H), 1553, 1547 (Ar), 1351 (P=O), 1267, 1169 (P=O-C), 1052, 1029 (C=O-C) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.12 (t, *J* = 6.8 Hz, 3H, CH₃), 1.18 (t, *J* = 6.8 Hz, 3H, CH₃), 3.80 (s, 6H, 2CH₃O), 3.91–4.06 (m, 4H, CH₂), 4.77 (dd, *J* = 6.4 Hz, *J* = 24.0 Hz, 1H, PCH), 5.02 (t, *J* = 8.0 Hz, 1H, NH), 5.80 (s, 1H, pyrimidine-H), 6.51 (d, *J* = 8.0 Hz, 1H, ArH), 6.71 (t, *J* = 7.6 Hz, 1H, ArH), 6.94–7.01 (m, 3H, ArH), 7.07 (d, *J* = 7.6 Hz, 1H, ArH), 7.39 (t, *J* = 7.6 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.18. Anal. Calcd for C₂₃H₂₇FN₃O₆P: C, 56.21; H, 5.54; N, 8.55. Found: C, 56.04; H, 5.48; N, 8.63.

Data for compound **IVt** (R = Et, X = O, Ar = 4-ClC₆H₄): light yellow oil; yield, 79%; IR (KBr) ν 3356 (NH), 2979 (Ar—H), 1567, 1543 (Ar), 1359 (P=O), 1272, 1161 (P—O—C), 1045, 1028 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3H, CH₃), 1.19 (t, *J* = 6.8 Hz, 3H, CH₃), 3.81 (s, 6H, 2CH₃O), 3.90–4.06 (m, 4H, CH₂), 4.75 (d, *J* = 24.4 Hz, 1H, PCH), 4.98 (br s, 1H, NH), 5.80 (s, 1H, pyrimidine-H), 6.49 (d, *J* = 8.0 Hz, 1H, ArH), 6.71 (t, *J* = 7.6 Hz, 1H, ArH), 6.95 (t, *J* = 7.6 Hz, 1H, ArH), 7.07 (d, *J* = 7.6 Hz, 1H, ArH), 7.25 (d, *J* = 8.0 Hz, 2H, ArH), 7.35 (d, *J* = 6.4 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 20.92. Anal. Calcd for C₂₃H₂₇ClN₃O₆P: C, 54.39; H, 5.36; N, 8.27. Found: C, 54.13; H, 5.31; N, 8.33.

Data for compound **IVu** (R = Et, X = O, Ar = 4-CH₃C₆H₄): light yellow oil; yield, 66%; IR (KBr) ν 3341 (NH), 2994 (Ar—H), 1573, 1560, 1497 (Ar), 1362 (P=O), 1271, 1177 (P—O—C), 1047, 1026 (C—O—C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.10 (t, *J* = 6.6 Hz, 3H, CH₃), 1.17 (t, *J* = 6.6 Hz, 3H, CH₃), 2.28 (s, 3H, CH₃), 3.65–3.73 (m, 1H, CH₂), 3.78 (s, 6H, 2CH₃O), 3.87–3.95 (m, 2H, CH₂), 3.98–4.03 (m, 1H, CH₂), 4.75 (d, *J* = 24.0 Hz, 1H, PCH), 5.68 (br s, 1H, NH), 5.78 (s, 1H, pyrimidine-H), 6.55 (d, *J* = 7.8 Hz, 1H, ArH), 6.67 (t, *J* = 7.2 Hz, 1H, ArH), 6.93 (t, *J* = 7.8 Hz, 1H, ArH), 7.04 (d, *J* = 7.8 Hz, 1H, ArH), 7.07 (d, *J* = 7.2 Hz, 2H, ArH), 7.27 (d, *J* = 7.2 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.25; EI-MS (70 eV) *m/z* (%) 487.3 (M⁺, 4.8), 351 (24.2), 350 (100), 258 (4.2), 210 (15.8). Anal. Calcd for C₂₄H₃₀N₃O₆P: C, 59.13; H, 6.20; N, 8.62. Found: C, 59.31; H, 6.28; N, 8.50.

Data for compound IVv (R = Et, X = O, Ar = $4 \cdot NO_2C_6H_4$): white solid; yield, 64%; mp, 115.4–117.3 °C; IR (KBr) ν 3362 (NH), 2999 (Ar—H), 1570, 1564, 1492 (Ar), 1357 (P=O), 1266, 1171 (P–O–C), 1046, 1028 (C–O–C) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H, CH₃), 1.20 (t, *J* = 7.2 Hz, 3H, CH₃), 3.80 (s, 6H, 2CH₃O), 3.83–3.88 (m, 1H, CH₂), 3.98–4.04 (m, 3H, CH₂), 4.88 (dd, *J* = 6.6 Hz, *J* = 25.2 Hz, 1H, PCH), 5.08 (t, *J* = 7.8 Hz, 1H, NH), 5.82 (s, 1H, pyrimidine-H), 6.40 (d, *J* = 7.8 Hz, 1H, ArH), 6.75 (t, *J* = 7.8 Hz, 1H, ArH), 6.95 (t, *J* = 7.8 Hz, 1H, ArH), 7.10 (d, *J* = 7.8 Hz, 1H, ArH), 7.61 (d, *J* = 7.2 Hz, 2H, ArH), 7.16 (d, *J* = 7.2 Hz, 2H, ArH); ³¹P NMR (CDCl₃, 162 MHz) δ 21.03. Anal. Calcd for C₂₄H₂₇N₄O₈P: C, 53.28; H, 5.25; N, 10.81. Found: C, 53.17; H, 5.35; N, 10.98.

Herbicidal Activity Assays. All of the herbicidal activity assays (in vitro and in vivo) were performed in the bioactive activity evaluation platform at Syngenta Jealott's Hill International Research Centre.

Herbicidal Plate Assays (in Vitro). The compounds were tested for herbicidal activity against *Arabidopsis thaliana* at 10 mg/L and

Table 3. Herbicide Activity of Some Compounds I (in Vivo, Glass House Screen, GH2)^a

					posteme	rgence				symp	tomology				pre-em	ergence			s	ymptome	logy
compd	dose (g/ha)	Abutilon theophrasti	Bidens pilosa	Chenopodium album	Kochia scoparia	Echinochloa crus galli	Setaria Faberi	Eleusine indica	Sorghum halepense	-	2	Abutilon theophrasti	Bidens pilosa	Chenopodi- um album	Kochia scoparia	Echinochloa crus galli	Setaria Faberi	Eleusine indica	Sorghum halepense	-	5
Ib	1000	70	10	96	90	70	70	70	60	ST	NC	50	10	80	80	70	70	60	70	ST	C
Ic	1000	70	0	80	80	60	70	60	60	ST	NC	40	0	70	80	60	60	70	NC	ST	C
Ig	1000	50	30	100	80	60	60	60	60	ST	NC	70	50	80	80	70	70	20	70	\mathbf{ST}	IJ
li	1000	20	0	70	90	60	70	60	20	ST	NC	0	0	70	20	50	50	40	0	ST	C
Ik	1000	0	0	100	80	60	40	10	40	NC	ST	0	0	70	20	40	60	60	50	ST	BL
In	1000	30	0	70	70	60	60	50	20	ST	NC	50	0	70	20	40	60	40	0	\mathbf{ST}	
mesotrione	62.5	80	40	70	70	70	60	70	60	BL	NC	80	80	90	20	80	50	06	50	BL	ž
atrazine	300	70	20	70	50	100	100	90	60	NC	ST	40	20	NC	30	06	100	100	80	ß	ST
glyphosate	1000	80	90	100	100	60	80	60	50	NC	ST										
acetochlor	250											0	0	60	0	06	06	100	90	\mathbf{ST}	ž
^a Results fron germination	n testing (inhibition	in the GH2 ; CL, chlor	screen tosis; B	, with positiv L, bleaching.	e control	s. Scores are	: given a	s percent	: phytoto	aicity s	core. Hei	bicide sym	ptomo	ogies are g	jven as a	phytotoxici	ty type:	NC, nec	rosis; ST, s	tunting	G

	Aphis spe	cies (mixed- 1000 1	population r ng/L)	nortality,	Plutel	lla xylostella 500 m	(larval mortang/L)	ality,	Diabr	otica balteat 500 1	a (larval mort ng/L)	ality,
compd	Rep1	Rep2	Rep3	av	Rep1	Rep2	Rep3	av	Rep1	Rep2	Re p 3	av
IVs	0	99	99	66	0	0	0	0	0	0	0	0
IVt	99	99	99	99	0	0	0	0	0	99	0	33
IVI	0	0	0	0	99	99	99	99	0	0	0	0
thiamethoxam	99	99	99	99	0	0	0	0	99	99	99	99
indoxacarb	0	0	0	0	99	99	99	99	99	99	99	99

against *Poa annua* at 32 mg/L. Test plates were stored for 7 days in a controlled environment cabinet. They were scored as 0 or 99, where 99 means significant herbicidal effect and 0 means no effect. The herbicidal activity is summarized in Table 1.

Herbicide Glasshouse Screening (in Vivo, GH1). The substances were dissolved in dimethyl sulfoxide (DMSO) for storage. Subsamples to be tested were dried down and formulated into spray solution for application. The compounds were tested for pre- and postemergence activity against four weed species, with the compounds applied at 1000 g/ha. The plants were then stored in the glasshouse for 12 days. The weeds tested were *Amaranthus retroflexus, Stellaria media, Lolium perenne,* and *Digitaria sanguinalis.* Assessments were made of pecent phytotoxicity and converted to a banded score between 0 and 100, where complete control of the target is 100 and 0 is no control. Acetochlor, atrazine, mesotrione, and glyphosate were used as positive controls for the test. The herbicidal activity is summarized in Table 2.

Herbicide Glasshouse Screening (in Vivo, GH2). The substances were dissolved in DMSO for storage. Subsamples to be tested were dried down and formulated into spray solution for application. The compounds were tested for pre- and postemergence activity against a range of weed species (dicotolydon plant weeds *Chenopodium album, Abutalon theophrasti, Koschia scoparia,* and *Bidens pilosa;* monocotolydon plant weeds *Echinochloa crus-galli, Setaria fabari, Eleusine indica,* and *Sorghum halapense*), with the compounds applied at 1000 g/ha. The plants were then stored in the glasshouse for 12 days. Assessments were made of percent phytotoxicity and converted to a banded score between 0 and 100, where complete control of the target is 100 and 0 is no control. Acetochlor, atrazine, mesotrione, and glyphosate were used as positive controls for the test. The herbicidal activity is summarized in Table 3.

Insecticide Assays. All of the insecticidal assays were carried out in the bioactive activity evaluation platform at Syngenta Jealott's Hill International Research Centre. The compounds were tested for activity against an aphid species at 1000 mg/L on a leaf-piece-based assay and against *Plutella xylostella* and *Diabrotica balteata* at 500 mg/L in artificial diet assays. Chemicals were applied to feeding aphids or prior to infestation with *P. xylostella* and *D. balteata* larvae. Mortality was assessed relative to control wells using a two-band system (0 or 99 where 99 = significant mortality and 0 = no effect), 3–6 days after the treatments depending on the assay. In addition to the test compounds, thiamethoxam and indoxacarb as the positive control compounds were included in each insecticide assays. For all screens, data were recorded for replicates and averaged. The insecticidal activity is summarized in Table 4.

Mode of Action Investigation. *Methodology.* The mode of action screen (MOA1) comprises a series of biochemical, cell-based, and whole plant assays that enable scientists at Syngenta to determine if test compounds have any of the major herbicide modes of action. Compounds are tested only once in MOA1 (i.e., there is no duplicate or replicate), so the IC_{50} values are just an approximation.

Compounds **Ib**, **Ic**, **Ig**, and **Ii** did not give any specific MOA in MOA1 as it was inactive in all of the assays; for example, compounds **Ib** and **Ig** did not give any specific MOA in MOA1 as it was inactive in all of the assays apart from some activity on tobacco cells ($EC_{50} = 1 \text{ mg/L}$, 0.4 mg/L, respectively) and some weak injury on *Arabidospsis* seedlings ($EC_{50} = 36 \text{ mg/L}$, 1 mg/L respectively) and tobacco seedlings ($EC_{50} = 36 \text{ mg/L}$, 18 mg/L, respectively), so it suggested

that these compounds perhaps have novel herbicidal modes of action. Further herbicidal mode of action determination is underway at Syngenta Jealott's Hill International Research Centre.

RESULTS AND DISCUSSION

Synthesis. Series of novel α -amino phosphonate derivatives containing a pyrimidinyl moiety, **I**, **II**, **III**, and **IV**, were designed and synthesized by Lewis acid (magnesium perchlorate) catalyzed Mannich-type reaction of benzoaldehyde containing a pyrimidinyl group, substituted benzylamine, and phosphites. It was found that Lewis acid (magnesium perchlorate) has a large effect on the rate of the reaction and yields of products; without the use of the catalyst, the rates of the reaction were remarkably slowed and the yields were very low, too (about 20%). The structures of target compounds **I–IV** were determined by their spectral data (IR, ¹H NMR, ³¹P NMR, EI-MS, or ESI-MS) and elemental analyses.

Herbicidal Activities and Structure–Activity Relationships. The results of herbicidal activities, in vitro and in vivo (GH1, GH2), of these compounds are listed in Tables 1, 2, and 3, respectively. To our delight, most compounds I exhibited good herbicidal activities in vivo (Tables 2 and 3). However, their meta-position and para-position pyrimidin-2-oxy-substituted structural isomers II and III and their analogues IV did not display any herbicidal activities in vivo (GH1; data not listed), although some of them displayed good selectivity inhibitory activity against *Arabidopsis thaliana* at a concentration of 10 mg/L in vitro (Table 1).

For the in vivo (GH1) herbicidal activity, it was found that compounds Ib, Ic, Ig, Ii, Is, and Iv displayed 100% inhibition against Amaranthus retroflexus at the dose of 1000 g/ha in postemergence treatment. Moreover, both compounds Is and It showed 100% inhibition against Lolium perenne at the dose of 1000 g/ha in postemergence treatment. Furthermore, all compounds I exhibited better inhibition against the four plants tested in postemergence treatment than in pre-emergence one. Finally, compounds Ib, Ic, Ig, Is, and It displayed good broadspectrum herbicidal activities against the four plants in both post- and pre-emergence treatments. As for the preliminary structure-activity relationships, it was shown that the different phosphonic acid esters affected the herbicidal activity significantly; phosphonic acid methyl and ethyl esters were universally advantageous for the herbicidal activities compared with the butyl and phenyl esters. However, the electronic effects of substituent on the benzene ring have no remarkable effect on the herbicidal activity. Both electron-donating (Ig, 4-methoxy-substituted) and electron-withdrawing compounds (Ic, 4-nitro-substituted; Is and It, 4-fluoro-substituted) displayed as good herbicidal activity; even nonsubstituted compound Ib also exhibited good herbicidal activity.

As for the in vivo (GH2) herbicidal activity of I, as shown in Table 3, all of the tested compounds (Ib, Ic, Ig, Ii, Ik, and In)

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showed better inhibition activity against *Chenopodium album* and *Kochia scoparia* than against the other six plants (*Abutilon theophrasti, Bidens pilosa, Echinochloa crus galli, Setaria faberi, Eleusine indica,* and *Sorghum halepense*) at the dose of 1000 g/ha in both post- and pre-emergence treatments; for instance, both compounds **Ig** and **Ik** displayed 100% inhibition against *Chenopodium album* in the postemergence treatment. However, these test compounds exhibited weak herbicidal activity against *Bidens pilosa* relative to the other seven plants in both post- and pre-emergence treatments, except for compound **Ig**, which displayed 50% inhibition in the pre-emergence treatment. Further herbicidal activity evaluation in a lower dose and mode of action investigation are underway at Syngenta Jealott's Hill International Research Centre.

Insecticidal Activities. It is worth noting that some of the analogues IV showed selective insecticidal activities (Table 4), although compounds IV did not display any herbicidal activities in vivo. For example, compounds IVs and IVt exhibited insecticidal activity against *Aphis* species to some extent at the concentration of 1000 mg/L. Moreover, the sulfur analogue IVI showed insecticidal activity against *Plutella xylostella* at the concentration of 500 mg/L. Further insecticidal activity study will be performed and will be reported in due course.

In summary, α -amino phosphonic acids and their ester derivatives, as bioisosteres of natural amino acids, exhibited versatile biological activities. To find novel high-activity and low-toxicity herbicide lead compounds with novel herbicidal modes of action, four series of novel α -amino phosphonate derivatives containing a pyrimidinyl moiety I, II, III, and IV were designed and synthesized by Lewis acid (magnesium perchlorate) catalyzed Mannich-type reaction of aldehydes, amines, and phosphites. The bioassay (in vivo, GH1 and GH2) showed that most compounds I exhibited good selective herbicidal activities. However, their structural isomers II and III and analogues IV did not display any herbicidal activities in vivo, although some of them displayed selectivity inhibitory activity against Arabidopsis thaliana in vitro. Interestingly, compounds IVs, IVt, and IVI possessed selective insecticidal activities against Aphis species or Plutella xylostella, respectively. Their preliminary herbicidal mode of action and structureactivity relationships were also investigated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.Sb02335.

Synthetic procedures for the intermediates and the target compounds methods, data of intermediates 1a-1c, 2a-2b, and title compounds I–IV, and ¹H NMR spectra of I–IV (PDF)

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Funding

We are grateful to the National Natural Science Foundation of China (No. 21342004), self-determined research funds of CCNU from the colleges' basic research and operation of MOE (No. CCNU14A02007), and the Syngenta Ph.D. (postgraduate) program for support of this work.

Article

Notes

The authors declare no competing financial interest.

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