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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, ^{1}H NMR, ^{31}P 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 **IVl** 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 high-efficiency 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 CO_2H vs tetrahedral PO_3H_2), 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-enol-pyruvyl-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-(2-fluorophenyl)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 pyriminobac-methyl 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

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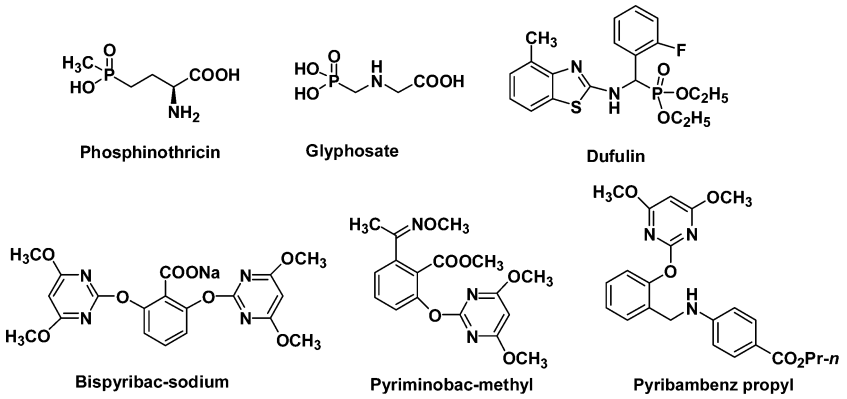
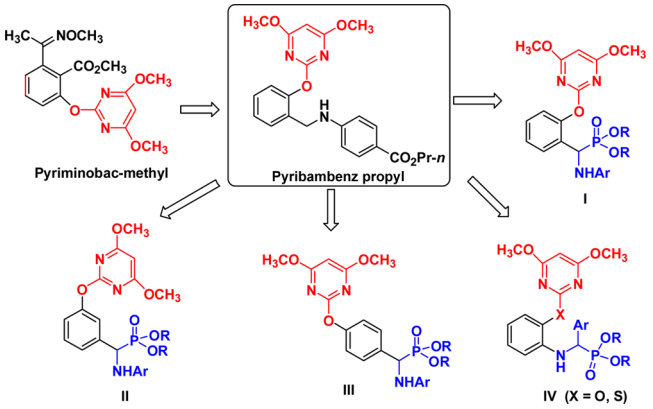


Figure 1. Structures of commercial α-amino phosphonic acid and pyrimidine pesticides.

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. ^{1}H and ^{31}P NMR spectra were performed on a Varian Mercury-PLUS400 (400 MHz) or Varian Mercury Plus-600 (600 MHz) spectrometer at room temperature in $CDCl_3$ with TMS and 85% H_3PO_4 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-(4,6-dimethoxypyrimidin-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 $Mg(ClO_4)_2$ (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-FC_6H_4): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.06 (t, J = 7.8 Hz, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 3.70–3.74 (m, 1H, CH_2), 3.79 (s, 6H, $2CH_3O$), 3.88–3.94 (m, 1H, CH_2), 4.17–4.22 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}FN_3O_6P$: 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-FC_6H_4): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.46 (d, J = 10.8 Hz, 3H, OCH_3), 3.80 (s, 6H, $2CH_3O$), 3.88 (d, J = 10.8 Hz, 3H, OCH_3), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{21}H_{23}FN_3O_6P$: 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-FC_6H_4): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.71 (s, 6H, $2CH_3O$), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{31}H_{27}FN_3O_6P$: C, 63.37; H, 4.63; N, 7.15. Found: C, 63.16; H, 4.58; N, 7.22.

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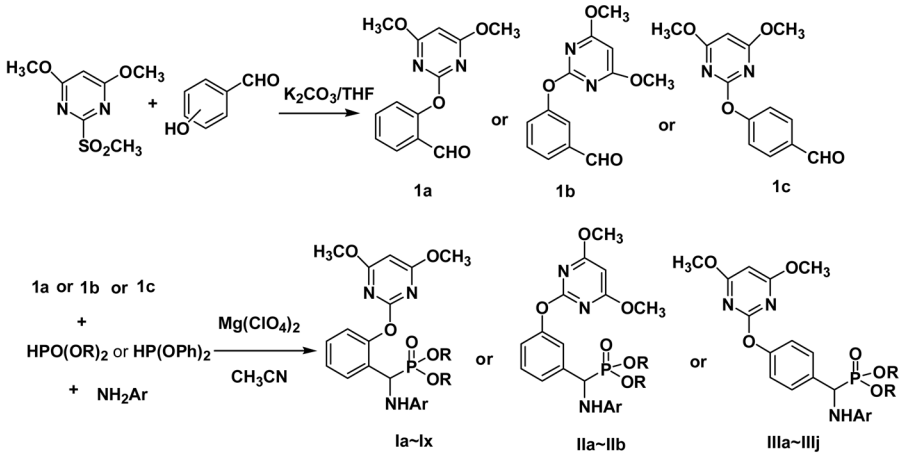
Scheme 2. Synthetic Route of Title Compounds I−III



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-Br-C_6H_4
Ig	Me	4-CH_3O-C_6H_4	**Ih**	Et	4-CH_3O-C_6H_4	**Ii**	Me	2-Cl-C_6H_4
Ij	Et	2-Cl-C_6H_4	**Ik**	Me	3-Br-C_6H_4	**Il**	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**	*n*-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-Br-C_6H_4	**Iw**	Et	4-CN-C_6H_4	**Ix**	Et	4-EtOCO-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-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_6H_3	**IIIi**	Me	4-Cl-C_6H_4	**IIIj**	Et	2-F-C_6H_4

Data for compound **Iv** (R = Et, Ar = 2-BrC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.11 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 3.65−3.68 (m, 1H, CH_2), 3.81 (s, 6H, $2CH_3O$), 3.96−3.99 (m, 1H, CH_2), 4.18−4.20 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}BrN_3O_6P$: 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-CNC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.06 (t, J = 7.2 Hz, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 3.68−3.72 (m, 1H, CH_2), 3.81 (s, 6H, $2CH_3O$), 3.90−3.94 (m, 1H, CH_2), 4.15−4.20 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{24}H_{27}N_4O_6P$: 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-EtOCOC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.07 (t, J = 7.2 Hz, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 1.33 (t, J = 7.8 Hz, 3H, CH_3), 3.71−3.74 (m, 1H, CH_2), 3.80 (s, 6H, $2CH_3O$), 3.92−3.95 (m, 1H, CH_2), 4.20 (q, J = 7.2 Hz, 2H, CH_2), 4.28 (q, J = 7.2 Hz, 2H, CH_2), 5.21 (br s, 1H, NH), 5.28 (d, J = 7.8 Hz, J = 24.0 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); ^{31}P NMR ($CDCl_3$, 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 $C_{26}H_{32}N_3O_8P$: 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-FC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.12 (t, J = 7.8 Hz, 3H, CH_3), 1.29 (t, J = 7.8 Hz, 3H, CH_3), 3.70 (s, 6H, $2CH_3O$), 3.71−3.74 (m, 1H, CH_2), 3.93−3.97 (m, 1H, CH_2), 4.10−4.14 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}FN_3O_6P$: 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-BrC_6H_4): 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),

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1068, 1024 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.19 (t, J = 7.8 Hz, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 3.73 (s, 6H, $2CH_3O$), 3.82−3.86 (m, 1H, CH_2), 4.00−4.14 (m, 3H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}BrN_3O_6P$: 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-FC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.13 (t, J = 7.8 Hz, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 3.69−3.74 (m, 1H, CH_2), 3.77 (s, 6H, $2CH_3O$), 3.94−3.98 (m, 1H, CH_2), 4.10−4.16 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}FN_3O_6P$: 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-BrC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.19 (t, J = 7.2 Hz, 3H, CH_3), 1.28 (t, J = 7.8 Hz, 3H, CH_3), 3.76 (s, 6H, $2CH_3O$), 3.81−3.85 (m, 1H, CH_2), 4.00−4.16 (m, 3H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}BrN_3O_6P$: 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-ClC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 3.65−3.72 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.93−3.97 (m, 1H, CH_2), 4.10−4.15 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 243 MHz) δ, 21.80. Anal. Calcd for $C_{23}H_{27}ClN_3O_6P$: 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-$CH_3C_6H_4$): 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 ($CDCl_3$, 600 MHz) δ 1.13 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.71−3.74 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.93−3.99 (m, 1H, CH_2), 4.06−4.17 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 243 MHz) δ 21.58. Anal. Calcd for $C_{24}H_{30}N_3O_6P$: 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-$NO_2C_6H_4$): 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 ($CDCl_3$, 600 MHz) δ 1.13 (t, J = 7.2 Hz, 3H, CH_3), 1.31 (t, J = 7.2 Hz, 3H, CH_3), 3.65−3.71 (m, 1H, CH_2), 3.79 (s, 6H, $2CH_3O$), 3.93−3.98 (m, 1H, CH_2), 4.11−4.18 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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-BrC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 3.65−3.72 (m, 1H, CH_2), 3.77 (s, 6H, $2CH_3O$), 3.92−3.98 (m, 1H, CH_2), 4.08−4.16 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 243 MHz) δ 21.47. Anal. Calcd for $C_{23}H_{27}BrN_3O_6P$: 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 = C_6H_5): 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 ($CDCl_3$, 600 MHz) δ 1.13 (t, J = 10.8 Hz, 3H, CH_3), 1.29 (t, J = 10.8 Hz, 3H, CH_3), 3.66−3.74 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.93−3.99 (m, 1H, CH_2), 4.08−4.17 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 243 MHz) δ 21.76. Anal. Calcd for $C_{23}H_{28}N_3O_6P$: 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-$Cl_2C_6H_3$): 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 ($CDCl_3$, 600 MHz) δ 1.18 (t, J = 10.8 Hz, 3H, CH_3), 1.28 (t, J = 10.8 Hz, 3H, CH_3), 3.79 (s, 6H, $2CH_3O$), 3.80−3.83 (m, 1H, CH_2), 3.98−4.17 (m, 3H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 243 MHz) δ 19.98. Anal. Calcd for $C_{23}H_{26}Cl_2N_3O_6P$: 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-ClC_6H_4): 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 ($CDCl_3$, 400 MHz) δ 3.48 (d, J = 10.4 Hz, 3H, OCH_3), 3.77 (s, 6H, $2CH_3O$), 3.79 (d, J = 10.4 Hz, 3H, OCH_3), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 23.49. Anal. Calcd for $C_{21}H_{23}ClN_3O_6P$: 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-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 ($CDCl_3$, 400 MHz) δ 1.16 (t, J = 7.2 Hz, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 3.77 (s, 6H, $2CH_3O$), 3.80−3.84 (m, 1H, CH_2), 3.95−4.03 (m, 1H, CH_2), 4.05−4.16 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 20.73. Anal. Calcd for $C_{23}H_{27}FN_3O_6P$: 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

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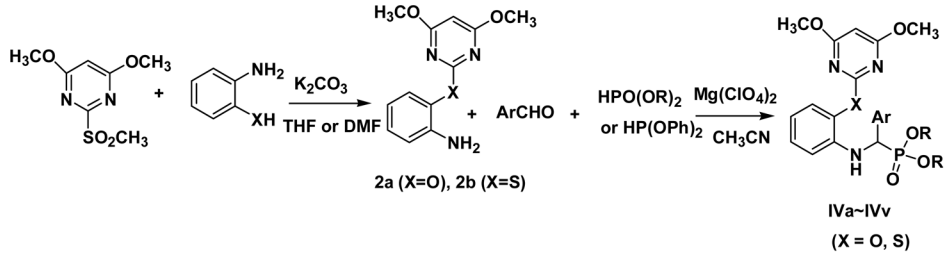
Scheme 3. Synthetic Route of Title Compounds IV



Compd.	R	X	Ar	Compd.	R	X	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_6H_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	**IVl**	Et	S	4-NO_2-C_6H_4
IVm	Et	S	2,4-$(CH_3O)_2$-C_6H_3	**IVn**	Et	S	2,4-Cl_2-C_6H_3
IVo	Et	S	4-HO-C_6H_4	**IVp**	Et	O	C_6H_5
IVq	Et	O	2-Cl-C_6H_4	**IVr**	Et	O	2-F-C_6H_4
IVs	Et	O	4-F-C_6H_4	**IVt**	Et	O	4-Cl-C_6H_4
IVu	Et	O	4-CH_3-C_6H_4	**IVv**	Et	O	4-NO_2-C_6H_4

anhydrous $Mg(ClO_4)_2$ (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 = C_6H_5): 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 ($CDCl_3$, 600 MHz) δ 1.10 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.64 (s, 6H, $2CH_3O$), 3.70−3.74 (m, 1H, CH_2), 3.89−3.95 (m, 2H, CH_2), 3.99−4.02 (m, 1H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{28}N_3O_5PS$: 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-$CH_3C_6H_4$): 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 ($CDCl_3$, 600 MHz) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.64 (s, 6H, $2CH_3O$), 3.72−3.76 (m, 1H, CH_2), 3.90−3.95 (m, 2H, CH_2), 3.99−4.03 (m, 1H, CH_2), 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), 7.22 (d, J = 7.8 Hz, 2H, ArH), 7.45 (d, J = 7.8 Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 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 $C_{24}H_{30}N_3O_5PS$: 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-$CH_3OC_6H_4$): 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 ($CDCl_3$, 600 MHz) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.64 (s, 6H, $2CH_3O$), 3.71−3.75 (m, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.88−3.95 (m, 2H, CH_2), 3.97−4.03 (m, 1H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{24}H_{30}N_3O_6PS$: 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-FC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.13 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.65 (s, 6H, $2CH_3O$), 3.76−3.79 (m, 1H, CH_2), 3.91−3.96 (m, 2H, CH_2), 4.00−4.02 (m, 1H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}FN_3O_5PS$: 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-FC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.10 (t, J = 6.6 Hz, 3H, CH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_3), 3.60 (s, 6H, $2CH_3O$), 3.78−3.81 (m, 1H, CH_2), 3.93−3.97 (m, 1H, CH_2), 4.05−4.12 (m, 2H, CH_2), 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,

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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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}FN_3O_5PS$: 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-ClC_6H_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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.07 (t, J = 7.2 Hz, 3H, CH_3), 1.24 (t, J = 7.2 Hz, 3H, CH_3), 3.60 (s, 6H, $2CH_3O$), 3.66−3.73 (m, 1H, CH_2), 3.87−3.94 (m, 1H, CH_2), 4.04−4.13 (m, 2H, CH_2), 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), 6.69 (t, J = 7.2 Hz, 1H, ArH), 7.10 (t, J = 7.8 Hz, 1H, ArH), 7.18 (d, J = 7.8 Hz, 2H, ArH), 7.31 (d, J = 7.8 Hz, 1H, ArH), 7.36 (d, J = 7.8 Hz, 1H, ArH), 7.44 (d, J = 7.2 Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}ClN_3O_5PS$: 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-ClC_6H_4): white solid; yield, 78%; mp, 143.2−144.4 °C; IR (KBr) ν 3359 (NH), 2980 (Ar—H), 1584, 1553 (Ar), 1370 (P═O), 1285, 1193 (P—O—C), 1049, 1024 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.14 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.66 (s, 6H, $2CH_3O$), 3.78−3.84 (m, 1H, CH_2), 3.91−3.98 (m, 2H, CH_2), 4.00−4.04 (m, 1H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}ClN_3O_5PS$: 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-ClC_6H_4): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.52 (d, J = 10.2 Hz, 3H, OCH_3), 3.64 (d, J = 10.8 Hz, 3H, OCH_3), 3.66 (s, 6H, $2CH_3O$), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{21}H_{23}ClN_3O_5PS$: 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-ClC_6H_4): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.63 (s, 6H, $2CH_3O$), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{31}H_{27}ClN_3O_5PS$: C, 60.05; H, 4.39; N, 6.78. Found: C, 59.87; H, 4.44; N, 6.97.

Data for compound **IVj** (R = Et, X = S, Ar = 4-BrC_6H_4): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.14 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.66 (s, 6H, $2CH_3O$), 3.78−3.85 (m, 1H, CH_2), 3.91−4.04 (m, 3H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 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 $C_{23}H_{27}BrN_3O_5PS$: 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-$NO_2C_6H_4$): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.16 (t, J = 7.2 Hz, 3H, CH_3), 1.20 (t, J = 7.2 Hz, 3H, CH_3), 3.66 (s, 6H, $2CH_3O$), 3.86−3.93 (m, 1H, CH_2), 3.95−4.09 (m, 2H, CH_2), 4.13−4.20 (m, 1H, CH_2), 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), 7.47 (t, J = 7.8 Hz, 1H, ArH), 7.50 (d, J = 7.2 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}N_4O_7PS$: C, 51.68; H, 5.09; N, 10.48. Found: C, 51.87; H, 5.23; N, 10.61.

Data for compound **IVl** (R = Et, X = S, Ar = 4-$NO_2C_6H_4$): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.17 (t, J = 7.2 Hz, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3), 3.69 (s, 6H, $2CH_3O$), 3.86−3.92 (m, 1H, CH_2), 3.93−3.97 (m, 1H, CH_2), 3.99−4.07 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{27}N_4O_7PS$: 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) ν 3345 (NH), 2951 (Ar—H), 1578, 1541 (Ar), 1350 (P═O), 1283, 1184 (P—O—C), 1055, 1028 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.08 (t, J = 7.2 Hz, 3H, CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_3), 3.59 (s, 6H, $2CH_3O$), 3.69−3.73 (m, 1H, CH_2), 3.75 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.89−3.92 (m, 1H, CH_2), 4.00−4.10 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{25}H_{32}N_3O_7PS$: 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-$Cl_2C_6H_3$): 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}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3), 1.24 (t, J = 7.2 Hz, 3H, CH_3), 3.63 (s, 6H, $2CH_3O$), 3.76−3.82 (m, 1H, CH_2), 3.91−3.97 (m, 1H, CH_2), 4.04−4.13 (m, 2H, CH_2), 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), 7.20 (t, J = 8.4 Hz, 1H, ArH), 7.25 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H, ArH), 7.39 (s, 1H, ArH), 7.45 (d, J = 9.0 Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 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),

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Table 1. Herbicide Activity of Some Compounds I–III (in Vitro, Plate Method, Inhibition Percent)[a]

compd	*Arabidopsis thaliana* (10 mg/L)			*Poa annua* (32 mg/L)			compd	*Arabidopsis thaliana* (10 mg/L)			*Poa annua* (32 mg/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 sample was tested against each plant three times.

Table 2. Herbicide Activity of Some Compounds I–IV (in Vivo, Glass House Screen, GH1)[a,b]

		postemergence				pre-emergence					
compd	dopse (g/ha)	*Amaranthus retroflexus*	*Lolium perenne*	*Stellaria media*	*Digitaria sanguinalis*	*Amaranthus retroflexus*	*Lolium perenne*	*Stellaria media*	*Digitaria sanguinalis*	symptomology	
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

[a]Scores 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. [b]Compounds **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-HOC_6H_4): 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 ($CDCl_3$, 600 MHz) δ 1.15 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.63 (s, 6H, $2CH_3O$), 3.71–3.74 (m, 1H, CH_2), 3.78–3.83 (m, 1H, CH_2), 3.89–4.03 (m, 2H, CH_2), 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), 7.07 (d, J = 8.4 Hz, 2H, ArH), 7.16 (t, J = 7.8 Hz, 1H, ArH), 7.45 (d, J = 7.8 Hz, 1H, ArH), 7.96 (br s, 1H, OH); ^{31}P NMR ($CDCl_3$, 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 $C_{23}H_{28}N_3O_6PS$: 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 ($CDCl_3$, 400 MHz) δ 1.09 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.66–3.74 (m, 1H, CH_2), 3.80 (s, 6H, $2CH_3O$), 3.88–4.06 (m, 3H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 21.03. Anal. Calcd for $C_{23}H_{28}N_3O_6P$: 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-ClC_6H_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 ($CDCl_3$, 600 MHz) δ 1.06 (t, J = 7.2 Hz, 3H, CH_3), 1.24 (t, J = 7.2 Hz, 3H, CH_3), 3.64–3.71 (m, 1H, CH_2), 3.79 (s, 6H, $2CH_3O$), 3.86–3.92 (m, 1H, CH_2), 4.05–4.14 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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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Table 3. Herbicide Activity of Some Compounds I (in Vivo, Glass House Screen, GH2)[a]

		postemergence								symptomology		pre-emergence								symptomology	
compd	dose (g/ha)	*Abutilon theophrasti*	*Bidens pilosa*	*Chenopodium album*	*Kochia scoparia*	*Echinochloa crus galli*	*Setaria Faberi*	*Eleusine indica*	*Sorghum halepense*	1	2	*Abutilon theophrasti*	*Bidens pilosa*	*Chenopodium album*	*Kochia scoparia*	*Echinochloa crus galli*	*Setaria Faberi*	*Eleusine indica*	*Sorghum halepense*	1	2
Ib	1000	70	10	90	90	70	70	70	60	ST	NC	50	10	80	80	70	70	60	70	ST	CL
Ic	1000	70	0	80	80	60	70	60	60	ST	NC	40	0	70	80	60	60	70	NC	ST	CL
Ig	1000	50	30	100	80	60	60	60	60	ST	NC	70	50	80	80	70	70	70	70	ST	CL
Ii	1000	20	0	70	90	60	70	60	20	ST	NC	0	0	70	70	50	50	40	0	ST	CL
Ik	1000	0	0	100	80	60	40	10	40	NC	ST	0	0	70	70	40	60	60	50	ST	BL
In	1000	30	0	70	70	60	60	50	20	ST	NC	50	0	70	70	40	60	40	0	ST	
mesotrione	62.5	80	40	70	70	70	60	70	60	BL	NC	80	80	90	70	80	50	90	50	BL	NC
atrazine	300	70	20	70	50	100	100	90	60	NC	ST	40	20	NC	30	90	100	100	80	GI	ST
glyphosate	1000	80	90	100	100	60	80	60	50	NC	ST										
acetochlor	250											0	0	60	0	90	90	100	90	ST	NC

[a]Results from testing on the GH2 screen, with positive controls. Scores are given as percent phytotoxicity score. Herbicide symptomologies are given as a phytotoxicity type: NC, necrosis; ST, stunting; GI, germination inhibition; CL, chlorosis; BL, bleaching.

$C_{23}H_{27}ClN_3O_6P$: 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-FC_6H_4): 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 ($CDCl_3$, 400 MHz) δ 1.09 (t, J = 6.8 Hz, 3H, CH_3), 1.23 (t, J = 6.8 Hz, 3H, CH_3), 3.65−3.72 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.87−3.97 (m, 1H, CH_2), 4.04−4.13 (m, 2H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 20.34. Anal. Calcd for $C_{23}H_{27}FN_3O_6P$: 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-FC_6H_4): 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 ($CDCl_3$, 400 MHz) δ 1.12 (t, J = 6.8 Hz, 3H, CH_3), 1.18 (t, J = 6.8 Hz, 3H, CH_3), 3.80 (s, 6H, $2CH_3O$), 3.91−4.06 (m, 4H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 20.18. Anal. Calcd for $C_{23}H_{27}FN_3O_6P$: 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-ClC_6H_4): 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 ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 7.2 Hz, 3H, CH_3), 1.19 (t, J = 6.8 Hz, 3H, CH_3), 3.81 (s, 6H, $2CH_3O$), 3.90−4.06 (m, 4H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 20.92. Anal. Calcd for $C_{23}H_{27}ClN_3O_6P$: 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-$CH_3C_6H_4$): 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 ($CDCl_3$, 600 MHz) δ 1.10 (t, J = 6.6 Hz, 3H, CH_3), 1.17 (t, J = 6.6 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.65−3.73 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.87−3.95 (m, 2H, CH_2), 3.98−4.03 (m, 1H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 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 $C_{24}H_{30}N_3O_6P$: 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-$NO_2C_6H_4$): 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 ($CDCl_3$, 600 MHz) δ 1.16 (t, J = 7.2 Hz, 3H, CH_3), 1.20 (t, J = 7.2 Hz, 3H, CH_3), 3.80 (s, 6H, $2CH_3O$), 3.83−3.88 (m, 1H, CH_2), 3.98−4.04 (m, 3H, CH_2), 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); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 21.03. Anal. Calcd for $C_{24}H_{27}N_4O_8P$: 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

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Table 4. Insecticidal Activity of Compounds IVs, IVt, and IVl

	Aphis species (mixed-population mortality, 1000 mg/L)				*Plutella xylostella* (larval mortality, 500 mg/L)				*Diabrotica balteata* (larval mortality, 500 mg/L)			
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
IVl	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 mg/L, 0.4 mg/L, respectively) and some weak injury on *Arabidospsis* seedlings (EC_{50} = 36 mg/L, 1 mg/L respectively) and tobacco seedlings (EC_{50} = 36 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, ^{1}H NMR, ^{31}P 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 broad-spectrum 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 **IVl** 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 **IVl** possessed selective insecticidal activities against *Aphis* species or *Plutella xylostella*, respectively. Their preliminary herbicidal mode of action and structure–activity 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.5b02335.

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

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Notes

The authors declare no competing financial interest.

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