Synthesis and Biological Activity of 1-(Substituted phenoxyacetoxy)-1-(pyridin-2-yl or thien-2-yl)methylphosphonates

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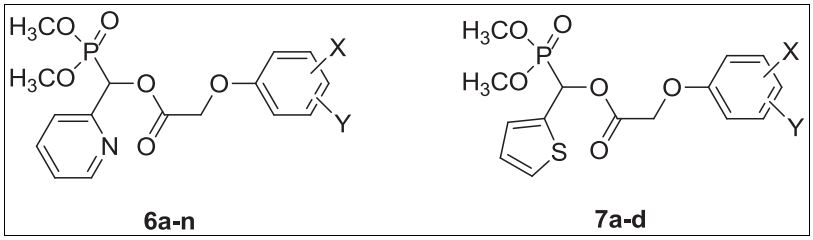

A series of novel *O*,*O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(pyridin-2-yl or thien-2-yl)methylphosphonates **6a–n** and **7a–d** were synthesized. Their structures were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The results of preliminary bioassays show that some of the title compounds exhibit moderate to good herbicidal and fungicidal activities. For example, the title compounds **6a**, **6c**, **6l**, **6m**, and **7d** possess 90–100% inhibition against most of the tested plants at the dosage of 1500 g ai/ha, whereas the title compounds **6b**, **6g–h** and **6n** possess 92–100% inhibition against *Fusarium oxysporum*, *Phyricularia grisea*, *Botrytis cinereapers*, *Gibberella zeae*, *Sclerotinia sclerotiorum*, and *Cercospora beticola* at the concentration of 50 mg/L.

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INTRODUCTION

The application of agrochemicals to protect vegetable and cereal crops is a virtual and convenient approach for modern agriculture. This has provided healthy crops and increased yields as well as economic benefits for decades. The main purpose of the research for agrochemicals is to develop novel active compounds with lower application doses, high selectivity, and benign environment [1,2]. Substituted pyridine and thiophene derivatives, as an important class of agrochemicals, have played a major role in crop protection. And as typical heterocyclic groups, pyridinyl and thienyl are often introduced in the design of bioactive compounds [3–12].

On the other hand, α-substituted alkylphosphonate derivatives have received considerable attention in medicine and pesticide chemistry because of their biological activities over the past two decades [13–17]. Especially, in our previous work, a series of 1-(substituted phenoxyacetoxy) alkylphosphonates, as potent pyruvate dehydrogenase complex inhibitors, were synthesized and showed notable herbicidal activities [18–23]. However, our previous work was not devoted to the synthesis of heterocycle-containing 1-(substituted phenoxyacetoxy)alkylphosphonates. Hence, as part of our ongoing work aimed at searching for new herbicidal and fungicidal compounds, we thought that the introduction of pyridinyl and thienyl groups into the parent structure may result in the improvement of bioactivity. Herein, we report the synthesis and biological activities of the phosphonates **6** and **7** (Scheme 1).

RESULTS AND DISCUSSION

The title compounds **6a–n** and **7a–d** were prepared by condensation of intermediates **2a–b** with substituted phenoxyacetyl chlorides **5** in the presence of triethylamine as a base in chloroform (**Scheme** 1). The intermediates **2a–b** were prepared according to the reported methods [23–26]. The substituted phenoxyacetic acids **4** could be easily synthesized starting from the corresponding substituted phenols and ethyl 2-bromoacetate in good yields.

The structures of **6a–n** and **7a–d** were characterized by ^{1}H NMR, IR, MS, and elemental analysis. The proton signal corresponding to the two methoxy groups (–OCH_3) attached with phosphorus appears as two doublet at δ 3.68 ± 0.04 and 3.81 ± 0.04, respectively. The differentiation of the chemical shifts of the two methyl hydrogens due to the low rate of environmental exchange caused by the slow rotation of the P–C bond, and the magnetic nucleus phosphorus makes the signal of both methyls split into a doublet. In **7a–d**, the signal corresponding to the methylene group (–CH_2–) flanked by the phenoxy group, and carbonyl group appears as a quartet, the outside peaks smaller in size, which belongs to the AB system with the difference in chemical shift between the two mutually coupled protons A and B. However, at the extreme, when A and B have exactly the same chemical shift, the outside peaks disappear, and the inside peaks merge into a singlet, exemplified by **6a–n** series. The corresponding IR spectrum revealed normal absorption bands at ~1760 (C═O) and ~3050 (Ar–H) cm^{-1}. The EI

mass spectra of the title compounds **6** and **7** revealed the existence of the molecular ion peaks, which were in good accordance with the given structures of products.

Biological activities

Herbicidal activity. The preliminary herbicidal activity of **6a–n** and **7a–d** was evaluated against *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass) at the concentration of 100 and 10 mg/L using the known procedure [23]. And 2,4-dichlorophenoxy acetic acid (2, 4-D), a commercially available herbicide, was selected as a positive control. As shown in Table 1, **6a–6c**, **6l–6m**, **7a**, and **7d** displayed notable herbicidal activity against the tested plants, with more than 90% inhibitory rate to the growth of the stem and the root at the concentration of 10 mg/L. The title compounds showed higher inhibitory activities against the growth of the root than that of the stem. For example, the compounds **6d–6i** showed 75–89% inhibitory rate against the root of *E. crusgalli* at the dosage of 10 mg/L, but only 4–56% inhibitory rate against the stem of *E. crusgalli* at the same dosage. Comparing herbicidal activities among the title compounds in Table 1, it was found that the X and Y groups have great impact on the herbicidal activity. The title compounds with 2,4-Cl_2, 2-CH_3-4-Cl, 2-Cl-4-F, and 3-CF_3 as X and Y (**6a–b**, **6l–m**, **7a**, and **7d**) show higher inhibitory rate (>90%) against the root of the tested plants at the concentration of 10 mg/L.

On the basis of the preliminary bioassays, **6a–g**, **6l–n** and **7a–d** were selected for further bioassay for pre-emergence and post-emergence herbicidal activity on *B. napus* (rape), *Amaranthus mangostanus* (amaranth), *Medicago sativa* (lucerne), *E. crusgalli* (barnyard grass), and *Digitaria sanguinalis* (crabgrass). As shown in Table 2, it was found that the title compounds **6a**, **6l**, **6m** and **7d** showed much better activity than the other compounds, which is agreement

Scheme 1. Synthetic route of compounds **6a–n** and **7a–d**.

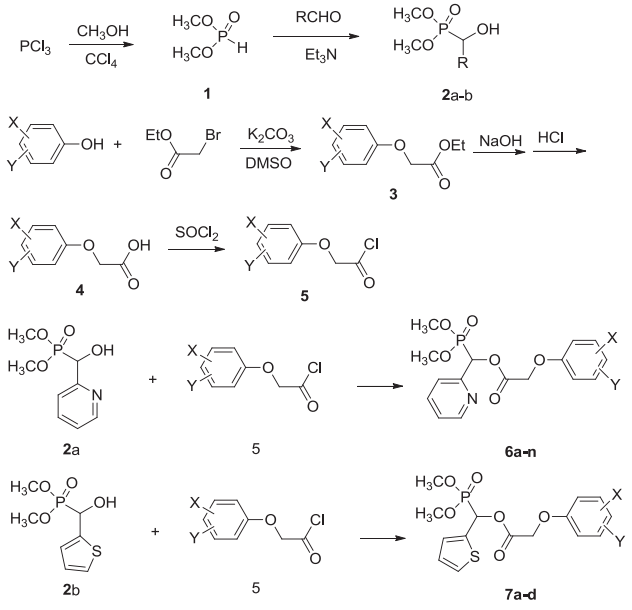

Table 1

Structure and herbicidal activity of compounds 6 and 7.

			Relative inhibition (stem%/root%)			
			[a]EC		[a]BN	
Compound	X	Y	100 mg/L	10 mg/L	100 mg/L	10 mg/L
6a	2-Cl	4-Cl	98/100	95/100	100/100	95/99
6b	3-CF_3	H	80/96	51/90	90/95	90/95
6c	4-Cl	H	95/97	90/90	96/98	90/95
6d	4-F	H	90/95	48/85	90/97	88/88
6e	2-Cl	5-CH_3	70/86	40/75	89/93	79/80
6f	3-CH_3	4-Cl	75/83	30/75	85/97	80/80
6g	2-Cl	3-Cl	78/80	40/80	88/95	82/85
6h	2-Cl	6-Cl	86/94	56/89	83/99	14/68
6i	2-F	H	39/92	4/81	57/93	22/62
6j	2-F	4-F	13/94	22/64	95/99	49/87
6k	3-F	H	22/92	22/75	76/97	5/50
6l	2-Cl	4-F	91/100	81/100	100/100	89/99
6m	2-CH_3	4-Cl	52/100	48/100	100/100	92/100
6n	4-CF_3	H	13/100	61/89	97/99	43/83
7a	3-CF_3	H	88/95	61/93	92/95	90/91
7b	3-CH_3	4-Cl	70/80	31/70	90/95	85/88
7c	2-F	H	20/94	25/65	90/99	40/83
7d	2-Cl	4-F	92/100	61/95	100/100	90/99
2,4-D			34/98	33/98	94/100	94/99

[a]EC for *Echinochloa crusgalli*; BN for *Brassica napus*.

Table 2

The herbicidal activity of compounds 6 and 7 (1500 g ai/ha).

			[a]BN		[a]AM		[a]MS		[a]EC		[a]DS	
Compound	X	Y	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
6a	2-Cl	4-Cl	89	76	93	90	94	41	87	42	98	39
6b	3-CF_3	H	84	63	51	45	49	91	31	15	68	22
6c	4-Cl	H	90	60	69	100	82	41	79	49	92	59
6d	4-F	H	81	79	51	50	46	58	30	24	82	31
6e	2-Cl	5-CH_3	6	43	9	21	3	29	11	52	11	37
6f	3-CH_3	4-Cl	59	50	66	44	76	41	66	22	73	55
6g	2-Cl	3-Cl	0	19	22	52	26	25	19	0	16	4
6l	2-Cl	4-F	95	90	96	95	94	90	80	30	85	25
6m	2-CH_3	4-Cl	95	81	83	100	88	47	89	46	92	39
6n	4-CF_3	H	60	69	50	41	40	56	20	15	40	25
7a	3-CF_3	H	54	72	62	54	57	61	29	0	62	41
7b	3-CH_3	4-Cl	63	45	66	53	88	34	48	5	62	14
7c	2-F	H	18	10	9	0	0	21	4	0	21	19
7d	2-Cl	4-F	97	100	100	100	100	96	83	39	91	45
2,4-D			93	94	94	99	92	91	73	95	70	92

[a]BN for *Brassica napus*; AM for *Amaranthus mangostanus*; MS for *Medicago sativa*; EC for *Echinochloa crusgalli*; DS for *Digitaria sanguinalis*.

with the results in the preliminary bioassays. And the title compounds **6a**, **6l**, **6m**, and **7d** exhibited notable pre-emergence inhibitory effects against all the weed species, with more than 80% inhibitory rate. Especially, **6l** and **7d** showed excellent herbicidal activity against the dicotyledonous weeds, such as *B. napus*, *A. mangostanus* and *M. sativa*, with more than 90% inhibitory for pre-emergence and post-emergence at the dosage of 1500 g ai/ha, which is comparable with 2,4-D. However, **6l** and **7d** showed weaker inhibitory activity in comparison with 2,4-D for post-emergence against the monocotyledonous plants, such as *E. crusgalli* and *D. sanguinalis*. These findings suggested that the compounds **6l** and **7d** had a higher level of selectivity between the monocotyledonous and dicotyledonous plants, especially for post-emergence.

Fungicidal activity. The fungicidal activities of **6a–n** and **7a–d** were evaluated by the classic plate method at the concentration of 50 mg/L, which was described in the experimental part. The six fungi *Fusarium oxysporum* (Fusarium wilt), *Phyricularia grisea* (Rice blast), *Botrytis cinereapers* (Gray mold), *Gibberella zeae* (Telomorph), *Sclerotinia sclerotiorum* (Sclerotiniose) and *Cercospora beticola* (Brown spot) belong to the group of field fungi and were isolated from corresponding crops. As listed in Table 3, most of compounds display moderate to good fungicidal activity against the aforementioned six fungi. For example, the compounds **6b**, **6g**, **6h**, and **6n** possessed high fungicidal activity and broad spectrum against all the target fungi with 90–100% inhibition effect. It was found that the X and Y groups on the phenoxy ring had great impact on the fungicidal activity. The 2,3-Cl_2 and 2,6-Cl_2 di-substitution on the phenoxy ring was the most promotive, followed by 2-Cl-5-CH_3, 3-CH_3-4-Cl, 2,4-F_2, and 2-Cl-4-F. The fungicidal activity could also be greatly enhanced by introducing 3-CF_3 or 4-CF_3 on the phenoxy ring. In the case of single halo substituted derivatives like **6i** and **6k**, with halo substitution at *ortho* and *meta* position in phenoxy ring showed better activity compared with that substituted at *para* position (**6c** and **6d**). When the X and Y groups were kept constant, compounds **6b**, **6f**, **6i**, and **6l** exhibited much higher fungicidal activity than compounds **7a–d**, indicating that pyridinyl group introduced to the parent structure was more beneficial for the improvement of fungicidal activity than the thienyl group.

In conclusion, a series of novel *O*,*O*-dimethyl 1-(substituted phenoxyacetoxy)-1-(pyridn-2-yl or thien-2-yl) methylphosphonates **6a–n** and **7a–d** were designed and synthesized. The results of preliminary bioassays showed that most of the title compounds exhibited moderate to good herbicidal activity at the dosage of 1500 g ai/ha. In addition, the compounds **6b**, **6g**, **6h**, and **6n** also possessed high fungicidal activity and broad spectrum against all the tested fungi with 90–100% inhibition effect. These results indicated that the title compounds **6** and **7** could be modified and used as lead compounds for further study.

EXPERIMENTAL

Chemicals and reagents were obtained from commercial sources and all of the solvents were dried and purified by standard techniques prior to use. Column chromatography was carried out with Merck silica gel (200–300 mesh). Melting points (mp) were measured on a X-4 melting point apparatus (Beijing, China) and were uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer Fourier transform infrared spectrophotometer (USA). ^{1}H NMR was recorded on Varian XL-300 spectrometer at 300 MHz or Varian XL-400 spectrometer (Salt Lake City, USA) at 400 MHz using tetramethylsilane as internal standard (solvent $CDCl_3$). Chemical shifts (δ) are given in parts per million, coupling constants (J) are in Hertz, and

Table 3

Fungicidal activity of compounds 6 and 7.

			50 mg/L					
Compound	X	Y	[a]FO	[a]PG	[a]BC	[a]GZ	[a]SS	[a]CB
6a	2-Cl	4-Cl	22	38	64	53	74	26
6b	3-CF_3	H	93	96	100	100	100	100
6c	4-Cl	H	44	46	57	26	72	37
6d	4-F	H	33	65	84	53	99	55
6e	2-Cl	5-CH_3	79	97	99	79	100	84
6f	3-CH_3	4-Cl	96	97	100	70	100	98
6g	2-Cl	3-Cl	96	100	100	95	100	94
6h	2-Cl	6-Cl	92	100	100	98	100	100
6i	2-F	H	58	94	99	91	100	94
6j	2-F	4-F	92	97	100	88	93	100
6k	3-F	H	92	97	100	84	100	94
6l	2-Cl	4-F	88	100	100	95	100	100
6m	2-CH_3	4-Cl	58	71	91	51	95	39
6n	4-CF_3	H	96	100	100	97	100	100
7a	3-CF_3	H	59	62	98	71	98	67
7b	3-CH_3	4-Cl	52	69	98	56	98	56
7c	2-F	H	70	69	95	68	97	59
7d	2-Cl	4-F	48	42	95	65	98	44

[a]FO for *Fusarium oxysporum*; PG for *Phyricularia grisea*; BC for *Botrytis cinereapers*; GZ for *Gibberella zeae*; SS for *Sclerotinia sclerotiorum*; CB for *Cercospora beticola*.

multiplicities are implicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS spectra were analyzed on a Finnigan TRACE spectrometer (Ramsey, USA) and API2000LC/MS (Framingham, USA). Elemental analyses were performed by a Vario EL III elemental analyzer (Hanau, Germany).

General procedure for the synthesis of 2a–b. *O*,*O*-Dimethyl 1-hydroxy-1-(pyridin-2-yl)methylphosphonate **2a** and 1-hydroxy-1-(thien-2-yl)methylphosphonate **2b** could be prepared by the reaction of dimethyl phosphite **1** and pyridin-2-carbaldehyde or thien-2-carbaldehyde in chloroform using triethylamine as catalyst in yields of 80–90% according to literatures [23–26].

General procedure for the synthesis of 4 and 5. The substituted phenoxyacetic acid **4** was synthesized by a standard method [23,27]. A mixture containing substituted phenoxyacetyl acid **4** (4.0 mmol) and thionyl chloride (3 mL) was added into a 25 mL flask and refluxed for 5–6 h. Excess thionyl chloride was evaporated off under reduced pressure, and a light yellow oil **5** was obtained with a yield of 85–90%.

General procedure for the synthesis of 6a–n and 7a–d. A solution of substituted phenoxyacetyl chlorides **5** (3.3 mmol) in chloroform (15 mL) was added to a stirred mixture of **2a** or **2b** (3 mmol) and triethylamine (3.3 mmol) in chloroform (20 mL) at 0–5°C. The resultant mixture was stirred for 3–5 h at room temperature and then for 1–2 h at 40°C. The chloroform layer was washed with 0.1 M hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried, and concentrated. The residue was purified by column chromatography on silica gel and elution with petroleum ether/acetone (4:1, v/v) to give the corresponding pure title compounds **6a–n** and **7a–d**. Their structures were confirmed by ^{1}H NMR, IR, MS, and elemental analysis. And the physicochemical properties and spectroscopic data for compounds **6a–n** and **7a–d** are as follows.

O,O-Dimethyl 1-[(2,4-dichlorophenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6a). White solid; yield, 88%; mp, 105–106°C; IR (KBr, cm^{-1}): ν 3056, 2963, 2852, 1766, 1591, 1478, 1451, 1265, 1190, 1027, 926, 755. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (d, 3H, –OCH_3, J = 9.9 Hz), 3.80 (d, 3H, –OCH_3, J = 9.9 Hz), 4.88 (s, 2H, –OCH_2CO–), 6.36 (d, 1H, –OCHP, J = 13.8 Hz), 6.81 (d, 1H, 6-phenyl-H, J = 8.8 Hz), 7.14 (dd, 1H, 5-phenyl-H, J = 2.5 Hz, J = 2.5 Hz), 7.27 (d, 1H, 5-pyrinyl-H, J = 8.3 Hz), 7.38 (d, 1H, 3-phenyl-H, J = 2.5 Hz), 7.45 (d, 1H, 3-pyrinyl-H, J = 7.7 Hz), 7.69–7.75 (m, 1H, 4-pyrinyl-H), 8.63 (s, 1H, 6-pyrinyl-H); ^{31}P NMR (120 MHz $CDCl_3$): δ 8.5; EI-MS *m/z* (%): 419 (M^+, 13.91), 220 (65.58), 216 (36.89), 203 (7.56), 200 (60.25), 175 (60.80), 162 (100), 146 (27.15), 109 (50.31), 94 (6.68), 93 (40.49), 79 (18.54). *Anal*. Calcd for $C_{16}H_{16}Cl_2NO_6P$: C, 45.74; H, 3.84; N, 3.33. Found: C, 45.97; H, 3.79; N, 2.94.

O,O-Dimethyl 1-[(3-trifluoromethylphenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6b). White solid; yield, 71%; mp, 79–80°C; IR (KBr, cm^{-1}): ν 3076, 2964, 2852, 1784, 1608, 1495, 1441, 1248, 1178, 1030, 938, 754. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (d, 3H, –OCH_3, J = 11.3 Hz), 3.80 (d, 3H, –OCH_3, J = 11.3 Hz), 4.87 (s, 2H, –OCH_2CO–), 6.38 (d, 1H, –OCHP, J = 13.8 Hz), 7.08–7.46 (m, 6H, 2, 4, 5 and 6-phenyl-H, 3 and 5- pyrinyl-H), 7.71–7.72 (m, 1H, 4-pyrinyl-H), 8.61–8.64 (m, 1H, 6-pyrinyl-H); EI-MS *m/z* (%): 419 (M^+ + 1, 16.56), 244 (72.49), 216 (12.52), 201 (27.18), 175 (56.34), 145 (100), 127 (23.75), 109 (61.20), 94 (8.12), 93 (68.93), 79 (50.46), 75 (11.22), 63 (15.56). *Anal*. Calcd for $C_{17}H_{17}F_3NO_6P$: C, 48.70; H, 4.09; N, 3.34. Found: C, 48.61; H, 4.04; N, 3.39.

O,O-Dimethyl1-[(4-chlorophenoxy)acetoxy]-1-(pyridin-2-yl) methylphosphonate (6c). White solid; yield, 76%; mp, 124–125°C; IR (KBr, cm^{-1}): ν 3069, 2955, 2850, 1777, 1589, 1495, 1447, 1255, 1172, 1038, 945, 772. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (d, 3H, –OCH_3, J = 10.7 Hz), 3.80 (d, 3H, –OCH_3, J = 10.7 Hz), 4.80 (s, 2H, –OCH_2CO–), 6.37 (d, 1H, –OCHP, J = 13.8 Hz), 6.85 (dd, 2H, 2 and 6-phenyl-H, J = 2.5 Hz, J = 6.8 Hz), 7.21 (dd, 2H, 3 and 5-phenyl-H, J = 2.5 Hz, J = 6.8 Hz), 7.27 (d, 1H,

5-pyrinyl-H, $J = 8.4$ Hz), 7.45 (d, 1H, 3-pyrinyl-H, $J = 7.9$ Hz), 7.68–7.75 (m, 1H, 4-pyrinyl-H), 8.62 (d, 1H, 6-pyrinyl-H, $J = 4.8$ Hz); EI-MS *m/z* (%): 385 ($M^+ + 1$, 7.52), 258 (16.56), 244 (61.27), 216 (7.05), 201 (25.40), 140 (37.78), 127 (5.05), 109 (73.14), 94 (7.19), 93 (100), 79 (52.33), 75 (34.88), 63 (20.18). *Anal*. Calcd for $C_{16}H_{17}ClNO_6P$: C, 49.82; H, 4.44; N, 3.63. Found: C, 49.90; H, 4.21; N, 3.66.

O,O-Dimethyl 1-[(4-fluorophenoxy)acetoxy]-1-(pyridin-2-yl) methylphosphonate (6d). Yellow solid; yield, 67%; mp, 68–70°C; IR (KBr, cm^{-1}): *v* 3059, 2959, 2857, 1767, 1630, 1507, 1440, 1254, 1179, 1050, 933, 775. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (d, 3H, $–OCH_3$, $J = 10.7$ Hz), 3.80 (d, 3H, $–OCH_3$, $J = 10.7$ Hz), 4.79 (s, 2H, $–OCH_2CO–$), 6.37 (d, 1H, –OCHP, $J = 13.8$ Hz), 6.84–6.88 (m, 2H, 2 and 6-phenyl-H), 6.89–6.99 (m, 2H, 3 and 5-phenyl-H), 7.25–7.30 (m, 1H, 5-pyrinyl-H), 7.45 (d, 1H, 3-pyrinyl-H, $J = 7.9$ Hz), 7.68–7.72 (m, 1H, 4-pyrinyl-H), 8.60–8.63 (m, 1H, 6-pyrinyl-H); EI-MS *m/z* (%): 369 ($M^+ + 1$, 1.10), 244 (7.12), 216 (1.23), 201 (3.36), 170 (52.30), 148 (2.27), 125 (45.29), 109 (8.43), 95 (100), 93 (20.33), 79 (20.25), 75 (31.95), 63 (17.03). *Anal*. Calcd for $C_{16}H_{17}FNO_6P$: C, 52.04; H, 4.64; N, 3.79. Found: C, 51.88; H, 4.61; N, 3.68.

O,O-Dimethyl 1-[(2-chloro-5-methylphenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6e). White solid; yield, 78%; mp, 76–77°C; IR (KBr, cm^{-1}): *v* 3049, 2952, 2853, 1754, 1629, 1493, 1441, 1222, 1182, 1054, 936, 778. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3Ph), 3.72 (d, 3H, $–OCH_3$, $J = 9.0$ Hz), 3.80 (d, 3H, $–OCH_3$, $J = 9.0$ Hz), 4.88 (s, 2H, $–OCH_2CO–$), 6.38 (d, 1H, –OCHP, $J = 13.5$ Hz), 6.67 (d, 1H, 6-phenyl-H, $J = 1.2$ Hz), 6.74–6.77 (m, 1H, 4-phenyl-H), 7.23–7.30 (m, 2H, 3-phenyl-H, 5-pyrinyl-H), 7.44 (d, 1H, 3-pyrinyl-H, $J = 8.0$ Hz), 7.68–7.74 (m, 1H, 4-pyrinyl-H), 8.60–8.63 (m, 1H, 6-pyrinyl-H); EI-MS *m/z* (%): 399 ($M^+ + 1$, 0.82), 216 (1.51), 200 (8.69), 183 (1.64), 155 (8.17), 125 (8.54), 109 (9.44), 95 (36.66), 93 (23.52), 79 (100), 75 (9.49), 63 (19.17). *Anal*. Calcd for $C_{17}H_{19}ClNO_6P$: C, 51.08; H, 4.79; N, 3.50. Found: C, 50.94; H, 4.93; N, 3.25.

O,O-Dimethyl 1-[(4-chloro-5-methylphenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6f). White solid; yield, 74%; mp, 83–85°C; IR (KBr, cm^{-1}): *v* 3058, 2957, 2854, 1776, 1593, 1482, 1435, 1258, 1167, 1035, 935, 772. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, kCH_3Ph), 3.71 (d, 3H, $–OCH_3$, $J = 10.8$ Hz), 3.83 (d, 3H, $–OCH_3$, $J = 10.8$ Hz), 4.79 (s, 2H, $–OCH_2CO–$), 6.37 (d, 1H, –OCHP, $J = 13.8$ Hz), 6.66–6.70 (m, 1H, 6-phenyl-H), 6.79 (d, 1H, 2-phenyl-H, $J = 3.1$ Hz), 7.19–7.30 (m, 2H, 3-phenyl-H, 5-pyrinyl-H), 7.40–7.44 (m, 1H, 3-pyrinyl-H), 7.68–7.74 (m, 1H, 4-pyrinyl-H), 8.61–8.63 (m, 1H, 6-pyrinyl-H); EI-MS *m/z* (%): 399 (M^+, 33.17), 258 (41.95), 244 (99.57), 216 (17.44), 201 (47.25), 200 (20.85), 182 (10.15), 155 (38.74), 125 (75.49), 109 (81.07), 94 (10.36), 93 (100), 79 (67.15), 75 (8.30), 63 (34.44). *Anal*. Calcd for $C_{17}H_{19}ClNO_6P$: C, 51.08; H, 4.79; N, 3.50. Found: C, 50.83; H, 4.54; N, 3.52.

O,O-Dimethyl 1-[(2,3-dichlorophenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6g). White solid; yield, 66%; mp, 115–116°C; IR (KBr, cm^{-1}): *v* 3077, 2957, 2852, 1779, 1586, 1468, 1443, 1252, 1173, 1053, 946, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, 3H, $–OCH_3$, $J = 11.2$ Hz), 3.80 (d, 3H, $–OCH_3$, $J = 11.2$ Hz), 4.92 (s, 2H, $–OCH_2CO–$), 6.37 (d, 1H, –OCHP, $J = 14.0$ Hz), 6.78 (dd, 1H, 6-phenyl-H, $J = 2.4$ Hz, $J = 2.4$ Hz), 7.11–7.13 (m, 2H, 4 and 5-phenyl-H), 7.28–7.29 (m, 1H, 5-pyrinyl-H), 7.45–7.48 (m, 1H, 3-pyrinyl-H), 7.70–7.74 (m, 1H, 4-pyrinyl-H), 8.63 (d, 1H, 6-pyrinyl-H, $J = 4.4$ Hz); EI-MS *m/z* (%): 419 (M^++1, 5.85), 258 (18.10), 244 (100), 216 (12.35), 201 (18.31), 200 (7.69), 182 (4.07), 175 (30.65), 162 (5.65), 145 (26.52), 109 (67.98), 94 (6.31), 93 (71.43), 79 (41.83), 75 (13.80), 63 (19.00); *Anal*. Calcd for $C_{16}H_{16}Cl_2NO_6P$: C, 45.47; H, 3.84; N, 3.33. Found: C, 45.80; H, 3.63; N, 3.38.

O,O-Dimethyl 1-[(2,6-dichlorophenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6h). White solid; yield, 68%; mp,125–126°C; IR (KBr, cm^{-1}): *v* 3074, 2947, 2849, 1738, 1630, 1512, 1458, 1222, 1156, 1048, 939, 785; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, 3H, $–OCH_3$, $J = 10.8$ Hz), 3.81 (d, 3H, $–OCH_3$, $J = 10.8$ Hz), 4.92 (s, 2H, $–OCH_2CO–$), 6.37 (d, 1H, –OCHP, $J = 14.0$ Hz), 6.78 (dd, 1H, 4-phenyl-H, $J = 2.8$ Hz, $J = 2.8$ Hz), 7.11–7.13 (m, 2H, 3 and 5-phenyl-H), 7.28–7.29 (m, 1H, 5-pyrinyl-H), 7.45–7.47 (m, 1H, 3-pyrinyl-H), 7.72–7.73 (m, 1H, 4-pyrinyl-H), 8.63 (d, 1H, 6-pyrinyl-H, $J = 4.4$ Hz); EI-MS *m/z* (%): 419 (M^++1, 1.05), 258 (23.60), 244 (62.50), 216 (7.49), 201 (16.83), 200 (5.30), 182 (4.64), 175 (27.45), 162 (16.04), 145 (34.46), 109 (100), 94 (7.74), 93 (70.77), 79 (58.37), 75 (22.27), 63 (38.56); *Anal*. Calcd for $C_{16}H_{16}Cl_2NO_6P$: C, 45.47; H, 3.84; N, 3.33. Found: C, 45.82; H, 3.65; N, 3.38.

O,O-Dimethyl 1-[(2-fluorophenoxy)acetoxy]-1-(pyridin-2-yl) methylphosphonate (6i). Yellow oil; yield, 63%; n_D^{20} 1.5062; IR (KBr, cm^{-1}): *v* 3070, 2959, 2855, 1771, 1591, 1505, 1437, 1263, 1182, 1036, 942, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, 3H, $–OCH_3$, $J = 9.6$ Hz), 3.81 (d, 3H, $–OCH_3$, $J = 9.6$ Hz), 4.82 (s, 2H, $–OCH_2CO–$), 6.39 (d, 1H, –OCHP, $J = 14.0$ Hz), 6.63–6.71 (m, 3H, 3, 4 and 6-phenyl-H), 7.21–7.29 (m, 2H, 3-phenyl-H, 5-pyrinyl-H), 7.44–7.47 (m, 1H, 3-pyrinyl-H), 7.72–7.73 (m, 1H, 4-pyrinyl-H), 8.63 (d, 1H, 6-pyrinyl-H, $J = 4.4$ Hz); EI-MS *m/z* (%): 369 ($M^+ + 1$, 1.52), 216 (2.44), 201 (4.98), 148 (7.10), 125 (52.34), 109 (76.83), 94 (12.68), 93 (100), 79 (54.16), 75 (29.13), 63 (17.20); *Anal*. Calcd for $C_{16}H_{17}FNO_6P$: C, 52.04; H, 4.64; N, 3.79. Found: C, 51.89; H, 4.39; N, 3.83.

O,O-Dimethyl 1-[(2,4-difluorophenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6j). Yellow oil; yield, 67%; n_D^{20} 1.5183; IR (KBr, cm^{-1}): *v* 3059, 2960, 2856, 1771, 1590, 1515, 1437, 1267, 1174, 1036, 965, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, 3H, $–OCH_3$, $J = 10.8$ Hz), 3.80 (d, 3H, $–OCH_3$, $J = 10.8$ Hz), 4.85 (s, 2H, $–OCH_2CO–$), 6.36 (d, 1H, –OCHP, $J = 13.6$ Hz), 6.76–6.98 (m, 3H, 3, 5 and 6-phenyl-H), 7.28–7.29 (m, 1H, 5-pyrinyl-H), 7.45–7.48 (m, 1H, 3-pyrinyl-H), 7.70–7.75 (m, 1H, 4-pyrinyl-H), 8.61 (d, 1H, 6-pyrinyl-H, $J = 4.8$ Hz); EI-MS *m/z* (%): 387 ($M^+ + 1$, 5.12), 244 (28.45), 201 (10.73), 143 (59.47), 113 (46.76), 109 (69.39), 94 (10.67), 93 (100), 79 (51.89), 75 (6.92), 63 (31.99); *Anal*. Calcd for $C_{16}H_{16}F_2NO_6P$: C, 49.62; H, 4.16; N, 3.62. Found: C, 49.67; H, 4.18; N, 3.53.

O,O-Dimethyl 1-[(3-fluorophenoxy)acetoxy]-1-(pyridin-2-yl) methylphosphonate (6k). Yellow solid; yield, 66%; mp,79–80°C; IR (KBr, cm^{-1}): *v* 3072, 2962, 2850, 1774, 1591, 1493, 1450, 1254, 1188, 1054, 940, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, 3H, $–OCH_3$, $J = 10.4$ Hz,), 3.79 (d, 3H, $–OCH_3$, $J = 10.4$ Hz,), 4.81 (s, 2H, $–OCH_2CO–$), 6.39 (d, 1H, –OCHP, $J = 13.6$ Hz), 6.63–6.71 (m, 3H, 2, 4 and 6-phenyl-H), 7.21–7.29 (m, 2H, 5-phenyl-H, 5-pyrinyl-H), 7.44–7.47 (m, 1H, 3-pyrinyl-H), 7.71–7.72 (m, 1H, 4-pyrinyl-H), 8.63 (d, 1H, 6-pyrinyl-H, $J = 4.8$ Hz); EI-MS *m/z* (%): 369 ($M^+ + 1$, 4.64), 258 (10.51), 244 (88.45), 216 (11.62), 201 (24.99), 170 (11.29), 148 (8.17), 125 (54.51), 109 (59.36), 95 (100), 93 (80.93), 79 (49.99), 75 (31.87), 63 (14.67); *Anal*. Calcd for $C_{16}H_{17}FNO_6P$: C, 52.04; H, 4.64; N, 3.79. Found: C, 51.66; H, 4.40; N, 3.79.

O,O-Dimethyl 1-[(2-chloro-4-fluorophenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6l). White solid; yield, 74%;

mp,124–126°C; IR (KBr, cm^{-1}): *v* 3073, 2963, 2851, 1775, 1592, 1493, 1449, 1254, 1188, 1054, 967, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, 3H, –OCH_3, *J* = 11.8 Hz), 3.81 (d, 3H, –OCH_3, *J* = 11.8 Hz), 4.92 (s, 2H, –OCH_2CO–), 6.36 (dd, 1H, –OCHP, *J* = 1.6 Hz, *J* = 1.6 Hz), 6.81 (dd, 1H, 6-phenyl-H, *J* = 1.2 Hz, *J* = 1.2 Hz), 7.13–7.16 (m, 1H, 5-phenyl-H), 7.29 (s, 1H, 5-pyrinyl-H), 7.39 (s, 1H, 3-phenyl-H), 7.44–7.46 (m, 1H, 3-pyrinyl-H), 7.72 (t, 1H, 4-pyrinyl-H, *J* = 7.6 Hz), 8.62 (s, 1H, 6-pyrinyl-H); EI-MS *m/z* (%): 403 (M^+, 0.65), 204 (17.61), 159 (27.85), 146 (69.10), 129 (44.29), 109 (18.59), 94 (23.37), 93 (23.49), 79 (2.73), 75 (17.70), 63 (19.17); *Anal*. Calcd for $C_{16}H_{16}ClFNO_6P$: C, 47.60; H, 3.99; N, 3.47. Found: C, 47.29; H, 4.26; N, 3.30.

O,O-Dimethyl 1-[(4-chloro-2-methylphenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6m). White solid; yield, 77%; mp, 75–77°C; IR (KBr, cm^{-1}): *v* 3013, 2963, 2850, 1767, 1592, 1493, 1432, 1264, 1177, 1047, 939, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3Ph), 3.71 (d, 3H, –OCH_3, *J* = 10.4 Hz), 3.80 (d, 3H, –OCH_3, *J* = 10.4 Hz), 4.82 (s, 2H, –OCH_2CO–), 6.37 (d, 1H, –OCHP, *J* = 14.0 Hz), 6.63 (d, 1H, 6-phenyl-H, *J* = 8.8 Hz), 7.05 (d, 1H, 5-phenyl-H, *J* = 8.4 Hz), 7.13 (s, 1H, 5-pyrinyl-H), 7.28 (s, 1H, 3-phenyl-H), 7.39–7.41 (m, 1H, 3-pyrinyl-H), 7.72 (t, 1H, 4-pyrinyl-H, *J* = 7.6 Hz), 8.62 (d, 1H, 6-pyrinyl-H, *J* = 4.4 Hz); EI-MS *m/z* (%): 399 (M^+ + 1, 31.22), 216 (21.72), 201 (77.68), 182 (5.68), 155 (35.00), 141 (43.45), 125 (72.49), 109 (78.91), 108 (100), 94 (12.15), 93 (98.32), 79 (74.73), 75 (8.92), 63 (31.67); *Anal*. Calcd for $C_{17}H_{19}ClNO_6P$: C, 51.08; H, 4.79; N, 3.50. Found: C, 50.78; H, 4.99; N, 3.28.

O,O-Dimethyl 1-[(4-trifluoromethylphenoxy)acetoxy]-1-(pyridin-2-yl)methylphosphonate (6n). White solid; yield, 68%; mp, 73–74°C; IR (KBr, cm^{-1}): *v* 3081, 2964, 2859, 1784, 1593, 1494, 1441, 1248, 1177, 1052, 940, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, 3H, –OCH_3, *J* = 11.2 Hz), 3.80 (d, 3H, –OCH_3, *J* = 11.2 Hz), 4.88 (s, 2H, –OCH_2CO–), 6.38 (d, 1H, –OCHP, *J* = 13.6 Hz), 7.09–7.47 (m, 6H, 2, 3, 5 and 6-phenyl-H, 3 and 5-pyrinyl-H), 7.73 (t, 1H, 4-pyrinyl-H, *J* = 7.6 Hz), 8.64 (d, 1H, 6-pyrinyl-H, *J* = 4.4 Hz); EI-MS *m/z* (%): 419(M^+ + 1, 0.71), 244 (19.55), 220 (16.39), 216 (4.54), 201 (27.32), 175 (41.83), 162 (25.40), 145 (100), 127 (27.99), 109 (34.71), 94 (8.17), 93 (32.41), 79 (49.51), 75 (33.08), 63 (36.80); *Anal*. Calcd for $C_{17}H_{17}F_3NO_6P$: C, 48.70; H, 4.09; N, 3.34. Found: C, 48.42; H, 4.03; N, 3.35.

O,O-Dimethyl 1-[(3-trifluoromethylphenoxy)acetoxy]-1-(thien-2-yl)methylphosphonate (7a). Yellow solid; yield, 72%; mp, 74–75°C; IR (KBr, cm^{-1}): *v* 3083, 2926, 2855, 1763, 1593, 1494, 1444, 1275, 1173, 1026, 936, 724; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (d, 3H, –OCH_3, *J* = 10.7 Hz), 3.81 (d, 3H, –OCH_3, *J* = 10.7 Hz), 4.74, 4.79 (q, AB system, 2H, OCH_2O, *J* = 16.5 Hz), 6.54 (d, 1H, –OCHP, *J* = 13.5 Hz), 7.00–7.11 (m, 3H, 6-phenyl-H, 3 and 4-thienyl-H), 7.24–7.30 (m, 2H, 2 and 4-phenyl-H), 7.36–7.42 (m, 2H, 5-thienyl-H, 5-phenyl-H); ^{31}P NMR(120 MHz $CDCl_3$): δ 6.3; EI-MS *m/z* (%): 424 (M^+, 10.10), 220 (26.21), 205 (19.30), 175 (100), 162 (14.19), 145 (76.58), 133 (3.44), 109 (11.00), 94 (2.55), 93 (65.31), 75 (4.58), 63 (7.41), 44 (15.86); *Anal*. Calcd for $C_{16}H_{16}F_3O_6PS$: C, 45.29; H, 3.80; Found: C, 45.06; H, 3.91.

O,O-Dimethyl 1-[(4-chloro-5-methylphenoxy)acetoxy]-1-(thien-2-yl)methylphosphonate (7b). Yellow solid; yield, 88%; mp, 74–75°C; IR (KBr, cm^{-1}): *v* 3076, 2931, 2852, 1766, 1599, 1489, 1435, 1249, 1174, 1027, 928, 725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3Ph), 3.68 (d, 3H, –OCH_3, *J* = 10.7 Hz), 3.81 (d, 3H, –OCH_3, *J* = 10.7 Hz), 4.66, 4.70 (q, AB system, 2H, OCH_2O, *J* = 16.5 Hz), 6.53 (d, 1H, –OCHP, *J* = 13.6 Hz), 6.62–6.66 (m, 1H, 6-phenyl-H), 6.74 (d, 1H, 2-phenyl-H, *J* = 2.7 Hz), 7.00–7.04 (m, 1H, 3-thienyl-H), 7.20 (d, 1H, 3-phenyl-H, *J* = 8.7 Hz), 7.26–7.29 (m, 1H, 4-thienyl-H), 7.37–7.39 (m, 1H, 5-thienyl-H); EI-MS *m/z* (%): 404 (M^+, 13.21), 369 (25.58), 325 (60.90), 250 (25.94), 219 (45.97), 205 (100), 200 (44.18), 155 (86.48), 142 (37.21), 125 (74.54), 109 (60.10), 94 (17.03), 93 (99.00), 75 (8.28), 63 (49.59), 44 (22.09); *Anal*. Calcd for $C_{16}H_{18}ClO_6PS$: C, 47.47; H, 4.48; Found: C, 47.19; H, 4.46.

O,O-Dimethyl 1-[(2-fluorophenoxy)acetoxy]-1-(thien-2-yl) methylphosphonate (7c). White solid; yield, 72%; mp, 73–74°C; IR (KBr, cm^{-1}): *v* 3082, 2954, 2846, 1763, 1613, 1510, 1433, 1261, 1180, 1025, 929, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, 3H, –OCH_3, *J* = 10.8 Hz), 3.78 (d, 3H, –OCH_3, *J* = 10.8 Hz), 4.73, 4.79 (q, AB system, 2H, OCH_2O, *J* = 16.5 Hz), 6.51 (d, 1H, –OCHP, *J* = 13.8 Hz), 6.82–7.10 (m, 5H, 3, 4, 5 and 6-phenyl-H, 3-thienyl-H), 7.23–7.24 (m, 1H, 4-thienyl-H), 7.34 (d, 1H, 5-thienyl-H, *J* = 5.2 Hz); EI-MS *m/z* (%): 374 (M^+, 27.44), 221 (46.69), 205 (54.49), 170 (37.80), 125 (100), 112 (68.67), 109 (21.14), 94 (6.10), 93 (98.49), 75 (17.29), 63 (14.08), 44 (13.56); *Anal*. Calcd for $C_{15}H_{16}FO_6PS$: C, 48.13; H, 4.31; Found: C, 48.32; H, 4.16.

O,O-Dimethyl 1-[(2-chloro-4-fluorophenoxy)acetoxy]-1-(thien-2-yl)methylphosphonate (7d). Yellow solid; yield, 78%; mp, 68–70°C; IR (KBr, cm^{-1}): *v* 3086, 2962, 2857, 1762, 1603, 1494, 1450, 1249, 1188, 1026, 938, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (d, 3H, –OCH_3, *J* = 10.8 Hz), 3.81 (d, 3H, –OCH_3, *J* = 10.8 Hz), 4.74, 4.78 (q, AB system, 2H, OCH_2O, *J* = 16.5 Hz), 6.54 (d, 1H, –OCHP, *J* = 13.6 Hz), 6.80–6.82 (m, 1H, 6-phenyl-H), 6.87–6.88 (m, 1H, 3-thienyl-H), 7.01–7.03 (m, 1H, 5-phenyl-H), 7.12–7.39 (m, 3H, 4 and 5-thienyl-H, 3-phenyl-H,); EI-MS *m/z* (%): 408 (M^+, 29.31), 271 (8.29), 221 (34.20), 205 (98.18), 159 (89.16), 129 (74.48), 111 (100), 93 (95.69), 79 (39.73), 75 (9.63), 63 (21.54), 45 (20.46); *Anal*. Calcd for $C_{15}H_{15}ClFO_6PS$: C, 44.07; H, 3.70; Found: C, 43.90; H, 3.56.

Biological activity testing. The preliminary herbicidal activity of title compounds **6a–n** and **7a–d** was measured according to the modified method described previously [12]. A set amount of each sample was dissolved in *N*, *N*-dimethylformamide (DMF) to which a drop of an emulsifier, Tween 80, was added. The solution was then diluted with water until it reached the concentrations required. The amounts of DMF and the emulsifier were set as low as possible but still sufficient to make a uniform emulsion even at high concentrations. A solution (5 mL) was placed on a filter paper (diameter = 5.5 cm) in Petri dishes (diameter = 9.0 cm), and 10 rape seeds were placed on the filter paper after soaking in water for 6 h. The Petri dishes were kept at 28°C for 3 days with 10 h of lighting and 14 h in the dark. The experiments were conducted in three replicates. The lengths of roots and shoots were measured after 72 h of treatment, and the growth inhibitory rate related to untreated control was determined.

Then some of the title compounds **6** and **7** were selected for further test against dicotyledonous weeds such as *B. napus*, *A. mangostanus*, and *M. sativa* and monocotyledonous weeds such as *E. crusgalli* and *D. sanguinalis* at the dosage of 1500 g ai/ha according to the method described in [21,23]. Plastic pots were packed with sandy clay loam soil and water was added up to 3 cm in depth. About 15–20 seeds of plants were sown in the soil at a depth of 5 mm and grown at 20–25°C for a few days. The diluted solution of each compound containing acetone and Tween 80 were applied into the pots at 1500 g ai/ha. Twenty days later,

the pre-emergence, the activity was visually evaluated. At the post-emergence, the solution was applied to the foliage of plants grown at two or three leaves with a sprayer at the rate of 1500 g ai/ha. All the treatments were replicated three times in a completely randomized design. The test plants were harvested 20 days after sowing, and determined for fresh weight. The post-emergence herbicidal activity against each weed was evaluated.

The fungicidal activity measurement method was adapted from [11]. The phosphonates were dissolved in DMF (0.5–1.0 mL) to the concentration of 1000 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50°C. The mixtures were poured into Petri dish. After the dishes were cooled, the solidified plates were incubated with 4-mm mycelium disk, inverted, and incubated at 28°C for 48 h. Distilled water was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibitory rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibitory rate (%), T is the treatment group fungi settlement radius (mm), and C is the radius of the blank control.

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