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Article

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Synthesis and Herbicidal Activity of *α*-(Substituted Phenoxybutyryloxy or Valeryloxy)alkylphosphonates and 2-(Substituted Phenoxybutyryloxy)alkyl-5,5-dimethyl-1,3,2-dioxaphosphinan-2-one

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ABSTRACT: Based on our work on the modification of alkylphosphonates **1**, a series of *α*-(substituted phenoxybutyryloxy or valeryloxy)alkylphosphonates (**4-5**) and 2-(substituted phenoxybutyryloxy)alkyl-5,5-dimethyl-1,3,2-dioxaphosphinan-2-one (**6**) was designed and synthesized. The bioassay results indicated that fourteen of title compounds **4** exhibited significant post-emergence herbicidal activity against velvetleaf, common amaranth and false daisy at 150 g ai/ha. Compounds **5** were inactive against all the tested weeds. Compounds **6** exhibited moderate to good inhibitory effect against the tested dicotyledonous weeds. Structure-activity relationship (SAR) analyses showed that the length of the carbon chain as linking bridge had a great effect on the herbicidal activity. Broad spectrum test of compounds **4-1**, **4-2**, **4-9**, **4-30** and **4-36** were carried out at 75 g ai/ha. Especially, **4-1** exhibited 100% inhibition activity against the tested dicotyledonous weeds, which was higher than that of glyphosate.

KEYWORDS: synthesis; herbicide; structure-activity relationship; phosphonate; modification; crop selectivity

INTRODUCTION

Alkylphosphonate derivatives have attracted more and more interest due to their potential biological activity, and they are intensely used in agricultural and pharmaceutical chemistry.[1-5] For the purpose of developing novel herbicides against new targets, we have ever synthesized series of alkylphosphonates **1** (Figure 1), and some of them displayed excellent herbicidal or fungicidal activities.[6] Among alkylphosphonates **1**, clacyfos, as a selective post-emergence herbicide, displayed outstanding herbicidal activity on the broad-leaved weeds.[6] Based on the structure of compounds **1**, compounds **2** have been designed and synthesized by the introduction of some heterocycles such as furanic and pyridinic groups into the R^3 group of the general structure **1**. Among the compounds **2**, compound **HWS** showed the most effective activity against broadleaved weeds at 50 g ai/ha. Furthermore, compounds **3** have been designed and synthesized by the introduction of a cyclophosphonate moiety into the phosphonate part of structure **1**. The compounds **3-2** and **3-3** showed high activity with an inhibition effect of 70−100 % at 75 g ai/ha against all the tested broadleaf weeds and against tested dicotyledons, such as velvetleaf, leaf mustard, and false daisy, which indicated that they could be developed as a selective post-emergence herbicides. [7]

The structural skeleton of **1** was used as the lead compound. An acetoxy (CH_2COO) group served as the linker and connected the phosphonate and phenoxy moieties in **1**. To explore the relationship between the length of the linking bridge and the herbicidal activity, compounds **4** and **5**, as shown in the Figure 1, were designed and synthesized by replacing the acetoxy group with a butyryloxy group and a valeryloxy group, respectively. As a comparison, compounds **6** were designed by introducing a cyclophosphonate moiety into the phosphonate part of lead compound **1**. In this work, we report the syntheses and characterization of novel

alkylphosphonates **4**, **5** and **6**, and they are evaluated for their herbicidal activities and safety to some crops.

MATERIALS AND METHODS

Chemicals

Chemicals and reagents were obtained from commercial sources Sinopharm Chemical Reagent Co., Ltd. (SCRC, Shanghai, China) and used as received. FT-IR spectra were measured on a Perkin-Elmer FT-IR spectrometer (PerkinElmer, Mass., USA). NMR spectra were obtained using Varian XL-400 (Varian, Calif., USA) or Varian XL-600 (Varian, Calif., USA) spectrometer using $CDCl_3$ as solvents and TMS as an internal standard. Chemical shifts (δ) were expressed in parts per million downfield from the internal standard. The mass spectra were recorded using a Finnigen TRACE spectrometer (Applied Biosystems, Mass., USA) and API2000LC/MS (Applied Biosystems, Mass., USA). Elemental analysis was carried out using a Vario EL III elemental analyzer (Elementar, Hanau, Germany).

Synthesis Procedures

Synthesis of Compounds 8a-f.

Compounds **8a-f** were prepared according to our earlier reported method with minor modifications.[8-12] To a solution of appropriate phosphite **7** (1.0 equiv) and aldehydes (1.0 equiv) in chloroform (10 mL), triethylamine (0.5 equiv) was added at 0^{o}C to afford compounds **8a-f**.

Synthesis of Compounds 10 and 11a-g

The intermediate **10** was prepared according to procedures reported in the literature.[13] The intermediate **10** (4.0 mmol) was dissolved in thionyl chloride (3 mL). Then N,N-dimethylformamide (5% mol) was added and the reaction mixture was allowed to heat at reflux for 5-6 h. Thionyl chloride was removed under reduced pressure to afford light yellow oils **11a-g**

with yields of 85-90%.

Synthesis of Compounds 18a-b.

Following the procedure described for **8a-f**, compounds **18a-b** were obtained with yields of 60-90%. Compounds **18a-b** have been reported in the literature.[7]

Synthesis of Compounds 16.

The intermediate **16** was prepared according to procedures reported in the literature. [14-15] The substituted 3-phenoxypropanol **12** was obtained from substituted phenol and 1-chloro-3-hydroxypropane according to the methods given in the literature.[8] To a stirred solution of substituted 3-phenoxypropanol **12** (1.0 equiv) and triethylamine (1.2 equiv) in dichloromethane (DCM, 10mL), cooled to 0-5 ^{o}C, methanesulfonyl chloride (1.2 equiv) in DCM (5 mL) was added dropwise. The reaction mixture was allowed to heat at 30-35^{o}C for 3-5 h. The solution was filtered and the filtration was evaporated under reduced pressure to afford crude product **13**, and then, a solution of sodium ethoxide (1.0 equiv) in ethanol (10 mL) was added to the crude and allowed to heat at reflux for 2 h. Then diethyl malonate (1.0 equiv) was added dropwise over 60 min period. The resulting mixture was refluxed for 5-8 h at 70-80 ^{o}C, and filtered, the filtration was evaporated under reduced pressure to afford crude product **14** without further purification (Figure 3). The intermediate **14** was added to aqueous NaOH (2M, 80 mL). The resulting mixture was allowed to stir for 18 h at 30-35^{o}C, and then acidified by 5% HCl. The acid **15** was precipitated, filtered off, and subsequently washed with H_2O, then dissolved into dimethylformamide (10 mL) and refluxed for 8 h at 110-120 ^{o}C and cooled to 25-30^{o}C. Then ice water (30 mL) was added to the mixture, and the precipitate was filtered off. A colorless crystal **16** was obtained with a yield of 90-96% (Figure 3). [14-15]

Synthesis of Compounds 17a-c.

Following the procedure described for **11a-g**, the substituted phenoxyvaleryloxy chlorides **17a-c** were afforded as light yellow oils with yields of 71-84%.

Synthesis of Compounds 4-1−4-42.

To a solution of intermediate **8a-f** (1.0 equiv) and triethylamine (1.1 equiv) in chloroform (20 mL), cooled to 0-5 ^{o}C, a solution of substituted phenoxybutanoyl chlorides **11a-g** (1.1 equiv) in chloroform (15 mL) was added dropwise. The mixture was allowed to stir at 25-30 ^{o}C for 3-5 h, and then at 40-45 ^{o}C for 1-2 h. The chloroform layer was washed with 5% HCl, saturated sodium bicarbonate, and brine, dried, and concentrated. The residue was purified by flash chromatography (2:1, petroleum ether/acetone) to afford title compounds **4-1−4-42**.

Synthesis of Compounds 5-1-5-6.

Following the procedure described for **4-1-4-42**, compounds **5-1-5-6** were obtained.

Synthesis of Compounds 6-1-6-6.

Following the procedure described for **4-1-4-42**, compounds **6-1-6-6** were obtained.

RESULTS AND DISCUSSION

Synthesis

The intermediates **8-18** were prepared according to procedures reported in the literature.[9-12] The ethyl substituted phenoxybutanoate **9** were synthesized by the reaction of substituted phenols and ethyl 4-bromobutanoate with potassium carbonate as the catalyst. Substituted phenoxybutanoic acids **10** were prepared by hydrolyzing the corresponding intermediates **9** in the presence of sodium hydrate as a base.

In triethylamine or pyridine, with chloroform as solvent, the target compounds **4** and **5** were synthesized from the reaction of intermediates **8** with substituted phenoxybutanoyl chlorides **11** and substituted phenoxyvaleryloxy chlorides **17**, respectively (Figure 2 and 3). In triethylamine

or pyridine, with chloroform as solvent, the target compounds **6** were synthesized from the reaction of intermediates **18** and substituted phenoxybutanoyl chlorides **11** (Figure 4). The structures of the target compounds **4**, **5** and **6** were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS and elemental analysis. The target compounds **4**, **5** and **6** exhibit some characteristic peaks at δ = 3.60-3.84 (m or dd, 6H, 2×P-O-CH_3) and δ = 5.28-6.31 (d or t or m, 1H, P-CH) in the ^{1}H NMR. A typical carbon resonance at δ_C 168.56-173.72 in the ^{13}C NMR spectra of **4** also confirms the presence of a carbon-oxygen double bond. The typical phosphorus resonance in the ^{31}P NMR spectra of **4**, **5** and **6** reveals the presence of a phosphorus center coupled to an adjacent CH at δ_P 16.16-23.28, 20.09-24.07 and 9.98-15.58, respectively.

Greenhouse Herbicidal Activity and Crop Selectivity

All the title compounds were tested at 150 g ai/ha for post-emergence herbicidal activity on barnyard grass (*Echinochloa crusgalli*), green bristlegrass (*Setaira viridis*), crab grass (*Digitaria sanguinalis*), velvetleaf (*Abutilon theophrasti*), slender amaranth (*Amaranthus retroflexus*) and false daisy (*Eclipta prostrata*). Clacyfos was selected as a control. As shown by the data in Table 1, we see that all of compounds **4** with 2-NO_2 or 4-NO_2 substitution on the phenoxybenzene ring were inactive against all of the tested weeds, while other compounds **4** exhibited weak to excellent activity against dicotyledonous weeds and were almost inactive against the tested monocotyledonous weeds. Compounds **4-1**−**4-3, 4-8**−**4-9, 4-15, 4-19, 4-22**, **4-24**, **4-30**, **4-31** and **4-36**−**4-38** exhibited significant herbicidal activity against velvetleaf, slender amaranth and false daisy. It is worthwhile to note that compounds **4-1**, **4-2**, **4-9**, **4-22** and **4-30** displayed remarkable herbicidal activity on the tested broad-leaved weeds with an 85-100% inhibition, which was equal to that of clacyfos against the tested dicotyledons with an 85-100% inhibition at 150 g ai/ha. Especially, the herbicidal activity of compounds **4-1** and **4-9** against velvetleaf, leaf

mustard and false daisy were 100% inhibition effect at 150 g ai/ha. All of the compounds **5** were inactive against all of tested plants at 150 g ai/ha, no matter what the substitution groups (R, X and Y) were. As shown by the data in Table 2, all of title compounds **6** displayed outstanding herbicidal activity against dicotyledonous weeds equal to clacyfos. Interestingly, the herbicidal activity of compounds **6** against monocotyledonous weeds with values of 10-30% inhibition at the same rate were better than those of compounds **4** and that of clacyfos with values of zero at 150 g ai/ha.

Comparing the data shown in Table 1, title compounds **4** with 2,4-Cl_2 or 4-Cl-2-CH_3 as X and Y (such as **4-1**, **4-2**, **4-8**, **4-9**, **4-19**, **4-20**, **4-22**, **4-23**, **4-29**, **4-30**, **4-36** and **4-37**) exhibited significant herbicidal activity (more than 80% inhibition) against the tested dicotyledons for post-emergence treatment at 150 g ai/ha, regardless of different substituents in the R^1 moiety (such as CH_3, CH_2CH_3, *n*-Pr and Ph) and R moiety (such as CH_3 and CH_2CH_3). The 2,4-Cl_2 or 4-Cl-2-CH_3 substitution on the phenoxybenzene ring was the most promotive followed by 4-Cl or 4-Cl-3-CH_3. The nitro group substitution on the phenoxybenzene ring resulted in inactive against all of the tested weeds, no matter what other groups served as R^1 and R moieties.

Bioassay results indicated that compounds **5** showed no herbicidal activity against all tested plants at 150 g ai/ha in post-emergence treatment, regardless of the different substituents R, R^1 and X, Y. As shown by the data in Table 2, all of the compounds **6** exhibited 60-85% inhibition against dicotyledonous weeds at 150 g ai/ha in post-emergence treatment, no matter what the different of substituents R, R^1 and X, Y. However, compounds **6** exhibited a 10-30% herbicidal inhibition against all of the tested monocotyledons, which is better than that of clacyfos without activity against the tested monocotyledons.

The SAR analysis of compounds **4** implied that the carbon chain with three carbon atoms

between carbonyl and phenoxy moiety seemed to have a favorable effect on herbicidal activity, in this case substituents X and Y on the phenoxy-benzene ring still greatly affected the activity. Compounds **4** with 2,4-Cl_2 or 4-Cl-2-CH_3 as X and Y especially exhibit much higher herbicidal activity. However, compounds **5** with a four-member carbon chain as linking bridge resulted in a loss of activity against all of the tested weeds even 2,4-Cl_2 or 4-Cl-2-CH_3 as X and Y on the phenoxy-benzene ring.

It was found that **4-1**, **4-2**, **4-9**, **4-30** and **4-36** displayed much higher herbicidal activity than that of other compounds at 150 g ai/ha, so these compounds were chosen for a broad spectrum test to confirm their activity and potential application. They were tested at the rates of 75 and 150 g ai/ha for post-emergence herbicidal activity against velvetleaf, false daisy, field mustard, tomato, leaf mustard, glory, common vetch, goosefoot, ball cabbage, common amaranth, radish, monarch redstem and sheathed monochoria herb. As shown by the data in Table 3, the herbicidal activities and spectra of **4-1**, **4-2**, **4-9**, **4-30** and **4-36** were comparable with that of glyphosate. The title compound **4-1** showed especially higher herbicidal activity than glyphosate against velvetleaf, field mustard, leaf mustard, glory, common vetch, goosefoot, ball cabbage, common amaranth radish, monarch redstem and sheathed monochoria herb at 75 g ai/ha.

Furthermore, the crop selectivity of **4-1**, **4-2**, **4-9**, **4-20**, **4-22** and **4-23** were also tested. As shown by the data in Table 4, the compounds were harmless to wheat and maize by post-emergence application at 450 g ai/ha, which indicated that these compounds could be developed as potential herbicides used in wheat and maize fields.

In summary, three series of novel α-(substituted phenoxybutyryloxy or valeryloxy)alkylphosphonates **4-5** and 2-(substituted phenoxybutyryloxy)alkyl-5,5-dimethyl-1,3,2-dioxaphosphinan-2-one derivatives **6** were designed and synthesized based on the

structural modification of **1**, and their post-emergence herbicidal activity against six species of weeds were evaluated. Structure-activity relationship (SAR) analyses indicated that a three-member carbon chain as linking bridge in the modified structure had a favorable effect on herbicidal activity against the tested dicotyledons, and the herbicidal activity of compound could be further increased by a reasonable combination of X, Y and R in the parent structure **4**. The title compounds **5** with a four-member carbon chain showed no activity against all of the tested weeds. Compounds **6** containing a phosphorus-heterocyclic ring showed lower herbicidal activity against the tested dicotyledons compared with those of compounds **4**. Title compound **4-1** was found to possess high activity and a broad spectrum against all of the tested broadleaf weeds with a 70-100% inhibition effect at 75 g ai/ha; furthermore, it is very safe for wheat and maize at 450 g ai/ha. These findings demonstrate that **4-1** could be as a potential selective post-emergence herbicide for further development.

ASSOCIATED CONTENT

Supporting Information

Structures were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS and elemental analysis. The physicochemical properties and spectroscopic data of all title compounds are provided. Bioassay methods for greenhouse herbicidal activity and crop selectivity are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Ning, L. H.; Wang, W.; Liang, Y. J.; Pneg, H.; Fu, Li-W.; He, H. W. Synthesis and cytotoxicity of *O,O′*-dialkyl {[2-(substituted phenoxy)acetamido](substituted phenyl)methyl}phosphonates. *Eur. J. Med. Chem*. **2012**, *48*, 379-384.

(2) Roy, N. K.; Nidiry, E. S. J.; Vasu, K.; Bedi, S.; Lalljee, B.; Singh, B. Quantitative structure−activity relationship studies of *O,O*-bisaryl alkyl phosphonate fungicides by Hansch approach and principal component analysis. *J. Agric. Food. Chem.* **1996**, *44*, 3971-3976.

(3) Forlani, G.; Giberti, S.; Berlicki, L.; Petrollino, D.; Kafarski, P. Plant P5C reductase as a new target for aminomethylenebisphosphonates. *J. Agric. Food. Chem.* **2007**, *55*, 4340-4347.

(4) Forlani, G.; Occhipinti, A.; Berlicki, L.; DziedzioŁa, G.; Wieczorek, A.; Kafarski, P. Tailoring the structure of aminobisphosphonates to target plant P5C reductase. *J. Agric. Food. Chem.* **2008**, *56*, 3193-3199.

(5) Cox, J. M.; Hawkes, T. R.; Bellini, P.; Ellis, R. M.; Barrett, R.; Swanborough, J. J.; Russell, S. E.; Walker, P. A.; Barnes, N. J.; Knee, A. J.; Lewis, T.; Davies, P. R. The design and synthesis of inhibitors of imidazoleglycerol phosphate dehydratase as potential herbicides. *J. Pestic. Sci.* **1997**, *50*, 297-311.

(6) He, H. W.; Yuan, J. L.; Peng, H.; Chen, T.; Shen, P.; Wan, S. Q.; Li, Y. J.; Tan, H. L.; He, Y. H.; He, J. B.; Li, Y. Studies of *O*,*O*-dimethyl *α*-(2,4-dichlorophenoxyacetoxy)ethylphosphonate (HW02) as a new herbicide. 1. Synthesis and herbicidal activity of HW02 and analogues as novel inhibitors of pyruvate dehydrogenase complex. *J. Agric. Food. Chem.* **2011**, *59*, 4801-4813.

(7) Wang, W.; He, H. W.; Zuo, N.; Peng, H. Synthesis and herbicidal activity of 2-[(substituted phenoxyacetoxy)alkyl]-5,5-dimethyl-1,3,2-dioaphosphinan-2-one containing fluorine. *J. Fluorine Chem*. **2012**, *42*, 24-28.

(8) Gancarz, R.; Wielkopolski, W.; Jaskulska, E.; Kafarski, P; Lejczzak, B.; Mastalerz, P.; Wieczorek, J. S. Phosphonic analogues of morphactine. Part IV: 9-aminofluoren-9-ylphosphine oxides. *Pestic. Sci.**1985***, *16*, 234–238.

(9) Kumaraswamy, S.; Selvi, R. S.; Swamy, K. C. K. Synthesis of new *α*-hydroxy-, *α*-halogeno- and vinylphosphonates derived from 5,5-dimethyl-1,3,2-dioxaphosphinan-2-one, *Synthesis*. **1997**, *2*, 207-211.

(10) Wang, C. B.; Xu, C.; Tan, X. S.; Peng, H.; He, H. W. The asymmetric synthesis of chiral cyclic *α*-hydroxy phosphonates and quaternary cyclic *α*-hydroxy phosphonates. *Org. Biomol. Chem*. **2012**, *10*, 1680-1685.

(11) Muthiah, C.; Kumar, K. P.; Mani, C. A.; Swamy, K. C. K. Chlorophosphonates: inexpensive precursors for stereodefined chloro-substituted olefins and unsymmetrical disubstituted acetylenes. *J. Org. Chem.* **2000**, *65*, 3733–3737.

(12) He, H. W.; Wang, T.; Yuan, J. L. Synthesis and herbicidal activities of methyl-1-(2,4-dichloro-phenoxyacetoxy)alkylphosphonatemonosalts. *J. Organomet. Chem.* **2005**, *690*, 2608-2613.

(13) Xie, Q. L.; Zheng, J. Y. Synthesis and structure of tricyclohexyistannane aromatoxyacetares. *Chin. J. Org. Chem.* **1991**, *11*, 82-87.

(14) Wen, R. Chapter 2: Alkylation Reaction. In *Organic Reactions for Drug Synthesis*, 3; Chemical Industry Press: Beijing, China, 2002; 44-51.

(15) Huang, X.; Wang, Y., G.; Chen, Z. C. Chapter 5: Alcohol and Phenol. In *New Organic Synthetic Chemistry*, 1; Chemical Industry Press: Beijing, China, 2002; 196-203.

253 **FIGURE CAPTIONS**

254 **Table 1.** Herbicidal activity of compounds **4-1-4-42.**

255 **Table 2.** Herbicidal activity of compounds **6-1-6-6.**

256 **Table 3.** Broad spectra bioassay of compounds **4-1, 4-2, 4-9, 4-30** and **4-36**.

257 **Table 4.** Crop selectivity of compounds **4-1**, **4-2**, **4-9**, **4-20**, **4-22** and **4-23**

258 **Figure 1.** Chemical modification of lead structure **1.**

259 **Figure 2.** Synthetic route of α-(substituted phenoxybutyryloxy)alkylphosphonates **4-1-4-42.**

260 **Figure 3**. Synthetic route of α-(substituted phenoxyvaleryloxy)alkylphosphonates **5-1-5-6.**

261 **Figure 4.** Synthetic route of 2-(substituted phenoxybutyryloxy)alkyl-5,5-dimethyl-1,3,2-

262 dioxaphosphinan-2-one **6-1-6-6.**

263 **Table 1.** Herbicidal activity of compounds **4-1-4-42.**

Compd.	R^1	R	X	Y	post-emergence, 150 g ai/ha					
					EC[a]	SV[a]	DS[a]	AT[a]	BJ[a]	EP[a]
4-1	Me	Me	2-Cl	4-Cl	0	0	0	100	100	100
4-2	Me	Me	2-Me	4-Cl	0	0	30	95	98	100
4-3	Me	Me	4-Cl	H	0	30	30	70	70	70
4-7	Me	Me	3-Me	4-Cl	0	30	0	60	60	40
4-8	Me	Et	2-Cl	4-Cl	30	0	0	100	100	75
4-9	Me	Et	2-Me	4-Cl	40	30	30	100	100	100
4-10	Me	Et	4-Cl	H	50	30	20	70	60	60
4-13	Me	Et	3-Me	4-Cl	0	0	0	70	60	60
4-15	Me	Pr	4-Cl	H	30	30	30	75	70	70
4-19	Me	Pr	2-Cl	4-Cl	40	20	20	100	100	80
4-20	Me	Pr	2-Me	4-Cl	0	0	0	100	80	50
4-21	Me	Pr	3-Me	4-Cl	0	0	0	30	60	50
4-22	Me	Ph	2-Cl	4-Cl	30	0	0	85	100	100
4-23	Me	Ph	2-Me	4-Cl	0	0	0	95	80	60
4-24	Me	Ph	4-Cl	H	50	50	40	75	70	75
4-27	Me	Ph	3-Me	4-Cl	0	0	0	60	40	40
4-29	Et	Me	2-Cl	4-Cl	0	0	0	85	80	60
4-30	Et	Me	2-Me	4-Cl	50	30	30	100	90	90
4-31	Et	Me	4-Cl	H	40	50	50	100	85	70

4-34	Et	Me	3-Me	4-Cl	0	0	0	60	60	60
4-36	Et	Ph	2-Cl	4-Cl	30	0	20	100	80	80
4-37	Et	Ph	2-Me	4-Cl	40	0	0	100	80	70
4-38	Et	Ph	4-Cl	H	50	60	50	100	80	70
4-41	Et	Ph	3-Me	4-Cl	30	30	20	80	70	60
Clacyfos					0	0	0	100	85	90

[a]EC for *Echinochloa crusgalli*; SV for *Setaira viridis*; DS for *Digitaria sanguinalis*; AT for *Abutilon theophrasti*; BJ for *Brassica juncea*; EP for *Eclipta prostrate.*

n.b.: Compounds **4-4**, **4-5**, **4-6**, **4-11**, **4-12**, **4-14**, **4-16**, **4-17**, **4-18**, **4-25**, **4-26**, **4-28**, **4-32**, **4-33**, **4-35**, **4-39**, **4-40** and **4-42** with no herbicidal activity against all the tested weeds were not listed in the **Table 1**.

269 **Table 2.** Herbicidal activity of compounds **6-1-6-6.**

Compd.	R	X	Y	post-emergence, 150 g ai/ha					
				EC[a]	SV[a]	DS[a]	AT[a]	BJ[a]	EP[a]
6-1	Me	2-Cl	4-Cl	30	30	30	85	85	80
6-2	Me	2-Me	4-Cl	30	30	30	85	80	80
6-3	Me	4-Cl	H	30	30	30	80	70	60
6-4	Ph	2-Cl	4-Cl	30	30	20	75	75	90
6-5	Ph	2-Me	4-Cl	10	10	10	80	75	80
6-6	Ph	4-Cl	H	20	20	20	75	50	75
	Clacyfos			0	0	0	100	85	90

270 [a]EC for *Echinochloa crusgalli*; SV for *Setaira viridis*; DS for *Digitaria sanguinalis*; AT for

271 *Abutilon theophrasti*; BJ for *Brassica juncea*; EP for *Eclipta prostrate.*

272 **Table 3.** Broad spectra bioassay of compounds **4-1, 4-2, 4-9, 4-30** and **4-36**.

Compd.	Rate	Post-emergence												
	g ai/ha	AT[a]	EC[a]	BC[a]	SL[a]	BJ[a]	PC[a]	VS[a]	CA[a]	BO[a]	AR[a]	RS[a]	AB[a]	MK[a]
4-1	150	100	100	90	90	95	100	100	90	85	100	95	100	100
	75	100	70	70	80	90	100	100	80	80	90	80	100	100
4-2	150	95	100	80	80	100	100	75	75	60	80	85	100	90
	75	80	60	80	70	80	100	75	70	50	80	90	90	85
4-9	150	100	100	70	70	100	100	70	75	70	90	60	100	100
	75	80	60	60	60	90	100	60	70	50	80	50	100	90
4-30	150	100	90	60	70	100	100	70	80	70	75	50	50	50
	75	70	70	60	50	70	80	60	60	60	70	30	0	40
4-36	150	100	80	80	95	85	100	80	80	80	80	90	70	100
	75	\	\	60	70	85	100	70	70	80	70	80	70	90
glyphosate	150	100	100	80	85	80	60	95	90	80	90	65	100	100
	75	80	90	70	85	30	60	95	70	70	90	60	100	100

273 [a]AT for *Abutilon theophrasti*; EC for *Eclipta prostrata*; BC for *Brassica chinensis* L.; SL for
274 *Solanum lycopersicum*; BJ for *Brassica juncea*; PC for *Pharbitis nil* (L.) *Choisy*; VS for *Vicia*
275 *sativa* L.; CA for *Chenopodium album*; BO for *Brassica oleracea*; AR for *Amaranthus*
276 *retroflexus*; RS for *Raphanus sativus L.*; AB for *Ammannia baccifera L.*; MK for *Monochoria*
277 *vaginalis* (BL.) *Kunth*

278

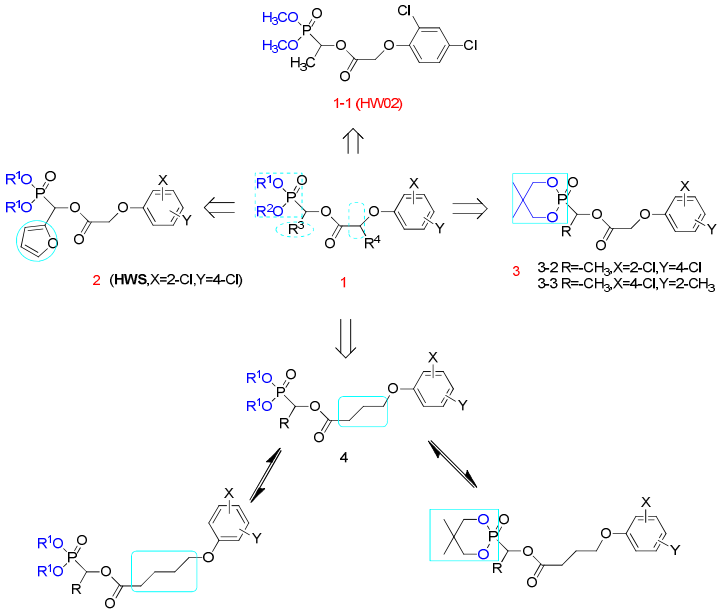
279

280 **Table 4.** Crop selectivity of compounds **4-1**, **4-2**, **4-9**, **4-20**, **4-22** and **4-23**

Compd.	R	R^1	X	Y	Crops (percent inhibition, 450 g ai/ha）[a]					
					wheat	rice	maize	cotton	soybean	rape
4-1	Me	Me	2-Cl	4-Cl	0	31-50	0	11-30	11-30	31-50
4-2	Me	Me	2-Me	4-Cl	0	31-50	0	11-30	11-30	31-50
4-9	Me	Et	2-Me	4-Cl	0	0	0	11-30	11-30	0
4-20	Me	Pr	2-Me	4-Cl	0	31-50	0	11-30	11-30	31-50
4-22	Me	Ph	2-Cl	4-Cl	0	11-30	0	11-30	11-30	11-30
4-23	Me	Ph	2-Me	4-Cl	0	31-50	0	11-30	11-30	31-50

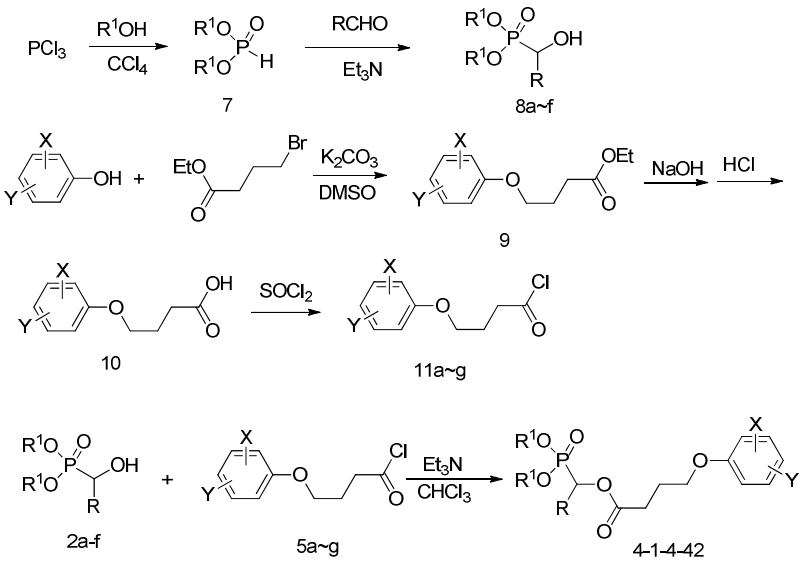
281 [a]>10%, not safe to crops; 0-10%, safe to crops.

282 **Figure 1.** Chemical modification of lead structure **1.**



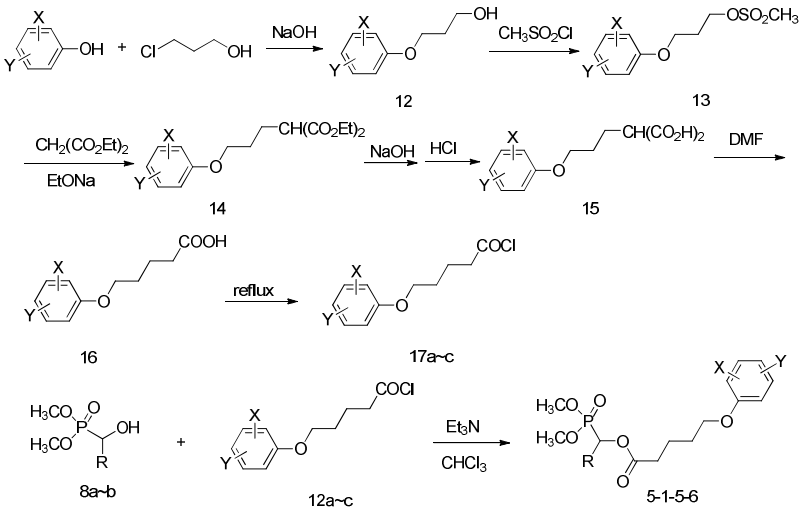
283

284 **Figure 2.** Synthetic route of *α*-(substituted phenoxybutyryloxy)alkylphosphonates **4-1-4-42.**



285

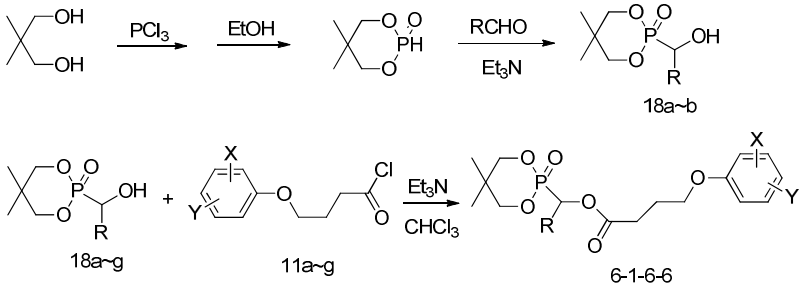
286 **Figure 3**. Synthetic route of *α*-(substituted phenoxybutyryloxy)alkylphosphonates **5-1-5-6.**



287

288 **Figure 4.** Synthetic route of 2-(substituted phenoxybutyryloxy)alkyl-5,5-dimethyl-1,3,2-

289 dioxaphosphinan-2-one **6-1-6-6.**



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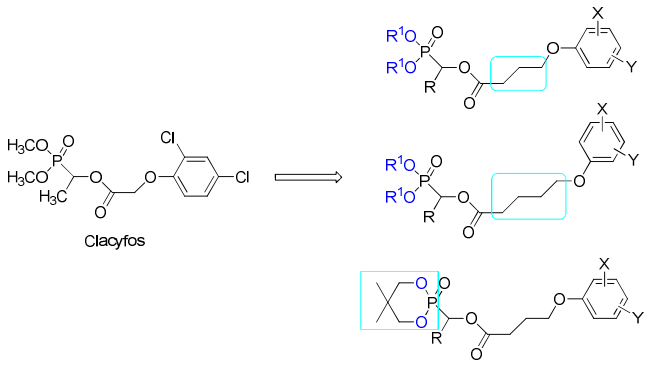

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