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Synthesis and Biological Activity of Novel 1-(Substituted Phenoxyacetoxy) Alkyl Phosphonates and Phosphinates

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Abstract

*To investigate the influence of nitro group on the biological activity of phenoxyacetoxy phosphonates and phosphinates, a series of novel 1-(substituted phenoxyacetoxy) alkyl phosphonates and phosphinates were synthesized and screened for herbicidal activity and plant growth regulatory activity. Compounds **5a, 5b** and **5j** exhibited notable bioactivity. Results indicated that nitro groups had a great influence on the biological activity, and the improvement of biological activity required a reasonable combination of a nitro group and other substituents.*

Introduction

It is known that substituted phenoxyacetic acid derivatives possess herbicidal activity.[1-3] Some acetylphosphinates and acetylphosphonates showed modest herbicidal activity due to their inhibition against pyruvate dehydrogenase complex (PDHc).[4,5] In recent years, we have been engaged in designing agrochemicals utilizing a biochemically rational approach.[6,7] The general structure (1) shown in Fig. 1, which possessed significant herbicidal activities, could act as a leading structure for herbicide design and some of them also showed plant growth regulatory activity.

Structure modification of (1) has been attempted by introducing different substituents R, X and Y to the phosphonates.[8,9] However, none of our previous work was devoted towards examining the effects of nitro group substituents on herbicidal activity and plant growth regulatory activity. Here, we would like to introduce the NO_2 group in R, NO_2 and Cl as X or/and Y into the phosphonates and their corresponding phosphinates to explore the effects on bioactivity. A novel series of 1-

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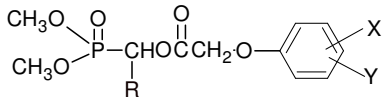
(substituted phenoxyacetoxy) alkyl phosphonates and phosphinates were synthesized and screened for herbicidal activity and plant growth regulatory activity.

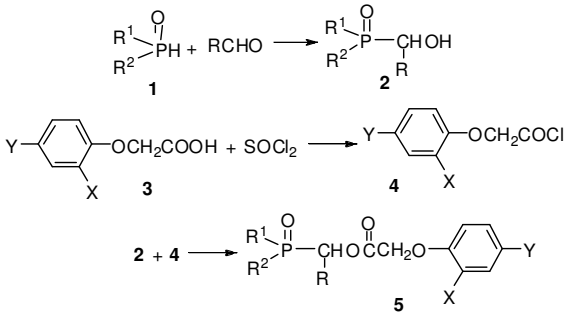


(1)

Figure 1: The general structure of O,O-dimethyl 1-(substituted phenoxyacetoxy) alkyl phosphonates.

Experimental Methods

Melting points were determined with an X4 melting-point apparatus and were uncorrected. Refractive index was measured with an Abbe refractometer at 20°C. Elemental analyses were performed with a PE-2400 elemental analysis apparatus. IR spectra were obtained with a Perkin-Elmer-983 spectrometer. ^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer with TMS as internal standard and $CDCl_3$ as solvent. Column chromatography (30×3 cm column) was carried out using silica gel. 2,4–Dichlorophenoxy acetic acid was purchased from Yancheng Huilong Chemical Co. Ltd, China. All other chemicals and solvents used were of reagent grade. Compounds **1**, **2**, **3** and **4**, as shown in Scheme 1, were prepared according to the literature.[1, 10-15]



"X, Y = Cl, NO_2, R = n-Pr, Ph, m-NO_2Ph, p-NO_2Ph, R^1 = OCH_3, CH_3, R^2 =OCH_3"

Scheme 1: Synthetic pathway of 1-(substituted phenoxyacetoxy) alkyl phosphonates and phosphinates

General synthetic procedure for compound 5

To a stirred and cooled solution of the appropriate *α*-hydroxyalkyl phosphonate or phosphinate (0.01 mol) in 10 ml chloroform and 0.8 ml pyridine, substituted phenoxyacetyl chloride (0.012 mol) dissolved in 10 ml chloroform was added slowly to keep the reaction temperature below 10°C. The resultant mixture was stirred at an ambient temperature for 4-6 h, washed successively with 1% NaOH (3×10 ml) and saturated NaCl (2×10 ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column

chromatography on silica gel using acetone+petroleum ether (1+1) as an eluent to give **5a-n**.

Methods of bioassay

(a) Herbicidal activity test in Greenhouse

Plastic pots were packed with sandy clay loam soil and water was added up to 3 cm in depth. Plant seeds were sown in the pots, and a diluted suspension of each compound containing acetone and Tween 80 was applied into the pots at 0.225 gm^{-2}. Five days later, the pre-emergence herbicidal activity against each plant was visually evaluated. The solution of the chemicals tested was applied to the foliage of plants grown at the 2-3 leaves stage with a sprayer at the rate of 0.225 g m^{-2} with a spelling volume of 100 ml m^{-2}. Test plants were harvested 15 days after treatment. The fresh weights of aerial parts of each plant were measured. The post-emergence herbicidal activity against each plant was evaluated. Each experiment was replicated two times.

(b) Determination of IC_{50}

A compound with a certain concentration was dissolved in acetone and placed on a filter paper (5.5 cm diameter) in Petri dishes (9 cm), and 10 cucumber seeds were placed on the filter paper after soaking in water for 6 h. The Petri dishes with cucumber seeds were placed in a LRH-250-G lighting culture tank at 28^{o}C for 3 days with 10 h of lighting and 14 h in the dark. After 6 days of cultivation, the inhibition percentage was calculated by the corresponding control using the length of the taproot or stem as an indicator. Three replications per concentration were performed. According to the average inhibition of cucumber root or stem at five concentrations for each compound, IC_{50} was estimated by regression analysis using the logarithm of concentration and a probit of corresponding inhibition percentage.

The wheat coleoptile test and Cucumber cotyledon test procedures were the same as described in the literature[16].

Results and Discussion

Chemistry

Compound **1** is O,O-dimethyl phosphite or O-methyl methyl phosphite. O,O-Dimethyl phosphite was used directly as obtained commercially or prepared by the reaction of phosphorus trichloride and methanol.[17] O-methyl methyl phosphite was synthesized in two-step sequence starting from phosphorus trichloride, methyl iodide and aluminium trichloride.[10,11] Compound **2** was prepared by addition of compound **1** to the desired aldehyde using triethylamine as catalyst in yields of 53-86%.[12,13] Compound **3** could be easily synthesized according to the literature

procedures,[1,14,15] starting from substituted phenol and 2-chloroacetic acid or 2-bromoacetic ester in yields of 68-75%.

The preparation of the title compounds involved the condensation of substituted phenoxyacetyl chloride **4** and *O,O*-dimethyl 1-hydroxylalkyl phosphonates or *O*-methyl 1-hydroxylalkyl methyl phosphinates **2**. The synthetic pathway is outlined in Scheme 1 and the structures of **5a-n** are given in Table 1.

All new compounds were identified by ^{1}H NMR (Table 2), IR (Table 3) and elemental analysis (Table 1). In the ^{1}H NMR spectra of **5a-n**: the protons in the P-C moieties and P-OCH_3 moiety display doublets, which are due to coupling with the phosphorus. All the main functional groups were characterized using IR spectra. A strong absorption near 1760 cm^{-1} was identified for the C=O. A sharp, weak band at 3050-3100 cm^{-1} accounted for the C-H stretching of the benzene ring. A strong peak at around 1250 cm^{-1} accounted for P=O in phosphonates, and at around 1180 cm^{-1} for P=O in phosphinates. Two strong peaks at 1520 cm^{-1} and at 1350 cm^{-1} were the evidence for the NO_2 stretching.

*Table 1: Yield, melting point or refractive index and elemental analysis data of compounds (**5a-n**).*

Compd.	R^1	R	X	Y	Yield[a]	Mp (°C)	Analysis Found (Calcd.) (%)		
					(%)	n_D^{20}	C	H	N
5a	OCH_3	*m*-NO_2Ph	Cl	Cl	52	92-93[b]	43.93(43.96)	3.78(3.45)	3.16(3.02)
5b	OCH_3	*p*-NO_2Ph	Cl	Cl	54	126-127[b]	43.74(43.96)	3.82(3.45)	3.18(3.02)
5c	OCH_3	*m*-NO_2Ph	NO_2	H	51	86-87	46.49(46.36)	4.09(3.86)	6.31(6.36)
5d	OCH_3	*p*-NO_2Ph	NO_2	H	55	162-163	46.83(46.36)	4.21(3.86)	6.44(6.36)
5e	OCH_3	Ph	H	NO_2	61	157-158	51.60(51.65)	4.57(4.56)	3.47(3.54)
5f	OCH_3	*m*-NO_2Ph	H	NO_2	52	93-94	46.25(46.36)	4.02(3.86)	6.41(6.36)
5g	OCH_3	*n*-Pr	H	NO_2	66	33-34	46.36(46.54)	6.06(5.54)	4.32(3.88)
5h	OCH_3	Ph	H	Cl	76	95-97	53.55(53.07)	4.22(4.72)	
5i	OCH_3	*m*-NO_2Ph	H	Cl	80	80-84	47.01(47.51)	3.97(3.26)	3.02(3.26)
5j	CH_3	*m*-NO_2Ph	Cl	Cl	82	1.5550	45.76(45.56)	3.18(3.60)	2.96(3.12)
5k	CH_3	*n*-Pr	Cl	Cl	84	97-99	45.40(45.55)	5.10(5.19)	
5l	CH_3	*m*-NO_2Ph	NO_2	H	80	1.5403	47.90(48.12)	4.13(4.04)	6.55(6.60)
5m	CH_3	*n*-Pr	NO_2	H	68	1.5122	48.85(48.70)	5.98(5.84)	4.26(4.05)
5o	CH_3	*m*-NO_2Ph	Cl	NO_2	57	60-62	44.51(44.50)	3.65(3.52)	6.22(6.10)

[a] *Yields are based on products purified by column chromatography.*
[b] *Data are previously published by us.*[18]

Biological Assays

The herbicidal activity of title compounds **5a-n** was evaluated at a rate of 0.225 g m^{-2} in a set of experiments in greenhouse. They were tested for pre-emergence and post-emergence inhibitory effects against *Echinochloa Crusgalli Beava* (barngard grass), *Digitaria Sanguinalis scop* (ascendant crabgrass), *Brassica napus L.* (rape), *Cirsium arvensis* (thistle), and *Cucumis sativa L.* (cucumber). The results are listed in Table 4.

*Table 2: ^{1}H NMR spectral properties of compounds (**5a-n**).*

Compd.	^{1}H NMR ($CDCl_3$/TMS), δ
5a[a]	3.88 (dd, 6H, 2-OCH_3), 5.09 (s, 2H.-OCH_2-), 5.67(d, 1H,-CHP-), 7.03-8.16 (m, 7H, C_6H_3+C_6H_4)
5b[a]	3.86(dd, 6H, 2-OCH_3), 5.01 (s, 2H, -OCH_2-), 5.92(d, 1H, -CHP-), 7.00-8.02 (m, 7H, C_6H_3+C_6H_4)
5c	3.76-3.82 (dd, 6H, 2-OCH_3), 4.98 (s, 2H, -OCH_2-), 6.36 (d, 1H, -CHP-), 7.02-8.30 (m, 8H, C_6H_4+C_6H_4)
5d	3.92-3.95 (dd, 6H, 2-OCH_3), 4.87 (s, 2H.-OCH_2-), 6.34 (d, 1H,-CHP-), 7.15-8.17 (m, 8H, C_6H_4+C_6H_4)
5e	3.58-3.66 (dd, 6H, 2-OCH_3), 4.82 (s, 2H, -OCH_2-), 6.19 (d, 1H, -CHP-), 6.84-8.16 (m, 9H, C_6H_4+C_6H_5)
5f	3.66-3.78 (dd, 6H, 2-OCH_3), 4.88 (s, 2H, -OCH_2-), 6.29 (d, 1H, -CHP-), 6.90-8.22 (m, 8H, C_6H_4+C_6H_4)
5g	0.92 (t. 3H, -CH_3), 1.25-2.02 (m, 4H, 2-CH_2-), 3.70-3.84 (dd, 6H, 2-OCH_3), 4.80 (s, 2H, -OCH_2-), 5.22-5.46 (m, 1H, -CHP-), 6.90-8.22 (m, 4H, -C_6H_4)
5h	3.62-3.71 (dd, 6H, 2-OCH_3), 4.73 (s, 2H, -OCH_2-), 6.25 (d, 1H, -CHP-), 6.81-7.46 (m, 9H, C_6H_5+C_6H_4)
5i	3.72-3.82 (dd, 6H, 2-OCH_3), 4.79 (s, 2H, -OCH_2-), 6.34 (d, 1H, -CHP-), 6.81-8.29 (m, 8H, C_6H_4+C_6H_4)
5j	1.39-1.54 (dd. 3H, -CH_3), 3.61-3.74 (dd, 3H, -OCH_3), 4.97 (s, 2H, -OCH_2-), 6.27-6.42 (dd, 1H, -CHP-), 6.82-8.28 (m, 7H, C_6H_4+C_6H_3)
5k	0.90-0.97 (t, 3H, -CH_3), 1.34-1.41 (dd, 3H, -CH_3), 1.46-1.80 (m, 4H, 2-CH_2-), 3.65-3.79 (dd, 3H, -OCH_3), 4.78 (s, 2H, -OCH_2-), 5.30-5.48 (m, 1H, -CHP-), 6.75-7.41 (m, 3H, C_6H_3)
5l	1.32-1.54 (dd. 3H, -CH_3), 3.55-3.73 (dd, 3H, -OCH_3), 4.96 (s, 2H, -OCH_2-), 6.16-6.36 (t, 1H, -CHP-), 6.95-8.17 (m, 8H, C_6H_4+C_6H_4)
5m	0.83-0.98 (t, 3H, -CH_3), 1.32-1.50 (dd. 3H, -CH_3), 1.62-1.98 (m, 4H, 2-CH_2-), 3.57-3.77 (dd, 3H, -OCH_3), 4.81 (s, 2H, -OCH_2-), 5.16-5.44 (m, 1H, -CHP-), 6.94-7.86 (m, 4H, C_6H_4)
5n	1.41-1.51 (dd. 3H, -CH_3), 3.65-3.74 (dd, 3H, -OCH_3), 5.06 (s, 2H, -OCH_2-), 6.26-6.38 (dd, 1H, -CHP-), 6.94-8.35 (m, 7H, C_6H_4+C_6H_3)

[a] *Data are previously published by us.*[18]

As Table 4 indicates, there were remarkable differences among the herbicidal activity of the title compounds. Compounds **5a, 5b, 5h-5k** showed much better activity than that of compounds **5c-5g, 5l-5n.** In particular, compounds **5a, 5b, 5j, 5k** showed 100% inhibitory effect against dicotyledon (*Brassica napus L., Cirsium arvensis, Cucumis sativ L.*) for post-emergence. Compounds **5j, 5k** also exhibited 83.3-100% inhibitory effect against monocotyledon (*Echinochloa Crusgalli Beava, Digitaria Sanguinalis scop*) for both pre-emergence and post-emergence.

Table 3: IR spectral properties of compounds ***5a-n*** *(ν/cm^{-1}).*

Compd.	Ar-H	R-H	C=O	C=C	C-NO_2	P=O	C-O-C	P-O-C	P-C
5a[a]	3028	2952	1774	1580	1533	1235	1170	1035	758
		2845		1460	1352				
5b[a]	3043	2958	1773	1578	1521	1257	1176	1056	751
		2858		1472	1348				
5c	3046	2951	1787	1590	1528	1253	1178	1037	745
		2856		1497	1350				
5d	3030	2950	1780	1580	1520	1250	1183	1055	749
		2849		1454	1352				
5e	3072	2961	1770	1591	1507	1267	1173	1048	748
		2858		1448	1346				
5f	3082	2955	1787	1592	1525	1269	1171	1058	752
		2852		1439	1344				
5g	3084	2960	1767	1593	1516	1261	1178	1032	751
		2855		1496	1344				
5h	3072	2956	1776	1596		1256	1165	1029	752
		2855		1492					
5i	3020	2959	1769	1595	1534	1223	1172	1037	733
		2857		1492	1354				
5j	3061	2944	1758	1579	1542	1170	1102	1038	1300
		2872		1474	1350				889
5k	3061	2958	1764	1587		1180	1108	1034	1307
		2873		1488					876
5l	3058	2941	1762	1579	1528	1169	1115	1031	1305
		2856		1490	1341				889
5m	3084	2961	1764	1587	1525	1188	1112	1038	1303
		2876		1487	1353				875
5n	3087	2954	1775	1585	1524	1171	1126	1032	1288
	3043	2853		1489	1341				877

[a] *Data are previously published by us.*[18]

Among all the compounds, compound **5j** showed the highest activity, which exhibited 97.3-100% post-emergence inhibitory activity and 90.0-100% pre-emergence inhibition against all the test plants in greenhouse. Compound **5o** also listed in Table 4 was employed to discuss herbicidal activity. It was obtained from our previous work.[19] Based on the preliminary bioassays, title compounds were tested for IC_{50} values against the growth of *Cucumis Sativa L.* The results are listed in Table 5.

According to the IC_{50} value shown in Table 5, the IC_{50} results corresponded well to the results in Table 1. Compounds **5a, 5b, 5h-5k**, for which the IC_{50} values were less than 11.2 μM, showed higher inhibitory activity, whereas compounds **5c-5g, 5l-5n**, for which the IC_{50} values were more than 109 μM, exhibited low inhibitory activity against the growth of the root and stem of *Cucumis sativa L.* Compound **5a** displayed the highest inhibitory activity against the growth of the root of *Cucumis sativa L.* (IC_{50} = 0.00343 μM) and compound **5b** displayed the highest

inhibitory activity against the growth of the stem of *Cucumis sativa L.* (IC_{50} = 2.22 μM).

From the data in Tables 4 and 5, we noticed that NO_2 as X or Y on the benzene ring had greater influence on the herbicidal activity. Such herbicidal activity could be enhanced by introducing 2-Cl-4-Cl to the benzene ring, whereas the introduction of X or Y as NO_2 resulted in a sharp decrease in their herbicidal activity towards test plants. As a typical example, the herbicidal activity of compounds **5a** and **5j** (X and Y as 2-Cl-4-Cl, R^1 as OCH_3 or CH_3, R as *m*-NO_2Ph) was much higher than that of compounds **5c** and **5l** (X and Y as 2-NO_2-4-H, R^1 as OCH_3 or CH_3, R as *m*-NO_2Ph). However, the introduction of a nitro group as R had a favorable effect on herbicidal activity when X or/and Y as Cl, such as in compounds **5a, 5b, 5i,** and **5j**. The structure of R^1 bounded to P had also great influence on the herbicidal activity. The herbicidal activity could be further enhanced by introducing R^1 as CH_3 to P. For instance, the herbicidal activity of phosphinates **5j** and **5k** (X and Y as 2-Cl-4-Cl, R^1 as CH_3, R as *m*-NO_2Ph or *n*-Pr) was higher than that of phosphonates **5a** and **5o** (X and Y as 2-Cl-4-Cl, R^1 as OCH_3, R as *m*-NO_2Ph or *n*-Pr) against the test plants, especially on monocotyledon.

Table 4: The herbicidal activity of the title compounds (0.225 g m^{-2}, relative inhibition of growth %)[a]

Compd.	*Ech.*		*Dig.*		*Bra.*		*Cir.*		*Cuc.*	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
5a	-52.9	-28.0	-47.5	-26.2	-57.8	-100	-100	-100	-96.4	-100
5b	-41.1	-44.0	-53.9	-35.2	-100	-100	-100	-100	-99.0	-100
5c	-2.3	0	-6.7	-0.3	-0.9	0	-6.7	+5.2	-0.3	-20.0
5d	-4.1	-17.3	0	0	-5.4	-1.2	-7.9	+4.8	-9.8	-10.6
5e	-0.8	0	0	+5.2	+2.8	-5.5	+17.6	+7.3	+6.7	-5.3
5f	+1.1	+2.5	-5.3	-0.3	+16.7	+1.1	+3.9	+2.5	+20.0	-5.3
5g	-15.0	-9.6	-0.1	-2.6	+19.4	-20.3	+2.9	+5.4	+6.7	-5.3
5h	-80.9	-70.5	-98.5	-47.3	-91.7	-72.2	/	/	/	/
5i	-94.7	-46.3	-84.6	-9.2	-97.7	-94.4	/	/	/	/
5j	-90	-97.3	-100	-100	-100	-100	-90.9	-100	-100	-100
5k	-90	-94.6	-83.3	-100	-100	-100	-54.5	-100	-100	-100
5l	+5	-27.0	0	0	-7.1	-21.6	0	0	0	0
5m	-5	-2.7	0	0	+2.8	0	-36.4	/	/	/
5n	+20	0	0	-28.6	+11.3	+15.7	-36.4	-35.7	/	+22.7
5o	-70	-52.5	-75.0	-55.0	-99.5	-100	-98.9	-100	-99.0	-100

[a] *Ech: Echinochloa Crusgalli Beava; Dig: Digitaria Sanguinalis scop; Bra: Brassica napus L.; Cir: Cirsium arvensis; Cuc: Cucumis sativ L.; pre: pre-emergence; post: post-emergence; -: inhibition on the growth of plants; +: stimulation on the growth of plants; /: As there was not enough sample for the test, the data were unavailable.*

Table 5: The IC_{50} of the title compounds against Cucumis sativa L (μM).

Compd.	Inhibition on cucumber Root (IC_{50})	Inhibition on cucumber stem (IC_{50})
5a	0.00343	5.02
5b	0.112	2.22
5c	>11364	>1818
5d	423	446
5e	222	190
5f	296	922
5g	207	109
5h	1.03	6.89
5i	0.471	4.24
5j	0.283	3.48
5k	0.455	11.2
5l	3193	>2781
5m	3052	>4200
5n	1160	>2379

Title compounds were tested for plant growth regulatory activity by wheat (*Triticum aestivum L.*) coleoptiles and cucumber (*Cucumis satival L.*) cotyledon test.[18] The results are listed in Table 6. As there were not enough samples for compounds **5h** and **5i**, the data were not available.

As seen from Table 6, compound **5b** showed the highest inhibitory activity towards the growth of wheat coleoptile at 100 μg ml^{-1}. However, compounds **5a, 5j-m** exhibited high stimulating activity at 10 μg ml^{-1} towards the growth of wheat coleoptile, which was higher than that of the standard comparison reagent IAA. All of the phosphonates **5a-g** showed no effect or weak effect on the growth of cucumber cotyledon root at 10 μg ml^{-1}, whereas phosphinates **5j** and **5k** had 100% inhibitory effect on the growth of cucumber cotyledon root at 10 μg ml^{-1}.

It was also found that the plant growth regulatory activity of phosphinates (e.g. **5j**, **5k** and **5l**) was higher than its corresponding phosphonates (e.g. **5a, 5o** and **5c)** at 10 μg ml^{-1}. The NO_2 and Cl as X or/and Y in the benzene ring also had different influence on the plant growth regulatory activity. For example, the stimulating activity of compounds **5a** and **5j** (X and Y as 2-Cl-4-Cl, R^1 as OCH_3 or CH_3, R as *m*-NO_2Ph) was much higher than that of compounds **5c** and **5l** (X and Y as 2-NO_2-4-H, R^1 as OCH_3 or CH_3, R as *m*-NO_2Ph) on the growth of wheat coleoptile at 10 μg ml^{-1}. These observations show that the bioactivity of the title compounds highly depends upon X and Y on the benzene ring and the R^1 bounded to P.

Table 6: The plant growth regulating activity of the title compounds (%)[a]

Compd.	Wheat coleoptile		Cucumber cotyledon root
	100 μg ml^{-1}	10 μg ml^{-1}	10 μg ml^{-1}
5a	-1.1	+26.3	0
5b	-26.3	-5.3	0
5c	+3.2	-9.5	0
5d	+10.5	+5.3	+4.3
5e	+11.6	-13.7	0
5f	+5.3	+17.9	0
5g	+7.4	+15.8	+4.3
5j	+1.1	+41.0	-100
5k	+12.5	+29.7	-100
5l	+17.2	+22.7	-30.8
5m	+23.9	+41.0	-23.1
5n	-15.2	-3.8	+37.5
5o	-25.4	+4.4	/
ABA	-18.4		
IAA		+20.0	

[a] *-: inhibition on the growth of plants; +: stimulation on the growth of plants; /: the data was unavailable. ABA: Abscisic acid, and IAA: Indole-3-acetic acid as standard comparison reagents.*

Conclusions

Above results indicate that there were remarkably different effects on bioactivity by introducing nitro group in R or/and as X or Y into the phosphonates and phosphinates. The introduction of a nitro group as X or Y resulted in low bioactivity, especially low herbicidal activity. However, the introduction of a nitro group in R had a favorable effect on bioactivity. Excellent herbicidal activity and plant growth regulatory activity were achieved in the compounds **5a, 5b, 5j** with NO_2 in R, X and Y as 2-Cl-4-Cl and R^1 as OCH_3 or CH_3. So we can conclude that the introduction of a nitro group as X or Y is not beneficial to bioactivity of the title compounds. The satisfactory herbicidal activity and plant growth regulatory activity of the title compounds could be achieved by introducing a nitro group in R with a reasonable combination of X, Y and R^1. These results provided some interesting hints for further study of structure modification and structure-activity relationship of these compounds.

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