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α-(Substituted-phenoxyacetoxy)-α-heterocyclylmethylphosphonates: Synthesis, Herbicidal Activity, Inhibition on Pyruvate Dehydrogenase Complex (PDHc), and Application as Postemergent Herbicide against Broadleaf Weeds

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Supporting Information

ABSTRACT: Pyruvate dehydrogenase complex (PDHc) is the site of action of a new class of herbicides. On the basis of the previous work for *O,O′*-dimethyl α-(substituted-phenoxyacetoxy)alkylphosphonates (**I**), further synthetic modifications were made by introducing a fural and a thienyl group to structure **I**. A series of α-(substituted-phenoxyacetoxy)-α-heterocyclylmethylphosphonate derivatives (**II**) were synthesized as potential inhibitors of PDHc. The postemergent activity of the title compounds **II** was evaluated in greenhouse experiments. The in vitro efficacy of **II** against PDHc was also examined. Compounds **II** with fural as R^3 and 2,4-dichloro as X and Y showed significant herbicidal activity and effective inhibition against PDHc from plants. *O,O′*-Dimethyl α-(2,4-dichlorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate **II-17** had higher inhibitory potency against PDHc from *Pisum sativum* than against PDHc from *Oryza sativa* in vitro and was most effective against broadleaf weeds at 50 and 300 ai g/ha. **II-17** was safe for maize and rice even at the dose of 900−1200 ai g/ha. Field trials at different regions in China showed that **II-17** (**HWS**) could control a broad spectrum of broad-leaved and sedge weeds at the rate of 225−375 ai g/ha for postemergent applications in maize fields. **II-17** (**HWS**) displayed potential utility as a selective herbicide.

KEYWORDS: *α-(2,4-dichlorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate, herbicide, pyruvate dehydrogenase, weed control*

INTRODUCTION

The discovery of new herbicides and new herbicidal targets is an interesting challenge to crop protection chemistry. Pyruvate dehydrogenase complex (PDHc), which catalyzes the oxidative decarboxylation of pyruvate and the subsequent acetylation of coenzyme A (CoA) to acetyl coenzyme A,[1,2] has been known to be one target enzyme attacked by some herbicidally active compounds.[3−5] PDHc is a multienzyme complex composed of three enzymes [E_1 (pyruvate decarboxylase), E_2 (dihydrolipoamide acetyltransferase), E_3 (dihydrolipoamide dehydrogenase)] and six cofactors (thiamin diphosphate, lipoic acid, FAD, NAD^+, CoA, and Mg^{2+}). They are responsible for the conversion of pyruvate to acetyl coenzyme A. The first step of the multistep process is catalyzed by the E_1 component (PDHc E_1) that promotes the decarboxylation of pyruvate using thiamin pyrophosphate (TPP) and Mg^{2+} as cofactors.[6−8] PDHc E_1 as a target is of interest in new herbicide design.

Sodium methylacetylphosphonate, a phosphorus-containing analogue of pyruvic acid, was reported to be a PDHc E_1 inhibitor by Kluger and Pike in 1977.[9] Baillie et al., in 1988,[3,10] reported that these compounds showed modest herbicidal activity, and it was demonstrated that susceptible plants died as a direct result of inhibition on PDHc, which was concerned only with the fist step of a series of the reaction from pyruvate to acetyl coenzyme A.[3,4] However these acylphosphinates, acylphosphonates, and relative compounds were not candidates for commercial development of herbicides. Although some exhibited good activity, 80−100% inhibition against weeds at the rate of 2.8 kg/ha, these compounds had unacceptable phytotoxicity to the crops at rates that gave good weed control.[3,4] Furthermore, some PDHc E1 inhibitors also exhibited adverse mammalian toxicity.[11−13]

We have attempted to design novel PDHc E1 inhibitors with high herbicidal potency for several years. Diethyl α-(substituted-phenoxyacetoxy)alkylphosphonates were identified as scaffolds for lead structures.[3] High inhibitory potencies against PDHc and herbicidal activities could be achieved by introducing a small methoxy (MeO) group as R^1 and R^2 in the phosphonate moiety. *O,O′*-Dimethyl α-(2,4-dichlorophenoxyacetoxy)ethylphosphonate (clacyfos, HW02) was found to be an effective inhibitor of PDHc E1 from plants and showed potential utility as a herbicide.[14] These results encouraged us to further explore PDHc E1 inhibitors possessing effective herbicidal activities.

To find new inhibitors of PDHc E1, the synthesis strategy was focused on modifications of the *O,O′*-dimethyl α-(substituted-phenoxyacetoxy)alkylphosphonate (**I**) scaffold. As

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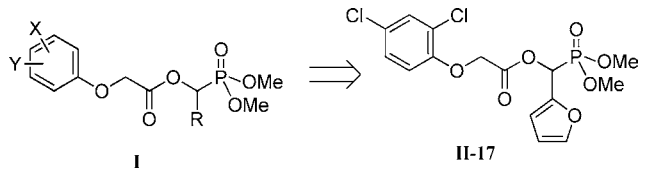
many heterocyclic compounds have remarkable biological properties, fural and thienyl groups as R were introduced to **I** to form title compounds **II** (Scheme 1). It is very interesting to examine their herbicidal activity and their inhibition against plant PDHc.

Scheme 1. Chemical Modification of Lead Structure I



I **II-17**

Here, we report the synthesis, herbicidal activities, and inhibitions against plant PDHc of a series of α-(substituted-phenoxyacetoxy)-α-heterocyclylmethylphosphonate derivatives. Compound **II-17** (**HWS**) and some analogues showed potential utility as a herbicide against broadleaf weeds.

MATERIALS AND METHODS

Synthesis Procedures. All solvents used were absolutely anhydrous. Pyridine and sodium iodide were dried in an oven prior to the reaction. Column chromatography was carried out with Merck silica gel (230−400 mesh). Thin layer chromatography (TLC) was performed on silica gel GF-254. ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer at 300 MHz, Mercury-plus400 at 400 MHz or on a Varian NMR System 600 at 600 MHz, using tetramethylsilane as an internal standard. Chemical shifts (δ) were given in (DMSO) parts per million, coupling constants (J) were given in hertz, and multiplicities were indicated by s (single), d (double), t (triplet), q (quartet), qn (quintet), and m (multiplet). IR spectra were recorded on a Perkin-Elmer-983 spectrometer. Peaks were reported in cm^{-1} with indicated relative intensities: s (strong, 67−100%), m (medium, 34−66%), and w (weak, 0−33%). MS were measured on a Finnigan TRACE spectrometer and API2000LC/MS. Elemental analysis was performed on a Vario EL III element analyzer. Melting points were measured on an Electrothermal melting-point apparatus and were uncorrected.

The procedures for the preparation of compounds **II-1−15**, **II-20−33**, and **II-37** are given below. Detailed synthetic methods for other compounds have been reported elsewhere.[14−17]

*General Procedure for the Preparation of O,O′-Dimethyl α-(Substituted-phenoxyacetoxy)-α-heterocyclylmethylphosphonates **II-1−15**, **II-21**, **II-23−26**, **II-28**, **II-30−31**, **II-33**, and **II-37**.* A solution of substituted phenoxyacetyl chlorides **M-2** (0.022 mol) in trichloromethane (10 mL) was added to a stirred mixture of *O,O′*-dimethyl α-hydroxy-α-heterocyclylmethylphosphonates **M-1** (0.02 mol) and pyridine (0.022 mol) in trichloromethane (25 mL) at 10−25 °C. The resultant mixture was stirred for 3−5 h at ambient temperature and then for 1−3 h at 40−45 °C. The trichloromethane layer was washed with 0.1 M HCl, saturated sodium hydrogen carbonate solution, and brine, dried, and concentrated. The residue was purified through a silica gel column eluted with petroleum ether/acetone (2:1, v/v) to give the corresponding pure title compounds **II-1−15**, **II-21**, **II-23−26**, **II-28**, **II-30**, **I-31**, **II-33**, and **II-37**.

*O,O′-Dimethyl α-(phenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-1**):* white solid; yield, 80.8%; mp, 69.9−70.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73−3.84 (dd, 6H, J = 11.2 Hz, 2 × OCH_3), 4.72 (d, 1H^a, J = 16.4 Hz, OCH_2CO), 4.74 (d, 1H^b, J = 16.4 Hz, OCH_2CO), 6.27 (d, 1H, J = 13.2 Hz, OCHP), 6.40−7.48 (m, 8H, C_6H_5 + C_4H_3O). Anal. Calcd for $C_{15}H_{17}O_7P$: C, 52.95; H 5.04. Found: C, 52.69; H, 4.75.

*O,O′-Dimethyl α-(3-methylphenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-2**):* white solid; yield, 82.3%; mp, 51.9−52.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 3.74−3.84 (dd, 6H, J = 11.2 Hz, 2 × OCH_3), 4.70 (d, 1H^a, J = 16.4 Hz, OCH_2CO), 4.74 (d, 1H^b, J = 16.4 Hz, OCH_2CO), 6.41 (d, 1H, J = 13.2 Hz, OCHP), 6.63−7.49 (m, 7H, C_6H_4 + C_4H_3O). Anal. Calcd for $C_{16}H_{19}O_7P$: C, 54.24; H 5.41. Found: C, 54.66; H, 5.09.

*O,O′-Dimethyl α-(4-methylphenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-3**):* white solid; yield, 85.2%; mp, 55.8−56.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 3.73−3.84 (dd, 6H, J = 11.2 Hz, 2 × OCH_3), 4.63 (d, 1H^a, J = 16.4 Hz, OCH_2CO), 4.67 (d, 1H^b, J = 16.4 Hz, OCH_2CO), 6.41 (d, 1H, J = 13.2 Hz, OCHP), 6.63−7.47 (m, 7H, C_6H_4 + C_4H_3O). Anal. Calcd for $C_{16}H_{19}O_7P$: C, 54.24; H 5.41. Found: C, 54.37; H, 5.47.

*O,O′-Dimethyl α-(2.3-dimethylphenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-4**):* white solid; yield, 85.2%; mp, 57.3−57.8 °C; IR (KBr, cm^{-1}) ν 3108, 1770, 1305, 1263, 1180, 1125, 1027, 966, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.26 (s, 3H, 2 × CH_3), 3.73−3.83 (dd, 6H, J = 11.2 Hz, 2 × OCH_3), 4.71 (d, 1H^a, J = 16.4 Hz, OCH_2CO), 4.72 (d, 1H^b, J = 16.4 Hz, OCH_2CO), 6.40 (d, 1H, J = 13.2 Hz, OCHP), 6.42−7.48 (m, 6H, C_6H_3 + C_4H_3O). Anal. Calcd for $C_{17}H_{21}O_7P$: C, 55.44; H, 5.75. Found: C, 55.46; H, 5.34.

*O,O′-Dimethyl α-(4-chloro-3-methylphenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-5**):* yellow solid; yield, 69%; mp, 54.7−55.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H, CH_3), 3.74−3.83 (m, 6H, 2 × OCH_3), 4.68 (d, 2H, J = 9.6 Hz, OCH_2CO), 6.38 (d, 1H, J = 15.6 Hz, OCHP), 6.41−7.47 (m, 6H, C_6H_3 + C_4H_3O); EI-MS m/z (%) 388 (M$^+$, 5), 279 (10), 229 (21), 213 (12), 161 (23), 159 (75), 129 (15), 120 (13), 119 (57), 109 (13), 105 (13), 95 (13), 93 (100);. Anal. Calcd for $C_{16}H_{18}ClO_7P$: C, 49.43; H, 4.67. Found: C, 49.62; H, 4.41.

*O,O′-Dimethyl α-(4-bromophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-6**):* yellow solid; yield, 68%; mp, 53.5−54.7 °C; IR (KBr, cm^{-1}) ν 3081, 2912, 1959, 1736, 1581, 1489, 1430, 1283, 1175, 1064, 930, 755; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74−3.86 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.64 (s, 2H, OCH_2CO), 6.39 (d, 1H, J = 13.2 Hz, OCHP), 6.50−7.44 (m, 7H, C_6H_4 + C_4H_3O); EI-MS m/z (%) 417 (M$^+$, 2), 232 (11), 230 (12), 206 (14), 198 (11), 196 (11), 174 (23), 172 (23), 127 (12), 119 (12), 111 (10), 110 (98), 109 (23), 97 (100), 96 (57), 95 (93), 94 (11), 93 (20), 81 (11), 80 (66), 79 (49). Anal. Calcd for $C_{15}H_{16}BrO_7P$: C, 42.98; H, 3.85. Found: C, 42.76; H, 3.57.

*O,O′-Dimethyl α-(2-chlorophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-7**):* yellow solid; yield, 66%; mp, 51.5−52.2 °C; IR (KBr, cm^{-1}) ν 2960, 2855, 1741, 1589, 1485, 1449, 1236, 1170, 1041, 931, 755; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74−3.83 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.79 (d, 2H, J = 8.4 Hz, OCH_2CO), 6.41 (d, 1H, J = 15.2 Hz, OCHP), 6.41−7.47 (m, 7H, C_6H_4 + C_4H_3O); EI-MS m/z (%) 374 (M$^+$, 2), 205 (10), 189 (11), 188 (27), 186 (74), 151 (38), 150 (15), 143 (25), 141 (76), 130 (32), 129 (11), 128 (100), 127 (18), 111 (63), 99 (32), 77 (42). Anal. Calcd for $C_{15}H_{16}ClO_7P$: C, 48.08; H, 4.30. Found: C, 47.76; H, 4.63.

*O,O′-Dimethyl α-(4-cyanophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-8**):* yellow solid; yield, 64%; mp, 57.4−58.9 °C; IR (KBr, cm^{-1}) ν 3181, 2961, 1717, 1587, 1512, 1450, 1287, 1170, 1041, 941, 760; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74−3.83 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.77 (s, 2H, OCH_2CO), 6.37 (d, 1H, J = 15.0 Hz, OCHP), 6.43−7.59 (m, 7H, C_6H_4 + C_4H_3O); EI-MS m/z (%) 365 (M$^+$+1, 5), 200 (17), 198 (48), 196 (53), 177 (10), 167 (9), 149 (12), 146 (54), 134 (11), 133 (13), 132 (37), 119 (71), 110 (61), 109 (31), 102 (15), 101 (15), 99 (13), 97 (35), 96 (30), 95 (28), 86 (100), 64 (79). Anal. Calcd for $C_{16}H_{16}NO_7P$: C, 52.61; H, 4.42. Found: C, 52.54; H, 4.53.

*O,O′-Dimethyl α-(3-trifluoromethylphenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-9**):* yellow solid; yield, 68%; mp, 78−79 °C; IR (KBr, cm^{-1}) ν 3132, 2960, 2852, 1766, 1594, 1494, 1456, 1251, 1173, 1033, 932, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73−3.82 (dd, 6H, J = 10.1 Hz, 2 × OCH_3), 4.75 (d, 1H^a, J = 16.4, OCH_2CO), 4.78 (d, 1H^b, J = 16.4, OCH_2CO), 6.39 (d, 1H, J = 11.0 Hz, OCHP), 6.42−7.47 (m, 7H, C_6H_4 + C_4H_3O); EI-MS m/z (%) 408 (M$^+$, 58.76), 220 (41.56), 205 (80.88), 203 (16.18), 189 (87.31), 175 (100), 162 (37.61), 145 (82.39), 133 (10.65), 109 (68.68), 94 (28.33), 93 (97.13), 75 (17.91), 63 (23.73), 44 (18.02). Anal. Calcd for $C_{16}H_{16}F_3O_7P$: C, 47.07; H, 3.95. Found: C, 46.75; H, 3.54.

*O,O′-Dimethyl α-(4-trifluoromethylphenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-10**):* yellow oil; yield, 67%; n_D^{20} 1.5182; IR (KBr, cm^{-1}) ν 3029, 2962, 2854, 1732, 1594, 1494, 1456, 1284, 1124, 1065, 928, 743; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74−3.80 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.79 (d, $1H^a$, J = 16.4, OCH_2CO), 4.82 (d, $1H^b$, J = 16.4, OCH_2CO), 6.38 (d, 1H, J = 13.6 Hz, OCHP), 6.84−7.28 (m, 3H, C_4H_3O), 7.43−8.64 (m, 4H, C_6H_4); EI-MS m/z (%) 408 (M^+, 32.26), 220 (31.76), 205 (60.18), 203 (11.11), 189 (89.91), 175 (100), 162 (47.31), 145 (52.49), 133 (13.62), 109 (64.28), 94 (48.13), 93 (93.12), 75 (13.31), 63 (25.74), 44 (13.62). Anal. Calcd for $C_{16}H_{16}F_3O_7P$: C, 47.07; H, 3.95. Found: C, 47.58; H, 3.54.

*O,O′-Dimethyl α-(2-fluorophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-11**):* light yellow oil; yield, 66%; mp, 56−58 °C; IR (KBr, cm^{-1}) ν 3124, 2931, 2857, 1765, 1613, 1510, 1435, 1263, 1181, 1029, 933, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72−3.82 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.76 (d, $1H^a$, J = 16.5 Hz, OCH_2CO), 4.78 (d, $1H^b$, J = 16.5 Hz, OCH_2CO), 6.38 (d, 1H, J = 14.7 Hz, OCHP), 6.61−6.94 (m, 3H, C_4H_3O), 6.95−7.45 (m, 4H, C_6H_4); EI-MS m/z (%) 358 (M^+, 25.35), 205 (66.71), 189 (52.99), 170 (56.31), 125 (100), 112 (67.01), 109 (32.14), 95 (81.46), 93 (83.55), 75 (20.13), 63 (10.65), 44 (23.52). Anal. Calcd for $C_{15}H_{16}FO_7P$: C, 50.29; H, 4.50. Found: C, 50.67; H, 4.38.

*O,O′-Dimethyl α-(2,4-difluorophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-12**):* yellow solid; yield, 70%; mp, 52.2−53.7 °C; IR (KBr, cm^{-1}) ν 3032, 2916, 2854, 1768, 1589, 1564, 1480, 1257, 1179, 1028, 940, 755; ^1H NMR (600 MHz, $CDCl_3$) δ 3.74−3.86 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.67 (s, 2H, OCH_2CO), 6.39 (d, 1H, J = 15.2 Hz, OCHP), 6.50−7.43 (m, 3H, C_4H_3O), 6.87−6.96 (m, 4H, C_6H_4); EI-MS m/z (%) 376 (M^+, 2), 258 (25), 214 (34), 213 (25), 157 (11), 155 (36), 141 (12), 127 (10), 125 (25), 120 (13), 119 (34), 105 (17), 93 (100), 91 (25). Anal. Calcd for $C_{15}H_{15}F_2O_7P$: C, 47.88; H, 4.02. Found: C, 47.69; H, 4.33.

*O,O′-Dimethyl α-(4-chloro-2-fluorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-13**):* yellow oil; yield, 70%; n_D^{20} 1.4387; IR (KBr, cm^{-1}) ν 2960, 2856, 1747, 1592, 1502, 1441, 1272, 1197, 1047, 931, 763; ^1H NMR (600 MHz, $CDCl_3$) δ 3.73−3.86 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.70 (s, 2H, OCH_2CO), 5.95 (d, 1H, J = 13.2 Hz, OCHP), 6.39−6.90 (m, 3H, C_4H_3O), 7.03−7.44 (m, 3H, C_6H_4); EI-MS m/z (%) 392 (M^+, 7), 206 (11), 205 (45), 204 (14), 189 (68), 161 (18), 159 (59), 148 (13), 146 (36), 145 (11), 131 (13), 129 (24), 127 (16), 117 (13), 111 (12), 110 (23), 109 (37), 97 (21), 93 (100). Anal. Calcd for $C_{15}H_{15}ClFO_7P$: C, 45.88; H, 3.85. Found: C, 46.03; H, 3.56.

*O,O′-Dimethyl α-(2-chloro-4-fluorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-14**):* yellow solid; yield, 70%; mp 62.0−63.5 °C; IR (KBr, cm^{-1}) ν 3123, 2960, 2846, 1721, 1589, 1495, 1424, 1246, 1192, 1044, 929, 751; ^1H NMR (600 MHz, $CDCl_3$) δ 3.71−3.80 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.77 (d, 2H, J = 7.8 Hz, OCH_2CO), 6.37 (d, 1H, J = 15.0 Hz, OCHP), 6.41−6.76 (m, 3H, C_4H_3O), 7.14−7.47 (m, 3H, C_6H_4); EI-MS m/z (%) 392 (M^+, 6), 204 (10), 189 (4), 159 (11), 146 (19), 129 (19), 109 (100), 95 (55), 93 (34), 79 (77), 63 (24), 44 (8); $[\alpha]_D^{20}$ = −48.3° (c 0.57, $CHCl_3$). Anal. Calcd for $C_{15}H_{15}ClFO_7P$: C, 45.88; H, 3.85. Found: C, 45.73; H, 3.69.

*O,O′-Dimethyl α-(2,4,5-trichlorophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (**II-15**):* yellow solid; yield, 69%; mp 57.3−58.7 °C; IR (KBr, cm^{-1}) ν 3099, 2959, 2856, 1745, 1586, 1479, 1438, 1285, 1139, 1044, 938, 766; ^1H NMR (600 MHz, $CDCl_3$) δ 3.74−3.86 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.71 (s, 2H, OCH_2CO), 6.39 (d, 1H, J = 15.6 Hz, OCHP), 6.51−7.49 (m, 5H, C_6H_2 + C_4H_3O); EI-MS m/z (%) 442 (M^+ + 1, 3), 256 (12), 254 (13), 213 (8), 210 (24), 209 (25), 206 (9), 205 (59), 200 (11), 198 (34), 196 (38), 190 (10), 189 (69), 180 (17), 179 (15), 169 (12), 167 (13), 147 (10), 146 (14), 145 (19), 143 (14), 127 (18), 111 (12), 110 (33), 109 (45), 97 (40), 96 (31), 95 (53), 93 (100), 81 (32), 79 (26). Anal. Calcd for $C_{15}H_{14}Cl_3O_7P$: C, 40.61; H, 3.18. Found: C, 40.78; H, 3.48.

*O,O′-Dimethyl α-(2,3-dimethylphenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-21**):* yellow solid; yield, 71%; mp 54.6−55.9 °C; IR (KBr, cm^{-1}) ν 3054, 2956, 2854, 1737, 1583, 1470, 1423, 1245, 1127, 1047, 920, 773; ^1H NMR (600 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.73−3.89 (dd, 6H, J = 10.2 Hz, 2 × OCH_3), 4.72 (d, 2H, J = 12.0 Hz, OCH_2CO), 6.55 (d, 1H, J = 15.6 Hz, OCHP), 6.80−7.03 (m, 3H, C_4H_3S), 7.29−7.38 (m, 3H, C_6H_3); EI-MS m/z (%) 384 (M^+, 3), 222 (14), 205 (7), 198 (8), 180 (13), 177 (18), 133 (11), 132 (26), 131 (20), 121 (21), 119 (31), 113 (75), 112 (79), 111 (100), 110 (79), 109 (14), 79 (55). Anal. Calcd for $C_{17}H_{21}O_6PS$: C, 53.12; H, 5.51. Found: C, 52.93; H, 5.57.

*O,O′-Dimethyl α-(4-bromophenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-23**):* yellow solid; yield, 70%; mp 52.5−53.9 °C; IR (KBr, cm^{-1}) ν 3119, 2957, 2853, 1774, 1580, 1488, 1447, 1239, 1168, 1026, 948, 747; ^1H NMR (600 MHz, $CDCl_3$) δ 3.70−3.79 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.71 (s, 2H, OCH_2CO), 6.54 (d, 1H, J = 13.2 Hz, OCHP), 6.75−7.03 (m, 3H, C_4H_3S), 7.28−7.40 (m, 4H, C_6H_4); EI-MS m/z (%) 434 (M^+, 3), 221 (15), 219 (10), 205 (70), 187 (22), 185 (23), 177 (14), 157 (16), 155 (18), 132 (22), 119 (25), 112 (17), 111 (38), 110 (11), 109 (13), 102 (15), 97 (27), 93 (100), 77 (15). Anal. Calcd for $C_{15}H_{16}BrO_6PS$: C, 44.07; H, 3.70. Found: C, 44.56; H, 3.57.

*O,O′-Dimethyl α-(2-chlorophenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-24**):* yellow solid; yield, 66%; mp 54.2−55.8 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 3.75−3.82 (dd, 6H, J = 10.2 Hz, 2 × OCH_3), 4.73 (s, 2H, OCH_2CO), 6.88 (d, 1H, J = 8.4 Hz, OCHP), 6.97−7.17 (m, 3H, C_4H_3S), 7.21−7.40 (m, 4H, C_6H_4); EI-MS m/z (%) 390 (M^+, 5), 279 (9), 229 (18), 213 (13), 161 (32), 159 (68), 129 (12), 120 (12), 119 (62), 109 (13), 105 (16), 95 (15), 93 (100), 91 (21). Anal. Calcd for $C_{15}H_{16}ClO_6PS$: C, 47.47; H, 4.48. Found: C, 47.22; H, 4.21.

*O,O′-Dimethyl α-(4-chlorophenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-25**):* yellow solid; yield, 66%; mp 48.1−49.9 °C; IR (KBr, cm^{-1}) ν 3080, 2929, 2852, 1766, 1500, 1486, 1431, 1243, 1174, 1024, 923, 721; ^1H NMR (600 MHz, $CDCl_3$) δ 3.70−3.80 (dd, 6H, J = 10.2 Hz, 2 × OCH_3), 4.77 (s, 2H, OCH_2CO), 6.54 (d, 1H, J = 13.8 Hz, OCHP), 6.80−7.04 (m, 3H, C_4H_3S), 7.19−7.40 (m, 4H, C_6H_4); EI-MS m/z (%) 390 (M^+, 30.65), 220 (31.33), 205 (73.53), 186 (8.94), 141 (54.45), 128 (19.52), 111 (62.08), 109 (63.15), 94 (18.13), 93 (100), 75 (37.76), 63 (47.41), 44 (13.50). Anal. Calcd for $C_{15}H_{16}ClO_6PS$: C, 47.47; H, 4.48. Found: C, 47.70; H, 4.53.

*O,O′-Dimethyl α-(4-cyanophenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-26**):* yellow solid; yield, 74%; mp 52.4−53.9 °C; IR (KBr, cm^{-1}) ν 3109, 2957, 2850, 1742, 1605, 1509, 1453, 1247, 1041, 914, 732; ^1H NMR (600 MHz, $CDCl_3$) δ 3.74−3.82 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.70 (s, 2H, OCH_2CO), 6.90 (d, 1H, J = 8.4 Hz, OCHP), 6.97−7.02 (m, 3H, C_4H_3S), 7.19−7.61 (m, 4H, C_6H_4); EI-MS m/z (%) 381 (M^+, 11), 222 (8), 177 (66), 133 (13), 132 (100), 119 (89), 113 (43), 112 (34), 111 (51), 110 (46), 104 (24), 102 (68), 80 (27), 79 (34). Anal. Calcd for $C_{16}H_{16}NO_6PS$: C, 50.39; H, 4.23. Found: C, 50.62; H, 4.49.

*O,O′-Dimethyl α-(4-trifluoromethylphenoxyacetoxy)-α-(thien-2-yl)methylphosphonate (**II-28**):* yellow solid; yield, 76%; mp 54−56 °C; IR (KBr, cm^{-1}) ν 3082, 2959, 2856, 1771, 1616, 1519, 1446, 1264, 1167, 1035, 904, 712; ^1H NMR (300 MHz, $CDCl_3$) δ 3.69−3.79 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.75 (d, $1H^a$, J = 16.5 Hz, OCH_2CO), 4.79 (d, $1H^b$, J = 16.5 Hz, OCH_2CO), 6.55 (d, 1H, J = 13.6 Hz, OCHP), 6.92−7.03 (m, 3H, C_4H_3S), 7.27−7.55 (m, 4H, C_6H_4); EI-MS m/z (%) 424 (M^+, 15.63), 221 (11.84), 205 (82.46), 175 (73.08), 162 (3.72), 145 (90.83), 133 (5.58), 109 (76.50), 94 (3.69), 93 (100), 79 (29.55), 75 (8.88), 63 (16.48), 45 (17.77). Anal. Calcd for $C_{16}H_{16}F_3O_6PS$: C, 45.29; H, 3.80. Found: C, 44.93; H, 3.64.

*O,O′-Dimethyl α-(2,4-difluorophenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-30**):* yellow solid; yield, 67%; mp 52.5−53.9 °C; IR (KBr, cm^{-1}) ν 3083, 2956, 2850, 1763, 1606, 1510, 1430, 1258, 1178, 1025, 930, 753; ^1H NMR (600 MHz, $CDCl_3$) δ 3.71−3.80 (dd, 6H, J = 10.8 Hz, 2 × OCH_3), 4.75 (d, 2H, J = 17.4 Hz, OCH_2CO), 6.53 (d, 1H, J = 13.8 Hz, OCHP), 6.75−6.90 (m, 3H, C_4H_3S), 6.91−7.30 (m, 3H, C_6H_3); EI-MS m/z (%) 392 (M^+, 6), 222 (11), 186 (26), 151 (13), 143 (10), 141 (27), 130 (32), 128 (38), 113 (83), 112 (61), 111 (100), 110 (66), 109 (10), 80 (43), 77 (42). Anal. Calcd for $C_{15}H_{15}F_2O_6PS$: C, 45.92; H, 3.85. Found: C, 45.69; H, 3.73.

*O,O′-Dimethyl α-(4-chloro-2-fluorophenoxyacetoxy)-α-(thien-2-yl)methylphosphonate (**II-31**):* yellow solid; yield, 67%; mp 49.5−50.7 °C; IR (KBr, cm^{-1}) ν 3087, 2959, 2856, 1745, 1592, 1502, 1438, 1270, 1138, 1044, 930, 765; ^1H NMR (600 MHz, $CDCl_3$) δ 3.71−3.80

(dd, 6H, J = 10.2 Hz, 2 × OCH_3), 4.78 (d, 2H, J = 13.2 Hz, OCH_2CO), 6.53 (d, 1H, J = 13.2 Hz, OCHP), 6.81−6.88 (m, 3H, C_4H_3S), 7.14−7.39 (m, 3H, C_6H_3); EI-MS m/z (%) 408 (M^+ + 1, 7), 206 (11), 205 (45), 204 (14), 189 (68), 161 (18), 159 (59), 148 (13), 146 (36), 145 (11), 131 (13), 129 (24), 127 (16), 117 (13), 111 (12), 110 (23), 109 (37), 97 (21), 93 (100). Anal. Calcd for $C_{15}H_{15}ClFO_6PS$: C, 44.18; H, 3.46. Found: C, 44.56; H, 3.57.

*O,O′-Dimethyl α-(2,4,5-trichlorophenoxyacetoxy)-α-(thien-2-yl)-methylphosphonate (**II-33**):* yellow solid; yield, 69%; mp 56.1−57.6 °C; IR (KBr, cm^{-1}) ν 3101, 2956, 2854, 1744, 1586, 1479, 1431, 1231, 1138, 1042, 938, 767; ^1H NMR (600 MHz, $CDCl_3$) δ 3.75−3.83 (dd, 6H, J = 8.4 Hz, 2 × OCH_3), 4.71 (s, 2H, OCH_2CO), 6.96 (d, 1H, J = 13.6 Hz, OCHP), 7.01−7.17 (m, 3H, C_4H_3S), 7.33−7.48 (m, 2H, C_6H_2); EI-MS m/z (%) 457 (M^+ − 1, 29), 255 (27), 253 (30), 209 (16), 200 (30), 198 (88), 197 (17), 196 (100), 194 (14), 111 (92), 110 (66), 109 (28), 80 (42), 79 (37). Anal. Calcd for $C_{15}H_{14}Cl_3O_6PS$: C, 39.19; H, 3.07. Found: C, 39.22; H, 3.45.

*O,O′-Dimethyl α-(3-trifluoromethylphenoxyacetoxy)-α-(pyrid-2-yl)methylphosphonate (**II-37**):* white solid, yield, 71%, mp 79−80 °C; IR (KBr) cm^{-1} ν 3076, 2852, 1784, 1608, 1495, 1248, 1178, 1030, 1330, 754; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66−3.79 (dd, 6H, J = 11.3 Hz, 2 × OCH_3), 4.87 (s, 2H, OCH_2CO), 6.38 (d, 1H, J = 13.8 Hz, OCHP), 7.08−7.37 (m, 4H, C_6H_4), 7.29−8.63 (m, 4H, C_5H_4N); MS(EI) 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.

*Synthetic Procedure for Sodium O-Methyl α-(2,4-Dichlorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-20**).* A solution of *O,O′*-dimethyl-α-(2,4-dichlorophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate (0.02 mol) and oven-dried sodium iodide (0.02 mol) in molecular sieve (4 A) dried acetone (40 mL) was stirred and refluxed under nitrogen for 10 h. The solution was evaporated at reduced pressure. The residual solid was recrystallized from dichloromethane to afford the pure product as a white solid. The salts were isolated directly in 95% yields.

O,O′-Dimethyl α-(2,4-dichlorophenoxyacetoxy)-α-(furan-2-yl)-methylphosphonate was prepared according to the methods previously reported.[15]

*Sodium O-Methyl α-(2,4-dichlorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**I-20**):* white solid; yield 95%; mp 99−100 °C; IR (KBr) cm^{-1} ν 3104, 2958, 2852, 1742, 1646, 1601, 1485, 1216, 1078, 1053, 938, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37(d, 3H, J = 9.7 Hz, OCH_3), 4.89 (d, $1H^a$, J = 14.6 Hz, OCH_2CO), 4.94 (d, $1H^b$, J = 9.7 Hz, OCH_2CO), 5.88 (d, 1H, J = 12.6 Hz, OCHP), 6.38−7.26 (m, 3H, C_4H_3O), 7.00−7.54 (m, 3H, C_6H_3); MS (EI) m/z 416 (M^+, 0.1), 234 (6.14), 220 (19.40), 199 (61.55), 175 (2.37), 174 (35.20), 164 (100), 145 (26.05), 132 (35.61), 110 (36.97), 108 (35.91), 96 (10.49). Anal. Calcd for $C_{14}H_{12}Cl_2NaO_6P$: C, 40.31; H, 2.90. Found: C, 40.06; H, 2.96.

Herbicide Activity Assay. *Greenhouse Experiments.* According to the modified method described previously,[18,19] the herbicidal activity was evaluated in a greenhouse with 15 weed species. Tested plants were *Brassica campestris* (leaf mustard), *Abutilon theophrasti* (chingma abutilon), *Amaranthus retroflexus* (amaranth pigweed), *Amaranthus spinosus* (spiny amaranth), *Eclipta prostrata* (white eclipta), *Amaranthus ascendens* (emarginate amaranth), *Chenopodium album* (lambsquarters), *Polygonum aviculare* (common knotgrass), *Portulaca oleracea* (common purslane), *Echinochloa crusgalli* (barnyard grass), *Beta vulgaris* (sugar beet), *Pisum sativum* (pea), *Brassica campestris* (rape), *Oryza sativa* (rice), and *Zea mays* (maize).

The emulsions of purified compounds were prepared by dissolving them in 100 μL of acetone with the addition of a drop of Tween 20 and proper water. A mixture of the same amount of water, acetone, and Tween 20 was used as the control. At pre-emergence, plastic pots were packed with sandy clay loam soil. Water was added up to 3 cm in depth. In the pot, about 15−20 plant seeds were sown in the soil at a depth of 5 mm and sprayed with the test compound solution. Twenty days later, the pre-emergence herbicidal activity against each weed was visually evaluated.

At postemergence, the solution of the chemicals tested was applied to the foliage of plants grown at 2−3-leaf stage with a sprayer at the rate of 50−1200 ai g/ha with a spilling volume of 1000 L/ha.

All of the treatments were in triplicate and in a completely randomized design. The tested plants were harvested 20 days after sowing and determined for fresh weight. The postemergence herbicidal activity against each weed was evaluated. The growth inhibition percentages of roots and aerial parts were calculated in relation to the mass of the roots and aerial parts of the control, respectively.

The inhibitory effect of compounds on the growth of plants at a dose was measured as percentage change in each plant weight compared to that of the control, such as 0% (no effect or not significantly different from the control) or 100% (completely killed).

The IC_{50} values of the title compounds were determined for the toxicity of inhibition to root growth of *B. campestris* (rape) by the following method: A defined amount of tested compounds dissolved in acetone was poured on a filter paper in Petri dishes (9 cm), and 10 *B. campestris* seeds after soaking in water for 6 h were placed on the filter paper. The Petri dishes with *B. campestris* seeds were placed in a lighting incubator (LRH-250-G) at 28 °C for 3 days with 10 h of lighting and 14 h in the dark. After 3 days of treatment, the inhibition percentage was calculated in comparison with the corresponding control using the length of the taproot as an indicator. Three replications of each concentration were performed. According to the average percentage of inhibition of *B. campestris*'s root at five concentrations for each tested compound (different IC_{50} values were determined at different ranges of five concentrations), the IC_{50} values were estimated by regression analysis using the logarithm of the concentration and probit of corresponding inhibition percentage. Detailed data are in the Supporting Information.

Enzyme Assays. The activity of PDHc could be determined by a sensitive spectrophotometric assay according to refs 3 and 20−22. In this procedure, PDHc could be conveniently assayed by measuring the rate of appearance of product reduced nicotinamide adenine dinucleotide (NADH) that absorbs at 340 nm.[23,24] If the reaction is prevented by an inhibitor, there will be a corresponding decrease in absorbance compared with the control.

Preparation of *P. sativum* (Pea) Mitochondria. The preparation of pea mitochondria was carried out according to the procedure of Reid et al.[25] *P. sativum* seeds were soaked in water overnight and grown at room temperature in the dark until the shoots were 20−30 cm in height. The shoots were cut into small pieces (about 10 mm) and frozen for 1 h in a refrigerator. The shoots were then ground with a mortar and pestle in 3 times the volume of 50 mM Tris-HCl buffer (pH 7.4) containing 0.25 M glucose, 3 mM EDTA, and 0.75 mM BSA. The homogenate was filtered through several layers of cheesecloth and centrifuged at 10000*g* for 15 min. The supernatant was centrifuged at 27000*g* for 45 min. The resulting pellet was resuspended in the grinding medium and centrifuged at 27000*g* for 45 min. The surface of the pellet was washed with ice water, then resuspended in acetone or ethanol at −20 °C, centrifuged at 27000*g* for 20 min, and resuspended and centrifuged an additional three times in cold acetone. The final pellet was dried with a stream of air and stored at −20 °C.

Preparation of Enzyme Sample. The powder of mitochondria in acetone was resuspended in 25 mM Tes buffer (pH 7.4) containing 200 μM thiamin pyrophosphate (TPP), 5 mM dithiothreitol (DTT), and 2 mM $MgSO_4$ at a final concentration of 20 mg/mL and ground thoroughly with a glass homogenizer. The homogenate was centrifuged at 27000*g* for 15−20 min. The supernatant was used as an enzyme solution.

Inhibition of *P. sativum* (Pea) PDHc. Six samples of enzyme solution (0.5 mL) were taken. One of them was added to water as the control, whereas the rest were mixed with the test compounds at final concentrations of 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} g/mL, separately. The mixtures were incubated at 25 °C for 25 min. An aliquot (10 μL) of the mixture was added at various times to 1 mL of reaction mixture containing 25 mM Tes (pH 7.4), 1 mM $MgCl_2$, 1 mM cysteine, 1 mM

Scheme 2. Synthetic Routes of α-(Substituted-phenoxyacetoxy)heterocyclylmethylphosphonates (II)

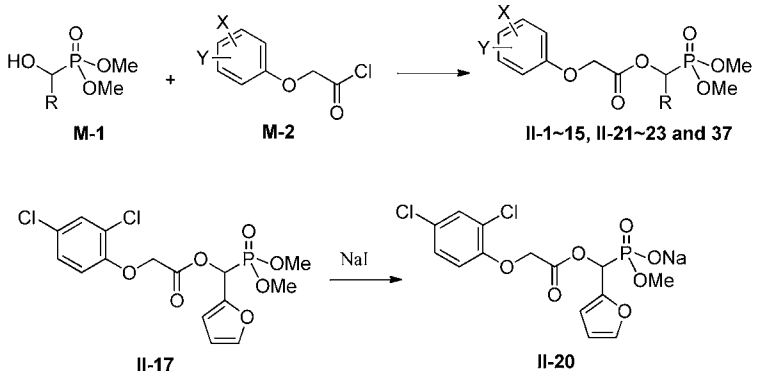
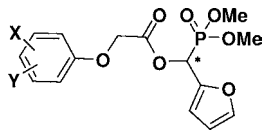


Table 1. Structures and Post-emergence Herbicidal Activities of II-1−II-19[a,b]



no.	X	Y	*Bra*[c]	*Abu*[c]	*Ama*[c]	*Ecl*[c]
II-1	H	H	28 ± 2	22 ± 5	6 ± 2	31 ± 2.5
II-2	H	3-Me	37 ± 3	39 ± 2	36 ± 2	30 ± 5
II-3	H	4-Me	36 ± 2	32 ± 1	23 ± 2	30 ± 2
II-4	2-Me	3-Me	40 ± 2	50 ± 5	50 ± 2	30 ± 3
II-5	3-Me	4-Cl	80 ± 1	80 ± 2	80 ± 1	75 ± 2
II-6	H	4-Br	75 ± 2	40 ± 5	60 ± 2	60 ± 2
II-7	H	2-Cl	40 ± 0	0	40 ± 5	30 ± 2
II-8	H	4-CN	40 ± 2	40 ± 2	50 ± 2	30 ± 5
II-9	H	3-CF_3	0	0	0	0
II-10	H	4-CF_3	0	0	0	0
II-11	H	2-F	75 ± 2	40 ± 2	60 ± 3	60 ± 2
II-12	2-F	4-F	60 ± 2	40 ± 5	50 ± 5	40 ± 5
II-13	2-F	4-Cl	75 ± 2	70 ± 3	60 ± 5	70 ± 1
II-14	2-Cl	4-F	85 ± 2	75 ± 3	90 ± 0	75 ± 0
II-15	2,4-Cl_2	5-Cl	85 ± 1	75 ± 2	75 ± 2	80 ± 1
II-16	2-Cl	3-Cl	30 ± 2	20 ± 5	25 ± 5	35 ± 5
II-17	2-Cl	4-Cl	95 ± 2	95 ± 1	95 ± 0	90 ± 0
II-18	H	4-Cl	75 ± 2	75 ± 2	70 ± 1	70 ± 1
II-19	2-Me	4-Cl	85 ± 2	80 ± 0	80 ± 0	60 ± 2
clacyfos (**HW02**)	2-Cl	4-Cl	92 ± 2	95 ± 1	91 ± 2	90 ± 2
2,4-D			92.5 ± 2.5	93 ± 0	92 ± 2	90 ± 1

[a]Synthetic methods for compounds: **II-16**, **II-17**, **II-18**, **II-19**;[15] **HW02**.[14] [b]Inhibition (%) of plant growth at a dose of 150 ai g/ha in a greenhouse for postemergence herbicidal activity. [c]*Bra*, *Brassica campestris*; *Abu*, *Abutilon theophrasti*; *Ama*, *Amaranthus retroflexus*; *Ecl*, *Eclipta prostrate*.

oxidized nicotinamide adenine dinucleotide (NAD^+), 0.13 mM CoA (Na salt form), and 4 mM TPP, followed by the addition of 0.3 mL (1 mM) of sodium pyruvate as a substrate to start the reaction in a total volume of 3 mL. After 1 min at 25 °C for temperature equilibration, the rate of formation of NADH was continuously monitored at 340 nm on a spectrophotometer. Three or five replications per concentration were performed and averaged, and the inhibitor concentration giving 50% inhibition (IC_{50}) was calculated.

Assays of rice PDHc were also carried out according to the same method as for peas.

RESULTS AND DISCUSSION

Synthesis. In general, two synthetic routes can be used to obtain *O*,*O*′-dialkyl α-(substituted-phenoxyacetoxy)-alkylphosphonates.[14] Here *O*,*O*′-dimethyl α-(substituted-phenoxyacetoxy)-α-heterocyclylmethylphosphonates (**II**) were synthesized by the condensation of *O*,*O*′-dimethyl α-hydroxy-α-heterocyclylmethylphosphonates (**M-1**) and substituted phenoxyacetyl chloride (**M-2**). Sodium *O*-methyl α-(2,4-dichlorophenoxyacetoxy)-α-(furan-2-yl)methylphosphonate (**II-20**) was synthesized by dealkylation of the dimethyl phosphonate **II-17** using NaI (Scheme 2). The reaction for the target phosphonates **II** required a temperature near room temperature in anhydrous solvents using a weak base such as pyridine, due to **II** containing a carboxylic ester group, which is sensitive to acid or base. *O*,*O*′-Dimethyl α-(fluoro- or trifluoromethyl-substituted-phenoxyacetoxy)-α-heterocyclylmethylphosphonates were obtained by condensation of **M-1** with the corresponding fluorophenoxyacetyl chloride or trifluoromethyl phenoxyacetyl chloride **M-2**, which were prepared from fluoro-substituted phenoxyacetic acids or trifluoromethyl-substituted phenoxyacetic acids. Fluoro- or trifluoromethyl-substituted phenoxyacetic acids were prepared in satisfactory

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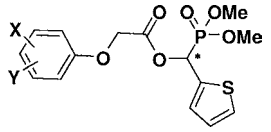
Table 2. Structures and Postemergence Herbicidal Activities of II-21−II-36[a,b]



no.	X	Y	dose (ai g/ha)	*Bra*[c]	*Abu*[c]	*Ama*[c]	*Ecl*[c]
II-21	2-Me	3-Me	150	0	0	40 ± 2	0
			450	0	0	40 ± 3	0
II-22	3-Me	4-Cl	150	0	0	50 ± 2	50 ± 2
			450	60 ± 2	60 ± 2	60 ± 1	70 ± 1
II-23	H	4-Br	150	70 ± 5	50 ± 0	50 ± 2	60 ± 2
			450	75 ± 2	70 ± 3	60 ± 2	70 ± 1
II-24	H	2-Cl	150	0	0	0	0
			450	30 ± 5	40 ± 5	50 ± 2	60 ± 1
II-25	H	4-Cl	150	70 ± 2	70 ± 2	70 ± 5	70 ± 3
			450	90 ± 0	85 ± 2	80 ± 0	85 ± 1
II-26	H	4-CN	150	30 ± 5	30 ± 2	40 ± 5	0
			450	40 ± 0	40 ± 2	40 ± 1	30 ± 2
II-27	H	3-CF_3	150	30 ± 2	20 ± 4	20 ± 2	15 ± 0
II-28	H	4-CF_3	150	20 ± 2	15 ± 0	20 ± 5	30 ± 5
II-29	H	2-F	150	0	0	15 ± 2	20 ± 0
II-30	2-F	4-F	150	70 ± 0	60 ± 3	60 ± 5	60 ± 5
			450	80 ± 2	75 ± 3	70 ± 3	60 ± 2
II-31	2-F	4-Cl	150	70 ± 2	70 ± 5	70 ± 2	70 ± 1
			450	75 ± 2	75 ± 0	75 ± 0	70 ± 2
II-32	2-Cl	4-F	150	75 ± 2	70 ± 1	90 ± 0	80 ± 0
			450	95 ± 2	90 ± 1	100 ± 0	90 ± 2
II-33	2,4-Cl_2	5-Cl	150	80 ± 2	80 ± 2	80 ± 0	80 ± 0
			450	95 ± 2	85 ± 2	90 ± 0	85 ± 0
II-34	2-Cl	3-Cl	150	0	0	40 ± 2	40 ± 3
			450	40 ± 5	40 ± 2	60 ± 1	50 ± 0
II-35	2-CH_3	4-Cl	150	80 ± 2	60 ± 2	80 ± 5	75 ± 0
			450	95 ± 2	90 ± 0	100 ± 0	85 ± 1
II-36	2-Cl	4-Cl	150	90 ± 1	90 ± 2	90 ± 2	80 ± 2
			450	100 ± 0	100 ± 0	100 ± 0	100 ± 0
2,4-D			150	92.5 ± 2	93 ± 0	92 ± 2	90 ± 1
clacyfos (**HW02**)	2-Cl	4-Cl	150	92 ± 2	95 ± 1	91 ± 2	90 ± 2
			450	100 ± 0	100 ± 0	100 ± 0	100 ± 0

[a]Synthetic methods for compounds: **II-34**, **II-35**, **II-36**;[15] **HW02**,[14] **II-22**, **II-27**, **II-29**, **II-32**.[17] [b]Inhibition (%) of the plant growth at a dose of 150 or 450 ai g/ha in greenhouse for postemergence herbicidal activity. [c]*Bra*, *Brassica campestris*; *Abu*, *Abutilon theophrasti*; *Ama*, *Amaranthus retroflexus*; *Ecl*, *Eclipta prostrate*.

yields by the reaction of fluoro- or trifluoromethyl-substituted phenols with ethyl bromoacetate.[14]

Herbicidal Activity and Inhibition on PDHc. Most **II** compounds were tested at a rate of 150 or 450 ai g/ha for postemergence herbicidal activity on *B. campestris*, *A. theophrasti*, *A. retroflexus*, *E. prostrate*, *Brassica juncea*, *P. sativum*, *E. crusgalli*, and *O. sativa*. The results are listed in Tables 1− 3.

By comparison of activities among compounds **II-1**−**II-19** and **II-21**−**II-36** in Tables 1 and 2, it could be found that substituents X and Y on the phenoxybenzene ring greatly affected the activity. Compounds **II-17** and **II-36** with 2,4-dichloro as X and Y exhibited the best herbicidal activity against

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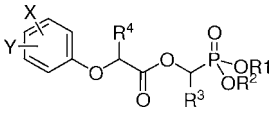
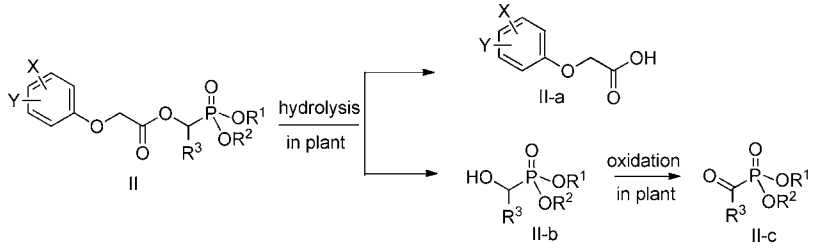
Table 3. Herbicidal Activity of Some Title Compounds I and II[a] and Their Inhibitory Activity against PDHc from Plant in Vitro



no.	R^1	R^2	R^3	X	Y	*Ech*[b]	*Ory*[b]	*Ama*[b]	*Bra*[b]	*Pis*[b]	IC_{50} (μM)
II-17 (HWS)	Me	Me	2-Furyl	2-Cl	4-Cl	25 ± 5.0	10 ± 0	96.5 ± 1.5	100 ± 0	90 ± 5.0	28.25,[c] 703.88[d]
II-37	Me	Me	pyridyl	H	3-CF_3	0	0	60 ± 5.0	77.5 ± 2.5	0	>2300[c]
II-20	Na	Me	2-Furyl	2-Cl	4-Cl	50 ± 5.0	45 ± 5.0	92.5 ± 2.5	100	98 ± 1	6.96,[c] 41.14[d]
II-20-a[e] (2,4-D)						35 ± 4.0	37.5 ± 2.5	100 ± 0	100 ± 0	97.5 ± 2.5	>4530[c]
II-20-b[e]						17.5 ± 2.5	N	N	0	0	>4670[c]
II-20-c[e]						25.0 ± 5.0	N	N	25 ± 5.0	35 ± 1	389[c]
I-1 (HW02)	Me	Me	Me	2-Cl	4-Cl	35 ± 4.0	0	100 ± 0	100 ± 0	97.5 ± 2.5	18.19,[c (15)] 867.33[d (15)]
I-2	Na	Me	H	2-Cl	4-Cl	10 ± 5.0	12 ± 2	93 ± 2.0	92. ± 1.5	52.5 ± 2.5	29.14,[d (25)]
I-3	Na	Me	Me	2-Cl	4-Cl	50 ± 0	27 ± 2	100 ± 0	98 ± 2.0	71.5 ± 3.5	0.29[d]
I-4	Na	Me	C_2H_5	2-Cl	4-Cl	30 ± 5.0	27 ± 2.5	94.5 ± 1.5	97 ± 1.0	90 ± 5.0	18.87[d]
I-5	Na	Me	n-C_3H_7	2-Cl	4-Cl	45 ± 0	22 ± 2.5	96 ± 0	97 ± 0	77.5 ± 2.5	3.26[d]

[a]Synthetic methods for compounds: **I-2**, **I-3**, **I-4**, **I-5**.[16] Inhibition (%) of the plant growth for postemergence at a dose of 450 ai g/ha in a greenhouse; N, not tested. [b]*Ech*, *Echinochloa crusgalli*; *Ory*, *Oryza sativa*; *Ama*, *Amaranthus retroflexus*; *Bra*, *Brassica juncea*; *Pis*, *Pisum sativum*. [c]IC_{50} values against PDHc from *Pisum sativum* in vitro [d]IC_{50} values against PDHc from *Oryza sativa* in vitro [e]The structures of **II-20-a**, **II-20-b**, and **II-20-c** are given in Table 4.

Scheme 3. Proposed Metabolic Pathways of α-(Substituted-phenoxyacetoxy)heterocyclylmethylphosphonates (II) in Plants



dicotyledons for postemergence at a dose of 150 ai g/ha irrespective of the difference of fural and thienyl group as R^1 moiety. Compounds with 2-Cl,4-F; 2,4,5-Cl_3; or 2-Me,4-Cl as X and Y showed modest herbicidal activities. However, compounds with other groups as X and Y or no substituent on the phenoxybenzene ring had weak herbicidal activities or were almost inactive.

Inhibitory activities for postemergence of some title compounds **I** and **II** were further examined against *E. crusgalli*, *O. sativa*, *A. retroflexus*, *B. juncea*, and *P. sativum* at a dose of 450 ai g/ha in a greenhouse. The results showed that all compounds with 2,4-dichloro as X and Y exhibited good inhibition against dicotyledons, but they were weak against monocotyledons (Table 3).

To examine structure−activity relationships, inhibitory potencies of compounds **I** and **II** against plant PDHc were also tested. The IC_{50} values of the tested compounds are listed in Table 3. The results suggested that substituents R^1, R^2, R^3, X, and Y had a great influence on the inhibitory potency. All compounds **I** and **II** with 2,4-dichloro as X and Y showed significant inhibition against plant PDHc (Table 3). Compounds **II-17** and **II-20** with 2,4-dichloro as X and Y exhibited powerful potency against *P. sativum* (pea) PDHc in vitro; however, **II-37** with 3-CF_3 on the phenoxybenzene ring was much less active against *P. sativum* PDHc.

When X and Y on **I** and **II** were chloro (2,4-Cl), the potency was greatly enhanced by modifications of R^1, R^2, and R^3 in the phosphonate moiety. When the MeO group at the phosphorus atom was replaced by NaO (X, Y, R^3, and R^4 are kept constant), the potency against PDHc was also greatly improved (Table 3). Phosphonic acid monosodium salts **II-20** (IC_{50} = 41.14 μM) and **I-3** (IC_{50} = 0.29 μM) displayed higher inhibitory potency against *O. sativa* PDHc than their corresponding phosphonates **II-17** (IC_{50} = 703.88 μM) and **I-1** (IC_{50} = 867 μM). **I-3** exhibited best inhibitory potency against *O. sativa* PDHc in vitro among the compounds listed in Table 3. However, monosodium salt **II-20** with a fural group as R^3 showed weaker activity against *O. sativa* PDHc than compounds **I-2**, **I-3**, **I-4**, and **I-5** with H or alkyl groups as R^3. The results indicate that the potency improvement requires an optimal combination of R^1, R^2, R^3, X, and Y.

Relationships of Herbicidal Activity and Inhibitory Potency against PDHc. The herbicidal activity correlated well with the inhibitory potency against PDHc. Both inhibitory potency against PDHc and herbicidal activity were highly dependent upon the structure and position of substituents X and Y in the phenoxyacetyl substructure. It was found that 2- and 4-positions in the benzene ring were the most essential sites for substitution, which greatly enhanced both inhibitory potency against PDHc and herbicidal activity. This result is in agreement with the results of molecular docking and 3D-QSAR studies on binding of the title compounds to PDH E1.[15]

Tables 1−3 show that compounds **II-17** and **II-20** with 2,4-Cl_2 as X and Y, MeO (NaO) as R^1O and R^2O, and fural as R^3 showed higher inhibitions against dicotyledons PDHc and also higher herbicidal activities against dicotyledons than the other compounds.

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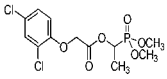
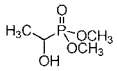
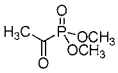
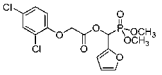
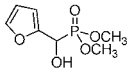
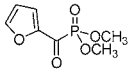
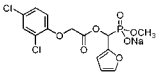
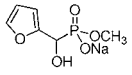
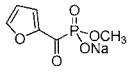
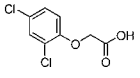
It is noteworthy that **II-17** showed higher inhibition against *P. sativum* PDHc than *O. sativa* in vitro, as well as higher inhibitory activity against *P. sativum* than *O. sativa* in vivo and weak activity against the monocot weed *E. crusgalli* by the herbicide activity assay in a greenhouse (Table 3). **II-17** has particularly better selectivity between *P. sativum* and *O. sativa* than **II-20**, **I-3**, **I-4**, and **I-5**. **II-17** can selectively inhibit the growth of dicotyledonous plants due to the selective inhibition of the PDHc.

We proposed a metabolic pathway of α-(substituted-phenoxyacetoxy)alkylphosphonates in plants when the title compounds were initially designed. **II** may be metabolized to substituted phenoxyacetic acids (**II-a**) as auxin-type herbicide and acylphosphonates (**II-c**) as inhibitors of PDHc to show herbicidal activity after hydrolysis and oxidation by some esterases and oxidases in plants (Scheme 3). **II-20**, for example, was presumably metabolized to **II-20-a** (2,4-D), **II-20-b**, and **II-20-c** (Table 4) in vivo. The herbicidal activity of **II-20** might, therefore, come from the effects of both possible metabolic products **II-20-a** and **II-20-c**. To examine this hypothesis, **II-20-a** (2,4-D), **II-20-b**, and **II-20-c** were prepared, and their inhibitory potencies against *P. sativum* PDHc in vitro were tested (Table 3). Greenhouse tests were also done for the inhibitory activity against the growth of *P. sativum* (pea), *B. juncea* (leaf mustard), *A. retroflexus* (common amaranth), *E. crusgalli* (barnyard grass), *O. sativa* (rice) (Table 3), and *B. campestris* (rape) (Table 4) in vivo.

Table 4. Inhibitory Potency against *Brassica campestris* (Rape)[a,b]

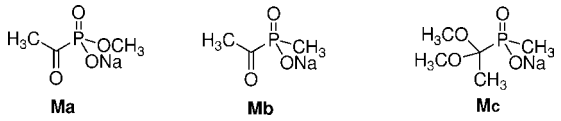
Compd.	Structure	*Brassica campestris* IC_{50}[a] (μM)	Post[b]	pre[b]
I-1 (HW-02)		0.0344	98±2	96±1
I-1-b		2404.248	30±5	36±5
I-1-c		1875.671	45±5	34±4
II-17		0.0418	92±2	94±1
II-17-b		> 4672	20±3	25±5
II-17-c		236.848	50±5	56±2
II-20		0.0396	95±1	96±2
II-20-b		> 4672	20±5	23±5
II-20-c		3245	30±2	20±3
II-a		0.0556	90±2	98±1

[a]Inhibitory activity against rape root growth. [b]Inhibition (%) on the rape growth at a dose of 450 ai g/ha in a greenhouse for postemergence and pre-emergence.

II-20-b and **II-20-c** had much lower inhibitions against *P. sativum* PDHc in vitro than **II-20** and they were inactive against *P. sativum* and other tested dicotyledonous plants in vivo (Tables 3 and 4). Although **II-20-a** (2,4-D) showed a high activity against *P. sativum* and other tested dicotyledonous plants in vivo, it was almost inactive against *P. sativum* PDHc in vitro. These results indicate that the compound **II-20** itself is responsible for the both inhibitory potency against *P. sativum* in vitro and in vivo. **II-20** is also responsible for the herbicidal activity against tested broadleaf plants in vivo. To further confirm the herbicidal effects of possible metabolic products of compounds **II**, inhibitions of compounds **I-1** and **II-17** and their possible metabolic products, such as **I-1-b**, **I-1-c**, **II-17-b**, and **II-17-c**, against a set of plants were also determined. The results in Tables 3 and 4 show that **II-17**, **II-20**, and **I-1** displayed high activities against all tested dicotyledonous plants at a dose of 450 ai g/ha in a greenhouse; however, the possible metabolic products **II-20-b**, **II-20-c**, **II-17-b**, **II-17-c**, **I-1-b**, and **I-1-c** had very weak activity against all tested dicotyledonous plants in the same assay.

Baillie et al.[3] reported that compound **Ma** was a good competitive inhibitor of PDHc from pea (IC_{50} = 70 μM) and compound **Mb** (Scheme 4) killed plants by virtue of a primary effect on PDHc E1.[3] These compounds showed postemergence herbicidal activity at the rate of 2800 ai g/ha due to their inhibition against PDHc. The most active compound, **Mc** (Scheme 4), exhibited 80−100% inhibition against weeds at the rate of 2800 ai g/ha, and it was extensively evaluated in many field trials. **Mc**, however, was not selected as a candidate for commercial development due to an unacceptable phytotoxicity to the crops at rates that gave good weed control. In the present work, both herbicidal activity and inhibition to PDHc of the compounds were greatly increased by optimizing the structure of the phosphonate molecule. Compounds **II-17**, **II-20**, and **I-1**−**I-5** exhibited higher inhibitory activity and higher post-emergence herbicidal activity than compounds **Ma** and **Mc**.

Scheme 4. Structures of Some PDHc Inhibitors



The structure of **II-17** was confirmed by X-ray diffraction analysis,[26] and was selected as a representative compound for mammal (rat) toxicity tests according to the pesticide standard procedure. **II-17** exhibited a low toxicity against rat (LD_{50}, percutaneous, >2000 mg/kg; oral, 2700−3000 mg/kg). **II-17** also has a low toxicity to bees, birds, fishes, and the silkworm. The herbicidal activity and selectivity of **II-17** at the dose of 50−1200 ai g/ha were further examined. **II-17** exhibited excellent herbicidal activity against broadleaf weeds *P. aviculare*, *A. ascendens*, *C. album* , and *A. spinosus* at doses of 100−300 ai g/ha (Table 5). The dicotyledonous crops sugar beet and pea were susceptible to **II-17** at doses of 50 and 450 ai g/ha, respectively, whereas the monocot crops maize and rice displayed high tolerance to **II-17** even at doses of 900−1200 ai g/ha. The results indicate that **II-17** is safe for maize and rice and a useful selective herbicide for broadleaf weed control in monocot crop fields. On the basis of the above preliminary

Table 5. Herbicidal Activity of II-17 (HWS) for Postemergence (Relative Inhibition of Growth Percent)[a]

dose (ai g/ha)	*P. aviculare*	*A. ascendens*	*C. album*	*A. spinosus*	*B. vulgaris*	*Z. mays*	*O. sativa*
50	70 ± 3	100 ± 0	80 ± 1	60 ± 1	80 ± 3	N	N
100	83 ± 2	100 ± 0	90 ± 0	90 ± 3	80 ± 0	N	N
200	85 ± 5	100 ± 0	100 ± 0	98 ± 2	98 ± 1	0	N
300	91 ± 2	100 ± 0	100 ± 0	98 ± 2	98 ± 1	0	0
450	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	0	0
600	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	0	0
900	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	0	0
1200	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	10 ± 2	20 ± 2

[a]Evaluation in a greenhouse test. N, not tested.

Table 6. Herbicidal Effect of 30% HWS EC against Primary Broad-Leaved Weeds in Maize Fields at Different Regions in China[a]

	control rate of weed numbers after 30 days (%)		control rate of weed weight after 30 days (%)		control rate of weed numbers after 30 days (%)		control rate of weed weight after 30 days (%)	
dose (ai g/ha)	field trial 1[b]	field trial 2[b]	field trial 1[b]	field trial 2[b]	field trial 3[c]	field trial 4[d]	field trial 3[c]	field trial 4[d]
225	84.77	96.13	85.87	99.82				
300	91.91	96.32	95.09	99.71	91.7	89.4	90.5	94.7
375	97.61	98.77	98.59	99.91	92.9	93.4	92.4	96.4
450	100.0	99.67	100.0	99.97	94.9	94.2	94.5	97.3
900	100.0	99.21	100.0	99.96	96.1	95.1	96.5	97.7

[a]Inhibitory potency (%) on the growth of weeds at different doses was measured as percentage change in weed fresh weight or weed numbers compared to that of the control after 30 days by using 30% **HWS**. EC, values are the average of four experiments. [b]The data for field trials 1 and 2 are the average values of inhibitory potency (%) against all weeds including *Portulaca oleracea, Amaranthus retroflexus, Acalypha australis,* and *Eclipta prostrate* in maize fields at Shandong in China. [c]The data for field trial 3 are the average values of inhibitory potency (%) against all weeds including *Rotala indica, Lindernia procumbens, Polygonum aviculare, Amaranthus spinosus, Chenopodium serotinum,* and *Portulaca oleracea* in maize fields at Shaoxing in China. [d]The data for field trial 4 are the average values of inhibitory potency (%) against all weeds including *Polygonum flaccidum, Chenopodium album,* and *Alternanthera philoxeroides* in maize fields at Shaoxing in China.

research, compound **II-17** (code number for development, **HWS**) as a potential herbicide was further evaluated and developed. Herbicidal effects of 30% **HWS** EC against primary broad-leaved weeds in maize fields at Shandong and Shaoxing in China are listed in Table 6. It showed good herbicidal effect against 12 weeds including *P. oleracea, A. retroflexus, A. australis, E. prostrate, R. indica, L. procumbens, P. aviculare, A. spinosus, C. serotinum, P. flaccidum, C. album, A. philoxeroides* in maize fields and *A. philoxeroides* in maize fields. Field trials in different regions of China showed that **HWS** could control a broad spectrum of broad-leaved and sedge weeds at rates of 225−375 g/ha for postemergence in maize fields.

Conclusion. The results showed that when a fural group as R^3 was introduced to *O,O′*-dimethyl *α*-(2,4-dichlorophenoxyacetoxy)methylphosphonate, the compounds showed significant herbicidal activity and effective inhibition against plant PDHc. This showed that the fural group was beneficial to herbicidal activity. *O,O′*-Dimethyl *α*-(2,4-dichlorophenoxyacetoxy)-*α*-(furan-2-yl)methylphosphonate (**II-17**) as an effective inhibitor against PDHc from *P. sativum* was found to be the most effective compound with excellent herbicidal activity against broadleaf weeds at 100−450 ai g/ha and had a good selectivity for monocotyledonous crops. There is good agreement between enzyme inhibition and herbicidal activity. The results indicated **II-17** can control a broad spectrum of broad-leaved and sedge weeds at rates of 225−375 ai g/ha for postemergence weed management with good selectivity in maize fields. The results of this study also suggest that PDHc can be a new target for new herbicide design and development.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Source of seeds used for bioassays, regression equation, and *R* values for the IC_{50} values. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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