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Synthesis and Herbicidal Activity of Diphenyl Ether Derivatives Containing Unsaturated Carboxylates

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ABSTRACT: A series of novel diphenyl ether derivatives containing unsaturated carboxylates were designed and synthesized. Their structures were identified by ^{1}H nuclear magnetic resonance and elemental analyses. The bioassays indicated that the compounds **5b** and **5c** exhibited good herbicidal activities against velvetleaf at a concentration of 30−40 g/hm^2. The relationship between structure and herbicidal activity was also discussed. Among unsaturated carboxylates group, butenoate is the most promising one. Amonst them, 4-ethoxy-4-oxobutenyl 5-(2-chloro-4-(trifluoromethyl)phenoxy)-2-nitrobenzoate **5b** was identified as the most promising candidate due to its high protoporphyrinogen IX oxidase inhibition effect (pI_{50} = 6.64) and good herbicidal activity against broadleaf weeds with selectivity to soybean and low toxicity to mammals.

KEYWORDS: Protoporphyrinogen oxidase, diphenyl ether, unsaturated carboxylate, synthesis, herbicide

INTRODUCTION

As the last common enzyme in the biosynthesis pathway leading to heme and chlorophyll synthesis, protoporphyrinogen IX oxidase (PPO) has been identified as one of the most significant targets for several chemical families of herbicides such as diphenyl ethers (DPEs) and *N*-phenyl phthalimides that have been available in the commercial market for many years.[1−7] The protoporphyrinogen oxidase enzyme catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by molecular oxygen. Inhibition of the PPO results in the accumulation of enzyme product protoporphyrin IX. In the presence of light, protoporphyrin IX generates large amounts of single oxygen, which results in peroxidation of the usaturated bonds of fatty acids found in membranes.[8] The end result of this peroxidation process is the loss of membrane integrity and leakage, pigment breakdown, and necrosis of the leaf that results in the death of plant.[9]

DPEs are the first group of commercial herbicides targeting PPO, among which nitrofen (**1a**) (Figure 1) is the first product that entered market in the early 1960s. Following the discovery of herbicidal activity of nitrofen, intense research by several companies resulted in a vast number of highly active and diverse agrochemicals.[10−15] Replacement of the aromatic 4-chloro group with the lipophilic trifluoromethyl group, as is the case with acifluorfen, resulted in a significant improvement in biological activity; 2-chloro-4-(trifluoromethyl)benzene became the dominant substitution pattern for the DPEs. Many 4-CF_3-DPEs incorporated alkoxycarbonyl, carbamoyl groups into the 3-position of phenyl ring and have been found to show high activities since the development of acifluorfen, as shown in Figure 2. Among them, fluoroflycofen-ethyl, fomesafen, and lactofen have been successfully commercialized (Figure 1). However, there are some defects in DPEs such as high use rate and low selectivity for crops.

Extensive studies of the 1-, 3-, 8-, 9-positions of the phenyl ring of DPEs revealed very specific electronic, steric, and lipophilic

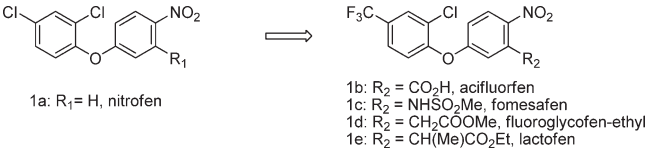

Figure 1. Evolution of DPE herbicides.

requirements for chemical groups at these positions.[11] Position 9 should be substituted by electronegative groups to increase the electrostatic interaction with Arg98.[16,17] Position 9 should also be occupied by bulky groups with hydrogen bond acceptor atoms to form van der Waals and hydrogen bond interactions with the surrounding residues. DPEs need somewhat lipophilic groups that interact with lipophilic areas of the target. Substituents at position 9 have an important effect not only on the activity but also on the crop selectivity.[11] In previous work, we added a lipophilic group unsaturated carboxylate in the acifluorfen, and compounds **2a**−**3** were synthesized (Figure 2), which showed higher herbicidal activities against broadleaf weeds than acifluorfen (**1e**).[18] Therefore, as a continuation of our research work on the development of new DPEs with low use rate and high selectivity for crops, we are very interested in the DPE derivatives containing unsaturated carboxylates, as shown in Figure 3. Herein, we report the detailed synthesis and herbicidal activities of series **3**−**5** and also the relationship between their structures and herbicidal activity.

MATERIALS AND METHODS

Synthetic Procedures. Melting points were measured using a RY-1 melting point apparatus (TaiKe Co.) and are uncorrected. ^{1}H NMR

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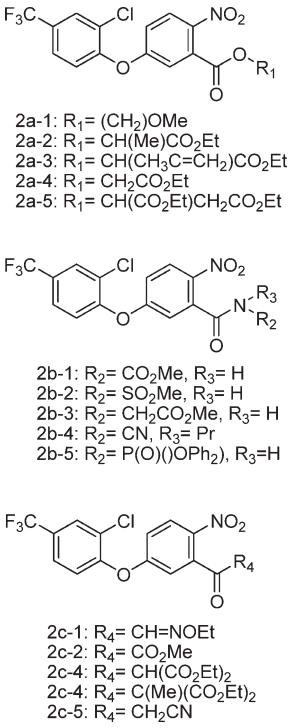


Figure 2. Structural modifications of 4-CF3-DPEs: 3-alkoxycarbonyl and 3-carbamoyl derivatives.

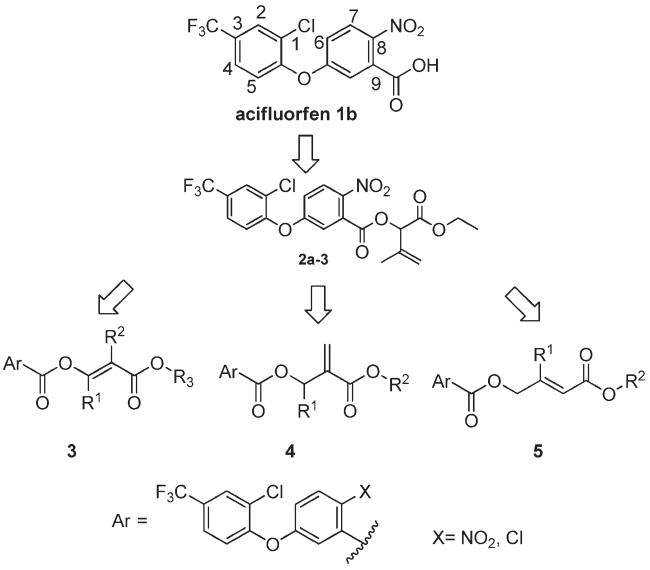


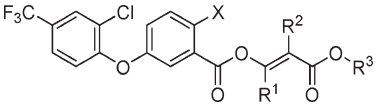
Figure 3. Design of novel DPE compounds.

spectra were recorded on a Bruker-300 (Bruker Co.) spectrometer using tetraamethylsilane as an internal reference. Chemical shift values (δ) were given in ppm. Elemental analyses were performed on a Yanaco Corder MT-3 (Yanaco Co. Ltd.) elemental analyzer. X-ray diffraction analyses were measured on a Siemens P4 diffractometer. The solvents were used directly without further purification.

General Synthetic Procedure for 3a−k. To a solution of substituted benzoic acid **6** (10 mmol) in dichloromethane (10 mL) were added (13 mmol) oxalyl dichloride and two drops of *N*,*N*-dimethylformamide in an ice−water bath. The reaction was stirred at room temperature for 2 h, and then, the solvent was removed under reduced pressure and afforded acyl chloride **7**. The acyl chloride was used directly without further purification. Then, to a stirred solution of acetoacetate **8** (10 mmol) and Et_3N (12 mmol) in dichloromethane was added a solution of acyl chloride **7** in dichloromethane at 0 °C. The reaction mixture was stirred for 2 h, and then, the solvent was removed under reduced pressure, and the residue was purified by silica gel (65 g) column chromatography (1:10 ethyl acetate/petroleum ether) to afford the title compounds. The melting points, yields, and elemental analyses of compounds **3a−k** are listed in Table 1. The ^{1}H NMR analyses of compounds **3a−k** are listed in Table 2.

General Synthetic Procedure for 4a−c. A mixture of substituted benzoic acid **6** (1 mmol), K_2CO_3 (1.2 mmol) and 2-(bromomethyl) acrylate **10** (1.1 mmol) was stirred in *N*,*N*-dimethylformamide at 40 °C. The mixture was allowed to react at this temperature until the starting material was consumed [monitored by thin-layer chromatography (TLC)]. The mixture was poured into water. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were

Table 1. Melting Points, Yields, and Elemental Analyses of Compounds 3a−k



							elemental analysis (%, calcd)		
compd	X	R^1	R^2	R^3	mp (°C)	yield (%)	C	H	N
3a	NO_2	CH_3	H	CH_3	98−99, white solid	65	49.69 (49.64)	2.83 (2.85)	3.09 (3.05)
3b	NO_2	CH_3	H	CH_3CH_2	98−100, white solid	68	50.71 (50.70)	3.22 (3.19)	2.99 (2.96)
3c	NO_2	CH_3	H	$CH_3OCH_2CH_2$	yellow oil	66	49.08 (49.04)	3.13 (3.09)	2.87 (2.86)
3d	NO_2	CH_3	H	$(CH_3)_3C$	yellow oil	63	52.69 (52.65)	3.82 (3.88)	2.83 (2.79)
3e	NO_2	CH_3	H	CH_2═CH−CH_2	yellow oil	66	51.92 (51.92)	3.11 (3.13)	2.88 (2.89)
3f	NO_2	CH_3	CH_3	CH_3CH_2	79−81, white solid	70	51.71 (51.75)	3.51 (3.50)	2.87 (2.92)
3g	NO_2	CF_3	H	CH_3CH_2	111−112, white solid	69	45.50 (45.52)	2.29 (2.33)	2.65 (2.66)
3h	NO_2	C_2H_5	H	CH_3	yellow oil	50	50.71 (50.70)	3.17 (3.19)	3.01 (2.96)
3i	NO_2	n-C_3H_7	H	CH_3CH_2	yellow oil	51	52.65 (52.68)	3.82 (3.83)	2.79 (2.75)
3j	Cl	CH_3	H	CH_3CH_2	yellow oil	63	51.87 (51.86)	3.29 (3.26)	
3k	Cl	CH_3	CH_3	CH_3CH_2	yellow oil	60	52.90 (52.85)	3.63 (3.59)	

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Table 2. ^{1}H NMR of Compounds 3a−k

compd	δ (ppm)
3a	2.49 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.87 (s, H, CH), 7.09 (dd, J = 2.4 and 6.3 Hz, 1H, Ar−H), 7.19 (d, J = 2.4 Hz, 1H, Ar−H), 7.28 (d, J = 8.7 Hz, 1H, Ar−H), 7.64 (dd, J = 2.1 and 6.6 Hz, 1H, Ar−H), 7.83 (d, J = 1.8 Hz, 1H, Ar−H), 8.11 (d, J = 8.7 Hz, 1H, Ar−H)
3b	1.29 (t, J = 7.2 Hz, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.20 (q, J = 7.2 Hz, 2H, OCH_2), 5.86 (s, 1H, CH), 7.10 (dd, J = 2.7 and 6.6 Hz, 1H, Ar−H), 7.19 (d, J = 2.4 Hz, 1H, Ar−H), 7.29 (d, J = 8.7 Hz, 1H, Ar−H), 7.64 (dd, J = 2.1 and 8.7 Hz, 1H, Ar−H), 7.83 (d, J = 2.4 Hz, 1H, Ar−H), 8.12 (d, J = 8.7 Hz, 1H, Ar−H)
3c	2.49 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 3.62 (t, J = 7.5 Hz, Hz, 2H, CH_2), 4.30 (t, J = 7.5 Hz, 2H, CH_2), 5.92 (s, 1H, C═CH), 7.09−7.19 (m, 2H, Ar−H), 7.28 (d, J = 8.4 Hz, 1H, Ar−H), 7.65 (d, J = 9 Hz, 1H, Ar−H), 7.84 (d, J = 1.8 Hz, 1H, Ar−H), 8.12 (d, J = 9 Hz, 1H, Ar−H)
3d	1.49 (s, 9H, CH_3), 2.41 (s, 3H, CH_3), 5.74 (s, 1H, C═CH), 7.11 (d, J = 8.7 Hz, 1H, Ar−H), 7.26 (d, J = 9 Hz, 1H, Ar−H), 7.55−7.56 (m, 2H, Ar−H), 7.57 (d, J = 8.4 Hz, 1H, Ar−H), 7.83 (d, J = 9 Hz, 1H, Ar−H)
3e	2.46 (s, 3H, CH_3), 4.64−4.67 (m, 2H, CH_2), 5.24−5.38 (m, 2H), 5.87−5.99 (m, 2H), 7.11 (dd, J = 1.5 and 6.6 Hz, 1H, Ar−H), 7.20 (d, 1H, J = 8.7 Hz, Ar−H), 7.56−7.62 (m, 2H, Ar−H), 7.78 (dd, J = 1.8 and 8.4 Hz, 1H, Ar−H), 7.86 (dd, J = 1.5 and 6.6 Hz, 1H, Ar−H)
3f	1.32 (t, J = 7.2 Hz, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.25 (q, J = 7.2 Hz 2H, CH_2), 7.11 (dd, J = 1.5 and 6.9 Hz, 1H, Ar−H), 7.21 (d, J = 6.9 Hz, 1H, Ar−H), 7.57 (d, J = 8.4 Hz, 1H, Ar−H), 7.78 (d, J = 2.1 Hz, 1H, Ar−H), 7.96 (dd, J = 2.1 Hz, 1H, Ar−H), 7.94 (d, J = 1.5 and 6.9 Hz, 1H, Ar−H)
3g	1.25 (t, J = 7.5 Hz, 3H, CH_3), 4.21 (q, J = 7.5 Hz, 2H, CH_2), 6.48 (s, 1H, CH), 7.14 (dd, J = 3 and 6.6 Hz, 1H, Ar−H), 7.21 (d, J = 8.4 Hz, 1H, Ar−H), 7.56−7.61 (m, 2H, Ar−H), 7.78 (d, J = 2.1 Hz, 1H, Ar−H), 7.97 (d, J = 8.4 Hz, 1H, Ar−H)
3h	1.14 (t, J = 6.9 Hz, 3H, CH_3), 2.92 (q, J = 6.9 Hz, 2H, CH_2), 3.74 (s, 3H, CH_3), 5.91 (s, 1H, C═CH), 7.09 (dd, J = 6.6 Hz, 1H, Ar−H), 7.22 (d, J = 2.4 Hz, 1H, Ar−H), 7.29 (d, J = 2.4 Hz, 1H, Ar−H), 7.63−7.81 (m, 2H, Ar−H), 8.11 (d, J = 8.1 Hz, 1H, Ar−H)
3i	0.98 (t, J = 7.2 Hz, 3H, CH_3), 1.27 (t, J = 7.5 Hz, 3H, CH_3), 1.59 (q, J = 7.5 Hz, 2H, CH_2), 2.88 (q, J = 7.2 Hz, 2H, CH_2), 4.20 (q, J = 7.5 Hz, 2H, CH_2), 5.84 (s, 1H, C═CH), 7.11 (d, J = 8.7 Hz, 1H, Ar−H), 7.18 (d, J = 2.4 Hz, 1H, Ar−H), 7.56−7.62 (m, 2H, Ar−H), 7.84 (d, J = 2.4 Hz, 1H, Ar−H), 7.87 (d, J = 8.7 Hz, 1H, Ar−H)
3j	1.27 (t, J = 7.5 Hz, 3H, CH_3) 2.47 (s, 3H, CH_3), 4.19 (q, J = 7.5 Hz, 2H, CH_2), 5.83 (s, 1H), 7.04−7.09 (m, 2H, Ar−H), 7.48−7.52 (m, 3H, Ar−H), 7.77 (d, J = 8.7 Hz, 1H, Ar−H)
3k	0.87 (t, J = 7.5 Hz, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.22 (q, J = 7.5 Hz, 2H, CH_2), 7.06 (d, J = 8.7 Hz, 1H, Ar−H) ,7.74−7.52 (m, 2H, Ar−H), 7.76 (d, J = 3 Hz, 1H, Ar−H), 7.98 (d, J = 8.4 Hz, 1H, Ar−H), 8.27 (d, J = 8.7 Hz, 1H, Ar−H)

washed with a solution of saturated $NaHCO_3$ and NaCl and dried over anhydrous magnesium sulfate. Then, the solvent was removed under reduced pressure, and the residue was purified by silica gel (65 g) column chromatography (1:20 ethyl acetate/petroleum ether) to afford the title compounds. The apperance, yields, and elemental analyses of compounds **4a**−**c** are listed in Table 4. The ^{1}H NMR analyses of compounds **4a**−**c** are listed in Table 5.

General Synthetic Procedure for 4d−e. To a stirred solution of α-(hydroxymethyl)acrylate **11** (10 mmol) and Et_3N (12 mmol) in dichloromethane was added a solution of acyl chloride **7** in dichloromethane at 0 °C. The reaction mixture was stirred for 2 h, and then, the solvent was removed under reduced pressure, and the residue was purified by silica gel (65 g) column chromatography (1:10 ethyl acetate/petroleum ether) to afford the title compounds. The appearance, yields, and elemental analyses of compounds **4d**−**e** are listed in Table 4. The ^{1}H NMR analyses of compounds **4d**−**e** are listed in Table 5.

General Synthetic Procedure for 5a−h. To a stirring solution of substituted benzoic acid **6** (1 mmol) and K_2CO_3 (1.2 mmol) in *N*,*N*-dimethylformamide, 4-bromobutenates **12** (1.1 mmol) was added at room temperature. The mixture was allowed to react at 40 °C until the starting material was consumed (monitored by TLC). The mixture was poured into water. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with a solution of saturated $NaHCO_3$ and NaCl and dried over anhydrous magnesium sulfate. Then, the solvent was removed under reduced pressure, and the residue was purified by silica gel (65 g) column chromatography (1:10 ethyl acetate/petroleum ether) to afford the title compounds. The appearance, yields, and elemental analyses of compounds **5a**−**h** are listed in Table 7. The ^{1}H NMR analyses of compounds **5a**−**h** are listed in Table 8.

Biological Assay. Barnyard (*Echinochloa crusgalli*), crabgrass (*Digitaria sanguinalis*), foxtail (*Setaria glauca*), velvetleaf (*Abutilon theophrasti*), common purslane (*Portulaca oleracea*), redroot amaranth (*Amaranthus retroflexus*), dayflower (*Commelina communis*), and heartleaf cocklebur (*Xanthius strumarium*) were used for the test. The seeds were allowed to germinate and grow for 14 days. Test plants were selected for uniformity, size, and stage of development and then treated with the test compound, returned to the greenhouse, and watered. The plants not treated with the compound under evaluation were used as a control. The compound to be evaluated was dissolved in acetone and sprayed using a carrier volume equivalent to 187 L per hectare at 2000 to 30 g/hm^2. Two weeks after application of the test compounds, the state of the plants was observed. Each species was evaluated on a scale of 0−100 in which 0 equals no activity and 100 equals total control. The average control of the three plant species was calculated.

Inhibitory Activity in Vitro against PPO. The pI_{50} values against PPO of compounds **5b** and acifluorfen were assayed according to the procedure reported.[19−22]

RESULTS AND DISCUSSION

Synthesis. Compounds **6** were synthesized as described by the literature.[23,24] The 3-benzoxy acrylate derivatives of **3a**−**k** were prepared according to the Scheme 1.[25,26] Acetoacetate was reacted with acyl chloride **7** to give O-acylated products **3** and C-acylated products **9**. The solvent had a great effect on the reaction procedure. The major product was the O-acylated one in the polar aprotic solvent, such as DMF. However, the major product was C-acylated one in the less polar aprotic solvent, such as toluene. The structure of compound **3a** was further conformed by the X-ray diffraction (Figure 4). The compound **3a** exists as the *E* configuration.

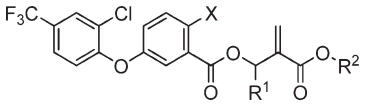
(2-Bromomethyl)-acrylate derivatives of **10** were prepared starting from diethyl malonate according to the literature's procedures.[27,28] Substituted benzoic acid was reacted with **10** giving 2-(benzoxy) alkyl acrylate **4a**−**c** (Scheme 2). The reaction was carried out in a polar aprotic solvent like DMF at 40 °C using potassium carbonate as the base. Aldehyde and acrylate were

Table 3. Herbicidal Activities of Compounds 3a−k[a]

compd	Clog *P*	dosage (g/hm^2)	BYG	CRB	VEL
3a	5.7	1000	80	95	100
		200	50	80	75
		40	15	5	25
3b	6.4	1000	60	98	100
		200	40	90	85
		40	10	80	10
3c	5.8	1000	80	75	100
		200	30	35	100
		40	20	30	98
3d	7.1	1000	45	40	75
		200	30	15	50
		40	5	5	30
3e	6.6	1000	25	35	40
		200	5	5	0
3f	6.7	1000	25	55	100
		200	15	50	35
		40	10	20	0
3g	6.5	1000	35	50	60
		200	0	0	0
3h	6.4	1000	35	15	10
		200	0	5	0
3i	7.4	1000	35	15	0
		200	5	5	0
3j	6.0	1000	95	25	100
		200	20	20	90
		40	0	10	50
3k	6.1	1000	25	30	100
		200	20	25	90
		40	0	0	5
acifluorfen	4.9	1000	90	10	100
		200	50	0	95
		40	20	0	50

[a] 0 equals no activity; 100 equals total control. BYG, barnyard (*E. crusgalli*); CRB, crabgrass (*D. sanguinalis*); and VEL, velvetleaf (*Abutilon thophrasti*). CLog *P* was predicted by ChemBioDraw 11.0.

Table 4. Appearance, Yields, and Elemental Analyses of Compounds 4a−e



						elemental analysis (%, calcd)		
compd	X	R^1	R^2	apperance	yield (%)	C	H	N
4a	Cl	H	CH_3	yellow oil	75	50.77 (50.80)	2.95 (2.92)	
4b	Cl	H	CH_2CH_3	yellow oil	81	51.87 (51.86)	3.27 (3.26)	
4c	Cl	H	$CH_2CH_2CH_3$	yellow oil	80	52.84 (52.85)	3.64 (3.59)	
4d	Cl	CH_3	CH_2CH_3	yellow oil	76	52.88 (52.85)	3.63 (3.59)	
4e	NO_2	CH_3	CH_2CH_3	yellow oil	83	51.70 (51.71)	3.56 (3.51)	2.91 (2.87)

subjected to Baylis−Hillman reaction with DABCO as the catalyst to give α-(hydroxymethyl)acrylate analogues **11**.[29] The title compounds of 2-(benzoxy) alkyl acrylate **4d**−**e** were prepared by the reaction of benzoyl chloride with Baylis−Hillman adducts **11** in dichloromethane using Et_3N as the acid acceptor (Scheme 3).

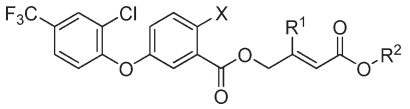
Table 5. ^{1}H NMR of Compounds 4a−e

compd	δ (ppm)
4a	3.73 (s, 3H, OCH_3), 4.81 (s, 2H, OCH_2), 5.96 (s, 1H, C═CH), 6.37 (s, 1H, C═CH), 7.02−7.09 (m, 2H, Ar−H), 7.44−7.55 (m, 3H, Ar−H), 7.66 (d, J = 8.4 Hz, 1H, Ar−H)
4b	1.31 (t, J = 7.5 Hz, 3H, CH_3), 4.24 (q, J = 7.5 Hz, 2H, OCH_2), 5.06 (s, 2H, OCH_2), 5.93 (s, 1H, C═CH), 6.44 (s, 1H, C═CH), 7.07 (dd, J = 2.4 and 9 Hz, 1H, Ar−H), 7.26 (d, J = 7.5 Hz, 1H, Ar−H), 7.17 (d, J = 3 Hz, 1H, Ar−H), 7.62 (d, J = 6.9 Hz, 1H, Ar−H), 7.83 (d, J = 2.1 Hz, 1H, Ar−H), 8.04 (d, J = 9 Hz, 1H, Ar−H)
4c	0.95−0.98 (m, 3H, CH_3), 1.66−1.73 (m, 2H, CH_2), 4.11−4.17 (m, 2H, CH_2), 5.95 (s, 1H), 6.37 (s, 1H), 7.02−7.09 (m, 2H, Ar−H), 7.48−7.52 (m, 3H, Ar−H), 7.763 (d, J = 2.1 Hz, 1H, Ar−H)
4d	1.31 (t, J = 6.9 Hz, 3H, CH_3), 1.50 (d, J = 6.3 Hz, 3H, CH_3), 4.24 (q, J = 6.9 Hz, 2H, OCH_2), 5.06 (q, J = 6.3 Hz, 1H, OH), 5.93 (s, 1H, C=CH), 6.44 (s, 1H, C═CH), 7.07 (dd, J = 2.1 and 9 Hz, 1H, Ar−H), 7.26 (d, J = 7.5 Hz, 1H, Ar−H), 7.15 (d, J = 3 Hz, 1H, Ar−H), 7.62 (d, J = 6.9, 1H, Ar−H), 7.82 (d, J = 2.1 Hz, 1H, Ar−H), 8.04 (d, J = 9 Hz,1H, Ar−H)
4e	1.31 (t, J = 6.9 Hz, 3H, CH_3), 1.53 (d, J = 6.3 Hz, 3H, CH_3), 4.24 (q, J = 6.9 Hz, 2H, OCH_2), 5.05 (q, J = 6.3 Hz, 1H, OH), 5.94 (s, 1H, C=CH), 6.36 (s, 1H, C═CH), 7.07 (dd, J = 3 and 8.7 Hz, 1H, Ar−H), 7.15 (d, J = 3 Hz, 1H, Ar−H), 7.26 (d, J = 9 Hz, 1H, Ar−H), 7.62 (d, J = 9 Hz, 1H, Ar−H), 7.81 (d, J = 1.8 Hz, 1H, Ar−H), 8.04 (d, J = 9 Hz, 1H, Ar−H)

Table 6. Herbicidal Activities of Compounds 4a−e

compd	Clog P	dosage (g/hm^2)	BYG	CRB	VEL
4a	6.1	1000	75	30	100
		200	15	25	98
		40	5	10	10
4b	6.6	1000	90	95	100
		200	20	70	100
		40	10	40	30
4c	7.1	1000	75	35	100
		200	10	30	100
		40	5	10	20
4d	6.9	1000	95	40	100
		200	20	35	75
		40	0	0	5
4e	6.3	1000	30	90	100
		200	20	70	50
		40	10	25	5
acifluorfen	4.9	1000	90	10	100
		200	50	0	95
		40	20	0	50

Table 7. Appearance, Yields, and Elemental Analyses of Compounds 5a−h



						elemental analysis (%, calcd)		
compd	X	R^1	R^2	appearance	yield (%)	C	H	N
5a	NO_2	H	CH_3	yellow oil	85	49.69 (49.64)	2.86 (2.85)	3.04 (3.05)
5b	NO_2	H	CH_2CH_3	yellow oil	80	50.71 (50.70)	3.21 (3.19)	2.93 (2.96)
5c	NO_2	H	$CH_2CH_2CH_3$	yellow oil	80	51.76 (51.71)	3.54 (3.51)	2.85 (2.87)
5d	NO_2	H	$CH(CH_3)CH_3$	yellow oil	79	51.68 (51.71)	3.56 (3.51)	2.90 (2.87)
5e	NO_2	H	$CH_2CH_2CH_2CH_3$	yellow oil	80	52.69 (52.65)	3.86 (3.82)	2.75 (2.79)
5f	NO_2	H	CH_2CH═CH_2	yellow oil	70	51.88 (51.92)	3.15 (3.11)	2.85 (2.88)
5g	NO_2	CH_3	CH_2CH_3	yellow oil	67	51.68 (51.71)	3.56 (3.51)	2.90 (2.87)
5h	Cl	H	CH_2CH_3	yellow oil	70	51.87 (51.86)	3.30 (3.26)	

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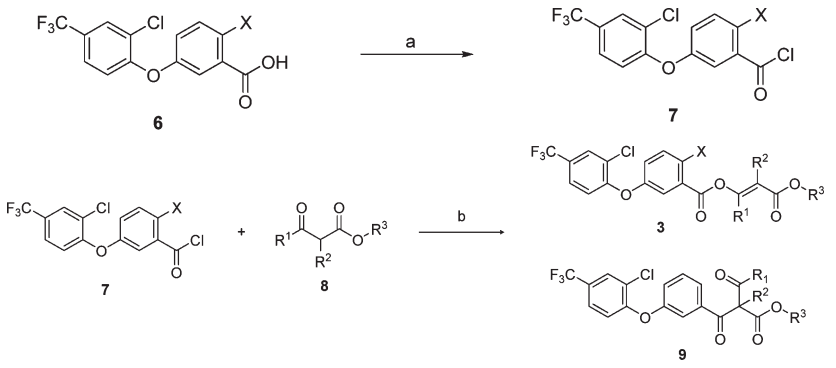
Table 8. ^{1}H NMR of Compounds 5a−h

compd	δ (ppm)
5a	3.74 (s, 3H, OCH_3), 4.98 (q, J = 4.8 Hz, 2H, OCH_2), 6.06 (d, J = 15.6 Hz, 1H, CH═), 6.94−7.02 (m, 1H, ═CH), 7.09 (dd, J = 2.7 and 8.7 Hz, 1H, Ar−H), 7.16 (d, J = 3 Hz, 1H, Ar−H), 7.27 (d, J = 8.4 Hz, 1H, Ar−H), 7.63 (dd, J = 1.8 and 8.4 Hz, 1H, Ar−H), 7.82 (d, J = 2.1 Hz, 1H, Ar−H), 8.07 (d, J = 8.7 Hz, 1H, Ar−H)
5b	1.29 (t, J = 7.5 Hz, 3H, CH_3), 4.21 (q, J = 7.5 Hz, 2H, OCH_2), 4.98 (q, J = 4.8 Hz, 2H, OCH_2), 6.06 (d, J = 15.6 Hz, 1H, CH═), 6.93−7.01 (m, 1H, ═CH), 7.09 (dd, J = 3 and 8.7 Hz, 1H, Ar−H), 7.16 (d, J = 3 Hz, 1H, Ar−H), 7.27 (d, J = 8.7 Hz, 1H, Ar−H), 7.63 (d, J = 8.4 Hz, 1H, Ar−H), 7.82 (d, J = 2.4 Hz, 1H, Ar−H), 8.07 (d, J = 8.7 Hz, 1H, Ar−H)
5c	0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.60−1.72 (m, 2H, CH_2) 4.12−4.18 (m, 2H, OCH_2), 4.98 (q, J = 4.8 Hz, 2H, OCH_2), 6.06 (d, J = 15.6 Hz, 1H, CH═), 6.92−7.01 (m, 1H, ═CH), 7.08 (dd, J = 3 and 8.7 Hz, 1H, Ar−H), 7.16 (d, J = 3 Hz, 1H, Ar−H), 7.26 (d, J = 8.7 Hz, 1H, Ar−H), 7.62 (d, J = 8.4 Hz, 1H, Ar−H), 7.82 (d, J = 2.4 Hz, 1H, Ar−H), 8.06 (d, J = 8.7 Hz, 1H, Ar−H)
5d	1.26−1.28 (m, 6H, CH_3), 4.98 (q, J = 4.8 Hz, 2H, OCH_2), 5.06−5.09 (m, 1H, CH), 6.03 (d, J = 15.6 Hz, 1H, CH═), 6.92−6.97 (m, 1H, ═CH), 7.09 (dd, J = 3 and 9 Hz, 1H, Ar−H), 7.16 (d, J = 2.7 Hz, 1H, Ar−H), 7.27 (dd, J = 2.4 and 6 Hz, 1H, Ar−H), 7.62 (d, J = 9 Hz, 1H, Ar−H), 7.82 (d, J = 2.1 Hz, 1H, Ar−H), 8.07 (d, J = 8.7 Hz, 1H, Ar−H)
5e	0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.362−1.54 (m, 2H, CH_2), 1.60−1.67 (m, 2H CH_2), 4.15 (q, J = 7.2 Hz, 2H, OCH_2), 4.98 (q, J = 4.8 Hz, 2H, OCH_2), 6.03 (d, J = 15.6 Hz, CH═), 6.97−6.93 (m,1H, ═CH), 6.99 (dd, J = 2.4 and 6 Hz, 1H, Ar−H), 7.10 (d, J = 3 Hz, 1H, Ar−H), 7.27 (dd, J = 2.4 and 6 Hz, 1H, Ar−H), 7.63 (d, J = 9 Hz, 1H, Ar−H) 7.83 (d, J = 2.1 Hz, 1H, Ar−H), 8.06 (d, J = 8.7 Hz, 1H, Ar−H)
5f	4.66−4.69 (m, 1H, OCH_2), 5.01−5.12 (m, 1H, OCH_2), 5.30−5.82 (m, 2H, C═CH_2), 5.91−5.98 (m, 1H, CH═), 6.11 (d, J = 15.6 Hz, 1H, CH═), 7.01−7.06 (m, 1H, ═CH), 7.09 (dd, J = 3 and 8.7 Hz, 1H, Ar−H), 7.16 (d, J = 2.4 Hz, 1H, Ar−H), 7.28 (d, J = 8.1 Hz, 1H, Ar−H), 7.63 (dd, J = 2.1 and 6.3 Hz, 1H, Ar−H), 7.82 (d, J = 1.8 Hz, 1H, Ar−H), 8.07 (d, J = 9.0 Hz, 1H, Ar−H)
5g	1.29 (t, J = 7.5 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.16 (q, J = 7.5 Hz, 2H, OCH_2), 5.47 (s, 2H, OCH_2), 5.83 (s, 1H, C═CH), 7.08 (dd, J = 3 and 6 Hz, 1H, Ar−H), 7.16 (d, J = 3 Hz, 1H, Ar−H), 7.27 (d, J = 7.2 Hz, 1H, Ar−H), 7.63 (dd, J = 1.8 and 6.6 Hz, 1H, Ar−H), 7.82 (d, J = 1.8 Hz, 1H, Ar−H), 8.03 (d, J = 9.0 Hz, 1H, Ar−H)
5h	1.30 (t, J = 6.9 Hz, 3H, CH_3), 4.22 (q, J = 6.9 Hz, 2H, CH_2), 4.99 (q, J = 4.8 Hz, 2H, CH_2), 6.14 (d, J = 15.6 Hz, 1H, C═CH), 6.99−7.11 (m, 3H), 7.27−7.52 (m, 3H, Ar−H), 7.77 (d, J = 2.4 Hz, H, Ar−H)

Scheme 1[a]



[a] Reagents and conditions: (a) Oxalyl dichloride/CH_2Cl_2, DMF(cat). (b) Et_3N, dichloromethane.

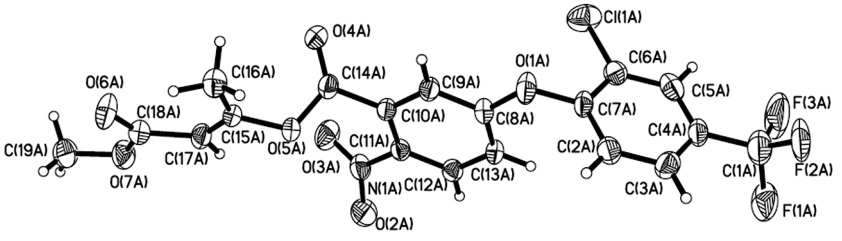
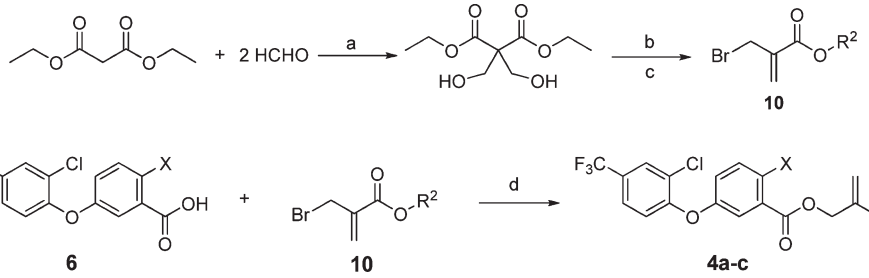


Figure 4. Crystal structure of compound **3a**.

4-Bromobutenates **12** can be prepared from butenates via a halgenated reaction with NBS. The title compounds 4-benzoxy−butenates **5a−h** were synthesized via intermediate **6** as shown in Scheme 4.

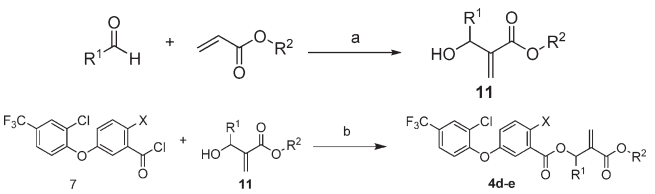
Structure−Activity Relationship. The results of herbicidal activities are listed in Tables 3, 6, and 9. In general, these compounds exhibited higher herbicidal activities against broadleaf

Scheme 2[a]



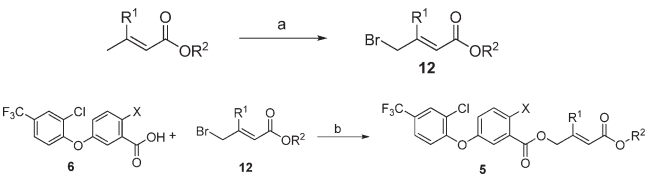
[a] Reagents and conditions: (a) $KHCO_3$, H_2O. (b) HBr (40%). (c) Alcohol/toulene, H_2SO_4(cat). (d) K_2CO_3, DMF.

Scheme 3[a]



[a] Reagents and conditions: (a) DABCO, 1,4-dioxane. (b) Et_3N, CH_2Cl_2.

Scheme 4[a]



[a] Reagents and conditions: (a) NBS/AIBN (cat), CCl_4. (b) K_2CO_3, DMF.

Table 9. Herbicidal Activities of Compound 5a−h

compd	Clog *P*	dosage (g/hm^2)	BYG	CRB	VEL
5a	5.5	480	80	90	100
		120	60	80	95
		30	10	20	30
5b	6.0	480	70	90	100
		120	50	80	99
		30	40	60	95
5c	6.4	480	70	90	100
		120	40	80	100
		30	10	70	95
5d	6.5	480	80	90	100
		120	60	85	95
		30	30	80	80
5e	7.1	480	40	85	95
		120	20	80	90
		30	10	70	90
5f	6.3	2000	60	55	100
		1000	30	25	80
5g	6.5	1000	35	20	100
		200	20	10	100
		40	5	10	90
5h	6.7	1000	85	70	100
		200	45	30	100
		40	15	20	98
acifluorfen	4.9	1000	90	10	100
		200	50	0	95
		40	10	0	55

Table 10. Herbicidal Spectrum of Compound 5b and Acifluorfen[a]

species	**5b** (40 g/hm^2)	acifluorfen (400 g/hm^2)
barnyard grass (*E. crusgalli*, BYG)	C	C
crabgrass (*D. sanguinalis*, CRB)	B	B
foxtail (*S. glauca*, FOX)	C	C
velvetleaf (*A. theophrasti*, VEL)	A	B
common purslane (*P. oleracea*, CMP)	A	A
redroot amaranth (*A. retroflexus*, RDA)	A	A
dayflower (*C. communis*, DAY)	C	C
heartleaf cocklebur (*X. strumarium*, HLC)	B	C

[a] A equals 95−100% control, B equals 70−95%control, and C equals below 70% control.

weeds than grass in postemergent application. Some compounds showed good herbicidal activities such as compounds **5b** and **5c**, which showed higher herbicidal activities as compared to the commercialized compound acifluorfen.

From the biological assay results in Table 3, compound **3c** was found to be the most active. A summary of results is outlined in Figure 5 against velvetleaf. We first focused our attention on the influence of substituent R^3 to the herbicidal activity. Compounds with methoxyethyl group (**3c**) exhibited higher herbicidal activity than that with methyl (**3a**) and ethyl (**3b**), while the compounds with *t*-butyl (**3d**) and allyl (**3e**) groups were less active. The structure−activity relationships for the substituents R^1 and R^2 were also investigated. Elongation of the alkyl group at R^1 reduced the activity. Compounds with hydrogen atom at R^2 gave a better herbicidal activity than methyl group. Replacement of the nitro group (**3b**) by chlorine atom (**3j**) caused a slight increase in activity.

Table 6 shows herbicidal activities of compounds, and a summary of results is outlined in Figure 6 against velvetleaf. These data showed that efficacy was strongly influenced by the

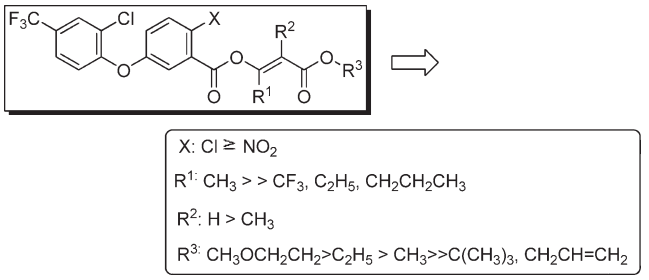


Figure 5. Structure−activity relationships for 3-benzoxy acrylate derivatives **3** against velvetleaf.

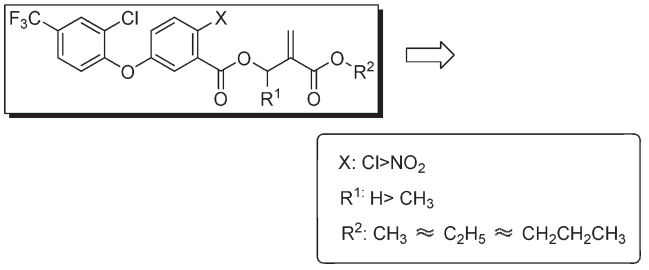


Figure 6. Structure−activity relationships for 2-(benzoxy) alkyl acrylate derivatives **4** against velvetleaf.

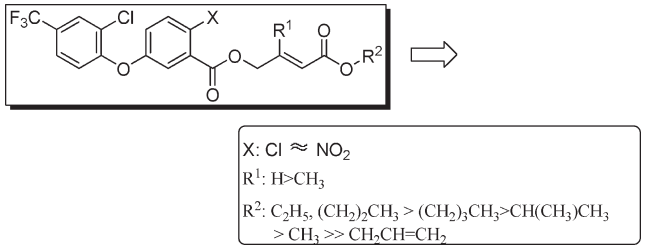


Figure 7. Structure−activity relationships for 4-benzoxy-butenoate derivatives **5** against velvetleaf.

Table 11. Crop Selectivity (Postemergence)

	g/hm^2		
compd	LD_{90} for velvetleaf	LD_{10} for soybean	crop selectivity index
5b	19.4	63.0	3.2
acifluorfen	137.4	461.8	3.4

group R^1, while the hydrogen atom (**4a**) is better than methyl group (**4d**) for R^1. Compounds with methyl and ethyl groups at R^2 exhibited an equal activity. Replacement of the nitro group (**4e**) by chlorine atom (**4d**) caused an obvious increase in activity.

From the biological assay results in Table 9, compounds **5b** and **5c** exhibited higher herbicidal activities, while **5f** was obviously less active than **5b**. A summary of results is outlined in Figure 7 against velvetleaf. A compound with a hydrogen atom (**5a**) on R^1 shows a higher activity than that with a methyl group (**5h**). The effect at R^2 on the herbicidal activity was investigated with the compounds **5a**−**f**. Compounds with an ethyl group (**5b**) and propyl group (**5c**) exhibited higher herbicidal activities than those with isopryl (**5d**) and methyl (**5a**) groups. Introduction of an allyl group (**5f**) caused a significant decrease in the activity. Replacement of the nitro group (**5b**) by chlorine atom gave **5h**, which was as active as **5b**.

Lipophilicity as Clog *P* was predicted by ChemBioDraw 11.0 as shown in Tables 3, 6, and 9. There are some extent correlations between herbicidal activity and lipophilicity. The appropriate lipophilicity is essential for the herbicidal activity; the Clog *P* of title compounds with potent herbicidal activity was between 5.8 and 6.1. If the Clog *P* is too small or too big, the efficiency is lower.

Deeply Studies of Compound 5b. Compound **5b** was the most interesting compound in our primary screening. It was further evaluted for inhibitory activity against PPO, herbicidal spectrum, crop selectivity, field performance, and acute toxicity.

Inhibitory activity against PPO results showed that compound **5b** exhibited stronger inhibition than acifluorfen in vitro. The pI_{50} values against PPO of compound **5b** and acifluorfen were 6.64 and 4.51, respectively. Compound **5b**'s PPO inhibitory activity correlated well with its herbicidal activities.

The herbicidal spectrum results showed that compound **5b** exhibited higher herbicidal activities against broadleaf weeds than grass as shown in Table 10. Compound **5b** showed good herbicidal activities against velvetleaf, common purslane, and redroot amaranth at 40 g/hm^2. As shown in Table 11, compound **5b** exhibits good herbicidal activity on broadleaf weeds with selectivity for soybean, and the selectivity index for soybean is 3.2, which is commensurate to acifluorfen (3.4).

Compound **5b** was primary field tested in soybeans and wheat. As shown in Table 12, postemergence field application of **5b** at 100 g/hm^2 demonstrated good broadleaf weed control, with soybean tolerance, but low selectivity to wheat. Compound **5b** showed good herbicidal activities against velvetleaf, common purslane, and redroot amaranth at 100 g/hm^2, while acifluorfen achieving the same efficacy at 400 g/hm^2. Soybean plants eventually outgrew initial injury at 7 days after application.

Table 12. Herbicidal Activities in Field Tests of 5b[a]

compd	dosage (g/hm^2)	BYG	CRB	HLC	VEL	DAY	soybean	wheat
5b	25	0	5	40	65	35	5	10
	100	55	60	98	100	95	10	25
acifluorfen	100	25	10	80	85	60	5	0
	400	80	55	100	100	100	10	15

[a] 0 equals no activity; 100 equals total control. BYG, barnyard (*E. crusgalli*); CRB, crabgrass (*D. sanguinalis*); HLC, heartleaf cocklebur (*X. strumarium*); VEL, velvetleaf (*A. thophrasti*); and DAY, dayflower (*C. communis*).

Table 13. Acute Toxicity

acute toxicity test	species	results
oral LD_{50} (mg kg^{-1})	rat	2330 (male)
		2330 (female)
dermal	rat	>2150 (male)
		>2150 (female)
skin irritation	rabbit	nonirritating
eye irritation	rabbit	minimally irritating
skin sensitization	guinea pig	nonsensitizing
Ames		negative

As shown in Table 13, the acute toxicity results show that compound **5b**'s acute toxicity to mammals is low.

In conclusion, a series of novel DPE derivatives were designed and synthesized containing unsaturated carboxylates, and some title compounds exhibited good herbicidal activities against velvetleaf. Among unsaturated carboxylates group, butenate is the most promising one. Compound **5b** was identified as the most promising candidate due to its high PPO inhibition effect ($pI_{50} = 6.64$) and good herbicidal activity against broadleaf weeds with selectivity for soybean and low toxicity to mammals and thus is worth further study.

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