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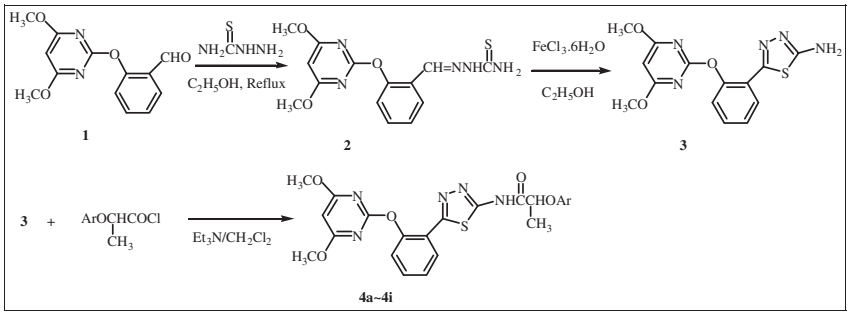
Received August 2, 2012
DOI 10.1002/jhet.1853
Published online 18 November 2013 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel *N*-{5-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazol-2-yl}2-aroxy-propanamides were designed and synthesized by the multistep reactions. 2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-benzaldehyde (**1**) reacted with aminothiourea to yield **2**, which undergoes ring closure to give 5-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazol-2-amine (**3**) in the presence of ferric chloride in refluxing ethanol. **3** reacted with 2-aroxy-propionyl chlorides to give the target compounds **4a–4i** in moderate to good yields. Their structures were confirmed by IR, ^{1}H-NMR, EIMS, and elemental analyses. The preliminary bioassay indicated that some of them displayed moderate to good selective herbicidal activity against *Brassica campestris L.* at the concentration of 100 mg/L. However, these compounds did not possess inhibitory activity against *Echinochloa crus-galli* at the tested concentrations.

J. Heterocyclic Chem., **51**, 432 (2014).

INTRODUCTION

Recently, pyrimidinyl salicylic acid derivatives, which acted as inhibitors of branched chain amino acids (acetolactate synthase (ALS) or acetohydroxyacid synthase (AHAS)) synthase, have been found to be effective herbicides against barnyard grass in different growth stages including pre-emergence treatment and excellent safety on transplanted rice crops, animals, fish, and so forth [1–5]. To date, several pyrimidyl carboxylic acid derivatives such as bispyribac-sodium and pyriminobac-methyl, have been used as commercially herbicides (Figure 1), which are widely used in agriculture and plant protection around the world. On the other hand, 1,3,4-thiadiazole derivatives possessed a wide range of pharmaceutical or agrochemical activities, such as anticancer [6], antiviral [7], antibacterial [8], antimicrobial, and anti-inflammatory activities [9]; some of them exhibited good fungicidal [10] and herbicidal activities [11]. To find novel lead compound with good herbicidal activity, we designed and synthesized a series of novel *N*-{5-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazol-2-yl} 2-aroxy-propanamides, according to the pesticide metabolism, which might be hydrolyzed to 2-(4,6-dimethoxy-pyrimidin-2-yloxy)-benzoic acid and 2-aroxy propionic acid in plant tissues; both of them are effective herbicides. Their herbicidal activities against *Brassica campestris L.* and *Echinochloa crus-galli* (*in vitro*) were evaluated in this study. Herein, we would like to report the synthesis and herbicidal activities of the title compounds **4a–4i** in this article (Scheme 1).

RESULTS AND DISCUSSION

4,6-Dimethoxypyrimidin-2-yl-methylsulfone reacted with salicyl aldehyde in the presence of potassium carbonate to give 2-(4,6-dimethoxypyrimidin-2-yloxy)benzaldehyde (**1**) in 94% yield. **1** reacted with aminothiourea to form semicarbazone (**2**), which undergoes annulation in the presence of $FeCl_3$ to give 5-amino-2-[2-(4,6-dimethoxypyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazole (**3**) in moderate yield. The target compounds **4** were synthesized by the condensations of **3** with 2-aroxy-propionyl chlorides in the presence of Et_3N at RT in moderate to good yields.

The structures of all of the target compounds were characterized by ^{1}H-NMR, IR spectra, and elemental analyses; some of them were determined by EIMS spectrum, which were listed in the Experimental Section. In the ^{1}H-NMR spectra of **4**, the methyl protons exhibited as a doublet at approximately 1.70, whereas the methine proton displayed as a quartet at approximately 5.0. The two methoxy groups of the pyrimidine ring and the pyrimidine proton also showed as a singlet with the chemical shift at approximately

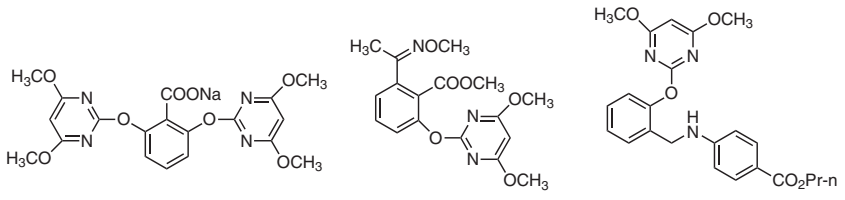


Figure 1. Structures of some commercial pyrimidinyl carboxylic acid and pyrimidinyl benzylamine herbicides.

Scheme 1. Synthetic route to compounds **4a–4i**.

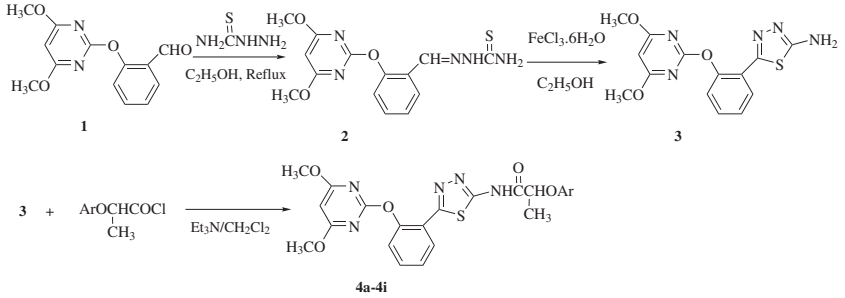


Table 1

Herbicidal activity of compounds **4a–4i** (growth inhibition rate %).

	Brassica campestris root test		*Echinochloa crus-galli* cup test	
Compd.	10 μg/mL	100 μg/mL	10 μg/mL	100 μg/mL
4a	46.4	75.0	0	0
4b	20.3	65.4	0	0
4c	0	27.6	0	20.0
4d	31.8	59.8	0	5.0
4e	0	33.0	0	0
4f	24.0	64.2	0	20.0
4g	6.2	42.4	0	15.0
4h	0	0	0	0
4i	61.0	87.6	0	0
Bispyribac-sodium	65.6	69.8	46.9	72.4

3.8 and 5.8, respectively; however, the amino proton displayed a wide singlet with the chemical shift δ at the range of 10 and 11.5. The IR spectra of **4** revealed NH at 3450 cm^{-1}, whereas the signal of 1700 cm^{-1} is attributed to C=O absorption, and 1350 and 1220 cm^{-1} can be attributed to C—O—C absorption bands. The mass spectra of the target compounds **4** shows moderate molecular ion peak and anticipated fragmentation ion peaks.

Herbicidal activity. The preliminary herbicidal activities of compounds **4** were evaluated, against two representative targets, oil rape and barnyard grass, at concentrations of 100 and 10 mg/L, according to a literature method [12]. The results were listed in Table 1. The results showed that these compounds exhibited moderate selective herbicidal activity against *B. campestris L.* at the concentration of 100 mg/L. However, these compounds displayed weak inhibitory activity against *E. crus-galli* at different concentration. For example, compounds **4a**, **4b**, **4f**, and **4i** possessed 75.0%, 65.4%, 64.2%, and 87.6% inhibitory activities against *B. campestris L.* at the concentration of 100 mg/L. As for the preliminary structure-activity relationships, the substituents of the benzene ring have some effects on their herbicidal activity. For example, 2,4-dichloro substituted compound (**4i**) exhibits the strongest activity, which shows as good herbicidal activity as the control drug—bispyribac-sodium—did. Secondly, varying substituents of the aromatic ring at the different position have some effects on the herbicidal activity. For example, 4-fluoro substituted one (**4f**) shows better activity than 3-fluoro one (**4c**). However, as for electron-donating substituents, 3-methyl substituted one displays stronger activity than 4-methyl substituted one (**4g**). Further exploring of structure-activity relationships needs more experimental results to support. Further biological activity (*in vivo*) investigations are on the way.

In conclusion, a series of novel *N*-{5-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazol-2-yl}2-aroxy-propanamides (**4**) were designed and synthesized by the multistep reactions. Their structures were determined by IR, ^{1}H-NMR, EIMS, and elemental analyses. The preliminary bioassay indicated that some of them displayed moderate selective herbicidal activity against *B. campestris L* at the concentration of 100 mg/L.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus (Shanghai, China) and are uncorrected. ^{1}H-NMR spectra was recorded with a Varian Mercury PLUS 400 (400 MHz) or PLUS 600 (600 MHz) spectrometer (Palo Alto, CA) with TMS as the internal reference and $CDCl_3$ or DMSO-d_6 as the solvent, whereas mass spectra were measured on a Finnigan Trace MS 2000 spectrometer (Finnigan Cooperation, CA) at 70 eV using EI method. IR spectra were measured by a Nicolet NEXUS470 spectrometer (ThermoNicolet Corporation, USA). Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer (Elementar Cooperation, Germany). 2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-benzaldehyde (**1**) and 2-aroxy-propionyl chlorides can be prepared according to a reported method [13,14], respectively. All of the solvents and materials were reagent grade and purified as required.

Synthesis of 5-amino-2-[2-(4,6-dimethoxypyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazole (3) [11c]. 2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-benzaldehyde (**1**) (5 g, 19 mmol), aminothiourea (1.75 g, 19 mmol), and anhydrous ethanol (70 mL) were added to a 100-mL three-necked flask; the mixture was allowed to be stirred at RT for 0.5 h and then was stirred under reflux for 4 h. After the mixture was cooled to RT, the white solid was filtered and washed with ethanol (5 mL) to give **2** as white solid (6 g, 94% yield). mp 184–185°C.

2 (4.25 g, 12 mmol), $FeCl_3.6H_2O$ (12 g, 44 mmol), and anhydrous methanol (45 mL) were added to a 100-mL three-necked flask; the mixture were allowed to be stirred under reflux for 8 h. After most of ethanol was removed under vacuum, water (100–150 mL) was added; the solid was filtered and washed with water (50 mL × 3); **3** was obtained as gray brown solid (3.5 g, 88% yield). mp 161–162°C; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 3.76 (s, 6H), 5.41 (br, 2H), 5.78 (s, 1H), 7.22 (d, J = 7.8 Hz, 1H, ArH), 7.30 (t, J = 8.4 Hz, 1H, ArH), 7.41 (t, J = 7.2 Hz, 1H, ArH), 7.78 (d, J = 7.2 Hz, 1H, ArH). *Anal*. Calcd for $C_{14}H_{13}N_5O_3S$: C, 50.75; H, 3.95; N, 21.14. Found: C, 50.87; H, 3.99; N, 21.01.

General procedure for the synthesis of *N*-{5-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-phenyl]-[1,3,4]thiadiazol-2-yl} 2-aroxy-propanamides (4). 3 (1.66 g, 5 mmol), Et_3N (0.5 mL), and anhydrous CH_2Cl_2 (10 mL) were added to a 50-mL three-necked flask, the solution of 2-aroxy-propionyl chloride (5 mmol) in CH_2Cl_2 (2 mL) was added dropwise slowly in an ice bath. After the addition completed, the mixture was allowed to be stirred at RT for 3–4 h till the reaction finished (monitored by TLC). After the removal of the solvent followed by column chromatography of the crude product on silica gel using a mixture of petroleum ether (60–90°C) and ethyl acetate (v/v, 2:1) as the eluent, compounds **4** were obtained as white or light yellow solids in 62–75% yields.

Compound 4a. **4a** (Ar=C_6H_5): white solid, yield: 71%, mp 170–171°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.68 (d, J = 6.8 Hz, 3H, CH_3), 3.83 (s, 6H, 2 × OCH_3), 5.01 (q, J = 6.8 Hz, 1H, CH), 5.80 (s, 1H, pyrimidine-H), 6.95 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 7.2 Hz, 1H), 7.28–7.37 (m, 4H), 7.49 (t, J = 7.2 Hz, 1H), 8.36 (d, J = 7.6 Hz, 1H), 10.48 (br, 1H, NH); IR (KBr) ν: 3441 (NH), 2935 (ArH), 1718 (C=O), 1608, 1565, 1510 (Ar), 1358, 1220 (C—O—C) cm^{-1}; EIMS (70 eV): *m/z* 479.5 (M^+, 27.6), 464.5 (10.7), 358 (27.0), 331 (11.6), 299 (9.8), 258 (15.5), 195 (15.9), 139 (13.1), 136 (11.3), 121 (57.6), 116 (15.9), 108 (14.6), 94 (15.9), 93 (24.4), 77 (100). *Anal*. Calcd for $C_{23}H_{21}N_5O_5S$: C, 57.61; H, 4.41; N, 14.61. Found: C, 57.42; H, 4.46; N, 14.75.

Compound 4b. **4b** (Ar=2-BrC_6H_4): white solid, yield: 62%, mp 182–183°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.74 (d, J = 6.8 Hz, 3H, CH_3), 3.83 (s, 6H, 2 × OCH_3), 5.00 (q, J = 6.8 Hz, 1H, CH), 5.80 (s, 1H, pyrimidine-H), 6.95 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 7.6 Hz, 1H), 10.35 (br, 1H, NH); IR (KBr) ν: 3436 (NH), 2931 (ArH), 1697 (C=O), 1603, 1560, 1512 (Ar), 1355, 1196 (C—O—C) cm^{-1}. *Anal*. Calcd for $C_{23}H_{20}BrN_5O_5S$: C, 49.47; H, 3.61; N, 12.54. Found: C, 49.61; H, 3.83; N, 12.67.

Compound 4c. **4c** (Ar=3-FC_6H_4): white solid, yield: 75%, mp 176–177°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.70 (d, J = 6.4 Hz, 3H, CH_3), 3.84 (s, 6H, 2 × OCH_3), 5.01 (q, J = 6.4 Hz, 1H, CH), 5.81 (s, 1H, pyrimidine-H), 6.68–6.75 (m, 3H), 722–7.38 (m, 3H), 7.50 (t, J = 8.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 10.64 (br, 1H, NH); IR (KBr) ν: 3452 (NH), 2959 (ArH), 1686 (C=O), 1612, 1571, 1488 (Ar), 1362, 1210, 1192 (C—O—C) cm^{-1}. *Anal*. Calcd for $C_{23}H_{20}FN_5O_5S$: C, 55.53; H, 4.05; N, 14.08. Found: C, 55.39; H, 4.16; N, 13.92.

Compound 4d. **4d** (Ar=3-$CH_3C_6H_4$): white solid, yield: 74%, mp 162–163°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.67 (d, J = 6.8 Hz, 3H, CH_3), 2.30 (s, 3H), 3.83 (s, 6H, 2 × OCH_3), 5.02 (q, J = 6.4 Hz, 1H, CH), 5.81 (s, 1H, pyrimidine-H), 6.75 (t, J = 6.8 Hz, 2H), 6.83 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 10.70 (br, 1H, NH); IR (KBr) ν: 3464 (NH), 2936 (ArH), 1715 (C=O), 1605, 1561, 1506 (Ar), 1342, 1225 (C—O—C) cm^{-1}; EIMS (70 eV): *m/z* 493.5 (M^+, 29.6), 478 (5.8), 358 (30.4), 299 (9.9), 258 (22.3), 195 (12.8), 139 (12.6), 136 (12.0), 135 (51.1), 119 (13.1), 116 (14.5), 108 (21.3), 107 (22.8), 91 (100). *Anal*. Calcd for $C_{24}H_{23}N_5O_5S$: C, 58.41; H, 4.70; N, 14.19. Found: C, 58.56; H, 4.52; N, 14.33.

Compound 4e. **4e** (Ar=4-ClC_6H_4): white solid, yield: 65%, mp 174–175°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.70 (d, J = 6.8 Hz, 3H, CH_3), 3.83 (s, 6H, 2 × OCH_3), 5.08 (q, J = 6.8 Hz, 1H, CH), 5.81 (s, 1H, pyrimidine-H), 6.90 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 8.0 Hz, 2H), 7.49 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 11.46 (br, 1H, NH); IR (KBr) ν: 3458 (NH), 2940 (ArH), 1712 (C=O), 1608, 1565, 1502 (Ar), 1341, 1227 (C—O—C) cm^{-1}; EIMS (70 eV): *m/z* 513 (M^+, 40.0), 498 (13.8), 482 (29.9), 358 (48.9), 258 (76.5), 195 (40.7), 157 (42.4), 155 (76.9), 139 (48.0), 130 (22.6), 128 (40.9), 127 (44.9), 116 (30.3), 113 (36.3), 111 (100), 91 (69.5), 69 (33.6). *Anal*. Calcd for $C_{23}H_{20}ClN_5O_5S$: C, 53.75; H, 3.92; N, 13.63. Found: C, 53.70; H, 3.84; N, 13.88.

Compound 4f. **4f** (Ar=4-FC_6H_4): white solid, yield: 68%, mp 168–170°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.67 (d, J = 6.8 Hz, 3H, CH_3), 3.84 (s, 6H, 2 × OCH_3), 4.96 (q, J = 7.2 Hz, 1H, CH), 5.81 (s, 1H, pyrimidine-H), 6.91 (dd, J = 4.4 Hz, J = 9.2 Hz, 2H), 7.00 (t, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H), 10.61 (br, 1H, NH); IR (KBr) ν: 3468 (NH), 2921 (ArH), 1707 (C=O), 1612, 1559, 1506 (Ar), 1345, 1218 (C—O—C) cm^{-1}. *Anal*. Calcd for $C_{23}H_{20}FN_5O_5S$: C, 55.53; H, 4.05; N, 14.08. Found: C, 55.30; H, 4.16; N, 14.29.

Compound 4g. **4g** (Ar=4-$CH_3C_6H_4$): white solid, yield: 70%, mp 172–173°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.64 (d, J = 6.8 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.83 (s, 6H, 2 × OCH_3), 4.92 (q, J = 7.2 Hz, 1H, CH), 5.81 (s, 1H, pyrimidine-H), 6.84 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 10.13 (br, 1H, NH);

IR (KBr) ν: 3439 (NH), 2920 (ArH), 1684 (C=O), 1612, 1569, 1508 (Ar), 1352, 1222, 1195 (C—O—C) cm^{-1}; EIMS (70 eV): *m/z* 493 (M^+, 12.5), 387 (40.3), 386 (14.8), 358 (33.8), 331 (17.2), 258 (74.3), 218 (16.8), 195 (22.8), 139 (18.6), 135 (59.4), 108 (32.7), 107 (41.9), 91 (100), 69 (26.8). *Anal*. Calcd for $C_{24}H_{23}N_5O_5S$: C, 58.41; H, 4.70; N, 14.19. Found: C, 58.65; H, 4.61; N, 14.03.

Compound 4h. **4h** (Ar=4-$CH_3OC_6H_4$): light yellow solid, yield: 75%, mp 161–163°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.64 (d, J = 6.8 Hz, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.83 (s, 6H, $2 \times OCH_3$), 4.88 (q, J = 6.8 Hz, 1H, CH), 5.80 (s, 1H, pyrimidine-H), 6.83 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 10.33 (br, 1H, NH); IR (KBr) ν: 3440 (NH), 2928 (ArH), 1681 (C=O), 1613, 1572, 1505 (Ar), 1357, 1225, 1190 (C—O—C) cm^{-1}; EIMS (70 eV): *m/z* 509 (M^+, 19.7), 387 (16.1), 386 (60.4), 358 (54.6), 331 (20.4), 299 (17.4), 259 (15.7), 258 (36.8), 195 (13.2), 151 (29.4), 139 (19.8), 135 (32.2), 124 (28.0), 123 (100), 121 (10.5), 92 (44.8), 77 (52.5). *Anal*. Calcd for $C_{24}H_{23}N_5O_6S$: C, 56.57; H, 4.55; N, 13.74. Found: C, 56.77; H, 4.30; N, 13.56.

Compound 4i. **4i** (Ar=2,4-$Cl_2C_6H_3$): white solid, yield: 63%, mp 187–189°C; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 1.71 (d, J = 7.2 Hz, 3H, CH_3), 3.83 (s, 6H, $2 \times OCH_3$), 4.95 (q, J = 6.6 Hz, 1H, CH), 5.80 (s, 1H, pyrimidine-H), 6.92 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.50 (t, J = 7.8 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 10.43 (br, 1H, NH); IR (KBr) ν: 3441 (NH), 2934 (ArH), 1676 (C=O), 1605, 1574, 1501 (Ar), 1342, 1228, 1184 (C—O—C) cm^{-1}. *Anal*. Calcd for $C_{23}H_{19}Cl_2N_5O_5S$: C, 50.37; H, 3.49; N, 12.77. Found: C, 50.14; H, 3.24; N, 12.52.

Herbicidal activity testing. The herbicidal activity measurement method was adapted according to a literature method [13].

Acknowledgment. This work was supported by the Natural Science Foundation of China (No. 20872046) and the Natural Science Foundation of Hubei Province (No. 2008CDB086).

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