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Synthesis and Herbicidal Activities of Novel 3-N-Substituted Amino-6-methyl-4-(3-trifluoromethylphenyl)pyridazine Derivatives

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4-(3-Trifluoromethylphenyl)pyridazine is a new series of compounds with bleaching and herbicidal activities. Starting from ethyl 2-(3-trifluoromethylphenyl)acetate, an important intermediate **7** was synthesized in five steps with a moderate total yield of 51.5% in a safe and practical way. Twenty-six novel 3-N-substituted amino-6-methyl-4-(3-trifluoromethylphenyl)pyridazine derivatives were synthesized and evaluated through a *Spirodela polyrrhiza* test and greenhouse test. Some compounds can completely inhibit Chl at 1 μg/mL and exhibit equal or higher herbicidal activities with the commercial bleaching herbicide diflufenican against dicotyledonous plants at a rate of 75 g/ha.

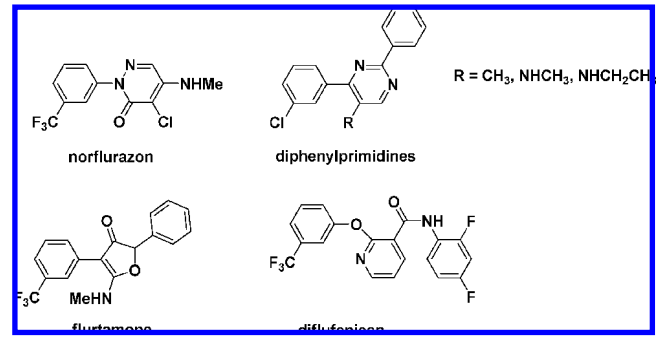
KEYWORDS: 3-Trifluoromethylphenyl; pyridazine; herbicidal activity; bleaching activity; synthesis

INTRODUCTION

Carotenoids are essential components for the assembly of the photosynthetic apparatus of green plants. A lack of carotenoid synthesis, which is inhibited by corresponding compounds, may lead to typical bleaching symptoms in plants. Commercially important bleaching herbicides are found among the phytoene desaturase inhibitors (*1, 2*).

Typical and efficient bleaching compounds possess a central five- or six-membered heterocycle carrying one or two substituted phenyl rings in which a 3-trifluoromethylphenyl group is a common structure in all compounds (*2*). In our previous work (*3*), it was indicated that **1** showed better bleaching and herbicidal activities, with a Chl inhibition of >80% at 10 μg/mL for most of compounds and that **1a**,**b** controlled >80% *Digitaria adscendens* at 300 g/ha (*3*). This series of compounds fits quite well into the characteristics of an optimized inhibitor of phytoene desaturase in which it has a 3-trifluoromethylphenyl ring, a central heterocycle, and additional substituents (*2*).

In some series of PDS (phytoene desaturase) inhibitors, the substituted amino group is important for activity. Norflurazon, a PDS inhibitor having a central pyridazinone ring and methylamino group at the 5-position of the central ring, can control annual grasses at 1−8 kg/ha (*4*). When the methylamino group was replaced by an amino or methoxy group, the bleaching activity was decreased (*5*). Another PDS inhibitor that is amino-substituted is flurtamone; it possesses a methylamino group at the central dihydrofuranone ring and controls annual broad grass at 250−500 g/ha. For diphenylpyrimidines, modification of the 5-substituent from CH_3 to CH_3NH or to CH_3CH_2NH increased the inhibitory properties considerably (*6*). We also noticed some higher active PDS inhibitors such as diflufenican, used at 125−250 g/ha, in which the central heterocycle carried two substituted phenyl rings.



With the previous options in mind and to find more highly active compounds, compounds **1** were modified by the replacement of pyridazinone with a pyridazine ring, and substituted aryl amino or arylalkyl amino groups in the 3-position of the pyridazine were introduced to give compounds **2**. The bioassay

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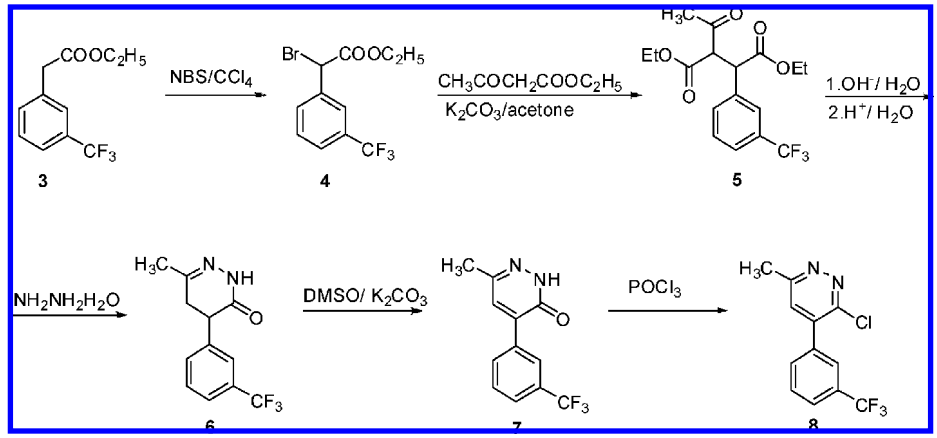
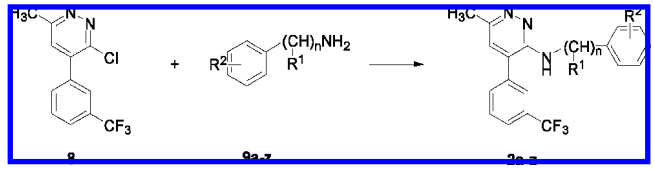
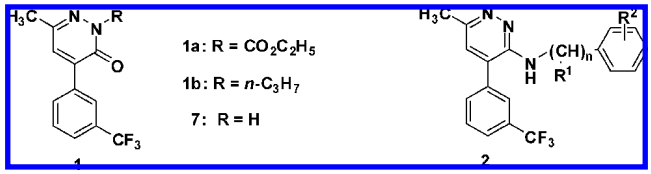
Scheme 1. Synthetic Route to Compound **8**



Scheme 2. Synthetic Route to the Title Compounds **2**



results showed that compounds **2** have a higher level of bleaching and herbicidal activities than compounds **1** using a *S. polyrrhiza* test and a greenhouse test. Some compounds can completely inhibit chlorophyll (Chl) at 1 μg/mL and exhibit equal or higher herbicidal activities with commercial bleaching of the herbicide diflufenican against dicotyledonous plants at a rate of 75 g/ha.



In a previous paper, the important intermediate **7** was synthesized through 3-(trifluoromethylphenyl)magnesium bromide, and the yield was low (38.6%) (*3*). Herein, we report a new method for the preparation of intermediate **7** from ethyl 2-(3-trifluoromethylphenyl)acetate in five steps with a moderate total yield of 51.5% (**Scheme 1**).

MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were recorded in a deuterochloroform solution with a Bruker AC-P500 (300 MHz) or an Oxford AS400 (400 MHz) instrument, using tetramethylsilane as an internal standard. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyzer. Melting points were determined using a Thomas−Hoover melting-point apparatus and were uncorrected. Yields were not optimized (**Schemes 1** and **2**).

Synthesis of Ethyl 2-Bromo-2-(3-trifluoromethylphenyl)acetate (4). A mixture of ethyl 2-(3-trifluoromethylphenyl)acetate (23.2 g, 0.100 mol) and *N*-bromosuccinimide (18.7 g, 0.105 mol) in 100 mL of dry carbon tetrachloride was stirred at room temperature, and then a catalytic amount of 48% hydrobromic acid was added. The mixture was stirred at reflux until the orange color faded. The solid was filtered off, and the filtrate was concentrated to give a colorless liquid (30.6 g) in 98.4% yield. ^{1}H NMR (300 MHz) δ: 1.30 (t, J_H = 7.2 Hz, 3H, CH_3), 4.24−4.28 (m, 2H, CH_2), 5.35 (s, 1H, CH), 7.51 (t, J_H = 7.6 Hz, 1H, ArH), 7.62 (d, J_H = 7.8 Hz, 1H, ArH), 7.77 (d, J_H = 7.8 Hz, 1H, ArH), 7.81 (s, 1H, ArH).

Synthesis of Diethyl 2-Acetyl-3-(3-trifluoromethylphenyl)succinate (5). A mixture of ethyl 2-bromo-2-(3-trifluoromethylphenyl)acetate (16.5 g, 50 mmol), 3-oxo-butyric acid ethyl ester (6.5 g, 50 mmol), and anhydrous potassium carbonate (7.6 g, 55 mmol) was dissolved in 100 mL of dry acetone and refluxed for 2 h. The resulting mixture was cooled and concentrated in vacuo. Water (50 mL) was added and extracted 3 times with dichloromethane (3 × 75 mL). The organic phase was washed twice with saturated brine (2 × 50 mL) and concentrated in vacuo. Crude diethyl 2-acetyl-3-(3-trifluoromethylphenyl)succinate (**5**) was obtained without further purification and can be used in the next step.

Synthesis of 6-Methyl-4-(3-trifluoromethylphenyl)-4,5-dihydro-2*H*-pyridazin-3-one (6). To the crude product of diethyl 2-acetyl-3-(3-trifluoromethylphenyl)succinate (**5**) was added a sodium hydroxide solution (1 M, 100 mL), and then the resulting mixture was refluxed for 2 h. After being cooled to room temperature, concentrated hydrochloric acid was added dropwise until the pH was 1. The reaction mixture was stirred at room temperature for 1 h and then extracted 3 times with dichloromethane (3 × 75 mL). The organic phase was dried over magnesium sulfate. After the solvent was distilled off, the residue was dissolved in 70 mL of ethanol, and 85% hydrazine hydrate (2.9 g, 50 mmol) was added dropwise. The mixture was refluxed for 3 h. After being cooled, the mixture was slowly added to 250 mL of ice water in which a light yellow solid was formed. The solid was filtered and dried to give a yellow solid (7.13 g) in 55.7% yield. ^{1}H NMR (400 MHz) δ: 2.09 (s, 3H, CH_3), 2.72−2.87 (m, 2H, CH_2), 3.73−3.77 (m, 1H, CH), 7.43 (d, J_H = 7.6 Hz, 1H, ArH), 7.48−7.51 (m, 2H, 2ArH), 7.57 (d, J_H = 8.0 Hz, 1H, ArH), 8.48 (s, 1H, NH).

Synthesis of 6-Methyl-4-(3-trifluoromethylphenyl)-2*H*-pyridazin-3-one (7). Compound **6** (0.51 g, 2.0 mmol) was added to a mixture of potassium carbonate powder (0.28 g, 2.0 mmol) and 30 mL of anhydrous dimethyl sulfoxide. The reaction mixture was stirred at room temperature for 24 h and then poured into 50 mL of water and neutralized with 15% diluted hydrochloric acid until the pH was 7. The mixture was extracted with ether (5 × 20 mL). The combined organic layer was washed with saturated brine (2 × 50 mL), dried over magnesium sulfate, and concentrated under a vacuum to give a white solid (0.48 g) in 94.0% yield. ^{1}H NMR (400 MHz) δ: 2.42 (s, 3H, CH_3), 7.32 (s, 1H, pyridazinone), 7.59 (t, J_H = 7.8 Hz, 1H, ArH), 7.69 (d, J_H = 7.6 Hz, 1H, ArH), 8.02 (s, 1H, ArH), 8.10 (d, J_H = 7.6 Hz, 1H, ArH), 11.77 (s, 1H, NH).

Synthesis of 3-Chloro-6-methyl-4-(3-trifluoromethylphenyl)pyridazine (8). Compound **7** (2.00 g, 7.9 mmol) was dissolved in 40 mL of dry phosphorous oxychloride. The reaction mixture was refluxed

for 2 h, and then the excess phosphorous oxychloride was removed by distillation. The residue was poured into ice water (200 mL) while being stirred to give a white solid. The mixture was neutralized with 20% sodium hydroxide until the pH was 7. The solid was collected by filtration and dried in vacuo to give a white solid (2.10 g) in 98.0% yield. mp 125−126 °C; ^{1}H NMR (300 MHz) δ: 2.78 (s, 3H, CH_3), 7.32 (s, 1H, ArH), 7.62−7.78 (m, 4H, 4ArH); Anal. calcd for $C_{12}H_8ClF_3N_2$: C 52.86, H 2.96, N 10.27; found: C 52.82, H 3.03, N 10.04.

General Synthetic Procedures for Target Compounds 2a−j. Compound **8** (0.5 mmol) and the corresponding **9** (2.5 mmol) were mixed together and heated to 190 °C for 20 h in a sealed reactor (*7*). After cooling to room temperature, the residue was purified on a silica gel column eluted with petroleum ether (60−90 °C)/ethyl acetate (1:1) to give **2a−j**.

General Synthetic Procedures for Target Compounds 2k−z. Compound **8** (0.5 mmol) and the corresponding **9** (2.5 mmol) were mixed together and heated to 160 °C for 4 h in a sealed reactor. After cooling to room temperature, the residue was purified on a silica gel column eluted with petroleum ether (60−90 °C)/ethyl acetate (2:1) to give **2k−z**.

Data for **2a**: Yield, 58.3%; mp, 162−164 °C. ^{1}H NMR (400 MHz) δ: 2.59 (s, 3H, CH_3), 4.51−4.62 (b, 1H, NH), 4.76 (d, 1H, J_H = 5.2 Hz, CH_2), 6.94 (s, 1H, pyridazine), 7.26−7.36 (m, 5H, 5ArH), 7.61−7.70 (m, 4H, 4ArH); Anal calcd for $C_{19}H_{16}F_3N_3$: C 66.46, H 4.70, N 12.24; found: C 66.29, H 5.00, N 12.40.

Data for **2b**: Yield, 67.2%; mp, 95−97 °C. ^{1}H NMR (300 MHz) δ: 2.32 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.49−4.52 (b, 1H, NH), 4.71 (d, 1H, J_H = 5.4 Hz, CH_2), 6.93 (s, 1H, pyridazine), 7.12 (d, 2H, J_H = 7.8 Hz, 2ArH), 7.25 (d, 2H, J_H = 8.1 Hz, 2ArH), 7.60−7.69 (m, 4H, 4ArH); Anal calcd for $C_{20}H_{18}F_3N_3$: C 67.22, H 5.08, N 11.76; found: C 67.38, H 4.94, N 11.60.

Data for **2c**: Yield, 54.2%; mp, 83−85 °C. ^{1}H NMR (300 MHz) δ: 2.61 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.42−4.53 (b, 1H, NH), 4.70 (d, 1H, J_H = 5.1 Hz, CH_2), 6.85−6.88 (m, 2H, 2ArH), 6.95 (s, 1H, pyridazine), 7.28−7.32 (m, 2H, 2ArH), 7.63−7.71 (m, 4H, 4ArH); Anal calcd for $C_{20}H_{18}F_3N_3O$: C 64.34, H 4.86, N 11.25; found: C 64.17, H 4.98, N 11.09.

Data for **2d**: Yield, 64.9%; mp, 130−131 °C. ^{1}H NMR (300 MHz) δ: 2.58 (s, 3H, CH_3), 4.64−4.82 (m, 3H, NH + CH_2), 6.93−7.72 (m, 9H, 9ArH); Anal calcd for $C_{19}H_{15}F_4N_3$: C 63.16, H 4.18, N 11.63; found: C 63.10, H 4.10, N 11.73.

Data for **2e**: Yield, 72.2%; mp, 88−90 °C. ^{1}H NMR (300 MHz) δ: 2.59 (s, 3H, CH_3), 4.57−4.61 (b, 1H, NH), 4.72 (d, 1H, J_H = 5.7 Hz, CH_2), 6.95 (s, 1H, pyridazine), 7.28−7.32 (m, 4H, 4ArH), 7.62−7.73 (m, 4H, 4ArH); HRMS (ESI) for $[C_{19}H_{15}ClF_3N_3 + 1]^+$, calcd: 378.0995; found: 378.0997.

Data for **2f**: Yield, 73.7%; mp, 99−101 °C. ^{1}H NMR (300 MHz) δ: 2.58 (s, 3H, CH_3), 4.82 (d, 1H, J_H = 5.7 Hz, CH_2), 4.89−4.93 (b, 1H, NH), 6.93 (s, 1H, pyridazine), 7.20−7.22 (m, 2H, 2ArH), 7.32−7.37 (m, 1H, ArH), 7.56−7.74 (m, 5H, 5ArH); Anal calcd for $C_{19}H_{15}ClF_3N_3$: C 60.40, H 4.00, N 11.12; found: C 60.60, H 4.10, N 10.92.

Data for **2g**: Yield, 83.3%; mp, 178−180 °C. ^{1}H NMR (300 MHz) δ: 1.54 (d, 3H, J_H = 5.4 Hz, CH_3), 2.56 (s, 3H, CH_3), 4.49−4.56 (b, 1H, NH), 5.45−5.55 (m, 1H, CH), 6.90 (s, 1H, pyridazine), 7.22−7.37 (m, 5H, 5ArH), 7.63−7.73 (m, 4H, 4ArH); Anal calcd for $C_{20}H_{18}F_3N_3$: C 67.22, H 5.08, N 11.76; found: C 67.30, H 5.18, N 11.59.

Data for **2h**: Yield, 68.4%; mp, 101−103 °C. ^{1}H NMR (300 MHz) δ: 1.51 (d, 3H, J_H = 6.9 Hz, CH_3), 2.56 (s, 3H, CH_3), 4.48−4.51 (b, 1H, NH), 5.40−5.47 (m, 1H, CH), 6.91−7.01 (m, 3H, 3ArH), 7.30−7.35 (m, 2H, 2ArH), 7.58−7.75 (m, 4H, 4ArH); Anal calcd for $C_{20}H_{17}F_4N_3$: C 64.00, H 4.56, N 11.19; found: C 64.04, H 4.33, N 11.16.

Data for **2i**: Yield, 61.5%; mp, 118−120 °C. ^{1}H NMR (300 MHz) δ: 1.50 (d, 3H, J_H = 6.9 Hz, CH_3), 2.55 (s, 3H, CH_3), 4.42−4.51 (b, 1H, NH), 5.35−5.47 (m, 1H, CH), 6.91 (s, 1H, pyridazine), 7.24−7.31 (m, 4H, 4ArH), 7.54−7.76 (m, 4H, 4ArH); Anal calcd for $C_{20}H_{17}ClF_3N_3$; C 61.31, H 4.37, N 10.72; found: C 61.08, H 4.20, N 10.48.

Data for **2j**: Yield, 66.7%; mp, 124−126 °C. ^{1}H NMR (300 MHz) δ: 2.58 (s, 3H, CH_3), 2.96 (t, 2H, J_H = 6.6 Hz, CH_2), 3.78−3.84 (m, 2H, CH_2), 4.08−4.34 (b, 1H, NH), 6.88 (s, 1H, pyridazine), 7.12−7.26 (m, 5H, 5ArH), 7.39 (d, 1H, J_H = 7.8 Hz, ArH), 7.50−7.55 (m, 2H, 2ArH), 7.67 (d, 1H, J_H = 7.8 Hz, ArH); Anal calcd for $C_{20}H_{18}F_3N_3$: C 67.22, H 5.08, N 11.76; found: C 67.15, H 5.26, N 11.60.

Data for **2k**: Yield, 54.5%; mp, 140−141 °C. ^{1}H NMR (300 MHz) δ: 2.66 (s, 3H, CH_3), 6.28 (s, 1H, NH), 6.98−7.07 (m, 2H, 2ArH), 7.23−7.30 (m, 2H, 2ArH), 7.55−7.78 (m, 6H, 6ArH); Anal calcd for $C_{18}H_{14}F_3N_3$: C 65.65, H 4.28, N 12.76; found: C 65.40, H 4.46, N 12.51.

Data for **2l**: Yield, 70.6%; mp, 136−137 °C. ^{1}H NMR (400 MHz) δ: 2.07 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 6.20 (s, 1H, NH), 6.92−7.16 (m, 4H, 4ArH), 7.23−7.30 (m, 2H, 2ArH), 7.63−7.75 (m, 4H, 4ArH), 8.03 (d, 1H, J_H = 8.0 Hz, ArH); Anal calcd for $C_{19}H_{16}F_3N_3$: C 66.46, H 4.70, N 12.24; found: C 66.40, H 4.68, N 12.10.

Data for **2m**: Yield, 58.5%; mp, 118−119 °C. ^{1}H NMR (300 MHz) δ: 2.31 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 6.24 (s, 1H, NH), 6.82 (d, 1H, J_H = 7.5 Hz, ArH), 7.06 (s, 1H, ArH), 7.16 (t, 1H, J_H = 7.8 Hz, ArH), 7.21 (d, 1H, J_H = 7.8 Hz, ArH), 7.64−7.77 (m, 4H, 4ArH); Anal calcd for $C_{19}H_{16}F_3N_3$: C 66.46, H 4.70, N 12.24; found: C 66.50, H 4.43, N 12.20.

Data for **2n**: Yield, 64.7%; mp, 147−148 °C. ^{1}H NMR (300 MHz) δ: 2.29 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.20 (s, 1H, NH), 7.04 (s, 1H, ArH), 7.09 (d, 2H, J_H = 8.1 Hz, 2ArH), 7.45 (d, 2H, J_H = 8.4 Hz, 2ArH), 7.64−7.77 (m, 4H, 4ArH); Anal calcd for $C_{19}H_{16}F_3N_3$: C 66.46, H 4.70, N 12.24; found: C 66.20, H 4.85, N 11.97.

Data for **2o**: Yield, 55.6%; mp, 144−145 °C. ^{1}H NMR (300 MHz) δ: 2.05 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.09 (s, 1H, NH), 6.93−7.05 (m, 3H, 3ArH), 7.61−7.87 (m, 5H, 5ArH); Anal calcd for $C_{20}H_{18}F_3N_3$: C 67.22, H 5.08, N 11.76; found: C 67.03, H 5.10, N 11.64.

Data for **2p**: Yield, 61.1%; mp, 156−157 °C. ^{1}H NMR (300 MHz) δ: 2.66 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 6.81−7.07 (m, 4H, 4ArH), 7.35 (s, 1H, NH), 7.69−7.83 (m, 4H, 4ArH), 8.82−8.86 (m, 1H, ArH); Anal calcd for $C_{19}H_{16}F_3N_3O$: C 63.51, H 4.49, N 11.69; found: C 63.40, H 4.40, N 11.85.

Data for **2q**: Yield, 66.7%; mp, 136−137 °C. ^{1}H NMR (300 MHz) δ: 2.63 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.13 (s, 1H, NH), 6.83 (d, 2H, J_H = 9.0 Hz, 2ArH), 7.03 (s, 1H, ArH), 7.45 (d, 2H, J_H = 9.0 Hz, 2ArH), 7.66−7.76 (m, 4H, 4ArH); Anal calcd for $C_{19}H_{16}F_3N_3O$: C 63.51, H 4.49, N 11.69; found: C 63.44, H 4.30, N 11.69.

Data for **2r**: Yield, 57.1%; mp, 116−117 °C. ^{1}H NMR (300 MHz) δ: 2.68 (s, 3H, CH_3), 6.67 (s, 1H, NH), 6.93−7.19 (m, 4H, 4ArH), 7.72−7.76 (m, 4H, 4ArH), 8.66−8.71 (m, 1H, ArH); Anal calcd for $C_{18}H_{13}F_4N_3$: C 62.25, H 3.77, N 12.10; found: C 62.10, H 3.95, N 12.05.

Data for **2s**: Yield, 51.4%; mp, 163−164 °C. ^{1}H NMR (300 MHz) δ: 2.65 (s, 3H, CH_3), 6.20 (s, 1H, NH), 6.95−7.06 (m, 3H, 3ArH), 7.49−7.54 (m, 2H, 2ArH), 7.68−7.79 (m, 4H, 4ArH); Anal calcd for $C_{18}H_{13}F_4N_3$: C 62.25, H 3.77, N 12.10; found: C 62.19, H 3.71, N 12.34.

Data for **2t**: Yield, 58.3%; mp, 98−99 °C. ^{1}H NMR (400 MHz) δ: 2.68 (s, 3H, CH_3), 6.90−8.86 (m, 10H, 9ArH + NH); Anal calcd for $C_{18}H_{13}ClF_3N_3$: C 59.43, H 3.60, N 11.55; found: C 59.40, H 3.76, N 11.39.

Data for **2u**: Yield, 63.9%; mp, 139−140 °C. ^{1}H NMR (300 MHz) δ: 2.67 (s, 3H, CH_3), 6.31 (s, 1H, NH), 6.95−7.41 (m, 4H, 4ArH), 7.68−7.79 (m, 5H, 5ArH); Anal calcd for $C_{18}H_{13}ClF_3N_3$: C 59.43, H 3.60, N 11.55; found: C 59.50, H 3.40, N 11.58.

Data for **2v**: Yield, 52.8%; mp, 164−166 °C. ^{1}H NMR (300 MHz) δ: 2.66 (s, 3H, CH_3), 6.27 (s, 1H, NH), 7.08 (s, 1H, ArH), 7.24 (d, 2H, J_H = 9.0 Hz, 2ArH), 7.55 (d, 2H, J_H = 8.7 Hz, 2ArH), 7.68−7.80 (m, 4H, 4ArH); Anal calcd for $C_{18}H_{13}ClF_3N_3$: C 59.43, H 3.60, N 11.55; found: C 59.20, H 3.50, N 11.54.

Data for **2w**: Yield, 48.8%; mp, 147−148 °C. ^{1}H NMR (300 MHz) δ: 2.68 (s, 3H, CH_3), 6.28 (s, 1H, NH), 7.10−7.14 (m, 3H, 3ArH), 7.46−7.50 (m, 1H, ArH), 7.68−7.82 (m, 5H, 5ArH); Anal calcd for $C_{18}H_{13}BrF_3N_3$: C 52.96, H 3.21, N 10.29; found: C 52.71, H 3.26, N 10.31.

Data for **2x**: Yield, 36.6%; mp, 175−176 °C. ^{1}H NMR (300 MHz) δ: 2.66 (s, 3H, CH_3), 6.26 (s, 1H, NH), 7.08 (s, 1H, ArH), 7.39 (d, 2H, J_H = 9.0 Hz, 2ArH), 7.51 (d, 2H, J_H = 9.0 Hz, 2ArH), 7.67−7.80 (m,

4H, 4ArH); Anal calcd for $C_{18}H_{13}BrF_3N_3$: C 52.96, H 3.21, N 10.29; found: C 52.70, H 3.45, N 10.05.

Data for **2y**: Yield, 52.5%; mp, 113−114 °C. ^{1}H NMR (300 MHz) δ: 2.68 (s, 3H, CH_3), 6.42 (s, 1H, NH), 7.12 (s, 1H, ArH), 7.25 (d, 1H, J_H = 7.5 Hz, ArH), 7.39 (t, 1H, J_H = 8.1 Hz, ArH), 7.69−7.83 (m, 6H, 6ArH); Anal calcd for $C_{19}H_{13}F_6N_3$: C 57.44, H 3.30, N 10.58; found: C 57.28, H 3.24, N 10.61.

Data for **2z**: Yield, 56.1%; mp, 148−149 °C. ^{1}H NMR (300 MHz) δ: 2.67 (s, 3H, CH_3), 6.29 (s, 1H, NH), 7.09 (s, 1H, ArH), 7.14 (d, 2H, J_H = 8.4 Hz, 2ArH), 7.60 (d, 2H, J_H = 9.0 Hz, 2ArH), 7.68−7.80 (m, 4H, 4ArH); Anal calcd for $C_{19}H_{13}F_6N_3O$: C 55.21, H 3.17, N 10.17; found: C 54.99, H 3.39, N 10.28.

Bioassays. The herbicidal activities of title compounds **2a**−**z** and reported compounds **1a**,**b** were evaluated using a previously reported procedure (*3*).

Inhibition of Growth and Chlorophyll Determination in S. polyrrhiza. S. polyrrhiza was cultivated aseptically in a medium as described in the literature (*8*). A *N*,*N*-dimethylformamide solution of the compound to be tested was applied on a piece of filter paper as droplets. After evaporation of solvent for 15 min, the filter paper was placed into an Erlenmeyer flask with 15 mL of fresh medium. The flask was then shaken for more than 10 min before 10 fronds were inoculated into each flask. Cultures of fronds were performed at 23−26 °C with a 16 h light to 8 h dark photoperiod and a light intensity of ca. 45 μE m^{-2} s^{-1}. The test was terminated after 7 days of cultivation. The mixture of the same amount of *N*,*N*-dimethylformamide and fresh medium was used as a control. The changes in Chl content of fronds in each flask were analyzed and recorded as a percentage of the control.

Chl was measured according to the method described in ref *9*. Briefly, Chl in plant materials was extracted with 96% ethanol overnight at 4 °C. After brief centrifugation, the supernatant was used to measure the OD at 665 and 649 nm, respectively. The content of Chl in plant material was finally calculated by the following formula: Chl content = $(6.10A_{665} + 20.04A_{649}) \times$ total volume of extract/FW (μg/g).

Glasshouse Tests. The emulsions of purified compounds were prepared by being dissolved in 100 μL of *N*,*N*-dimethylformamide with the addition of a small amount of Tween 20 and water. The mixture of the same amount of water, *N*,*N*-dimethylformamide, and Tween 20 was used as a control. The solutions of test compounds were sprayed using a laboratory belt sprayer delivering a 750 L/ha spray volume.

Pre-emergence. Sandy clay (100 g) in a plastic box (11 cm × 7.5 cm × 6 cm) was wetted with water. Sprouting seeds (*15*) of the weed under test were planted in fine earth (0.6 cm depth) in the glasshouse and sprayed with the test compound solution at 750 g/ha.

Postemergence. Seedlings (one leaf and one stem) of the weed were sprayed with the test compound solution at 750, 600, 300, 150, or 75 g/ha. For both methods, the fresh weights of the aboveground portions were determined 24 days later, and the percent inhibition relative to the controls was calculated. There were two replicates for each treatment.

RESULTS AND DISCUSSION

Synthesis. In a previous paper (*3*), intermediate **7** was synthesized through 3-(trifluoromethylphenyl)magnesium bromide, and the yield was low (38.6%). Literature references mentioning detonations of trifluoromethylphenyl Grignard reagents surfaced (*10, 13*). Pfizer scientists reported a violent explosion of 3-(trifluoromethylphenyl)magnesium bromide, resulting in extensive laboratory damage (*14*). Another report mentioned the detonation of 4-(trifluoromethylphenyl)magnesium bromide resulting in destruction of a factory and loss of life (*15*). The trifluoromethylphenyl moiety is frequently encountered in pharmaceutical drug, catalysts, and synthetic intermediates (*16*), so we need a safe and reliable preparation of this valuable intermediate. In this paper, we explored another way to synthesize intermediate **7**. Starting with (3-trifluoromethylphenyl)acetic acid ethyl ester **3**, it can be converted easily to **4** by bromization with 98.4% yield. Further reaction of **4** with acetylacetic ether could proceed readily in the presence of K_2CO_3 to give **5**, which can be used for the next step without purification. Pyridazinone **6** was synthesized from **5** by hydrolysis, decarboxylation, and ring closure reactions with hydrazine hydrate in 55.7% yield. Compound **7** was obtained by the dehydrogenation of **6** with K_2CO_3/DMSO in 94.0% yield. Compound **8** was synthesized by the reaction of **7** with phosphorous oxychloride in high yield (98.0%). Compounds **2a**−**z** were obtained by heating **8** with the corresponding amine via a neat reaction. The title compounds were identified by ^{1}H NMR. The measured elemental analyses are also consistent with the corresponding calculated values.

Table 1. Activities of Compounds against *S. polyrrhiza*

				Chl inhibition (%)	
compd	*n*	R^2	R^1	10 μg/mL	1 μg/mL[a]
2a	1	H	H	86	83
2b	1	4-CH_3	H	74	34
2c	1	4-OCH_3	H	84	51
2d	1	2-F	H	81	77
2e	1	4-Cl	H	85	25
2f	1	2-Cl	H	90	73
2g	1	H	CH_3	63	31
2h	1	4-F	CH_3	79	47
2i	1	4-Cl	CH_3	23	15
2j	2	H	H	100	100
2k	0	H		100	100
2L	0	2-CH_3		83	65
2m	0	3-CH_3		100	100
2n	0	4-CH_3		96	95
2o	0	2,4-$(CH_3)_2$		72	69
2p	0	2-OCH_3		82	62
2q	0	4-OCH_3		100	100
2r	0	2-F		100	100
2s	0	4-F		100	100
2t	0	2-Cl		100	82
2u	0	3-Cl		100	100
2v	0	4-Cl		100	87
2w	0	3-Br		100	100
2x	0	4-Br		63	59
2y	0	3-CF_3		100	100
2z	0	4-OCF_3		83	65
1a	R = $CO_2C_2H_5$			100	−
1b	R = *n*-C_3H_7			90	−
diflufenican				94	90

[a] Error of these number is 2%. −: not tested.

Biological Assay. *S. polyrrhiza* (L.) Schleiden, which is the largest duckweed (giant duckweed) in the Lemnaceae family, frequently is used to determine the potential impacts of heavy metals and other pollutants in environmental risk assessments. It is a sensitive plant that could exhibit effects when treated in low concentrations (*17, 18*). Herein, we used it to evaluate the bleaching activities of the title compounds (**Table 1**). In addition, the herbicidal activities also were bioassayed in the glasshouse on four weeds representative of monocotyledonous and dicotyledonous plants (**Tables 2** and **4**) (*3, 19, 20*). Through these tests, we can comprehensively evaluate the bleaching and herbicidal activities of the title compounds.

In our previous work, novel 4-(3-trifluoromethylphenyl)pyridazinone derivatives were synthesized, and bioassay results indicated that modification of the hydrogen atom at N2 in the pyridazinone ring of **7** can increase the activities. Most of these compounds can inhibit Chl biosynthesis at 10 μg/mL, and some compounds control more than 80% *D. adscendens* at 300 g/ha in pre-emergence applications (*3*). To find more high activity compounds and further investigate the structure−activity relationship of the 3-position in the pyridazine ring, the title compounds were synthesized by the replacement of pyridazinone

Table 2. Herbicidal Activities of Compounds (Percent Inhibition)[a] in Greenhouse Test (750 g/ha)

		Brassica campestris		*Amaranthus retroflexus*		*Echinochioa crus-galli*		*Digitaria adscendens*	
compd	log P[b]	pre	post	pre	post	pre	post	pre	post
2a	5.55	0	30	4	27	0	8	7	23
2b	6.04	16	20	31	2	78	0	64	54
2c	5.42	0	14	2	18	22	0	0	8
2d	5.71	24	49	8	44	0	10	0	24
2e	6.11	7	27	3	44	9	15	0	18
2f	6.11	0	34	36	33	3	26	1	29
2g	5.87	12	0	10	7	10	43	12	54
2h	6.03	13	0	1	1	14	0	28	57
2i	6.43	2	8	16	17	13	27	11	67
2j	5.83	0	45	16	30	4	13	27	11
2k	5.78	48	99[c]	33	60[c]	43	15	43	0
2L	6.27	7	86[c]	0	38	0	10	11	1
2m	6.27	18	79[c]	81[c]	64[c]	8	29	7	6
2n	6.27	82[c]	99[c]	90[c]	85[c]	0	2	17	18
2o	6.76	10	22	0	0	0	25	7	11
2p	5.66	9	6	4	30	0	11	0	0
2q	5.66	13	44	55	27	5	28	2	89
2r	5.94	18	100[c]	0	100[c]	0	21	15	40
2s	5.94	8	88[c]	19	85[c]	2	23	0	0
2t	6.34	9	93[c]	10	41	2	24	0	19
2u	6.34	3	63	12	38	0	7	0	5
2v	6.34	18	100[c]	0	100[c]	0	0	0	0
2w	6.61	14	17	0	30	0	0	0	0
2x	6.61	26	36	54	45	15	13	14	26
2y	6.71	0	96[c]	0	95[c]	0	8	0	0
2z	7.31	0	50	35	26	0	21	5	35
1a[d]	2.81	87[c]	55	100[c]	61	46	0	100[c]	13
1b[d]	3	61	6	51	28	82[c]	5	100[c]	19
diflufenican	4.99	71	98[c]	90[c]	100[c]	94[c]	67	100[c]	83[c]

[a] Error of these numbers is 2%. [b] Calculated by ChemBioDraw Ultra 11.0. [c] Leaves emerged after treatments were completely white. [d] Application rate 600 g/ha.

Table 3. MR Value of Substitutent

R^2	H	F	Cl	Br	CH_3	OCH_3	CF_3	OCF_3
MR	1.03	0.92	6.03	8.88	5.65	7.87	5.02	7.86

with a pyridazine ring and the introduction of a substituted amino group in the 3-position.

As shown in **Table 1**, some compounds showed excellent bleaching activities; for example, **2j**, **2k**, **2m**, **2q**, **2r**, **2s**, **2u**, **2w**, and **2y** can inhibit the synthesis of Chl completely (Chl inhibition = 100%) at 1 μg/mL, which is better than diflufenican. At the same time, it can be seen that the target compounds in which the amines are (un)substituted phenyl amines ($n = 0$) mostly showed a better bleaching activity than (un)substituted benzyl amines ($n = 1$) (e.g., Chl inhibition: **2k** > **2a**; **2n** > **2b**; **2q** > **2c**; **2r** > **2d**; **2v** > **2e**; and **2t** > **2f** at 10 or 1 μg/mL). When the substituted amines are α-methylbenzyl amines, the bleaching activity is much lower (e.g., Chl inhibition: **2a** > **2g** and **2e** > **2i** at 10 or 1 μg/mL). The activity of **2j** in which the amine is phenethyl amine ($n = 2$) is better than **2a**. Within the (un)substituted phenyl derivatives (**2k**−**z**), meta-substituted compounds always displayed better bleaching activities. For example, **2m**, **2u**, **2w**, and **2y**, which have meta substituents, can completely inhibit the synthesis of Chl at 1 μg/mL.

From the biological assay results in **Table 2**, it was found that compounds with (un)substituted phenyl amine in the 3-position of the pyridazine ring have a higher level of herbicidal activities. As compared to **1** and **2**, **1** showed better activities in pre-emergence applications. However, from **2k**−**z**, most of the compounds exhibited more efficient activities in postemergence applications against dicotyledonous plants *B. campestris* and *A. retroflexus*. For example, **2v** (**Table 4**) can control (inhibition >80%) *B. campestris* at the rate of 150 g/ha in postemergence applications, which is different from **1a** and **1b** (*3*). Modification of the structure **1** to **2** increased the overall lipophilicity of the molecule, which can be measured by log P (*21*). Log P listed in **Table 2** showed that compounds **2** have larger values than **1a**,**b**. This may result in the difference in their activities and application times.

Table 4. Herbicidal Activities of Compounds (Percent Inhibition)[a] in Greenhouse (Postemergence Treatment)

compd	rate (g/ha)	*B. campestris*	*A. retroflexus*	compd	rate (g/ha)	*B. campestris*	*A. retroflexus*
2k	600	92[b]	61[b]	**2s**	600	93[b]	64[b]
	300	84[b]	43[b]		300	83[b]	55[b]
	150	74[b]	41[b]		150	58[b]	43[b]
	75	66[b]	18		75	55[b]	32
2m	600	42[b]	52[b]	**2v**	600	90[b]	66[b]
	300	30	25		300	89[b]	60[b]
	150	0	23		150	87[b]	45[b]
					75	52[b]	42[b]
2n	600	59[b]	59[b]	**2y**	600	88[b]	54[b]
	300	54[b]	28		300	79[b]	42[b]
	150	39	17		150	72[b]	37[b]
					75	48[b]	32
2r	600	96[b]	75[b]	diflufenican	600	98[b]	100[b]
	300	88[b]	58[b]		300	94[b]	74[b]
	150	67[b]	48[b]		150	88[b]	70[b]
	75	60[b]	39[b]		75	44[b]	41[b]

[a] Error of these numbers is 2%. [b] Leaves emerged after treatments were completely white.

Among the 26 compounds, compounds with $n = 0$ showed better herbicidal activities than the others. For example, **2r**, **2v**, and **2y** can control (inhibition >95%) *B. campestris* and *A. retroflexus* in postemergence treatment, and **2n** exhibited good herbicidal activities (inhibition >80%) against dicotyledonous plants *B. campestris* and *A. retroflexus* both in postemergence and in pre-emergence treatments. When n was 1 or 2, the corresponding compounds' herbicidal activities (such as **2a**−**i**) decreased remarkably. It is well-known that steric properties are one of the factors affecting biological activities of compounds. The tolerance of enzymes and receptors for the bulkiness of substrates and drugs to which they are exposed is a problem of great concern in biomedicinal/biochemical studies. MR may be crude but provides useful measures of bulk (*21*). As compared to **2k**, with the introduction of F at the ortho position, the activity increased, but bulkier substitutions (**Table 3**) (e.g., **2l**, R^2 = 2-CH_3; **2p**, R^2 = 2-OCH_3; and **2t**, R^2 = 2-Cl) decreased activity. When R_2 is at the meta position, CH_3 (**2m**) and CF_3 (**2y**) were better than other bulkier substitutions (e.g., **2u**, R^2 = 3-Cl and **2w**, R^2 = 3-Br). At the para position, the substituent can be bulkier, and **2n** (R^2 = 4-CH_3), **2s** (R^2 = 4-F), and **2v** (R^2 = 4-Cl) exhibited better activity than **2x** (R^2 = 4-Br) and **2z** (R^2 = 4-OCF_3). These results indicate that the appropriate bulkiness substituent at the right position is very important for the herbicidal activity of the compounds. Footnote *c* in **Table 2** indicates that leaves emerged after treatments were completely white, which is the character of bleaching herbicide. As compared to diflufenican, some of these compounds (e.g., **2r**, **2s**, **2v**, and **2y**) showed better selectivity to dicotyledonous plants in postemergence treatment, and further study on their selective application in crops is planned.

From **Tables 1** and **2**, we notice that most compounds that showed better herbicidal activities in greenhouse tests had equal bleaching activities in the *S. polyrrhiza* test (e.g., **2k**, **2m**, **2n**,

2r, **2s**, **2v**, and **2y**). Nevertheless, some compounds with a larger Chl inhibition value did not exhibit a higher herbicidal efficacy (e.g., **2j**, **2q**, **2u**, and **2w**). These results may be because different plant species exhibited different sensitivities to the same compound, and *S. polyrrhiza* is a sensitive plant, so it can detect activities in low concentrations.

Target compounds that showed excellent herbicidal activities against *B. campestris* and *A. retroflexus* also were bioassayed at decreasing rates in postemergence (**Table 4**). Compounds **2k**, **2r**, **2s**, **2v**, and **2y** exhibited equal or higher herbicidal activities against *B. campestris* with diflufenican at a rate of 75 g/ha. Compounds **2r** and **2v** showed equal activities with diflufenican against *A. retroflexus* at 75 g/ha. These results indicate that changing the structure **1** by replacement of pyridazinone with a pyridazine ring and introducing (un)substituted phenyl amino groups in the 3-position of the pyridazine can enhance herbicidal activities.

In conclusion, we described here a practical and safe procedure for the preparation of intermediate **7** from ethyl 2-(3-trifluoromethylphenyl)acetate in five steps with a moderate total yield of 51.5%. Twenty-six novel 3-N-substituted amino-6-methyl-4-(3-trifluoromethylphenyl)pyridazine derivatives were synthesized. The results of bioassays showed that some of these title compounds exhibited equal or higher herbicidal activities against dicotyledonous plants *B. campestris* and *A. retroflexus* in postemergence treatments with diflufenican at a rate of 75 g/ha. It was found that a suitable substituent amine at the 3-position of the pyridazine ring was essential for a high herbicidal activity. All results in this paper will be very useful for later research.

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