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# Design and Syntheses of Novel *N*-(Benzothiazol-5-yl)-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and *N*-(Benzothiazol-5-yl)isoindoline-1,3-dione as Potent Protoporphyrinogen Oxidase Inhibitors

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**ABSTRACT:** Discovery of protoporphyrinogen oxidase (PPO, EC 1.3.3.4) inhibitors has been one of the hottest research areas in the field of herbicide development for many years. As a continuation of our research work on the development of new PPO-inhibiting herbicides, a series of novel *N*-(benzothiazol-5-yl)-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-diones (**1a**−**p**) and *N*-(benzothiazol-5-yl)isoindoline-1,3-diones (**2a**−**h**) were designed and synthesized according to the ring-closing strategy of two *ortho*-substituents. The bioassay results indicated that some newly synthesized compounds exhibited higher PPO inhibition activity than the control of sulfentrazone. Compound **1a**, *S*-(5-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-6-fluorobenzothiazol-2-yl) *O*-methyl carbonothioate, was identified as the most potent inhibitor with $k_i$ value of 0.08 $\mu$M, about 9 times higher than that of sulfentrazone ($k_i$ = 0.72 $\mu$M). Further green house assay showed that compound **1b**, methyl 2-((5-(1,3-dioxo-4,5,6,7-tetrahydro-1H-isoindol-2(3*H*)-yl)-6-fluorobenzothiazol-2-yl)thio)acetate, exhibited herbicidal activity comparable to that of sulfentrazone even at a concentration of 37.5 g ai/ha. In addition, among six tested crops, wheat exhibited high tolerance to compound **1b** even at a dosage of 300 g ai/ha. These results indicated that compound **1b** might have the potential to be developed as a new herbicide for weed control of wheat field.

**KEYWORDS:** protoporphyrinogen oxidase, 4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, isoindoline-1,3-dione, benzothiazole, herbicide

## INTRODUCTION

Protoporphyrinogen oxidase (PPO, E.C. 1.3.3.4) is the last enzyme in the common tetrapyrrole biosynthesis pathway before the pathway branches toward chlorophyll (in plant) and heme (in animal) synthesis.[1] PPO has been identified as one of the most significant targets for several chemical families of herbicides such as diphenylethers,[2] phenylpyrazoles,[3] oxadiazoles,[4] triazolinones,[5] thiadiazoles,[6] pyrimidineones,[7] oxazolidinediones,[8] isoxazoles,[9] and *N*-phenyl phthalimides[10] that have been introduced into market for many years. These PPO-inhibiting herbicides can cause peroxidative destruction of cellular membrane and bleaching of plant tissues in the presence of light. In contrast to the other herbicides, PPO inhibitors have many advantages such as low toxicity, low use-rate (10−50 g ai/ha), broad herbicidal spectrum (active against both monocotyledon and dicotyldon weeds), quick onset of action (necrosis within 24 h), long lasting effect and other environmentally benign characteristics (e.g., low toxicity).[11]

Among the existing PPO inhibitors, *N*-phenyl phthalimide has been a very interesting and hot research area due to its broad structural diversity.[12−16] As shown in Figure 1, chlorphthalim is the pioneering compound of the *N*-phenyl phthalimide family. Structural optimization of chlorphthalim has resulted in the discovery of a lot of structurally diverse commercial compounds, such as cinidon-ethyl,[17] flumiclorac-pentyl,[18,19] and flumioxazin.[20,21] It has been established that *N*-phenyl phthalimide has a common structural feature of *N*-2,4,5-trisubstituted phenylnitrogen to obtain optimum herbicidal activity. We are very interested in the structure of flumioxazin, which integrated its *ortho*-substituents at the 4- and 5-positions into a heterocycle of 2*H*-benzo[1,4]oxazin-3(4*H*)-one.

It is well-known that the derivatives of benzothiazole always possess a wide range of biological activities including antitumor, antiviral, antimicrobial, and antiglutamate properties.[22−25] Some of benzothiazole derivatives have also been widely used in agriculture. For example, bentaluron, chlobenthiazone and TCMTB have been used as commercial fungicides for many years[26,27] (Figure 2). In addition, some 2-benzothiazole thioether derivatives also possess anticandious, antimicrobacterial, photosynthesis-inhibiting, fungicidal, insecticidal and herbicidal properties.[28−31] Previously, we have designed and discovered some benzothiazole-type ring-closing analogues of oxadiargyl with high PPO-inhibiting activity and green house herbicidal activity.[32] Therefore, as a continuation of our research work on the development of new PPO inhibitors,[13−15,32−36] we are very interested in the design and synthesis of *N*-phenyl phthalimide bearing benzothiazole substructure, *N*-(benzothiazol-5-yl)-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione **1a**−**p** as shown in Figure 3. As a comparison, we also synthesized some *N*-(benzothiazol-5-yl)- isoindoline-1,3-dione derivatives **2a**−**h**. Herein, we report the detailed syntheses,

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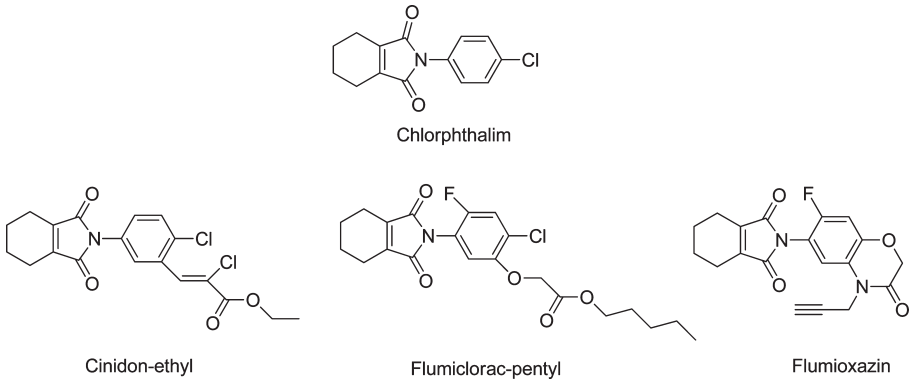


**Figure 1.** Chemical structures of some commercial *N*-phenyl phthalimides.

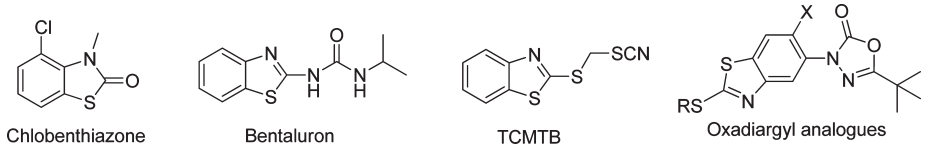


**Figure 2.** Chemical structures of some typical benzothiazole derivatives.

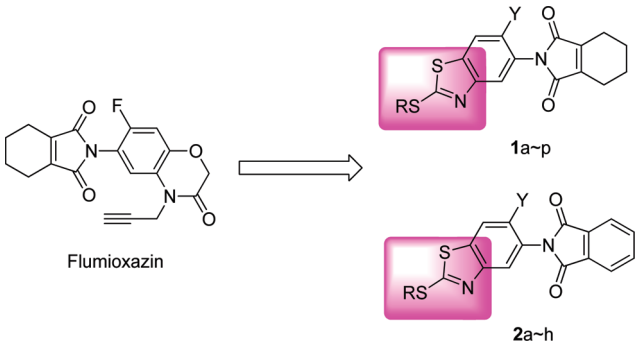


**Figure 3.** Design strategy of the title compounds.

PPO inhibition activity and herbicidal activities of compounds **1a**−**p** and **2a**−**h**, and the results indicate that these compounds display good PPO inhibition activity and promising herbicidal activity.

## MATERIALS AND METHODS

All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried in a routine way and redistilled before use. $^1$H NMR spectra were recorded on a VARIAN Mercury-Plus 600 or 400 spectrometer in $CDCl_3$ or DMSO-$d_6$ with TMS as the internal reference. Mass spectral data were obtained on a ThermoFisher Mass platform DSQII by electrospray ionization (ESI-MS). Elemental analyses were performed on a Vario EL III elementary analysis instrument. Melting points were taken on a Buchi B-545 melting point apparatus and are uncorrected.

**Preparation of 2,4-Disubstituted 5-Nitroanilines (4a and 4b).** A solution of $HNO_3$ (2.77 g, 44 mmol) in concentrated $H_2SO_4$ (43.1 g, 440 mmol) was added dropwise to a stirred mixture of **3a**,**b** (40 mmol) and concentrated $H_2SO_4$ (200 mL) in an ice bath (−20 °C). The complete addition took about 15 min. After stirring for 3 h, the solution was slowly poured into a mixture of ice and water (1000 mL). The resulted solid was collected by filtration and washed with water (2 L), then dried to give the desired solid products.

*Data for* ***4a***. Yield: 46%; mp 102.3−104.5 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 4.26 (bs, 2H), 7.41 (d, $J$ = 10.2 Hz, 1H), 7.43 (d, $J$ = 6.6 Hz, 1H); EI-MS 233.9 $(M)^+$.

*Data for* ***4b***. Yield: 42%; mp 101.3−103.9 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.38 (bs, 2H), 7.32 (s, 1H), 7.44 (s, 1H); EI-MS 206.8 $(M)^+$.

**Preparation of 6-Fluoro-2-mercapto-5-nitrobenzothiazole (5a) and 6-Chloro-2-mercapto-5-nitrobenzothiazole (5b).** Potassium *O*-ethyl carbonodithioate (90 mmol, 14.43 g) was dissolved in 300 mL of DMF, and then, compound **4a**,**b** was added. The resulted mixture was heated to a temperature of 80−85 °C. After the reaction completed according to the TLC detection, the solution was slowly poured into 500 mL of water and acidified with concentrated hydrogen chloride to pH = 1−2. The resulted solid was filtered off, dried, and recrystallized to afford compound **5a** or **5b**.

*Data for* ***5a***. Yield: 66%; mp 190.1−191.3 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 7.85 (d, $J$ = 6.6 Hz, 1H), 8.02 (d, $J$ = 11.4 Hz, 1H), 14.11(bs, 1H); ESI-MS 229.0 $(M - H)^-$.

*Data for* ***5b***. Yield: 87%; mp 230.3−232.1 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 7.84 (s, 1H), 8.17 (s, 1H), 14.24 (bs, 1H); ESI-MS 245.0 $(M - H)^-$.

**Preparation of 6-Fluoro-2-mercapto-5-aminobenzothiazole (6a) and 6-Chloro-2-mercapto-5-aminobenzothiazole (6b).** Fe powder was added portionwise to a stirred solution of $NH_4Cl$ (0.83 g) and **5a**,**b** (10.4 mmol) in a mixture of EtOH/$H_2O$ (v/v: 10:1, 220 mL) at reflux temperature. After TLC detection showing that reaction was finished, the reaction mixture was filtered and concentrated to dryness. The residue was dissolved in water (200 mL) and extracted with EtOAc (200 mL), and the organic phase was washed with brine (150 mL), dried, filtered, and then concentrated to give the desired solid products.

*Data for* ***6a***. Yield: 31%; mp 250.1−252.3 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 5.54 (s, 2H), 6.73 (d, $J$ = 9.0 Hz, 1H), 7.39(d, $J$ = 10.2 Hz, 1H), 13.43(bs, 1H); ESI-MS 199.0 $(M - H)^-$.

*Data for* ***6b***. Yield: 76%; mp 256.7−258.4 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 5.69 (s, 2H), 6.77 (s, 1H), 7.56 (s, 1H), 13.47 (bs, 1H); ESI-MS 216.9 $(M + H)^+$.


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**Preparation of 2-(6-Fluoro-2-mercaptobenzothiazol-5-yl)-4,5,6,7-tetrahydro-1*H*- isoindole-1,3(2*H*)-dione (7a) and 2-(6-Chloro-2-mercaptobenzothiazol-5-yl)-4,5,6,7- tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (7b).** A solution of compound **6a** (or **6b**) (13.7 mmol) and 4,5,6,7-tetrahydroisobenzofuran-1,3-dione (2.31 g, 15.2 mmol) in glacial acetic acid (160 mL) was refluxed for about 3 h. After the reaction was complete according to the TLC detection, the solution was slowly poured into 500 mL of water. The resulting mixture was stirred until the solid appeared. Then, after filtration, the obtained solid was dried and recrystallized to afford compound **7a** or **7b**.

*Data for* ***7a***. Yield: 58%; mp 283.4−285.2 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 1.75 (s, 4H), 2.35 (s, 4H), 7.34 (d, $J$ = 6.6 Hz, 1H), 7.87 (d, $J$ = 9.0 Hz, 1H), 14.00 (bs, 1H); ESI-MS 333.0 $(M - H)^-$.

*Data for* ***7b***. Yield: 77%; mp 296.3−298.4 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 1.75 (s, 4H), 2.36 (s, 4H), 7.40 (s, 1H), 8.07 (s, 1H), 14.09 (bs, 1H); ESI-MS 348.9 $(M - H)^-$.

**General Procedure for the Preparation of the Title Compounds 1a−p.** $K_2CO_3$ powder (0.33 g, 2.4 mmol) was added to a solution of **7a** (or **7b**) (1.2 mmol) in acetone (20 mL). After stirring for 10 min at room temperature, halogen derivative (RX, 1.8 mmol) in acetone solution was added dropwise to the mixture. The resulted mixture reacted for about 30 min and then was filtered and concentrated. The residue was purified *via* flash chromatography to give the pure products **1a−p** in yields of 43−76%.

*Data for* ***1a***. Yield: 55%; mp 176−178 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.85 (s, 4H), 2.47 (s, 4H), 4.00 (s, 3H), 7.72 (d, $J$ = 9.0 Hz, 1H), 7.88 (d, $J$ = 6.0 Hz, 1H); ESI-MS 393.0 $(M + H)^+$. Anal. Calcd for $C_{17}H_{13}FN_2O_4S_2$: C, 52.03; H, 3.34; N, 7.14. Found: C, 51.82; H, 3.30; N, 6.93.

*Data for* ***1b***. Yield: 43%; mp 86−87 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.85 (s, 4H), 2.46 (s, 4H), 3.79 (s, 3H), 4.17 (s, 2H), 7.58 (d, $J$ = 9.0 Hz, 1H), 7.72 (d, $J$ = 6.0 Hz, 1H); ESI-MS 407.1 $(M + H)^+$. Anal. Calcd for $C_{18}H_{15}FN_2O_4S_2$: C, 53.19; H, 3.72; N, 6.89. Found: C, 53.34; H, 3.90; N, 6.71.

*Data for* ***1c***. Yield: 48%; mp 98−99 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.28 (t, $J$ = 7.2 Hz, 3H), 1.85 (s, 4H), 2.46 (s, 4H), 4.15 (s, 2H), 4.23 (q, $J$ = 7.2 Hz, 2H), 7.58 (d, $J$ = 9.0 Hz, 1H), 7.71 (d, $J$ = 6.6 Hz, 1H); ESI-MS 421.1 $(M + H)^+$. Anal. Calcd for $C_{19}H_{17}FN_2O_4S_2$: C, 54.27; H, 4.08; N, 6.66. Found: C, 54.47; H, 4.36; N, 6.65.

*Data for* ***1d***. Yield: 66%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.26 (t, $J$ = 7.2 Hz, 3H), 1.70 (d, $J$ = 7.8 Hz, 3H), 1.85 (s, 4H), 2.46 (s, 4H), 4.21 (q, $J$ = 7.2 Hz, 2H), 4.66 (q, $J$ = 7.2 Hz, 1H), 7.59 (d, $J$ = 9.0 Hz, 1H), 7.73 (d, $J$ = 6.0 Hz, 1H); ESI-MS 435.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}FN_2O_4S_2$: C, 55.28; H, 4.41; N, 6.45. Found: C, 55.27; H, 4.59; N, 6.27.

*Data for* ***1e***. Yield: 49%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.27 (d, $J$ = 6.6 Hz, 6H), 1.85 (s, 4H), 2.46 (s, 4H), 4.11 (s, 2H), 5.08−5.10 (m, 1H), 7.58 (d, $J$ = 8.4 Hz, 1H), 7.70 (d, $J$ = 6.6 Hz, 1H); ESI-MS 435.0 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}FN_2O_4S_2$: C, 55.28; H, 4.41; N, 6.45. Found: C, 55.50; H, 4.70; N, 6.28.

*Data for* ***1f***. Yield: 60%; mp 124−125 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.47 (s, 9H), 1.85 (s, 4H), 2.46 (s, 4H), 4.06 (s, 2H), 7.58 (d, $J$ = 9.0 Hz, 1H), 7.70 (d, $J$ = 6.0 Hz, 1H); ESI-MS 435.0 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}FN_2O_4S_2$: C, 55.28; H, 4.41; N, 6.45. Found: C, 55.46; H, 4.60; N, 6.34.

*Data for* ***1g***. Yield: 66%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 7.2 Hz, 3H), 1.66−1.68 (m, 2H), 1.85 (s, 4H), 2.46 (s, 4H), 4.13 (t, $J$ = 7.2 Hz, 2H), 4.16 (s, 2H), 7.58 (d, $J$ = 8.4 Hz, 1H), 7.72 (d, $J$ = 6.0 Hz, 1H); ESI-MS 435.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}FN_2O4S_2$: C, 55.28; H, 4.41; N, 6.45. Found: C, 55.01; H, 4.60; N, 6.41.

*Data for* ***1h***. Yield: 60%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.27 (t, $J$ = 7.2 Hz, 3H), 1.85 (s, 4H), 2.46 (s, 4H), 2.90 (t, $J$ = 7.2 Hz, 2H),3.58 (t, $J$ = 7.2 Hz, 2H), 4.17 (q, $J$ = 7.2 Hz, 2H), 7.58 (d, $J$ = 9.0 Hz, 1H), 7.72 (d, $J$ = 6.0 Hz, 1H); ESI-MS 435.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}FN_2O_4S_2$: C, 55.28; H, 4.41; N, 6.45. Found: C, 55.24; H, 4.71; N, 6.33.

*Data for* ***1i***. Yield: 48%; mp 176−178 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.86 (s, 4H), 2.47 (s, 4H), 4.01 (s, 3H), 7.87 (s, 1H), 8.04 (s, 1H); ESI-MS 408.9 $(M + H)^+$. Anal. Calcd for $C_{17}H_{13}ClN_2O_4S_2$: C, 49.94; H, 3.20; N, 6.85. Found: C, 50.00; H, 3.31; N, 6.75.

*Data for* ***1j***. Yield: 49%; mp 166−167 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.40 (t, $J$ = 7.2 Hz, 3H), 1.86 (s, 4H), 2.47 (s, 4H), 4.45 (q, $J$ = 7.2 Hz, 2H), 7.87 (s, 1H), 8.04 (s, 1H); ESI-MS 421.3 $(M - H)^-$. Anal. Calcd for $C_{18}H_{15}ClN_2O_4S_2$: C, 51.12; H, 3.58; N, 6.62. Found: C, 51.26; H, 3.67; N, 6.36.

*Data for* ***1k***. Yield: 76%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.28 (t, $J$ = 7.2 Hz, 3H), 1.86 (s, 4H), 2.47 (s, 4H), 4.16 (s, 2H), 4.23 (q, $J$ = 7.2 Hz, 2H), 7.72 (s, 1H), 7.89 (s, 1H); ESI-MS 437.2 $(M + H)^+$. Anal. Calcd for $C_{19}H_{17}ClN_2O_4S_2$: C, 52.23; H, 3.92; N, 6.41. Found: C, 52.19; H, 4.12; N, 6.31.

*Data for* ***1l***. Yield: 54%; mp 151−152 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.26 (t, $J$ = 7.2 Hz, 3H), 1.70 (d, $J$ = 7.2 Hz, 3H), 1.86 (s, 4H), 2.47 (s, 4H), 4.20 (q, $J$ = 7.2 Hz, 2H), 4.67 (q, $J$ = 7.2 Hz, 1H), 7.73 (s, 1H), 7.90 (s, 1H); ESI-MS 451.0 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}ClN_2O_4S_2$: C, 53.27; H, 4.25; N, 6.21. Found: C, 53.44; H, 3.97; N, 6.41.

*Data for* ***1m***. Yield: 48%; mp 115−116 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.21 (t, $J$ = 7.2 Hz, 3H), 1.76 (s, 6H), 1.85 (s, 4H), 2.46 (s, 4H), 4.18 (q, $J$ = 7.2 Hz, 2H), 7.77 (s, 1H), 7.91 (s, 1H); ESI-MS 465.0 $(M + H)^+$. Anal. Calcd for $C_{21}H_{21}ClN_2O_4S_2$: C, 54.24; H, 4.55; N, 6.02. Found: C, 54.46; H, 4.67; N, 6.26.

*Data for* ***1n***. Yield: 48%; mp 88−89 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.26 (t, $J$ = 7.2 Hz, 3H), 1.86 (s, 4H), 2.47 (s, 4H), 2.90 (t, $J$ = 7.2 Hz, 2H), 3.59 (t, $J$ = 7.2 Hz, 2H), 4.17 (q, $J$ = 7.2 Hz, 2H), 7.73 (s, 1H), 7.88 (s, 1H); ESI-MS 451.0 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}ClN_2O_4S_2$: C, 53.27; H, 4.25; N, 6.21. Found: C, 53.26; H, 4.69; N, 6.17.

*Data for* ***1o***. Yield: 55%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.25 (t, $J$ = 7.2 Hz, 3H), 1.85 (s, 4H), 2.15−2.17 (m, 2H), 2.47 (s, 4H), 2.49 (t, $J$ = 7.2 Hz, 2H), 3.40 (t, $J$ = 7.2 Hz, 2H), 4.13 (q, $J$ = 7.2 Hz, 2H), 7.72 (s, 1H), 7.88 (s, 1H); ESI-MS 465.0 $(M + H)^+$. Anal. Calcd for $C_{21}H_{21}ClN_2O_4S_2$: C, 54.24; H, 4.55; N, 6.02. Found: C, 54.49; H, 4.58; N, 5.83.

*Data for* ***1p***. Yield: 69%; mp 114−117 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.85 (s, 4H), 2.47 (s, 4H), 3.79 (s, 3H), 4.18 (s, 2H), 7.73 (s, 1H), 7.89 (s, 1H); ESI-MS 421.3 $(M - H)^-$. Anal. Calcd for $C_{18}H_{15}ClN_2O_4S_2$: C, 51.12; H, 3.58; N, 6.62. Found: C, 51.29; H, 3.84; N, 6.43.

**Preparation of 2-(2,4-Disubstituted phenyl)isoindoline-1,3-dione (8a and 8b).** A solution of 2,4-disubstituted aniline (100 mmol) and phthalic anhydride (15.5 g, 105 mmol) in 150 mL of glacial acetic acid was refluxed for about 2 h. Then, the solution was slowly poured into 1000 mL of water (1000 mL). After stirring for about 30 min, the resulting solid was collected by filtration, washed with water (3 × 100 mL), and then dried to give to the desired solid products.

*Data for* ***8a***. Yield: 96%; mp 163.5−164.2 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J$ = 9.0 Hz, 1H), 7.56 (dd, $J_1$ = 1.8 Hz, $J_2$ = 9.0 Hz, 1H), 7.75 (d, $J$ = 1.8 Hz, 1H), 7.82 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H), 7.97 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H); EI-MS 358.8 $(M + Na)^+$.

*Data for* ***8b***. Yield: 81%; mp 133.0−134.8 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.26 (d, $J$ = 15.2 Hz, 2H), 7.31 (d, $J$ = 6.4 Hz, 1H), 7.81 (dd, $J_1$ = 2.4 Hz, $J_2$ = 5.4 Hz, 2H), 7.97 (dd, $J_1$ = 2.4 Hz, $J_2$ = 5.4 Hz, 2H); ESI-MS: 274.2 $(M - H)^-$.

**Preparation of 2-(2,4-Disubstituted phenyl)-5-nitroisoindoline-1,3-dione (9a and 9b).** A solution of $HNO_3$ (3.52 g, 55 mmol) in concentrated $H_2SO_4$ (48.5 g, 495 mmol) was added dropwise to a stirred mixture of **8a** (or **8b**) (50 mmol) and concentrated $H_2SO_4$

(180 mL) in an ice bath (−15 °C). The complete addition took about 15 min. After stirring for 3 h, the solution was slowly poured into a mixture of ice and water (1000 mL). The resulting solid was collected by filtration, washed with water (3 × 500 mL), and then dried to give to the desired solid products.

*Data for* ***9a***. Yield: 90%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.86 (dd, $J_1$ = 3.6 Hz, $J_2$ = 5.4 Hz, 2H), 7.98−8.01 (m, 4H); EI-MS 380.4 $(M)^+$.

*Data for* ***9b***. Yield: 88%; mp 191.5−193.7 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 9.0 Hz, 1H), 7.86 (dd, $J_1$ = 3.6 Hz, $J_2$ = 5.4 Hz, 2H), 8.00 (dd, $J_1$ = 2.4 Hz, $J_2$ = 5.4 Hz, 2H), 7.52 (d, $J$ = 7.2 Hz, 1H); EI-MS 320.4 $(M)^+$.

**Preparation of 2-(2,4-Disubstituted phenyl)-5-aminoisoindoline-1,3-dione (10a and 10b).** Fe powder (5.6 g, 99 mmol) was added portionwise to a stirred solution of $NH_4Cl$ (4 g, 74 mmol), **9a** (or **9b**) (49.7 mmol) in a mixture of EtOH/$H_2O$ (v/v: 10:1, 220 mL) at refluxing temperature. After TLC detection showed that reaction was finished, the reaction mixture was filtered and concentrated to dryness. The residue was dissolved in water (200 mL) and extracted with EtOAc (200 mL), and the organic phase was washed with brine (150 mL), dried, filtered, and then concentrated to give the desired solid products.

*Data for* ***10a***. Yield: 37%; mp 180.2−182.5 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 4.25 (bs, 2H), 6.73 (s, 1H), 7.61 (s, 1H), 7.80 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H), 7.96 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H); EI-MS 349.4 $(M)^+$.

*Data for* ***10b***. Yield: 44%; mp 165.2−167.3 °C; $^1$H NMR(600 MHz, $CDCl_3$) $\delta$ 4.05 (bs, 2H), 6.73 (d, $J$ = 6.6 Hz, 1H), 7.21 (d, $J$ = 9.0 Hz, 1H), 7.80 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H), 7.96 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H); ESI-MS 290.7 $(M + H)^+$.

**Preparation of 2-(2-Mercapto-6-chlorobenzothiazol-5-yl)isoindoline-1,3-dione (11a) and 2-(2-Mercapto-6-fluorobenzothiazol-5-yl)isoindoline-1,3-dione (11b).** Potassium *O*-ethyl carbonodithioate (50 mmol, 8.0 g) was dissolved in 160 mL of DMF, and then, compound **10a** (or **10b** (25 mmol) was added. The resulting mixture was heated to refluxing temperature. After the reaction was complete according to the TLC detection, the solution was slowly poured into 500 mL of water and acidified with concentrated hydrogen chloride to pH = 1−2. The resulted solid was filtered off, dried, and recrystallized to afford compound **11a** or **11b**.

*Data for* ***11a***. Yield: 95%; mp 303.2−305.6 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 7.63 (s, 1H), 7.96 (s, 2H), 8.02 (s, 2H), 8.12 (s, 1H), 14.14 (bs, 1H); EI-MS 346.5 $(M)^+$.

*Data for* ***11b***. Yield: 85%; mp 335.1−337.2 °C; $^1$H NMR (600 MHz, DMSO) $\delta$ 7.54 (d, $J$ = 6.0 Hz, 1H), 7.21−7.96 (m, 3H), 8.01−8.03 (m, 2H), 14.04 (bs, 1H); EI-MS 330.0 $(M)^+$.

**General Procedure for the Preparation of the Title Compounds 2a−h.** $K_2CO_3$ powder (0.33 g, 2.4 mmol) was added to a solution of **11a** (or **11b**) (1.2 mmol) in acetone (20 mL). After stirring for 10 min at room temperature, halogen derivative (RX, 1.8 mmol) in acetone solution was added dropwise to the mixture. The resulting mixture reacted for about 30 min and then was filtered and concentrated. The residue was purified *via* flash chromatography to give the pure products **2a**−**h** in yields of 42−71%.

*Data for* ***2a***. Yield: 70%; mp 153−155 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.40 (t, $J$ = 7.2 Hz, 3H), 4.45 (q, $J$ = 7.2 Hz, 2H), 7.77 (d, $J$ = 8.4 Hz, 1H), 7.83−7.84 (m, 2H), 8.00 (s, 3H); ESI-MS 403.2 $(M + H)^+$. Anal. Calcd for $C_{18}H_{11}FN_2O_4S_2$: C, 53.72; H, 2.76; N, 6.96. Found: C, 53.87; H, 2.49; N, 6.84.

*Data for* ***2b***. Yield: 67%; mp 140−142 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 3.80 (s, 3H), 4.19 (s, 2H), 7.65 (d, $J$ = 7.2 Hz, 1H), 7.84 (s, 3H), 8.00 (s, 2H); ESI-MS 403.4 $(M + H)^+$. Anal. Calcd for $C_{18}H_{11}FN_2O_4S_2$: C, 53.72; H, 2.76; N, 6.96. Found: C, 53.51; H, 2.66; N, 6.71.

*Data for* ***2c***. Yield: 62%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.26 (t, $J$ = 7.2 Hz, 3H), 1.71 (d, $J$ = 7.2 Hz, 3H), 4.24 (q, $J$ = 7.2 Hz, 2H), 4.67 (q, $J$ = 7.2 Hz, 1H), 7.65 (d, $J$ = 8.4 Hz, 1H), 7.82−7.85 (m, 3H), 7.99 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H); EI-MS 430.6 $(M)^+$. Anal. Calcd for $C_{20}H_{15}FN_2O_4S_2$: C, 55.80; H, 3.51; N, 6.51. Found: C, 55.50; H, 3.71; N, 6.70.

*Data for* ***2d***. Yield: 59%; mp 137−139 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.27 (d, $J$ = 6.0 Hz, 6H), 4.13 (s, 2H), 5.09−5.11 (m, 1H), 7.65 (d, $J$ = 9.0 Hz, 1H), 7.81−7.84 (m, 3H), 7.99−8.00 (m, 2H); EI-MS 452.7 $(M + Na)^+$. Anal. Calcd for $C_{20}H_{15}FN_2O_4S_2$: C, 55.80; H, 3.51; N, 6.51. Found: C, 55.76; H, 3.30; N, 6.27.

*Data for* ***2e***. Yield: 71%; mp 119−121 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 7.2 Hz, 3H), 1.65−1.71 (m, 2H), 4.14 (t, $J$ = 6.6 Hz, 2H), 4.18 (s, 2H), 7.64 (d, $J$ = 9.0 Hz, 1H), 7.83−7.84 (m, 3H), 7.99 (m, 2H); EI-MS 453.4 $(M + Na)^+$. Anal. Calcd for $C_{20}H_{15}FN_2O_4S_2$: C, 55.80; H, 3.51; N, 6.51. Found: C, 55.92; H, 3.34; N, 6.72.

*Data for* ***2f***. Yield: 45%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.27 (t, $J$ = 6.9 Hz, 3H), 2.91 (t, $J$ = 6.9 Hz, 2H), 3.60 (t, $J$ = 6.9 Hz, 2H), 4.17 (q, $J$ = 6.9 Hz, 2H), 7.63 (d, $J$ = 8.4 Hz, 1H), 7.82−7.85 (m, 3H), 7.99 (dd, $J_1$ = 3.0 Hz, $J_2$ = 5.4 Hz, 2H); EI-MS 430.4 $(M)^+$. Anal. Calcd for $C_{20}H_{15}FN_2O_4S_2$: C, 55.80; H, 3.51; N, 6.51. Found: C, 55.66; H, 3.13; N, 6.72.

*Data for* ***2g***. Yield: 48%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.26 (t, $J$ = 7.2 Hz, 3H), 1.72 (d, $J$ = 7.2 Hz, 3H), 4.22 (q, $J$ = 7.2 Hz, 2H), 4.69 (q, $J$ = 7.2 Hz, 1H), 7.83−7.84 (m, 3H), 7.95 (s, 1H), 7.99−8.00 (m, 2H); EI-MS 446.0 $(M)^+$. Anal. Calcd for $C_{20}H_{15}ClN_2O_4S_2$: C, 53.75; H, 3.38; N, 6.27. Found: C, 53.80; H, 2.98; N, 6.33.

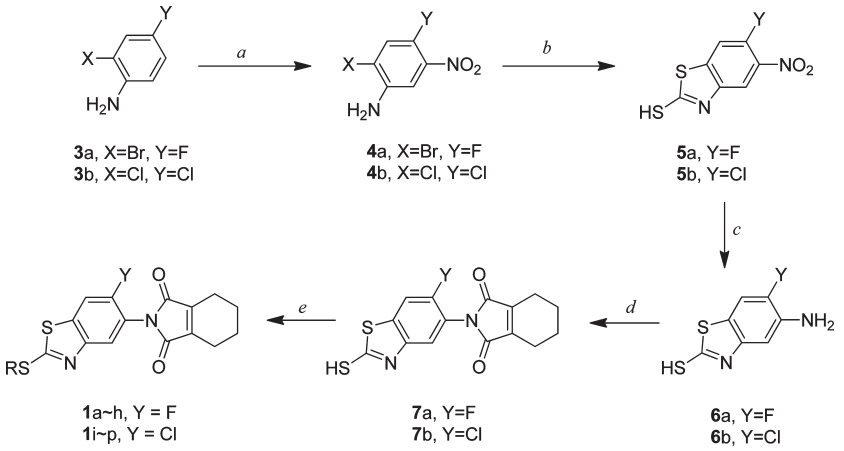
*Data for* ***2h***. Yield: 42%; oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.27 (t, $J$ = 7.2 Hz, 3H), 2.91 (t, $J$ = 6.9 Hz, 2H), 3.60 (t, $J$ = 6.9 Hz, 2H), 4.17 (q, $J$ = 7.2 Hz, 2H), 7.83−7.84 (m, 3H), 7.94 (s, 1H), 7.99−8.01 (m, 2H); ESI-MS 446.8 $(M + H)^+$. Anal. Calcd for $C_{20}H_{15}ClN_2O_4S_2$: C, 53.75; H, 3.38; N, 6.27. Found: C, 53.49; H, 3.87; N, 6.37.

**Enzyme Expression, Purification and Inhibition Kinetic Analysis.** The expression of the recombinant human PPO enzyme was performed according to the reported methods,[37−39] which have been described in detail previously.[32] Because the product of the enzymatic reaction has a maximum excitation wavelength at 410 nm and a maximum emission wavelength at 630 nm, the PPO activity can be assayed by fluorescence as described previously.[40−43] The concentration of protoporphyrinogen IX was determined by the difference of the absorption of protoporphyrin IX before and after the complete enzyme oxidation of the substrate monitored by UV−vis spectrophotometer at a wavelength of 410 nm. The concentration of protoporphyrin IX was calculated from the calibration graph. In assays, the inhibitors were dissolved in dimethyl sulfoxide (DMSO). The final concentration ranged from 0.005 $\mu$M to 250 $\mu$M. The enzymatic reaction rate was measured in 100 mM potassium phosphate (pH = 7.5), 5 mM DTT, 1 mM EDTA, Tween 80 (0.03%, v/v), 200 mM imidazole, 5 $\mu$M FAD, and approximately 0−40 $\mu$g of protein. The reaction was initiated by adding the substrate (0−6.5 $\mu$M) to the assay mixture, and the formation of protoporphyrin IX was monitored at room temperature using a fluorescence detector with the excitation and emission wavelengths set to 410 and 631 nm, respectively. The kinetic parameters were evaluated by Sigma Plot software 10.0 (SPSS, Chicago, IL, USA). $IC_{50}$ was determined by measuring PPO activity over a range of inhibitor concentrations at a single substrate concentration. $IC_{50}$ values were calculated by fitting $v$ versus [I] data to a single binding site model described by eq 1,

$$y = \min + \frac{\max - \min}{1 + 10^{\log IC_{50} - x}} \quad (1)$$

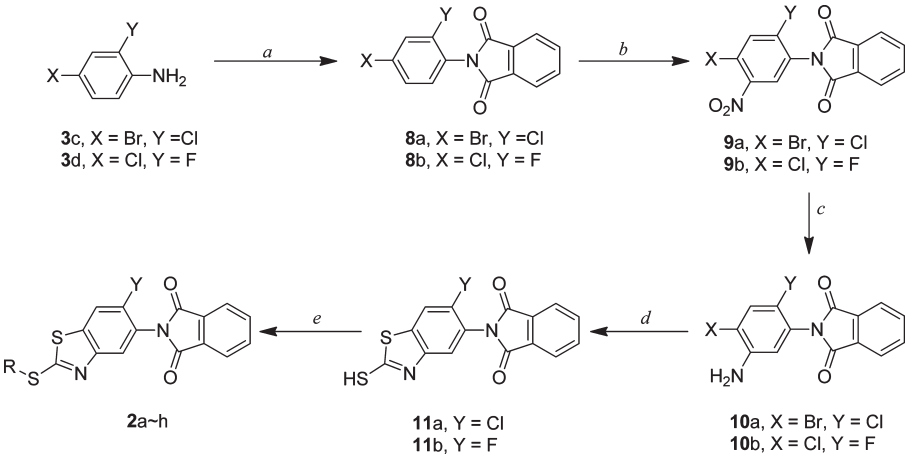
where $y$ is the percentage of maximal rate, max and min are the $y$ values at which the curve levels off, $x$ is the logarithm of inhibitor concentration, and $IC_{50}$ is the inhibitor concentration that elicits 50% of the total inhibition. As described before,[44] calculated $K_i$ value is obtained by applying the following relationship, which exists for competitive inhibition among $K_i$, $K_m$, and $IC_{50}$ at any saturating

**Scheme 1. Synthetic Route for the Title Compounds 1a−p**[a]




[a] Reagents and conditions: (a) $HNO_3$/concd $H_2SO_4$, −20 °C; (b) $CH_3CH_2OCS(S)K$, DMF; HCl (6 N); (c) Fe, $NH_4Cl$, EtOH/$H_2O$, reflux; (d) 4,5,6,7-tetrahydroisobenzofuran-1,3-dione, reflux, HOAc; (e) RX, $K_2CO_3$, acetone, rt.

**Scheme 2. Synthetic Route for the Title Compounds 2a−h**[a]




[a] Reagents and conditions: (a) isobenzofuran-1,3-dione, HOAc, reflux; (b) $HNO_3$/concd $H_2SO_4$, 0 °C; (c) Fe, $NH_4Cl$, EtOH/$H_2O$, reflux; (d) $CH_3CH_2OCS(S)K$, DMF; 6 N HCl; (e) RX, $K_2CO_3$, acetone, rt.

substrate concentration ($S$).

$$K_i = \frac{IC_{50}}{S/K_m + 1} \quad (2)$$

**Greenhouse Herbicidal Activities.** The herbicidal activities of compounds **1a**−**p**, **2a**, **2d**, and **2e** against monocotyledon weeds such as *Echinochloa crus-galli* (EC), *Digitaria sanguinalis* (DS), and *Setaria faberii* (SF), and dicotyldon weeds such as *Amaranthus retroflexus* (AR), *Eclipta prostrate* (EP), *Brassica juncea* (BJ) and *Abutilon theophrasti* (AT) were evaluated according to a previously reported procedure.[32,45−47] Sulfentrazone was selected as a positive control. All test compounds were formulated as a 100 g/L emulsified concentrates by using DMF as solvent and Tween-80 as emulsification reagent. The concentrated formulas were diluted with water to the required concentration and applied to pot-grown plants in a greenhouse. The soil used was a clay soil, pH 6.5, 1.6% organic matter, 37.3% clay particles, and CEC 12.1 mol/kg. The rate of application (g ai/ha) was calculated by the total amount of active ingredient in the formulation divided by the surface area of the pot. Plastic pots with a diameter of 9.5 cm were filled with soil to a depth of 8 cm. Approximately 20 seeds of the tested weeds were sown in the soil at a depth of 1−3 cm and grown at a temperature of 15−30 °C in a greenhouse. The air relative humidity is 50%. The diluted formulation solutions were applied for postemergence treatment, dicotyledon weeds were treated at the 2-leaf stage and monocotyledon weeds were treated at the 1-leaf stage, respectively. The postemergence application rate was 150 g ai/ha. Untreated seedlings were used as the control group, and the solvent (DMF + Tween-80) treated seedlings were used as the solvent control group. Herbicidal activity was evaluated visually 15 days post treatment. The results of herbicidal activities are shown in Table 2, three replicates per treatment.

**Crop Selectivity**[33,48]**.** Conventional rice, soybean, cotton, wheat, rape and maize were respectively planted in plots (diameter = 12 cm) containing test soil and grown in a greenhouse at 20−25 °C. After the plants had reached the 4-leaf stage, the spraying treatment was conducted at different dosages by diluting the formulation of compound **1b** with water. The visual injury and growth state of the individual plant


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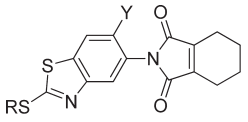
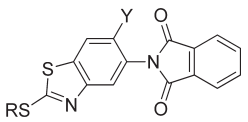
**Table 1. PPO Inhibition Activity of the Title Compounds 1a−p and 2a−h**



**1**a~h, Y = F
**1**i~p, Y = Cl



**2**a~f, Y = F
**2**g~h, Y = Cl

| no. | Y | R | $k_i$ ($\mu$M) |
|---|---|---|---|
| **1a** | F | $COOCH_3$ | 0.08 ± 0.01 |
| **1b** | F | $CH_2COOCH_3$ | 1.22 ± 0.15 |
| **1c** | F | $CH_2COOC_2H_5$ | 0.25 ± 0.03 |
| **1d** | F | $CH(CH_3)COOC_2H_5$ | 0.29 ± 0.07 |
| **1e** | F | $CH_2COOCH(CH_3)_2$ | 0.21 ± 0.01 |
| **1f** | F | $CH_2COOC(CH_3)_3$ | 0.18 ± 0.01 |
| **1g** | F | $CH_2COOCH_2CH_2CH_3$ | 0.28 ± 0.03 |
| **1h** | F | $CH_2CH_2COOC_2H_5$ | 0.11 ± 0.01 |
| **1i** | Cl | $COOCH_3$ | 0.52 ± 0.05 |
| **1j** | Cl | $COOC_2H_5$ | 0.47 ± 0.07 |
| **1k** | Cl | $CH_2COOC_2H_5$ | 1.66 ± 0.28 |
| **1l** | Cl | $CH(CH_3)COOC_2H_5$ | 0.80 ± 0.15 |
| **1m** | Cl | $C(CH_3)_2COOC_2H_5$ | 1.66 ± 0.48 |
| **1n** | Cl | $CH_2CH_2COOC_2H_5$ | 0.32 ± 0.01 |
| **1o** | Cl | $CH_2CH_2CH_2COOC_2H_5$ | 0.75 ± 0.11 |
| **1p** | Cl | $CH_2COOCH_3$ | 3.92 ± 0.54 |
| **2a** | F | $COOC_2H_5$ | 0.51 ± 0.02 |
| **2b** | F | $CH_2COOCH_3$ | 2.25 ± 0.21 |
| **2c** | F | $CH(CH_3)COOC_2H_5$ | 132.0 ± 9.90 |
| **2d** | F | $CH_2COOCH(CH_3)_2$ | 1.50 ± 0.06 |
| **2e** | F | $CH_2COOCH_2CH_2CH_3$ | 1.24 ± 0.01 |
| **2f** | F | $CH_2CH_2COOC_2H_5$ | 5.52 ± 1.49 |
| **2g** | Cl | $CH(CH_3)COOC_2H_5$ | 85.90 ± 8.00 |
| **2h** | Cl | $CH_2CH_2COOC_2H_5$ | 3.76 ± 0.10 |
| sulfentrazone | | | 0.72 ± 0.01 |

were observed at regular intervals. The final evaluation for crop safety of compound **1b** was conducted by visual observation in 30 days after treatment on the 0−100 scale.

## RESULTS AND DISCUSSION

**Synthesis of the Title Compounds.** As shown in Scheme 1, the target compound **1a**−**p** was prepared by a five-step synthetic route using 2,4-disubstituted aniline as starting materials. After nitration, cyclization and reduction reactions, the 2,4-disubstituted aniline was transformed into the key intermediate 2-mercapto-5-aminobenzothiazole (**6a**,**b**). Then, the key intermediates **6a**,**b** reacted with 4,5,6,7-tetrahydroisobenzofuran-1,3-dione to afford 2-(2-mercaptobenzothiazol-5-yl)-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**7a**,**b**) in acceptable yields. Finally, intermediate **7a**−**c** reacted with various alkylation reagents to give the target compounds **1a**−**p** in yields of 43−76%. In addition, the synthetic route for compound **2a**−**h** was as shown in Scheme 2, which also used 2,4-disubstituted aniline as starting materials. 2,4-Disubstituted-aniline reacted with phthalic anhydride to afford 2-(2,4-disubstituted phenyl) isoindoline-1,3-diones (**8a** and **8b**), which suffered nitration,

**Table 2. Herbicidal Activity of Compounds 1a−p, 2a, 2d and 2e**

| | postemergence,150 g ai/ha | | | | | |
|---|---|---|---|---|---|---|
| no. | EC[a] | DS | SF | AR | EP | BJ[b] or AT[c] |
| **1a** | −[d] | − | − | +++ | +++ | +++ |
| **1b** | ++ | ++ | ++ | +++ | +++ | +++ |
| **1c** | ++ | ++ | ++ | +++ | + | − |
| **1d** | ++ | ++ | ++ | +++ | +++ | +++ |
| **1e** | ++ | ++ | + | +++ | +++ | ++ |
| **1f** | − | ++ | − | +++ | +++ | +++ |
| **1g** | ++ | ++ | − | +++ | +++ | ++ |
| **1h** | + | + | − | +++ | +++ | +++ |
| **1i** | − | − | − | ++ | ++ | − |
| **1j** | − | − | − | + | + | − |
| **1k** | − | − | − | +++ | ++ | − |
| **1l** | − | − | − | ++ | ++ | − |
| **1m** | − | − | − | +++ | ++ | − |
| **1n** | − | − | − | ++ | ++ | ++ |
| **1o** | − | − | − | +++ | ++ | − |
| **1p** | − | − | − | ++ | ++ | − |
| **2a** | − | − | − | +++ | +++ | +++ |
| **2d** | − | − | − | +++ | ++ | +++ |
| **2e** | − | − | + | +++ | − | +++ |
| sulfentrazone | ++ | ++ | − | +++ | +++ | +++ |

[a] EC for *E. crusgalli*, DS for *D. sanguinalis*, SF for *S. faberii*, AR for *A. retroflexus*, EP for *E. prostrate*, BJ *for B. juncea* and AT for *A. theophrasti*. [b] Compounds **1a**−**p** were tested against BJ. [c] Compounds **2a**, **2d** and **2e** were tested against AT. [d] Rating system for the growth inhibition percentage: +++, 80%; ++, 60−79%; +, 50−59%; −, <50%

subsequent reduction and final cyclization reactions to give the key intermediates 2-(2-mercapto-6-chlorobenzothiazol-5-yl)isoindoline-1,3-dione (**11a**) and 2-(2-mercapto-6- fluorobenzothiazol-5-yl)isoindoline-1,3-dione (**11b**). Then, these two intermediates reacted with various alkylation reagents to give the target compounds **2a**−**h** in yields of 42−71%. The structures of all intermediates and title compounds were confirmed by elemental analyses, $^1$H NMR and ESI-MS spectral data.

**PPO Inhibition Activity.** The $k_i$ values against human PPO of the synthesized compounds **1a**−**p** and **2a**−**h** are listed in Table 1. Sulfentrazone, a commercial PPO inhibitor, was used as a control. As shown in Table 1, compounds **1a**−**h** with a fluoro atom at the 6-position always displayed higher PPO-inhibiting activity than the corresponding compounds **1i**−**p** with a chloro atom at the 6-position. Except for compounds **1b**, **1k**, **1m**, **1o** and **1p**, all other compounds **1** displayed higher PPO-inhibiting activity than sulfentrazone. The most promising one is compound **1a**, whose $k_i$ value against human PPO is 0.08 $\mu$M. This result indicates that compound **1a** shows 9 times higher PPO-inhibiting activity than the control compound. In addition, from Table 1 we can also conclude that compound **1** has higher PPO-inhibiting activity than the corresponding compound **2** bearing the same R and Y groups. However, different from the series of compounds **1a**−**p**, compounds **2** bearing a fluoro substituent at the 6-position were found to show lower PPO-inhibiting activity than the corresponding compounds **2** bearing a chloro atom at the 6-position. For


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**Table 3. Further Herbicidal Testing of Compound 1b (Postemergence)**

| | dosage (g ai/ha) | EC[a] | DS | SF | AR | EP | AT | BJ |
|---|---|---|---|---|---|---|---|---|
| **1b** | 37.5 | −[b] | − | − | +++ | +++ | +++ | + |
| | 75 | + | + | − | +++ | +++ | +++ | + |
| | 150 | ++ | ++ | ++ | +++ | +++ | +++ | +++ |
| sulfentrazone | 37.5 | + | + | − | +++ | +++ | +++ | ++ |
| | 75 | + | + | − | +++ | +++ | +++ | +++ |
| | 150 | ++ | ++ | − | +++ | +++ | +++ | +++ |

[b] Rating system for the growth inhibition percentage: +++, 80%; ++, 60−79%; +, 50−59%; −, <50% [a] EC for *E. crusgalli*, DS for *D. sanguinalis*, SF for *S. faberii*, AR for *A. retroflexus*, EP for *E. prostrate*, AT for *A. theophrasti*, BJ *for B. juncea*.

**Table 4. Crop Selectivity of Compound 1b**

| dosage (g ai/ha) | rice | cotton | soybean | maize | rape | wheat |
|---|---|---|---|---|---|---|
| 75 | / | / | / | / | / | 0 |
| 150 | 60 | 80 | 50 | 40 | 50 | 0 |
| 300 | / | / | / | / | / | 0 |

example, the activities of compounds **2c** (R = $CH(CH_3)COOC_2H_5$, Y = F, $k_i$ = 132.0 $\mu$M) and **2f** (R = $CH_2CH_2COOC_2H_5$, Y = F, $k_i$ = 5.52 $\mu$M) are about 1.54 times and 1.47 times lower than those of compounds **2g** (R = $CH(CH_3)COOC_2H_5$, Y = Cl, $k_i$ = 85.9 $\mu$M) and **2h** (R = $CH_2CH_2COOC_2H_5$, Y = Cl, $k_i$ = 3.76 $\mu$M), respectively. In addition, Table 1 clearly indicates that the optimum R group is $COOCH_3$ or $COOC_2H_5$, while the optimum Y groups are F for 4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione derivatives (**1a**−**p**) and Cl for isoindoline-1,3-dione derivatives (**2a**−**h**), respectively.

**Greenhouse Herbicidal Activities.** The postemergence herbicidal activities of compounds which displayed high PPO-inhibition activity ($k_i$ < 2.0 $\mu$M) were tested in a greenhouse at a concentration of 150 g ai/ha; sulfentrazone was also selected as a control. As shown in Table 2, most of the compounds were not found to display promising herbicidal activities at a concentration of 150 g ai/ha against monocotyledon weeds such as *E. crus-galli*, *D. sanguinalis*, and *S. faberii*. However, compounds **1b**, **1c**, and **1d** showed moderate herbicidal activity against these monocotyledon weeds at the same concentration. Fortunately, some compounds bearing a fluoro atom at 6-position, such as **1a**, **1b**, **1d**, **1e**, **1f**, **1g**, and **1h**, exhibited high and broad spectrum herbicidal activity (>80% inhibition) at a concentration of 150 g ai/ha against dicotyldon weeds such as *A. retroflexus*, *E. prostrate*, and *B. juncea*. On the contrary, compounds **1i**, **1j**, **1k**, and **1l**, which contained a chloro atom at the 6-position, showed much lower herbicidal activity against the tested weeds. Besides, compound **2a** showed high herbicidal activities (>80% inhibition) at a concentration of 150 g ai/ha against dicotyldon weeds such as *A. retroflexus*, *E. prostrate*, and *A. theophrasti*, and compounds **2d** and **2e** exhibited high herbicidal activities (>80% inhibition) against *A. retroflexus* and *E. prostrate*.

From Table 2 we can conclude that the inhibition rate of compound **1b** against *E. crus-galli*, *A. retroflexus*, *E. prostrate*, and *B. juncea* is over 80%, and against *D. sanguinalis* and *S. faberii* it is over 60%, which indicated that compound **1b** displayed the broadest spectrum herbicidal activity at a concentration of 150 g ai/ha. Therefore, compound **1b** was selected for further testing, and the results are listed in Table 3, which indicate clearly that compound **1b** showed comparable herbicidal activity and spectrum as sulfentrazone. Even at a dosage as low as 37.5 g ai/ha, compound **1b** still exhibited high herbicidal activity against *A. retroflexus*, *E. prostrate*, and *A. theophrasti*. In addition, we also tested the crop selectivity of compound **1b** as shown in Table 4. Among six tested crops, only wheat exhibited high tolerance to compound **1b** by postemergence application at the dosages of 75−300 g ai/ha, whereas rice, cotton, soybean, maize, and rape are susceptible at a dosage of 150 g ai/ha (Table 4). Even at a dosage of 300 g ai/ha, wheat still exhibited tolerance to compound **1b**, which indicated that compound **1b** might be developed as a potential herbicide used for weed control in wheat field.

In summary, a series of novel *N*-(benzothiazol-5-yl)-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-diones (**1a**−**p**) and *N*-(benzothiazol-5-yl)isoindoline-1,3-diones (**2a**−**h**) were designed and synthesized as potential PPO inhibitors. The results of *in vitro* and greenhouse testing indicated that some newly synthesized compounds had good PPO inhibition activity and herbicidal activities at a concentration of 150 g ai/ha. Most interestingly, compound **1a**, *S*-(5-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-6-fluorobenzothiazol-2-yl) *O*-methyl carbonothioate, showed the highest PPO-inhibiting activity with a $k_i$ value of 0.08 $\mu$M, about 9 times higher than that of sulfentrazone ($k_i$ = 0.72 $\mu$M). Further greenhouse testing indicated that compound **1b**, methyl 2-((5-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-6-fluorobenzothiazol-2-yl)thio)acetate, showed comparable herbicidal activity even at a concentration of 37.5 g ai/ha. Additional crop selectivity testing showed that wheat exhibited high tolerance to compound **1b** even at a dosage of 300 g ai/ha. These results indicate that compound **1b** might have the potential to be developed as a new herbicide for wheat field.

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