Design, Synthesis and Herbicidal Activities of Tetrahydroisoindoline-1,3-dione Derivatives Containing Alkoxycarbonyl Substituted 2-Benzoxazolinone

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Several different alkoxycarbonyl-substituted 2-benzoxazolinone moieties have been incorporated into a tetrahydroisoindoline-1,3-dione scaffold to provide 25 compounds (1a–1u and 2a–2d). The structures of these compounds were confirmed by ¹H and ¹³C NMR, HRMS and X-ray single-crystal diffraction. Some of these compounds (1g, 1h, 1j, 1k) exhibited excellent herbicidal activities against *Abutilon theophrasti, Amaranthus retroflexus* and *Echinochloa crus-galli* at a rate of 375 g AI•ha⁻¹. Among them, compounds 1h and 1j displayed the best post-emergence herbicidal effect against *Abutilon theophrasti* with ED₅₀ values of 1.8 and 5.3 g AI•ha⁻¹, respectively, which are superior to that of the commercial acifluorfen (44.3 g AI•ha⁻¹). Field trials demonstrated that compound 1h exhibited similar herbicidal activity to a high concentration atrazine, and found to be safer for maize than atrazine. The results of this study therefore show that compound 1h could potentially be used as a post-emergence herbicide for maize fields.

Keywords synthesis, tetrahydroisoindoline-1,3-dione, benzoxazolinone, protoporphyrinogen oxidase, herbicidal activity

Introduction

Chemical herbicides have been used successfully for several decades to achieve convenient and economical weed control in agricultural practices.^[1] Unfortunately, however, the overuse of herbicides has inevitably resulted in the evolution of herbicide-resistant weeds, which represents a significant threat to the security and stability of food supplies.^[2] According to the results of a recent survey from the Herbicide Resistance Action Committee, there are currently 404 unique cases (species×site of action) throughout the world of herbicide resistant weeds, however only six weed species have been found to be resistant to protoporphyrinogen oxidase (PPO, EC 1.3.3.4) inhibiting herbicides up to 2014.^[2,3] PPO-inhibiting herbicides, such as saflu-fenacil^[4] and flumioxazin,^[5] could be used as part of a multi-component approach for the management of re-sistant biotypes,^[6] such as glyphosate resistance weeds,^[7] which has stimulated our interest in the discovery of novel PPO inhibitors.^[8]

Research towards the development of novel phenyl heterocycles as PPO inhibitors has intensified during the

last two decades, and resulted in several different heterocyclic compound families,^[9] including tetrahydrophthalimides, oxadiazolinones, triazolinones, thiadiazoles, pyrazoles and uracils. Phenyl heterocycles usually possess a 2,4,5-trisubstituted phenyl group as a common structural feature, which is required to obtain high her-bicidal activity.^[10] Following on from the discovery and development of new PPO inhibitors, a novel class of benzoheterocycle herbicides was obtained when the substituents at 4 and 5 positions of the characteristic phenyl ring were linked together to yield a broad range of benzoheterocycles,^[11] including flumioxazin,^[5] benzimidazole^[12] and benzothiazole derivatives^[13] (Figure 1). Flumioxazin, whose core scaffold is based on a tetrahydrophthalimide skeleton, exhibited a high level herbicidal activity towards annual broadleaf weeds at a very low dosage. Despite its promising activity, there are several limitations associated with the use of flumioxazin. For example, flumioxazin can cause injury to maize, barley, wheat and rice, and can only be applied as a pre-emergence herbicide.^[14] With this in mind, there is therefore considerable interest in the design of new tetrahydrophthalimide derivatives with both post-

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emergence herbicidal activity and good crop safety properties.

Benzoxazolinones are a group of secondary metabolites found in cereals that play an important role in defense of cereals against pests, diseases and weeds.^[15] For example, 2-benzoxazolinone (BOA) and 6-methoxy-2-benzoxazolinone (MBOA) are well known allelochemicals, which exhibit phytotoxicity against the germination and early growth of several plant species^[16] (Figure 1). BOA has also been studied for its herbicidal potential.^[15,17] It was envisaged that the incorporation of a benzoxazolinone ring into a tetrahydrophthalimide moiety could be used as promising strategy for the identification of novel herbicidal compounds. It is noteworthy that a large number of herbicidal compounds contain an alkoxycarbonyl group,^[18] and it was therefore envisaged that the incorporation of an alkoxycarbonyl group into the benzoxazolinone-substituted tetrahydrophthalimides described above would lead to enhanced levels of lipophilicity, which would favor translocation.^[19] Based on these considerations, we designed and synthesized a series of N-(2-benzoxazolinone-5-yl)-4,5,6,7-tetrahydroisoindole-1,3-diones 1a - 1u. For comparison, we also synthesized the corresponding N-(2-benzoxazolinone-6-yl)-4,5,6,7-tetrahydroisoindole-1,3-dione compounds 2a - 2d. Herein, we have described the synthesis of these compounds and the subsequent evaluation of their herbicidal activities.

Experimental

General

All reagents were purchased from commercial suppliers, and used directly without further purification. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ on a Bruker DPX300 spectrometer (Bruker, Fallanden, Switzerland), using tetramethylsilane as internal standard. High-resolution mass spectrometry

(HRMS) was recorded on an Agilent G1969A spectrometer (Agilent Technologies, Santa Clara, CA, USA). X-ray diffraction was performed on a Rigaku MM007-HF diffractometer (Rigaku, Tokyo, Japan) equipped with a Saturn724+ detector using graphite monochromated Mo K α radiation (λ =0.71073 Å). The melting points were obtained utilizing a Stuart melting point apparatus (Bibby Scientific Limited, Staffordshire, UK) and were uncorrected.

General procedure for preparation of intermediates 10 and 11

Synthesis of 6-fluorobenzo[d]oxazol-2(3H)-one (4a) A solution of triphosgene (8.2 g, 27.5 mmol) in THF (50 mL) was added in a dropwise manner to a solution of compound 3a (10.0 g, 78.7 mmol) and pyridine (12.5 g, 158.0 mmol) in THF (150 mL) at 5 °C, and the resulting mixture was stirred at this temperature for 30 min before being warmed to room temperature and stirred for a further 3 h. The reaction was then evaporated to dryness under vacuum to give a residue, which was partitioned between a saturated aqueous solution of NaHCO₃ and ethyl acetate. The aqueous layer was collected and extracted with ethyl acetate, and the combined organic extracts were washed with brine and dried over MgSO₄. The solvent was then removed under vacuum to give the crude product, which was recrystallized from a 1 : 1 (V/V) mixture of petroleum ether and ethyl acetate to give 4a as a yellow solid (8.4 g, yield 70%); m.p. 192.6-193.3 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ : 11.68 (s, 1H), 7.33 (dd, J=8.6, 2.4 Hz, 1H), 7.14-6.93 (m, 2H).

Synthesis of 6-fluoro-5-nitrobenzo[d]oxazol-2(3H)-one (5a) HNO₃ (60%, 8.9 g, 84.8 mmol) was added in dropwise manner to a solution of compound 4a (10.0 g, 65.3 mmol) in 80% H₂SO₄ (180 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then poured into a mixture of



Figure 1 Design strategy for compounds 1 and 2.

ice and water (1800 mL), and the resulting solid was filtered, rinsed with water, and dried to afford **5a** as a brown solid (11.9 g, yield 92%); m.p. 179.7–181.1 °C; ¹H NMR (300 MHz, DMSO- d_6) δ : 12.22 (s, 1H), 7.78 (s, 1H), 7.75 (d, J=4.4 Hz, 1H).

Synthesis of 5-amino-6-fluorobenzo[d]oxazol-2(3H)-one (6a) Compound 5a (10.3 g, 52.2 mmol) and NH₄Cl (4.2 g) were added to a 1 : 1 (V/V) mixture of C₂H₅OH and H₂O (250 mL), and the resulting suspension was heated at 60 °C until all of the solid material had dissolved. Fe powder (8.7 g) was then added to the reaction in a portionwise manner, and the resulting mixture was heated at reflux for 3 h until the reaction was complete. The hot mixture was then filtered immediately, and the filtrate was concentrated under vacuum and poured into cold water (500 mL). The resulting solid was collected by filtration and washed with water, then dried to afford **6a** as a black solid (5.9 g, yield 67%); m.p. 189.4-191.0 °C; ¹H NMR (300 MHz, DMSO- d_6) δ : 11.26 (s, 1H), 7.13 (d, J=10.5 Hz, 1H), 6.51 (d, J=8.0 Hz, 1H), 4.98 (s, 2H).

Synthesis of 2-(6-fluoro-2-oxo-2,3-dihydrobenzo-[d]oxazol-5-yl)-4,5,6,7-tetrahydro-1*H*-isoindole-1,3-(2*H*)-dione (10a) Compound 6a (3 g, 17.8 mmol) and 4,5,6,7-tetrahydroisobenzofuran-1,3-dione (3.2 g, 21.3 mmol) were added to glacial acetic acid (80 mL), and the resulting mixture was heated at reflux for 12 h. The reaction was then cooled to ambient temperature and slowly poured into a mixture of ice and water (400 mL). The resulting solid was collected by filtration and washed with water, then dried to afford **10a** as a brown solid (3.9 g, yield 72%); m.p. 207.0–208.3 °C; ¹H NMR (300 MHz, CDCl₃) δ : 11.82 (s, 1H), 7.56 (d, *J*= 9.3 Hz, 1H), 7.17 (d, *J*=6.5 Hz, 1H), 2.39–2.31 (m, 4H), 1.79–1.70 (m, 4H).

Intermediates **10b**, **11** were synthesized according to the method described for **10a**, and their characterization data are given in the Supporting Information.

General procedure for preparation of the target compounds 1 and 2

A halogenated carboxylate (3.0 mmol) was added to a mixture of compound 10 (or 11) (2.5 mmol) and anhydrous K_2CO_3 (2.5 mmol) in acetone (10 mL), and the resulting mixture was heated at reflux for 3 h. The reaction was then cooled to room temperature and filtered. The resulting filtrate was then evaporated to dryness to give a residue, which was purified by flash chromatography over silica gel eluting with a 10 : 1 (*V*/*V*) mixture of petroleum ether and ethyl acetate to give the title compounds 1a-1u and 2a-2d. The data for compound 1h are shown below, and the data for other title compounds are given in the Supporting Information.

Scheme 1 Synthetic route for the construction of compounds 1a - 1u and 2a - 2d



Reagents and conditions: (i) pyridine, triphosgene, THF, 5 °C; (ii) HNO₃/conc. H₂SO₄, 0 °C; (iii) Fe, NH₄Cl, C₂H₅OH/H₂O, reflux; (iv) 4,5,6,7-tetrahydroisobenzofuran-1,3-dione, HOAc, reflux; (v) RX, K₂CO₃, acetone, reflux.

Ethyl 2-(5-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-6-fluoro-2-oxobenzo[*d*]oxazol-3(2*H*)yl)propanoate (1h) White solid; yield 68%; m.p. 111.8–112.4 °C; ¹H NMR (300 MHz, CDCl₃) δ : 7.17 (d, *J*=8.5 Hz, 1H, Ar-H), 6.87 (d, *J*=6.1 Hz, 1H, Ar-H), 5.04 (q, *J*=7.4 Hz, 1H, CH), 4.27–4.19 (m, 2H, OCH₂), 2.49–2.38 (m, 4H, 2×CH₂), 1.89–1.78 (m, 4H, CH₂CH₂), 1.72 (d, *J*=7.4 Hz, 3H, CHCH₃), 1.24 (t, *J*=7.1 Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ : 168.81, 154.09 (d, *J*_{C-F}=246.8 Hz), 153.60, 142.36 (d, *J*_{C-F}=13.0 Hz), 142.35, 125.89, 115.12 (d, *J*_{C-F}=15.5 Hz), 110.38, 100.21 (d, *J*_{C-F}=27.3 Hz), 62.28, 51.75, 21.16, 20.17, 14.81, 13.92; HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₂₀H₂₀FN₂O₆: 403.1300; found 403.1304.

Greenhouse herbicidal activity

The herbicidal activities of compounds 1a - 1u and 2a-2d were tested against monocotyledon weeds (*i.e.*, Echinochloa crus-galli and Digitaria sanguinalis) and broadleaf weeds (i.e., Abutilon theophrasti and Amaranthus retroflexus) using a previously published procedure.^[20] Acifluorfen was used as a positive control. All of the test compounds were dissolved in 100 μ L of N,N-dimethylformamide (DMF) containing a couple of drops of Tween 20, and the resulting solutions were sprayed onto pot-grown plants. The rate of application (g AI•ha⁻¹) was calculated according to the total amount of active ingredient in the formulation divided by the surface area of the pot. Plastic pots with a diameter of 6 cm were filled with soil to a depth of 8 cm. Approximately 15 seeds of selected weeds were sown in the soil at the depth of 1-3 cm and grown at 20-30 °C in a greenhouse. The formulation solutions were applied for pre-emergence treatment 24 h after the seeds had been sown. For post-emergence treatment, the broadleaf weeds were treated at the two-leaf stage, whereas the monocotyledon weeds were treated at the one-leaf stage. The pre- and post-emergence application rate was set at 375 g AI•ha⁻¹. A mixture containing the same amount of water, DMF and Tween 20 was sprayed as the solvent control. Each treatment was conducted in triplicate. The fresh weights of the aerial parts of the plant were measured 10 d after treatment, and the percentage inhibition value was used to describe the control efficiency of the compounds.

ED₅₀ values of some compounds against *Echinochloa crus-galli* and *Abutilon theophrasti* were calculated with SPSS 17.0 software.

Crop selectivity

Conventional crops of rice, soybean, cotton, wheat and maize were planted separately in plastic pots (diameter 9 cm) filled with soil and grown in a greenhouse at 20–25 °C. After the plants had reached the 4-leaf stage, the test compounds were applied at a dosage of 300 or 150 g AI•ha⁻¹ for the post-emergence evaluation of the test compounds. Each experiment was conducted in triplicate. After 15 d, the crop safety was determined by visually comparing the injury caused by the test treatments relative to the untreated controls.

Field trials

The field trials were carried out at Yangtze University, Jingzhou City (Hubei Province, South China). The soil used in this study was a loam soil containing 1.48% organic matter, and the pH of the soil was 7.4. The maize variety Luoyu No. 8 was planted in the soil, and the treated plots were arranged in a random block array with four replicates. Compound **1h** was formulated as a 10% emulsifiable concentrate, and the commercial herbicide 38% atrazine SC was used as a positive control. The application rate for the post-emergence treatment was varied from 100 to 300 g AI•ha⁻¹. The weed numbers were measured at regular intervals, and the final fresh weights of the aerial portions of the weeds were also measured. The percentage of inhibition relative to the water-sprayed control group was calculated. The control effects expressed as percentages were arcsine transformed to homogenize any variance prior to analysis, and those of the different spraying treatments were examined using Duncan's multiple range test.

Results and Discussion

Synthesis

As shown in Scheme 1, the target compounds 1a -1u were prepared via a five-step linear sequence starting from either 2-amino-5-fluorophenol (3a) or 2-amino-5chlorophenol (3b). By performing the cyclization reaction with BTC, compounds **3a** and **3b** were converted to the corresponding 6-substituted-benzo[d]oxazol-2(3H)ones 4a and 4b, respectively. Subsequent nitration and reduction reactions gave the corresponding 5-amino-6substituted benzo[d]oxazol-2(3H)-one intermediates 6a and **6b**, which were reacted with 4,5,6,7-tetrahydroisobenzofuran-1.3-dione to afford the 2-(2-oxo-2.3-dihydrobenzo[d]oxazol-5-yl)-4,5,6,7-tetrahydro-1H-isoindole-1,3(2H)-dione intermediates 10a and 10b in moderate yields. Finally, intermediates 10a and 10b were reacted with various alkylating agents to give the target compounds 1a-1u in yields of 56%-80%. Intermediate 11 was prepared from 2-amino-4-chloro-5nitrophenol. Compounds 2a-2d were prepared from intermediate 11 in yields of 55% - 76% according to the alkylation procedure used for the preparation of compounds 1a-1u.

Halogenated alkylation reagents generally prefer to react with nitrogen atoms through *N*-alkylation reaction in the target compounds preparation. However, these reagents can also react through *O*-alkylation reactions.^[21] To further confirm the structures of the target compounds, The crystal structure of **1h** is shown in Figure 2,^[22] which unambiguously demonstrates that the target compounds were *N*-alkylation products.



Figure 2 Crystal structure of compound 1h.

Greenhouse herbicidal activity and structure-activity relationships

The herbicidal activities of compounds 1a - 1u and 2a-2d were evaluated against monocotyledon weeds (E. crus-galli and D. sanguinalis) and broadleaf weeds (A. theophrasti and A. retroflexus) in a greenhouse at different rates. All of the compounds were initially tested at a rate of 375 g AI•ha⁻¹ for their pre-emergence and post-emergence herbicidal activities. As shown in Table 1, compounds 1a - 1n (X = F) generally displayed greater herbicidal activities than the corresponding chlorine-containing compounds 1o - 1u (X=Cl). Furthermore, compounds 2a - 2d showed no detectable activity in the pre- or post-emergence activity studies. Compounds 1a-1u were found to be more potent towards dicotyledon weeds than monocotyledons, and the activities observed in the post-emergence treatment group were generally better than those observed in the pre-emergence treatment group. For example, most of the compounds belonging to series 1 displayed 100% control in the post-emergence treatment group against A. *theophrasti*. Among them, compounds 1g, 1h, 1j and 1k also exhibited 100% control against *E. crus-galli* and *A*. retroflexus. Unfortunately, however, these compounds displayed poor herbicidal activity against D. sanguinalis. Taken together, these results indicated that the conformation of the scaffold is critical to the activities of these compounds. For example, compounds belonging to series 1 gave much higher levels of inhibitory activity than the corresponding compounds belonging to series 2 bearing the same R group. Meanwhile, the structure of R substituent also exerts a significant influence over the herbicidal activities of the compounds belonging to series 1. The introduction of a longer chain between the

ester carbon and the core structure had a favorable effect on the inhibitory activity, as demonstrated by the following trend in the activity of these compounds: 1i $(CH_2CH_2CH_2CO_2C_2H_5) > 1i (CH_2CH_2CO_2C_2H_5) > 1c$ $(CH_2CO_2C_2H_5)$. However, compounds 1m and 1n, which both had an unsaturated C=C bond in their R group, displayed decreased herbicidal activities compared with their saturated analogues 1j and 1i. The introduction of a methyl or ethyl group at the α -position of the ester group generally led to a significant increase in the herbicidal activities of the corresponding compounds, as exemplified by the following trend in the activities of these compounds: 1g (CH(CH₃)CO₂CH₃), 1h (CH(CH₃)CO₂C₂H₅), 1k (CH(C₂H₅)CO₂C₂H₅)>>1a $(CO_2C_2H_5)$, **1b** $(CH_2CO_2CH_3)$, **1c** $(CH_2CO_2C_2H_5)$. This rule was also found to be applicable to the chlorinated derivatives (*i.e.*, 1q, 1r, 1t, 1u>10, 1p, 1s).

Table 1 Herbicidal activities (inhibition ratings of 0-100) of compounds 1a-1u and 2a-2d at 375 g AI·ha⁻¹

| No | D | AT^{a} | | AR | | EC | | DS | |
|-----------|--|------------------|-------------------|-----|------|-----|------|-------|------|
| | | pre ^b | post ^b | pre | post | pre | post | pre j | post |
| 1a | $CO_2C_2H_5$ | 0 | 82 | C | 86 | 0 | 10 | 0 | 10 |
| 1b | CH ₂ CO ₂ CH ₃ | 15 | 100 | 35 | 30 | 0 | 15 | 0 | 15 |
| 1c | $CH_2CO_2C_2H_5$ | 10 | 100 | 20 | 24 | 0 | 10 | 0 | 5 |
| 1d | CH ₂ CO ₂ CH ₂ CH ₂ CH ₃ | 0 | 100 | 20 | 0 | 0 | 15 | 0 | 5 |
| 1e | CH ₂ CO ₂ CH(CH ₃) ₂ | 10 | 100 | C | 15 | 0 | 10 | 0 | 10 |
| 1f | CH ₂ CO ₂ C(CH ₃) ₃ | 20 | 100 | 99 | 52 | 40 | 62 | 84 | 0 |
| 1g | CH(CH ₃)CO ₂ CH ₃ | 85 | 100 | 99 | 100 | 20 | 100 | 42 | 27 |
| 1h | CH(CH ₃)CO ₂ C ₂ H ₅ | 96 | 100 | 99 | 100 | 40 | 100 | 35 | 53 |
| 1i | $CH_2CH_2CO_2C_2H_5$ | 29 | 100 | 90 | 27 | 10 | 45 | 35 | 50 |
| 1j | $CH_2CH_2CH_2CO_2C_2H_5$ | 100 | 100 | 100 | 100 | 0 | 99 | 49 | 51 |
| 1k | CH(C ₂ H ₅)CO ₂ C ₂ H ₅ | 100 | 100 | 100 | 100 | 60 | 100 | 28 | 24 |
| 11 | CH(C ₂ H ₅)CO ₂ C(CH ₃) ₃ | 20 | 100 | 80 | 0 | 25 | 20 | 87 | 25 |
| 1m | CH ₂ CHCHCO ₂ C ₂ H ₅ | 0 | 100 | 53 | 0 | 20 | 50 | 0 | 30 |
| 1n | CH ₂ C(CH ₂)CO ₂ C ₂ H ₅ | 0 | 100 | 50 | 0 | 10 | 20 | 0 | 40 |
| 10 | $CH_2CO_2C_2H_5$ | 0 | 0 | C | 0 | 0 | 0 | 0 | 0 |
| 1p | $CH_2CO_2C(CH_3)_3$ | 0 | 5 | 10 | 0 | 0 | 10 | 0 | 0 |
| 1q | CH(CH ₃)CO ₂ CH ₃ | 15 | 100 | 40 | 0 | 0 | 5 | 0 | 50 |
| 1r | CH(CH ₃)CO ₂ C ₂ H ₅ | 0 | 100 | 5 | 0 | 0 | 0 | 0 | 60 |
| 1s | $CH_2CH_2CO_2C_2H_5$ | 5 | 15 | C | 0 | 0 | 0 | 0 | 5 |
| 1t | $CH_2CH_2CH_2CO_2C_2H_5$ | 0 | 89 | C | 0 | 0 | 15 | 0 | 0 |
| 1u | CH(C ₂ H ₅)CO ₂ C ₂ H ₅ | 15 | 100 | 39 | 10 | 0 | 15 | 0 | 0 |
| 2a | $CH_2CO_2C_2H_5$ | 0 | 0 | C | 0 | 0 | 0 | 0 | 0 |
| 2b | $CH_2CO_2C(CH_3)_3$ | 0 | 0 | C | 0 | 0 | 10 | 0 | 0 |
| 2c | CH(CH ₃)CO ₂ CH ₃ | 5 | 0 | C | 0 | 0 | 0 | 0 | 0 |
| 2d | $CH_2CH_2CH_2CO_2C_2H_5$ | 0 | 0 | C | 0 | 0 | 5 | 15 | 0 |
| aci | fluorfen | 50 | 100 | 97 | 97 | 65 | 87 | 100 | 65 |

^{*a*} AT, *Abutilon theophrasti*; AR, *Amaranthus retroflexus*; EC, *Echinochloa crus-galli*; DS, *Digitaria sanguinalis*. ^{*b*} pre: preemergence; post: post-emergence.

Compounds 1h and 1j that showed excellent levels

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of activity were chosen for further testing their ED_{50} values. As shown in Table 2, compound **1h** exhibited better herbicidal activity against *A. theophrasti* and *E. crus-galli* (ED₅₀ value of 1.8 and 48.4 g AI-ha⁻¹, respectively) than compound **1j** (ED₅₀ values of 5.3 and 74.2 g AI-ha⁻¹, respectively). Notably, their activities against *A. theophrasti* were found to be far superior to the commercial herbicide acifluorfen (ED₅₀ value of 44.3 g AI-ha⁻¹). Furthermore, the results of the crop safety test showed that compound **1h** was safe for rice, wheat and maize at a dosage of 150 g AI-ha⁻¹ (Table 3), whereas the same rate of flumioxazin led to damage in all five of the crops tested in the current study. Even at an application rate of 300 g AI-ha⁻¹, maize still exhibited high tolerance towards compound **1h**.

Table 2 ED₅₀ values of compounds **1h**, **1j** and acifluorfen $(\text{post-emergence})^a$

| Commit | Abutilon theoph | rasti | Echinochloa crus-galli | | | |
|-------------|------------------|------------------|------------------------|------------------|--|--|
| Compa. | y=bx+a | ED ₅₀ | y=bx+a | ED ₅₀ | | |
| 1h | y = 1.48x - 0.38 | 1.8 | y = 0.89x - 1.50 | 48.4 | | |
| 1j | y = 1.02x - 0.74 | 5.3 | y = 0.81x - 1.52 | 74.2 | | |
| acifluorfen | y = 3.24x - 5.34 | 44.3 | / ^b | | | |
| | | | 1 | | | |

^{*a*} ED₅₀, 50% effective dose, the unit is g AI•ha⁻¹. ^{*b*}/, not tested.

Table 3 Crop selectivities of compound 1h and flumioxazin(post-emergence)

| Compd. | Dose ^a | Rice | White | Maize | Cotton | Soybean |
|-------------|-------------------|----------------|-------|-------|--------|---------|
| 1h | 150 | $+^{b}$ | + | _ | ++ | ++ |
| | 300 | / ^c | / | - | / | / |
| flumioxazin | 150 | ++ | ++ | ++ | ++ | ++ |

^{*a*} the unit is g AI•ha⁻¹. ^{*b*} Rating system for injury: ++, injury> 10%; +, injury=1%-10%; -, no injury. ^{*c*}/: not tested.

Table 4Herbicidal effects of compound **1h** in a maize field(Jingzhou, China)

| Commd | Dose ^{<i>a</i>} | Control effect of weed number ^{<i>b</i>} /% | | Control after 28 | Maize injury/% | |
|----------|--------------------------|--|------|---------------------|-------------------|-----|
| Compa. | | 7 d ^c | 14 d | Weed number | Weed weight | 7 d |
| 1h | 100 | 75 | 71 | 74 | 70 | 0 |
| | 200 | 82 | 80 | 87 | 83 | 0 |
| | 300 | 88 | 86 | 88 | 91 | 0 |
| atrazine | 800 | 90 | 92 | 91 | 85 | 10 |

^{*a*} The unit is g AI•ha⁻¹. ^{*b*} These data are the average values of inhibitory activity against all of the weeds tested, including *Amaranthus retroflexus*, *Eclipta prostrata*, *Echinochloa crus-galli*, *Convolvulus arvensis*, *Acalypha australis* and *Polygonum hydropiper* in maize field. ^{*c*} The number of days after the spraying of the herbicides.

Herbicidal activity of 1h in a field trial

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Compound 1h, which exhibited excellent herbicidal

activity and crop selectivity in the greenhouse field test, was evaluated further in a maize field trial. As shown in Table 4, 10% of the EC of **1h** showed good control effects against broadleaf weeds and some grass weeds at dosages in the range of 200-300 g AI•ha⁻¹. The 7-day herbicidal effect (88% control) of **1h** at 300 g AI•ha⁻¹ was almost equal to that of atrazine (90% control) at 800 g AI•ha⁻¹. Compound **1h** was also found to be safer for maize than atrazine (10% injury). 28 d after being sprayed onto the plants, compound **1h** still exhibited a higher level of activity (91% control) towards the weight of the weeds than atrazine (85% control). Most notably, compound **1h** showed a long lasting control effect, and there was no significant difference between the levels of control observed at 14 and 28 d.

Conclusions

Two series of tetrahydroisoindoline-1,3-diones have been designed and synthesized containing an alkoxycarbonyl substituted 2-benzoxazolinone moiety. The results of greenhouse tests indicated that some of these newly synthesized compounds exhibited excellent herbicidal activities against *A. theophrasti, A. retroflexus* and *E. crus-galli*. Compound **1h** was identified as the most promising candidate of all of the compounds tested because of its good post-emergence herbicidal activity and excellent selectivity for maize. Further field trials indicated that compound **1h** possessed similar herbicidal activity to atrazine, as well as a long duration of control efficacy. These results therefore suggest that compound **1h** could be a potential candidate for the development of a new post-emergence herbicide for use in maize fields.

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