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# Synthesis and Herbicidal Activity of Isoindoline-1,3-dione Substituted Benzoxazinone Derivatives Containing a Carboxylic Ester Group

Ming-Zhi Huang,*,† Fei-Xian Luo,‡ Hong-Bo Mo,‡ Ye-Guo Ren,† Xiao-Guang Wang,† Xiao-Ming Ou,† Man-Xiang Lei,† Ai-Ping Liu,† Lu Huang,† and Man-Cai Xu‡

†National Engineering Research Center for Agrochemicals, Hunan Research Institute of Chemical Industry, Changsha 410007, People's Republic of China, and ‡Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education of China), Hunan Normal University, Changsha 410081, People's Republic of China

A carboxylic ester group was introduced to three series of isoindolinedione substituted benzoxazinone derivatives. Some of these analogues exhibited good herbicidal activities, and the injury symptoms against weeds included leaf cupping, crinkling, bronzing, and necrosis, typical of protox inhibitor herbicides. Structurally, they were classified as Chemical Group **A** (4-carboxylic ester group-6-isoindolinyl-benzoxazinones), **B** (4-carboxylic ester group-7-isoindolinyl-benzoxazinones), and **C** (4-carboxylic ester group-6- tetrahydroisoindolinyl-benzoxazinones). All of the tested compounds were structurally confirmed by $^1$H NMR, IR, mass spectroscopy, and elemental analysis. Preliminary bioassay data of these three classes of compounds showed that, in general, the order of the herbicidal effectiveness is **C** > **A** > **B**. Several of the lead compounds, for example, **C10** (methyl 2-(6-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-7-fluoro-2-methyl-3-oxo-2*H*-benzo[*b*][1,4] oxazin-4(3*H*)-yl) propano-ate), **C12** (ethyl 2-(6-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-7-fluoro-2- methyl-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl) propanoate), and **C13** (ethyl 2-(6-(1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindol-2(3*H*)-yl)-7-fluoro-2-methyl-3-oxo-2H-benzo-[*b*][1,4]oxazin-4(3*H*)-yl) butanoate), exhibited greater than 80% control at 75 g a.i./ha in both pre- and postemergence treatments against dicotyledonous weeds, such as *Abutilon theophrasti* Medic, *Chenopodium album* L., and *Amaranthus ascendens* L., and monocotyledon weeds, such as *Digitaria sanguinalis* L., Echinochloa crus-galli L., and *Setaria viridis* L. On the basis of advanced screening tests and crop selectivity, compounds **C10**, **C12**, and **C13** are safer to crops than flumioxazin. Compounds **C10**, **C12**, and **C13** are potent to develop as pre-emergent herbicides used in peanut, soybean, maize, and cotton fields.

**KEYWORDS: Benzoxazinone; isoindoline-1; 3-dione substituted carboxylic ester derivatives; protox inhibitor; synthesis; herbicidal activity**

## INTRODUCTION

Flumioxazin (*1*, *2*) and thidiazimin (*3*) are commercial herbicides with their mode of action classified as protoporphyrinogen oxidase (protox) inhibitors. Protoporphyrinogen oxidase is an enzyme in the chlorophyll biosynthetic pathway (*4*−*7*). Flumioxazin and thidiazimin contain benzoxazinone as the core substructure. These benzoxazinone-type herbicides contain a substituted-(2*H*)-1,4-benzoxazin-3(4*H*)-one connected with a heterocyclic ring group as a common structural feature (**Figure 1**). On the side of heterocyclic ring moiety, a large number of heteroatom derivatives, including tetrahydrophthalimides, tetraconimides, oxazolinones, inmidazolidinediones, oxadiazolinones, pyrazoles, triazolidinediones, thiazolidinones, triazolinones, thiadiazolines, triazoles, tetrazolinones, trifluoromethyluracils, and other 6-membered cyclic imides were synthesized. The most optimal heterocyclic ring is the tetrahydrophthalimides connected at the 6-position of the benzoxazinone system (*8*, *9*). On the side of the substituted benzoxazinone moiety, analogues with various substituents at C-2 and N-4 of the oxazinone ring and at positions of C-5, C-6, C-7, and C-8 have been reported. The different substituent combinations on the aromatic ring, including methoxy, methoxycarbonyl, fluorine, chlorine, and trifluoromethyl, were introduced at different positions. It has been recognized that the optimal substituent is the fluorine at the 7-position (*10*). However, the structural combination of the C-2 and N-4 of the oxazine ring, a main element affecting the herbicidal activity of benzoxazinones, has attracted the intense attention of many

*To whom correspondence should be addressed. Tel: (+86)731-85357883. Fax: (+86)731-85959000. E-mail: huang-mz@163.com.


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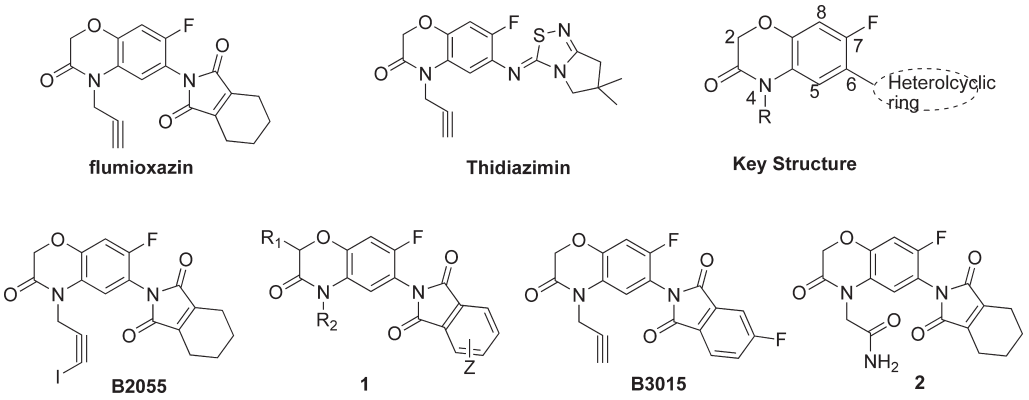
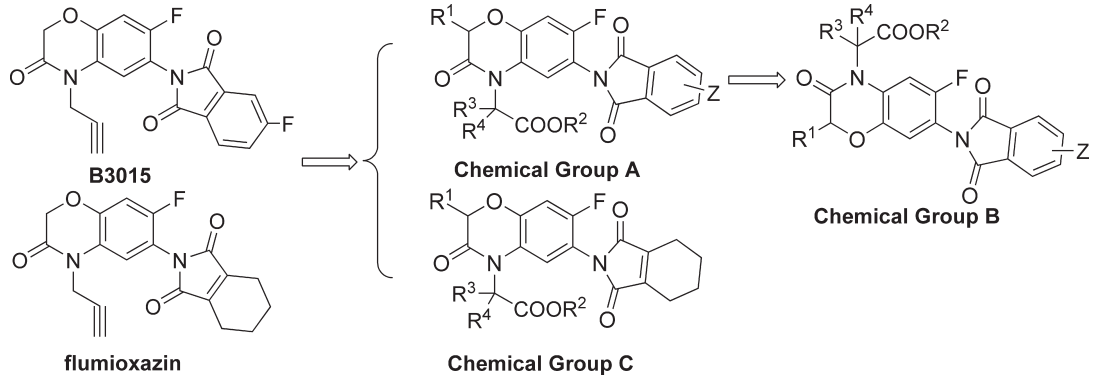



**Figure 1.** Chemical structure of flumioxazin, thidiazimin, **B2055**, **B3015**, **1**, **2**, and the key structure.

**Scheme 1.** Design Strategy for the Target Compounds




researchers. Most of the modification and optimization has been focused on the substituents at the N-4 position of the oxazine ring, ranging from propargyl, alkyl, halopropargyl, hydroxy, and alkoxy to substituted amino, carboxy amine, and so forth. (*11*−*13*).

In our previous work, we modified the structure of flumioxazin and its iodo-analogue **B2055** (*14*) by the replacement of the tetrahydro-isoindolinedione moiety with isoindolinedione, which resulted in the synthesis of analogues of N-4-substituted-benzoxazinyl-isoindoline-1,3-dione **1** (*15*), as shown in **Figure 1**. Among these analogues, the promising compound **B3015** provided $>80\%$ control at 75 g a.i. $ha^{-1}$ in both pre- and post emergence treatments against both dicotyledonous weeds such as *A. theophrasti* Medic, *C. album* L., and *A. ascendens* L., and monocotyledonous weeds such as *D. sanguinalis* L., *E. crus-galli* L., and *S. Viridis* L. The $IC_{50}$ values of **B3015** for the postemergence control of velvetleaf and crabgrass were comparable to those of flumioxazin.

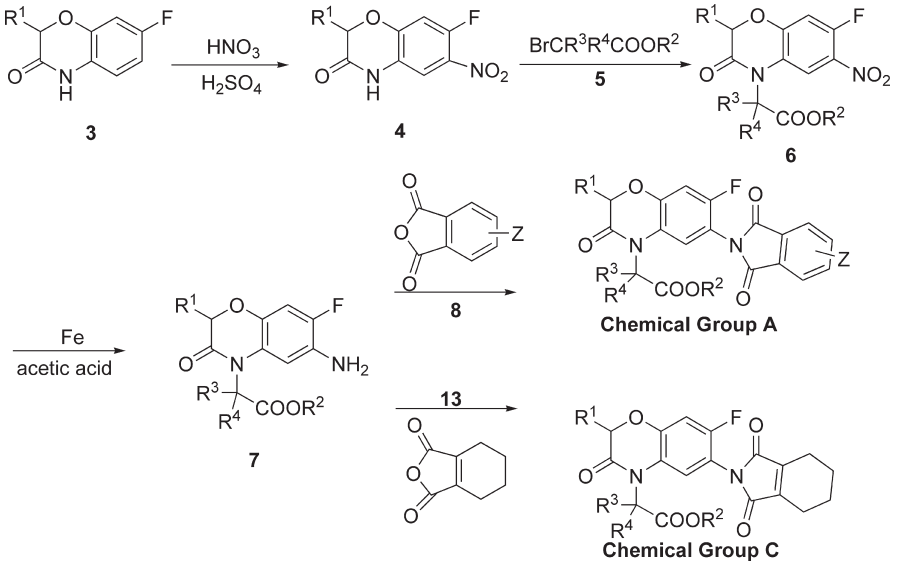
It was reported that compound **2** with N-4-acetamido substitution had also shown some promising herbicidal activities, which were synthesized from the corresponding intermediates with the N-4-carboxylic ester group by Kume's research group (*16*). To our surprise, however, the herbicidal activities of these intermediates with N-4-carboxylic ester group have not been reported. Since the carboxylic ester group is an essential group contained many commercial herbicidal products, such as fluazifop-butyl, haloxyfop-phenyl, cinidon-ethyl, chlorimuron-ethyl, and pyraflufen-ethyl (*17*, *18*), an optimization program was carried out by introducing the carboxylic ester group to the N-4 position of the oxazin ring of lead compounds flumioxazin and **B3015** with the hope that more novel compounds with promising herbicidal activities may be achieved. As depicted in **Scheme 1**, for the first time, targeted compounds in Chemical Groups **A** (4-carboxylic ester group-6-isoindolinyl-benzoxazinones), **B** (4-carboxylic ester group-7-isoindolinyl-benzoxazinones), and **C** (4-carboxylic ester group-6-tetrahydroisoindolinyl-benzoxazinones) were designed on the principle of molecular diversity and synthesized. Their structures were characterized by $^1$H NMR, IR, mass spectroscopy, and elemental analysis. Their herbicidal activities against monocotyledons and dicotyledons in pre- and postemergence were determined.

## MATERIALS AND METHODS

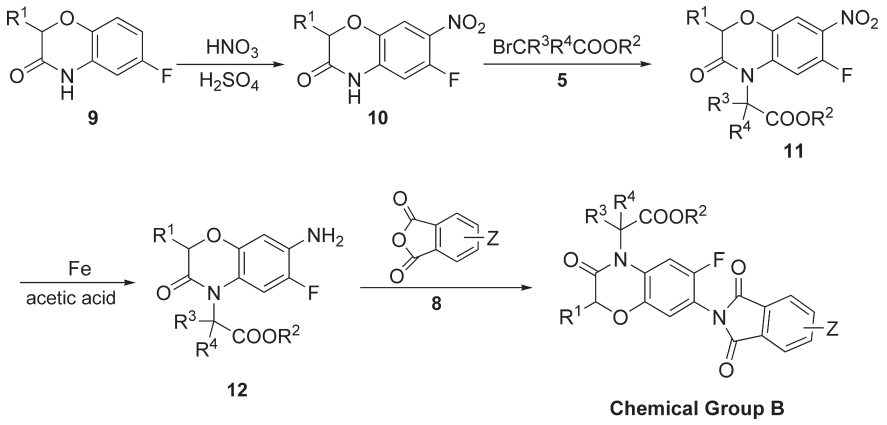
Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. The cross-linking degree of the amino resin is 1%. $^1$H NMR spectra were obtained with a Varian INOVA300 spectrometer using tetramethylsilane (TMS) as internal standard and deuterochloroform or dimethyl-$d_6$ sulfoxide as solvent. LC-mass spectra were recorded with an HP 1100 LC-MS using negative or positive ion scan mode. IR spectra were recorded in potassium bromide disks with a PE System 2000 FTIR spectrophotometer. Elemental analyses were carried out with a PE CHNS/O 2400 II elemental analyzer. Uncorrected melting points were taken on a WRS-1 melting point apparatus.

**Synthesis and Synthetic Methods.** Target compounds in Chemical Groups **A** and **C**, as shown in **Scheme 2**, were synthesized by the reaction of phthalic anhydride **8** (4,5,6,7-tetrahydrophthalic anhydride **13**) with appropriate 2-(6-amino-7-fluoro-2-substituted-3-oxo-2*H*-benzo[*b*][1,4]-oxazin-4(3*H*)-yl)-2-substituted acetate **7**, which were prepared in three steps from the intermediate 2-substituted benzoxazinone **3**: (a) nitrating benzoxazine derivatives with a $HNO_3-H_2SO_4$ mixture; (b) N-carboxy esterification of nitrobenzoxazine derivatives with appropriate 2-bromo-2-substituted-carboxy esters **5**; (c) and reduction of N-substituted nitrobenzoxazinone derivatives **6** with iron powder as reducing reagent and acetic acid as solvent. Target compounds in Chemical Group **B** were synthesized by the reaction of (substituted) phthalic anhydride **8** with an appropriate

**Scheme 2.** General Synthetic Route for the Target Compounds in Chemical Group **A** and Chemical Group **C**




**Scheme 3.** General Synthetic Route for the Target Compounds in Chemical Group **B**




2-(6-fluoro-7-amino-2- substituted-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)-2-substituted-acetate **12**. As shown in **Scheme 3**, compound **12** was prepared using the same procedure as **7**, but the starting substrates were **9** (*14*), which were obtained from 4-fluoro-2-nitrophenol.

All of the key intermediates, 7-fluoro-2-substituted-benzoxazinones **3**, 7-fluoro-6-nitro-2-substituted-benzoxazinones **4**, 6-fluoro-2-substituted-benzoxazinones **9**, and 6-fluoro-5-nitro-2-substituted-benzoxazinones **10**, were prepared according to the reported literature (*14*).

*General Synthetic Procedure for 2-(7-Fluoro-6-nitro-2-substituted-3-oxo-2H-benzo[b][1,4] oxazin-4(3H)-yl)-2-substituted Acetate* ***6***. Anhydrous potassium bicarbonate (6 mmol) was added to a solution of 7-fluoro-6-nitro-2-substituted-benzoxazineone **4** (4 mmol) in acetone. After stirring for 15 min at room temperature, a solution of 2-bromocarboxylic ester **5** (4 mmol) in acetone (20 mL) was added dropwise to the reaction mixture, then was heated under reflux for 3 h. After cooling to room temperature, the mixture was poured into ice water. The solid residue was filtered, washed three times with water, and dried to yield 2-(7-fluoro-6-nitro-2-substituted-3-oxo-2*H*-benzo[*b*] [1,4]oxazin-4(3*H*)-yl)-2-substituted acetate **6** as solid with the yield of 62−83%.

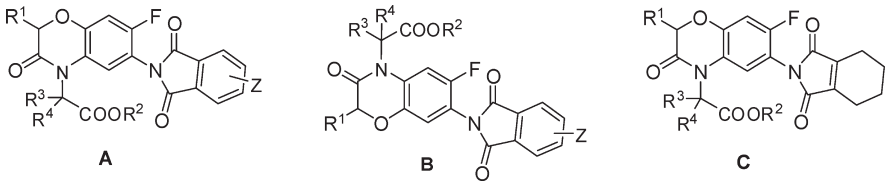
*General Synthetic Procedure for 2-(6-Amino-7-fluoro-2-substituted-3-oxo-2H-benzo[b][1,4] oxozin-4(3H)-yl)-2-substituted Acetate 7*. A solution of compound **6** in acetic acid (5 mL) was added dropwise to a mixture of iron powder (10 mmol) and acetic acid (20 mL) at 60 °C and the mixture heated under reflux for 1 h. After cooling to room temperature, the iron powder was filtered off, and the filtrate was poured into water. The solid residue was filtered, washed three times with water, and dried to yield 2-(6-amino-7-fluoro-2-substituted-3-oxo-2*H*-benzo[*b*][1,4]oxozin-4(3*H*)-yl)-2-substituted-acetate **7** as a solid with a yield of 50−69%.

The synthetic procedure for the intermediates, compounds **11** and **12**, were prepared the aforementioned method.

*General Synthetic Procedure for 2-(6-(1,3-Dioxo-isoindolin-2-yl)-7-fluoro-2-substituted-3- oxo-2,3-dihydrobenzo[b][1,4]-oxazin-4-yl)-2-substituted Acetate: Compunds in Chemical Group* ***A***. A mixture of compound **7** (1.5 mmol) and (substituted) phthalic anhydride **8** (1.8 mmol) in acetic acid (30 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated sodium bicarbonate solutionc and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 6:1 petroleum ether (60−90 °C)/ethyl acetate as eluent to yield the target compound in Chemical Group **A** as a yellow solid.

*General Synthetic Procedure for 2-(7-(1,3-Dioxo-isoindolin-2-yl)-6-fluoro-2-substituted-3-oxo-2,3-dihydro-benzo[b][1,4]-oxazin-4-yl)-2-substituted Acetate: Compounds in Chemical Group* ***B***. A mixture of compound **12** (1.5 mmol) and (substituted) phthalic anhydride **8** (1.8 mmol) in acetic acid (30 mL) was heated under reflux for 3.5 h. After cooling to room temperature, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 6:1 petroleum ether (60−90 °C)/ethyl acetate as eluent to yield target compounds in Chemical Group **B** as white solids.

**Table 1.** Chemical Structures, Physical Characteristics, Yields, Mass Spectrum, and Elemental Analysis Data of New Compounds in Groups **A**, **B**, and **C**



A B C

| compd | chemical structure | | | | | formula | m.p.(°C) | yield (%) | MS (*m*/*z*) | elemental analyses (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Z | | | | | C(Calcd) | H(Calcd) | N(Calcd) |
| A1 | H | $CH_3$ | H | H | | $C_{19}H_{13}FN_2O_6$ | 242−243 | 78 | 385 [M + H] | 59.09 (59.38) | 3.32 (3.41) | 7.38 (7.29) |
| A2 | H | $C_2H_5$ | H | H | | $C_{20}H_{15}FN_2O_6$ | 201−203 | 75 | 399 [M + H] | 60.11 (60.30) | 3.78 (3.80) | 7.20 (7.03) |
| A3 | H | $CH_3$ | H | $CH_3$ | | $C_{20}H_{15}FN_2O_6$ | 181−183 | 72 | 397 [M − H] | 60.23 (60.30) | 3.67 (3.80) | 7.22 (7.03) |
| A4 | H | $C_2H_5$ | H | H | 5,6-2Cl | $C_{20}H_{13}Cl_2FN_2O_6$ | 193 −194 | 52 | 465 [M − H] | 51.59 (51.41) | 2.90 (2.80) | 6.00 (6.00) |
| A5 | H | $C_2H_5$ | H | $CH_3$ | 5-$NO_2$ | $C_{21}H_{16}FN_3O_8$ | 184−186 | 71 | 456 [M − H] | 55.05 (55.15) | 3.35 (3.53) | 9.30 (9.19) |
| A6 | H | $C_2H_5$ | H | $CH_3$ | 5,6-2Cl | $C_{21}H_{15}Cl_2FN_2O_6$ | 163−164 | 65 | 479 [M − H] | 52.41 (52.41) | 3.29 (3.14) | 5.64 (5.82) |
| A7 | H | $C_2H_5$ | H | $CH_3$ | 5-$CH_3$ | $C_{22}H_{19}FN_2O_6$ | 179−181 | 53 | 425 [M − H] | 61.69 (61.97) | 4.50 (4.49) | 6.78 (6.57) |
| A8 | H | $C_2H_5$ | H | H | 5-$CH_3$ | $C_{21}H_{17}FN_2O_6$ | 172−174 | 60 | 411 [M − H] | 61.43 (61.16) | 4.20 (4.16) | 6.62 (6.79) |
| A9 | H | $C_2H_5$ | H | H | 5-$NO_2$ | $C_{20}H_{14}FN_3O_8$ | 181−182 | 51 | 442 [M − H] | 54.48 (54.18) | 3.30 (3.18) | 9.29 (9.48) |
| B1 | H | $C_2H_5$ | H | H | | $C_{20}H_{15}FN_2O_6$ | 260−261 | 53 | 397 [M − H] | 60.05 (60.30) | 3.77 (3.80) | 7.27 (7.03) |
| B2 | H | $C_2H_5$ | H | H | 5-$CH_3$ | $C_{21}H_{17}FN_2O_6$ | 218−219 | 66 | 411 [M − H] | 61.99 (61.97) | 4.54 (4.49) | 6.67.(6.57) |
| B3 | H | $C_2H_5$ | H | $CH_3$ | 5,6-2Cl | $C_{21}H_{15}Cl_2FN_2O_6$ | 167−168 | 60 | 479 [M − H] | 52.65 (52.41) | 3.44 (3.14) | 5.73 (5.82) |
| C1 | H | $CH_3$ | H | H | | $C_{19}H_{17}FN_2O_6$ | 172−174 | 64 | 389 [M + H] | 58.49 (58.76) | 4.40 (4.41) | 7.43 (7.21) |
| C2 | H | $CH_3$ | H | $CH_3$ | | $C_{20}H_{19}FN_2O_6$ | 187−189 | 70 | 403 [M + H] | 59.88 (59.70) | 4.87 (4.76) | 6.89 (6.96) |
| C3 | H | $CH_3$ | H | $C_2H_5$ | | $C_{21}H_{21}FN_2O_6$ | 159−160 | 58 | 415 [M − H] | 60.77 (60.57) | 5.18 (5.08) | 6.65 (6.73) |
| C4 | H | $C_2H_5$ | H | H | | $C_{20}H_{19}FN_2O_6$ | 116−118 | 61 | 403 [M + H] | 59.87 (59.70) | 4.80 (4.76) | 6.90 (6.96) |
| C5 | H | $C_2H_5$ | H | $CH_3$ | | $C_{21}H_{21}FN_2O_6$ | 204−206 | 67 | 415 [M − H] | 60.39 (60.57) | 5.08 (5.08) | 6.87 (6.73) |
| C6 | H | $C_2H_5$ | H | $C_2H_5$ | | $C_{22}H_{23}FN_2O_6$ | 164−166 | 58 | 429 [M − H] | 61.59 (61.39) | 5.48 (5.39) | 6.42 (6.51) |
| C7 | H | $C_2H_5$ | H | $C_6H_5$ | | $C_{26}H_{23}FN_2O_6$ | 150−151 | 56 | 477 [M − H] | 65.37 (65.27) | 4.84 (4.85) | 5.77 (5.85) |
| C8 | $CH_3$ | $C_2H_5$ | $CH_3$ | $CH_3$ | | $C_{23}H_{25}FN_2O_6$ | 147−150 | 71 | 443 [M − H] | 62.36 (62.15) | 5.87 (5.67) | 6.05 (6.30) |
| C9 | $CH_3$ | $CH_3$ | H | H | | $C_{20}H_{19}FN_2O_6$ | 166−167 | 72 | 401 [M − H] | 59.42 (59.70) | 4.75 (4.76) | 7.08 (6.96) |
| C10 | $CH_3$ | $CH_3$ | H | $CH_3$ | | $C_{21}H_{21}FN_2O_6$ | 128−130 | 69 | 415 [M − H] | 60.47 (60.57) | 5.18 (5.08) | 6.62 (6.73) |
| C11 | $CH_3$ | $C_2H_5$ | H | H | | $C_{21}H_{21}FN_2O_6$ | 132−134 | 65 | 415 [M − H] | 60.29 (60.57) | 5.04 (5.08) | 6.96 (6.73) |
| C12 | $CH_3$ | $C_2H_5$ | H | $CH_3$ | | $C_{22}H_{23}FN_2O_6$ | 167−169 | 73 | 429 [M − H] | 61.57 (61.39) | 5.48 (5.39) | 6.36 (6.51) |
| C13 | $CH_3$ | $C_2H_5$ | H | $C_2H_5$ | | $C_{23}H_{25}FN_2O_6$ | 127−128 | 68 | 443 [M − H] | 62.43 (62.15) | 5.79 (5.67) | 6.20 (6.30) |
| C14 | $CH_3$ | $C_2H_5$ | H | $C_6H_5$ | | $C_{27}H_{25}FN_2O_6$ | 168−171 | 57 | 491 [M − H] | 65.65 (65.85) | 5.02 (5.12) | 5.77 (5.69) |

*General Synthetic Procedure for 2-(6-(1,3-Dioxo-4,5,6,7-tetrahydro-1H-isoindol-2(3H)-yl)-7-fluoro2-substituted-3-oxo-2,3-dihydro-benzo[b][1,4]oxazin-4-yl)-2-substituted Acetate: Compounds in Chemical Group C*. A mixture of compound **7** (1.5 mmol) and 4,5,6,7-tetrahydrophthalic anhydride **13** (1.8 mmol) in acetic acid (30 mL) was heated under reflux for 3.5 h. After cooling to room temperature, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated sodium bicarbonate solution, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 6:1 petroleum ether (60−90 °C)/ethyl acetate as eluent to yield target compounds in Chemical Group **C** as slight yellow solids.

**Biological Activity (*15*) .** Test compounds were formulated as 100 g/L emulsified concentrates by using DMF as solvent and TW-80 as emulsification reagent. The stock solutions 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, 1.7% organic matter, 37.5% clay particles, and CEC of 12.9 cmol/kg. The rate of application [grams of active ingredient (ai) per hectare] was calculated by the total amount of active ingredient in the formulation divided by the surface area of the pot.

**Determination of Preliminary Herbicidal Activity against Dicotyledonous Weeds and Monocotyledonous Weeds.** Plastic pots (9-cm diameter) were filled with soil to a depth of 6 cm. Approximately 20 seeds of *Abutilon theophrasti* Medic (AT), *Chenopodium album* L. (CA), *Amaranthus ascendens* L. (AA), *Digitaria sanguinalis* L. (DS), *Echinochloa crus-galli* L. (EC), and *Setaria viridis* L. (SV) were sown in the soil at a depth of 5-mm and grown at 22−25 °C in a greenhouse. The diluted formulation test solutions were applied to pre-emergence treatment 24 h after weeds were sown. For the postemergence treatment, dicotyledonous weeds were treated at the 2-leaf stage, and monocotyledonous weeds were treated at the 1-leaf stage. The pre- and postemergence application rates were 75 g of ai/ha. Untreated seedlings were used as the control group, while the solvent (DMF)-treated seedlings were used as the solvent control group. Each treatment was conducted in triplicate. After cultivation for 15 days, the herbicidal activity on test weeds was evaluated by visually comparing the weed growth inhibition of all test treatments with untreated controls, calculated as the average of the triplicates, and rated on the basis of percentage of weed growth inhibition using the following rating system: ++, > 80%; +, 50−80%; − < 50%.

**Determination of Advanced Herbicidal Activity.** Six kinds of weeds such as *Abutilon theophrasti* Medic (AT), *Amaranthus spinosus* L. (AS), *Chenopodium album* L.(CA), *Digitaria sanguinalis* L. (DS), *Echinochloa crus-galli* L. (EC), and *Setaria viridis* L. (SV) were used for the advanced herbicidal screening test of compounds **C10**, **C12**, and **C13**. The bioassay process was the same as the above-described method for determining the preliminary herbicidal activity, but the treatment dosage was reduced to 7.5, 15, and 37.5 g a.i./ha. Each treatment was conducted in triplicate, and the bioassay result was reported as the average of the percentage of weed growth inhibition for the triplicates. The significance of differences of the herbicidal activity for all treatments were subjected to statistical analysis using Duncan's multiple range test with $P = 0.05$.

**Determination of Crop Selectivity.** The seeds of peanut (*Arachis hypogaea*), rice (*Oryza sativa* L.), wheat (*Triticum aestivum* L.), maize (*Zea mays* L.), cotton (*Gossypium* spp.), soybean (*Glycine max*), and rape (*Brassica campestris* L.) were sown in plastic pots (9-cm diameter) filled with soil to a depth of 6 cm and grown at 22−25 °C in the greenhouse. Test compounds were applied at the dosage of 300, 150, 75, and 37.5 g a.i./ha at the pre-emergence stage and at the dosage of 60, 30, 15, and 7.5 g a.i./ha for the postemergence evaluation. Each treatment was conducted in triplicate.

After cultivation for 15 days, the crop selectivity was evaluated by visually comparing the crop phytotoxicity of all test treatments with untreated controls, calculated as the average of the triplicates, and rated on the basis of percentage of crop growth inhibition using the following rating system: ++, >10% growth inhibition; +, 1−10% growth inhibition; −, no growth inhibition.

## RESULTS AND DISCUSSION

**Synthesis and Structure Characterization.** *Reduction Reaction.* The reduction of nitro to amines can be achieved by several methods (*19*−*22*) including (a) reduced iron powder/acetic acid, (b) high pressure hydrogen gas, (c) $SnCl_2$/HCl, and (d) $(NH_4)_2S$/$Na_2S$. For the small scale reduction reaction to prepare intermediates **7** or **12**, we used the method of iron/acetic acid conditions. Although the yield was not very high, its mild condition (the reaction was generally completed within 40 min at 55−65 °C reaction temperature) served well as a laboratory method. For the larger scale preparation of compound **7** (>100 g), however, we have used catalytic hydrogenation of compound **6** in an autoclave. Although the reaction time is more than 5 h, the yield can reach 90%.

*Synthesis of Target Compounds in Chemical Groups **A**, **B**, and **C**.* The target compounds in Chemical Groups **A**, **B**, or **C**, which were depicted in the last step reaction in **Schemes 2** and **3** can be prepared by the condensation of compound **7** or **12** with a 20% molar excess of appropriate anhydride **8** or **13**. After the reaction was completed, the workup procedure was usually undertaken in the following way: amino resin, an anhydride scavenger, was added to the reaction mixture and was stirred at 80 °C for 6 h. The mixture was then cooled down to room temperature, and the resin was filtered off. The filtrate was poured into ice water and extracted with ethyl acetate several times. The combined organic layer was washed sequentially with water, saturated sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate and filtration, the solution was concentrated in vacuo to give a target product. However, the results from the HPLC (using 1:4 methanol/purified water as flow phase) indicated that the chemical purity was usually below 85%. Further purification of the target compounds in Chemical Group **A**, **B**, or **C** should be undertaken by column chromatography. The procedure was not an economic and convenient method to purify target compounds. Therefore column chromatography purification method has been adopted directly, while more target compounds in Chemical Group **A**, **B**, or **C** were synthesized.

**Table 1** summarizes the chemical structures, physical characteristics, yields, mass spectrum, and elemental analysis data of three novel series of compounds in Chemical Groups **A**, **B**, and **C**. $^1$H NMR data are listed in **Table 2**. All compounds had characteristic IR absorbances at 1707−1736 $cm^{-1}$ (carbonyl in benzoxazinyl moiety), 1679−1705 $cm^{-1}$ (carbonyl in isoindolin-1,3-dione moiety), and 1710−1769 $cm^{-1}$ (carbonyl in N-substituted carboxylic ester moiety), respectively.

*Preliminary Herbicidal Activity.* As shown in **Table 3**, several compounds exhibited high herbicidal activity. The injury symptoms against weeds included leaf cupping, crinkling, bronzing, and necrosis, typical of protox inhibitor herbicides (*23*, *24*). Several interesting characteristics of these target compounds may be pointed out as follows.

First, among the three series of compounds, compounds in Group **C** had greater herbicidal activity than compounds in Groups **A** and **B**, and compounds in Group **B** had no detectable activity in the conditions tested, either in pre- or postemergency.

Second, compounds in Group **C** were more potent against dicotyledonous weeds than monocotyledonous ones. All of the tested 14 compounds in the Group **C** series had more than 80% control at 75 g of ai/ha in postemergence treatment against dicotyledonous weeds such as *A. theophrasti* Medic, *C. album* L., and *A. ascendens* L. Among them, compounds **C4**, **C5**, **C9**, **C10**, **C11**, **C12**, and **C13** also exhibited more than 80% control in pre-emergence treatment against dicotyledonous weeds such as *A. theophrasti* Medic, *C. album* L., and *A. ascendens* L.

Third, compounds in Group **C** had some herbicidal activity against monocotyledons, and the activity in postemergence treatment was better than that in pre-emergence treatment. Among all of the tested 14 compounds, **C2**, **C5**, **C10**, **C12**, and **C13** had more than 80% control at 75 g of ai/ha in postemergence treatments against monocotyledonous weeds such as *D. sanguinalis* L., *E. crus-galli* L., and *S. viridis* L., while compound **C7** had more than 80% control against *D. sanguinalis* L. and *S. viridis* L. Compounds **C10**, **C12**, **C13**, and **C14** had same herbicidal efficiency in pre-emergence treatments against monocotyledonous weeds.

Fourth, several compounds in Group **A** showed herbicidal activity against dicotyledonous weeds in postemergence treatment. For example, compounds **A1**, **A2**, and **A3** showed more than 80% control against dicotyledonous weeds such as *A. theophrasti* Medic, *C. album* L., and *A. ascendens* L., and compound **A7** showed more than 80% control against *A. theophrasti* Medic.

Finally, comparable to flumioxazin and **B3015**, compounds **C10**, **C12**, and **C13** also possess more than 80% control at 75 g a.i./ha in both pre- and postemergence treatments against both dicotyledonous weeds and monocotyledonous weeds. It is demonstrated that the introduction of the carboxylic ester to the N-4 position of benzoxazinone can also enhance the herbicidal efficacy of benzoxazinones.

*Preliminary Structure−Activity Relationship Study.* Some interesting structure−activity relationship may be drawn from **Tables 1** and **3**. The substituted position of newly synthesized carboxylic ester derivatives of isoindoline-1,3-dione-substituted benzoxazine can sufficiently influence the herbicidal activity. For example, when the substituted position of isodoline-1,3-dione was changed from the 6-position to 7-position, the resulting compounds had almost no herbicidal activity.

Furthermore, from all 9 compounds of Group **A**, their herbicidal activities were not influenced by the substituted group on the ring of isoindoline. For example, activity was not increased when a methyl, nitro, or chloro group was introduced onto the isoindoline ring.

Changing the substitution from isoindoline-1,3-dione to 1,3-dioxo-4,5,6,7-tetrahydro-1*H*-isoindolin-2-yl significantly increased the herbicidal activity. For example, the herbicidal activity of compound **C1**, **C2**, or **C4** was higher than that of corresponding compound **A1**, **A3**, or **A2**, respectively.

The introduction of a methyl group on the 2-position of the benzoxazine ring was propitious to enhance the herbicidal activity in soil treatments. For example, compound **C10**, **C12**, or **C13** against mono- and dicotyledons exhibited higher herbicidal activities than compound **C2**, **C5**, or **C6**, respectively.

The number of alkyl groups on the carboxyl carbon connected to the N atom of the benzoxazine ring of the carboxylic ester derivatives also influenced the herbicidal activity. If there was only one methyl or ethyl group substituted on the carboxy carbon, then it increased the herbicidal activity against the monocotyledon. For example, except for compound **C3**, the herbicidal activity of compound **C2**, **C5**, **C10**, or **C12** against monocotyledons was higher than that of compound **C1**, **C4**, **C9**,

**Table 2.** $^1$H NMR Data of the New Compounds in Chemical Groups **A**, **B**, and **C**

| compd | $^1$H NMR, $\delta$(300 MHz,$CDCl_3$, ppm) |
|---|---|
| **A1** | 3.78 (s, 3H, $OCH_3$), 4.65 (s, 2H, $NCH_2$), 4.75(s, 2H, $OCH_2$), 6.72 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.97 (d, 1H, *J* = 9.9 Hz, O-Ph-H), 7.80−7.83 (m, 2H, Ar-H), 7.95−7.98 (m, 2H, Ar-H) |
| **A2** | 1.27 (t, 3H, *J* = 7.2 Hz, $CH_3$), 4.23 (q, 2H, *J* = 7.2 Hz, $CH_2$), 4.64 (s,2H, $NCH_2$), 4.75(s, 2H, $OCH_2$), 6.73 (d, 1H, *J* = 6.6 Hz, OPh-H), 6.98 (d, 1H, *J* = 9.6 Hz, O-Ph-H), 7.81−7.84 (m, 2H, Ar-H), 7.96−7.99 (m, 2H, Ar-H) |
| **A3** | 1.64 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 3.76 (s, 3H, $OCH_3$), 4.69 (q, 2H, *J* = 15 Hz, $OCH_2$), 5.36 (q, 1H, *J* = 7.2 Hz, NCH), 6.78 (d, 1H, *J* = 6.6 Hz, Ar-H), 6.98 (d, 1H, *J* = 9.9 Hz, Ar-H), 7.81−7.84 (m, 2H, Ar-H), 7.96−7.98 (m, 2H, Ar-H) |
| **A4** | 1.26 (t, 3H, *J* = 6.9 Hz, $CH_2CH_3$), 4.24 (q, 2H, *J* = 6.9 Hz, $CH_2CH_3$), 4.63 (s, 2H, $NCH_2$), 4.75 (s, 2H, $OCH_2$), 6.70 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.97 (d, 1H, *J* = 9.6 Hz, O-Ph-H), 8.04 (s, 2H, Ar-H) |
| **A5** | 1.22 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 1.63 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 4.20−4.25(m, 2H, $CH_2CH_3$), 4.74 (q, 2H, *J* = 14.7 Hz, $OCH_2$), 5.39 (q, 1H, *J* = 7.5 Hz, NCH), 6.81 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 7.01 (d, 1H, *J* = 9.6 Hz, O-Ph-H), 8.17 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.71 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.79 (s, 1H, Ar-H) |
| **A6** | 1.21 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 1.63 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 4.20−4.24(m, 2H, $CH_2CH_3$), 4.68 (q, 2H, *J* = 15 Hz, $OCH_2$), 5.35 (q, 1H, *J* = 6.9 Hz, NCH), 6.78 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.98 (d, 1H, *J* = 9.6 Hz, O-Ph-H), 8.04 (s, 2H, Ar-H) |
| **A7** | 1.21 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 1.63 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 2.59 (s, 3H, Ph−$CH_3$), 4.20−4.24(m, 2H, $CH_2CH_3$), 4.68 (q, 2H, *J* = 15 Hz, $OCH_2$), 5.31 (q, 1H, *J* = 7.2 Hz, NCH), 6.80 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.97 (d, 1H, *J* = 9.6 Hz, O-Ph-H), 7.61 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 7.84 (d, 1H, *J* = 7.8 Hz, Ar-H) |
| **A8** | 1.26 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 2.56 (s, 1H, $CH_3$−Ph), 4.23 (q, 2H, *J* = 7.5 Hz, $CH_3CH_2$), 4.63 (s, 3H, $OCH_2$), 4.73 (s, 2H, $NCH_2$), 6.72 (d, 1H, *J* = 6.9 Hz, OPh-H), 6.95 (d, 1H, *J* = 9.6 Hz, OPh-H), 7.61 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 7.83 (d, 1H, *J* = 7.8 Hz, Ar-H) |
| **A9** | 1.27 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 4.23 (q, 2H, *J* = 7.2 Hz, $CH_3CH_2$), 4.63 (s, 3H, $OCH_2$), 4.76 (s, 2H, $NCH_2$), 6.73 (d, 1H, *J* = 6.9 Hz, OPh-H), 6.98 (d, 1H, *J* = 9.6 Hz, OPh-H), 7.99−8.25 (m, 3H, Ar-H) |
| **B1** | 1.32 (t, 3H, *J* = 7.2 Hz, $CH_3$), 4.28 (q, 2H, *J* = 7.2 Hz, $CH_2$), 4.64 (s,2H, $NCH_2$), 4.73 (s, 2H, $OCH_2$), 6.69 (d, 1H, *J* = 10.2 Hz, OPh-H), 7.04 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 7.81−7.83 (m, 2H, Ar-H), 7.96−7.99 (m, 2H, Ar-H) |
| **B2** | 1.32 (t, 3H, *J* = 7.2 Hz, $CH_3$), 2.56 (s, 1H, $CH_3$-Ph), 4.28 (q, 2H, *J* = 7.2 Hz, $CH_2$), 4.63 (s,2H, $NCH_2$), 4.72 (s, 2H, $OCH_2$), 6.68 (d, 1H, *J* = 10.5 Hz, OPh-H), 7.03 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 7.61−7.86 (m, 3H, Ar-H) |
| **B3** | 1.24 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 1.65 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 4.22−4.26(m, 2H, $CH_2CH_3$), 4.64−4.76 (q, 2H, $OCH_2$), 5.37 (q, 1H, *J* = 6.9 Hz, NCH), 6.68 (d, 1H, *J* = 10.2 Hz, O-Ph-H), 7.03 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 8.04 (s, 2H, Ar-H) |
| **C1** | 1.81−1.85 (m, 4H, $CH_2CH_2$), 2.41−2.45 (m, 4H, 2*$CH_2$), 3.77 (s, 3H, $OCH_3$), 4.63 (s, 2H, $NCH_2$), 4.72 (s, 2H, $OCH_2$), 6.61 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.91 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C2** | 1.62 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 1.82−1.86 (m, 4H, $CH_2CH_2$), 2.42−2.46 (m, 4H, 2*$CH_2$), 3.75 (s, 3H, $OCH_3$), 4.68 (q, 2H, *J* = 15 Hz, $OCH_2$), 5.36 (q, 1H, *J* = 7.2 Hz, NCH), 6.65 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.92 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C3** | 0.91 (t, 3H, *J* = 7.5 Hz, $CH_2CH_3$), 1.81−1.85 (m, 4 H, $CH_2CH_2$), 2.00−2.32 (d*m, 2H, −$CH_2$−), 2.41−2.45 (m, 4H, 2*$CH_2$), 3.74 (s, 3H, $OCH_3$), 4.68(q, 2H, *J* = 15 Hz, $OCH_2$), 5.36 (q, 1H, *J* = 7.2 Hz, NCH), 6.67 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.92 (d, 1H, *J* = 9.6 Hz, O-Ph-H) |
| **C4** | 1.26 (t, 3H, *J* = 7.5 Hz, $CH_2CH_3$), 1.82−1.84 (m, 4H, $CH_2CH_2$), 2.42−2.43 (m, 4H, 2*$CH_2$), 4.23(q, 2H, *J* = 6 Hz, $CH_2CH_3$), 4.61 (s, 2H, $OCH_2$), 4.71 (s, 2H, $NCH_2$), 6.61 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.91(d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C5** | 1.22 (t, 3H, *J* = 7.5 Hz, $CH_2CH_3$), 1.63 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 1.83−1.84 (m, 4H, $CH_2CH_2$), 2.40−2.48 (m, 4H, 2*$CH_2$), 4.18−4.25 (m, 2H, $CH_2CH_3$), 4.70 (q, 2H, *J* = 15 Hz, $OCH_2$), 5.29 (q, 1H, *J* =7.2 Hz, NCH), 6.68 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.93 (d, 1 H, *J* = 9.9 Hz, O-Ph-H) |
| **C6** | 0.91 (t, 3H, *J* = 7.5 Hz, $CH_2CH_3$), 1.20 (t, 3H, *J* = 7.2 Hz, $OCH_2CH_3$), 1.81−1.85 (m, 4H, $CH_2CH_2$), 2.00−2.29 (d*m, 2H, −$CH_2$−), 2.41−2.45 (m, 4H, 2*$CH_2$), 4.16−4.25 (m, 2H, $OCH_2CH_3$), 4.68 (q, 2H, *J* = 15 Hz, $OCH_2$), 5.31−5.36 (m, 1H, NCH), 6.70 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.92 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C7** | 1.20 (t, 3H, *J* = 6.9 Hz, $OCH_2CH_3$), 1.77−1.81 (m, 4H, $CH_2CH_2$), 2.36−2.38 (m, 4H, 2*$CH_2$), 4.21−4.33 (m, 2H, $OCH_2CH_3$), 4.76 (q, 2H, *J* = 15 Hz, $OCH_2$), 6.41 (s, 1H, NCH), 6.66 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.91 (d, 1H, *J* = 9.9 Hz, O-Ph-H), 7.32−7.37 (m, 5H, Ph-H) |
| **C8** | 1.31 (t, 3H, *J* = 6.9 Hz, $OCH_2CH_3$), 1.46 (s, 6H, $C(CH_3)_2$), 1.62 (d, 3H, *J* = 6.6 Hz, $CHCH_3$), 1.83−1.84 (m, 4H, $CH_2CH_2$), 2.41−2.45 (m, 4H, 2*$CH_2$), 4.12−4.21 (m, 2H, $OCH_2CH_3$), 4.81−4.82 (m, 1H, $CHCH_3$), 6.61 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.91(d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C9** | 1.61 (d, 3H, *J* = 6.9 Hz, $OCHCH_3$), 1.83−1.84 (m, 4H, $CH_2CH_2$), 2.41−2.45 (m, 4H, 2*$CH_2$), 3.77 (s, 3H, $OCH_3$), 464 (q, 2H, *J* = 15.6 Hz, $NCH_2$), 4.74−4.76 (m, 1H, $OCHCH_3$), 6.58 (d, 1H, *J* = 6.3 Hz, O-Ph-H), 6.91 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C10** | 1.57 (d, 3H, *J* = 6.9 Hz, $NCHCH_3$), 1.60 (d, 3H, *J* = 7.5 Hz, $OCHCH_3$), 1.81−1.85 (m, 4H, $CH_2CH_2$), 2.42−2.46 (m, 4H, 2*$CH_2$), 3.74 (s, 3H, $OCH_3$), 4.73 (2*q, 1H, *J* = 6.9 Hz, $OCHCH_3$), 4.74−4.76 (m, 1H, $OCHCH_3$), 5.35−5.38 (m, 1H, NCH), 6.63 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.91 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C11** | 1.25 (t, 3H, *J* = 7.2 Hz, $OCH_2CH_3$), 1.60 (d, 3H, *J* = 6.9 Hz, $OCHCH_3$), 1.81−1.85 (m, 4H, $CH_2CH_2$), 2.41−2.45 (m, 4H, 2*$CH_2$), 4.23 (q, 2H, *J* = 7.2 Hz, $OCH_2CH_3$), 4.58 (q, 2H, *J* = 6.9 Hz, $NCH_2$), 4.76 (q, 1H, *J* = 6.9 Hz, $OCHCH_3$), 6.59 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.90 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C12** | 1.20 (t, 3H, *J* = 7.2 Hz, $OCH_2CH_3$), 1.53−1.61 (m, 6H, $NCHCH_3$, $OCHCH_3$), 1.82−1.85 (m, 4H, $CH_2CH_2$), 2.41−2.45 (m, 4H, 2*$CH_2$), 4.16−4.25 (m, 2H, $OCH_2CH_3$), 4.68 (2*q, 1H, *J* = 6.9 Hz, $OCHCH_3$), 5.32 (2*q, 1H, *J* = 7.2 Hz, $NCHCH_3$), 6.66 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.91 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C13** | 0.94 (t, 3H, *J* = 7.2 Hz, $CHCH_2CH_3$), 1.22 (t, 3H, *J* = 7.2 Hz, $OCH_2CH_3$), 1.60 (d, 3H, *J* = 6.9 Hz, $OCHCH_3$), 1.82−1.86 (m, 4H, $CH_2CH_2$), 2.01−2.29 (d*m, 2H, $CHCH_2CH_3$), 2.42−2.46 (m, 4H, 2*$CH_2$), 4.17−4.26 (m, 2H, $OCH_2CH_3$), 4.68 (2*q, 1H, *J* = 6.9 Hz, $OCHCH_3$), 5.32−5.36 (m, 1H, NCH), 6.69 (d, 1H, *J* = 6.6 Hz, O-Ph-H), 6.91 (d, 1H, *J* = 9.9 Hz, O-Ph-H) |
| **C14** | 1.19 (t, 3H, *J* = 6.9 Hz, $OCH_2CH_3$), 1.66 (d, 3H, *J* = 6.9 Hz, $OCHCH_3$), 1.78−1.82 (m, 4H, $CH_2CH_2$), 2.35−2.39 (m, 4H, 2*$CH_2$), 4.17−4.32 (m, 2H,$OCH_2CH_3$), 4.75−4.87 (m, 1H, $OCHCH_3$), 6.47 (s, 1H, NCH), 6.60 (d, 1H, *J* = 6.9 Hz, O-Ph-H), 6.90 (d, 1H, *J* = 9.6 Hz, O-Ph-H), 7.30−7.39 (m, 5H, Ph-H) |

or **C11**, respectively. However, when a compound contains two substituents, the herbicidal activity decreased dramatically. As an example, compound **C8** exhibited much lower herbicidal activity than compounds **C10** and **C12**.

*Advanced Screening Test and Crop Selectivity of Compounds **C10**, **C12**, and **C13***. On the basis of the herbicidal activity primary test, compounds **C10**, **C12**, and **C13** show promising activities comparable to those of flumioxazin. In order to further assess the herbicidal activity of those compounds, **C10**, **C12**, and **C13** were selected as interesting leads for advanced screening tests. As shown in **Table 4**, at the dosage of 7.5−37.5 g a.i./ha, all of the three compounds exhibited 100% control against dicotyledon weeds such as *Abutilon theophrasti* Medic, *Amaranthus spinosus* L., and *Chenopodium album* L. in postemergence treatment, and their herbicidal activity compared with that of flumioxazin exhibited no significant differences at $P = 0.05$ on the basis of a Duncan's multiple range test (DMRT). However, they did not have good activity to inhibit monocotyledon weeds such as *Digitaria sanguinalis* L., *Echinochloa crus-galli* L., and *Setaria viridis* L. As applied in pre-emergence, they also had more than 90% control against docotyledon weeds such as *Amaranthus spinosus* L. and *Chenopodium album* L. but less activity against *Abutilon theophrasti* Medic. Only, at the dosage of 37.5 g a.i./ha, compound **C10** had 80% control against *Echinochloa crus-galli* L. and *Setaria viridis* L.; compound **C12** had 80% control against *Digitaria sanguinalis* L.

**Table 3.** Preliminary Herbicidal Activity of New Compounds in Groups **A**, **B**, and **C**

| | pre-emergence activity (75 g a.i./ha) | | | | | | postemergence activity (75 g a.i./ha) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | AT[a] | CA | AA | DS | EC | SV | AT | CA | AA | DS | EC | SV |
| **A1** | +[b] | + | + | − | − | − | ++ | ++ | ++ | − | − | − |
| **A2** | + | + | + | − | − | − | ++ | ++ | ++ | − | − | − |
| **A3** | − | − | − | − | − | − | ++ | ++ | ++ | + | + | + |
| **A4** | − | − | − | − | − | − | + | + | + | − | − | − |
| **A5** | − | + | − | − | − | − | − | − | − | − | − | − |
| **A6** | − | − | − | − | − | − | − | + | − | − | − | − |
| **A7** | − | + | − | − | − | − | ++ | − | − | − | − | − |
| **A8** | − | − | − | − | − | − | + | + | + | − | − | − |
| **A9** | − | − | − | − | − | − | + | + | + | − | − | − |
| **B1** | − | − | − | − | − | − | − | − | − | − | − | − |
| **B2** | − | − | − | − | − | − | − | − | − | − | − | − |
| **B3** | − | − | − | − | − | − | − | − | − | − | − | − |
| **C1** | + | + | + | − | − | − | ++ | ++ | ++ | + | + | + |
| **C2** | ++ | + | + | − | − | − | ++ | ++ | ++ | ++ | ++ | ++ |
| **C3** | − | − | − | − | − | − | ++ | ++ | ++ | + | − | + |
| **C4** | ++ | ++ | ++ | − | − | − | ++ | ++ | ++ | − | − | − |
| **C5** | ++ | ++ | ++ | + | − | + | ++ | ++ | ++ | ++ | ++ | ++ |
| **C6** | ++ | + | + | + | + | + | ++ | ++ | ++ | + | + | + |
| **C7** | + | ++ | ++ | + | − | + | ++ | ++ | ++ | ++ | + | ++ |
| **C8** | − | − | + | − | − | − | ++ | ++ | ++ | + | + | + |
| **C9** | ++ | ++ | ++ | − | − | − | ++ | ++ | ++ | + | − | + |
| **C10** | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| **C11** | ++ | ++ | ++ | − | − | − | ++ | ++ | ++ | − | − | − |
| **C12** | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| **C13** | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| **C14** | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | + | − | + |
| **B3015** | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| flumioxazin | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |

[a] AT, *Abutilon theophrasti* Medic; CA, *Chenopodium album* L.; AA, *Amaranthus ascendens* L.; DS, *Digitaria sanguinalis* L.; EC,r *Echinochloa crus-galli* L.; SV, *Setaria viridis* L. [b] Rating system for the growth inhibition percentage: ++, >80%; +, 80−50%; − for <50%.

**Table 4.** Biological Activity of Compounds **C10**, **C12**, and **C13** against AT, AS, CA, DS, EC, and SV

| | | postemergence activity (%) | | | | | | pre-emergence activity (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | dosage (g ai/ha) | AT[a] | AS | CA | DS | EC | SV | AT | AS | CA | DS | EC | SV |
| **C10** | 7.5 | 100 a[b] | 100 a | 100 a | 10 h | 10 e | 10 g | 50 e | 100 a | 100 a | 0 e | 0 f | 0 f |
| | 15 | 100 a | 100 a | 100 a | 20 g | 30 d | 50 d | 60 d | 100 a | 100 a | 10 d | 10 e | 10 e |
| | 37.5 | 100 a | 100 a | 100 a | 60 d | 50 c | 80 b | 70 c | 100 a | 100 a | 50 b | 80 a | 80 a |
| **C12** | 7.5 | 100 a | 100 a | 100 a | 20 g | 10 e | 20 f | 0 h | 90 c | 100 a | 0 e | 0 f | 0 f |
| | 15 | 100 a | 100 a | 100 a | 30 g | 30 d | 30 e | 0 h | 95 b | 100 a | 40 c | 10 e | 40 d |
| | 37.5 | 100 a | 100 a | 100 a | 50 e | 50 c | 50 d | 20 g | 100 a | 100 a | 80 a | 30 d | 60 b |
| **C13** | 7.5 | 100 a | 100 a | 100 a | 40 f | 0 f | 20 f | 0 h | 100 a | 100 a | 0 e | 0 f | 0 f |
| | 15 | 100 a | 100 a | 100 a | 50 e | 0 f | 30 e | 40 f | 100 a | 100 a | 0 e | 0 f | 0 f |
| | 37.5 | 100 a | 100 a | 100 a | 70 c | 50 c | 70 c | 70 c | 100 a | 100 a | 0 e | 0 f | 0 f |
| flumioxazin | 7.5 | 100 a | 100 a | 100 a | 80 b | 50 c | 80 b | 50 e | 100 a | 100 a | 0 e | 0 f | 0 f |
| | 15 | 100 a | 100 a | 100 a | 90 a | 70 b | 90 a | 80 b | 100 a | 100 a | 50 b | 50 c | 50 c |
| | 37.5 | 100 a | 100 a | 100 a | 95 a | 80 a | 95 a | 100 a | 100 a | 100 a | 80 a | 70 b | 80 a |

[a] AT, *Abutilon theophrasti* Medic; AS, *Amaranthus spinosus* L.; CA, *Chenopodium album* L.; DS, *Digitaria sanguinalis* L.; EC, *Echinochloa crus-galli* L.; SV, *Setaria viridis* L. [b] Numbers in a longitudinal column followed by the same letter exhibited no significant differences at $P = 0.05$ based on Duncan's multiple range test (DMRT).

**C10**, **C12**, and **C13** were chosen for further evaluation of their crop selectivity in comparison with that of flumioxazin. The phytotoxicity to the seven crops are listed in **Table 5**. Surprisingly, at the pre-emergence treatment, compounds **C10**, **C12**, and **C13** are all safer to the crops than flumioxazin, and the safety ranking among the three compounds are **C13** > **C12** > **C10**; at the dosage of 37.5−300 g a.i./ha, all of the three compounds are safe to peanuts and soybean, and **C12** and **C13** have no injury to maize and cotton. Compound **C10** is not safe to maize and cotton at the dosage of 300 g a.i./ha, having more than 10% growth inhibition; but all of the three compounds, being similar to flumioxazin, are not good to rice, wheat, and rape. At the postemergent treatment, compounds **C10**, **C12**, **C13**, and flumioxazin are not safe to all tested crops. From all herbicidal test data, compounds **C10**, **C12**, and **C13** show development potential as a pre-emergent herbicide in crops such as peanut, soybean, maize, and cotton.

In this article, we describe the synthesis and herbicidal activity of three series of isoindoline-1,3-dione substituted benzoxazinone derivatives containing a carboxylic ester group as a new class of protox inhibitors. The preliminary structure−activity relationships were also analyzed upon the basis of the preliminary bioassay data. The advanced screening test and crop selectivity data showed that compounds **C10**, **C12**, and **C13** had promising activities comparable to that of the lead compound flumioxazin. All of the three compounds are much safer to crops than flumioxazin. Compounds **C10**, **C12**, and **C13** can be developed as potential pre-emergent herbicides for use in peanut, soybean, maize, and cotton fields.

**Table 5.** Phytotoxicity of Compounds **C10**, **C12**, **C13**, and Flumioxazin to Crops (Pre-Emergence)

| cmpd | dosage (g ai/ha) | PEA [a] | SOY | COT | MAI | WHE | RIC | RAP |
|---|---|---|---|---|---|---|---|---|
| **C10** | 37.5 | −[b] | − | − | − | − | ++ | ++ |
| | 75 | − | − | − | − | ++ | ++ | ++ |
| | 150 | − | − | − | − | ++ | ++ | ++ |
| | 300 | − | − | ++ | ++ | ++ | ++ | ++ |
| **C12** | 37.5 | − | − | − | − | − | ++ | ++ |
| | 75 | − | − | − | − | − | ++ | ++ |
| | 150 | − | − | − | − | ++ | ++ | ++ |
| | 300 | − | − | − | − | ++ | ++ | ++ |
| **C13** | 37.5 | − | − | − | − | − | − | ++ |
| | 75 | − | − | − | − | − | − | ++ |
| | 150 | − | − | − | − | − | ++ | ++ |
| | 300 | − | − | − | − | ++ | ++ | ++ |
| flumioxazin | 37.5 | − | − | − | − | ++ | ++ | ++ |
| | 75 | − | ++ | − | + | ++ | ++ | ++ |
| | 150 | − | ++ | − | + | ++ | ++ | ++ |
| | 300 | − | ++ | ++ | ++ | ++ | ++ | ++ |

[a] PEA, peanut; SOY, soybean; COT, cotton; MAI, maize; WHE, wheat; RIC, rice; RAP, rape. [b] Rating system for phytoxity: ++, >10% growth inhibition; +, 1−10% growth inhibition; −, no growth inhibition.

## LITERATURE CITED


(1) Nandihalli, U. B.; Duke, S. O. Structure−activity relationship of protoporphyrinogen oxidase inhibiting herbicides. *ACS Symp. Ser.* **1994**, *559*, 133–146.

(2) Kwon, J. W.; Armbrust, K. L.; Grey, T. L. Hydrolysis and photolysis of flumioxazin in aqueous buffer solutions. *Pest Manag. Sci.* **2004**, *60*, 939–943.

(3) Etheridge, J. R. Synergistic Herbicidal Composition. U.S. Patent 5108488, 1992.

(4) Dayan, F. E.; Duke, S. O. Phytotoxicity of Protoporphyrinogen Oxidase Inhibitors: Phenomenology, Mode of Action and Mechanisms of Resistance. In *Herbicide Activity: Toxicology, Biochemistry and Molecular Biology*; Roe, R. M., Burton, J. D., Kuhr, R. J., Eds.; IOS Press: Washington, DC, 1997; pp 11−35.

(5) Dayan, F. E.; Duke, S. O.; Reddy, K. N.; Hamper, B. C.; Leschinsky, K. L. Effects of isoxazole herbicideson protoporphyrinogen oxidase and porphyrin physiology. *J. Agric. Food Chem.* **1997**, *45*, 967–975.

(6) Corradi, H. R.; Corrigall, A. V.; Boix, E.; Mohan, C. G.; Sturrock, E. D.; Meissner, P. N.; Acharya, K. R. Crystal structure of protoporphyrinogen oxidase from *Myxococcus xanthus* and its complex with the inhibitor acifluorfen. *J. Biol. Chem.* **2006**, *281*, 38625–38633.

(7) Koch, M.; Breithaupt, C.; Kiefersauer, R.; Freigang, J.; Huber, R.; Messerschmidt, A. Crystal structure of protoporphyrinogen IX oxidase: a key enzyme in haem and chlorophyll biosynthesis. *EMBO J.* **2004**, *23*, 1720–1728.

(8) Hirai, K. Structural Evolution and Synthesis of Diphenyl Ethers, Cyclic Imides and Related Compounds. In *Peroxidizing Herbicides*; Boger, P., Wakabayashi, K., Eds.; Springer: Berlin, 1999; pp 29−61.

(9) Theodoridis, G. Protoporphyrinogen-IX-oxidase Inhibitors. In *Modern Crop Protection Compounds*; Kraomer, W., Schirmer, U.; , Eds.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007; pp 153−182.

(10) Macías, F. A.; De Siqueira, J. M.; Chinchilla, N.; Marín, D.; Varela, R. M.; Molinillo, J. M. G. New herbicide models from benzoxazinones: Aromatic ring functionalization effects. *J. Agric. Food Chem.* **2006**, *54*, 9843–9851.

(11) Macías, F. A.; Marín, D.; Oliveros-Bastidas, A.; Chinchilla, D.; Simonet, A. M.; Molinillo, J. M. G. Isolation and synthesis of benzoxazinones and related compounds. *J. Agric. Food Chem.* **2006**, *54*, 991–1000.

(12) Macías, F. A.; Marín, D.; Oliveros-Bastidas, A.; Castellano, D.; Simonet, A. M.; Molinillo, J. M. G. Structure-activity relationship (SAR) studies of benzoxazinones, their degradation products and analogues. Phytotoxicity on standard target species (STS). *J. Agric. Food Chem.* **2005**, *53*, 538–548.

(13) Macías, F. A.; Marín, D.; Oliveros-Bastidas, A.; Castellano, D.; Simonet, A. M.; Molinillo, J. M. G. Structure-activity (SAR) studies of benzoxazinones, their degradation products, and analogues. Phytotoxicity on problematic weeds *Avena fatua* L. and *Lolium rigidum* Gaud. *J. Agric. Food Chem.* **2006**, *54*, 1040–1048.

(14) Hou, Z. K.; Ren, Y. G.; Huang, M. Z.; Lei, M. X.; Ou, X. M.; Zang, K. B.; Wang, X. G.; Liu, A. P. Heterocyclic Substituted Benzo[b]-[1,4]oxazine Derivatives and Their Bioactivity. CN 03118226.7, **2003**.

(15) Huang, M. Z.; Huang, K. L.; Ren, Y. G.; Lei, M. X.; Huang, L.; Hou, Z. K.; Liu, A. P.; Ou, X. M. Synthesis and herbicidal activity of 2-(7-fluoro-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-6-yl)-isoindoline-1,3-diones. *J. Agric. Food Chem.* **2005**, *53*, 7908–7914.

(16) Liu, C. L. *The World Pesticide Manual: herbicides*; Chemical Industry Press: Beijing, China, 2002; pp 23−227.

(17) Unger, T. A. *Pesticide Synthesis Handbook*; Noyes Publications: Park Ridge, NJ, 1996.

(18) Kume,T.; Goto, T.; Kamochi, A.; Yagi, S. Benzoxazine Derivative, Process and Intermediates for Its Preparation and Its Use As Herbicide. EP 0290863, 1988.

(19) Petra, S. A.; Anderluh, M.; Ilas, J.; Mravljak, J.; Dolenc, Sollner; Stegnar, M.; Kikelj, M.; Toward, D. a novel class of antithrombotic compounds with dual function. Discovery of 1,4-benzoxazin-3(4H)-one derivatives possessing thrombin inhibitory and fibrinogen receptor antagonistic activities. *J. Med. Chem.* **2005**, *48*, 3110–3113.

(20) Tabarrini, O.; Manfroni, G.; Fravolini, A.; Cecchetti, V.; Sabatini, S.; De Clercq, E.; Rozenski, J.; Canard, B.; Dutartre, H.; Paeshuyse, J.; Neyts, J. Synthesis and anti-BVDV activity of acridones as new potential antiviral agents. *J. Med. Chem.* **2006**, *49*, 2621–2627.

(21) Liu, Ch. C. Research progress in synthesis of p-aminophenol by reduction from nitrobenzene. *Appl. Chem. Ind.* (*in Chinese*) **2001**, *30* (6), 3–5.

(22) Boschelli, D. H.; Ye, F.; Wang, Y. D.; Dutia, M.; Johnson, S.; Wu, B.; Karen, M.; Dennis, W. P.; Deanna, Y.; Mairead, Y.; Mark, T.; Kim, A.; Carolyn, D.; Carlo, E.; Jay, G.; Janet, G.; Judy, L.; Jennifer, M.; Frank, B. Optimization of 4-phenylamino-3-quinolinecarbonitriles as potent inhibitors of src kinase activity. *J. Med. Chem.* **2001**, *44*, 3965–3977.

(23) Johnson, W. O.; Kollman, G. E.; Swithenbank, C.; Yih, R. Y. RH-6201 (Blazer): a new broad spectrum herbicide for post-emergence use in soybean. *J. Agric. Food Chem.* **1978**, *26*, 285–286.

(24) Dayan, F. E.; Weete, J. D.; Duke, S. O.; Hancock, H. G. Soybean (*Glycine max*) cultivar differences in response to sulfentrazone. *Weed Sci.* **1997**, *45*, 634–641.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