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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

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The mode of action of 2-(7-fluoro-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-4,5,6,7-tetrahydro-2*H*-isoindoline-1,3-diones, including the commercial herbicide flumioxazin, had been identified as inhibition of protoporphyrinogen oxidase (protox). As part of continuous efforts to search for new herbicides with high efficacy, broad-spectrum activity, and safety to crops, flumioxazin and its iodo analogue (**B2055**) were used as lead compounds for further optimization. Series of novel compounds were prepared by multistep synthetic procedures starting from 5-fluoro-2-nitrophenol. All of the test compounds were structurally confirmed by ^{1}H NMR, IR, mass spectroscopy, and elemental analysis. Preliminary bioassay data showed that some of them possess commercial levels of herbicidal activity comparable to those of other protox-inhibiting herbicides. One of the best compounds, 5-fluoro-2-(7-fluoro-3-oxo-4-(prop-2-ynyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)isoindoline-1,3-dione (**8e**), has IC_{50} values for velvetleaf (*Abutilon theophrasti* Medic) and crabgrass (*Digitaria sanguinalis*) comparable to thos of **B2055**. With respect to crop selectivity, compound **8e** is similar to flumioxazin. Compound **8e** is safe to cotton and maize at a rate of 150 g of active ingredient (ai)/ha or less when applied at pre-emergent stage, and it has the best safety to wheat among the tested crops, showing no injury after post-emergent application at 7.5−30 g of ai/ha.

KEYWORDS: Benzo[*b*][1,4]oxazin-6-yl-isoindoline-1,3-dione; protox inhibitor; synthesis; herbicidal activity; *Digitaria sanguinalis*; *Abutilon theophrasti* Medic

INTRODUCTION

Herbicides inhibiting protoporphyrinogen oxidase (protox) have been commercialized for nearly 40 years. Thousands of active compounds exhibiting this mode of action have been synthesized (*1*−*5*). On the basis of their chemical structures, these compounds can be classified as diphenyl ethers (*6*, *7*), benzoxazinones (*8*), phenyl imides (*9*−*12*), triazolinones (*13*), tetrazolinones (*14*), oxadiazolones (*15*), thiadiazolidines (*16*), isothiazolones (*17*), and arylpyrroles (*18*). 2-(7-Fluoro-3-oxo-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazin-6-yl)-4,5,6,7-tetrahydro-2*H*-isoindoline-1,3-diones are a class of phenylimide protox-inhibiting herbicides (*19*, *20*). The commercial product of this class is flumioxazin (*21*, *22*), which was developed by the Sumitomo Chemical Co. In our previous work, we showed that a new compound, *B2055* (*23*), an iodo analogue of flumioxazin, can be applied as a postemergent herbicide; it exhibited better selectivity to crops than flumioxazin at the same dosage rate. However, the manufacturing cost for **B2055** is much higher because of a lack of readily available starting materials and the complexity of its manufacturing process. To search for additional promising active compounds in this area, we continued our effort to modify the structures of lead compounds flumioxazin and **B2055** by the replacement of the 4,5,6,7-tetrahydro-2*H*-isoindoline-1,3-dione moiety with (substituted) 2*H*-isoindoline-1,3-dione (**Scheme 1**). A new series of 2-(7-fluoro-3-oxo-4-substituted-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)isoindoline-1,3-diones (**8**) analogues were synthesized, and their structures were characterized by ^{1}H NMR, IR, mass spectroscopy, and elemental analysis. Their herbicidal activity (reported as IC_{50} values) against velvetleaf (*Abutilon theophrasti* Medic) and crabgrasses (*Digitaria sanguinalis*) was determined. The crop selectivity of one compound (**8e**), which has a high herbicidal activity, was evaluated, and qualitative structure−activity relationships of the synthesized compounds based on the test IC_{50} values are also discussed.

MATERIALS AND METHODS

Proton 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 ion scan mode. IR spectra were recorded in potassium bromide disks with a PE System

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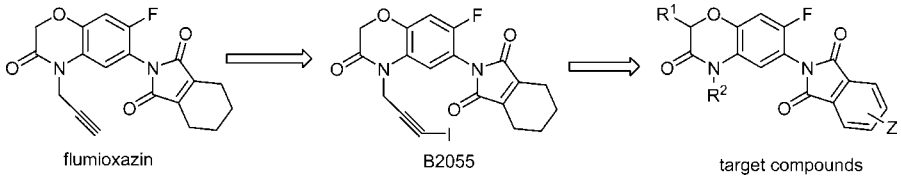
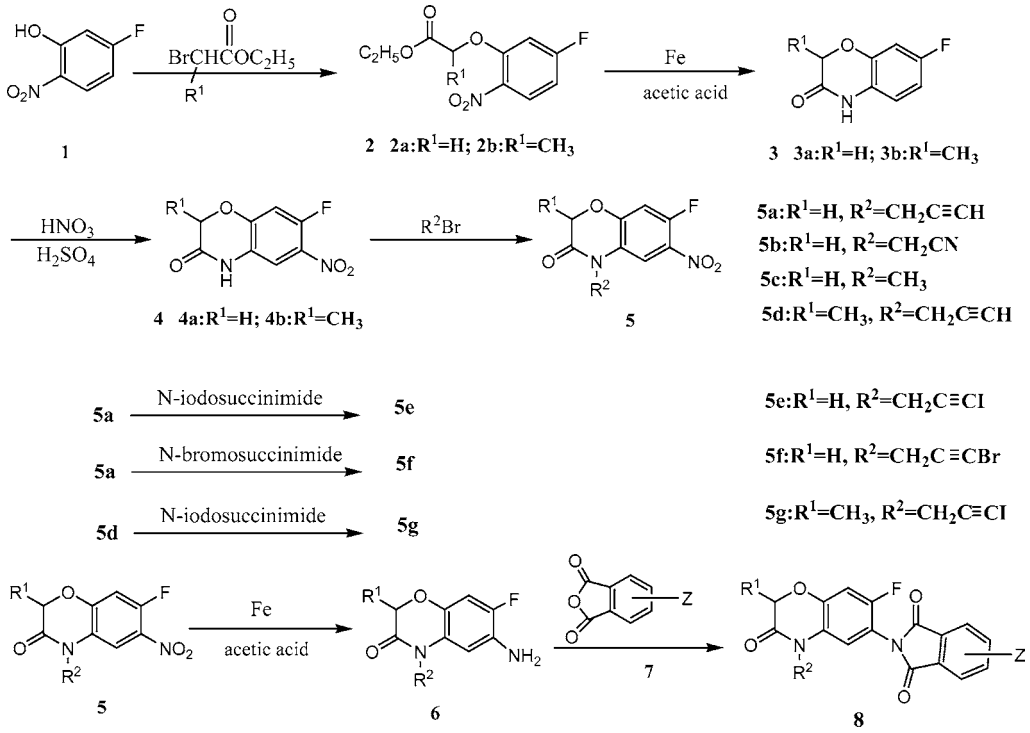
Scheme 1. Design Strategy for the Target Compounds



Scheme 2. General Synthetic Route for the Target Compounds



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. Compound **B2055** was synthesized according to a procedure modified from the literature (*23*). As shown in **Scheme 2**, the target compounds were synthesized by the reaction of (substituted) phthalic anhydride(s) with an appropriate 6-amino-7-fluoro-4-substututed-2*H*-3(4*H*)-benzo[*b*][1,4]oxazinone, which was prepared in five steps from 5-fluoro-2-nitrophenol: (a) the etherification of 5-fluoro-2-nitrophenol with ethyl 2-bromoacetate or ethyl 2-bromopropanoate; (b) the reductive ring closure of phenoxyacetate esters in the presence of iron powder and acetic acid as solvent; (c) nitrating benzoxazine derivatives with a $HNO_3-H_2SO_4$ mixture; (d) N-alkylation of nitrobenzoxazine derivatives with an appropriate bromide and/or the further halogenation reaction of the obtained compounds with *N*-halosuccinimide; (e) and the reduction of N-substituted nitrobenzoxazine derivatives with iron powder as reducing agent and acetic acid as solvent.

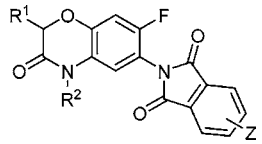
All of the key intermediates—ethyl 2-(5-fluoro-2-nitrophenoxy)-propanoate or ethyl 2-(5-fluoro-2- nitrophenoxy) acetate **2a**,**b**, 7-fluoro-2-substituted-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones **3a**,**b**, 7-fluoro-6-nitro-2-substituted-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones **4a**,**b**, 2,4-disubstituted-7-fluoro-6-nitro-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones **5a**,**d**, and 6-amino-7-fluoro-4-substututed-2*H*-3(4*H*)-benzo[*b*][1,4]oxazinone **6**—were prepared according to the reported literature (*24*−*28*). The following modified procedure was used to prepare 3-(3-haloprop-2-ynyl)-2-benzoxazolone derivatives (*29*): 7-fluoro-4-(3-haloprop-2-ynyl)-6-nitro-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones **5e**−**g** were obtained by the reaction of 7-fluoro-6-nitro-4-(prop-2-ynyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one **5a** or **5d** with *N*-halosuccinimide in a polar solvent such as *N*,*N*-dimethylformamide (DMF) in the presence of a catalytic amount of silver nitrate.

*General Synthetic Procedure for 7-Fluoro-4-(3-haloprop-2-ynyl)-6-nitro-2H-benzo[b][1,4] oxazin-3(4H)-one (**5e**−**g**).* To a stirred mixture of 7-fluoro-6-nitro-4-(prop-2-ynyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one **5a** or **5d** (12.0 mmol), anhydrous DMF (20 mL), and silver nitrate (0.20 g) was added dropwise *N*-bromo(iodo)succinimide (12.6 mmol). After stirring at room temperature for 4 h, the mixture was poured into water, which was then 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 to yield 7-fluoro-4-(3-haloprop-2-ynyl)-6-nitro-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones **5e**−**g** as pale yellow solids.

*General Synthetic Procedure for 6-Amino-7-fluoro-4-substituted-2H-3(4H)-benzo[b][1,4] oxazinone (**6**).* A solution of 7-fluoro-6-nitro-4-substituted-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one **5** (20 mmol) in acetic acid (50 mL) and water (5 mL) was added dropwise to a mixture of iron powder (100 mmol) and 5% aqueous acetic acid (50 mL) at 65 °C, and the mixture was heated under reflux for 1 h. After cooling to room temperature, the iron powder was filtered off, and the filtrate was mixed with 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 to yield 6-amino-7-fluoro-4-substituted-2*H*-3(4*H*)-benzo[*b*][1,4]oxazinone **6** with the yield of 65−87%, which was used in the next step without further purification.

*General Synthetic Procedure for 2-(7-Fluoro-3-oxo-4-substituted-3,4-dihydro-2H-benzo[b][1,4] oxazin-6-yl)isoindoline-1,3-dione (**8**).* A mixture of 6-amino-7-fluoro-4-substituted-2*H*-3(4*H*)-benzo[*b*][1,4]-oxazinone **6** (1 mmol) and (substituted) phthalic anhydride **7** (1.3 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 solution, and

Table 1. Chemical Structures, Physical Characteristics, Yield, and Elemental Analysis Data of New Compounds **8**



	chemical structure						elemental analysis (%)		
compd	R^1	R^2	Z	formula	mp (°C)	yield[a] (%)	C (calcd)	H (calcd)	N (calcd)
8a	H	CH_2CCH		$C_{19}H_{11}FN_2O_4$	276–278	74	65.04 (65.15)	3.20 (3.17)	8.02 (8.00)
8b	H	CH_2CN		$C_{18}H_{10}FN_3O_4$	257–259	68	61.60 (61.54)	2.81 (2.87)	11.96 (11.96)
8c	H	CH_2CC–I		$C_{19}H_{10}FIN_2O_4$	217–218	62	48.02 (47.92)	1.96 (2.12)	5.96 (5.88)
8d	H	CH_2CC–Br		$C_{19}H_{10}BrFN_2O_4$	247–248	64	53.31 (53.17)	2.35 (2.35)	6.60 (6.53)
8e	H	CH_2CCH	5-F	$C_{19}H_{10}F_2N_2O_4$	221–222	70	61.70 (61.96)	2.69 (2.74)	7.69 (7.61)
8f	H	CH_2CCH	4-F	$C_{19}H_{10}F_2N_2O_4$	243–246	67	61.73 (61.96)	2.70 (2.74)	7.70 (7.61)
8g	H	CH_2CCH	5-CH_3	$C_{20}H_{13}FN_2O_4$	219–221	75	65.87 (65.93)	3.71 (3.60)	7.54 (7.69)
8h	H	CH_2CCH	4-CH_3	$C_{20}H_{13}FN_2O_4$	254–256	71	65.82 (65.93)	3.59 (3.60)	7.80 (7.69)
8i	H	CH_2CCH	4-NO_2	$C_{19}H_{10}FN_3O_6$	245–246	69	57.60 (57.73)	2.61 (2.55)	10.49 (10.63)
8j	H	CH_3	5-F	$C_{17}H_{10}F_2N_2O_4$	218–220	66	59.18 (59.31)	2.84 (2.93)	8.20 (8.14)
8k	H	CH_3	4-F	$C_{17}H_{10}F_2N_2O_4$	260–262	63	59.20 (59.31)	2.87 (2.93)	8.18 (8.14)
8l	H	CH_2CC–I	4-F	$C_{19}H_9F_2IN_2O_4$	214–216	58	45.96 (46.18)	1.82 (1.84)	5.72 (5.67)
8m	CH_3	CH_2CCH	4-F	$C_{20}H_{12}F_2N_2O_4$	206–208	68	62.80 (62.83)	3.25 (3.16)	7.27 (7.33)
8n	CH_3	CH_2CCH		$C_{20}H_{13}FN_2O_4$	232–233	73	65.84 (65.93)	3.55 (3.60)	7.73 (7.69)
8o	CH_3	CH_2CCH	5-CH_3	$C_{21}H_{15}FN_2O_4$	181–183	70	66.74 (66.66)	3.91 (4.00)	7.25 (7.40)
8p	CH_3	CH_2CC–I		$C_{20}H_{12}FIN_2O_4$	196–198	60	48.86 (49.00)	3.91 (2.47)	5.65 (5.71)
8q	CH_3	CH_2CC–I	4-F	$C_{20}H_{11}F_2IN_2O_4$	206–208	63	47.40 (47.27)	2.13 (2.18)	5.69 (5.51)
8r	CH_3	CH_2CC–I	5-CH_3	$C_{21}H_{14}FIN_2O_4$	189–191	65	49.95 (50.02)	2.91 (2.80)	5.48 (5.56)

[a] Yield after purification by column chromatography on silica gel.

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 the eluent to yield 2-(7-fluoro-3-oxo-4-substituted-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazin-6-yl)isoindoline-1,3-dione **8** as solid.

Biological Activity. Test compounds were formulated as 100 g/L emulsified concentrates by using DMF as solvent and TW-80 as emulsification reagent. The concentrates 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 of 12.1 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 Herbicidal Activity against Dicotyledon Weeds and Monocotyledon Weeds. Plastic pots (~9-cm diameter) were filled with soil to a depth of 6 cm. Approximately 20 seeds of velvetleaf (*Abutilon theophrasti* Medic), fat hen (*Chenopodium album* L.), redroot pigweed (*Amaranthus ascedense* L.), crabgrass (*Digitaria sanguinalis* L.), barnyard grass (*Echinochloa crus-galli* L.), and green foxtail (*Setaria viridis* L.) were sown in the soil at the depth of 5 mm and grown at 22−25 °C in a greenhouse. The diluted formulation test solutions were applied for pre-emergence treatment 24 h after weeds were sown. For postemergence treatment, dicotyledon weeds were treated at the two-leaf stage and monocotyledon weeds were treated at the one-leaf stage. The pre- and postemergence application rates were 75 g of ai/ha. Untreated seedlings were used as the control group, and the solvent (DMF)-treated seedlings were used as the solvent control group. Herbicidal activity was evaluated visually 15 days post-treatment. Biological activity was rated on the basis of percentage of weed growth inhibition using the following rating system: ++, >80%; +, 50−80%; −, <50%.

Determination of IC_{50} Values for A. theophrasti Medic and D. sanguinalis. Seeds of *A. theophrasti* Medic and *D. sanguinalis* were sown in plastic pots (~9-cm diameter), which were filled with soil to a depth of 6 cm and cultivated in the greenhouse. Test compounds were applied at dosage rates of 150, 75, 37.5, 18.75, 9.38, 4.69, 2.35, and 1.17 g of ai/ha when *D. sanguinalis* and *A. theophrasti* Medic had grown to the one- or two-leaf stage, respectively. Untreated seedlings were used as the control group, and the solvent (DMF)-treated seedlings were used as the solvent control group. After cultivation for 15 days, the herbicidal activity on test weeds was evaluated as follows: the aerial parts of the test plants were cut off and weighed (fresh weight), and the percentage of growth inhibition was calculated with the following equation:

$$\text{growth inhibition (\%)} = 100 \times (\text{fresh wt of control} - \text{fresh wt of treatment})/\text{fresh wt of control}$$

The test data were subjected to statistical analysis using DPS software (*30*), and their IC_{50} values were calculated.

Determination of Crop Selectivity. Approximately 10 seeds of 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, respectively, 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 dosage rates of 150, 75, 30, 15, and 7.5 g of ai/ha at pre-emergence stage and at dosage rates of 30, 15, and 7.5 g of ai/ha for the postemergence evaluation. After cultivation for 15 days, the crop selectivity was evaluated according to the phytotoxicity of crops by comparing visually all test treatments with untreated controls using the following rating system: ++, >10% growth inhibition; +, 1−10% growth inhibition; −, no growth inhibition.

RESULTS AND DISCUSSION

Synthesis and Structure Characterization. Compounds **8** could be also prepared by the following method: first, obtain 6-amino-7-fluoro-2*H*-3(4*H*)-benzo[*b*][1,4]oxazinone by the reduction reaction of 7-fluoro-6-nitro-2-substituted-2*H*-benzo[*b*]-[1,4]oxazin-3(4*H*)-ones **4a**,**b**; second, synthesize 2-(7-fluoro-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)isoindoline-1,3-dione by the reaction of 6-amino-7-fluoro-2*H*-3(4*H*)-benzo-[*b*][1,4]oxazinone with an appropriate (substituted) phthalic anhydride(s); third, prepare the target compounds **8** by further N-alkylation reaction. However, we chose the synthetic route shown as **Scheme 2** to reduce experimental workload to synthesize a great deal of compounds. **Table 1** summarizes the chemical structures, physical characteristics, yields, and elemental analysis data of the new compounds **8**. MS, ^{1}H NMR,

Table 2. MS, ^{1}H NMR, and IR Data of Compounds **8**

compd	MS[a] (*m*/*e*)	^{1}H NMR($CDCl_3$), δ	IR υ (cm^{-1})
8a	349	2.30–2.31 (m, 1, ≡CH), 4.69 (s, 2, NCH_2), 4.70 (s, 2, OCH_2), 6.97(d, 1, J = 10 Hz, O–Ph–H), 7.17 (d, 1, J = 6 Hz, O–Ph–H), 7.83–7.85 (m, 2, ID[b]–H), 7.88–8.00 (m, 2, ID–H)	3296 (s), 3060 (w), 2987 (w), 2128 (w), 1734 (vs), 1693 (vs), 1608 (m), 1525 (s), 1461(m), 1390 (s), 1281 (s), 1035 (m), 875 (s), 721 (s)
8b	350	4.75 (s, 2, NCH_2), 4.84 (s, 2, OCH_2), 7.02 (d, 1, J = 10 Hz, O–Ph–H), 7.05 (d, 1, J = 7 Hz, O–Ph–H), 7.81–7.84 (m, 2, ID–H), 7.96–7.99 (m, 2, ID–H)	3092 (w), 3061 (w), 3003 (w), 2891 (w), 2858 (w), 2256 (w), 1733 (vs), 1699 (vs), 1616 (m), 1530 (s), 1458 (m), 1387 (s), 1275 (s), 1043 (m), 876 (s), 719 (s)
8c	475	4.71 (s, 2, NCH_2), 4.81 (s, 2, OCH_2), 6.95 (d, 1, J = 9.6 Hz, O–Ph-H), 7.12 (d, 1, J = 7 Hz, O–Ph–H), 7.81–7.84 (m, 2, ID–H), 7.98–8.01 (m, 2, ID–H)	3061 (w), 2962 (w), 2924 (w), 2189 (w), 1731 (vs), 1709 (vs), 1609 (m), 1525 (s), 1458 (m), 1391 (s), 1278 (s), 1037 (m), 882 (s), 722 (s)
8d	428	4.70 (s, 2, NCH_2), 4.85 (s, 2, OCH_2), 7.27 (d, 1, J = 10 Hz, O–Ph–H), 7.51 (d, 1, J = 7 Hz, O–Ph–H), 7.94–7.97 (m, 2, ID–H), 8.02–8.05 (m, 2, ID–H)	3022 (w), 2974 (w), 2922 (w), 2219 (w), 1731 (vs), 1698 (vs), 1609 (m), 1526 (s), 1459 (m), 1390 (s), 1279 (s), 1039 (m), 883 (s), 721 (s)
8e	367	2.29–2.31 (m, 1, ≡CH), 4.68 (s, 2, NCH_2), 4.71 (s, 2, OCH_2), 6.95 (d, 1, J = 10 Hz, O–Ph–H), 7.15 (d, 1, J = 7 Hz, O–Ph–H), 7.45–7.51 (m, 1, ID-H), 7.52–7.66 (m, 1, ID–H), 7.96–8.01 (m, 1, ID–H)	3297 (s), 3078 (w), 2123 (w), 1728 (vs), 1700 (vs), 1614 (m), 1527 (s), 1459 (m), 1389 (s), 1278 (s), 1036 (m), 857 (m), 746 (s)
8f	367	2.29–2.30 (m, 1, ≡CH), 4.68 (s, 2, NCH_2), 4.71 (s, 2, OCH_2), 6.95 (d, 1, J = 10 Hz, O–Ph–H), 7.15 (d, 1, J = 7 Hz, O–Ph–H), 7.45–7.46 (m, 1, ID–H), 7.79–7.84 (m, 2, ID–H)	3269 (s), 3063 (w), 2957 (m), 2923 (s), 2853 (m), 2123 (w), 1729 (vs), 1693 (vs), 1610 (m), 1517 (s), 1461 (m), 1390 (s), 1285 (s), 1032 (m), 878 (m), 749 (s)
8g	363	2.28–2.30 (m, 1, ≡CH), 2.56 (s, 3, CH_3), 4.68 (s, 2, NCH_2), 4.69 (s, 2, OCH_2), 6.94(d, 1, J = 10 Hz, O–Ph–H), 7.15 (d, 1, J = 7 Hz, O–Ph–H), 7.61 (d, 1, J = 8 Hz, ID-H), 7.78 (s, 1, ID–H), 7.84–7.87 (d, 1, J = 8 Hz, ID–H)	3298 (s), 3059 (w), 2974 (w), 2927 (w), 2120 (w), 1721 (vs), 1699 (vs), 1615 (m), 1524 (s), 1457 (m), 1388 (s), 1277 (s), 1031 (m), 846 (m), 742 (s)
8h	363	2.28–2.30 (m, 1, ≡CH), 2.76 (s, 3, CH_3), 4.68 (s, 2, NCH_2), 4.70 (s, 2, OCH_2), 6.95 (d, 1, J = 10 Hz, O–Ph–H), 7.15 (d, 1, J = 7 Hz, O–Ph–H), 7.56 (d, 1, J = 8 Hz, ID–H), 7.67 (t, 1, ID–H), 7.80 (d, 1, J = 7 Hz, ID–H)	3282 (s), 3060 (w), 2983 (m), 2904 (w), 2858 (w), 2124 (w), 1719 (vs), 1687 (vs), 1611 (m), 1526 (s), 1460 (m), 1395 (s), 1283 (s), 1036 (m), 869 (m), 739 (s)
8i	394	2.29–2.31 (m, 1, ≡CH), 4.69 (s, 2, NCH_2), 4.72 (s, 2, OCH_2), 6.96 (d, 1, J = 9 Hz, O–Ph–H), 7.16 (d, 1, J = 7 Hz, O–Ph–H), 7.99–8.04 (m, 1, ID–H), 8.19–8.26 (m, 2, ID–H)	3271 (s), 3057 (w), 2125 (w), 1741 (vs), 1692 (vs), 1616 (m), 1541 (s), 1524 (s), 1456 (m), 1389 (s), 1358 (s), 1278 (s), 1035 (m), 865 (m)
8j	343	3.35 (s, 3, NCH_3), 4.69 (s, 2, OCH_2), 6.90 (d, 1, J = 7 Hz, O–Ph–H), 6.93 (d, 1, J = 11 Hz, O–Ph–H), 7.46–7.50 (m, 1, ID–H), 7.80–7.86 (m, 2, ID–H)	3069 (m), 2942 (w), 2909 (w), 2867 (w), 1733 (vs), 1688 (vs), 1610 (m), 1527 (s), 1483 (s), 1386 (s), 1261 (s), 1025 (m), 872 (s), 745 (s)
8k	343	3.35 (s, 3, NCH_3), 4.70 (s, 2, OCH_2), 6.91 (d, 1, J = 7 Hz, O–Ph–H), 6.94 (d, 1, J = 10 Hz, O–Ph–H), 7.47–7.52 (m, 1, ID–H), 7.81–7.85 (m, 2, ID–H)	3070 (m), 2942 (w), 2911 (w), 2868 (w), 1732 (vs), 1689 (vs), 1611 (m), 1527(s), 1484 (s), 1387 (s), 1261 (s), 1025 (m), 872 (s), 746 (s)
8l	493	4.71 (s, 2, NCH_2), 4.81 (s, 2, OCH_2), 6.95 (d, 1, O–Ph–H), 7.10 (d, 1, O–Ph–H), 7.46–7.49 (m, 1, Ar–H), 7.81–7.84 (m, 2, Ar–H)	3083 (w), 2972 (w), 2184 (w), 1724 (vs), 1690 (vs), 1611 (m), 1526 (s), 1457 (m), 1392 (s), 1279 (s), 1036 (m), 865 (m), 746 (s)
8m	381	1.62 (d, 3, J = 7 Hz, CH_3), 2.28–2.30 (m, 1, ≡CH), 4.56–4.79 (m, 3, OCH, NCH_2), 6.95 (d, 1, J = 10 Hz, O–Ph–H), 7.13 (d, 1, J = 7 Hz, O–Ph-H), 7.45–7.51 (m, 1, ID–H), 7.81–7.84 (m, 2, ID–H)	3270 (s), 3077 (w), 2989 (w), 2942 (w), 2870 (w), 2122 (w), 1730 (vs), 1696 (vs), 1612 (m), 1523 (s), 1453 (m), 1390 (s), 1277 (s), 1032 (m), 865 (m), 746 (s)
8n	363	1.63 (d, 3, J = 7 Hz, CH_3), 2.28–2.29 (m, 1, ≡CH), 4.57–4.79 (m, 3, OCH, NCH_2), 6.95 (d, 1, J = 10 Hz, O–Ph–H), 7.14 (d, 1, J = 7 Hz, O–Ph–H), 7.83 (d, 2, ID–H), 7.98 (d, 2, ID–H)	3299 (s), 3062 (w), 2987 (w), 2952 (w), 2126 (w), 1692 (vs), 1608 (m), 1527 (s), 1457 (m), 1392 (s), 1281 (s), 1028 (m), 871 (m), 723 (s)
8o	377	1.62 (d, 3, J = 7 Hz, CH_3), 2.27–2.29 (m, 1, ≡CH), 2.57 (s, 3, ID–CH_3), 4.56–4.79 (m, 3, OCH, NCH_2), 6.94 (d, 1, J = 10 Hz, O–Ph–H), 7.13 (d, 1, J = 7 Hz, O–Ph–H), 7.61 (d, 1, J = 8 Hz, ID–H), 7.78 (s, 1, ID–H), 7.85 (d, 1, J = 8 Hz, ID–H)	3272 (s), 3066 (w), 2992 (w), 2943 (w), 2122 (w), 1727 (vs), 1698 (vs), 1615 (m), 1526 (s), 1447 (m), 1390 (s), 1279 (s), 1025 (m), 872 (m), 741 (s)
8p	489	1.63 (d, 3, J = 7 Hz, CH_3), 4.67–4.94 (m, 3, OCH, NCH_2), 6.94 (d, 1, J = 10 Hz, O–Ph–H), 7.10 (d, 1, J = 7 Hz, O–Ph–H), 7.81–7.86 (m, 2, ID–H), 7.97–8.01 (m, 2, ID–H)	3063 (w), 2992 (w), 2941 (w), 2190 (w), 1728 (vs), 1705 (vs), 1609 (m), 1523 (s), 1454 (m), 1387 (s), 1275 (s), 1032 (m), 864 (m), 723 (s)
8q	507	1.63 (d, 3, J = 7 Hz, CH_3), 4.66–4.93 (m, 3, OCH, NCH_2), 6.94 (d, 1, J = 10 Hz, O–Ph–H), 7.08 (d, 1, J = 7 Hz, O–Ph–H), 7.46–7.52 (m, 1, ID–H), 7.80–7.84 (m, 2, ID–H)	3077 (w), 2989 (w), 2942 (w), 2870 (w), 2193 (w), 1724 (vs), 1693 (vs), 1611 (m), 1523 (s), 1452 (m), 1388 (s), 1274 (s), 1031 (m), 867 (m), 745 (s)
8r	503	1.62 (d, 3, J = 7 Hz, CH_3), 2.57 (s, 3, ID–CH_3), 4.66–4.93 (m, 3, OCH, NCH_2), 6.93 (d, 1, J = 10 Hz, O–Ph–H), 7.09 (d, 1, J = 7 Hz, O–Ph–H), 7.61 (d, 1, J = 8 Hz, ID–H), 7.79 (s, 1, ID–H), 7.86 (d, 1, J = 8 Hz, ID–H)	3070 (w), 2987 (w), 2941 (w), 2872 (w), 2190 (w), 1714 (vs), 1693 (vs), 1613 (m), 1524 (s), 1453 (m), 1389 (s), 1274 (s), 1033 (m), 878 (m), 741 (s)

[a] Scan by negative ion method. [b] ID, isoindolinedione.

Table 3. Preliminary Herbicidal Activity[a,b] and IC_{50}[c] Value against *A. theophrasti* Medic and *D. sanguinalis* L. of Compounds **8**

	pre-emergence activity (75 g of ai/ha)						postemergence activity (75 g of ai/ha)						IC_{50}	
compd	AT	CA	AA	DS	EC	SV	AT	CA	AA	DS	EC	SV	AT	DS
8a	++	++	++	++	−	−	++	++	++	++	++	++	7.5	17
8b	−	−	−	−	−	−	−	−	−	+	−	−	92	57
8c	++	++	++	++	−	+	++	++	++	+	−	+	3.9	68
8d	−	−	−	−	−	−	−	−	−	−	−	−	121	314
8e	++	++	++	++	++	++	++	++	++	++	++	++	3.6	4.8
8f	++	++	++	++	++	++	++	++	++	++	++	++	23	20
8g	−	−	−	−	−	−	++	++	++	++	+	−	28	31
8h	−	−	−	−	−	−	−	−	−	+	+	−	87	63
8i	−	−	−	−	−	−	−	−	−	−	−	−	300	210
8j	−	−	−	−	−	−	−	−	−	−	−	−	161	172
8k	+	+	+	−	−	−	++	++	++	−	−	−	45	>1800
8l	++	++	++	−	−	−	++	++	++	++	++	++	7.2	40
8m	++	++	++	++	++	++	++	++	++	++	++	++	7.7	42
8n	++	++	++	−	−	−	++	++	++	−	−	−	7.5	161
8o	++	++	++	−	−	−	++	++	++	−	−	−	18	393
8p	++	++	++	++	++	++	++	++	++	+	−	−	7.4	60
8q	++	++	++	−	−	−	++	++	++	−	−	−	7.5	238
8r	++	++	++	−	−	−	++	++	++	−	−	−	30	>1800
B2055	++	++	++	++	++	++	++	++	++	++	++	++	2.3	3.8
flumioxazin	++	++	++	++	++	++	++	++	++	++	++	++	1.0	2.5

[a] AT, *A. theophrasti* Medic; CA, *C. album* L.; AA, *A. ascedense* L.; DS, *D. sanguinalis* L.; EC, *E. crus-galli* L.; SV, *S. viridis* L. [b] Rating system for the growth inhibition percentage: ++, >80%; +, 50–80%; −, <50%. [c] Inhibitive concentration (g of ai/ha) to obtain 50% growth inhibition.

and IR data are listed in **Table 2**. All compounds **8** showed the characteristic IR absorbances at 1687−1705 cm^{-1} (carbonyl in benzoxazinyl moiety) and 1714−1741 cm^{-1} (carbonyl in isoindolin-1,3-dione moiety), respectively.

Preliminary Herbicidal Activity. As shown in **Table 3**, some compounds **8** show high herbicidal activity. For example, compounds **8e**, **8f**, and **8m** have >80% herbicidal efficiency at 75 g of ai/ha in both pre- and postemergence treatments against both dicotyledon weeds such as *A. theophrasti* Medic, *C. album* L., and *A. retroflexus* L. and monocotyledon weeds such as *D. sanguinalis* L., *E. crus-galli* L., and *S. viridis* L. The injury symptoms include leaf cupping, crinkling, bronzing, and necrosis, typical of protox inhibitor herbicides (*31*). Some compounds **8**, such as **8c**, **8l**, and **8n**−**r**, exhibit better herbicidal efficacy on dicotyledon weeds than on monocotyledon weeds in both pre- and postemergence treatments. Compound **8a** has pre-emergence herbicidal activity against dicotyledon weeds and postemergence herbicidal activity against monocotyledon weeds. Against monocotyledon weeds, **8l** has no pre-emergence activity, and **8p** has no postemergence activity. Compounds **8g** and **8k** have just postemergence herbicidal activity against dicotyledon weeds. Among the prepared compounds, compounds **8b**, **8d**, and **8h**−**j** have no or very low herbicidal activity.

IC_{50} Values. Our main interest is to develop a new postemergence herbicidal protox inhibitor. To evaluate their postemergence bioactivity, the IC_{50} values of compounds **8** for *A. theophrasti* Medic and *D. sanguinalis* were determined, and the test data are listed also in **Table 3**.

The results show that most of the compounds **8** have high growth inhibition activity against *A. theophrasti* Medic. For example, compounds **8c** and **8e** have IC_{50} values of <4 g of ai/ha, and the IC_{50} values for compounds **8a**, **8f**, **8g**, and **8k**−**r** range from 7.2 to 45 g of ai/ha. However, compounds **8b**, **8d**, and **8h**−**j** exhibit lower activity, and their IC_{50} values are >87 g of ai/ha.

The results indicate also that some compounds **8** exhibit high growth inhibition activity against *D. sanguinalis*. For example, compound **8e** has an IC_{50} value comparable to that of **B2055**. The highly active compounds **8a**, **8f**, **8g**, **8l**, and **8m** have IC_{50} values ranging from 17 to 42 g of ai/ha. The active compounds **8b**, **8c**, **8h**, and **8p** have IC_{50} values ranging from 57 to 63 g of ai/ha. For other inactive compounds, their IC_{50} values are >160 g of ai/ha.

From a comparison of the IC_{50} values with the preliminary herbicidal activity for postemergence treatments in **Table 3**, it is easy to conclude that, except for **8g** and **8p** against monocotyledon weeds, the IC_{50} values of compounds **8** for *A. theophrasti* Medic and *D. sanguinalis* are correlative to their preliminary herbicidal activity against the test dicotyledon and monocotyledon weeds, respectively. Among all of the prepared compounds **8**, compound **8e** has herbicidal activity comparable to that of **B2055**.

Qualitative Structure−Activity Relationships. In the general formula for compounds **8**, the structural change includes three parts, that is, R^1 moiety, R^2 moiety, and Z moiety. As shown in **Table 3**, the variance of R^1, R^2, and Z can affect herbicidal activity, and there are some interesting structure−activity relationships based on the test IC_{50} values for *A. theophrasti* Medic and *D. sanguinalis*.

R^1 Moiety. When R^2 and Z are unchanged, the herbicidal activities of the synthesized compounds are influenced by the substituent group R^1. In general, transformation of the R^1 group from a hydrogen atom to a methyl group cannot increase the IC_{50} value for *A. theophrasti* Medic; for example, IC_{50} values are correlated as follows: **8a** = **8n**, **8f** > **8m**, **8g** > **8o**, and **8l** ≈ **8q**, but there is an exception, IC_{50} **8c** < **8p**. It is very interesting that the potency against *D. sanguinalis* is reversed; the IC_{50} values become generally greater, for example, IC_{50} **8a** < **8n**, **8f** < **8m**, **8g** < **8o**, and **8l** < **8q**, and IC_{50} **8c** > **8p** is an exception, too. Therefore, the changing R^1 group from a hydrogen atom to methyl can increase the herbicidal activity of compounds **8** against dicotyledon weeds.

R^2 Moiety. When R^1 and Z are kept unchanged, the IC_{50} value of the synthesized compounds **8** is influenced by substitution group R^2. When prop-2-ynyl is changed to isocyanomethylene, 3-iodoprop-2-ynyl, 3-bromoprop-2-ynyl, or methyl, the IC_{50} value of the corresponding compound for *D. sanguinalis* increases; for example, IC_{50} **8a** < **8b** < **8c** < **8d**, **8e** < **8j**, **8f** < **8l**, **8m** < **8q**, **8o** < **8r**; there is an exception, IC_{50} **8n** > **8p**.

Changing R^2 from prop-2-ynyl to isocyanomethylene, 3-

Table 4. Phytotoxicity[a−c] of Compound **8e** and Flumioxazin to Crops

	dosage	pre-emergence						postemergence					
compd	(g of ai/ha)	COT	SOY	RAP	RIC	WHE	MAI	COT	SOY	RAP	RIC	WHE	MAI
8e	7.5	−	−	−	−	−	−	++	++	++	−	−	+
	15	−	−	−	+	−	−	++	++	++	++	−	+
	30	−	−	++	++	−	−	++	++	++	++	−	++
	75	−	−	++	++	++	−	NT	NT	NT	NT	NT	NT
	150	−	++	++	++	++	−	NT	NT	NT	NT	NT	NT
flumioxazin	7.5	−	−	−	++	−	−	++	++	++	++	++	++
	15	−	−	−	++	++	−	++	++	++	++	++	++
	30	−	−	++	++	++	−	++	++	++	++	++	++
	75	−	++	++	++	++	+	NT	NT	NT	NT	NT	NT
	150	−	++	++	++	++	+	NT	NT	NT	NT	NT	NT

[a] Rating system for phytotoxicity: ++, >10% growth inhibition; +, 1–10% of growth inhibition; −, no growth inhibition. [b] COT, cotton; SOY, soybean; RAP, rape; RIC, rice; WHE, wheat; MAI, maize. [c] NT, no test.

bromoprop-2-ynyl, or methyl can also increase the IC_{50} value of the corresponding compound for *A. theophrasti* Medic; for example, IC_{50} **8a** < **8b** < **8d**, **8e** < **8j**, **8o** < **8r**. It is interesting that changing R^2 from prop-2-ynyl to 3-iodoprop-2-ynyl generally decreases the IC_{50} value; for example, IC_{50} **8a** > **8c**, **8f** > **8l**, **8m** ≈ **8q**, **8n** ≈ **8p**, but there is an exception, IC_{50} **8o** < **8r**. It should be concluded that changing R^2 from prop-2-ynyl to 3-iodoprop-2-ynyl can also increase the herbicidal activity of compounds **8** against dicotyledon weeds.

Z Moiety. When R^1 and R^2 are unchanged, the changes of group Z and its substituted position influence the IC_{50} value of compounds **8**. In general, compounds **8** with a substituent group at the 5-position of isoindoline-1,3-dione exhibit higher herbicidal activity against both *A. theophrasti* Medic and *D. sanguinalis* than the corresponding isomer with the same group at the 4-position, and the following order in the influence of group Z on the IC_{50} value could be summarized: IC_{50} 5-F < H ≤ 4-F < 5-CH_3 < 4-CH_3 < 4-NO_2. For example, IC_{50} correlation for *A. theophrasti* Medic and *D. sanguinalis* is **8e** < **8a** < **8f** < **8g** < **8h** < **8i**, **8p** < **8q** < **8r**, but there are three exceptions: IC_{50} for *A. theophrasti* Medic **8j** > **8k**, and IC_{50} for *D. sanguinali* **8c** > **8l** and **8n** > **8m**.

Crop Selectivity of Compound 8e. On the basis of the preliminary herbicidal activities of compounds **8** against dicotyledon weeds and monocotyledon weeds and their IC_{50} values for *A. theophrasti* Medic and *D. sanguinalis*, compound **8e** was chosen for further evaluation on its crop selectivity, in comparison with flumioxazin. The phytotoxicity data of compound **8e** and flumioxazin to six crops are listed in **Table 4**.

As a whole, the crop selectivity of compound **8e** is similar to that of flumioxazin, although **8e** was slightly safer to rice, wheat, and maize than the latter. Compound **8e**, like flumioxazin, is safer to crops when used pre-emergence than when used postemergence. For example, applied at the pre-emergence stage, it is safe to cotton and maize at 150 g of ai/ha, to soybean at 75 g of ai/ha, to wheat at 30 g of ai/ha, and to rape at 15 g of ai/ha. When applied postemergence, it has >10% growth inhibition to cotton, soybean, and rape at 7.5 g of ai/ha, to rice at 15 g of ai/ha, and to maize at 30 g of ai/ha. Compound **8e** has the best safety to wheat among the tested crops postemergently, showing no injury to wheat at 7.5−30 g of ai/ha.

In this paper, we have described the synthesis and herbicidal activity of a series of 2-(7-fluoro-3-oxo-4-substituted-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)isoindoline-1,3-diones as a new class of protox inhibitors. The preliminary bioassay data show that some of them, for example, **8e**, have promising herbicidal activities comparable to that of lead compound **B2055**. Further investigation on herbicidal activity and crop selectivity in vivo for compound **8e** is underway in our group.

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