Design and Syntheses of Novel Phthalazin-1(2*H*)-one Derivatives as Acetohydroxyacid Synthase Inhibitors

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A series of 2-substituted-8-(4,6-dimethoxypyrimidin-2-yloxy)-4-methylphthalazin-1-one derivatives, **7a**–**7w**, were designed via an ortho-substituent cyclization strategy to discover a new herbicidal lead structure. These compounds were synthesized by a seven-step route using 3-hydroxy-acetophenone as a starting material. Determination of the K_i values against wild-type *A. thaliana* acetohydroxyacid synthase (AHAS) (EC 4.1.3.18) indicated that some of the compounds displayed good enzyme inhibition activity comparable to that of KIH-6127. The further preliminary bioassay data on weeds showed that the synthesized compounds exhibited typical injury symptoms of AHAS-inhibiting herbicides, and some of them showed broad-spectrum and high herbicidal activities in postemergence treatments against *Echinochloa crusgalli*, *Digitaria sanguinalis*, *Setaria viridis*, *Brassica juncea*, *Amaranthus retroflexus*, and *Chenopodium album* at an application rate of 150 g ai/ha. To our knowledge, this is the first report of methylphthalazin-1-one derivatives as AHAS inhibitors.

KEYWORDS: Acetohydroxyacid synthase (AHAS); methylphthalazin-1-one; herbicide

INTRODUCTION

Acetohydroxyacid synthase (AHAS, also known as acetolactate synthase; EC 2.2.1.6, formerly EC 4.1.3.18), which is known to catalyze the biosynthesis of branched-chain amino acids including valine, leucine, and isoleucine, has been identified as the action target of herbicidal sulfonylureas, imidazolinones, triazolopyrimidines, and pyrimidinylbenzoates (*1*, *2*). AHAS-inhibiting herbicides have been widely and rapidly adopted because they exhibit a number of advantages such as low rates, low mammalian toxicity, broad-spectrum weed control, and flexible application timing in a wide variety of crops, but new herbicides are still needed to combat herbicide resistance (*3*−*5*).

Pyrimidinylbenzoates, such as bispyriba-sodium (*6*), pyriminobac-methyl (KIH-6127) (*7*−*9*), and pyriftalid (*10*) (**Chart 1**), have been found to be particularly effective herbicides at dosages of 30−90 g/ha against barnyard grass over a wide range of growth stages including pre-emergence application. These compounds have conferred excellent safety on transplanted rice crops, animals and fish, etc. From both agricultural and environmental points of view, pyrimidinylbenzoates can be used as a lead structure for further herbicidal development. The objective of this study was to design and synthesize novel compounds by structural modification of pyrimidinylbenzoates via a cyclization strategy (**Scheme 1**).

MATERIALS AND METHODS

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification, as all solvents were redistilled before use. ^{1}H NMR spectra were recorded on a Mercury-Plus 400 spectrometer in CDCl$_3$ with TMS as the internal reference. MS spectra were determined using a TraceMS 2000 organic mass spectrometer. Elemental analyses were performed on a Vario EL III elemental analysis instrument. Melting points were measured on a Buchi B-545 melting point apparatus and are uncorrected. Intermediates 2−6 were prepared according to the reported methods (*7*, *8*), and the detailed procedures can be found in the Supporting Information.

Preparation of 8-(4,6-Dimethoxypyrimidin-2-yloxy)-4-methylphthalazin-1(2H)-one (7a). To a 250-mL round-bottom flask were gradually added 3.0 g (7.9 mmol) of methyl 2-(4,6-dimethoxypyrimidin-2-yloxy)-6-(2-methyl-1,3-dioxolan-2-yl)-benzoate (**6**), 1.26 g (11.9 mmol) of hydrazine hydrochloride, and 200 mL of methanol. The resulting mixture was stirred at room temperature for 24 h and then concentrated on a rotary evaporator; the crude product obtained was poured into 300 mL of water and extracted with chloroform (100 mL × 3). The combined chloroform extracts were washed with brine (100 mL × 2), dried with anhydrous magnesium sulfate, and filtered off

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Chart 1.   Structures of Some Commercial Herbicides Related to the Present Study

Bispyribac-sodium   Pyriminobac-methyl   Pyriftalid
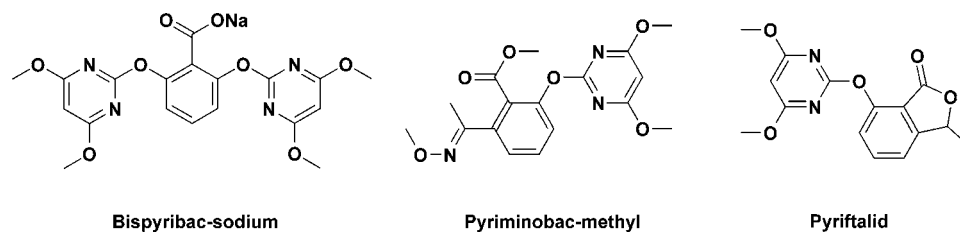
by suction, and the solvent was evaporated to give crude, white crystals of **7a** that could be purified by recrystallization from toluene. Yield 88%. mp 225−227 °C. ^{1}H NMR (CDCl$_3$): δ 2.58 (s, 3H, CH$_3$), 3.77 (s, 6H, 2 × OCH$_3$), 5.75 (s, 1H, PyHet-H), 7.53 (d, J = 8.0 Hz, 1H, 7′-ArH), 7.67 (d, J = 8.0 Hz, 1H, 5′-ArH), 7.86 (t, J = 8.0 Hz, 1H, 6′-ArH), 9.56 (s, 1H, N−H). EI MS: m/z (%) 314 (M$^+$, 100), 299 (40), 283 (75), 256 (16), 226 (45), 173 (21), 144 (12), 101 (13). Anal. Calcd for C$_{15}$H$_{14}$N$_4$O$_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.06; H, 4.32; N, 17.62.

General Procedure for the Synthesis of Target Compounds 7b−7w. A solution of **7a** (1 mmol) and NaH (60%, dispersion in mineral oil) (1.2 mmol) in *N,N*-dimethylformamide (DMF) (10 mL) was stirred at room temperature for 0.5 h, and halogenated compound (1.1 mmol) was then added. The reaction was continued for 9−24 h at room temperature. The mixture was poured into 200 mL of water, extracted with ethyl acetate (50 mL × 3), dried with anhydrous magnesium sulfate, and filtered off by suction, and the solvent was evaporated to give the crude product, which was then purified by chromatography on silica using petroleum ether/ethyl acetate as the eluent to give the target compounds. Example data for **7b** are included here, and data for **7c−7w** can be found in the Supporting Information.

Data for 7b. Yield 93%. mp 106−108 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.61 (s, 3H, CH$_3$), 3.77 (s, 6H, 2 × OCH$_3$), 4.68 (d, J = 6.0 Hz, 2H, CH$_2$), 5.14−5.18 (m, 2H, =CH$_2$), 5.75 (s, 1H, PyHet-H), 5.93−5.70 (m, 1H, =CH), 7.50 (d, J = 8.0 Hz, 1H, 7′-ArH), 7.65 (d, J = 8.0 Hz, 1H, 5′-ArH), 7.83 (t, J = 8.0 Hz, 1H, 6′-ArH). EI MS: m/z (%) 356 ([M + 2]$^+$, 28), 354 (M$^+$, 69), 339 (33), 284 (45), 258 (26), 256 (48), 229 (20), 138 (36), 88 (65), 69 (39), 40.8 (100). Anal. Calcd for C$_{18}$H$_{18}$N$_4$O$_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.33; H, 5.39; N, 15.65.
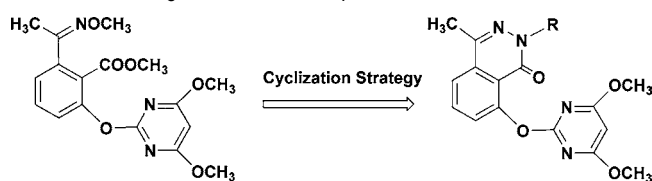
X-ray Diffraction. Colorless blocks of **7m** (0.50 mm × 0.25 mm × 0.20 mm) were coated on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 27.00; 20552 measured reflections; 4578 independent reflections (R_{int} = 0.0615), of which 4477 had $|F_o|$ > $2|F_o|$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.9704; T_{max} = 0.9869). The structure was solved by direct methods using SHELXS-97 (*11*); all other calculations were performed with Bruker SAINT System and Bruker SMART programs (*12*). Full-matrix least-squares refine-

ment based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0742P)^2 + 0.059P]$ gave final values of R = 0.0481, ωR = 0.1388, and GOF(F) = 1.066 for 332 variables and 2237 contributing reflections; maximum shift/error = 0.024(3), max/min residual electron density = 0.217/−0.189 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Biological Assay. *AHAS Inhibition Activity.* The K_i values of compounds **7a−7w** against wild-type *A. thaliana* acetohydroxyacid synthase (AHAS, EC 4.1.3.18) were determined according to the methods reported previously (*13, 14*); KIH-6127 was used as a control, and the results were listed in **Table 1**.

Herbicidal Activities on Weeds. The herbicidal activities of compounds 7a−7w against *Echinochloa crusgalli* (EC), *Digitaria sanguinalis* (DS), *Setaria viridis* (SV), *Brassica juncea* (BJ), *Amaranthus retroflexus* (AR), and *Chenopodium album* (CA) were evaluated according to a previously reported procedure (*15*). All test compounds were formulated as 100 g/L emulsified concentrates using DMF as the solvent and TW-80 as an 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 with pH 6.5, 1.6% organic matter, 37.3% clay particles, and a CEC of 12.1 cmol/kg. The rate of application (g ai/ha) was calculated by the total amount of active ingredient in the formulation divided by the surface area of the pot. Plastic pots with a diameter of 9.5 cm were filled with soil to a depth of 8 cm. Approximately 20 seeds of *Echinochloa crusgalli* (EC), *Digitaria sanguinalis* (DS), *Setaria viridis* (SV), *Brassica juncea* (BJ), *Amaranthus retroflexus* (AR), and *Chenopodium album* (CA) were sown in the soil at a depth of 1−33 cm and grown at 15−30 °C in a greenhouse. The diluted formulation solutions were applied for pre-emergence treatment 24 h after the 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 estimated as 150 g ai/ha. Untreated seedlings were used as the control group, and solvent- (DMF-) treated seedlings were used as the solvent control group. Herbicidal activity was evaluated visually 15 days posttreatment. Biological activity was rated on the basis of the percentage of weed growth inhibition using the following rating system: ++ for >80%, + for 50−80%, and − for <50%. The DMF control displayed no herbicidal activity, and the results are reported in **Table 1**.
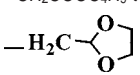
RESULTS AND DISCUSSION

Synthesis and Structure Characterization. As shown in **Scheme 2**, intermediates **2−6** were prepared readily using 3-hydroxyacetophenone as the starting material according to the reported methods (*7, 8*). The deprotection of intermediate **6** afforded compound **8** successfully in our hands (**Scheme 3**); however, according to the reported methods (*16−18*), the

Scheme 1.   Design of the Title Compounds

Phthalazin-1(2H)-one Derivatives as AHAS Inhibitors

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Table 1. Ahas Inhibition Activities and Herbicidal Activities of Compounds **7a**–**7w**

compd	R	K_i^c (10^{-4} M)	pre-emergence (150 g ai/ha)^{a,b}						post-emergence (150 g ai/ha)					
			EC	DS	SV	BJ	AR	CA	EC	DS	SV	BJ	AR	CA
7a	H	7.89	−	−	−	−	−	−	++	++	++	−	++	+
7b	−CH$_2$CHCH$_2$	52.5	−	−	−	−	−	−	++	+	++	−	++	+
7c	−CH$_2$COOC$_2$H$_5$	5.57	−	−	−	−	−	−	++	+	++	−	++	+
7d	−C$_2$H$_5$	16.8	−	−	−	−	−	−	++	++	++	−	++	+
7e	−CH$_2$Ph	8.22	−	−	−	−	−	−	−	−	−	−	−	−
7f	−CH$_2$Ph(2-F-4-Br)	4.20	−	−	−	−	−	−	−	−	−	−	−	−
7g	−CH$_2$Ph(2,6-F$_2$)	6.34	−	−	−	−	−	−	−	−	−	−	−	−
7h	−CH$_2$Ph(2,4-F$_2$)	10.40	−	−	−	−	−	−	+	−	+	+	++	−
7i	−CH$_2$Ph(3-F)	14.00	−	−	−	−	−	−	−	−	−	−	−	−
7j	−CH$_2$Ph(2-Br)	3.62	−	−	−	−	−	−	−	−	−	−	−	−
7k	−CH$_2$Ph(3-Br)	7.59	−	−	−	−	−	−	+	+	+	+	++	−
7l	−CH$_2$Ph(4-Br)	3.10	−	−	−	−	−	−	−	−	−	−	−	−
7m	−CH$_2$Ph(4-Me)	6.37	−	−	−	−	−	−	−	−	−	−	−	−
7n	−CH$_2$Ph(4-Cl)	2.03	−	−	−	−	−	−	−	−	−	−	−	−
7o	−CH$_2$Ph(2-NO$_2$-5-Me)	3.10	−	−	−	−	−	−	+	−	+	+	++	+
7p	−CH$_2$Ph(2-Cl)	2.10	−	−	−	−	−	−	−	−	−	−	−	−
7q	−CH$_2$Ph(3-Cl)	2.16	−	−	−	−	−	−	+	−	−	+	++	+
7r	−CH$_2$Ph(2-Me)	2.62	−	−	−	−	−	−	−	−	+	+	++	+
7s	−C$_4$H$_9$-n	4.41	−	−	−	−	−	−	+	−	+	+	++	++
7t	−C$_3$H$_7$-n	16.6	−	−	−	−	−	−	+	+	+	+	++	+
7u	−COPh(4-Et)	7.10	−	−	−	−	−	−	+	−	+	+	++	+
7v	−CH$_2$COOC$_4$H$_9$-t	15.6	−	−	−	−	−	−	−	−	−	−	−	−
7w	—H$_2$C⟨dioxolane⟩	7.78	−	−	−	−	−	−	+	+	++	+	++	+
KIH-6127		0.49	−	−	−	−	−	−	++	++	ND^d	ND	++	++

^{a} EC, *Echinochloa crusgalli*; DS, *Digitaria sanguinalis*; SV, *Setaria viridis*; BJ, *Brassica juncea*; AR, *Amaranthus retroflexus*; and CA, *Chenopodium album*. ^{b} Rating system for the growth inhibition percentage: ++, >80%; +, 50–80%; −, <50%. ^{c} The K_i values were determined against wild-type *A. thaliana* acetolactate synthase (EC 4.1.3.18). ^{d} Not determined.

reaction of compound 8 with hydrazine hydrochloride or hydrazine hydrate failed to give the target intermediate **7a**. Fortunately, we found that intermediate **6** reacts directly with 1.5 equiv of hydrazine hydrochloride in CH$_3$OH solution at room temperature to afford **7a** in a good yield (88%). This reaction proceeded smoothly because of the possible mechanism that forms aldehyde in situ by condensation with hydrazine before the side reaction takes place. The alkylation of **7a** with various halogenated compounds in the presence of sodium hydrogen in DMF solution afforded the target compounds **7b**−**7v** smoothly in yields of 41−97%. The structures of all intermediates and target compounds were confirmed by elemental analyses and ^{1}H NMR and EI-MS spectral data. In addition, the crystal structure of **7m** was determined by X-ray diffraction

Scheme 2
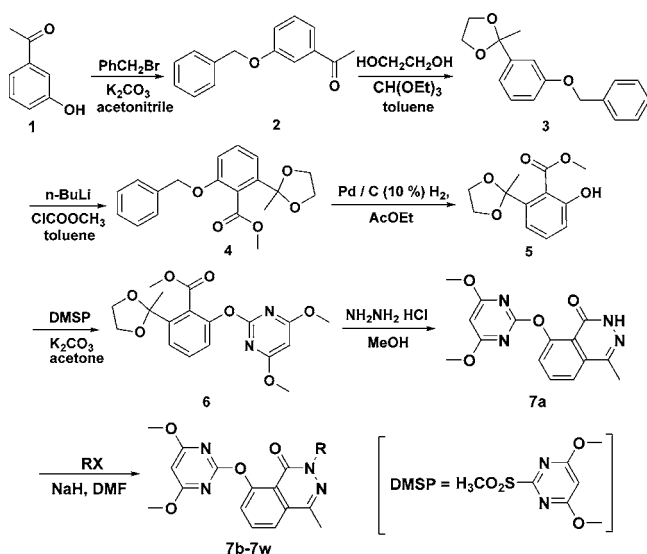
analysis. As shown in **Figure 1**, the backbone of phthalazin-1(2H)-one is coplanar, whereas the plane of 4,6-dimethoxypyrimidinyl and the phenyl group are orthogonal and located on the same side of phthalazin-1(2H)-one plane.

AHAS Inhibitory Activity. In the general formula for compounds **7**, the structural change focused on R. Although all compounds exhibited lower enzyme inhibitory activity than KIH-6127, the variance of R affected the AHAS inhibition activity of compound **7** and displayed some interesting structure−activity relationships. As shown in **Table 1**, the steric and electrostatic property of substituents R seems to be the most significant factor determining the enzyme inhibition activity. In general, compounds containing benzyl substituents displayed higher enzyme inhibition activity than compounds bearing alkyl substituents. For example, the K_i values of compounds **7n**, **7p**, and **7q** ($K_i = 2.03 \times 10^{-4}$M, 2.10×10^{-4}M, and 2.16×10^{-4}M, respectively) were close to that of KIH-6127 ($K_i = 0.49 \times 10^{-4}$M). Compounds **7b**, **7d**, **7t**, and **7v** had K_i values over 10.0×10^{-4}M, while only two compounds (**7h** and **7i**) among benzyl derivatives presented K_i values over 10.0×10^{-4}M. Within benzyl derivatives, 3′-position substituted compounds always displayed lower enzyme inhibition activities than 2′ and 4′ position substituted compounds. Additionally, the electrostatic effect on the enzyme inhibition activity seemed to be very complex. Chlorine derivatives displayed higher activity than the bromine and fluorine derivatives. Some compounds with electron-withdrawing groups (**7g**, **7h**, **7i**, **7u**, **7v**, and **7w**) exhibited lower activities ($K_i > 6.0 \times 10^{-4}$M), while some compounds with electron-withdrawing groups (**7c**, **7f**, and **7o**) presented relatively high enzyme inhibitory activity ($K_i < 6.0 \times 10^{-4}$M).

Herbicidal Activity and Structure−Activity Relationship. **Table 1** indicates that no compounds displayed herbicidal activity in pre-emergence treatments against the six tested weeds,

Scheme 3
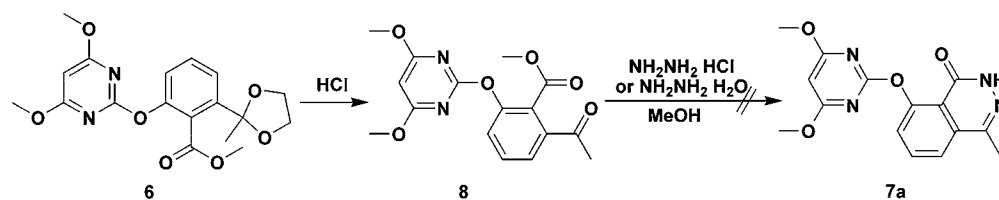
whereas some compounds showed high herbicidal activity in postemergence treatments. These results indicate that the target compounds might be degraded easily by organisms in soil. In addition, injury symptoms showed the typical characteristics of AHAS-inhibiting herbicides. Most of the compounds (**7a**−**7d**, **7h**, **7k**, **7o**, **7q**−**7u**, and **7w**) displayed over 80% inhibition activity against the growth of *Amaranthus retroflexus* at the application rate of 150 g ai/ha, and some compounds (**7a**−**7d**) exhibited broad-spectrum herbicidal activity in postemergence treatments. For example, compounds **7a** and **7d** showed excellent activities against *E. crusgalli*, *D. sanguinalis*, *S. viridis*, and *A. retroflexus*, whereas compounds **7b** and **7c** showed excellent activities against *E. crusgalli*, *S. viridis*, and *A. retroflexus*.

Although the benzyl group of R was favorable to the enzyme inhibition activity, it did not prove favorable for herbicidal activity against *E. crusgalli*, *D. sanguinalis*, *S. viridis*, *B. juncea*, and *C. album*. For example, compound **7a**, with the smallest group (R = H), displayed a low enzyme inhibition activity but a broad-spectrum and high herbicidal activity in postemergence treatments. Compound **7n** (R = 4′-ClC$_6$H$_4$CH$_2$) showed the highest AHAS-inhibiting activity but no herbicidal activity in both pre- and postemergence treatments. In addition, the same complex electrostatic effect on the in vitro activity was also observed on the in vivo activity. For example, some compounds with electron-withdrawing groups (**7f**, **7g**, **7i**, and **7v**) did not display herbicidal activity against the tested weeds, whereas some compounds with electron-withdrawing groups (**7c**, **7h**, **7o**, **7u**, and **7w**) displayed good herbicidal activity against most tested weeds, especially *A. retroflexus*. Furthermore, we can conclude from **Table 1** that AHAS from different species exhibited different sensitivities to the same inhibitors. For example, compound **7h** (R = 2′,4′-F$_2$C$_6$H$_3$CH$_2$) displayed a low in vitro activity ($K_i = 10.40 \times 10^{-4}$ M) but showed over 80% herbicidal efficiency against *A. retroflexus* in postemergence treatments. Compound **7g** (R = 2′,6′-F$_2$C$_6$H$_3$CH$_2$) displayed a higher enzyme inhibition activity ($K_i = 6.34 \times 10^{-4}$M) than

7h, but it showed no in vivo activity in both pre- and postemergence treatments.

In conclusion, we have demonstrated the molecular design, syntheses, and biological activities of a series of 8-(4,6-dimethoxypyrimidinyl-2-oxy)-4-methylphthalazin-1(2H)-ones as a new class of AHAS inhibitors. The preliminary bioassay data showed that some of the synthesized compounds manifested promising AHAS-inhibiting and herbicidal activities in postemergence treatments comparable to that of KIH-6127 and, moreover, that phthalazin-1(2H)-one could be used as a new lead structure for the development of AHAS-inhibiting herbicides. Further investigations on structural optimization and herbicidal activities, especially with respect to resistant weeds and in vivo crop selectivity of this class of compounds, is underway.

Supporting Information Available: Preparation of compounds **2**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

LITERATURE CITED

(1) Duggleby, R. G.; Pang, S. S. Acetohydroxyacid synthase. *J. Biochem. Mol. Biol.* **2000**, *33* (1), 1−36.

(2) Yang, G. F.; Liu, H. Y.; Yang, H. Z. QSAR and 3D-QSAR analysis of structurally diverse ALS inhibitors: Sulfonylureas and triazolopyrimidine-2-sulfonamides. *Pestic. Sci.* **1999**, *55*, 1143−1150.

(3) Burgos, N. R.; Kuk. Y. I.; Talbert, R. E. *Amaranthus palmeri* resistance and differential tolerance of *Amaranthus palmeri* and *Amaranthus hybridus* to ALS-inhibitor herbicides. *Pest Manag. Sci.* **2001**, *57*, 449−457.

(4) Stetter, J., Ed. *Herbicides Inhibiting Branched Chain Amino Acid Biosynthesis*; Chemistry of Plant Protection 10; Springer: New York, 1994.

(5) Whitcomb, C. E. An introduction to ALS-inhibiting herbicides. *Toxicol. Ind. Health* **1999**, *15* (1−2), 231−239.

(6) Wada, N.; Hamamatsu, S. K.; Toyokawa, Y. Pyrimidine derivatives and herbicidal method and compositions. U.S. Patent 4,-906,285, 1990.

(7) Tamaru, M.; Saito, Y. Study of new herbicide KIH-6127. Part I. Novel synthesis of methyl 6-acetylsalicylate as a key intermediate for the preparation of 6-acetylpyrimidin-2-yl salicylates and analogues. *Pestic. Sci.* **1996**, *47*, 125−130.

(8) Tamaru, M.; Takehi, T.; Masuyama, N.; Hanai, R. Studies of the new herbicide KIH-6127. Part II. Synthesis and herbicidal activity of 6-acyl pyrimidin-2-yl salicylates and analogues against barnyard grass. *Pestic. Sci.* **1996**, *47*, 327−335.

(9) Tamaru, M.; Masuyama, N.; Sato, M.; Takabe, F.; Inoue, J. Studies of the new herbicide KIH-6127. Part III. Synthesis and structure−activity studies of analogues of KIH-6127 against barnyard grass (*Echinochloa oryzicola*). *Pestic. Sci.* **1997**, *49*, 76−84.

(10) Christoph, L.; Jean-Pierre, O. Pyrimidine and triazine derivatives with herbicidal and plant growth regulating properties. World Patent WO 9105781, 1991.

(11) Sheldrick, G. M. *SHELXS97*; University of Göttingen: Germany, 1997.

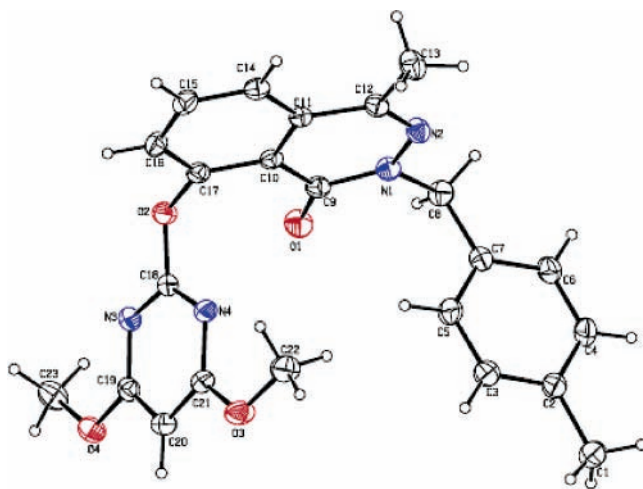(12) *SAINT* and *SMART*; Bruker AXS: Madison, WI, 2003.

Figure 1. Molecular structure of **7m**.

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(13) Xi, Z.; Niu, C. W.; Li, Q. X.; Ouyang, Z.; Ban, S. R. Studies on Herbicide Design through Mutation on Herbicidal Target−Acetohydroxyacid Synthase(I). Enzyme Kinetics of Wild Type and Mutants of *E. coli* AHAS II. *Chinese J. Pestic. Sci.* **2005**, *7* (3), 215−220.

(14) Chang, A. K.; Duggleby, R. G. Expression, purification and characterization of *Arabidopsis thaliana* acetohydroxyacid synthase. *Biochem. J.* **1997**, *327*, 161−169.

(15) Hang, 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-2H-benzo[b][1,4]-oxazin-6-yl)isoindoline-1,3-diones. *J. Agric. Food Chem.* **2005**, *53*, 7908−7914.

(16) Lefkaditis, D. A.; Nicolaides, D. N.; Papageorgiou, G. K.; Stephanidou-Stephana, J. Synthesis of Acenaphtho[1.2-*x*]heterocycles and Spiro[acenaphthylene 1-isoxazoles]. *J. Heterrocycl. Chem.* **1990**, *27*, 227−236.

(17) Marciano, D.; Baud Huin, M.; Zinger, B.; Goldberg, I.; Kosower, E. M. Bimanes. 25. The Synthesis and Structures of Tricyclic Bimanes (*μ*-(Cn)-*syn*-(CH$_2$, CH$_3$ or C1)B). *J. Am. Chem. Soc.* **1990**, *112,* 7320−7328.

(18) Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Mantellini, F. Aspects of the Chemistry of Functionalized 1-Phenylpyrazoles Available from 1,2-Diaza-1,3-butadienes and 2-Phenylazo-1,3-dicarbonyl Compounds. *Tetrahedron Lett.* **1999**, *40*, 3891−3894.