

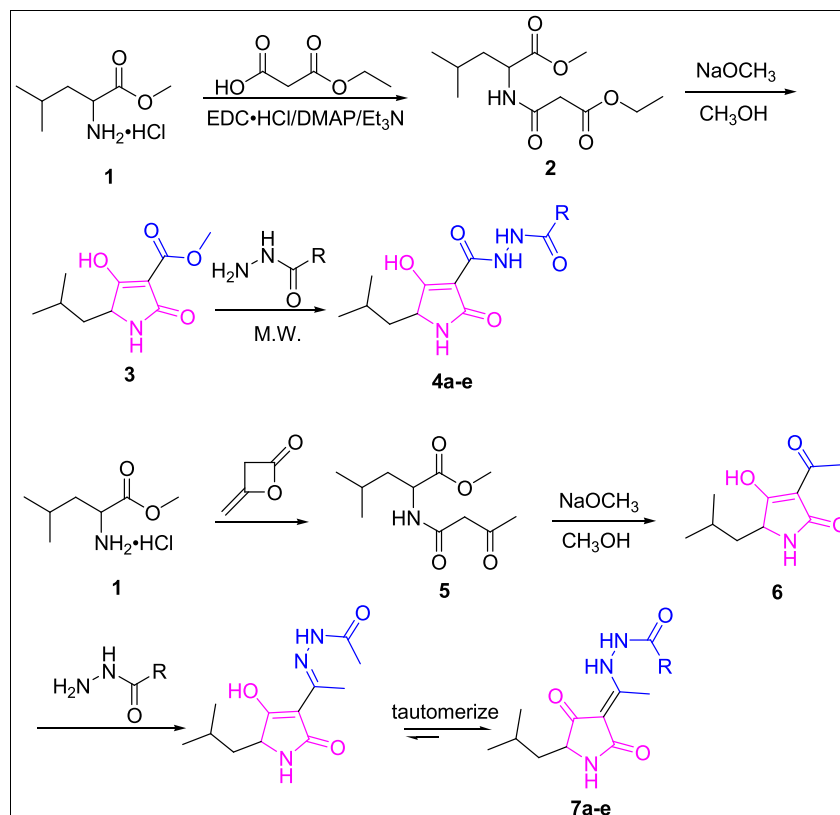
Yu-Xiu Liu,^a Zhi-Peng Cui,^a Yong-Hong Li,^a Yu-Cheng Gu,^b and Qing-Min Wang^{a*}^aState Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China^bSyngenta, Jealott's Hill International Research Centre, Bracknell, Berks, RG42 6EY, UK

*E-mail: wangqm@nankai.edu.cn

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With the aim of optimizing the structure of tenuazonic acid and improving the herbicidal activity, hydrazine moieties were introduced to the 3-position of pyrrolidine-2,4-dione scaffold of tenuazonic acid. 3-Hydrazido-pyrrolidine-2,4-dione compounds (**4a-e**) were prepared from corresponding carboxylates and hydrazines via a microwave-assisted amidation, whereas 3-hydrazono compounds (**7a-e**) were prepared from corresponding 3-acetyl pyrrolidine-2,4-dione. Both of the two structures also exhibited herbicidal activities, especially against the dicotyledonous species amaranth pigweed (*Amaranthus retroflexus*), but with different structure-activity relationship.

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INTRODUCTION

Tenuazonic acid (TeA) (Figure 1, **TeA**), first isolated in 1957 from the culture filtrates of a fungal strain of *Alternaria tenuis* [1,2], was found to have versatile bioactivities including antitumor, antiviral, antibacterial activities, and so on [3]. TeA was also found to have phytotoxic effects on a wide range of plants including weed species and crop plants [3]. On the basis of the 2,4-diketone structure of TeA, series of analogs were designed and synthesized to improve their herbicidal activity, of which 3-[(α -hydroxy-substituted)

benzylidene]pyrrolidine-2,4-diones (Fig. 1, **A**) were the most successful representatives [4,5]. They exhibited good herbicidal activities especially against the monocotyledonous plants *Echinochloa crus-galli* and *Digitaria sanguinalis* in preemergence treatments. 3-(1-Substituted-amino)ethylidene-1*H*-pyrrolidine-2,4-diones [6] (Fig. 1, **B**) and 3-(1-(alkyloxyamino)ethylidene)-1*H*-pyrrolidine-2,4-diones [7,8] (Fig. 1, **C**) were also found to exhibit significant herbicidal activity. However, these compounds may combine with different targets therefore have different weed control mechanisms [5,9,10].

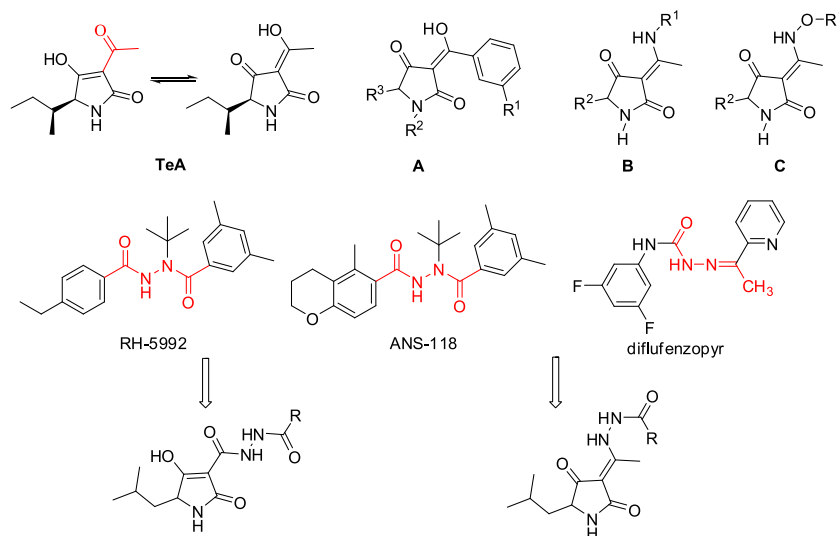


Figure 1. Tenuazonic acid (**TeA**) and designed herbicidal analogs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In this paper, we also focus our attention on the substituent at the 3-position of the pyrrolid-2,4-dione unit, which is reported to play an important role in the herbicidal activity and mode of action. Hydrazines were introduced into the 3-position of the pyrrolid-2,4-dione to prepare hydrazide and hydrozone compounds (Fig. 1). Hydrazides and hydrozones are common structure fragments widespread in pesticide molecules. In the hydrazine compounds, the most successful example may be the diacylhydrazine insect growth regulators such as RH-5992 [11] and ANS-118 [12] (Fig. 1). Hydrazone compound diflufenzopyr [13], which bearing both urea and hydrazone structure (Fig. 1), was mainly used for broadleaf weeds and gramineous weeds control in corn field at a dosage of 13.3–26.2 g/hm. We wish the introduction of hydrazide and hydrozone group to 3-position of the pyrrolid-2,4-dione bring novel herbicidal activity or other unknown bioactivity.

Herein, we report the synthesis and bioactivities of these compounds, and the preliminary structure-herbicidal activity relationships are discussed.

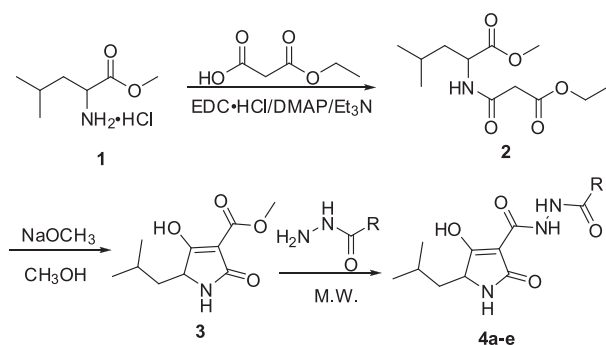
easily decarboxylated when refluxing, microwave irradiation was used for the reaction with hydrazines to reduce the reaction time. Under this condition, the hydrazidation was completed within only 15 min and gave 3-hydrazido products (**4a–e**) in acceptable yields. Representative alkyl, aryl, and alkoxyhydrazides were selected to prepare the target compounds to investigate their influence on herbicidal activity.

The 3-hydrazono compounds (**7a–e**) were synthesized by the condensation of 5-isobutyl-3-acetyl-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (**6**) with the corresponding hydrazides (Scheme 2). Compound **6** [18] was prepared from leucine methyl ester hydrochloride and diketene using similar strategy as compound **3**. It was reported that when alkylamines reacting with compound **6**, the alkylamines were definitely to condense with the carbonyl of the 3-acetyl group rather than at the carbonyl at the 4-position [6]; thus, hydrazides were speculated to condense with compound **6** in the same way. Furthermore, compounds **7** have multiple

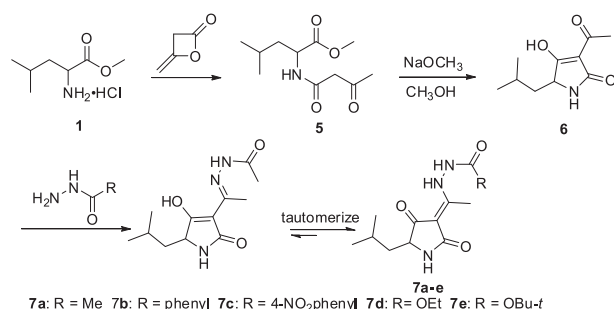
RESULT AND DISCUSSION

Synthesis. The 3-hydrazido compounds (**4a–e**) were synthesized from leucine methyl ester hydrochloride (**1**) in three steps (Scheme 1). Compound **1** reacted with monomalonate in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, triethyl amine, and catalytic amount of DMAP to give amidation product (**2**), which was treated with sodium methoxide via a Dieckmann cyclization to afford methyl 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carboxylate (**3**) [14,15]. Because the carboxylate of **3** at the 3-position was

Scheme 1. Synthesis of compounds **4a–e**.



4a: R=Me **4b:** R=phenyl **6c:** R=4-NO₂-phenyl **4d:** R=OEt **4e:** R=OBu-*t*

Scheme 2. Synthesis of compounds **7a–e**.

tautomers, of which the enamine form drawn in Scheme 2 would be the most likely form according to similar structures [6,20].

Herbicidal activity. Comparing with **TeA**, the 3-hydrazido compounds (**4a–e**) gave relatively better herbicidal activities; especially *N*-arylcarbonyl compounds **4b** and **4c** gave 55% of herbicidal inhibition against the amaranth pigweed, higher than the hydrophilic *N*-acetyl compound (**4a**), the *N*-*t*-butoxycarbonyl compound (**4e**), and *N*-ethoxycarbonyl compound (**4d**). The 3-hydrazono compounds (**7a–e**) showed better herbicidal activity against both dicotyledonous species rape and amaranth pigweed, but the structure-activity relationships were opposite to those observed for the compounds **4a–e**. The compounds **7b** and **7c**, with arylcarbonyl groups on the nitrogen, gave weaker activity than *N*-acetyl compound (**7a**) and the *N*-alkoxycarbonyl compounds **7e** and **7d** (the herbicidal activities above 45% in Table 1 are showed in bold style). However, all the target compounds did not exhibit any herbicidal activity against monocot weeds, thus showed obvious herbicidal selectivity.

The compounds were also tested the fungicidal, insecticidal, and acaricidal activities; but most of them did not exhibit much such activities, only compound **7b** showed

Table 1

Herbicidal activity of synthesized compounds (1.5 kg/ha, percent inhibition).

Compounds	Postemergence treatment (1.5 kg/ha)			
	Rape	Amaranth pigweed	Barnyard grass	Hairy crabgrass
TeA	10	0	20	0
4a	15	25	10	0
4b	15	55	0	10
4c	5	55	10	0
4d	20	25	0	0
4e	10	35	5	0
7a	50	55	15	0
7b	30	0	5	30
7c	35	25	15	0
7d	25	50	10	0
7e	20	45	0	0

a motility of 60% against oriental armyworm by using dip-leaf method at a concentration of 600 mg/kg.

In summary, 3-hydrazido and 3-hydrazono-pyrrolidine-2,4-dione compounds were designed and synthesized to investigate the influence of group at 3-position of pyrrolidine-2,4-dione on the bioactivity including herbicidal activity. The 3-hydrazido (**4**) and the hydrazono compounds (**7**) also showed herbicidal activity, especially against dicotyledonous species amaranth pigweed, which pointed a specific direction for further investigation.

EXPERIMENTAL

Instruments. ¹H-NMR spectra were obtained using a Bruker AV400 spectrometer (Switzerland) or a Varian Mercury Plus 400 spectrometer (US) in CDCl₃ or d₆-DMSO solution with TMS as the internal standard. Chemical shift values (δ) are given in parts per million. Elemental analyses were determined on an Elementar vario EL CUBE elemental analyzer (Germany). HRMS data were obtained on a Ionspec 7.0T Fourier transform ion cyclotron resonance mass spectrometer (FTICR MS) instrument (US). Microwave-assisted syntheses were carried out with CEM Discover-S Microwave Synthesizer (US). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Technical Instruments Co., Beijing, China) and were uncorrected. All of the anhydrous solvents were dried and distilled by using standard techniques. **TeA** was prepared according published procedure, and the structure and purity was assured by comparing with literature [14–16].

Methyl 2-(3-ethoxy-3-oxopropanamido)-4-methylpentanoate (2). To a stirred solution of L-leucine methyl ester hydrochloride (18.07 g, 100 mmol) in dichloromethane (200 mL) at 0°C was successively added triethylamine (10.12 g, 100 mmol), monomethyl malonate (13.2 g, 100 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (20.13 g, 105 mmol). The mixture was stirred over night at RT, then washed with 1M hydrochloric acid and brine, dried over anhydrous sodium sulfate, and evaporated to give compound **2** (20.13 g, 78.4%) as colorless oil.

Synthesis of methyl 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1H-pyrrole-3-carboxylate (3). Metal sodium (0.26 g, 11.47 mmol) was added to anhydrous methanol (10 mL). After sodium disappeared, compound **2** (3.50 g, 13.50 mmol) was added, and the mixture was refluxed for 1.5 h and then was concentrated. The resulting solid was dissolved in water and washed with dichloromethane. Then, the aqueous solution was acidified with 2M HCl and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to give compound **3** (1.23 g, 64.8%) as a white solid. mp 98–100°C (lit. [17] 98–101°C). ¹H-NMR (400 MHz, CDCl₃) δ 0.99 (d, *J* = 6.0 Hz, 6H, CH(CH₃)₂), 1.45–1.53 (m, 1H, CH₂CH), 1.71–1.85 (m, 2H, CH₂CH + CH(CH₃)₂), 3.93 (s, 3H, OCH₃), 4.18–4.21 (m, 1H, CHNH), 5.77 (br, 1H, NH).

2,5-Dihydro-4-hydroxy-5-isobutyl-2-oxo-1H-pyrrole-3-carbohydrazides (4). A substituted hydrazide (5.0 mmol) and several drops of acetic acid were added to a solution of compound **3** (1.07 g, 5.0 mmol) in THF (20 mL), and the mixture was stirred at 100°C for 15 min with microwave heating at 100 W. The

reaction mixture was then concentrated, the residue was dissolved in EtOAc and washed with diluted hydrochloric acid then brine, dried over anhydrous sodium sulfate, evaporated, and recrystallized in ethyl acetate to give compound **4**.

Data for *N*'-acetyl-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carbohydrazide (4a**).** Yield, 50.6%. White solid; mp 175–177°C. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 0.88 (d, *J* = 6.8 Hz, 6H, CH(CH₃)₂), 1.36–1.52 (m, 2H, CH₂CH), 1.72–1.84 (m, 1H, CH(CH₃)₂), 1.84 + 1.93 + 2.08 (s, 0.36 + 1.06 + 1.61 = 3H, COCH₃), 3.02 (br, 2H, NHNH), 3.99–4.23 (m, 1H, CHNH), 8.34 + 8.38 + 8.47 (br s, 0.54 + 0.36 + 0.07 = 1H, NH), 9.75 + 10.06 + 10.19 (br s, 0.54 + 0.36 + 0.07 = 1H, OH). HRMS for C₁₁H₁₆N₃O₄ (M – H)[–]: 254.1146. Found: 254.1140.

Data for *N*'-benzoyl-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carbohydrazide (4b**).** Yield, 45.3%. White solid; mp 202–204°C. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 0.92 (d, *J* = 6.4 Hz, 6H, CH(CH₃)₂), 1.23–1.32 (m, 1H, CH₂CH), 1.63–1.70 (m, 1H, CH₂CH), 1.78–1.88 (m, 1H, CH(CH₃)₂), 3.99–4.05 (m, 1H, CHNH), 4.48 (s, 1H, NH), 7.31 (br, 1H, NH), 7.50 (t, *J* = 7.2 Hz, 2H, ArH), 7.58 (t, *J* = 7.2, 1H, ArH), 7.87 (d, *J* = 7.2 Hz, 2H, ArH), 8.75 (br, 1H, NH), 10.50 (br, 1H, OH). HRMS for C₁₆H₁₈N₃O₄ (M – H)[–]: 316.1303. Found: 316.1300.

Data for 2,5-dihydro-4-hydroxy-*N*'-(4-nitrobenzoyl)-5-isobutyl-2-oxo-1*H*-pyrrole-3-carbohydrazide (4c**).** Yield, 48.1%. White solid; mp 149–152°C. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 0.92 (d, *J* = 6.8 Hz, 6H, CH(CH₃)₂), 1.25–1.32 (m, 1H, CH₂CH), 1.63–1.70 (m, 1H, CH₂CH), 1.76–1.90 (m, 1H, CH(CH₃)₂), 4.02–4.07 (m, 1H, CHNH), 4.56 (br, 1H, NH), 7.36 (br, 1H, NH), 8.10 (d, *J* = 8.8 Hz, 2H, ArH), 8.35 (d, *J* = 8.8 Hz, 2H, ArH), 8.86 (br, 1H, NH), 10.84 (br, 1H, OH). HRMS for C₁₆H₁₇N₄O₆ (M – H)[–]: 361.1154. Found: 361.1149.

Data for 2,5-dihydro-*N*'-ethoxycarbonyl-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carbohydrazide (4d**).** Yield, 63.2%. White solid; mp 204–205°C. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 0.88 (d, *J* = 6.0 Hz, 6H, CH(CH₃)₂), 1.22 (t, *J* = 5.4 Hz, 3H, CH₂CH₃), 1.35–1.49 (m, 2H, CH₂CH), 1.73–1.84 (m, 1H, CH(CH₃)₂), 3.00 (s, 1H, NH), 3.42 (br, 1H, NH), 4.02–4.17 (m, 3H, CH₂CH₃ + CHNH), 8.33 (br, 1H, NH), 9.90 (br, 1H, OH). HRMS for C₁₂H₁₈N₃O₅ (M – H)[–]: 284.1252. Found: 284.1255.

Data for *N*'-(tert-butoxycarbonyl)-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carbohydrazide (4e**).** Yield, 67.7%. White solid; mp 159–161°C. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 0.87–0.92 (m, 6H, CH(CH₃)₂), 1.24–1.34 (m, 1H, CH₂CH), 1.41 (s, 9H, (CH₃)₃), 1.52–1.59 (m, 1H, CH₂CH), 1.75–1.85 (m, 1H, CH(CH₃)₂), 4.06–4.16 (m, 1H, CHNH), 5.22 (br, 1H, NH), 8.34 (br, 1H, NH), 8.88 (br, 1H, NH), 9.33 (br, 1H, OH). HRMS for C₁₄H₂₂N₃O₅ (M – H)[–]: 312.1565. Found: 312.1561.

Synthesis of *N*-acetoacetyl leucine methyl ester (5**).** To a stirred solution of leucine methyl ester hydrochloride (3.67 g, 20 mmol) in dichloromethane (30 mL) at 0°C, a solution of triethylamine (2.12 g, 21 mmol) in dichloromethane (10 mL) was added. Diketene 1.80 g (21 mmol) in dichloromethane (15 mL) was added dropwise, and then the reaction was stirred in an ice bath over night. Water was added to the reaction mixture, and then the organic layer was separated, washed twice with water, dried over anhydrous sodium sulfate, filtrated, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (petroleum–ethyl acetate = 2:1) to give **5** as a colorless oil (4.35 g, yield 86.5%). ¹H-NMR (400 MHz, CDCl₃) δ 0.95 (br, 6H, CH(CH₃)₂), 1.57–1.70 (m, 3H, CH(CH₃)₂), 2.28 (s, 3H, COCH₃), 3.46 (s, 2H, COCH₂), 3.74 (s, 3H, COOCH₃), 4.59–4.62 (m, 1H, CHNH), 7.33 (d, *J* = 6.4 Hz, 1H, NH).

Synthesis of 5-isobutyl-3-acetyl-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (6**).** To a methanol solution of sodium methoxide (sodium (78 mg, 3.4 mmol) in 10 mL dry methanol) was added a solution of **5** (0.92 g, 4.0 mmol) in dry methanol. The mixture was heated under reflux for 1 h and then concentrated. The residue was diluted with ice water and extracted twice with dichloromethane. The aqueous layer was then carefully acidified with 2*M* hydrochloric acid in ice bath and then extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was recrystallized from petroleum and ethyl acetate to give compound **6** as a white solid (0.49 g, 70.3%). mp 108–111°C (lit. [18], 133–134°C). ¹H-NMR (400 MHz, CDCl₃) δ 0.97 (br, 6H, CH(CH₃)₂), 1.42–1.50 (m, 1H, CH(CH₃)₂), 1.70–1.80 (m, 2H, CH₂CH), 2.46 (s, 3H, COCH₃), 3.86 (d, *J* = 10.0 Hz, 1H, CHNH), 6.49 (br, 1H, NH).

General procedure for the synthesis of compounds (7**).** To a stirred EtOH solution of **6** (5 mmol) was added a hydrazide (5 mmol), and the reaction mixture was heated under reflux for 2 h. After cooling, it was concentrated, and the residue was dissolved in EtOAc and washed successively with dilute hydrochloric acid and then brine, dried over anhydrous sodium sulfate, evaporated, and recrystallized to give the compounds (**7**).

Data for *N*'-(1-(5-isobutyl-2,4-dioxopyrrolidin-3-ylidene)ethyl)acetohydrazide (7a**).** Yield, 69.7%. White solid; mp 168–169°C. ¹H-NMR (400 MHz, CD₃OD) δ 0.95–0.98 (m, 6H, CH(CH₃)₂), 1.36–1.45 (m, 1H, CH₂CH), 1.57–1.67 (m, 1H, CH₂CH), 1.78–1.90 (m, 1H, CH(CH₃)₂), 2.08 (s, 3H, COCH₃), 2.48 + 2.52 (s, 3H, CCH₃), 3.76–3.85 (m, 1H, CHNH). HRMS for C₁₂H₁₈N₃O₃ (M – H)[–]: 252.1454. Found: 252.1357.

Data for *N*'-(1-(5-isobutyl-2,4-dioxopyrrolidin-3-ylidene)ethyl)benzohydrazide (7b**).** Yield, 56.3%. White solid; mp 188–190°C. ¹H-NMR (400 MHz, CD₃OD) δ 0.97–1.00 (m, 6H, CH(CH₃)₂), 1.40–1.47 (m, 1H, CH(CH₃)₂), 1.61–1.69 (m, 1H, CH₂CH), 1.81–1.91 (m, 1H, CH₂CH), 2.55 + 2.59 (s, 3H, CCH₃), 3.79–3.89 (m, 1H, CHNH), 7.55 (t, *J* = 7.6 Hz, 2H, ArH), 7.65 (t, *J* = 7.6 Hz, 1H, ArH), 7.93 (d, *J* = 7.6 Hz, 2H, ArH). HRMS for C₁₇H₂₀N₃O₃ (M – H)[–]: 314.1510. Found: 314.1515.

Data for *N*'-(1-(5-isobutyl-2,4-dioxopyrrolidin-3-ylidene)ethyl)-4-nitrobenzohydrazide (7c**).** Yield, 67.6%. White solid; mp 225°C. ¹H-NMR (400 MHz, CD₃OD) δ 0.97–1.00 (m, 6H, CH(CH₃)₂), 1.40–1.47 (m, 1H, CH(CH₃)₂), 1.59–1.71 (m, 1H, CH₂CH), 1.81–1.92 (m, 1H, CH₂CH), 2.58 + 2.61 (s, 3H, N=CCH₃), 3.80–3.90 (m, 1H, CHNH), 8.15 (d, *J* = 8.4 Hz, 2H, ArH), 8.41 (d, *J* = 8.4 Hz, 2H, ArH). HRMS for C₁₇H₁₉N₄O₅ (M – H)[–]: 359.1361. Found: 359.1362.

Data for ethyl *N*'-(1-(5-isobutyl-2,4-dioxopyrrolidin-3-ylidene)ethyl)-hydrazinecarboxylate (7d**).** Yield, 53.6%. White solid; mp 147–149°C. ¹H-NMR (400 MHz, CD₃OD) δ 0.95–0.98 (m, 6H, CH(CH₃)₂), 1.31 (t, 3H, *J* = 7.2 Hz, CH₂CH₃), 1.36–1.44 (m, 1H, CH(CH₃)₂), 1.58–1.66 (m, 1H, CH₂CH), 1.78–1.89 (m, 1H, CH₂CH), 2.49 + 2.52 (s, 3H, N=CCH₃), 3.80 (m, 1H, CHNH), 4.23 (q, *J* = 7.2 Hz, 2H, OCH₂). HRMS for C₁₃H₂₀N₃O₄ (M + Na)⁺: 306.1424. Found: 306.1423.

Data for tert-butyl *N*'-(1-(5-isobutyl-2,4-dioxopyrrolidin-3-ylidene)ethyl)-hydrazinecarboxylate (7e**).** Yield, 52.7%. White solid; mp 159–161°C. ¹H-NMR (400 MHz, CD₃OD) δ 0.95–0.98 (m, 6H, CH(CH₃)₂), 1.36–1.43 (m, 1H, CH(CH₃)₂),

1.52 (s, 9H, C(CH₃)₃), 1.58–1.67 (m, 1H, CH₂CH), 1.77–1.89 (m, 1H, CH₂CH), 2.49+2.52 (s, 3H, N=CHCH₃), 3.75–3.84 (m, 1H, CHNH). HRMS for C₁₅H₂₅N₃O₄ (M – H)[–]: 310.1772. Found: 310.1779.

Herbicide screening. The glasshouse herbicidal activities of compounds (**4a–e**) and (**7a–e**) were evaluated using a standard procedure in Nankai University [19]. Two dicotyledonous species, namely rape (*Brassica napus* L.) and amaranth pigweed (*Amaranthus retroflexus*), and two monocotyledonous weeds, barnyard grass (*Echinochloa crus-galli* (L.) Beauv) and hairy crabgrass (*Digitaria sanguinalis* L. Scop.), were used as herbicidal targets. Purified compounds were dissolved in 100 μL of *N,N*-DMF with the addition of a little Tween 20 and then were sprayed using a laboratory belt sprayer delivering a 750 L/ha spray volume. The dosage (activity ingredient) for each compound corresponded to 1.5 kg/ha. Compounds were sprayed immediately after seed planting (preemergence treatment) or after the expansion of the first true leaf (postemergence treatment). The mixture of same amount of water, *N,N*-DMF, and Tween 20 was sprayed as the control. Each treatment was triplicated. The fresh weight of the aforementioned ground tissues was measured 10 days after treatment. The inhibition percent was used to describe the control efficiency of the compounds. The activity numbers in Table 1 represented the percent displaying herbicidal damage as compared with the control, where complete control of the target is 100 and no control is 0. Each treatment was performed three times. The deviation of values was ±5%.

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