Synthesis and Biological Activities of 3-Substituted Analogues of Tenuazonic Acid

Yu-Xiu Liu,[a] Zhi-Peng Cui,[a] Hua-Ping Zhao,[a] Yong-Hong Li,[a] Yu-Cheng Gu,[b] and Qing-Min Wang[a]*

[a]State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China
[b]Syngenta, Jealott's Hill International Research Centre, Bracknell, Berks RG42 6EY, United Kingdom
*E-mail: wang98h@263.net

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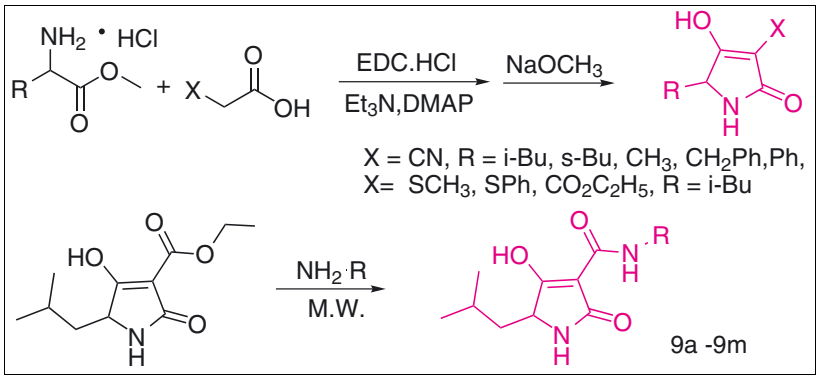

A series of tenuazonic acid analogues in which the acetyl group was replaced with electron-withdrawing substituents have been synthesized with the aim of obtaining molecules with various bioactivities. Substituents such as cyano, sulfonyl, and amido were introduced at the 3-position of the pyrrolidine-2,4-dione nucleus of tenuazonic acid. 3-Cyano and sulfonyl pyrrolidine-2,4-dione compounds (**2** and **6**) were prepared via a Dieckmann cyclization as key step. 3-Amido pyrrolidine-2,4-dione compounds (**9**) were prepared by a microwave-assisted amidation reaction from corresponding 3-carboxylate derivative. The target compounds were evaluated; their herbicidal, fungicidal, and insecticidal activities, and the preliminary bioassay data showed that some 3-cyanopyrrolidine-2,4-diones **2** gave good insecticidal activity, whereas some 3-amido compounds **9** exhibited moderate to strong fungicidal activity against *Pythium dissimile* at 20 mg/L.

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INTRODUCTION

Tenuazonic acid (TeA) (Fig. 1, **TeA**) was first isolated in 1957 from the culture filtrates of a fungal strain of *Alternaria tenuis* [1,2]. Since then, it has also been found in many plant materials such as olives, sunflower seeds, peppers, tobacco, rice, and melons. It has been evaluated against a variety of targets and shows antitumor, antiviral, and antibacterial activities. In agrochemical research, TeA was found to have phytotoxic effects on a wide range of plants including weed species and crop plants [3].

The structure of TeA was extensively modified to provide various structures with different bioactivities [4–14], of which we were interested in the compounds with herbicidal activities. 3-[(α-Hydroxy substituted) benzylidene]pyrrolidine-2,4-diones (Fig. 1, **A**) [10,11] exhibited good herbicidal activity especially against the monocotyledonous plants *Echinochloa crus-galli* and *Digitaria sanguinalis* in preemergence treatments. Their mode of action was proposed to be inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD), based on the triketone core structure that is similar to that in the commercial herbicide mesotrione, and the bleaching effect on leaves of the test plants. Another two series of compounds, 3-(1-substituted amino)ethylidene-1*H*-pyrrolidine-2,4-diones [12] (Fig. 1, **B**) and 3-(1-(alkyloxyamino) ethylidene)-1*H*-pyrrolidine-2,4-diones [13,14] (Fig. 1, **C**), were also found to exhibit significant herbicidal activity. But extensive studies on their mode of action indicated that TeA and some of its analogues strongly inhibit photosynthesis by blocking electron flow from plastoquinone Q_A to Q_B on the acceptor side of photosystem II [15–18]. So, these compounds seem to act against more than one target, and minor changes to the structure may alter their ability to bind to different enzymes, leading to different herbicidal characteristics.

In this article, we also focus our attention on the substituent at the 3-position of the pyrrolid-2,4-dione unit, which was reported to play an important role in the herbicidal activity and mode of action. The electron-withdrawing cyano, sulfonyl, and amido groups were introduced at the 3-position of the pyrrolidine-2,4-dione nucleus of TeA to investigate the herbicidal activity (**2**, **6**, and **9** in Fig. 1). To efficiently synthesize the

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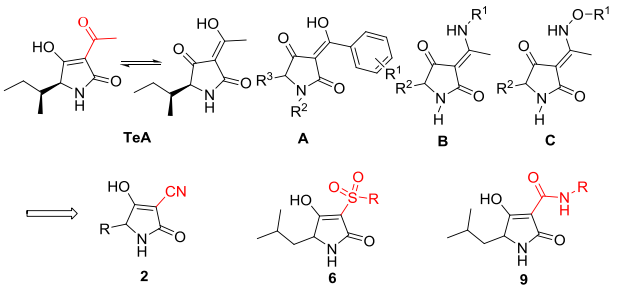


Figure 1. Tenuazonic Acid (TeA) and designed herbicidal analogues.

compounds and compare with each other, *s*-butyl group at the 5-positon of the compounds was changed to *i*-butyl group. Herein, we report the synthesis and herbicidal activity of these compounds. Their fungicidal and insecticidal activities were also evaluated and reported.

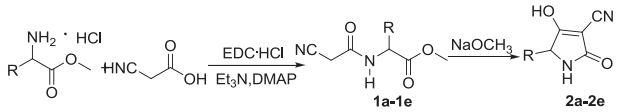
RESULTS AND DISCUSSION

Synthesis. The 3-cyano analogue of TeA (**2a**) was synthesized from leucine methyl ester hydrochloride and cyanoacetic acid. These materials condensed in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl), triethylamine, and a catalytic amount of DMAP to form the amide **1a**, which was treated with sodium methoxide to afford the 3-cyano analogue **2a** via Dieckmann cyclization. **2b–2e** were synthesized according to the same procedure but using different amino acids as the starting materials (Scheme 1).

Similarly, 3-phenylthio- and 3-methylthio analogues of TeA (**5a** and **5b**) were synthesized from corresponding (phenylthio)acetic acid (**3a**) and (methylthio)acetic acid (**3b**) using same strategy. **3a** was prepared from sodium chloroacetate and thiophenol, whereas **3b** was synthesized from 2-mercaptoacetic acid and iodomethane [19]. To obtain higher yield for Dicekmann cyclization step, potassium *t*-butoxide was used instead of sodium methoxide. 3-Phenylsulfonyl and 3-methylsulfonyl analogues **6a** and **6b** were prepared, respectively, from **5a** and **5b** by oxidation with H_2O_2 (Scheme 2).

The 3-amido compounds (**9a–9m**) were synthesized from the key intermediate methyl 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carboxylate (**8**) [20]. Because the ester **8** was easily decarboxylated during the long heating period when reacting with amines, microwave irradiation was used for this step to reduce the reaction time according to literature [20]. Under these conditions, the reactions completed within only 15 min and gave products in acceptable yields. For the preparation of the amides **9**, representative alkylamines, arylamines, benzylamines, isoxazole-5-methylamines, and substituted ethanolamines were chosen (Scheme 3).

Scheme 1. Synthesis of 3-cyano compounds **2**.



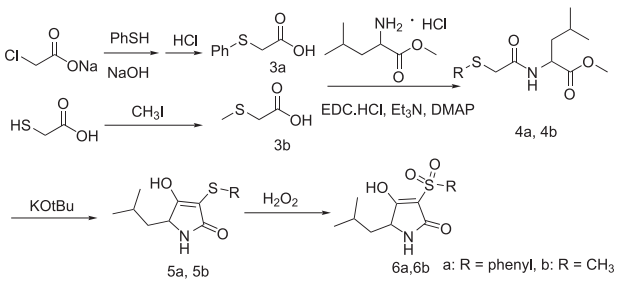
a: R = *i*-Bu, **b**: R = *s*-Bu, **c**: R = CH_3, **d**: R = CH_2Ph, **e**: R = Ph

The herbicidal activities of compounds **2**, **5**, **6**, and **9** against four representative species (two dicot species and two monocot species, see herbicidal assay method) at a dose of 1.5 kg/ha were evaluated. Unfortunately, none of the compounds gave notable herbicidal activity whatever in preemergence treatments or postemergence treatments (the mentioned compounds exhibited herbicidal inhibitory activity no more than 20% at a dose of 1.5 kg/ha). It is worth mentioning that although the 3-amido compounds **9** did not exhibit high herbicidal activity, some of the compounds (**9a**, **9c**, and **9e**) slightly bleached the leaves of the weeds in the assay for herbicidal activity, which suggested compounds **9** may bind to HPPD, but with very low binding energy.

Selected compounds were evaluated for fungicidal activity in mycelial growth tests or in leaf-piece assays (Table 1). The amide analogues of TeA **9** exhibited significantly higher fungicidal activity against *Pythium dissimile* than the other compounds. Activity was higher when the R group is propyl or 4-Cl–phenyl (**9b** and **9d**). When R is an arylmethylene group, activity varied depending on both the aryl group and the substituent on the aromatic ring. For example, the 4-fluoro-benzyl amide (**9f**) exhibited higher activity than the benzyl amide (**9e**), and the 3-phenylisooxazol-5-methylene amide (**9h**) gave much higher activity than the 3-(4-methoxyphenyl) and 3-(4-trifluorophenyl)-isooxazol-5-methylene amides (**9i** and **9j**). In addition, some compounds of the series **9** also showed slight fungicidal activity against *Septoria tritici* and *Uromyces viciae-fabae*.

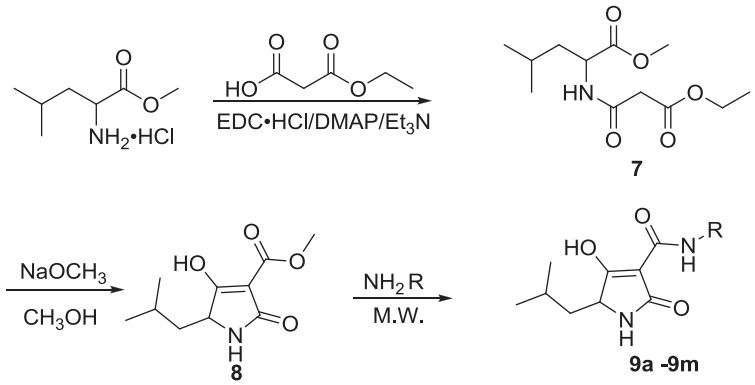
Representative compounds were tested for their insecticidal and acaricidal activities. The 3-cyano compound **2a** was the first of this type to be tested and gave some insecticidal activity against cotton bollworm, oriental armyworm, and corn borer at 600 mg/L and mosquito larvae at 5 mg/L.

Scheme 2. Synthesis of 3-sulfonyl compounds **6**.



a: R = phenyl, b: R = CH_3

Scheme 3. Synthesis of 3-amido compounds **9**.



9a R = CH_3
9b R = *n*-C_3H_7
9c R = *t*-C_4H_9
9d R = *p*-ClC_6H_4
9e R = $C_6H_5CH_2$
9f R = *p*-$FC_6H_4CH_2$
9g R = 3-*i*-propylisoxazol-5-methylene
9h R = 3-phenyl-isoxazol-5-methylene
9i R = 3-(4-methoxyphenyl)-isoxazol-5-methylene
9j R = 3-(4-trifluoromethylphenyl)-isoxazol-5-methylene
9k R = 1-hydroxy-2-methylpropan-2-yl
9l R =2-hydroxy-1-phenylethyl
9m R = 1-(4-t-butylphenyl)-2-hydroxyethyl

Table 1

Fungicidal activities of compounds.

	Pythium dissimile (20 mg/L)	*Septoria tritici* (100 mg/L)	*Uromyces viciae-fabae* (100 mg/L)
2a	0	0	0
5a	0	0	0
6a	0	33	0
9a	55	0	27
9b	99	18	0
9c	55	18	55
9d	99	18	0
9e	27	0	27
9f	55	18	0
9h	77	0	0
9i	0	0	0
9j	0	33	0
9k	27	18	0
9m	27	0	0

Its analogues **2b–2e** were then prepared and evaluated. Like **2a**, all these compounds exhibited slight insecticidal activity against cotton bollworm (30–60% mortality at 600 mg/L). Other compounds did not exhibit notable insecticidal activity, and none of the compounds gave acaricidal activity against the adult mite, the larvae, or the eggs of spider mite (*Tetranychus cinnabarinus*).

In summary, 3-cyano, 3-sulfonyl, and 3-amido pyrrolidine-2,4-dione compounds were synthesized to investigate the bioactivity. 3-Amido pyrrolidine-2,4-dione compounds (**9**) exhibited good fungicidal activity against *P. dissimile* at 20 mg/L, which provided good leading products for further extension. 3-Cyano pyrrolidine-2,4-dione compounds (**2**) exhibited insecticidal activity against cotton bollworm (30–60% mortality at 600 mg/L). But none of the compounds showed significant herbicidal activity, which verified the fact that the herbicidal activity was largely influenced by the 3-substituent.

EXPERIMENTAL

Instruments. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer (Switzerland) or at 400 MHz using a Varian Mercury Plus400 spectrometer (US) in $CDCl_3$ or DMSO-d_6 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 FTICR-MS Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) instrument (Ionspec 7.0T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Technical Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized. All of the anhydrous solvents were dried and distilled by using standard techniques.

Synthesis of methyl 2-(2-cyanoacetamido)-4-methylpentanoate (1a). To a stirred solution of cyanoacetic acid (4.25 g, 50 mmol) in dichloromethane (120 mL) was added leucine methyl ester hydrochloride (9.18 g, 50 mmol). To this solution were added triethylamine (5.06 g, 50 mmol) and DMAP (0.31 g, 2.5 mmol) at 0°C. After the mixture was stirred at 0°C for 0.5 h, EDC·HCl (10.06 g, 52.5 mmol) was added, and then, the mixture was stirred overnight at room temperature. The mixture was then washed successively with 1*M* hydrochloric acid and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give compound **1a** (9.28 g, yield 88.4%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 6.4 Hz, 6H, $CH(CH_3)_2$), 1.58–1.73 (m, 3H, CH_2CH), 3.23 (s, 2H, CH_2CN), 3.74 (s, 3H, OCH_3), 4.62–4.67 (m, 1H, CHNH), 7.19 (br s, 1H, NH).

Compounds **1b–1e** were prepared according to the procedure used for compound **1a**.

Data for methyl 2-(2-cyanoacetamido)-3-methylpentanoate (1b). Yield 82.9%. An oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–0.96 (m, 6H, CH_2CH_3 + $CHCH_3$), 1.17–1.24 (m, 1H, CH_2CH_3), 1.40–1.50 (m, 1H, CH_2CH_3), 1.89–1.99 (m, 1H, $CHCH_3$), 3.43 (s, 2H, CH_2CN), 3.77 (s, 3H, OCH_3), 4.59 (dd, J = 4.8 Hz, 8.4 Hz, 1H, CHNH), 6.60 (br s, 1H, NH).

Data for methyl 2-(2-cyanoacetamido)propanoate (1c). Yield 77.4%. A white solid; mp 67–69°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, J = 7.2 Hz, 3H, $CHCH_3$), 3.41 (s, 2H, CH_2CN), 3.79 (s, 3H, OCH_3), 4.56–4.63 (m, 1H, CHNH), 6.60 (br, 1H, NH).

Data for methyl 2-(2-cyanoacetamido)-3-phenylpropanoate (1d). Yield 87.2%. A white solid; mp 110–111°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09–3.22 (m, 2H, CH_2CH), 3.33 (s, 2H, CH_2CN), 3.36 (s, 3H, OCH_3), 4.82–4.89 (m, 1H, CHNH), 6.40 (br s, 1H, NH), 7.10 (d, J = 7.2 Hz, 2H, ArH), 7.30–7.41 (m, 3H, ArH).

Data for methyl 2-(2-cyanoacetamido)-2-phenylacetate (1e). Yield 85.3%. A white solid; mp 131–133°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 1H, CH_2CN), 3.41 (s, 1H, CH_2CN), 3.75 (s, 3H, OCH_3) 5.54 (d, J = 7.2 Hz, 1H, CHNH), 7.05 (br s, 1H, NH), 7.30–7.41 (m, 5H, ArH).

Synthesis of 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carbonitrile (2a). To a methanol solution of sodium methoxide from sodium (0.23 g, 10 mmol) in dry methanol (10 mL) was added a solution of compound **1a** (2.32 g, 10 mmol) in dry toluene. The mixture was heated under reflux for 1.5 h, cooled, and diluted with water, and the two phases were separated. The organic layer was washed twice with water. The combined aqueous layers were carefully acidified with 2*M* hydrochloric acid and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*, and recrystallized in ethyl acetate to give compound **2a** (1.29 g, 72.8%) as a white solid. mp 173–175°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (d, J = 6.4 Hz, 6H, $CH(CH_3)_2$), 1.23–1.30 (m, 1H, $CHCH_2$), 1.52–1.58 (m, 1H, $CHCH_2$), 1.70–1.80 (m, 1H, $CH(CH_3)_2$), 4.00–4.10 (m, 1H, CHNH), 8.05 (br s, 1H, NH). HRMS (ESI) for $C_9H_{13}N_2O_2$ $(M+H)^+$ Calcd 181.0972. Found 181.0972.

Compounds **2b–2e** were prepared according to same procedure as compound **2a**.

Data for 5-sec-butyl-2,5-dihydro-4-hydroxy-2-oxo-1H-pyrrole-3-carbonitrile (2b). Yield 68.3%. A white solid; mp 210–212°C (ref [21]: 212–214°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.92 (d, J = 7.2 Hz, 3H, $CHCH_3$), 0.99–1.06 (m, 1H, CH_2CH_3), 1.14–1.24 (m, 1H, CH_2CH_3), 1.80–1.88 (m, 1H, $CHCH_3$), 4.02 (d, J = 2.4 Hz, 1H, CHNH), 7.98 (br, 1H, NH). HRMS (ESI) for $C_9H_{13}N_2O_2$ $(M+H)^+$ Calcd 181.0972. Found 181.0972.

Data for 2,5-dihydro-4-hydroxy-5-methyl-2-oxo-1H-pyrrole-3-carbonitrile (2c). Yield 52.9%. A white solid; mp 216–218°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 3H, CH_3), 4.02–4.12 (m, 1H, CHNH), 7.92 (br, 1H, NH). HRMS (ESI) for $C_6H_7N_2O_2$ $(M+H)^+$ Calcd 139.0502. Found 139.0504.

Data for 5-benzyl-2,5-dihydro-4-hydroxy-2-oxo-1H-pyrrole-3-carbonitrile (2d). Yield 66.4%. A white solid; mp 222–225°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89–3.03 (m, 2H, CH_2CH), 4.37 (t, J = 4.8 Hz, 1H, CHNH), 7.16 (d, J = 6.8 Hz, 2H, ArH), 7.19–7.29 (m, 3H, ArH), 7.91 (br, 1H, NH). HRMS (ESI) for $C_{12}H_{11}N_2O_2$ $(M+H)^+$ Calcd 215.0815. Found 215.0816.

Data for 2,5-dihydro-4-hydroxy-2-oxo-5-phenyl-1H-pyrrole-3-carbonitrile (2e). Yield 69.0%. A white solid; mp 209–210°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H, CHNH), 7.25 (d, J = 7.2 Hz, 2H, ArH), 7.29–7.41 (m, 3H, ArH). HRMS (ESI) for $C_{11}H_9N_2O_2$ $(M+H)^+$ Calcd 201.0659. Found 201.0659.

Synthetic procedure for 2-(phenylthio)acetic acid (3a). To a solution of thiophenol 5.51 g (50 mmol) and sodium hydroxide (2.0 g, 50 mmol) in 95% ethanol (80 mL) was added slowly a solution of sodium chloroacetate (5.83 g, 50 mmol) in water (40 mL). After stirring at room temperature for 3 h, the mixture was refluxed for another 1 h, cooled to room temperature, and acidified with 6*M* HCl to pH = 2. Removal of ethanol and filtration gave **3a** (4.20 g, yield 50.0%) as a white rod-shape crystal. mp 63–64°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 2H), 7.23–7.28 (m, 1H), 7.32 (t, J = 6.8 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H).

Synthetic procedure for compound 2-(methylthio)acetic acid (3b). A 2*M* NaOH (200 mL) was added to a suspension of 2-mercaptoacetic acid (80%, 11.51 g, 100 mmol) in ethanol (40 mL) at 0°C; after stirring for 1 h, iodomethane (7.0 mL, 17.03 g, 120 mmol) was added, and the stirring was continued for 2 h at room temperature, then ethanol was removed under reduced pressure. The solution was acidified with 2*M* HCl and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was distilled (98–100°C/5–6 mmHg) to afford **3b** (9.08 g, yield 85.5%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.24 (s, 2H).

Synthetic procedure for methyl 2-(2-(phenylthio) acetamido)- 4-methylpentanoate (4a) and methyl 2-(2-(methylthio)acetamido)- 4-methylpentanoate (4b). To a stirred solution of **3a** or **3b** (85.54 mmol) in dichloromethane (120 mL) at 0°C were successively added leucine methyl ester hydrochloride (16.32 g, 89.82 mmol), triethylamine (9.09 g, 89.82 mmol), and DMAP (3.14 g, 25.66 mmol). The mixture was stirred at 0°C for 0.5 h, and then, EDC·HCl (17.22 g, 89.82 mmol) was added. The solution was stirred overnight at room temperature and then washed with 1*M* HCl and brine, dried over anhydrous sodium sulfate, and evaporated to give compound **4a** or **4b**. Recrystallization from petroleum ether and ethyl acetate gave white crystals.

Data for 4a. Yield 92.6%; mp 63–65°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J = 6.4 Hz, 6H), 1.29–1.39 (m, 1H), 1.43–1.50 (m, 1H), 1.55–1.62 (m, 1H), 3.72 (d, J = 17.2 Hz, 1H), 3.68 (s, 3H), 3.62 (d, J = 17.2 Hz, 1H), 4.55–4.62 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.20–7.23 (m, 1H), 7.28–7.33 (m, 4H).

Data for 4b. Yield 88.6%; mp 69–70°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 5.6 Hz, 6H), 1.58–1.74 (m, 3H), 2.17 (s, 3H), 3.23 (s, 2H), 3.75 (s, 3H), 4.62–4.68 (m, 1H), 7.19 (d, J = 7.6 Hz, 1H).

Synthetic procedure for 4-hydroxy-5-isobutyl-3-(methylthio)-1*H*-pyrrol-2(5*H*)-one (5a) and 4-hydroxy-5-isobutyl-3-(phenylthio)-1*H*-pyrrol-2(5*H*)-one (5b). *t*-BuOK (4.48 g, 40 mmol) was added to a solution of compound **4a** or **4b** (40 mmol) in THF (120 mL). After refluxed for 1.5 h, the reaction mixture was concentrated to give white solid. The solid was dissolved in water and washed with dichloromethane. Then, the aqueous solution was acidified with 2*M* HCl and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was recrystallized from ethanol and ethyl acetate to give compound **5a** or **5b** as colorless crystal.

Data for 5a. Yield 91.6%; mp 150°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ *0*.92–0.94 (m, 6H, $(CH_3)_2$), 1.28–1.34 (m, 1H, $CH(CH_3)_2$), 1.61–1.68 (m, 1H, CH_2), 1.79–1.88 (m, 1H, CH_2), 4.08–4.14 (m, 1H, CHNH), 7.08–7.12 (m, 3H, Ar–H), 7.27 (t, J = 7.7 Hz, 2H, Ar–H), 7.88 (br, 1H, NH), 12.18

(br, 1H, O**H**). HRMS for $C_{14}H_{16}NO_2S$ $(M-H)^-$: 262.0907. Found: 262.0900.

Data for 5b. Yield 55.3%; mp 146–148°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87–0.90 (m, 6H, $(CH_3)_2$), 1.15–1.22 (m, 1H, $CH(CH_3)_2$), 1.54–1.60 (m, 1H, CH_2), 1.71–1.83 (m, 1H, CH_2), 2.15 (s, 3H), 3.88–3.96 (m, 1H, CHNH), 7.75 (br, 1H, NH), 11.38 (br, 1H, OH). HRMS (ESI) for $C_9H_{14}NO_2S$ $(M-H)^-$: 200.0751. Found: 200.0750.

Synthetic procedure for 4-hydroxy-5-isobutyl-3-(phenylsulfonyl)-1*H*-pyrrol-2(5*H*)-one (6a) and 4-hydroxy-5-isobutyl-3-(methylsulfonyl)-1*H*-pyrrol-2(5*H*)-one (6b). H_2O_2 (30%, 0.92 g, 24 mmol) was added to a suspension of compound **5a** or **5b** (1.0 mmol) in acetic acid (5 mL). After stirring at 35°C for 2 h, the reaction solution was concentrated. The residue was recrystallized from ethanol and ethyl acetate to give white powder **6a** or **6b**.

Data for 6a. Yield 84.8%; mp 150°C decomp; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83–0.85 (m, 6H, $(CH_3)_2$), 1.18–1.24 (m, 1H, $CH(CH_3)_2$), 1.54–1.60 (m, 1H, CH_2), 1.66–1.75 (m, 1H, CH_2), 3.95–4.02 (m, 1H, CHNH), 7.56–7.67 (m, 3H, Ar–H), 7.91 (d, J = 7.2 Hz, 3H, ArH + NH). HRMS (ESI) for $C_{15}H_{20}NO_5S$ $(M+CH_3OH-H)^-$: 294.0806. Found: 294.0814.

Data for 6b. Yield 25.3%; mp 231°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (d, J = 7.2 Hz, 6H, $(CH_3)_2$), 1.28–1.35 (m, 1H, $CH(CH_3)_2$), 1.50–1.57 (m, 1H, CH_2), 1.73–1.85 (m, 1H, CH_2), 3.34 (s, 3H, SCH_3), 4.14–4.17 (m, 1H, CHNH), 8.78 (br, 1H, NH), 15.12 (br, 1H, OH). HRMS for $C_{10}H_{20}NO_5S$ $(M+CH_3OH+H)^+$: 234.0795. Found: 234.0794.

Methyl 2-(3-ethoxy-3-oxopropanamido)-4-methylpentanoate (7). To a stirred solution of leucine methyl ester hydrochloride (18.07 g, 100 mmol) in dichloromethane (200 mL) at 0°C were successively added triethylamine (10.12 g, 100 mmol), monomethyl malonate (13.2 g, 100 mmol), and EDC·HCl (20.13 g, 105 mmol). The mixture was stirred overnight at room temperature, then washed with 1*M* hydrochloric acid and brine, dried over anhydrous sodium sulfate, and evaporated to give compound **7** (20.13 g, 78. 4%) as colorless oil.

Synthesis of methyl 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole- 3-carboxlate (8). Metal sodium (0.26 g, 11.47 mmol) was added to anhydrous methanol (10 mL). After sodium disappeared, compound **7** (3.50 g, 13.50 mmol) was added, and the mixture was refluxed for 1.5 h then was concentrated. The resulting solid was dissolved in water and washed with dichloromethane. Then, the aqueous solution was acidified with 2*M* 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 **8** (1.23 g, 64.8%) as a white solid. mp 98–100°C (lit. [20] 98–101°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.0 Hz, 6H, $CH(CH_3)_2$), 1.45–1.53 (m, 1H, CH_2CH), 1.71–1.85 (m, 2H, $CH_2CH + CH(CH_3)_2$), 3.93 (s, 3H, OCH_3), 4.18–4.21 (m, 1H, CHNH), 5.77 (br, 1H, NH).

General synthetic procedure for 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1*H*-pyrrole-3-carboxamides (9). To a 35-mL microwave reaction tube were added a substituted amine (5.0 mmol) and compound **8** (1.07 g, 5.0 mmol) in THF (20 mL), and the tube was sealed and stirred at 100°C for 15 min with microwave heating at 100 W. The reaction mixture was then concentrated; the residue was dissolved in ethyl acetate and washed with diluted hydrochloric acid then brine, dried over anhydrous sodium sulfate, evaporated, and recrystallized from ethyl acetate to give compound **9**.

Data for 2,5-dihydro-4-hydroxy-5-isobutyl-N-methyl-2-oxo-1H-pyrrole- 3-carboxamide (9a). Yield 66.0%. A white solid; mp 129°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.00 (m, 6H, CH $(CH_3)_2$), 1.41–1.52 (m, 1H, CH_2), 1.69–1.86 (m, 2H, $CH_2 + CH$ $(CH_3)_2$), 2.93 (d, J = 4.4 Hz, 3H, NCH_3), 4.12–4.20 (m, 1H, CHNH), 6.06 (br, 1H, NH), 7.52 (br, 1H, NH), 8.07 (br, 1H, OH). HRMS for $C_{10}H_{15}N_2O_3$ $(M-H)^-$: 211.1088. Found: 211.1085.

Data for 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-N-propyl-1H-pyrrole-3-carboxamide (9b). Yield 43.5%. A white solid; mp 123–125°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–1.00 (m, 9H, $CH(CH_3)_2 + CH_2CH_3$), 1.42–1.49 (m, 1H, $CHCH_2$), 1.56–1.66 (m, 2H, CH_2CH_3), 1.71–1.85 (m, 2H, $CHCH_2 + CH$ $(CH_3)_2$), 3.2 (q, J = 6.8 Hz, 2H, NCH_2), 4.12–4.16 (m, 1H, CHNH) 5.97 (br, 1H, NH), 7.59 (br, 1H, NH), 9.92 (br, 1H, OH). HRMS for $C_{12}H_{19}N_2O_3$ $(M-H)^-$: 239.1401. Found: 239.1408.

Data for N-tert-butyl-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1H-pyrrole- 3-carboxamide (9c). Yield 72.5%. A white solid; mp 195–198°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.00 (m, 6H, $CH(CH_3)_2$), 1.39–1.48 (m, 10H, $C(CH_3)_3 + CH(CH_3)_2$), 1.69–1.89 (m, 2H, $CHCH_2$), 4.07–4.13 (m, 1H, CHNH), 5.87 (br, 1H, NH), 7.53 (br, 1H, NH), 7.94 (br, 1H, OH). HRMS for $C_{13}H_{21}N_2O_3$ $(M-H)^-$: 253.1558. Found: 253.1552.

Data for N-(4-Chlorophenyl)-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo- 1H-pyrrole-3-carboxamide (9d). Yield 59.1%. A white solid; mp 160°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.0 Hz, 6H, $CH(CH_3)_2$), 1.46–1.56 (m, 1H, $CH(CH_3)_2$), 1.76–1.87 (m, 2H, $CHCH_2$), 4.22–4.26 (m, 1H, CHNH), 5.91 (br, 1H, NH), 7.31 (d, J = 8.8 Hz, 2H, ArH), 7.31 (d, J = 8.8 Hz, 2H, ArH), 7.53 (br, 1H, NH), 9.57 (br, 1H, OH). HRMS for $C_{15}H_{16}ClN_2O_3$ $(M-H)^-$: 307.0855. Found: 307.0862.

Data for N-benzyl-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1H-pyrrole- 3-carboxamide (9e). Yield 68.1%; A white solid; mp 168–171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–0.99 (m, 6H, $CH(CH_3)_2$), 1.41–1.49 (m, 1H, $CH(CH_3)_2$), 1.71–1.84 (m, 2H, $CHCH_2$), 4.14–4.17 (m, 1H, CHNH), 4.55 (d, J = 6.4 Hz, 2H, $NHCH_2$), 5.84 (br, 1H, NH), 6.43 (br, 1H, OH or CHCO), 7.27–7.36 (m, 5H, ArH), 7.94 (br, 1H, NH). HRMS for $C_{16}H_{19}N_2O_3$ $(M-H)^-$: 287.1401. Found: 287.1403.

Data for N-(4-fluorobenzyl)-2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1H-pyrrole- 3-carboxamide (9f). Yield 65.4%. A white solid; mp 173–175°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–1.01 (m, 6H, $CH(CH_3)_2$), 1.41–1.51 (m, 1H, $CH(CH_3)_2$), 1.69–1.82 (m, 2H, $CHCH_2$), 3.28 (br, 1H, CHCO), 4.12–4.19 (m, 1H, CHNH), 4.51 (d, J = 6.0 Hz, 2H, $NHCH_2$), 5.71 (br, 1H, NH), 6.99–7.05 (m, 2H, ArH), 7.26–7.31 (m, 2H, ArH), 7.94 (br, 1H, NH). HRMS for $C_{15}H_{16}FN_2O_3$ $(M-H)^-$: 305.1307. Found: 305.1302.

Data for 2,5-dihydro-4-hydroxy-5-isobutyl-N-((3-isopropylisoxazol-5-yl)methyl)- 2-oxo-1H-pyrrole-3-carboxamide (9g). Yield 46.2%. A white solid; mp 167–170°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86–0.92 (m, 6H, $CH(CH_3)_2$), 1.18–1.21 (m, 6H, $CH(CH_3)_2$), 1.26–1.34 (m, 1H, CH_2CH), 1.51–1.60 (m, 1H, CH_2CH), 1.71–1.87 (m, 1H, $CH(CH_3)_2$), 2.90–3.03 (m, 1H, $CH(CH_3)_2$), 3.88–3.94 (m, 0.54H, CHNH) + 4.06–4.03 (m, 0.46H, CHNH), 4.28 (d, J = 5.8 Hz, 1.08H, $NHCH_2$), +4.55 (d, J = 5.8 Hz, 0.92H, $NHCH_2$), 4.30 (s, 0.54H, CHCO), 6.27 (s, 0.54H, Ar–H), + 6.35 (s, 0.46H, Ar–H), 7.12–7.16 (m, 1H, NH), 8.32 (br, 0.46H, NH) 8.55 (br, 0.54H, NH). HRMS for $C_{16}H_{22}N_3O_4$ $(M-H)^-$: 320.1616. Found: 320.1619.

Data for 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-N-((3-phenylisoxazol-5-yl)methyl)-1H-pyrrole-3-carboxamide (9h). Yield 38.1%. A white solid; mp 217°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.01 (m, 6H, $CH(CH_3)_2$), 1.44–1.53 (m, 1H, $CH(CH_3)_2$),

1.73–1.87 (m, 2H, CHC**H**$_2$), 4.18–4.22,(m, 1H, C**H**NH), 4.63 (s, 1H, C**H**CO), 4.72 (d, J = 6.4 Hz, 2H, NHC**H**$_2$), 5.74 (br, 1H, N**H**), 6.53 (s, 1H, C**H**), 7.43–7.45 (m, 3H, Ar**H**), 7.77–7.80 (m, 2H, Ar**H**), 8.12 (t, J = 6.4 Hz, 1H, N**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.2, 25.6, 34.3, 40.6, 55.3, 98.0, 100.4, 126.9, 128.8, 128.9, 130.1, 162.6, 166.1, 169.0, 170.5, 186.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87–0.91 (m, 6H, CH(C**H**$_3$)$_2$), 1.17–1.25 (m, 1H, CHC**H**$_2$), 1.55–1.63 (m, 1H, CHC**H**$_2$), 1.73–1.84 (m, 1H, C**H**(CH$_3$) $_2$), 3.93 (d, J = 9.6 Hz, 1H, C**H**NH), 4.39 (d, J = 6.4 Hz, 2H, NHC**H**$_2$), 4.51 (s, 1H, CHCO), 6.96 (s, 1H, C**H**), 7.13 (br, 1H, N**H**), 7.23 (t, J = 6.4 Hz, 1H, N**H**), 7.46–7.55 (m, 3H, Ar**H**), 7.82–7.90 (m, 2H, Ar**H**). HRMS for $C_{19}H_{20}N_3O_4$ $(M-H)^-$: 354.1459. Found: 354.1453.

Data for 2,5-dihydro-4-hydroxy-5-isobutyl-N-((3-(4-methoxyphenyl)isoxazol-5-yl)methyl)-2-oxo-1H-pyrrole-3-carboxamide (9i). Yield 33.2%. A white solid; mp 205°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87–0.91 (m, 6H, CH(CH$_3$)$_2$), 1.17–1.24 (m, 1H, C**H**$_2$CH), 1.55–1.62 (m, 1H, C**H**$_2$CH), 1.73–1.83 (m, 1H, C**H**(CH$_3$)$_2$), 3.81 (s, 3H, OC**H**$_3$), 3.91–3.96 (m, 1H, C**H**NH), 4.36 (d, J = 5.6 Hz, 2H, NHC**H**$_2$), 4.50 (s, 1H, C**H**CO), 6.89 (s, 1H, C**H**), 7.02–7.08 (m, 2H, Ar**H**), 7.13 (br, 1H, N**H**), 7.23 (t, J = 5.6 Hz, 1H, N**H**), 7.80 (d, J = 8.8 Hz, 2H, Ar**H**). HRMS for $C_{20}H_{22}N_3O_5$ $(M-H)^-$: 384.1565. Found: 384.1558.

Data for N-((3-(4-(trifluoromethyl)phenyl)isoxazol-5-yl) methyl)- 2,5-dihydro-4-hydroxy-5-isobutyl-2-oxo-1H-pyrrole-3-carboxamide (9j). Yield 39.5%. A white solid; mp 209–211°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87–0.91 (m, 6H, CH(C**H**$_3$)$_2$), 1.18–1.27 (m, 1H, C**H**$_2$CH), 1.55–1.62 (m, 1H, C**H**$_2$CH), 1.70–1.84 (m, 1H, C**H**(CH$_3$)$_2$), 3.91–3.98 (m, 1H, C**H**NH), 4.42 (d, J = 5.6 Hz, 2H, NHC**H**$_2$), 4.52 (s, 1H, C**H**CO), 7.09 (s, 1H, C**H**), 7.15 (br, 1H, N**H**), 7.25 (t, J = 5.6 Hz, 1H, N**H**), 7.89 (d, J = 8.2 Hz, 2H, Ar**H**), 8.11 (d, J = 8.2 Hz, 2H, Ar**H**). HRMS for $C_{20}H_{19}F_3N_3O_4$ $(M-H)^-$: 422.1333. Found: 422.1329.

Data for 2,5-dihydro-4-hydroxy-N-(1-hydroxy-2-methylpropan-2-yl)-5-isobutyl-2-oxo-1H-pyrrole-3-carboxamide (9k). Yield 51.5%. A white solid; mp 168°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.01(m, 6H, CH(C**H**$_3$)$_2$), 1.36 (s, 6H, C(C**H**$_3$)$_2$), 1.42–1.48 (m, 1H, CHC**H**$_2$), 1.70–1.87 (m, 2H, CHC**H**$_2$ + C**H**(CH$_3$)$_2$), 3.63 (s, 2H, OC**H**$_2$), 4.12–4.17 (m, 1H, C**H**NH), 6.25 (br, 2H, OH), 6.36 (br, 1H, N**H**), 7.83 (br, 1H, N**H**). HRMS for $C_{13}H_{21}N_2O_4$ $(M-H)^-$: 269.1507. Found: 269.1501.

Data for 2,5-dihydro-4-hydroxy-N-(2-hydroxy-1-phenylethyl)-5-isobutyl-2-oxo-1H-pyrrole-3-carboxamide (9l). Yield 67.8%. A white solid; mp 137–139°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95–1.00 (m, 6H, CH(C**H**$_3$)$_2$), 1.38–1.49 (m, 1H, CHC**H**$_2$), 1.64–1.86 (m, 2H, CHC**H**$_2$ + C**H**(CH$_3$)$_2$), 3.88–3.93 (m, 2H, OC**H**$_2$), 4.12–4.18 (m, 1H, C**H**NH), 5.05(s, 2H, OH), 5.13–5.21 (m, 1H, C**H**CH$_2$O), 6.23 (br, 1H, N**H**), 7.30–7.39 (m, 5H, Ar**H**), 8.27 (br, 1H, N**H**). HRMS for $C_{17}H_{21}N_2O_4$ $(M-H)^-$: 317.1507. Found: 317.1513.

Data for N-(1-(4-tert-butylphenyl)-2-hydroxyethyl)-2,5-dihydro-4-hydroxy- 5-isobutyl-2-oxo-1H-pyrrole-3-carboxamide (9m). Yield 55.3%. A white solid; mp 189–191°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–1.01 (m, 6H, CH(C**H**$_3$)$_2$), 1.30 (s, 9H, C(C**H**$_3$)$_3$), 1.43–1.50 (m, 1H, CHC**H**$_2$), 1.71–1.84 (m, 2H, CHC**H**$_2$ + C**H**(CH$_3$)$_2$), 3.28 (s, 2H, OH), 3.90 (d, J = 5.6 Hz, 2H, OC**H**$_2$), 4.12–4.18 (m, 1H, C**H**NH), 5.14 (dd, J = 5.6 Hz, 7.2 Hz, 1H, C**H**CH$_2$O), 5.82 (br, 1H, N**H**), 7.27 (d, J = 7.2 Hz, 2H, Ar**H**), 7.38 (d, J = 7.2 Hz, 2H, Ar**H**), 8.24 (br, 1H, N**H**). HRMS for $C_{21}H_{29}N_2O_4$ $(M-H)^-$: 373.2133. Found: 373.2128.

Herbicidal assay. The glasshouse herbicidal activities of compounds **2**, **5**, **6**, and **9** were evaluated using a previously reported procedure. 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 auto-spray tower (3WPSH-500D, Nanjing Research Institute for Agricultural Mechanization, Nanjing, China) 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 above 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%.

Fungicidal assay. Selected compounds were evaluated in mycelial growth tests in artificial media against water mould (*Pythium dissimile*), early blight fungus (*Alternaria solani*), and noble rot fungus (*Botrytis cinerea*, *Botryotinia fuckeliana*) at rate of 20 mg/L). The compounds were also evaluated in leaf-piece assays, at rates of 200 mg/L for potato late blight fungus (*Phytophthora infestans*) on tomato and 100 mg/L for speckled leaf blotch fungus (*S. tritici*) on wheat and rust fungus (*U. viciae-fabae*) on bean. Chemicals were applied to leaf-pieces prior to inoculation with spores of the pathogen or incorporated into the growth medium for the artificial media assays. The plates were stored in controlled environment cabinets for between 4 and 14 days, depending on the assay, after which mycelia growth or disease inhibition was assessed. Each well was scored using a three-banded system, with complete inhibition of mycelia growth or disease symptoms scored as 99, partial inhibition as 55, and no inhibition as 0. Each assay contained two replicates for each rate, except the *S. tritici* assay that contained three replicates.

Insecticidal and acaricidal assay. Selected compounds were evaluated for insecticidal activities on representative test organisms reared in the laboratory, such as diamondback moth (*Plutella xylostella*), beet armyworm (*Laphygma exigua* Hübner), cotton bollworm (*Helicoverpa armigera*), oriental armyworm (*Mythimna separata*), corn borer (*Ostrinia nubilalis*), bean aphid (*Aphis craccivora*), and mosquito larvae (*Culex pipiens pallens*). Acaricidal activities against eggs, larvae, and adults of spider mite (*T. cinnabarinus*) were also tested. Stock solutions of each test compound was prepared in DMF at a concentration of 200 mg/L and then diluted to the required concentration with water containing Tween-20. Testing was carried out using the leaf-dip method, with the exception of the test with mosquito larvae, which was tested in solution. Assessments were made on a dead/alive basis. Evaluations were based on a percentage scale of 0–100, where 0 equals no activity and 100 equals total kill. Each treatment was performed three times. The deviation of values was ±5%. The detailed assay methods can be found in the literature [22].

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