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Synthesis of Piperine Analogs Containing Isoxazoline/Pyrazoline Scaffold and Their Pesticidal Bioactivities

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Abstract

In continuation of our program to discover new potential pesticidal agents, thirty-one piperine analogs containing isoxazoline/pyrazoline scaffold were prepared, and confirmed by infrared spectra, proton/carbon-13 nuclear magnetic resonance spectra, and high-resolution mass spectra. The structures of compounds **VIIb** and **VIIIc** were further determined by ^{1}H-^{1}H COSY spectra. Especially the configuration of compound **VIIIc** was unambiguously confirmed by single-crystal X-ray diffraction. Their pesticidal activities were evaluated against three serious and typically crop-threatening agricultural pests, *Tetranychus cinnabarinus* Boisduval (spider mite), *Mythimna separata* Walker (Oriental armyworm) and *Plutella xylostella* Linnaeus (diamondback moth). Compounds **VIIIb** and **VIIIc** exhibited greater than 40 folds more potent acaricidal activity than the lead compound piperine against *T. cinnabarinus*. Notably, compounds **VIa**–**c** exhibited more pronounced oral toxicity against *P. xylostella* than toosendanin; compounds **VIb** and **VIc** displayed more promising growth inhibitory activity against *M. separata* than toosendanin. It demonstrated that the methylenedioxy and isoxazoline scaffolds were important for the oral toxicity and growth inhibitory activity against *P. xylostella* and *M. separata*, respectively; the ethylenedioxy and isoxazoline scaffolds were vital for the acaricidal activity against *T. cinnabarinus*. Moreover, compounds **VIb**, **VIIf** and **VIIIc** showed very low toxicity against NRK-52E cells.

KEYWORDS: Piperine, Structural modification, Acaricidal activity, Oral toxicity, Growth inhibitory activity

INTRODUCTION

Tetranychus cinnabarinus Boisduval (spider mite), *Mythimna separata* Walker (Oriental armyworm) and *Plutella xylostella* Linnaeus (diamondback moth) are three serious and typical agriculture-threatening pests, and their outbreaks can result in a significant loss of crops.[1-4] For instance, due to the intermittent outbreaks of third-generation larvae of *M. separata* occurring in 2012, nearly 4 million hectares of crops in China were entirely lost.[5] On the other hand, because of extensive and unreasonable application of synthetic agrochemicals to deal with pests outbreaks, currently, resistances in pest populations, and negative impacts on human health and environment have been simultaneously developed.[6-12] Therefore, discovery of the potential alternatives to efficiently control pests for crop protection is highly urgent. Natural products could play an important role for affording lead compounds in the discovery of pesticide candidates.[13-26]

Piperine (Figure 1) is isolated as a simple alkaloid from *Piper nigrum* Linn., and exhibits lots of biological properties such as anti-inflammatory, antimicrobial, antitumor, and pesticidal activities.[27,28] In addition, molecules containing isoxazoline (**I**) or pyrazoline (**II**, Figure 1) fragment show antimicrobial, fungicidal, mosquitocidal, anti-Alzheimer, anti-cancer, monoamine oxidase inhibitory, pesticidal, or anti-inflammatory activities.[29-39] Previously, we studied isoxazolopodophyllic acid-based esters (**III**, Figure 1), isoxazolopodophyllol-based esters (**IV**, Figure 1) and isoxazolopodophyllal-based hydrazones (**V**, Figure 1) from podophyllotoxin, and found some derivatives showed more promising insecticidal activity than toosendanin, a commercial botanical insecticide isolated from *Melia azedarach*.[40,41] Based upon the above results, and in continuation of our program aimed at the development of new potential pesticidal agents,[42-44] therefore, a series of piperine analogs containing

isoxazoline/pyrazoline scaffold (**VI**–**IX**, Figure 1) were prepared. Their insecticidal and acaricidal activities were evaluated against *M. separata*, *T. cinnabarinus* and *P. xylostella*.

MATERIALS AND METHODS

Chemicals. All reagents and solvents were of reagent grade or purified according to standard methods before use. All the different substituted acetophenone, hydroxylamine hydrochloride, all the different substituted phenylhydrazine hydrochloride, piperidine, lithium aluminium hydride ($LiAlH_4$), aluminum chloride ($AlCl_3$), manganese dioxide (MnO_2), sodium hydride (NaH) and trimethyl phosphonoacetate were purchased from Aladdin Chemistry Co., Ltd. (Shanghai, China). *N*,*N*-Dimethylformamide (DMF), ethyl acetate (EA), petroleum ether (PE), dichloroethane (DCE), dichloromethane (DCM), absolute methanol (MeOH), and absolute ethanol (EtOH) were analytical-grade and purchased from Bodi Chemical Co., Ltd. (Tianjin, China). Malonic acid, pyridine, potassium carbonate (K_2CO_3), ammonium chloride (NH_4Cl), anhydrous sodium sulfate (Na_2SO_4), sodium chloride (NaCl), sodium hydroxide (NaOH) and potassium hydroxide (KOH) were purchased from Kelong Chemical Reagent Co., Ltd. (Chengdu, China). Hydrochloric acid (HCl) and sulfuric acid (H_2SO_4) were purchased from Luoyang Chemical Reagent Factory (Luoyang, China). Analytical thin-layer chromatography (TLC) was performed on silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China). Silica gel column chromatography was performed with silica gel 200−300 mesh (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China). An intermediate, (2*E*,4*E*)-5-(1,3-benzodioxol-5-yl)-2,4-pentadienal (**2**, 37% yield for four steps from piperine (**1**)) (Figure 2), was prepared as previously described.[28]

Instruments. Melting point (mp) was determined using the XT-4 digital melting point apparatus (Beijing Tech Instrument Ltd., Beijing, China). Infrared (IR) spectra were measured

by a TENSOR 27 spectrometer (Bruker, Ettlingen, Germany). Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were carried out on an Avance III 500 MHz equipment (Bruker, Karlsruhe, Germany). High-resolution mass spectra (HRMS) were carried out on a LTQ FT Ultra instrument (Thermo Fisher Scientific Inc., MA). X-ray crystallography was recorded on a SMART APEX II equipment (Bruker, Karlsruhe, Germany).

General Procedure for Synthesis of Compounds 4a–c. A solution of (2*E*,4*E*)-5-(1,3-benzodioxol-5-yl)-2,4-pentadienal (**2**, 2.0 mmol), appropriate substituted acetophenone (2.0 mmol) and KOH (0.4 mmol) in EtOH (10 mL) was stirred at room temperature for 2–11 h. When the reaction was complete checked by TLC analysis, the precipitate was collected by filtration, washed with water (2 mL×2) and EtOH (1 mL×2), and dried to afford compounds **4a–c** in 57–76% yields.

Data for Compound **4a**: Yield: 57%, yellow solid. Mp: 132–134 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, J = 7.0 Hz, 2H), 7.46–7.57 (m, 4H), 6.98–7.01 (m, 2H), 6.90 (dd, J = 1.0, 8.0 Hz, 1H), 6.67–6.79 (m, 4H), 6.52–6.57 (m, 1H), 5.98 (s, 2H). HRMS (ESI): Calcd for $C_{20}H_{17}O_3$ ($[M+H]^+$), 305.1172; found, 305.1172.

Data for Compound **4b**: Yield: 76%, yellow solid. Mp: 145–147 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (dd, J = 5.5, 8.5 Hz, 2H), 7.55 (dd, J = 11.5, 14.5 Hz, 1H), 7.13–7.16 (m, 2H), 6.95–6.99 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.68–6.79 (m, 4H), 6.56 (dd, J = 11.5, 14.0 Hz, 1H), 5.98 (s, 2H). HRMS (ESI): Calcd for $C_{20}H_{16}O_3F$ ($[M+H]^+$), 323.1078; found, 323.1077.

Data for Compound **4c**: Yield: 69%, yellow solid. Mp: 140–142 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (d, J = 8.0 Hz, 2H), 7.50–7.56 (m, 1H), 7.45 (d, J = 7.5 Hz, 2H), 6.89–6.99 (m, 3H), 6.68–6.83 (m, 4H), 6.50–6.57 (m, 1H), 5.98 (s, 2H). HRMS (ESI): Calcd for

$C_{20}H_{16}O_3Cl$ ($[M+H]^+$), 339.0782; found, 339.0782.

Synthesis of 2,3-Dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (6). A solution of 3,4-dihydroxybenzaldehyde (**5**, 0.087 mol), DCE (0.174 mol) and K_2CO_3 (0.174 mol) in DMF (150 mL) was stirred at 105 °C. After 4 h, the mixture was cooled and filtered. The filtered cake was washed with EA (100 mL). The filtrate was diluted with water (100 mL) and extracted with EA (200 mL×3). The combined organic phase was washed by brine (200 mL×3), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (PE:EA = 4:1–2:1, v/v) to afford compound **6** in 90% yield as a white solid. *Data for Compound* **6**: CAS: 29668-44-8. Mp: 49–51°C (lit., mp 51°C).[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.82 (s, 1H), 7.39–7.40 (m, 2H), 6.97–6.99 (m, 1H), 4.33–4.34 (m, 2H), 4.28–4.30 (m, 2H).

Synthesis of Methyl (*E*)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylate (8). A solution of compound **6** (0.047 mol), malonic acid (0.07 mol) and piperidine (1.4 mL) in pyridine (14 mL) was stirred at 85 °C. When the reaction was complete checked by TLC analysis after 6 h, the mixture was cooled to room temperature and poured into ice water (30 mL). Then the pH value was adjusted to pH 5–6 by 1 M aq. HCl. The precipitate was collected by filtration and washed with ice water to afford (*E*)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylic acid (**7**) as a white solid, which was used directly for the next step without further purification. When a solution of compound **7** (0.036 mol) and conc. H_2SO_4 (fourteen drops) in MeOH (100 mL) was refluxed for 12 h, the mixture was cooled to room temperature and the white precipitate (**8**) was collected by filtration. *Data for Compound* **8**: Yield: 85% (for two steps from compound **6** to **8**). Mp: 66–68 °C (lit., mp 66–68 °C).[46] ^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.59 (d, J = 16.0 Hz, 1H), 7.01–7.05 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 16.0 Hz, 1H), 4.26–4.28 (m, 4H), 3.78 (s, 3H).

Synthesis of (*E*)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylaldehyde (10). A solution of compound **8** (0.035 mol) in THF (100 mL) was added dropwise to a well-stirred suspension of $LiAlH_4$ (0.105 mol) and $AlCl_3$ (0.035 mol) in dry THF (30 mL) at 0 °C. The mixture was stirred at this temperature for 2 h and quenched by dropwise addition of ice water (2 mL). The solid was removed by filtration and washed with DCM/MeOH (5:1, v/v). The filtrate was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography to afford compound **9** in 81% yield as a light yellow oil. Subsequently, a solution of compound **9** (0.03 mol) and MnO_2 (0.30 mol) in dry THF (100 mL) was refluxed for 4 h. The solid was removed by filtration and washed with DCM. The filtrate was concentrated *in vacuo*, and purified by silica gel column chromatography (PE:EA:DCM = 5:1:1, v/v/v) to give compound **10** in 52% yield as a white solid. *Data for Compound* **10**: CAS: 261913-24-0. Mp: 69–71 ^{o}C (lit., not reported).[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.65 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 16.0 Hz, 1H), 7.06–7.10 (m, 2H), 6.91 (d, J = 8.5 Hz, 1H), 6.59 (dd, J = 7.5, 15.5 Hz, 1H), 4.30–4.31 (m, 2H), 4.27–4.29 (m, 2H).

Synthesis of Methyl (*2E,4E*)-5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)penta-2,4-dienoate (11). To a stirred solution of NaH (0.044 mol) (60% dispersion in mineral oil) in dry THF (180 mL) was added trimethyl phosphonoacetate (0.026 mol) dropwise at 0 °C. After adding, a solution of compound **10** (0.022 mol) in dry THF (50 mL) was added to the above mixture at 0 °C. When the reaction was complete checked by TLC analysis after 1.5 h, it was quenched with saturated aq. NH_4Cl (15 mL). Water (50 mL) was added to the solution, which

was extracted with EA (100 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (PE:EA = 5:1–3:1, v/v) to afford compound **11** in 90% yield as a white solid. *Data for Compound* **11**: Mp: 91–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (dd, J = 10.5, 15.0 Hz, 1H), 6.94–6.98 (m, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.68–6.80 (m, 2H), 5.95 (d, J = 15.0 Hz, 1H), 4.25–4.28 (m, 4H), 3.76 (s, 3H).

Synthesis of (*2E,4E*)-5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)penta-2,4-dienal (13). A solution of compound **11** (0.015 mol) in THF (80 mL) was added dropwise to a well-stirred suspension of $LiAlH_4$ (0.045 mol) and $AlCl_3$ (0.015 mol) in dry THF (20 mL) at 0°C. After adding, the reaction mixture was stirred at this temperature for 2 h and quenched by dropwise addition of ice water (2 mL). The solid was removed by filtration and washed with DCM/MeOH (5/1, v/v). The filtrate was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford compound **12**, which was used directly for the next step without further purification. A solution of compound **12** (0.01 mol) and MnO_2 (0.10 mol) in dry THF (60 mL) was refluxed for 4 h. The solid was removed by filtration and washed with DCM. The filtrate was concentrated *in vacuo*, and purified by silica gel column chromatography (PE:EA:MeOH = 10:2:1, v/v/v) to afford compound **13** as a yellow solid. *Data for Compound* **13**: Yield: 51% (for two steps from compound **11** to **13**). Mp: 114–115 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.59 (d, J = 8.0 Hz, 1H), 7.20–7.25 (m, 1H), 6.99–7.02 (m, 2H), 6.81–6.91 (m, 3H), 6.24 (dd, J = 8.0, 15.5 Hz, 1H), 4.26–4.29 (m, 4H).

General Procedure for Synthesis of Compounds 14a–c. A solution of compound **13** (2.0 mmol), appropriate substituted acetophenone (2.0 mmol) and KOH (0.4 mmol) in EtOH (10 mL) was stirred at room temperature for 8–12 h. When the reaction was complete checked by

158 TLC analysis, the precipitate was collected, washed with water (2 mL×2) and EtOH (1
159 mL×2), and dried to afford compounds **14a–c** in 65–72% yields.

160 *Data for Compound* **14a**: Yield: 65%, yellow solid. Mp: 134–136 ^{o}C. ^{1}H NMR (500 MHz,
161 $CDCl_3$) δ: 7.96 (d, J = 7.5 Hz, 2H), 7.46–7.57 (m, 4H), 6.94–7.00 (m, 3H), 6.74–6.84 (m, 3H),
162 6.67 (d, J = 14.5 Hz, 1H), 6.51–6.56 (m, 1H), 4.27 (s, 4H). HRMS (ESI): Calcd for $C_{21}H_{19}O_3$
163 ($[M+H]^+$), 319.1329; found, 319.1328.

164 *Data for Compound* **14b**: Yield: 71%, yellow solid. Mp: 168–170 ^{o}C. ^{1}H NMR (500 MHz,
165 $CDCl_3$) δ: 7.97–8.00 (m, 2H), 7.50–7.56 (m, 1H), 7.12–7.16 (m, 2H), 6.94–6.98 (m, 3H),
166 6.74–6.84 (m, 3H), 6.68 (d, J = 14.5 Hz, 1H), 6.55 (t, J = 12.5 Hz, 1H), 4.27 (s, 4H). HRMS
167 (ESI): Calcd for $C_{21}H_{18}FO_3$ ($[M+H]^+$), 337.1234; found, 337.1239.

168 *Data for Compound* **14c**: Yield: 72%, yellow solid. Mp: 152–154 ^{o}C. ^{1}H NMR (500 MHz,
169 $CDCl_3$) δ: 7.89–7.93 (m, 2H), 7.45–7.55 (m, 3H), 6.96–7.01 (m, 3H), 6.74–6.84 (m, 3H),
170 6.68 (d, J = 11.5 Hz, 1H), 6.50–6.55 (m, 1H), 4.27 (s, 4H). HRMS (ESI): Calcd for
171 $C_{21}H_{18}ClO_3$ ($[M+H]^+$), 353.0939; found, 353.0937.

172 **General Procedure for Synthesis of Compounds VIa–c and VIIIb,c**. A mixture of
173 compounds **4a**–**c** or **14b,c** (0.2 mmol), hydroxylamine hydrochloride (0.5 mmol), and NaOH
174 (1.2 mmol) in absolute EtOH (2 mL) was stirred at room temperature for 3 h and then at
175 65 °C for 6–9 h. When the reaction was complete checked by TLC analysis, the mixture was
176 cooled and filtered. The filtered cake was washed with ice water (1 mL×2) and cold EtOH (1
177 mL×2), and then dried to afford compounds **VIa–c** and **VIIIb,c** in 5–45% yields. Exemplary
178 data for compounds **VIa** and **VIIIb** are as follows:

179 *Data for Compound* **VIa**: Yield: 23%, pale yellow solid. Mp: 125–127 ^{o}C. IR cm^{-1} (KBr):

3024, 2921, 2851, 1502, 1488, 1445, 1252, 1041, 988, 759, 692; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.67–7.69 (m, 2H), 7.45–7.46 (m, 3H), 7.15 (s, 1H), 6.86–6.92 (m, 2H), 6.83 (dd, J = 10.5, 15.5 Hz, 1H, H-3'), 6.61 (d, J = 15.5 Hz, 1H, H-4'), 6.50 (dd, J = 11.0, 15.0 Hz, 1H, H-2'), 6.01 (s, 2H, OCH_2O), 5.91 (dd, J = 7.5, 15.0 Hz, 1H, H-1'), 5.20–5.25 (m, 1H, H-5), 3.63 (dd, J = 10.5, 16.5 Hz, 1H, H-4), 3.25 (dd, J = 9.0, 17.0 Hz, 1H, H-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 157.2, 148.3, 147.6, 133.85, 133.80, 131.7, 131.2, 130.5, 129.9, 129.2, 127.0, 126.7, 122.1, 108.8, 105.8, 101.6, 81.9, 40.4. HRMS (ESI): Calcd for $C_{26}H_{18}O_3N$ ($[M+H]^+$), 320.1281; found, 320.1281.

Data for Compound **VIIIb**: Yield: 45%, pale yellow solid. Mp: 198–200 ^{o}C. IR cm^{-1} (KBr): 3000, 2920, 2875, 1604, 1457, 1295, 1069, 988, 865, 668; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.71–7.74 (m, 2H), 7.28–7.31 (m, 2H), 6.99 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.75–6.82 (m, 2H), 6.57 (d, J = 15.5 Hz, 1H, H-4'), 6.44–6.49 (m, 1H, H-2'), 5.91 (dd, J = 7.5, 15.0 Hz, 1H, H-1'), 5.19–5.24 (m, 1H, H-5), 4.23 (s, 4H, OCH_2CH_2O), 3.62 (dd, J = 10.5, 16.5 Hz, 1H, H-4), 3.24 (dd, J = 8.5, 17.0 Hz, 1H, H-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.4 (J = 246.2 Hz), 156.4, 143.96, 143.91, 133.8, 133.6, 131.0, 130.7, 129.4 (J = 8.7 Hz), 126.6, 126.5, 120.3, 117.7, 116.4 (J = 22.5 Hz), 115.1, 82.1, 64.6, 64.5, 40.4. HRMS (ESI): Calcd for $C_{27}H_{24}O_2N_2Br$ ($[M+H]^+$), 487.1016; found, 487.1015.

General Procedure for Synthesis of VIIa–m and IXa–m. A mixture of compounds **4a**–**c** or **14a**–**c** (0.2 mmol), substituted phenylhydrazine hydrochlorides (**15a**–**e**, 0.5 mmol), and NaOH (1.2 mmol) in absolute EtOH (2 mL) was stirred at room temperature for 3 h and then at 65 °C for 6–9 h. When the reaction was complete checked by TLC analysis, the mixture was cooled and filtered. The filtered cake was washed with ice water (1 mL×2) and cold EtOH (1 mL×2), and then dried to afford compounds **VIIa–m** and **IXa–m** in 27–87% yields.

Exemplary data for compounds **VIIa,b** and **IXa,b** are as follows:

Data for Compound **VIIa**: Yield: 59%, pale yellow solid. Mp: 106–108 ^{o}C. IR cm^{-1} (KBr): 3023, 2895, 1595, 1492, 1251, 1038, 984, 749, 691; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.73–7.75 (m, 2H), 7.45 (t, J = 7.0 Hz, 2H), 7.35–7.38 (m, 1H), 7.22–7.25 (m, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 1.0 Hz, 1H), 6.83–6.88 (m, 2H), 6.72–6.78 (m, 2H), 6.53 (d, J = 15.5 Hz, 1H), 6.46 (dd, J = 10.5, 15.0 Hz, 1H), 5.99 (s, 2H), 5.84 (dd, J = 7.5, 15.0 Hz, 1H), 5.00–5.05 (m, 1H), 3.67 (dd, J = 11.5, 17.0 Hz, 1H), 3.14 (dd, J = 6.0, 17.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 148.5, 148.3, 147.4, 145.2, 132.9, 132.6, 132.4, 131.8, 129.3, 129.1, 126.9, 126.2, 126.1, 126.0, 121.9, 119.2, 113.9, 108.8, 105.6, 101.5, 62.1, 40.3. HRMS (ESI): Calcd for $C_{26}H_{23}O_2N_2$ ([M+H]$^+$), 395.1754; found, 395.1753.

Data for Compound **VIIb**: Yield: 87%, pale yellow solid. Mp: 117–119 ^{o}C. IR cm^{-1} (KBr): 3018, 2888, 1506, 1446, 1254, 1044, 982, 820, 690; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.74 (d, J = 7.5 Hz, 2H), 7.36–7.44 (m, 3H), 7.07–7.14 (m, 5H), 6.84–6.89 (m, 2H), 6.78 (dd, J = 10.5, 15.0 Hz, 1H), 6.53 (d, J = 15.5 Hz, 1H), 6.47 (dd, J = 10.5, 15.0 Hz, 1H), 6.00 (s, 2H), 5.83 (dd, J = 7.5, 15.0 Hz, 1H), 4.97–5.02 (m, 1H), 3.66 (dd, J = 11.5, 17.0 Hz, 1H), 3.14 (dd, J = 6.0, 17.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 157.4 (J = 233.7 Hz), 148.8, 148.2, 147.4, 142.1, 132.9, 132.8, 132.6, 132.5, 131.8, 129.2, 129.1, 126.9, 126.1, 121.9, 115.9 (J = 22.5 Hz), 115.2 (J = 7.5 Hz), 108.8, 105.7, 101.5, 62.8, 40.5. HRMS (ESI): Calcd for $C_{26}H_{22}O_2N_2F$ ([M+H]$^+$), 413.1660; found, 413.1659.

Data for Compound **IXa**: Yield: 72%, pale yellow solid. Mp: 170–172 ^{o}C. IR cm^{-1} (KBr): 3024, 2926, 1596, 1508, 1379, 1290, 1068, 988, 750, 692; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.74 (d, J = 7.0 Hz, 2H), 7.36–7.42 (m, 3H), 7.14–7.22 (m, 4H), 6.89–6.92 (m, 2H), 6.78 (d, J = 6.0 Hz, 2H), 6.72 (dd, J = 11.0, 15.0 Hz, 1H), 6.40–6.48 (m, 2H), 5.86 (dd, J = 7.0, 14.5 Hz,

1H), 5.00–5.02 (m, 1H), 4.21 (s, 4H), 3.67 (dd, J = 11.5, 16.5 Hz, 1H), 3.13 (dd, J = 5.5, 17.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 148.5, 145.2, 143.9, 143.7, 132.9, 132.65, 132.62, 132.4, 130.8, 129.3, 129.1, 126.9, 126.1, 120.1, 119.2, 117.6, 115.0, 113.8, 64.6, 64.5, 62.1, 40.4. HRMS (ESI): Calcd for $C_{27}H_{25}O_2N_2$ ($[M+H]^+$), 409.1911; found, 409.1910.

Data for Compound **IXb**: Yield: 33%, Yellow solid. Mp: 100–102 ^{o}C. IR cm^{-1} (KBr): 3013, 2922, 1579, 1507, 1446, 1384, 1288, 1068, 988, 822, 691; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.74 (d, J = 7.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.35–7.38 (m, 1H), 7.05–7.19 (m, 5H), 6.95 (s, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.75 (dd, J = 11.0, 15.5 Hz, 1H), 6.41–6.49 (m, 2H), 5.84 (dd, J = 7.5, 15.0 Hz, 1H), 4.96–5.01 (m, 1H), 4.21 (s, 4H), 3.66 (dd, J = 11.5, 17.0 Hz, 1H), 3.14 (dd, J = 6.0, 17.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 157.4 (J = 233.7 Hz), 148.7, 143.9, 143.7, 142.1, 132.8, 132.7, 132.6, 132.4, 130.8, 129.2, 129.1, 126.9, 126.1, 120.1, 117.6, 115.9 (J = 21.2 Hz), 115.2 (J = 7.5 Hz), 115.0, 64.6, 64.4, 62.8, 40.5. HRMS (ESI): Calcd for $C_{27}H_{24}O_2N_2F$ ($[M+H]^+$), 427.1816; found, 427.1816.

Biological Assay.

Acaricidal Activity of Compounds ***4a–c, 14a–c, VIa–c, VIIa–m, VIIIb,c*** *and* ***IXa–m*** *against Tetranychus cinnabarinus.*[48,49] The acaricidal activity of compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** against the female adults of *T. cinnabarinus* was assessed by slide-dipping method. Spirodiclofen (a commercial acaricidal agent) was used as a positive control. The solutions of compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c**, **IXa**–**m** and spirodiclofen were prepared in acetone/deionized water (v/v = 1/1) at 0.5 mg/mL. For each compound, 90−120 healthy and size-consistency female adults of spider mites (30−40 mites per group) were selected. 30−40 spider mites were adfixed dorsally in two lines to a strip of double-coated masking tape on a microscope slide by using a small brush. Then the slides

were dipped into the corresponding solution for 5 s, and taken out. Excess solutions on the slides were removed by filter paper. The slides treated with acetone/deionized water (v/v = 1/1) alone were used as a blank control group (CK). The experiment was carried out at 26 ± 1°C and 60−80% relative humidity (RH), and on 14 h/10 h (light/dark) photoperiod. The results were checked by binocular dissecting microscope. Their mortalities were recorded at 48 h and 72 h after treatment. Their corrected mortality rate values were calculated as follows: corrected mortality rate (%) = ($T - C$) × 100/(100% − C); C is the mortality rate of CK, and T is the mortality rate of the treated *T. cinnabarinus*.

*Oral Toxicity of Compounds **4a–c, 14a–c, VIa–c, VIIa–m, VIIIb,c** and **IXa–m** against Plutella xylostella.*[16] Thirty 3rd-instar larvae of *P. xylostella* were chosen as the tested insects for each compound. The solutions of compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c**, **IXa**–**m** and toosendanin (a positive control) were prepared in acetone at 20 mg/mL. The corresponding solution (1 μL) was added to a fresh Brassica oleracea leaf disc (0.5×0.5 cm), and dried. A fresh Brassica oleracea leaf disc was treated by acetone alone as the blank control group (CK). One piece of the above discs was offered to and consumed by each insect, which was raised in each well of 12- or 24-well culture plates for 48 h (temperature: 25 ± 2 °C; RH: 65–80%; photoperiod: light/dark = 16 h/8 h). Their corrected mortality rate values were calculated as follows: corrected mortality rate (%) = ($T - C$) × 100/(100% − C); C is the mortality rate of CK, and T is the mortality rate of the treated *P. xylostella*.

*Growth Inhibitory Activity of Compounds **4a–c, 14a–c, VIa–c, VIIa–m, VIIIb,c** and **IXa–m** against Mythimna separata.*[50,51] Thirty early 3rd-instar larvae of *M. separata* were chosen as the tested insects for each compound. The solutions of compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c**, **IXa**–**m** and toosendanin (a positive control) were prepared in acetone at 1

mg/mL. After dipped into the corresponding solution for 3 s, wheat leaf discs (1×1 cm) were taken out, and dried. Wheat leaf discs were treated by acetone alone as the blank control group (CK). Several above discs were added to each culture dish (ten insects per dish). Once the discs were consumed, additional ones were added. After 48 h, the rest of compound-soaked discs was cleaned out, and the untreated ones were added till the end of pupae (temperature: 25 ± 2 °C; RH: 65–80%; photoperiod: light/dark = 12 h/12 h). Their corrected mortality rate values were calculated as follows: corrected mortality rate (%) = (T − C) × 100/ (100% − C); C is the mortality rate of CK, and T is the mortality rate of the treated *M. separata*.

Cytotoxic Assay.

Normal rat kidney tubular epithelial cells (NRK-52E) were purchased from the Chinese Academy of Sciences Cell Bank (Shanghai, China). NRK-52E cells, maintained in a 37 °C humidified incubator with 5% CO_2, were grown in high glucose Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% (v/v) fetal bovine serum (FBS), 100 U/mL penicillin and 100 μg/mL streptomycin.[52] The cell line was routinely cultured in 6-well plate and trypsinized using trypsin/ethylenediaminetetraacetic acid (EDTA) when the cells reached approximately 80% confluence. The cytotoxicity of compounds **VIb**, **VIIf** and **VIIIc** was evaluated using the Cell Counting Kit-8 (CCK-8, Dojindo Laboratories, Japan) assay.[53,54] NRK-52E cells were seeded at a density of 5000 cells per well of 96-well plate and incubated at 37 °C in a atmosphere of 5% CO_2 for 24 h. The DMEM was discarded, and replaced with 200 μL DMEM containing candidate compounds at various concentrations. The DMEM without NRK-52E cells and compounds was as a blank group. After incubation for 24 h, 10 μL CCK-8 was added. After 1–2 h at 37 °C, the OD (optical density) value of each well was

measured using an enzyme linked immunosorbent assay (ELISA) hybrid microplate reader at a wavelength of 450 nm. Cell survival rate values were calculated as follows: cell survival rate (%) = $(OD_{treated} - OD_{blank})/(OD_{control} - OD_{blank}) \times 100$

RESULTS AND DISCUSSION

Synthesis. As shown in Figure 2, firstly, an intermediate, (2*E*,4*E*)-5-(1,3-benzodioxol-5-yl)-2,4-pentadienal (**2**) was obtained in 37% yield for four steps from piperine (**1**) as described previously.[28] Then, compounds **4a**–**c** were smoothly prepared by reaction of compound **2** with appropriate substituted acetophenone in the presence of KOH.[55] On the other hand, as described in Figure 3, reaction of 3,4-dihydroxybenzaldehyde (**5**) with DCE in the presence of K_2CO_3 gave 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (**6**).[56] Compound **6** then reacted with malonic acid in the presence of piperidine and pyridine to afford (*E*)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylic acid (**7**),[57] which was esterified with methanol catalyzed by conc. sulfuric acid to give methyl (*E*)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylate (**8**) in 85% yield for two steps from compound **6** to **8**.[28] Next, compound **8** reacted with $LiAlH_4$ and $AlCl_3$ to produce compound **9** in 81% yield, which was further oxidized by MnO_2 to afford (*E*)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylaldehyde (**10**) in 52% yield.[28] Subsequently, reaction of compound **10** with trimethyl phosphonoacetate in the presence of NaH gave methyl (*2E,4E*)-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)penta-2,4-dienoate (**11**) in 90% yield.[58] Compound **11** reacted with $LiAlH_4$ and $AlCl_3$ to produce compound **12**, which was oxidized by MnO_2 to afford (*2E,4E*)-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)penta-2,4-dienal (**13**) in 51% yield for two steps from compound **11** to **13**.[28] Finally, compounds **14a**–**c** were

easily prepared by reaction of compound **13** with appropriate substituted acetophenone in the presence of KOH.[55] As described in Figures 4 and 5, piperine analogs **VIa**–**c** and **VIIIb,c** were obtained by reaction of compounds **4a**–**c** or **14b,c** with hydroxylamine hydrochloride in the presence of NaOH;[55] piperine analogs **VIIa**–**m** and **IXa**–**m** were synthesized by reaction of compounds **4a**–**c** or **14a**–**c** with different phenylhydrazine hydrochlorides (**15a**–**e**) in the presence of NaOH.[45] Their structures were determined by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

The assignments of the chemical shifts for the protons were further determined by ^{1}H-^{1}H COSY spectra. As shown in Figure 6, the ^{1}H-^{1}H COSY correlation of H-5 and H-1' of compound **VIIb** indicated that its configuration should be as **A**. Similarly, the ^{1}H-^{1}H COSY correlation of H-5 and H-1' of compound **VIIIc** demonstrated that its configuration should be as **B** (Figure S1). Especially three-dimensional structure of compound **VIIIc** was determined by X-ray crystallography (Figure 7). It clearly showed that the nitrogen atom of the isoxazoline fragment was on the same side of the 4-chlorophenyl. Crystallographic data (excluding structure factors) of compound **VIIIc** was deposited at the CCDC (Cambridge Crystallographic Data Centre) with deposition numbers of 1585248.

Pesticidal Activities. The acaricidal activity of compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** against the female adults of *T. cinnabarinus* was evaluated by slide-dipping method at a concentration of 0.5 mg/mL. As shown in Table 1, compounds **VIa**, **VIb**, **VIIf**, **VIIg**, **VIIl**, **VIIIb**, **VIIIc**, **IXf**, and **IXl** exhibited more potent acaricidal activity when compared with piperine (**1**). The 72 h mortality rates (MRs) of compounds **VIa**, **VIb**, **VIIf**, **VIIg**, **VIIl**, **VIIIb**, **VIIIc**, **IXf**, and **IXl** against *T. cinnabarinus* were 45.4%, 41.0%, 48.5%, 47.7%, 46.0%, 56.7%, 63.7%, 46.7% and 42.9%, respectively; whereas the 72 h MR

of compound **1** against *T. cinnabarinus* was only 12.1%. Among them, compound **VIIIc** showed the most promising acaricidal activity. Compared with andrographolide-related esters and quinolinomatrine derivatives,[50,59] herein piperine analogs generally exhibited more potent acaricidal activity. For piperine analogs containing isoxazoline scaffold (e.g., **VIb,c** and **VIIIb,c**), the ethylenedioxy group was an important factor for increasing the acaricidal activity. For example, the 72 h MRs of compounds **VIb,c** (containing the methylenedioxy group) against *T. cinnabarinus* were 41.0% and 26.7%, respectively; whereas the 72 h MRs of compounds **VIIIb,c** (containing the ethylenedioxy group) against *T. cinnabarinus* were 56.7% and 63.7%, respectively. However, for piperine analogs containing pyrazoline scaffold (**VIIa-m** and **IXa-m**), their ethylenedioxy or methylenedioxy group to the acaricidal activity was not very obvious. It was noteworthy that when introduction of two fluorine or chlorine atoms on the two phenyl rings of compound **VIIa** or **IXa**, respectively, four promising compounds **VIIf,l** and **IXf,l** were obtained; and the 72 h MRs of compounds **VIIf,l** and **IXf,l** against *T. cinnabarinus* were 48.5%, 46.0%, 46.7% and 42.9%, respectively.

As described in Table 2, the LC_{50} values of nine potent compounds against *T. cinnabarinus* were assessed. The LC_{50} values of **VIa**, **VIb**, **VIIf**, **VIIg**, **VIIl**, **VIIIb**, **VIIIc**, **IXf**, and **IXl** were 0.67, 0.82, 0.60, 0.60, 0.63, 0.42, 0.38, 0.65, and 0.72 mg/mL, respectively. Especially compounds **VIIIb** and **VIIIc** exhibited 41 or 45 folds more pronounced activity than compound **1** (LC_{50} value: 17.3 mg /mL). The LC_{90} values of **VIIIb** and **VIIIc** were 1.22, and 1.23 mg/mL, respectively (LC_{90} value of compound **1**: 49.9 mg /mL).

As shown in Table 3, the oral toxicity of compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** against *P. xylostella* treated at 20 μg/larvae was described at 24 h and 48 h, respectively. Compounds **VIa**–**c**, **VIIb**, **VIIf**, **VIIg**, and **VIIIc** showed the good activity

against *P. xylostella*, and their corresponding 48 h MRs were 62.1%, 72.4%, 69.0%, 55.2%, 58.6%, 51.7%, and 51.7%, respectively; whereas the 48 h MR of compound **1** was only 27.6%. Among them, compounds **VIa**–**c** exhibited more promising oral toxicity than toosendanin. Interestingly, for piperine analogs containing isoxazoline scaffold (e.g., **VIb,c** and **VIIIb,c**), the methylenedioxy group was an vital factor for increasing the oral toxicity. For example, the 48 h MRs of compounds **VIIIb,c** (containing the ethylenedioxy group) against *P. xylostella* were 44.8% and 51.7%, respectively; whereas the 48 h MRs of compounds **VIb,c** (containing the methylenedioxy group) against *P. xylostella* were 72.4% and 69.0%, respectively. Similarly, for piperine analogs containing pyrazoline scaffold (**VIIa**–**m** and **IXa**–**m**), the methylenedioxy group was also an important factor for the good oral toxicity. Compounds **VIIa**–**m** (containing the methylenedioxy group) generally displayed more promising activity than compounds **IXa**–**m** (containing the ethylenedioxy one). Additionally, when the hydrogen atom (R^2) of **VIIa** was substituted by a fluorine atom, the 48 h MR of the corresponding compound **VIIb** was increased from 31.1% to 55.2%; when two hydrogen atoms (R^1, R^2) of **VIIa** were substituted by two fluorine atoms or the fluorine and chlorine atoms, respectively, the corresponding compounds **VIIf** (48 h MR: 58.6%) and **VIIg** (48 h MR: 51.7%) also showed the activity better than compound **VIIa** (48 h MR: 31.1%).

As shown in Table 4, compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** were tested for their growth inhibitory activity against *M. separata* at 1 mg/mL. Compounds **VIa**–**c**, **VIIf**–**h**, and **VIIIb**,**c** showed the good activity with the final mortality rates (FMRs) greater than 50%. Especially compounds **VIb** and **VIc** displayed the most pronounced activity. The FMRs of **VIb** and **VIc** were 62.1%, and 65.5%, respectively; whereas the FMR of compound **1** was 41.4%. The symptoms for the treated *M. separata* during the larval, pupal and adult

periods were observed as the same as previously described.[48,50,51] For instance, the dead larvae with thin and wrinkled bodies (Figure S2), the malformed and dead pupae (Figure S3), and the malformed moths (Figure S4) appeared at three different growth stages, respectively. However, the percentages of FMRs of the treated *M. separata* at three growth stages were different (Figure 8). The percentages of FMRs at the larval stage of compounds **VIa**–**c**; **VIIf**–**g**; and **VIIIb**,**c** were greater than 45%; especially the percentage of FMR at the larval stage of compound **VIIh** was greater than 78%. Whereas the percentages of FMRs at the pupal stage of compounds **VIa**–**c**; **VIIf**–**g**; and **VIIIb**,**c** were at the range of 2.7%–26.7%. These results were different to those of 2′(2′,6′)-(di)chloropicropodophyllotoxins derivatives, and more than half of their FMRs were generally at the pupal stage.[2]

Additionally, as described in Table 4, in general, piperine analogs containing isoxazoline scaffold (**VIa**–**c** and **VIIIb,c**) showed more potent activity against *M. separata* than those containing pyrazoline scaffold (**VIIa**–**m** and **IXa**–**m**). For piperine analogs containing isoxazoline scaffold, the methylenedioxy group was an important factor for the growth inhibitory activity. The FMRs of compounds **VIb,c** (containing the methylenedioxy group) against *M. separata* were 62.1% and 65.5%, respectively; whereas the FMRs of compounds **VIIIb,c** (containing the ethylenedioxy one) against *M. separata* were 51.7% and 58.6%, respectively. Among compounds **VIIa**–**m**, when two hydrogen atoms (R^1,R^2) of **VIIa** were substituted by two fluorine atoms or the fluorine and chlorine/bromine atoms, respectively, the corresponding compounds **VIIf** (FMR: 51.7%), **VIIg** (FMR: 51.7%) and **VIIh** (FMR: 55.2%) exhibited more pronounced activity than compound **VIIa** (FMR: 27.6%).

Finally, the toxicity of compounds **VIb**, **VIIf** and **VIIIc** was evaluated against NRK-52E cells. It is noteworthy that compounds **VIb**, **VIIf** and **VIIIc** showed very low toxicity to

NRK-52E cells, and their CC_{50} values were 186.2, > 200, and 127.0 μg/mL, respectively.

In conclusion, a series of piperine analogs containing isoxazoline (**VIa**–**c** and **VIIIb,c**)/pyrazoline (**VIIa**–**m** and **IXa**–**m**) scaffold were prepared, and their structures were characterized by infrared spectra, nuclear magnetic resonance spectra, and high-resolution mass spectra. Moreover, the configuration of compound **VIIIc** was further determined by single-crystal X-ray diffraction. Their pesticidal activities were evaluated against three serious and typically crop-threatening agricultural pests, *T. cinnabarinus*, *M. separata* and *P. xylostella*. Among them, compounds **VIIIb** and **VIIIc** showed greater than 40-fold more pronounced acaricidal activity than their precursor piperine against *T. cinnabarinus*. Compounds **VIa**–**c** exhibited more potent oral toxicity than piperine and toosendanin against *P. xylostella*. Compounds **VIb** and **VIc** displayed more promising growth inhibitory activity than piperine and toosendanin against *M. separata*. In general, piperine analogs containing isoxazoline scaffold (e.g., **VIa**–**c** and **VIIIb,c**) showed more potent pesticidal activities than those containing pyrazoline scaffold (e.g., **VIIa**–**m** and **IXa**–**m**). The methylenedioxy and isoxazoline scaffolds were the important factors for piperine analogs exhibiting good oral toxicity and growth inhibitory activity; on the contrary, the ethylenedioxy and isoxazoline scaffolds were the vital factors for piperine analogs showing good acaricidal activity. This will lay the foundation for further structural modifications and application of piperine analogs as pesticidal agents for agriculture.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: Spectra of ^{1}H NMR and ^{13}C NMR, and data on ^{1}H NMR, ^{13}C NMR, HRMS, IR, and

melting points of target compounds.

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Notes

The authors declare no competing financial interest.

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Figure Captions.

Figure 1. Chemical structures of piperine (**1)**, podophyllotoxin, isoxazoline (**I)**, pyrazoline (**II)**, isoxazoline derivatives of podophyllotoxin (**III**–**V**), and target compounds **VI**–**IX**.

Figure 2. Synthesis of intermediates (**4a**–**c**) from piperine (**1**).

Figure 3. Synthesis of intermediates (**14a**–**c**) from 3,4-dihydroxybenzaldehyde (**5**).

Figure 4. Synthesis of piperine analogs containing isoxazoline/pyrazoline scaffold (**VIa**–**c** and **VIIa**–**m**).

Figure 5. Synthesis of piperine analogs containing isoxazoline/pyrazoline scaffold (**VIIIb**,**c** and **IXa**–**m**).

Figure 6. ^{1}H-^{1}H COSY spectrum of compound **VIIb** (structure **A** is the right isomer).

Figure 7. X-ray crystal structure of compound **VIIIc**.

Figure 8. The percentages of the final mortality rates (FMRs) at three different growth stages of compounds **VIa**–**c**; **VIIf**–**h**; **VIIIb**,**c**; and toosendanin against *M. separata*.

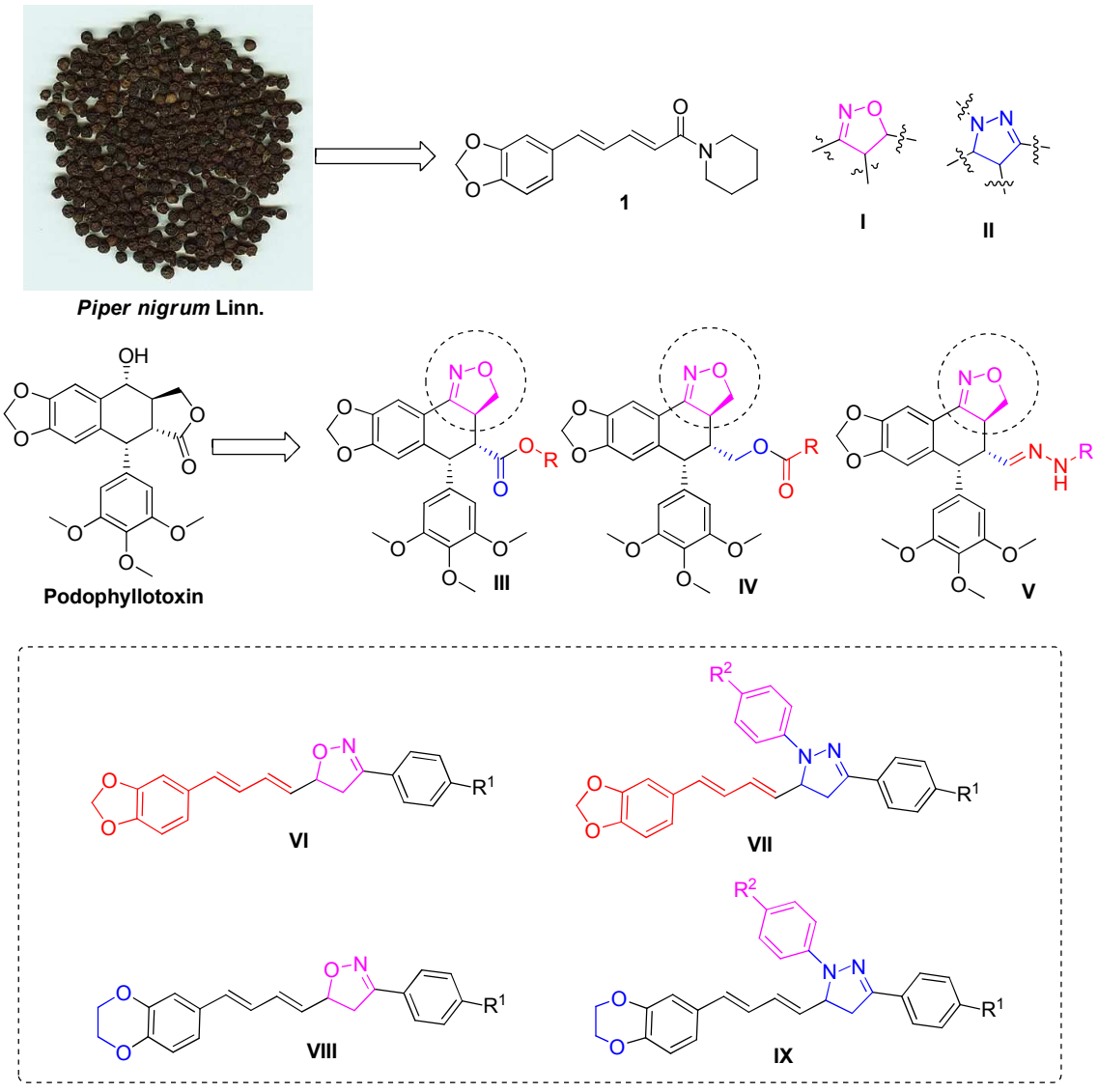

Piper nigrum Linn.
1
I
II
Podophyllotoxin
III
IV
V
VI
VII
VIII
IX

Figure 1.

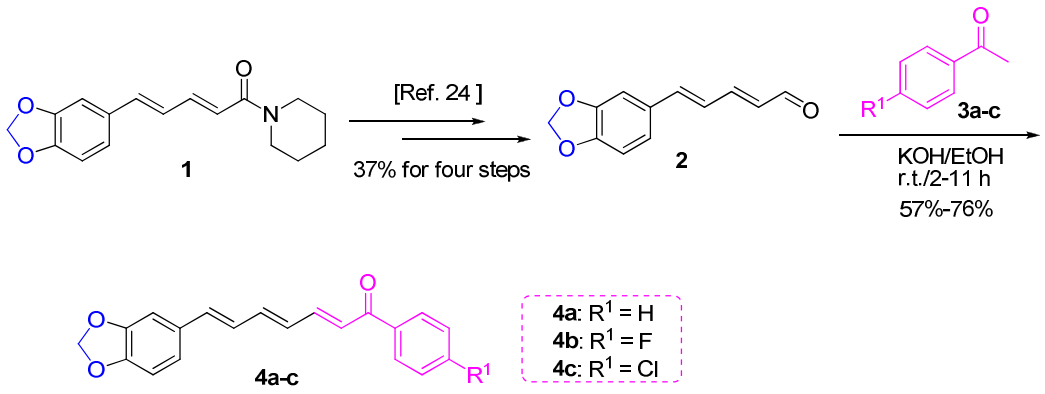

[Ref. 24]
37% for four steps
1
2
3a-c
KOH/EtOH
r.t./2-11 h
57%-76%
4a-c
4a: R1 = H
4b: R1 = F
4c: R1 = Cl

Figure 2.

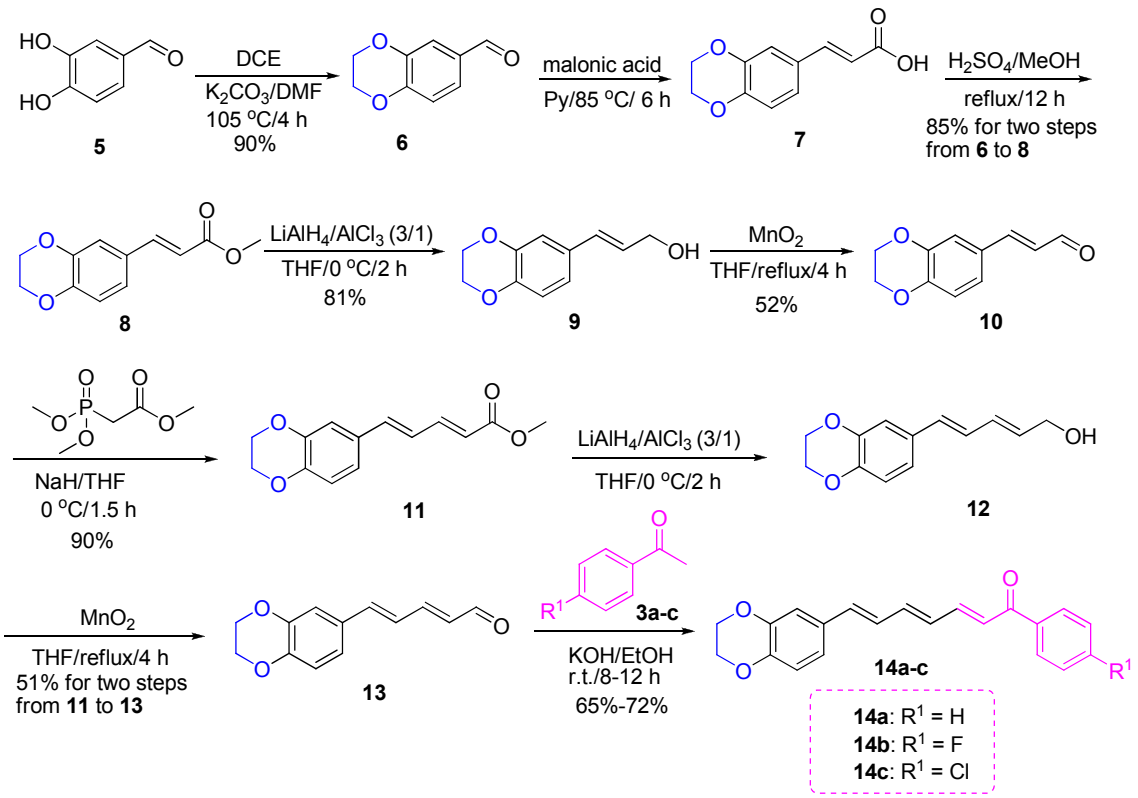

HO
HO
O
5
DCE
K2CO3/DMF
105 °C/4 h
90%
O
O
O
6
malonic acid
Py/85 °C/ 6 h
O
O
O
OH
7
H2SO4/MeOH
reflux/12 h
85% for two steps
from 6 to 8
O
O
O
O
8
LiAlH4/AlCl3 (3/1)
THF/0 °C/2 h
81%
O
OH
9
MnO2
THF/reflux/4 h
52%
O
O
O
10
O
O
O
O
NaH/THF
0 °C/1.5 h
90%
O
O
O
11
LiAlH4/AlCl3 (3/1)
THF/0 °C/2 h
OH
12
MnO2
THF/reflux/4 h
51% for two steps
from 11 to 13
O
O
13
R1
O
3a-c
KOH/EtOH
r.t./8-12 h
65%-72%
O
O
O
R1
14a-c
14a: R1 = H
14b: R1 = F
14c: R1 = Cl

Figure 3.

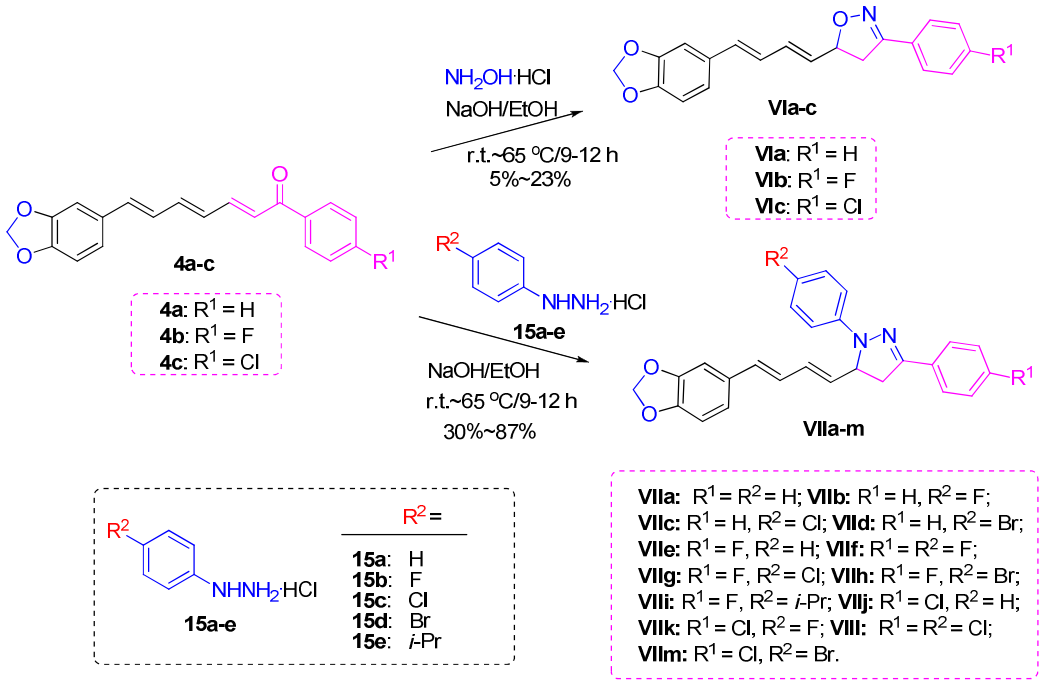

NH2OH·HCl
NaOH/EtOH
r.t.~65 °C/9-12 h
5%~23%
VIa-c
VIa: R1 = H
VIb: R1 = F
VIc: R1 = Cl
4a-c
4a: R1 = H
4b: R1 = F
4c: R1 = Cl
15a-e
NaOH/EtOH
r.t.~65 °C/9-12 h
30%~87%
VIIa-m
R2 =
15a: H
15b: F
15c: Cl
15d: Br
15e: i-Pr
VIIa: R1 = R2 = H; VIIb: R1 = H, R2 = F;
VIIc: R1 = H, R2 = Cl; VIId: R1 = H, R2 = Br;
VIIe: R1 = F, R2 = H; VIIf: R1 = R2 = F;
VIIg: R1 = F, R2 = Cl; VIIh: R1 = F, R2 = Br;
VIIi: R1 = F, R2 = i-Pr; VIIj: R1 = Cl, R2 = H;
VIIk: R1 = Cl, R2 = F; VIIl: R1 = R2 = Cl;
VIIm: R1 = Cl, R2 = Br.

Figure 4.

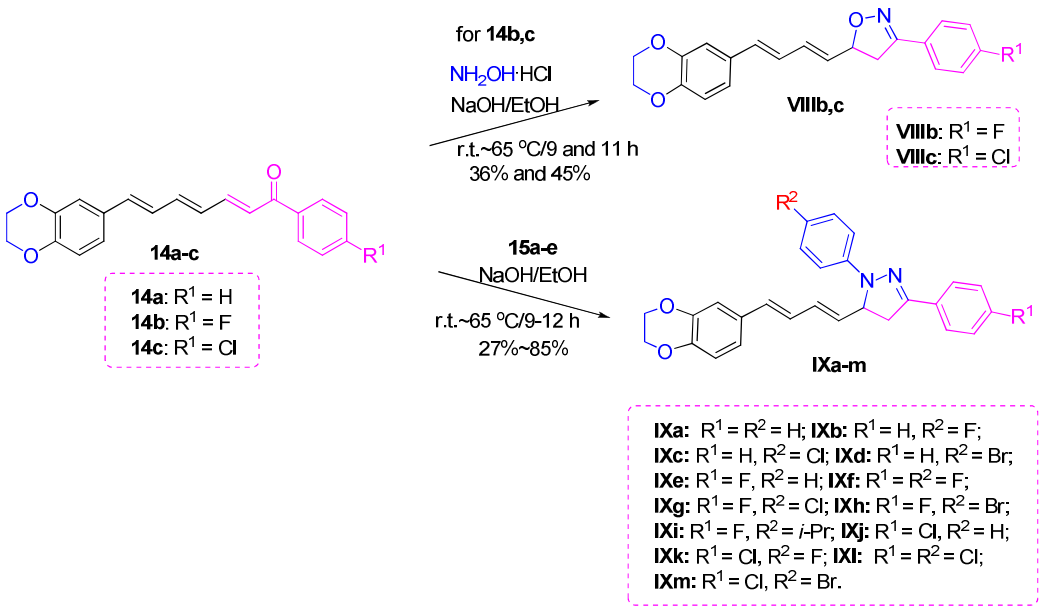

for 14b,c
NH2OH·HCl
NaOH/EtOH
r.t.~65 °C/9 and 11 h
36% and 45%
VIIIb,c
VIIIb: R1 = F
VIIIc: R1 = Cl
14a-c
14a: R1 = H
14b: R1 = F
14c: R1 = Cl
15a-e
NaOH/EtOH
r.t.~65 °C/9-12 h
27%~85%
IXa-m
IXa: R1 = R2 = H; IXb: R1 = H, R2 = F;
IXc: R1 = H, R2 = Cl; IXd: R1 = H, R2 = Br;
IXe: R1 = F, R2 = H; IXf: R1 = R2 = F;
IXg: R1 = F, R2 = Cl; IXh: R1 = F, R2 = Br;
IXi: R1 = F, R2 = i-Pr; IXj: R1 = Cl, R2 = H;
IXk: R1 = Cl, R2 = F; IXl: R1 = R2 = Cl;
IXm: R1 = Cl, R2 = Br.

Figure 5.

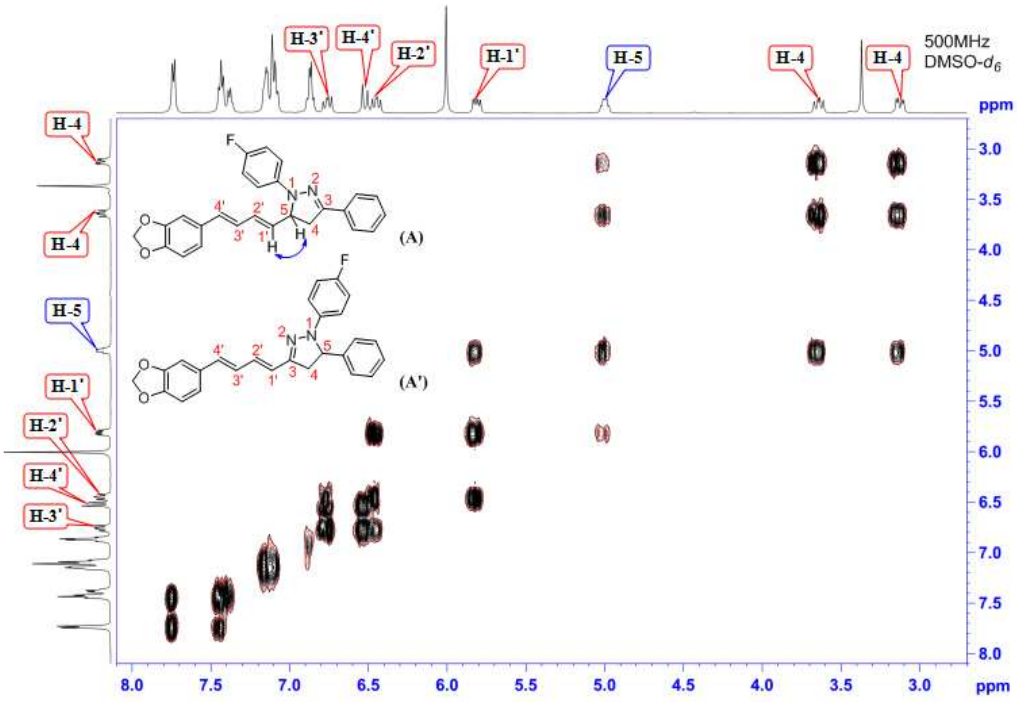

H-3'
H-4'
H-2'
H-1'
H-5
H-4
H-4
500MHz
DMSO-d_6
ppm
H-4
H-4
H-5
H-1'
H-2'
H-4'
H-3'
(A)
(A')
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

Figure 6.

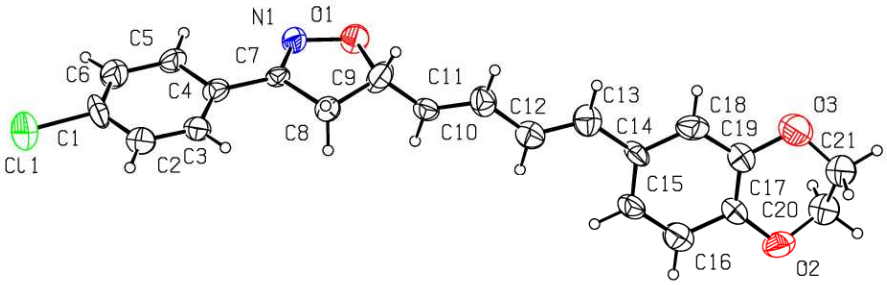

N1
O1
C5
C7
C6
C4
C9
C11
C12
C13
C18
O3
C14
C19
C21
C1
C8
C10
Cl1
C2
C3
C15
C17
C20
C16
O2

Figure 7.

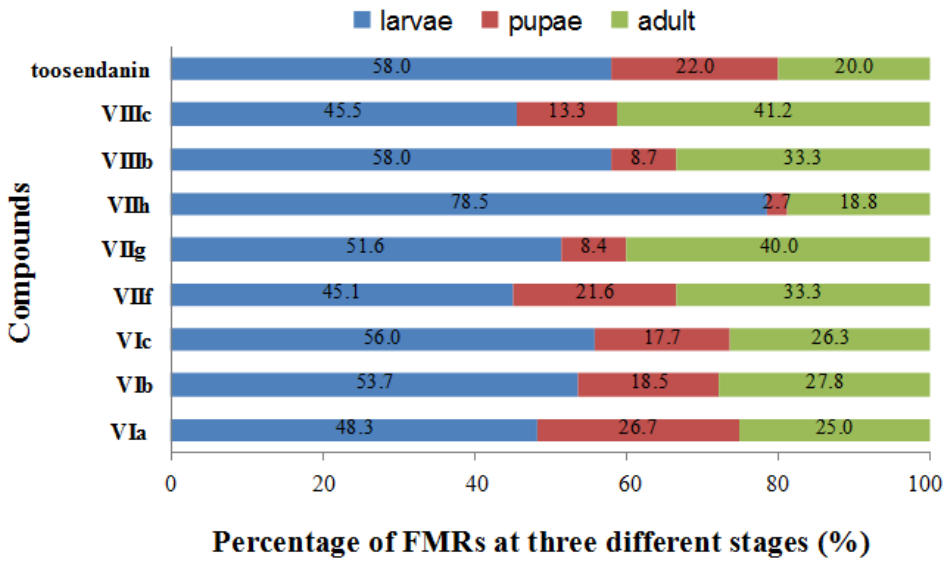

larvae
pupae
adult
toosendanin
VIIIc
VIIIb
VIIh
VIIg
VIIf
VIc
VIb
VIa
58.0
22.0
20.0
45.5
13.3
41.2
58.0
8.7
33.3
78.5
2.7
18.8
51.6
8.4
40.0
45.1
21.6
33.3
56.0
17.7
26.3
53.7
18.5
27.8
48.3
26.7
25.0
Compounds
0
20
40
60
80
100
Percentage of FMRs at three different stages (%)

Figure 8.

Table 1. Acaricidal Activity of Compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** against *T. cinnabarinus* Treated at a Concentration of 0.5 mg/mL[a]

Compound	Corrected mortality rate (%)	
	48 h	72 h
4a	10.3 ± 1.6	19.7 ± 2.6 lm[b]
4b	3.5 ± 1.4	18.1 ± 3.2 lm
4c	3.7 ± 1.3	16.9 ± 2.9 mn
14a	6.1 ± 1.4	27.7 ± 1.5 hij
14b	4.8 ± 1.6	20.0 ± 1.7 lm
14c	11.3 ± 1.4	26.8 ± 1.0 hijk
VIa	13.6 ± 1.2	45.4 ± 1.5 cd
VIb	13.9 ± 1.0	41.0 ± 1.3 de
VIc	7.4 ± 0.8	26.7 ± 0.2 hijk
VIIa	14.5 ± 0.2	26.1 ± 0.8 ijk
VIIb	16.2 ± 0.5	31.4 ± 0.7 ghi
VIIc	7.4 ± 0.5	26.5 ± 0.3 hijk
VIId	5.9 ± 0.8	30.0 ± 1.2 ghi
VIIe	12.0 ± 0.4	32.4 ± 0.4 gh
VIIf	18.2 ± 0.5	48.5 ± 1.5 c
VIIg	9.1 ± 0.4	47.7 ± 0.8 c
VIIh	5.4 ± 0.9	35.6 ± 1.7 fg
VIIi	13.0 ± 0.9	21.5 ± 1.4 klm
VIIj	20.4 ± 1.4	31.3 ± 0.8 ghi
VIIk	13.0 ± 1.4	32.4 ± 0.6 gh
VIIl	12.3 ± 0.4	46.0 ± 0.6 cd
VIIm	9.6 ± 0.6	30.3 ± 0.8 ghi
VIIIb	11.2 ± 0.8	56.7 ± 1.6 b
VIIIc	33.0 ± 1.1	63.7 ± 2.1 a
IXa	14.5 ± 0.3	21.2 ± 1.2 klm
IXb	15.2 ± 1.0	33.6 ± 0.8 g
IXc	10.1 ± 0.9	35.5 ± 0.9 fg
IXd	8.8 ± 0.7	31.3 ± 1.0 ghi
IXe	11.0 ± 1.1	39.5 ± 0.4 ef
IXf	18.2 ± 0.7	46.7 ± 0.5 c
IXg	12.9 ± 0.8	35.4 ± 0.7 fg
IXh	10.4 ± 0.2	35.0 ± 0.5 fg
IXi	7.4 ± 0.3	12.6 ± 1.3 n
IXj	8.8 ± 0.7	23.7 ± 1.3 jkl
IXk	15.9 ± 0.4	30.4 ± 0.1 ghi
IXl	18.2 ± 0.7	42.9 ± 2.0 cde
IXm	16.8 ± 1.0	34.6 ± 0.5 fg
Piperine (**1**)	7.8 ± 0.9	12.1 ± 1.1 n
Spirodiclofen	29.5 ± 0.4	68.0 ± 1.1 a

[a]Values are the mean ± SE of three replicates. [b]Multiple range test using Duncan's test ($p < 0.05$). The same

letters denote treatments not significantly different from each other.

Table 2. LC_{50} and LC_{90} Values of Nine Compounds against *T. cinnabarinus*

Compound	Linear regression equation	LC_{50} (mg/mL)	LC_{90} (mg/mL)	r
VIa	Y = 1.4835X + 5.2553	0.67	1.72	0.9811
VIb	Y = 1.6447X + 5.1422	0.82	1.66	0.9913
VIIf	Y = 1.6078X + 5.3527	0.60	1.52	0.9934
VIIg	Y = 1.2561X + 5.2786	0.60	2.23	0.9966
VIIl	Y = 1.2552X + 5.2470	0.63	1.81	0.9758
VIIIb	Y = 1.8481X + 5.6946	0.42	1.22	0.9992
VIIIc	Y = 1.6670X + 5.6904	0.38	1.23	0.9942
IXf	Y = 1.3138X + 5.2386	0.65	1.66	0.9844
IXl	Y = 1.4868X + 5.2117	0.72	1.63	0.9974
Piperine (**1**)	Y = 1.5426X + 3.0902	17.30	49.9	0.9801
Spirodiclofen	Y = 1.7924X + 6.1435	0.23	0.92	0.9909

Table 3. Oral Toxicity of Compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** against *P. xylostella* Treated at 20 μg/Larvae[a]

Compound	Corrected mortality rate (%)	
	24 h	48 h
4a	3.3 ± 2.7	20.7 ± 2.7 lm[b]
4b	10.0 ± 0	27.6 ± 0 jklm
4c	6.7 ± 2.7	24.2 ± 2.7 klm
14a	3.3 ± 2.7	17.3 ± 0 m
14b	3.3 ± 2.7	20.7 ± 2.7 lm
14c	6.7 ± 2.7	17.3 ± 0 m
VIa	23.3 ± 2.7	62.1 ± 2.7 bc
VIb	40.0 ± 0	72.4 ± 2.7 a
VIc	36.7 ± 2.7	69.0 ± 0 ab
VIIa	16.7 ± 2.7	31.1 ± 2.7 ijkl
VIIb	10.0 ± 4.7	55.2 ± 2.7 cde
VIIc	10.0 ± 4.7	48.3 ± 4.7 defg
VIId	10.0 ± 0	41.4 ± 2.7 fghi
VIIe	16.7 ± 2.7	34.5 ± 2.7 hijk
VIIf	20.0 ± 4.7	58.6 ± 4.7 cd
VIIg	6.7 ± 2.7	51.7 ± 2.7 cdef
VIIh	10.0 ± 4.7	48.3 ± 0 defg
VIIi	6.7 ± 2.7	41.4 ± 2.7 fghi
VIIj	16.7 ± 2.7	34.5 ± 2.7 hijk
VIIk	6.7 ± 2.7	44.8 ± 2.7 efgh
VIIl	20.0 ± 4.7	38.0 ± 4.7 ghij
VIIm	10.0 ± 4.7	24.2 ± 2.7 klm
VIIIb	6.7 ± 2.7	44.8 ± 2.7 efgh
VIIIc	26.7 ± 2.7	51.7 ± 2.7 cdef
IXa	10.0 ± 0	20.7 ± 2.7 lm
IXb	0 ± 0	41.4 ± 2.7 fghi
IXc	6.7 ± 2.7	34.5 ± 2.7 hijk
IXd	6.7 ± 2.7	24.2 ± 2.7 klm
IXe	3.3 ± 2.7	24.2 ± 2.7 klm
IXf	13.3 ± 2.7	48.3 ± 0 defg
IXg	6.7 ± 2.7	20.7 ± 2.7 lm
IXh	6.7 ± 2.7	44.8 ± 2.7 efgh
IXi	3.3 ± 2.7	24.2 ± 2.7 klm
IXj	3.3 ± 2.7	20.7 ± 2.7 lm
IXk	6.7 ± 2.7	38.0 ± 0 ghij
IXl	20.0 ± 4.7	38.0 ± 0 ghij
IXm	16.7 ± 2.7	44.8 ± 2.7 efgh
Piperine (**1**)	6.7± 2.7	27.6 ± 0 jklm
Toosendanin	13.3 ± 2.7	55.2 ± 2.7 cde

[a]Values are the mean ± SE of three replicates. [b]Multiple range test using Duncan's test ($p < 0.05$). The

same letters denote treatments not significantly different from each other.

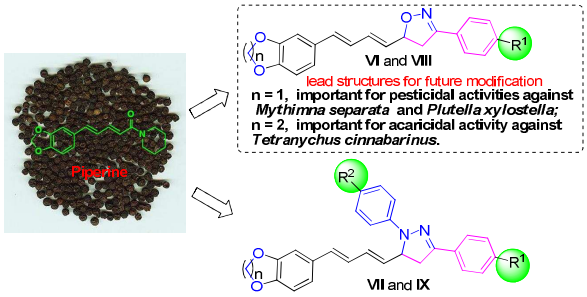
Table 4. Growth Inhibitory Activity of Compounds **4a**–**c**, **14a**–**c**, **VIa**–**c**, **VIIa**–**m**, **VIIIb**,**c** and **IXa**–**m** against *M. separata* on Leaves Treated at a Concentration of 1 mg/mL[a].

Compound	Corrected mortality rate (%)		
	10 days	25 days	35 days
4a	6.7 ± 2.7	13.8 ± 2.7	17.2 ± 0 lmn[b]
4b	6.7 ± 2.7	20.7 ± 2.7	20.7 ± 2.7 klmn
4c	16.7 ± 2.7	20.7 ± 5.4	24.1 ± 2.7 jklm
14a	3.3 ± 2.7	10.3 ± 2.7	10.3 ± 2.7 n
14b	20.0 ± 0	20.7 ± 2.7	24.1 ± 2.7 jklm
14c	13.3 ± 2.7	13.8 ± 2.7	13.8 ± 2.7 mn
VIa	23.3 ± 2.7	37.9 ± 0	55.2 ± 2.7 abcd
VIb	20.0 ± 0	44.8 ± 2.7	62.1 ± 2.7 ab
VIc	36.7 ± 2.7	48.3 ± 0	65.5 ± 2.7 a
VIIa	3.3 ± 2.7	27.6 ± 4.7	27.6 ± 4.7 ijkl
VIIb	16.7 ± 2.7	27.6 ± 4.7	48.3 ± 0 cdef
VIIc	10.0 ± 4.7	34.5 ± 2.7	44.8 ± 2.7 defg
VIId	13.3 ± 2.7	31.0 ± 2.7	37.9 ± 0 fghi
VIIe	6.7 ± 2.7	27.6 ± 0	34.5 ± 2.7 ghij
VIIf	13.3 ± 2.7	34.5 ± 2.7	51.7 ± 2.7 bcde
VIIg	23.3 ± 2.7	20.7 ± 2.7	51.7 ± 2.7 bcde
VIIh	40.0 ± 4.7	41.4 ± 2.7	55.2 ± 2.7 abcd
VIIi	16.7 ± 2.7	20.7 ± 2.7	24.1 ± 2.7 jklm
VIIj	16.7 ± 2.7	31.0 ± 2.7	37.9 ± 0 fghi
VIIk	13.3 ± 2.7	20.7 ± 2.7	48.3 ± 0 cdef
VIIl	23.3 ± 5.4	31.0 ± 2.7	41.4 ± 2.7 efgh
VIIm	26.7 ± 2.7	27.6 ± 4.7	37.9 ± 0 fghi
VIIIb	26.7 ± 2.7	31.0 ± 2.7	51.7 ± 0 bcde
VIIIc	20.0 ± 4.7	27.6 ± 4.7	58.6 ± 0 abc
IXa	23.3 ± 2.7	27.6 ± 4.7	27.6 ± 4.7 ijkl
IXb	26.7 ± 2.7	41.4 ± 2.7	44.8 ± 2.7 defg
IXc	10.0 ± 0	24.1 ± 2.7	37.9 ± 4.7 fghi
IXd	6.7 ± 2.7	27.6 ± 4.7	31.0 ± 2.7 hijk
IXe	23.3 ± 2.7	31.0 ± 2.7	31.0 ± 2.7 hijk
IXf	23.3 ± 2.7	34.5 ± 2.7	48.3 ± 0 cdef
IXg	16.7 ± 2.7	27.6 ± 4.7	44.8 ± 2.7 defg
IXh	20.0 ± 4.7	27.6 ± 4.7	41.4 ± 2.7 efgh
IXi	20.0 ± 0	24.1 ± 2.7	34.5 ± 2.7 ghij
IXj	26.7 ± 5.4	34.5 ± 2.7	34.5 ± 2.7 ghij
IXk	16.7 ± 5.4	24.1 ± 2.7	41.4 ± 5.4 efgh
IXl	13.3 ± 2.7	20.7 ± 2.7	37.9 ± 4.7 fghi
IXm	30.0 ± 0	34.5 ± 2.7	41.4 ± 2.7 efgh
Piperine (**1**)	16.7 ± 2.7	31.0 ± 2.7	41.4 ± 2.7 efgh
Toosendanin	23.3 ± 2.7	31.0 ± 2.7	51.7 ± 2.7 bcde

[a]Values are the mean ± SE of three replicates. [b]Multiple range test using Duncan's test ($p < 0.05$). The same

letters denote treatments not significantly different from each other.

TOC graphic


Piperine
VI and VIII
lead structures for future modification
n = 1, important for pesticidal activities against
Mythimna separata and Plutella xylostella;
n = 2, important for acaricidal activity against
Tetranychus cinnabarinus.
VII and IX