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Semisynthesis of esters and oxime esters/sulfonates from furyl-ring-based acetylation derivatives of fraxinellone as insecticidal agents†

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In continuation of our program to discover new natural-product-based crop protection agents, we prepared a series of esters and oxime esters/sulfonates from furyl-ring-based acetylation derivatives as pesticidal agents by structural modification of fraxinellone, a biorenewable degraded limonoid isolated from Meliaceae and Rutaceae plants. The structural assignment was based on the spectroscopic and X-ray analysis data. Their insecticidal activity was evaluated against a crop-threatening agricultural insect pest, *Mythimna separata* Walker. Among all derivatives, compounds **9a** and **10i** exhibited the most promising pesticidal activity. Their structure–activity relationships were also discussed.

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Introduction

Oriental armyworm (*Mythimna separata* Walker) is a terrible lepidopteran insect pest, and its infestations are hard to control.^{1,2} In 2012, approximately 4 million hectares of crops were completely lost in China due to the intermittent outbreaks of *M. separata*.³ Obviously, lots of chemical pesticides had to be extensively applied to deal with insect pest outbreaks, however, it ultimately led to insect pests resistance, and human health and environmental problems.^{4–7} Consequently, research and development of new potential alternatives to effectively and selectively control insect pests is extremely desirable.

Fraxinellone (**1**, Fig. 1), a biorenewable degraded limonoid, is isolated from many Meliaceae and Rutaceae plants, and exhibits a variety of interesting properties, including the anti-inflammatory bowel disease,⁸ neuroprotective,⁹ and insecticidal activities.^{10–13} In our previous reports, compound **1** was modified at its C-4/C-10 positions, and some fraxinellone-based oxime esters¹⁴ (**I** and **II**, Fig. 1) and esters¹⁵ (**III** and **IV**, Fig. 1) displayed higher insecticidal activity than toosendanin against pre-third-instar larvae of *Mythimna separata*. In addition, to the best of our knowledge, little attention has been paid to the structural modifications on the C-ring (furyl-ring) of compound **1** as pesticidal agents. Based upon the above results, and in

continuation of our program to discover biorenewable fraxinellone-based pesticides, herein we wanted to prepare a series of new esters/oxime esters from furyl-ring-based acetylation derivatives of fraxinellone (**V** and **VI**, Fig. 1) as insecticidal agents against *M. separata* *in vivo*.

Materials and methods

General

All chemical reagents were purchased and utilized without further purification. Melting point (mp) was determined using the XT-4 digital mp apparatus. Optical rotation was measured using an Autopol III automatic polarimeter. Infrared (IR) spectra were measured by a TENSOR 27 spectrometer. Proton nuclear magnetic resonance spectra (¹H NMR) were measured with the Avance 400 or 500 MHz equipment. 5'-Acetylfraxinellone (**2**) and 2'-acetylfraxinellone (**3**) were prepared according to our previous paper.¹⁶

Synthesis of compound 4

To a stirred solution of **2** (0.5 mmol) in methanol at 0–5 °C, NaBH₄ (1 mmol) was slowly added. After addition, the reaction mixture was stirred at 0–5 °C for 1.5 h. Then the solvent was removed, and the residue was dissolved in CH₂Cl₂ (50 mL). The mixture was washed by brine (20 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Finally, the crude product was purified by preparative thin-layer chromatography (PTLC) to give **4** as a white solid in 72% yield.

Data for 4 (isomer α : β = 1 : 1). Mp 96–98 °C; [α]_D²⁰ = –27 (c 3.0 mg mL^{–1}, acetone); IR cm^{–1}: 3402, 2933, 2896, 1748, 1673, 1671, 1205, 978; ¹H NMR (400 MHz, CDCl₃) δ: 7.40 (s, 1H, H-2'), 6.20 (s, 1H, H-4'), 4.86–4.89 (m, 1H, –OH(CH)CH₃), 4.83 (s, 1H,

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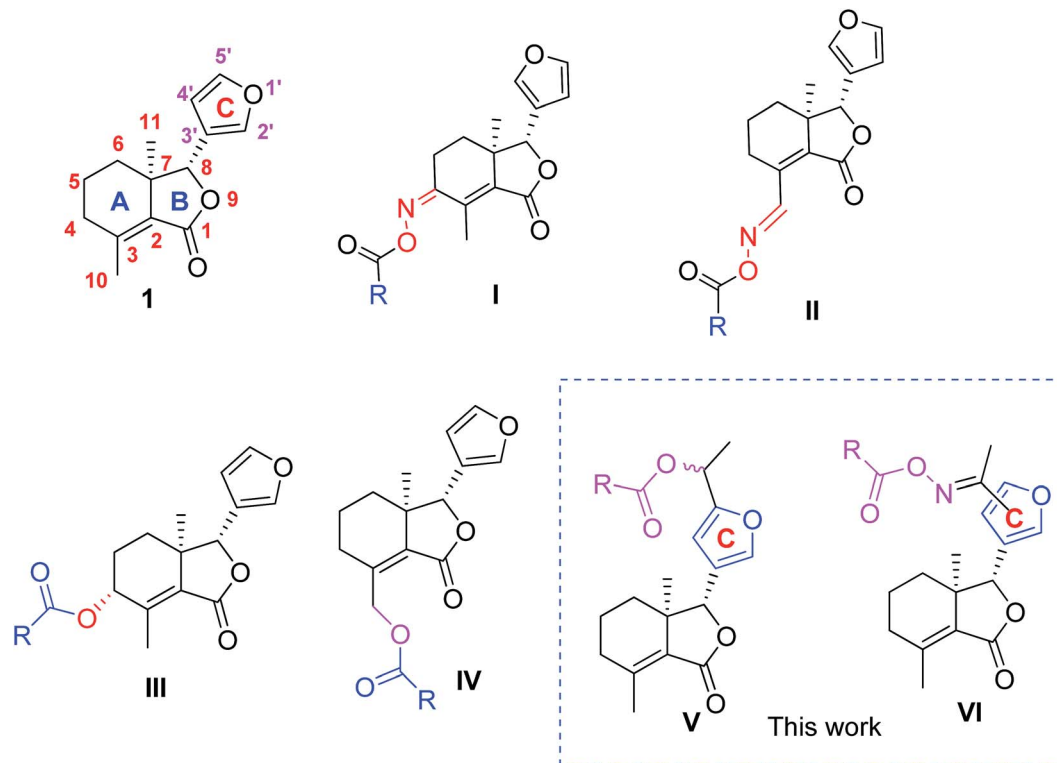


Fig. 1 Chemical structures of fraxinellone (1), and its derivatives (I–VI).

H-8), 2.12–2.31 (m, 2H, H-4), 2.11 (s, 3H, H-10), 2.03 (s, 1H, –OH), 1.71–1.87 (m, 3H, H-5, 6), 1.55 (s, 1.5H, –OH(CH)CH₃), 1.53 (s, 1.5H, –OH(CH)CH₃), 1.40–1.46 (m, 1H, H-6), 0.87 (s, 3H, H-11). HRMS (ESI): calcd for C₁₆H₂₁O₄ ([M + H]⁺), 277.1434; found, 277.1433.

General procedure for synthesis of compounds 5 and 6

A mixture of 2 or 3 (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol), and pyridine (2 mmol) in absolute ethanol (10 mL) was refluxed. When the reaction was complete according to TLC analysis, the solvent was removed under reduced pressure. Finally, the crude product was purified by PTLC to give 5 (72% yield) or 6 (82% yield) as a white solid.

Data for 5. Mp 176–178 °C; $[\alpha]_D^{20} = -25$ (c 3.8 mg mL⁻¹, acetone); IR cm⁻¹: 3265, 2961, 2922, 2855, 1746, 1264, 1049, 901; ¹H NMR (400 MHz, CDCl₃) δ: 7.49 (s, 1H, H-2'), 6.59 (s, 1H, H-4'), 4.87 (s, 1H, H-8), 2.17–2.32 (m, 6H, –CH₃, –OH and H-4), 2.13 (s, 3H, H-10), 1.72–1.84 (m, 3H, H-5, 6), 1.42–1.48 (m, 1H, H-6), 0.87 (s, 3H, H-11). HRMS (ESI): calcd for C₁₆H₂₀O₄N ([M + H]⁺), 290.1387; found, 290.1387.

Data for 6. Mp 186–188 °C; $[\alpha]_D^{20} = 88$ (c 4.1 mg mL⁻¹, acetone); IR cm⁻¹: 3300, 2957, 2925, 2852, 1727, 1670, 1272, 1218, 984; ¹H NMR (500 MHz, CDCl₃) δ: 7.43 (s, 1H, H-5'), 7.31 (s, 1H, –OH), 6.61 (d, J = 1.5 Hz, 1H, H-4'), 5.59 (s, 1H, H-8), 2.21–2.26 (m, 4H, –CH₃ and H-4), 2.08–2.16 (m, 4H, H-4, 10), 1.75–1.77 (m, 1H, H-5), 1.58–1.68 (m, 3H, H-5, 6), 0.92 (s, 3H, H-11). HRMS (ESI): calcd for C₁₆H₂₀O₄N ([M + H]⁺), 290.1387; found, 290.1385.

General procedure for synthesis of compounds 8b–j, 9a–j and 10a–j

A mixture of the corresponding acid (7, 0.28 mmol), *N,N*-dicyclohexylcarbodiimide (DCC, 0.28 mmol), 4-dimethylaminopyridine (DMAP, 0.04 mmol), and 4, 5 or 6 (0.2 mmol) in dry CH₂Cl₂ (10 mL) was stirred at room temperature. When the reaction was complete according to TLC analysis, the mixture was diluted by CH₂Cl₂ (30 mL), washed by HCl (0.1 mol L⁻¹, 15 mL), 5% NaHCO₃ (15 mL) and brine (15 mL), dried over anhydrous Na₂SO₄, concentrated *in vacuo*, and purified by PTLC to give products 8b–j, 9a–j and 10a–j. The example data of 8b–e, 9a–e and 10a–e were described as follows, whereas the data of 8f–j, 9f–j and 10f–j were shown in the ESI.†

Data for 8b. Yield: 70%, colorless liquid; $[\alpha]_D^{20} = -17$ (c 3.1 mg mL⁻¹, acetone); IR cm⁻¹: 2951, 2924, 2853, 1754, 1717, 1451, 1265, 1205, 1048; ¹H NMR (400 MHz, CDCl₃) δ: 8.04 (d, J = 8.0 Hz, 2H, –Ph), 7.54 (t, d, J = 7.6 Hz, 1H, –Ph), 7.41–7.45 (m, 3H, –Ph, H-2'), 6.35 (s, 1H, H-4'), 6.16–6.21 (m, 1H, –O(CH)CH₃), 4.84 (s, 1H, H-8), 2.24–2.31 (m, 2H, H-4), 2.12 (s, 3H, H-10), 1.79–1.83 (m, 3H, H-5, 6), 1.71 (d, J = 2.4 Hz, 1.5H, –OH(CH)CH₃), 1.69 (d, J = 2.4 Hz, 1.5H, –OH(CH)CH₃), 1.40–1.47 (m, 1H, H-6), 0.86–0.87 (m, 3H, H-11). HRMS (ESI): calcd for C₂₃H₂₈O₅N ([M + NH₄]⁺), 398.1962; found, 398.1959.

Data for 8c. Yield: 81%, colorless liquid; $[\alpha]_D^{20} = -18$ (c 3.2 mg mL⁻¹, acetone); IR cm⁻¹: 2952, 2923, 2853, 1756, 1716, 1267, 1047; ¹H NMR (400 MHz, CDCl₃) δ: 7.92 (d, J = 8.0 Hz, 2H, –Ph), 7.43 (s, 1H, H-2'), 7.22 (d, J = 8.0 Hz, 2H, –Ph), 6.33 (d, J = 2.4 Hz, 1H, H-4'), 6.14–6.19 (m, 1H, –O(CH)CH₃), 4.84 (s, 1H, H-8), 2.40 (s, 1H, –PhCH₃), 2.17–2.30 (m, 2H, H-4), 2.12 (s, 3H, H-



10), 1.73–1.83 (m, 3H, H-5, 6), 1.70 (d, $J = 2.4$ Hz, 1.5H, $-\text{OH}(\text{CH})\text{CH}_3$), 1.68 (d, $J = 2.4$ Hz, 1.5H, $-\text{OH}(\text{CH})\text{CH}_3$), 1.39–1.47 (m, 1H, H-6), 0.86–0.87 (m, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{30}\text{O}_5\text{N}$ ($[\text{M} + \text{NH}_4]^+$), 412.2118; found, 412.2115.

Data for 8d. Yield: 98%, colorless liquid; $[\alpha]_{\text{D}}^{20} = -18$ (c 3.2 mg mL⁻¹, acetone); IR cm⁻¹: 2952, 2923, 2853, 1743, 1713, 1606, 1258, 1165; ¹H NMR (400 MHz, CDCl₃) δ : 7.99 (d, $J = 9.2$ Hz, 2H, -Ph), 7.43 (s, 1H, H-2'), 6.89 (d, $J = 8.8$ Hz, 2H, -Ph), 6.33 (s, 1H, H-4'), 6.12–6.17 (m, 1H, $-\text{O}(\text{CH})\text{CH}_3$), 4.84 (s, 1H, H-8), 3.85 (s, 3H, $-\text{OCH}_3$), 2.15–2.31 (m, 2H, H-4), 2.12 (s, 3H, H-10), 1.79–1.83 (m, 3H, H-5, 6), 1.69 (d, $J = 2.4$ Hz, 1.5H, $-\text{OH}(\text{CH})\text{CH}_3$), 1.67 (d, $J = 2.4$ Hz, 1.5H, $-\text{OH}(\text{CH})\text{CH}_3$), 1.39–1.47 (m, 1H, H-6), 0.84–0.86 (m, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{27}\text{O}_6$ ($[\text{M} + \text{H}]^+$), 411.1802; found, 411.1802.

Data for 8e. Yield: 73%, white solid, mp 158–160 °C; $[\alpha]_{\text{D}}^{20} = -23$ (c 4.1 mg mL⁻¹, acetone); IR cm⁻¹: 2953, 2923, 2852, 1755, 1719, 1266, 1048, 855; ¹H NMR (400 MHz, CDCl₃) δ : 8.04–8.08 (m, 2H, -Ph), 7.44 (s, 1H, H-2'), 7.08–7.12 (m, 2H, -Ph), 6.35 (s, 1H, H-4'), 7.08–7.12 (m, 2H, -Ph), 6.13–6.18 (m, 1H, $-\text{O}(\text{CH})\text{CH}_3$), 4.84 (s, 1H, H-8), 2.16–2.31 (m, 2H, H-4), 2.13 (s, 3H, H-10), 1.79–1.83 (m, 3H, H-5, 6), 1.70 (d, $J = 2.4$ Hz, 1.5H, $-\text{OH}(\text{CH})\text{CH}_3$), 1.69 (d, $J = 2.4$ Hz, 1.5H, $-\text{OH}(\text{CH})\text{CH}_3$), 1.40–1.47 (m, 1H, H-6), 0.86–0.87 (m, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{27}\text{O}_5\text{NF}$ ($[\text{M} + \text{NH}_4]^+$), 416.1868; found, 416.1862.

Data for 9a. Yield: 78%, white solid, mp 89–90 °C; $[\alpha]_{\text{D}}^{20} = -23$ (c 4.0 mg mL⁻¹, acetone); IR cm⁻¹: 2940, 2873, 1755, 1675, 1205, 1046, 909; ¹H NMR (500 MHz, CDCl₃) δ : 8.04 (d, $J = 8.5$ Hz, 1H, Ar-H), 8.86 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.80 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.43–7.56 (m, 5H, Ar-H and H-2'), 6.81 (s, 1H, H-4'), 4.82 (s, 1H, H-8), 4.27 (s, 2H, $-\text{CH}_2\text{C}_{10}\text{H}_7$), 2.14–2.29 (m, 2H, H-4), 2.12 (s, 3H, $-\text{CH}_3$), 2.02 (s, 3H, H-10), 1.77–1.85 (m, 2H, H-5, 6), 1.69–1.73 (m, 1H, H-5), 1.39–1.44 (m, 1H, H-6), 0.80 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{28}\text{H}_{28}\text{O}_5\text{N}$ ($[\text{M} + \text{H}]^+$), 458.1962; found, 458.1962.

Data for 9b. Yield: 72%, white solid, mp 200–202 °C; $[\alpha]_{\text{D}}^{20} = -10$ (c 3.4 mg mL⁻¹, acetone); IR cm⁻¹: 2926, 2853, 1743, 1676, 1250, 1048, 907; ¹H NMR (500 MHz, CDCl₃) δ : 8.10 (dd, $J = 8.0, 1.5$ Hz, 2H, Ar-H), 7.60–7.63 (s, 2H, Ar-H and H-2'), 7.48 (t, $J = 8.0$ Hz, 2H, Ar-H), 6.97 (s, 1H, H-4'), 4.89 (s, 1H, H-8), 2.46 (s, 3H, $-\text{CH}_3$), 2.27–2.32 (m, 1H, H-4), 2.18–2.21 (m, 1H, H-4), 2.14 (s, 3H, H-10), 1.84–1.87 (m, 2H, H-5, 6), 1.73–1.77 (m, 1H, H-5), 1.44–1.49 (m, 1H, H-6), 0.87 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{24}\text{O}_5\text{N}$ ($[\text{M} + \text{H}]^+$), 394.1649; found, 394.1648.

Data for 9c. Yield: 64%, white solid, mp 160–162 °C; $[\alpha]_{\text{D}}^{20} = -28$ (c 3.4 mg mL⁻¹, acetone); IR cm⁻¹: 2940, 2872, 1745, 1675, 1260, 1049, 911; ¹H NMR (500 MHz, CDCl₃) δ : 7.99 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.61 (s, 1H, H-2'), 7.28 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.96 (s, 1H, H-4'), 4.88 (s, 1H, H-8), 2.45 (s, 3H, $-\text{PhCH}_3$), 2.44 (s, 3H, $-\text{CH}_3$), 2.26–2.32 (m, 1H, H-4), 2.18–2.21 (m, 1H, H-4), 2.14 (s, 3H, H-10), 1.85–1.87 (m, 2H, H-5, 6), 1.73–1.79 (m, 1H, H-5), 1.45–1.49 (m, 1H, H-6), 0.87 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{26}\text{O}_5\text{N}$ ($[\text{M} + \text{H}]^+$), 408.1805; found, 408.1804.

Data for 9d. Yield: 73%, white solid, mp 150–152 °C; $[\alpha]_{\text{D}}^{20} = -21$ (c 3.2 mg mL⁻¹, acetone); IR cm⁻¹: 2954, 2923, 2853, 1739, 1607, 1265, 1047, 957; ¹H NMR (500 MHz, CDCl₃) δ : 8.06 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.62 (s, 1H, H-2'), 6.96 (d, $J = 9.0$ Hz, 2H, Ar-H), 6.95 (s, 1H, H-4'), 4.88 (s, 1H, H-8), 3.88 (s, 3H, $-\text{OCH}_3$), 2.44 (s, 3H, $-\text{CH}_3$), 2.17–2.32 (m, 2H, H-4), 2.14 (s, 3H, H-10), 1.84–

1.88 (m, 2H, H-5, 6), 1.74–1.77 (m, 1H, H-5), 1.44–1.49 (m, 1H, H-6), 0.87 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6\text{N}$ ($[\text{M} + \text{H}]^+$), 424.1755; found, 424.1754.

Data for 9e. Yield: 61%, white solid, mp 184–186 °C; $[\alpha]_{\text{D}}^{20} = -28$ (c 3.3 mg mL⁻¹, acetone); IR cm⁻¹: 2934, 2871, 1748, 1673, 1601, 1257, 1047, 910; ¹H NMR (500 MHz, CDCl₃) δ : 8.12–8.15 (m, 2H, Ar-H), 7.61 (s, 1H, H-2'), 7.15 (t, $J = 8.5$ Hz, 2H, Ar-H), 6.97 (s, 1H, H-4'), 4.89 (s, 1H, H-8), 2.45 (s, 3H, $-\text{CH}_3$), 2.19–2.32 (m, 2H, H-4), 2.14 (s, 3H, H-10), 1.85–1.87 (m, 2H, H-5, 6), 1.73–1.77 (m, 1H, H-5), 1.45–1.49 (m, 1H, H-6), 0.87 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{23}\text{O}_5\text{NF}$ ($[\text{M} + \text{H}]^+$), 412.1555; found, 412.1556.

Data for 10a. Yield: 75%, white solid, mp 70–71 °C; $[\alpha]_{\text{D}}^{20} = 82$ (c 3.3 mg mL⁻¹, acetone); IR cm⁻¹: 2952, 2924, 2853, 1752, 1207, 908; ¹H NMR (500 MHz, CDCl₃) δ : 8.01 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.87 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.81–7.82 (m, 1H, Ar-H), 7.43–7.56 (m, 5H, Ar-H and H-5'), 6.66 (d, $J = 1.5$ Hz, 1H, H-4'), 5.69 (s, 1H, H-8), 4.22 (s, 2H, $-\text{CH}_2\text{C}_{10}\text{H}_7$), 2.14–2.19 (m, 2H, H-4), 2.11 (s, 3H, $-\text{CH}_3$), 2.09 (s, 3H, H-10), 1.87–1.93 (m, 1H, H-5), 1.68–1.72 (m, 1H, H-6), 1.50–1.60 (m, 2H, H-5, 6), 0.88 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{28}\text{H}_{28}\text{O}_5\text{N}$ ($[\text{M} + \text{H}]^+$), 458.1962; found, 458.1956.

Data for 10b. Yield: 80%, white solid, mp 146–148 °C; $[\alpha]_{\text{D}}^{20} = 110$ (c 3.6 mg mL⁻¹, acetone); IR cm⁻¹: 2961, 2922, 2910, 1754, 1449, 1247, 978; ¹H NMR (500 MHz, CDCl₃) δ : 8.08 (d, $J = 7.0$ Hz, 2H, Ar-H), 7.60 (t, $J = 7.5$ Hz, 1H, Ar-H), 7.55 (d, $J = 1.5$ Hz, 1H, H-5'), 7.48 (t, $J = 8.0$ Hz, 2H, Ar-H), 6.73 (d, $J = 2.0$ Hz, 1H, H-4'), 5.85 (s, 1H, H-8), 2.49 (s, 3H, $-\text{CH}_3$), 2.21–2.23 (m, 2H, H-4), 2.14 (s, 3H, H-10), 2.05–2.12 (m, 1H, H-5), 1.80–1.84 (m, 1H, H-6), 1.63–1.66 (m, 2H, H-5, 6), 0.96 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{24}\text{O}_5\text{N}$ ($[\text{M} + \text{H}]^+$), 394.1649; found, 394.1645.

Data for 10c. Yield: 75%, white solid, mp 174–176 °C; $[\alpha]_{\text{D}}^{20} = 111$ (c 4.3 mg mL⁻¹, acetone); IR cm⁻¹: 2954, 2923, 2851, 1745, 1459, 1376, 1049, 980; ¹H NMR (500 MHz, CDCl₃) δ : 7.96 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.54 (d, $J = 1.5$ Hz, 1H, H-5'), 7.28 (d, $J = 8.0$ Hz, 2H, Ar-H), 6.73 (d, $J = 1.5$ Hz, 1H, H-4'), 5.84 (s, 1H, H-8), 2.48 (s, 3H, $-\text{CH}_3$), 2.44 (s, 3H, $-\text{PhCH}_3$), 2.21–2.24 (m, 2H, H-4), 2.14 (s, 3H, H-10), 2.05–2.09 (m, 1H, H-5), 1.80–1.83 (m, 1H, H-6), 1.62–1.66 (m, 2H, H-5, 6), 0.95 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{26}\text{O}_5\text{N}$ ($[\text{M} + \text{H}]^+$), 408.1805; found, 408.1802.

Data for 10d. Yield: 70%, white solid, mp 120–122 °C; $[\alpha]_{\text{D}}^{20} = 110$ (c 3.4 mg mL⁻¹, acetone); IR cm⁻¹: 2954, 2924, 2853, 1747, 1252, 1049; ¹H NMR (500 MHz, CDCl₃) δ : 8.03 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.53 (d, $J = 2.0$ Hz, 1H, H-5'), 6.96 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.72 (d, $J = 1.5$ Hz, 1H, H-4'), 5.84 (s, 1H, H-8), 3.88 (s, 3H, $-\text{OCH}_3$), 2.48 (s, 3H, $-\text{CH}_3$), 2.21–2.24 (m, 2H, H-4), 2.14 (s, 3H, H-10), 2.05–2.12 (m, 1H, H-5), 1.81–1.84 (m, 1H, H-6), 1.62–1.66 (m, 2H, H-5, 6), 0.95 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6\text{N}$ ($[\text{M} + \text{H}]^+$), 424.1755; found, 424.1750.

Data for 10e. Yield: 74%, white solid, mp 142–144 °C; $[\alpha]_{\text{D}}^{20} = 126$ (c 3.0 mg mL⁻¹, acetone); IR cm⁻¹: 2947, 2929, 2871, 1747, 1602, 1250, 1051, 913; ¹H NMR (500 MHz, CDCl₃) δ : 8.09–8.11 (m, 2H, Ar-H), 7.55 (d, $J = 2.0$ Hz, 1H, H-5'), 7.15–7.19 (m, 2H, Ar-H), 6.73 (d, $J = 1.5$ Hz, 1H, H-4'), 5.83 (s, 1H, H-8), 2.49 (s, 3H, $-\text{CH}_3$), 2.21–2.24 (m, 2H, H-4), 2.14 (s, 3H, H-10), 2.04–2.10 (m, 1H, H-5), 1.80–1.83 (m, 1H, H-6), 1.62–1.68 (m, 2H, H-5, 6), 0.96 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{23}\text{O}_5\text{NF}$ ($[\text{M} + \text{H}]^+$), 412.1555; found, 412.1554.

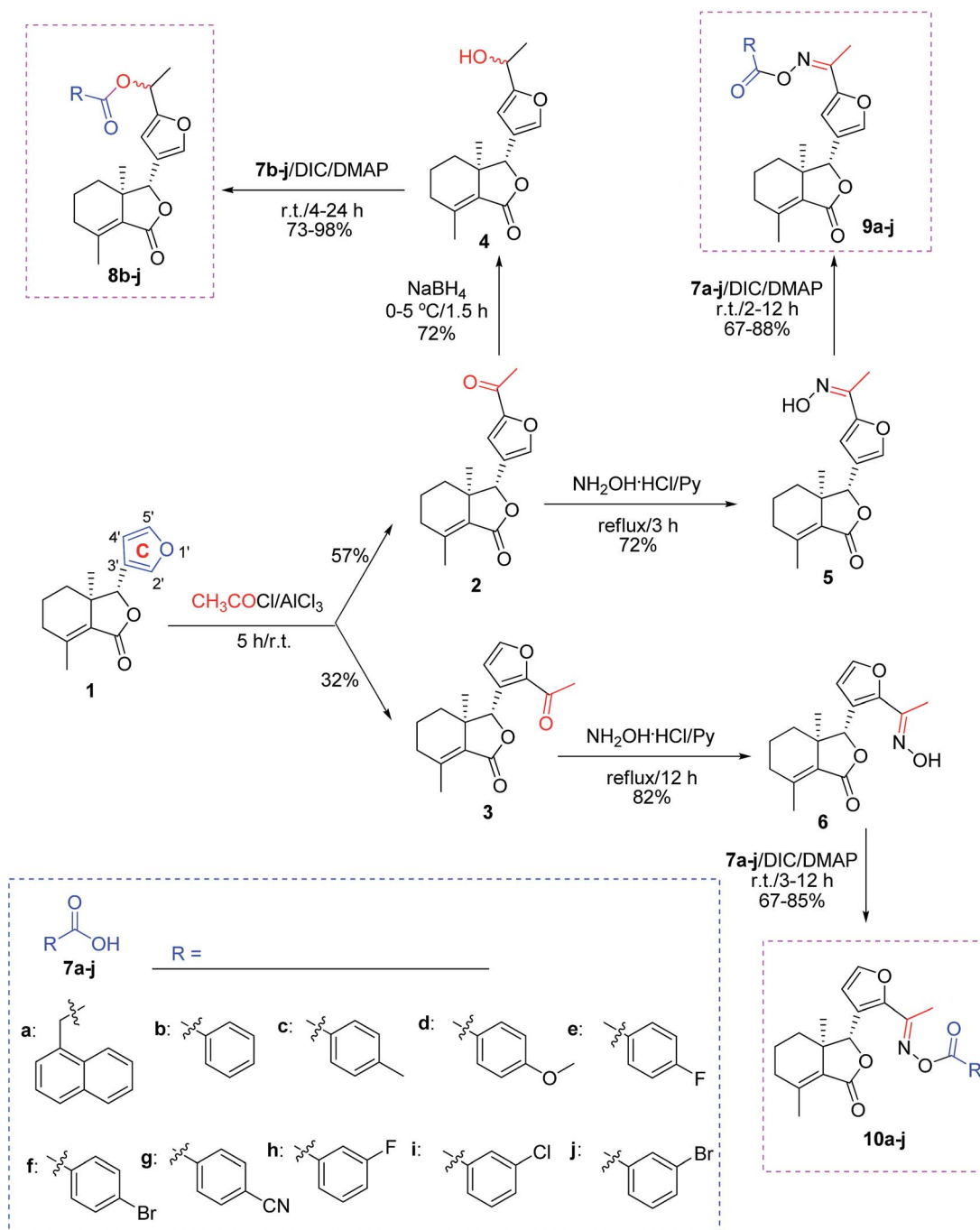


General procedure for synthesis of compounds **11** and **12**

To a stirred solution of NaH (1.26 mmol) in dry tetrahydrofuran (THF, 10 mL) at $-15\text{ }^{\circ}\text{C}$ was slowly added compound **5** or **6** (0.18 mmol). After addition, the reaction mixture was stirred at $-15\text{ }^{\circ}\text{C}$ for 10 min. Then, benzenesulfochloride (0.72 mmol) were added. When the reaction was complete according to TLC analysis, saturated aqueous NaHCO_3 (15 mL) was added to the mixture, which was extracted with CH_2Cl_2 ($3 \times 40\text{ mL}$). Finally, the combined organic phase was dried over anhydrous Na_2SO_4 ,

filtered, concentrated under reduced pressure, and purified by PTLC to give **11** (78% yield) or **12** (48% yield) as a white solid.

Data for 11. Mp $144\text{--}146\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} = -14$ (c 3.3 mg mL^{-1} , acetone); IR cm^{-1} : 2952, 2924, 2851, 1752, 1450, 1185, 986; ^1H NMR (400 MHz, CDCl_3) δ : 8.01 (d, $J = 8.8\text{ Hz}$, 2H, Ar-H), 7.65 (d, $J = 7.6\text{ Hz}$, 1H, Ar-H), 7.54–7.60 (m, 3H, Ar-H and H-2'), 7.34 (s, 1H, H-4'), 4.89 (s, 1H, H-8), 2.19–2.34 (m, 5H, $-\text{CH}_3$ and H-4), 2.15 (s, 3H, H-10), 1.73–1.88 (m, 3H, H-5, 6), 1.49–1.56 (m, 1H, H-6), 0.84 (s, 3H, H-11). HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{24}\text{O}_6\text{NS}$ ($[\text{M} + \text{H}]^+$), 430.1319; found, 430.1316.



Scheme 1 Synthesis of esters (**8b-j**) and oxime esters (**9a-j** and **10a-j**) from furyl-ring-based acetylation derivatives of fraxinellone.



Data for 12. Mp 100–101 °C; $[\alpha]_D^{20} = -5$ (*c* 4.2 mg mL⁻¹, acetone); IR cm⁻¹: 2955, 2921, 2869, 1750, 1378, 1191, 846; ¹H NMR (500 MHz, CDCl₃) δ : 8.01 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.90 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.74 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.66 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.59 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.54 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.12 (s, 1H, H-4'), 5.27 (s, 1H, H-8), 2.21–2.26 (m, 2H, H-4), 2.12 (s, 3H, -CH₃), 2.07 (s, 3H, H-10), 1.78–1.80 (m, 2H, H-5, 6), 1.58–1.61 (m, 1H, H-5), 1.47–1.52 (m, 1H, H-6), 0.57 (s, 3H, H-11). HRMS (ESI): calcd for C₂₈H₂₈O₈NS₂ ([M + H]⁺), 570.1251; found, 570.1240.

X-ray crystallography

Five three-dimensional structures of compounds **4** (α -OH isomer), **5**, **6**, **9c** and **10e** were confirmed by X-ray crystallography. Crystallographic data (excluding structure factors) of **4** (α -OH isomer), **5**, **6**, **9c** and **10e** were deposited at the Cambridge Crystallographic Data Centre (CCDC[†]) with deposition numbers of 1524889, 1524890, 1524891, 1524894, and 1524893, respectively.

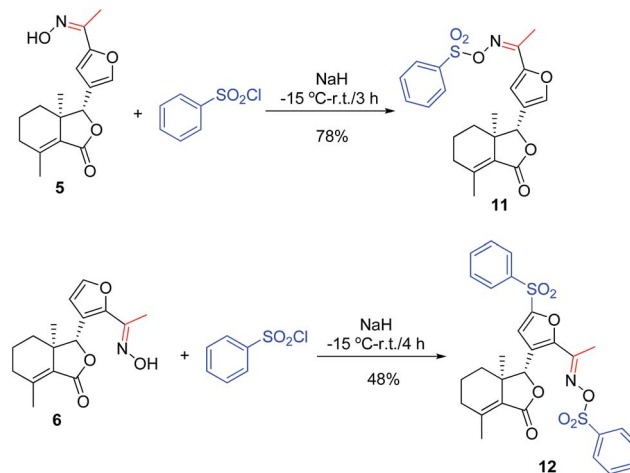
Biological assay

Growth inhibitory activity of 1, 4–6, 8b–j, 9a–j, 10a–j, 11 and 12 against *Mythimna separata*. Thirty early 3rd-instar larvae of *M. separata* were chosen as the tested insects for each compound. Solutions of **1**, **4–6**, **8b–j**, **9a–j**, **10a–j**, **11**, **12** and toosendanin (a positive control) were prepared in acetone at 1 mg mL⁻¹. 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: *L/D* = 12/12 h). Their corrected mortality rate values were calculated as follows: corrected mortality rate (%) = $(T - C) \times 100 / (100\% - C)$; *C* is the mortality rate of CK, and *T* is the mortality rate of the treated *M. separata*.^{15,17}

Results and discussion

Synthesis

As shown in Scheme 1, first, 5'-acetylfraxinellone (**2**) and 2'-acetylfraxinellone (**3**) were prepared by reaction of fraxinellone (**1**) with acetyl chloride in the presence of AlCl₃.¹⁶ Then, reduction of 5'-acetylfraxinellone (**2**) with NaBH₄ gave compound **4** ($\alpha/\beta = 1/1$, which was determined by ¹H NMR). Hydroxylamine hydrochloride reacted with **2** or **3** to easily afford the corresponding oximes **5** and **6**, respectively. Finally, in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), the corresponding acid **7** reacted with **4**, **5** or **6** to produce target products **8b–j**, **9a–j** and **10a–j**, respectively. On the other hand, as described in Scheme 2, compounds **5** and **6** reacting with benzenesulfochloride was also investigated. When **5** reacted with benzenesulfochloride (4 equiv.), oxime sulfonate **11** was afforded; when **6** reacted with benzenesulfochloride (4 equiv.), interestingly, oxime sulfonate **12** containing 5'-phenylsulfonyl was produced. Their structures were well determined by melting



Scheme 2 Synthesis of oxime sulfonates (**11** and **12**).

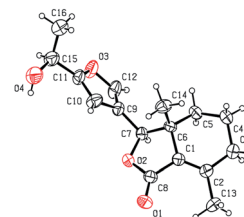


Fig. 2 X-ray crystal structure of compound **4** (α -OH isomer).

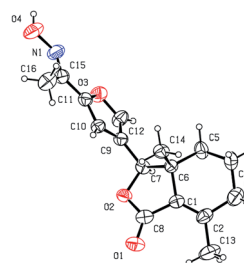


Fig. 3 X-ray crystal structure of compound **5**.

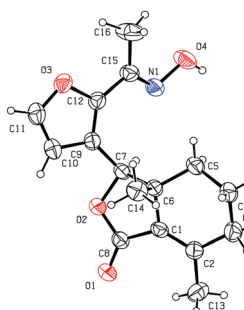


Fig. 4 X-ray crystal structure of compound **6**.

points, optical rotation, IR, and ¹H NMR. More importantly, five compounds **4** (α -OH isomer), **5**, **6**, **9c** and **10e** were further testified by X-ray crystallography (Fig. 2–6). As shown in Fig. 2, the hydroxyethyl was at the 5'-position on the furfuryl ring, and the OH



group was in α position; as shown in Fig. 3 and 4, the corresponding oxime groups of **5** and **6** were at the 5' and 2'-position on the furyl ring, respectively; as described in Fig. 5 and 6, the 4-methylphenylcarboxyloxy of **9c** and the 4-fluorophenylcarboxyloxy of **10e** were at the 5' and 2'-position on the furyl ring, respectively.

Comparison of partial ^1H NMR spectra of compounds **9b**, **10b**, **11**, and **12** was described in Fig. 7. Assignment of the position of a phenylsulfonyl group on the furyl ring of **12** was

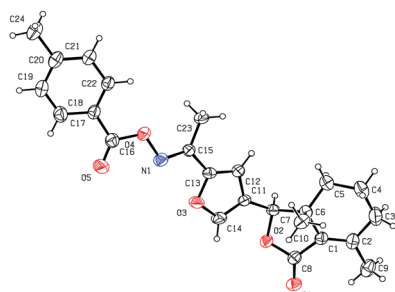


Fig. 5 X-ray crystal structure of compound **9c**.

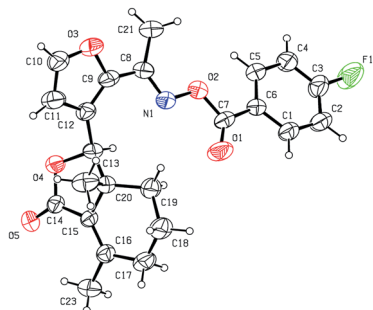


Fig. 6 X-ray crystal structure of compound **10e**.

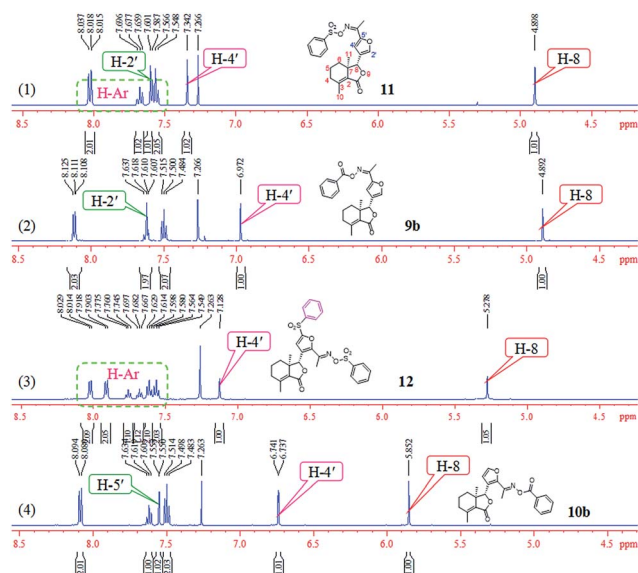


Fig. 7 Comparison of partial ^1H NMR spectra of compounds **9b**, **10b**, **11**, and **12**.

based on the chemical shift. If the phenylsulfonyl group was at the 4'-position on the furyl ring, the corresponding chemical shift of H-5' will be greater than 7.342 ppm; here the chemical shift was 7.128 ppm, which belonged to H-4', so the phenylsulfonyl group was at the 5'-position on the furyl ring of **12**.

Insecticidal activity

As described in Table 1, the growth inhibitory activity of compounds **1**, **4–6**, **8b–j**, **9a–j**, **10a–j**, **11** and **12** against *M. separata* was tested at 1 mg mL^{-1} . Toosendanin, a commercial insecticide derived from *Melia azedarach*, was used as the positive control. Leaves treated with acetone alone were used as a blank control group. Compounds **9a**, **9c**, **9j**, **10h** and **10i** displayed more potent insecticidal activity than toosendanin. For example, the final mortality rates (FMRs) of **9a**, **9c**, **9j**, **10h** and **10i** were 57.1%, 50.0%, 50.0%, 50.0%, and 57.1%, respectively; whereas the FMRs of **1** and toosendanin were 42.9% and 46.4%, respectively. The

Table 1 Growth inhibitory activity of compounds **1**, **4–6**, **8b–j**, **9a–j**, **10a–j**, **11** and **12** against *M. separata* on leaves treated with a concentration of 1 mg mL^{-1}

| Compound | Corrected mortality rate (mean \pm SD, %) | | |
|---------------|---|----------------|----------------|
| | 10 days | 20 days | 35 days |
| 1 | 10.0 \pm 0 | 13.3 \pm 3.3 | 42.9 \pm 3.3 |
| 4 | 13.3 \pm 3.3 | 26.7 \pm 3.3 | 39.3 \pm 3.3 |
| 5 | 13.3 \pm 3.3 | 13.3 \pm 3.3 | 42.9 \pm 3.3 |
| 6 | 23.3 \pm 3.3 | 33.3 \pm 3.3 | 46.4 \pm 5.8 |
| 8b | 6.7 \pm 3.3 | 10.0 \pm 0 | 35.7 \pm 5.8 |
| 8c | 20.0 \pm 0 | 26.7 \pm 3.3 | 42.9 \pm 3.3 |
| 8d | 16.7 \pm 3.3 | 16.7 \pm 3.3 | 21.4 \pm 3.3 |
| 8e | 10.0 \pm 0 | 13.3 \pm 3.3 | 21.4 \pm 3.3 |
| 8f | 10.0 \pm 5.8 | 6.7 \pm 6.7 | 35.7 \pm 0 |
| 8g | 26.7 \pm 3.3 | 33.3 \pm 6.7 | 39.3 \pm 3.3 |
| 8h | 16.7 \pm 3.3 | 16.7 \pm 3.3 | 42.9 \pm 3.3 |
| 8i | 26.7 \pm 3.3 | 33.3 \pm 3.3 | 42.9 \pm 3.3 |
| 8j | 13.3 \pm 3.3 | 13.3 \pm 3.3 | 32.1 \pm 3.3 |
| 9a | 20.0 \pm 5.8 | 23.3 \pm 6.7 | 57.1 \pm 0 |
| 9b | 36.7 \pm 3.3 | 36.7 \pm 3.3 | 46.4 \pm 5.8 |
| 9c | 16.7 \pm 3.3 | 20.0 \pm 5.8 | 50.0 \pm 3.3 |
| 9d | 13.3 \pm 3.3 | 13.3 \pm 3.3 | 46.4 \pm 5.8 |
| 9e | 30.0 \pm 0 | 33.3 \pm 3.3 | 42.9 \pm 3.3 |
| 9f | 6.7 \pm 3.3 | 13.3 \pm 3.3 | 32.1 \pm 6.7 |
| 9g | 26.7 \pm 3.3 | 26.7 \pm 3.3 | 39.3 \pm 3.3 |
| 9h | 13.3 \pm 3.3 | 16.7 \pm 3.3 | 35.7 \pm 0 |
| 9i | 3.3 \pm 3.3 | 10.0 \pm 0 | 46.4 \pm 5.8 |
| 9j | 10.0 \pm 0 | 10.0 \pm 0 | 50.0 \pm 3.3 |
| 10a | 13.3 \pm 3.3 | 13.3 \pm 3.3 | 46.4 \pm 5.8 |
| 10b | 10.0 \pm 0 | 13.3 \pm 3.3 | 35.7 \pm 5.8 |
| 10c | 20.0 \pm 0 | 23.3 \pm 3.3 | 42.9 \pm 3.3 |
| 10d | 6.7 \pm 3.3 | 6.7 \pm 3.3 | 39.3 \pm 3.3 |
| 10e | 20.0 \pm 0 | 30.0 \pm 0 | 42.9 \pm 3.3 |
| 10f | 26.7 \pm 3.3 | 26.7 \pm 3.3 | 42.9 \pm 3.3 |
| 10g | 23.3 \pm 3.3 | 30.0 \pm 0 | 42.9 \pm 3.3 |
| 10h | 13.3 \pm 3.3 | 26.7 \pm 3.3 | 50.0 \pm 3.3 |
| 10i | 13.3 \pm 3.3 | 20.0 \pm 0 | 57.1 \pm 5.8 |
| 10j | 26.7 \pm 3.3 | 30.0 \pm 0 | 46.4 \pm 0 |
| 11 | 6.7 \pm 3.3 | 13.3 \pm 3.3 | 25.0 \pm 5.8 |
| 12 | 16.7 \pm 6.7 | 23.3 \pm 3.3 | 42.9 \pm 3.3 |
| Toosendanin | 6.7 \pm 3.3 | 16.7 \pm 3.3 | 46.4 \pm 5.8 |
| Blank control | 0 \pm 0 | 0 \pm 0 | 6.7 \pm 3.3 |



symptoms for the treated *M. separata* during the larval, pupation and adult periods were observed by the same way as our previous reports.^{14,15,17} For example, the dead larvae with thin and wrinkled bodies, the malformed and dead pupae, and the malformed moths also appeared during the above three stages.

Additionally, the structure–activity relationships of tested compounds were also observed. When compared with toosendanin, all esters (**8b–j**) and oxime sulfonates (**11** and **12**) exhibited less potent insecticidal activity. To 5'-oxime esters (**9a–j**), introduction of the electron-withdrawing groups on the phenyl of **9b** usually resulted in the less active compounds (except **9i,j**); for instance, the FMRs of **9e–h** were 42.9%, 32.1%, 39.3% and 35.7%, respectively. On the contrary, to 2'-oxime esters (**10a–j**), compounds containing the electron-withdrawing groups generally showed more potent insecticidal activity than those containing the electron-donating ones. For example, the FMRs of **10e–j** were all greater than 42.9%, especially the FMR of **10i** was 57.1%. Previously, we noticed that introduction of a (1-naphthylacetyl)oxy group at the C-4 position of the podophyllotoxin derivatives could lead to promising compounds;^{18–20} in this paper, introduction of a (1-naphthylacetyl)oxy group to **5** or **6** also produced the potent compounds **9a** and **10a**, respectively. So this suggested that the (1-naphthylacetyl)oxy group could be introduced into other natural products in the future.

Conclusions

In summary, we have semisynthesized a series of esters and oxime esters/sulfonates from furyl-ring-based acetylation derivatives of fraxinellone as pesticidal agents. Especially the steric structures of five products were assigned by X-ray analysis data. Their insecticidal activity was evaluated against a crop-threatening agricultural insect pest, *M. separata*. Among all derivatives, especially compounds **9a** and **10i** exhibited the most promising pesticidal activity. Their structure–activity relationships were also observed. It will pave the way for further structural modifications of fraxinellones as biorenewable pesticidal agents for agriculture.

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