

## Research Article

# Research on Crystal Structure and Fungicidal Activity of the Amide Derivatives Based on the Natural Products Sinapic Acid and Mycophenolic Acid

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Structural optimization based on natural products is an important and effective way to discover new green pesticides. Here, two series of amide derivatives based on sinapic acid and mycophenolic acid were designed in combination with the fungicidal natural product piperlongumine and synthesized by preparing the carboxylic acid into acyl chloride and then reacting with the corresponding aromatic amines, respectively. The resulting structures were successively characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS. The crystal structures of molecules I-4 and II-5 were analyzed for structure validation. The in vitro inhibitory activity indicated that most of the target products exhibited fungicidal activity equivalent to or even better than fluopyram against *Physalospora piricola*. The in vivo fungicidal activity demonstrated that the compounds I-5 and II-4 displayed almost the same preventative activity as carbendazim and fluopyram at 200 μg mL<sup>-1</sup>. The TEM observation revealed that the fungicidal activity of the target molecules against *Physalospora piricola* may be due to the influence on the mitochondria in the cell structure. These results will provide valuable theoretical guidance for developing the new green fungicides.

## 1. Introduction

Agrochemicals are important production materials for agricultural production, and their development plays an important role in ensuring national food security, agricultural product quality, ecological environment safety, and public health [1]. However, the continuous application of traditional chemical fungicides has produced many negative effects including ecological environment pollution, pathogen resistance, and poison for beneficial insects and microorganisms [2, 3]. Therefore, the development of efficient, safe, low residual, and environmentally friendly green

fungicides has become the inevitable trend for pesticide innovation [4, 5].

The discovery of lead compounds and the exploration of mechanism of action are the key to the development and innovation of fungicides. Structural optimization based on natural products has become an effective way to develop new green fungicides, which has important guiding significance for practicing new development concepts and promoting green development of agrochemicals [6–11]. For example, coumoxystrobin was successfully developed based on natural products strobilurin and coumarin (Figure 1) [12]. Moreover, natural product strobilurin A-derived

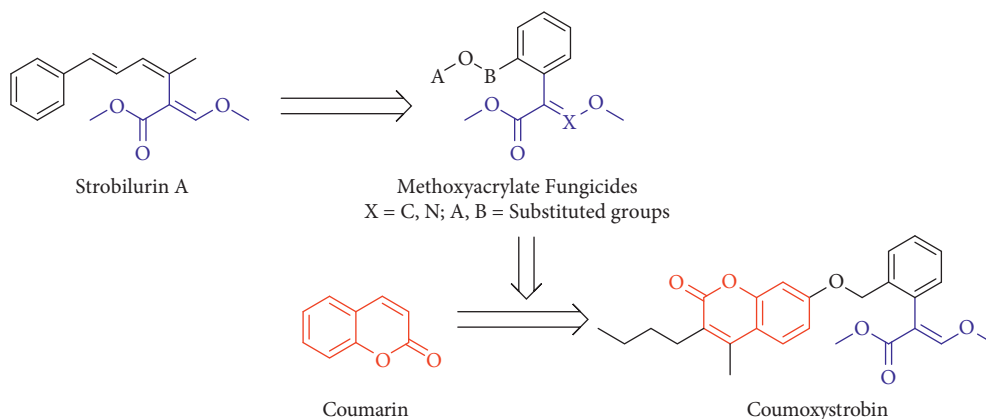


FIGURE 1: Methoxyacrylate fungicides and coumoxystrobin successfully developed based on natural product strobilurin A.

methoxyacrylate fungicides have occupied the top position in the market sales of fungicides [6].

Mycophenolic acid (MPA) was discovered by Gosio in 1893 in a strain of *Penicillium* fungus and was found to possess broad biological activity such as antifungal, antiviral, anticancer, and antipsoriasis properties [13, 14]. Sinapic acid is widely distributed in the plants and belongs to hydroxycinnamic acid. Furthermore, commercial fungicides dimethomorph, pyrimorph, and flumorph were successively developed based on natural product cinnamic acid (Figure 2) [15–18]. In this project, combined with the structure of fungicidal natural product piperlongumine [19, 20], two series of amide compounds based on natural products sinapic acid and mycophenolic acid were designed, synthesized, and evaluated their fungicidal activity against the common agricultural pathogens (Figure 3).

## 2. Experimental Materials and Methods

**2.1. Materials and Equipment.** The materials and reagents used in the organic synthesis reactions were of analytical grade and purchased from Energy Chemical and Bide Pharmatech Ltd. Melting points were measured on a X-5 binocular microscope (Yuhua Co., Ltd., China).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were provided on a AVANCE NEO-500 MHz spectrometer (Bruker, Germany). HRMS was recorded on a Xevo G2-XS QToF spectrometer (Waters, USA). X-ray crystal structure was determined on a D8 Venture diffractometer (Bruker, Germany). The purification of target compounds was performed by the column chromatography on silica gel (200–300 mesh).

**2.2. Preparation of the Target Molecules.** (*E*)-2,6-dimethoxy-4-(3-oxo-3-(phenylamino)prop-1-en-1-yl)phenyl acetate (**I-1**) was synthesized as follows. Thionyl chloride (2.38 g, 20.0 mmol) was added dropwise to a mixture of (*E*)-3-(4-acetoxy-3,5-dimethoxyphenyl) acrylic acid (1.06 g, 4.0 mmol) and DMF (3 drops) in DCM (20 mL). The reaction was stirred for 6 h at room temperature and concentrated in vacuo to sufficiently remove the solvent and excess thionyl chloride. The resulting acyl chloride was

immediately dissolved in anhydrous DCM (3 mL) and then added dropwise at room temperature to a mixture of aniline (0.45 g, 4.8 mmol) and trimethylamine (0.81 g, 8.0 mmol) in anhydrous DCM (25 mL). The reaction was stirred overnight and poured into a mixture of DCM and water (150 mL, v/v = 1/1). The DCM layer was separated by extraction and washed successively with dilute hydrochloric acid and potassium carbonate aqueous solution. The obtained solution was dried over anhydrous sodium sulfate, filtered, and concentrated. The provided residue was purified by silica gel chromatography using petroleum ether/ethyl acetate (v/v = 1/1) as eluent to provide **I-1** (yield 68%). Molecules **I-2–I-5** and **II-1–II-5** were prepared similarly.

(*E*)-2,6-dimethoxy-4-(3-oxo-3-(phenylamino)prop-1-en-1-yl)phenyl acetate (**I-1**): white solid, yield 68%, m.p. 125–127°C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (s, 1H, NH), 7.63–7.57 (m, 3H, Ph-H, and CH), 7.34 (t,  $J = 7.9$  Hz, 2H, Ph-H), 7.12 (t,  $J = 7.4$  Hz, 1H, Ph-H), 6.68 (s, 2H, Ph-H), 6.39 (d,  $J = 15.4$  Hz, 1H, CH), 3.78 (s, 6H,  $(\text{OCH}_3)_2$ ), 2.37 (s, 3H,  $\text{COCH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.0, 163.8, 152.3, 141.7, 138.2, 133.2, 130.1, 129.1, 124.4, 121.4, 119.8, 104.7, 56.2, 20.5. Found,  $m/z$ : 342.1333  $[\text{M}+\text{H}]^+$ .  $\text{C}_{19}\text{H}_{20}\text{NO}_5$ . Calculated,  $m/z$ : 342.1336.

(*E*)-2,6-dimethoxy-4-(3-oxo-3-((2-(trifluoromethyl)phenyl)amino)prop-1-en-1-yl)phenyl acetate (**I-2**): white solid, yield 60%, m.p. 143–145°C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (d,  $J = 7.9$  Hz, 1H, Ph-H), 7.68 (d,  $J = 15.4$  Hz, 1H, CH), 7.66–7.57 (m, 3H, NH, and Ph-H), 7.27–7.24 (m, 1H, Ph-H), 6.80 (s, 2H, Ph-H), 6.47 (d,  $J = 15.4$  Hz, 1H, CH), 3.87 (s, 6H,  $(\text{OCH}_3)_2$ ), 2.36 (s, 3H,  $\text{COCH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 163.8, 152.5, 143.2, 135.4, 135.4, 133.0, 132.6, 130.4, 126.1 (q,  $J_{\text{C-F}} = 5.4$  Hz), 124.5, 124.4, 124.2 (q,  $J_{\text{C-F}} = 273.4$  Hz), 120.5, 104.7, 56.3, 20.5. Found,  $m/z$ : 410.1208  $[\text{M}+\text{H}]^+$ .  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{NO}_5$ . Calculated,  $m/z$ : 410.1210.

(*E*)-4-(3-((2,3-dichlorophenyl)amino)-3-oxoprop-1-en-1-yl)-2,6-dimethoxyphenyl acetate (**I-3**): white solid, yield 64%, m.p. 114–116°C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (dd,  $J = 7.5, 2.2$  Hz, 1H, Ph-H), 7.89 (s, 1H, NH), 7.67 (d,  $J = 15.4$  Hz, 1H, CH), 7.27–7.23 (m, 2H, Ph-H), 6.78 (s, 2H, Ph-H), 6.53 (d,  $J = 15.4$  Hz, 1H, CH), 3.86 (s, 6H,  $(\text{OCH}_3)_2$ ), 2.36 (s, 3H,  $\text{COCH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6,

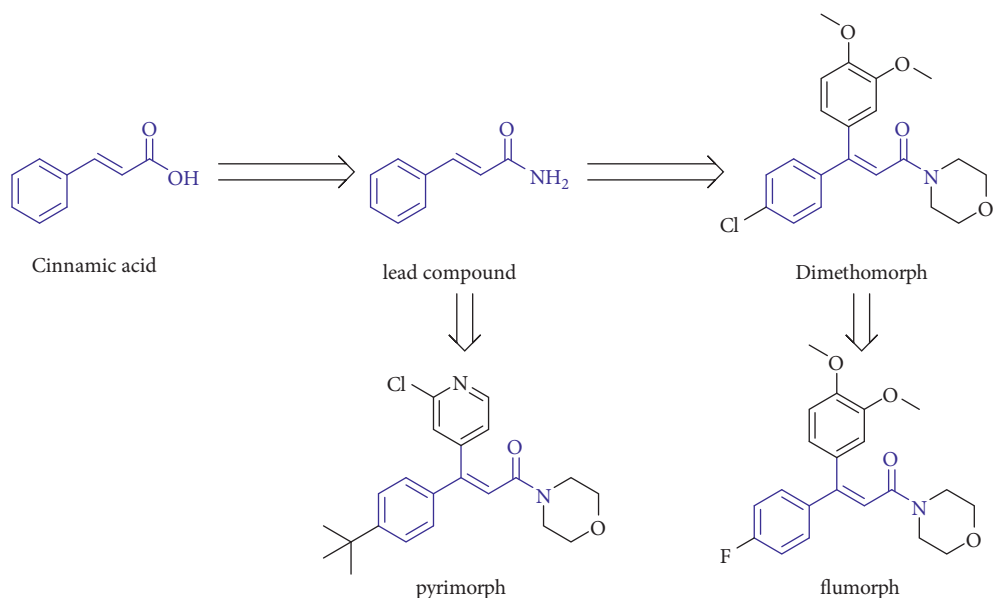


FIGURE 2: Cinnamic acid amide fungicides successfully developed based on natural product cinnamic acid.

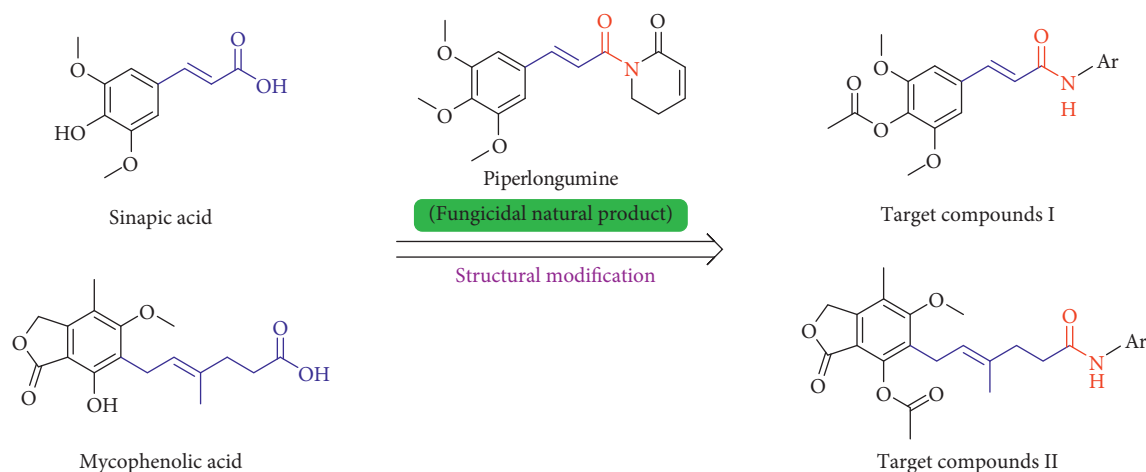


FIGURE 3: Molecular design strategy in this project.

163.7, 152.4, 143.2, 136.4, 132.8, 132.6, 130.4, 127.9, 125.3, 121.2, 120.6, 119.6, 104.7, 56.2, 20.5. Found,  $m/z$ : 410.0555  $[M+H]^+$ .  $C_{19}H_{18}Cl_2NO_5$ . Calculated,  $m/z$ : 410.0557.

(*E*)-2,6-dimethoxy-4-(3-((2-methoxy-5-methylphenyl)amino)-3-oxoprop-1-en-1-yl)phenyl acetate (**I-4**): white solid, yield 72%, m.p. 153–155°C.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.35 (s, 1H, NH), 7.93 (s, 1H, Ph-H), 7.65 (d,  $J=15.4$  Hz, 1H, CH), 6.86 (dd,  $J=8.2, 1.4$  Hz, 1H, Ph-H), 6.80–6.78 (m, 3H, Ph-H), 6.52 (d,  $J=15.4$  Hz, 1H, CH), 3.89 (s, 3H,  $OCH_3$ ), 3.87 (s, 6H,  $(OCH_3)_2$ ), 2.35 (s, 3H,  $COCH_3$ ), 2.33 (s, 3H, Ph- $CH_3$ ).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  168.6, 163.4, 152.4, 145.9, 141.6, 133.2, 130.8, 130.1, 127.5, 124.1, 121.7, 120.7, 109.8, 104.6, 56.2, 55.9, 21.0, 20.5. Found,  $m/z$ : 386.1594  $[M+H]^+$ .  $C_{21}H_{24}NO_6$ . Calculated,  $m/z$ : 386.1598.

(*E*)-4-(3-((3-isopropoxyphenyl)amino)-3-oxoprop-1-en-1-yl)-2,6-dimethoxyphenyl acetate (**I-5**): white solid,

yield 68%, m.p. 122–124°C.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.61 (d,  $J=15.4$  Hz, 1H, CH), 7.51 (s, 1H, Ph-H), 7.41 (s, 1H, NH), 7.21 (t,  $J=8.1$  Hz, 1H, Ph-H), 7.03 (d,  $J=7.8$  Hz, 1H, Ph-H), 6.71 (s, 2H, Ph-H), 6.67 (dd,  $J=8.2, 1.8$  Hz, 1H, Ph-H), 6.40 (d,  $J=15.4$  Hz, 1H, CH), 4.57 (hept,  $J=6.1$  Hz, 1H,  $\underline{CH(CH_3)_2}$ ), 3.81 (s, 6H,  $(OCH_3)_2$ ), 2.36 (s, 3H,  $COCH_3$ ), 1.34 (d,  $J=6.1$  Hz, 6H,  $\underline{CH(CH_3)_2}$ ).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  168.9, 163.7, 158.6, 152.3, 149.3, 141.9, 139.3, 133.1, 130.1, 129.7, 121.3, 112.3, 111.8, 104.6, 70.0, 56.2, 22.1, 20.5. Found,  $m/z$ : 400.1753  $[M+H]^+$ .  $C_{22}H_{26}NO_6$ . Calculated,  $m/z$ : 400.1755.

(*E*)-6-methoxy-7-methyl-5-(3-methyl-6-oxo-6-(phenylamino)hex-2-en-1-yl)-3-oxo-1,3-dihydroisobenzofuran-4-yl acetate (**II-1**): white solid, yield 66%, m.p. 160–162°C.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.53 (s, 1H, NH), 7.33 (d,  $J=7.8$  Hz, 2H, Ph-H), 7.18 (t,  $J=7.9$  Hz, 2H, Ph-H), 7.01 (t,

$J = 7.4$  Hz, 1H, Ph-H), 5.15 (t,  $J = 6.9$  Hz, 1H, CH), 5.01 (s, 2H, OCH<sub>2</sub>Ph), 3.70 (s, 3H, OCH<sub>3</sub>), 3.35 (d,  $J = 7.1$  Hz, 2H, PhCH<sub>2</sub>), 2.40 (s, 3H, COCH<sub>3</sub>), 2.38–2.35 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.06 (s, 3H, Ph-CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 169.9, 168.4, 162.6, 146.1, 145.5, 138.1, 134.6, 129.2, 128.5, 123.7, 123.0, 122.5, 119.6, 113.2, 68.4, 61.2, 36.1, 34.4, 23.5, 20.8, 16.8, 11.7. Found,  $m/z$ : 438.1907 [M+H]<sup>+</sup>. C<sub>25</sub>H<sub>28</sub>NO<sub>6</sub>. Calculated,  $m/z$ : 438.1911.

(*E*)-6-methoxy-7-methyl-5-(3-methyl-6-oxo-6-((2-(trifluoromethyl)phenyl) amino)hex-2-en-1-yl)-3-oxo-1,3-dihydroisobenzofuran-4-yl acetate (**II-2**): white solid, yield 70%, m.p. 93–95°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.09 (d,  $J = 7.6$  Hz, 1H, Ph-H), 7.58 (d,  $J = 7.8$  Hz, 1H, Ph-H), 7.51 (t,  $J = 7.8$  Hz, 1H, Ph-H), 7.38 (s, 1H, NH), 7.21 (t,  $J = 7.6$  Hz, 1H, Ph-H), 5.19 (t,  $J = 6.4$  Hz, 1H, CH), 5.11 (s, 2H, OCH<sub>2</sub>Ph), 3.77 (s, 3H, OCH<sub>3</sub>), 3.36 (d,  $J = 6.8$  Hz, 2H, PhCH<sub>2</sub>), 2.51–2.44 (m, 2H, CH<sub>2</sub>), 2.41 (t,  $J = 7.4$  Hz, 2H, CH<sub>2</sub>), 2.37 (s, 3H, COCH<sub>3</sub>), 2.19 (s, 3H, Ph-CH<sub>3</sub>), 1.83 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 169.0, 168.2, 162.6, 146.2, 145.9, 135.2, 134.3, 132.8, 129.1, 126.0 (q,  $J_C-F = 5.4$  Hz), 125.1, 124.8, 124.5, 122.9, 122.8, 113.5, 68.3, 61.2, 36.1, 34.7, 23.6, 20.5, 16.3, 11.8. Found,  $m/z$ : 506.1781 [M+H]<sup>+</sup>. C<sub>26</sub>H<sub>27</sub>F<sub>3</sub>NO<sub>6</sub>. Calculated,  $m/z$ : 506.1785.

(*E*)-5-(6-((2,3-dichlorophenyl)amino)-3-methyl-6-oxohex-2-en-1-yl)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-4-yl acetate (**II-3**): white solid, yield 67%, m.p. 149–151°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.24 (dd,  $J = 6.5, 2.9$  Hz, 1H, Ph-H), 7.67 (s, 1H, NH), 7.18 (s, 1H, Ph-H), 7.17 (dd, 1H,  $J = 8.5, 3.5$  Hz, Ph-H), 5.20 (td,  $J = 6.9, 1.1$  Hz, 1H, CH), 5.12 (s, 2H, OCH<sub>2</sub>Ph), 3.74 (s, 3H, OCH<sub>3</sub>), 3.36 (d,  $J = 6.8$  Hz, 2H, PhCH<sub>2</sub>), 2.51 (t,  $J = 7.6$  Hz, 2H, CH<sub>2</sub>), 2.42 (t,  $J = 7.4$  Hz, 2H, CH<sub>2</sub>), 2.39 (s, 3H, COCH<sub>3</sub>), 2.16 (s, 3H, Ph-CH<sub>3</sub>), 1.84 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.8, 169.1, 168.2, 162.6, 146.2, 145.9, 136.2, 134.2, 132.6, 129.0, 127.7, 125.1, 122.9, 119.7, 113.5, 68.3, 61.1, 36.2, 34.6, 23.6, 20.6, 16.5, 11.8. Found,  $m/z$ : 506.1129 [M+H]<sup>+</sup>. C<sub>25</sub>H<sub>26</sub>Cl<sub>2</sub>NO<sub>6</sub>. Calculated,  $m/z$ : 506.1132.

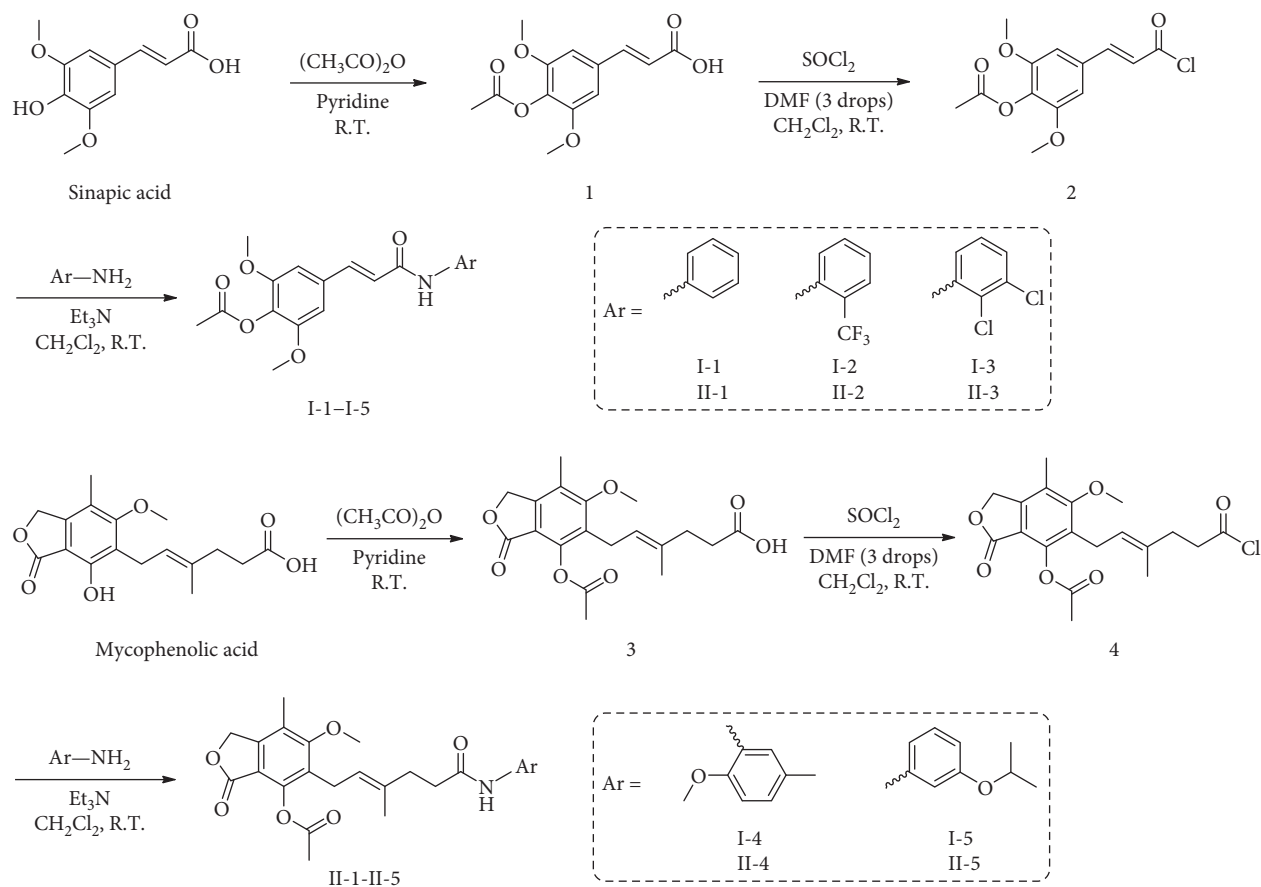
(*E*)-6-methoxy-5-(6-((2-methoxy-5-methylphenyl) amino)-3-methyl-6-oxohex-2-en-1-yl)-7-methyl-3-oxo-1,3-dihydroisobenzofuran-4-yl acetate (**II-4**): white solid, yield 74%, m.p. 113–115°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.14 (s, 1H, NH), 7.69 (s, 1H, Ph-H), 6.79 (dd,  $J = 8.2, 1.1$  Hz, 1H, Ph-H), 6.71 (d,  $J = 8.3$  Hz, 1H, Ph-H), 5.16 (t,  $J = 6.4$  Hz, 1H, CH), 5.10 (s, 2H, OCH<sub>2</sub>Ph), 3.81 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.35 (d,  $J = 6.8$  Hz, 2H, PhCH<sub>2</sub>), 2.46–2.38 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.37 (s, 3H, COCH<sub>3</sub>), 2.27 (s, 3H, Ph-CH<sub>3</sub>), 2.17 (s, 3H, Ph-CH<sub>3</sub>), 1.83 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 169.0, 168.3, 162.6, 146.1, 145.9, 145.7, 134.7, 130.4, 129.2, 127.3, 123.6, 122.9, 122.3, 120.4, 113.4, 109.6, 68.3, 61.2, 55.7, 36.4, 34.8, 23.6, 20.9, 20.5, 16.5, 11.8. Found,  $m/z$ : 506.1129 [M+H]<sup>+</sup>. C<sub>27</sub>H<sub>32</sub>NO<sub>7</sub>. Calculated,  $m/z$ : 506.1132.

(*E*)-5-(6-((3-isopropoxyphenyl)amino)-3-methyl-6-oxohex-2-en-1-yl)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-4-yl acetate (**II-5**): white solid, yield 58%, m.p. 89–91°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 (s, 1H, NH), 7.12 (s, 1H, Ph-H), 7.05 (t,  $J = 8.1$  Hz, 1H, Ph-H), 6.75 (dd,  $J = 8.0, 0.9$  Hz, 1H, Ph-H), 6.56 (dd,  $J = 8.2, 1.8$  Hz, 1H, Ph-H), 5.15 (t,  $J = 6.9$  Hz, 1H, CH), 5.05 (s, 2H, OCH<sub>2</sub>Ph),

4.48 (dt,  $J = 12.1, 6.1$  Hz, 1H, OCH), 3.71 (s, 3H, OCH<sub>3</sub>), 3.35 (d,  $J = 7.1$  Hz, 2H, PhCH<sub>2</sub>), 2.41 (s, 3H, COCH<sub>3</sub>), 2.40–2.31 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.08 (s, 3H, Ph-CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>), 1.30 (d,  $J = 6.1$  Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 169.8, 168.4, 162.5, 158.2, 146.2, 145.6, 139.2, 134.6, 129.2, 129.1, 123.0, 122.5, 113.2, 111.8, 111.6, 107.1, 70.0, 68.4, 61.2, 36.2, 34.4, 23.5, 22.0, 20.8, 16.8, 11.7. Found,  $m/z$ : 496.2326 [M+H]<sup>+</sup>. C<sub>28</sub>H<sub>34</sub>NO<sub>7</sub>. Calculated,  $m/z$ : 496.2330.

**2.3. X-Ray Crystal Structure Determination.** The crystals of the target compounds **I-4** and **II-5** were cultivated from a mixed solvent of methanol, ethyl acetate, and n-hexane, respectively. All measurements were made on a Bruker D8 Venture diffractometer with *Mo-K $\alpha$*  radiation ( $\lambda = 0.71073$  Å). The crystal data of the compound **I-4** were collected at 298 K, and the colorless crystal is of monoclinic system, space group *C 2/c*, with  $a = 28.208$  (3),  $b = 11.1670$  (12),  $c = 14.0948$  (14) Å,  $\alpha = 90^\circ$ ,  $\beta = 114.242$  (4)°,  $\gamma = 90^\circ$ ,  $V = 4048.3$  (7) Å<sup>3</sup>,  $Z = 8$ ,  $F(000) = 1712$ , density (calculated) = 1.324 g/cm<sup>3</sup>, and linear absorption coefficient 0.100 mm<sup>-1</sup>. All of the non-H atoms were refined anisotropically by full-matrix least-squares to give the final  $R = 0.0493$  and  $wR = 0.1153$  ( $w = 1/[\sigma^2(F_o^2) + (0.0465P)^2 + 2.2020P]$ , where  $P = (F_o^2 + 2F_c^2)/3$ ) with  $S = 1.064$  using the SHELXL program. The crystal data of the compound **II-5** were collected at 298(2) K, and the colorless crystal is of monoclinic system, space group *P2<sub>1</sub>/n*, with  $a = 15.3461$  (16),  $b = 10.3766$  (11),  $c = 16.0494$  (17) Å,  $\alpha = 90^\circ$ ,  $\beta = 95.683$  (2)°,  $\gamma = 90^\circ$ ,  $V = 2543.2$  (5) Å<sup>3</sup>,  $Z = 4$ ,  $F(000) = 1056$ , density (calculated) = 1.294 g/cm<sup>3</sup>, and linear absorption coefficient 0.093 mm<sup>-1</sup>. All of the non-H atoms were refined anisotropically by full-matrix least-squares to give the final  $R = 0.0625$  and  $wR = 0.1565$  ( $w = 1/[\sigma^2(F_o^2) + (0.0001P)^2 + 0.9874P]$ , where  $P = (F_o^2 + 2F_c^2)/3$ ) with  $S = 1.044$  using the SHELXL program. The crystal structures were solved by direct methods with SHELXS-2014/6 program.

**2.4. Fungicidal Activity Measurement.** With fluopyram and carbendazim as positive controls, the mycelial growth inhibition method was used to determine the in vitro inhibitory activities of the target compounds against common agricultural pathogens according to the previously reported procedures [21, 22], and each treatment was repeated at least three times. The tested pathogens include *Rhizoctonia solani* (RS), *Gibberella zeae* (GZ), *Botrytis cinerea* (BC), *Physalospora piricola* (PP), *Cercospora circumscissa* Sacc. (CS), *Colletotrichum capsici* (CC), *Alternaria kikuchiana* Tanaka (AK), and *Alternaria* sp. (AS). The in vivo fungicidal activity of compounds **I-5** and **II-4** against *Physalospora piricola* was performed on apples referring to literature methods [23]. The target molecule (5.0 mg) was dissolved in dimethyl sulfoxide (30  $\mu$ L) and diluted with 0.1% Tween-80 aqueous solution to provide the test stock solution (200  $\mu$ g·mL<sup>-1</sup>), which was sprayed with the same volume on healthy apples. Subsequently, the fungi cake containing *Physalospora piricola* with a diameter of 7 mm was inoculated. After cultivation at 25°C for 5 days, the average lesion area was



SCHEME 1: The synthetic procedures for the target molecules I and II.

measured to calculate the preventative activity. Each in vivo fungicidal activity screening was carried out for at least five repeats.

**2.5. Transmission Electron Microscope (TEM) Investigation.** *Physalospora piricola* hyphae were obtained by incubation in PDB medium at  $25^\circ\text{C}$  for 72 h and centrifugation at 7000 rpm for 3 min, which were then resuspended in PDB medium to treat with compounds **I-5** and **II-4** ( $200\ \mu\text{g}\cdot\text{mL}^{-1}$ ) for 24 h, respectively. Subsequently, the treated hyphae were provided by centrifugation and fixed with 2.5% glutaraldehyde. The ultrastructure observation of the hyphae treated with compounds **I-5** and **II-4** ( $200\ \mu\text{g}\cdot\text{mL}^{-1}$ ) was performed by Shiyanjia Lab on a TEM according to the standard procedures.

### 3. Results and Discussion

**3.1. Organic Synthesis.** Herein, the important intermediates and target molecules **I-1-I-5** and **II-1-II-5** were provided referring to the reported procedures (Scheme 1). In the preparation of target compound **I-1-I-5**, the phenolic hydroxyl group in sinapic acid was firstly reacted with acetic anhydride to produce (*E*)-3-(4-acetoxy-3,5-dimethoxyphenyl)acrylic acid [24], which was further reacted with thionyl chloride under the catalyzed condition of DMF (3

drops) to provide (*E*)-3-(4-acetoxy-3,5-dimethoxyphenyl)acrylic chloride. Finally, the target compound **I-1-I-5** was synthesized by reacting the acyl chloride **2** with the corresponding aromatic amines, respectively. In addition, the condensing reagents such as EDCI-HOBt, HATU-DIEA, or TBTU-DIEA were also taken to explore the condensation of the carboxylic acid **1** and substituted aromatic amines; however, the yields of the products were low. The target compound **II-1-II-5** was obtained according to the same steps described above. Subsequently, the obtained structures were identified and characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and HRMS.

**3.2. Crystal Structure Analysis.** The crystal structure analysis is beneficial in investigating the physical and chemical properties of the molecules. In this study, several crystal structure characteristics were also illustrated through the crystal structures and packing of molecules **I-4** and **II-5** (Figure 4, CCDC numbers 2095769 and 2095768). The selected bond lengths and angles are presented in Table 1, and the selected dihedral angles are shown in Table 2. From the data, the sum of bond angles  $\text{C}(4)\text{-C}(3)\text{-H}(3)$ ,  $\text{C}(2)\text{-C}(3)\text{-C}(4)$ , and  $\text{C}(2)\text{-C}(3)\text{-H}(3)$  in compound **I-4** was  $360^\circ$ , indicating the  $sp^2$  hybridization state of atom  $\text{C}(3)$ . Similarly, the atoms  $\text{C}(2)$  in **I-4** and  $\text{C}(17)$  in **II-5** also adopted  $sp^2$  hybridization state. The torsion angle of  $\text{C}(8)\text{-C}(7)\text{-O}(3)\text{-}$

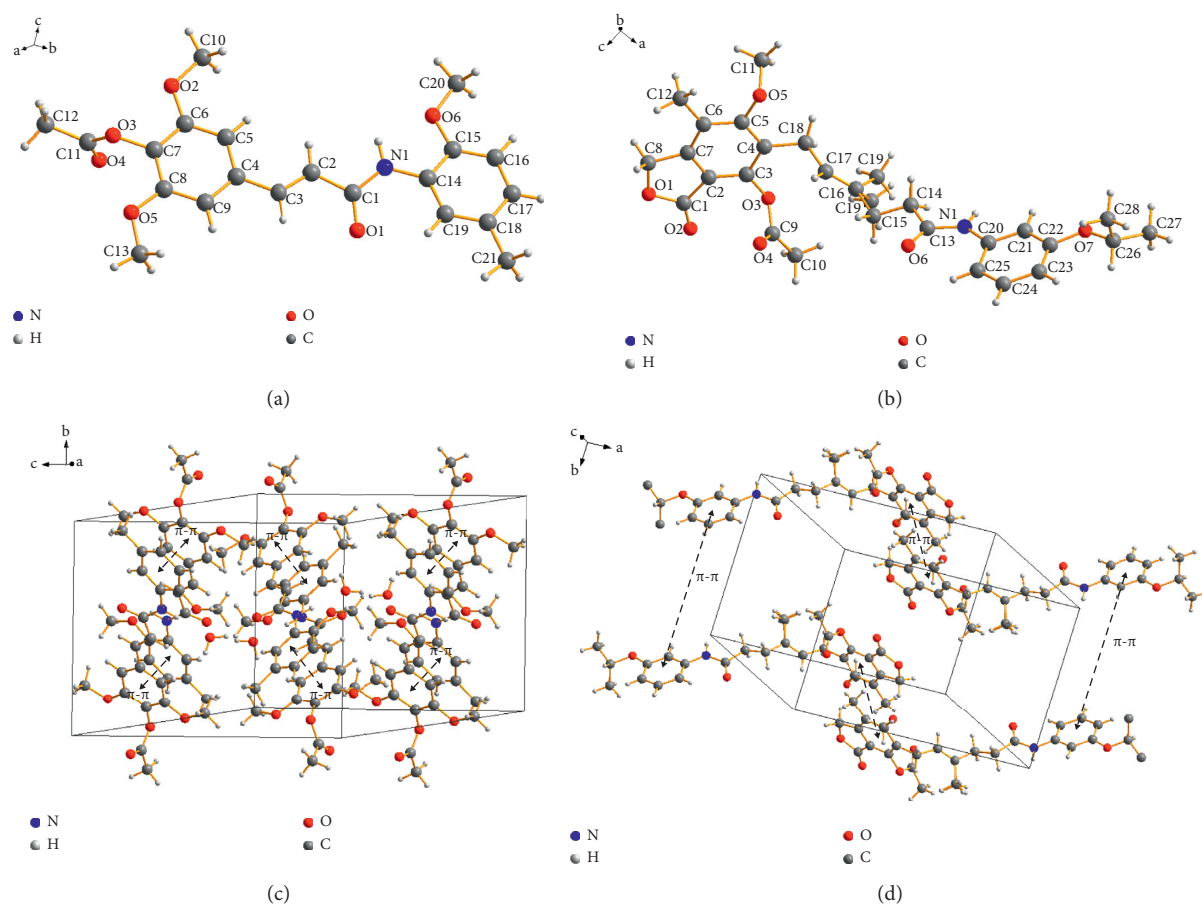


FIGURE 4: Crystal structures of I-4 (a) and II-5 (b), and crystal packing of I-4 (c) and II-5 (d).

TABLE 1: Selected bond lengths (Å) and bond angles (°) for the compounds I-4 and II-5.

Compound I-4		Compound II-5	
Bond	Dist.(Å)	Bond	Dist.(Å)
C(1) = O(1)	1.209(3)	C(1) = O(2)	1.193(4)
C(1)–N(1)	1.332(3)	C(1)–O(1)	1.339(4)
C(11) = O(4)	1.182(3)	C(3)–O(3)	1.385(4)
C(11)–O(3)	1.327(3)	C(9) = O(4)	1.175(5)
C(2) = C(3)	1.309(3)	C(9)–O(3)	1.354(4)
C(8)–O(5)	1.351(3)	C(13) = O(6)	1.200(4)
C(15)–O(6)	1.351(3)	C(13)–N(1)	1.339(4)
C(4) = C(5)	1.376(3)	C(5)–O(5)	1.367(4)
C(1)–C(2)	1.456(3)	N(1)–C(20)	1.390(4)
C(3)–C(4)	1.444(3)	C(4) = C(5)	1.394(4)
C(4) = C(9)	1.378(3)	C(22)–O(7)	1.364(3)
C(14) = C(15)	1.383(3)	C(16) = C(17)	1.285(4)
C(14) = C(19)	1.369(3)	C(17)–C(18)	1.482(4)
C(18)–C(21)	1.484 (4)	C(15)–C(16)	1.478(5)
Bond angles	(°)	Bond angles	(°)
C(1)–C(2)–C(3)	121.6(2)	O(1)–C(1)–C(2)	108.4(3)
C(2)–C(3)–C(4)	127.0(2)	O(2)–C(1)–C(2)	130.1(3)
C(4)–C(5)–C(6)	120.2(2)	C(1)–C(2)–C(7)	108.1(3)
C(14)–C(15)–C(16)	119.3(3)	C(16)–C(17)–C(18)	129.0(3)
O(3)–C(11)–O(4)	122.6(2)	C(15)–C(16)–C(17)	122.4(3)

TABLE 1: Continued.

Compound I-4		Compound II-5	
Bond	Dist.(Å)	Bond	Dist.(Å)
O(1)–C(1)–N(1)	122.9(2)	O(6)–C(13)–N(1)	123.7(3)
O(1)–C(1)–C(2)	122.1(2)	C(13)–N(1)–C(20)	129.6(3)
N(1)–C(1)–C(2)	114.9(2)	C(20)–C(21)–C(22)	120.9(3)
C(8)–O(5)–C(13)	117.7(2)	C(2)–C(3)–C(4)	120.7(3)
C(6)–O(2)–C(10)	117.7(2)	C(4)–C(18)–C(17)	114.2(3)
C(15)–O(6)–C(20)	119.2(2)	C(5)–O(5)–C(11)	115.1(3)
C(3)–C(4)–C(5)	121.7(2)	C(22)–O(7)–C(26)	120.4(3)

TABLE 2: Selected dihedral angles (°) for the compounds I-4 and II-5.

Compounds	Groups	Dihedral angles (°)
I-4	Benzene ring {C(4)–C(9)}	Benzene ring {C(14)–C(19)}
I-4	Benzene ring {C(4)–C(9)}	Ester group {C(11) = O(4)}
I-4	Benzene ring {C(4)–C(9)}	Amide group {C(1)–N(1)}
I-4	Benzene ring {C(14)–C(19)}	Ester group {C(11) = O(4)}
I-4	Benzene ring {C(14)–C(19)}	Amide group {C(1)–N(1)}
II-5	Benzene ring {C(2)–C(7)}	Benzene ring {C(20)–C(25)}
II-5	Benzene ring {C(2)–C(7)}	Ester group {C(1) = O(2)}
II-5	Benzene ring {C(2)–C(7)}	Ester group {C(9) = O(4)}
II-5	Benzene ring {C(2)–C(7)}	Amide group {C(13)–N(1)}
II-5	Benzene ring {C(20)–C(25)}	Ester group {C(1) = O(2)}
II-5	Benzene ring {C(20)–C(25)}	Ester group {C(9) = O(4)}
II-5	Benzene ring {C(20)–C(25)}	Amide group {C(13)–N(1)}

C(11) in compound **I-4** was  $-92.8(3)^\circ$ , revealing that the plane of ester group was clearly vertical with the adjacent benzene ring. In compound **II-5**, the ester group plane consisted of O(1)–C(1)–O(2) was coplanar with the adjacent benzene ring, resulting in the existing conjugation effect between these two planes. However, the ester group plane composed of O(3)–C(9)–O(4) and the adjacent benzene ring were apparently nonplanar, with a dihedral angle of  $74.830(111)^\circ$ . The dihedral angle between the two benzene rings in compound **I-4** was  $6.505(75)^\circ$ , indicating that these two benzene rings were approximately coplanar. However, the two benzene rings in compound **II-5** were nearly vertical, with a dihedral angle of  $84.911(77)^\circ$ . In addition, the amide plane was almost coplanar with the two benzene rings in compound **I-4**, with the dihedral angles of  $13.111(183)^\circ$  and  $19.106(159)^\circ$ , respectively. In compound **II-5**, the dihedral angle between the amide plane and the benzene ring consisted of C(20)–C(25) was  $12.284(189)^\circ$ , while the amide plane and the benzene ring consisted of C(2)–C(3) were obviously vertical with the dihedral angle of  $89.604(238)^\circ$ . From the crystal packing, the  $\pi$ - $\pi$  interactions occurred between the benzene rings of the adjacent molecules, which strengthen the integration of the crystal molecules (Figures 4(c) and 4(d)).

**3.3. Fungicidal Inhibitory Activity.** The in vitro inhibitory activities of the target compounds against the common agricultural pathogens were investigated, and the results are shown in Table 3. From the data, most of the target

compounds exhibited weak-to-moderate fungicidal activity against *Gibberella zeae*, *Rhizoctonia solani*, *Botrytis cinerea*, *Cercospora circumscissa* Sacc, *Alternaria kikuchiana* Tanaka, *Colletotrichum capsici*, and *Alternaria* sp. However, all compounds showed moderate-to-good fungicidal activity against *Physalospora piricola*, even better than fluopyram. For example, compounds **I-1**, **I-4**, and **I-5** exhibited higher inhibitory activity than fluopyram, with the inhibitory rates of 76.2%, 73.3%, and 73.5%, respectively. It can be concluded that the compounds **I-1–I-5** and **II-1–II-5** displayed high selectivity for the fungicidal activity against *Physalospora piricola*. In terms of the relationship between the structures and the initial inhibitory activity, the structural modification had different effects on the inhibitory activities of target compounds against the different pathogens. For example, compared with the electron-withdrawing trifluoromethyl and chlorine groups, the introduction of the electron-donating methyl, methoxy, or isopropoxy group at the benzene ring was beneficial to improving the fungicidal activity of **I-4** and **I-5** against *Physalospora piricola*. For instance, the inhibition rates of compounds **I-4** and **I-5** were 73.3% and 73.5%, respectively, which were apparently higher than those of compounds **I-2** and **I-3**. However, this structural modification had no significant effects on the inhibitory activity of the compounds **II-2–II-5** against *Physalospora piricola*. To further investigate the fungicidal activity of the target compounds against *Physalospora piricola*, the  $EC_{50}$  values were measured and the results are exhibited in Table 4. It could be found that most of the target compounds exhibited fungicidal activity equivalent to or even better than

TABLE 3: In vitro inhibitory activity of the target compounds at 50  $\mu\text{g}\cdot\text{mL}^{-1}$ .

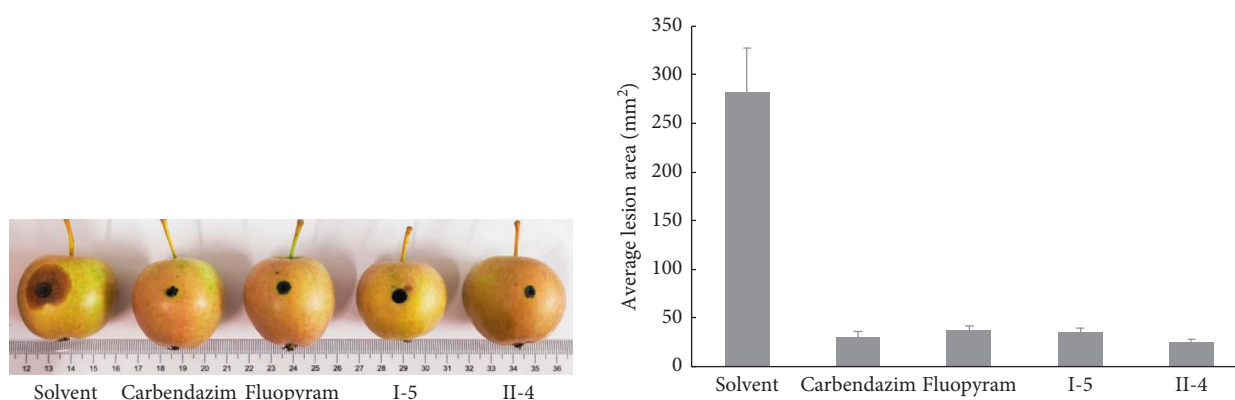
Compounds	Inhibition rate (%)							
	GZ	RS	BC	CS	PP	AK	CC	AS
I-1	12.9 ± 0.28**	7.0 ± 0.61**	24.7 ± 0.25	36.5 ± 0.59**	76.2 ± 0.66**	27.9 ± 0.34	14.5 ± 0.81**	17.2 ± 0.46**
I-2	11.8 ± 0.51**	7.4 ± 0.41**	22.2 ± 0.50	19.7 ± 0.51**	53.9 ± 0.83**	31.0 ± 0.43	1.7 ± 0.64**	12.1 ± 0.77
I-3	29.9 ± 0.32**	3.2 ± 0.30**	4.2 ± 0.55**	20.1 ± 0.81**	54.8 ± 0.79**	29.1 ± 0.67	7.5 ± 0.71**	16.2 ± 0.35**
I-4	41.7 ± 0.42**	2.7 ± 0.13**	22.2 ± 0.32	22.5 ± 0.60**	73.3 ± 0.85**	38.5 ± 0.32**	10.1 ± 0.61**	20.1 ± 0.46**
I-5	24.6 ± 0.55**	8.3 ± 0.31**	14.0 ± 0.51**	24.3 ± 0.65**	73.5 ± 0.56**	34.4 ± 0.34**	5.5 ± 0.71**	16.5 ± 0.55**
II-1	36.1 ± 0.38**	9.4 ± 0.61**	23.6 ± 0.26	17.3 ± 0.51**	45.2 ± 0.11**	31.1 ± 0.34	8.8 ± 0.59**	15.8 ± 0.46**
II-2	28.2 ± 0.57**	21.9 ± 0.52**	27.4 ± 0.25	23.0 ± 0.60**	55.9 ± 0.39**	28.5 ± 0.24	3.3 ± 0.81**	16.5 ± 0.35**
II-3	16.8 ± 0.48**	19.0 ± 0.31**	24.4 ± 0.25	19.7 ± 0.51**	55.3 ± 0.59**	25.6 ± 0.83	13.7 ± 0.71**	26.9 ± 0.54**
II-4	35.9 ± 0.38**	19.5 ± 0.57**	20.1 ± 0.51**	14.1 ± 0.40**	57.2 ± 0.39**	41.1 ± 0.67**	3.3 ± 0.30**	25.9 ± 0.58**
II-5	19.8 ± 0.30**	24.8 ± 0.44**	13.8 ± 0.76**	19.5 ± 0.56**	56.1 ± 0.43**	18.8 ± 0.49**	5.6 ± 0.38**	10.3 ± 0.47**
Fluopyram	100	56.6 ± 0.31**	100.0**	85.5 ± 0.51**	53.2 ± 0.73**	100**	60.1 ± 0.31**	100**
Carbendazim	100	100	24.6 ± 0.74	27.8 ± 0.47	100	27.1 ± 0.34	100	12.4 ± 0.49

GZ, *Gibberella zeae*; RS, *Rhizoctonia solani*; BC, *Botrytis cinerea*; CS, *Cercospora circumscissa* Sacc.; PP, *Phylospora piricola*; AK, *Alternaria kikuchiana* Tanaka; CC, *Colletotrichum capsici*; AS, *Alternaria* sp. Asterisk (\*) means significant differences among different treatments. \*, significant at the  $p < 0.05$  level, and \*\*, significant at the  $p < 0.01$  level compared with carbendazim.

TABLE 4: Medium effective concentration ( $EC_{50}$ ,  $\mu\text{g}\cdot\text{mL}^{-1}$ ) values of the target compounds against *Phylospora piricola*.

Compounds	Regression equation	Correlation coefficient ( $r$ )	$EC_{50}$ (95% confidence interval)
I-1	$y = 1.26x + 3.35$	0.9918	20.4 (17.7–23.7) **
I-2	$y = 1.00x + 3.51$	0.9903	30.7 (26.2–36.0) **
I-3	$y = 1.52x + 2.81$	0.9911	27.3 (23.5–31.7) **
I-4	$y = 1.83x + 2.33$	0.9908	28.6 (24.6–33.3) **
I-5	$y = 1.27x + 3.42$	0.9876	17.4 (14.4–21.0) **
II-1	$y = 1.78x + 1.67$	0.9824	74.2 (54.1–101.7) **
II-2	$y = 1.90x + 1.83$	0.9993	46.9 (44.8–49.2) **
II-3	$y = 1.10x + 3.44$	0.9835	25.7 (20.9–31.5) **
II-4	$y = 1.54x + 2.88$	0.9919	23.9 (20.8–27.6) **
II-5	$y = 2.46x + 1.41$	0.9823	28.8 (23.2–35.7) **
Fluopyram	$y = 1.07x + 3.42$	0.9951	30.4 (27.2–34.0) **
Carbendazim			<3.125

Asterisk (\*) means significant differences among different treatments. \*, significant at the  $p < 0.05$  level, and \*\*, significant at the  $p < 0.01$  level compared with carbendazim.

FIGURE 5: In vivo fungicidal activity of compounds I-5 and II-4 against *Phylospora piricola*-infected apples at 200  $\mu\text{g}\cdot\text{mL}^{-1}$ .

fluopyram, with the  $EC_{50}$  values of compounds I-1, I-5, and II-4 to 20.4  $\mu\text{g}\cdot\text{mL}^{-1}$ , 17.4  $\mu\text{g}\cdot\text{mL}^{-1}$ , and 23.9  $\mu\text{g}\cdot\text{mL}^{-1}$ , respectively.

Subsequently, the in vivo fungicidal activity of sinapic amide I-5 and mycophenolic amide II-4 against

*Phylospora piricola* was performed on apples at 200  $\mu\text{g}\cdot\text{mL}^{-1}$ , and the results are displayed in Figure 5. From the data, the compounds I-5 and II-4 exhibited almost the same preventative activity as carbendazim and fluopyram at 200  $\mu\text{g}\cdot\text{mL}^{-1}$ , with the inhibition rates of carbendazim,



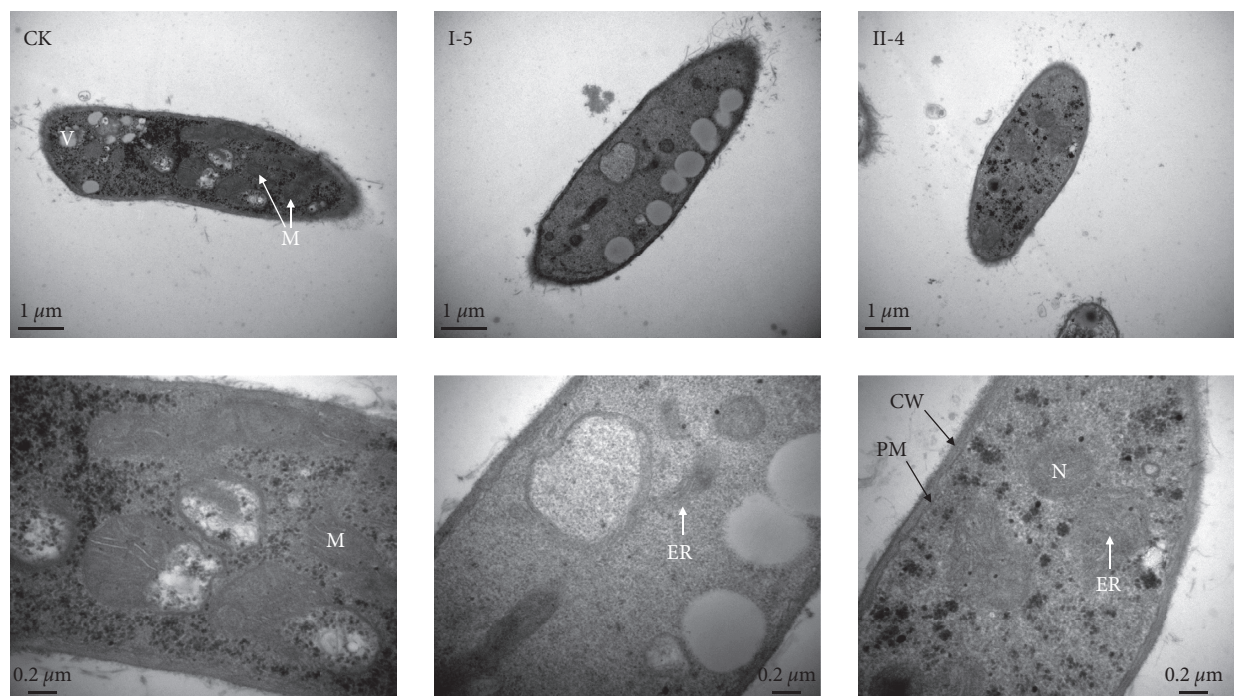


FIGURE 6: TEM investigation of *Physalospora piricola* hyphae treated with I-5 and II-4. CW: cell wall; PM: plasma membrane; N: nucleus; V: vacuole; M: mitochondria; ER: endoplasmic reticulum.

fluopyram, I-5, and II-4 to 90.8%, 86.9%, 87.6%, and 91.1%, respectively.

**3.4. TEM Observation.** To further explore the effects of molecules I-5 and II-4 on the hyphae, the ultrastructure of *Physalospora piricola* hyphae treated with distilled water, compounds I-5 and II-4 ( $200 \mu\text{g}\cdot\text{mL}^{-1}$ ), was observed on a TEM, and the results are illustrated in Figure 6. From the data, the cell wall and plasma membrane of the cell structures in the control and tested groups were normal, and mitochondria could be clearly observed in the control group. However, the mitochondria in the cell structure treated with I-5 and II-4 were blurred or even disappeared. Based on this, it could be speculated that the fungicidal activity of the target compounds against *Physalospora piricola* may be due to the influence of I-1–I-5 and II-1–II-5 on the mitochondria in the cell structure.

#### 4. Conclusion

In summary, two series of sinapic acid-derived and mycophenolic acid-derived amide derivatives were designed and synthesized. The obtained structures were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HRMS, and X-ray crystal diffraction. The in vitro and in vivo fungicidal activity screening indicated that compared with other tested pathogens, most of the target compounds exhibited excellent fungicidal activity against *Physalospora piricola*, of which the compounds I-5 and II-4 displayed almost the same preventative activity as carben-dazim and fluopyram at  $200 \mu\text{g}\cdot\text{mL}^{-1}$ . The TEM observation further revealed that the fungicidal activity of the target compounds against *Physalospora piricola* may be due to the influence on the mitochondria in the cell structure.

#### Data Availability

The data used to support the findings of this study are included within the article and the supplementary information file(s). Crystallographic data for the structures reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre under the CCDC numbers: 2095769 (compound I-4) and 2095768 (compound II-5). Copies of these data can be obtained free of charge from [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

#### Conflicts of Interest

There are no conflicts of interest to declare.

#### Acknowledgments

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#### Supplementary Materials

The supporting information contained X-ray crystal data of the compounds I-4 and II-5, and  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and

HRMS spectra of target compounds **I-1-I-5** and **II-1-II-5**.  
(*Supplementary Materials*)

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