Design, synthesis, and bioactivity of ferulic acid derivatives containing an β-amino alcohol

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Abstract

Background: Plant diseases caused by viruses and bacteria cause huge economic losses due to the lack of effective control agents. New potential pesticides can be discovered through biomimetic synthesis and structural modification of natural products. A series of ferulic acid derivatives containing an β-amino alcohol were designed and synthesized, and their biological activities were evaluated.

Result: Bioassays results showed that the EC50 values of compound D24 against Xanthomonas oryzae pv. oryzae (Xoo) was 14.5 μg/mL, which was better than that of bismethiazol (BT, EC50 = 16.2 μg/mL) and thiodiazole copper (TC, EC50 = 44.5 μg/mL). The in vivo curative and protective activities of compound D24 against Xoo were 50.5% and 50.1%, respectively. The inactivation activities of compounds D2, D3 and D4 against tobacco mosaic virus (TMV) at 500 μg/mL were 89.1, 93.7 and 89.5%, respectively, superior to ningnanmycin (93.2%) and ribavirin (73.5%). In particular, the EC50 value of compound D3 was 38.1 μg/mL, and its molecular docking results showed that compound D3 had a strong affinity for TMV-CP with a binding energy of −7.54 kcal/mol, which was superior to that of ningnanmycin (−6.88 kcal/mol).

Conclusions: The preliminary mechanism research results indicated that compound D3 may disrupt the three-dimensional structure of the TMV coat protein, making TMV particles unable to self-assemble, which may provide potential lead compounds for the discovery of novel plant antiviral agents.

Keywords: Ferulic acid derivatives, β-amino alcohol, Synthesized, Antiviral activity, Antibacterial activity

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Introduction
Plant pathogens, pests and various abiotic stresses cause serious losses to agricultural production, and are significant problems in achieving agricultural sustainability [1]. So far, more than 1000 plant viruses have been reported [2]. Plant viruses cause huge economic losses to agriculture all over the world every year, amounting to a loss of about $60 billion (USD) in global annual crop yield [2, 3]. Cucumber mosaic virus (CMV) and tobacco mosaic virus (TMV) are the most common plant viruses. TMV infects crops easily and can overwinter on a variety of plants, and few antiviral drugs can effectively control TMV infection [3, 4]. Plant pathogenic bacteria include *Xanthomonas oryzae* pv. *oryzae* (Xoo), which causes rice bacterial blight with crop yield loss of up to 50% [5, 6], and *Xanthomonas axonopodis* pv. *citri* (Xac), which causes citrus canker [7]. Extant pesticides for these diseases are ineffective, so new pesticides need to be discovered.

Natural products are a potential alternative for developing new pesticides thanks to their low toxicity to mammals, easy decomposition, environmental friendliness, and unique mode of action [8, 9]. One such product is ferulic acid (FA), the most abundant phenolic acid in the plant. It is cross-linked with polysaccharides and lignin in the structure of the cell wall. It is abundant in *Angelica sinensis*, *Cimicifuga* spp. and *Ligusticum chuanxiong*, and can be isolated from fruits, vegetables, grains, and coffee beans [2, 4, 10]. Ferulic acid, an α, β-unsaturated carboxylic acid structure, has antiviral properties [11–14]. Some phenolic plant extracts containing ferulic acid can inhibit pathogenic bacteria like *Shigella sonnei*, *Bacillus pneumoniae*, *Escherichia coli*, *Citrobacter*, and *Pseudomonas aeruginosa* [15–19]. In addition, the antioxidant effect of ferulic acid has been verified in several acute and chronic pathologies, such as intestinal ischemia, cardiovascular disease, skin disease, and diabetes [20, 21]. Ferulic acid also has anti-inflammatory [22], anti-cancer activity [23, 24], and is a free radical scavenger and an inhibitor or depolymerizer of amyloid structure [20]. Some of the active compounds containing ferulic acid scaffold are shown in Fig. 1A.

The β-amino alcohol fragment is a common substructure used as a chiral ligand or an auxiliary in asymmetric synthesis, and plays an important role in pharmaceutical chemistry, medicine and organic synthesis [25–28]. A large part of the literature on asymmetric amino hydroxylation focuses on its application in the synthesis of bioactive compounds, many β-amino alcohol derivatives have widely been concerned for their good biological activity [29, 30]. Including antiviral [31], antibacterial [32, 33], antioxidative [34], anti-inflammatory [35], anti-proliferative [36], and anti-cancer [37] properties. Some of the active compounds containing β-amino alcohol scaffold are exemplified in Fig. 1B.
In conclusion, biomimetic synthesis and structural modification of lead compounds of natural products are used to find new pesticides with strong biological activity. In the work described in this paper, ferulic acid derivatives were designed and synthesized in search of highly active compounds, providing potential lead compounds for the discovery of novel plant bactericides and antivirals. Ferulic acid was used as the lead compound, and an \( \beta \)-amino alcohol structure was created by etherifying the phenolic hydroxyl site with an appropriate pesticide molecule. This process synthesized a series of ferulic acid derivatives containing an \( \beta \)-amino alcohol (Fig. 2), and evaluated the antibacterial and antiviral activities of the target compounds.

**Materials and methods**

All reagents and solvents were purchased from commercial companies without further purification and drying. Melting points of synthetic compounds were determined using an XT-4 micro melting point instrument (Beijing Tech Instrument Co., China). All reactions were monitored by thin-layer chromatography (TLC) and identified by UV. The data for \(^1\)H, \(^13\)C and \(^19\)F NMR of title compounds were obtained with AVANCE III HD 400 MHz (Bruker Corporation, Switzerland) or JEOL-ECX 500 MHz (Japan Electronics Corporation), and used TMS as an internal standard at room temperature. High-resolution mass spectrometer (HR-MS) data was conducted using an Orbitrap LC–MS instrument (Q-Exative, Thermo Scientific™, USA).

**Experimental Chemistry**

Compounds D1–D24 can be easily obtained by reported methods [34, 38]. The synthetic preparation for the target compounds is depicted in Scheme 1. Under alkaline conditions, methyl ferulate A is substituted with epichlorohydrin B to obtain intermediate C. Then, intermediate C undergoes a ring-opening reaction with different substituted amines to obtain target compounds D1–D24.

**General procedure for the preparation of intermediate C**

Methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (A) (2.00 g, 1 mmol), anhydrous K$_2$CO$_3$ (1.59 g, 1.2 mmol) and KI (0.79 g, 0.5 mmol) were dissolved in DMF and stirred at room temperature for 2-3 h. Then to this solution was added epichlorohydrin (B) (1.07 g, 1.2 mmol) and refluxed for 5–6 h. After completion of the reaction, the resulted mixture was diluted with water and...
extracted with ethyl acetate, the organic layer was dried over by Na\(\text{SO}_4\) and concentrated under vacuum. The residue was purified by silica gel chromatography with petroleum ether/ethyl acetate (8:1), concentrated eluent to give solid intermediate C.

**General procedure for the preparation of target compounds D1–D24**

Methyl (E)-3-(3-methoxy-4-(oxiran-2-ylmethoxy)phenyl) acrylate (C) (150.00 mg, 1 mmol) and various substituted aniline (284.13 mg, 4 mmol) were dissolved in ethanol (6 mL) and refluxed for 6–8 h. Upon completion of the reaction, and an appropriate amount of water was added to the system to get white solid, the precipitate was collected by filtration. Then crude compound was subjected to column chromatography with petroleum ether/ethyl acetate (3:1) to afford target compounds D1–D24. Their structures were identified by \(^1\text{H NMR}, ^{13}\text{C NMR}, ^{19}\text{F NMR}, \text{and HR-MS.}\)

**Scheme 1** The synthetic route of the target compounds D1–D24
Methyl(E)-3-(4-(2,4-difluorophenylamino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D2)

Yield 80%; White solid; m.p. 69–71 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 15.9 Hz, 1H), 7.14–7.01 (m, 2H), 6.88 (d, J = 8.2 Hz, 1H), 6.83–6.64 (m, 3H), 6.32 (d, J = 15.9 Hz, 1H), 4.33–4.26 (m, 1H), 4.13 (ddd, J = 16.0, 9.7, 5.0 Hz, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.37 (dd, J = 19.2, 12.8, 5.5 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 154.5 (dd, J = 21.6, 8.3 Hz), 110.1, 103.5 (dd, J = 26.6, 22.8 Hz), 72.0, 68.4, 55.7, 51.7, 46.6. ¹⁹F NMR (376 MHz, CDCl₃) δ −125.26, −131.24. HRMS (ESI⁺) m/z Calcd for C₂₁H₂₂F₂NO₅ [M+H]⁺ 358.16490; Found 358.16492.

Methyl(E)-3-(4-(3-(2-chloro-4-fluorophenylamino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D3)

Yield 83%; White solid; m.p. 71–73 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 16.0 Hz, 1H), 7.14–7.03 (m, 3H), 6.93–6.84 (m, 2H), 6.66 (dd, J = 9.0, 5.0 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 4.30 (dq, J = 6.6, 4.4 Hz, 1H), 4.13 (qd, J = 9.7, 5.1 Hz, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.38 (ddd, J = 19.6, 12.8, 5.7 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 154.6 (dd, J = 238.1, 11.1 Hz), 151.2 (dd, J = 242.3, 11.7 Hz), 149.9, 149.6, 144.5, 133.1 (dd, J = 11.7, 2.9 Hz), 128.3, 122.3, 116.0, 113.6, 112.5 (dd, J = 8.8, 4.4 Hz), 110.6 (dd, J = 21.6, 3.8 Hz), 110.1, 103.5 (dd, J = 26.6, 22.8 Hz), 72.0, 68.4, 55.7, 51.7, 46.6. ¹⁹F NMR (376 MHz, CDCl₃) δ −125.26, −131.24. HRMS (ESI⁺) m/z Calcd for C₂₁H₂₂F₂NO₅ [M+H]⁺ 358.16490; Found 358.16492.

Methyl(E)-3-(4-(3-((5-fluoro-2-methylphenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D4)

Yield 60%; White solid; m.p. 104–105 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 16.0 Hz, 1H), 7.11–7.04 (m, 2H), 6.96 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.39–6.30 (m, 3H), 4.32 (ddd, J = 10.3, 6.5, 4.0 Hz, 1H), 4.13 (ddd, J = 16.1, 9.7, 5.1 Hz, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.36 (ddd, J = 19.6, 12.8, 5.6 Hz, 2H), 2.10 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 162.7 (d, J = 240.3 Hz), 149.9, 149.7, 147.3 (d, J = 10.4 Hz), 144.5, 130.6 (d, J = 9.8 Hz), 128.4, 122.3, 117.9 (d, J = 2.7 Hz), 116.0, 113.8, 110.1, 103.1 (d, J = 21.1 Hz), 97.5 (d, J = 26.2 Hz), 72.0, 68.3, 55.7, 51.7, 46.2, 16.8. ¹⁹F NMR (376 MHz, CDCl₃) δ −115.66. HRMS (ESI⁺) m/z Calcd for C₂₁H₂₂FNO₅ [M+H⁺]⁺ 390.17113; Found 390.17099.
**Methyl(E)-3-(4-(2-hydroxy-3-((2,4,5-trifluorophenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D8)**

Yield 87%; White solid; m.p. 112–114 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J$ = 15.9 Hz, 1H), 7.11–7.03 (m, 2H), 6.92–6.82 (m, 2H), 6.58 (dt, $J$ = 12.2, 7.9 Hz, 1H), 6.33 (d, $J$ = 15.9 Hz, 1H), 4.37 (s, 1H, OH), 4.27 (d, $J$ = 4.1 Hz, 1H), 4.12 (dd, $J$ = 15.7, 9.6, 5.0 Hz, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.45–3.23 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.7, 149.8, 149.6, 147.0 (dd, $J$ = 15.4, 13.0, 3.2 Hz), 146.3 (dd, $J$ = 12.6, 10.0, 7.56 Hz), 144.6, 140.8 (dd, $J$ = 26.0, 13.9, 11.4 Hz), 134.5, 128.5, 122.4, 116.1, 113.6, 110.2, 104.8 (t, $J$ = 23.3 Hz), 100.8 (dd, $J$ = 23.6, 4.0 Hz), 71.7, 68.4, 55.6, 51.7, 46.5. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –137.98, –142.42, –139.85. HRMS (ESI+ m/z Calcd for C$_{20}$H$_{19}$F$_6$NO$_5$K [M+K]$^+$ 450.09252; Found 450.09174.

**Methyl(E)-3-(4-((3-bromo-3-fluorophenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D9)**

Yield 75%; Yellow solid; m.p. 125–127 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J$ = 15.9 Hz, 1H), 7.22 (d, $J$ = 8.3 Hz, 1H), 7.10–7.01 (m, 2H), 6.85 (d, $J$ = 8.3 Hz, 1H), 6.41 (dd, $J$ = 11.1, 2.6 Hz, 1H), 6.34–6.32 (m, 2H), 4.24 (dd, $J$ = 10.3, 6.2, 4.3 Hz, 1H), 4.15–4.03 (m, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.41–3.19 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.5, 159.9 (d, $J$ = 244.1 Hz), 149.8, 149.7, 149.3 (d, $J$ = 9.8 Hz), 144.5, 133.4, 128.5, 122.5, 116.2, 113.7, 110.5 (d, $J$ = 1.8 Hz), 110.2, 100.9 (d, $J$ = 26.2 Hz), 95.2 (d, $J$ = 21.1 Hz), 72.1, 68.3, 55.9, 51.8, 46.4. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –107.03. HRMS (ESI+ m/z Calcd for C$_{20}$H$_{20}$F$_3$NO$_5$K [M+K]$^+$ 450.09252; Found 450.09174.

**Methyl(E)-3-((4-(2-hydroxy-3-((4-methyl-3-fluorophenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D10)**

Yield 95%; Purple solid; m.p. 64–66 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J$ = 15.9 Hz, 1H), 7.11–7.04 (m, 2H), 6.89 (d, $J$ = 8.3 Hz, 1H), 6.72–6.67 (m, 2H), 6.61 (d, $J$ = 8.5 Hz, 1H), 6.32 (d, $J$ = 15.9 Hz, 1H), 4.32 (ddd, $J$ = 10.6, 6.8, 4.1 Hz, 1H), 4.13 (dd, $J$ = 16.2, 9.7, 5.1 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.34 (ddd, $J$ = 19.3, 12.6, 5.6 Hz, 2H), 2.17 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.6, 152.1, 150.0, 149.6, 144.6, 140.1, 128.2, 124.9, 122.4, 116.9, 115.9, 113.5, 111.6, 111.5, 110.1, 72.2, 68.4, 55.8, 55.7, 51.6, 47.3, 17.7. HRMS (ESI+ m/z Calcd for C$_{22}$H$_{25}$FNO$_5$ [M+H]$^+$ 426.15228; Found 426.15213.

**Methyl(E)-3-((4-(3-((3-fluorophenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D11)**

Yield 93%; White solid; m.p. 107–109 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J$ = 16.0 Hz, 1H), 7.15–7.02 (m, 2H), 6.87 (d, $J$ = 8.2 Hz, 1H), 6.33 (d, $J$ = 15.9 Hz, 1H), 6.20–6.10 (m, 3H), 4.59 (s, 1H, OH), 4.33–4.22 (m, 1H), 4.10 (ddd, $J$ = 15.8, 9.6, 4.9 Hz, 2H), 3.90 (s, 3H), 3.80 (m, 1H), 7.11 (d, $J$ = 2.2 Hz, 1H), 7.09 (d, $J$ = 1.4 Hz, 1H), 7.07 (d, $J$ = 1.7 Hz, 1H), 6.90 (d, $J$ = 5.1 Hz, 1H), 6.89–6.85 (m, 1H), 6.34 (d, $J$ = 15.9 Hz, 1H), 4.33–4.27 (m, 1H), 4.22–4.08 (m, 2H), 3.93 (s, 3H), 3.81 (s, 3H), 3.46 (dd, $J$ = 12.5, 4.3 Hz, 1H), 3.31 (dd, $J$ = 12.5, 6.2 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.5, 149.7, 149.6, 148.2 (d, $J$ = 254.9 Hz), 148.2 (d, $J$ = 23.3 Hz), 137.4, 128.7, 122.3, 119.9 (d, $J$ = 7.1 Hz), 118.9 (d, $J$ = 22.3 Hz), 116.2, 113.8, 110.2, 108.0 (d, $J$ = 3.1 Hz), 72.2, 68.1, 55.8, 51.7, 46.7. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –132.70. HRMS (ESI+ m/z Calcd for C$_{20}$H$_{20}$F$_3$NO$_5$K [M+K]$^+$ 421.14056; Found 421.14011.
Yield 82%; White solid; m.p. 77–78 °C. 1H NMR (400 MHz, CDCl3) δ 7.63 (d, J = 16.0 Hz, 1H), 7.12–6.98 (m, 3H), 6.88 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 4.80 (s, 3H), 3.97 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 3.57 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.28 (s, 3H), 3.20 (s, 3H), 3.13 (s, 3H), 3.05 (s, 3H), 2.97 (s, 3H), 2.89 (s, 3H), 2.80 (s, 3H), 2.72 (s, 3H), 2.64 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.84 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.72 (s, 3H), 0.64 (s, 3H), 0.56 (s, 3H), 0.48 (s, 3H), 0.40 (s, 3H), 0.32 (s, 3H), 0.24 (s, 3H), 0.16 (s, 3H), 0.08 (s, 3H), 0.00 (s, 3H). HRMS (ESI+) m/z Calcd for C23H30BrNO5 [M+H]^+ 502.0512; Found 502.05151.

Yield 92%; Pink solid; m.p. 77–78 °C. 1H NMR (400 MHz, CDCl3) δ 7.63 (d, J = 16.0 Hz, 1H), 7.12–6.98 (m, 3H), 6.88 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 4.80 (s, 3H), 3.97 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 3.57 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.28 (s, 3H), 3.20 (s, 3H), 3.13 (s, 3H), 3.05 (s, 3H), 2.97 (s, 3H), 2.89 (s, 3H), 2.80 (s, 3H), 2.72 (s, 3H), 2.64 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.84 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.72 (s, 3H), 0.64 (s, 3H), 0.56 (s, 3H), 0.48 (s, 3H), 0.40 (s, 3H), 0.32 (s, 3H), 0.24 (s, 3H), 0.16 (s, 3H), 0.08 (s, 3H), 0.00 (s, 3H). HRMS (ESI+) m/z Calcd for C23H30BrNO5 [M+H]^+ 502.0512; Found 502.0515.
Yield 93%; White solid; m.p. 123–125 °C. 1H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 16.0 Hz, 1H), 7.12–7.04 (m, 2H), 6.93 (dd, J = 30.9, 16.0, 8.6 Hz, 2H), 6.46 (ddd, J = 12.7, 6.7, 2.8 Hz, 1H), 6.38–6.27 (m, 2H), 4.30–4.22 (m, 1H), 4.11 (dd, J = 15.9, 9.6, 5.0 Hz, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.30 (ddd, J = 19.1, 12.7, 5.4 Hz, 2H). 13C NMR (100 MHz, CDCl₃) δ 167.6, 149.9, 149.6, 144.6, 144.5, 134.6, 128.4, 127.1, 122.4, 120.4, 118.5, 116.0, 113.7, 110.1, 108.5, 72.1, 68.3, 55.8, 51.7, 46.5, 13.5. HRMS (ESI+) m/z Calcd for C₂₃H₂₆ClNO₅Na [M+Na]⁺ 428.12352; Found 428.12292.

Methyl(E)-3-(4-(3,4-difluorophenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D22)

Methyl(E)-3-(4-(3-((3-chloro-4-fluorophenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D23)

Methyl(E)-3-(4-(3-((4-chloro-2-methylphenyl)amino)-2-hydroxypropoxy)-3-methoxyphenyl)acrylate (D24)

Yield 81%; White solid; m.p. 99–101 °C. 1H NMR (400 MHz, CDCl₃) δ 7.62 (d, J = 15.9 Hz, 1H), 7.13–6.98 (m, 4H), 6.87 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 4.31 (ddd, J = 10.7, 6.7, 4.2 Hz, 1H), 4.11 (dd, J = 16.1, 9.7, 5.1 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.35 (ddd, J = 19.5, 12.7, 5.6 Hz, 2H), 2.12 (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 167.6, 149.9, 149.6, 144.6, 144.5, 129.8, 128.3, 126.6, 124.4, 122.4, 122.0, 116.0, 113.6, 111.1, 110.2, 72.0, 68.3, 55.8, 51.7, 46.5, 17.3. HRMS (ESI+) m/z Calcd for C₂₁H₂₁F₂N₂O₅Na [M+Na]⁺ 416.12800; Found 416.12744.

In vivo antibacterial activity test

The curative and protective activities in potted plants of compound D24 against rice bacterial leaf blight were determined by Schaad's method [40, 41]. Dimethyl sulfoxide (DMSO) was used as a negative control, and the commercial bactericides thiodiazole copper (TC) and bismethiozol (BT) were used as positive controls. Add 4 mL nutrient broth (NB) medium, 1 mL test compound or commercial bactericides (the final concentration of the solution is 100 and 50 µg/mL), and 40 µL Xoo or Xac bacterial solution into the 15 mL test tube. Test the EC₅₀ value of the target compounds when the concentration was 100, 50, 25, 12.5, 6.25 µg/mL, respectively. Then incubated the above sample solution in a shaker (180 rpm, 28 ± 1 °C) for about 24–48 h, until the negative control grew to the logarithmic phase. Measure the optical density at 595 nm (OD₅₉₅) with a microplate reader (turbidity correction value = ODValue of medium containing bacteria − ODMedium value without bacteria), and the calculation formula for the inhibition rate I was: \( I = (C − T)/C \times 100\% \). C represented the corrected absorbance value of the untreated NB medium, and T represented the corrected absorbance value of the treated NB medium. Each experiment was tested for three times.
after spraying, the rice leaves were inoculated with *Xoo* that had grown to the logarithmic growth stage. Then they were placed in a plant growth room (28 °C and 90% RH) for 14 days to determine the disease index of rice leaves. The control efficiency of compound D24’s curative and protective activities $I(\%) = (1 - T/C) \times 100\%$, where $C$ was the disease index of the negative control group, and $T$ was the disease index of the treatment group.

### In vitro antibacterial activity of the target compounds against *Xoo* and *Xac*

| Compd | **Xoo** Inhibition rate (%) | **Xac** Inhibition rate (%) |
|-------|-----------------------------|-----------------------------|
|       | 100 μg/mL | 50 μg/mL | 100 μg/mL | 50 μg/mL |
| D1    | 26.5±1.9 | 21.8±1.2 | 47.4±1.9 | 32.1±1.8 |
| D2    | 35.6±2.1 | 31.8±3.8 | 55.3±0.5 | 45.9±3.3 |
| D3    | 77.8±2.8 | 66.4±2.7 | 68.2±2.7 | 48.7±1.9 |
| D4    | 28.2±2.7 | 28.0±1.1 | 25.2±0.2 | 15.7±2.6 |
| D5    | 72.0±1.3 | 55.0±1.2 | 22.5±3.7 | 21.4±0.9 |
| D6    | 35.2±0.9 | 17.1±3.0 | 29.7±4.5 | 22.4±4.7 |
| D7    | 66.5±1.8 | 47.9±1.0 | 74.5±2.3 | 60.0±2.5 |
| D8    | 25.3±1.8 | 19.9±2.2 | 31.9±3.5 | 27.8±2.6 |
| D9    | 47.4±1.3 | 32.8±2.9 | 36.2±2.2 | 12.0±4.8 |
| D10   | 26.8±3.6 | 23.6±2.7 | 33.1±2.6 | 29.9±0.1 |
| D11   | 33.0±1.2 | 32.4±1.6 | 68.5±3.5 | 45.3±1.8 |
| D12   | 22.7±1.8 | 22.6±3.7 | 33.5±1.0 | 33.0±0.7 |
| D13   | 34.5±2.4 | 26.8±1.3 | 28.6±1.9 | 15.4±3.1 |
| D14   | 36.7±4.4 | 22.9±1.1 | 26.7±4.0 | 12.6±3.3 |
| D15   | 43.4±2.9 | 26.4±1.0 | 57.9±3.2 | 45.9±1.9 |
| D16   | 42.2±0.6 | 26.4±3.1 | 31.1±3.9 | 19.8±4.2 |
| D17   | 20.6±1.8 | 8.7±2.8 | 28.2±3.8 | 12.8±2.6 |
| D18   | 32.9±2.1 | 30.0±0.8 | 27.7±4.1 | 263.2±24 |
| D19   | 24.9±3.5 | 19.8±2.0 | 25.1±1.3 | 14.2±4.3 |
| D20   | 34.2±0.6 | 5.2±2.2 | 344.1±6 | 209.0±1.1 |
| D21   | 38.6±2.6 | 37.7±1.8 | 260.0±3.0 | 21.6±3.0 |
| D22   | 89.1±3.7 | 68.0±1.1 | 28.6±1.3 | 126.5±3.5 |
| D23   | 79.9±10.0 | 63.6±3.6 | 285.7±2.2 | 23.1±3.5 |
| D24   | 90.7±0.8 | 80.5±2.7 | 259.1±5 | 21.7±3.7 |
| BT†   | 90.1±2.3 | 80.2±1.3 | 64.6±1.9 | 51.2±1.4 |
| TC†   | 65.7±0.9 | 46.9±2.6 | 76.8±0.7 | 65.2±2.0 |

Average of three replicates

† The commercial agricultural antibacterial agents bismethiazol (BT) and thiodiazole copper (TC) were used as positive control

### Results and discussion

#### Antibacterial activity in vitro screening of target compounds

On the basis of previous work, the antibacterial activity of the target compounds was tested by turbidity method [15, 16, 39]. The preliminary results of the in vitro antibacterial activities of target compounds D1–D24 against *Xoo* and *Xac* are shown in Table 1. Some compounds showed moderate antibacterial activity. Compound D24 showed good inhibitory activity against *Xoo* (90.7% and 80.6% at concentrations of 100 and 50 μg/mL, respectively), similar to BT (90.1% and 80.2%, respectively). The antibacterial activity of compounds D3, D5, D7, D22, and D23 against *Xoo* was higher than that of TC (65.7% and 46.9% at concentrations of 100 and 50 μg/mL, respectively). Compounds D2, D3, D7, D11, and D15 had moderate antibacterial activity against *Xac* at 100 μg/mL, with the inhibitory activity of compounds D3, D7 and D11 slightly higher than that of BT (which was 64.6%). To further quantify the antibacterial activity, the concentration values for 50% of maximal effect (EC50) were determined for select compounds (Table 2). The EC50 values of compounds D22 and D24 on *Xoo* were 14.5 and 16.2 μg/mL, respectively, which were better than that of TC (44.5 μg/mL) and similar to that of BT (16.2 μg/mL). Compounds D3, D7 and D11 had inhibitory effects on *Xac*, and their EC50 values (37.3, 29.4 and 45.6 μg/mL, respectively) were slightly better than the EC50 of BT (46.8 μg/mL).
Table 2 Antibacterial activities of some target compounds against Xoo and Xac in vitro

| Compd | Xoo | Xac |
|-------|-----|-----|
|       | Regression equation | R² | EC₅₀ (µg/mL) | Regression equation | R² | EC₅₀ (µg/mL) |
| D1    | y = 0.84x + 3.9 | 0.99 | 20.3 ± 0.9 | y = 0.54x + 3.8 | 0.94 | 122.9 ± 4.9 |
| D2    | y = 0.87x + 3.7 | 0.93 | 27.1 ± 2.5 | y = 0.78x + 3.5 | 0.97 | 74.2 ± 3.9 |
| D3    | y = 1.16x + 3.0 | 0.98 | 45.4 ± 1.3 | y = 0.92x + 3.5 | 0.96 | 37.3 ± 1.4 |
| D5    | y = 1.33x + 3.3 | 0.95 | 16.2 ± 1.5 | y = 1.13x + 3.3 | 0.99 | 29.4 ± 4.1 |
| D7    | y = 1.62x + 3.0 | 0.98 | 16.2 ± 3.4 | y = 0.83x + 3.6 | 0.95 | 46.8 ± 5.0 |
| D11   | y = 0.93x + 3.4 | 0.97 | 44.5 ± 3.4 | y = 1.04x + 3.5 | 0.95 | 23.8 ± 4.9 |
| D15   |               |     |              |               |     |              |
| D22   |               |     |              |               |     |              |
| D23   |               |     |              |               |     |              |
| D24   |               |     |              |               |     |              |
| BT    |               |     |              |               |     |              |
| TC    |               |     |              |               |     |              |

Average of three replicates
* The commercial agricultural antibacterial agents bismuthiazol (BT) and thiodiazole copper (TC) were used as positive control agents

Table 3 The protective activity of compound D24 against Xanthomonas oryzae pv. oryzae in vivo at 200 µg/mL

| Treatment | 14 days after spraying |
|-----------|------------------------|
|           | Morbidity (%) | Disease Index (%) | Control efficiency (%) |
| D24       | 100          | 42.2D         | 50.1A                 |
| BTb       | 100          | 45.8C         | 45.8B                 |
| TCb       | 100          | 47.6B         | 43.7C                 |
| CKc       | 100          | 84.6A         |                       |

* Statistical analysis was conducted by the analysis of variance method under the conditions of equal variances assumed (P > 0.05) and equal variances not assumed (P < 0.05). Different uppercase letters indicate the values of protection activity with significant difference among different treatment groups at P < 0.05

* Commercial bactericides bismuthiazol (BT) and thiodiazole copper (TC) were used as positive control agents

Table 4 The curative activity of compound D24 against Xanthomonas oryzae pv. oryzae in vivo at 200 µg/mL

| Treatment | 14 days after spraying |
|-----------|------------------------|
|           | Morbidity (%) | Disease Index (%) | Control efficiency (%) |
| D24       | 100          | 42.8C         | 50.5A                 |
| BTb       | 100          | 45.8B         | 47.1B                 |
| TCb       | 100          | 46.6B         | 46.1C                 |
| CKc       | 100          | 86.7A         |                       |

* Statistical analysis was conducted by the analysis of variance method under the conditions of equal variances assumed (P > 0.05) and equal variances not assumed (P < 0.05). Different uppercase letters indicate the values of protection activity with significant difference among different treatment groups at P < 0.05

* Commercial bactericides bismuthiazol (BT) and thiodiazole copper (TC) were used as positive control agents

* Negative control

Antibacterial activity in vivo
Based on its promising antibacterial activity in vitro, the in vivo activity of compound D24 against rice bacterial leaf blight at 200 µg/mL was determined, and the results are shown in Tables 3 and 4, and Fig. 3. The protective activity of D24 was 50.1%, higher than that of BT (45.8%) and TC (43.7%). Compound D24 also had good curative activity (50.5%), superior to that of BT (47.1%) and TC (46.1%).

Anti-TMV activity in vivo screening of target compounds
The inhibitory effect of ferulic acid derivatives D1–D24 on TMV was further studied based on the method of literature and the previous work of antiviral activity test [1, 12, 42]. The bioassay results indicated that most of the compounds exhibited moderate to good anti-TMV activity at 500 µg/mL, as shown in Table 5. The curative activities of compounds D1, D5, D12, D13, D18, D21, and D24 were 56.1, 59.3, 59.8, 53.9, 45.5, 74.0, and 74.1%, respectively, which were better than that of ribavirin (44.8%). Compounds D21 and D24 (74.0 and 74.1%, respectively) showed slightly higher curative activity than ningnanmycin (70.0%). Compounds D3, D4, D5, D7, D9, D14, D18, D20, and D24 exhibited good protective activity (respectively 54.6, 52.6, 59.6, 53.1, 70.7, 74.3, 68.1, 51.9, and 54.9%), higher than ribavirin (50.0%). Compounds D9, D14 and D18 (70.7, 74.3 and 68.1%, respectively) showed better activity...
than ningnanmycin (65.3%). Most of the compounds showed excellent inactivation activity against TMV compared to ribavirin (73.5%). Notably, compound D3 (93.7%) was slightly better than ningnanmycin (93.2%). The EC$_{50}$ values of the inactivation activity of some compounds were tested, and the results are shown in Table 6. In particular, the EC$_{50}$ value of compound D3 was 38.1 μg/mL, which was higher than that of ningnanmycin (EC$_{50}$ = 39.2 μg/mL).

**Autodocking and MD simulation**

Based on previous work [43, 44], the interaction between the active target compounds and TMV coat protein (TMV-CP) (PDB 97 code: 1E17) was investigated. The binding mode of compound D3 and TMV-CP was studied by molecular docking, and the results are shown in Fig. 4. Compound D3 has a strong affinity for TMV-CP with a binding energy of $-7.54$ kcal/mol, which is better than that of ningnanmycin ($-6.88$ kcal/mol). Binding to the active site of TMV-CP was achieved through amino acid residues that play a key role in the self-assembly of TMV-CP, including GLY137, ASN73, THR136, VAL75, SER143 and VAL260 (Fig. 4A and B). Among them, there is a strong hydrogen bond interaction between compound D3 and key residues (GLY137 and ASN73), the bond lengths of which are 3.1 Å and 2.9 Å, respectively, and GLY137 also interacts with ningnanmycin. The carbon atoms of compound D3 and ningnanmycin interact with THR136 and VAL75 residues through hydrophobic bonds, and a halogen bond is formed between D3 and SER143. Therefore, compound D3 may be the same as ningnanmycin, disrupting the three-dimensional structure of TMV-CP, making TMV particles unable to self-assemble, thereby achieving antiviral effects.

Molecular dynamics (MD) simulations were used to evaluate the stability of compound D3 and ningnanmycin. Under simulated conditions, the root-mean-square deviation (RMSD) of the atom from its initial position was measured and recorded (Fig. 4C and D). The interaction of other binding site residues affects the energy and geometric characteristics, so that the ligand obtains a stable conformation at the active site.
**Table 5** Antiviral activities of target compounds against TMV in vivo at 500 μg/mL

| Compd | Curative activity (%) | Protective activity (%) | Inactivation activity (%) |
|-------|-----------------------|-------------------------|---------------------------|
| D1    | 56.1±0.8              | 49.9±3.9                | 76.9±1.4                  |
| D2    | 31.8±4.8              | 41.8±3.5                | 89.1±3.8                  |
| D3    | 37.5±0.8              | 54.6±2.5                | 93.7±1.9                  |
| D4    | 38.8±4.5              | 52.6±4.5                | 89.5±1.5                  |
| D5    | 59.3±0.7              | 59.6±4.9                | 72.9±2.7                  |
| D6    | 25.1±2.7              | 35.1±0.1                | 73.0±1.7                  |
| D7    | 31.8±0.7              | 53.1±0.5                | 74.2±2.8                  |
| D8    | 40.9±2.7              | 47.2±0.8                | 85.2±3.1                  |
| D9    | 31.5±3.6              | 70.7±5.0                | 84.9±1.9                  |
| D10   | 38.4±3.3              | 31.4±1.1                | 84.3±4.9                  |
| D11   | 35.4±1.0              | 34.2±0.1                | 74.1±2.0                  |
| D12   | 598±13                | 399±1.1                 | 612±0.3                   |
| D13   | 53.9±4.7              | 398±4.9                 | 714±0.4                   |
| D14   | 218±4.5               | 743±3.7                 | 812±2.5                   |
| D15   | 323±4.5               | 350±2.4                 | 827±3.3                   |
| D16   | 22.5±4.8              | 190±3.7                 | 849±3.4                   |
| D17   | 33.6±2.5              | 439±2.2                 | 825±3.6                   |
| D18   | 45.5±3.2              | 681±3.3                 | 841±4.5                   |
| D19   | 346±2.1               | 437±3.6                 | 856±4.2                   |
| D20   | 42.8±0.1              | 519±1.6                 | 818±0.7                   |
| D21   | 740±4.0               | 415±2.1                 | 601±0.1                   |
| D22   | 202±1.7               | 436±2.5                 | 668±0.7                   |
| D23   | 402±3.6               | 549±2.7                 | 745±1.5                   |
| D24   | 741±1.9               | 474±2.6                 | 742±0.8                   |
| Ribavirin | 448±1.2            | 500±1.8                 | 735±1.6                   |
| Ningnanmycin | 700±3.8            | 653±2.5                 | 932±0.5                   |

a All active values are the average of three duplicates.

**Table 6** EC<sub>50</sub> of some target compounds anti-TMV activity

| Compd   | Regression equation | R² | EC<sub>50</sub> of inactivation activity<sup>a</sup> |
|---------|---------------------|----|---------------------------------|
| D2      | y = 1.33x + 2.6    | 0.99 | 56.8 ± 4.4                   |
| D3      | y = 1.26x + 3.0    | 0.96 | 38.1 ± 1.4                   |
| D4      | y = 1.29x + 2.7    | 0.98 | 52.5 ± 4.4                   |
| D8      | y = 1.15x + 2.9    | 0.99 | 57.3 ± 2.9                   |
| D19     | y = 1.12x + 3.0    | 0.99 | 57.9 ± 4.0                   |
| Ningnanmycin<sup>b</sup> | y = 1.37x + 2.8 | 0.99 | 39.2 ± 3.8                   |

<sup>a</sup> All active values are the average of three replicates.
<sup>b</sup> Ningnanmycin was used as the control.

**Structure–activity relationship analysis**

The preliminary structure–activity relationship (SAR) indicated that different substituents of ferulic acid compounds had a strong influence on their activity against Xoo, Xac and TMV. According to Table 1, the position and number of substituted fluorine atoms on the aromatic ring had a significant effect on the inhibition of Xoo. When the substituents are two fluorine atoms at the same time, the activity of the compounds towards Xoo is different: D22 (R = 3,4-di-F-Ph) > D14 (R = 3,5-di-F-Ph) > D2 (R = 2,4-di-F-Ph). The introduction of chlorine atoms to the electron-withdrawing group improved the activity of the compound: D24 (R = 3-Cl-4-F-Ph) and D3 (R = 2-Cl-4-F-Ph) > D13 (R = 3-CH₂-4-F-Ph) and D1 (R = 2-CH₂-4-F-Ph). Compounds with weak electron-withdrawing effects at the same position had higher activity: D23 (R = 4-Cl-2-CH₃-Ph), D18 (R = 4-Br-2-CH₃-Ph) > D1 (R = 4-F-2-CH₃-Ph). The introduction of substituents on the benzene ring helps to improve the antibacterial activity against Xac: D7 (R = 4-Cl-3-F-Ph) > D11 (R = 3-NO₂-4-F-Ph) > D3 (R = 2-CH₂-5-F-Ph) > D15 (R = 5-CH₂-2-F-Ph) > D2 (R = 2,4-di-F-Ph) > D1 (R = 2-CH₂-4-F-Ph) > D5 (R = Ph).

Different halogens and positions influenced the activity of the compound: D7 (R = 4-Cl-3-F-Ph) > D9 (R = 4-Br-3-F-Ph), D3 (R = 2-Cl-4-F-Ph) > D24 (R = 3-Cl-4-F-Ph).

According to Table 5, increasing the number of fluorine atoms increased the curative activity against TMV, particularly in the case of 2,4 substituted difluoride: D8 (R = 2,4,5-tri-F-Ph) > D2 (R = 2,4-di-F-Ph) > D14 (R = 3,5-di-F-Ph), D22 (R = 3,4-di-F-Ph). The electron-withdrawing at the same position is more active than the electron-donating, and the compound with a strong electron-withdrawing effect were more active: D1 (R = 4-F-2-CH₃-Ph) > D18 (R = 4-Br-2-CH₃-Ph), D23 (R = 4-Cl-2-CH₃-Ph) > D10 (R = 4-CH₃-2-CH₃-Ph). The protective activity sequence of compounds with two electron-withdrawing substituents on the benzene ring was as follows: D14 (R = 3,5-di-F-Ph) > D9 (R = 4-Br-3-F-Ph) > D3 (R = 2-Cl-4-F-Ph) > D7 (R = 4-Cl-3-F-Ph) > D20 (R = 4-I-2-F-Ph) > D24 (R = 3-Cl-4-F-Ph) > D22 (R = 3,4-di-F-Ph) > D2 (R = 2,4-di-F-Ph) > D6 (R = 4-F-3-CF₃-Ph) > D11 (R = 3-NO₂-4-F-Ph).

The electron-donating group on the benzene ring can improve the inactivation activity of the compound: D19 (R = 3,4-di-OCH₃-2-Ph) > D10 (R = 4-OCH₃-2-CH₃-Ph) > D17 (R = 4-CH(CH₃)₂-Ph) > D5 (R = Ph). The same halogen introduced at different positions had different activities: D4 (R = 5-F-2-CH₃-Ph) > D1 (R = 4-F-2-CH₃-Ph), D23 (R = 4-Cl-2-CH₃-Ph) > D21 (R = 3-Cl-2-CH₃-Ph). In general, the R substituents of the compounds resulting in better anti-TMV activity or inhibition of Xoo and Xac frequently contained fluorne atoms. The introduction of fluorine atoms into compounds is known to effectively alter conformation, membrane permeability, lipophilicity, metabolic pathways, and pharmacokinetic properties, and can improve biological activity in many
cases [45, 46]. However, it is also affected by other factors such as the position of the substituent and the influence of other substituents on the fluorine atom, which leads to changes in the activity of the compound.

**Conclusion**

In summary, a series of ferulic acid derivatives containing a β-amino alcohol were designed and synthesized, and the biological activities of the target compounds were evaluated. Bioassays results showed that compound D24 had a good inhibitory effect on Xoo, which was superior to the commercial bactericide BT and TC. The inhibitory effect of compound D7 on Xac was also higher than BT and close to TC. As compound D3 (EC₅₀ = 39.2 μg/mL) had good passivating activity against TMV, the interaction of the ligand molecules with TMV-CP was explored by molecular docking and molecular dynamics simulations. The results of molecular docking indicated that compound D3 was inserted into the active site of TMV-CP through amino acid residues, and had a strong affinity for TMV-CP with a binding energy of −7.54 kcal/mol, which was superior to the commercial antiviral agent ningnanmycin (−6.88 kcal/mol). Therefore, the three-dimensional structure of the TMV coat protein may be disrupted by the compounds D3 and ningnanmycin, preventing the TMV particles from self-assembling and thus producing a potent antiviral effect. The synthetic compounds in this work may provide potential lead compounds for the discovery of novel plant fungicides and antivirals.

**Abbreviations**

Xoo: Xanthomonas oryzae Pv. oryzae; Xac: Xanthomonas axonopodis Pv. citri; TMV: Tobacco mosaic virus; FA: Ferulic acid; TC: Thiodiazole copper; BT: Bismethiazol; 1H NMR: 1H nuclear magnetic resonance; 13C NMR: 13C nuclear magnetic resonance; 19F NMR: 19F nuclear magnetic resonance; HRMS: High-resolution mass spectrum.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13065-022-00828-8.

Additional file 1. 1H NMR, 13C NMR, 19F NMR, and HR-MS spectra of the title compounds D1–D24.
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Author contributions
Synthesis: AD; Bio-assay: AD and LY; Data curation: AD, LY, ZZ; Computational chemistry and the analysis of docking: YH; Writing—original draft: AD; Project administration: JW; Writing—review and editing: AD, ZZ and JW. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article (and its Additional file 1).

Declarations

Ethics approval and consent to participate
In this study, all the experimental research on plants were conducted under the guidelines set by the Institutional Bioethics Committee, Guizhou University. All the plants (tobacco and rice) were cultivated in our greenhouse. The Xoo, Xac were isolated from the rice plant; tobacco mosaic virus (TMV) was isolated from the tobacco plant; all the plants were growth in the field without uprooting. For our studied purpose, permission was granted by the owner of the field. These microorganisms were identified and preserved by Prof. Xiangyang Li in our laboratory.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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