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Sulfonate derivatives bearing an amide unit: design, synthesis and biological activity studies

You-hua Liu^{1†}, Chang-kun Li^{1†}, Mao-yu Nie¹, Fa-li Wang¹, Xiao-li Ren¹, Lin-hong Jin¹ and Xia Zhou^{1*}

Abstract

Pest disasters which occurs on crops is a serious problem that not only cause crop yield loss or even crop failure but can also spread a number of plant diseases. Sulfonate derivatives have been widely used in insecticide and fungicide research in recent years. On this basis, a series of sulfonate derivatives bearing an amide unit are synthesized and the biological activities are evaluated. The bioassay results showed that compounds **A**₈, **A**₁₃, **A**₁₆, **B**₁, **B**₃, **B**₄, **B**₅, **B**₁₀, **B**_{12–20}, **C**₃, **C**₅, **C**₉, **C**₁₀, **C**₁₄, **C**₁₅, **C**₁₇ and **C**₁₉ showed 100% activity at a concentration of 500 µg/mL against the *Plutella xylostella* (*P. xylostella*). Among them, **B**₁₅ which contains a thiadiazole sulfonate structure still shows 100% activity at 50 µg/mL concentration against *P. xylostella* and had the lowest median lethal concentration (LC₅₀) (7.61 µg/mL) among the target compounds. Further mechanism studies are conducted on compounds with better insecticidal activity. Molecular docking results shows that **B**₁₅ formed hydrophobic interactions π-π and hydrogen bonds with the indole ring of Trp532 and the carboxyl group of Asp384, respectively, with similar interaction distances or bond lengths as those of diflubenzuron. Moreover, chitinase inhibition assays are performed to further demonstrate its mode of action. In addition, the anti-bacterial activity of the series of compounds is also tested and the results showed that the series of compounds has moderate biological activity against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*), with inhibition rates of 91%, 92% and 92%, 88% at the concentration of 100 µg/mL, respectively. Our study indicates that **B**₁₅ can be used as a novel insecticide for crop protection.

Keywords Sulfonate derivatives, Synthesis, Pesticides, Biological activity

Introduction

Agricultural pests are the most important impact factors that threaten crops. They often cause serious quality and yield losses in agricultural production [1, 2]. Become potential “carriers” while feeding on susceptible plants, spreading more serious diseases to the plants. Among agricultural pests, the *P. xylostella* is one of the most challenging pests to control, infesting cruciferous crops and causing up to \$4.5 billion in losses annually [3]. Since crops are threatened not only by agricultural pests but also by crop pathogens, the focus of addressing these issues is on effective disease and pest management.

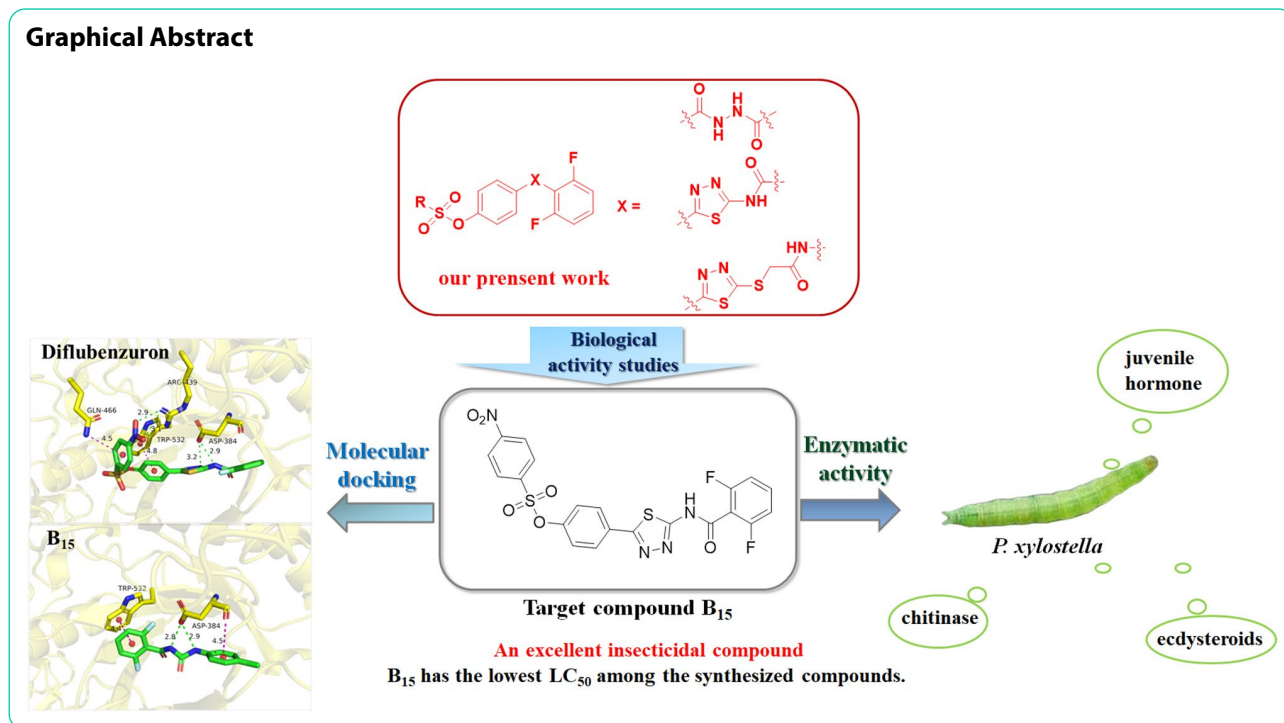
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Therefore, different types of pesticides such as fungicides/bactericides, insecticides, are applied to manage the corresponding pests and diseases [4]. However, 4.6 million tons of pesticides are used worldwide every year, with about 90% of them unable to be used properly and ending up in vulnerable farming systems, leading to an excessive build-up of harmful residues in crops [5–11]. Hence, the development of novel insecticidal agents is particularly important to reduce impacts on agroecosystem diversity.

Sulfonate derivatives have been widely studied owing to their strong affinity for lipids, which can easily cross the plant cuticle to perform their biological activities [12, 13]. Aryl sulfonate esters have been widely used for agricultural and pharmaceutical research due to their antiviral [14, 15], antibacterial [16], antifungal [17], insecticidal [18], and anticancer [19] properties. And more aryl sulfonate compounds with high efficacy in insecticidal, antibacterial, and antiviral activities can be obtained by structural modification [20, 21], such as, genite, irosustat, chlorfenson and nimrod, etc. In recent years, 1,3,4-thiadiazole derivatives and amide derivatives have become a major focus for the development of novel bactericides, insecticides, and fungicides [22–26], and a number of commercial agents containing thiadiazole/amide structures have been discovered and commercialized, such as bismethiazol, thiodiazole copper, boscalid, diflubenzuron, and chlorantraniliprole, etc. [21]. In view of the above, a series of novel sulfonate derivatives containing 1,3,4-thiadiazole/amide backbone was designed

and synthesized for further development of efficient and active lead compounds (Fig. 1) and evaluated for their biological activities. To our delight, most of the title compounds showed average biological activity against bacteria but most of the target compounds exhibited moderate to excellent insecticidal activity. The high insecticidal activity of the compounds was validated by further preliminary mechanism of action studies and molecular docking.

Results and discussion

Chemical synthesis

The synthetic route of target compounds is shown in Scheme 1. 4-hydroxybenzhydrazide produce intermediate A-1 by nucleophilic substitution reaction with acyl chloride, and intermediate A-1 is sulfonated with sulfonyl chloride to produce target compounds A₁–A₁₈ (Scheme 1A). 4-hydroxybenzhydrazide produce amino thiourea compounds by addition reaction with potassium thiocyanide under acidic condition, and intermediate B-1 produce target compounds B₁–B₂₀ (Scheme 1B) by cyclization reaction. Intermediate B-2 is formed by cyclization of intermediate B-1, and intermediate B-3 is sulfonated with sulfonyl chloride to form target compounds B₁–B₂₀. The synthesis route of target compounds C₁–C₂₀ is shown in Scheme 1C. 4-hydroxybenzhydrazide reacts with carbon disulfide in a condensation reaction to form intermediate C-1 under alkaline conditions. Intermediate C-1 is cyclized to form intermediate C-2, intermediate C-2 and C-3 react with nucleophilic

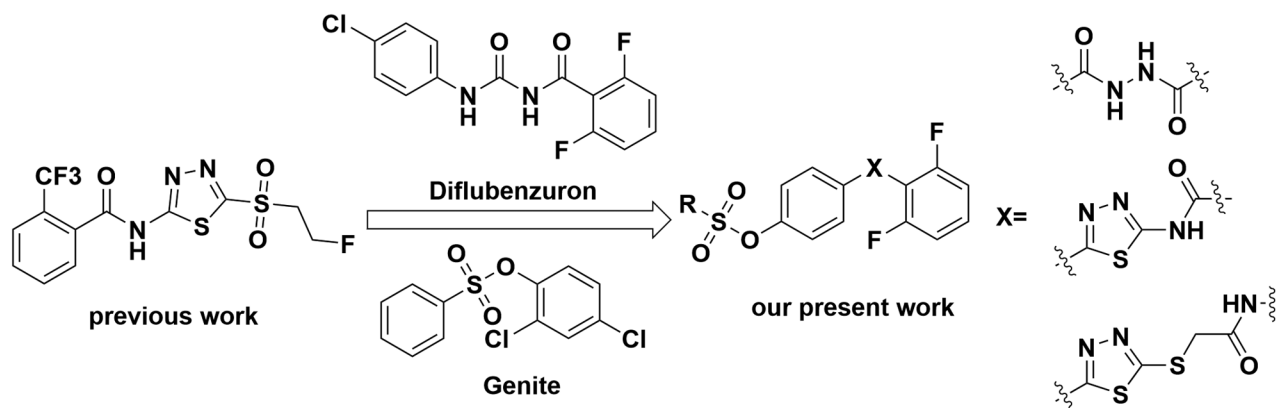


Fig. 1 Design strategy for target compounds

substitution to form intermediate C-4, intermediate C-4 and sulfonyl chloride react with sulfonation to form the target compound C₁-C₂₀. The chemical structures of all the target compounds, A₁-A₁₈, B₁-B₂₀ and C₁-C₂₀, have been confirmed by ¹H NMR, ¹³C NMR spectroscopy and high-resolution mass spectrometry. Physicochemical properties are provided in supporting information.

Insecticidal activity

The insecticidal activities of the target compounds are shown in Table 1, where diflubenzuron is used as a positive control. It can be seen that most of the target compounds show excellent insecticidal activities against both *P. xylostella* and *Myzus persicae*. Among them, compounds A₈, A₁₃, A₁₆, B₁, B₃, B₄, B₅, B₁₀, B₁₂₋₂₀, C₃, C₅, C₉, C₁₀, C₁₄, C₁₅, C₁₇ and C₁₉ all show 100% mortality against *P. xylostella* at a concentration of 500 μg/mL, and compounds B₁₅, C₁₄, C₁₅, C₁₇ and C₁₉ show insecticidal activity against the *P. xylostella* of more than 80% at 50 μg/mL, notably compound B₁₅ still show 100% mortality against *P. xylostella* at both 50 and 500 μg/mL concentrations.

In order to assess the insecticidal potency, the compounds that showed more than 90% mortality at 50 μg/mL concentration are further investigated to obtain their half lethal concentration (LC₅₀). As shown in Table 2, B₁₅, C₁₄, C₁₅, C₁₇ and C₁₉ show better insecticidal activity against *Plutella xylostella* with LC₅₀ values ranging from 7 to 19 μg/mL as compared to diflubenzuron with LC₅₀ value of 24.08 μg/mL. Among them, B₁₅ is the compound with the highest mortality against *Plutella xylostella* with an LC₅₀ value of 7.61 μg/mL, which was about three times more active than that of diflubenzuron.

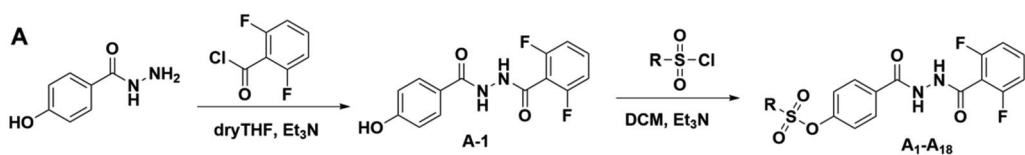
Changes of chitinase, juvenile hormone and ecdysteroids in *P. xylostella*

The growth and development of insects are mainly affected by chitinase, and the interaction of juvenile hormone and ecdysteroids also affects the activity and content of chitinase, which in turn affects the metamorphosis

and development of insects. In order to further evaluate the possible insecticidal mechanism of action of compound B₁₅, it firstly is observed the morphological changes of *P. xylostella* feeding on drug-containing leaves, and then tested the effects of compound B₁₅ on chitinase, juvenile hormone and ecdysteroids of *P. xylostella*. It can be seen that *P. xylostella* in the treated group after feeding on the drug-containing leaves over time the death of the worms is accompanied by body stiffness, as compared to that of diflubenzuron as a positive control (Fig. 2). To further explore the possible mechanism of action of the title compound in killing the insects, we test the changes in chitinase, juvenile hormone and ecdysteroids in *P. xylostella* after feeding on the drug-containing leaves (Fig. 3). The inhibition of *P. xylostella* chitinase activity by compound B₁₅ shows a tendency of increasing and then decreasing, and the inhibition of chitinase activity is most obvious at 12 h, whereas the inhibition of chitinase activity by diflubenzuron is almost non-existent (Fig. 3a). The effect of compound B₁₅ on juvenile hormones appears to follow the same trend as its effect on chitinase activity (Fig. 3b). The levels of ecdysteroids are higher in both compound B₁₅ and diflubenzuron-treated *P. xylostella* than in the blank control group (CK), and there is no inhibition of ecdysteroids by compound B₁₅ and diflubenzuron (Fig. 3c). Chitinase plays an important role in the growth and development of insects, and this result suggests that compound B₁₅ may prevent *P. xylostella* from completing the normal metamorphosis and development process by inhibiting the activity of chitinase, leading to its death.

Molecular docking

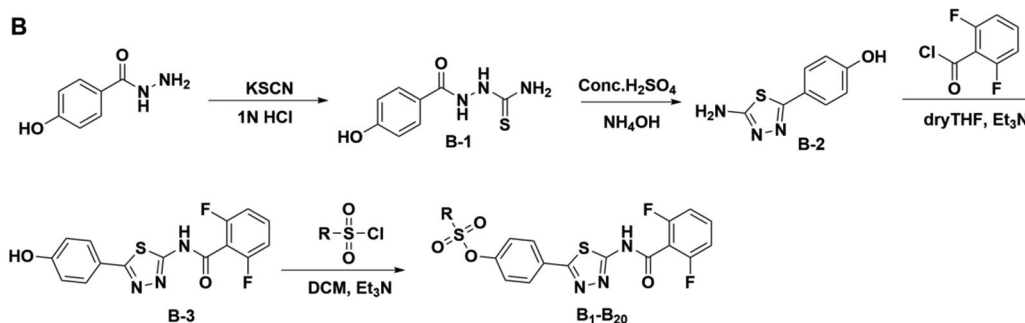
Chitin is essential in insect growth and development, and it has been shown that the title compound disrupts chitinase activity, which in turn may cause dysregulation of chitin synthesis and catabolism in insects; therefore, the chitinase-related protein (PDB ID: 6JMA) has been selected to be used for molecular docking. In order



A₁ : R=-phenyl
 A₂ : R=2-F-phenyl
 A₃ : R=3-F-phenyl
 A₄ : R=4-F-phenyl
 A₅ : R=3,4-difluorophenyl
 A₆ : R=2,6-difluorophenyl

A₇ : R=2-Cl-phenyl
 A₈ : R=3-Cl-phenyl
 A₉ : R=4-Cl-phenyl
 A₁₀ : R=2-Br-phenyl
 A₁₁ : R=3-Br-phenyl
 A₁₂ : R=4-Br-phenyl

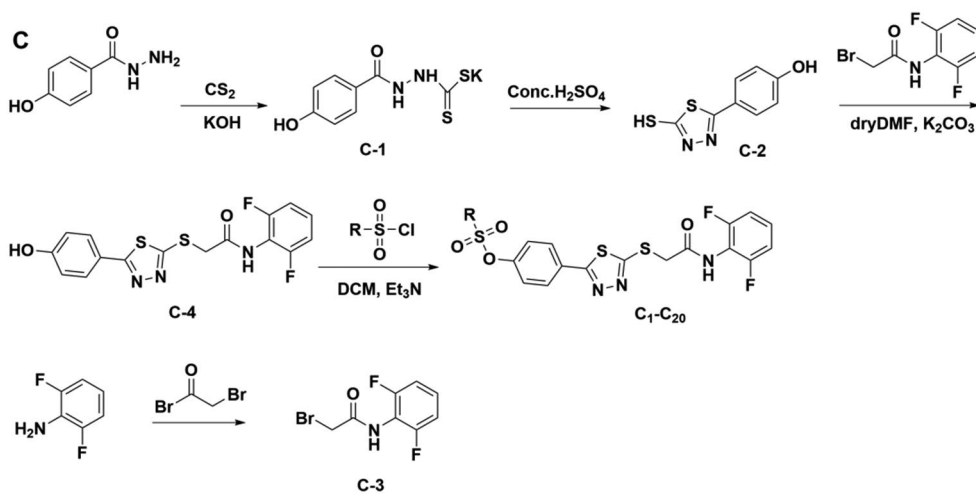
A₁₃ : R=4-NO₂-phenyl
 A₁₄ : R=4-CN-phenyl
 A₁₅ : R=4-CF₃-phenyl
 A₁₆ : R=4-OCH₃-phenyl
 A₁₇ : R=4-CH₃-phenyl
 A₁₈ : R=4-C(CH₃)₃-phenyl



B₁ : R=-phenyl
 B₂ : R=2-F-phenyl
 B₃ : R=3-F-phenyl
 B₄ : R=4-F-phenyl
 B₅ : R=3,4-difluorophenyl
 B₆ : R=2,6-difluorophenyl
 B₇ : R=-Pentafluorophenyl

B₈ : R=2-Cl-phenyl
 B₉ : R=3-Cl-phenyl
 B₁₀ : R=4-Cl-phenyl
 B₁₁ : R=2,4,6-trichlorophenyl
 B₁₂ : R=2-Br-phenyl
 B₁₃ : R=3-Br-phenyl
 B₁₄ : R=4-Br-phenyl

B₁₅ : R=4-NO₂-phenyl
 B₁₆ : R=4-CN-phenyl
 B₁₇ : R=4-CF₃-phenyl
 B₁₈ : R=4-OCH₃-phenyl
 B₁₉ : R=4-CH₃-phenyl
 B₂₀ : R=4-C(CH₃)₃-phenyl



C₁ : R=-phenyl
 C₂ : R=2-F-phenyl
 C₃ : R=3-F-phenyl
 C₄ : R=4-F-phenyl
 C₅ : R=3,4-difluorophenyl
 C₆ : R=2,6-difluorophenyl
 C₇ : R=-Pentafluorophenyl

C₈ : R=2-Cl-phenyl
 C₉ : R=3-Cl-phenyl
 C₁₀ : R=4-Cl-phenyl
 C₁₁ : R=2,4,6-trichlorophenyl
 C₁₂ : R=2-Br-phenyl
 C₁₃ : R=3-Br-phenyl
 C₁₄ : R=4-Br-phenyl

C₁₅ : R=4-NO₂-phenyl
 C₁₆ : R=4-CN-phenyl
 C₁₇ : R=4-CF₃-phenyl
 C₁₈ : R=4-OCH₃-phenyl
 C₁₉ : R=4-CH₃-phenyl
 C₂₀ : R=4-C(CH₃)₃-phenyl

Scheme 1 Synthetic routes for the target compounds

Table 1 Insecticidal activity of title compounds **A**₁-**A**₁₈, **B**₁-**B**₂₀ and **C**₁-**C**₂₀ against *P. xylostella* and *Myzus persicae*

Compd.	<i>P. xylostella</i>		<i>Myzus persicae</i>
	500 µg/mL (%) ^a	50 µg/mL (%) ^a	500 µg/mL (%) ^a
A ₁	90.00 ± 0.00	73.33 ± 5.77	36.67 ± 5.77
A ₂	93.33 ± 5.77	70.00 ± 10.00	16.67 ± 5.77
A ₃	80.00 ± 10.00	33.33 ± 5.77	26.67 ± 5.77
A ₄	80.00 ± 0.00	70.00 ± 0.00	60.00 ± 10.00
A ₅	76.67 ± 5.77	30.00 ± 0.00	83.33 ± 5.77
A ₆	76.67 ± 11.55	30.00 ± 10.00	6.67 ± 5.77
A ₇	80.00 ± 0.00	23.33 ± 5.77	16.67 ± 5.77
A ₈	100	50.00 ± 10.00	20.00 ± 0.00
A ₉	93.33 ± 5.77	60.00 ± 0.00	33.33 ± 5.77
A ₁₀	73.33 ± 11.55	26.67 ± 11.55	40.00 ± 0.00
A ₁₁	86.67 ± 5.77	20.00 ± 0.00	23.33 ± 11.55
A ₁₂	66.67 ± 5.77	63.33 ± 5.77	26.67 ± 5.77
A ₁₃	100	53.33 ± 5.77	53.33 ± 5.77
A ₁₄	86.67 ± 5.77	53.33 ± 5.77	66.67 ± 5.77
A ₁₅	90.00 ± 0.00	60.00 ± 10.00	66.67 ± 11.55
A ₁₆	100	60.00 ± 0.00	50.00 ± 10.00
A ₁₇	40.00 ± 0.00	13.33 ± 5.77	23.33 ± 5.77
A ₁₈	93.33 ± 5.77	73.33 ± 5.77	6.67 ± 5.77
B ₁	100	76.67 ± 5.77	30.00 ± 0.00
B ₂	90.00 ± 10.00	20.00 ± 0.00	3.33 ± 5.77
B ₃	100	40.00 ± 10.00	10.00 ± 0.00
B ₄	100	50.00 ± 0.00	36.67 ± 5.77
B ₅	100	40.00 ± 0.00	86.67 ± 5.77
B ₆	86.67 ± 5.77	10.00 ± 0.00	23.33 ± 5.77
B ₇	96.67 ± 5.77	40.00 ± 10.00	26.67 ± 5.77
B ₈	93.33 ± 5.77	36.67 ± 11.55	10.00 ± 0.00
B ₉	86.67 ± 11.55	13.33 ± 5.77	46.67 ± 5.77
B ₁₀	100	700.00 ± 0.00	26.67 ± 5.77
B ₁₁	93.33 ± 5.77	26.67 ± 5.77	20.00 ± 0.00
B ₁₂	100	43.33 ± 5.77	13.33 ± 11.55
B ₁₃	100	43.33 ± 5.77	16.67 ± 5.77
B ₁₄	100	66.67 ± 5.77	80.00 ± 10.00
B ₁₅	100	100	50.00 ± 10.00
B ₁₆	100	70.00 ± 10.00	20.00 ± 10.00
B ₁₇	100	50.00 ± 0.00	30.00 ± 0.00
B ₁₈	100	66.67 ± 5.77	26.67 ± 5.77
B ₁₉	100	60.00 ± 0.00	36.67 ± 5.77
B ₂₀	100	46.67 ± 5.77	30.00 ± 0.00
C ₁	86.67 ± 11.55	76.67 ± 5.77	10.00 ± 0.00
C ₂	70.00 ± 10.00	6.67 ± 5.77	16.67 ± 5.77
C ₃	100	50.00 ± 10.00	13.33 ± 11.55
C ₄	93.33 ± 5.77	83.33 ± 5.77	16.67 ± 5.77
C ₅	100	53.33 ± 5.77	83.33 ± 5.77
C ₆	86.67 ± 5.77	23.33 ± 5.77	26.67 ± 5.77
C ₇	73.33 ± 11.55	30.00 ± 10.00	50.00 ± 10.00
C ₈	93.33 ± 5.77	30.00 ± 0.00	6.67 ± 5.77
C ₉	100	36.67 ± 5.77	10.00 ± 0.00
C ₁₀	100	70.00 ± 10.00	50.00 ± 10.00
C ₁₁	76.67 ± 5.77	20.00 ± 0.00	20.00 ± 0.00
C ₁₂	96.67 ± 5.77	36.67 ± 5.77	3.33 ± 5.77
C ₁₃	83.33 ± 5.77	10.00 ± 0.00	16.67 ± 5.77
C ₁₄	100	93.33 ± 5.77	30.00 ± 10.00

Table 1 (continued)

Compd.	<i>P. xylostella</i>		<i>Myzus persicae</i>
	500 µg/mL (%) ^a	50 µg/mL (%) ^a	500 µg/mL (%) ^a
C ₁₅	100	90.00 ± 0.00	36.67 ± 5.77
C ₁₆	83.33 ± 5.77	66.67 ± 5.77	26.67 ± 5.77
C ₁₇	100	93.33 ± 5.77	23.33 ± 11.55
C ₁₈	93.33 ± 5.77	66.67 ± 5.77	33.33 ± 5.77
C ₁₉	100	90.00 ± 10.00	16.67 ± 5.77
C ₂₀	66.67 ± 5.77	33.33 ± 5.77	40.00 ± 0.00
Diflubenzuron	100	80.00 ± 0.00	3.00 ± 5.77

^aAll results are expressed as mean ± SD.

Table 2 LC₅₀ values of some compounds with excellent insecticidal activity against the *P. xylostella*

Compd.	<i>Plutella xylostella</i>		
	Regression eq.	R ²	LC ₅₀ (µg/mL) ^a
B ₁₅	y = 2.59x + 2.72	0.98	7.61 ± 1.62
C ₁₄	y = 3.23x + 0.88	0.99	18.85 ± 3.46
C ₁₅	y = 2.79x + 1.70	0.97	15.28 ± 2.52
C ₁₇	y = 3.47x + 0.70	0.97	17.38 ± 3.16
C ₁₉	y = 2.73x + 1.69	0.99	16.37 ± 3.41
Diflubenzuron	y = 2.34x + 1.77	0.99	24.08 ± 2.31

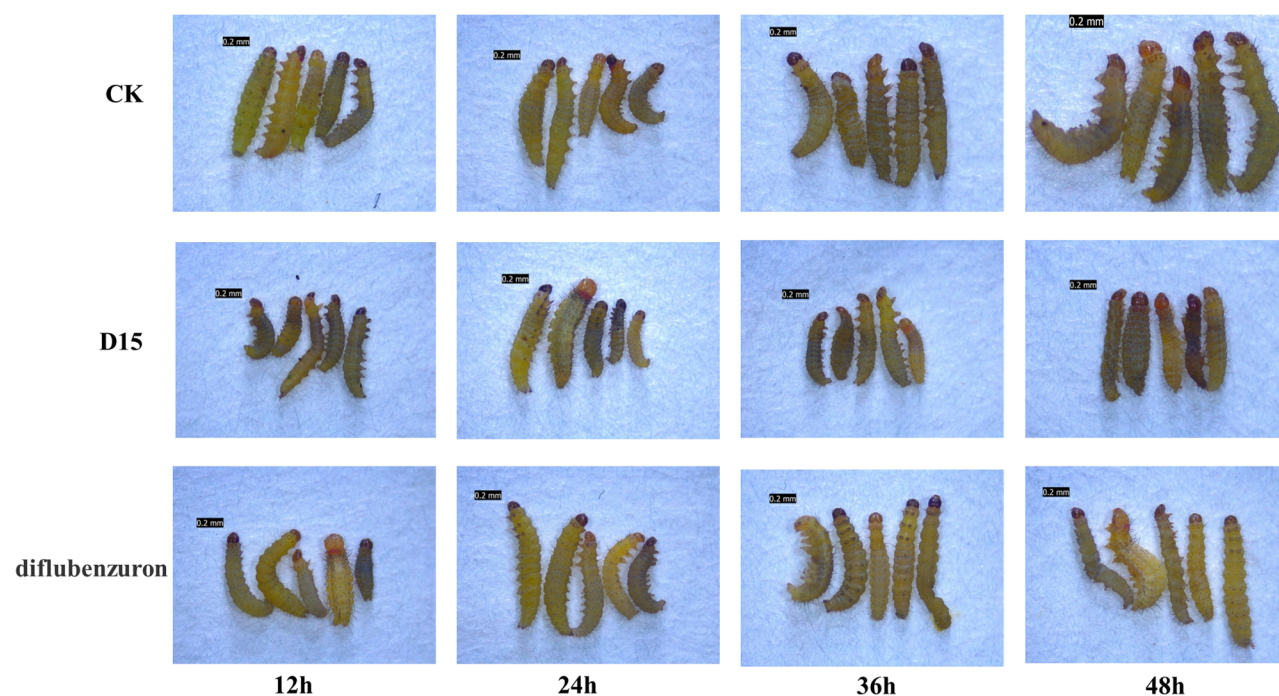
^aAll results are expressed as mean ± SD.

to verify the possible insecticidal mechanism of the title compound B₁₅, it is docked at the theoretical binding site of the chitinase protein, diflubenzuron is used as a positive control. The interactions of B₁₅ and diflubenzuron with the chitinase protein are shown in Fig. 4. In the docking complex of diflubenzuron and chitinase protein

(Fig. 4A) the two N atoms of the amide bond form two hydrogen bonds (2.8 Å and 2.9 Å) with the key residue ASP384, which is essential for the binding of the inhibitor and chitinase protein. The benzene ring forms a π-π stacking interaction with residues TRP532 and ASP384 (4.4 Å and 4.5 Å). As shown in Fig. 4B, the thiazole ring and amide bond of B₁₅ forms two hydrogen bonds (3.2 Å and 2.9 Å) with ASP384 as well as the nitro group on the benzene ring with ARG239 (2.9 Å and 3.1 Å), which is two more than that of the diflubenzuron. The benzene ring forms a π-π stacking interaction with ARG439 and GLN466 (4.8 Å and 4.5 Å), respectively. All these differences explain the more active insecticidal activity of B₁₅ against the *P. xylostella* than that of diflubenzuron.

In vitro antibacterial activity

In order to explore the effect of the synthesized target compounds beyond insecticides, antibacterial activity

**Fig. 2** Morphological changes of the *P. xylostella* feeding on the drug-containing leaves at different time periods

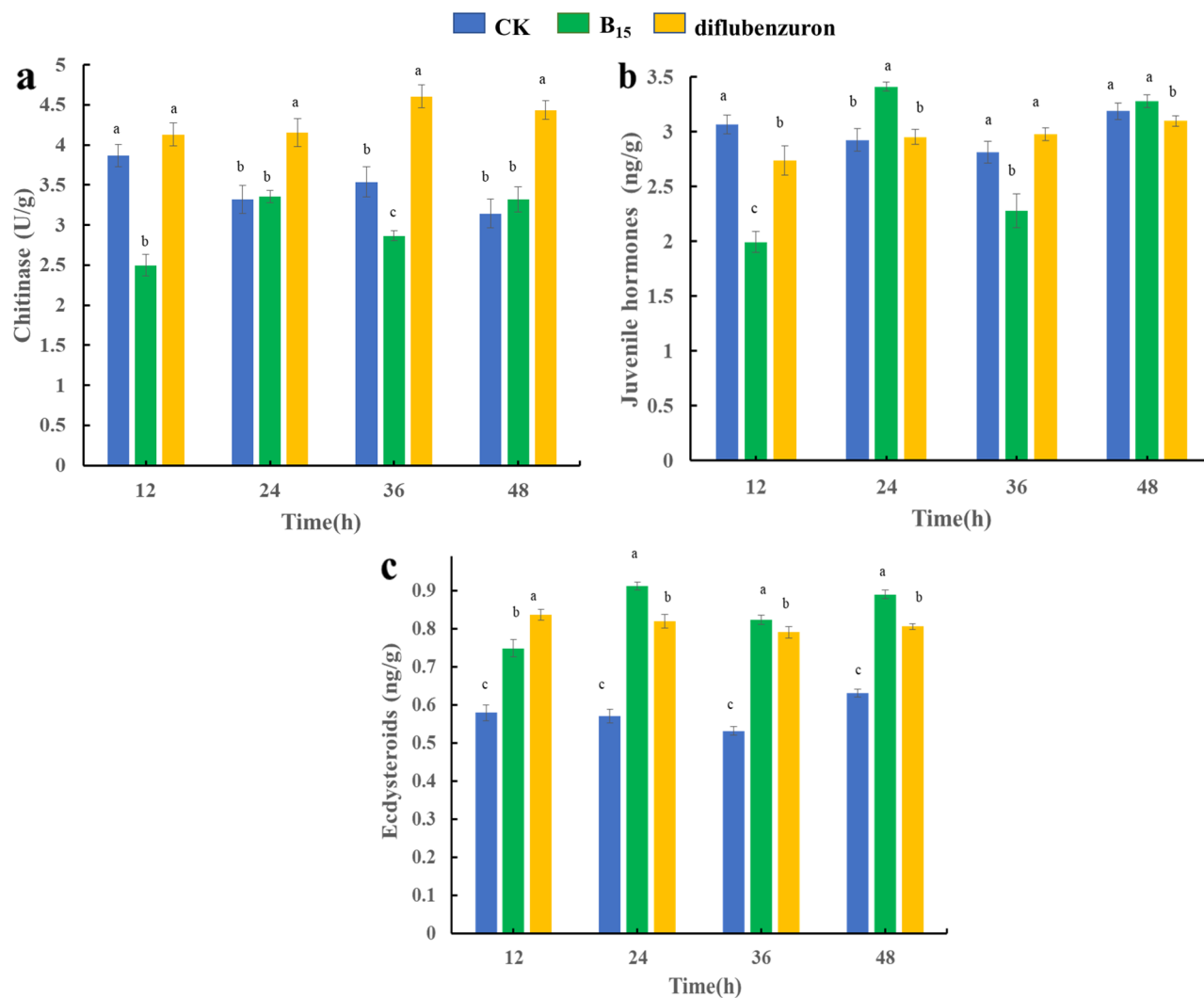


Fig. 3 Graphical representations of changes in chitinase, juvenile hormone and ecdysteroids in the *P. xylostella* feeding on drug-containing leaves. Values are the means and standard deviations of three independent experiments. Different lowercase letters indicate values with significant differences among different treatment groups, according to one-way ANOVA ($P < 0.05$)

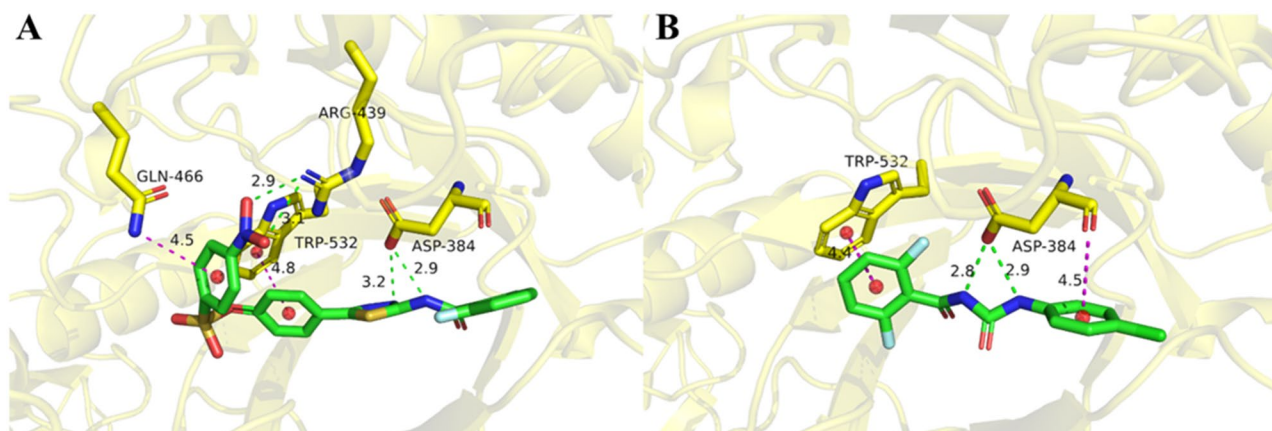


Fig. 4 Molecular docking diagram of diflubenzuron (A) and compound B₁₅ (B)

experiments are carried out. The antibacterial activities of the title compounds in vitro are shown in Table 3. Most of the compounds show moderate inhibitory activity against the tested bacteria. Among them, some of the compounds show a good inhibitory activity against *Xoo* and *Xoc*, and compounds **A₄** and **C₄** both showed more than 90% inhibitory activity against *Xoo* at a concentration of 100 $\mu\text{g/mL}$. Then, we test the EC_{50} values of those title compounds that showed better activity against *Xoo* and *Xoc*, the EC_{50} values of antibacterial activity of compound **A₄** and compound **C₄** against *Xoo* are 24.87 and 30.04 $\mu\text{g/mL}$, respectively. The EC_{50} values of compounds **A₄**, **A₁₅**, **A₁₆**, **B₇**, **C₄** and **C₇** of that inhibitory activity against *Xoc* are 30.12, 39.59, 18.75, 67.9, 43.85 and 54.56 $\mu\text{g/mL}$, respectively (Table 4).

Conclusion

In summary, 58 novel series of sulfonate derivatives containing an amide backbone were designed and synthesized. They have been evaluated for their antibacterial and insecticidal activities. The results of the bioactivity tests indicated that the compounds show fair antibacterial activity, but most of them showed good insecticidal activity against the *P. xylostella*. Among them, compound **B₁₅** showed the best insecticidal activity against *P. xylostella* with LC_{50} of 7.61 $\mu\text{g/mL}$, which is much lower than the control agent diflubenzuron. Further preliminary studies on the insecticidal mechanism indicated that compound **B₁₅** may exert its insecticidal activity by inhibiting chitinase and juvenile preserving hormone in the body of the *P. xylostella*, and this result was also consistent with the molecular docking experiments. Therefore, compound **B₁₅** may be a promising insecticide candidate.

Materials and methods

Equipment and materials

Melting points of new compounds were determined on an X-4 digital display micro melting point apparatus (Henan, Gongyi Yuhua Instrument Co., Ltd, China) and were uncorrected. The NMR spectra of the title compounds were obtained on a JEOL-ECX500 apparatus (JEOL, Japan) or a Bruker Biospin AG-400 apparatus (Bruker Corporation, Germany) using tetramethylsilane as the internal standard. High-resolution mass spectra were recorded with a Thermo Scientific UltiMate 3000 spectrometer (Thermo Fisher Scientific, USA). Optical density was recorded on a Cytation™ 5 multi-mode readers (BioTek Instruments, USA). All chemical reagents were obtained from commercial suppliers. All strains used (*Xoo*, *Xac*, *Psa* and *Xoc*) and the test insects (*Plutella xylostella* and *Myzus persicae*) were provided by the laboratory of Guizhou University. All ELISA kits were obtained from commercial suppliers (Jiangsu Meimian Industrial Co., Ltd, China).

Preparation procedure of intermediate compounds

Synthesis of intermediate **A-1**: following the method described in the literature [27], 4-hydroxybenzhydrazide (65.7 mmol) and Et_3N (131.4 mmol) were added to a clean 250 mL three-necked flask with tetrahydrofuran (130 mL), at 25 °C. Then 2,6-difluorobenzoyl chloride (65.7 mmol) was added to the mixture at ice bath. The reaction would be accomplished quickly in 5 min (monitored by TLC). Then the reaction mixture was quenched by adding 100 mL H_2O and extracted with ethyl acetate (100mL \times 3). The collected organic phase was extracted with NaOH solution and the water phase was adjusted to pH=4–5 with diluted hydrochloric acid. Then ethyl acetate was added to extract and concentrate to get the crucial solid, which was then recrystallized with anhydrous ethanol to obtain white crystal intermediate **A-1** (yield, 76%).

Synthesis of intermediate **B-1**: following the method described in the literature [28], 4-hydroxybenzhydrazide (65.7 mmol) was added into a clean 250 mL three-necked flask with 120 mL of 1 M HCl solution at room temperature. After stirring for 15 min, all the solid was dissolved. Then potassium thiocyanate (131.4 mmol) was added and the mixture was heated at 100 °C for 8 h until the reaction completion as monitored by TLC. The system was cooled to room temperature and a large amount of white solid appeared. The solid product was filtered and washed by water for three times and ethanol once, and then recrystallized in anhydrous ethanol to obtain intermediate **B-1**, with yield of 57.6%.

Synthesis of intermediate **B-2**: following the method in the literature [28], intermediate **B-1** (28.4 mmol) was added into a clean 50 mL three-neck flask at 25 °C followed with H_2SO_4 (20 mL) while stirring. After 6 h the reaction was completed. Then the reaction mixture was slowly poured into crushed ice, and 25% ammonia water was added to adjust the solution to pH=8–10 during stirring and a large amount of white solid precipitated. The precipitate was filtered and washed with water three times and dried. The solid was then recrystallized in anhydrous ethanol to obtain intermediate **B-2**, with yield of 32.8%.

Synthesis of intermediate **B-3**: following the method in the literature [29], intermediate **B-2** (9.3 mmol) and Et_3N (18.6 mmol) were added to 20 mL tetrahydrofuran in a clean 50 mL three-neck flask and stirred for 15 min at 25 °C. Next in an ice bath, 2,6-difluorobenzoyl chloride (9.3 mmol) was slowly added and then the mixture was stirred at room temperature till reaction was completed according to TLC. Then the reaction mixture was quenched by adding 20 mL H_2O and extracted with ethyl acetate (20 mL \times 3). The collected organic phase was extracted with

Table 3 *In vitro* antibacterial activity results of the title compounds

Compd.	Xoo		Xoc		Xac		Psa	
	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$
A ₁	18.56±1.33	21.11±1.15	70.33±2.53	36.20±1.10	35.03±1.23	26.05±1.03	27.91±3.15	12.88±1.51
A ₂	33.16±0.93	22.78±0.76	53.43±1.81	27.27±2.09	46.87±2.78	23.03±1.14	21.12±2.52	11.64±0.99
A ₃	41.16±1.21	36.85±1.35	41.63±2.19	26.16±1.20	46.03±1.24	20.18±2.48	18.52±2.46	10.43±1.44
A ₄	90.59±3.32	39.67±1.45	66.67±1.54	40.19±1.27	39.00±2.34	23.96±3.30	22.37±2.01	12.62±2.05
A ₅	42.74±1.47	10.73±1.00	78.15±1.54	45.45±1.44	49.00±4.50	25.08±1.32	12.94±2.54	8.12±2.06
A ₆	13.46±1.15	33.51±1.58	66.99±1.66	40.19±1.66	56.64±1.34	34.49±1.03	10.16±1.45	8.69±4.39
A ₇	39.67±1.85	58.58±1.40	56.94±1.27	36.20±4.45	42.63±0.94	28.86±3.40	20.10±1.46	8.31±2.45
A ₈	13.28±1.30	38.79±2.06	69.06±1.10	49.76±0.83	52.54±3.02	25.55±1.03	16.06±2.20	9.75±1.42
A ₉	11.79±1.52	65.00±2.71	60.29±1.27	37.16±1.20	42.44±2.37	27.06±4.71	15.07±2.86	6.61±2.08
A ₁₀	68.78±3.86	20.99±3.56	45.45±2.91	24.72±1.68	35.08±1.36	28.68±1.53	9.53±0.34	5.63±2.04
A ₁₁	21.78±1.76	23.17±1.05	61.08±1.46	41.47±2.92	34.89±2.14	26.85±2.92	14.78±4.83	5.52±1.21
A ₁₂	64.69±1.19	52.67±1.10	56.78±2.46	33.97±2.53	30.08±1.67	24.97±3.74	9.79±1.69	5.29±2.59
A ₁₃	31.35±0.50	32.41±1.92	35.41±2.09	23.13±1.00	36.45±2.92	19.03±1.13	20.28±2.92	11.75±3.73
A ₁₄	17.89±1.94	61.91±1.14	85.96±1.68	37.00±1.46	32.39±1.82	24.50±4.05	10.23±1.69	6.31±3.95
A ₁₅	15.58±2.17	54.32±2.61	94.74±0.48	72.41±1.00	40.84±3.92	25.73±1.49	13.24±3.88	5.18±4.77
A ₁₆	63.76±2.72	25.74±4.09	100	84.69±2.91	31.26±2.30	28.04±2.64	10.01±2.54	5.70±3.51
A ₁₇	10.96±0.60	34.26±4.29	49.92±2.64	33.33±1.93	49.71±1.96	27.60±1.64	0.55±2.92	0.91±2.61
A ₁₈	11.49±0.59	27.92±3.26	55.50±4.78	45.30±1.00	42.16±0.90	19.39±1.58	2.86±0.61	0
B ₁	68.78±3.86	25.15±4.24	48.00±0.35	32.67±1.33	60.79±2.65	40.40±1.25	9.29±0.71	5.47±1.03
B ₂	20.99±3.56	8.07±4.66	38.00±0.53	25.80±0.20	49.56±2.50	35.68±1.25	14.25±2.15	7.70±1.28
B ₃	44.22±2.02	5.13±2.52	35.07±0.12	29.67±0.12	66.22±3.18	43.71±1.43	15.14±1.53	6.32±1.04
B ₄	23.30±1.02	0	42.07±0.42	27.47±0.81	43.52±2.41	30.81±1.03	2.89±2.15	2.98±0.46
B ₅	21.78±1.76	0	41.53±0.31	22.33±0.31	69.24±1.73	40.18±1.47	5.97±4.45	1.38±2.15
B ₆	23.17±1.05	11.18±4.12	41.53±0.90	31.40±1.40	58.34±2.20	35.71±4.68	29.9±1.23	14.84±1.39
B ₇	64.69±1.19	39.33±0.34	65.33±0.31	33.73±1.15	47.58±2.67	30.77±1.04	9.02±4.04	6.84±1.84
B ₈	52.67±1.10	8.78±0.81	39.40±1.06	28.93±0.83	49.19±2.94	26.92±2.54	27.09±1.09	10.6±1.34
B ₉	31.35±0.50	8.24±1.18	41.93±0.31	29.80±0.35	15.36±2.22	34.52±3.95	6.48±0.71	2.98±2.84
B ₁₀	32.41±1.92	7.91±2.08	30.27±0.81	24.80±0.20	47.49±1.39	39.39±1.27	4.10±4.52	0
B ₁₁	17.89±1.94	12.11±0.75	43.80±0.72	31.13±0.42	31.02±0.99	22.41±1.59	2.50±3.73	0
B ₁₂	61.91±1.14	13.26±1.43	38.73±0.76	21.27±0.12	15.78±1.86	4.86±1.59	3.98±1.84	0
B ₁₃	15.58±2.17	21.88±1.52	35.13±0.76	29.00±1.06	35.27±2.52	24.04±1.78	2.58±1.95	0
B ₁₄	54.32±2.61	13.91±0.98	41.60±0.35	33.00±0.20	30.36±2.62	20.07±2.31	0	0
B ₁₅	63.76±2.72	15.28±0.81	44.40±1.40	28.93±0.31	45.55±2.37	39.24±1.03	0	0
B ₁₆	25.74±4.09	13.48±1.16	41.00±1.25	18.27±0.23	37.25±1.28	30.45±3.00	0	0
B ₁₇	10.96±0.60	0	52.20±1.11	37.60±0.40	58.43±1.20	32.72±1.08	0	0
B ₁₈	34.26±4.29	14.13±2.54	47.73±0.31	27.93±0.12	63.10±2.92	35.60±2.60	11.94±2.23	8.00±2.09
B ₁₉	11.49±0.59	3.82±0.41	53.00±0.35	39.47±0.61	63.67±2.89	32.86±1.03	5.27±2.65	4.69±2.96
B ₂₀	27.92±3.26	6.87±0.59	38.27±0.61	23.60±0.20	47.77±1.81	22.27±2.07	5.89±2.48	3.87±1.63
C ₁	65.43±0.49	35.33±1.47	58.62±1.39	31.90±0.74	52.52±1.45	41.19±1.43	38.96±1.27	22.22±1.75
C ₂	55.81±2.43	43.24±1.15	39.60±1.25	18.00±0.54	49.85±1.05	38.96±1.61	41.39±2.37	24.72±2.40
C ₃	64.67±1.57	26.86±0.57	34.56±1.24	25.77±1.87	62.74±1.22	49.04±1.22	29.65±1.15	11.11±0.98
C ₄	92.10±1.29	71.62±0.16	87.93±0.54	51.19±1.25	64.96±1.00	46.07±2.23	32.43±3.23	16.11±1.15
C ₅	42.48±2.31	26.00±1.48	41.24±0.47	24.06±1.84	49.33±2.26	36.52±1.41	26.94±2.41	11.67±1.91
C ₆	59.62±1.44	29.43±1.74	38.24±2.28	26.52±1.44	43.41±1.34	38.67±1.33	11.88±1.50	0
C ₇	82.19±1.44	47.71±0.86	84.12±1.84	41.04±0.31	62.89±2.04	46.37±2.06	52.22±1.82	34.44±0.94
C ₈	57.81±1.08	31.05±3.00	36.33±1.99	20.45±0.54	58.44±1.02	34.81±1.70	26.81±1.88	10.56±0.94
C ₉	56.48±1.90	28.76±1.44	42.40±2.37	34.08±1.03	62.30±2.27	52.15±1.12	38.19±1.26	27.57±1.39
C ₁₀	66.19±1.90	38.19±1.44	48.53±2.37	33.06±1.30	58.15±1.48	49.93±1.12	25.97±1.07	15.63±0.95
C ₁₁	59.14±1.78	32.29±1.74	51.74±1.14	28.02±0.71	56.07±2.58	48.74±1.61	11.94±1.54	3.96±0.95
C ₁₂	61.43±1.31	40.29±0.57	30.88±0.54	25.97±1.34	57.56±2.12	37.26±1.48	17.29±2.32	1.67±1.91
C ₁₃	68.19±1.67	40.57±1.25	32.58±1.03	22.22±1.79	53.56±1.02	39.63±2.02	1.53±1.70	1.18±1.03

Table 3 (continued)

Compd.	Xoo		Xoc		Xac		Psa	
	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$	100 $\mu\text{g/mL}(\%)^a$	50 $\mu\text{g/mL}(\%)^a$
C ₁₄	55.33 ± 1.00	34.38 ± 3.08	46.35 ± 1.39	34.01 ± 2.46	44.15 ± 3.70	36.44 ± 2.31	39.86 ± 2.23	24.51 ± 1.22
C ₁₅	69.81 ± 3.57	31.71 ± 0.49	23.38 ± 1.93	14.45 ± 1.18	55.41 ± 2.57	44.52 ± 2.25	46.04 ± 2.76	37.43 ± 1.92
C ₁₆	54.00 ± 1.31	24.76 ± 1.47	38.17 ± 1.39	20.04 ± 1.14	54.15 ± 3.03	44.81 ± 3.03	35.76 ± 1.67	11.67 ± 1.85
C ₁₇	55.33 ± 1.00	35.52 ± 1.29	70.28 ± 1.55	41.24 ± 1.13	48.59 ± 2.06	45.85 ± 1.03	9.65 ± 1.70	1.74 ± 1.59
C ₁₈	63.62 ± 1.94	36.86 ± 0.49	47.99 ± 0.83	26.58 ± 1.02	53.63 ± 1.81	43.48 ± 2.45	2.71 ± 2.18	0
C ₁₉	62.19 ± 0.87	36.19 ± 0.72	76.35 ± 1.70	43.08 ± 1.05	54.74 ± 0.68	44.52 ± 3.34	7.78 ± 1.89	3.61 ± 1.48
C ₂₀	74.00 ± 1.31	39.43 ± 1.87	29.65 ± 1.06	18.13 ± 0.92	50.44 ± 1.02	39.26 ± 2.63	7.36 ± 1.03	0
BT	100	77.00 ± 1.46	84.00 ± 2.36	42.00 ± 2.13	57.00 ± 1.18	41.00 ± 0.64	/	/
TZ	/	/	/	/	97.00 ± 2.64	40.00 ± 1.70	60.00 ± 3.24	42.00 ± 1.13
TC	100	54.00 ± 1.12	62.00 ± 2.48	33.00 ± 2.41	40.00 ± 0.57	27.00 ± 2.32	37.00 ± 2.80	22.00 ± 1.70

^aAll results are expressed as mean ± SD.

Table 4 EC₅₀ values of some compounds with better inhibitory activity against Xoo, Xoc

Compd.	Xoo	Xoc				
	Regression eq.	R ²	EC ₅₀ ($\mu\text{g/mL}$) ^a	Regression eq.	R ²	EC ₅₀ ($\mu\text{g/mL}$) ^a
A ₄	y = 1.83x + 2.44	0.96	24.87 ± 1.22	y = 2.15x + 1.81	0.95	30.12 ± 1.03
A ₁₅	-	-	-	y = 4.19x - 1.69	0.99	39.59 ± 1.44
A ₁₆	-	-	-	y = 2.16x + 2.25	0.95	18.75 ± 1.16
B ₇	y = 1.27x + 2.69	0.96	66.88 ± 2.23	y = 2.42x + 0.57	0.97	67.90 ± 1.90
C ₄	y = 1.58x + 2.66	0.97	30.04 ± 2.01	y = 3.15x - 0.17	0.99	43.85 ± 2.28
C ₇	-	-	-	y = 3.90x - 1.78	0.99	54.56 ± 1.58
BT	y = 2.21x + 1.91	0.99	25.12 ± 1.03	y = 1.39x + 2.38	0.98	76.38 ± 3.23
TC	y = 1.41x + 2.66	0.99	45.81 ± 1.72	y = 1.50x + 1.82	0.94	130.49 ± 2.50

^aAll results are expressed as mean ± SD.

NaOH solution, and the water phase was adjusted to pH = 4–5 with diluted hydrochloric acid. Then ethyl acetate was added to extract and concentrate to get the crucial solid, which was then recrystallized with anhydrous ethanol to obtain intermediate B-3, with yield of 61.4%.

Synthesis of intermediate C-1: following the published methods [28], 4-hydroxybenzhydrazide (32.8 mmol), KOH (49.2 mmol), and 80 mL of ethanol were added sequentially to a 150 mL three-neck flask at room temperature. The solids were dissolved after 10 min stirring. The CS₂ (49.2 mmol) was slowly added into the mixture in an ice bath. The mixture was stirred overnight at room temperature. The reaction solution was becoming, and till the reaction completed as indicated by TLC. Solid products appeared in the solution, filtered and washed by ethanol to obtain intermediate C-1, with yield 92%. The intermediate C-1 was subjected directly to the next reaction without recrystallization.

Synthesis of Intermediate C-2: following the published methods [28], intermediate C-1 (7.5 mmol) was slowly added to the ice-cold H₂SO₄ (15 mL) in 50 mL three-neck flask while stirring. The reaction was kept stirring for 4 h at an ice-water bath and poured into crushed ice. The newly appeared precipitate product

was filtered to dissolve in a 20% NaOH aqueous solution. After insoluble substances were excluded, and the solution was acidified with diluted hydrochloric acid and got a precipitate, which was then filtered, washed by water and dried to obtain intermediate C-2, with a yield of 76.1%.

Synthesis of intermediate C-3: following the method described in the literature [30], 2,6-difluoroaniline (38.7 mmol) was added into 80 mL of 1,4-dioxane in a 150 mL three-necked flask and dissolved after stirring for 10 min. Then bromoacetyl bromid (50.3 mmol) early dissolved in dry dioxane (15 mL), was added dropwise to the above solution at 0 °C then mixture was stirred at room temperature for 5 h. Finally, the reaction mixture was poured into cold water, precipitate appeared, which was then filtered, washed by water and dried to obtain intermediate C-3, with a yield of 64%.

Synthesis of intermediate C-4: as reported [31], a mixture of thiazole intermediate C-2 (15.6 mmol), anhydrous potassium carbonate (23.4 mmol), and the corresponding amide intermediate C-3 (17.2 mmol) was added to dimethylformamide (80 mL) in a 150 mL three-necked flask at 25 °C. The mixture was stirred for 4 h (monitored by TLC). Then, the reaction solution was poured into 80 mL cold water, and got

precipitates, which was filtered, washed by water and dried to (intermediate C-4) was obtained, with a yield of 67.1%.

General procedure of target compound A₁-A₁₈, B₁-B₂₀,

C₁-C₂₀

For all target compounds, the final synthetic procedure was an esterification between the substituted benzene sulfonyl chloride and A-1, B-3 or C-4 respectively. And the reaction condition was completely same. Here, compound A series was taken for example to illustrate the reaction procedure. Intermediate A-1 (1.7 mmol) and triethylamine (5.1 mmol) were added and dissolved in 20 mL of dichloromethane in a clean 50 mL three-necked flask at room temperature. To the flask, different substituted benzene sulfonyl chloride (2.1 mmol) was added accordingly. The mixture was stirred overnight till the reaction was completed (monitored by TLC). The reaction was quenched with 20 mL water. Then ethyl acetate was added to extract and concentrate to get the crude solid, which was purified by the column chromatography (dichloromethane: methanol=50:1, v/v) and obtained the title compounds A₁-A₁₈ with a yield in the range of 70-96%. For title compound B₁-B₂₀, the yield ranged 74-90% and C₁-C₂₀ 68-95%.

Insecticidal assay

The insecticidal activity of compounds against *P. xylostella* and *Myzus persicae* was evaluated according to our previously reported methods [21]. After soaked in a solution of 500 and 50 µg/mL of compounds A₁-A₁₈, B₁-B₂₀ and C₁-C₂₀, diflubenzuron (positive control), or no compound (blank control) for 10s, the fresh cabbage discs (6 cm in diameter) were air-dried and placed in 9 cm petri dishes lined with wet filter paper. Ten *P. xylostella*/*Myzus persicae* (third instar larvae) were placed in the petri dishes and the survival insect individual was recorded after 72 h. The mortality rate was determined by the number of survival larvae comparing to the initial number. Compounds that were active at this concentration were further tested at 5 lower gradient concentrations (6.25, 12.5, 25.00, 50.00 and 100.00 µg/mL) to get LC₅₀. Each treatment was repeated three times. The data were analyzed with probit analysis to obtain LC₅₀ values. All experiments were conducted at 25 °C using laboratory reared test insects and were repeated according to statistical requirements. The death rate was estimated by calculating the ratio of the number of insects killed to the initial number.

The adjusted mortality rate (%) is as follows:

Adjusted mortality rate (%) = (death rate in the treatment group - death rate in the blank control group)/(1 - death rate in the blank control group) × 100.

Effect of highly active compound on chitinase, juvenile hormone and ecdysteroids in *P. xylostella*

Fresh cabbage discs (6 cm in diameter) were first soaked in a solution of 50 µg/mL of highly active compound for 10 s, air-dried and placed in a 9 cm petri dish lined with wet filter paper. Ten third instar larvae of *P. xylostella* were placed in the petri dishes and samples were taken and stored at -80 °C after 12, 24, 36 and 48 h of feeding by *P. xylostella*. Chitinase, juvenile hormone, and ecdysteroids activities were determined by MicroplateReader using commercial ELISA kits following the manufacturer's instructions. Each experiment was repeated three times. The blank control group was treated with distilled water containing 0 µg/mL of the compounds, and the positive control was selected as diflubenzuron that is a commercially available insecticide.

Molecular docking

A molecular docking station was built using the Ledge program according to the literature [32], the crystal structure of chitinase (PDB: 6JMA) of the *P. xylostella* was downloaded from the Protein Data Bank (<https://www.pdb.org>, accessed on 10 February 2023) and was processed with Pymol [33]. The molecular structures of highly active compound and diflubenzuron were drawn using ChemBioDraw Ultra 14.0 software and were optimized to minimize energy. A 17.5×15.3×14.7 docking box was generated with the Carboxin Standard in the protein as the center, and the docking station generated 20 ligand conformations with an RMSD less than 1.0 Å. The docking results were visualized in 3D by the Pymol software v.2.4.0.

Antibacterial activity assay

According to previously reported procedures [21], the title compounds A₁-A₁₈, B₁-B₂₀, C₁-C₂₀ were tested in vitro against *Xoo*, *Xoc*, *Xac* and *Psa* at concentrations of 100 and 50 µg/mL respectively. The commercial fungicides Bismethiazol (BT), Zinc Thiazole (TZ) and Thiodiazole copper (TC) were selected as positive controls. The solution containing no compound was set as negative control (CK). Compounds that were active at this concentration were further tested at 5 lower gradient concentrations (6.25, 12.50, 25.00, 50.00 and 100.00 µg/mL) to get EC₅₀. Each treatment was repeated three times. The inhibitory effect of compounds on bacteria was calculated based on optical density values using the following formula.

$$I (\%) = (CK - T) / T \times 100.$$

I (%) denotes the inhibition rate. CK denotes the OD value of the treatment with solvent with no tested compound. T denotes the OD value of the treatment in tested compound group.

Statistical analyses

All trials were performed in triplicate, and the results of each trial are shown as mean \pm standard deviation (SD). Analyses of variance (ANOVAs) were performed using SPSS Statistics 24.0 with and without the assumption of equal variance (with $P > 0.05$ taken as the significance level for both). Significant differences between treatment groups are indicated using various lowercase letters.

Abbreviations

Xoo	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i>
Xoc	<i>Xanthomonas oryzae</i> pv. <i>oryzicola</i>
Xac	<i>Xanthomonas axonopodis</i> pv. <i>citri</i>
Psa	<i>Pseudomonas syringae</i> pv. <i>actinidiae</i>
<i>P. xylostella</i>	<i>Plutella xylostella</i>
LC ₅₀	median lethal concentration
EC ₅₀	median effect concentration
TLC	thin-layer chromatography
BT	bismerthiazol
TZ	zinc thiazole
TC	thiodiazole copper
OD	optical density
ELISA	enzyme-linked immunosorbent assay
PDB	protein data bank

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13065-024-01151-0>.

Supplementary Material 1

Author contributions

Y.L. and C.L. wrote the main manuscript text and F.W., M.N., and X.R. prepared figures. X.Z. and L.J. prepared the final draft of the paper. All authors reviewed the manuscript.

Funding

This work was supported by the National Nature Science Foundation of China [grant numbers 21967006].

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.
Not applicable.

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Received: 7 February 2024 / Accepted: 22 February 2024

Published online: 06 March 2024

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