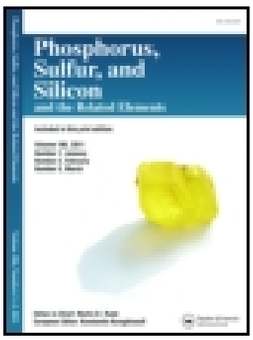

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# Novel pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties: Design, synthesis, and insecticidal activity

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**ABSTRACT**

A series of novel pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties were designed, synthesized, and evaluated for their insecticidal activity. Bioassays indicated that some of the target compounds exhibited good insecticidal activities against *Plutella xylostella* (*P. xylostella*), *Vegetable aphids* (*V. aphids*), and *Empoasca vitis* (*E. vitis*). In particular, compound (*E*)-2-((5-(2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)-*N*′-(4-(trifluoromethyl)-benzylidene)acetohydrazide (**6s**) revealed excellent insecticidal activities against *P. xylostella*, *V. aphids,* and *E. vitis* with the 50% lethal concentration ($LC_{50}$) values of 5.23, 7.07, and 1.61 mg/L, respectively, which were similar to or even better than those of chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin. These results indicated that novel pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties could be developed as novel and promising insecticides.

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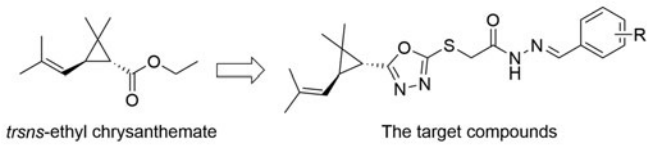
**GRAPHICAL ABSTRACT**




## Introduction

In recent years, crop damage from harmful pests has become more and more common and traditional pesticides application can often lead to the development of resistance pests, thus bringing about enormous losses in crop production.[1,2] Nowadays, some insecticides, such as fluobendiamide, chlorpyrifos, tebufenozide, RH-5849, chlorantraniliprole, have been used to control plant harmful pests in agricultural production.[3,4] However, the long-term use of available traditional insecticides not only leads to the drug resistance but also results in a harmful influence on the safety of environment and plants. Therefore, the development of novel and promising insecticides with a new mode of action is an urgent task.

Hydrazone, a highly efficient pharmacophore and widely used in drug design, has demonstrated significant insecticidal,[5,6] fungicidal,[7,8] antibacterial,[9,10] antioxidant,[9] anti-tumor,[10] anticonvulsant,[11,12] anti-inflammatory,[13,14] antimalarial,[15] and anti-tuberculosis [16–18] activities. Meanwhile, 1,3,4-oxadiazole and their derivatives, an important class of heterocyclic derivatives, represented a key structure in pharmaceutical and pesticide chemistry due to their wide range of bioactivities including antifungal,[19,20] antibacterial,[21–24] insecticidal,[25] herbicidal,[26] anticancer,[27] anti-HIV-1,[28] antihepatitis,[29] antitumor,[30] and anti-inflammatory [31] activities. In addition, recent works have highlighted that the thioether group is a highly efficient pharmacophore that is widely concerned in the research of new pesticide creation due to their wide range of biological activities, such as antifungal,[32] antibacterial,[24] antiviral,[33] nematicidal,[24,34] and insecticidal [35] activities.

Esbiothrin is one of the most important insecticides derived from natural sources. Its molecular framework is ethyl chrysanthemate which is the main component isolated from the natural plant pyrethrum.[36] Literature reports that ethyl chrysanthemate is a natural insecticide with good insecticidal activity, high efficiency, low toxicity, broad spectrum, good biodegradability, environmentally friendly, and harmless to humans and animals.[36] However, due to the instability of ultraviolet light in natural light, it is greatly

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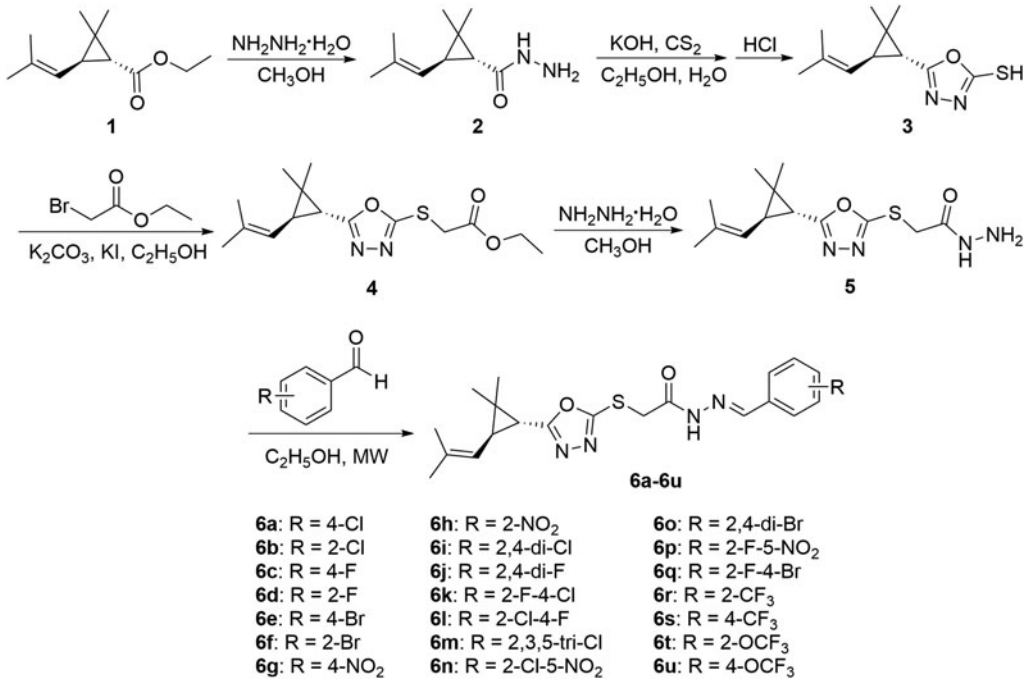


**Scheme 1.** Synthetic route of the target compounds **6a—6u**.

limited in the wide application, limited to the use of indoor health pest control. Since the successful development of the first light-stable pyrethroid insecticide Phenothrin in the 1970s, which has been widely used in agricultural pest control. However, due to their repellent effect on bees, high toxic to silkworms and natural enemies, pyrethroid insecticides cannot be used in orchards, silkworm breeding and surrounding areas, rice fields, rivers, ponds and surrounding areas.[37] In order to solve the light stability and reduce the harm to aquatic organisms of pyrethroid insecticides, many chemists optimized the molecular structure of ethyl chrysanthemate by introducing new active groups into the molecular structure to build a novel family of pyrethroid insecticides, such as cypermethrin, fenpropathrin, *cis*-cypermethrin, deltamethrin, fenvalerate.

To develop highly active and readily available insecticidal inhibitors, in this study, we aim to introduce the hydrazone and 1,3,4-oxadiazole thioether moieties to the *trans*-ethyl chrysanthemate skeleton to build a novel family of bioactive molecules against *Plutella xylostella* (*P. xylostella*), *Vegetable aphids* (*V. aphids*), and *Empoasca vitis* (*E. vitis*). To the best of our knowledge, it is the first report on the insecticidal activity of pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties.

## Results and discussion

### Chemistry

The synthetic route of the target compounds **6a**–**6u** was depicted in Scheme 1. As shown in Scheme 1, using *trans*-ethyl chrysanthemate as the starting material, the intermediates **2**–**5** was prepared according to the reported methods.[19–24] The target compounds **6a**–**6u** were obtained under microwave irradiation reaction at 90 °C and 150 W for 30 min with the yields of 81.3–87.3%, and confirmed their structures by IR, $^1$H NMR, $^{13}$C NMR, ESI-MS, and elemental analysis.

The $^1$H NMR spectra of the title compounds **6a**–**6u** exhibited a singlet at 11.77–12.12 and 8.00–8.43 ppm, which indicated the presence of −NH− and −N=CH−, respectively. A doublet at 5.00–5.01 ppm indicated the presence of −C=CH−. Meanwhile, typical chemical shifts at 173.74–159.25 ppm in the $^{13}$C NMR spectra confirmed the presence of oxadiazole ring and C = O. In addition, the IR spectra exhibited characteristic absorption near 2970−2950, 2920, 1680, and 1570 cm$^{-1}$, which indicated the presence of –$CH_3$, –$CH_2$–, C = C, and C = N, respectively.

### Biological evaluations

In this study, the insecticidal activities of the target compounds **6a**–**6u** against *P. xylostella*, *V. aphids*, and *E. vitis* were evaluated using the previously reported methods.[38–41] The commercial insecticides of chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin, which were commonly used in China, were used as the positive controls and evaluated at the same conditions. The results of the preliminary bioassays, as listed in **Table S 1 (Supplemental Materials)**, indicated that the target compounds **6a**–**6u** showed good insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* at the concentration of 500 mg/L, with the inhibitory effect values of 53.33–100.00%, 53.33–100.00%, and 56.67–100.00%, respectively. Meanwhile, **Table S 1** also showed that compounds **6c**, **6d**, **6j**, **6k**, **6l**, **6m**, **6p**, **6q**, **6r**, **6s**, **6t**, and **6u** exhibited significant insecticidal activities against *P. xylostella* and *E. vitis*, with a value of 100.00% at the concentrations of 500 mg/L. Similar, compounds **6j**, **6m**, **6r**, **6s**, **6t**, and **6u** exhibited significant insecticidal activity against *V. aphids*, with a value of 100.00% at the

concentrations of 500 mg/L, which were equally to those of chlorpyrifos (100.00%), beta cypermethrin (100.00%), spinosad (100.00%), and azadirachtin (100.00%).

The 50% lethal concentration ($LC_{50}$) values of the target compounds as well as the commercial pesticides chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin against *P. xylostella, V. aphids*, and *E. vitis* were also determined and presented in **Table S 2 (Supplemental Materials)**. **Tables S2** showed that the target compounds **6a–6u** exhibited insecticidal activities against *P. xylostella, V. aphids*, and *E. vitis* with the $LC_{50}$ values of 2.23–312.42, 7.07–334.77, and 1.61–266.58 mg/L, respectively. Especially, compound **6s** revealed the best insecticidal activities against *P. xylostella, V. aphids*, and *E. vitis* with the $LC_{50}$ values of 5.23, 7.07, and 1.61 mg/L, respectively, which were similar to or even better than those of chlorpyrifos (7.71, 11.37, and 6.25 mg/L, respectively), beta cypermethrin (12.77, 8.41, and 4.67 mg/L, respectively), spinosad (4.88, 13.55, and 7.93 mg/L, respectively), and azadirachtin (10.22, 18.28, and 14.34 mg/L, respectively). These results indicated that novel pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties could be developed as novel and promising insecticides.

### Structure-activity relationship analysis

Based on the insecticidal activities of the target compounds against *P. xylostella*, *V. aphids,* and *E. vitis*, shown in **Table S 2**, the preliminary structure-activity relationship (SAR) showed that the type and position of the substituent group R at the phenyl ring had an important effect on the insecticidal activities of the target compounds. First, with the presence of electron-drawing groups (–$CF_3$, –$OCF_3$, and –F) at 2 and/or 4-position of phenyl, the corresponding compounds presented better bioactivities against *P. xylostella*, *V. aphids,* and *E. vitis* in the order of **6s** > **6e**, **6r** > **6f**, and **6j** > **6i**. Second, compared with the same electron withdrawing group on phenyl, the insecticidal activities against *P. xylostella*, *V. aphids,* and *E. vitis* of the corresponding compounds with the R substituent group at 4-position is higher than those of at 2-position in the order of **6a** > **6b**, **6c** > **6d**, and **6s** > **6r**.

## Experimental

### General methods

The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer (Bruker, Rheinstetten, Germany) in KBr disk. $^1$H NMR and $^{13}$C NMR (solvent DMSO-$d_6$) spectral analyses were performed on a Bruker DRX-400 NMR spectrometer (Bruker, Rheinstetten, Germany) at room temperature using TMS as an internal standard. Elemental analysis was carried out using an Elemental Vario-III CHN analyzer (Elementar, Hanau, German). Mass spectral studies were conducted on an Agilent 5973 organic mass spectrometer (Agilent Technologies, Palo Alto, Canada). Microwave experiments were carried out using a CEM Discover Labmate microwave apparatus (300 W with ChemDriver Software). Analytical TLC was performed on silica gel $GF_{254}$ (200–300 mesh). All solvents were dried by standard methods in advance and distilled before use. The Supplemental Materials contains sample $^1$H, $^{13}$C NMR and IR spectra for products **6a–6u** (Figures S 1–S 84).

### Preparation of the key intermediate 5

As shown in Scheme 1, a mixture of *trans*-ethyl chrysanthemate (19.6 g, 100 mmol) and 80% hydrazine hydrate (18.8 g, 300 mmol) was dissolved in anhydrous ethanol (50 mL) in a 250 mL of reaction flask. Then, the mixture was further reacted at 100 °C for 18 h. Upon completion of the reaction (monitored by TLC), the mixture was concentrated and dried under vacuum, the intermediate **2** was obtained after recrystallization from ethanol.

A mixture of intermediate **2** (18.2 g, 100 mmol) and KOH (8.4 g, 150 mmol) were dissolved in anhydrous ethanol (150 mL) in a 500 mL of reaction flask. Then, $CS_2$ (22.8 g, 300 mmol) was added dropwise to completely dissolve the reaction mixture under stirring at room temperature. Upon completion of addition, the reaction solution was continuously stirred for 18 h at 72 °C. The solvent was removed under reduced pressure, and the obtained mixture was adjusted to pH = 4−5 with diluted HCl. The residue was dried and the intermediate **3** was attained after recrystallization from ethanol.

A mixture of intermediate **3** (22.4 g, 100 mmol), anhydrous $K_2CO_3$ (13.8 g, 100 mmol), and KI (1.7 g, 10 mmol) was dissolved in anhydrous ethanol (150 mL) in a 500 mL of reaction flask. Then, ethyl bromoacetate (25.1 g, 150 mmol) was added dropwise to completely dissolve the reaction mixture under stirring at room temperature. Upon completion of addition, the reaction solution was continuously stirred at 72 °C. Upon completion of the reaction (monitored by TLC), the mixture was concentrated under vacuum, followed by filtration. The residue was dried and the intermediate **4** was obtained after recrystallization from ethanol.

To a solution of intermediate **4** (31.0 g, 100 mmol) in anhydrous ethanol (50 mL), 80% hydrazine hydrate (18.8 g, 300 mmol) was slowly added at room temperature. Then, the mixture was further reacted at 100 °C for 10 h. The solvent was removed under reduced pressure, and the crude product was further recrystallized from ethanol to obtain the key intermediate **5**.

### Preparation of the target compounds 6a−6u

To a 50 mL round-bottom flask fitted with a magnetic stirring bar, intermediate **5** (3.0 g, 1 mmol) and the solution of substituted benzaldehyde (1.2 mmol) in anhydrous ethanol (10 mL) were added in order, then the round-bottom flask was sealed and placed in the synthetic reactor and reacted under microwave irradiation at 90 °C with 150 W for 20 min. Upon completion of the reaction (monitored by

TLC), the mixture was concentrated under vacuum and purified after recrystallization from ethanol to obtain the target compounds **6a**−**6u**. The physical characteristics, IR, $^1$H NMR, $^{13}$C NMR, ESI-MS, and elemental analysis data for all the target compounds **6a**–**6u** are shown in Supplementary Materials, and the data for the representative compound **6s** are shown below.

*(E)-2-((5-(2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(4-(trifluoromethyl)benzylidene)acetohydrazide* (**6s**). White solid; mp 156−157 °C; yield 84.1%; $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 12.06 (s, 1 H, −N = CH−), 8.27 − 8.31 (q, 2 H, Ar−H), 8.13 (s, 1 H, −NH−), 7.97 (d, 2 H, $J$ = 11.60 Hz, Ar−H), 5.01 (d, 1 H, $J$ = 10.40 Hz, −C = CH−), 4.60 (s, 1 H, $-CH_2-$), 4.17 (s, 1 H, $-CH_2-$), 1.97−2.06 (m, 2 H, 2 × −CH−), 1.67 (d, 6 H, $J$ = 13.20 Hz, 2 × $-CH_3$), 1.15 (s, 3 H, $-CH_3$), 1.08 (s, 3 H, $-CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 168.98, 167.82, 163.80, 162.64, 148.33, 145.38, 142.23, 140.65, 135.36, 128.61, 128.39, 124.52, 121.40, 39.40, 35.23, 31.54, 27.71, 26.50, 25.79, 21.64, 18.73; IR (KBr, cm$^{-1}$) $\nu$: 3419, 3214, 3075, 2923, 2875, 1705, 1687, 1616, 1563, 1524, 1488, 1457, 1410, 1362, 1343, 1326, 1236, 1186, 1108, 1081, 1009, 992, 973, 956, 882, 855, 836, 750, 726; Anal. Calcd for $C_{21}H_{23}F_3N_4O_2S$: C 55.74%, H 5.12%, F 12.60%, N 12.38%; found: C 55.96%, H 5.33%, F 12.73%, N 12.48%; ESI-MS: 452.0 $[M + H]^+$.

### Insecticidal biological assay

All bioassays were performed on test organisms reared in the lab and repeated at 25 ± 1 °C according to statistical requirements. Mortalities were corrected using Abbott's formula.[21,22] Evaluations were based on a percentage scale (0 = no activity and 100% = complete eradication). Chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin were used as controls, and the solvent water was used as blank control. Three replicates and at least five concentrations were performed for each experiment and mortalities were determined after 72 h.

### Insecticidal activity against P. xylostella

Fresh cabbage discs (diameter 2 cm) were dipped into the prepared solutions containing compounds **6a**−**6u** for 10 s, dried in air and placed in a petri dish (diameter 9 cm) lined with filter paper. Thirty larvae of second-instar *P. xylostella* were carefully transferred to the petri dish, and placed in the artificial climate chamber with a light-dark period of 14:10 h at 25 ± 1 °C and 75% relative humidity.

### Insecticidal activity against V. aphids

The agar was mixed with distilled water to form agar solution with 1.3% mass fraction. 5 ml liquid agar was absorbed by a micropipette and added into a culture dish 5 cm in diameter and 2 cm in height. The liquid agar was cooled and solidified. Fresh cabbage discs (diameter 4 cm) were dipped into the prepared solutions containing compounds **6a** − **6u** for 10 s, dried in air and placed the back face up in the agar-coated petri dish above. Thirty larvae of third-instar *V. aphids* were carefully transferred to the petri dish, sealed with a perforated fresh-keeping film, and placed in the artificial climate chamber with a light-dark period of 14:10 h at 25 ± 1 °C and 75% relative humidity.

### Insecticidal activity against E. vitis

Fresh the tender tea shoots (length 13 cm) were dipped into the prepared solutions containing compounds **6a**−**6u** for 10 s, dried in air and wrapped with wet cotton and parafilm film, then packed in test tube (3 × 20 cm). Ten tender tea stems were placed in each test tube. Thirty larvae of second-third-instar *E. vitis* were carefully transferred to the tube. Finally, the opening of the tube was wrapped with gauze and placed in the artificial climate chamber with a light-dark period of 14:10 h at 25 ± 1 °C and 75% relative humidity.

## Conclusions

In conclusion, a series of novel pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties were designed and synthesized. Bioassays indicated that some of the target compounds exhibited better insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis*. Especially, compound **6s** revealed the best insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* which were similar to or even better to those of chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin. Our research demonstrated that novel pyrethrin derivatives containing hydrazone and 1,3,4-oxadiazole thioether moieties could effectively control *P. xylostella*, *V. aphids*, and *E. vitis*. Furthermore, according to the requirements of pesticide registration in China, further field studies on the photostability, biological efficacies, crop safety, and toxicities of compound **6s** as insecticidal candidates will be performed in our next work.

## Acknowledgement

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## Conflicts of interest

The authors declare no conflict of interest.

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