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ORIGINAL PAPER

Design, synthesis, and biological evaluation of novel pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties as active insecticidal agents

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Abstract

To discover and develop novel active molecules, in this study, a series of novel pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties were designed and synthesized. Bioassay results revealed that some of the target compounds possessed good insecticidal activities against *Plutella xylostella* (*P. xylostella*), *Vegetable aphids* (*V. aphids*), and *Empoasca vitis* (*E. vitis*), respectively, which were even better than those of the commercial insecticidal agents chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin. The results favored our rational design intention and provide a new class of small-molecule inhibitors available for the development of active insecticidal agents targeting *P. xylostella*, *V. aphids*, and *E. vitis.*

Keywords Pyrethrin · *trans*-Ethyl chrysanthemate · 1,3,4-Oxadiazole · Thioether · Insecticidal activity

Introduction

For years, crop damage from harmful pests (e.g., *Plutella xylostella* (*P. xylostella*), *Vegetable aphids* (*V. aphids*), and *Empoasca vitis* (*E. vitis*)) has become more common and the continued application of traditional pesticides can often lead to the development of more resistant pests, thus bringing about enormous losses in crop production (Talekar and Shelton 1993). However, the application of traditional pesticides is not effective, resulting in high residues or negative impact on the environment. Therefore, finding novel insecticidal agents remains a daunting task in pesticide science.

The pyrethrum plants (*Tanacetum cinerariifolium,* family Asteraceae) synthesize a class of compounds called pyrethrins, which serve as efficient insecticides and have been used by people for pest control since ancient times since they are harmless to people and most vertebrates (Casida 1973; Casida and Quistad 1995; Katsuda 1999). However, early varieties, such as natural pyrethroids, are easily decomposed and ineffective under light, and are only suitable for indoor pest control. Many scientists have conducted long-term studies to find out the unstable parts of the molecular structure, which are easily decomposed by light. In the early 1970s, they made a breakthrough in the structural changes and synthesized the first photostable permethrin for pest control in agriculture and forestry. Since then, there have been many varieties of photostable pyrethrin insecticides, for example, allethrin, permethrin, fenpropathrin, cypermethrin, deltamethrin, and lambda-cyhalothrin, which have the advantages of good biodegradability, environmental friendliness and harmlessness to humans and livestock, were developed (Holan and Reimund 1982; Poulter et al. 1977).

1,3,4-Oxadiazole derivatives belong to an important class of heterocyclic compounds and attracted more and more attention in the development of pesticides (Suwiński

Zaibo Yang and Pei Li contributed equally to this work.

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and Szczepankiewicz 2008). In the past few years, lots of 1,3,4-oxadiazole derivatives with better bioactivity have been developed by pesticide chemistry companies that possessed good prospects for commercialization. Different classes of oxadiazoles possess an extensive spectrum of pharmacological activities such as antimalarial (Hutt et al. 1970), anti-inflammatory (Omar et al. 1996), anticonvulsant (Zarghi et al. 2005), analgesic (Husain and Ajmal 2009), antibacterial (Xu et al. 2012), antitumor (Luo et al. 2012), herbicidal (Zhang et al. 2016), and antifungal (Xu et al. 2013; Liu et al. 2008; Yang et al. 2007) 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. In the past few years, great progress has been made in the synthesis of thioether compounds, and the biological activity research has found that compounds containing thioether group have a wide range of biological activities, such as anti-cancer (Shen et al. 2013; Yang et al. 2007), antibacterial (Bao et al. 2013; Li et al. 2018), nematocidal (Li et al. 2018), and antivirus (Long et al. 2008) activities. In the previous work, many of 1,3,4-oxadiazole derivatives containing a thioether group were synthesized and bioassay results showed that the target compounds revealed good antifungal (Shi et al. 2019), antibacterial (Li et al. 2018), antiviral (Gan et al. 2016), nematicidal (Li et al. 2018; Chen et al. 2018), and insecticidal (Guo et al. 2017) activities.

To aid the development of highly active novel compounds, as shown in Fig. 1, we aimed to introduce the 1,3,4-oxadiazole and thioether groups into the pyrethrin structure to design and synthesize a series of novel pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties as active insecticidal agents.

Materials and methods

General information

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 $CDCl_3$ or 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). 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}. Column chromatographic purification was carried out using silica gel. All solvents were dried by standard methods in advance and distilled before use.

Synthesis of (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carbohydrazide (2)

As shown in Scheme 1, intermediate **2** was prepared via hydrazidation reaction according to the reported methods (Xu et al. 2012; Li et al. 2018; Gan et al. 2016; Chen et al. 2018). A mixture of *trans*-ethyl chrysanthemate (100 mmol) and hydrazine hydrate (300 mmol) was dissolved with 50 mL of anhydrous ethanol in 250-mL reaction flask and reacted at 100 °C for 18 h. The residue was dried and obtained after recrystallization from ethanol to obtain intermediate **2**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.21 (s, 1H, –NH–), 4.88 (d, 1H, J = 8.00 Hz, –C=CH–), 3.91 (s, 2H, $–NH_2$), 2.09 (t, 1H, J = 2.00 Hz, –CH–), 1.76 (d, 1H, J = 2.00 Hz, –CH–), 1.24 (s, 3H, $–CH_3$), 1.23 (s, 3H, $–CH_3$), 1.11 (s, 3H, $–CH_3$), 1.09 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 172.6, 135.3, 121.3, 34.8, 30.8, 28.9, 25.9, 22.2, 20.3, 18.5.

Synthesis of 5-((1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazole-2-thiol (3)

Intermediate **3** was prepared via cyclization reaction according to the reported methods (Xu et al. 2012; Li et al. 2018; Gan et al. 2016; Chen et al. 2018). A mixture of 100 mmol intermediate **2** and 150 mmol KOH was dissolved in 150 mL of anhydrous ethanol in 500-mL reaction flask. Then 300 mmol of CS_2 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. Then the solvent was removed under reduced pressure, a certain amount of water was added to terminate the reaction, and the obtained mixture was adjusted to pH 4–5 with HCl. A large amount

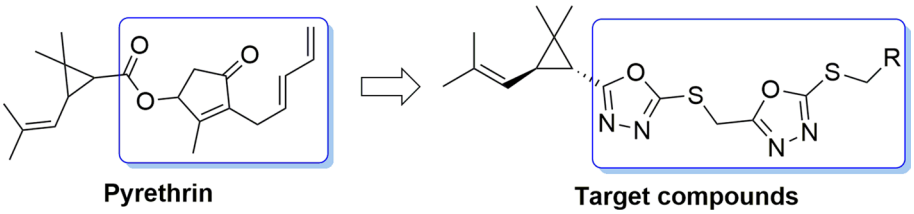
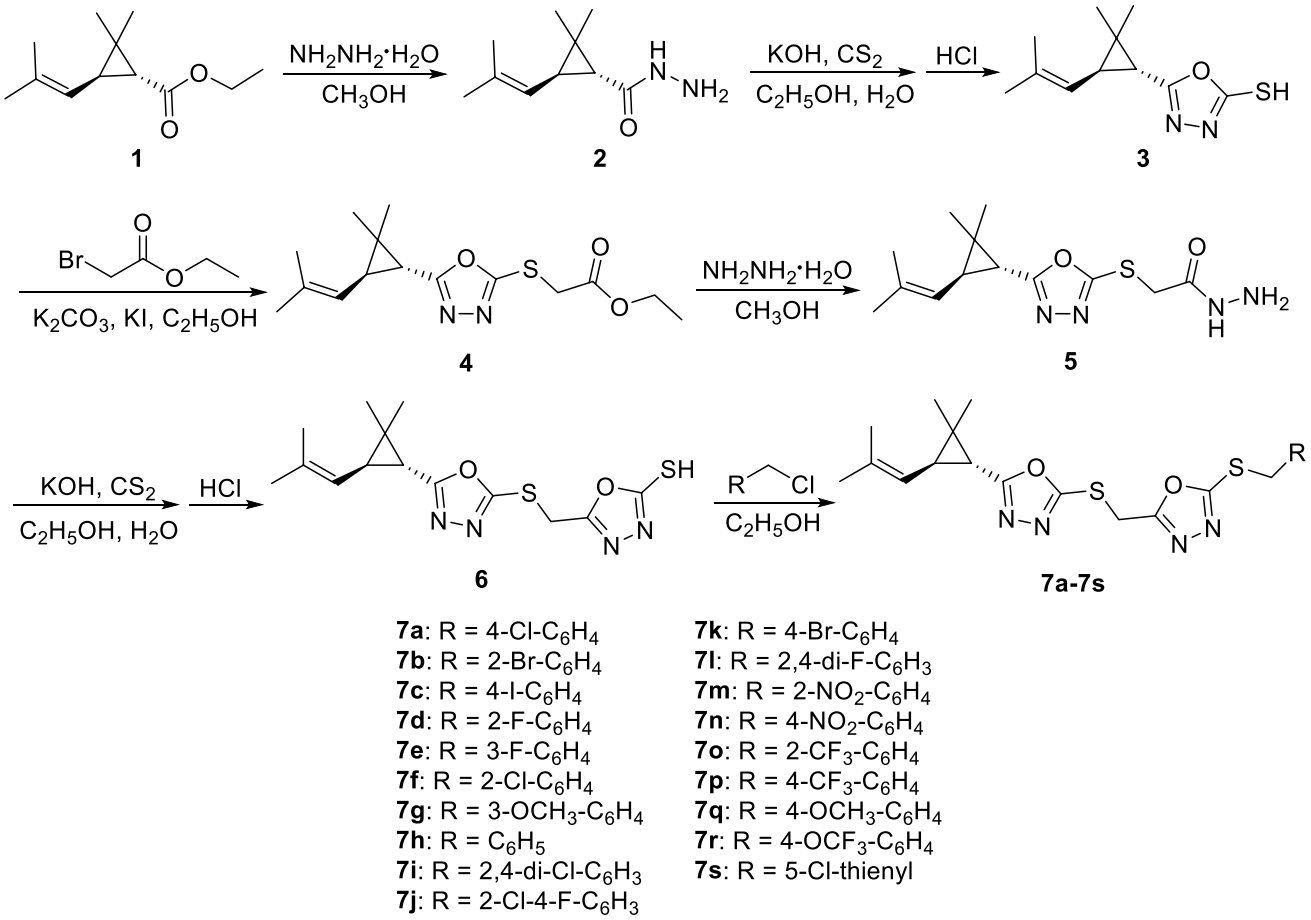


Fig. 1 Design route of the target compounds **7a**–**7s**



Scheme 1 Synthetic route of the target compounds **7a**–**7s**

of solid was precipitated, followed by filtration. The residue was dried and intermediate **3** was attained after recrystallization with ethanol. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 14.34 (s, 1H, –SH), 5.01 (d, 1H, J = 8.00 Hz, –C=CH–), 1.99 (t, 1H, J = 5.60 Hz, –CH–), 1.92 (d, 1H, J = 5.20 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.01 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 177.9, 163.8, 135.6, 121.1, 30.8, 27.7, 26.3, 25.8, 21.4, 21.4, 18.7.

Synthesis of ethyl 2-((5-((1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)acetate (4)

Intermediate **4** was prepared via thioetherification reaction according to the reported methods (Xu et al. 2012; Li et al. 2018; Chen et al. 2018). A mixture of 100 mmol intermediate **3**, 100 mmol anhydrous K_2CO_3 and 10 mmol KI was dissolved with 150 mL of anhydrous ethanol in 500-mL reaction flask. Then 150 mmol of ethyl 2-bromoacetate was added dropwise to completely dissolve the reaction mixture under stirring at room temperature. Upon completion of the reaction (monitored by TLC), the mixture was concentrated under vacuum, followed by filtration. The residue was dried and intermediate **4** was obtained after recrystallization from ethanol. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 5.03 (d, 1H, J = 6.40 Hz, –C=CH–), 4.18–4.11 (m, 4H, 2×–CH_2–), 2.08 (t, 1H, J = 4.40 Hz, –CH–), 2.01 (d, 1H, J = 4.00 Hz, –CH–), 1.71 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.17 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.08 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 135.7, 121.7, 62.3, 34.48, 31.8, 28.1, 26.7, 26.1, 24.4, 21.9, 19.0, 14.7.

Synthesis of 2-((5-((1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl) thio)acetohydrazide (5)

Intermediate **5** was prepared via hydrazidation reaction according to the reported methods (Xu et al. 2012; Li et al. 2018; Gan et al. 2016; Chen et al. 2018). To a solution of intermediate **4** (100 mmol) in anhydrous ethanol (50 mL), 300 mmol of 98% hydrazine hydrate was slowly added at room temperature. Then the mixture further reacted at 100 °C for 10 h. The solvent was removed under reduced

pressure, and the residue was washed with water and anhydrous ethanol. The obtained crude product was further recrystallized and dried, giving intermediate **5**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.26 (s, 1H, –NH–), 4.96 (d, 1H, J = 8.80 Hz, –C=CH–), 3.92 (s, 2H, –NH_2), 3.82 (s, 2H, –CH_2–), 2.18 (t, 1H, J = 8.00 Hz, –CH–), 1.74 (s, 3H, –CH_3), 1.73 (s, 3H, –CH_3), 1.22 (s, 3H, –CH_3), 1.19 (s, 3H, –CH_3), 0.87 (d, 1H, J = 7.60 Hz, –CH–); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 168.7, 168.1, 163.2, 136.6, 120.3, 33.3, 32.1, 28.3, 27.2, 25.6, 21.5, 21.4, 18.6.

Synthesis of 5-(((5-((1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole-2-thiol (6)

Intermediate **6** was prepared via cyclization reaction according to the reported methods (Xu et al. 2012; Li et al. 2018; Gan et al. 2016; Chen et al. 2018). A mixture of 100 mmol intermediate **5** and 150 mmol KOH was dissolved in 150 mL of anhydrous ethanol in 500-mL reaction flask. Then 300 mmol of CS_2 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. Subsequently, the solvent was removed under reduced pressure; a certain amount of water was added to end the reaction, and the resulting mixture was adjusted to pH 4–5 with HCl. A large amount of solid was precipitated, followed by filtration. The residue was dried and intermediate **6** was obtained after recrystallization from ethanol. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 14.58 (s, 1H, –SH), 5.03 (d, 1H, J = 8.00 Hz, –C=CH–), 4.62 (s, 2H, –CH_2–), 2.09 (d, 1H, J = 5.20 Hz, –CH–), 2.00 (t, 1H, J = 5.60 Hz, –CH–), 1.71 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.17 (s, 3H, –CH_3), 1.07 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.3, 167.9, 135.4, 121.5, 34.2, 31.6, 27.7, 26.5, 25.9, 21.7, 18.8, 14.5.

Synthesis of the target compounds 7a–7s

Target compounds **7a–7s** were synthesized based on the previously reported method (Xia et al. 2016). To a 50-mL round-bottom flask fitted with a magnetic stirring bar, intermediate **6** (1 mmol) and anhydrous ethanol (5 mL) were added. Then the solution of RCH_2Cl (1.2 mmol) in anhydrous ethanol (5 mL) was added dropwise to the above solution, which was sealed and placed in the synthetic reactor and irradiated in microwave at 90 °C and 150 W for 15 min. Upon completion of the reaction (monitored by TLC), the mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (ethyl acetate:petroleum ether = 1:8).

The structures of the target compounds **7a**–**7s** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. The physical characteristic data of intermediates **2–5** and the target compounds **7a–7s** are shown in Table 1, and the IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis data for all target compounds **7a–7s** are shown below.

2-((4-Chlorobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole (**7a**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.46–7.36 (m, 4H, Ar–H), 5.03 (d, 1H, J = 8.00 Hz, –C=CH–), 4.76 (s, 2H, –SCH_2–), 4.48 (s, 2H, –SCH_2–), 2.07 (t, 1H, J_1 = 2.00 Hz, J_2 = 5.60 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.71 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 163.8, 161.0, 135.7, 133.4, 132.0, 128.5, 124.4, 121.3, 37.3, 31.7, 27.9, 26.5, 26.2, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 3435.71, 3207.99, 3125.45, 3062.84, 2951.48, 2924.04, 2870.22, 1686.57, 1573.02, 1484.92, 1463.02, 1439.26, 1376.41, 1280.32, 1221.45, 1153.65, 1114.64, 1075.64, 1042.39, 1022.65, 955.02, 895.10, 852.51, 755.34, 714.29; Anal. calcd for $C_{21}H_{23}ClN_4O_2S_2$: C 54.47%, H 5.01%, N 12.10%, found: C 54.65%, H 5.27%, N 12.33%.

2-((4-Bromobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole (**7b**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.66 (dd, 1H, J_1 = 1.20 Hz, J_2 = 8.00 Hz, Ar–H), 7.56 (dd, 1H, J_1 = 1.60 Hz, J_2 = 7.60 Hz, Ar–H), 7.36–7.32 (m, 1H, Ar–H), 7.28–7.24 (m, 1H, Ar–H), 5.02 (d, 1H, J = 7.60 Hz, –C=CH–), 4.76 (s, 2H, –SCH_2–), 4.55 (s, 2H, –SCH_2–), 2.01 (t, 1H, J_1 = 6.00 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.9, 164.1, 161.0, 137.8, 136.9, 135.4, 131.7, 121.3, 94.4, 35.7, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.8; IR (KBr, cm^{-1}) ν: 3566.53, 2969.90, 2951.68, 2925.95, 2880.26, 1748.28, 1731.01, 1680.80, 1659.98, 1643.26, 1621.68, 1573.51, 1327.02, 1253.34, 1152.45, 1116.62, 1070.57, 1012.08, 971.19, 803.86, 749.82, 721.40; Anal. calcd for $C_{21}H_{23}BrN_4O_2S_2$: C 49.70%, H 4.57%, N 11.04%; found: C 49.83%, H 4.69%, N 11.22%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-5-(((5-((4-iodobenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7c**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.67 (d, 2H, J = 8.40 Hz, Ar–H), 7.22 (d, 2H, J = 8.00 Hz, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.74 (s, 2H, –SCH_2–), 4.42 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 6.00 Hz, J_2 = 7.60 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.02 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.9, 164.1, 161.0, 137.8, 136.9, 131.7, 121.3, 94.4, 35.7, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.8; IR (KBr, cm^{-1}) ν: 3648.26, 3566.52, 2951.28, 2924.76, 2874.06, 1680.99, 1573.49, 1483.67, 1399.41, 1377.89,

Table 1 Physical characteristics data of intermediates **2**–**5** and the target compounds **7a**–**7s**

Compounds	Molecular formula	Form	Yield (%)	R_f value	mp (°C)
2	$C_{10}H_{18}N_2O$	Gray-white solid	83.2	0.10	126.7–127.5
3	$C_{11}H_{16}N_2OS$	White solid	83.4	0.20	104.6–105.3
4	$C_{15}H_{22}N_2O_3S$	Pale yellow liquid	86.1	0.55	–
5	$C_{13}H_{20}N_4O_2S$	White solid	93.0	0.10	158.9–159.3
6	$C_{14}H_{18}N_4O_2S_2$	Brown-yellow viscous liquid	85.0	0.20	–
7a	$C_{21}H_{23}ClN_4O_2S_2$	Pale yellow liquid	78.9	0.45	–
7b	$C_{21}H_{23}BrN_4O_2S_2$	Pale yellow liquid	80.6	0.45	–
7c	$C_{21}H_{23}IN_4O_2S_2$	Pale yellow liquid	80.7	0.45	–
7d	$C_{21}H_{23}FN_4O_2S_2$	Pale yellow liquid	80.9	0.45	–
7e	$C_{21}H_{23}FN_4O_2S_2$	Pale yellow liquid	82.6	0.46	–
7f	$C_{21}H_{23}ClN_4O_2S_2$	Pale yellow liquid	81.7	0.45	–
7g	$C_{22}H_{26}N_4O_3S_2$	Pale yellow liquid	83.9	0.45	–
7h	$C_{21}H_{24}N_4O_2S_2$	Pale yellow liquid	81.6	0.45	–
7i	$C_{21}H_{22}Cl_2N_4O_2S_2$	Pale yellow liquid	82.3	0.44	–
7j	$C_{21}H_{22}ClFN_4O_2S_2$	Pale yellow liquid	79.8	0.44	–
7k	$C_{21}H_{23}BrN_4O_2S_2$	Pale yellow liquid	82.4	0.45	–
7l	$C_{21}H_{22}F_2N_4O_2S_2$	Pale yellow liquid	83.8	0.45	–
7m	$C_{21}H_{23}N_5O_4S_2$	Pale yellow liquid	84.6	0.45	–
7n	$C_{21}H_{23}N_5O_4S_2$	Pale yellow liquid	85.1	0.45	–
7o	$C_{22}H_{23}F_3N_4O_2S_2$	Pale yellow liquid	82.9	0.44	–
7p	$C_{22}H_{23}F_3N_4O_2S_2$	Pale yellow liquid	82.7	0.43	–
7q	$C_{22}H_{26}N_4O_3S_2$	Pale yellow liquid	83.7	0.45	–
7r	$C_{22}H_{23}F_3N_4O_3S_2$	Pale yellow liquid	81.9	0.45	–
7s	$C_{19}H_{21}ClN_4O_2S_3$	Pale yellow liquid	82.1	0.42	–

1327.09, 1275.08, 1252.05, 1152.62, 1059.61, 1008.00, 970.19, 852.78, 831.78, 800.83, 751.58, 720.17; Anal. calcd for $C_{21}H_{23}IN_4O_2S_2$: C 45.49%, H 4.18%, N 10.10%; found: C 45.61%, H 4.35%, N 10.22%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((2-fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7d**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.50–7.46 (m, 1H, Ar–H), 7.39–7.33 (m, 1H, Ar–H), 7.23–7.13 (m, 2H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.50 (s, 2H, –SCH_2–), 2.07 (t, 1H, J_1 = 6.00 Hz, J_2 = 7.60 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 163.8, 161.0, 135.4, 131.8, 130.7, 125.0, 123.8, 123.7, 121.3, 116.1, 115.9, 31.7, 30.2, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2951.87, 2926.12, 2875.23, 1617.68, 1574.08, 1490.99, 1478.16, 1378.65, 1234.21, 1152.61, 1095.62, 1014.51, 969.56, 758.91; Anal. calcd for $C_{21}H_{23}FN_4O_2S_2$: C 56.48%, H 5.19%, N 12.55%; found: C 56.61%, H 5.32%, N 12.64%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((3-fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7e**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.39–7.33 (m, 1H, Ar–H), 7.29–7.25 (m, 2H, Ar–H), 7.14–7.09 (m, 1H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.74 (s, 2H, –SCH_2–), 4.49 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.03 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.8, 164.2, 161.0, 139.9, 135.4, 131.0, 130.9, 125.6, 121.3, 116.1, 115.2, 115.0, 35.6, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2952.33, 2926.37, 2878.52, 1673.14, 1616.99, 1574.33, 1487.15, 1448.06, 1378.47, 1326.66, 1259.20, 1151.69, 1074.52, 1013.73, 970.15, 945.88, 886.14, 768.57, 743.17; Anal. calcd for $C_{21}H_{23}FN_4O_2S_2$: C 56.48%, H 5.19%, N 12.55%; found: C 56.65%, H 5.38%, N 12.69%.

2-((2-Chlorobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl) thio)methyl)-1,3,4-oxadiazole (**7f**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.67 (dd, 1H, J_1 = 1.20 Hz, J_2 = 8.00 Hz, Ar–H), 7.56 (dd, 1H, J_1 = 1.60 Hz, J_2 = 7.60 Hz, Ar–H), 7.36–7.32 (m, 1H, Ar–H), 7.28–7.24 (m, 1H, Ar–H), 5.02 (d, 1H, J = 7.60 Hz, –C=CH–), 4.76 (s, 2H, –SCH_2–), 4.55 (s, 2H, –SCH_2–), 2.07 (t, 1H, J_1 = 6.00 Hz, J_2 = 8.00 Hz, –CH–), 2.01 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 163.8,

161.0, 135.4, 134.1, 133.7, 132.0, 130.4, 127.9, 121.3, 34.6, 31.7, 27.9, 26.5, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2925.45, 2738.40, 1669.47, 1621.45, 1574.02, 1474.93, 1445.90, 1378.22, 1327.47, 1282.16, 1251.40, 1153.28, 1053.56, 1037.99, 1016.06, 969.19, 854.23, 761.34, 734.58; Anal. calcd for $C_{21}H_{23}ClN_4O_2S_2$: C 54.47%, H 5.01%, N 12.10%; found: C 54.63%, H 5.19%, N 12.27%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((3-methoxybenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7g**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.23 (t, 1H, J_1 = 7.60 Hz, J_2 = 8.00 Hz, Ar–H), 7.01–6.96 (m, 2H, Ar–H), 6.87–6.84 (m, 1H, Ar–H), 5.02 (d, 1H, J_1 = 8.00 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.45 (s, 2H, –SCH_2–), 3.73 (s, 3H, –OCH_3), 2.07 (t, 1H, J_1 = 6.00 Hz, J_2 = 7.60 Hz, –CH–), 2.01 (d, 1H, J = 6.00 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.05 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.8, 164.3, 161.0, 159.7, 138.2, 135.4, 130.1, 121.6, 121.3, 115.1, 113.8, 36.2, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2928.18, 2836.09, 1600.44, 1574.71, 1487.99, 1475.30, 1378.18, 1322.32, 1297.46, 1268.98, 1152.23, 1046.13, 970.64, 871.48, 853.47, 783.92, 735.24; Anal. calcd for $C_{22}H_{26}N_4O_3S_2$: C 57.62%, H 5.71%, N 12.22%; found: C 57.79%, H 5.83%, N 12.47%.

2-(Benzylthio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio) methyl)-1,3,4-oxadiazole (**7h**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.40 (d, 2H, J = 6.80 Hz, Ar–H), 7.34–7.27 (m, 3H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.47 (s, 2H, –SCH_2–), 2.07 (t, 1H, J_1 = 5.60 Hz, J_2 = 7.60 Hz, –CH–), 2.01 (d, 1H, J = 5.20 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.8, 164.3, 161.0, 136.8, 135.4, 129.4, 129.0, 128.2, 121.3, 31.7, 27.9, 26.5, 26.1, 25.8, 25.7, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2951.66, 2925.33, 2872.17, 2737.72, 1669.25, 1573.68, 1475.48, 1454.71, 1378.11, 1326.74, 1251.62, 1153.65, 1072.11, 1014.75, 968.69, 853.54, 766.49; Anal. calcd for $C_{21}H_{24}N_4O_2S_2$: C 58.85%, H 5.64%, N 13.07%; found: C 58.98%, H 5.81%, N 13.26%.

2-((2,4-Dichlorobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole (**7i**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.66 (d, 1H, J = 2.00 Hz, Ar–H), 7.57 (d, 1H, J = 8.40 Hz, Ar–H), 7.39 (m, 1H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.74 (s, 2H, –SCH_2–), 4.53 (s, 2H, –SCH_2–), 2.05 (t, 1H, J_1 = 6.00 Hz, J_2 = 7.60 Hz, –CH–), 1.99 (d, 1H, J = 5.20 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.67 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.03 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.1, 163.6, 161.0, 135.4, 134.7, 133.4, 129.6, 128.0, 121.3, 34.0, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2951.90, 2925.89, 2878.88, 1574.12, 1473.52, 1416.80, 1379.54, 1326.76, 1251.41, 1152.57, 1116.67, 1098.96, 1051.37, 1013.05, 970.43, 867.48, 848.09, 751.94, 733.04; Anal. calcd for $C_{21}H_{22}Cl_2N_4O_2S_2$: C 50.70%, H 4.46%, N 11.26%; found: C 50.83%, H 4.59%, N 11.47%.

2-((2-Chloro-4-fluorobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole (**7j**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.61 (q, 1H, Ar–H), 7.50 (dd, 1H, J_1 = 2.40 Hz, J_2 = 8.80 Hz, Ar–H), 7.22–7.17 (m, 1H, Ar–H), 5.02 (d, 1H, J = 6.40 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.54 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.1, 163.7, 160.8, 135.4, 134.6, 133.4, 130.6, 121.3, 117.6, 117.3, 115.2, 115.0, 34.0, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2952.92, 2925.87, 2876.65, 1602.22, 1575.59, 1490.24, 1417.72, 1397.51, 1378.47, 1327.51, 1250.91, 1235.20, 1154.22, 1043.56, 1016.19, 969.64, 911.99, 857.67, 823.06, 752.55; Anal. calcd for $C_{21}H_{22}ClFN_4O_2S_2$: C 52.44%, H 4.61%, N 11.65%; found: C 52.59%, H 4.78%, N 11.74%.

2-((2-Bromobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl) thio)methyl)-1,3,4-oxadiazole (**7k**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.51 (dd, 2H, J_1 = 2.00 Hz, J_2 = 6.80 Hz, Ar–H), 7.38 (d, 2H, J = 5.60 Hz, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.45 (s, 2H, –SCH_2–), 2.07 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.71 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.03 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 163.8, 161.0, 135.7, 135.4, 133.4, 132.0, 130.7, 128.5, 124.4, 121.3, 37.3, 31.7, 27.9, 26.5, 26.2, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2924.88, 1572.73, 1475.15, 1441.87, 1378.02, 1327.17, 1280.47, 1249.87, 1153.55, 1045.65, 1026.65, 968.93, 854.36, 761.43, 729.81; Anal. calcd for $C_{21}H_{23}BrN_4O_2S_2$: C 49.70%, H 4.57%, N 11.04%; found: C 49.89%, H 4.68%, N 11.24%.

2-((2,4-Difluorobenzyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole (**7l**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.58–7.52 (m, 1H, Ar–H), 7.29–7.24 (m, 1H, Ar–H), 7.07–7.02 (m, 1H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.48 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.67 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.03 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 163.7, 161.0, 135.4, 133.1, 133.0, 133.0, 132.9, 121.3, 112.2, 112.0, 104.8, 104.6, 104.3, 31.7, 29.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν:

2953.74, 2925.38, 1618.69, 1603.91, 1574.21, 1478.22, 1436.33, 1378.44, 1327.83, 1279.01, 1252.07, 1138.63, 1088.94, 1015.69, 968.20, 850.14, 819.19, 751.84, 731.97; Anal. calcd for $C_{21}H_{22}F_2N_4O_2S_2$: C 54.29%, H 4.77%, N 12.06%; found: C 54.41%, H 4.85%, N 12.23%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((2-nitrobenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7m**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.11 (d, 1H, J = 8.00 Hz, Ar–H), 7.72 (d, 2H, J = 4.00 Hz, Ar–H), 7.63–7.59 (m, 1H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.75 (d, 4H, J = 5.60 Hz, 2 × –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.03 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 164.1, 161.0, 148.1, 135.4, 134.7, 133.0, 132.4, 130.1, 125.8, 121.3, 34.0, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2925.47, 1609.93, 1574.43, 1525.20, 1477.17, 1446.98, 1341.84, 1311.63, 1253.38, 1152.38, 1074.17, 1015.35, 969.47, 857.04, 807.88, 788.77, 756.08; Anal. calcd for $C_{21}H_{23}N_5O_4S_2$: C 53.26%, H 4.90%, N 14.79%; found: C 53.37%, H 4.99%, N 14.83%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((4-nitrobenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7n**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.19 (d, 2H, J = 8.80 Hz, Ar–H), 7.71 (d, 2H, J = 8.80 Hz, Ar–H), 5.01 (d, 1H, J = 8.00 Hz, –C=CH–), 4.74 (s, 2H, –SCH_2–), 4.61 (s, 2H, –SCH_2–), 2.05 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 1.99 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.67 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.08 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 163.9, 161.0, 147.3, 145.2, 135.4, 130.8, 124.1, 121.3, 35.3, 31.6, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2925.41, 1668.89, 1600.31, 1573.95, 1522.03, 1478.50, 1378.08, 1345.92, 1253.14, 1153.44, 1110.93, 1015.72, 969.35, 893.17, 858.67, 801.75, 756.42; Anal. calcd for $C_{21}H_{23}N_5O_4S_2$: C 53.26%, H 4.90%, N 14.79%; found: C 53.39%, H 4.98%, N 14.84%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((2-(trifluoromethyl)benzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7o**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.78–7.55 (m, 1H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.76 (s, 2H, –SCH_2–), 4.64 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 6.00 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.67 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.1, 163.7, 160.9, 135.5, 135.4, 134.5, 133.5, 132.4, 129.3, 127.7, 127.4, 126.8, 123.3, 121.3, 33.5, 31.7, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2926.17, 1606.81, 1573.96, 1477.83, 1451.62, 1378.71, 1315.75, 1151.78, 1119.90, 1059.78, 1036.93, 898.61, 853.53, 769.12; Anal. calcd for $C_{22}H_{23}F_3N_4O_2S_2$: C 53.21%, H 4.67%, N 11.28%; found: C 53.31%, H 4.76%, N 11.34%.

2-(2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-5-(((5-((4-(trifluoromethyl)benzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7p**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.67 (q, 4H, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.74 (s, 2H, –SCH_2–), 4.56 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 6.00 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.67 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.02 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.9, 164.0, 161.0, 142.1, 135.4, 130.3, 129.1, 128.8, 128.6, 129.2, 125.9, 125.9, 121.3, 35.5, 31.6, 27.9, 26.5, 26.1, 25.8, 21.7, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2926.74, 1618.03, 1574.20, 1477.86, 1418.38, 1378.74, 1324.36, 1165.28, 1127.04, 1067.05, 1019.07, 969.36, 850.06, 753.24; Anal. calcd for $C_{22}H_{23}F_3N_4O_2S_2$: C 53.21%, H 4.67%, N 11.28%; found: C 53.32%, H 4.75%, N 11.33%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((4-methoxybenzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7q**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.33 (d, 2H, J = 8.80 Hz, Ar–H), 6.87 (d, 2H, J = 8.80 Hz, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.75 (s, 2H, –SCH_2–), 4.42 (s, 2H, –SCH_2–), 3.72 (s, 3H, –OCH_3), 2.07 (t, 1H, J_1 = 5.60 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.6, 164.7, 164.4, 161.0, 159.3, 135.4, 130.8, 128.5, 121.3, 114.4, 55.5, 36.0, 31.6, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2929.32, 1610.35, 1574.35, 1513.62, 1474.91, 1378.20, 1319.89, 1303.22, 1246.74, 1153.81, 1033.17, 969.61, 835.98, 752.70; Anal. calcd for $C_{22}H_{26}N_4O_3S_2$: C 57.62%, H 5.71%, N 12.22%; found: C 57.73%, H 5.89%, N 12.33%.

2-((1R,3R)-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropyl)-5-(((5-((4-(trifluoromethoxy)benzyl)thio)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-oxadiazole (**7r**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.55 (d, 2H, J = 8.80 Hz, Ar–H), 7.32 (d, 2H, J = 8.00 Hz, Ar–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.74 (s, 2H, –SCH_2–), 4.51 (s, 2H, –SCH_2–), 2.06 (t, 1H, J_1 = 5.60 Hz, J_2 = 7.60 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.67 (s, 3H, –CH_3), 1.15 (s, 3H, –CH_3), 1.03 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 164.9, 164.2, 161.0, 148.2, 136.7, 135.3, 131.4, 121.5, 121.3, 35.3, 31.6, 27.9, 26.5, 26.1, 25.8, 21.5, 21.5, 18.7; IR (KBr, cm^{-1}) ν: 2927.02, 1574.39, 1508.63, 1477.28, 1379.16, 1260.68, 1221.26, 1196.82, 1164.00, 1019.58, 969.56, 921.84, 853.09, 751.06; Anal. calcd for $C_{22}H_{23}F_3N_4O_3S_2$: C 51.55%, H 4.52%, N 10.93%; found: C 51.66%, H 4.59%, N 10.98%.

2-(((5-Chlorothiophen-2-yl)methyl)thio)-5-(((5-((1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)

cyclopropyl)-1,3,4-oxadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole (**7s**). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 6.96 (d, 1H, J = 3.60 Hz, thiophyl–H), 6.93 (d, 1H, J = 4.00 Hz, thiophyl–H), 5.02 (d, 1H, J = 8.00 Hz, –C=CH–), 4.76 (s, 2H, –SCH_2–), 4.68 (s, 2H, –SCH_2–), 2.07 (t, 1H, J_1 = 6.00 Hz, J_2 = 8.00 Hz, –CH–), 2.00 (d, 1H, J = 5.60 Hz, –CH–), 1.70 (s, 3H, –CH_3), 1.68 (s, 3H, –CH_3), 1.16 (s, 3H, –CH_3), 1.04 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 168.5, 165.0, 164.0, 161.0, 138.9, 135.4, 128.6, 128.4, 126.9, 121.3, 31.7, 31.4, 27.9, 26.5, 26.1, 25.8, 21.6, 21.5, 18.8; IR (KBr, cm^{-1}) ν: 2971.43, 2925.47, 1621.69, 1573.10, 1476.76, 1447.48, 1405.46, 1377.82, 1330.90, 1249.89, 1229.18, 1153.24, 1062.45, 1015.46, 994.54, 969.13, 853.57, 798.32, 736.27; Anal. calcd for $C_{19}H_{21}ClN_4O_2S_3$: C 48.65%, H 4.51%, N 11.94%; found: C 48.73%, H 4.68%, N 12.17%.

Insecticidal biological assay

In this study, the insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* were performed using previously reported procedures (Cahill et al. 1995; Feng et al. 2010; Sudoi 1998; Subaharan and Regupathy 2000; Wang et al. 2006; Zhao et al. 2010). 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. Evaluations were based on a percentage scale (0 = no activity and 100 = complete eradication). Commercial agents of chlorpyrifos, beta cypermethrin, spinosad and azadirachtin were used as controls, and water was used as blank control. Three replicates and at least five concentrations were performed for each experiment and the 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 **6** and **7a**–**7s** 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 at 25 ± 1 °C with a light–dark period of 14:10 h and a relative humidity of 75%.

Insecticidal activity against *V. aphids*

The agar was mixed with distilled water to form agar solution with 1.3% mass fraction, and 5 mL liquid agar was taken in a micropipette and added into a culture dish 5 cm in diameter and 2 cm in height. Then the liquid agar was cooled and solidified. Fresh cabbage discs (diameter 4 cm) were dipped in the prepared solutions containing compounds **6** and **7a**–**7s** for 10 s, dried in air and placed the back face up in the agar-coated Petri dish. 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 at 25 ± 1 °C with a light–dark period of 14:10 h and a relative humidity of 75%.

Insecticidal activity against *E. vitis*

Fresh the tender tea shoots (length 13 cm) were dipped in the prepared solutions containing compounds **6** and **7a**–**7s** for 10 s, dried in air, wrapped with wet cotton and parafilm, and then packed in test tube (3 × 20 cm). Ten tender tea stems were placed in each test tube and 30 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 at 25 ± 1 °C with a light–dark period of 14:10 h and a relative humidity of 75%.

Results and discussion

Chemical

In this study, the synthetic route of the target compounds **7a**–**7s** is depicted in Scheme 1. The target compounds **7a**–**7s** were synthesized from *trans*-ethyl chrysanthemate **1** in six steps including hydrazidation, cyclization, and thioetherification reactions according to the reported methods (Xu et al. 2012; Li et al. 2018; Gan et al. 2016; Chen et al. 2018; Xia et al. 2016). As shown in Scheme 1, *trans*-ethyl chrysanthemate **1** was reacted with 80% hydrazine hydrate in alcohol at reflux condition to obtain intermediate **2**. Then a mixture of intermediate **2**, KOH and CS_2 was reacted in a mixture of ethanol and H_2O at reflux condition and acidified with HCl to produce intermediate **3**. Intermediate **3** and ethyl bromoacetate were reacted in anhydrous ethanol at reflux condition to produce intermediate **4**. Intermediate **4** was reacted with 80% hydrazine hydrate in alcohol at reflux conditions to produce intermediate **5**. With that intermediate **5**, KOH and CS_2 were reacted in a mixture of ethanol and H_2O at reflux condition and acidified with HCl to produce the key intermediate **6**. Finally, intermediate **6** and RCH_2Cl were reacted in anhydrous ethanol under microwave irradiation at 90 °C with 150 W to obtain the target compounds **7a**–**7s**, and confirmed their structures by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

The main characteristic of the ^{1}H NMR spectra of the title compounds was the presence of a low-frequency downfield singlet at δ 6.87–8.19 and δ 5.01–5.03 ppm, which indicated the presence of phenyl and –C=CH– protons, respectively. Two –SCH_2– groups showed absorption peaks of ^{1}H NMR spectra at 4.74–4.76 and 4.42–4.68 ppm, respectively. Meanwhile, typical chemical shifts at 168.6–160.8 ppm in the ^{13}C

NMR spectra confirmed the presence of oxadiazole ring. In addition, the IR spectra exhibited characteristic absorption near 1570 cm^{-1}, which indicated the presence of C=N vibrations. The absorptions near 2950, 2920, and 1680 cm^{-1} were attributed to the presence of $–CH_3$, $–CH_2–$, and C=C groups, respectively.

Biological evaluations

The results of the preliminary bioassays, as can be seen from Table 2, showed that compounds **6** and **7a**–**7s** had moderate to good insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* at the concentration of 500 mg/L. Especially, compounds **7j**, **7l**, **7o**, **7p**, **7r**, and **7s** displayed excellent insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* at the concentration of 500 mg/L, with the inhibitory activity value of 100%, which was equal to the commercial agents of chlorpyrifos, beta cypermethrin, spinosad, and azadirachtin. Meanwhile, the 50% lethal concentration (LC_{50}) values were also determined and are presented in Tables 3, 4, and 5. Table 3 shows that compounds **7l**, **7p**, **7r**, and **7s** revealed better bioactivities against *P. xylostella*, with the LC_{50} values of 4, 2, 2, and 1 mg/L, respectively, which were superior to those of the commercial insecticidal agents chlorpyrifos (8 mg/L), beta cypermethrin (13 mg/L), spinosad (5 mg/L) and azadirachtin (10 mg/L). Meanwhile, Table 4 shows that compounds **7j**, **7l**, **7o**, **7p**, **7r**, and **7s** revealed better bioactivities against *V. aphids*, with the LC_{50} values of 5, 3, 3, 2, 2, and 1 mg/L, respectively, than chlorpyrifos (11 mg/L), beta cypermethrin (8 mg/L), spinosad (14 mg/L) and azadirachtin (18 mg/L). In addition, Table 5 shows that compounds **7o**, **7p**, **7r**, and **7s** revealed better bioactivities against *V. aphids*, with the LC_{50} values of 3, 1, 2, and 1 mg/L, respectively, than chlorpyrifos (6 mg/L), beta cypermethrin (5 mg/L), spinosad (8 mg/L) and azadirachtin (14 mg/L). Especially, compound **7s** revealed the best insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* with the LC_{50} values of 1, 1, and 1 mg/L, respectively. These results indicated that pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties could be developed as novel and promising insecticides.

Table 2 The insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* of the target compounds at 500 mg/L

Compounds	Insecticidal activity (%)		
	P. xylostella	*V. aphids*	*E. vitis*
6	60 ± 2.1	65 ± 1.0	64 ± 0.8
7a	93 ± 0.8	93 ± 1.0	97 ± 1.0
7b	90 ± 0.7	90 ± 0.8	90 ± 0.9
7c	83 ± 0.9	80 ± 0.8	83 ± 0.7
7d	90 ± 0.9	93 ± 0.9	93 ± 0.8
7e	100 ± 1.1	97 ± 1.0	100 ± 1.0
7f	87 ± 0.7	83 ± 0.7	90 ± 0.7
7g	70 ± 0.7	73 ± 0.6	77 ± 0.7
7h	73 ± 0.8	80 ± 0.8	80 ± 0.8
7i	100 ± 0.9	97 ± 1.0	100 ± 1.1
7j	100 ± 1.1	100 ± 1.0	100 ± 1.1
7k	80 ± 0.7	80 ± 0.7	83 ± 0.8
7l	100 ± 1.2	100 ± 1.0	100 ± 1.2
7m	70 ± 0.6	73 ± 0.7	80 ± 0.7
7n	87 ± 0.9	83 ± 0.9	87 ± 0.8
7o	100 ± 1.0	100 ± 1.2	100 ± 1.1
7p	100 ± 1.2	100 ± 1.1	100 ± 1.2
7q	73 ± 0.7	80 ± 0.9	80 ± 0.8
7r	100 ± 1.0	100 ± 1.1	100 ± 1.0
7s	100 ± 1.1	100 ± 1.2	100 ± 1.2
Chlorpyrifos	100 ± 1.4	100 ± 1.4	100 ± 1.5
Beta cypermethrin	100 ± 1.4	100 ± 1.5	100 ± 1.6
Spinosad	100 ± 1.6	100 ± 1.6	100 ± 1.5
Azadirachtin	100 ± 1.2	100 ± 1.3	100 ± 1.7

Table 3 The LC_{50} values of the target compounds against *P. xylostella*

Compounds	$y = ax + b$	LC_{50} (mg/L)	r
6	$y = 0.43x + 4.11$	124 ± 3.2	0.99
7a	$y = 0.72x + 4.21$	12 ± 0.9	0.98
7b	$y = 0.86x + 3.83$	23 ± 1.3	0.97
7c	$y = 0.78x + 3.79$	36 ± 2.3	0.98
7d	$y = 0.82x + 4.06$	14 ± 1.4	0.99
7e	$y = 1.08x + 4.06$	7 ± 1.0	0.98
7f	$y = 0.89x + 3.53$	44 ± 2.6	0.98
7g	$y = 0.92x + 3.17$	99 ± 3.1	0.98
7h	$y = 0.73x + 3.61$	78 ± 2.6	0.98
7i	$y = 1.25x + 3.91$	7 ± 0.9	0.98
7j	$y = 1.34x + 3.91$	6 ± 0.9	0.98
7k	$y = 0.84x + 3.55$	52 ± 2.1	0.99
7l	$y = 1.23x + 4.29$	4 ± 0.4	0.97
7m	$y = 0.48x + 4.17$	53 ± 2.7	0.99
7n	$y = 0.85x + 3.75$	30 ± 2.6	0.98
7o	$y = 1.19x + 4.30$	4 ± 0.5	0.98
7p	$y = 1.02x + 4.79$	2 ± 0.4	0.99
7q	$y = 0.92x + 3.17$	99 ± 3.1	0.98
7r	$y = 1.05x + 4.62$	2 ± 0.4	0.97
7s	$y = 0.92x + 4.90$	1 ± 0.5	0.99
Chlorpyrifos	$y = 1.07x + 4.05$	8 ± 0.7	0.98
Beta cypermethrin	$y = 1.32x + 3.53$	13 ± 0.9	0.98
Spinosad	$y = 1.27x + 4.13$	5 ± 0.7	0.99
Azadirachtin	$y = 1.06x + 3.93$	10 ± 0.9	0.96

Table 4 The LC_{50} values of the target compounds against *V. aphids*

Compounds	$y=ax+b$	LC_{50} (mg/L)	r
6	$y=0.49x+3.98$	124 ± 2.0	0.99
7a	$y=0.70x+4.17$	15 ± 1.0	0.97
7b	$y=0.90x+3.72$	26 ± 2.3	0.98
7c	$y=0.76x+3.82$	35 ± 2.2	0.99
7d	$y=0.73x+4.25$	11 ± 1.0	0.99
7e	$y=0.66x+4.38$	9 ± 1.0	0.99
7f	$y=0.95x+3.46$	42 ± 2.2	0.99
7g	$y=1.00x+2.94$	114 ± 3.2	0.99
7h	$y=1.26x+2.57$	86 ± 3.2	0.99
7i	$y=0.87x+4.16$	9 ± 0.9	0.98
7j	$y=1.21x+4.11$	5 ± 0.8	0.99
7k	$y=0.87x+3.48$	55 ± 2.7	0.99
7l	$y=1.01x+4.51$	3 ± 0.4	0.99
7m	$y=0.74x+3.69$	59 ± 2.2	0.98
7n	$y=0.70x+4.01$	26 ± 1.5	0.99
7o	$y=1.10x+4.43$	3 ± 0.4	0.99
7p	$y=0.96x+4.82$	2 ± 0.5	0.99
7q	$y=0.82x+3.38$	93 ± 3.1	0.97
7r	$y=0.94x+4.75$	2 ± 0.4	0.98
7s	$y=0.80x+4.91$	1 ± 0.3	0.99
Chlorpyrifos	$y=1.95x+2.94$	11 ± 1.1	0.98
Beta cypermethrin	$y=1.58x+3.54$	8 ± 1.0	0.97
Spinosad	$y=1.84x+2.92$	14 ± 1.1	0.99
Azadirachtin	$y=2.41x+1.96$	18 ± 1.2	0.98

Table 5 The LC_{50} values of the target compounds against *E. vitis*

Compounds	$y=ax+b$	LC_{50} (mg/L)	r
6	$y=0.48x+3.97$	147 ± 3.1	0.98
7a	$y=0.83x+4.21$	9 ± 0.9	0.96
7b	$y=0.69x+4.25$	12 ± 1.1	0.96
7c	$y=0.70x+4.01$	26 ± 2.2	0.99
7d	$y=0.53x+4.42$	12 ± 1.4	0.99
7e	$y=1.37x+3.85$	7 ± 0.8	0.98
7f	$y=1.15x+3.08$	47 ± 2.2	0.99
7g	$y=1.12x+2.68$	118 ± 3.4	0.98
7h	$y=1.06x+2.95$	85 ± 2.9	0.98
7i	$y=1.11x+4.10$	6 ± 0.6	0.96
7j	$y=1.12x+4.15$	6 ± 0.5	0.99
7k	$y=1.06x+3.11$	60 ± 2.2	0.99
7l	$y=0.99x+4.42$	4 ± 0.5	0.99
7m	$y=1.29x+2.63$	70 ± 3.0	0.98
7n	$y=0.93x+3.57$	35 ± 2.5	0.98
7o	$y=1.45x+4.28$	3 ± 0.5	0.97
7p	$y=0.92x+4.90$	1 ± 0.4	0.99
7q	$y=1.23x+2.65$	82 ± 3.0	0.97
7r	$y=1.25x+4.61$	2 ± 0.3	0.97
7s	$y=0.86x+4.97$	1 ± 0.3	0.97
Chlorpyrifos	$y=1.15x+4.09$	6 ± 0.8	0.98
Beta cypermethrin	$y=1.35x+4.10$	5 ± 0.6	0.98
Spinosad	$y=1.58x+3.58$	8 ± 0.7	0.99
Azadirachtin	$y=1.62x+3.13$	14 ± 1.1	0.98

Structure–activity relationship analysis

As an extension of this approach, based on the insecticidal activities of the title compounds against *P. xylostella*, *V. aphids,* and *E. vitis* indicated in Tables 2, 3, 4, and 5, the preliminary structure–activity relationship (SAR) was deduced. First, the insecticidal activities against *P. xylostella*, *V. aphids,* and *E. vitis* of the target compounds **7a**–**7s** were better than that of compound **6**. Second, the type and position of the substituent group at the phenyl had an important effect on the insecticidal activity of the target compounds; compared with the same substituent group on phenyl, the insecticidal activities against *P. xylostella*, *V. aphids,* and *E. vitis* of the corresponding compounds with the substituent group at 4-position are higher than those of at 2-position in the order of **7a** > **7f**, **7n** > **7m**, and **7p** > **7o**; the electron-withdrawing groups at the phenyl could increase the insecticidal activities against *P. xylostella*, *V. aphids,* and *E. vitis* of the corresponding compounds in the order of **7e** > **7h** > **7g**.

Conclusions

In conclusion, 19 novel pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties were designed and synthesized. Bioassay results revealed that some of the target compounds possessed better insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis*, respectively. To the best of our knowledge, this is the first report on the insecticidal activities against *P. xylostella*, *V. aphids*, and *E. vitis* of this series of pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties and the present work demonstrated that series of pyrethrin derivatives containing 1,3,4-oxadiazole and thioether moieties can be used to develop potential agrochemicals. Furthermore, according to the requirements of pesticide registration in China, further field studies on the photostability, biological efficacies, crop safety, and toxicities of compound **7s** as insecticidal candidates will be performed in our next work.

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