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Synthesis and bioactivity of sulfide derivatives containing 1,3,4-oxadiazole and pyridine

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Abstract: A series of novel sulfide derivatives containing 1,3,4-oxadiazole and pyridine were synthesized, characterized, and tested for their antibacterial activity against tobacco bacterial wilt and rice bacterial blight and for insecticidal activity toward diamondback moth. The results showed that some compounds had good insecticidal and bactericidal activity, e.g., the activities of compounds **6e** and **6g**–**6j** toward tobacco bacterial wilt were much better than those of commercial thiodiazole-copper, and some of the synthesized compounds possessed good insecticidal activity against *Plutella xylostella*. Compounds **6d**, **6h**, **6j**, **6l**, **6p**, **6r**, and **6p** displayed over 93% activity at 500 mg L^{-1}.

Key words: Sulfide derivative, 1,3,4-oxadiazole, pyridine, synthesis, antibacterial activity, insecticidal activity

1. Introduction

Bacterial disease in crops is extremely difficult to prevent due to the lack of effective antibacterial agents. The threats from bacterial diseases in crops are still a big challenge for humans. For example, *Xanthomonas oryzae* pv. *oryzae* (Xoo) is one of the most seriously harmful bacterial diseases in rice.[1] The infection caused by this disease may result in blighting of leaves and more than 10% yield loss of rice.[2] Currently, only a few measurements are available for bacterial diseases, including chemical and biological methods and the use of resistant cultivars and lines, among which bismerthiazol and thiodiazole-copper are the main chemical antimicrobial agents. However, their efficacy is not ideal. Therefore, the development of new antibacterial agents against harmful bacterial diseases in crops remains a daunting task in pesticide science.

Derivatives of sulfides, which are an important class of bioactive compounds with a wide spectrum of activities, have attracted more attention in the preparation of pesticides in recent years. They are employed as antiinflammatory,[3] anticancer,[4,5] anti-HIV-1,[6] insecticidal,[7,8] herbicidal,[9] fungicidal,[10] and antibacterial agents.[11–16] Some compounds with good antibacterial activity against Xoo and *Xanthomonas oryzae* pv. *oryzae* (Xoc) have been reported by our group.[13–16]

1,3,4-Oxadiazole, an important heterocycle, possesses a broad spectrum of biological and pharmaceutical activities,[17–20] which have attracted growing attention because of their good herbicidal, insecticidal,[21–24] antifungal,[25–29] and antibacterial activity.[13–16,30,31] Some of the 1,3,4-oxadiazole derivatives (such as the compounds in the Figure) were treated as pesticide candidates. In 2014, a series of 1,3,4-oxadiazole derivatives with sulfone substructures were reported by Li et al., and many of the compounds showed excellent activity

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against the plant pathogenic bacteria Xoo and Xoc.[14] More recently, Wang et al. reported a variety of 1-aryl-4-hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives bearing 1,3,4-oxadiazole moiety by placing the 1-aryl-4-hydroxy-1*H*-pyrrol-2(5*H*)-one at the 2-position of 1,3,4-oxadiazole through a sulfide linkage. Some of the synthesized compounds showed excellent antibacterial activity against plant pathogenic bacteria including Xoo, *Ralstonia solanacearum*, and *Xanthomonas axonopodis* pv. *citri*.[15] Moreover, as an important pyridine derivative, the scaffold of 3-methyl-4-(2,2,2-trifluoroethoxy)pyridine has also received close attention due to the fluorine atoms in its structure. Many compounds with this substructure showed good activity for both pharmaceutical and agrochemical applications.[7,32–37]

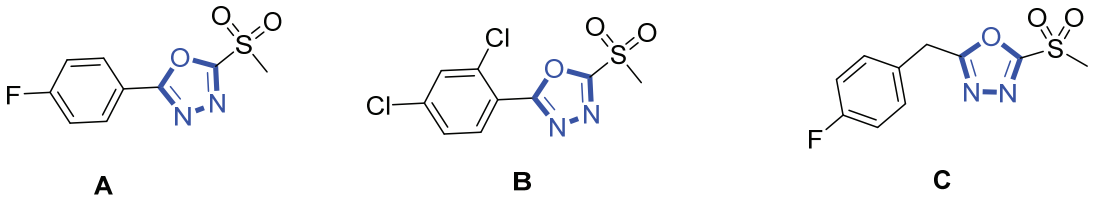


Figure. Pesticide candidates containing 1,3,4-oxadiazole.

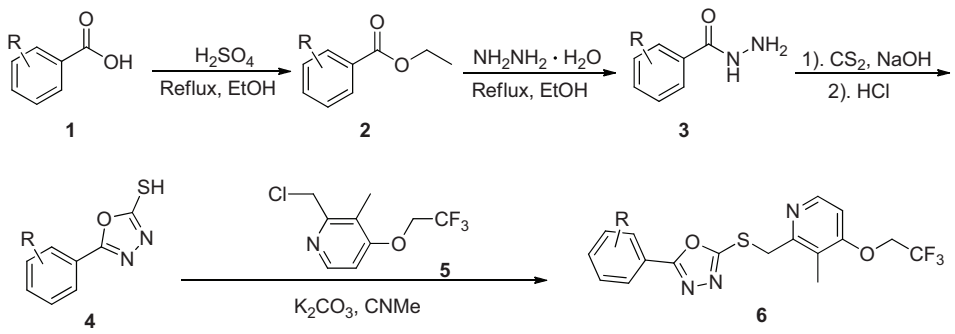
Encouraged by the information above, and in continuation of works on sulfide derivatives and interesting sulfides,[7,8] a series of new sulfide derivatives containing both 1,3,4-oxadiazole and pyridine moieties was designed and synthesized by introducing 3-methyl-4-(2,2,2-trifluoroethoxy)pyridine into the 2-position of 1,3,4-oxadiazole via a sulfide linkage. The antibacterial and insecticidal activities of these target compounds were evaluated and the results indicated that some of the synthesized compounds showed good bioactivity.

2. Results and discussion

2.1. Synthesis

The synthetic route of the sulfide derivatives is drawn in the Scheme. First, substituted ethyl benzoate (**2**) was prepared by treatment of substituted benzoic acid with ethanol in the presence of concentrated sulfuric acid, which further reacted with hydrazine hydrate (80%) in good yield to get substituted benzoyl hydrazine in excellent yield. Substituted 5-phenyl-1,3,4-oxadiazole-2-thiol (**4**) was synthesized via ring-closure reaction of substituted benzoyl hydrazine **3** with CS_2 in the presence of NaOH.[14,15] Subsequently, thioetherification of substituted 5-phenyl-1,3,4-oxadiazole-2-thiol was carried out by treatment of **4** with 2-(chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride in the presence of K_2CO_3 in excellent yield as described in our previous work.[7,8]

Take compound **6g** as an example. It can be seen from the ^{1}H NMR spectrum of compound **6g** that at δ 8.36 ppm is H adjacent to the N atom on the pyridine ring, and it is coupled by the H atom in the meta position, split into a doublet, with coupling constant $J = 5.7$ Hz. The H in the N position of the pyridine ring appears at δ 8.36 ppm. Due to the H coupling of the ortho position, it is divided into double peaks, and the coupling constant is $^1J = 5.7$ Hz. At δ 7.87 ppm is H on the benzene ring and it is bimodal with a coupling constant of $^2J = 2.2$ Hz. Both δ 7.37 ppm and δ 7.35 ppm are H on the benzene ring. Due to the coupling of H atoms with each other, they are split into d peaks with a coupling constant of $^3J = 2.2$ Hz. At δ 6.69 ppm is H on the pyridine ring. Due to the ortho-H coupling, the split is divided into double peaks, and the coupling constant is $^4J = 5.6$ Hz; δ 4.76 ppm is a single peak, which is -CH_2-, and -CH_2- connected to CF_3 is affected



6a: R = 3,5-Cl_2; **6b:** R = 4-CH_2CH_3; **6c**: R = 3-I; **6d**: R = H;
6e: R = 4-F; **6f**: R = 4-I; **6g**: R = 5-Cl-2-CH_3; **6h**: R = 2-CF_3;
6i: R = 4-CF_3; **6j**: R = 2,4-$(CH_3)_2$; **6k**: R = 3-$N(CH_3)_2$; **6l**: R = 3-Cl;
6m:R = 3-Br; **6n**: R = 3-Cl-4-CH_3; **6o**: R = 4-Cl -3-F; **6p**: R = 3-CH_3;
6q: R = 4-Br; **6r**: R = 4-Br -2-F; **6s**: R = 2-F; **6t**: R = 3 -CF_3;
6u: R = 4-Cl; **6v**: R = 5-Br-2-Cl: **6w**:R = 2-OCH_3.

Scheme. The synthesis of target sulfide derivatives containing 1, 3, 4-oxadiazole and pyridine.

by 3 couplings of F atoms, split into quadruple peaks, with coupling constant $J_{F-H} = 7.8$ Hz. It appears at δ 4.41 ppm. In the ^{13}C NMR spectrum (for example, compound **6d**), due to the presence of CF_3, the C atom is also split into a quartet, and C in the -CF_3 group appears at δ 122.98 ppm. In the vicinity, the coupling constant is $^1J_{C-F} = J = 277.9$ Hz, and the C linked to the -CF_3 group is also split into a quartet, with δ 65.52 ppm coupling constant $^2J_{C-F} = 36.3$ Hz.

2.2. Antibacterial activity

2.3. Inhibitory activity of compounds against rice bacterial blight

Using bismerthiazol as a positive control, the inhibitory activities of the synthesized compounds against Xoo were evaluated by turbidity method at concentrations of 100 mg L^{-1} and 50 mg L^{-1}. The results in Table 1 indicate that compounds **6a**, **6j**, **6k**, **6l**, **6n**, **6q**, and **6u** possess potential bacteriostatic activity against Xoo, with inhibition rates of 60.7%, 58.4%, 52.2%, 56.8%, 53.8%, 59.2%, and 64.2%, respectively. The antibacterial activity of compound **6u** was equivalent to the positive control, bismerthiazol (66.0%). When the concentration was 50 mg L^{-1}, the activities of **6h**, **6j**, **6n**, **6o**, and **6t** were 43.8%, 36.2%, 33.1%, 34.8%, and 41.3%, respectively. Compounds **6h**, **6j**, and **6t** showed slightly higher activity than that of bismerthiazol (33.3%).

2.3.1. Inhibitory activity of compounds against tobacco bacterial wilt

The bacteriostatic activity against tobacco bacterial wilt (*Ralstonia solanacearum*) as listed in Table 2 indicated that some of synthesized compounds show good bacteriostatic activity against *Ralstonia solanacearum*. Compounds **6e**, **6g**, **6h**, **6i**, **6j**, and **6r** showed 60% activity at 100 mg L^{-1}, and the inhibition rates of the other compounds were as high as 73.8%, which was much higher than that of thiodiazole-copper (31.5%). When the concentration was 50 mg L^{-1}, most of the synthesized compounds displayed better inhibition rates than that of thiodiazole-copper, whereby the inhibition rate of compound **6v** was as high as 59.0%.

Table 1. Inhibition of target compounds against *Xanthomonas oryzae* pv. *oryzae*.

Compound	Concentration		Compound	Concentration	
	100 mg L^{-1}	50 mg L^{-1}		100 mg L^{-1}	50 mg L^{-1}
6a	60.7	17.9	**6m**	25.5	1.7
6b	28.0	27.9	**6n**	53.8	33.1
6c	1.6	0.6	**6o**	43.8	34.8
6d	0	0	**6p**	30.4	3.6
6e	22.1	18.1	**6q**	59.2	16.8
6f	25.1	10.3	**6r**	26.3	8.1
6g	24.6	22.5	**6s**	34.6	6.4
6h	49.2	43.8	**6t**	45.7	41.3
6i	10.1	10.9	**6u**	64.2	22.8
6j	58.4	36.2	**6v**	26.0	0
6k	52.2	30.6	**6w**	21.0	18.0
6l	56.8	44.1	Bismerthiazol	66.0	33.2

Table 2. Inhibitory effects of target compounds on *Ralstonia solanacearum*.

Compound	Concentration		Compound	Concentration	
	100 mg L^{-1}	50 mg L^{-1}		100 mg L^{-1}	50 mg L^{-1}
6a	53.6	33.3	**6m**	23.6	22.2
6b	0	0	**6n**	52.3	47.5
6c	23.2	13.8	**6o**	53.1	51.2
6d	0	0	**6p**	36.8	28.5
6e	73.8	58.6	**6q**	38.6	30.3
6f	0	0	**6r**	67.9	53.0
6g	66.5	50.3	**6s**	33.1	30.9
6h	65.8	41.4	**6t**	39.3	24.3
6i	67.5	53.0	**6u**	57.0	40.3
6j	60.3	43.6	**6v**	66.1	59.0
6k	30.3	0	**6w**	63.1	55.2
6l	9.3	0	Thiodiazole-copper	31.5	9.4

2.4. Insecticidal activity

The bioassay results against *Plutella xylostella* are presented in Table 3. Some of the compounds possessed weak to good bioactivities. For instance, compounds **6d**, **6f**, **6h**, **6i**, **6j**, **6l**, **6p**, **6r**, and **6p** displayed activities of over 93% at 500 mg L^{-1}. When the concentration was 200 mg L^{-1}, the activities of compounds **6h**, **6j**, and **6l** were still over 85%, and most of the compounds (**6d**, **6f**, **6i**, **6q**, **6t**, etc.) showed moderate activity. However, the activities were sharply decreased when the concentration was 100 mg L^{-1}. Preliminary structure-activity relationship analysis indicated that the insecticidal activity can be enhanced by introducing groups of trifluoromethyl (**6h**, **6i**, **6t**) in the benzene ring, while the introduction of ethyl (**6b**) or iodine (**6c**) could

sharply decrease the insecticidal activities. However, the quantitative structure-activity relationship is not very clear. Further studies are currently underway to establish a definite structure-activity relationship.

Table 3. Insecticidal activity of title compounds against *P. xylostella*.

Comp.	Concentrations, mg L^{-1}			Comp.	Concentrations, mg L^{-1}		
	500	250	100		500	250	100
6a	57%	32%	0	**6m**	56%	34%	12%
6b	27%	0%	/	**6n**	23%	0%	/
6c	17%	0%	/	**6o**	54%	26%	0%
6d	100%	77%	20%	**6p**	97%	46%	13%
6e	53%	22%	13%	**6q**	84%	50%	12%
6f	93%	75%	23%	**6r**	97%	62%	23%
6g	23%	0%	/	**6s**	20%	0%	0%
6h	100%	87%	27%	**6t**	87%	72%	23%
6i	90%	53%	15%	**6u**	87%	54%	10%
6j	100%	87%	24%	**6v**	97%	68%	23%
6k	37%	16%	0%	**6w**	56%	18%	0%
6l	93%	85%	13%	Chlorantraniliprole	100%	100%	100%

2.5. Conclusions

In this article, 23 novel pyridine-containing 1,3,4-oxadiazole sulfide derivatives were designed and synthesized. The bacteriostatic activities against tobacco bacterial wilt (*Ralstonia solanacearum*) and rice bacterial blight (Xoo) were tested using the turbidity method. The results indicated that the synthesized compounds showed good antibacterial activities against tobacco bacterial wilt and rice bacterial blight. The results of insecticidal activity indicated that some of the synthesized compounds showed good insecticidal activities; for instance, compounds **6d**, **6h**, **6j**, **6l**, **6p**, **6r**, and **6p** displayed over 93% activity at 500 mg L^{-1}. The sulfide derivatives containing 1,3,4-oxadiazole and pyridine could be considered as lead structures for the discovery of novel pesticide molecules. Further studies for structural optimization and bioactivity testing are underway in our laboratory.

3. Experimental

3.1. Materials

All reactants and starting materials were purchased from Accela ChemBio Co., Ltd. (Shanghai, China). The NMR spectra were recorded on a JEOL ECX500 NMR spectrometer (JEOL Ltd., Tokyo, Japan) with ^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz, and ^{19}F NMR at 471 MHz operating at room temperature. The ^{1}H NMR chemical shifts were measured relative to $CDCl_3$ as the internal reference ($CDCl_3$: δ = 7.26 ppm, DMSO-d6: δ = 2.50 ppm). The ^{13}C NMR chemical shifts were given using $CDCl_3$ as the internal standard ($CDCl_3$: δ = 77.2 ppm, DMSO-d6: δ = 39.5 ppm). High-resolution mass spectra (HR-MS) were recorded on an Orbitrap LC–MS instrument (Q-Exative, Thermo Scientific, USA). Melting points were determined with X-4 and are uncorrected. The process of the reaction was monitored by TLC.

3.2. Preparation of the intermediate

Intermediate **4** (5-substituted-1,3,4-oxadiazole-2-thiol) was prepared using previously reported protocols.[14,15]

3.3. General synthetic procedures for compounds 6a–6w

A mixture of substituted phenyl-1,3,4-oxadiazole-2-thiol (**4**) (0.2 g, 1 mmol), 2-(chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (**5**) (1.1 mmol), and K_2CO_3 (0.5 mmol) in acetonitrile was stirred under reflux and the reaction was monitored with TLC. After completion of the reaction, the mixture was concentrated in vacuum and the residue was poured into 20 mL of water, filtered, and dried to obtain the target compounds.

2-(3,5-Dichlorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6a**): White solid; yield, 88.6%; mp 148–149 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.5 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.56 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 5.5 Hz, 1H), 4.76 (s, 2H), 4.41 (q, J = 7.7 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.53, 163.45, 161.69, 154.32, 148.19, 138.10, 133.92, 131.68, 131.27, 127.68, 123.06 (q, J = 263.9 Hz), 121.56, 121.37, 105.91, 65.53 (q, J = 36.7 Hz), 37.38, 10.76; ^{19}F NMR (471 MHz, chloroform-D) δ –73.64; HR-MS (ESI): Calculated for $C_{17}H_{12}O_2N_3Cl_2F_3S$ $[M+H]^+$: 450.00418, found: 450.00521.

2-(4-Ethylphenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6b**): White solid; yield, 80.9%; mp 181–182 °C; ^{1}H NMR (500 MHz, Chloroform-D) δ 8.35 (d, J = 5.6 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 5.6 Hz, 1H), 4.74 (s, 2H), 4.40 (q, J = 7.8 Hz, 2H), 2.71 (q, J = 7.6 Hz, 2H), 2.34 (s, 3H), 1.26 (t, J = 7.7, 6.4 Hz, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 166.11, 164.13, 161.68, 154.63, 148.50, 148.19, 128.64, 126.88, 121.43, 121.17, 122.98 (q, J = 277.0 Hz), 105.85, 65.52 (q, J = 36.5 Hz), 37.34, 29.16, 15.31, 10.78. ^{19}F NMR (471 MHz, chloroform-D) δ –73.67; HR-MS (ESI): Calculated for $C_{19}H_{18}O_2N_3F_3S[M+H]^+$: 410.11446, found: 410.11340.

2-(3-Iodophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6c**): White solid; yield, 69.5%; mp 140–141 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 7.9 Hz, 1H), 8.35 (s, 1H), 7.95 (m, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 6.69 (d, J = 5.7 Hz, 1H), 4.75 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.11, 164.41, 161.71, 154.39, 148.17, 140.59, 135.39, 130.73, 125.89, 125.55, 122.97 (q, J = 277.6 Hz), 121.42, 105.91, 94.37, 65.53 (q, J = 36.4 Hz), 37.41, 10.79; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS (ESI): Calculated for $C_{17}H_{13}O_2N_3F_3SI$ $[M+H]^+$: 507.97980, found: 507.97888.

2-(((3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-5-phenyl-1,3,4-oxadiazole (**6d**): White solid; yield, 86.3%; mp 160–161 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.6 Hz, 1H), 8.02 (m, 2H), 7.54 (m, 3H), 6.68 (d, J = 5.6 Hz, 1H), 4.75 (s, 2H), 4.40 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.93, 164.56, 161.68, 154.53, 148.18, 131.73, 129.12, 126.80, 123.74, 122.98 (q, J = 277.9 Hz), 121.40, 105.87, 65.52 (q, J = 36.3 Hz), 37.36, 10.77; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS (ESI): Calculated for $C_{17}H_{14}O_2N_3F_3S$ $[M+H]^+$: 382.08316, found: 382.08209.

2-(4-Fluorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6e**): White solid; yield, 65.2%; mp 101–102 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.30 (d, J = 4.0 Hz, 1H), 7.25 (d, J = 3.7 Hz, 2H), 7.07 (m, 2H), 6.66 (d, J = 4.0 Hz, 1H), 4.65 (s, 2H), 4.39 (q, J = 7.7, 4.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 166.30, 165.09, 162.30 (d, J = 246.3 Hz), 161.66, 154.42, 148.12, 130.55 (d, J = 8.1 Hz), 129.43, 122.97 (q, J = 278.0 Hz), 121.32, 115.89 (d, J = 21.7 Hz), 105.85, 65.50

(q, J = 36.4 Hz), 31.17, 10.70; ^{19}F NMR (471 MHz, chloroform-D) δ –73.68, –114.68; HR-MS (ESI): Calculated for $C_{17}H_{13}O_2N_3F_4S$ $[M+H]^+$: 400.07374, found: 400.07446.

2-(4-Iodophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6f**): White solid; yield, 53.0%; mp 172–173 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (s, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 6.69 (s, 1H), 4.75 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.35, 164.94, 161.73, 154.37, 148.13, 138.41, 128.13, 122.76 (q, J = 277.3 Hz), 106.36 (s), 105.90 (s), 98.57 (s), 65.53 (q, J = 36.6 Hz), 45.32, 37.33, 10.79; ^{19}F NMR (471 MHz, chloroform-D) δ –73.62; HR-MS(ESI): Calculated for $C_{17}H_{13}O_2N_3F_3SI$ $[M+H]^+$: 507.97980, found: 507.97903.

2-(5-Chloro-2-methylphenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6g**): White solid; yield, 59.3%; mp 129–130 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.36 (d, J = 5.7 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 4.76 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.66 (s, 2H), 2.34 (s, 2H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.01, 164.66, 161.70, 154.46, 148.21, 136.82, 133.18, 132.00, 131.09, 128.47, 124.17, 121.38, 105.91, 65.53 (q, J = 36.5 Hz), 37.39, 29.80, 21.71, 10.77; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS (ESI): Calculated for $C_{18}H_{15}ClF_3N_3O_2S$ $[M+H]^+$: 430.05984, found: 430.05884.

2-(2-Trifluoromethyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6h**): White solid; yield, 99.1%; mp 124–125 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.28 (d, J = 5.5 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.90–7.83 (m, 2H), 7.09 (d, J = 5.5 Hz, 1H), 4.89 (q, J = 8.5 Hz, 2H), 4.78 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d6) δ 165.75, 163.53, 161.13, 161.13, 154.30, 148.19, 133.80, 133.06, 132.41, 127.78, 127.73, 122.75 (q, J = 39.2 Hz), 121.76, 120.20, 107.68, 65.53 (q, J = 36.5 Hz), 37.64, 10.58; ^{19}F NMR (471 MHz, chloroform-D) δ –59.82, –73.65; HR-MS (ESI): Calculated for $C_{18}H_{13}O_2N_3F_6S$ $[M+H]^+$: 450.07054, found: 450.06937.

2-(4-Trifluoromethyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6i**): White solid; yield 82.6%; mp 152–153 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 6.69 (d, J = 5.6 Hz, 1H), 4.77 (s, 1H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.63, 164.72, 161.70, 154.29, 148.19, 133.31 (q, J = 33.2 Hz), 127.10, 126.21, 126.18, 124.40 (q, J = 82.9 Hz), 122.98 (q, J = 105.8 Hz), 121.38, 105.92, 65.53 (q, J = 36.5 Hz), 37.43, 10.78; ^{19}F NMR (471 MHz, chloroform-D) δ –62.95, –73.66; HR-MS (ESI): Calculated for $C_{18}H_{13}O_2N_3F_6S$ $[M+H]^+$: 450.07054, found: 450.06949.

2-(2,4-Dimethylphenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6j**): White solid; yield, 86.3%; mp 145–146 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 4.2 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.11 (d, J = 7.9 Hz, 1H), 6.67 (d, J = 4.3 Hz, 1H), 4.75 (s, 2H), 4.40 (q, J = 7.8 Hz, 2H), 2.64 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 166.32, 163.77, 161.67, 154.64, 148.19, 141.66, 138.25, 132.56, 128.84, 126.99, 122.99 (q, J = 278.0 Hz), 121.39, 120.02, 105.85, 65.52 (q, J = 36.3 Hz), 37.30, 22.10, 21.49, 10.76; ^{19}F NMR (471 MHz, chloroform-D) δ –73.64; HR-MS (ESI): Calculated for $C_{19}H_{18}O_2N_3F_3S$ $[M+H]^+$: 410.11446, found: 410.11359.

N,*N*-Dimethyl-3-(5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazol-2-yl) aniline (**6k**): White solid; yield, 78.5%; mp 150–151 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.27 (d, J = 5.6 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.16 (s, 1H), 7.08 (d, J = 5.7 Hz, 1H), 6.92 (d,

J= 8.4 Hz, 1H), 4.88 (dd, J= 16.4, 8.7 Hz, 2H), 4.74 (s, 2H), 2.93 (s, 6H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d6) δ 166.33, 164.07, 161.62, 154.70, 151.06, 148.24, 130.51, 124.12 (s), 123.73 (dd, J= 272.1, 151.7 Hz), 120.27, 116.14, 114.35, 109.43, 107.61, 65.18 (q, J= 25.2 Hz), 40.46, 37.56, 10.67; ^{19}F NMR (471 MHz, DMSO-d6) δ -72.60; HR-MS (ESI): Calculated for $C_{19}H_{19}O_2N_4F_6S$ $[M+H]^+$: 425.12536, found: 425.12442.

2-(3-Chlorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6l**): White solid; yield, 74.2%; mp 116–117 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.5 Hz, 1H), 8.00 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.43 (t, J = 8.7 Hz, 1H), 6.68 (d, J= 5.3 Hz, 1H), 4.76 (s, 2H), 4.40 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.16, 164.76, 161.69, 154.39, 148.19, 135.27, 131.76, 130.49, 126.77, 125.35, 124.87, 122.97 (q, J= 277.0 Hz), 121.38, 105.90, 65.53 (d, J= 36.3 Hz), 37.43, 10.78; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS (ESI): Calculated for $C_{17}H_{13}O_2N_3F_3SCl$ $[M+H]^+$: 416.04419, found: 416.04327.

2-(3-Bromophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6m**): White solid; yield, 67.3%; mp 120– 21 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.36 (d, J= 5.7 Hz, 1H), 8.16 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.65 (d, J= 9.0 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 6.69 (d, J= 5.6 Hz, 1H), 4.76 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 164.62, 164.37, 161.69, 154.36, 148.20, 134.70, 130.73, 129.63, 125.53, 125.33, 123.06, 122.98 (q, J = 277.6 Hz), 121.39, 105.89, 65.50 (q, J = 36.7 Hz), 37.42, 10.78; ^{19}F NMR (471 MHz, chloroform-D) δ –73.65; HR-MS (ESI): Calculated for $C_{17}H_{13}O_2N_3F_3SBr$ $[M+H]^+$: 459.99367, found: 459.99292.

2-(3-Chloro-4-methylphenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6n**): White solid; yield, 61.2%; mp 158–159 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J= 5.6 Hz, 1H), 7.98 (d, J= 1.6 Hz, 1H), 7.80 (dd, J= 7.9, 1.7 Hz, 1H), 7.35 (d, J= 8.0 Hz, 1H), 6.68 (d, J = 5.6 Hz, 1H), 4.74 (s, 2H), 4.41 (q, J= 7.8 Hz, 2H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 164.91, 164.73, 161.68, 154.46, 148.19, 140.22, 135.28, 131.66, 127.20, 124.89, 122.98 (q, J= 277.8 Hz), 122.82, 121.40, 65.52 (q, J= 36.6 Hz), 37.41, 20.41, 10.78; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS (ESI): Calculated for $C_{18}H_{15}O_2N_3F_3SCl$ $[M+H]^+$: 430.05984, found: 430.05899.

2-(4-Chloro-3-fluorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6o**): White solid; yield, 83.2%; mp 158–160 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.27 (d, J= 5.7 Hz, 1H), 7.97 (d, J= 9.6 Hz, 1H), 7.81 (d, J= 1.8 Hz, 2H), 7.09 (d, J= 5.7 Hz, 1H), 4.89 (q, J= 8.3 Hz, 2H), 4.78 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d6) δ 165.27, 161.64, 157.00, 154.45, 148.22, 132.58, 124.26 (d, J = 3.9 Hz), 123.92, 122.97 (q, J= 278.0 Hz), 120.28, 120.00, 115.43, 115.24, 107.68, 65.36 (dd, J = 28.0, 14.9 Hz), 37.68, 10.67; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66, –112.81; HR-MS (ESI): Calculated for $C_{17}H_{12}O_2N_3F_4SCl$ $[M+H]^+$: 434.03476, found: 434.03384.

2-(((3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-5-(m-tolyl)-1,3,4-oxadiazole (**6p**): White solid; yield, 85.6%; mp 140–141 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.27 (d, J= 5.4 Hz, 1H), 7.76 (s, 1H), 7.74 (d, J= 7.7 Hz, 1H), 7.45 (t, J= 7.6 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.08 (d, J = 5.6 Hz, 1H), 4.89 (q, J = 8.6 Hz, 2H), 4.76 (s, 2H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d6) δ 165.75, 164.33, 161.64, 154.63, 148.23, 139.50, 133.21, 129.89, 127.22, 124.12, 122.97 (q, J= 278.0 Hz), 123.52, 120.30, 107.65, 65.52 (q, J= 36.2 Hz), 37.66, 21.34, 10.67; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS (ESI): Calculated for $C_{18}H_{16}O_2N_3F_3S$ $[M+H]^+$: 396.09881, found: 396.09805.

2-(4-Bromophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6q**): White solid; yield, 78.4%; mp 183–184 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.7 Hz, 1H), 7.88 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.75 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.20, 164.94, 161.69, 154.40, 148.18, 132.48, 128.20, 126.41, 122.97 (q, J = 278.0 Hz), 122.64, 121.39, 105.89, 65.52 (q, J = 36.7 Hz), 37.39, 10.78; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66; HR-MS(ESI): Calculated for $C_{17}H_{13}O_2N_3F_3SBr$ $[M+H]^+$: 459.99367, found: 459.99292.

2-(4-Bromo-2-fluorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6r**): White solid; yield, 60.8%; mp 171–172 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.34 (d, J = 5.6 Hz, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 0.8 Hz, 1H), 6.68 (d, J = 5.6 Hz, 1H), 4.76 (s, 2H), 4.41 (q, J = 7.4 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.46, 161.96 (d, J = 5.4 Hz), 161.69, 159.51 (d, J = 263.5 Hz), 154.34, 148.18, 130.35, 128.31, 126.66 (d, J = 8.9 Hz), 122.97 (q, J = 277.6 Hz), 121.40, 120.83 (d, J = 23.9 Hz), 111.42 (d, J = 12.1 Hz), 105.90, 65.52 (q, J = 36.1 Hz), 37.35, 10.76; ^{19}F NMR (471 MHz, chloroform-D) δ –73.66, –106.98; HR-MS (ESI): Calculated for $C_{17}H_{12}O_2N_3F_4SBr$ $[M+H]^+$: 477.98425, found: 477.98325.

2-(2-Fluorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6s**): White solid; yield, 85.3%; mp 124–125 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.6 Hz, 1H), 8.11 – 7.88 (m, 1H), 7.52 (dddd, J = 8.6, 7.1, 5.1, 1.8 Hz, 1H), 7.28 (dt, J = 8.0, 4.1 Hz, 1H), 7.25–7.21 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.76 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.12, 162.62 (d, J = 5.9 Hz), 161.69, 159.95 (d, J = 258.5 Hz), 154.49, 148.20, 133.49 (d, J = 8.3 Hz), 129.63, 124.71 (d, J = 3.4 Hz), 122.98 (q, J = 277.6 Hz), 121.42, 117.07 (d, J = 20.7 Hz), 112.29 (d, J = 11.6 Hz), 105.87, 65.52 (q, J = 72.6, 36.2 Hz), 37.33, 10.76; ^{19}F NMR (471 MHz, chloroform-D) δ –73.68, –109.53; HR-MS(ESI): Calculated for $C_{17}H_{13}O_2N_3F_4S$ $[M+H]^+$: 400.07374, found: 400.07281.

2-(((3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-5-(3-(trifluorom-ethyl)phenyl)-1,3,4-oxadiazole (**6t**): White solid; yield, 88.6%; mp 125–126 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.34 (dd, J = 5.5, 2.9 Hz, 1H), 7.99 (t, J = 6.6 Hz, 1H), 7.57–7.41 (m, 2H), 7.38–7.08 (m, 1H), 6.68 (dd, J = 5.4, 2.9 Hz, 1H), 4.75 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.11, 162.63, 160.97, 158.91, 154.43, 148.19, 132.16 (q, J = 314.8 Hz), 129.61, 124.70, 123.69 (q, J = 173.1 Hz), 122.75 (q, J = 31.0 Hz), 121.40, 116.98, 112.20, 105.89, 65.50 (q, J = 36.5 Hz), 37.31, 10.75; ^{19}F NMR (471 MHz, chloroform-D) δ –73.68, –109.55; HR-MS (ESI): Calculated for $C_{18}H_{13}O_2N_3F_6S$ $[M+H]^+$: 450.07054, found: 450.06949.

2-(4-Chlorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6u**): White solid; yield, 73.9%; mp 185–186 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.75 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.10, 164.89, 161.68, 154.40, 148.18, 137.99, 129.52, 128.07, 122.97 (q, J = 277.7 Hz), 122.21, 121.38, 105.89, 65.52 (q, J = 36.7 Hz), 37.40, 10.78; ^{19}F NMR (471 MHz, chloroform-D) δ –73.68; HR-MS (ESI): Calculated for $C_{17}H_{13}O_2N_3F_3SCl$ $[M+H]^+$: 416.04419, found: 416.04306.

2-(5-Bromo-2-chlorophenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1,3,4-oxadiazole (**6v**): White solid; yield, 87.8%; mp 140–141 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.6

Hz, 1H), 8.09 (d, J= 2.3 Hz, 1H), 7.55 (dd, J = 8.6, 2.2 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 6.68 (d, J= 5.7 Hz, 1H), 4.76 (s, 2H), 4.41 (q, J= 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 165.77, 162.95, 161.69, 154.30, 148.20, 135.24, 133.44, 132.75, 132.07, 124.54, 122.97 (q, J = 278.0 Hz), 121.38, 120.69, 105.93, 65.53 (q, J= 72.5, 36.3 Hz), 37.41, 10.77; ^{19}F NMR (471 MHz, chloroform-D) δ –73.67; HR-MS (ESI): Calculated for $C_{17}H_{12}BrClF_3N_3O_2S$ $[M+H]^+$: 494.95470, found: 494.95361.

2-(2-Methoxyphenyl)-5-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl)methyl)thio)-1,3,4-oxadiazole (**6w**): White solid; yield, 79.4%; mp 124–125 °C; ^{1}H NMR (500 MHz, chloroform-D) δ 8.35 (d, J = 5.6 Hz, 1H), 7.87 (dd, J= 7.7, 1.7 Hz, 1H), 7.48 (ddd, J= 8.4, 7.5, 1.7 Hz, 1H), 7.05 (td, J= 7.6, 1.0 Hz, 2H), 7.04 (d, J= 8.4 Hz, 1H), 6.67 (d, J = 5.7 Hz, 1H), 4.75 (s, 2H), 4.40 (q, J= 7.8 Hz, 2H), 3.94 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, chloroform-D) δ 164.61, 164.14, 161.67, 157.85, 154.74, 148.19, 133.09, 130.38, 122.99 (q, J = 278.2 Hz), 121.46, 120.78, 112.91, 111.98, 105.81, 65.51 (q, J= 36.4 Hz), 56.06, 37.24, 10.77; ^{19}F NMR (471 MHz, chloroform-D) δ –73.68; HR-MS (ESI): Calculated for $C_{18}H_{16}F_3N_3O_3S$ $[M+H]^+$: 412.09372, found: 412.09296.

3.4. Biological assays

3.4.1. Antibacterial activity

The turbidity method was used to carry out biological activity tests.[14] When rice bacterial blight was determined, leaf cumin was used as the control agent. When the tobacco bacterial wilt bacteria were used, thiodiazole-copper was used as the control agent and warm water was used as the blank control. Three parallels, using the following formulas, were used to calculate the bacterial inhibition rate:

Corrected OD value = OD value of bacteria-containing medium – OD value of sterile medium

Inhibition rate = (OD value of corrected control medium broth – corrected OD value of toxic medium) / corrected OD value of control medium broth × 100%

3.4.2. Insecticidal activity

Previously reported protocols[7,8] were used to test the insecticidal activities against *Plutella xylostella*. Fresh cabbage discs (diameter of 2 cm) were dipped in the prepared solutions containing the synthesized compounds for 10 s, dried in air, and placed in a petri dish lined with filter paper. Ten larvae of the second instar of *Plutella xylostella* were carefully transferred to the petri dishes. Chlorantraniliprole was used as a positive control; three replicates were performed for each experiment. Mortality was calculated after 72 h. Evaluations of mortality were calculated on a percentage scale (0 = no activity and 100 = complete eradication) at 5% intervals.

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