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Article

Trifluoromethylpyridine 1,3,4-Oxadiazole Derivatives: Emerging Scaffolds as Bacterial Agents

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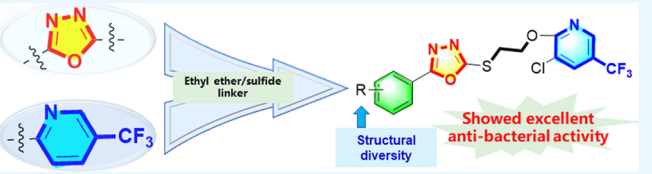
ABSTRACT: A new class of trifluoromethylpyridine 1,3,4-oxadiazole derivatives (**6a−6v**) was obtained, and their antibacterial activities were evaluated. Some of them exhibited good activity, particularly **6a,** which had the highest in vitro activity against *Ralstonia solanacearum* (*R. solanacearum*) and *Xanthomonas axonopodis* pv. *citri* (*Xac*). The half-maximal effective concentrations (EC_{50}) were 26.2 and 10.11 μg/mL, respectively, which were lower than those of commercial thiodiazole copper (97.2 and 35.3 μg/mL, respectively). Furthermore, **6q** showed much higher activity against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) with an EC_{50} value of 7.2 μg/mL; this was superior to bismerthiazol (57.2 μg/mL). Collectively, our findings provide a foundation for the development of trifluoromethylpyridine 1,3,4-oxadiazole derivatives.



INTRODUCTION

Bacterial diseases of plants can bring extensive reductions in crop quality and yield and continue to pose a significant threat to crop production.[1] For example, *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) can cause serious outbreaks of bacterial blight disease in rice and often result in serious diseases; thus, in severe cases, the crop yield can be reduced by 50%.[2,3] Moreover, as the most aggressive pathogens, tobacco bacterial wilt, which is caused by *Ralstonia solanacearum* (*R. solanacearum*), and citrus ulcer, which is caused by *Xanthomonas axonopodis* pv. *citri* (*Xac*), are very destructive bacterial diseases and can cause serious reductions in the global yield of tobacco and citrus fruit. It is very hard to regulate these diseases once plants have been infected.[4−7] At present, pesticides remain as the most economical and effective treatment for controlling agricultural diseases. Although bismerthiazol, thiodiazole copper, and zinc thiazole have been used broadly to prevent plant bacterial diseases,[8] however, the resistance or cross-resistance of pathogens progressively increases and limits the existing pesticides' therapeutic effects.[9] Consequently, there is a severe shortage of agrochemicals for the treatment of bacterial diseases, and there is an urgent need to develop new active molecules with high activity.

As a highly efficient pharmacophore, 1,3,4-oxadiazole is not only used widely in drug design but also has extensive biological activities,[10,11] such as antibacterial,[12] herbicidal,[13] anti-inflammatory,[14] and insecticidal[15] properties. Furthermore, the molecules that contain 1,3,4-oxadiazole show excellent antibacterial activities against a number of plant bacterial pathogens, including *R. solanacearum*,[16] *Xoo*,[17] and *Xac*.[18] In previous research, plenty of 1,3,4-oxadiazole derivatives were synthesized and evaluated (Figure 1);[19−26] some of these were confirmed to exhibit good antibacterial activities.

Furthermore, the trifluoromethylpyridine ring has drawn much attention in novel pesticide creation[27,28] and has desirable biological activities, including antibacterial, weeding, and insecticidal[28] properties. We synthesized a class of 1,3,4-oxadiazole compounds that contained trifluoromethylpyridine and exhibited antibacterial and insecticidal activities (Figure 1).[29,30] In addition, there are related reports described in world patents that relate to trifluoromethylpyridine-containing compounds.[31]

We considered previous research relating to 1,3,4-oxadiazole and the advantageous structure of trifluoromethylpyridine and attempted to use this information to develop novel and efficient antibacterial agents. Herein, by incorporating ethyl ether and sulfide linkers, a series of trifluoromethylpyridine 1,3,4-oxadiazole derivatives was designed and synthesized and their activities against *R. solanacearum*, *Xoo* and *Xac* were evaluated. Collectively, some of them showed high levels of antibacterial activities to be used as lead compounds for bactericides.

RESULTS AND DISCUSSION

Chemistry. As shown in Figure 2, benzoic acids **1a−1v** with different substituents underwent an esterification reaction with ethanol to give intermediates **2a−2v**. Intermediates **2a−**

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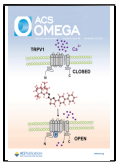

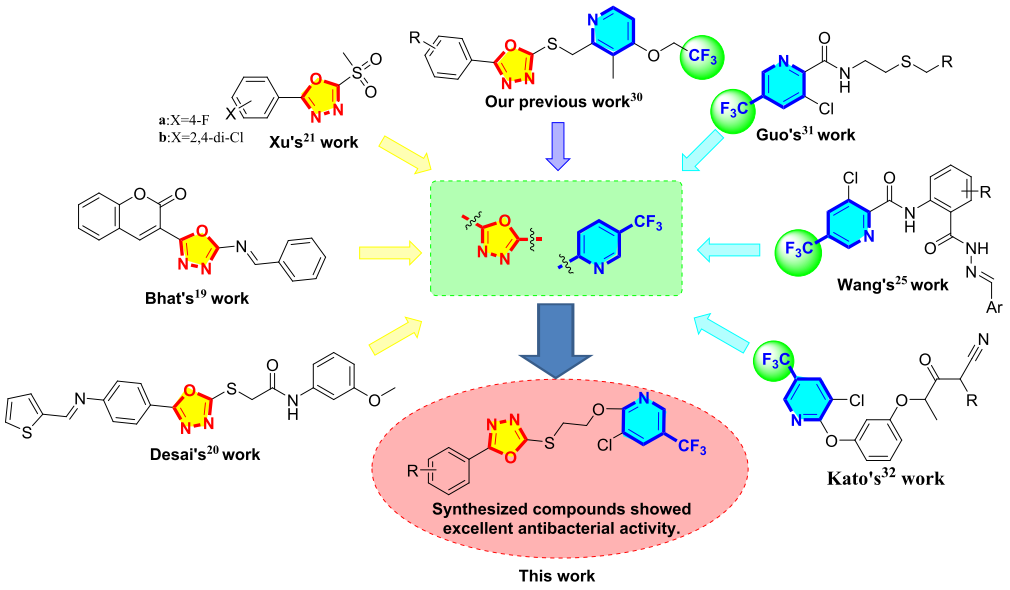

Figure 1. Design of compounds **6a**−**6v**.

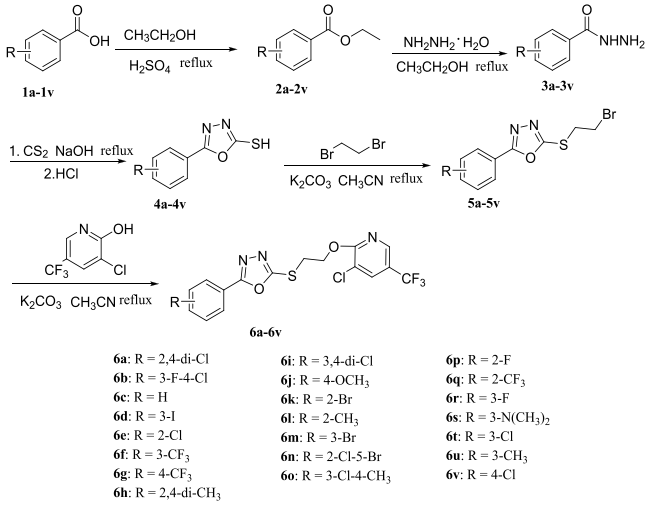

Figure 2. Synthesis route of the target compounds **6a**−**6v**.

2v then underwent hydrazinolysis with hydrazine hydrate to give intermediates **3a**−**3v**. Under basic conditions, intermediates **3a**−**3v** underwent a ring-closing reaction with carbon disulfide to give intermediates **4a**−**4v**. In the reflux state, **4a**−**4v** and 1,2-dibromoethane rapidly underwent a substitution reaction to give intermediates **5a**−**5v**. Using acetonitrile as the solvent, the intermediates **5a**−**5v** and 3-chloro-5-(trifluoromethyl) pyridin-2-ol were reacted for approximately 1.5 h under reflux to give the corresponding target compounds **6a**−**6v**. The structures of the target compounds were characterized by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and ^{19}F NMR spectroscopy and high-resolution mass spectrometry (HRMS).

Antibacterial Activity In Vitro. The results shown in Table 1 indicated that some of the title compounds showed higher activities against *R. solanacearum*, *Xac*, and *Xoo* than commercial bactericides at concentrations of 50 and 100 μg/mL. At 50 μg/mL, compounds **6a** and **6o** showed the highest activities against *R. solanacearum* (71.3 and 67.3%, respectively); these activities were superior to that of thiodiazole copper (TDC, 39.1%). At 100 μg/mL, compounds **6a**, **6d**, **6i**, **6j**, and **6m** demonstrated good activities against *Xac*: the inhibition rates were 97.7, 88.2, 88.3, 96.8, and 89.8%, respectively. These activities were better than that of TDC (72.1%). Moreover, at a concentration of 100 μg/mL, the 1,3,4-oxadiazole trifluoromethylpyridine-containing compounds **6o**, **6q**, and **6t** showed higher inhibitory activities of 91.5, 100, and 91.9%, respectively, against *Xoo*; these activities were better than bismerthiazol (BMT, 64.6%).

Next, the EC_{50} values of the 1,3,4-oxadiazole trifluoromethylpyridine-containing compounds against *R. solanacearum*, *Xac*, and *Xoo* were further evaluated. The results shown in Tables 2, 3, and 4 revealed that the EC_{50} values against *R. solanacearum* for compounds **6a** and **6o** were 26.2 and 26.3 μg/mL, respectively; these were much lower than that of TDC (97.2 μg/mL). Meanwhile, compounds **6a** and **6b** showed excellent inhibitory activities against *Xac*, with EC_{50} values of 10.1 and 11.6 μg/mL, respectively; these activities were better than that for TDC (35.5 μg/mL). Furthermore, the target molecules **6o** and **6q** also revealed better inhibitory activities against *Xoo*, with EC_{50} values of 12.7 and 7.2 μg/mL, respectively; these activities were lower than that of the commercial agent BMT (57.2 μg/mL).

SAR Analysis. According to the data of antibacterial evaluation shown in Tables 1 to 4, Structure-Activity Relationship (SAR) analysis showed that different substitutions on the benzene ring could change the antibacterial activity. Compounds **6a**−**6v** exhibited better activities against *R. solanacearum* when R was 2,4-dichloro or 3-chloro-4-methyl. The activities against *Xac* were maximal when the substituents of the benzene ring were 2,4-dichloro, 3-iodine, and 2-chloro; the activities of 3-chloro, 4-chloro, and 3,4-dichloro were lower than that of 2,4-dichloro. Furthermore, the activities against *Xoo* were slightly higher than other substitutions when the substituent on the benzene ring was 3-chloro-4-methyl, 2-trifluoromethyl, and 3-chloro. When the 2-position of the benzene ring was substituted with trifluoromethyl, the antibacterial activity was better than the substitution of other positions. When the 3-position was substituted with a chlorine atom, the activity was higher than those at the 2- and 4-

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Table 1. In Vitro Antibacterial Activities of the Target Compounds against *R. Solanacearum*, *Xac*, and *Xoo*

		inhibition rate/%					
		R. solanacearum		*Xac*		*Xoo*	
compounds	*R*	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
6a	2,4-*di*-Cl	79.0 ± 3.4	71.3 ± 1.6	97.7 ± 4.2	75.6 ± 3.1	56.8 ± 1.1	26.1 ± 2.6
6b	3-F-4-Cl	81.2 ± 5.1	60.1 ± 2.9	74.8 ± 0.9	65.1 ± 1.7	18.3 ± 2.8	12.7 ± 2.1
6c	H	63.3 ± 3.6	56.0 ± 3.2	79.3 ± 1.3	70.9 ± 2.5	36.2 ± 2.0	20.1 ± 1.4
6d	3-I	52.0 ± 4.0	41.9 ± 2.7	88.2 ± 5.5	74.2 ± 3.7	82.1 ± 4.1	63.6 ± 2.9
6e	2-Cl	60.5 ± 3.8	51.8 ± 2.1	72.0 ± 2.7	67.5 ± 4.1	31.5 ± 0.8	12.8 ± 0.6
6f	3-CF_3	56.3 ± 3.6	43.0 ± 2.9	83.2 ± 2.2	77.1 ± 3.6	61.6 ± 4.2	49.4 ± 2.6
6g	4-CF_3	88.7 ± 4.8	63.1 ± 2.7	84.3 ± 4.2	80.9 ± 3.2	30.4 ± 1.3	9.9 ± 0.8
6h	2,4-*di*-CH_3	66.9 ± 4.1	59.3 ± 2.2	84.4 ± 3.0	76.7 ± 5.3	44.4 ± 2.8	23.3 ± 2.1
6i	3,4-*di*-Cl	83.8 ± 3.5	64.8 ± 2.6	88.3 ± 4.6	77.6 ± 4.3	53.0 ± 3.6	20.7 ± 1.8
6j	4-OCH_3	21.8 ± 3.5	12.3 ± 1.9	96.8 ± 4.5	81.9 ± 2.3	83.3 ± 2.6	51.8 ± 3.5
6k	2-Br	45.6 ± 3.6	41.2 ± 4.1	79.0 ± 3.7	72.9 ± 1.9	39.3 ± 2.4	34.5 ± 1.8
6l	2-CH_3	52.4 ± 4.6	37.6 ± 3.7	84.1 ± 3.2	69.7 ± 3.2	85.6 ± 1.9	61.9 ± 1.5
6m	3-Br	49.3 ± 3.3	30.5 ± 3.9	89.8 ± 2.6	70.9 ± 2.9	69.8 ± 3.2	49.2 ± 2.5
6n	2-Cl-5-Br	58.4 ± 2.7	39.9 ± 1.5	80.4 ± 2.7	54.9 ± 3.4	88.4 ± 1.6	65.9 ± 2.8
6o	3-Cl-4-CH_3	89.4 ± 4.1	67.3 ± 2.3	76.2 ± 3.1	62.9 ± 3.7	91.5 ± 2.3	76.6 ± 2.4
6p	2-F	68.2 ± 2.2	52.5 ± 3.1	78.5 ± 2.5	59.9 ± 2.7	82.4 ± 2.0	72.1 ± 3.5
6q	2-CF_3	78.3 ± 2.4	64.7 ± 3.8	81.6 ± 1.5	50.5 ± 2.6	100.0	94.6 ± 2.6
6r	3-F	50.5 ± 1.7	41.3 ± 2.3	63.8 ± 3.4	41.1 ± 3.3	78.2 ± 3.1	69.2 ± 1.8
6s	3-$N(CH_3)_2$	60.2 ± 2.3	45.9 ± 3.8	66.9 ± 2.9	41.9 ± 2.7	71.4 ± 2.5	55.5 ± 2.8
6t	3-Cl	59.3 ± 4.2	46.4 ± 3.7	69.6 ± 5.0	58.5 ± 3.2	91.9 ± 3.7	70.2 ± 3.4
6u	3-CH_3	78.2 ± 3.1	53.5 ± 3.4	65.2 ± 3.5	47.5 ± 3.0	84.6 ± 3.5	51.3 ± 4.2
6v	4-Cl	83.3 ± 4.6	60.1 ± 2.9	78.7 ± 4.6	59.4 ± 2.4	76.8 ± 4.1	56.4 ± 2.3
TDC[a]		61.8 ± 2.7	39.1 ± 4.3	72.1 ± 3.0	45.2 ± 1.8	NT[c]	NT[c]
BMT[b]		NT[c]	NT[c]	NT[c]	NT[c]	64.6 ± 2.6	38.4 ± 1.8

[a]Thiodiazole copper. [b]Bismerthiazol. [c]NT = not tested.

Table 2. EC_{50} Values of In Vitro Antibacterial Activities of the Target Compounds against *R. Solanacearum*

compounds	*R*	regression equation	*r*	EC_{50}[a]/(μg/mL)
6a	2,4-*di*-Cl	$y = 1.0296x + 3.4628$	0.9672	26.2 ± 2.6
6b	3-F-4-Cl	$y = 0.7747x + 3.8775$	0.9851	38.1 ± 4.3
6g	4-CF_3	$y = 1.0824x + 1.7437$	0.9883	39.5 ± 1.8
6h	2,4-di-CH_3	$y = 2.0983x + 1.1979$	0.9903	42.4 ± 3.6
6i	3,4-*di*-Cl	$y = 1.3506x + 2.9760$	0.9859	35.2 ± 3.5
6o	3-Cl-4-CH_3	$y = 1.9795x + 2.1882$	0.9945	26.3 ± 1.6
6p	2-F	$y = 2.1409x + 1.3962$	0.9008	48.2 ± 2.4
6q	CF_3	$y = 1.9419x + 2.0093$	0.9869	34.7 ± 1.9
6u	3-Cl-4-CH_3	$y = 1.7576x + 2.1969$	0.9964	46.4 ± 3.5
6v	4-Cl	$y = 1.8389x + 2.0386$	0.9886	40.8 ± 2.5
TDC[b]		$y = 1.8727x + 1.8973$	0.9831	97.2 ± 2.7

[a]Average of three replicates. [b]Thiodiazole copper.

Table 3. EC_{50} Values of In Vitro Antibacterial Activities of the Target Compounds against *Xac*

compounds	*R*	regression equation	*r*	EC_{50}[a]/(μg/mL)
6a	2,4-*di*-Cl	$y = 1.208x + 3.7858$	0.8308	10.1 ± 3.7
6d	3-I	$y = 1.0141x + 3.9213$	0.9364	11.6 ± 3.1
6f	3-CF_3	$y = 2.5575 + 0.3133$	0.9228	43.9 ± 1.3
6g	4-CF_3	$y = 1.1588x + 3.3050$	0.9525	29.1 ± 2.5
6h	2,4-*di*-CH_3	$y = 2.7059x + 0.2196$	0.9168	38.4 ± 2.5
6i	3,4-*di*-Cl	$y = 1.6804x + 2.5760$	0.9782	27.7 ± 1.8
6j	4-OCH_3	$y = 2.0733x + 2.0249$	0.9766	27.2 ± 1.6
6k	2-Br	$y = 2.0095x + 2.1709$	0.9896	25.6 ± 2.5
6l	2-CH_3	$y = 1.3378x + 2.9349$	0.9672	31.5 ± 1.6
6m	3-Br	$y = 1.4360x + 2.9071$	0.9907	28.7 ± 2.7
6n	2-Cl-5-Br	$y = 2.9492x + 0.1740$	0.8857	43.3 ± 3.1
6p	2-F	$y = 2.4451x + 1.1452$	0.9203	37.7 ± 1.9
6q	2-CF_3	$y = 1.3491x + 2.9377$	0.9207	33.8 ± 4.1
6v	4-Cl	$y = 2.0645x + 1.4369$	0.9015	43.2 ± 2.6
TDC[b]		$y = 1.9591x + 1.9678$	0.9905	35.3 ± 3.6

[a]Average of three replicates. [b]Thiodiazole copper.

positions. However, the quantity and structure of the derivatives were too poor to derive accurate SAR data.

In summary, we identified several compounds exhibiting high activities against *R. solanacearum*, *Xac*, and *Xoo*. These results demonstrated that the novel trifluoromethylpyridine-containing 1,3,4-oxadiazoles can be considered as new antibacterial agents and laid a foundation for controlling plant bacterial diseases.

MATERIALS AND METHODS

Chemicals. All reagents and solvents were obtained from TCI (Tokyo, Japan) and Accela (Shanghai, China) and used without further purification.

Instruments. The newly synthesized compounds were characterized using an Avance III HD 400 MHz NMR spectrometer (Bruker Corp., Fallanden, Switzerland) and a Q Exactive HRMS (Thermo Scientific, Missouri, USA). The

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Table 4. EC_{50} Values of In Vitro Antibacterial Activities of the Target Compounds against *Xoo*

compounds	*R*	regression equation	*r*	EC_{50}[a]/(μg/mL)
6d	3-I	$y = 3.3335x + 0.0259$	0.8686	31.0 ± 2.1
6j	4-OCH_3	$y = 1.209x + 3.2895$	0.8913	25.9 ± 1.9
6l	2-CH_3	$y = 1.2336x + 2.885$	0.9843	31.8 ± 2.2
6m	3-Br	$y = 1.4044x + 3.1919$	0.9532	37.4 ± 3.4
6n	2-Cl-5-Br	$y = 1.2398x + 3.4224$	0.9318	18.7 ± 2.6
6o	3-Cl-4-CH_3	$y = 1.4399x + 3.0211$	0.9589	12.7 ± 1.5
6p	2-F	$y = 0.9939x + 3.5244$	0.9936	30.5 ± 2.3
6q	2-CF_3	$y = 1.0854 + 4.0720$	0.9362	7.2 ± 1.2
6r	3-F	$y = 3.1403x + 0.0508$	0.9090	37.7 ± 1.6
6s	3-$N(CH_3)_2$	$y = 1.649x + 2.4165$	0.9968	36.8 ± 1.8
6t	3-Cl	$y = 3.0771x + 1.6031$	0.9599	12.7 ± 2.1
6u	3-CH_3	$y = 1.6466x + 2.2633$	0.9457	35.9 ± 2.5
6v	4-Cl	$y = 1.0725x + 3.8219$	0.9779	12.6 ± 2.5
BMT[b]		$y = 1.4719x + 2.4134$	0.9664	57.2 ± 5.3

[a]Average of three replicates. [b]Bismerthiazol.

melting points were determined using an XT4 binocular microscope (Beijing Tech Instrument Co., China).

Preparation of Intermediates 2a−2v. First, 5 g of substituted benzoic acid was added to 30 mL of absolute ethanol and 2 mL of concentrated sulfuric acid (2 mL) and refluxed for approximately 10 h, as described in the literature.[32] After the reaction was completed, the anhydrous ethanol was distilled off under a reduced pressure, and the reaction solution was poured into water. An aqueous sodium carbonate solution was then added and the pH was adjusted to >7, and then the solution was extracted with ethyl acetate, and the organic phase was collected, dried with $MgSO_4$, and evaporated to obtain **2a−2v**.

Preparation of Intermediates 3a−3v. According to the literature,[33] intermediates **3a−3v** could be obtained. First, a certain amount of **2a−2v** (1 equivalent, equiv) was added to a certain amount of absolute ethanol as a solvent. Next, we added 80% hydrazine hydrate (2 equiv) and stirred under reflux for 10 min. After the reaction was completed, ethanol was distilled off under a reduced pressure, and the preparation was refrigerated for 12 h. The solid precipitate was then filtered off with suction, washed with water, and dried, thus creating intermediates **3a−3v**.

Preparation of Intermediates 4a−4v. Intermediates **4a−4v** were prepared according to previously reported methods.[34] First, we weighed intermediates **3a−3v** (1 equiv) and sodium hydroxide (1.5 equiv, dissolved in a certain amount of water). Next, we used absolute ethanol as a solvent with stirring at room temperature for 20 min. Carbon disulfide (2 equiv) was added dropwise to the system. Then, the reaction was kept at room temperature for about 1 h, followed by heating under reflux for 12 h. After completion of the reaction, the resulting solution was concentrated under a reduced pressure and poured into water, and the resulted mixture was stirred with glass rod and filtered out the impurities. Then the mother liquor was adjusted to pH < 7 with dilute hydrochloric acid. The solids were precipitated, filtered off with suction, and dried to obtain intermediates **4a−4v**.

Preparation of Intermediates 5a−5v. Intermediates **5a−5v** were prepared in accordance with the method described in the literature.[35] First, we weighed intermediates **4a−4v** and anhydrous potassium carbonate using an analytical method. Next, we used acetonitrile as the solvent and heated the mixture to reflux for approximately 1 h. After 1 h, the speed of the reaction was increased to the maximum, and 1,2-dibromoethane was quickly added to the reaction system. The reaction was completed after approximately 1 min. After the temperature of the system was lowered, the contents of the system were poured into water and extracted with dichloromethane, and the organic phases were collected, dried over anhydrous $MgSO_4$ for 2 h, filtered with suction, subjected to column chromatography with petroleum ether/ethyl acetate (10:1), and finally dried under vacuum to obtain the intermediates **5a−5v**.

Synthesis of the Target Compounds 6a−6v. 3-Chloro-5-(trifluoromethyl) pyridin-2-ol (1 equiv), anhydrous potassium carbonate (2.2 equiv), potassium iodide (0.5 equiv), and acetonitrile as the solvents were heated under reflux for approximately 1.5 h. Then, the intermediates **5a−5v** were added to the reaction system. After the reaction was completed, the system was purified by column chromatography with petroleum ether/ethyl acetate (15:1) to obtain the target compounds **6a−6v**. The data of **6u** are shown below.

*2-((2-((3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)-thio)-5-(4-chlorophenyl)-1,3,4-oxadiazole (**6u**).* White solid; mp 128−129 °C; yield 61.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.81 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.42−7.33 (m, 2H), 4.56 (t, *J* = 6.5 Hz, 2H), 3.69 (t, *J* = 6.5 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.45, 162.93, 158.35, 139.07, 136.39 (q, *J* = 5.2 Hz), 133.62 (q, *J* = 2.3 Hz), 132.83, 129.04, 127.41, 127.20, 123.87, 123.01, 122.56 (q, *J* = 270.6 Hz), 109.32 (q, *J* = 35.7 Hz), 50.74, 30.14, 21.32. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.16. HRMS (ESM): calculated for $C_{17}H_{13}ClF_3N_3O_2S$ $[M + H]^+$: 416.04362, found: 416.04419.

Antibacterial Activity. *Antibacterial Activity in Vitro.* The in vitro antibacterial activity against *R. solanacearum*, *Xac*, and *Xoo* was evaluated using the turbidimeter test.[36] All samples were dissolved with dimethyl sulfoxide and diluted with 1‰ Tween-20 to obtain a test solution. Thiodiazole copper solution was used as a positive control for *R. solanacearum* and *Xac*. BMT solution was used as a positive control drug for *Xoo*. Test tubes were filled with 5 mL of culture medium and test solution; we then added the logarithmic bacterial solution (40 μL) to the test tubes. The test tubes were then placed in a constant temperature shaker (temperature: 28 °C, speed: 180 rpm). *Xoo* was shaken for

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36−48 h, *Xac* was shaken for 24−36 h, and *R. solanacearum* was shaken for 16−24 h. After the logarithmic growth period, the optical density (OD) values of all bacterial liquids were measured with a microplate reader at a wavelength of 595 nm, and the inhibition rate of the tested drugs on bacteria was calculated based on the measured OD values. All experiments were repeated three times. The inhibition rate was calculated using the following equation, where the corrected turbidity value of the negative control group was expressed as X and the turbidity value of the treatment group was expressed as Y.

$$\text{Inhibition rate}\ (\%) = (X - Y)/X \times 100$$

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04472.

Characterization data, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra, and HRMS data for the target compounds (PDF)

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Notes

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■ REFERENCES

(1) Huang, N.; Angeles, E. R.; Domingo, J.; Magpantay, G.; Singh, S.; Zhang, G.; Kumaravadivel, N.; Bennett, J.; Khush, G. S. Pyramiding of bacterial blight resistance genes in rice: Marker-assisted selection using RFLP and PCR. *Theor. Appl. Genet.* **1997**, *95*, 313−320.

(2) Lakshmanan, V.; Thangaraj, M.; Ponnusamy, B.; Santhiraka, S.; Kannan, R.; Regunathan, U.; Selvaraj, S. Antibacterial activity of *Rhizophora apiculata* leaf extract for the management of rice bacterial blight disease. *J. Plant Pathol.* **2019**, *18*, 39−46.

(3) Gao, Y.; Zhong, X.; Li, Q.; Qian, J. J.; Xiao, N.; Chen, J. M. ZmXa21-L gene encodes a plant receptor-like kinases (RLKs) protein that enhances resistance to bacterial blight in rice. *Physiol. Mol. Plant. Pathol.* **2019**, *108*, No. 101429.

(4) Pandiyaraj, P.; Singh, T.; Reddy, K. M.; Sadashiva, A.; Dhananjaya, M.; Samuel, D. K.; Venugopala, R.; Reddy, D. Evaluation of brinjal (*Solanum melongena* L.) germplasm for yield and bacterial wilt (*Ralstonia solanacearum*) disease resistance. *Int. J. Chem. Stud.* **2019**, *7*, 836−838.

(5) Hayward, A. C. Biology and epidemiology of bacterial wilt caused by *Pseudomonas solanacearum*. *Annu. Rev. Phytopathol.* **1991**, *29*, 65−87.

(6) Graham, J. H.; Gottwald, R.; Cubero, J.; Achor, D. S. *Xanthomonas axonopodis* pv. *citri*: factors affecting successful eradication of citrus canker. *Mol. Plant. Pathol.* **2004**, *5*, 1−15.

(7) Wang, M. W.; Zhu, H. H.; Wang, P. Y.; Zeng, D.; Wu, Y. Y.; Liu, L. W.; Wu, Z. B.; Li, Z.; Yang, S. Synthesis of Thiazolium-Labeled 1,3,4-Oxadiazole Thioethers as Prospective Antimicrobials: In Vitro and in Vivo Bioactivity and Mechanism of Action. *J. Agric. Food Chem.* **2019**, *67*, 12696−12708.

(8) Liu, D. Y.; Zhang, J.; Zhao, L.; He, W. J.; Liu, Z. J.; Gan, X. H.; Song, B. A. First Discovery of Novel Pyrido[1,2-*a*] Pyrimidinone Mesoionic Compounds as Antibacterial Agents. *J. Agric. Food Chem.* **2019**, *67*, 11860−11866.

(9) Lei, J.; Sun, L. C.; Huang, S. Y.; Zhu, C. H.; Li, P.; He, J.; Mackey, V.; Coy, D. H.; He, Q. Y.The Antimicrobial Peptides and Their Potential Clinical Applications. *Am. J. Transl. Res.* **2019**, *11*, 3919−3931.

(10) Zhang, M. Z.; Mulholland, N.; Beattie, D.; Irwin, D.; Gu, Y. C.; Chen, Q.; Yang, G. F.; Clough, J. Synthesis and antifungal activity of 3-(1,3,4-oxadiazol-5-yl) -indoles and 3-(1,3,4-oxadiazol-5-yl)methyl-indoles. *Eur. J. Med. Chem.* **2013**, *63*, 22−32.

(11) Ahsan, M. J.; Choupra, A.; Sharma, R. K.; Jadav, S. S.; Padmaja, P.; Hassan, M. Z.; al-Tamimi, A. B. S.; Geesi, M. H.; Bakht, M. A. Rationale Design, Synthesis, Cytotoxicity Evaluation, and Molecular Docking Studies of 1,3,4-oxadiazole Analogues. *Anti-Cancer Agents Med. Chem.* **2018**, *18*, 121−138.

(12) Chen, Q.; Zhu, X. L.; Jiang, L. L.; Liu, Z. M.; Yang, G. F. Synthesis, antifungal activity and CoMFA analysis of novel 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives. *Eur. J. Med. Chem.* **2008**, *43*, 595−603.

(13) Yu, W.; Zhai, Z. W.; Wedge, D. E.; Duke, S. O.; Wu, H. K.; Weng, J. Q.; Tan, C. X.; Zhang, Y. G.; Liu, X. H. Synthesis and biological activity of novel 1,3,4-oxadiazole derivatives containing a pyrazole moiety. *Res. Chem. Intermed.* **2019**, *45*, 5989−6001.

(14) Tajik, H.; Dadras, A. Synthesis and herbicidal activity of novel 5-chloro-3-fluoro-2-phenoxypyridines with a 1,3,4-oxadiazole ring. *J. Pestic. Sci.* **2011**, *36*, 27−32.

(15) Yang, Z. B.; Li, P.; He, Y. J.; Luo, J.; Zhou, J.; Wu, Y. H.; Chen, L. T. Design, synthesis, and biological evaluation of novel pyrethrin derivatives containing 1, 3, 4- oxadiazole and thioether moieties as active insecticidal agents. *Chem. Pap.* **2020**, *74*, 1621−1632.
(16) Su, S. H.; Zhou, X.; Zhou, Y.; Liao, G. P.; Shi, L.; Yang, X. Synthesis and biological evaluation of novel sulfone derivatives containing 1,3,4-oxadiazole moiety. *World J. Org. Chem.* **2014**, *2*, 18−27.
(17) Zheng, Y. T.; Zhang, T. T.; Wang, P. Y.; Wu, Z. B.; Zhou, L.; Ye, Y. Q.; Zhou, X.; He, M.; Yang, S. Synthesis and bioactivities of novel 2-(thioether/sulfone)-5-pyrazolyl-1,3,4-oxadiazole derivatives. *Chin. Chem. Lett.* **2017**, *28*, 253−256.
(18) Wu, W. N.; Gao, M. N.; Tu, H.; Ouyang, G. P. Synthesis and antibacterial activity of novel substituted purine derivatives. *J. Heterocyclic Chem.* **2016**, *53*, 2042−2048.
(19) Bhat, M. A.; Al-Omar, M. A.; Siddiqui, N. Antimicrobial activity of Schiff bases of coumarin-incorporated 1,3,4-oxadiazole derivatives: an in vitro evaluation. *Med. Chem. Res.* **2013**, *22*, 4455−4458.
(20) Desai, N. C.; Kotadiya, G. M. Microwave-assisted synthesis of benzimidazole bearing 1,3,4-oxadiazole derivatives: screening for their in vitro antimicrobial activity. *Med. Chem. Res.* **2014**, *23*, 4021−4033.
(21) Xu, W. M.; Song, B. A.; Yang, S.; He, J.; He, M.; Hu, D. Y.; Jin, L. H.; Zhao, Y.; Wang, Z. C.; Bai, S.; Wang, J. 2-Substituent-5- (2,4-dichlorophenyl)-1,3,4-oxadiazole derivatives, synthesis method and application thereof. CN 101812034, 2010.
(22) Tian, K.; Li, X. Q.; Zhang, L.; Gan, Y. Y.; Meng, J.; Wu, S. Q.; Wan, J. L.; Xu, Y.; Cai, C. T.; Ouyang, G. P.; Wang, Z. C. Synthesis of novel indole derivatives containing double 1,3,4-oxadiazole moiety as efficient bactericides against phytopathogenic bacterium *Xanthomonas oryzae*. *Chem. Pap.* **2019**, *73*, 17−25.
(23) Xu, W. M.; He, J.; He, M.; Han, F. F.; Chen, X. H.; Pan, Z. X.; Wang, J.; Tong, M. G. Synthesis and Antifungal Activity of Novel Sulfone Derivatives Containing 1,3,4-Oxadiazole Moieties. *Molecules* **2011**, *16*, 9129−9141.
(24) Xu, W. M.; Han, F. F.; He, M.; Hu, D. Y.; He, J.; Yang, S.; Song, B. A. Inhibition of Tobacco Bacterial Wilt with Sulfone Derivatives Containing an 1,3,4-Oxadiazole Moiety. *J. Agric. Food Chem.* **2012**, *60*, 1036−1041.
(25) Wang, Y. Y.; Xu, F. Z.; Luo, D. X.; Guo, S. X.; He, F.; Dai, A. L.; Song, B. A.; Wu, J. Synthesis of Anthranilic Diamide Derivatives Containing Moieties of Trifluoromethylpyridine and Hydrazone as Potential Anti-Viral Agents for Plants. *J. Agric. Food Chem.* **2019**, *67*, 13344−13352.
(26) Xu, W. M.; Yang, S.; Bhadury, P.; He, J.; He, M.; Gao, L. L.; Hu, D. Y.; Song, B. A. Synthesis and bioactivity of novel sulfone derivatives containing 2,4-dichlorophenyl substituted 1,3,4-oxadiazole/thiadiazole moiety as chitinase inhibitor. *Pest. Biochem. Physiol.* **2011**, *101*, 6−15.
(27) Haga, T.; Tsujii, Y.; Hayashi, K.; Kimura, F.; Sakashita, N.; Fujikawa, K. Trifluoromethylpyridines as Building Blocks for New Agrochemicals. *ACS Symp. Ser.* **1991**, *443*, 107−119.
(28) Burriss, A.; Edmunds, J. F.; Emery, D.; Hall, R. G.; Jacob, O.; Schaetzer, J. The importance of trifluoromethyl pyridines in crop protection. *Pest Manage. Sci.* **2018**, *74*, 1228−1238.
(29) Yu, G.; Chen, S.; He, F.; Luo, D.; Zhang, Y.; Wu, J. Synthesis and bioactivity of sulfide derivatives containing 1,3,4-oxadiazole and pyridine. *Turk. J. Chem.* **2019**, *43*, 1075−1085.
(30) Guo, S. X.; He, F.; Dai, A. L.; Zhang, R. F.; Chen, S. H.; Wu, J. Synthesis and biological activities of novel trifluoromethylpyridine amide derivatives containing sulfur moieties. *RSC Adv.* **2020**, *10*, 35658−35670.
(31) Kato, S.; Itahana, H.; Ishizaki, M. D.; Furuki, M.; Yamaguchi, M.; Ohmuro, F.; Nagata, S.; Ohara, E.; Kitajima, T. Preparation of 4-(aryl oxy- or heterocyclyl oxy) - 3- oxobutyronitrile derivatives as antibacterial agents. WO 9600570, 1996.
(32) Zhang, C. R.; Wang, L.; Ge, Y. L.; Ju, X. L. Synthesis of oxazole, benzoxazole and 1,3,4-oxadiazole sulfur ethers and determination of their antitumor activity. *Chin. J. Organ. Chem.* **2007**, *27*, 1432−1437.
(33) Ali, M. A.; Shaharyar, M. Oxadiazole mannich bases: Synthesis and antimycobacterial activity. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3314−3316.
(34) Gan, X. H.; Hu, D. Y.; Li, P.; Wu, J.; Chen, X. W.; Xue, W.; Song, B. A. Design, synthesis, antiviral activity and three-dimensional quantitative structure-activity relationship study of novel 1,4-pentadien-3-one derivatives containing the 1,3,4-oxadiazole moiety. *Pest Manage. Sci.* **2016**, *72*, 534−543.
(35) Wang, C. H.; Xie, X. R.; Liu, W. S.; Hou, G. G.; Sun, J. F.; Zhao, F.; Cong, W.; Li, H. J.; Xin, W. Y. Quaternary ammonium salts substituted by 5-phenyl-1,3,4-oxadiazole-2-thiol as novel antibacterial agents with low cytotoxicity. *Chem. Biol. Drug Des.* **2017**, *90*, 943−952.
(36) Dalgaard, P.; Ross, T.; Kamperman, L.; Neumeyer, K.; McMeekin, T. A. Estimation of bacterial growth rates from turbidimetric and viable count data. *Int. J. Food Microbiol.* **1994**, *23*, 391−404.

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