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Design, synthesis, and antibacterial activity against rice bacterial leaf blight and leaf streak of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivative

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ABSTRACT

A series of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivatives were synthesized and evaluated for their antibacterial activities against rice bacterial leaf blight and leaf streak caused by *Xanthomonas oryzae pv. oryzae* and *Xanthomonas oryzae pv. oryzicolaby* via the turbidimeter test in vitro. Antibacterial bioassay results indicated that most compounds demonstrated good inhibitory effect antibacterial bioactivities against rice bacterial leaf blight and leaf streak. Among the title compounds, compound **6c** demonstrated the best inhibitory effect against rice bacterial leaf blight and leaf streak with half-maximal effective concentration (EC_{50}) values of 1.07 and 7.14 μg/mL, respectively, which were even better than those of commercial agents such as Bismerthiazol and Thiediazole Copper. In vivo antibacterial activities tests at greenhouse conditions demonstrated that the controlling effect of compounds **6c** (43.5%) and **6g** (42.4%) against rice bacterial leaf blight were better than those of Bismerthiazol (25.5%) and Thiediazole Copper (37.5%).

Rice is one of the most important staple crops worldwide. Unfortunately, its production is constrained by several bacterial diseases. Rice bacterial leaf blight and leaf streak caused by pathogens such as *Xanthomonas oryzae pv. oryzae* (*Xoo*) and *Xanthomonas oryzae pv. oryzicola* (*Xoc*) are the most important and well-known bacterial diseases of rice in rice-growing countries.[1–4] The infection caused by these two diseases at the maximum tillering stage results in blighting of leaves. A yield loss of at least 10% caused by these two diseases has been reported in the past 30 years.[5,6] Currently, only a few control methods are available for bacterial rice diseases, including chemical and biological methods and the use of resistant cultivars and lines.[7] Therefore, searching for new antibacterial agents remains a daunting task in pesticide science.

1,3,4-Oxadiazole/thiadiazole, a privileged structure, represents a key motif in heterocyclic chemistry and is important in medicinal chemistry because of its ability to exhibit a wide range of pharmacological activities. Recently, derivatives of 1,3,4-oxadiazole/thiadiazole have been reported for their antibacterial,[8,9] antifungal,[10–14] inflammatory,[15] antianxiety,[16] and antitubercular activities.[17] Meanwhile, sulfone derivatives are also known to exhibit a wide spectrum of biological activities because the sulfone group is an important core found in many biologically active compounds with a wide range of biological activities including antibacterial,[8,9] antifungal,[18] insecticidal,[19] antiviral,[20] herbicidal,[21] anticancer,[22] anti-HIV-1,[23] antihepatitis,[24] antitumor,[25] and anti-inflammatory properties.[26]

In 2005, Guimaraes, and co-workers performed molecular modeling and pharmacokinetic studies to demonstrate that the introduction of a 1,3,4-oxadiazole ring to the inhibitors can change their polarity, flexibility, and metabolic stability. Moreover, the 1,3,4-oxadiazole scaffold can also function as acceptors of hydrogen bonds formation, which enables its use as an isosteric

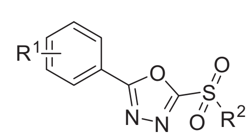

Figure 1. Compounds that were reported against tobacco bacterial wilt and tomato bacterial wilt.

Abbreviations: Xoo, Xanthomonas oryzae pv. oryzae; *Xoc, Xanthomonas oryzae pv. oryzicolaby*; EC_{50}, half-maximal effective concentration; ^1H NMR, ^1H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; IR, infrared spectroscopy; SAR, structure–activity relationship.

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substituent for amide or ester groups.[27] In addition, in our previous study, we have reported a series of sulfone derivatives containing the 1,3,4-oxadiazole moiety (Fig. 1), which showed potent antibacterial activities against tobacco bacterial wilt and tomato bacterial wilt.[8,9] Based on these findings, we aim to introduce a benzyl fragment, which could enhance the flexibility of the molecular backbone to combine with the receptor protein molecular of pathogenic bacteria, and a sulfone fragment to the 1,3,4-oxadiazole/thiadiazole skeleton to build a novel family of bioactive molecules.

In this letter, we reported the synthesis and characterization of several sulfone derivatives containing the 1,3,4-oxadiazole/thiadiazole moiety, and bioassay results demonstrated that several of the title compounds exhibited the best inhibitory effect against rice bacterial leaf blight and leaf streak caused by pathogens *Xoo* and *Xoc*. In order to develop highly active and readily available bacteria inhibitors, the structure–activity relationship (SAR) derived from antibacterial activities of compounds was also discussed. To the best of our knowledge, this is the first report of sulfone derivatives containing the 1,3,4-oxadiazole/thiadiazole moiety with potent controlling effect against rice bacterial leaf blight and leaf streak.

Compounds **6a** to **6′h** were synthesized, as shown in Scheme 1, based on previously described methods.[8–10] Using phenylacetic acid as the starting material, compounds **6a** to **6′h** were synthesized in five steps including esterification, hydrazidation, cyclization, thioetherification and oxidation. The physical characteristics, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis data for all synthesized compounds are reported in the Supplementary data, and the representative data for **6c** are shown below.

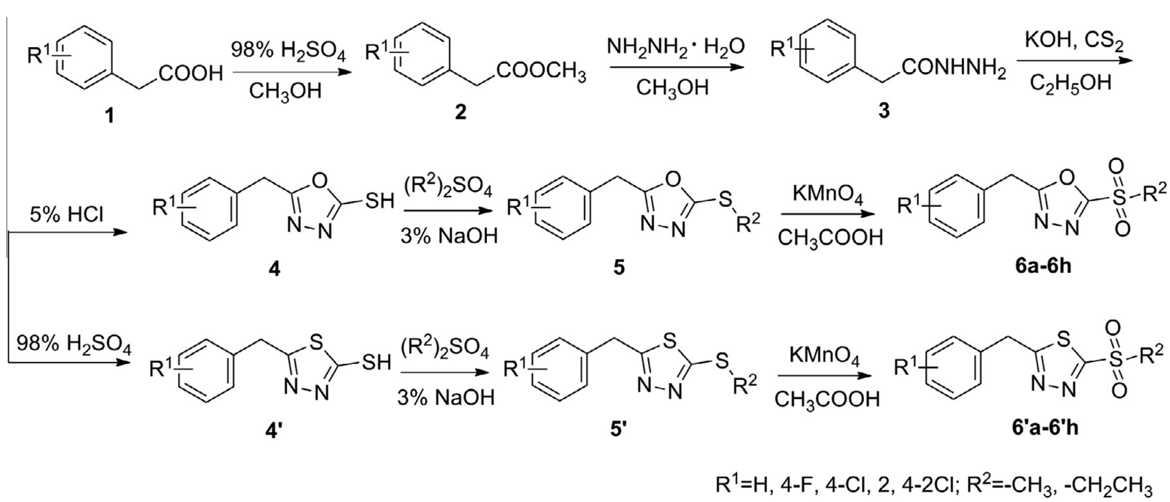
*2-(Methyl sulfonyl)-5-(4-fluorobenzyl)-1,3,4-oxadiazole (**6c**):* white solid; mp 139–140 °C; yield 65.3%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 7.39–7.20 (m, 4H, Ar-H), 4.59 (s, 2H, Ar-CH_2-), 3.59 (s, 3H, –CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 175.52, 169.89, 136.32, 132.71, 131.47, 129.40, 43.49, 34.89; IR (KBr, cm^{-1}) v: 3021, 2932, 1593, 1554, 1341, 1155; Anal. Calcd for $C_{10}H_9FN_2O_3S$: C, 46.85; H, 3.55; N, 10.95. Found: C, 46.87; H, 3.54; N, 10.93.

In this study, the inhibitory effect of the synthesized series of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivatives was evaluated for their antibacterial activities in vitro against rice bacterial leaf blight and leaf streak via the turbidimeter test.[8,28] For comparison, the activities of Bismerthiazol and Thiediazole Copper were evaluated at the same conditions. The results of the preliminary bioassays, as indicated in Tables 1 and 2, showed that compounds **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6g**, **6h** and **6′a** exhibited significant inhibition effects against rice bacterial leaf blight and leaf streak, and a control efficacy of 100% was observed at 200 and 100 μg/mL, which were even better than those of Bismerthiazol and Thiediazole Copper.

The half-maximal effective concentration (EC_{50}) values of the synthesized compounds as well as for Bismerthiazol and Thiediazole Copper were presented in Tables 1 and 2. Table 1 showed that compounds **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6g** and **6h** inhibited rice bacterial leaf blight in vitro with the EC_{50} values of 2.93, 5.78, 1.07, 19.61, 12.23, 25.28, 1.96 and 4.72 μg/mL, respectively. Meanwhile, Table 2 indicated that compounds **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6g** and **6h** inhibited rice bacterial leaf streak with the EC_{50} values of 10.08, 16.62, 7.14, 13.37, 17.68, 33.88, 8.45 and 25.61 μg/mL, respectively. Among the title compounds, **6c** demonstrated the best inhibitory effect against rice bacterial leaf blight and leaf streak with EC_{50} values of 1.07 and 7.14 μg/mL, respectively, which were even better than those of Bismerthiazol and Thiediazole Copper.

To determine the effect of antibacterial potency in vivo, the antibacterial bioassay of compounds **6c** and **6g** against rice bacterial leaf blight were performed via the leaf-cutting method[29] at greenhouse conditions at a concentration of 200 μg/mL. Bismerthiazol and Thiediazole Copper, the most successful registered bactericides for plant in China, were used as positive control samples. The results, as listed in Table 3, indicated that compounds **6c** and **6g** have potent controlling effect against rice bacterial leaf blight at 43.5% and 42.4%, respectively, which were better than those of Bismerthiazol (25.5%) and Thiediazole Copper (37.5%). The data were statistically analyzed via ANOVA (least significant difference), and the results showed that no significant differences ($p > 0.05$) exist between each of the commercial agents and compounds **6c** and **6g** 15 days after spraying.

As an extension of this approach, the synthesis and structure–activity relationships were deduced on the basis of the activity values in Tables 1 and 2. Three main conclusions were drawn. First, the presence of the –H or –F groups at 4-position and the –Cl group at 2,4-positions of benzyl in the corresponding compounds presented good antibacterial activities against rice bacterial leaf blight and leaf streak. The activities of the compounds followed the order **6c** > **6e**, **6a** > **6e**, **6g** > **6e** and **6′c** > **6′e**, **6′a** > **6′e**, **6′g** > **6′e** (Tables 1 and 2). Second, compared with the same substituent on benzyl, methyl was replaced with ethyl at the R^2 substituent group caused a decrease in the activity against rice bacterial leaf blight and leaf streak in the order **6a** > **6b**, **6c** > **6d** and **6′a** > **6′b**, **6′c** > **6′d** (Tables 1 and 2). Third, compared with the same substituent on benzyl and the R^2 substituent group, the activities of 1,3,4-oxadiazole sulfone derivatives were superior to those of 1,3,4-thiadiazole sulfone



Scheme 1. Synthetic route of **6a**–**6h** and **6′a**–**6′h**.

Table 1
Inhibition effect of the compounds against rice bacterial leaf blight

No.	Compounds		Inhibition (%)		Toxic regression equation	r	EC_{50} (μg/mL)
	R^1	R^2	200 (μg/mL)	100 (μg/mL)			
6a	H	$-CH_3$	100 ± 0.45	100 ± 0.32	$y = 1.558x + 4.410$	0.98	2.39 ± 0.56
6b	H	$-CH_2CH_3$	100 ± 0.18	100 ± 0.24	$y = 1.679x + 3.721$	0.96	5.78 ± 0.66
6c	4-F	$-CH_3$	100 ± 0.16	100 ± 0.81	$y = 1.409x + 4.958$	0.97	1.07 ± 0.68
6d	4-F	$-CH_2CH_3$	100 ± 0.65	100 ± 0.82	$y = 1.327x + 3.285$	0.99	19.61 ± 1.98
6e	4-Cl	$-CH_3$	100 ± 0.22	100 ± 0.34	$y = 2.045x + 2.776$	0.99	12.23 ± 1.45
6f	4-Cl	$-CH_2CH_3$	100 ± 0.78	100 ± 0.54	$y = 1.773x + 2.513$	0.99	25.28 ± 2.24
6g	2,4-2Cl	$-CH_3$	100 ± 0.58	100 ± 0.26	$y = 1.593x + 4.535$	0.99	1.96 ± 0.99
6h	2,4-2Cl	$-CH_2CH_3$	100 ± 0.66	100 ± 0.57	$y = 2.002x + 3.650$	0.99	4.72 ± 1.10
6′a	H	$-CH_3$	100 ± 0.21	100 ± 0.16	$y = 1.733x + 2.196$	0.99	41.50 ± 4.45
6′b	H	$-CH_2CH_3$	100 ± 0.43	86 ± 1.78	$y = 2.351x + 1.177$	0.98	42.28 ± 3.87
6′c	4-F	$-CH_3$	100 ± 0.46	80 ± 2.48	$y = 1.708x + 2.270$	0.97	39.66 ± 2.91
6′d	4-F	$-CH_2CH_3$	87 ± 1.22	67 ± 3.34	$y = 2.346x + 0.677$	0.99	69.62 ± 5.21
6′e	4-Cl	$-CH_3$	91 ± 0.46	65 ± 2.48	$y = 2.470x + 0.468$	0.98	68.36 ± 4.48
6′f	4-Cl	$-CH_2CH_3$	75 ± 1.11	58 ± 1.87	$y = 1.925x + 1.268$	0.99	86.84 ± 5.18
6′g	2,4-2Cl	$-CH_3$	100 ± 1.64	100 ± 2.83	$y = 2.225x + 1.518$	0.99	36.72 ± 4.67
6′h	2,4-2Cl	$-CH_2CH_3$	56 ± 3.78	43 ± 4.55	$y = 1.451x + 1.892$	0.99	138.67 ± 6.87
Bismerthiazol			72 ± 0.65	54 ± 1.23	$y = 1.499x + 2.052$	0.98	92.61 ± 2.15
Thiediazole Copper			64 ± 2.76	43 ± 3.15	$y = 1.540x + 1.788$	0.98	121.82 ± 3.59

Table 2
Inhibition effect of the compounds against rice bacterial leaf streak

No.	Compounds		Inhibition (%)		Toxic regression equation	r	EC_{50} (μg/mL)
	R^1	R^2	200 (μg/mL)	100 (μg/mL)			
6a	H	$-CH_3$	100 ± 0.12	100 ± 0.34	$y = 1.750x + 3.244$	0.97	10.08 ± 1.22
6b	H	$-CH_2CH_3$	100 ± 0.54	100 ± 0.67	$y = 2.213x + 2.299$	0.99	16.62 ± 2.78
6c	4-F	$-CH_3$	100 ± 0.98	100 ± 0.21	$y = 2.107x + 3.201$	0.99	7.14 ± 0.97
6d	4-F	$-CH_2CH_3$	100 ± 0.26	100 ± 0.28	$y = 1.830x + 2.939$	0.98	13.37 ± 1.59
6e	4-Cl	$-CH_3$	100 ± 0.67	100 ± 0.98	$y = 1.818x + 2.732$	0.97	17.68 ± 2.87
6f	4-Cl	$-CH_2CH_3$	100 ± 0.34	100 ± 0.65	$y = 1.300x + 3.011$	0.96	33.88 ± 3.56
6g	2,4-2Cl	$-CH_3$	100 ± 0.55	100 ± 0.78	$y = 1.837x + 3.297$	0.99	8.45 ± 1.65
6h	2,4-2Cl	$-CH_2CH_3$	100 ± 0.43	100 ± 0.31	$y = 1.506x + 2.879$	0.97	25.61 ± 2.54
6′a	H	$-CH_3$	100 ± 0.32	100 ± 0.21	$y = 1.429x + 2.838$	0.99	32.58 ± 2.12
6′b	H	$-CH_2CH_3$	92 ± 0.77	86 ± 1.43	$y = 2.549x + 0.706$	0.98	48.37 ± 5.25
6′c	4-F	$-CH_3$	88 ± 1.22	71 ± 3.76	$y = 2.222x + 1.059$	0.98	59.38 ± 2.79
6′d	4-F	$-CH_2CH_3$	70 ± 6.32	61 ± 2.98	$y = 1.801x + 1.526$	0.99	84.90 ± 5.19
6′e	4-Cl	$-CH_3$	80 ± 0.46	52 ± 2.48	$y = 2.076x + 0.972$	0.99	87.15 ± 4.81
6′f	4-Cl	$-CH_2CH_3$	68 ± 3.45	49 ± 2.48	$y = 1.802x + 1.268$	0.99	117.77 ± 7.54
6′g	2,4-2Cl	$-CH_3$	100 ± 2.32	86 ± 2.32	$y = 2.293x + 1.419$	0.99	36.45 ± 2.75
6′h	2,4-2Cl	$-CH_2CH_3$	52 ± 4.11	31 ± 2.65	$y = 1.368x + 1.827$	0.99	208.66 ± 7.49
Bismerthiazol			57 ± 5.56	35 ± 6.76	$y = 1.349x + 2.058$	0.97	151.66 ± 5.98
Thiediazole Copper			35 ± 4.31	15 ± 2.11	$y = 2.313x - 0.623$	0.99	269.80 ± 7.11

Table 3
Inhibition effect of testing compounds against rice bacterial leaf blight at greenhouse conditions at 200 μg/mL

Compounds	15 Days after spraying		
	Morbidity (%)	Disease index (%)	Control efficiency[c] (%)
6c	100	52.0	43.5 ± 3.4c
6g	100	53.0	42.4 ± 2.1c
Bismerthiazol	100	68.5	25.5 ± 1.7b
Thiediazole Copper	100	57.5	37.5 ± 3.3a
CK1[a]	0.0	0.0	100.0 ± 0.0c
CK2[b]	100.0	92.0	/

[a] CK1: blank control sample.
[b] CK2: negative control sample.
[c] Statistical analysis was conducted via the ANOVA method at a condition of equal variances assumed ($p > 0.05$) and equal variances not assumed ($p < 0.05$). Different lowercase letters indicate the values of inhibition and EC_{50} with significant difference among different treatment groups at $p < 0.05$.

derivatives and followed the order **6a** > **6′a** and **6c** > **6′c** (Tables 1 and 2).

In conclusion, we synthesized a series of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivatives, evaluated their antibacterial activities against rice bacterial leaf blight and leaf streak via the turbidimeter test in vitro, and assayed their controlling effect against rice bacterial leaf blight based on the leaf-cutting method at greenhouse conditions in vivo. Antibacterial bioassay results indicated that most compounds demonstrated excellent inhibitory effect antibacterial bioactivities against rice bacterial leaf blight and leaf streak. The antibacterial tests showed that when the presence of the –H or –F groups at 4-position and the –Cl group at 2,4-positions of benzyl and methyl at the R^2 substituent group were attached to the 2,5-position of oxadiazole/thiadiazole, the corresponding compounds presented good antibacterial activities. In vivo antibacterial activities tests at greenhouse conditions demonstrated that the controlling effect of compounds **6c** and **6g** against rice bacterial leaf blight were better than those of Bismerthiazol and Thiediazole Copper. This work demonstrated that 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivatives can be used to develop potential bactericides for plants.

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Supplementary data

Supplementary data (which contain information on the synthesis, characterization, and bioactivity test methods of the title compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.02.060.

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