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Author: Yu-Tao Zheng Teng-Teng Zhang Pei-Yi Wang Zhi-Bing Wu Lei Zhou Yi-Qiang Ye Xiang Zhou Ming He Song Yang

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Original article

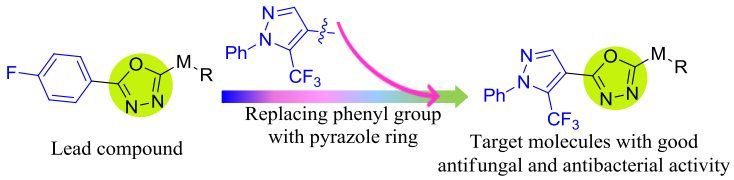
Synthesis and bioactivities of novel 2-(thioether/sulfone)-5-pyrazolyl-1,3,4-oxadiazole derivatives

Yu-Tao Zheng [a †], Teng-Teng Zhang [a †], Pei-Yi Wang [a], Zhi-Bing Wu [a], Lei Zhou [a], Yi-Qiang Ye [a], Xiang Zhou [a], Ming He [a], Song Yang [a,b *]

[a] *State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals, Guizhou University, Guiyang 550025, China.*
[b] *College of Pharmacy, East China University of Science & Technology, Shanghai 550025, China.*

* Corresponding author.
E-mail address: jhzx.msm@gmail.com
† These two authors contribute equally to this work.

Graphical Abstract



By introducing the pyrazole moiety into the 5-position of 1,3,4-oxadiazole, a series of novel 2-(thioether/sulfone)-5-pyrazolyl-1,3,4-oxadiazole derivatives were synthesized. Among them, the EC_{50} values of **6c**, **7a**, **7b** and **7c** against *Xanthomonas oryzae pv. oryzae* were within 16.6 and 65.7 μg/mL, which were better than those of commercial agricultural antibacterial product bismerthiazol and thiodiazole copper. While compounds **7a**, **7b**, and **7c** exerted comprehensive antifungal activity toward five plant fungi, which were comparable with that of hymexazol.

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ABSTRACT

By introducing the pyrazole moiety into the 5-position of 1,3,4-oxadiazole, a series of novel 2-(thioether/sulfone)-5-pyrazolyl-1,3,4-oxadiazole derivatives were synthesized. Preliminary bioassays suggested that target compounds exhibited appreciable activity against pathogenic bacteria *Xanthomonas oryzae pv. oryzae* (*Xoo*) and five phytopathogenic fungi *in vitro*. Among them, the half-maximal effective concentration (EC_{50}) values of **6c**, **7a**, **7b** and **7c** against *Xoo* were within 16.6 μg/mL and 65.7 μg/mL, which were better than those of commercial agricultural antibacterial bismerthiazol (92.6 μg/mL) and thiodiazole copper (121.8 μg/mL). While compounds **7a**, **7b**, and **7c** exerted comprehensive antifungal activity toward five plant fungi, which were comparable with that of hymexazol. The results demonstrated that this kind of compounds can be further studied and developed as promising antifungal and antibacterial agents.

Keywords: Pyrazole 1,3,4-Oxadiazole Synthesis Antibacterial *Antifung*

1. Introduction

Heterocyclic substructures have been extensively studied for their powerful applications in construction of bioactive compounds [1-4]. Among them, pyrazole ring as an important functional group has already been used in the development of pharmaceuticals and agrochemicals due to its derivatives bearing multitudinous bioactivities, including anti-inflammatory, antitumor, herbicidal, insecticidal, antifungal, and antibacterial activities [5-13]. Furthermore, some pyrazole compounds have already been commercialized as fungicides, like sedaxane (Syngenta, 2005), isopyrazam (Syngenta, 2006), bixafen (Bayer, 2005), and fluxapyroxad (BASF, 2008) [14-17]. As another crucial scaffold, 1,3,4-oxadiazole, has exerted promising applications in creating new agrochemicals on account of the diverse bioactivities of its derivatives [18-21]. In our previous work, we had found a series of new 1,3,4-oxadiazole sulfone compounds (structure depicted in Fig. 1, lead compound) with high antibacterial/fungicidal bioactivities [22-24]. In order to find new structures with antibacterial/antifungal bioactivities, the two functional moieties of pyrazole and 1,3,4-oxadiazole were combined into one molecule by replacing the phenyl group to pyrazole moiety at the 5-position of the lead compound, as shown in Fig. 1. All the title compounds were bioassayed against pathogenic bacteria *Xanthomonas oryzae pv. oryzae* (*Xoo*) and five phytopathogenic fungi.

2. Experimental

All the chemicals were purchased from Aladdin and used as received. The organic solvents were distilled before used. NMR spectra were obtained by using a JEOL-ECX-500 apparatus. Chemical shifts were reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (*J*) were reported in Hz and referred to apparent peak multiplications. MS data were recorded on an Agilent ESI-MSD Trap (VL) mass instrument.

*2.1 General synthetic procedures for the target compounds (**6a-6o**) and (**7a-7i**)*

A solution of carbon disulfide (0.015 mol) in ethanol (10 mL) was added dropwise to the mixture of compound 4 (0.01 mol) and potassium hydroxide (0. 012 mol) in ethanol (40 mL) at room temperature. Then, the reaction mixture was heated under reflux with stirring for 8 h. After the reaction was completed, ethanol was evaporated to give unpurified intermediate **5**. An appropriate halohydrocarbon (0.01 mol) was added to the solution of unpurified intermediate **5** in water (20 mL) and the mixture was stirred for 1 h at room temperature. The solid was filtered, purified by column chromatography using a mixture of petroleum ether and ethyl acetate (10:1) as the eluent, and then the pure target compounds (**6a-6o**) were obtained.

The compound (**6a-6i**) (5 mmol) and acetic acid (15 mL) were added to a 50 mL three-neck round-bottom flask equipped with a magnetic stirrer. The resulting solution was stirred for 10 min when a clear solution was obtained, and then 7% $KMnO_4$ solution (5 mmol) was added dropwise at room temperature and the progress of the reaction was monitored by thin layer chromatography (TLC) using petroleum ether : ethyl acetate (3:1). After the reaction was completed, 10% $NaHSO_3$ solution was added to deoxidize the unreacted $KMnO_4$. The resulted solid was filtered, washed with water, from which the pure compounds (**7a-7i**) can be obtained by column chromatography using a mixture of petroleum ether and ethyl acetate (15:1) as the eluent.

2.2 In vitro antibacterial bioassay (turbidimeter test)

In our study, all the synthesized target compounds were evaluated for their antibacterial activities against *Xoo* by the turbidimeter test *in vitro*. Dimethylsulfoxide in sterile distilled water served as a blank control, Bismerthiazol and Thiodiazole Copper served as the positive controls. Approximately 40 μL of solvent NB (1.5 g beef extract, 2.5 g peptone, 0.5 g yeast powder, 5.0 g glucose, and 500 mL distilled water; pH = 7.0–7.2) containing *Xoo*, incubated on the phase of logarithmic growth, was added to 5 mL of solvent NB containing the test compounds and positive control. The inoculated test tubes were incubated at 28 ± 1 °C and continuously shaken at 180 rpm for 24-48 h until the bacteria were incubated on the logarithmic growth phase. The growth of the cultures was monitored on a microplate reader by measuring the optical density at 595 nm (OD_{595}) given by turbiditycorrected values = $OD_{\text{bacterial wilt}} - OD_{\text{no bacterial wilt}}$, and the inhibition rate I was calculated by $I = (C - T)/C \times 100\%$. C is the corrected turbidity values of bacterial growth on untreated NB (blank control), and T is the corrected turbidity values of bacterial growth on treated NB. The experiment was repeated three times.

3. Results and discussion

The synthesis and structures of (**6a-6o**), and (**7a-7i**) are shown in scheme 1. Briefly, ethyltrifluoroacetoacetate (**1**) was treated with triethoxymethane to give intermediate (*E*)-2-trifluoroacetyl-3-ethoxy-2-propenoate (**2**), followed by the cyclocondensation reaction to provide an important intermediate ethyl 1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**3**) containing pyrazole group in 82% yield. Next, the hydrazide **4** was obtained through refluxing **3** in hydrazine hydrate with the yield of 94%. A subsequent reaction with carbon disulfide in the presence of potassium hydroxide leaded to the formation of the crucial intermediate **5** containing 1,3,4-oxadiazole. Finally, the corresponding target thioethers (**6a-6o**) were achieved *via* thioetherification with halogenated agents in good yields ranging from 76% to 85%, and subsequently converted into the corresponding sulfones (**7a-7i**) by oxidizing the related thioether at room temperature. All the structures were confirmed by ^{1}H NMR, ^{13}C NMR, and MS (detailed information see supplementary data).

In our study, we first evaluated the antibacterial activity of all the title compounds *via* turbidmeter test [25-27] against pathogenic bacteria *Xanthomonas oryzae pv. oryzae* (*Xoo*), which was considered as one of devastative bacteria against rice in rice-growing countries. Meanwhile, the commercial agricultural antibacterial bismerthiazol (BT) and thiodiazole copper (TC) were employed for the comparison of bioactivity *in vitro*. Preliminary bioassays revealed that most of the target compounds exerted appreciable inhibition bioactivity against *Xoo* in the dosage of 200 or 100 μg/mL (Table 1). Among them, compounds **6c**, **6e**, **6f**, **6j**, **7a**, **7b**, and **7c** gives the inhibition rate above 72.3% against *Xoo* in the dosage of 200 μg/mL, which were better than that of BT (72.1%) and TC (64.2%); while compounds **6c**, **6f**, **7a**, **7b**, and **7c** offers better inhibition rate above 66.2% against *Xoo* than that of BT (53.7%) and TC (43.1%) in the dosage of 100 μg/mL. The half-maximal effective concentration (EC_{50}) values of **6c**, **7a**, **7b**, and **7c** were detected as 47.5, 31.6, 65.7, and 16.6 μg/mL, respectively, which were obviously better than that of commercial bactericides (92.6 or 121.8 μg/mL). Based on the above results, among all the thioether compounds (**6a-6o**), the isopropyl group compound (**6c**) exhibited the best bioactivity against *Xoo* than the other groups, while for benzyl thioether compounds, 4-methylbenzyl thioether (**6f**) gives superior activity than the other substituted benzyl in the dosage of 200 μg/mL or 100 μg/mL. For sulfone compounds, the antibacterial activity of alkyl sulfone compounds (such as **7a** ~ **7c**) was dramatically better than the benzyl derivatives.

The antifungal activity of (**6a-6o**) and (**7a-7i)** was examined *via* the poison plate technique [28] against five phytopathogenic fungi, *Gibberella zeae* (*G. z.*), *Fusarium oxysporum* (*F. o.*), *Cytospora mandshurica* (*C. m.*), *Sclertinia sclerotiorum* (*S. s.*), and *Rhizoctonia solani* (*R. s.*) at the concentrate of 100 μg/mL, Meanwhile, the commercial agricultural antifungal Hymexazol (HM) and Carbendazim (CB) were employed for the comparison of bioactivity. As shown in table 2, compounds **7a** and **7c** were observed having comprehensive antifungal activity with the inhibition rate ranging from 53.8% to 75.5% against the five kinds of fungi, which were comparable to the commercial fungicide HM. It is worth pointing out that compound **6j** exerted good antifungal activity with the inhibition rate of 86.4% against *S. sclerotiorum*. In comparison of **6a** and **7a**, **6b** and **7b**, **6c** and **7c**, **6d** and **7d**, **6f** and **7f**, the antifungal activity was improved after oxidizing the thioether into the sulfone, further suggested sulfonyl group as a crucial functional group may improve the bioactivity of the target compound. It can be seen that compound **7a** showed the strongest antifungi activity against the five phytopathogenic fungi.

3. Conclusion

In summary, a series of 2-(thioether/sulfone)-5-pyrazolyl-1,3,4-oxadiazole derivatives containing both pyrazole moiety and 1,3,4-oxadiazole moiety were designed and synthesized, and which antibacterial activity and antifungal activity were evaluated *via* turbidmeter test or the poison plate technique *in vitro*. Compounds **6c**, **7a**, **7b** and **7c** showed good inhibition effects against *Xoo* with the EC_{50} values ranging from 16.6 μg/mL to 65.7 μg/mL, which were better than those of commercial agricultural antibacterial bismerthiazol (92.6 μg/mL) and thiediazole copper (121.8 μg/mL). Meanwhile, compounds **7a**, **7b**, and **7c** exerted good antifungal activities against five plant fungi, which were comparable to that of HM. The results demonstrated that this kind of compounds can be further studied and developed as promising antifungal and antibacterial agents.

Acknowledgment

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Supplementary data

Experimental characterization data of (**6a-6o**) and (**7a-7i**); ^{1}H NMR, ^{13}C NMR and Mass Spectra of **6a**, **6d**, **7a**, and **7d** (Figure S1-S12). This material is available free of charge *via* the internet at http://www.elsevier.com/.

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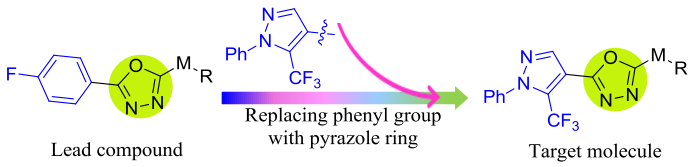
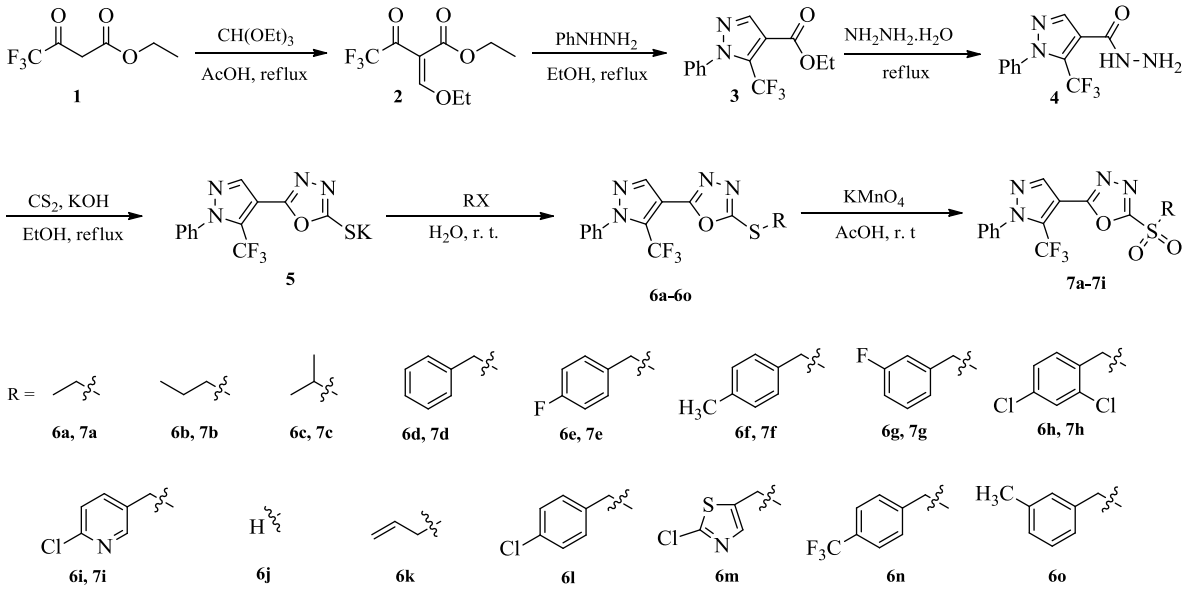


Fig. 1. Design strategy of the target compounds.



Scheme 1. Synthetic route of 2-(thioether/sulfone)-5-pyrazolyl-1,3,4-oxadiazole derivatives (**6a-6o**) and (**7a-7i**).

Table 1. Inhibition effect of sulfides/sulfones against *Xoo*.

Compd.	Inhibition rate (%)		Compounds	Inhibition rate (%)		Compd.	Regression equation	r	EC_{50} (μg/mL)
	200 μg/mL	100 μg/mL		200 μg/mL	100 μg/mL				
6a	55.2 ± 2.8	36.5 ± 2.7	**7a**	98.9 ± 0.3	97.8 ± 0.9	**6c**	y=1.647x+2.238	0.96	47.5±4.3
6b	50.3 ± 2.4	26.7 ± 1.9	**7b**	100.0 ± 0.3	100.0 ± 0.2	**7a**	y=2.345x+1.482	0.96	31.6±1.2
6c	93.8 ± 0.3	83.2 ± 0.3	**7c**	100.0 ± 0.6	96.9 ± 0.5	**7b**	y=1.258x+2.712	0.99	65.7±3.8
6d	69.3 ± 3.6	33.8 ± 1.7	**7d**	50.8 ± 2.7	45.0 ± 3.9	**7c**	y=3.419x+0.832	0.96	16.6±0.2
6e	77.5 ± 1.2	49.1 ± 4.3	**7e**	67.7 ± 3.6	48.0 ± 3.8	BT	y=1.499x+2.052	0.98	92.6±2.1
6f	84.3 ± 0.8	66.2 ± 3.9	**7f**	51.5 ± 4.1	40.0 ± 3.6	TC	y=1.540x +1.788	0.98	121.8±3.6
6g	50.2 ± 2.1	34.3 ± 3.5	**7g**	48.3 ± 2.8	34.2 ± 4.8				
6h	66.2 ± 1.9	40.1 ± 1.9	**7h**	57.7 ± 3.3	38.4 ± 4.3				
6i	53.2 ± 2.2	38.4 ± 2.8	**7i**	34.5 ± 3.1	12.8 ± 4.9				
6j	72.3 ± 1.7	39.3 ± 1.7	**6m**	55.6 ± 1.4	31.9 ± 2.9				
6k	59.8 ± 3.5	45.8 ± 2.2	**6n**	59.4 ± 1.8	48.7 ± 3.4				
6l	68.5 ± 3.0	43.2 ± 0.7	**6o**	56.2 ± 1.9	40.9 ± 2.1				
BT	72.1 ± 0.7	53.7 ± 1.2	TC	64.2 ± 2.8	43.1 ± 3.2				

Table 2. Inhibition effect of sulfides/sulfones at 100 μg/mL against five phytopathogenic fungi.

Compd.	Inhibition rate (%)					Compd.	Inhibition rate (%)				
	G. z.	*F. o.*	*C. m.*	*S. s.*	*R. s.*		*G. z.*	*F. o.*	*C. m.*	*S. s.*	*R. s.*
6a	53.7±2.8	36.1±1.9	38.7±2.1	57.3±2.9	54.6±2.6	**7a**	59.9±1.8	72.4±2.8	70.9±2.4	72.3±2.2	75.5±2.1
6b	39.1±2.4	30.1±2.6	34.4±1.4	47.1±2.3	46.7±2.1	**7b**	45.6±3.1	51.2±1.7	57.8±1.5	62.0±2.3	59.6±3.4
6c	44.1±1.9	48.3±2.2	28.0±1.6	25.6±1.4	47.0±2.0	**7c**	53.8±2.8	70.2±3.2	64.4±2.1	70.1±2.9	69.8±2.4
6d	15.4±1.4	0	0	10.0±1.7	17.0±2.1	**7d**	23.4±1.7	34.2±1.9	25.8±1.8	22.5±2.3	31.7±1.1
6e	17.4±1.7	0	14.3±1.8	14.0±2.4	13.5±1.8	**7e**	0	0	0	13.6±1.4	0
6f	13.1±1.5	0	0	0	13.1±1.9	**7f**	41.5±1.5	52.2±2.3	38.9±2.0	36.4±2.2	35.8±2.1
6g	16.6±1.5	16.6±1.6	6.1±1.4	0	11.9±1.4	**7g**	0	0	0	13.2±1.5	0
6h	0	0	0	7.2±1.7	0	**7h**	0	0	0	12.0±2.4	0
6i	11.7±1.4	8.3±1.7	14.7±1.8	29.0±2.3	17.4±1.8	**7i**	11.7±1.3	25.8±1.8	23.2±1.7	23.1±2.2	17.2±1.9
6j	23.5±1.8	51.6±2.4	29.6±1.6	86.4±4.9	33.5±1.8	**6m**	11.1±1.4	9.4±1.6	19.0±1.8	0	21.6±2.0
6k	35.3±1.7	26.7±1.7	27.1±1.7	53.8±2.7	50.5±2.1	**6n**	10.9±1.6	0	7.2±1.7	0	6.0±2.8
6l	11.7±1.4	0	8.2±1.6	13.3±2.2	12.1±1.7	**6o**	10.9±1.6	18.5±1.7	0	0	14.4±1.5
HM	72.2±3.6	62.1±2.5	66.1±2.1			CB	100	100	100	100	100