Accepted Manuscript

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PII: S1001-8417(19)30366-3
DOI: https://doi.org/10.1016/j.cclet.2019.06.037
Reference: CCLET 5068

To appear in: *Chinese Chemical Letters*

Received date: 14 May 2019
Revised date: 15 June 2019
Accepted date: 19 June 2019

Please cite this article as: Shi J, Luo N, Ding M, Bao X, Synthesis, *in vitro* antibacterial and antifungal evaluation of novel 1,3,4-oxadiazole thioether derivatives bearing the 6-fluoroquinazolinylpiperidinyl moiety, *Chinese Chemical Letters* (2019), https://doi.org/10.1016/j.cclet.2019.06.037

Communication

Synthesis, *in vitro* antibacterial and antifungal evaluation of novel 1,3,4-oxadiazole thioether derivatives bearing the 6-fluoroquinazolinylpiperidinyl moiety

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Graphical abstract

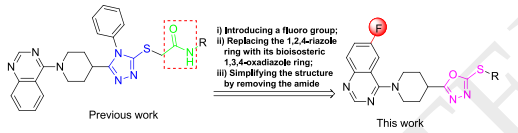
ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1,3,4-Oxadiazole thioether
Fluoroquinazolinylpiperidinyl
Synthesis
Antibacterial activity
Antifungal activity

ABSTRACT

A series of structurally novel 1,3,4-oxadiazole thioether derivatives (**6a**–**6z**) containing a 6-fluoroquinazolinylpiperidinyl moiety were designed and synthesized using pharmacophore hybrid approach, and their structures were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectra. Among them, the structure of compound **6d** was further corroborated *via* single-crystal X-ray diffraction analysis. *In vitro* antibacterial bioassays showed that compounds **6a**, **6g**, **6u** and **6v** possessed EC_{50} values of 30.4, 30.6, 27.5 and 26.0 μg/mL against phytopathogenic bacterium *Xanthomonas oryzae* pv. *oryzae*, respectively, which were significantly superior to that of commercially-available bactericide Bismerthiazol (85.1 μg/mL). Moreover, *in vitro* antifungal bioassays indicated that seven compounds demonstrated broad-spectrum fungicidal acitivties against six types of phytopathogenic fungi at 50 μg/mL. The present work showed the potential of 1,3,4-oxadiazole thioether derivatives carrying a 6-fluoroquinazolinylpiperidinyl moiety as effective antimicrobial agents for crop protection, deserving further investigations in the future.



Twenty-six 6-fluoroquinazolinylpiperidinyl-containing 1,3,4-oxadiazole thioether derivatives were designed and synthesized as agricultural antimicrobial agents. The structure of compound **6d** was confirmed by single-crystal X-ray diffraction analysis. Compounds **6a**, **6g**, **6u** and **6v** exhibited higher antibacterial efficacy against *Xoo* than commercial bactericide Bismerthiazol.

Plant diseases have long been recognized as a serious threat to global agricultural production. Among them, phytopathogenic bacteria and fungi are difficult to control and cause enormous crop yield losses per year [1,2]. For instance, *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) is a pathogen responsible for rice bacterial leaf blight, which can reduce rice yield by up to 50% under certain conditions [3]. On the other hand, it is well-known that fungal diseases remain the biggest threat to global agricultural industry at all times [2]. Compared with other methods, chemical control has some unique advantages, including high effectiveness, low cost and convenient application. However, some severe problems had emerged due to long-term unreasonable utilization of the existing antimicrobial agents, such as

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growing germicide resistances, decreasing control effects and environmental pollution [4,5]. Therefore, the search of new and more efficient agricultural germicides is still an urgent task in the field of crop protection.

Previous studies had shown that 1,3,4-oxadiazole thioether derivatives possessed a wide range of pesticidal activities, including antibacterial [6–8], nematicidal [9], antifungal [10], and anti-TMV activities [11]. Generally speaking, the presence of thioether group in bioactive molecules was believed to increase the hydrophilicity and provide an additional hydrogen-bond accepting site for ligand-protein binding, which were favorable for improving the pesticide-likeness [12,13]. On the other hand, quinazoline ring was one of the most significant nitrogen-containing heterocycles, occupying an important position in medicine and pesticide chemistry [14]. Some quinazoline-based drugs and pesticides have been on the market for many years, like anticancer drugs Gefitinib and Vandetanib, acaricide Fenazaquin and sympatholytic drug Prazosin (Fig. 1). As is known, the method of pharmacophore hybridization [15,16] is quite practical for the discovery of new drugs/pesticides as it can provide multiple interacton sites within a single molecule to interact with relevant proteins of pathogenic microorganisms. Tiodazosin (Fig. 1), a potent competitive postsynaptic α-adrenergic receptor antagonist, is just an excellent example of the delicate combination of 1,3,4-oxadiazole thioether group and quinazoline backbone *via* a piperazinyl carbonyl linkage.

In our previous work [4], a series of 1,2,4-triazole thioether derivatives containing both quinazolinylpiperidinyl moiety and acetamide group were synthesized and some compounds exhibited better antibacterial activities against *Xoo in vitro*, relative to control agent Bismerthiazol. Unfortunately, nearly all the compounds failed to display notable fungicidal activity against tested phytopathogenic fungi at 50 μg/mL. In fact, antimicrobial capabilities of this class of compounds were less satisfied on the whole. As we all know, the introduction of fluoro group into bioactive molecules can improve the lipophilicity, bioavailability and metabolic stability [17–21]. Based on the aforementioned considerations as well as our prior work [4], we thus designed a series of 1,3,4-oxadiazole thioether derivatives containing the 6-fluoroquinazolinylpiperidinyl moiety using pharmacophore hybridization method (with the capacity to overcome the resistance, reducing the toxicity and improve the pharmacokinetic properties) [22] and also took account of the following points: (a) replacing the 1,2,4-triazole ring by its bioisosteric 1,3,4-oxadiazole ring; (b) introducing a fluoro group into the quinazoline backbone; (c) simplifying the final structure by removing the amide group (Fig. 2).

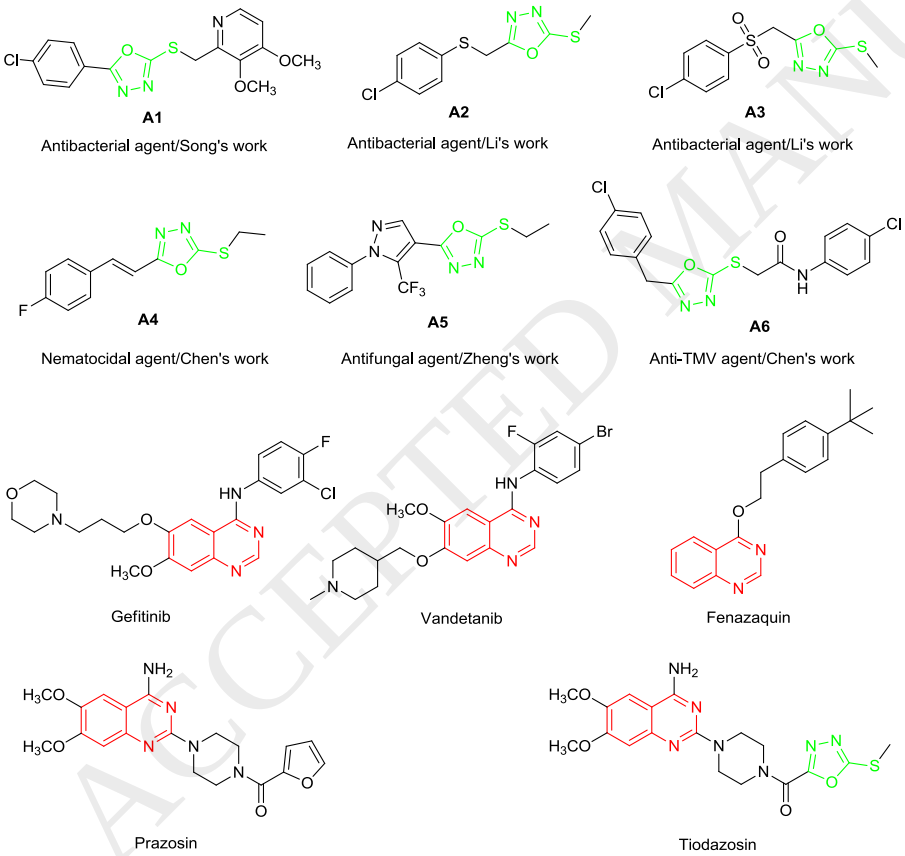


Fig. 1. Some representative bioactive molecules containing either the 1,3,4-oxadiazole thioether group or a quinazoline moiety.

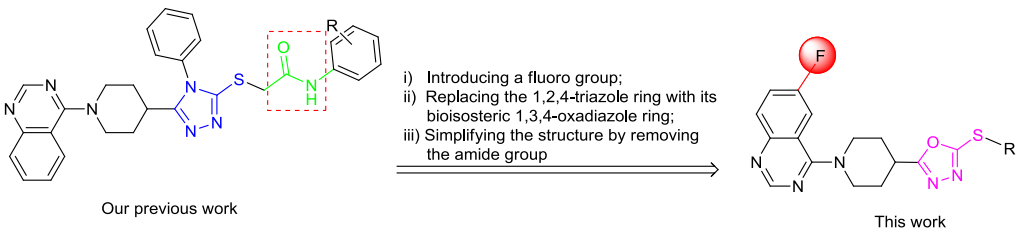
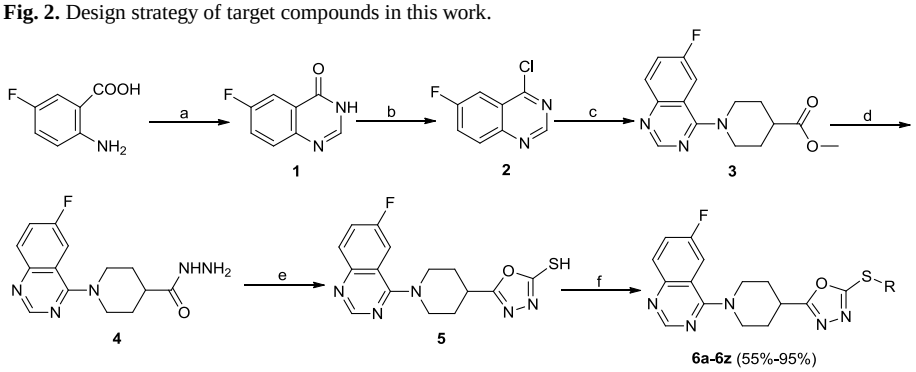


Fig. 2. Design strategy of target compounds in this work.



6a R = $PhCH_2$; **6b** R = 2-CH_3PhCH_2; **6c** R = 3-CH_3PhCH_2; **6d** R = 4-CH_3PhCH_2; **6e** R = 4-$C(CH_3)_3PhCH_2$; **6f** R = 2-OCH_3PhCH_2; **6g** R = 3-OCH_3PhCH_2; **6h** R = 4-OCH_3PhCH_2; **6i** R = 2-$FPhCH_2$; **6j** R = 3-$FPhCH_2$; **6k** R = 4-$FPhCH_2$; **6l** R = 2-$ClPhCH_2$; **6m** R = 3-$ClPhCH_2$; **6n** R = 4-$ClPhCH_2$; **6o** R = 2-CF_3PhCH_2; **6p** R = 3-CF_3PhCH_2; **6q** R = 4-CF_3PhCH_2; **6r** R = 2-NO_2PhCH_2; **6s** R = 3-NO_2PhCH_2; **6t** R = 4-NO_2PhCH_2; **6u** R = 2-$CNPhCH_2$; **6v** R = 3-$CNPhCH_2$; **6w** R = 4-$CNPhCH_2$; **6x** R = 4-OCF_3PhCH_2; **6y** R = CH_3; **6z** R = CH_3CH_2.

Scheme 1. Synthesis of target compounds **6a**–**6z**. Reagents and conditions: (a) $HCONH_2$, reflux, 7 h; (b) $SOCl_2$, DMF, reflux, 5 h; (c) methyl 4-piperidinecarboxylate, 1,4-dioxane, reflux, 7 h; (d) hydrazine hydrate, MeOH, r.t., overnight; (e) i) NaOH, EtOH, CS_2, r.t. 15 min then reflux 8 h; ii) 10% HCl, pH 5.5; (f) RX, K_2CO_3, CH_3CN, r.t., 8-12 h.

Synthetic procedures for target compounds **6a**–**6z** were depicted in Scheme 1. First, 4-chloro-6-fluoroquinazoline **2** [23] was reacted with methyl 4-piperidinecarboxylate in 1,4-dioxane solution to afford ester **3**, which was then subjected to hydrazinolysis for the preparation of hydrazide **4**. Next, hydrazide **4** was treated with CS_2 under basic conditions and then acidified to furnish oxadiazole-thiol **5**. Finally, target compounds **6a**–**6z** were readily obtained in 55%–95% yield by reaction of thiol **5** with various halogenated hydrocarbons in K_2CO_3/CH_3CN system at room temperature. The structures of target compounds **6a**–**6z** were fully characterized by ^1H NMR, ^{13}C NMR and HRMS spectra. Detailed synthetic procedures, characterization data and spectral copies of intermediates **3–5** and target compounds **6a–6z** are available in Supporting information. Fortunately, a single crystal of compound **6d** suitable for X-ray diffraction analysis (Fig. 3) was obtained by slow evaporation of a DMF solution of **6d** at room temperature.

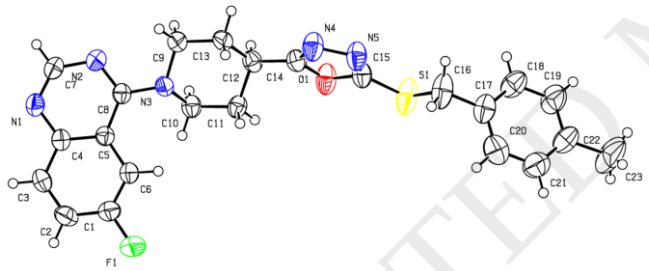


Fig. 3. Crystal structure of compound **6d** (CCDC 1913061).

In vitro inhibition activities of target compounds **6a**–**6z** and intermediates **3**–**5** against three pathogenic bacteria *Xoo*, *Rs* (*Ralstonia solanacearum*) and *Xac* (*Xanthomonas axonopodis* pv. *citri*) were assessed based on the turbidimetric method [4,24], with commercially-available agrobactericides Bismerthiazol (BMT) and Thiodiazole-copper (TDC) as positive control agents. As listed in Table 1, some of the target compounds demonstrated significantly better antibacterial efficacy towards the pathogens under the tested concentrations, relative to control agents. For example, compounds **6a**, **6g**, **6h**, **6n**, **6u** and **6v** showed the inhibition ratios of 96.8%, 90.9%, 85.1%, 85.5%, 91.8% and 92.9% against *Xoo* at 100 μg/mL, respectively, which were considerably superior to that of control BMT (58.4%). Unfortunately, only two compounds within the series (namely compounds **6u** and **6v**) were found to possess a comparable inhibition activity against *Xac* at 100 μg/mL, in comparison to control BMT (62.0%). As far as the bacterium *Rs* was concerned, compounds **6g**, **6h**, **6n** and **6u** had more potent inhibition efficacies of 74.7%, 76.0%, 72.8% and 81.6% at 100 μg/mL, respectively, compared with control agents BMT (46.1%) and TDC (32.3%).

In consideration of outstanding antibacterial activites exhibited by most of the target compounds against *Xoo*, EC_{50} values (half-maximal effective concentration) of all the target compounds were further determined. As summarized in Table 1, more than half of the target compounds had a clearly lower EC_{50} value than control BMT. It was noteworthy that compounds **6a**, **6g**, **6h**, **6i**, **6k**, **6l**, **6n**, **6u** and **6v** possessed EC_{50} values of 30.4, 30.6, 36.5, 37.1, 39.4, 41.1, 36.1, 27.5 and 26.0 μg/mL, respectively, over two times more potent than control BMT (85.1 μg/mL). A preliminary structure-activity relationship analysis demonstrated the following findings: (a) The introduction of strong electron-withdrawing groups in the benzene ring of benzyl group was detrimental to antibacterial activity, like -CF_3, -NO_2 and -OCF_3 groups; (b) The presence of a cyano group at the 2- or 3-position of the benzyl group (compounds **6u** and **6v**) was found to be most beneficial to bactericidal activity against *Xoo*, which may be attributed to the formation of an additional hydrogen bond between cyano group (being a strong hydrogen-bond acceptor) and relevant bacterial protein [25]; (c) The presence of a mono-halogen

substituent (such as -F and -Cl) on the phenyl ring was helpful to antibacterial activity on the whole, in comparison with other substituents; (d) The existence of sterically bulky *tert*-butyl group (**6e**), strong electron-withdrawing -OCF_3 (**6x**) or 3-NO_2 (**6s**) groups or ethyl thioether unit (**6z**) in the target compounds led to the weakest antibacterial effect.

In vitro antifungal activities of target compounds **6a–6z** and intermediates **3–5** were also evaluated using the mycelial growth rate method [4,5], against six types of phytopathogenic fungi. As shown in Table 2, some of the target compounds displayed a pronounced fungicidal effect against certain fungi at 50 μg/mL. For example, compounds **6a**, **6c**, **6d**, **6g**, **6h**, **6j**, **6m**, **6n**, **6q**, **6y** and **6z** exhibited a significant antifungal activity towards *G. zeae*, slightly higher or similar to that of control Hymexazol (53.6%). Concerning the fungus *C. gloeosporioides*, only compounds **6a** and **6h** were found to exhibit comparable antifungal activities to control Hymexazol (71.8%). It should be noted that seven compounds (including **6a**, **6c**, **6g**, **6h**, **6m**, **6n** and **6z**) possessed broad-spectrum fungicidal activities against all six fungi, having an inhibition ratio of >50% in nearly every case.

Table 1
Antibacterial activities of target compounds **6a**−**6z** and intermediates **3**, **4** as well as **5** against phytopathogenic bacteria *Xoo*, *Xac* and *Rs*.

Compd.	*Xoo*					*Xac*		*Rs*	
	Inhibition ratio[a] (%)		Regression equation	*r*	EC_{50} (μg/mL)	Inhibition ratio[a] (%)		Inhibition ratio[a] (%)	
	100μg/mL	50 μg/mL				100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
3	30.7 ± 1.6	14.2 ± 1.9	--	--	--	23.9 ± 0.9	10.6 ± 1.3	17.1 ± 3.6	9.8 ± 2.3
4	28.3 ± 1.4	17.1 ± 0.6	--	--	--	16.4 ± 1.7	9.3 ± 2.4	23.4 ± 2.0	16.1 ± 1.2
5	43.4 ± 1.0	21.2 ± 2.2	--	--	--	21.8 ± 2.0	16.5 ± 1.2	25.7 ± 1.8	15.5 ± 2.1
6a	96.8 ± 0.2	65.6 ± 1.4	$y = 2.7085x + 0.9825$	0.9909	30.4 ± 0.7	35.8 ± 3.2	21.6 ± 1.3	50.0 ± 3.9	22.1 ± 2.4
6b	63.4 ± 3.6	41.3 ± 3.4	$y = 1.7089x + 1.9594$	0.9974	60.2 ± 4.3	14.8 ± 2.5	5.4 ± 1.4	19.5 ± 5.7	7.8 ± 3.5
6c	54.9 ± 3.3	33.4 ± 1.8	$y = 1.4324x + 2.2107$	0.9947	88.6 ± 4.6	38.4 ± 0.6	18.3 ± 1.3	12.8 ± 2.6	6.4 ± 5.3
6d	70.8 ± 1.8	53.3 ± 2.4	$y = 1.7623x + 2.0284$	0.9893	48.6 ± 3.2	18.6 ± 0.2	7.2 ± 2.4	42.7 ± 1.3	23.1 ± 4.6
6e	31.0 ± 4.2	18.2 ± 0.7	$y = 0.9886x + 2.5081$	0.9839	331.4 ± 4.7	7.6 ± 1.9	6.4 ± 3.5	10.8 ± 3.3	5.0 ± 3.7
6f	37.8 ± 2.5	19.9 ± 4.8	$y = 1.3549x + 1.9345$	0.9870	183.0 ± 2.5	8.8 ± 2.1	6.4 ± 2.8	21.4 ± 2.1	10.6 ± 4.1
6g	90.9 ± 2.3	60.6 ± 3.9	$y = 2.1665x + 1.7826$	0.9843	30.6 ± 1.1	50.7 ± 0.4	22.4 ± 2.5	74.7 ± 0.9	41.2 ± 0.9
6h	85.1 ± 3.5	53.0 ± 1.5	$y = 2.0453x + 1.8040$	0.9845	36.5 ± 2.5	43.4 ± 1.5	20.3 ± 2.9	76.0 ± 2.7	55.4 ± 2.9
6i	81.5 ± 1.3	52.4 ± 2.1	$y = 1.9648x + 1.9164$	0.9827	37.1 ± 0.7	36.8 ± 3.0	13.7 ± 0.7	59.4 ± 2.0	26.7 ± 2.7
6j	57.1 ± 1.8	37.2 ± 4.6	$y = 1.5037x + 2.2127$	0.9873	71.4 ± 5.2	13.1 ± 1.2	9.0 ± 2.4	48.6 ± 5.0	20.3 ± 4.2
6k	80.5 ± 2.7	53.6 ± 1.4	$y = 1.8808x + 1.9995$	0.9885	39.4 ± 3.3	36.4 ± 2.6	17.8 ± 1.7	47.4 ± 2.5	23.2 ± 3.9
6l	74.7 ± 3.0	57.6 ± 2.6	$y = 1.7419x + 2.1897$	0.9914	41.1 ± 4.6	40.3 ± 2.0	16.3 ± 2.3	54.4 ± 4.0	42.8 ± 4.3
6m	62.3 ± 2.0	39.5 ± 2.9	$y = 1.4215x + 2.3019$	0.9896	79.1 ± 1.6	4.5 ± 0.7	2.6 ± 0.5	46.7 ± 1.4	20.8 ± 6.6
6n	85.5 ± 3.9	57.8 ± 2.0	$y = 2.0647x + 1.7851$	0.9808	36.1 ± 0.8	47.7 ± 3.7	19.1 ± 1.1	72.8 ± 1.7	48.8 ± 1.6
6o	54.7 ± 3.9	40.5 ± 1.4	$y = 1.3587x + 2.4589$	0.9718	74.2 ± 0.5	13.3 ± 0.9	3.8 ± 1.0	38.5 ± 4.2	24.7 ± 4.4
6p	37.1 ± 2.3	25.0 ± 1.6	$y = 1.2077x + 2.2092$	0.9923	204.6 ± 7.0	10.8 ± 1.3	2.4 ± 2.5	17.3 ± 5.7	7.2 ± 5.7
6q	44.7 ± 4.6	34.4 ± 1.8	$y = 1.2503x + 2.3077$	0.9873	142.3 ± 4.2	21.7 ± 2.6	4.6 ± 2.2	33.5 ± 4.6	18.7 ± 5.4
6r	43.9 ± 4.0	29.0 ± 3.1	$y = 1.2646x + 2.3341$	0.9912	128.3 ± 6.0	32.3 ± 2.9	14.6 ± 4.1	22.0 ± 2.1	7.1 ± 4.6
6s	22.3 ± 2.9	14.6 ± 3.3	$y = 0.8778x + 2.4234$	0.9689	861.6 ± 3.2	9.5 ± 2.9	7.0 ± 3.6	2.4 ± 1.9	1.1 ± 2.5
6t	43.4 ± 2.7	16.3 ± 2.0	$y = 1.1709x + 2.2939$	0.9523	204.7 ± 6.0	3.9 ± 2.4	2.0 ± 2.4	11.9 ± 5.3	7.1 ± 4.8
6u	91.8 ± 2.1	61.7 ± 2.7	$y = 2.2407x + 1.7743$	0.9888	27.5 ± 0.8	62.9 ± 2.7	30.4 ± 2.0	81.6 ± 2.5	54.9 ± 4.0
6v	92.9 ± 3.6	68.6 ± 2.4	$y = 2.3508x + 1.6742$	0.9849	26.0 ± 0.3	66.1 ± 3.3	37.9 ± 2.6	59.1 ± 2.7	44.9 ± 5.5
6w	38.3 ± 1.0	18.6 ± 3.0	$y = 1.3643x + 1.9461$	0.9980	173.1 ± 8.4	9.1 ± 2.3	6.4 ± 1.6	42.0 ± 1.2	25.2 ± 5.9
6x	25.8 ± 3.8	12.3 ± 1.6	$y = 1.0166x + 2.1887$	0.9742	582.6 ± 8.8	7.8 ± 3.8	6.1 ± 1.4	12.5 ± 4.9	9.8 ± 4.5
6y	67.6 ± 2.5	38.6 ± 2.2	$y = 1.5722x + 2.2044$	0.9792	60.0 ± 4.0	42.1 ± 2.3	23.4 ± 3.1	39.4 ± 0.9	24.8 ± 1.6
6z	23.4 ± 3.2	15.6 ± 2.3	$y = 0.9823x + 2.3156$	0.9832	540.6 ± 7.7	33.6 ± 2.0	19.0 ± 1.6	30.2 ± 2.0	26.9 ± 2.2
BMT[b]	58.4 ± 2.2	35.5 ± 1.7	$y = 1.5404x + 2.0271$	0.9808	85.1 ± 1.7	62.0 ± 1.5	28.7 ± 0.9	46.1 ± 1.6	36.9 ± 4.8
TDC[b]	NT[c]	NT[c]	--	--	--	NT[c]	NT[c]	32.3 ± 3.9	23.6 ± 2.4

[a] The average of three trials.
[b] Commercial bactericides Bismerthiazol (BMT) and Thiodiazole-copper (TDC) were used as positive control agents.
[c] NT: not tested.

Table 2
Antifungal activities of target compounds **6a**-**6z** and intermediates **3**, **4** and **5** at 50 μg/mL.

Compd.	Inhibition ratio[a] (%)					
	GZ	CG	PI	VD	SS	CM
3	18.6 ± 1.1	14.1 ± 2.1	15.0 ± 1.5	27.9 ± 2.6	13.1 ± 0.7	9.0 ± 0.8
4	9.6 ± 1.9	0	8.8 ± 2.1	2.8 ± 0.9	4.3 ± 0.9	0
5	27.6 ± 2.2	9.8 ± 1.2	23.0 ± 1.3	6.5 ± 1.0	12.9 ± 1.2	10.5 ± 2.5
6a	55.7 ± 0.8	64.9 ± 1.0	65.8 ± 2.4	68.6 ± 0.7	63.0 ± 2.3	52.2 ± 2.6
6b	21.1 ± 0.2	28.9 ± 1.3	38.9 ± 1.0	13.2 ± 1.5	33.2 ± 1.1	10.4 ± 0.9
6c	51.9 ± 2.3	52.1 ± 1.9	55.0 ± 1.7	70.0 ± 1.3	54.1 ± 1.0	47.8 ± 3.9
6d	61.6 ± 0.6	51.8 ± 1.3	58.4 ± 2.1	48.8 ± 2.8	54.8 ± 0.7	29.7 ± 1.3
6e	31.9 ± 2.2	16.0 ± 2.5	26.2 ± 0.3	17.0 ± 3.2	14.4 ± 1.1	4.8 ± 2.1
6f	1.6 ± 1.6	16.4 ± 1.5	11.4 ± 1.0	2.8 ± 0.9	20.1 ± 1.0	3.0 ± 1.0
6g	56.7 ± 2.8	50.8 ± 2.6	53.0 ± 1.7	71.6 ± 1.1	51.4 ± 0.6	43.9 ± 0.5
6h	56.2 ± 2.0	68.7 ± 0.8	56.8 ± 1.5	76.4 ± 1.5	66.1 ± 1.1	55.4 ± 2.4
6i	29.8 ± 1.7	46.6 ± 0.3	44.4 ± 0.9	51.0 ± 0.9	39.1 ± 1.1	33.7 ± 1.5
6j	47.8 ± 2.2	49.6 ± 0.6	56.0 ± 1.1	65.9 ± 1.0	43.1 ± 1.6	38.2 ± 8.3
6k	21.1 ± 1.8	37.9 ± 0.4	43.8 ± 1.3	65.4 ± 2.1	32.2 ± 2.0	42.2 ± 1.4
6l	22.4 ± 1.2	46.9 ± 1.1	45.7 ± 1.4	63.8 ± 0.3	28.9 ± 1.2	46.1 ± 2.8
6m	59.5 ± 1.5	43.2 ± 2.1	50.9 ± 1.9	62.3 ± 1.1	46.0 ± 0.9	47.5 ± 1.9
6n	53.3 ± 0.9	50.9 ± 0.9	49.6 ± 1.2	65.0 ± 1.6	35.6 ± 2.0	47.9 ± 1.1
6o	46.8 ± 2.0	40.1 ± 2.8	53.9 ± 0.7	63.0 ± 1.9	32.3 ± 4.2	17.2 ± 3.4
6p	20.5 ± 2.0	24.4 ± 0.5	35.8 ± 1.9	32.1 ± 1.1	19.3 ± 1.0	16.5 ± 2.4

6q	56.5 ± 1.9	17.3 ± 2.8	51.8 ± 0.7	23.8 ± 1.4	54.7 ± 0.5	25.6 ± 1.4
6r	12.4 ± 1.6	21.6 ± 1.1	20.1 ± 1.1	28.1 ± 1.3	15.6 ± 1.4	19.5 ± 0.9
6s	2.9 ± 2.0	6.8 ± 2.1	18.9 ± 1.9	8.4 ± 2.8	7.8 ± 1.6	7.5 ± 1.2
6t	9.6 ± 0.9	15.2 ± 1.3	23.9 ± 2.2	28.1 ± 2.2	6.8 ± 1.1	11.0 ± 2.0
6u	43.5 ± 1.2	32.7 ± 2.8	42.5 ± 0.9	73.7 ± 1.4	31.2 ± 0.9	33.4 ± 1.3
6v	9.9 ± 1.0	17.3 ± 2.1	12.8 ± 0.8	34.1 ± 2.6	9.5 ± 0.4	17.3 ± 1.5
6w	22.9 ± 1.5	15.2 ± 1.3	23.9 ± 2.2	15.2 ± 1.3	12.5 ± 2.0	13.9 ± 1.0
6x	21.1 ± 1.8	44.6 ± 1.9	35.2 ± 2.9	48.1 ± 1.9	32.5 ± 0.8	39.4 ± 4.6
6y	50.3 ± 0.5	37.8 ± 1.6	25.5 ± 2.8	32.1 ± 2.1	34.2 ± 3.3	34.5 ± 5.5
6z	55.1 ± 1.7	52.6 ± 0.9	36.0 ± 1.3	79.1 ± 3.0	48.5 ± 0.4	51.3 ± 2.9
Hymexazol[b]	53.6 ± 1.4	71.8 ± 1.4	67.5 ± 0.8	86.2 ± 2.3	73.8 ± 2.6	59.8 ± 2.2

GZ: *Gibberella zeae*; CG: *Colletotrichum gloeosporioides*; PI: *Phytophthora infestans*; VD: *Verticillium dahlia*; SS: *Sclerotinia sclerotiorum*; CM: *Cytospora mandshurica*.

[a] The average of three trials.

[b] The commercial agrofungicide Hymexazol was utilized as a positive control agent.

In summary, a series of novel 6-fluoroquinazolinylpiperidinyl-containig 1,3,4-oxadiazole thioether derivatives were evaluated as agricultural antimicrobial agents. *In vitro* antibacterial bioassays indicated that compounds **6a**, **6g**, **6u** and **6v** had significantly higher inhibiton activity against phytopathogenic bacterium *Xoo*, relative to commercially-available bactericide Bismerthiazol. Additionally, *in vitro* antifungal assays showed that seven compounds demonstrated broad-spectrum fungicidal activities against tested phytopathogenic fungi at 50 μg/mL. The present work demonstrated the potential of fluoroquinazolinylpiperidinyl-containing 1,3,4-oxadiazole thioether derivatives as effective antimicrobial agents for crop protection, deserving more considerations in future studies.

Acknowledgments

This work was financially supported by Young Top-Notch Talent Support Program of Guizhou Provincial Education Department (No. 2018038), Guizhou Provincial High-Level Overseas Talents Innovation and Enterpreneurship Program (No. 201809) and Breeding Program of Guizhou University (No. 20185781).

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