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Communication

Novel 1,3,5-thiadiazine-2-thione derivatives containing a hydrazide moiety: Design, synthesis and bioactive evaluation against phytopathogenic fungi *in vitro* and *in vivo*

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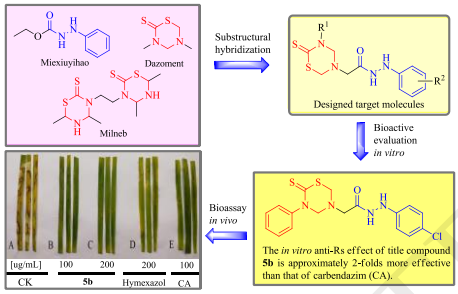
Graphical abstract



A series of novel 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety were designed, synthesized and evaluated for their biological activities against phytopathogenic fungi. The antifungal bioassays indicated that the title compound **5b** impressively displayed the obvious selectivity and specificity aganist *Rhizoctonia solani* (Rs) *in vitro* and *in vivo*. The above researches provide a significant reference for the further structural optimization of 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety as potential fungicides.

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ABSTRACT

A series of novel 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety were designed, synthesized and evaluated for their antifungal activities against Rhizoctonia solani *(Rs),* Fusarium graminearum *(Fg),* Botrytis cinerea *(Bc) and* Colletotrichum capsici *(Cc). The* in vitro *antifungal bioassays indicated that most of title compounds displayed good selectivity and specificity aganist Rs relative to Fg, Bc and Cc. Strikingly, the title compound* N'*-(4-chlorophenyl)-2-(5-phenyl-6-thioxo-1,3,5-thiadiazinan-3-yl)acethydrazide (***5b***) obviously inhibited the Rs growth* in vitro *with the* EC_{50} *value of 0.24 μg/mL,*

which is approximately 2-folds more effective than the commercialized fungicide carbendazim (0.55 μg/mL). The in vivo *anti-Rs effects of title compound* ***5b*** *were further evaluated on rice leaves with control efficacies of 98.58% at 200 μg/mL and 61.27% at 100 μg/mL. The above researches provide a significant reference for the further structural optimization of 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety as potential fungicides.*

Keywords:
1,3,5-Thiadiazine-2-thione
Hydrazide
Crop protection
Antifungal activity

Rhizoctonia solani

Grains, vegetables and fruits are important food sources that are tremendously threatened by the infection of plant pathogenic fungi [1]. These pathogenic fungi, such as *Rhizoctonia solani* (Rs), *Fusarium graminearum* (Fg), *Botrytis cinerea* (Bc) and *Colletotrichum capsici* (Cc), not only lead annually to agricultural yield reductions of at least 10% [2], but also pose huge risks to food security and human health by generating hazardous mycotoxins in infected crops [3]. Nowadays, the rational application of commercialized fungicides is regarded as the most effective approach to alleviate agricultural disease outbreaks caused by phytopathogenic fungi [4,5]. For example, carbendazim, penthiopyrad and azoxystrobin were developed as the highly-efficient and broad-spectrum fungicides that were widely used to reduce the losses of agricultural economies in last decades. However, the long-term application of existing agricultural fungicides not only leads to the rapid deterioration of fungal resistance [6], but also generates the harmful influences on the environment and non-target organisms [7,8]. Therefore, it remains a challenge in agricultural sciences to develop highly-efficient and broad-spectrum fungicides with a novel molecular structure [9,10].

Featuring high lipid solubilities and desirable enzymatic hydrolyzation within living organisms [11,12], 1,3,5-thiadiazine-2-thione derivatives were documented to possess various bioactivities including anti-proliferative [13], antibacterial [14], antiepileptic [15], antifungal [16], antileishmanial [17], antimalarial [18], antitubercular [19], trypanocidal [20], antioxidant [21] and herbicidal [22] properties. Recent practical studies on 1,3,5-thiadiazine-2-thione derivatives showed that this type of nonaromaic heterocycles exhibited desirable inhibition effects against phytopathogenic fungi, bacteria and nematodes. As the important bioactive molecules bearing a 1,3,5-thiadiazine-2-thione fragment, milneb and dazoment (Fig. 1) were respectively developed as agricultural fungicide and acaricide over the last three decades [23,24]. Meanwhile, Mao *et al*. conducted the antibacterial evaluation of dazoment against *Ralstonia solanacearum* in field trials and found dazoment could be used as an alternative bactericide to control ginger bacterial wilt [25]. Subsequently, Hwang *et al.* also found that dazoment could effectively manage agricultural diseases caused by the soil-borne fungal pathogens *Plasmodiophora brassicae*, *Fusarium avenaceum*, *Pythium ultimum* and *Rhizoctonia silani* [26]. However, to the best of our knowledge, 1,3,5-thiadiazine-2-thione derivatives except milneb and dazoment were rarely reported on their structural modifications and agricultural bioactivities.

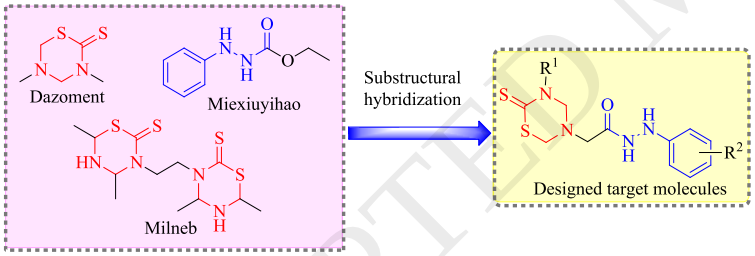
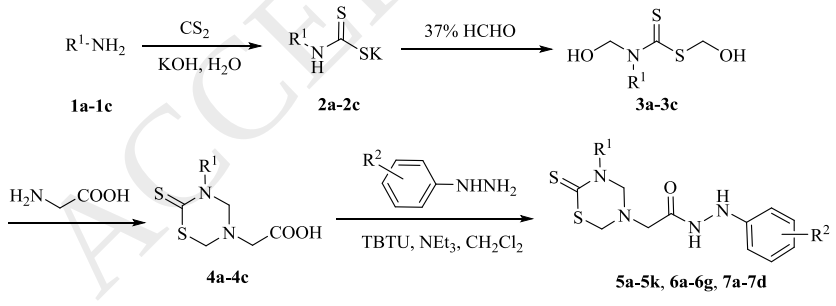


Fig. 1. Design strategy of title compounds.



1a, **2a**, **3a**, **4a**, **5a-5k**: R^1 = Ph
1b, **2b**, **3b**, **4b**, **6a-6g**: R^1 = Bn
1c, **2c**, **3c**, **4c**, **7a-7d**: R^1 = 4-FPh

5a, **6a**, **7a**: R^2 = 4-F
5d, **6d**, **7d**: R^2 = 4-CF_3
5g, **6g**: R^2 = 2,4-di-Cl
5j: R^2 = 2-F

5b, **6b**, **7b**: R^2 = 4-Cl
5e, **6e**: R^2 = 4-Me
5h: R^2 = 2,4,6-tri-Cl
5k: R^2 = 2-Cl

5c, **6c**, **7c**: R^2 = 4-Br
5f, **6f**: R^2 = 4-OMe
5i: R^2 = H

Scheme 1. Synthesis route of title compounds.

Hydrazide derivatives are significant nitrogenous compounds that exhibit herbicidal [27], anticancer [28], antimalarial [29], anti-inflammatory [30], antiviral [31], antibacterial [32], antifungal [33], anticoagulant [34] and insecticidal [35] bioactivities. Among these

bioactive hydrazide derivatives, arylhydrazide derivatives have recently attracted tremendous interests from biologists and chemists due to their excellent inhibition effects against various phytopathogenic fungi. For example, ethyl 2-phenylhydrazine-1-carboxylate named miexiuyihao (Fig. 1) was developed as the systemic fungicide that was mainly applied in effectively controlling wheat stripe rust [36]. Recently, Wang *et al.* reported that arylhydrazide derivatives bearing a 1,2,3-triazole moiety exhibited fine systemic conductions and effectively inhibited the energy generation of various plant fungi [37]. In addition, our previous studies also found that 2-(4-oxoquinazolin-3(4*H*)-yl)-*N'*-phenylacetohydrazide derivatives exhibited the impressive anti-phytopathogenic effects against Rs and Fg *in vitro* [38].

Based on the above-mentioned outstanding fungicidal activities and excellent properties of 1,3,5-thiadiazine-2-thione and hydrazide derivatives, the aims of this work are to: (i) construct novel bioactive molecules by combinating the 1,3,5-thiadiazine-2-thione fragment with the hydrazide substructure, as shown in Fig. 1, which could enhance the molecular lipid solubility within organisms and improve the combining capacity with receptor proteins; (ii) generate a series of novel 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety (Scheme 1) and evaluate their antifungal activities *in vitro* against Rs, Fg, Bc and Cc; and (iii) investigate their *in vivo* anti-Rs effects and perform their structure-activity relationship (SAR) analysis against the above tested fungi.

As shown in Scheme 1, the nucleophilic reaction of the primary amide **1** (aniline, *para*-fluoroaniline or benzylamine) with carbon disulfide in sodium hydroxide solution generated the substituted potassium carbamodithioate **2** that directly reacted with formaldehyde to synthesize the substituted *N*-hydroxymethyl-*S*-hydroxymethyl carbamodithioate **3**. The substituted 2-(6-thioxo-1,3,5-thiadiazinan-3-yl)acetic acid **4** was conveniently synthesized by the nucleophilic substitution of an intermediate **3** with glycine in phosphate buffer (pH 7.8). Using *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluroniumtetrafluoroborate (TBTU) as the catalyst and triethylamine as the acid binding agent, the intermediates **4** reacted with substituted phenylhydrazines to obtain the target compounds **5**–**7** with good yields ranging from 31% to 88%. The obtained 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety were confirmed *via* corresponding FT-IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. The relevant spectroscopic data of synthesized compounds **5**–**7** were collected and presented in Supporting information.

Using the agricultural fungicides carbendazim, penthiopyrad and azoxystrobin as positive controls, the *in vitro* antifungal effects of title compounds against Rs, Fg, Bc and Cc were evaluated by a mycelium growth rate method [5,10,37–43]. As shown in Table 1, the title compounds **5b**, **6a**–**6c** and **7a**–**7c** exhibited impressive anti-Fg effects *in vitro*, with the corresponding EC_{50} values of 2.11, 2.34, 2.17, 2.82, 1.49, 1.19 and 1.73 μg/mL. Meanwhile, the title compounds **5a**–**5e**, **5g**, **6a**–**6c**, **6g** and **7a**–**7c** obviously inhibited Bc *in vitro* with the EC_{50} values of 1.38, 0.85, 0.66, 2.57, 2.26, 2.08, 2.03, 1.43, 2.13, 2.62, 1.75, 1.10 and 1.44 μg/mL, respectively. In addition, Table 1 also showed that the title compounds **5d**, **5g**, **5h**, **5j**, **6d**, **6g** and **7d** had obvious anti-Cc effects, with the corresponding EC_{50} values of 2.29, 2.88, 0.70, 2.12, 0.70, 1.59 and 1.41 μg/mL. Strikingly, the anti-Rs EC_{50} values of title compounds **5b**, **5c**, **6d**, **7b**, **7c** and **7d** reached 0.24, 0.44, 0.25, 0.28, 0.35 and 0.46 μg/mL, respectively, which are better than that of carbendazim (0.55 μg/mL).

Table 1 showed that most of title compounds displayed good selectivity and specificity *in vitro* aganist Rs relative to Fg, Bc and Cc. Impressively, the title compound **5b** obviously inhibited the Rs growth *in vitro* with the EC_{50} value of 0.24 μg/mL, which is approximately 2-folds more effective than the commercialized fungicide carbendazim (0.55 μg/mL). Aiming to further investigate the application values of title compounds as agricultural fungicides, the *in vivo* anti-Rs effects of title compound **5b**, carbendazim and hymexazol were evaluated on rice leaves by a detached leaf assay [44]. As shown in Table 2 and Fig. 2, the *in vivo* anti-Rs control efficacy of title compound **5b** at 100 μg/mL was 61.27%, which is inferior to that of carbendazim at 100 μg/mL (98.08%). Meanwhile, the *in vivo* bioassay results in Table 2 also presented that the title compound **5b** obviously inhibited the Rs growth on rice leaves at 200 μg/mL with an impressive control efficacy of 98.58%, which is obviously better than hymexazol at the same concentration of 200 μg/mL (54.90%). The *in vivo* bioassay research provides a significant reference for the practical application of 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety in agricultures.

Table 1
In vitro antifungal EC_{50} values of title compounds **5**–**7** (μg/mL).[a]

Compd.	Rs	Fg	Bc	Cc
5a	0.76 ± 1.05	3.16 ± 1.54	1.38 ± 0.91	8.09 ± 0.79
5b	0.24 ± 0.16	2.11 ± 1.12	0.85 ± 0.50	3.75 ± 0.87
5c	0.44 ± 0.27	3.66 ± 2.51	0.66 ± 0.41	4.31 ± 0.87
5d	0.81 ± 0.35	8.43 ± 5.58	2.57 ± 0.74	2.29 ± 0.50
5e	4.14 ± 2.29	5.16 ± 1.68	2.26 ± 0.63	35.42 ± 5.34
5f	19.06 ± 5.60	10.48 ± 1.59	11.10 ± 6.02	86.45 ± 8.67
5g	1.86 ± 0.56	10.68 ± 0.53	2.08 ± 0.82	2.88 ± 0.92
5h	10.03 ± 3.86	72.67 ± 8.62	48.00 ± 7.02	0.70 ± 0.21
5i	3.35 ± 0.79	9.44 ± 7.11	9.14 ± 6.16	45.28 ± 4.20
5j	1.53 ± 0.32	17.81 ± 7.14	7.88 ± 4.78	2.12 ± 0.51
5k	2.10 ± 0.76	54.31 ± 8.67	48.13 ± 9.15	7.99 ± 2.62
6a	0.62 ± 0.51	2.34 ± 0.72	2.03 ± 0.71	3.31 ± 0.88
6b	0.77 ± 0.56	2.17 ± 1.27	1.43 ± 0.43	4.44 ± 1.84
6c	0.82 ± 0.32	2.82 ± 0.97	2.13 ± 1.18	3.44 ± 1.07
6d	0.25 ± 0.39	7.84 ± 1.47	4.12 ± 1.54	0.70 ± 0.27
6e	1.81 ± 1.11	4.53 ± 1.94	6.39 ± 1.42	19.06 ± 4.93
6f	4.98 ± 1.29	7.11 ± 2.78	6.50 ± 3.05	25.62 ± 7.94
6g	0.86 ± 0.39	5.13 ± 1.93	2.62 ± 0.96	1.59 ± 0.67
7a	0.82 ± 0.18	1.49 ± 0.27	1.75 ± 0.30	16.04 ± 6.66

7b	0.28 ± 0.16	1.19 ± 0.49	1.10 ± 0.25	8.03 ± 3.05
7c	0.35 ± 0.33	1.73 ± 1.08	1.44 ± 0.23	11.78 ± 2.04
7d	0.46 ± 0.41	9.02 ± 2.73	3.78 ± 1.71	1.41 ± 0.70
Carbendazim	0.55 ± 0.61	0.54 ± 0.56	-	-
Penthiopyrad	-	-	0.82 ± 0.86	-
Azoxystrobin	-	-	-	0.44 ± 0.48

[a]Values are the average of three replicates.

Table 2
In vivo anti-Rs control efficacies of bioactive compounds on rice leaves.[a]

Compd.	Treatment (μg/mL)	Lesion length (cm)	Control efficacy (%)
5b	100	3.83 ± 2.48	61.27
5b	200	0.14 ± 0.47	98.58
Hymexazol	200	4.46 ± 2.76	54.90
Carbendazim	100	0.19 ± 0.52	98.08
Blank control	-	9.89 ± 5.32	-

[a]Values are the average of 10 replicates.

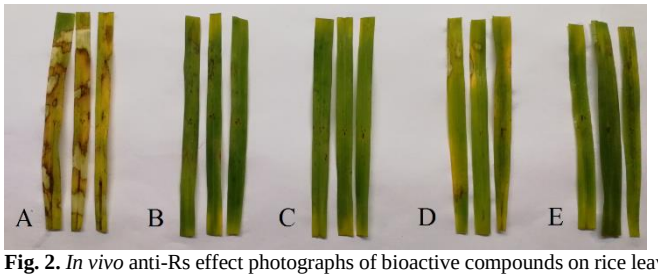


Fig. 2. *In vivo* anti-Rs effect photographs of bioactive compounds on rice leaves. (A) Blank control; (B) **5b** at 100 μg/mL; (C) **5b** at 200 μg/mL; (D) Hymexazol at 200 μg/mL; (E) Carbendazim at 100 μg/mL.

As shown in Table 1, introducing different substituents at R^1 and R^2 positions greatly influenced the inhibition effects of title compounds against phytopathogenic fungi. Based on the bioassay results in Table 1, some structure-activity relationships were analyzed and presented as below. First, all title compounds except **5e**, **5f** and **5h** exhibited better inhibition effects against Rs than that against Fg, Bc and Cc. Second, most of title compounds bearing a Bn group at R^1 position, such as **6a**, **6d**, **6e**, **6f** and **6g**, displayed better anti-Rs and anti-Cc effects than those bearing a Ph (**5a**, **5d**, **5e**, **5f** and **5g**) or 4-FPh (**7a** and **7d**) fragment at R^1 position. Third, the bioassay results in Table 1 showed that a presence of 4-FPh group at R^1 position overall enhanced the anti-Fg effects of title compounds. For example, the anti-Fg EC_{50} values of title compounds **7a**, **7b** and **7c** (R^1 = 4-FPh) respectively reached 1.49, 1.19 and 1.73 μg/mL, which are better than that of title compounds **5a**, **5b** and **5c** (R^1 = Ph; 3.16, 2.11 and 3.66 μg/mL) as well as **6a**, **6b** and **6c** (R^1 = Bn; 2.34, 2.17 and 2.82 μg/mL). Forth, when R^1 was substituted with a Ph group, the anti-Bc EC_{50} values of obtained compounds **5a**–**5d** were 1.38, 0.85, 0.66 and 2.57 μg/mL, respectively, which are better than that of title compounds **6a**–**6d** (R^1 = Bn; 2.03, 1.43, 2.13 and 4.12 μg/mL) and **7a**–**7d** (R^1 = 4-FPh; 1.75, 1.10, 1.44 and 3.78 μg/mL). Fifth, introducing a 4-F, 4-Cl or 4-Br group at R^2 position greatly improved the antifungal effects of title compounds against Rs, Fg and Bc. Table 1 showed that the title compounds containing a 4-F (**5a**, **6a** and **7a**), 4-Cl (**5b**, **6b** and **7b**) or 4-Br (**5c**, **6c** and **7c**) group at R^2 position exhibited better inhibition effects against Rs, Fg and Bc than those molecules bearing a 4-CF_3 (**5d**, **6d** and **7d**), 4-Me (**5e** and **6e**), 4-OMe (**5f** and **6f**), 2,4-di-Cl (**5g** and **6g**), 2,4,6-tri-Cl (**5h**), H (**5i**), 2-F (**5j**) or 2-Cl (**5k**) group at R^2 position.

In conclusion, aiming to search for novel bioactive molecules with anti-phytopathogenic effects, a series of novel 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety were designed and synthesized, and their structures were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. Antifungal bioassays *in vitro* indicated that most of target compounds displayed good selectivity and specificity aganist Rs relative to Fg, Bc and Cc. Strikingly, six title compounds **5b**, **5c**, **6d**, **7b**, **7c** and **7d** exhibited remarkable antifungal activities against Rs *in vitro*, with corresponding EC_{50} values of 0.24, 0.44, 0.25, 0.28, 0.35 and 0.46 μg/mL, which are obviously better than carbendazim (0.55 μg/mL). The *in vivo* anti-Rs effects of title compound **5b** as a key representative were further evaluated on rice leaves to investigate the application potentials of title compounds as agricultural fungicides. The *in vivo* anti-Rs control efficacies of title compound **5b**, which reached 98.58% at 200 μg/mL and 61.27% at 100 μg/mL, indicate that 1,3,5-thiadiazine-2-thione derivatives bearing a hydrazide moiety may have the research value of further structural optimization.

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