Design, Synthesis, and Biological Activity of Novel Triazole Sulfonamide Derivatives Containing a Benzylamine Moiety

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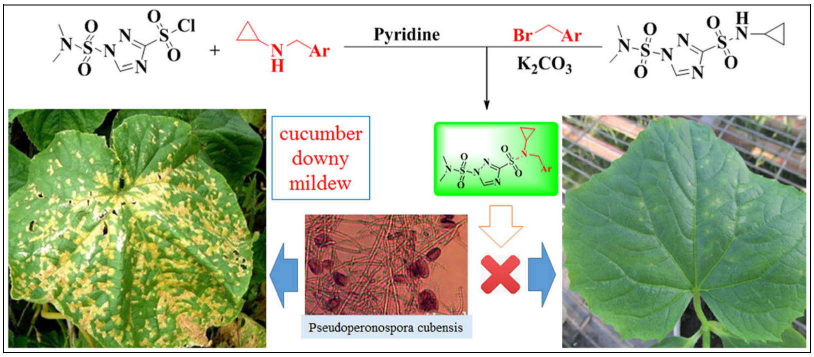

The triazole sulfonamide played a very important role in the field of research of new agrochemical compounds as a novel heterocyclic compound with lack of reported resistance. For the research on the innovative triazole sulfonamide fungicide effective against cucumber downy mildew (CDM), the present article designed an array of 1,2,4-triazole-1,3-disulfonamide derivatives. The derivatives were synthesized *via* coupling multiple benzylamine with triazole sulfonamide groups. ^{1}H-NMR, ^{13}C-NMR, and LC–MS spectrometry were used to characterize these synthesized compounds. Most of these derivatives exhibited better fungicidal activities than that of the commercial cyanosole using bioassays. In particular, compounds **6g** and **6h** showed the best fungicidal activity against CDM (EC_{50} = 6.91 and 10.62 mg/L). Comparative experiments demonstrated that the fungicidal activity of **6g** and **6h** was better than the commercial pesticides amisulbrom and cyanosole. According to the study, the compound **6g** had a giant application potential on fungicide against CDM.

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INTRODUCTION

Fungicides are an integral part of agrochemicals and interpret a critical role in agricultural production *via* improving crop quality and output as well as quality of life [1–3]. They have been employed to control varieties of plant disease and found a wide utilization in major crops: vegetables, fruits, and rice, and so forth [4]. In the past 10 years from 2006 to 2016, the compound annual growth rate (+5.5%) of fungicides was the highest, followed by pesticides (+4.8%) and herbicides (+3.0%). In 2017, fungicides even accounted for 28.6% of the $54.419bn pesticide market [5]. Nevertheless, it is inevitable that drug resistance is always developing with the extensive application of the fungicides [6,7]. The fungicides having a definitive mechanism of action can be classified into more than 50 groups according to the target site. Among them, more than 40 target sites have been reported to pose a moderate to high risk of resistance to many common classes of fungicides, which involve most fungicide structures [8]. There is an urgent need to find fungicide candidates with new mode of action to solve this trouble.

Triazole sulfonamide is an electron transport inhibitor against mitochondrial complex III (MET III) [9–12]. It is one of the few fungicides that have not reported drug resistance [13–16]. Amisobromide is an excellent representative of triazole sulfonamide fungicides targeted at MET III, and its chemical construction is obviously different from that of commercial fungicides [17–21]. What is more, it is relatively safe for nontarget organisms. There is no problem on cross-resistance with most of conventional fungicides. The earlier properties indicate that triazole sulfonamide is a promising candidate for the discovery of novel fungicides [22–28].

Aromatic groups are generally existed in a number of agricultural drugs such as (aryloxy)phenoxypropionate herbicides, amide insecticides, prothioconazole, and amisulbrom. Compounds containing aromatic group are of great interest because of their highly biological activity especially in agricultural fungicide. Triazole sulfonamide groups are employed, act as pharmacophore, and play a significant role in fungicide, such as amisulbrom, which can be highly active against blight and downy mildew. Inspired by the success of triazole sulfonamide with benzene heterocycle compounds, we have pursued the synthesis of triazole and benzylamine analogues.

Pseudoperonospora cubensis is a type of water mold known for giving rise to downy mildew on melons such as loofah, cantaloupe, cucumber, zucchini, pumpkin, and watermelon. Since 2004, it has become one of the most baleful diseases in cucumber production. The revival in toxicity has caused great anxious and vast economic damages for growers. Moreover, downy mildew of other cucurbit crops remains an annual obstacle. Therefore, it is urgent to develop novel structure with high activity in oomycetes disease [29,30]. In our current research, we sought to exploit novel triazole sulfonamide derivatives with ideal fungicidal activity against cucumber downy mildew (CDM) by coupling diverse benzylamine with triazole sulfonamide units, with the purpose of finding a new fungicide candidate.

RESULTS AND DISCUSSION

Chemistry. Synthesis of the derivatives of 1,2,4-triazole-1,3-disulfonamide is shown in Scheme 1. The target compound contains two modes, the first consisting of two groups: a triazole disulfonamide moiety and a benzylamine part. At first, 3-mercapto-1,2,4-triazole (**1**) was adopted as a starting material to give triazolesulfonyl chloride *via* three steps. The intermediate triazole thiosulfonate is obtained by reaction of **1** with benzenesulfonyl chloride. It reacts with another molecule thiol and produces symmetrical disulfides (**2**) in the presence of pyridine. Then, **2** was reacted with *N*,*N*-dimethylsulfamoyl chloride to obtain **3** using potassium carbonate as a base. Next, oxidation of the disulfide is carried out by bubbling chlorine into an aqueous solution containing ethylic acid, and the triazolesulfonyl chloride **4** was given. Benzylamine was synthesized by condensation reaction of properly substituted aromatic aldehydes with cyclopropylamine, and the intermediate **5** was obtained. The assembly of the triazolesulfonyl chloride and various benzylamine furnished the designed product **6** in extremely high yield.

Another method was **4** as the starting material, occurring condensation reaction with cyclopropylamine to generate the vital intermediate **7**. Finally, the designed product **8** was obtained by coupling the intermediate **7** with various benzyl bromides with a good yield.

Fungicidal activity. The living pot experiments indicated that almost half of the synthesized derivatives had good inhibitory activity against CDM. Different triazole sulfonamide derivatives contained benzylamine moiety and expressed significant differences of activity. Several compounds exhibited complete control against CDM according to Table 1. **6a–6d**, **6g–6j**, **6p**, **8a–8d** had an inhibition activity of 100% at the concentration of 200 mg/L. Besides, **6a**, **6b**, **6g**, **6h**, **6i**, **6j**, **6p**, and **8d** remained the same complete control at the concentration of 100 mg/L. Especially it was worth to mention that **6g**

Scheme 1. Synthetic route of target compounds. Reagents and conditions: (a) benzenesulfonyl chloride, pyridine, CH_2Cl_2, 20°C, 12 h; (b) dimethylsulfamoyl chloride, 0 to 20°C, 30 min–15 h; (c) Cl_2, $CH_2Cl_2/CH_3COOH/H_2O$ = 1:2:1 (v:v:v), 0°C, 2 h; (d) $MgSO_4$, CH_2Cl_2, 20°C, 12 h, then be reduced by $NaBH_4$ in methanol for 2 h; (e) pyridine, tetrahydrofuran, 20°C, 12 h; (f) triethylamine, tetrahydrofuran, 20°C, 12 h; (g) K_2CO_3, *N*,*N*-dimethylformamide, 20°C, 12 h.

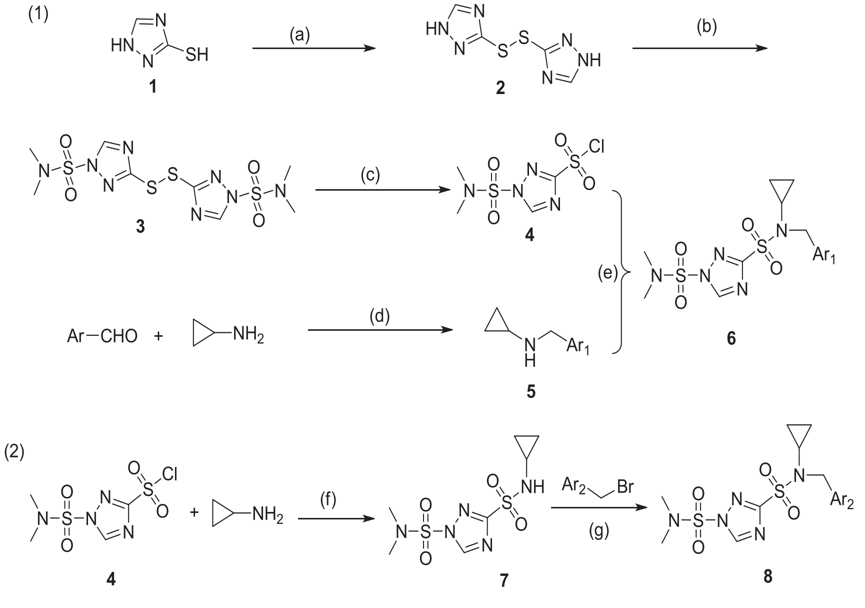
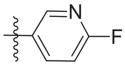
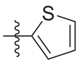
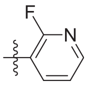
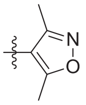
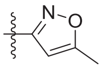
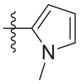
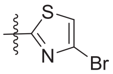
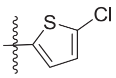
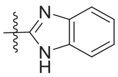
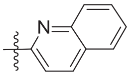
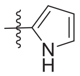
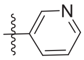
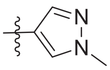
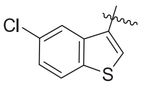


Table 1

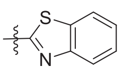
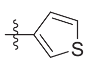
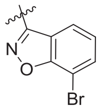
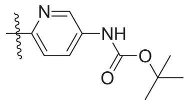
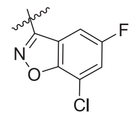
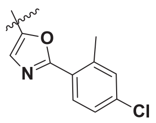
The inhibitory activity of the title compounds against cucumber downy mildew.

		Cucumber downy mildew % inhibition (mg/L)					
Example	Ar	200	100	50	25	12.5	6.25
6a		100	100	80	30	0	0
6b		100	100	80	70	30	0
6c		100	90	80	60	10	0
6d		100	90	50	20	0	0
6e		30	10	0	0	0	0
6f		50	20	0	0	0	0
6g		100	100	100	90	70	50
6h		100	100	100	80	60	30
6i		100	100	80	50	40	30
6j		100	100	60	20	0	0
6k		50	20	0	0	0	0
6l		80	60	20	0	0	0
6m		60	30	0	0	0	0
6n		30	0	0	0	0	0

(*Continues*)

Table 1

(Continued)

Example	Ar	Cucumber downy mildew % inhibition (mg/L)					
		200	100	50	25	12.5	6.25
6o		90	50	30	0	0	0
6p		100	100	80	60	20	0
8a		100	60	30	0	0	0
8b		100	90	50	20	0	0
8c		100	80	50	20	0	0
8d		100	100	60	30	0	0
Amisulbrom		100	100	95	85	45	30
Cyanosole		100	80	50	20	5	0

and **6h** remained in complete control even at the concentration of 50 mg/L; on this level, amisulbrom and cyanosole exclusively existed at 95 and 50% control. Derivatives **6g** and **6h** showed better fungicidal activity against CDM than amisulbrom and cyanosole, respectively, at the concentration of 6.25 and 12.5 mg/L. In addition, **6b**, **6c**, and **6i** showed moderate inhibition rates, which were 30, 10, and 40%, respectively.

Preliminary antibacterial test against CDM at different concentrations revealed that compounds **6g** and **6h** had excellent potency. Thus, we selected these all active compounds for further evaluation. Besides, we selected amisulbrom and cyanosole as positive contrast, for they were the most effective and frequently used fungicide and they had good control activity against CDM. The EC_{50} values calculated and derived from inhibition of fungi earlier were shown in Table 2.

As shown in Table 2, compounds **6g** (EC_{50} = 6.910 mg/L) and **6h** (EC_{50} = 10.123 mg/L) exhibited the best inhibitory activity against CDM than that of amisulbrom (EC_{50} = 11.309 mg/L) and cyanosole (EC_{50} = 48.522 mg/L), thus emerging as new lead compounds for antibacterial research. Among the five-membered heterocycle derivatives **6b**, **6d–6h**, **6k**, **6m**, and **6p**, brominated heterocyclic ring **6g** showed the best activity, while alkenyl heterocycle **6e** displayed the lowest inhibitory effect, indicating that single halogen substitution on the ring and multiple substitutions within the ring probably had a positive effect on bioactivity. The quantitative structure–activity relationship of aromatic ring or coupling derivatives showed irregularity but lower activity than five-membered heterocycle on the whole. The earlier results indicated that the heterocycle formation may impact the antibacterial activity of these compounds, aromatic ring or more complex coupling was favorable to inhibitory effect. The main difference between **6g** and **6h** lay in the number of the substitution atom within heterocycle, which indicated that the substitution within ring is important for keeping high antibacterial activity.

Table 2

Determination of activity of different agents on cucumber downy mildew.

Example	Toxic regression equation	EC_{50} (mg/L)	95% confidence interval (mg/L)	χ^2	*P*
6a	$Y = -8.189 + 5.388X$	33.102	30.548–35.856	3.444	0.486
6b	$Y = -4.253 + 3.238X$	20.579	13.814–29.544	21.079	0.000
6c	$Y = -4.424 + 3.075X$	27.463	18.243–40.075	22.040	0.000
6d	$Y = -6.531 + 3.916X$	46.529	42.370–51.112	5.352	0.253
6e	$Y = -7.561 + 3.077X$	286.627	230.811–422.083	1.719	0.787
6f	$Y = -8.365 + 3.667X$	191.159	168.755–226.228	3.920	0.417
6g	$Y = -2.078 + 2.487X$	6.846	5.488–8.087	3.854	0.426
6h	$Y = -2.819 + 2.797X$	10.189	8.835–11.538	6.567	0.161
6i	$Y = -2.392 + 1.981X$	16.124	7.891–26.624	23.348	0.000
6j	$Y = -8.039 + 5.009X$	40.252	33.879–48.013	8.034	0.090
6k	$Y = -8.365 + 3.667X$	191.159	168.755–226.228	3.920	0.417
6l	$Y = -6.511 + 3.304X$	96.020	77.477–121.627	8.057	0.089
6m	$Y = -8.392 + 3.808X$	159.907	130.361–216.132	7.627	0.106
6n	$Y = -7.667 + 3.038X$	334.225	218.026–493.161	7.932	0.094
6o	$Y = -6.692 + 3.441X$	88.062	67.898–117.446	12.122	0.016
6p	$Y = -4.769 + 3.479X$	23.493	18.330–19.893	10.864	0.028
8a	$Y = -8.397 + 4.472X$	75.442	58.145–98.755	14.897	0.005
8b	$Y = -6.531 + 3.916X$	46.529	42.370–51.112	5.352	0.253
8c	$Y = -5.903 + 3.474X$	50.056	40.704–61.679	8.120	0.087
8d	$Y = -7.081 + 4.492X$	37.690	29.012–49.179	15.082	0.005
Amisulbrom	$Y = -2.788 + 2.645X$	11.329	9.836–12.849	6.561	0.161
Cyanosole	$Y = -5.215 + 3.103X$	47.942	43.145–53.346	5.152	0.272

The indoor pot experiment further demonstrated that **6g** might have more excellent protective and curative activity than amisulbrom (Fig. 1). The structural optimum design and field trials of **6g** were still being investigated, as well as the synthesis of analogues. The results suggested that compound **6g** exhibited better fungicidal activities against CDM than that of the commercial fungicides amisulbrom and cyanosole (EC_{50} = 11.309 and 48.522 mg/L). It was the optimal structure with EC_{50} value of 6.910 mg/L and worth further research and optimization. The development of resistance could be delayed by the discovery of new triazole disulfonamide fungicides, which could also contribute to resistance management. Current results provide support for the development of triazole disulfonamide as novel agrochemicals.

EXPERIMENTAL

Materials and methods. All commercially purchased reagents could be used directly not having any purification. A VARIAN Mercury-Plus 400 spectrometer (varian Inc., Palo Alto, California, USA) was applied to record ^{1}H-NMR spectra in $CDCl_3$ or DMSO-d_6, and tetramethylsilane was adopted to be an internal reference. The VARIAN Mercury-Plus 400 (100 MHz) spectrometer was used to record ^{13}C-NMR spectra in $CDCl_3$ or DMSO-d_6. The chemical shifts (δ) of ^{13}C-NMR were obtained by adopting the middle line of the triplet of $CDCl_3$ as 77.0 ppm. Several abbreviations were adopted to indicate multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

Chemical synthesis. ***1H-1,2,4-Triazole-3-thiol (1).*** In a 100-mL flask, 24.92 g (520.0 mmol) of formic acid was added to 25.0 mL of water and then 20.02 g (220.0 mmol) of 1-aminothiourea was poured. The temperature was increased to 105°C for half an hour and then slowly cooled to room temperature. After further dropping to −10°C, the crystal was slowly decrystallized, and finally, the aldehyde 1-aminothiourea was obtained by using filtration and drying the solid. Then aldehyde aminethiourea (11.90 g 100.0 mmol), K_2CO_3 (26.50 g, 250.0 mmol), and water (125.0 mL) were put in a 250-mL single-mouth bottle. The temperature was increased to 100°C for 4 h and then lowered to 25°C slowly; the pH was regulated to 4 to 5 using diluted HCl aqueous, and this mixture was stirred at −10°C to slowly decrystallize. The crystallized product was filtered and dried to gain white powder 5.60 g, yield 55%.

1,2-di(1H-1,2,4-Triazol-3-yl)disulfane (2). Dry pyridine 3.95 g (50.0 mmol) was added into 50-mL dichloromethane (DCM) with 5.05 g (50.0 mmol) of 3-mercapto-1,2,4-triazole, which was agitated mechanically. This solution earlier was cooled to 0°, followed by adding 4.42 g (25.0 mmol) of benzenesulfonyl chloride into the mixture in 1 h. The mixture was reacted at 25°C for 15 h without ice bath. DCM was concentrated under reduced pressure, and the residue was washed with distilled water (50 mL) and acetic ether (30 mL) for 1 h, and then the precipitate was filtered and washed by water (25 mL) and acetic ether (20 mL) in sequence. The precipitate was dried at 70°C to provide 4.50 g (90%) of desired 3,3′-(dithiobis)-1,2,4-triazole [31].

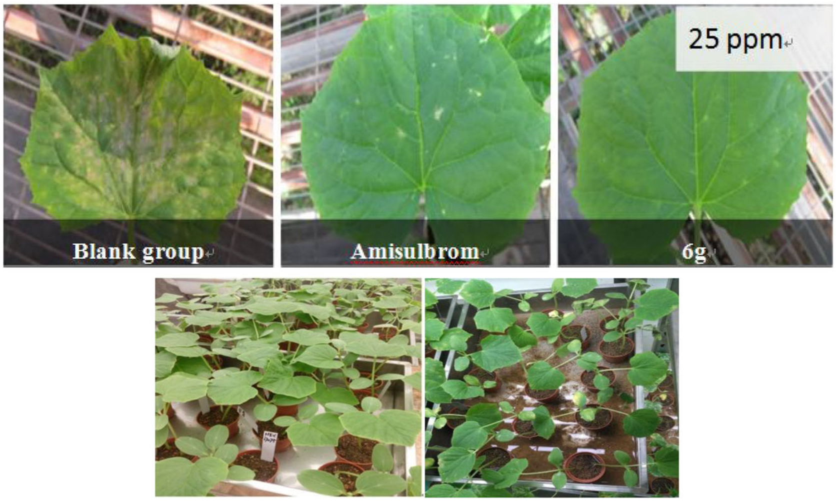


Figure 1. Comparison of indoor pot experiment. [Color figure can be viewed at wileyonlinelibrary.com]

3,3′-Disulfanediylbis(N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide) (3). Potassium carbonate 5.52 g (40.0 mmol) and 4.00 g (20.0 mmol) of bis[1,2,4-triazole-3-yl]disulfide were mixed into 50 mL of dimethylformamide, and the temperature was cooled to 10°C. *N*,*N*-Dimethylsulfamoyl chloride 3.16 g (22.0 mmol) was added to the reaction system as drops, and the temperature was controlled between 15 and 30°C over 2 h. Next, 30 mL of DCM was poured into reaction mixture, followed by adding 50.0 mL of 10% hydrochloric acid into the resulting solution at a temperature ranging from 20 to 25°C. A DCM solution having 7.44 g of title product was obtained from the collected organic phase in 90% yield [32].

1-(N,N-Dimethylsulfamoyl)-1H-1,2,4-triazole-3-sulfonyl chloride (4). After adding 50 mL of water into 30 mL of DCM solution containing 7.05 g (17.0 mmol) of previous product, the system was cooled to 0°. Chlorine was bubbled into the solution, and the temperature was controlled ranging from 10 to 15°C over 2 h followed by adding 10 mL of ethylic acid. Organic layer by phase separation was washed with 20 mL of H_2O (three times) after the reaction was completed. A DCM solution containing 8.25 g of title product was obtained in 89% yield [33].

General chemical synthesis of compound (5). Add aromatic aldehyde (12.0 mmol), cyclopropylamine (1.71 g, 30.0 mmol), $MgSO_4$ (3.60 g, 30.0 mmol), and DCM (30 mL) to a 250-mL three-necked bottle. The imine intermediate was afforded according to filtration and removal of solvent by evaporator and dissolved in methyl alcohol (22.0 mL). Sodium borohydride (0.46 g, 12.0 mmol) was slowly put in solution, and this reaction system was reacted at 25°C over 2 h. The solid was purified through gel column chromatography followed by evaporating the solvent to give pure product **5** [34].

General chemical synthesis of compound (6). Compound (**5**) (2.0 mmol), pyridine (0.24 g, 3.0 mmol), and tetrahydrofuran (10 mL) were mixed into a 50-mL three-necked flask and stirred at an ice bath. A mixture of **4** (0.55 g, 2.0 mmol) and tetrahydrofuran (12.0 mL) was added dropwise over 10 min, and the system was reacted at 25°C over 2 h. Residue was purified through flash chromatography after evaporating the solvent to give **6** [35,36].

N_3-Cyclopropyl-N_3-((6-fluoropyridin-3-yl)methyl)-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6a). White solid (78%). mp 95–98°C. ^{1}H-NMR: δ (ppm) 8.63 (s, 1H), 8.20 (s, 1H), 7.93 (dt, 1H), 6.94 (dd, 1H), 4.59 (s, 2H), 3.09 (s, 6H), 2.53–2.48 (m, 1H), 0.87–0.83 (m, 2H), 0.82–0.77 (m, 2H). ^{13}C-NMR: δ 163.40 (d, J = 240.2 Hz), 163.00, 147.63 (d, J = 14.9 Hz), 146.19, 141.88, 129.50 (d, J = 4.7 Hz), 109.67, 51.47, 38.90, 30.76, 7.53. HRMS (EI): $C_{13}H_{17}FN_6O_4S_2$ $(M)^+$ calcd. 404.0737; found 404.0735.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-(thiophen-2-ylmethyl)-1H-1,2,4-triazole-1,3-disulfonamide (6b). White solid (74%). mp 93–96°C.^{1}H-NMR: δ (ppm) 8.55 (s, 1H), 7.23 (d, 1H), 6.99 (d, 1H), 6.93–6.91 (m, 1H), 4.76 (s, 2H), 3.09 (s, 6H), 2.71–2.66 (m, 1H), 0.99–0.95 (m, 2H), 0.87–0.82 (m, 2H). ^{13}C-NMR: δ 163.32, 145.94, 137.56, 128.09, 126.78, 126.04, 48.95, 38.92, 30.44, 7.87. HRMS (EI): $C_{12}H_{17}N_5O_4S_3$ $(M)^+$ calcd. 391.0443; found 391.0444.

N_3-Cyclopropyl-N_3-((2-fluoropyridin-3-yl)methyl)-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6c). White solid (76%). mp 104–106°C. ^{1}H-NMR: δ (ppm) 8.62 (s, 1H), 8.16 (d, 1H), 8.00–7.96 (m, 1H), 7.24–7.21 (m, 1H), 4.64 (s, 2H), 3.09 (s, 6H), 2.64–2.59 (m, 1H), 0.86–0.83 (m, 2H), 0.81–0.75 (m, 2H). ^{13}C-NMR: δ 163.40 (d, J = 240.2 Hz), 163.00, 147.63 (d, J = 14.9 Hz), 146.19, 141.88, 129.50, 109.67, 51.47, 38.90, 30.76, 7.53.

HRMS (EI): $C_{13}H_{17}FN_6O_4S_2$ $(M)^+$ calcd. 404.0737; found 404.0737.

N_3-Cyclopropyl-N_3-((3,5-dimethylisoxazol-4-yl)methyl)-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6d). White solid (80%). mp 106–108°C. ^{1}H-NMR: δ (ppm) 8.63 (s, 1H), 4.38 (s, 2H), 3.09 (s, 6H), 2.58–2.55 (m, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 0.86–0.83 (m, 2H), 0.78–0.73 (m, 2H). ^{13}C-NMR: δ 168.09, 162.92, 159.67, 146.16, 108.83, 43.92, 38.85, 30.73, 11.23, 10.32, 7.52. HRMS (EI): $C_{13}H_{20}N_6O_5S_2$ $(M)^+$ calcd. 404.0937; found 404.0938.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-((5-methylisoxazol-3-yl)methyl)-1H-1,2,4-triazole-1,3-disulfonamide (6e). White solid (67%). mp 107–109°C. ^{1}H-NMR: δ (ppm) 8.63 (s, 1H), 6.11 (s, 1H), 4.58 (s, 2H), 3.09 (s, 6H), 2.66–2.61 (m, 1H), 2.41 (s, 3H), 0.92–0.88 (m, 2H), 0.82–0.77 (m, 2H). ^{13}C-NMR: δ 170.09, 162.85, 160.09, 146.13, 101.69, 46.14, 38.91, 31.05, 12.21, 7.53. HRMS (EI): $C_{12}H_{18}N_6O_5S_2$ $(M)^+$ calcd. 390.0780; found 390.0783.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-((1-methyl-1H-pyrrol-2-yl)methyl)-1H-1,2,4-triazole-1,3-disulfonamide (6f). White solid (75%). mp 94–97°C. ^{1}H-NMR: δ (ppm) 8.62 (s, 1H), 6.59 (s, 1H), 6.09 (s, 1H), 6.00 (s, 1H), 4.58 (s, 2H), 3.68 (s, 3H), 3.08 (s, 6H), 2.43–2.36 (m, 1H), 0.73–0.68 (m, 4H). ^{13}C-NMR: δ 162.81, 146.08, 125.25, 123.32, 111.38, 106.91, 46.81, 38.90, 34.07, 29.95, 7.18. HRMS (EI): $C_{13}H_{20}N_6O_4S_2$ $(M)^+$ calcd. 388.0987; found 388.0984.

N_3-((4-Bromothiazol-2-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6g). White solid (73%). mp 83–85°C. ^{1}H-NMR: δ (ppm) 8.63 (s, 1H), 7.47 (s, 1H), 4.73 (s, 2H), 3.09 (s, 6H), 2.64–2.56 (m, 1H), 0.97–0.92 (m, 2H), 0.88–0.83 (m, 2H). ^{13}C-NMR: δ 162.88, 146.18, 142.47, 137.25, 137.20, 46.69, 38.91, 30.53, 7.75. HRMS (EI): $C_{11}H_{15}BrN_6O_4S_3$ $(M)^+$ calcd. 469.9500; found 469.9506.

N_3-((5-Chlorothiophen-2-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6h). White solid (77%). mp 108–109°C. ^{1}H-NMR: δ (ppm) 8.60 (s, 1H), 6.78 (d, 1H), 6.74 (d, 1H), 4.65 (s, 2H), 3.08 (s, 6H), 2.69–2.64 (m, 1H), 0.98–0.94 (m, 2H), 0.87–0.83 (m, 2H). ^{13}C-NMR: δ 163.19, 146.03, 136.68, 130.39, 127.38, 125.81, 49.34, 38.90, 30.46, 7.82. HRMS (EI) $C_{12}H_{16}ClN_5O_4S_3$ $(M)^+$ calcd. 425.0053; found 425.0051.

N_3-((1H-Benzo[d]imidazol-2-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6i). White solid (70%). mp 111–114°C. ^{1}H-NMR: δ (ppm) 9.40 (s, 1H), 7.40–7.52 (m, 2H), 7.12–7.20 (m, 2H), 4.73 (s, 3H), 2.95 (s, 6H), 2.53–2.56 (m, 1H), 0.69–0.73 (m, 4H). ^{13}C-NMR: δ 169.98, 161.19, 151.87, 135.56, 126.32, 122.79, 53.05, 38.90, 31.91, 7.66. HRMS (EI): $C_{15}H_{19}N_7O_4S_2$ $(M)^+$ calcd. 425.0940; found 425.0941.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-(quinolin-2-ylmethyl)-1H-1,2,4-triazole-1,3-disulfonamide (6j). White solid (65%). mp 123–125°C. ^{1}H-NMR: δ (ppm) 8.63 (s, 1H), 8.81 (d, 1H), 7.97 (d, 1H), 7.84 (d, 1H), 7.73 (dd, 1H), 7.65 (d, 1H), 7.56 (t, 1H), 4.91 (s, 2H), 3.05 (s, 6H), 2.84–2.79 (m, 1H), 0.87–0.83 (m, 2H), 0.75–0.70 (m, 2H). ^{13}C-NMR: δ 163.02, 157.04, 147.40, 146.15, 136.98, 129.76, 128.96, 127.67, 127.38, 126.61, 119.97, 56.99, 38.90, 31.75, 7.39. HRMS (EI): $C_{17}H_{20}N_6O_4S_2$ $(M)^+$ calcd. 436.0987; found 436.0985.

N_3-((1H-Pyrrol-2-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6k). White solid (74%). mp 102–104°C. ^{1}H-NMR: δ (ppm) 8.93 (s, 1H), 8.63 (s, 1H), 6.77 (s, 1H), 6.11 (s, 1H), 6.08 (s, 1H), 4.55 (s, 2H), 3.08 (s, 6H), 2.54–2.51 (m, 1H), 0.93–0.89 (m, 2H), 0.81–0.75 (m, 2H). ^{13}C-NMR: δ 163.23, 146.22, 125.60, 118.90, 109.10, 107.97, 47.55, 38.90, 30.29, 7.42. HRMS (EI) $C_{12}H_{18}N_6O_4S_2$ $(M)^+$ calcd. 374.0831; found 374.0832.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-(pyridin-3-ylmethyl)-1H-1,2,4-triazole-1,3-disulfonamide (6l). White solid (70%). mp 98–101°C. ^{1}H-NMR: δ (ppm) 8.64 (s, 1H), 8.37 (s, 1H), 8.16 (d, $J = 4.4$ Hz, 1H), 8.10–8.06 (m, 1H), 7.26–7.24 (m, 1H), 4.62 (s, 2H), 3.08 (s, 6H), 2.64–2.59 (m, 1H), 0.86–0.82 (m, 2H), 0.82–0.74 (m, 2H). ^{13}C-NMR: δ 162.88, 163.31, 148.16, 144.18, 140.49, 121.79, 119.76, 48.01, 38.95, 31.56, 7.51. HRMS (EI): $C_{13}H_{18}N_6O_4S_2$ $(M)^+$ calcd. 386.0831; found 386.0830.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-((1-methyl-1H-pyrazol-4-yl)methyl)-1H-1,2,4-triazole-1,3-disulfonamide (6m). White solid (68%). mp 90–91°C. ^{1}H-NMR: δ (ppm) 8.55 (s, 1H), 7.34 (s, 1H), 7.30 (s, 1H), 4.42 (s, 2H), 3.81 (s, 3H), 3.05 (s, 6H), 2.59–2.54 (m, 1H), 0.96–0.92 (m, 2H), 0.84–0.80 (m, 2H). ^{13}C-NMR: δ 163.81, 146.09, 131.89, 125.32, 115.38, 46.56, 44.07, 38.90, 29.09, 7.15. HRMS (EI): $C_{12}H_{19}N_7O_4S_2$ $(M)^+$ calcd. 389.0940; found 389.0943.

N_3-((5-Chlorobenzo[b]thiophen-3-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6n). White solid (68%). mp 183–187°C. ^{1}H-NMR: δ (ppm) 8.62 (s, 1H), 7.96 (s, 1H), 7.79 (d, 1H), 7.53 (s, 1H), 7.35 (d, 1H), 4.80 (s, 2H), 3.07 (s, 6H), 2.58–2.55 (m, 1H), 0.86–0.82 (m, 2H), 0.77–0.72 (m, 2H). ^{13}C-NMR: δ 163.01, 146.04, 139.12, 138.53, 130.86, 130.32, 128.28, 125.10, 123.82, 121.69, 48.59, 38.90, 31.18, 7.59. HRMS (EI): $C_{16}H_{18}ClN_5O_4S_3$ $(M)^+$ calcd. 475.0209; found 475.0210.

N_3-(Benzo[d]thiazol-2-ylmethyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (6o). White solid (72%). mp 145–148°C. ^{1}H-NMR: δ (ppm) 8.63 (s, 1H), 7.96 (d, 1H), 7.89 (d, 1H), 7.50 (t, 1H), 7.42 (t, 1H), 5.02 (s, 2H), 3.07 (s, 6H), 2.84–2.79 (m, 1H), 1.03–0.99 (m, 2H), 0.86–0.81 (m, 2H). ^{13}C-NMR: δ 167.86, 162.63, 152.99, 146.15, 135.56, 126.22, 125.41, 123.09, 121.77, 53.05, 38.92, 31.89, 7.65. HRMS (EI): $C_{15}H_{18}N_6O_4S_3$ $(M)^+$ calcd. 442.0552; found 442.0555.

N_3-Cyclopropyl-N_1,N_1-dimethyl-N_3-(thiophen-3-ylmethyl)-1H-1,2,4-triazole-1,3-disulfonamide (6p). White solid

(76%). mp 91–94°C. ^{1}H-NMR: δ (ppm) 8.57 (s, 1H), 7.26–7.20 (m, 2H), 7.06 (d, J = 4.8 Hz, 1H), 4.57 (s, 2H), 3.07 (s, 6H), 2.63–2.58 (m, 1H), 0.92–0.88 (m, 2H), 0.81–0.76 (m, 2H). ^{13}C-NMR: δ 163.30, 146.07, 136.41, 128.03, 125.95, 124.19, 49.38, 38.89, 30.61, 7.60. HRMS (EI): $C_{12}H_{17}N_5O_4S_3$ (M)$^+$ calcd. 391.0443; found 391.0443.

N_3-Cyclopropyl-N_1,N_1-dimethyl-1*H*-1,2,4-triazole-1,3-disulfonamide (7). Under a nitrogen atmosphere, cyclopropylamine (1.25 g, 22.0 mmol), *N*,*N*-diethylethanamine (2.22 g, 22.0 mmol), and hydrofuran (30 mL) were mixed into a 250-mL flask, stirred at 0°C, and added dropwise with 20 mL of hydrofuran solution of **4** (5.48 g, 20.0 mmol) over 10 min and then eluted with white smoke. The reaction system was reacted at 25°C for 2 h. The mixture was filtered and dried after finishing the reaction to obtain a white solid compound 4.45 g, yield 75% [37].

General chemical synthesis of compound (8). In a 50-mL single-mouth bottle, **7** (0.74 g, 2.5 mmol), K_2CO_3 (0.62 g, 4.5 mmol), and *N*,*N*-dimethylformamide (15 mL) were added successively at room temperature, followed by adding benzyl bromide (3.0 mmol) slowly to the system and stirred for about 2 h. The residue was purified through column chromatography followed by evaporating the solvent of the reaction to obtain pure compound **8** [38].

N_3-((7-Bromobenzo[d]isoxazol-3-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (8a). White solid (75%). mp 129–132°C. ^{1}H-NMR: δ (ppm) 8.65 (s, 1H), 7.94 (d, 1H), 7.75 (d, 1H), 7.28–7.24 (m, 1H), 5.00 (s, 2H), 3.09 (s, 6H), 2.65–2.60 (m, 1H), 0.86–0.82 (m, 2H), 0.80–0.75 (m, 1H). ^{13}C-NMR: δ 162.50, 160.88, 155.10, 146.22, 133.22, 125.55, 121.66, 121.33, 102.63, 46.05, 38.91, 31.22, 7.41. HRMS (EI): $C_{15}H_{17}BrN_6O_5S_2$ (M)$^+$ calcd. 503.9885; found 503.9887.

tert-Butyl-(6-((N-cyclopropyl-1-(N,N-dimethylsulfamoyl)-1H-1,2,4-triazole-3-sulfonamido)methyl)pyridin-3-yl)carbamate (8b). White solid (78%). mp 113–116°C. ^{1}H-NMR: δ (ppm) 8.61 (s, 1H), 7.80 (d, 1H), 7.63 (t, 1H), 7.20 (s, 1H), 7.05 (d, 1H), 4.56 (s, 2H), 3.05 (s, 6H), 2.75–2.72 (m, 1H), 1.52 (s, 9H), 0.92–0.84 (m, 2H), 0.75–0.70 (m, 2H). ^{13}C-NMR: δ 163.27, 154.70, 152.17, 151.23, 145.98, 138.80, 116.95, 110.80, 81.09, 55.64, 38.88, 31.45, 28.22, 7.57. HRMS (EI): $C_{18}H_{27}N_7O_6S_2$ (M)$^+$ calcd. 501.1464; found 501.1460.

N_3-((7-Chloro-5-fluorobenzo[d]isoxazol-3-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (8c). White solid (77%). mp 118–121°C. ^{1}H-NMR: δ (ppm) 8.66 (s, 1H), 7.62 (dd, 1H), 7.40 (dd, 1H), 4.97 (s, 2H), 3.10 (s, 6H), 2.63–2.58 (m, 1H), 0.86–0.76 (m, 4H). ^{13}C-NMR: δ 162.39, 158.42, 157.74, 155.30, 146.26, 121.92, 119.36, 116.53, 106.08, 45.89, 38.91, 31.29, 7.35. HRMS (EI): $C_{15}H_{16}ClFN_6O_5S_2$ (M)$^+$ calcd. 478.0296; found 478.0299.

N_3-((2-(4-Chloro-2-methylphenyl)oxazol-5-yl)methyl)-N_3-cyclopropyl-N_1,N_1-dimethyl-1H-1,2,4-triazole-1,3-disulfonamide (8d). White solid (66%). mp 135–137°C. ^{1}H-NMR: δ (ppm) 8.56 (s, 1H), 8.01 (s, 1H), 7.81 (d, 1H), 7.36 (s, 1H), 7.32 (d, 1H), 4.90 (s, 2H), 3.08 (s, 6H), 2.85–2.80 (m, 1H), 2.66 (s, 3H), 1.02–0.98 (m, 2H), 0.91–0.86 (m, 2H). ^{13}C-NMR: δ 164.91, 162.33, 161.47, 146.15, 140.35, 137.57, 131.79, 130.23, 126.60, 120.98, 44.99, 38.86, 31.16, 21.87, 8.06. HRMS (EI): $C_{18}H_{21}ClN_6O_5S_2$ (M)$^+$ calcd. 500.0703; found 500.0706.

Biological evaluation. Antifungal activity was tested on CDM with the living pot assay. The sample with effective concentration causing a 50% control effect (EC_{50}) was determined subsequently. The commercial antifungal agents amisulbrom and cyanosole, produced in China by the Shanghai Nongle Biological Products Co., Ltd., were used as the positive control. Meanwhile, the sterile water was maintained as negative control. When cultivating the cucumber seeds (*Cucumis sativus* L.) to the single-leaf and single-heart stage, this host plant was sprayed with the test solution (compounds dissolved in dimethylformamide to 1% emulsifiable concentrate) by a homemade sprayer. The leaves of these plants were inoculated by sporangium suspension 24 h later cultured in China by Shenyang Sinochem Agrochemicals R&D Co. Ltd. from *P. cubensis* fungus at 2–3 × 10^5 spores/mL using double action 0.3-mm spray gun (0.1 MPa) named PS289 Procon Boy WA (GSI, Tokyo, Japan). After staying in a humid house (21°C, relative humidity = 100%, dark) for 24 h. These infected cucumber plants were shift to a greenhouse (21°C, relative humidity = 95%). Three repeated experiments were carried out, and every compound evaluated the activity by visual check after 5 days. The results were presented in the scope of 0% (blank control) to 100% (total control). The inhibitory property (%) = [(viability of the no control − viability of the total control) viability of the no control] × 100. DPS version 14.5 was used to calculate the EC_{50} values.

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