Received: 3 December 2019 | Revised: 16 January 2020 | Accepted: 2 February 2020

DOI: 10.1002/jhet.3932

WILEY

ARTICLE

Discovery of a new fungicide by screening triazole sulfonylhydrazone derivatives and its downy mildew inhibition in cucumber

Yitao Li | **Jian Lin** | **Wenqiang Yao** | **Guoliang Gao** | **Dewang Jing** | **Yang Wu**

Dongguan HEC Pesticides R&D Co., Ltd., Dongguan 523871, Guangdong, People's Republic of China

Correspondence
Jian Lin, Dongguan HEC Pesticides R&D Co., Ltd., Dongguan 523871, Guangdong, People's Republic of China.
Tel +86-076985315888-5575
Email: linjian@hec.cn

Abstract

Downy mildew is a very important detrimental disease that lead reduced to fruits and vegetables. Due to the continuous growth of drug resistance, finding novel fungicides with dissimilar modes of function from present fungicides for controlling downy mildew are imminent. This work is an extension of our preceding research on the original triazole sulfonamide derivatives lead compound. Triazole sulfonamide as a remarkable nitrogen-containing heterocyclic compound opposed cucumber downy mildew (CDM) develops a quite vital part in the sphere of the study of new farm chemicals. The existing report designs a certain amount of 1,2,4-triazole-1,3-disulfonamide derivatives. Hydrazones have obtained extensive attention in the field of pharmaceutical due to its unique chemical structure and remarkable activity (insecticidal, antibacterial, antifungal and herbicidal). By means of coupling numerous hydrazone with triazole sulfonyl chloride groups, 24 novel derivatives were synthesized. Spectrum analysis of LC-MS, ^{1}H NMR and ^{13}C NMR were used for characterizing these new compounds. Compared with commercial Cyazofamid using bioassays, most of these compounds displayed preferable fungicidal activities. Moreover, compounds **8q** illustrated the greatest CDM resistance (EC_{50} = 7.776 mg/L). Field efficacy trials revealed that compound **8q** fungicidal activity was higher than the purchased agrochemical Cyazofamid and Amisulbrom. Thus, the research declared that **8q** displayed a great potential for the application of fungicide against CDM.

1 | INTRODUCTION

Plant diseases caused by pathogenic fungi seriously affect production and quality of crops in agriculture worldwide.[1–3] As for example, downy mildew is one of the most highly destructive diseases that cause serious damage to fruits, vegetables and other economic crops such as muskmelon, grape, cucumber, spinach, radish and scallion etcetera.[4,5] Among them, cucumber downy mildew (CDM), caused by *Pseudoperonospora cubensis*, is a devastating disease found in cucumber. Due to the rapid onset and seriousness of the disease, over 50% cucumber yield can be seriously decreased if the CDM is not prevented in time.[6] Chemical fungicide applications are, and will remain, the most effective tools for CDM management. However, the frequent use and misuse of fungicides inevitably lead to developing serious resistance.[7–9] It has been reported that the pathogen has

evolved resistance within 2 y of a new fungicide usage.[10] Thus, there is an urgent need for discovering and developing new fungicides with innovative structures and improved activities for the crop protection.

Triazole sulfonamide is a new anti-mitochondrial complex III (MET III) electron transport inhibitor, exhibiting a variety of important pharmacological and agricultural activities for promising lead derivation and novel agrochemical development.[11–18] Their derivatives Amisulbrom have also been developed as commercial fungicides against downy mildew and *Phytophthora infestans*.[19–23] It is worth mentioning that Amisulbrom is comparatively secure for non-target creatures. Moreover, it is not worry about the cross-resistance of most commercial fungicides. Therefore, the above characteristics revealed that triazole sulfonamide could be a potent antifungal lead scaffold for fungicides discovery.[24–30] On the other hand, hydrazones (iNHN=C-1) are known as biologically active fragements, which are widely used as a scaffold in agricultural chemistry.[31–33] It has been reported that derivatives of hydrazones are shown to possess a wide range of biological activities, such as antifungal, antibacterial, insecticidal, herbicidal, antiviral and anticancer activities.[34–39] Heretofore, some pharmaceutical companies have developed dozens of fungicides, insecticides, plant growth regulators such as benquinox, hydramethylnon and diflufenzopyr.[40–42] All of the findings inspired us to design the bioactive structures with these functional motifs as potential agrochemical leads for plant disease control.

In a previous work, we reported an array of triazole sulfonamide derivatives using the intermediate derivatization method (IDM). Bioactivity assay showed that compound **9** (Figure 1) exhibited promising antifungal activities against CDM in greenhouse with an ideal EC_{50} value of 6.91 mg/L. However, compound **9** did not perform well in field efficacy trials.[43] In this study, to continue our previous work, a series of novel structures that combine triazole sulfonamide and hydrazone moieties together were designed and synthesized to produce the corresponding compounds with the anticipation of creating several promising antifungal agents. Antifungal activities were evaluated in vivo against CDM. Fortunately, compound **8q** (Figure 1) was finally identified and showed excellent fungicidal activity toward CDM. Futhermore, compound **8q** was tested as a potent candidate with activity against *P. cubensis* in the cucumber field. This novel structure may represent a new efficient antifungal alternative that can be used to control CDM.

2 | RESULTS AND DISCUSSION

2.1 | Chemistries

Design of the derivatives of target compound was revealed in Scheme 1. The target compound embodys two portions: one is the triazole-disulfonamide and another is the hydrazone part. First, the **1** was regarded as a raw material to obtain **4** by means of three steps. Then the intermediate **2** consist of **1** and benzenesulfonyl chloride. And with that, another part thiol reacts with it and produces symmetrical disulfides **2** when pyridine existed. After that, *N*,*N*-dimethylsulfamoyl chloride reacted with **2** to acquire **3** using K_2CO_3 as the base. Then, oxidation of the disulfide is carried out by blowing chlorine to the aqueous solution containing DCM, and the intermediate **4** was achieved. Through condensation reaction of appropriately substituted aromatic aldehyde or ketone and hydrazine, so the important intermediate **7** was acquired. The triazole sulfonyl chloride and various hydrazone provide the designed product **8** in excellent yield.

2.2 | Antifungal activity

The indoor pot tests displayed that practically more than 50% of the composed ramifications have cracking inhibitory activity counter cucumber downy mildew. Various triazole sulfonamide ramifications comprised benzylamine moiety conveyed obviously activity difference. Several target compounds showed high domination against CDM based on Table 1. Among **8a-8x** have a repression activity of 100% when the concentration is

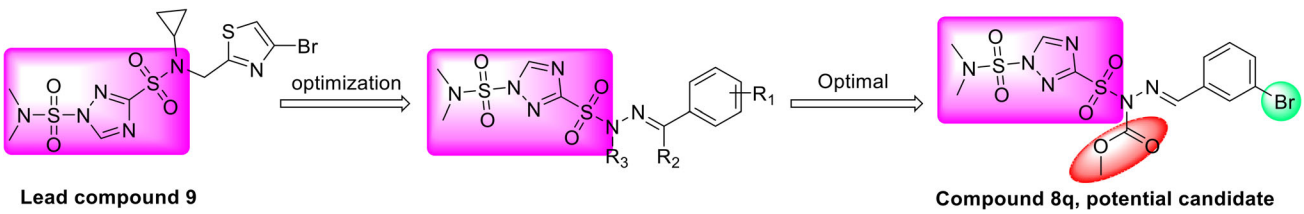
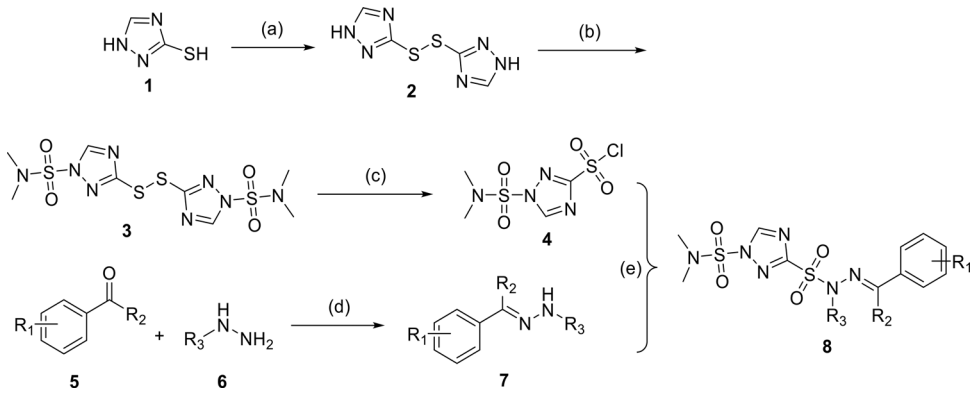


FIGURE 1 A conspectus of the majorization devise of new triazolesulfonamide derivatives and the optimized potential fungicide candidate **8q**



SCHEME 1 Methods for synthesizing target compound. Conditions and reagents: (A) Pyridine, benzenesulfonyl Chloride, CH_2Cl_2, 12 h, 20°C; (B) Dimethylsulfamoyl chloride, 30 min to 15 h, 0 to 20°C; (C) Cl_2, (v:v:v)CH_2Cl_2/CH_3COOH/ H_2O = 1:2:1, 2 h, 0°C; (D) $MgSO_4$, CH_2Cl_2, 20°C,12 h; (E) Tetrahydrofuran, pyridine, 12 h, 20°C

200 mg/L. But also, **8a, 8b, 8p, 8q, 8t, 8u** kept the same entire control at the concentration of 100 mg/L. Particularly it should be noted that **8q** maintained positive dominate even if the concentration is 50 mg/L, at this horizontal, Cyazofamid and Amisulbrom merely existed 50% and 95% dominate. Compound **8q** revealed the same fungicidal activity for CDM than Cyazofamid and Amisulbrom separately if the concentration is 12.5 and 6.25 mg/L.

Initial antibacterial examine against cucumber downy mildew at the various concentration showed that active compounds **8q** had unexceptionable effectiveness. Therefore we opted all these positive ramifications for further appraision. But also, we chose Cyazofamid and Amisulbrom as frontage contrast, and they are the most efficacious commonly used fungicide and they had excellent dominate activity aimed at cucumber downy mildew.

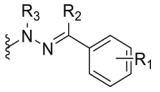
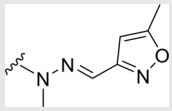
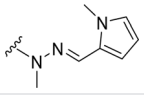
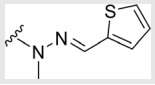
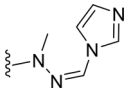
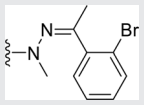
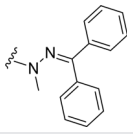
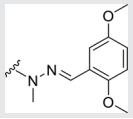
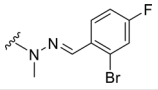
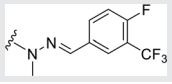
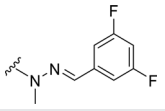
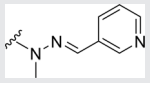
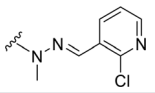
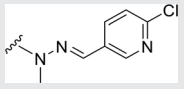
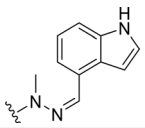
To further analyze the structure-activity relationships, we transformed the activity results to EC_{50} values. As shown in Table 2, we tested some aromatic heterocycle derivatives **8a-8d**, and we found *N*-methylpyrrole **8b** exhibited the good activity. Inserting a -CH_3 group (for compound **8e**) to R_2 dramatically reduced the antifungal ability, revealing that substituent of this position was not recommended in improving biological activity. The fusion of a substituent with greater steric hindrance (for compound **8f**, **8n**, **8o**) decreased bioactivity, suggesting that relatively rigid and hydrophobic aromatic rings are not conducive to the improvement of activity. A similar decreased activity can be observed after replacing the -CH_3 on R_3 group into a relatively rigid aromatic ring (for compound **8u**, **8v**, **8w**, **8x**). The introduction of pyridine rings to R_1 group (for compound **8k**, **8l**, **8m**) showed relatively lower biological activity, which is also demostrated with methyl ester-bearing compounds (for compound **8s**, **8t**). Comparison of the electronic property revealed that the introduction of a strong electron-donating group (4-OCH_3, for compound **8g**) and electron-withdrawing group (3-CF_3, for compound **8i**) on the benzene ring of R_1 group had no significant effect in promoting antifungal activity. Compound **8p** (2-Cl-3,4-F) exhibited high activity, which was better than that of compound **8h** (2-Br-4-F) and **8j** (3-F-5-F), suggesting that halogen type and quantity on the benzene ring of R_1 group could contribute to the antifungal activity against CDM. It can be observed that changing -CH_3 substituent to methyl ester substituent on R_3 group could lead to significant changes in the activity. Among them, 3-bromobenzene-containing compound **8q** exhibited the strongest antifungal activity against CDM with EC_{50} value of 7.776 mg/L, which was even stronger than that of Cyazofamid (EC_{50} = 48.522 mg/L) and Amisulbrom (EC_{50} = 11.309 mg/L). It may become a new lead compound for antifungal research. All results exhibited that the antifungal effect of traget compounds against CDM can be affected by multifarious factors, such as the type of the substituent, the position of substituents, the type of halogen on the benzene ring.

2.3 | Analysis of field efficacy trials

Many cucumber leaves were covered with yellow mould layer in the blank space, following their DI values raised from 4.17 to 19.53. Cucumber leaves treated with synthetic active compounds can be well controlled. DI values are in the range of 2.25 and 6.36. These efficacies of compound **8q** on cucumber downy mildew in cucumber fields are shown in Table 3. Compared with high (6.67 g ai/667 m^2) and low (3.33 g ai/667 m^2) positive control Amisulbrom, the effect of applying **8q** showed better control effect. In order to control cucumber downy mildew in the field, the recommended dosage applications of compound 8q is 6.67 g ai/667 m^2 three times a week.

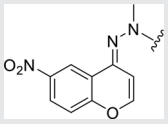
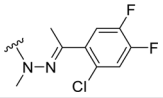
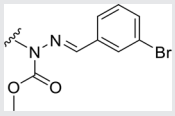
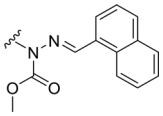
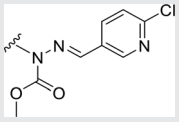
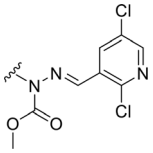
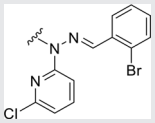
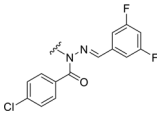
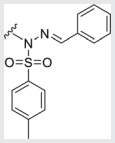
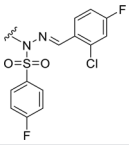
The field efficacy trials further indicated that **8q** may has better therapeutic and protective activity than Amisulbrom (Figure 2). The structural optimization field and devise test of **8q** were yet under exploration, and synthesis of analogs. The outcomes showed that active compound **8q**, displayed the fungicide activity against CDM

TABLE 1 In vivo fungicidal activity of target compounds against cucumber downy at differett concentrations

		Cucumber downy mildew					
		% inhibition (mg/L)					
Examples		200	100	50	25	12.5	6.25
8a		80	75	60	30	0	0
8b		100	100	80	70	30	0
8c		100	90	80	60	10	0
8d		100	90	50	20	0	0
8e		80	10	0	0	0	0
8f		100	20	0	0	0	0
8g		100	70	40	0	0	0
8h		100	100	60	30	20	0
8i		90	60	20	0	0	0
8j		90	80	60	20	0	0
8k		100	20	0	0	0	0
8l		100	60	20	0	0	0
8m		100	30	0	0	0	0
8n		100	20	0	0	0	0

(Continues)

TABLE 1 (Continued)

		Cucumber downy mildew					
		% inhibition (mg/L)					
8o		100	50	30	0	0	0
8p		100	100	80	70	50	30
8q		100	100	100	80	60	50
8r		100	80	70	50	20	0
8s		80	70	50	20	0	0
8t		80	75	60	30	0	0
8u		95	90	60	20	0	0
8v		100	80	0	0	0	0
8w		100	60	20	0	0	0
8x		100	90	80	0	0	0
Amisulbrom		100	100	95	85	45	30
Cyazofamid		100	80	50	20	5	0

was better than commercial fungicides Cyazofamid and Amisulbrom. The expandment of repellency may be postponed through the exploration of novel triazole disulfonamide fungcides, which will also help resist administration. Present outcomes supply sustains the exploration of triazole disulfonamide as a new agricultural chemical.

3 | EXPERIMENTALS

3.1 | Materials and means

All of the commercially available reagents can be used immediately without purification. ^{1}H and ^{13}C NMR characterization data were collected at 300 K on a VARIAN

TABLE 2 Determination of activity of different agents on cucumber downy mildew

Examples	Toxic regression equation	EC_{50} (mg/L)	95% confidence interval (mg/L)
8a	Y = −6.510 + 3.773X	53.159	28.519-110.651
8b	Y = −7.289 + 5.590X	20.134	12.773-30.666
8c	Y = −7.764 + 5.443X	26.688	17.627-39.879
8d	Y = −11.457 + 6.863X	46.708	38.086-57.354
8e	Y = −17.064 + 7.837X	150.476	118.990-203.737
8f	Y = −16.978 + 8.186X	118.556	74.002-221.857
8g	Y = −13.873 + 7.623X	66.059	47.631-92.718
8h	Y = −8.100 + 5.336X	32.954	18.999-56.829
8i	Y = −13.195 + 6.789X	87.845	79.744-97.014
8j	Y = −8.388 + 4.927X	50.413	35.560-72.674
8k	Y = −16.978 + 8.186X	118.556	74.002-221.857
8l	Y = −16.186 + 8.474X	81.313	65.370-101.288
8m	Y = −16.955 + 8.289X	111.062	77.502-169.885
8n	Y = −16.978 + 8.186X	118.556	74.002-221.857
8o	Y = −13.598 + 7.111X	81.698	51.857-134.008
8p	Y = −3.658 + 3.318X	12.660	7.113-18.818
8q	Y = −3.341 + 3.751X	7.776	2.824-12.209
8r	Y = −6.062 + 4.081X	30.571	18.789-48.917
8s	Y = −7.129 + 3.950X	63.797	41.860-104.535
8t	Y = −6.510 + 3.773X	53.159	28.519-110.651
8u	Y = −10.089 + 6.097X	45.149	35.534-57.519
8v	Y = −25.021 + 13.113X	80.926	68.594-93.275
8w	Y = −16.186 + 8.474X	81.313	65.370-101.288
8x	Y = −17.452 + 10.636X	43.747	7.478-127.024
Amisulbrom	Y = −4.861 + 4.614X	11.309	8.242-14.566
Cyazofamid	Y = −9.132 + 5.417X	48.522	39.494-59.850

Mercury-Plus 400 spectrometer (varian Inc., Palo Alto, CA) operating at 400.0 and 100.0 MHz (respectively) with chemical shifts reported in parts per million relative to $CHCl_3$. Several abridgations put to used show that multiplicity as follow, s: singlet, t: triplet, d: doublet, br: broad, m: multiplet.

3.2 | The synthesis of intermediate compound (1)

At the 250 mL double-mouth bottle, 14.32 g (320.0 mmol) of the formic acid was added to 35.0 mL of deionized water, after that pour in 14.32 g (160.0 mmol) of 1-aminothiourea. The temperature was raised to 100°C for 1 h, after that andantely cooled to 25°C. Then further downing to −5°C, and crystal was tardily decrystallized, lastly, then aldehyde was getted through filtrating and drying. After that water (85.0 mL), aldehyde aminethiourea (8.90 g 70.0 mmol) and K_2CO_3 (16.50 g, 150.0 mmol) were mixed in a 150 mL double-mouth bottle. Then the temperature was raised to 110°C at 3.0 h, and subsequently lowered to room tempurature, and then the mixture was mixed at −15°C to tardily decrystallize. Then filtering and dring to get white solid 3.42 g, yield 65%.

3.3 | The synthesis of intermediate compound (2)

2.95 g of (40.0 mmol) pyridine was added to 100 mL DCM with 4.12 g (40.0 mmol) of **(1)**. And the solution lower the temperature to zero, and so that by tardily putting 3.42 g (20.0 mmol) in benzenesulfonyl chloride at 2 h. And the mixture was reacted at room tempurature for 12.0 h. DCM was concentrated under decreased pressure and the dregs was washed with

TABLE 3 Efficacy of Compound **8q** against cucumber downy mildew in field

Compd	Rate (g ai/667 m^2)	BaseDi[a]	afterDI[b]	Field efficacy (%)	DD[c] 5%	DD[c] 1%
8q	3.33	4.08	4.98	74.61	bcd	cde
	6.67	2.98	2.25	84.10	aA	aA
Amisulbrom	3.33	4.58	6.36	70.91	cde	def
	6.67	3.82	3.81	79.35	AB	AB
CK	ND[d]	4.17	19.53	ND	ND	ND

[a]Base disease index.
[b]Disease index after used compound.
[c]Significant difference a, b, c, d, and e, distinct difference at 95% of confidence limits. A, B, distinct difference at 99% of confidence limits.
[d]ND = not detected.

FIGURE 2 Comparison of field efficacy trials

water (40 mL) and EA (20 mL) for 2 h, after the precipitate filtering, and washing by water (35 mL) and EA (30 mL) according to priority. Then the accumulation was dried at 60°C to acquire 3.50 g (88%) of the aim product.[44]

3.4 | The synthesis of intermediate compound (3)

4.52 g (34.0 mmol) of K_2CO_3 and 3.00 g (15.0 mmol) of **(2)** were mixed in 100 mL of DMF, then the temperature cooling to 6°C. Added 2.16 g (12.0 mmol) of *N*,*N*-dimethylsulfamoyl chloride to the reaction mixture slowly and temperature was dominated between 20 and 25°C over 3 h. Then, 20 mL of DCM add to the reaction system, next in importance adding 60.0 mL of 15% HCl to the system at the temperature from 15 to 30°C. After that 6.44 g of target product was getted from the cumulative organic phase get 3.20 g (78%).[45]

3.5 | The synthesis of intermediate compound (4)

50 mL of DCM solution embodying 8.05 g (19.0 mmol) of the product **3**, after adding 60 mL of water to the system and then cooled to 0°C. Then, the chlorine was bubbling, and the temperature and the solution was dominated from 15 to 25°C over 2.0 h, after that adding 15 mL of EA. Washing with 25 mL of H_2O to organic layer when the reaction was accomplished. After that 7.25 g of target product was acquired in 88% yield.[46]

3.6 | The synthesis of intermediate compound (7)

Adding aromatic ketone or aromatic aldehyde (14.2 mmol), DCM (25 mL) and $MgSO_4$ (3.40 g, 26.0 mmol) to a 150 mL three-neck bottle, and the reaction system was reacted at room temperature over 10.0 h, after that adding 25 mL of EA. Separating the organic layer and washing with 25 mL

of H_2O after the reaction was accomplished. The residue with purification by silica gel column chromatography as eluent the product **7** was obtained.[47]

3.7 | The synthesis of active compound (8)

7 (3.0 mmol), pyridine (0.34 g, 3.5 mmol) and THF (15 mL) were blended to a 100 mL double-mouth bottle, stirred at 0°C. The THF (15.0 mL) and compound of **4** (0.65 g, 3.5 mmol) were added tardily over 15 min, and the reaction system is stirred at room temperature over 3.0 h. The residue with purification by silica gel column chromatography as eluent the product **8** was acquired.[48,49]

(E)-N,N-dimethyl-3-((1-methyl-2-((5-methylisoxazol-3-yl)-methylene)hydrazinyl)sulfonyl)-1H-1,2,4-triazole-1-sulfonamide (**8a**). White solid (58%). Melting points: 84-88°C. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.76 (s, 1H), 6.35 (s, 1H), 3.56 (s, 3H), 3.04 (s, 6H), 2.39 (s, 3H). ^{13}C NMR: δ 171.02, 160.72, 160.27, 148.87, 135.70, 99.24, 38.76, 34.78, 12.11. HRMS (EI): $C_{10}H_{15}N_7O_5S_2$ $(M)^+$ calcd. 378.0576; found 378.0572.

(E)-N,N-dimethyl-3-((1-methyl-2-((1-methyl-1H-pyrrol-2-yl)methylene)hydrazinyl)sulfonyl)-1H-1,2,4-triazole-1-sulfonamide (**8b**). White solid (45%). Melting points: 96-98°C. ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1H), 7.82 (s, 1H), 6.72 (s, 1H), 6.47 (dd, J = 3.6, 1.4 Hz, 1H), 6.15-6.10 (m, 1H), 3.78 (s, 3H), 3.43 (s, 3H), 3.03 (s, 6H). ^{13}C NMR: δ 162.47, 155.78, 148.45, 130.47, 127.65, 117.45, 62.58, 53.18, 38.72, 14.56. HRMS (EI): $C_{11}H_{17}N_7O_4S_2$ $(M)^+$ calcd. 376.0856; found 376.0859.

(E)-N,N-dimethyl-3-((1-methyl-2-(thiophen-2-ylmethylene)-hydrazinyl)sulfonyl)-1H-1,2,4-triazole-1-sulfonamide (**8c**). White solid (36%). Melting points: 93-96°C. ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.03 (s, 1H), 7.36 (d, J = 5.0 Hz, 1H), 7.31-7.26 (m, 1H), 7.04 (dd, J = 4.9, 3.8 Hz, 1H), 3.52 (s, 3H), 3.00 (s, 6H). ^{13}C NMR: δ 160.85, 148.75, 141.99, 138.73, 131.94, 129.66, 128.32, 38.74, 35.33. HRMS (EI): $C_{10}H_{14}N_6O_4S_3$ $(M)^+$ calcd. 379.0239; found 379.0236.

(Z)-3-((2-((1H-imidazol-1-yl)methylene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8d**). White solid (41%). Melting points: 103-107°C. ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 1H), 7.74 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.44 (s, 1H), 3.32 (m, 3H), 2.95 (s, 6H). ^{13}C NMR: δ 162.47, 155.78, 148.45, 130.47, 127.65, 62.58, 38.72, 14.56. HRMS (EI): $C_9H_{14}N_8O_4S_2$ $(M)^+$ calcd. 363.0579; found 363.0577.

(Z)-3-((2-(1-(2-bromophenyl)ethylidene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8e**). White solid (52%). Melting points: 113-117°C. ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 1H), 7.74 (s, 1H), 7.64 (s, 1H), 7.62 (dd, J = 7.1, 2.1 Hz, 2H), 3.32 (m, 3H), 3.53 (s, 3H), 2.95 (s, 6H). ^{13}C NMR: δ 177.39, 159.33, 148.60, 139.46, 133.38, 131.66, 130.05, 128.24, 120.06, 38.88, 38.73, 21.02. HRMS (EI): $C_{13}H_{17}BrN_6O_4S_2$ $(M)^+$ calcd. 464.9936; found 464.9937.

3-((2-(diphenylmethylene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8f**). White solid (55%). Melting points: 123-125°C. ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.61 (s, 1H), 8.10 (s, 1H), 7.47 (ddd, J = 12.3, 8.7, 5.0 Hz, 6H), 7.32 (d, J = 7.5 Hz, 2H), 3.03 (s, 6H), 2.92 (s, 3H). ^{13}C NMR: δ 171.61, 159.63, 154.04, 148.71, 130.32, 129.23, 128.78, 38.87, 38.66. HRMS (EI): $C_{18}H_{20}N_6O_4S_2$ $(M)^+$ calcd. 449.0987; found 449.0984.

(E)-3-((2-(2,5-dimethoxybenzylidene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8g**). White solid (62%). Melting points: 103-106°C. ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.12 (s, 1H), 7.34 (d, J = 3.1 Hz, 1H), 6.91 (dd, J = 9.0, 3.2 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.55 (s, 3H), 2.99 (s, 6H). ^{13}C NMR: δ 163.83, 162.19, 160.72, 148.88, 143.12, 137.96, 110.20, 106.10, 105.75, 38.70, 34.84. HRMS (EI): $C_{14}H_{20}N_6O_6S_2$ $(M)^+$ calcd. 433.0886; found 433.0884.

(E)-3-((2-(2-bromo-4-fluorobenzylidene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8h**). White solid (53%). Melting points: 115-119°C. ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.00 (s, 1H), 7.94 (dd, J = 8.8, 6.2 Hz, 1H), 7.34-7.29 (m, 1H), 7.09-7.00 (m, 1H), 3.59 (s, 3H), 3.04 (s, 6H). ^{13}C NMR: δ 164.38, 161.87, 160.75, 148.84, 142.46, 129.69 (d, *J* = 9.7 Hz), 124.23 (d, *J* = 10.2 Hz), 120.52, 116.35, 38.74, 34.79. HRMS (EI): $C_{12}H_{14}BrFN_6O_4S_2$ $(M)^+$ calcd. 468.9686; found 468.9684.

(E)-3-((2-(4-fluoro-3-(trifluoromethyl)benzylidene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8i**). White solid (43%). Melting points: 109-112°C. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.87 (t, J = 7.4 Hz, 2H), 7.73 (s, 1H), 7.23 (t, J = 9.1 Hz, 1H), 3.56 (s, 3H), 3.04 (s, 6H). ^{13}C NMR: δ 160.77, 148.85, 143.38, 133.74 (d, *J* = 9.1 Hz), 131.48 (d, *J* = 3.4 Hz), 126.22 (d, *J* = 4.8 Hz), 123.69, 118.64, 60.20, 38.69, 34.33. HRMS (EI): $C_{13}H_{14}F_4N_6O_4S_2$ $(M)^+$ calcd. 459.0454; found 459.0452.

(E)-3-((2-(3,5-difluorobenzylidene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8j**). White solid (36%). Melting points: 101-105°C. ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 7.62 (s, 1H), 7.17 (d, J = 5.9 Hz, 2H), 6.82 (t, J = 7.6 Hz, 1H), 3.56 (s, 3H), 3.05 (s, 6H). ^{13}C NMR: δ 163.83 (d, *J* = 13.3 Hz), 162.19 (d, *J* = 13.3 Hz), 160.72, 143.12, 137.96 (t, *J* = 9.9 Hz), 106.10, 105.75, 38.70, 34.84. HRMS (EI): $C_{12}H_{14}F_2N_6O_4S_2$ $(M)^+$ calcd. 409.0486; found 409.0488.

(E)-N,N-dimethyl-3-((1-methyl-2-(pyridin-3-ylmethylene)hydrazinyl)sulfonyl)-1H-1,2,4-triazole-1-sulfonamide (**8k**). White solid (48%). Melting points:

115-119°C. ^{1}H NMR ($CDCl_3$) δ 8.75 (d, J = 1.3 Hz, 1H), 8.62 (s, 1H), 8.58 (dd, J = 4.7, 1.3 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.34-7.27 (m, 1H), 3.57 (s, 3H), 3.01 (s, 6H). ^{13}C NMR: δ 160.82, 154.07, 150.36, 148.86, 146.72, 142.84, 135.08, 124.93, 38.75, 34.91. HRMS (EI): $C_{11}H_{15}N_7O_4S_2$ $(M)^+$ calcd. 374.0627; found 374.0625.

(E)-3-((2-((2-chloropyridin-3-yl)methylene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8l**). White solid (42%). Melting points: 120-125°C. ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.40 (dd, J = 4.6, 1.8 Hz, 1H), 8.27 (dd, J = 7.8, 1.7 Hz, 1H), 7.98 (s, 1H), 7.28 (t, J = 6.2 Hz, 1H), 3.62 (s, 3H), 3.05 (s, 6H). ^{13}C NMR: δ 160.69, 151.52, 149.78, 148.89, 139.79, 136.59, 128.49, 38.76, 34.78. HRMS (EI): $C_{11}H_{14}ClN_7O_4S_2$ $(M)^+$ calcd. 408.0237; found 408.0235.

(E)-3-((2-((6-chloropyridin-3-yl)methylene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8m**). White solid (57%). Melting points: 124-128°C. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.52 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.4, 2.3 Hz, 1H), 7.71 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 3.58 (s, 3H), 3.05 (s, 6H). ^{13}C NMR: δ 160.76, 151.74, 149.46, 148.82, 141.84, 137.04, 129.73, 125.22, 38.73, 34.77. HRMS (EI): $C_{11}H_{14}ClN_7O_4S_2$ $(M)^+$ calcd. 408.0237; found 408.0235.

(Z)-3-((2-((1H-indol-4-yl)methylene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8n**). White solid (42%). Melting points: 114-118°C. ^{1}H NMR ($CDCl_3$) δ 11.21 (s, 1H), 9.37 (s, 1H), 8.36 (d, J = 7.3 Hz, 1H), 8.24 (s, 2H), 7.91 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H),3.72 (s, 3H), 2.81 (s, 6H). ^{13}C NMR: δ 163.97, 162.33, 160.89, 148.78, 144.27, 140.72, 129.99, 128.87, 117.97, 113.67, 34.82. HRMS (EI): $C_{14}H_{17}N_7O_4S_2$ $(M)^+$ calcd. 412.0783; found 412.0784.

(Z)-N,N-dimethyl-3-((1-methyl-2-(6-nitro-4H-chromen-4-ylidene)hydrazinyl)sulfonyl)-1H-1,2,4-triazole-1-sulfonamide (**8o**). White solid (46%). Melting points: 132-137°C. ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 1H), 7.74 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.62 (dd, *J* = 7.1, 2.1 Hz, 2H), 3.32 (m, 3H), 2.95 (s, 6H). ^{13}C NMR: δ 169.92, 161.43, 148.35, 141.11, 132.66, 130.47, 127.65, 127.17, 61.30, 39.06, 38.52, 36.87. HRMS (EI): $C_{14}H_{15}N_7O_7S_2$ $(M)^+$ calcd. 458.0474; found 458.0477.

(E)-3-((2-(1-(2-chloro-4,5-difluorophenyl)ethylidene)-1-methylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8p**). White solid (53%). Melting points: 115-118°C. ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1H), 7.34 (dd, J = 9.9, 8.4 Hz, 1H), 7.26 (dd, J = 10.3, 7.7 Hz, 1H), 3.23 (s, 3H), 3.07 (s, 6H), 2.59 (s, 3H). ^{13}C NMR: δ 174.45, 164.26159.26, 151.07 (d, *J* = 13.4 Hz), 149.44 (t, *J* = 13.3 Hz), 148.62, 147.84 (d, *J* = 12.5 Hz), 126.90 (dd, *J* = 8.9, 3.2 Hz), 120.02 (d, *J* = 20.8 Hz), 119.08 (d, *J* = 19.9 Hz), 38.72, 20.69. HRMS (EI): $C_{13}H_{15}ClF_2N_6O_4S_2$ $(M)^+$ calcd. 457.0253; found 457.0256.

Methyl(E)-2-((6-chloropyridin-2-yl)methylene)-1-((1-(N,N-dimethylsulfamoyl)-1H-1,2,4-triazol-3-yl)sulfonyl)hydrazine-1-carboxylate (**8q**). White solid (64%). Melting points: 132-136°C. ^{1}H NMR ($CDCl_3$) δ 13.79 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.58 (dd, J = 4.7, 1.4 Hz, 1H), 7.85 (dd, J = 8.2, 1.5 Hz, 1H), 7.32 (dd, J = 8.2, 4.7 Hz, 1H), 3.91 (s, 3H), 2.99 (s, 6H). ^{13}C NMR: δ160.76, 151.74, 149.46, 148.82, 141.84, 137.04, 129.73, 125.22, 108.34, 38.73, 34.77. HRMS (EI): $C_{12}H_{14}ClN_7O_6S_2$ $(M)^+$ calcd. 452.0136; found 452.0132.

Methyl(E)-1-((1-(N,N-dimethylsulfamoyl)-1H-1,2,4-triazol-3-yl)sulfonyl)-2-(naphthalen-1-ylmethylene) hydrazine-1-carboxylate (**8r**). White solid (57%). Melting points: 138-142°C. ^{1}H NMR ($CDCl_3$) δ 9.97 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.47 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 7.1 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.56 (dt, J = 20.7, 7.7 Hz, 2H), 2.99 (s, 6H), 2.41 (s, 3H). ^{13}C NMR: δ162.13, 154.51, 144.20, 133.99, 130.51, 130.11, 129.21, 127.56, 126.65, 125.98, 124.47, 116.98, 112.47, 52.49, 38.72, 14.56. HRMS (EI): $C_{17}H_{18}N_6O_6S_2$ $(M)^+$ calcd. 467.0729; found 467.0725.

Methyl(E)-2-((6-chloropyridin-2-yl)methylene)-1-((1-(N,N-dimethylsulfamoyl)-1H-1,2,4-triazol-3-yl)sulfonyl)hydrazine-1-carboxylate (**8s**). White solid (47%). Melting points: 128-133°C. ^{1}H NMR ($CDCl_3$) δ 13.79 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.58 (dd, J = 4.7, 1.4 Hz, 1H), 7.85 (dd, J = 8.2, 1.5 Hz, 1H), 7.32 (dd, J = 8.2, 4.7 Hz, 1H), 3.91 (s, 3H), 2.99 (s, 6H). ^{13}C NMR: δ160.76, 151.74, 149.46, 148.82, 141.84, 137.04, 129.73, 125.22, 108.34, 38.73, 34.77. HRMS (EI): $C_{12}H_{14}ClN_7O_6S_2$ $(M)^+$ calcd. 452.0136; found 452.0138.

Methyl(E)-2-((2,5-dichloropyridin-3-yl)methylene)-1-((1-(N,N-dimethylsulfamoyl)-1H-1,2,4-triazol-3-yl)sulfonyl) hydrazine-1-carboxylate (**8t**). White solid (35%). Melting points: 136-139°C. ^{1}H NMR ($CDCl_3$) δ 13.79 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.58 (dd, J = 4.7, 1.4 Hz, 1H), 7.32 (dd, J = 8.2, 4.7 Hz, 1H), 3.91 (s, 3H), 2.99 (s, 6H). ^{13}C NMR: δ163.76, 152.74, 145.46, 141.82, 137.04, 129.73, 123.22, 105.34, 39.73, 35.77. HRMS (EI): $C_{12}H_{13}C_{l2}N_7O_6S_2$ $(M)^+$ calcd. 485.9746; found 485.9748.

(E)-3-((2-(2-bromobenzylidene)-1-(6-chloropyridin-2-yl) hydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8u**). White solid (41%). Melting points: 141-143°C. ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 8.00 (s, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.30-7.23 (m, 1H), 2.98 (s, 6H). ^{13}C NMR: δ162.13, 154.51, 144.20, 133.99, 130.51, 130.11, 129.21, 127.56, 126.65, 125.98, 124.47, 116.98, 112.47, 52.49, 38.72. HRMS (EI): $C_{16}H_{15}BrClN_7O_4S_2$ $(M)^+$ calcd. 547.9499; found 547.9497.

(E)-3-((1-(4-chlorobenzoyl)-2-(3,5-difluorobenzylidene) hydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8v**). White solid (52%). Melting points: 134-137°C. ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 8.75 (s, 1H), 7.85 (t, J = 8.2 Hz, 3H), 7.43 (d, J = 8.5 Hz, 2H), 7.13 (dd, J = 8.3, 2.3 Hz, 1H), 7.06-6.98 (m, 1H), 3.08 (s, 6H). ^{13}C NMR: δ 164.04 (d, *J* = 13.5 Hz), 163.61, 162.40 (d, *J* = 13.0 Hz), 156.20, 149.84, 145.45, 133.95, 130.30, 129.17, 120.41, 114.31, 106.46, 34.78. HRMS (EI): $C_{18}H_{15}ClF_2N_6O_5S_2$ $(M)^+$ calcd. 533.0202; found 533.0204.

(E)-3-((2-benzylidene-1-tosylhydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8w**). White solid (45%). Melting points: 123-127°C. ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.60 (s, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 6.9 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 3.05 (s, 6H), 2.48 (s, 3H). ^{13}C NMR: δ 173.28, 160.76, 148.65, 146.84, 142.54, 133.95, 132.14, 130.32, 129.70, 129.32, 38.72, 34.77, 21.70. HRMS (EI): $C_{18}H_{20}N_6O_6S_3$ $(M)^+$ calcd. 513.0606; found 513.0604.

(E)-3-((2-(2-chloro-4-fluorobenzylidene)-1-((4-fluorophenyl)sulfonyl)hydrazinyl)sulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide (**8x**). White solid (49%). Melting points: 129-132°C. ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1H), 8.64 (s, 1H), 8.06 (ddd, J = 15.0, 8.8, 5.6 Hz, 3H), 7.25 (ddd, J = 10.8, 8.3, 3.4 Hz, 4H), 7.13-7.05 (m, 1H), 3.08 (s, 6H). ^{13}C NMR: δ 173.28, δ 164.04 (d, *J* = 13.5 Hz), 163.61, 162.40 (d, *J* = 13.0 Hz), 153.24, 151.66, 146.84, 133.95(d, *J* = 11.5 Hz), 132.14, 130.32, 129.70, 129.32, 38.72, 34.77. HRMS (EI): $C_{17}H_{15}ClF_2N_6O_6S_3$ $(M)^+$ calcd. 568.9872; found 568.9874.

3.8 | Biological evaluation

Antifungal activity of cucumber downy mildew (CDM) was tested by in vivo experiment. The test compounds with a valid density resulting in a 50% Control effect (EC_{50}) was firmed afterwards. The positive control Cyazofamid and Amisulbromand were purchased from Shanghai Sinopharm Chemical reagent Co. Ltd. Meanwhile, the pure water was preserved as no control of fungus. Breeding the seeds (Cucumber Cucumissativus L.) to the one-heart and one-leaf section, the seedlings were spouted with the experiment mixture (test chemicals dissolved in DMF to 1% emulsifiable concentrate [EC]) through a home-made sprayeron. The seedlings leaves were 24 h later cultivated and embeded by Sporangium suspension in China by Shenyang Sinochem Agrochemicals R&D Co. Ltd. from *Pseudoperonosporacubensis* fungus at 2-3 × 10^5 spores per milliliter applying double action 0.3 mm spray gun (0.1 Mpa) called PS289 Procon Boy WA (GSI, Tokyo, Japan). Remaining in a humidity house (24 ± 1°C, RH = 100%, dark) for 24 h later, cucumber seedlings were migrated to a greenhouse (18-30°C, RH = 95%) after infection. Three duplicated experiments were advanced and every composite was assessed the activity via visual inspection after 5 days. The consequents were expressed e range from 0% (no control) to 100% (complete control). The inhibitory rate (%) = [(viability of the no control-viability of the total control)/viability of the no control] × 100. DPS version 15.0 was made use of calculating the EC_{50} values.

3.9 | Field efficacy trials of activity compound (8q)

According to the in vivo cucumber downy mildew inhibitory activity, the field test of cucumber further verified the efficacy of compound **8q** to valid its fungicidal activity. The activity compound **8q** was prepared as 10% emulsifiable concentrate and diluted with water to 3.33 g ai/667 m^2 and 6.67 g ai/667 m^2 for application. In the early onset of cucumber downy mildew, the activity compound **8q** was uniformly sprayed on the cucumbers. Amisulbrom (10%, emulsifiable concentrate) was used as the positive control, and an equal amount of water was used as the blank. Depending on the disease level of the investigated leaves, the disease indexes (DI) and control efficacies were calculated. The control efficacy (CE) was calculated by the formula CE (%) = $[1 - CK_0 \times pt_1/(CK_1 \times pt_0)] \times 100$, and DI was evaluated by the formula $DI = \Sigma(A \times B) \times 100/(C \times 9)$, where CK_0 (control check) shows that the disease index of the blank before the pesticide application, and CK_1 shows the DI after the application of pesticide, *A* is the number of diseased leaves, *B* is the corresponding disease level, *C* is the total number of leaves investigated, pt_1 show that the disease index of the pesticide-treatment group after compound application, and pt_0 is the disease index of the pesticide treatment group before compound application. The statistical analysis of control effects was established via variance analysis and reverse arcsine transformation. In addition, the significant difference was compared by LRS method between each treatment.[50]

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical support of the research institute of Shenzhen Dongyangguang Industry Co., Ltd.

ORCID

Jian Lin https://orcid.org/0000-0003-0789-5567
Dewang Jing https://orcid.org/0000-0001-5359-0049

REFERENCES

[1] M. C. Fisher, N. J. Hawkins, D. Sanglard, S. Gurr, *J. Sci.* **2018**, *360*, 739.
[2] Y. Y. Wu, W. B. Shao, J. J. Zhu, Z. Q. Long, L. W. Liu, P. Y. Wang, Z. Li, S. Yang, *J. Agric. Food Chem.* **2019**, *67*, 13892.
[3] G. Z. Yang, J. K. Zhu, X. D. Yin, Y. F. Yan, Y. L. Wang, X. F. Shang, Y. Q. Liu, Z. M. Zhao, J. W. Peng, H. Liu, *J. Agric. Food Chem.* **2019**, *67*, 11340.
[4] A. Y. Guan, M. A. Wang, J. L. Yang, L. Z. Wang, Y. Xie, J. Lan, C. L. Liu, *J. Agric. Food Chem.* **2017**, *65*, 10829.
[5] J. Gabaston, E. Cantos-Villar, B. Biais, P. Waffo-Teguo, E. Renouf, M. Corio-Costet, T. Richard, J. Mérillon, *J. Agric. Food Chem.* **2017**, *65*, 2711.
[6] W. Z. Wang, P. P. Teng, F. M. Liu, T. T. Fan, Q. R. Peng, Z. Y. Wang, T. Y. Hou, *J. Agric. Food Chem.* **2019**, *67*, 12904.
[7] X. L. Zhu, M. M. Zhang, J. J. Liu, J. M. Ge, G. F. Yang, *J. Agric. Food Chem.* **2015**, *63*, 3377.
[8] M. A. Ghannoum, L. B. Rice, *Clin. Microbiol. Rev.* **1999**, *12*, 501.
[9] P. F. Zhang, A. Y. Guan, X. L. Xia, X. F. Sun, S. Y. Wei, J. L. Yang, J. F. Wang, Z. N. Li, J. Lan, C. L. Liu, *J. Agric. Food Chem.* **2019**, *67*, 11893.
[10] W. l. Jian, D. H. He, P. G. Xi, X. W. Li, *J. Agric. Food Chem.* **2015**, *63*, 9963.
[11] A. R. Crofts, *Annu. Rev. Physiol.* **2004**, *66*, 689.
[12] H. Kim, D. Xia, C. A. Yu, J. Z. Xia, A. M. Kachurin, L. Zhang, L. Yu, J. Deisenhofer, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 8026.
[13] C. Hunte, S. Solmaz, H. Palsdottir, T. Wenz, *Results Probl. Cell Differ.* **2008**, *45*, 253.
[14] E. A. Berry, M. Guergova-Kuras, L. S. Huang, A. R. Croft, *Annu. Rev. Biochem.* **2003**, *69*, 1005.
[15] Y. Pan, D. Gao, C. G. Zhan, *J. Am. Chem. Soc.* **2008**, *130*, 5140.
[16] R. Horsefield, V. Yankovskaya, G. Sexton, W. Whittingham, K. Shiomi, S. Omura, B. Byrne, G. Cecchini, S. Iwata, *J. Biol. Chem.* **2006**, *281*, 11357.
[17] G. F. Hao, F. Wang, H. Li, X. L. Zhu, W. C. Yang, L. S. Huang, J. W. Wu, E. A. Berry, G. F. Yang, *J. Am. Chem. Soc.* **2012**, *134*, 11168.
[18] Y. M. Xiao, L. Esser, F. Zhou, C. Li, Y. H. Zhou, C. A. Yu, Z. H. Qin, D. Xia, *Plos One* **2014**, *9*, 93765.
[19] F. Wang, H. Li, L. Wang, W. C. Yang, J. W. Wu, G. F. Yang, *Bioorg. Med. Chem.* **2011**, *19*, 4608.
[20] E. Berry, L. Huang, *Biochim. Biophys. Acta* **2011**, *1807*, 1349.
[21] L. S. Huang, J. T. Shen, A. C. Wang, E. A. Berry, *Biochim. Biophys. Acta* **2006**, *1757*, 1073.
[22] P. Mitchell, *J. Theor. Biol.* **1976**, *62*, 267.
[23] E. A. Berry, L. S. Huang, D. W. Lee, F. Daldal, K. Nagai, N. Minagawa, *Biochim. Biophys. Acta* **2010**, *1797*, 360.
[24] W. C. Yang, H. Li, F. Wang, X. L. Zhu, G. F. Yang, *ChemBioChem* **2012**, *13*, 1542.
[25] E. Maklashina, G. Cecchini, *Biochim. Biophys. Acta* **2010**, *1797*, 1877.
[26] M. Ueki, K. Machida, M. Taniguchi, *Curr. Opin. Anti-Infect. Invest. Drugs* **2000**, *2*, 387.
[27] D. W. Bartett, J. M. Clough, C. R. A. Godfrey, J. R. Godwin, A. A. Hall, S. P. Heaney, *Maund. S. J. Pestic Outlook* **2011**, *12*, 143.
[28] Imamura, K.; Mitomo, K.; Yamada, N.; Yamamoto, K.; Teraoka, T.; Sakanaka, O.; Kurihara, H.; Taniguchi M. *PCT International Application* WO2000026191 2000.
[29] Roman, F. N.; Vors, J. P.; Villier, A.; Lachaise, H.; Mousques, A.; Hartmann, B.; Hutin, P.; Molina, J. L.; Muller, B. *PCT International Application* WO2001049666 2001.
[30] Bacque, E.; Barriere, J. C.; Vors, J. P.; Nieto, R. F.; Villier, A. *PCT International Application* WO2001049667 2001.
[31] V. K. Pandey, A. Dwivedi, O. P. Pandey, S. K. Sengupta, *J. Agric. Food Chem.* **2008**, *56*, 10779.
[32] N. Aggarwal, R. Kumar, C. Srivastva, P. Dureja, J. M. Khurana, *J. Agric. Food Chem.* **2010**, *58*, 3056.
[33] M. Zhang, Z. C. Dai, S. S. Qian, J. Y. Liu, Y. Xiao, A. M. Lu, H. L. Zhu, J. X. Wang, Y. H. Ye, *J. Agric. Food Chem.* **2014**, *62*, 9637.
[34] M. E. Ahmed, B. A. Abdel, M. T. Ghattas, *Farmaco (Lausanne)* **1999**, *54*, 56.
[35] H. M. Tawfeeq, R. F. Muslim, O. H. Abid, M. N. Owaid, *Acta Chim. Slov.* **2019**, *66*, 552.
[36] M. A. Salama, A. L. G. Saad, *Delta J. Sci.* **1991**, *15*, 53.
[37] Scola, D.A. *US patent application US3362994 A 19680109*.
[38] N. V. Galaiko, I. A. Tolmacheva, V. V. Grishko, L. V. Volkova, E. N. Prevozchikova, S. A. Pestereva, *Bioorg Khim* **2010**, *36*, 556.
[39] X. Chen, L. Guo, Q. Ma, W. Chen, W. Fan, J. Zhang, *Molecules* **2019**, *24*, 2950.
[40] J. E. Sheridan, V. Vachrabhorn, *NZ J Agric. Res.* **1968**, *11*, 812.
[41] N. M. Mallipudi, S. J. Stout, A. H. Lee, E. J. Orloski, *J. Agric. Food Chem.* **1986**, *34*, 1050.
[42] Chollet, R.; Bozeman, L.L, *European Patent Application* EP 795269 1997 A1.
[43] Y. T. Li, W. Q. Yao, J. Lin, F. L. Li, Y. Wu, J. X. Xu, *J. Heterocyclic Chem.* **2019**, *56*, 2170.
[44] Hegde, S. G.; Mahoney, M. D. *US Patent Application* US6461997 2002 B1.
[45] Fukuda, K.; Kondo, Y.; Makabe, T.; Tanaka, N.; Utsunomiya, T. Sakurai Y *European Patent Application* EP 1829872 2007 A1.
[46] Adnan, M. M. M.; Robert, C. A.; Ramesh, G. S.; Hari, A.; Avor, K.; Qabaja, G.; Guo, X. C.; Gupta, S.; Jones, D. R.; Chen, X. *PCT International Application* WO2003075921 2003 A2.
[47] J. D. Christopher, T. M. Williams, K. Hamilton, T. J. O'Neill, E. Rands, K. S. Koblan, N. E. Kohl, J. B. Gibbs, S. L. Graham, G. D. Hartman, A. I. Oliff, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1345.
[48] S. K. Khim, J. Bauman, J. Evans, B. Freeman, B. King, T. Kirkland, M. Kochanny, D. Lentz, A. Liang, L. Mendoza, G. Phillips, J. L. Tseng, R. G. Wei, H. Ye, L. Yu, J. Parkinson, W. Guilford, *J. Bioorg. Med. Chem. Lett.* **2008**, *18*, 3895.
[49] T. KaTo, I. Okamoto, A. Tanatani, T. Hatano, M. Uchiyama, H. Kagechika, H. Masu, K. Katagiri, M. Tominaga, K. Yamaguchi, I. Azumaya, *Org. Lett.* **2006**, *8*, 5017.
[50] L. Chen, Y. J. Zhu, Z. J. Fan, X. F. Guo, Z. M. Zhang, J. H. Xu, Y. Q. Song, M. Y. Yurievich, N. P. Belskaya, V. A. Bakulev, *J. Agric. Food Chem.* **2017**, *65*, 745.

How to cite this article: Li Y, Lin J, Yao W, Gao G, Jing D, Wu Y. Discovery of a new fungicide by screening triazole sulfonylhydrazone derivatives and its downy mildew inhibition in cucumber. *J Heterocyclic Chem*. 2020;1–11. https://doi.org/10.1002/jhet.3932