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Study on a new type of high efficient amide compound fungicides against soybean rust

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ABSTRACT

Amide compounds have received considerable interest in agricultural chemistry due to a novel action mode, extremely high activity against a broad spectrum of soybean rust, low acute toxicity to mammals, and environmentally benign characteristics. A series amide compounds were synthesized and characterized by ^{1}H NMR and ^{13}C NMR, which were evaluated against plant diseases caused by *Phakopsora Pachyrhizi*. The results show that when the concentration of the amide compound was over 10 ppm, the fungicidal activities on soybean rust were more than 90%. Especially, the fungicide 11 exhibits excellent activity at a low concentration, which provides some hints for further investigation on structure modification. Those amide compounds would play an important role in the control of agriculture and forestry, especially the pathogen of soybean rust in the foreseeable future.

Introduction

Soybean rust is caused by *Phakopsora Pachyrhizi* fungus, which may lead to the loss of 10% to 15% of soybean production [1]. Seriously, the loss may sharply decrease to 50% in rainy years. The disease was first found in Africa in the mid-1990s. The pathogen was first discovered in Japan in 1902 and then throughout tropical and subtropical Asia and Oceania in the early 20th century [1]. It then explosively expanded to Paraguay and western Parana, Brazil, and throughout South America within three years [2,3]. In 2004, soybean rust also spread in the continental United States [4].

Claudia Godoy, the Embrapa scientist, said that soybean rust pathogens were becoming less sensitive to different fungicides. The activities of some pesticides have reduced to 20% from 90%. In the worst case, farmers have to intensify spraying to ten times in order to control the disease. In Brazil, more than three fungicides need to be applied each season, which increase annual cost to $2 billion [5]. Undoubtedly, excessive use of fungicides will cause serious consequences, such as increased resistance of fungal strains. Recently research explained that excessive use of fungicides has caused seriously resistance of *Phakopsora Pachyrhizi* fungi and other fungal pathogens to pyrazole fungicides [6]. After using fungicides for several years, the effectiveness of DMI against *Phakopsora Pachyrhizi* fungi was significantly reduced in Brazil [7–9].

Amide fungicides are widely used for the highly effective fungicidal activity [10]. In terms of chemical structure classification they can be divided into carboxylic acid amides, mandelic acid and phenylamides and divided into biosynthesis inhibitors and biooxidation inhibitors according to the mechanism of action. Amide fungicides performed outstanding effects on downy mildew on soybean, cucumber, millet, potato and eggplant caused by Phytophthora. Unfortunately, after using for a period of time,the fungicides will be gradually out of severce. Therefore, it is urgent to develop some innovative compounds displaying excellent fungicidal activity against soybean rust.

Carboxin Standard was the earliest commercial product launched of the Amide fungicides in 1966. Thereafter, many new fungicides have being developed with good activity. So far, there are 19 commercial fungicides, divided into 9 categories [11]. Due to long-term use, many pathogens have exhibited extremely resistant to carboxamide fungicides, such as Alternaria alternate [12,13], Botrytis cinerea [14,15], Podosphaera xanthii [16], and Mycosphaerella graminicola.[17–19] Thus, it is necessary to develop new fungicides with excellent performance [20–24].

Xiong [25] has designed and synthesized a series of novel succinate ubiquinone oxidoreductase (SQR) inhibitors containing pyrazole-carboxamide. The evaluation showed good SQR inhibitory activities against Fusarium solani and Pythium brevis with the concentration 200 mg/L. Specially, Compound A showed the most excellent SQR inhibitory activity, with a Ki value of

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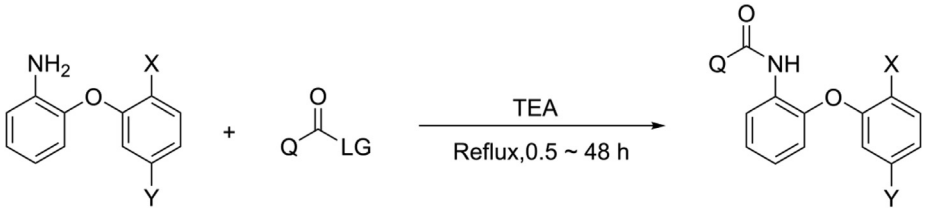
Table 1
Amide fungicides **1**–**12**.



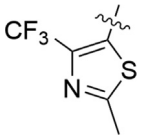
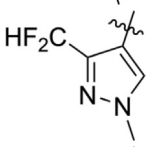
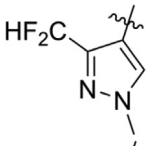
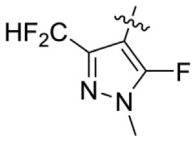
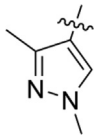
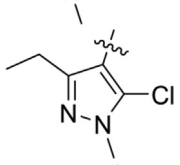
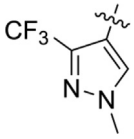
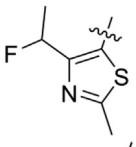
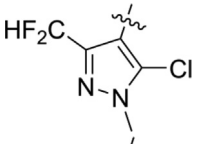
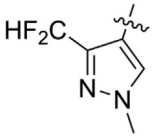
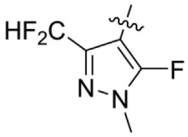
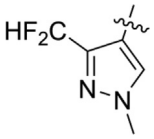
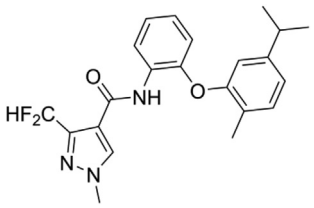
Product	Q	X	Y	Yield[a] (%)
1		Isopropyl	methyl	37
2		Isopropyl	methyl	85
3		methyl	methyl	87
4		Isopropyl	methyl	76.7
5		Isopropyl	methyl	59
6		Isopropyl	methyl	73
7		Isopropyl	methyl	75
8		Isopropyl	methyl	49
9		Isopropyl	methyl	69.3
10		*Tert*-butyl	methyl	79

Table 1 (*continued*)

Product	Q	X	Y	Yield[a] (%)
11		*Tert*-butyl	methyl	73.9
12		*Tert*-butyl	Isopropyl	77

[a] Isolated yield.

0.081 μM, which was about 4 times stronger than pentathion (Ki = 0.307 μM).



Compound **A**

A series of novel 1,2,4-triazole derivatives with 4-(4-substituted phenyl)piperazine side chain based on the structure of lanosterol 14α-demethylase (CYP51) were developed by Xu [26]. By measuring the minimum inhibitory concentration, antifungal activities against eight human pathogenic fungi are evaluated in vitro. Nearly all the compounds are more resistant to Candida albicans than fluconazole.

Depressively, these fungicides play poor activity at low concentration. Therefore, it is very important to develop more effective fungicides at low concentration. This paper presents the design and synthesis for a class of amide compounds. Exhilaratingly, the amide compounds perform unexpectedly high fungicidal activities against plant diseases caused by oomycetes, ascomycetes, basidiomycetes or deuterium bacteria.

Experimental section

In this work, 12 novel amide compounds based on compound **A** were designed and the related structures are in Table 1. The synthetic process of amide fungicides are shown in Scheme 1.

Results and discussion

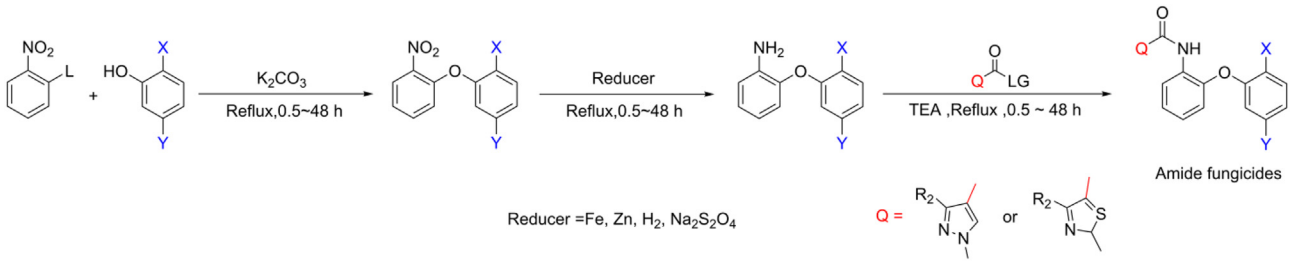
*Fungicidal activities of amide fungicides **1**–**12***

The samples were dissolved in a little solvent and diluted with water containing 0.1% Tween 80. Two-leaf stage soybean was cultivated in a greenhouse as a test host plant of *Phakopsora Pachyrhizi*. The results of the survey referred to the *Key Manual of Plant Disease*. The activities against soybean rust of amide fungicides **1**–**12** and compound **A** were tested in Table 2.

Relationship between fungicidal activities and structure of amide fungicides

In Fig. 1, the activities between amide fungicide 1 (thiazole) and 7 (pyrazole) were compared in A. At high concentrations, nearly no significant differences of fungicidal activities played, but the fungicidal activity of 7 at low concentration improved significantly. Therefore, the fungicidal activity with pyrazole was higher than that of the thiazole. In order to investigate the fungicidal activities of halogen substitution on pyrazole the bactericidal activities of amide fungicides 2, 4, and 9 were discussed. At high concentrations, the fungicidal activities of the three compounds were equivalent, but the fungicidal activities at low concentrations with Cl and unsubstituted showed no activities. And the fungicidal activities with F substitution was 20, so the sequence of fungicidal activities of halogen substitution on pyrazole was F > Cl > unsubstituted.

Similarly, the activities of amide fungicides **2** with methyl, **5** with difluoromethyl and **7** with trifluoromethyl were also compared that the activities of amide fungicide **5** with difluoromethyl at low concentrations were better than that of trifluoromethyl and methyl. Then the fungicidal activities of amide fungicides **6** and **9** substituted with alkane groups were also investigated in the presence of halogen substitution on pyrazole. The result showed that



Scheme 1. The synthesis of the amide fungicides 1–12. (**R_2** is difluoromethyl or a trifluoromethyl; **X** is selected among a C2-C12 alkyl; **Y** is selected among a C1-C6 alkyl; **LG** represents a readily detachable group such as a chlorine or a bromine, alkoxy or acyloxy; **L** represents a group susceptible to nucleophilic reaction, such as fluorine or chlorine).

Table 2
Fungicidal activity of amide fungicides **1**–**12** and compound **A**.

Product	Fungicidal activities at different concentrations		
	10 ppm	1 ppm	0.1 ppm
1	100	95	0
2	100	90	0
3	95	40	0
4	100	95	20
5	85	20	0
6	80	20	0
7	100	95	30
8	85	20	0
9	100	100	0
10	100	100	20
11	100	100	70
12	100	45	0
A	40	0	0

the fungicidal activities of compound with difluoromethyl were better than that with ethyl.

The fungicidal activities of amide fungicides **2**, **10**, and **12** substituted by phenoxy group were also studied. It displayed that at the Y position the fungicidal activities with tertiary butyl radical at low concentrations was better than Propyl radical. Similarly, amide fungicides **10** and **12** were studied that the fungicidal activities of compound substituted with methyl at X position were superior to isopropyl at low concentrations.

Therefore, the amide fungicide **11** exhibited higher fungicidal activities than amide fungicides **4** and **10** (result shown in Fig. 2).

The structure differences between amide fungicides **4** and **11** were that amide fungicide **4** was substituted by isopropyl while amide fungicide **11** was substituted by *tert*-butyl at the Y position respectively. The amide fungicide **10** had no halogen on pyrazole, while the amide fungicide **11** owned F. It could be speculated from

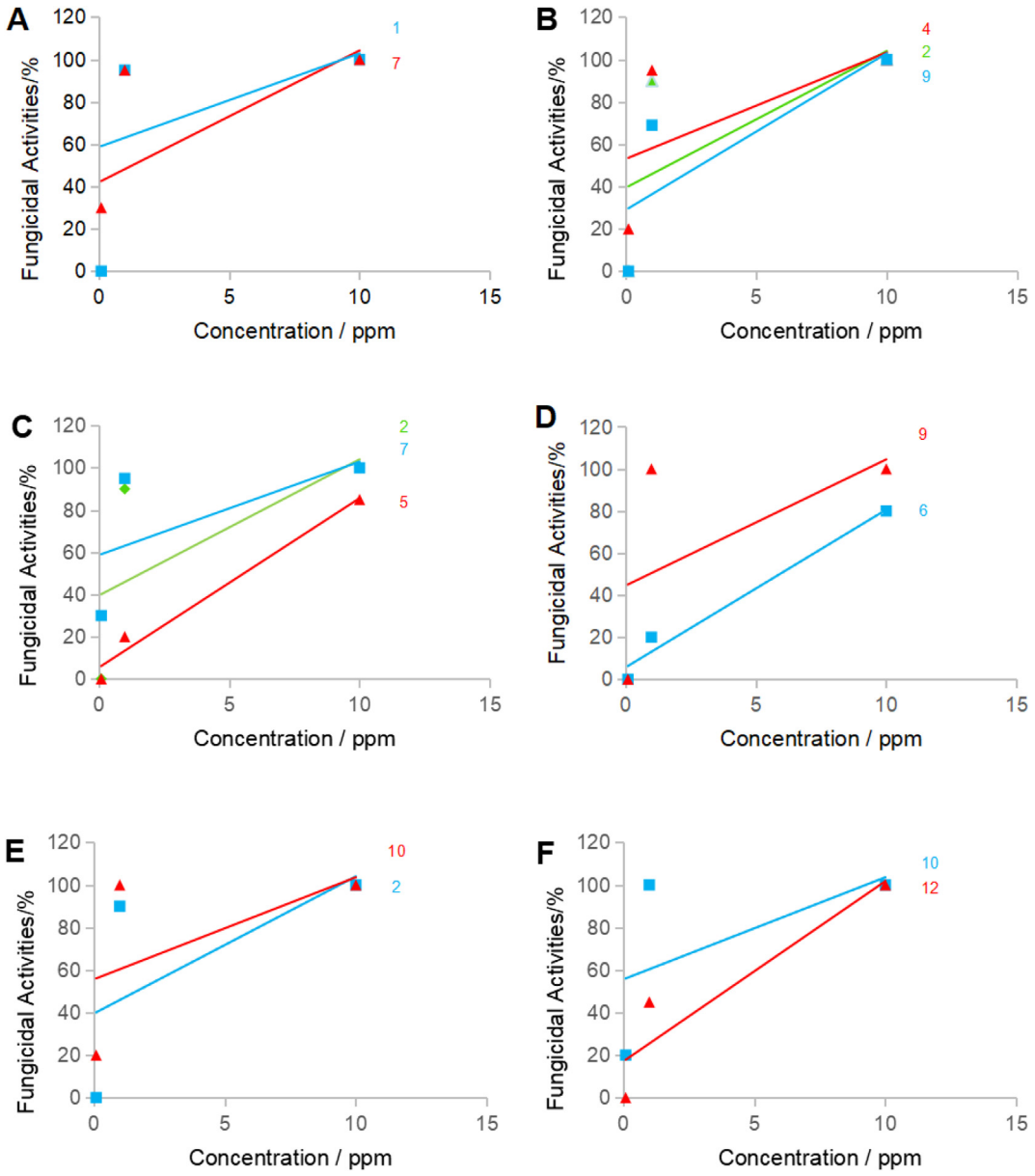


Fig. 1. Comparison of fungicidal activities between similar structures. (A) The comparison of the fungicidal activities between thiazole and pyrazole;(B) The comparison of fungicidal activities of halogen substitution on the pyrazole; (C) R_2 is the comparison of the fungicidal activities among methyl, difluoromethyl and trifluoromethyl; (D) R_2 is the comparison of the fungicidal activities between difluoromethyl and ethyl; (E) Y is the comparison of the fungicidal activities between *tert*-butyl and isopropyl; (F) X is the comparison of the fungicidal activities between methyl and isopropyl.

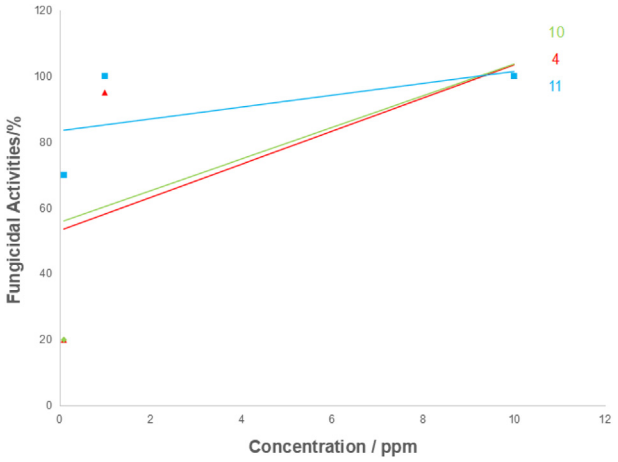


Fig. 2. Comparison of fungicidal activities of amide fungicides **4**, **10** and **11**.

Fig. 1 that these three amide fungicides exhibited excellent fungicidal activities at high concentrations. However, at low concentrations, the amide fungicide **11** could reach 70% of fungicidal activities, while amide fungicides **4** and **10** were only 20%, which were much lower than the amide fungicide **11**.It could be speculated that the excellent activity of amide fungicide **11** at low concentration was benefit of its special structure.

In conclusion of the data of fungicidal activities, amide fungicides **1**–**12** exhibited excellent activity on the control of soybean rust. Specially amide fungicide **11** exhibited best fungicidal activities of soybean rust at a low concentration, which was a hopeful fungicide.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152745.

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