DOI:10.1021/jf1006193

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

5-Methyl-1,2,3-thiadiazoles Synthesized via Ugi Reaction and Their Fungicidal and Antiviral Activities

Qingxiang Zheng,[‖] Na Mi,[‖] Zhijin Fan,* Xiang Zuo,[‖] Haike Zhang, Huan Wang, and Zhikun Yang

State Key Laboratory of Elemento-Organic Chemistry, Nankai University, 94 Weijin Road, Nankai District, Tianjin 300071, People's Republic of China. [‖]These authors contributed equally to this work.

1,2,3-Thiadiazoles, an important synthetic active substructure, are nowadays becoming one of the important branches in novel pesticide development. To develop pesticide candidates with diverse biological activities and probe their structure−activity relationship, three series of 5-methyl-1,2,3-thiadiazoles were rationally designed and synthesized using a simple and convenient one-step synthetic procedure via Ugi reaction. Biological activities of the target compounds including fungicidal activity, antivirus activity in vitro and in vivo, and systemic acquired resistance were systematically evaluated. The results indicated that compound $\mathbf{III_{10}}$ showed broad-spectrum of activities against most fungi tested, and compounds $\mathbf{I_{10}}$ and $\mathbf{II_{17}}$ showed excellent potential antivirus activities as compared to positive control agent ribavirin. The preliminary structure−activity relationship was also discussed. The results of these studies indicated that the 5-position-substituted 1,2,3-thiadiazoles exhibited good antivirus activity and were worthy of further study in pesticide development.

KEYWORDS: 5-Methyl-1,2,3-thiadiazole; systemic acquired resistance; Ugi reaction; fungicide

INTRODUCTION

Derivatives of 1,2,3-thiadiazole with a wide variety of biological activities including antivirus activity (*1*, *2*), systemic acquired resistance (*3*, *4*), fungicide activity (*3*, *5*−*8*), insecticide activity (*9*), and herbicide activity (*10*) were reported in the past decade. Moreover, the properties of easy breakdown of the 1,2,3-thiadiazole ring into low molecular weight compounds through release of N_2 favor the use of its derivatives as environmentally friendly pesticide candidates with low toxicity (*11*). The chemistry of 5-substituted 1,2,3-thiradiazoles has been well studied in our previous work (*3*, *12*, *13*). These papers address the issues of these compounds and their biological activities. The results proved that our strategy for pesticide development by combining other bioactive moieties with a 1,2,3-thiadiazole moiety at the 5-position really did work. However, derivatives at the 4-position of the 1,2,3-thiadiazole ring were seldom synthesized and considered in pesticide development.

On the basis of the consideration above, the following characteristics are highly desirable for our studies on this field: (i) a compound containing a 1,2,3-thiadiazole ring with a functional group at the 4-position should be easily modified; (ii) as an intermediate, this compound should be conveniently synthesized; (iii) the substitution at the 4-position of the 1,2,3-thiadiazole ring should be inert to most reactions so that the modifications at the 5-position would not be affected; (iv) a rapid and efficient modification measure is preferred for our subsequent bioactivity tests and structure−activity relationship studies.

*Author to whom correspondence should be addressed (phone +86-22-23504367; fax +86-22-23503627; e-mail fanzj@nankai.edu.cn).

Part of our previous studies on lead derivation by Ugi four-component condensation reaction (U-4CR) indicated that Ugi four-component condensation is an efficient and convenient green method to combine several active moieties into one molecule, and it could be convenient to implement structural modification via alternation of diverse starting materials (*12*). On the basis of the fact that 4-methyl-1,2,3-thiadiazole-containing 3-(trifluoromethyl)phenyl and 2-methylphenyl derivatives possessed potentially wide spectra of fungicidal activity, 4-methyl-1,2,3-thiadiazole-containing 3-(trifluoromethyl)phenyl and 4-hydroxyphenyl derivatives possessed good potential direct antivirus activities against TMV in vitro and because replacement of the Cl atom by a F atom improved their direct inhibition activities against TMV in vitro, 4-methyl-1,2,3-thiadiazole-containing phenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3-nitrophenyl, 4-nitrophenyl, 2-methylphenyl, and 4-hydroxyphenyl derivatives possessed good potential bioactivities in vivo including protection, inactivation, curative, and induction activities against TMV (*12*), there was an expectation that the activity of 5-methyl-1,2,3-thiadiazole also deserved further studies.

Moreover, the compounds obtained through U-4CR with α-amino acylamide skeletons showed considerable bioactivities. These are particularly useful with respect to the above parameters (iv). Generally, U-4CR refers to the reaction among an amine, a carbonyl compound (aldehyde or ketone), an isocyanide, and a carboxylic acid to provide a single condensation product (*14*−*17*). On the basis of an overall consideration of the above factors (i, ii, and iii), 5-methyl-1,2,3-thiadiazole-4-carboxylic acid was synthesized as the intermediate with carboxylic acid as the functional group. To obtain compounds with potential bioactivities and

 Published on Web 06/17/2010

study the structure−activity relationship, like our previous work (*12*), 3-chloro-4-methylbenzenamine and 3-fluoro-4-methylbenzenamine were chosen as the amine components, and substituted benzaldehydes were chosen as the carbonyl components; two series including isopropyl isocyanide and cyclohexyl isocyanide were chosen as the isocyanide components, respectively. This will provide useful information for the study of the structure−activity relationship of these new structures.

To continue our ongoing program to develop 1,2,3-thiadiazoles with biologically interesting compounds, here we report the synthesis and fungicidal activities, antivirus activity in vitro and in vivo, and systemic acquired resistance of 5-methyl-1,2,3-thiadiazole-4-carboxamides including N-((isopropylcarbamoyl)(aryl)methyl)-N-(3-chloro-4-methylphenyl)-5-methyl-1,2,3-thiadiazole-4-carboxamides (**Series I**), N-((isopropylcarbamoyl)(aryl)methyl)-N-(3-fluoro-4-methylphenyl)-5-methyl-1,2,3-thiadiazole-4-carboxamides (**Series II**) and N-((cyclohexylcarbamoyl)(aryl)methyl)-N-(3-fluoro-4-methylphenyl)-5-methyl-1,2,3-thiadiazole-4-carboxamides (**Series III**). The results indicated that compound $\mathbf{III_{10}}$ showed broad-spectrum of activities against several fungi tested, and compound $\mathbf{I}_{10}$ and $\mathbf{II}_{17}$ showed excellent potential antivirus activities as compared with ribavirin. The 5-position substituted 1,2,3-thiadiazoles are worthy of further studies. Their preliminary structure−activity relationship is also discussed here.

EXPERIMENTAL METHODS

Equipment for Structural Characterization. Melting points of all compounds were determined on an X-4 binocular microscope (Gongyi Tech. Instrument Co., Henan, China), and the thermometer was not corrected. Proton NMR spectra were obtained using a Bruker Avance-400 MHz spectrometer, and chemical shift values (δ) were reported as parts per million with deutero-dimethyl sulfoxide (DMSO-d_6) or $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. HRMS data were obtained on an FTICR-MS Varian 7.0T FTICR-MS instrument. All solvents and liquid reagents were of analytical reagent grade and were dried in advance and distilled before use. Flash column chromatography purification was carried out by using silica gel.

Preparation of Isopropyl Isocyanide and Cyclohexyl Isocyanide. *N*-Isopropylformamide was prepared by reflux of 78.2 g (1.3 mol) of isopropylamine and 130.0 g (1.8 mol) of ethyl formate for 16 h; 91.1 g of *N*-isopropylformamide was collected through distillation under reduced pressure with a yield of 79%. A solution of 43.6 g (0.5 mol) of isopropylformamide in 237.3 g (3.0 mol) of refined pyridine was cooled to 0 °C, followed by the addition of 46.1 g (0.3 mol) of phosphorus oxychloride dropwise for 1 h under an ice bath. After the solution was then heated to 60 °C and stirred for 30 min, it was cooled to 0−5 °C again. Fifty milliliters of pentane and 200 mL of ice−water were added to the solution with violent stirring. The organic phase was collected, and the aqueous phase was extracted with 30 mL portions of pentane by four times. The organic phase was dried by sodium sulfate, and 10.88 g of colorless foul-smelling liquid isopropylisonitrile was obtained by distillation with a yield of 31%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37−1.39 (m, 6H, J = 2.0 Hz, CH_3), 3.72−3.80 (m, 1H, CH).

The preparation of cyclohexyl isocyanide was conducted according to the procedures as described in refs *12* and *18*. Cyclohexylisocyanide was obtained as a colorless foul-smelling liquid with a yield of 73%.

Preparation of 5-Methyl-1,2,3-thiadiazolyl-4-carboxylic Acid. 5-Methyl-1,2,3-thiadiazole-4-carboxylic acid was prepared according to the description in ref *19*.

General Synthetic Procedure for 5-Methyl-1,2,3-thiadiazole-4-carboxamides via U-4CR. 3-Chloro-4-methylbenzenamine (0.47 g, 3.0 mmol), 5-methyl-1,2,3-thiadiazole-4-carboxylic acid (0.43 g, 3.0 mmol), and isopropyl isocyanide (0.20 g, 2.8 mmol) were added to a solution of benzaldehyde (0.35 g, 3.0 mmol) in 10 mL of methanol in sequence. The color of the mixture grew darker during this procedure. The solution was then stirred for another 1 h at room temperature; afterward, removal of solvent under reduced pressure and purification by flash column chromatography on silica gel using ethyl acetate and petroleum ether (60−90 °C; 1:3) as an eluent were performed to obtain the product. The yields, physical properties, and ^{1}H NMR and HRMS data of the target compounds are listed in **Table 1**.

Biological Screening. Biological activities of the target compounds including fungicide and direct antivirus activities such as protection, inactivation, curative effect and systemic acquired resistance were evaluated systematically according to the standard operation practice (SOP) as described in ref *3* and the following procedures.

Fungicide Screening. Preliminary screening was conducted by a fungal growth inhibition method according to reference using potato dextrose agar (PDA) as cultivation medium (*3*). Fungi used in this studies included *Alternaria solani* (AS), *Botrytis cinerea* (BC), *Cercospora arachidicola* (CA), *Cercospora beticola* (CB), *Colletotrichum lagenarium* (CL), *Fusarium oxysporum* (FO), *Gibberella zeae* (GZ), *Puccinia triticina* Eriks (PT), *Phytophthora infestans* (Mont) de Bary (PI), *Physalospora piricola* (PP), *Pellicularia sasakii* (PS), and *Rhizoctonia solani* (RS).

Systemic Acquired Resistance Screening. Systemic acquired resistance of the target compounds was detected using tobacco against the tobacco mosaic virus (TMV) system as described in ref *3*. The induction activity was evaluated using the antivirus inhibition ratio, which was calculated by the average number of viral inflammations on the inoculated leaves with the corresponding control accordingly. Tiadinil (TDL) and ribavirin were chosen as positive control and negative control, respectively, and all compounds tested were conducted at 100 and 50 μg/mL, respectively.

Protective Effects of the Target Compounds against TMV in Vivo. Healthy fresh tobacco leaves growing at six-leaf age were selected for the tests. The compound solution was smeared on the whole leaves, and then the leaves were dried in the greenhouse. After 12 h, TMV at a concentration of 5.88×10^{-2} μg/mL was inoculated on the upper three leaves using the conventional juice-robbing method, and the solvent was smeared on the lower three leaves as a control. The local lesion numbers were then recorded 2−3 days after inoculation. For each compound, three repetitions were conducted. Most compounds tested were conducted at 500 and 100 μg/mL, respectively. Only a few compound tests were conducted at 500 and 200 μg/mL, respectively.

Inactivation Effect of the Target Compounds against TMV in Vivo. Healthy fresh tobacco leaves growing at six-leaf age were selected for the tests. TMV virus at a concentration of 5.88×10^{-2} μg/mL was inhibited by mixing with the target compound solution at the same volume for 30 min. Then the mixture was inoculated on the upper three leaves using the conventional juice-robbing method, and the solvent was smeared on the lower three leaves as a control. The local lesion numbers were then recorded 2−3 days after inoculation. For each compound, three repetitions were conducted. All compounds tested were conducted at 500 and 100 μg/mL, respectively.

Curative Effect of Target Compounds on TMV in Vivo. Healthy fresh tobacco leaves growing at six-leaf age were selected for the tests. TMV at a concentration of 5.88×10^{-2} μg/mL was inoculated on the whole leaves using the conventional juice-robbing method. After the leaves were dried in the greenhouse, the compound solution was smeared on the upper three leaves, and the solvent was smeared on the lower three leaves as control. The local lesion numbers were then recorded 2−3 days after inoculation. For each compound, three repetitions were conducted. All compounds tested were conducted at 500 and 100 μg/mL, respectively.

The activities of protection, inactivation, and curative effects against TMV were calculated by the average number of viral inflammations on the inoculated leaves with the corresponding control according to eq 1

$$Y = \frac{\mathrm{CK} - A}{\mathrm{CK}} \times 100 \quad (1)$$

where Y is the antivirus inhibition ratio (protection, inactivation, and curative effects in vivo) (%), CK is the average number of viral inflammations on the control leaves in vivo, and A is the average number of viral inflammations on the target compound treated leaves in vivo.

RESULTS AND DISCUSSION

Preparation of the New Derivatives of 5-Methyl-1,2,3-thiadiazole-4-carboxylic Acid via U-4CR. All structures of the title compounds synthesized were confirmed by ^{1}H NMR and HRMS.

Table 1. Yields, Physical Properties, and ^{1}H NMR and HRMS Data of the Target Compounds

compd	yield (%)	appearance and mp (°C)	^{1}H NMR, δ (solvent)	HRMS (*m*/*z*)
I_1	71	white crystal, 163	1.15 (dd, 6H, *J* = 6.6 Hz, *J* = 24.6 Hz, CH_3), 2.15 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.13−4.21 (m, 1H, *J* = 6.8 Hz, CH), 5.51 (d, 1H, *J* = 7.6 Hz, NH), 6.20 (s, 1H, PhCH), 6.81−7.28 (m, 7H, Ph) ($CDCl_3$)	$[M + Na^+]$: 465.1128; found: 465.1119
I_2	36	light yellow crystal, 203−204	1.19 (dd, 6H, *J* = 6.8 Hz, *J* = 29.6 Hz, CH_3), 2.18 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.14−4.22 (m, 1H, *J* = 6.8 Hz, CH), 5.86 (d, 1H, *J* = 7.6 Hz, NH), 6.23 (s, 1H, PhCH), 6.80−7.82 (m, 3H, Ph−H), 7.49 (d, 2H, *J* = 8.8 Hz, Ph−H), 8.12 (d, 2H, *J* = 8.8 Hz, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 510.0979; found: 510.0973
I_3	68	light yellow crystal, 189−190	1.204 (dd, 6H, *J* = 6.8 Hz, *J* = 29.6 Hz, CH_3), 2.177 (s, 3H, Ph−CH_3), 2.722 (s, 3H, CH_3), 4.152−4.237 (m, 1H, *J* = 6.8 Hz, CH), 5.872 (d, 1H, *J* = 7.6 Hz, NH), 6.261 (s, 1H, PhCH), 6.839−7.129 (m, 3H, Ph−H), 7.457 (t, 1H, *J* = 8.0 Hz, Ph−H), 7.633 (d, 1H, *J* = 7.6 Hz, Ph−H), 8.138−8.154 (d, 2H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 510.0979; found: 510.0970
I_4	72	white crystal, 178−179	1.15 (dd, 6H, *J* = 6.8 Hz, *J* = 24.6 Hz, CH_3), 2.15 (s, 3H, Ph−CH_3), 2.73 (s, 3H, CH_3), 4.09−4.19 (m, 1H, *J* = 6.8 Hz, CH), 5.89 (d, 1H, *J* = 7.6 Hz, NH), 6.77 (s, 1H, PhCH), 6.86−7.95 (m, 7H, Ph-H) ($CDCl_3$)	$[M + Na^+]$: 510.0979; found: 510.0972
I_5	52	white crystal, 170−171	1.16 (dd, 6H, *J* = 6.6 Hz, *J* = 27.4 Hz, CH_3), 2.18 (s, 3H, Ph−CH_3), 2.69 (s, 3H, CH_3), 4.11−4.21 (m, 1H, *J* = 6.8 Hz, CH), 5.59 (d, 1H, *J* = 7.6 Hz, NH), 6.14 (s, 1H, PhCH), 6.80−7.26 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 499.0738; found: 499.0726
I_6	59	white crystal, 165−166	1.17 (dd, 6H, *J* = 6.6 Hz, *J* = 30.0 Hz, CH_3), 2.18 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.13−4.23 (m, 1H, *J* = 6.8 Hz, CH), 5.61 (d, 1H, *J* = 7.6 Hz, NH), 6.12 (s, 1H, PhCH), 6.83−7.27 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 499.0738; found: 499.0735
I_7	52	white crystal, 162−163	1.19 (dd, 6H, *J* = 6.4 Hz, *J* = 35.6 Hz, CH_3), 2.11 (s, 3H, Ph−CH_3), 2.68 (s, 3H, CH_3), 4.16−4.24 (m, 1H, *J* = 6.8 Hz, CH), 5.65 (br, 1H, *J* = 7.6 Hz, NH), 6.63 (s, 1H, PhCH), 6.76−7.36 (m, 7H, Ph-H) ($CDCl_3$)	$[M + Na^+]$: 499.0738; found: 499.0736
I_8	65	white crystal, 172−173	1.15 (dd, 6H, *J* = 6.8 Hz, *J* = 29.6 Hz, CH_3), 2.16 (s, 3H, Ph−CH_3), 2.69 (s, 3H, CH_3), 4.11−4.19 (m, 1H, *J* = 6.8 Hz, CH), 5.61 (d, 1H, *J* = 7.6 Hz, NH), 6.19 (s, 1H, PhCH), 6.79−7.22 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 483.1034; found: 483.1024
I_9	53	white crystal, 164	1.17 (dd, 6H, *J* = 6.4 Hz, *J* = 24.8 Hz, CH_3), 2.17 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.11−4.21 (m, 1H, *J* = 6.8 Hz, CH), 5.64 (d, 1H, *J* = 7.6 Hz, NH), 6.11 (s, 1H, PhCH), 6.85−7.30 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 483.1034; found: 483.1025
I_{10}	61	white needle crystal, 167−168	1.19 (dd, 6H, *J* = 6.4 Hz, *J* = 29.2 Hz, CH_3), 2.14 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.15−4.24 (m, 1H, *J* = 6.8 Hz, CH), 5.67 (br, 1H, NH), 6.48 (s, 1H, PhCH), 6.81−7.32 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 483.1034; found: 483.1030
I_{11}	41	white needle crystal, 203	1.17 (dd, 6H, *J* = 6.4 Hz, *J* = 27.2 Hz, CH_3), 2.18 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.10−4.22 (m, 1H, *J* = 6.8 Hz, CH), 5.69 (d, 1H, *J* = 7.2 Hz, NH), 6.19 (s, 1H, PhCH), 6.81−7.32, 7.80−7.82 (m, 3H, Ph−H), 7.41 (d, 2H, *J* = 8.4 Hz, Ph−H), 7.54 (d, 2H, *J* = 8.4 Hz, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 533.1002; found: 533.1004
I_{12}	63	white needle crystal, 170−171	1.18 (dd, 6H, *J* = 6.8 Hz, *J* = 33.2 Hz, CH_3), 2.16 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.14−4.23 (m, 1H, *J* = 6.8 Hz, CH), 5.68 (d, 1H, *J* = 7.2 Hz, NH), 6.26 (s, 1H, PhCH), 6.81−7.55 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 533.1002; found: 533.0996
I_{13}	51	white solid, 113−115	1.15 (dd, 6H, *J* = 6.8 Hz, *J* = 58.8 Hz, CH_3), 2.14 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.11−4.21 (m, 1H, *J* = 6.8 Hz, CH), 5.36 (d, 1H, *J* = 7.6 Hz, NH), 6.61 (s, 1H, PhCH), 6.78−7.17 (m, 3H, Ph−H), 7.16 (d, 1H, *J* = 8.0 Hz, Ph−H), 7.25 (t, 1H, *J* = 7.6 Hz, Ph−H), 7.37 (t, 1H, *J* = 7.6 Hz, Ph−H), 7.70 (d, 1H, *J* = 8.0 Hz, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 533.1002; found: 533.0988
I_{14}	52	white crystal, 145−146	1.14 (dd, 6H, *J* = 6.6 Hz, *J* = 27.0 Hz, CH_3), 2.17 (s, 3H, Ph−CH_3), 2.31 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.12−4.22 (m, 1H, *J* = 6.8 Hz, CH), 5.47 (d, 1H, *J* = 7.6 Hz, NH), 6.16 (s, 1H, PhCH), 6.82−7.16 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 479.1284; found: 479.1275
I_{15}	46	white crystal, 148−149	1.14 (dd, 6H, *J* = 6.4 Hz, *J* = 23.6 Hz, CH_3), 2.16 (s, 3H, Ph−CH_3), 2.27 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.12−4.21 (m, 1H, *J* = 6.8 Hz, CH), 5.51 (br, 1H, NH), 6.16 (s, 1H, PhCH), 6.81−7.15 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 479.1284; found: 479.1276
I_{16}	27	white crystal, 189−190	1.16 (dd, 6H, *J* = 6.8 Hz, *J* = 24.8 Hz, CH_3), 2.11 (s, 3H, Ph−CH_3), 2.49 (s, 3H, Ph−CH_3), 2.69 (s, 3H, CH_3), 4.15−4.24 (m, 1H, *J* = 6.8 Hz, CH), 5.41 (d, 1H, *J* = 7.2 Hz, NH), 6.57 (s, 1H, PhCH), 6.73−7.19 (m, 7H, Ph−H) ($CDCl_3$)	$[M + H^+]$: 457.1465; found: 457.1454
I_{17}	33	white crystal, 178−179	1.15 (dd, 6H, *J* = 6.8 Hz, *J* = 27.2 Hz, CH_3), 2.16 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.11−4.21 (m, 1H, *J* = 6.8 Hz, CH), 5.53 (d, 1H, *J* = 7.6 Hz, NH), 5.75 (s, 1H, OH), 6.13 (s, 1H, PhCH), 6.72 (d, 2H, *J* = 8.4 Hz, Ph−H), 6.84−6.80 (m, 2H, Ph−H), 7.07 (d, 2H, *J* = 8.4 Hz, Ph−H), 7.16 (br, 1H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 481.1077; found: 481.1070
I_{18}	51	white crystal, 203−204	1.13 (dd, 6H, *J* = 6.4 Hz, *J* = 23.2 Hz, CH_3), 2.16 (s, 3H, Ph−CH_3), 2.67 (s, 3H, CH_3), 4.11−4.22 (m, 1H, *J* = 6.8 Hz, CH), 5.86 (d, 1H, *J* = 8.0 Hz, NH), 6.10 (s, 1H, PhCH), 6.64−6.84 (m, 5H, Ph−H), 6.94 (s, 1H, OH), 7.09 (t, 1H, *J* = 7.8 Hz, Ph−H), 7.209 (s, 1H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 481.1077; found: 481.1072
I_{19}	19	white crystal, 178−179	1.22 (dd, 6H, *J* = 6.4 Hz, *J* = 15.2 Hz, CH_3), 2.19 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.15−4.23 (m, 1H, *J* = 6.8 Hz, CH), 6.19 (s, 1H, PhCH), 6.21 (s, 1H, OH), 6.76−7.21 (m, 7H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 481.1077; found: 481.1078
II_1	52	white crystal, 172−173	1.16 (dd, 6H, *J* = 6.8 Hz, *J* = 24.0 Hz, CH_3), 2.06 (d, 3H, *J* = 1.6 Hz, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.13−4.23 (m, 1H, CH), 5.49 (d, 1H, *J* = 7.6 Hz, NH), 6.23 (s, 1H, Ph−CH), 6.72−6.87 (m, 3H, Ph−H), 7.21−7.28 (m, 5H, Ph−H) ($CDCl_3$)	$[M + Na^+]$: 449.1423; found: 449.1423

Table 1. Continued

compd	yield (%)	appearance and mp (°C)	^{1}H NMR, δ (solvent)	HRMS (*m*/*z*)
II$_2$	59	white crystal, 174	1.20 (dd, 6H, *J* = 6.4 Hz, *J* = 30.0 Hz, CH_3), 2.08 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.13−4.23 (m, 1H, CH), 5.80 (d, 1H, *J* = 7.6 Hz, NH), 6.26 (s, 1H, Ph−CH), 6.69−6.90 (m, 3H, Ph−H), 7.49 (d, 2H, *J* = 8.4 Hz, Ph−H), 8.12 (d, 2H, *J* = 8.8 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 494.1274; found: 494.1261
II$_3$	46	white crystal, 156−157	1.19 (dd, 6H, *J* = 6.4 Hz, *J* = 30.4 Hz, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.15−4.23 (m, 1H, CH), 5.92 (d, 1H, *J* = 7.6 Hz, NH), 6.31 (s, 1H, Ph−CH), 6.73−6.84 (m, 3H, Ph−H), 7.44 (t, 1H, *J* = 8.0 Hz, Ph−H), 7.62 (d, 1H, *J* = 7.6 Hz, Ph−H), 8.12−8.14 (d, 2H, Ph−H) ($CDCl_3$)	[M + Na^+]: 494.1274; found: 494.1266
II$_4$	65	white solid, 148−169	1.16 (dd, 6H, *J* = 6.4 Hz, *J* = 24.8 Hz, CH_3), 2.05 (s, 3H, Ph−CH_3), 2.75 (s, 3H, CH_3), 4.13−4.21 (m, 1H, CH), 5.79 (d, 1H, *J* = 7.2 Hz, NH), 6.78−6.91 (m, 4H, Ph−CH and Ph), 7.47 (t, 1H, *J* = 8.0 Hz, Ph−H), 7.43−7.96 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 494.1274; found: 494.1262
II$_5$	63	white solid, 147−148	1.16 (dd, 6H, *J* = 6.4 Hz, *J* = 26.8 Hz, CH_3), 2.08 (d, 3H, *J* = 1.6 Hz, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.14−4.23 (m, 1H, CH), 5.51 (d, 1H, *J* = 7.6 Hz, NH), 6.17 (s, 1H, Ph−CH), 6.70−6.89 (m, 3H, Ph−H), 7.17−7.25 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 483.1034; found: 483.1034
II$_6$	55	white solid, 171−172	1.18 (dd, 6H, *J* = 6.4 Hz, *J* = 25.6 Hz, CH_3), 2.08 (d, 3H, *J* = 1.6 Hz, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.13−4.23 (m, 1H, CH), 5.57 (d, 1H, *J* = 8.0 Hz, NH), 6.14 (s, 1H, Ph−CH), 6.73−6.88 (m, 3H, Ph−H), 7.11−7.28 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 483.1034; found: 483.1033
II$_7$	63	white solid, 173	1.19 (dd, 6H, *J* = 6.4 Hz, *J* = 35.2 Hz, CH_3), 2.02 (s, 3H, Ph−CH_3), 2.68 (s, 3H, CH_3), 4.16−4.25 (m, 1H, CH), 5.62 (d, 1H, *J* = 8.0 Hz, NH), 6.65 (s, 1H, Ph−CH), 6.70−6.95 (m, 3H, Ph−H), 7.03−7.36 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 483.1034; found: 483.1031
II$_8$	54	white solid, 145−146	1.16 (dd, 6H, *J* = 6.4 Hz, *J* = 28.4 Hz, CH_3), 2.08 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.16−4.23 (m, 1H, CH), 5.52 (d, 1H, *J* = 6.8 Hz, NH), 6.21 (s, 1H, Ph−CH), 6.69−6.85 (m, 3H, Ph−H), 6.92−7.23 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 467.1329; found: 467.1329
II$_9$	56	white solid, 162−163	1.17 (dd, 6H, *J* = 6.4 Hz, *J* = 25.2 Hz, CH_3), 2.07 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.12−4.21 (m, 1H, CH), 5.66 (d, 1H, *J* = 7.6 Hz, NH), 6.17 (s, 1H, Ph−CH), 6.73−7.25 (m, 7H, Ph-H) ($CDCl_3$)	[M + Na^+]: 467.1329; found: 467.1325
II$_{10}$	75	white solid, 173−174	1.18 (dd, 6H, *J* = 6.4 Hz, *J* = 29.2 Hz, CH_3), 2.04 (d, 3H, *J* = 0.8 Hz, Ph−CH_3), 2.69 (s, 3H, CH_3), 4.16−4.24 (m, 1H, CH), 5.67 (d, 1H, *J* = 7.2 Hz, NH), 6.50 (s, 1H, Ph−CH), 6.76−7.24 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 467.1329; found: 467.1325
II$_{11}$	57	white solid, 173−174	1.18 (dd, 6H, *J* = 6.4 Hz, *J* = 26.0 Hz, CH_3), 2.08 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.14−4.22 (m, 1H, CH), 5.65 (d, 1H, *J* = 7.2 Hz, NH), 6.21 (s, 1H, Ph−CH), 6.70−6.90 (m, 3H, Ph−H), 7.41 (d, 2H, *J* = 8.0 Hz, Ph−H), 7.54 (d, 2H, *J* = 8.0 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 517.1297; found: 517.1286
II$_{12}$	53	white solid, 144−145	1.18 (dd, 6H, *J* = 6.8 Hz, *J* = 32.4 Hz, CH_3), 2.07 (s, 3H, Ph−CH_3), 2.72 (s, 3H, CH_3), 4.15−4.23 (m, 1H, CH), 5.63 (d, 1H, *J* = 8.0 Hz, NH), 6.28 (s, 1H, Ph−CH), 6.69−6.82 (m, 3H, Ph−H), 7.37−7.55 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 517.1297; found: 517.1293
II$_{13}$	55	white solid, 147−148	1.15 (dd, 6H, *J* = 6.8 Hz, *J* = 57.2 Hz, CH_3), 2.04 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.12−4.20 (m, 1H, CH), 5.35 (d, 1H, *J* = 7.2 Hz, NH), 6.62 (s, 1H, Ph−CH), 6.74 (s, 3H, Ph−H), 7.16−7.25 (m, 2H, Ph−H), 7.37 (t, 1H, *J* = 7.2 Hz, Ph−H), 7.70 (d, 1H, *J* = 8.0 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 517.1297; found: 517.1289
II$_{14}$	50	white solid, 171−172	1.14 (dd, 6H, *J* = 6.4 Hz, *J* = 21.2 Hz, CH_3), 2.07 (d, 3H, *J* = 1.6 Hz, Ph−CH_3), 2.30 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.12−4.22 (m, 1H, CH), 5.46 (d, 1H, *J* = 6.4 Hz, NH), 6.19 (s, 1H, Ph−CH), 6.72−6.87 (m, 3H, Ph−H), 7.05−7.11 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 463.1580; found: 463.1581
II$_{15}$	63	white solid, 166−167	1.15 (dd, 6H, *J* = 6.4 Hz, *J* = 22.8 Hz, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.27 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.13−4.23 (m, 1H, CH), 5.49 (d, 1H, *J* = 7.2 Hz, NH), 6.18 (s, 1H, Ph−CH), 6.72−6.87 (m, 3H, Ph−H), 6.96−7.14 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 463.1580; found: 463.1578
II$_{16}$	47	white solid, 201−202	1.17 (dd, 6H, *J* = 6.4 Hz, *J* = 23.6 Hz, CH_3), 2.02 (s, 3H, Ph−CH_3), 2.49 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.16−4.25 (m, 1H, CH), 5.36 (d, 1H, *J* = 7.2 Hz, NH), 6.57 (s, 1H, Ph−CH), 6.68−7.19 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 463.1580; found: 463.1571
II$_{17}$	48	white solid, 160−161	1.15 (dd, 6H, *J* = 6.4 Hz, *J* = 23.2 Hz, CH_3), 2.07 (d, 3H, *J* = 1.6 Hz, Ph−CH_3), 2.70 (s, 3H, CH_3), 4.13−4.22 (m, 1H, CH), 5.50 (d, 1H, *J* = 6.4 Hz, NH), 5.56 (s, 1H, OH), 6.16 (s, 1H, Ph−CH), 6.71 (d, 2H, *J* = 8.4 Hz, Ph−H), 6.76−6.86 (m, 3H, Ph−H), 7.07 (d, 2H, *J* = 8.8 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 465.1373; found: 465.1375
II$_{18}$	64	white solid, 202−203	1.17 (dd, 6H, *J* = 6.0 Hz, *J* = 25.2 Hz, CH_3), 1.98 (s, 3H, Ph−CH_3), 2.58 (s, 3H, CH_3), 3.95−3.98 (m, 1H, CH), 6.21 (s, 1H, Ph−CH), 6.53−7.01 (m, 7H, Ph−H), 8.17 (br, 1H, NH), 9.34 (s, 1H, OH) (DMSO-d_6)	[M + Na^+]: 465.1373; found: 465.1368
II$_{19}$	6	white solid, 154−156	1.22 (dd, 6H, *J* = 6.4 Hz, *J* = 13.6 Hz, CH_3), 2.09 (d, 3H, *J* = 1.2 Hz, Ph−CH_3), 2.71 (s, 3H, CH_3), 4.15−4.24 (m, 1H, CH), 6.19 (s, 1H, Ph−CH), 6.21 (s, 1H, NH), 6.71−7.21 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 465.1373; found: 465.1366
III$_1$	73	white solid, 173−174	1.02−1.97 (m, 10H, CH_3), 2.05 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.85−3.87 (m, 1H, CH), 5.56 (d, 1H, *J* = 7.6 Hz, NH), 6.26 (s, 1H, Ph−CH), 6.71−6.86 (m, 3H, Ph−H), 7.22−7.25 (m, 5H, Ph−H) ($CDCl_3$)	[M + Na^+]: 489.1736; found: 487.1732)

Table 1. Continued

compd	yield (%)	appearance and mp (°C)	^{1}H NMR, δ (solvent)	HRMS (*m*/*z*)
III$_2$	90	white solid, 181−182	1.06−2.02 (m, 10H, CH_3), 2.07 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 3.85−3.92 (m, 1H, CH), 5.85 (d, 1H, *J* = 7.6 Hz, NH), 6.27 (s, 1H, Ph−CH), 6.70−6.90 (m, 3H, Ph−H), 7.48 (d, 2H, *J* = 8.4 Hz, Ph−H), 8.12 (d, 2H, *J* = 8.4 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 534.1587; found: 534.1575
III$_3$	98	white solid, 183−184	1.09−2.03 (m, 10H, CH_3), 2.07 (s, 3H, Ph−CH_3), 2.72 (s, 3H, CH_3), 3.86−3.93 (m, 1H, CH), 5.92 (d, 1H, *J* = 7.2 Hz, NH), 6.31 (s, 1H, Ph−CH), 6.72−6.85 (m, 3H, Ph−H), 7.45 (t, 1H, *J* = 8.0 Hz, Ph−H), 7.63 (d, 1H, *J* = 7.6 Hz, Ph−H), 8.13, 8.15 (d, 2H, Ph−H) ($CDCl_3$)	[M + Na^+]: 534.1587; found: 534.1577
III$_4$	72	yellow solid, 113−115	1.10−1.99 (m, 10H, CH_3), 2.05 (s, 3H, Ph−CH_3), 2.74 (s, 3H, CH_3), 3.81−3.89 (m, 1H, CH), 5.88 (d, 1H, *J* = 7.2 Hz, NH), 6.78 (s, 1H, Ph−CH), 6.79−6.91 (m, 3H, Ph−H), 7.43−7.95 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 534.1587; found: 534.1579
III$_5$	97	white solid, 180−181	1.04−1.99 (m, 10H, CH_3), 2.08 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.82−3.89 (m, 1H, CH), 5.58 (d, 1H, *J* = 7.6 Hz, NH), 6.68 (s, 1H, Ph−CH), 6.78−6.89 (m, 3H, Ph−H), 7.17 (d, 2H, *J* = 8.4 Hz, Ph−H), 7.24 (d, 2H, *J* = 8.4 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 523.1347; found: 523.1339
III$_6$	77	white solid, 178−179	1.07−2.00 (m, 10H, CH_3), 2.08 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 3.83−3.91 (m, 1H, CH), 5.68 (d, 1H, *J* = 7.6 Hz, NH), 6.19 (s, 1H, Ph−CH), 6.73−6.88 (m, 3H, Ph−H), 7.10−7.27 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 523.1347; found: 523.1333
III$_7$	82	white solid, 176	1.07−2.04 (m, 10H, CH_3), 2.01 (s, 3H, Ph−CH_3), 2.68 (s, 3H, CH_3), 3.87−3.94 (m, 1H, CH), 5.62 (d, 1H, *J* = 7.6 Hz, NH), 6.66 (s, 1H, Ph−CH), 6.71−6.95 (m, 3H, Ph−H), 7.02−7.36 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 523.1347; found: 523.1333
III$_8$	92	white solid, 178	1.04−1.99 (m, 10H, CH_3), 2.07 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.85−3.87 (m, 1H, CH), 5.58 (d, 1H, *J* = 7.2 Hz, NH), 6.24 (s, 1H, Ph−CH), 6.68−7.22 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 507.1642; found: 507.1635
III$_9$	72	white solid, 176−177	1.06−1.99 (m, 10H, CH_3), 2.07 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.83−3.90 (m, 1H, CH), 5.67 (d, 1H, *J* = 7.2 Hz, NH), 6.19 (s, 1H, Ph−CH), 6.73−6.86 (m, 3H, Ph−H), 6.96−7.25 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 507.1642; found: 507.1637
III$_{10}$	60	white solid, 169−170	1.06−2.00 (m, 10H, CH_3), 2.04 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.86−3.93 (m, 1H, CH), 5.69 (d, 1H, *J* = 7.2 Hz, NH), 6.51 (s, 1H, Ph−CH), 6.75−7.24 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 507.1642; found: 507.1633
III$_{11}$	85	white solid, 176−177	1.06−2.00 (m, 10H, CH_3), 2.08 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.84−3.91 (m, 1H, CH), 5.70 (d, 1H, *J* = 7.2 Hz, NH), 6.23 (s, 1H, Ph−CH), 6.69−6.88 (m, 3H, Ph−H), 7.40 (d, 2H, *J* = 8.0 Hz, Ph−H), 7.53 (d, 2H, *J* = 8.0 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 557.1610; found: 557.1611
III$_{12}$	39	white solid, 160−161	1.05−2.00 (m, 10H, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 3.85−3.92 (m, 1H, CH), 5.70 (d, 1H, *J* = 7.6 Hz, NH), 6.31 (s, 1H, Ph−CH), 6.67−6.81 (m, 3H, Ph−H), 7.37−7.54 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 557.1610; found: 557.1610
III$_{13}$	84	white solid, 83−85	0.99−1.85 (m, 10H, CH_3), 2.04 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 3.82−3.89 (m, 1H, CH), 5.40 (d, 1H, *J* = 7.6 Hz, NH), 6.64 (s, 1H, Ph−CH), 6.73−7.24 (m, 5H, Ph−H), 7.36 (t, 1H, *J* = 7.6 Hz, Ph−H), 7.70 (d, 1H, *J* = 8.0 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 557.1610; found: 557.1597
III$_{14}$	90	white solid, 170	1.02−1.96 (m, 10H, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.30 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.84−3.86 (m, 1H, CH), 5.52 (d, 1H, *J* = 7.6 Hz, NH), 6.22 (s, 1H, Ph−CH), 6.71−6.86 (m, 3H, Ph−H), 7.05 (d, 2H, *J* = 8.0 Hz, Ph−H), 7.09 (d, 2H, *J* = 8.0 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 503.1893; found: 503.1892
III$_{15}$	65	white solid, 170	1.03−1.97 (m, 10H, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.27 (s, 3H, Ph−CH_3), 2.71 (s, 3H, CH_3), 3.83−3.90 (m, 1H, CH), 5.54 (d, 1H, *J* = 7.6 Hz, NH), 6.22 (s, 1H, Ph−CH), 6.70−6.86 (m, 3H, Ph−H), 6.95−7.14 (m, 4H, Ph−H) ($CDCl_3$)	[M + Na^+]: 503.1893; found: 503.1889
III$_{16}$	51	white solid, 178−179	1.03−1.97 (m, 10H, CH_3), 2.01 (s, 3H, Ph−CH_3), 2.49 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.85−3.93 (m, 1H, CH), 5.41 (d, 1H, *J* = 7.2 Hz, NH), 6.60 (s, 1H, Ph−CH), 6.69−7.19 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 503.1893; found: 508.1882
III$_{17}$	50	white solid, 148−149	1.03−1.96 (m, 10H, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.70 (s, 3H, CH_3), 3.84−3.86 (m, 1H, CH), 5.58 (d, 1H, *J* = 8.0 Hz, NH), 5.94 (d, 1H, *J* = 18.0 Hz, OH), 6.18 (s, 1H, Ph−CH), 6.71 (d, 2H, *J* = 8.4 Hz, Ph−H), 6.75−6.85 (m, 3H, Ph−H), 7.06 (d, 2H, *J* = 8.4 Hz, Ph−H) ($CDCl_3$)	[M + Na^+]: 505.1686; found: 505.1672
III$_{18}$	27	white solid, 183−184	1.05−1.95 (m, 10H, CH_3), 2.06 (s, 3H, Ph−CH_3), 2.62 (s, 3H, CH_3), 3.80−3.88 (m, 1H, CH), 6.07 (s, 1H, OH), 6.18 (s, 1H, Ph−CH), 6.61 (d, 1H, *J* = 7.6 Hz, NH), 6.75−7.23 (m, 7H, Ph−H) ($CDCl_3$)	[M + Na^+]: 505.1686; found: 505.1680

This study used U-4CR as the synthesis method via parallel synthesis, and the target compounds were proved to be easily synthesized and purified. Following the method developed in our previous study (*12*), we mixed an amine component and an aldehyde component first to get an intermediate imine, and then a carbonyl component was added in the mixture for certain time intervals before the addition of an isocyanide component. The amount of methanol added to the reaction was as small as possible, just enough to make the agitation effective. After all components were mixed, products usually precipitated in solvent within 1 h. To obtain high yields, we removed solvent under reduced pressure and then purified the products by column chromatography on silica gel using ethyl acetate and petroleum ether (60−90 °C) at 1:3 as an eluent. Generally, compounds in

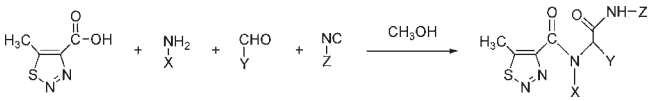
Table 2. Fungal Growth Inhibition by the Target Compounds (Percent)[a]

compd	AS	BC	CA	CB	CL	FO	GZ	PI	PP	PS	PT	RS
I_1	39	85	21	0	11	36	13	12	47	64	nd	nd
I_2	39	79	17	9	4	23	4	21	33	60	nd	nd
I_3	33	78	9	46	10	12	33	26	45	52	nd	nd
I_4	26	60	5	8	10	14	12	24	39	31	nd	nd
I_5	37	76	21	9	7	26	4	19	47	60	nd	nd
I_6	37	76	8	9	14	26	4	14	40	62	nd	nd
I_7	49	76	21	25	13	23	23	23	27	72	nd	nd
I_8	42	70	13	25	17	14	27	5	36	63	nd	nd
I_9	42	78	21	33	10	19	23	18	38	69	nd	nd
I_{10}	40	73	21	25	10	21	37	15	33	67	nd	nd
I_{11}	35	70	25	17	7	12	67	0	11	56	nd	nd
I_{12}	37	76	13	25	17	14	50	0	44	26	nd	nd
I_{13}	36	70	18	23	17	10	24	13	43	57	nd	nd
I_{14}	34	79	33	9	11	19	0	0	37	60	nd	nd
I_{15}	44	76	38	17	13	14	37	8	51	63	nd	nd
I_{16}	40	76	21	17	10	19	37	10	31	69	nd	nd
I_{17}	37	76	17	17	10	23	20	23	36	65	nd	nd
I_{18}	33	73	14	23	13	30	15	30	45	59	nd	nd
I_{19}	38	75	9	0	7	18	18	24	39	47	nd	nd
II_1	13	nd	9	0	14	nd	27	38	0	0	0	2
II_2	0	nd	27	25	0	nd	0	13	0	22	0	17
II_3	13	nd	27	25	29	nd	45	13	0	0	14	15
II_4	0	nd	0	25	14	nd	27	0	19	39	0	2
II_5	38	nd	0	13	14	nd	0	38	0	28	0	15
II_6	0	nd	0	13	0	nd	0	0	0	4	0	22
II_7	0	nd	0	0	14	nd	0	25	0	0	0	0
II_8	0	nd	0	25	0	nd	27	0	0	0	0	22
II_9	44	nd	27	25	57	nd	5	19	0	0	0	43
II_{10}	38	nd	0	13	14	nd	27	44	0	0	0	15
II_{11}	0	nd	0	25	0	nd	0	25	0	11	0	15
II_{12}	0	nd	27	25	14	nd	36	0	8	4	14	22
II_{13}	13	nd	9	13	36	nd	27	44	0	15	0	17
II_{14}	31	nd	45	25	29	nd	0	13	0	11	14	37
II_{15}	0	nd	9	25	0	nd	0	13	0	0	0	0
II_{16}	56	nd	36	0	50	nd	27	31	0	0	0	22
II_{17}	0	nd	0	0	0	nd	0	0	0	4	0	0
II_{18}	0	nd	0	11	14	nd	0	38	0	0	0	2
II_{19}	0	nd	0	0	50	nd	50	0	19	41	0	26
III_1	25	nd	18	0	0	nd	27	38	69	65	0	0
III_2	0	nd	45	25	14	nd	0	50	0	0	0	2
III_3	0	nd	0	25	0	nd	0	44	0	0	0	4
III_4	0	nd	27	25	0	nd	0	50	12	0	0	9
III_5	0	nd	18	13	0	nd	0	6	0	0	0	22
III_6	25	nd	27	25	0	nd	27	44	8	0	14	39
III_7	0	nd	0	0	0	nd	45	25	0	0	0	22
III_8	0	nd	9	0	14	nd	0	25	0	87	0	2
III_9	50	nd	27	25	43	nd	9	44	8	11	0	2
III_{10}	63	nd	55	25	57	nd	73	50	0	0	0	59
III_{11}	0	nd	0	0	14	nd	9	0	0	0	0	22
III_{12}	25	nd	27	25	29	nd	14	25	0	13	0	22
III_{13}	44	nd	0	25	14	nd	0	25	0	0	0	4
III_{14}	0	nd	27	25	14	nd	0	25	8	15	0	2
III_{15}	6	nd	0	25	0	nd	36	1	0	0	0	37
III_{16}	38	nd	0	25	29	nd	0	44	0	0	0	22
III_{17}	13	nd	45	25	36	nd	14	25	0	0	0	22
III_{18}	0	nd	0	25	0	nd	14	6	0	0	0	30
TDL	nd	67	18	40	nd	48	36	46	74	46	nd	1

[a] nd, not detected; AS, *Alternaria solani*; BC, *Botrytis cinerea*; CA, *Cercospora arachidicola*; CB, *Cercospora beticola*; CL, *Colletotrichum lagenarium*; FO, *Fusarium oxysporum*; GZ, *Gibberella zeae*; PI, *Phytophthora infestans* (Mont) de Bary; PP, *Physalospora piricola*; PS, *Pellicularia sasakii*; PT, *Puccinia triticina* Eriks; RS, *Rhizoctonia solani*; TDL, tiadinil.

series **III** had higher yields; this indicated that using cyclohexyl isocyanide as the isocyanide component could favor the reaction. Moreover, when 2-hydroxybenzaldehyde served as the carbonyl compound, the yields were pretty low, which indicated that the hydroxyl at the 2-position interfered with the interaction between amine and aldehyde.

Scheme 1. Molecule Structures and Synthesis of the Target Compounds[a]



[a] Series **I**: X = 3-chloro-4-methylphenyl, Z = isopropyl, Y = phenyl (I_1); 4-nitrophenyl (I_2); 3-nitrophenyl (I_3); 4-nitrophenyl (I_4); 4-chlorophenyl (I_5); 3-chlorophenyl (I_6); 2-chlorophenyl (I_7); 4-fluorophenyl (I_8); 3-fluorophenyl (I_9); 4-fluorophenyl (I_{10}); 4-(trifluoromethyl)phenyl (I_{11}); 3-(trifluoromethyl)phenyl (I_{12}); 2-(trifluoromethyl)phenyl (I_{13}); 4-methylphenyl (I_{14}); 3-methylphenyl (I_{15}); 2-methylphenyl (I_{16}); 4-hydroxyphenyl (I_{17}); 3-hydroxyphenyl (I_{18}); 2-hydroxyphenyl (I_{19}). Series **II**: X = 3-fluoro-4-methylphenyl, Z = isopropyl, Y = phenyl (II_1); 4-nitrophenyl (II_2); 3-nitrophenyl (II_3); 4-nitrophenyl (II_4); 4-chlorophenyl (II_5); 3-chlorophenyl (II_6); 2-chlorophenyl (II_7); 4-fluorophenyl (II_8); 3-fluorophenyl (II_9); 4-fluorophenyl (II_{10}); 4-(trifluoromethyl)phenyl (II_{11}); 3-(trifluoromethyl)phenyl (II_{12}); 2-(trifluoromethyl)-phenyl (II_{13}); 4-methylphenyl (II_{14}); 3-methylphenyl (II_{15}); 2-methylphenyl (II_{16}); 4-hydroxyphenyl (II_{17}); 3-hydroxyphenyl (II_{18}); 2-hydroxyphenyl (II_{19}). Series **III**: X = 3-fluoro-4-methylphenyl, Z = cyclohexyl, X = 3-fluoro-4-methylphenyl, Z = isopropyl, Y = phenyl (III_1); 4-nitrophenyl (III_2); 3-nitrophenyl (III_3); 4-nitrophenyl (III_4); 4-chlorophenyl (III_5); 3-chlorophenyl (III_6); 2-chlorophenyl (III_7); 4-fluorophenyl (III_8); 3-fluorophenyl (III_9); 4-fluorophenyl (III_{10}); 4-(trifluoromethyl)phenyl (III_{11}); 3-(trifluoromethyl)phenyl (III_{12}); 2-(trifluoromethyl)phenyl (III_{13}); 4-methylphenyl (III_{14}); 3-methylphenyl (III_{15}); 2-methylphenyl (III_{16}); 4-hydroxyphenyl (III_{17}); 3-hydroxyphenyl (III_{18}).

Biological Activity and Structure−Activity Relationship Study. *Fungicidal Activity*. The 12 fungi representing typical fungi often occurring in the Chinese agro-ecosystem including AS, BC, CA, CB, CL, FO, GZ, PI, PP, PS, PT, and RS were chosen for fungicide screening, and the results are shown in **Table 2**. All compounds showed a certain degree of fungicidal activity at 50 μg/mL. The results indicated that compounds belonging to series **I** showed high activities against BC and PS; most of them had inhibition activities above 70% against BC and 60% against PS, respectively. Especially, compound $\mathbf{I_1}$ had an inhibition activity of 85% against BC, and compound $\mathbf{III_8}$ had inhibition activity of 87% against PS. Moreover, compound $\mathbf{III_1}$ had inhibition activities of 69 and 65% against PP and PS, respectively. As the results describe above, most of the target compounds showed a very narrow spectrum against fungi tested; however, compound $\mathbf{III_{10}}$ showed a broad spectrum of activities against several fungi tested with inhibition activities of 55, 63, 73, 57, 59, and 50% against CA, AS, GZ, CL, RS, and PI, respectively. These results indicated that F- or CF_3-containing derivatives had good activity because of their special atom size and their characteristics with H to form a H bond with the potential target.

Structure and Fungicide Activity Relationship Study. All 56 5-methyl-1,2,3-thiadiazole derivatives with an α-amino acylamide skeleton synthesized were tested by fungicidal activity and direct antivirus activity in vitro screening. All of the results provided useful information to study the structure−activity relationship of these new structures shown in **Scheme 1**. Herein, the effect of substitutions at positions X and Y (**Scheme 1**) on the bioactivity were studied, respectively. At position X, we paid attention to the comparison of 3-chloro-4-methylphenyl with 3-fluoro-4-methylphenyl. At position Y, the substitutions at the substituted phenyl were compared with each other. Finally, at position Z, we compared cyclohexyl with isopropyl. Only significant effects are mentioned; if not, there was no significant structure−activity relationship observed on the bioactivity concerned.

For fungi PP, as described in **Figure 1**, at position X, compounds with 3-chloro-4-methylphenyl showed significantly better activity than the others. This indicated that a Cl atom here was the key factor favoring the bioactivity. For fungi PS, as described in **Figure 2**, at position X, compounds with 3-chloro-4-methylphenyl showed significantly better activity than the others.

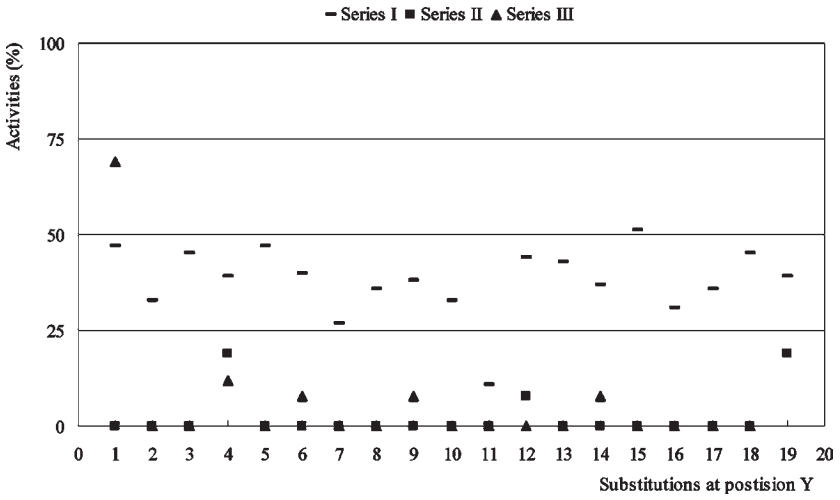


Figure 1. Parallel activity contrasts between series I, series II, and series III against PP. The inhibition activity was tested at 50 μg/mL and expressed in ordinate. The figures under the *X*-axis represent the substitutions at position Y in **Scheme 1**: 1 = phenyl; 2 = 4-nitrophenyl; 3 = 3-nitrophenyl; 4 = 4-nitrophenyl; 5 = 4-chlorophenyl; 6 = 3-chlorophenyl; 7 = 2-chlorophenyl; 8 = 4-fluorophenyl; 9 = 3-fluorophenyl; 10 = 4-fluorophenyl; 11 = 4-(trifluoromethyl)phenyl; 12 = 3-(trifluoromethyl)phenyl; 13 = 2-(trifluoromethyl)phenyl; 14 = 4-methylphenyl; 15 = 3-methylphenyl; 16 = 2-methylphenyl; 17 = 4-hydroxyphenyl; 18 = 3-hydroxyphenyl; 19 = 2-hydroxyphenyl. Compounds at the same abscissa had the same substitutions at position Y in **Scheme 1** and compounds belonged to the same series had the same substitutions at position X in **Scheme 1**.

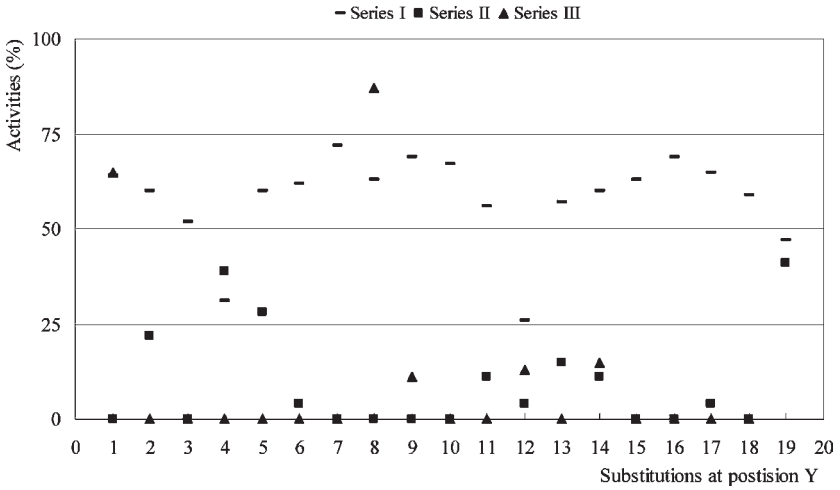


Figure 2. Parallel activity contrasts between series I, series II, and series III against PS. The inhibition activities were tested at 50 μg/mL. The figures under the abscissa are as explained in **Figure 1**.

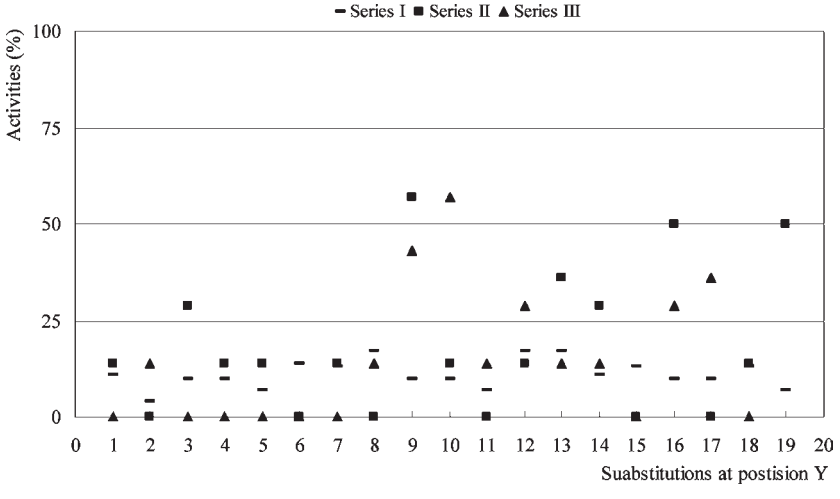


Figure 3. Parallel activity contrasts between series I, series II, and series III against CL. The inhibition activities were tested at 50 μg/mL. The figures under the abscissa are as explained in **Figure 1**.

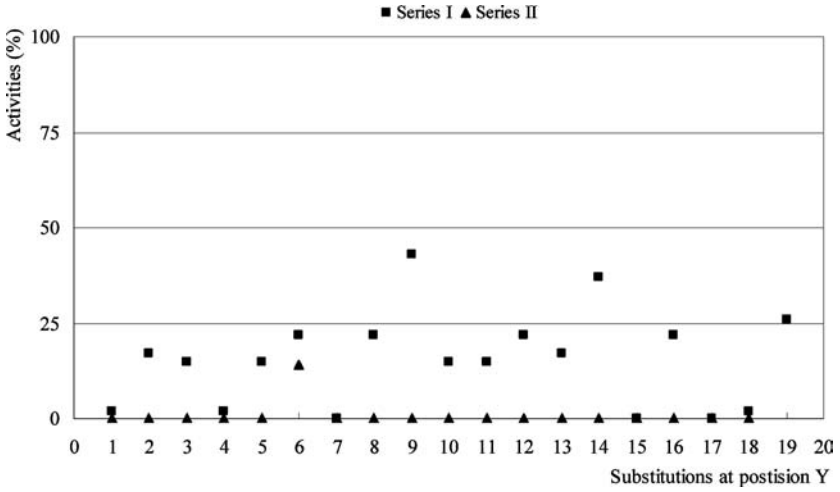


Figure 4. Parallel activity contrasts between series I, series II, and series III against RS. The inhibition activities were tested at 50 μg/mL. The figures under the abscissa are the same as explained in **Figure 1**.

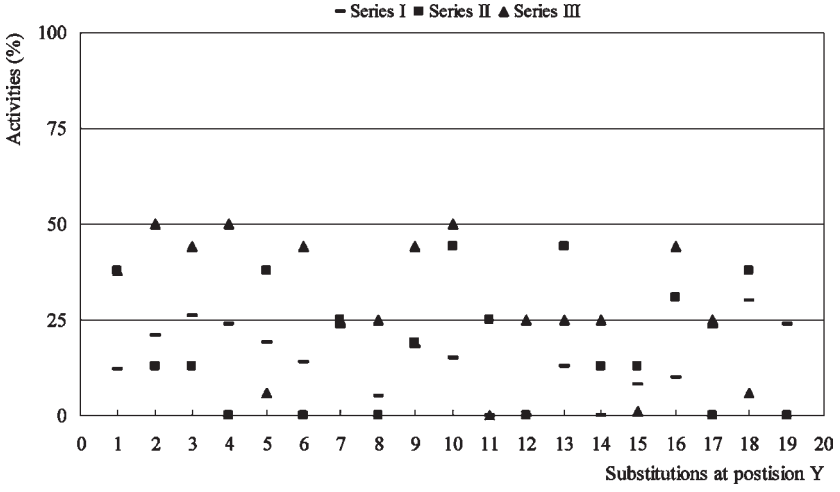


Figure 5. Parallel activity contrasts between series I, series II, and series III against PI. The inhibition activities were tested at 50 μg/mL. The figures under the abscissa are the same as explained in **Figure 1**.

This indicated that a Cl atom here was the key factor making contribution to the bioactivity. At position Y, compounds with phenyl and 4-fluorophenyl were better in most contrasts. For fungi CL, as described in **Figure 3**, at position X, compounds with 3-fluoro-4-methylphenyl showed significantly better activity than the others. This indicated that a F atom here was the key factor favoring the bioactivity. For fungi RS, as described in **Figure 4**, at position Z, compounds with isopropyl showed significantly better activity than the others. For fungi PI, as described in **Figure 5**, at position Z, compounds with cyclohexyl showed significantly better activity than the others.

Anti-TMV Activity in Vitro and in Vivo. TDL and ribavirin were used as two positive controls. The results of activity screening by half-leaf juice-robbing method against TMV indicated that (**Table 3**) most compounds showed a certain degree of direct inhibition activities against TMV in vitro with results lower than 50%. However, some compounds exhibited relatively higher activity; compounds $\mathbf{II_6}$, $\mathbf{III_2}$, and $\mathbf{III_{12}}$ had direct inhibition activities of 66, 70, and 72%, respectively, at 500 μg/mL, which were over twice as much as ribavirin did. They did not keep the high activity at 100 μg/mL. Only $\mathbf{III_1}$ and $\mathbf{II_{13}}$ had high activity at both 500 and 100 μg/mL. Their activities were $>70\%$ at 500 μg/mL and $>50\%$ at 100 μg/mL, significantly higher than those of the positive control agents. Compounds $\mathbf{III_1}$ and $\mathbf{II_{13}}$ are worthy of further study.

Moreover, 16 compounds were chosen for further evaluation of protection, inactivation, and curative and induction activities against TMV in vivo. The results in **Table 4** indicate that almost all of the compounds tested had good inactivation activity. Among these, compounds $\mathbf{I_{15}}$, $\mathbf{II_{10}}$, $\mathbf{III_6}$, and $\mathbf{III_8}$ had inactivation activities of 82, 74, 79, and 79%, respectively, at 500 μg/mL, and 72, 73, 69, and 69%, respectively, at 100 μg/mL, which were significantly better than the positive control agents. As for the protection, curative effect, and induction activities, most of them had lower activities than the positive control. However, some compounds stood out. Compound $\mathbf{II_{17}}$ had good protection activities of 76 and 71% at 500 and 100 μg/mL, respectively, and compound $\mathbf{I_{10}}$ had curative activities of 60 and 47% at 500 and 100 μg/mL, respectively, which were equal to or higher than that of the positive control. These results indicated that the title compounds had good potential of antifungal and anti-TMV bioactivities. There was observed no phytotoxicity to tobacco during the test courses of experiment.

Structure and Anti-TMV Activity Relationship Studies. No significant structure−activity relationship was observed. This indicated that the whole molecular structure played an important part in these activities rather than one moiety in the molecule.

Table 3. Inhibition Activities against TMV in Vitro

compd	concn (μg/mL)	activity (%)	compd	concn (μg/mL)	activity (%)	compd	concn (μg/mL)	activity (%)
I_1	200	30 ± 1	II_1	100	5 ± 4	III_1	100	51
	500	43 ± 3		500	15 ± 5		500	71 ± 3
I_2	200	14 ± 1	II_2	100	9 ± 8	III_2	100	8 ± 10
	500	19 ± 3		500	25 ± 11		500	70 ± 4
I_3	100	28 ± 11	II_3	100	4 ± 4	III_3	100	9 ± 10
	500	34 ± 13		500	14 ± 5		500	57 ± 4
I_4	100	19 ± 4	II_4	100	11 ± 10	III_4	100	5 ± 8
	500	59 ± 13		500	24 ± 10		500	11 ± 2
I_5	200	25	II_5	100	20 ± 8	III_5	100	8 ± 1
	500	32 ± 5		500	12 ± 2		500	14 ± 2
I_6	200	6 ± 1	II_6	100	32 ± 2	III_6	100	14 ± 6
	500	9 ± 1		500	66 ± 5		500	18 ± 9
I_7	200	3 ± 5	II_7	100	23 ± 5	III_7	100	16 ± 3
	500	8 ± 1		500	17 ± 2		500	53 ± 7
I_8	200	14 ± 3	II_8	100	18 ± 9	III_8	100	24 ± 2
	500	19 ± 7		500	51 ± 1		500	44 ± 5
I_9	100	34 ± 4	II_9	100	50	III_9	100	52 ± 1
	500	18 ± 3		500	30		500	30 ± 2
I_{10}	100	32 ± 5	II_{10}	100	16 ± 9	III_{10}	100	33 ± 1
	500	34 ± 5		500	46 ± 2		500	58 ± 1
I_{11}	200	32 ± 5	II_{11}	100	14 ± 2	III_{11}	100	27 ± 6
	500	34 ± 5		500	45 ± 2		500	36 ± 4
I_{12}	200	17	II_{12}	100	19 ± 1	III_{12}	100	35 ± 1
	500	41		500	51 ± 3		500	72 ± 11
I_{13}	200	29	II_{13}	100	57 ± 1	III_{13}	100	31 ± 6
	500	16		500	71 ± 5		500	20 ± 5
I_{14}	200	11	II_{14}	100	7 ± 3	III_{14}	100	21 ± 1
	500	21		500	31 ± 3		500	53 ± 11
I_{15}	200	18 ± 3	II_{15}	100	14 ± 3	III_{15}	100	44 ± 6
	500	34 ± 4		500	35 ± 1		500	29 ± 2
I_{16}	200	58	II_{16}	100	36 ± 8	III_{16}	100	13 ± 3
	500	12		500	55 ± 1		500	35 ± 5
I_{17}	200	0	II_{17}	100	26 ± 4	III_{17}	100	9 ± 2
	500	4		500	35 ± 1		500	34 ± 9
I_{18}	100	13 ± 8	II_{18}	100	4 ± 4	III_{18}	100	25 ± 2
	500	24 ± 2		500	20 ± 5		500	48 ± 1
I_{19}	100	18 ± 4	II_{19}	100	27 ± 7			
	500	23 ± 2		500	56 ± 1			
ribavirin	100	20 ± 2	tiadinil	100	25 ± 2			
	500	32 ± 1		500	48 ± 1			

Table 4. Antivirus in Vivo and Systemic Acquired Resistance Activity of the Title Compounds (Percent)

	protective effect (%)		curative effect (%)		inactivation effect (%)		induction effect (%)	
compd	500 μg/mL	100 μg/mL	500 μg/mL	100 μg/mL	500 μg/mL	100 μg/mL	100 μg/mL	50 μg/mL
I_1	57 ± 5	40 ± 2	46 ± 7	30 ± 4	65 ± 12	50 ± 4	41 ± 6	33 ± 9
I_{15}	48 ± 5	14 ± 5	40 ± 8	33 ± 4	82 ± 4	72 ± 4	49 ± 8	65 ± 3
I_{16}	38 ± 10	13 ± 6	42 ± 7	21 ± 3	50 ± 4	23 ± 8	0	37 ± 7
I_{17}	36 ± 2	8 ± 10	nd	nd	64 ± 5	50 ± 4	41 ± 3	23 ± 5
II_2	27 ± 10	26 ± 7	17 ± 4	0 ± 7	62 ± 8	65 ± 4	7 ± 7	66 ± 4
II_{10}	60 ± 6	27 ± 7	60 ± 6	47 ± 4	74 ± 9	73 ± 4	7 ± 8	59 ± 3
II_{13}	44 ± 5	5 ± 4	44 ± 5	32 ± 6	65 ± 4	67 ± 9	60 ± 6	30 ± 4
II_{17}	76 ± 5	71 ± 0	55 ± 4	28 ± 6	72 ± 4	51 ± 9	7 ± 8	36 ± 11
III_6	67	29 ± 8	40 ± 8	0	79 ± 4	69	22 ± 0	30 ± 5
III_8	17 ± 8	6 ± 7	52 ± 5	20 ± 10	79 ± 4	69 ± 8	41 ± 7	41 ± 16
III_{15}	8 ± 3	10 ± 5	38 ± 5	29 ± 7	69 ± 8	38 ± 8	54 ± 7	40 ± 8
III_{18}	44 ± 7	43 ± 5	57 ± 2	23 ± 2	67 ± 4	44 ± 4	76 ± 5	32 ± 9
tiadinil	75	57	58 ± 7	46 ± 8	59 ± 4	42 ± 4	52 ± 4	50 ± 6
ribavirin	59 ± 7	30 ± 7	nd	nd	59 ± 9	46 ± 8	28 ± 9	31 ± 9

ABBREVIATIONS USED

AS, *Alternaria solani*; BTH, acibenzolar-*S*-methyl; CA, *Cercospora arachidicola*; CB, *Cercospora beticola*; CL, *Colletotrichum lagenarium*; DMSO-d_6, deutero-, dimethyl sulfoxide; FO, *Fusarium oxysporum*; GZ, *Gibberella zeae*; ^{1}H NMR, hydrogen nuclear magnetic resonance; HRMS, high-resolution mass spectrometry; nd, not detected; PDA, potato dextrose agar; PG, *Phyricularia grisea*; PI, *Phytophthora infestans* (Mont) de Bary; PP, *Physalospora piricola*; PS, *Pellicularia sasakii*; RS, *Rhizoctonia solani*; SOP, standard operation practice; TDL, tiadinil; TMS, tetramethylsilane;

TMV, tobacco mosaic virus; U-4CR, Ugi four-component condensation reaction.

LITERATURE CITED

(1) Bloom, J. D.; Dushin, R. G.; Curran, K. J.; Donahue, F.; Norton, E. B.; Terefenko, E.; Jones, T. R.; Ross, A. A.; Feld, B.; Lang, S. A.; DiGrandi, M. J. Thiourea inhibitors of herpes viruses. Part 2: *N*-Benzyl-*N*′-arylthiourea inhibitors of CMV. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3401–3406.

(2) Bloom, J. D.; DiGrandi, M. J.; Dushin, R. G.; Curran, K. J.; Ross, A. A.; Norton, E. B.; Terefenko, E.; Jones, T. R.; Feld, B.; Lang, S. A. Thiourea inhibitors of herpes viruses. Part 1: Bis-(aryl)thiourea inhibitors of CMV. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2929–2932.

(3) Fan, Z. J.; Shi, Z. G.; Zhang, H. K.; Liu, X. F.; Bao, L. L.; Ma, L.; Zuo, X.; Zheng, Q. X.; Mi, N. Synthesis and biological activity evaluation of 1,2,3-thiadiazole derivatives as potential elicitors with highly systemic acquired resistance. *J. Agric. Food Chem.* **2009**, *57*, 4279–4286.

(4) Xu, Y. F.; Zhao, Z. J.; Qian, X. H.; Qian, Z. G.; Tian, W. H.; Zhong, J. J. Novel, unnatural benzo-1,2,3-thiadiazole-7-carboxylate elicitors of taxoid biosynthesis. *J. Agric. Food Chem.* **2006**, *54*, 8793–8798.

(5) Dong, W. L.; Xu, J. Y.; Liu, X. H.; Li, Z. M.; Li, B. J.; Shi, Y. X. Synthesis, crystal structure and biological activity of novel anthranilic diamides containing 1,2,3-thiadiazole. *Chem. J. Chinese Univ.* **2008**, *29*, 1990–1994.

(6) Tang, W. M.; He, X. Q.; Song, V. A.; Hu, D. Y.; Zhang, Z. G.; Sang, W. J.; Yang, S.; Jin, L. H. Synthesis and fungicidal activity of oleic amide and linoleic amide of N-heterocycle. *Chinese J. Org. Chem.* **2004**, *24*, 1288–1291.

(7) Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M.; Daneshtalab, M.; Shafiee, A. Synthesis and in vitro antifungal and cytotoxicity evaluation of substituted 4,5-dihydronaphtho[1,2-*d*][1,2,3]thia(or selena)-diazoles. *Farmaco* **2003**, *58*, 63–68.

(8) Moawad, E. B.; Yousif, M. Y.; Metwally, M. A. Synthesis of certain heteroaryl-fused pyrimidines and pyridines and Selena- and thiadiazoles with naphthyl substituent as potential antifungal agents. *Pharmazie* **1989**, *44*, 820–822.

(9) Nombela, G.; Pascual, S.; Aviles, M.; Guillard, E.; Muniz, M. Benzothiadiazole induces local resistance to *Bemisia tabaci* (*Hemiptera*:*Aleyrodidae*) in tomato plants. *J. Econ. Entomol.* **2005**, *98*, 2266–2271.

(10) Chen, Y. F.; Zhang, C. R.; Huang, X. Effect of TDZ on somatic embryogenesis of plant. *Plant Physiol. Commun.* **2006**, *42*, 127–133.

(11) Bakulev, V.; Mokrushin, V. Structures synthesis, and properties of 1,2,3-thiadiazoles (review). *Chem. Heterocycl. Compd.* **1986**, *22*, 811–827.

(12) Zuo, X.; Mi, N.; Fan, Z. J.; Zheng, Q. X.; Zhang, H. K.; Wang, H.; Yang, Z. K. Synthesis of 4-methyl-1,2,3-thiadiazole derivatives via Ugi reaction and their biological activities. *J. Agric. Food Chem.* **2010**, *58*, 2755–2762.

(13) Fan, Z. J.; Yang, Z. K.; Zhang, H. K.; Mi, N.; Wang, H.; Cai, F.; Zuo, X.; Zheng, Q. X.; Song, H. B. Synthesis, crystal structure, and biological activity of 4-methyl-1,2,3-thiadiazole-containing 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles. *J. Agric. Food Chem.* **2010**, *58*, 2630–2636.

(14) Domling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew Chem. Int. Ed.* **2000**, *18*, 3169–3210.

(15) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. Studies on isonitriles. *Angew. Chem.* **1959**, *71*, 386.

(16) Ugi, I.; Steinbruckner, C. Concerning a new condensation principle. *Angew. Chem.* **1960**, *72*, 267–268.

(17) Ugi, I. α-Addition of immonium ions and anions to isonitriles coupled with secondary reactions. *Angew. Chem.* **1962**, *74*, 9–22.

(18) Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. Cyclohexyl isocyanide. *Org. Synth.* **1961**, *41*, 13–15.

(19) Bakulev, V. A.; Dehaen, W. *The Chemistry of 1, 2, 3-thiadiazoles*; Wiley: New York, 2004.

Received for review February 19, 2010. Revised manuscript received June 5, 2010. Accepted June 6, 2010. This study was funded in part by grants from the National Natural Science Foundation of China (No. 20872071), the International Collaboration Program of the National Natural Science Foundation of China (No. 20911120069), the Tianjin Natural Science Foundation (10JCZDJC17500), the National Key Project for Basic Research (2010CB126105), and the Key Laboratory of Pesticide Chemistry and Application, Ministry of Agriculture (MOA), Beijing, People's Republic of China (No. MOAPCA200903).