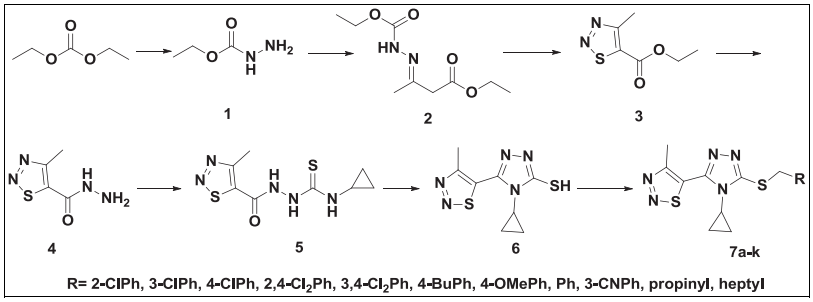
Cheng-Xia Tan,[a†] Yan-Xia Shi,[c†] Jian-Quan Weng,[a] Xing-Hai Liu,[a*] Wei-Guang Zhao,[b*] and Bao-Ju Li[c*]

[a]College of Chemical Engineering & Materials Sciences, Zhejiang University of Technology, Hangzhou, 310014, China
[b]State-Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, China
[c]Institute of Vegetables and Flowers, Chinese Academy of Agricultural Sciences, Beijing, 100014, China
*E-mail: xhliu@zjut.edu.cn or zwg@nankai.edu.cn or libj@mail.caas.net.cn
†Cheng-Xia Tan and Yan-Xia Shi contributed equally to this work.

Received December 7, 2011
DOI 10.1002/jhet.1656
Published online 2 December 2013 in Wiley Online Library (wileyonlinelibrary.com).



Starting from carbonic acid diethyl ester, a series of 1,2,4-triazole derivatives containing 1,2,3-thiadiazole were synthesized. Reactions were performed by microwave irradiation or ultrasonic irradiation as well as by conventional heating. The structure of title compounds was characterized by ^{1}H-NMR, MS, and elemental analyses. The fungicidal activities of these compounds were tested *in vivo*. Most of title compounds exhibited good antifungal activity against *Pseudoperonospora cubensis*. Some of title compounds displayed moderate antifungal activities against *Fusarium oxysporum*, *Pseudoperonospora cubensis*, *Sphaerotheca fuligenea*, *Corynespora cassiicola*, and *Xanthomonas axonopodis*.

J. Heterocyclic Chem., **51**, 690 (2014).

INTRODUCTION

Heterocyclic compounds have been received considerable attentions in recent years because of their pharmacological and pesticidal importance [1–3]. 1,2,3-Thiadiazole moiety has been claimed to have beneficial, medicinal, and agricultural applications, because of their exhibited excellent biological activities such as fungicidal [4], anti-HBV [5], herbicidal [6], anti-TMV [7], antihistaminic [8], antifungal [9], and antibacterial [10]. Also, they are useful intermediates in organic synthesis, and the 1,2,3-thiadiazole chemistry has been widely studied. For example, after the plant inducers such as thiadinal [11] and BTH [12] were discovered (Figure 1), 1,2,3-thiadiazoles pesticide has become one of the focuses of developing agrochemicals in academia and industries.

Furthermore, it is reported that 1,2,4-triazoles possess a diverse range of bioactivities in medicinal and agrochemical field, such as anticancer [13], anti-inflammatory [14], antimicrobial [15], herbicidal [16], and insecticidal [17] activity. Some compounds had been developed as commercial fungicides (Figure 2), such as triadimefon, triadimenol, flusilazole, and so on. Because of their diverse properties, 1,2,4-triazole fungicides may become one of the focuses in drug research.

In view of these facts mentioned earlier and also as a part of our work [18] on the synthesis of bioactive lead compounds, the title compounds were designed by introducing cyclopropane and 1,2,3-thiadiazole pharmacophore into 1,2,4-triazole scaffold. Some 1,2,4-triazole derivatives were synthesized and characterized by ^{1}H-NMR, MS, and elemental analysis. The biological activities of these compounds were tested *in vivo*.

RESULTS AND DISCUSSION

Synthesis and spectra. The synthesis procedures for title compound were shown in Scheme 1. The intermediate **6** is reacted with substituted benzyl chloride to afford intermediate **7** at RT for 24 h. To optimize the reaction condition and reaction times, microwave and ultrasonic irradiation were employed. NaOH/DMF/H_2O system was applied under microwave irradiation at 90°C for 10 min. Also, K_2CO_3/DMF condition was tried under ultrasound irradiation at RT for 50 min. The results are shown in Table 1. The proton magnetic resonance spectra of the triazoles have been recorded in $CDCl_3$. The triazole intermediates can exist either as a thione or the thiol tautomeric forms or as an equilibrium mixture of both forms, because they have a thioamide, —NH—C(═S) function. The chemical shift at δ 10.86 as a singlet may be due to SH proton, indicating that **6** existed not as thione but as the thiol tautomeric forms in solution [19]. The signal of CH_2 protons of thioether and sulfone neighboring to the triazole ring was observed at δ 4.73–4.53 ppm, respectively, except compound **7j** and **7k**. The chemical shifts around

© 2013 HeteroCorporation

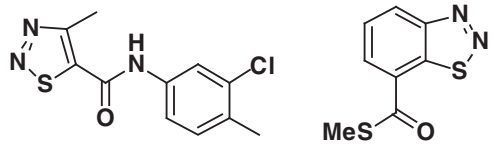


Figure 1. The commercial pesticides contain 1,2,3-thiadiazole group.

3.0 ppm are the methyl of 1,2,3-thiadiazole. All the title compounds of mass spectra are M + H peak.

Antifungal activity and SAR. The *in vivo* fungicidal results of title compounds against *Fusarium oxysporum*, *Pseudoperonospora cubensis*, *Sphaerotheca fuligenea*, *Corynespora cassiicola*, *Xanthomonas axonopodis*, *Pseudomonas syringae* pv. *lachrymans*, and *Rhizoctonia solanii* were listed in Table 2; thiophanate methyl, jinggangmeisu, and zhongshengmycin were used as a control. Lots of the title compounds showed good control efficacy of some of the test fungi at a concentration of 500 μg/mL. Meanwhile, all of these tested compounds were found safe for the cucumber plants. As shown in Table 1, compound **7c**, **7d**, **7f**, **7j**, and **7k** exhibited a significant inhibition effect against *P. cubensis*, and the fungicidal activities (control efficacy of 71–83%) were higher than those of thiophanate methyl, jinggangmeisu, and zhongshengmycin. All these compounds did not display obvious fungicidal activities against *R. solanii*. All of them were less effective than that of the control jinggangmeisu. Compound **7f**, **7i**, **7j**, and **7k** showed fair fungicidal activity (control effect 69.9–86.2%) against *F. oxysporum*. All of the four compounds were similar with that of thiophanate methyl. Compound **7d**, **7j**, and **7k**, held about 50% control effect against *S. fuligenea*. For the *X. axonopodis* and *P. syringae* pv. *lachrymans*, it was found that most of the compounds had moderate

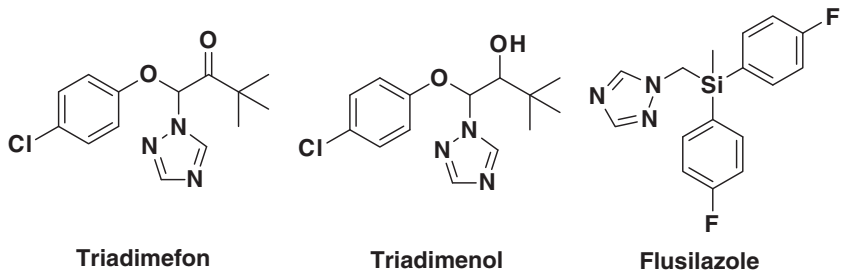


Figure 2. The commercial pesticides contain 1,2,4-triazole group.

Scheme 1. The synthetic route of title compounds.

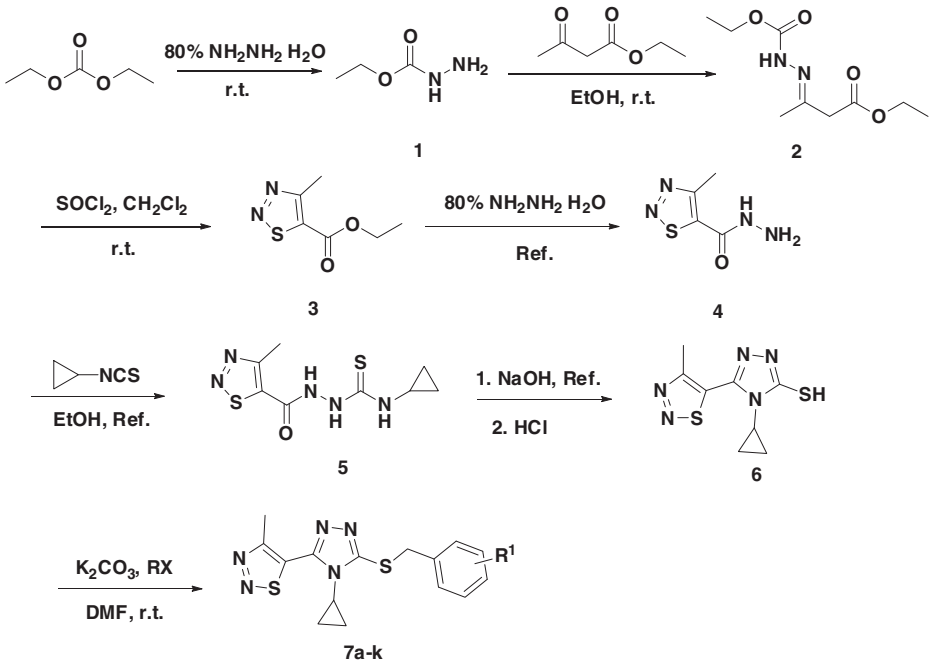


Table 1

The reaction condition of target compounds.

Compound	Condition		Time	Yield
7h	RT	K_2CO_3/DMF	24 h	83%
7h	US/RT	K_2CO_3/DMF	50 min	84%
7h	MW/90°C	K_2CO_3/DMF/H_2O	10 min	88%

US, ultrasonic; MW, microwave.

fungicidal activity, except that compound **7g** (78.02%) displayed moderate control effect against *X. axonopodis*, which was similar to that of the most active fungicide zhongshengmycin (87.86%). Compound **7c** showed moderate control effect (66.06%) against *C. cassiicola*, and it was had same level with zhongshengmycin (75.19%). In general, the *in vivo* fungicidal activity of compounds **7** indicated that the change of substituent affects the activity with the trend alkyl > aromatic. For example, **7j** and **7k** exhibited higher fungicidal activity than that of substituted benzene rings. In addition, the substituted benzene ring compound with *p*-Cl or 2,4-Cl_2 lead to higher fungicidal activity against *P. cubensis*.

CONCLUSIONS

In summary, we have synthesized some novel 1,2,4-triazole derivatives containing cyclopropane ring and 1,2,3-thiadiazole ring under conventional, microwave, and ultrasonic condition with good yields. The preliminary bioassays showed that some of the compounds had good antifungal activities.

EXPERIMENTAL

Instruments. Melting points were determined using an X-4 apparatus (Beijing, China) and uncorrected. ^{1}H-NMR spectra were measured on a AV 400 instrument (Bruker, Fallanden, Switzerland) using TMS as an internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument (San Jose, CA). Elemental analyses were performed on a Vario EL elemental analyzer (Hanau, Germany). Microwave activation was carried out with CEM Discover focused microwave (2450 MHz, 300 W; Matthews, NC). Ultrasonic activation was carried out with KQ-200KDB ultrasonic apparatus (Kunshan, Jiangsu, China). All the reagents are of analytical grade or freshly prepared before use.

General procedure. The title compounds were synthesized according to the route shown in Scheme 1, and the yields were not optimized.

Synthesis of intermediates.

Preparation of 4-methyl-1,2,3-thiadiazole-5-carbohydrazide. Intermediate 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide **4** was synthesized according to the literature [5]. A mixture of carbonic acid diethyl ester (11.8 g, 0.1 mol) and hydrazine hydrate (5.6 mL, 0.095 mol, 85%) was added into a 250 mL round-bottom flask equipped with a condenser. The reaction mixture was heated to 50°C, stirred for 20 min, and then stirred at RT for 30 h. Water, ethanol, and excess carbonic acid diethyl ester were distilled off under reduced pressure. After dryness, a white crystal ethyl hydrazinecarboxylate **1** (9.88 g) was obtained with a yield of 95%. A solution containing the compound **1** (6.36 g, 0.06 mol) in ethanol (16.7 mL) was added dropwise to a solution of ethyl acetoacetate (7.8 g, 0.06 mol) in ethanol (3.7 mL) slowly. After stirring for 6 h at RT, water and ethanol were distilled off under reduced pressure, and a white product ethyl 2-(4-ethoxy-4-oxobutan-2-ylidene) hydrazinecarboxylate **2** (12.8 g) was obtained with a yield of 99%. To a solution of 3-ethoxycarbonylhydrazonoacetic acid ethyl ester (12.8 g, 0.059 mol) in dichloromethane (25 mL), thionyl chloride (20 mL) was added dropwise in batches below 20°C. After stirring in an ice water bath for 1 h, the reaction mixture was permitted to stand for 20 h at RT. The excess thionyl chloride and dichloromethane were distilled off, and the remaining residue was subject to fractional distillation under reduced pressure. A slight yellowish oil ethyl 4-methyl-1,2,3-thiadiazole-5-carboxylate **3**

Table 2

Antifungal activity of title compounds (percent relative control efficacy) at 500 μg/mL.

No.	PC	PS	CC	FO	SF	XA	RS
7a	45.92	36.50	25.18	53.61	27.07	52.07	12.07
7b	68.54	20.39	27.59	53.61	17.73	34.04	6.66
7c	79.24	48.87	66.06	59.87	32.48	44.38	8.36
7d	83.04	57.47	55.99	58.62	47.23	59.57	4.97
7e	64.46	54.45	14.09	53.61	10.51	26.13	16.12
7f	78.89	54.48	53.72	72.41	29.57	49.95	10.84
7g	45.04	43.29	39.60	53.61	29.83	78.02	3.59
7h	54.02	43.55	48.01	66.14	50.11	14.25	8.36
7i	69.17	24.41	28.99	86.21	44.53	8.39	3.21
7j	71.07	6.47	21.38	69.91	58.58	43.03	4.51
7k	81.62	30.17	54.03	71.16	42.63	45.96	9.60
Thiophanate methyl	38.32	49.85	27.72	78.68	30.15	47.92	10.84
Jinggangmeisu	35.92	49.20	45.47	59.87	19.81	−3.15	93.84
Zhongshengmycin	8.04	75.19	65.13	28.53	65.08	87.86	10.18

PC, *Pseudoperonospora cubensis*; PS, *Pseudomonas syringae* pv. *lachrymans*; CC, *Corynespora cassiicola*; FO, *Fusarium oxysporum*; SF, *Sphaerotheca fuligenea*; XA, *Xanthomonas axonopodis*; RS, *Rhizoctonia solanii*.

(7.95 g) was obtained with a yield of 77%. A mixture of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester **3** (1.72 g, 10 mmol) and hydrazine hydrate (12 mmol) in 10 mL of methanol was stirred vigorously for 0.5 h at RT, the mixture was filtered, and the solid was washed with cold methanol. After drying, the solid was recrystallized from methanol to give intermediate 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide **4**.

Preparation of isothiocyanatocyclopropane. The isothiocyanatocyclopropane was synthesized according to the reference [19].

N-Cyclopropyl-2-(4-methyl-1,2,3-thiadiazole-5-carbonyl) hydrazinecarbothioamide (5). 4-Methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide **4** mixed with 1.5 g of isothiocyanatocyclopropane for refluxing about 3 h in ethanol. After cooling, lots of solid were obtained. The solid was filtered, dried, and recrystallized from methanol to give intermediate *N*-cyclopropyl-2-(4-methyl-1,2,3-thiadiazole-5-carbonyl)hydrazinecarbothioamide **5**: yellow crystal, yield 87.6%, mp 120–121°C, ^{1}H-NMR (400 M, $CDCl_3$): 0.40–0.79 (m, 4H, cyclopropane-CH_2), 2.78 (m, 1H, cyclopropane-CH), 3.31 (s, 3H, Me).

4-Cyclopropyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-4H-1,2,4-triazole-3-thiol (6). *N*-cyclopropyl-2-(4-methyl-1,2,3-thiadiazole-5-carbonyl) hydrazinecarbothioamide **5** (10 mmol) mixed with 15 mL, 2*N* NaOH for refluxing about 4 h. After cooling, 4*N* HCl was added, and lots of solid were obtained. The solid was filtered, dried, and recrystallized from methanol to give intermediate 4-cyclopropyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-4*H*-1,2,4-triazole -3-thiol **6**: yellow crystal, yield 85.6%, mp 205–209°C, ^{1}H-NMR (400 M, $CDCl_3$): 1.13–1.25 (m, 4H, cyclopropane-CH_2), 2.42 (s, 3H, Het—Me), 2.91–2.97 (m, 1H, cyclopropane-CH), 10.86 (br, 1H, SH).

General procedure for thioether. To a stirred solution of 4-cyclopropyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-4*H*-1,2,4-triazole-3-thiol **6** (1.5 g, 5.1 mmol) and K_2CO_3 (0.2 g, 5.6 mmol) in DMF (15 mL), a mixture of a substituted benzyl chloride (5.6 mmol) was added dropwise. The resulting mixture was stirred at RT for overnight. The mixture was poured into water. The precipitate formed was filtered off and recrystallized from petroleum ether/acetone to give **7** in good yields.

5-(5-((2-Chlorobenzyl)thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7a). This compound was obtained as white solid, yield 78.5%, mp 133–134°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.70–0.84 (m, 2H, cycloprane-CH_2), 1.09–1.15 (m, 2H, cycloprane-CH_2), 2.86–2.93 (m, 1H, cyclopropane-CH), 2.94 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 7.14 (s, 1H, Ph—H), 7.20–7.24 (m, 1H, Ph—H), 7.34 (d, J = 7.62 Hz, 1H, Ph—H), 7.58 (d, J = 7.24 Hz, 1H, Ph—H); ESI–MS: 365 $[M+1]^+$; Elemental analysis for $C_{15}H_{14}ClN_5S_2$: found C 49.56, H 3.65, N 19.44; Calcd C 49.51, H 3.88, N 19.25.

5-(5-((3-Chlorobenzyl)thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7b). This compound was obtained as white solid, yield 86.7%, mp 131–132°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.82–0.96 (m, 2H, cycloprane-CH_2), 1.21–1.26 (m, 2H, cycloprane-CH_2), 2.99 (s, 3H, CH_3), 3.03–3.18 (m, 1H, cyclopropane-CH), 4.62 (s, 2H, CH_2), 7.30–7.35 (m, 2H, Ph—H), 7.36–7.44 (m, 1H, Ph—H), 7.49 (s, 1H, Ph—H); ESI–MS: 365 $[M+1]^+$; Elemental analysis for $C_{15}H_{14}ClN_5S_2$: found C 49.56, H 3.78, N 19.13; Calcd C 49.51, H 3.88, N 19.25.

5-(5-((4-Chlorobenzyl)thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7c). This compound was obtained as white solid, yield 37.0%, mp 112–113°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.85–0.94 (m, 2H, cycloprane-CH_2), 1.20–1.25 (m, 2H, cycloprane-CH_2), 3.03 (s, 3H, CH_3), 3.04–3.12 (m, 1H, cyclopropane-CH), 4.60 (s, 2H, CH_2), 7.32 (d, J = 7.96 Hz, 2H, Ph—H), 7.45 (d, J = 7.96 Hz, 2H, Ph—H); ESI–MS: 365 $[M+1]^+$; Elemental analysis for $C_{15}H_{14}ClN_5S_2$: found C 49.87, H 3.99, N 19.34; Calcd C 49.51, H 3.88, N 19.25.

5-(4-Cyclopropyl-5-((2,4-dichlorobenzyl)thio)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7d). This compound was obtained as white solid, yield 89.3%, mp 114–115°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.81–0.91 (m, 2H, cycloprane-CH_2), 1.21–1.26 (m, 2H, cycloprane-CH_2), 3.03 (s, 3H, CH_3), 3.06–3.12 (m, 1H, cyclopropane-CH), 4.73 (s, 2H, CH_2), 7.22 (d, J = 8.27 Hz, 1H, Ph—H), 7.45 (s, 1H, Ph—H), 7.70 (d, J = 8.22 Hz, 1H, Ph—H); ESI–MS: 399 $[M+1]^+$; Elemental analysis for $C_{15}H_{13}Cl_2N_5S_2$: found C 45.33, H 3.43, N 17.66; Calcd C 45.23, H 3.29, N 17.58.

5-(4-Cyclopropyl-5-((3,4-dichlorobenzyl)thio)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7e). This compound was obtained as white solid, yield 88.5%, mp 95–96°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 1.06–1.13 (m, 2H, cycloprane-CH_2), 1.21–1.27 (m, 2H, cycloprane-CH_2), 3.03 (s, 3H, CH_3), 3.05–3.10 (m, 1H, cyclopropane-CH), 4.58 (s, 2H, CH_2), 7.38 (d, J = 8.35 Hz, 1H, Ph—H), 7.42(d, J = 8.12 Hz, 1H, Ph—H), 7.61 (s, 1H, Ph—H); ESI–MS: 399 $[M+1]^+$; Elemental analysis for $C_{15}H_{13}Cl_2N_5S_2$: found C 45.41, H 2.97, N 17.88; Calcd C 45.23, H 3.29, N 17.58.

5-(5-((4-(tert-Butyl)benzyl)thio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7f). This compound was obtained as white solid, yield 39.8%, mp 113–114°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.86–1.02 (m, 2H, cycloprane-CH_2), 1.08–1.13 (m, 2H, cycloprane-CH_2), 1.24 (s, 9H, CH_3), 2.92 (s, 3H, CH_3), 2.96–3.05 (m, 1H, cyclopropane-CH), 4.58 (s, 2H, CH_2), 7.19 (s, 2H, Ph—H), 7.24–7.28 (m, 1H, Ph—H), 7.31–7.39 (s, 1H, Ph—H); ESI–MS: 386 $[M+1]^+$; Elemental analysis for $C_{19}H_{23}N_5S_2$: found C 59.05, H 6.25, N 18.43; Calcd C 59.19, H 6.01, N 18.16.

5-(4-Cyclopropyl-5-((4-methoxybenzyl)thio)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7g). This compound was obtained as white solid, yield 87.3%, mp 119–120°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.89–0.94 (m, 2H, cycloprane-CH_2), 1.12–1.25 (m, 2H, cycloprane-CH_2), 3.02 (s, 3H, CH_3), 3.09–3.15 (m, 1H, cyclopropane-CH), 3.82 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2), 6.88 (d, J = 7.86 Hz, 2H, Ph—H), 7.41 (d, J = 7.86 Hz, 2H, Ph—H); ESI–MS: 360 $[M+1]^+$; Elemental analysis for $C_{16}H_{17}N_5OS_2$: found C 53.33, H 4.88, N 19.79; Calcd C 53.46, H 4.77, N 19.48.

5-(5-(Benzylthio)-4-cyclopropyl-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7h). This compound was obtained as white solid, yield 77.9%, mp 122–123°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.71–0.84 (m, 2H, cycloprane-CH_2), 1.08–1.14 (m, 2H, cycloprane-CH_2), 2.89–2.93 (m, 1H, cyclopropane-CH), 2.94 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 7.21–7.29 (m, 3H, Ph—H), 7.39 (m, 2H, Ph—H); ESI–MS: 330 $[M+1]^+$; Elemental analysis for $C_{15}H_{15}N_5S_2$: found C 54.44, H 4.76, N 21.01; Calcd C, 54.69; H, 4.59; N, 21.26.

3-(((4-Cyclopropyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzonitrile (7i). This compound was obtained as white solid, yield 82.1%, mp 133–134°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.79–0.83 (m, 2H, cycloprane-CH_2), 1.13–1.18 (m, 2H, cycloprane-CH_2), 2.95 (s, 3H, CH_3), 2.97–3.02 (m, 1H, cyclopropane-CH), 4.53 (s, 2H, CH_2), 7.37 (t, J = 7.22 Hz, 1H, Ph—H), 7.51 (d, J = 7.22 Hz, 1H, Ph—H), 7.71(t, J = 7.84 Hz, 2H, Ph—H); ESI–MS: 355 $[M+1]^+$; Elemental analysis for $C_{16}H_{14}N_6S_2$: found C 54.21, H 3.70, N 23.99; Calcd C, 54.22; H, 3.98; N, 23.71.

5-(4-Cyclopropyl-5-(prop-2-yn-1-ylthio)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7j). This compound was obtained as white solid, yield 76.8%, mp 107–108°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.78–0.94 (m, 2H, cycloprane-CH_2), 1.17–1.21 (m, 2H,

cycloprane-CH_2), 2.24 (s, 1H, CH), 2.95 (s, 3H, CH_3), 2.99–3.11 (m, 1H, cyclopropane-CH), 4.09 (s, 2H, CH_2); ESI–MS: 278 $[M+1]^+$; Elemental analysis for $C_{11}H_{11}N_5S_2$: found C 47.88, H 4.23, N 25.14; Calcd C, 47.63; H, 4.00; N, 25.25.

5-(4-Cyclopropyl-5-(octylthio)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole (7k). This compound was obtained as white solid, yield 80.5%, mp 67–68°C; ^{1}H-NMR (400 M, $CDCl_3$) δ: 0.79–0.86 (m, 5H, cycloprane-CH_2 and CH_2), 1.14–1.24 (m, 11H, cycloprane-CH_2 and CH_2), 1.36–1.44 (m, 2H, CH_2), 1.74–1.81 (m, 2H, CH_2), 2.95 (s, 3H, CH_3), 2.99–3.05 (m, 1H, cyclopropane-CH), 3.33 (t, 3H, CH_3); ESI–MS: 352 $[M+1]^+$; Elemental analysis for $C_{16}H_{25}N_5S_2$: found C 54.86, H 7.24, N 20.20; Calcd C, 54.67; H, 7.17; N, 19.92.

Antifungal activities assay. Antifungal activity of compounds **7a–k** against *F. oxysporum*, *P. cubensis*, *S. fuligenea*, *C. cassiicola*, *X. axonopodis*, *P. syringae* pv. *lachrymans*, and *R. solanii* were evaluated, and a potted plant test method was adopted. Germination was conducted by soaking cucumber seeds in water for 2 h at 50°C and then keeping the seeds moist for 24 h at 28°C in an incubator. When the radicles were 0.5 cm, the seeds were grown in plastic pots containing a 1:1 (v/v) mixture of vermiculite and peat. Cucumber plants used for inoculations were at the stage of two seed leaves. Tested compounds and commercial fungicides were sprayed with a hand spray on the surface of the seed leaves on a fine morning, at the standard concentration of 500 μg/mL. After 2 h, inoculations of *P. cubensis*, *S. fuligenea*, and *C. cassiicola* were carried out by spraying a conidial suspension; inoculation of *X. axonopodis* and *P. syringae* pv. *lachrymans* was carried out by spraying fungal suspension; inoculation of *R. solanii* was carried out by spraying a mycelial suspension; and inoculation of *F. oxysporum* was carried out by radicle soaking. The experiment was repeated four times. After inoculation, the plants were maintained at 18–30°C (mean temperature of 24°C and above 80% relative humidity). The fungicidal activity were evaluated when the nontreated cucumber plant (blank) fully developed symptoms. The area of inoculated treated leaves covered by disease symptoms was assessed and compared with that of nontreated ones to determine the average disease index. The relative control efficacy of compounds compared with the blank assay was calculated via the following equation:

$$\text{relative control efficacy } (\%) = (CK - PT)/CK \times 100\%$$

where CK is the average disease index during the blank assay, and PT is the average disease index after treatment during testing.

Acknowledgments. This work was supported by National Natural Science Foundation of China (No. 21002090, 21172124), The Key Innovation Team of Science and Technology in Zhejiang Province (2010R50018-06), and the National Key Technologies R&D Program (2011BAE06B03-01).

REFERENCES AND NOTES

[1] Liu, X. H.; Tan, C. X.; Weng, J. Q. Phosphorus Sulfur Silicon Relat Elem 2011, 186, 552–557.

[2] Liu, X. H.; Tan, C. X.; Weng, J. Q. Phosphorus Sulfur Silicon Relat Elem 2011, 186, 558–564.

[3] Liu, X. H.; Chen, P. Q.; Wang, B. L.; Dong, W. L.; Li, Y. H.; Xie, X. Q.; Li, Z. M. Chem Biol Drug Des 2010, 75, 228–232.

[4] Liu, X. H.; Weng, J. Q.; Tan, C. X. Asian J Chem 2011, 23, 4064–4066.

[5] Dong, W. L.; Liu, Z. X.; Liu, X. H.; Li, Z. M.; Zhao, W. G. Eur J Med Chem 2010, 45, 1919–1926.

[6] Tang, W.; Yu, Z. H.; Shi, D. Q. Phosphorus Sulfur Silicon Relat Elem 2010, 185, 2024–2029.

[7] Fan, Z. J.; Shi, Z. G.; Zhang, H. K.; Liu, X. F.; Bao, L. L.; Ma, L.; Zuo, X.; Zheng, Q. X.; Mi, N. J Agr Food Chem 2009, 57, 4279–4286.

[8] Shafiee, A.; Mohamadpour, M.; Abtahi, F.; Khoyi, A. J Pharm Sci 1981, 70, 510–513.

[9] Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M.; Shafiee, A.; Daneshtalab, M. Arch Pharm 2000, 333, 347–354.

[10] Kobori, T.; Fujita, M.; Yamamoto, R.; Hiyama, T.; Kondo, K.; Numata, K.; Sugita, K.; Akashi, T.; Kaneda, Y.; Nagate, T.; Hanada, K. Bioorg Med Chem Lett 1993, 3, 2225–2230.

[11] Tsubata, K.; Sanpei, O.; Takagi, K.; Umetani, K.; Uchikurohane, T.; Tajima, S. World Patent WO 992 3084 1999.

[12] Kunz, W.; Schurter, R.; Maetzke, T. Pestic Sci 1997, 50, 275–282.

[13] Bekircan, O. Asian J Chem 2009, 21, 1017–1023.

[14] Moise, M.; Sunel, V.; Profire, L.; Popa, M.; Desbrieres, J.; Peptu, C. Molecules 2009, 14, 2621–2631.

[15] Singh, R. J.; Singh, D. K. Asian J Chem 2010, 22, 2659–2663.

[16] Yin, K.; Jiang, L. H.; Zhou, H. X.; Huang, Y.; Xiang, J. N. Chin J Org Chem 2008, 28, 1016–1023.

[17] Liu, X. H.; Pan, L.; Ma, Y.; Weng, J. Q.; Tan, C. X.; Li, Y. H.; Shi, Y. X.; Li, B. J.; Li, Z. M.; Zhang, Y. G. Chem Biol Drug Des 2011, 78, 689–694.

[18] Liu, X. H.; Pan, L.; Tan, C. X.; Weng, J. Q.; Wang, B. L.; Li, Z. M. Pestic Biochem Physiol 2011, 101, 143–147.

[19] Liu, X. H.; Pan, L.; Weng, J. Q.; Tan, C. X.; Li, Y. H.; Wang, B. L.; Li, Z. M. Mol Divers 2012, 16, 251.