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Synthesis and Fungicidal Activity of Novel 2,5-Disubstituted-1,3,4-oxadiazole Derivatives

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ABSTRACT: A novel series of 1,3,4-oxadiazole derivatives containing a 5-phenyl-2-furan moiety were synthesized from the intermediates diacylhydrazine **3** and acylhydrazone **5** via an efficient approach under microwave irradiation in good yields. Their structures were characterized by IR, ^{1}H NMR, and elemental analysis. The antifungal tests indicated that the title compounds showed in vivo fungicidal activity against *Botrytis cinerea* and *Rhizoctonia solanii* at 500 μg/mL obviously. Some tested compounds even had a superiority effect over the commercial fungicides 40% Pyrimethanil SC and 3% Validamycin AS. The activity between the title compound and their precursors diacylhydrazine **3** and acylhydrazone **5** was also compared and discussed.

KEYWORDS: *2,5-disubstituted-1,3,4-oxadiazole, 5-phenyl-2-furan, fungicidal activity, microwave irradiation, synthesis*

1. INTRODUCTION

1,3,4-Oxadiazoles and their derivatives have a wide range of biological activities including antimicrobial,[1] antifungal,[2] insecticidal,[3] antitumor,[4] anti-inflammatory,[5] and antihypertensive[6] activities. The widespread use of 1,3,4-oxadiazoles as a scaffold in pesticidal and medicinal chemistry establishes this moiety as an important structural class.

The common synthetic method for these compounds is cyclodehydration of diacylhydrazines and their derivatives with dehydrants, such as phosphorus oxychloride,[7] trifluoroacetic anhydride,[8] thionyl chloride,[9] polyphosphoric acid,[10] and so on. However, the conventional route to cyclodehydration in dehydrants solution showed certain disadvantages; for example, (a) the reaction conditions for the synthesis of oxadiazoles involve longer durations of time, and (b) the yields of oxadiazoles are low. Recently, there has been growing interest in the application of microwave irradiation in chemical reaction enhancement, the salient features being improved reaction rates and increased yields.[11]

The furan ring is an electron-rich system that is amenable to various chemical reactions and easily forms hydrogen bonds with different kinds of biological enzymes. It was reported that the derivatives of 5-phenyl-2-furan showed broad-spectrum antibacterial,[12] plant growth regulator,[13] and herbicidal[14] activity, which also exhibited pharmacological properties, including serving as anti-inflammatory agents[15] and methionine aminopeptidase inhibitors.[16] Thus, 5-phenyl-2-furan was regarded as an active scaffold in drug design.

In our previous work, some benzoylureas,[17] acylhydrazones,[18] diacylhydrazines,[19] semicarbazide,[20] pyrazole, and 1,2,4-triazole[21] derivatives containing 5-phenyl-2-furan moiety were designed and synthesized. All of the compounds showed diverse and promising bioactivities such as insecticidal, fungicidal, and antitumor activities. In continuation of our research on the design and synthesis of bioactive compounds, a series of novel 1,3,4-oxadiazole derivatives containing 5-phenyl-2-furan moiety were designed (Scheme 1) and synthesized from the precursors diacylhydrazine **3** and acylhydrazone **5** via an efficient approach under microwave irradiation in good yields (Scheme 2). Their antifungal activities were evaluated, and the activity between the title compound and their precursors was also compared and discussed in this paper.

2. MATERIALS AND METHODS

2.1. Instruments. All of the melting points were determined with a Cole-Parmer melting point apparatus, while the thermometer was uncorrected. IR spectra were recorded on a NEXUS-470 FTIR (Nicolet) spectrometer with KBr pellets. ^{1}H NMR spectra were recorded with a Bruker DPX300 instrument, while tetramethylsilane was used as the internal standard. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. Elemental analysis, which was performed at the laboratory of the Institute of Chemistry, Chinese Academy of Sciences, was carried out with a Flash EA 1112 elemantal analyzer. Mass spectra were measured on a Bruker ESQUIRE-LC spectrometer. The microwave-assisted reaction was carried out with a CEM Microwave synthesizer (CEM Discover S-Class).

2.2. Synthetic Procedures. *2.2.1. General Synthetic Procedure for the Key Intermediates.* Intermediate **2** was synthesized from substituted aniline by Meerwein arylation reaction using the reported procedure.[17,22] Intermediates **3** and **5** were synthesized according to our previous literatures.[18,19]

N-(4-Bromobenzoyl)-*N*′-[5-(2′-chlorophenyl)-2-furoyl]hydrazine **3a** (R^1 = 4-Br; R^2 = 2-Cl): white powdery crystals; yield, 67.3%; mp 219−220 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.34 (d, *J* = 3.69 Hz, 1H, FuH), 7.39 (d, *J* = 3.69 Hz, 1H, FuH), 7.42−7.54 (m, 2H, ArH-Fu), 7.62 (dd, *J* = 7.83, 1.29 Hz, 1H, ArH-Fu), 7.75−7.79 (m, 2H, ArH), 7.86−7.89 (m, 2H, ArH), 8.23 (dd, *J* = 7.80, 1.73 Hz, 1H, ArH-Fu), 10.64 (s, 1H, NH), 10.66 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{12}BrClN_2O_3$: C, 51.52; H, 2.88; N, 6.68. Found: C, 51.52; H, 2.95; N, 6.67.

N-(4-methylbenzoyl)-*N*′-[5-(4′-chlorophenyl)-2-furoyl]hydrazine **3b** (R^1 = 4-CH_3; R^2 = 4-Cl): light yellow powdery crystals; yield, 56.3%; mp 242−244 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.23

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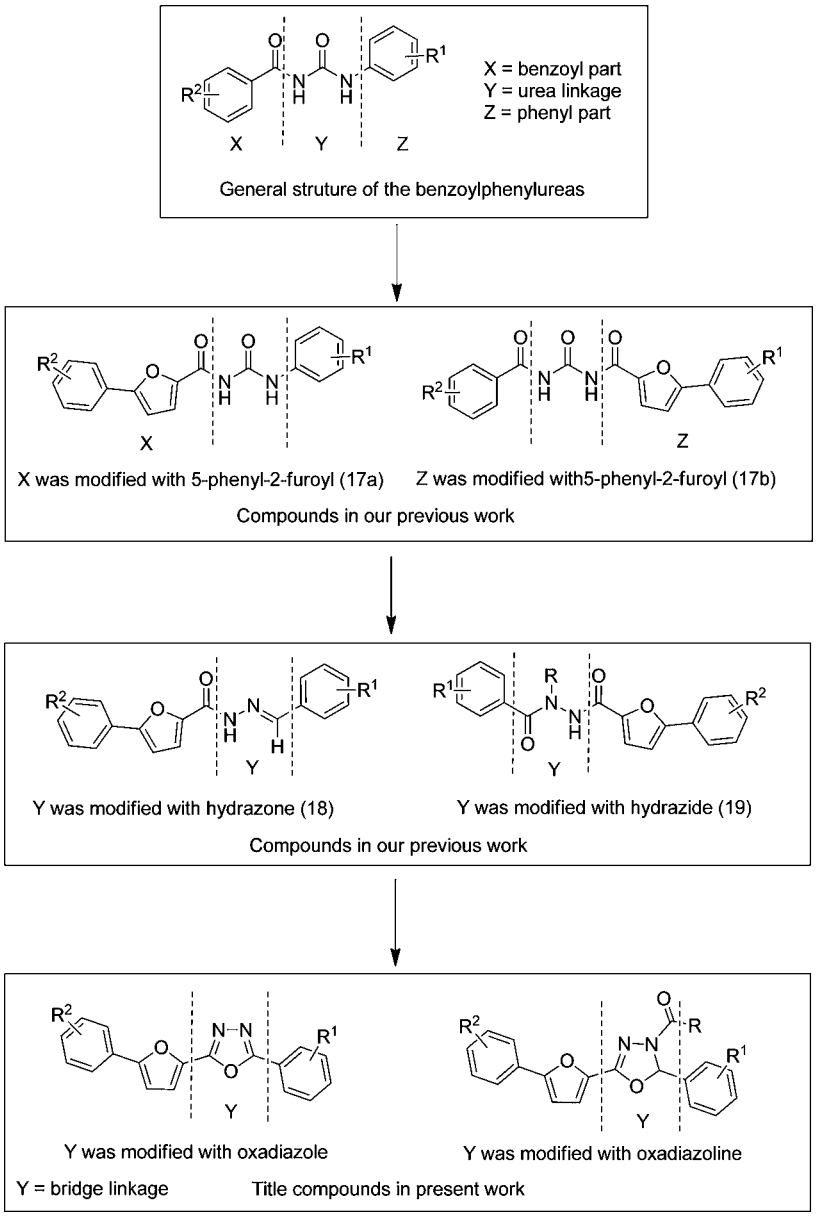
Scheme 1. Design Strategy for the Title Compounds



(d, J = 3.60 Hz, 1H, FuH), 7.34 (d, J = 3.63 Hz, 1H, FuH), 7.56−7.61 (m, 3H, 2ArH + ArH-Fu), 7.68−7.72 (m, 1H, ArH-Fu), 7.88−7.91 (m, 1H, ArH-Fu), 7.95 (t, J = 1.71 Hz, 1H, ArH-Fu), 7.99−8.02 (m, 2H, ArH), 10.66 (s, 2H, NHNH). Anal. calcd (%) for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.39; H, 4.39; N, 7.82.

N-(4-chlorobenzoyl)-*N*′-[5-(2′-nitrophenyl)-2-furoyl]hydrazine **3c** (R^1 = 4-Cl; R^2 = 2-NO_2): light yellow powdery crystals; yield, 79.8%; mp 193−194 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.96 (d, J = 3.66 Hz, 1H, FuH), 7.40 (d, J = 3.66 Hz, 1H, FuH), 7.60−7.64 (m, 2H, ArH), 7.70 (td, J = 7.77, 1.34 Hz, 1H, ArH-Fu), 7.84 (td, J = 7.65, 1.23 Hz, 1H, ArH-Fu), 7.91−7.95 (m, 2H, ArH), 8.00−8.04 (m, 2H, ArH-Fu), 10.59 (s, 1H, NH), 10.62 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{12}ClN_3O_5$: C, 56.04; H, 3.14; N, 10.89. Found: C, 55.92; H, 3.11; N, 10.87.

N-(4-methoxybenzoyl)-*N*′-[5-(2′-nitrophenyl)-2-furoyl]hydrazine **3d** (R^1 = 4-OCH_3; R^2 = 2-NO_2): yellow powdery crystals; yield, 69.7%; mp 197−198 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.95 (d, J = 3.63 Hz, 1H, FuH), 7.06 (d, J = 8.85 Hz, 2H, ArH), 7.38 (d, J = 3.66 Hz, 1H, FuH), 7.70 (td, J = 7.77, 1.17 Hz, 1H, ArH-Fu), 7.83 (td, J = 7.65, 1.04 Hz, 1H, ArH-Fu), 7.90 (d, J = 8.82 Hz, 2H, ArH), 8.00−8.04 (m, 2H, ArH-Fu), 10.37 (s, 1H, NH), 10.48 (s, 1H, NH). Anal. calcd (%) for $C_{19}H_{15}N_3O_6$: C, 59.84; H, 3.96; N, 11.02. Found: C, 59.85; H, 4.00; N, 11.02.

N-(4-ethoxybenzoyl)-*N*′-[5-(2′-nitrophenyl)-2-furoyl]hydrazine **3e** (R^1 = 4-OEt; R^2 = 2-NO_2): yellow powdery crystals; yield, 74.3%; mp 172−173 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.35 (t, J = 6.98 Hz, 3H, CH_3−C-O), 4.11 (q, J = 6.96 Hz, 2H, O−CH_2-C), 6.96 (d, J = 3.63 Hz, 1H, FuH), 7.04 (d, J = 8.88 Hz, 2H, ArH), 7.39 (d, J = 3.66 Hz, 1H, FuH), 7.69 (td, J = 7.76, 1.36 Hz, 1H, ArH-Fu), 7.83 (td, J = 7.68, 1.27 Hz, 1H, ArH-Fu), 7.89 (dd, J = 6.99, 1.88 Hz, 2H, ArH), 8.00−8.04 (m, 2H, ArH-Fu), 10.36 (s, 1H, NH), 10.49 (s, 1H, NH). Anal. calcd (%) for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.63. Found: C, 60.50; H, 4.38; N, 10.66.

N-(4-methoxybenzoyl)-*N*′-[5-(4′-nitrophenyl)-2-furoyl]hydrazine **3f** (R^1 = 4-OCH_3; R^2 = 4-NO_2): yellow powdery crystals; yield, 75.1%; mp 237−238 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 7.07 (d, J = 8.85 Hz, 2H, ArH), 7.40 (d, J = 3.69 Hz, 1H, FuH), 7.50 (d, J = 3.66 Hz, 1H, FuH), 7.92 (d, J = 8.88 Hz, 2H, ArH), 8.24 (d, J = 9.03 Hz, 2H, ArH-Fu), 8.36 (d, J = 9.03 Hz, 2H, ArH-Fu), 10.56 (brs, 2H, NHNH). Anal. calcd (%) for $C_{19}H_{15}N_3O_6$: C, 59.84; H, 3.96; N, 11.02. Found: C, 59.61; H, 3.98; N, 11.33.

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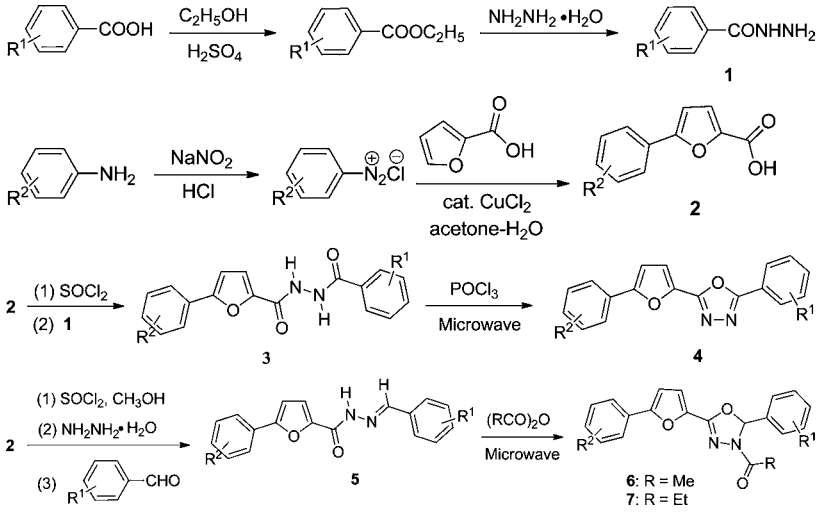
Scheme 2. General Synthetic Procedure for Title Compounds



N-(4-ethoxybenzoyl)-*N*′-[5-(4′-nitrophenyl)-2-furoyl]hydrazine **3g** (R^1 = 4-OEt; R^2 = 4-NO_2): yellow powdery crystals; yield, 85.2%; mp 252−253 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.36 (t, J = 6.96 Hz, 3H, CH_3−C-O), 4.12 (q, J = 6.96 Hz, 2H, O−CH_2-C), 7.05 (d, J = 8.88 Hz, 2H, ArH), 7.40 (d, J = 3.69 Hz, 1H, FuH), 7.50 (d, J = 3.66 Hz, 1H, FuH), 7.91 (d, J = 8.85 Hz, 2H, ArH), 8.24 (d, J = 9.00 Hz, 2H, ArH-Fu), 8.35 (d, J = 9.03 Hz, 2H, ArH-Fu), 10.40 (brs, 1H, NH), 10.67 (brs, 1H, NH). Anal. calcd (%) for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.63. Found: C, 60.75; H, 4.43; N, 10.89.

N-(2-chlorobenzoyl)-*N*′-[5-(4′-fluorophenyl)-2-furoyl]hydrazine **3h** (R^1 = 2-Cl; R^2 = 4-F): light yellow powdery crystals; yield, 65.1%; mp 191−192 °C. ^{1}H NMR(300 MHz, DMSO-d_6): δ 7.16 (d, J = 3.57 Hz, 1H, FuH), 7.33−7.39 (m, 3H, FuH + 2ArH-Fu), 7.48−7.58 (m, 4H, ArH), 8.05 (dd, J = 8.79, 5.42 Hz, 2H, ArH-Fu), 10.43 (s, 1H, NH), 10.69 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{12}FClN_2O_3$: C, 60.26; H, 3.37; N, 7.81. Found: C, 60.06; H, 3.43; N, 7.96.

Benzaldehyde 5-(4-chlorophenyl)-2-furoyl hydrazone **5a** (R^1 = H; R^2 = 4-Cl): light yellow needle crystals; mp 188−189 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26 (d, J = 3.63 Hz, 1H, FuH), 7.41−7.61 (m, 6H, FuH + 2ArH-Fu + 3ArH), 7.74−7.77 (m, 2H, ArH), 7.99−8.01 (m, 2H, ArH-Fu), 8.53 (s, 1H, CH═N), 11.86 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.44; H, 4.00; N, 8.61.

4-Bromobenzaldehyde-5-(2-chlorophenyl)-2-furoyl hydrazone **5b** (R^1 = 4-Br; R^2 = 2-Cl): light yellow powdery crystals; mp 189−190 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33 (d, J = 3.69 Hz, 1H, FuH), 7.42−7.56 (m, 3H, FuH + 2ArH-Fu), 7.61−7.74 (m, 5H, 4ArH + ArH-Fu), 8.15−8.17 (m, 1H, ArH-Fu), 8.50 (s, 1H, CH═N), 11.94 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{12}BrClN_2O_2$: C, 53.56; H, 3.00; N, 6.94. Found: C, 53.34; H, 3.19; N, 7.02.

4-Chlorobenzaldehyde-5-(2-fluorophenyl)-2-furoyl hydrazone **5c** (R^1 = 4-Cl; R^2 = 2-F): white powdery crystals; mp 209−210 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.05 (t, J = 3.48 Hz, 1H, ArH-Fu), 7.36−7.56 (m, 6H, 2FuH + 2ArH-Fu + 2ArH), 7.77−7.80 (m, 2H, ArH), 8.15−8.20 (m, 1H, ArH-Fu), 8.52 (s, 1H, CH═N), 11.96 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{12}ClFN_2O_2$: C, 63.08; H, 3.53; N, 8.17. Found: C, 63.22; H, 3.53; N, 8.51.

2-Chlorobenzaldehyde-5-(4-fluorophenyl)-2-furoyl hydrazone **5d** (R^1 = 2-Cl; R^2 = 4-F): yellow powdery crystals; mp 182−183 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.19 (d, J = 3.63 Hz, 1H, FuH), 7.35−7.57 (m, 6H, FuH + 2ArH-Fu + ArH), 8.04−8.07 (m, 3H, ArH + 2ArH-Fu), 8.92 (s, 1H, CH═N), 12.08 (s, 1H, NH). Anal. calcd (%) for $C_{18}H_{12}ClFN_2O_2$: C, 63.08; H, 3.53; N, 8.17. Found: C, 63.39; H, 3.65; N, 7.93.

2.2.2. General Procedure for the Synthesis of the Target Compounds ***4*** *by Conventional Method.* The mixture of the diacylhydrazines **3** (5 mmol) and phosphorus oxychloride (20 mL) was refluxed for 6−8 h. After it was cooled to room temperature, the reaction was quenched by addition of ice water. The precipitate was filtered, washed with water and dried, finally recrystallized from ethanol to afford the pure 2,5-disubstituted-1,3,4-oxadiazoles **4**.

2.2.3. General Procedure for the Synthesis of the Target Compounds ***4*** *by Microwave Radiation.* All reactions were carried out in a pressure tube, sealed with a Teflon septum. The mixture of the diacylhydrazines **3** (2 mmol) and phosphorus oxychloride (20 mL) was taken in the pressure tube. The pressure tube was introduced to the center of a CEM Discover microwave oven and irradiated for 10 min at 150 W (the reaction temperature was set to 105 °C). After completion of the reaction, the reaction mixture was allowed to cool, and then, it was poured slowly with stirring into ice water. The resulting precipitate was filtered, washed with water and dried, and finally recrystallized from ethanol to afford the corresponding 2,5-disubstituted-1,3,4-oxadiazoles **4**.

2.2.4. General Procedure for the Synthesis of the Target Compounds ***6*** *and* ***7*** *by Conventional Method.* The mixture of the acylhydrazones **5** (2 mmol) and the corresponding anhydrides (20 mL) was refluxed for 3−4 h. After it was cooled to room temperature, it was poured slowly with stirring into ice water. The precipitate was filtered, washed with water and dried, and finally recrystallized from ethanol to produce the pure 1,3,4-oxadiazolines **6** and **7**.

2.2.5. General Procedure for the Synthesis of the Target Compounds ***6*** *and* ***7*** *by Microwave Radiation.* All reactions were carried out in a pressure tube, sealed with a Teflon septum. The mixture of the acylhydrazones **5** (2 mmol) and acetic anhydride or propionic anhydride (20 mL) was taken in the pressure tube. The pressure tube was introduced to the center of a CEM Discover microwave oven and irradiated for 10 min at 150 W (for the solution of acetic anhydride, the reaction temperature was set to 155 °C; for the solution of acetic anhydride, the reaction temperature was set to 165 °C). After the reaction was completed, the reaction mixture was allowed to cool, and then, it was poured slowly with stirring into ice water. The resulting precipitate was filtered, washed with water and dried, and finally recrystallized from ethanol to produce the corresponding 1,3,4-oxadiazolines **6** and **7**.

All of the title compounds were solid. Their structures were confirmed by ^{1}H NMR, IR, MS, and elemental analysis. The data are listed in Tables 1 and 2.

2.3. Bioassays. Using pot culture test according to the references,[21,23] the in vivo fungicidal activities of the title compounds against *B. cinerea*, *Corynespora cassiicola*, *Cladosporium cucumerinum*, and *R. solanii* were evaluated in a greenhouse with four commercial fungicides, 40% Pyrimethanil SC, 75% Chlorothalonil WP, 40% Flusilazole EC, and 3% Validamycin AS, as controls. All of the strains were conserved in the Institute of Vegetable and Flowers, Chinese Academy of Agricultural

Table 1. Physical, MS, and Elemental Analysis Data of Title Compounds 4, 6, and 7

							elemental analysis (found %)		
compd	R^1	R^2	appearance	mp (°C)	yield (%)	MS/ESI *m/e* (%)	C	H	N
4a	4-Br	2-Cl	brown solid	175−176	79.5	424.1[M+Na]$^+$ (53)	53.83	2.51	6.97
						402.3[M+H]$^+$ (36)	(53.48)	(2.55)	(7.17)
4b	4-Me	4-Cl	light yellow solid	198−199	78.0	359.0[M+Na]$^+$ (40)	67.76	3.89	8.32
						337.0[M+H]$^+$ (57)	(67.65)	(3.91)	(8.06)
4c	4-Cl	2-NO_2	yellow solid	192−193	76.0	389.8[M+Na]$^+$ (100)	58.79	2.74	11.43
						367.9[M+H]$^+$ (43)	(58.59)	(2.80)	(11.14)
4d	4-OMe	2-NO_2	yellow solid	150−151	72.0	385.9[M+Na]$^+$ (100)	62.81	3.61	11.57
						364.0[M+H]$^+$ (47)	(62.53)	(3.70)	(11.48)
4e	4-OEt	2-NO_2	brown solid	155−156	74.0	399.9[M+Na]$^+$ (100)	63.66	4.01	11.14
						377.9[M+H]$^+$ (66)	(63.42)	(4.10)	(11.10)
4f	4-OMe	4-NO_2	yellow solid	236−237	79.0	364.1[M+H]$^+$ (57)	62.81	3.61	11.57
							(62.54)	(3.65)	(11.45)
4g	4-OEt	4-NO_2	yellow solid	214−215	80.2	378.2[M+H]$^+$ (56)	63.66	4.01	11.14
							(63.59)	(4.11)	(11.04)
4h	2-Cl	4-F	gray solid	166−167	80.4	341.3[M+H]$^+$ (69)	63.45	2.96	8.22
							(63.50)	(3.13)	(8.01)
6a	H	4-Cl	yellow solid	169−170	84.6	389.4[M+Na]$^+$(88)	65.49	4.12	7.64
							(65.55)	(4.14)	(7.70)
6b	4-Br	2-Cl	light yellow solid	154−155	86.8	468.2[M+Na]$^+$(93)	53.90	3.17	6.29
							(53.94)	(3.14)	(6.17)
6c	4-Cl	2-F	light yellow solid	166−167	79.5	407.2[M+Na]$^+$(100)	62.43	3.67	7.28
							(62.43)	(3.62)	(7.56)
6d	2-Cl	4-F	white solid	162−163	76.9	407.2[M+Na]$^+$(100)	62.43	3.67	7.28
							(62.28)	(3.60)	(7.44)
7a	4-Br	2-Cl	white solid	165−166	84.3	498.9[M+K]$^+$ (6.0)	54.86	3.51	6.09
						483.0[M+Na]$^+$ (100)	(54.60)	(3.62)	(6.14)
7b	2-Cl	4-F	white solid	175−176	82.8	437.0[M+K]$^+$ (9.7)	63.24	4.04	7.02
						421.2[M+Na]$^+$ (100)	(63.05)	(4.09)	(7.03)

Science (Beijing, China). *B. cinerea*, *C. cassiicola*, *C. cucumerinum*, and *R. solanii* were maintained on potato dextrose agar (PDA) medium at 4 °C. The culture plates were cultivated at 24 ± 1 °C. 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, which will be inoculated with *B. cinerea*, *C. cassiicola*, *C. cucumerinum*, and *R. solanii* at the standard concentration of 500 μg/mL. Three replicates were used per treatment.

After the leaves were dried, inoculations of *C. cassiicola* and *C. cucumerinum* were carried out by spraying a conidial suspension, and inoculations of *B. cinerea* and *R. solanii* were carried out by spraying a mycelial suspension. The experiment was repeated three times. After inoculation, the plants were maintained at 24 ± 1 °C and above 80% relative humidity.

The fungicidal activity was evaluated when the nontreated cucumber plant (blank) fully developed symptoms. The area of inoculated treated leaves covered by disease symptoms was assessed and compared to that of nontreated ones to determine the average disease index. The relative control efficacy of compounds compared to the blank assay was calculated via the following equation:

$$I\ (\%) = [(\mathrm{CK} - \mathrm{PT})/\mathrm{CK}] \times 100\%$$

where *I* is the relative control efficacy, CK is the average disease index during the blank assay, and PT is the average disease index after treatment during testing.

3. RESULTS AND DISCUSSION

3.1. Synthesis. The synthetic route of title compounds **4**, **6**, and **7** is shown in Scheme 2. Title compounds were obtained from the diacylhydrazines **3** or acylhydrazones **5** by cyclodehydration reaction in the dehydrants phosphorus oxychloride or anhydride. To establish the general validity of the newly developed method, several selected one-pot microwave-assisted syntheses were carried out. This method appeared to be expeditious and economical, with a wide range of applications. The reaction was found to proceed smoothly under microwave irradiation within 10 min, whereas 3−8 h was required under conventional reflux condition in $POCl_3$ or the corresponding anhydride (Table 3). The products were isolated by simple cold aqueous workup followed by precipitation and were finally purified by recrystallization wherever necessary, to afford pure 2,5-disubstituted-1,3,4-oxadiazole (oxadiazolines). The yield was raised from 8 to 18.6% as compared to the conventional method. The present method, which was more rapid and simple than the conventional method, is a good contribution to microwave-assisted synthetic methodologies.

3.2. Fungicidal Activity. The in vivo fungicidal results of the compounds against *R. solanii*, *B. cinerea*, *C. cassiicola*, and *C. cucumerinum* are listed in Table 4. Not only the title compounds but also the intermediates diacylhydrazine and acylhydrazone showed promising results in inhibiting the mycelial growth of the test fungi especially against *B. cinerea* and *R. solanii* at 500 μg/mL. Meanwhile, all of these tested compounds were found safe for the plants. The comparison of the fungicidal activity of compounds for four test fungi to those of commercial fungicides leads to the following conclusions: (a) Compounds **3c** and **4c** exhibited a significant inhibition effect against *R. Solanii*, and the fungicidal activities (control efficacy of 95.56 ± 4.05 and 94.38 ± 3.60%) were equal to the active

Table 2. ^{1}H NMR and IR Data of Title Compounds 4, 6, and 7

compd	^{1}H NMR δ (ppm, DMSO-d_6, 300 MHz)	IR (cm^{-1})
4a	7.30−7.40 (m, 4H, 2ArH-Ox + 2FuH), 7.49 (dd, *J* = 7.93, 1.27 Hz, 1H, ArH-Fu), 7.69 (dd, *J* = 6.78, 1.88 Hz, 2H, ArH-Ox), 8.00−8.08 (m, 3H, 2ArH-Ox + ArH-Fu)	1599.3, 1475.5, 1458.4, 1406.9, 1087.2, 1024.3
4b	2.45 (s, 3H, CH_3), 6.83 (d, *J* = 3.65 Hz, 1H, FuH), 7.28 (d, *J* = 3.65 Hz, 1H, FuH), 7.34 (d, *J* = 7.95 Hz, 2H, ArH-Ox), 7.42 (dd, *J* = 6.72, 2.02 Hz, 2H, ArH-Fu), 7.75 (dd, *J* = 6.71, 2.01 Hz, 2H, ArH-Fu), 8.03 (dd, *J* = 6.49, 1.75 Hz, 2H, ArH-Ox)	1615.0, 1554.8, 1487.7, 1457.9, 1279.5, 1090.8, 1027.9
4c	6.85 (d, *J* = 3.69 Hz, 1H, FuH), 7.34 (d, *J* = 3.70 Hz, 1H, FuH), 7.51−7.58 (m, 3H, ArH-Fu + 2ArH-Ox), 7.81−7.90 (m, 2H, ArH-Fu), 8.08 (dd, *J* = 6.77, 2.06 Hz, 2H, ArH-Ox)	1510, 1490, 1370, 1090
4d	3.90 (s, 3H, OCH_3), 6.84 (d, *J* = 3.70 Hz, 1H, FuH), 7.02−7.05 (m, 2H, ArH-Ox), 7.30 (d, *J* = 3.68 Hz, 1H, FuH), 7.53−7.56 (m, 1H, ArH-Fu), 7.65−7.68 (m, 1H, ArH-Fu), 7.81 (dd, *J* = 6.65, 1.14 Hz, 1H, ArH-Fu), 7.90 (d, *J* = 6.65, 1.22 Hz, 1H, ArH-Fu), 8.07 (dd, *J* = 6.90, 2.15 Hz, 2H, ArH-Ox)	1610, 1510, 1490, 1370, 1290, 1250, 1180, 1010
4e	1.46 (t, *J* = 6.99 Hz, 3H, CH_3-C-O), 4.12 (q, *J* = 6.99 Hz, 2H, O-CH_2-C), 6.83 (d, *J* = 3.68 Hz, 1H, FuH), 7.00−7.03 (m, 2H, ArH-Fu), 7.29 (d, *J* = 3.71 Hz, 1H, FuH), 7.53−7.56 (m, 1H, ArH-Ox), 7.65−7.68 (m, 1H, ArH-Ox), 7.81 (dd, *J* = 6.79, 1.27 Hz, 1H, ArH-Ox), 7.90 (dd, *J* = 6.44, 1.41 Hz, 1H, ArH-Ox), 8.06 (dd, *J* = 6.91, 2.05 Hz, 2H, ArH-Fu)	1610, 1520, 1490, 1370, 1260, 1190, 1030
4f	3.91 (s, 3H, OCH_3), 7.03−7.07 (m, 3H, FuH + 2ArH-Ox), 7.33 (d, *J* = 3.69 Hz, 1H, FuH), 7.95−8.00 (m, 2H, ArH-Fu), 8.07−8.12 (m, 2H, ArH-Ox), 8.29−8.35 (m, 2H, ArH-Fu)	1607.6, 1518.5, 1492.1, 1337.3, 1264.9, 1175.4, 1017.5
4g	1.47 (t, *J* = 6.98 Hz, 3H, CH_3-C-O), 4.13 (q, *J* = 6.98 Hz, 2H, O-CH_2-C), 7.03 (dd, *J* = 6.90, 2.01 Hz, 2H, ArH-Ox), 7.06−7.33 (d, *J* = 3.70 Hz, 1H, FuH), 7.97 (dd, *J* = 6.96, 1.94 Hz, 2H, ArH-Fu), 8.08 (dd, *J* = 6.86, 2.01 Hz, 2H, ArH-Ox), 8.32 (dd, *J* = 6.99, 1.92 Hz, 2H, ArH-Fu)	1603.3, 1515.1, 1477.1, 1340.8, 1302.1, 1274.7, 1154.7, 1015.0
4h	6.80 (d, *J* = 3.66 Hz, 1H, FuH), 6.80−7.18 (m, 2H, ArH-Fu), 7.32 (d, *J* = 3.63 Hz, 1H, FuH), 7.44−7.51 (m, 2H, ArH-Ox), 7.57−7.60 (m, 1H, ArH-Ox), 7.79−7.83 (m, 2H, ArH-Fu), 8.07−8.10 (m, 1H, ArH-Ox)	1602.6, 1544.5, 1499.8, 1474.4, 1461.8, 1229.6, 1159.1, 1095.8, 1036.7
6a	2.80 (s, 3H, $COCH_3$), 7.18 (s, 1H, OxH), 7.26 (d, *J* = 3.72 Hz, 1H, FuH), 7.29 (d, *J* = 3.70 Hz, 1H, FuH), 7.45−7.56 (m, 7H, 5ArH-Ox + 2ArH-Fu), 7.82 (dd, *J* = 6.69, 1.99 Hz, 2H, ArH-Fu)	1661.4, 1520.5, 1479.1, 1447.2, 1363.2, 1330.0, 1218.1, 1090.2, 1024.2
6b	2.26 (s, 3H, $COCH_3$), 7.20 (s, 1H, OxH), 7.31 (d, *J* = 3.75 Hz, 1H, FuH), 7.34 (d, *J* = 3.77 Hz, 1H, FuH), 7.45−7.52 (m, 4H, 2ArH-Ox + 2ArH-Fu), 7.61−7.68 (m, 3H, 2ArH-Ox + ArH-Fu), 7.86−7.88 (m, 1H, ArH-Fu)	1657.6, 1594.6, 1521.7, 1469.5, 1422.6, 1372.9, 1356.2, 1329.3, 1215.6, 1164.2, 1119.1, 1028.7
6c	2.52 (s, 3H, $COCH_3$), 7.13 (t, *J* = 3.57 Hz, 1H, FuH), 7.36−7.39 (m, 2H, ArH-Fu), 7.54−7.57 (m, 3H, 2ArH-Ox + ArH-Fu), 7.64 (d, *J* = 3.82 Hz, 1H, FuH), 7.83−7.87 (m, 3H, 2ArH-Ox + ArH-Fu), 8.35 (s, 1H, OxH)	1694.5, 1511.3, 1482.1, 1366.1, 1304.8, 1292.8, 1215.1, 1174.8, 1088.8, 1040.5
6d	2.54 (s, 3H, $COCH_3$), 7.31 (d, *J* = 3.85 Hz, 1H, FuH), 7.34−7.40 (m, 2H, ArH-Fu), 7.47−7.56 (m, 3H, ArH-Ox), 7.69 (d, *J* = 3.86 Hz, 1H, FuH), 7.90−7.95 (m, 2H, ArH-Fu), 8.04−8.07 (m, 1H, ArH-Ox), 8.51 (s, 1H, OxH)	1659.0, 1487.9, 1445.8, 1359.4, 1262.7, 1228.6, 1157.9, 1053.0, 1027.0
7a	1.05 (t, *J* = 6.94 Hz, 3H, CH_3C), 2.66 (q, *J* = 7.49 Hz, 2H, CO-CH_2-C), 7.20 (s, 1H, OxH), 7.31 (d, *J* = 3.76 Hz, 1H, FuH), 7.34 (d, *J* = 3.76 Hz, 1H, FuH), 7.45−7.52 (m, 4H, 2ArH-Ox + 2ArH-Fu), 7.61−7.68 (m, 3H, 2ArH-Ox + ArH-Fu), 7.85−7.88 (m, 1H, ArH-Fu)	1654.6, 1490.7,1468.8, 1440.3, 1266.6, 1215.4, 1025.3
7b	1.06 (t, *J* = 7.50 Hz, 3H, CH_3C), 2.68 (q, *J* = 7.39 Hz, 2H, CO-CH_2-C), 7.19 (d, *J* = 3.69 Hz, 1H, FuH), 7.26 (d, *J* = 3.69 Hz, 1H, FuH), 7.30−7.36 (m, 3H, OxH + 2ArH-Fu), 7.45−7.52 (m, 3H, ArH-Ox), 7.56−7.59 (m, 1H, ArH-Ox), 7.83−7.88 (m,2H, ArH-Fu)	1656.3, 1491.6, 1440.1, 1234.3, 1219.9, 1163.0, 1021.5, 837.2, 789.9, 758.9, 611.4

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Table 3. Comparison between Conventional Heating Method and Microwave-Assisted Method for the Synthesis of Title Compounds 4, 6, and 7 in Terms of Time and Yield

	conventional		microwave	
compd	time (min)	yield (%)	time (min)	yield (%)
4a	480	68.4	10	79.5
4b	360	65.6	10	78.0
4c	420	62.7	10	76.0
4d	480	58.3	10	72.0
4e	480	61.4	10	74.0
4f	420	65.6	10	79.0
4g	480	68.5	10	80.2
4h	480	66.9	10	80.4
6a	210	73.6	10	84.6
6b	180	74.3	10	86.8
6c	210	69.4	10	79.5
6d	210	65.4	10	76.9
7a	240	76.3	10	84.3
7b	210	64.2	10	82.8

fungicide 3% Validamycin AS (93.68 ± 3.21%). The variances between pre- and postcyclization had a great effect on the fungicidal activity against *R. solanii*. For compound **4**, the activity of most compounds before cyclization was higher than cyclic 1,3,4-oxadiazoles. For example, the activities of compounds **3a** and **3h** were 49.42 ± 2.25 and 69.35 ± 3.02%, and after cyclization, the activities of **4a** and **4h** were decreased to −1.16 ± 0.09 and 25.54 ± 1.14%. For compounds **6** and **7**, the activities of cyclic 1,3,4-oxadiazolines were higher than the corresponding ring-opening ones. For example, the activity of compound **5a** was 10.20 ± 0.20%, and after cyclizatio, the activities of **6a** and **7a** were increased to 69.09 ± 3.00 and 63.87 ± 2.02%. The difference between R^1 and R^2 also affected the fungicidal activity against *R. solanii*. When R^2 was 2-NO_2, such as **3c**, **3e**, **4c**, and **4e** displayed higher fungicidal activity. (b) Some compounds exhibited good control efficacy against *B. cinerea* (exceeding 70% efficacy rate), which had a higher activity than 40% Pyrimethanil SC (69.57 ± 3.35%). It was worthy to note that compounds **3h**, **5b**, and **4d**, whose efficacy rates were 89.57 ± 3.39, 91.76 ± 3.30, and 92.68 ± 3.46%, respectively, were found to be much more effective as compared to the fungicide 40% Pyrimethanil SC (69.57 ± 3.35%) against *B. cinerea*. The variances between pre- and postcyclization had no obvious relationship with the fungicidal activity against *B. cinerea*. (c) For *C. cassiicola*, compounds **3c**, **4a**, and **4e** exhibited favorable fungicidal activities of 66.09 ± 3.02, 90.59 ± 3.09, and 74.71 ± 4.05%, respectively. Compound **4a** had almost the same activity as that of 75% Chlorothalonil WP against *C. cassiicola* (93.53 ± 3.20%). (d) All of the compounds showed lower effects against *C. cucumerinum* than the fungicide 40% Flusilazole EC (95.56 ± 3.20%).

The change of the Y moiety in Scheme 1 could bring a variant of bioactivity. The designed urea derivatives from that of benzoylphenyl urea (BPU) showed good larvicidal activity.[17] When it was changed to the hydrazide and hydrazone moieties, the bioactive spectra were broadened and not only showed promising insecticidal activity but also exhibited obvious fungicidal

Table 4. Fungicidal Activities of Compounds 3−7 against Four Fungus Species at 500 μg/mL in Vivo

			control efficacy (%)			
compd	R^1	R^2	*C. cucumerinum*	*C. cassiicola*	*B. cinerea*	*R. solanii*
3a	4-Br	2-Cl	14.20 ± 1.02	8.24 ± 0.75	24.64 ± 2.26	49.42 ± 2.25
3b	4-Me	4-Cl	29.80 ± 2.25	50.87 ± 2.62	4.35 ± 1.10	19.80 ± 1.75
3c	4-Cl	2-NO_2	14.44 ± 1.71	66.09 ± 3.02	79.58 ± 4.00	95.56 ± 4.05
3d	4-OMe	2-NO_2	2.61 ± 0.42	28.35 ± 2.24	35.50 ± 2.37	56.45 ± 3.20
3e	4-OEt	2-NO_2	10.00 ± 2.00	18.82 ± 1.15	−43.27 ± 1.02	78.93 ± 2.25
3f	4-OMe	4-NO_2	57.89 ± 3.35	36.36 ± 2.26	29.90 ± 2.03	24.45 ± 1.52
3g	4-OEt	4-NO_2	28.35 ± 2.25	38.24 ± 2.38	79.13 ± 3.61	71.90 ± 1.05
3h	2-Cl	4-F	30.32 ± 3.05	34.26 ± 3.12	89.57 ± 3.39	69.35 ± 3.02
4a	4-Br	2-Cl	17.90 ± 1.75	90.59 ± 3.09	−2.61 ± 0.22	−1.16 ± 0.09
4b	4-Me	4-Cl	5.85 ± 0.55	28.24 ± 2.00	42.38 ± 3.02	24.13 ± 1.11
4c	4-Cl	2-NO_2	17.20 ± 2.13	15.17 ± 2.05	−30.02 ± 1.02	94.38 ± 3.60
4d	4-OMe	2-NO_2	15.00 ± 2.23	48.61 ± 3.02	92.68 ± 3.46	48.48 ± 4.05
4e	4-OEt	2-NO_2	8.89 ± 1.10	74.71 ± 4.05	33.75 ± 1.62	65.58 ± 4.05
4f	4-OMe	4-NO_2	12.35 ± 1.15	10.59 ± 1.15	47.83 ± 3.02	−3.97 ± 0.75
4g	4-OEt	4-NO_2	16.48 ± 2.03	25.49 ± 2.02	77.78 ± 4.03	63.47 ± 2.03
4h	2-Cl	4-F	7.78 ± 1.14	27.94 ± 2.11	76.52 ± 4.11	25.54 ± 1.14
5a	H	4-Cl	−8.10 ± 0.75	50.78 ± 2.25	11.00 ± 0.00	10.20 ± 0.20
5b	4-Br	2-Cl	19.75 ± 1.74	28.79 ± 2.10	91.76 ± 3.30	57.85 ± 2.02
5c	4-Cl	2-F	37.30 ± 3.02	−3.05 ± 0.95	27.00 ± 1.60	−5.20 ± 0.15
5d	2-Cl	4-F	−22.00 ± 1.15	13.87 ± 2.07	72.00 ± 2.00	8.00 ± 0.20
6a	4-Br	2-Cl	45.61 ± 3.05	35.29 ± 2.12	70.71 ± 3.35	69.09 ± 3.00
6b	4-Br	2-Cl	16.67 ± 2.01	32.03 ± 1.15	23.23 ± 2.11	14.30 ± 1.14
6c	4-Cl	2-F	31.11 ± 2.01	28.85 ± 2.20	18.89 ± 2.25	66.28 ± 2.65
6d	2-Cl	4-F	40.00 ± 3.20	28.72 ± 2.26	76.28 ± 4.06	31.03 ± 2.11
7a	4-Br	2-Cl	23.98 ± 2.11	41.18 ± 3.01	13.91 ± 1.19	63.87 ± 2.02
7b	2-Cl	4-F	31.48 ± 2.65	46.75 ± 2.62	−24.90 ± 1.12	52.33 ± 1.25
acetone	(control)		3.18 ± 0.75	5.23 ± 0.88	1.53 ± 0.21	2.22 ± 0.79
fungicides[a]			95.56 ± 3.20 a	93.53 ± 3.20 b	69.57 ± 3.35 c	93.68 ± 3.21 d

[a]Control fungicides: a, 40% Flusilazole EC; b, 75% Chlorothalonil WP; c, 40% Pyrimethanil SC; and d, 3% Validamycin AS.

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and antitumor activities.[18,19] In the present work, while the hydrazide and hydrazone were cyclodehydrated to the corresponding 1,3,4-oxadiazole and oxadiazoline derivatives, the in vivo fungicidal activity was maintained. Especially, when Y was 1,3,4-oxadiazoline, its activity was improved to a certain extent. The evaluation of the further fungicidal bioassay and other tests about the bioactive spectra is under going.

In summary, a novel series of 1,3,4-oxadiazole derivatives containing a 5-phenyl-2-furan moiety were synthesized by an efficient approach with microwave irradiation in good yields. Their antifungal tests indicated that most of the title compounds and the intermediates diacylhydrazine and acylhydrazone showed fungicidal activity obviously against *B. cinerea* and *R. solanii* at 500 μg/mL in vivo. Meanwhile, all of the tested compounds were found safe for the plants. Among the tested compounds, some showed superiority over the commercial fungicides during the present studies. These compounds could be lead compounds for further discovery of fungicides.

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Notes

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REFERENCES

(1) (a) Suresh Kumar, G. V.; Rajendraprasad, Y.; Mallikarjuna, B. P.; Chandrashekar, S. M.; Kistayya, C. Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents. *Eur. J. Med. Chem.* **2010**, *45* (5), 2063−2074. (b) Farshori, N. N.; Banday, M. R.; Ahmad, A.; Khan, A. U.; Rauf, A. Synthesis, characterization, and *in vitro* antimicrobial activities of 5-alkenyl/hydroxyl-alkenyl-2-phenylamine-1,3,4-oxadiazoles and thiadiazoles. *Bioorg. Med. Chem. Lett.* **2010**, *20* (6), 1933−1938.

(2) (a) Khanum, S. A.; Shashikanth, S.; Sathyanarayana, S. G.; Lokesh, S.; Deepak, S. A. Synthesis and antifungal activity of 2-azetidinonyl-5-(2-benzoylphenoxy) methyl-1,3,4-oxadiazoles against seed-borne pathogens of *Eleusine coracana* (L.) Gaertn. *Pest Manage. Sci.* **2009**, *65* (7), 776−780. (b) Ishii, M.; Jorge, S. D.; de Oliveira, A. A.; Palace-Berl, F.; Sonehara, I. Y.; Pasqualoto, K. F. M.; Tavares, L. C. Synthesis, molecular modeling and preliminary biological evaluation of a set of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole as potential antibacterial, anti-Trypanosoma cruzi and antifungal agents. *Bioorg. Med. Chem.* **2011**, *19* (21), 6292−6301. (c) Xu, W. M.; Han, F. F.; He, M.; Hu, D. Y.; He, J.; Yang, S.; Song, B. A. Inhibition of Tobacco Bacterial Wilt with Sulfone Derivatives Containing an 1,3,4-Oxadiazole Moiety. *J. Agric. Food Chem.* **2012**, *60* (4), 1036−1041.

(3) Cui, Z. N.; Yang, L.; Li, X. C.; Wang, Z.; Yang, X. L. Progress in the study on the synthesis and the activities as insect growth regulators of 2,5-disubstituted 1,3,4-oxadiazoles. *Chin. J. Org. Chem.* **2006**, *26* (12), 1647−1656.

(4) (a) Bondock, S.; Adel, S.; Etman, H. A.; Badria, F. A. Synthesis and antitumor evaluation of some new 1,3,4-oxadiazole-based heterocycles. *Eur. J. Med. Chem.* **2012**, *48*, 192−199. (b) Somani, R. R.; Shirodkar, P. Y.; Kadam, V. J. Synthesis and anticancer evaluation of some newer 2,5-disubstituted-1,3,4-oxadiazole analogues. *Lett. Drug Des. Discovery* **2008**, *5* (6), 364−368. (c) Aboraia, A. S.; Abdel-Rahman, H. M.; Mahfouz, N. M.; EL-Gendy, M. A. Novel 5-(2- hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: Promising anticancer agents. *Bioorg. Med. Chem.* **2006**, *14* (4), 1236−1246.

(5) (a) Chavan, R. S.; Nirmal, D. A.; Bhosale, A. V. Synthesis and biological evaluation of 1,3,4-oxadiazole derivatives as novel analgesic and antiinflammatory agents. *Asian J. Chem.* **2011**, *23* (9), 3919−3922. (b) Jayashankar, B.; Lokanath Rai, K. M.; Baskaran, N.; Sathish, H. S. Synthesis and pharmacological evaluation of 1,3,4-oxadiazole bearing bis(heterocycle) derivatives as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem.* **2009**, *44* (10), 3898−3902.

(6) Bankar, G. R.; Nampurath, G. K.; Nayak, P. G.; Bhattacharya, S. A possible correlation between the correction of endothelial dysfunction and normalization of high blood pressure levels by 1,3,4-oxadiazole derivative, an L-type Ca^{2+} channel blocker in deoxycorticosterone acetate and NG-nitro-L-arginine hypertensive rats. *Chem.-Biol. Interact.* **2010**, *183* (2), 327−331.

(7) Vansdadia, R. N.; Roda, K. P.; Parekh, H. Studies on 1,3,4-oxadiazoles. Part X. Preparation and antimicrobial activity of 2-aryl-5-p-phenylsulfophenyl-1,3,4- oxadiazoles. *J. Indian Chem. Soc.* **1988**, *65* (11), 809−811.

(8) Liras, S.; Allen, M. P.; Segelstein, B. E. A mild method for the preparation of 1,3,4-oxadiazoles: Triflic anhydride promoted cyclization of diacylhydrazines. *Synth. Commun.* **2000**, *30* (3), 437−443.

(9) Al-Talib, M.; Tashtoush, H.; Odeh, N. A convenient synthesis of alkyl and aryl substituted bis-1,3,4-oxadiazoles. *Synth. Commun.* **1990**, *20* (12), 1811−1817.

(10) Wang, S.; Li, Z. T.; Hua, W. T. Synthesis and characterization of fully conjugated schiff base macrocycles containing 1,3,4-oxadiazole moiety. *Synth. Commun.* **2002**, *32* (21), 3339−3345.

(11) (a) Polshettiwar, V.; Varma, R. S. Greener and expeditious synthesis of bioactive heterocycles using microwave irradiation. *Pure Appl. Chem.* **2008**, *80* (4), 777−790. (b) Chauveau, E.; Marestin, C.; Schiets, F.; Mercier, R. Synthesis of 2,4,5-triarylimidazoles in aqueous solution, under microwave irradiation. *Green Chem.* **2010**, *12* (6), 1018−1022. (c) Insuasty, B.; Garcia, A.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J. Synthesis of novel 6,6a,7,8-tetrahydro-5*H*-naphtho [1,2-e]pyrimido[4,5-b][1,4] diazepines under microwave irradiation as potential anti-tumor agents. *Eur. J. Med. Chem.* **2010**, *45* (7), 2841−2846.

(12) (a) Owens, R. G. Plant disease control by 5-nitrofuran derivatives in relation to chemical structure. *Contrib. Boyce Thompson Inst.* **1959**, *20*, 141−149. (b) Kupchik, E. J.; Pisano, M. A.; Whalen, S. M.; Lynch, J. Synthesis and antimicrobial activity of triorganotin 5-nitro-2-furoates. *J. Pharm. Sci.* **1982**, *71* (3), 311−314.

(13) (a) Wei, T.; Chen, J.; Wang, X.; Yang, S. Studies on the synthesis and biological activity of *N*-aryl-*N*′-(5-aryl-2-furoyl)thiourea derivatives. *Chem. J. Chin. Univ.* **1992**, *13* (9), 1217−1221. (b) Chen, J.; Wei, T.; Wang, X.; Yang, S. Studies on the synthesis and biological activity of *N*-aryl-*N*′-(5-aryl-2-furoyl)thiourea derivatives. *Chin. Chem. Lett.* **1991**, *2* (6), 433−436.

(14) (a) Ke, S.; Wei, T.; Xue, S.; Duan, L.; Li, J. Phase transfer catalyzed synthesis under ultrasonic irradiation and bioactivity of *N*′-(4,6-disubstituted-pyrimidin-2- yl)-*N*-(5-aryl-2- furoyl) thiourea derivatives. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2005**, *44B* (9), 1957−1960. (b) Xue, S.; Ke, S.; Duan, L.; Li, J. Ultrasonically irradiated synthesis and bioactivity of 5,7-disubstituted-2-(5-aryl-2-furoylimino)-[1,2,4]-thiadiazolo[2,3-a]pyrimidine derivatives. *Chin. J. Org.Chem.* **2004**, *24* (12), 1610−1613. (c) Xue, S.; Bian, W. Method for preparation and application of 2-(5-*o*-chlorophenyl-2-furoylamino)-acetamidopyrimidine derivatives. CN 101220022 A, 2008.

(15) (a) Kort, M. E.; Drizin, I.; Gregg, R. J.; Scanio, M. J. C.; Shi, L.; Gross, M. F.; Atkinson, R. N.; Johnson, M. S.; Pacofsky, G. J.; Thomas, J. B.; Carroll, W. A.; Krambis, M. J.; Liu, D.; Shieh, C. C.; Zhang, X. F.; Hernandez, G.; Mikusa, J. P.; Zhong, C. M.; Joshi, S.; Honore, P.; Roeloffs, R.; Marsh, K. C.; Murray, B. P.; Liu, J. R.; Werness, S.; Faltynek, C. R.; Krafte, D. S.; Jarvis, M. F.; Chapman, M. L.; Marron, B. E. Discovery and Biological Evaluation of 5-Aryl-2-furfuramides, Potent and Selective Blockers of the Nav1.8 Sodium Channel with Efficacy in Models of Neuropathic and Inflammatory Pain. *J. Med. Chem.* **2008**, *51* (3), 407−416. (b) Burch, H. A.; White, R. E.; Wright,

G. C.; Goldenberg, M. M. Phenylfurans. IV: Spasmolytic 3-diethylamino-2,2-(dimethyl) propyl esters of 5-substituted phenyl-2-furancarboxylic acids. *J. Pharm. Sci.* **1980**, *69* (1), 107−110.

(16) (a) Ye, Q. Z.; Xie, S. X.; Huang, M.; Huang, W. J.; Lu, J. P.; Ma, Z. Q. Metalloform-Selective Inhibitors of Escherichia coli Methionine Aminopeptidase and X-ray Structure of a Mn(II)-Form Enzyme Complexed with an Inhibitor. *J. Am. Chem. Soc.* **2004**, *126* (43), 13940−13941. (b) Vedantham, P.; Zhang, M.; Gor, P. J.; Huang, M.; Georg, G. I; Lushington, G. H.; Mitscher, L. A.; Ye, Q. Z.; Hanson, P. R. Studies Towards the Synthesis of Methionine Aminopeptidase Inhibitors: Diversification Utilizing a ROMP-Derived Coupling Reagent. *J. Comb. Chem.* **2008**, *10* (2), 195−203.

(17) (a) Yang, X. L.; Wang, D. Q.; Chen, F. H.; Ling, Y.; Zhang, Z. N. The synthesis and larvicidal activity of *N*-aroyl-*N*′-(5-aryl-2-furoyl) ureas. *Pestic. Sci.* **1998**, *52*, 282−286. (b) Yang, X. L.; Ling, Y.; Wang, D. Q.; Chen, F. H. The synthesis and biological activity of *N*-phenyl-*N*′-(5-phenyl-2-furoyl) ureas. *Chin. J. Synth. Chem.* **2002**, *10*, 510−512. (c) Cui, Z. N.; Zhang, L.; Huang, J.; Li, Y.; Ling, Y.; Yang, X. L. 3D-QSAR studies on diacyl urea derivatives containing furan moiety. *Acta Chim. Sin.* **2008**, *66* (12), 1417−1423.

(18) (a) Cui, Z. N.; Li, Y.; Huang, J.; Ling, Y.; Cui, J. R.; Wang, R. Q.; Yang, X. L. New Class of Potent Antitumor Acylhydrazone Derivatives Containing Furan. *Eur. J. Med. Chem.* **2010**, *45* (12), 5576−5584. (b) Cui, Z. N.; Yang, X. L.; Shi, Y. X.; Uzawa, H.; Cui, J. R.; Dohi, H.; Nishida, Y. Molecular design, synthesis and bioactivity of glycosyl hydrazine and hydrazone derivatives: Notable effects of the sugar moiety. *Bioorg. Med. Chem. Lett.* **2011**, *21* (23), 7193−7196.

(19) (a) Cui, Z. N.; Wang, Z.; Li, Y.; Zhou, X. Y.; Ling, Y.; Yang, X. L. Synthesis of 5-(chlorophenyl)-2-furancarboxylic acid 2-(benzoyl)-hydrazide derivatives and determination of their insecticidal activity. *Chin. J. Org. Chem.* **2007**, *27* (10), 1300−1304. (b) Cui, Z. N.; Huang, J.; Li, Y.; Ling, Y.; Yang, X. L.; Chen, F. H. Synthesis and bioactivity of novel *N*,*N*′-diacylhydrazine derivatives containing furan(I). *Chin. J. Chem.* **2008**, *26* (5), 916−922. (c) Li, X. C.; Yang, X. L.; Cui, Z. N.; Li, Y.; He, H. W.; Ling, Y. Synthesis and Bioactivity of Novel *N*,*N*′-Diacylhydrazine Derivatives Containing Furan(II). *Chin. J. Chem.* **2010**, *28* (7), 1233−1239. (d) Cui, Z. N.; Zhang, L.; Huang, J.; Yang, X. L.; Ling, Y. Synthesis and Bioactivity of Novel *N*,*N*′-Diacylhydrazine Derivatives Containing Furan(III). *Chin. J. Chem.* **2010**, *28* (7), 1257−1266. (e) Zhang, L.; Cui, Z. N.; Yin, B.; Yang, G. F.; Ling, Y.; Yang, X. L. QSAR and 3D-QSAR studies of the diacylhydrazine derivatives containing furan rings based on the density functional theory. *Sci. China Chem.* **2010**, *53* (6), 1322−1331.

(20) Cui, Z. N.; Ling, Y.; Li, B. J.; Li, Y. Q.; Rui, C. H.; Cui, J. R.; Shi, Y. X.; Yang, X. L. Synthesis and Bioactivity of *N*-benzoyl-*N*′-[5-(2′-substituted phenyl)-2- furoyl] semicarbazide Derivatives. *Molecules* **2010**, *15* (6), 4267−4282.

(21) Cui, Z. N.; Shi, Y. X.; Cui, J. R.; Ling, Y.; Li, B. J.; Yang, X. L. Synthesis and Bioactivities of Novel Pyrazole and Triazole Derivatives Containing 5-Phenyl-2-Furan. *Chem. Biol. Drug Des.* **2012**, *79* (1), 121−127.

(22) Krutosikova, A.; Kovac, J.; Sykora, V. Furan derivatives. LIII. Synthesis of 5-aryl-2-furancarboxylic acids. *Collect. Czech. Chem. Commun.* **1974**, *39* (7), 1892−1897.

(23) (a) Shi, Y. X.; Yuan, L. P.; Zhang, Y. B.; Li, B. J. Fungicidal activity of novel fungicide chlorphenomizole and efficacy in controlling main diseases on vegetable in field. *Chin. J. Pestic. Sci.* **2007**, *9* (2), 126−130. (b) Wang, B. L.; Shi, Y. X.; Ma, Y.; Liu, X. H.; Li, Y. H.; Song, H. B.; Li, B. J.; Li, Z. M. Synthesis and Biological Activity of Some Novel Trifluoromethyl-Substituted 1,2,4- Triazole and Bis(1,2,4-Triazole) Mannich Bases Containing Piperazine Rings. *J. Agric. Food Chem.* **2010**, *58* (9), 5515−5522. (c) Liu, X. H.; Shi, Y. X.; Ma, Y.; Zhang, C. Y.; Dong, W. L.; Pan, L.; Wang, B. L.; Li, B. J.; Li, Z. M. Synthesis, antifungal activities and 3D QSAR study of *N*-(5-substituted-1,3,4- thiadiazol-2-yl) cyclopropanecarbox-amides. *Eur. J. Med. Chem.* **2009**, *44* (7), 2782−2786. (d) Zhang, C. Y.; Liu, X. H.; Wang, B. L.; Wang, S. H.; Li, Z. M. Synthesis and antifungal activities of new pyrazole derivatives *via* 1,3-dipolar cycloaddition reaction. *Chem. Biol. Drug Des.* **2010**, *75* (5), 489−493.