Benzamides Substituted with Quinoline-Linked 1,2,4-Oxadiazole: Synthesis, Biological Activity and Toxicity to Zebrafish Embryo

Bin-Long Sun, Ying-Ying Wang, Sen Yang, Min-Ting Tu, Ying-Ying Shao, Yi Hua, Yi Zhou and Cheng-Xia Tan *

College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China; zark725@163.com (B.-L.S.); wyy1252909407@163.com (Y.-Y.W.); y17764528124@163.com (S.Y.); tt1239803789@163.com (M.-T.T.); s2901692009@163.com (Y.-Y.S.); huayi3181@gmail.com (Y.H.); 2112101265@zjut.edu.cn (Y.Z.)
* Correspondence: tanchengxia@zjut.edu.cn; Tel./Fax: +86-571-8832-0238

Abstract: To develop new compounds with high activity, broad spectrum and low-toxicity, 17 benzamides substituted with quinoline-linked 1,2,4-oxadiazole were designed using the splicing principle of active substructures and were synthesized. The biological activities were evaluated against 10 fungi, indicating that some of the synthetic compounds showed excellent fungicidal activities. For example, at 50 mg/L, the inhibitory activity of 13p (3-Cl-4-Cl substituted, 86.1%) against Sclerotinia sclerotiorum was superior to that of quinoxyfen (77.8%), and the inhibitory activity of 13f (3-CF$_3$ substituted, 77.8%) was comparable to that of quinoxyfen. The fungicidal activities of 13f and 13p to Sclerotinia sclerotiorum were better than that of quinoxyfen (14.19 mg/L), with EC$_{50}$ of 6.67 mg/L and 5.17 mg/L, respectively. Furthermore, the acute toxicity of 13p was 19.42 mg/L, classifying it as a low-toxic compound.

Keywords: quinoline; synthesis; 1,2,4-oxadiazole; biological activity; toxicity

1. Introduction

Possessing different biological activity, heterocyclic structures like nitrogen-containing heterocyclic [1,2] and oxygen-containing heterocyclic are important features in synthetic pesticides for their high efficiency, various biological activities, and diversity of possible substituents. Quinoline is a versatile group, a privileged scaffold, and an outstanding fused heterocyclic compound [3]. Apart from their applications in medicine [4], quinoline derivatives have shown potential in pesticides, such as insecticidal [5–7], herbicidal [8] and fungicidal activities [9–12]. As the bioisostere of the amide, the 1,2,4-oxadiazole heterocycle has good hydrolytic and metabolic properties [13], and exhibits a wide range of biological activities in the field of pesticides [14–19]. In addition, there have already been quite a few products containing quinoline or 1,2,4-oxadiazole scaffold launched successively, including quinoxyfen [20], ipflufenoquin [21], quinmerac, tioxazafen and oxolamine (Figure 1).

In our efforts to develop potent fungicides, we have previously reported the synthesis and biological activity studies of 1,2,4-oxadiazole-substituted benzamide derivatives [22,23]. Some of them exhibited good fungicidal activities. In view of the facts mentioned above, to further improve the fungicidal activities of these compounds, we designed (Figure 2) a series of novel 1,2,4-oxadiazole-substituted benzamides using the splicing principle of active substructures and synthesized them by introducing a quinoline scaffold at the 5-position of 1,2,4-oxadiazole. The chemical structures of these new compounds were confirmed by ¹H-NMR, ¹³C-NMR, and HRMS, their fungicidal activities were studied and a toxicity test with zebrafish embryo was performed.
Molecules 2022, 27, x  

would hydrolyzed readily than ester groups under alkaline condition (Scheme 2).

Table 1. Effects of reaction conditions on the synthesis of compound 5.

| Entry | Oxidant      | Solvent | Reaction Time/h | Yield/% |
|-------|--------------|---------|-----------------|---------|
| 1     | H$_2$O$_2$   | MeCN    | 4               | /       |
| 2     | MnO$_2$      | THF     | 10              | 43.5    |
| 3     | K$_2$S$_2$O$_8$/H$_2$SO$_4$ | MeCN | 4               | 86.5    |

The synthesis of amine oxime 9 was similar to our previous procedures [23]. It should be noted that this reaction could not be carried out for a long time to avoid the form of amide by-products. Afterwards, intermediate 12 was prepared from compound 9 via cyclization, hydrolysis, and condensation reaction. In addition, the hydrolysis reaction was carried out under acidic condition to avoid by-products as chlorine-substituted alkanes would hydrolyzed readily than ester groups under alkaline condition (Scheme 2).
Molecules 2022, 27, x...0 under alkaline condition. Finally, Williamson ether synthesis of compound 5 with 12 formed the target compounds 13.

2.2. Spectrum Analysis of Target Compounds

All the target compounds were confirmed by $^1$H-NMR, $^{13}$C-NMR, and HRMS. The target compound 13f was taken as an example to conduct spectrum analysis. In the $^1$H-NMR spectra of 13f, the $-\text{NH}-$ proton signal was found at $\delta$ 10.75 ppm. In addition, the single peak at 6.04 ppm was the peak of $-\text{CH}_2-$ between ether bond and 1,2,4-oxadiazoles. In the $^{13}$C-NMR spectra of compound 13f, the appearances of signals at 167.83 ppm and 165.40 ppm were assigned to the carbons of the 1,2,4-oxadiazole ring. In the HRMS spectrum, the calculated value of the ion peak of this compound was [M + Na]$^+$ 559.0546, and the measured value was [M + Na]$^+$ 559.0549. The absolute error was within 0.003.

2.3. Biological Activities of Target Compounds

The results of the fungicidal activities test of the target compounds against 10 fungi are shown in Table 2. At 50 mg/L, all the target compounds 13a–13q were found to exhibit certain inhibitory activity against the 10 fungi tested. Overall, the target compounds showed better inhibitory activity against Sclerotinia sclerotiorum, ranging from 47.2% to
86.1%. Among them, the inhibitory rate of compound 13p (86.1%) was superior to the control drug quinoxyfen (77.8%), and the inhibitory rate of compound 13f was 77.8%, which was similar to quinoxyfen. In addition, the inhibition rates of compounds 13a, 13b, 13d and 13o against Sclerotinia sclerotiorum were 75.0%, 72.2%, 75.0% and 75.0%, respectively, which are slightly lower than that of quinoxyfen. Other compounds also exhibited moderate inhibitory activity (47.2–69.4%). For Alternaria solani, Gibberella zeae, Phytophthora capsica and Physalospora piricola, some compounds possessed better inhibitory activities than quinoxyfen, but their inhibition rates were less than 50%. As can be seen from Table 3, the EC50 of compounds 13f and 13p against Sclerotinia sclerotiorum were 6.67 mg/L and 5.17 mg/L, respectively, which were significantly superior to quinoxyfen (14.19 mg/L).

Structure–activity relationship (SAR) results for these target compounds showed that when the substituent of the benzene ring was 3-CF3 or 3,4-(Cl)2, their inhibitory activities were obviously superior to others. Overall, electron withdrawing groups are beneficial to inhibitory activity.

Table 2. Fungicidal activities of compounds 13a–13q at 50 mg/L.

| Compounds | R       | Fungicidal Activities (Inhibition Rate %) |
|-----------|---------|------------------------------------------|
| 13a       | H       | 7.1  3.2  20.0  25.0  75.0  30.4  6.3  11.5  6.7  15.4 |
| 13b       | 2-CH3   | 14.3 16.1  6.7  18.8  72.2  21.7  6.3  11.5  13.3  26.9 |
| 13c       | 3-CH3   | 21.4  9.7  20.0  9.4  69.4  30.4  6.3  11.5  6.7  11.5 |
| 13d       | 4-CH3   | 21.4  9.7  20.0  9.4  75.0  34.8  25.0  15.4  6.7  11.5 |
| 13e       | 4-t-Bu  | 35.7 19.4 33.3 18.8 55.6 17.4 25.0 15.4 13.3 30.8 |
| 13f       | 3-CF3   | 21.4 32.3 20.0 18.8 77.8 21.7 6.3 3.8 20.0 15.4 |
| 13g       | 2-F     | 21.4 45.2 20.0 18.8 69.4 21.7 8.3 7.7 6.7 34.6 |
| 13h       | 3-F     | 14.3 38.7 20.0 31.3 69.4 34.8 4.2 7.7 6.7 38.5 |
| 13i       | 4-F     | 21.4 6.5 20.0 34.4 47.2 8.7 10.4 3.8 13.3 38.5 |
| 13j       | 4-Cl    | 21.4 3.2 6.7 31.3 55.6 30.4 4.2 3.8 6.7 11.5 |
| 13k       | 4-Br    | 35.7 19.4 33.3 18.8 55.6 21.7 39.6 19.2 20.0 26.9 |
| 13l       | 4-I     | 35.7 29.0 33.3 31.3 55.6 8.7 35.4 3.8 13.3 19.2 |
| 13m       | 2,4-di-CH3 | 35.7 45.2 20.0 28.1 50.0 17.4 4.2 7.7 20.0 19.2 |
| 13n       | 2,6-di-CH3 | 35.7 25.8 20.0 18.8 58.3 34.8 18.8 7.7 13.3 38.5 |
| 13o       | 3-Cl-2-CH3 | 35.7 38.7 33.3 18.8 75.0 30.4 8.3 7.7 20.0 38.5 |
| 13p       | 3-Cl-4-Cl | 7.1  48.4 33.3 31.3 86.1 21.7 35.4 11.5 26.7 38.5 |
| 13q       | 2-F-4-F | 14.3 32.3 20.0 25.0 66.7 13.0 10.4 7.7 13.3 19.2 |
| quinoxyfen |         | 35.7 45.2 46.7 9.4 77.8 30.4 25.0 42.3 33.3 38.5 |

Note: Alternaria solani (AS), Gibberella zeae (GZ), Pyricularia oryae (PO), Phytophthora capsica (PC), Sclerotinia sclerotiorum (SS), Botrytis cinerea (BC), Rizocotinia solani (RS), Fusarium oxysporum (FO), Cercospora arachidicola (CA), Physalospora piricola (PP). All the data were determined three times.

Table 3. EC50 of compounds 13f, 13p and quinoxyfen to Sclerotinia sclerotiorum (SS).

| Compounds | y = a + bx | r²      | EC50(mg L⁻¹) |
|-----------|------------|---------|--------------|
| 13f       | y = 1.0563x + 4.1298 | 0.9845  | 6.67         |
| 13p       | y = 1.0992x + 4.2153 | 0.9938  | 5.17         |
| quinoxyfen | y = 1.5356x + 3.2309 | 0.9784  | 14.19        |

2.4. Toxicity to Zebrafish Embryo

According to the fungicidal activity results (Figure 3), we selected compound 13p with better activity to study the lethal and teratogenic effects exposure on zebrafish embryos from 6 to 96 hpf (hours post fertilization). When the concentration of 13p was below 40 mg/L, the mortality rate increased sharply as the concentration increased. Afterwards, the mortality rate exceeded 90% at 40 mg/L. The resulting LC50 value for compound 13p was 19.42 mg/L, and it was classified as a low-toxic compound [24].
As the time and concentration increased, zebrafish embryos showed obvious developmental delay (Figure 4), such as bent spine, pericardial cyst, yolk cyst and even malformation. At 72 hpf, compared to the control group, the zebrafish embryo exposed at 10 mg/L and 20 mg/L showed obvious yolk cyst. At 96 hpf, pericardial cyst and bent spine appeared on the zebrafish embryo exposed at 10 mg/L and 20 mg/L.

Figure 4. Zebrafish embryo malformation after exposure to compound 13p. Note: BS, bent spine; PC, pericardial cyst; YC, yolk cyst.

3. Experimental Section

3.1. General Information

Melting points were determined using an X-4 digital microscopic melting point detector (Taike, Beijing, China) and the thermometer was uncorrected. $^1$H-NMR and $^{13}$C-NMR spectra were measured on BRUKER Avance 500 MHz spectrometer (Bruker 500 MHz, Fallanden, Switzerland) using CDCl$_3$ or DMSO as the solvent. High-resolution electrospray mass spectra (HR-ESI–MS) were determined using an UPLC H CLASS/QTOF G2 XS mass spectrometer (Waters, Milford, CT, USA). All the reagents were analytical grade or synthesized in our laboratory. The characterization data for all synthetic compounds are provided in the Supplementary Materials.

Ethics statement: The Institutional Animal Care and Use Committee (IACUC) at Wenzhou Medical University (SYXK 2019-0009, 4 April 2019 to 4 April 2024) approved our study plan for proper use of zebrafish. All studies were carried out in strict accordance with the guidelines of the IACUC. All dissections were performed on ice, and all efforts were made to minimize suffering.

Table 3. EC50 of compounds 13f, 13p and quinoxyfen to Sclerotinia sclerotiorum (SS) in rice. The regression equations are $y = 1.5356x + 3.2309$, $y = 1.0992x + 4.2153$ and $y = 0.9784x + 5.17$ respectively. Note: $y$ represents the malformation rate, $x$ represents the concentration. The equations are as follows: $y = 1.5356x + 3.2309$, $y = 1.0992x + 4.2153$, and $y = 0.9784x + 5.17$.

| Concentration (mg/L) | 24hpf | 48hpf | 72hpf | 96hpf |
|----------------------|-------|-------|-------|-------|
| Control              | ![Control](image) | ![Control](image) | ![Control](image) | ![Control](image) |
| 5mg/L                | ![5mg/L](image) | ![5mg/L](image) | ![5mg/L](image) | ![5mg/L](image) |
| 10mg/L               | ![10mg/L](image) | ![10mg/L](image) | ![10mg/L](image) | ![10mg/L](image) |
| 20mg/L               | ![20mg/L](image) | ![20mg/L](image) | ![20mg/L](image) | ![20mg/L](image) |

Figure 3. Zebrafish embryo mortality rates after exposure to 13p.
3.2. Synthesis

3.2.1. Ethyl 3-((3,5-dichlorophenyl)amino)propanoate (2)

3,5-dichloroaniline 1 (16.20 g, 0.10 mol) and ethyl acrylate (30.00 g, 0.30 mol) were sequentially added to a three-necked flask, heated, and stirred until dissolved completely. The mixture of MSA (1.44 g) and water (2.70 g) was added dropwise, then reacted at 60 °C for 16 h. After the reaction was completed, the mixture was cooled to room temperature, unreacted ethyl acrylate was removed under reduced pressure. The remnant was dissolved in toluene (300 mL) and washed with HCl. Finally, the organic layer was dried with anhydrous MgSO\textsubscript{4} and evaporated to give 23.60 g yellow solid. Yield: 90.0%, m.p. 72–74 °C; \textsuperscript{1}H-NMR (500 MHz, Chloroform-d) \(\delta\) 6.69 (t, \(J = 1.7\) Hz, 1H), 6.48 (d, \(J = 1.8\) Hz, 2H), 4.18 (q, \(J = 7.1\) Hz, 2H), 3.42 (t, \(J = 6.2\) Hz, 2H), 2.61 (t, \(J = 6.2\) Hz, 2H), 1.29 (t, \(J = 7.1\) Hz, 3H).

3.2.2. 3-((3,5-Dichlorophenyl)amino)propanoic Acid (3)

Ethyl 3-((3,5-dichlorophenyl)amino)propanoate 2 (31.32 g, 0.12 mol), methanol (50 mL) and NaOH (20%, 32.00 g) were added to a three-necked flask and reacted at 60 °C for 1 h. Methanol was removed under reduced pressure followed by the addition of water (100 mL). Afterwards, we adjusted the pH to 2–3 with HCl and white solid precipitate was obtained (24.50 g). Yield: 85%, m.p. 102–103 °C.

3.2.3. 5,7-Dichloro-2,3-dihydroquinolin-4(1H)-one (4)

To a three-necked flask, we added PPA (10.00 g) and heated at 90 °C for 0.5 h. Then, 3-((3,5-dichlorophenyl)amino)propanoic acid 3 (4.66 g, 0.02 mol) was added slowly and reacted at 150 °C for 5 h. To the stirred solution, water (100 mL) was added to precipitate yellow solid after the mixture was cooled to room temperature. The crude product was filtered, sequentially washed with petroleum ether and saturated aqueous NaHCO\textsubscript{3} solution, and dried to obtain 4.30 g solid. Yield: 94%, m.p. 184–185 °C.

3.2.4. 5,7-Dichloro-4-hydroxyquinoline (5)

Conc. H\textsubscript{2}SO\textsubscript{4} (2.00 g) was added slowly to a solution of compound 4 (5.00 g, 23.00 mmol) in acetonitrile (35.00 g). Afterwards, K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (8.00 g) was added when the temperature reached 50 °C. The mixture was then reflux for 4 h. TLC was used to track the reaction progress. After the reaction was completed, the mixture was cooled to room temperature to precipitate solid. The solid was filtered, washed with water, and dried to obtain product 5 (4.60 g). Yield: 93.4%.

3.2.5. Methyl-3-(N-hydroxycarbamimidoyl)benzoate (9)

The synthesis of intermediate 9 was performed with reference to our previous work.

3.2.6. Methyl 3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)benzoate (10)

To a three-necked flask, we added intermediate 9 (0.97 g, 5.00 mmol), triethylamine (1.20 g, 12.00 mmol) and dry toluene (100 mL). Stirring was started at 0 °C for 2 h followed by the dropwise addition of chloroacetyl chloride (0.58 g, 5.20 mmol). This was then reacted at 0 °C for another 3 h. The mixture was further heated to reflux for about 2 h. The mixture was then cooled to room temperature and sequentially washed with water and saturated sodium chloride solution. The organic layer was dried with Na\textsubscript{2}SO\textsubscript{4} and the solvent was removed to give 0.93 g yellow solid. Yield: 73.8%; \textsuperscript{1}H-NMR (500 MHz, Chloroform-d) \(\delta\) 8.75 (s, 1H), 8.28 (d, \(J = 7.8\) Hz, 1H), 8.20 (d, \(J = 7.8\) Hz, 1H), 7.59 (t, \(J = 7.8\) Hz, 1H), 4.78 (s, 2H), 3.97 (s, 3H).

3.2.7. 3-(5-(Chloromethyl)-1,2,4-oxadiazol-3-yl)benzoic Acid (11)

Compound 10 (5.00 g, 0.02 mol), CH\textsubscript{3}COOH (30 mL), and HCl (30 mL) were added to a three-necked flask and reacted at 70 °C for 3 h. After the reaction was completed, the mixture was cooled to room temperature to precipitate white solid. The white solid was filtered, washed with water, and dried to give compound 11 (4.45 g). Yield: 93.6%, m.p.
Molecules 2022, 27, 3946

179–182 ºC; 1H NMR (400 MHz, DMSO-d6) δ 13.34 (s, 1H), 8.53 (s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 5.19 (s, 2H).

3.2.8. Synthesis of Intermediate (12)

The solution of compound 11 (0.24 g, 1.00 mmol) in SOCl2 (5 mL) was reacted at reflux for 3 h. The SOCl2 was removed and THF (30 mL) was added subsequently. Then, the mixture of substituted aniline (1.20 mmol), triethylamine (2.5 mmol) and THF (1 mL) was added dropwise under ice bath. Stirred overnight, separated by column chromatography to give intermediate 12.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-phenylbenzamide 12a. Yellow solid, yield 79.4%, m.p. 103–104 ºC; 1H-NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 8.60 (s, 1H), 8.22 (t, J = 9.0 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 7.9 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 5.23 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 176.33, 168.18, 165.05, 139.41, 136.45, 131.42, 130.36, 130.06, 129.09, 126.82, 126.36, 124.37, 121.03, 34.21; HRMS calcd for C16H12ClN3O2 [M + H]+ 314.0691, found 314.0698.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(o-tolyl)benzamide 12b. Yellow solid, yield 77.5%, m.p. 95–96 ºC; 1H-NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 8.64 (t, J = 1.8 Hz, 1H), 8.24 (d, J = 7.7 Hz, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.27–7.17 (m, 2H), 5.23 (s, 2H), 2.26 (s, 3H); 13C-NMR (126 MHz, DMSO-d6) δ 176.32, 168.20, 164.91, 136.69, 136.07, 134.33, 131.31, 130.81, 130.32, 130.09, 127.17, 126.89, 126.64, 126.50, 126.41, 34.22, 18.39; HRMS calcd for C17H13ClN3O2 [M + H]+ 328.0847, found 328.0856.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(m-tolyl)benzamide 12c. White solid, yield 69.7%, m.p. 98–100 ºC; 1H-NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.60 (d, J = 1.8 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 5.23 (s, 2H), 2.33 (s, 3H); 13C-NMR (126 MHz, DMSO-d6) δ 176.32, 168.18, 164.96, 139.33, 138.25, 136.49, 131.40, 130.32, 130.05, 128.92, 126.78, 126.35, 125.06, 121.55, 118.20, 34.21, 21.66; HRMS calcd for C17H13ClN3O2 [M + H]+ 328.0847, found 328.0857.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(p-tolyl)benzamide 12d. White solid, yield 73.8%, m.p. 113–116 ºC; 1H-NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.59 (s, 1H), 8.24–8.18 (m, 2H), 7.75 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 5.23 (s, 2H), 2.29 (s, 3H); 13C-NMR (126 MHz, DMSO-d6) δ 176.31, 168.19, 164.82, 136.89, 136.51, 133.35, 131.36, 130.26, 130.02, 129.47, 126.78, 126.34, 121.04, 34.21, 20.97; HRMS calcd for C17H13ClN3O2 [M + H]+ 328.0847, found 328.0854.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(4-(tert-butyl)phenyl)benzamide 12e. White solid, yield 75.7%, m.p. 125–127 ºC; 1H-NMR (500 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.21 (d, J = 7.7 Hz, 1H), 8.15 (s, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.64–7.54 (m, 3H), 7.39 (d, J = 8.3 Hz, 2H), 4.76 (s, 2H), 1.34 (s, 9H); 13C-NMR (126 MHz, DMSO-d6) δ 167.72, 167.21, 164.88, 150.40, 146.74, 136.83, 136.53, 131.31, 130.51, 130.01, 126.94, 126.34, 125.71, 124.92, 120.74, 111.70, 41.05, 34.55, 31.67, 19.01, 12.96; HRMS calcd for C20H21ClN3O2 [M + H]+ 370.1317, found 370.1327.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(3-(trifluoromethyl)phenyl)benzamide 12f. Yellow solid, yield 66.4%, m.p. 141–145 ºC; 1H-NMR (500 MHz, DMSO-d6) δ 10.80 (s, 1H), 8.63 (d, J = 1.8 Hz, 1H), 8.31–8.17 (m, 3H), 8.10 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 5.23 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 167.60, 167.19, 165.40, 150.37, 140.21, 135.87, 131.37, 130.86, 130.33, 130.02 (d, J = 11.5 Hz), 126.97, 126.43, 125.69, 124.85, 124.38, 123.52, 120.63 (d, J = 3.8 Hz), 116.99 (d, J = 4.0 Hz), 111.72, 41.03, 18.98, 12.90; HRMS calcd for C17H13ClF3N3O2 [M + H]+ 382.0565, found 382.0576.
3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(2-fluorophenyl)benzamide 12h. Yellow solid, yield 78.6%, m.p. 123–127 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 8.92 (t, J = 1.5 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.82–7.74 (m, 2H), 7.60 (d, J = 8.2 Hz, 1H), 7.45–7.37 (m, 1H), 6.97 (t, J = 8.5 Hz, 1H), 5.23 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 167.10, 166.68, 164.79, 162.97, 161.05, 149.86, 140.67 (d, J = 11.3 Hz), 135.55, 130.85, 130.20 (d, J = 10.1 Hz), 129.53, 126.45, 125.89, 124.34, 116.06, 111.22, 110.29 (d, J = 21.1 Hz), 107.08 (d, J = 26.3 Hz), 40.54, 18.49, 12.40; HRMS calcd for C16H12ClFN3O2 [M + H]+ 332.0597, found 332.0604.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(3-fluorophenyl)benzamide 12i. Yellow solid, yield 67.1%, m.p. 132–133 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.57 (s, 1H), 8.60 (s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.86–7.80 (m, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 8.9 Hz, 2H), 5.23 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 167.68, 167.21, 165.00, 159.86, 157.95, 150.39, 136.29, 135.74, 131.32, 130.63, 130.06, 126.91, 124.38, 124.90 (d, J = 7.8 Hz), 115.69 (d, J = 22.2 Hz), 111.70, 41.05, 19.00, 12.95; HRMS calcd for C16H12ClIF3N3O2 [M + H]+ 331.0597, found 332.0601.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(4-fluorophenyl)benzamide 12j. Yellow solid, yield 79.3%, m.p. 149–151 °C; 1H-NMR (500 MHz, DMSO-d6) δ 8.50 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.67–7.57 (m, 3H), 7.34 (d, J = 8.8 Hz, 2H), 4.78 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 167.67, 167.23, 165.08, 150.41, 135.52, 135.35, 131.37, 130.86, 130.20, 130.17, 130.08, 129.09, 128.20, 128.00, 127.05, 126.47, 124.93, 111.70, 41.05, 19.01, 12.96; HRMS calcd for C16H12ClF3N3O2 [M + H]+ 348.0301, found 348.0312.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(4-bromophenyl)benzamide 12k. Yellow solid, yield 73.4%, m.p. 153–155 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 8.59 (s, 1H), 8.24 (d, J = 7.7 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.82–7.73 (m, 3H), 7.56 (d, J = 8.7 Hz, 2H), 5.23 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 167.61, 167.18, 165.27, 150.37, 140.89, 135.99, 133.43, 131.36, 130.77, 130.05, 126.96, 124.80, 124.03, 120.34, 119.22, 111.72, 41.04, 18.99, 12.91; HRMS calcd for C16H12ClBrF3N3O2 [M + H]+ 391.9796, found 391.9802.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(4-iodophenyl)benzamide 12l. Yellow solid, yield 68.8%, m.p. 141–143 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.59 (s, 1H), 8.58 (d, J = 1.7 Hz, 1H), 8.23 (d, J = 7.7 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 5.22 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 167.69, 167.25, 165.21, 150.41, 138.39, 136.23, 131.42, 130.75, 130.12, 129.04, 128.02, 126.96, 126.41, 124.94, 122.49, 111.70, 41.06, 19.01, 12.98; HRMS calcd for C16H12ClI3N3O2 [M + H]+ 439.9657, found 439.9668.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(2-dimethylphenyl)benzamide 12m. White solid, yield 69.5%, m.p. 114–117 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.11 (s, 1H), 8.63 (s, 1H), 8.22 (d, J = 7.8 Hz, 2H), 7.75 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.10 (s, 1H), 7.04 (d, J = 7.9 Hz, 1H), 5.22 (s, 2H), 2.30 (s, 3H), 2.21 (s, 3H); 13C-NMR (126 MHz, DMSO-d6) δ 167.68, 167.24, 165.21, 150.41, 138.81, 136.22, 131.96, 131.41, 130.76, 130.12, 126.96, 126.41, 124.93, 122.85, 116.11, 111.70, 41.06, 19.01, 12.97; HRMS calcd for C16H17ClN3O2 [M + H]+ 342.1004,
3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(2,6-dimethylphenyl)benzamide 12n. White solid, yield 64.9%, m.p. 138–140 °C; 1H-NMR (500 MHz, DMSO-d₆) δ 10.43 (s, 1H), 8.63 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.16 (s, 1H), 7.81–7.74 (m, 2H), 7.61 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H); 13C-NMR (126 MHz, DMSO-d₆) δ 167.70, 167.18, 165.20, 150.41, 139.29, 137.80, 136.25, 131.41, 130.53, 130.11, 128.24, 127.28, 126.88, 124.88, 111.69, 41.03, 19.00, 18.53, 12.92; HRMS calcd for C₁₇H₁₇ClN₃O₂ [M + H]+ 362.0458, found 362.0459.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(3-chloro-2-methylphenyl)benzamide 12o. White solid, yield 63.7%, m.p. 121–124 °C; 1H-NMR (500 MHz, DMSO-d₆) δ 10.44 (s, 1H), 8.63 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.68–7.57 (m, 1H), 7.39 (t, J = 9.8 Hz, 1H), 7.15 (t, J = 8.5 Hz, 1H), 5.23 (s, 2H); 13C-NMR (126 MHz, DMSO-d₆) δ 167.67, 167.21, 165.13, 150.39, 138.31, 135.64, 134.30, 132.73, 131.37, 130.77, 130.14, 127.42, 127.39, 127.02, 126.43, 126.40, 124.90, 41.05, 19.00, 15.83, 12.95; HRMS calcd for C₁₆H₁₁ClF₂N₂O₂ [M + H]+ 381.9911, found 381.9921.

3-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-N-(4,3-dichlorophenyl)benzamide 12p. Yellow solid, yield 69.9%, m.p. 138–140 °C; 1H-NMR (500 MHz, DMSO-d₆) δ 10.72 (s, 1H), 8.59 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.16 (s, 1H), 7.81–7.74 (m, 2H), 7.61 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H); 13C-NMR (126 MHz, DMSO-d₆) δ 167.70, 167.18, 164.58, 150.38, 136.06, 135.85, 135.54, 131.11, 130.53, 130.11, 128.24, 127.28, 126.88, 124.88, 111.69, 41.03, 19.00, 18.53, 12.92; HRMS calcd for C₁₆H₁₁Cl₂N₂O₂ [M + H]+ 390.0502, found 390.0511.

3.2.9. Synthesis of Target Compound 13

5,7-dichloro-4-hydroxyquinoline 5 (0.21 g, 1.00 mmol), intermediate 12 (1.00 mmol), K₂CO₃ (0.35 g) and DMF (10 mL) were added to a round bottom flask. The mixture was reacted at 60 °C for 5 h. Afterwards, the mixture was cooled to room temperature and poured into water (100 mL) then extracted with ethyl acetate. The extraction was dried over anhydrous MgSO₄ and filtered. After that the filtration was concentrated and separated by column chromatography to give target compounds 13.
3-((5-(5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(m-tolyl)benzamide 13c. Yellow solid, yield 65.6%, HPLC 93.26%, m.p. 113.04, 48.64; HRMS calcd for C_{25}H_{29}Cl_{2}N_{2}O_{4} [M + H]^+ 505.0829, found 505.0831.

3-((5-(5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-ethylbenzamide 13d. Yellow solid, yield 63.7%, HPLC 94.00%, m.p. 117.04 (s, 1H), 8.47 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.12–8.05 (m, 2H), 7.88 (d, J = 1.5 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 1.5 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 6.20 (d, J = 7.9 Hz, 1H), 6.04 (s, 2H); HRMS calcd for C_{26}H_{33}Cl_{2}N_{2}O_{4} [M + H]^+ 505.0832, found 505.0832.

3-((5-(5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(4-(tert-butyl)phenyl)benzamide 13e. Yellow solid, yield 65.1%, HPLC 96.69%, m.p. 113.04, 48.64; HRMS calcd for C_{26}H_{33}Cl_{2}N_{2}O_{4} [M + H]^+ 505.0832, found 505.0832.

3-((5-(5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(2-fluorophenyl)benzamide 13g. Yellow solid, yield 59.6%, HPLC 96.30%, m.p. 113.04, 48.64; HRMS calcd for C_{25}H_{16}Cl_{2}F_{2}N_{2}O_{4} [M + H]^+ 509.0578, found 509.0581.

3-((5-(5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(3-fluorophenyl)benzamide 13h. Yellow solid, yield 59.3%, HPLC 91.69%, m.p. 113.04, 48.64; HRMS calcd for C_{25}H_{16}Cl_{2}F_{2}N_{2}O_{4} [M + H]^+ 509.0578, found 509.0581.
Molecules 2022, 27, 3946

Yellow solid, yield 61.6%, HPLC 92.59%, m.p. 246–248 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 8.47 (s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 5.8 Hz, 1H), 7.88 (s, 1H), 7.77–7.68 (m, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.50 (s, 1H), 7.43–7.36 (m, 1H), 6.95 (t, J = 7.0 Hz, 1H), 6.20 (d, J = 7.5 Hz, 1H), 6.04 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 175.99, 175.96, 167.83, 165.29, 163.45, 161.53, 144.58, 143.58, 141.09 (d, J = 10.9 Hz), 136.84, 136.03, 135.01, 134.18, 131.30, 130.69 (d, J = 11.3 Hz), 130.09, 129.86, 126.76 (d, J = 7.1 Hz), 121.82, 116.61, 116.11, 113.04, 110.82 (d, J = 21.0 Hz), 107.64 (d, J = 26.0 Hz), 48.63; HRMS calcd for C25H16Cl2N3O3 [M + H]+ 509.0578, found 509.0583.

3-(5-(((5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-(4-fluorophenyl)benzamide 13k. Yellow solid, yield 63.8%, HPLC 91.72%, m.p. 263–264 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.57 (s, 1H), 8.47 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.87 (s, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.73–7.68 (m, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.49 (s, 1H), 6.20 (d, J = 7.8 Hz, 1H), 6.04 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 175.99, 175.95, 167.84, 165.14, 144.58, 143.59, 138.29, 136.84, 136.10, 135.00, 131.28, 130.57, 130.07, 128.99, 128.04, 127.86, 127.64, 126.31, 122, 121.82, 116.12, 113.04, 48.63; HRMS calcd for C25H16Cl2BrN3O3 [M + H]+ 525.0282, found 525.0283.

3-(5-(((5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-(4-iodophenyl)benzamide 13l. Yellow solid, yield 66.6%, HPLC 94.60%, m.p. 211–214 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.04 (s, 1H), 8.49 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 8.12–8.05 (m, 2H), 7.89 (s, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.50 (s, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.08 (s, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 6.03 (s, 2H), 2.28 (s, 3H), 2.18 (s, 3H); 13C-NMR (126 MHz, DMSO-d6) δ 175.97, 175.94, 167.90, 164.93, 144.58, 143.61, 136.83, 134.59, 131.90, 131.28, 130.57, 130.06, 129.87, 126.78, 126.74, 126.31, 122.87, 121.83, 116.12, 113.04, 48.63; HRMS calcd for C25H16Cl2I3N4O3 [M + H]+ 616.9639, found 616.9642.
found 519.0986.

3-(5-((5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(2,6-dimethylphenyl) benzamide 13n. Yellow solid, yield 63.5%, HPLC 95.45%, m.p. 227–228 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.51 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 8.09–8.06 (m, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.13 (s, 3H), 6.20 (d, J = 7.9 Hz, 1H), 6.04 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 175.95, 167.89, 164.65, 144.57, 143.59, 136.83, 136.00, 135.87, 135.46, 135.00, 130.98, 130.34, 130.13, 129.88, 128.21, 127.25, 126.76, 126.72, 126.38, 121.82, 116.14, 113.03, 48.63, 18.47; HRMS calcd for C27H21Cl2N4O3 [M + H]+ 519.0985, found 519.0983.

3-(5-((5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(3-chloro-2-methylphenyl)benzamide 13o. Yellow solid, yield 49.8%, HPLC 93.20%, m.p. 241–244 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 8.49 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 1.9 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 6.20 (d, J = 7.9 Hz, 1H), 6.03 (s, 3H), 2.23 (s, 3H); 13C-NMR (126 MHz, DMSO-d6) δ 176.04, 175.93, 167.84, 165.13, 144.60, 143.63, 138.26, 136.83, 135.62, 134.99, 134.28, 132.71, 131.27, 130.59, 130.16, 127.38, 126.86, 126.74, 126.38, 121.83, 116.17, 113.04, 99.99, 48.64, 15.77; HRMS calcd for C26H19Cl3N4O3 [M + H]+ 539.0439, found 539.0446.

3-(5-((5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(3,4-dichlorophenyl) benzamide 13p. Yellow solid, yield 51.4%, HPLC 94.83%, m.p. 265–269 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.47 (s, 1H), 8.17–8.10 (m, 3H), 8.08 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.77–7.69 (m, 2H), 7.62 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 6.04 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 176.02, 175.96, 167.79, 165.30, 144.59, 143.58, 139.46, 136.84, 135.72, 135.00, 131.34, 130.99, 130.79, 130.14, 126.77, 126.74, 126.36, 125.87, 122.09, 121.82, 120.85, 116.13, 113.04, 48.64; HRMS calcd for C25H15Cl2N4O3 [M + H]+ 558.9893, found 558.9899.

3-(5-((5,7-dichloroquinolin-4-yl)oxy)methyl)-1,2,4-oxadiazol-3-yl)-N-(2,4-difluorophenyl) benzamide 13q. Brown solid, yield 47.9%, HPLC 93.53%, m.p. 235–237 °C; 1H-NMR (500 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.50 (s, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.63–7.56 (m, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.40–7.33 (m, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.20 (d, J = 7.9 Hz, 1H), 6.03 (s, 2H); 13C-NMR (126 MHz, DMSO-d6) δ 176.00, 175.97, 167.82, 165.14, 159.30 (d, J = 11.5 Hz), 157.55 (d, J = 12.8 Hz), 155.56 (d, J = 12.7 Hz), 144.40, 143.58, 136.85, 135.17, 134.99, 131.33, 130.75, 130.17, 129.00 (d, J = 12.2 Hz), 126.84, 126.74, 126.35, 121.81, 116.12, 113.03, 111.70 (d, J = 18.6 Hz), 104.85, 48.65; HRMS calcd for C25H15Cl2F2N4O3 [M + H]+ 527.0484, found 527.0487.

3.3. Biological Activity and Toxicity Determination

The fungicidal activities were investigated in the National Pesticide Engineering Research Center, Nankai University, according to reference [25], and the results of the activity test are shown in Table 2. The toxicity was determined according to Ref. [26].

Through acute exposure, we assessed the toxicity of compound 13p on zebrafish embryo. According to the preliminary exposure experiments, a series of gradient concentrations of compound 13p was set on the basis of mortality rates in the range of 10–95%. LC50 values for zebrafish embryos exposed to compound 13p from 24 to 96 hpf: control (0 mg/L of 13p), 5, 10, 20 mg/L of 13p. The LC50 (median lethal concentration) values were computed by the Boltzmann equation [26,27]. The observational indexes included mortality rate and teratogenic effects.
4. Conclusions

In conclusion, a total of 17 novel benzamides containing quinoline-linked 1,2,4-oxadiazole moiety were designed using splicing principle of active substructures and synthesized via Williamson ether synthesis. The structures of target compounds were confirmed by $^1$H NMR, $^{13}$C NMR, and HRMS. The bioassay results showed that 13a–13q displayed certain inhibitory activity against 10 fungi tested, especially 13f and 13p. It is worth mentioning that the fungicidal activities of 13f and 13p to Sclerotinia sclerotiorum were better than quinoxyfen (14.19 mg/L) with EC$_{50}$ of 6.67 mg/L and 5.17 mg/L, and their inhibition rates were equal (77.8%) or higher (86.1%) than quinoxyfen (77.8%) at 50 mg/L. Moreover, the acute toxicity of 13p was 19.42 mg/L, which was classified as a low-toxic compound. Hence, these compounds could potentially be lead compounds for further study.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27123946/s1. Figures S1–S17: $^1$H-NMR spectra of 13a–q; Figures S18–S34: $^{13}$C-NMR spectra of 13a–q; Figures S35–S51: ESI-HRMS spectra of 13a–q.

Author Contributions: B.-L.S., Y.-Y.W., S.Y., M.-T.T., Y.-Y.S., Y.H., Y.Z. carried out experimental work, B.-L.S. prepared the manuscript, C.-X.T. designed the material and supervised the project. C.-X.T. revised the paper. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

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