

Communication

Microwave-Assisted Synthesis and Antifungal Activity of Some Novel Thioethers Containing 1,2,4-Triazole Moiety

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Abstract: A series of novel thioether derivatives containing 1,2,4-triazole moiety were designed and synthesized from 4-chlorophenol and ethyl 2-chloroacetate as starting materials by multi-step reactions under microwave irradiation, and their structures were characterized by ¹H-NMR, MS and elemental analysis. The antifungal activity of title compounds was determined. The results indicated that some of title compounds exhibited moderate antifungal activity.

Keywords: thioether; 1,2,4-triazole; microwave assistant synthesis; antifungal activity

1. Introduction

In recent years, heterocycles had been attracted in medicinal or pesticidal importance due to its wide and spectrum activity [1–6]. The 1,2,4-triazole compounds represent an important nitro-containing heterocycles with extensively bioactivities [7–10], such as anti-inflammatory activity [11], anticancer

activity [12], anti-oxidation activity [13,14], herbicidal activity [15], antifungal activity [16,17], antiurease activity [18], antidepressant activity [19] and so on. Moreover, 1,2,4-triazole substructure was found in many commercial pesticide or drugs, especially in antifungal medicines (Figure 1). It is an important research field for developing novel 1,2,4-triazole derivatives. Meanwhile, the phenoxy nucleus is key fragment in many herbicides [20]. For example, it is reported that 2,4-dichlorophenoxyacetylhydrazines exhibited excellent antifungal or herbicidal activity.

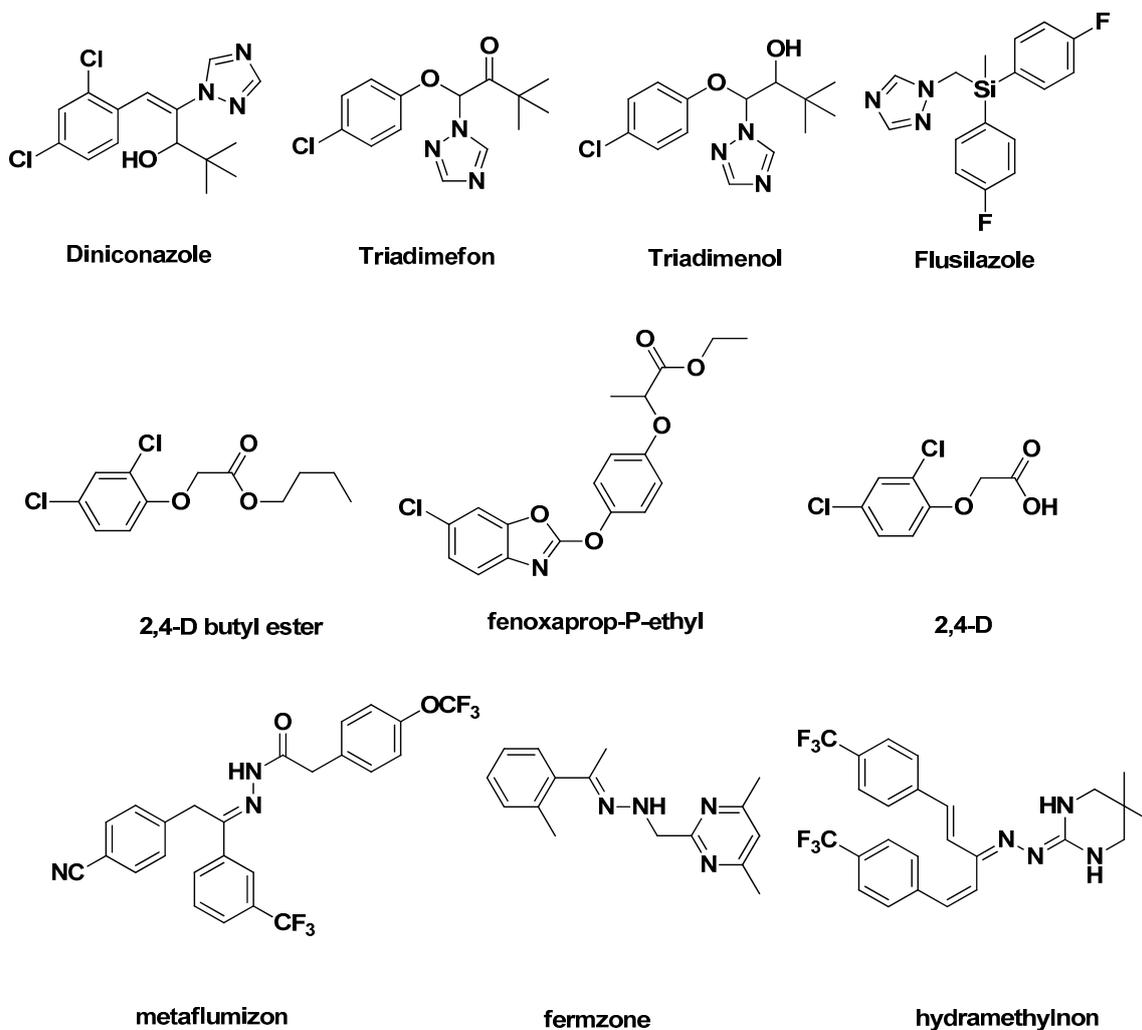


Figure 1. Some representative commercial drugs or pesticides.

On the other hand, 1,2,4-triazole-thiones are useful intermediates in the field of drug design and discovery. According to the rule of bioisostere, when the oxygen atom was replaced by sulfur atom, the biological activity will be improved. So far, many bioactive 1,2,4-triazole-thioether or 1,2,4-triazole-thione derivatives have been reported. For example, Polucci and co-authors synthesized a series of alkylsulfanyl-1,2,4-triazoles, which exhibited excellent anticancer activity [21]. Another interesting reference reported that a series of 1,2,4-triazole-thioether derivatives containing benzothiazinone and benzoxazinone moiety displayed excellent activity as non-glucoside SGLT2 inhibitors [22]. Also, we had synthesized some interesting 1,2,4-triazole-thioether derivatives containing 1,2,3-thiadiazole [23] or pyridine [24] moiety, and these compounds possessed good antifungal activity.

Kochikyan and co-workers [25] reported the synthesis method about 1,2,4-triazole-3-thiols and their *S*-substituted derivatives.

Microwave-assisted technique is a green method in current organic synthesis [26–28]. It is attractive offering reduced pollution, low cost and high yields. The method can often shorten the reaction time. In recent years, many references had been reported this method. For example, MW-assisted synthesis heterocycles have been conducted successfully earlier [29,30].

In view of all these facts and as continuation of our research on bioactive compounds [31–33], herein a series of novel thioether derivatives containing 1,2,4-triazole moiety were synthesized under microwave irradiation. The antifungal activity of title compounds was tested.

2. Results and Discussion

2.1. Synthesis

The ethyl 2-(4-chlorophenoxy)acetate was obtained from 4-chlorophenol and ethyl 2-chloroacetate catalyzed by KI at reflux condition. The KI was used as catalyst in order to increase the yield of ethyl 2-(4-chlorophenoxy)acetate. The ethyl 2-(4-chlorophenoxy)acetate reacted with 85% hydrazine hydrate to give 2-(4-chlorophenoxy)acetohydrazide at refluxing condition. Then the 2-(4-chlorophenoxy)acetohydrazide reacted with isothiocyanatobenzene. Then 2-(2-(4-chlorophenoxy)acetyl)-*N*-phenylhydrazinecarbothioamide was collected easily by filtered. The key intermediate 5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol was cyclized under alkaline condition, such as NaOH, then the concentrate HCl was added to this solution. The key intermediatethiol is reacted with substituted benzyl chloride or alkylchloride to afford title compounds. The microwave-assisted synthesis and conventional method was also employed in this experiment. NaOH/DMF/H₂O system was applied under microwave irradiation. The best reaction condition is at 90 °C for 15 min under microwave irradiation synthesis. Taking the compound **5b** as example, we can see that the yield is higher than that of conventional method, also the reaction time is shorter from Table 1.

Table 1. Comparison of yields of **5b** through methods with or without microwave irradiation.

No.	Method	Time	Temperature/°C	Yield/%
5b	No-MW	24 h	r.t.	78
5b	No-MW	10 min	90	42
5b	MW	10 min	90	79
5b	MW	15 min	90	81
5b	MW	20 min	90	81

2.2. Antifungal Activities

The *in vivo* fungicidal results of title compounds against *Pythium ultimum* Trow, *Phytophthora infestans* (Mont.) de Bary, *Corynespora cassiicola*, *Botrytis cinerea* and *Rhizoctonia solani* were listed in Table 2, Zhongshengmycin, Dimethomorph, Procymidone, Chlorothalonil and Validamycin were used as controls. As shown in Table 2, some of the title compoundsshowed good control efficacy against *Pythium ultimum* Trow at a concentration of 100 µg/mL, such as compound **5a** (66.7%), **5b** (55.6%), **5h** (55.6%) and **5i** (55.6%), which is better than that of control. While some of them exhibited low activity

against *Pythium ultimum* Trow. For example, compound **5c** (−88.9%), **5d** (−111.1%), **5e** (−55.6%), **5j** (−33.3%), **5k** (−122.2%) held no inhibitory against *Pythium ultimum* Trow. On the opposite, these compounds can increase the fungal growth. For this fungal *Pythium ultimum* Trow, the control Zhongshengmycin also cannot inhibit it. For the fungal *Corynespora cassiicola*, the compound **5c** (46.2%), **5d** (46.2%), **5e** (61.3%) and **5f** (50.9%) displayed excellent inhibition respectively. They exhibited the same inhibitory as that of the control chlorothalonil (45.9%). All the title compounds exhibited no inhibition effect against *Rhizoctonia solani* and *Phytophthora infestans* (Mont.) de Bary. Only compound **5a** (3.9%), **5c** (6.7%) and **5k** (10.6%) displayed weak inhibitory against *Rhizoctonia solani*. The control procymidone also exhibited no activity against *Rhizoctonia solani*. Surprisingly, most of these compounds showed stimulate growth activity against *Botrytis cinerea*, except compound **5c** (23.8%), **5d** (19.9%) and **5e** (19.9%).

Table 2. The antifungal activity of title compounds *in vivo* at 100 ppm (%).

No.	<i>Pythium ultimum</i>	<i>Phytophthora infestans</i>	<i>Corynespora cassiicola</i>	<i>Botrytis cinerea</i>	<i>Rhizoctonia solani</i>
5a	66.7 ± 2.15	−0.8 ± 0.08	4.1 ± 1.02	−25.4 ± 1.32	3.9 ± 0.05
5b	55.6 ± 1.65	−0.8 ± 0.02	−0.9 ± 0.06	−11.9 ± 0.98	0.0 ± 0.00
5c	−88.9 ± 2.03	−0.8 ± 0.09	46.2 ± 2.05	23.8 ± 1.05	6.7 ± 0.07
5d	−111.1 ± 2.78	−0.8 ± 0.01	46.2 ± 2.12	19.9 ± 0.96	0.0 ± 0.00
5e	−55.6 ± 0.89	−0.8 ± 0.04	61.3 ± 1.89	19.9 ± 1.01	0.0 ± 0.00
5f	11.1 ± 0.78	−0.8 ± 0.03	50.9 ± 1.66	−16.7 ± 0.88	0.0 ± 0.00
5g	0.0 ± 0.00	−0.8 ± 0.04	41.4 ± 1.15	−16.7 ± 0.79	0.0 ± 0.00
5h	55.6 ± 1.35	−0.5 ± 0.04	37.8 ± 1.25	−56.3 ± 1.22	0.0 ± 0.00
5i	55.6 ± 1.62	−0.8 ± 0.02	24.9 ± 2.16	−15.8 ± 1.14	0.0 ± 0.00
5j	−33.3 ± 1.01	0.3 ± 0.04	42.2 ± 1.14	−46.6 ± 0.38	0.0 ± 0.00
5k	−122.2 ± 3.05	3.3 ± 0.05	16.2 ± 1.18	1.6 ± 0.06	10.6 ± 0.52
Zhongshengmycin	0.0 ± 0.00	-	-	-	-
Dimethomorph	-	97.8 ± 2.07	-	-	-
Chlorothalonil	-	-	45.9 ± 1.77	-	-
Procymidone	-	-	-	−7.6 ± 0.68	-
Validamycin	-	-	-	-	62.5 ± 2.13

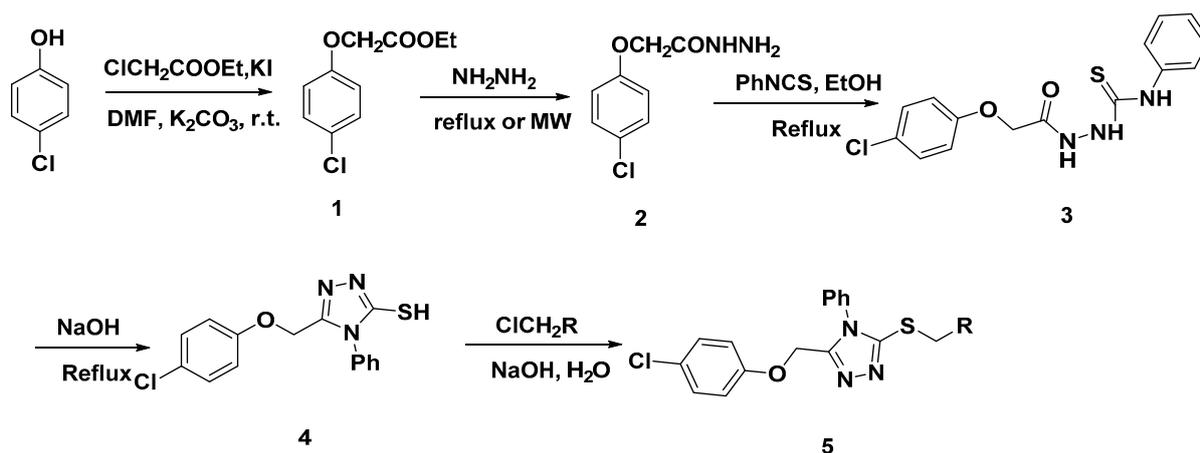
3. Experimental Section

3.1. Instruments

Melting points were recorded using an X-4 apparatus and uncorrected (Beijing Tech Instrument Co., Beijing, China). ¹H-NMR spectra were performed on a Bruker AV-400 instrument (Bruker, Fallanden, Switzerland) using TMS as an internal standard and CDCl₃ as the solvent. Elemental analyses were determined on a Vario EL elemental analyzer (Elementar, Hanau, Germany). All the reagents are of analytical grade or freshly prepared before use.

3.2. Synthesis

The synthetic procedure for title compound is shown in Scheme 1.



Scheme 1. The synthetic route of title compounds.

3.2.1. Synthesis of Ethyl 2-(4-chlorophenoxy)acetate (**1**)

4-Chlorophenol (0.1 mol), acetone (40 mL), ethyl 2-chloroacetate (0.12 mol), K_2CO_3 (16.56 g, 0.12 mol) and catalytic amount of KI were added to a 100 mL three-necked flask, then the mixture was stirred at reflux. The reaction was monitored by GC until the start material 1a disappeared completely. The mixture was poured into ice water and extracted with ethyl acetate (3×50 mL) and then dried by anhydrous Na_2SO_4 and evaporated to dryness to get crude solid **1**.

3.2.2. Synthesis of 2-(4-Chlorophenoxy)acetohydrazide (**2**)

A mixture of ethyl 2-(4-chlorophenoxy)acetate (1.44 g, 10 mmol) and 85% hydrazine hydrate (2 mL, 35 mmol) was heated under reflux for 6 h. The mixture was cooled to room temperature, filtered, washed with cool ethyl acetate, then dried to give white solid 2-(4-chlorophenoxy)acetohydrazide **2**, yield 83%.

3.2.3. Synthesis of 2-(2-(4-Chlorophenoxy)acetyl)-*N*-phenylhydrazinecarbothioamide (**3**)

A mixture of 2-(4-chlorophenoxy)acetohydrazide (10 mmol) with isothiocyanatobenzene (10 mmol) was refluxed for 5 h in ethanol. After cooling down to room temperature, the products were obtained and recrystallized from methanol to give **3**, yield 95%.

3.2.4. Synthesis of 5-((4-Chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**4**)

A mixture of compound (**3**) (10 mmol) in aqueous NaOH solution (5 mL, 2 N) was refluxed for 4 h. After cooling down to room temperature, HCl aqueous solution (4 N) was added to afford a large amount of precipitate. The solid was filtered, dried and recrystallized from methanol to give intermediate **4**, yield 88%.

3.2.5. General Procedure for Thioether (**5**)

A CEM designed 10 mL pressure-rated vial was charged with DMF (5 mL), **4** (1 mmol), RCH_2Cl (1.1 mmol) and NaOH (1.2 mmol). The mixture was irradiated in a CEM Discover Focused Synthesizer (150 W, 90 °C, 200 psi, 15 min). The mixture was cooled to room temperature by passing compressed

air through the microwave cavity for 2 min. It was poured into cold ice (40 mL) and the formed precipitate was filtered. The crude solid was recrystallized from EtOH to give the title compounds **5a**. All the other compounds are synthesized according to the procedure (Scheme 1).

3-(butylthio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5a** yield 87%, m.p. 140–141 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 0.85 (t, 3H, CH₃), 1.34 (q, 2H, CH₂), 1.62 (m, 2H, CH₂), 3.12 (m, 2H, CH₂), 3.12 (t, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.90 (d, *J* = 8.2 Hz, 2H, Ph), 7.27 (d, *J* = 8.2 Hz, 2H, Ph), 7.45–7.55 (m, 5H, Ar-H). ESI-MS: 375 [M + H]⁺; Elemental analysis for C₁₉H₂₀ClN₃OS: found C 60.98, H 5.56, N 11.43; calcd. C, 61.03; H, 5.39; N, 11.24.

3-(benzylthio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5b** yield 81%, m.p. 104–105 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.38 (s, 2H, SCH₂), 5.08 (s, 2H, OCH₂), 6.87 (d, *J* = 8.0 Hz, 2H, Ph), 7.27–7.20 (m, 8H, Ph), 7.51 (m, 4H, Ph). ESI-MS: 409 [M + H]⁺; Elemental analysis for C₂₂H₁₈ClN₃OS: found C 64.44, H 4.53, N 10.98; calcd. C, 64.78; H, 4.45; N, 10.30.

3-((4-chlorobenzyl)thio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5c** yield 77%, m.p. 108–109 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.38 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88 (d, *J* = 8.2 Hz, 2H, Ph), 7.05–7.19 (m, 2H, Ph), 7.27–7.37 (m, 6H, Ph), 7.50–7.52 (m, 3H, Ph). ESI-MS: 443 [M + H]⁺; Elemental analysis for C₂₂H₁₇Cl₂N₃OS: found C 59.83, H 3.97, N 9.45; calcd. C, 59.73; H, 3.87; N, 9.50.

3-((4-bromobenzyl)thio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5d** yield 68%, m.p. 99–100 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.35 (s, 2H, SCH₂), 5.08 (s, 2H, OCH₂), 6.88 (d, *J* = 8.2 Hz, 2H, Ph), 7.27–7.33 (m, 6H, Ph), 7.45–7.52 (m, 6H, Ph). ESI-MS: 488 [M + H]⁺; Elemental analysis for C₂₂H₁₇BrClN₃OS: found C 53.97, H 3.31, N 8.99; calcd. C, 54.28; H, 3.52; N, 8.63.

3-((2-chlorobenzyl)thio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5e** yield 77%, m.p. 108–109 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.44 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88 (d, *J* = 8.2 Hz, 2H, Ph), 7.08–7.19 (m, 2H, Ph), 7.27–7.39 (m, 6H, Ph), 7.50–7.52 (m, 3H, Ph). ESI-MS: 443 [M + H]⁺; Elemental analysis for C₂₂H₁₇Cl₂N₃OS: found C 59.63, H 3.97, N 9.45; calcd. C, 59.73; H, 3.87; N, 9.50.

3-((4-chlorophenoxy)methyl)-5-((4-methoxybenzyl)thio)-4-phenyl-4*H*-1,2,4-triazole **5f** yield 82%, m.p. 122–123 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 3.72 (s, 3H, OCH₃), 4.33 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.82 (d, *J* = 6.8 Hz, 2H, Ph), 6.88 (d, *J* = 6.8 Hz, 2H, Ph), 7.21–7.33 (m, 6H, Ph), 7.50–7.52 (m, 3H, Ph). ESI-MS: 439 [M + H]⁺; Elemental analysis for C₂₃H₂₀ClN₃O₂S: found C 63.12, H 4.75, N 9.86; calcd. C, 63.08; H, 4.60; N, 9.59.

3-((4-chlorophenoxy)methyl)-5-((2,4-dichlorobenzyl)thio)-4-phenyl-4*H*-1,2,4-triazole **5g** yield 81%, m.p. 120–121 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.41 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88 (d, *J* = 8.0 Hz, 2H, Ph), 7.27 (d, *J* = 8.0 Hz, 2H, Ph), 7.28–7.33 (m, 3H, Ph), 7.46–7.58 (m, 5H, Ph). ESI-MS: 478 [M + H]⁺; Elemental analysis for C₂₂H₁₆Cl₃N₃OS: found C 55.22, H 3.07, N 8.51; calcd. C, 55.42; H, 3.38; N, 8.81.

4-(((5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)benzotrile **5h** yield 79%, m.p. 123–124 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.46 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88 (d, *J* = 6.8 Hz, 2H, Ph), 7.27 (d, *J* = 6.8 Hz, 2H, Ph), 7.34–7.74 (m, 9H, Ph). ESI-MS: 434 [M + H]⁺; Elemental analysis for C₂₃H₁₇ClN₄OS: found C 63.88, H 3.90, N 13.04; calcd. C, 63.81; H, 3.96; N, 12.94.

3-((3-chlorobenzyl)thio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5i** yield 77%, m.p. 108–109 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.37 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88 (d, *J* = 8.7 Hz, 2H, Ph), 7.27 (d, *J* = 8.7 Hz, 2H, Ph), 7.33–7.35 (m, 3H, Ph), 7.51–7.62 (m, 5H, Ph). ESI-MS: 443 [M + H]⁺; Elemental analysis for C₂₂H₁₇Cl₂N₃OS: found C 59.54, H 3.97, N 9.45; calcd. C, 59.73; H, 3.87; N, 9.50.

3-((4-chlorophenoxy)methyl)-5-((2-fluorobenzyl)thio)-4-phenyl-4*H*-1,2,4-triazole **5j** yield 83%, m.p. 110–111 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 4.37 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88 (d, *J* = 7.8 Hz, 2H, Ph), 7.10–7.52 (m, 11H, Ph). ESI-MS: 427 [M + H]⁺; Elemental analysis for C₂₂H₁₇ClFN₃OS: found C 62.89, H 3.88, N 9.86; calcd. C, 62.04; H, 4.02; N, 9.87.

3-((4-(tert-butyl)benzyl)thio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **5k** yield 81%, m.p. 62–63 °C; ¹H-NMR (DMSO-*d*₆, 400 MHz), δ: 1.25(s, 9H, Bu), 4.33 (s, 2H, SCH₂), 5.09 (s, 2H, OCH₂), 6.88(d, *J* = 8.6 Hz, 2H, Ph), 7.17(d, *J* = 8.0 Hz, 2H, Ph), 7.24–7.29 (m, 5H, Ph), 7.48–7.52 (m, 4H, Ph). ESI-MS: 465 [M + H]⁺; Elemental analysis for C₂₆H₂₆ClN₃OS: found C 67.13, H 5.75, N 9.23; calcd. C, 67.30; H, 5.65; N, 9.06.

3.3. Antifungal Activity

Antifungal activity of compounds **5a–5k** against *Pythium ultimum* Trow, *Phytophthora infestans* (Mont.) de Bary, *Corynespora cassiicola*, *Botrytis cinerea* and *Rhizoctonia solani* were evaluated according to reference [3]. 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 cotyledons, and tomato plants were five euphyllas. Tested compounds and commercial fungicides were sprayed with a hand sprayer on the surface of the leaves and on a fine morning, at the standard concentration of 100 µg/mL, and each plant was sprayed compounds and commercial fungicides 200 µL. Dimethomorph, Fludioxonil, Chlorothalonil, Validamycin, Zhongshengmycin were used as a control. After 2 h, inoculations of *Phytophthora infestans*, *Corynespora cassiicola* and *Botrytis cinerea* were carried out by spraying fungal spore suspension with 1 × 10⁴ spore/mL, inoculation of *Rhizoctonia solani* and *Pythium ultimum* were carried out by spraying mycelial suspension of 2 × 10⁴ CFU/mL, which was smashed with IKA T10 basic ULTRA-TURRAX[®] (Guangzhou, China). Each kind of inoculum was sprayed 300 µL/plant. Each treatment was replicated 4 times. After inoculation, the plants were maintained at 18–30 °C (mean temperature of 24 °C and above 80% relative humidity (RH)). The antifungal activity were evaluated when the nontreated 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:

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

where *CK* is the average disease index during the blank assay and *PT* is the average disease index after treatment during testing. All experiments were replicated three times.

4. Conclusions

Some interesting thioether derivatives containing 1,2,4-triazole moiety were designed and synthesized. Their structures were confirmed by NMR, MS and elemental analysis. The primarily antifungal activities showed that some of them exhibited excellent antifungal activities.

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Author Contributions

Li-Jing Min, Yan-Xia Shi, Hong-Ke Wu and Zhao-Hui Sun carried out experimental work, Li-Jing Min prepared the manuscript, Xing-Hai Liu, Bao-Ju Li and Yong-Gang Zhang designed the material and supervised the project.

Conflicts of Interest

The authors declare no conflict of interest.

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