Synthesis and Antimicrobial Activity of Novel 2-Substituted Phenoxy-*N*-(4-substituted Phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl) acetamide Derivatives

Guo-Ping Liao, Xia Zhou,* Wei Xiao, Yan Xie, and Lin-Hong Jin*

State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025 People's Republic of China

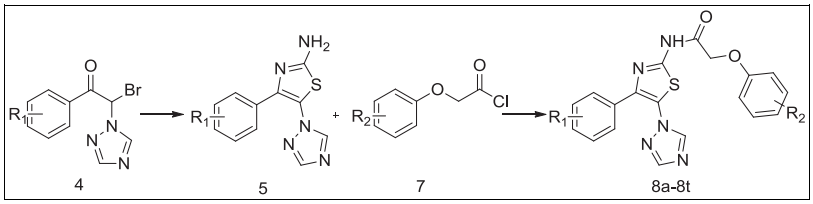
*E-mail: zhouxia_j@126.com; linhong_j@126.com

Additional Supporting Information may be found in the online version of this article.

Received April 13, 2016

DOI 10.1002/jhet.2737

Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



A series of 2-substituted phenoxy-*N*-(4-substituted phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazole-2-yl)acetamide derivatives **8a–8t** was synthesized by the reaction of phenoxyacetyl chloride **7** with intermediate 4-substituted phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine **5**. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR, MS, IR, and elemental analyses. The synthesized compounds were also screened for their antimicrobial activity against three types of plant fungi (*Gibberella zeae*, *Phytophthora infestans*, and *Paralepetopsis sasakii*) and two kinds of bacteria [*Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas axonopodis* pv. *citri* (*Xac*)] showing promising results. In particular, **8b**, **8f**, **8g**, and **8h** exhibited excellent antibacterial activity against *Xoo*, with 50% effective concentration (EC_{50}) values of 35.2, 80.1, 62.5, and 82.1 μg/mL, respectively, which are superior to the commercial antibacterial agent bismerthiazol (89.9 μg/mL). The preliminary structure–activity relationship studies of these compounds are also briefly described.

INTRODUCTION

Thiazole moiety serves as an active core for various bioactive molecules. Its derivatives have widespread application as useful biological agents, such as insecticidal [1], antibacterial [2–4], antifungal [5,6], herbicidal [7,8], anticancer [9,10], antioxidant [11,12], and anti-inflammatory [13]. Specifically, a large number of thiazole derivatives, for example, thiabendazole, ethaboxam, thifluzamide, and metsulfovax, have already been commercialized as potent fungicides [14–16]. Therefore, the synthesis of novel thiazole-incorporated heterocyclic compounds continues to draw significant interest in scientific community.

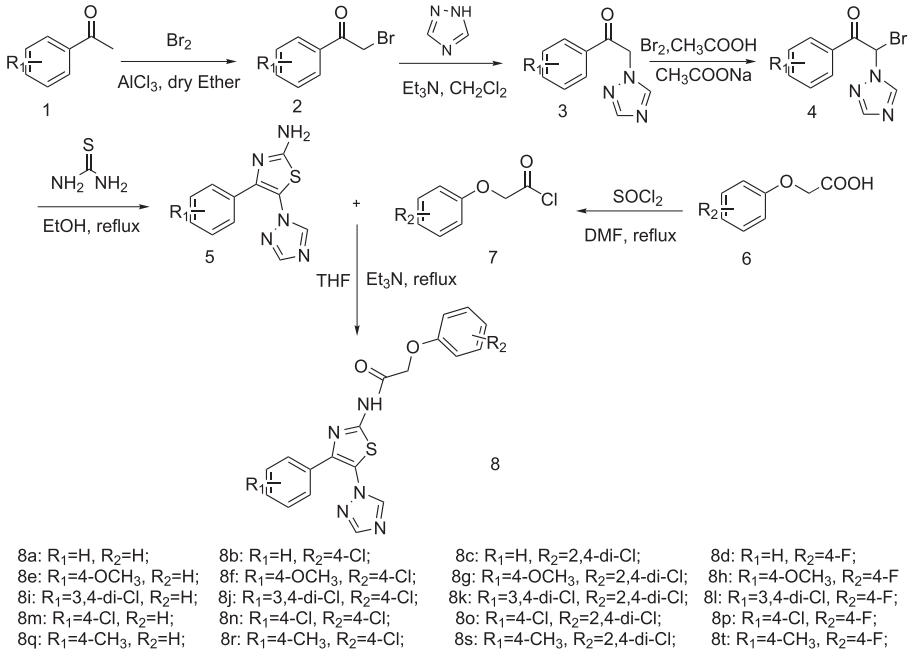
On the other hand, 1,2,4-triazole derivatives exhibit broad-spectrum bioactivity and are widely used in agrochemicals [17–25] and pharmaceuticals [26–28]. Fungicides containing triazoles, for example, flusilazole, triadimenol, and propiconazole, are the most effective plant protection agents against plant pathogens such as *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) or *Gibberella zeae* at present [29].

Plant fungi (*G. zeae*, *Phytophthora infestans*, and *Paralepetopsis sasakii*) and plant bacteria [*Xoo* and *Xanthomonas axonopodis* pv. *citri* (*Xac*)] colonize various crops that are essential for human nutrition such as wheat, rice, potato, and citrus. Infected plants are accompanied with yield losses and adverse effects on crop quality. Derivatives containing thiazole or triazole units can exhibit a good inhibition for those plant diseases [6,29]. In addition, incorporation of phenoxyacetamide moiety can also serve as an effective approach for enhancing antifungal activity [30]. Fascinated by these investigations, we explored to develop a practical synthetic route to phenoxyacetamides bearing both a triazole and a thiazole heterocyclic unit. Herein, we report the preparation of a series of novel 2-substituted phenoxy-*N*-(4-substituted-phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide derivatives and the subsequent evaluation of their biological activity against plant pathogenic fungi and bacteria.

RESULTS AND DISCUSSION

Synthesis. The synthetic procedure adopted to obtain the target compounds **8a–8t** is shown in Scheme 1. The intermediate 2-bromo-1-phenylenthanone (**2**) was synthesized from acetophenone (**1**) by reacting with bromine in liquid phase using aluminum chloride as catalyst in ice bath [31]. Then, (**2**) was submitted to 1,2,4-triazole and trimethylamine to obtain the 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (**3**) [32]. The 2-bromo-1-phenyl-2-bromo-(1*H*-1,2,4-triazol-1-yl)ethanone (**4**) can

Scheme 1. Synthetic route to compounds **8a–8t**.



8a: R_1=H, R_2=H; 8b: R_1=H, R_2=4-Cl; 8c: R_1=H, R_2=2,4-di-Cl; 8d: R_1=H, R_2=4-F;
8e: R_1=4-OCH_3, R_2=H; 8f: R_1=4-OCH_3, R_2=4-Cl; 8g: R_1=4-OCH_3, R_2=2,4-di-Cl; 8h: R_1=4-OCH_3, R_2=4-F
8i: R_1=3,4-di-Cl, R_2=H; 8j: R_1=3,4-di-Cl, R_2=4-Cl; 8k: R_1=3,4-di-Cl, R_2=2,4-di-Cl; 8l: R_1=3,4-di-Cl, R_2=4-F;
8m: R_1=4-Cl, R_2=H; 8n: R_1=4-Cl, R_2=4-Cl; 8o: R_1=4-Cl, R_2=2,4-di-Cl; 8p: R_1=4-Cl, R_2=4-F;
8q: R_1=4-CH_3, R_2=H; 8r: R_1=4-CH_3, R_2=4-Cl; 8s: R_1=4-CH_3, R_2=2,4-di-Cl; 8t: R_1=4-CH_3, R_2=4-F;

be obtained by bromination of 1-phenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**3**) reacting with liquid bromine with anhydrous sodium acetate and glacial acetic acid [33]. The key intermediate 4-phenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-amine (**5**) was synthesized by 1-phenyl-2-bromo-(1H-1,2,4-triazol-1-yl)ethanone cyclizing with thiourea and absolute ethyl alcohol under reflux condition. The 2-phenoxyacetyl chloride (**7**) can be acquired easily from 2-phenoxyacetic acid. The target compound 2-phenoxyl-*N*-(4-phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (**8**) was synthesized by reaction between 2-phenoxyacetyl chloride (**7**) dissolved in anhydrous THF and 4-phenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-amine (**5**) in the presence of catalyst trimethylamine.

The structure of the title compounds **8a–8t** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The IR spectrum of **8a–8t** displayed the absorption bands between 3474.2 and 3050.5 cm^{-1} corresponding to N-H and Ph-H, as well as 1685.4–1650.6 cm^{-1} corresponding to C=O function. The ^{1}H NMR spectrum of **8a** in DMSO-d_6 displayed a singlet at δ 12.92 ppm that corresponds to H–N–C=O functionality, a singlet at δ 8.80 and 8.32 ppm belonged to thiazole ring-CH=N proton, and the multiplet at δ 7.36–7.31, 7.30–7.27, and 7.01–6.93 ppm that corresponds to phenyl-H functionality. A singlet that appeared at δ 4.91 ppm was observed because of the protons of CH_2 group. The chemical shifts at 168.52 and 66.42 ppm in ^{13}C NMR confirmed the existence of C=O and CH_2 groups, respectively. Final confirmation was obtained from electrospray ionization (ESI) mass spectra, which exhibited molecular ion peak of compounds **8a–8t** that corresponded well with their respective molecular formulae.

Antifungal bioactivity. The antifungal activity of all synthesized compounds was tested against three pathogenic fungi, *G. zeae*, *P. infestans*, and *P. sasakii* by the poison plate technique [34]. All target compounds were dissolved in DMSO (1 mL) and diluted with sterile distilled water containing 0.1% Tween-20 (9 mL) to prepare the 500 μg/mL stock solution before mixing with molten potato dextrose agar (PDA; 90 mL) below 60°C. The compounds were tested at a concentration of 50 μg/mL for the initial screening. All fungi were poured into sterilized Petri dishes in PDA at 26.5 ± 0.5°C for 4 days to make new mycelium for antifungal activity test. Then, mycelia dishes of approximately 4 mm in diameter were cut from the culture medium. A mycelium was obtained using a germ-free inoculated plate incubated at 26.5 ± 0.5°C for 4–5 days. DMSO in sterile distilled water containing 0.1% tween served as a negative control, whereas hymexazol served as a positive control. Each treatment condition consisted of three replicates. Radial growth diameter of the fungal colonies was measured twice by cross-bracketing method; then, the data were statistically analyzed. Inhibitory effects of the test compounds *in vitro* on these fungi were calculated by the formula:

$$\text{Inhibition rate}\ (\%) = [(CK - T)/(CK - 4\ \text{mm})] \times 100$$

where *CK* means the average diameter of fungal growth in the negative control and *T* means the average diameter of fungi on treated PDA.

The inhibitory effects of the synthesized compounds on the three phytopathogenic fungi were illustrated in Table 1. The inhibition rates of target compounds **8a–8t** against *G. zeae*, *P. infestans*, and *P. sasakii* displayed the inhibition rates ranged 12.40–50.53%, 9.11–44.23%, and 0.95–36.28% at 50 μg/mL, respectively. The inhibition rates of 50 μg/mL of hymexazol on the corresponding fungi were 52.23%, 63.54%, and 52.61%, respectively. The target products have weak to moderate antifungal activity against *G. zeae*. In particular, **8p** showed potent antifungal activity with inhibition rate (50.53%) against *G. zeae* compared with hymexazol (52.23%) at 50 μg/mL.

Antibacterial bioactivity. All of the target compounds were tested for *in vitro* antibacterial activity against *Xoo* and *Xac* by turbidimeter test [35]. The target compounds were dissolved in 150 μL of DMSO and diluted with sterile distilled water containing 0.1% Tween-20 (4 mL) to prepare 1000 and 500 μg/mL of stock solution. DMSO in sterile distilled water containing 0.1% Tween-20 served as the negative control. Commercial agricultural antibacterial bismerthiazol served as a positive control. Approximately 1 mL of stock solution was added to 4 mL of nontoxic liquid medium (nutrient broth (NB), 3 g of beef extract, 5 g of peptone, 1 g of yeast powder, 10 g of glucose, and 1000 mL of distilled water, pH 7.0 to 7.2) in tubes. Then, approximately 40 μL of NB containing *Xoo* or *Xac* was added to 5 mL of solvent NB containing compounds, DMSO, or bismerthiazol. Then, the inoculated test tubes were incubated at 30 ± 1°C with continuous shaking at 180 rpm for 24 h. The growth of bacterial culture was monitored with a spectrophotometer by measuring the optical density at 600 nm (OD_{600}). The inhibitory rate of bacterial culture growth was calculated using the following equation:

$$I\ (\%) = (CK - T)/CK \times 100$$

where "*CK*" implies the value of the corrected optical density of bacterial growth on untreated NB (negative control) and "*T*" means the value of corrected optical density of bacterial growth on treated NB; "*I*" denotes the inhibition rate.

Antibacterial bioassay results indicated that, in general, most compounds under investigation were associated with excellent inhibitory effect antibacterial bioactivities against *Xoo* and *Xac*. As shown in Table 2, almost all of them exhibited excellent antibacterial activity against *Xoo* and *Xac* at 200 or 100 μg/mL. In particular, compounds **8b**, **8f**, **8g**, **8h**, **8p**, and **8q** showed high antibacterial activity against *Xoo* or *Xac* at 200 and 100 μg/mL. Among them, **8b**, **8f**, **8g**, and **8h** were highlighted for their significant inhibition effects with inhibition rates of 90.3–100% at 200 μg/mL and 77.6–98.2% at 100 μg/mL against *Xoo*, which were much higher than that of commercial bactericide bismerthiazol exhibiting the rates of 72.4% and 54.2%, respectively.

Table 1
Antifungal activities of the title compounds **8a–8t** at a concentration of 50 μg/mL.

Compound	R_1	R_2	Average values of inhibition rate (%)[a] *G. zeae*	*P. infestans*	*P. sasakii*
8a	H	H	30.22 ± 0.85	15.94 ± 0.85	0.95 ± 1.23
8b	H	4-Cl	45.23 ± 0.90	38.28 ± 1.42	30.12 ± 0.59
8c	H	2,4-di-Cl	21.19 ± 0.76	36.57 ± 1.68	25.48 ± 2.62
8d	H	4-F	35.40 ± 1.11	23.59 ± 0.91	9.58 ± 0.69
8e	4-OCH3	H	40.63 ± 1.26	35.42 ± 1.28	29.45 ± 2.78
8f	4-OCH3	4-Cl	42.65 ± 1.06	44.23 ± 1.28	35.69 ± 2.08
8g	4-OCH3	2,4-di-Cl	42.32 ± 1.17	40.62 ± 2.54	20.50 ± 0.66
8h	4-OCH3	4-F	44.62 ± 0.84	32.41 ± 0.77	36.28 ± 0.98
8i	3,4-di-Cl	H	30.66 ± 2.45	36.45 ± 1.00	19.60 ± 0.73
8j	3,4-di-Cl	4-Cl	40.63 ± 1.39	33.45 ± 2.08	20.06 ± 0.71
8k	3,4-di-Cl	2,4-di-Cl	45.00 ± 1.52	42.18 ± 0.63	20.93 ± 1.32
8l	3,4-di-Cl	4-F	22.52 ± 0.84	16.46 ± 0.72	13.35 ± 1.60
8m	4-Cl	H	12.40 ± 1.84	21.41 ± 0.54	19.63 ± 0.72
8n	4-Cl	4-Cl	41.36 ± 0.93	21.27 ± 1.99	16.56 ± 0.90
8o	4-Cl	2,4-di-Cl	31.09 ± 1.56	17.50 ± 0.96	16.61 ± 0.92
8p	4-Cl	4-F	50.53 ± 1.72	36.85 ± 0.60	8.53 ± 0.81
8q	4-CH3	H	35.00 ± 1.62	28.01 ± 0.1	31.14 ± 0.92
8r	4-CH3	4-Cl	25.63 ± 0.92	15.82 ± 0.62	12.14 ± 0.70
8s	4-CH3	2,4-di-Cl	40.94 ± 1.89	34.82 ± 0.98	35.89 ± 1.42
8t	4-CH3	4-F	29.42 ± 0.93	9.11 ± 0.98	7.77 ± 0.95
Hymexazol[b]			52.23 ± 2.86	63.54 ± 2.41	52.61 ± 4.10

[a]Average of three replicates.
[b]The commercial agricultural fungicide hymexazol was used for comparison of antifungal activity.

Table 2

Antibacterial activities of compounds **8a–8t** against *Xanthomonas oryzae* pv. *oryzae* and *Xanthomonas axonopodis* pv. *citri*.

	Average values of inhibition rate (%)[a]			
	Xanthomonas oryzae pv. *oryzae*		*Xanthomonas axonopodis* pv. *citri*	
Compound	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL
8a	67.8 ± 1.0	60.2 ± 1.3	67.8 ± 2.1	48.2 ± 1.5
8b	100.0 ± 1.8	98.2 ± 2.2	80.2 ± 1.2	64.1 ± 1.8
8c	23.8 ± 1.2	11.7 ± 0.8	42.2 ± 1.7	20.3 ± 1.1
8d	42.2 ± 0.9	26.0 ± 0.8	60.2 ± 1.2	44.8 ± 1.3
8e	47.3 ± 3.6	39.2 ± 4.0	30.4 ± 1.4	15.1 ± 2.3
8f	95.2 ± 1.5	78.1 ± 2.1	80.2 ± 2.1	57.4 ± 1.6
8g	100.0 ± 3.0	99.0 ± 1.2	55.2 ± 2.6	31.3 ± 3.1
8h	90.3 ± 2.2	77.6 ± 1.4	66.1 ± 0.8	46.8 ± 1.6
8i	75.0 ± 2.0	67.4 ± 4.1	40.2 ± 2.1	21.0 ± 1.6
8j	31.2 ± 1.8	26.6 ± 1.3	65.6 ± 2.4	43.2 ± 1.2
8k	33.9 ± 1.7	21.3 ± 1.5	56.8 ± 2.5	33.6 ± 1.0
8l	35.1 ± 1.5	28.9 ± 1.1	28.4 ± 4.2	16.3 ± 1.2
8m	30.0 ± 1.2	26.9 ± 1.9	66.8 ± 2.5	48.2 ± 3.6
8n	86.8 ± 1.7	61.3 ± 2.1	60.2 ± 1.1	48.2 ± 3.6
8o	37.0 ± 1.5	28.9 ± 1.1	40.0 ± 1.1	27.2 ± 1.4
8p	81.7 ± 1.8	60.8 ± 1.4	100.0 ± 1.2	75.3 ± 2.7
8q	85.5 ± 2.0	79.0 ± 1.5	70.1 ± 2.2	52.8 ± 1.6
8r	12.1 ± 2.2	9.6 ± 1.9	30.2 ± 1.2	23.8 ± 2.2
8s	44.6 ± 1.6	24.3 ± 1.1	79.6 ± 2.2	54.3 ± 1.3
8t	63.4 ± 1.1	50.8 ± 1.5	60.0 ± 1.1	34.2 ± 2.5
Bismerthiazol[b]	72.4 ± 3.1	54.2 ± 1.2	77.5 ± 1.4	50.0 ± 2.2

[a]Average of three replicates.
[b]The commercial agricultural antibacterial agent bismerthiazol was used for comparison of antibacterial activity.

Further investigations were conducted with previously reported compounds possessing excellent activity against *Xoo* for their 50% inhibition concentration (EC_{50}) values (Table 3). EC_{50} values of compounds **8b**, **8f**, **8g**, and **8h** are 35.2, 80.1, 62.5, and 82.1 μg/mL, respectively, which appeared to be more potent than the commercial bactericide bismerthiazol (89.9 μg/mL).

On the basis of the activity values in Table 2, a preliminary conclusion of the structure–activity relationships could be deduced. Some suitably substituted monohalogenated and dihalogenated alkoxyphenyl derivatives (R_2 = 4-Cl, 4-F, 2,4-di-Cl) exhibited good antibacterial activities against *Xoo* and *Xac*. For example, **8g**, **8f**, **8h**, **8n**, **8q**, and **8p** displayed higher activity against *Xoo* and *Xac* than those without bearing a similar halogen substituent; the observed bioactivities of the compounds followed the order **8b** > **8g** > **8f** > **8h** > **8n** > **8q** > **8p** on *Xoo* and **8p** > **8b** > **8f** > **8q** > **8h** > **8n** on *Xac* (Table 2). On the other hand, for the same type of R_2 substitutions, the substituent effect in the phenyl ring attached to the thiazole moiety revealed that a methoxy group at the 4-position of the ring (R_1 = 4-OCH_3) was superior to those mono or dichloro substituents at 4-position or 2,4- position (R_1 = 4-Cl or 2,4-di-Cl); the activity against *Xoo* for these representative compounds followed the order **8f**, **8g**, **8h** ($R_1 = OCH_3$) > **8n**, **8o**, **8p** (R_1 = 4-Cl) > **8i**, **8j**, **8k** (2,4-Cl). In general, it may be derived that chlorinated alkoxyphenyl derivatives and 4-methoxy group in the aromatic ring attached to thiazole exert a significant role in promoting activity. Thus, compounds **8b**, **8g**, **8f**, and **8h** showed potent antibacterial activities against *Xoo* and *Xac*, being higher than the rest. The effects of electron-withdrawing substituent chlorine seem more prominent in enhancing activity.

It is worthwhile to note that the intermediate compound **5** incorporating the thiazole moiety showed potent antibacterial activities (data not given). Nevertheless,

Table 3

Inhibitory effect of compounds **8b**, **8f**, **8g**, and **8h** against *Xanthomonas oryzae* pv. *oryzae*.[a]

Compound	EC_{50} (μg/mL)	Toxic regression eq.	*R*
8b	35.2 ± 5.6	$y = 2.1427x + 0.8711$	0.9904
8f	80.1 ± 5.4	$y = 1.3583x + 2.4143$	0.9529
8g	62.5 ± 7.8	$y = 1.9088x + 1.572$	0.9824
8h	82.1 ± 4.0	$y = 2.0736x + 1.0295$	0.9967
Bismerthiazol[b]	89.9 ± 5.5	$y = 2.0757x + 0.9445$	0.9888

[a]Average of three replicates.
[b]The commercial agricultural antibacterial agent bismerthiazol was used for comparison of antibacterial activity.

amidation of intermediate **5** by acyl chloride to generate **7** does not necessarily lead to enhancement of antibacterial activity. There is no apparent rational for incorporating phenoxyacetamide [30] as the basis to improve bioactivity.

The antibacterial results showed that the presence of 4-chloro, 4-fluoroalkoxyphenyl, and 2,4-dichloroalkoxyphenyl as well as 4-methoxyphenylthiazole units in the target compound was primarily responsible for increasing antibacterial activity. The present work demonstrated that 2-substituted phenoxy-*N*-(4-substituted phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide derivatives have significant potential for developing potent plants bactericides.

CONCLUSION

In conclusion, a series of novel 2-substituted phenoxy-*N*-(4-substituted phenyl-5-(1*H*-1,2,4-triazol-1-yl) thiazol-2-yl)acetamide derivatives were synthesized and bioassayed for their antifungal activity against *G. zeae*, *P. infestans*, and *P. sasakii* and antibacterial activities against *Xoo* and *Xac in vitro*. The study revealed that all of the derivatives exhibited weak to good active against the tested fungus, with compound **8p** showing high antifungal activity. While most of the compounds demonstrated excellent inhibitory effects against *Xoo* and *Xac*, in particular, compounds **8b**, **8f**, **8g**, and **8h** revealed superior activities compared with commercial bactericide bismerthiazol against *Xoo*.

This work demonstrated that 2-substituted phenoxy-*N*-(4-substituted phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide derivatives are of great potential for developing plants bactericides.

EXPERIMENTAL

All of the reagents and solvents were purchased from Aladdin (Shanghai, China) and used without further purifications. The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., Beijing, China). The progress of the reactions as well as the purity of compounds was monitored by thin-layer chromatography (TLC) with GF_{254} silica-gel precoated sheets using hexane/ethyl acetate (EA) as eluent; prepared TLC and column chromatographic purification were performed on silica gel using petroleum ether (PE)/EA as eluent. The IR spectra were recorded on FTIR model SHIMADZU-8400S grating infrared spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR (solvent DMSO-d_6) spectral analyses were performed on a JEOL-ECX 500 NMR at room temperature using TMS as an internal standard.

General procedure for synthesis of 4-phenyl-5-(1H-1,2,4-triazol-1-yl)-2-amine (5a). A mixture of 2-bromo-1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (5.0 mmol) and thiourea (7.5 mmol) was refluxed in ethanol for 8 h. The progress of the reaction was monitored by TLC (mobile phase, PE : EA = 1:1, vol.); after completion, the solvent was neutralized with ammonium hydroxide (15%). The mixture was allowed to stand overnight; the precipitated solid was filtered, washed with water, and recrystallized from ethanol to afford compound **5a**.

General procedure for synthesis of phenoxyacetyl chloride (7a). A solution of 2.28 g (1.5 mmol) of phenoxyacetic acid was dissolved in 10 mL of $SOCl_2$, and the catalytic amounts of DMF were added. The mixture was heated at reflux for 5 h. After completion of the reaction, the excess thionyl chloride ($SOCl_2$) was removed under vacuum, and light yellow oil (**7**) (0.23 g) was obtained by fractional distillation under reduced pressure with a yield of 90%.

General procedure for synthesis of 2-phenoxy-N-(4-phenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8a). To a stirred solution of 4-phenyl-5-(1*H*-1,2,4-triazol-1-yl)-2-amine (5a) (1 mmol) and triethylamine (1.5 mmol) in dry THF (15 mL), a solution of phenoxyacetyl chloride (1.2 mmol) in dry THF (15 mL) was added drop by drop for 30 min at room temperature. The mixture was stirred for 6 h. After completion of the reaction, the resultant triethylamine hydrochloride was filtered, and the filtrate was evaporated in vacuo to give an oily residue. The residue was purified by column chromatograph using PE : EA (5:1) as eluate to afford the target compound **8a**.

2-Phenoxy-N-(4-phenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8a). A white solid; yield 57.2%; mp 216–218°C; IR (KBr): *v* 3475, 3127, 2360,1683, 1533, 1495, 1270, 950, 765, 697 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.91 (s, 1H, NH), 8.79 (s, 1H, 5-Thiazole-H), 8.32 (s, 1H, 3-Thiazole-H), 7.36–7.31 (m, 3H, Ph-H), 7.30–7.27 (m, 2H, Ph-H), 7.25–7.21 (m, 2H, Ph-H), 7.01–6.93 (m, 3H, Ph-H), 4.91 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.52, 158.15, 155.27, 153.68, 148.00, 144.77, 132.36, 130.11, 129.47, 129.32, 127.70, 121.86, 121.18, 115.06, 66.42; MS (ESI, *m/z*): 400.1 ([M + Na]$^+$); *Anal*. Calcd. for $C_{19}H_{15}N_5O_2S$: C, 60.46; H, 4.01; N, 18.56; Found: C, 60.52; H, 4.05; N, 18.23.

2-(4-Chlorophenoxy)-N-(4-phenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8b). A white solid; yield 54.6%; mp 228–230°C, IR (KBr): *v* 3474, 3099, 2358, 1685, 1534, 1442, 1235, 1069, 950, 689 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.92 (s, 1H, NH), 8.80 (s, 1H, 5-Thiazole-H), 8.32 (s, 1H, 3-Thiazole-H), 7.37–7.31 (m, 5H, Ph-H), 7.25–7.20 (m, 2H, Ph-H), 7.02–6.97 (m, 2H, Ph-H), 4.92 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.25, 157.04, 155.25, 153.70, 148.03, 144.77, 132.33, 129.85, 129.49, 129.34, 127.65, 125.56, 121.18, 116.93, 66.67; MS (ESI, *m/z*): 434.1 ([M + Na]$^+$); *Anal*. Calcd. for

$C_{19}H_{14}ClN_5O_2S$: C, 55.41; H, 3.43; N, 17.00; Found: C, 54.87; H, 3.51; N, 17.16.

2-(2,4-Dichlorophenoxy)-N-(4-phenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8c). A white powder; yield 59.0%; mp 187–189°C; IR (KBr): *v* 3384, 3050, 2361, 1770, 1537, 1483, 1433, 1288, 1103, 944, 769 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.97 (s, 1H, NH), 8.79 (s, 1H, 5-Thiazole-H), 8.32 (s, 1H, 3-Thiazole-H), 7.59 (d, J = 2.8 Hz, 1H, Ph-H), 7.39–7.30 (m, 4H, Ph-H), 7.25–7.18 (m, 2H, Ph-H), 7.10 (d, J = 8.8 Hz, 1H, Ph-H), 5.06 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.69, 155.31, 153.69, 152.93, 148.41, 144.78, 132.34, 130.02, 129.48, 129.34, 128.61, 127.65, 125.74, 122.95, 115.90, 67.26; MS (ESI, *m/z*): 469.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{19}H_{13}Cl_2N_5O_2S$: C, 51.13; H, 2.94; N, 15.69; Found: C, 51.89; H, 2.88; N, 15.55.

2-(4-Fluorophenoxy)-N-(4-phenyl-5-(1H-1,2,4-triazol-1-yl) thiazol-2-yl)acetamide (8d). A white solid; yield 50.3%; mp 199–201°C; IR (KBr): *v* 3383, 3121, 2360, 1684, 1538, 1503, 1253, 1085, 950, 765, 697 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.92 (s, 1H, NH), 8.79 (s, 1H, 5-Thiazole-H), 8.32 (s, 1H, 3-Thiazole-H), 7.38–7.30 (m, 3H, Ph-H), 7.27–7.20 (m, 2H, Ph-H), 7.16–7.09 (m, 2H, Ph-H), 7.02–6.95 (m, 2H, Ph-H), 4.91 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.40, 158.39, 156.51, 155.24, 154.51, 153.69, 147.77, 144.74, 132.35, 132.35, 129.48, 129.33, 127.70, 121.20, 116.55, 116.49, 116.35, 67.29; MS (ESI, *m/z*): 418.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{19}H_{14}FN_5O_2S$: C, 57.71; H, 3.57; N, 17.71; Found: C, 58.23; H, 3.46; N, 17.65.

N-(4-(4-Methoxyphenyl)5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)-2-phenoxyacetamide (8e). A white solid; yield 55.2%; mp 170–172°C; IR (KBr): *v* 3344, 3121, 2365, 1609, 1416, 1260, 1176, 1082, 949, 835, 761 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.87 (s, 1H, NH), 8.79 (s, 1H, 5-Thiazole-H), 8.32 (s, 1H, 3-Thiazole-H), 7.32–7.25 (m, 2H, Ph-H), 7.18–7.14 (m, 2H, Ph-H), 6.98–6.94 (m, 2H, Ph-H), 6.92–6.87 (m, 2H, Ph-H), 4.90 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.43, 160.15, 158.15, 155.08, 153.67, 148.06, 144.73, 130.11, 129.07, 124.80, 121.85, 119.51, 115.06, 114.75, 66.41, 55.73; MS (ESI, *m/z*): 430.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{20}H_{17}N_5O_3S$: C, 58.96; H, 4.21; N, 17.19; Found: C, 59.06; H, 4.16; N, 17.21.

2-(4-Chlorophenoxy)-N-(4-(4-methoxyphenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8f). A yellow solid; yield 59.3%; mp 236–238°C; IR (KBr): *v* 3441, 2932, 2364, 1671, 1541, 1489, 1240, 1175, 1075, 950, 845, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.89 (s, 1H, NH), 8.79 (s, 1H, 5-Thiazole-H), 8.32 (s, 1H, 3-Thiazole), 7.33 (d, J = 7.0 Hz, 2H, Ph-H), 7.15 (d, J = 5.9 Hz, 2H, Ph-H), 6.99 (d, J = 7.1 Hz, 2H, Ph-H), 6.89 (d, J = 6.8 Hz, 2H, Ph-H), 4.91 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.15, 160.14, 157.05, 155.04, 153.68, 148.07, 144.74, 129.84, 129.06, 125.56, 124.77, 119.52, 116.93, 114.75, 66.67, 55.73. MS (ESI, *m/z*): 464.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{20}H_{16}ClN_5O_3S$: C, 54.36; H, 3.65; N, 15.85; Found: C, 54.21; H, 3.65; N, 15.78.

2-(2,4-Dichlorophenoxy)-N-(4-(4-methoxyphenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8g). A pale yellow solid; yield 61.7%; mp 158–160°C; IR (KBr): *v* 3440, 3134, 2934, 1665, 1538,1260, 1175, 1082, 948, 834 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.92 (s, 1H, NH), 8.81 (s, 1H, 5-Thiazole-H), 8.34 (s, 1H, 3-Thiazole-H), 7.57 (d, J = 9.6 Hz, 1H, Ph-H), 7.36–7.30 (m, 1H, Ph-H), 7.15 (d, J = 7.7 Hz, 2H, Ph-H), 7.10 (d, J = 8.8 Hz, 1H, Ph-H), 6.89 (d, J = 8.7 Hz, 2H, Ph-H), 5.06 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.56, 160.17, 155.02, 153.69, 152.94, 148.06, 144.75, 130.02, 129.05, 128.60, 125.64, 124.78, 122.85, 119.52, 115.69, 114.76, 67.24, 55.73; MS (ESI, *m/z*): 498.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{20}H_{15}Cl_2N_5O_3S$: C, 50.43; H, 3.17; N, 14.70; Found: C, 51.03; H, 3.21; N, 14.62.

2-(4-Fluorophenoxy)-N-(4-(4-methoxyphenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8h). A yellow solid; yield 54.3%; mp 229–231°C; IR (KBr): *v* 3442, 3127, 2928, 1681, 1541, 1272, 1071, 951, 831, 755 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.85 (s, 1H, NH), 8.79 (s, 1H, 5-Thiazole-H), 8.34 (s, 1H, 3-Thiazole-H), 7.15 (d, J = 7.9 Hz, 2H, Ph-H), 7.10 (d, J = 23.8 Hz, 2H, Ph-H), 6.98 (d, 2H, J = 21.1 Hz, Ph-H), 6.89 (d, J = 7.2 Hz, 2H, Ph-H), 4.88 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.34, 160.14, 158.37, 156.52, 155.06, 154.49, 153.68, 148.06, 144.73, 129.07, 124.78, 119.51, 115.45, 114.74, 67.02, 55.72; MS (ESI, *m/z*): 448.0 ($[M+Na]^+$); *Anal*. Calcd. for $C_{20}H_{16}FN_5O_3S$: C, 56.46; H, 3.76; N, 16.46; Found: C, 56.45; H, 3.76; N, 16.28.

N-(4-(3,4-Dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)-2-phenoxyacetamide (8i). A yellow solid; yield 57.6%; mp 192–1194°C; IR (KBr): *v* 3393, 3119, 1687, 1695, 1532, 1284, 1241, 949, 769, 673 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.97 (s, 1H, NH), 8.86 (s, 1H, 5-Thiazole-H), 8.36 (s, 1H, 3-Thiazole-H), 7.63 (d, J = 8.5 Hz, 1H, Ph-H), 7.44 (d, J = 2.1 Hz, 1H, Ph-H), 7.34–7.23 (m, 2H, Ph-H), 7.10 (s, J = 8.5, 1H, Ph-H), 7.00–6.92 (m, 3H, Ph-H), 4.92 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.69, 158.12, 155.58, 153.92, 148.06, 142.04, 132.85, 132.08, 131.73, 130.11, 129.55, 127.59, 122.56, 121.89, 115.08, 66.43; MS (ESI, *m/z*): 468.0 ($[M+Na]^+$); *Anal*. Calcd. for $C_{19}H_{13}Cl_2N_5O_2S$: C, 51.13; H, 2.94; N, 15.69; Found: C, 50.66; H, 3.01; N, 15.52.

2-(4-Chlorophenoxy)-N-(4-(3,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8j). A pale yellow solid; yield 45.2%; mp 218–220°C; IR (KBr): *v* 3409, 3110,

2904, 1680, 1699, 1490, 1243, 1077, 951, 825, 673 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.95 (s, 1H), 8.85 (s, 1H, 5-Thiazole-H), 8.35 (d, 1H, 3-Thiazole-H), 7.63 (d, J = 8.5 Hz, 1H, Ph-H), 7.44 (d, J = 2.1 Hz, 1H, Ph-H), 7.36–7.30 (m, 2H, Ph-H), 7.11 (s, 1H, Ph-H), 7.02–6.97 (m, 2H, Ph-H), 4.91 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.51, 157.03, 155.81, 153.89, 148.01, 141.98, 132.86, 132.06, 131.67, 129.81, 129.53, 127.54, 125.57, 122.45, 116.83, 66.78; MS (ESI, *m/z*): 481.9 ($[M+H]^+$); *Anal*. Calcd. for $C_{19}H_{12}Cl_3N_5O_2S$: C, 47.47; H, 2.52; N, 14.57; Found: C, 48.03; H, 2.50; N, 14.64.

2-(2,4-Dichlorophenoxy)-N-(4-(3,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8k). A white solid; yield 57.3%; mp 212–214°C; IR (KBr): *v* 3382, 3026, 1703, 1532, 1480, 1287, 1136, 1075, 945, 875, 786 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 13.02 (s, 1H, NH), 8.87 (s, 1H, 5-Thiazole-H), 8.36 (s, 1H, 3-Thiazole-H), 7.62 (m, 2H, Ph-H), 7.42 (s, 1H, Ph-H), 7.34 (s, 1H, Ph-H), 7.10 (m, 2H, Ph-H), 5.07 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.81, 155.54, 153.93, 152.91, 148.07, 142.06, 132.81, 132.10, 131.75, 130.03, 129.50, 128.60, 127.58, 125.78, 122.97, 122.55, 120.00, 115.72, 67.55; MS (ESI, *m/z*): 415.9 ($[M+Na]^+$); *Anal*. Calcd. for $C_{19}H_{11}Cl_4N_5O_2S$: C, 44.29; H, 2.15; N, 13.59; Found: C, 44.22; H, 2.20; N, 14.06.

N-(4-(3,4-Dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazole-2-yl)-2-(4-fluorophenoxy)acetamide (8l). A pale red solid; yield 58.9%; mp 191–193°C; IR (KBr): *v* 3415, 3050, 1696, 1565, 1506, 1278, 1196, 1098, 955, 828, 670 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.95 (s, 1H, NH), 8.86 (s, 1H, 5-Thiazole-H), 8.36 (s, 1H, 3-Thiazole-H), 7.63 (dd, J = 8.4, 2.4 Hz, 1H, Ph-H), 7.44 (d, J = 1.6 Hz, 1H, Ph-H), 7.18–7.07 (m, 3H, Ph-H), 7.04–6.95 (m, 2H, Ph-H), 4.89 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.58, 158.40, 156.52, 155.56, 154.47, 153.92, 148.05, 142.03, 132.84, 132.09, 131.72, 129.55, 127.57, 122.57, 116.54, 116.36, 67.30; MS (ESI, *m/z*): 464.0 ($[M+H]^+$); *Anal*. Calcd. for $C_{19}H_{12}Cl_2FN_5O_2S$: C, 49.15; H, 2.61; N, 15.08; Found: C, 49.06; H, 2.68; N, 15.21.

N-(4-(4-Chlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)-2-phenoxyacetamide (8m). A pale red solid; yield 55.8%; mp 196–198°C; IR (KBr): *v* 3387, 3117, 1681, 1597, 1540, 1287, 1233, 1142, 1081, 948, 838, 761 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.96 (s, 1H, NH), 8.82 (s, 1H, 5-Thiazole-H), 8.33 (s, 1H, 3-Thiazole-H), 7.43 (d, J = 8.6 Hz, 2H, Ph-H), 7.36–7.26 (m, 2H, Ph-H), 7.22 (d, J = 8.6 Hz, 2H, Ph-H), 7.01–6.92 (m, 3H, Ph-H), 4.91 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.59, 158.12, 155.40, 153.82, 148.01, 143.49, 134.14, 131.21, 130.11, 129.47, 129.45, 121.86, 121.65, 115.05, 66.38; MS (ESI, *m/z*): 413.3 ($[M+H]^+$); *Anal*. Calcd. for $C_{19}H_{14}ClN_5O_2S$: C, 55.41; H, 3.43; N, 17.00; Found: C, 54.25; H, 3.56; N, 17.10.

2-(4-Chlorophenoxy)-N-(4-(4-chlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8n). A yellow solid; yield 51.1%; mp 234–1236°C; IR (KBr): *v* 3421, 3118, 2925, 1684, 1502, 1285, 1200, 1072, 953, 832, 759 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.94 (s, 1H, NH), 8.82 (s, 1H, 5-Thiazole-H), 8.33 (s, 1H, 3-Thiazole-H), 7.48–7.37 (m, 2H, Ph-H), 7.27–7.18 (m, 2H, Ph-H), 7.17–7.06 (m, 2H, Ph-H), 7.03–6.93 (m, 2H, Ph-H), 4.89 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.50, 158.37, 156.49, 155.39, 154.47, 153.82, 148.00, 143.49, 134.14, 131.20, 129.46, 121.66, 116.52, 116.37, 67.01; MS (ESI, *m/z*): 447.8 ($[M+H]^+$). *Anal*. Calcd. for $C_{19}H_{13}C_{12}N_5O_2S$: C, 51.13; H, 2.94; N, 15.69; Found: C, 51.46; H, 2.88; N, 15.62.

N-(4-(4-Chlorophenyl)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)-2-(2,4-dichlorophenoxy)acetamide (8o). A yellow solid; yield 62.5%; mp 215–217°C; IR (KBr): *v* 3379, 3102, 2906, 1696, 1539, 1484, 1289, 1079, 1001, 945, 840, 773 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 13.02 (s, 1H, NH), 8.82 (s, 1H, 5-Thiazole-H), 8.33 (s, 1H, 3-Thiazole-H), 7.60 (d, J = 2.5 Hz, 1H, Ph-H), 7.43 (d, J = 8.5 Hz, 2H, Ph-H), 7.34 (m, 1H, Ph-H), 7.21 (d, J = 8.5 Hz, 2H, Ph-H), 7.09 (d, J = 8.9 Hz, 1H, Ph-H), 5.06 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.71, 155.35, 153.83, 152.89, 148.02, 143.50, 134.15, 131.17, 130.02, 129.49, 129.42, 128.60, 125.73, 122.91, 121.62, 115.65, 67.63; MS (ESI, *m/z*): 481.9 ($[M+H]^+$); *Anal*. Calcd. for $C_{19}H_{12}Cl_3N_5O_2S$: C, 47.47; H, 2.52; N, 14.57; Found: C, 47.50; H, 2.52; N, 14.57.

N-(4-(4-Chloropheny)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)-2-(4-fluorophenoxy)acetamide (8p). A pale yellow solid; yield 61.3%; mp 232–234°C; IR (KBr): *v* 3455, 3118, 1683, 1539, 1503, 1281, 1201, 1071, 953, 832 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.94 (s, 1H, NH), 8.82 (s, 1H, 5-Thiazole-H), 8.33 (s, 1H, 3-Thiazole-H), 7.45–7.39 (m, 2H, Ph-H), 7.26–7.19 (m, 2H, Ph-H), 7.16–7.07 (m, 2H, Ph-H), 7.02–6.94 (m, 2H, Ph-H), 4.89 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.54, 158.38, 156.50, 155.40, 154.42, 154.42, 147.88, 143.48, 134.15, 131.21, 129.45, 121.77, 116.50, 116.35, 67.81; MS (ESI, *m/z*): 430.1 ($[M+H]^+$); *Anal*. Calcd. for $C_{19}H_{13}ClFN_5O_2S$: C, 53.09; H, 3.05; N, 16.29; Found: C, 53.21; H, 3.02; N, 16.15.

2-Phenoxy-N-(4-(p-toly)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8q). A pale yellow solid; yield 66.4%; mp 219–221°C; IR (KBr): *v* 3453, 2940, 1676, 1540, 1288, 1081, 949, 824, 759 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.90 (s, 1H, NH), 8.77 (s, 1H, 5-Thiazole-H), 8.31 (s, 1H, 3-Thiazole-H), 7.32–7.26 (m, 2H, Ph-H), 7.12 (m, 4H, Ph-H), 6.97–6.93 (m, 3H, Ph-H), 4.91 (s, 2H, CH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.47, 158.15, 155.17, 153.64, 148.01, 144.91, 139.09, 130.10, 129.89, 127.58, 121.85, 120.54, 120.00, 115.06, 66.41, 21.33; MS (ESI, *m/z*): 392.1 ($[M+H]^+$); *Anal*. Calcd. for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89; Found: C, 61.40; H, 4.35; N, 17.74.

2-(4-Chlorophenoxy)-N-(4-(p-toly)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8r). A red solid; yield 62.1%; mp 242–244° C; IR (KBr): *v* 3441, 2924, 1540, 1490, 1243, 1076, 952, 826, 695 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 13.00 (s, 1H, NH), 8.78 (s, 1H, 5-Thiazole), 8.33 (s, 1H, 3-Thiazole-H), 7.33 (d, J = 8.9 Hz, 2H, Ph-H), 7.17–7.08 (m, 4H, Ph-H), 7.03–6.96 (m, 2H, Ph-H), 4.92 (s, 2H, CH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.19, 157.04, 155.16, 153.63, 148.00, 144.91, 139.08, 129.90, 129.84, 129.58, 127.57, 125.58, 120.56, 117.08, 66.60, 21.31; MS (ESI, *m/z*): 426.8 ($[M+H]^+$); *Anal*. Calcd. for $C_{20}H_{16}ClN_5O_2S$: C, 56.40; H, 3.79; N, 16.44; Found: C, 56.20; H, 3.83; N, 16.40.

2-(2,4-Dichlorophenoxy)-N-(4-(p-toly)-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl)acetamide (8s). A pale red solid; yield 64.3%; mp 215–1217°C; IR (KBr): *v* 3380, 3076, 1698, 1536, 1478, 1267, 1103, 943, 826, 768, 650 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.94 (s, 1H, NH), 8.76 (s, 1H, 5-Thiazole-Hx), 8.31 (s, 1H, 3-Thiazole-H), 7.58 (d, J = 1.8 Hz, 1H, Ph-H), 7.34 (m, 1H, Ph-H), 7.14 (d, J = 8.3 Hz, 2H, Ph-H), 7.10 (m, J = 8.6, 3H, Ph-H), 5.06 (s, 2H, CH_2), 2.24 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.58, 155.10, 153.64, 152.94, 148.00, 144.92, 139.10, 130.02, 129.90, 129.57, 128.60, 127.58, 125.76, 122.98, 120.56, 115.72, 67.26, 21.33; MS (ESI, *m/z*): 460.1 ($[M+H]^+$); *Anal*. Calcd. for $C_{20}H_{15}Cl_2N_5O_2S$: C, 52.18; H, 3.28; N, 15.21; Found: C, 52.18; H, 3.16; N, 15.32.

2-(4-Fluorophenoxy)-N-(4-(p-toly)-5-(1H-1,2,4-triazol-1-yl) thiazol-2-yl)acetamide (8t). A pale red solid; yield 57.4%; mp >250°C; IR (KBr): *v* 3431, 3120, 2923, 1672, 1540, 1505, 1200, 1072, 953, 831 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.90 (s, 1H, NH), 8.78 (s, 1H, 5-Thiazole-H), 8.32 (d, 1H, 3-Thiazole-H), 7.16–7.09 (m, 6H, Ph-H), 7.01–6.93 (m, 2H, Ph-H), 4.87 (s, 2H, CH_2), 2.24 (d, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.38, 158.37, 156.49, 155.17, 154.49, 153.66, 148.02, 144.91, 139.10, 129.88, 129.57, 127.58, 120.67, 116.55, 116.52, 116.46, 116.37, 65.90, 19.82; MS (ESI, m/z): 432.1 ($[M+Na]^+$); *Anal*. Calcd. for $C_{20}H_{16}FN_5O_2S$: C, 58.67; H, 3.94; N, 17.10; Found: C, 58.44; H, 4.05; N, 17.10.

Acknowledgments. This work was supported by the Excellent Young Science and Technology Talent Cultivation Plan (201122) and the National Natural Science Foundation "synthesis and antibacterial activity of novel amide derivatives" (20962005).

REFERENCES AND NOTES

[1] Dai, H.; Yu, H. B.; Qin, X.; Wang, T. T.; Zhang, X.; Qin, Z. F.; Fang, J. X. Chin J Org Chem 2013, 33, 1104.

[2] Qin, Y. J.; Wang, P. F.; Makawana, J. A.; Wang, Z. C.; Wang, Z. N.; Gu, Y.; Jing, A. Q.; Zhu, H. L. Bioorg Med Chem Lett 2014, 24, 5279.

[3] Parekh, N. M.; Juddhawala, K. V.; Rawal, B. M. Med Chem Res 2013, 22, 2737.

[4] Liaras, K.; Geronikaki, A.; Glamoclija, J.; Ciric, A.; Sokovic, M. Bioorg Med Chem 2011, 19, 3135.

[5] Zhu, Y. Q.; Wang, D. Y.; Yuan, Y. W.; Ma, Y.; Zou, X. M.; Yang, H. Z. Chin J Org Chem 2012, 32, 2115.

[6] Chen, C. J.; Song, B. A. Agrochemicals 2005, 44, 53.

[7] Shen, F.; Hu, A. X.; Luo, X. F.; Ye, J.; Ou, X. M. Chin J Org Chem 2012, 32, 388.

[8] Mo, W. Y.; Shi, Y. X.; He, J. B.; Li, B. J.; Peng, H.; He, H. J Heterocyclic Chem 2016, 53, 183.

[9] Koppireddi, S.; Chilaka, D. R. K.; Avula, S.; Komsani, J. R.; Kotamraju, S.; Yadla, R. Bioorg Med Chem Lett 2014, 24, 5428.

[10] Grozav, A.; Gaina, L. I.; Pileczki, V.; Crisan, O.; Silaghi-Dumitrescu, L.; Therrien, B.; Zaharia, V.; Berindan-Neagoe, I. Int J Mol Sci 2014, 15, 22059.

[11] Kumar, M. A.; An, T. N. M.; Lee, I. J.; Pare, S.; Lee, K. D. Phosphorus Sulfur Silicon 2015, 190, 1160.

[12] An, T. N. M.; Kumar, M. A.; Chang, S. H.; Kim, M. Y.; Kim, J. A.; Lee, K. D. Bull Korean Chem Soc 2014, 35, 1619.

[13] Suh, J.; Yum, E. K.; Cheon, H. G.; Cho, Y. S. Chem Biol Drug Des 2012, 80, 90.

[14] Hu, D. Y.; Song, B. A.; He, W. J Synth Chem 2006, 14, 319.

[15] He, X. L. World Pestic 2005, 37, 58.

[16] Tomlin, C. D. S. The Pesticide Manual, 12th edn.; BCPC: Hampshire, UK, 2005, pp 901.

[17] Xu, L. Z.; Li, W. H.; Li, K.; Qin, Y. Q.; Li, C. L.; Hou, B. R. Chin J Org Chem 2005, 25, 1594.

[18] Liu, B. J.; Tao, W. F.; Dai, H.; Jin, Z.; Fang, J. X. Heteroatom Chem 2007, 18, 376.

[19] Moreno, M. M.; Arredondo, Y.; Pleixats, R. J Heterocyclic Chem 1992, 29, 1557.

[20] Zhang, Z. P.; Zhou, S. F.; Li, T. R.; Jiang, L. Chinese Chem Lett 2012, 23, 1381.

[21] Zhang, M.; Luo, X. A.; Zhu, D. Z.; Zhang, X. P.; Liu, F.; Fang, J. X.; Liu, J. B. Chin J Org Chem 2013, 33, 1955.

[22] Zhang, S. L.; Chang, J. J.; Damu, G. L. V.; Geng, R. X.; Zhou, C. H. Med Chem Commun 2013, 4, 839.

[23] Desai, N. C.; Shihora, P. N.; Rajpara, K. M.; Joshi, V. V.; Vaghani, H. V.; Satodiya, H. M.; Dodiya, A. M. Med Chem Res 2012, 21, 2981.

[24] Xiong, Q. Z.; Lin, X. F.; Liu, J. H.; Bi, L.; Bao, X. P. Chin J Org Chem 2012, 32, 1255.

[25] Shang, J.; Wang, W. M.; Li, Y. H.; Song, H. B.; Li, Z. M.; Wang, J. G. J Agric Food Chem 2012, 60, 8286.

[26] Wang, L. Y.; Tseng, W. C.; Wu, T. S. Bioorg Med Chem Lett 2011, 21, 5358.

[27] Cui, Z. N.; Shi, Y. X.; Cui, J. R.; Ling, Y.; Li, B. J.; Yang, X. L. Chem Biol Drug Des 2012, 79, 121.

[28] Kücükgüzel, S. G.; Cikla-Süzgün, P. Eur J Med Chem 2015, 97, 830.

[29] Klix, M. B.; Verreet, J. A.; Beyer, M. Crop Prot 2007, 26, 683.

[30] Spatz, D. M. United States patent 4672065 1987.

[31] Zhang, Y. J.; Shen, L. L.; Cheon, H. G.; Xu, Y. N.; Jeong, J. H. Arch Pharm Res 2014, 37, 588.

[32] Oh, K.; Nakai, K.; Yamana, K.; Yoshizawa, Y. J Pestic Sci 2012, 37, 80.

[33] Liu, J. B.; Dai, H.; Fang, J. X. Synth Commun 2011, 41, 3197.

[34] Tarun, K. C.; Prem, D. J. J Agric Food Chem 2006, 54, 2129.

[35] Li, P.; Yin, J.; Xu, W. M.; Wu, J.; He, M.; Hu, D. Y.; Yang, S.; Song, B. A. Chem Biol Drug Des 2003, 82, 546.