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Design, Synthesis, and Acaricidal/Insecticidal Activities of Oxazoline Derivatives Containing a Sulfur Ether Moiety

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Supporting Information

ABSTRACT: On the basis of etoxazole, a series of novel 2-(2,6-difluorophenyl)-4-(4-substituted phenyl)-1,3-oxazolines containing a sulfur ether moiety were designed and synthesized via the key intermediate *N*-(1-(4-(bromomethyl)phenyl)-2-chloroethyl)-2,6-difluorobenzamide. The bioassay results showed that most of these designed target compounds exhibited excellent acaricidal activity against both the eggs and larvae of *Tetranychus cinnabarinus*, especially the eggs. Among compounds with high activity against the eggs of mites, the LC_{50} values of **2**, **11**, **17**, and **19** were 0.0003, 0.0002, 0.0005, and 0.0008 mg L^{-1}, respectively, much lower than that of etoxazole (0.0089 mg L^{-1}). Compound **2** was chosen to evaluate the acaricidal activity in the field, and the results displayed that at a concentration of 22 mg kg^{-1}, **2** had a much better control effect than etoxazole against both *T. cinnabarinus* and *P. latus* on eggplant. Some compounds also showed good insecticidal activities against oriental armyworm and mosquito. On the basis of our research, the newly found structure−activity relationship may guide the development of new acaricides/pesticides that are required in the agriculture market.

KEYWORDS: *2,4-diphenyl-1,3-oxazolines, acaricidal activity, insecticidal activity, thioether, structure−activity relationship*

INTRODUCTION

To overcome the global food shortage, the emergence of pesticide resistance, pollution, and the accumulation of pesticides in food products and water supplies, researchers are compelled to develop novel pesticides with unique modes of actions coupled with a high degree of activity on targeted pests and low toxicity to nontarget organisms (including many beneficial arthropods).[1,2] Etoxazole (Figure 1) is the only commercial acaricide/insecticide belonging to the chemical class of 2,4-diphenyl-1,3-oxazolines, discovered by Kyoyu Agri Co., Ltd. (formerly Yashima Chemical Industry Co., Ltd.) and launched to the market in 1998.[3,4] The acaricidal and insecticidal mode of action of the 2,4-diphenyl-1,3-oxazolines (such as the commercial acaricide etoxazole) is chitin biosynthesis inhibition,[5] which is similar to that of benzoylphenylureas (BPUs) (Figure 1), the well-known class of insect chitin biosynthesis inhibitors.[6,7] Chitin is an important component only in insect cuticles and fungal cell walls but not in higher plants and mammals, so insect chitin synthesis inhibitors show high bioactivity on target pests and low toxicity to nontarget organisms and are safe to humans, livestock, insects' natural enemies, and the ecological environment.[1,8,9] Oxazoline derivatives have attracted considerable attention for decades because of the above advantages and their unique mechanism of action.

There are three parts (parts A, B, and C) to the 2,4-diphenyl-1,3-oxazoline structure (Figure 1). Recently, our research group reported the synthesis and acaricidal/insecticidal activities of oxazoline compounds in which a substituted phenoxy or a different alkoxy group was fixed at the para position of the 4-phenyl moiety (part C), optionally with Cl, methyl, or ethoxy at the ortho position and/or meta position. Most of the designed compounds showed excellent acaricidal activity, and the results also showed that the positions and types of substituents on the 4-phenyl moiety of 1,3-oxazolines had a great influence on the acaricidal and insecticidal activities.[10,11] In 2014, we further reported a series of 1,3-oxazolines with an oxime ether substituent at the para position of the 4-phenyl moiety. The bioassay results indicated that all of the target compounds exhibited considerable acaricidal activity against *T. cinnabarinus*. The acaricidal mechanism of action of the target compounds and etoxazole were studied with a fluorescence polarization method, which showed that they could bind to the site of the sulfonylurea receptor (SUR) and therefore inhibit chitin synthesis.[12]

Inspired by these reports, herein we report a series of oxazoline derivatives containing a sulfur ether moiety at the para position of 4-phenyl group. The bioactivities of the target compounds were evaluated, and the structure−activity relationship of these compounds is shown in this paper. The preparation of key intermediate *N*-(1-(4-(bromomethyl)phenyl)-2-chloroethyl)-2,6-difluorobenzamide is also modified to be more suitable for scale-up.

MATERIALS AND METHODS

Instruments and Chemicals. Reagents (analytically or chemically pure) were purchased from commercial sources and used as received. All anhydrous solvents were dried and distilled by standard techniques just before use. Reaction progress was monitored by thin-layer chromatography on silica gel GF254 with ultraviolet (UV) detection. Melting points were obtained using an X-4 binocular microscope melting point (mp) apparatus and are uncorrected. Yields were not optimized. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded utilizing a Bruker AV400 spectrometer with $CDCl_3$ as solvent and tetramethylsilane as

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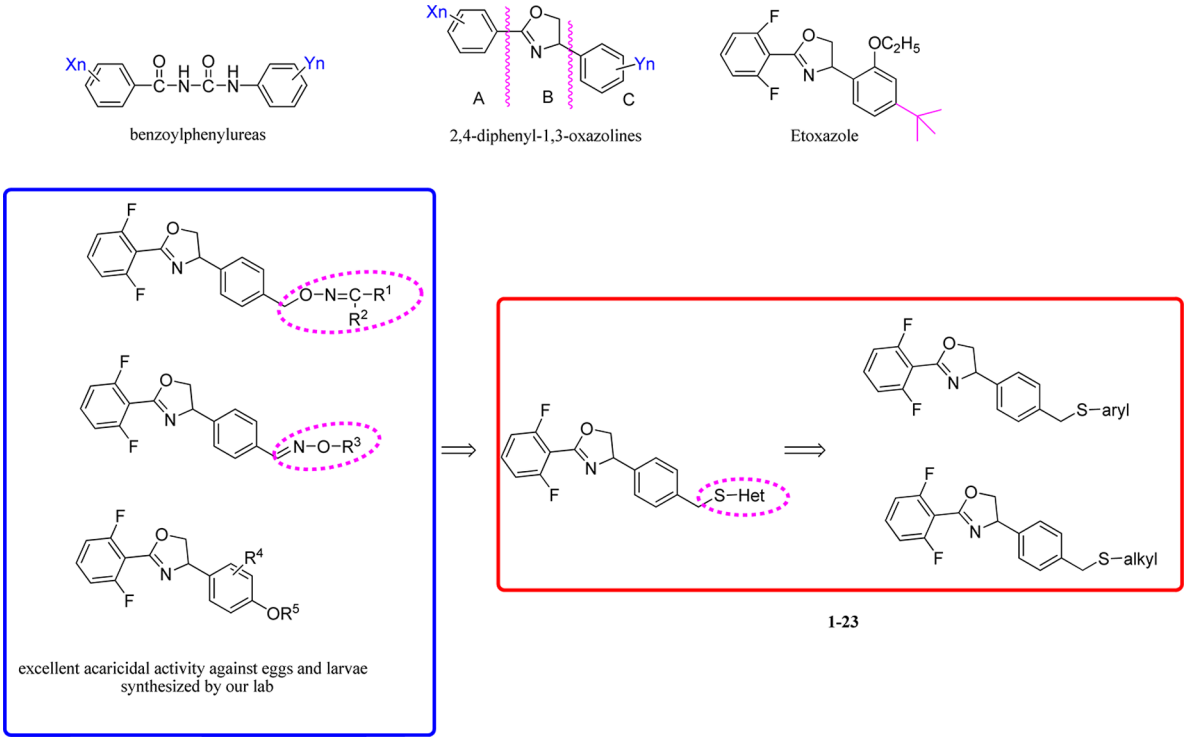

Figure 1. Chemical structure and the design of the target compounds.

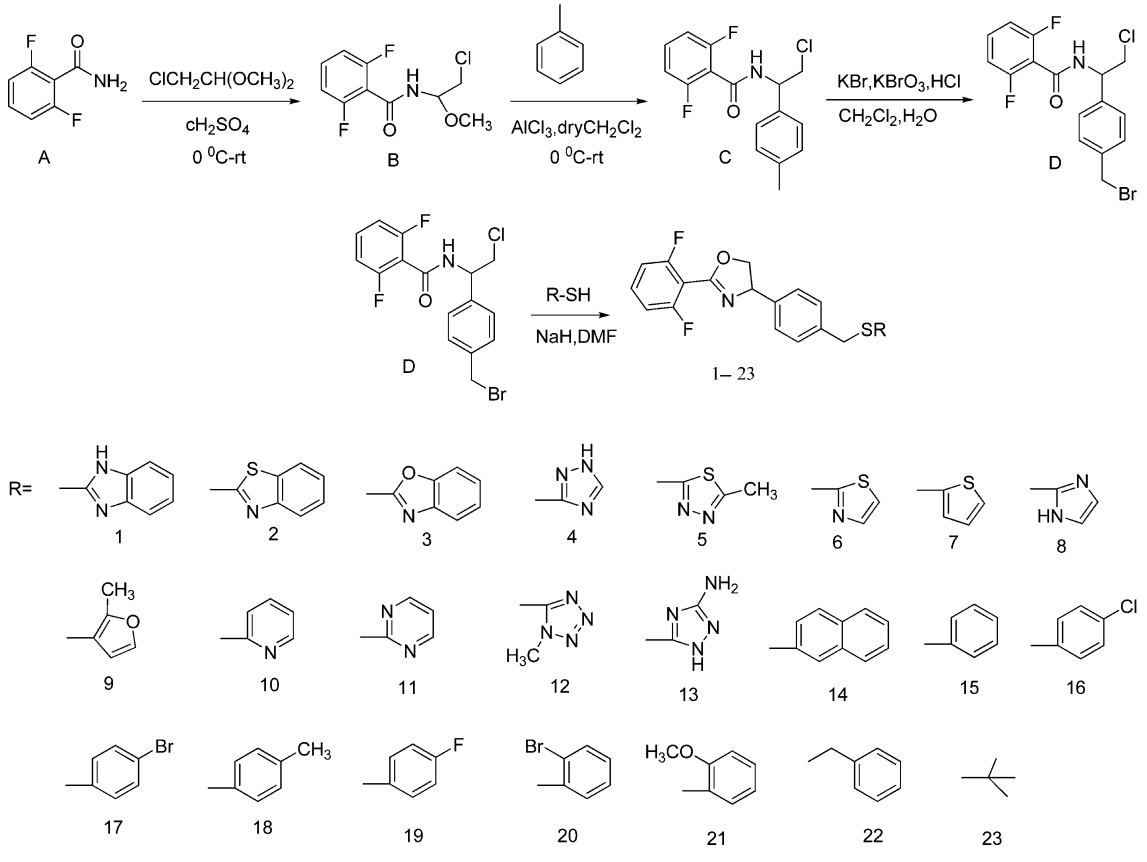

Figure 2. Synthetic procedure for the target compounds **1**−**23**.

internal standard. Chemical shifts (δ) are given in parts per million (ppm). High-resolution mass spectra (HRMS) were obtained with a Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) spectrometer (ionspec, 7.0T).

Procedure for the Synthesis of the Target Compounds 1−23 (Figure 2). *Synthesis of N-(2-Chloro-1-methoxyethyl)-2,6-difluorobenzamide (B).* To a solution of 2,6-difluorobenzamide **A** (7.15 g, 0.046 mol) in dimethylchloroacetal (22.68 g, 0.184 mol) under stirring

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Table 1. Acaricidal Activity of the Target Compounds against *T. cinnabarinus*

	activities(%) against eggs at concentration (mg L^{-1})					activities (%) against larvae at concentration (mg L^{-1})				
compd	100	50	25	2.5	1	100	50	25	2.5	1
1	100	100	79	20	–	90	80	78	62	–
2	100	100	100	100	100	100	100	100	100	38
3	100	100	100	100	100	100	100	100	100	20
4	80	67	50	18	–	100	50	36	–	–
5	100	100	100	86	50	100	100	83	70	41
6	100	100	100	100	100	100	100	90	87	21
7	100	100	100	100	95	100	100	92	91	0
8	100	100	100	35	–	100	82	75	39	0
9	100	100	100	66	30	100	100	80	72	0
10	100	100	100	100	100	100	100	100	100	27
11	100	100	100	100	100	100	100	100	100	17
12	100	100	100	34	–	100	100	82	30	–
13	100	97	91	53	10	100	80	10	–	–
14	100	100	100	89	77	100	100	100	93	15
15	100	100	100	89	81	100	100	100	100	15
16	100	100	100	100	100	100	100	100	100	30
17	100	100	100	100	100	100	100	77	76	22
18	100	100	100	85	78	100	92	83	75	26
19	100	100	100	100	97	100	100	92	81	30
20	100	100	100	100	100	100	100	100	98	0
21	100	100	100	100	100	100	100	87	85	57
22	100	100	100	100	100	100	100	90	70	45
23	100	100	100	100	100	100	100	100	86	0
etoxazole	100	100	100	100	100	100	100	100	85	30

below 0 °C was added dropwise concentrated sulfuric acid (3 mL), and then the reaction mixture was stirred at room temperature until the reaction was complete, indicated by TLC. Water was added, and then the reaction mixture was extracted with dichloromethane. The combined organic phase was washed with water and saturated brine successively, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. To the residue was added *n*-hexane (50 mL), and the mixture was stirred overnight at 0 °C and filtered to give **B** (10.20 g, yield 90%).

*Synthesis of N-(2-Chloro-1-p-tolylethyl)-2,6-difluorobenzamide (**C**).* To a solution of amide acetal **B** (2.0 g, 0.008 mol) in anhydrous dichloromethane (25 mL) was added toluene (0.89 g, 0.0096 mol), and the mixture was cooled to 0 °C. $AlCl_3$ was added to the mixture, and then the reaction mixture was stirred at room temperature overnight until the reaction was complete as indicated by TLC. The mixture was poured into ice−water. After the organic phase was separated, the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with saturated brine, dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude product, which was purified by recrystallization using petroleum ether and ethyl acetate to give **C** (2.36 g, yield 95%).

The synthetic procedure for *N*-(1-(4-(bromomethyl)phenyl)-2-chloroethyl)-2,6-difluorobenzamide (**D**) was performed according to published literature.[12]

Synthesis of 4-(4-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)phenyl)-2-(2,6-difluorophenyl)-4,5-dihydrooxazole (**1**): A mixture of 1*H*-benzo[*d*]imidazole-2-thiol (0.19 g, 1.3 mmol) in 10 mL of dry DMF was cooled below 0 °C. To this solution was added sodium hydride (0.12 g, 5.2 mmol). The reaction mixture was stirred below 0 °C for 30 min, and then compound **D** (0.5 g, 1.3 mmol) was added. The reaction progress was monitored by TLC until the reaction was complete. The mixture was extracted with ethyl acetate three times, and the combined organic phase was washed with water three times, dried with anhydrous sodium sulfate, and filtered. After the solvent was removed under reduced pressure, the residue was purified by flash chromatography on silica gel with petroleum ether and ethyl acetate (v/v = 2:1) to give the target compound **1** (0.25 g, yield 46%).

Compounds **2**−**23** were synthesized according to a procedure similar to that used for compound **1**. The physical data in detail can be found in the Supporting Information.

Biological Assay. All biological assays were performed on representative test organiams prepared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[13] Percentage mortalities were evaluated based on a percentage scale of 0−100, in which 0 indicates no activity and 100 indicates total kill. The standard deviations of the tested biologocal values were ±5%. LC_{50} values were calculated by probit analysis.[14]

Acaricidal Activity against Eggs of Spider Mites (*T. cinnabarinus*). The acaricidal activities of all target compounds **1**−**23** and etoxazole as the standard compound against the eggs of spider mites (*T. cinnabarinus*) were measured by the leaf-dip method.[15−18] Sieva bean plants (*Phaseolus vulgaris* L.) with primary leaves expanded to 10 cm were selected and cut back to one plant per pot. A small piece was cut from a leaf taken from the main colony and placed on each leaf of the test plants to allow the female mites to move to the test leaves and lay eggs. The size of the piece was tuned to obtain about 60−100 eggs per leaf. The leaves were kept for no more than 24 h before treatment. The mite-egg-infested leaves were dipped into the test solution for 3 s with agitation and set in the hood to dry, and then they were placed in a tube (10 cm inner diameter) lined with a piece of filter paper. Three replicates were carried out, and percentage mortalities were evaluated 4 days after treatment.

Acaricidal Activity against Larvae of Spider Mites (*T. cinnabarinus*). The acaricidal activities against the larvae of spider mites (*T. cinnabarinus*) were measured by the leaf-dip method.[17−20] Mite-egg-infested leaves (choose the leaves with the eggs layed on the same day) were kept at 25 °C for 4 days, and then they were cut and put on the test leaves as described above. After 1 day, the larvae were hatched and moved to the fresh leaves. Each leaf had about 60−100 mites. The leaf was cut and dipped into the test solution for 3 s with agitation, set in the hood to dry, and then placed in a tube (10 cm inner diameter) lined with a piece of filter paper. Three replicates were carried out, and percentage mortalities were evaluated 4 days after treatment.

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Larvicidal Activity against Oriental Armyworm. The larvicidal activities of the target compounds **1**−**23** against oriental armyworm were tested by foliar application using the reported produre.[21] For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were examined 4 days after treatment. Each treatment was carried out three times. Etoxazole as the control compound was tested under the same conditions.

Larvicidal Activity against Mosquito. The larvicidal activities of the target compounds **1**−**23** against mosquito were tested by using the reported procedure.[22] Compounds **1**−**23** were prepared in different concentrations by dissolving **1**−**23** in acetone and adding distilled water. Then 20 fourth-instar mosquito larvae were put into 10 mL of the test solutions and raised for 8 days. The results are expressed by death percentage. Etoxazole as the control compound was tested under the same conditions.

Evaluation of Acaricidal Activity in the Field. The field trials were carried out between June and July in 2015. The trial against *T. cinnabarinus* in an eggplant field was performed in the trial area of Institute of Plant Protection, Tianjin Academy of Agricultural Science, Tianjin City, China. Moreover, the trial against *Polyphagotarsonemus latus Banks* (*P. latus*) also in an eggplant field was performed in the trial area of Institute of Plant Protection, College of Agriculture, Yangtze University, Jingzhou City. The treatment plots of eggplants were designed in a random block array with four replicates. The untreated plots served as a blank control. A formulation of compound **2** and etoxazole (1% emulsifiable concentrates (ECs)) was prepared in our research group. They were diluted to 10, 15, or 22 mg L^{-1} before use. The control effects expressed as percentages were arcsine transformed to homogenize variances before analysis, in which different spraying treatments were examined using analysis of variance (ANOVA).[23]

RESULT AND DISCUSSION

Synthesis. The synthetic procedure of the target compounds **1**−**23** is shown in Figure 2. 2,6-Difluorobenzamide (**A**) reacted with chloroacetaldehyde dimethyl acetal under catalysis from H_2SO_4, giving **B**. Friedel−Crafts alkylation of **B** with toluene afforded compound **C**. Compound **D** was prepared through bromination of **C** using NaBr/$NaBrO_3$, in which the reaction temperature was strictly controlled between 0 and 5 °C to reduce the generation of byproducts. Different substituted thiophenols or mercaptans were treated with sodium hydride in DMF and then reacted with **D** to afford the target compounds **1**−**23** in moderate yields (28−71%) via cyclization and substitution in one pot. The whole route has only four steps, much shorter than the route for previously reported oxazoline derivatives.[10,12]

Biological Activity. Table 1 shows acaricidal activities of the target compounds **1**−**23** and commercial etoxazole against eggs and larvae of spider mites (*T. Cinnabarinus*). The results indicated that all compounds exhibited good acaricidal activities. When the substituent at the para position of the 4-phenyl moiety was a benzo heterocyclic moiety (e.g., compounds **1**, **2**, and **3**), the activities of compounds **2** [bearing a (benzothiazol-2-yl)thiomethyl group] and **3** [bearing a (benzooxazol-2-yl)-thiomethyl group] against eggs and larvae of spider mites were slightly higher than those of **1** [bearing a (benzoimidazolyl)-thiomethyl group]. For compounds **4**−**9**, **12**, and **13**, the para position of the 4-phenyl group was substituted with a five-membered heterocyclic moiety; for example, compounds **5**−**7** and **9** bear a thiodiazole, thiazole, thiophene, and furan moiety, respectively, and showed better acaricidal activities than that of the others. For compounds **10** and **11**, the para position of the 4-phenyl moiety was substituted with a pyridinethiomethyl group and a pyrimidinethiomethyl group, respectively, and also displayed good activities. Compounds **15**−**21** bear a substituted benzene ring. The acaricidal activities of compound **15** (bearing an unsubstituted benzene ring) were near those of **14** which bears a naphthalene ring. Compounds bearing halogen (**16**, **17**, **19**, and **20**) or methoxy (**21**) on the benzene ring showed better activities than those of the compound bearing a methyl substituent (**18**) on the benzene ring; for **22** and **23** the para position of the 4-phenyl moiety was alkyl-substituted and also had excellent activity against eggs but had relatively poor activity against larvae.

Gernerally, all compounds exhibited better ovicidal activity than larvicidal activity. Compounds **2**, **3**, **6**, **7**, **10**, **11**, **16**, **17**, and **19**−**23** gave 100% mortality against eggs at 1 mg L^{-1}, so these compounds were further assayed at lower concentrations and LC_{50} values were calculated (Table 2). LC_{50} values of the target compounds **2** and **3**, substituted at the para position of 4-phenyl moiety with a (benzothiazole)thiomethyl group and (benzooxazole)thiomethyl group, respectively, were 0.0003 mg L^{-1} and 0.0037 mg L^{-1}, both lower than that of other heterocyclic aryl sulfide compounds and etoxazole (0.0089 mg L^{-1}). **6**, which bears a thiazole moiety, had better activity than **7**, which bears a thiophene. **11**, which bears a pyrimidinethiomethyl group, exhibited excellent activity (LC_{50} 0.0002 mg L^{-1}). Among the three compounds with a (para-substituted halogen)-phenylthiomethyl group, compound **17** (with a bromine atom at the para position of the phenyl, LC_{50} 0.0005 mg L^{-1}) and **19** (bearing a fluorine atom, LC_{50} 0.0008 mg L^{-1}) exhibited ovicidal activities higher than those of compound **16**, which bears a chloro atom (LC_{50} 0.0224 mg L^{-1}). Compounds **20** and **21**, which bear a bromine group and a methoxy group, respectively, at the ortho position of the phenyl, showed the same level of ovicidal activities (LC_{50} 0.0051 and 0.0043 mg L^{-1}, respectively). Moreover, LC_{50} values of compounds **22** and **23**, para substituted at 4-phenyl with a benzylthio methyl group and a *tert*-butylthio methyl group, respectively, were 0.0013 mg L^{-1} and 0.0056 mg L^{-1}, also lower than that of etoxazole.

Table 2. LC_{50} of Acaricidal Activity against Eggs of *T. cinnabarinus*

	activities (%) at concentration (mg L^{-1})				
compd	0.1	0.01	0.001	0.0001	LC_{50} (mg L^{-1})
2	97	90	53	45	0.0003 ± 0.0001
3	97	92	49	0	0.0037 ± 0.0009
6	95	51	30	0	0.0077 ± 0.0024
7	72	48	30	0	0.0223 ± 0.0048
10	80	45	0	0	0.0265 ± 0.0127
11	89	82	68	40	0.0002 ± 0.0001
16	83	66	0	0	0.0224 ± 0.0080
17	100	79	55	33	0.0005 ± 0.0001
19	74	64	50	42	0.0008 ± 0.0001
20	83	70	50	0	0.0051 ± 0.0010
21	85	72	55	0	0.0043 ± 0.0008
22	82	71	47	28	0.0013 ± 0.0009
23	82	66	49	0	0.0056 ± 0.0011
etoxazole	79	51	34	0	0.0089 ± 0.0028

The insecticidal activities of the target compounds **1**−**23**, and the control compound etoxazole, against oriental armyworm and mosquito larvae are listed in Table 3. The structure−activity relationship is different from that of acaricidal activity, and the structure−activity relationships between mosquito larvae and oriental armyworm are also different. It was found that

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Table 3. Insecticidal Activity of the Target Compounds against Oriental Armyworm and Mosquito

	activities (%) against oriental armyworm at concentration (mg L^{-1})			activities (%) against mosquito at concentration (mg L^{-1})			
compd	600	200	100	10	5	2	1
1	100	60	–	100	100	100	30
2	100	20	–	50	–	–	–
3	100	40	–	65	–	–	–
4	100	40	–	60	–	–	–
5	100	70	–	70	–	–	–
6	100	40	–	100	100	100	20
7	100	60	–	75	–	–	–
8	70	–	–	50	–	–	–
9	65	–	–	75	–	–	–
10	100	100	40	100	100	100	80
11	100	60	–	100	20	–	–
12	50	–	–	100	0	–	–
13	100	60	–	100	100	20	–
14	100	100	40	40	–	–	–
15	100	100	70	30	–	–	–
16	100	100	60	100	40	–	–
17	100	60	–	70	–	–	–
18	100	100	60	40	–	–	–
19	100	100	70	100	60	–	–
20	100	100	60	100	60	–	–
21	100	60	–	60	–	–	–
22	60	–	–	30	–	–	–
23	100	100	60	100	0	–	–
etoxazole	100	100	60	100	0	–	–

compounds **1**, **6**, **10**, **11**, and **13**, para substituted at 4-phenyl with a heterocyclic alkyl sulfide moiety, had insecticidal activities against mosquito much higher than that of etoxazole, whereas their activities against oriental armyworm were lower than that of etoxazole. By contrast, compounds **15**, **16**, **18**, **19**, **20**, and **23**, para substituted with an aryl alkyl sulfide moiety, showed the same level or slightly higher activities than that of etoxazole.

Combining the comprehensive analysis of bioactivity and LC_{50} values of the target compounds, compound **2**, which gave excellent acaricidal activity in the laboratory, was chosen to evaluate the acaricidal activity in the field (Table 4). One percent ECs of **2** and etoxazole were separately prepared and evaluated for the control of *P. latus* on eggplants in Jingzhou City (Hubei Province, South China), and *T. cinnabarinus* on eggplants in Tianjin City (North China). They were diluted to 10, 15, or 22 mg kg^{-1} before use, and equivalent amounts of solution were sprayed to each test field in the same site. It was shown that at a concentration of 22 mg kg^{-1}, **2** had a control effect much better than that of etoxazole against *P. latus*. The data of the field trial against *P. latus* in Jingzhou showed that, 1 day after the spray, the control efficiency of 1% **2** EC against *P. latus* at 22 mg kg^{-1} was 83%, whereas etoxazole was 75% under the same condition; 3 days after the spray, the control efficiency was 88% and 83%, respectively. This meant that the speed of action of **2** was faster than that of etoxazole. Seven days after the spray, the control efficiency of **2** was 90%, obviously much better than that of etoxazole (84%). The control efficiencies of **2** at 22 mg kg^{-1} were all greater than 80% after 1 day, 3 days, and 7 days spray, indicating that it had a certain control and persistent effect. Similarly, for *T. cinnabarinus* in Tianjin, **2** at concentrations of 10, 15, and 22 mg kg^{-1}, all showed an excellent control effect and persistent effect. Fourteen days after the spray, the control efficiency of **2** against *T. cinnabarinus* at 10 mg kg^{-1} still remained at 92%. It should be mentioned that in both of the field trials, **2** had no adverse effect on the growth of eggplants under all processing concentrations. Therefore, it was suggested that **2** showed a certain field application prospect.

In summary, a series of 2,4-diphenyl-1,3-oxazolines containing a sulfur ether moiety at the para position of the 4-phenyl group were designed and synthesized based on the SARs of etoxazole derivatives. Their acaricidal activities against eggs and larvae of *T. cinnabarinus* and insecticidal activities against oriental armyworm and mosquito larvae were tested. The results of the bioassay indicated that certain compounds displayed acaricidal activities higher than that of commercial etoxazole, especially against eggs of spider mites, and some compounds also showed insecticidal activity. So the modification of the substituents at the para site of the 4-phenyl moiety of 2,4-diphenyl-1,3-oxazolines influenced the acaricidal and insecticidal activity but with different structure−activity relationships. In the field trial, compound **2** exhibited acaricidal activity against both *T. cinnabarinus* and *P. latus* better than that of etoxazole at the same or lower concentrations, showing an excellent field application prospect.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.5b04126.

The physical data of compounds **B**, **C**, **D**, and target compounds **1**−**23** (PDF)

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Table 4. Effect of Acaricidal Program on Spider Mites in the Field in 2015

		% effect of **2**				% effect of etoxazole			
target and trial sites	dose mg kg^{-1}	1 day[c]	3 days[c]	7 days[c]	14 days[c]	1 day[c]	3 days[c]	7 days[c]	14 days[c]
P. latus on eggplant, Jingzhou, Hubei Province[a]	10	69	73	82	–	–	–	–	–
	15	71	80	85	–	–	–	–	–
	22	83	88	90	–	75	83	84	–
T. cinnabarinus on eggplant, Tianjin City[b]	10	67	84	94	92	–	–	–	–
	15	72	87	97	95	–	–	–	–
	22	75	90	97	96	77	91	91	88

[a]The amount sprayed is about 500 g ha^{-1}. [b]The amount sprayed is about 750 g ha^{-1}. [c]The number of days between spraying insecticides and investigating the effects.

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Notes

The authors declare no competing financial interest.

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