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Article

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Design, Synthesis, Acaricidal/Insecticidal Activity, and Structure-Activity Relationship (SAR) Studies of Novel Oxazolines Containing Sulfone/Sulfoxide Groups Based on the Sulfonylurea Receptor Protein Binding Site

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ABSTRACT

Enormous compounds containing sulfone/sulfoxide groups have been used in a variety of fields, especially in drug and pesticide design. To search for novel environmentally benign and ecologically safe pesticides with unique modes of action, a series of 2,4-diphenyl-1,3-oxazolines containing sulfone/sulfoxide groups as chitin synthesis inhibitors (CSI) were designed and synthesized, on the basis of sulfonylurea receptor protein (SUR) binding site for CSI. Their structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The acaricidal and insecticidal activities of the new compounds were evaluated. It was found that most of the target compounds displayed wonderful acaricidal activities against spider mite (*Tetranychus cinnabarinus*) larvae and eggs. Especially **I-4**, **II-3** and **II-4** displayed higher activities than commercial etoxazole at a concentration of 2.5 mg L^{-1}. And some target compounds exhibited insecticidal activities against lepidopteran pests. The present work demonstrated that these compounds containing sulfone/sulfoxide groups could be considered as potential candidates for the development of novel acaricides in the future.

KEYWORDS: 2,4-diphenyl-1,3-oxazoline, sulfone, sulfoxide, acaricidal/insecticidal activity, structure-activity relationship

INTRODUCTION

In the future human is still facing the problem of food, one of the most serious problems. In order to get the most food production, we have been trying our best to prevent and control the threats from weeds, pests, and diseases. Among these threats, the control of mites and insects is of extremely importance. Mites are small in size and have extremely short life cycle, powerful reproductive potential, wide hosts, and are easy to develop resistance, so mites are very difficult to prevent and control.[1-3] To cope with the serious challenge of insect resistance and stricter environmental regulation, scientists have been dedicated in innovating novel potent insecticides with new mechanisms of action and eco-friendly properties. The use of pesticides can bring numerous benefits and make a significant contribution to the lifestyles we have come to expect.

Sulfonylurea receptor (SUR) protein is one of the families of ATP-binding cassette transporter (ABC transporter).[4] So far, the crystal structure of SUR protein has not been parsed out. Antidiabetics glibenclamide and glipizide containing sulfone functional groups, are the second generation of sulfonylurea receptor inhibitor, defined a bipartite binding site in SUR (A site and B site). Of the molecules the sulfonylurea group was speculated to interact with site A, while the amide group associated with site B, presenting a "L" shape of the molecular conformation. The amino acid residues of SUR could possibly form hydrogen bonds with functional groups of the molecules, therefore SUR acts as hydrogen bond donors (**Figure 1**).[5] In 2004, Matsumura and co-workers by isotope labeling experiments found that the

benzoylurea insecticide diflubenzuron and antidiabetic glibenclamide both targeted SUR protein in *Drosophila melanogaster* and *Blattella germanica*; such binding made chitin not be biosynthesized normally.[6,7] In 2012, Leeuwen et al also utilized the technology of calcofluor white (CFW) staining to demonstrate that etoxazole indeed inhibited chitin biosynthesis in *T. urticae*.[8] According to the similarity in the action mechanism of the 2,4-diphenyl-1,3-oxazolines and benzoylureas, both belonging to chitin synthesis inhibitors (CSI),[9,10] our research group preliminarily determined the binding affinity of etoxazole and oxazoline derivatives to SUR in vitro by fluorescence polarization method, and found that the trend of their binding affinity was almost consistent with their acaricidal activities against *T. cinnabarinus* in vivo. Therefore, it was verified that oxazoline derivatives including etoxazole could bind with SUR then resulting in the inhibition of chitin biosynthesis in mite body.[11] We speculated the interaction between oxazoline derivatives and SUR was carried out possible by forming hydrogen bonds.

Most of sulfone/sulfoxide compounds possess a broad spectrum of bioactivities, such as insecticidal,[12] antifungal,[13,14] herbicidal,[15,16] antitumor,[17,18] anti-HIV-1[19] and antitubercular[20,21] activities et al, especially in the field of pesticides. For example, Aventis Company developed a sulfoxide insecticide named as fipronil (**Figure 1**) which possesses a broad spectrum of bioactivity against *Myzus persicae*, *Empoasca*, *Musca domestica*, larvae of lepidopteran and hymenopteran pests; Japanese Pesticide Co., Ltd. and Bayer Crop Science Company jointly developed a new sulfone-containing insecticide flubendiamide (**Figure 1**) as the first ryanodinne

receptor inhibitor which gave excellent larvicidal activity on lepidopteran pests, such as cotton bollworm. Sulfone/sulfoxide groups containing oxygen atom(s) which are good hydrogen bond acceptor. From this point, the introduction of sulfone/sulfoxide groups into certain insecticides might increase the binding property between the insecticide and potent receptor. Inspired by the above viewpoints, based on the molecular mechanism of action of oxazolines acaricides, we developed an idea that introducing sulfone/sulfoxide groups to oxazolines acaricides to increase the binding ability, then a series of 2,4-diphenyl-1,3-oxazolines containing sulfone/sulfoxide group at the para position of 4-phenyl were designed and synthesized. The acaricidal/insecticidal activities of these novel compounds were evaluated to test the idea, and the structure-activity relationships were analyzed.

MATERIALS AND METHODS

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

General Synthesis. The reagents were all analytically or chemically pure

purchased from commercial sources and were used as received. All anhydrous solvents were dried and distilled by standard techniques just before use. All the sulfides were prepared by the reaction of N-(1-(4-(bromomethyl)phenyl)-2-chloroethyl)-2,6-difluorobenzamide with thiophenol or mercaptan according to the literature method.[22] The synthetic route is given in **Figure 2**.

General Synthetic Procedure for the Target Compounds **I-1**–**I-13** and **II-1**–**II-9** (Figure 2).

Synthesis of 2-(2,6-difluorophenyl)-4-(4-((naphthalen-2-ylsulfonyl)methyl)phenyl)-4,5-dihydrooxazole (**I-1**). To a solution of 2-(2,6-difluorophenyl)-4-(4-((naphthalen-2-ylthio)methyl)phenyl)-4,5-dihydrooxazole (0.5 g, 1.16 mmol) in 20 mL dichloromethane was successively added trifluoroacetic acid (1.25 mL) and 30% hydrogen peroxide (0.5 mL, 3.94 mmol) at room temperature. The progress of the reaction was monitored by TLC until the reaction was complete. The reaction mixture was added sodium hydrogen sulfite (1.5 g, 14.42 mmol) and stirred for 1 h at room temperature to decompose excess hydrogen peroxide. The aqueous phase was separated and then extracted with dichloromethane twice. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered. After the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel and eluted with petroleum ether and ethyl acetate (v/v = 4:1) to give the target compound **I-1**.[23]

Compounds **I-2**−**I-13** were prepared according to the method used for compound **I-1**. The physical data in detail are included in the Supporting Information.

Synthesis of 2-(2,6-difluorophenyl)-4-(4-((naphthalen-2-ylsulfinyl)methyl)phenyl)-4,5-dihydrooxazole (**II-1**). To a solution of 2-(2,6-difluorophenyl)-4-(4-((naphthalen-2-ylthio)methyl)phenyl)-4,5-dihydrooxazole (0.42 g, 0.97 mmol) in dichloromethane (20 mL) under stirring was successively added glacial acetic acid (1.05 mL) and 30% hydrogen peroxide (0.4 mL, 3.15 mmol). The reaction mixture was monitored by TLC. Excess hydrogen peroxide was destroyed by adding 1.5 g sodium hydrogen sulfite and stirred for 1 h at room temperature. Then the organic phase was separated, and the aqueous phase was extracted by dichloromethane (2 ×20 mL). The organic layer was washed with saturated brine and dried with anhydrous sodium sulfate, then filtered. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel and eluted with petroleum ether and ethyl acetate (v/v = 1:1) to give the target compound **II-1**.[24]

Synthesis of 2-(2,6-difluorophenyl)-4-(4-(p-tolylsulfinylmethyl)phenyl)-4,5-dihydrooxazole (**II-2**). To a solution of 2-(2,6-difluorophenyl)-4-(4-(p-tolylthiomethyl)phenyl)-4,5-dihydrooxazole (0.43 g, 1.09 mmol) in 15 mL acetonitrile was added Dess-Martin Periodinane (0.46 g, 1.09 mmol). Then the reaction mixture was stirred at 0 °C for 0.5 h and slowly warmed to

room temperature. The progress of the reaction was monitored by TLC. The resulting mixture was added water, extracted with ethyl acetate (3 ×15 mL), the combined organic phase was washed with dilute hydrochloric acid, an aqueous sodium carbonate solution and saturated brine successively. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified by recrystallization using petroleum ether and ethyl acetate to give the target compound **II-2**.

Compounds **II-3**−**II-9** were synthesized by a method similar to that used for compound **II-1**. Their physical data are included in the Supporting Information.

Biological Assay. Detailed bioassay procedures for spider mites[25-30] and various insects[31-34] were discribed in published literature and are also included in the Supporting Information. According to statistical requirements each bioassay was repeated at least three times. The error of the experimments was 5%. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula. Evaluation were based on a percentage scale of 0−100, where 0 equals no activity and 100 equals total kill. For comparative purpose, etoxazole was tested under the same conditions.

RESULT AND DISCUSSION

Chemistry

Synthesis. Sulfides were obtained by the reaction of the key intermediate N-(1-(4-(bromomethyl)phenyl)-2-chloroethyl)-2,6-difluorobenzamide with thiophenol or mercaptan on the basis of the previous report. Both sulfones **I-1**–**I-13** and

sulfoxides **II-1**–**II-9** were synthesized from corresponding sulfides by oxidation with H_2O_2 but in the presence of different acid. Sulfone compounds (**I-1**–**I-13**) were prepared by oxidation of sulfides with H_2O_2/CF_3COOH;[23] the reaction occured at room temperature, and the raw material was disappeared quickly once hydrogen peroxide was added. Sulfoxide compounds (**II-1**–**II-9**) were prepared from sulfides by oxidation with H_2O_2/CH_3COOH; H_2O_2 was added under the ice bath, and the reaction need for the whole night to complete. The reaction required 3 equivalent of H_2O_2 as oxidant and CH_3COOH as catalyst to prevent over-oxidation; when using 1,2-dichloroethane as solvent, very little sulfone compound was detected by TLC when raw material was consumed completely. **II** could also be prepared by oxidation of corresponding sulfide with Deiss-Martin oxidant, but the yield of the reaction (**II-2** as an example) was not high.

Structure. There has a "prochirality" concept in ^{1}H-NMR spectra of sulfoxide compounds **II-1**–**II-9**. That is to say, sulfoxide compound contains a lone pair of electrons on the sulfur atom, so it is a chiral compound. Therefore the two hydrogen atoms on the CH_2 linked to sulfoxide group are chemical non-equivalent atoms and should give differnet chemical shift. To be specific, the CH_2 connected to sulfoxide group of **II-2** displays two duplicate peaks at 3.98 and 4.08 ppm in ^{1}H-NMR spectrum, with a coupling constant of 12.4 Hz. Correspondingly, this compound exhibits two set of peaks in ^{13}C-NMR spectrum. In contrast, there is no such situation in sulfone compounds. The CH_2 connected to sulfone group of **I-2** shows only a single peak in ^{1}H-NMR, and one set of peaks occur in ^{13}C-NMR spectrum.

177 Biological Activity and Structure-Activity Relationship. *Activities*
178 *against Spider Mite (T. cinnabarinus) Larvae.* The acaricidal activities of the
179 target compounds **I-1**–**I-13**, **II-1**–**II-9** and commercial etoxazole as the contrast
180 compound against the eggs and larvae of spider mite (*T. cinnabarinus*) were evaluated.
181 The results (Table 1) indicated that most of the target sulfones or sulfoxides possessed
182 excellent activities against *T. cinnabarinus* larvae. To be specific, compounds with a
183 4-halophenyl sulfonyl (**I-3**, **I-4**, **I-5**) or a sulfinyl (**II-3**, **II-4**, **II-5**) at the para site of
184 the 4-phenyl of 2,4-diphenyl-1,3-oxazolines all had good acaricidal activities;
185 componds **I-7** and **II-7** which had a 2-bromophenyl sulfonyl and a 2-bromophenyl
186 sulfinyl moiety, respectively, also had higher activities than 2-methoxyphenyl sulfonyl
187 and sulfinyl compounds **I-6** and **II-6**. Tertiary butyl sulfonyl derivative **I-8** and
188 tertiary butyl sulfinyl derivative **II-8** had higher activities than benzyl sulfonyl
189 compound **I-9** and benzyl sulfinyl compound **II-9**, although the substituents were all
190 alkyl moieties. Compounds with heterocyclic aryl sulfonyl at the para site of the
191 4-phenyl moiety of 2,4-diphenyl-1,3-oxazolines (**I-10**–**I-13**) did not have good
192 acaricidal activities against spider mite larvae at most concentrations, but **I-11**
193 exhibited comparable acaricidal activity as etoxazole at 1 mg L^{-1}. In all, compounds
194 **I-2**, **I-3**, **II-5**, **I-8** and **II-8** showed activities as high as etoxazole, whereas compounds
195 **II-3**, **I-4**, **II-4**, **I-5** and **II-7** exhibited a little higher activities. The LC_{50}, LC_{90} values
196 of compounds **II-3** and **II-4** are given in Table 2. Both compounds showed lower
197 concentrations than commercial etoxazole.

198 *Activities against Spider Mite (T. cinnabarinus) Eggs.* The results of

acaricidal activities given in Table 1 indicated that most of the target sulfone or sulfoxide compounds possessed moderate to excellent activities against *T. cinnabarinus* eggs. Compounds **I-1**, **II-1**, **I-2**, **II-3**, **II-4**, **I-5**, **II-5**, **II-7**, **I-8**, **II-8**, **II-9**, **I-10** and **I-11** showed the same level of mortality of *T. cinnabarinus* eggs as etoxazole, and compound **I-4** bearing a 4-fiuorophenyl sulfonyl at the para site of the 4-phenyl moiety exhibited higher activity than etoxazole: the mortality of **I-4** was 100%, 82% at 2.5 mg L^{-1} and 1 mg L^{-1}, respectivily, but etoxazole gave only 90% and 63% at the same concentrations. Whatever for larvae or eggs, when the subsitiuents attached to sulfonyl or sulfinyl were the same, some sulfones exhibited better acaricidal activities than sulfoxides, but some were on the contrary; no rules to follow. Among the compounds bearing heterocyclic aryl sulfonyl groups, **I-11** (bearing a benzothiazole sulfonyl) was the only compound whose activity was excellent against spider mite eggs. Then, the LC_{50}, LC_{90} values of compound **I-4** were tested and are given in Table 3, which showed the LC_{90} value of **I-4** was about two times lower than etoxazole.

It is worth mentioning that compounds **I-2**, **I-4**, **II-4**, **I-5**, **II-7**, **I-8** and **II-8** gave good activities against both spider mite eggs and larvae.

Insecticidal Activities against Lepidopteran Pests and Mosquito Larvae. Table 4 shows the insecticidal activities of the target compounds **I-1**–**I-13**, **II-1**–**II-9** and etoxazole against lepidopteran pests larvae (oriental armyworm, cotton bollworm and corn borer) and mosquito larvae,. It could be seen that most of the target compound exhibited certain insecticidal activities but were much lower than etoxazole, Nevertheless, there are still some compounds with good activities that could be found.

Compound **II-7** exhibited excellent activity against cotton bollworm and corn borer, higher than etoxazole. This compound also gave excellent activity against spider mite eggs and larvae. Compounds **I-5**, **I-7** and **I-11** showed higher activities against mosquito than etoxazole, although they only had moderate activities against the other three insects.

In summary, a series of 2,4-diphenyl-1,3-oxazolines containing sulfone/sulfoxide groups were designed and synthesized, on the basis of sulfonylurea receptor protein binding site for CSI. The results of the bioassay showed that whatever sulfones or sulfoxides they all exhibited considerable acaricidal activities against the eggs and larvae of spider mite. Especially **I-4** (containing a 4-fluorophenyl sulfonyl group at the para position of 4-phenyl) gave very high activity against spider mite eggs; the mortality was 82% at 1 mg L^{-1}. **II-3** and **II-4** (containing a 4-chlorophenyl and a 4-fluorophenyl sulfinyl group, respectively) showed excellent activity against spider mite larvae; the mortality was 87%, 83% at 1 mg L^{-1}, respectively, all better than etoxazole. We speculate sulfone/sulfoxide groups enhance the binding between the compound and target site, and fluorine atom can change charge distribution of the molecules, strengthen the lipotropy, which all are beneficial to the improvement of the activity. It indicated that based on the target site to design pesticide molecules is reasonable.

ASSOCIATED CONTENT

Supporting Information. The physical data of target compounds **I-1**–**I-13**, **II-1**–**II-9** can be found in Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Figure Captions

Figure 1 The Design of the Target Compounds.

Figure 2 General Synthetic Procedure for the Target Compounds **I-1**−**I-13** and **II-1**−**II-9** and Chemical Structures of the Target Compounds.

Figure 1

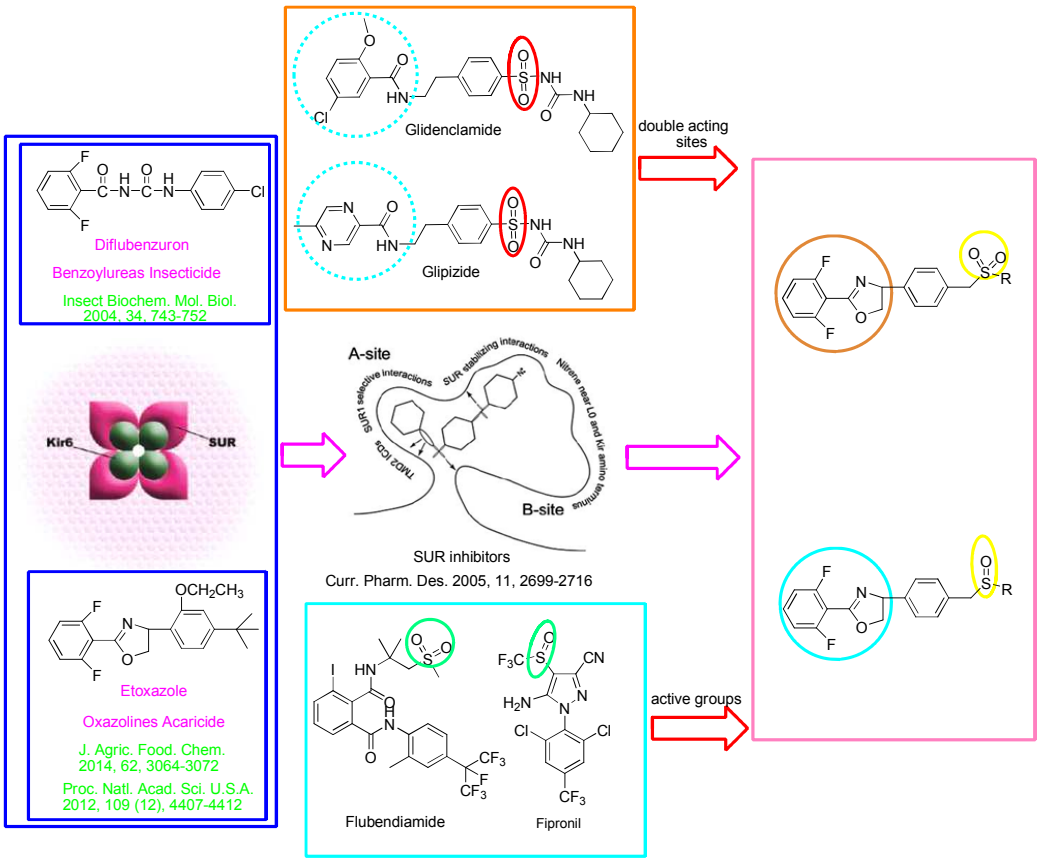
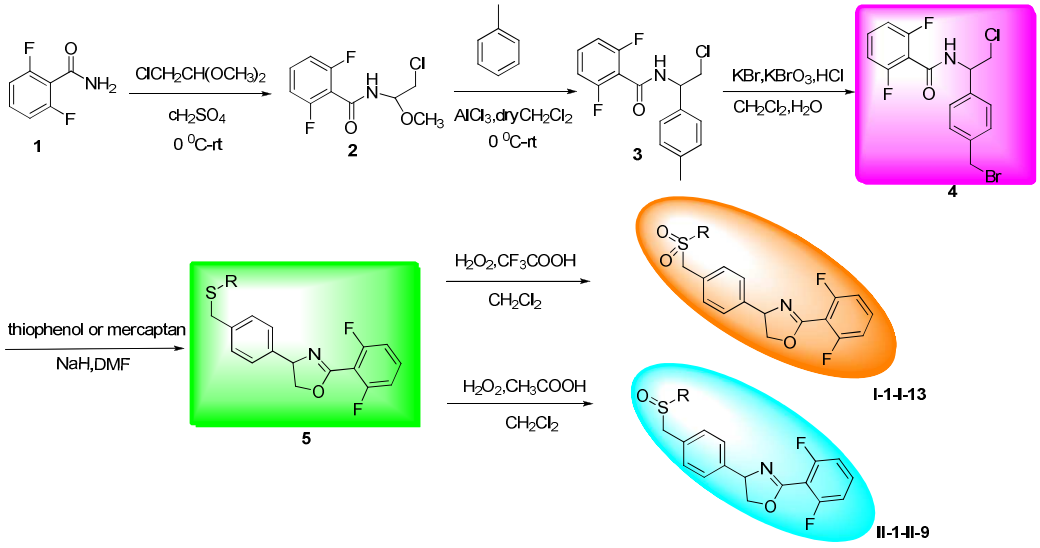
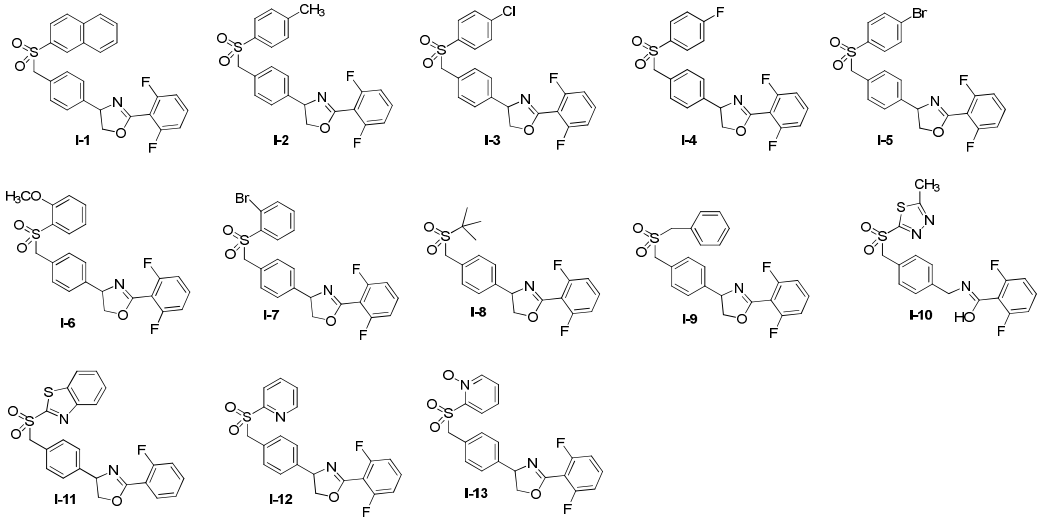

Diflubenzuron
Benzoylureas Insecticide
Insect Biochem. Mol. Biol. 2004, 34, 743-752
Kir6
SUR
Etoxazole
Oxazolines Acaricide
J. Agric. Food. Chem. 2014, 62, 3064-3072
Proc. Natl. Acad. Sci. U.S.A. 2012, 109 (12), 4407-4412
Glidenclamide
Glipizide
double acting sites
A-site
B-site
SUR inhibitors
Curr. Pharm. Des. 2005, 11, 2699-2716
Flubendiamide
Fipronil
active groups

Figure 2



Chemical structures of **I-1-I-13**



Chemical structures of **II-1-II-9**

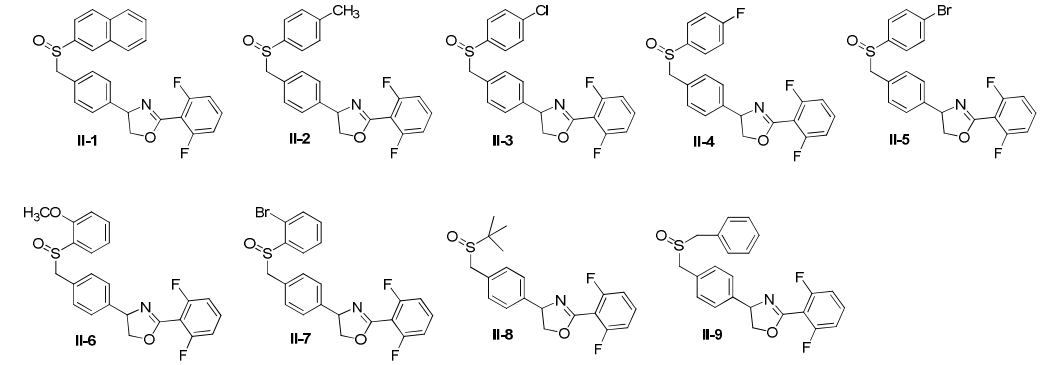


Table 1 Acaricidal Activities of the Target Compounds against Spider Mite

	Mortality (%) against larvae					Mortality (%) against eggs				
Conc. ($mg\ L^{-1}$)	100	50	25	2.5	1	100	50	25	2.5	1
I-1	100	87	75	66	53	100	100	100	95	67
II-1	100	89	80	73	49	100	100	100	93	63
I-2	100	100	100	88	79	100	100	100	93	73
II-2	100	89	80	71	68	94	86	73	61	49
I-3	100	100	100	89	78	100	100	84	78	51
II-3	100	100	100	96	87	100	100	89	75	66
I-4	100	100	100	91	80	100	100	100	100	82
II-4	100	100	100	96	83	100	100	100	89	67
I-5	100	100	100	95	86	100	100	100	91	64
II-5	100	100	100	87	76	100	89	77	75	66
I-6	85	73	60	44	—	100	100	88	51	40
II-6	89	76	61	57	48	100	100	100	84	50
I-7	100	100	86	36	—	100	100	84	72	30
II-7	100	100	100	93	88	100	100	100	94	63
I-8	100	100	100	89	78	100	100	100	89	67
II-8	100	100	100	91	79	100	100	100	92	65
I-9	100	78	69	54	—	100	83	74	62	43

II-9	93	84	79	64	23	100	100	100	90	67
I-10	100	85	64	50	—	100	100	89	75	71
I-11	100	92	83	79	77	100	100	100	93	63
I-12	90	76	68	57	36	100	92	82	73	45
I-13	94	89	79	76	72	100	89	77	41	—
Etoxazole	100	100	100	88	77	100	100	100	90	63

Table 2 LC_{50}, LC_{90} Values of **II-3**, **II-4**, and **Etoxazole** against Larvae of Spider Mite

compd	y=ax + b	LC_{50} (mg L^{-})	LC_{90} (mg L^{-})	correlation coefficient
II-3	y=2.24x + 5.85	0.42	1.55	0.9697
II-4	y=2.93x + 5.69	0.58	1.58	0.9770
Etoxazole	y=2.49x + 5.27	0.78	2.53	0.9841

Table 3 LC_{50}, LC_{90} Values of **I-4** and **Etoxazole** against Eggs of Spider Mite

compd	y=ax + b	LC_{50}(mg L^{-})	LC_{90}(mg L^{-})	correlation coefficient
I-4	y=6.20x + 6.15	0.65	1.05	0.9956
Etoxazole	y=2.43x + 5.32	0.74	2.48	1.0000

Table 4 Insecticidal Activities of the Target Compounds (Mortality, Percent)

compd	cotton bollworm (600 mg L^{-1})	corn borer (600 mg L^{-1})	oriental armyworm (600 mg L^{-1})	mosquito (10 mg L^{-1})
I-1	80	65	50	10
II-1	65	65	70	5
I-2	40	40	75	70
II-2	45	35	70	10
I-3	55	40	40	5
II-3	45	35	65	25
I-4	80	75	40	15
II-4	15	5	35	5
I-5	55	45	25	100/40[c]
II-5	75	65	70	10
I-6	35	25	70	5
II-6	50	45	80	25
I-7	55	50	10	100/100[c]/20[d]
II-7	100/100[a]/60[b]	100/100[a]/80[b]	30	70
I-8	45	40	15	25
II-8	65	55	80	5
I-9	35	30	75	50

II-9	25	10	45	20
I-10	40	30	50	10
I-11	65	65	50	100/60[c]
I-12	75	70	15	25
I-13	65	60	65	10
Etoxazole	100/100[a]/40[b]	100/100[a]/30[b]	100/100[a]/0[b]	100/0[c]

[a] Activities at 200 mg L^{-1}. [b] Activities at 100 mg L^{-1}. [c] Activities at 5 mg L^{-1}. [d] Activities at 2 mg L^{-1}.

TOC graphic

Agrochemical Bioregulators