JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Agricultural and Environmental Chemistry

Synthesis and Acaricidal/Insecticidal Activities Evaluation of Novel Oxazolines Containing Sul#liminyl Moieties and Derivatives

Xiuling Yu, Yu Zhang, Yuxiu Liu, Yongqiang Li, and Qingmin Wang

J. Agric. Food Chem., **Just Accepted Manuscript** • Publication Date (Web): 24 Mar 2019

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis and Acaricidal/Insecticidal Activities Evaluation of Novel Oxazolines Containing Sulfiliminyl Moieties and Derivatives

Xiuling Yu[1], Yu Zhang[1], Yuxiu Liu[1],* Yongqiang Li[1] and Qingmin Wang[1,2]*

[1] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China

[2]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China

* Corresponding authors. Tel: +86-(0)22-23503952; Fax: +86-(0)22-23503952; Qingmin Wang, E-mail: wangqm@nankai.edu.cn Yuxiu Liu, E-mail: liuyuxiu@nankai.edu.cn

ABSTRACT

Sulfimides and sulfoximines are highly relevant for medicinal chemistry and crop protection, as the resulting products can reveal interesting bioactivities. Herein, we report the design and synthesis of a series of novel 2,4-diphenyl-1,3-oxazolines containing sulfiliminyl and sulfoximinyl moieties. The acaricidal and insecticidal activities of the new compounds were evaluated and indicated that these compounds exhibited excellent acaricidal activities against spider mite larvae and eggs. The LC_{50} values of **6a-7**, **6b-3**, **6b-4**, **6c-2** and **6c-4** against larvae of spider mite were about 4 to 6 times lower than commercial insecticide etoxazole (0.0221 mg L^{-1}), and the LC_{50} value of **6a-4** against eggs of spider mite was 0.0006 mg L^{-1}, which was ten times lower than etoxazole (0.0063 mg L^{-1}). At the same time, most of the compounds showed insecticidal activity though their structure-activity relationships were different. Oxazolines containing N-cyano sulfiliminyl moiety at the *para* position of 4-phenyl group exhibited better insecticidal activities against cotton bollworm and corn borer than etoxazole, while the compounds containing groups derived from sulfiliminyl and sulfoximinyl had weak insecticidal activities. This research again proved that the substituent type at the *para* site of 4-phenyl moiety have a decisive role on its biological activity and insecticidal spectrum.

KEYWORDS: 2,4-diphenyl-1,3-oxazoline, etoxazole, sulfimides, sulfoximines acaricidal/insecticidal activity, structure-activity relationship

INTRODUCTION

Phytophagous mites are common pests on agricultural production. There are about dozens of phytophagous mites in our country, including the most destructive *Tetranychus urticae (Koch)*, and *Panonychus citri (Mcgregor)*; they mainly cause damage to crops such as cottons, vegetables, fruit trees, tea trees and wheats. Mites not only feed on plant juices, but also spread plant pathogens and viruses thus resulting in huge decrease in agricultural production.[1]

Now, the application of acaricides is still one of the effective methods to prevent and control agricultural spider mites. But the frequent use and misuse of acaricide caused more and more resistance of the mites.[2] In order to deal with the growing insect resistance problem, low toxic, highly efficient and environment friendly acaricides with unique structure and novel mechanism of action are still needed to continuously introduce to the market, which also is a difficult task and huge challenge for pesticide chemists.

Sulfimides ($R^1R^2S{=}NR$) and sulfoximines ($R^1R^2S(O){=}NR$) are mono-aza analogues of sulfoxides and sulfones, respectively. Sulfoximines have been applied with great success in asymmetric synthesis,[3] and more recently, much attention has been focused on their bioactive profiles in crop protection and drug development.[3-7] For example, sulfoximines can be modified at the nitrogen atom, which allows improving the solubility of the corresponding molecules.[8,9] Sulfoxaflor (Figure 1) aroused our interests in that it has a sulfoximine group linked to N-cyano and exhibited excellent insecticidal activities.[10] Sulfilimines, possessing a nitrogen substituent and a free

electron pair at the sulfur atom, are intermediates in the sulfoximine synthesis and have shown interesting insecticidal activities.[6b,11] Furthermore, sulfilimines should also be similar in properties to the corresponding sulfoximines but they have not been extensively examined for use in agrochemical research, except that some sulfiliminyl derivatives were reported to exhibit herbicidal properties.[12] The sulfilimine moiety was postulated to have a small hydrophilic core as well as a hydrogen bond acceptor site, thus when it was introduced into compounds, the novel structures might bring us unknown, interesting bioactivities.

Etoxazole (Figure 1) is the only commercial acaricides/insecticides belonging to the chemical class of 2,4-diphenyl-1,3-oxazolines. The acaricidal and insecticidal structure-activity relationships of etoxazole analogues showed that the substituent type at the *para* site of 4-phenyl moiety has a decisive role on their biological activities and insecticidal spectrum.[13,14] In 2015, we reported 2,4-diphenyl-1,3-oxazolines containing sulfur ether moiety which exhibited excellent acaricidal activities.[15] In consideration of the above viewpoints, a series of 2,4-diphenyl-1,3-oxazolines were designed by introducing the sulfiliminyl and sulfoximinyl group into the *para* position of 4-phenyl moiety, and the synthesis are shown in Figure 1. Their acaricidal/insecticidal activities were evaluated accordingly, and the structure-activity relationships were discussed.

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). InfraRed (IR) was conducted with a MAGNA-560 FTIR (Nicolet).

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 **5** were synthesized according to the method reported in our previous publication.[13] The synthetic route is given in Figure 2.

General Synthetic Procedure for the Target Compounds **6a**, **6b**, **6c**, **6d**, and **6e** (Figure 2).

Synthesis of 2-(2,6-difluorophenyl)-4-(4-((naphthalen-2-yl-N-cyanosulfilimidoyl)methyl)phenyl)-4,5-dihydrooxazole (**6a-1**). A mixture of 2-(2,6-difluorophenyl)-4-(4-((naphthalen-2-ylthio)methyl)phenyl)-4,5-dihydrooxazole (0.2 g, 0.46 mmol) and cyanamide (0.02 g, 0.51 mmol) in 20 mL of acetonitrile was cooled below 0 °C. To this solution was added iodobenzene diacetate (0.15 g, 0.46 mmol) all at once. The reaction mixture was allowed to stir below 0 °C for 10 min and slowly warmed to room temperature; the progress of the reaction was monitored

by TLC. Excess oxidant was destroyed by adding 5 mL of 2.5% aqueous sodium hydrogen sulfite, and then the solution was added dichloromethane and water. 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, and filtered. After the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to give the target compound **6a-1**.[16-19]

Compounds **6a-2**−**6a-10** were prepared according to the method used for compound **6a-1**. The physical data in detail are included in the Supporting Information.

Synthesis of 2-(2,6-difluorophenyl)-4-(4-(p-tolyl-N-trifluoroacetylsulfilimidoylmethyl)phenyl)-4,5-dihydrooxazole (**6b-2**). To a solution of 2-(2,6-difluorophenyl)-4-(4-(p-tolyl-N-cyanosulfilimidoylmethyl)phenyl)-4,5-dihydro oxazole (**6a-2**) (0.50 g, 1.15 mmol) in 20 mL dichloromethane, trifluoroacetic anhydride (TFAA) (0.72 g, 3.44 mmol) was added dropwise at room temperature. Then the reaction mixture was stirred continuously until the raw material disappeared (monitored by TLC). The resulting mixture was washed with water, the organic phase was separated, and the aqueous phase was extracted by dichloromethane (2 ×20 mL). The combined organic layer was washed with saturated brine and dried with anhydrous sodium sulfate, then filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with

petroleum ether and ethyl acetate (v/v = 3:1) to give the target compound **6b-2**.[20]

Compounds **6b-1**, **6b-3**−**6b-7**, **6b-9** were synthesized by a method similar to that used for compound **6b-2**. Their physical data are included in the Supporting Information.

Synthesis of 2-(2,6-difluorophenyl)-4-(4-(p-tolyl-NH-sulfoximidoyl methyl)phenyl)-4,5-dihydrooxazole (**6c-2**). A solution of 2-(2,6-difluorophenyl)-4-(4-(p-tolyl-N-trifluoroacetylsulfilimidoylmethyl)phenyl)-4,5 -dihydrooxazole (**6b-2**) (0.42 g, 0.83 mmol) in 20 mL ethanol was added 3-chloroperoxybenzoic acid (m-CPBA) at 0 °C. Potassium carbonate (0.34 g, 2.49 mmol) aqueous solution was added dropwise to the above mixture. The progress of the reaction was monitored by TLC until the reaction was complete. The reaction mixture was concentrated under reduced pressure. The resulting mixture was added dichloromethane and water, the organic phase was separated, and the aqueous phase was extracted by dichloromethane (2 ×20 mL). The combined organic layer was washed with saturated brine, dried with anhydrous sodium sulfate, and then filtered. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give the target compound **6c-2**.[21]

The synthesis procedure of **6c-1**, **6c-4** and **6c-5** was similar to that of compound **6c-2**. The physical data in detail are included in the Supporting Information.

Synthesis of 2-(2,6-difluorophenyl)-4-(4-(N-cyanosulfoximidoyl methyl)phenyl)-4,5-dihydrooxazole (**6d**). The synthesis procedure of compounds **6d-1**−**6d-5**, **6d-8**, **6d-9** was similar to that of compound **6c-2** using intermediate

133 **6a-1**−**6a-5**, **6a-8**, **6a-9**, respectively, as materials. Their physical data are included in
134 the Supporting Information.

135 Synthesis of 2-(2,6-difluorophenyl)-4-(4-(p-tolyl-N-carbamoylsulfoximidoyl
136 methyl)phenyl)-4,5-dihydrooxazole (**6e-2**). To a solution of
137 2-(2,6-difluorophenyl)-4-(4-(p-tolyl-N-cyanosulfoximidoylmethyl)phenyl)-4,5-dihydr
138 ooxazole (**6d-2**) (0.44 g, 0.97 mmol) in 20 mL dichloromethane, trifluoroacetic acid
139 (0.33 g, 2.91 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at
140 0 °C until the reactant disappeared (monitored by TLC). The resulting mixture was
141 washed with water. The organic phase was separated and then the aqueous phase was
142 extracted with dichloromethane twice. The combined organic layer was washed with
143 saturated brine, dried with anhydrous sodium sulfate, and then filtered. The solvent
144 was concentrated in vacuo, and the residue was purified by silica gel column
145 chromatography to give the target compound **6e-2**.[21]

146 The synthesis procedure of **6e-1**, **6e-3**−**6e-5** was similar to that of compound **6e–2**.
147 The physical data in detail can be found in the Supporting Information.

148 Biological Assay. Detailed bioassay procedures for spider mites[22-24] and various
149 insects[25,26] were carried out according to the published literature and can also be
150 found in the Supporting Information. According to statistical requirements each
151 bioassay was repeated at least three times. The error of the experimments was 5%.
152 Assessments were made on a dead/alive basis, and mortality rates were corrected
153 using Abbott's formula. Evaluation were based on a percentage scale of 0−100, where
154 0 equals no activity and 100 equals total kill. For comparative purpose, etoxazole was

tested under the same conditions.

RESULT AND DISCUSSION

Chemistry

Synthesis. A series of sulfides **5** were initially prepared according to the previously reported literature in moderate yields. The treatment of the sulfides with cyanamine as a nitrogen source and iodobenzene diacetate as an oxidant in acetonitrile led efficiently to corresponding N-cyanosulfilimines **6a** in considerable yields. However, when there is a heterocyclic ring connected with the sulfur atom in **5**, most of the oxidation step could not occur; only one compound **6a-10** was obtained, in which the sulfur atom was connected with a thiadiazole ring. It is worth mentioning that these novel compounds are much stable, as they are easily handled and stored for weeks at room temperature without degradation.

Then the N-cyanosulfilimidoyl group of **6a** was derived to provide more diverse groups. The replacement of cyano of the sulfiliminyl moiety with trifluoroacetyl group could bring changes in physical, chemical, and biological properties of the whole molecule.[25-30] So firstly N-trifluoroacetyl sulfilimines **6b** were synthesized by treating **6a** with trifluoroacetic anhydride (TFAA) at room temperature. But the product **6b-8** was not obtained using this method. This is probably because the steric hindrance of tertiary butyl is unfavorable factor for the synthesis.

Subsequently, we conducted the oxidation reaction of **6b**. Surprisingly, the oxidation of **6b** with m-CPBA didn't afford the desired N-trifluoroacetylsulfoximines, but afforded sulfoximine compounds **6c**. The compounds **6b** bearing a 4-phenyl group

177 at the sulfur atom all converted to the corresponding sulfoximines (**6c-1**, **6c-2, 6c-4**
178 and **6c-5**), while both compounds **6b-6** (bearing a 2-methoxylphenyl group) and **6b-7**
179 (bearing a 2-bromophenyl group) were not oxidized under the synthetic procedure
180 because of the ortho steric hindrance.

181 Direct oxidation of **6a** with m-CPBA could afford N-cyanosulfoximines **6d**.
182 Interestingly, the oxidation of **6a-6** and **6a-7** gave the same compound:
183 4-(2-(2,6-difluorophenyl)-4,5-dihydrooxazol-4-yl)benzaldehyde; it was reported that
184 the oxidation at sulfur is hindered by the adjacent ortho substituent and the removal of
185 the NCN group occurs in an unusual reductive transformation.[21] Finally,
186 N-cyanosulfoximines **6d** were treated with trifluoroacetic acid (TFA) in
187 dichloromethane under an ice bath to produce N-acylaminosulfilimines **6e**.

188 Structure. The novel structures of the target compounds have been identified by
189 ^{1}H NMR, ^{13}C NMR and HRMS. Since there are four different groups connected with
190 sulfur atom in each of the structures, the two hydrogen atoms on the methylene linked
191 to sulfur atom are chemical non-equivalent atoms and therefore give different
192 chemical shift in ^{1}H-NMR spectrum. Correspondingly, these compounds also exhibit
193 two sets of peaks in ^{13}C-NMR spectrum.

194 Biological Activity and Structure-Activity Relationship. *Activities
195 against Spider Mite (T. cinnabarinus) Eggs and Larvae.* The acaricidal
196 activities of the compounds **6a-6e** and etoxazole (as control) against the eggs and
197 larvae of spider mite (*T. cinnabarinus*) were tested and the data are listed in Table 1.
198 Most oxazolines **6a** (containing N-cyanosulfilimidoyl group) exhibited good to

199 excellent ovicidal and larvicidal activities. Compounds **6a-1** (containing
200 N-cyano-S-naphthylsulfilimidoyl group), **6a-2**−**6a-5** (containing
201 N-cyano-S-(4-substituted phenyl)sulfilimidoyl group), and **6a-8** (containing
202 N-cyano-S-t-butylsulfilimidoyl group) showed comparable ovicidal activities to that
203 of etoxazole. Especially, the mortality of **6a-4** (containing a
204 N-cyano-S-(4-fluorophenyl)sulfilimidoyl group) was 86% at the concentration of 0.01
205 mg/L, but etoxazole showed only a mortality of 67% at the same concentration.
206 Further test showed the LC_{50} value of **6a-4** (0.0006 mg L^{-1}) was about ten times lower
207 than etoxazole (0.0063 mg L^{-1}) (Table 2). The ovicidal activities of compound **6a-7**
208 (containing N-cyano-S-2-brominephenyl sulfilimidoyl) were much better than that of
209 compound **6a-6** (containing N-cyano-S-2-methoxylphenyl sulfilimidoyl), and both of
210 them had higher larvicidal activities than etoxazole.

211 Other oxazolines (**6b**−**6e**) derived from corresponding **6a** also exhibited excellent
212 acaricidal activities, but with no obvious structure-activity relationships.

213 In N-trifluoroacetylsulfilimines **6b**, the larvicidal activities of compounds **6b-3**
214 **(**containing 4-chlorophenyl) on sulfur atom and **6b-4 (**containing 4-flluorophenyl)
215 were much better than etoxazole, and **6b-2**, **6b-5, 6b-7** and **6b-9** also displayed good
216 larvicidal activity. Meanwhile, the ovicidal activities of **6b-4** and **6b-7 (**containing
217 2-brominephenyl**)** on sulfur atom were as good as etoxazole. The activities of
218 NH-sulfoximines **6c** against mite eggs were not as good as etoxazole, but the
219 activities against mite larvae of compounds **6c-2** (containing 4-methylphenyl on sulfur
220 atom) and **6c-4** (containing 4-flluorophenyl) were higher than etoxazole.

N-cyanosulfoximine **6d-4** containing 4-flluorophenyl on sulfur atom had good activities against both mite eggs and larvae. The acaricidal activities of N-carbamoyl-sulfoximines **6e-4** and **6e-5** were pretty good. N-trifluoroacetylsulfilimine **6b-4**, NH-sulfoximine **6c-4**, N-cyanosulfoximine **6d-4**, and N-carbamoyl-sulfoximine **6e-4** containing 4-fluorophenyl all showed wonderful acaricidal activities against mite both eggs and larvae, while **6b-5**, **6c-5**, **6d-5** and **6e-5** containing 4-brominephenyl exhibited better larvicidal activities but weaker ovicidal activities. The LC_{50}, LC_{90} values of compounds **6a-7**, **6b-3**, **6b-4**, **6c-2** and **6c-4** against larvae of spider mite are given in Table 3. These compounds showed lower concentrations than commercial etoxazole. LC_{50} of **6c-2** was 0.0039 mg L^{-1}, much lower than etoxazole (0.0221 mg L^{-1}).

Insecticidal Activities against Lepidopteran Pests and Mosquito Larvae. The insecticidal activities of the target compounds **6a−6e** and etoxazole against mosquito larvae and lepidopteran pests larvae (oriental armyworm, cotton bollworm and corn borer) are listed in Tables 4 and 5. As shown in Tables, most compounds exhibited more or less insecticidal activities at the preliminary screening concentration. The inhibitory activities of **6b**, **6c**, **6d**, **6e** series were superior to **6a** series and etoxazole for mosquito larvae, but were weaker than **6a** series compounds and etoxazole for cotton bollworm and corn borer. Compounds **6c-1**、**6d-1**、**6e-1**、**6d-3** and **6c-4** exhibited excellent activities against mosquito larvae; among these compounds, **6d-1** and **6e-1** showed a morality of 60% and 20% at 0.5 mg/L, respectively; the moralities of **6d-3** and **6c-4** were 20% and 60% at 0.25 mg/L

243 respectively; etoxazole gave a death rate of only 20% at 2 mg/L. Compounds **6a-4**
244 and **6a-5** displayed 50% and 40% insecticidal activities against cotton bollworm, 40%
245 and 60% insecticidal activities against corn borer at the concentration of 100 mg/L,
246 but etoxazole only showed insecticidal activities of 40% and 35% against cotton
247 bollworm and corn borer respectively.

248 In summary, by introducing N-cyanosulfiliminyl moieties into
249 2,4-diphenyl-1,3-oxazolines and further derivation steps, a series of novel oxazoline
250 derivatives with sulfilimine functional groups were designed and synthesized. Their
251 acaricidal activities against spider eggs and larvae, insecticidal activities against
252 oriental armyworm, cotton bollworm, corn borer and mosquito larvae were evaluated.
253 The bioassay results of N-cyano sulfilimine oxazolines indicated that compounds
254 **6a-1**−**6a-10** exhibited good to excellent acaricidal activities, among them compound
255 **6a-4** (containing a N-cyano-S-(4-fluorophenyl)sulfilimidoyl group) displayed highest
256 morality against eggs, the LC_{50} value (0.0006 mg L^{-1}) was about ten times lower than
257 etoxazole (0.0063 mg L^{-1}); the LC_{50} of the acaricidal activity against spider larvae of
258 compound **6a-7** (containing 2-brominephenyl on sulfur atom) was 0.0056 mg L^{-1},
259 also much lower than etoxazole (0.0221 mg L^{-1}); especially compounds **6a-5**, **6a-6**,
260 **6a-7** gave outstanding acaricidal activities against both spider eggs and larvae. In **6b**、
261 **6c**、**6d**、**6e** series, compounds **6b-3**, **6b-4**, **6c-2** and **6c-4** had much better larvicidal
262 activities than etoxazole; their LC_{50} values were 0.0058 mg L^{-1}, 0.0055 mg L^{-1}, 0.0039
263 mg L^{-1}, 0.0041 mg L^{-1} respectively. The insecticidal activities of **6a** series compounds
264 showed that the target compounds displayed excellent activities against cotton

bollworm and corn borer, but the activities against oriental armyworm and mosquito larvae were weak. **6b**, **6c**, **6d**, **6e** series compounds all showed wonderful insecticidal activities against mosquito larvae. It was further concluded that the present research indicated that the introduction of sulfiliminyl moieties into the 2,4-diphenyl-1,3-oxazolines maintained or improved biological activities. Some of the target compounds might be potential candidates for further investigation.

ASSOCIATED CONTENT

Supporting Information. The physical data of target compounds **6a-1−6a-10, 6b-1−6b-7, 6b-9, 6c-1−6c-2, 6c-4−6c-5, 6d-1−6d-5, 6d-8−6d-9, 6e-1−6e-5** can be found in Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

Phone: +86-(0)22-23503952. Fax: +86-(0)22-23503952. Qingmin Wang, E-mail: wangqm@nankai.edu.cn; Yuxiu Liu, E-mail: liuyuxiu@nankai.edu.cn

Funding Sources

This work was supported by the National Key Research and Development Program of China (No. 2016YFD0300708) and the National Natural Science Foundation of China (21772102).

Notes

The authors declare no competing financial interest.

287 REFERENCES

288 (1) Van Leeuwen, T.; Vontas, J.; Tsagkarakou, A.; Dermauw, W.; Tirry, L. Acaricide
289 resistance mechanisms in the two-spotted spider mite Tetranychus urticae and
290 other important Acari: a review. *Insect Biochem. Mol. Biol.* **2010**, *40*, 563–572.
291 (2) Croft, B. A.; van de Baan, H. E. Ecological and genetic factors influencing
292 evolution of pesticide resistance in tetranychid and phytoseiid mites. *Exp. Appl.*
293 *Acarol.* **1988**, *4*, 277–300.
294 (3) a) Johnson, C. R. Utilization of sulfoximines and derivatives as reagents for
295 organic synthesis. *Acc. Chem. Res.* **1973**, *6*(10), 341–347.
296 b) Reggelin, M.; Zur, C. Sulfoximines: Structures, properties and synthetic
297 applications. *Synthesis* **2000**, *2000*(1), 1–64.
298 c) Okamura, H.; Bolm, C. Sulfoximines: synthesis and catalytic applications. *Chem.*
299 *Lett.* **2004**, *33*, 482–487.
300 d) Bentley, R. Role of sulfur chirality in the chemical processes of biology. *Chem. Soc.*
301 *Rev.* **2005**, *34*, 609–624.
302 e) Bolm, C. in: Asymmetric synthesis with chemical and biological methods, (Eds.: D.
303 Enders, K.-E. Jaeger), Wiley-VCH, Weinheim, **2007**, pp 149–176.
304 f) Gais, H.-J. Development of new methods for asymmetric synthesis based on
305 sulfoximines. *Heteroat. Chem.* **2007**, *18*, 472–481.
306 g) Worch, C.; Mayer, A. C.; Bolm, C. in: Organosulfur chemistry in asymmetric
307 synthesis, (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, pp 209–229.
308 h) Bizet, V.; Kowalczyk, R.; Bolm, C. Fluorinated sulfoximines: syntheses, properties

and applications. *Chem. Soc. Rev.* **2014**, *43*, 2426–2538.

i) Hendriks, C. M. M.; Nürnberg, P.; Bolm, C. Zolimidine Analogues: The synthesis of imidazo[1,2-α]pyridine-based sulfilimines and sulfoximines. *Synthesis* **2015**, *47*, 1190–1194.

j) Hendriks, C. M. M.; Bohmann, R. A.; Bohlem, M.; Bolm, C. N-Alkylations of NH-Sulfoximines and NH-Sulfondiimines with alkyl halides mediated by potassium hydroxide in dimethyl sulfoxide. *Adv. Synth. Catal.* **2014**, *356*, 1847–1852.

(4) a) Zhu, Y.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. Discovery and characterization of sulfoxaflor, a novel insecticide targeting sap-feeding pests. *J. Agric. Food Chem.* **2011**, *59*(7), 2950–2957.

b) Babcock, J. M.; Gerwick, C. B.; Huang, J. X.; Loso, M. R.; Nakamura, G.; Nolting, S. P.; Rogers, R. B.; Sparks, T. C.; Thomas, J.; Watson, G. B.; Zhu, Y. M. Biological characterization of sulfoxaflor, a novel insecticide. *Pest Manag. Sci.* **2011**, *67*(3), 328–334.

c) Watson, G. B.; Loso, M. R.; Babcock, J. M.; Hasler, J. M.; Letherer, T. J.; Young, C. D.; Zhu, Y.; Casida, J. E.; Sparks, T. C. Novel nicotinic action of the sulfoximine insecticide sulfoxaflor. *Insect. Biochem. Mol. Biol.* **2011**, *41*, 432–439.

d) Sparks, T. C.; Loso, M. R.; Watson, G. B.; Babcock, J. M.; Kramer, V. J.; Zhu, Y.; Nugent, B. M.; Thomas, J. D. in: Modern crop protection compounds, 2nd edn., Vol. 3, (Eds.: W. Kraemer, U. Schirmer, P. Jeschke, M. Witschel), Wiley-VCH, Weinheim,

2012, pp 1226–1237.

e) Park, S. J.; Baars, H.; Mersmann, S.; Buschmann, H.; Baron, J. M.; Amann, P. M.; Czaja, K.; Hollert, H.; Bluhm, K.; Redelstein, R.; Bolm, C. N-Cyano sulfoximines: COX inhibition, anticancer activity, cellular toxicity, and mutagenicity. *ChemMedChem* **2013**, *8*, 217–220.

(5) a) Lücking, U. Sulfoximines: a neglected opportunity in medicinal chemistry. *Angew. Chem. Int. Ed.* **2013**, *52*(36), 9399–9408.

b) Christine, V. B.; Hendriks, M. M.; Bolm, C. Sulfur imidations: access to sulfimides and sulfoximines. *Chem. Soc. Rev.* **2015**, *44*, 3378–3390.

(6) a) Gnamm, C.; Jeanguenat, A.; Dutton, A. C.; Grimm, C.; Kloer, D. P.; Crossthwaite, A. J. Novel diamide insecticides: sulfoximines, sulfonimidamides and other new sulfonimidoyl derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22(11)*, 3800–3806.

b) Bland, D. C.; Ross, R. Jr.; Johnson, P. L.; Johnson, T. C. Insecticidal N-substituted sulfilimine and sulfoximine pyridine N-oxides. U.S. Patent 20140005234, **2014**.

(7) a) Foote, K. M.; Wilhelmus, J.; Nissink, M.; Turner, P. Morpholino pyrimidines and their use in therapy. W.O. Patent 2011154737, **2011**.

b) Lücking, U.; Boehnke, N.; Scholz, A.; Lienau, P.; Siemeister, G.; Boemer, U.; Kosemund, D.; Bohlmann, R. N-(pyridine-2-yl)pyrimidin-4-amine derivatives containing a sulfoximine group. W.O. Patent 2014076111, **2014**.

(8) Lücking, U.; Jautelat, R.; Krüger, M.; Brumby, T.; Lienau, P.; Schäfer, M.; Briem, H.; Schulze, J.; Hillisch, A.; Reichel, A.; Wengner, A. M.; Siemeister, G. The Lab

Oddity Prevails: Discovery of Pan-CDK inhibitor (*R*)-*S*-cyclopropyl-*S*-(4-{[4-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)sulfoximide (BAY 1000394) for the Treatment of Cancer. *ChemMedChem* **2013**, *8*(7), 1067–1085.

(9) Goldberg, F. W.; Kettle, J. G.; Xiong, J.; Lin, D. G. General synthetic strategies towards *N*-alkyl sulfoximine building blocks for medicinal chemistry and the use of dimethylsulfoximine as a versatile precursor. *Tetrahedron* **2014**, *70*(37), 6613–6622.

(10) Zhu, Y. M.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. Discovery and characterization of sulfoxaflor, a novel insecticide targeting sap-feeding pests. *J. Agric. Food Chem*. **2011**, *59*(7), 2950–2957.

(11) a) Zhou, S.; Gu, Y. C.; Liu, M.; Wu, C. C.; Zhao, Y.; Jia, Z. H.; Wang, B. L.; Xiong, L. X.; Yang, N.; Li, Z. M. Insecticidal activities of chiral *N*-trifluoroacetyl sulfilimines as potential ryanodine receptor modulators. *J. Agric. Food Chem.* **2014**, *62*(46), 11054–11061.

b) Zhou, S.; Yan, T.; Li, Y. X.; Jia, Z. H.; Wang, B. L.; Zhao, Y.; Qiao, Y. Y.; Xiong, L. X.; Li, Y. Q.; Li, Z. M. Novel phthalamides containing sulfiliminyl moieties and derivatives as potential ryanodine receptor modulators. *Org. Biomol. Chem.* **2014**, *12*, 6643–6652.

(12) Furukawa, N.; Oae, S. Sulfilimines. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 260–270.

(13) Suzuki, J.; Ishida, T.; Shibuya, I.; Toda, K. Development of a new acaricide, Etoxazole. *J. Pestic. Sci.* **2001**, *26*, 215–223.

(14) Suzuki, J.; Ishida, T.; Kikuchi, Y.; Morikawa, C.; Tsukidate, Y.; Tanji, I.; Ota, Y.; Toda, K. Synthesis and activity of novel acaricidal/insecticidal 2,4-diphenyl-1,3-oxazolines. *J. Pestic. Sci.* **2002**, *27*, 1–8.

(15) Yu, X. L.; Liu, Y. X.; Li, Y. Q.; Wang, Q. M. Design, synthesis, and acaricidal/insecticidal activities of oxazoline derivatives containing a sulfur ether moiety. *J. Agric. Food Chem.* **2015**, *63*, 9690–9095.

(16) Loso, M. R.; Nugent, B. M.; Huang, J. X.; Rogers, R. B.; Zhu Y.; Rogers, R. B.; et al. Preparation of insecticidal N-substituted (6-haloalkylpyridin-3-yl) alkyl sulfoximines. WO 2007095229, **2007**.

(17) Podhorez, D. E.; Ross, R., Jr.; McConnell, J. R. Process for the preparation of certain substituted sulfilimines. U.S. 20080207910, **2008**.

(18) Bland, D. C.; Adaway, T. J.; Podhorez, D. E. Process for the preparation of certain substituted sulfilimines. U.S. 819322, **2012**.

(19) Huang, J. X.; Rogers, R. B.; Orr, N.; Sparks, T. C.; Clifford, J. M.; Loso, M. R.; Zhu Y.; Meade, T. A method to control insects resistant to common insecticides. WO 2007149134, **2007**.

(20) García Mancheno, O.; Bistri, O.; Bolm, C. Iodine and metal-free synthesis of N-cyano sulfilimines: novel and easy access of NH sulfoximines. *Org. Lett.* **2007**, *9*, 3809−3811.

(21) Barry, N.; Brondel, N.; Lawrence, S. E.; Maguire, A. R. Synthesis of aryl benzyl

397 *N*H-sulfoximines. *Tetrahedron* **2009**, *65*, 10660–10670.

398 (22) Sun, R. F.; Li, Y. Q.; Xiong, L. X.; Liu, Y. X.; Wang, Q. M. Design, synthesis,

399 and insecticidal evaluation of new benzoylureas containing isoxazolines and isoxazole

400 group. *J. Agric. Food Chem.* **2011**, *59*, 4851–4859.

401 (23) Kuhn, D. G.; Kameswaran, V. Insecticidal, acaricidal and molluscicidal

402 1-(substituented)thioalkylpyrroles. U.S. Patent 5302383, **1993**.

403 (24) Wang, Y. J.; Ou, X. M.; Pei, H.; Lin, X. M.; Yu, K. Toxicities of novel

404 insecticide chlorfenpyr against several insects in lab. *Agrochem. Res. Appl.* **2006**, *10*,

405 20–23.

406 (25) Hsu, A. C.; Murphy, R. A.; Aller, H. E.; Hamp, D. W.; Weinstein, B. Insecticidal

407 N'-substituented-N,N'-disubstituentedhydrazines. U.S. Patent 5117057, **1992**.

408 (26) Chen, L.; Huang, Z. Q.; Wang, Q. M.; Shang, J.; Huang, R. Q.; Bi, F. C.

409 Insecticidal benzoylphenylurea-S-carbamate: a new propesticide with two effects of

410 both benzoylphenylureas and carbamates. *J. Agric. Food Chem.* **2007**, *55*, 2659–2663.

411

Figure Captions

Figure 1 The Design of the Target Compounds.

Figure 2 General Synthetic Procedure for the Target Compounds **6a−6e**. Reagent and conditions: (a) $PhI(OAc)_2$, NH_2CN, CH_3CN, 0 °C to rt, (b) $(CF_3CO)_2O$, CH_2Cl_2, 0 °C to rt, (c) m-CPBA, K_2CO_3, EtOH, 0 °C to rt, (d) CF_3COOH, CH_2Cl_2, ice bath.

Figure 1

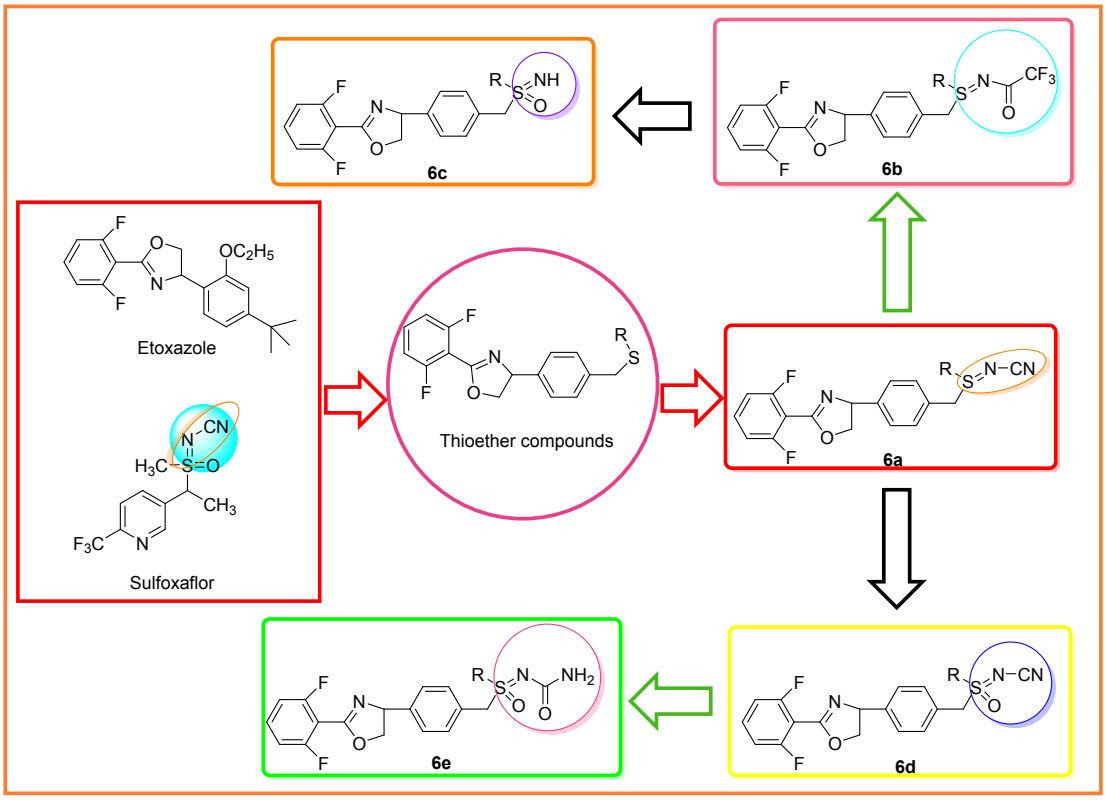
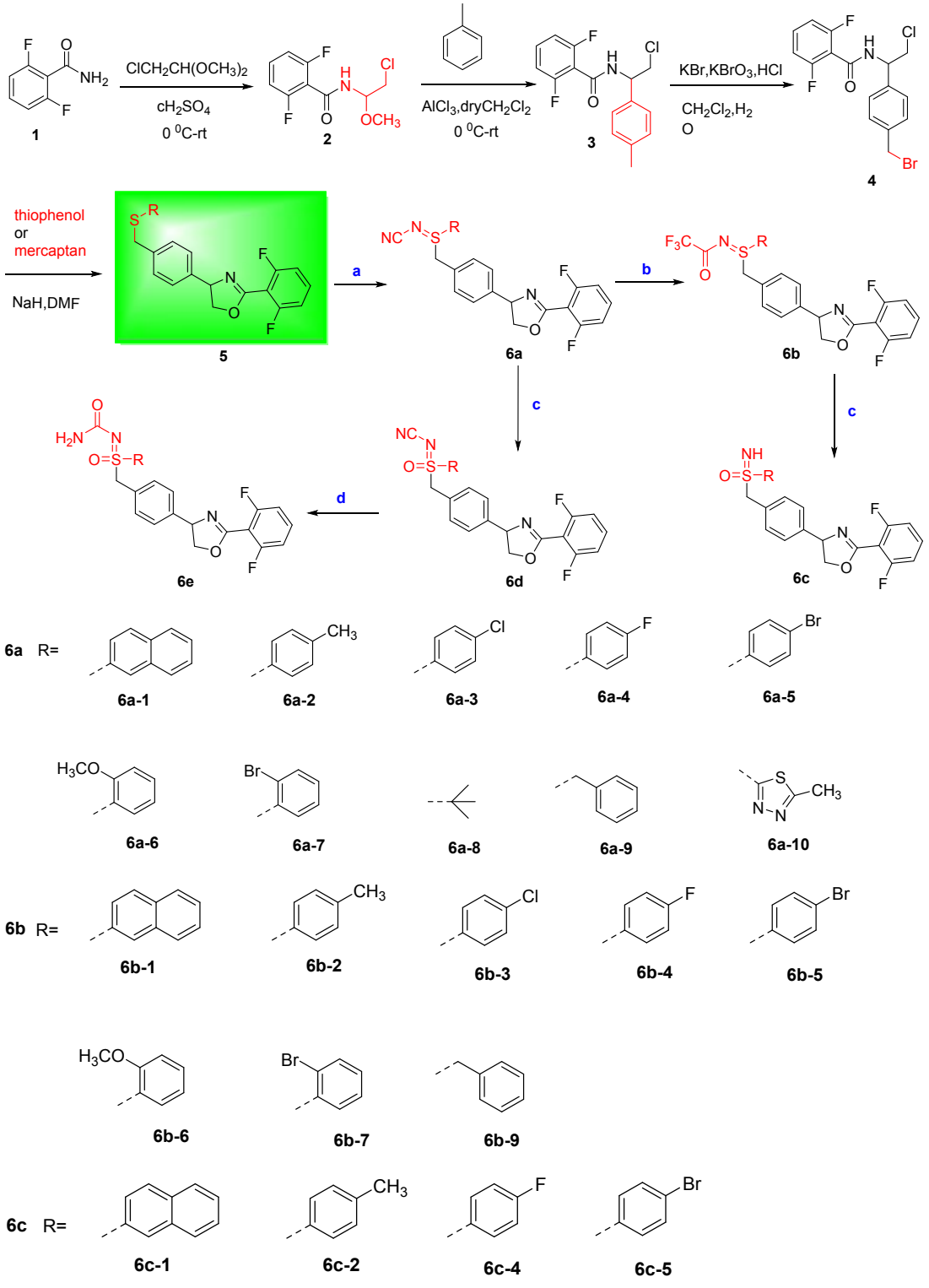


Figure 2


ClCH2CH(OCH3)2
cH2SO4
0 0C-rt
AlCl3,dryCH2Cl2
0 0C-rt
KBr,KBrO3,HCl
CH2Cl2,H2O
thiophenol
or
mercaptan
NaH,DMF
a
b
c
d
1
2
3
4
5
6a
6b
6c
6d
6e
6a R=
6a-1
6a-2
6a-3
6a-4
6a-5
6a-6
6a-7
6a-8
6a-9
6a-10
6b R=
6b-1
6b-2
6b-3
6b-4
6b-5
6b-6
6b-7
6b-9
6c R=
6c-1
6c-2
6c-4
6c-5

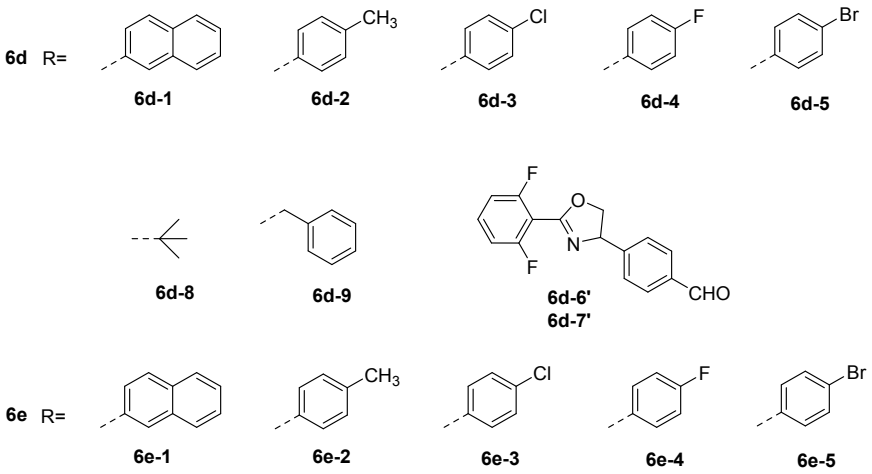


Table 1 Acaricidal Activities of the Target Compounds against Spider Mite

compd	activities (%) against eggs at concentration (mg L^{-1})	activities (%) against larvae at concentration (mg L^{-1})

	100	50	25	2.5	1	0.1	0.01	100	50	25	2.5	1	0.1	0.01
6a-1	100	100	100	100	91	83	52	100	100	100	94	88	72	65
6a-2	100	100	100	90	83	72	61	100	100	91	84	64	48	21
6a-3	100	100	100	96	88	79	51	100	100	100	95	89	76	50
6a-4	**100**	**100**	**100**	**100**	**100**	**100**	**86**	100	100	100	83	67	52	—
6a-5	100	100	100	100	100	89	50	100	100	100	100	81	69	55
6a-6	100	100	90	79	67	54	0	100	100	100	100	96	88	66
6a-7	100	100	100	100	100	90	48	**100**	**100**	**100**	**100**	**100**	**81**	**69**
6a-8	100	100	100	100	95	88	56	100	100	100	86	78	69	54
6a-9	100	92	81	73	67	49	0	100	100	90	79	63	48	27
6a-10	100	100	92	79	66	54	36	100	100	100	92	87	75	63
6b-1	100	100	100	100	93	82	79	100	100	100	93	88	67	59
6b-2	100	100	100	95	89	77	30	100	100	100	100	86	79	61
6b-3	100	100	100	100	93	67	49	**100**	**100**	**100**	**100**	**100**	**84**	**74**
6b-4	100	100	100	100	100	82	71	**100**	**100**	**100**	**100**	**100**	**81**	**77**
6b-5	100	100	93	85	76	62	51	100	100	100	100	96	86	74
6b-6	100	100	100	90	77	61	51	100	100	91	84	75	69	49
6b-7	100	100	100	100	100	85	71	100	100	100	100	91	78	53
6b-9	100	100	100	93	85	70	43	100	100	100	100	92	84	79
6c-1	100	100	100	92	85	75	64	100	100	100	91	79	62	47
6c-2	100	100	100	93	80	76	66	**100**	**100**	**100**	**100**	**100**	**87**	**70**
6c-4	100	100	100	100	87	76	69	**100**	**100**	**100**	**100**	**100**	**89**	**66**
6c-5	100	100	100	100	92	87	63	100	100	100	100	96	81	55
6d-1	100	100	100	100	93	88	61	100	100	100	92	78	61	50
6d-2	100	100	88	72	61	49	17	100	94	86	77	61	44	31
6d-3	100	100	100	91	82	71	64	100	100	92	80	71	63	58
6d-4	100	100	100	100	100	86	76	100	100	100	100	90	77	72
6d-5	100	100	100	100	89	74	56	100	100	100	100	93	79	59
6d-8	100	100	100	100	93	81	62	100	100	100	90	83	75	68
6d-9	100	100	100	87	79	60	39	100	100	100	90	83	72	60
6e-1	100	100	94	82	63	46	30	100	100	100	89	83	76	61
6e-2	100	100	100	95	83	72	59	100	100	100	93	81	72	60
6e-3	100	100	94	78	61	53	48	100	100	100	100	89	76	68
6e-4	100	100	100	100	100	85	63	100	100	100	100	89	76	54
6e-5	100	100	100	100	100	88	79	100	100	100	100	95	82	70
Etox-azole	100	100	100	100	100	84	67	100	100	100	100	85	67	49

Table 2 LC_{50}, LC_{90} Values of **6a-4** and Etoxazole against Eggs of Spider Mite

compd	y=ax + b	LC_{50}(mg L^{-1})	LC_{90}(mg L^{-1})	correlation coefficient

6a-4	y=1.47x + 9.77	0.0006	0.0043	0.9655
Etoxazole	y=2.43x + 5.32	0.0063	0.0455	0.9437

Table 3 LC_{50}, LC_{90} Values of **6a-7**, **6b-3**, **6b-4**, **6c-2**, **6c-4**, and Etoxazole against Larvae of Spider Mite

compd	y=ax + b	LC_{50} (mg L^{-1})	LC_{90} (mg L^{-1})	correlation coefficient
6a-7	y=1.40x + 8.17	0.0056	0.0452	0.9466
6b-3	y=1.46x + 8.27	0.0058	0.0434	0.9580
6b-4	y=1.42x + 8.22	0.0055	0.0434	0.9447
6c-2	y=1.33x + 8.21	0.0039	0.0357	0.9533
6c-4	y=1.35x + 8.24	0.0041	0.0358	0.9606
Etoxazole	y=0.66x + 6.10	0.0221	1.8293	0.9855

Table 4 Insecticidal Activity of the Target Compounds against Mosquito

activities (%) against mosquito at concentration (mg L^{-1})					
10	5	2	1	0.5	0.25

compd						
6a-1	30	—	—	—	—	—
6a-2	100	100	40	—	—	—
6a-3	45	—	—	—	—	—
6a-4	10	—	—	—	—	—
6a-5	30	—	—	—	—	—
6a-6	5	—	—	—	—	—
6a-7	70	—	—	—	—	—
6a-8	25	—	—	—	—	—
6a-9	5	—	—	—	—	—
6a-10	15	—	—	—	—	—
6b-1	40	—	—	—	—	—
6c-1	100	100	20	—	—	—
6d-1	100	100	100	100	60	—
6e-1	100	100	100	100	20	—
6b-2	65	—	—	—	—	—
6c-2	20	—	—	—	—	—
6d-2	50	—	—	—	—	—
6e-2	50	60	75	—	—	—
6b-3	50	—	50	—	—	—
6d-3	100	100	100	100	100	20
6e-3	100	0	—	—	—	—
6b-4	20	—	—	—	—	—
6c-4	100	100	100	100	100	60
6d-4	100	60	—	—	—	—
6e-4	50	—	—	—	—	—
6b-5	100	100	0	—	—	—
6c-5	50	—	—	—	—	—
6d-5	100	20	—	—	—	—
6e-5	20	—	—	—	—	—
6b-6	40	—	—	—	—	—
6b-7	30	—	—	—	—	—
6d-8	50	—	—	—	—	—
6b-9	60	—	—	—	—	—
6d-9	100	20	—	—	—	—
Etoxazole	100	100	20	—	—	—

Table 5 Insecticidal Activities of the Target Compounds (Mortality, Percent)

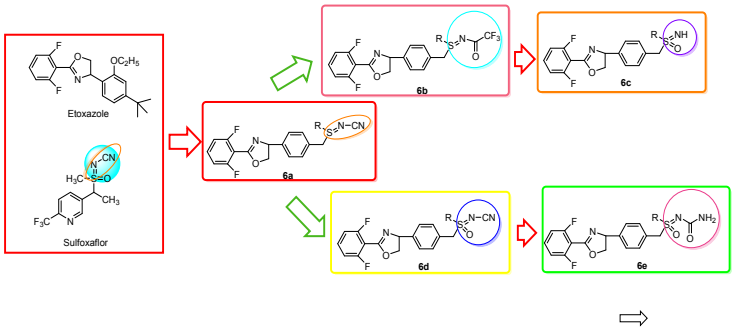
compd	cotton bollworm (600 mg L^{-1})	corn borer (600 mg L^{-1})	oriental armyworm (600 mg L^{-1})

6a-1	55	45	30
6a-2	80	85	45
6a-3	85	80	75
6a-4	100/100[a]/50[b]	100/100[a]/40[b]	50
6a-5	100/100[a]/40[b]	100/100[a]/60[b]	20
6a-6	65	60	75
6a-7	100/60[a]	100/80[a]	30
6a-8	75	70	50
6a-9	60	45	45
6a-10	85	80	20
6b-1	0	0	25
6c-1	20	15	10
6d-1	20	5	10
6e-1	50	50	45
6b-2	50	45	75
6c-2	0	10	5
6d-2	70	65	40
6e-2	15	25	20
6b-3	0	5	20
6d-3	15	20	25
6e-3	0	10	50
6b-4	30	15	5
6c-4	35	45	70
6d-4	10	25	20
6e-4	5	10	20
6b-5	0	5	20
6c-5	0	0	5
6d-5	0	15	30
6e-5	5	10	20
6b-6	0	10	5
6b-7	15	15	15
6d-8	0	0	5
6b-9	25	35	50
6d-9	25	10	20
Etoxazole	100/100[a]/40[b]	100/100[a]/35[b]	100/100[a]/60[b]

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

TOC graphic

Agrochemical Bioregulators


Etoxazole
Sulfoxaflor
6a
6b
6c
6d
6e