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# The Study of Novel Sulfilimines as Potential Insects Modulators

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## Abstract

This paper describes the novel sulfiliminyl structures as potential control of the $Ca^{2+}$ influx within the Ryanodine Receptor of insect body. Referring to commercial Flubendiamide structural composition, *N*-cyano, *N*-trifluroacetyl and *N*-acylamino sulfiliminyl moieties were firstly introduced into dicarboxamides scaffolds. The chiral sulfilimines especially exhibited significant insecticidal activities. The investigation of chirality impact on bioactivity was also systemically studied.

**Keywords:** Insecticides; Sulfilimines; Ryanodine receptor; Chirality

In order to protect the food supply and combat against insects resistance, the discovery of eco-friendly and effective insecticides with new mode of action is highly critical in agrochemcial research [1-2]. The ryanodine receptor (RyR) within insects is a non-voltage gated calcium channel, which is located in the sarcoplasmic reticulum and regulates the release of intracellular calcium stores critical for muscle contraction [2-4]. Up to date, there are three commercial products namely Flubendiamide [5], (Figure 1A ), Chloranthraniliprole (B) and Cyantranidliprole (C) [6-7], all of which have highly potent effects on insect RyRs.

With the rapid development of organic sulfur compounds, their industrial applications have expanded widely in the field of pharmaceuticals, agrochemicals and other industrial materials. One of the successful examples by Syngenta in diamide research was the discovery of sulfoximines as insecticides [8]. Considering its similarity to sulfoximines, sulfilimines have aroused considerable attention in recent years. Despite their rather short history, several sulfiliminyl derivatives have been known to be good herbicides as well as excellent tranquilizers [9]. However, the application of sulfimines in insecticide research has not been explored before.

In 2012 our research group firstly reported a series of new phthalamides containing sulfiliminyl moieties [10-12]. Most *N*-cyano, *N*-trifluroacetyl and *N*-acylamino sulfilimines exhibited good to excellent activity against oriental armyworm. Especially compound D (Figure 1) displayed 100% larvicidal activities at 0.25 mg/l , which reached the same larvicidal level as Flubendiamide. Later, Fan et al. [13] reported that anthranilic diamides structures containing *N*-cyano sulfiliminyl moieties also could maintain the activity. The results prompted us to look for new structures with better insecticidal potency by structure optimization.

Recently, Nihon Nohyaku reported several chiral diamides structures with mono methyl substituent in the aliphatic side chain [14]. While sulfur chirality [15] was not explored in diamides research. As chiral agrochemicals have played an increasing important role in sales market, which also have received considerable attention worldwide [16-17]. Based on the above viewpoints, two chiral centers containing carbon and sulfur were firstly introduced into dicarboxamides scaffolds. Four configurations were designed, synthesized and evaluated against oriental armyworm and diamondback moth for their insecticidal activities [18-21]. The biological assessment showed that some of these sulfilimines possessed impressive activities against oriental armyworm with $LC_{50}$ values of compounds E, F and G (Figure 2) as 0.0504, 0.0699, 0.1052 $mg{\cdot}L^{-1}$ (Table 1), respectively, lower than Flubendiamide (0.1230 $mg{\cdot}L^{-1}$). Interestingly the chiral *N*-cyano isomers expressed their

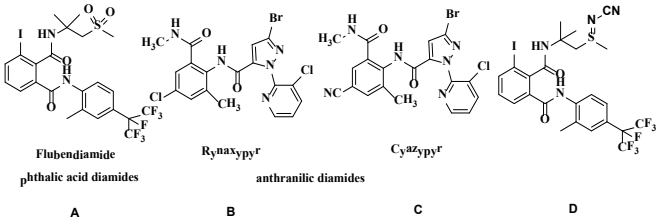


**Figure 1:** The Structures of Commercial Diamides Products and Sulfiliminyl Phthalamide

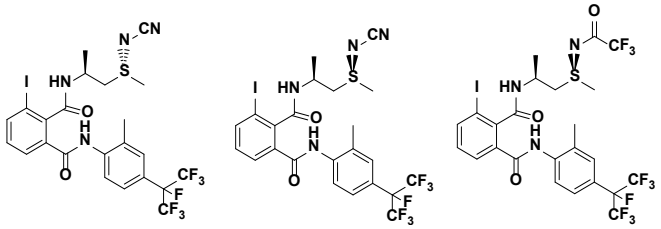

**Figure 2:** Structures of Chiral N-CN and N-COCF3 Sulfilimines.

sequence of activity as (Sc, Ss) ≥ (Sc, Rs)>>(Rc, Ss)>(Rc, Rs), while in *N*-trifluroacetylsulfilimines the sequence as (Sc, Rs) ≥ (Sc, Ss)>>(Rc, Ss)>(Rc, Rs). It was indicated that carbon chirality influenced bioactivity stronger than sulfur, propably due to the synergistic effect involved. For diamondback moth, in *N*-cyano sulfilimines the sequence as (Sc, Ss)>(Sc, Rs), where indicated that the sulfur chirality influenced the activities greater than carbon inversely. It is interesting to point out that several chiral isomers showed much higher activity than Flubendiamide.

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| Comp. | $LC_{50}$ (mg·L$^{-1}$) | | | |
|---|---|---|---|---|
| | y=a+bx | R | $LC_{50}$ | $LC_{95}$ |
| E | y=7.4089+1.8566x | 0.9885 | 0.0504 | 0.3877 |
| F | y=7.5886+2.2397x | 0.9402 | 0.0699 | 0.3790 |
| G | y=8.6832+3.7658x | 0.9914 | 0.1052 | 0.2876 |
| Flubendiamide | y=7.4237+2.6428x | 0.9945 | 0.1230 | 0.5160 |

**Table 1:** $LC_{50}$ Values of Compounds E, F, G and Flubendiamide against Oriental Armyworm.

We postulated that the improvement of insecticidal activity propably required a coordination of both carbon and sulfur chirality and chiral sulfiliminyl moiety was considered to be an essential element for high larvicidal activity. The further design including computional approach [22] and the chiral sulfiliminyl anthranilic diamides will be continued in our future work.

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