REVIEW

The Study of Novel diamide Insecticides: Chiral Sulfilimines

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Novel insecticidal chiral phthalamides containing *N*-cyano and *N*-trifluroacetyl sulfiliminyl moieties were firstly described coupled with their insecticidal activity against oriental armyworm and diamondback moth. The chirality of carbon and sulfur impact on bioactivity was systemically studied.

Keywords: phthaldiamide insecticides; chiral; sulfilimines; ryanodine receptor

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Due to the resistance and environmental issues involved, there is an increasing requirement for novel insecticides with new mechanisms of action. The insecticidal phthaldiamides constitute a new category of crop protection agents, which act on insect ryanodine receptor (RyR) and exhibit distinct pharmacological characteristics [1-4]. Additionally the diamides have broader insecticidal spectra, excellent toxicity and eco-friendly profiles, which have aroused interests worldwide [5].

Currently, almost a third of all agrochemicals are chiral compounds, with a trend that appears to be arising [6-7]. However, in the research of phthalamides only few literatures reported chiral diamides structures, one patent [8] mentioned compound **A** with high insecticidal activity. A series of phthaldiamides including its Rc counterpart (Figure 1 **B**), the related racemic compound and structures with none methyl (Figure1 **C**) were deliberatively synthesized in our laboratory to compare with the commercial Flubendiamide (Figure1 **D**). From our own bioassay experiments, it was concluded that compound **A** gave slightly better bioactivity against diamondback moth than **D**. The results prompted us to systemically explore the new frontier of novel chiral phthalamides structures, which might bring us some unknown biological properties

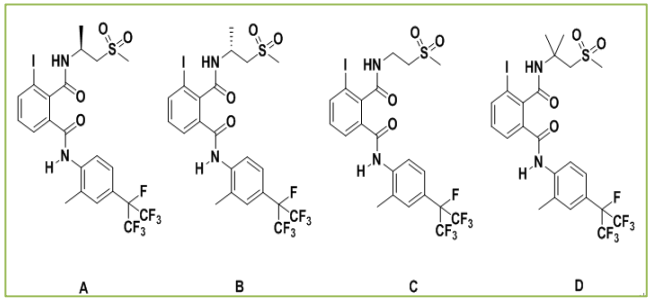

Figure 1. The scheme of molecular design for dicarboxamides analogues.

The sulfimines have been reported to be tranquillizers

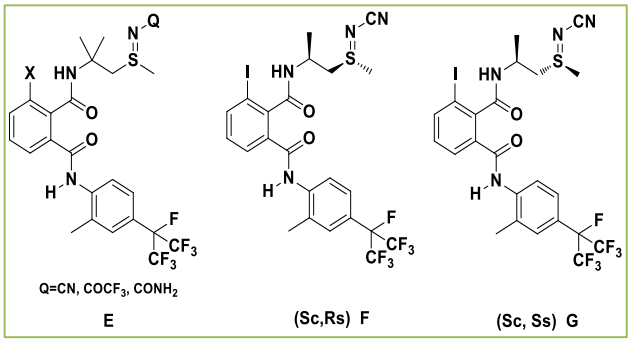

Figure 2. The structures of some reported Sulfilimines.

as well as herbicides, yet the systematic research on sulfimines in insecticides remain to be explored. In 2012, a series of new phthalamides containing sulfiliminyl moieties (Figure 2 **E**) have been firstly reported by our research group [9], some of which showed same larvicidal level as that of commercial flubendiamide [10-11]. The biological assessment encourage us to look for new structures with excellent insecticidal properties. As chirality becoming an important factor to consider, inaddition to the chiral carbon mentioned above, we introduced another chiral sulfur center into the phathalamide structures. To explore the chirality impact on larvicidal activity, the related racemic compounds and its different Sc and Rc counterparts were evaluated against oriental armyworm for their larvicidal activity. The bioassay clearly revealed that the carbon chirality influenced greater than sulfur.

As there are two chiral centers in the structure, four configurations were obtained in our experimental work. It was the first time to report novel optical active configuration introduced into dicarboxamides scaffolds containing sulfiliminyl moieties (Figure 3) [12-13]. The bioassay results elucidated that several compounds showed significant larvicidal activities. These *N*-cyano sulfiliminyl optical isomers had different impact on biological activity against oriental armyworm following the sequence as (Sc, Ss) ≥ (Sc, Rs) >> (Rc, Ss) > (Rc, Rs), while for *N*-trifluroacetyl optical isomers, the sequence was (Sc, Rs) ≥ (Sc, Ss) >> (Rc, Ss) > (Rc, Rs). The reason that carbon chirality influenced the activities stronger than sulfur might be due to the synergism involved. Compound **F** (Figure 2) and **G** (Figure 2) with LC_{50} values 0.0504 and 0.0699 $mg \cdot L^{-1}$ respectively, reached the higher activity than Flubendiamide (0.1230 $mg \cdot L^{-1}$). For diamondback moth, *N*-cyano sulfilimines exerted the sequence of activity as (Sc, Ss) > (Sc, Rs) where inversely the sulfur chirality influenced the activities greater than carbon. In particular, some title compounds gave much higher activity than Flubendiamide, two of which showed a death rate of 100%

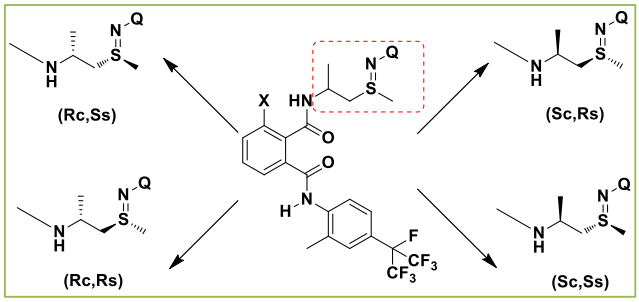

Figure 3. The molecular design for chiral sufilimines.

and 80% at 10^{-6} mg/L (while flubendiamide with a death rate of0% at 10^{-4} mg/L), where there is a more than a hundred fold preference. It was postulated that a coordination of both carbon and sulfur chirality might improve their insecticidal activity.

Most *N*-trifluoroacetyl sulfilimines showed higher activities than corresponding *N*-cyano sulfilimines, probably due to their better solubility and hydrophobic properties. From Comparative Molecular Field Analysis Calculation, it was found that stereoisomers with Ss configurations containing strong electron withdrawing groups as CN, $COCF_3$ are critical to maintain their excellent activity. So other electron with drawing groups such as $CONH_2$, NO_2 et al. have drawn our attention in our further work. The corresponding sulfoximines will also be explored.

Conflicting interests

The authors have declared that no competing interests exist.

Acknowledgements

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