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新型含 *N*-$COCF_3$ 硫亚胺取代的手性双酰胺类化合物的合成与生物活性研究

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摘要 邻苯二甲酰胺类化合物是一类作用于鱼尼丁受体的特殊杀虫剂, 它具有高效、低毒、作用机制独特、对环境友好、对哺乳动物十分安全等优异的特点. 为了探索新颖的结构, 设计合成了一系列碳硫双手性 *N*-$COCF_3$ 硫亚胺类化合物, 并通过熔点、^{1}H NMR、高分辨率质谱(HRMS)和比旋光度进行了化合物表征. 同时也探索了这些结构对东方粘虫的活性并总结了其构效关系. 初步的生测结果表明, 某些化合物对东方粘虫显示出良好的杀虫活性. 这些异构体的杀虫活性顺序为(S_c,R_s)≥(S_c,S_s). 值得一提的是, 在苯胺部分中含有 2-CH_3-4-Cl 的化合物比具有 3-CF_3 的化合物具有更好的生物活性. 该研究为进一步研究含有硫亚胺结构的邻苯二甲酰胺类化合物提供了重要信息.

关键词 手性; 硫亚胺; 生物活性; 鱼尼丁受体; 邻苯二甲酰胺类

Synthesis and Insecticidal Activities of Novel Optically Active Dicarboxamides Containing *N*-Trifluoroacetyl Sulfulimiyl Substituents

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Abstract Dicarboxamide is a class of special insecticide targeting at Ryanodine Receptor (RyR) with potent activity, new mode of action and eco-friendly characteristics in modern pest control. To explore new structures acting on RyR, a series of new dual chiral *N*-$COCF_3$ sulfiliminyl derivatives were designed, synthesized, and characterized by melting point, ^{1}H NMR, high-resolution mass spectrometry (HRMS) and optical polarimeter. Their insecticidal activity against oriental armyworm (*Pseudaletia separata* Walker) were evaluated and the structure-activity relationship were summarized. The bioactivity revealed that some compounds showed favourable insecticidal activities against oriental armyworm. The sequence of these isomers' insecticidal activity was (S_c,R_s)≥(S_c,S_s). It was worth noting that compounds containing 2-CH_3-4-Cl in the anilide moiety gave better activity than the compounds with 3-CF_3. The study provided some important information for the further research of sulfiliminyl dicarboxamides.

Keywords chirality; sulfilimine; bioactivity; ryanodine receptor; dicarboxamides

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1 Introduction

As one of the most important second messagers in cells, Ca^{2+} is closely concerned with some physiological activities. During the modern agrochemical innovation program for insect control, Ryanodine Receptor (RyR) has been considered as an ideal target for its regulatory functions of Ca^{2+},[1] which had become a hot spot in agrochemistry. As we all know, there were three commercial diamides insecticides namely Flubendiamide,[2] Chlorantraniliprole[3] and Cyantraniliprole[4] targeting on RyR, which had potent efficiency, low toxicity, unique mechanism, no-cross resistance to traditional insecticides, safety to mammals and ecological environment.

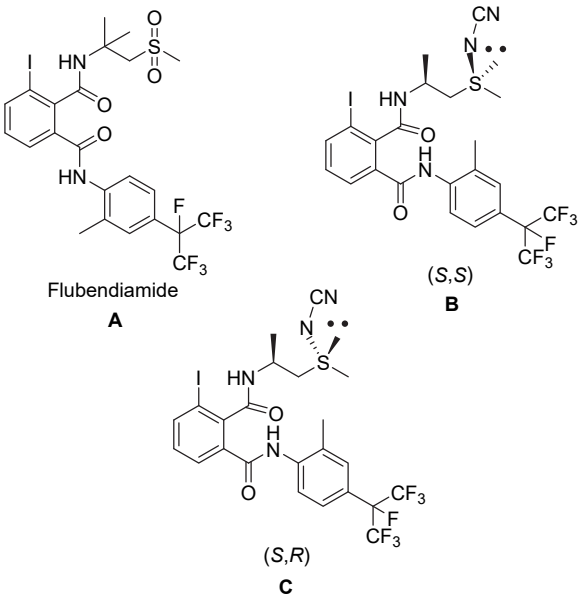


Figure 1 Structures of Flubendiamide (**A**) and *N*-cyano sulfilimine (**B**)

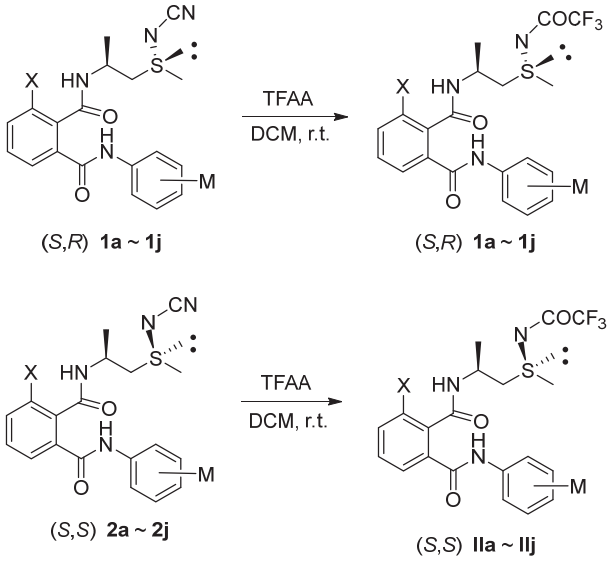
Previously, we reported dual chiral scaffolds containing sulfiliminyl substituents and their excellent larvacidal activities.[5-17] Some compounds showed the same activity level as Flubendiamide for oriental armyworm. Surprisingly, for diamondback moths, other sulfiliminyl derivatives gave higher activity than Flubendiamide. The bioassay results gave our suggestion that dual chiral sulfiliminyl substituent was helpful to improve the larvacidal activity, which inspired us to research the further modifications of these structures. At the same time, we found that some *N*-$COCF_3$ sulfilimines gave better activity than the corresponding *N*-CN sulfilimines to a certain extent.

Referring to collective information and our previous work, 16 novel *N*-$COCF_3$ sulfilimines containing 3-CF_3, 2-CH_3-4-Cl or 2,3,4-F_3 with the replacement of heptafluoroisopropyl group in the anilide moiety were designed and synthesized in order to systematically explore the structure-activity relationship of this category of dual chiral sulfilimines. The bioassay evaluation against oriental armyworm was discussed as well.

2 Results and discussion

2.1 Synthesis

N-$COCF_3$ sulfilimines can be easily prepared from the corresponding *N*-CN sulfilimines in high yield. The preparation of title compounds was shown in Scheme 1. All the target compounds have been identified by melting point, ^1H NMR, HRMS and optical polarimeter.



a: X=I, M=3-CF_3; **b**: X=NO_2, M=3-CF_3; **c**: X=Cl, M=3-CF_3; **d**: X=F, M=3-CF_3; **e**: X=Br, M=3-CF_3; **f**: X=H, M=3-CF_3; **g**: X=I, M=2-CH_3- 4-Cl; **h**: X=NO_2, M=2-CH_3-4-Cl; **i**: X=NO_2, M=2,3,4-F_3

Scheme 1 Synthesis of target compounds

2.2 Larvicidal activity against oriental armyworm

The larvicidal activities of compounds **Ia**~**Ij**, **Iia**~**IIj** and commercial Flubendiamide against oriental armyworm were summarized in Tables 1 and 2. The bioassay results indicated that most of the compounds showed moderate larvicidal activity. For the most part, the bioactivity law of these isomers is (S_c,R_s)≥(S_c,S_s), which is in accordance with SARs in our previous studies (S_c,R_s)≥(S_c,S_s)≫(R_c,R_s)>(R_c,S_s).[8] As seen in these diastereomers, these structures showed similar activities **Ie** (S_c,R_s) vs **IIe** (S_c,S_s), **If** (S_c,R_s) vs **IIf** (S_c,S_s), **Ig** (S_c,R_s) vs **IIg** (S_c,S_s), **Ih** (S_c,R_s) vs **IIh** (S_c,S_s). For others, **Ia** (S_c,R_s) showed 60% bioactivity at 100 mg•L^{-1}, **IIa** (S_c,S_s) gave better insecticidal activity than **Ia** (20%, 10 mg•L^{-1}). Surprisingly, **Id** (S_c,R_s) gave a mortality rate of 20% at 50 mg•L^{-1}, while **IId** (S_c,S_s) exhibited 40% insecticidal activity at 200 mg•L^{-1}. These bioassay results indicated that sulfur chirality could affect the biological activities to a certain extent.

As shown in Table 1, it was found that compounds **Ig**, **IIa** and **IIg** showed 40%, 20% and 25% activities at 25 mg•L^{-1}, respectively. As a result, the compound **Ig** containing iodine substituent in the aromatic moiety showed the best larvicidal activity. It was worth noting that compounds containing 2-CH_3-4-Cl in the anilide moiety gave better activity than the compounds with 3-CF_3. From Table 1, it

Table 1 Insecticidal activities of compounds **Ia**～**Ii**, **IIa**, **IIc**～**IIg** and Flubendiamide against oriental armyworm

Compd.	Larvicidal activity (%) at conc. (mg•L^{-1})				
	200	100	50	25	10
Ia	100	60			
Ib	30				
Ic	100	60			
Id	100	100	20	0	
Ie	100	100	60	20	
If	40				
Ig	100	100	100	100	40
Ih	100	100	30		
Ii	55				
IIa	100	100	100	100	20
IIc	50				
IId	40				
IIe	100	100	40	0	
IIf	40				
IIg	100	100	100	100	25
IIh	100	100	60		
Flubendiamide	100	100	100	100	100

Table 2 LC_{50} values of compounds **Ia**, **Ib**, **If**, **Ig**, **Ih**, **IIa**, **IIg**, **IIh** and Flubendiamide against oriental armyworm

Compd.	LC_{50}/(mg•L^{-1})			
	y=a+bx	R	LC_{50}	LC_{95}
Ia	y=0.2758+2.6470x	0.9726	60.9216	254.7882
Ib	y=−1.8087+2.6912x	0.9837	338.8469	1384.2087
If	y=−4.7357+3.9709x	0.9440	282.9624	734.4319
Ig	y=1.3515+3.8835x	0.9446	8.6994	23.0697
Ih	y=1.6886+2.0064x	0.9501	44.7156	295.3081
IIa	y=−3.7613+7.8288x	0.9950	13.1557	21.3412
IIg	y=−1.7923+6.0046x	0.9701	13.5261	25.4158
IIh	y=−1.4049+3.8814x	0.9676	44.6843	118.5586
Fluben-diamide	y=7.4237+2.6428x	0.9945	0.1230	0.5160

was also concluded that most *N*-$COCF_3$ sulfilimines showed better activity than the corresponding *N*-CN sulfilimines. As shown in Table 2, the LC_{50} value of **Ig** was 8.6994 mg•L^{-1}, while Flubendiamide was 0.1230 mg•L^{-1}.

2.3 Molecule docking result

Lin *et al.*[18] reported that the crystal structure of ryanodine receptor *N*-terminal domain from *Plutella xylostella* reveals two potential species-specific insecticide-targeting sites. Based on these findings, we performed molecular docking studies on **Ib** and **Ig** in the potential binding pockets of the *N*-terminal domain of ryanodine receptor. The docking results show that **Ib** has a worse predicted binding free energy in pocket 2 (Table 3), while **Ig** has a better predicted binding free energy in pocket 2 than in pocket 1 (Table 4). The interaction between compound **Ib** and the ryanodine receptor was shown in Figure 2. From Figure 2, the interaction between the compound **Ib** and the ryanodine receptor has less hydrogen bond interaction with residues Thr30 and Asp164 and π-π interactions with the residue His195. As shown in Figure 3, the carbonyl oxygen atom of **Ig** forms hydrogen bond interaction with the residues His195. The nitrogen atom of the sulfulimiyl group and the residue Thr30 form a hydrogen bond interaction. At the same time, the hydrogen atom of the imine group forms a hydrogen bond interaction with the residue Asp164. In addition, the phenyl group of **Ig** forms a π-π interactions with the residue His195. The formation of hydrogen bonds and π-π interaction facilitates the binding between ryanodine receptors and the **Ig**.

Table 3 Docking results of compound **Ib** in different pockets of the ryanodine receptor *N*-terminal domain of Plutella xylostella

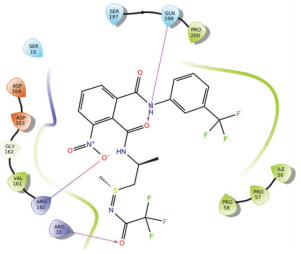
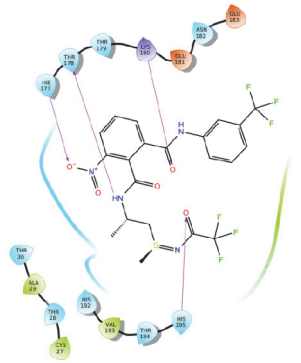
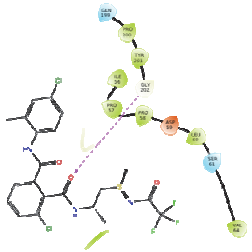
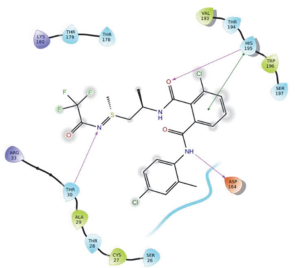
Pocket	Docking score (kcal•mol^{-1})	2D diagram
1	−3.54	
2	−4.86	

Table 4 Docking results of compound **Ig** in different pockets of the ryanodine receptor *N*-terminal domain of Plutella xylostella

Pocket	Docking score/ (kcal•mol^{-1})	2D diagram
1	−3.89	
2	−5.07	

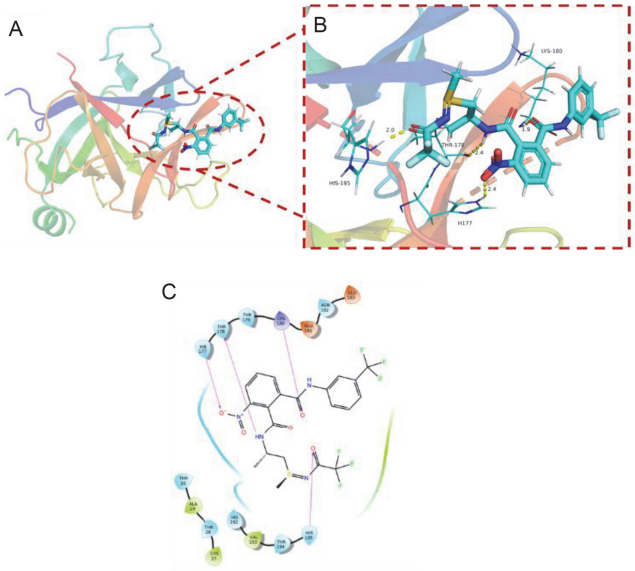


Figure 2 Molecule docking of **Ib** (A and B) dealed with PyMol soft and 2D diagram C depicted by Schrödinger 2017

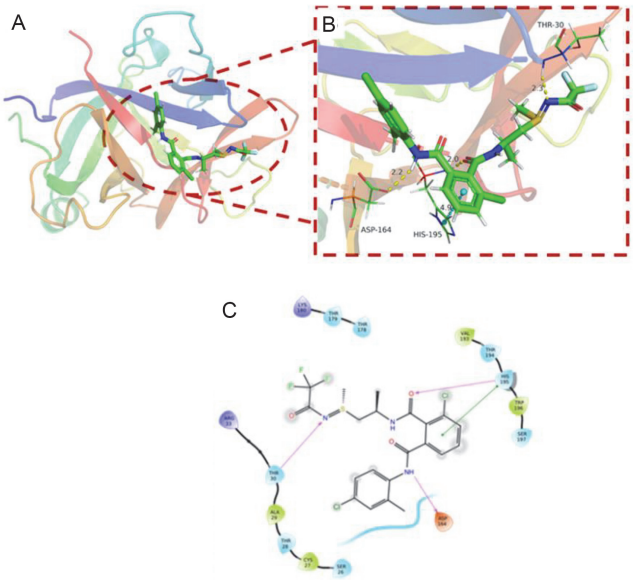


Figure 3 Molecule docking of compound **Ig** (A and B) dealed with PyMol soft and 2D diagram C depicted by Schrödinger 2017

3 Conclusions

In summary, a series of new dual chiral *N*-$COCF_3$ sulfiliminyl derivatives were designed, synthesized and evaluated against oriental armyworm for their insecticidal activities. The bioassay results revealed that some title compounds possessed favorable activities following the sequence as (S_c,R_s)≥(S_c,S_s). It was worth mentioning that compounds containing 2-CH_3-4-Cl in the anilide moiety gave superior activity comparing with the compounds containing 3-CF_3. The study provided some important information for the further drug design of sulfiliminyl dicarboxamides.

4 Experimental section

4.1 Instruments and materials

The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instrument Co., Beijing, China) and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300MHz (Bruker AC-P 300 spectrometer) or 400MHz (Bruker AV 400 spectrometer) in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as internal standard. Elemental analyses were performed on a Vario EL elemental analyzer. HRMS data were obtained on a Varian QFT-ESI. Optical rotations were measured with a Perkin-Elmer 341 polarimeter at 20 ℃. Reagents were all analytically pure. All solvents and liquid reagents were dried by standard methods and distilled before use. Insecticide Flubendiamide was used only as a control, synthesized according to the literature.[2]

4.2 General synthetic procedure for compounds **1a**～**1j** and **2a**～**2j**

1a～**1j** and **2a**～**2j** were synthesized in moderate yields by the method previously published in the literature.[7] The melting point and ^{1}H NMR data were consistent with the literature. These phthalamide derivatives were synthesized in high yield by the method reported in the literature.[8]

(*S*,*R*)-3-Iodo-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)pthalamide (**Ia**): White solid, yield 89.34%. m.p. 188～191 ℃; $[\alpha]_D^{20}$ + 50.6 (*c* 10, EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.63 (s, 1H, Ar-NH), 8.81 (d, J=8.0 Hz, 1H, CNH), 8.15 (s, 1H, Ar-H), 8.05 (d, J=7.8 Hz, 1H, Ar-NH), 7.94 (d, J=7.9 Hz, 1H, Ar-H), 7.76 (d, J=7.5 Hz, 1H, Ar-H), 7.58 (t, J=7.8 Hz, 1H, Ar-H), 7.45 (d, J=7.3 Hz, 1H, Ar-H), 7.31 (t, J=7.7 Hz, 1H, Ar-H), 4.31 (d, J=6.2 Hz, 1H, NCH), 3.46～3.39 (m, 1H, SCH_2), 3.28 (dd, J=12.5, 5.2 Hz, 1H, SCH_2), 2.84 (s, 3H, SCH_3), 1.25 (d, J=6.3 Hz, 3H, CCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.6, 165.5, 165.0～164.3 (m), 141.5, 141.0, 139.7, 135.7, 130.3, 130.0, 129.8～128.9 (m), 127.3, 125.4, 123.3 (m), 120.1, 118.4, 115.8 (m), 95.3 , 51.6, 40.7, 28.3, 19.1. HRMS calcd. for $C_{21}H_{18}F_6IN_3O_3SH$ $[M+H]^+$ 633.0091; found 633.0082.

(*S*,*R*)-3-Nitro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**Ib**): White solid, yield 89.57%. m.p. 114～116 ℃; $[\alpha]_D^{20}$ +15.4 (*c* 5, MeOH); ^{1}H NMR (400 MHz, DMSO- d_6) δ: 10.88 (s, 1H, Ar-NH), 9.04 (d, J=8.1 Hz, 1H, CNH), 8.26 (d, J=8.2 Hz, 1H, Ar-H), 8.15 (s, 1H, Ar-H), 8.10 (d, J=7.5 Hz, 1H, Ar-H), 7.93 (d, J=8.2 Hz, 1H, Ar-H), 7.83 (t, J=7.9 Hz, 1H, Ar-H), 7.61 (t, J=7.9 Hz, 1H, Ar-H), 7.48 (d, J=7.6 Hz, 1H, Ar-H), 4.32～4.24 (m, 1H, NCH), 3.39 (m, 1H, SCH_2), 3.27 (dd, J=12.7, 5.7 Hz, 1H, SCH_2), 2.83 (s, 3H, SCH_3), 1.19 (d, J=6.6 Hz, 3H, CCH_3). HRMS calcd for $C_{21}H_{18}F_6N_4O_5SH$ $[M+H]^+$ 553.0975; found 553.0971.

(*S*,*R*)-3-Chloro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**Ic**): White solid, yield 90.24%. $[\alpha]_D^{20}$ −1.0 (*c* 3.1,

DMF); m.p. 206～208 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H, Ar-NH), 8.91 (d, J=8.4 Hz, 1H, CNH), 8.14 (s, 1H, Ar-H), 7.94 (d, J=8.3 Hz, 1H, Ar-H), 7.74～7.68 (m, 2H, Ar-H), 7.59 (td, J=7.9, 3.9 Hz, 2H, Ar-H), 7.46 (d, J=7.7 Hz, 1H, Ar-H), 4.38～4.29 (m, 1H, NCH), 3.38～3.37 (m, 1H, SCH_2), 3.29 (dd, J=12.7, 5.4 Hz, 1H, SCH_2), 2.84 (s, 3H, SCH_3), 1.23 (d, J=6.7 Hz, 3H, CCH_3). HRMS calcd for $C_{21}H_{18}ClF_6N_3O_3SH$ $[M+H]^+$ 542.0735; found 542.0739.

(*S*,*R*)-3-Fluoro-N^2-(1-(*N*-trifluoroacetyl-*S*-methyl-sulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**Id**): White solid, yield 90.84%. $[\alpha]_D^{20}$ −26.2 (*c* 5, $(CH_3)_2CO$); m.p. 152～154 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.76 (s, 1H, Ar-NH), 8.96 (d, J=8.2 Hz, 1H, -CNH), 8.14 (s, 1H, Ar-H), 7.93 (d, J=7.7 Hz, 1H, Ar-H), 7.62～7.58 (m, 3H, Ar-H), 7.49～7.45 (m, 2H, Ar-H), 4.38～4.30 (m, 2H, NCH), 3.38 (d, J=8.3 Hz, 1H, SCH_2), 3.32 (dd, J=12.7, 5.5 Hz, 1H, SCH_2), 2.85 (s, 3H, SCH_3), 1.24 (d, J=6.7 Hz, 3H, CCH_3). HRMS calcd for $C_{21}H_{18}F_7N_3O_3SH$ $[M+H]^+$ 526.1030; found 526.1035.

(*S*,*R*)-3-Bromo-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**Ie**): White solid, yield 91.17%. $[\alpha]_D^{20}$ −8.8 (*c* 5, $(CH_3)_2CO$); m.p. 207～209 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.68 (d, J=8.3 Hz, 1H, Ar-NH), 8.88 (t, J=9.5 Hz, 1H, -CNH), 8.15 (s, 1H, Ar-H), 7.95 (d, J=8.0 Hz, 1H, Ar-H), 7.79～7.74 (m, 1H, Ar-H), 7.73～7.68 (m, 1H, Ar-H), 7.63～7.55 (m, 2H, Ar-H), 7.46 (d, J=7.8 Hz, 1H, Ar-H), 4.37～4.31 (m, 1H, -NCH), 3.47～3.38 (m, 1H, SCH_2), 3.29 (d, J=7.3 Hz, 1H, SCH_2), 2.85 (s, 3H, SCH_3), 1.24 (d, J=6.5 Hz, 3H, CCH_3). HRMS calcd for $C_{21}H_{18}BrF_6N_3O_3SH$ $[M+H]^+$ 586.0229; found 586.0225.

(*S*,*R*)-N^2-(1-(*N*-Trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**If**): White solid, yield 89.49%. m.p. 143～146 ℃; $[\alpha]_D^{20}$ +44.8 (*c* 10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H, Ar-NH)), 8.79 (d, J=8.4 Hz, 1H, CNH), 8.20 (s, 1H, Ar-H), 7.92 (d, J=7.8 Hz, 1H, Ar-H), 7.68～7.56 (m, 5H, Ar-H), 7.44 (d, J=7.6 Hz, 1H, Ar-H), 4.39～4.30 (m, 1H, NCH), 3.48～3.41 (m, 1H, SCH_2), 3.37～3.35 (m, 1H, SCH_2), 2.86 (s, 3H, SCH_3), 1.28 (d, J=6.6 Hz, 3H, CCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.4, 167.3, 165.0～164.0 (m), 140.1, 136.4, 135.5, 130.0, 129.9, 129.8～128.9 (dd, J=25.6, 19.1 Hz), 129.2, 127.8, 127.6, 125.5, 122.9, 119.6, 118.4, 115.5, 52.3, 41.1, 28.5, 19.6. HRMS calcd for $C_{21}H_{19}F_6N_3O_3SH$ $[M+H]^+$ 508.1124; found 508.1123.

(*S*,*R*)-3-Iodo-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(4-chloro-2-methylphenyl)phthalamide (**Ig**): White solid, yield 91.70%. m.p. 109～111 ℃; $[\alpha]_D^{20}$ + 16.0 (*c* 10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.83 (s, 1H, Ar-NH), 8.82 (d, J=8.1 Hz, 1H, CNH), 8.03 (d, J=7.8 Hz, 1H, Ar-H), 7.78 (d, J=7.5 Hz, 1H, Ar-H), 7.45 (d, J=8.5 Hz, 1H, Ar-H), 7.35～7.24 (m, 4H, Ar-H), 4.30 (dt, J=13.6, 7.0 Hz, 1H, NCH), 3.42～3.37 (m, 1H, SCH_2), 3.29 (dd, J=12.6, 5.6 Hz, 1H, SCH_2), 2.79 (s, 3H, SCH_3), 2.25 (s, 3H, $ArCH_3$), 1.24 (d, J=6.5 Hz, 3H, CCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.8, 165.2, 164.4 (m), 141.6, 140.8, 135.7, 135.3, 135.0, 130.3, 129.9, 129.6, 127.3 (d, J=11.01 Hz), 125.8 118.4, 115.5, 95.4, 51.8, 40.8, 28.4, 19.0, 17.6. HRMS calcd for $C_{21}H_{20}ClIF_3N_3O_3SH$ $[M+H]^+$ 613.9984; found 613.9978.

(*S*,*R*)-3-Nitro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(4-chloro-2-methylphenyl)phthalamide (**Ih**): White solid, yield 90.79%. m.p. 104～107 ℃; $[\alpha]_D^{20}$ − 36.2 (*c* 10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H, Ar-NH), 9.02 (d, J=7.8 Hz, 1H, CNH), 8.25 (d, J=8.2 Hz, 1H, Ar-H), 8.11 (d, J=7.5 Hz, 1H, Ar-H), 7.83 (t, J=7.9 Hz, 1H, Ar-H), 7.50 (d, J=8.4 Hz, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.29 (d, J=8.3 Hz, 1H, Ar-H), 4.34～4.24 (m, 1H, NCH), 3.37～3.35 (m, 1H, SCH_2), 3.29～3.26 (m, 1H, SCH_2), 2.80 (s, 3H, SCH_3), 2.29 (s, 3H, $ArCH_3$), 1.20 (d, J=6.5 Hz, 3H, CCH_3); HRMS calcd for $C_{21}H_{20}ClF_3N_4O_5SH$ $[M+H]^+$ 533.0868; found 533.0867.

(*S*,*R*)-3-Nitro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(2,3,4-trifluorophenyl)phthalamide (**Ii**): White solid, yield 88.84%. m.p. 108～111 ℃; $[\alpha]_D^{20}$ +0.8 (*c* 1, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.61 (s, 1H, Ar-NH), 9.00 (d, J=8.0 Hz, 1H, CNH), 8.26 (d, J=8.1 Hz, 1H, Ar-H), 8.08 (d, J=7.6 Hz, 1H, Ar-H), 7.83 (d, J=8.0 Hz, 1H, Ar-H), 7.56 (d, J=8.0 Hz, 1H, Ar-H), 7.34 (dd, J=17.6, 8.2 Hz, 1H, Ar-H), 4.31～4.22 (m, 1H, NCH), 3.37 (d, J=8.0 Hz, 1H, CH_2), 3.28 (dd, J=12.7, 5.8 Hz, 1H, SCH_2), 2.81 (s, 3H, SCH_3), 1.20 (d, J=6.7 Hz, 3H, CCH_3); HRMS calcd for $C_{20}H_{16}F_6N_4O_5SH$ $[M+H]^+$ 539.0819; found 539.0816.

(*S*,*S*)-3-Iodo-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**IIa**): White solid, yield 90.14%. m.p. 144～146 ℃; $[\alpha]_D^{20}$ −20.6 (*c* 5, MeOH); ^{1}H NMR (400 MHz, DMSO- d_6) δ: 10.64 (s, 1H, Ar-NH), 8.65 (d, J=6.7 Hz, 1H, CNH), 8.14 (s, 1H, Ar-H), 8.04 (d, J=6.3 Hz, 1H, Ar-H), 7.94 (d, J=6.4 Hz, 1H, Ar-H), 7.73 (d, J=7.3 Hz, 1H, Ar-H), 7.58 (t, J=8.0 Hz, 1H, Ar-H), 7.46 (d, J=6.0 Hz, 1H, Ar-H), 7.30 (t, J=7.2 Hz, 1H, Ar-H), 4.31 (m, 1H, NCH), 3.40～3.35 (m, 2H, SCH_2),2.81 (s, 3H, SCH_3), 1.27 (d, J=5.2 Hz, 3H, CCH_3); HRMS calcd for $C_{21}H_{18}F_6IN_3O_3SH$ $[M+H]^+$ 633.0091; found 633.0081.

(*S*,*S*)-3-Chloro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**IIc**): White solid, yield 92.27%. m.p. 76～77 ℃; $[\alpha]_D^{20}$ − 18.4 (*c* 5, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.71 (s, 1H, Ar-NH), 8.73 (d, J=8.0 Hz, 1H, CNH), 8.14 (s, 1H, Ar-H), 7.93 (d, J=7.9 Hz, 1H, Ar-H), 7.74～7.66 (m, 2H, Ar-H), 7.58 (dd, J=16.6, 8.7 Hz, 2H, Ar-H), 7.46 (d, J=7.8 Hz, 1H, Ar-H), 4.37～4.29 (m, 1H, NCH), 3.34～3.31 (m, 2H, SCH_2), 2.81 (s, 3H, SCH_3), 1.24 (d, J=6.7 Hz, 3H, CCH_3). HRMS calcd for $C_{21}H_{18}ClF_6N_3O_3SH$ $[M+H]^+$ 542.0735; found 542.0739.

(*S*,*S*)-3-Fluoro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**IId**): White solid, yield 87.89%. m.p. 92～94 ℃; $[\alpha]_D^{20}$ +12.4 (*c* 5, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-

d_6) δ: 10.76 (s, 1H, Ar-NH), 8.78 (d, J=7.8 Hz, 1H, CNH), 8.15 (s, 1H, Ar-H), 7.93 (d, J=7.4 Hz, 1H, Ar-H), 7.60 (d, J =7.9 Hz, 3H, Ar-H), 7.47 (t, J=8.8 Hz, 2H, Ar-H), 4.38～4.29 (m, 1H, NCH), 3.36 (d, J=6.8 Hz, 2H, SCH_2), 2.83 (s, 3H, SCH_3), 1.26 (d, J=6.5 Hz, 3H, CCH_3). HRMS calcd for $C_{21}H_{18}F_7N_3O_3SH$ $[M+H]^+$ 526.1030; found 526.1035.

(*S*,*S*)-3-Bromo-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**IIe**): White solid, yield 89.64 %. m.p. 86～88 ℃; $[\alpha]_D^{20}$ +29.6 (*c* 5, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.69 (s, 1H, Ar-NH), 8.71 (d, J=8.1 Hz, 1H, CNH), 8.14 (s, 1H, Ar-H), 7.93 (d, J=8.2 Hz, 1H, Ar-H), 7.74 (d, J=12.0 Hz, 1H, Ar-H), 7.69 (d, J=9.4 Hz, 1H, Ar-H), 7.63～7.54 (m, 2H, Ar-H), 7.47 (t, J=7.2 Hz, 1H, Ar-H), 4.33 (m, 1H, NCH), 3.35 (d, J=2.6 Hz, 2H, SCH_2), 2.82 (s, 3H, SCH_3), 1.25 (d, J=6.7 Hz, 3H, CCH_3); HRMS calcd for $C_{21}H_{18}BrF_6N_3O_3SH$ $[M+H]^+$ 586.0229; found 586.0225.

(*S*,*S*)-N^2-(1-(*N*-Trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(3-(trifluoromethyl)phenyl)phthalamide (**IIf**): White solid, yield 90.39%. m.p.181～182 ℃; $[\alpha]_D^{20}$ +84.0 (*c* 10, EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.69 (s, 1H, Ar-NH), 8.58 (d, J=8.0 Hz, 1H, -CNH), 8.20 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.66～7.62 (m, 1H, Ar-H), 7.61～7.55 (m, 4H, Ar-H), 7.43 (d, J=7.7 Hz, 1H, Ar-H), 4.31 (dt, J=14.0, 6.8 Hz, 1H, NCH), 3.40 (d, J=6.8 Hz, 2H, SCH_2), 2.84 (s, 3H, SCH_3), 1.27 (d, J=6.7 Hz, 3H, CCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.4, 167.3, 165.3 ～ 164.3 (m), 140.2, 136.4, 135.7, 129.9, 129.8, 129.7～128.9 (m), 127.8, 127.6, 125.5, 123.0, 122.8, 119.6, 118.3, 115.5, 51.8, 41.3, 29.5, 19.9. HRMS calcd for $C_{21}H_{19}F_6N_3O_3SH$ $[M+H]^+$ 508.1124; found 508.1123.

(*S*,*S*)-3-Iodo-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(4-chloro-2-methylphenyl)phthalamide (**IIg**): White solid, yield 90.12%. m.p. 117～121 ℃; $[\alpha]_D^{20}$ +64.4 (*c* 5, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.84 (s, 1H, Ar-NH), 8.65 (d, J=7.8 Hz, 1H, CNH), 8.02 (d, J=7.8 Hz, 1H, Ar-H), 7.75 (d, J=7.4 Hz, 1H, Ar-H), 7.46 (d, J=8.5 Hz, 1H, Ar-H), 7.32 (d, J=4.6 Hz, 1H, Ar-H), 7.30～7.22 (m, 2H, Ar-H), 4.31 (dt, J=13.9, 7.0 Hz, 1H, CH), 3.34～3.29 (m, 2H, SCH_2), 2.76 (s, 3H, SCH_3), 2.25 (s, 3H, $ArCH_3$), 1.28 (d, J=6.7 Hz, 3H, CCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.8, 165.3, 164.5 (m), 141.6, 140.7, 135.9, 135.3, 135.0, 130.2, 129.9, 129.7, 127.2 (d, J=13.3 Hz), 125.8, 118.4, 115.5, 95.0, 52.1, 41.6, 29.7, 19.6, 17.6. HRMS calcd for $C_{21}H_{20}ClIF_3$- N_3O_3SH $[M+H]^+$ 613.9984; found 613.9978.

(*S*,*S*)-3-Nitro-N^2-(1-(*N*-trifluoroacetyl-*S*-methylsulfinimidoyl)-propan-2-yl)-N^1-(4-chloro-2-methylphenyl)phthalamide (**IIh**): White solid, yield 91.76%. m.p. 112～115 ℃; $[\alpha]_D^{20}$ +63.4 (*c* 5, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.08 (s, 1H, Ar-NH), 8.85 (d, J=7.5 Hz, 1H, CNH), 8.23 (d, J=8.1 Hz, 1H, Ar-H), 8.09 (d, J=7.5 Hz, 1H, Ar-H), 7.81 (t, J=7.9 Hz, 1H, Ar-H), 7.50 (d, J=8.4 Hz, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.29 (d, J=8.0 Hz, 1H, Ar-H), 4.32～4.20 (m, 1H, NCH), 3.29 (d, J=7.7 Hz, 2H, SCH_2), 2.77 (s, 3H, SCH_3), 2.28 (s, 3H, $ArCH_3$), 1.24 (d, J=6.5 Hz, 3H, CCH_3); HRMS calcd for $C_{21}H_{20}ClF_3N_4O_5$-SH $[M+H]^+$ 533.0868; found 533.0867.

4.4 Biological assay

All biological assays were carried out on representative test organisms prepared in the laboratory. The bioassay experiments were repeated at (25±1) ℃ according to statistical needs. Assessments were conducted on the basis of dead/alive, and mortality rates were corrected applying Abbott's formula.[19] Percentage mortalities were evaluated based on a percentage scale of 0～100, in which 0 indicates no activity and 100 indicates total kill. Error of the bioassay experiments was 5%. LC_{50} values were calculated by probit analysis.[20]

Larvicidal activity against oriental armyworm (*Mythimna separate* Walker): The insecticidal activity of compounds **Ia**～**Ii**, **IIa**, **Iic**～**IIg** and Flubendiamide were evaluated using the reported procedure. The insecticidal activity is outlined in Table 1. LC_{50} values of compounds **Ia**, **Ig**, **Ij**, **IIa**, **IIg**, **IIj** and Flubendiamide are shown in Table 2.

Molecular docking: Crystal structure of diamondback moth ryanodine receptor *N*-terminal domain[18] (PDB ID: 5Y9V) was downloaded from the RCSB Protein Data Bank (PDB). The protein structure was then prepared using the Protein Preparation Wizard[21] module in Schrödinger 2017 to remove all crystallographic water molecules and ligand, correct side chains with missing atoms, add hydrogen atoms and assign protonation states and partial charges with the OPLS_2005 force field for covalent docking studies. Compounds **Ib** and **Ig** were prepared using the LigPrep[22] module of the Schrödinger 2017 molecular modeling package to add hydrogen atoms, convert 2D structures to 3D, generate stereoisomers and determine the ionization state at pH (7.0±2.0) with Epik[23]. Energy minimized 3D structures were obtained using an OPLS_2005 force field. ConfGen[24] with default parameters was utilized to generate conformers for the compounds **Ib** and **Ig**. A grid-file calculation was generated using the Receptor Grid Generation6 module in Schrödinger, which created a grid in the protein, specifically the active site, which was searched when performing the docking simulations. The standard precision (SP) of Ligand Docking module in Schrödinger 2017 was used to perform the docking of compounds **Ib**, **Ig** and ryanodine receptor, respectively.

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