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Original article

The exploration of chiral *N*-cyano sulfiliminyl dicarboxamides on insecticidal activities

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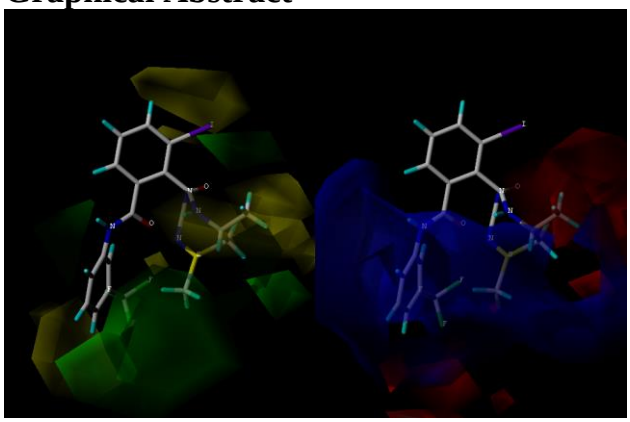
Graphical Abstract



The results indicated that these groups such as 3-CF_3, 2-CH_3-4-Cl or 2, 3, 4-trifluro were inefficient to replace heptafluoroisopropyl group for high larvicidal activity, which provided some guidance for the further modifications of sulfiliminyl dicarboxamides.

ABSTRACT
Due to new mechanism of action and ecofriendly characteristics, dicarboxamide insecticides have attracted more and more attentions in modern pest management. A series of 20 dual chiral N-cyano sulfilimines containing two centers (carbon and sulfur) were designed and synthesized. All title compounds were determined by ^{1}H NMR, high-resolution mass spectrometry (HRMS) and optical polarimeter. The preliminary results indicated that some of them exhibited favourable insecticidal activities against oriental armyworm (Pseudaletia separata Walker). These isomers exhibited different impact on activity following the sequence as (Sc, Ss) ≥ (Sc, Rs), and the rule of title compounds' activity against oriental armyworm was 3-CF_3 ≥ 2-CH_3-4-Cl > 2, 3, 4-trifluro in the anilide moiety. The results indicated that these groups such as 3-CF_3, 2-CH_3-4-Cl or 2, 3, 4-trifluro were inefficient to replace heptafluoroisopropyl group for high larvicidal activity, which provided some guidance for the further modifications of sulfiliminyl dicarboxamides.

Keywords:
Dual chiral
Sulfilimines
Insecticidal activity
Ryanodine receptor
Dicarboxamides

1. Introduction

With the modern agro-chemical means for pest control, crop production has made considerable progress. During the last century, a large number of insecticides including the organochlorines, organophosphates, carbamates, pyrethroids and neonicotinoids have been introduced to the market. However, some of these chemicals have brought undesired environmental and health problems [1]. Persistent

application of the insecticides with the same mode of action induced insecticide resistance has become a problem. Therefore, it is necessary to discover new insecticides with novel mechanisms of action [2]. As an ideal biological target for insecticide research, ryanodine receptor (RyR) has aroused considerable interests in integrated strategies for the development of agro-chemistry. Recently, the first commercial RyR insecticide, flubendiamide [3-4] (Fig. 1), was developed by Nihon Nohyaku jointly with Bayer and was brought to the market in 2007 [5-6]. In particular, flubendiamide [7-8] has been developed as a highly potent insecticide against lepidopteran insects [9-10].

In our previous work [11-12], dual chiral scaffolds containing sulfiliminyl substituents and their larvacidal activities were reported. For oriental armyworm, some compounds reached the same high level as flubendiamide, with LC_{50} values 0.0504 (B) and 0.0699 (C) mg/L, lower than that of flubendiamide (0.1230 mg/L) [13]. Other sulfilimine derivatives exhibited higher activity against diamondback moths than flubendiamide [14]. The previous results implied that the introduction of the dual chiral *N*-cyano sulfiliminyl substituent was favorable for the larvacidal activity. The results prompted us to explore the further structural modifications. It is well-known that heptafluoroisopropyl iodide is an expensive material for the synthesis of flubendiamide. To reduce production costs, it is necessary to identify cheaper replacement of heptafluoroisopropyl iodide. What is more, the new structure also maintains excellent insecticidal activity after the replacement of heptafluoroisopropyl group.

Enlightened by the above research, 20 novel dual chiral *N*-cyano sulfiliminyl phthalamide derivatives with these groups including 3-CF_3, 2-CH_3-4-Cl or 2, 3, 4-trifluro in the anilide moiety were designed and synthesized. All title compounds were determined by ^{1}H NMR, high-resolution mass spectrometry and optical polarimeter. The preliminary structure-activity relationship (SAR) was discussed as well.

2. Results and discussion

2.1 Synthesis

N-cyano sulfilimines can be easily obtained by sulfides in 95% ~ 99% yield with the ratio of diastereoselectivity 6:4. The synthetic method of these title compounds were shown in Scheme 1.

The title compounds have been determined by melting point, ^{1}H NMR, HRMS and optical polarimeter. The ^{1}H NMR data of *N*-cyano sulfilimines were characteristic between two diastereoisomers. The active proton signals of –NHCO- in the anilide moiety were observed at 9.83-10.88 ppm in DMSO-d_6. However, the chemical shifts of the active proton signals on the amide bridge in the aliphatic amide moiety were at δ 8.76-9.02 and δ 8.58-8.87 ppm in DMSO-d_6, respectively.

2.2 Crystal structure analysis

The crystal structure of **If** had been shown in the literature previously reported [13]. The crystal structure (0.20 mm x 0.18 mm x 0.12 mm) of compound **Ih** was cultivated from the solvent DMSO, which was selected and mounted on Rigaku Saturn 724 CCD diffractometer equipped with a graphite-monochromatic Mo*Ká* radiation (*ë* = 0.71073 Å). The data were collected at 293(2) K to a maximum θ value of 25.02 with the following index ranges: $-4 \le h \le 5$, $-26 \le k \le 26$ and $-27 \le l \le 27$. A total of 21057 integrated reflections were collected and 4473 with R_{int} = 0.0638 were independent, of which 3581 with $I > 2ó$ (*I*) were observed. The structure was resolved by direct methods with the *SHELXL-97* program [14]. Refinements were done by the full-matrix least-squares on F^2 with *SHELXL-97*. The crystal is of orthorhombic system with P2(1)2(1)2(1) space group. X-ray single crystal diffraction was shown in Fig. 2 with the following crystallographic parameters: a = 4.8338(10) Å, b = 22.320 (5) Å, c = 23.512(5) Å, α = 90 °, β = 90 °, γ = 90°, V = 2536.8(9) Å^3, Z = 4, Dc =1.414 mg/m^3, μ = 0.358 mm^{-1}, F (000) = 1128, R = 0.0797, *w*R = 0.1802, final R factor = 6.29%, final *w*R factor = 16.27%, absolute structure parameter = 0.06 (11). All the bond length and bond angle were in normal range, the N(5)-C(20) bond length of 1.172Å is intermediate between C=N(1.34-1.38 Å) and C≡N(1.14-1.16Å) may be due to the conjugation effect of S(1)=N(4). The torsion angles of S(1)-N(4)-C(20)-N(5) is 172.6 °, which indicates that the S(1)=N(4) and N(5)≡C(20) are not coplanar in the molecular structure.

2.3 Structure-activity relationship (SAR)

2.3.1 Larvicidal activity against oriental armyworm.

The larvicidal activities of compounds **5f**–**5j**, **Ia**–**Ij**, **IIa**–**IIj** and flubendiamide against oriental armyworm were shown in Table 1 and Table 2. Most title compounds showed moderate larvicidal activity against oriental armyworm. In general, the sequence of these isomers' activity is (Sc, Ss) ≥ (Sc, Rs), which is consistent with SARs described in our previous report ((Sc, Ss) ≥ (Sc, Rs) >> (Rc, Ss) > (Rc, Rs)) [13]. As shown in Table 1, **IIk** (Sc, Ss) exhibited 50% insecticidal activity at 10 mg/L, while **Ik** (Sc, Rs) gave a mortality rate of 30% at 50 mg/L. At concentration of 50 mg/L, **IIq** (Sc, Ss) (100%) possessed better insecticidal activity than **Iq** (Rc, Rs) (0%). These observations indicated that the influence of sulfur chirality on biological activities is self-evident.

From Table 1, we could find that compounds **5g**, **IIa** and **IIg** exhibited 100%, 80% and 60% activities at 25 mg/L, respectively. It was worth noting that **5g** gave the mortality of 40% at 5 mg/L. Furthermore, the iodine substituents (**5g**, **IIa** and **IIg**) showed the best larvicidal activity. For compounds with CF_3 group in the anilide moiety, **I** showed the best activity, **Br** as well as **Cl**, and **F** substituent possessed similar biological activity against oriental armyworm. As shown in Table 1, these title compounds exerted the sequence of biological activity as 3-CF_3 ≥ 2-CH_3-4-Cl > 2, 3, 4-trifluro in the anilide moiety. From Table 2, it was found that the LC_{50} value of **IIa** was 12.8448 mg/L, higher than that of Flubendiamide (0.1230 mg/L).

2.3.2 CoMFA analysis by SYBYL

With the purpose of increasing the calculated sample, the published compounds (**Ia**, **Ib**, **IIa**, **IIb**, **IId**) [13] and the novel compounds **Ia**, **Ig**, **Ij**, **IIa**, **IIg**, **IIj** were selected for 3D-QSAR model. The above compounds were prepared with *SYBYL* program, the conformations with minimum energy were evaluated by Tripos force field and Gasteiger-Hükel charges in advance. The most active molecule published **Ia** was used as a template to align the training samples by align database, the common skeleton was overlapped very well. The pIC_{50} was the activity data, and the negative logarithms of LC_{50} data were shown in Table 2. Then the 3D-QSAR model CoMFA was developed successfully. The Fig. 3 showed the CoMFA steric and electrostatic contour map. Partial least-squares analysis gives a satisfactory R^2 value of 0.952 and Q^2 value of 0.867 with 2 components, which indicates a valid and stable CoMFA model.

The left of the Fig. 3 is the steric field, the green regions mean that bulky substituents can increase the insecticidal activity, while yellow regions mean that the bulky substituents reduce the activity. From the Fig. 3, a large green region is found surrounding the $CF(CF_3)_2$ group, indicating that bulky substituents are preferred here. For instance, insecticidal activity of published compounds **Ia**, **Ib**, **IIa**, **IIb** and **IId** [13] with $CF(CF_3)_2$ group are higher than compounds **Ia**, **Ig**, **Ij**, **IIa**, **IIg**, **IIj** with other less bulky substituents. The right of the Fig. 3 is the electrostatic field, the red regions indicate that electronegative substituents will increase the insecticidal activity, while blue regions mean that electropositive substituents will increase the insecticidal activity. Here, red area near the CF_3 group, indicating a electronegative substituent will increase the activity, such as compound **IIa** has higher activities than compound **Ig**, **Ij**, **IIg** and **IIj**.

3. Conclusion

In conclusion, 20 novel optically active *N*-cyano sulfilimines were designed, synthesized and evaluated against oriental armyworm (*Pseudaletia separata* Walker) for their insecticidal activities. The results of bioassay indicated that most target compounds possessed favorable activities against oriental armyworm. For oriental armyworm, these isomers exhibited different impact on biological activity following the sequence as (Sc, Ss) ≥ (Sc, Rs), which was in accordance with SARs described in our previous report [13]. And the rule of activity against oriental armyworm was 3-CF_3 ≥ 2-CH_3-4-Cl > 2, 3, 4-trifluro in the anilide moiety. The results indicated that these groups including 3-CF_3, 2-CH_3-4-Cl or 2, 3, 4-trifluro in the anilide moiety might not be essential for favorable larvicidal activity, which provided some guidance for the further modifications of sulfiliminyl dicarboxamides.

4. Experimental

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 300 MHz (Bruker AC-P 300 spectrometer) or 400 MHz (Bruker AV 400 spectrometer) in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as internal standard, and chemical shift (δ) in (ppm) (s = singlet, d = doublet, t = triplet, m = multiplet). Elemental analyses were performed on a Vario EL elemental analyzer. HRMS data were obtained on a Varian QFT-ESI. Optical rotations were measured with Perkin-Elmer 341 polarimeter at 20 °C. GC-MS were recorded on HP 5973 MSD with 6890 GC Flash chromatography with silica gel (200-300 mesh). 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]. Compounds 3-substituented anhydride **1** **[**15-16], (*S*)-1-(methylthio)propan -2- amine **2** [17] were synthesized according to the methods reported in the literatures.

*4.2 General synthetic procedure for compounds **5a-j***

5a-j were synthesized in moderate yields by the method previously published in the literature [18]. The melting point and ^{1}H NMR data were consistent with the literature.

(*S*)-*N*^{1}-(1-(Methylthio)propan-2-yl)-*N*^{2}-(3-(trifluoromethyl)phenyl)phthalamide **5f**: White solid; yield 72.91%; mp 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H, Ar-NH), 8.36 (d, 1H, *J* = 7.7 Hz, -CNH), 8.22 (s, 1H, Ar-H), 7.90 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.58 (m, 5H, Ar-H), 7.44 (d, 1H, *J* = 7.0 Hz, Ar-H), 4.08 – 3.98 (m, 1H, -NCH), 2.66 (dd, 1H, *J* = 13.0, 6.3 Hz, -SCH_2), 2.54-2.53 (m, 1H, -SCH_2), 2.05 (s, 3H, -SCH_3), 1.19 (d, 3H, *J* = 6.3 Hz, -CCH_3).

(*S*)-*N*^{1}-(4-Chloro-2-methylphenyl)-3-iodo-*N*^{2}-(1-(methylthio)propan-2-yl)phthalamide **5g**: White solid; yield 61.74%; mp 209-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H, Ar-NH), 8.01 (d, 1H, *J* = 9.3 Hz, Ar-H), 7.94 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.73 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.18 (t, 3H, *J* = 8.0 Hz, Ar-H), 6.38 (d, 1H, *J* = 8.1 Hz, -CNH), 4.35 – 4.27 (m, 1H, -NCH), 2.63 (dd, 1H, *J* = 13.5, 6.0 Hz, -SCH_2), 2.56 (dd, 1H, *J* = 13.5, 6.3 Hz, -SCH_2), 2.29 (s, 3H, -SCH_3), 1.97 (s, 3H, $ArCH_3$), 1.25 (d, 3H, *J* = 6.6 Hz, -CCH_3).

(*S*)-*N*^{1}-(4-Chloro-2-methylphenyl)-*N*^{2}-(1-(methylthio)propan-2-yl)-3-nitrophthalamide **5h**: White solid; yield 55.23%%; mp 224-226 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s, 1H, Ar-NH), 8.63 (d, 1H, *J* = 7.6 Hz, -CNH), 8.20 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.04 (d, 1H, *J* = 7.3 Hz, Ar-H), 7.78 (t, 1H, *J* = 7.8 Hz, Ar-H), 7.54 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.36 (s, 1H, Ar-H), 7.30 (d, 1H, *J* = 7.9 Hz, Ar-H), 3.97 (m, 1H, -NCH), 2.63 (dd, 1H, *J* = 12.9, 4.3 Hz, -SCH_2), 2.37 – 2.32 (m, 1H, -SCH_2), 2.28 (s, 3H, -SCH_3), 2.02 (s, 3H, $ArCH_3$), 1.11 (d, 3H, *J* = 6.3 Hz, -CCH_3).

(*S*)-3-Iodo-*N*^{2}-(1-(methylthio)propan-2-yl)-*N*^{1}-(2,3,4-trifluorophenyl)phthalamide **5i**: White solid; yield 61.48%; mp 160-162 °C; ^{1}H NMR (400 MHz, DMSO−d_6): δ 10.21 (s, 1H, Ar-NH), 8.44 (d, 1H, *J* = 7.8 Hz, -CNH), 8.02 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.69 (d, 1H, *J* =

7.4 Hz, Ar-H), 7.51 (s, 1H, Ar-H), 7.39 – 7.32 (m, 1H, Ar-H), 7.26 (t, 1H, *J* = 7.7 Hz, Ar-H), 3.99 (dd, 1H, *J* = 12.7, 6.5 Hz, -NCH), 2.69 (dd, 1H, *J* = 13.2, 4.8 Hz, -SCH_2), 2.37 (dd, 1H, *J* = 13.1, 8.7 Hz, -SCH_2), 2.02 (s, 3H, -SCH_3), 1.15 (d, 3H, *J* = 6.5 Hz, -CCH_3).

(*S*)-*N*^{2}-(1-(Methylthio)propan-2-yl)-3-nitro-*N*^{1}-(2,3,4-trifluorophenyl)phthalamide **5j**: White solid; yield 67.52%; mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H, Ar-NH), 8.63 (d, 1H, *J* = 7.7 Hz, -CNH), 8.22 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.02 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.79 (s, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 7.39 (d, 1H, *J* = 9.0 Hz, Ar-H), 3.95 (d, 1H, *J* = 6.2 Hz, -NCH), 2.65 (dd, 1H, *J* = 13.1, 4.6 Hz, -SCH_2), 2.35 (dd, 1H, *J* = 13.0, 8.5 Hz, -SCH_2), 2.04 (s, 3H, -SCH_3), 1.12 (d, 3H, *J* = 6.5 Hz, -CCH_3).

4.3 General synthetic procedure for title compounds

These phthalamide derivatives were synthesized in moderate yield by the method reported in the literature [13].

(*S*,*R*)-3-Iodo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)p-thalamide **Ia**: White solid; yield 73.41%; mp 194-195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H, Ar-NH), 8.81 (d, 1H, *J* = 6.9 Hz, -CNH), 8.15 (s, 1H, Ar-H), 8.05 (d, 1H, *J* = 6.8 Hz, Ar-H), 7.93 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.75 (d, 1H, *J* = 6.3 Hz, Ar-H), 7.59 (d, 1H, *J* = 6.7 ,13.2Hz, Ar-H), 7.46 (d, 1H, *J* = 6.6 Hz, Ar-H), 7.32 (d, 1H, *J* = 5.9, 12.4 Hz, Ar-H), 4.25 (m, 1H, -NCH), 3.26 – 3.17 (m, 2H, -SCH_2), 2.81 (s, 3H, -SCH_3), 1.27 (d, 3H, *J* = 4.4 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}F_3IN_4O_2S$ ([M + H]$^+$), 563.0220; found, 563.0216. $[\alpha]^{20}_D$= -86.4(*c*=0.5, DMF).

(*S*,*R*)-3-Nitro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide **Ib**: White solid; yield 69.94%; mp 108-110 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H, Ar-NH), 9.02 (d, 1H, *J* = 7.9 Hz, -CNH), 8.25 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.15 (s, 1H, Ar-H), 8.09 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.93 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.83 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.62 (t, 1H, *J* = 7.9 Hz, Ar-H), 7.49 (d, 1H, *J* = 7.6 Hz, Ar-H), 4.22 (dt, 1H, *J* = 13.5, 6.7 Hz, -NCH), 3.30 (dd, 1H, *J* = 12.7, 6.1 Hz, -SCH_2), 3.17 (dd, 1H, *J* = 12.7, 7.3 Hz, -SCH_2), 2.81 (s, 3H, -SCH_3), 1.22 (d, 3H, *J* = 6.6 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}F_3N_5O_4S$ ([M + H]$^+$), 482.1105; found, 482.1103. $[\alpha]^{20}_D$=-12.0(*c*=0.07, $(CH_3)_2CO$).

(*S*,*R*)-3-Chloro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide **Ic**: White solid; yield 68.43%; mp 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H, Ar-NH), 8.91 (d, 1H, *J* = 8.1 Hz, -CNH), 8.14 (s, 1H, Ar-H), 7.94 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.72 (dd, 2H, *J* = 10.9, 7.9 Hz, Ar-H), 7.59 (dd, 2H, *J* = 12.9, 5.0 Hz, Ar-H), 7.47 (d, 1H, *J* = 7.7 Hz, Ar-H), 4.27 (dt, 1H, *J* = 14.5, 7.4 Hz, -NCH), 3.34 – 3.31 (m, 1H, -SCH_2), 3.21 (dd, 1H, *J* = 12.6, 7.7 Hz, -SCH_2), 2.83 (s, 3H, -SCH_3), 1.25 (d, 3H, *J* = 6.7 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}ClF_3N_4O_2S$ ([M + H]$^+$), 417.0864; found, 471.0868. $[\alpha]^{20}_D$=-1.0(*c*=0.33, $(CH_3)_2CO$)

(*S*,*R*)-3-Fluoro-*N*^{2}-(1-(*N*-cyano-*S*-methyl-sulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide **Id**: White solid; yield 70.62%; mp 179-181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H, Ar-NH), 8.97 (d, 1H, *J* = 8.1 Hz, -CNH), 8.15 (s, 1H, Ar-H), 7.95 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.64 – 7.59 (m, 3H, Ar-H), 7.49 (dd, 2H, *J* = 11.4, 8.6 Hz, Ar-H), 4.34 – 4.25 (m, 1H, -NCH), 3.35 (m, 1H, -SCH_2), 3.22 (dd, 1H, *J* = 12.7, 7.4 Hz, -SCH_2), 2.85 (s, 3H, -SCH_3), 1.28 (d, 3H, *J* = 6.7 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}F_4N_4O_2S$ ([M + H]$^+$), 455.1160; found, 455.1162. $[\alpha]^{20}_D$= -61.2(*c*=0.5, $(CH_3)_2CO$).

(*S*,*R*)-3-Bromo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide **Ie**: White solid; yield 71.25%; mp 182-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H, Ar-NH), 8.90 (d, 1H, *J* = 8.2 Hz, -CNH), 8.14 (s, 1H, Ar-H), 7.94 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.72 (ddd, 2H, *J* = 9.6, 9.0, 4.2 Hz, Ar-H), 7.59 (dt, 2H, *J* = 9.8, 8.0 Hz, Ar-H), 7.49 (dd, 1H, *J* = 15.1, 7.5 Hz, Ar-H), 4.31 – 4.22 (m, 1H, -NCH), 3.33 – 3.31 (m, 1H, -SCH_2), 3.20 (dd, 1H, *J* = 12.6, 7.7 Hz, -SCH_2), 2.82 (s, 3H, -SCH_3), 1.25 (d, 3H, *J* = 6.7 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}BrF_3N_4O_2S$ ([M + H]$^+$), 515.0359; found, 515.0356. $[\alpha]^{20}_D$= -0.6(*c*=0.18, DMF).

(*S*,*R*)-*N*^{2}-(1-(*N*-Cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide **If**: White solid; yield 59.86%; mp 74-78 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.69 (s, 1H, Ar-NH), 8.76 (d, 1H, *J* = 7.6 Hz, -CNH), 8.21 (s, 1H, Ar-H), 7.91 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.66 – 7.57 (m, 5H, Ar-H), 7.44 (d, 1H, *J* = 7.4 Hz, Ar-H), 4.35 – 4.25 (m, 1H, -NCH), 3.38-3.36 (m, 1H, -SCH_2), 3.29 – 3.21 (m, 1H, -SCH_2), 2.83 (s, 3H, -SCH_3), 1.29 (d, 3H, *J* = 5.6 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{19}F_3N_4O_2S$ ([M + H]$^+$), 437.1254; found, 437.1252. $[\alpha]^{20}_D$= -29.8(*c*=1, MeOH)

(*S*,*R*)-3-Iodo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(4-chloro-2-methylphenyl)phthalamide **Ig**: White solid; yield 64.24%; mp 133-134 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ 9.83 (s, 1H, Ar-NH), 8.80 (d, 1H, *J* = 7.2 Hz, -CNH), 8.03 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.77 (d, 1H, *J* = 6.6 Hz, Ar-H), 7.44 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.35 (s, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 4.25 (m, 1H, -NCH), 3.29 (m, 1H, -SCH_2), 3.20 (d, 1H, *J* = 6.5 Hz, -SCH_2), 2.71 (s, 3H, -SCH_3), 2.25 (s, 3H, $ArCH_3$), 1.26 (d, 3H, *J* = 5.8 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{20}ClIN_4O_2S$ ([M + H]$^+$), 543.0113; found, 543.0107. $[\alpha]^{20}_D$= -32.2(*c*=1, MeOH).

(*S*,*R*)-3-Nitro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(4-chloro-2-methylphenyl)phthalamide **Ih**: White solid; yield 63.84%; mp 184-185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.09 (s, 1H, Ar-NH), 9.02 (d, 1H, *J* = 7.6 Hz, -CNH), 8.25 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.11 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.83 (t, 1H, *J* = 7.9 Hz, Ar-H), 7.48 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.38 (s, 1H, Ar-H), 7.32 (d, 1H, *J* = 8.2 Hz, Ar-H), 4.24 (dt, 1H, *J* = 13.1, 6.5 Hz, -NCH), 3.28 (dd, 1H, *J* = 12.7, 5.8 Hz, -SCH_2), 3.17 (dd, 1H, *J* = 12.7, 6.7 Hz, -SCH_2), 2.74 (s, 3H, -SCH_3), 2.30 (s, 3H, $ArCH_3$), 1.23 (d, 3H, *J* = 6.6 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{20}ClN_5O_4S$ ([M + H]$^+$), 462.0998; found, 462.0994. $[\alpha]^{20}_D$= -44.8(*c*=0.5, MeOH).

(*S*,*R*)-3-Iodo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(2,3,4-trifluorophenyl)phthalamide **Ii**: White solid; yield 71.09%; mp 159-162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (s, 1H, Ar-NH), 8.78 (d, 1H, *J* = 6.7 Hz, -CNH), 8.05 (d, 1H, *J* = 7.2 Hz, Ar-H), 7.75 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.39 – 7.26 (m, 3H, Ar-H), 4.24 (m, 1H, -NCH), 3.32 – 3.28 (m, 1H, -SCH_2),

3.23-3.18 (m, 1H, -SCH_2), 2.78 (s, 3H, -SCH_3), 1.27 (d, 3H, *J* = 5.7 Hz, -CCH_3). HRMS calcd. for $C_{19}H_{16}F_3IN_4O_2S$ ([M + H]$^+$), 549.0064; found, 549.0067. $[\alpha]^{20}_D$ =+1.2(*c*=1, DMF).

(*S*,*R*)-3-Nitro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(2,3,4-trifluorophenyl)phthalamide, **Ij**: White solid; yield 63.48%; mp 160-163 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.63 (s, 1H, Ar-NH), 9.00 (d, 1H, *J* = 7.7 Hz, -CNH), 8.26 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.08 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.82 (t, 1H, *J* = 7.9 Hz, Ar-H), 7.54 (s, 1H, Ar-H), 7.41 – 7.34 (m, 1H, Ar-H), 4.25 – 4.17 (m, 1H, -NCH), 3.29 (dd, 1H, *J* = 12.7, 5.9 Hz, -SCH_2), 3.17 (dd, 1H, *J* = 12.6, 7.0 Hz, -SCH_2), 2.80 (s, 3H, -SCH_3), 1.23 (d, 3H, *J* = 6.6 Hz, -CCH_3). HRMS calcd. for $C_{19}H_{16}F_3N_5O_4S$ ([M + H]$^+$), 468.0948; found, 468.0946. $[\alpha]^{20}_D$= +10.0(*c*=1, DMF).

(*S*,*S*)-3-Iodo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide, **IIa**: White solid; yield 26.59%; mp 147-149 °C; ^{1}H NMR (400 MHz, DMSO) *δ* 10.63 (s, 1H, Ar-NH), 8.64 (d, *J* = 7.1 Hz, 1H, -CNH), 8.15 (s, 1H, Ar-H), 8.04 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.93 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.73 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.59 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.46 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.30 (t, *J* = 7.3 Hz, 1H, Ar-H), 4.23 (m, 1H, -NCH), 3.31 – 3.16 (m, 2H, -SCH_2), 2.76 (s, 3H, -SCH_3), 1.26 (d, *J* = 5.8 Hz, 3H, -CCH_3). HRMS calcd for $C_{20}H_{18}F_3IN_4O_2S$ ([M + H]$^+$), 563.0220; found, 563.0216. $[\alpha]^{20}_D$= +28.6(*c*=0.2, MeOH).

(*S*,*S*)-3-Nitro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide, **IIb**: White solid; yield 30.06%; mp 105-107 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.87 (s, 1H, Ar-NH), 8.87 (d, 1H, *J* = 7.7 Hz, -CNH), 8.25 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.17 (s, 1H, Ar-H), 8.08 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.94 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.83 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.62 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.49 (d, 1H, *J* = 7.7 Hz, Ar-H), 4.21 (m, 1H, -NCH), 3.25 (dd, 1H, *J* = 13.2, 9.4 Hz, -SCH_2), 3.16 (dd, 1H, *J* = 13.3, 4.4 Hz, -SCH_2), 2.77 (s, 3H, -SCH_3), 1.23 (d, 3H, *J* = 6.7 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}F_3N_5O_4S$ ([M + H]$^+$), 482.1105; found, 482.1103. $[\alpha]^{20}_D$= +8.0(*c*=0.1, MeOH).

(*S*,*S*)-3-Chloro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide, **IIc**: White solid; yield 31.57%; mp 148-150 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.64 (s, 1H, Ar-NH), 8.72 (d, *J* = 4.2 Hz, 1H, -CNH), 8.15 (s, 1H, Ar-H), 7.89 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.71 – 7.66 (m, 2H, Ar-H), 7.62 – 7.54 (m, 2H, Ar-H), 7.46 (d, *J* = 7.7 Hz, 1H, Ar-H), 4.24-4.21 (m, 1H, -NCH), 3.29 – 3.17 (m, 2H, -SCH_2), 2.78 (s, 3H, -SCH_3), 1.22 (d, *J* = 6.7 Hz, 3H, -CCH_3). HRMS calcd. for $C_{20}H_{18}ClF_3N_4O_2S$ ([M + H]$^+$), 471.0864; found, 471.0868. $[\alpha]^{20}_D$= -+51.6(*c*=0.5, $(CH_3)_2CO$).

(*S*,*S*)-3-Fluoro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide, **IId**: White solid; yield 29.38%; mp 110-112 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.74 (s, 1H, Ar-NH), 8.76 (d, 1H, *J* = 7.9 Hz, -CNH), 8.15 (s, 1H, Ar-H), 7.94 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.60 (dd, 3H, *J* = 10.5, 6.0 Hz, Ar-H), 7.47 (t, 2H, *J* = 8.9 Hz, Ar-H), 4.29-4.22 (m, 1H, -NCH), 3.28 (dd, 1H, *J* = 13.2, 9.5 Hz, -SCH_2), 3.21 (dd, 1H, *J* = 13.2, 4.5 Hz, -SCH_2), 2.80 (s, 3H, -SCH_3), 1.26 (d, 3H, *J* = 6.7 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}F_4N_4O_2S$ ([M + H]$^+$), 455.1160; found, 455.1162. $[\alpha]^{20}_D$= +76.8(*c*=0.5, $(CH_3)_2CO$).

(*S*,*S*)-3-Bromo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide, **IIe**: White solid; yield 28.75%; mp 201-203 °C;^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.72 (s, 1H, Ar-NH), 8.73 (s, 1H, -CNH), 8.15 (s, 1H, Ar-H), 7.93 (d, 1H, *J* = 8.9 Hz, Ar-H), 7.73 – 7.66 (m, 2H, Ar-H), 7.63 – 7.54 (m, 2H, Ar-H), 7.46 (d, 1H, *J* = 7.7 Hz, Ar-H), 4.29 – 4.20 (m, 1H, -NCH), 3.32 – 3.30 (m, 1H, -SCH_2), 3.23 (dd, 1H, *J* = 13.4, 7.1 Hz, -SCH_2), 2.78 (s, 3H, -SCH_3), 1.24 (d, 3H, *J* = 6.7 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{18}BrF_3N_4O_2S$ ([M + H]$^+$), 515.0359; found, 515.0356. $[\alpha]^{20}_D$= +59.2(*c*=0.29, DMF).

(*S*,*S*)-*N*^{2}-(1-(*N*-Cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(3-(trifluoromethyl)phenyl)phthalamide, **IIf**: White solid; yield 40.14%; mp 85-87 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.68 (s, 1H, Ar-NH), 8.58 (d, 1H, *J* = 7.2 Hz, -CNH), 8.20 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.59 (d, 5H, *J* = 5.9 Hz, Ar-H), 7.44 (d, 1H, *J* = 7.2 Hz, Ar-H), 4.27 (m, 1H, -NCH), 3.29 (d, 2H, *J* = 9.6 Hz, -SCH_2), 2.81 (s, 3H, -SCH_3), 1.27 (d, 3H, *J* = 6.6 Hz, -CCH_3). $C_{20}H_{19}F_3N_4O_2S$. HRMS calcd. for $C_{20}H_{19}F_3N_4O_2S$ ([M + H]$^+$), 437.1254; found, 437.1252. $[\alpha]^{20}_D$= +45.1(*c*=1, MeOH).

(*S*,*S*)-3-Iodo-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(4-chloro-2-methylphenyl)phthalamide, **IIg**: White solid; yield 35.76%; mp 109-111 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 9.81 (s, 1H, Ar-NH), 8.64 (d, 1H, *J* = 6.3 Hz, -CNH), 8.02 (d, 1H, *J* = 6.3 Hz, Ar-H), 7.74 (s, 1H, Ar-H), 7.47 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.35 (s, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 4.22 (m, 1H, -NCH), 3.29 – 3.22 (m, 1H, -SCH_2), 3.16 (d, 1H, *J* = 11.9 Hz, -SCH_2), 2.71 (s, 3H, -SCH_3), 2.26 (s, 3H, $ArCH_3$), 1.27 (d, 3H, *J* = 4.1 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{20}ClIN_4O_2S$ ([M + H]$^+$), 543.0113; found, 543.0107. $[\alpha]^{20}_D$= +115.6(*c*=1, MeOH)

(*S*,*S*)-3-Nitro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(4-chloro-2-methylphenyl)phthalamide, **IIh**: White solid; yield 36.16%; mp 129-130 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.06 (s, 1H, Ar-NH), 8.84 (d, 1H, *J* = 7.5 Hz, -CNH), 8.23 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.08 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.82 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.50 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.36 (s, 1H, Ar-H), 7.30 (d, 1H, *J* = 8.3 Hz, Ar-H), 4.18 (m, 1H, -NCH), 3.26 – 3.18 (m, 1H, -SCH_2), 3.13 (dd, 1H, *J* = 13.2, 4.1 Hz, -SCH_2), 2.71 (s, 3H, -SCH_3), 2.28 (s, 3H, $ArCH_3$), 1.24 (d, 3H, *J* = 6.6 Hz, -CCH_3). HRMS calcd. for $C_{20}H_{20}ClN_5O_4S$ ([M + H]$^+$), 462.0998; found, 462.0994. $[\alpha]^{20}_D$= +24.0(*c*=0.2, MeOH).

(*S*,*S*)-3-Nitro-*N*^{2}-(1-(*N*-cyano-*S*-methylsulfinimidoyl)-propan-2-yl)-*N*^{1}-(2,3,4-trifluorophenyl)phthalamide, **IIj**: White solid; yield 36.52%; mp 168-170 °C;^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 10.60 (s, 1H, Ar-NH), 8.85 (d, 1H, *J* = 7.5 Hz, -CNH), 8.25 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.06 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.81 (t, 1H, *J* = 7.9 Hz, Ar-H), 7.58 (s, 1H, Ar-H), 7.37 (dd, 1H, *J* = 17.7, 8.7 Hz, Ar-H), 4.18 (m, 1H, -NCH), 3.27 – 3.20 (m, 2H, -SCH_2), 3.15 (dd, 1H, *J* = 13.2, 4.3 Hz, -SCH_2), 2.77 (s, 3H, -SCH_3), 1.24 (d, 3H, *J* = 6.6 Hz, -CCH_3). HRMS calcd for $C_{19}H_{16}F_3N_5O_4S$ ([M + H]$^+$), 468.0948; found, 468.0946. $[\alpha]^{20}_D$= -86.4(*c*=0.5, DMF).

4.4 X-ray diffraction

The crystals of compound **If** and **Ih** were established, and X-ray intensity data were measured at 298K on a Bruker SMART 1000 CCD area detector diffraction meter with graphite monochromated Mo Kα radiation (λ=0.71073 Å). All hydrogen atoms were observed and placed at their calculated positions with a fixed value of their isotropic displacement parameters.

4.5 Biological assay

All biological assays were carried out on representative test organisms prepared in the laboratory. The bioassay experiments were repeated at 25 ± 1 ºC 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].

4.5.1 Larvicidal activity against oriental armyworm (Mythimna separate Walker)

The insecticidal activity of compounds **5f**–**5j**, **Ia**–**Ij**, **IIa**–**IIj** and Flubendiamide were evaluated using the reported procedure [21]. 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.

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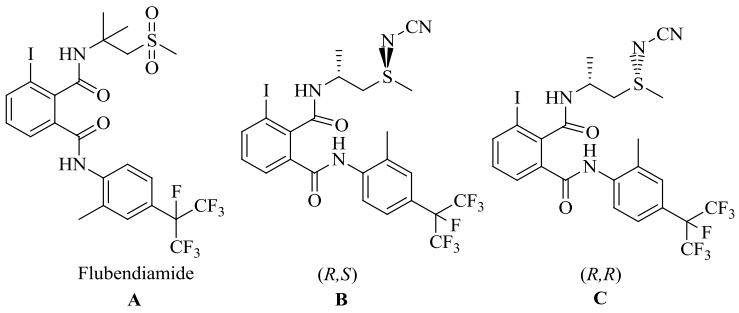


Fig. 1. The structures of Flubendiamide (A) and N-cyano sulfilimine (B)

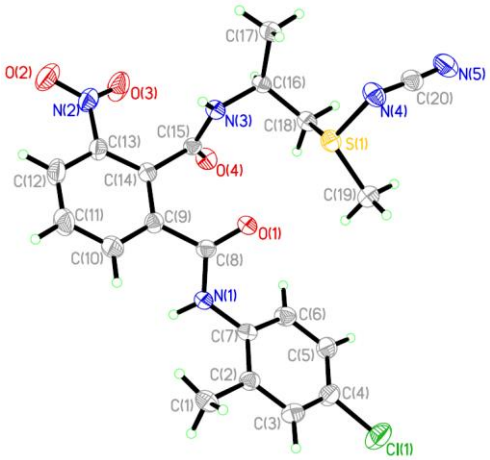


Fig. 2. Crystal structure of compound **Ih**

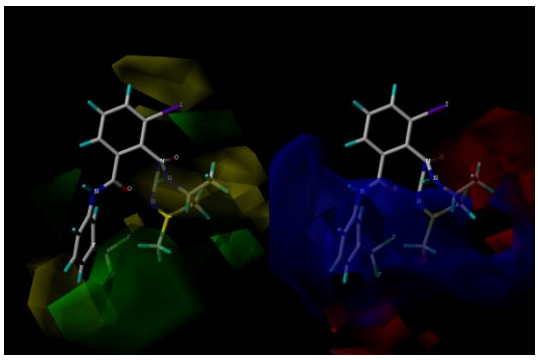
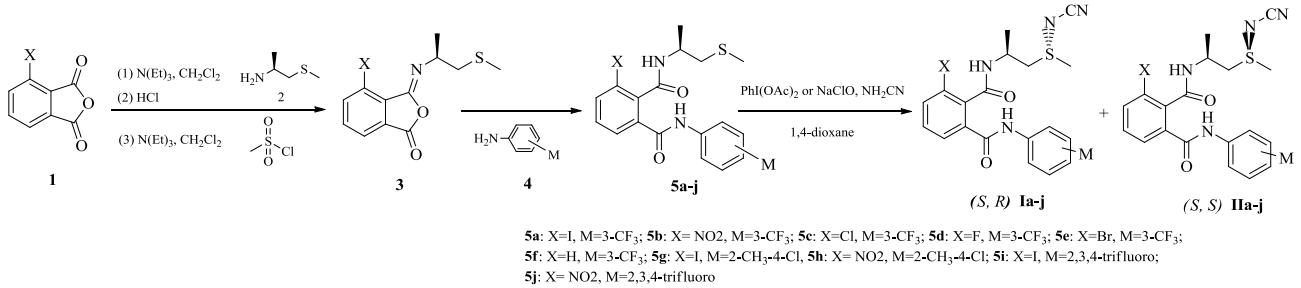


Fig. 3. The CoMFA results of compound **Ia**



5a: X=I, M=3-CF_3; **5b**: X= NO2, M=3-CF_3; **5c**: X=Cl, M=3-CF_3; **5d**: X=F, M=3-CF_3; **5e**: X=Br, M=3-CF_3; **5f**: X=H, M=3-CF_3; **5g**: X=I, M=2-CH_3-4-Cl, **5h**: X= NO2, M=2-CH_3-4-Cl; **5i**: X=I, M=2,3,4-trifluoro; **5j**: X= NO2, M=2,3,4-trifluoro

Scheme 1 The synthetic procedure of Title Compounds

Table 1

Insecticidal activities of compounds **5f-5j**, **Ia-Ij**, **IIa-IIj** and flubendiamide against oriental armyworm

Compd.	Larvicidal activity (%) at conc. (mg/L)					
	200	100	50	25	10	5
5f	10					
5g	100	100	100	100	100	40
5h	100	60				
5i	75					
5j	20					
Ia	100	100	30			
Ib	10					
Ic	100	100	40	15		
Id	50					
Ie	100	100	40			
If	35					
Ig	100	40				
Ih	100	20				
Ii	50					
Ij	25					
IIa	100	100	100	80	50	
IIb	10					
IIc	100	100	60			
IId	40					
IIe	100	100	60	10		
IIf	35					
IIg	100	100	100	60		
IIi	30					
IIj	30					
flubendiamide	100	100	100	100	100	100

Table 2.

LC50 values of compounds **ia**, **ig**, **ij**, **iia**, **iig**, **iij** and flubendiamide against oriental armyworm

Compd.	y=a+bx	R	LC_{50} ($mg \cdot L^{-1}$)	LC_{95} ($mg \cdot L^{-1}$)
Ia	y=1.2188+1.8661x	0.9809	106.2315	808.5173
Ig	y=-12.2716+8.0423x	0.9747	140.4774	224.9744
Ij	y=-3.8711+3.4239x	0.9527	389.8511	1178.4100
IIa	y=3.4424+1.4049x	0.9761	12.8448	190.3473
IIg	y=-3.6189+3.3477x	0.9115	375.4853	1163.9502
IIj	y=0.1006+2.0568x	0.9521	241.0443	1519.9492
flubendiamide	y=7.4237+2.6428x	0.9945	0.1230	0.5160