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Investigation of the "methyl" impact on bio-activity of dicarboxamides as potential ryanodine receptor activators

Ruyi Jin[1], Weibin Xie[2], Linshan Li[2], Huangong Li[2], Na Yang[2], Yuxin Li[2], Lixia Xiong[2], Yu Zhao[2], Zhengming Li[2], Sha Zhou[2,*]

[1]College of Pharmacy, Shaanxi University of Chinese Medicine, Xi'an/Xianyang, China 712046

[2]State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China

Abstract: To investigate the impact of methyl group in dicarboxamides on bioactivity as ryanodine receptor activators, compound B and C were designed, synthesized and evaluated against oriental armyworm (Pseudaletia separata Walker) and diamondback moth (Plutella xylostella (L.)) for their insecticidal activity. All structures were characterized by 1H NMR, 13C NMR and HRMS and their relative absolute configurations were confirmed by chiral HPLC and optical polarimeter. The bioassay results showed that the number of methyl group incorporated in the dicarboxamide structures have clearly impact on each biological activity following the sequence as di-methyl (A) ~ mono-methyl (B) > no methyl group (C). The optical isomer of S configuration (D) originated from structure B showed stronger activity than R configuration (E), as well as higher activity against diamondback moth (Plutella xylostella (L.)) than the corresponding A. Through mode of action study by whole-cell patch-clamp revealed that these compounds released stored calcium ions from endoplasmic reticulum. It was concluded that chiral carbon with S configuration in the aliphatic amido side chain of dicarboxamide might be a critical factor from the standpoint of molecular design strategy.

Keywords: Methyl group; Insecticidal; activities; Flubendiamide; Chiral; Absolute configuration

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*Corresponding Author: Sha Zhou, zhousha@nankai.edu.cn

1. Introduction

Ryanodine is a natural structurally complex alkaloid (Figure 1), which had been utilized as a botanical insecticide. However, many attempts to generate synthetic commercial analogues of ryanodine have been unsuccessful. Moreover, its mammalian toxicity has precluded its agricultural use [1-2]. In 2007, the first synthetic insecticide Flubendiamide (A) targeting at new insect Ryanodine Receptor (RyR) was marketed by Nihon Nohyaku and Bayer, which had a novel mode of action for controlling *lepidopterous* pests [3-10]. Afterwards some modified structures (Figure 1) have been reported, which mainly focused on the phthaloyl moiety, sulfonylalkyl group in the aliphatic amide moiety and heptafluoroisopropyl group in the anilide moiety [11].

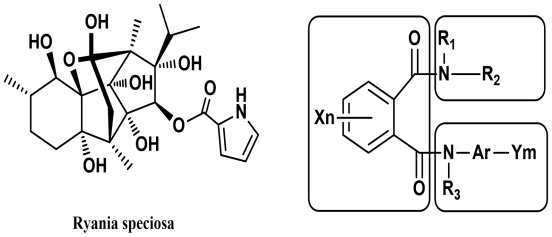


Figure 1. The Structure of Ryania speciosa and Structural Modification.

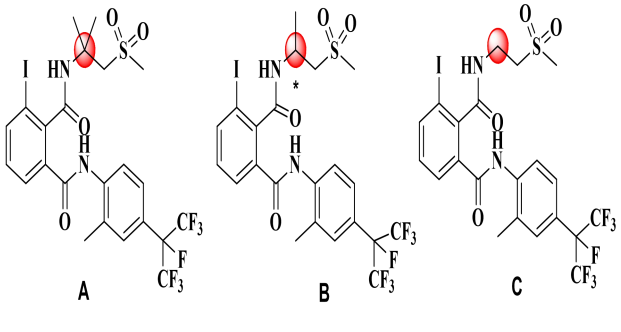


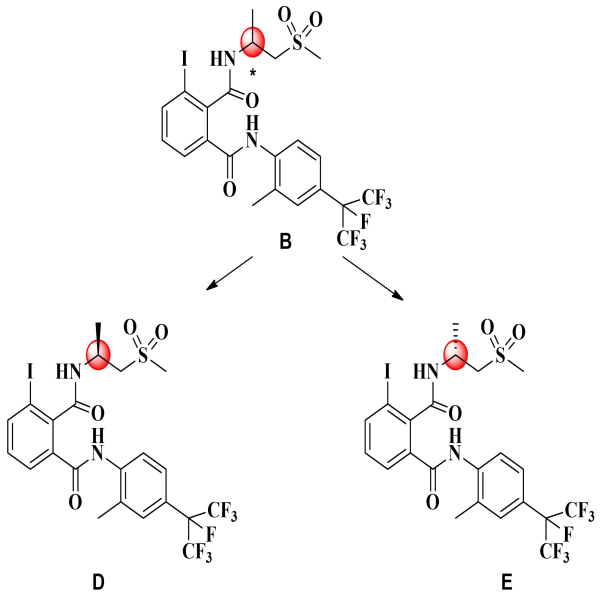
Figure 2. The scheme of molecular design.

It is hard to predict what will happen on insecticidal activities when the number of methyl group in sulfonylalkyl group varies (n = 0, 1 or 2).

Furthermore, the S configuration of structure B (Figure 2) was reported to be active against beet armyworm (*Spodoptera exigua*) [12-13]. It is also interesting to notice what will be the difference of both enantiomers from B.

Compounds A (Flubendiamide), B, C, D and E were synthesized in our Lab. Their activities against oriental armyworm (Pseudaletia separata Walker) and diamondback moth (Plutella xylostella (L.)) were evaluated and compared accordingly. Effects of title

compounds on Calcium Channels of Neurons from S.exigua were further explored. The relating structure-activity relationship was discussed.

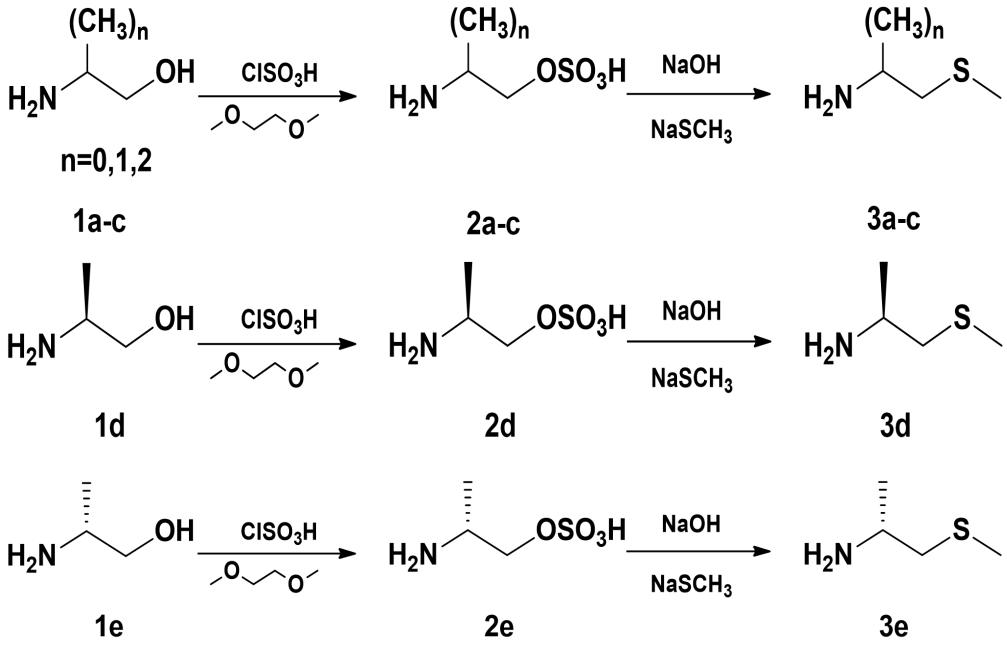


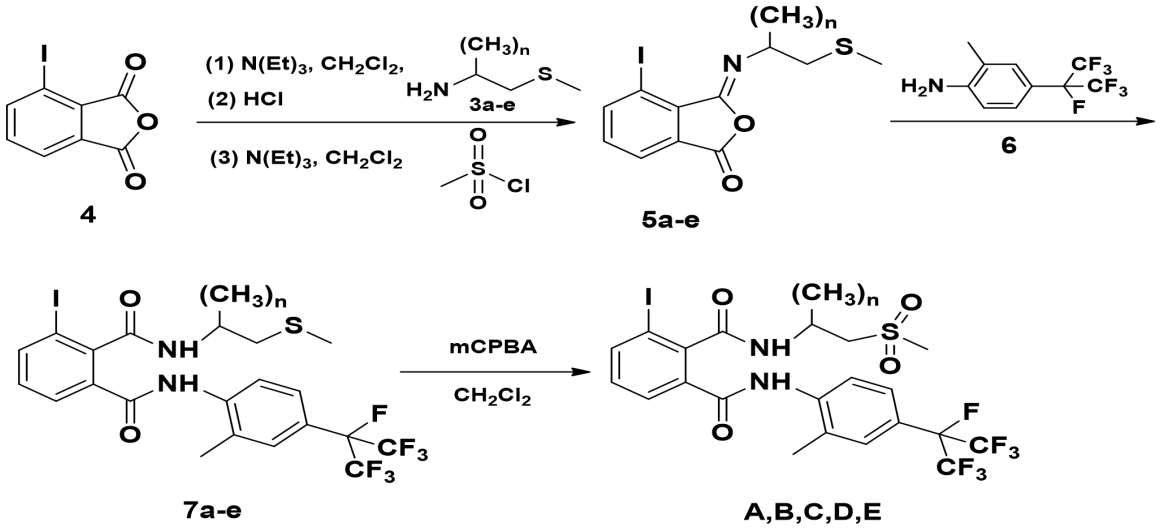
Scheme 1. Synthetic route of B, D, E structures.

2. Materials and Methods

2.1 Instruments and Materials

The melting points determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instrument Co.,Beijing, China) uncorrected. Infrared spectra recorded on a Nicolet MAGNA-560 spectrophotometer as KBr tablets. 1H NMR and 13C NMR spectra recorded at 300MHz (Bruker AC-P 300 spectrometer) or 400MHz (Bruker AV 400 spectrometer) in CDCl3 or DMSO-d6 solution with tetramethylsilane as internal standard, and chemical shift (δ) in (ppm). Elemental analyses performed on a Vario EL elemental analyzer. HRMS data by Varian QFT-ESI. Optical rotations measured with Perkin-Elmer 341 polarimeter at 20 oC. HPLC analysis performed on Shimadzu CTO-10AS by using a Chirapak AD-H and AS-H column from Daicel Chemical Inustries. GC-MS recorded on HP 5973 MSD with 6890 GC Flash chromatography with silica gel (200-300 mesh). Reagents all analytically pure. All solvents and liquid reagents dried by standard methods and distilled before use. Commercial insecticides Flubendiamide was used only as control, synthesized according to the literature [14]. Compounds aliphatic amine, 3a-e [15], 3-iodophthalic anhydride 4 [16-18], 2-methyl-4-(perfluoropropan-2-yl) aniline 6 were synthesized referring to literature [19].





Scheme 2. Synthetic route of title structures.

2.1.1 Synthesis of intermediate compounds

Data for 1-(methylthio)propan-2-amine **3d-e**, pale yellow liquid, yield 57.8%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (dqd, *J* = 8.4, 6.3, 4.5 Hz, 1H), 2.42 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.19 (dd, *J* = 13.2, 8.4 Hz, 1H), 1.95 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H);

(S)-1-(methylthio)propan-2-amine **3d**, $[\alpha]^{20}_D$=+30.13 (c=53.7, $CHCl_3$);

(R)-1-(methylthio)propan-2-amine **3e**, $[\alpha]^{20}_D$=-29.79 (c=53.2, $CHCl_3$);

2.1.2 General procedure for the Synthesis of compound 5a-e

The intermediate 5a-e was synthesized by the reaction of 3-iodophthalic anhydride 4 with 1-(methylthio)propan-2-amine 3a-e in dichloromethane, followed by cyclization by methylsulfonyl chloride in dichloromethane. Compound 5a-e was identified by GC-MS. The reaction solution was used in the subsequent reaction without workup [14].

2.1.3 General procedure for the Synthesis of compounds 7a-e

To the above reaction solution of 5a-e in dichloromethane was added 2-methyl-4-(perfluoropropan-2-yl) aniline 6. The reaction mixture stirred for an additional hour under ice bath and then warmed to room temperature. The reaction progress was monitored by TLC. The compounds were purified by silica gel column chromagraphy [20].

These phthalamide derivatives (7a-b, 7d-e) were synthesized in moderate yields. The melting point and ^{1}H NMR data were consistent with the literature [7, 21].

Data for 3-iodo-N^1-(2-methyl-4-(perfluoropropan-2-yl)phenyl)-N^2- (2-(methylthio)ethyl)phthalamide (**7c**) white solid, yield: 52%; mp. 164-166 °C (dec.), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H, ArNH), 8.26 (d, *J* = 8.6 Hz, 1H, ArH), 7.97 (d, *J* = 7.9 Hz, 1H, ArH), 7.78 (d, *J* = 7.7 Hz, 1H, ArH), 7.44 (d, *J* = 14.2 Hz, 2H, ArH), 7.22 (t, *J* = 7.9 Hz, 1H, ArH), 6.55 (t, *J* = 5.6 Hz, 1H, -CNH), 3.61 (q, *J* = 6.2 Hz, 2H, -NCH_2), 2.66 (t, *J* = 6.4 Hz, 2H, -SCH_2), 2.38 (s, 3H, $ArCH_3$), 1.98 (s, 3H, -SCH_3).

2.1.4 General procedure for the Synthesis of target compounds

To a solution of 8 (0.5 mmol) in dichloromethane (10 mL) was added 3-chloroperoxybenzoic acid (mCPBA) (1.65 mmol). The reaction was carried out at room temperature, monitored by TLC. After the disappearance of 7a-e, the mixture poured into water; the product extracted with chloroform. The organic layer washed with an aqueous sodium hydrosulfite and sodium carbonate solution respectively, and dried over anhydrous sodium sulfate. The solvent removed under reduced pressure, the residue was purified by column chromatrography [14].

Data for 3-iodo-N^1-(2-methyl-4-(perfluoropropan-2-yl)phenyl)-N^2-(1-(methylsulfonyl)propan-2-yl) phthalamide B. white solid, Yield: 90%; mp 116-119 °C, ^{1}H NMR (400 MHz, $CDCl_3$) 8.25 (s, 1H, NH), 8.20 (d, *J* = 8.3 Hz, 1H, ArH), 7.97 (d, *J* = 7.9 Hz, 1H, ArH), 7.70 (d, *J* = 7.7 Hz, 1H, ArH), 7.45 (d, *J* = 8.0 Hz, 2H, ArH), 7.21 (t, *J* = 7.8 Hz, 1H, ArH), 6.71 (d, *J* = 7.8 Hz, 1H, NH), 4.60 (dt, *J* = 12.9, 6.5 Hz, 1H, CH), 3.34 (dd, *J* = 14.2, 4.8 Hz, 1H, CH_2), 3.15 (dd, *J* = 14.2, 6.1 Hz, 1H, CH_2), 2.70 (s, 3H, $ArCH_3$), 2.37 (s, 3H, -SCH_3), 1.50 (d, *J* = 6.9 Hz, 3H, -CCH_3). ^{13}C NMR δ 169.00, 165.00, 142.11, 139.96, 138.31, 135.37, 131.13, 129.21, 128.37, 124.39, 127.90, 123.02, 121.95, 94.02, 77.35, 76.72, 58.26, 42.53, 41.94, 19.64, 18.06. HRMS (ESI) calcd for:

$C_{22}H_{20}F_7IN_2O_4S$, $(M+H)^+$, 669.0142, found 669.0149.

Data for 3-iodo-N^1-(2-methyl-4-(perfluoropropan-2-yl)phenyl)-N^2-(2-(methylsulfonyl)ethyl)phthal- amide C. white solid, Yield: 82%; mp 119-121 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.6 Hz, 1H, NH), 8.15 (s, 1H, ArH), 7.99 (d, *J* = 7.9 Hz, 1H, ArH), 7.73 (d, *J* = 7.7 Hz, 1H, ArH), 7.46 (d, *J* = 13.0 Hz, 2H, ArH), 7.23 (t, *J* = 7.9 Hz, 1H, ArH), 6.87 (t, *J* = 7.5 Hz, 1H, NH), 3.93 (dd, *J* = 11.5, 6.0 Hz, 2H, -NCH_2), 3.22-3.26 (m, 2H, SCH_2), 2.71 (s, 3H, $ArCH_3$), 2.37 (s, 3H, -SCH_3), HRMS (ESI) calcd for: $C_{21}H_{18}F_7IN_2O_4S$, 676.9818, $(M+Na)^+$, Found 676.9812.

Data for (S)-3-iodo- N^1-(2-methyl-4-(perfluoropropan-2-yl)phenyl)-N^2-(1-(methylsulfonyl)propan- 2-yl) phthalamide D white solid, Yield: 89%; mp 118-119 °C, $[\alpha]^{20}_D$=-2.4 (c=10.0, EtOAc), ($[\alpha]^{20}_D$=-0.39 (c=1.03, $CHCl_3$)) *(16)*. ^{1}H NMR (400 MHz, $CDCl_3$) 8.25 (s, 1H, NH), 8.20 (d, *J* = 8.3 Hz, 1H, ArH), 7.97 (d, *J* = 7.9 Hz, 1H, ArH), 7.70 (d, *J* = 7.7 Hz, 1H, ArH), 7.45 (d, *J* = 8.0 Hz, 2H, ArH), 7.21 (t, *J* = 7.8 Hz, 1H, ArH), 6.71 (d, *J* = 7.8 Hz, 1H, NH), 4.60 (dt, *J* = 12.9, 6.5 Hz, 1H, CH), 3.34 (dd, *J* = 14.2, 4.8 Hz, 1H, CH_2), 3.15 (dd, *J* = 14.2, 6.1 Hz, 1H, CH_2), 2.70 (s, 3H, $ArCH_3$), 2.37 (s, 3H, -SCH_3), 1.50 (d, *J* = 6.9 Hz, 3H, -CCH_3). ^{13}C NMR δ 169.00, 165.00, 142.11, 139.96, 138.31, 135.37, 131.13, 129.21, 128.37, 124.39, 127.90, 123.02, 121.95, 94.02, 77.35, 76.72, 58.26, 42.53, 41.94, 19.64, 18.06, HRMS (ESI) calcd for: $C_{22}H_{20}F_7IN_2O_4S$, $(M+H)^+$, 669.0142, found 669.0149. The ee was determined by HPLC using a Chiralpak AD-H column [hexane/i-PrOH (80:20)], flow rate 1.0 ml min^{-1} (97.8% ee)

Data for (R)-3-iodo-N^1-(2-methyl-4-(perfluoropropan-2-yl)phenyl)-N^2-(1-(methylsulfonyl)propan-2-yl) phthalamide (**E**) white solid, mp 118-120 °C,Yield 88%, $[\alpha]^{20}_D$=+2.3 (c=10, EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, NH), 8.17 (d, *J* = 9.0 Hz, 1H, ArH), 7.96 (d, *J* = 7.9 Hz, 1H, ArH), 7.69 (d, *J* = 7.6 Hz, 1H, ArH), 7.44 (d, *J* = 6.3 Hz, 2H, ArH), 7.20 (t, *J* = 7.8 Hz, 1H, ArH), 6.78 (d, *J* = 7.9 Hz, 1H, NH,), 4.58 (dt, *J* = 12.8, 6.5 Hz, 1H, CH), 3.33 (dd, *J* = 14.2, 4.7 Hz, 1H, CH_2), 3.14 (dd, *J* = 14.2, 6.1 Hz, 1H, CH_2), 2.68 (s, 3H, $ArCH_3$), 2.36 (s, 3H, -SCH_3), 1.49 (d, *J* = 6.9 Hz, 3H, -CCH_3).^{13}C NMR δ 169.13, 165.13, 142.23, 140.11, 138.43, 135.48, 131.23, 129.37, 128.49, 127.98, 124.51, 123.05, 122.12, 94.15, 77.48, 76.84, 58.38, 42.65, 42.02, 19.76, 18.18, HRMS (ESI) calcd for: $C_{22}H_{20}F_7IN_2O_4S$, $(M+H)^+$, 669.0142, found 669.0149, The ee was determined by HPLC using a Chiralpak AD-H column [hexane/i-PrOH (80:20)], flow rate 1.0 ml min^{-1} (99.2% ee).

2.2 Biological Assay

All bioassays were performed on representative test organisms reared in greenhouse. The bioassay was replicated 3 times at 25±1 oC according to statistical requirements. Assessments were made on a dead/alive basis, and morality rates corrected using Abbott's formula. Evaluations were based on a percentage scale of 0-100, in which 0 = no activity and 100 = total kill. The standard deviation of the tested biological values were ± 5%.

Larvicidal Activity against Oriental Armyworm (Pseudaletia separata Walker) The larvicidal activity evaluated according to reported leaf-dip method [22]. Their activity is summarized in Table 1.

Larvicidal Activity against Diamondback Moth (Plutella xylostella L.) The larvicidal activity of the title compounds and Flubendiamide as control against diamondback moth was tested by the leaf-dip method using the reported procedure [23-24]. The insecticidal activity is summarized in Table 2.

Table 1 Insecticidal Activity against Oriental Armyworm of Title Compounds

Compd.	larvicidal activity (%) at conc. (mg·L^{-1})										
	200	100	50	25	10	5	2.5	1	0.5	0.25	0.1
B	100	100	100	100	100	100	100	100	100	100	20
C	100	100	100	100	50						
D	100	100	100	100	100	100	100	100	100	100	30
E	100	100	100	100	100	100	100	100	100	100	
Flubendiamide (A)			100	100	100	100	100	100	100	100	50

Table 2 Insecticidal Activity against Diamondback moth of Title Compounds

Compd.	larvicidal activity (%) at conc. (mg·L^{-1})							
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}
B	100	100	100	100	100	100	43	14
C	100	100	100	86	57			
D	100	100	100	100	100	100	100	50
E	100	100	100	100	57			
Flubendiamide (A)			100	100	100	100	57	14

3. Results and Discussions

The novel structures of title compounds have been characterized by melting point, 1H NMR, 13C NMR, HRMS. Chiral configurations were also characterized by chiral HPLC and optical polarimeter. All spectral and analytical data were consistent with the assigned structures, also the same results of the FT-IR spectra identifying D and E. It showed two characteristic vibration bands at 3453 cm-1 and 3265 cm-1 for N-H stretching. The strong peaks at 1647-1443 cm-1 are ascribed to the C=O group as well. After trying with various solvents, crystals of these chiral compounds were finally obtained in binary solvent mixture (iso-propanol and n-heptane or acetone and n-hexane). X-ray approach was undertaken to elucidate the structural configuration of D and E crystals obtained in this laboratory repetitively for scores of times, due to its lacking high-angle diffraction spots and instability of the crystals at the testing condition, the X-ray experiment data regrettably can not be provided.

3.1 Structure-Activity Relationship (SAR)

3.1.1 Larvicidal Activity against Oriental Armyworm (Pseudaletia separata Walker)

The larvicidal activities of compounds against oriental armyworm were listed in Table 1, from which it was found that the insecticidal activity of structure B was close to the commercial Flubendiamide. Compared with A and B, C with no methyl group exhibited moderate activities. As a result, the number of methyl group had clearly bestowed different impact on each biological activity following the sequence as di-methyl ~ mono-methyl > no methyl group in a decreasing order. Further investingaion of bio-activity of each optical isomer (D or E), it was found that **D** exhibited 30% larvicidal activity at 0.1 mgL^{-1} against oriental armyworm, which reached the similar larvicidal level of flubendiamide (A). However, its enantiomer, compound E showed inferior activity at a concentration of 0.1 mg L^{-1}. Considering our previous work, the chirality was essential for activity in sulfilimine and sulfoximine, among which S configurations gave better activity than R counterparts[25]. The results clearly indicated that chirality plays a critical role in bioactivity in this class of dicarboxamides.

3.1.2 Larvicidal Activity against Diamondback Moth (Plutella xylostella L.)

The larvicidal activities against diamondback moth of the title compounds were shown in Table 2. From which we can see that most compounds showed excellent larvicidal activities (100% at 0.001 mg L^{-1}). In comparison of A, B, C, of which B had reached the high activity level as A (Flubendiamide) and behaved much better than C. The bioassay further showed that B (with S configuration) has superior larvicidal activity against diamondback moth than Flubendiamide at a extreme low rate as 10^{-8} mg L^{-1}. Compared with D, E (with R configuration) showed inferior activity. It was concluded that chiral carbon with S configuration in the aliphatic amido side chain of dicarboxamide might be a critical factor from the standpoint of molecular design strategy.

3.2 Effect of title compound on Calcium Channels of Neurons from beet armyworm (Spodoptera exigua)

As in our previous paper [26-27], the neurons of beat armyworm (*Spodoptera exigua)* were chosen for the study of the calcium transduction mechanism by imaging technique on beet armyworm. These novel compounds involved in the calcium concentration were tested**.** Fluorescence values were expressed as F/F0, F0 being the resting (or baseline) fluorescence, and F the change in fluorescence from baseline after the drug application with insecticidal activity were tested. The effects on the calcium homeostasis of beet armyworm were studied after the neurons loading with fluo-3 AM.

Figure1 shows the change of [Ca^{2+}]i versus recording time when the neurons were treated with flubendiamide, B, C, D and E. Application of novel compounds to isolated beet armyworm neurons caused an increase in the cytosolic calcium concentration. The

peaks of calcium concentration were elevated to 107.68 ± 3.61 % (n = 9), 106.54 ± 3.12 % (n = 9), 103.30 ± 1.83 % (n = 9), 107.90 ± 3.29 % (n = 9) and 106.41 ± 2.58 % (n = 9) of the initial value when the cells were treated with 100 mgL^{-1} flubendiamide, B, C, D and E respectively. From these experiment results, it can be concluded that these compounds could increase the intracellular Ca^{2+} through activate the calcium channel in the ER. The elevations of Ca^{2+} concentrations were due to release from internal stores. On the other hand, compared insecticide bioactivities against oriental armyworms with the $[Ca^{2+}]i$, we found the recorded $[Ca^{2+}]i$ (F/F0) had a good positive correlation.

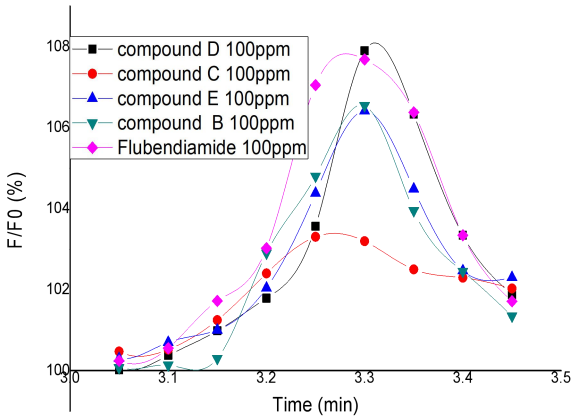


Figure 3. The change of $[Ca^{2+}]_i$ versus recording time when the neurons were treated with flubendiamide, B, C, D and E. The central neurons of *S. exigua* third larvae were dyed by loading with fluo-3 AM.

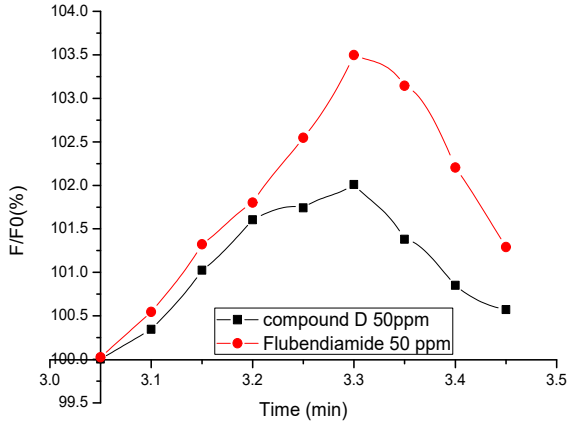


Figure 4. Effects of 50 ppm of flubendiamide and D on $[Ca^{2+}]_i$ in the central neurons of *S. exigua* when extracellular Ca^{2+} was in absence (EGTA replace Ca^{2+}). The central neurons of *S. exigua* third larvae were dyed by loading with fluo-3 AM.

Figure 2 exhibits change of $[Ca^{2+}]i$ versus recording time when the neurons were treated with 50 ppm of D and flubendiamide. Compared with figure 1, the peak of $[Ca^{2+}]i$ were decreased to 103.51 ± 3.25 % (n = 9) and 102.01 ± 1.29 % (n = 9) of the initial value after the neurons treated with 50 ppm flubendiamide and compound D shorter than 20 seconds respectively. From Figure 1 and 2, in estimation of F/FO value on nerve neurons of Noctuids pests, D curve seems lower than flubendiamide.

4. Conclusions

It is the first report of the investigation of the methyl group impact on bio-activity of dicarboxamides, as well as the R configuration (E) in this class of structures. The biological assessment indicated that the number of methyl group has clearly bestowed different impact on biological activity following the sequence as di-methyl ~ mono-methyl > no methyl group. Within the B structure the S optical isomer (D) behaved better than its R counterpart (E). It was worth noting that D exhibited excellent insecticidal activities against oriental armyworm and diamondback moth comparable to the commercial Flubendiamide (A), as even better in certain case. The whole-cell patch-clamp technique indicated that these compounds released stored calcium ions from endoplasmic reticulum. Our research denoted that compound D could be considered as a potential novel RyR activator. It was concluded that chiral carbon with S configuration in the aliphatic amido side chain of dicarboxamide might be a critical factor from the standpoint of molecular design strategy in search of novel insecticides.

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Notes

The authors declare no competing financial interest.

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