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Synthesis and Insecticidal Activities of Novel Phthalic Acid Diamides

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In order to discover novel insecticides with the new action mode on ryanodine receptor (RyR), a series of novel phthalic acid diamide derivatives were designed and synthesized. All compounds were characterized by ^{1}H NMR spectra and HRMS. The preliminary results of biological activity assessment indicated that some title compounds exhibited excellent insecticidal activities against *Mythimna separata*, *Spodoptera exigua*, and *Plutella xylostella*. The title compound 3-nitro-*N*-cyclopropyl-*N'*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (**4a**) was more efficient against diamondback moths than the control (chlorantraniliprole). The effects of some title compounds on intracellular calcium of neurons from the *Spodoptera exigua* proved that the title compounds were RyR activators.

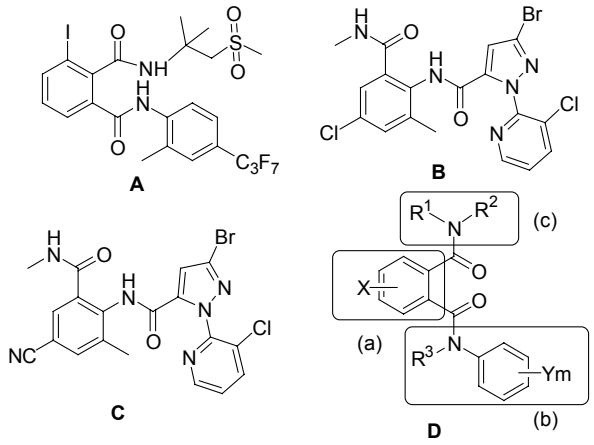
Keywords phthalic acid diamides, insecticidal activity, ryanodine receptor, activators

Introduction

In order to overcome resistance and ecobiological problems associated with conventional insecticides, there is an urgent need to discover novel potent insecticides with a new action mode.[1] The ryanodine receptor (RyR) represents a new target to study in integrated strategies for pest management.[2,3] To date, there are only three commercial products targeting the RyR, namely: flubendiamide (Scheme 1, **A**),[4] chlorantraniliprole (Rynaxypyr) (Scheme 1, **B**) and cyantraniliprole (Cyazypyr) (Scheme 1, **C**).[5,6] They stabilise insect RyR channels to the open state, evoke massive calcium release from intracellular stores and then disrupt calcium homeostasis, and possess distinct pharmacological characteristics.[7]

Since the discovery of phthalic acid diamides, most modifications can be categorized into three substructures (Scheme 1, **D**): the phthalic acid moiety (a), aromatic amide moiety (b) and aliphatic amide moiety (c).[8] In previous work, most modifications are related to parts a and b.[9-13] However, less research has been devoted to the modification of part c, it has been reported that the biological activity of such compounds can be affected by changing the aliphatic amide skeleton to a large extent.[12,14,15] In consideration of the above viewpoints, a series of novel phthalic acid diamides containing heptafluoroisopropylaniline were synthesized as shown in Scheme 2. Their bioactivity against oriental armyworms (*Mythimna separata*), beet armyworms (*Spodoptera exigua*) and diamondback moths (*Plutella xylostella*) were tested accordingly. The effect of these compounds on intracellular calcium concentration in the central neurons isolated from the third instar of *Spodoptera exigua* was studied by calcium imaging technique as well.[16]

Scheme 1 Chemical structures of compounds **A**—**D**



Experimental

Materials and instruments

^{1}H NMR spectra were recorded on a Bruker 400

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MHz or 300 MHz nuclear magnetic resonance spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as internal standard. High resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. The melting points were determined on an X-4 melting point apparatus. All the reagents were of analytical grade.

General procedure for the synthesis of intermediates 2 and 3

Synthetic route of the intermediates (compounds **2** and **3**) was shown in Scheme 2. They were synthesized according to the methods reported in the literature[13,17] with some modification.

3-Nitrophthalic anhydride (2) Yield 98.7%, yellow solid, m.p. 160—162 ℃ (lit. 163—165 ℃).[18]

2-(2-Methyl-4-(perfluoropropan-2-yl)phenyl)-4-nitro-isoindoline-1,3-dione (3) Yield 91.5%, yellow solid, m.p. 146—148 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, $^3J_{HH}$=7.50 Hz, 1H, Ar-H), 8.21 (d, $^3J_{HH}$=8.14 Hz, 1H, Ar-H), 8.02 (t, $^3J_{HH}$=7.80 Hz, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.59 (d, $^3J_{HH}$=8.50 Hz, 1H, Ar-H), 7.36 (d, $^3J_{HH}$=8.42 Hz, 1H, Ar-H), 2.30 (s, 3H, Ar-CH_3).

General procedure for the synthesis of compounds 4a—4c

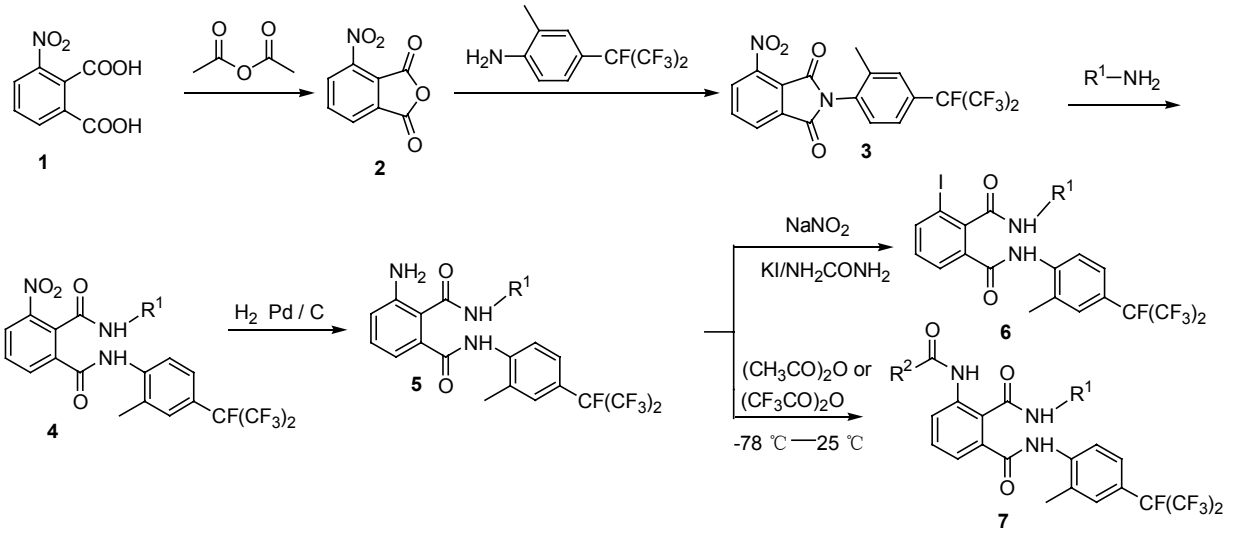
Synthetic route of title compounds was shown in Scheme 2. The synthetic procedure was described below.

To a solution of compound **3** (0.50 mmol) and potassium carbonate (10 mg) in 10 mL of tetrahydrofuran, aliphatic amine (0.50 mmol) in 5 mL of tetrahydrofuran was added dropwise at the room temperature. The resulting mixture was then stirred for 1—12 h and monitored by TLC. After evaporation, extracted twice with 20 mL of dichloromethane, the combined organic layer was sequentially washed with 1 mol/L HCl, saturated sodium bicarbonate solution and brine. The resulting solution was dried and evaporated to give the crude residue, which was further purified by flash chromatography on silica gel with petroleum/ethyl acetate (4∶1, volume ratio) to afford the title compounds **4a**—**4c**.

3-Nitro-*N*-cyclopropyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (4a) Yield 61.7%, white solid, m.p. 218—220 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, 1H, Ar-NH), 8.28 (d, $^3J_{HH}$=8.10 Hz, 1H, Ar-H), 8.08 (d, $^3J_{HH}$=7.42 Hz, 1H, Ar-H), 7.69 (t, $^3J_{HH}$=7.90 Hz, 1H, Ar-H), 7.54—7.41 (m, 2H, Ar-H), 6.28 (s, 1H, N**H**CHCH$_2$CH$_2$), 2.86—2.77 (m, 1H, C**H**CH$_2$CH$_2$), 2.42 (s, 3H, Ar-CH$_3$), 0.84—0.74 (m, 2H, CHCH$_2$C**H**$_2$), 0.59—0.50 (m, 2H, CHC**H**$_2$CH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.1, 146.8, 139.2, 137.2, 133.6, 133.0, 131.5, 130.0, 127.1, 125.6, 125.5, 123.2, 121.9, 121.7, 119.0, 118.7, 22.5, 18.0, 5.3. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M + Na]$^+$) 530.0921, found 530.0934.

3-Nitro-*N*-butyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (4b) Yield 65.2%, white solid, m.p. 224—226 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, 1H, Ar-N**H**), 8.37 (d, $^3J_{HH}$=8.82 Hz, 1H, Ar-H), 8.30 (d, $^3J_{HH}$=8.40 Hz, 1H, Ar-H), 8.13 (d, $^3J_{HH}$=7.74 Hz, 1H, Ar-H), 7.72 (t, $^3J_{HH}$=8.00 Hz, 1H, Ar-H), 7.48 (d, $^3J_{HH}$=9.20 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 6.09 (s, 1H, N**H**CH$_2$CH$_2$CH$_2$CH$_3$), 3.41 (dd, $^3J_{HH}$=13.30, $^4J_{HH}$=6.82 Hz, 2H, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.40 (s, 3H, Ar-CH$_3$), 1.47—1.40 (m, 2H, CH$_2$C**H**$_2$-CH$_2$CH$_3$), 1.28—1.18 (m, 4H, CH$_2$C**H**$_2$CH$_2$CH$_3$), 0.73 (t, $^3J_{HH}$=7.30 Hz, 3H, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.1, 163.7, 146.8, 139.2, 137.2, 133.0, 132.9, 131.4, 130.0, 127.2, 125.4, 125.0, 123.3, 121.6, 121.4, 118.7, 38.9, 30.5, 19.5, 17.9, 13.4. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M + Na]$^+$) 546.1234, found 546.1242.

Scheme 2 Synthesis of compounds **4**, **5**, **6**, **7**



4a, **5a**, **6a**: R^1 = cyclopropyl; **4b**, **5b**, **6b**: R^1 = *n*-butyl; **4c**, **5c**, **6c**: R^1 = *i*-amyl; **7a**: R^1 = cyclopropyl, R^2 = CH_3; **7b**: R^1 = *n*-butyl, R^2 = CH_3; **7c**: R^1 = *i*-amyl, R^2 = CH_3; **7d**: R^1 = *n*-butyl, R^2 = CF_3; **7e**: R^1 = *i*-amyl, R^2 = CF_3

3-Nitro-*N*-isopentyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (4c) Yield 58.4%, white solid, m.p. 230—231 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (s, 1H, Ar-N**H**), 8.36 (d, $^3J_{HH}$=8.72 Hz, 1H, Ar-H), 8.29 (d, $^3J_{HH}$=8.20 Hz, 1H, Ar-H), 8.10 (d, $^3J_{HH}$=7.70 Hz, 1H, Ar-H), 7.70 (t, $^3J_{HH}$=8.00 Hz, 1H, Ar-H), 7.48 (d, $^3J_{HH}$=8.82 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 6.14 (t, $^3J_{HH}$ = 5.62 Hz, 1H, N**H**CH_2CH_2-$CH(CH_3)_2$), 3.42 (q, $^3J_{HH}$=6.60 Hz, 2H, NHC**H**$_2CH_2$-$CH(CH_3)_2$), 2.40 (s, 3H, Ar-CH_3), 1.54—1.48 (m, 1H, $NHCH_2CH_2C$**H**$(CH_3)_2$), 1.30 (q, $^3J_{HH}$=7.20 Hz, 2H, $NHCH_2C$**H**$_2CH(CH_3)_2$), 0.72 (d, $^3J_{HH}$=6.60 Hz, 6H, $NHCH_2CH_2CH(C$**H**$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 164.6, 145.6, 138.0, 136.4, 134.5, 130.1, 128.0, 126.4, 124.2, 123.4, 123.2, 122.1, 121.8, 119.2, 119.0, 38.9, 37.7, 25.4, 22.0, 18.0. HRMS calcd for $C_{23}H_{21}F_7N_3O_4$ ([M−H]$^-$) 536.1426, found 536.1421.

General procedure for the synthesis of compounds 5a—5c

Synthetic route of title compounds was shown in Scheme 2. The synthetic procedure was described below.

Compounds **4** (0.50 mmol) in 200 mL methanol were placed into a flask and stirred at 60 ℃ until dissolved completely and then 10% Pd/C (0.05 mmol) was added. The mixture was intensively stirred under H_2 at 60 ℃ for 1—4 h, monitored with TLC and then filtered. The resulting solution was evaporated to give the crude product. It was further purified by flash chromatography on silica gel with petroleum/ethyl acetate (2∶1, volume ratio) to afford the title compounds **5a**—**5c**.

3-Amino-*N*-cyclopropyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (5a) Yield 85.3%, white solid, m.p. 164—167 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (d, $^3J_{HH}$=8.50 Hz, 1H, Ar-N**H**), 7.54 (s, 1H, Ar-N**H**), 7.49 (d, $^3J_{HH}$=8.72 Hz, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 7.24 (t, $^3J_{HH}$=8.00 Hz, 1H, Ar-H), 6.93 (d, $^3J_{HH}$=7.42 Hz, 1H, Ar-H), 6.81 (d, $^3J_{HH}$=8.10 Hz, 1H, Ar-H), 6.42 (s, 1H, N**H**$CHCH_2CH_2$), 4.66 (s, 2H, Ar-N**H**$_2$), 2.74—2.86 (m, 1H, C**H**CH_2CH_2), 2.33 (s, 3H, Ar-CH_3), 0.76—0.69 (m, 2H, CHC**H**$_2CH_2$), 0.30—0.35 (m, 2H, $CHCH_2C$**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.0, 168.0, 145.9, 138.3, 135.6, 131.0, 128.4, 127.8, 124.5, 122.8, 122.6, 121.3, 119.0, 118.5, 118.0, 117.0, 23.1, 18.0, 6.4. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M + Na]$^+$) 500.1179, found 500.1174.

3-Amino-*N*-butyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (5b) Yield 95.6%, white solid, m.p. 159—161 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, $^3J_{HH}$=8.62 Hz, 1H, Ar-H), 7.61 (s, 1H, Ar-N**H**), 7.51 (d, $^3J_{HH}$=8.80 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.31 (d, $^3J_{HH}$=7.34 Hz, 1H, Ar-H), 7.00 (d, $^3J_{HH}$=7.34 Hz, 1H, Ar-H), 6.85 (d, $^3J_{HH}$=7.90 Hz, 1H, Ar-H), 6.27 (s, 1H, N**H**$CH_2CH_2CH_2CH_3$), 4.63 (s, 2H, Ar-N**H**$_2$), 3.33 (q, $^3J_{HH}$=6.50 Hz, 2H, NHC**H**$_2CH_2$-CH_2CH_3), 2.35 (s, 3H, Ar-CH_3), 1.38—1.31 (m, 2H, $NHCH_2C$**H**$_2CH_2CH_3$), 1.27—1.16 (m, 2H, $NHCH_2$-CH_2C**H**$_2CH_3$), 0.71 (t, $^3J_{HH}$=7.20 Hz, 3H, $NHCH_2$-CH_2CH_2C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 168.0, 145.7, 138.5, 135.5, 130.9, 128.2, 127.8, 124.5, 122.6, 122.4, 121.2, 119.3, 118.6, 118.4, 117.2, 39.9, 31.5, 20.0, 17.9, 13.4. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 516.1492, found 516.1495.

3-Amino-*N*-isopentyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (5c) Yield 81.7%, white solid, m.p. 95—97 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.33 (s, 1H, Ar-N**H**), 7.99 (dd, $^3J_{HH}$=13.82, $^4J_{HH}$=7.3 Hz, 2H, Ar-H), 7.50 (s, 1H, Ar-H), 7.49 (d, $^3J_{HH}$=7.90 Hz, 1H, Ar-H), 7.17 (t, $^3J_{HH}$=7.80 Hz, 1H, N**H**$CH_2CH_2CH(CH_3)_2$), 6.83 (t, $^3J_{HH}$=7.50 Hz, 2H, Ar-H), 5.29 (s, 2H, Ar-N**H**$_2$), 3.13 (q, $^3J_{HH}$=6.80 Hz, 2H, NHC**H**$_2CH_2CH(CH_3)_2$), 2.35 (s, 3H, Ar-CH_3), 1.48—1.36 (m, 1H, $NHCH_2CH_2C$**H**$(CH_3)_2$), 1.15 (q, $^3J_{HH}$=7.00 Hz, 2H, $NHCH_2C$**H**$_2CH(CH_3)_2$), 0.63 (d, $^3J_{HH}$=16.40, 6H, $NHCH_2CH_2CH(C$**H**$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 167.9, 145.7, 138.5, 135.5, 130.9, 128.0, 127.8, 124.5, 122.6, 122.4, 121.1, 119.3, 118.6, 118.4, 117.2, 38.4, 38.2, 25.5, 22.0, 17.9. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 530.1649, found 530.1646.

General procedure for the synthesis of compounds 6a—6c

Synthetic route of title compounds was shown in Scheme 2. The synthetic procedure was described below.

To a solution of compound **5** (0.5 mmol) in 20 mL 20% diluted hydrochloric acid at 0 ℃, sodium nitrite (1.00 mmol) dissolved in 5 mL of water was added dropwise. The resulting mixture was stirred for 2 h and 0.1 g urea was added. After the mixture was intensively stirred for 15 min, an aqueous solution of KI (0.6 mmol) was added dropwise. The resulting mixture was then stirred for 2 h at room temperature and monitored by TLC. The solution was extracted with CH_2Cl_2 (30 mL×3) and dried over Na_2SO_4. After filtration, the solvent was evaporated to give the crude product. It was further purified by flash chromatography on silica gel with petroleum/ethyl acetate (4∶1, volume ratio) to afford the title compounds **6a**—**6c**.

3-Iodo-*N*-cyclopropyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (6a) Yield 22.8%, white solid, m.p. 210—211 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (s, 1H, Ar-NH), 8.11 (d, $^3J_{HH}$=8.42 Hz, 1H, Ar-H), 7.90 (d, $^3J_{HH}$=7.70 Hz, 1H, Ar-H), 7.65 (d, $^3J_{HH}$=7.42 Hz, 1H, Ar-H), 7.42 (s, 2H, Ar-H), 7.13 (t, $^3J_{HH}$=7.70 Hz, 1H, Ar-H), 6.63 (s, 1H, N**H**$CHCH_2$-CH_2), 2.87—2.76 (m, 1H, C**H**CH_2CH_2), 2.38 (s, 3H, Ar-CH_3), 0.85—0.75 (m, 2H, CHC**H**$_2CH_2$), 0.66—0.56 (m, 2H, $CHCH_2C$**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.5, 154.6, 143.4, 139.4, 135.8, 135.0, 132.4, 131.5, 128.8, 127.1, 125.3, 123.2, 121.2, 121.0, 119.0, 115.8, 31.5, 17.8, 6.2. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 611.0037, found 611.0039.

3-Iodo-*N*-butyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (6b) Yield 76.4%, white solid, m.p. 210—212 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (s, 1H, Ar-NH), 8.36 (d, $^3J_{HH}$=8.70 Hz, 1H, Ar-H), 7.99 (d, $^3J_{HH}$=7.92 Hz, 1H, Ar-H), 7.81 (d, $^3J_{HH}$=7.74 Hz, 1H, Ar-H), 7.46 (d, $^3J_{HH}$=8.90 Hz, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.23 (t, $^3J_{HH}$=8.00 Hz, 1H, Ar-H), 6.02 (t, $^3J_{HH}$=5.60 Hz, 1H, N**H**$CH_2CH_2CH_2CH_3$), 3.40 (q, $^3J_{HH}$=6.70 Hz, 2H, NHC**H**$_2CH_2CH_2CH_3$), 2.38 (s, 3H, Ar-CH_3), 1.51—1.41 (m, 2H, $NHCH_2C$**H**$_2CH_2CH_3$), 1.30—1.21 (m, 2H, $NHCH_2CH_2C$**H**$_2CH_3$), 0.73 (t, $^3J_{HH}$=7.30 Hz, 3H, $NHCH_2CH_2CH_2C$**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 165.2, 141.9, 140.2, 138.5, 135.2, 130.9, 129.2, 129.1, 127.9, 124.3, 122.8, 122.6, 121.5, 119.3, 93.5, 40.2, 31.1, 20.0, 18.1, 13.4. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 627.0350, found 627.0357.

3-Iodo-*N*-isopentyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (6c) Yield 58.5%, white solid, m.p. 198—200 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (s, 1H, Ar-NH), 8.26 (d, $^3J_{HH}$=8.42 Hz, 1H, Ar-H), 7.94 (d, $^3J_{HH}$=7.90 Hz, 1H, Ar-H), 7.72 (d, $^3J_{HH}$=7.70 Hz, 1H, Ar-H), 7.43 (d, $^3J_{HH}$=8.84 Hz, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.17 (t, $^3J_{HH}$=7.80 Hz, 1H, Ar-H), 6.35 (s, 1H, N**H**$CH_2CH_2CH(CH_3)_2$), 3.41 (q, $^3J_{HH}$=6.70 Hz, 2H, NHC**H**$_2CH_2CH(CH_3)_2$), 2.38 (s, 3H, Ar-CH_3), 1.56—1.46 (m, 1H, $NHCH_2CH_2C$**H**$(CH_3)_2$), 1.33 (q, $^3J_{HH}$=7.10 Hz, 2H, $NHCH_2C$**H**$_2CH(CH_3)_2$), 0.73 (d, $^3J_{HH}$=16.40, 6H, $NHCH_2CH_2CH(C$**H**$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 165.2, 141.9, 140.2, 138.5, 135.2, 130.9, 129.1, 129.0, 127.9, 124.3, 122.8, 122.6, 121.4, 119.3, 93.5, 38.7, 38.0, 25.5, 22.0, 18.0. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M + Na]$^+$) 641.0506, found 641.0509.

General procedure for the synthesis of compounds 7a—7c

Synthetic route of title compounds was shown in Scheme 2. The synthetic procedure was described below.

Compound **5** (0.50 mmol) in 10 mL acetic anhydride was stirred at room temperature for 10 min. The reaction mixture was filtered and the residue was dissolved in ethyl acetate. The solution was sequentially washed with saturated sodium bicarbonate solution, brine and dried over Na_2SO_4. After filtration, the solvent was evaporated to give the products **7a**—**7c**.

3-Acetamido-*N*-cyclopropyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (7a) Yield 95.6%, white solid, m.p. 204—206 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.07 (s, 1H, Ar-NH), 8.36 (d, $^3J_{HH}$=8.20 Hz, 1H, Ar-H), 8.26 (d, $^3J_{HH}$=8.92 Hz, 1H, Ar-H), 7.59 (s, 1H, N**H**$COCH_3$), 7.50 (d, $^3J_{HH}$=7.42 Hz, 1H, Ar-H), 7.46 (d, $^3J_{HH}$=10.80 Hz, 2H, Ar-H), 7.31 (d, $^3J_{HH}$=7.5 Hz, 1H, Ar-H), 6.78 (s, 1H, N**H**$CHCH_2CH_2$), 2.87—2.78 (m, 1H, C**H**CH_2CH_2), 2.33 (s, 3H, Ar-CH_3), 2.19 (s, 3H, $NHCOC$**H**$_3$), 0.79—0.72 (m, 2H, CHC**H**$_2$-CH_2), 0.45—0.37 (m, 2H, $CHCH_2C$**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.8, 167.2, 166.5, 139.6, 136.1, 135.1, 133.2, 130.4, 128.9, 127.2, 126.8, 125.1, 124.0, 123.3, 121.4, 121.2, 119.0, 23.4, 22.5, 17.9, 5.6. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 542.1285, found 542.1279.

3-Acetamido-*N*-butyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (7b) Yield 96.8%, white solid, m.p. 190—192 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (s, 1H, Ar-NH), 8.35 (d, $^3J_{HH}$=8.22 Hz, 1H, Ar-H), 8.31 (d, $^3J_{HH}$=8.62 Hz, 1H, Ar-H), 7.66 (s, 1H, N**H**$COCH_3$), 7.52—7.42 (m, 3H, Ar-H), 7.33 (d, $^3J_{HH}$=7.62 Hz, 1H, Ar-H), 6.73 (t, $^3J_{HH}$=6.50 Hz, 1H, N**H**$CH_2CH_2CH_2CH_3$), 3.32 (q, $^3J_{HH}$=6.50 Hz, 1H, C**H**$CH_2CH_2CH_3$), 2.32 (s, 3H, Ar-CH_3), 2.18 (s, 3H, $NHCOC$**H**$_3$), 1.41—1.28 (m, 2H, CHC**H**$_2CH_2CH_3$), 1.24—1.15 (m, 2H, $CHCH_2C$**H**$_2CH_3$), 0.71 (t, $^3J_{HH}$=7.30 Hz, 3H, $CHCH_2CH_2C$**H**$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.8, 166.5, 165.9, 139.6, 136.0, 135.1, 132.5, 130.3, 128.8, 127.1, 126.7, 124.6, 124.0, 123.3, 121.2, 120.1, 119.0, 38.8, 30.9, 23.4, 19.5, 17.9, 13.4. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M + Na]$^+$) 558.1598, found 558.1598.

3-Acetamido-*N*-isopentyl-*N′*-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (7c) Yield 93.4%, white solid, m.p. 195—197 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (s, 1H, Ar-N**H**), 8.37 (t, $^3J_{HH}$=8.02 Hz, 2H, Ar-H), 7.67 (s, 1H, N**H**$COCH_3$), 7.54—7.42 (m, 3H, Ar-H), 7.35 (d, $^3J_{HH}$=7.60 Hz, 1H, Ar-H), 6.69 (t, $^3J_{HH}$=5.20 Hz, 1H, N**H**$CH_2CH_2CH(CH_3)_2$), 3.35 (q, $^3J_{HH}$=6.20 Hz, 2H, NHC**H**$_2CH_2CH(CH_3)_2$), 2.34 (s, 3H, Ar-CH_3), 2.19 (s, 3H, $NHCOC$**H**$_3$), 1.53—1.43 (m, 1H, $NHCH_2CH_2C$**H**$(CH_3)_2$), 1.25 (q, $^3J_{HH}$=7.20 Hz, 2H, $NHCH_2C$**H**$_2CH(CH_3)_2$), 0.74 (d, $^3J_{HH}$=6.60, 6H, $NHCH_2CH_2CH(C$**H**$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 167.4, 167.3, 138.3, 135.9, 134.9, 130.6, 128.7, 127.9, 125.1, 124.8, 124.4, 123.4, 123.1, 122.9, 121.7, 119.3, 38.6, 38.0, 25.6, 24.6, 22.1, 17.9. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M + Na]$^+$) 572.1755, found 572.1755.

General procedure for the synthesis of compounds 7d and 7e

Synthetic route of title compounds was shown in Scheme 2. The synthetic procedure was described below.

Compound **5** (0.50 mmol) and 15 mL tetrahydrofuran were placed into a flask and stirred at −78 ℃ and then trifluoroacetic anhydride (0.6 mmol) was added dropwise. The temperature of the reaction mixture was warmed to room temperature within 4 h and the mixture was then stirred for another 4 h, monitored by TLC. The reaction mixture was poured into the water and filtered. The residue was dissolved in ethyl acetate. The solution was sequentially washed with saturated sodium bicarbonate solution, brine and dried over Na_2SO_4. After filtration, the solvent was evaporated to give the products **7d** and **7e**.

3-Trifluoroacetamido-*N*-butyl-*N′*-[2-methyl-4-

(perfluoropropan-2-yl)phenyl]phthalamide (7d) Yield 67.1%, white solid, m.p. 200—202 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.74 (s, 1H, N**H**$COCF_3$), 8.52 (d, $^3J_{HH}$=8.30 Hz, 1H, Ar-H), 8.31 (d, $^3J_{HH}$=8.52 Hz, 1H, Ar-H), 7.61 (t, $^3J_{HH}$=8.00 Hz, 1H, Ar-H), 7.52 (d, $^3J_{HH}$=11.20 Hz, 1H, Ar-H), 7.50 (s, 1H, Ar-N**H**), 7.47—7.40 (m, 2H, Ar-H), 6.92 (t, $^3J_{HH}$=4.84 Hz, 1H, N**H**$CH_2CH_2CH_2CH_3$), 3.36 (q, $^3J_{HH}$=6.80 Hz, 1H, C**H**$CH_2CH_2CH_3$), 2.32 (s, 3H, Ar-CH_3), 1.41—1.31 (m, 2H, CHC**H**$_2CH_2CH_3$), 1.24—1.14 (m, 2H, $CHCH_2$-C**H**$_2CH_3$), 0.71 (t, $^3J_{HH}$=7.30 Hz, 3H, $CHCH_2CH_2$-C**H**$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.2, 165.1, 155.3, 139.5, 136.7, 133.0, 132.1, 131.8, 129.5, 128.4, 127.1, 126.9, 125.0, 123.2, 121.4, 121.2, 119.0, 114.4, 38.8, 30.8, 19.5, 17.9, 13.3. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 612.1315, found 612.1319.

3-Trifluoroacetamido-*N*-isopentyl-*N*′-[2-methyl-4-(perfluoropropan-2-yl)phenyl]phthalamide (7e) Yield 58.4%, white solid, m.p. 177—179 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.73 (s, 1H, N**H**$COCF_3$), 8.51 (d, $^3J_{HH}$=8.02 Hz, 1H, Ar-H), 8.32 (d, $^3J_{HH}$=7.64 Hz, 1H, Ar-H), 7.60 (t, $^3J_{HH}$=5.84 Hz, 1H, Ar-H), 7.51 (s, 2H, Ar-H), 7.46 (s, 1H, Ar-NH), 7.43 (d, $^3J_{HH}$=6.82 Hz, 1H, Ar-H), 6.87 (s, 1H, N**H**$CH_2CH_2CH(CH_3)_2$), 3.37 (q, $^3J_{HH}$=5.30 Hz, 2H, NHC**H**$_2CH_2CH(CH_3)_2$), 2.32 (s, 3H Ar-CH_3), 1.50—1.37 (m, 1H, $NHCH_2CH_2C$**H**$(CH_3)_2$), 1.24 (q, $^3J_{HH}$=5.70 Hz, 2H, $NHCH_2C$**H**$_2CH(CH_3)_2$), 0.72 (d, $^3J_{HH}$=4.12, 6H, $NHCH_2CH_2CH(C$**H**$_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.2, 165.1, 155.3, 139.5, 136.7, 133.0, 132.6, 132.2, 129.5, 128.4, 127.2, 126.6, 124.7, 123.3, 121.3, 121.1, 117.3, 114.4, 37.5, 37.2, 24.7, 22.0, 17.9. HRMS calcd for $C_{21}H_{16}F_7N_3O_4Na$ ([M+Na]$^+$) 626.1472, found 626.1469.

Biological assay

Insecticidal activities against oriental armyworms, beet armyworms and diamondback moths were performed on test organisms reared in a greenhouse. The bioassay was replicated at 25 ℃ according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected applying Abbott's formula.[19] Evaluation was based on a percentage scale of 0—100, where 0 equals no activity and 100 equals total kill. Error of the experiments was 5%. For comparative purposes, chlorantraniliprole was tested as control under the same conditions. The insecticidal activity is summarized in Tables 1, 2 and 3.

Larvicidal activity against oriental armyworms

The insecticidal activities of compounds **4a**—**4c**, **5a**—**5c**, **6a**—**6c**, **7a**—**7e** and chlorantraniliprole were evaluated using the reported procedure.[20] The insecticidal activity against oriental armyworms was tested by foliar application; individual corn (Tangyu 10, Zeamays L.) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 2 d after treatment. Each treatment was replicated three times.

Larvicidal activity against beet armyworms

The larvicidal activities of compounds **4a**—**6a**, **6b** and chlorantraniliprole were tested by the artificial feeddip method.[21] At first, a solution of each test sample in DMSO (AR, purchased from AlfaAesar) at a concentration of 200 mg/L was prepared and then diluted to the required concentration with water (distilled). 2 g feed was placed individually into beakers and then was sprayed with the test solution. The resulting feed was infested with ten third-instar beet armyworms larvae. Percentage mortalities were evaluated 2 d after treatment. Each treatment was performed three times.

Larvicidal activity against diamondback moths

The larvicidal activity of compounds **4a** and the control chlorantraniliprole was tested by the leafdip method. At first, a solution of each test sample in DMF (AR, purchased from AlfaAesar) at a concentration of 200 mg/L was prepared and then diluted to the required concentration with water (distilled). Leaf disks (6 cm×2 cm) were cut from fresh cabbage leaves and then were sprayed with the test solution for 3 s and allowed to dry. The resulting leaf disks were placed individually into glass tubes. Each disk was infested with seven second-instar diamondback moth larvae. Percentage mortalities were evaluated 2 d after treatment. Each treatment was performed three times.

Isolation of neural cells

Spodoptera exigua were initially obtained from shallot fields in Tianjin City, China and reared indoors in climatic chambers on an agar-based semisynthetic diet at (27±1) ℃, (75±5)% relative humidity, and a LD 16∶8 h photocycle.[22] The insects were reared for two generations prior to the experiment. Third instar larvae of *S. exigua* were first anaesthetized with 70% ethanol and their thoracic and abdomen ganglia were removed and placed in saline. The thoracic and abdomen ganglia were transferred to a solution containing 0.3% trypsin for 6 min at 28 ℃, plated into a 35 mm culture dish containing 1 mL of improved L-15 Leibovitz culture medium supplemented with fetal calf serum (15%, *V*∶*V*)[23] and then mechanically dissociated by repeated trituration using a fire-polished Pasteur pipette. The cultures were maintained at 27 ℃ for 2 h to allow the cell to adhere to the dish. All procedures were carried out under sterile conditions.

Calcium imaging

Calibration of the fluorescence signal was achieved by using the method of Takahashi *et al.*[24] with some modifications. The attached neurones were rinsed in standard physiological saline [(mmol•L^{-1}): 150 NaCl, 4 KCl, 2 $MgCl_2$, 2 $CaCl_2$, 10 HEPES, buffered to pH 6.9] and then incubated in the dark for 45 min at 28 ℃ in

standard external saline containing the dye fluo-3-AM (Sigma, 10 μmol•L^{-1}) or incubated in the dark for 5 h at 28 ℃ in external saline [(mmol•L^{-1}): 150 NaCl, 4 KCl, 2 $MgCl_2$, 2 EGTA, 10 HEPES, buffered to pH 6.9] containing the dye fluo-5N (Invitrogen, 5 μmol•L^{-1}). After dye loading cells were again rinsed in physiological saline twice. For full depletion of thapsigargin-sensitive stores, cells were incubated with 1 μmol•L^{-1} thapsigargin for 10 min. Calcium ratio imaging studies were conducted using the imaging system coupled to an inverted fluorescence microacope with a Fluor 40× oil immersion objective (Olympus IX71). Cells were excited at 488 nm and the 530 nm fluorescence emission acquired using a CCD (Image Pro-6.0) data analysis. Each experiment was repeated at least six times. The data were analysed using Spss Inc, version 17.0 and Microcal Origin, version 8.0 (Origin Lab Corp., Northampton, MA). Results were expressed as mean± SD (n=number of cells). Statistical significance was determined by using Student's paired or unpaired t-tests. Fluorescence values were expressed as F/F_0, F_0 being the resting (or baseline) fluorescence, and F the change in fluorescence from baseline after the drug application.

Results and Discussion

Synthesis

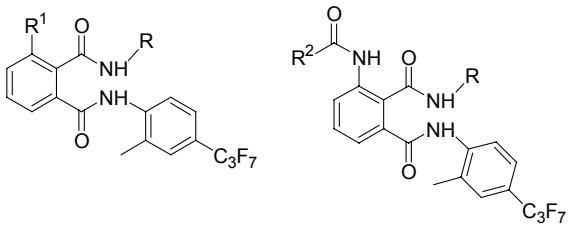
The synthetic procedures of the title compounds were shown in Scheme 2. The intermediates **2** and **3** were synthesized referring to a reported methods.[13,17] Compound **3** reacted with the aliphatic amides to give compounds (**4a**—**4c**) regioselectively, which was result of the electron-withdrawing effect of the nitro-group. However, the syntheses of compounds **4** and **5** were significantly influenced by the structures of the aliphatic amides. The reactions would not be progressed when the aliphatic amide is *tert*-butylamine. Finally, the compounds (**7a**—**7c**) were successfully obtained at room temperature in high yields, but the compounds (**7d**, **7e**) were obtained at −78 ℃ in moderate yields. The different reaction conditions and yields suggested that the electron withdrawing effect of anhydride significantly influenced the reactions.

The synthetic compounds were confirmed by ^{1}H NMR and HRMS. All spectral and analytical data were consistent with the assigned structures.

Larvicidal activities against oriental armyworm

The larvicidal activity against oriental armyworms was summarized in Table 1. In general, most of the compounds showed moderate potency against oriental armyworms at 200 mg/L. Compound **4a** exhibited the best activity (100% mortality at 10 mg/L). In order to study different substituents in the 3-substituted position of the phthalic acid moiety (Scheme 1, D) on the activity, five kinds of substituents were introduced. When R were fixed as one aliphatic group, the nitro-substituent showed comparably higher activity than amino and halogen substituents. For example, the trend of bioactivity is **4a**＞**6a**＞**5a**. Also, when the substituents of the 3-substituted position were acetyl or trifluoroacetyl groups, their activities were comparably low, which indicated that the larger substituents in the 3-substituted position were negative on the activity. The cyclopropanamine, *n*-butylamine, isopentylamine were introduced to examine their different effects on the activity. It was observed that the cyclopropanamine showed the best activity.

Table 1 Insecticidal activities of title compounds against oriental armyworms



Comp.	R	R^1	R^2	Larvicidal activity/%		
				200 mg/L	100 mg/L	50 mg/L
4a	cyclopropyl	NO_2		100	100	100[c]
4b	*n*-butyl	NO_2		80	—[b]	—[b]
4c	*i*-amyl	NO_2		40	—[b]	—[b]
5a	cyclopropyl	NH_2		100	40	—[b]
5b	*n*-butyl	NH_2		80	—[b]	—[b]
5c	*i*-amyl	NH_2		60	—[b]	—[b]
6a	cyclopropyl	I		100	100	80
6b	*n*-butyl	I		100	100	60
6c	*i*-amyl	I		10	—[b]	—[b]
7a	cyclopropyl		CH_3CO	100	60	—[b]
7b	*n*-butyl		CH_3CO	40	—[b]	—[b]
7c	*i*-amyl		CH_3CO	20	—[b]	—[b]
7d	*n*-butyl		CF_3CO	40	—[b]	—[b]
7e	*i*-amyl		CF_3CO	50	—[b]	—[b]
control[a]				100	100	100[c]

[a] Chlorantraniliprole. [b] Not tested. [c] 10 mg/L.

Larvicidal activities against beet armyworms

The insecticidal activities of compounds **4a**—**6a** and **6b** against beet armyworms were shown in Table 2. Most of them had higher activity against beet armyworms than against oriental armyworms. Meanwhile, the activity of **4a** was 40% at 2.5 mg/mL, higher than that of the other listed compounds, which indicated that the compound **4a** was also the most sensitive compound against beet armyworms.

Larvicidal activities against diamondback moths

The insecticidal activity and LC_{50} values of compound **4a** against diamondback moth were listed in Table 3. The activity of **4a** was 86% at 0.05 mg/L and

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Table 2 Insecticidal activities of title compounds against beet armyworms

Comp.	Larvicidal activity (%) at a concentration of (mg/L)						
	200	100	50	25	10	5	2.5
4a	100	100	100	100	100	100	40
5a	100	100	100	100	90	70	10
6a	100	100	100	100	60	40	20
6b	100	100	100	100	100	90	30
control[a]	100	100	100	100	100	100	100

[a] Chlorantraniliprole.

Table 3 Insecticidal activities (%) and LC_{50} values of title compound **4a** against diamondback moths

Comp.	Larvicidal activity			LC_{50}		
	1[b]	0.1[b]	0.05[b]	$y=a+bx$	LC_{50}[b]	R
4a	100	86	86	$y=8.05+1.61x$	0.0127	0.9913
Control[a]	100	100	71	$y=8.77+2.34x$	0.0246	0.9924

[a] Chlorantraniliprole. [b] in mg/L.

the LC_{50} value was 0.0127 mg/L, higher than that of chlorantraniliprole (71% at 0.05 mg/L and LC_{50} value was 0.0246 mg/L). It was indicated that the title compound **4a** was more sensitive against diamondback moths than the chlorantraniliprole.

The effects of 4a, 5a and 7b on intracellular calcium of neurons from the *Spodoptera exigua*

Figure 1 illustrated the change of $[Ca^{2+}]_i$ vs. recording time when the neurons were treated with **4a**, **5a** and **7b**. The peak values of $[Ca^{2+}]_i$ were (131.163±3.48)%, (114.049±4.37)%, (105.883±4.81)% and (96.6±5.69)% of the initial value by the end of 10 min recording when the cells were treated with 200 mg/L **4a**, 100 mg/L **4a**, 100 mg/L **5a** and 100 mg/L **7b** respectively. Compared with the control [(99.91±2.56)%], compounds **4a** and **5a** induced $[Ca^{2+}]_i$ increase without extracellular Ca^{2+} ($n=6$) and compound **7c** at 100 mg/L has no effect on intracellular calcium concentration.

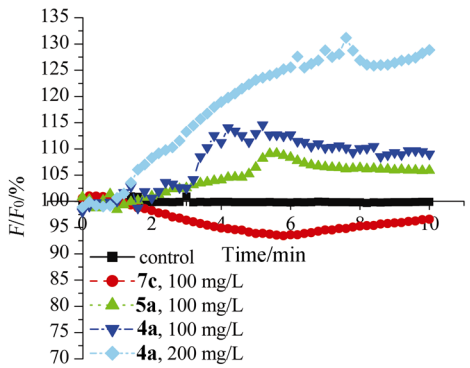

Figure 1 Effect of different concentrations of **4a**, **5a** and **7b** on $[Ca^{2+}]_i$ in the central neurones of *S. exigua* when extracellular calcium was in absence.

It indicated that compounds **4a** and **5a** could activate the calcium release channel in the endoplasmic reticulum (ER) membrane. Figure 1 also indicated that the recorded $[Ca^{2+}]_i$ treated with **4a** was in a concentration-dependent manner and the activities had a good positive correlation with the F/F_0.

There were two kinds of calcium release channels in the ER membrane, namely RyR and IP_3R Ca^{2+} channels.[25] After dye loading with fluo-5N, primary cultured neurones incubated with 1 μmol•L^{-1} thapsigargin 10 min were pretreated with heparin (10 mg/mL, a competitive antagonist of IP_3) to test which pathway was involved in elevation of $[Ca^{2+}]_i$. When external Ca^{2+} was free, blockade of IP_3 receptors with heparin and depletion of intracellular calcium store with thapsigargin, compound **4a** 100 mg/L and 200 mg/L induced $[Ca^{2+}]_i$ decrease to (81.25±4.26)% and (89.34±5.76)%, respectively. These data proved that compound **4a** stimulated $[Ca^{2+}]_i$ via RyR pathway in the central neurones of *S. exigua* third larvae.

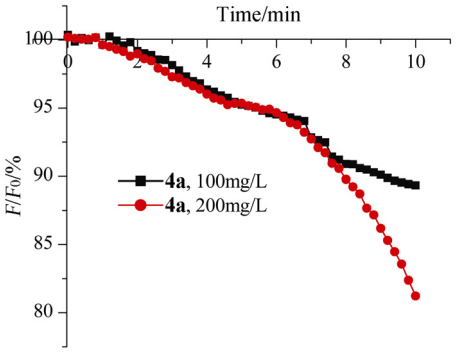

Figure 2 Effect of treatments with different concentrations of **4a** on intracellular Ca^{2+} at different time when extracellular Ca^{2+} was in absence (EGTA replace Ca^{2+}). Panel indicated that intracellular Ca^{2+} decreased by 100 mg/L and 200 mg/L of **4a**. It means the ryanodine receptor would be the action target of **4a**.

Conclusions

In conclusion, four novel series of phthalic acid diamides (14 compounds) were synthesized, and their structures were characterized and confirmed by ^1H NMR and HRMS. The biological activities of new compounds were evaluated. The results indicated that some compounds especially compound **4a** exhibited favorable larvicidal activities against oriental armyworms and beet armyworms. Meanwhile, the LC_{50} value of compound **4a** against diamondback moth was lower than the control indicating that the title compound **4a** was more efficient against diamondback moths than the control. The effects of some title compounds on intracellular calcium of neurons from the *Spodoptera exigua* proved that the title compounds were the activators of the RyR. Also, the experiment of intracellular calcium of neurons provided us a new rapid detection method of the target compound activities.

Acknowledgement

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