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ORIGINAL PAPER

Synthesis, structure and insecticidal activity of some novel amides containing *N*-pyridylpyrazole

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Abstract A novel series of amides containing *N*-pyridylpyrazole were designed and synthesized. All of the compounds were characterized and confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The single crystal structure of **9d** was determined by X-ray diffraction. The bioassay tests showed that the title compounds exhibited good insecticidal activities against *Mythimna separata* Walker, *diamondback moth* and *Laphygma exigua* Hübner.

Keywords Amide · *N*-pyridylpyrazole · Synthesis · Crystal structure · Insecticidal activity

Introduction

Due to the capability of insects to rapidly develop resistance, the discovery of agents that act on new biochemical targets is an important tool for effective pest management. Calcium channels, in particular, the ryanodine receptors (RyR) represent an attractive biological target for insect control and thus offer excellent promise in integrated pest management strategies [1]. Recently, two new classes of insecticidals, phthalic acid diamides and anthranilic diamides have been discovered with exceptional insecticidal activity on a range of Lepidoptera, which exhibit their action by binding to RyR and activating the uncontrolled release of calcium stores [2–4]. Since then diamides have been the focus of synthesis activities within the agrochemical industry. Anthranilic diamides and their chemistry have recently attracted considerable attention to the field of novel agricultural insecticides, owing to their prominent insecticidal activity, unique modes of action and good environmental profiles [5–9].

Anthranilic diamide insecticide is characterized by a three-part chemical structure as shown in Fig. 1a: (**X**) an anthraniloyl moiety, (**Y**) an aromatic acyl moiety and (**Z**) an aliphatic amide moiety. Notably, anthranilic diamides contain *N*-pyridylpyrazole in the second section (**Y**) showed significantly better activity than other heterocyclic derivatives [10, 11]. Work in this area has led to the discovery of Rynaxypyr^{TM}, a highly potent and selective activator of insect RyR with exceptional activity on a broad range of Lepidoptera, as the first new insecticide from this class (Fig. 1b) [12]. In our previous work, when the *N*-pyridylpyrazole ring was replaced with 1,2,3-thiadiazole [13] or triazolopyrimidine [14], the insecticidal activities were eliminated, and when the modification of insecticidal anthranilic diamides with an ester group substituting an amide group in the aliphatic amide moiety, the insecticidal activities decreased markedly [15]. Thus, these results suggest that *N*-pyridylpyrazole (**Y**) and aliphatic amide (**Z**) in anthranilic diamides play an important role in its insecticidal activities. Suramin (Fig. 2), a polysulphonated naphtylurea contains diamide structures which is similar with anthranilic diamide insecticides, was a RyR modulating agent [16]. However, unlike anthranilic diamides, the diamide structure in Suramin was not ortho-position but

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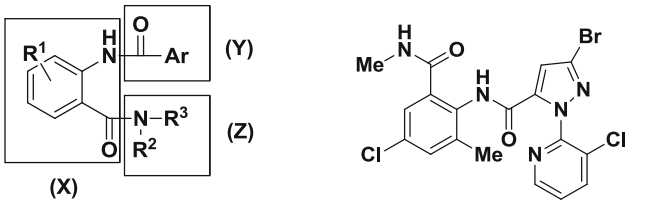


(a) General formula **(b)** Rynaxypyr™

Fig. 1 Chemical structures of anthranilic diamide insecticides

meta-position. Encouraged by these reports, we developed an idea that the replacement of the ortho-diamide structure of Rynaxypyr™ with a meta-diamide or a para-diamide could obtain novel analog with high insecticidal activities. Enlightened by all of the descriptions above, to further explore the comprehensive structure–activity relationships about the insecticidal activity, a series of novel meta-diamide and para-diamide analog containing *N*-pyridylpyrazole were designed and synthesized as shown in Schemes 1 and 2.

Experimental

Instruments

Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. ^{1}H NMR

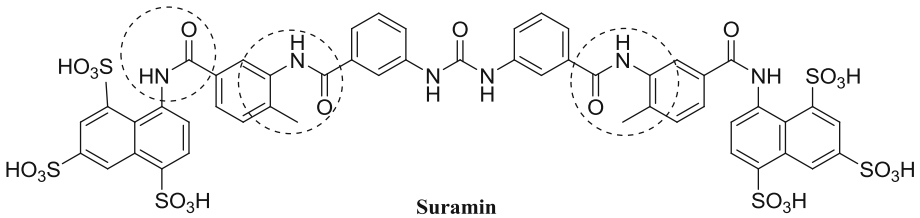
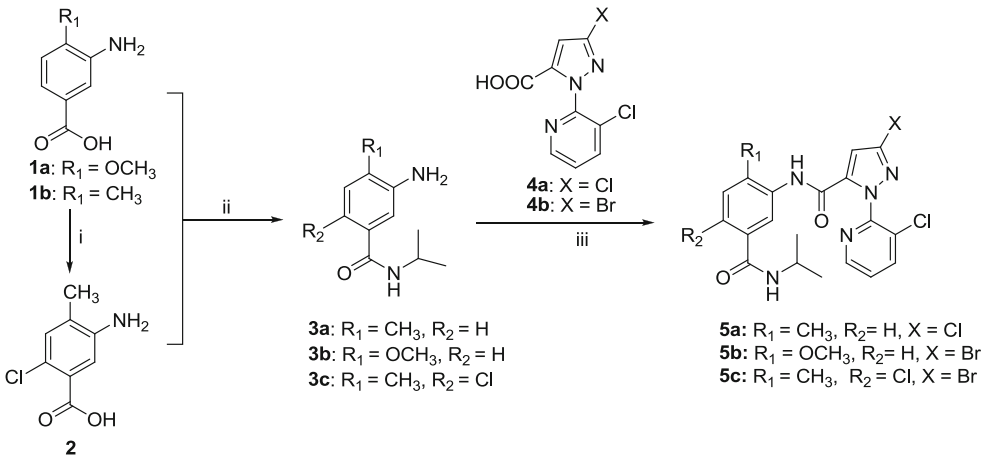
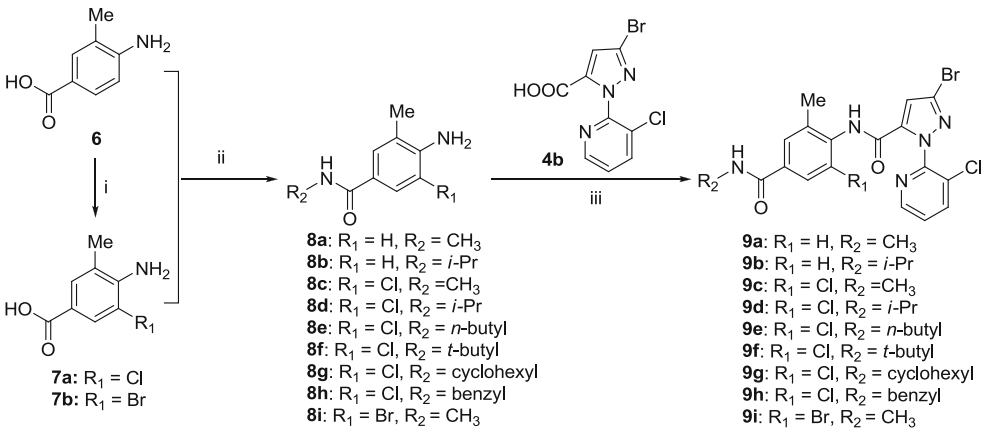


Fig. 2 Suramin, a RyR modulating agent



Scheme 1 Synthetic pathway to amides containing *N*-pyridylpyrazole derivatives **5a–5c**. Reagents and conditions: (*i*) *N*-chlorosuccinimide (NCS), DMF; (*ii*) $SOCl_2$, *i*-$PrNH_2$; (*iii*) CH_2Cl_2, oxalyl chloride, DMF



Scheme 2 Synthetic pathway to amides containing *N*-pyridylpyrazole derivatives **9a–9i**. Reagents and conditions: (*i*) *N*-Chlorosuccinimide (NCS), DMF/*N*-bromosuccinimide (NBS), DMF; (*ii*) $SOCl_2$, R_2NH_2; (*iii*) CH_2Cl_2, oxalyl chloride, DMF

spectra were obtained on Bruker AC-P500 spectrometer (300 MHz; Bruker, Fallanden, Switzerland) and Bruker Avance 400 spectrometer (400 MHz; Bruker) using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were obtained on Bruker Avance 400 spectrometer (100 MHz) with TMS as an internal standard. Elemental analyses were performed on a Vario EL elemental analyzer (Elementar, Hanau, Germany). IR spectra were obtained on a Bruker Vector 27 FT-IR spectrometer (Bruker, Ettlingen, Germany). Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. All chemicals or reagents were purchased from standard commercial suppliers: petroleum ether, bp 60–90 °C.

Synthesis of compounds

Synthesis of 5-amino-2-chloro-4-methylbenzoic acid ***2***

To a solution of **1** (3.02 g, 20 mmol) in DMF (30 ml) was added the NCS (2.8 g, 21 mmol) and the mixture was stirred for 1 h at 100 °C, cooled to room temperature, left to stand overnight, and then slowly poured into ice-water (100 ml) to precipitate a white solid. The solid was filtered and dried to obtain the synthesis of 5-amino-2-chloro-4-methylbenzoic acid **2** (2.51 g, 34 %), m.p. 162–163 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.76 (s, 3H, CH_3), 6.63 (br. s, 2H, NH_2), 7.20–7.25 (m, 1H, Ar–H), 7.66–7.68 (m, 1H, Ar–H).

General method for preparing intermediates ***3a–3c***

To the substituted benzoic acid **2** (10 mmol) was added thionyl chloride (30 mmol) and the mixture was refluxed for 3 h to give acid chloride. A solution of isopropylamine (20 mmol) in THF (20 ml) was dropwised and this mixture was vigorously stirred at room temperature for overnight. Subsequently, the reaction mixture was diluted with water and extracted several times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on a silica gel using petroleum ether and ethyl acetate as the eluent to afford the compounds **3a–3c**.

3-amino-N-isopropyl-4-methylbenzamide 3a

The compound was obtained in 86.5 % yield as a white solid; m.p. 122–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (d, 6H, $J = 6.8$ Hz, $CH(\underline{CH_3})_2$), 2.19 (s, 3H, CH_3), 3.71 (br. s, 2H, NH), 4.21–4.30 (m, 1H, $\underline{CH}(CH_3)_2$), 5.87 (br. s, 1H, NH), 6.96-7.07 (m, 2H, Ar–H), 7.13 (d, 1H, $J = 1.6$ Hz, Ar–H).

3-amino-N-isopropyl-4-methoxybenzamide 3b

The compound was obtained in 72.1 % yield as a white solid; m.p. 94–96 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, 6H, $J = 6.4$ Hz, $CH(\underline{CH_3})_2$), 3.87 (s, 3H, OCH_3), 4.20–4.28 (m, 1H, $\underline{CH}(CH_3)_2$), 5.87 (br. s, 1H, NH), 6.74 (d, 1H, $J = 8.3$ Hz, Ar–H), 7.06 (dd, 1H, $J = 2.1$, 8.0 Hz, Ar–H), 7.15 (d, 1H, $J = 2.4$ Hz, Ar–H).

5-amino-2-chloro-N-isopropyl-4-methylbenzamide 3c

The compound was obtained in 56.5 % yield as a white solid; m.p. 160–165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (d, 6H, $J = 6.8$ Hz, $CH(\underline{CH_3})_2$), 2.21 (s, 3H, CH_3), 4.15 (br. s, 2H, NH), 4.24–4.33 (m, 1H, $\underline{CH}(CH_3)_2$), 5.71 (br. s, 1H, NH), 6.83 (d, 1H, $J = 7.6$ Hz, Ar–H), 6.98 (d, 1H, $J = 8.0$ Hz, Ar–H).

General method for preparing title compounds ***5a–5c***

Oxalyl chloride (3 mmol) and DMF (2 drop) was added to a solution of 3-halo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid **4** (1 mmol) in 20 ml of CH_2Cl_2. The mixture was stirred at room temperature for 3 h. Then the solvent was evaporated to give the crude acyl chloride. To an ice-water bath cooled solution of 2 (1.2 mmol) in CH_2Cl_2 (20 ml), acyl chloride and diisopropylethylamine (1 mmol) were added dropwise, then further stirring for 12 h at room temperature. Subsequently, the mixture was added another 20 ml CH_2Cl_2, then washed by HCl, $NaHCO_3$, NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography on a silica gel using petroleum ether and ethyl acetate as the eluent to afford the compounds **5a–5c**.

3-chloro-1-(3-chloropyridin-2-yl)-N-(5-(isopropylcarbamoyl)-2-methylphenyl)-1H-pyrazole-5-carboxamide 5a

The compound was obtained in 82.5 % yield as a white solid; m.p. 128–132 °C; IR ν_{max}(KBr), cm^{-1}: 3,343 (NH), 3,258 (NH), 1,680 (C=O), 1,636 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, 6H, $J = 6.8$ Hz, $CH(\underline{CH_3})_2$), 2.28 (s, 3H, CH_3), 4.15–4.23 (m, 1H, $\underline{CH}(CH_3)_2$), 5.90 (d, 1H, $J = 8.4$ Hz, NH), 6.92 (s, 1H, pyrazolyl-H), 7.21 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.39 (dd, 1H, $J = 4.8$, 8.4 Hz, pyridyl—H), 7.51 (dd, 1H, $J = 1.6$, 8.0 Hz, Ar–H), 7.60 (s, 1H, Ar–H), 7.90 (dd, 1H, $J = 1.6$, 8.4 Hz, pyridyl-H), 8.39 (dd, 1H, $J = 1.2$, 4.4 Hz, pyridyl-H), 8.55 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.69, 155.32, 148.30, 147.17, 139.32, 138.93, 138.54, 136.05, 134.84, 128.74, 128.51, 127.80, 126.90, 126.68, 122.87, 110.66, 40.21, 26.29, 18.51. ESI–MS (*m/z*): 433.74 $(M + H)^+$. Elemental analysis for $C_{20}H_{19}Cl_2N_5O_2$: found C 55.31, H 4.60, N 15.94; calcd. C 55.57, H 4.43, N 16.20.

3-bromo-1-(3-chloropyridin-2-yl)-N-(5-(isopropylcarbamoyl)-2-methoxyphenyl)-1H-pyrazole-5-carboxamide 5b

The compound was obtained in 79.6 % yield as a white solid; m.p. 202–203 °C; IR ν_{max}(KBr), cm^{-1}: 3,341 (NH), 3,266 (NH), 1,676 (C=O), 1,635 (C=O), 1,142 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (d, 6H, $J = 6.8$ Hz, CH($\underline{CH_3}$)$_2$), 3.97 (s, 3H, OCH_3), 4.18–4.27 (m, 1H, $\underline{CH}$(CH_3)$_2$), 5.87 (d, 1H, $J = 7.6$ Hz, NH), 6.90 (s, 1H, pyrazolyl-H), 6.95 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.45 (dd, 1H, $J = 4.8$, 8.0 Hz, pyridyl-H), 7.71 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.93 (d, 1H, $J = 8.0$ Hz, pyridyl-H), 8.43 (br.s, 1H, NH), 8.49 (s, 1H, Ar–H), 8.51 (d, 1H, $J = 4.4$ Hz, pyridyl-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.32, 155.48, 154.39, 148.35, 147.13, 139.36, 139.30, 133.92, 127.92, 126.80, 126.71, 126.31, 125.04, 124.49, 110.92, 110.65, 55.99, 40.92, 22.34. ESI–MS (*m/z*): 494.10 $(M + H)^+$. Elemental analysis for $C_{20}H_{19}BrClN_5O_3$ found C 48.45, H 4.17, N 14.19; calcd. C 48.75, H 3.89, N 14.21.

3-bromo-N-(4-chloro-5-(isopropylcarbamoyl)-2-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 5c

The compound was obtained in 45.3 % yield as a white solid; m.p. 144–147 °C; IR ν_{max}(KBr), cm^{-1}: 3,336 (NH), 3,243 (NH), 1,675 (C = O), 1,633 (C = O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (d, 6H, $J = 6.8$ Hz, CH($\underline{CH_3}$)$_2$), 2.16 (s, 3H, CH_3), 4.25–4.33 (m, 1H, $\underline{CH}$(CH_3)$_2$), 5.81 (d, 1H, $J = 7.6$ Hz, NH), 7.21 (d, 1H, $J = 8.0$ Hz, Ar–H), 6.92 (s, 1H, pyrazolyl-H), 7.39 (dd, 1H, $J = 4.8$, 8.4 Hz, pyridyl—H), 7.51 (dd, 1H, $J = 1.6$, 8.0 Hz, Ar–H), 7.60 (s, 1H, Ar–H), 7.90 (dd, 1H, $J = 1.6$, 8.4 Hz, pyridyl—H), 8.39 (dd, 1H, $J = 1.2$, 4.4 Hz, pyridyl-H), 8.55 (br.s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.20, 155.41, 148.35, 145.78, 139.50, 137.73, 137.68, 133.05, 131.67, 128.34, 128.19, 127.84, 127.12, 125.67, 124.55, 110.34, 41.78, 21.39, 17.80. ESI–MS *(m/z)*: 510.21 (M-H). Elemental analysis for $C_{20}H_{19}BrClN_5O_3$: found C 47.25, H 3.29, N 13.58; calcd. C 46.99, H 3.55, N 13.70.

4-amino-3-halo-5-methylbenzoic acid 7a and 7b

The intermediate **7** was synthesized according to the methods described in synthesis of 5-amino-2-chloro-4-methylbenzoic acid **2**.

4-amino-3-chloro-5-methylbenzoic acid 7a

The compound was obtained in 69.6 % yield as a white solid; m.p. > 197 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 5.75 (s, 2H, NH_2), 7.55 (s, 1H, Ar–H), 7.77 (s, 1H, Ar–H), 12.37 (br. s, 1H, COOH).

4-amino-3-bromo-5-methylbenzoic acid 7b

The compound was obtained in 78.3 % yield as a white solid; m.p. > 230 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.14 (s, 3H, CH_3), 5.80 (s, 2H, NH_2), 7.50 (s, 1H, Ar–H), 7.60 (s, 1H, Ar–H), 12.34 (br. s, 1H, COOH).

General method for preparing intermediates ***8a–8i***

To 4-amino-3-halo-5-methylbenzoic acid **7** (10 mmol) was added thionyl chloride (30 mmol) and the mixture was refluxed for 3 h to give acid chloride. A solution of isopropylamine (20 mmol) in THF (20 ml) was dropwised and this mixture was vigorously stirred at room temperature for overnight. Subsequently, the reaction mixture was diluted with water and extracted several times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on a silica gel using petroleum ether and ethyl acetate as the eluent to afford the compounds **8a–8i**.

4-amino-N-3-dimethylbenzamide 8a

The compound was obtained in 58.9 % yield as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H, CH_3), 2.95 (d, 3H, $J = 4.8$ Hz, NH$\underline{CH_3}$), 5.87 (br. s, 2H, NH), 6.20 (br. s, 1H, NH), 6.62 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.43 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.50 (s, 1H, Ar–H).

4-amino-N-isopropyl-3-methylbenzamide 8b

The compound was obtained in 86.7 % yield as a white solid; m.p. 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (d, 6H, $J = 6.6$ Hz, CH($\underline{CH_3}$)$_2$), 2.11 (s, 3H, CH_3), 3.83 (br. s, 2H, NH), 4.13–4.25 (m, 1H, $\underline{CH}$(CH_3)$_2$), 5.73 (br. s, 1H, NH), 6.57 (d, 1H, $J = 8.1$ Hz, Ar–H), 7.37 (dd, 1H, $J = 2.1$, 8.4 Hz, Ar–H), 7.43 (d, 1H, $J = 1.5$ Hz, Ar–H).

4-amino-3-chloro-N-5-dimethylbenzamide 8c

The compound was obtained in 83.5 % yield as a white solid; m.p. 222–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.13 (s, 3H, CH_3), 2.68 (d, 3H, $J = 4.4$ Hz, NH$\underline{CH_3}$), 5.52 (s, 2H, NH_2), 7.44 (s, 1H, Ar–H), 7.58 (s, 1H, Ar–H), 8.09 (br, 1H, $\underline{NH}CH_3$).

4-amino-3-chloro-N-isopropyl-5-methylbenzamide 8d

The compound was obtained in 94.7 % yield as a white solid; m.p. 194–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

1.24 (d, 6H, $J = 6.4$ Hz, CH($\underline{CH_3}$)$_2$), 2.22 (s, 3H, CH_3), 4.20–4.30 (m, 1H, $\underline{CH}(CH_3)_2$), 4.30 (br. s, 2H, NH), 5.76 (br. s, 1H, NH), 7.41 (s, 1H, Ar–H), 7.56 (d, 1H, $J = 1.6$ Hz, Ar–H).

4-amino-N-butyl-3-chloro-5-methylbenzamide 8e

The compound was obtained in 72.2 % yield as a white solid; m.p. 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 1.27–1.38 (m, 2H, $\underline{CH_2}CH_3$), 1.47–1.55 (m, 2H, $\underline{CH_2}CH_2CH_3$), 2.15 (s, 3H, CH_3), 3.34 (q, 2H, $J = 7.2$ Hz, NH$\underline{CH_2}CH_2$), 3.64 (br, 2H, NH), 5.88 (br.s, 1H, NH), 7.34 (s, 1H, Ar–H), 7.50 (s, 1H, Ar–H).

4-amino-N-tert-butyl-3-chloro-5-methylbenzamide 8f

The compound was obtained in 65.3 % yield as a white solid; m.p. 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 9H, C($\underline{CH_3}$)$_3$), 2.16 (s, 3H, CH_3), 4.04 (br. s, 2H, NH), 5.75 (br. s, 1H, NH), 7.30 (d, 1H, $J = 0.8$ Hz, Ar–H), 7.45 (d, 1H, $J = 2.0$ Hz, Ar–H).

4-amino-3-chloro-N-cyclohexyl-5-methylbenzamide 8g

The compound was obtained in 91.3 % yield as a white solid; m.p. 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19–2.04 (m, 10H, cyclohexyl-H), 2.24 (s, 3H, CH_3), 3.92–3.99 (m, 1H, cyclohexyl-H), 4.31 (br, 2H, NH_2), 5.80 (d, 1H, $J = 6.4$ Hz, NH), 7.43 (s, 1H, Ar–H), 7.57 (s, 1H, Ar–H).

4-amino-N-benzyl-3-chloro-5-methylbenzamide 8 h

The compound was obtained in 69.5 % yield as a white solid; m.p. 121–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, CH_3), 4.00 (br, 2H, NH_2), 4.53 (d, 2H, $J = 5.2$ Hz, CH_2), 6.24 (br, 1H, NH), 7.19–7.30 (m, 5H, Ar–H), 7.37 (s, 1H, Ar–H), 7.54 (s, 1H, Ar–H).

4-amino-3-bromo-N-5-dimethylbenzamide 8i

The compound was obtained in 91.8 % yield as a white solid; m.p. 220–225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.17 (s, 3H, CH_3), 2.72 (d, 3H, $J = 4.4$ Hz, NH$\underline{CH_3}$), 5.47 (s, 2H, NH_2), 7.50 (s, 1H, Ar–H), 7.77 (s, 1H, Ar–H), 8.12 (br, 1H, NH).

General method for preparing title compounds 9a-9i

Oxalyl chloride (3 mmol) and DMF (2 drop) was added to a solution of 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid **4b** (1 mmol) in 20 ml of CH_2Cl_2. The mixture was stirred at room temperature for 3 h. Then the solvent was evaporated to afford the crude acyl chloride. To an ice-water bath cooled solution of **8** (1.2 mmol) in CH_2Cl_2 (20 ml), acyl chloride and diisopropylethylamine (1 mmol) were added dropwise, then further stirring for 12 h at room temperature. Subsequently, the mixture was added another 20 ml CH_2Cl_2, then washed by HCl, $NaHCO_3$, NaCl, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography on a silica gel using petroleum ether and ethyl acetate as the eluent to afford the compounds **9a–9i**.

3-bromo-1-(3-chloropyridin-2-yl)-N-(2-methyl-4-(methylcarbamoyl)phenyl)-1H-pyrazole-5-carboxamide 9a

The compound was obtained in 68.2 % yield as a white solid; m.p. 112–115 °C; IR ν_{max}(KBr), cm^{-1}: 3,300 (NH), 3,155 (NH), 1,660 (C=O), 1,642 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3H, CH_3), 2.98 (d, 3H, NH$\underline{CH_3}$), 6.11 (br, 1H, $\underline{NH}CH_3$), 6.97 (s, 1H, pyrazolyl-H), 7.40–7.45 (m, 2H, pyridyl-H, Ar–H), 7.60 (s, 1H, Ar–H), 7.77 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.91 (dd, 1H, $J = 1.6$, 8.0 Hz, pyridyl-H), 8.01 (br.s, 1H, NH), 8.47 (dd, 1H, $J = 1.6$, 4.8 Hz, pyridyl-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.73, 155.47, 148.42, 147.30, 139.53, 138.92, 138.52, 136.22, 134.54, 129.76, 128.49, 127.98, 126.30, 126.01, 123.89, 110.57, 26.28, 18.27. ESI–MS (*m*/*z*): 484.27 (M^+ Cl)$^-$. Elemental analysis for $C_{18}H_{15}BrClN_5O_2$: found C 47.96, H 3.21, N 15.87; calcd. C 48.18, H 3.37, N 15.61.

3-bromo-1-(3-chloropyridin-2-yl)-N-(4-(isopropylcarbamoyl)-2-methylphenyl)-1H-pyrazole-5-carboxamide 9b

The compound was obtained in 66.0 % yield as a white solid; m.p. 230–232 °C; IR ν_{max}(KBr), cm^{-1}: 3,335 (NH), 3,200 (NH), 1,680 (C=O), 1,632 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (d, 6H, $J = 6.4$ Hz, CH($\underline{CH_3}$)$_2$), 2.24 (s, 3H, CH_3), 4.21changed to n dash4.29 (m, 1H, $\underline{CH}(CH_3)_2$), 5.89 (d, 1H, $J = 7.2$ Hz, NH), 7.05 (s, 1H, pyrazolyl-H), 7.37–7.43 (m, 2H, pyridyl-H, Ar–H), 7.52 (s, 1H, Ar–H), 7.65 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.89 (d, 1H, $J = 8.0$ Hz, pyridyl-H), 8.25 (br.s, 1H, NH), 8.47 (d, 1H, $J = 4.4$ Hz, pyridyl-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.82, 155.46, 148.42, 147.27, 139.42, 138.70, 138.47, 136.12, 134.31, 129.55, 128.47, 127.97, 126.25, 125.96, 123.72, 110.63, 42.09, 22.83, 18.24. ESI–MS (*m*/*z*): 511.90 (M^+ Cl$^-$). Elemental analysis for $C_{20}H_{19}BrClN_5O_2$: found C 50.70, H 3.84, N 14.38; calcd. C 50.39, H 4.02, N 14.69.

3-bromo-N-(2-chloro-6-methyl-4-(methylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9c

The compound was obtained in 67.0 % yield as a white solid; m.p. 227–230 °C; IR ν_{max}(KBr), cm^{-1}: 3,348 (NH),

3,224 (NH), 1,677 (C=O), 1,632 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.19 (s, 3H, CH_3), 2.99 (d, 3H, $J = 3.6$ Hz, NH$\underline{CH_3}$), 6.19 (br, 1H, $\underline{NH}CH_3$), 7.19 (s, 1H, pyrazolyl-H), 7.32 (s, 1H, Ar–H), 7.37 (dd, 1H, $J = 4.8$, 8.0 Hz, pyridyl-H), 7.44 (s, 1H, Ar–H), 7.85 (d, 1H, $J = 7.6$ Hz, pyridyl-H), 8.36 (br.s, 1H, NH), 8.46 (d, 1H, $J = 4.0$ Hz, pyridyl-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.81, 155.41, 148.30, 147.18, 139.33, 138.87, 138.44, 134.53, 134.51, 132.02, 127.90, 127.81, 126.93, 126.69, 125.62, 110.71, 26.30, 18.27. ESI–MS (*m/z*): 517.97 ($M + Cl^-$). Elemental analysis for $C_{18}H_{14}BrCl_2N_5O_2$: found C 44.46, H 2.77, N 14.19; calcd. C 44.75, H 2.92, N 14.47.

3-bromo-N-(2-chloro-4-(isopropylcarbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9d

The compound was obtained in 82.4 % yield as a white solid; m.p. 157–160 °C; IR ν_{max}(KBr), cm^{-1}: 3,338 (NH), 3,220 (NH), 1,677 (C=O), 1,632 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (d, 6H, $J = 6.4$ Hz, CH($\underline{CH_3}$)$_2$), 2.21 (s, 3H, CH_3), 4.00-4.04 (m, 1H, $\underline{CH}$(CH_3)$_2$), 7.41 (s, 1H, pyrazolyl-H), 7.62 (dd, 1H, $J = 4.8$, 8.0 Hz, pyridyl-H), 7.72 (d, 1H, $J = 1.2$ Hz, Ar–H), 7.82 (s, 1H, Ar–H), 8.18 (dd, 1H, $J = 1.6$, 8.0 Hz, pyridyl-H), 8.32 (d, 1H, $J = 7.6$ Hz, $\underline{NH}CH_3$), 8.51 (dd, 1H, $J = 1.6$, 4.8 Hz, pyridyl-H), 10.54 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.50, 155.40, 148.31, 147.18, 139.32, 138.90, 138.33, 134.78, 134.46, 131.92, 128.04, 127.80, 126.93, 126.68, 125.74, 110.71, 41.23, 22.23, 18.22. ESI–MS (*m/z*): 512.09 $(M + H)^+$. Elemental analysis for $C_{20}H_{18}BrCl_2N_5O_2$: found C 46.90, H 3.67, N 13.76; calcd. C 46.99, H 3.55, N 13.70.

3-bromo-N-(4-(butylcarbamoyl)-2-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9e

The compound was obtained in 46.2 % yield as a white solid; m.p. 232–234 °C; IR ν_{max}(KBr), cm^{-1}: 3,340 (NH), 3,123 (NH), 1,681 (C=O), 1,632 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 1.27–1.36 (m, 2H, $\underline{CH_2}CH_3$), 1.45–1.53 (m, 2H, $\underline{CH_2}CH_2CH_3$), 2.22 (s, 3H, CH_3), 3.24 (q, 2H, $J = 6.4$ Hz, NH$\underline{CH_2}CH_2$), 7.43 (s, 1H, pyrazolyl-H), 7.63 (dd, 1H, $J = 4.4$, 8.0 Hz, pyridyl-H), 7.72 (s, 1H, Ar–H), 7.81 (s, 1H, Ar–H), 8.19 (d, 1H, $J = 8.0$ Hz, pyridyl-H), 8.51–8.54 (m, 1H, pyridyl-H,1H, NH), 10.54 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.25, 155.41, 148.30, 147.19, 139.34, 138.87, 138.40, 134.67, 134.50, 131.97, 127.98, 127.80, 126.94, 126.71, 125.67, 110.71, 31.08, 19.62, 18.26, 13.71. ESI–MS (*m/z*): 559.87 (M^+ Cl^-). Elemental analysis for $C_{21}H_{20}BrCl_2N_5O_2$: found C 47.90, H 4.01, N 13.24; calcd. C 48.02, H 3.84, N 13.33.

3-bromo-N-(4-(tert-butylcarbamoyl)-2-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9f

The compound was obtained in 77.1 % yield as a white solid; m.p. 207–210 °C; IR ν_{max}(KBr), cm^{-1}: 3,434 (NH), 3,246 (NH), 1,688 (C=O), 1,650 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.36 (s, 9H, C($\underline{CH_3}$)$_3$), 2.22 (s, 3H, CH_3), 7.43 (s, 1H, pyrazolyl-H), 7.62 (dd, 1H, $J = 4.8$, 8.4 Hz, pyridyl-H), 7.68 (s, 1H, Ar–H), 7.78 (s, 1H, Ar–H), 7.88 (br.s, 1H, NH), 8.19 (dd, 1H, $J = 1.2$, 8.0 Hz, pyridyl-H), 8.51 (dd, 1H, $J = 1.6$, 4.8 Hz, pyridyl-H), 10.52 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.42, 155.39, 148.31, 147.17, 139.32, 138.93, 138.15, 135.79, 134.24, 131.75, 128.11, 127.79, 126.92, 126.67, 125.87, 110.68, 51.03, 28.46, 18.18. ESI–MS (*m/z*): 525.96 (M^+ H^+). Elemental analysis for $C_{21}H_{20}BrCl_2N_5O_2$: found C 47.89, H 3.97, N 13.01; calcd. C 48.02, H 3.84, N 13.33.

3-bromo-N-(2-chloro-4-(cyclohexylcarbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9g

The compound was obtained in 70.9 % yield as a white solid; m.p. 175–178 °C; IR ν_{max}(KBr), cm^{-1}: 3,340 (NH), 3,194 (NH), 1,678 (C=O), 1,638 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10–1.81 (m, 10H, cyclohexyl—H), 2.22 (s, 3H, CH_3), 3.73 (br, 1H, CH), 7.43 (s, 1H, pyrazolyl-H), 7.62 (dd, 1H, $J = 4.8$, 8.0 Hz, pyridyl-H), 7.73 (s, 1H, Ar–H), 7.82 (s, 1H, Ar–H), 8.19 (d, 1H, $J = 7.2$ Hz, pyridyl-H), 8.30 (d, 1H, $J = 8.0$ Hz, NH), 8.51 (d, 1H, $J = 4.4$ Hz, pyridyl-H), 10.54 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.48, 155.39, 148.30, 147.17, 139.32, 138.90, 138.32, 134.81, 134.45, 131.89, 128.07, 127.79, 126.92, 126.68, 125.76, 110.70, 48.54, 32.33, 25.24, 24.89, 18.21. ESI–MS (*m/z*): 551.96 $(M + H)^+$. Elemental analysis for $C_{23}H_{22}BrCl_2N_5O_2$: found C 49.97, H 4.03, N 12.34; calcd. C 50.11, H 4.02, N 12.70.

N-(4-(benzylcarbamoyl)-2-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9h

The compound was obtained in 42.3 % yield as a white solid; m.p. 247–250 °C; IR ν_{max}(KBr), cm^{-1}: 3,306 (NH), 3,213 (NH), 1,671 (C=O), 1,641 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.23 (s, 3H, CH_3), 4.46 (d, 2H, $J = 6.0$ Hz, CH_2), 7.22-7.35 (m, 5H, Ar–H), 7.44 (s, 1H, pyrazolyl-H), 7.62 (dd, 1H, $J = 4.8$, 8.4 Hz, pyridyl-H),

7.79 (s, 1H, Ar–H), 7.88 (s, 1H, Ar–H), 8.19 (dd, 1H, $J = 1.2$, 8.0 Hz, pyridyl-H), 8.52 (dd, 1H, $J = 1.6$, 4.8 Hz, pyridyl-H), 9.15 (t, 1H, $J = 6.0$ Hz, NH), 10.57 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.41, 155.40, 148.28, 147.18, 139.33, 139.27, 138.85, 138.50, 134.73, 134.28, 132.05, 128.29. 128.09, 127.79, 127.26, 126.93, 126.82, 126.70, 125.79, 110.70, 42.75, 18.25. ESI–MS (*m/z*): 560.83 (M^+ H^+). Elemental analysis for $C_{24}H_{18}BrCl_2N_5O_2$: found C51.28, H 3.53, N 12.19; calcd. C 51.51, H 3.24, N 12.52.

3-bromo-N-(2-bromo-6-methyl-4-(methylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide 9i

The compound was obtained in 56.7 % yield as a white solid; m.p. 238–240 °C; IR ν_{max}(KBr), cm^{-1}: 3,331 (NH), 3,121 (NH), 1,665 (C=O), 1,632 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.23 (s, 3H, CH_3), 2.76 (d, 3H, $J = 4.4$ Hz, NHC$\underline{H_3}$), 7.43 (s, 1H, pyrazolyl-H), 7.62 (dd, 1H, $J = 4.8$, 8.0 Hz, pyridyl-H), 7.75 (s, 1H, Ar–H), 7.95 (s, 1H, Ar–H), 8.19 (dd, 1H, $J = 1.6$, 8.0 Hz, pyridyl-H), 8.51 (dd, 1H, $J = 1.2$, 4.8 Hz, pyridyl-H), 8.55 (br, 1H, $\underline{NH}CH_3$), 10.55 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.08, 155.45, 148.37, 147.20, 139.87, 138.98, 138.34, 134.83, 134.75, 132.05, 128.17, 127.90, 127.03, 126.79, 125.93, 110.72, 26.27, 18.23. ESI–MS (*m/z*): 527.84 $(M + H)^+$. Elemental analysis for $C_{18}H_{14}Br_2ClN_5O_2$: found C 41.09, H 2.63, N 13.00; calcd. C 40.98, H 2.67, N 13.27.

Biological assay

All bioassays were performed on representative test organisms reared in the laboratory, which were repeated at 25 ± 1 °C according to the statistical requirements. The detailed procedure was described as follows. The leaf dipping assay method was used for oriental armyworm (*Mythimna separata* Walker) tests, in which the corn leaves were dipped into a test solution for 20 s and allowed to dry. The treated diet was placed in a 7 cm diameter Petri dish, and 10 fourth-instar oriental armyworm larvae were released into the Petri dish. The symptoms of affected larvae were observed at 24 h after the application, and percentage mortalities were evaluated 72 h after treatment. The immersion method assay was used for *Culex pipiens pallens* tests, and concentrations of test compounds were adjusted by serial dilution of a stock solution of the compounds in acetone. Each compound in acetone was suspended in distilled water, 10 early fourth-instar larvae of *Culex pipiens pallens* were put into glass cups (125 ml) containing each test solution (100 ml). Larvicidal activity was evaluated 72 h after treatment. For comparative purposes, Rynaxypyr^{TM} was tested under the same conditions. All treatments were replicated three times.

Results and discussion

Synthesis

The synthesis procedures for title compounds **5a–5c** were shown in Scheme 1. The intermediate 5-amino-2-c4hloro-4-methylbenzoic acid **2** was prepared by halogenation of commercially available 3-amino-4-methylbenzoic acid **1b** with *N*-chlorosuccinimide [17]. Compound **2** was aminated with appropriate amines to give intermediates **3** [18]. The acid intermediate pyrazole carboxylic acids **4**, which were previously synthesized [19], were treated with oxalyl chloride at reflux to give acid chloride, which was then reacted with **3** to afford the title compounds **5a–5c**. The title compounds **9a–9i** were synthesized in a similar method as described for the synthesis compounds **5a–5c**, as shown in Scheme 2.

Crystal structure

The structure of compound **9d** was further confirmed by single crystal X-ray diffraction analysis (Fig. 3). Compound **9d** consists of pyrazole ring, pyridine ring, benzene ring and a molecule of ethyl acetate according to X-ray single-crystal structure determination. All the C–N distances are typically for a single bond in the range of 1.321–1.463 Å. The C=O distance is 1.230(4), 1.238(4) and 1.216(4) Å, which are typically for a double bond. In the molecular structure of title compound, the three rings (benzene ring, pyridine ring and pyrazole ring) are nearly vertically with θ angle of 94.9°(benzene ring vs. pyridine ring), 105.8° (pyrazole ring vs. pyridine), 62.5°(pyrazole

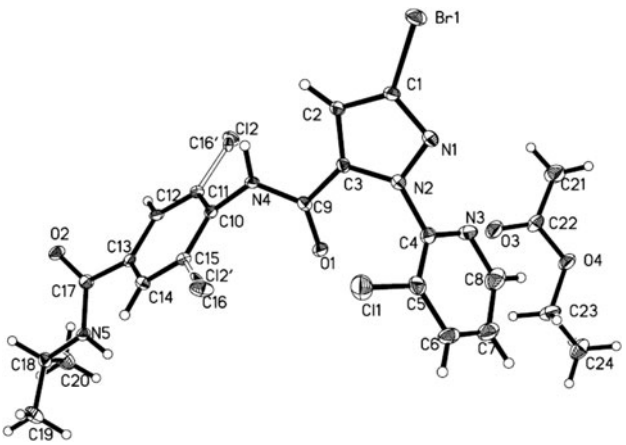


Fig. 3 Crystal structure of **9d**

Table 1 Insecticidal activities data of title compounds (mortality/%)

Compd.	*Mythimna separata* Walker						*Culex pipiens pallens*
	μg ml^{-1}/death rate (%)						μg ml^{-1}/death rate (%)
	200	100	50	25	10	5	2
5a	0						0
5b	0						0
5c	30						50
9a	100	100	60	20			0
9b	30						10
9c	100	100	100	100	100	40	10
9d	100	70	60				0
9e	100	100	100	60			30
9f	0						10
9g	0						30
9h	100	100	100	100	100	0	10
9i	100	100	100	100	100	0	50
Rynaxypyr™						100	100

ring vs. benzene ring), respectively. The average bond lengths and bond angles of the phenyl ring [20–24], the pyrazole ring [25, 26], pyridine ring [27, 28] and the amide bond [29–32] are normal.

Insecticidal activities and structure–activity relationship (SAR)

The insecticidal activities of these synthesized amides containing *N*-pyridylpyrazole were determined in vivo. The results are summarized in Table 1. All these meta-substituted diamines **(5a–5c)** did not display obvious insecticidal activities against *Lepidoptera* insect [Oriental Armyworm (*Mythimna separata* Walker)]. The death rates are 0 at 200 μg·ml^{-1} except compound **5c** with 30 %. Compared with compounds **5a–5c**, the para-substituted diamines **(9a–9i)** displayed better insecticidal activities against Oriental Armyworm, and some structure–activity relationships for R_1 and R_2 variation can be observed from the results. The R_1 chloro-substituted or bromin-substituted amides **(9c, 9d** and **9i)** displayed more potent insecticidal activities than the corresponding non-substituted analog **(9a** and **9b)**. For example, compound **9c** exhibited excellent activity against Oriental Armyworm at 10 μg·ml^{-1}, even at 5 μg·ml^{-1}. In addition, the methyl substitution at R_2 was more favored than isopropyl group due to the significant higher potencies observed in R_2 methyl substituted amines **(9a** and **9c)** than the corresponding isopropyl substituted analog **(9b** and **9d)**, but the insecticidal activity disappeared when the R_2 was substituted with *t*-butyl or cyclohexyl group **(9f** and **9 g)**. Besides, the R_2 benzyl substituted amine **(9 h)** also displayed potent insecticidal activity against Oriental Armyworm. As shown in Table 1, no significant larvicidal activities were found of these compounds against *Culex pipiens pallens.*

Figure 4 shows the symptoms of larvae affected by the title compounds and commercial Rynaxypyr™. Insects treated with the title compound **9c** showed abnormal symptoms such as body contraction, vomiting, feeding cessation, body thickening and shortening, which are similar to the larvae treated with commercial Rynaxypyr™. These results suggest that the title compounds exhibit their activity by activating insect RyR.

For the compound **9a**, **9b**, **9c**, **9d**, **9h**, **9i**, further bioassay was conducted against *diamondback moth* and *Laphygma exigua* Hübner. The results are summarized in Table 2. At a dose of 25 μg ml^{-1}, all these compounds have good insecticidal activity against *diamondback moth* and *Laphygma exigua* Hübner, which can be compared with that of the control Rynaxypyr™.

In summary, a series of amides containing *N*-pyridylpyrazole were synthesized and assessed for their insecticidal activities. Several synthesized compounds exhibited significant insecticidal activity against Oriental Armyworm, and these compounds also show good insecticidal activity against *diamondback moth* and *Laphygma exigua* Hübner. The SAR study reveals that substitutions R_1 and R_2 in para-diamide analog containing *N*-pyridylpyrazole are important for the insecticidal activity,

Fig. 4 Symptoms of fourth-instar larvae of *Mythimna separata* Walker treated by leaf dipping. (**a**) Untreated; (**b**) Rynaxypyr™ at 10 μg·ml^{-1}, 36 h after application; (**c**) **9c** at 10 μg·ml^{-1}, 36 h after application

Table 2 Insecticidal activities data of title compounds (mortality/%)

Compd.	*Diamondback moth*				*Laphygma exigua* Hübner			
	μg ml^{-1}/death rate (%)				μg ml^{-1}/death rate (%)			
	200	100	50	25	200	100	50	25
9a	100	100	100	100	100	100	100	100
9b	100	100	98	92	100	100	100	96
9c	100	100	100	100	100	100	100	97
9d	100	100	100	100	100	100	95	91
9h	100	100	100	100	–[a]	–	–	–
9i	100	100	100	100	100	100	100	100
Rynaxypyr™	–	–	100	100	–	–	100	100

[a] Not tested

compound **9c**, with the chlorine substitution at R_1 and the methyl substitution at R_2, showed the most potence insecticidal activity against Oriental Armyworm. It was also revealed that not only ortho-diamide compounds (anthranilic diamides) showed prominent insecticidal activity but also para-diamide analog showed excellent insecticidal activity, and exhibited their activity by activating insect RyR. The studies described herein provided a powerful complement to the SARs of diamide insecticides, and provided useful information for further investigation of the mechanism of action.

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