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Synthesis, crystal structure and biological activity of a novel anthranilic diamide insecticide containing allyl ether

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Abstract In search of environmentally benign insecticides with high activity, low toxicity and low residue, a series of novel anthranilic diamides containing allyl ether were designed and synthesized. All the compounds were characterized by ^{1}H NMR spectroscopy, HRMS or elemental analysis. The single crystal structure of **18e** was determined by X-ray diffraction. The insecticidal activities of the new compounds were evaluated. The results showed that some compounds exhibited excellent insecticidal activities against Lepidoptera pests. Among this series compounds, **18l** showed 100 % larvicidal activity against *Mythimna separate* Walker and *Plutella xylostella Linnaeus* at the test concentration.

Keywords Anthranilic diamide · Ryanodine receptor · Synthesis · Insecticidal activity

Introduction

Resistance has often been a problem or a potential problem for insecticides and is one of the most important reasons why insecticides with a new mode of action have been desired [1]. The ryanodine receptor (RyR) derives its name from the plant metabolite ryanodine (**A**), a natural insecticide from *Ryania speciosa*, known to modify calcium channels [2–5]. As ryanodine is a potent natural insecticide, it has been conjectured that RyRs would provide an excellent target for insect control. The phthalic dimides [6–8] from Nihon Nohyaku, and the anthranilic diamides [9–12]

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from Dupont, are the first synthetic classes of potent activators of insect RyRs. The recent commercial introduction of RyR insecticides flubendiamide (**B**) and chlorantraniliprole (**C**), is significant in the field of crop protection, and particularly important in light of the ability of insects to rapidly develop resistance and the need for safe and effective pesticides that act at new biochemical targets [13, 14].

Owing to their prominent insecticidal activity, unique modes of action and good environmental profiles, anthranilic diamides and their chemical synthesis have recently attracted considerable attention in the field of novel agricultural insecticides. There are many reports in the literature on the modification of the anthranilic diamides [15–18], with the most modification related to a variation of the substitution pattern in part of the aliphatic amide moiety. Although less research has been devoted to the modification of the anthraniloyl skeleton, it has been reported that the biological activity of such compounds can be affected by changing the anthraniloyl skeleton to a large extent [19]. In continuation of our research on biologically active heterocycles [20], a series of novel anthranilic diamides containing allyl ether were designed and synthesized, and their insecticidal activities were tested. The results showed that some compounds exhibited moderate insecticidal activities against *Mythimna separate* Walker and *Plutella xylostella Linnaeus.*

Experimental

Materials and methods

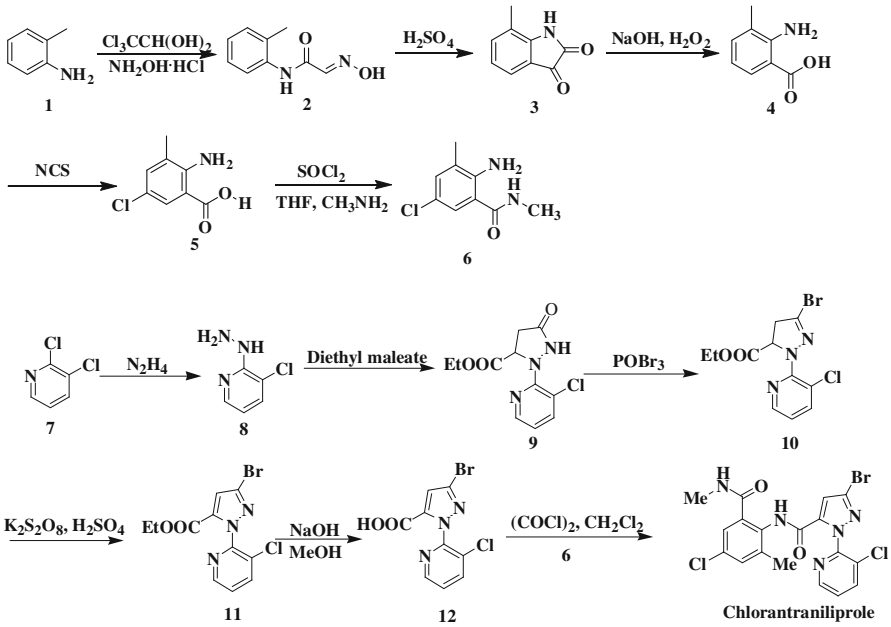
^{1}H NMR spectra were obtained at 400 MHz using a Bruker AV400 spectrometer or Varian Mercury Plus400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in ppm. Elemental analyses were determined on a Yanaco CHN Corder MT-3 elemental analyzer. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments, Beijing, China) and were uncorrected. All solvents and liquid reagents were dried by standard methods and distilled before use.

General procedures

Chlorantraniliprole was prepared according to the route shown in Scheme 1. The title compounds **18** were synthesized from compound **17** and the appropriate intermediate **14** (obtained from the intermediate **13** and corresponding amine; see Table 1) in dry tetrahydrofuran using triethylamine as base as shown in Scheme 2.

Synthetic procedure for 2-amino-3-methyl-benzoic acid (**4**)

Compound **4** was prepared according to the literature [13]. Chloralhydrate (8.1 g, 55 mmol, 1.1 equiv) and Na_2SO_4 (71.0 g, 0.5 mol, 10 equiv) were dissolved in water (200 mL) in a three-neck 500-mL round-bottom flask. The solution was stirred with a mechanical stirrer and heated to 40 °C until the mixture became clear.

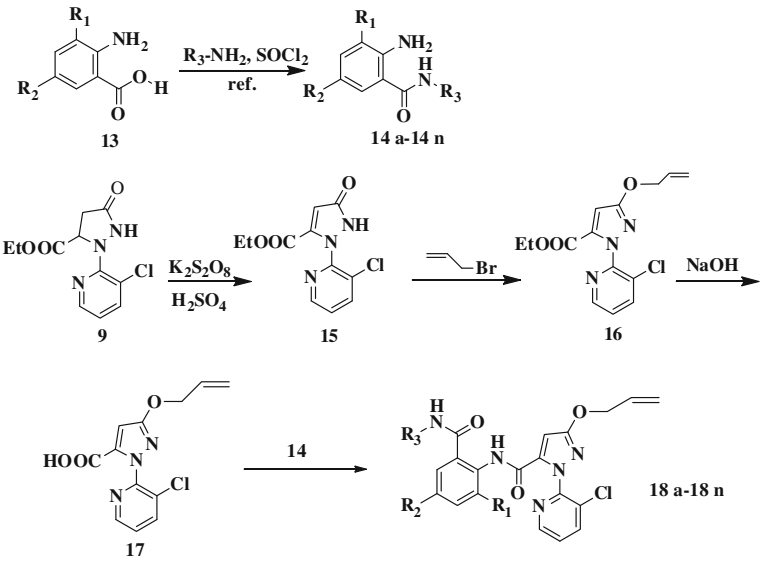


Scheme 1 General synthetic route of the chlorantraniliprole

Table 1 Melting points and yields of the compounds **14a–14n**

Compd.	R_1	R_2	R_3	m.p. (°C)	Yield (%)
14a	CH_3	Cl	*n*-propyl	119–121	88.0
14b	CH_3	Cl	*n*-butyl	87–88	77.9
14c	CH_3	Cl	*i*-butyl	117–122	68.1
14d	CH_3	Cl	Cyclohexyl	167–168	89.2
14e	H	Cl	*n*-propyl	120–122	79.3
14f	H	Cl	*i*-propyl	161–162	58.0
14g	H	Cl	Cyclopropyl	143–145	61.9
14h	H	Cl	*n*-butyl	108–110	66.4
14i	H	Cl	Cyclohexyl	179–181	56.9
14j	CH_3	H	*n*-propyl	88–90	70.2
14k	CH_3	H	*i*-propyl	137–139	70.2
14l	CH_3	H	Cyclopropyl	118–120	80.0
14m	CH_3	Br	*i*-propyl	161–163	71.4
14n	CH_3	Br	Cyclopropyl	157–159	63.8

A warm solution of the commercial *o*-toluidine **1** (5.4 g, 50 mmol) in water (50 mL) and an aqueous solution of concentrated HCl (5.32 g, 4.5 mL, 52.5 mmol, 1.05 equiv.) was added, followed by a warm solution of hydroxylamine hydrochloride (10.4 g, 0.15 mol, 3.0 equiv.) in water (45 mL). The mixture was heated to reflux under vigorous stirring, allowed to reflux for 10 min, and then cooled to room



Scheme 2 General synthetic route of the title compounds **18a–18n**

temperature. The product precipitated out of solution, and after standing overnight, the solid was collected and dried to obtain 2-hydroxyimino-*N*-*o*-tolyl-acetamide.

Sulfuric acid (60 mL) was heated in a three-neck 250-mL round-bottom flask to 60 °C and then removed. The dry 2-hydroxyimino-*N*-*o*-tolyl-acetamide (**2**) was added in portions with stirring over 30 min so that the temperature did not exceed 70 °C. The mixture was then heated to 80 °C for 20 min, then allowed to cool to room temperature. The reaction mixture was poured over crushed ice (100 g) and left to stand for 1 h, yielding a crude precipitate that was collected by suction filtration. The product was washed with water (2 × 50 mL) and filtered to give crude 7-methyl-1*H*-indole-2,3-dione, which was directly used for the next step without further purification.

To a stirred suspension of compound **3** in a 5 % aqueous sodium hydroxide solution (150 mL) (this mixture was cooled to 0 °C) was added dropwise a 30 % aqueous hydrogen peroxide solution (150 mL). The reaction mixture was stirred at 50 °C for 30 min and then allowed to reach room temperature. The filtered solution was acidified to pH 4 with an aqueous 1 N hydrochloric acid solution, and a tan precipitate was collected by filtration, washed thoroughly with cold water, and dried under vacuum to afford 2-amino-3-methyl-benzoic acid (**4**). The overall yield of compound **4** was 25.6 %, m.p. 173–174 °C. ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 7.61 (d, J = 8.0 Hz, 1H, Ph-H), 7.15 (d, J = 7.0 Hz, 1H, Ph-H), 6.50 (m, 1H, Ph-H), 2.09 (s, 3H, CH_3).

Synthetic procedure for 2-amino-5-chloro-3-methyl-benzoic acid (**5**)

2-amino-5-chloro-3-methylbenzoic acid (**5**) was prepared according to the literature [14]. To a solution of 2-amino-3-methylbenzoic acid (10 g, 66 mmol) in DMF (40 mL) was added *N*-chlorosuccinimide (8.8 g, 66 mmol) and the reaction mixture

was heated to 100 °C for 40 min. The reaction was cooled to room temperature and let stand overnight. The reaction mixture was then slowly poured into ice-water (150 mL) to precipitate a white solid. The solid was filtered and washed with water (3 × 50 mL) and then taken up in ethyl acetate (600 mL). The ethyl acetate solution was dried over magnesium sulfate, evaporated under reduced pressure and the residual solid was washed with ether (3 × 30 mL) to afford intermediate 2-amino-5-chloro-3-methylbenzoic acid (**5**): white solid, m.p. 196–197 °C (dec.) yield 76.0 %; ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 7.53 (s, 1H, Ph-H), 7.21 (s, 1H, Ph-H), 2.09 (s, 3H, CH_3).

Synthesis of intermediates 2-amino-5-chloro-3,*N*-dimethyl-benzamide (**6**)

2-Amino-5-chloro-3,*N*-dimethyl-benzamide (**6**) was prepared according to the literature [15]. Into a 100-mL round-bottomed flask was placed 2-amino-5-chloro-3-methylbenzoic acid (**5**) (3.7 g, 20 mmol) and then 50 mL of thionyl chloride was added. The resulting mixture was refluxed for 3 h. The mixture was evaporated in vacuo to dryness and then 60 mL of THF was added. To this solution was added dropwise a solution 50 g of 25 % aqueous methylamine solution under an ice bath. The resulting solution was allowed to stand at room temperature for 12 h and then water (200 mL) was added. The yellow precipitate was collected by filtration and dried to give 2.36 g (59.3 %) of compound **6**, m.p. 130–132 °C. ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.16 (d, J = 2.2 Hz, 1H, Ph-H), 7.09 (d, J = 1.6 Hz, 1H, Ph-H), 6.01 (br, 1H, NH), 5.52 (br, 2H, NH_2), 2.95 (d, J = 4.8 Hz, 3H, $NHCH_3$), 2.13 (s, 3H, CH_3).

Synthetic procedure for (3-chloro-pyridin-2-yl)-hydrazine (**8**)

To a suspension of 2,3-dichloropyridine 7 (100.0 g, 0.676 mol) in anhydrous ethanol (420 mL) was added 50 % hydrazine hydrate (280 mL, 2.884 mol). The resulting mixture was refluxed for 36 h, and then cooled to room temperature. The product precipitated out of solution, the white crystal was collected by filtration, washed thoroughly with cold ethanol and dried to give white crystals (74.4 g, 76.8 %), m.p. 163–164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.09 (d, J = 3.9 Hz, 1H, pyridyl-H); 7.47 (d, J = 8.1 Hz, 1H, pyridyl-H); 6.64 (dd, J_1 = 3.9 Hz, J_2 = 8.1 Hz, 1H, pyridyl-H); 6.21 (s, 1H, NH); 3.97 (br. s, 2H, NH_2).

Synthetic procedure for 2-(3-chloro-pyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (**9**)

To 200 mL of absolute ethanol in a 500-mL three-necked round-bottomed flask was added 6.9 g (0.3 mol) of sodium cut in pieces of suitable size. When all the sodium has reacted, the mixture was heated to reflux and (3-chloro-pyridin-2-yl)-hydrazine (**8**) (39.82 g, 0.277 mol) was added. The mixture was refluxed for 10 min, then diethyl maleate (51.65 g, 0.3 mol) was added dropwise. The resulting orange–red solution was held at reflux for 30 min. After being cooled to 65 °C, the reaction

mixture was treated with glacial acetic acid (30 g, 0.51 mol). The mixture was diluted with water (30 mL). After removal of most of the solvent, the residue was treated with water (300 mL). The slurry formed was dissolved in aqueous ethanol (70 %, 200 mL) and was stirred thoroughly. The solid was collected by filtration, washed with aqueous ethanol (50 %, 3 × 50 mL) to give 2-(3-chloro-pyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (**9**) (36.6 g, 49.0 %), m.p. 132–134 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.18 (s, 1H, NH); 8.25 (d, $J = 4.8$ Hz, 1H, pyridyl-H); 7.91 (d, $J = 7.4$ Hz, 1H, pyridyl-H); 7.18 (dd, $J_1 = 4.8$ Hz, $J_2 = 7.4$ Hz, 1H, pyridyl-H); 4.81 (d, $J = 9.8$ Hz, 1H, CH); 4.17 (q, $J = 7.0$ Hz, 2H, OCH_2); 2.89 (dd, $J_1 = 9.8$ Hz, $J_2 = 16.8$ Hz, 1H, CH_2–H); 2.34 (d, $J = 16.8$ Hz, 1H, CH_2–H); 1.20 (t, $J = 7.0$ Hz, 3H, CH_3).

5-Bromo-2-(3-chloro-pyridin-2-yl)-3,4-dihydro-2*H*-pyrazole-3-carboxylic acid ethyl ester (**10**)

To a solution of 2-(3-chloro-pyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (**9**) (27 g, 0.1 mol) in acetonitrile (300 mL) was added phosphorous oxybromide (34.4 g, 0.12 mmol). The reaction mixture was refluxed for 5 h, then 250 mL of solvent was removed by distillation. The concentrated reaction mixture was slowly poured into saturated aq. Na_2CO_3 (250 mL) and was stirred vigorously for 30 min. The resulting mixture was extracted with CH_2Cl_2 (2 × 250 mL), the organic extract was separated, dried, filtered, concentrated and purified by silica gel chromatography to afford 5-bromo-2-(3-chloro-pyridin-2-yl)-3,4-dihydro-2*H*-pyrazole-3-carboxylic acid ethyl ester (**10**) (31.0 g, 93.0 %), m.p. 59–60 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.10 (d, $J = 4.4$ Hz, 1H, pyridyl-H); 7.83 (d, $J = 7.7$ Hz, 1H, pyridyl-H); 6.98 (dd, $J_1 = 4.4$ Hz, $J_2 = 7.7$ Hz, 1H, pyridyl-H); 5.17 (dd, $J_1 = 8.7$ Hz, $J_2 = 11.8$ Hz, 1H, CH); 4.08 (q, $J = 7.0$ Hz, 2H, OCH_2); 3.27 (dd, $J_1 = 8.7$ Hz, $J_2 = 17.6$ Hz, 1H, CH_2–H); 3.57 (dd, $J_1 = 11.8$ Hz, $J_2 = 17.6$ Hz, 1H, CH_2–H); 1.12 (t, $J = 7.0$ Hz, 3H, CH_3).

Synthetic procedure for 5-bromo-2-(3-chloro-pyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid ethyl ester (**11**)

To a solution of 5-bromo-2-(3-chloro-pyridin-2-yl)-3,4-dihydro-2*H*-pyrazole-3-carboxylic acid ethyl ester (**10**) (17 g, 51 mmol) in acetonitrile (250 mL) was added sulfuric acid (98 %, 10 g, 102 mmol). After being stirred for several minutes, the reaction mixture was treated with $K_2S_2O_8$ (21 g, 76.5 mmol) and was refluxed for 4.5 h. After being cooled to 60 °C, the mixture was filtered to remove a fine filter cake which was washed with acetonitrile (30 mL). The filtrate was concentrated to 100 mL, then was added slowly to water (250 mL) under stirring. The solid was collected by filtration, washed with acetonitrile (3 × 30 mL), water (30 mL), and then dried to give 5-bromo-2-(3-chloro-pyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid ethyl ester (**11**) (15.6 g, 92.7 %), m.p. 117–118 °C. ^{1}H NMR ($CDCl_3$, 300 M) δ: 8.52 (d, $J = 4.8$ Hz, 1H, pyridyl-H); 7.92 (d, $J = 8.1$ Hz, 1H, pyridyl-H); 7.45 (dd, $J_1 = 4.8$ Hz, $J_2 = 8.1$ Hz, 1H, pyridyl-H); 6.95 (s, 1H, pyrazolyl-H); 4.24 (q, $J = 7.2$ Hz, 2H, CH_2); 1.21 (t, $J = 7.2$ Hz, 3H, CH_3).

Synthetic procedure for 5-bromo-2-(3-chloro-pyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (**12**)

To a mixture of the ethyl 5-bromo-2-(3-chloro-pyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid ethyl ester (**11**) (15.6 g, 47.2 mmol) in methanol (120 mL) was added aqueous sodium hydroxide solution (60 mL, 1 mol L^{-1}). The solution was stirred at room temperature for 6 h, then was concentrated in vacuo to about 50 mL. The concentrated mixture was diluted with H_2O (150 mL), and washed with ethyl acetate (150 mL). The aqueous solution was acidified using concentrated hydrochloric acid to pH = 2. The solid was collected by filtration, washed with ether (30 mL), and then dried to give 5-bromo-2-(3-chloro-pyridin-2-yl)-2*H*-pyrazole-3-carboxylic acid (**12**) (12.75 g, 89.3 %), m.p. 197–200 °C. ^{1}H NMR ($CDCl_3$, 300 M) δ: 8.52 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.8$ Hz, 1H, pyridyl-H); 7.94 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.1$ Hz, 1H, pyridyl-H); 7.48 (dd, 1H, $J = 4.8$, 8.1 Hz, pyridyl-H); 7.10 (s, 1H, pyrazolyl-H).

Synthetic procedure for chlorantraniliprole

Chlorantraniliprole was prepared according to the literature [16, 17]. To a suspension of *N*-pyridylpyrazole acid **12** (0.30 g, 1 mmol) in dichloromethane (20 mL) was added oxalyl chloride (0.38 g, 3 mmol), followed by dimethylformamide (2 drops). The solution was stirred at room temperature. After 6 h, the mixture was concentrated in vacuo to obtain the crude acid chloride. The crude acid chloride in dichloromethane (20 mL) was added slowly to a stirred solution of 2-amino-5-chloro-3,*N*-dimethyl-benzamide (**6**) (0.24 g, 1.2 mmol) in dichloromethane (20 mL) in an ice bath. After 20 min, ethyl-diisopropyl-amine (0.13 g, 1 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 12 h. The solution was diluted with CH_2Cl_2 (20 mL), and washed with 1 N aq. HCl solution (10 mL), saturated aq. $NaHCO_3$ (10 mL), and brine (10 mL). The organic extract was separated, dried, filtered, and concentrated and purified by silica gel chromatography to afford the chlorantraniliprole. (0.43 g, 89.3 %), m.p. 197–200 °C. ^{1}H NMR ($CDCl_3$, 400 M) δ: 10.10 (br. s, 1H, NH); 8.46 (dd, $J_1 = 1.6$ Hz, $J_2 = 4.8$ Hz, 1H, pyridyl-H); 7.85 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.38 (dd, $J_1 = 4.8$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.24 (d, $J = 2.0$ Hz, 1H, Ph-H); 7.21 (d, $J = 2.0$ Hz, 1H,Ph-H); 7.11 (s, 1H, pyrazolyl-H); 6.15–6.18 (m, 1H, NHCO); 2.95 (d, $J = 4.9$ Hz, 2H, $NHCH_3$); 2.17 (s, 3H, CH_3).

Synthetic procedure for 2-amino-5-chloro-3-methyl-*N*-propyl-benzamide (**14a**)

Compound **13** was synthesized according to the same method of compound **5**. To a 100-mL round-bottomed flask was placed 2-amino-5-chloro-3-methylbenzoic acid (**5**) (5.0 g, 27 mmol) and then 50 mL of thionyl chloride was added. The resulting mixture was refluxed for 3 h. The mixture was evaporated in vacuo to dryness and then 40 mL of THF was added. The solution was added slowly to a stirred solution of propylamine (15.8 g, 270 mmol) in tetrahydrofuran (40 mL) in an ice bath. The resulting solution was allowed to stir at room temperature for 12 h. Then, the

solution was concentrated in vacuo and diluted with ethyl acetate (150 mL), and washed with water (3 × 50 mL). The organic extract was separated, dried, filtered, and concentrated and purified by silica gel chromatography to afford the desired title compound **14a**.

Compounds **14b–14n** were prepared by similar method above using the appropriate substrates. The melting points and yields of compounds **14a–14n** are listed in Table 1. The ^{1}H NMR data are listed in Table 2.

Synthetic procedure for 2-(3-chloro-pyridin-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole-3- carboxylic acid ethyl ester (**15**)

To a solution of 2-(3-chloro-pyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (**9**) (10 g, 37 mmol) in acetonitrile (150 mL) was added sulfuric acid (98 %, 7.2 g, 74 mmol). After being stirred for several minutes, the reaction mixture was treated with $K_2S_2O_8$ (15 g, 56 mmol) and was refluxed for 4.5 h. After being cooled to 60 °C, the mixture was filtered to remove a fine filter cake which was washed with acetonitrile (30 mL). The filtrate was concentrated and poured into ice water (200 mL). The aqueous layer was extracted with dichloromethane (3 × 150 mL). The organic layer was washed with water (3 × 100 mL) and dried over anhydrous sodium sulfate. Then, the ethyl acetate was concentrated. The residue was purified by column chromatography over silica gel using petroleum ether (60–90 °C) and ethyl acetate as the eluent to afford the 2-(3-chloro-pyridin-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid ethyl ester (**15**). (6.2 g, 62.4 %), m.p. 136–138 °C. ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.35 (s, 1H, NH); 8.52 (d, $J = 4.4$ Hz, 1H, pyridyl-H); 7.90 (d, $J = 8.0$ Hz, 1H, pyridyl-H); 7.43 (dd, $J_1 = 4.4$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 6.36 (s, 1H, pyrazolyl-H); 4.19 (q, 2H, $J = 7.2$ Hz, CH_2); 1.19 (t, 3H, $J = 7.2$ Hz, CH_3).

Synthetic procedure for ethyl 3-(allyloxy)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylate (**16**)

The ester **16** was prepared according to the literature [7]. Compound **15** (2.0 g, 7.5 mmol) was dissolved in 30 mL of dry dimethylformamide, and potassium carbonate (1.52 g, 11.0 mmol) was added. The mixture was heated to 40 °C. The allyl bromide (1.08 g, 9 mmol) in dry dimethylformamide (5 mL) was added slowly to the mixture. The solution was warmed at 100 °C and stirred for 3 h and poured into ice water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 40 mL). The organic layer was washed with water (3 × 40 mL) and dried over anhydrous sodium sulfate. Then, the ethyl acetate was concentrated. The residue was purified by column chromatography on a silica gel using petroleum ether (60–90 °C) and ethyl acetate as the eluent to afford the ethyl 3-(allyloxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylate (**16**). (2.11 g, 91 %), ^{1}H NMR ($CDCl_3$, 400 M) δ: 8.51 (dd, $J_1 = 1.6$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 7.90 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.41 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 6.48 (s, 1H, pyrazolyl-H); 6.05–6.12 (m, 1H, CH=); 5.33–5.38 (m,

Table 2 ^{1}H NMR of the compounds **14a–14n**

Compd.	^{1}H NMR δ (ppm)
14a	(400 MHz, DMSO-d_6), δ: 8.37 (br, 1H, CONH); 7.41 (d, J = 1.8 Hz, 1H, Ph-H); 7.13 (d, J = 1.8 Hz, 1H, Ph-H); 6.32 (s, 2H, $PhNH_2$); 3.14–3.17 (m, 2H, $NHCH_2$); 2.08 (s, 3H, $PhCH_3$); 1.50–1.52 (m, 2H, CH_2CH_3); 0.88 (t, J = 7.4 Hz, 3H, CH_2CH_3)
14b	(400 MHz, DMSO-d_6), δ: 8.34 (br, 1H, CONH); 7.41 (d, J = 1.8 Hz, 1H, Ph-H); 7.12 (d, J = 1.8 Hz, 1H, Ph-H); 6.32 (s, 2H, $PhNH_2$); 3.19–3.22 (m, 2H, $NHCH_2$); 2.08 (s, 3H, $PhCH_3$); 1.45–1.52 (m, 2H, CH_2); 1.29–1.36 (m, 2H, CH_2CH_3); 0.89 (t, J = 7.3 Hz, 3H, CH_2CH_3)
14c	(400 MHz, DMSO-d_6), δ: 8.38 (br, 1H, CONH); 7.42 (d, J = 2.0 Hz, 1H, Ph-H); 7.14 (d, J = 2.0 Hz, 1H, Ph-H); 6.29 (s, 2H, $PhNH_2$); 3.01–3.03 (m, 2H, $NHCH_2$); 2.08 (s, 3H, $PhCH_3$); 1.77–1.88 (m, 1H, $CH(CH_3)_2$); 0.88 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$)
14d	(400 MHz, $CDCl_3$), δ: 7.05–7.14 (m, 2H, Ph-H); 5.81 (br, 1H, NH); 5.46 (br, 2H, NH_2); 3.82–3.94 (m, 1H, cyclohexyl-H); 2.13 (s, 3H, CH_3); 1.18–2.04 (m, 10H, cyclohexyl-H)
14e	(400 MHz, DMSO-d_6), δ: 8.34–8.36 (m, 1H, CONH); 7.53 (d, J = 2.4 Hz, 1H, Ph-H); 7.15 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, Ph-H); 6.70 (d, J = 8.7 Hz, 1H, Ph-H); 6.54 (s, 2H, $PhNH_2$); 3.13–3.16 (m, 2H, $NHCH_2$); 1.46–1.53 (m, 2H, CH_2CH_3); 0.87 (t, J = 7.2 Hz, 3H, CH_2CH_3)
14f	(400 MHz, DMSO-d_6), δ: 8.11–8.13 (m, 1H, CONH); 7.54 (d, J = 2.4 Hz, 1H, Ph-H); 7.15 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, Ph-H); 6.70 (d, J = 8.8 Hz, 1H, Ph-H); 6.50 (s, 2H, $PhNH_2$); 4.01–4.09 (m, 1H, CH); 1.14 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$)
14g	(400 MHz, DMSO-d_6), δ: 8.35–8.37 (m,1H, CONH); 7.53 (d, J = 2.4 Hz, 1H, Ph-H); 7.20 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H, Ph-H); 6.76 (d, J = 8.8 Hz, 1H, Ph-H); 6.61 (s, 2H, $PhNH_2$); 2.82–2.88 (m, 1H, cyclopropyl-H); 0.69–0.74 (m,2H, cyclopropyl-H); 0.58–0.62 (m, 2H, cyclopropyl-H)
14h	(400 MHz, DMSO-d_6), δ: 8.30–8.32 (m, 1H, CONH); 7.51 (d, J = 2.0 Hz, 1H, Ph-H); 7.15 (dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 1H, Ph-H); 6.70 (d, J = 8.7 Hz, 1H, Ph-H); 6.53 (s, 2H, $PhNH_2$); 3.17–3.19 (m, 2H, $NHCH_2$); 1.42–1.51 (m, 2H, CH_2CH_2); 1.26–1.35 (m, 2H, CH_2CH_3); 0.89 (t, J = 7.2 Hz, 3H, CH_2CH_3)
14i	(400 MHz, DMSO-d_6), δ: 8.10–8.12 (m, 1H, CONH); 7.52 (d, J = 2.0 Hz, 1H, Ph-H); 7.14 (dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 1H, Ph-H); 6.69 (d, J = 8.7 Hz, 1H, Ph-H); 6.47 (s, 2H, $PhNH_2$); 3.67–3.70 (m, 1H, NHCH); 1.08–1.79 (m, 10H, cyclohexyl-H)
14j	(400 MHz, DMSO-d_6), δ: 8.20–8.22 (m, 1H, CONH); 7.35 (d, J = 7.6 Hz, 1H, Ph-H); 7.06 (d, J = 7.2 Hz, 1H, Ph-H); 6.45–6.49 (m,1H, Ph-H); 6.18 (s, 2H, $PhNH_2$); 3.14–3.19 (m, 2H, $NHCH_2$); 2.07 (s, 3H, $PhCH_3$); 1.46–1.55 (m, 2H, CH_2CH_3); 0.88 (t, J = 7.4 Hz, 3H, CH_2CH_3)
14k	(400 MHz, DMSO-d_6), δ: 8.19–8.21 (m, 1H, CONH); 7.33 (d, J = 7.6 Hz, 1H, Ph-H); 7.05 (d, J = 7.0 Hz, 1H, Ph-H); 6.46–6.49 (m,1H, Ph-H); 6.11 (s, 2H, $PhNH_2$); 4.22–4.30 (m, 1H, CH); 2.18 (s, 3H, CH_3); 1.25 (m, 6H, J = 6.6 Hz, $CH(CH_3)_2$)
14l	(400 MHz, DMSO-d_6), δ: 8.18 (s, 1H, CONH); 7.30 (d, J = 7.6 Hz, 1H, Ph-H); 7.05 (d, J = 6.8 Hz, 1H, Ph-H); 6.43–6.47 (m, 1H, Ph-H); 6.21 (s, 2H, $PhNH_2$); 2.78–2.80 (m, 1H, cyclopropyl-H); 2.07 (s,3H, $PhCH_3$); 0.65–0.67 (m, 2H, CH_2CH_2, cyclopropyl-H); 0.53–0.55 (m, 2H, CH_2CH_2, cyclopropyl-H)
14m	(400 MHz, $CDCl_3$), δ: 7.24-7.31 (m, 1H, Ar–H); 7.24-7.25 (m, 1H, Ar–H);5.87 (br, 1H, NH); 4.20-4.26 (m, 1H, CH); 2.19 (s, 3H, CH_3); 1.26 (d, 6H, J = 6.4 Hz, CH_3)
14n	(400 MHz, $CDCl_3$), δ: 7.08–7.12 (m, 2H, Ph-H); 6.03 (br, 1H, NH); 5.43–5.64 (br, 2H, NH_2); 2.68–2.72 (m, 1H, cyclopropyl-H); 2.02 (s, 3H, CH_3); 0.71–0.76 (m, 2H, cyclopropyl-H); 0.46–0.50 (m, 2H, cyclopropyl-H)

2H, $=CH_2$); 4.78 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 4.22 (q, $J = 7.2$ Hz, 2H, CH_2CH_3); 1.22 (t, $J = 7.2$ Hz, 3H, CH_2CH_3).

Synthetic procedure for 3-(allyloxy)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (**17**)

To a mixture of the compound **16** (2.11 g, 7.5 mmol) in methanol (20 mL) was added aqueous sodium hydroxide solution (10 mL, 1 mol L^{-1}). The solution was stirred at room temperature for 6 h, then was concentrated in vacuo to about 5 mL. The concentrated mixture was diluted with H_2O (40 mL), and washed with ethyl acetate (20 mL). The aqueous solution was acidified using concentrated hydrochloric acid to pH = 2. The solid was collected by filtration, washed with ether (10 mL), and then dried to give 3-(allyloxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**17**) (1.69 g, 73.3 %), m.p. 138–140 °**C**. ^{1}H NMR (DMSO-d_6, 400 M) δ: 8.50 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 7.90 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.40 (dd, $J_1 = 4.7$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 6.52 (s, 1H, pyrazolyl-H); 6.05–6.12 (m, 1H, CH=); 5.33–5.38 (m, 2H, $=CH_2$); 4.76 (d, $J_{HH} = 5.6$ Hz, 2H, $CH_2CH=$).

Synthetic procedure for the title compounds **18a–18n**

To a suspension of *N*-pyridylpyrazole acid **17** (1 mmol) in dichloromethane (20 mL) was added oxalyl chloride (3 mmol) and dimethylformamide (2 drops). The solution was stirred at ambient temperature for 4 h. Then, the mixture was concentrated in vacuo to give the crude acid chloride. The crude acid chloride in tetrahydrofuran (25 mL) was added slowly to a stirred solution of **14** (1.2 mmol) and triethylamine (1.2 mmol) in tetrahydrofuran (15 mL). The mixture was stirred at ambient temperature for 8 h. Then, the solution was concentrated in vacuo and diluted with CH_2Cl_2 (60 mL), and washed with 1 N aq. HCl solution (15 mL), saturated aq. $NaHCO_3$ (15 mL), and brine (15 mL). The organic extract was separated, dried, filtered, and concentrated and purified by silica gel chromatography to afford the desired title compound **18a–18n**.

3-(allyloxy)-N-(4-chloro-2-methyl-6-(propylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18a**): White crystal, yield, 58.3 %; m.p. 209–211 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.78 (s, 1H, CONH); 8.35–8.38 (m, 1H, pyridyl-H); 7.73 (d, $J = 7.8$ Hz, 1H, pyridyl-H); 7.23 (dd, $J_1 = 4.0$ Hz, $J_2 = 7.8$ Hz, 1H, pyridyl-H); 7.18 (s, 1H, Ph-H); 7.14 (s, 1H, Ph-H); 6.42 (s, 1H, pyrazolyl-H); 6.01–6.04 (m, 1H, $NHCH_2$); 5.94–5.99 (m, 1H, CH=); 5.19–5.35 (m, 2H, $=CH_2$); 4.73 (d, $J_{HH} = 5.6$ Hz, 2H, $CH_2CH=$); 3.24–3.27 (m, 2H, CH_2NH); 2.12(s, 3H, $PhCH_3$); 1.51–1.54 (m, 2H, CH_2CH_3); 0.88 (t, $J = 6.9$ Hz, 3H, CH_2CH_3); Anal. Calcd. for $C_{23}H_{23}Cl_2N_5O_3$ (%): C, 56.57; H, 4.75; N, 14.34. Found: C, 56.68; H, 4.78; N, 14.13.

3(allyloxy)-N-(2-(butylcarbamoyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18b**): White crystal, yield, 52.2 %; m.p. 183–185 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.81(s, 1H, CONH); 8.35–8.38 (m, 1H, pyridyl-H); 7.73 (d, $J = 7.5$ Hz, 1H, pyridyl-H); 7.22–7.24 (m, 1H, pyridyl-H); 7.14

(s, 1H, Ph-H); 7.10 (s, 1H, Ph-H); 6.46 (s, 1H, pyrazolyl-H); 6.07–6.12 (m, 1H, $NHCH_2$); 5.97–6.02 (m, 1H, CH=); 5.19–5.36 (m, 2H, $=CH_2$); 4.72 (s, 2H, $CH_2CH=$); 3.25–3.28 (m, 2H, $NHCH_2$); 2.10 (s, 3H, $PhCH_3$); 1.42–1.45 (m, 2H, CH_2CH_2); 1.26–1.28 (m, 2H, CH_2CH_2); 0.85 (t, $J = 7.0$ Hz, 3H, CH_2CH_3); The value of HRMS $[M+Na]^+$ for $C_{24}H_{25}Cl_2N_5O_3$:524.1227. Found: 524.1224

3-(allyloxy)-N-(4-chloro-2-(isobutylcarbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18c**): White crystal, yield, 58.2 %; m.p. 233–234 °C; ^1H NMR ($CDCl_3$, 400 M) δ: 9.77 (s, 1H, CONH); 8.35–8.38 (m, 1H, pyridyl-H); 7.74 (d, $J = 7.5$ Hz, 1H, pyridyl-H); 7.22–7.26 (m, 1H, pyridyl-H); 7.18 (s, 1H, Ph-H); 7.13 (d, 1H, Ph-H); 6.42 (s, 1H, pyrazolyl-H); 6.04–6.08 (m, 1H, $NHCH_2$); 5.97–6.02 (m, 1H, CH=); 5.20–5.38 (m, 2H, $=CH_2$); 4.73 (s, 2H, $CH_2CH=$); 3.10–3.13 (m, 2H, $NHCH_2$); 2.12 (s, 3H, $PhCH_3$); 1.73–1.76 (m, 1H, $CHCH_2$); 0.86 (d, $J = 6.2$ Hz, 6H, $(CH_3)_2$); Anal. Calcd. for $C_{24}H_{25}Cl_2N_5O_3$ (%): C, 57.38; H, 5.02; N, 13.94. Found: C, 57.46; H, 4.84; N, 13.85.

3-(allyloxy)-N-(4-chloro-2-(cyclohexylcarbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18d**): White crystal, yield, 55.0 %; m.p. 142–144 °C; ^1H NMR ($CDCl_3$, 400 M) δ: 9.83 (s, 1H, CONH); 8.39 (d, $J = 4.7$ Hz, 1H, pyridyl-H); 7.78 (d, $J = 8.0$ Hz, 1H, pyridyl-H); 7.28 (dd, $J_1 = 4.7$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.18 (s, 1H, Ph-H); 7.13 (s, 1H, Ph-H); 6.41 (s, 1H, pyrazolyl-H); 5.97–6.01 (m, 1H, NHCH); 5.86–5.93 (m, 1H, CH=); 5.18–5.37 (m, 2H, $=CH_2$); 4.71 (d, $J_{HH} = 5.6$ Hz, 2H, $CH_2CH=$); 3.68–3.71 (m, 1H, NHCH); 2.13 (s, 3H, $PhCH_3$); 1.95–1.98 (m, 2H, CH_2); 1.84–1.86 (m, 2H, CH_2); 1.47–1.49 (m, 2H, CH_2); 1.22–1.24 (m, 2H, CH_2); 1.01–1.03 (m, 2H, CH_2); The value of HRMS $[M+Na]^+$ for $C_{26}H_{27}Cl_2N_5O_3$: 550.1383. Found: 550.1383.

3-(allyloxy)-N-(4-chloro-2-(propylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18e**): colourless oil, yield,61.7 %; ^1H NMR ($CDCl_3$, 400 M) δ: 12.02 (s, 1H, CONH); 8.42 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 8.37–7.40 (m, 1H, Ph-H); 7.81 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.26–7.36 (m, 3H, pyridyl-H, Ph-H); 6.45 (s, 1H, pyrazolyl-H); 6.15–6.18 (m, 1H, NH); 6.00–6.09 (m, 1H, CH=); 5.20–5.35 (m, 2H, $=CH_2$); 4.73 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 3.33–3.36 (m, 2H, $NHCH_2$); 1.59–1.61 (m, 2H, CH_2CH_2); 0.96 (t, $J = 7.4$ Hz, 3H, CH_2CH_3); The value of HRMS $[M+Na]^+$ for $C_{22}H_{21}Cl_2N_5O_3$: 496.0914. Found: 496.0917.

3-(allyloxy)-N-(4-chloro-2-(isopropylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18f**): White crystal, yield, 53.6 %; m.p. 188–190 °C; ^1H NMR ($CDCl_3$, 400 M) δ: 12.15 (s, 1H, CONH); 8.52 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 8.46 (d, $J = 9.0$ Hz, 1H, Ph-H); 7.93 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.33–7.45 (m, 3H, pyridyl-H, Ph-H); 6.53 (s, 1H, pyrazolyl-H); 6.10–6.13 (m, 1H, NH); 6.04–6.11 (m, 1H, CH=); 5.24–5.42 (m, 2H, $=CH_2$); 4.80 (d, $J_{HH} = 5.6$ Hz, 2H, $CH_2CH=$); 4.27–4.30 (m, 1H, NHCH); 1.31 (d, $J = 6.6$ Hz, 6H, $(CH_3)_2$); Anal. Calcd. for $C_{22}H_{21}Cl_2N_5O_3$ (%): C, 55.71; H, 4.46; N, 14.76. Found: C, 55.64; H, 4.55; N, 14.68.

3-(allyloxy)-N-(4-chloro-2-(cyclopropylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18g**): White crystal, yield, 47.9 %; m.p. 195–196 °C; ^1H NMR ($CDCl_3$, 400 M) δ: 12.05 (s, 1H, CONH); 8.42 (dd, $J_1 = 1.2$ Hz, $J_2 = 4.7$ Hz,

1H, pyridyl-H); 8.38 (d, $J = 9.0$ Hz, 1H, Ph-H); 7.80 (dd, $J_1 = 1.2$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.24–7.34 (m, 3H, pyridyl-H, Ph-H); 6.48 (s, 1H, pyrazolyl-H); 6.23–6.25 (m, 1H, NH); 6.00–6.09 (m, 1H, CH=); 5.00–5.16 (m, 2H, $=CH_2$); 4.72 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 2.80–2.83(m, 1H, NHCH); 0.85–0.87(m, 2H, CH_2CH_2); 0.58–0.60 (m, 2H, CH_2CH_2); The value of HRMS $[M+Na]^+$ for $C_{22}H_{19}Cl_2N_5O_3$: 494.0757. Found: 494.0758.

3-(allyloxy)-N-(2-(butylcarbamoyl)-4-chlorophenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18h**): White crystal, yield, 46.2 %; m.p. 196–198 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 12.03 (s, 1H, CONH); 8.40 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 8.36 (d, $J = 9.0$ Hz, 1H, Ph-H); 7.79 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.24–7.39 (m, 3H, pyridyl-H, Ph-H); 6.43 (s, 1H, pyrazolyl-H); 6.18–6.20 (m, 1H, NH); 5.95–6.04 (m, 1H, CH=); 5.14–5.37 (m, 2H, $=CH_2$); 4.71 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 3.35–3.38 (m, 2H, $NHCH_2$); 1.50–1.53 (m, 2H, CH_2CH_2); 1.32–1.34 (m, 2H, CH_2CH_2); 0.89 (t, $J = 7.2$ Hz, 3H, CH_2CH_3); The value of HRMS $[M+Na]^+$ for $C_{23}H_{23}Cl_2N_5O_3$: 510.1070. Found: 510.1066.

3-(allyloxy)-N-(4-chloro-2-(cyclohexylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18i**): White crystal, yield, 54.8 %; m.p. 145–147 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 12.04 (s, 1H, CONH); 8.42 (dd, $J_1 = 1.4$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 8.39 (d, $J = 9.0$ Hz, 1H, Ph-H); 7.80 (dd, $J_1 = 1.4$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.26–7.34 (m, 3H, pyridyl-H, Ph-H); 6.45 (s, 1H, pyrazolyl-H); 6.02–6.04 (m, 1H, NH); 5.86–5.93 (m, 1H, CH=); 5.13–5.25 (m, 2H, $=CH_2$); 4.73 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 3.87–3.89 (m, 2H, CH_2); 1.95–1.97 (m, 2H, CH_2); 1.70–1.72 (m, 2H, CH_2); 1.60–1.62 (m, 2H, CH_2); 1.36–1.38 (m, 2H, CH_2); 1.18–1.20 (m, 2H, CH_2); The value of HRMS $[M+Na]^+$ for $C_{25}H_{25}Cl_2N_5O_3$: 536.1227. Found: 536.1236.

3-(allyloxy)-1-(3-chloropyridin-2-yl)-N-(2-methyl-6-(propylcarbamoyl)phenyl)-1H-pyrazole-5-carboxamide (**18j**): White crystal, yield, 49.6 %; m.p. 177–179 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.96 (s, 1H, CONH); 8.38 (dd, $J_1 = 1.4$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 7.62 (dd, $J_1 = 1.4$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.15–7.26 (m, 3H, pyridyl-H, Ph-H); 7.06–7.08 (m, 1H, Ph-H); 6.41 (s, 1H, pyrazolyl-H); 6.08–6.10 (m, 1H, NHCH); 6.00–6.07 (m, 1H, CH=); 5.21–5.39 (m, 2H, $=CH_2$); 4.73 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 3.25–3.27 (m, 2H, CH_2CH_2); 2.15 (s, 3H, $PhCH_3$);1.50–1.52 (m, 2H, CH_2CH_2); 1.19 (t, $J = 7.2$ Hz, 3H, CH_2CH_3); Anal. Calcd. for $C_{23}H_{24}Cl_2N_5O_3$ (%): C, 60.86; H, 5.33; N, 15.43. Found: C, 60.62; H, 5.30; N, 15.17.

3-(allyloxy)-1-(3-chloropyridin-2-yl)-N-(2-(isopropylcarbamoyl)-6-methylphenyl)-1H-pyrazole-5-carboxamide (**18k**): White crystal, yield, 63.3 %; m.p. 158–160 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.97 (s, 1H, CONH); 8.38 (d, $J = 4.4$ Hz, 1H, pyridyl-H); 7.74 (dd, $J_1 = 1.8$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.15–7.24 (m, 3H, pyridyl-H, Ph-H); 7.04–7.06 (m, 1H, Ph-H); 6.43 (s, 1H, pyrazolyl-H); 6.01–6.06 (m, 1H, CH=); 5.92–5.96 (m, 1H, NHCH); 5.21–5.38 (m, 2H, $=CH_2$); 4.73 (d, $J_{HH} = 5.5$ Hz, 2H, $CH_2CH=$); 4.09–4.11 (m, 1H, CH); 2.26 (s, 3H, $PhCH_3$); 1.12(d, $J = 6.0$ Hz, 6H, $(CH_3)_2$); The value of HRMS $[M+Na]^+$ for $C_{23}H_{24}ClN_5O_3$: 476.1460. Found: 476.1462.

3-(allyloxy)-1-(3-chloropyridin-2-yl)-N-(2-(cyclopropylcarbamoyl)-6-methylphenyl)-1H-pyrazole-5-carboxamide (**18l**): White crystal, yield, 52.3 %; m.p. 183–185 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.92 (s, 1H, CONH); 8.39 (d, $J_1 = 1.4$ Hz, $J_2 = 4.7$ Hz, 1H, pyridyl-H); 7.74 (dd, $J_1 = 1.4$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.20–7.26 (m, 3H, pyridyl-H, Ph-H); 7.05–7.10 (m, 1H, Ph-H); 6.42 (s, 1H, pyrazolyl-H); 6.14–6.16 (m, 1H, NH); 6.03–6.06 (m, 1H, CH=); 5.19–5.33 (m, 2H, =CH_2); 4.73 (d, $J_{HH} = 5.5$ Hz, 2H, CH_2CH=); 2.74–2.76 (m, 1H, CH); 2.15 (s, 3H, PhCH_3); 1,55–1.57 (m, 2H, CH_2CH_2); 0.79–0.81 (m, 2H, CH_2CH_2); The value of HRMS $[M+Na]^+$ for $C_{23}H_{22}ClN_5O_3$: 474.1303. Found: 474.1295.

3-(allyloxy)-N-(4-bromo-2-(isopropylcarbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (**18m**): White crystal, yield, 55.8 %; m.p. 181–182 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.97 (s, 1H, CONH); 8.46 (dd, $J_1 = 1.6$ Hz, $J_2 = 4.8$ Hz, 1H, pyridyl-H); 8.39 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H, pyridyl-H); 7.38–7.40 (m, 1H, Ph-H); 7.31–7.35 (m, 2H, pyridyl-H, Ph-H); 6.56 (s, 1H, pyrazolyl-H); 6.05–6.14 (m, 1H, CH=); 5.94–5.96 (m, 1H, NH); 5.33–5.48 (m, 2H, =CH_2); 4.81 (d, $J_{HH} = 5.5$ Hz, 2H, CH_2CH=); 4.16–4.18 (m, 1H, CH); 2.19 (s, 3H, PhCH_3); 1.21 (d, $J = 6.6$ Hz, 6H, $(CH_3)_2$); The value of HRMS $[M+Na]^+$ for $C_{23}H_{23}BrClN_5O_3$: 554.0565. Found: 554.0569.

N-(4-bromo-2-methyl-6-(propylcarbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-3-methoxy-1H-pyrazole-5-carboxamide (**18n**): White crystal, yield, 42.1 %; m.p. 235–236 °C; ^{1}H NMR ($CDCl_3$, 400 M) δ: 9.91 (s, 1H, CONH); 8.46 (s, 1H, pyridyl-H); 7.83 (d, $J = 7.6$ Hz, 1H, pyridyl-H); 7.32–7.37 (m, 3H, pyridyl-H, Ph-H); 6.64 (s, 1H, pyrazolyl-H); 6.38–6.40 (m, 1H, NH); 6.08–6.15 (m, 1H, CH=); 5.29–5.48 (m, 2H, =CH_2); 4.82 (d, $J_{HH} = 3.7$ Hz, 2H, CH_2CH=); 2.78–2.81 (m, 1H, CH); 2.17 (s, 3H, PhCH_3); 0.84–0.86 (m, 2H, CH_2CH_2); 0.55–0.58 (m, 2H, CH_2CH_2); The value of HRMS $[M+Na]^+$ for $C_{23}H_{21}BrClN_5O_3$: 552.0409. Found: 552.0402.

Crystal structure

Compound **18e** was recrystallized from ethyl acetate/petroleum ether to give a colorless crystal suitable for X-ray single-crystal diffraction. The crystal with dimensions of 0.20 × 0.18 × 0.12 mm was mounted on a rigaku saturn diffractometer with a graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) by using a Phi scan modes at 113(2) K in the range of $2.36° \leq \theta \leq 25.01°$. The crystals are Monoclinic, space group P2(1)/*n* with $a = 8.0423(16)$ Å, $b = 17.238(3)$ Å, $c = 16.648(3)$ Å, $\alpha = 90°$, $\beta = 97.77(3)°$, $\gamma = 90°$, $V = 2{,}286.7(8)$ Å^3, $Z = 4$, $F(000) = 452$, $D_c = 1.378$ g/cm^3, $\mu = 0.32$ cm^{-1}. A total of 15,151 reflections were collected, of which 4,029 were independent ($R_{int} = 0.0468$) and 2,826 were observed with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 program [21] and the empirical absorption corrections were applied to all intensity data. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were determined with theoretical calculations and refined isotropically. The final full-matrix least squares refinement gave $R1 = 0.068$ and $wR2 = 0.211$ ($w = 1/[\sigma^2(F_o^2) + (0.1265P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$), $S = 1.05$, $(\Delta/\sigma)_{max} = 0.004$, $\Delta\rho_{max} = 0.69$ and $\Delta\rho_{min} = -0.37$ e Å^{-3}. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography.

Biological assay

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula. Evaluations are based on a percentage scale of 0–100 in which 0 equals no activity and 100 equals total kill.

Insecticidal activity against oriental armyworm (*Mythimna separata*); The insecticidal activities of the title compounds **18a–18n** against oriental armyworm were evaluated using the reported procedure [22]. The insecticidal activity against oriental armyworm was tested by foliar application, individual corn 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 10 fourth-instar Oriental armyworm larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed three times. For comparative purposes, chlorantraniliprole was tested under the same conditions. The results were summarized in Table 3.

Insecticidal activity against diamond-back moth (*Plutella xylostella Linnaeus*): The insecticidal activities of the title compounds **18a–18n** against diamondback moth were evaluated using the leaf disc assay [23]. The leaf discs (5 × 3 cm) were cut from fresh cabbage leaves and then dipped into the test solution for 15 s. After air-drying, the treated leaf discs were placed individually into boxes (80 cm^3), and then the second-instar diamondback moth larvae were transferred to the Petri dish.

Table 3 Insecticidal activities against oriental armyworm of the title compounds **18a–18n** and chlorantraniliprole

Compd.	Larvicidal activity (%) at conc. (mg kg^{-1})							
	200	100	50	25	10	5	2.5	1
18a	100	100	100	100	100	60		
18b	100	100	100	100	40			
18c	100	100	60					
18d	100	100	60					
18e	0							
18f	100	50						
18g	0							
18h	0							
18i	0							
18j	100	100	20					
18k	100	100	100	100	20			
18l	100	100	100	100	100	100	100	40
18m	100	100	100	100	100	100	100	20
18n	100	100	100	60				
Chlorantraniliprole	100	100	100	100	100	100	100	100

Table 4 Insecticidal activities against diamond-back moth of the title compounds **18a–18n** and chlorantraniliprole

Compd.	Larvicidal activity (%) at conc. (mg kg^{-1})				
	50	20	10	5	1
18a	100	100	100	100	40
18b	100	100	100	0	0
18c	100	100	40		
18d	100	100	0		
18f	100	100	100	0	0
18g	100	100	60	0	
18h	0				
18i	40				
18j	100	100	100	0	
18k	100	100	0		
18l	100	100	100	100	50
18m	100	100	100	100	0
18n	100	100	100	100	0
Chlorantraniliprole	100	100	100	100	100

Three replicates (seven larvae per replicate) were carried out. The commercial insecticide chlorantraniliprole was used as a standard. The results were summarized in Table 4.

Results and discussion

Synthesis

In the present work, the synthesis of two series novel anthranilic diamide derivatives as well as their insecticidal activities against three lepidopterous pests were studied. The target allyl ether compounds **18a–18n** were synthesized by a simple and convenient four-step procedure starting from the key intermediate 2-(3-chloropyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (**9**). Compound **9** was oxidized to give pyrazolone **15** in low yield. The compound **15** was reacted with allyl bromide in dry dimethylformamide to yield ethyl 3-(allyloxy)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylate (**16**). Then, compound **16** was hydrolyzed to give the key intermediate 3-(allyloxy)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (**17**). The title compounds **18** were synthesized from compound **17** and the appropriate intermediate **14** (obtained from the intermediate **13** and corresponding amine—see Table 1) in dry tetrahydrofuran using triethylamine as base.

Crystal structure analysis

The structure of compound **18e** was further confirmed by single crystal X-ray diffraction analysis (Figs. 1, 2). In the molecular structure of title compound, the three ring (benzene ring, pyridine ring and pyrazole ring) are nearly vertically with θ angle of 83.2° (benzene ring vs. pyridine ring), 87.3° (pyrazole ring vs. pyridine), respectively, but the pyrazole ring is planar with the benzene ring (12.3°). The average bond lengths and bond angles of the phenyl ring [24–28], the pyrazole ring [29], the pyridine ring [30], and the amide bond [31–35] are normal. The intermolecular edge-to-face π–π stacking appears between the pyridine ring and the phenyl ring in another adjacent molecule, in which the distance of H_2O and the centroid of phenyl ring is 3.298 Å. These interactions can help to further stabilize the crystal structure. The title compound has an extensive network of hydrogen bonding involving the two acceptor N atoms. In the *bc* plane, they are linked together by N–H···O hydrogen bonds, also the intramolecular N–H···O hydrogen-bonding sequence is repeated to form a ring.

Biological activity

Table 3 shows the insecticidal activities of the title compounds **18a**–**18n** and chlorantraniliprole against oriental armyworm. The results of insecticidal activities given in Table 3 indicated that most of the title compounds exhibited excellent activity against oriental armyworm. For instance, the insecticidal activities of

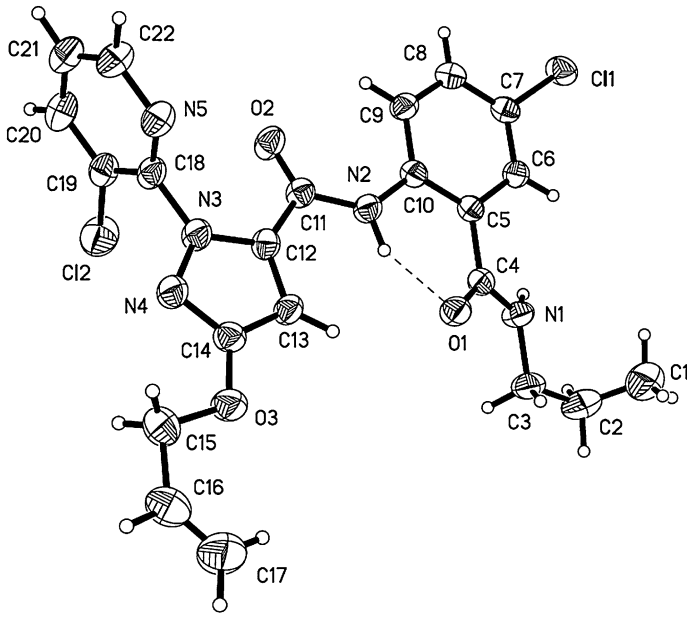


Fig. 1 Molecular structure of the compound **18e**

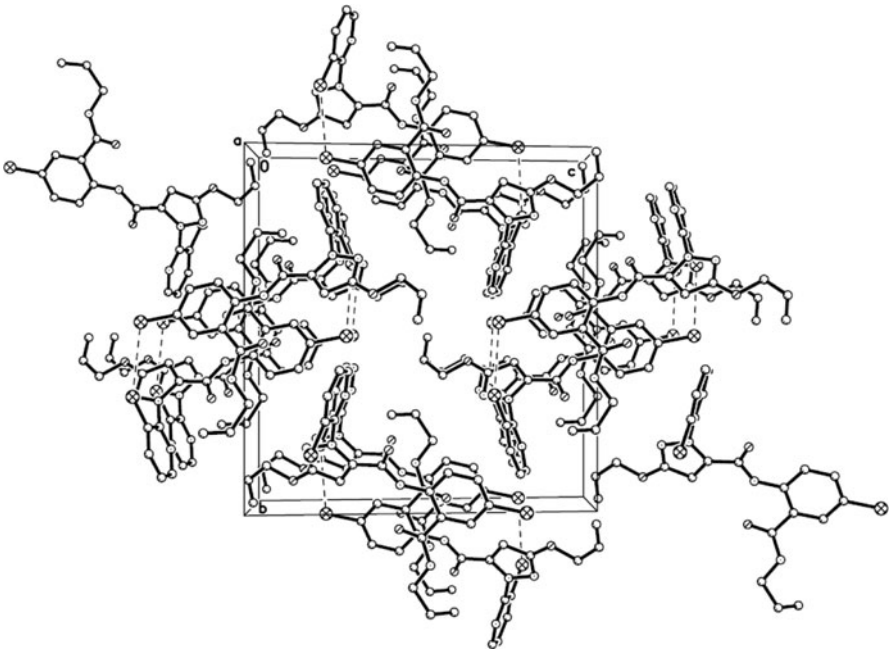


Fig. 2 Packing diagram of the compound **18e**

compounds **18a**, **18l** and **18m** against oriental armyworm at 5 mg kg^{-1} were 100 %. Moreover, compounds **18l** and **18m** still exhibited good insecticidal activity against oriental armyworm when the concentration was reduced to 2.5 mg kg^{-1}.

Table 4 shows the insecticidal activities of the title compounds **18a**–**18n** and chlorantraniliprole against diamond-back moth. The results indicate that the title compounds have good insecticidal activities against diamond-back moth. For instance, the insecticidal activities of compounds **18a**, **18l**, **18m** and **18n** against diamond-back moth at 5 mg kg^{-1} were 100 %.

From Tables 3 and 4, we can see that the larvicidal activities of the title compounds appeared to be strongly associated with the substituent R and its position on the benzene. Methyl-substituted at ortho- and chloro-substituted at para is very important for increasing activity. Further studies on structural optimization and structure–activity relationships of these anthranilic diamide derivatives are in progress.

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