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Design, Synthesis and Biological Activities of Novel Anthranilic Diamide Insecticide Containing Trifluoroethyl Ether

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Two series of novel anthranilic diamide insecticide containing trifluoroethyl ether were designed and synthesized, and their structures were characterized by ^{1}H NMR spectroscopy, elemental analysis and single crystal X-ray diffraction analysis. The insecticidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal activities. The insecticidal activities of compounds **19a**, **19b**, **19d**, **19g**, **19k** and **19m** against oriental armyworm at 2.5 mg•kg^{-1} were 100%. The larvicidal activities of **19a**, **19b**, **19c**, **19d**, **19e**, **19g** and **19n** against diamond-back moth were 100% at 0.1 mg•kg^{-1}. Surprisingly, most of them still exhibited perfect insecticidal activity against diamond-back moth when the concentration was reduced to 0.05 mg•kg^{-1}, which was higher than the commercialized Chlorantraniliprole.

Keywords anthranilic diamide, ryanodine receptor, trifluoroethyl ether, insecticidal activity

Introduction

Resistance has often been a problem or a potential problem for insecticide and is one of the most important reasons why insecticides with a new mode of action have been desired.[1] Recently, two new classes of insecticidal 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 ryanodine receptors and activating the uncontrolled release of calcium stores.[2] Since then diamides have be the focus of synthesis activities within the agrochemical industry. Anthranilic diamides and their chemistry have recently attracted considerable attention in the field of novel agricultural insecticides, owing to their prominent insecticidal activity, unique modes of action and good environmental profiles.[3,4] Anthranilic diamides act on the sarcosplasmic reticulum of cardiac and skeletal muscle cells to open internal calcium stores causing muscle contraction, paralysis, and death.[5,6]

Anthranilic diamide insecticide is characterized by a three-part chemical structure as shown in Figure 1: (A) an anthraniloyl moiety, (B) an aromatic acyl moiety and (C) an aliphatic amide moiety. Notably, anthranilic diamides containing *N*-pyridylpyrazole in the second section (B) showed significantly better activity than other heterocyclic derivatives. Work in this area has led to the discovery of Chlorantraniliprole, a highly potent and selective activator of insect ryanodine receptors with exceptional activity on a broad range of Lepidoptera. As the first new insecticide from this class (Figure 1),[7] Chlorantraniliprole demonstrates field use-rates that are significantly less than current commercial standards, varying from 50 g/ha to less than 1 g/ha and with good safety toward beneficial insects. In addition to possessing extremely high levels of potency on insects, Chlorantraniliprole shows remarkable safety to mammals as a result of poor intrinsic activity on mammalian ryanodine receptors with a margin of selectivity of the order of 10^3.

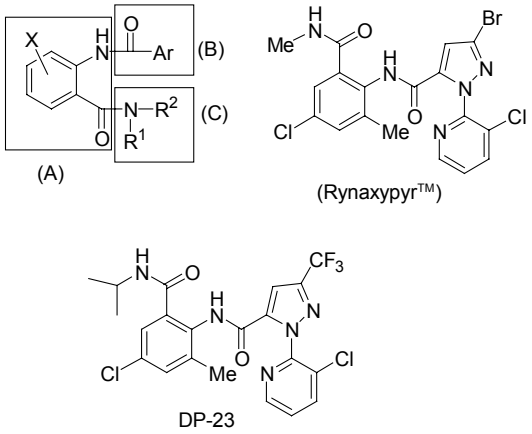

Figure 1 Chemical structures of anthranilic diamides insecticides.

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Recently, anthranilic diamides derivatives have drawn much attention in insecticidal research due to their significant bioactivity. In addition, many investigations have indicated that introducing the F or CF_3 group into heterocyclic molecules mostly results in the improvement of physical, chemical and biological properties.[8-11] It was reported that a series of fluorinated derivatives of anthranilic diamides displayed an insecticidal activity comparable or superior to that of Chlorantraniliprole. The synthesis and insecticidal evaluation of DP-23 have been reported and the results of bioassay showed that it exhibit excellent larvicidal activity (Figure 1).[12]

Encouraged by these reports, an idea was developed that the introduction of a trifluoroethyl ether substituent into the Chlorantraniliprole molecules by substituting the halogen atoms on the pyrazole ring could improve biological properties. Therefore, in a search for new anthranilic diamide insecticides with improved profiles, two series of anthranilic diamide derivatives containing trifluoroethyl ether were designed and synthesized.

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. 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 Co., Beijing, China) and were uncorrected. All solvents and liquid reagents were dried by standard methods and distilled before use.

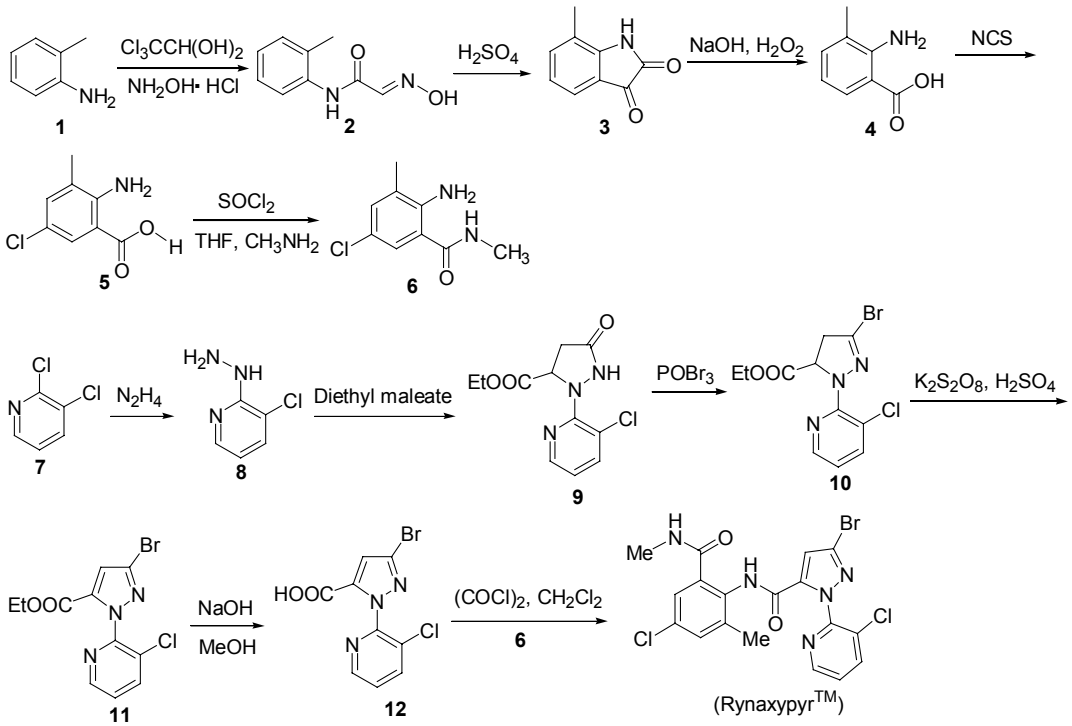
General procedures

Chlorantraniliprole was prepared according to the route shown in Scheme 1. The title compounds **19** and **20** were synthesized from compound **18** and the appropriate intermediate **14** or **15** (obtained from the intermediate **13** and corresponding alcohol or amine – see Table 1) in dry tetrahydrofuran using triethylamine as base as shown in Scheme 2.

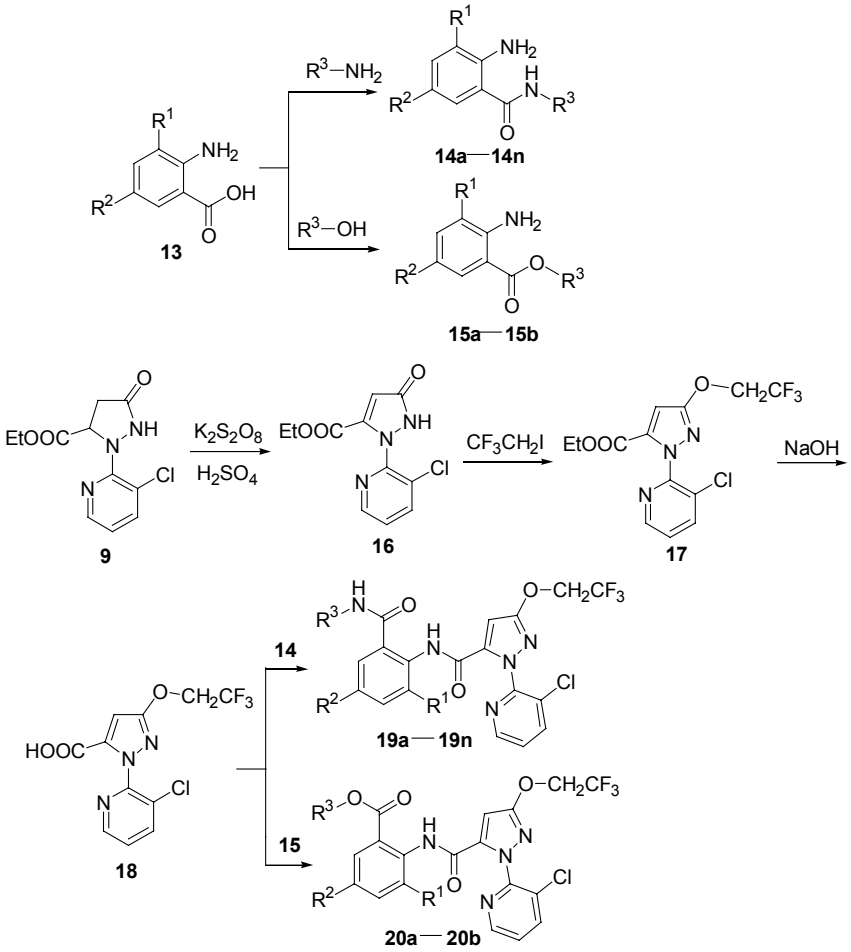
Synthetic procedure for 2-amino-3-methyl-benzoic acid (4)

Compounds **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 ℃ until the mixture became clear. 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.) were 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 temperature. The product precipitated out of solution, and after standing overnight, the solid were collected and dried to obtain 2-hydroxyimino-*N*-*o*-tolyl-acetamide.

Scheme 1



Scheme 2



Sulfuric acid (60 mL) was heated in a three-neck 250 mL round-bottom flask to 60 ℃ 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 ℃. The mixture was then heated to 80 ℃ 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 (50 mL×2) 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 ℃, and added dropwise a 30% aqueous hydrogen peroxide solution (150 mL). The reaction mixture was stirred at 50 ℃ for 30 min and then allowed to reach room temperature. The filtered solution was acidified to pH 4 with an aqueous 1 mol•L^{-1} 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 ℃. ^{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), 6.48—6.51 (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 ℃ 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 (50 mL×3) 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 (30 mL×3) to afford intermediate 2-amino-5-chloro-3-methylbenzoic acid (**5**): White solid, m.p. 196—197 ℃ (dec.), yield 76.0%; ^{1}H NMR (DMSO, 400 MHz) δ: 7.53 (s, 1H, Ph-H), 7.21 (s, 1H, Ph-H), 2.09 (s, 3H, CH_3).

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

N-Methyl 2-amino-5-chloro-3-methyl-benzamide (**6**)

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was prepared according to the literature.[15] To a 100 mL round-bottomed flask was placed 2-amino-5-chloro-3-methylbenzoic acid (**5**) (3.7 g, 20 mmol) and then was added 50 mL of thionyl chloride. 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 50 g of 25% aqueous methylamine solution under an ice bath. The resulting solution was allowed to stir 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 ℃; ^{1}H NMR ($CDCl_3$, 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 s, 1H, NH), 5.52 (br s, 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 ℃; ^{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=3.9, 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 ℃, 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 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%, 50 mL×3) 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 ℃; ^{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=4.8, 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=9.8, 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 (250 mL×2), 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 ℃; ^{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=4.4, 7.7 Hz, 1H, pyridyl-H), 5.17 (dd, J=8.7, 11.8 Hz, 1H, CH), 4.08 (q, J=7.0 Hz, 2H, OCH_2), 3.27 (dd, J=8.7, 17.6 Hz, 1H, CH_2-H), 3.57 (dd, J=11.8, 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 ℃, the mixture was filtered, the filter cake 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 (30 mL×3), 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 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) 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=4.8, 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 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.52 (dd, J=1.5, 4.8 Hz, 1H, pyridyl-H), 7.94 (dd, J=1.5, 8.1 Hz, 1H, pyridyl-H), 7.48 (dd, J=4.8, 8.1 Hz, 1H, pyridyl-H), 7.10 (s, 1H, pyrazolyl-H).

Synthetic procedure for Chlorantraniliprole

Chlorantraniliprole was prepared according to the literatures.[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 mol•L^{-1} 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 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.10 (br s, 1H, NH), 8.46 (dd, J=1.6, 4.8 Hz, 1H, pyridyl-H), 7.85 (dd, J=1.6, 8.0 Hz, 1H, pyridyl-H), 7.38 (dd, J=4.8, 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)

To a 100 mL round-bottomed flask was placed 2-amino-5-chloro-3-methylbenzoic acid (**5**) (5.0 g, 27 mmol) and then was added 50 mL of thionyl chloride. 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 (50 mL×3). 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** and **15a**—**15b** were prepared by similar method above using the appropriate substrates. The melting points and yields of compounds **14** and **15** are listed in Table 1. The ^{1}H NMR data are listed in Table 2.

Table 1 Melting points and yields of the compounds **14a**—**14n** and **15a**—**15b**

Compd.	R^1	R^2	R^3	m.p./℃	Yield/%
14a	CH_3	Cl	*n*-propyl	119—121	88.0
14b	CH_3	Cl	cyclopropyl	122—124	92.4
14c	CH_3	Cl	*n*-butyl	87—88	77.9
14d	CH_3	Cl	*i*-butyl	117—122	68.1
14e	CH_3	Cl	cyclohexyl	167—168	89.2
14f	H	Cl	*n*-propyl	120—122	79.3
14g	H	Cl	*i*-propyl	161—162	58.0
14h	H	Cl	cyclopropyl	143—145	61.9
14i	H	Cl	*n*-butyl	108—110	66.4
14j	H	Cl	cyclohexyl	179—181	56.9
14k	CH_3	H	*n*-propyl	88—90	70.2
14l	CH_3	H	*i*-propyl	137—139	70.2
14m	CH_3	H	cyclopropyl	118—120	80.0
14n	CH_3	H	cyclohexyl	158—159	69.6
15a	CH_3	Cl	methyl	33—35	52.9
15b	CH_3	Br	methyl	50—53	47.6

Synthetic procedure for 2-(3-chloro-pyridin-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid ethyl ester (16)

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 min, the reaction mixture was treated with $K_2S_2O_8$ (15g, 56 mmol) and was refluxed for 4.5 h. After being cooled to 60 ℃, the mixture was filtered, the filter cake was washed with acetonitrile (30 mL). The filtrate was concentrated and poured into ice water (200 mL). The aqueous layer was extracted with dichloromethane (150 mL×3). The organic layer was washed with water (100 mL×3) 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 ℃) 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 (**16**). (6.2 g, 62.4%), m.p. 136—138 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) 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=4.4, 8.0 Hz, 1H, pyridyl-H), 6.36 (s, 1H, pyrazolyl-H), 4.19 (q, J=7.2 Hz, 2H, CH_2), 1.19 (t, J=7.2 Hz, 3H, CH_3).

Synthetic procedure for 2-(3-chloro-pyridin-2-yl)-5-(2,2,2-trifluoro-ethoxy)-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid ethyl ester (17)

The ester **17** was prepared according to the literature.[7] Compound **16** (1.0 g, 3.7 mmol) was dissolved in 30 mL of dry dimethylformamide, and potassium

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Table 2 ^{1}H NMR of the compounds **14a**—**14n** and **15a**—**15b**

Compd.	^{1}H NMR δ
14a	(400 MHz, DMSO-d_6) δ: 8.37 (br s, 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, $CDCl_3$) δ: 7.08—7.10 (m, 2H, Ph-H), 6.10 (br s, 1H, NH), 5.60 (br s, 2H, NH_2), 2.80—2.86 (m, 1H, cyclopropyl-H), 2.13 (s, 3H, CH_3), 0.84—0.87 (m, 2H, cyclopropyl-H), 0.58—0.62 (m, 2H, cyclopropyl-H)
14c	(400 MHz, DMSO-d_6) δ: 8.34 (br s, 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)
14d	(400 MHz, DMSO-d_6) δ: 8.38 (br s, 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, $CH(CH_3)_2$)
14e	(400 MHz, $CDCl_3$) δ: 7.05—7.14 (m, 2H, Ph-H), 5.81 (br s, 1H, NH), 5.46 (br s, 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)
14f	(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=8.7, 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)
14g	(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=8.8, 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, $CH(CH_3)_2$)
14h	(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=8.8, 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)
14i	(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=8.7, 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)
14j	(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=8.7, 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)
14k	(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)
14l	(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 (d, J=6.6 Hz, 6H, $CH(CH_3)_2$)
14m	(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)
14n	(400 MHz, $CDCl_3$) δ: 6.56—7.19 (m, 3H, Ph-H), 5.90 (br s, 1H, NH), 5.53 (br s, 2H, NH_2), 3.88—3.97 (m, 1H, cyclohexyl-H), 2.15 (s, 3H, CH_3), 1.15—2.03 (m, 10H, cyclohexyl-H)
15a	(400 MHz, DMSO-d_6) δ: 7.56 (s, 1H, Ph-H), 7.26 (s, 1H, Ph-H), 6.33 (br s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 2.12 (s, 3H, CH_3)
15b	(400 MHz, DMSO-d_6) δ: 7.80 (s, 1H, Ph-H), 7.21 (s,1H, Ph-H), 5.78 (br s, 2H, NH_2), 3.84 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3)

carbonate (0.76 g, 5.5 mmol) was added. The mixture was heated to 100 ℃. The 2,2,2-trifluoroiodoethane (0.94 g, 4.4 mmol) in dry dimethylformamide (5 mL) was added slowly to the mixture. The solution was warmed at 100 ℃ and stirred for 3 h and poured into ice water (50 mL). The aqueous layer was extracted with ethyl acetate (40 mL×3). The organic layer was washed with water (40 mL×3) 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 ℃) and ethyl acetate as the eluent to afford the 2-(3-chloro-pyridin-2-yl)-5-(2,2,2-trifluoro-ethoxy)-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid ethyl ester (**17**). (1.28 g, 99%), m.p. 63—65 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.52 (dd, J=1.6, 4.8 Hz, 1H, pyridyl-H), 7.91 (dd, J=1.6, 8.0 Hz, 1H, pyridyl-H), 7.43 (dd, 1H, J=4.8, 8.0 Hz, 1H, pyridyl-H), 6.54 (s, 1H, pyrazolyl-H), 4.66 (q, J=16.4 Hz, 2H, CH_2CF_3), 4.20 (q, J=7.2 Hz, 2H, CH_2), 1.22 (t, J=7.2 Hz, 3H, CH_3).

Synthetic procedure for 2-(3-chloro-pyridin-2-yl)-5-(2,2,2-trifluoro-ethoxy)-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid (18)

To a mixture of the compound **17** (1.28 g, 3.6 mmol) in methanol (20 mL) was added aqueous sodium hydroxide solution (5 mL, 1 mol•L^{-1}). The solution was stirred at room temperature for 6 h, then was concen-

trated *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 2-(3-chloro-pyridin-2-yl)-5-(2,2,2-trifluoro-ethoxy)-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid (**18**) (0.84 g, 71.3%), m.p. 165—167 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.51 (dd, J=1.6, 4.8 Hz, 1H, pyridyl-H); 7.92 (dd, J=1.6, 8.0 Hz, 1H, pyridyl-H); 7.44 (dd, 1H, J=4.8, 8.0 Hz, pyridyl-H); 6.59 (s, 1H, pyrazolyl-H); 4.65 (q, J=16.4 Hz, 2H, CH_2CF_3).

Synthetic procedure for the title compounds 19 and 20

To a suspension of *N*-pyridylpyrazole acid **18** (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** or **15** (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 mol•L^{-1} 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 compounds **19** and **20**. The melting points, yields, and elemental analyses of compounds **19** and **20** are listed in Table 3. The ^{1}H NMR data are listed in Table 4.

Biological assay

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at (25±1) ℃ 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 **19a**—**19n** and **20a**—**20b** against oriental armyworm were evaluated using the reported procedure.[18,19] 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 d after treatment. Each treatment was performed three times. For comparative purposes, Chlorantraniliprole was tested under the same conditions. The results were summarized in Table 5.

Insecticidal activity against diamond-back moth (*Plutella xylostella Linnaeus*) The insecticidal activities of the title compounds **19a**—**19n** against diamondback moth were evaluated using the leaf disc assay.[20] The leaf discs (5 cm×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. Three replicates (seven larvae per replicate) were carried out. The commercial insecticide Chlorantraniliprole was used as a standard. The results were summarized in Table 6.

Table 3 The melting points, yields and elemental analyses of the title compounds **19** and **20**

Compd.	R^1	R^2	R^3	m.p./℃	Yield/%	Elemental analysis (%) calcd. (found)		
						C	H	N
19a	CH_3	Cl	*n*-propyl	200—201	59.9	49.82 (49.66)	3.80 (3.92)	13.21 (13.22)
19b	CH_3	Cl	cyclopropyl	211—213	62.7	50.02 (49.92)	3.43 (3.78)	13.26 (13.21)
19c	CH_3	Cl	*n*-butyl	173—175	67.6	50.75 (50.56)	4.07 (3.99)	12.87 (12.98)
19d	CH_3	Cl	*i*-butyl	220—221	63.9	50.75 (50.81)	4.07 (4.11)	12.87 (12.81)
19e	CH_3	Cl	cyclohexyl	160—162	58.7	52.64 (52.54)	4.24 (4.41)	12.28 (12.24)
19f	H	Cl	*n*-propyl	102—104	60.5	48.85 (48.77)	3.51 (3.55)	13.56 (13.29)
19g	H	Cl	*i*-propyl	186—188	70.1	48.85 (48.79)	3.51 (3.46)	13.56 (13.40)
19h	H	Cl	cyclopropyl	198—199	56.9	49.04 (49.40)	3.14 (3.47)	13.62 (13.07)
19i	H	Cl	*n*-butyl	96—98	63.2	49.82 (49.70)	3.80 (3.84)	13.21 (13.10)
19j	H	Cl	cyclohexyl	145—146	66.7	51.81 (51.93)	3.99 (4.06)	12.59 (13.45)
19k	CH_3	H	*n*-propyl	185—187	67.0	53.29 (53.41)	4.27 (4.11)	14.12 (13.97)
19l	CH_3	H	*i*-propyl	177—179	69.3	53.29 (53.22)	4.27 (4.35)	14.12 (14.40)
19m	CH_3	H	cyclopropyl	172—173	54.8	53.50 (53.25)	3.88 (4.09)	14.18 (13.94)
19n	CH_3	H	cyclohexyl	147—149	64.7	56.03 (56.07)	4.70 (4.60)	13.07 (13.08)
20a	CH_3	Cl	methyl	50—52	69.1	47.73 (47.99)	3.00 (2.85)	11.13 (11.01)
20b	CH_3	Br	methyl	40—42	65.4	43.86 (43.90)	2.76 (3.02)	10.23 (10.45)

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Table 4 ^{1}H NMR of the title compounds **19a**—**19n** and **20a**—**20b**

Compd.	^{1}H NMR (400 MHz, $CDCl_3$) δ
19a	9.97 (s, 1H, CONH), 8.38 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 7.75 (dd, J=8.0, 1.6 Hz, 1H, pyridyl-H), 7.27 (dd, J=8.0, 4.8 Hz, 1H, pyridyl-H, 1H), 7.14 (s, 1H, Ph-H), 7.10 (s, 1H, Ph-H), 6.58 (s, 1H, pyrazolyl-H), 6.09—6.11 (m, 1H, $NHCH_2$), 4.60 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.23—3.25 (m, 2H, CH_2NH), 2.10 (s, 3H, $PhCH_3$), 1.47—1.48 (m, 2H, CH_2CH_3), 0.87 (t, J=7.0 Hz, 3H, CH_2CH_3)
19b	10.02 (s, 1H, CONH), 8.45 (dd, J=4.4, 1.6 Hz, 1H, pyridyl-H), 7.82 (dd, J=8.0, 1.6 Hz, 1H, pyridyl-H, 1H), 7.34 (dd, J=8.0, 4.4 Hz, 1H, pyridyl-H, 1H), 7.17 (s, 1H, Ph-H), 7.10 (s, 1H, Ph-H), 6.74 (s, 1H, pyrazolyl-H), 6.42—6.44 (m, 1H, PhCONH), 4.67 (q, J=8.2 Hz, 2H, CH_2CF_3), 2.77—2.79 (m, 1H, CH), 2.15 (s, 3H, $PhCH_3$), 0.82—0.84 (m, 2H, CH_2CH_2), 0.53—0.55 (m, 2H, CH_2CH_2)
19c	9.99 (s, 1H, CONH), 8.39 (dd, J=4.4, 1.2 Hz, 1H, pyridyl-H), 7.77 (dd, J=8.0, 1.6 Hz, 1H, pyridyl-H), 7.29 (dd, J=8.0, 4.4 Hz, 1H, pyridyl-H), 7.27 (s, 1H, Ph-H), 7.15 (s, 1H, Ph-H), 6.55 (s, 1H, pyrazolyl-H), 6.10—6.12 (m, 1H, PhCONH), 4.60 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.30—3.32 (m, 2H, $NHCH_2$), 2.14 (s, 3H, $PhCH_3$), 1.53—1.55 (m, 2H, CH_2CH_2), 1.32—1.34 (m, 2H, CH_2CH_3), 0.89 (t, J=7.2 Hz, 3H, CH_2CH_3)
19d	10.04 (s, 1H, CONH), 8.47 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 7.84 (dd, J=8.0, 1.6 Hz, 1H, pyridyl-H), 7.36 (dd, J=8.0, 4.8 Hz, 1H, pyridyl-H), 7.27 (s, 1H, Ph-H), 7.22 (s, 1H, Ph-H), 6.59 (s, 1H, pyrazolyl-H), 6.19—6.21 (m, 1H, PhCONH), 4.68 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.21—3.23 (m, 2H, CH_2NH), 2.19 (s, 3H, $PhCH_3$), 1.84—1.86 (m, 1H, CH), 0.95 (d, J=6.7 Hz, 6H, $CH(CH_3)_2$)
19e	10.06 (s, 1H, CONH), 8.47 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 7.84 (dd, J=8.0, 1.6 Hz, 1H, pyridyl-H), 7.35 (dd, J=8.0, 4.8 Hz, 1H, pyridyl-H), 7.26 (s, 1H, Ph-H), 7.20 (s, 1H, Ph-H), 6.60 (s, 1H, pyrazolyl-H), 5.95—5.97 (m, 1H, PhCONH), 4.69 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.85—3.87 (m, 1H, CH), 2.19 (s, 3H, $PhCH_3$), 1.96—1.98 (m, 2H, cyclohexanyl-H), 1.73—1.75 (m, 2H, cyclohexanyl-H), 1.63—1.65 (m, 2H, cyclohexanyl-H), 1.38—1.40 (m, 2H, cyclohexanyl-H), 1.18—1.21 (m, 2H, cyclohexanyl-H)
19f	12.24 (s, 1H, CONHPh), 8.52 (d, J=4.0 Hz, 1H, pyridyl-H), 8.46—8.48 (m, 1H, Ph-H), 7.92 (d, J=6.8 Hz, 1H, pyridyl-H), 7.37—7.48 (m, 3H, pyridyl-H, Ph-H), 6.61 (s, 1H, pyrazolyl-H), 6.33—6.35 (m, 1H, PhCONH), 4.69 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.44—3.46 (m, 2H, $NHCH_2$), 1.66—1.68 (m, 2H, CH_2CH_2), 1.01 (t, J=6.8 Hz, 3H, CH_2CH_3)
19g	12.26 (s, 1H, CONHPh), 8.50 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 8.47 (d, J=8.9 Hz, 1H, Ph-H), 7.92 (d, J=8.0 Hz, 1H, pyridyl-H), 7.42—7.45 (m, 2H, pyridyl-H, Ph-H), 7.34 (d, J=9.0 Hz, 1H, Ph-H), 6.58 (s, 1H, pyrazolyl-H), 6.05—6.06 (m, 1H, PhCONH), 4.66 (q, J=8.2 Hz, 2H, CH_2CF_3), 4.27—4.29 (m, 1H, CH), 1.30 (d, J=6.4 Hz, 6H, $CH(CH_3)_2$)
19h	12.27 (s, 1H, CONHPh), 8.52 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 8.46 (d, J=8.9 Hz, 1H, Ph-H), 7.93 (d, J=8.0 Hz, 1H, pyridyl-H), 7.44—7.48 (m, 2H, pyridyl-H, Ph-H), 7.35 (d, J=9.0 Hz, 1H, Ph-H), 6.62 (s, 1H, pyrazolyl-H), 6.37—6.39 (m, 1H, PhCONH), 4.68 (q, J=8.2 Hz, 2H, CH_2CF_3), 4.27—4.29 (m, 1H, CH), 0.95—0.99 (m, 2H, CH_2CH_2), 0.66—0.69 (m, 2H, CH_2CH_2)
19i	12.15 (s, 1H, CONHPh), 8.52 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 8.45 (d, J=8.9 Hz, 1H, Ph-H), 7.93 (d, J=8.0 Hz, 1H, pyridyl-H), 7.42—7.46 (m, 2H, pyridyl-H, Ph-H), 7.33—7.35 (m, 1H, Ph-H), 6.51 (s, 1H, pyrazolyl-H), 6.14—6.16 (m, 1H, PhCONH), 4.60 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.31—3.33 (m, 2H, $NHCH_2$), 1.53—1.56 (m, 2H, CH_2CH_2), 1.32—1.37 (m, 2H, CH_2CH_3), 0.90 (t, J=7.2 Hz, 3H, CH_2CH_3)
19j	12.26 (s, 1H, CONH), 8.52 (dd, J=4.8, 1.6 Hz, 1H, pyridyl-H), 8.48 (d, J=9.0 Hz, 1H, Ph-H), 7.89 (d, J=1.2 Hz, 1H, pyridyl-H), 7.40—7.45 (m, 2H, pyridyl-H, Ph-H), 7.33—7.35 (m, 1H, Ph-H), 6.60 (s, 1H, pyrazolyl-H), 6.20—6.23 (m, 1H, PhCONH), 4.68 (q, J= 8.2 Hz, 2H, CH_2CF_3), 3.95—3.97 (m, 1H, CH), 1.78—1.81 (m, 2H, cyclohexanyl-H), 1.68—1.70 (m, 2H, cyclohexanyl-H), 1.43—1.45 (m, 2H, cyclohexanyl-H), 1.28—1.30 (m, 2H, cyclohexanyl-H), 1.19—1.22 (m, 2H, cyclohexanyl-H)
19k	10.10 (s, 1H, CONH), 8.39 (dd, J=4.7, 1.5 Hz, 1H, pyridyl-H), 7.75 (dd, J=8.0, 1.5 Hz, 1H, pyridyl-H), 7.36 (dd, J=8.0, 4.7 Hz, 1H, pyridyl-H), 7.25—7.28 (m, 1H, Ph-H), 7.17—7.20 (m, 1H, Ph-H), 7.07—7.10 (m, 1H, Ph-H), 6.48 (s, 1H, pyrazolyl-H), 6.05—6.08 (m, 1H, PhCONH), 4.61 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.26—3.28 (m, 2H, CH_2NH), 2.15 (s, 3H, $PhCH_3$), 1.51—1.55 (m, 2H, CH_2CH_3), 0.89 (t, J=7.2 Hz, 3H, CH_2CH_3)
19l	8.54 (s, 1H, CONH), 8.38 (dd, J=4.7, 1.4 Hz, 1H, pyridyl-H), 7.92 (dd, J=8.0, 1.4 Hz, 1H, pyridyl-H), 7.53—7.55 (m, 1H, Ph-H), 7.42—7.45 (m, 1H, Ph-H), 7.39 (dd, J=8.0, 4.7 Hz, 1H, pyridyl-H), 7.21—7.23 (m, 1H, Ph-H), 6.54 (s, 1H, pyrazolyl-H), 6.03—6.06 (m, 1H, PhCONH), 4.69 (q, J=8.3 Hz, 2H, CH_2CF_3), 4.20—4.22 (m, 1H, CH), 2.30 (s, 3H, $PhCH_3$), 1.16 (d, J=6.6 Hz, 6H, $CH(CH_3)_2$))
19m	10.16 (s, 1H, CONH), 8.38 (d, J=4.8 Hz, 1H, pyridyl-H), 7.76 (d, J=8.0 Hz, 1H, pyridyl-H), 7.27 (dd, J=4.8, 8.0 Hz, 1H, pyridyl-H), 7.13—7.15 (m, 1H, Ph-H), 7.00—7.05 (m, 2H, Ph-H), 6.57 (s, 1H, pyrazolyl-H), 6.44—6.46 (m, 1H, PhCONH), 4.61 (q, J=8.2 Hz, 2H, CH_2CF_3), 2.64—2.65 (m, 1H, CH), 2.10 (s, 3H, $PhCH_3$), 0.72—0.74 (m, 2H, CH_2CH_2), 0.40—0.43 (m, 2H, CH_2CH_2)

Continued

Compd.	^{1}H NMR (400 MHz, $CDCl_3$) δ
19n	10.22 (s, 1H, CONH), 8.47 (dd, J=4.7, 1.5 Hz, 1H, pyridyl-H), 7.83 (dd, J=8.0, 1.5 Hz, 1H, pyridyl-H), 7.34 (dd, J=8.0, 4.7 Hz, 1H, pyridyl-H), 7.26—7.27 (m, 1H), 7.22—7.25 (m, 1H), 7.14—7.15 (m, 1H), 6.61 (s, 1H, pyrazolyl-H), 6.21—6.23 (m, 1H, PhCONH), 4.69 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.86—3.88 (m, 1H CH), 2.23 (s, 3H, $PhCH_3$), 1.94—1.96 (m, 2H, cyclohexanyl-H), 1.73—1.75 (m, 2H, cyclohexanyl-H), 1.63—1.66 (m, 2H, cyclohexanyl-H), 1.38—1.40 (m, 2H, cyclohexanyl-H), 1.18—1.21 (m, 2H, cyclohexanyl-H)
20a	10.02 (s, 1H, CONH), 8.45 (d, J=4.5 Hz, 1H, pyridyl-H), 7.80 (d, J=1.7 Hz, 1H, pyridyl-H), 7.34—7.37 (m, 3H, pyridyl-H, Ph-H), 6.56 (s, 1H, pyrazolyl-H), 6.54—6.57 (m, 1H, PhCONH), 4.68 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.91 (s, 3H, OCH_3), 2.21 (s, 3H, $PhCH_3$)
20b	10.03 (s, 1H, CONH), 8.45 (dd, J=4.6, 1.4 Hz, 1H, pyridyl-H), 7.92—7.94 (m, 1H, Ph-H), 7.84 (dd, J=7.8, 1.4 Hz, 1H, pyridyl-H), 7.51—7.53 (m, 1H, Ph-H), 7.36 (dd, J=4.6, 1.4 Hz, 1H, pyridyl-H), 6.56 (s, 1H, pyrazolyl-H), 4.69 (q, J=8.2 Hz, 2H, CH_2CF_3), 3.91 (s, 3H, OCH_3), 2.20 (s, 3H, $PhCH_3$)

Table 5 Insecticidal activities against oriental armyworm of the title compounds **19a**—**19n**, **20a**—**20b** and Chlorantraniliprole

Compd.	larvicidal activity (%) at conc (mg•kg^{-1})									
	200	100	50	25	10	5	2.5	1	0.5	0.25
19a	100	100	100	100	100	100	100	40		
19b	100	100	100	100	100	100	100	100	100	40
19c	100	100	100	100	100	100	70	0		
19d	100	100	100	100	100	100	100	50		
19e	100	100	100	100	100	100	30			
19f	100	100	100	40						
19g	100	100	100	100	100	100	100	80	0	
19h	100	100	100	100	100	80	0			
19i	80	20								
19j	20									
19k	100	100	100	100	100	100	100	40		
19l	100	100	100	100	0					
19m	100	100	100	100	100	100	100	100	20	
19n	100	100	100	100	100	50				
20a	100	90	30							
20b	90	10								
Chlorantraniliprole	100	100	100	100	100	100	100	100	100	100

Insecticidal activity against beet armyworm (*Laphygma exigua Hubner*) The insecticidal activities of the title compounds **19a**—**19n** against beet armyworm were tested by the leaf-dip method using the reported procedure.[21] Leaf discs (1.8 cm diameter) were cut from fresh cabbage leaves and then were dipped into the test solution for 15 s. After air-drying, the treated leaf discs were placed in a Petri dish (9 cm diameter). Each dried treated leaf disc was infested with seven third-instar beet armyworm larvae. Percentage mortalities were evaluated 3 d after treatment. Leaves treated with water and acetone were provided as controls. Each treatment was performed three times. For comparative purposes, Chlorantraniliprole was tested under the same conditions. The results were summarized in Table 7.

Table 6 Insecticidal activities against diamond-back moth of the title compounds **19a**—**19n** and Chlorantraniliprole

Compd.	larvicidal activity (%) at conc (mg•kg^{-1})								
	50	20	10	5	1	0.5	0.25	0.1	0.05
19a	100	100	100	100	100	100	100	100	100
19b	100	100	100	100	100	100	100	100	100
19c	100	100	100	100	100	100	100	100	100
19d	100	100	100	100	100	100	100	100	100
19e	100	100	100	100	100	100	100	100	100
19f	100	100	100	100	40		100	100	57
19g	100	100	100	100	100	100			
19h	100	100	100	100	0				
19i	100	100	100	0	0				
19j	100	100	60	80	0				
19k	100	100	100	100	100	100	43		
19l	100	100	100	0	0				
19m	100	100	100	100	100	100	100	43	
19n	100	100	100	100	100	100	100	100	100
Chlorantraniliprole	100	100	100	100	100	100	100	43	0

Results and Discussion

Synthesis

In the present work, the synthesis of two series of novel anthranilic diamide derivatives as well as their insecticidal activities against three lepidopterous pests were studied. The target trifluoroethyl ether compounds **19** and **20** were synthesized by a simple and convenient four-step procedure starting from the key intermediate 2-(3-chloro-pyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (**9**). Compound **9** was oxidized to give pyrazolone **16** in low yield. The compound **16** was reacted with 2,2,2-trifluoroiodoethane in dry dimethylformamide to yield 1-(2-chloro-5-pyridylmethyl)-2-cyanoiminoimidazolidine (**17**). Then compound **17** was hydrolyzed to give the key intermediate 2-(3-chloro-pyridin-2-yl)-5-(2,2,2-trifluoro-ethoxy)-2,5-dihydro-1*H*-pyrazole-3-carboxylic acid (**18**). The title compounds **19** and **20** were synthesized from

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Table 7 Insecticidal activities against beet armyworm of the title compounds **19a**—**19n** and Chlorantraniliprole

Compd.	larvicidal activity (%) at conc (mg•kg^{-1})				
	20	5	2	1	0.5
19a	100	100	100	100	57
19b	100	100	100	100	86
19c	100	100	28		
19d	100	83			
19e	100	83			
19f	100	50			
19g	100	100	57		
19h	100	100	71		
19i	0				
19j	0				
19k	67				
19l	0				
19m	100	100	86		
19n	50				
Chlorantraniliprole	100	100	100	100	100

compound **1**8 and the appropriate intermediate **14** or **15** (obtained from the intermediate **13** and corresponding alcohol or amine – see Table 1) in dry tetrahydrofuran using triethylamine as base.

Crystal structure analysis

Compound **19g** was recrystallized from ethyl acetate/petroleum ether to give colorless crystal suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a=11.976(2) Å, b=14.274(3) Å, c=14.350(3) Å, α=90°, β=111.73(3)°, γ=90°, μ=0.344 mm^{-1}, V=2278.6(8) Å^3, Z=4, D_x=1.505 Mg•m^{-3}, F(000)=1056, T=113(2) K, 3.06°≤θ≤25.02°, and the final R factor, R_1=0.0431, wR_2=0.1048. The crystal is monoclinic.

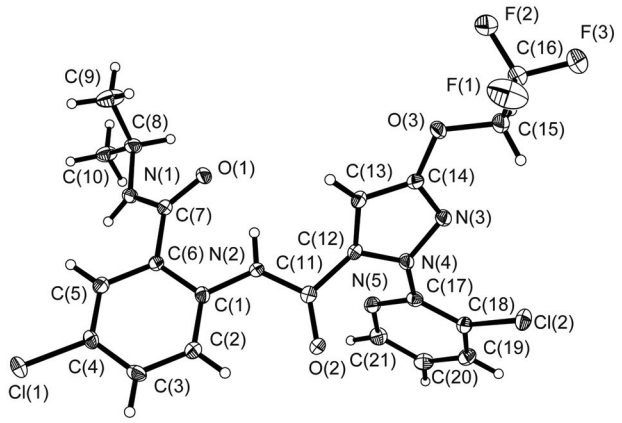

Figure 2 Molecular structure of the compound **19 g**

The molecular structure of **19g** contains the following three-plane subunit: the benzene ring C(1)—C(6) (*p1*), the pyridine ring C(17)-C(21)-N(5) (*p*2), and the pyrazole ring (*p*3). The dihedral angel between the plane of the pyridine ring *p*2 and the plane of the pyrazole ring *p*3 is about 44.0°. The crystal packing structure of this compound is shown in Figure 3.

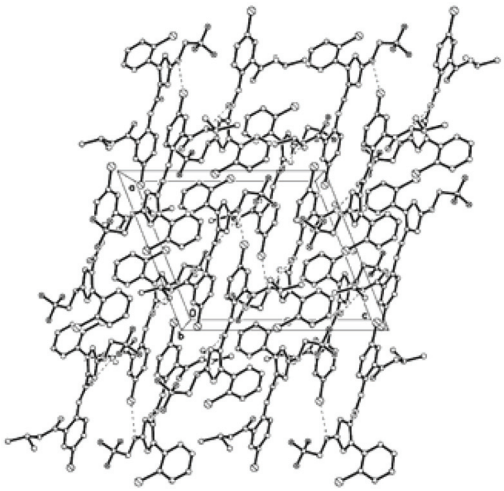

Figure 3 Packing diagram of the compound **19g**

Biological activity

Table 5 shows the insecticidal activities of the title compounds **19a**—**19n** and **20a**—**20b** and Chlorantraniliprole against oriental armyworm. The results of insecticidal activities given in Table 5 indicated that most of the title compounds exhibited excellent activity against oriental armyworm comparable to the commercialized Chlorantraniliprole. For instance, the insecticidal activities of compounds **19a**, **19b**, **19d**, **19g**, **19k** and **19m** against oriental armyworm at 2.5 mg•kg^{-1} were 100%. Moreover, some of them still exhibited good insecticidal activity against oriental armyworm when the concentration was reduced to 1 mg•kg^{-1}.

Table 6 shows the insecticidal activities of the title compounds **19a**—**19n** and Chlorantraniliprole against diamond-back moth. The results indicate that the title compounds **19** have excellent insecticidal activities against diamond-back moth and that some of the title compounds **19** exhibit higher larvicidal activities than the commercialized Chlorantraniliprole. For example, the larvicidal activities of **19a**, **19b**, **19c**, **19d**, **19e**, **19g**, and **19n** against diamond-back moth were 100% at 0.1 mg•kg^{-1}, whereas the corresponding commercial insecticide Chlorantraniliprole caused 43% mortality at this concentration. Surprisingly, most of them still exhibited perfect insecticidal activity against diamond-back moth when the concentration was reduced to 0.05 mg•kg^{-1}, which was higher than the commercialized Chlorantraniliprole.

Table 7 shows the insecticidal activities of the title compounds **19a**—**19n** and Chlorantraniliprole against beet armyworm. The results indicated that most of the title compounds exhibited good activity against beet armyworm. Compounds **19b** exhibited moderate insec-

ticide activity against beet armyworm and had >80% mortality at 0.5 mg•kg^{-1}.

From the data presented in Table 5, we found that the bioactivities of the second series **20** were weaker than that of the first series **19**. Therefore the amide-substituted analogue showed a higher insecticidal activity than did the corresponding ester-substituted analogue. Among those compounds, replacing the nitrogen atom with oxygen atom resulted in decreased insecticidal activity. From Tables 5—7, we can also 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* are very important for increasing activity. Further studies on structural optimization and structure-activity relationships of these anthranilic diamide derivatives are in progress.

Conclusions

In summary, two series of novel anthranilic diamide insecticide containing trifluoroethyl ether were designed and synthesized with structures characterized by ^{1}H NMR spectroscopy, single crystal X-ray diffraction analysis and elemental analysis. The insecticidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal activities. Surprisingly, most of them still exhibited perfect insecticidal activity against diamond-back moth when the concentration was reduced to 0.05 mg•kg^{-1}, which was higher than the commercialized Chlorantraniliprole.

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