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Communication

Synthesis and structure-insecticidal activity relationship of novel phenylpyrazole carboxylic acid derivatives containing fluorine moiety

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ABSTRACT

A series of novel phenylpyrazole carboxylic acid derivatives containing fluorine moiety, *i.e.,* diamides **11**, simple aryl-bearing amides **12** and acylthioureas **14** were successfully synthesized based on the key fluoro-containing phenylpyrazole acid intermediate. The new compounds were identified and confirmed by melting point, ^{1}H NMR, ^{13}C NMR and elemental analysis or HRMS. The bioassay results indicated that some of the compounds possessed excellent insecticidal activities towards oriental armyworm, diamondback moth and corn borer at low concentrations. For examples, compounds **11a**, **11e**–**g** and **14b** exhibited remarkable larvicidal activities with LC_{50} values of 0.13 – 0.39 mg/L and 0.0002 – 0.0014 mg/L against oriental armyworm and diamondback moth, respectively, were comparable with those of the control chlorantraniliprole. Particularly, **11e** were found superior to chlorantraniliprole in oriental armyworm tests (LC_{50}: 0.23 mg/L *vs.* 0.26 mg/L); **11a**, **11e**, **11f** and **14c** in diamondback moth tests with LC_{50} values of 0.0002 mg/L, 0.0002 mg/L, 0.0008 mg/L and 0.0005 mg/L, respectively, were more effective than that of chlorantraniliprole. In addition, **12a** also showed a promising insecticidal potential and development/optimization advantage. Compounds **11a**, **11e–g**, **12a**, **14b** and **14c** could be considered as possible new leading structures for further study. The SAR investigation indicated that the compounds with fluorine motif (*e.g.*, -F, -CF_2H, -CF_3) held apparently favorable insecticidal potentials, which provided useful guidance for further design/development of new phenylpyrazole-containing agrochemicals.

With the increase of the world population as well as the food, feed and water consumption, and the decrease of the average cultivatable land resources all over the world, how to high efficiently improve the crop production based on the limited farmlands available is becoming an urgent problem. The agrochemicals that are used to control various crop pests, weeds and diseases undoubtedly exert very important roles in solving this increasingly prominent issue. However, there always accompanies negative effects more or less during the use of agrochemicals such as pollution to the eco-environment, long term residue period and the resistance problem. Therefore the innovation for new agrochemicals with novel structures and excellent bioactivities is a permanent subject for the pesticide researchers [1,2].

N-Pyridylpyrazole derivatives have received continuous concerns since the early of this century owing to their significant biological activities in agriculture applications. The most noticeable agrochemicals of this kind of compounds are the DuPont's famous insecticides chlorantraniliprole and cyantraniliprole (targeting at insect RyR) which both contain the anthranilic diamide and *N*-pyridylpyrazole structural characteristics [3–5]. Moreover, cyclaniliprole that recently has been developed by Ishihara Sangyo Kaisha is another insecticide of such kind [6,7]. Because of their potential insecticidal activities towards a variety of Lepidopera, Coleoptera and Diptera pests, and some other good properties as well (high efficiency, ecologically safe, less resistance, *etc.*), their structural modifications and the bioactivity evaluation of the synthesized compounds have become a research hot topic in recent years [8–16].

Based on the structures of pyridylpyrazole-containing anthranilic diamides, our previous research work have shown that the substitution of Br-containing pyridylpyrazole group with CF_3-containing (chloronitro)phenylpyrazole group [17] (Fig. 1,**A**), or replacing amide bridge by acylthiourea bridge (giving rise to the CF_3CH_2O-containing pyridylpyrazole acylthiourea derivative) [18] (Fig. 1,**B**) could retain or increase the insecticidal activities of the parent structure towards the test larvae of *Mythimna separata*

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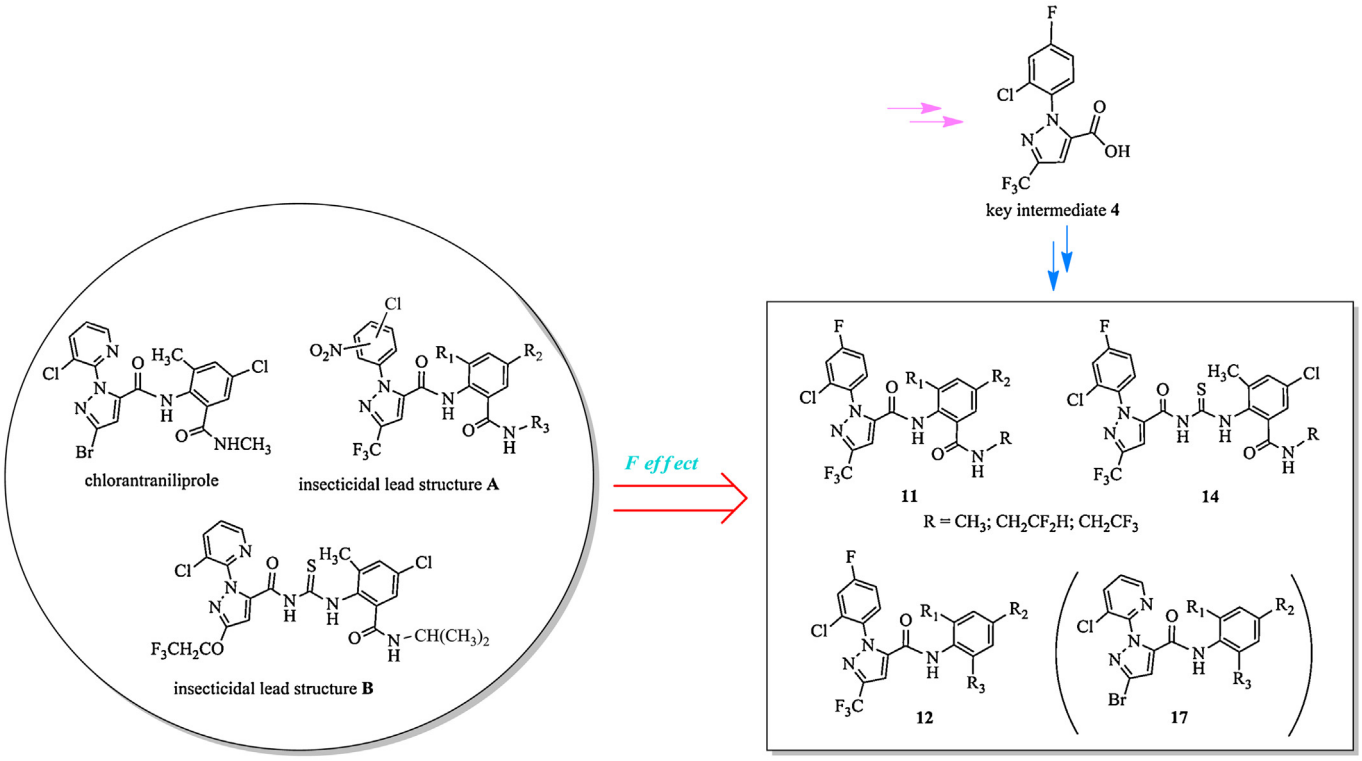
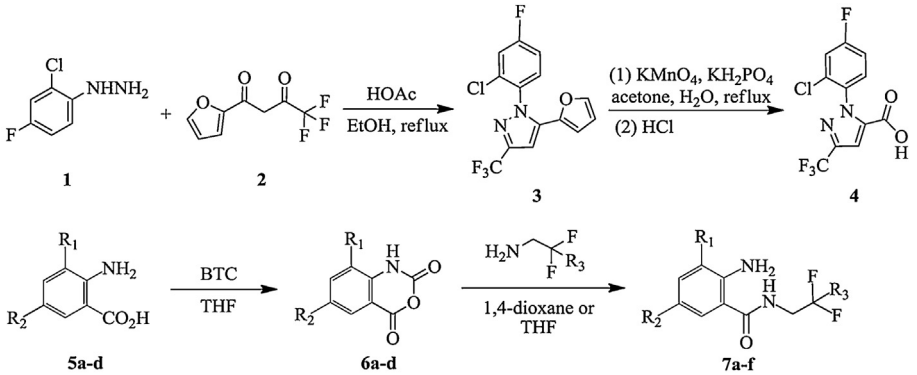


Fig. 1. The design strategy for the title new phenylpyrazole carboxylic acid derivatives containing fluorine moiety.

Walker and *Plutella xylostella* L. at low dose concentrations. Encouraged by these information and with the aim of further looking for new insecticidal agrochemicals, a series of novel phenylpyrazole carboxylic acid derivatives containing fluorine moiety, *i.e.*, diamides **11**, simple aryl-bearing amides **12** and acylthioureas **14** were synthesized in this paper based on the key intermediate (chlorofluoro)phenyl(CF_3)pyrazole acid (a F effect strategy), which is displayed in Fig. 1. It should be noted that some similar anthranilic diamide analogues have been involved in previous patents by Lahm *et al.* [19–21], however the new pyrazole carboxylic acid derivatives ((di)amides and acylthioureas) with 2-chloro-4-fluorophenyl motif were first reported in this article. It is also worth noting that several fluorine-containing groups (CH_2CF_2H, CH_2CF_3) were introduced into the aliphatic amide part of the structures of these diamide and acylthiourea derivatives (**11** and **14**), which is an obvious innovation towards the situations in previous literatures [17,19–22]. The insecticidal activities of all the new synthesized title derivatives were systematically investigated against *Mythimna separata* Walker, *Plutella xylostella* L. and *O. nubilalis* at different dose concentrations in this research. In addition, to further study the structure-activity relationship for the simple aryl-containing amide derivatives **12**, chloropyridyl(Br) pyrazole amides **17** as contrasts were also synthesized and bioassayed.

As shown the synthetic procedure in Scheme 1, the key intermediate 1-(2-chloro-4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid (**4**) was prepared. A mixture of (2-chloro-4-fluorophenyl) hydrazine (**1**, 140 mmol) and 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (**2**, 153 mmol) in glacial acetic acid (150 mL) was refluxed for 5 h with TLC monitoring. After cooling down, the mixture was concentrated under reduced pressure. The residue was added saturated Na_2CO_3 aq. (50 mL), and



5a, **6a**: R_1=CH_3; **5b**, **6b**: R_1=Cl;
5c, **6c**: R_1=CH_3, R_2=Cl; **5d**, **6d**: R_1=R_2=Cl

7a: R_1=CH_3, R_2=R_3=H; **7b**: R_1=Cl, R_2=R_3=H;
7c: R_1=Cl, R_2=H, R_3=F; **7d**: R_1=CH_3, R_2=Cl, R_3=H;
7e: R_1=CH_3, R_2=Cl, R_3=F; **7f**: R_1=R_2=Cl, R_3=H

Scheme 1. Synthetic route of the intermediate **4** and the intermediates **7a**–**f**.

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then extracted with ethyl acetate (3 × 20 mL). The organic phase was combined, washed with brine and dried over anhydrous Na_2SO_4, successively. After solvent removal, the residue was conducted to column chromatography with petroleum ether and ethyl acetate (6:1, v/v) as solvents to afford the furylpyrazole intermediate **3** as a yellow sticky oil, yield 84%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, 1H, J = 8.8, 5.6 Hz, Ph-H), 7.41 (d, 1H, J =1.2 Hz, furyl-H), 7.32 (dd, 1H, J = 8.0, 2.8 Hz, Ph-H), 7.14–7.19 (m, 1H, Ph-H), 6.93 (s, 1H, pyrazole-H), 6.34 (dd, 1H, J = 3.2, 1.6 Hz, Ph-H), 5.85 (d, 1H, J =3.6 Hz, furyl-H).

To a three-necked flask furylpyrazole intermediate **3** (52.8 mmol), potassium dihydrogen phosphate (68.4 mmol), acetone (100 mL) and water (200 mL) were added. Potassium permanganate (285 mmol) was then added to the above mixture in small portions under stirring. After completion of addition, the reaction system was refluxed for 1 h and cooled down. The mixture was filtered. The filtrate was acidized with concentrated hydrochloric acid, then extracted with ethyl acetate (3 × 30 mL). The organic phase was combined and dried over anhydrous Na_2SO_4. After solvent removal, the residue was conducted to column chromatography using petroleum ether and ethyl acetate (3:1, v/v) as solvents to afford the (chlorofluoro)phenyl(CF_3)pyrazole acid intermediate **4** as a white solid, yield 56%, mp 149 – 150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (br, 1H, COOH), 7.45 (dd, 1H, J = 8.8, 5.2 Hz, Ph-H), 7.35 (s, 1H, pyrazole-H), 7.28 (dd, 1H, J = 8.0, 2.4 Hz, Ph-H), 7.12–7.17 (m, 1H, Ph-H).

6,8-Disubstituted-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (**6a**–**d**) (Scheme 1) was prepared from 2-amino-3,5-disubstituted-benzoic acid (**5a**–**d**) and triphosgene following the procedure of Hanusek *et al.* [23]. 2-Amino-5-chloro-*N*,3-dimethylbenzamide (**9**) was prepared by literature method *via* $SOCl_2$ acylation and aminolysis successively, based on the starting material 2-amino-3-methyl-5-chlorobenzoic acid [14]. The intermediate 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (**15**) was prepared *via* multi steps according to the procedure in literature [18,24].

2-Amino-3,5-disubstituted-*N*-(2,2-difluoroethyl)/(2,2,2-trifluoroethyl)benzamide (**7a**–**f**) (Scheme 1) were prepared referring to a similar procedure in literature [14,23]. A mixture of the benzooxazinedione intermediate **6** (5 mmol), 2,2-difluoroethan-1-amine or 2,2,2-trifluoroethan-1-amine (15 mmol) and 1,4-dioxane or tetrahydrofuran (30 mL) was reacted for 6 – 8 h with TLC monitoring. After solvent removal under reduced pressure, the residue was purified by recrystallization or column chromatography using petroleum ether/ethyl acetate (5:1, v/v) as solvents to afford the new intermediate **7**.

(Chlorofluoro)phenyl(CF_3)pyrazole acid **4** (0.8 mmol), oxalyl chloride (3.2 mmol) and dry DCM (15 mL) were mixed and stirred for 2 min at room temperature. Two drops of DMF were added to the above solution. The reaction system was stirred for further 3.5 h at room temperature, and then concentrated under reduced pressure to give crude intermediate pyrazole carbonyl chloride **8** as a yellow solid, which was directly used to do the next step reaction without purification.

The crude acyl chloride **8** (0.8 mmol) was dissolved in dry DCM (8 mL) and was added dropwise to a stirred solution of 2-amino-5-chloro-*N*,3-dimethylbenzamide **9** or 2-amino-3,5-disubstituted-*N*-(2,2-difluoroethyl)/(2,2,2-trifluoroethyl)benzamide (**7a**–**f**) (0.76 mmol) and Et_3N (0.96 mmol) in DCM (20 mL). The system was reacted for 10 h at room temperature, and washed with hydrochloric acid, saturated $NaHCO_3$ aq. and brine, successively. The organic phase was combined and dried over anhydrous Na_2SO_4. After solvent removal, the residue was conducted to column chromatography using petroleum ether and ethyl acetate (10:1, v/v) as solvents to afford the title compounds **11a**–**g** (Scheme 2) as a white solid.

A solution of 2,4,6-trisubstitutedphenylamine (**10**, 0.8 mmol) in pyridine (10 mL) was added to the flask containing the crude acyl chloride **8** (0.8 mmol) which was prepared from the procedure described above, and the mixture was refluxed for 3 – 5 h. After cooling down, the mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 15 mL). The extracts were combined and washed with hydrochloric acid (2 × 10 mL) and brine, successively. The organic phase was dried over anhydrous Na_2SO_4. After solvent removal, the residue was further purified by recrystallization from ethanol to afford the title compounds **12a**–**c** (Scheme 2) as a solid.

The crude acyl chloride **8** (0.85 mmol) prepared from the above procedure was dissolved in dry aectonitrile (8 mL) and the solution was added dropwise to a stirred mixture of KSCN (2.13 mmol) and PEG-400 (2 drops) in dry acetonitrile (15 mL). The mixture was stirred for 1 h at room temperature and filtered. To the filtrate (*i.e.*, acyl isothiocyanate **13** in CH_3CN), aminobenzamide intermediate **9** or **7d** or **7e** (0.8 mmol) was added in small portions. The system was reacted for further 4 h at room temperature (TLC monitoring) and concentrated under reduced pressure. The residue was then made purification *via* column chromatography using petroleum ether and ethyl acetate (4:1, v/v) as solvents to afford the title compounds **14a**–**c** (Scheme 2) as a white solid.

Using the similar synthetic procedure of compounds **12a** and **b**, 3-bromo-*N*-(2,4,6-trisubstitutedphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**17a** and **b**) with chloropyridyl(Br) pyrazole acid **15** as acid material (Scheme 3).

As shown in Scheme 1, the key intermediate (chlorofluoro) phenyl(CF_3)pyrazole acid **4** was first prepared *via* a nucleophilic addition-elimination-based cyclization of (2-chloro-4-fluorophenyl)hydrazine **1** and trifluoromethyl- and furyl-containing 1,3-dione **2** in boiling acetic acid and $KMnO_4$-oxidation of the generated new furylpyrazole intermediate **3** with good yield. The nucleophilic substitution reaction of benzooxazinedione intermediate **6** and difluoroethylamine or trifluoroethylamine high effectively gave rise to the new intermediate **7** (76%–95%) (Scheme 1). It is worth noting that the synthesis and the structural characterization of the intermediates **4** and **7** were first reported in this article (Supporting information).

Based on the key acid intermediate **4**, the diamide derivatives **11a**–**g** and the amide derivatives **12a**–**c** were smoothly synthesized *via* $(COCl)_2$-acylation and aminolysis using corresponding aminobenzamide or amine intermediates, respectively (Scheme 2); the acyl chloride intermediate **8** reacted with KSCN under PEG-400 catalyzing in CH_3CN gave the acyl isothiocyanate intermediate **13**, which further reacted with aminobenzamide intermediate **9** or **7d** or **7e** leading to the desired acylthiourea compounds **14a**–**c** (Scheme 2).

Moreover, the amide derivatives **17a** and **b** also could be obtained in satisfactory yield *via* similar reaction conditions as those of **12a**–**c**, that is, the acyl chloride **16** which derived from the chloropyridyl(Br)pyrazole acid **15** reacted with 2,4,6-trisubstitutedphenylamine **10a** or **10b** in pyridine under reflux for 3 – 5 h (Scheme 3).

The synthesized title compounds were identified and confirmed by melting point, ^{1}H NMR and ^{13}C NMR spectra (Supporting information). The measured elemental analysis or high-resolution mass spectroscopy data were also consistent with the corresponding calculated values (Supporting information). In the ^{1}H NMR of these synthesized new compounds, (di)amide or acylthiourea derivatives, the active proton (NH) signals mainly showed up one or two or three groups of peaks at very downfield with the chemical shift of 6.36–12.12 ppm. As bearing fluoro-containing group, some proton or carbon resonance absorption peaks in most of the compounds obviously appeared characteristic spin coupling and splitting of fluorine atom. For examples, the proton signals of

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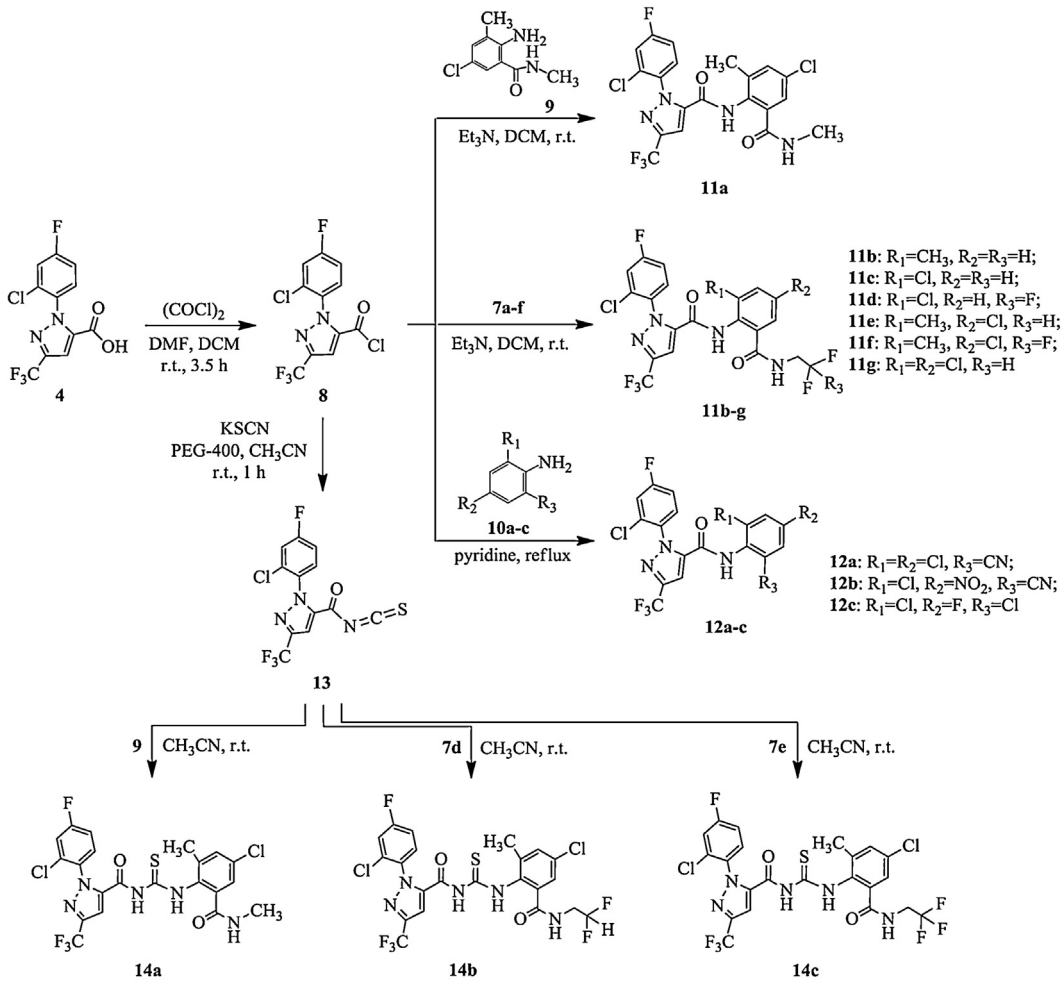
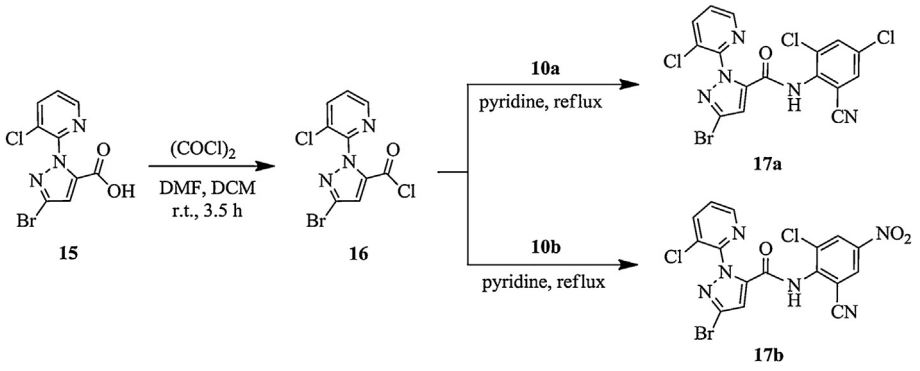


Scheme 2. Synthetic route of the title compounds **11a**–**g**, **12a**–**c** and **14a**–**c**.

CF_2H and CH_2 in CH_2CF_2H-containing compounds **11c** and **11e** showed up "tt" peaks ($^2J_{FH}$ =56.0 Hz, $^3J_{HH}$ =4.0 Hz) at δ ~5.90 ppm, and multiplet peaks at 3.36 – 3.75 ppm, respectively; the proton signals of CH_2 in CH_2CF_3-containing compounds **11f** and **14c** showed up multiplet peaks at 3.60 – 4.40 ppm; the carbon signals of the CF_2H and CH_2 groups in CH_2CF_2H-containing compounds **11e**, **11 g** and **14b** appeared at δ ~114 ppm and ~42 ppm as triplet peaks ($^1J_{FC}$ ≈ 241 Hz) and triplet peaks ($^2J_{FC}$ ≈ 26 Hz), respectively; the carbon signals of the CF_3 and CH_2 groups in CH_2CF_3-containing compounds **11d**, **11f** and **14c** appeared at δ ~123 ppm and ~40 ppm as quartet peaks ($^1J_{FC}$ ≈ 279 Hz) and quartet or multiplet peaks ($^2J_{FC}$ ≈ 34 Hz), respectively. In addition, in the ^{13}C NMR of acylthiourea derivatives **14a**–**c**, the carbon signals of C=S and two C=O groups were observed at δ ~180 ppm, ~166 ppm and ~157 ppm, respectively; around this region, it also appeared doublet peaks at δ ~162.5 ppm, ascribing to the benzene carbon that connects to the fluorine atom.

The insecticidal activities of compounds **11**, **12**, **14** and **17** against oriental armyworm (*Mythimna separata* Walker), corn borer (*O. nubilalis*) and diamondback moth (*Plutella xylostella* L.) were tested in a greenhouse according to the reported methods [17,18,25–27], and the detailed procedures are presented in the Supporting information.

As shown in Table 1, initially all the tested compounds exhibited 100% lethality rate against oriental armyworm at a concentration



Scheme 3. Synthetic route of the compounds **17a** and **b**.

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Table 1
Larvicidal activity of the title compounds and chlorantraniliprole against oriental armyworm (*Mythimna separata* Walker) and corn borer (*O. nubilalis*).

Compd.	Activity (%) against *Mythimna separata* Walker at conc. (mg/L)					Activity (%) against *O. nubilalis* at conc. (mg/L)			
	100	5	2.5	0.5	0.25	100	50	25	5
11a	100	100	100	100	20.0	100	100	100	65.0
11b	100	50.0 (10 mg/L)	n.t.*	n.t.	n.t.	100	25.0	n.t.	n.t.
11c	100	100	15.0	n.t.	n.t.	100	100	35.0	n.t.
11d	100	40.0 (10 mg/L)	n.t.	n.t.	n.t.	100	10.0	n.t.	n.t.
11e	100	100	100	80.0	60.0	100	100	100	70.0
11f	100	100	100	60.0	33.3	100	100	100	65.0
11 g	100	100	100	100	96.7	100	100	100	100
12a	100	66.8	33.3	n.t.	n.t.	100	100	40.0	n.t.
12b	100	60.0 (50 mg/L)	n.t.	n.t.	n.t.	60.0 (200 mg/L)	n.t.	n.t.	n.t.
12c	100	100	30.0	n.t.	n.t.	100	100	20.0	n.t.
14a	100	70.0 (10 mg/L)	n.t.	n.t.	n.t.	100	20.0	n.t.	n.t.
14b	100	100	100	100	96.7	100	100	100	100
14c	100	30.0 (10 mg/L)	n.t.	n.t.	n.t.	100	10.0	n.t.	n.t.
17a	100	80.0 (25 mg/L)	n.t.	n.t.	n.t.	70.0	n.t.	n.t.	n.t.
17b	100	40.0 (50 mg/L)	n.t.	n.t.	n.t.	60.0 (200 mg/L)	n.t.	n.t.	n.t.
Chlorantraniliprole	100	100	100	70.0	50.0	100	100	100	50.0

* n.t.: not test.

of 100 mg/L. By further determination at lower concentrations, most of the diamide derivatives **11a**–**g** and the acylthiourea derivatives **14a**–**c** could still display remarkable insecticidal activities, *e.g.*, compounds **11a**, **11c**, **11e**–**g** and **14b** possessed 100% larvicidal activities against oriental armyworm at 5 mg/L; compounds **11a**, **11e**–**g** and **14b** pleasingly showed 20.0%–96.7% activity at 0.25 mg/L. In particular, compounds **11e**, **11g** and **14b** whose lethality rate are 60.0%, 96.7% and 96.7%, respectively, were more effective than the control chlorantraniliprole (50.0%). The (chlorofluoro)phenyl(CF_3)pyrazole amide derivatives (with simple phenyl motif) **12a**–**c** and chloropyridyl(Br)pyrazole amide derivatives **17a** and **b** also exhibited favorable insecticidal activities against oriental armyworm. Especially, **12a** and **12c** at 2.5 mg/L held lethality rate of 33.3% and 30.0%, respectively. From Table 1, it also can be seen that compounds **11a**–**g**, **12a**, **12c** and **14a**–**c** can totally kill the test larvae of corn borer at 100 mg/L concentration (100%). Remarkably, compounds **11a**, **11e**–**g** and **14b** whose lethality rates at 5 mg/L are 65.0%, 70.0%, 65.0%, 100% and 100%, respectively were more effective than the control chlorantraniliprole (50.0%).

As shown in Table 2, all the synthesized compounds displayed excellent insecticidal activities against diamondback moth at 200 mg/L and 100 mg/L concentrations. At lower dosage, compounds **11a**, **11e**–**g**, **14b** and **14c** had 100% insecticidal activities at the concentration of 0.1 mg/L; particularly, these six compounds also possessed 20.0%–75.0% lethality rate at 0.0005 mg/L, near to even higher than that of chlorantraniliprole (40.0%).

Table 2
Larvicidal activity of the title compounds and chlorantraniliprole against diamondback moth (*Plutella xylostella* L.).

Compd.	Larvicidal activity (%) at conc. (mg/L)						
	200	100	10	1	0.1	0.001	0.0005
11a	100	100	100	100	100	90.0	55.0
11b	100	100	90.0	80.0	60.0	n.t.*	n.t.
11c	100	100	90.0	60.0	n.t.	n.t.	n.t.
11d	100	100	100	90.0	60.0	n.t.	n.t.
11e	100	100	100	100	100	90.0	75.0
11f	100	100	100	100	100	70.0	45.0
11 g	100	100	100	100	100	65.0	30.0
12a	100	100	100	100	50.0	20.0 (0.01 mg/L)	n.t.
12b	100	80.0	50.0	n.t.	n.t.	n.t.	n.t.
12c	100	80.0	50.0	n.t.	n.t.	n.t.	n.t.
14a	100	100	100	100	90.0	60.0 (0.01 mg/L)	n.t.
14b	100	100	100	100	100	50.0	20.0
14c	100	100	100	100	100	80.0	40.0
17a	100	100	100	80.0	n.t.	n.t.	n.t.
17b	100	85.0	60.0	n.t.	n.t.	n.t.	n.t.
Chlorantraniliprole	100	100	100	100	100	70.0	40.0

* n.t.: not test.

By analyzing the insecticidal activities of the synthesized title compounds corresponding to their structures, the following relationships could be found: (i) When R_2 and R_3 of compounds **11b**–**g** are fixed as H or Cl and H, respectively, the R_1 group in corresponding compounds against oriental armyworm and corn borer shows an activity trend: Cl > CH_3 (*e.g.*, in Table 1, **11c** > **11b**; **11g** > **11e**). Interestingly, such situation is somewhat different from that against diamondback moth, that is, CH_3 > Cl (*e.g.*, in Table 2, **11b** > **11c**; **11e** > **11g**). (ii) When R_1=Cl and R_2=H, R_3 group in the corresponding compounds against oriental armyworm and corn borer shows the activity sequence of H > F (**11c** > **11d**); when R_1=CH_3 and R_2=Cl, the activity trend for R_3 group is H > F (**11e** > **11f**; **14b** > **14c**), that is, CH_2CF_2H group is better than CH_2CF_3 group in aliphatic amide motif. (iii) Against diamondback moth, it shows a reverse trend for R_3 group, that is F > H (CH_2CF_3 is better than CH_2CF_2H). (iv) Comparing the diamide derivatives **11a**, **11e** and **11f**, it was found that CH_2CF_2H group in the respective types of structures is better than CH_3 group for the increase of the insecticidal activities. Such situation is particularly obvious in the cases of **14a** and **14b** against all the three kinds of test larvae, which indicates the introduction of F atom to the alkyl chain of aliphatic amide motif could greatly increase the insecticidal activity of the parent structures. (v) When bearing the same substituents R_1, R_2 and R_3 in the phenylamine motif, (chlorofluoro)phenyl(CF_3) pyrazole group displayed apparent superiority relative to the chloropyridyl(Br)pyrazole group for the contribution to the insecticidal activities (*e.g.*, **12a** > **17a**; **12b** > **17b**). Whereas, when R_1=Cl, R_3=CN both in **12a** and **b** and **17a** and **b**, the R_2 group indicates an activity sequence of Cl > NO_2.

On the whole, compounds with CH_3/Cl, Cl and $CONHCH_2CF_2H$ groups at benzene ring's 2-, 4- and 6- positions of phenylamine part both in diamide derivatives **11** and acylthiourea derivatives **14** showed the excellent insecticidal activities. In addition, (chlorofluoro)phenyl(CF_3)pyrazole amide derivatives **12a** and **12c** that contain simple groups, *i.e.*, 2,4-Cl_2-6-CN-phenyl and 2,6-Cl_2-4-F-phenyl, respectively, exhibited a favorable and promising insecticidal potentials. Such substituents favorability corresponding to the insecticidal activity or SAR contrast could be well reflected and illustrated as shown in Figs. 2 and 3. An insecticidal activity enhancement of fluorine-containing groups that linked with the

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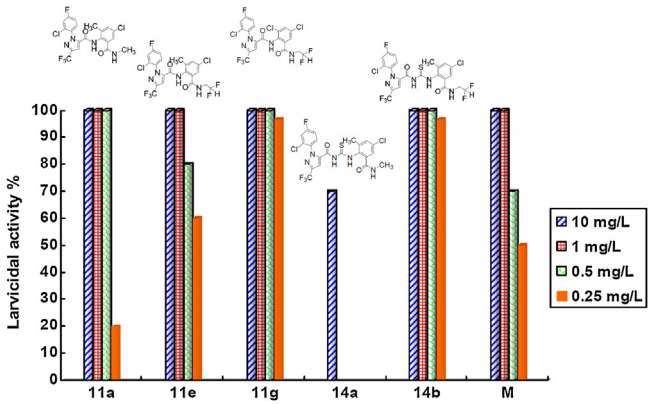

Fig. 2. The larvicidal activity contrast diagram of compounds **11a**, **11e**, **11 g**, **14a**, **14b** and chlorantraniliprole (**M**) against oriental armyworm (*Mythimna separata* Walker) at different test concentrations.

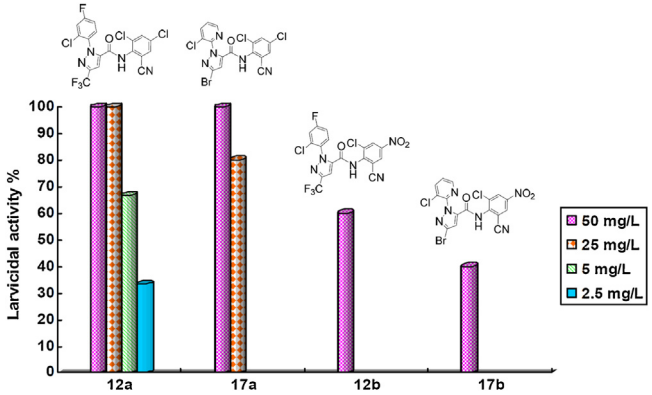

Fig. 3. The larvicidal activity contrast diagram of compounds **12a**, **12b**, **17a** and **17b** against oriental armyworm (*Mythimna separata* Walker) at different test concentrations.

aliphatic amide part of both diamide and acylthiourea derivatives was apparently found in Fig. 2 [*e.g.*, **11 g** (CH_2CF_3), **11e** (CH_2CF_2H) > **11a** (CH_3); **14b** (CH_2CF_2H) >> **14a** (CH_3)]. Also in Fig. 3, when other part of the compounds was fixed as the same, (chlorofluoro)phenyl (CF_3)pyrazole has greater contribution than chloropyridyl(Br) pyrazole group for the activity (*i.e.*, **17a** > **12a**; **17b** > **12b**). Obviously, the introduction of fluorine moiety both in pyrazole and phenyl rings promoted the insecticidal activity, which is possibly due to the effect of F atom or polyfluoro group by means of improving lipophilicity, metabolic stability and subsequent insecticidal activity of the corresponding compounds [28].

Based on the preliminary bioassay results, some compounds with good insecticidal activities were made further investigation on LC_{50} values. From Table S1 (Supporting information) we can see that compounds **11a**, **11e**–**g** and **14b** exhibited remarkable larvicidal activities against oriental armyworm with LC_{50} value of 0.13 – 0.39 mg/L, comparable with that of chlorantraniliprole (0.26 mg/L and 0.11 mg/L at respective batch). Particularly, **11e** held LC_{50} value of 0.23 mg/L (LC_{95} = 0.88 mg/L), superior to chlorantraniliprole which had a LC_{50} value of 0.26 mg/L (LC_{95} = 1.79 mg/L) under the same test conditions. Those compounds mentioned above also exhibited excellent larvicidal activities against diamondback moth with LC_{50} value of 0.0002 – 0.0014 mg/L (Table S2 in Supporting information). Among which, **11a**, **11e**, **11f** and **14c** whose LC_{50} values are 0.0002 mg/L, 0.0002 mg/L, 0.0008 mg/L and 0.0005 mg/L, respectively, were more effective than that of chlorantraniliprole (0.0014 mg/L and 0.0006 mg/L at respective batch). **11 g** and **14b** also had favorable activities with LC_{50} values of 0.0008 mg/L and 0.0014 mg/L, respectively. In addition, compound **12a** possessed LC_{50} values of 3.41 mg/L and 0.12 mg/L against oriental armyworm and diamondback moth, respectively, showing a promising insecticidal potential and development/optimization advantage considering its comparatively simple structural characteristics.

In summary, a series of novel phenylpyrazole carboxylic acid derivatives containing fluorine moiety, *i.e.*, diamides **11**, simple aryl-bearing amides **12** and acylthioureas **14** were successfully synthesized based on the key fluorine-containing phenylpyrazole acid intermediate. The new compounds were identified and confirmed by melting point, ^{1}H NMR, ^{13}C NMR and elemental analysis or HRMS. The bioassay results showed that some of the title compounds possessed excellent insecticidal activities towards oriental armyworm, diamondback moth and corn borer at low concentrations and could be considered as possible new leading insecticides for further study. For examples, compounds **11a**, **11e**–**g** and **14b** exhibited remarkable larvicidal activities with LC_{50} value of 0.13 – 0.39 mg/L against oriental armyworm and 0.0002 – 0.0014 mg/L against diamondback moth, respectively, and were comparable with those of the control insecticide chlorantraniliprole. Particularly, **11e** held LC_{50} value of 0.23 mg/L, were superior to chlorantraniliprole in oriental armyworm tests; **11a**, **11e**, **11f** and **14c** in diamondback moth tests with LC_{50} values of 0.0002 mg/L, 0.0002 mg/L, 0.0008 mg/L and 0.0005 mg/L, respectively, were more effective than that of chlorantraniliprole. In addition, simple aryl-bearing amide derivative **12a** of the title compounds also showed a promising insecticidal potential and development/optimization advantage. The investigation on structure-insecticidal activity relationship of these novel compounds indicated that the compounds with fluorine motif (*e.g.*, -F, -CF_2H, -CF_3) held apparently favorable insecticidal potentials, which provided useful guidance for further design/development of new phenylpyrazole-containing agrochemicals.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.07.064.

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