Design, Synthesis and Insecticidal Evaluation of Novel Pyrazolecarboxamides Containing Cyano Substituted *N*-Pyridylpyrazole†

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12 novel pyrazolecarboxamides containing cyano substituted *N*-pyridylpyrazole were synthesized, and their structures were characterized by ^{1}H NMR and HRMS techniques. Their evaluated insecticidal activities against oriental armyworm (*Mythimna separata*) indicated that the cyano-containing pyrazolecarboxamides exhibited moderate insecticidal activities. Compounds **6i** and **6k** showed comparable higher activity than corresponding anthranilic diamide **6m**.

Keywords cyano, insecticidal activity, *N*-pyridylpyrazole, anthranilic diamide, pyrazolecarboxamide

Introduction

The discovery of novel insecticide with a new mode of action is crucial to overcome resistance and eco-biological problems associated with some conventional insecticides. The ryanodine receptors (RyR), which regulates calcium ion channel in insect nerve synpase, has represented one of the attractive biological target for pest control strategies.[1] The commercial chlorantraniliprole (**A**),[2,3] which has a typical anthranilic diamide structure, was developed by DuPont Co. and exhibited exceptional insecticidal activity on a broad range of Lepidoptera, Coleoptera, Diptera and Isoptera.[4]

The anthranilic diamide structure has been characteristic to chlorantraniliprole, yet the insecticidal activity of simpler structures that eliminate the aliphatic amide moiety has been little reported. Pyrazolecarboxamide (**B**) reported by DuPont Co. with a simpler structure, still showed high activity against Lepidoptera.[5] The introduction of a cyano group to replace the 4-halo substituent led to the discovery of cyantraniliprole (Cyazypyr, **C**),[6] which had improved plant mobility and increased spectra of insect control. In this article, based on our previous work,[7] a new cyano substituted *N*-pyridylpyrazole carboxylic acid was synthesized. Further derivatization of this compound led to 12 novel pyrazolecarboxamides as shown in Scheme 1. The bioactivity against oriental armyworm was tested accordingly.

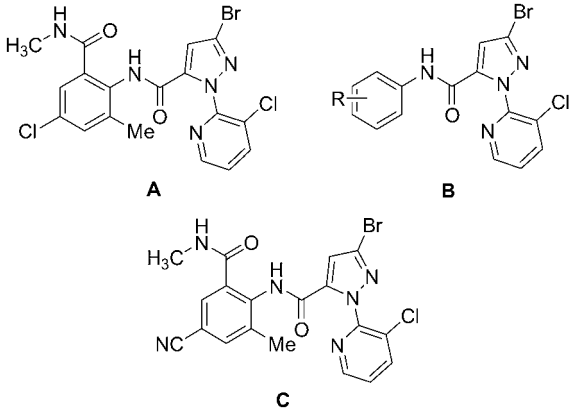

Figure 1 Chemical structures of compounds **A**—**C**.

Experimental

Materials and instruments

^{1}H NMR spectra were recorded at 400 MHz using a Bruker AC-400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized. Reagents were all analytically or chemically pure. Substituted anilines **5a**—**5l** were purchased from Alfa Aesar. All solvents and liquid reagent were dried

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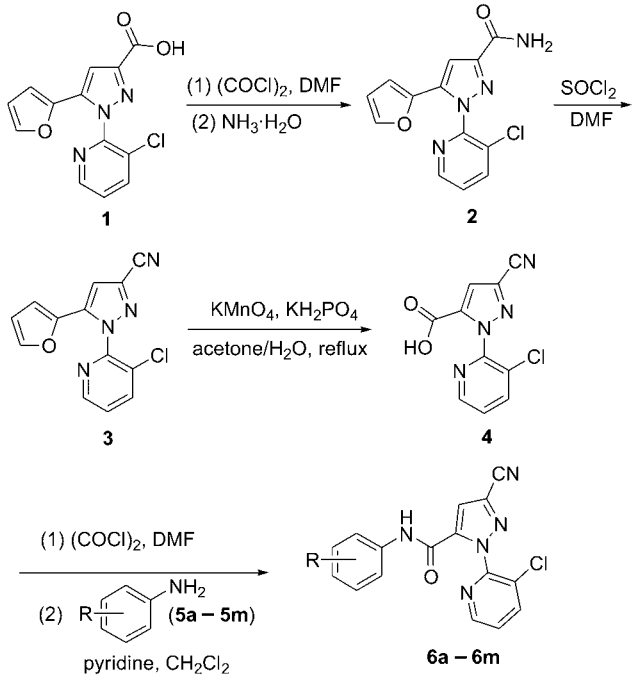
Scheme 1 General synthetic procedure of compounds **6a**—**6m**



by standard methods in advance and distilled before use. Chlorantraniliprole was synthesized according to the literature[8] and used as the control.

General procedure

The intermediate 1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylic acid (**1**) was synthesized according to our previous work.[7] 2-Amino-5-chloro-*N*,3-dimethylbenzamide (**5m**) was synthesized by the method reported by Dong *et al.*[8] The title compounds were prepared as shown in Scheme 1.

1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxamide (2) Compound **1** (1.0 mmol) was dissolved in 25 mL of dichloromethane. Under vigorous stirring, oxalyl chloride (1.5 mmol) and a drop of DMF were added successively. After stirring at room temperature for 3 h, the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 10 mL of THF, and added dropwise to an ice-cold solution of ammonium hydroxide (0.5 mL) in 10 mL of THF. After completion, the mixture was left to warm to ambient temperature and stirred for another 40 min. Then the yellow suspension was poured into 50 mL of water and extracted by ethyl acetate (30 mL×3). The combined extracts were washed with 2 mol/L hydrochloric acid and brine successively. The yellow solution was dried and evaporated to give the title compound as a yellow solid, yield 85.0%. m.p. 151—153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (dd, ^4J=1.6 Hz, J=4.8 Hz, 1H, Ar-H), 7.97 (dd, ^4J=1.4 Hz, J=8.2 Hz, 1H, Ar-H), 7.52 (dd, J=4.4, 8.0 Hz, Ar-H), 7.32 (d, J=1.6 Hz, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 6.84 (s, 1H, CONH), 6.34 (dd, J=1.8, 3.4 Hz, 1H, Ar-H), 6.05 (s, 1H, Ar-H), 5.67(s, 1H, CONH).

1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carbonitrile (3) The title compound was synthesized according to the method reported by Saitoh *et al.*[9] Thionyl dichloride (2.0 mmol) was added dropwise to an ice-cold solution of compound **2** (1.0 mmol) in 30 mL of DMF with the temperature maintained below 5 ℃ throughout. The reaction was stirred at 5 ℃ for 45 min and then 2 h at ambient temperature. Then the mixture was poured into 50 mL of ice water with stirring for 0.5 h and gray powder was precipitated. After filtration and recrystallization, the title compound **3** was obtained as white solid, yield 65.8%, m.p. 92—94 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J=4.4 Hz, 1H, Ar-H), 7.99 (d, J=8.0 Hz, 1H, Ar-H), 7.54 (dd, J=4.8, 7.6 Hz, 1H, Ar-H), 7.37 (s, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 6.36 (s, 1H, Ar-H), 6.00 (d, J=3.2 Hz, 1H, Ar-H).

1-(3-Chloropyridin-2-yl)-3-cyano-1*H*-pyrazole-5-carboxylic acid (4) The furan moiety was oxidized by the procedure reported by Varnes *et al.*[10] $KMnO_4$ (5.0 mmol) and KH_2PO_4 (3.0 mmol) were added successively to a solution of compound **3** (1.0 mmol) in 20 mL of acetone and 20 mL of water. The mixture was refluxed for 1 h, then filtrated and washed with 20 mL of hot water. The filtrate was acidified to pH 2, then most of the acetone was evaporated *in vacuo*. The resulting solution was extracted with ethyl acetate. Organic layer was combined and dried with sodium sulfate. The solution was evaporated to give the crude product, which was recrystallized with petroleum ether and ethyl acetate (V∶V=2∶1) to give the title carboxylic acid as a yellow solid, yield 55.6%. m.p. 237—239 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (d, J=4.4 Hz, 1H, Ar-H), 8.32 (d, J=8.4 Hz, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.75 (dd, J=4.8, 8.0 Hz, 1H, Ar-H).

General synthetic procedure of 6a—6m Compound **4** (0.5 mmol) was dissolved in 20 mL of dichloromethane under stirring, oxalyl chloride (0.8 mmol) and a drop of DMF were added successively. After stirring for 2 h at room temperature, dichloromethane was removed *in vacuo*. The residue was dissolved in 20 mL of dichloromethane, and then added dropwise to an ice-cold solution of substituted anilines **5a**—**5m** (0.5 mmol), pyridine (0.5 mmol) in 20 mL of dichloromethane. The mixture was stirred at room temperature for 2 h before it was washed with 2 mol/L hydrochloric acid, saturated sodium bicarbonate solution and brine successively. The organic layer was dried with sodium sulfate and evaporated. The residue was subjected to flash chromatography on silica gel with *V*(petroleum ether)∶*V*(ethyl acetate)=1∶1 to give the title compounds **6a**—**6m**.

6a: Yield 75.0%; white solid, m.p. 209—211 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (d, J=4.8 Hz, 1H, Ar-H), 8.36 (s, 1H, CONH), 8.22 (d, J=8.0 Hz, 1H, Ar-H), 7.97 (d, J=8.4 Hz, 1H, Ar-H), 7.51 (dd, J=4.6, 7.6 Hz, Ar-H), 7.41 (d, J=8.0 Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.26—7.23 (m, 1H, Ar-H), 7.11 (t, J=7.8 Hz, 1H, Ar-H). HRMS calcd for $C_{16}H_9Cl_2N_5O$ ([M—

H]$^-$) 356.0111, found 356.0113.

6b: Yield 90.9%; white solid, m.p. 185—187 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (dd, ^4J=2.0 Hz, J=6.4 Hz, 1H, Ar-H), 7.92 (dd, ^4J=2.0 Hz, J=11.8 Hz, 1H, Ar-H), 7.88 (s, 1H, CONH), 7.53 (d, J=9.6 Hz, 1H, Ar-H), 7.45 (dd, J=6.4, 10.8 Hz, 1H, Ar-H), 7.19—7.15 (m, 4H, Ar-H), 2.24 (s, 3H, Ar-CH_3). HRMS calcd for $C_{17}H_{12}ClN_5O$ ([M—H]$^-$) 336.0658, found 336.0666.

6c: Yield 55.0%; white solid, m.p. 200—202 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.77 (s, 1H, CONHAr), 8.55 (d, J=4.4 Hz, 1H, Ar-H), 8.40 (d, J=7.6 Hz, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.79 (d, J=7.6 Hz, 1H, Ar-H), 7.74—7.67 (m, 2H, Ar-H), 7.56 (t, J=7.6 Hz, 1H, Ar-H), 7.43 (d, J=7.6 Hz, 1H, Ar-H). HRMS calcd for $C_{17}H_9ClF_3N_5O$ ([M — H] $^-$) 390.0375, found 390.0371.

6d: Yield 93.3%; white solid, m.p. 209—212 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.35 (s, 1H, CONHAr), 8.55 (d, J=4.4 Hz, 1H, Ar-H), 8.24 (d, J=8.0 Hz, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 7.67 (dd, J=4.8, 8.0 Hz, 1H, Ar-H), 7.14—7.08 (m, 3H, Ar-H), 2.14 (s, 6H, Ar-CH_3). HRMS calcd for $C_{18}H_{14}ClN_5O$ ([M—H]$^-$) 350.0814, found 350.0819.

6e: Yield 60.4%; white solid, m.p. 212—213 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.98 (s, 1H, CONHAr), 8.55 (d, J=4.8 Hz, 1H, Ar-H), 8.24 (d, J=8.0 Hz, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.69 (dd, J=4.6, 8.0 Hz, 1H, Ar-H), 7.57 (d, J=8.0 Hz, 2H, Ar-H), 7.40 (t, J=8.0 Hz, 1H, Ar-H). HRMS calcd for $C_{16}H_8Cl_3N_5O$ ([M—H]$^-$) 389.9733, found 389.9728.

6f: Yield 75.2%; white solid, m.p. 173—174 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.46 (s, 1H, CONHAr), 8.55 (dd, ^4J=1.2 Hz, J=4.8 Hz, 1H, Ar-H), 8.26 (dd, ^4J=1.2 Hz, J=8.0 Hz, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.70 (dd, J=4.6, 8.2 Hz, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.25 (s, 2H, Ar-H), 2.18 (s, 3H, Ar-CH_3). HRMS calcd for $C_{17}H_{11}Cl_2N_5O$ ([M — H] $^-$) 370.0268, found 370.0272.

6g: Yield 45.7%; white solid, m.p. 98—101 ℃; ^{1}H NMR (400 MHz, $CHCl_3$) δ: 8.50 (dd, ^4J=2.0 Hz, J=6.4 Hz, 1H, Ar-H), 8.20 (s, 1H, CONH), 8.10 (s, 1H, Ar-H), 8.03—8.02 (m, 2H, Ar-H), 7.98 (dd, ^4J=2.0 Hz, J=10.8 Hz, 1H, Ar-H), 7.51 (dd, J=6.0, 10.8 Hz, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 2.41 (s, 3H, Ar-CH_3). HRMS calcd for $C_{17}H_{11}ClN_6O_3$ ([M—H]$^-$) 381.0508, found 381.0507.

6h: Yield 48.0%; white solid, m.p. 202—204 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.87 (s, 1H, CONHAr), 8.56 (dd, ^4J=1.2 Hz, J=4.8 Hz, 1H, Ar-H), 8.26 (dd, ^4J=1.2 Hz, J=8.0 Hz, 1H, Ar-H), 8.27 (d, ^4J=1.2 Hz, J=8.0 Hz, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.70 (dd, J=4.8, 8.2 Hz, 1H, Ar-H). HRMS calcd for $C_{16}H_7Cl_4N_5O$ ([M — H] $^-$) 423.9932, found 423.9331.

6i: Yield 50.4%; white solid, m.p. 187—189 ℃; ^{1}H NMR (400 MHz, $CHCl_3$) δ: 8.48 (d, J=4.8 Hz, 1H, Ar-H), 7.92 (d, J=8.0 Hz, 1H, Ar-H), 7.91 (s, 1H, CONH), 7.46 (dd, J=4.8, 8.0 Hz, 1H, Ar-H), 7.38 (s, 2H, Ar-H), 7.33 (s, 1H, Ar-H). HRMS calcd for $C_{16}H_7Cl_4N_5O$ ([M−H]$^-$) 423.9332, found 423.9328.

6j: Yield 60.7%; white solid, m.p. 165—167 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (s, 1H, CONH), 8.53 (d, J=4.8 Hz, 1H, Ar-H), 7.99 (d, J=8.0 Hz, 1H, Ar-H), 7.78—7.76 (m, 1H, Ar-H), 7.52 (dd, J=4.8, 8.4 Hz, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 6.97—6.90 (m, 1H, Ar-H). HRMS calcd for $C_{16}H_7ClF_3N_5O$ ([M − H]$^-$) 376.0219, found 376.0219.

6k: Yield 68.5%; white solid, m.p. 180—182 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, J=4.4 Hz, 1H, Ar-H), 7.92 (d, J=8.0 Hz, 1H, Ar-H), 7.82 (s, 1H, CONH), 7.46 (dd, J=4.4, 7.6 Hz, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.19 (d, J=7.2 Hz, 1H, Ar-H), 6.89 (t, J=8.6 Hz, 1H, Ar-H). HRMS calcd for $C_{16}H_7BrClF_2N_5O$ ([M−H]$^-$) 435.9418, found 435.9418.

6l: Yield 80.4%; white solid, m.p. 167—169 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.81 (s, 1H, CONHAr), 8.56 (dd, ^4J=1.2 Hz, J=4.8 Hz, 1H, Ar-H), 8.30 (dd, ^4J=1.0 Hz, J=8.0 Hz, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.72 (dd, J=4.4, 8.0 Hz, 1H, Ar-H), 7.68 (d, J=8.8 Hz, 2H, Ar-H), 7.43 (d, J=8.8 Hz, 2H, Ar-H). HRMS calcd for $C_{16}H_9ClIN_5O$ ([M−H]$^-$) 447.9468, found 447.9464.

6m: Yield 65.8%; white solid, m.p. 220—222 ℃ (lit.[11] m.p. 182—184 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.34 (s, 1H, CONHAr), 8.49 (dd, ^4J=1.4 Hz, J=4.6 Hz, 1H, Ar-H), 7.91 (dd, ^4J=1.4 Hz, J=8.0 Hz, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 7.72 (dd, J=4.6, 8.2 Hz, 1H, Ar-H), 7.25 (d, ^4J=2.0 Hz, 1H, Ar-H), 7.23 (d, ^4J=2.0 Hz, 1H, Ar-H), 6.15 (d, J=4.8 Hz, 1H, CON**H**CH_3), 2.96 (d, J=4.8 Hz, 3H, CONHC**H**$_3$), 2.17 (s, 3H, Ar-CH_3).

Biological activity

Insecticidal activities against oriental armyworm (*Mythimna separata*) were performed in the greenhouse. The bioassay was operated at (25±1) ℃ according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected according to Abbott's formula.[12] Percent mortality was evaluated. Error of the experiments was 5%. For comparative purpose, compound **6m**[11] and chlorantraniliprole were tested as control under the same conditions.

The insecticidal activities of compounds **6a**—**6m** and chlorantraniliprole were evaluated using the reported procedure.[8] 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. Then every 10 fourth-instar oriental armyworm larvae were put into each dish. Percent mortalities were evaluated 2 d after treatment. Each treatment was replicated for three times.

Results and discussion

Insecticidal activity

The insecticidal activities of compounds **6a**—**6m**

and chlorantraniliprole against oriental armyworm was summarized in Table 1.

Table 1 Insecticidal activities of compounds **6a**—**6m** and chlorantraniliprole against oriental armyworm.

Compd.	R	Larvicidal activity/%			
		200 mg/L	100 mg/L	50 mg/L	20 mg/L
6a	2-Cl	0			
6b	2-CH_3	40			
6c	2-CF_3	0			
6d	2,6-$(CH_3)_2$	100	100	50	
6e	2,6-Cl_2	100	100	60	
6f	2-CH_3,4-Cl	100	100	100	0
6g	2-CH_3,4-NO_2	100	100	0	
6h	2,4,5-Cl_3	100	100	0	
6i	2,4,6-Cl_3	100	100	100	60
6j	2,3,4-F_3	0			
6k	2,4-F_2,6-Br	100	100	100	80
6l	4-I	0			
6m	2-$CONHCH_3$, 4-Cl,6-CH_3	100	100	100	40
Chlorantraniliprole					100

In general, different substitutes in the benzene ring suggested the activity sequence as 2,4,6-substituted (**6i** and **6k**)＞2,6- or 2,4-substituted (**6d**—**6h**)＞monosubstituted (**6a**—**6c** and **6l**). The 2,3,5-trichloro substituted compound **6h** showed the activity of 100% at 100 mg/L, but the 2,3,4-trifluro substituted compound **6g** had no effect at the test concentration. Surprisingly, compounds **6i** and **6k** showed comparable higher activity than the corresponding cyano-containing anthranilic diamide **6m**, but still lower than chlorantraniliprole.

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