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Synthesis and Insecticidal Activities of Novel Anthranilic Diamides Containing Modified *N*-Pyridylpyrazoles

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In order to look for novel insecticides targeting the ryanodine receptor, four new series of anthranilic diamides containing modified *N*-pyridylpyrazoles were designed and synthesized. All of the compounds were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS. The single crystal structure of **10c** was determined by X-ray diffraction. Their insecticidal activities against oriental armyworm (*Mythimna separata*) and diamondback moth (*Plutella xylostella*) indicated that most of the compounds showed moderate to high activities at the tested concentration, while compound **19** showed comparable higher activity at the concentration of 0.125 mg/L. The preliminary structure−activity relationship (SAR) was discussed.

KEYWORDS: Anthranilic diamides; *N*-pyridylpyrazole; insecticidal activity

INTRODUCTION

In order to overcome resistance and ecobiological problems associated with conventional insecticides, there was an urgent need to discover novel potent insecticides with a new mode of action. In the past decade, Dupont discovered the anthranilic diamides (*1*), which originated from the insecticidal phthalic diamides and are highly potent and selective activators of the insect ryanodine receptor (*2*). The insect ryanodine receptor is a nonvoltage-gated calcium channel and regulates the release of intracellular calcium stores critical for muscle contraction (*3*). Until now, two representive molecules, chlorantraniliprole (Rynaxypyr; DPX-E2Y45) (**Figure 1**, **A**) and cyantraniliprole (Cyazypyr) (**B**) have been marketed (*4*, *5*). Both compounds show exceptional insecticidal activity on a broad range of Lepidopera, Coleoptera, Diptera, and Isoptera insects (*2*). In addition to larvicidal activity, chlorantraniliprole has been found to have significant ovicidal activity among some Lepidoperan pests (*6*).

Since the discovery of anthranilic diamides, most modification can be categorized into three substructures (**C**): the *N*-pyridylpyrazole moiety (a) (*7*−*9*), anthraniloyl moiety (b) (*10*−*12*), and aliphatic amide moiety (c) (*13*−*15*). In previous work, most modifications were related to parts b and c. The most successful example is cyantraniliprole (Cyazypyr) (**B**) (*10*), which replaced a cyano group of the 4-halo substituent of the former anthranilic diamides. Improved plant mobility and increased spectrum has been reported for this new compound (*2*). However, the pyrazole heterocycle in the *N*-pyridylpyrazole moiety (a), which is a key pharmacophore in this kind of compounds, was not much altered in the previous patents, and most variation was focused on the 3-substituted position, with halogen and trifluoromethyl. Other substitutes, such as alkoxy (*8*), oxime ether (*7*), and heteroaromatic substituents (*9*) were reported in individual patents. In particular, two series of general structures **D** and **E** reported by Bayer AG showed high larvicidal activity against Lepidopera (*7*) (*9*). Consequently, the general structures **F**, **G**, **H**, and **I** were designed through a bioisosterism approach (*16*). In this article, four novel series of anthranilic diamides containing *N*-pyridylpyrazole were synthesized as shown in **Schemes 1**−**7**. Their bioactivity against oriental armyworms and diamondback moths were tested accordingly. The preliminary structure−activity relationships (SAR) were also discussed.

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MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker AV 400 spectrometer (Bruker CO., Switzerland) in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard, and chemical shift values (δ) were given in ppm. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. Flash chromatography was performed with silica gel (200−300 mesh). 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. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. Chlorantraniliprole was used as the control and synthesized according to the literature (*17*).

Ethyl-4-(2-furyl)-2,4-dioxobutanoate (3). Sodium (2.58 g, 112.0 mmol) was dissolved in 300 mL of anhydrous ethanol. To this ice-cooled solution of sodium ethoxide, the orange red solution containing diethyl oxalate (32.74 g, 224.0 mmol) and 2-acetylfurane (12.32 g, 111.9 mmol) in 50 mL of anhydrous ethanol was added dropwise with stirring. The resulting mixture was stirred at room temperature, and a large amount of solid powder was formed. The reaction was stirred for 2 h until the solution became a gray solid. Then 2 mol/L hydrochloric acid was added until pH 2 was obtained. The mixture was poured into 200 mL of water, and a yellow solid was precipitated. The resulting suspension was filtered, and the filter cake was washed with 50 mL of water. After drying under infrared light, 16.30 g of ethyl-4-(2-furyl)-2,4-dioxobutanoate (**3**) was obtained as a yellow solid powder; yield, 69.3%; mp 78−80 °C (literature: mp 88−89 °C) (*18*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.50 (br s, 1H, OH), 7.69

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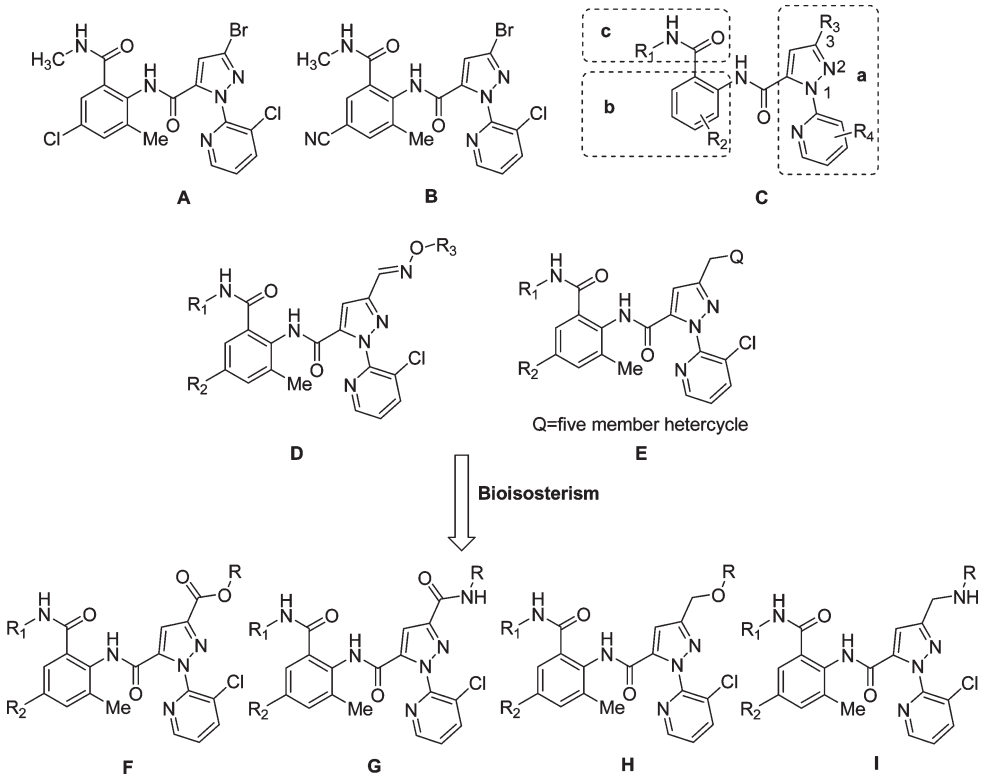
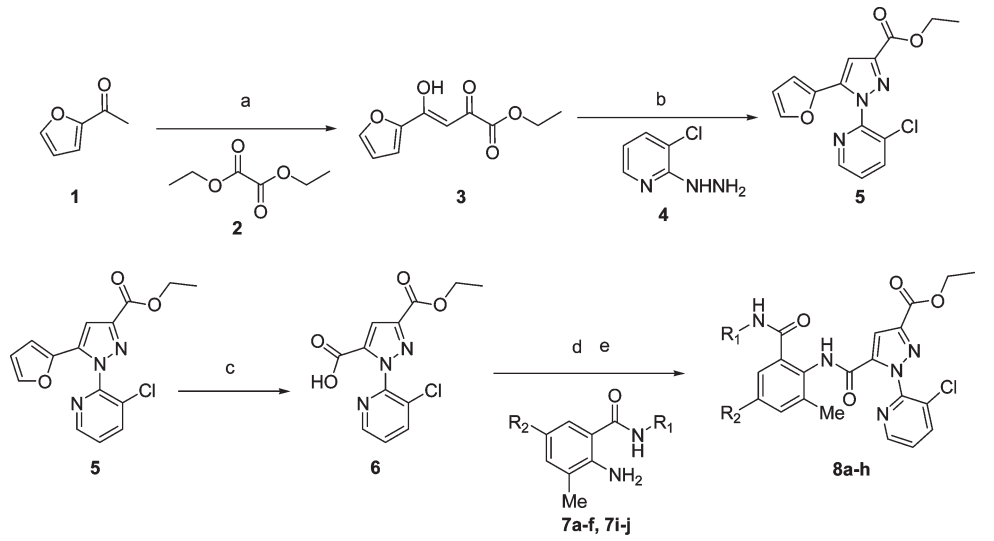


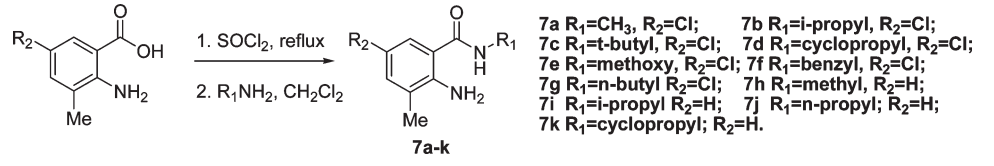
Figure 1. Chemical structures of compounds **A-I**.

Scheme 1. Synthetic Route of Title Compounds **8a**−**h**



Reagents and conditions: (a) EtOH, NaOEt; (b) AcOH, reflux; (c) $KMnO_4$, acetone/H_2O, reflux; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) **7a**−**f**, **7i**−**j**, pyridine, CH_2Cl_2.

Scheme 2. Synthesis of Compounds **7a**−**k**

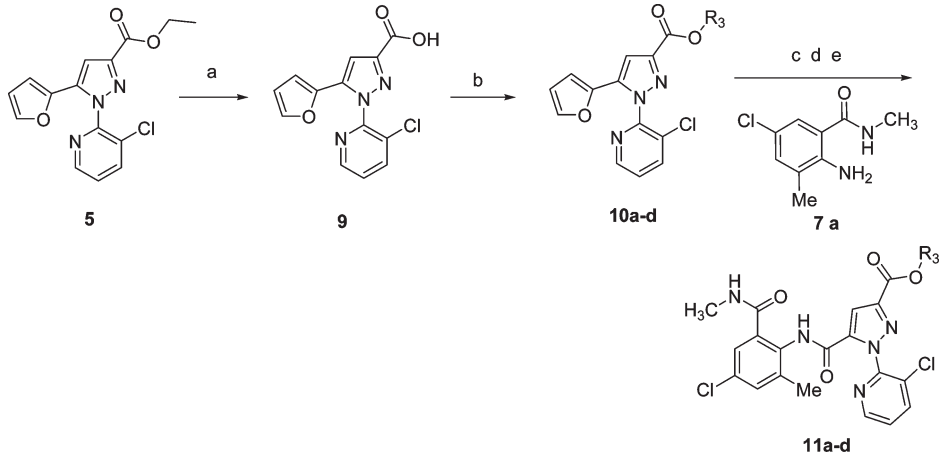


7a R_1=CH_3, R_2=Cl; **7b** R_1=i-propyl, R_2=Cl; **7c** R_1=t-butyl, R_2=Cl; **7d** R_1=cyclopropyl, R_2=Cl; **7e** R_1=methoxy, R_2=Cl; **7f** R_1=benzyl, R_2=Cl; **7g** R_1=n-butyl R_2=Cl; **7h** R_1=methyl, R_2=H; **7i** R_1=i-propyl R_2=H; **7j** R_1=n-propyl; R_2=H; **7k** R_1=cyclopropyl; R_2=H.

(s, 1H, Ar−H), 7.35 (d, 1H, $^3J_{HH}$ = 3.6 Hz, Ar−H), 6.94 (s, 1H, CH), 6.62 (dd, 1H, $^3J_{HH}$ = 1.0 Hz, $^3J_{HH}$ = 3.4 Hz, Ar−H), 4.39 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 1.41 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3).

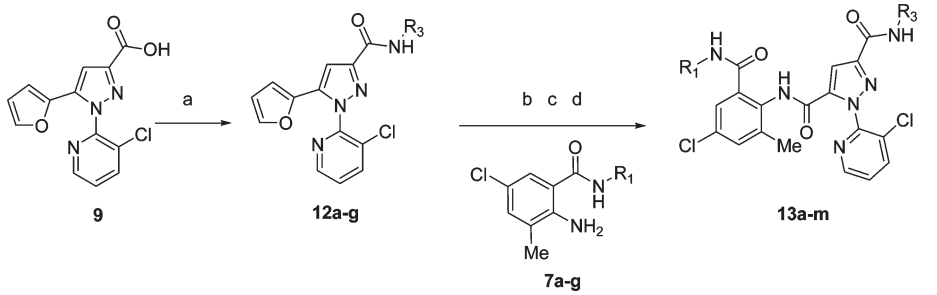
Ethyl 1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (5). Ethyl-4-(2-furyl)-2,4-dioxobutanoate (**3**) (27.34 g, 0.13 mol) and 3-chloro-2-hydrazinylpyridine (**4**) (23.25 g, 0.16 mol) were added to 350 mL of acetic acid. The resulting red solution was refluxed for 0.5 h. The mixture was permitted to cool to room temperature and then poured into 300 g of ice water with stirring. A lot of red powder was precipitated. The precipitate was filtered and washed with 100 mL of water. After drying under

Scheme 3. Synthetic Route of Title Compounds **11a−d**



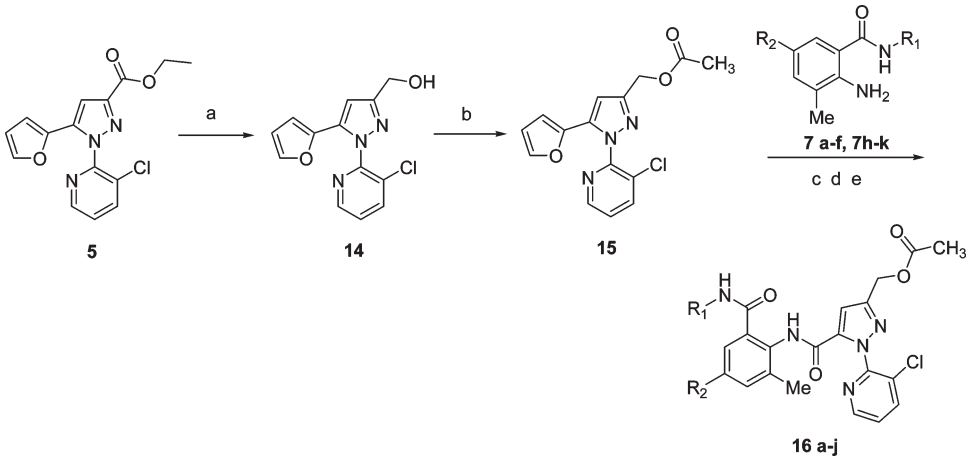
Reagents and Conditions: (a) NaOH, MeOH/H_2O; (b) alcohol, cat. DMAP, DCC, CH_2Cl_2; (c) $KMnO_4$, acetone/H_2O, reflux; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) **7a**, pyridine, CH_2Cl_2.

Scheme 4. Synthetic Route of Title Compounds **13a−m**



Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, then R_3NH_2; (b) $KMnO_4$, KH_2PO_4, acetone/H_2O, reflux; (c) $(COCl)_2$, DMF, CH_2Cl_2; (d) **7a−g**, pyridine, CH_2Cl_2.

Scheme 5. Synthetic Route of Title Compounds **16a−j**



Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) acetyl chloride, pyridine, CH_2Cl_2; (c) $KMnO_4$, acetone/H_2O, reflux; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) **7a−f**, **7h−k**, pyridine, CH_2Cl_2.

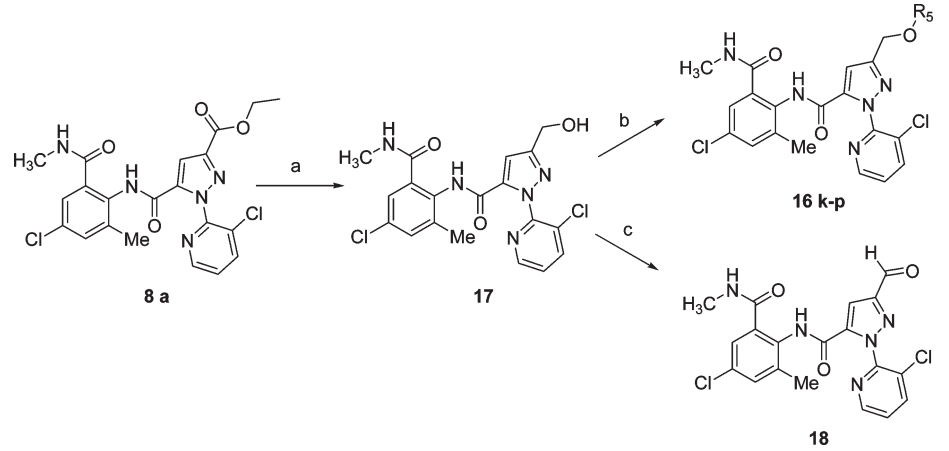
infrared light, the red powder was dissolved in 100 mL of ethyl acetate, the undissolved material was filtered, and the filtrate was concentrated in vacuo to afford a brown powder, 35.11 g; yield, 85.0%; mp 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 4.8 Hz, Ar−H), 7.94 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.4 Hz, Ar−H), 7.49 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.4 Hz, Ar−H), 7.34 (d, 1H, $^3J_{HH}$ = 1.2 Hz, Ar−H), 7.20 (s, 1H, Ar−H), 6.34 (dd, 1H, $^3J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 3.0 Hz, Ar−H), 5.99 (d, 1H, $^3J_{HH}$ = 3.2 Hz, Ar−H), 4.45 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 1.42 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3).

General Synthetic Procedure for Compounds 7a−k. 2-Amino-3-methylbenzamide derivatives **7a−k** were synthesized in moderate yield by the method reported by Dong et al. (**Scheme 2**) (*19*). The melting point and ^{1}H NMR data of **7a−d**, **7g**, and **7i−k** were consistent with the literature (*19*) (*20*).

2-Amino-5-chloro-*N*-methoxy-3-methylbenzamide (7e). Yellow solid, yield 65.0%, mp 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H, NHO), 7.15 (d, 1H, $^4J_{HH}$ = 2.4 Hz, Ar−H), 7.13 (s, 1H, Ar−H), 5.49 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 2.14 (s, 3H, Ar−CH_3).

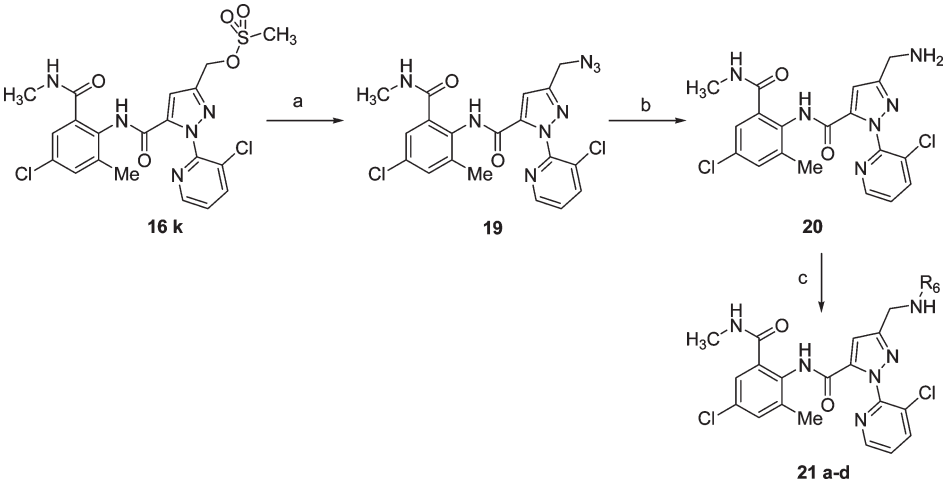
2-Amino-*N*-benzyl-5-chloro-3-methylbenzamide (7f). White solid, yield 70.3%, mp 119−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.26 (m, 5H, Ph-H), 7.18 (d, 1H, $^4J_{HH}$ = 2.4 Hz, Ar−H), 7.11 (d, 1H, $^4J_{HH}$ = 1.6 Hz, Ar−H), 6.26 (s, 1H, NH), 5.59 (s, 2H, NH_2), 4.59 (d, 2H, $^3J_{HH}$ = 5.6 Hz, CH_2), 2.15 (s, 3H, Ar−CH_3).

Scheme 6. Synthetic Route of Title Compounds **16k−p** and **18**



Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) acid chloride or acid anhydride, pyridine, CH_2Cl_2; (c) PCC, CH_2Cl_2.

Scheme 7. Synthetic Route of Title Compounds **21a−d**



Reagents and conditions: (a) NaN_3, acetone/H_2O, room temperature; (b) H_2, 10% Pd/C, MeOH, room temperature; (c) acid chloride or acid anhydride, pyridine, CH_2Cl_2.

2-Amino-*N*,3-dimethylbenzamide (7h). White solid, yield 50.1%, mp 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.13 (d, 1H, $^3J_{HH}$ = 7.2 Hz, Ar−H), 6.59 (t, 1H, $^3J_{HH}$ = 7.6 Hz, Ar−H), 6.06 (s, 1H, NH), 5.57 (s, 2H, NH_2), 2.98 (d, 3H, $^3J_{HH}$ = 4.8 Hz, NH*CH*$_3$), 2.17 (s, 3H, Ar−CH_3).

General Synthetic Procedure for Compounds 8a−h. *1-(3-Cl-2-Pyridinyl)-3-ethoxycarbonyl-1H-pyrazole-5-carboxylic Acid* (**6**). To a mixture of ethyl 1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (**5**) (6.35 g, 20.0 mmol) in 100 mL of acetone and 100 mL of water, $KMnO_4$ (22.12 g, 0.140 mol) was added in small portions. During the addition, the temperature rose, and the mixture was refluxed without additional heating. When the addition was complete, the reaction was heated and refluxed for 30 min. The resulting mixture was filtered and washed with 50 mL of hot water. The filtrate was acidified with 2 mol/L HCl and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were dried with Na_2SO_4 and evaporated to give the crude product, which was further purified with recrystallization (ethanol) to give the title compound as a yellow solid, 3.01 g; yield 50.1%, mp 234−236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 4.6 Hz, Ar−H), 7.92 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.55 (s, 1H, Ar−H), 7.47 (dd, 1H, $^3J_{HH}$ = 4.6 Hz, $^3J_{HH}$ = 8.2 Hz, Ar−H), 4.45 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 1.41 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3).

Carboxylic acid (**6**) (1.0 mmol) and oxalyl chloride (2.0 mmol) were added to 20 mL of CH_2Cl_2, followed by one drop of DMF. The mixture was stirred for 1 h at room temperature. Then the solvent was evaporated and dissolved with 10 mL of THF. The solution was added dropwise to an ice-cold solution of 2-amino-3-methylbenzamide derivatives (**7a−f**, **7i−j**) (1.0 mmol) and pyridine (1.1 mmol) in 10 mL of THF. The reaction was stirred at room temperature for 1 h and then evaporated, dissolved in ethyl acetate (30 mL), and washed with 1 mol/L hydrochloric acid (2 × 30 mL) and saturated sodium bicarbonate solution (2 × 30 mL). The organic layer was dried and evaporated. Silica gel flash chromatography, eluting with a gradient of petroleum ether/ethyl acetate (1:1 to 2:1), gave the title compounds **8a−h**.

1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylic Acid (9). Compound (**5**) (23.13 g, 72.8 mmol) was added to a mixture of 100 mL of methanol and 50 mL of water and NaOH (3.50 g, 87.4 mmol). The resulting red solution was stirred at room temperature for 6 h, then most of the solvent was evaporated. The concentrated mixture was diluted with 100 mL water and washed with ethyl acetate (30 mL × 3). The aqueous layer was acidified with 2 mol/L hydrochloric acid to pH 2. The yellow precipitate was collected by filtration, washed with water (30 mL), and then dried to give pyrazolecarboxylic acid (**9**), 16.01 g; yield 75.9%, mp 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 4.8 Hz, Ar−H), 7.97 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.52 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.35 (d, 1H, $^3J_{HH}$ = 1.2 Hz, Ar−H), 7.26 (s, 1H, Ar−H), 6.35 (dd, 1H, $^3J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 3.6 Hz, Ar−H), 6.03 (d, 1H, $^3J_{HH}$ = 3.2 Hz, Ar−H).

General Synthetic Procedure for 1-(3-*Cl*-2-Pyridinyl)-5-(2-furyl)-1*H*-pyrazole-3-carboxylic Acid Ester 10a−d. DCC (1.1 mmol) was added to a yellow solution of compound **9** (1.0 mmol), alkyl alcohol (2.0 mmol), and DMAP (0.1 mmol) in 20 mL of dichloromethane. After 4 h, the reaction was complete, then the mixture was filtered, and the filtrate was evaporated. The residue was applied to column chromatography by eluting with petroleum ether/ethyl acetate (3:1) to give title compounds **10a−d**.

Butyl 1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (10a). Yield 86.5%, white solid, mp 66−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, $^3J_{HH}$ = 4.4 Hz, Ar−H), 7.93 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.51−7.48 (m, 1H, Ar−H), 7.34 (s, 1H, Ar−H), 7.19 (s, 1H, Ar−H), 6.64 (d, 1H, $^3J_{HH}$ = 1.6 Hz, Ar−H), 5.99 (s, 1H, Ar−H), 4.39 (t, 2H, $^3J_{HH}$ = 6.8 Hz, OCH_2), 1.82−1.74 (m, 2H, OCH_2CH_2), 1.51−1.41 (m, 2H, $CH_2CH_2CH_3$), 0.96 (t, 3H, $^3J_{HH}$ =7.4 Hz, $CH_2CH_2CH_3$).

Isopropyl 1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (10b). Yield 83.5%, white solid, mp 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, $^3J_{HH}$ = 4.4 Hz, Ar−H), 7.93 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.49 (dd, 1H, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 7.8 Hz, Ar−H), 7.34 (s, 1H, Ar−H), 7.19 (s, 1H, Ar−H), 6.33 (s, 1H, Ar−H), 5.98 (d, 1H, $^3J_{HH}$ = 2.8, Ar−H), 5.37−5.31 (m, 1H, OCH), 1.40 (dd, 6H, $^3J_{HH}$ = 6.0 Hz, $CH(CH_3)_2$).

Benzyl 1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (10c). Yield 80.1%, white solid, mp 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, 1H, $^3J_{HH}$ = 4.0 Hz, Ar−H), 7.93 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.49−7.47 (m, 3H, Ar−H), 7.39−7.33 (m, 4H, Ar−H), 7.20 (s, 1H, Ar−H), 6.33 (d, 1H, $^3J_{HH}$ = 1.6, Ar−H), 5.97 (d, 1H, $^3J_{HH}$ = 2.8 Hz, Ar−H), 5.43 (s, 2H, OCH_2).

Cyclohexyl 1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (10d). Yield 83.0%, white solid, mp 133−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, $^3J_{HH}$ = 4.0 Hz, Ar−H), 7.93 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ar−H), 7.49 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 7.6 Hz, Ar−H), 7.34 (s, 1H, Ar−H), 7.18 (s, 1H, Ar−H), 6.33 (d, 1H, $^3J_{HH}$ = 1.2 Hz, Ar−H), 5.98 (s, 1H, Ar−H), 5.10−5.05 (m, 1H, OCH), 2.04−2.01(m, 2H, cyclohexyl), 1.82−1.79 (m, 2H, cyclohexyl), 1.64−1.56 (m, 3H, cyclohexyl), 1.46−1.37 (m, 2H, cyclohexyl),1.30−1.25 (m, 1H, cyclohexyl).

General Synthetic Procedure for Compounds 11a−d. Compounds **11a−d** were prepared from corresponding pyrazolecarboxylic acid ester **10a−d** by the procedure reported for compound **8**. The overall yield was based on ester **10a−d**.

General Synthetic Procedure for Compounds 12a−g. To a suspension of 1-(3-*Cl*-2-pyridinyl)-5-(2-furyl)-1*H*-pyrazole-3-carboxylic acid (**9**) (1.50 g, 5.2 mmol) in 25 mL of dichloromethane was added oxalyl chloride (7.8 mmol) and a drop of dimethylformamide. After stirring for 3 h, the solution became red and clear, then the solvent was evaporated. The resulting acyl chloride was dissolved in 20 mL of THF and added dropwise to a 0 °C solution of alkyl amine or aniline (15.6 mmol) in 30 mL of THF. The reaction was complete after 1 h of stirring at room temperature. Then most of the solvent was evaporated, and 40 mL of 1 mol/L hydrochloric acid solution was added to the residue. The mixture was extracted with ethyl acetate; the extracts were washed with 1 mol/L hydrochloric acid solution, saturated sodium bicarbonate solution, and brine. The ethyl acetate solution was dried with Na_2SO_4 and evaporated to give the title compounds **12a−g**.

1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-*N*-methyl-1*H*-pyrazole-3-carboxamide (12a). Yield 85.6%, yellow solid, mp 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, 1H, $^3J_{HH}$ = 4.4, Ar−H), 7.96 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.51 (dd, 1H, $^3J_{HH}$ = 4.6 Hz, $^3J_{HH}$ = 7.8 Hz, Ar−H), 7.32 (s, 1H, Ar−H), 7.20 (s, 1H, Ar−H), 6.93 (s, 1H, CONH), 6.34 (s, 1H, Ar−H), 6.05 (d, 1H, $^3J_{HH}$ = 3.2 Hz, Ar−H), 2.98 (d, 1H, $^3J_{HH}$ = 5.2, CH_3).

***N*-Benzyl-1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxamide (12b).** Yield 89.0%, yellow solid, mp 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, $^3J_{HH}$ = 3.6 Hz, Ar−H), 7.94 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.49 (dd, 1H, $^3J_{HH}$ = 4.4 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.36−7.23 (m, 8H, Ar−H, CONH), 7.15 (s, 1H, Ar−H), 6.80 (s, 1H, CONH), 6.34 (d, 1H, $^3J_{HH}$ = 1.6 Hz, Ar−H), 6.05 (d, 1H, $^3J_{HH}$ = 3.2 Hz, Ar−H), 4.63 (d, 2H, $^3J_{HH}$ = 6.0 Hz, CH_2).

1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-*N*-isopropyl-1*H*-pyrazole-3-carboxamide (12c). Yield 88.7%, yellow solid, mp 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (dd, 1H, $^4J_{HH}$= 1.4 Hz, $^3J_{HH}$ = 4.6 Hz, Ar−H), 7.94 (dd, 1H, $^4J_{HH}$ = 1.2 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.51 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.31 (d, 1H, $^3J_{HH}$ = 1.6 Hz, Ar−H), 7.19 (s, 1H, Ar−H), 6.77 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CONH), 6.34 (dd, 1H, $^3J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 3.4 Hz, Ar−H), 6.04 (d, 1H, $^3J_{HH}$ = 3.6 Hz, Ar−H), 4.34−4.23 (m, 1H, CH), 1.24 (d, 6H, $^3J_{HH}$ = 6.8 Hz, $CH(CH_3)_2$).

***N*-*tert*-Butyl-1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxamide (12d).** Yield 93.1%, yellow solid, mp 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 4.4 Hz, Ar−H), 7.95 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.51 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.31 (d, 1H, $^4J_{HH}$ = 1.6 Hz, Ar−H), 7.15 (s, 1H, Ar−H), 6.81 (s, 1H, CONH), 6.34 (dd, 1H, $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 3.4 Hz, Ar−H), 6.03 (d, 1H, $^3J_{HH}$ = 3.6 Hz, Ar−H), 1.46 (s, 9H, $C(CH_3)_3$).

1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-*N*-phenyl-1*H*-pyrazole-3-carboxamide (12e). Yield 87.6%, yellow solid, mp 179−181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H, CONH), 8.62 (d, 1H, $^3J_{HH}$ = 4.4 Hz, Ar−H), 7.99 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.68 (d, 2H, $^3J_{HH}$ = 7.6 Hz, Ar−H), 7.54 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.37−7.33 (m, 3H, Ar−H), 7.29 (s, 1H, Ar−H), 7.12 (t, 1H, $^3J_{HH}$ = 7.4 Hz, Ar−H), 6.36 (d, 1H, $^3J_{HH}$ = 1.2 Hz, Ar−H), 6.08 (d, 1H, $^3J_{HH}$ = 3.2 Hz, Ar−H).

1-(3-Chloropyridin-2-yl)-*N*-cyclohexyl-5-(furan-2-yl)-1*H*-pyrazole-3-carboxamide (12f). Yield 92.0%, yellow solid, mp 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, 1H, $^3J_{HH}$ = 4.8 Hz, Ar−H), 7.95 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ar−H), 7.50 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.30 (s, 1H, Ar−H), 7.19 (s, 1H, Ar−H), 6.81 (d, 1H, $^3J_{HH}$ = 7.6 Hz, CONH), 6.33 (dd, 1H, $^3J_{HH}$ = 1.8, $^3J_{HH}$ = 3.4 Hz, Ar−H), 6.04 (d, 1H, $^3J_{HH}$ = 2.8, $^3J_{HH}$ = 7.6 Hz, Ar−H), 4.00−3.92 (m, 1H, NH*CH*), 2.04−2.00 (m, 2H, cyclohexyl), 1.76−1.61 (m, 3H, cyclohexyl), 1.44−1.35 (m, 2H, cyclohexyl), 1.27−1.18 (m, 3H, cyclohexyl).

***N*-Butyl-1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxamide (12g).** Yield 91.2%, white solid, mp 101−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 4.6 Hz, Ar−H), 7.95 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.50 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.31 (d, 1H, $^3J_{HH}$ = 1.6 Hz, Ar−H), 7.19 (s, 1H, Ar−H), 6.92 (br s, 1H, CONH), 6.34 (dd, 1H, $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 3.4 Hz, Ar−H), 6.05 (s, 1H, $^3J_{HH}$ = 3.2 Hz, Ar−H), 3.43 (q, 2H, $^3J_{HH}$ = 6.8 Hz, NHCH_2), 1.61−1.54 (m, 2H, $CH_2CH_2CH_2$), 1.44−1.35 (m, 2H, $CH_2CH_2CH_3$), 0.93 (t, 3H, $^3J_{HH}$ = 7.4 Hz, CH_3).

General Synthetic Procedure for Compounds 13a−m. To a mixture of compound **12** (10.0 mmol) and KH_2PO_4 (50.0 mmol) in 30 mL of acetone and 30 mL of water, $KMnO_4$ (50.0 mmol) was added in two portions. The mixture was then refluxed for 0.5 h and filtered. The filter cake was washed with 50 mL of hot water. The filtrate was acidified with 2 mol/L HCl and extracted with CH_2Cl_2 (3 × 25 mL). The extracts were dried with Na_2SO_4 and evaporated. The crude pyrazolecarboxylic acid was obtained as a yellow powder (2.50 g), which was used directly in the next step without further purification.

Oxalyl chloride (1.5 mmol) was added to a mixture of the crude pyrazolecarboxylic acid (1.0 mmol) in 15 mL of dichloromethane, followed by a drop of dimethylformamide. The mixture was stirred at room temperature for 1 h, and the solvent was evaporated. The residue was dissolved in 15 mL of dichloromethane, and the solution was added dropwise to an ice-cold solution of 2-amino-3-methylbenzamide derivatives (**7a−g**) (1.0 mmol) and pyridine (1.0 mmol) in 20 mL of dichloromethane. After 2 h, the reaction was complete, and 30 mL of dichloromethane was added. The solution was washed with 1 mol/L hydrochloric acid solution, saturated sodium bicarbonate solution, and brine. The dichloromethane solution was dried and evaporated, and the residue was applied to a flash column chromatography by eluting with petroleum ether/ethyl acetate (1:2) to give title compounds **13a−m**. The overall yield was the based on **12a−g**.

(1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazol-3-yl)methanol (14). To a 0 °C solution of ethyl 1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (**5**) (3.0 mmol) in 30 mL of THF, $LiAlH_4$ (6.0 mmol) was added in small portions. The reaction was mentained at 0 °C and monitored with TLC. After 0.5 h, the reaction was complete, and the mixture was poured into 100 g of ice-water. The yellow suspension was acidified with 1 mol/L hydrochloric acid solution until pH 7 was obtained. The aqueous layer was extracted with ethyl acetate, and the extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was subjected to flash chromatography on silica gel with petroleum ether/ethyl acetate (1:1) to give the title compound as a white solid. Yield 60.3%, mp 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 4.6 Hz, Ar−H), 7.92 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 8.2 Hz, Ar−H), 7.44 (dd, 1H, $^3J_{HH}$ = 4.6 Hz, $^3J_{HH}$ = 8.2 Hz, Ar−H), 7.32 (d, 1H, $^3J_{HH}$ = 1.2 Hz, Ar−H), 6.71 (s, 1H, Ar−H), 6.32 (dd, 1H, $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 3.4 Hz, Ar−H), 5.98 (s, $^3J_{HH}$ = 3.6 Hz, Ar−H), 4.80 (s, 2H, Ar−CH_2), 2.20 (br s, 1H, OH).

(1-(3-Chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazol-3-yl)methyl Acetate (15). A solution of acetyl chloride (1.5 mmol) in 10 mL of dichloromethane was added dropwise to an ice-cold solution of (1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazol-3-yl)methanol (**14**) (1.5 mmol) and triethylamine (1.5 mmol) in 20 mL of dichloromethane. The resulting mixture was warmed to room temperature and monitored with TLC. The reaction was then quenched with water, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined extracts were washed with 1 mol/L hydrochloric acid solution, dried over anhydrous sodium sulfate, and concentrated to give the title compound **15** as a yellow oil. Yield 87.6%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (dd, 1H, $^4J_{HH}$ = 2.2 Hz, $^3J_{HH}$ = 6.2 Hz, Ar−H), 7.93 (dd, 1H, $^4J_{HH}$ = 2.0 Hz, $^3J_{HH}$ = 10.8 Hz, Ar−H), 7.46 (dd, 1H, $^3J_{HH}$ = 6.2 Hz, $^3J_{HH}$ = 10.6 Hz, Ar−H), 7.32 (d, 1H, $^3J_{HH}$ = 2.0 Hz, Ar−H), 6.74 (s, 1H, Ar−H), 6.33 (dd, 1H, $^3J_{HH}$ = 2.6 Hz, $^3J_{HH}$ = 4.6 Hz, Ar−H), 5.22 (s, 2H, Ar−CH_2), 2.14 (s, 3H, CH_3)

General Synthetic Procedure for Compounds 16a−j. The title compounds were prepared from compound **15** by the procedure described for compounds **13a−m** with **7a−f** and **7h-k** substituted for **7a−g**. The overall yield was based on that of compound **15**.

***N*-(2-(Methylcarbamoyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-3-(hydroxymethyl)-1*H*-pyrazole-5-carboxamide (17).** To a solution of compound **8a** (1.0 mmol) in 20 mL of THF at 0 °C was added lithium aluminum hydride (2.0 mmol) in small portions. After stirring for 0.5 h at 0 °C, the mixture was poured into 100 mL of ice-water, then acidified with 1 mol/L HCl. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was subjected to flash chromatography on silica gel with ethyl acetate to give the title compound **17** as a white solid; yield 85.0%, mp 131−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H, CONHAr), 8.41 (d, 1H, $^3J_{HH}$ = 4.4 Hz, Ar−H), 7.82 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.35 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.29 (s, 1H, Ar−H), 6.99 (s, 1H, Ar−H), 6.97 (s, 1H, Ar−H), 6.53 (s, 1H, *NH*CH_3), 4.79 (s, 2H, Ar−CH_2), 3.99 (br s, 1H, OH), 2.82 (d, 3H, $^3J_{HH}$ = 4.0 Hz, NH*CH_3*), 2.01 (s, 3H, Ar−CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 157.9, 155.2, 150.0, 146.6, 138.7, 137.7, 136.9, 133.7, 131.6, 130.4, 129.2, 125.4, 125.0, 124.9, 108.1, 58.5, 27.0, 17.9. HRMS calcd for $C_{19}H_{17}{}^{35}Cl_2N_5O_3Na$ ([M + Na] $^+$), 456.0595; found, 456.0601; calcd for $C_{19}H_{17}{}^{35}Cl^{37}ClN_5O_3Na$ ([M + Na] $^+$), 458.0566; found, 458.0572; calcd for $C_{19}H_{17}{}^{37}Cl_2N_5O_3Na$ ([M + Na] $^+$), 460.0555; found, 460.0547.

General Synthetic Procedure for Compounds 16k−p. To a solution of compound **17** (0.50 mmol) in 20 mL of dichloromethane at 0 °C was added triethylamine (0.50 mmol), then acid chloride or acid anhydride (0.50 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and monitored with TLC. Then 20 mL of water was added to quench the reaction followed by extracting the aqueous layer with dichloromethane (2 × 20 mL). The combined extracts were sequentially washed with 1 mol/L HCl, saturated sodium bicarbonate solution, and brine. The resulting solution was dried and evaporated to give the crude residue, which was further purified by flash chromatography on silica gel with petroleum/ethyl acetate (1:3) to afford the title compounds **16k−p**.

***N*-(2-(Methylcarbamoyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-3-formyl-1*H*-pyrazole-5-carboxamide (18).** A solution of compound **17** (0.3 mmol) in 20 mL of dichloromethane was added in one portion to the suspension of PCC (pyridinium chlorochromate, 0.6 mmol) in 20 mL of dichloromethane. The mixture was stirred for 1.5 h at room temperature, and 20 mL of ether was added, then the mixture was stirred for an additional 0.5 h. The resulting black suspension was filtered, and the insoluble residue was washed with ether whereupon it became a black granular solid. The combined organic solution was passed through a short pad of silica gel, and the colorless solution was evaporated to afford the title compound as a white solid; yield 83.1%, mp 184−187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H, CHO), 10.11 (s, 1H, CONHAr), 8.50 (d, 1H, $^3J_{HH}$ = 4.4 Hz, Ar−H), 7.91 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.67 (s, 1H, Ar−H), 7.44 (dd, 1H, $^3J_{HH}$ = 4.6 Hz, $^3J_{HH}$ = 7.8 Hz, Ar−H), 7.20 (s, 1H, Ar−H), 7.18 (s, 1H, Ar−H), 6.24 (d, 1H, $^3J_{HH}$ = 3.6 Hz, CO*NH*CH_3), 2.96 (d, 3H, $^3J_{HH}$ = 4.4 Hz, NH*CH_3*), 2.19 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 168.4, 156.9, 151.8, 149.3, 147.0 (2C), 139.0 (2C), 138.6, 132.8, 132.3, 131.4, 128.9, 126.1, 124.5, 107.2, 26.9, 18.7. HRMS calcd for $C_{19}H_{15}{}^{35}Cl_2N_5O_3Na$ ([M + Na] $^+$), 454.0447; found, 454.0444; calcd for $C_{19}H_{15}{}^{35}Cl^{37}ClN_5O_3Na$ ([M + Na] $^+$), 456.0428; found, 456.0416; calcd for $C_{19}H_{15}{}^{37}Cl_2N_5O_3Na$ ([M + Na] $^+$), 458.0433; found, 458.0391.

***N*-(2-(Methylcarbamoyl)-4-chloro-6-methylphenyl)-3-(azidomethyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (19).** To a solution of compound **16k** (0.5 mmol) in acetone (10 mL) and water (10 mL) at room temperature, sodium azide (1.5 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 20 h. Additional water (30 mL) was added, and a lot of white solid was precipitated. The mixture was filtered, washed with water, and dried to afford the title compound as a white solid; yield 85.0%, mp 151−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H, CONHAr), 8.47 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 4.8 Hz, Ar−H), 7.86 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.38 (dd, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.23 (s, 1H, Ar−H), 7.21 (s, 1H, Ar−H), 7.13 (s, 1H, Ar−H), 6.24 (s, 1H, *NH*CH_3), 4.52 (s, 2H, Ar−CH_2), 2.93 (d, 3H, $^3J_{HH}$ = 4.8 Hz, NH*CH_3*), 2.19 (s, 3H, Ar−CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 157.2, 149.6, 148.9, 146.8, 138.9, 138.6, 138.4, 132.9, 132.4, 132.0, 131.8, 129.1, 125.6, 124.4, 107.5, 47.8, 26.9, 18.9. HRMS calcd for $C_{19}H_{16}{}^{35}Cl_2N_8O_2Na$ ([M + Na] $^+$), 481.0661; found, 481.0666; calcd for $C_{19}H_{16}{}^{35}Cl^{37}ClN_8O_2Na$ ([M + Na] $^+$), 483.0634; found, 483.0637; calcd for $C_{19}H_{16}{}^{37}Cl_2N_8O_2Na$ ([M + Na] $^+$), 485.0609; found, 485.0612.

***N*-(2-(Methylcarbamoyl)-4-chloro-6-methylphenyl)-3-(aminomethyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (20).** A mixture of compound **19** (2.3 mmol) and 10% Pd/C (0.10 g) in methanol (20 mL) was stirred under H_2 at room temperature for 4 h, then filtered. The resulting solution was evaporated to give the crude product. It was further purified by recrystallization with the mixture solvent of ethyl acetate/petroleum ether (1:1) to give the title compound as a white solid; yield 90.3%, mp 139−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (br s, 1H, CONHAr), 8.45 (dd, 1H, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 4.8 Hz, Ar−H), 7.83 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.35 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 8.0 Hz, Ar−H), 7.17 (s, 1H, Ar−H), 7.16 (s, 1H, Ar−H), 7.06 (s, 1H, Ar−H), 6.35 (s, 1H, *NH*CH_3), 4.03 (s, 2H, *CH_2*NH_2), 2.90 (d, 3H, $^3J_{HH}$ = 4.8, NH*CH_3*), 2.14 (s, 3H, Ar−CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 157.2, 149.6, 148.9, 146.8, 138.9, 138.6, 138.4, 132.9, 132.4, 132.0, 131.8, 129.1, 125.6, 124.4, 107.5, 47.8, 26.9, 18.9. HRMS calcd for $C_{19}H_{18}{}^{35}Cl_2N_6O_3Na$ ([M + Na] $^+$), 433.0935; found, 433.0941; calcd for $C_{19}H_{18}{}^{35}Cl^{37}ClN_6O_3Na$ ([M + Na] $^+$), 435.0905; found, 435.0913; calcd for $C_{19}H_{18}{}^{37}Cl_2N_6O_3Na$ ([M + Na] $^+$), 437.0878; found, 437.0886.

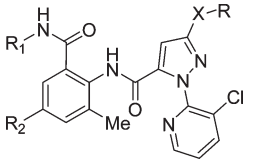
General Synthetic Procedure for Compounds 21a−d. To a solution of compound **20** (0.4 mmol) in 15 mL of THF at 0 °C was added triethylamine (0.4 mmol), then acid chloride or acid anhydride (0.4 mmol) in 10 mL of THF was added dropwise. The resulting mixture was stirred at room temperature for 2 h. Cold 1 mol/L HCl (30 mL) was added to quench the reaction, and the mixture was stirred for an additional 10 min. A lot of white solid was precipated, then the mixture was filtered, washed with 1 mol/L HCl, and dried to give the crude residue, which was further purified by recrystallization with the mixture solvent of ethyl acetate/petroleum ether (2:1) to give the title compounds **21a−d**.

Biological Assay. Insecticidal activities against oriental armyworms (*Mythimna separata*) and diamondback moths (*Plutella xylostella*) were performed on test organisms reared in a greenhouse. The bioassay was replicated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected applying Abbott's formula (*21*). Evaluation was based on a percentage scale of 0−100, where 0 equals no activity, and 100 equals total kill. Error of the experiments was 5%. For comparative purposes, chlorantraniliprole was tested as control under the same conditions. The insecticidal activity is summarized in **Tables 1**, **2**, and **3**.

Larvicidal Activity against Oriental Armyworms. The insecticidal activities of compounds **8a−h**, **11a−d**, **13a−m**, **17**, **16a−p**, **19**, **20**, and **21a−d** and chlorantraniliprole were evaluated using the reported procedure (*17*). The insecticidal activity against oriental armyworms was tested by foliar application; individual corn (Tangyu 10, *Zea mays L.*) 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 with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was replicated three times.

Larvicidal Activity against Diamondback Moths. The larvicidal activity of compounds **13c−d**, **16a−d**, **16h**, **19**, and **21c** and the control chlorantraniliprole was tested by the leafdip method. At first, a solution of each test sample in DMF (AR, purchased from Alfa

Table 1. Insecticidal Activities of Compounds **8a**−**h**, **11a**−**d**, **13a**−**m**, **16a**−**p**, **17**, **18**, **19**, **20**, and **21a**−**d** and Chlorantraniliprole against Oriental Armyworms



					larvicidal activity (%) at a concentration of (mg/L)						
comp.	R_1	R_2	X	R	200	100	50	20	10	5	2.5
8a	CH_3	Cl	COO	CH_2CH_3	80						
8b	$CH(CH_3)_2$	Cl	COO	CH_2CH_3	70						
8c	$C(CH_3)_3$	Cl	COO	CH_2CH_3	100	100	70				
8d	cyclopropyl	Cl	COO	CH_2CH_3	100	100	80				
8e	OCH_3	Cl	COO	CH_2CH_3	50						
8f	$PhCH_2$	Cl	COO	CH_2CH_3	20						
8g	$CH(CH_3)_2$	H	COO	CH_2CH_3	100	100	60				
8h	$(CH_2)_2CH_3$	H	COO	CH_2CH_3	100	100	60				
11a	CH_3	Cl	COO	$(CH_2)_3CH_3$	80						
11b	CH_3	Cl	COO	$CH(CH_3)_2$	80						
11c	CH_3	Cl	COO	$PhCH_2$	100	40					
11d	CH_3	Cl	COO	cyclohexyl	100	40					
13a	CH_3	Cl	CONH	CH_3	100	60					
13b	$CH(CH_3)_2$	Cl	CONH	CH_3	100	60					
13c	$C(CH_3)_3$	Cl	CONH	CH_3	100	100	100	100	100	40	
13d	cyclopropyl	Cl	CONH	CH_3	100	100	100	100	20		
13e	OCH_3	Cl	CONH	CH_3	0						
13f	$PhCH_2$	Cl	CONH	CH_3	100	60					
13g	$(CH_2)_3CH_3$	Cl	CONH	CH_3	100	20					
13h	CH_3	Cl	CONH	$PhCH_2$	100	100	100	20			
13i	CH_3	Cl	CONH	$CH(CH_3)_2$	100	100	100	60			
13j	CH_3	Cl	CONH	$C(CH_3)_3$	100	100	100	40			
13k	CH_3	Cl	CONH	Ph	100	100	100	0			
13l	CH_3	Cl	CONH	cyclohexyl	0						
13m	CH_3	Cl	CONH	$(CH_2)_3CH_3$	100	100	100	20			
16a	CH_3	Cl	CH_2O	$COCH_3$	100	100	100	100	0		
16b	$CH(CH_3)_2$	Cl	CH_2O	$COCH_3$	100	100	100	100	20		
16c	$C(CH_3)_3$	Cl	CH_2O	$COCH_3$	100	100	100	100	100	20	
16d	cyclopropyl	Cl	CH_2O	$COCH_3$	100	100	100	100	0		
16e	OCH_3	Cl	CH_2O	$COCH_3$	100	0					
16f	$PhCH_2$	Cl	CH_2O	$COCH_3$	100	100	100	40			
16g	CH_3	H	CH_2O	$COCH_3$	100	60					
16h	$CH(CH_3)_2$	H	CH_2O	$COCH_3$	100	100	100	100	0		
16i	cyclopropyl	H	CH_2O	$COCH_3$	100	100	100	40			
16j	$(CH_2)_2CH_3$	H	CH_2O	$COCH_3$	100	100	100	40			
16k	CH_3	Cl	CH_2O	SO_2CH_3	100	100	100	40			
16l	CH_3	Cl	CH_2O	Tosyl	100	100	100	80			
16m	CH_3	Cl	CH_2O	$COCF_3$	100	100	100	20			
16 n	CH_3	Cl	CH_2O	$CO(CH_2)_3Cl$	100	100	100	60			
16o	CH_3	Cl	CH_2O	acetoxy acetyl	100	100	100	40			
16p	CH_3	Cl	CH_2O	COPh	100	100	100	40			
17	CH_3	Cl	CH_2O	H	100	100	100	60			
18	CH_3	Cl	CHO		100	40					
19	CH_3	Cl	CH_2N_3		100	100	100	100	100	100	40
20	CH_3	Cl	CH_2NH	H	20						
21a	CH_3	Cl	CH_2NH	$COCH_3$	100	100	100	0			
21b	CH_3	Cl	CH_2NH	SO_2CH_3	100	60					
21c	CH_3	Cl	CH_2NH	$COCF_3$	100	100	100	100	100	40	
21d	CH_3	Cl	CH_2NH	COPh	20						
control[a]					100	100	100	100	100	100	100

[a] Chlorantraniliprole.

Aesar) at a concentration of 200 mg/L was prepared and then diluted to the required concentration with water (distilled). Leaf disks (6 cm × 2 cm) were cut from fresh cabbage leaves and then were sprayed with the test solution for 3 s and allowed to dry. The resulting leaf disks were placed individually into glass tubes. Each disk was infested with seven second-instar diamondback moth larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed three times.

RESULTS AND DISCUSSION

Synthesis. The syntheses of compounds **8a**−**h** and **11a**−**d** are shown in **Schemes 1** and **3**. Ethyl-4-(2-furyl)-2,4-dioxobutanoate

Table 2. Insecticidal Activities of Compounds **13c**−**d**, **16a**−**d**, **16h**, **19**, and **21c** and Chlorantraniliprole against Diamondback Moths

	larvicidal activity (%) at a concentration of (mg/L)							
comp.	20	10	5	2.5	1	0.5	0.25	0.125
13c	100	100	100	100	100	85	30	0
13d	50	0						
16a	100	90	70	45	0			
16b	100	100	95	60	0			
16c	100	100	100	95	70	50	25	0
16d	100	100	100	90	60	40	0	
16h	100	60	0					
19	100	100	100	100	100	100	75	45
21c	100	100	100	100	80	40	0	
control[a]	100	100	100	100	100	100	100	100

[a] Chlorantraniliprole.

Table 3. LC_{50} Values of Compound **19** and Chlorantraniliprole against Diamondback Moths

comp.	$y = a + bx$	LC_{50} (mg/L)	R
19	$y = 10.91 + 4.63x$	0.05	0.94
chlorantraniliprole	$y = 13.75 + 3.61x$	0.0038	0.93

(**3**) was synthesized according to the reported method with minor improvements (*18*). The pure product was easily obtained after filtration instead of extraction and distillation as the literature described. Then compound **3** was condensed with 3-chloro-2-hydrazinylpyridine (**4**) to regioselectively give compound **5**. The furan moiety was oxidized with potassium permanganate to afford the corresponding carboxylic acid (**6**) (*22*). Compound **6** was converted to the acyl chloride by treatment with oxalyl chloride and coupled with 2-amino-3-methylbenzamide derivatives (**7a**−**f**, **7i**−**j**) in the presence of pyridine in THF to afford the title compounds **8a**−**h**. Saponification of the pyrazole ester (**5**) afforded compound **9**, which was coupled with acohol to afford corresponding esters (**10a**−**d**) (*23*). Oxidation of the furan moiety, acid chloride formation, and subsequent coupling to 2-amino-3, *N*-methylbenzamide (**7a**) afforded the title compounds **11a**−**d**.

The synthesis of compounds **13a**−**m** is shown in **Scheme 4**. Carboxylic acid (**9**) was treated with oxalyl chloride and then coupled with excessive amine to provide amides **12a**−**g**. At first, the furan moiety was oxidized with potassium permanganate directly by the same procedure shown in **Scheme 1**, but it failed to give the carboxylic acid. It was found that the oxidation of this kind of compounds needs a small portion of sodium dihydrogen phosphate (5%) (*24*). We propose that the main reason is that the reactant was decomposed under the basic conditions because of the oxidation of potassium permanganate. After examing reaction conditions, the carboxylic acid was obtained with potassium permanganate and potassium dihydrogen phosphate (both were 5 equivalents). Then the carboxylic acid was coupled with 2-amino-3-methylbenzamide derivatives (**7a**−**g**) to provide the title compounds **13a**−**m**.

The title compounds **16a**−**p** and **18** were prepared as shown in **Schemes 5** and **6**. In order to find the SAR, two different synthetic pathways were used. First, acetate compounds **16a**−**j** were synthesized from intermediate **5**. Compound **5** was reduced with lithium aluminum hydride to provide alcohol **14**, which in turn underwent acetylation to give compound **15** in high yield. Then the title compounds **16a**−**j** were obtained by a procedure similar to that shown in **Scheme 1**. Second, compounds **16k**−**p** were synthesized from compound **8a**. It was found that **8a** can be regioselectively reduced with lithium aluminum hydride to provide alcohol **17** with high yield. Then, the alcohol **17** was easily

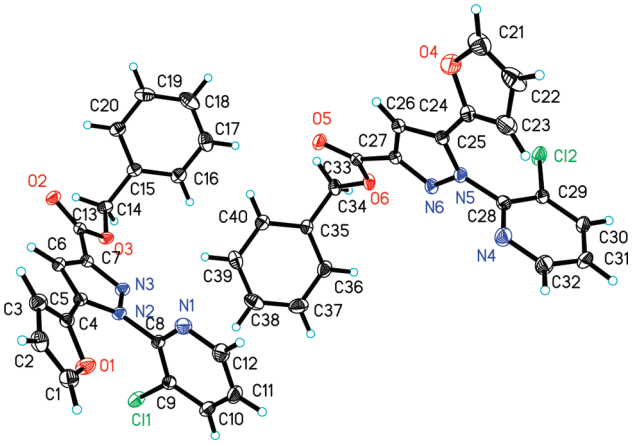


Figure 2. Molecular structure of compound **10c**.

acylated with different acylating agents to give the title compounds **16k**−**p**. In addition, the formyl product **18** was obtained by the oxidation of compound **17** with PCC as an oxidant (*25*).

The title compounds **21a**−**d** were synthesized from compound **16k** as shown in **Scheme 6**. The mesyl group of compound **16k** was displaced with sodium azide (*26*), followed by catalytic hydrogenation to provide the primary amine **20**. Compound **20** was allowed to couple with various acid chlorides or anhydride to afford the final products **21a**−**d**.

Structure of Compound 10c. Benzyl 1-(3-chloropyridin-2-yl)-5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (**10c**) was confirmed by ^{1}H NMR and the melting point. Santos Fustero et al. reported that two *N*-arylpyrazole isomers were formed by the condensation of aryl hydrazines and 1,3-diketones in different reaction conditions (*27*). In order to verify the regioselectivity in the pyrazole (compound **5**) formation, compound **10c**, the derivative of compound **5**, was recrystallized from a mixture of ethyl acetate and petroleum ether (60−90 °C) to give a colorless crystal for X-ray single-crystal diffraction. It could be seen from the X-ray single-crystal figure (**Figure 2**) that the pyrazole formation was regioselective, and two conformers were found due to the different dihedral angle between the furan ring and the pyrazole ring (*28*).

Structure−**Activity Relationship (SAR).** *Larvicidal Activities against Oriental Armyworms*. The larvicidal activity against oriental armyworms is summarized in **Table 1**. In general, most of the compounds showed moderate potency against oriental armyworms. In order to examine different substituents in the 3-substituted position of pyrazole, four kinds of bioisosterism groups (**Figure 1**, F−I) were introduced. When R_1 and R_2 were fixed as CH_3 and Cl, respectively, compounds **21c**, **16a**, **13i**, and **11c**−**d** showed comparable higher activity in each series, and the sequence was **21c** > **16a** > **13i** > **11c**−**d**. Furthermore, different substituents in each series had different effects on the activity. On the one hand, different amide groups had great impact on the activity in the **G** and **I** series. For example, compound **21c** showed much higher activity than compound **21d**; while compound **13i** showed 60% activity at the concentration of 20 mg/L, its analogue **13l** showed no activity even at the concentration of 200 mg/L. On the other hand, different ester groups had little effect on insecticidal activity. For example, in the H series, **16a** and **16k**−**p** had similar activity at the concentration of 20 mg/L. The main reason was probably due to the metabolic degradation of ester groups in the insect. The ester hydrolysis productions of the **H** series were compound **17**; therefore, they had similar activity. However, the ester hydrolysis productions of the **F** series were carboxylic acids; therefore, their activity was comparably low, which was consistent with the results obtained before (*17*).

Surprisingly, replacement of the mesylate ester with the azide (**19**) indicated an increase of the activity, while the oxidation product **18** of compound **17** showed somewhat less activity.

Different substitutions in the aliphatic amide moiety were introduced to investigate their influence on the insecticidal activity. The bioactivity of compounds **13a**−**m**, where X and R were fixed as $CONHCH_3$, indicated the sequence C $(CH_3)_3$ > cyclopropyl > CH $(CH_3)_2$ > $PhCH_2$ > CH_3 > OCH_3 in the aliphatic amide moiety, while compounds **16a**−**f** showed a similar trend. The methyl amides, which showed the highest toxicity in previous SARs (*4*), did not show the greater levels of insecticidal activity this time. On the contrary, the *t*-butyl amides (**8c**, **13c**, and **16c**) tended to show greater levels of insecticidal activity than other substituents, and the second were the cyclopropyl amides (**8d**, **13d**, and **16d**). Furthermore, the methoxy amides (**8e**, **13e**, and **16e**) showed very low activity, which did not correlate to the results obtained before (*29*). In addition, the chloro-substituted compounds in the **H** series (compounds **16a**−**p**) showed better activity than the corresponding nonchloro compounds, such as compounds **16a** and **16g**, **16b** and **16h**, and **16d** and **16i**.

Larvicidal Activities against Diamondback Moths. **Table 2** shows the insecticidal activity of compounds **13c**−**d**, **16a**−**d**, **16h**, **19**, and **21c** against diamondback moth. The acitivity of **19** was 45% at 0.125 mg/mL, higher than that of the other listed compounds. But its LC_{50} was 0.05 mg/mL, still lower than that of chlorantraniliprole (0.0038 mg/mL, **Table 3**). It was also observed that the *t*-butyl amides (**13c** and **16c**) showed higher activity than their anologues. The acitivity of compounds **16a**−**d** and **16 h**, where X and R were fixed as CH_2O and $COCH_3$, respectively, indicated the trend $C(CH_3)_3$ > cyclopropyl > $CH(CH_3)_2$ > CH_3 (R_2 = Cl) > CH_3 (R_2 = H). Surprisingly, the compound **13d**, which had favorable activity against oriental armyworms (100% at 20 mg/mL), shows relatively lower activity against diamondback moths (50% at 20 mg/mL). In addition, compound **21c** showed a 40% death rate at 0.5 mg/mL.

In summary, four novel series of anthranilic diamides containing modified *N*-pyridylpyrazoles were synthesized, and their structures were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS. The single crystal structure of **10c** confirmed the regioselectivity in the pyrazole formation. The larvicidal activities against oriental armyworms and diamondback moths of these anthranilic diamides were evaluated. The results of the larvicidal activities indicated that most compounds exhibited favorable larvicidal activities against oriental armyworms and diamondback moths. The preliminary structure−activity relationship of the title compounds indicated that the improvement of insecticidal activity required a reasonable combination of both substituents in the pyrazole ring and the aliphatic amide moiety. The azide compound **19** showed the highest activity in the list compounds, and *t*-butyl amides tended to show greater levels of insecticidal activity than other amides in the aliphatic amide moiety.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, HRMS, and melting point data for compounds **8a**−**h**, **11a**−**d**, **13a**−**m**, **16a**−**p**, and **21a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

LITERATURE CITED

(1) Lahm, G. P.; Selby, T. P.; Frendenberger, J. H.; et al. Insecticidal anthranilic diamides: A new class of potent ryanodine receptor activators. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4898−4906.

(2) Lahm, G. P.; Cordova, D.; Barry, J. D. New and selective ryanodine receptor activators for insect control. *Bioorg. Med. Chem*. **2009**, *17*, 4127−4133.

(3) David, B. S.; Daniel, C.; Timothy, R. C. Insect ryanodine receptors: molecular targets for novel pest control chemicals. *Invert Neurosci*. **2008**, *8*, 107−119.

(4) Lahm, G. P.; Stevenson, T. M.; Selby, T. P.; et al. Rynaxypyr™: A new insecticidal anthranilic diamide that acts as a potent and selective ryanodine receptor activator. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6274−6279.

(5) Selby, T. P.; Lahm, G. P.; Stevenson, T. M.; et al. *Abstracts of Papers, 236th National Meeting of the American Chemical Society, Philadelphia, PA*, American Chemical Society: Washington, DC, **2008**.

(6) DuPont Rynaxypyr_ Insect Control Technical Bulletin: http://www2.dupont.com/Production_Agriculture/en_US/assets/downloads/pdfs/Rynaxypyr_Tech_Bulletin.pdf.

(7) Alig, B.; Fischer, R.; Gesing, R. F. E.; Hense, A.; Kruger, B.; Losel, P.; Arnold, C. Anthranilamides. WO 2006000336 A2, 2006.

(8) Alig, B.; Fischer, R.; Funke, C.; et al. Anthranilic acid diamide derivative with hetero-aromatic and hetero-cyclic substituents. WO 2007144100 A1, 2007.

(9) Lahm, G. P. Preparation of novel anthranilamides useful for controlling invertebrate pests. WO 2006023783 A1, 2006.

(10) Hughes, K. A.; Lahm, G. P.; Selby, T. P.; Stevenson, T. M. Cyano anthranilamide insecticides. WO 04067528 A1, 2004.

(11) Loiseleur, O.; Hall, R. G.; Stoller, A. D.; et al. Novel insecticides. WO 2009024341 A2, 2009.

(12) Loiseleur, O.; Durieux, P.; Trah, S.; et al. Pesticides containing a bicyclic bisamide structure. WO 2007093402 A1, 2007.

(13) Kruger, B.; Hense, A.; Alig, B.; et al. Dioxazine- and oxadiazine-substituted arylamides. WO 2007031213 A1, 2007.

(14) Jeanguenat A.; O'sullivan, A. C. Anthranilamide derivatives as insecticides. WO 2006061200 A1, 2006.

(15) Muehlebach, M.; Craig, G. W. N-Cyanoalkylanthranilamides as insecticides. WO 2008064891 A1, 2006.

(16) Lima, L. M. A.; Barreiro, E. J. Bioisosterism: A useful strategy for molecular modification and drug design. *Curr. Med. Chem*. **2005**, *12* (1), 23−49.

(17) Dong, W. L.; Xu, J. Y.; Xiong, L. X.; Liu, X. H.; Li, Z. M. Synthesis, structure and biological activities of some novel anthranilic acid esters containing *N*-pyridylpyrazole. *Chin. J. Chem*. **2009**, *27*, 579−586.

(18) Gardner, T. S.; Wenis, E.; Lee, J. Synthesis of 5-substituted 3-isoxazolecarboxylic acid hydrazides and derivatives. *J. Org. Chem*. **1961**, *26*, 1514−1518.

(19) Dong, W. L.; Liu, X. H.; Xu, J. Y.; Li, Z. M. Design and synthesis of novel anthranilic diamides containing 5,7-dimethyl[1,2,4]triazolo-[1,5-*a*]pyrimidine. *J. Chem. Res*. **2008**, *9*, 530−533.

(20) Kornet, M. J. Synthesis and anti convulsant activity of 3-alkyl-3, 4-dihydro-2(1*H*)-quinazolinones. *J. Heterocyclic Chem*. **1992**, *29*, 103−105.

(21) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol*. **1925**, *18*, 265−267.

(22) Pruitt, J. R.; Pinto, D. J. P.; Galemmo, R. A., Jr.; et al. Discovery of 1-(2-aminomethylphenyl)-3-trifluoromethyl-N-[3-fluoro-2′-(aminosulfonyl)-[1,1′-biphenyl)]-4-yl]-1*H*-pyrazole-5-carboxamide (DPC602), a potent, selective, and orally bioavailable factor Xa inhibitor. *J. Med. Chem*. **2003**, *46*, 5298−5315.

(23) Otera, J. Reaction of Alcohols with Carboxylic Acids and Their Derivatives. In *Esterification*; Otera, J., Eds.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; pp 21−23.

(24) Varnes, J. G.; Wacker, D. A.; Jacobson, I. C.; et al. Design, structure-activity relationship, and pharmacokinetic profile of pyrazole-based indoline factor Xa inhibitors. *Bioorg. Med. Chem. Lett*. **2007**, *17* (23), 6481−6488.

(25) Corey, E. J.; Suggs, J. W. Pyridinium chlorochromate: an efficient reagent for oxidation of primary and secondary alcohols to carbonyl compounds. *Tetrahedron Lett*. **1975**, *31*, 2647−2650.

(26) Tai, C. L.; Hung, M. S.; Pawar, V. D.; et al. Design, synthesis, and biological evaluation of novel alkenylthiophenes as potent and selective CB1 cannabinoid receptor antagonists. *Org. Biomol. Chem*. **2008**, *6*, 447−450.

(27) Fustero, S.; Roman, R.; Sanz-Cervera, J. F.; et al. Improved regioselectivity in pyrazole formation through the use of fluorinated alcohols as solvents: synthesis and biological activity of fluorinated tebufenpyrad analogs. *J. Org. Chem.* **2008**, *73*, 3523−3529.

(28) Supplementary material CCDC-784747 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB 21EZ, UK. Fax: +44−1223−336033. E-mail: deposit@ccdc.cam.ac.uk.

(29) Liu, A. P.; Hu, Z. B.; Wang, Y. J.; et al. Preparation of pyrazole containing 2-amino-*N*-oxybenzamide compounds as pesticides. CN 101337959 A, 2009.

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