

Synthesis, Insecticidal Activities, and SAR Studies of Novel Pyridylpyrazole Acid Derivatives Based on Amide Bridge Modification of Anthranilic Diamide Insecticides

Bao-Lei Wang, Hong-Wei Zhu, Yi Ma, Li-Xia Xiong, Yong-Qiang Li, Yu Zhao, Ji-Feng Zhang, You-Wei Chen, Sha Zhou, and Zheng-Ming Li*

State-Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

S Supporting Information

ABSTRACT: Anthranilic diamides are one of the most important classes of modern agricultural insecticides. To discover new structure-modified compounds with high activity, series of novel carbonyl thioureas, carbonyl ureas, oxadiazoles, carbonyl thiophosphorylureas, oxadiazole-containing amides, and thiazoline-containing amides were designed through the modification of the amide bridge based on the structure of chlorantraniliprole and were synthesized, and bioassays were carried out. The compounds were characterized and confirmed by melting point, IR, ¹H NMR, and elemental analyses or HRMS. Preliminary bioassays indicated that some compounds exhibited significant insecticidal activities against oriental armyworm, diamondback moth, beet armyworm, corn borer, and mosquito. Among them, trifluoroethoxyl-containing carbonyl thiourea **20a** showed best larvicidal activity against oriental armyworm, with LC₅₀ and LC₉₅ values of 0.1812 and 0.7767 mg/L, respectively. Meanwhile, **20c** and **20e** showed 86 and 57% death rates against diamondback moth at 0.005 mg/L, and the LC₅₀ values of the two compounds were 0.0017 and 0.0023 mg/L, respectively, which were lower than that of the control chlorantraniliprole. The relationship between structure and insecticidal activity was discussed, and the HF calculation results indicated that the carbonyl thiourea moiety plays an important role in the insecticidal activity. The present work demonstrated that the trifluoroethoxyl-containing carbonyl thioureas can be used as lead compounds for further development of novel insecticides.

KEYWORDS: *pyridylpyrazole acid derivative, synthesis, insecticidal activity*

INTRODUCTION

Synthetic pesticides play important roles for controlling pests harmful to crop growth in the current agricultural system. To overcome resistance and ecobiological problems associated with conventional insecticides, there is an urgent need to discover novel potent insecticides with new modes of action and ecofriendly properties such as easy degradability to nontoxic residues, harmlessness to human beings, and benefits in meeting the demands of crop protection.

The ryanodine receptor (RyR), also known as the calcium ion channel receptor, has been regarded as one of the potential targets for novel insecticide discovery since it was found that natural ryanodine possessed insecticidal activity.^{1–3} In the past decade, Nippon Kayaku Co., Ltd., found the phthalic diamide insecticide flubendiamide targeting insect RyR.⁴ Also, DuPont discovered the anthranilic diamides,⁵ which originated from the insecticidal phthalic diamides as highly potent and selective activators of the insect RyR.⁶ Until now, two representative phthalic diamides, chlorantraniliprole (Rynaxypyr; DPX-E2Y45) and cyantraniliprole (Cyazypyr) (Figure 1) have been marketed.^{7,8} These compounds show exceptional insecticidal activity on a broad range of Lepidoptera, Coleoptera, Diptera, and Isoptera insects.⁶ In addition to larvicidal activity, chlorantraniliprole has been found to have significant ovicidal activity among some Lepidopteran pests.⁹

Since the discovery of phthalic diamides and anthranilic diamides, compounds with such structural features and their

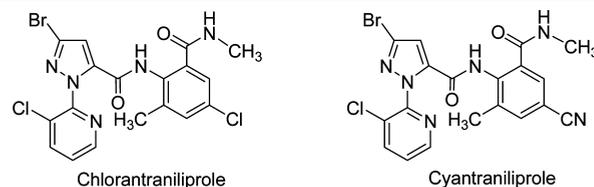


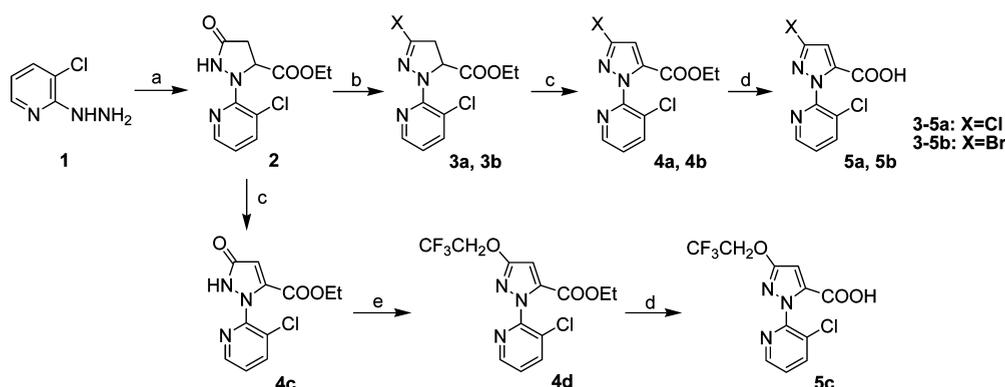
Figure 1. Chemical structures of anthranilic diamide insecticides.

chemical synthesis have attracted considerable attention.^{10,11} There are two amide moieties in the structures of flubendiamide and chlorantraniliprole, respectively. In previous work, most modifications for chlorantraniliprole were related to the benzene moiety and the *N*-pyridylpyrazole heterocycle moiety. The most successful example is cyantraniliprole (Cyazypyr),⁸ which replaced a cyano group of the 4-Cl substituent of the former chlorantraniliprole. However, the modification for the two amide moieties was relatively seldom reported, especially the alteration of the amide bridge, a key pharmacophore that links the benzene ring and the *N*-pyridylpyrazole heterocycle, was not much reported in previous patents. It is known that acylurea or acylthiourea compounds, representing an important class of

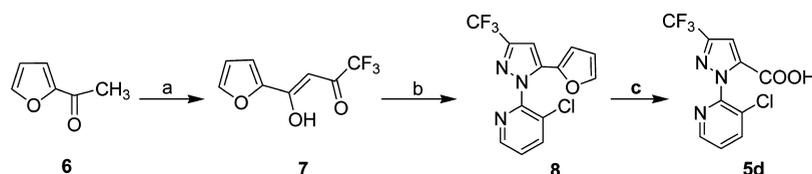
Received: March 22, 2013

Revised: May 17, 2013

Accepted: May 20, 2013

Scheme 1. Synthesis of Compounds 5a–c^a

^aReagents and conditions: (a) diethyl maleate, NaOEt, EtOH, reflux; (b) POCl₃ or POBr₃, MeCN, 80 °C; (c) K₂S₂O₈, H₂SO₄, MeCN, reflux; (d) (i) aqueous NaOH, MeOH and (ii) aqueous HCl; and (e) CF₃CH₂I, K₂CO₃, DMF, 100 °C.

Scheme 2. Synthesis of Compound 5d^a

^aReagents and conditions: (a) NaOCH₃, ethyl trifluoroacetate; (b) 3-chloro-2-hydrazinylpyridine (1), AcOH, reflux; and (c) KMnO₄, acetone/H₂O, reflux.

biologically active molecules, such as benzoylphenylureas (e.g., diflubenzuron), are a familiar type of insect growth regulators (IGRs), which have attracted considerable attention for decades because of their unique mode of action and low toxicity to nontarget organisms (beneficial arthropods).^{12–14} We also found some *N*-pyridylpyrazole acylthioureas showed favorable insecticidal activities in our preliminary research, which encouraged us to further synthesize novel compounds with bridge-modified structure.¹⁵ Heterocycles such as oxadiazole, thiazoline, and other heterocycles are important pharmacophores for insecticidal molecular design. Given these considerations, series of novel compounds were designed by changing the amide bridge to carbonyl thiourea, carbonyl urea, oxadiazole, carbonyl thiophosphorylurea, and thiazoline amide moieties with a substituted *N*-pyridylpyrazole ring based on the structure of chlorantraniliprole and were synthesized successfully as shown in Schemes 1–9. Their insecticidal activities against oriental armyworm, diamond-back moth, beet armyworm, corn borer, and mosquito were tested accordingly. The preliminary structure–activity relationship (SAR) was also discussed.

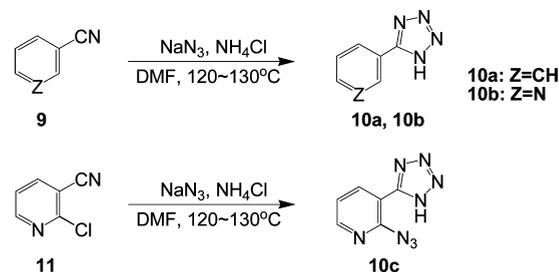
MATERIALS AND METHODS

Instruments and Materials. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instrument Co., Beijing, China) and were uncorrected. Infrared spectra were recorded on a Nicolet MAGNA-560 spectrophotometer as KBr tablets. ¹H NMR spectra were recorded at 300 MHz using a Bruker AC-P300 spectrometer or 400 MHz using a Bruker AV 400 spectrometer (Bruker Co., Switzerland) in CDCl₃ or DMSO-*d*₆ solution with tetramethylsilane as the internal standard, and chemical shift values (δ) were given in parts per million (ppm). Elemental analyses were performed on a Vario EL elemental analyzer. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument.

Flash chromatography was performed with silica gel (200–300 mesh). Reagents were all analytically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. 5-Methyl-1*H*-tetrazole was purchased from Adamas Reagent Co., Ltd. 2-Aminoethanol and 1-amino-2-propanol were purchased from Aladdin Reagent Database Inc. Commercial insecticides chlorantraniliprole and diflubenzuron were used only as contrast compounds and synthesized according to the literature.^{16,17}

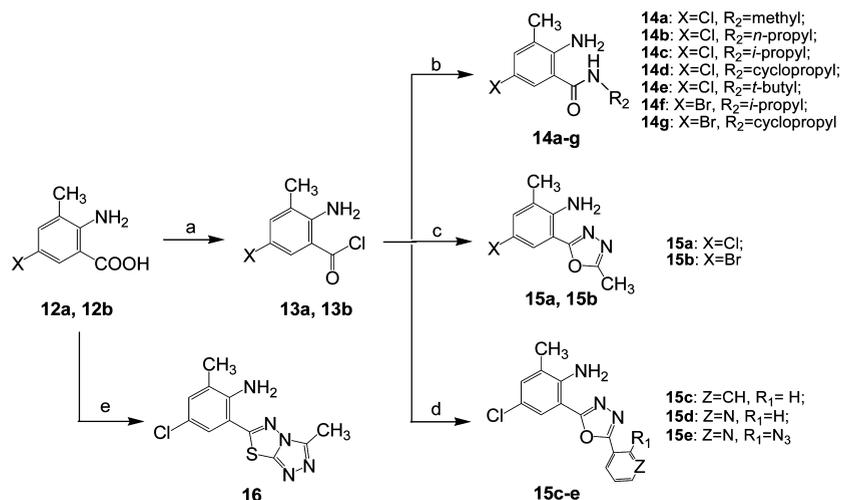
Synthetic Procedures. 4-Amino-5-methyl-4*H*-1,2,4-triazole-3-thiol was prepared according to the literature.¹⁸ The key intermediate pyrazole carboxylic acid (5a–d) was synthesized from the material 3-chloro-2-hydrazinylpyridine (1) or 2-acetylfuran (6) referring to the literature^{15,19,20} (Schemes 1 and 2). 2-Amino-3,5-disubstituted-benzamide derivatives (14a–g) were synthesized with 2-amino-3,5-disubstituted-benzoic acids (12) as materials in moderate yield according to the method reported by Dong et al.²¹ (Scheme 4).

Scheme 3. Synthesis of Compounds 10a–c



Synthesis of Intermediate Tetrazole Derivatives (10a–c).²²

To a solution of benzonitrile (20 mmol) in *N,N*-dimethylformamide (DMF) (25 mL) was added ammonium chloride (40 mmol) and sodium azide (40 mmol), and the resultant slurry was vigorously stirred at 120 °C for 2–3 h. After cooling to room temperature, the mixture was filtered, and the solid was washed with DMF. The filtrates were combined and the DMF was removed in vacuo. To the residue was added water (30 mL), the mixture was adjusted to pH 2–3 with

Scheme 4. Synthesis of Compounds 14a–g, 15a–e, and 16^a

^aReagents and conditions: (a) SOCl₂, reflux; (b) R₂NH₂, CH₂Cl₂; (c) 5-methyl-1H-tetrazole, Py, 100–110 °C; (d) compounds 10a–c, Py, 1,4-dioxane, 100–110 °C; and (e) 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol, POCl₃, reflux.

concentrated HCl, and the solid was collected by filtration and washed with water and acetone successively to afford 5-phenyl-1H-tetrazole (10a) as white crystals: yield 68%, mp 213–215 °C (lit.²⁵ mp 215–216 °C).

3-Cyanopyridine was used as material to afford 3-(1H-tetrazol-5-yl)pyridine (10b) as white crystals: yield 54%, mp 240–242 °C (lit.²² mp 239–241 °C).

2-Chloro-3-cyanopyridine was used as material to afford 2-azido-3-(1H-tetrazol-5-yl)pyridine (10c) as a light yellow solid: yield 52%; mp 245–247 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (t, *J* = 7.2 Hz, 1H, Py-H), 8.60 (d, *J* = 7.2 Hz, 1H, Py-H), 9.55 (d, *J* = 7.2 Hz, 1H, Py-H). HRMS calcd for C₆H₄N₈ ([M – H][–]), 187.0481; found, 187.0490.

Synthesis of Oxadiazole-Containing Substituted Aniline (15a, 15b). A mixture of 2-amino-5-halo-3-methylbenzoic acid (12, 10 mmol) with thionyl chloride (SOCl₂) (15 mL) was refluxed for 3–5 h and condensed under reduced pressure to give the corresponding crude carbonyl chloride (13), which was immediately dissolved in dry toluene (10 mL) and added to a solution of 5-methyl-1H-tetrazole (9.5 mmol) in dry pyridine (20 mL) with stirring at room temperature. The mixture was then stirred at 100–110 °C for 2–3 h, the solvent was removed in vacuo, the residue was added to a 10% Na₂CO₃ solution (30 mL) and stirred for 5 min, and the solid was filtered, washed with water, and recrystallized with 95% EtOH to give compound 15a or 15b.

4-Chloro-2-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)aniline (15a): brown solid; yield 69%; mp 150–153 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.19 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 6.64 (br, 0.67H, NH₂), 7.24 (d, *J* = 1.6 Hz, 1H, Ph-H), 7.49 (d, *J* = 1.6 Hz, 1H, Ph-H).

4-Bromo-2-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)aniline (15b): yellow solid; yield 72%; mp 133–136 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.22 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 5.91 (br, 2H, NH₂), 7.27 (d, *J* = 2.0 Hz, 1H, Ph-H), 7.75 (d, *J* = 2.0 Hz, 1H, Ph-H).

Synthesis of Oxadiazole-Containing Substituted Aniline (15c–e). A mixture of 2-amino-5-chloro-3-methylbenzoic acid (12a, 5 mmol) with SOCl₂ (7 mL) was refluxed for 3 h and condensed under reduced pressure to give a crude carbonyl chloride (13a), which was immediately dissolved in 1,4-dioxane (5 mL) and added to a solution of tetrazole derivative (10a–c, 4 mmol) in dry pyridine (10 mL) with stirring. The mixture was further stirred at 100 °C for 4–6 h, the solvent was removed in vacuo, the residue was added to a 10% Na₂CO₃ solution (20 mL) and stirred for 5 min, and the solid was filtered, washed with water, and recrystallized with a mixed solvent of EtOH and DMF to give the product.

4-Chloro-2-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline (15c): yellow crystal; yield 51%; mp 205–208 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.21 (s, 3H, CH₃), 6.75 (br, 0.71H, NH₂), 7.29 (s, 1H,

Ph-H), 7.62–7.68 (m, 3H, Ph-H), 7.83 (d, *J* = 2.0 Hz, 1H, Ph-H), 8.19 (t, *J* = 2.0 Hz, 2H, Ph-H).

4-Chloro-2-methyl-6-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)aniline (15d): yellow crystal; yield 84%; mp 202–205 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.22 (s, 3H, CH₃), 6.75 (br, 0.85H, NH₂), 7.30 (s, 1H, Ph-H), 7.67 (dd, *J*₁ = 8.0 Hz, *J*₂ = 4.4 Hz, 1H, Py-H), 7.89 (s, 1H, Ph-H), 8.57 (d, *J* = 7.6 Hz, 1H, Py-H), 8.83 (d, *J* = 4.4 Hz, 1H, Py-H), 9.37 (s, 1H, Py-H).

2-(5-(2-Azidopyridin-3-yl)-1,3,4-oxadiazol-2-yl)-4-chloro-6-methylaniline (15e): yellow solid; yield 78%; mp 254–256 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.24 (s, 3H, CH₃), 6.82 (br, 2H, NH₂), 7.34 (d, *J* = 2.0 Hz, 1H, Ph-H), 7.67 (t, *J* = 7.2 Hz, 1H, Py-H), 7.85 (d, *J* = 2.0 Hz, 1H, Ph-H), 8.79 (d, *J* = 7.2 Hz, 1H, Py-H), 9.59 (d, *J* = 7.2 Hz, 1H, Py-H). HRMS calcd for C₁₄H₁₀ClN₇O ([M + Na]⁺), 350.0533; found, 350.0530.

Synthesis of 4-Chloro-2-methyl-6-(3-methyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)aniline (16). A mixture of 2-amino-5-chloro-3-methylbenzoic acid (12a, 2 mmol), 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol (2 mmol), and phosphorus oxychloride (POCl₃) (7 mL) was refluxed for 5 h and condensed under reduced pressure. The residue was poured into ice–water, and the mixture was adjusted to pH 10–11 with 30% sodium hydroxide solution. The solid was collected by filtration, washed with water, and recrystallized with DMF–H₂O to afford compound 16 as a yellow solid: yield 47%; mp 266–268 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.20 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 6.56 (br, 2H, NH₂), 7.31 (s, 1H, Ph-H), 7.36 (s, 1H, Ph-H).

Synthesis of 1-(3-Chloro-2-pyridyl)-3-(substituted)-1H-pyrazole-5-carbonyl chloride (17a–d). To a suspension of pyrazole carboxylic acid (5) (1 mmol) in 25 mL of dichloromethane were added successively oxalyl chloride (4 mmol) and two drops of DMF under vigorous stirring. After stirring at room temperature for 3 h, the solution was evaporated to dryness in vacuo, and the residue, that is, the crude pyrazole carbonyl chloride, was obtained as a yellow powder (100%), which was used directly in the next step without further purification.

General Synthetic Procedure for *N'*-(2,4,6-Trisubstituted-phenyl)-*N*-(1-(3-chloro-2-pyridyl)-3-halo-1H-pyrazole-5-carbonyl)thiourea (19a–n). To a mixture of 0.24 g (2.5 mmol) of potassium thiocyanate (KSCN) in 15 mL of dry acetonitrile were added two drops of polyethylene glycol-400 (PEG-400), and the mixture was stirred at room temperature for 5 min to give a homogeneous solution; then, the solution of crude pyrazole carbonyl chloride (17a or 17b) (1 mmol) in 5 mL of dry acetonitrile was added. After stirring at room temperature for 40 min, the mixture was filtered to give the acetonitrile solution of pyrazole carbonyl isothiocyanate (18a or 18b), and then the 2,4,6-trisubstituted aniline (0.85 mmol) was added. After stirring for a further 3–4 h at room temperature, the reaction mixture was evaporated

in vacuo, and the residue was subjected to column chromatography on silica gel with petroleum ether and ethyl acetate as solvents to give product (19a–n).

General Synthetic Procedure for *N*-(4-Halo-2-methyl-6-(substituted-carbamoyl)phenylcarbamothioyl)-1-(3-chloropyridin-2-yl)-3-(2,2,2-trifluoroethoxy)-1*H*-pyrazole-5-carboxamide (20a–g). To a mixture of 0.24 g (2.5 mmol) of KSCN in 15 mL of dry acetonitrile were added two drops of PEG-400, and the mixture was stirred at room temperature for 5 min to give a homogeneous solution; then, the solution of crude pyrazole carbonyl chloride (17c) (1 mmol) in 5 mL of dry acetonitrile was added. After stirring at room temperature for 40 min, the reaction was filtered to give the acetonitrile solution of pyrazole carbonyl isothiocyanate (18c), and then the amino compound (14a–g) (0.85 mmol) was added; after stirring at room temperature for another 3–4 h, the reaction mixture was evaporated in vacuo, and the residue was subjected to column chromatography on silica gel with petroleum ether and ethyl acetate as solvents to give product.

General Synthetic Procedure for 3-Substituted-*N*-(4-halo-2-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (21a–c). To a mixture of oxadiazole-containing substituted aniline (15a or 15b) (0.95 mmol) and triethylamine (1 mmol) in dichloromethane (15 mL) was added the solution of pyrazole carbonyl chloride (17b or 17c, 1 mmol) in dry dichloromethane (7 mL) at 0–5 °C. The reaction mixture was then stirred at room temperature for 3–4 h and washed with 5% NaHCO₃ solution and water successively. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was subjected to column chromatography on silica gel with petroleum ether and ethyl acetate as solvents to give product.

General Synthetic Procedure for *N*-(2-(5-(2-Azidopyridin-3-yl)-1,3,4-oxadiazol-2-yl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (22). The synthesis was similar to that of compounds 21a–c. Using oxadiazole-containing aniline (15e) and pyrazole carbonyl chloride (17b) as materials, compound 22 was obtained as a yellow solid.

General Synthetic Procedure for *N'*-(4-Chloro-2-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-*N*-(1-(3-chloro-2-pyridyl)-3-bromo-1*H*-pyrazole-5-carbonyl)thiourea (23). The procedure was similar to those of 19 and 20. Using 15a as substituted aniline material, compound 23 was obtained as a yellow solid.

General Synthetic Procedure for 3-Halo-*N*-(4-chloro-2-methyl-6-(5-aryl-1,3,4-oxadiazol-2-yl)phenylcarbamothioyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (24a–c). The synthesis was similar with those of 19 and 20. Using 15c or 15d as substituted aniline material, compounds 24a–c were obtained.

Synthesis of 3-Substituted-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (25a, 25b). To a suspension of pyrazole carboxylic acid (5b or 5d) (8 mmol) in 50 mL of dichloromethane were added successively oxalyl chloride (17 mmol) and two drops of DMF. After stirring at room temperature for 3–4 h, the solution was evaporated. The resulting carbonyl chloride was dissolved in 50 mL of dry tetrahydrofuran (THF) and added to a mixture of aqueous ammonia (25%) (40 mmol) and water (100 mL) at 0 °C. After stirring overnight, a large amount of solid formed and was filtered, which was further purified by a silica gel column eluted with petroleum ether and ethyl acetate to give the pyrazole carboxamide. 25a: white solid; yield 84%; mp 200–202 °C. 25b: white solid; yield 77%; mp 183–185 °C.

General Synthetic Procedure for 3-Bromo-*N*-(4-chloro-2-methyl-6-(5-substituted-1,3,4-oxadiazol-2-yl)-phenylcarbamoyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (26a, 26b). A suspension of compound 25 (1 mmol) in 20 mL of 1,2-dichloroethane and oxalyl chloride (1.1 mmol) was heated to reflux and kept for 2 h. After the mixture had cooled slightly, oxadiazole-containing aniline (15a or 15d) was added, and the mixture was further refluxed for 1–2 h. After cooling, the produced precipitate was filtered and washed with 1,2-dichloroethane and ethyl acetate successively to give product.

General Synthetic Procedure for *O,O*-Dimethyl 3-Substituted-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbonylcarbamoylphosphoramidothioate (27a, 27b). The procedure was similar

to that of 26 using 93% spermine as amine material, and the solid filtered was washed with 1,2-dichloroethane to give pure product.

General Synthetic Procedure for 2-(3-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-5-substituted-1,3,4-oxadiazole (28, 29a–c). A mixture of pyrazole carboxylic acid (5b, 1.5 mmol) with SOCl₂ (10 mL) was refluxed for 4 h and condensed under reduced pressure to give carbonyl chloride (17b), which was immediately dissolved in dry toluene (7 mL) and added to a solution of 5-methyl-1*H*-tetrazole or compound 10 (1.2 mmol) in dry pyridine (10 mL) with stirring. The mixture was further stirred at 100–110 °C for 2 h and cooled to room temperature, and water (50 mL) was added. The mixture was then extracted with ethyl acetate (10 mL × 4), and the extracts were dried with anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was recrystallized with 95% EtOH to give product.

Synthesis of 6-(3-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-3-methyl-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole (30). A mixture of pyrazole carboxylic acid (5b, 2 mmol) and 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol (2 mmol) in POCl₃ (7 mL) was refluxed for 5 h and condensed under reduced pressure. The residue was poured into ice–water, and the mixture was adjusted to pH 10–11 with 30% sodium hydroxide solution. The solid was collected by filtration, washed with water, and recrystallized with DMF–H₂O to afford compound 30 as pink crystals.

Synthesis of 1-(2-Hydroxyethyl/hydroxypropyl)-3-(2,4,6-trisubstituted-phenyl)thiourea (32a–d). According to the method in the literature,²⁴ to a solution of 1,3,5-trisubstituted-2-isothiocyanatobenzene (31a–c, 4 mmol) in diethyl ether (15 mL) was added 2-aminoethanol or 1-amino-2-propanol (4.5 mmol), and the mixture was refluxed for 1–2 h. The produced precipitate was filtered and washed with diethyl ether to give compound 32 as a white solid, which was used for following reaction without purification.

Synthesis of 5-Substituted-*N*-(2,4,6-trisubstituted-phenyl)-4,5-dihydrothiazol-2-amine (33a–d). The intermediate thiourea (32, 3 mmol) was mixed with concentrated HCl (8 mL) and refluxed for 2 h. The reaction solution was diluted with water (15 mL) and decolorized by activated charcoal. After cooling to room temperature, the mixture was adjusted to pH ~10 with aqueous sodium hydroxide (6 mol/L), and the solid was collected by filtration, washed with water and recrystallized with EtOH–H₂O to afford compound 33.

33a: white crystal; yield 40%; mp 117–119 °C (lit.,²⁵ mp 118–119 °C).

33b: white crystal; yield 46%; mp 124–126 °C (lit.,²⁴ mp 124–125 °C).

33c: white crystal; yield 65%; mp 165–166 °C (lit.,²⁴ mp 165.5–166 °C).

33d: white crystal; yield 42%; mp 122–123 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.44 (d, *J* = 6.8 Hz, 3H, CH₃), 3.34 (dd, *J*₁ = 10.0 Hz, *J*₂ = 6.4 Hz, 1H, CH₂), 3.78 (dd, *J*₁ = 10.0 Hz, *J*₂ = 6.4 Hz, 1H, CH₂), 3.88 (m, 1H, CH), 6.80 (s, 1H, NH), 7.30 (s, 2H, Ph–H).

General Synthetic Procedure for 3-Substituted-1-(3-chloropyridin-2-yl)-*N*-(5-substituted-4,5-dihydrothiazol-2-yl)-*N*-(2,4,6-trisubstituted-phenyl)-1*H*-pyrazole-5-carboxamide (34a–e). The synthesis was similar to the synthesis of compounds 21a–c. Using thiazoline-containing aniline (33) and pyrazole carbonyl chloride (compound 17b or 17c) as materials, compound 34 was obtained.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.²⁶ Evaluations were based on a percentage scale of 0–100, in which 0 = no activity and 100 = total kill. The standard deviations of the tested biological values were ±5%. LC₅₀ and LC₉₅ values were calculated by probit analysis.²⁷

Larvicidal Activity against Oriental Armyworm (*Mythimna separata* Walker) and Corn Borer (*Ostrinia nubilalis*). The larvicidal activity of the title compounds and contrast compounds chlorantraniliprole and diflubenzuron against oriental armyworm and corn borer was tested according to the leaf-dip method using the reported procedure.²⁸ Leaf disks (about 5 cm) were cut from fresh corn

Table 1. Larvicidal Activity of Compounds and Chlorantraniliprole against Oriental Armyworm (*Mythimna separata* Walker) at 200 mg/L Concentration

compd	larvicidal activity (%)	compd	larvicidal activity (%)						
15a	20	19e	10	20a	100	22	100	29a	0
15b	16.7	19f	20	20b	100	23	100	29b	10
15c	36.7	19g	10	20c	100	24a	0	29c	0
15d	23.3	19h	0	20d	100	24b	0	30	13.3
15e	6.67	19i	20	20e	100	24c	0	34a	30
16	10	19j	30	20f	100	26a	60	34b	16.7
19a	20	19k	40	20g	100	26b	10	34c	50
19b	20	19l	10	21a	100	27a	10	34d	6.67
19c	100	19m	20	21b	100	27b	10	34e	10
19d	100	19n	10	21c	43.3	28	33.3	control ^a	100

^achlorantraniliprole.**Table 2. Larvicidal Activity of Compounds, Chlorantraniliprole, and Diflubenzuron against Oriental Armyworm (*Mythimna separata* Walker)**

compd	larvicidal activity (%) at									
	100 mg/L	50 mg/L	25 mg/L	10 mg/L	5 mg/L	2.5 mg/L	1 mg/L	0.5 mg/L	0.25 mg/L	
19c	100	100	20	0						
19d	100	100	100	15						
20a	100	100	100	100	100	100	100	100	40	
20b	100	100	100	100	0					
20c	100	100	100	100	40					
20d	100	100	100	100	0					
20e	100	100	100	100	100	40				
20f	100	100	100	100	0					
20g	100	100	100	100	100	100	80			
21a	100	60		0						
21b	30			0						
22	100	60		0						
23	100	40		0						
26a	0									
34c	10									
diflubenzuron	100	100	100	100	100	40				
chlorantraniliprole	100	100	100	100	100	100	100	100	70 ^a	

^aAt a concentration of 0.1 mg/L.**Table 3. Larvicidal Activity of Compounds, Diflubenzuron, and Chlorantraniliprole against Diamondback Moth (*Plutella xylostella* L.)**

compd	larvicidal activity (%) at									
	50 mg/L	25 mg/L	10 mg/L	2.5 mg/L	1.25 mg/L	0.125 mg/L	0.1 mg/L	0.01 mg/L	0.005 mg/L	
19c	90		57							
19d	43		0							
20a		100		100	100	100	71	43	29	
20c		100		100	100	100	100	100	86	
20e		100		100	100	100	100	71	57	
20g		100		100	100	86	71	30	0	
22	100		60							
23	100		60							
26a	29									
34c	29									
diflubenzuron		29		0						
chlorantraniliprole		100		100	100	86	100	86	57	

leaves and then were dipped into the test solution for 3–5 s. After air drying, the treated leaf disks were placed individually into a glass-surface vessel (7 cm). Each dried treated leaf disk was infested with 10 third-instar oriental armyworm or corn borer larvae. Percentage mortalities were evaluated 4 days after treatment. Leaves treated with acetone were

provided as controls. Each treatment was performed three times. The insecticidal activity is summarized in Tables 1, 2, and 4.

Larvicidal Activity against Diamondback Moth (*Plutella xylostella* L.) and Beet Armyworm (*Laphygma exigua* Hübner). The larvicidal activity of the title compounds and contrast compounds chlorantraniliprole and diflubenzuron against diamondback moth and

Table 4. Larvicidal Activity of Compounds 20a, 20c, 20e, 20g, Diflubenzuron, and Chlorantraniliprole against Beet Armyworm (*Laphygma exigua* Hübner) and Corn Borer (*O. nubilalis*)

compd	<i>L. exigua</i> Hübner		<i>O. nubilalis</i>	
	concn (mg/L)	larvicidal activity (%)	concn (mg/L)	larvicidal activity (%)
20a	10	0	25	100
	1	0	10	60
20c	10	70	25	100
	1	60	10	60
	0.1	40		
20e	10	80	25	100
	1	60	10	60
	0.1	40		
20g	10	20	25	30
	1	0		
diflubenzuron	10	0	25	20
	1	0		
chlorantraniliprole	10	80	25	100
	1	80	10	80
	0.1	40		

beet armyworm was tested by the leaf-dip method using the reported procedure.^{29,30} Leaf disks (5 cm × 3 cm) were cut from fresh cabbage leaves and then dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into boxes (80 cm). Each dried treated leaf disk was infested with 30 third-instar beet armyworm or 30 second-instar diamondback moth larvae. Percentage mortalities were evaluated 3 days after treatment. Leaves treated with water and acetone were provided as controls. Each treatment was performed three times. The insecticidal activity is summarized in Tables 3 and 4.

Larvicidal Activity against Mosquito (*Culex pipiens pallens*).

The larvicidal activity of the title compounds and contrast compounds against mosquito were evaluated by using the reported procedure.³¹ The compounds were prepared to different concentrations by dissolving the compounds in acetone and adding distilled water. Then 20 fourth-instar mosquito larvae were put into 10 mL of the test solution and raised for 8 days. Each treatment was performed three times. The biological data in Table 5 were the average value of the three tested values. The results

Table 5. Larvicidal Activity of Compounds 19c, 19d, 20a–g, Diflubenzuron, and Chlorantraniliprole against Mosquito (*Culex pipiens pallens*)

compd	larvicidal activity (%) at			
	2 mg/L	1 mg/L	0.5 mg/L	0.25 mg/L
19c	20			
19d	0			
20a	100	100	40	
20b	100	60	20	
20c	60			
20d	50			
20e	60			
20f	30			
20g	50			
diflubenzuron	100	100	30	
chlorantraniliprole	100	100	100	100

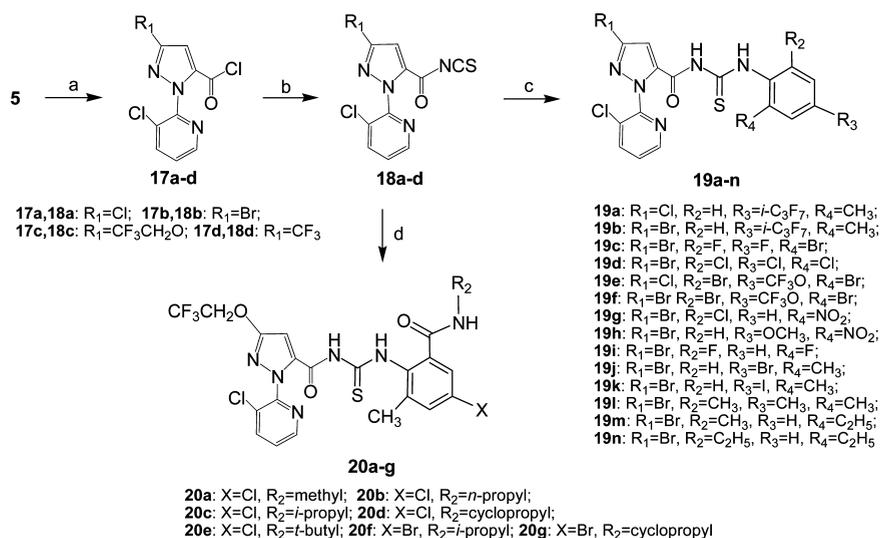
were expressed by death percentage. For comparative purposes, chlorantraniliprole and diflubenzuron were tested under the same conditions.

Hartree–Fock (HF) Calculation. The structures of compounds 20a, 20c and chlorantraniliprole were selected as the initial structures, whereas the HF/6-31G (d,p)³² method in the Gaussian 03 package³³ was used to optimize their structures. Vibration analysis showed that the optimized structures were in accordance with the minimum points on the potential energy surfaces. All of the convergent precisions were the system default values, and all of the calculations were carried out on the NanKai-Star supercomputer.

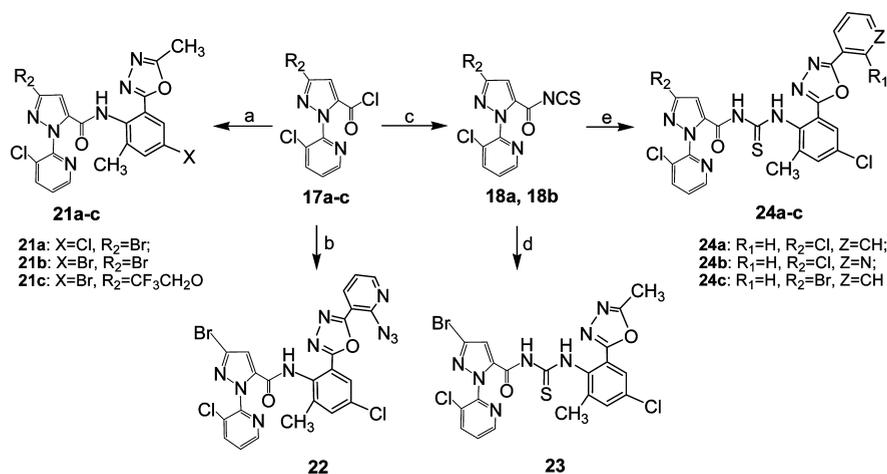
RESULTS AND DISCUSSION

Chemistry. The tetrazole compounds (10a, 10b) were prepared according to the literature²² by heating cyano-containing compound 9 with 2 equiv of sodium azide and ammonium chloride in DMF with satisfactory yields. When using 2-chloro-3-cyanopyridine as material, we did not obtain the desired 2-chloro-3-(1*H*-tetrazol-5-yl)pyridine; however, 2-azido-3-(1*H*-tetrazol-5-yl)pyridine (10c), which is a novel biheterocyclic compound containing eight nitrogen atoms, was obtained. This result indicated that the chloro atom in the 2-position of pyridine can be substituted by nucleophilic reagent N₃[−] during cyclization of the cyano group with hydrazoic acid, and the reactivity of the −Cl group may be increased by its neighboring −CN group of the material or tetrazole group of its product, so the −Cl group could be easier to leave. Tetrazole compound (5-methyl-1*H*-tetrazole or 10a, 10b) reacted with 3,5-disubstituted-2-amino benzoyl chloride (13) in pyridine, undergoing a Huisgen reaction to give oxadiazole-containing substituted aniline (15a–d) with the amino group conserved. Similarly, azido-containing tetrazole compound (10c) can also undergo such reaction to afford corresponding oxadiazole-containing substituted aniline (15e). The azido group is not affected in the following reactions, too, which can be confirmed by ¹H NMR and HRMS of their products (22 and 29c). Moreover, 2-amino-5-chloro-3-methylbenzoic acid (12a) and 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol refluxed in POCl₃ to successfully give corresponding fused heterocyclic substituted aniline (16) via a cyclization reaction. The reaction of oxadiazole-containing aniline (15a, 15b, 15e) with pyrazole carbonyl chloride can give oxadiazole-containing amide (21a–c, 22), whereas it is difficult for compound 16 to undergo this reaction to afford acylation product, which may be because of the very weak solubility and weak reactivity of fused heterocyclic aniline 16.

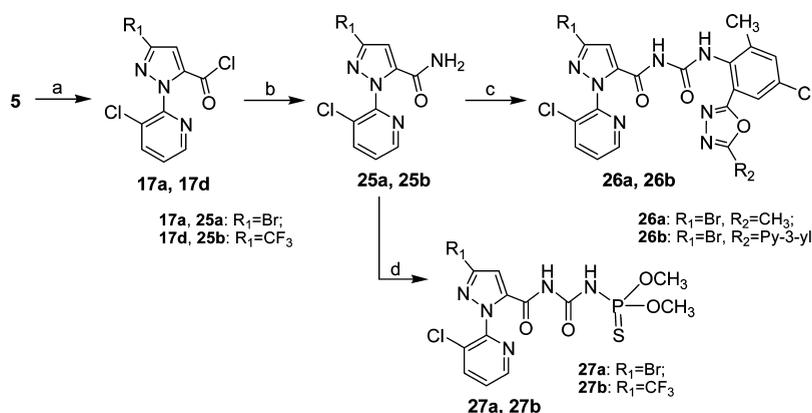
There are some common methods for synthesizing the carbonyl thioureas, for example, carbonyl chloride compound refluxes with thiocyanate in acetone³⁴ or reacts with thiocyanate catalyzed by PEG-600 in methane dichloride at room temperature³⁵ to produce carbonyl isothiocyanate, which further reacts with amine to give carbonyl thiourea. In our experiments for the syntheses of carbonyl thioureas (19, 20, 23, and 24a–c), a PEG-400 PTC method was adopted (illustrated in Scheme 5 and Scheme 6). Pyrazole carbonyl chloride (5) was prepared from the reaction of pyrazole acid with oxalyl chloride, and it was treated with potassium thiocyanate under the conditions of solid–liquid phase transfer catalysis using a small amount of PEG-400 as the catalyst to give pyrazole carbonyl isothiocyanate (18) at room temperature. This compound does not need to be isolated, and it was treated immediately with 2,4,6-trisubstituted anilines or 2-amino-3-methylbenzamide derivatives (14a–g) to give compound 19 or 20 in good to excellent yields.

Scheme 5. Synthesis of Compounds 19a–n and 20a–g^a

^aReagents and conditions: (a) (COCl)₂, DMF, CH₂Cl₂; (b) KSCN, PEG-400, CH₃CN; (c) substituted aniline, CH₃CN; and (d) compd 14a–g, CH₃CN.

Scheme 6. Synthesis of Compounds 21a–c, 22, 23, and 24a–c^a

^aReagents and conditions: (a) compd 15a or 15b, Et₃N, CH₂Cl₂; (b) compd 15e, Et₃N, CH₂Cl₂; (c) KSCN, PEG-400, CH₃CN; (d) compd 15a, CH₃CN; and (e) compd 15c or 15d, CH₃CN

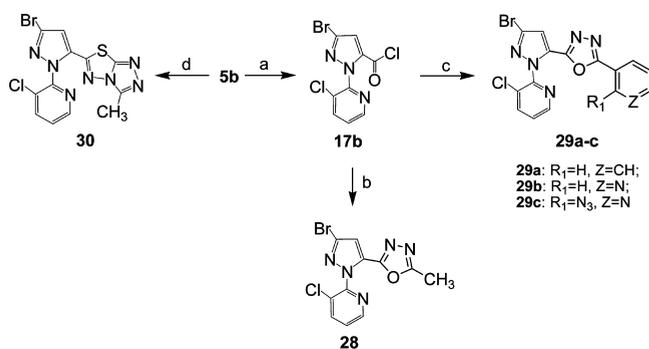
Scheme 7. Synthesis of Compounds 26a, 26b, 27a, and 27b^a

^aReagents and conditions: (a) (COCl)₂, DMF, CH₂Cl₂; (b) NH₃·H₂O; (c) (i) (COCl)₂, ClCH₂CH₂Cl, reflux, and (ii) compd 15a or 15d; and (d) (i) (COCl)₂, ClCH₂CH₂Cl, reflux, and (ii) 93% spermine.

Compounds **26** were synthesized, as shown in Scheme 7. Pyrazole carboxylic acid **5** was converted to amide **25** by reaction with oxalyl chloride and then aqueous ammonia. Compound **25** was then refluxed with oxalyl chloride in 1,2-dichloroethane to give its corresponding pyrazole carbonyl isocyanate derivative, which coupled with amines **15** to afford the compounds **26**. Similarly, using 93% spermine as amine material the carbonyl thiophosphorylureas **27** were obtained.

The reaction of tetrazole compound (5-methyl-1*H*-tetrazole or **10**) with pyrazole carbonyl chloride **17b** in pyridine led to oxadiazole compound (**28**, **29**; Scheme 8) by a Huisgen reaction, whereas pyrazole carboxylic acid **5b** directly reacted with 4-amino-5-methyl-4*H*-1,2,4-triazol-3-thiol in POCl₃ to afford the fused heterocyclic compound **30**.

Scheme 8. Synthesis of Compounds **28**, **29a–c**, and **30**^a

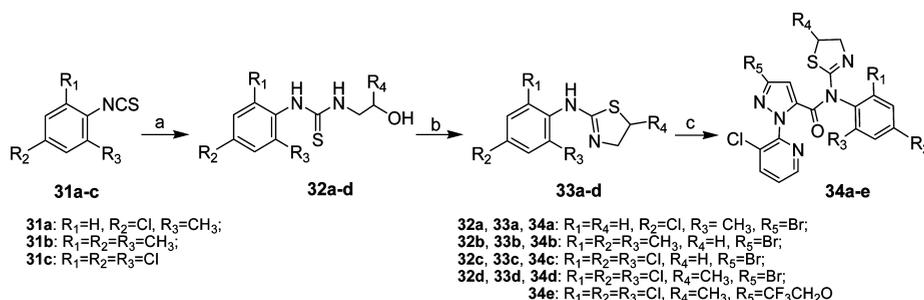


^aReagents and conditions: (a) SOCl₂, benzene, reflux; (b) 5-methyl-1*H*-tetrazole, Py, 100–110 °C; (c) compd **10a–c**, Py, 1,4-dioxane, 100–110 °C; and (d) 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol, POCl₃, reflux.

Referring to the literature method reported by He et al.,²⁴ thiazoline amines (**33**) were prepared by a cyclization reaction in a concentrated HCl solution of hydroxyethylthiourea or hydroxypropylthiourea (**32**), which derived from the condensation of isothiocyanate (**31**) with 2-aminoethanol or 1-amino-2-propanol. Then compound **33** reacted with pyrazole acyl chloride (**17**) using Et₃N as deacid reagent to give acylation product (**34**; Scheme 9).

The novel structures of these title compounds have been characterized by melting point, ¹H NMR, and elemental analyses or HRMS; several compounds with typical structures were also characterized by IR spectra. All spectral and analytical data were consistent with the assigned structures. The infrared spectrum of

Scheme 9. Synthesis of Compounds **34a–e**^a



^aReagents and conditions: (a) 2-aminoethanol or 1-amino-2-propanol, Et₂O; (b) (i) concentrated HCl, reflux, and (ii) NaOH; and (c) compd **17b** or **17c**, Et₃N, dry THF.

carbonyl thiourea compounds **19a**, **20a–g**, **23**, and **24a–c** showed absorption bands at 3143–3446 cm⁻¹ for N–H stretching. The strong peaks at 1742–1579 cm⁻¹ are ascribed to the C=O group and C=N group of heterocyclic ring skeleton as well. The characteristic stretching vibrations ν (C=S) and ν (C–N) appeared at 1273–1369 and 1152–1167 cm⁻¹, respectively. In the ¹H NMR spectra of compounds **19a–n** and **20a–g**, the proton signals of –NHCO– and –NHCS– on the carbonyl thiourea bridge were observed at δ 9.73–10.42 and 11.08–12.48 as a singlet, respectively. The trifluoroethoxy protons (–OCH₂CF₃) of compounds **20a–g**, **21c**, and **34e** appeared at δ 4.65–4.92 as a quartet due to “F” splitting, whereas the methoxyl protons ((CH₃O)₂P(=S)–) of compound **27** appeared at δ ~3.85 as a doublet owing to “P” splitting. Another N–H proton signal of the amide moiety (–CONHR₂) in compounds **20a–g** was observed at δ 6.32–6.64. As for compounds **26** and **27**, the two active proton signals (N–H) appeared at δ 9.67–9.93 and 10.75–11.53 as a singlet, respectively.

Structure–Activity Relationship (SAR). Larvicidal Activity against Oriental Armyworm. The larvicidal activity of compounds against oriental armyworm is summarized in Tables 1 and 2. All of the compounds were initially tested at a concentration of 200 mg/L, and consequently the compounds with high insecticidal potency were investigated further at low concentration. From Table 1, we can see that at 200 mg/L, carbonyl thiourea compounds **19c**, **19d**, **20a–g**, and **23** showed 100% larvicidal activities, oxadiazole-containing amide compounds **21a–c** and **22** exhibited 43.3–100% activities, and oxadiazole-containing carbonyl urea **26a** and thiazoline-containing amide **34c** possessed 60 and 50% activities, respectively. Other compounds including novel carbonyl thiophosphorylureas **27** and intermediates oxadiazole-containing or fused heterocyclic substituted aniline **15** and **16** showed comparably lower activity and were not tested further. From Table 2, we can see that compounds **20a–g** also showed 100% larvicidal activity against oriental armyworm even at the concentration of 10 mg/L. At lower concentration, for example, 2.5 mg/L, **20a** and **20g** still exhibited excellent larvicidal activity (100%), and were more potent than the contrast diflubenzuron (2.5 mg/L, 40%). Especially, **20a** showed 100 and 40% larvicidal activities at concentrations of 0.5 and 0.25 mg/L, respectively. Its LC₅₀ and LC₉₅ values correspondingly were 0.1812 and 0.7767 mg/L, lower than those of chlorantraniliprole (0.0276 and 0.2004 mg/L, respectively, Table 6). The bioactivity of compounds **20a–e**, when R₁ was fixed as Cl, indicated the sequence of larvicidal

Table 6. LC₅₀ and LC₉₅ Values of Compound 20a and Chlorantraniliprole against Oriental Armyworm

compd	$y = a + bx$	R	LC ₅₀ (mg/L)	LC ₉₅ (mg/L)
20a	$y = 6.93 + 2.60x$	0.98	0.1812	0.7767
chlorantraniliprole	$y = 7.98 + 1.91x$	0.91	0.0276	0.2004

activity was $\text{CH}_3 > \text{C}(\text{CH}_3)_3 > \text{CH}(\text{CH}_3)_2 > \text{CH}_3\text{CH}_2\text{CH}_2$, cyclopropyl in the aliphatic amide moiety (R_2).

Larvicidal Activity against Diamondback Moth. Table 3 shows that the bioassay results against diamondback moth at 1.25 mg/L, compounds 20a, 20c, 20e, 20g were more effective than diflubenzuron (2.5 mg/L, 0%). At 0.125 mg/L the four compounds have the same or better larvicidal activity than chlorantraniliprole (86–100%). Even at 0.005 mg/L, 20e showed 57% activity and reached the same larvicidal level as chlorantraniliprole. It was worth noting that 20c showed a death rate of 86% at 0.005 mg/L, which is more effective than chlorantraniliprole (57%) against diamondback moth. The LC₅₀ value of 20a was 0.0054 mg/L, higher than that of chlorantraniliprole (0.0045 mg/L, Table 7). The LC₅₀ values

Table 7. LC₅₀ Values of Compounds 20a, 20c, 20e, and Chlorantraniliprole against Diamondback Moth

compd	$y = a + bx$	R	LC ₅₀ (mg/L)
20a	$y = 15.11 + 4.46x$	0.99	0.0054
20c	$y = 10.79 + 2.09x$	0.97	0.0017
20e	$y = 15.22 + 3.87x$	0.92	0.0023
chlorantraniliprole	$y = 18.06 + 5.57x$	0.97	0.0045

of 20c and 20e were 0.0017 and 0.0023 mg/L, respectively, lower than that of chlorantraniliprole (0.0045 mg/mL, Table 7), which were in accordance with the results in Table 3. The activities of compounds 20a, 20c, and 20e, where R_1 was fixed as Cl, indicated the trend $\text{CH}(\text{CH}_3)_2 > \text{C}(\text{CH}_3)_3 > \text{CH}_3$ in the aliphatic amide moiety (R_2).

Larvicidal Activity against Beet Armyworm. The larvicidal activity of 20a, 20c, 20e, and 20g against beet armyworm at different concentrations is summarized in Table 4. It was found that only 20c and 20e exhibited a 40% death rate at 0.1 mg/L, similar to that of chlorantraniliprole. Surprisingly, 20a and 20g, with excellent activity against oriental armyworm (100% at 2.5 mg/L), showed no activity against beet armyworm at 1 mg/L.

Larvicidal Activity against Corn Borer. From Table 4, it was found that 20a, 20c, and 20e possessed 100% death rate against corn borer at 25 mg/L, more effective than 20g (30%) and diflubenzuron (20%) as well. All three compounds exhibited a 60% death rate at 10 mg/L, which was somewhat less effective than chlorantraniliprole (80%).

Larvicidal Activity against Mosquito. The larvicidal activity of 19c, 19d, and 20a–g against mosquitoes is summarized in Table 5, from which we can see that 20a–g exhibited significant larvicidal activity and showed a 30–100% death rate at 2 mg/L. 20a and 20b showed 40 and 20% activity against mosquitoes at 0.5 mg/L, respectively, lower than that of chlorantraniliprole but similar to that of diflubenzuron (0.5 mg/L, 30%).

HF Calculation. According to the frontier molecular orbital theory, HOMO and LUMO are the two most important factors that affect the bioactivities of compounds. HOMO has the priority to provide electrons, whereas LUMO accepts electrons first.^{36–38} Thus, a study of the frontier orbital energy can provide some useful information for the active mechanism. We therefore

calculated the frontier molecular orbital of representative compounds 20a and 20c that have good insecticidal activity against oriental armyworm and diamondback moth with chlorantraniliprole as contrast by means of HF (Hartree–Fock).

The energies of LUMO, HOMO, and HOMO-1 of 20a, 20c and chlorantraniliprole are listed in Table 8 and the LUMO and

Table 8. Energies of LUMO, HOMO, and HOMO-1 of 20a, 20c and Chlorantraniliprole (Hartree)

	20a	20c	chlorantraniliprole
LUMO	−0.20895	−0.20902	−0.09190
HOMO	−0.29959	−0.29961	−0.25188
HOMO-1	−0.30856	−0.308448	−0.25569

HOMO maps of 20a, 20c and chlorantraniliprole are shown in Figure 2. Taking HF calculation results, there is something in common between 20a and 20c in the LUMO and HOMO maps. In the HOMO of 20a and 20c, electrons are mainly delocalized on the benzene ring and the thiourea group, especially the latter. However, when electron transitions take place, some electrons in the HOMO will enter into the LUMO;³⁷ then, in the LUMO of 20a and 20c, the electrons will mainly be delocalized on the aromatic rings [benzene ring, pyrazole ring (including O atom of trifluoroethoxy group in the 3-position of pyrazole) and pyridine ring] and the carbonyl thiourea group. It was observed that the carbonyl thiourea moiety in both of the molecules (20a, 20c) makes a major contribution to the activity. These are largely through hydrophobic interaction and are most obvious in the HOMO maps (especially the S atom of the bridge). Comparing with those of chlorantraniliprole, we can see that the LUMO of chlorantraniliprole mainly contains three aromatic rings and the amide bridge group, which is similar to that of 20a and 20c, whereas the HOMO contains the pyrazole ring, the pyridine ring, and a small part of the amide bridge (mainly the N atom). The frontier molecular orbitals are located on the main groups, the atoms of which can easily bind with the receptor.³⁸ Thus, it can be concluded that the three aromatic rings of compounds 20a and 20c and chlorantraniliprole as well may contribute activity through π – π and hydrophobic interactions; meanwhile, the carbonyl thiourea bridge that links the benzene and pyrazole rings of the compounds also plays an important role in the insecticidal activity, like the amide bridge group of chlorantraniliprole, which may contribute activity through hydrophobic interaction.

In summary, series of novel amide bridge modified compounds containing pyridylpyrazole were conveniently synthesized on the basis of the structures of anthranilic diamide insecticides, and their structures were characterized and confirmed by melting point, IR, ¹H NMR, and elemental analyses or HRMS. The insecticidal activities against oriental armyworm, diamondback moth, beet armyworm, corn borer, and mosquito of these heterocycle compounds were evaluated. The bioassay results indicated that carbonyl urea, oxadiazole, carbonyl thiophosphorylurea, and thiazoline-containing amide compounds showed weak insecticidal activity against oriental armyworm, whereas part of the carbonyl thiourea and oxadiazole-containing amide compounds exhibited significant larvicidal activity against oriental armyworm, and some of them showed favorable activity against mosquito, diamondback moth, beet armyworm, and corn borer. In general, carbonyl thiourea compounds 20a, 20c, and 20e exhibited comparably outstanding activity compared with others, even prior to the contrasts. In

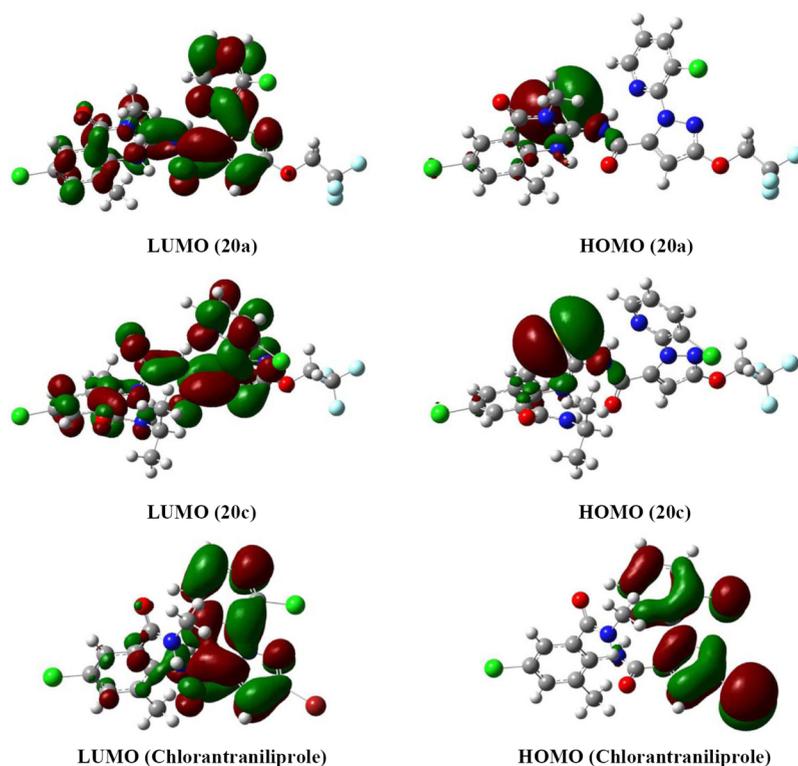


Figure 2. LUMO and HOMO maps for compounds **20a**, **20c**, and chlorantraniliprole from HF calculations. The green parts represent positive molecular orbital, and the red parts represent negative molecular orbital.

some cases, **20c** and **20e** had better larvicidal effects against diamondback moth than chlorantraniliprole. The preliminary structure–activity relationship of compounds was discussed, and the HF calculation results indicated that the carbonyl thiourea moiety of the compounds **20a** and **20c** plays an important role in the insecticidal activity. It is worth noting that the change of the amide bridge in chlorantraniliprole to carbonyl thiourea can keep the insecticidal activities at a low concentration in our earlier studies,¹⁵ whereas the introduction of both carbonyl thiourea and trifluoroethoxyl moieties to such a structure can increase the insecticidal activities in this study, such as in the case of **20c** and **20e**. The present work demonstrated that the trifluoroethoxy-containing carbonyl thioureas can be used as lead compounds for the development of new insecticidal structures.

■ ASSOCIATED CONTENT

Supporting Information

¹H NMR, HRMS, or elemental analyses and melting point data for compounds **19a–n**, **20a–g**, **21a–c**, **22**, **23**, **24a–c**, **26a**, **26b**, **27a**, **27b**, **28**, **29a–c**, **30**, and **34a–e** (³¹P NMR and IR data for part compounds). This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +86-22-23503732. E-mail: nkzml@vip.163.com.

Funding

This work was supported by the National Basic Research Program of China (No. 2010CB126106), the National Key Technologies Research and Development Program (2011BAE06B05-3), the National Natural Science Foundation of China (No. 20872069), and the Tianjin Natural Science Foundation (No. 11JCYBJC04500).

Notes

The authors declare no competing financial interest.

■ REFERENCES

- (1) Rogers, E. F.; Koniuszy, F. R.; Shavel, J., Jr.; Folkers, K. Plant insecticides. I. Ryanodine, a new alkaloid from *Ryania speciosa*. *J. Am. Chem. Soc.* **1948**, *70*, 3086–3088.
- (2) Kuna, S.; Heal, R. E. Toxicological and pharmacological studies on the powdered stem of *Ryania speciosa*, a plant insecticide. *J. Pharmacol. Exp. Ther.* **1948**, *93*, 407–413.
- (3) Procita, L. Some pharmacological actions of ryanodine in the mammal. *J. Pharmacol. Exp. Ther.* **1958**, *123*, 296–305.
- (4) Tohnishi, M.; Nakao, H.; Furuya, T.; Seo, A.; Kodama, H.; Tsubata, K. Flubendiamide, a new insecticide characterized by its novel chemistry and biology. *J. Pestic. Sci.* **2005**, *30*, 354–360.
- (5) Lahm, G. P.; Selby, T. P.; Frendenberger, J. H.; Stevenson, T. M.; Myers, B. J.; Seburyamo, G.; Smith, B. K.; Flexner, L.; Clark, C. E.; Cordova, D. Insecticidal anthranilicdiamides: a new class of potent ryanodine receptor activators. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4898–4906.
- (6) Lahm, G. P.; Cordova, D.; Barry, J. D. New and selective ryanodine receptor activators for insect control. *Bioorg. Med. Chem.* **2009**, *17*, 4127–4133.
- (7) 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.
- (8) Hughes, K. A.; Lahm, G. P.; Selby, T. P.; Stevenson, T. M. *Cyano anthranilamide insecticides*. WO 2004067528 A1, 2004.
- (9) DuPont Rynaxypyr Insect Control Technical Bulletin; http://www2.dupont.com/Production_Agriculture/en_US/assets/downloads/pdfs/Rynaxypyr_Tech_Bulletin.pdf.
- (10) Gewehr, M.; Puhl, M.; Dickhaut, J.; Bastiaans, H. M. M.; Anspaugh, D. D.; Kuhn, D. G.; Oloumi-Sadeghi, H.; Armes, N.; Armers, N. *Pesticidal mixtures*. WO 2007082841 A2, 2007.

- (11) Muehlebach, M.; Jeanguenat, A.; Hall, R. G. *Novel insecticides*. WO 2007080131 A2, 2007.
- (12) Xu, X. Y.; Qian, X. H.; Li, Z.; Huang, Q. C.; Chen, G. Synthesis and insecticidal activity of new substituted *N*-aryl-*N'*-benzoylthiourea compounds. *J. Fluorine Chem.* **2003**, *121*, 51–54.
- (13) Yoon, C. J.; Yang, O. S.; Kang, H.; Kim, G. H. Insecticidal properties of bistrifluron against sycamore lace bug, *Corythucha ciliata* (Hemiptera: Tingidae). *J. Pestic. Sci.* **2008**, *33*, 44–50.
- (14) Sun, R. F.; Li, Y. Q.; Lü, M. Y.; Xiong, L. X.; Wang, Q. M. Synthesis, larvicidal activity, and SAR studies of new benzoylphenylureas containing oxime ether and oxime ester group. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4693–4699.
- (15) Zhang, J.-F.; Xu, J.-Y.; Wang, B.-L.; Li, Y.-X.; Xiong, L.-X.; Li, Y.-Q.; Ma, Y.; Li, Z.-M. Synthesis and insecticidal activities of novel anthranilic diamides containing acylthiourea and acylurea. *J. Agric. Food Chem.* **2012**, *60*, 7565–7572.
- (16) 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.
- (17) Schneider, L.; Graham, D. E. *Method of making N-[(4-chlorophenyl)arnino]carbonyl-2,6-difluorobenzamide*. U.S. 4117009-A, 1978.
- (18) George, T.; Mehta, D. V.; Tahilramani, R.; David, J.; Talwalker, P. K. Synthesis of some s-triazoles with potential analgesic and antiinflammatory activities. *J. Med. Chem.* **1971**, *14*, 335–338.
- (19) Xu, J.; Dong, W.; Xiong, L.; Li, Y.; Li, Z. Design, synthesis and biological activities of novel amides (sulfonamides) containing *N*-pyridylpyrazole. *Chin. J. Chem.* **2009**, *27*, 2007–2012.
- (20) Lahm, G. P.; Selby, T. P.; Stevenson, T. M.; George, P. L.; Philip, L. G.; Paul, S. T.; Martin, S. T. *Arthropodocidal anthranilamides*. WO 2003015519 A1, 2003.
- (21) 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.
- (22) Denton, T. T.; Zhang, X.; Cashman, J. R. 5-Substituted, 6-substituted, and unsubstituted 3-heteroaromatic pyridine analogues of nicotine as selective inhibitors of cytochrome P-450 2A6. *J. Med. Chem.* **2005**, *48* (1), 224–239.
- (23) David, A.; Romina, B.; Francesco, F.; Ferdinando, P.; Luigi, V. TBAF-catalyzed synthesis of 5-substituted 1*H*-tetrazoles under solventless conditions. *J. Org. Chem.* **2004**, *69* (8), 2896–2898.
- (24) He, H.-D.; Tu, S.-Z. Synthesis and structure-activity relationship of analogs of intravenous anesthetic-xylazine. *Chinese J. Pharm.* **1992**, *23* (5), 208–211.
- (25) Hirashima, A.; Yoshii, Y.; Eto, M. Synthesis and biological activity of 2-aminothiazolines and 2-mercaptothiazolines as octopaminergic agonists. *Agric. Biol. Chem.* **1991**, *55* (10), 2537–2545.
- (26) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267.
- (27) Raymond, M. Presentation d'un programme basic'analyse log-probit pour micro-ordinateur. *Cah. ORSTOM Ser. Ent. Med. Parasitol.* **1985**, *23*, 117–121.
- (28) Wu, Y. D.; Shen, J. L.; Chen, J.; Lin, X. W.; Li, A. M. Evaluation of two resistance monitoring methods in *Helicoverpa armigera*: topical application method and leaf dipping method. *Zhiwu Baohu* **1996**, *22* (5), 3–6.
- (29) Ma, H.; Wang, K. Y.; Xia, X. M.; Zhang, Y.; Guo, Q. L. The toxicity testing of five insecticides to different instar larvae of *Spodoptera exigua*. *Xiandai Nongyao* **2006**, *5*, 44–46.
- (30) Busvine, J. R. *Recommended Methods for Measurement of Pest Resistance to Pesticides*; FAO Plant Production and Protection Paper 21; FAO: Rome, Italy, 1980; pp 3–13 and 119–122.
- (31) Chen, L.; Huang, Z. Q.; Wang, Q. M.; Shang, J.; Huang, R. Q.; Bi, F. C. Insecticidal benzoylphenylurea-*S*-carbamate: a new propenesticide with two effects of both benzoylphenylureas and carbamates. *J. Agric. Food Chem.* **2007**, *55*, 2659–2663.
- (32) Scott, A. P.; Radom, L. Harmonic vibrational frequencies: an evaluation of Hartree–Fock, Moeller–Plesset, quadratic configuration interaction, density functional theory, and semiempirical scale factors. *J. Phys. Chem.* **1996**, *100*, 16502–16513.
- (33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; et al. *Gaussian 03*, revision C01; Gaussian, Inc.: Wallingford, UK, 2004.
- (34) Nitulescu, G. M.; Draghici, C.; Missir, A. V. Synthesis of new pyrazole derivatives and their anticancer evaluation. *Eur. J. Med. Chem.* **2010**, *45*, 4914–4919.
- (35) Liu, X.-H.; Zhang, C.-Y.; Guo, W.-C.; Li, Y.-H.; Chen, P.-Q.; Wang, T.; Dong, W.-L.; Wang, B.-L.; Sun, H.-W.; Li, Z.-M. Synthesis, bioactivity and SAR study of *N'*-(5-substituted-1,3,4-thiadiazol-2-yl)-*N*-cyclopropylformyl-thioureas as ketol-acid reductoisomerase inhibitors. *J. Enzym. Inhib. Med. Chem.* **2009**, *24* (2), 545–552.
- (36) Chen, P. Q.; Liu, X. H.; Sun, H. W.; Wang, B. L.; Li, Z. M.; Lai, C. M. Molecular simulation studies of interactions between ketol-acid reductoisomerase and its inhibitors. *Acta Chem. Sinica* **2007**, *65*, 1693–1701.
- (37) Liu, X.-H.; Zhao, W.-G.; Wang, B.-L.; Li, Z.-M. Synthesis, bioactivity and DFT structure–activity relationship study of novel 1,2,3-thiadiazole derivatives. *Res. Chem. Intermed.* **2012**, *38* (8), 1999–2008.
- (38) Liu, X.-H.; Pan, L.; Tan, C.-X.; Weng, J.-Q.; Wang, B.-L.; Li, Z.-M. Synthesis, crystal structure, bioactivity and DFT calculation of new oxime ester derivatives containing cyclopropane moiety. *Pestic. Biochem. Physiol.* **2011**, *101*, 143–147.