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

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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, $^1$H 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 $LC_{50}$ and $LC_{95}$ 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 $LC_{50}$ 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 representive 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 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

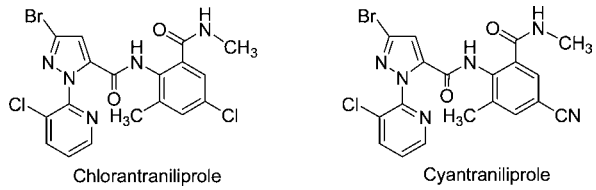


**Figure 1.** Chemical structures of anthranilic diamide insecticides.

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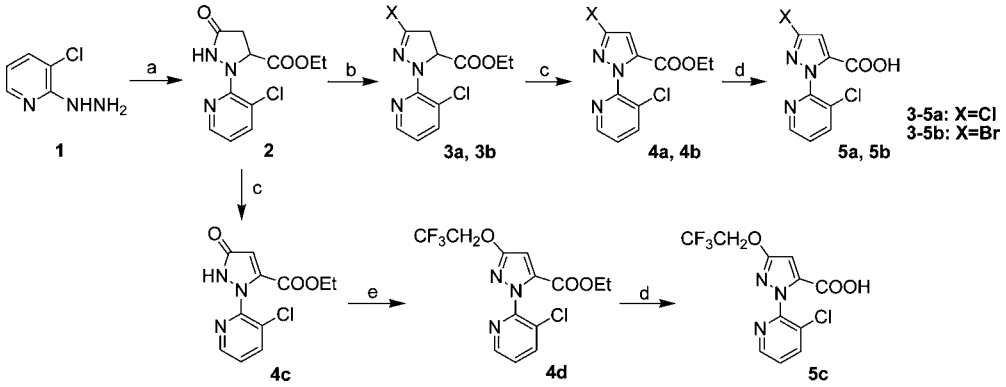
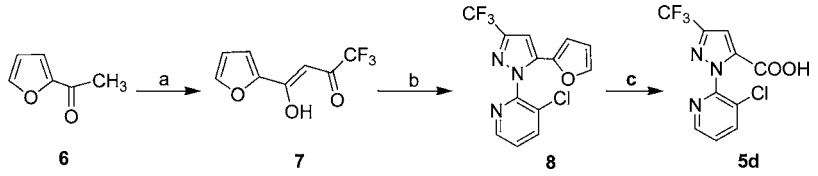
**Scheme 1. Synthesis of Compounds 5a−c**[a]




[a]Reagents and conditions: (a) diethyl maleate, NaOEt, EtOH, reflux; (b) $POCl_3$ or $POBr_3$, MeCN, 80 °C; (c) $K_2S_2O_8$, $H_2SO_4$, MeCN, reflux; (d) (i) aqueous NaOH, MeOH and (ii) aqueous HCl; and (e) $CF_3CH_2I$, $K_2CO_3$, DMF, 100 °C.

**Scheme 2. Synthesis of Compound 5d**[a]




[a]Reagents and conditions: (a) $NaOCH_3$, ethyl trifluoroacetate,; (b) 3-chloro-2-hydrazinylpyridine (**1**), AcOH, reflux; and (c) $KMnO_4$, acetone/$H_2O$, 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, diamondback moth, beet armyworm, corn borer, and mosquito were tested accordingly. The preliminary structure−activity relationship (SAR) was also discussed.

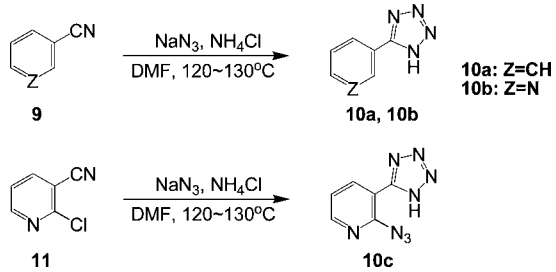
## MATERIALS AND METHODS

**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. $^1$H 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 $CDCl_3$ or DMSO-$d_6$ solution with tetramethylsilane as the internal standard, and chemical shift values ($\delta$) 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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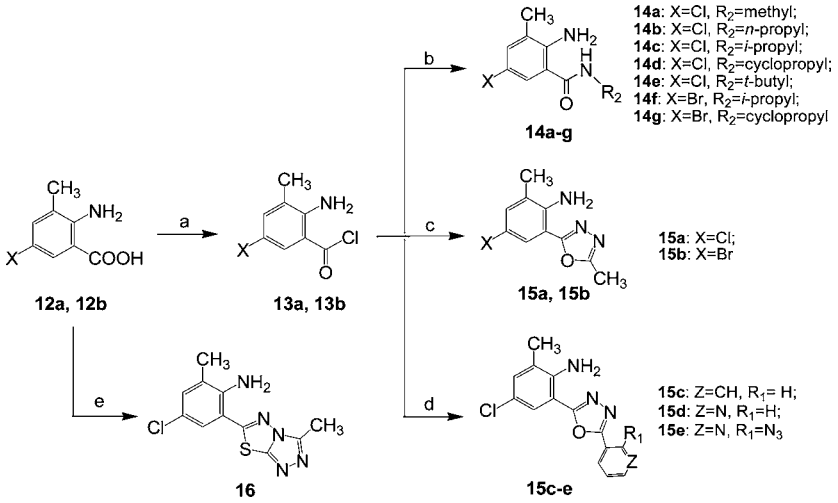
**Scheme 4. Synthesis of Compounds 14a−g, 15a−e, and 16**[a]




[a]Reagents and conditions: (a) $SOCl_2$, reflux; (b) $R_2NH_2$, $CH_2Cl_2$; (c) 5-methyl-1*H*-tetrazole, Py, 100−110 °C; (d) compounds **10a−c**, Py, 1,4-dioxane, 100−110 °C; and (e) 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol, $POCl_3$, reflux.

concentrated HCl, and the solid was collected by filtration and washed with water and acetone successively to afford 5-phenyl-1*H*-tetrazole (**10a**) as white crystals: yield 68%, mp 213−215 °C (lit.[23] mp 215−216 °C).

3-Cyanopyridine was used as material to afford 3-(1*H*-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-(1*H*-tetrazol-5-yl)pyridine (**10c**) as a light yellow solid: yield 52%; mp 245−247 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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 $C_6H_4N_8$ ($[M - H]^-$), 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 ($SOCl_2$) (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-1*H*-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% $Na_2CO_3$ 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; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.19 (s, 3H, $CH_3$), 2.58 (s, 3H, $CH_3$), 6.64 (br, 0.67H, $NH_2$), 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; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.22 (s, 3H, $CH_3$), 2.62 (s, 3H, $CH_3$), 5.91 (br, 2H, $NH_2$), 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 $SOCl_2$ (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% $Na_2CO_3$ 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; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.21 (s, 3H, $CH_3$), 6.75 (br, 0.71H, $NH_2$), 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; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.22 (s, 3H, $CH_3$), 6.75 (br, 0.85H, $NH_2$), 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; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.24 (s, 3H, $CH_3$), 6.82 (br, 2H, $NH_2$), 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 $C_{14}H_{10}ClN_7O$ ($[M + Na]^+$), 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-4*H*-1,2,4-triazole-3-thiol (2 mmol), and phosphorus oxychloride ($POCl_3$) (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−$H_2O$ to afford compound **16** as a yellow solid: yield 47%; mp 266−268 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.20 (s, 3H, $CH_3$), 2.67 (s, 3H, $CH_3$), 6.56 (br, 2H, $NH_2$), 7.31 (s, 1H, Ph−H), 7.36 (s, 1H, Ph−H).

**Synthesis of 1-(3-Chloro-2-pyridyl)-3-(substituted)-1*H*-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-1*H*-prazole-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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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% $NaHCO_3$ 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*-prazole-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 caboxamide. **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 mmmol) with $SOCl_2$ (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 $POCl_3$ (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−$H_2O$ to afford compound **30** as pink crystals.

**Synthesis of 1-(2-Hydroxyethyl/hyroxypropyl)-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−$H_2O$ 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; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.44 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 3.34 (dd, $J_1$ = 10.0 Hz, $J_2$ = 6.4 Hz, 1H, $CH_2$), 3.78 (dd, $J_1$ = 10.0 Hz, $J_2$ = 6.4 Hz, 1H, $CH_2$), 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%. $LC_{50}$ and $LC_{95}$ 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 (%) | compd | larvicidal activity (%) | 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 |

[a]chlorantraniliprole.

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

| | larvicidal activity (%) at | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| compd | 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] |

[a]At a concentration of 0.1 mg/L.

**Table 3. Larvicidal Activity of Compounds, Diflubenzuron, and Chlorantraniliprole against Diamondback Moth (*Plutella xylostella* L.)**

| | larvicidal activity (%) at | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| compd | 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


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

| | *L. exigua* Hübner | | *O. nubilalis* | |
|---|---|---|---|---|
| compd | 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 were expressed by death percentage. For comparative purposes, chlorantraniliprole and diflubenzuron were tested under the same conditions.

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

| | larvicidal activity (%) at | | | |
|---|---|---|---|---|
| compd | 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 |

**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 package[33] 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 literature [22] 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 $N_3^-$ 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 oxadizole-containing substituted aniline (**15e**). The azido group is not affected in the following reactions, too, which can be confirmed by $^1$H 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 $POCl_3$ 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 acetone[34] or reacts with thiocyanate catalyzed by PEG-600 in methane dichloride at room temperature[35] 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.


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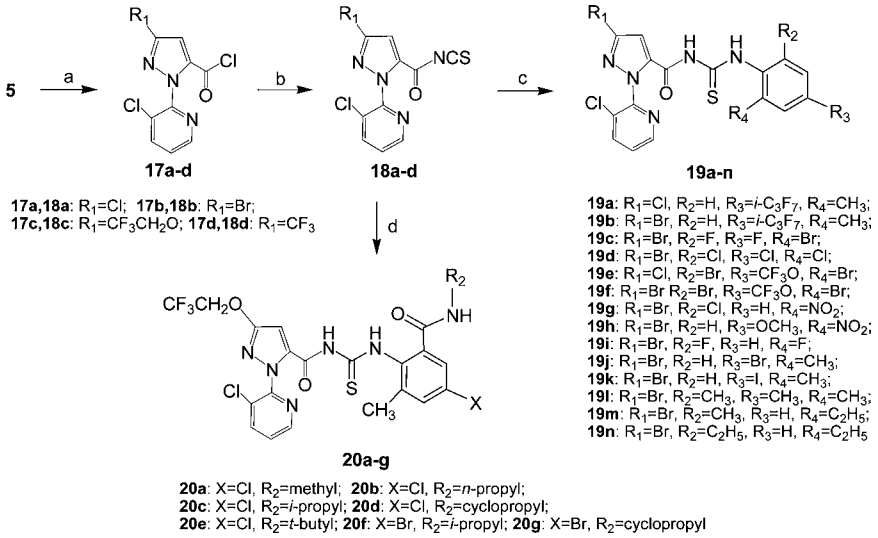
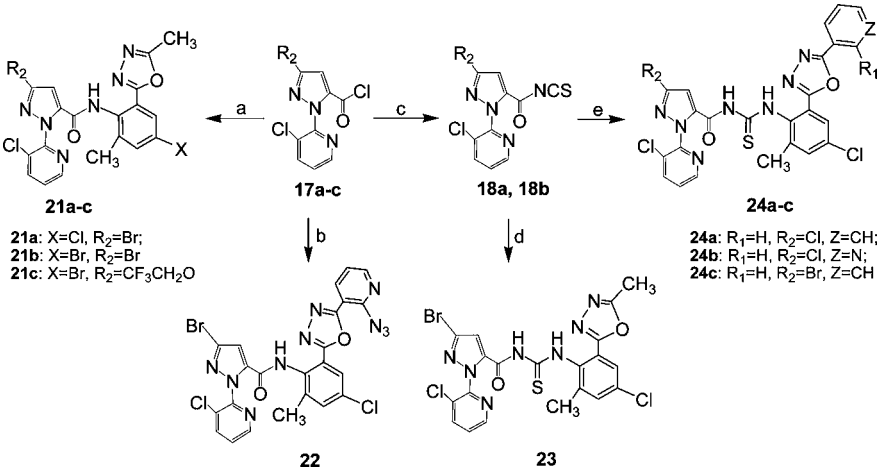
**Scheme 5. Synthesis of Compounds 19a−n and 20a−g**[a]



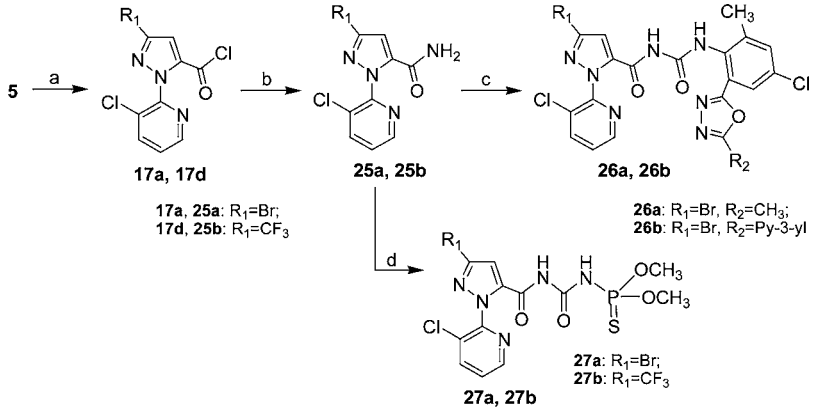

[a]Reagents and conditions: (a) $(COCl)_2$, DMF, $CH_2Cl_2$; (b) KSCN, PEG-400, $CH_3CN$; (c) substituted aniline, $CH_3CN$; and (d) compd **14a−g**, $CH_3CN$.

**Scheme 6. Synthesis of Compounds 21a−c, 22, 23, and 24a−c**[a]




[a]Reagents and conditions: (a) compd **15a** or **15b**, $Et_3N$, $CH_2Cl_2$; (b) compd **15e**, $Et_3N$, $CH_2Cl_2$; (c) KSCN, PEG-400, $CH_3CN$; (d) compd **15a**, $CH_3CN$; and (e) compd **15c** or **15d**, $CH_3CN$

**Scheme 7. Synthesis of Compounds 26a, 26b, 27a, and 27b**[a]




[a]Reagents and conditions: (a) $(COCl)_2$, DMF, $CH_2Cl_2$; (b) $NH_3{\cdot}H_2O$; (c) (i) $(COCl)_2$, $ClCH_2CH_2Cl$, reflux, and (ii) compd **15a** or **15d**; and (d) (i) $(COCl)_2$, $ClCH_2CH_2Cl$, reflux, and (ii) 93% spermine.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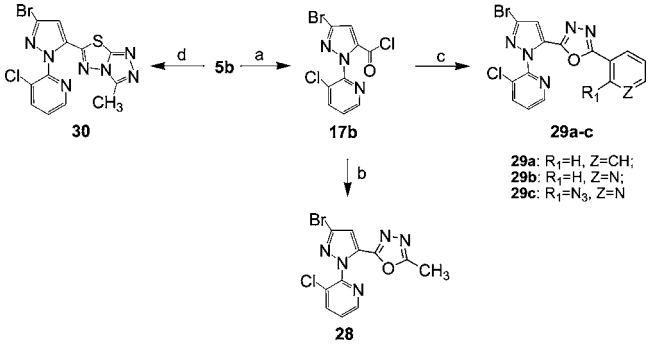
Compounds **26** were synthesized, as shown in Scheme 7. Pyrazole carboxylic acid **5** was converted to amide **25** by reaction with oxalyl chloride and then aqueous ammonia. Compound **25** was then refluxed with oxalyl chloride in 1,2-dichloroethane to give its corresponding pyrazole carbonyl isocyanate 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 $POCl_3$ to afford the fused heterocyclic compound **30**.

**Scheme 8. Synthesis of Compounds 28, 29a−c, and 30**[a]



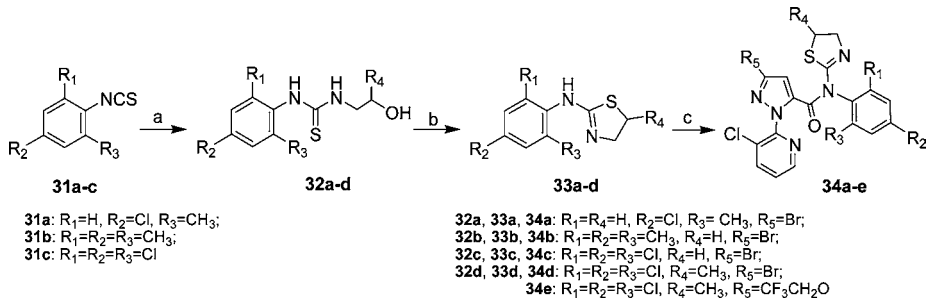

[a]Reagents and conditions: (a) $SOCl_2$, benzene, reflux; (b) 5-methyl-1*H*-tetrazole, Py, 100−110 °C; (c) compd **10a−c**, Py, 1,4-dioxane, 100−110 °C; and (d) 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol, $POCl_3$, reflux.

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 $Et_3N$ 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 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 $\nu$ (C═S) and $\nu$ (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 $\delta$ 9.73−10.42 and 11.08−12.48 as a singlet, respectively. The trifluoroethoxyl protons ($-OCH_2CF_3$) of compounds **20a−g**, **21c**, and **34e** appeared at $\delta$ 4.65−4.92 as a quartet due to "F" splitting, whereas the methoxyl protons ($(CH_3O)_2P(=S)-$) of compound **27** appeared at $\delta$ ∼3.85 as a doublet owing to "P" splitting. Another N—H proton signal of the amide moiety ($-CONHR_2$) in compounds **20a−g** was observed at $\delta$ 6.32−6.64. As for compounds **26** and **27**, the two active proton signals (N—H) appeared at $\delta$ 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 $LC_{50}$ and $LC_{95}$ 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 $R_1$ was fixed as Cl, indicated the sequence of larvicidal

**Scheme 9. Synthesis of Compounds 34a−e**[a]




[a]Reagents and conditions: (a) 2-aminoethanol or 1-amino-2-propanol, $Et_2O$; (b) (i) concentrated HCl, reflux, and (ii) NaOH; and (c) compd **17b** or **17c**, $Et_3N$, dry THF.


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**Table 6. $LC_{50}$ and $LC_{95}$ 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 $CH_3$ > $C(CH_3)_3$ > $CH(CH_3)_2$ > $CH_3CH_2CH_2$, 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 $LC_{50}$ value of **20a** was 0.0054 mg/L, higher than that of chlorantraniliprole (0.0045 mg/L, Table 7). The $LC_{50}$ values

**Table 7. $LC_{50}$ 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 $CH(CH_3)_2$ > $C(CH_3)_3$ > $CH_3$ 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 trifluoroethyloxyl 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 $\pi-\pi$ 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


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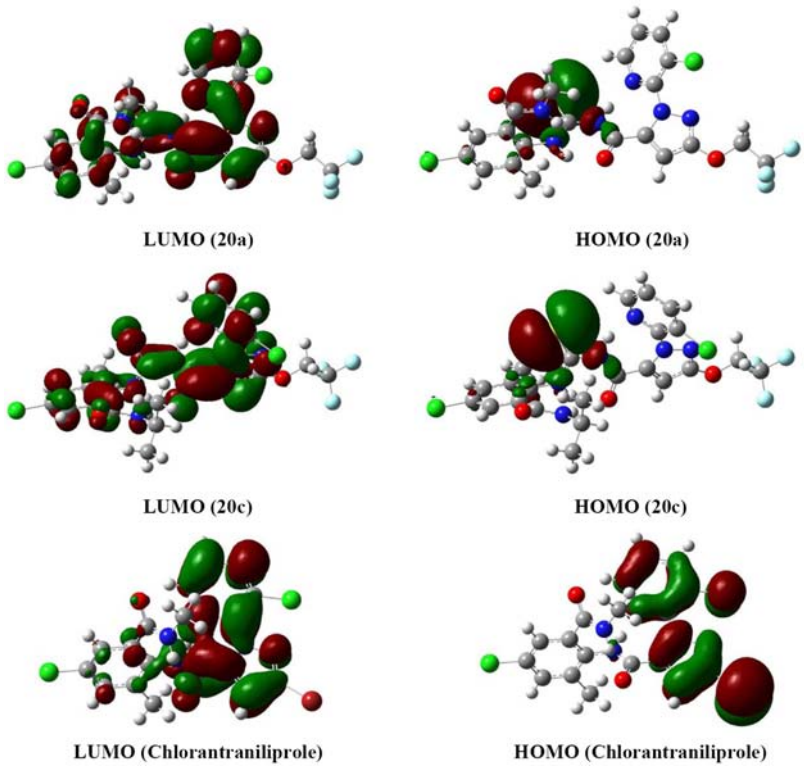


**Figure 2.** LUMO and HOMO maps for compounds **20a**, **20c**, and chlorantraniliprole from HF calculations. The green parts represent positive molecular orbital, and the red parts represent negative molecular orbital.

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

$^{1}$H 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** ($^{31}$P NMR and IR data for part compounds). This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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