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Synthesis and Insecticidal Activity of Novel *N*-Pyridylpyrazole Carbonyl Thioureas

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A series of novel *N*-pyridylpyrazole carbonyl thioureas were designed and synthesized. Their structures were characterized by melting points, ^{1}H NMR, IR and elemental analysis or HRMS. The bioassay tests indicated that some of these compounds exhibited moderate insecticidal activity against *Mythimna separata* Walker and *Culex pipiens pallens*. Among 17 compounds, **5n** and **5p** showed 100% larvicidal activity against *Mythimna separata* Walker at the test concentration of 100 mg/L.

Keywords carbonyl thiourea, insecticidal activity, *N*-pyridylpyrazole

Introduction

The use of synthetic pesticides is an essential element for fighting serious crop damage from harmful pests in both guarantee of food supply and prevention of disease transmission. However, over time, some pests become pesticide-resistant due to annual applications. In addition, due to environmental concerns associated with the accumulation of pesticides in food products and water supplies, there is a great demand for environmentally friendly products that act on new biochemical targets. A new class of insecticides has been discovered, the anthranilic diamides, that provide exceptional control through action on a novel target, the ryanodine receptor. Chlorantraniliprole (Rynaxypyr^{TM}) (Dupont's) is the first new insecticide from the anthranilic diamides, characterized by its high levels of insecticidal activity and low toxicity to mammals attributed to a high selectivity for insect over mammalian ryanodine receptors.[1] Owing to their prominent insecticidal activity, unique modes of action and good environmental profiles, anthranilic diamides and their chemical synthesis have recently attracted considerable attention in the field of novel agricultural insecticides.[2-5]

There were lots of literatures reported for the modification of the anthranilic diamides,[6-9] but the modifications on the amide bridge that links two aryl rings were relatively seldom reported,[10,11] which encouraged us to synthesize some other novel compounds with such bridge-modified structure. In order to find more potent insecticidal compounds and continue our work, in this paper, according to the structure of chlorantraniliprole, a series of novel carbonyl thiourea title compounds containing *N*-pyridylpyrazole heterocycles were designed through a variation of the amide bridge of such general structure of anthranilic diamides to the carbonyl thiourea bridge (Figure 1) and synthesized as shown in Scheme 1. The bioactivity against *Mythimna separata* Walker and *Culex pipiens pallens* was tested accordingly. The preliminary structure-activity relationships were also discussed using a conformation analysis method.

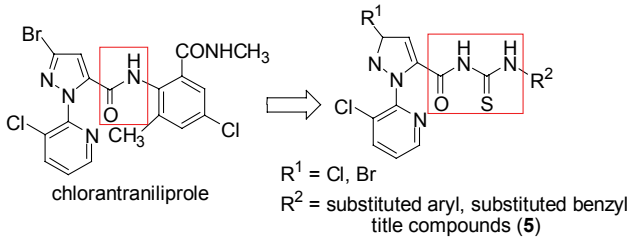

Figure 1 Design of the title compounds.

Experimental

Materials and instruments

The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments 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 or 400 MHz using a Bruker AC-P 300 or AV 400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal

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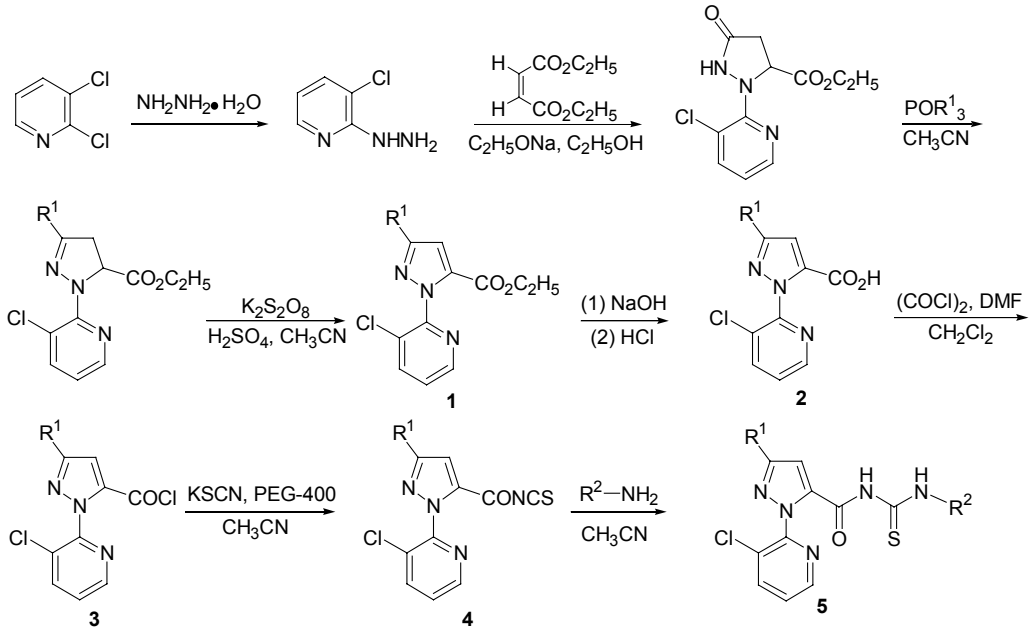
Scheme 1 General synthetic route for title compounds **5a**—**5q**



standard. Elemental analyses were performed on a Vario EL elemental analyzer. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. Reagents were all analytically or chemically pure. Substituted anilines and 3,5-bis(trifluoromethyl)benzylamine were purchased from Alfa Aesar and Aladdin-Reagent. All solvents were dried by standard methods in advance and distilled before use. Chlorantraniliprole was synthesized according to the literature[12] and used as the control.

General procedure

Ethyl 2-amino-5-ethyl-thiophene-5-carboxylate was synthesized by the method reported by literature.[13] The intermediates ethyl 3-chloro-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylate (**1a**) and ethyl 3-bromo-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylate (**1b**) were synthesized according to our previous work.[14] The title compounds were prepared as shown in Scheme 1.

3-Chloro-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylic acid (2a) To a solution of ester **1a** (5.42 g, 19 mmol) in 30 mL of methanol and 15 mL of water, 3 mL of aq. sodium hydroxide (w=50%) was added, and the mixture was stirred at room temperature for 3 h, then concentrated. The concentrated mixture was diluted with 30 mL water, and washed with 20 mL of ethyl acetate to remove organic impurities. The aqueous phase was acidified to pH 2 using concentrated hydrochloric acid to give 4.6 g of acid **2a**: white solid, yield 94%, m.p. 199—201 ℃ (Lit.[14] 200—201 ℃).

With the same procedure using ester **1b** as material, 3-bromo-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylic acid (**2b**) could also be prepared: light yellow solid, yield 89%, m.p. 198—200 ℃ (Lit.[14] 197—200 ℃).

3-Substituted-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carbonyl chloride (3) Compound **2** (1.0 mmol) was suspended in 25 mL of dichloromethane. Under vigorous stirring, oxalyl chloride (4 mmol) and two drops of DMF were added successively. After stirring at room temperature for 3—4 h, the mixture was evaporated to dryness *in vacuo*, the residue, that is, the crude pyrazolecarbonyl chloride was obtained as a yellow powder (100%), which was used directly in the next step without further purification.

***N′*-Substituted-*N*-(3-substitued-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carbonyl)thiourea (5)** To a mixture of 0.24 g (2.5 mmol) of KSCN in 15 mL of dry acetonitrile, two drops of PEG-400 were added, and the mixture was stirred at room temperature for 5 min to give a homogeneous solution, then, the solution of crude pyrazole carbonyl chloride **3** (1 mmol) in 5 mL of dry acetonitrile was added. After stirring at room temperature for 40 min, the mixture was filtrated to give the acetonitrile solution of pyrazole carbonyl isothiocyanate (**4**), and then the substituted amine (0.85 mmol) was added, after stirring at room temperature for another 3—4 h, the 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 the title compounds.

***N′*-(2-Trifluoromethylphenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-chloro-1*H*-prazole-5-carbonyl] thiourea (5a)** Yield 61%; light yellow solid, m.p. 183—185 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (s, 1H, Pyrazol-H), 7.40—7.50 (m, 2H, Ph-H), 7.61 (t, J=8.0 Hz, 1H,

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Ph-H), 7.69 (d, J=8.0 Hz, 1H, Ph-H), 7.84 (d, J=8.0 Hz, 1H, Py-H), 7.99 (d, J=8.0 Hz, 1H, Py-H), 8.56 (d, J=4.4 Hz, 1H, Py-H), 10.03 (s, 1H, NH), 11.81 (s, 1H, NH). HRMS calcd for $C_{17}H_{10}Cl_2F_3N_5OS$ 481.9833, found 481.9829 $[M+Na]^+$.

***N′*-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[1-(3-chloro-2-pyridyl)-3-chloro-1*H*-prazole-5-carbonyl]-thiourea (5b)** Yield 67%; light yellow solid, m.p. 177—179 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (s, 1H, Pyrazol-H), 7.54 (dd, J_1=8.0 Hz, J_2=4.8 Hz, 1H, Py-H), 7.70 (s, 1H, Ph-H), 8.03 (d, J=8.4 Hz, 1H, Py-H), 8.14 (s, 2H, Ph-H), 8.67 (d, J=4.0 Hz, 1H, Py-H), 10.20 (s, 1H, NH), 12.22 (s, 1H, NH). Anal. calcd for $C_{18}H_9Cl_2F_6N_5OS$: C 40.93, H 1.72, N 13.26; found C 40.95, H 2.14, N 13.21.

***N′*-(4-Fluoro-3-nitrophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-chloro-1*H*-prazole-5-carbonyl] thiourea (5c)** Yield 56%; yellow solid, m.p. 139—141 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (s, 1H, Pyrazol-H), 7.26—7.32 (m, 1H, Ph-H), 7.53 (dd, J_1=7.2 Hz, J_2=5.2 Hz, 1H, Py-H), 7.90—7.92 (m, 1H, Ph-H), 8.01 (d, J=8.0 Hz, 1H, Py-H), 8.41 (d, J=5.2 Hz, 1H, Ph-H), 8.61 (d, J=4.0 Hz, 1H, Py-H), 10.07 (s, 1H, NH), 12.04 (s, 1H, NH). Anal. calcd for $C_{16}H_9Cl_2FN_6O_3S$: C 42.21, H 1.99, N 18.46; found C 41.93, H 2.32, N 18.62.

***N′*-(2-Methylphenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5d)** Yield 65%; light yellow solid, m.p. 179—181 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 7.09 (s, 1H, Pyrazol-H), 7.22—7.26 (m, 3H, Ph-H), 7.46—7.50 (m, 1H, Ph-H), 7.57 (d, J=4.8 Hz, 1H, Py-H), 7.97 (dd, J_1=10.4 Hz, J_2=2.0 Hz, 1H, Py-H), 8.56 (d, J=2.0 Hz, 1H, Py-H), 9.85 (s, 1H, NH), 11.51 (s, 1H, NH). Anal. calcd for $C_{17}H_{13}BrClN_5OS$: C 45.30, H 2.91, N 15.54; found C 45.11, H 2.84, N 15.59.

***N′*-(2-Trifluoromethylphenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5e)** Yield 50%; white solid, m.p. 181—183 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (s, 1H, Pyrazol-H), 7.40—7.50 (m, 2H, Ph-H), 7.58—7.71 (m, 2H, Ph-H), 7.84 (d, J=10.0 Hz, 1H, Py-H), 7.98 (d, J=10.4 Hz, 1H, Py-H), 8.56 (d, J=4.4 Hz, 1H, Py-H), 10.03 (s, 1H, NH), 11.81 (s, 1H, NH). Anal. calcd for $C_{17}H_{10}BrClF_3N_5OS$: C 40.46, H 2.00, N 13.88; found C 40.18, H 1.69, N 13.92.

***N′*-(2-Chlorophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5f)** Yield 73%; white solid, m.p. 188—189 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (s, 1H, Pyrazol-H), 7.19—7.34 (m, 2H, Ph-H), 7.42—7.51 (m, 2H, Ph-H), 7.98 (dd, J_1=10.8 Hz, J_2=2.0 Hz, 1H, Py-H), 8.21 (d, J=10.8 Hz, 1H, Py-H), 8.57 (dd, J_1=6.4 Hz, J_2=2.0 Hz, 1H, Py-H), 10.00 (s, 1H, NH), 11.97 (s, 1H, NH). Anal. calcd for $C_{16}H_{10}BrCl_2N_5OS$: C 40.79, H 2.14, N 14.86; found C 40.35, H 1.89, N 14.87.

***N′*-(2-Nitrophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5g)** Yield 51%; yellow solid, m.p. 190—191 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (s, 1H, Pyrazol-H), 7.38—7.69 (m, 3H, Ph-H), 7.99 (d, J=10.8 Hz, 1H, Py-H), 8.10 (dd, J_1=11.2 Hz, J_2=1.6 Hz, 1H, Py-H), 8.36 (d, J=10.8 Hz, 1H, Py-H), 8.57 (d, J=4.4 Hz, 1H, Ph-H), 10.42 (s, 1H, NH), 12.34 (s, 1H, NH). HRMS calcd for $C_{16}H_{10}BrClN_6O_3S$ 502.9305, found 502.9303$[M+Na]^+$.

***N′*-[3-Ethoxycarbonyl-5-ethyl-2-thienyl]-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl]-thiourea (5h)** Yield 81%; yellow solid, m.p. 216—218 ℃; IR (KBr) v: 3399, 3140 (N—H), 1712, 1682 (C=O, C=N), 1279 (C=S), 1177 (C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.29 (t, J=7.2 Hz, 3H, CH_3), 1.30 (t, J=7.5 Hz, 3H, CH_3), 2.74 (q, J=7.5 Hz, 2H, CH_2), 4.33 (q, J=7.2 Hz, 2H, CH_2), 7.02 (s, 1H, Pyrazol-H), 7.17 (s, 1H, Thiophene-H), 7.49 (dd, J_1=8.1 Hz, J_2=4.8 Hz, 1H, Py-H), 8.00 (dd, J_1=8.1 Hz, J_2=1.5 Hz, 1H, Py-H), 8.61 (dd, J_1=4.8 Hz, J_2=1.5 Hz, 1H, Py-H), 10.57 (s, 1H, NH), 14.19 (s, 1H, NH). Anal. calcd for $C_{19}H_{17}BrClN_5O_3S_2$: C 42.04, H 3.16, N 12.90; found C 41.76, H 3.19, N 12.68.

***N′*-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl]-thiourea (5i)** Yield 56%; light yellow solid, m.p. 182—184 ℃; IR (KBr) v: 3315, 3164 (N—H), 1678, 1644 (C=O, C=N), 1277 (C=S), 1162 (C—N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (s, 1H, Pyrazol-H), 7.54 (dd, J_1=7.6 Hz, J_2=4.8 Hz, 1H, Py-H), 7.71 (s, 1H, Ph-H), 8.02 (d, J=8.4 Hz, 1H, Py-H), 8.14 (s, 2H, Ph-H), 8.66 (d, J=4.8 Hz, 1H, Py-H), 10.14 (s, 1H, NH), 12.21 (s, 1H, NH). Anal. calcd for $C_{18}H_9BrClF_6N_5OS$: C 37.75, H 1.58, N 12.23; found C37.99, H 2.15, N 12.34.

***N′*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl]-thiourea (5j)** Yield 59%; white solid, m.p. 171—173 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.95 (d, J=5.6 Hz, 2H, CH_2), 7.04 (s, 1H, Pyrazol-H), 7.48 (dd, J_1=7.6 Hz, J_2=5.6 Hz, 1H, Py-H), 7.75—7.81 (m, 3H, Ph-H), 7.97 (d, J=8.0 Hz, 1H, Py-H), 8.55 (d, J=4.4 Hz, 1H, Py-H), 9.76 (s, 1H, NH), 10.54 (br s, 1H, NH). Anal. calcd for $C_{19}H_{11}BrClF_6N_5OS$: C 38.89, H 1.89, N 11.94; found C 39.08, H 2.14, N 12.43.

***N′*-(4-Fluoro-3-nitrophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5k)** Yield 51%; yellow solid, m.p. 136—138 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (s, 1H, Pyrazol-H), 7.26—7.32 (m, 1H, Ph-H), 7.53 (t, J=5.6 Hz, 1H, Py-H), 7.91 (d, J=6.8 Hz, 1H, Ph-H), 8.01 (d, J=8.4 Hz, 1H, Py-H), 8.41 (d, J=6.0 Hz, 1H, Ph-H), 8.60 (d, J=4.0 Hz, 1H, Py-H), 10.04 (s, 1H, NH), 12.04 (s, 1H, NH). Anal. calcd for $C_{16}H_9BrClFN_6O_3S$: C 38.46, H 1.82, N 16.82; found C 38.55, H 2.16, N 16.74.

***N′*-(4-Trifluoromethoxylphenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5l)** Yield 86%; light yellow solid, m.p. 158—160 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (s, 1H, Pyrazol-H), 7.21 (d, J=8.4 Hz, 2H, Ph-H), 7.50 (dd, J_1=8.0 Hz, J_2=4.8 Hz, 1H, Py-H), 7.65 (d, J=8.4 Hz, 2H, Ph-H),

7.99 (d, J=8.0 Hz, 1H, Py-H), 8.60 (d, J=3.2 Hz, 1H, Py-H), 9.81 (s, 1H, NH), 11.90 (s, 1H, NH). Anal. calcd for $C_{17}H_{10}BrClF_3N_5O_2S$: C 39.21, H 1.94, N 13.45; found C 39.06, H 2.19, N 13.14.

***N′*-(2,3,4-Trifluorophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5m)** Yield 62%; yellow solid, m.p. 183—185 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96—7.03 (m, 1H, Ph-H), 7.11 (s, 1H, Pyrazol-H), 7.50 (dd, J_1=8.0 Hz, J_2=4.4 Hz, 1H, Py-H), 7.76—7.81 (m, 1H, Ph-H), 8.00 (dd, J_1=8.0 Hz, J_2=1.2 Hz, 1H, Py-H), 8.58 (dd, J_1=4.4 Hz, J_2=1.2 Hz, 1H, Py-H), 10.06 (s, 1H, NH), 11.76 (s, 1H, NH). HRMS calcd for $C_{16}H_8BrClF_3N_5OS$: 489.9352, found 489.9348 $[M+H]^+$.

***N′*-(2,6-Dimethylphenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5n)** Yield 71%; white solid, m.p. 202—204 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.23 (s, 6H, CH_3), 7.09 (d, J=7.6 Hz, 2H, Ph-H), 7.10 (s, 1H, Pyrazol-H), 7.18 (t, J=7.6 Hz, 1H, Ph-H), 7.49 (dd, J_1=8.0 Hz, J_2=4.4 Hz, 1H, Py-H), 7.98 (d, J=8.0 Hz, 1H, Py-H), 8.57 (d, J=4.4 Hz, 1H, Py-H), 9.75 (s, 1H, NH), 11.16 (s, 1H, NH). Anal. calcd for $C_{18}H_{15}BrClN_5OS$: C 46.52, H 3.25, N 15.07; found C 46.09, H 3.37, N 14.86.

***N′*-(4-Phenoxylphenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5o)** Yield 52%; yellow solid, m.p. 164—166 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (s, 1H, Pyrazol-H), 6.97—7.54 (m, 10H, Ph-H+Py-H), 7.98 (d, J=8.0 Hz, 1H, Py-H), 8.58 (d, J=4.4 Hz, 1H, Py-H), 9.69 (s, 1H, NH), 11.77 (s, 1H, NH). Anal. calcd for $C_{22}H_{15}BrClN_5O_2S$: C 49.97, H 2.86, N 13.24; found C 49.61, H 2.39, N 13.52.

***N′*-(2-Methyl-4-nitrophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5p)** Yield 60%; yellow solid, m.p. 193—194 ℃; IR (KBr) ν: 3419, 3180 (N—H), 1687, 1616 (C=O, C=N), 1273 (C=S), 1141 (C—N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 7.13 (s, 1H, Pyrazol-H), 7.51 (dd, J_1=8.0 Hz, J_2=4.8 Hz, 1H, Py-H), 8.01 (d, J=8.0 Hz, 1H, Py-H), 8.10 (d, J=8.8 Hz, 1H, Ph-H), 8.13 (s, 1H, Ph-H), 8.22 (d, J=8.8 Hz, 1H, Ph-H), 8.59 (d, J=4.0 Hz, 1H, Py-H), 10.20 (s, 1H, NH), 11.93 (s, 1H, NH). Anal. calcd for $C_{17}H_{12}BrClN_6O_3S$: C 41.19, H 2.44, N 16.95; found C 41.18, H 2.78, N 16.94.

***N′*-(2,4-Dichlorophenyl)-*N*-[1-(3-chloro-2-pyridyl)-3-bromo-1*H*-prazole-5-carbonyl] thiourea (5q)** Yield 48%; white solid, m.p. 198—200 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (s, 1H, Pyrazol-H), 7.29—7.30 (m, 1H, Ph-H), 7.44—7.51 (m, 2H, Ph-H), 7.99 (dd, J_1=10.4 Hz, J_2=1.6 Hz, 1H, Py-H), 8.23 (d, J=12.0 Hz, 1H, Py-H), 8.57 (dd, J_1=6.0 Hz, J_2=1.6 Hz, 1H, Py-H), 10.09 (s, 1H, NH), 11.99 (s, 1H, NH). HRMS calcd for $C_{16}H_9BrCl_3N_5OS$: 503.8855, found 503.8852 $[M+H]^+$.

Biological activity

Insecticidal activities against oriental armyworm (*Mythimna separate* Walker) were performed in the greenhouse.[15] The bioassay was operated at (25±1) ℃ according to statistical requirements. The compounds were dissolved in acetone to test at varying concentrations. For each fourth-instar larva of oriental armyworm, 0.306 μL of tested solution was applied to the thoracic tergite with a platinum loop. After treatment, the insects were then transferred to their standard rearing conditions. Mortalities were calculated 72 h after treatment. Each treatment was performed three times.

Insecticidal activity was examined against mosquito (*Culex pipiens pallens*).[15] One milliliter of differently concentrated solution of each compound was added to 99 mL of water to get different concentrations of tested solutions. Then, 20 fourth-instar mosquito larva were put into 10 mL of the test solution and raised for 2 d, and the results were expressed by death percentage.

Conformation analysis

Molecular modeling was performed using the Sybyl 6.91 software of Tripos running on an SGI (Silicon Graphics, Inc.) workstation and the conformation optimization for the lowest energy has been done according to our previous works.[6,17] The control chlorantraniliprole, owing to its excellent larvicidal activity, was used as a template to build the molecular structures of compounds **5f** and **5p** which represent the weakest and the best active molecules in this series, respectively. Each structure was fully geometry optimized using a conjugate gradient procedure based on the TRIPOS force field and Gasteiger and Hückel charges. Because these compounds share some common skeleton, non-hydrogen atoms of *N*-pyridylpyrazole and CONH groups were used for superposition with the corresponding atoms of the template structure to analyze the optimized conformation differences between compound **5f** or **5p** and chlorantraniliprole.

Results and Discussion

Synthesis and structure characterization

The synthetic route of title compounds is illustrated in Scheme 1. Pyrazole carbonyl chloride (**3**) was prepared from the reaction of pyrazole acid with oxalyl chloride, and it was treated with potassium thiocyanate under the condition of solid-liquid phase transfer catalysis using a small amount of polyethylene glycol-400 (PEG-400) as the catalyst to give pyrazole carbonyl isothiocyanate (**4**). This compound does not need to be isolated and it was treated immediately with amines to obtain the title compounds (**5**) in good yields. The novel structures of these compounds synthesized have been characterized by melting points, ^{1}H NMR, IR and elemental analysis or HRMS.

In the ^{1}H NMR spectra of **5**, the two active proton signals of NHCO and NHCS on carbonyl thiourea bridge in most cases were observed at δ 9.69—10.42 and δ 10.54—12.34, respectively. Whereas in the situation of compound **5h**, they were observed at δ 10.57 and

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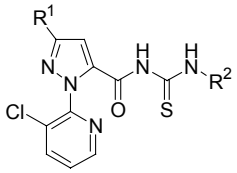
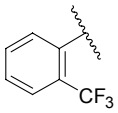
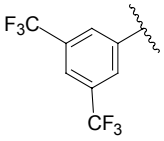
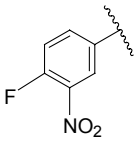
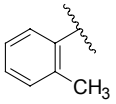
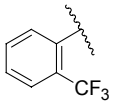
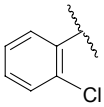
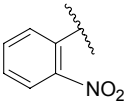
14.19, respectively. The latter has a very high chemical shift value, which may be produced by a SH group, that is, the compound **5h** may be more stable in chloroform-d_6 solution as a carbonyl isothiourea derivative. However, the IR spectrum demonstrated the carbonyl thiourea structure of **5h**. In addition, the aromatic proton of pyrazole ring appeared at δ 6.98—7.12 as a singlet. Compounds **5i** and **5p** were selected to further investigate the IR spectrum characterization of this kind of compounds. The infrared spectrum of the compounds showed absorption bands at 3164—3419 cm^{-1} for N—H stretching. The strong peaks at 1616—1687 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) appear at 1273—1277 and 1141—1162 cm^{-1}, respectively.

Insecticidal activity

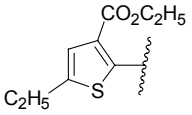
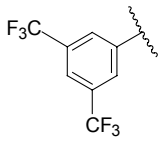
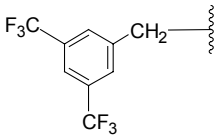
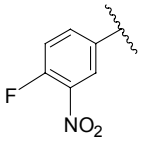
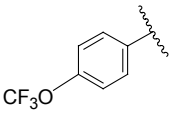
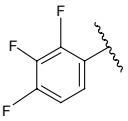
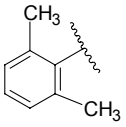
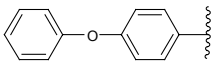
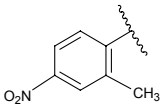
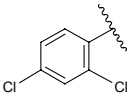
Biological evaluation results of the title compounds were listed in Table 1. Some of them exhibited certain insecticidal activity against *Mythimna separata* Walker. The larvicidal activity of **5q** was 80% and 30% at the concentration of 200 and 100 mg/L, respectively. While the larvicidal activity of **5n** and **5p** were 100%, 100%, 40% and 100%, 100%, 60% at 200, 100 and 50 mg/L separately. In addition, in the same table we can see that some of the compounds had weak insecticidal activity (10%—30%) against *Culex pipiens pallens* at 2 mg/L.

Table 1 Insecticidal activity data of title compounds (% mortality)



Compd.	R^1	R^2	*Mythimna separata* Walker			*Culex pipiens pallens*
			200 mg/L	100 mg/L	50 mg/L	2 mg/L
5a	Cl		50	nt[b]	nt	0
5b	Cl		10	nt	nt	nt
5c	Cl		20	nt	nt	nt
5d	Br		0	nt	nt	nt
5e	Br		10	nt	nt	0
5f	Br		0	nt	nt	30
5g	Br		10	nt	nt	30

Continued

Compd.	R^1	R^2	*Mythimna separata* Walker			*Culex pipiens pallens*
			200 mg/L	100 mg/L	50 mg/L	2 mg/L
5h	Br		30	nt	nt	0
5i	Br		20	nt	nt	Nt
5j	Br		10	nt	nt	Nt
5k	Br		10	nt	nt	Nt
5l	Br		10	nt	nt	Nt
5m	Br		20	nt	nt	Nt
5n	Br		100	100	40	10
5o	Br		10	nt	nt	Nt
5p	Br		100	100	60	20
5q	Br		80	30	nt	30
Control[a]			100	100	100	100

[a] Chlorantraniliprole; [b] nt = not tested.

To further explore the structure-activity relationship on the basis of the data against *Mythimna separata* Walker, a conformation analysis method was performed. Compounds **5f** and **5p** which represent the weakest and the best active molecules in this series, respectively, were selected to compare the optimized conformation with that of chlorantraniliprole. From Figure 2, we can see that the sulfur atom and oxygen atom on the carbonyl thiourea bridge of this series compounds are on the opposite positions. Meanwhile, owing to the better flexibility of carbonyl thiourea bridge than the amide bridge, the substituted phenyl parts of two kinds of compounds showed apparent difference in space after conformation optimization and superposition. The chlorine atom on benzene ring of compound **5f** is far away from the CH_3NHCO group of chlorantraniliprole, while

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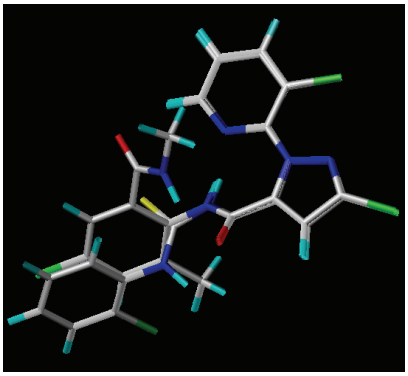
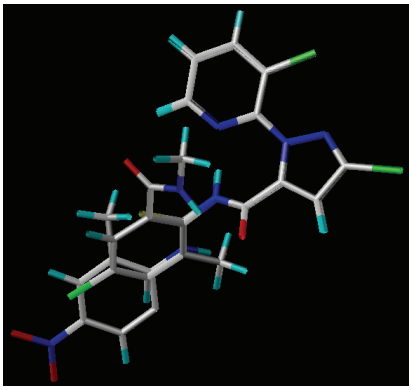


(a)



(b)

Figure 2 Superposition of **5f** with chlorantraniliprole (a) and **5p** with chlorantraniliprole (b).

the methyl group on benzene ring of compound **5p** is near to the CH_3NHCO group of chlorantraniliprole, furthermore the nitro group is also in the similar position of the chlorine atom on the benzene ring of chlorantraniliprole. **5f** exhibited no larvicidal activity, while **5p** showed relatively high larvicidal activity. All these results showed that the existence of more bulky group on *ortho* and *para* position of amino group on the benzene ring of the title compounds is favorable, however it is also essential that the optimized conformation maintains the more bulky group of the title compounds locating in appropriate position for a better matching with that of chlorantraniliprole in space. These may be the possible reasons for the low and high activity of compounds **5f** and **5p**, respectively.

In summary, a series of novel *N*-pyridylpyrazole carbonyl thioureas were synthesized and bioassayed. Among 17 compounds, **5n** and **5p** showed 100% larvicidal activity against *Mythimna separata* Walker at the test concentration of 100 mg/L. Though the most active **5p** showed less effect against *Mythimna separata* Walker than the control chlorantraniliprole, its novel structure and favorable larvicidal activity make it a promising compound for further studies.

Acknowledgement

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