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Design, Synthesis and Biological Activities of Novel Amides (Sulfonamides) Containing *N*-Pyridylpyrazole

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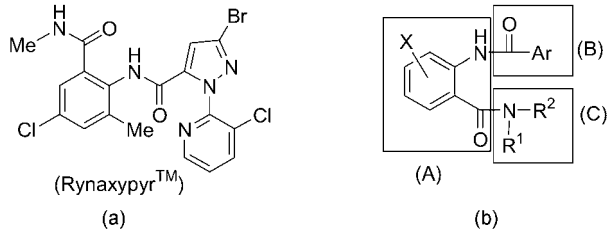
In search of environmentally benign insecticides with high activity, low toxicity and low residual effects, a series of novel amides (sulfonamides) containing *N*-pyridylpyrazole were designed and synthesized. Their chemical structures were characterized by ^{1}H NMR, MS and elemental analysis or HRMS. The bioassay tests indicated that some of these compounds exhibited moderate insecticidal activities against *Mythimna separata* Walker and *Culex pipiens pallens*.

Keywords amide, sulfonamide, *N*-pyridylpyrazole, insecticidal activity

Introduction

Anthranilic diamide,[1,2] discovered by Dupont, is a promising class of novel insecticides which exhibit their action by binding to insect ryanodine receptors (RyR) and activating the uncontrolled release of calcium stores.[3,4] As shown in Scheme 1 (a), anthranilic diamide insecticides could be characterized by a three-part chemical structure: an anthraniloyl moiety (A), an aromatic acyl moiety (B) and an aliphatic amide moiety (C). It was reported that anthranilic diamides containing *N*-pyridylpyrazole in the second section (B) showed better activity than other heterocyclic derivatives.[5] Work in this area has led to the discovery of Rynaxypyr^{TM} (Scheme 1 (b)),[6] a highly potent and selective activator of insect RyR with exceptional activity on a broad range of Lepidoptera, as the first new insecticide from this class.

Scheme 1 Chemical structures of anthranilic diamide insecticides



Structural modification of anthranilic diamide has attracted considerable attention in the field of insecticidal research.[7-14] Most modification was related to a variation of the substitution pattern in part of the aliphatic amide moiety. Although less research has been devoted to the modification of the anthraniloyl skeleton, it has been reported that the biological activity of such compounds can be affected by changing the anthraniloyl skeleton to a large extent.[15] In continuation of our research on biologically active heterocycles,[16] a series of new amides (sulfonamides) containing *N*-pyridylpyrazole were synthesized and their insecticidal activity was tested. The results showed that some compounds exhibited moderate insecticidal activities against *Mythimna separata* Walker and *Culex pipiens pallens*.

Experimental

Materials and instruments

All melting points were measured on an X-4 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker AC-400 instrument using TMS as an internal standard. Elemental analyses were performed on a Yanaco MT-3 CHN elemental analyzer. HRMS data were obtained on a FTICR-MS instrument (Ionspec 7.0T). All the reagents were of analytical reagent grade.

General procedure

The title compounds were prepared as shown in Scheme 2. The key intermediate **6** was synthesized according to the reference.[17]

3-Chloro-2-hydrazylpyridine (2) To a suspension of 2,3-dichloropyridine **1** (100.0 g, 0.676 mol) in anhydrous ethanol (420 mL) was added 50% hydrazine hydrate (280 mL, 2.884 mol). The resulting mixture was refluxed for 36 h, and then cooled to room temperature.

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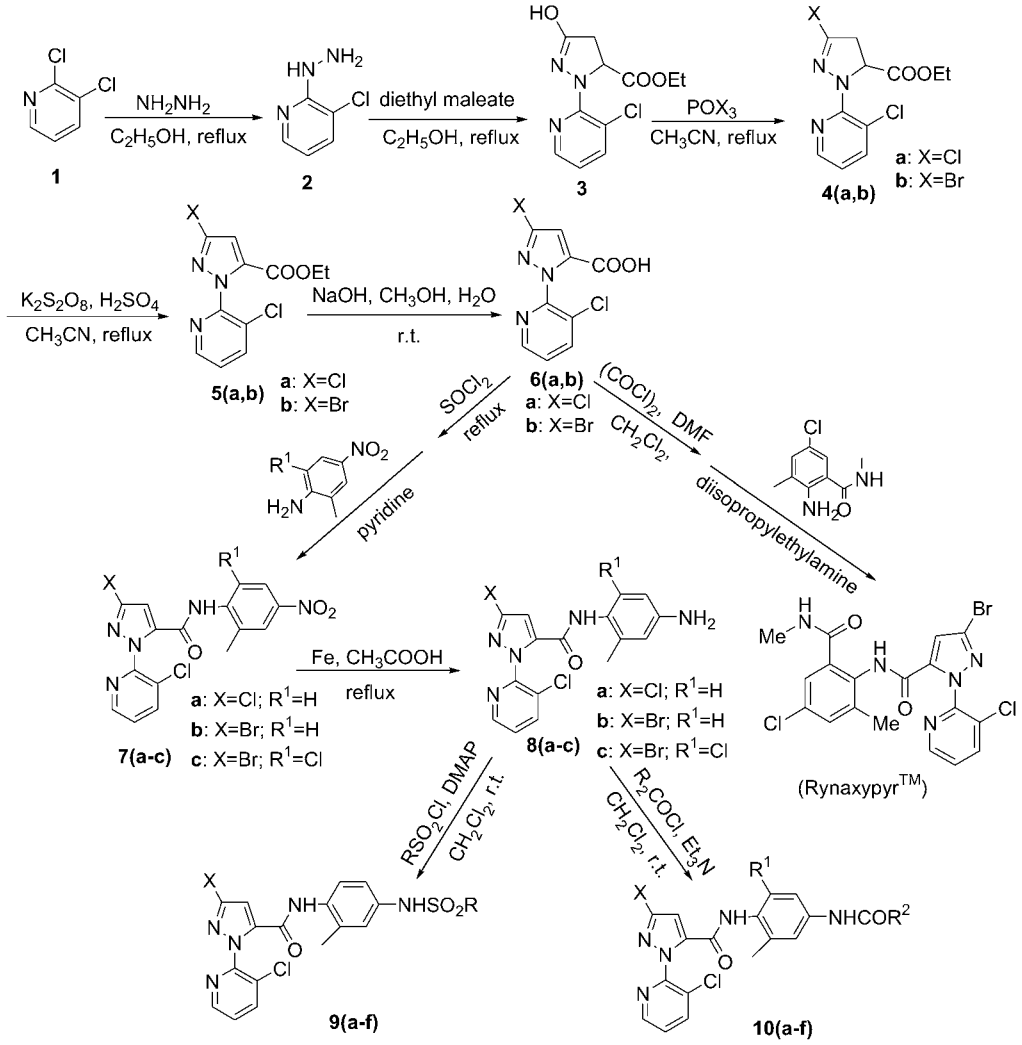
Scheme 2 Synthesis of title compounds (**9a**—**9f** and **10a**—**10f**)



9a: X=Cl, R=C_6H_5; **9b**: X=Cl, R=*p*-$CH_3C_6H_4$; **9c**: X=Cl, R=*p*-ClC_6H_4; **9d**: X=Br, R=C_6H_5; **9e**: X=Br, R=*p*-$CH_3C_6H_4$; **9f**: X=Br, R=*p*-ClC_6H_4; **10a**: X=Cl, R^1=H, R^2=C_6H_5; **10b**: X=Cl, R^1=H, R^2=$C_6H_5CH_2$; **10c**: X=Cl, R^1=H, R^2=CH_3; **10d**: X=Br, R^1=H, R^2=C_6H_5; **10e**: X=Br, R^1=H, R^2=$C_6H_5CH_2$; **10f**: X=Br, R^1=Cl, R^2=$C_6H_5CH_2$

The product precipitated out of solution, the white crystal was collected by filtration, washed thoroughly with cold ethanol and dried to give white crystals (74.4 g, 76.8%), m.p. 163—164 ℃.

Ethyl 1-(3-chloro-2-pyridyl)-3-pyrazolidinone-5-carboxylate (3) A solution of sodium ethoxide (9.0%, 480 mL, 0.551 mol) was heated to reflux. It was then treated with **2** (74.4 g, 0.519 mol). The mixture was refluxed for 10 min, then diethyl maleate (96 mL, 0.596 mol) was added dropwise. The resulting orange-red solution was held at reflux for 30 min. After being cooled to 65 ℃, the reaction mixture was treated with glacial acetic acid (54 mL, 0.956 mol). A precipitate formed, which was isolated via filtration, washed with aqueous ethanol (40%, 50 mL×3) to afford a yellow powder (82.2 g, 58.7%, m.p. 132—134 ℃).

Ethyl 3-chloro-1-(3-chloro-2-pyridyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (4a) To a solution of **3** (27 g, 0.100 mol) in acetonitrile (300 mL) was added $POCl_3$ (15 g, 0.150 mol). The reaction mixture was refluxed for 3.5 h, then concentrated. The concentrated reaction mixture was slowly poured into saturated aq. Na_2CO_3 (250 mL) and then stirred vigorously for 30 min. The resulting mixture was extracted with CH_2Cl_2 (250 mL×2), the organic layer was separated, dried, filtered, concentrated and purified by silica gel chromatography to afford a yellow oil (28.2 g, 98.0%).

Ethyl 3-bromo-1-(3-chloro-2-pyridyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (**4b**) could also be prepared with similar results using $POBr_3$ as the bromination reagent: yellow oil (32.6 g, 98.0%).

Ethyl 3-chloro-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylate (5a) To a solution of **4a** (28.2 g, 0.098 mol) in acetonitrile (500 mL) was added sulfuric acid (98%, 9.8 mL, 0.196 mol). After being stirred for several minutes, the reaction mixture was treated with $K_2S_2O_8$ (38.9 g, 0.144 mol) and refluxed for 3.5 h. After being cooled to 60 ℃, the mixture was filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated to 100 mL, then added slowly to water

(250 mL) under stirring. The solid (27.1 g, 96.7%, m.p. 109—110 ℃) was collected by filtration.

Ethyl 3-bromo-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylate (**5b**) could also be prepared with the same procedure: yellow solid (92.7%), m.p. 117—118 ℃.

3-Chloro-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylic acid (6a) A mixture of **5a** (27.1 g, 0.095 mol), methanol (100 mL), H_2O (50 mL) and NaOH (50%, 12 mL, 0.120 mol) was stirred at room temperature for 3 h, then concentrated. The concentrated mixture was diluted with H_2O (100 mL), and washed with ethyl acetate (100 mL). The aqueous phase was acidified to pH 2 using concentrated hydrochloric acid to get a white solid (23.3 g, 95.3%), m.p. 200—201 ℃.

3-Bromo-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxylic acid (**6b**) could also be prepared with the same procedure (90.3%), m.p. 197—200 ℃.

3-Chloro-*N*-(2-methyl-4-nitrophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (7a) To a 100 mL round-bottomed flask were placed **6a** (9.98 g, 0.0387 mol) and then added 50 mL of thionyl chloride. The resulting mixture was refluxed for 6—8 h, and evaporated *in vacuo* to obtain the crude acid chloride. The solution of crude acid chloride in dichloromethane (150 mL) was added slowly to a stirred solution of 2-methyl-4-nitroaniline (6.82 g, 0.0449 mol) in dichloromethane (100 mL) at 0 ℃. After 5 min, pyridine (3.55 g, 0.0449 mol) was added dropwise. The solution was warmed to room temperature and stirred for 24 h, diluted with dichloromethane (60 mL), and washed with 1 mol•L^{-1} aq. HCl solution, water, and brine. The organic extract was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1∶5) to obtain the yellow product (7.90 g, 52.1%), m.p. 189—190 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.43 (s, 3H, CH_3), 6.85 (s, 1H, pyrazolyl-H), 7.47 (dd, J=4.8, 9.0 Hz, 1H, pyridyl-H), 7.95—8.11 (m, 4H, Ar-H and NH), 8.17 (d, J=8.0 Hz, 1H, pyridyl-H), 8.49 (d, J=4.8 Hz, 1H, pyridyl-H); ESI-MS *m*/*z*: 390.1 (M−H^+). Anal. calcd for $C_{16}H_{11}Cl_2N_5O_3$: C 49.28, H 2.96, N 17.81; found C 49.00, H 2.83, N 17.86.

The compounds **7b** and **7c** were obtained similarly following the above procedure.

3-Bromo-*N*-(2-methyl-4-nitrophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (7b) Yellow solid, yield 62.3%, m.p. 185—187 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.35 (s, 3H, CH_3), 7.49 (s, 1H, pyrazolyl-H), 7.61—7.67 (m, 2H, ArH), 8.06 (dd, J=4.2, 4.4 Hz, 1H, ArH), 8.17 (dd, J=4.4, 8.8 Hz, 1H, pyridyl-H), 8.22 (d, J=8.8 Hz, 1H, pyridyl-H), 8.53 (dd, J=1.5, 4.5 Hz, 1H, pyridyl-H), 10.57 (s, 1H, NH); FT-ESI-MS calcd for $C_{16}H_{11}BrClN_5O_3$ 435.9805, found 435.9507 $[M+H]^+$.

3-Bromo-*N*-(2-methyl-6-chloro-4-nitrophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (7c) Yellow solid, yield 48.6%, m.p. 107—109 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.32 (s, 3H, CH_3), 7.46 (s, 1H, pyrazolyl-H), 7.63 (dd, J=4.2, 4.4 Hz, 1H, Ar-H), 8.18—8.23 (m, 2H, Ar-H and pyridyl-H), 8.35 (d, J=7.8 Hz, 1H, pyridyl-H), 8.52 (dd, J=1.5, 4.5 Hz, 1H, pyridyl-H), 10.78 (s, 1H, NH); ESI-MS *m*/*z*: 470.2 (M−H^+). Anal. calcd for $C_{16}H_{10}BrCl_2N_5O_3$: C 40.86, H 2.26, N 14.81; found C 40.79, H 2.14, N 14.87.

3-Chloro-*N*-(2-methyl-4-aminophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (8a) Mill scale (2.24 g, 0.040 mol) was added to a stirred suspension of **7a** (3.91 g, 0.010 mol) in water (20 mL). After 10 min, HOAc (1.22 g, 0.020 mol) was added dropwise, and the reaction mixture was heated to reflux for 1 h, cooled to room temperature, treated to pH=8 with ammonia solution and filtered. The residue was washed with warm THF and filtered. The filtrate was concentrated to get yellow solid (3.36 g, 92.7%), m.p. 271—273 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.98 (s, 3H, CH_3), 5.00 (s, 2H, NH_2), 6.31—6.38 (m, 2H, Ar-H), 6.76 (d, J=8.0 Hz, 1H, Ar-H), 7.27 (s, 1H, pyrazolyl-H), 7.60 (dd, J=4.2, 8.4 Hz, 1H, pyridyl-H), 8.16 (dd, J=1.6, 8.8 Hz, 1H, pyridyl-H), 8.49 (dd, J=1.4, 4.2 Hz, 1H, pyridyl-H), 9.58 (s, 1H, NH); FT-ESI-MS calcd for $C_{16}H_{13}Cl_2N_5O$ 384.0396, found 384.0389 $[M+Na]^+$.

The compounds **8b** and **8c** were obtained similarly following the above procedure.

3-Bromo-*N*-(2-methyl-4-aminophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (8b) Yellow solid, yield 89.6%, m.p. 270—272 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.01 (s, 3H, CH_3), 5.00 (s, 2H, NH_2), 6.34—6.41 (m, 2H, Ar-H), 6.79 (d, J=7.8 Hz, 1H, Ar-H), 7.34 (s, 1H, pyrazolyl-H), 7.63 (d, J=4.2 Hz, 1H, pyridyl-H), 8.18 (d, J=8.2 Hz, 1H, pyridyl-H), 8.50 (d, J = 3.2 Hz, pyridyl-H), 9.84 (s, 1H, NH); FT-ESI-MS calcd for $C_{16}H_{13}BrClN_5O$ 406.0064, found 406.0065 $[M+H]^+$.

3-Bromo-*N*-(2-methyl-4-amino-6-chlorophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (8c) Yellow solid, yield 90.6%, m.p. 246—248 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.02 (s, 3H, CH_3), 5.34 (s, 2H, NH_2), 6.41 (s, H, Ar-H), 6.48 (s, H, Ar-H), 7.36 (s, 1H, pyrazolyl-H), 7.62 (dd, J=4.0, 7.8 Hz, 1H, pyridyl-H), 8.18 (d, J=8.2 Hz, 1H, pyridyl-H), 8.51 (d, J=3.8 Hz, pyridyl-H), 9.97 (s, 1H, NH); ESI-MS *m*/*z*: 440.2 (M−H^+). Anal. calcd for $C_{16}H_{12}BrCl_2N_5O$ C 43.85, H 2.56, N 15.81; found C 43.57, H 2.74, N 15.88.

3-Chloro-*N*-[2-methyl-4-(benzenesulfonamido)-phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (9a) To a solution of **8a** (0.80 g, 0.002 mol) in dichloromethane were added phenylsulfonyl chloride (0.35 g, 0.002 mol) and DMAP (0.24 g, 0.002 mol). The reaction mixture was stirred for 16 h then diluted with dicholoromethane (100 mL) and washed with 1 mol•L^{-1} aq. HCl (100 mL) and water (100 mL). The organic extract was separated, dried ($MgSO_4$), filtered, and concentrated. Then the residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1∶5) to obtain the white product (0.45 g, 45%), m.p. 179—181 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.07 (s, 3H, CH_3), 6.93 (d, J=8.0 Hz, 1H,

Ar-H), 6.96 (s, 1H, pyrazolyl-H), 7.06 (d, J=8.4 Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.56—7.76 (m, 6H, Ar-H and pyridyl-H), 8.17 (d, J=8.0 Hz, 1H, pyridyl-H), 8.49 (d, J=4.8 Hz, 1H, pyridyl-H), 10.09 (s, 1H, NH), 10.27 (s, 1H, NH); ESI-MS *m/z*: 500.2 ($M-H^+$). Anal. calcd for $C_{22}H_{17}Cl_2N_5O_3S$: C 52.73, H 3.66, N 13.75; found C 52.60, H 3.41, N 13.94.

The title compounds **9b**—**9f** were obtained similarly following the above procedure.

3-Chloro-*N*-[2-methyl-4-(*p*-toluenesulfonamido)-phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (9b) White solid, yield 43%, m.p. 147—149 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.00 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 6.84 (d, J=8.0 Hz, 1H, Ar-H), 6.91 (s, 1H, pyrazolyl-H), 7.01 (d, J=8.4 Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.35—7.62 (m, 5H, Ar-H and pyridyl-H), 8.16 (d, J=8.0 Hz, 1H, pyridyl-H), 8.48 (d, J=4.7 Hz, 1H, pyridyl-H), 10.03 (s, 1H, NH), 10.19 (s, 1H, NH); ESI-MS *m/z*: 514.2 ($M-H^+$). Anal. calcd for $C_{23}H_{19}Cl_2N_5O_3S$: C 53.60, H 3.41, N 13.42; found C 53.49, H 3.71, N 13.56.

3-Chloro-*N*-[2-methyl-4-(*p*-chlorobenzenesulfonamido)phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (9c) White solid, yield 62%, m.p. 208—209 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.05 (s, 3H, CH_3), 6.90 (d, J=8.0 Hz, 1H, Ar-H), 6.94 (s, 1H, pyrazolyl-H), 7.06 (d, J=8.8 Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.58—7.61 (m, 5H, Ar-H and pyridyl-H), 8.16 (d, J=8.0 Hz, 1H, pyridyl-H), 8.47 (d, J=4.8 Hz, 1H, pyridyl-H), 10.10 (s, 1H, NH), 10.37 (s, 1H, NH); ESI-MS *m/z*: 536.2 ($M-H^+$). Anal. calcd for $C_{22}H_{16}Cl_3N_5O_3S$: C 48.95, H 3.24, N 12.80; found C 49.22, H 3.00, N 13.05.

3-Bromo-*N*-[2-methyl-4-(benzenesulfonamido)-phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (9d) White solid, yield 52%, m.p. 198—200 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.03 (s, 3H, CH_3), 6.89 (d, J=8.0 Hz, 1H, Ar-H), 6.93 (s, 1H, pyrazolyl-H), 7.02 (d, J=8.4 Hz, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.49—7.73 (m, 6H, Ar-H and pyridyl-H), 8.16 (d, J=8.0 Hz, 1H, pyridyl-H), 8.47 (d, J=4.8 Hz, 1H, pyridyl-H), 10.07 (s, 1H, NH), 10.27 (s, 1H, NH); ESI-MS *m/z*: 546.2 ($M-H^+$). Anal. calcd for $C_{22}H_{17}BrClN_5O_3S$: C 48.12, H 3.10, N 13.09; found C 48.32, H 3.13, N 12.81.

3-Bromo-*N*-[2-methyl-4-(*p*-toluenesulfonamido)-phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (9e) White solid, yield 48%, m.p. 198—200 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.03 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.88 (d, J=8.0 Hz, 1H, Ar-H), 6.93 (s, 1H, pyrazolyl-H), 7.01 (d, J=8.2 Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.32—7.62 (m, 5H, Ar-H and pyridyl-H), 8.16 (d, J=8.0 Hz, 1H, pyridyl-H), 8.50 (d, J=4.8 Hz, 1H, pyridyl-H), 10.07 (s, 1H, NH), 10.21 (s, 1H, NH); ESI-MS *m/z*: 560.1 ($M-H^+$). Anal. calcd for $C_{23}H_{19}BrClN_5O_3S$: C 48.95, H 3.68, N 12.39; found C 49.25, H 3.41, N 12.49 .

3-Bromo-*N*-[2-methyl-4-(*p*-chlorobenzenesulfonamido)phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (9f) White solid, yield 59%, m.p. 227—229 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.10 (s, 3H, CH_3), 6.88 (d, J=8.0 Hz, 1H, Ar-H), 6.94 (s, 1H, pyrazolyl-H), 7.05 (d, J=8.8 Hz, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.58—7.62 (m, 5H, Ar-H and pyridyl-H), 8.16 (d, J=8.0 Hz, 1H, pyridyl-H), 8.47 (d, J=4.8 Hz, 1H, pyridyl-H), 10.08 (s, 1H, NH), 10.34 (s, 1H, NH); ESI-MS *m/z*: 580.2 ($M-H^+$). Anal. calcd for $C_{22}H_{16}BrCl_2N_5O_3S$: C 45.49, H 2.84, N 11.93; found C 45.46, H 2.77, N 12.05.

3-Chloro-*N*-(2-methyl-4-benzamidophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (10a) To a solution of **8a** (0.80 g, 0.002 mol) in dichloromethane were added benzoylchloride (0.32 g, 0.002 mol), triethylamine (0.24 g, 0.002 mol). The reaction mixture was stirred for 3 h, diluted with dichloromethane (100 mL) and washed with 1 mol•L^{-1} aq. HCl (100 mL) and water (100 mL). The organic extract was separated, dried ($MgSO_4$), filtered, and concentrated and the residue purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1∶5) to obtain the white solid (0.615 g, 66%), m.p. 231—233 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.19 (s, 3H, CH_3), 6.93 (d, J=8.0 Hz, 1H, Ar-H), 6.96 (s, 1H, pyrazolyl-H), 7.06 (d, J=8.4 Hz, 1H, Ar-H), 7.52—8.00 (m, 7H, Ar-H and pyridyl-H), 8.20 (d, J = 4.4 Hz, 1H, pyridyl-H), 8.53 (d, J=4.4 Hz, 1H, pyridyl-H), 10.19 (s, 1H, NH), 10.23 (s, 1H, NH). FT-ESI-MS calcd for $C_{23}H_{17}Cl_2N_5O_2$ 488.0644, found 488.0652 $[M+Na]^+$.

The title compounds **10b** — **10f** were obtained similarly following the above procedure.

3-Chloro-*N*-(2-methyl-4-phenylacetamidophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (10b) White crystals; yield 61%; m.p. 240—242 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.15 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 7.17 (d, J=8.2 Hz, 1H, Ar-H), 7.30—7.51 (m, 9H, Ar-H, pyrazolyl-H and pyridyl-H), 8.17 (d, J=4.4 Hz, 1H, pyridyl-H), 8.49 (d, J=4.4 Hz, 1H, pyridyl-H), 10.11 (s, 1H, NH), 10.14 (s, 1H, NH). FT-ESI-MS calcd for $C_{24}H_{18}Cl_2N_4O_2$ 502.0803, found 502.0808 $[M+H]^+$.

3-Chloro-*N*-(2-methyl-4-acetamidophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (10c) White crystals, yield 63%, m.p. 229—231 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.02 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 7.11 (d, J=8.0 Hz, 1H, Ar-H), 7.34—7.64 (m, 4H, Ar-H, pyridyl-H and pyrazolyl-H), 8.19 (d, J=4.4 Hz, 1H, pyridyl-H), 8.51 (d, J=4.4 Hz, 1H, pyridyl-H), 9.90 (s, 1H, NH), 10.13 (s, 1H, NH). ESI-MS *m/z*: 604.1 ($M-H^+$). FT-ESI-MS calcd for $C_{24}H_{19}BrClN_5O_5S$ 426.0500, found 426.0495 $[M+Na]^+$.

3-Bromo-*N*-(2-methyl-4-benzamidophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (10d) White solid, yield 72%, m.p. 236—238 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.18 (s, 3H, CH_3), 7.18 (d, J=8.2 Hz, 1H, Ar-H), 7.42 (s, 1H, pyrazolyl-H), 7.52—7.95 (m, 8H, Ar-H and pyridyl-H), 8.20 (d, J=4.4 Hz, 1H, pyridyl-H), 8.50 (d, J=4.4 Hz, 1H, pyridyl-H), 10.17 (s, 1H, NH), 10.22 (s, 1H, NH). FT-ESI-MS calcd

for $C_{23}H_{17}BrClN_5O_2$ 532.0155, found 532.0146 $[M+Na]^+$.

3-Bromo-*N*-(2-methyl-4-phenylacetamidophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (10e) White solid, yield 68%, m.p. 244—246 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.13 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 7.12 (d, J=8.2 Hz, 1H, Ar-H), 7.25—7.41 (m, 9H, Ar-H, pyrazolyl-H and pyridyl-H), 8.20 (d, J= 4.4 Hz, 1H, pyridyl-H), 8.50 (d, J = 4.4 Hz, 1H, pyridyl-H), 10.12 (s, 1H, NH), 10.14 (s, 1H, NH). FT-ESI-MS calcd for $C_{24}H_{19}BrClN_5O_2$ 524.0477, found 524.0483 $[M+Na]^+$.

3-Bromo-*N*-(2-methyl-4-phenylacetamido-6-chlorophenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide (10f) White solid, yield 62%, m.p. 231—233 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.15 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 7.15 (d, J=8.4 Hz, 1H, Ar-H), 7.14—7.39 (m, 8H, Ar-H, pyrazolyl-H and pyridyl-H), 8.20 (d, J=4.2 Hz, 1H, pyridyl-H), 8.50 (d, J=4.4 Hz, 1H, pyridyl-H), 10.11 (s, 1H, NH), 10.15 (s, 1H, NH). ESI-MS *m*/*z*: 558.2 ($M-H^+$). Anal. calcd for $C_{24}H_{18}BrCl_2N_5O_2$: C 51.42, H 3.02, N 12.34; found C 51.54, H 3.24, N 12.52.

Rynaxypyr™ Rynaxypyr™ was prepared according to the literature.[18] To a suspension of *N*-pyridylpyrazole acid **6b** (0.30 g, 0.001 mol) in dichloromethane (20 mL) was added oxalyl chloride (0.38 g, 0.003 mol), followed by dimethylformamide (2 drops). The solution was stirred at room temperature for 6 h, then concentrated to obtain the crude acid chloride. The crude acid chloride in dichloromethane (10 mL) was added slowly to a stirred solution of 2-amino-5-chloro-*N*,3-dimethylbenzamide (0.24 g, 0.0012 mmol) in dichloromethane (20 mL) in an ice bath. After 20 min, diisopropylethylamine (1.29 g, 0.001 mol) was added dropwise. The solution was warmed to room temperature, stirred for 12 h, diluted with dichloromethane (20 mL), and washed with 1 mol•L^{-1} aq. HCl solution (10 mL), saturated aq. $NaHCO_3$ (10 mL), and brine (10 mL). The organic extract was separated, dried, filtered, concentrated, and purified by silica gel chromatography to afford the desired product, m.p. 239—240 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.17 (s, 3H, CH_3), 2.95 (d, 3H, J=4.9 Hz, CH_3), 6.17 (d, J=5.2 Hz, 1H, NH), 7.11 (s, 1H, pyrazolyl-H), 7.21 (d, J=2.0 Hz, 1H, Ar-H), 7.24 (d, J=2.0 Hz, 1H, Ar-H), 7.38 (dd, J=4.8, 8.0 Hz, 1H, pyridyl-H), 7.85 (dd, J=1.6, 8.0 Hz, 1H, pyridyl-H), 8.46 (dd, J=1.6, 4.8 Hz, 1H, pyridyl-H), 10.10 (brs, 1H, NH).

Biological activity

Contact toxicity was examined against oriental armyworm (*Mythimna separate* Walker).[19] 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*).[19] 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.

Results and discussion

Synthesis

The synthesis of **7** involves a condensation reaction of **6** with $SOCl_2$ followed by amidation with substituted aniline. In this step, compounds **7** were formed in a low yield when the reaction was carried out with triethylamine or 4-dimethylamino-pyridine (DMAP) as the acid acceptor. However, on changing the acid acceptor to pyridine, the compounds **7** were formed in 52.1% yield**.** It was postulated that the basicity of the acid acceptor might play an important role in the systhesis of **7**. The compounds **8** without further purification were reacted with sulfonyl chloride or carboxylic acid chloride in the presence of DMAP or triethylamine to give the title compounds (**9a**—**9f** and **10a**—**10f**). In our experiments, we found that the reactivity of carboxylic acid chlorides was higher than benzenesulfonyl chlorides and the yields of the compounds had the same change.

Insecticidal activities

Biological evaluation results of the title compounds are listed in Table 1.

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

No.	*Mythimna separata* Walker				*Culex pipiens pallens*
	200 mg•L^{-1}	100 mg•L^{-1}	50 mg•L^{-1}	25 mg•L^{-1}	2 mg•L^{-1}
9a	20	nt[a]	nt[a]	nt[a]	0
9b	10	nt[a]	nt[a]	nt[a]	30
9c	10	nt[a]	nt[a]	nt[a]	0
9d	10	nt[a]	nt[a]	nt[a]	0
9e	30	nt[a]	nt[a]	nt[a]	10
9f	30	nt[a]	nt[a]	nt[a]	0
10a	0	nt[a]	nt[a]	nt[a]	0
10b	100	80	10	nt[a]	0
10c	40	nt[a]	nt[a]	nt[a]	0
10d	0	nt[a]	nt[a]	nt[a]	0
10e	100	80	40	nt[a]	10
10f	100	100	70	30	10
Rynaxypyr™	100	100	100	100	100

[a] Not tested.

Some of them exhibited certain insecticidal activities against oriental armyworm. The larvicidal activities of

10f were 100%, 70% and 30% at 100, 50 and 25 mg•L^{-1} separately. The larvicidal activities of **10b** and **10e** were 80% at 100 mg•L^{-1}. Some of them had weak insecticidal activities against *Culex pipiens pallens*. The larvicidal activities of some compounds were 10%—30% at 2 mg•L^{-1}. In these results, we found that the insecticidal activities of title compounds containing phenylacetyl moiety were quite better than others.

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