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Original article

Design, synthesis and insecticidal activities of novel acetamido derivatives containing *N*-pyridylpyrazole carboxamides

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ABSTRACT

A series of novel acetamido derivatives containing *N*-pyridylpyrazole carboxamides was designed and synthesized by increasing the amide bridge of chlorantraniliprole using acetamido moieties and introducing different aryl substitutions. The target compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. Bioassays indicated that some of the synthesized compounds exhibited strong insecticidal activity against *Plutella xylostella*. Compounds **5e**, **5g** and **5v** were the most potent, with LC_{50} values of 23.72, 2.04, and 20.01 mg/L, respectively. The insecticidal activity of compound **5g** was higher than that of chlorpyrifos (LC_{50} = 7.25 mg/L), a commonly used insecticide. These results indicate that novel acetamido derivatives containing *N*-pyridylpyrazole carboxamides can effectively control *P. xylostella*.

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1. Introduction

Plutella xylostella, one of the most widespread and harmful Lepidoptera pests, poses significant threats to cruciferous vegetables, such as cabbage, cauliflower and turnip, in many parts of the world. It has been causing an estimated annual loss of US $1 billion in economic crops throughout the world since the early 1990s [1,2]. A significant challenge faced by farmers is that *P. xylostella* is difficult to prevent and control due to its strong resistance to currently available pesticides [3–6].

Chlorantraniliprole (Fig. 1), a novel insecticide that acts on ryanodine receptors, was discovered and commercialized by DuPont Ltd [7]. It shows excellent insecticidal activity against *P. xylostella* and has low toxicity to mammals [8]. In recent years, the chemical structure of chlorantraniliprole has received considerable attention, and a large number of active compounds have been obtained by modifying chlorantraniliprole at its 1-(3-chloropyridyl) pyrazole moiety (**I**), substituted phenyl moiety (**II**), aliphatic amide moiety (**III**) and the amide bridge (**IV**) [9]. For instance, the bromine atom on the pyrazole ring (**I**) can be replaced by cyano, trifluoromethyl, methoxy, perfluoroethoxy and ethynyloxy moieties [10–13], while the benzene ring can be replaced by benzofuran, quinoline and naphthalene [14,15]. Cyantraniliprole (Fig. 1), another anthranilic diamide insecticide, was discovered by changing the chlorine at position 5 of the substituted phenyl moiety (**II**) to a cyano group [16]. Moreover, cyano group [17], oxadiazoles, thiadiazoles [18], and substituted hydrazinecarbonyl (or carbamoyl) have been used to replace the methylcarbamoyl group in the aliphatic amide moiety (**III**) of chlorantraniliprole [19–26]. More recently, several compounds with high insecticidal activities have been obtained by changing the amide bridge (**IV**) to acylthiourea and acylurea moieties [9,27]. Thus, the sub-structure of *N*-pyridylpyrazole carboxamide is an important factor in our search for anthranilic diamide insecticides.

Acetamido derivatives have been reported to possess good flexibility due to the presence of $-CH_2-$ groups [28]. They have also been paid close attention due to their antimicrobial [29], anticonvulsant [30], antitumor [31], anticancer [32], insecticidal [33], and antifungal activities [34]. Among agrochemicals, sub-structures of acetamido groups can be found in the structure of several insecticides (e.g., dimethoate and omethoate) and herbicides (e.g.,

Abbreviations: P. xylostella, *Plutella xylostella*; mp, melting point; IR, infrared; ^{1}H NMR, proton nuclear magnetic resonance; ^{13}C NMR, carbon nuclear magnetic resonance; LC_{50}, median lethal concentration; SAR, structure–activity relationship.

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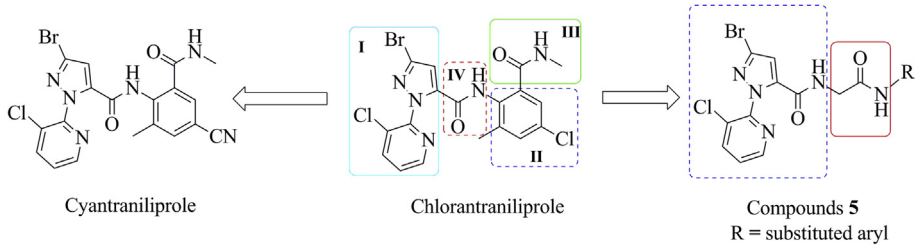


Fig. 1. Design of the title compound **5**.

propanil). Thus, widespread use of acetamido as a scaffold in pesticide and medicinal chemistry establishes this moiety as an important structural class.

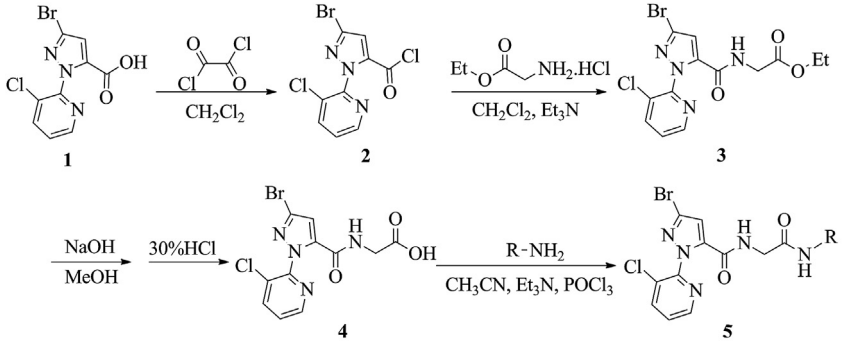
In order to obtain novel acetamido derivatives (Scheme 1) with potential insecticidal activity, we sought to retain the substructure of *N*-pyridylpyrazole carboxamides, increase the amide bridge by introducing an acetamido moiety, then introduce different substituted aryls. A series of novel acetamido derivatives containing *N*-pyridylpyrazole carboxamides (**5**) was designed (Fig. 1) and synthesized. Structures of all synthesized compounds were characterized by ^{1}H NMR and ^{13}C NMR, infrared spectroscopy, and elemental analysis. Results of bioassays indicate that most synthesized compounds exhibit strong insecticidal activities against *P. xylostella*. In particular, the compounds **5e**, **5g**, and **5v** exhibited 100% insecticidal activity at 250 mg/L. Compound **5g** showed >60% insecticidal activity at 6.25 mg/L with an LC_{50} value of 2.04 mg/L, indicating that its insecticidal activity was much higher than that of chlorpyrifos (LC_{50} = 7.25 mg/L), a commonly used pesticide.

2. Results and discussion

2.1. Chemistry

The synthesis protocol for obtaining the title compounds is depicted in Scheme 1. Intermediates **1** and **2** were prepared according to previously reported methods [35]. Firstly, compound **3** was prepared using intermediates **2** and glycine ethyl ester hydrochloride in dry dichloromethane. Compound **3** was hydrolyzed in aqueous sodium hydroxide and the pH was adjusted to 3 using 5% hydrochloric acid to obtain compound **4**. The title compounds (**5a**–**5w**) were finally prepared in a single step by treatment of compound **4** with different substituted amines in the presence of triethylamine and phosphorus oxychloride for 30 min in refluxing acetonitrile. As reported previously, amides can be prepared via reaction of chloride (prepared first from acids) with amines [36] or condensation of acid with amines in the presence of a condensing agent (such as DCC, EDC, and DIC) [37–39]. However, these methods usually involve long reaction steps and reaction time, and require difficult post-processing steps. In the present work, the amides were prepared in a single step as described previously [40]. This method offered several advantages, such as short reaction time, relatively high yield and simple post-processing. Moreover, yields of amide preparation could be enhanced by aromatic amines containing electron donating groups (such as, $-OCF_3$, $-SCF_3$, and $-OCH_2CH_3$ groups) likely due to the strong alkaline system provided by these amines (e.g., yields for **5a**, **5b** and **5m** were 90.8%, 90.1% and 90.3%, respectively). Consistent with this idea, amines that exhibited lower yields contained electron withdrawing groups (such as, $-NO_2$, $-Cl$) and possessed weaker alkaline properties.

All synthesized compounds (**5a**–**5w**) were characterized based on their spectroscopic data. IR absorption bands near 3329–3300 cm^{-1} and 3255–3245 cm^{-1} confirmed the presence of N–H



R = 4-OCF_3-Ph (5a), 4-SCF_3-Ph(5b), 3,5-di-CF_3-Ph(5c), 4-Cl-Ph(5d), 2,6-di-Cl-4-CF_3-Ph(5e), 2-Cl-4-CH_3-Ph(5f), 2-NO_2-Ph(5g), 4-NO_2-Ph(5h), 2-CH_3-5-Cl-Ph(5i), 3-CF_3-4-Cl-Ph(5j), 2-CN-Ph(5k), 4-CH_3-Ph(5l), 4-OCH_2CH_3-Ph(5m), 3,4-di-Cl-Ph(5n), 3,4-di-CH_3-Ph(5o), 3-F-Ph(5p), 3-Cl-Ph(5q), 3-Cl-4-F-Ph(5r), 3-CF_3-4-F-Ph(5s), 2,5-di-Cl-Ph(5t), 5-CH_3-1*H*-Pyrazol-3-yl(5u), 2-Cl-4-CH_3-Pyridin-3-yl(5v), 2-Cl-Pyridin-3-yl(5w).

Scheme 1. General synthetic route for title compounds **5a**–**5w**.

Table 1
Insecticidal activities of compounds **3**, **5a**–**5w**, chlorantraniliprole, chlorpyrifos and avermectin against *Plutella xylostella*.

Compound	R_1	Insecticidal activity (%) at indicated concentrations (mg/L)						
		500	250	100	50	25	12.5	6.25
5a	4-OCF_3-Ph	100	76.7	40	/	/	/	/
5b	4-SCF_3-Ph	53.3	30	/	/	/	/	/
5c	3,5-di–CF_3–Ph	86.7	60	/	/	/	/	/
5d	4-Cl-Ph	100	83.3	46.7	/	/	/	/
5e	2,6-di-Cl-4-CF_3-Ph	100	100	100	83.3	50.0	/	/
5f	2-Cl-4-CH_3-Ph	86.7	56.7	/	/	/	/	/
5g	2-NO_2-Ph	100	100	93.3	86.7	76.7	70	66.7
5h	4-NO_2-Ph	86.7	66.7	36.7	/	/	/	/
5i	2-CH_3-5-Cl-Ph	43.3	/	/	/	/	/	/
5j	3-CF_3-4-Cl-Ph	63.3	33.3	/	/	/	/	/
5k	2-CN-Ph	86.7	76.7	53.3	/	/	/	/
5l	4-CH_3-Ph	40	/	/	/	/	/	/
5m	4-OCH_2CH_3-Ph	30	/	/	/	/	/	/
5n	3,4-di-Cl-Ph	26.7	/	/	/	/	/	/
5o	3,4-di-CH_3-Ph	26.7	/	/	/	/	/	/
5p	3-F-Ph	23.3	/	/	/	/	/	/
5q	3-Cl-Ph	6.7	/	/	/	/	/	/
5r	3-Cl-4-F-Ph	16.7	/	/	/	/	/	/
5s	3-CF_3-4-F-Ph	23.3	/	/	/	/	/	/
5t	2,5-di-Cl-Ph	90.0	76.7	56.7	/	/		/
5u	5-CH_3-1*H*-Pyrazol-3-yl	100	73.3	56.7	/	/	/	/
5v	2-Cl-4-CH_3-Pyridin-3-yl	100	100	73.3	63.3	56.7	46.7	/
5w	2-Cl-Pyridin-3-yl	100	83.3	53.3	/	/	/	/
3		90	60	/	/	/	/	/
Chlorantraniliprole		/	/	100	100	100	100	100
Chlorpyrifos		/	/	100	90	83.3	66.7	43.3
Avermectin		/	/	100	100	100	100	100
CK		0	0	0	0	0	0	0

in two amides. Ar–H appeared in the range of 3100–2920 cm^{-1}. Presence of two amide functional groups [41] in their structures was noted based on appearance of bands at 1720–1690 cm^{-1} and 1670–1650 cm^{-1}. For the compound **5k**, absorption peak of the cyano group appeared at 2225 cm^{-1}. In the ^1H NMR spectra of the title compounds, a broad signal peak that appeared at the lowest field of 10.83–9.24 ppm corresponded with the $-CH_2CONHAr-$ proton influenced by the aromatic ring. Hence, the chemical shift of $-CONHCH_2-$ appeared as a triplet at 9.35–9.15 ppm, and the pyrazole-H proton mainly appeared as a doublet at 7.34–7.30 ppm. The chemical shift of $-NHCH_2CO-$ was influenced by its carbonyl group and nitrogen atoms, and it appeared as a doublet at 4.10–3.90 ppm. Moreover, in the ^{13}C NMR spectra, the carbon resonance frequencies of the two C=O were at 168.73–166.38 ppm (adjacent to pyrazole) and at 157.71–157.47 ppm (near the "$-CH_2-$" group). Finally, the $-CH_2-$ group appeared at 43.38–42.50 ppm.

Table 2
LC_{50} values for insecticidal activity against *Plutella xylostella*.

Compound	$y = a + b\,x$	LC_{50} (mg/L)	R
5a	$y = 0.39 + 2.21\,x$	121.60	0.99
5b	$y = 1.36 + 1.33\,x$	539.22	0.98
5c	$y = 0.16 + 2.15\,x$	180.90	0.99
5d	$y = 1.07 + 2.01\,x$	90.27	0.99
5e	$y = 0.82 + 3.03\,x$	23.72	0.99
5f	$y = 1.65 + 1.50\,x$	168.52	0.98
5g	$y = 4.77 + 0.75\,x$	2.04	0.96
5h	$y = 0.96 + 1.87\,x$	144.43	0.99
5j	$y = 1.14 + 1.49\,x$	395.61	0.97
5k	$y = 3.07 + 1.07\,x$	63.48	0.97
5t	$y = 1.53 + 1.90\,x$	65.90	0.97
5u	$y = 1.91 + 1.64\,x$	76.76	0.99
5v	$y = 4.01 + 0.76\,x$	20.01	0.99
5w	$y = 0.82 + 2.09\,x$	99.34	0.99
Chlorpyrifos	$y = 3.60 + 1.62\,x$	7.25	0.99

2.2. Insecticidal activity

Insecticidal activities of compounds **5a**–**5w** against *P. xylostella* are shown in Table 1. The commercial insecticides chlorantraniliprole, chlorpyrifos, and avermectins were used as standards. In general, most of the compounds (i.e., **5a**, **5d**, **5e**, **5g**, **5u**, **5v**, and **5w**) showed 100% insecticidal activity at 500 mg/L. The insecticidal activities of compounds **5e**, **5g**, and **5v** were still 100% at 250 mg/L, while compounds **5e** and **5g** displayed >90% insecticidal activity at 100 mg/L. The insecticidal activity of compound **5g** was over 65% at 6.25 mg/L. For comparison, the LC_{50} value of chlorpyrifos (a commonly used insecticide) and some title compounds were also determined. The results are listed in Table 2.

The LC_{50} values of compounds **5d**, **5e**, **5g**, **5k**, **5t**, **5u**, **5v** and **5w** were less than 100 mg/L (Table 2). In particular, the compounds **5e**, **5g** and **5v** exhibited excellent insecticidal activities, with LC_{50} values of 23.72, 2.04, and 20.01 mg/L, respectively. The compound **5g** showed much higher insecticidal activity than commercial chlorpyrifos (LC_{50} = 7.25 mg/L). As revealed by data in Tables 1 and 2, when R was substituted with a benzene ring, the insecticidal activity of the title compounds could be enhanced by the groups 2-nitro, 2,6-dichloro-4-trifluoromethyl and 4-chloro. In addition, introduction of heterocyclic rings (i.e., pyridine and pyrazole) increased its insecticidal activity against *P. xylostella*. Interestingly, a compound containing an ester group (**3**) was found to have 90% insecticidal activity against *P. xylostella* at 500 mg/L.

3. Conclusion

Twenty-three novel acetamido derivatives (**5a**–**5w**) containing *N*-pyridylpyrazole carboxamides were designed and synthesized based on the sub-structure of chlorantraniliprole. These compounds were characterized and confirmed by ^1H NMR, ^{13}C NMR, IR, and elemental analysis. A preliminary evaluation of the insecticidal

activities of the synthesized compounds was conducted. Most compounds exhibited excellent toxic effects against *P. xylostella*. In particular, the LC_{50} values of compounds **5e**, **5g**, and **5v** were 23.72, 2.04, and 20.01 mg/L, respectively. Notably, compound **5g** showed much higher insecticidal activity than chlorpyrifos (LC_{50} = 7.25 mg/L). Preliminary SAR analysis indicated that the 2-nitro, 2,6-dichloro-4-trifluoromethyl, and 4-chloro groups on the benzene ring (in the R group) had positive influence on the insecticidal activity of synthesized compounds. Moreover, introduction of a heterocyclic ring (pyridine and pyrazole) could enhance their insecticidal effects against *P. xylostella*.

4. Materials and methods

4.1. Instruments

Unless otherwise stated, all reagents and reactants (analytically or chemically pure) were purchased from commercial suppliers. Melting points were uncorrected and determined using an XT-4 binocular microscope (Beijing Tech Instrument Co., China). ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a JEOL ECX 500 NMR spectrometer (JEOL Ltd., Japan) operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR using $CDCl_3$ or dimethyl sulfoxide (DMSO) as a solvent and tetramethylsilane as an internal standard. IR spectra were recorded in KBr on an IR Prestige-21 spectrometer (Shimadzu Corporation, Japan). Elemental analysis was performed on an Elemental Vario-III CHN analyzer (Elementar, Germany). The reactions were monitored by thin liquid chromatography (TLC). Analytical TLC was performed on silica gel GF 254. All solvents were dried by standard methods and distilled before use.

4.2. General procedure

Ethyl 2-(3-substituted-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamido) acetate (intermediates **1**) and 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbonyl chloride (interme diates **2**) were synthesized as previously described [35]. The title compounds were prepared as shown in Scheme 1.

4.2.1. General procedure for the preparation of compound *3*

To a mixture of glycine ethyl ester hydrochloride (3.35 g, 24.0 mmol) in dry dichloromethane (50 mL), triethylamine (2.43 g, 24.0 mmol) was added. The resulting mixture was stirred at 0 °C for 5 min. Then, intermediate **2** (6.42 g, 20 mmol) in dry dichloromethane (20 mL) was added. After stirring at room temperature for 30 min, the mixture was concentrated and filtered to obtain 6.30 g of compound **3**. The physical and chemical properties of compound **3** are as follows: Phase, white solid; mp, 126–127 °C; yield, 81.3%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 8.49 (dd, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 4.60 Hz, 1H, 6-Pyridine-H), 7.91 (dd, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 8.00 Hz, 1H, 4-Pyridine-H), 7.42 (dd, $^4J_{HH}$ = 4.60 Hz, $^3J_{HH}$ = 8.00 Hz, 1H, 5-Pyridine-H), 6.83 (s, 1H, 4-Pyrazole-H), 6.81 (t, J = 5.75 Hz, 1H, −CONHCH$_2$−), 4.24 (q, J = 6.85 Hz, 2H, −CH$_2$−CH$_3$), 4.07 (d, J = 5.45 Hz, 2H, −NH−CH$_2$−), 1.29 (t, J = 6.85 Hz, 3H, −CH$_3$); Anal. calcd for $C_{13}H_{12}BrClN_4O_3$ (386): C, 40.33%; H, 3.23%; N, 14.39%. Found: C, 40.28%; H, 3.12%; N, 14.45%.

4.2.2. General procedure for the preparation of compound *4*

To a solution of compound **3** (6.00 g, 15.5 mmol) in 30 mL of methanol, sodium hydroxide (0.74 g, 18.6 mmol) in water (5.0 mL) was added, and the mixture was stirred at room temperature for 3 h and concentrated. The resulting mixture was diluted with 30 mL water, and acidified to pH 3 using 5% hydrochloric acid to obtain 4.6 g of compound **4**. The physical and chemical properties of compound **4** are as follows: Phase, light yellow solid; mp, 223–225 °C; yield, 94%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 12.69 (br, 1H, −COOH), 9.17 (t, 1H, J = 5.75 Hz, −CONHCH$_2$−), 8.50 (dd, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 4.55 Hz, 1H, 6-Pyridine-H), 8.19 (dd, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 8.05 Hz, 1H, 4-Pyridine-H), 7.64 (dd, $^4J_{HH}$ = 4.50 Hz, $^3J_{HH}$ = 8.05 Hz, 1H, 5-Pyridine-H), 7.27 (s, 1H, 4-Pyrazole-H), 3.83 (d, J = 5.70 Hz, 2H, −NH−CH$_2$−); Anal. calcd for $C_{11}H_8BrClN_4O_3$ (358): C, 36.57%; H, 2.43%; N, 15.65%. Found: C, 36.74%; H, 2.24%; N, 15.58%.

4.2.3. General synthetic procedure for obtaining compounds *5a–5w*

Compound **4** (0.1 mmol), 4-(trifluoromethoxy) aniline (0.1 mmol), and triethylamine (0.1 mmol) were dissolved in CH_3CN (15 mL) with stirring, and $POCl_3$ (0.1 mmol) was dissolved in CH_3CN (5 mL) and then added dropwise. After stirring and refluxing for 2 h, CH_3CN was removed *in vacuo*. The mixture was washed with saturated sodium bicarbonate solution. The solution was filtered to obtain a crude product, which was recrystallized with ethanol to obtain the title compound **5a**.

Target compounds **5b**–**5w** were prepared using similar procedures as those described above for compound **5a**. The melting point, yield, IR, ^{1}H NMR, ^{13}C NMR and elemental analyses data for **5a** are shown below, and those for compounds **5b**–**5w** can be found in the Supporting Information.

Data for 3-bromo-1-(3-chloropyridin-2-yl)-N-(2-oxo-2-((4-(trifluoromethoxy)phenyl)amino)ethyl)-1H-pyrazole-5-carboxamide (**5a**). Phase, white solid; mp, 212–214 °C; yield, 90.1%; IR (KBr, cm^{-1}) ν: 3309.8, 3251.9, 3107.3, 3076.4, 2927.9, 1714.7, 1664.5, 1543.0, 1506.3, 1467.8, 1294.2; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 10.24 (s, 1H, −CONH−), 9.18 (t, 1H, J = 5.75 Hz, −CONHCH$_2$−), 8.50 (dd, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 4.60 Hz, 1H, 6-Pyridine-H), 8.19 (dd, $^4J_{HH}$ = 1.15 Hz, $^3J_{HH}$ = 8.00 Hz, 1H, 4-Pyridine-H), 7.67 (s, 1H, Ph-H), 7.65 (s, 1H, Ph-H), 7.63 (dd, $^4J_{HH}$ = 4.60 Hz, $^3J_{HH}$ = 8.05 Hz, 1H, 5-Pyridine-H), 7.33 (s, 1H, Ph-H), 7.32 (s, 1H, Ph-H), 7.30 (s, 1H, 4-Pyrazole-H), 3.98 (d, J = 5.70 Hz, 2H, −CH$_2$−); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 167.71, 157.61, 149.26, 147.58, 144.09, 139.71, 139.61, 138.50, 128.64, 127.21, 127.16, 122.20, 120.95, 119.62, 110.67, 43.14; Anal. calcd for $C_{18}H_{12}BrClF_3N_5O_3$ (517): C, 41.50%; H, 2.47%; N, 13.77%. Found: C, 41.68%; H, 2.33%; N, 13.50%.

4.3. Insecticidal activity

Insecticidal activities were measured on representative test organisms reared in the laboratory. According to statistical requirements, the bioassay was repeated at 25 ± 1 °C [42]. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula [43]. Evaluations were based on a percentage scale of 0–100, in which 0 corresponds to no activity and 100 corresponds to total mortality. The insecticidal activities of compounds **5a**–**5w** against third instar larvae of *P. xylostella* were evaluated according to a previously reported procedure [44,45]. Fresh cabbage discs (diameter: 2 cm) were dipped into the prepared solutions containing compounds **5a**–**5w** for 10 s, air-dried, and then placed in a Petri dish (diameter: 9 cm) lined with filter paper. Then, ten third instar larvae of *P. xylostella* were carefully transferred to the Petri dish. Each assay was conducted in triplicate. Mortality was calculated 72 h after treatment. The control groups were treated with distilled water containing TW-80 (0.1 mL/L). Commercial insecticides (i.e., chlorantraniliprole, chlorpyrifos, and avermectins) were tested and compared under the same conditions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.06.023. These data include MOL files and InChiKeys of the most important compounds described in this article.

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