Design, synthesis, and insecticidal activity of novel neonicotinoid derivatives containing N-oxalyl groups

Yu Zhao, Yongqiang Li, Suhua Wang, and Zhengming Li*

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China
E-mail: nkzml@vip.163.com

Abstract

Two series of novel neonicotinoid derivatives containing N-oxalyl groups were designed and synthesized, and their structures were characterized by ^{1}H NMR spectroscopy, high-resolution mass spectroscopy, elemental analysis and single crystal X-ray diffraction analysis. The insecticidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal activities. The insecticidal activities of compounds **13c**, **13d**, **13g**, **13h**, and **13i** against bean aphids at 12.5 mg kg^{-1} were 100%; the insecticidal activities against bean aphids of the derivative **13 c, 13d, 13g**, **13h**, and **14h** were comparable to imidacloprid at 6.25 mg kg^{-1}. Surprisingly, the results indicated that the activity of ethyl 2-(3-((6-chloropyridin-3-yl)methyl)-2-(nitroimino)imidazolidin-1-yl)-2-oxoacetate (**13b**) against bean aphids at 6.25 mg kg^{-1} was 96%, which was higher than the commercialized imidacloprid.

Keywords: Neonicotinoid, N-oxalyl derivatives, synthesis, insecticidal activity, bean aphid, imidacloprid

Introduction

Since the introduction of imidacloprid (**1**) in the 1980s as an insecticide for crop protection,[1] neonicotinoid insecticides have been rapidly developed worldwide for controlling insects because of their high potency, low mammalian toxicity, broad insecticidal spectra, and good systemic properties. Neonicotinoids, which interact with nicotinic acetylcholine receptors (nAChR), have a higher affinity for the insect receptor than for the mammalian receptor and are relatively safe toward mammals and aquatic life.[2-5] Imidacloprid (**1**), the first neonicotinoid insecticide acting on a nAChR, has been widely used to control not only various plant pests, but also fleas on cats and

dogs, and termites.[6-8] Following imidacloprid, thiamethoxam (**2**), thiacloprid (**3**), acyclic neonicotinoid insecticides, dinotefuran (**4**), acetamiprid (**5**), nitenpyram (**6**), and clothianidin (**7**) have been registered as agricultural insecticides.[9-14] These six products were developed by replacing the pyridine ring with a thiazole ring or a saturated heterocyclic ring, changing the nitroimino group to an isoelectronic nitromethylene or cyanoimine group, or reconstructing the imidazolidine ring with bioisosteric cyclic or acyclic moieties.[15] All of these compounds were characterized by their high insecticidal activities against insects and relative safety toward mammals and aquatic life.[16-19]

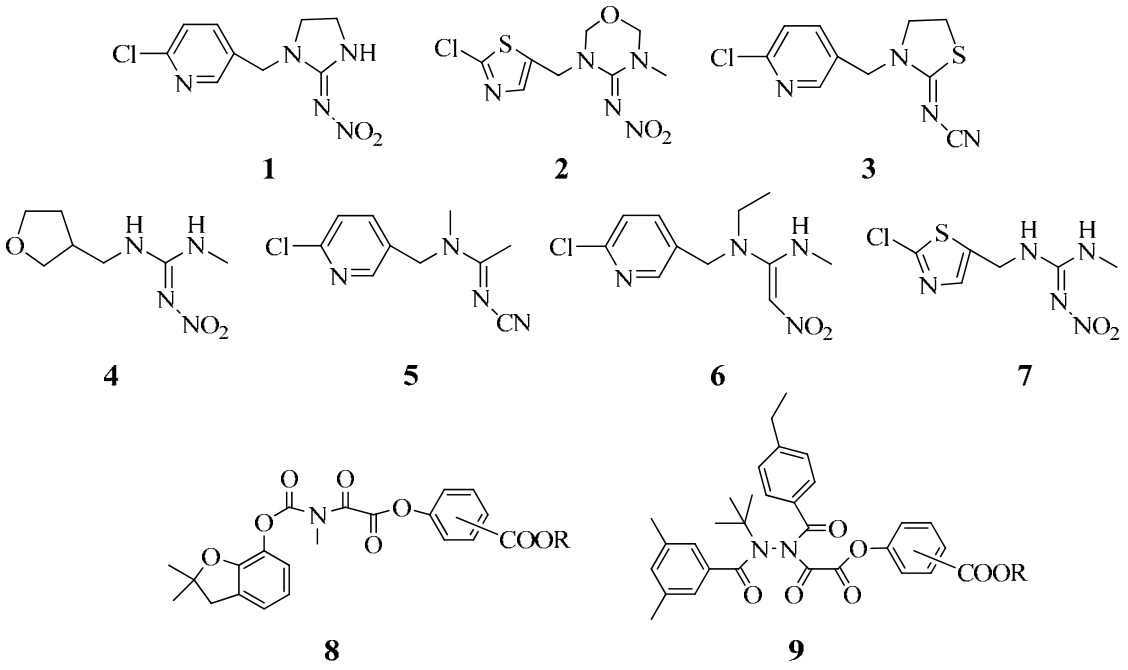


Figure 1. Seven commercialized neonicotinoid compounds and two reported *N*-oxalyl derivatives.

The activity spectrum of a pesticide is often determined by the physical properties of the compound, and it is possible to develop a compound of new style by attaching an appropriate functional group to a present insecticide. Moreover, the physical properties of an insecticidal compound may be manipulated to obtain products with other selected types of activity by proper selection of the derivative moiety.[20] It was reported that N-oxalyl derivatives of carbofuran containing a carboxylic acid or ester substituent (**8**) displayed an insecticidal activity comparable or superior to that of carbofuran.[21] The synthesis and insecticidal evaluation of novel N-oxalyl derivatives of tebufenozide (**9**) have been reported and the results of bioassay showed that they exhibit excellent larvicidal activity (Figure 1).[22]

Encouraged by these reports, an idea was developed that the introduction of an oxalyl substituent into some neonicotinoid molecules by substituting the hydrogen on the nitrogen atom could

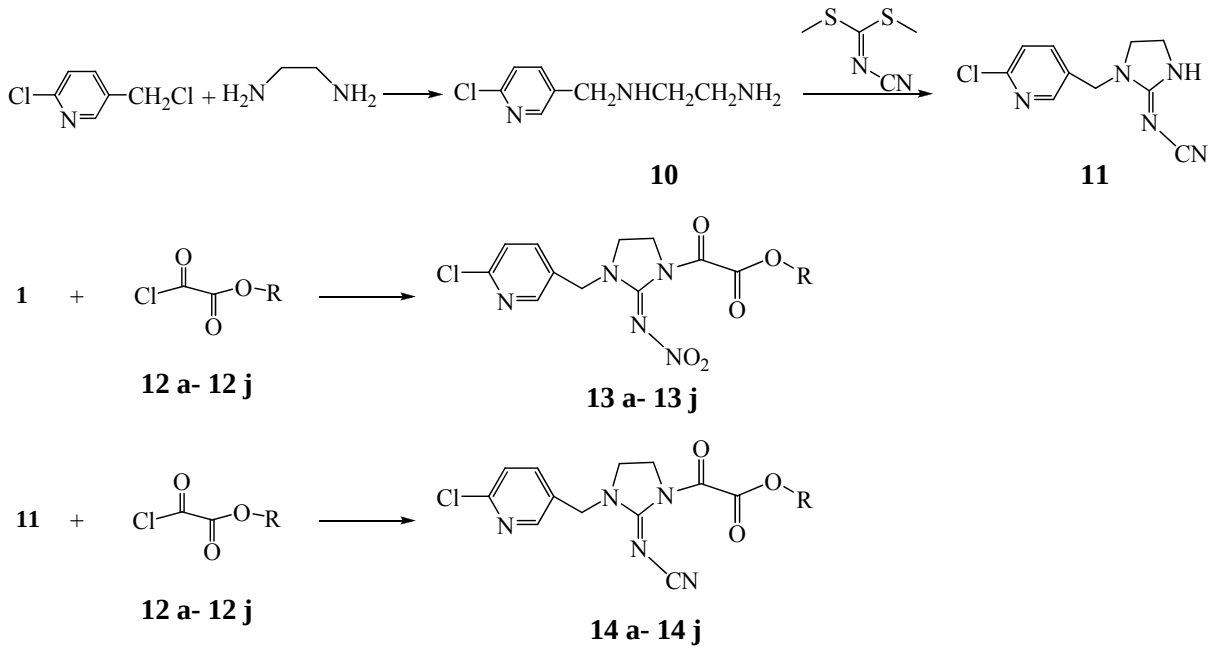
improve biological properties and decrease resistance. Therefore, in a search for new neonicotinoid insecticide with improved profiles, two series of neonicotinoid derivatives containing *N*-oxalyl groups were designed and synthesized as shown in Scheme 1.

Results and Discussion

Synthesis

In the present work, the synthesis of two series novel N-oxalyl derivatives of neonicotinoid compounds as well as their insecticidal activities against bean aphids were studied. Imidacloprid (**1**) was prepared according to the literature.[23-25] The title compounds **13** were synthesized from imidacloprid (**1**) and the appropriate alkyloxyoxalyl chloride (**12**) (obtained from the corresponding alcohol and oxalyl chloride – see Table 1) in dry dimethylformamide using sodium hydride as base as shown in Scheme 1. The target N-oxalyl derivatives of neonicotinoid compounds **14** were synthesized by a simple and convenient four-step procedure starting from 2-chloro-5-chloromethylpyridine and ethylenediamine. The compound (**10**) was reacted with dimethyl cyanodithioimidocarbonate in ethanol to yield 1-(2-chloro-5-pyridylmethyl)-2-cyanoiminoimidazolidine (**11**).

The reaction of **11** and **12** using the method described above for compounds **13** afforded the title compounds **14**. The melting points, yields, and elemental analyses of compounds **13** and **14** are listed in Table 2. The ^{1}H NMR data are listed in Table 3.



Scheme 1. General synthetic route of the title compounds **13 a-13 j** and **14 a- 14 j**.

Insecticidal activity

Table 4 shows the insecticidal activities of the title compounds **13** and **14** and imidacloprid against bean aphids. The results of insecticidal activities given in Table 4 indicated that most of the title compounds exhibited excellent activity against bean aphids, comparable to the commercialized imidacloprid. For instance, the insecticidal activities of compounds **13 c, 13 d, 13 g, 13 h,** and **13 i** against bean aphids at 12.5 mg kg^{-1} were 100%. Moreover, some of them still exhibited good insecticidal activity against bean aphids when the concentration was reduced to 6.25 mg kg^{-1}. Surprisingly, the results indicated that the activity of compound **13 b** against bean aphids at 6.25 mg kg^{-1} was 96%, which was higher than the commercialized imidacloprid; and the activity of compound **13 h** was 81% at 6.25 mg kg^{-1}, which was equal to imidacloprid.

From the data presented in Table 4, we found that the bioactivities of the second series **14** were weaker than that of the first series **13**. Therefore the nitroimino-substituted analogue showed a higher insecticidal activity than did the corresponding cyanoimine-substituted analogue. Among those compounds, replacing the nitroimino group with cyanoimine group resulted in decreased insecticidal activity.

Compounds **13 a- 13 g**, 1**4 a, 14 b** and **14 d** exhibited good insecticide activity against bean aphids and had > 90% mortality at 25 mg kg^{-1}. The allyl esters **13 h** and **14 h** exhibited the highest insecticidal activity in their respective series, comparable to that of the control imidacloprid. Further studies on structural optimization and structure-activity relationships of these *N*-oxalyl derivatives are in progress.

Conclusions

In summary, two series of novel neonicotinoid derivatives containing N-oxalyl group were designed and synthesized with structures characterized by ^{1}H NMR spectroscopy, high-resolution mass spectroscopy, elemental analysis and single crystal X-ray diffraction analysis. The insecticidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited good insecticidal activities, and that substitution of the hydrogen atom at N in the imidazolidine ring of the parent compounds by oxalate may be a feasible approach to improving activity profiles of neonicotinoids. Most of the new derivatives retain the insecticidal activity of the parent compounds and some, such as derivative **13 b,** increase the activity. The modification of the imidazolidine ring of the parent compounds offers a promising prospect and highly active analogues are expected to be found by further work.

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. HRMS data was obtained on a FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. All solvents and liquid reagents were dried by standard methods and distilled before use. Imidacloprid (**1**) was prepared according to the literatures.[23-25]

Synthetic procedure for 1-(2-chloro-5-pyridylmethyl)-2-cyanoiminoimidazolidine (11). 2-Chloro-5-chloromethylpyridine (4.86 g, 0.03 mol) in acetonitrile (30 mL) was added dropwise to a mixture of ethylenediamine (9.0 g, 0.15 mol) and potassium carbonate (4.2 g, 0.03 mol) at 25 ^{o}C. After stirring for 10 hours at room temperature, the reaction mixture was poured into ice water (30 mL), and extracted with dichloromethane (3 × 30 mL). The organic layer was washed successively with water (3 × 20 mL) and brine (20 mL), and then dried over anhydrous sodium sulfate. The solvent was evaporated to give *N*-(2-chloro-5-pyridylmethyl)ethylenediamine (**10**) as a colorless oil, which was directly used for the next step without further purification. The yield was 43%.

N-(2-Chloro-5-pyridylmethyl)ethylenediamine (**10**) (3.71 g, 0.02 mol) and dimethyl cyanodithioimidocarbonate (2.92 g, 0.02 mol) were added to ethanol (50 mL), and the mixture was gradually heated with stirring and subsequently refluxed for 3 hours. After the reaction, ethanol was distilled off under reduced pressure, whereupon the residue solidified. The solidified residue was pulverized and washed with a mixture of ether (10 mL) and a small amount of ethanol (1 mL). The amount of product yielded after drying was 2.88 g. The yield was 71%. Melting point 153-155 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.30 (d, $^4J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.66 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.35 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 6.34 (s, 1H, NH); 4.41 (s, 2H, Py-CH_2); 3.63 (t, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2-N); 3.49 (t, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2-NH).

Synthetic procedure for alkyloxyoxalyl chlorides 12 a-12 j[26]

The appropriate alcohol (0.1 mol) was added dropwise over 20 minutes to an excess of oxalyl chloride (0.2 mol) at 0 ^{o}C. When the addition was complete, the mixture was allowed to warm to room temperature for 2 hours. Excess oxalyl chloride was removed by vacuum distillation. Further distillation affords alkyloxyoxalyl chloride **12 a-12 j**. The boiling points, yields of compounds **12 a- 12 j** were listed in Table 1.

Table 1. Boiling points, yields, of the compounds **12 a- 12 j**

Compd.	R	b.p. (℃)	Yield (%)
12 a	methyl	118-120	75
12 b	ethyl	132-135	79
12 c	*n*-propyl	150-152	77
12 d	*i*-propyl	149-151	71
12 e	*n*-butyl	77-79 (3 mmHg)	66
12 f	*i*-butyl	75-76 (3 mmHg)	60
12 g	*s*-butyl	76-78 (3 mmHg)	64
12 h	allyl	63-66 (3 mmHg)	84
12 i	benzyl	93-95 (3 mmHg)	58
12 j	2-methoxyethyl	97-99 (3 mmHg)	60

General synthetic procedure for the title compounds 13 a- 13 j

Imidacloprid (**1**) (0.01 mol) was dissolved in dry dimethylformamide (30 mL) and sodium hydride (0.011 mol) was added at 10 °C. The mixture was stirred at room temperature until the generation of hydrogen ceased. Then, alkyloxyoxalyl chloride (**12**) (0.011 mol) was added, and the mixture was stirred at 30 °C. for 5 hours, and poured into ice water (50 mL). The aqueous layer was extracted with dichloromethane (3×40 mL). The dichloromethane layer was washed with water (3×40 mL) and dried over anhydrous sodium sulfate. Then the dichloromethane was concentrated. The residue was purified by column chromatography over silica gel using petroleum ether (60-90 °C) and ethyl acetate as the eluent to afford the title compounds **13 a- 13 j**. The melting points, yields, and elemental analyses of compounds **13 a- 13 j** are listed in Table 2. The ^{1}H NMR data are listed in Table 3.

The title compounds **14 a- 14 j** can be prepared using the same method. The melting points, yields, and elemental analyses of compounds **14 a- 14 j** are also listed in Table 2. The ^{1}H NMR data are listed in Table 3.

Table 2. Melting points, yields, and elemental analyses of the title compounds **13 a- 13 j** and **14 a- 14 j**

Compd.	R	mp (℃)	Yield (%)	Elemental Analysis (%) calcd. (found)		
				C	H	N
13 a	methyl	86-88	68	42.18 (41.93)	3.54 (3.69)	20.50 (20.53)
13 b	ethyl	121-123	56	43.89 (43.99)	3.97 (3.89)	19.69 (19.75)
13 c	*n*-propyl	88-90	59	45.48 (45.51)	4.36 (4.49)	18.94 (18.84)
13 d	*i*-propyl	103-104	79	45.48 (45.50)	4.36 (4.32)	18.94 (18.88)
13 e	*n*-butyl	82-84	43	46.94 (46.95)	4.73 (4.62)	18.25 (18.02)
13 f	*i*-butyl	102-104	57	46.94 (47.09)	4.73 (4.63)	18.25 (18.29)
13 g	*s*-butyl	110-112	35	46.94 (46.96)	4.73 (4.89)	18.25 (18.13)
13 h	allyl	86-87	73	45.72 (45.70)	3.84 (4.00)	19.04 (18.93)
13 i	benzyl	113-115	72	51.75 (51.55)	3.86 (3.89)	16.76 (16.87)
13 j	2-methoxyethyl	75-77	74	43.59 (43.46)	4.18 (4.24)	18.15 (17.98)
14 a	methyl	133-135	41	48.53 (48.32)	3.76 (3.95)	21.77 (21.79)
14 b	ethyl	153-155	82	50.08 (50.09)	4.20 (4.29)	20.86 (20.71)
14 c	*n*-propyl	159-161	62	51.51 (51.41)	4.61 (4.48)	20.02 (20.09)
14 d	*i*-propyl	179-181	61	51.51 (51.40)	4.61 (4.83)	20.02 (19.97)
14 e	*n*-butyl	146-148	55	386.0096 (386.0090)[a]		
14 f	*i*-butyl	139-141	69	52.82 (52.89)	4.99 (5.05)	19.25 (19.26)
14 g	*s*-butyl	100-102	71	52.82 (52.81)	4.99 (5.09)	19.25 (19.23)
14 h	allyl	102-104	75	51.81 (51.70)	4.06 (4.03)	20.14 (19.94)
14 i	benzyl	oil	46	420.0834 (420.0836)[a]		
14 j	2-methoxyethyl	oil	56	388.0783 (388.0788)[a]		

[a] The value of HRMS $[M + Na]^+$.

Table 3. ^{1}H NMR of the title compounds **13 a- 13 j** and **14 a- 14 j**

Compd.	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)
13 a	8.36 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 4.62 (s, 2H, Py-CH_2); 4.16 (t, $^3J_{HH}$ = 6.9 Hz, 2H, CH_2-CH_2); 3.91 (s, 3H, CH_3); 3.67 (t, $^3J_{HH}$ = 6.9 Hz, 2H, CH_2-CH_2)
13 b	8.36 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.75 (dd, $^3J_{HH}$ =8.3 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.3 Hz, 1H, Py-H); 4.61 (s, 2H, Py-CH_2); 4.35 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2); 4.15 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3)
13 c	8.36 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.42 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 4.61 (s, 2H, Py-CH_2); 4.23 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OCH_2); 4.16 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.75 (m, 2H, CH_2CH_3); 0.97 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3)
13 d	8.36 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.38 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.14 (m, 1H, OCH); 4.60 (s, 2H, Py-CH_2); 4.14 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.34 (d, $^3J_{HH}$ = 6.3 Hz, 6H, $CH(CH_3)_2$)
13 e	8.36 (d, $^4J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 4.61 (s, 2H, Py-CH_2); 4.29 (t, $^3J_{HH}$ = 6.8 Hz, 2H, OCH_2); 4.14 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.66 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.71 (m, 2H, OCH_2CH_2); 1.41 (m, 2H, CH_2CH_3); 0.95 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3)
13 f	8.36 (d, $^4J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.75 (dd, $^3J_{HH}$ =8.3 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 4.61 (s, 2H, Py-CH_2); 4.15 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2-CH_2); 4.10 (d, $^3J_{HH}$ = 6.7 Hz, 2H, OCH_2); 3.67 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2-CH_2); 2.05 (m, 1H, CH_2CH); 0.98 (d, $^3J_{HH}$ = 6.7 Hz, 6H, $(CH_3)_2$)
13 g	8.36 (d, $^4J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.3 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 4.96 (m, 1H, OCH); 4.60 (s, 2H, Py-CH_2); 4.14 (t, $^3J_{HH}$ = 8.3 Hz, 2H, CH_2-CH_2); 3.67 (t, $^3J_{HH}$ = 8.3 Hz, 2H, CH_2-CH_2); 1.68 (m, 2H, CH_2CH_3); 1.31 (d, $^3J_{HH}$ = 6.3 Hz, 3H, $CHCH_3$); 0.93 (t, $^3J_{HH}$ = 7.5 Hz, 3H, CH_2CH_3)
13 h	8.36 (d, $^4J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.39 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.95 (m, 1H, CH=); 5.37 (m, 2H, =CH_2); 4.75 (d, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2CH=); 4.61 (s, 2H, Py-CH_2); 4.16 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.68 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2)
13 i	8.32 (d, $^4J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.69 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 7.35 (m, 5H, Ph); 5.27 (s, 2H, Ph-CH_2); 4.56 (s, 2H, Py-CH_2); 4.09 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.61 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2)
13 j	8.36 (d, $^4J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.74 (dd, $^3J_{HH}$ =8.2 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Py-H); 4.60 (s, 2H, Py-CH_2); 4.43 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $COOCH_2$); 4.14 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.68 (t, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2);

	3.66 (t, $^{3}J_{HH}$ = 4.8 Hz, 2H, CH_2OCH_3); 3.38 (s, 3H, CH_3)
14 a	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.81 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.43 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.06 (s, 2H, Py-CH_2); 3.96 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.92 (s, 3H, CH_3); 3.67 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2)
14 b	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.3 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.40 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.07 (s, 2H, Py-CH_2); 4.40 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H, OCH_2); 3.96 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.40 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3)
14 c	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.43 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.07 (s, 2H, Py-CH_2); 4.29 (t, $^{3}J_{HH}$ = 6.8 Hz, 2H, OCH_2); 3.96 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.77 (m, 2H, CH_2CH_3); 1.01 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3)
14 d	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.83 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.44 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.26 (m, 1H, OCH); 5.08 (s, 2H, Py-CH_2); 3.96 (t, $^{3}J_{HH}$ = 8.1 Hz, 2H, CH_2-CH_2); 3.65 (t, $^{3}J_{HH}$ = 8.1 Hz, 2H, CH_2-CH_2); 1.39 (d, $^{3}J_{HH}$ = 6.3 Hz, 6H, $CH(CH_3)_2$)
14 e	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.44 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.08 (s, 2H, Py-CH_2); 4.34 (t, $^{3}J_{HH}$ = 6.8 Hz, 2H, OCH_2); 3.97 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.72 (m, 2H, OCH_2CH_2); 1.44 (m, 2H, CH_2CH_3); 0.96 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3)
14 f	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.3 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.43 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.07 (s, 2H, Py-CH_2); 4.11 (d, $^{3}J_{HH}$ = 6.6 Hz, 2H, OCH_2); 3.97 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.67 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 2.07 (m, 1H, CH_2CH); 1.00 (d, $^{3}J_{HH}$ = 6.8 Hz, 6H, $(CH_3)_2$)
14 g	8.38 (d, $^{4}J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.44 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.08 (m, 1H, OCH); 5.07 (s, 2H, Py-CH_2); 3.96 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.66 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 1.71 (m, 2H, CH_2CH_3); 1.37 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, $CHCH_3$); 0.98 (t, $^{3}J_{HH}$ = 7.4 Hz, 3H, CH_2CH_3)
14 h	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.6 Hz, 1H, Py-H); 7.43 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 6.00 (m, 1H, CH=); 5.42 (m, 2H, $=CH_2$); 5.07 (s, 2H, Py-CH_2); 4.82 (d, $^{3}J_{HH}$ = 6.2 Hz, 2H, CH_2CH=); 3.96 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.66 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2)
14 i	8.38 (d, $^{4}J_{HH}$ = 2.3 Hz, 1H, Py-H); 7.80 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.41 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 7.33 (m, 5H, Ph); 5.20 (s, 2H, Ph-CH_2); 4.05 (s, 2H, Py-CH_2); 3.93 (t, $^{3}J_{HH}$ = 7.9 Hz, 2H, CH_2-CH_2); 3.63 (t, $^{3}J_{HH}$ = 7.9 Hz, 2H, CH_2-CH_2)
14 j	8.38 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, Py-H); 7.82 (dd, $^{3}J_{HH}$ =8.2 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H, Py-H); 7.43 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py-H); 5.07 (s, 2H, Py-CH_2); 4.51 (t, $^{3}J_{HH}$ = 4.6 Hz, 2H, $COOCH_2$); 3.95 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.70 (t, $^{3}J_{HH}$ = 4.6 Hz, 2H, CH_2OCH_3); 3.65 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H, CH_2-CH_2); 3.44 (s, 3H, CH_3)

Crystal structure analysis

Compound **14 b** was recrystallized from ethyl acetate/petroleum ether to give colorless crystal suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a = 8.397(2) Å, b = 8.397(2) Å, c = 12.476(3) Å, α = 90°, β = 108.602(3)°, γ = 90°, μ = 0.274 mm^{-1}, V = 1523.8(6) $Å^3$, Z = 4, D_x = 1.464 mg m^{-3}, F (000) = 696, T = 113(2) K, 2.17° ≤ θ ≤ 27.86°, and the final R factor, R_1 = 0.0374, ωR_2 = 0.1060. The crystal is monoclinic.

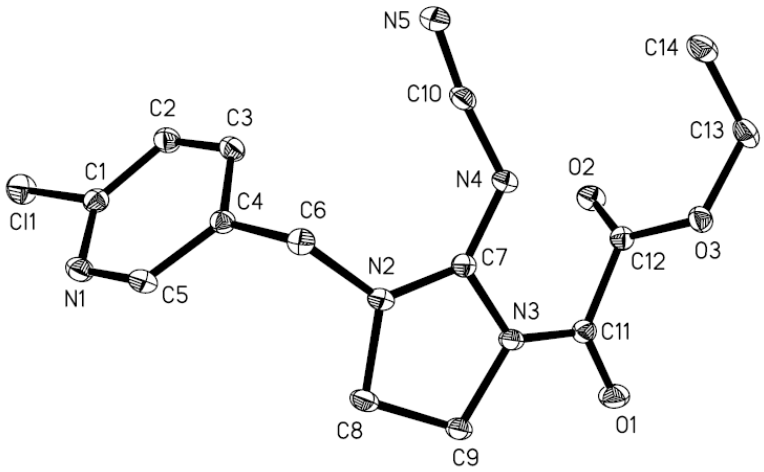


Figure 2. Molecular structure of the compound **14 b**.

The crystal structure of compound **14 b** is shown in Figure 2. The bond length of C(7)-N(2) [1.3275(18) Å] and C(7)-N(3) [1.3902(17) Å] are shorter than the normal C-N single bond (1.49 Å), which suggest that the electron density is delocalized among N(4)-C(7)-N(2) and N(3). The atoms N(4)-C(7)-N(2) and N(3) are close to planar. The dihedral angel between the plane of the pyridine ring and the plane of the imidazole ring is about 106.4°. The crystal packing structure of this compound is shown in Figure 3.

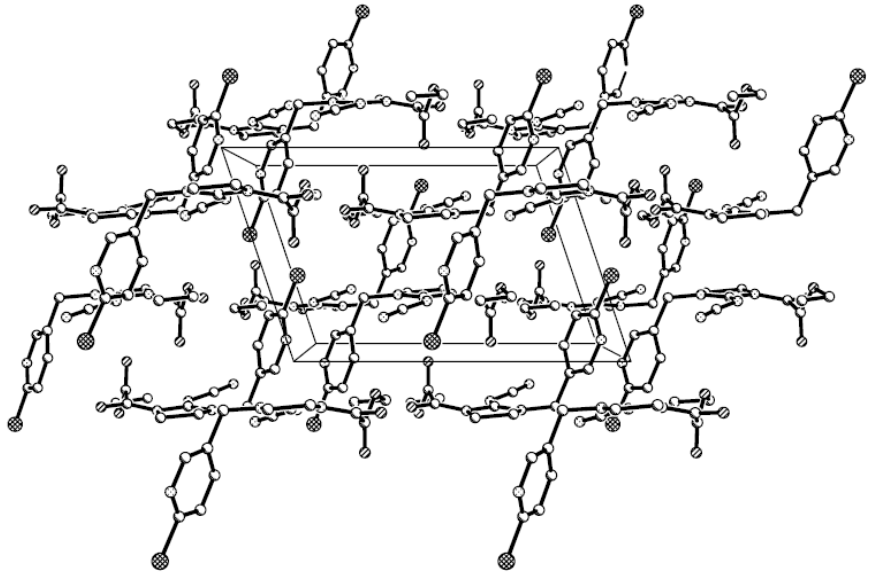


Figure 3. Packing diagram of the compound **14 b**.

Biological assay

All compounds were dissolved in acetone and diluted with water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 200.0, 100.0, 50.0, 25.0, 12.5 and 6.25 mg kg^{-1} and others for bioassays. The bioassay was repeated at 25 ± 1 ^{o}C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[27] Evaluations are based on a percentage scale of 0-100 which 0 equals no activity and 100 equals total kill.

The insecticidal activities of the title compounds **13 a- 13 j, 14 a- 14 j** and imidacloprid against the bean aphids were evaluated. Bean aphids were dipped according to a slightly modified FAO dip test.[28] The tender shoots of soybean with 40~60 healthy apterous adult aphids were dipped in the diluted solutions of the compounds for 5 s, the superfluous fluid removed, and placed in the conditioned room (25 ± 1 ^{o}C, 50% RH). Mortality were calculated 48 h after treatment. Each treatment was performed three times. Water containing Triton X-100 (0.1 mg kg^{-1}) was used as control. The commercial insecticide imidacloprid was used as a standard. Mortality was calculated after 48 h, and data were corrected and subjected to probit analysis as before. The results of the insecticidal activity of the title compounds **13 a- 13 j, 14 a- 14 j** and imidacloprid were summarized in Table 4.

Table 4. Insecticidal activities of compounds **13 a-13 j** and **14 a-14 j** against bean aphids

Compd.	larvicidal activity (%) at conc (mg kg^{-1})					
	200	100	50	25	12.5	6.25
13 a	100	100	100	98	92	74
13 b	100	100	100	97	96	96
13 c	100	100	100	100	100	73
13 d	100	100	100	100	100	74
13 e	100	100	100	100	88	
13 f	100	100	100	94	88	
13 g	100	100	100	100	100	72
13 h	100	100	100	100	100	81
13 i	100	100	100	100	100	66
13 j	100	100	100	98		
14 a	100	100	100	96	80	
14 b	100	100	100	91	79	
14 c	92					
14 d	100	100	100	92	90	60
14 e	100	100	98	78		
14 f	100	100	95	79	44	
14 g	100	100	100	89		
14 h	100	100	100	95	93	69
14 i	95					
14 j	100	100	100	80		
Imidacloprid	100	100	100	100	100	83

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