Synthesis and Insecticidal Activities of Chlorothiazolyl Analogs of Nitromethylene Neonicotinoids with Tetrahydropyridine Fixed *cis*-Configuration

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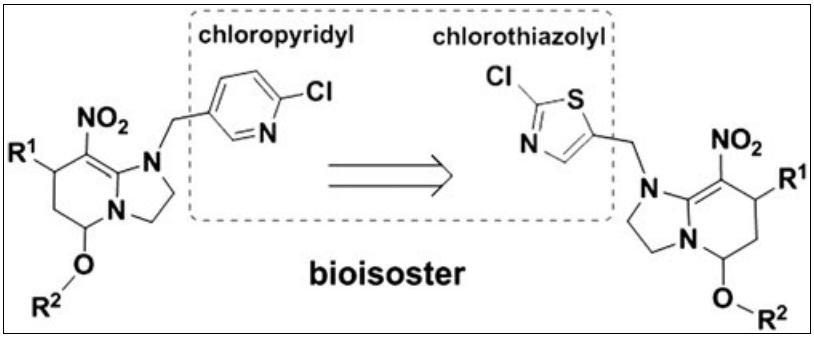

The chlorothiazolyl moiety was an effective bioisoster of chloropyridyl in pesticide molecular design. Replacement of chloropyridyl in *cis*-nitromethylene neonicotinoids with chlorothiazolyl generated the chlorothiazolyl counterpart of nitromethylene neonicotinoids with tetrahydropyridine fixed *cis*-configuration. Bioassay against cowpea aphis (*Aphis craccivora*) indicated that the chlorothiazolyl analogs could maintain the high insecticidal activity.

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INTRODUCTION

The thiazole ring is present in various natural compounds and many synthetic bioactive compounds [1–3]. A number of structure-activity studies have confirmed that thiazole ring was indispensable requirement relate to its biological activity [4–7]. In neonicotinoid insecticides molecular design, the replacement of chloropyridyl moiety by a chlorothiazolyl resulted in the discovery of second-generation neonicotinoids (thiamethoxam and clothianidin) characterized by thiazole motif (Fig. 1) [8–10]. Other researches concerning pesticides have also confirmed that chlorothiazolyl skeleton was an effective bioisoster of chloropyridyl and other heterocycles, and introduction of this bioisoster can often acquire desirable bioactivities [11–15].

Previously, we devoted ourselves to the research on *cis*-neonicotinoids and discovered several series of *cis*-neonicotinoids [16]. Recently, we described the syntheses of chloropyridyl nitromethylene neonicotinoids **6** (Fig. 2) with tetrahydropyridine fixed *cis*-configuration and their excellent insecticidal activities which were slightly weaker than that of imidacloprid [17,18]. Among these *cis*-neonicotinoids, compound **7** (commercial name Paichongding) has been commercialized in China this year. However, bioactivities of chlorothiazolyl analogs of compounds **6** were ambiguous. As a continuation of our work and with the aim of enhancing the insecticidal activities of this kind of compounds, we herein report the synthesis and insecticidal activities of a series of chlorothiazolyl analogs of *cis*-neonicotinoids **8**. Bioassay showed that some of the candidates showed excellent activities against cowpea aphids (Table 1).

RESULTS AND DISCUSSION

The target compound **8** were synthesized according to our previously reported procedures (Scheme 1). From the starting material, 2-chloro-4-(chloromethyl)thiazole **9**, cyclic nitromethylene intermediate **11** was prepared by amination followed by subsequent cyclization. Treatment of **11** with crotonaldehyde or cinnamaldehyde in acetonitrile at 40–50°C employing glacial acetic acid as catalyst afforded hexahydroimidazo[1,2-α]pyridine derivatives **12**. The bicyclic nature of the structures **12** clearly followed from ^{1}H NMR data indicating the disappearance of singlet of C=C–H and N–H in intermediate **11**. A presumed reaction pathway from **11** to **12** was outlined briefly in Scheme 1. The reactions were initiated by Michael addition via electrophilic attack of C=C double bond by α, β-unsaturated aldehydes**,** and then the intramolecular electrophilic attack on the nitrogen atom underwent with the formation of

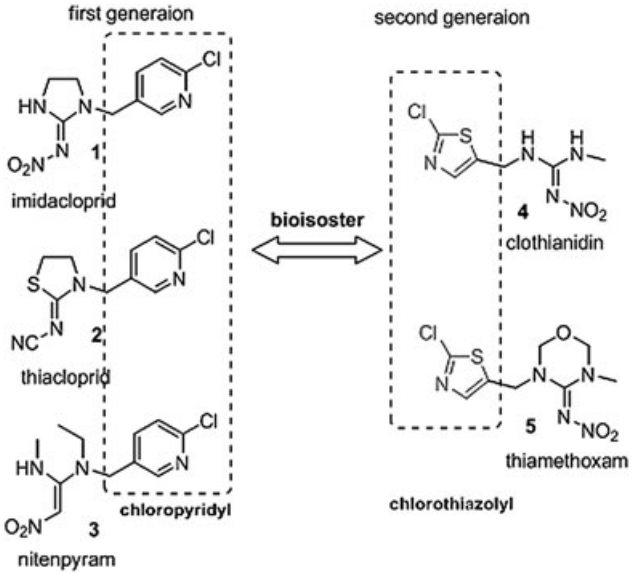


Figure 1. Chlorothiazolyl was an effective bioisoster of chloropyridyl in neonicotinoids.

target compounds. In this cyclization to hexahydroimidazo [1,2-α]pyridine, both C=**C**–NO_2 and nitrogen in imidazolidine acted as the nucleophilic centre. The reaction of **11** with crotonaldehyde could generate byproduct **13** by elimination of H_2O from compound **12a** in elevated temperature. Further study showed that compound **12a** could convert to **13** in dichloromethane catalyzed by lewis acid $BF_3{\cdot}Et_2O$ in good yields (80%). The structures of the compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

As chloropyridyl series compounds **6** showed high activities against the homopteran insects, we selected the cowpea aphis (*Aphis craccivora*) to evaluate the insecticidal activity of compounds **8a**-**v**. Some chlorothiazolyl analogs exhibited good activity against cowpea aphis, but somewhat lower than that of imidacloprid. For the effects of the R^2, the longer alkyl group could attenuate activities. For the substituents R^1, replacement of methyl with phenyl led to almost total loss of activities (methyl analogs demonstrated much high potency than the corresponding phenyl analogs). These structure-activity relationship observations associated with the substituents R^1 and R^2 are similar to that of the chloropyridyl analogs. Here, compound **8d**, the counterpart of commercialized compound Paichongding, gave the highest activities, which was consistent with the chloropyridyl insecticides **6** in bioactivity tendency. **8a**, **8c**, **8d**, **8e** (LC_{50} = 25.80, 22.90, 19.21, 29.58 mg L^{-1}, respectively) had somewhat higher activity than Paichongding (LC_{50} = 33.66 mg L^{-1}), indicating that chlorothiazolyl moiety was an effective replacement for chloropyridyl. Interestingly, hydroxyl-eliminated compound **13** also have excellent activity (LC_{50} = 67.02 mg L^{-1}).

CONCLUSION

In summary, a series of chlorothiazolyl analogs of nitromethylene neonicotinoids with tetrahydropyridine fixed *cis*-configuration were synthesized and their insecticidal activities were evaluated. Some chlorothiazolyl analogs showed significant activity against cowpea aphis, which further confirmed that chlorothiazolyl was a good bioisoster of chloropyridyl.

EXPERIMENTAL

Unless otherwise noted, all reagents and solvents were used as received from commercial suppliers. Yields were not optimized. Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Combustion analyses for elemental composition were made with an Elementar vario EL III. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light.

General synthetic procedure for 12a and 12b. Compound **12a** and **12b** were synthesized according to the procedure reported previously [18]. To a mixture of compound **11** (0.51 g, 2 mmol) were added crotonaldehyde or cinnamaldehyde (2.2 mmol), acetonitrile (20 mL), and a drop of glacial acetic acid. The reaction was carried out at 40°C, and the progress of the reaction was monitored by TLC. After completion, the precipitated product was filtered, washed, and dried to obtain the corresponding product.

General synthetic procedure for 8a–v. To a solution of compound **12a** or **12b** (1 mmol) were added various alcohols (5 mmol), dichloromethane (30 mL), and a drop of concentrated hydrochloric acid. The mixture was refluxed and

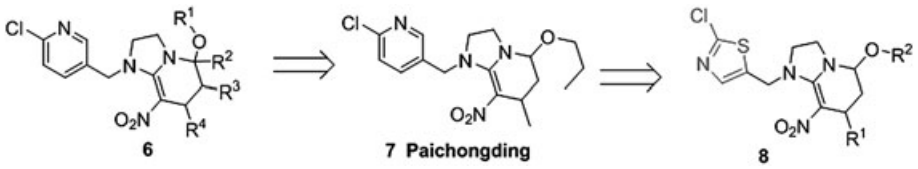
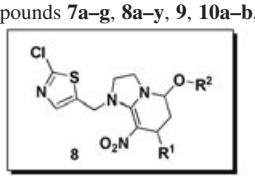
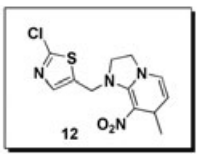


Figure 2. Nitromethylene neonicotinoids with tetrahydropyridine fixed *cis*-configuration.

Table 1

Insecticidal activities of compounds **7a–g**, **8a–y**, **9**, **10a–b**, **11a–b**, **12**, **13**, and imidacloprid against pea aphids.





Compound	R^1	R^2	Mortality(%) (500 mg/L)	LC_{50} (mg/L)
8a	Methyl	H	100	25.80
8b	Methyl	Methyl	100	59.87
8c	Methyl	Ethyl	100	22.90
8d	Methyl	*n*-Propyl	100	19.21
8e	Methyl	*iso*-Propyl	100	29.58
8f	Methyl	*n*-Butyl	60.1	n.t.[a]
8g	Methyl	*n*-pentyl	95.3	336.49
8h	Methyl	iso-Butyl	73.4	n.t.
8i	Methyl	*iso*-pentyl	69.6	n.t.
8j	Methyl	*tert*-Butyl	100	160.97
8k	Methyl	Cyclohexyl	0	n.t.
8l	Methyl	Chloroethyl	100	96.72
8m	Methyl	Methoxyethyl	33.3	n.t.
8n	Methyl	Ethoxyethyl	76.4	n.t.
8o	Methyl	Benzyl	91.5	174.03
8p	Methyl	Allyl	100	96.57
8q	Phenyl	Methyl	0	n.t.
8r	Phenyl	Ethyl	0	n.t.
8s	Phenyl	*n*-Propyl	49.2	n.t.
8t	Phenyl	*iso*-Propyl	0	n.t.
8u	Phenyl	*n*-Butyl	0	n.t.
8v	Phenyl	*iso*-Butyl	0	n.t.
13			100	67.02
Paichongding			100	33.66
Imidacloprid			100	7.90

[a]n.t., not tested.
[b]Compounds from our previous article.

the progress of the reaction was monitored by TLC. After complete, the mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography on silica gel, eluting with dichloromethane/acetone to afford pure products.

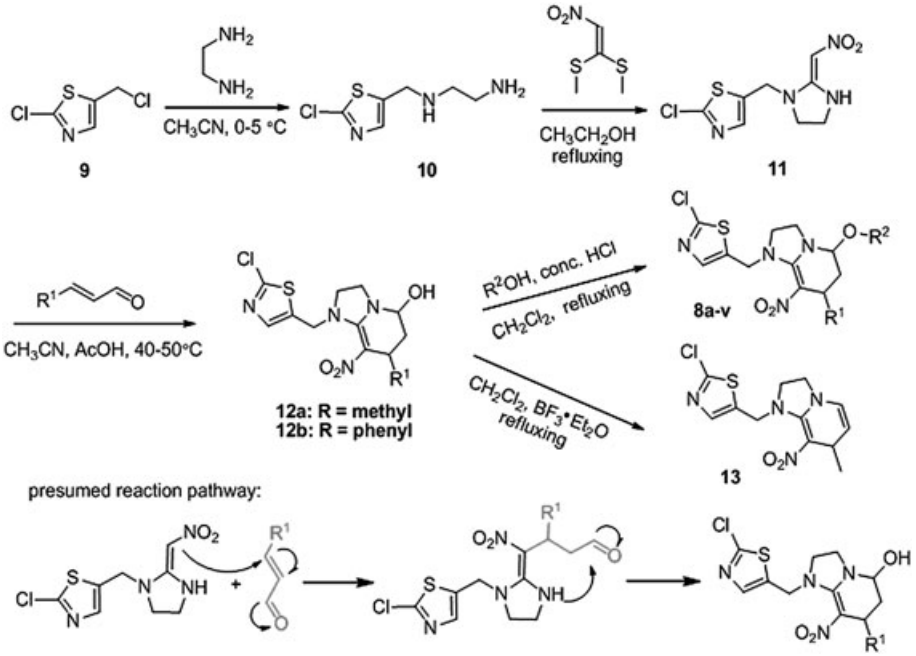
1-((2-Chlorothiazol-5-yl)methyl)-7-methyl-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridin-5-ol (8a). Grey white solid, yield 52%. mp = 198.2–200.0°C; IR (KBr): 3205, 2908, 2369, 1683, 1560, 1346, 1148, 981, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.63 (s, 1H), 6.30 (d, 1H, J = 6.2 Hz), 4.78-4.83 (m, 2H), 4.68 (d, 1H, J = 15.4 Hz), 3.54-3.70 (m, 4H), 3.12-3.17 (m, 1H), 1.89-1.95 (m, 1H), 1.68-1.74 (m, 1H), 1.12 (t, 1H, J = 6.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 158.1, 152.0, 141.6, 136.8, 109.4, 77.1, 75.8, 49.0, 48.1, 45.0, 28.1, 19.9; HRMS (EI+) calcd for $C_{12}H_{15}N_4O_3^{35}ClS$ (M^+), 330.0553; found, 330.0537; calcd for $C_{12}H_{15}N_4O_3^{37}ClS$ (M^+), 332.0524; found, 332.0505. Anal. Calcd. for $C_{12}H_{15}N_4O_3ClS$: C, 43.57; H, 4.57; N, 16.94. Found. C, 43.68; H, 4.59; N, 16.88 %.

2-Chloro-5-((5-methoxy-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8b). Yellow solid, yield 63%, mp = 111.8–113.5°C; IR (KBr): 3032, 2968, 1549, 1425, 1322, 1136, 1062, 961, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 4.92 (dd, 1H, J_1 = 0.9 Hz, J_2 = 15.4 Hz), 4.72 (d, 1H, J = 15.4 Hz), 4.40-4.42 (m, 1H), 3.95-4.02 (m, 1H), 3.69-3.76 (m, 1H), 3.45-3.60 (m, 3H), 3.40 (s, 3H), 1.95-2.06 (m, 2H), 1.29 (d, 1H, J = 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 154.1, 140.7, 135.1, 110.3, 86.2, 55.7, 48.7, 48.5, 45.8, 32.2, 28.2, 19.2 ppm; HRMS (EI+) calcd for $C_{13}H_{17}N_4O_3S^{35}Cl$ (M^+), 344.0710; found, 344.0705; calcd for $C_{13}H_{17}N_4O_3S^{37}Cl$ (M^+), 346.0680; found, 346.0658. Anal. Calcd. for $C_{13}H_{17}N_4O_3ClS$: C, 45.28; H, 4.97; N, 16.25. Found. C, 45.18; H, 4.79; N, 16.36 %.

2-Chloro-5-((5-ethoxy-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8c). Yellow solid, yield 85%, mp 118.1–119.9°C; IR (KBr): 2962, 1555, 1314, 1134, 1062, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 4.91 (d, 1H, J = 15.6 Hz), 4.69 (d, 1H, J = 15.6 Hz), 4.49 (t, 1H, J = 3.2 Hz), 3.94-4.00 (m, 1H), 3.68-3.72 (m, 1H), 3.47-3.64 (m, 4H). 3.44-3.66 (m, 1H), 1.98-2.00 (m, 2H), 1.29 (d, 3H, J = 6.8), 1.23 (t, 3H, J = 6.8); ^{13}C NMR (100 MHz, DMSO-d_6): 157.9, 154.1, 140.8, 135.1, 110.4, 83.0, 63.9, 48.9, 48.8, 45.4, 36.0, 27.7, 19.8, 15.3; HRMS (EI+) calcd for $C_{14}H_{19}N_4O_3^{35}ClS$ (M^+), 358.0866; found, 358.0858. Anal. Calcd. for $C_{14}H_{19}N_4O_3ClS$: C, 48.86; H, 5.34; N, 15.61. Found. C, 48.95; H, 5.39; N, 15.68 %.

2-Chloro-5-((7-methyl-8-nitro-5-propoxy-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8d). Yellow solid, yield 79%, mp 93.4–94.8°C; IR (KBr): 2962, 1554, 1521, 1146, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 4.91

Scheme 1



(d, 1H, J = 15.6 Hz), 4.70 (d, 1H, J = 15.2 Hz), 4.48 (t, 1H, J = 1.6 Hz), 3.97-4.00 (m, 1H), 3.70-3.73 (m, 1H), 3.50-3.57 (m, 4H), 3.39-3.49 (m, 1H),1.97-2.00 (m, 2H), 1.58-1.63 (m, 2H), 1.29 (d, 3H, J = 6.8), 0.94 (t, 3H, J = 7.2); ^{13}C NMR (100 MHz, DMSO-d_6): 156.4, 154.0, 140.6, 135.3, 110.3, 85.0, 70.3, 49.7, 48.5, 45.7, 33.2, 28.3, 23.0, 19.3, 10.6; HRMS (EI+) calcd for $C_{15}H_{21}N_4O_3^{35}ClS$ (M^+), 372.1023; found, 372.1023. Anal. Calcd. for $C_{15}H_{21}N_4O_3ClS$: C, 48.32; H, 5.68; N, 15.03. Found. C, 48.28; H, 5.75; N, 15.11 %.

2-Chloro-5-((5-isopropoxy-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8e). Yellow solid, yield 75%, mp 115.7–119.8°C; IR (KBr): 2926, 2881, 1554, 1346, 1261, 1190, 1131,1038, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 4.90 (d, 1H, J = 15.6 Hz), 4.69 (d, 1H, J = 14.8 Hz), 4.57 (t, 1H, J = 4.4Hz), 3.76-3.97 (m, 1H), 3.50-3.72 (m, 4H), 3.32-3.37 (m, 1H), 2.03-2.10 (m, 1H), 1.75-1.86 (m, 1H), 1.24 (d, 3H, J = 6.8), 1.15 (d, 6H, J = 6.0); ^{13}C NMR (100 MHz, DMSO-d_6): 158.0, 153.8, 140.8, 139.2, 110.4, 82.3, 71.0, 50.0, 46.8, 44.9, 37.0, 27.9, 22.6, 22.4, 19.6; HRMS (EI+) calcd for $C_{15}H_{21}N_4O_3^{35}ClS$ (M^+), 372.1023; found, 372.1007. Anal. Calcd. for $C_{15}H_{21}N_4O_3ClS$: C, 48.32; H, 5.68; N, 15.03. Found. C, 48.40; H, 5.78; N, 15.06%.

5-((5-Butoxy-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)-2-chlorothiazole (8f). Yellow solid, yield 72%, mp 100.2–101.8°C; IR (KBr): 2955, 2859, 1551, 1514, 1350, 1209, 1083, 923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 4.93 (d, 1H, J = 15.2 Hz), 4.70 (d, 1H, J = 15.2 Hz), 4.48 (t, 1H, J = 3.6 Hz), 3.94-4.03 (m, 1H), 3.70-3.73 (m, 1H), 3.50-3.57 (m, 4H), 3.43-3.49 (m, 1H), 1.98-2.00 (m, 2H), 1.56-1.60 (m, 2H), 1.36-1.42 (m, 2H), 1.30 (d, 3H, J = 6.8), 0.94 (t, 3H, J = 7.2); ^{13}C NMR (100 MHz, DMSO-d_6): 157.9, 154.0, 140.7, 135.1, 110.4, 83.1, 68.3, 48.9, 48.7, 46.4, 35.8, 31.7, 27.8, 19.8, 19.2, 13.8; HRMS (EI+) calcd for $C_{16}H_{23}N_4O_3^{35}ClS$ (M^+), 386.1179; found, 386.1161. Anal. Calcd. for $C_{16}H_{23}N_4O_3ClS$: C, 49.67; H, 5.99; N, 14.48. Found. C, 49.52; H, 5.81; N, 14.40 %.

2-Chloro-5-((7-methyl-8-nitro-5-(pentyloxy)-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8g). Yellow solid, yield 65%, mp 94.2–95.0°C; IR (KBr): 2956, 2874, 1562, 1503, 1413, 1209, 1142, 1079, 1046, 938, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 4.93 (d, 1H, J = 15.2 Hz), 4.73 (d, 1H, J = 15.2 Hz), 4.54 (t, 1H, J = 3.6Hz), 3.70-3.80 (m, 2H), 3.45-3.57 (m, 4H), 3.36-3.38 (m, 1H), 2.14-2.17 (m, 1H), 1.78-1.80 (m, 1H), 1.54-1.69 (m, 2H), 1.26-1.34 (m, 7H), 0.88-0.91 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 157.8, 154.1, 140.7, 135.1, 110.4, 83.1, 68.6, 48.9, 48.7, 45.3, 35.8, 29.4, 28.2, 19.8, 14.0; HRMS (EI+) calcd for $C_{17}H_{25}N_4O_3^{35}ClS$ (M^+), 400.1336; found, 400.1336. Anal. Calcd. for $C_{17}H_{25}N_4O_3ClS$: C, 50.93; H, 6.29; N, 13.97. Found. C, 50.96; H, 6.33; N, 14.09%.

2-Chloro-5-((5-isobutoxy-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8h). Yellow solid, yield 68%, mp 116.8–119.7°C; IR (KBr): 3089, 2970, 1655, 1562, 1499, 1343, 1284, 1105, 1057, 912, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 4.92 (d, 1H, J = 15.2 Hz), 4.67 (d, 1H, J = 15.2 Hz), 4.52 (t, 1H, J = 3.6Hz), 3.59-3.80 (m, 2H), 3.35-3.57 (m, 2H), 3.20-3.35 (m, 3H), 2.11-2.13 (m, 1H), 1.75-1.80 (m, 2H), 1.23-1.26 (m, 3H), 0.85-0.92 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 157.9, 153.8, 140.8, 135.3, 110.3, 83.3, 75.3, 48.9, 48.7, 45.5, 35.8, 28.6, 27.8, 19.8, 19.2, 18.2; HRMS (EI+) calcd for $C_{16}H_{23}N_4O_3^{35}ClS$ (M^+),386.1179; found, 386.1180. Anal. Calcd. for $C_{16}H_{23}N_4O_3ClS$: C, 49.67; H, 5.99; N, 14.48. Found. C, 49.56; H, 5.88; N, 14.39%.

2-Chloro-5-((5-(isopentyloxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8i). Yellow solid, yield 63%, mp 131.7–133.0°C; IR (KBr): 3089, 2926, 2852, 1536, 1347, 1042, 868, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 4.91 (d, 1H, J = 15.2 Hz), 4.68-4.72 (m, 1H), 4.47 (t, 1H, J = 3.6Hz), 3.95-3.97 (m, 1H), 3.70-3.72 (m, 1H), 3.44-3.59

(m, 5H), 1.97-1.98 (m, 2H), 1.59-1.70 (m, 1H), 1.44-1.49 (m, 2H), 1.28 (d, 3H, J = 6.8), 0.90 (d, 6H, J = 3.6); ^{13}C NMR (100 MHz, DMSO-d_6): 156.4, 154.0, 140.6, 135.2, 110.3, 85.0, 67.0, 48.7, 48.5, 45.7, 38.5, 33.1, 28.3, 24.9, 22.5, 22.4, 19.2; HRMS (EI+) calcd for $C_{17}H_{25}N_4O_3^{35}ClS$ (M^+), 400.1336; found, 400.1336. Anal. Calcd. for $C_{17}H_{25}N_4O_3ClS$: C, 50.93; H, 6.29; N, 13.97. Found. C, 50.81; H, 6.16; N, 13.92%.

5-((5-tert-Butoxy-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)-2-chlorothiazole (8j). Yellow solid, yield 45%, mp 148.8–154.3°C; IR (KBr): 2956, 2926, 2867, 1551, 1525, 1417, 1343, 1298, 1261, 1206, 1139, 1076, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 4.92 (d, 1H, J = 15.2 Hz), 4.71 (t, 1H, J = 4.4Hz), 4.66 (d, 1H, J = 15.2 Hz), 3.88-3.93 (m, 1H), 3.65-3.70 (m, 1H), 3.38-3.54 (m, 3H), 2.09-2.14 (m, 1H), 1.79-1.85 (m, 1H), 1.33 (d, 3H, J = 6.8), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.4, 154.0, 140.7, 135.2, 110.1, 78.2, 75.1, 48.6, 48.6, 45.2, 38.5, 31.2, 28.8, 28.4, 19.8; HRMS (EI+) calcd for $C_{16}H_{23}N_4O_3^{35}ClS$ (M^+), 386.1179; found, 386.1175. Anal. Calcd. for $C_{16}H_{23}N_4O_3ClS$: C, 49.67; H, 5.99; N, 14.48. Found. C, 49.72; H, 6.06; N, 14.59%.

2-Chloro-5-((5-(cyclohexyloxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8k). Yellow solid, yield 56%, mp 139.6–154.8°C; IR (KBr): 2956, 2881, 1573, 1506, 1413, 1295, 1261, 1206, 1142, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 4.92 (d, 1H, J = 15.2 Hz), 4.67 (d, 1H, J = 15.2 Hz), 4.57 (t, 1H, J = 3.2Hz), 3.94-3.96 (m, 1H), 3.70-3.72 (m, 1H), 3.39-3.55 (m, 4H), 2.00-2.03 (m, 1H), 1.71-1.92 (m, 5H), 1.28-1.30 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): 156.6, 153.9, 140.6, 135.3, 110.1, 82.7, 48.6, 48.5, 45.3, 35.1, 32.9, 32.0, 28.4, 25.4, 23.8, 19.6; HRMS (EI+) calcd for $C_{18}H_{25}N_4O_3^{35}ClS$ (M^+),412.1336; found, 412.1337. Anal. Calcd. for $C_{18}H_{25}N_4O_3ClS$: C, 52.36; H, 6.10; N, 13.57. Found. C, 52.20; H, 6.01; N, 13.38%.

2-Chloro-5-((5-(2-chloroethoxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8l). Yellow solid, yield 80%, mp 121.6–122.7°C; (KBr): 2956, 2919, 2889, 1555, 1517, 1417, 1369, 1206, 1142, 1079, 1046, 935, 853, 756, 701, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 4.91 (d, 1H, J = 15.2 Hz), 4.70 (d, 1H, J = 15.6 Hz), 4.60 (t, 1H, J = 3.2Hz), 4.01-4.06 (m, 1H), 3.83-3.87 (m, 1H), 3.63-3.3.74 (m, 4H), 3.48-3.59 (m, 3H), 2.00-2.02 (m, 2H),1.28 (d, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 156.0, 154.0, 140.7, 135.1, 110.2, 68.4, 48.8, 48.5, 45.7, 43.2, 32.8, 28.1, 19.2; HRMS (EI+) calcd for $C_{14}H_{18}N_4O_3^{35}Cl_2S$ (M^+), 392.0477; found, 392.0435. Anal. Calcd. for $C_{14}H_{18}N_4O_3Cl_2S$: C, 42.75; H, 4.61; N, 14.25. Found. C, 42.76; H, 4.65; N, 14.29%.

2-Chloro-5-((5-(2-methoxyethoxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8m). Yellow solid, yield 86%, mp 110.7–112.1°C; IR (KBr): 3022, 2993, 2933, 2874, 2822, 1566, 1514, 1417, 1321, 1261, 1213, 1139, 1076, 1050, 1027, 938, 853, 753, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 4.94 (d, 1H, J = 15.2 Hz), 4.72 (d, 1H, J = 15.2 Hz), 4.67 (t, 1H, J = 3.6Hz), 3.87-3.90 (m, 1H), 3.70-3.74 (m, 1H), 3.63-3.65 (m, 2H), 3.50-3.55 (m, 4H), 3.38-3.40 (m, 2H), 3.36 (S, 3H), 2.16-2.21 (m, 1H), 1.79-1.83 (m, 1H), 1.27 (d, 3H, J = 6.8Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 154.8, 154.2, 141.2, 135.0, 122.1, 115.6, 108.2, 49.3, 48.2, 46.5, 31.8, 21.5; HRMS (EI+) calcd for $C_{15}H_{21}N_4O_4^{35}ClS$ (M^+), 388.0972; found, 388.0940. Anal. Calcd. for $C_{15}H_{21}N_4O_4ClS$: C, 46.33; H, 5.44; N, 14.41. Found. C, 46.037; H, 5.36; N, 14.29%.

2-Chloro-5-((5-(2-ethoxyethoxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8n). Yellow solid, yield 83%, Mp 118.0–120.4°C; IR (KBr): 3015, 2963, 2926, 2881, 1558, 1514, 1417, 1339, 1324, 1265, 1139, 1072, 1046, 938, 753, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 4.94 (d, 1H, J = 15.2 Hz), 4.73 (d, 1H, J = 15.2 Hz), 4.69 (t, 1H, J = 3.6Hz), 3.89-3.92 (m, 1H), 3.70-3.73 (m, 1H), 3.64-3.66 (m, 2H), 3.37-3.57 (m, 6H), 2.16-2.21 (m, 1H), 1.77-1.82 (m, 1H), 1.27 (d, 3H, J = 6.4Hz), 1.20 (t, 3H, J = 6.8Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 157.8, 154.1, 140.7, 135.2, 110.4, 83.5, 70.0, 67.5, 66.8, 48.9, 48.7, 45.1, 35.6, 27.8, 19.8, 15.2; HRMS (EI+) calcd for $C_{16}H_{23}N_4O_4^{35}ClS$ (M^+), 402.1129; found, 402.1163. Anal. Calcd. for $C_{16}H_{23}N_4O_4ClS$: C, 47.70; H, 5.75; N, 13.91. Found. C, 47.62; H, 5.78; N, 19.90 %.

5-((5-(Benzyloxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)-2-chlorothiazole (8o). Yellow solid, yield 65%, mp 146.1–148.6°C; IR (KBr): 2956, 2926, 2874, 1555, 1517, 1413, 1324, 1265, 1209, 1139, 1076, 1046, 990, 860, 753, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.27-7.38 (m, 5H), 4.96 (d, 1H, J = 15.6 Hz), 4.51-4.69 (m, 5H), 3.39-3.69 (m, 5H), 2.22-2.27 (m, 1H), 1.76-1.79 (m, 1H), 1.30 (d, 3H, J = 6.4Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 157.9, 154.1, 140.8, 140.7, 137.1, 135.0, 128.7, 128.2, 127.5, 110.3, 82.5, 70.4, 48.8, 45.5, 36.2, 27.6, 20.0; HRMS (EI +) calcd for $C_{19}H_{21}N_4O_3^{35}ClS$ (M^+), 420.1023; found, 420.1017. Anal. Calcd. for $C_{19}H_{21}N_4O_3ClS$: C, 54.22; H, 5.03; N, 13.31. Found. C, 54.29; H, 5.06; N, 13.35 %.

5-((5-(Allyloxy)-7-methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)-2-chlorothiazole (8p). Yellow solid, yield 75%, mp 105.7–106.9°C; IR (KBr): 3000, 2956, 2919, 2881, 1567, 1517, 1417, 1350, 1213, 1142, 1053, 938, 849, 742, 701, 593 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1H), 5.86-5.90 (m, 1H), 5.22-5.33 (m, 2H), 4.91 (d, 1H, J = 15.6 Hz), 4.70 (d, 1H, J = 15.6 Hz), 4.55 (t, 1H, J = 3.6Hz), 4.00-4.10 (m, 3H), 3.46-3.72 (m, 4H), 1.99-2.01 (m, 2H), 1.30 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 156.3, 154.0, 140.7, 135.2, 133.5, 118.0, 110.4, 84.2, 69.3, 48.7, 48.5, 45.7, 33.2, 28.2, 19.3; HRMS (EI+) calcd for $C_{15}H_{19}N_4O_3^{35}ClS$ (M^+), 370.0866; found, 370.0868. Anal. Calcd. for $C_{15}H_{19}N_4O_3ClS$: C, 48.58; H, 5.16; N, 15.11. Found. C, 48.60; H, 5.28; N, 15.01%.

2-Chloro-5-((5-methoxy-8-nitro-7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8q). Yellow solid, yield 78%, mp 206.7–208.3°C; IR (KBr): 3030, 2963, 2933, 2881, 1558, 1514, 1413, 1324, 1261, 1206, 1135, 1046, 979, 953, 753, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.14-7.32 (m, 5H), 5.11 (d, 1H, J = 14.8 Hz), 4.80 (d, 1H, J = 15.2 Hz), 4.48 (t, 1H, J = 7.2Hz), 4.39 (t, 1H, J = 3.6Hz), 3.62-3.87 (m, 4H), 3.38 (s, 3H), 2.36-2.43 (m, 1H), 2.03-2.09 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 157.8, 154.1, 140.7, 135.1, 110.4, 83.1, 68.6, 48.9, 48.7, 45.3, 35.8, 29.5, 28.2, 27.8, 22.4, 19.8, 14.0; HRMS (EI+) calcd for $C_{18}H_{19}N_4O_3^{35}ClS$ (M^+), 406.0866; found, 406.0867. Anal. Calcd. for $C_{18}H_{19}N_4O_3ClS$: C, 53.13; H, 4.71; N, 13.77. Found. C, 53.31; H, 4.90; N, 13.86%.

2-Chloro-5-((5-ethoxy-8-nitro-7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8r). Yellow solid, yield 76%, Mp 182.6–184.1°C; IR (KBr): 2956, 2926, 2867, 1555, 1517, 1417, 1321, 1213, 1139, 1072, 1046, 749, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.14-7.31 (m, 5H), 5.10(d, 1H, J = 15.2 Hz), 4.80 (d, 1H, J = 15.2 Hz), 4.49 (t, 1H, J = 7.6Hz), 4.45 (t, 1H, J = 3.6Hz), 3.79-3.84 (m, 2H), 3.53-3.59 (m, 4H), 2.35-2.38 (m, 1H), 2.02-2.10 (m, 1H),1.21-1.24 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 157.9, 154.1, 143.7, 140.8, 135.0,

128.6, 126.5, 126.4, 108.1, 82.9, 64.1, 49.3, 49.0, 45.3, 39.0, 37.1, 15.3; HRMS (EI+) calcd for $C_{19}H_{21}N_4O_3{}^{35}ClS$ (M^+), 420.1023; found, 420.1023. Anal. Calcd. for $C_{19}H_{21}N_4O_3ClS$: C, 54.22; H, 5.03; N, 13.31. Found. C, 54.18; H, 5.08; N, 13.35%.

2-Chloro-5-((8-nitro-7-phenyl-5-propoxy-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8s). Yellow solid, yield 72 %, mp 177.6–181.3°C; IR (KBr): 2948, 2881, 1569, 1514, 1417, 1358, 1321, 1261, 1213, 1139, 1076, 1053, 753, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.14-7.31 (m, 5H), 5.09 (d, 1H, J = 15.2 Hz), 4.80 (d, 1H, J = 15.2 Hz), 4.50 (t, 1H, J = 7.6Hz), 4.44 (t, 1H, J = 3.6Hz), 3.79-3.85 (m, 2H), 3.42-3.63 (m, 4H), 2.35-2.38 (m, 1H), 2.03-2.14 (m, 1H), 1.58-1.63 (m, 3H), 0.93 (t, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 157.8, 154.1, 143.7, 140.8, 135.1, 128.6, 126.5, 126.4, 108.1, 83.0, 70.3, 49.3, 49.0, 45.3, 39.0, 37.0, 20.0, 10.5; HRMS (EI+) calcd for $C_{20}H_{23}N_4O_3{}^{35}ClS$ (M^+), 434.1179; found, 434.1199. Anal. Calcd. for $C_{20}H_{23}N_4O_3ClS$: C, 55.23; H, 5.33; N, 12.88. Found. C, 55.11; H, 5.26; N, 12.98%.

2-Chloro-5-((5-isopropoxy-8-nitro-7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8t). Yellow solid, yield 67%, mp 175.4–181.2°C; IR (KBr): 2993, 2956, 2919, 2867, 2807, 1566, 1525, 1413, 1331, 1261, 1209, 1142, 1050, 979, 842, 752, 595 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.69 (s, 1H), 7.11-7.24 (m, 5H), 4.97 (d, 1H, J = 15.2 Hz), 4.75 (d, 1H, J = 15.6 Hz), 4.72 (d, 1H, J = 3.2Hz), 4.06-4.11 (m, 1H), 3.66-3.82 (m, 4H), 3.33 (s, 1H), 2.20-2.25 (m, 1H), 1.74-1.81 (m, 1H), 1.11 (t, 6H, J = 6.0Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 158.3, 152.1, 145.9, 141.8, 136.5, 128.5, 127.0, 126.1, 123.9, 107.3, 80.5, 70.3, 49.5, 48.6, 46.2, 23.0, 22.9; HRMS (EI+) calcd for $C_{20}H_{23}N_4O_3{}^{35}ClS$ (M^+), 434.1179; found, 434.1179. Anal. Calcd. for $C_{20}H_{23}N_4O_3ClS$: C, 55.23; H, 5.33; N, 12.88. Found. C, 55.08; H, 5.16; N, 12.75%.

5-((5-Butoxy-8-nitro-7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)-2-chlorothiazole (8u). Yellow solid, yield 65%, mp 144.7–146.8°C; IR (KBr): 2948, 2911, 2867, 1567, 1521, 1317, 1206, 1076, 979, 842, 756, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.14-7.31 (m, 5H), 5.09 (d, 1H, J = 15.2 Hz), 4.80 (d, 1H, J = 15.2 Hz), 4.50 (t, 1H, J = 7.2Hz), 4.43 (t, 1H, J = 3.6Hz), 3.79-3.86 (m, 2H), 3.45-3.63 (m, 4H), 2.33-2.38 (m, 1H), 2.08-2.11 (m, 1H), 1.53-1.60 (m, 2H), 1.34-1.40 (m, 2H), 0.93 (t, 3H, J = 7.6Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 158.1, 150.9, 143.7, 140.8, 135.1, 128.6, 126.5, 126.4, 108.1, 83.0, 68.4, 49.3, 49.0, 45.3, 39.0, 36.9, 31.8, 19.2, 13.8; HRMS (EI+) calcd for $C_{21}H_{25}N_4O_3{}^{35}ClS$ (M^+), 448.1336; found, 448.1313. Anal. Calcd. for $C_{21}H_{25}N_4O_3ClS$: C, 56.18; H, 5.61; N, 12.48. Found. C, 56.34; H, 5.76; N, 12.61%.

2-Chloro-5-((5-isobutoxy-8-nitro-7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-1(5H)-yl)methyl)thiazole (8v). Yellow solid, yield 62%, mp 176.2–176.9°C; IR (KBr): 3015, 2904, 2881, 1644, 1562, 1521, 1499, 1406, 1336, 1261, 1187, 1135, 1046, 920, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.13-7.31 (m, 5H), 5.08 (d, 1H, J = 15.2 Hz), 4.82 (d, 1H, J = 15.2 Hz), 4.51 (t, 1H, J = 7.2Hz), 4.43 (t, 1H, J = 3.6Hz), 3.79-3.87 (m, 2H), 3.20-3.63 (m, 4H), 2.34-2.37 (m, 1H), 2.10-2.12 (m, 1H), 1.83-1.86 (m, 1H), 0.91 (d, 6H, J = 6.8Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 157.8, 154.1, 143.6, 140.8, 135.0, 128.6, 127.1, 126.5, 126.4, 108.1, 83.2, 75.3, 49.3, 49.0, 45.2, 39.0, 36.8, 28.7, 19.2; HRMS (EI+) calcd for $C_{21}H_{25}N_4O_3{}^{35}ClS$ (M^+), 448.1336; found, 448.1333. Anal. Calcd. for $C_{21}H_{25}N_4O_3ClS$: C, 56.18; H, 5.61; N, 12.48. Found. C, 56.25; H, 5.68; N, 12.52%.

Synthetic procedure for 13. To a solution of compound **12a** (1 mmol) were added dichloromethane (30 mL), and a drop of $BF_3{\cdot}Et_2O$. The mixture was refluxed and monitored by TLC. After complete, the mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography on silica gel, eluting with dichloromethane/acetone to afford pure products. Yellow solid, yield 56%, mp = 187.0–188.9°C; IR (KBr): 2956, 2919, 2867, 1666, 1632, 1555, 1347, 1198, 1146, 1079, 1042, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 5.90 (d, 1H, J = 7.60Hz), 5.31 (t, 1H, J = 6.4Hz), 4.99 (d, 1H, J = 15.6 Hz), 4.78 (d, 1H, J = 15.6 Hz), 3.70–3.95 (m, 4H), 3.55–3.61 (m, 1H), 1.12 (d, 3H); HRMS (EI+) calcd for $C_{12}H_{13}N_4O_2{}^{35}ClS$ (M^+), 312.0488; found, 312.0451. calcd for $C_{12}H_{13}N_4O_2{}^{35}ClS$ (M^+), 314.0418; found, 314.0401. Anal. Calcd. for $C_{12}H_{13}N_4O_2ClS$: C, 46.08; H, 4.19; N, 17.91. Found. C, 46.15; H, 4.31; N, 17.89%.

Insecticidal test for cowpea aphids (Aphis craccivora). The activities of insecticidal compounds against cowpea aphids were tested by leaf-dip method. The horsebean plant leaves with 40-60 apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s and the excess dilution was sucked out with filter paper, and the burgeons were placed in the conditioned room (25 ± 1°C, 50% RH). Water containing Triton X-100 (0.1 mg L^{-1}) was used as control. The mortality rates were evaluated 24 h after treatment. Each treatment had three repetitions and the data were adjusted and subjected to probit analysis as before.

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