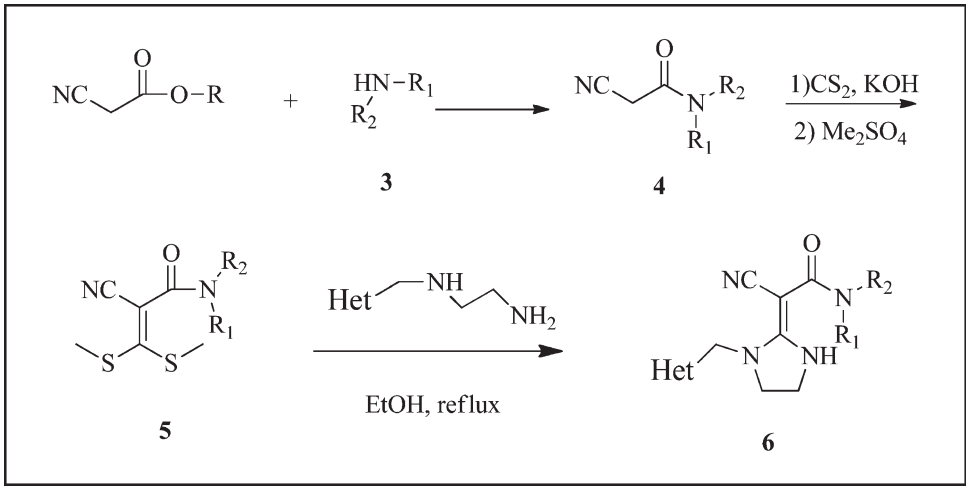
Synthesis and Insecticidal Activities of Novel Neonicotinoid Analogs Bearing an Amide Moiety

Jian Wu, Song Yang,* Bao-An Song, Pinaki S. Bhadury, De-Yu Hu, Song Zeng, and Hua-Peng Xie

State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, People's Republic of China
*E-mail: songbaoan22@yahoo.com

Received July 15, 2010
DOI 10.1002/jhet.663
Published online 19 April 2011 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel neonicotinoid analogs containing an amide moiety were synthesized, characterized, and subsequently evaluated for their insecticidal activity. According to the preliminary bioassay, the compounds **6c**, **6e**, **6f**, **6j**, **6n**, and **6r** exhibited > 50% activity against *Nilaparvata lugens* at 100 mg/L. Amongst the active compounds, **6f** and **6r** revealed insecticidal activities similar to that displayed by standard buprofezin.

J. Heterocyclic Chem., **48**, 901 (2011).

INTRODUCTION

Neonicotinoids, an interesting class of insecticides known to act on the central nervous system of insects, are widely used in agriculture due their broad spectrum activity and low mammalian toxicity [1–3]. Generally, they are believed to bind at a specific site called acetylcholine receptor (nAChR) and are relatively safe toward mammals and aquatic species [2,4–6]. The most commonly available neonicotinoid insecticides include acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam [7–17]. Amongst them, imidacloprid is possibly the most widely used insecticide in the worldwide market and is obtained by structural modification of lead compound NTN32692 (Fig. 1). The essential structural feature of these insecticides is the presence of a strong electron withdrawing pharmcaphoric group such as CN or NO_2 [16,18,19].

Because insecticidal activity of certain synthetic amides has revealed significant promise in recent past [20–24], we decided to retain the basic structure of a cyano neonicotinoid and then incorporate an amide moiety to the α-carbon to generate lead structures with potent activities. Based on this hypothesis, 18 novel analogs of neonicotinoids (**6a–6r**) were prepared (Scheme 1). All the compounds were unequivocally characterized by IR, NMR, and elemental analysis. Preliminary biological evaluation showed that most of the compounds exhibited insecticidal activity against *Nilaparvata lugens* to a certain extent. Among them, compounds **6f**, **6j**, and **6r** showed considerable promise (activity > 60%) at 100 mg/L.

RESULTS AND DISCUSSION

The synthetic route to the title compounds is demonstrated in Scheme 1. N^1-((6-chloropyridin-3-yl)methyl)-ethane-1,2-diamine and N^1-((2-chlorothiazol-5-yl) methyl) ethane-1,2-diamine were synthesized by reacting 2-chloro-5-(chloromethyl) pyridine [or 2-chloro-5-(chloromethyl)thiazole] with ethane-1,2-diamine, in accordance with the known synthetic protocols described in the

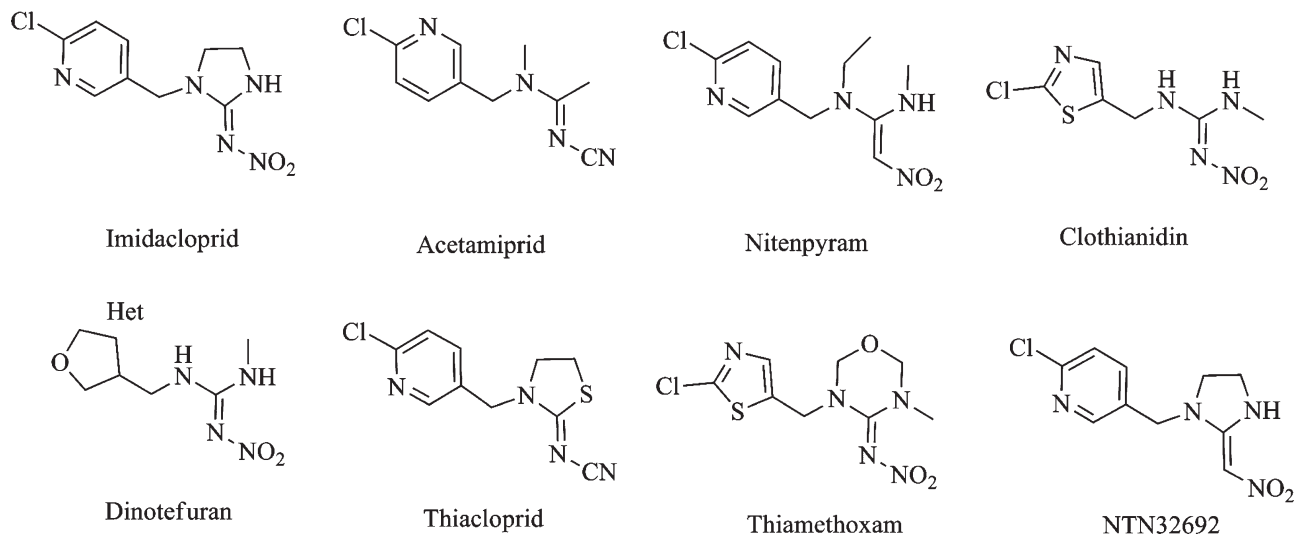


Figure 1. The structures of common neonicotinoid insecticides and lead compound NTN32629.

literature [7,9,11]. 2-Cyanoacetamide and *N*-benzyl-2-cyanoacetamide were easily prepared from ethyl 2-cyanoacetate by using standard procedure [25], whereas 2-cyano-*N*,*N*-dimethylacetamide could be obtained by the treatment of ethyl (or methyl) 2-cyanoacetate with dimethylamine [26,27] or by flash vacuum thermolysis of

Scheme 1. Synthetic route of compounds **6a**–**6r**.

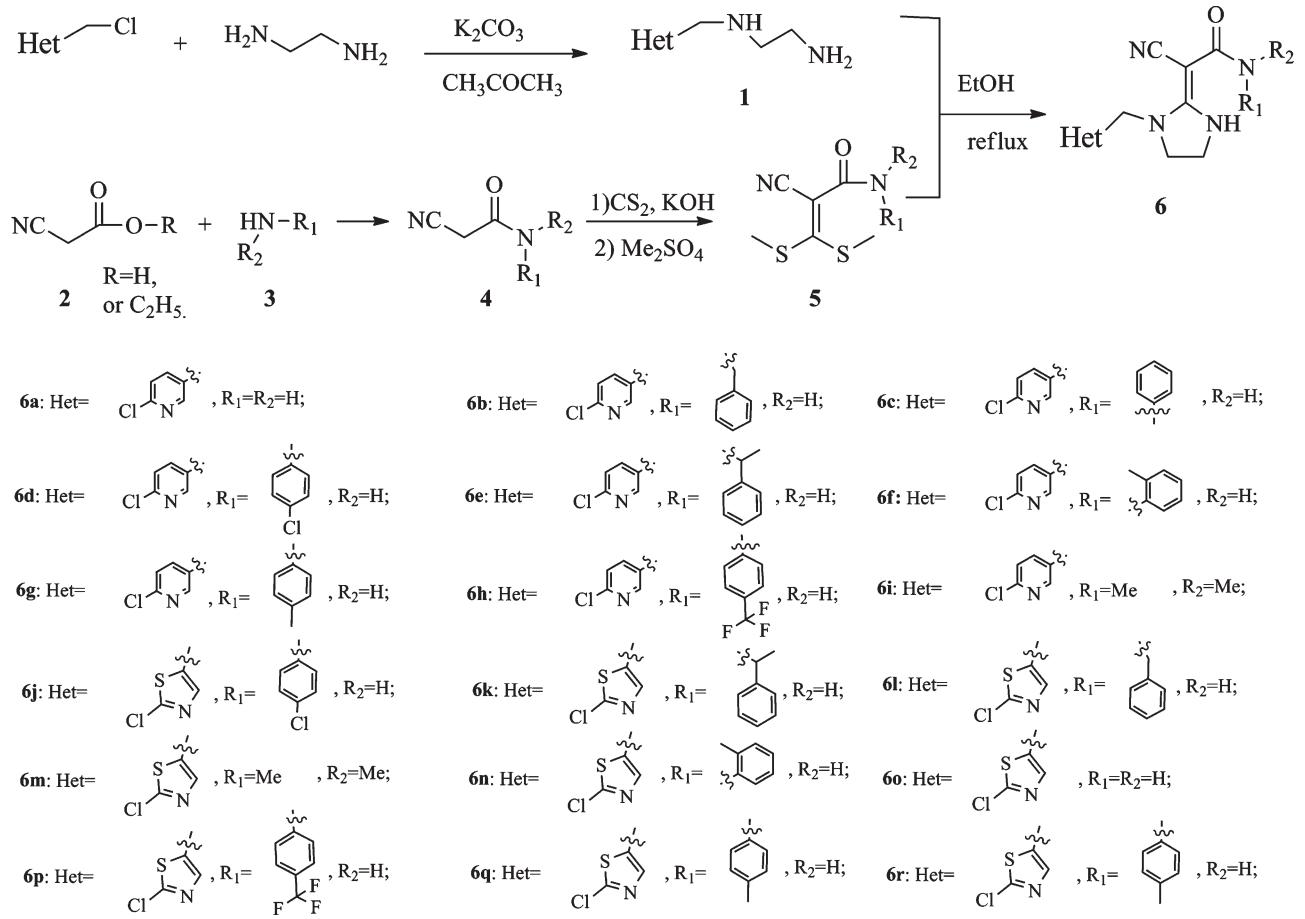


Table 1

The insecticidal activities of compounds **6a–6r** against *Nilaparvata lugens* at 100 mg/L.

Compounds	Mortality (%)	Compounds	Mortality (%)	Compounds	Mortality (%)
6a	33.2	**6h**	41.7	**6o**	26.6
6b	33.3	**6i**	40.0	**6p**	25.0
6c	56.7	**6j**	60.0	**6q**	25.0
6d	22.4	**6k**	33.3	**6r**	65.0
6e	53.3	**6l**	28.3	**Buprofezin**	71.7
6f	68.3	**6m**	25.0		
6g	30.0	**6n**	50.0		

Meldrum's acid (5-((dimethylamino)(isopropylamino)-methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione) [28]. Alternatively, this intermediate could also be accessed in 77% yield by refluxing a mixture of 2-cyanoacetamide and dimethyl sulfate in acetonitrile for 7 h in the presence of K_2CO_3. The rest of the N-substituted-2-cyanoacetamides were obtained in excellent yields when 2-cyanoacetic acid and an appropriate amine were refluxed for 3–4 h in 1,2-dichloroethane in the presence of $POCl_3$. The key intermediates **5** were prepared by successive treatment of N-substituted-2-cyanoacetamides **(4)** with carbon disulfide/KOH and dimethyl sulfate as described in previous reports [25,29]. Because of the high solubility of potassium salt generated from **4**, water could be used successfully as solvent for these reactions. The product (**5**) was subsequently precipitated form the reaction system in excellent yields after adding dimethyl sulfate.

Finally, the title neonicotinoids **6a–6r** incorporating an amide moiety were obtained under mild conditions in good yields by reacting 2-cyano-*N*-substituted-acetamide (**5**) with amine **1** in refluxing ethanol. These reactions are presumably initiated by nucleophilic attack followed by expulsion of two molecules of methylmercaptan [9,25,29].

All the synthesized compounds (**6a–6r**) were characterized on the basis of their spectroscopic data. The IR absorption bands near 3350–3250 cm^{-1}, 3100–3000 cm^{-1}, 1610–1650 cm^{-1}, and 2170 cm^{-1} confirmed the presence of N—H, Ar—H, amide, and CN functional groups, respectively. In the ^{1}H-NMR spectra of the title compounds, the CON—H proton appeared as a broad singlet at 9.00–8.60; the aromatic protons revealed the expected multiplet pattern near 6.64–8.40, the methylene (—CH_2—) proton signals were observed as a singlet near 4.90 and —CH_2CH_2— protons of the imidazolidine ring showed up as a multiplet near 3.40–3.70.

The insecticidal activity of compounds **6a–6r** against *Nilaparvata lugens* was assayed by the reported method [30]. Buprofezin, one of the proven commercial agents for controlling *Nilaparvata lugens*, was used as the reference insecticidal agent. The results provided in Table 1 indicate that most of the prepared compounds have moderate insecticidal activity against *Nilaparvata lugens* at 100 mg/L. The mortality rates of compounds **6a–6r** were in the range 25.0–68.3%. Amongst these compounds, **6f**, **6j**, and **6r** showed considerable promise with insecticidal activity of 68.3%, 60.0% and 65.3% at 100 mg/L, respectively, being comparable with that exhibited by buprofezin (71.7%). Although, a definite structure activity relationship could not be established with the limited experimental data and available compounds, it appears that incorporation of aniline, *o*-toluidine, or *p*-chloroaniline unit into the general structure of neonicotinoids might have a positive influence in enhancing the insecticidal activity of the final product.

In conclusion, preparation and characterization of a series of novel neonicotinoid analogs bearing both cyano and amide pharmacophoric units are demonstrated. Some of the synthesized compounds were shown to exhibit moderate activity (>50%) against *Nilaparvata lugens* at 100 mg/L by preliminary biological activity test. In particular, compounds **6f** and **6r** which were almost as effective as that of Buprofezin hold considerable promise to be used as potential insecticides in future. Further studies are currently underway to establish a definite structure activity relationship.

EXPERIMENTAL

General procedures. Unless otherwise stated, all the reagents and reactants were purchased from commercial suppliers; melting points were uncorrected and determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL ECX 500 NMR spectrometer at room temperature operating at 500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR by using $CDCl_3$ or DMSO as solvents and TMS as an internal standard; infrared spectra were recorded in KBr on a Bruker VECTOR 22 spectrometer; elemental analysis was performed on an Elemental Vario-III CHN analyzer. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF_{254}.

Intermediates **1** were prepared according to the reported methods [7,9,11]. 2-Cyanoacetamide and *N*-benzyl-2-

cyanoacetamide were synthesized from ethyl 2-cyanoacetate by following the described procedure [25].

2-Cyano-*N*,*N*-dimethylacetamide. To a well stirred solution of 2-cyanoacetamide (1.68 g, 20 mmol) in acetonitrile (20 mL) was added potassium carbonate (1 g) and dimethyl sulfate (4 g, 32 mmol). The resulting mixture was heated under reflux for 7 h, then cooled to room temperature and filtered off. The solvent was removed in vacuum to afford a crude oil, which was stored overnight to obtain a crystalline solid. The pure *N*,*N*-dimethylcyanoacetamide was finally obtained by washing the solid with ether, 1.73 g; yield: 77%; mp: 64–66°C (lit. [26], mp: 58°C; lit. [27], mp: 68°C; lit. [28], mp: 62°C).

General procedure for the preparation of 5. To a mixture of N-substituted-2-cyanoacetamides (1 mmol) and carbon disulfide (1.2 mmol) in ethanol (10 mL) was slowly added a solution of potassium hydroxide (2.5 mmol) in ethanol (5 mL) at 0°C. The resulting mixture was warmed to room temperature and stirred for 2–3 h. The potassium salt formed was separated by filtration and then dissolved in water (15 mL). Dimethyl sulfate was added into the system, the precipitated solid was easily separated from the reaction mixture to afford (**5**) in good yields.

General procedure for the preparation of 6a–6r. A mixture of intermediate **5** (1 mmol) and **1** (1 mmol) was stirred in refluxing ethanol (10 mL). The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature to afford a crystalline solid which was filtered off and recrystallized from ethanol. The physical and spectral data for **6a–6r** are listed below.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyanoacetamide (6a). White solid; yield: 73%; mp: 197–199°C; IR (KBr): ν 3320.0, 3258.9, 3025.5, 2958.8, 2920.0, 2179.9, 1655.4, 1610.5, 1569.1, 1524.8, 1456.5 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 9.35 (br, 1H, N—H), 8.36 (d, J = 2.30 Hz, 1H, pyridine-H), 7.78 (dd, J = 2.30 Hz, J = 8.60 Hz, 1H, pyridine-H), 7.57 (d, J = 8.00 Hz, 1H, pyridine-H), 6.4 (br, 1H, NH_2), 4.85 (s, 2H, CH_2), 3.51–3.53 (m, 4H, CH_2CH_2); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 170.56, 163.98, 149.91, 149.27, 139.20, 132.69, 124.86, 121.91, 52.36, 49.60, 47.31, 41.86. Anal. Calc. for $C_{12}H_{12}ClN_5O$: C, 51.07; H, 4.36; N, 25.22. Found: C, 51.47; H, 4.45; N, 25.33.

N-Benzyl-2-(1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyanoacetamide (6b). Light yellow solid; yield: 80%; mp: 197–199°C; IR (KBr): ν 3360.0, 3251.9, 3030.1, 2956.8, 2924.0, 2169.92, 1653, 1610.5, 1568.1, 1521.8, 1458.1 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 9.52 (br, 1H, N—H), 8.32 (d, J = 2.30 Hz, 1H, pyridine-H), 7.68 (dd, J = 2.85 Hz, 8.60 Hz, 1H, N—H), 7.25–7.37 (m, 6H, 6Ar—H), 6.18 (t, J = 5.15 Hz, 1H, NH), 4.88 (s, 2H, CH_2), 4.47 (d, J = 5.70 Hz, 2H, CH_2), 3.47–3.63 (m, 4H, CH_2CH_2); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 168.57, 163.70, 151.58, 148.96, 138.80, 138.46, 130.44, 128.74, 127.56, 127.40, 124.87, 121.55, 53.37, 49.21, 47.69, 43.66, 41.42; Anal. Calc. for $C_{19}H_{18}ClN_5O$: C, 62.04; H, 4.93; N, 19.04. Found: C, 62.14; H, 4.70; N, 19.06.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-phenylacetamide (6c). Light yellow solid; yield: 75%; mp: 164–165°C; IR (KBr): ν 3323.3, 3288.6, 3057.1, 2924.0, 2877.7, 2181.4, 1616.3, 1564.2, 1506.4, 1458.1 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.51 (br, 1H, N—H), 8.34 (d, J = 2.30 Hz, 1H, pyridine-H), 7.71 (dd, J = 2.30 Hz, 8.05 Hz, 1H, pyridine-H), 7.57 (br, 1H, N—H), 7.45 (d, J = 7.45 Hz, 2H, 2Ph—H), 7.39 (d, J = 8.00 Hz, 1H, pyridine-H), 7.31 (t, J = 8.05, 2H, 2Ph—H), 7.08 (t, J = 7.45, 1H, Ph—H), 4.92 (s, 2H, CH_2), 3.51–3.67 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.99, 163.80, 151.65, 148.97, 138.42, 138.16, 130.32, 129.00, 124.92, 123.97, 121.35, 120.49, 54.17, 49.24, 47.77, 41.47; Anal. Calc. for $C_{18}H_{16}ClN_5O$: C, 61.10; H, 4.56; N, 19.79. Found: C, 60.78; H, 4.77; N, 19.54.

N-(4-Chlorophenyl)-2-(1-((6-chloropyridin-3-yl)methyl) imidazolidin-2-ylidene)-2-cyanoacetamide (6d). Light yellow solid; yield: 72%; mp: 182–183.5°C; IR (KBr): ν 3290.5, 3045.6, 2899.0, 2854.6, 2179.5, 1635.6, 1562.3, 1535.6, 1458.1 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.45 (br, 1H, N—H), 8.34 (d, J = 2.30 Hz, 1H, pyridine-H), 7.71 (dd, 1H, J = 2.90 Hz, 8.60 Hz, 1H, pyridine-H), 7.55 (br, 1H, N—H), 7.26–7.41 (m, 5H, 5Ar—H), 4.93 (s, 2H, CH_2), 3.52–3.69 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.90, 163.72, 151.72, 148.95, 138.38, 136.79, 130.19, 128.99, 128.88, 124.93, 121.61, 121.21, 54.18, 49.25, 47.75, 41.48; Anal. Calc. for $C_{18}H_{15}Cl_2N_5O$: C, 55.68; H, 3.89; N, 18.04. Found: C, 55.79; H, 3.59; N, 17.94.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(1-phenylethyl)acetamide (6e). Light yellow solid; yield: 70%; mp: 141–143°C; IR (KBr): ν 3342.6, 3078.3, 3039.8, 2966.5, 2927.9, 2893.2, 2175.7, 1616.3, 1508.3, 1477.4 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.49 (br, 1H, N—H), 8.32 (d, J = 2.30 Hz, 1H, pyridine-H), 7.70 (dd, J = 2.85 Hz, 8.05 Hz, 1H, pyridine-H), 7.23–7.37 (m, 7H, 7Ar—H), 6.0 (d, J = 7.45, 1H, N—H), 5.05–5.08 (m, 1H, N—CH), 4.88 (s, 2H, CH_2), 3.44–3.60 (m, 4H, CH_2CH_2), 1.50 (d, J = 6.85 Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 167.87, 163.68, 151.57, 148.97, 144.14, 138.46, 130.47, 128.73, 127.21, 125.90, 124.86, 121.62, 53.37, 49.27, 49.16, 47.67, 41.35, 22.78; Anal. Calc. for $C_{20}H_{20}ClN_5O$: C, 62.91; H, 5.28; N, 18.34. Found: C, 62.74; H, 4.96; N, 17.99.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(o-tolyl)acetamide (6f). Light yellow solid; yield: 76%; mp: 155.2–156.5°C; IR (KBr): ν 3423.6, 3319.4, 3047.5, 2968.4, 2906.7, 2166.0, 1639.4, 1558.4, 1508.3, 1448.5 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.50 (br, 1H, N—H), 7.35 (s, 1H, pyridine-H), 7.05–7.45 (m, 6H, 6Ar—H), 4.99 (s, 2H, CH_2), 3.51–3.67 (m, 4H, CH_2CH_2), 2.29 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 167.03, 163.74, 151.62, 148.97, 138.45, 130.56, 130.37, 129.69, 126.65, 124.91, 124.80, 123.01, 121.48, 54.08, 49.25, 47.77, 41.47, 17.88; Anal. Calc. for $C_{19}H_{18}ClN_5O$: C, 62.04; H, 4.93; N 19.04. Found: C, 62.09; H, 4.72; N, 18.77.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(p-tolyl)acetamide (6g). Light yellow solid; yield: 75%; mp: 191–193°C; IR (KBr): ν 3309.8, 3057.1, 2953.2, 2922.1, 2179.5, 1335.5, 1606.7, 1558.4, 1500.0, 1458.2 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.51 (br, 1H, N—H), 8.34 (d, J = 2.85 Hz, 1H, pyridine-H), 7.71 (dd, J = 2.90 Hz, 8.60 Hz, 1H, pyridine-H), 4.97 (s, 2H, CH_2), 7.51 (br, 1H, NH), 7.39 (d, J = 8.60 Hz, pyridine-H), 7.32 (d, J = 7.70, 2H, 2Ph—H), 7.10 (d, J = 8.05, 2H, 2Ph—H), 4.91 (s, 2H, CH_2), 3.49–3.66 (m, 4H, CH_2CH_2), 2.31 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.97, 163.79, 151.61, 148.97, 138.44, 135.50, 133.64, 130.38, 129.50, 124.91, 121.45, 120.72, 54.05, 49.23, 47.75, 41.46, 20.93; Anal. Calc. for $C_{19}H_{18}ClN_5O$: C, 62.04; H, 4.93; N, 19.04. Found: C, 62.14; H, 4.70; N, 19.06.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(4-(trifluoromethyl)phenyl)acetamide (6h). Light yellow solid; yield: 74%; mp: 178–180°C; IR (KBr): ν 3346.5,

3307.9, 3086.1, 3051.3, 2893.2, 2181.4, 1643.3, 1560.4, 1500.6, 1462.0 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.43 (br, 1H, N—H), 8.35 (d, J = 2.30 Hz, 1H, pyridine-H), 7.69–7.71 (m, 2H, N—H + pyridine-H), 7.59 (d, J = 8.55 Hz, 2H, 2Ph—H), 7.55 (d, J = 9.15 Hz, 2H, 2Ph—H), 7.39 (d, J = 9.15 Hz, 2H, 2Ph—H), 4.97 (s, 2H, CH_2), 7.51 (br, 1H, NH), 7.39 (d, J = 8.55 Hz, 1H, pyridine-H), 4.93 (s, 2H, CH_2), 3.53–3.70 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.99, 163.70, 151.72, 148.93, 141.47, 138.36, 130.13, 126.23, 126.20, 125.51, 125.36, 125.25, 124.93, 123.20, 121.07, 119.57, 54.39, 49.28, 47.75, 41.49; Anal. Calc. for $C_{19}H_{15}ClF_3N_5O$: C, 54.10; H, 3.58; N, 16.60. Found: C, 54.20; H, 3.27; N, 16.32.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N,N-dimethylacetamide (6i). Light yellow solid; yield: 75%; mp: 104.0–105.5°C; IR (KBr): ν 3296.3, 3086.4, 2924.0, 2171.8, 1636.5, 1575.84, 1558.48, 15.6.4, 1481.3 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.03 (br, 1H, N—H), 8.34 (d, J = 2.30 Hz, 1H, pyridine-H), 7.76 (dd, J = 2.30 Hz, 8.60 Hz, 1H, pyridine-H), 7.35 (d, J = 8.55 Hz, 1H, pyridine-H), 4.87 (s, 2H, CH_2), 3.49–3.63 (m, 4H, CH_2CH_2), 3.03 (s, 6H, $2CH_3$); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 170.76, 166.28, 151.46, 149.04, 138.68, 130.54, 124.75, 121.14, 52.60, 49.63, 48.44, 41.37, 38.36; Anal. Calc. for $C_{22}H_{19}ClN_4O_4S_2$: C, 52.53; H, 3.81; N, 11.14. Found: C, 52.94; H, 3.29; N, 11.62.

N-(4-Chlorophenyl)-2-(1-((2-chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyanoacetamide (6j). Light yellow solid; yield: 72%; mp: 201–203°C; IR (KBr): ν 3329.4, 3269.3, 3050.0, 2960.7, 2877.9, 2187.2, 1643.3, 1566.2, 1527.6, 1494.8 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.42 (br, 1H, N—H), 7.55 (br, 1H, N—H), 7.54 (s, 1H, thiazole-H), 7.40 (d, J = 9.15 Hz, 2H, 2Ph—H), 7.28 (d, J = 9.15 Hz, 2H, 2Ph—H), 5.03 (s, 2H, CH_2), 3.58–3.68 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.69, 163.31, 153.45, 141.05, 136.75, 134.26, 128.99, 128.93, 121.62, 121.20, 54.57, 48.90, 43.35, 41.43; Anal. Calc. for $C_{16}H_{13}Cl_2N_5OS$: C, 48.74; H, 3.32; N, 17.76. Found: C, 48.9; H, 3.24; N, 17.74.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(1-phenylethyl)acetamide (6k). Light yellow solid; yield: 73%; mp: 129.5–131.5°C; IR (KBr): ν 3327.2, 3032.1, 2976.1, 2887.4, 2177.8, 1610.5, 1564.2, 1509.0, 1417.8 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.45 (br, 1H, N—H), 7.51 (s, 1H, thiazole-H), 7.24–7.35 (m, 5H, 5Ph—H), 6.0 (d, J = 7.45 Hz, 1H, N—H), 5.00–5.06 (m, 1H, N-CH), 4.96 (s, 2H, CH_2), 3.44–3.60 (m, 4H, CH_2CH_2), 1.50 (d, J = 6.90 Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 167.67, 163.25, 153.30, 144.10, 140.87, 134.58, 128.54, 127.22, 125.90, 121.61, 53.80, 49.31, 48.83, 43.30, 41.31, 22.798; Anal. Calc. for $C_{18}H_{18}ClN_5OS$: C, 55.74; H, 4.68; N, 18.06; Found: C, 55.92; H, 4.87; N, 18.26.

N-Benzyl-2-(1-((2-chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyanoacetamide (6l). Light yellow solid; yield: 73%; mp: 181–183°C; IR (KBr): ν 3250.0, 3032.1, 2926.0, 2169.9, 1614.4, 1570.0, 1514.1, 1483.2, 1296.1 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.49 (br, 1H, N—H), 7.51 (s, 1H, thiazole-H), 7.25–7.35 (m, 5H, 5Ph—H), 6.20 (t, J = 5.75 Hz, 1H, N—H), 4.99 (s, 2H, CH_2), 4.48 (d, J = 5.75, 2H, CH_2), 3.55–3.62 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 168.36, 163.27, 153.32, 140.92, 138.74, 134.54, 128.74, 127.55, 127.42, 121.53, 53.80, 48.88, 43.67, 43.32, 41.37; Anal. Calc. for $C_{22}H_{19}ClN_4O_4S_2$: C, 52.53; H, 3.81; N, 11.14. Found: C, 52.94; H, 3.29; N, 11.62.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N,N-dimethylacetamide (6m). Light yellow solid; yield: 76%; mp: 135.2–136.6°C; IR (KBr): ν 3290.5, 2906.7, 2164.3, 1604.7, 1548.8, 1498.6, 1485.1, 1458.1 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.00 (br, 1H, NH), 7.53 (s, 1H, thiazole-H), 5.00 (s, 2H, CH_2), 3.57–3.59 (m, 4H, CH_2CH_2), 3.06 (s, 6H, $2CH_3$); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 170.45, 165.83, 153.18, 141.01, 134.45, 121.06, 53.18, 49.16, 43.77, 41.31, 38.33; Anal. Calc. for $C_{12}H_{14}ClN_5OS$: C, 46.23; H, 4.53; N, 22.46. Found: C, 46.30; H, 4.33; N, 22.2.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(o-tolyl)acetamide (6n). Light yellow solid; yield: 72%; mp: 174.5–175.8°C; IR (KBr): ν 3321.4, 3282.8, 3024.8, 2936.0, 2879.7, 2171.8, 1616.2, 1568.1, 1473.6, 1458.1 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.47 (br, 1H, NH), 7.54 (s, 1H, thiazole-H), 7.04–7.76 (m, 4H, 4Ph—H), 7.49 (br, 1H, NH), 5.00 (s, 2H, CH_2), 3.56–3.65 (m, 4H, CH_2CH_2), 2.30 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.81, 163.31, 153.39, 141.00, 136.12, 134.45, 130.57, 129.68, 126.66, 124.84, 123.00, 121.46, 54.48, 48.90, 43.37, 41.43, 17.88; Anal. Calc. for $C_{17}H_{16}ClN_5OS$: C, 54.61; H, 4.31; N, 18.73. Found: C, 54.72; H, 3.94; N, 18.51.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyanoacetamide (6o). Light yellow solid; yield: 70%; mp: 206.1–208.5°C; IR (KBr): ν 3360.0, 3184.4, 2972.3, 2889.3, 2187.2, 1636.4, 1608.6, 1558.4, 15.5.0 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 9.31 (br, 1H, NH), 7.69 (s, 1H, thiazole-H), 6.47 (br, 2H, NH_2), 4.97 (s, 2H, CH_2), 3.47–3.53 (m, 4H, CH_2CH_2); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 170.27, 163.59, 151.32, 141.47, 136.52, 121.94, 52.85, 48.99, 43.11, 41.80; Anal. Calc. for $C_{10}H_{10}ClN_5OS$: C, 42.33; H, 3.55; N, 24.68. Found: C, 42.15; H, 3.49; N, 24.32.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(4-(trifluoromethyl)phenyl)acetamide (6p). White solid; yield: 68%; mp: 164.0–165.8°C; IR (KBr): ν 3282.8, 2980.0, 2899.0, 2181.4, 1647.2, 1564.2, 1508.3, 1483.2 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.41 (br, 1H, NH), 7.70 (s, 1H, thiazole-H), 7.54–7.60 (m, 5H, 4Ph—H + NH), 5.04 (s, 2H, CH_2), 3.60–3.70 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.77, 163.29, 153.49, 141.39, 141.09, 134.17, 126.26, 126.23, 125.35, 123.19, 121.07, 119.58, 54.76, 48.91, 43.55, 41.46; Anal. Calc. for $C_{17}H_{13}ClF_3N_5OS$: C, 47.72; H, 3.06; N, 16.37. Found: C, 47.75; H, 2.92; N, 16.41.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-(p-tolyl)acetamide (6q). Yellow solid; yield: 78%; mp: 197.1–198.5°C; IR (KBr): ν 3305.9, 3282.8, 3049.4, 2974.2, 2922.1, 2885.5, 2187.2, 1624.0, 1575.8, 1506.4, 1479.4 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.48 (br, 1H, NH), 7.53 (s, 1H, thiazole-H), 7.52 (br, 1H, NH), 7.31 (d, J = 8.60 Hz, 2H, 2Ph—H), 7.12 (d, J = 8.60 Hz, 2H, 2Ph—H), 5.02 (s, 2H, CH_2), 3.55–3.65 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.75, 163.36, 153.38, 140.99, 135.46, 134.46, 133.69, 129.50, 121.44, 120.72, 54.46, 48.22, 43.36, 41.41, 20.94; Anal. Calc. for $C_{17}H_{16}ClN_5OS$: C, 54.61; H, 4.31; N, 18.73. Found: C, 54.73; H, 4.29; N, 19.18.

2-(1-((2-Chlorothiazol-5-yl)methyl)imidazolidin-2-ylidene)-2-cyano-N-phenylacetamide (6r). Yellow solid; yield: 73%; mp: 181.8–182.8°C; IR (KBr): ν 3300.2, 3055.2, 3047.5, 2968.4, 2906.7, 2166.0, 1639.4, 1558.4, 1508.3, 1448.5 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.48 (br, 1H, NH), 7.57 (s 1H, NH), 7.53 (s, 1H, thiazole-H), 7.44 (d, J = 8.05 Hz, 2H,

2Ph—H), 7.31 (t, $J = 8.00$ Hz, 2H, 2Ph—H), 7.09 (t, $J = 7.44$ Hz, 1H, Ph—H), 5.03 (s, 2H, CH_2), 3.56–3.66 (m, 4H, CH_2CH_2); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 166.77, 163.38, 153.42, 141.01, 138.11, 134.39, 129.00, 124.04, 121.35, 120.49, 54.57, 48.88, 43.37, 41.42; Anal. Calc. for $C_{16}H_{14}ClN_5OS$: C, 53.41; H, 3.92; N, 19.46. Found: C, 53.73; H, 3.69; N, 19.28.

Biological assay. The compounds under investigation were dissolved in 2 mL DMSO and diluted with water containing TWEEN-20 (0.1 mg /L) to generate a final concentration of 100.0 mg/L. About 15 rice plants (~10 cm lengths) with roots were dipped for 10 sec in the solution of the compound being tested. Then, the plants were air-dried and the rice roots were wrapped in moist cotton. The plants were subsequently placed into a tumbler, and 20 *Nilaparvata lugens* were introduced into it. The treated insects were maintained at a temperature of 27°C ± 1°C. For each compound, three repetitions were measured; water containing TWEEN-20 (0.1 mg/L) and DMSO was used as control, and the mortality rates were assessed after 72 h.

Acknowledgments. The authors gratefully acknowledge the National Natural Science Foundation of China (No. 20872021) and the Agricultural Scientific and Technological Project of Guizhou Province in China (No. 20103068) for providing the financial support.

REFERENCES AND NOTES

[1] Nishimura, K.; Kanda, Y.; Okazawa, A.; Ueno, T. Pestic Biochem Physiol 1994, 50, 51.

[2] Mori, K.; Okumoto, T.; Kawahara, N.; Ozoe, Y. Pest Manag Sci 2002, 58, 190.

[3] Bai, D. L.; Lummis, S. C. R.; Leicht, W.; Breer, H.; Sattelle, D. B. Pestic Sci 1991, 33, 197.

[4] Leech, C. A.; Jewess, P.; Marshall, J.; Sattelle, D. B. FEBS Lett 1991, 290, 90.

[5] Liu, M. Y.; Casida, J. E. Pestic Biochem Physiol 1993, 46, 40.

[6] Zhang, A. G.; Kayser, H.; Maienfisch, P.; Casida, J. E. J Neurochem 2000, 75, 1294.

[7] Shao, X. S.; Zhang, W. W.; Peng, Y. Q.; Li, Z.; Tian, Z. Z.; Qian, X. H. Bioorg Med Chem Lett 2008, 18, 6513.

[8] Shao, X. S.; Fu, H.; Xu, X. Y.; Xu, X. L.; Liu, Z. W.; Li, Z.; Qian, X. H. J Agric Food Chem 2010, 58, 2696.

[9] Shao, X. S.; Li, Z.; Qian, X. H.; Xu, X. Y. J Agric Food Chem 2009, 57, 951.

[10] Xu, X.; Bao, H.; Shao, X.; Zhang, Y.; Yao, X.; Liu, Z.; Li, Z. Insect Mol Biol 2010, 19, 1.

[11] Shao, X. S.; Xu, Z. P.; Zhao, X. F.; Xu, X. Y.; Tao, L. M.; Zhong, L.; Qian, X. H. J Agric Food Chem 2010, 58, 2690.

[12] Zhao, X. F.; Shao, X. S.; Zou, Z. Y.; Xu, X. Y. J Agric Food Chem 2010, 58, 2746.

[13] Zhao, Y.; Li, Y. Q.; Wang, S. H.; Li, Z. M. ARKIVOC 2009, 11, 152.

[14] Sun, C. W.; Yang, D. R.; Xing, J. H.; Wang, H. F.; Jin, J.; Zhu, J. J Agric Food Chem 2010, 58, 3415.

[15] Zhang, W. W.; Yang, X. B.; Chen, W. D.; Xu, X. Y.; Li, L.; Zhai, H. B.; Li, Z. J Agric Food Chem 2010, 58, 2741.

[16] Ohno, I.; Tomizawa, M.; Aoshima, A.; Kumazawa, S.; Kagabu, S. J Agric Food Chem 2010, 58, 4999.

[17] Tian, Z. Z.; Shao, X. S.; Li, Z.; Qian, X. H.; Huang, Q. C. J Agric Food Chem 2007, 55, 2288.

[18] Ohno, I.; Tomizawa, M.; Durkin, K. A.; Naruse, Y.; Casida, J. E.; Kagabu, S. Chem Res Toxicol 2009, 22, 476.

[19] Tomizawa, M.; Lee, D. L.; Casida, J. E. J Agric Food Chem 2000, 48, 6016.

[20] Kai, A.; Wakita, T.; Katsuta, H.; Yoshida, K.; Tsukada, H.; Takahashi, Y.; Kawahara, N.; Nomura, M.; Daido, H.; Kawahara, N. C.; Kei, Y.; Akiyosi, K.; Hidetaka, C.; Takeo, W.; Yuseuke, T. Eur. Pat. 1,911,751 (2006); Chem Abstr 2006, 146, 100426.

[21] Stevenson, T. M.; Stevenson, M. Jpn. Pat. 2,005,529,937 (2003); Stevenson, T. M.; Stevenson, M. Chem Abstr 2003, 140, 14039.

[22] Wakita, T.; Daido, H.; Kai, A.; Kawahara, N.; Yoshida, K. Jpn. Pat. 2,007,099,761 (2007); Chem Abstr 2007, 146, 441501.

[23] Yoshida, K.; Kobayashi, Y.; Nomura, M.; Kawahara, N.; Daido, H.; Inomata, S.; Kei, Y. Eur. Pat. 1,916,236 (2006); Chem Abstr 2006, 146, 100426.

[24] Yoshida, K.; Wakita, T.; Katsuta, H.; Kai, A.; Chiba, Y.; Takahashi, K.; Kato, H.; Kawahara, N.; Nomura, M.; Daido, H.; Maki, J.; Banba, S.; Hiba, Y. Eur. Pat. 1,714,958 (2005); Chem Abstr 2005, 143, 211723.

[25] Long, N.; Cai, X. J.; Song, B. A.; Yang, S.; Chen, Z.; Bhadury, P. S.; Hu, D. Y.; Jin, L. H.; Xue, W. J Agric Food Chem 2008, 56, 5242.

[26] Tkachenko, V. V.; Tregub, N. G.; Knyazev, A. P.; Mezheritskii, V. V. Zh Org Khim 1990, 26, 638.

[27] Basheer, A.; Yamataka, H.; Ammal, S. C.; Rappoport, Z. J Org Chem 2007, 72, 5297.

[28] Bencheikh, A.; Chuche, J.; Manisse, N.; Pommelet, J. C.; Netsch, K. P.; Lorencak, P.; Wentrup, C. J Org Chem 1991, 56, 970.

[29] Wang, Q. M.; Sun, H. K.; Cao, H. Y.; Cheng, M. R.; Huang, R. Q. J Agric Food Chem 2003, 51, 5030.

[30] Wang, Y. H.; Chen, J.; Zhu, Y. C.; Ma, C. Y.; Huang, Y.; Shen, J. L. Pest Manag Sci 2008, 64, 1278.