JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

J. Agric. Food Chem. **2009,** *57,* 951–957 **951**

Design, Synthesis, and Insecticidal Activities of Novel Analogues of Neonicotinoids: Replacement of Nitromethylene with Nitroconjugated System

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To replace nitromethylene pharmacophore with a nitroconjugated system, a series of novel neonicotinoid analogues bearing five-membered aromatic heterocycles were designed and synthesized. Bioassays indicated that some of the synthesized compounds exhibited higher insecticidal activities than imidacloprid against cowpea aphids (*Aphis craccivora*), armyworm (*Pseudaletia separate* Walker), *Nephotettix bipunctatus* (Fabricius), and small brown rice planthopper (*Laodelphasx striatellus*). Exhilaratingly, the activity levels of derivatives **13a** and **13j** rivaled that of imidacloprid.

KEYWORDS: Neonicotinoids; nitromethylene; imidacloprid; insecticide

INTRODUCTION

Neonicotinoids, targeting insect nicotinic acetylcholine receptors (nAChRs) (*1, 2*), have attracted considerable attention for decades and represent a new generation of synthetic insecticides as they combine unique properties allowing them to be the fastest growing synthetic insecticides on the market (*3*). Some of these unique properties are a broad-spectrum insecticidal activity, low application rate, novel mode of action, and favorable safety profile; as well, they lack cross-resistance to other insecticides (*4, 5*). Imidacloprid (*1*), the first commercialized neonicotinoid, has the largest sales of any insecticide worldwide (*6*). Neonicotinoids are increasingly used in crop protection and animal health care due to the decrease in effectiveness of organophosphorus and carbamate derivatives. However, significant increases in resistance were observed in a range of species after frequent field applications (*7*−*14*). Therefore, the development of neonicotinoids with new chemical structures and high insecticidal activities is highly desirable.

According to the chemical structures of neonicotinoids developed in the past several decades, the common molecular structural features of neonicotinoids consist of four sections: (1) aromatic heterocycle, (2) flexible linkage, (3) hydroheterocyles or guanidine/amidine, and (4) electron-withdrawing segment (**Scheme 1**) (*15*). A major emphasis on searching for new neonicotinoids has involved the modification of the electron-withdrawing segment C═X. It has been proved that nitromethylene is one of the most effective electron-withdrawing segments, and neonicotinoids bearing this scaffold are called "nitromethylene neonicotinoids", such as 6-Cl-PMNI (*2*), nitenpyram (*3*), and compound **4** (*16*−*19*). The double bond in the nitromethylene group plays a crucial role in its modes of action; it can stabilize the planarity of the pharmacophore and form a conjugation system that facilitates electron flow toward the nitro group (*20*−*22*). Furthermore, all of the commercialized neonicotinoids have a C═N or C═C double bond, so it is believed that the double bond is indispensable to this kind of compound. Interestingly, *N*-((6-chloropyridin-3-yl)methyl)-3-(dimethylamino)-*N*,*N*′-dimethyl-2-nitroacrylamidine (*5*) discovered by Dow Agrosciences (*23*), into which the conjugated double bond was introduced, also showed high insecticidal activities. This special structure feature revealed that replacement of the double bond by a conjugated system might be the tactic to obtain novel analogues with high activities.

In a previous study, we found that 6-Cl-PMNI could react with α,β-unsaturated aldehydes to give nitromethylene compounds **7** with high insecticidal activities (*15*, *24*), but when

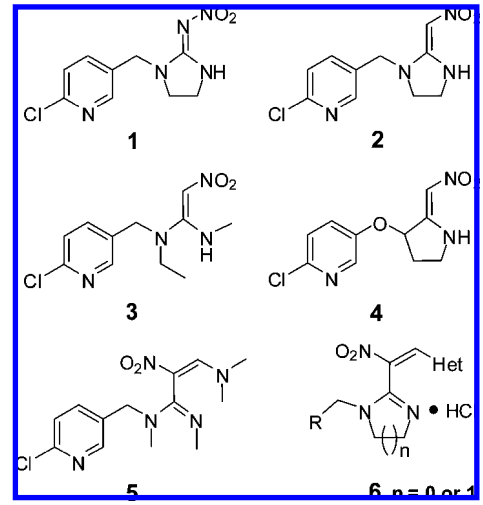

Figure 1. Structures of imidacloprid, nitromethylene neonicotinoids, and neonicotinoids with nitroconjugated system.

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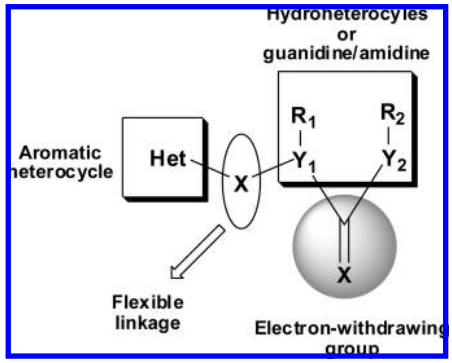
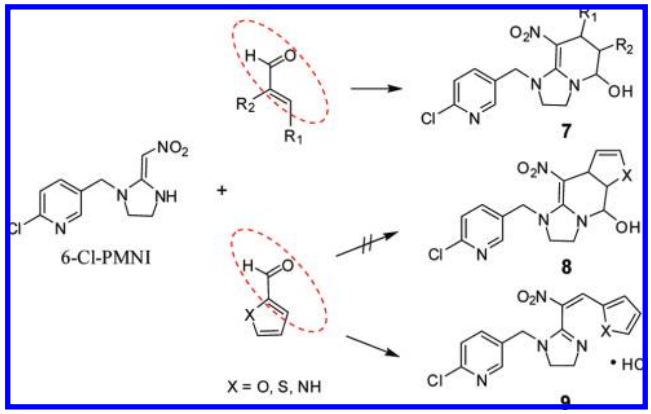
10.1021/jf803305f CCC: $40.75
Published on Web 01/12/2009

Scheme 1. General Structure of Neonicotinoids



Scheme 2. Reaction of Nitromethylene Compound 6-Cl-PMNI with α,β-Unsaturated Aldehydes and Five-Membered Aromatic Aldehydes



five-membered aromatic aldehydes were used as the replacement of α,β-unsaturated aldehydes, compounds **9** rather than **8** were obtained (**Scheme 2**). Enlightened by all of the descriptions above, we herein designed and synthesized a series of novel neonicotinoid analogues (*6*) bearing nitroconjugated double bond and five-membered heterocycles.

MATERIALS AND METHODS

Instruments. Melting points (mp) were recorded on a Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H NMR, ^{13}C NMR, and 2D NMR (HMBC and HMQC) spectra were recorded on a Bruker WP-500SY (500 MHz) or a Bruker AM-400 (400 MHz) spectrometer with DMSO-d_6 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.

Synthetic Procedures. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized.

General Synthetic Procedure for 13a−n, 14a−e, and 18a−c. Concentrated hydrochloric acid (0.15 mL) was added to a stirred mixture of compound **2** (**12** or **17a–c**) (4 mmol), five-membered aromatic aldehyde (6 mmol), and acetonitrile (20 mL). The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC. After completion, the product was precipitated. The precipitate was filtered, washed with dichloromethane, and dried to give the corresponding product.

(Z)-2-Chloro-5-((2-(2-(furan-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13a****:* yield, 93%; mp 200.4−201.6 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.74 (s, 1H), 8.74 (s, 1H), 8.23 (d, J = 2.4 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 7.68−7.71 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 6.92 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.67 (d, J = 15.6 Hz, 1H), 4.08−4.18 (m, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.7, 153.2, 150.7, 150.3, 144.9, 140.3, 131.1, 129.7, 129.5, 126.2, 124.7, 115.6, 49.7, 46.9, 44.5; HRMS (ES+) calcd for $C_{15}H_{14}N_4O_3{}^{35}Cl$ (M + H)$^+$, 333.0754; found, 333.0761; calcd for $C_{15}H_{14}N_4O_3{}^{37}Cl$ (M + H)$^+$, 335.0725; found, 335.0766. Anal. Calcd for $C_{15}H_{14}N_4O_3Cl_2$: C, 48.80; H, 3.82; N, 15.18. Found: C, 48.08; H, 3.51; N, 15.47.

(Z)-2-Chloro-5-((2-(2-(5-methylfuran-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13b****:* yield, 91%; mp 205.6−206.4 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.55 (s, 1H), 8.63 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.70 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.77 (d, J = 3.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 6.28 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H), 4.78 (d, J = 15.2 Hz, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.11−4.13 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 164.2, 159.0, 150.7, 150.3, 143.7, 140.4, 132.3, 130.4, 129.5, 124.7, 124.5, 113.2, 49.7, 46.8, 44.6, 14.4; HRMS (EI+) calcd for $C_{16}H_{15}N_4O_3{}^{35}Cl$ (M$^+$), 346.0833; found, 346.0834; calcd for $C_{16}H_{15}N_4O_3{}^{37}Cl$ (M$^+$), 348.0803; found, 348.0812.

(Z)-2-Chloro-5-((2-(2-(5-ethylfuran-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13c****:* yield, 62%; mp 167.7−168.2 °C; ^{1}H NMR (400 Mz, DMSO-d_6): δ 11.50 (s, 1H), 8.65 (s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.67−7.70 (m, 2H), 7.49 (dd, J_1 = 0.4 Hz, J_2 = 8.0 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 4.76 (d, J = 15.2 Hz, 1H), 4.70 (d, J = 15.2 Hz, 1H), 4.04−4.19 (m, 4H), 2.60−2.76 (m, 2H), 1.13 (t, J = 15.2, 3H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 169.0, 159.0, 150.7, 150.4, 143.6, 140.4, 132.3, 130.6, 129.4, 124.7, 124.5, 111.8, 49.7, 46.8, 44.6, 21.8, 14.4; HRMS (EI+) calcd for $C_{17}H_{17}N_4O_3{}^{35}Cl$ (M$^+$), 360.0989; found, 360.0989; calcd for $C_{17}H_{17}N_4O_3{}^{37}Cl$ (M$^+$), 362.0960; found, 360.0974.

(Z)-2-Chloro-5-((2-(2-(4,5-dimethylfuran-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13d****:* yield, 58%; mp 190.1−191.0 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.52 (s, 1H), 8.57 (s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 7.69 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.54 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 15.2 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.05−4.16 (m, 4H), 2.28 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 160.8, 159.1, 150.6, 150.3, 142.5, 140.3, 130.1, 129.5, 124.7, 123.9, 122.0, 49.8, 46.8, 44.5, 12.6, 9.6; HRMS (EI+) calcd for $C_{17}H_{17}N_4O_3{}^{35}Cl$ (M$^+$), 360.0989; found, 360.0990; calcd for $C_{17}H_{17}N_4O_3{}^{37}Cl$ (M$^+$), 362.0960; found, 360.0979.

(Z)-(5-(2-(1-((6-Chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-2-nitrovinyl)furan-2-yl)methanol hydrochloric acid salt ***13e****:* yield, 72%; mp 172.0−172.5 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.42 (s, 1H), 8.69 (s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 7.72 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.67 (d, J = 3.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 3.6 Hz, 1H), 4.80 (d, J = 15.2 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.52 (d, J = 2.8 Hz, 2H), 4.14−4.19 (m, 2H), 4.04−4.10 (m, 2H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 166.5, 158.9, 150.7, 150.3, 144.1, 140.3, 131.2, 130.8, 129.5, 125.3, 124.7, 112.5, 56.4, 49.7, 46.9, 44.5; HRMS (ES+) calcd for $C_{16}H_{16}N_4O_4{}^{35}Cl$ (M + H)$^+$, 363.0815; found, 363.0830; calcd for $C_{16}H_{16}N_4O_4{}^{37}Cl$ (M + H)$^+$, 365.0831; found, 365.0829.

(Z)-2-Chloro-5-((2-(2-(5-chlorofuran-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13f****:* yield, 77%; mp 189.3−190.4 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 12.05 (s, 1H), 8.72 (s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 4.0 Hz, 1H), 7.72 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 3.6 Hz, 1H), 4.79 (d, J = 15.2 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 4.13−4.23 (m, 2H), 3.99−4.09 (m, 2H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.3, 150.8, 150.3, 145.2, 144.6, 140.4, 131.4, 130.2, 129.3, 126.6, 124.7, 113.2, 49.9, 46.8, 44.8; HRMS (EI+) calcd for $C_{15}H_{12}N_4O_3{}^{35}Cl_2$ (M$^+$), 366.0286; found, 366.0286; calcd for $C_{15}H_{12}N_4O_3{}^{37}Cl_2$ (M$^+$), 370.0227; found, 370.0227.

(Z)-2-Chloro-5-((2-(2-(5-bromofuran-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13g****:* yield 79%; mp 205.6−207.5 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.15 (s, 1H), 8.74 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 4.0 Hz, 1H), 7.72 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 3.6 Hz, 1H), 4.81 (d, J = 15.2 Hz, 1H), 4.75 (d, J = 15.2 Hz, 1H), 4.14−4.23 (m, 2H), 4.00−4.10 (m, 2H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.4, 150.8, 150.3, 145.3, 144.5, 140.4, 131.6, 130.2,

129.2, 126.5, 124.7, 113.2, 50.0, 46.9, 44.9; HRMS (ES+) calcd for $C_{15}H_{13}N_4O_3{}^{35}Cl^{79}Br$ $(M + H)^+$, 410.9860; found, 410.9855; calcd for $C_{15}H_{13}N_4O_3{}^{35}Cl^{81}Br$ $(M + H)^+$, 412.9839; found, 412.9849; calcd for $C_{15}H_{13}N_4O_3{}^{37}Cl^{79}Br$ $(M + H)^+$, 412.9830; found, 412.9849; calcd for $C_{15}H_{13}N_4O_3{}^{37}Cl^{81}Br$ $(M + H)^+$, 414.9810; found, 414.9800.

(Z)-2-Chloro-5-((2-(1-nitro-2-(5-nitrofuran-2-yl)vinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13h****:* yield, 90%; mp 162.5−162.9 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.80 (s, 1H), 8.92 (s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 7.89 (d, J = 4.0 Hz, 1H), 7.83 (d, J = 4.0 Hz, 1H), 7.74 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 4.89 (d, J = 15.2 Hz, 1H), 4.71 (d, J = 15.2 Hz, 1H), 4.10−4.19 (m, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 157.6, 150.4, 145.4, 144.6, 140.5, 131.5, 131.1, 130.1, 129.2, 128.6, 124.8, 114.3, 50.2, 46.9, 45.2; HRMS (EI+) calcd for $C_{15}H_{12}N_5O_5{}^{35}Cl$ (M^+), 377.0527; found, 377.0518; calcd for $C_{15}H_{12}N_5O_5{}^{37}Cl$ (M^+) (M^+), 379.0497; found, 379.0524.

(Z)-2-Chloro-5-((2-(2-(furan-3-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13i****:* yield, 69%; mp 175.3−175.9 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.86 (s, 1H), 8.86 (s, 1H), 8.70 (s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.02 (s, 1H), 7.71 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 0.8 Hz, 1H), 4.75 (d, J = 15.2 Hz, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.05−4.25 (m, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 157.9, 154.9, 150.8, 150.6, 148.2, 140.7, 137.8, 129.2, 128.9, 124.8, 116.8, 108.7, 49.7, 46.9, 44.6; HRMS (EI+) calcd for $C_{15}H_{13}N_4O_3{}^{35}Cl$ (M^+), 332.0676; found, 332.0676; calcd for $C_{15}H_{13}N_4O_3{}^{37}Cl$ (M^+), 334.0674; found, 334.0651.

(Z)-2-Chloro-5-((2-(1-nitro-2-(thiophen-2-yl)vinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13j****:* yield, 90%; mp 188.8−189.7 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 12.11 (s, 1H), 9.18 (s, 1H), 8.37 (d, J = 4.8 Hz, 1H), 8.27 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 3.6 Hz, 1H), 7.71 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 4.4 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.15 (s, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 157.8, 150.8, 150.6, 143.2, 140.6, 140.4, 139.3, 131.4, 130.6, 129.1, 127.2, 124.7 49.7, 46.9, 44.8; HRMS (EI+) calcd for $C_{15}H_{13}N_4O_2S^{35}Cl$ (M^+), 348.0448; found, 348.0446; calcd for $C_{15}H_{13}N_4O_2S^{37}Cl$ (M^+), 350.0418; found, 350.0431. Anal. Calcd for $C_{15}H_{14}N_4O_2SCl_2$: C, 46.76; H, 3.66; N, 14.54. Found: C, 46.80; H, 3.42; N, 14.72.

(Z)-5-((2-(2-(4-Bromothiophen-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)-2-chloropyridine hydrochloric acid salt ***13k****:* yield, 88%; mp 161.0−162.0 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 12.19 (s, 1H), 9.13 (s, 1H), 8.46 (s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 1.2 Hz, 1H), 7.72 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 4.83 (d, J = 15.2 Hz, 1H), 4.69 (d, J = 15.2 Hz, 1H), 4.15 (s, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 155.6, 149.2, 148.9, 141.8, 139.0, 136.3, 134.8, 130.9, 127.4, 126.8, 123.1, 110.8, 48.2, 45.3, 43.2; HRMS (ES+) calcd for $C_{15}H_{13}N_4O_2S^{79}Br^{35}Cl$ $(M + H^+)$, 426.9631; found, 426.9640; calcd for $C_{15}H_{13}N_4O_2S^{81}Br^{35}Cl$ $(M + H^+)$, 428.9611; found, 428.9631; calcd for $C_{15}H_{13}N_4O_2S^{79}Br^{37}Cl$ $(M + H^+)$, 428.9602; found, 428.9631; calcd for $C_{15}H_{13}N_4O_2S^{81}Br^{37}Cl$ $(M + H^+)$, 430.9581; found, 430.9594.

(Z)-2-Chloro-5-((2-(2-(5-methylthiophen-2-yl)-1-nitrovinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13l****:* yield, 64%; mp 170.7−171.3 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 9.10 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 3.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.67 (d, J = 15.2 Hz, 1H), 4.11−4.17 (m, 4H), 2.60 (s, 3H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 157.9, 156.6, 150.8, 150.6, 144.7, 140.6, 139.4, 129.7, 129.6, 129.2, 125.6, 124.7, 49.6, 46.9, 44.6, 16.6; HRMS (EI+) calcd for $C_{16}H_{15}N_4O_2S^{35}Cl$ (M^+), 362.0604; found, 362.0604; calcd for $C_{16}H_{15}N_4O_2S^{37}Cl$ (M^+), 364.0575; found, 364.0564.

(Z)-2-Chloro-5-((2-(1-nitro-2-(thiophen-3-yl)vinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13m****:* yield, 35%; mp 95.8−96.1 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.89 (s, 1H), 8.62 (s, 1H), 8.23 (s, 1H), 7.80 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 4.8 Hz, 1H), 4.66−4.77 (m, 2H), 4.08−4.24 (m, 4 H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.3, 150.7, 150.5, 141.4, 140.6, 139.4, 130.9, 130.1, 129.1, 128.7, 127.3, 124.7 49.7, 46.9, 44.7; HRMS (EI+) calcd for $C_{15}H_{13}N_4O_2S^{35}Cl$ (M^+), 348.0448; found, 348.0444.

(Z)-2-Chloro-5-((2-(1-nitro-2-(1H-pyrrol-2-yl)vinyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine hydrochloric acid salt ***13n****:* yield, 51%; mp 239.0−240.1 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 12.96 (s, 1H), 11.49 (br, s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.68−7.71 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.54 (t, J = 2.0 Hz, 1H), 4.70 (d, J = 15.2 Hz, 1H), 4.62 (d, J = 15.2 Hz, 1H), 4.01−4.23 (m, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 159.2, 150.7, 150.5, 140.6, 134.4, 132.9, 129.3, 124.7, 122.8, 121.2, 116.0, 49.4, 46.9, 44.4; HRMS (EI+) calcd for $C_{15}H_{14}N_5O_2{}^{35}Cl$ (M^+), 331.0836; found, 331.0825; calcd for $C_{15}H_{14}N_5O_2{}^{37}Cl$ (M^+), 333.0807; found, 333.0815.

(Z)-1-((6-chloropyridin-3-yl)methyl)-2-(2-(furan-2-yl)-1-nitrovinyl)-1,4,5,6-tetrahydropyrimidine hydrochloric acid salt ***14a****:* yield, 24%; mp 126.3−127.2 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.31 (s,1H), 8.61 (s, 1H), 8.22−8.23 (m, 2H), 7.64−7.68 (m, 2H), 7.47 (d, J = 8.2 Hz, 1H), 6.90 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H), 4.84 (d, J = 15.6 Hz, 1H), 4.68 (d, J = 15.6 Hz, 1H), 3.62−3.74 (m, 2H), 3.54 (s, 2H), 2.06−2.16 (m, 2H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 153.6, 152.9, 150.5, 150.1, 145.2, 140.0, 131.6, 129.8, 129.4, 129.0, 124.6, 115.4, 55.2, 52.8, 46.5, 18.1; HRMS (EI+) calcd for $C_{16}H_{15}N_4O_3{}^{35}Cl$ (M^+), 346.0833; found, 346.0831; calcd for $C_{16}H_{15}N_4O_3{}^{37}Cl$ (M^+), 348.0803; found, 348.0818.

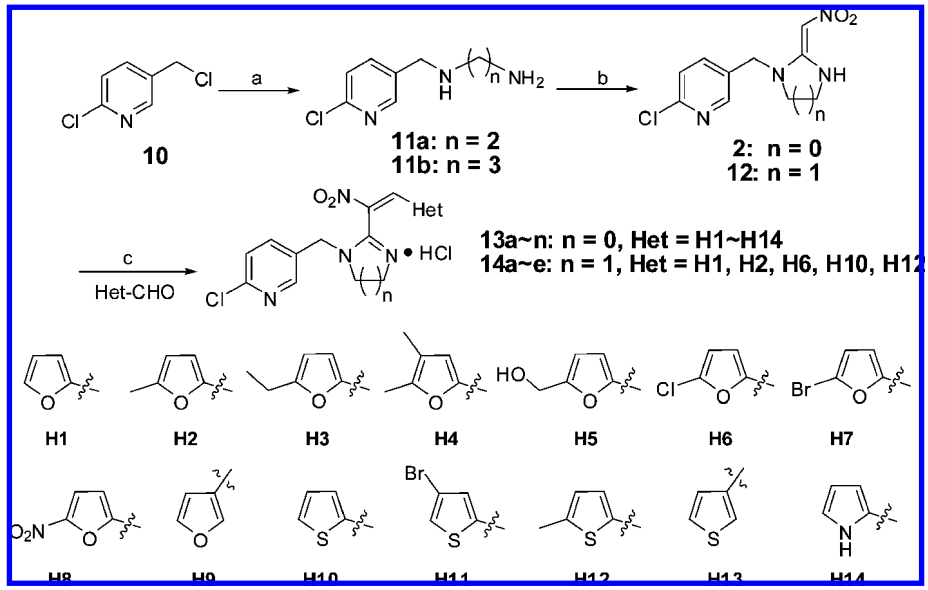
(Z)-1-((6-Chloropyridin-3-yl)methyl)-2-(2-(5-methylfuran-2-yl)-1-nitrovinyl)-1,4,5,6-tetrahydropyrimidine hydrochloric acid salt ***14b****:* yield, 75%; mp 213.7−213.9 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.31 (s, 1H), 8.48 (s, 1H), 8.25 (d, J = 2.4 Hz, 1H), 7.68 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 3.6 Hz, 1H), 4.84 (d, J = 15.2 Hz, 1H), 4.69 (d, J = 15.2 Hz, 1H), 3.64−3.77 (m, 2H), 3.52 (s, 2H), 2.41 (s, 3H), 2.04−2.09 (m, 2H); ^{13}C NMR (100 Mz, DMSO-*d6*) δ 163.8, 153.8, 150.5, 150.2, 144.2, 140.1, 131.6, 130.1, 129.9, 128.9, 124.6, 112.9, 52.8, 46.8, 18.3, 14.2; HRMS (EI+) calcd for $C_{17}H_{17}N_4O_3{}^{35}Cl$ (M^+), 360.0989; found, 360.0989; calcd for $C_{17}H_{17}N_4O_3{}^{37}Cl$ (M^+), 362.0960; found, 362.0969.

(Z)-1-((6-Chloropyridin-3-yl)methyl)-2-(2-(5-chlorofuran-2-yl)-1-nitrovinyl)-1,4,5,6-tetrahydropyrimidine hydrochloric acid salt ***14c****:* yield, 43%; mp 235.5−236.1 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 10.88 (s, 1H), 8.59 (s, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.69−7.72 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 4.0 Hz, 1H), 4.89 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 3.72−3.74 (m, 2H), 3.53−3.54 (m, 2H), 2.04−2.18 (m, 2H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 153.4, 150.7, 150.2, 145.1, 144.8, 140.1, 131.9, 130.9, 129.7, 128.4, 124.6, 113.1, 52.9, 47.0, 18.0; HRMS (ES+) calcd for $C_{16}H_{14}N_4O_3{}^{35}Cl_2$ $(M + H)^+$, 381.0521; found, 381.0503; calcd for $C_{16}H_{14}N_4O_3{}^{35}Cl^{37}Cl$ $(M + H)^+$, 383.0492; found, 383.0480; calcd for $C_{16}H_{14}N_4O_3{}^{37}Cl_2$ $(M + H)^+$, 385.0462; found, 385.0479.

(Z)-1-((6-Chloropyridin-3-yl)methyl)-2-(1-nitro-2-(thiophen-2-yl)vinyl)-1,4,5,6-tetrahydropyrimidine hydrochloric acid salt ***14d****:* yield, 69%; mp 160.5−161.3 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.74 (s, 1H), 9.06 (s, 1H), 8.33 (dt, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.10 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H), 7.68 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H), 7.48 (dd, J_1 = 0.4 Hz, J_2 = 8.2 Hz, 1H), 7.42 (dd, J_1 = 4.0 Hz, J_2 = 5.0 Hz, 1H), 4.88 (d, J = 15.2 Hz, 1H), 4.70 (d, J = 15.2 Hz, 1H), 3.71 (t, J = 5.6, 2H), 3.55−3.62 (m, 2H), 2.06−2.26 (m, 2H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 152.7, 150.7, 150.5, 143.0, 140.4, 140.0, 137.6, 132.4, 131.7, 130.4, 129.4, 124.6, 52.9, 46.6, 17.9; HRMS (EI+) calcd for $C_{16}H_{15}N_4O_2S^{35}Cl$ (M^+), 362.0605; found, 362.0604; calcd for $C_{16}H_{15}N_4O_2S^{37}Cl$ (M^+), 364.0575; found, 364.0580.

(Z)-1-((6-Chloropyridin-3-yl)methyl)-2-(2-(5-methylthiophen-2-yl)-1-nitrovinyl)-1,4,5,6-tetrahydropyrimidine hydrochloric acid salt ***14e****:* yield, 15%; mp 208.6−209.4 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 11.57 (s, 1H), 8.96 (s, 1H), 8.27 (d, J = 1.6 Hz, 1H), 7.98 (d, J = 3.6 Hz, 1H), 7.70 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 4.88 (d, J = 15.6 Hz, 1H), 4.69 (d, J = 15.6 Hz, 1H), 3.66−3.77 (m, 2H), 3.55−3.63 (m, 2H), 2.61 (s, 3H), 2.21−2.26 (m, 1H), 2.05−2.10 (m, 1H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 156.1, 152.9, 150.7, 150.4, 144.3, 140.4, 137.7, 131.2, 129.8, 129.5, 129.5, 124.6, 52.8, 46.6, 18.0, 16.6; HRMS (EI+) calcd for

Scheme 3[a]



[a] Reagents and conditions: (a) ethane-1,2-diamine or propane-1,3-diamine, CH_3CN, 0−5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, CH_3CH_2OH, refluxing; (c) CH_3CN, various aldehyde, concentrated HCl, rt.

$C_{17}H_{17}N_4O_2S^{35}Cl$ (M^+), 376.0761; found, 376.0762; calcd for $C_{17}H_{17}N_4O_2S^{37}Cl$ (M^+), 378.0731; found, 378.0728.

(Z)-1-Benzyl-2-(2-(furan-2-yl)-1-nitrovinyl)-4,5-dihydro-1H-imidazole hydrochloric acid salt ***18a****:* yield, 56%; mp 185.7−187.8 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.74 (s, 1H), 8.25 (s, 1H), 7.72 (d, J = 3.2 Hz, 1H), 7.31−7.32 (m, 3H), 7.17−7.19 (m, 2H), 6.93 (d, J = 1.6 Hz, 1H), 4.67 (d, J = 15.2 Hz, 1H), 4.56 (d, J = 15.2 Hz, 1H), 4.00−4.15 (m, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.4, 153.2, 145.0, 133.8, 131.0, 129.6, 129.2, 128.8, 128.7, 126.4, 115.6, 50.3, 49.5, 44.4; HRMS (EI+) calcd for $C_{16}H_{15}N_3O_3$ (M^+), 297.1113; found, 297.1113.

(Z)-1-(4-Chlorobenzyl)-2-(2-(furan-2-yl)-1-nitrovinyl)-4,5-dihydro-1H-imidazole hydrochloric acid salt ***18b****:* yield, 51%; mp 194.8−195.1 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.74 (s, 1H), 8.22 (s, 1H), 7.76 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.93 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H), 4.71 (d, J = 15.2 Hz, 1H), 4.57 (d, J = 15.2 Hz, 1H), 4.01−4.15 (m, 4H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.6, 153.2, 145.0, 133.5, 132.9, 131.2, 130.7, 129.7, 129.2, 126.3, 115.6, 49.5, 44.4; HRMS (EI+) calcd for $C_{16}H_{14}N_3O_3{}^{35}Cl$ (M^+), 331.0724; found, 331.0724; calcd for $C_{16}H_{14}N_3O_3{}^{37}Cl$ (M^+), 333.0694; found, 333.0716.

(Z)-1-((2-Chlorothiazol-5-yl)methyl)-2-(2-(furan-2-yl)-1-nitrovinyl)-4,5-dihydro-1H-imidazole hydrochloric acid salt ***18c****:* yield, 63%; mp 198.2−198.7 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.75 (s, 1H), 8.19 (s, 1H), 7.71 (d, J = 3.2 Hz, 1H), 7.61 (s, 1H), 6.92−6.93 (m, 1H), 4.97 (s, 2H), 4.13 (s, 4 H); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.4, 153.2, 152.2, 145.0, 142.9, 133.6, 131.2, 129.7, 126.0, 115.7, 49.3, 44.6, 42.3; HRMS (EI+) calcd for $C_{13}H_{11}N_4O_3S^{35}Cl$ (M^+), 338.0240; found, 338.0240; calcd for $C_{13}H_{11}N_4O_3S^{37}Cl$ (M^+), 340.0211; found, 340.0213.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. All compounds were dissolved in *N*,*N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 500.0, 250.0, and 125.0 mg L^{-1} and others for bioassays. For comparative purposes, imidacloprid was tested under the same conditions.

Insecticidal Test for Cowpea Aphids (Aphis craccivora). The activities of insecticidal compounds against cowpea aphids were tested by leaf-dip method according to our previously reported procedure (*15*, *25*). 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; 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.

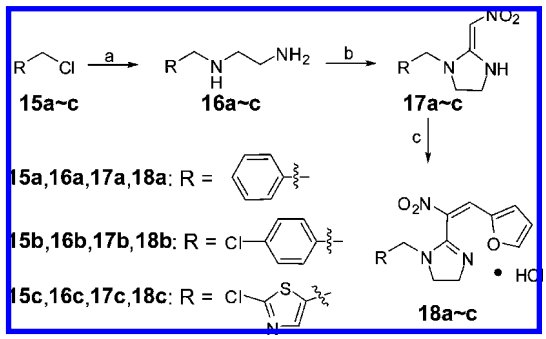
Insecticidal Test for Armyworm (Pseudaletia separate Walker). The activities of insecticidal compounds against armyworm were tested using previously reported procedures (*26*, *27*). The insecticidal activity against armyworm was tested by foliar application. Individual corn (*Zea mays*) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the compound solution and exposed to dry. The dishes were infested with 10 second-instar larvae and placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis as before.

Insecticidal Test for Small Brown Rice Planthopper (Laodelphasx striatellus) and Nephotettix bipunctatus (Fabricius). The activities of insecticidal compounds against brown rice planthopper and *N. bipunctatus* (Fabricius) were tested using the dipping method previously reported (*28*). Rice plants (Shanyou 63) at tillering to booting stage were pulled out, and the rice stems (about 10 cm lengths) with roots were cut and air-dried to remove excess water. Three rice stems were dipped in appropriate solutions of the tested compound for 30 s. After the rice stems had been air-dried, the rice roots was wrapped in moistened cotton. Then the rice stems were placed into a tumbler. Thirty *L. striatellus* or *N. bipunctatus* were introduced into the tumbler, and the treated insects were maintained at a temperature of 27 ± 1 °C. The distilled water only was used as control for each chemical. Each process was repeated three times, and the mortality rates were evaluated 48 h after treatment. The data were adjusted and subjected to probit analysis as before.

RESULTS AND DISCUSSION

Synthesis. The synthetic procedures for the title compounds are depicted in **Schemes 3** and **4**. Starting from **10** and **15a**−**c**, a set of diamines **11a**−**b** and **16a**−**c**, nitromethylene **2**, **12**, and **17a**−**c** were prepared following the procedure reported previously (*29*). Then compounds **2**, **12**, and **17a**−**c** could readily react with various five-membered aromatic aldehydes catalyzed by concentrated hydrochloric acid to give the title compounds **13a**−**n**, **14a**−**e**, and **18a**−**c** at room temperature. The amount of hydrochloric acid should be strictly controlled to allow the

Scheme 4[a]



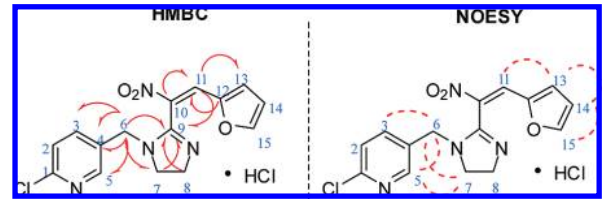
[a] Reagents and conditions: (a) ethane-1,2-diamine, CH_3CN, 0−5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, CH_3CH_2OH, refluxing; (c) CH_3CN, furan-2-carbaldehyde, concentrated HCl, rt.

product to precipitate from the reaction mixture. When the reaction took place at high temperature (>60 °C), a large amount of tar was produced and the yield was rather low (<10%). Unexpectedly, six-membered aromatic aldehydes, such as 2-pyridinaldehyde, 3-pyridinaldehyde, benzaldehyde, 4-methoxybenzaldehyde, and 4-nitrobenzaldehyde, could not react with intermediate **2** to provide the corresponding compounds, which might be due to the low electrophilic reactivities of these compounds. Attempts to synthesize the corresponding products by using aliphatic aldehydes (trifluoroacetaldehyde, butyraldehyde, and cyclohexanecarbaldehyde) were also unsuccessful even if the reaction mixture was heated to reflux.

The structures of all synthesized compounds were confirmed by NMR and HRMS. A broad peak at δ 11−12.5 in the ^{1}H NMR spectra of all the compounds and elemental analyses of **13a** and **13j** showed that the target compounds were obtained as hydrochloric acid salts. Moreover, heteronuclear chemical shift correlation experiments (HMBC, HMQC, and NOESY) were performed to assign all of the signals of the ^{13}C NMR spectrum and to confirm the assignments made for the ^{1}H NMR spectrum. A complete assignment of the proton signals and selected HMBC and NOESY correlations of compound **13a** is shown in **Table 1**.

Bioassay. *Insecticidal Activities against Cowpea Aphids (Aphis craccivora) and Armyworm (Pseudaletia separate Walker).* **Table 2** shows the insecticidal activities of the title compounds against cowpea aphids and armyworm. Most of the title compounds showed excellent insecticidal activities against cowpea aphids, and some of them were as active as or more so than imidacloprid. For example, the LC_{50} values of compounds **13a**, **13c**, **13i**, **13j**, **13l**, and **18c** were 0.00372, 0.00182, 0.00446, 0.00423, 0.00311, and 0.00350 mmol L^{-1}, respectively, whereas that of imidacloprid was only 0.03502 mmol L^{-1}. Against armyworm, the title compounds also had high insecticidal activities, whereas the activities of imidacloprid were weak, which implied that introduction of the five-membered aromatic heterocycles improved the insecticidal activities against not only homoptera insects but also lepidoptera insects. Unexpectedly, compound **13d** demonstrated high insecticidal activity against cowpea aphids but was inactive against armyworm, whereas **13k** and **13m** had very low or no activity. The insecticidal activities of the six-membered ring analogues **14a**−**e** were lower than those of the corresponding five-membered ring compounds. Replacement of 2-chloro-5-pyridine in **13a** with 2-chloro-5-thiazole to generate analogue **18c** maintained high insecticidal activities because the 2-chloro-5-thiazole unit has been shown to be an effective bioisosteric replacement for the 2-chloro-5-pyridine, whereas benzyl analogue **18a** and 4-chlorobenzyl analogue **18b** showed low insecticidal activities as anticipated.

Table 1. NMR Data and HMBC and NOESY Correlations of Compound **13a**



atom no.	δ_H (m, J in Hz)	δ_C	HMBC (δ_H to δ_C)	NOESY
1		150.7		
2	7.49 (d, 8.4)	124.7	1, 3, 4	
3	7.68−7.71(m)	140.3	1, 2, 6	6
4		129.5		
5	8.23 (d, 2.4)	150.3	1, 2, 3, 4, 6	6, 7
6	4.78 (d, 15.6)	46.9	3, 4, 5, 7, 9	5, 7
	4.67 (d, 15.6)			
7	4.08−4.18 (m)	49.7	8, 9	5, 6
8	4.08−4.18 (m)	44.5	7, 9	
9		158.7		
10		126.2		
11	8.74 (s)	131.1	9, 10, 12, 13	13
12		144.9		
13	7.68−7.71(m)	129.7	11, 12, 14,15	11, 14
14	6.92 (dd, 1.6, 3.6)	115.6	12, 13, 15	13, 15
15	8.20 (d, 1.2)	153.2	12, 13, 14	14

Table 2. Insecticidal Activities of Compounds **13a**−**n**, **14a**−**e**, and **18a**−**c** and Imidacloprid against Cowpea Aphids (*Aphis craccivora*) and Armyworm (*Pseudaletia separate* Walker)

			A. craccivora		*P. separate* Walker	
compd	*n*	Het[a]	mortality (%, 500 mg L^{-1})	LC_{50} (mmol L^{-1})	mortality (%, 500 mg L^{-1})	LC_{50} (mmol L^{-1})
13a	0	**H1**	100	0.00372	100	0.02470
13b	0	**H2**	100	0.00634	100	0.05313
13c	0	**H3**	100	0.00182	100	0.09790
13d	0	**H4**	100	0.00465	0	nt[b]
13e	0	**H5**	100	0.01058	100	0.03387
13f	0	**H6**	100	0.00754	100	0.03761
13g	0	**H7**	100	0.00730	100	0.03973
13h	0	**H8**	100	0.01109	100	0.06954
13i	0	**H9**	100	0.00446	100	0.05530
13j	0	**H10**	100	0.00423	100	0.05288
13k	0	**H11**	0	nt	0	nt
13l	0	**H12**	100	0.00311	100	0.02965
13m	0	**H13**	31.9	nt	0	nt
13n	0	**H14**	100	0.01117	100	0.03967
14a	1	**H1**	100	0.07642	16.7	nt
14b	1	**H2**	100	0.6975	33.3	nt
14c	1	**H6**	100	0.06091	96.7	nt
14d	1	**H10**	100	0.02050	73.3	nt
14e	1	**H12**	100	0.02464	63.3	nt
18a			0	nt	46.6	nt
18b			98.0	0.23440	67.2	nt
18c			100	0.00350	100	0.10727
imidacloprid			100	0.03502	nt	nt

[a] Het, five-membered aromatic heterocycles. [b] nt, not tested.

Insecticidal Activities against Nephotettix bipunctatus (Fabricius). Considering the bioassay results described above, compounds **13a**, **13b**, **13e**, **13g**, **13h**, and **13j** were selected to further evaluate the activities against *N. bipunctatus* (Fabricius), and the results are shown in **Table 3**. The results indicated that all compounds except **13h** possessed higher insecticidal activities than imidacloprid against *N. bipunctatus* (Fabricius). Especially, compounds **13a**, **13e**, and **13j** exhibited 16.0-, 18.8-, and 17.1-fold potency compared with imidacloprid, respectively.

Table 3. Insecticidal Activities of Compounds **13a**, **13b**, **13e**, **13g**, **13h**, and **13j** and Imidacloprid against *Nephotettix bipunctatus* (Fabricius)

compd	$y = a + bx$	LC_{50} (mmol L^{-1})	toxic ratio[a]
13a	$y = 5.5133 + 1.5925x$	0.00130	16.0
13b	$y = 4.7336 + 1.4034x$	0.00405	5.2
13e	$y = 5.5617 + 1.5613x$	0.00111	18.8
13g	$y = 4.9021 + 1.7913x$	0.00254	8.2
13h	$y = 2.9553 + 1.1326x$	0.15430	0.1
13j	$y = 5.4564 + 1.3838x$	0.00122	17.1
imidacloprid	$y = 4.2828 + 0.9880x$	0.02086	1

[a] Toxic ratio is defined as the ratio of imidacloprid's LC_{50} value for baseline toxicity and the compounds' LC_{50} value.

Table 4. Insecticidal Activities of Compounds **13a** and **13j** and Imidacloprid against Small Brown Rice Planthopper (*Laodelphasx striatellus*)

compd	$y = a + bx$	LC_{50} (mmol L^{-1})	toxic ratio[a]
13a	$y = 4.2260 + 1.8230x$	0.00723	6.9
13j	$y = 3.8342 + 1.5961x$	0.01397	3.6
imidacloprid	$y = 2.7972 + 1.9958x$	0.04980	1

[a] Toxic ratio is defined as the ratio of imidacloprid's LC_{50} value for baseline toxicity and the compounds' LC_{50} value.

Insecticidal Activities against Small Brown Rice Planthopper (Laodelphasx striatellus). **Table 4** shows the insecticidal activities of compounds **13a** and **13j** and imidacloprid against small brown rice planthopper. The results show that the insecticidal activities of compounds **13a** and **13j** against small brown rice planthopper were 6.9- and 3.6-fold as high as that of imidacloprid on the basis of the LC_{50} value.

In conclusion, a series of a novel class of neonicotinoids, in which the common nitromethylene pharmacophore was replaced by a nitroconjugated system, were designed and synthesized. Most of the compounds exhibited excellent insecticidal activities against cowpea aphids (*A. craccivora*), armyworm (*P. separate* Walker), *N. bipunctatus* (Fabricius), and small brown rice planthopper (*L. striatellus*), and some of them showed higher activities than imidacloprid, which implied that replacement of nitromethylene by the nitroconjugated system was feasible to obtain novel neonicotinoids analogues with high activities. In particular, derivatives **13a** and **13j**, as two field-testing candidates, showed much higher insecticidal activities than imidacloprid. Further field trial and structural modifications of compounds **13a** and **13j** are underway.

LITERATURE CITED

(1) Tomizawa, M.; Casida, J. E. Neonicotinoid insecticide toxicology: mechanisms of selective action. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 247–268.

(2) Matsuda, K.; Shimomura, M.; Ihara, M.; Akamatsu, M.; Sattelle, D. B. Neonicotinoids show selective and diverse actions on their nicotinic receptor targets: electrophysiology, molecular biology, and receptor modeling studies. *Biosci., Biotechnol., Biochem.* **2005**, *69*, 1442–1452.

(3) Tomizawa, M.; Casida, J. E. Selective toxicity of neonicotinoids attributable to specificity of insect and mammalian nicotinic receptors. *Annu. Rev. Entomol.* **2003**, *48*, 339–364.

(4) Tomizawa, M.; Talley, T.; Maltby, D.; Durkin, K. A.; Medzihradszky, K. F.; Burlingame, A. L.; Taylor, P.; Casida, J. E. Mapping the elusive neonicotinoid binding site. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 9075–9080.

(5) Kagabu, S.; Ishihara, R.; Nishimura, K.; Naruse, Y. Insecticidal and neuroblocking potencies of variants of the imidazolidine moiety of imidacloprid-related neonicotinoids and the relationship to partition coefficient and charge density on the pharmacophore. *J. Agric. Food Chem.* **2007**, *55*, 812–818.

(6) Mencke, N.; Jeschke, P. Therapy and preventions of parasitic insects in veterinary medicine using imidacloprid. *Curr. Top. Med. Chem.* **2002**, *2*, 701–715.

(7) Nauen, R.; Denholm, I. Resistance of insect pests to neonicotinoid insecticides: current status and future prospects. *Arch. Insect Biochem. Physiol.* **2005**, *58*, 200–215.

(8) Nauen, R.; Elbert, A. Resistance of *Bemisia tabaci* (Homoptera: Aleyrodidae) to insecticides in southern Spain with special reference to neonicotinoids. *Pest Manag. Sci.* **2000**, *56*, 60–64.

(9) Reyes, M.; Franck, P.; Charmillot, P. J.; Ioriatti, C.; Olivares, J.; Pasqualini, E.; Sauphanor, B. Diversity of insecticide resistance mechanisms and spectrum in European populations of the codling moth *Cydia pomonella*. *Pest Manag. Sci.* **2007**, *63*, 890–902.

(10) Liu, Z. W.; Han, Z. J.; Wang, Y. C.; Zhang, L. C.; Zhang, H. W.; Liu, C. J. Selection for imidacloprid resistance in *Nilaparvata lugens*: cross-resistance patterns and possible mechanisims. *Pest Manag. Sci.* **2003**, *59*, 1355–1359.

(11) Ninsin, K. D. Acetamiprid resistance and cross-resistance in the diamondback moth, *Plutella xylostella*. *Pest Manag. Sci.* **2004**, *60*, 839–841.

(12) Sanchez, D. M.; Hollingworth, R. M.; Grafius, E. J.; Moyer, D. D. Resistance and cross-resistance to neonicotinoid insecticides and spinosad in the Colorado potato beetle, *Leptinotarsa decemlineata* (Say) (Coleoptera: Chrysomelidae). *Pest Manag. Sci.* **2006**, *62*, 30–37.

(13) Gorman, K. G.; Devine, G.; Bennison, J.; Coussons, P.; Punchard, N.; Denholm, I. Report of resistance to the neonicotinoid insecticide imidacloprid in *Trialeurodes vaporariorum* (Hemiptera: Aleyrodidae). *Pest Manag. Sci.* **2007**, *63*, 555–558.

(14) Kristensen, M.; Jespersen, J. B. Susceptibility to thiamethoxam of *Musca domestica* from Danish livestock farms. *Pest Manag. Sci.* **2008**, *64*, 126–132.

(15) Tian, Z. Z.; Shao, X. S.; Li, Z.; Qian, X. H. Synthesis, insecticidal activity, and QSAR of novel nitromethylene neonicotinoids with tetrahydropyridine fixed *cis* configuration and exo-ring ether modification. *J. Agric. Food Chem.* **2007**, *55*, 2288–2292.

(16) *Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor*; Yamamoto, I., Casida, J. E., Eds.; Springer-Verlag: Tokyo, Japan, 1999; pp 177−209.

(17) Shiokawa, K.; Tsuboi, S.; Kagabu, S.; Moriya, K. Nitromethylene derivatives, intermediates, and their preparation as insecticides. Eur. Patent Appl. EP 163855, 1985.

(18) Markley, L. D.; Sparks, L. C.; Dripps, J. E.; Gifford, J. M. Compounds useful as insecticides, compounds useful as acaricides processes to use and make same. PCT Int. Appl. WO218339, 2002.

(19) Jeschke, P. In *Insecticides Design Using Advanced Technologies*; Ishaaya, I., Nauen, R., Horowitz, A. R., Eds.; Springer Verlag: The Netherlands, 2007; pp 151−195.

(20) Kagabu, S.; Matsuno, H. Chloronicotinyl insecticides. 8: Crystal and molecular structures of imidacloprid and analogous compounds. *J. Agric. Food Chem.* **1997**, *45*, 276–281.

(21) Tomizawa, M.; Zhang, N. J.; Durkin, K. A.; Olmstead, M. M.; Casida, J. E. The Neonicotinoid electronegative pharmacophore plays the crucial role in the high affinity and selectivity for the *Drosophila* nicotinic receptor: an anomaly for the nicotinoid cation−π interaction model. *Biochemistry* **2003**, *42*, 7819–7827.

(22) Wang, Y. L.; Cheng, J. G.; Qian, X. H.; Li, Z. Actions between neonicotinoids and key residues of insect nAChR based on an ab initio quantum chemistry study: hydrogen bonding and cooperative $\pi-\pi$ interaction. *Bioorg. Med. Chem.* **2007**, *15*, 2624–2630.

(23) Samaritoni, J. G. Compounds useful as pesticides PCT Int. Appl. WO 2004/056178, 2004.

(24) Li, Z.; Qian, X. H.; Shao, X. S.; Xu, X. Y.; Tian. Z. Z.; Huang, Q. C. Preparation method and use of compounds having high biocidal activities. PCT Int. Appl. WO 2007/101369.

(25) Tian, Z. Z.; Jiang, Z. X.; Li, Z.; Song, G. H.; Huang, Q. C. Syntheses and biological activities of octahydro-1*H*-cyclopenta[*d*]pyrimidine derivatives. *J. Agric. Food Chem*. **2007**, *55*, 143–147.

(26) Wei, S.; Qian, X. H.; Zhang, R.; Song, G. H. Synthesis and quantitative structure−activity relationships of new 2,5-disubstituted-1,3,4-oxadiazoles. *J. Agric. Food Chem*. **2001**, *49*, 143–130.

(27) Li, C.; Wang, Q. M.; Huang, R. Q.; Mao, C. H.; Shang, J.; Bi, F. C. Synthesis and insecticidal evalution of propesticides of benzoylphenylureas. *J. Agric. Food Chem.* **2005**, *49*, 38–41.

(28) Wang, Y. H.; Chen, J.; Zhu, Y. C.; Ma, C. Y.; Huang, Y.; Shen, J. L. Susceptibility to neonicotinoids and risk of resistance development in the brown planthopper, *Nilaparvata lugens* (Stål) (Homoptera: Delphacidae). *Pest Manag. Sci*. **2008**, *64*, 1278–1284.

(29) Kagabu, S.; Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K. 1-(6-Halonicotinyl)-2-nitromethylene-imidazolidines as potential new insecticides. *Biosci., Biotechnol., Biochem*. **1992**, *56*, 362–363.

Received for review October 22, 2008. Revised manuscript received December 8, 2008. Accepted December 8, 2008. This work was financially supported by the National Natural Science Foundation of China (20502006, 2087203) and the National High Technology Research and Development Program of China (863 Program, 2006AA10A201). We appreciate partial support from the Shanghai Foundation of Science and Technology (073919107, 064319022), Shanghai Leading Academic Discipline Project, Project B507.

JF803305F