

Divalent and Oxabridged Neonicotinoids Constructed by Dialdehydes and Nitromethylene Analogues of Imidacloprid: Design, Synthesis, Crystal Structure, and Insecticidal Activities[†]

XUSHENG SHAO,[§] HUA FU,[‡] XIAOYONG XU,^{*,§} XINGLEI XU,[§] ZEWEI LIU,[#] ZHONG LI,^{*,§}
AND XUHONG QIAN[§]

[§]Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China, [#]Key Laboratory of Monitoring and Management of Plant Disease and Insect, Ministry of Agriculture, Nanjing Agricultural University, Tongwei Road 6, Nanjing 210095, China, and [‡]Department of Applied Chemistry, Chemical Engineering College, Qinghai University, Xining 810016, China

A series of divalent and oxabridged neonicotinoids were synthesized by reactions of nitromethylene analogues of imidacloprid and dialdehydes, and their structures were confirmed by ¹H NMR, ¹³C NMR, high-resolution mass spectroscopy, and X-ray diffraction analysis. The bioassays indicated that some of them were endowed with excellent insecticidal activities against cowpea aphid (*Aphis craccivora*), armyworm (*Pseudaletia separata* Walker), and brown planthopper (*Nilaparvata lugens*). Divalent neonicotinoid **6** and oxabridged **8a** had higher activities than imidacloprid against cowpea aphids and armyworm; furthermore, the activity of **8a** was 40.4-fold higher than that of imidacloprid against imidacloprid-resistant brown planthopper.

KEYWORDS: Neonicotinoids; dialdehydes; imidacloprid; insecticide; oxabridge

INTRODUCTION

The past decades have witnessed the great power and versatile ability of neonicotinoids as a novel class of insecticides (1, 2), which account for 18% of world insecticide sales with a turnover of \$1.7 billion in 2006 (3). By virtue of novel modes of action (targeting insect nicotinic acetylcholine receptors (nAChRs)) (4–6), low mammalian toxicity, broad insecticidal spectra, and good systemic properties (7, 8), neonicotinoids are increasingly used in crop protection and animal health care against a broad spectrum of sucking and biting insects. Since their inception about 30 years ago, the development of neonicotinoids with novel structures and higher insecticidal activities has provoked continuing interest; for example, divalent neonicotinoids (9, 10), proinsecticides of imidacloprid (11), neonicotinoids with extended N-substituted-imine (12), neonicotinoid substituents forming a water bridge (13), and crown-capped imidacloprid (14) have consecutively appeared in the literature in recent years. Furthermore, the discoveries of high-resolution crystal structures of AChBP–neonicotinoid complexes have promoted the receptor structure guided neonicotinoid design (4, 12, 13, 15). Despite the tremendous amount of effort invested in the development of neonicotinoids, it is still essential to explore novel neonicotinoid candidates, because significant increases in resistance have been

observed in a range of species after frequent field applications (16–23).

The rationale for our molecular design involved the use of fused heterocycles or bulky groups to fix the direction of the nitro group, which was one of the most important groups in neonicotinoids. Fortunately, our foray into this arena met with encouraging insecticidal activities, and some novel neonicotinoids with high activities happened to be discovered (24–28). In our previous studies, it was found that 6-Cl-PMNI (**1**) could react with various α,β -unsaturated aldehydes to give high-insecticidal compounds **2** with tetrahydropyridine fixed *cis*-configuration (26, 27), and it could also react with five-membered aromatic aldehydes to give compounds **3** with bulky groups fixed in the direction of the nitro group, which showed higher insecticidal activities than imidacloprid (28). It is noteworthy that toward α,β -unsaturated aldehydes and five-membered aromatic aldehydes, C1 or N1 in 6-Cl-PMNI acted as nucleophilic centers.

Inspired by the promising results described above, we next turned our attentions to reactions of dialdehydes with 6-Cl-PMNI with a view to incorporate dialdehydes to 6-Cl-PMNI and search for high insecticidal neonicotinoids. Fortunately, different fates of dialdehydes upon reacting with 6-Cl-PMNI were observed due to the two electrophilic aldehyde groups in dialdehydes. Herein, for the sake of comparison and extending our studies, we report the synthesis and insecticidal activities of divalent and oxabridged neonicotinoids constructed by dialdehydes and nitromethylene analogues of imidacloprid.

[†]Part of the ECUST-Qian Pesticide Cluster.

*Corresponding authors [telephone + 86 21 64253540; fax +86 21 64252603; e-mail (Z.L.) lizhong@ecust.edu.cn or (X.X.) xyxu@ecust.edu.cn].

MATERIALS AND METHODS

Instruments. Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with CDCl_3 or $\text{DMSO}-d_6$ 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. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. X-ray diffraction was performed with a Bruker Smart 1000.

Synthesis. The general synthetic methods for compounds **4**, **5**, **6**, **8a–d**, and **9a–d** are depicted in Schemes 2–5. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized. All reactions were carried out under a protective atmosphere of drying nitrogen or utilizing a calcium chloride tube.

4-(1-((6-Chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-1-(1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-1,4-dinitrobut-3-en-2-ol (4). A mixture of compound **1** (2.54 g, 10 mmol), 40% oxalaldehyde aqueous solution (4 mL, 30 mmol), and acetonitrile (50 mL) was stirred at room temperature. After it was stirred for about 1 h, concentrated hydrochloric acid (0.20 mL) was added to the reaction mixture. The progress of the reaction was monitored by TLC. After completion, the solvent was removed under reduced pressure. The obtained residue was added to methanol (20 mL), and then the product was precipitated. The precipitate was filtered, washed with dichloromethane, and dried to give the corresponding product as a white solid: yield, 58%; mp, 164.6–165.3 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 9.01 (s, 1H), 8.41 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.80–7.86 (m, 2H), 7.51–7.54 (m, 2H), 6.50 (d, J = 7.2 Hz, 1H), 5.34 (d, J = 15.2 Hz, 1H), 5.18 (d, J = 15.2 Hz, 1H), 4.84 (dd, J_1 = 2.4 Hz, J_2 = 7.2 Hz, 1H), 4.77 (d, J = 16.8 Hz, 1H), 4.67 (d, J = 16.8 Hz, 1H), 3.98 (d, J = 2.4 Hz, 1H), 3.86–3.95 (m, 2H), 3.61–3.80 (m, 5H), 3.40–3.47 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 162.7, 158.7, 148.3, 148.2, 148.0, 147.7, 138.1, 137.7, 130.9, 130.2, 123.1, 123.0, 102.5, 101.4, 81.4, 53.8, 52.6, 49.4, 48.8, 46.4, 41.2, 41.0. HRMS (ES+) calcd for $\text{C}_{22}\text{H}_{23}\text{N}_8\text{O}_5^{35}\text{Cl}_2$ (M + H) $^+$, 549.1168; found, 549.1178; calcd for $\text{C}_{22}\text{H}_{23}\text{N}_8\text{O}_5^{35}\text{Cl}^{37}\text{ClNa}$ (M + H) $^+$, 551.1139; found, 551.1152; calcd for $\text{C}_{22}\text{H}_{23}\text{N}_8\text{O}_5^{37}\text{Cl}_2$ (M + H) $^+$, 553.1109; found, 553.1108.

2-Chloro-5-((2-(4-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-2-methoxy-1,4-dinitrobut-3-enylidene)imidazolidin-1-yl)methyl)pyridine (5). To a mixture of compound **4** (1.1 g, 2 mmol), methanol (10 mL), and dichloromethane (30 mL) was added three drops of concentrated hydrochloric acid. The resulting mixture was refluxed for 10 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 3:1) to afford the desired products as a brown solid: yield, 20%; mp, 170.2–170.6 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.84 (s, 1H), 8.38–8.39 (m, 2H), 7.81–7.86 (m, 2H), 7.50–7.55 (m, 2H), 5.37 (d, J = 15.4 Hz, 1H), 5.14 (d, J = 15.4 Hz, 1H), 4.69 (s, 2H), 4.62 (d, J = 2.2 Hz, 1H), 3.83–4.01 (m, 3H), 3.67–3.82 (m, 5H), 3.50–3.58 (m, 1H), 3.20 (s, 3H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 164.0, 161.1, 150.0, 149.9, 149.6, 149.3, 139.7, 139.3, 132.4, 132.0, 124.7, 124.6, 104.0, 102.3, 90.8, 55.4, 55.1, 54.4, 52.9, 50.8, 48.1, 45.5, 42.7. HRMS (ES+) calcd for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_5^{35}\text{Cl}_2\text{Na}$ (M + Na) $^+$, 585.1144; found, 585.1113; calcd for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_5^{35}\text{Cl}^{37}\text{ClNa}$ (M + Na) $^+$, 587.1115; found, 587.1104; calcd for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_5^{37}\text{Cl}_2\text{Na}$ (M + Na) $^+$, 589.1085; found, 589.1110.

2-Chloro-5-((2-(5-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-1,5-dinitropenta-1,4-dienyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine (6). Malonaldehyde was prepared according to the previously reported procedure (29). 1,1,3,3-Tetramethoxypropane (2.2 g, 13 mmol) was stirred with 5.0 mL of 2.0 M HCl for 1.5 h. Then compound **1** (2.54 g, 10 mmol) was added followed by 30 mL of acetonitrile, and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, the pH value of the filtrate was adjusted to 7–8 by triethylamine, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 2:1) to afford the desired

product as a brown solid: yield, 39%; mp, 136.5–137.8 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.34 (d, J = 2.4 Hz, 2H), 7.82 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.96 (t, J = 2.8 Hz, 2H), 4.81 (d, J = 15.8 Hz, 2H), 4.44 (d, J = 15.8 Hz, 2H), 3.92–3.97 (m, 4H), 3.65–3.72 (m, 2H), 3.49–3.56 (m, 2H), 1.92–1.93 (m, 2H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.3, 147.9, 147.8, 138.0, 130.9, 122.7, 104.8, 502, 48.9, 48.5, 48.5, 28.1. HRMS (ES+) calcd for $\text{C}_{23}\text{H}_{23}\text{N}_8\text{O}_4^{35}\text{Cl}_2$ (M + H) $^+$, 545.1219; found, 545.1201; calcd for $\text{C}_{23}\text{H}_{23}\text{N}_8\text{O}_4^{35}\text{Cl}^{37}\text{Cl}$ (M + H) $^+$, 547.1190; found, 547.1178; calcd for $\text{C}_{23}\text{H}_{23}\text{N}_8\text{O}_4^{37}\text{Cl}_2$ (M + H) $^+$, 549.1160; found, 549.1181.

General Synthetic Procedure for 8a–d. Succinaldehyde was prepared according to the previously reported procedure (30). A mixture of 2,5-diethoxytetrahydrofuran (2 g, 12.5 mmol) and HCl aqueous solution (0.1 M, 10 mL) was heated to 90 °C for 1 h and then cooled to room temperature. Acetonitrile (40 mL), compound **1** or **7a–c** (10 mmol), and anhydrous Na_2SO_4 (3 g) were successively added, and the obtained mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, the mixture was filtered to remove Na_2SO_4 , and then the pH value of the filtrate was adjusted to 7–8 by triethylamine and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 3:1) to afford the desired products **8a–d**.

Data for 8a: yield, 53%; mp, 149.0–150.0 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.35 (d, J = 2.4 Hz, 1H), 7.81 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 5.36–5.39 (s, 2H), 5.00 (d, J = 15.6 Hz, 1H), 4.68 (d, J = 15.6 Hz, 1H), 3.57–3.73 (m, 4H), 1.94–2.04 (m, 4H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.6, 149.7, 149.6, 139.7, 132.6, 124.5, 109.6, 87.0, 75.1, 51.2, 50.3, 46.6, 31.9, 31.7; HRMS (ES+) calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3^{35}\text{Cl}$ (M + H) $^+$, 323.0911; found, 323.0912; calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3^{37}\text{Cl}$ (M + H) $^+$, 325.0811; found, 325.0895; calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_3^{35}\text{ClNa}$ (M + Na) $^+$, 345.0730; found, 345.0722; calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_3^{37}\text{ClNa}$ (M + Na) $^+$, 347.0701; found, 347.0692.

Data for 8b: yield, 56%; mp, 136.5–138.0 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 7.47 (s, 1H), 5.61 (d, J = 5.2 Hz, 1H), 5.28 (d, J = 15.4 Hz, 1H), 5.16 (d, J = 5.00 Hz, 1H), 4.70 (d, J = 15.4 Hz, 1H), 3.66–3.82 (m, 3H), 3.54–3.61 (m, 1H), 2.22–2.29 (m, 1H), 2.12–2.21 (m, 2H), 1.99–2.07 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 154.6, 154.3, 140.6, 135.1, 110.4, 87.4, 75.4, 49.6, 47.9, 46.5, 31.8, 31.8. HRMS (ES+) calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3^{35}\text{Cl}$ (M + H) $^+$, 329.0475; found, 329.0475; calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3^{37}\text{Cl}$ (M + H) $^+$, 331.0446; found, 331.0461.

Data for 8c: yield, 58%; mp, 149.0–149.8 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 7.28–7.39 (m, 5H), 5.66 (d, J = 4.3 Hz, 1H), 5.14 (d, J = 4.5 Hz, 1H), 4.92–5.01 (m, 2H), 3.57–3.74 (m, 3H), 3.47–3.53 (m, 1H), 2.30–2.34 (m, 1H), 2.13–2.22 (m, 2H), 2.00–2.07 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.5, 135.9, 128.9, 128.2, 128.1, 87.7, 75.6, 54.4, 48.9, 47.2, 31.8, 31.6. HRMS (ES+) calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$ (M + H) $^+$, 287.1270; found, 287.1272.

Data for 8d: yield, 38%; mp, 140.0–140.9 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 7.27–7.34 (m, 4H), 5.63 (d, J = 5.4 Hz, 1H), 5.14 (d, J = 5.2 Hz, 1H), 5.04 (d, J = 15.1 Hz, 1H), 4.78 (d, J = 15.1 Hz, 1H), 3.62–3.73 (m, 3H), 3.45–3.51 (m, 1H), 2.26–2.31 (m, 1H), 2.11–2.21 (m, 2H), 1.98–2.07 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.3, 134.4, 133.9, 129.6, 129.0, 110.2, 87.6, 75.5, 53.9, 49.2, 47.0, 31.8, 31.7. HRMS (ES+) calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3^{35}\text{Cl}$ (M + H) $^+$, 322.0958; found, 322.0972; calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3^{37}\text{Cl}$ (M + H) $^+$, 324.0929; found, 324.0938.

General Synthetic Procedure for 9a–d. A mixture of compound **1** or **7a–c** (10 mmol), 25% glutaraldehyde aqueous solution (4 mL), and acetonitrile (50 mL) was stirred at room temperature. After it had been stirred for about 30 min, concentrated hydrochloric acid (0.20 mL) was added to the reaction mixture. The progress of the reaction was monitored by TLC. After completion, the pH value of the filtrate was adjusted to 7–8 by triethylamine, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 3:1) to afford the desired products **9a–d**.

Data for 9a: yield, 76%; mp, 174.7–175.4 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.38 (dd, J_1 = 0.6 Hz, J_2 = 2.4 Hz, 1H), 7.84 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.52 (dd, J_1 = 0.6 Hz, J_2 = 8.4 Hz, 1H), 5.12 (s, 1H), 5.04–5.05 (m, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.71 (d, J = 15.6 Hz, 1H), 3.62–3.74 (m, 4H), 1.66–1.81 (m, 4H), 1.51–1.55 (m, 1H), 1.32–1.44 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 156.6, 149.7, 149.6, 139.7, 132.9, 124.5, 105.8, 81.7, 68.9, 51.7, 50.0, 46.3, 28.8, 27.2, 14.8. HRMS (EI+)

calcd for $C_{15}H_{17}N_4O_3^{35}Cl$ (M^+), 336.0989; found, 336.0988; calcd for $C_{15}H_{17}N_4O_3^{37}Cl$ (M^+), 338.0960; found, 338.0968.

Data for 9b: yield, 62%; mp, 159.1–160.5 °C; 1H NMR (400 Mz, DMSO- d_6) δ 7.48 (s, 1H), 5.30 (d, J = 3.2 Hz, 1H), 5.24 (d, J = 15.4 Hz, 1H), 4.98 (s, 1H), 4.78 (d, J = 15.4 Hz, 1H), 3.76–3.87 (m, 1H), 3.60–3.71 (m, 3H), 2.12 (d, J = 14.0 Hz, 1H), 1.82–1.96 (m, 2H), 1.64–1.77 (m, 2H), 1.48–1.60 (m, 1H); ^{13}C NMR (100 Mz, DMSO- d_6) δ 155.7, 154.1, 140.5, 135.6, 107.0, 82.7, 69.4, 49.4, 48.3, 46.2, 29.4, 26.5, 14.9. HRMS (EI+) calcd for $C_{13}H_{15}N_4O_3S^{35}Cl$ (M^+), 342.0553; found, 342.0548; calcd for $C_{13}H_{15}N_4O_3S^{37}Cl$ (M^+), 344.0524; found, 344.0564.

Data for 9c: yield, 77%; mp, 180.5–181.2 °C; 1H NMR (400 Mz, DMSO- d_6) δ 7.29–7.37 (m, 5H), 5.33 (d, J = 3.1 Hz, 1H), 5.02 (d, J = 15.0 Hz, 1H), 4.95 (s, 1H), 4.85 (d, J = 15.0 Hz, 1H), 3.68–3.75 (m, 1H), 3.48–3.64 (m, 3H), 2.14 (d, J = 13.1 Hz, 1H), 1.81–1.93 (m, 2H), 1.51–1.70 (m, 3H); ^{13}C NMR (100 Mz, DMSO- d_6) δ 156.6, 136.4, 128.8, 128.3, 128.0, 106.7, 83.0, 69.7, 54.8, 48.6, 46.7, 29.5, 26.5, 15.0. HRMS (EI+) calcd for $C_{16}H_{19}N_3O_3$ (M^+), 301.1426; found, 301.1429.

Data for 9d: yield, 70%; mp, 156.9–158.3 °C; 1H NMR (400 Mz, DMSO- d_6) δ 7.29–7.34 (m, 4H), 5.33 (d, J = 4.0 Hz, 1H), 5.05 (d, J = 15.1 Hz, 1H), 4.96 (s, 1H), 4.75 (d, J = 15.1 Hz, 1H), 3.66–3.73 (m, 1H), 3.55–3.60 (m, 3H), 2.14 (d, J = 13.6 Hz, 1H), 1.82–1.95 (m, 2H), 1.51–1.71 (m, 3H); ^{13}C NMR (100 Mz, DMSO- d_6) δ 156.5, 134.9, 133.8, 129.7, 129.0, 106.8, 83.0, 69.6, 54.4, 48.9, 46.6, 29.6, 26.5, 15.0. HRMS (EI+) calcd for $C_{16}H_{18}N_3O_3^{35}Cl$ (M^+), 335.1037; found, 335.1044; calcd for $C_{16}H_{18}N_3O_3^{37}Cl$ (M^+), 337.1007; found, 337.1036.

X-ray Diffraction. Compound **8a** was recrystallized by slow evaporation from dichloromethane to afford a suitable single crystal. Colorless blocks of **8a** (0.421 mm $\times$ 0.369 mm $\times$ 0.327) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo K α radiation (λ = 0.71073 Å; θ_{max} = 25.50; 7954 measured reflections; 2958 independent reflections (R_{int} = 0.0985). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.7954 and T_{max} = 1.0000). The structure was solved by direct methods with SHELXS-97 (31). All other calculations were performed with Bruker SAINT System and Bruker SMART programs (32). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0903P)^2 + 0.0000P]$ gave final values of R = 0.0744, ωR = 0.1670, and GOF (F) = 0.977 for 213 variables and 2958 contributing reflections. Maximum shift/error = 0.000(3) and max/min residual electron density = 0.510/−0.522 e Å $^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Compound **9a** was recrystallized by slow evaporation from dichloromethane to afford a suitable single crystal. Colorless blocks of **9a** (0.468 mm $\times$ 0.391 mm $\times$ 0.229) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo K α radiation (λ = 0.71073 Å; θ_{max} = 27.00; 8730 measured reflections; 3254 independent reflections (R_{int} = 0.0649). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.84981 and T_{max} = 1.0000). The structure was solved by direct methods with SHELXS-97. All other calculations were performed with Bruker SAINT System and Bruker SMART programs. Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0585P)^2 + 0.1852P]$ gave final values of R = 0.0482, ωR = 0.1193, and GOF (F) = 1.032 for 208 variables and 3254 contributing reflections. Maximum shift/error = 0.000(3) and max/min residual electron density = 0.280/−0.215 e Å $^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

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 Aphid (*Aphis craccivora*). The activities of insecticidal compounds against cowpea aphid were tested by leaf-dip method according to our previously reported procedure (25, 26). 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; burgeons were placed in a 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.

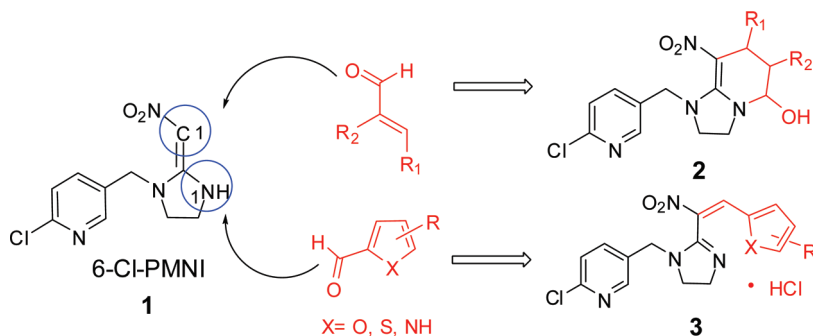
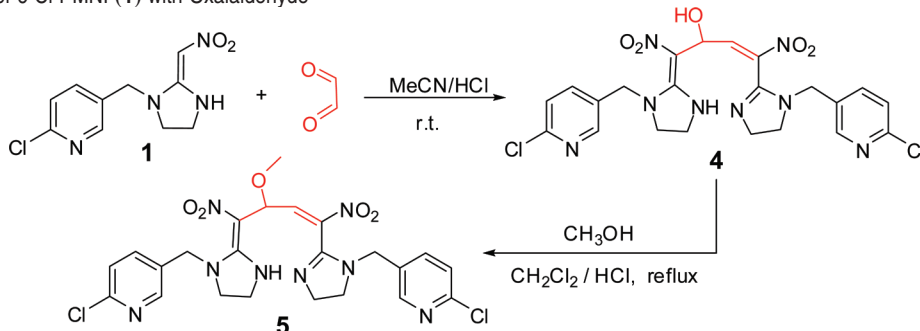
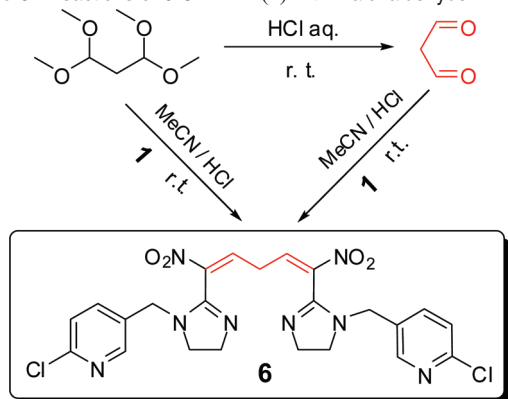
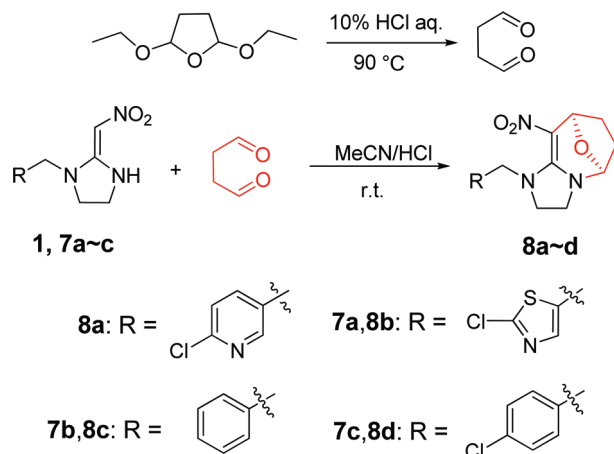
Insecticidal Test for Armyworm (*Pseudaletia separata* Walker). The activities of insecticidal compounds against armyworm were tested using previously reported procedures (33, 34). The insecticidal activity against armyworm was tested by foliar application. Individual corn (*Zea mays*) leaves were placed 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 Brown Planthopper (*Nilaparvata lugens*). The bioassay against brown planthopper followed the microtopical application technique reported by Nagata (35). Macropterous adult females (2–3 days old, unmated) were used as test animals. Insecticidal compounds were diluted to a series of concentrations with acetone. Under carbon dioxide anesthesia, a droplet (0.08 μ L) of insecticide solution was applied topically to the prothorax notum of test hoppers with a hand microapplicator (Burkard Manufacturing Co. Ltd., Rickmansworth, U.K.). About 30 insects were treated at each concentration, and every treatment was repeated three times. The controls used acetone instead of insecticide solution. The treated insects were reared on seedlings cultured soilless in the rearing box (20 $\times$ 20 $\times$ 10 cm) at 25 ± 1 °C and 16/8 h light/dark. The results were checked after 48 h. LD $_{50}$ values were determined on the basis of standard probit analysis.

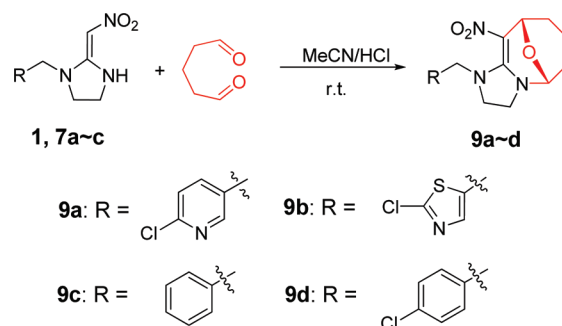
RESULTS AND DISCUSSION

Synthesis. Compounds **1** and **7a–c** were prepared according to the literature (36). **1** and **7a–c** were cyclic β -nitroenamines, which consist of push–pull ethylene systems with a donor (amine) at one end and an acceptor (nitro) at the other end of the ethylene. These nitroenamines manifest themselves as common enamines in electrophilic reactions and could react with a variety of electrophiles, with electrophilic attack proceeding at either or both of two nucleophilic centers (C1 and N1 in **Scheme 1**) (36–40). Shiokawa et al. made tremendous efforts on the chemical derivatizations of cyclic nitroenamine units by attack of the electrophile (such as sulfurizocyanatidic chloride, thiocyanogen, phenyl isocyanate, benzoyl isothiocyanate, and acrylate), and some neonicotinoid derivatives with desirable activities were found (40). Dialdehydes bearing two electrophilic centers are good electrophiles, which could readily react with cyclic β -nitroenamine. The synthetic procedures for the title compounds are depicted in **Schemes 2–5**.

Initially, the reaction of compound **1** with oxalaldehyde in acetonitrile catalyzed by concentrated hydrochloric acid at room temperature was investigated; the reaction proceeded smoothly, and a white powder was precipitated from the reaction mixture (**Scheme 2**). Analysis of the isolated precipitate by NMR showed the formation of 1:2 condensation compound **4**. HRMS lent further support for formation of divalent compound **4**. 1H NMR spectra of compound **4** showed the signal of NH at 9.01 ppm, which agreed with the one in compound **1** (8.90 ppm). Complete disappearance of the OH signal at 3.98 ppm on deuteration showed the existence of a hydroxyl group in **4**. To further confirm the structure of **4**, the etherization of **4** by methanol was carried out in refluxing dichloromethane catalyzed by concentrated HCl, and compound **5** was formed as expected. When malonaldehyde was subjected to reaction with **1** according to the aforementioned reaction conditions, a novel type of divalent neonicotinoid **6** was generated. Different from compound **4**, no hydroxyl group was

Scheme 1. Reactions of 6-Cl-PMNI (**1**) with α,β -Unsaturated Aldehydes and Five-Membered Aromatic Aldehydes**Scheme 2.** Reactions of 6-Cl-PMNI (**1**) with Oxalaldehyde**Scheme 3.** Reactions of 6-Cl-PMNI (**1**) with Malonaldehyde**Scheme 4.** Reactions of 6-Cl-PMNI (**1**) with Succinaldehyde

retained in compound **6**. The latter observation revealed that reaction of **1** with 1,1,3,3-tetramethoxypropane in acetonitrile catalyzed by concentrated hydrochloric acid at room temperature

Scheme 5. Reactions of 6-Cl-PMNI (**1**) with Glutaraldehyde

could also proceed to afford **6** (Scheme 3), which provided one-pot operation for the procurement of compound **6**. Previously, Kagabu also reported some divalent neonicotinoids, in which two imidacloprid molecules were coupled between two nitrogen atoms on the imidazoline (**9**), whereas linking two carbon atoms as described here could be another way to construct novel divalent neonicotinoids.

Subsequently, we embarked on reaction of **1** with succinaldehyde. Commercially available 2,5-diethoxytetrahydrofuran was stirred in 0.1 M HCl at 90 °C, affording succinaldehyde, and this mixture was used immediately without further purification. Upon treatment of **1** with succinaldehyde in the presence of hydrochloric acid in acetonitrile at room temperature, a white powder was obtained after column chromatography. The product was found to be a peculiar oxabridged compound **8a** rather than a divalent compound on the basis of its spectral and analytical data. Reaction of glutaraldehyde with **1** was accomplished under identical conditions, affording the oxabridged compound **9a** in 76% yield. Oxabridged compounds **8b-d** and **9b-d**, analogues of **8a** and **9a**, respectively, were easily obtained under similar conditions.

Crystal Structure Analysis. The oxabridged structure of compounds **8a** and **9a** was unambiguously confirmed by X-ray crystallographic diffraction analysis (Figures 1 and 2), which

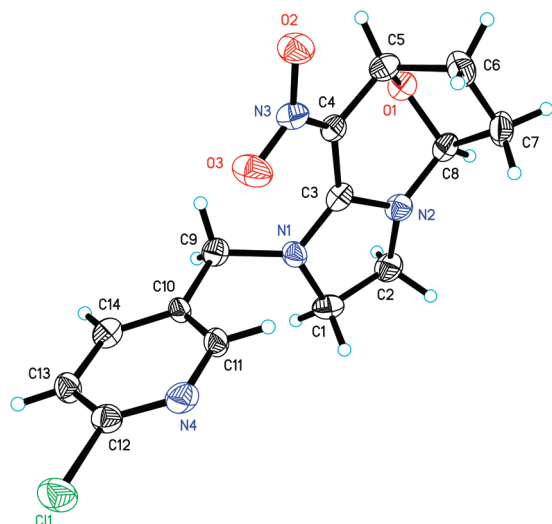


Figure 1. ORTEP drawing of **8a** with the atom-labeling scheme. Ellipsoids are drawn at the 30% probability level.

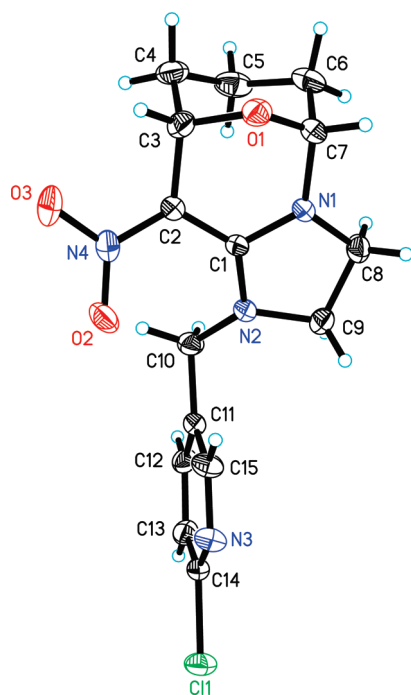


Figure 2. ORTEP drawing of **9a** with the atom-labeling scheme. Ellipsoids are drawn at the 30% probability level.

successfully provided the most convincing evidence for their proposed molecular structures. Although most key bond angles and distances are comparable for compounds **8a** and **9a**, rather surprisingly, the torsion angles of the chains containing oxygen are considerably different. When the torsion angle of **8a** was positive, the corresponding one of **9a** was negative and vice versa. For **8a**, the nitrogen atom in the pyridine ring and the oxygen atom pointed in opposite directions, whereas these two atoms in **9a** were oriented in the same direction.

Insecticidal Activities. Table 1 shows the insecticidal activities of the title compounds against cowpea aphid and armyworm. Divalent compound **4** showed moderate insecticidal activity against cowpea aphid at 500 mg L⁻¹ and high activity against armyworm with an LC₅₀ value of 0.19271 mmol L⁻¹. The etherified product **5** also had high insecticidal activity against cowpea aphid. Divalent compound **6** not only exhibited higher

Table 1. Insecticidal Activities of Compounds **4**, **5**, **6**, **8a–d**, and **9a–d** and Imidacloprid against Cowpea Aphid (*Aphis craccivora*) and Armyworm (*Pseudaletia separata* Walker)

compd	<i>Aphis craccivora</i>		<i>Pseudaletia separata</i> Walker	
	mortality (%, 500 mg L ⁻¹)	LC ₅₀ (mmol L ⁻¹)	mortality (%, 500 mg L ⁻¹)	LC ₅₀ (mmol L ⁻¹)
4	78.1	nt ^a	100	0.19471
5	97.7	nt	100	nt
6	100	0.00951	100	0.02798
8a	100	0.00471	100	0.03873
8b	100	0.00883	100	0.04956
8c	13.6	nt	0	nt
8d	95.7	nt	0	nt
9a	87.3	nt	0	nt
9b	98.2	nt	0	nt
9c	55.6	nt	0	nt
9d	38.9	nt	0	nt
imidacloprid	100	0.03502	100	0.12549
6-Cl-PMNI	100	0.00512	100	0.07087

^a Not tested.

Table 2. Insecticidal Activities of Compounds **8a** and **9a** and Imidacloprid against Imidacloprid-Resistant Brown Planthopper (*Nilaparvata lugens*)

strain	compd	$y = a + bx$	LC ₅₀ (ng/pest)	toxic ratio ^a
sensitive	8a	$y = 7.3127 + 2.0474x$	0.0742 ± 0.0106	1.77
	9a	$y = 3.9543 + 1.6936x$	4.1440 ± 0.6136	0.32
	imidacloprid	$y = 7.1823 + 2.4778x$	0.1316 ± 0.0154	1.00
resistant	8a	$y = 5.4068 + 1.3225x$	0.4925 ± 0.0811	50.00
	9a	$y = 3.1320 + 1.4613x$	18.9795 ± 2.3501	1.17
	imidacloprid	$y = 2.5873 + 1.7930x$	22.1614 ± 3.7522	1.00

^a Toxic ratio is defined as the ratio of the imidacloprid's LC₅₀ value for baseline toxicity and the compounds' LC₅₀ value.

activity than imidacloprid against cowpea aphid, but also had excellent activity against armyworm, which indicated that linkage of the two molecules in this way could maintain the insecticidal activities.

Oxabridged compound **8a** constructed by succinaldehyde demonstrated remarkable activities, which were higher than that of imidacloprid, against cowpea aphid (LC₅₀ = 0.00471 mmol L⁻¹) and armyworm (LC₅₀ = 0.03873 mmol L⁻¹). Intriguingly, the insecticidal activity of compound **8a** against imidacloprid-resistant brown planthopper was 50-fold higher than that of imidacloprid based on the value of LC₅₀, and **9a** also exhibited higher activity than imidacloprid (Table 2). The higher insecticidal activity of **8a** than imidacloprid might be attributed to the improved hydrophobicity. Replacement of 2-chloro-5-pyridine in **8a** with 2-chloro-5-thiazole to generate analogue **8b** maintained high insecticidal activity, which was consistent with the fact that the 2-chloro-5-thiazole unit has been proved to be an effective bioisosteric replacement for the 2-chloro-5-pyridine. Benzyl analogue **8c** and 4-chlorobenzyl counterpart **8d** showed low insecticidal activities as anticipated. Unexpectedly, compound **9a** constructed by glutaraldehyde had moderate activity against cowpea aphid but was inactive against armyworm. Analogues **9c** and **9d** also exhibited weak activities against cowpea aphid but no activity against armyworm. The volume or conformation of substituent at the N3-atom on the imidazoline had an influence on activities (1, 7, 10, 41), and the difference of ring size and conformation between **8a** and **9a** could possibly account in part for the higher potency of **8a** than of **9a**.

In conclusion, a series of divalent and oxabridged neonicotinoids were designed and synthesized by incorporating dialdehydes to nitromethylene analogues of imidacloprid. The bioassays showed that some of the compounds exhibited excellent insecticidal activities against cowpea aphid and armyworm. Further bioassay demonstrated that compound **8a** displayed a 50-fold higher activity against imidacloprid-resistant brown planthopper than imidacloprid. Oxabridged **8a** constructed by succinaldehyde had better activities than **9a** constructed by glutaraldehyde. Studies on the modes of action of **8a** and further field trials and structural modifications of compound **8a** are underway.

Supporting Information Available: CIF data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

LITERATURE CITED

- (1) *Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor*; Yamamoto, I., Casida, J. E., Eds.; Springer-Verlag: Tokyo, Japan, 1999; pp 177–209.
- (2) Jeschke, P. In *Insecticides Design Using Advanced Technologies*; Ishaaya, I., Nauen, R., Horowitz, A. R., Eds.; Springer-Verlag: Dordrecht, The Netherlands, 2007; pp 151–195.
- (3) Nauen, R.; Denholm, I.; Dennehy, T.; Nichols, R. News from the front line: reports from the global workshop on the stewardship of neonicotinoid insecticides, Honolulu, Hawaii, 5–6 June 2008. *Pest Manag. Sci.* **2008**, *64*, 1082–1083.
- (4) Talley, T. T.; Harel, M.; Hibbs, R. E.; Radić, Z.; Tomizawa, M.; Casida, J. E.; Taylor, P. Atomic interactions of neonicotinoids agonist with AChBP: Molecular recognition of the distinctive electronegative pharmacophore. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 7606–7611.
- (5) Tomizawa, M.; Maltby, D.; Talley, T. T.; Durkin, K. A.; Medzihradsky, K. F.; Burlingame, A. L.; Taylor, P.; Casida, J. E. Atypical nicotinic agonist bound conformations conferring subtype selectivity. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 1728–1732.
- (6) Ohno, I.; Tomizawa, M.; Durkin, K. A.; Naruse, Y.; Casida, J. E.; Kagabu, S. Molecular features of neonicotinoids pharmacophore variants interacting with the insect nicotinic receptor. *Chem. Res. Toxicol.* **2009**, *22*, 476–482.
- (7) Tomizawa, M.; Casida, J. E. Molecular recognition of neonicotinoid insecticide: the determinants of life or death. *Acc. Chem. Res.* **2009**, *42*, 260–269.
- (8) Jeschke, P.; Nauen, R. Neonicotinoids – from zero to hero in insecticide chemistry. *Pest Manag. Sci.* **2008**, *64*, 1084–1098.
- (9) Kagabu, S.; Itazu, Y.; Nishimura, K. Preparation of alkylene-tethered acyclic divalent neonicotinoids and their insecticidal activities for American cockroach (*Periplaneta americana* L.). *J. Pest. Sci.* **2004**, *29*, 40–42.
- (10) Ohno, I.; Tomizawa, M.; Durkin, K. A.; Casida, J. E.; Kagabu, S. Bis-neonicotinoids insecticides: observed and predicted binding interactions with the nicotinic receptor. *Bioorg. Med. Chem.* **2009**, *19*, 3449–3452.
- (11) Ohno, I.; Hirata, K.; Ishida, C.; Ihara, M.; Matsuda, K.; Kagabu, S. Proinsecticide candidates *N*-(5-methyl-2-oxo-1, 3-dioxol-4-yl)methyl derivatives of imidacloprid and 1-chlorothiazolylmethyl-2-nitroimino-imidazolidine. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4500–4503.
- (12) Tomizawa, M.; Kagabu, S.; Ohno, I.; Durkin, K. A.; Casida, J. E. Potency and selectivity of trifluoroacetylmino and pyrazinoylimino nicotinic insecticides and their fit at a unique binding site niche. *J. Med. Chem.* **2008**, *51*, 4213–4218.
- (13) Ohno, I.; Tomizawa, M.; Durkin, K. A.; Casida, J. E.; Kagabu, S. Neonicotinoids substituents forming a water bridge at the nicotinic acetylcholine receptor. *J. Agric. Food Chem.* **2009**, *57*, 2436–2440.
- (14) Kagabu, S.; Takagi, M.; Ohno, I.; Mikawa, T.; Miyamoto, T. Crown-capped imidacloprid: a novel design and insecticidal activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2947–2948.
- (15) Ihara, M.; Okajima, T.; Yamashita, A.; Oda, T.; Hirata, K.; Nishiwaki, H.; Morimoto, T.; Akamatsu, M.; Ashikawa, Y.; Kuroda, S.; Mega, R.; Kuramitsu, S.; Sattelle, D. B.; Matsuda, K. Crystal structures of *Lymnaea stagnalis* AChBP in complex with neonicotinoids insecticides imidacloprid and clothianidin. *Invert. Neurosci.* **2008**, *8*, 71–81.
- (16) Nauen, R.; Denholm, I. Resistance of insect pests to neonicotinoid insecticides: current status and future prospects. *Arch. Insect Biochem. Physiol.* **2005**, *58*, 200–215.
- (17) 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.
- (18) 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.
- (19) 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 mechanisms. *Pest Manag. Sci.* **2003**, *59*, 1355–1359.
- (20) Ninsin, K. D. Acetamiprid resistance and cross-resistance in the diamondback moth, *Plutella xylostella*. *Pest Manag. Sci.* **2004**, *60*, 839–841.
- (21) 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.
- (22) 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.
- (23) Kristensen, M.; Jespersen, J. B. Susceptibility to thiamethoxam of *Musca domestica* from Danish livestock farms. *Pest Manag. Sci.* **2008**, *64*, 126–132.
- (24) Tian, Z. Z.; Li, Z.; Huang, Q. C.; Xu, X. Y.; Yu, T.; Wu, Y. L.; Qian, X. H. Synthesis and bioactivities of novel neonicotinoids dioxolane compounds. *J. Chem. Res. (S)* **2006**, *10*, 620–622.
- (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) 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.
- (27) Shao, X. S.; Zhang, W. W.; Peng, Y. Q.; Li, Z.; Tian, Z. Z.; Qian, X. H. *cis*-Nitromethylene neonicotinoids as new nicotinic family: synthesis, structural diversity and insecticidal evaluation of hexahydroimidazo[1, 2- α]pyridine. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6513–6516.
- (28) Shao, X. S.; Li, Z.; Qian, X. H.; Xu, X. Y. Design, synthesis and insecticidal activities of novel analogues of neonicotinoids: replacement of nitromethylene with nitro-conjugated system. *J. Agric. Food Chem.* **2009**, *57*, 951–957.
- (29) Sands, R. D. Reaction of dimethyl 3-oxoglutarate with 1,3-dicarbonyl compounds. *J. Org. Chem.* **1983**, *48*, 3362–3363.
- (30) Fakstorp, B. J.; Raleigh, D.; Schniepp, L. E. Preparation and reactions of dialkoxytetrahydrofurans. *J. Am. Chem. Soc.* **1950**, *72*, 869–874.
- (31) Sheldrick, G. M. *SHELXTL (Version 5.0)*; University of Göttingen: Göttingen, Germany, 2001.
- (32) Bruker. SMART (Version 5.628). *SAINT (Version 6.45)*, and *SADABS*; Bruker AXS Inc.: Madison, WI, 2001.
- (33) 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*, 143–150.
- (34) Li, C.; Wang, Q. M.; Huang, R. Q.; Mao, C. H.; Shang, J.; Bi, F. C. Synthesis and insecticidal evaluation of propeptides of benzoylphenylureas. *J. Agric. Food Chem.* **2005**, *49*, 38–41.
- (35) Nagata, T. Insecticide resistance and chemical control of the rice planthopper, *Nilaparvata lugens* Stål. *Bull. Kyushu Natl. Agric. Exp. Stn.* **1982**, *22*, 49–164.

- (36) 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.
- (37) Rajappa, S. Nitroenamines: an update. *Tetrahedron* **1999**, *55*, 7065–7114 and references cited therein.
- (38) Komoto, I.; Seko, S. A new synthesis of β -nitroenamines by amination of nitroolefins with methoxyamines. *J. Chem. Soc., Perkin Trans. I* **1998**, 2957–2976.
- (39) Nazarenko, K. G.; Shvidenko, K. V.; Pinchuk, A. M.; Tolmachev, A. A. The reaction of cyclic nitroenamines with isocyanates. Synthesis of 1,6-polymethylene-6-nitromethyl-1,3,5-triazine-2,4-dione derivatives. *Monatsch. Chem.* **2005**, *136*, 211–215.
- (40) Aoki, I.; Tabuchi, T.; Minamida, I. Insecticidal nitro-substituted heterocyclic compounds. U.S. Patent 5122527, 1992.
- (41) Matsuda, K.; Shimomura, M.; Ihara, M.; Akamatsu, M.; Sattelle, D. B. Neonicotinoids show selective and diverse actions on their nicotinic receptor target: electrophysiology, molecular biology, and

receptor modeling studies. *Biosci., Biotechnol., Biochem.* **2005**, *69*, 1442–1452.

Received for review July 21, 2009. Revised manuscript received November 4, 2009. Accepted November 19, 2009. This work was financially supported by the National Basic Research Program of China (973 Program, 2010CB126100), the National High Technology Research and Development Program of China (863 Program, 2006AA10A201), the National Science Foundation China Program Grant (20872034), and the Program for New Century Excellent Talents in University (NCET070284). This work was also partly supported by the Shanghai Foundation of Science and Technology (08391911600, 0XD1401300, 073919107), the grant “Application of Nuclear Techniques in Agriculture” from the Chinese Ministry of Agriculture (Grant 200803034), and the Shanghai Leading Academic Discipline Project, Project B507.111 Project B07023.