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Design, Synthesis, and Particular Biological Behaviors of Chain-Opening Nitromethylene Neonicotinoids with Cis Configuration

Siyuan Lu, Xusheng Shao, Zhong Li, Zhiping Xu,* Shishuai Zhao, Yinli Wu, and Xiaoyong Xu*

Shanghai Key Laboratory of Chemistry Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

ABSTRACT: On the basis of the structure of heterocyclic-fused cis configuration derivatives and chain-opening neonicotinoids, two series of novel chain-opening tetrahydropyridine analogues were designed and synthesized. The preliminary bioassay tests were determined on cowpea aphid (*Aphis craccivora*) and armyworm (*Pseudaletia separata* Walker). The results showed that some of the target compounds exhibited repellent effects, whereas others showed good insecticidal activities.

KEYWORDS: *chain-opening, neonicotinoids, repellent effects, cis configuration, tetrahydropyridine*

INTRODUCTION

Neonicotinoids, as the fourth-generation insecticides after organophosphorus, carbamates, and pyrethroids, are the fastest growing synthetic insecticides on the market.[1] Their global sales reached U.S. $2.632 billion in 2009 and accounted for 23.7% of total market share of insecticides in 2008,[2] which were expected to take the biggest market of insecticides. With a thorough comprehension of the action mechanism, neonicotinoids are a class of insecticides targeting the insect nicotinic acetylcholine receptors (nAChRs).[3,4]

There are four common molecular features of neonicotinoids: (1) an aromatic heterocycle, (2) flexible linkage, (3) hydroheterocycles or guanidine/amidine, and (4) an electron-withdrawing group.[5] According to the structural characteristics of the third feature, the commercialized neonicotinoids can be subdivided into two categories: (1) cyclic compounds, including imidacloprid **1** (Figure 1), thiacloprid **2** (Figure 1), and thiamethoxam **3** (Figure 1); and (2) acyclic neonicotinoids, including nitenpyram **4** (Figure 1), acetamiprid **5** (Figure 1), clothianidin **6** (Figure 1), dinotefuran **7** (Figure 1), and sulfoxaflor **8** (Figure 1). Generally, compared with cyclic ones, acyclic neonicotinoids, which are defined as ring-opening or chain-opening neonicotinoids, exhibit a broader insecticidal spectrum.[6,7] The acyclic diamine skeleton was considered to be an effective bioisostere of imidazolidine and other heterocycles,[8] which made it possible for the reconstruction of an acyclic bioisostere to often acquire desirable bioactivities .

In previous work, we had reported the synthesis, bioactivities, and mode of action of nitromethylene neonicotinoids with fixed cis configuration.[9] The nitro group was fixed to form the cis configuration through the introduction of a tetrahydropyridine ring, which helps to improve the photostability. The preliminary bioassay results showed that their insecticidal activities against resistant strain brown planthopper were higher than that of imidacloprid.[5] Accordingly, it attracted us to investigate what chain-opening analogues of cis configuration nitromethylene neonicotinoids would provide.

To further explore the bioactivities of chain-opening analogues of cis configuration nitromethylene neonicotinoids, two series of compounds with tetrahydropyridine-fused neonicotinoids were designed and synthesized. Series 1 (see Table 1) was designed and synthesized on the basis of the structures of nitenpyram **4** (Figure 2) and acetamiprid **5** (Figure 2), wherein the substituent R_3 was an alkyl group. In the design of series 2, R_3 was replaced by a hydrogen atom as found in the structures of clothianidin **6** (Figure 2) and dinotefuran **7** (Figure 2).

In this paper, the syntheses of two series of chain-opening nitromethylene neonicotinoids and their particular biological behaviors or bioactivities are reported.

MATERIALS AND METHODS

Instrumentation and Chemicals. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Melting points (mp) were recorded on a Büchi B540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 MHz) or Bruker WP-400SY (400 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra were recorded under electron impact (70 eV) conditions using a MicroMass GCT CA 055 instrument. Combustion analyses for elemental composition were made with an Elementar vario EL III. GC mass spectra were recorded using a HP 6890 gas chromatograph and HP 5973 mass selective detector. 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. *Synthesis of Series 1 (Scheme 1). N-((6-Chloropyridin-3-yl)methyl)ethanamine (**19**).* Compound **19** was prepared as described in the literature[10] in 70.3% yield: GC-MS, *m*/*z* (%) 170 ([M]$^+$, 20), 155 (80), 126 (100), 114 (10), 90 (12).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-1-(methylthio)-2-nitroethenamine (**20**).* Compound **20** was prepared as described in the literature[11] in 18.5% yield: GC-MS, *m*/*z* (%) 242 ([M]$^+$ − 46, 53), 227 (15), 213 (100), 169 (45), 155 (28), 141 (29), 126 (91), 90 (12).

*N-Methyl-1-(methylthio)-2-nitroethenamine (**22**).* To the solution of compound **21** (15.0 g, 90 mmol) in acetonitrile (50 mL) was added dropwise 60−75% aqueous methanamine (4.7 g, 90 mmol) at 0

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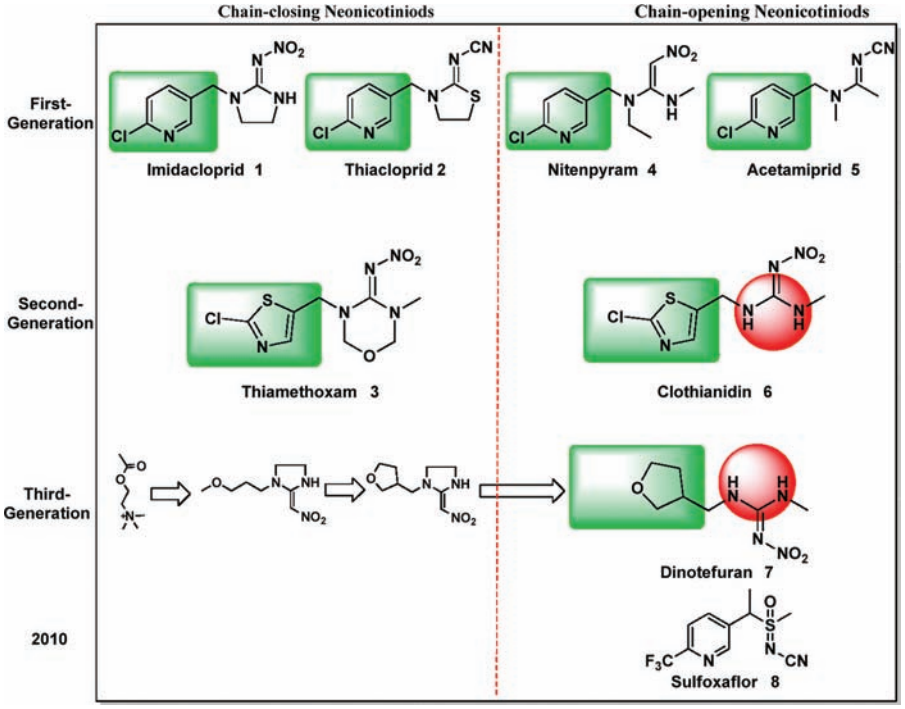

Figure 1. Commercialized neonicotinoids.

°C, and the resulting solution was stirred at room temperature for 24 h. The reaction was evaporated to dryness, and the residue was purified by chromatography over silica gel (petroleum ether/ethyl acetate, 1:1) to give 4.7 g (35.1% yield) of **22** as a yellow solid: GC-MS, *m*/*z* (%) 148 ($[M]^+$, 30), 101 (100), 84 (23), 55 (96).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-N-methyl-2-nitroethene-1,1-diamine (**23**).* Method 1. *N*-((6-Chloropyridin-3-yl)-methyl)-*N*-ethyl-*N*-methyl-2-nitroethene-1,1-diamine was prepared as described in the literature[11] in 29.5% yield: mp, 78.5−80.1 °C.

Method 2. A mixture of compound **22** (5.00 g, 34 mmol), compound **19** (5.78 g, 34 mmol), and AgOAc (5.8 g, 17 mmol) in anhydrous ethanol (30 mL) was stirred at 25 °C and monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure followed by chromatography purification on silica gel (dichloromethane/ethanol, 25:1) to give 4.0 g (38.1% yield) of **23** as a yellow solid: mp, 78.1−79.6 °C.

*6-(((6-Chloropyridin-3-yl)methyl)(ethyl)amino)-1-methyl-5-nitro-1,2,3,4-tetrahydropyridin-2-ol (**10a**).* To a mixture of compound **23** (0.3 g, 1.1 mmol), acrylaldehyde (0.21 mL, 3.3 mol), and acetonitrile (10 mL) were added two drops of $BF_3{\cdot}Et_2O$. The resulting solution was stirred at 40 °C for 4 h, evaporated to dryness, and purified by chromatography over silica gel (dichloromethane/acetone, 1:1) to give 0.05 g (18.0% yield) of **10a** as a pale white solid: mp, 165.1−168.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.77 (d, J = 5.4 Hz, 0.5H), 7.58 (d, J = 5.4 Hz, 0.5H), 7.31 (d, J = 8.2 Hz, 1H), 4.81 (s, 1H), 4.44−4.50 (m, 2H), 4.16 (d, J = 14.4 Hz, 0.5H), 4.14(d, J = 14.4 Hz, 0.5H), 2.96−3.26 (m, 2H), 2.96 (s, 3H), 2.70−2.88 (m, 2H), 1.92−2.05 (m, 2H), 1.16−1.26 (m, 3H); IR (KBr, cm^{-1}) 3200, 1560, 1507, 1461, 1381, 730; MS (ES+) calcd for $C_{14}H_{20}{}^{35}ClN_4O_3$ $(M + H)^+$, 327 (found, 327).

*N-((6-Chloropyridin-3-yl)methyl)-6-ethoxy-N-ethyl-1-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**10b**).* To a solution of compound **10a** (0.3 g, 0.9 mmol) in ethanol (10 mL) were added two drops of $BF_3{\cdot}Et_2O$. The resulting solution was refluxed for 6 h and then evaporated to dryness. The residue was purified by chromatography over silica gel (dichloromethane/acetone, 5:1) to give 0.06 g (18.8% yield) of **10b** as a yellow solid:[12] mp, 131.1−133.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 7.5 Hz, 0.5H), 7.64 (d, J = 7.5 Hz, 0.5H), 7.3 (d, J = 8.2 Hz, 1H), 4.35−4.48 (m, 2H), 4.18 (d, J = 14.9 Hz, 0.5H), 4.15 (d, J = 14.9 Hz, 0.5H), 2.94−3.52 (m, 4H), 2.89 (s, 3H), 2.75 (t, J = 7.7 Hz, 2H), 1.82−2.00 (m, 2H), 1.08−1.27 (m, 6H); IR (KBr, cm^{-1}) 2891, 1559, 1469, 1380, 1281, 1246, 1249, 1096, 729; HRMS (EI+) calcd for $C_{16}H_{23}{}^{35}ClN_4O_3$ (M^+), 354.1459 (found, 354.1452).

*General Synthetic Procedure for **10c−e** and **11a−e**.* A catalytic amount of $BF_3{\cdot}Et_2O$ was added to the mixture of compound **23** (0.3 g, 1.1 mmol), acrylaldehyde or crotonaldehyde (3.3 mmol), and the corresponding alcohol (10 mL), and then the mixture was heated to 40 °C. The resulting solution was stirred at 40 °C and monitored by TLC. The reaction was evaporated to dryness, and the residue was purified by chromatography over silica gel (dichloromethane/acetone, 1:1) to give the corresponding product.[13]

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-6-methoxy-1-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**10c**):* yield, 16.0%; mp, 151.1−155.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J = 1.9 Hz, 1H), 7.83 (d, J = 6.9 Hz, 0.5H), 7.62 (d, J = 6.9 Hz, 0.5H), 7.32 (d, J = 7.8 Hz, 1H), 4.26−4.49 (m, 2H), 4.09−4.23 (m, 1H), 2.94−3.29 (m, 5H), 2.91 (s, 3H), 2.73 (m, 2H), 1.78−2.04 (m, 2H), 1.23 (m, 3H); IR (KBr, cm^{-1}) 2899, 1561, 1505, 1281, 1096, 729; HRMS (ES+) calcd for $C_{15}H_{21}N_4O_3{}^{35}ClNa$ $(M + Na)^+$, 363.1200 (found, 363.1196); calcd for $C_{15}H_{21}N_4O_3{}^{37}ClNa$ $(M + Na)^+$, 365.1170 (found, 365.1186).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-1-methyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine (**10d**):* yield, 17.8%; mp, 110.1−114.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 1.7 Hz, 1H), 7.79 (d, J = 7.3 Hz, 0.5H), 7.61 (d, J = 7.3 Hz, 0.5H), 7.29 (d, J = 8.2 Hz, 1H), 4.32−4.45 (m, 2H), 4.21 (d, J = 14.8 Hz, 0.5H), 4.09 (d, J = 14.8 Hz, 0.5H), 2.86−3.51 (m, 4H), 2.86 (s, 3H), 2.72 (m, 2H), 1.79−1.99 (m, 2H), 1.54 (m, 2H), 1.19 (t, J = 6.9 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H); IR (KBr, cm^{-1}) 2900, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 730; HRMS (ES+) calcd for $C_{17}H_{26}N_4O_3{}^{35}Cl$ $(M + H)^+$, 369.1693 (found, 369.1667); calcd for $C_{17}H_{26}N_4O_3{}^{37}Cl$ $(M + H)^+$, 371.1664 (found, 371.1671).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-6-isopropoxy-1-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**10e**):* yield, 19.8%; mp, 112.8−116.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.78 (d, J = 7.6 Hz, 0.5H), 7.67 (d, J = 7.6 Hz, 0.5H), 7.32 (d, J = 7.8 Hz, 1H), 4.40−4.46 (m, 2H), 4.17 (t, J = 16.2 Hz, 1H), 2.87−3.58 (m, 6H), 2.71−2.77 (m, 2H), 1.83−1.94 (m, 2H), 1.09−1.22 (m, 9H); IR (KBr, cm^{-1}) 2897, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 730; HRMS

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Table 1. Compounds of Series 1 and 2

compd	R_1	R_2	R_3	R_4
10a	H	H	ethyl	methyl
10b	H	ethyl	ethyl	methyl
10c	H	methyl	ethyl	methyl
10d	H	*n*-propyl	ethyl	methyl
10e	H	isopropyl	ethyl	methyl
11a	methyl	methyl	ethyl	methyl
11b	methyl	ethyl	ethyl	methyl
11c	methyl	*n*-propyl	ethyl	methyl
11d	methyl	isopropyl	ethyl	methyl
11e	methyl	allyl	ethyl	methyl
12a	H	methyl	methyl	methyl
12b	H	ethyl	methyl	methyl
12c	H	*n*-propyl	methyl	methyl
12d	H	isopropyl	methyl	methyl
12e	H	allyl	methyl	methyl
13a	methyl	methyl	methyl	methyl
13b	methyl	ethyl	methyl	methyl
13c	methyl	*n*-propyl	methyl	methyl
13d	methyl	isopropyl	methyl	methyl
14a	methyl	ethyl	H	methyl
14b	methyl	*n*-propyl	H	methyl
14c	methyl	isopropyl	H	methyl
15a	ethyl	methyl	H	methyl
15b	ethyl	ethyl	H	methyl
15c	ethyl	*n*-propyl	H	methyl
15d	ethyl	isopropyl	H	methyl
16a	methyl	methyl	H	ethyl
16b	methyl	ethyl	H	ethyl
16c	methyl	*n*-propyl	H	ethyl
16d	methyl	isopropyl	H	ethyl
17a	ethyl	methyl	H	ethyl
17b	ethyl	ethyl	H	ethyl
17c	ethyl	*n*-propyl	H	ethyl
17d	ethyl	isopropyl	H	ethyl

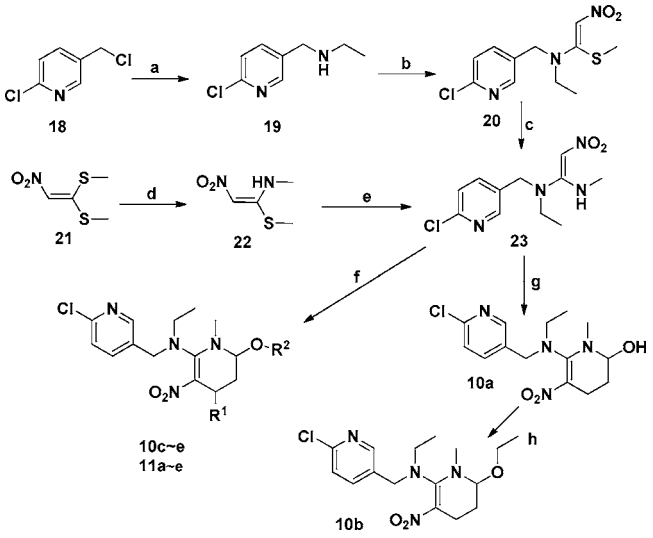
(ES+) calcd for $C_{17}H_{25}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 391.1513 (found, 391.1513); calcd for $C_{17}H_{25}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 393.1483 (found, 393.1512).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-6-methoxy-1,4-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**11a**):* yield, 22.7%; mp, 125.1−129.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.95 (d, J = 5.0 Hz, 0.5H), 7.50 (d, J = 5.0 Hz, 0.5H), 7.29 (d, J = 7.8 Hz, 1H), 4.30−4.47 (m, 2H), 4.20 (m, 1H), 3.02−3.41 (m, 5H), 2.95 (s, 3H), 2.28 (m, 1H), 1.59−1.69 (m, 2H), 1.30 (t, J = 6.7 Hz, 3H), 0.98−1.18 (m, 3H); IR (KBr, cm^{-1}) 2900, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 730; HRMS (ES+) calcd for $C_{16}H_{23}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 377.1356 (found, 377.1324); calcd for $C_{16}H_{23}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 379.1327 (found, 379.1336).

*N-((6-Chloropyridin-3-yl)methyl)-6-ethoxy-N-ethyl-1,4-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**11b**):* yield, 21.5%; mp, 120.1−123.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.95 (d, J = 5.0 Hz, 0.5H), 7.50 (d, J = 5.0 Hz, 0.5H), 7.29 (d, J = 7.8 Hz, 1H), 4.24−4.48 (m, 3H), 3.24−3.53 (m, 4H), 2.95 (s, 3H), 2.25−2.29 (m, 1H), 1.56−1.68 (m, 2H), 1.28 (m, 3H), 1.15 (t, J = 5.8 Hz, 3H), 0.98−1.07 (m, 3H); IR (KBr, cm^{-1}) 2900, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 730; HRMS (ES+) calcd for $C_{17}H_{25}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 391.1513 (found, 391.1513); calcd for $C_{17}H_{25}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 393.1483 (found, 393.1518).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-1,4-dimethyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine (**11c**):* yield, 22.8%; mp, 118.1−121.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.98 (d, J = 7.0 Hz, 0.5H), 7.50 (d, J = 7.0 Hz, 0.5H), 7.29 (d, J = 7.9 Hz, 1H), 4.53−4.28 (m, 3H), 3.03−3.41 (m, 4H), 2.95 (s, 3H), 2.28 (m, 1H), 1.51−1.69 (m, 2H), 1.51 (m, 2H), 1.28 (t, J = 8.7 Hz, 3H), 0.99−1.11 (m, 3H), 0.84 (t, J = 7.2 Hz, 3H); IR (KBr, cm^{-1}) 2900, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 730; HRMS (ES+) calcd for

Scheme 1. Preparation of Compounds 10a−11e of Series 1[a]



[a]Reagents and conditions: (a) ethylamine, MeCN, 0−5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, EtOH, refluxing; (c) methylamine, EtOH, refluxing; (d) methylamine, EtOH, refluxing; (e) compound **19**, AgOAc, EtOH, 25 °C; (f) acrylaldehyde or crotonaldehyde, corresponding alcohol, $BF_3{\cdot}Et_2O$, 40 °C; (g) acrylaldehyde, MeCN, $BF_3{\cdot}Et_2O$, 40 °C; (h) EtOH, $BF_3{\cdot}Et_2O$, 40 °C.

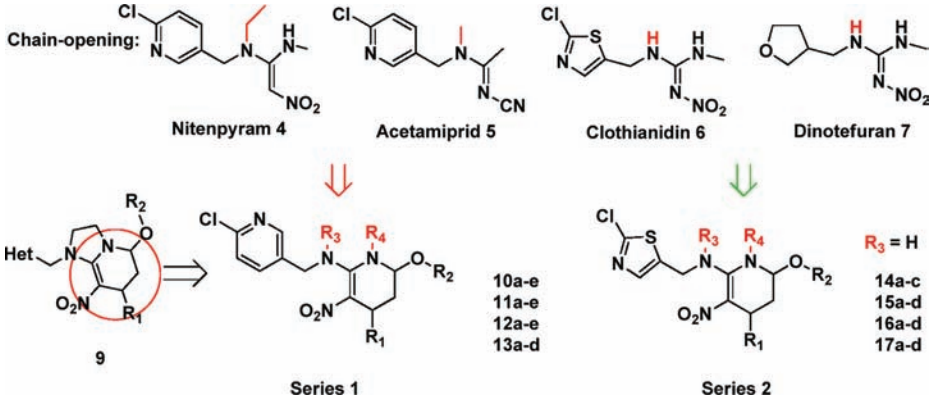


Figure 2. Chemical structures of cyclic and acyclic neonicotinoids, **9**, and its acyclic analogues.

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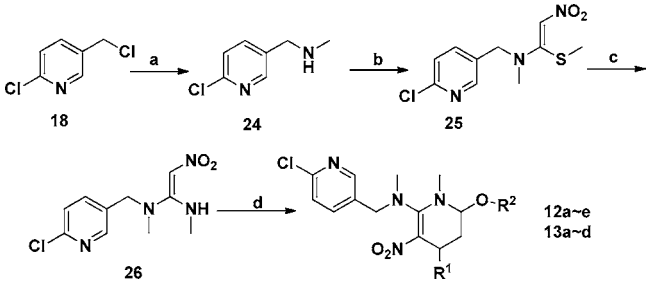
$C_{18}H_{28}N_4O_3{}^{35}Cl$ (M + H)$^+$, 383.1850 (found, 383.1815); calcd for $C_{18}H_{28}N_4O_3{}^{37}Cl$ (M + H)$^+$, 385.1820 (found, 385.1841).

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-6-isopropoxy-1,4-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**11d**):* yield, 23.2%; mp, 104.1−107.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.99 (d, J = 7.6 Hz, 0.5H), 7.51 (d, J = 7.6 Hz, 0.5H), 7.31 (d, J = 6.3 Hz, 1H), 4.25−4.49 (m, 3H), 3.06−3.67 (m, 3H), 2.95 (s, 3H), 2.22 (m, 1H), 1.54−1.72 (m, 2H), 1.28 (t, J = 6.69 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H), 1.07 (d, J = 6.1 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H); IR (KBr, cm^{-1}) 2896, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 729; HRMS (ES+) calcd for $C_{18}H_{28}N_4O_3{}^{35}Cl$ (M + H)$^+$, 383.1850 (found, 383.1831); calcd for $C_{18}H_{28}N_4O_3{}^{37}Cl$ (M + H)$^+$, 385.1820 (found, 385.1867).

*6-(Allyloxy)-N-((6-chloropyridin-3-yl)methyl)-N-ethyl-1,4-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine (**11e**):* yield, 25.5%; mp, 111.9−116.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.96 (d, J = 7.2 Hz, 0.5H), 7.50 (d, J = 7.2 Hz, 0.5H), 7.31 (d, J = 8.2 Hz, 1H), 5.75−5.83 (m, 1H), 5.15−5.24 (m, 2H), 4.28−4.49 (m, 3H), 3.77−4.02 (m, 2H), 3.01−3.36 (m, 2H), 2.92 (s, 3H), 2.28−2.32 (m, 1H), 1.56−1.78 (m, 2H), 1.28 (t, J = 6.1 Hz, 3H); IR (KBr, cm^{-1}) 2896, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 729; HRMS (ES+) calcd for $C_{18}H_{25}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 403.1513 (found, 403.1520); calcd for $C_{18}H_{25}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 405.1483 (found, 405.1486).

*General Synthetic Procedure for **12a−e** and **13a−d** (Scheme 2).* Compounds **24**, **25**, and **26** were synthesized following the same route as **19**, **20**, and **21**.[10,11] A catalytic amount of $BF_3{\cdot}Et_2O$ was added to the mixture of compound **26** (0.3 g, 1.1 mmol), acrylaldehyde or crotonaldehyde (3.3 mmol), and the corresponding alcohol (10 mL). Then the resulting solution was stirred at 40 °C, and the progress of the reaction was monitored by TLC. The reaction mixture was concentrated by rotary evaporator, and the residue was purified by chromatography on silica gel (dichloromethane/acetone, 1:1) to give the corresponding product.

Scheme 2. Preparation of Compounds 12a−13d of Series 1[a]



[a]Reagents and conditions: (a) methylamine, MeCN, 0−5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, EtOH, refluxing; (c) methylamine, EtOH, refluxing; (d) acrylaldehyde or crotonaldehyde, corresponding alcohol, $BF_3{\cdot}Et_2O$, 40 °C.

*N-((6-Chloropyridin-3-yl)methyl)-6-methoxy-N,1-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **12a**::* yield, 26.9%; mp, 101.2−104.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.72 (m, 0.5H), 7.61 (m, 0.5H), 7.34 (d, J = 8.1 Hz, 1H), 4.31−4.50 (m, 2H), 4.15 (m, 1H), 3.29−3.34 (m, 3H), 2.91 (s, 3H), 2.76 (m, 5H), 1.84−2.09 (m, 2H); IR (KBr, cm^{-1}) 2900, 1561, 1508, 1458, 1380, 1281, 1248, 1096, 730; HRMS (ES+) calcd for $C_{14}H_{19}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 349.1043 (found, 349.1013); calcd for $C_{14}H_{19}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 351.1014 (found, 351.1017).

*N-((6-Chloropyridin-3-yl)methyl)-6-ethoxy-N,1-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **12b**:* yield, 25.8%; mp, 94.3−98.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 4.35−4.39 (m, 2H), 4.14−4.17 (m, 1H), 3.38−3.49 (m, 2H), 2.88 (s, 3H), 2.76 (m, 5H), 1.84−1.87 (m, 2H), 1.17 (t, J = 6.9 Hz, 3H); IR (KBr, cm^{-1}) 2896, 1561, 1507, 1458, 1383, 1282, 1248, 1096, 730; HRMS (ES+) calcd for $C_{15}H_{21}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 363.1200 (found, 363.1189); calcd for $C_{15}H_{21}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 365.1170 (found, 365.1176).

*N-((6-Chloropyridin-3-yl)methyl)-N,1-dimethyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine **12c**:* yield, 21.4%; mp, 80.1−84.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J = 2.2 Hz, 1H), 7.63 (m, 1H), 7.33 (d, J = 8.2 Hz, 1H), 4.39−4.50 (m, 2H), 4.18 (m, 1H), 3.33−3.39 (m, 3H), 2.89 (s, 3H), 2.75 (m, 5H), 1.88−2.07 (m, 2H), 1.51−1.58 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); IR (KBr, cm^{-1}) 2896, 1561, 1507, 1458, 1381, 1281, 1248, 1096, 729; HRMS (ES+) calcd for $C_{16}H_{23}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 377.1356 (found, 377.1336); calcd for $C_{16}H_{23}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 379.1327 (found, 379.1295).

*N-((6-Chloropyridin-3-yl)methyl)-6-isopropoxy-N,1-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **12d**:* yield, 21.7%; mp, 85.2−89.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J = 2.1 Hz, 1H), 7.66 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 4.36−4.49 (m, 2H), 4.18 (m, 1H), 3.64 (m, 1H), 2.88 (s, 3H), 2.75−2.79 (m, 5H), 1.92 (m, 2H), 1.15 (d, J = 5.7 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H); IR (KBr, cm^{-1}) 2896, 1562, 1507, 1458, 1381, 1281, 1248, 1096, 729; HRMS (ES+) calcd for $C_{16}H_{23}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 377.1356 (found, 377.1352); calcd for $C_{16}H_{23}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 379.1327 (found, 379.1326).

*6-(Allyloxy)-N-((6-chloropyridin-3-yl)methyl)-N,1-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **12e**:* yield, 22.2%; mp, 76.0−80.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.62−7.75 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 5.83 (m, 1H), 5.19−5.25 (m, 2H), 3.93−4.55 (m, 5H), 2.89 (s, 3H), 2.78 (m, 2H), 2.75 (s, 3H), 1.86−2.10 (m, 2H); IR (KBr, cm^{-1}) 2901, 1562, 1507, 1458, 1381, 1281, 1248, 1096.34, 729; HRMS (ES+) calcd for $C_{16}H_{21}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 375.1200 (found, 375.1201); calcd for $C_{16}H_{21}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 377.1170 (found, 377.1175).

*N-((6-Chloropyridin-3-yl)methyl)-6-methoxy-N,1,4-trimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **13a**:* yield, 31.6%; mp, 126.1−130.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.85 (m, 0.5H), 7.52 (m, 0.5H), 7.33 (d, J = 7.9 Hz, 1H), 4.24−4.61 (m, 3H), 3.27 (m, 3H), 2.96 (s, 3H), 2.81 (s, 3H), 2.35 (m, 1H), 1.65 (m, 2H), 1.11−1.29 (m, 3H); IR (KBr, cm^{-1}) 2896, 1562, 1507, 1459, 1381, 1281.07, 1248, 1100, 727; HRMS (ES+) calcd for $C_{15}H_{21}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 363.1200 (found, 363.1202); calcd for $C_{15}H_{21}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 365.1170 (found, 365.1189).

*N-((6-Chloropyridin-3-yl)methyl)-6-ethoxy-N,1,4-trimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **13b**:* yield, 25.1%; mp, 126.1−129.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.83−7.86 (m, 0.5H), 7.52−7.53 (m, 0.5H), 7.32 (d, J = 8.2 Hz, 1H), 4.25−4.57 (m, 3H), 3.34−3.38 (m, 2H), 2.95 (s, 3H), 2.79 (s, 3H), 2.28−2.33 (m, 1H), 1.64 (m, 2H), 1.13−1.29 (m, 6H); IR (KBr, cm^{-1}) 2896, 1562, 1507, 1459, 1381, 1281, 1248, 1096, 727; HRMS (ES+) calcd for $C_{16}H_{23}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 377.1356 (found, 377.1333); calcd for $C_{16}H_{23}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 379.1326 (found, 379.1327).

*N-((6-Chloropyridin-3-yl)methyl)-N,1,4-trimethyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine **13c**:* yield, 32.7%; mp, 102.1−105.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.52−7.88 (m, 1H), 7.32 (d, J = 7.6 Hz, 1H), 4.30−4.59 (m, 3H), 3.25−3.39 (m, 2H), 2.95 (s, 3H), 2.80 (s, 3H), 2.30−2.35 (m, 1H), 1.63−2.09 (m, 2H), 1.51 (m, 2H), 1.14−1.29 (m, 3H), 0.84 (t, J = 6.9 Hz, 3H); IR (KBr, cm^{-1}) 2899, 1562, 1507, 1459, 1381, 1281, 1248, 1096, 730; HRMS (ES+) calcd for $C_{17}H_{25}N_4O_3Na^{35}Cl$ (M + Na)$^+$, 391.1513 (found, 391.1487); calcd for $C_{17}H_{25}N_4O_3Na^{37}Cl$ (M + Na)$^+$, 393.1483 (found, 393.1482).

*N-((6-Chloropyridin-3-yl)methyl)-6-isopropoxy-N,1,4-trimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **13d**:* yield, 30.1%; mp, 108.1−111.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.53−7.89 (m, 1H), 7.33 (d, J = 5.6 Hz, 1H), 4.34−4.80 (m, 3H), 3.26 (m, 1H), 2.94 (s, 3H), 2.79 (s, 3H), 2.24−2.29 (m, 1H), 1.28−2.04 (m, 2H), 1.10−1.26 (m, 6H), 1.06 (m, 3H); IR (KBr, cm^{-1}) 2897, 1562, 1508, 1459.79, 1381, 1281, 1248, 1096, 731; HRMS (ES+) calcd for $C_{17}H_{26}N_4O_3{}^{35}Cl$ (M + H)$^+$, 369.1649 (found, 369.1669); calcd for $C_{17}H_{26}N_4O_3{}^{35}Cl$ (M + H)$^+$, 371.1664 (found, 371.1690).

Synthesis of Series 2 (Scheme 3). *(2-Chlorothiazol-5-yl)-methanamine (**28**).* Compound **28** was prepared as described in the literature[14] in 32.4% yield: GC-MS, m/z(%) 148 ([M]$^+$, 15), 132 (9), 113 (100), 96 (1).

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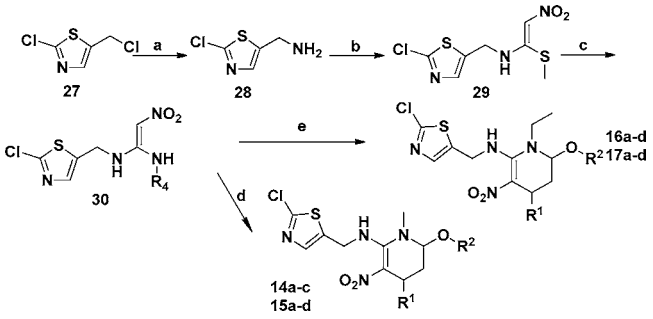
Scheme 3. Preparation of Series 2[a]



[a]Reagents and conditions: (a) $NH_3 \cdot H_2O$, EtOH, room temperature; (b) 1,1-bis(methylthio)-2-nitroethene, EtOH, refluxing; (c) methylamine or ethylamine, EtOH, refluxing; (d) CH_2Cl_2, crotonaldehyde or *trans*-2-pentenal, corresponding alcohol, $BF_3 \cdot Et_2O$, 20 °C; (e) CH_2Cl_2, crotonaldehyde or *trans*-2-pentenal, corresponding alcohol, $BF_3 \cdot Et_2O$, 20 °C.

*N-((2-Chlorothiazol-5-yl)methyl)-1-(methylthio)-2-nitroethenamine (**29**).* Compound **29** was prepared as described in the literature[15] in 63.8% yield: MS (ES+) calcd for $C_7H_8{}^{35}ClN_3O_2S_2$ (M^+), 265 (found, 265).

*N-((2-Chlorothiazol-5-yl)methyl)-N-methyl-2-nitroethene-1,1-diamine (**30**).* Compound **30** was prepared as described in the literature.[15]

*General Synthetic Procedure for **14a–c, 15a–d, 16a–d** and **17a–d**.* A mixture of compound **30** (0.375 g, 1.5 mmol), crotonaldehyde or *trans*-2-pentenal (3.3 mmol), and the corresponding alcohol (5 mL) in CH_2Cl_2 (10 mL) was stirred and cooled to 20 °C, and then a catalytic amount of $BF_3 \cdot Et_2O$ was added to the mixture. The resulting solution was stirred at 20 °C, and the progress of the reaction was monitored by TLC. The reaction was evaporated to dryness, and the residue was purified by chromatography over silica gel (dichloromethane/acetone, 12:1) to give the corresponding product.

*N-((2-Chlorothiazol-5-yl)methyl)-6-ethoxy-1,4-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **14a**:* yield, 14.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 7.49 (s, 1H), 4.59–4.62 (m, 2H), 4.45 (dd, J_1 = 4.4 Hz, J_2 = 7.6 Hz, 1H), 3.38–3.48 (m, 2H), 3.11 (s, 3H), 1.91–1.98 (m, 1H), 1.13–1.33 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 152.5, 139.5, 136.8, 116.4, 88.4, 62.7, 42.3, 40.4, 34.2, 25.9, 17.4, 15.3.; HRMS (ES+) calcd for $C_{13}H_{20}N_4O_3S^{35}Cl$ (M + H)$^+$, 347.0945 (found, 347.0946); calcd for $C_{13}H_{20}N_4O_3S^{37}Cl$ (M + H)$^+$, 349.0915 (found, 349.0932).

*N-((2-Chlorothiazol-5-yl)methyl)-1,4-dimethyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine **14b**:* yield, 13.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.48 (s, 1H), 4.59–4.64 (m, 2H), 4.39 (s, 1H), 3.29–3.47 (m, 2H), 3.12 (s, 3H), 1.83–1.96 (m, 1H), 1.56–1.63 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H), 1.08–1.15 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.4, 139.4, 137.0, 116.9, 89.0, 70.7, 42.3, 38.3, 31.5, 27.4, 22.9, 18.3, 10.7; HRMS (ES+) calcd for $C_{14}H_{22}N_4O_3S^{35}Cl$ (M + H)$^+$, 361.1101 (found, 361.1112); calcd for $C_{14}H_{22}N_4O_3S^{37}Cl$ (M + H)$^+$, 363.1072 (found, 363.1082).

*N-((2-Chlorothiazol-5-yl)methyl)-6-isopropoxy-1,4-dimethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **14c**:* yield, 14.7%; mp, 117.7–118.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 7.49 (s, 1H), 4.57–4.60 (m, 2H), 4.49 (dd, J_1 = 5.2 Hz, J_2 = 6.8 Hz, 1H), 3.18–3.23 (m, 1H), 3.10 (s, 3H), 1.91–1.94 (m, 1H), 1.15–1.22 (m, 2H), 1.22 (d, J = 4 Hz, 3H), 1.18 (d, 3H), 1.6 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3, 152.5, 139.5, 136.8, 116.4, 88.4, 62.7, 42.3, 40.4, 34.2, 25.9, 17.4, 15.3; IR (KBr, cm^{-1}) 2962, 1573, 1524, 1354, 1357, 1276, 1172, 1059, 919, 748; HRMS (ES+) calcd for $C_{14}H_{22}N_4O_3NaS^{35}Cl$ (M + Na)$^+$, 383.0921 (found, 383.0930); calcd for $C_{14}H_{22}N_4O_3NaS^{37}Cl$ (M + Na)$^+$, 385.0891 (found, 385.0880).

*N-((2-Chlorothiazol-5-yl)methyl)-4-ethyl-6-methoxy-1-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **15a**:* yield, 15.2%; mp, 101.0–102.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 7.49 (s, 1H), 4.59–4.62 (m, 2H), 4.39 (dd, J_1 = 4.8 Hz, J_2 = 8.4 Hz, 1H), 3.26 (s, 3H), 3.11 (s, 3H), 2.02–2.11 (m, 1H), 1.88–1.93 (m, 1H), 1.68–1.73 (m, 1H), 1.24–1.32 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 152.5, 139.5, 136.8, 116.4, 89.5, 53.9, 42.3, 40.5, 32.0, 29.9, 24.3, 11.5; IR (KBr, cm^{-1}) 2962, 1595, 1409, 1335, 1212, 1134, 1049, 963, 863; HRMS (ES+) calcd for $C_{13}H_{20}N_4O_3S^{35}Cl$ (M + H)$^+$, 347.0945 (found, 347.0951); calcd for $C_{13}H_{20}N_4O_3S^{37}Cl$ (M + H)$^+$, 349.0915 (found, 349.0926).

*N-((2-Chlorothiazol-5-yl)methyl)-6-ethoxy-4-ethyl-1-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **15b**:* yield, 14.3%; mp, 103.0–103.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.49 (s, 1H), 4.58–4.64 (m, 2H), 4.44 (dd, J_1 = 4.8 Hz, J_2 = 8.4 Hz, 1 H), 3.03–3.19 (m, 2H), 3.11 (s, 3H), 2.07–2.13 (m, 1H), 1.85–1.92 (m, 1H), 1.65–1.74 (m, 1H), 1.19–1.27 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.4, 139.5, 136.8, 116.3, 88.6, 62.5, 42.3, 40.3, 32.1, 30.7, 24.2, 15.3, 11.5; IR (KBr, cm^{-1}) 2970, 1585, 1524, 1409, 1335, 1276, 1146, 1059, 912, 748; HRMS (ES+) calcd for $C_{14}H_{22}N_4O_3S^{35}Cl$ (M + H)$^+$, 361.1101 (found, 361.1107); calcd for $C_{14}H_{22}N_4O_3S^{37}Cl$ (M + H)$^+$, 363.1072 (found, 363.1076).

*N-((2-Chlorothiazol-5-yl)methyl)-4-ethyl-1-methyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine **15c**:* yield, 14.2%; mp, 89.0–91.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.50 (s, 1H), 4.59–4.64 (m, 2H), 4.45 (dd, J_1 = 4.8 Hz, J_2 = 8.4 Hz, 1H), 3.29–3.36 (m, 2H), 3.11 (s, 3H), 2.08–2.13 (m, 1H), 1.84–1.91 (m, 1H), 1.68–1.75 (m, 1H), 1.24–1.32 (m, 2H), 0.92–0.96 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.5, 139.5, 136.8, 116.4, 88.7, 68.6, 42.3, 40.3, 32.1, 30.6, 24.3, 23.0, 11.5, 10.6; IR (KBr, cm^{-1}) 2955, 1587, 1406, 1331, 1209, 1138, 1059, 904, 748; HRMS (ES+) calcd for $C_{15}H_{24}N_4O_3S^{35}Cl$ (M + H)$^+$, 375.1179 (found, 375.1245); calcd for $C_{15}H_{24}N_4O_3S^{37}Cl$ (M + H)$^+$, 377.1228 (found, 377.1212).

*N-((2-Chlorothiazol-5-yl)methyl)-4-ethyl-6-isopropoxy-1-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **15d**:* yield, 13.4%; mp, 105.2–105.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 7.50 (s, 1H), 4.57–4.60 (m, 2H), 4.46 (dd, J_1 = 4.8 Hz, J_2 = 8.8 Hz, 1H), 3.33–3.36 (m, 1H), 3.10 (s, 3H), 2.10–2.14 (m, 1H), 1.83–1.86 (m, 1H), 1.69–1.75 (m, 1H), 1.25–1.31 (m, 2H), 1.20 (d, J = 4 Hz, 3H), 1.18 (d, J = 4 Hz, 3H), 0.95 (t, J = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.4, 139.6, 136.7, 116.4, 87.3, 70.4, 42.3, 40.1, 32.2, 32.1, 25.4, 24.2, 22.8, 11.6; IR (KBr, cm^{-1}) 2962, 1613, 1509, 1409, 1357, 1224, 1149, 1045, 919, 748; HRMS (ES+) calcd for $C_{15}H_{23}{}^{35}ClN_4NaO_3S$ (M + Na)$^+$, 397.1077 (found, 397.1064); calcd for $C_{15}H_{23}{}^{37}ClN_4NaO_3S$ (M + Na)$^+$, 399.1048 (found, 399.1020).

*N-((2-Chlorothiazol-5-yl)methyl)-1-ethyl-6-methoxy-4-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **16a**:* yield, 15.9%; mp, 150.4–151.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.49 (s, 1H), 4.58 (s, 2H), 4.38 (dd, J_1 = 4.8 Hz, J_2 = 7.2 Hz, 1H), 3.35–3.42 (m, 2H), 3.28 (s, 3H), 1.98–2.05 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.27–1.31 (m, 1H), 1.09–1.17 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 141.4, 134.1, 117.8, 85.1, 53.8, 50.9, 46.5, 42.1, 33.4, 25.5, 17.7, 15.9; IR (KBr, cm^{-1}) 2962.96, 1584.22, 1509.98, 1432.02, 1413.46, 1205.57, 1779.58, 1038.52, 942.00, 748.96; HRMS (ES+) calcd for $C_{13}H_{19}{}^{35}ClN_4NaO_3S$ (M + Na)$^+$, 369.0764 (found, 369.0758); calcd for $C_{13}H_{19}{}^{37}ClN_4NaO_3S$ (M + Na)$^+$, 371.0735 (found, 371.0719).

*N-((2-Chlorothiazol-5-yl)methyl)-6-ethoxy-1-ethyl-4-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine **16b**:* yield, 15.5%; mp, 94.1–94.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 7.46 (s, 1H), 4.52–4.69 (m, 2H), 4.52–4.69 (m, 1H), 3.48–3.53 (m, 2H), 3.33–3.38 (m, 2H), 1.93–1.97 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.20–1.29 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 153.1, 140.4, 135.7, 87.3, 63.8, 46.6, 42.0, 31.3, 27.0, 18.5, 15.8, 15.1; IR (KBr, cm^{-1}) 2977, 1591, 1532, 1458, 1368, 1276, 1179, 1049, 949, 774; HRMS (ES+) calcd for $C_{14}H_{22}N_4O_3S^{35}Cl$ (M + H)$^+$, 361.1101 (found, 361.1103); calcd for $C_{14}H_{22}N_4O_3S^{37}Cl$ (M + H)$^+$, 363.1072 (found, 363.1072).

*N-((2-Chlorothiazol-5-yl)methyl)-1-ethyl-4-methyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine **16c**:* yield, 15.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.46 (s, 1H), 4.55–4.69 (m, 2H),

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4.51 (t, J = 2.8 Hz, 1H), 3.42 (t, J = 6.4 Hz, 2H), 3.33−3.38 (m, 2H), 1.93−1.97 (m, 1H), 1.59−1.67 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.20−1.29 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 153.0, 140.4, 135.6, 117.1, 87.5, 70.2, 46.7, 42.0, 31.3, 27.0, 18.5, 22.9, 18.6, 15.8, 10.8; HRMS (ES+) calcd for $C_{15}H_{24}N_4O_3S^{35}Cl$ $(M + H)^+$, 375.1258 (found, 375.1256); calcd for $C_{15}H_{24}N_4O_3S^{37}Cl$ $(M + H)^+$, 377.1228 (found, 377.1268).

N-((2-Chlorothiazol-5-yl)methyl)-1-ethyl-6-isopropoxy-4-methyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine ***16d:*** yield, 13.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H), 7.47 (s, 1H), 4.57 (s, 2H), 4.50 (dd, J_1 = 4.0 Hz, J_2 = 6.8 Hz, 1H), 3.69−3.75 (m, 1H), 3.36−3.41 (m, 2H), 1.95−2.00 (m, 1H), 1.91−1.93 (m, 2H), 1.72−1.79 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.14 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 153.2, 141.1, 134.5, 117.9, 82.7, 69.0, 46.3, 42.0, 31.5, 27.2, 23.0, 18.6, 15.9, 14.1; HRMS (ES+) calcd for $C_{15}H_{24}N_4O_3S^{35}Cl$ $(M + H)^+$, 375.1258 (found, 375.1255); calcd for $C_{15}H_{24}N_4O_3S^{37}Cl$ $(M + H)^+$, 377.1228 (found, 377.1230).

N-((2-Chlorothiazol-5-yl)methyl)-1,4-diethyl-6-methoxy-3-nitro-1,4,5,6-tetrahydropyridin-2-amine ***17a:*** yield, 14.6%; mp, 117.1−119.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 7.48 (s, 1H), 4.59 (s, 2H), 4.38 (t, J = 6.0 Hz, 1H), 3.25−3.30 (m, 2H), 3.28 (s, 3H), 1.92−1.95 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.20−1.32 (m, 2H), 0.96−1.08 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 153.3, 141.4, 133.9, 117.2, 85.0, 53.5, 46.2, 42.1, 31.7, 29.8, 24.5, 15.9, 11.3; IR (KBr, cm^{-1}) 2955, 1584, 1509, 1450, 1376, 1261, 1187, 967, 748; HRMS (ES+) calcd for $C_{14}H_{21}N_4O_3S^{35}ClNa$ $(M + Na)^+$, 383.0921 (found, 383.0913); calcd for $C_{14}H_{21}N_4O_3S^{37}ClNa$ $(M + Na)^+$, 385.0891 (found, 385.0879).

N-((2-Chlorothiazol-5-yl)methyl)-6-ethoxy-1,4-diethyl-3-nitro-1,4,5,6-tetrahydropyridin-2-amine ***17b:*** yield, 17.0%; mp, 103.1−103.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.46 (s, 1H), 4.59 (s, 2H), 4.43 (dd, J_1 = 5.6 Hz, J_2 = 7.2 Hz, 1H), 3.40−3.51 (m, 2H), 3.32−3.40 (m, 2H), 1.90−1.94 (m, 1H), 1.37 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.14−1.29 (m, 2H), 0.93−1.06 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.2, 141.3, 134.1, 117.1, 84.0, 61.9, 46.0, 42.2, 31.8, 30.4, 24.5, 15.9, 15.3, 11.3; IR (KBr, cm^{-1}) 2970.37, 1584.22, 1521.11, 1446.87, 1342.92, 1187.01, 1049.65, 956.84, 745.24; HRMS (ES+) calcd for $C_{15}H_{24}N_4O_3S^{35}Cl$ $(M + H)^+$, 375.1258 (found, 375.1251); calcd for $C_{15}H_{24}N_4O_3S^{37}Cl$ $(M + H)^+$, 377.1228 (found, 377.1241).

N-((2-Chlorothiazol-5-yl)methyl)-1,4-diethyl-3-nitro-6-propoxy-1,4,5,6-tetrahydropyridin-2-amine ***17c:*** yield, 13.8%; mp, 90.2−91.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.47 (s, 1H), 4.59 (s, 2H), 4.44 (dd, J_1 = 5.2 Hz, J_2 = 7.2 Hz, 1H), 3.36 (t, J = 6.8 Hz, 2H), 3.27−3.33 (m, 2H), 1.91−1.96 (m, 1H), 1.58−1.62 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.20−1.33 (m, 2H), 0.98−1.07 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.2, 141.3, 134.1, 117.1, 84.0, 67.9, 46.0, 42.1, 31.8, 30.4, 24.5, 23.0, 15.9, 11.3, 10.7; IR (KBr, cm^{-1}) 2955, 1587, 1517, 1342, 1298, 1227, 1135, 1038, 956, 748; HRMS (ES+) calcd for $C_{16}H_{26}N_4O_3S^{35}Cl$ $(M + H)^+$, 389.1414 (found, 389.1401); calcd for $C_{16}H_{26}N_4O_3S^{37}Cl$ $(M + H)^+$, 391.1385 (found, 391.1373).

N-((2-Chlorothiazol-5-yl)methyl)-1,4-diethyl-6-isopropoxy-3-nitro-1,4,5,6-tetrahydropyridin-2-amine ***17d:*** yield, 13.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.46 (s, 1H), 4.58 (s, 2H), 4.48 (dd, J_1 = 5.2 Hz, J_2 = 8.4 Hz, 1H), 3.34−3.42 (m, 2H), 3.24−3.27 (m, 1H), 1.89−1.95 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H), 1.20−1.33 (m, 2H), 0.94−1.07 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.2, 141.1, 134.4, 117.2, 82.8, 69.0, 46.0, 42.0, 31.9, 30.0, 27.2, 24.5, 23.0, 15.9, 11.3; HRMS (ES+) calcd for $C_{16}H_{26}N_4O_3S^{35}Cl$ $(M + H)^+$, 389.1414 (found, 389.1411); calcd for $C_{16}H_{26}N_4O_3S^{37}Cl$ $(M + H)^+$, 391.1385 (found, 391.1394).

Biological Assay. According to statistical requirements, the bioassay was repeated three times at 25 ± 1 °C. All compounds were dissolved in *N*,*N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with 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.

Insecticidal Test for Cowpea Aphid (*Aphis craccivora*). The insecticidal activities of title compounds against cowpea aphid (*A. craccivora*) were tested according to the previously reported procedure.[5,16] Horsebean seedlings with 40−60 healthy apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s, and then the shoots were placed in a conditioned room (25 ± 1 °C, 50% relative humidity (RH)). Water containing Triton X-100 (0.1 mg L^{-1}) was used as control. The mortality rates were assessed after 24 h. Each treatment had three repetitions, and the data were corrected and subjected to probit analysis.

Bioassay on the Repellent Effects on Cowpea Aphid (*A. craccivora*). To understand the responses of aphid to title compounds, a Y-tape selective olfactometer was used for examination in the laboratory.[17] Horsebean seedlings without aphids were dipped in diluted solution of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s and then allowed to dry. The treated horsebean seedlings were put in one arm of the olfactometer, and the control ones were put in the other side arm. Apterous adult aphids were transferred into the third arm by brush. The olfactometer was covered with black cloth in the conditioned room (25 ± 1 °C, 50% RH). The number of adults in each arm was counted 1 h later. Each treatment had three repetitions, and the data were analyzed by ANOVA.

Insecticidal Test for Armyworm (*Pseudaletia separata* Walker). The insecticidal activities of title compounds against armyworm (*P. separata* Walker) were tested according to a previously reported procedure[18] by foliar application. Individual corn (*Zea mays*) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were sprayed with the solution containing compounds and allowed to dry. The dishes were infested with 10 second-instar larvae and then placed in a conditioned room (25 ± 1 °C, 50% RH); 48 h later, the mortality rates were assessed. Each treatment had three repetitions, and the data were corrected and subjected to probit analysis as before.

RESULTS AND DISCUSSION

Synthesis. Two methods were tried to synthesize the intermediate **23**. Using method 1, the reaction was carried out at 0 °C and the yield was 29.5%. By comparison with method 1, method 2 had a higher yield of 38.1%. However, a precipitate of Ag_2S formed in the reaction, which needed additional workup. Thus, method 1 was chosen to synthesize **23**.

When the target compounds were synthesized, the reaction was very complicated and there were many byproducts, which resulted in <5% yield. To optimize this reaction, several kinds of catalysts, including protonic acid and Lewis acid, such as $AlCl_3$, HCl, BF_3, CH_3COOH, and H_2SO_4, were studied. In view of increasing yield (10%) and simplicity of workup, $BF_3{\cdot}Et_2O$ was used as catalyst. The solvent of this reaction was also optimized; various solvents such as polar and nonpolar ones were employed, including MeCN, THF, DMF, alcohols, and dichloromethane. The result showed that dichloromethane was suitable to carry out the reaction. Furthermore, the reaction temperature was the vital factor for the synthesis of titled compounds. The reaction temperature was varied from 0 to 40 °C; it was observed that temperatures over 25 °C would lead to the formation of much more corresponding hydroxyl, eliminating byproducts, namely, 1,4-dihydropyridine analogues. The reaction temperature must be controlled below 25 °C.

After optimization, the factors in this reaction, such as temperature, catalyst, and solvent, were fixed and gave relatively higher yield. For compounds **10a−13d**, the yield reached 16.0−32.7%, whereas the yields of **14a−17d** were 13.4−17.0%. Compared to the synthesis of compounds **10a−13d**, the synthesis of compounds **14a−17d** was more difficult. Although an improvement of reaction time and temperature was tried

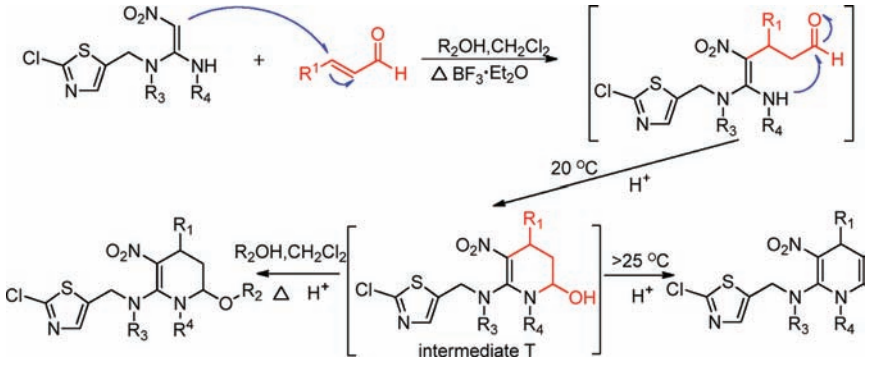

Figure 3. Mechanism to synthesize series 2.

and one-pot multicomponent reaction was also used to increase the yield and simplify the process, and even microwave synthesis was also carried out, it is still hard to get a higher yield during the synthesis of chain-opening nitromethylene neonicotinoids with cis configuration.

On the basis of our synthesis experience of this reaction, the main reason for very low yield was supposed. As shown in Figure 3, it was observed that the reaction not only for compounds **10a−13d** but also for **14a−17d** finished with high conversion monitored by TLC, but many spots of the product were observed on the TLC plate, which almost became a long line. A relatively low yield was obtained due to the accompanying side reactions of Michael addition, cyclization reaction, elimination reaction, and etherification. Several byproducts containing intermediates T and hydroxyl-eliminating products were isolated by column chromatography, and their structures were confirmed. Especially, the hydroxyl-eliminating compounds were the main products in the reaction. In addition, the conversion rate of the etherification reaction was also very low. Therefore, it was difficult to synthesize and separate target compounds. How to decrease the hydroxyl elimination reaction was the key problem of synthesis. Further optimization is in progress.

Biological Activities. Compounds **10a−13d** in series 1 exhibited rather poor insecticidal activity against cowpea aphid (*A. craccivora*) at 500 mg L^{-1}. The insecticidal activities are shown in Table 2, with **11b** showing the highest insecticidal activity of 31.8%. Compared with cyclic counterparts, these chain-opening molecules in series 1 all exhibited much reduced insecticidal activity against cowpea aphid.[9] Interestingly, we noted that the cowpea aphids fell down and crawled far away from the horsebean seedling after 24 h. This observation initiated our interest in investigating the repellent effects of these compounds. We chose compound **11b** as representative and found that its repellent percentage to apterous adults was 66.4 ± 8.6%, which is very interesting. There is no report of the repellent activities of known neonicotinoids such as nitenpyram, which has the same structure scaffold and does not have cis configuration present in compound **10−13**. Studies on the mechanism of repellent effects of this series of compounds are currently under investigation. This work would be helpful for the discovery of new leading compounds.

Table 2. Insecticidal Activities of Compounds 10a−13d against Cowpea Aphid (*Aphis craccivora*)

compd	*A. craccivora* mortality (%) at 500 mg L^{-1}	compd	*A. craccivora* mortality (%) at 500 mg L^{-1}
10a	16.2	**12a**	21.6
10b	17.7	**12b**	23.3
10c	24.3	**12c**	15.2
10d	23.7	**12d**	17.6
10e	15.3	**12e**	15.8
11a	27.6	**13a**	23.4
11b	31.8	**13b**	17.1
11c	27.2	**13c**	28.3
11d	25.8	**13d**	25.9
11e	19.5		

The insecticidal activities of compounds **14a−17d** of series 2 against cowpea aphid (*A. craccivora*) are shown in Table 3. Compounds **14b**, **14c**, and **15c** showed improved insecticidal activity against cowpea aphid with LC_{50} values of 0.05681, 0.08422, and 0.03855 mmol L^{-1}, respectively, compared to Paichongding, a commercial cis configuration cyclic compound with an LC_{50} of 0.09176 mmol L^{-1}(Table 3).[19] The bioactivities increased by 1.1−2.4-fold. Moreover, compared to other cyclic compounds with a pyridine (PYTP)[19] or thiazole ring (TZTP), with LC_{50} values of 0.26218 and 0.19001 mmol L^{-1}, respectively, the bioactivities of chain-opening series 2 also increased. Although the bioactivities of series 2 against cowpea aphid were lower than that of imidacloprid, the series 2 compounds could display better bioactivities against resistant strain brown planthopper similar to other known cis configuration analogues, such as Paichongding.

Aliphatic and aromatic substituents were available for R_3 and R_4. On the basis of the study of Akayama and co-workers, aliphatic substituted compounds exhibited higher insecticidal activities than those bearing an aromatic group.[20] Therefore, aromatic substituents were not chosen in this work.

The structural difference between compounds in series 1 (**10a−13d**) and 2 (**14a−17d**) was the substituent R_3. When R_3 is a hydrogen atom as in series 2, compounds exhibited better activities than those with a methyl or ethyl group as in series 1. It suggested that this position is important for the increase of bioactivity of chain-opening cis configuration neonicotinoids compounds.

At the same time, we also found that its substituent effect was different from that in the structure of commercialized nitenpyram. The effect of substituent of nitenpyram showed that methyl and ethyl groups have good bioactivities, with an LC_{95} value of 40 ppm against green rice leafhopper planthopper, whereas replacing those groups with a hydrogen atom decreases bioactivities, giving an LC_{95} value of >200 ppm.[20] When R_3 changed from a hydrogen atom to methyl and then ethyl, the larger the substituent was, the lower the

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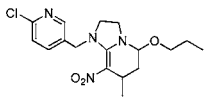
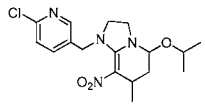
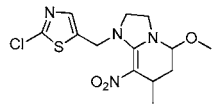
Table 3. Insecticidal Activities of Compounds 14a−c, 15a−d, 16b−d, and 17a−d against Cowpea Aphid (*Aphis craccivora*)

Compd.	*Aphis craccivora* mortality (%) 500mg L^{-1}	*Aphis craccivora* LC_{50} (mmol L^{-1})
14a	93.2	0.16218
14b	100	0.05681
14c	100	0.08422
15a	97.4	0.12188
15b	96.4	0.10578
15c	88.5	0.03855
15d	83.6	nt
16b	85.2	nt
16c	94.6	nt
16d	75	nt
17a	84.5	nt
17b	84	0.15298
17c	93.4	nt
17d	84.3	0.13882
Imidacloprid	100	0.03090
 **Paichongding**	100	0.09176
 **PYTP**	100	0.26218
 **TZTP**	100	0.19001

bioactivity was. Substituents on the nitrogen atom of the tetrahydropyridine ring (R_4) were important for improving activities of compounds **14a−17d**, and different substituents resulted in distinct difference of bioactivities. Especially, the bioactivity with the methyl group was better than that with the ethyl group. It also suggested that the sterics of R_3 and R_4 are likely playing a role in enhancing bioactivity. More analogues will be synthesized to further evaluate the substituent effect.

As for the substituent R_2, an *n*-propyl group led to slightly higher activity than an *iso*-propyl group did, whereas both are much better than methyl or ethyl analogues as exhibited by compounds **14a−c**. Compounds **14b** and **14c** displayed comparable LC_{50} values of f 0.5681 and 0.8422 mmol L^{-1}, respectively, which are considerably higher than that of compound **14a**. To further support this observation, other compounds with *n*-propyl at R_2 including compounds **15−17** all exhibit higher mortality, which displayed the same rule as the ring-closing tetrahydropyridine compounds.[19] However, compared with substituents R_4, the influence of R_2 on bioactivities is less profound.

Because some of our nitromethylene neonicotinoids with fixed cis configuration in previous work showed good insecticidal activities against army worm, the insecticidal activity of compounds **14a−c** against armyworm (*P. separata* Walker) at 500 mg L^{-1} was also measured. Mortalities of these three compounds were all 100% with LC_{50} values at 0.40864, 0.21781, and 0.25702 mmol L^{-1}, respectively. Although the bioactivities were not as high as those of other cis configuration neonicotiniods,[21,22] they are still promising candidates for further modifications against army worm (*P. separata* Walker).

In conclusion, two series of chain-opening nitromethylene neonicotinoids with cis configuration were designed and synthesized. Compared with cyclic ones, they showed obvious differences. The bioassays showed that some of the compounds exhibited unique repellent effects and other compounds showed better insecticidal activities against cowpea aphid and armyworm than cyclic compounds. Compound **15c** exhibited the highest insecticidal activity against cowpea aphid among the synthesized compounds; the LC_{50} value was 0.03855 mmol L^{-1}. Further studies on the particular biological behavior of compounds **10a−13d** are underway.

AUTHOR INFORMATION

Corresponding Author

*(X.X.) Phone: +86-21-64252945. Fax: +86-21-64252603. E-mail: xyxu@ecust.edu.cn. (Z.X.) Phone:+86-21-64253979. Fax: +86-21-64252603. E-mail: zhipingxu@ecust.edu.cn.

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