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Synthesis, Insecticidal Activity, and QSAR of Novel Nitromethylene Neonicotinoids with Tetrahydropyridine Fixed *cis* Configuration and Exo-Ring Ether Modification

ZHONGZHEN TIAN, XUSHENG SHAO, ZHONG LI,* XUHONG QIAN,* AND QINGCHUN HUANG

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, P.O. Box 544, Shanghai 200237, People's Republic of China

To keep the nitro group in the *cis* position, a series of nitromethylene neonicotinoids containing a tetrahydropyridine ring with exo-ring ether modifications were designed and synthesized. All of the compounds were characterized and confirmed by ^{1}H NMR, high-resolution mass spectroscopy, elemental analysis, and IR. The bioassay tests showed that some of them exhibited good insecticidal activities against pea aphids. On the basis of 10 nitromethylene derivatives, the quantitative structure−bioactivity relationship (QSAR) was analyzed and established. The results suggested that AlogP98 and Dipole_Mopac might be the important parameters related with biological activities.

KEYWORDS: Nitromethylene; tetrahydropyridine; *cis* position; QSAR

INTRODUCTION

Since imidacloprid (**1a**) was reported as an insecticide in the 1980s (*1*), neonicotinoid insecticides have rapidly grown and become a new chemical class of insecticides in recent years because of their novel structure and mode of action compared with conventional insecticides, such as organophosphates, carbamates, and synthetic pyrethroids (*2*). Following imidacloprid, thiamethoxam (*3*), dinotefuran (*4*), acyclic neonicotinoid insecticides, acetamiprid (*5*), nitenpyram (*6*), and clothianidin (*7*) have been registered as agricultural insecticides. All of these compounds were characterized by their high insecticidal activities against insects and relative safety toward mammals and aquatic life (*8*, *9*).

Neonicotinoid insecticides have many common molecular features. The notable feature is that the compounds contain four sections: aromatic heterocycle, flexible linkage, hydroheterocyles or guanidine/amidine, and electron-withdrawing group as shown in **Figure 1**. Another interesting feature is the configuration: the electron-withdrawing groups of NO_2 or CN linked to a C═C or C═N bond can exist in either of the two configurations (*trans* or *cis*), but X-ray crystallographic study showed that the heteroaromatic moiety in neonicotinoids (**1a** and **1b** in **Figure 2**) was only in the *trans* configuration relative to the electron-withdrawing tip (*10*). The related calculation also revealed that the *trans E* isomer form is also predominant in both gaseous and aqueous phases (*11*). In addition, the previous study of binding model presumed by Casida (*11*) and Sattelle (*12*) was based on *trans* configuration. Interestingly, the dicyclic neonicotinoid analogue containing a tetrahydropyrimidine ring,

Figure 1.

6-methyl-1-[(6-chloro-3-pyridinyl)methyl]-1,2,3,5,6,7-hexahydro-8-nitroimidazo[1,2-*c*]pyrimidine (**1c** in **Figure 2**), which was discovered by Bayer in 1992, in which the nitro group is *cis* to the chloropyridinylmethyl moiety, also showed high biological activity (*13*), which implied that neonicotinoids in the *cis* configuration might bind to the receptor in a different way.

On the other hand, although 6-Cl-PMMI (**1b**) in the *trans* configuration exhibits an insecticidal activity similar to that of imidacloprid (*14*), its photoinstability (*15*) and weak hydrophobicity (*16*) limited its use in crop protection. Herein, to find the diversity of nitromethylene neonicotinoids with a *cis* nitro configuration, our interest is to design novel neonicotinoids by introducing a tetrahydropyridine ring into the lead compound to fix the nitro moiety in the *cis* position (**1d** in **Figure 2**) and synthesize a series of new nitromethylene compounds. We expected that the new structure could not only overcome its photoinstability through fusing another ring but also adjust hydrophobicity by *exo*-ring ether modifications. This paper describes the synthesis and biological activities of a number of nitromethylene derivatives containing hydropyridine targeted to assess the potential use of a dicyclic ring system in neonicotinoid compounds.

To further explore the influential factor for the bioactivities of these compounds (**1d**), the quantitative structure−activity relationships of 10 compounds were studied, and satisfactory

* Authors to whom correspondence should be addressed (e-mail xhqian@ecust.edu.cn).

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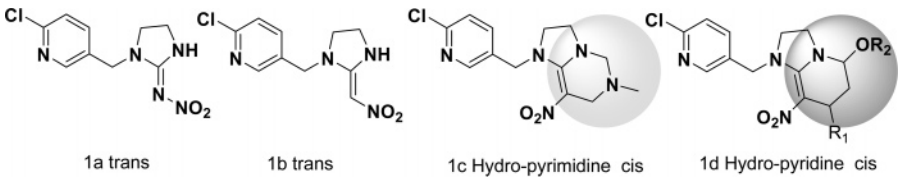


Figure 2.

quantitative structure−activity relationship (QSAR) equations were established.

MATERIALS AND METHODS

Synthetic Procedures. All melting points (mp) were obtained with a Büchi Melting Point B540 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 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) condition using a MicroMass GCT CA 055 instrument. Combustion analyses for elemental composition were made with an Elementar vario EL III. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

General Synthetic Procedure for 4 and 5. To a mixture of compound **1b** (0.51 g, 2 mmol) were added olefin aldehyde (2.2 mmol), acetonitrile (20 mL), and a drop of concentrated hydrochloric acid. The reaction was carried out at 40 °C, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure, and the crude oil was purified by flash chromatography to give the corresponding product.

General Synthetic Procedure for 6a−s and 7a,b. To a solution of compound **4** or **5** (1 mmol) were added various alcohols (5 mmol), dichloromethane (30 mL), and a drop of concentrated hydrochloric acid. The mixture was refluxed for 10 h and then cooled to room temperature. The mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography on silica gel, eluting with dichloromethane/acetone to afford pure products.

*Data for **4**:* yield, 70%; mp 169.0−172.1 °C; ^{1}H NMR (DMSO), δ 8.38 (d, J_1 = 2.1 Hz, 1H, Py-H), 7.85 (dd, J_1 = 2.3 Hz, J_2 = 8.3 Hz, 1H, Py-H), 7.21 (d, J = 8.2 Hz, 1H, Py-H), 6.34 (d, J = 5.5 Hz, 1H, O−H), 4.86 (m, 1H, N−CH−O), 4.81 (d, 1H, J = 15.5 Hz, Py-CH_2), 4.52 (d, 1H, J = 15.5 Hz, Py-CH_2), 3.72−3.78 (m, 1H), 3.49−3.62 (m, 3H), 2.68−2.73 (m, 1H), 2.49−2.59 (m, 1H), 1.82−1.86 (m, 1H), 1.74−1.79 (m, 1H); IR (KBr, cm^{-1}) 3203, 2908, 1683, 1560, 1400, 1346, 1148. HRESI: calcd for $C_{13}H_{16}ClN_4O_3$ (MH^+), 311.0911; found, 311.0909.

*Data for **5**:* yield, 67%; mp 175.6−177.1 °C; ^{1}H NMR ($CDCl_3$), δ 8.32 (d, J_1 = 2.1 Hz, 1H, Py-H), 7.79 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.48 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.80 (q, 1H, N−CH−O), 4.71 (d, 1H, J = 15.5 Hz, Py-CH_2), 4.58 (d, 1H, J = 15.5 Hz, Py-CH_2), 3.66−3.74 (m, 2H), 3.55−3.62 (m, 2H), 3.10−3.12 (m, 1H), 1.88−1.94 (m, 1H), 1.68−1.73 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H, CH_3); IR (KBr, cm^{-1}) 3184, 1520, 1474, 1354, 1213, 1029; MS (EI, 1.08e3), *m*/*z* (%) 324 (M^+, 1), 291 (100), 208 (21), 246 (15), 210 (13), 126 (72), 90 (9). HRMS: calcd for $C_{14}H_{17}N_4O_3Cl$ (M^+), 324.0989; found, 324.0986.

*Data for **6a**:* yield, 83%; mp 154.0−156.4 °C; ^{1}H NMR (DMSO), δ 8.33 (d, J_1 = 2.2 Hz, 1H, Py-H), 7.90 (dd, J_1 = 2.5 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.34 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.95 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.59 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.48 (t, J = 3.0 Hz, 1H, N−CH−O), 3.85−3.91 (m, 1H), 3.58−3.64 (m, 2H), 3.50−3.54 (m, 1H), 3.39 (s, 3H, CH_3), 2.97−3.02 (m, 1H), 2.68−2.74 (m, 1H), 2.17−2.21 (m, 1H), 1.76−1.80 (m, 1H); IR (KBr, cm^{-1}) 2927, 1573, 1507, 1353, 1056; MS (EI, 1.90e4), *m*/*z* (%) 324 (M^+, 8), 294 (100), 278 (46), 246 (38), 210 (12), 126 (92), 90 (11). Anal. Calcd for $C_{14}H_{17}ClN_4O_3$: C, 51.78; H, 5.28; N, 17.25. Found: C, 51.95; H, 5.12; N, 17.04.

*Data for **6b**:* yield, 80%; mp 126.8−127.8 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, J_1 = 2.2 Hz, 1H, Py-H), 7.91 (dd, J_1 = 2.4 Hz, J_2 = 8.3 Hz, 1H, Py-H), 7.34 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.93 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.61 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.55 (t, J = 3.0 Hz, 1H, N−CH−O), 3.84−3.90 (m, 1H), 3.49−3.61 (m, 5H), 2.97−3.02 (m, 1H), 2.72−2.78 (m, 1H), 2.13−2.17 (m, 1H), 1.78−1.82 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H, CH_2CH_3); IR (KBr, cm^{-1}) 2987, 1572, 1500, 1316, 1157, 1034; MS (EI, 2.51e4), *m*/*z* (%) 338 (M^+, 5), 308 (90), 292 (33), 246 (59), 210 (19), 126 (100), 90 (12). Anal. Calcd for $C_{15}H_{19}ClN_4O_3$: C, 53.18; H, 5.65; N, 16.54. Found: C, 53.64; H, 5.57; N, 16.68.

*Data for **6c**:* yield, 66%; mp 115.7−117.6 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, J_1 = 2.4 Hz, 1H, Py-H), 7.90 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.33 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.94 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.60 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.56 (t, J = 3.0 Hz, 1H, N−CH−O), 3.86−3.92 (m, 1H), 3.64−3.68 (m, 5H), 2.95−3.00 (m, 1H), 2.69−2.76 (m, 1H), 2.13−2.18 (m, 1H), 1.75−1.82 (m, 1H), 1.57−1.64 (m, 2H, CH_2CH_3), 0.93 (t, 3H, J = 7.4 Hz, CH_3); IR (KBr, cm^{-1}) 2967, 1579, 1503, 1316, 1152, 1096; MS (EI, 1.34e4), *m*/*z* (%) 352 (M^+, 8), 322 (100), 306 (36), 246 (44), 210 (14), 126 (95), 90 (11). Anal. Calcd for $C_{14}H_{17}ClN_4O_3$: C, 54.47; H, 6.00; N, 15.88. Found: C, 54.57; H, 5.99; N, 15.55.

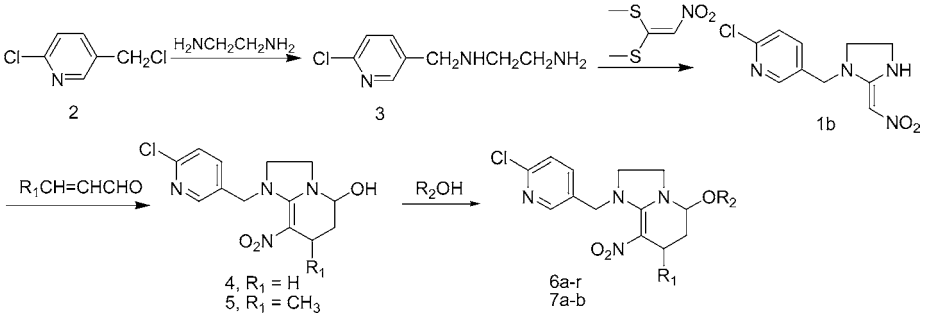
*Data for **6d**:* yield, 72%; mp 129.9−134.6 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, J_1 = 2.3 Hz, 1H, Py-H), 7.92 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py-H), 7.34 (d, J_2 = 8.3 Hz, 1H, Py-H), 4.89 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.63 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.59 (t, J = 3.1 Hz, 1H, N−CH−O), 3.82−3.86 (m, 1H), 3.70−3.75 (m, 1H), 3.50−3.56 (m, 3H), 2.98−3.03 (m, 1H), 2.73−2.79 (m, 1H), 2.05−2.09 (m, 1H), 1.81−1.85 (m, 1H), 1.20 (d, 6H, J = 6.0 Hz, $CHCH_3$); IR (KBr, cm^{-1}) 2946, 1560, 1334, 1246, 1123, 1070; MS (EI, 7.85e3), *m*/*z* (%) 352 (M^+, 10), 322 (99), 306 (33), 246 (30), 210 (18), 126 (100), 90 (14). HRMS: calcd for $C_{16}H_{21}N_4O_3Cl$ (M^+), 352.1302; found, 352.1303.

*Data for **6e**:* yield, 79%; mp 158.5−159.4 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J_1 = 2.2 Hz, 1H, Py-H), 7.90 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.34 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.94 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.66 (t, J = 2.8 Hz, 1H, N−CH−O), 4.60 (d, 1H, J = 15.1 Hz, Py-CH_2), 3.89−3.94 (m, 1H), 3.82−3.85 (m, 1H), 3.72−3.75 (m, 1H), 3.51−3.66 (m, 5H), 3.01−3.04 (m, 1H), 2.70−2.77 (m, 1H), 2.16−2.21 (m, 1H), 1.79−1.83 (m, 1H); IR (KBr, cm^{-1}) 3047, 1561, 1508, 1349, 1280, 1132; MS (EI, 4.11e4), *m*/*z* (%) 372 (M^+, 2), 342 (5), 326 (4), 246 (30), 210 (15), 126 (98), 90 (15), 31 (100). Anal. Calcd for $C_{15}H_{18}Cl_2N_4O_3$: C, 48.27; H, 4.86; N, 15.01. Found: C, 48.47; H, 4.94; N, 14.45.

*Data for **6f**:* yield, 86%; mp 131.1−132.9 °C; ^{1}H NMR ($CDCl_3$), δ 8.34 (d, J_1 = 1.8 Hz, 1H, Py-H), 7.88 (dd, J_1 = 2.2 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.34 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.95 (d, 1H, J = 15.2 Hz, Py-CH_2), 4.75 (s, 1H, N−CH−O), 4.59 (d, 1H, J = 15.2 Hz, Py-CH_2), 3.86−3.97 (m, 3H), 3.51−3.64 (m, 3H), 3.03−3.08 (m, 1H), 2.67−2.74 (m, 1H), 2.16−2.21 (m, 1H), 1.82−1.89 (m, 1H); IR (KBr, cm^{-1}) 3046, 1553, 1510, 1454, 1354, 1295, 1142, 1102; MS (EI, 1.13e4), *m*/*z* (%) 392 (M^+, 6), 362 (75), 346 (51), 246 (40), 210 (16), 126 (100), 90 (15). HRMS calcd for $C_{15}H_{16}F_3N_4O_3Cl$ (M^+), 392.0863; found, 392.0868.

*Data for **6g**:* yield, 72%; mp 86.7−88.2 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, J_1 = 1.5 Hz, 1H, Py-H), 7.92 (dd, J_1 = 2.0 Hz, J_2 = 8.3 Hz, 1H, Py-H), 7.34 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.92 (d, 1H, J = 15.0 Hz, Py-CH_2), 4.62 (d, 1H, J = 15.0 Hz, Py-CH_2), 4.53 (s, 1H, N−CH−O), 3.84−3.90 (m, 1H), 3.45−3.61 (m, 5H), 2.97−3.02 (m, 1H), 2.69−2.76 (m, 1H), 2.08−2.14 (m, 1H), 1.76−1.82 (m, 1H), 1.55−1.58 (m, 2H, CH_2), 1.37 (q, 2H, J = 7.5 Hz, CH_2CH_3), 0.92 (t, 3H, J = 7.4 Hz, CH_3); IR (KBr, cm^{-1}) 2899, 1573, 1493, 1454, 1308, 1149, 1089; MS (EI, 2.42e4), *m*/*z* (%) 366 (M^+, 4), 336 (95), 320 (29), 246 (29), 210 (10), 126 (100), 90 (9). HRMS: calcd for $C_{17}H_{23}N_4O_3Cl$ (M^+), 366.1459; found, 366.1465.

Scheme 1. General Synthetic Route for the Target Compound



Data for ***6h****:* yield, 66%; mp 93.6−95.4 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 2.3$ Hz, 1H, Py-H), 7.92 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.33 (d, $J_2 = 8.3$ Hz, 1H, Py-H), 4.92 (d, 1H, $J = 15.4$ Hz, Py-CH_2), 4.61 (d, 1H, $J = 15.5$ Hz, Py-CH_2), 4.58 (s, 1H, N−CH−O), 3.87−3.89 (m, 1H), 3.48−3.73 (m, 4H), 2.96−3.00 (m, 1H), 2.74−2.79 (m, 1H), 2.06−2.09 (m, 1H), 1.78−1.83 (m, 1H), 1.47−1.57 (m, 2H), 1.17 (d, 3H, $J = 6.1$ Hz, $CHCH_3$), 0.90 (t, 3H, $J = 7.3$ Hz, CH_2-CH_3); IR (KBr, cm^{-1}) 2972, 1573, 1560, 1513, 1460, 1328, 1175, 1056; MS (EI, 2.71e4), *m*/*z* (%) 366 (M^+, 7), 336 (100), 320 (27), 246 (30), 210 (17), 126 (100), 90 (8). HRMS: calcd for $C_{16}H_{21}ClN_4O_3$ (M^+), 252.1302; found, 252.1303. HRMS: calcd for $C_{17}H_{23}N_4O_3Cl$ (M^+), 366.1459; found, 366.1465.

Data for ***6i****:* yield, 68%; mp 118.8−120.8 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 2.1$ Hz, 1H, Py-H), 7.92 (dd, $J_1 = 2.3$ Hz, $J_2 = 8.3$ Hz, 1H, Py-H), 7.34 (d, $J_2 = 8.3$ Hz, 1H, Py-H), 4.92 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.63 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.52 (t, $J = 2.9$ Hz, 1H, N−CH−O), 3.84−3.90 (m, 1H), 3.48−3.60 (m, 3H), 3.22−3.29 (m, 2H), 2.98−3.03 (m, 1H), 2.70−2.77 (m, 1H), 2.13−2.17 (m, 1H), 1.78−1.87 (m, 2H), 0.91 (d, 6H, $J = 6.7$ Hz, $CH(CH_3)_2$); IR (KBr, cm^{-1}) 2989, 1573, 1533, 1348, 1288, 1169, 1016; MS (EI, 1.33e4), *m*/*z* (%) 366 (M^+, 7), 336 (100), 320 (35), 246 (31), 210 (12), 126 (65), 90 (8). HRMS: calcd for $C_{17}H_{23}N_4O_3Cl$ (M^+), 366.1459; found, 366.1458.

Data for ***6j****:* yield, 51%; mp 132.4−133.9 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 1.6$ Hz, 1H, Py-H), 7.93 (dd, $J_1 = 1.8$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.34 (d, $J_2 = 8.2$ Hz, 1H, Py-H), 4.88 (d, 1H, $J = 15.0$ Hz, Py-CH_2), 4.73 (s, 1H, N−CH−O), 4.62 (d, 1H, $J = 15.0$ Hz, Py-CH_2), 3.76−3.83 (m, 1H), 3.44−3.54 (m, 3H), 2.94−3.00 (m, 1H), 2.79−2.86 (m, 1H), 1.95−1.99 (m, 1H), 1.86−1.92 (m, 1H), 1.25 (s, 9H, $CH(CH_3)_3$); IR (KBr, cm^{-1}) 2966, 1559, 1507, 1396, 1328, 1175, 1056; MS (EI, 1.56e3), *m*/*z* (%) 366 (M^+, 5), 336 (39), 320 (17), 246 (36), 210 (21), 126 (100), 90 (19). HRMS: calcd for $C_{17}H_{23}N_4O_3Cl$ (M^+), 366.1459; found, 366.1451.

Data for ***6k****:* yield, 49%; mp 81.5−87.2 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 1.9$ Hz, 1H, Py-H), 7.92 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.34 (d, $J_2 = 8.3$ Hz, 1H, Py-H), 4.92 (d, 1H, $J = 15.0$ Hz, Py-CH_2), 4.62 (d, 1H, $J = 14.9$ Hz, Py-CH_2), 4.53 (s, 1H, N−CH−O), 3.85−3.88 (m, 1H), 3.46−3.59 (m, 5H), 2.98−3.02 (m, 1H), 2.71−2.77 (m, 1H), 2.13−2.17 (m, 1H), 1.77−1.82 (m, 1H), 1.57−1.59 (m, 2H, CH_2), 1.31−1.33 (m, 4H, $(CH_2)_2$), 0.90 (t, 3H, $J = 6.6$ Hz, CH_3); IR (KBr, cm^{-1}) 2960, 1560, 1513, 1388, 1308, 1275; MS (EI, 8.67e3), *m*/*z* (%) 380 (M^+, 9), 350 (100), 334 (43), 246 (46), 128 (28), 126 (99), 43 (36). HRMS: calcd for $C_{18}H_{25}N_4O_3Cl$ (M^+), 380.1615; found, 380.1601.

Data for ***6l****:* yield, 64%; mp 96.8−97.9 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 1.9$ Hz, 1H, Py-H), 7.91 (dd, $J_1 = 2.3$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.34 (d, $J_2 = 8.2$ Hz, 1H, Py-H), 4.92 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.62 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.52 (t, $J = 1.5$ Hz, 1H, N−CH−O), 3.86−3.88 (m, 1H), 3.48−3.60 (m, 5H), 2.96−3.02 (m, 1H), 2.72−2.75 (m, 1H), 2.13−2.17 (m, 1H), 1.78−1.79 (m, 1H), 1.68−1.71 (m, 1H), 1.45−1.49 (m, 2H), 0.90 (d, 6H, $J = 6.6$ Hz, $CH(CH_3)_2$); IR (KBr, cm^{-1}) 2946, 1566, 1513, 1454, 1341, 1175, 1056; MS (EI, 1.01e4), *m*/*z* (%) 380 (M^+, 10), 350 (100), 334 (37), 246 (43), 210 (15), 126 (72), 90 (9). HRMS: calcd for $C_{18}H_{25}N_4O_3Cl$ (M^+), 380.1615; found, 380.1647.

Data for ***6m****:* yield, 86%; mp 147.1−149.5 °C; ^{1}H NMR ($CDCl_3$), δ 8.31 (d, $J_1 = 2.0$ Hz, 1H, Py-H), 7.89 (dd, $J_1 = 2.2$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.31−7.39 (m, 6H, Py-H, Ph−H), 4.94 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.66 (d, 1H, $J = 12.4$ Hz, Ph−CH_2), 4.65 (s, 1H, N−CH−O), 4.55 (d, 1H, $J = 15.1$ Hz, Ph−CH_2), 4.53 (d, 1H, $J = 12.0$ Hz, Ph−CH_2), 3.73−3.76 (m, 1H), 3.41−3.49 (m, 3H), 3.01−3.06 (m, 1H), 2.77−2.84 (m, 1H), 2.20−2.25 (m, 1H), 1.78−1.83 (m, 1H); IR (KBr, cm^{-1}) 3043, 1579, 1503, 1316, 1152, 1096; MS (EI, 1.30e4), *m*/*z* (%) 400 (M^+, 3), 370 (35), 354 (11), 246 (27), 210 (11), 126 (25), 91 (100), 90 (6). HRMS: calcd for $C_{20}H_{21}N_4O_3Cl$ (M^+), 400.1302; found, 400.1325.

Data for ***6n****:* yield, 76%; mp 155.8−158.0 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 2.7$ Hz, 1H, Py-H), 8.32 (d, $J_3 = 2.8$ Hz, 1H, Py-H), 7.88 (dd, $J_1 = 2.5$ Hz, $J_2 = 8.3$ Hz, 1H, Py-H), 7.64 (dd, $J_3 = 2.4$ Hz, $J_4 = 8.2$ Hz, 1H, Py-H), 7.36 (d, $J_2 = 8.8$ Hz, 1H, Py-H), 7.34 (d, $J_4 = 9.0$ Hz, 1H, Py-H), 4.98 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.70 (t, 1H, $J = 2.6$ Hz, N−CH−O), 4.63 (d, 1H, $J = 12.1$ Hz, Py-CH_2), 4.55 (d, 1H, $J = 12.0$ Hz, Py-CH_2), 4.54 (d, 1H, $J = 15.2$ Hz, Py-CH_2), 3.76−3.82 (m, 1H), 3.47−3.59 (m, 3H), 3.02−3.06 (m, 1H), 2.72−2.79 (m, 1H), 2.22−2.26 (m, 1H), 1.81−1.85 (m, 1H); IR (KBr, cm^{-1}) 2979, 1570, 1553, 1474, 1334, 1275, 1216, 1082; MS (EI, 9.79e4), *m*/*z* (%) 435 (M^+, 2), 275 (23), 142 (65), 126 (100), 114 (64), 90 (22), 78 (67). HRMS: calcd for $C_{19}H_{19}N_5O_3Cl_2$ (M^+), 435.0865; found, 435.0888.

Data for ***6o****:* yield, 93%; mp 96.8−98.3 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 2.0$ Hz, 1H, Py-H), 7.90 (dd, $J_1 = 2.3$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.34 (d, $J_2 = 8.2$ Hz, 1H, Py-H), 4.98 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.86 (t, $J = 2.1$ Hz, 1H, N−CH−O), 4.58 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.19−4.29 (m, 2H), 3.89−3.95 (m, 1H), 3.57−3.64 (m, 2H), 3.47−3.53 (m, 1H), 3.00−3.05 (m, 1H), 2.69−2.75 (m, 1H), 2.50 (t, 1H, $J = 2.3$ Hz), 2.18−2.22 (m, 1H), 1.80−1.84 (m, 1H); IR (KBr, cm^{-1}) 2919, 1573, 1507, 1454, 1431, 1338, 1154, 1062; MS (EI, 5.16e3), *m*/*z* (%) 348 (M^+, 10), 318 (45), 302 (27), 246 (42), 210 (18), 126 (100), 90 (17). HRMS: calcd for $C_{16}H_{17}N_4O_3Cl$ (M^+), 348.0989; found, 348.1012.

Data for ***6p****:* yield, 91%; mp 97.8−100.3 °C; ^{1}H NMR ($CDCl_3$), δ 8.33 (d, $J_1 = 2.2$ Hz, 1H, Py-H), 7.91 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.2$ Hz, 1H, Py-H), 7.34 (d, $J_2 = 8.2$ Hz, 1H, Py-H), 5.32 (t, $J = 6.3$ Hz, 1H, N−CH−O), 4.91 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.60 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.57−4.58 (m, 1H), 4.01−4.08 (m, 2H), 3.85−3.89 (m, 1H), 3.49−3.58 (m, 3H), 2.99−3.04 (m, 1H), 2.72−2.78 (m, 1H), 2.15−2.19 (m, 1H), 1.79−1.81 (m, 1H), 1.77 (s, 3H, CH_3), 1.69 (s, 3H, CH_3); IR (KBr, cm^{-1}) 2934, 1572, 1508, 1467, 1316, 1175, 1187, 1067; MS (EI, 2.04e3), *m*/*z* (%) 378 (M^+, 6), 348 (33), 332 (12), 248 (100), 210 (26), 126 (95), 90 (21). HRMS: calcd for $C_{18}H_{23}N_4O_3Cl$ (M^+), 378.1459; found, 378.1432.

Data for ***6q****:* yield, 83%; mp 139.6−141.2 °C; ^{1}H NMR ($CDCl_3$), δ 8.32 (d, $J_1 = 2.1$ Hz, 1H, Py-H), 7.89 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.3$ Hz, 1H, Py-H), 7.27−7.39 (m, 6H), 6.62 (d, 1H, $J = 15.9$ Hz, Ph−CH_2), 6.22−6.28 (m, 1H, Ph−CH_2═CH), 4.96 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.67 (t, 1H, $J = 2.7$ Hz, N−CH−O), 4.57 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.26−4.30 (m, 1H, Ph−CH_2═CH−CH_2), 4.12−4.22 (m, 1H, Ph−CH_2═CH−CH_2), 3.86−3.92 (m, 1H), 3.45−3.61 (m, 3H), 3.01−3.06 (m, 1H), 2.76−2.83 (m, 1H), 2.19−2.24 (m, 1H), 1.78−1.85 (m, 1H); IR (KBr, cm^{-1}) 2906, 1573, 1553, 1321, 1261, 1142; MS (EI, 1.16e4), *m*/*z* (%) 426 (M^+, 2), 396 (10), 290 (10), 246 (12), 210 (5), 134 (17), 126 (23), 117 (100), 91 (23), 78 (10). HRMS: calcd for $C_{22}H_{23}N_4O_3Cl$ (M^+), 426.1459; found, 426.1473.

Data for ***6r****:* pale yellow liquid; yield, 66%; ^{1}H NMR ($CDCl_3$), δ 8.33 (s, 1H, Py-H), 7.91 (d, $J = 7.3$ Hz, 1H, Py-H), 7.34 (d, $J = 8.2$ Hz, 1H, Py-H), 4.92 (d, 1H, $J = 15.1$ Hz, Py-CH_2), 4.68 (s, 1H,

Table 1. Insecticidal Activities of Nitromethylene Derivatives Containing a Tetrahydropyridine Ring against Pea Aphids

compd	R_1	R_2	mortality (%) in vivo at 1 day concn (500 mg/L)	LC_{50} (mmol/L)
4	H	H	>90	0.188
5	CH_3	H	>90	0.097
6a	H	CH_3	>90	0.132
6b	H	C_2H_5	>90	0.096
6c	H	*n*-propyl	>90	0.105
6d	H	isopropyl	>90	0.260
6e	H	C_2H_5Cl	44.8	nt[a]
6f	H	CH_2CF_3	10.33	nt
6g	H	*n*-butyl	77.7	nt
6h	H	*sec*-butyl	<10	nt
6i	H	isobutyl	76.3	nt
6j	H	*tert*-butyl	72.8	nt
6k	H	*n*-pentyl	62.6	nt
6l	H	isopentyl	24.4	nt
6m	H	benzyl	>90	0.573
6n	H	2-chloro-5-methyl-pyridine	50	1.149
6o	H	propargyl	46.9	nt
6p	H	$CH_2CH{=}CH(CH_3)_2$	15.9	nt
6q	H	$CH_2CH{=}CHC_6H_5$	<10	nt
6r	H	$CH_2CH_2OC_2H_5$	10.2	nt
7a	CH_3	CH_3	>90	0.148
7b	CH_3	C_2H_5	>90	0.186
imidacloprid			>90	0.035

[a] Not tested.

N−CH−O), 4.61 (d, 1H, J = 15.1 Hz, Py-CH_2), 3.91−3.96 (m, 1H), 3.67−3.74 (m, 2H), 3.48−3.59 (m, 7H), 2.99−3.01 (m, 1H), 2.71−3.77 (m, 1H), 2.17−2.19 (m, 1H), 1.74−1.83 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H, CH_2CH_3); IR (KBr, cm^{-1}) 2972, 1553, 1511, 1334, 1176, 1061; MS (EI, 2.29e4), *m*/*z* (%) 382 (M^+, 4), 352 (93), 322 (38), 336 (22), 246 (43), 210 (11), 126 (100), 90 (9). HRMS: calcd for $C_{17}H_{23}N_4O_4Cl$ (M^+), 382.1408; found, 382.1412.

Data for ***7a****:* yield, 60%; mp 164.0−165.4 °C; ^{1}H NMR ($CDCl_3$), δ 8.32 (d, J_1 = 2.0 Hz, 1H, Py-H), 7.86 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.33 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.93 (d, 1H, J = 15.2 Hz, Py-CH_2), 4.60 (d, 1H, J = 15.2 Hz, Py-CH_2), 4.50 (q, 1H, N−CH−O), 3.81−3.85 (m, 1H), 3.72−3.74 (m, 1H), 3.60−3.62 (m, 1H), 3.52−3.55 (m, 1H), 3.36 (s, 3H, OCH_3), 3.33−3.35 (m, 1H), 2.19−2.25 (m, 1H), 1.73−1.78 (m, 1H), 1.23 (d, J = 6.6 Hz, 3H, CH_3); IR (KBr, cm^{-1}) 2936, 1563, 1506, 1454, 1320, 1077; MS (EI, 2.13e4), *m*/*z* (%) 338 (M^+, 1), 308 (9), 291 (100), 246 (9), 210 (7), 126 (38). HRMS: calcd for $C_{15}H_{19}N_4O_3Cl$ (M^+), 338.1146; found, 338.1150.

Data for ***7b****:* yield, 75%; mp 138.8−140.3 °C; ^{1}H NMR ($CDCl_3$), δ 8.31 (d, J_1 = 1.9 Hz, 1H, Py-H), 7.87 (dd, J_1 = 2.3 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.33 (d, J_2 = 8.2 Hz, 1H, Py-H), 4.89 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.62 (d, 1H, J = 15.1 Hz, Py-CH_2), 4.56 (q, 1H, N−CH−O), 3.82−3.84 (m, 1H), 3.68−3.71 (m, 1H), 3.49−3.56 (m, 4H), 3.37−3.38 (m, 1H), 2.16−2.21 (m, 1H), 1.76−1.81 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3); IR (KBr, cm^{-1}) 2959, 1546, 1511, 1392, 1316, 1078; MS (EI, 7.04e3), *m*/*z* (%) 352 (M^+, 2), 322 (15), 306 (8), 291 (100), 246 (13), 210 (9), 126 (42). HRMS: calcd for $C_{16}H_{21}N_4O_3Cl$ (M^+), 352.1302; found, 352.1306.

Biology Assay. All compounds were dissolved in acetone and diluted with water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 500.0, 250.0, 125.0 mg L^{-1} and others for bioassays.

Pea aphids (*Aphis craccivora*) were dipped according to a slightly modified FAO dip test (*17*). Tender shoots of soybean 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, the superfluous fluid was removed, and the shoots were placed in the conditioned room (23 ± 1 °C, 50% RH). Water containing Triton X-100 (0.1 mg L^{-1}) was used as control. Mortality was assessed after 24 h, and data were corrected and subjected to probit analysis as before.

Table 2. Activity (pLC_{50}) and Predicted Values for 10 Nitromethylene Derivatives Containing a Tetrahydropyridine Ring and Physicochemical Parameters for LINEAR Regression

compd	activity (pLC_{50} mmol/L)	eq 4 PLS predicted	V_m	AlogP98	dipole mag
4	6.73	7.190	256.03	2.77	11.09
5	7.01	6.926	272.87	3.23	10.96
6a	6.88	6.829	273.43	3.18	11.29
6b	7.02	6.878	290.44	3.53	10.89
6c	6.98	6.623	307.49	4.05	11.18
6d	6.59	6.610	307.00	3.91	11.48
6m	6.24	6.817	345.28	4.76	11.21
6n	5.94	5.682	354.81	4.49	13.07
7a	6.83	6.788	290.49	3.64	11.12
7b	6.73	6.761	256.03	3.99	11.00

RESULTS AND DISCUSSION

Synthesis. Starting from 2-chloro-5-chloromethylpridine, a set of *N*′-((5-chloropyridin-2-yl)methyl)ethane-1,2-diamine and nitromethylene **1b** were synthesized following the procedure reported previously (*18*). The further reaction of **1b** with acrylaldehyde or crotonaldehyde could proceed readily at 40 °C under catalysis of hydrochloric acid to give the target compound **4** or **5** (**Scheme 1**). Ether **6** or **7** was synthesized by the reaction of **4** or **5** with various alcohols in the presence of acid. The lower alcohols, allyl alcohol, propargyl alcohol, and benzyl alcohol, had higher reaction activity than the others. The structures of the title compounds were well characterized by ^{1}H NMR, HRMS, EA, and IR.

Biological Activity. Compounds **4**, **5**, **6a**−**d**, **6m**, **7a**, and **7b** exhibited good insecticide activity against pea aphids (**Table 1**) and had >90% mortality at 500 mg/L. Among those compounds, the bioactivities of **5**, **6b**, and **6c** were slightly weaker than that of imidacloprid. Compared with **6b**, the introduction of F and Cl elements into the ether-substituted group resulted in remarkably decreased insecticidal activity. For the effects of the R_2 substituent group, the modification of compound **4** with a longer alkyl group showed decreasing tendency in biological activity, and methyl and ethyl ether derivatives of compound **5** also exhibited about 2-fold less potency than compound **5**.

Structure−Activity Relationship. The bioactivities were quantitatively analyzed using physicochemical parameters and a regression method. All computations were done on Silicon Graphics workstation running on the IRIX 6.5 operating system. Relevant computational modules were accessed from the Drug Discovery Workbench (DDW) of Cerius^2 (version 4.8).

Physicochemical Parameters. To check which of the parameters were of importance for activity, several equations were obtained according different combinations of the parameters. The data matrix was analyzed by using the LINEAR method. The quality of each of the regression models was evaluated using the correlation coefficient (*r*).

As shown in **Table 1**, biological activities of compounds against pea aphids related strongly to the substituent groups R_1 and R_2. The activity was higher when the substituent was a lower alkyl group such as H, CH_3, ethyl, or propyl, whereas it decreased as the groups were extended. Therefore, the volume of compound may be an important factor for activity. To further explore the structural requirements for the activity of our compounds, quantitative structure−activity relationships (QSAR) analysis was performed. Considering the importance of hydrophobic and electrostatic properties, the dipole moment and ALogP98, as well as the volume, were selected as the descriptors.

The QSAR models by monoparameter regression analysis are below (eqs 1−3):

$$pLC_{50} = 9.42896 - 0.0091V_m$$
$$n = 10;\ r = 0.81;\ \text{XV } r = 0.63;\ \text{PRESS} = 0.683 \quad (1)$$

$$pLC_{50} = 8.18251 - 0.3960(\text{AlogP98})$$
$$n = 10;\ r = 0.68;\ \text{XV } r = 0.21;\ \text{PRESS} = 1.708 \quad (2)$$

$$pLC_{50} = 11.78269 - 0.4491(\text{Dipole\_Mopac})$$
$$n = 10;\ r = 0.81;\ \text{XV } r = 0.63;\ \text{PRESS} = 0.683 \quad (3)$$

From the above three models, all three descriptors were correlated with the pLC_{50} values. Correlation of three descriptors showed that V_m was highly correlated with AlogP98 (0.972) and Dipole_Mopac (0.648), whereas AlogP98 was more independent with Dipole_Mopac (0.46). Therefore, AlogP98 and Dipole_Mopac were selected for the biparameter regression analysis (eq 4).

$$pLC_{50} = 11.4825 - 0.2269(\text{AlogP98}) - 0.3473(\text{Dipole\_Mopac})$$
$$n = 10;\ r = 0.87;\ \text{XV } r = 0.56;\ \text{PRESS} = 0.771 \quad (4)$$

Equation 4 explained compounds' activities better than the former three equations. AlogP98 and Dipole_Mopac are the most important factors for the activities of our compounds. The lower AlogP98 and Dipole_Mopac values will result in higher bioactivities. Unfortunately, only 10 compounds' pLC_{50} values could be obtained, which limited the further QSAR analysis. However, our QSAR analysis revealed the essential structural requirement: The volumes of the R_1 and R_2 groups together with the molecular hydrophobic and electrostatic properties are strongly correlated with the activity.

In conclusion, we have demonstrated that the tetrahydropyridine nitromethylene derivatives for a nitro group in the *cis* position and exo-ring ether presented good insecticidal activity. Some of their compounds showed good insecticidal activities, and they have common features of hydropyridine, exo-ring ether, and *cis* configuration of the nitro group. Their structure−activity relationships showed that AlogP98 and Dipole_Mopac were the major factors for the biological activities of our designed compounds.

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