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Pyrrole- and Dihydropyrrole-Fused Neonicotinoids: Design, Synthesis, and Insecticidal Evaluation

Zhenjun Ye, Lina Shi, Xusheng Shao, Xiaoyong Xu, Zhiping Xu, and Zhong Li*

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

Supporting Information

ABSTRACT: Versatile pyrrole- and dihydropyrrole-fused neonicotinoids were obtained from cyclic and non-cyclic nitroeneamines. Anhydrous aluminum chloride ($AlCl_3$) exhibited high catalytic selectivity for the synthesis of the titled etherified compounds at room temperature and the eliminated products under reflux conditions. The target molecules have been identified on the basis of satisfactory analytical and spectral [^1H and ^{13}C nuclear magnetic resonance (NMR), high-resolution mass spectrometry (HRMS), and X-ray] data. All synthesized compounds have been screened for insecticidal activity. The preliminary insecticidal activity results showed that some of the aimed compounds displayed excellent insecticidal activity against cowpea aphids (*Aphis craccivora*).

KEYWORDS: *Pyrrole, dihydropyrrole, neonicotinoid, nAChR*

INTRODUCTION

α,β-Unsaturated enamine was reported as a typical 1,3-dipolar structure.[1] It underwent various addition reactions with the conjugate fragment of the electron-donating amino and electron-withdrawing substitute.[2] The reactions of α,β-unsaturated enamine with different functional groups afforded the corresponding five-, six-, and seven-membered cycloaddition products.[3−6]

Since the discovery of imidacloprid, the class of neonicotinoids has taken the biggest share in the insecticide market.[7−9] Several commercial neonicotinoid compounds were launched successively in the latest 2 decades, and they presented a broad spectrum performance in controlling various insects.[10−12] For all of that, seeking an insecticide with more effectiveness, lower toxicity, and environmentally friendly is an unremitting goal for all agrochemists.

On the basis of the research of a common neonicotinoid structure, it is recognized that four sections are essential for the construction of a neonicotinoid, namely, an aromatic heterocycle, a flexible linkage, a hydroheterocycle or guanidine/amidine, and an electron-withdrawing segment.[12] The early synthesized compound **3** showed apparent bioactivity and high affinity to nicotinic acetylcholine receptors (nAChRs).[6,13,14] Li et al. developed a series of systematic studies on moderating the neonicotinoids with fused tetrahydropyridine **4** and oxabridged rings **5** and **6**.[3,5,15] In this paper, we designed and synthesized compounds **7** and **8** that substituted pyrrole or dihydropyrrole cycles fused on the fragment of β-nitroenamine (Scheme 1). Interestingly, diverse target molecules were synthesized through different reaction conditions, and it was possible to selectively achieve the corresponding derivative compounds in high yields.

MATERIALS AND METHODS

Instruments. All melting points were obtained with a Büchi Melting Point B540 and are uncorrected. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ (parts per million) values. Coupling constants ^nJ are reported in hertz. High-resolution electron impact mass spectrometry (HR-EIMS) spectra were recorded under electron impact (70 eV) conditions using a MicroMass GCT CA 055 instrument. 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 Procedure for the Preparation of Compounds 10a−10e, 11, 12a−12c, 13a−13d, 14a−14f, and 15a−15c. *1-((6-Chloropyridin-3-yl)methyl)-5-methyl-7-nitro-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole-5,6-diol (**10a**).* Reactant **1** (2.030 g, 8.0 mmol), prepared using the previously reported method,[12] was dissolved in dichloromethane (20 mL), and then methylglyoxal **9** (8.8 mmol) was added. The mixture was stirred at room temperature for 1 h. The precipitate formed was filtered and washed with acetone to provide compound **10a** as a white solid (2.210 g, 84%). Melting point (mp) = 190.1−191.0 °C. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.40 (d, J = 1.6 Hz, 1H), 7.83 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.48 (d, J = 6.0 Hz, 1H), 5.37 (d, J = 15.2 Hz, 1H), 5.08 (d, J = 15.2 Hz, 1H), 4.68 (d, J = 6.0 Hz, 1H), 3.93−3.84 (m, 1H), 3.80 (q, J = 10.4 Hz, 1H), 3.43−3.36 (m, 2H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.1, 150.1, 149.8, 139.9, 132.5, 124.8, 108.5, 88.5, 81.8, 54.4, 48.3, 38.1, 20.1. High-resolution mass spectrometry (HRMS) (EI+) calcd for $C_{13}H_{16}N_4O_4{}^{35}Cl$ $(M + H)^+$, 327.0860; found, 327.0881; calcd for $C_{13}H_{16}N_4O_4{}^{37}Cl$ $(M + H)^+$, 329.0831; found, 329.0841.

Synthesis of the Target Molecules 10b−10e. Anhydrous aluminum chloride ($AlCl_3$, 0.2 mmol) was added to a solution of compound **10a** (2 mmol) in alcohol (20 mL). The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC. After completion, half of the solvent was removed and H_2O (20 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL), and the organic layer was washed with sodium dicarbonate aqueous solution and then brine, dried over

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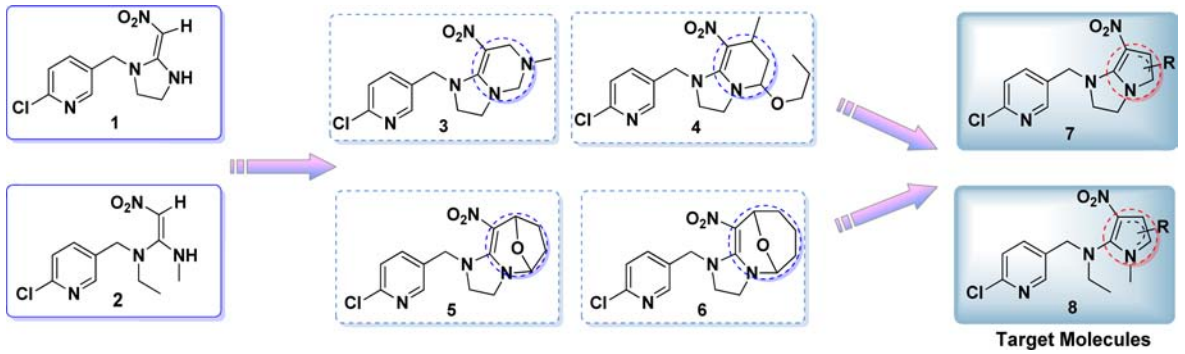
Scheme 1. Strategy To Synthesis Dihydropyrrole-Fused Neonicotinoids



anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the pure products.

*1-((6-Chloropyridin-3-yl)methyl)-5,6-dimethoxy-5-methyl-7-nitro-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole (**10b**).* Yield = 86%. Yellow solid. mp = 85.8−86.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 5.60 (d, J = 14.8 Hz, 1H), 4.83 (d, J = 14.8 Hz, 1H), 4.88 (s, 1H), 3.88 (m, 1H), 3.80 (q, J = 10.0 Hz, 1H), 3.60 (s, 3H), 3.51−3.41 (m, 2H), 3.20 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2, 151.5, 149.3, 139.5, 130.3, 124.8, 92.3, 86.4, 58.9, 54.0, 50.9, 49.3, 38.4, 30.9, 16.8. HRMS (ES+) calcd for $C_{15}H_{20}N_4O_4{}^{35}Cl$ (M + H)$^+$, 355.1173; found, 355.1156; calcd for $C_{15}H_{20}N_4O_4{}^{37}Cl$ (M + H)$^+$, 357.1144; found, 357.1143.

*1-((6-Chloropyridin-3-yl)methyl)-5,6-diethoxy-5-methyl-7-nitro-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole (**10c**).* Yield = 75%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, J = 1.6 Hz, 1H), 7.73 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 5.62 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 14.8 Hz, 1H), 4.83 (s, 1H), 3.88−3.74 (m, 1H), 3.69 (m, 1H), 3.47−3.31 (m, 1H), 3.23−3.10 (m, 1H), 1.38 (s, 3H), 1.15 (t, J = 6.8 Hz, 1H), 1.06 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 151.2, 149.3, 139.5, 130.5, 124.7, 106.4, 91.9, 85.7, 67.2, 58.5, 54.0, 49.2, 38.5, 17.6, 15.5, 15.3. HRMS (EI+) calcd for $C_{17}H_{23}N_4O_4{}^{35}Cl$ (M)$^+$, 382.1408; found, 382.1412; calcd for $C_{17}H_{23}N_4O_4{}^{37}Cl$ (M)$^+$, 384.1378; found, 384.1376.

*1-((6-Chloropyridin-3-yl)methyl)-5-methyl-7-nitro-5,6-dipropoxy-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole (**10d**).* Yield = 51%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 5.54 (d, J = 15.2 Hz, 1H), 4.75 (d, J = 15.2 Hz, 1H), 4.84 (s, 1H), 3.86−3.69 (m, 1H), 3.59 (q, J = 7.2 Hz, 1H), 3.39 (t, J = 8.8 Hz, 2H), 3.26 (q, J = 7.2 Hz, 1H), 3.06 (q, J = 7.2 Hz, 1H), 1.55 (q, J = 7.2 Hz, 2H), 1.45 (q, J = 7.2 Hz, 2H), 1.38 (s, 3H), 0.85 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 151.3, 149.3, 139.4, 130.5, 124.7, 106.5, 92.0, 85.7, 73.4, 64.5, 53.9, 49.2, 23.2, 23.0, 17.5, 10.6, 10.5. HRMS (EI+) calcd for $C_{19}H_{27}N_4O_4{}^{35}Cl$ (M)$^+$, 410.1721; found, 410.1743; calcd for $C_{19}H_{27}N_4O_4{}^{37}Cl$ (M)$^+$, 412.1691; found, 412.1717.

*5,6-Dibutoxy-1-((6-chloropyridin-3-yl)methyl)-5-methyl-7-nitro-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole (**10e**).* Yield = 43%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 5.57 (d, J = 14.8 Hz, 1H), 4.86 (s, 1H), 4.73 (d, J = 14.8 Hz, 1H), 3.84−3.70 (m, 3H), 3.65 (dd, J_1 = 15.6 Hz, J_2 = 6.8 Hz, 1H), 3.39 (dd, J_1 = 10.0 Hz, J_2 = 7.6 Hz, 2H), 3.32 (dd, J_1 = 14.8 Hz, J_2 = 6.4 Hz, 1H), 3.11 (dd, J_1 = 14.8 Hz, J_2 = 6.4 Hz, 1H), 1.57−1.49 (m, 2H), 1.45−1.40 (m, 2H), 1.38 (s, 3H), 1.32 (t, J = 7.2 Hz, 2H), 1.26 (t, J = 7.6 Hz, 2H), 0.85 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 151.5, 149.3, 139.6, 130.5, 124.8, 106.6, 92.1, 85.7, 71.7, 62.8, 54.0, 49.3, 38.4, 32.2, 31.8, 19.4, 19.3, 17.6, 13.9, 13.8. HRMS (EI+) calcd for $C_{21}H_{31}N_4O_4{}^{35}Cl$ (M)$^+$, 438.2034; found, 438.2032; calcd for $C_{21}H_{31}N_4O_4{}^{37}Cl$ (M)$^+$, 440.2004; found, 440.2021.

*1-((6-Chloropyridin-3-yl)methyl)-5-methyl-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6(5H)-one (**11**).* $AlCl_3$ (0.2 mmol) was added to a solution of compound **10a** (2 mmol) in acetone (20 mL). The reaction was carried out at room temperature and monitored by TLC. After completion, half of the solvent was removed and water (30 mL) was added. The mixture was extracted with dichloromethane (3 × 30 mL), and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the pure product **11**. Yield = 63%. Yellow solid. mp 137.4−138.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (d, J = 2.0 Hz, 1H), 7.76 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 5.23 (d, J = 15.2 Hz, 1H), 5.16 (d, J = 15.2 Hz, 1H), 3.95−3.87 (m, 2H), 3.81−3.74 (m, 1H), 3.71 (q, J = 6.8 Hz, 1H), 3.58 (q, J = 9.6 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7, 164.6, 151.8, 149.2, 138.9, 129.8, 124.9, 59.6, 52.6, 49.3, 43.5, 30.9, 14.9. IR (KBr, cm^{-1}): 2977.53, 1682.25, 1606.33, 1519.16, 1389.81, 1344.82. HRMS (EI+) calcd for $C_{13}H_{14}N_4O_3{}^{35}Cl$ (M + H)$^+$, 309.0754; found, 309.0741; calcd for $C_{13}H_{14}N_4O_3{}^{37}Cl$ (M)$^+$, 311.0725; found, 311.0733.

Synthesis of the Target Molecules 12a−12c. $AlCl_3$ (0.2 mmol) was added to a solution of compound **10a** (2 mmol) in diol solvents (20 mL). The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC. After completion, H_2O (200 mL) was added. The mixture was extracted with dichloromethane (3 × 30 mL), and the organic layer was washed with sodium dicarbonate aqueous solution and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the pure products.

*8-((6-Chloropyridin-3-yl)methyl)-4a-methyl-9-nitro-3,4a,6,7,8,9a-hexahydro-2H-[1,4]dioxino[2′,3′:4,5]pyrrolo[1,2-a]imidazole (**12a**).* Yield = 76%. White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (d, J = 2.4 Hz, 1H), 7.77 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 5.49 (d, J = 15.2 Hz, 1H), 5.02 (d, J = 15.2 Hz, 1H), 4.89 (s, 1H), 3.92−3.84 (m, 3H), 3.77−3.71 (m, 2H), 3.68−3.63 (m, 1H), 3.49−3.43 (m, 1H), 3.38−3.30 (m, 1H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 151.6, 149.3, 139.3, 130.3, 124.9, 106.3, 86.4, 80.0, 61.9, 61.1, 54.3, 49.2, 39.1, 20.6. HRMS (ES+) calcd for $C_{15}H_{17}N_4O_4{}^{35}Cl$ (M + H)$^+$, 352.0938; found, 352.0940; calcd for $C_{15}H_{17}N_4O_4{}^{37}Cl$ (M + H)$^+$, 354.0909; found, 354.0921.

*1-((6-Chloropyridin-3-yl)methyl)-4a-methyl-10-nitro-1,2,3,4a,6,7,8,9a-octahydro-[1,4]dioxepino[2′,3′:4,5]pyrrolo[1,2-a]-imidazole (**12b**).* Yield = 68%. White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 5.44 (d, J = 15.2 Hz, 1H), 4.98 (d, J = 15.2 Hz, 1H), 4.92 (s, 1H), 3.90−3.78 (m, 4H), 3.67−3.64 (m, 2H), 3.46−3.34 (m, 2H), 2.11−2.10 (m, 2H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 151.3, 149.3, 139.4, 130.6, 124.7, 104.0, 92.3, 89.6, 66.9, 63.4, 54.1, 49.2, 39.0, 32.9, 21.2. HRMS (ES+) calcd for $C_{16}H_{19}N_4O_4{}^{35}Cl$ (M + H)$^+$, 366.1095; found, 366.1091; calcd for $C_{16}H_{19}N_4O_4{}^{37}Cl$ (M + H)$^+$, 368.1065; found, 368.1084.

*1-((6-Chloropyridin-3-yl)methyl)-4a-methyl-11-nitro-2,3,4a,6,7,8,9,10a-octahydro-1H-[1,4]dioxocino[2′,3′:4,5]pyrrolo-[1,2-a]imidazole (**12c**).* Yield = 57%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, J = 2.4 Hz, 1H), 7.80 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 5.56 (d, J = 15.2 Hz, 1H), 4.96 (s, 1H), 4.90 (d, J = 15.2 Hz, 1H), 3.90−3.79 (m, 2H), 3.69−3.63 (m, 4H),

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3.51−3.44 (m, 2H), 1.72−1.59 (m, 6H), 1.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2, 151.2, 149.2, 139.5, 130.6, 124.8, 106.5, 92.1, 85.7, 71.5, 63.0, 62.2, 54.1, 49.2, 38.6, 29.3, 26.5, 17.5. HRMS (ES+) calcd for $C_{17}H_{21}N_4O_4{}^{35}Cl$ $(M + H)^+$, 380.1251; found, 380.1260; calcd for $C_{17}H_{21}N_4O_4{}^{37}Cl$ $(M + H)^+$, 382.1222; found, 382.1241.

Synthesis of the Target Molecules 13a−13d. $AlCl_3$ (0.2 mmol) was added to a solution of compound **10a** (2 mmol) in alcohol (20 mL). The reaction was warmed to reflux, and the progress of the reaction was detected by TLC. After 5−10 min, the color of the reaction mixture turned to wine red. H_2O (20 mL) was added, and the mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with sodium dicarbonate aqueous solution and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the pure products.

*1-((6-Chloropyridin-3-yl)methyl)-6-methoxy-5-methyl-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazole (**13a**).* Yield = 18%. Yellow solid. mp 119.4−120.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, J = 2.4 Hz, 1H), 7.73 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 4.95 (s, 2H), 3.91−3.86 (m, 2H), 3.79 (s, 3H), 3.75−3.70 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.0, 149.3, 143.1, 139.3, 136.9, 131.6, 124.6, 112.3, 110.2, 62.8, 53.0, 50.3, 42.8, 7.8. HRMS (EI+) calcd for $C_{14}H_{15}N_4O_3{}^{35}Cl$ $(M)^+$, 322.0833; found, 322.0833; calcd for $C_{14}H_{15}N_4O_3{}^{37}Cl$ $(M)^+$, 324.0803; found, 324.0816.

*1-((6-Chloropyridin-3-yl)methyl)-6-ethoxy-5-methyl-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazole (**13b**).* Yield = 36%. Yellow solid. mp 129.1−129.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, J = 2.0 Hz, 1H), 7.73 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 4.95 (s, 2H), 3.98 (q, J = 7.2 Hz, 2H), 3.91−3.87 (m, 2H), 3.74−3.70 (m, 2H), 2.02 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.0, 149.3, 143.1, 139.3, 135.5, 131.6, 124.6, 112.5, 110.6, 70.9, 53.0, 50.3, 42.8, 15.3, 7.8. HRMS (EI+) calcd for $C_{15}H_{17}N_4O_3{}^{35}Cl$ $(M)^+$, 336.0989; found, 336.0989; calcd for $C_{15}H_{17}N_4O_3{}^{37}Cl$ $(M)^+$, 338.0960; found, 338.0979.

*1-((6-Chloropyridin-3-yl)methyl)-5-methyl-7-nitro-6-propoxy-2,3-dihydro-1H-pyrrolo[1,2-a]imidazole (**13c**).* Yield = 60%. Yellow solid. mp 107.2−108.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, J = 2.4 Hz, 1H), 7.72 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 4.94 (s, 2H), 3.90−3.84 (m, 4H), 3.74−3.70 (m, 2H), 2.01 (s, 3H), 1.79−1.70 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.0, 149.3, 143.1, 139.3, 135.8, 131.7, 124.6, 112.5, 110.3, 77.2, 70.9, 53.0, 50.3, 42.8, 23.1, 10.4, 7.9. HRMS (EI+) calcd for $C_{16}H_{19}N_4O_3{}^{35}Cl$ $(M)^+$, 350.1146; found, 350.1141; calcd for $C_{16}H_{19}N_4O_3{}^{37}Cl$ $(M)^+$, 352.1116; found, 352.1116.

*6-Butoxy-1-((6-chloropyridin-3-yl)methyl)-5-methyl-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazole (**13d**).* Yield = 65%. Red solid. mp 83.8−84.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, J = 2.4 Hz, 1H), 7.73 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 4.95 (s, 2H), 3.93−3.86 (m, 4H), 3.73−3.70 (m, 2H), 2.02 (s, 3H), 1.76−1.69 (m, 2H), 1.53−1.44 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.1, 149.3, 143.1, 139.3, 135.9, 131.6, 124.6, 112.6, 110.3, 75.4, 53.0, 50.4, 42.8, 31.9, 19.1, 13.9, 7.9. HRMS (EI+) calcd for $C_{17}H_{21}N_4O_3{}^{35}Cl$ $(M)^+$, 364.1302; found, 364.1307; calcd for $C_{17}H_{21}N_4O_3{}^{37}Cl$ $(M)^+$, 366.1273; found, 366.1267.

*5-(((6-Chloropyridin-3-yl)methyl)(ethyl)amino)-1,2-dimethyl-4-nitro-2,3-dihydro-1H-pyrrole-2,3-diol (**14a**).* The fresh prepared nitenpyram **2**[16] (2.160 g, 8.0 mmol) was dissolved in dichloromethane (20 mL), and then methylglyoxal **9** (8.8 mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was added to 20 mL of water and extracted with CH_2Cl_2 3 times. The organic layers were combined and concentrated by rotary evaporation to provide the crude product **14a** as a yellow oil (1.760 g, 64%). HRMS (EI+) calcd for $C_{14}H_{20}N_4O_4{}^{35}Cl$ $(M + H)^+$, 343.1173; found, 343.1175; calcd for $C_{14}H_{20}N_4O_4{}^{37}Cl$ $(M + H)^+$, 345.1144; found, 345.1151.

Synthesis of the Target Molecules 14b−14f. $AlCl_3$ (0.2 mmol) was added to a solution of compound **14a** (2 mmol) in alcohol (20 mL). The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC. After completion, half of the solvent was removed and H_2O (20 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL), and the organic layer was washed with sodium dicarbonate aqueous solution and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the pure products.

*5-(((6-Chloropyridin-3-yl)methyl)(ethyl)amino)-3-methoxy-1,2-dimethyl-4-nitro-2,3-dihydro-1H-pyrrol-2-ol (**14b**).* Yield = 51%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, J = 1.6 Hz, 1H), 7.66 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 4.64 (d, J = 14.8 Hz, 1H), 4.54 (s, 1H), 4.50 (d, J = 14.8 Hz, 1H), 4.49 (s, 1H), 3.52 (s, 3H), 3.46−3.39 (m, 1H), 3.28−3.20 (m, 1H), 2.91 (s, 3H), 1.30 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 151.3, 148.9, 138.7, 130.9, 124.6, 111.2, 88.7, 81.5, 57.8, 52.0, 47.0, 28.7, 24.3, 14.1. HRMS (ES+) calcd for $C_{15}H_{21}N_4O_4{}^{35}Cl$ $(M)^+$, 356.1251; found, 356.1257; calcd for $C_{15}H_{21}N_4O_4{}^{37}Cl$ $(M)^+$, 358.1222; found, 358.1250.

*5-(((6-Chloropyridin-3-yl)methyl)(ethyl)amino)-3-ethoxy-1,2-dimethyl-4-nitro-2,3-dihydro-1H-pyrrol-2-ol (**14c**).* Yield = 43%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, J = 2.0 Hz, 1H), 7.66 (dd, J_1 = 8.0, J_2 = 2.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 4.61 (s, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.56 (s, 1H), 4.51 (d, J = 15.2 Hz, 1H), 3.76 (q, J = 6.8 Hz, 2H), 3.47−3.40 (m, 1H), 3.30−3.21 (m, 1H), 2.92 (s, 3H), 1.31 (s, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.21 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 151.2, 148.9, 138.7, 131.0, 124.6, 111.7, 88.5, 80.2, 66.1, 52.0, 47.1, 28.7, 24.3, 15.4, 14.1. HRMS (EI+) calcd for $C_{16}H_{23}N_4O_4{}^{35}Cl$ $(M)^+$, 370.1408; found, 370.1421; calcd for $C_{16}H_{23}N_4O_4{}^{37}Cl$ $(M)^+$, 372.1378; found, 372.1353.

*5-(((6-Chloropyridin-3-yl)methyl)(ethyl)amino)-1,2-dimethyl-4-nitro-3-propoxy-2,3-dihydro-1H-pyrrol-2-ol (**14d**).* Yield = 41%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 4.62 (s, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.55 (s, 1H), 4.50 (d, J = 15.2 Hz, 1H), 3.70−3.61 (m, 2H), 3.48−3.39 (m, 1H), 3.28−3.19 (m, 1H), 2.91 (s, 3H), 1.61−1.54 (m, 2H), 1.29 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 151.2, 148.9, 138.7, 131.0, 124.6, 111.6, 88.6, 80.2, 72.1, 51.9, 47.1, 28.7, 24.3, 23.0, 14.1, 10.5. HRMS (EI+) calcd for $C_{17}H_{25}N_4O_4{}^{35}Cl$ $(M)^+$, 384.1564; found, 384.1566; calcd for $C_{17}H_{25}N_4O_4{}^{37}Cl$ $(M)^+$, 386.1535; found, 386.1574.

*5-(((6-Chloropyridin-3-yl)methyl)(ethyl)amino)-3-isopropoxy-1,2-dimethyl-4-nitro-2,3-dihydro-1H-pyrrol-2-ol (**14e**).* Yield = 35%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 4.55 (s, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.53 (s, 1H), 4.43 (d, J = 15.6 Hz, 1H), 4.05−3.93 (m, 1H), 3.39−3.33 (m, 1H), 3.22−3.09 (m, 1H), 2.84 (s, 3H), 1.21 (s, 3H), 1.19−1.04 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 150.9, 148.9, 138.7, 131.1, 124.5, 111.8, 88.3, 78.8, 72.2, 51.9, 47.0, 28.6, 24.1, 23.1, 22.1, 14.0. HRMS (EI+) calcd for $C_{17}H_{25}N_4O_4{}^{35}Cl$ $(M)^+$, 384.1564; found, 384.1560; calcd for $C_{17}H_{25}N_4O_4{}^{37}Cl$ $(M)^+$, 386.1535; found, 386.1497.

*3-Butoxy-5-(((6-chloropyridin-3-yl)methyl)(ethyl)amino)-1,2-dimethyl-4-nitro-2,3-dihydro-1H-pyrrol-2-ol (**14f**).* Yield = 42%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 4.60 (s, 1H), 4.65 (d, J = 15.6 Hz, 1H), 4.52 (s, 1H), 4.49 (d, J = 15.6 Hz, 1H), 3.70−3.60 (m, 2H), 3.44−3.37 (m, 1H), 3.26−3.17 (m, 1H), 2.89 (s, 3H), 1.56−1.49 (m, 2H), 1.38−1.30 (m, 2H), 1.27 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 151.1, 148.9, 138.6, 131.0, 124.6, 111.6, 88.6, 80.3, 70.2, 51.9, 47.1, 31.8, 28.6, 24.2, 19.2, 14.1, 13.8. HRMS (EI+) calcd for $C_{18}H_{27}N_4O_4{}^{35}Cl$ $(M)^+$, 398.1721; found, 398.1731; calcd for $C_{18}H_{27}N_4O_4{}^{37}Cl$ $(M)^+$, 400.1691; found, 400.1715.

Synthesis of the Target Molecules 15a−15c. $AlCl_3$ (0.2 mmol) was added to a solution of fresh prepared compound **14a** (2 mmol) in alcohol (20 mL). The reaction was warmed to reflux, and the progress of the reaction was detected by TLC. After completion, half of the solvent was removed and H_2O (20 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL), and the organic layer was washed with sodium dicarbonate aqueous solution and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The

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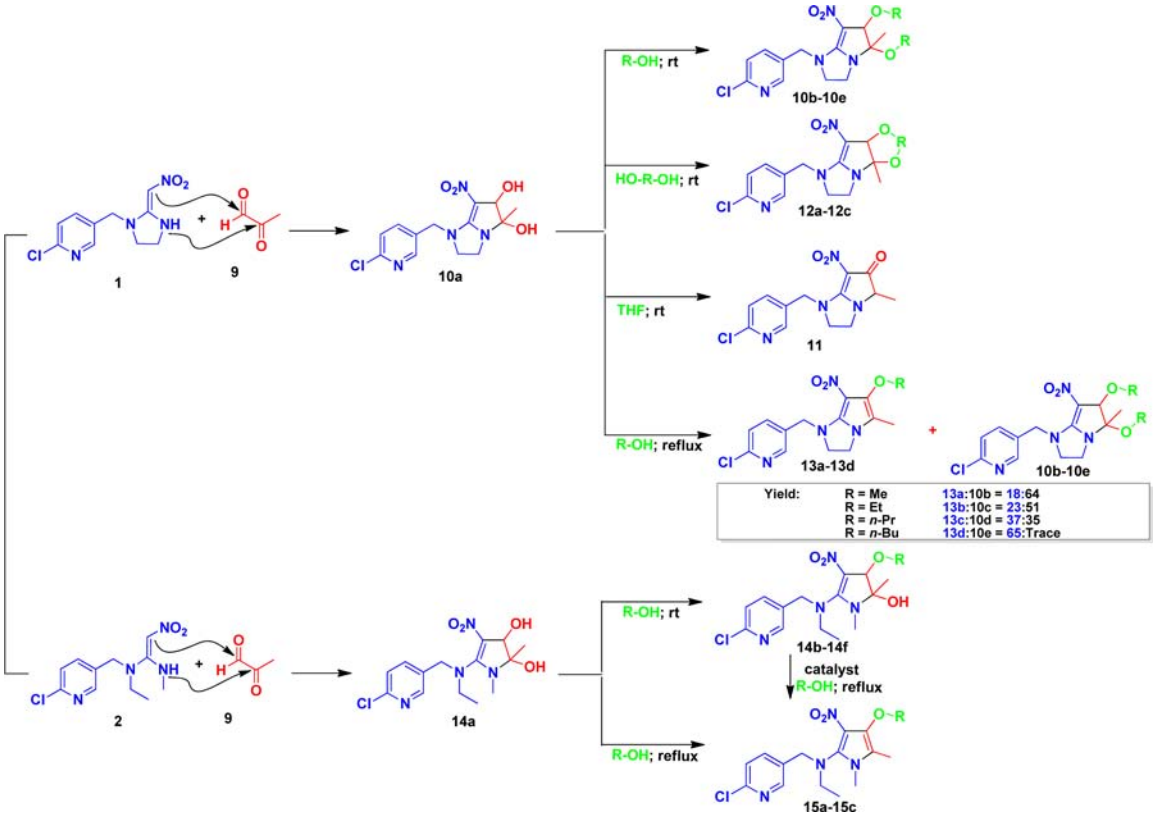
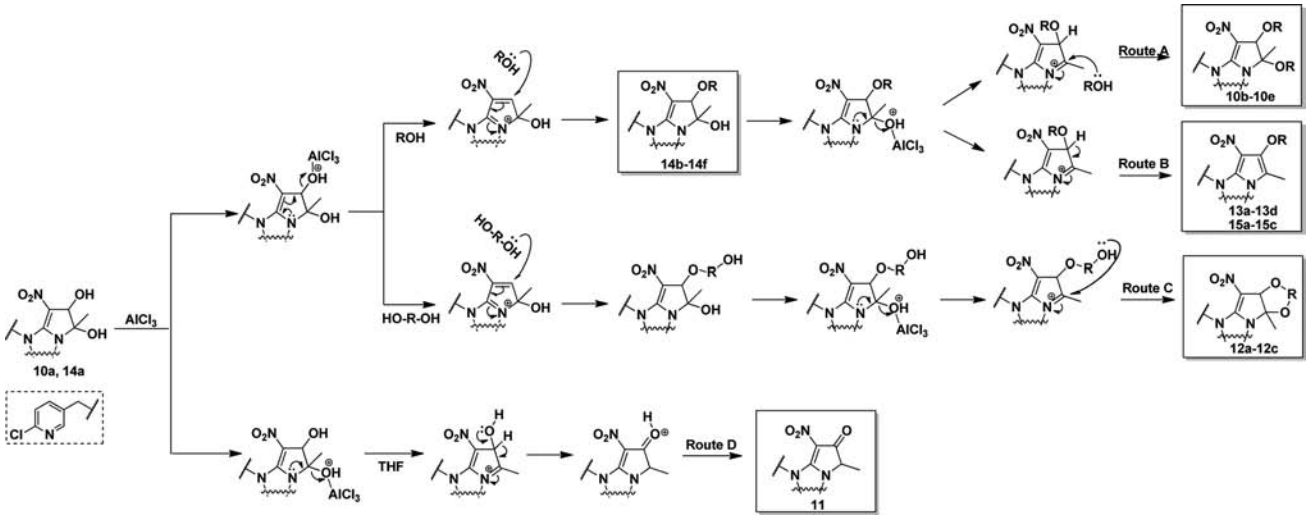
Scheme 2. Reaction Route To Synthesis the Target Compounds



Scheme 3. Presumed Synthetic Mechanism of the Target Compounds



residue was purified by silica gel column chromatography to give the pure products.

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-4-methoxy-1,5-dimethyl-3-nitro-1H-pyrrol-2-amine (**15a**).* Yield = 58%. Yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.30 (d, J = 2.0 Hz, 1H), 7.76 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 4.23 (s, 2H), 3.66 (s, 3H), 3.31 (s, 3H), 3.15−3.00 (m, 2H), 2.04 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.4, 149.6, 140.6, 135.7, 135.7, 134.0, 124.4, 122.6, 115.7, 62.5, 53.3, 47.2, 29.8, 13.9, 8.3. HRMS (EI+) calcd for $C_{15}H_{19}N_4O_3{}^{35}Cl$ $(M)^+$, 338.1146; found, 338.1137; calcd for $C_{15}H_{19}N_4O_3{}^{37}Cl$ $(M)^+$, 340.1116; found, 340.1121.

*N-((6-Chloropyridin-3-yl)methyl)-4-ethoxy-N-ethyl-1,5-dimethyl-3-nitro-1H-pyrrol-2-amine (**15b**).* Yield = 52%. Yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.27 (d, J = 2.0 Hz, 1H), 7.74 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 4.23 (s, 2H), 3.85 (q, J = 7.2 Hz, 2H), 3.30 (s, 3H), 3.15−3.00 (m, 2H), 3.13−3.00 (m, 2H), 2.02 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.4, 149.6, 140.6, 135.7, 134.3, 133.9, 124.4, 122.9, 116.1, 70.5, 53.3, 47.3, 29.9, 15.6, 13.9, 8.5. HRMS (EI+) calcd for $C_{16}H_{21}N_4O_3{}^{35}Cl$ $(M)^+$, 352.1302; found, 352.1299; calcd for $C_{16}H_{21}N_4O_3{}^{37}Cl$ $(M)^+$, 354.1273; found, 354.1282.

*N-((6-Chloropyridin-3-yl)methyl)-N-ethyl-1,5-dimethyl-3-nitro-4-propoxy-1H-pyrrol-2-amine (**15c**).* Yield = 49%. Yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.27 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 4.22 (s, 2H), 3.74 (q, J = 6.8 Hz, 2H), 3.30 (s, 3H), 2.02 (s, 3H), 1.68−1.59 (m, 2H), 0.95 (t, J = 6.8 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.4, 149.6, 140.6, 135.6, 134.6, 133.9, 124.4, 122.9, 115.8, 76.6, 53.3, 47.3, 29.8,

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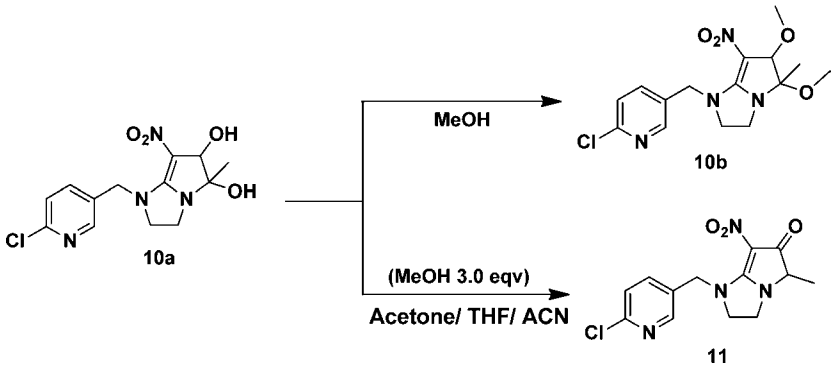
Table 1. Optimum Process To Synthesis the Target Molecules



entry	solvent	catalyst	catalyst amount (mol %)	temperature (°C)	time	yield (%)
1	MeOH	HCl	10	25	2 h	**10b**: 84
2	MeOH	none		25	24 h	nr
3	MeOH	$CoCl_2$	10	25	24 h	nr
4	MeOH	$CsCl_2$	10	25	24 h	nr
5	MeOH	$ZnCl_2$	10	25	24 h	nr
6	MeOH	$NiCl_2$	10	25	24 h	nr
7	MeOH	$FeCl_3$	10	25	45 min	**10b**: 79
8	MeOH	TsOH	10	25	1 h	**10b**: 78
9	MeOH	$BF_3{\cdot}Et_2O$	10	25	1.5 h	**10b**: 83
10	MeOH	$AlCl_3$	10	25	15 min	**10b**: 86
11	MeOH	$AlCl_3$	5	25	45 min	**10b**: 86
12	MeOH	$AlCl_3$	15	25	10 min	**10b**: 85
13	MeOH	$AlCl_3$	20	25	5 min	**10b**: 77
14	acetonitrile	$AlCl_3$	10	25	24 h	**11**: 16
15	acetone	$AlCl_3$	10	25	24 h	**11**: 19
16	1,4-dioxane	$AlCl_3$	10	25	24 h	**11**: 25
17	DMF	$AlCl_3$	10	25	24 h	**11**: 31
18	THF	$AlCl_3$	10	25	24 h	**11**: 35
19	THF	$AlCl_3$	10	25	24 h	**11**: 33
20	THF	$AlCl_3$	0	25	24 h	nr

23.1, 13.9, 10.8, 8.4. HRMS (EI+) calcd for $C_{17}H_{23}N_4O_3{}^{35}Cl$ $(M)^+$, 366.1459; found, 366.1458; calcd for $C_{17}H_{23}N_4O_3{}^{37}Cl$ $(M)^+$, 368.1429; found, 368.1446.

X-ray Diffraction Analysis. Compound **10b** was recrystallized by slow evaporation from a mixture of acetone and methanol to afford a suitable single crystal. Yellow blocks of compound **10b** (0.369 × 0.325 × 0.280 mm) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART charge-coupled device (CCD) area detector diffractometer with graphite monochromated Mo Kα radiation (λ = 0.710 73 Å); θ_{max} = 27.49; 18 236 measured reflections; 7031 independent reflections (R_{int} = 0.0626). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.8034, and T_{max} = 1.0000). The structure was solved by direct methods using SHELXS-97;[17] all other calculations were performed with the Bruker SAINT system and Bruker SMART programs.[18] Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0613P)^2 + 0.0371P]$ gave final values of R = 0.0457, ωR = 0.1097, and GOF (F) = 0.945 for 439 variables and 7031 contributing reflections. Maximum shift/error = 0.000(3), and maximum/minimum residual electron density = 0.292/−0.209 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Biology Assay. All compounds were dissolved in *N*,*N*-dimethylformamide (DMF, 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. The insecticidal activity of the synthetic compounds against cowpea aphids (*Aphis craccivora*) was tested according to our previous reported procedure.[4,19]

RESULTS AND DISCUSSION

Synthesis. Herein, two important *ortho*-dihydroxy-group-substituted intermediates **10a** and **14a** were designed and synthesized by reacting compound **1** or **2** with methylglyoxal **9** via aza−ene addition (Scheme 2).[20,21] Subsequently, the target products were smoothly and regioselectively prepared through etherification reaction, elimination reaction, cycloaddition reaction, and rearrangement reaction on the dihydroxy groups. The plausible mechanism was presumed in Scheme 3.[22]

During our attempt to obtain compound **10b**, the effect on the catalysts and the corresponding amounts were investigated while taking methanol as the reaction solvent. The results were listed in Table 1. Initially, the reaction was carried out with HCl (10 mol %) catalyzed and monitored by TLC, and the target compound **10b** was successfully acquired in a high yield. This encouraged us to optimize the etherification reaction with more candidate catalysts. The experimental results (entry 2 in Table 1) proved that it was infeasible to complete the reaction without any catalyst. Similar data were also achieved when $CoCl_2$, $CsCl_2$, $PdCl_2$, and $NiCl_2$ were tried as the catalysts. While screening for other protonic acids and Lewis acids, among which we found that $AlCl_3$ (10 mol %) presented satisfactory catalytic activity, the yield of compound **10b**

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reached 86% in 15 min. Further results proved that increasing or decreasing the amount of $AlCl_3$ would not lead to the improvement of the yield or shortening of the reaction time. However, when we tried to reduce the amount of methanol to 3.0 equiv, the reaction proceeded in another pathway. The ketone product **11** was formed rather than compound **10b** while using several other solvents [DMF, tetrahydrofuran (THF), acetone, etc.]. Further results proved that product **11** could also be obtained without methanol (entry 19 in Table 1). Among the candidate solvents, THF displayed a positive effect on generating compound **11**.

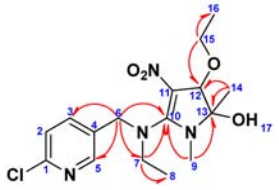
With the above optimized conditions in hand, we took various alcohols as the reactants as well as solvents to obtain the etherification of the dihydroxy group on the dihydropyrrole ring. A series of dietherified cyclic titled compounds **10b**−**10e** and **12a**−**12c** were gained, and the corresponding yields were decreased with the extension of the alkyl chains. However, when nitenpyram **2** was taken as the reactant, we obtained another series of non-cyclic neonicotinoid derivatives **14b**−**14f** with monohydroxyl-etherified products (Scheme 2). All of the synthesized compounds were confirmed by NMR and HRMS, and heteronuclear chemical shift correlation experiments [heteronuclear multiple-bond correlation (HMBC) and correlation spectroscopy (COSY)] were also performed to confirm the assignments of the ^{13}C and ^{1}H NMR spectra and to investigate the accurate structure of the compounds. A complete assignment of the proton signals and selected HMBC correlations of compound **14c** were shown in Table 2.

Dietherified compounds **10b**−**10e** were obtained in decreasing yields from compounds **10b** to **10e** at room temperature, which suggested that the dietherification selectivity was gradually weakened with the extension of the alkyl chains. Under reflux conditions, the dietherified compound **10b** was obtained accompanied with the forming of eliminated product **13a** (R = methyl). The yield of compound **13a** was low (yield = 18%), and compound **10b** was the main product (yield = 64%). Meanwhile, to the molecules **10e** and **13d** (R = *n*-Bu), compound **13d** was gained in a high yield (yield = 65%) with almost no compound **10e** produced (Scheme 2). Thus, different dietherified compounds and eliminated compounds with longer alkyl chains could also be selected with high yields. Further optimization on the catalyst proved that $AlCl_3$ possessed the ideal catalytic activity in terms of the reaction time as well as the yield.

With regard to the non-cyclic compound **14a**, one of the hydroxyl groups was successfully etherified at room temperature. The etherification reaction activity of the other hydroxyl group was poor (**14b**−**14f**). Meanwhile, the reaction was predominated by the eliminated process, and the eliminated compounds **15a**−**15c** were gained in relatively high yields without any dietherified molecule observed under reflux conditions.

Crystal Structure Analysis. Several characters of the structure were apparently presented in the crystal spectra (Figure 1). The pharmacophore nitromethylene group laid approximately in the same plane with the imidazoline ring,[23−25] and the torsion angle of N3−C3−C4−N2 was −9.7(6)°. A coplanar olefin−amine extended π electron was formed under the delocalization role of the lone pair electron on the amine and the withdrawing effect of the nitro group. It resulted that the C−N bond on the conjugation system bore the characteristic of C═N (imine).[26] The bond lengths of C4−N1 and C4−N2 were 1.35 and 1.34 Å, respectively, which were much shorter than the normal C−N (1.47 Å) but close to C═N (1.33 Å). Moreover, the double bond C3═C4 was apparently displaced with the ring tension of the fused five-membered dihydropyrrole cycle. In comparison to the infused molecule **1**, the corresponding bond angle for C3−C4−N2 enlarged from 117.1°[23] to 140.3(3)° and C3−C4−N1 changed from 128.3°[23] to 109.1(2)°. Meanwhile, O1 and O2 were

Table 2. NMR Data and HMBC Correlation of Compound 14c



atom number	δ_H (m, *J* in Hz)	δ_C	HMBC (δ_H to δ_C)
1		151.2	
2	7.32 (d, 8.0)	124.6	1, 3, 4
3	7.65 (dd, 2.0, 8.0)	138.7	1, 5, 6
4		131.0	
5	8.29 (d, 2.0)	148.9	1, 2, 3, 4, 6
6	4.51 (d, 15.6), 4.67 (d, 15.6)	51.9	3, 4, 5, 7, 10
7	3.40−3.48 (m), 3.20−3.29 (m)	47.1	3, 6, 8, 10
8	1.24 (t, 7.2)	14.1	7
9	2.92 (s)	28.7	10, 13
10		160.6	
11		111.7	
12	4.56 (s)	80.2	11, 14, 15
13		88.5	
14	1.30 (s)	24.3	12, 13
15	3.75 (q, 7.2)	66.1	12, 16
16	1.21 (t, 7.2)	15.4	15
17	4.60 (s)		

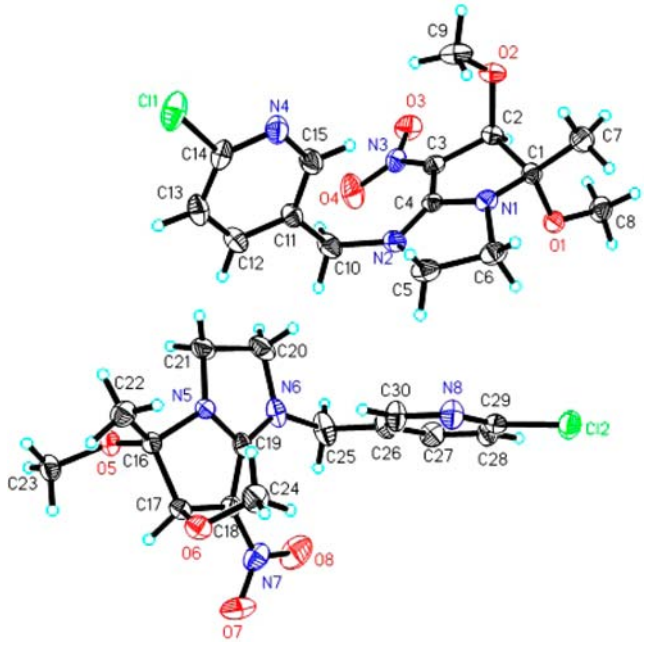


Figure 1. Crystal structure of compound **10b**.

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positioned in an opposite place over the dihydropyrrole ring, and O2 shared the same orientation with N4 on the pyridine cycle.

Insecticidal Activity. Table 3 lists the insecticidal activity of the titled compounds against cowpea aphid (*A. craccivora*).

Table 3. Insecticidal Activity Results of the Synthetic Compounds

	A. craccivora	
compound	mortality (%, 500 mg L^{-1})	LC_{50} (mg L^{-1})
10a	100	2.0
10b	100	0.7
10c	100	0.6
10d	100	0.8
10e	100	3.4
11	100	43.5
12a	100	10.0
12b	100	11.1
12c	100	14.8
13a	100	14.6
13b	100	37.3
13c	100	24.5
13d	100	39.5
14b	21.6	nt
14c	29.7	nt
14d	19.0	nt
14e	21.2	nt
14f	16.4	nt
15a	91	nt
15b	84	nt
15c	77	nt
imidacloprid	100	8.9

The bioassay results revealed that different structures of pyrrole- and dihydropyrrole-fused neonicotinoid analogues presented apparently different bioactivities. In general, the cyclic neonicotinoid derivatives displayed quite exciting insecticidal results (**10a−10e**, **12a−12c**, and **13a−13d** in Table 3). The mortality of all tested compounds reached 100% under the concentration of 500 mg L^{-1}. Some of the synthesized molecules showed 10-fold higher activities than imidacloprid (**10b−10d** in Table 3). In comparison to the unetherified dihydroxypyrrole **10a**, bioactivity improvements were achieved in the etherified compounds **10b−10d** and the extension of alkyl on the ether bond did not necessarily result in an increase in the activity (**10e** in Table 3). Nevertheless, the cyclizing of the two ether bonds would lead to the decrease in the bioactivity (**12a−12c**), which might have resulted from the rigid structure and steric effect of the fused tricyclic rings. The eliminated compounds **13a−13d** also presented moderate insecticidal performances. Incredibly, great disparity in insecticidal activity appeared between the non-cyclic fused ring compounds and cyclic fused ring compounds. According to the bioactivity results, no significant mortality was observed for the eliminated products **15a−15c** and monohydroxyl etherified products **14b−14f** under the concentration of 500 mg L^{-1}, and the corresponding LC_{50} values were not investigated (Table 3).

In conclusion, two important *ortho*-dihydroxy-group-substituted dihydropyyrole intermediates were designed and constructed. Versitile products, such as dihydroxy-etherified compounds, monohydroxyl-etherified compounds, ketone products, and eliminated products, were obtained through etherification reaction, elimination reaction, cycloaddition reaction, and rearrangement reaction on the dihydroxy groups. The target compounds were obtained in relatively high yields with the optimized reaction conditions. Dihydroxyl-etherified target compounds, monohydroxyl-etherified compounds, and eliminated compounds were obtained while taking cyclic or non-cyclic neonicotinoid as a reactant. All of the synthesized compounds were verified by ^{1}H and ^{13}C NMR and HRMS. Intriguingly, the insecticidal activity of the titled compounds was evaluated against cowpea aphid (*A. craccivora*), and the preliminary results indicated that those cyclic derivatives exhibited satisfactory insecticidal activity and LC_{50} values of molecules **10b−10d** were 10-fold higher than imidacloprid. Meanwhile, the synthesized non-cyclic compounds did not present satisfactory insecticidal activity. Further photostability evaluation and mode of action investigation of the titled compounds is in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR, IR, and HRMS spectra of the cyclic target compounds and crystallographic information files (CIFs) of compound **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Telephone: +86-21-64253540. Fax: +86-21-64252603. E-mail: lizhong@ecust.edu.cn.

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Notes

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