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Seven-Membered Azabridged Neonicotinoids: Synthesis, Crystal Structure, Insecticidal Assay, and Molecular Docking Studies

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Supporting Information

ABSTRACT: To study the influence of the ring sizes, 37 novel seven-membered azabridged neonicotinoid analogues were synthesized by reactions of nitromethylene analogues, succinaldehyde, and aniline hydrochlorides. Most of the title compounds presented higher insecticidal activities than that of imidacloprid (IMI), cycloxaprid (CYC), and eight-membered compounds against cowpea aphid (*Aphis craccivora*), armyworm (*Pseudaletia separata* Walker), and brown planthopper (*Nilaparvata lugens*), which indicated that introducing the structure of a seven-membered azabridge could significantly improve the insecticidal activities of neonicotinoid analogues. Docking study and binding mode analysis also revealed that introducing methyl group into position 2 of phenyl ring could increase the hydrophobic interactions with receptor, which implied that position 2 might be the key site to get high insecticidal compounds.

KEYWORDS: *cycloxaprid, seven-membered azabridge, neonicotinoids, insecticide*

INTRODUCTION

The nicotinic acetylcholine receptors (nAChRs) belong to the Cys-loop superfamily of agonist-gated ion channels.[1] They are widely distributed in the central nervous systems (CNS) and participated in regulating major physiological functions and pathophysiological processes.[2,3] The nAChRs mediate rapid excitatory neurotransmission and are the target of many toxicants, potential therapeutic agents,[4] and insecticides.[5]

The natural azabridged compound epibatidine (EPI) (Figure 1) is an extremely potent but nonselective nAChRs agonist[6]

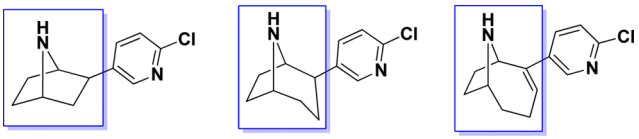

Figure 1. Ring expansion of epibatidine.

that has been subjected to numerous structure−activity relationship (SAR) studies. With the expansion of the bridged ring, the seven- and eight-membered compounds homoepibatidine[7] and UB-165[8] (Figure 1) were synthesized, respectively, and reported to show high affinity and selectivity for the $\alpha4\beta2$ receptor subtype, which means that the variation of bridged ring sizes could significantly influence the bioactivities. Moreover, to our best knowledge, such SAR studies were rarely reported in the exploration of potential neonicotinoid insecticides.

In our previous work, enlightened by two unexpected oxabridged compounds **A** and cycloxaprid (CYC)[9] (Figure 2), three series of eight-membered azabridged neonicotinoid

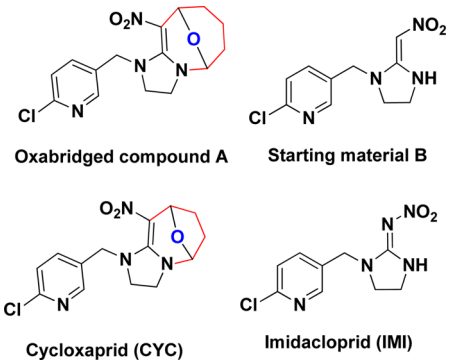

Figure 2. Oxabridged and neonicotinoid compounds.

analogues were designed and synthesized.[10] Most of the azabridged compounds displayed higher bioactivities than eight-membered oxabridged compound **A** against cowpea aphid (*Aphis craccivora*) and brown planthopper (*Nilaparvata lugens*), which indicated that changing the bridge atom from O to N could greatly affect the insecticidal activities.

To study the influence of ring sizes on insecticidal activities, in this paper, a series of seven-membered azabridged neonicotinoids were synthesized from starting material **B**, succinaldehyde, and aniline hydrochlorides (Scheme 1), followed with crystal structure, insecticidal assay, docking, and SAR analysis.

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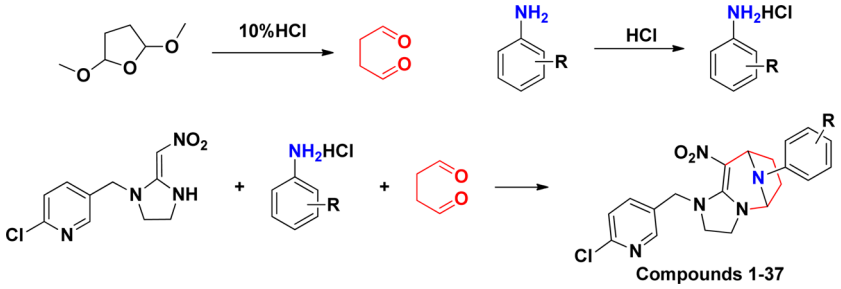
Scheme 1. Synthetic Routes of Compounds 1−37



MATERIALS AND METHODS

Instruments. All melting points were obtained with a Büchi Melting Point B540 and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker AM-400 spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent (^{1}H at 400 MHz and ^{13}C at 100 MHz) and TMS as the internal standard. Chemical shifts are reported in parts per million (δ). Coupling constants (J) are reported in hertz (Hz). High-resolution electron mass spectra (ESI-TOF) were performed on a Micromass LC-TOF spectrometer. 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 the Substituted Aniline Hydrochloride. The corresponding aniline (10 mmol) in ethyl acetate (15 mL) was cooled to 0 °C. A solution of concentrated HCl was dropwise added and the pH value of the reaction mixture adjusted to 1−2. After the addition was completed, precipitate was filtered and washed with less concentrated HCl and ethyl acetate. After drying under vacuum, the obtained corresponding aniline hydrochloride could be used without further purification.

Preparation of the Solution of Succinaldehyde. A mixture of 2,5-dimethoxydihydrofuran (0.290 g, 2.2 mmol) and 0.4 mL of 10% aqueous HCl was stirred at room temperature. After 12 h, the pH value of the mixture was adjusted to 2−3 by saturated aqueous $NaHCO_3$. The solution could be used directly in the next step.

General Synthetic Procedure for Compounds 1−37. A mixture of starting material **B** (2 mmol) and corresponding aniline hydrochloride (2.5 mmol) in acetonitrile (20 mL) was stirred at 0 °C. Then the solution of succinaldehyde was slowly added, and the reaction was monitored by TLC. After 1.5 h, the pH value of the mixture was adjusted to 7−8 by saturated aqueous $NaHCO_3$, and the solvent was removed under reduced pressure. Then, water was added, the mixture was extracted with dichloromethane (3 × 50 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 afford the corresponding product.

1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-phenyl-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (***1***)*:* yield, 44.8%; mp, 173−174 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 2.0 Hz, 1H), 7.30−7.20 (m, 4H), 6.94 (d, J = 8.0 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 5.62 (s, 1H), 5.26 (s, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 3.82−3.71 (m, 1H), 3.70−3.50 (m, 2H), 3.46−3.36 (m, 1H), 2.28−2.12 (m, 3H), 2.00−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 149.6, 149.6, 145.0, 138.9, 132.4, 129.7, 124.5, 120.6, 117.7, 109.3, 71.5, 56.9, 50.7, 49.7, 47.4, 31.5, 31.4; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}ClN_5O_2Na$ (M + Na)$^+$ 420.1203, found 420.1195; calcd for $C_{20}H_{20}{}^{37}ClN_5O_2Na$ (M + Na)$^+$ 422.1174; found 422.1186.

10-(4-Bromophenyl)-1-((6-chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (***2***)*:* yield, 84.0%; mp, 203−204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.27 (s, 2H), 6.91 (d, J = 8.4 Hz, 2H), 5.62 (s, 1H), 5.23 (s, 1H), 4.86 (d, J = 15.6 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 3.82−3.71 (m, 1H), 3.72−3.61 (m, 1H), 3.62−3.52 (m, 1H), 3.50−3.39 (m, 1H), 2.28−2.10 (m, 3H), 1.98−1.88 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.8, 149.7, 149.6, 144.5, 138.8, 132.3, 124.4, 119.9, 112.2, 109.0, 71.5, 57.1, 50.6, 49.8, 47.3, 31.6, 31.4; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}Cl^{79}BrN_5O_2$ (M + H)$^+$ 476.0489, found 476.0487; calcd for $C_{20}H_{20}{}^{37}Cl^{81}BrN_5O_2$ (M + H)$^+$ 480.0439, found 480.0447.

1-((6-Chloropyridin-3-yl)methyl)-10-(4-methoxyphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (***3***)*:* yield, 82.5%; mp, 177−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 2.0 Hz, 1H), 7.28−7.20 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 5.53 (s, 1H), 5.17 (s, 1H), 4.87 (d, J = 15.6 Hz, 1H), 4.57 (d, J = 15.6 Hz, 1H), 3.84−3.75 (m, 1H), 3.74 (s, 3H), 3.71−3.58 (m, 2H), 3.58−3.48 (m, 1H), 2.26−2.05 (m, 3H), 1.95−1.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 153.6, 149.6, 138.9, 138.5, 132.5, 124.5, 124.3, 118.9, 115.0, 109.2, 72.0, 55.5, 50.5, 49.5, 47.5, 31.6, 31.5, 15.6; HRMS (ES+) calcd for $C_{21}H_{22}{}^{35}ClN_5O_3Na$ (M + Na)$^+$ 450.1303, found 450.1324; calcd for $C_{21}H_{22}{}^{37}ClN_5O_3Na$ (M + Na)$^+$ 452.1279, found 452.1290.

1-((6-Chloropyridin-3-yl)methyl)-10-(4-fluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (***4***)*:* yield, 35.9%; mp, 165−166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 8.4, 1.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 8.8 Hz, 2H), 6.98−6.89 (m, 2H), 5.58 (s, 1H), 5.22 (s, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 3.82−3.71 (m, 1H), 3.70−3.61 (m, 1H), 3.61−3.51 (m, 1H), 3.50−3.39 (m, 1H), 2.29−2.07 (m, 3H), 1.97−1.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9 (d, J = 236.8 Hz), 155.8, 149.7, 149.6, 141.5 (d, J = 2.0 Hz), 139.0, 132.3, 124.3, 119.1 (d, J = 7.6 Hz), 116.1 (d, J = 22.1 Hz), 109.1, 71.9, 57.4, 50.7, 49.8, 47.3, 31.7, 31.5; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}ClFN_5O_2$ (M + H)$^+$ 416.1290, found 416.1278; calcd for $C_{20}H_{20}{}^{37}ClFN_5O_2$ (M + H)$^+$ 418.1260, found 418.1265.

1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(p-tolyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (***5***)*:* yield, 72.3%; mp, 183−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = 8.4, 1.6 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 7.2 Hz, 2H), 6.82 (d, J = 7.2 Hz, 2H), 5.57 (s, 1H), 5.20 (s, 1H), 4.86 (d, J = 15.2 Hz, 1H), 4.56 (d, J = 15.2 Hz, 1H), 3.84−3.70 (m, 1H), 3.72−3.59 (m, 1H), 3.58−3.47 (m, 1H), 3.47−3.36 (m, 1H), 2.24 (s, 3H), 2.23−2.03 (m, 3H), 1.97−1.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.8, 149.6, 149.6, 142.6, 139.0, 132.4, 130.1, 129.3, 124.4, 117.7, 109.3, 71.7, 57.0, 50.5, 49.7, 47.6, 31.5, 31.4, 20.6; HRMS (ES+) calcd for $C_{21}H_{23}{}^{35}ClN_5O_2$ (M + H)$^+$ 412.1540, found 412.1542; calcd for $C_{21}H_{23}{}^{37}ClN_5O_2$ (M + H)$^+$ 414.1511, found 414.1517.

1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(4-(trifluoromethyl)-phenyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]-azepine (***6***)*:* yield, 46.2%; mp, 190−191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 1.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.35 (dd, J = 8.4, 1.6 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 5.75 (s, 1H), 5.35 (s, 1H), 4.87 (d, J = 15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 3.83−3.73 (m, 1H), 3.73−3.56 (m, 2H), 3.53−3.42 (m, 1H), 2.31−2.14 (m, 3H), 2.01−1.91 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 149.7, 149.6, 148.4, 139.0, 132.3, 126.9 (d, J = 3.6 Hz), 125.2 (d, J = 270.9 Hz), 124.2, 120.6 (q, J = 32.0 Hz), 117.7, 109.0, 71.2, 57.0, 50.7, 50.0, 47.2, 31.6, 31.3; HRMS (ES+) calcd for $C_{21}H_{20}{}^{35}ClN_5O_2F_3$ (M + H)$^+$ 466.1258, found 466.1252; calcd for $C_{21}H_{20}{}^{37}ClN_5O_2F_3$ (M + H)$^+$ 468.1228, found 468.1225.

4-(1-((6-Chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepin-10-yl)benzonitrile (***7***)*:*

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yield, 89.4%; mp, 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.40 (dd, J = 8.0, 1.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 5.75 (s, 1H), 5.36 (s, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 3.82−3.43 (m, 4H), 2.31−2.10 (m, 3H), 2.01−1.89 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 154.5, 154.2, 153.7, 143.9, 138.8, 137.0, 129.1, 124.6, 122.8, 113.9, 106.8, 75.9, 61.7, 55.5, 54.9, 51.9, 36.4, 36.0; HRMS (ES+) calcd for $C_{21}H_{20}{}^{35}ClN_6O_2$ (M + H)$^+$ 423.1336, found 423.1337; calcd for $C_{21}H_{20}{}^{37}ClN_6O_2$ (M + H)$^+$ 425.1307, found 425.1313.

*10-(4-Chlorophenyl)-1-((6-chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**8**):* yield, 68.6%; mp, 200−201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 1.6 Hz, 1H), 7.30−7.18 (m, 4H), 6.91 (d, J = 8.0 Hz, 2H), 5.57 (s, 1H), 5.19 (s, 1H), 4.80 (d, J = 15.6 Hz, 1H), 4.54 (d, J = 15.6 Hz, 1H), 3.79−3.67 (m, 1H), 3.67−3.57 (m, 1H), 3.57−3.47 (m, 1H), 3.47−3.34 (m, 1H), 2.25−2.06 (m, 3H), 1.95−1.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 154.4, 154.4, 148.8, 143.7, 137.1, 134.2, 129.1, 129.1, 124.2, 113.8, 76.3, 62.0, 55.4, 54.6, 52.1, 36.4, 36.1; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}Cl_2N_5O_2$ (M + H)$^+$ 432.0994, found 432.0982; calcd for $C_{20}H_{20}{}^{37}Cl_2N_5O_2$ (M + H)$^+$ 436.0935, found 436.0940.

*1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(4-nitrophenyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**9**):* yield, 65.7%; mp, 234−235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 9.2 Hz, 2H), 8.05 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 8.4, 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 9.2 Hz, 2H), 5.80 (s, 1H), 5.43 (d, J = 5.6 Hz, 1H), 4.84 (d, J = 15.6 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 3.82−3.61 (m, 3H), 3.57−3.49 (m, 1H), 2.31−2.16 (m, 3H), 2.03−1.94 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.7, 151.0, 149.6, 149.3, 140.3, 139.3, 132.1, 126.0, 124.2, 117.3, 109.2, 71.2, 57.4, 50.7, 50.3, 47.1, 31.7, 31.2; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}ClN_6O_4$ (M + H)$^+$ 443.1235, found 443.1252; calcd for $C_{20}H_{20}{}^{37}ClN_6O_4$ (M + H)$^+$ 445.1205, found 445.1221.

*10-(2-Chlorophenyl)-1-((6-chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**10**):* yield, 75.8%; mp, 181−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 2.0 Hz, 1H), 7.69 (dd, J = 8.4, 2.4 Hz, 1H), 7.48−7.40 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 5.47 (s, 1H), 5.20 (s, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.74 (d, J = 15.6 Hz, 1H), 3.80−3.61 (m, 2H), 3.59−3.40 (m, 2H), 2.26−2.06 (m, 3H), 1.98−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 149.8, 149.7, 141.5, 139.7, 132.4, 131.3, 128.5, 126.0, 124.5, 124.4, 121.9, 108.5, 72.4, 58.7, 51.0, 49.9, 46.5, 31.7, 31.6; HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}Cl_2N_5O_2Na$ (M + Na)$^+$ 454.0808, found 454.0819; calcd for $C_{20}H_{19}{}^{37}Cl_2N_5O_2Na$ (M + Na)$^+$ 458.0754, found 458.0745.

*10-(2-Bromophenyl)-1-((6-chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**11**):* yield, 76.0%; mp, 181−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.0, 2.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.03−6.90 (m, 2H), 5.44 (s, 1H), 5.21 (s, 1H), 4.82 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 3.81−3.62 (m, 2H), 3.62−3.51 (m, 1H), 3.52−3.42 (m, 1H), 2.26−2.05 (m, 3H), 1.97−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 149.8, 149.8, 142.8, 139.8, 134.5, 132.4, 129.0, 125.1, 124.5, 122.3, 116.8, 108.4, 72.8, 59.0, 51.1, 50.0, 46.5, 31.7, 31.6; HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}Cl^{79}BrN_5O_2Na$ (M + Na)$^+$ 498.0303, found 498.0321; calcd for $C_{20}H_{19}{}^{37}Cl^{81}BrN_5O_2Na$ (M + Na)$^+$ 502.0258, found 502.0267.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2-fluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**12**):* yield, 42.1%; mp, 168−169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 1.6 Hz, 1H), 7.50 (dd, J = 8.0, 1.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.22−7.12 (m, 1H), 7.07−6.94 (m, 2H), 6.88−6.79 (m, 1H), 5.41 (s, 1H), 5.21 (s, 1H), 4.76 (d, J = 15.2 Hz, 1H), 4.69 (d, J = 15.2 Hz, 1H), 3.81−3.63 (m, 2H), 3.54−3.42 (m, 2H), 2.26−2.09 (m, 3H), 1.99−1.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.68, 154.09 (d, J = 243.2 Hz), 149.7, 149.6, 139.3, 132.4 (d, J = 9.0 Hz), 132.3, 125.5 (d, J = 3.1 Hz), 124.5, 122.9 (d, J = 8.0 Hz), 120.9 (d, J = 3.0 Hz), 116.7 (d, J = 20.9 Hz), 108.7, 72.5 (d, J = 8.2 Hz), 58.2 (d, J = 3.5 Hz), 50.9, 49.9, 46.8, 31.5, 31.2; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}ClFN_5O_2$ (M + H)$^+$ 416.1290, found 416.1293; calcd for $C_{20}H_{20}{}^{37}ClFN_5O_2$ (M + H)$^+$ 418.1260, found 418.1267.

*1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(o-tolyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**13**):* yield, 40.8%; mp, 155−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 1.6 Hz, 1H), 7.69 (dd, J = 8.4, 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.97−6.90 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.15 (s, 1H), 4.96 (s, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 3.75−3.58 (m, 2H), 3.56−3.36 (m, 2H), 2.27 (s, 3H), 2.24−2.04 (m, 3H), 1.93−1.84 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 154.6, 154.5, 147.9, 144.5, 137.2, 136.7, 135.0, 131.7, 129.3, 127.8, 124.4, 113.7, 77.5, 63.4, 55.7, 54.6, 51.4, 36.6, 36.3, 24.2; HRMS (ES+) calcd for $C_{21}H_{23}{}^{35}ClN_5O_2$ (M + H)$^+$ 412.1540, found 412.1535; calcd for $C_{21}H_{23}{}^{37}ClN_5O_2$ (M + H)$^+$ 414.1511, found 414.1513.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2-methoxyphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**14**):* yield, 42.5%; mp, 120−121 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.4, 2.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.01−6.92 (m, 2H), 6.82−6.75 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.58 (d, J = 5.2 Hz, 1H), 5.10 (d, J = 5.2 Hz, 1H), 4.74 (d, J = 16.4 Hz, 1H), 4.68 (d, J = 16.4 Hz, 1H), 3.83 (s, 3H), 3.78−3.57 (m, 2H), 3.40−3.36 (m, 1H), 3.30−3.23 (m, 1H), 2.26−1.99 (m, 3H), 1.96−1.84 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.8, 151.2, 149.8, 149.7, 139.4, 133.4, 132.4, 124.5, 122.9, 121.4, 119.6, 112.6, 108.9, 71.9, 58.0, 50.8, 49.7, 47.2, 31.6, 30.9, 15.6; HRMS (ES+) calcd for $C_{21}H_{23}{}^{35}ClN_5O_3$ (M + H)$^+$ 428.1489, found 428.1489; calcd for $C_{21}H_{23}{}^{37}ClN_5O_3$ (M + H)$^+$ 430.1460, found 430.1468.

*2-(1-((6-Chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepin-10-yl)benzonitrile (**15**):* yield, 52.6%; mp, 197−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 7.6, 1.6 Hz, 1H), 7.60 (dd, J = 8.0, 2.4 Hz, 1H), 7.56−7.49 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.56 (s, 1H), 5.49 (d, J = 5.2 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.72 (d, J = 15.6 Hz, 1H), 3.83−3.51 (m, 4H), 2.33−2.18 (m, 3H), 2.00−1.91 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.8, 149.8, 149.6, 147.6, 139.5, 135.2, 134.9, 132.3, 124.5, 122.8, 120.4, 118.7, 108.4, 103.2, 72.8, 59.1, 51.1, 50.1, 46.2, 31.9, 31.8; HRMS (ES+) calcd for $C_{21}H_{20}{}^{35}ClN_6O_2$ (M + H)$^+$ 423.1336, found 423.1338; calcd for $C_{21}H_{20}{}^{37}ClN_6O_2$ (M + H)$^+$ 425.1307, found 425.1299.

*1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(m-tolyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**16**):* yield, 64.6%; mp, 199−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 1.6 Hz, 1H), 7.24 (s, 2H), 7.15−7.07 (m, 1H), 6.78 (s, 1H), 6.76−6.68 (m, 2H), 5.60 (s, 1H), 5.24 (s, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 3.84−3.71 (m, 1H), 3.70−3.51 (m, 2H), 3.49−3.36 (m, 1H), 2.25 (s, 3H), 2.21−2.07 (m, 3H), 1.96−1.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.6, 149.6, 145.0, 138.9, 138.8, 132.5, 129.5, 124.4, 121.5, 118.3, 114.9, 109.3, 71.4, 56.9, 50.7, 49.6, 47.5, 31.5, 31.4, 21.9; HRMS (ES+) calcd for $C_{21}H_{23}{}^{35}ClN_5O_2$ (M + H)$^+$ 412.1540, found 412.1540; calcd for $C_{21}H_{23}{}^{37}ClN_5O_2$ (M + H)$^+$ 414.1511, found 414.1514.

*1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(3-(trifluoromethyl)-phenyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]-azepine (**17**):* yield, 69.8%; mp, 222−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 1.6 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.29−7.24 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.77 (s, 1H), 5.36 (s, 1H), 4.77 (d, J = 15.6 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 3.85−3.71 (m, 1H), 3.73−3.51 (m, 2H), 3.52−3.40 (m, 1H), 2.34−2.11 (m, 3H), 2.01−1.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.7, 149.5, 145.8, 138.9, 132.3, 130.8, 130.5 (d, J = 31.0 Hz), 126.0, 124.3, 121.5, 115.5 (dd, J = 298.6, 4.3 Hz), 108.9, 71.4, 57.2, 50.8, 49.8, 47.2, 31.6, 31.3; HRMS (ES+) calcd for $C_{21}H_{20}{}^{35}ClF_3N_5O_2$ (M + H)$^+$ 466.1258, found 466.1258; calcd for $C_{21}H_{20}{}^{37}ClF_3N_5O_2$ (M + H)$^+$ 468.1228, found 468.1232.

*1-((6-Chloropyridin-3-yl)methyl)-10-(3-methoxyphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**18**):*

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yield, 72.2%; mp, 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 8.0, 2.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.51−6.45 (m, 2H), 5.63 (s, 1H), 5.24 (s, 1H), 4.83 (d, J = 15.6 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 3.86−3.72 (m, 1H), 3.71 (s, 3H), 3.69−3.51 (m, 2H), 3.50−3.39 (m, 1H), 2.29−2.10 (m, 3H), 1.96−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 156.2, 149.6, 149.5, 146.4, 138.9, 132.5, 130.5, 124.4, 110.3, 109.2, 106.0, 103.9, 71.6, 57.0, 55.4, 50.8, 49.6, 47.4, 31.5; HRMS (ES+) calcd for $C_{21}H_{23}{}^{35}ClN_5O_3$ (M + H)$^+$ 428.1489, found 428.1489; calcd for $C_{21}H_{23}{}^{37}ClN_5O_3$ (M + H)$^+$ 430.1460, found 430.1465.

10-(3-Chlorophenyl)-1-((6-chloropyridin-3-yl)methyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**19**): yield, 59.6%; mp, 209−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 8.4, 2.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.03 (t, J = 2.0 Hz, 1H), 6.92 (dd, J = 8.0, 1.2 Hz, 1H), 6.88 (dd, J = 8.0, 1.6 Hz, 1H), 5.67 (s, 1H), 5.27 (s, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.62 (d, J = 15.6 Hz, 1H), 3.85−3.71 (m, 1H), 3.71−3.54 (m, 2H), 3.53−3.42 (m, 1H), 2.30−2.11 (m, 3H), 1.97−1.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.7, 149.5, 146.7, 138.9, 134.3, 132.4, 131.3, 124.4, 120.4, 117.4, 116.3, 108.9, 71.4, 57.0, 50.9, 49.8, 47.2, 31.6, 31.3; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}Cl_2N_5O_2$ (M + H)$^+$ 432.0994, found 432.0990; calcd for $C_{20}H_{20}{}^{37}Cl_2N_5O_2$ (M + H)$^+$ 436.0935, found 436.0942.

1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(3-nitrophenyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**20**): yield, 73.6%; mp, 221−222 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 2.4 Hz, 1H), 7.75−7.70 (m, 2H), 7.53−7.46 (m, 1H), 7.43−7.35 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 5.79 (s, 1H), 5.37 (d, J = 5.6 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 3.84−3.74 (m, 1H), 3.73−3.58 (m, 2H), 3.54−3.46 (m, 1H), 2.31−2.14 (m, 3H), 2.01−1.92 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.8, 149.6, 149.4, 146.3, 143.3, 139.1, 132.2, 131.0, 124.2, 124.2, 115.3, 111.9, 108.8, 71.5, 57.4, 50.8, 50.2, 47.1, 31.7, 31.3; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}ClN_6O_4$ (M + H)$^+$ 443.1235, found 443.1237; calcd for $C_{20}H_{20}{}^{37}ClN_6O_4$ (M + H)$^+$ 445.1205, found 445.1202.

1-((6-Chloropyridin-3-yl)methyl)-10-(3-fluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**21**): yield, 47.7%; mp, 205−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.4, 2.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (dd, J = 15.2, 8.0 Hz, 1H), 6.83−6.77 (m, 1H), 6.77−6.72 (m, 1H), 6.72−6.64 (m, 1H), 5.64 (s, 1H), 5.26 (d, J = 5.6 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.62 (d, J = 15.6 Hz, 1H), 3.83−3.71 (m, 1H), 3.71−3.56 (m, 2H), 3.54−3.43 (m, 1H), 2.29−2.11 (m, 3H), 1.97−1.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 156.1, 149.5, 148.4 (d, J = 260.8 Hz), 147.2, 139.0, 132.4, 131.3 (d, J = 9.9 Hz), 124.4, 113.6 (d, J = 2.4 Hz), 109.1, 107.1 (d, J = 21.1 Hz), 104.7 (d, J = 25.3 Hz), 71.5, 57.1, 50.8, 49.9, 47.2, 31.6, 31.3; HRMS (ES+) calcd for $C_{20}H_{20}{}^{35}ClFN_5O_2$ (M + H)$^+$ 416.1290, found 416.1279; calcd for $C_{20}H_{20}{}^{37}ClFN_5O_2$ (M + H)$^+$ 418.1260, found 418.1269.

1-((6-Chloropyridin-3-yl)methyl)-10-(3-fluoro-4-methoxyphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]-azepine (**22**): yield, 61.0%; mp, 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 1.6 Hz, 1H), 7.38 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 9.2 Hz, 1H), 6.93 (d, J = 14.0 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 5.54 (s, 1H), 5.17 (s, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.60 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H), 3.79−3.71 (m, 1H), 3.70−3.53 (m, 2H), 3.51−3.40 (m, 1H), 2.30−2.05 (m, 3H), 1.97−1.81 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 152.3 (d, J = 242.3 Hz), 149.6, 149.5, 141.3 (d, J = 11.0 Hz), 139.2 (d, J = 8.7 Hz), 139.1, 132.4, 124.3, 115.3 (d, J = 2.6 Hz), 113.2 (d, J = 2.8 Hz), 109.0, 106.5 (d, J = 21.7 Hz), 71.9, 57.4, 56.7, 50.7, 49.7, 47.3, 31.6, 31.4; HRMS (ES+) calcd for $C_{21}H_{22}{}^{35}ClFN_5O_3$ (M + H)$^+$ 446.1395, found 446.1389; calcd for $C_{21}H_{22}{}^{37}ClFN_5O_3$ (M + H)$^+$ 448.1366, found 448.1375.

1-((6-Chloropyridin-3-yl)methyl)-10-(2-fluoro-4-methylphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**23**): yield, 83.0%; mp, 174−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 1.6 Hz, 1H), 7.52 (dd, J = 8.0, 1.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 14.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.73−6.64 (m, 1H), 5.35 (s, 1H), 5.15 (s, 1H), 4.81 (d, J = 15.2 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 3.81−3.59 (m, 2H), 3.57−3.38 (m, 2H), 2.26 (s, 3H), 2.23−2.03 (m, 3H), 1.97−1.84 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.5, 153.8 (d, J = 243.1 Hz), 149.7, 149.6, 139.4, 132.5 (d, J = 7.7 Hz), 132.3, 129.7 (d, J = 8.9 Hz), 125.8, 124.4, 120.6, 117.2 (d, J = 20.8 Hz), 108.8, 72.5 (d, J = 8.0 Hz), 58.2, 50.7, 49.9, 46.9, 31.5, 31.2, 20.4; HRMS (ES+) calcd for $C_{21}H_{22}{}^{35}ClFN_5O_2$ (M + H)$^+$ 430.1446, found 430.1444; calcd for $C_{21}H_{22}{}^{37}ClFN_5O_2$ (M + H)$^+$ 432.1417, found 432.1416.

1-((6-Chloropyridin-3-yl)methyl)-10-(2,6-difluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**24**): yield, 34.2%; mp, 163−164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 2.4 Hz, 1H), 7.62 (dd, J = 8.0, 2.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.06−6.98 (m, 3H), 5.46−5.34 (m, 2H), 4.81 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 3.82−3.64 (m, 2H), 3.64−3.43 (m, 2H), 2.24−2.06 (m, 3H), 1.91−1.81 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.0 (d, J = 244.6 Hz), 155.5, 154.9 (d, J = 244.7 Hz), 149.7, 149.6, 139.4, 132.5, 124.5, 122.7 (t, J = 10.5 Hz), 121.6 (t, J = 12.5 Hz), 113.4 (d, J = 25.8 Hz), 113.4 (d, J = 11.7 Hz), 110.0, 73.2 (t, J = 5.4 Hz), 59.6 (t, J = 6.0 Hz), 51.0, 50.1, 46.4, 31.5, 31.1; HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}ClF_2N_5O_2$ (M + H)$^+$ 434.1195, found 434.1196; calcd for $C_{20}H_{19}{}^{37}ClF_2N_5O_2$ (M + H)$^+$ 436.1166, found 436.1173.

1-((6-Chloropyridin-3-yl)methyl)-10-(3,4-dichlorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**25**): yield, 64.7%; mp, 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.38 (dd, J = 8.0, 1.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 8.8, 2.0 Hz, 1H), 5.67 (s, 1H), 5.27 (d, J = 5.2 Hz, 1H), 4.84 (d, J = 15.6 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 3.81−3.71 (m, 1H), 3.72−3.55 (m, 2H), 3.56−3.45 (m, 1H), 2.28−2.09 (m, 3H), 1.98−1.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 149.7, 149.5, 145.4, 138.9, 132.3, 132.1, 131.4, 124.2, 122.2, 119.3, 118.1, 108.8, 71.5, 57.3, 50.8, 50.0, 47.1, 31.6, 31.3; HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}Cl_3N_5O_2$ (M + H)$^+$ 466.0604, found 466.0599; calcd for $C_{20}H_{19}{}^{37}Cl_3N_5O_2$ (M + H)$^+$ 472.0516, found 472.0512.

1-((6-Chloropyridin-3-yl)methyl)-10-(2,5-dimethoxyphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**26**): yield, 41.2%; mp, 125−126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.0, 2.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.53 (dd, J = 8.8, 2.8 Hz, 1H), 6.28 (d, J = 2.8 Hz, 1H), 5.63 (d, J = 4.8 Hz, 1H), 5.16 (d, J = 4.8 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.71 (d, J = 15.6 Hz, 1H), 3.77 (s, 3H), 3.76−3.68 (m, 1H), 3.65 (s, 3H), 3.64−3.56 (m, 1H), 3.45−3.34 (m, 2H), 2.25−2.02 (m, 3H), 1.93−1.82 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 154.0, 149.7, 149.5, 145.4, 139.2, 134.5, 132.5, 124.4, 113.8, 108.7, 107.1, 105.9, 71.9, 58.0, 56.6, 55.6, 50.8, 49.4, 47.0, 31.6, 30.9; HRMS (ES+) calcd for $C_{22}H_{25}{}^{35}ClN_5O_4$ (M + H)$^+$ 458.1595, found 458.1597; calcd for $C_{22}H_{25}{}^{37}ClN_5O_4$ (M + H)$^+$ 460.1566, found 460.1578.

1-((6-Chloropyridin-3-yl)methyl)-10-(2,3-dimethylphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**27**): yield, 41.1%; mp, 171−172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.0, 2.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 6.99−6.83 (m, 2H), 6.65 (d, J = 7.6 Hz, 1H), 5.03 (d, J = 4.4 Hz, 1H), 4.88 (d, J = 4.4 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 3.75−3.58 (m, 2H), 3.59−3.44 (m, 1H), 3.42−3.34 (m, 1H), 2.25−2.22 (m, 1H), 2.22 (s, 3H), 2.21−2.18 (m, 1H), 2.15 (s, 3H), 2.12−2.05 (m, 1H), 1.91−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 149.9, 149.8, 143.2, 139.8, 138.0, 132.4, 129.2, 126.0, 125.1, 124.5, 117.6, 109.0, 73.5, 59.1, 51.0, 49.8, 46.6, 31.8, 31.7, 20.8, 15.1; HRMS (ES+) calcd for $C_{22}H_{25}{}^{35}ClN_5O_2$ (M + H)$^+$ 426.1697, found 426.1692; calcd for $C_{22}H_{25}{}^{37}ClN_5O_2$ (M + H)$^+$ 428.1667, found 428.1678.

1-((6-Chloropyridin-3-yl)methyl)-10-(2,4-dimethylphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**28**): yield, 31.9%; mp, 157−158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 8.0, 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.09 (d, J = 3.6 Hz, 1H), 4.90 (d, J = 3.6 Hz, 1H), 4.80 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 3.76−3.59 (m, 2H), 3.59−

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3.46 (m, 1H), 3.45−3.37 (m, 1H), 2.23 (s, 3H), 2.21 (s, 3H), 2.19−2.00 (m, 3H), 1.93−1.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.8, 149.8, 140.6, 139.8, 132.5, 132.4, 131.7, 130.0, 127.2, 124.5, 119.6, 109.0, 72.9, 58.7, 50.9, 49.8, 46.7, 31.8, 31.5, 20.7, 19.3; HRMS (ES+) calcd for $C_{22}H_{25}{}^{35}ClN_5O_2$ (M + H)$^+$ 426.1697, found 426.1693; calcd for $C_{22}H_{25}{}^{37}ClN_5O_2$ (M + H)$^+$ 428.1667, found 428.1660.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2,5-dimethylphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**29**):* yield, 80.0%; mp, 157−158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.0, 2.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 7.2 Hz, 1H), 6.64 (s, 1H), 5.15 (d, J = 4.0 Hz, 1H), 4.99 (d, J = 4.0 Hz, 1H), 4.86 (d, J = 15.6 Hz, 1H), 4.68 (d, J = 15.6 Hz, 1H), 3.79−3.67 (m, 1H), 3.67−3.56 (m, 1H), 3.52−3.35 (m, 2H), 2.23 (s, 3H), 2.22−2.20 (m, 1H), 2.20 (s, 3H), 2.19−2.15 (m, 1H), 2.13−2.03 (m, 1H), 1.93−1.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.4, 149.7, 149.6, 143.1, 139.5, 135.8, 132.5, 131.8, 126.9, 124.4, 123.7, 120.4, 108.9, 72.8, 58.6, 51.1, 49.5, 46.7, 31.8, 31.5, 21.5, 19.1; HRMS (ES+) calcd for $C_{22}H_{25}{}^{35}ClN_5O_2$ (M + H)$^+$ 426.1697, found 426.1690; calcd for $C_{22}H_{25}{}^{37}ClN_5O_2$ (M + H)$^+$ 428.1667, found 428.1679.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2,5-dichlorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**30**):* yield, 46.8%; mp, 157−158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.4, 2.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.13 (dd, J = 8.4, 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 5.54 (s, 1H), 5.32 (d, J = 4.0 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 3.80−3.61 (m, 2H), 3.61−3.49 (m, 2H), 2.28−2.13 (m, 3H), 1.96−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.8, 149.6, 142.8, 139.4, 132.7, 132.6, 132.3, 124.6, 124.5, 124.0, 121.4, 107.9, 72.3, 58.7, 51.1, 49.8, 46.3, 31.6, 31.5; HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}Cl_3N_5O_2$ (M + H)$^+$ 466.0604, found 466.0591; calcd for $C_{20}H_{19}{}^{37}Cl_3N_5O_2$ (M + H)$^+$ 472.0516, found 472.0529.

*1-((6-Chloropyridin-3-yl)methyl)-10-(3,4-dimethylphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**31**):* yield, 66.1%; mp, 196−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.67−6.61 (m, 1H), 5.55 (d, J = 4.0 Hz, 1H), 5.20 (d, J = 4.8 Hz, 1H), 4.87 (d, J = 16.0 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 3.84−3.71 (m, 1H), 3.68−3.50 (m, 2H), 3.45−3.36 (m, 1H), 2.23−2.17 (m, 2H), 2.16 (s, 3H), 2.15 (s, 3H), 2.13−2.05 (m, 2H), 1.95−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 149.5, 149.5, 142.9, 138.9, 137.3, 132.4, 130.6, 128.2, 124.2, 119.0, 115.1, 109.4, 71.5, 57.0, 50.6, 49.5, 47.6, 31.5, 31.4, 20.3, 19.0; HRMS (ES-) calcd for $C_{22}H_{23}{}^{35}ClN_5O_2$ (M − H)$^+$ 424.1540, found 424.1543; calcd for $C_{22}H_{23}{}^{37}ClN_5O_2$ (M − H)$^+$ 426.1511, found 426.1516.

*1-((6-Chloropyridin-3-yl)methyl)-10-(3,5-dimethylphenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**32**):* yield, 53.2%; mp, 214−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.26−7.18 (m, 2H), 6.57 (s, 2H), 6.54 (s, 1H), 5.57 (d, J = 3.6 Hz, 1H), 5.22 (d, J = 4.8 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 3.82−3.73 (m, 1H), 3.69−3.52 (m, 2H), 3.47−3.37 (m, 1H), 2.20 (s, 6H), 2.18−2.03 (m, 3H), 1.95−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.6, 149.5, 145.0, 138.8, 138.6, 132.5, 124.3, 122.5, 115.5, 109.3, 71.4, 57.0, 50.7, 49.6, 47.6, 31.5, 31.4, 21.8; HRMS (ES-) calcd for $C_{22}H_{23}{}^{35}ClN_5O_2$ (M − H)$^+$ 424.1540, found 424.1543; calcd for $C_{22}H_{23}{}^{37}ClN_5O_2$ (M − H)$^+$ 426.1511, found 426.1517.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2,5-difluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**33**):* yield, 74.8%; mp, 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 8.0, 2.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.27−7.16 (m, 1H), 6.84−6.74 (m, 1H), 6.68−6.58 (m, 1H), 5.44 (s, 1H), 5.27 (s, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.69 (d, J = 15.6 Hz, 1H), 3.79−3.65 (m, 2H), 3.62−3.50 (m, 2H), 2.25−2.11 (m, 3H), 1.96−1.83 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ158.8 (d, J = 239.3 Hz), 155.8, 150.2 (d, J = 238.9 Hz), 149.8, 149.5, 139.2, 132.3, 124.4, 117.9 (d, J = 10.8 Hz), 117.7 (d, J = 10.4 Hz), 108.6 (d, J = 8.2 Hz), 108.5, 108.4 (d, J = 8.1 Hz), 107.8 (d, J = 27.7 Hz), 72.3 (d, J = 8.0 Hz), 58.3, 51.0, 50.1, 46.5, 31.4, 31.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ −115.94 to −116.56 (m, 1F), −127.09 to −127.39 (m, 1F); HRMS (ES+) calcd for $C_{20}H_{18}{}^{35}ClF_2N_5O_2Na$ (M + Na)$^+$ 456.1015, found 456.1021; calcd for $C_{20}H_{18}{}^{37}ClF_2N_5O_2Na$ (M + Na)$^+$ 458.0985, found 458.0995.

*1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(2,3,4,5-tetrafluorophenyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**34**):* yield, 51.3%; mp, 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 2.4 Hz, 1H), 7.61 (dd, J = 8.0, 2.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.80−6.69 (m, 1H), 5.42 (s, 1H), 5.26 (d, J = 4.8 Hz, 1H), 4.85 (d, J = 15.6 Hz, 1H), 4.66 (d, J = 15.6 Hz, 1H), 3.79−3.58 (m, 4H), 2.25−2.13 (m, 3H), 1.96−1.88 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.8, 148.2, 147.8, 137.9, 136.6, 130.6, 128.1, 125.5, 122.7, 117.0, 106.9, 101.4, 101.2, 70.7 (d, J = 6.5 Hz), 57.1 (d, J = 5.0 Hz), 49.3, 48.9, 44.7, 29.8, 29.6; ^{19}F NMR (376 MHz, DMSO-d_6) δ −138.96 to −139.37 (m, 1F), −149.38 to −149.60 (m, 1F), −156.26 (t, J = 21.3 Hz, 1F), −166.60 to −167.07 (m, 1F); HRMS (ES+) calcd for $C_{20}H_{16}{}^{35}ClF_4N_5O_2Na$ (M + Na)$^+$ 492.0826, found 492.0825; calcd for $C_{20}H_{16}{}^{37}ClF_4N_5O_2Na$ (M + Na)$^+$ 494.0797, found 494.0795.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2,4-difluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**35**):* yield, 56.4%; mp, 189−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 8.0, 2.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29−7.19 (m, 1H), 6.95−6.87 (m, 1H), 6.87−6.79 (m, 1H), 5.34 (d, J = 3.6 Hz, 1H), 5.16 (d, J = 3.6 Hz, 1H), 4.76 (d, J = 15.6 Hz, 1H), 4.70 (d, J = 15.6 Hz, 1H), 3.81−3.62 (m, 2H), 3.57−3.43 (m, 2H), 2.26−2.06 (m, 3H), 1.98−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.8 (d, J = 240.8 Hz), 156.6 (d, J = 240.8 Hz), 155.1, 153.4 (d, J = 246.9 Hz), 153.2 (d, J = 246.6 Hz), 149.3, 149.1, 139.0, 131.8, 128.8 (d, J = 3.4 Hz), 128.7 (d, J = 3.3 Hz), 123.9, 120.9 (d, J = 4.5 Hz), 120.8 (d, J = 4.2 Hz), 111.4 (d, J = 3.4 Hz), 111.2 (d, J = 3.3 Hz), 108.0, 105.1, 104.9 (d, J = 51.9 Hz), 72.0 (d, J = 7.4 Hz), 57.9 (d, J = 3.3 Hz), 50.4, 49.5, 46.2, 31.0, 30.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ −117.30 to −117.47 (m, 1F), −119.20 to −119.35 (m, 1F); HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}ClF_2N_5O_2$ (M + H)$^+$ 434.1195, found 434.1195; calcd for $C_{20}H_{19}{}^{37}ClF_2N_5O_2$ (M + H)$^+$ 436.1166, found 436.1156.

*1-((6-Chloropyridin-3-yl)methyl)-10-(2,3-difluorophenyl)-9-nitro-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**36**):* yield, 67.9%; mp, 193−194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 1.6 Hz, 1H), 7.53 (dd, J = 8.0, 1.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.09−6.94 (m, 2H), 6.75−6.59 (m, 1H), 5.44 (s, 1H), 5.25 (s, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.69 (d, J = 15.6 Hz, 1H), 3.81−3.64 (m, 2H), 3.61−3.47 (m, 2H), 2.26−2.10 (m, 3H), 1.99−1.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 150.7 (d, J = 243.7 Hz), 150.6 (d, J = 243.6 Hz), 149.3, 149.1, 142.0 (d, J = 245.1 Hz), 141.8 (d, J = 244.9 Hz), 138.9, 133.9 (d, J = 4.1 Hz), 131.8, 124.6 (dd, J = 8.6, 4.3 Hz), 123.9, 115.7, 109.7 (d, J = 17.3 Hz), 108.1, 72.0 (d, J = 7.5 Hz), 58.0 (d, J = 3.6 Hz), 50.4, 49.6, 46.1, 30.9, 30.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ −138.08 to −138.43 (m, 1F), −148.91 to −149.30 (m, 1F); HRMS (ES+) calcd for $C_{20}H_{19}{}^{35}ClF_2N_5O_2$ (M + H)$^+$ 434.1195, found 434.1185; calcd for $C_{20}H_{19}{}^{37}ClF_2N_5O_2$ (M + H)$^+$ 436.1166, found 436.1159.

*1-((6-Chloropyridin-3-yl)methyl)-9-nitro-10-(2,4,5-trifluorophenyl)-2,3,5,6,7,8-hexahydro-1H-5,8-epiminoimidazo[1,2-a]azepine (**37**):* yield, 77.9%; mp, 184−185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.4, 2.0 Hz, 1H), 7.57−7.48 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 6.90−6.80 (m, 1H), 5.38 (s, 1H), 5.24 (d, J = 4.8 Hz, 1H), 4.81 (d, J = 15.6 Hz, 1H), 4.70 (d, J = 15.6 Hz, 1H), 3.78−3.66 (m, 2H), 3.67−3.52 (m, 2H), 2.26−2.10 (m, 3H), 1.95−1.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.2, 149.3, 149.0, 138.9, 131.8, 123.8, 108.6 (d, J = 4.6 Hz), 108.4 (d, J = 4.6 Hz), 107.9, 106.9, 106.7 (d, J = 6.2 Hz), 106.4, 71.8 (d, J = 7.0 Hz), 58.0 (d, J = 4.8 Hz), 50.4, 49.7, 45.9, 30.8, 30.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ −122.75 to −123.04 (m, 1F), −141.06 to −141.51 (m, 1F), −144.07 to −144.38 (m, 1F); HRMS (ES+) calcd for $C_{20}H_{18}{}^{35}ClF_3N_5O_2$ (M + H)$^+$ 452.1101, found 452.1091; calcd for $C_{20}H_{18}{}^{37}ClF_3N_5O_2$ (M + H)$^+$ 454.1072, found 454.1087.

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X-ray Diffraction Analysis. Compound **1** was recrystallized by slow evaporation from a mixture of acetone, dichloromethane, and cyclohexane (1:1:1, v/v/v) to afford a suitable single crystal. Yellow blocks of compound **1** (0.29 mm × 0.21 mm × 0.14 mm) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 25.99°; 10716 measured reflections; 3627 independent reflections (R_{int} = 0.0475). Data were corrected for Lorentz and polarization effects and for absorption (t_{min} = 0.7050 and t_{max} = 1.0000). The structure was solved by direct methods using SHELXS-97;[11] all other calculations were performed with a Bruker SAINT System and Bruker SMART programs.[12] Full-matrix least-squares refinement based on F^2 using the weight of $1/ [\sigma^2 (F_0^2) + (0.0613P)^2 + 0.0371P]$ gave final values of R = 0.0542, ωR = 0.1462, and GOF (F) = 1.022 for 253 variables and 3627 contributing reflections. Maximum shift/error = 0.000(3) and max/min residual electron density = 0.530/−0.519 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. All compounds were dissolved in *N*,*N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 20 and 4 mg L^{-1} and others for bioassays. For comparative purposes, IMI and CYC were tested under the same conditions.

Insecticidal Test for Cowpea Aphid (*A. craccivora*). The insecticidal activity of synthetic compounds against cowpea aphid was tested by using the leaf-dip method.[13,14] Horsebean plant leaves with 30−40 apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s, and the excess dilution was sucked out with filter paper; the burgeons were placed in the conditioned room (25 ± 1 °C, 50% realtive humidity). Water containing Triton X-100 (0.1 mg L^{-1}) was used as control. The mortality rates were evaluated 24 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis as before.

Insecticidal Test for Armyworm (*Pseudaletia separata* Walker). The insecticidal activity against armyworm was tested by foliar application.[15−17] Individual corn (*Zea mays*) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the compound solution and allowed to dry. The dishes were infested with 10 third-instar larvae and placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis as before.

Insecticidal Test for Brown Planthopper (*N. lugens*). The insecticidal activity against brown planthopper was tested by foliar application. Rice seedlings were placed on moistened pieces of filter paper in Petri dishes. The dishes were infested with 30−40 third-instar larvae and then sprayed with the compound solutions (2.5 mL) using a Potter spray tower (pressure, 5 lb/in^2; settlement, 4.35 mg/cm^2). Samples were placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subject to probit analysis as before.

RESULTS AND DISCUSSION

Synthesis. To synthesize azabridged neonicotinoid compounds, the major obstacle was the synthetic methodology. Through comparison of the structures of the 1,3-dicarbonyl derivative and our starting material **B** (cyclic β-nitroenamine), similar nucleophilic centers were found in these two types of substances, which implied that the target compounds can be constructed in an intermolecular way involving primary amine hydrochlorides and dialdehydes.[10] Consequently, the commercialized glutaraldehyde was first chosen to synthesize eight-membered azabridged neonicotinoid analogues. Therefore, to obtain seven-membered azabridges, the preparation of succinaldehyde was the main task in this work.

Hitherto, various methods of acidic[17−23] and nonacidic hydrolysis[24] were reported to prepare succinaldehyde from commercially available and synthetic equivalent 2,5-dimethoxydihydrofuran (DMTHF). Furthermore, according to our previous study of eight-membered azabridges,[10] it was found that an acidic environment was conducive to the formation of azabridged neonicotinoid compounds. Thus, compound **3** was chosen to study the influence of the pH value, and the results are listed in Table 1.

Table 1. Optimization of Compound 3

entry	hydrolyzed succinaldehyde	time (h)	yield[a] (%)
1	pH 1−2	1.5	66.0
2	pH 2−3	1.5	82.5
3	pH 6−7	1.5	44.2
4	pH 8−9	1.5	tr[b]
5	pH 2−3	0.5	45.5
6	pH 2−3	5.0	26.2
7	pH 2−3	10.0	20.0
8	nonacidic[c]	1.5	60.1

[a]Isolated yields. [b]tr, trace. [c]See ref 24.

To begin with, the solution of succinaldehyde was used immediately after acidic hydrolysis of DMTHF. The reaction was monitored by TLC, and the target compound **3** was successfully acquired in a good yield (Table 1, entry 1), which encouraged us to optimize the pH value of succinaldehyde solution before it was used in the next step. From the experimental data in Table 1, it was observed that the pH value below 2 or above 3 would display relatively low yields (Table 1, entries 1−4). These results demonstrated that the pH value at 2−3 was more suitable to synthesize seven-membered azabridged compounds.

On the basis of this optimal condition, the reaction time was also investigated. The corresponding yields were increased, but decreased with the extension of time (Table 1, entries 2 and 5−7). Therefore, the reaction was carried out in 1.5 h, because the decomposition rate of our target compound was more rapid than the formation rate after a period of time. Eventually, the nonacidic condition was also studied (Table 1, entry 8). The succinaldehyde was prepared following literature procedures;[24] however, the corresponding yield was still lower than that of acid condition.

Crystal Structure Analysis. To provide more evidence for the proposed molecular structure and establish the conformation of the target compounds, compound **1** was recrystallized by slow evaporation and its single-crystal structure was determined by X-ray crystallography as illustrated in Figure 3.

Unlikely eight-membered compounds, the pyridine ring, and benzene ring of compound **1** pointed to the same direction. Compared with the *trans*-configuration of nitro in the crystal structure of IMI,[26] the nitro groups of compound **1** was in *cis*-configuration as anticipated. There are some characteristics of the bond lengths. For example, the bond lengths of C(9)—N(2) (1.35 Å) and C(9)—N(3) (1.34 Å) were obviously shorter than the typical C—N single bond (1.47 Å) but close to that of C=N (1.33 Å), owing to the transfer of the lone-pair electrons on the amines to C(10)=C(9) and the delocalization of the electrons extended as far as the electron-withdrawing

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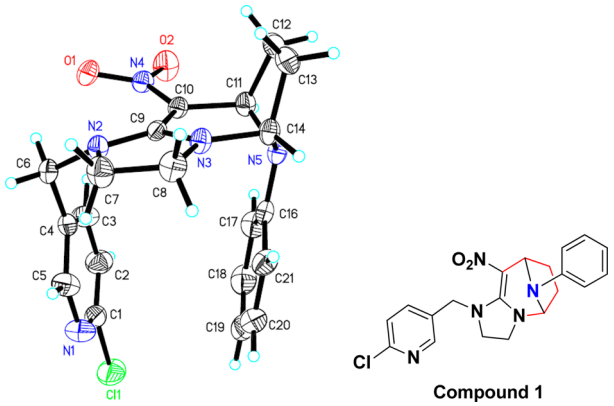

Figure 3. Crystal and chemical structures of compound **1**.

group ($-NO_2$), forming a coplanar olefin−amine π-electron network.[25,26] Moreover, it also made the bond lengths of C(10)═C(9) (1.41 Å) and C—NO_2 (C(10)—N(4); 1.36 Å) longer than that of normal C═C (1.34 Å) and shorter than that of typical C—NO_2 (C—N; 1.49 Å), respectively.

Insecticidal Activity. Table 2 lists the insecticidal activities of the title compounds against cowpea aphid (*A. craccivora*), brown planthopper (*N. lugens*), and armyworm (*P. separata* Walker). Most of the compounds exhibited significant insecticidal activities against these three species of pests. Compound **1** with no substituent on the phenyl group presented similar insecticidal activities against cowpea aphid and brown planthopper, but lower bioactivity against armyworm, compared with seven-membered oxabridged compound CYC (Table 3). Then, the substitution effect on insecticidal activities was investigated.

The compounds with various types of substitutions on position 4 of the phenyl group were first synthesized (**2**–**9**). The bioassay showed that introducing an electron-donating group (OMe and Me) (**3** and **5**) and a fluorine atom (**4**) could contribute to great improvement of activity against armyworm while presenting considerable activities against brown planthopper and cowpea aphid. Meanwhile, bringing in an electron-withdrawing group (CF_3, CN, NO_2) (**6**, **7**, and **9**), a bromine atom (**2**), or a chlorine atom (**8**) on the phenyl ring would decrease the activities against brown planthopper and cowpea aphid but increase the bioactivity against armyworm, compared with compound **1**.

On position 2 of the phenyl group, the compound with a cyano group (**15**) displayed relatively low insecticidal activities and the others (**10**–**14**) exhibited excellent bioactivities against the three species of pests, which confirmed that position 2 was the key substitution site for structural derivation to obtain high-activity molecules. Moreover, on the basis of the LC_{50} value in Table 3, with the radius of the halogen atom increasing (**10**–**12**), the insecticidal activities showed decreasing tendency against armyworm, but still higher than that of CYC and IMI. Notably, compounds **12** and **13** demonstrated the relatively higher bioactivities among the structures with substitution on position 2.

The insecticidal activities of all the compounds with a substituent on position 3 (**16**–**21**) were lower than that of compound **1** against brown planthopper and cowpea aphid. However, among these, compounds **16** and **21** presented relatively high bioactivities against the three species of pests. Combined with the discussion above, we could preliminarily conclude that introducing a methyl group and a fluorine atom on any site of the phenyl group was favorable to increase the insecticidal activities and that position 2 was an important site for obtaining high-activity compounds.

Therefore, further SAR study of two substitutions on the phenyl group was carried out. Initially, the combinations of fluorine atom with methoxy group (**22**) and methyl (**23**) were carried out. Unfortunately, the insecticidal activities against cowpea aphid and armyworm were decreased dramatically, which was not a good result for exploring a potential neonicotinoid insecticide with superior bioactivities against the three species of pests. Then, we turned our attention to dimethyl substitution on the phenyl group.

2,3-Dimethyl (**27**), 2,4-dimethyl (**28**), and 2,5-dimethyl groups (**29**) were introduced into the phenyl group; owing to the sterically hindered effect of the substituent, the

Table 2. Insecticidal Activities of Compounds 1−37

		mortality[a] (%)			
		P. separata Walker		*A. craccivora*	
compd	R	20 mg L^{-1}	4 mg L^{-1}	20 mg L^{-1}	4 mg L^{-1}
1	H	0	0	100	100
2	4-Br	0	0	100	100
3	4-OMe	80	10	100	100
4	4-F	80	10	100	100
5	4-Me	90	10	100	100
6	4-CF_3	60	0	100	80
7	4-CN	50	0	100	80
8	4-Cl	80	30	100	100
9	4-NO_2	0	0	0	0
10	2-Cl	80	10	100	100
11	2-Br	70	10	100	100
12	2-F	90	30	100	100
13	2-Me	80	30	100	100
14	2-OMe	80	30	100	100
15	2-CN	0	0	50	0
16	3-Me	40	0	100	100
17	3-CF_3	0	0	0	0
18	3-OMe	100	0	100	40
19	3-Cl	100	0	100	30
20	3-NO_2	80	0	100	0
21	3-F	50	0	100	70
22	3-F-4-OMe	100	0	100	0
23	2-F-4-Me	70	0	100	0
24	2,6-$(F)_2$	100	0	100	50
25	3,4-$(Cl)_2$	0	0	0	0
26	2,5-$(OMe)_2$	70	30	100	100
27	2,3-$(Me)_2$	80	20	100	100
28	2,4-$(Me)_2$	100	0	100	100
29	2,5-$(Me)_2$	90	50	100	100
30	2,5-$(Cl)_2$	70	0	100	90
31	3,4-$(Me)_2$	0	0	100	0
32	3,5-$(Me)_2$	80	10	100	80
33	2,5-$(F)_2$	80	0	90	70
34	2,3,4,5-$(F)_4$	0	0	0	0
35	2,4-$(F)_2$	30	0	100	95
36	2,3-$(F)_2$	90	30	100	95
37	2,4,5-$(F)_3$	80	0	100	90
CYC		40	0	100	100
IMI		40	0	100	100

[a]At 4 mg L^{-1}, the mortality of all compounds against brown planthopper (*Nilaparvata lugens*) was 100%.

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Table 3. LC_{50} Values of Some Compounds against Three Species of Pests

		LC_{50} (95% fiducial limits) (mg L^{-1})		
compd	R	*A. craccivora*	*N. lugens*	*P. separata* Walker
1	H	0.342 (0.256−0.438)	0.504 (0.427−0.597)	nt[a]
2	4-Br	0.574 (0.481−0.679)	1.015 (0.870−1.181)	nt
3	4-OMe	0.172 (0.064−0.270)	0.179 (0.140−0.221)	10.937 (9.526−12.536)
4	4-F	0.403 (0.341−0.464)	0.338 (0.239−0.450)	nt
5	4-Me	0.196 (0.158−0.233)	0.511 (0.439−0.591)	nt
6	4-CF_3	2.938 (2.433−3.602)	0.860 (0.721−1.029)	nt
7	4-CN	2.718 (2.241−3.324)	1.803 (1.544−2.111)	nt
8	4-Cl	2.469 (1.965−3.220)	0.558 (0.451−0.671)	7.550 (5.497−10.387)
10	2-Cl	0.412 (0.352−0.481)	0.232 (0.193−0.277)	10.984 (7.696−15.326)
11	2-Br	0.409 (0.343−0.487)	0.151 (0.119−0.183)	11.019 (9.436−12.845)
12	2-F	0.184 (0.149−0.219)	0.338 (0.239−0.450)	6.103 (4.590−7.823)
13	2-Me	0.396 (0.334−0.462)	0.129 (0.047−0.231)	6.762 (4.993−8.961)
14	2-OMe	0.419 (0.247−0.615)	0.178 (0.134−0.222)	nt
16	3-Me	0.421 (0.357−0.491)	0.831 (0.710−0.951)	nt
18	3-OMe	nt	0.418 (0.351−0.489)	nt
19	3-Cl	nt	0.429 (0.360−0.506)	nt
24	2,6-$(F)_2$	nt	0.395 (0.327−0.469)	nt
25	3,4-$(Cl)_2$	nt	0.859 (0.629−1.230)	nt
26	2,5-$(OMe)_2$	0.490 (0.325−0.702)	0.062 (0.041−0.082)	8.421 (6.037−11.292)
27	2,3-$(Me)_2$	0.864 (0.556−1.339)	0.279 (0.133−0.473)	9.549 (6.996−12.899)
28	2,4-$(Me)_2$	0.450 (0.229−0.744)	0.039 (0.006−0.077)	nt
29	2,5-$(Me)_2$	0.426 (0.156−0.793)	0.054 (0.033−0.077)	4.756 (3.510−6.374)
30	2,5-$(Cl)_2$	1.268 (0.855−1.982)	0.072 (0.045−0.099)	nt
CYC		0.435 (0.168−0.748)	0.383 (0.197−0.593)	26.692 (22.904−31.123)
IMI		0.634 (0.458−0.838)	1.089 (0.973−1.218)	34.078 (26.087−49.535)

[a]Not tested.

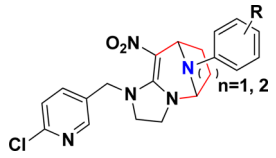
compound with a 2,6-dimethyl group could not be synthesized. Excitingly, compounds **28** (LC_{50} = 0.039 mg L^{-1}) and **29** (LC_{50} = 0.054 mg L^{-1}) displayed an improvement of about 1 order of magnitude over CYC (LC_{50} = 0.383 mg L^{-1}) in insecticidal activity against brown planthopper and an activity similar to that of **13** against cowpea aphid. Furthermore, the insecticidal activity of compound **29** was 7-fold higher than that of IMI against armyworm. Thus, we replaced the 2,5-dimethyl with 2,5-dimethoxy (**26**), 2,5-dichloro (**30**), and 2,5-difluoro (**33**) to study the variations of bioactivities. Compounds **26**, **30**, and **33** showed comparable activity against brown planthopper, but lower activities against armyworm and cowpea aphid, respectively, which implied that introducing disubstitution on positions 2 and 5 of the phenyl group could obtain a molecule with high activity against brown planthopper.

Difluoro- and multifluoro-substituted compounds were also studied (**24**, **33**−**37**). Compared with compound **12**, introducing multiple fluorine atoms into the phenyl group could not lead to the increase of bioactivities against three species of pests. Therefore, the substitution of a methyl group on the phenyl group was more favorable for the improvement of insecticidal activities than that of fluorine atoms.

Table 4 lists the comparison of insecticidal activities between eight-membered[10] and seven-membered compounds. At low concentration (4 and 20 mg L^{-1}), most seven-membered azabridged compounds showed apparently higher bioactivities than eight-membered compounds against the three species of pests. These results indicated that the ring size played a very important role in increasing the insecticidal activities.

Docking Study. A docking study was performed to explore the binding modes of our compounds. The crystal structure of the *Aplysia californica* acetylcholine binding protein (*Ac*-AChBP) complexed with IMI (PDB code 3C79) was selected to construct the binding models,[27] which showed high affinity with neonicotinoids and was a good prototype for investigating the binding mode of neonicotinoids.[28] For comparison, compounds **1** and **29** were built, minimized, and docked into

Table 4. Comparison of Insecticidal Activities between Eight- and Seven-Membered Compounds



		mortality (%)					
		N. lugens[a]		*A. craccivora*[a]		*P. separata* Walker[b]	
entry	R	*n* = 1	*n* = 2	*n* = 1	*n* = 2	*n* = 1	*n* = 2
1	H	100	0	100	20	0	0
2	4-Me	100	50	100	5	90	0
3	2-Me	100	0	100	30	80	0
4	3-Me	100	0	100	10	40	0
5	4-Br	100	0	100	0	0	0
6	2-F	100	0	100	20	90	0
7	2-Cl	100	0	100	30	80	0
8	2-Br	100	0	100	5	70	0
9	3-NO_2	100	0	0	15	80	0
10	4-NO_2	100	0	0	0	0	0
11	4-Cl	100	0	100	0	80	0
12	2,5-$(OMe)_2$	100	20	100	20	70	0

[a]At 4 mg L^{-1}. [b]At 20 mg L^{-1}.

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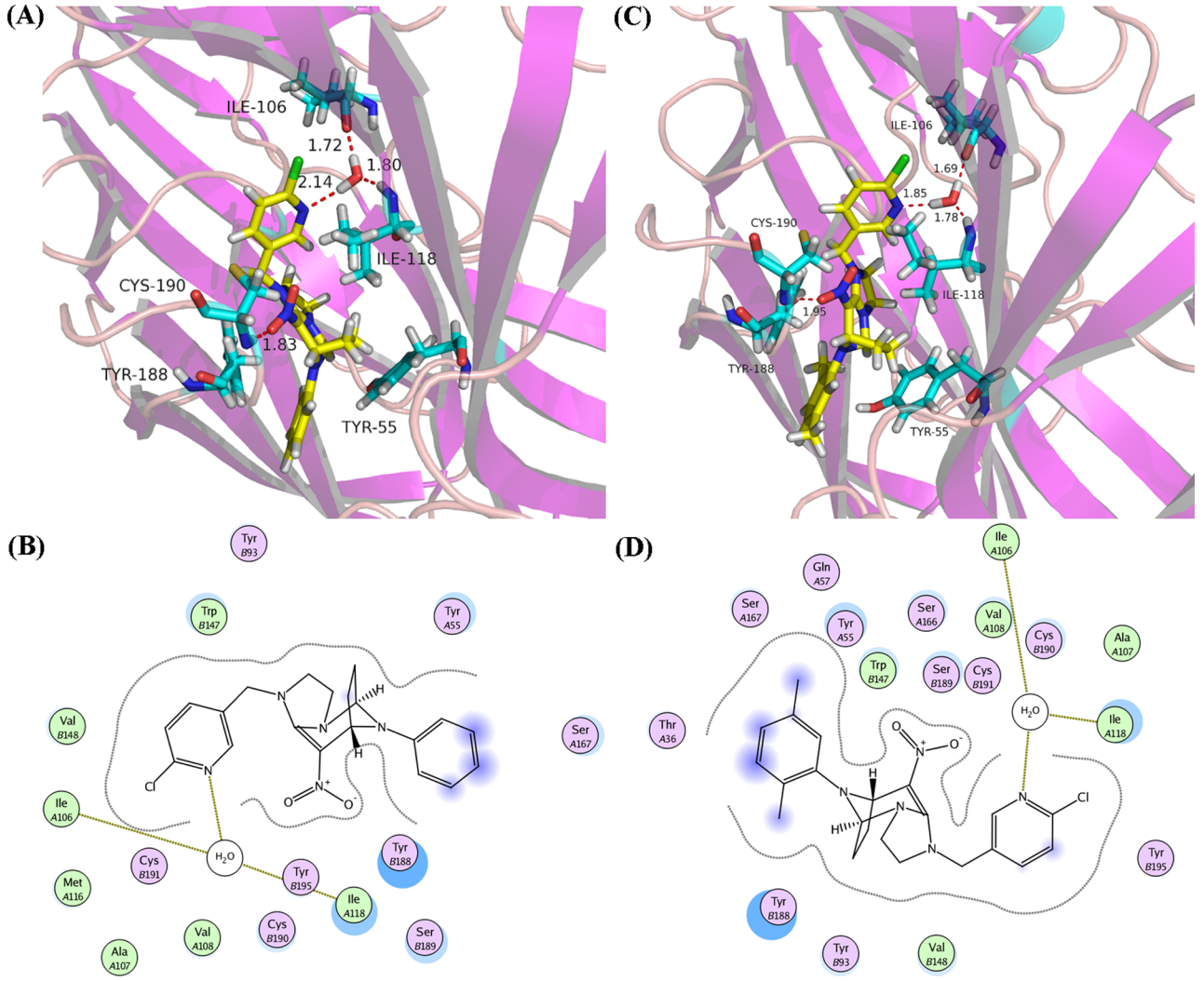

Figure 4. Binding modes of compounds **1** (A, B) and **29** (C, D).

the ligand binding pocket of *Ac*-AChBP by using the Induced Fit Docking approach, of which the IFDScore scoring function was selected to evaluate the docking results. All atoms within 20 Å around IMI in the 3C79 structure were selected as binding pocket and considered in the docking study. All computational studies were performed using Maestro 9.0 (Schrödinger, LLC, 2013).

The docking poses of compounds **1** and **29** were depicted in Figure 4. It was found that water bridged hydrogen bonding network played key roles for the ligands recognition, which has also been reported for the binding of IMI and other neonicotinoid compounds.[27,28] Also, N−H···O hydrogen bonds were observed between the peptide N−H of Cys190 and the nitro groups of compounds. The phenyl group inserted into the interspace between loop C and the adjacent subunit, and located between the Tyr188 and Tyr55. Comparing with compound **1**, the methyl group introduced into position 2 of phenyl group in compound **29** could improve the hydrophobic interactions with receptor (Figure 4B and 4D), which might be one of the reasons for the improvement of insecticidal activity.

In conclusion, 37 novel seven-membered azabridged neonicotinoid analogues were designed and synthesized. The pH value at 2−3 of hydrolyzed succinaldehyde solution was an optimized condition to synthesize target compounds in excellent yields. The bioassays showed that most of the compounds presented superior bioactivities to IMI and seven-membered oxabridged compound CYC against cowpea aphid, brown planthopper, and armyworm. Compared with IMI, compound **29** with 2,5-dimethyl group, displayed 7 fold and 20 fold higher activities against armyworm and brown planthopper, respectively. Moreover, seven-membered compounds showed much higher bioactivities against three species of pests than that of eight-membered azabridge neonicotinoids, which implied that the framework of a seven-membered azabridge could significantly improve the insecticidal activity of neonicotinoid analogues and was a very good lead structure to discover potential pesticides. Further studies on field testing of the title compounds are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic information files (CIF) of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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