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Design, Synthesis, Crystal Structure Analysis, and Insecticidal Evaluation of Phenylazoneonicotinoids

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Supporting Information

ABSTRACT: On the basis of research of the proposed modes of action between neonicotinoids and insect nicotinic acetylcholine receptor (nAChR), a series of phenylazoneonicotinoids were designed and synthesized to further promote the $\pi-\pi$ interaction between molecule and amino acid residues. The target compounds have been identified on the basis of satisfactory analytical and spectral (^{1}H NMR, ^{13}C NMR, HRMS, and X-ray) data. The preliminary results revealed that tiny differences in substitutes resulted in different configurations and great bioactivity variations. Some compounds with electron-donating groups on positions 2 and 6 of the phenyl ring presented higher insecticidal activity than imidacloprid against cowpea aphids (*Aphis craccivora*). The impressive crystal structure of the excellent insecticidal activity compound **9q** clearly proved that the functional electronegative pharmacophore was approximately vertical to the methyleneimidazolidine plane. The differences in the mode of interaction on nAChR of typical compounds **9h** and **9q** remain unclear.

KEYWORDS: phenylazo compounds, neonicotinoids, $\pi-\pi$ stacking, insecticide

INTRODUCTION

The insect nicotinic acetylcholine receptor (nAChR) is one of the most important targets for the insecticides[1,2] represented by neonicotinoid, which is used for crop protection and pet hygiene.[3,4] In the 1990s, imidacloprid **1** led to the booming and prosperous development of neonicotinoids[5] such as nitenpyram[6] **2** and dinotefuran[7] **3** (Figure 1). To date, it has attracted great attention for the characteristics of high efficiency, mammalian safety, low toxicity, no cross-resistance, and unique mode of action. Emerging as the fourth generation of pesticide replacing organophosphorus, carbamate, and pyrethroid compounds, neonicotinoids have taken the main share of the insecticidal market (in 2009, U.S. $2.632 billion) and have been used for insect control worldwide.[8,9] The newly launched neonicotinoid insecticide Sulfoxaflor[10] **4** potentially accounts for a market share of over U.S. $400 million.[11]

According to the crystal structure and three-dimensional arrangement of the pharmacophore, three various modes of action of neonicotinoids against nAChR were presumed successively by Yamamoto,[12] Kagabu,[13] and Casida.[14] Besides, Qian proposed a new mode of action by computational modeling in 2007, which demonstrated the importance of hydrogen bonding and cooperative $\pi-\pi$ interaction between the molecule and amino acid residues.[15] Afterward, two crystal structures of acetylcholine receptor binding protein−imidacloprid (AChBPs-IMI) complex disclosed that the $\pi-\pi$ stacking effect apparently appeared between the conjugated part of the molecule and the amino acid residues.[16,17] Meanwhile, the reported structures **5** and **6** with well-conjugated systems presented quite good activity[18,19] (Scheme 1).

Aiming at increasing the electron scope and density of the conjugated system, herein we introduce the diazene moiety into the structure of the nitromethylene molecule **7** to enhance the $\pi-\pi$ stacking interaction and explore the strategy of molecular design and synthesis to improve the bioactivity of the new chemical entities.

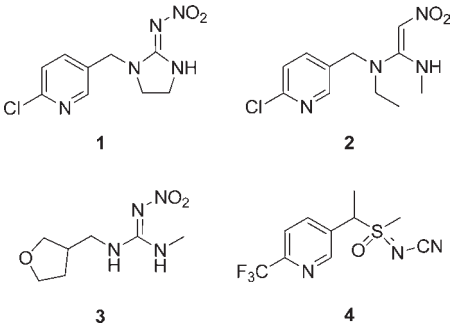

Figure 1. Some commercial neonicotinoid compounds.

MATERIALS AND METHODS

Instruments. All melting points were obtained with a Büchi Melting Point B540 (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Coupling constants ^nJ are reported in hertz. High-resolution electron mass (HR-EIMS) spectra were recorded under

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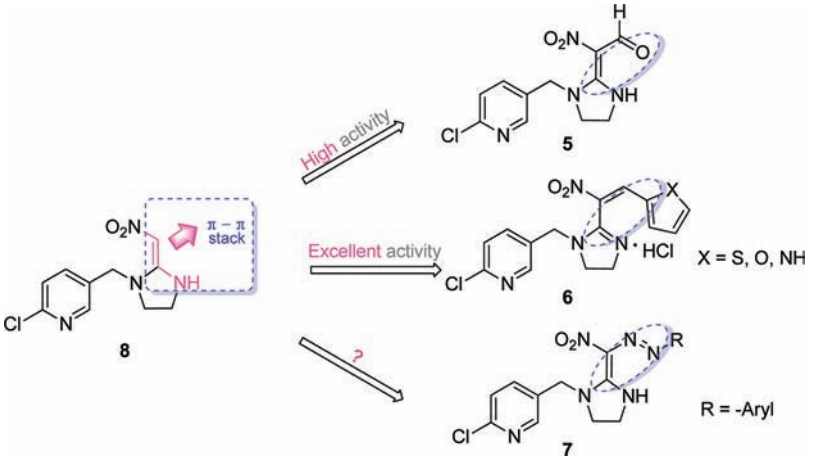
Scheme 1. Strategy To Improve the Conjugation Effect of the Neonicotinoid Analogues



electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized by an ultraviolet (UV) ZF-C analyzer.

General Synthetic Procedure for Compounds 9a−y and 11a−h . Substituted aniline (3.0 mmol) was added to a solution of concentrated HCl (0.73 mL, 9.0 mmol) in 2 mL of water, and the mixture was cooled to 0 °C; a 0 °C solution of $NaNO_2$ (3.15 mmol) in 3 mL water was dropwise added over a period of 5 min, maintaining the reaction temperature below 2 °C. After 15 min of stirring, the solution of diazonium salt was dropped into a reaction mixture of **8** or **10** (2.5 mmol) in 20 mL of acetone, which was immersed in a cooling bath set to 0 °C, and the reaction progress was monitored by TLC. On completion of the reaction, half of the solvent was evaporated under reduced pressure, and to the resulting mixture was added 15 mL of saturated $NaHCO_3$. The precipitate formed was filtered, washed with dichloromethane and water, and dried to provide the corresponding products.

*2-Chloro-5-(((E)-2-(nitro((E)-phenyldiazenyl)methylene)imidazolidin-1-yl)methyl)pyridine (**9a**):* yield, 71%; mp 149.5−150.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.0, 2.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 4.45 (s, 2H), 4.04−3.95 (m, 2H), 3.94−3.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 154.1, 150.4, 150.2, 140.2, 130.3, 129.4, 126.8, 125.5, 124.7, 121.0, 48.1, 47.4, 43.5. HRMS (ES+) calcd for $C_{16}H_{16}N_6O_2{}^{35}Cl$ $(M + H)^+$, 359.1023, found, 359.1031; calcd for $C_{16}H_{16}N_6O_2{}^{37}Cl$ $(M + H)^+$, 361.0994, found, 361.0993.

*2-Chloro-5-(((E)-2-(((E)-(4-fluorophenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9b**):* yield, 74%; mp 177.0−177.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.35 (s, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.60−7.45 (m, 3H), 7.21 (t, J = 8.4 Hz, 2H), 4.45 (s, 2H), 4.06−3.94 (m, 2H), 3.94−3.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1 (d, J = 243.0 Hz, 1C), 162.0, 150.8 (d, J = 3.0 Hz, 1C), 150.4, 150.2, 140.2, 130.3, 125.4, 124.7, 122.5 (d, J = 8.0 Hz, 1C), 116.1 (d, J = 23.0 Hz, 1C), 48.2, 47.4, 43.6. HRMS (ES+) calcd for $C_{16}H_{15}N_6O_2F^{35}Cl$ $(M + H)^+$, 377.0929, found, 377.0918; calcd for $C_{16}H_{15}N_6O_2F^{37}Cl$ $(M + H)^+$, 379.0900, found, 379.0910.

*2-Chloro-5-(((E)-2-(((E)-(2-fluorophenyl)diazenyl)(nitro)methylene)-imidazolidin-1-yl)methyl)pyridine (**9c**):* yield, 65%; mp 165.3−166.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.4, 2.4 Hz, 1H), 7.55−7.48 (m, 1H), 7.26−7.10 (m, 2H), 4.43 (s, 1H), 4.03−3.92 (m, 2H), 3.91−3.82 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 158.8, 156.3, 150.4, 150.2, 142.2 (d, J = 7.0 Hz, 1C), 140.2, 130.2, 127.4 (d, J = 8.0 Hz, 1C), 126.8, 124.9 (d, J = 3.0 Hz, 1C), 124.6, 118.1, 116.8 (d, J = 19.0 Hz, 1C), 48.2, 47.3, 43.7. HRMS (ES+) calcd for $C_{16}H_{15}N_6O_2F^{35}Cl$ $(M + H)^+$, 377.0929, found, 377.0928; calcd for $C_{16}H_{15}N_6O_2F^{37}Cl$ $(M + H)^+$, 379.0900, found, 379.0914.

*2-Chloro-5-(((E)-2-(((E)-(2,4-difluorophenyl)diazenyl)(nitro)methylene)-imidazolidin-1-yl)methyl)pyridine (**9d**):* yield, 63%; mp 177.8−178.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.32 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.54 (dd, J = 15.6, 8.8 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 10.0 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 4.43 (s, 1H), 4.05−3.91 (m, 2H), 3.92−3.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 160.5 (dd, J = 245.5, 11.5 Hz, 1C), 157.2 (dd, J = 252.7, 12.1 Hz, 1C), 150.4, 150.2, 140.1, 139.3 (dd, J = 7.2, 3.8 Hz, 1C), 130.2, 126.6, 124.5, 119.0 (d, J = 7.2 Hz, 1C), 112.1 (d, J = 18.9 Hz, 1C), 105.0, 48.2, 47.3, 43.7. HRMS (ES+) calcd for $C_{16}H_{14}N_6O_2F_2{}^{35}Cl$ $(M + H)^+$, 395.0835, found, 395.0830; calcd for $C_{16}H_{14}N_6O_2F_2{}^{37}Cl$ $(M + H)^+$, 397.0805, found, 397.0814.

*2-Chloro-5-(((E)-2-(((E)-(2,3-difluorophenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9e**):* yield, 66%; mp 164.2−164.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 8.0, 2.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.34−7.31 (m, 1H), 7.19−7.09 (m, 2H), 4.43 (s, 2H), 4.03−3.93 (m, 2H), 3.92−3.81 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 150.7 (dd, J = 242.4, 11.6 Hz, 1C), 150.4, 150.2, 145.3 (dd, J = 249.0, 14.0 Hz, 1C), 144.2, 140.1, 130.3, 127.3, 124.5, 124.3 (dd, J = 7.7, 4.8 Hz, 1C), 113.7 (d, J = 17.2 Hz, 1C), 113.5 (d, J = 1.8 Hz, 1C), 48.3, 47.3, 44.1. HRMS (ES+) calcd for $C_{16}H_{14}N_6O_2F_2{}^{35}Cl$ $(M + H)^+$, 395.0835, found, 395.0822; calcd for $C_{16}H_{14}N_6O_2F_2{}^{37}Cl$ $(M + H)^+$, 397.0805, found, 397.0821.

*2-Chloro-5-(((E)-2-(((E)-(3-chloro-4-fluorophenyl)diazenyl)(nitro)-methylene)imidazolidin-1-yl)methyl)pyridine (**9f**):* yield, 72%; mp 190.8−191.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.4, 2.4 Hz, 1H), 7.54 (dd, J = 7.2, 2.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.46−7.37 (m, 2H), 4.45 (s, 2H), 4.05−3.96 (m, 2H), 3.95−3.84 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 155.7 (d, J = 244.3 Hz, 1C), 151.46, 150.38, 150.16, 140.15, 130.19, 125.62, 124.63, 121.7 (d, J = 7.0 Hz, 1C), 121.22, 120.5 (d, J = 19.0 Hz, 1C), 117.6 (d, J = 22.0 Hz, 1C), 48.32, 47.40, 43.51. HRMS (ES+) calcd for $C_{16}H_{14}N_6O_2F^{35}Cl_2$ $(M + H)^+$, 411.0539, found, 411.0522; calcd for $C_{16}H_{14}N_6O_2F^{37}Cl_2$ $(M + H)^+$, 415.0480, found, 415.0516.

*2-Chloro-5-(((E)-2-(((E)-(2-chlorophenyl)diazenyl)(nitro)methylene)-imidazolidin-1-yl)methyl)pyridine (**9g**):* yield, 78%; mp 163.8−164.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.34 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 8.0, 2.4 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.33−7.29 (m, 1H), 7.21−7.09 (m, 1H), 4.45 (s, 2H), 4.04−3.92 (m, 2H), 3.92−3.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 150.4, 150.1, 150.0, 140.1, 130.5, 130.5, 130.3, 128.0, 127.4, 127.3, 124.6, 117.7,

48.5, 47.4, 44.2. HRMS (ES+) calcd for $C_{16}H_{15}N_6O_2{}^{35}Cl_2$ (M + H)$^+$, 393.0634, found, 393.0627; calcd for $C_{16}H_{15}N_6O_2{}^{37}Cl_2$ (M + H)$^+$, 397.0575, found, 397.0583.

*2-Chloro-5-((((E)-2-(((E)-(2,6-dichlorophenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9h**):* yield, 71%; mp 172.3−173.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.35 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.0, 2.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 4.52 (s, 2H), 4.04−3.91 (m, 2H), 3.90−3.75 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 150.4, 150.1, 149.0, 140.0, 130.5, 129.4, 127.7 126.9, 124.7, 55.4, 48.3, 47.5, 44.1. HRMS (ES+) calcd for $C_{16}H_{14}N_6O_2{}^{35}Cl_3$ (M + H)$^+$, 427.0244, found, 427.0229; calcd for $C_{16}H_{14}N_6O_2{}^{37}Cl_3$ (M + H)$^+$, 433.0155, found, 433.0199.

*5-((((E)-2-(((E)-(4-Bromophenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)-2-chloropyridine (**9i**):* yield, 81%; mp 175.4−176.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.0, 2.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 4.41 (s, 2H), 4.05−3.92 (m, 2H), 3.89−3.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 153.4, 150.3, 150.2, 140.2, 132.2, 130.5, 126.3, 124.6, 122.8, 118.8, 48.2, 47.4, 44.3. HRMS (ES+) calcd for $C_{16}H_{15}N_6O_2{}^{35}Cl^{79}Br$ (M + H)$^+$, 437.0128, found, 437.0113; calcd for $C_{16}H_{15}N_6O_2{}^{37}Cl^{81}Br$ (M + H)$^+$, 441.0078, found, 441.0077.

*2-Chloro-5-((((E)-2-(((E)-(2-iodophenyl)diazenyl)(nitro)methylene)-imidazolidin-1-yl)methyl)pyridine (**9j**):* yield, 69%; mp 173.7−174.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.0, 1.2 Hz, 1H), 7.77 (dd, J = 8.4, 2.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.44 (dd, J = 8.0, 1.6 Hz, 1H), 7.39−7.32 (m, 1H), 6.97−6.90 (m, 1H), 4.45 (s, 2H), 4.02−3.93 (m, 2H), 3.90−3.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 152.1, 150.4, 150.1, 140.1, 139.5, 130.5, 129.4, 128.4, 127.2, 124.7, 116.7, 99.9, 48.7, 47.5, 44.5. HRMS (ES+) calcd for $C_{16}H_{15}N_6O_2{}^{35}ClI$ (M + H)$^+$, 484.9990, found, 484.9978; calcd for $C_{16}H_{15}N_6O_2{}^{37}ClI$ (M + H)$^+$, 486.9960, found, 486.9968.

*2-Chloro-5-((((E)-2-(nitro((E)-(4-nitrophenyl)diazenyl)methylene)-imidazolidin-1-yl)methyl)pyridine (**9k**):* yield, 76%; mp 142.1−142.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.0 Hz, 1H), 4.38 (s, 2H), 3.96 (t, J = 10.0 Hz, 2H), 3.77 (t, J = 10.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 159.9, 150.1, 150.1, 143.5, 140.1, 131.0, 129.8, 125.4, 124.5, 120.6, 48.5, 47.4, 46.1. HRMS (ES+) calcd for $C_{16}H_{15}N_7O_4{}^{35}Cl$ (M + H)$^+$, 404.0874, found, 404.0878; calcd for $C_{16}H_{15}N_7O_4{}^{37}Cl$ (M + H)$^+$, 406.0845, found, 406.0850.

*2-Chloro-5-((((E)-2-(nitro((E)-(2-nitrophenyl)diazenyl)methylene)-imidazolidin-1-yl)methyl)pyridine (**9l**):* yield, 72%; mp 155.4−156.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.31 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.73 (dd, J = 8.0, 2.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 4.42 (s, 2H), 3.98−3.93 (m, 2H), 3.88−3.83 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 150.4, 150.1, 146.3, 146.2, 140.0, 132.9, 130.3, 127.5, 125.9, 124.7, 124.0, 118.1, 48.5, 47.3, 43.8. HRMS (ES+) calcd for $C_{16}H_{15}N_7O_4{}^{35}Cl$ (M + H)$^+$, 404.0847, found, 404.0879; calcd for $C_{16}H_{15}N_7O_4{}^{37}Cl$ (M + H)$^+$, 406.0845, found, 406.0846.

*2-Chloro-5-((((E)-2-(nitro((E)-o-tolyldiazenyl)methylene)imidazolidin-1-yl)methyl)pyridine (**9m**):* yield, 68%; mp 177.0−177.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.73 (dd, J = 8.0, 2.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 4.33 (s, 2H), 3.89 (t, J = 10.0 Hz, 2H), 3.72 (t, J = 10.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 151.9, 150.1, 145.0, 134.0, 133.9, 131.5, 131.1, 128.4, 126.6, 126.4, 124.5, 115.3, 48.6, 47.5, 46.0, 17.8. HRMS (EI+) calcd for $C_{17}H_{17}N_6O_2{}^{35}Cl$ (M)$^+$, 372.1102, found, 372.1106; calcd for $C_{17}H_{17}N_6O_2{}^{37}Cl$ (M)$^+$, 374.1072, found, 374.1120.

*2-Chloro-5-((((E)-2-(nitro((E)-p-tolyldiazenyl)methylene)imidazolidin-1-yl)methyl)pyridine (**9n**):* yield, 73%; mp 174.4−175.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.4, 2.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.42 (s, 1H), 4.03−3.90 (m, 2H), 3.90−3.77 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 152.1, 150.3, 150.2, 140.2, 136.2, 130.5, 129.9, 124.6, 120.9, 48.2, 47.4, 43.9, 21.2. HRMS (ES+) calcd for $C_{17}H_{18}N_6O_2{}^{35}Cl$ (M + H)$^+$, 373.1180, found, 373.1172; calcd for $C_{17}H_{18}N_6O_2{}^{37}Cl$ (M + H)$^+$, 375.1150, found, 375.1168.

*2-Chloro-5-((((E)-2-(((E)-(3,4-dimethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9o**):* yield, 75%; mp 173.9−174.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 8.0, 2.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.40 (s, 2H), 4.01−3.91 (m, 2H), 3.86−3.80 (m, 2H), 2.23 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 152.3, 150.3, 150.1, 140.1, 137.0, 135.2, 130.5, 130.4, 125.7, 124.6, 122.0, 118.6, 48.2, 47.4, 44.1, 20.0, 19.6. HRMS (ES+) calcd for $C_{18}H_{20}N_6O_2{}^{35}Cl$ (M + H)$^+$, 387.1336, found, 387.1332; calcd for $C_{18}H_{20}N_6O_2{}^{37}Cl$ (M + H)$^+$, 389.1307, found, 389.1322.

*2-Chloro-5-((((E)-2-(((E)-(2,3-dimethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9p**):* yield, 72%; mp 159.3−159.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 2.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 4.35 (s, 1H), 3.96−3.86 (m, 2H), 3.83−3.69 (m, 2H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 151.8, 150.2, 150.0, 140.0, 137.6, 132.8, 131.2, 128.0, 127.7, 125.8, 124.6, 113.3, 48.5, 47.4, 45.4, 20.2, 13.2. HRMS (ES+) calcd for $C_{18}H_{20}N_6O_2{}^{35}Cl$ (M + H)$^+$, 387.1336, found, 387.1320; calcd for $C_{18}H_{20}N_6O_2{}^{37}Cl$ (M + H)$^+$, 389.1307, found, 389.1320.

*2-Chloro-5-((((E)-2-(((E)-(2,6-dimethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9q**):* yield, 76%; mp 170.0−170.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.79 (dd, J = 8.0, 2.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 7.2 Hz, 2H), 6.98−6.94 (m, 1H), 4.48 (s, 2H), 4.02−3.92 (m, 2H), 3.93−3.84 (m, 2H), 2.23 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 151.4, 150.4, 150.1, 140.1, 130.5, 130.4, 129.17, 125.7, 125.6, 124.7, 48.2, 47.3, 43.6, 19.6. HRMS (ES+) calcd for $C_{18}H_{20}N_6O_2{}^{35}Cl$ (M + H)$^+$, 387.1336, found, 387.1339. calcd for $C_{18}H_{20}N_6O_2{}^{37}Cl$ (M + H)$^+$, 389.1307, found, 389.1322.

*2-Chloro-5-((((E)-2-(((E)-mesityldiazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9r**):* yield, 71%; mp =136.5−137.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.34 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.0, 2.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 16.4 Hz, 2H), 4.46 (s, 2H), 4.03−3.92 (m, 2H), 3.92−3.82 (m, 2H), 2.22 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 150.4, 150.1, 148.9, 140.1, 134.8, 130.5, 130.4, 129.9, 125.5, 124.7, 48.1, 47.2, 43.5, 21.0, 19.8. HRMS (ES+) calcd for $C_{19}H_{22}N_6O_2{}^{35}Cl$ (M + H)$^+$, 401.1493, found, 401.1488; calcd for $C_{19}H_{22}N_6O_2{}^{37}Cl$ (M + H)$^+$, 403.1463, found, 403.1482.

*2-Chloro-5-((((E)-2-(((E)-(2,6-dimethyl-4-(perfluoropropan-2-yl)-phenyl)diazenyl)(nitro)methylene) imidazolidin-1-yl)methyl)pyridine (**9s**):* yield, 78%; mp 130.1−130.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.0, 2.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.29 (s, 2H), 4.52 (s, 2H), 4.04−3.99 (m, 2H), 3.96−3.91 (m, 2H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 153.7, 150.5, 150.1, 140.0, 131.7, 130.3, 126.1, 125.8 (d, J = 98 Hz, 1C), 124.7, 121.0 (m, 1C), 92.5 (q, J = 32.1 Hz, 1C), 90.7 (q, J = 31.8 Hz, 1C), 48.3, 47.3, 43.4, 19.7. HRMS (ES+) calcd for $C_{21}H_{19}N_6O_2F_7{}^{35}Cl$ (M + H)$^+$, 555.1146, found, 555.1144; calcd for $C_{21}H_{19}N_6O_2F_7{}^{37}Cl$ (M + H)$^+$, 557.1117, found, 557.1133.

*2-Chloro-5-((((E)-2-(((E)-(2-ethyl-6-methylphenyl)diazenyl)(nitro)-methylene)imidazolidin-1-yl)methyl)pyridine (**9t**):* yield, 71%; mp 149.1−149.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 8.0, 2.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.11−6.90 (m, 3H), 4.48 (d, J = 17.2 Hz, 2H), 4.03−3.88 (m, 2H),

3.90−3.77 (m, 2H), 2.58 (q, J = 7.2 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 151.3, 150.4, 150.1, 140.1, 137.2, 130.7, 129.7, 129.2, 127.6, 126.1, 125.8, 124.7, 48.2, 47.3, 44.2, 25.5, 20.0, 16.1. HRMS (ES+) calcd for $C_{19}H_{22}N_6O_2{}^{35}Cl$ (M + H)$^+$, 401.1493, found, 401.1482; calcd for $C_{19}H_{22}N_6O_2{}^{37}Cl$ (M + H)$^+$, 403.1463, found, 403.1478.

*2-Chloro-5-(((E)-2-(((E)-(2,6-diethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9u**):* yield, 69%; mp 136.4−137.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.37 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 8.0, 2.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.03 (s, 3H), 4.49 (s, 2H), 4.05−3.92 (m, 2H), 3.92−3.81 (m, 2H), 2.57 (q, J = 7.2 Hz, 4H), 1.09 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 151.1, 150.5, 150.2, 140.2, 136.5, 130.4, 127.6, 126.1, 125.6, 124.8, 48.06, 47.2, 43.5, 25.6, 16.2. HRMS (ES+) calcd for $C_{20}H_{24}N_6O_2{}^{35}Cl$ (M + H)$^+$, 415.1649, found, 415.1649; calcd for $C_{20}H_{24}N_6O_2{}^{37}Cl$ (M + H)$^+$, 417.1620, found, 417.1636.

*2-Chloro-5-(((E)-2-(((E)-(2,6-diisopropylphenyl)diazenyl)(nitro)-methylene)imidazolidin-1-yl)methyl)pyridine (**9v**):* yield, 66%; mp 126.3−127.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 8.0, 2.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.12−7.08 (m, 3H), 4.49 (s, 2H), 3.98−3.94 (m, 2H), 3.88−3.84 (m, 2H), 3.04−2.97 (m, 1H), 1.09 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 151.0, 150.5, 150.0, 140.3, 140.1, 130.3, 126.1, 125.4, 124.7, 123.3, 48.1, 47.28, 43.3, 27.7, 24.1. HRMS (ES+) calcd for $C_{22}H_{28}N_6O_2{}^{35}Cl$ (M + H)$^+$, 443.1962, found, 443.1947; calcd for $C_{22}H_{28}N_6O_2{}^{37}Cl$ (M + H)$^+$, 445.1933, found, 445.1921.

*2-Chloro-5-(((E)-2-(((E)-(4-methoxyphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9w**):* yield, 74%; mp 165.3−166.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 8.0, 2.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H), 3.96−3.91 (m, 2H), 3.81−3.75 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 158.6, 150.2, 150.2, 148.2, 140.2, 130.8, 125.8, 124.6, 122.3, 114.6, 55.7, 48.1, 47.4, 44.5. HRMS (ES+) calcd for $C_{17}H_{18}N_6O_3{}^{35}Cl$ (M + H)$^+$, 389.1129, found, 389.1133; calcd for $C_{17}H_{18}N_6O_3{}^{37}Cl$ (M + H)$^+$, 391.1099, found, 391.1102.

*2-Chloro-5-(((E)-2-(((E)-(2-methoxyphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9x**):* yield, 71%; mp 151.7−152.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 8.4, 2.0 Hz, 1H), 7.19−7.15 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.94−6.89 (m, 2H), 4.43 (s, 2H), 3.98−3.92 (m, 2H), 3.87 (s, 1H), 3.86−3.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.09, 154.63, 150.38, 150.35, 143.34, 140.30, 130.23, 127.99, 126.51, 124.56, 121.14, 117.01, 113.51, 56.66, 48.18, 47.49, 43.48. HRMS (ES+) calcd for $C_{17}H_{18}N_6O_3{}^{35}Cl$ (M + H)$^+$, 389.1129, found, 389.1138; calcd for $C_{17}H_{18}N_6O_3{}^{37}Cl$ (M + H)$^+$, 391.1099, found, 391.1105.

*2-Chloro-5-(((E)-2-(((E)-(2,6-dimethoxyphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)pyridine (**9y**):* Yyield, 73%; mp 135.1−135.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 8.0 Hz, 1H), 7.76 (dd, J = 8.4, 2.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 4.49 (s, 2H), 3.95−3.89 (m, 2H), 3.83−3.78 (m, 2H), 3.63 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.54, 152.33, 150.28, 149.99, 139.93, 134.32, 130.72, 126.51, 124.59, 116.07, 105.62, 56.46, 48.34, 47.51, 43.43. HRMS (ES+) calcd for $C_{18}H_{20}N_6O_4{}^{35}Cl$ (M + H)$^+$, 419.1235, found, 419.1229; calcd for $C_{18}H_{20}N_6O_4{}^{37}Cl$ (M + H)$^+$, 421.1205, found, 421.1202.

*2-Chloro-5-(((E)-2-(nitro((E)-(4-nitrophenyl)diazenyl)methylene)-imidazolidin-1-yl)methyl)thiazole (**11a**):* yield, 65%; mp 157.3−157.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 9.2 Hz, 2H), 7.66 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 4.70 (s, 2H), 4.07−4.00 (m, 2H), 4.00−3.93 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 152.3, 144.4, 142.6, 134.2, 125.5, 120.6, 48.2, 43.8, 42.9. HRMS (ES+) calcd for $C_{14}H_{13}N_7O_4S^{35}Cl$ (M + H)$^+$, 410.0438, found, 410.0435; calcd for $C_{14}H_{13}N_7O_4S^{37}Cl$ (M + H)$^+$, 412.0409, found, 412.0411.

*2-Chloro-5-(((E)-2-(((E)-(2,6-dichlorophenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11b**):* Yyield, 63%; mp 141.0−142.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 7.66 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 8.0 Hz, 2H), 4.72 (s, 2H), 3.98−3.93 (m, 2H), 3.89−3.83 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 152.4, 148.9, 142.6, 134.7, 129.3, 127.7, 127.2, 125.9, 48.0, 43.6, 43.3. HRMS (ES+) calcd for $C_{14}H_{12}N_6O_2S^{35}Cl_3$ (M + H)$^+$, 432.9808, found, 432.9810; calcd for $C_{14}H_{12}N_6O_2S^{37}Cl_3$ (M+H)$^+$, 438.9720, found, 438.9730.

*2-Chloro-5-(((E)-2-(((E)-(2,3-dimethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11c**):* yield, 61%; mp 160.6−161.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 6.8 Hz, 1H), 4.55 (s, 2H), 3.96−3.84 (m, 2H), 3.84−3.76 (m, 2H), 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 151.8, 151.6, 141.8, 137.6, 136.1, 132.8, 128.1, 127.6, 125.8, 113.3, 48.3, 45.5, 43.1, 20.2, 13.3. HRMS (ES+) calcd for $C_{16}H_{18}N_6O_2S^{35}Cl$ (M + H)$^+$, 393.0900, found, 393.0904; calcd for $C_{16}H_{18}N_6O_2S^{37}Cl$ (M + H)$^+$, 395.0871, found, 495.0885.

*2-Chloro-5-(((E)-2-(((E)-(2,6-dimethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11d**):* yield, 68%; mp 152.4−153.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.66 (s, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.99−6.96 (m, 1H), 4.67 (s, 2H), 3.99−3.93 (m, 2H), 3.91−3.86 (m, 2H), 2.23 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 152.2, 151.4, 142.5, 134.9, 130.3, 129.2, 125.8, 125.6, 47.9, 43.5, 43.2, 19.5. HRMS (ES+) calcd for $C_{16}H_{18}N_6O_2S^{35}Cl$ (M + H)$^+$, 393.0900, found, 393.0894; calcd for $C_{16}H_{18}N_6O_2S^{37}Cl$ (M + H)$^+$, 395.0871, found, 395.0857.

*2-Chloro-5-(((E)-2-(((E)-mesityldiazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11e**):* yield, 70%; mp 127.8−129.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.65 (s, 1H), 6.84 (s, 2H), 4.63 (s, 2H), 3.98−3.89 (m, 2H), 3.87−3.78 (m, 2H), 2.22 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 152.0, 149.0, 142.3, 135.4, 134.8, 130.3, 129.9, 126.0, 47.9, 44.2, 43.2, 21.0, 19.7. HRMS (ES+) calcd for $C_{17}H_{20}N_6O_2S^{35}Cl$ (M + H)$^+$, 407.1057, found, 407.1062; calcd for $C_{17}H_{20}N_6O_2S^{37}Cl$ (M + H)$^+$, 409.1027, found, 409.1032.

*2-Chloro-5-(((E)-2-(((E)-(2,6-diethylphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11f**):* yield, 61%; mp 116.5−117.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.67 (s, 1H), 7.06−7.02 (m, 3H), 4.67 (s, 2H), 3.98−3.84 (m, 4H), 2.57 (q, J = 7.2 Hz, 4H), 1.09 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 152.2, 151.0, 142.6, 136.5, 134.8, 127.5, 126.1, 125.7, 47.8, 43.5, 43.1, 25.4, 16.1. HRMS (ES+) calcd for $C_{18}H_{22}N_6O_2S^{35}Cl$ (M + H)$^+$, 421.1213, found, 421.1199; calcd for $C_{18}H_{22}N_6O_2S^{37}Cl$ (M + H)$^+$, 423.1184, found, 423.1177.

*2-Chloro-5-(((E)-2-(((E)-(4-methoxyphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11g**):* yield, 66%; mp 162.3−163.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.65 (s, 1H), 7.49 (d, J = 9.2 Hz, 2H), 6.97 (d, J = 9.2 Hz, 2H), 4.62 (s, 2H), 4.02−3.92 (m, 2H), 3.92−3.85 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 158.8, 152.1, 148.0, 142.5, 134.8, 124.9, 122.4, 114.6, 55.8, 47.7, 43.4, 43.2. HRMS (ES+) calcd for $C_{15}H_{16}N_6O_3S^{35}Cl$ (M + H)$^+$, 395.1693, found, 395.0685; calcd for $C_{15}H_{16}N_6O_3S^{37}Cl$ (M + H)$^+$, 397.0664, found, 397.0683.

*2-Chloro-5-(((E)-2-(((E)-(2,6-dimethoxyphenyl)diazenyl)(nitro)methylene)imidazolidin-1-yl)methyl)thiazole (**11h**):* yield, 63%; mp 165.5−166.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.65 (s, 1H), 7.10 (t, J = 8.4 Hz, 1H), 6.68 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H), 3.91−3.86 (m, 2H), 3.81−3.73 (m, 2H), 3.63 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 152.3, 152.2, 142.2, 135.4, 126.6, 126.4, 105.6, 56.4, 48.2, 43.8, 43.3. HRMS (ES+) calcd for $C_{16}H_{18}N_6O_4S^{35}Cl$ (M + H)$^+$, 425.0799, found, 425.0799; calcd for $C_{16}H_{18}N_6O_4S^{37}Cl$ (M + H)$^+$, 427.0769, found, 427.0760.

X-ray Diffraction Analysis. Compound **9q** was recrystallized by slow evaporation from a mixture of acetone and methanol to afford a

suitable single crystal. Yellow blocks of **9q** (0.400 mm × 0.369 mm × 0.227 mm) were mounted on a quartz fiber and detected by Bruker Smart 1000 single-crystal diffraction. 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; 9673 measured reflections; 3607 independent reflections (R_{int} = 0.0748). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.55574 and T_{max} = 1.00000). The structure was solved by direct methods using SHELXS-97;[20] all other calculations were performed with a Bruker SAINT system and Bruker SMART programs.[21] Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0669P)^2 + 0.1381P]$ gave final values of R = 0.0526, ωR = 0.1343, and GOF (F) = 1.044 for 251 variables and 3607 contributing reflections. Maximum shift/error = 0.000(3), and max/min residual electron density = 0.355/−0.276 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Compound **9h** was recrystallized by slow evaporation from a mixture of acetone and methanol to afford a suitable single crystal. Yellow blocks of **9h** (0.369 mm × 0.317 mm × 0.223 mm) were mounted on a quartz fiber and detected by Bruker Smart 1000 single-crystal diffraction. 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} = 26.00; 9712 measured reflections; 3565 independent reflections (R_{int} = 0.0935). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.61673 and T_{max} = 1.00000). The structure was solved by direct methods using SHELXS-97; all other calculations were performed with a Bruker SAINT system and Bruker SMART programs. Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0824P)^2 + 0.0000P]$ gave final values of R = 0.0510, ωR = 0.1343, and GOF (F) = 0.985 for 249 variables and 3565 contributing reflections. Maximum shift/error = 0.000(3), and max/min residual electron density = 0.334/−0.360 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 (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 500.0, 250.0, and 125.0 mg L^{-1} and others for bioassays.

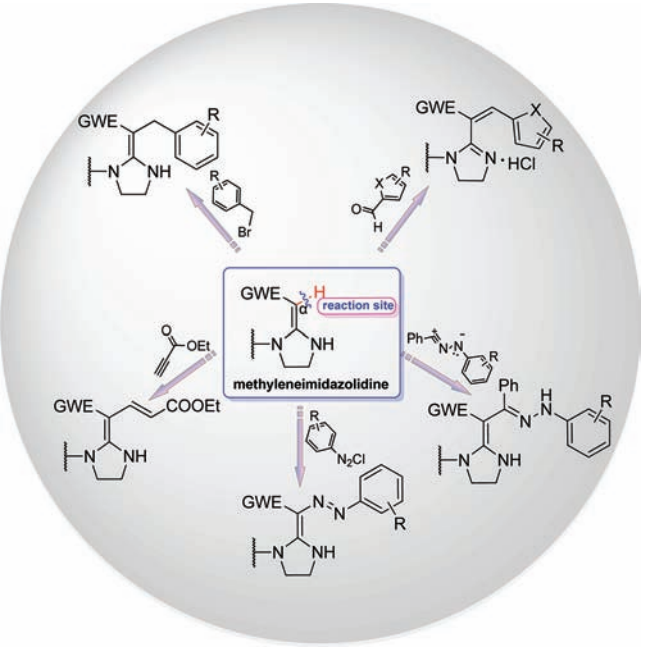
Insecticidal Test for Cowpea Aphids (Aphis craccivora). The insecticidal activities of the synthetic compounds against pea aphids (*A. craccivora*) were tested according to our previously reported procedure.[22,23]

RESULTS AND DISCUSSION

Synthesis. The double bond on the cyclic 1,1-enediamine bears the characteristic of high polarization resulting from the conjugation effect of an electron-withdrawing substituent and a strong electron-donating amino group.[24] The α-carbon is the first reaction site when the intermediate is attacked by the electrophilic reagents owing to the delocalization effect of the lone pair electron on the nitrogen atom.[25,26] Various adducting reactions of methyleneimidazolidine with electrophiles such as heterocyclic aldehyde, benzyl bromide, ethyl propiolate, diphenylnitrile imine, and diazonium salt proceed smoothly and have been reported previously,[18,25−29] which proved to us the possibility of synthesizing the phenylazoneonicotinoids by reaction with different substituted diazonium salts (Scheme 2).

The synthetic procedure for the title compounds is illustrated in Scheme 3. Starting from the substituted anilines, the diazonium salt solution was first prepared under 2 °C. The freshly prepared diazonium salt reacted with **8** or **10** to yield the corresponding phenylazo compounds, respectively.

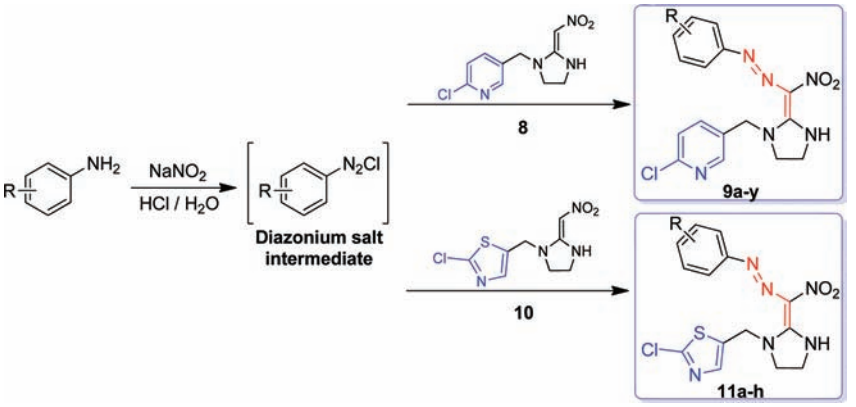
Scheme 2. Feasible Derivative Routes of the Methyleneimidazolidine Intermediate



Crystal Structure Analysis. The insecticidal activity of the target compounds varied greatly with the substituents on the benzene ring, which implied the requirement of specific spatial conformation. Comprehensive structural information of phenylazoneonicotinoid compounds **9h** (Figure 2a) and **9q** (Figure 2b) was provided by X-ray crystallographic diffraction analysis (see the Supporting Information). Obviously, the phenyl group with different substituents resulted in entirely different three-dimensional conformation. Selected bond lengths, bond angles, and torsional angles are given in Table 1.

To our best knowledge, face-to-face $\pi-\pi$ alignment is a rare phenomenon, and commonly π interaction is an offset or slipped stacking.[30] In structure **9h**, the plane of 2,6-dichlorophenyl and pyridine apparently formed a face-to-face stacked arrangement, where most of the ring-plane area overlapped. The centroid−centroid distance of the rings was 3.71 Å and an angle of 6.56° was formed between the ring normal of the pyridine plane and the vector between the ring centroids (Figure 2a). Unexpectedly, compound **9h** presented quite poor activity against the insect cowpea aphid (*A. craccivora*) compared with compound **8**. Intriguingly, compound **9q** with a (2, 6-dimethylphenyl)diazene moiety exhibited exciting insecticidal activity, and the crystal structure revealed extraordinary characteristics. According to the crystal structure of imidacloprid, Casida and Kagabu suggested that the coplanarity between the electronegative pharmacophore and the guanidine−amidine moiety is essential to obtain a high-activity molecule,[13,14,31] and the theory gained support from the commercial neonicotinoid compounds. Interestingly, in the structure of compound **9q**, a large torsion angle existed between the nitro group and the imidazoline plane, which brought some divergence with the classic theory. As shown in Figure 2b, the torsion angles of N(3)−C(1)−C(2)−N(5) and N(1)−N(2)−C(1)−N(3) were −104.5(2)° and 179.48(17)°, respectively. It

Scheme 3. Synthetic Route of the Target Molecules



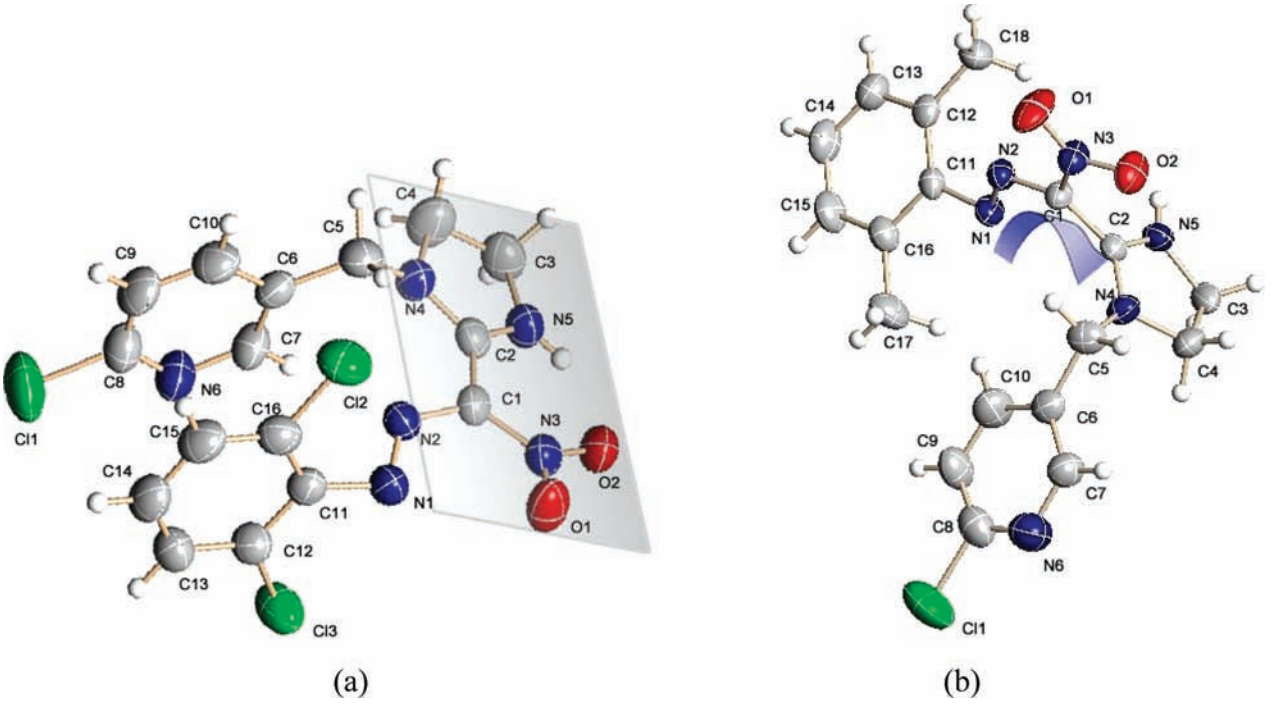


Figure 2. Crystal structures of compounds **9h** (a) and **9q** (b).

was regarded that the conjugation effect between the diazene moiety and methyleneimidazolidine was in the form of a Mobius strip. Evidently, no face-to-face $\pi-\pi$ interaction between pyridine and the 2,6-dimethylphenyl plane appeared, and these two rings shared the same plane from a large distance, which might due to the weaker stability of the π-deficient$-\pi$-rich system in **9q** compared with the π-deficient$-\pi$-deficient one in **9h**. However, the crystal configuration of **9q** does not convince us that it is the accurate configuration at the binding site, and the molecule would regulate its spacial conformation while interacting with nAChR. Herein, molecular binding research was also investigated to present a reasonable binding model (Figure 3).

Insecticidal Activities. Table 2 lists the insecticidal activities of the title compounds against cowpea aphid (*A. craccivora*). Compound **9a** with no substitution on the phenyl group presented low insecticidal activity. Introducing the halogen atoms did not contribute to great activity improvement of the corresponding compounds, and most of the halides exhibited unpleasing insecticidal effectiveness (**9c**−**j**) with the exception of compound **9b** (LC_{50} = 0.03720 mmol L^{-1}). Moreover, the structures with methyl groups on various substitution positions demonstrated entirely different insecticidal results. Positions 2 and 6 on the phenyl group were regarded as the two key substitution sites for structural derivation to obtain high-activity molecules. Compound **9q** (LC_{50} = 0.00426 mmol L^{-1}) displayed an improvement of about 1 order of magnitude over imidacloprid (LC_{50} = 0.03502 mmol L^{-1}) in insecticidal activity. Meanwhile, compared with **9r**, compound **9s** with a heptafluoroisopropyl moiety on position 4 had no activity, which confirmed to us that the substitution of an electron-withdrawing group on the phenyl ring would lead to a sharp decrease in the insecticidal activity. Replacing 2,6-dimethyl with 2,6-diethyl, 2,6-diisopropyl, or 2,6-dimethoxy

Table 1. Selected Bond Lengths, Bond Angles, and Torsional Angles of Compounds 9h and 9q

	bond lengths (Å)			bond angles (deg)			orsional angles (deg)	
	9h	9q		9h	9q		9h	9q
Cl(1)−C(8)	1.742(3)	1.756(3)	N(2)−N(1)−C(11)	110.38(19)	113.16(15)	C(11)−N(1)−N(2)−C(1)	−177.4(2)	−175.03(16)
N(1)−N(2)	1.266(3)	1.274(2)	N(1)−N(2)−C(1)	122.7(2)	115.38(15)	N(1)−N(2)−C(1)−N(3)	−4.5(3)	179.48(17)
N(1)−C(11)	1.434(3)	1.425(2)	C(2)−N(4)−C(5)	127.4(2)	127.18(17)	N(1)−N(2)−C(1)−C(2)	167.4(2)	8.5(3)
N(2)−C(1)	1.355(3)	1.361(2)	C(2)−N(4)−C(4)	110.3(2)	109.91(17)	O(1)−N(3)−C(1)−C(2)	170.2(2)	178.3(2)
N(3)−O(1)	1.226(3)	1.241(2)	C(5)−N(4)−C(4)	119.3(2)	121.62(17)	O(2)−N(3)−C(1)−C(2)	−10.3(3)	−1.5(3)
N(3)−O(2)	1.250(2)	1.274(2)	C(2)−N(5)−C(3)	112.7(2)	111.50(18)	C(3)−N(5)−C(2)−C(1)	174.5(2)	−179.62(18)
N(3)−C(1)	1.413(3)	1.364(2)	C(8)−N(6)−C(7)	116.3(2)	115.3(2)	C(5)−N(4)−C(2)−N(5)	−162.0(2)	176.4(2)
N(4)−C(2)	1.338(3)	1.314(2)	N(2)−C(1)−N(3)	124.8(2)	116.99(16)	C(5)−N(4)−C(2)−C(1)	21.6(4)	−4.0(3)
N(4)−C(5)	1.453(3)	1.453(3)	N(2)−C(1)−C(2)	115.21(19)	126.80(17)	C(4)−N(4)−C(2)−C(1)	−178.5(2)	−171.03(18)
N(4)−C(4)	1.467(3)	1.471(3)	N(3)−C(1)−C(2)	119.52(19)	115.65(16)	N(3)−C(1)−C(2)−N(5)	14.0(4)	−104.5(2)
N(5)−C(2)	1.317(3)	1.306(2)	N(5)−C(2)−N(4)	110.1(2)	111.96(17)	N(2)−C(1)−C(2)−N(4)	17.4(3)	−112.9(2)
N(5)−C(3)	1.453(3)	1.461(3)	N(5)−C(2)−C(1)	125.7(2)	123.24(18)	C(2)−N(4)−C(5)−C(6)	−102.5(3)	120.5(2)
N(6)−C(8)	1.315(3)	1.348(4)	N(4)−C(2)−C(1)	124.0(2)	124.79(17)	C(4)−N(4)−C(5)−C(6)	99.3(3)	−73.9(3)
N(6)−C(7)	1.340(3)	1.372(3)	N(5)−C(3)−C(4)	102.6(2)	101.95(16)	N(4)−C(5)−C(6)−C(7)	9.8(4)	117.0(2)
C(1)−C(2)	1.438(3)	1.474(3)	N(4)−C(4)−C(3)	104.1(2)	102.64(16)			
C(3)−C(4)	1.499(4)	1.523(3)	N(4)−C(5)−C(6)	115.3(2)	111.36(17)			
C(5)−C(6)	1.504(3)	1.510(3)	C(7)−C(6)−C(5)	124.1(2)	122.0(2)			
N(5)−H(5)···O(2)	1.97(2)	1.95(2)	N(5)−H(5)···O(2)	136(3)	156(2)			

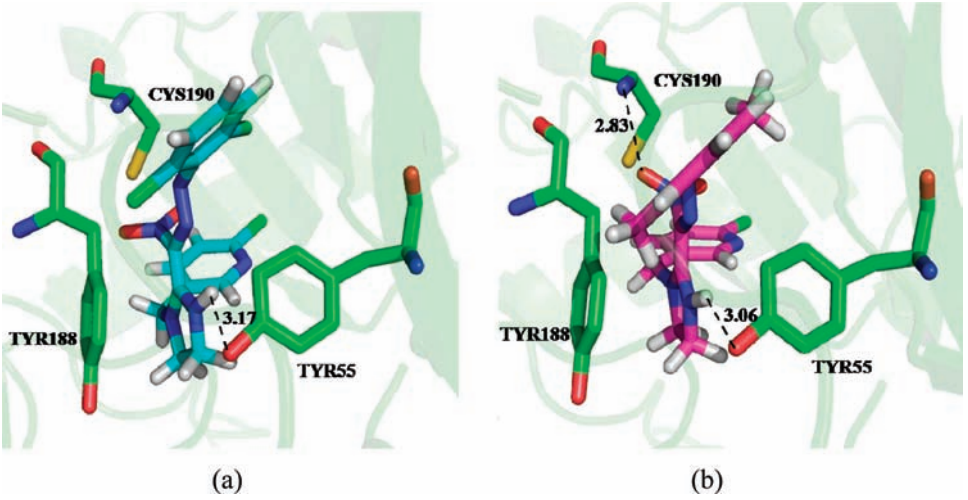


Figure 3. Molecular docking between AChBP and compounds **9h** (a) and **9q** (b).

also showed comparable activities (**9u**, **9v**, **9y**, respectively). Similar results were also acquired when 2-chloro-5-pyridine was modified with 2-chloro-5-thiazole, and the LC_{50} values of **11d**, **11e**, **11f**, **11h** were 0.00350, 0.01844, 0.01176, and 0.01464 mmol L^{-1}, respectively.

Docking Study. A molecular docking study was performed to investigate the interaction between receptor and compounds. Bearing numerous characteristics of nAChRs,[32] the crystal structure of AChBP was obtained from the Protein Data Bank (PDB code 3C79)[16] and prepared by adding hydrogen atoms, removing water, and extracting ligand using Maestro 7.5. Compounds **9h** and **9q** were built, minimized, and docked into the active site pocket of AChBP by using GOLD version 3.2 (The Cambridge Crystallographic Data Centre, Cambridge, U.K.), and the scoring function ChemScore was selected to evaluate the docking results. All atoms within 10 Å around the ligand (imidacloprid) in the 3C79 structure were selected as binding pocket and considered in the docking study. As illustrated in Figure 3, a $\pi-\pi$ stacking interaction was found between the plane of methyleneimidazolidine and the aromatic side chain of Tyr188. A N−H···O hydrogen bond was observed between the N−H of the imidazole ring and the phenol oxygen atom of Tyr55 (N···O distances of 3.17 and 3.06 Å for **9h** and **9q**, respectively). Although **9h** and **9q** showed quite different crystal structures, they showed a similar binding mode with the target from the docking results. However, the reason for their significant insecticidal activity differences is still unclear.

In conclusion, a series of phenylazoneonicotinoid compounds were designed and synthesized. The conjugation effect of the nitromethylene pharmacophore was enhanced by reaction with

Table 2. Insecticidal Activity Results of the Synthetic Compounds 9q−y and 11a−h

		Aphis craccivora			
		mortality (%)			LC_{50} (mmol L^{-1})
compd	R^a	500 mg L^{-1}	250 mg L^{-1}	125 mg L^{-1}	
9a	H	31.2	nt[b]	nt	nt
9b	4-F	100	100	100	0.03720
9c	2-F	13.0	nt	nt	nt
9d	2,4-F_2	12.2	nt	nt	nt
9e	2,3-F_2	25.1	nt	nt	nt
9f	4-F-3-Cl	8.6	nt	nt	nt
9g	2-Cl	7.1	nt	nt	nt
9h	2,6-Cl_2	6.5	nt	nt	nt
9i	4-Br	58.3	nt	nt	nt
9j	2-I	0	nt	nt	nt
9k	4-NO_2	4.7	nt	nt	nt
9l	2-NO_2	8.2	nt	nt	nt
9m	2-Me	52.5	nt	nt	nt
9n	4-Me	56.6	nt	nt	nt
9o	3,4-Me_2	19.7	nt	nt	nt
9p	2,3-Me_2	73.3	nt	nt	nt
9q	2,6-Me_2	100	100	100	0.00426
9r	2,4,6-Me_3	100	100	100	0.00499
9s	2,6-Me_2-4-F_7-i-Pr	12.2	nt	nt	nt
9t	2-Me-6-Et	100	100	100	0.00374
9u	2,6-Et_2	100	100	100	0.00280
9v	2,6-i-Pr_2	100	100	100	0.01375
9w	4-OMe	47.5	nt	nt	nt
9x	2-OMe	91.0	76.0	35.5	nt
9y	2,6-OMe_2	100	100	100	0.00990
11a	4-NO_2	12.1	nt	nt	nt
11b	2,6-Cl_2	18.2	nt	nt	nt
11c	2,3-Me_2	61.7	nt	nt	nt
11d	2,6-Me_2	100	100	100	0.00350
11e	2,4,6-Me_3	100	100	100	0.01523
11f	2,6-Et_2	100	100	100	0.01176
11g	4-OMe	11.8	nt	nt	nt
11h	2,6-OMe_2	100	100	100	0.01464
imidacloprid		100	100	100	0.03502

[a] See Scheme 3 for a substituent for R. [b] nt, not tested.

the diazonium salts. The bioassay results implied that some molecules displayed good insecticidal activities against cowpea aphids. In particular, most of the compounds with electron-donating groups on positions 2 and 6 of the phenyl ring presented excellent bioactivity, some of which were 10-fold higher than that of imidacloprid. The crystal structure of high-activity compound **9q** showed a large torsion angle between the pharmacophore and the methyleneimidazolidine plane. The preliminary computer-aided molecular docking result revealed that **9h** and **9q** shared similar binding configurations despite their great bioactivity disparity. Further studies on the mode of action (MoA) of **9q** and structural modifications are in progress.

■ ASSOCIATED CONTENT

Supporting Information. Crystallographic information files (CIFs) of compounds **9h** and **9q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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