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Design, Synthesis, and Synergistic Activity of Eight-Membered Oxabridge Neonicotinoid Analogues

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ABSTRACT: Insecticide synergists are sought-after due to their potential in improving the pesticide control efficacy with a reduced dose of an active ingredient. We previously reported that a cis-configuration neonicotinoid (IPPA08) exhibited specific synergistic activity toward neonicotinoid insecticides. In this study, we synthesized a series of structural analogues of IPPA08 by converting the pyridyl moiety of IPPA08 into phenyl groups, via facile double-Mannich condensation reactions between nitromethylene compounds and glutaraldehyde. All of the oxabridged neonicotinoid compounds were found to increase the toxicity of imidacloprid against *Aphis craccivora*. Notably, compound **25** at 0.75 mg/L lowered the LC_{50} value of imidacloprid against *A. craccivora* by 6.54-fold, while a 3.50-fold reduction of the LC_{50} value was observed for IPPA08. The results of bee toxicity test showed that compound **25** display selectivity in its effects on imidacloprid toxicity against the honey bee (*Apis mellifera* L.). In summary, replacing the pyridyl ring with a phenyl ring was a viable approach to obtain a novel synergist with oxabridged moiety for neonicotinoid insecticides.

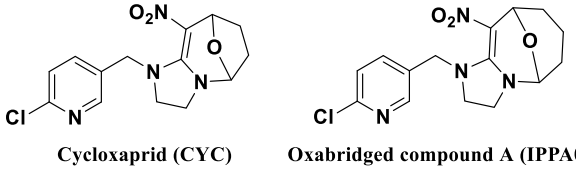
KEYWORDS: *neonicotinoid, insecticide synergist, imidacloprid, selectivity*

INTRODUCTION

Since the introduction of imidacloprid in the 1990s, neonicotinoid insecticides have played crucial roles in pest control due to their safety profile, insecticidal spectrum, and systemic properties.[1−3] Currently, neonicotinoids represent the largest insecticide group, accounting for over 25% of the global insecticide market.[4] However, the abusive use of neonicotinoids in the past three decades has brought about tough challenges, such as resistance and toxicity to honey bees.[5,6] Also, neonicotinoids are considered to have side effects on insect pollinators at sublethal concentrations through the potential uptake from crops and wild plants.[7,8] Recently, these concerns about sublethal effects of neonicotinoids on bees have led to a reevaluation of the overall biological safety of neonicotinoids in Europe and elsewhere.[9] Insecticide synergists are a potential solution for these issues. They can greatly enhance the activity of the existing pesticides and therefore lower the necessary dose of the active ingredient.

Cycloxaprid is a new class of neonicotinoid with a unique oxabridged substructure (Figure 1). It exhibited excellent activity, high selectivity, and good safety profiles, and was recently approved in China.[10−14] Interestingly, an eight-membered oxabridged homologue of cycloxaprid, i.e., IPPA08 (Figure 1), was almost inactive to insects and yet exhibited synergistic effects on traditional neonicotinoids, including imidacloprid, acetamiprid, thiacloprid, and clothianidin. We also find that IPPA08 presented little effects on the toxicities of dinotefuran and cycloxaprid. Also, IPPA08 did not display selectivity in its effects on imidacloprid toxicity against the honey bee (*A. mellifera* L.).[15,16] Therefore, we sought to modify the oxabridged structure, by changing the peripheral pyridyl ring into a phenyl ring, to further improve its synergistic activity as well as with selectivity and safety toward honey bees.

Herein, a focused library of eight-membered oxabridged compounds were synthesized from nitromethylene analogues and glutaraldehyde, and their structure−activity relationships (SARs) were thoroughly tested.



Cycloxaprid (CYC) Oxabridged compound A (IPPA08)

Figure 1. Oxabridged neonicotinoid compounds cycloxaprid (CYC) and IPPA08.

MATERIALS AND METHODS

Chemicals. Cycloxaprid, paichongding, and IPPA08 were synthesized and purified according to a literature procedure.[17] Other insecticides were purchased from Sigma-Aldrich (St. Louis, MO).

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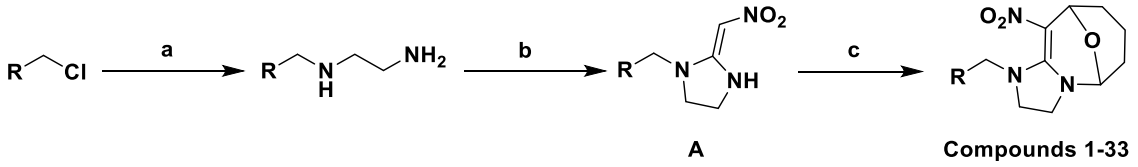
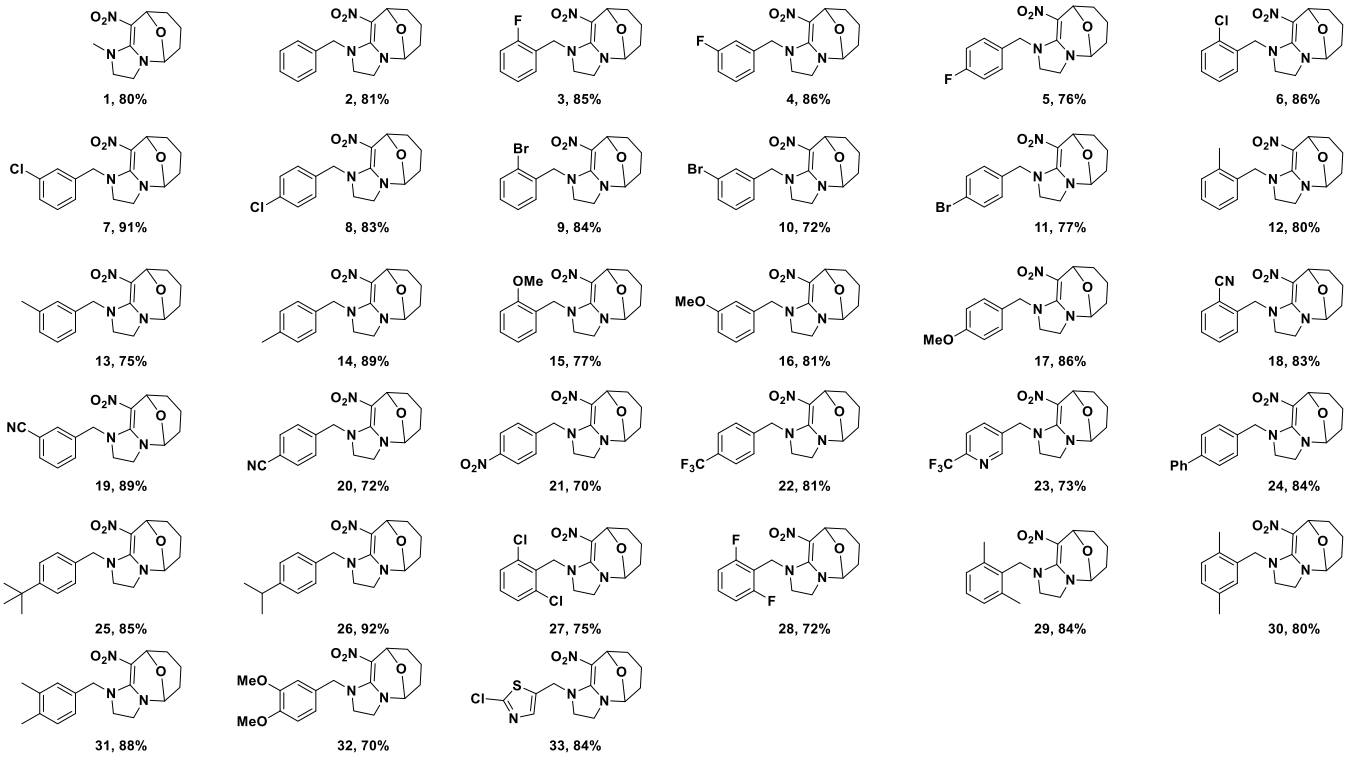
Scheme 1. Synthetic Routes of Target Compounds[a]



[a]Reagents and conditions: (a) ethane-1,2-diamine, CH_3CN, 0−5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, CH_3CH_2OH, refluxing; (c) glutaraldehyde, concentrated HCl, rt.

Table 1. Compounds 1−33



Experiment Design. First, we tested the standard curve of imidacloprid and calculated the LC_{30} (0.997 mg/L) and LC_{50} (1.72 mg/L) values. To screen out candidates with significant synergistic effect, the mortality of a mixture of imidacloprid (1 mg/L) with the new compounds at low concentrations (0.5, 1, 2, 4 mg/L) against *Aphis craccivora* was analyzed. To obtain the initial synergistic concentration **a** and the maximum synergistic concentration **b** (the minimum concentration when the mortality reaches the maximum), a further refined concentration gradient was performed. Finally, we assessed the LC_{50} of imidacloprid when the candidate compound is combined with imidacloprid at the initial synergistic concentration **a** and maximum synergistic concentration **b**, and compared with the blank to calculate the synergism ratio.

Insects and Bioassay. Cowpea Aphid (*A. craccivora*) is a susceptible strain from our laboratory, and the bioassay was carried out using the leaf dip bioassay.[18] Aqueous solution of each compound was prepared, to which 0.1% Triton X-100 (0.1 mg/L) as a surfactant and dimethyl sulfoxide (DMSO) as a solvent were added. The mixture was then diluted with 0.1% Triton X-100 (0.1 mg/L) to obtain a series concentrations of 4, 2, 1, and 0.5 mg/L and so on. Several adults of aphid were selected, avoiding light, and given a starvation treatment about an hour in the dark. Then, they were let to eat broad bean seedling until their mouthparts pierce the bean sprout (2−3 h). Then, the leaves of the horsebean plant, infested with 20−30 aphids, were dipped for 5 s in each concentration three times. This procedure was repeated three times in each group. After treatment, the burgeoning shoots were placed in a conditioned room (25 ± 1 °C, 50% RH). Water containing Triton X-100 (0.1 mg/L) was used as control. The mortality was recorded in 48 h. The data obtained were analyzed using Polo software (LeOra Software, Inc., Cary, NC) to determine the LC_{50} values.

Bee Toxicity Assay. Honey bees (*Apis mellifera* L.) were provided by Chinese Academy of Agricultural Sciences (Beijing, China), and a bioassay was performed following the Organization for Economic Cooperation and Development (OECD) method for contact toxicity and oral toxicity tests.[19]

Contact Assay. Honey bees (*A. mellifera* L.) were put into a dryer and anesthetized by 5 mL of diethyl ether for 3 min before the test. Then, solutions of different concentrations were added dropwise on the pronotum of the bees by a 1.00 μL microdropper. The bees were enclosed in the cage in time before the bees fully recovered and were fed with 33% honey water. The cage was put on the laboratory table and covered by a black cloth, and acetone was used as control.

Uptake Assay. Degrease cotton was dipped in diluted solutions of the chemicals, to which was added Tween 80 and diluted by 33% honey water until saturation. Then, the degrease cotton was spread on a gauze net in the cage and a 50 mL beaker was placed on the degrease cotton so that the honey bees (*A. mellifera* L.) could suck the liquid. The cage was placed on a laboratory table and covered by a black cloth. The amount of acetone with Tween 80 was the same as

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J. Agric. Food Chem. 2021, 69, 3005−3014

the maximum concentration of diluted solution. It was used as control.

The mortality rates and poisoning symptoms were recorded 24 and 48 h after treatment. The test data were processed by SPSS12.0 to obtain the LD_{50} (bee contact toxicity) for 24 and 48 h, and LD_{50} (bee oral toxicity) for 24 h and 48 h and 95% confidence intervals.

Instruments. All melting points were obtained with a Buchi 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 (electrospray ionization time-of-flight (ESI-TOF)) were performed on a Micromass liquid chromatography-TOF (LC-TOF) spectrometer. High-resolution mass spectra (HRMS) EI were recorded under 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 with ultraviolet (UV) light. All other solvents and reagents were obtained from commercial sources without further purification.

RESULTS

Synthesis. The synthetic route of the target compounds is summarized in Scheme 1. The structures of the title compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (ESI).

General Procedure for the Preparation of Compounds. A mixture of starting material A (nitromethylene analogues) (2 mmol) and concentrated hydrochloric acid (0.1 mL) in MeCN (6 mL) was stirred at room temperature. After 5 min of stirring, a 25% glutaraldehyde aqueous solution (1 mL) was added slowly. Then, the reaction mixture was stirred at 0 °C to room temperature and monitored by TLC. After completion, the pH value of the reaction mixture was adjusted to 7−8 by saturated aqueous $NaHCO_3$ and the solvent was removed under reduced pressure. The resulting mixture was extracted with dichloromethane (3 × 20 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 (DCM/MeOH as eluent) to afford the pure products (**1**−**33**, Table 1). The data of **1**−**33** are shown as follows.

*1-Methyl-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**1**).* Yield, 80%; mp, 109.8−110.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.11−4.99 (m, 2H), 3.86−3.56 (m, 4H), 3.14 (s, 3H), 1.84 (d, J = 13.4 Hz, 1H), 1.76−1.65 (m, 3H), 1.58−1.49 (m, 1H), 1.47−1.36 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.45, 104.44, 81.46, 68.64, 51.73, 45.97, 38.62, 28.56, 26.49, 14.45 ppm. HRMS (ESI) calcd for $C_{10}H_{16}N_3O_3$ $[M + H]^+$, 226.1192, found, 226.1193.

*1-Benzyl-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**2**).* Yield, 81%; mp, 154.5−155.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43−7.25 (m, 5H), 5.16−5.04 (m, 2H), 4.98 (d, J = 15.2 Hz, 1H), 4.78 (d, J = 15.2 Hz, 1H), 3.75−3.56 (m, 4H), 1.85−1.66 (m, 4H), 1.54−1.50 (m, 1H), 1.44−1.30 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.02, 137.01, 128.45, 127.75, 127.39, 105.35, 81.25, 68.52, 53.60, 49.15, 45.80, 28.23, 26.70, 14.33 ppm. HRMS (ESI) calcd for $C_{16}H_{20}N_3O_3$ $[M + H]^+$, 302.1505, found, 302.1506.

*1-(2-Fluorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**3**).* Yield, 85%; mp, 144.1−144.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38−7.35 (m, 2H), 7.23−7.19 (m, 2H), 5.12 (s, 1H), 5.03 (s, 1H), 4.97 (d, J = 15.8 Hz, 1H), 4.89 (d, J = 15.8 Hz, 1H), 3.82−3.54 (m, 4H), 1.80−1.61 (m, 4H), 1.52 (d, J = 13.8 Hz, 1H), 1.38−1.35 (m, 1H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ-118.36 (s, 1F) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.31, 155.99 (d, $J_{C\text{-}F}$ = 255.8 Hz, 1C), 129.88, 129.44, 124.59 (d, $J_{C\text{-}F}$ = 19.2 Hz, 1C), 123.87, 115.21 (d, $J_{C\text{-}F}$ = 3.9 Hz, 1C), 105.33, 81.24, 68.43, 49.44, 47.95, 45.83, 28.16, 26.78, 14.21 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3F$ $[M + H]^+$, 320.1410, found, 320.1411.

*1-(3-Fluorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**4**).* Yield, 86%; mp, 129.3−130.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53−7.03 (m, 4H), 5.07−5.01 (m, 3H), 4.75 (d, J = 15.6 Hz, 1H), 3.68 (d, J = 18.2 Hz, 4H), 1.90−1.29 (m, 6H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ-113.32 (s, 1F) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.42, 156.08 (d, $J_{C\text{-}F}$ = 255.1 Hz, 1C), 140.09, 130.32 (d, $J_{C\text{-}F}$ = 9.8 Hz, 1C), 123.69 (d, $J_{C\text{-}F}$ = 4.6 Hz, 1C), 114.44, 114.12, 105.30, 81.23, 68.45, 53.40, 49.37, 45.79, 28.25, 26.70, 14.32 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3F$ $[M + H]^+$, 320.1410, found, 320.1411.

*1-(4-Fluorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**5**).* Yield, 76%; mp, 143.3−144.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42−7.36 (m, 2H), 7.23−7.16 (m, 2H), 5.11 (s, 1H), 5.06 (d, J = 2.4 Hz, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 3.73−3.57 (m, 4H), 1.85−1.65 (m, 4H), 1.53 (d, J = 13.8 Hz, 1H), 1.43−1.29 (m, 1H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ-115.23 (s, 1F) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.52, 155.97 (d, $J_{C\text{-}F}$ = 249.2 Hz, 1C), 133.16, 129.89 (d, $J_{C\text{-}F}$ = 10.5 Hz, 1C), 115.18 (d, $J_{C\text{-}F}$ = 5.0 Hz, 1C), 105.34, 81.23, 68.48, 52.96, 49.14, 45.77, 28.23, 26.69, 14.33 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3F$ $[M + H]^+$, 320.1410, found, 320.1415.

*1-(2-Chlorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**6**).* Yield, 86%; mp, 130.4−131.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50−7.44 (m, 2H), 7.38−7.33 (m, 2H), 5.15 (s, 1H), 5.06 (d, J = 2.2 Hz, 1H), 4.94 (d, J = 16.4 Hz, 1H), 4.85 (d, J = 16.4 Hz, 1H), 3.82−3.61 (m, 4H), 1.88−1.66 (m, 4H), 1.64−1.40 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.46, 134.61, 131.68, 129.17, 129.00, 128.79, 127.26, 105.03, 81.30, 68.46, 52.55, 49.48, 45.91, 28.35, 26.76, 14.37 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3{}^{35}Cl$ $[M + H]^+$, 336.1115, found, 336.1113; calcd for $C_{16}H_{19}N_3O_3{}^{37}Cl$ $[M + H]^+$, 338.1085, found, 338.1089.

*1-(3-Chlorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**7**).* Yield, 91%; mp, 132.7−133.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39−7.34 (m, 4H), 5.13 (s, 1H), 5.07 (s, 1H), 5.00 (d, J = 15.4 Hz, 1H), 4.71 (d, J = 15.4 Hz, 1H), 3.76−3.58 (m, 4H), 1.86−1.66 (m, 4H), 1.54 (d, J = 13.8 Hz, 1H), 1.48−1.32 (m, 1H) ppm.^{13}C NMR (100 MHz, DMSO-d_6) δ 156.11, 139.69, 133.08, 130.24, 127.57, 127.30, 126.38, 105.30, 81.21, 68.44, 53.42, 49.37, 45.76, 28.22, 26.72, 14.31 ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3{}^{35}ClNa$ $[M + Na]^+$, 358.0934, found, 358.0933; calcd for $C_{16}H_{18}N_3O_3{}^{37}ClNa$ $[M + Na]^+$, 360.0905, found, 360.0903.

*1-(4-Chlorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**8**).* Yield, 83%; mp, 139.0−141.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42−7.36 (m, 2H), 7.23−7.16 (m, 2H), 5.11 (s, 1H), 5.06 (d, J = 2.4 Hz, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H),

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J. Agric. Food Chem. 2021, 69, 3005−3014

3.73−3.57 (m, 4H), 1.85−1.65 (m, 4H), 1.53 (d, J = 13.8 Hz, 1H), 1.43−1.29 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.03, 136.11, 131.94, 129.65, 128.36, 105.31, 81.24, 68.47, 53.17, 49.25, 45.79, 28.27, 26.67, 14.35 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3{}^{35}Cl$ $[M + H]^+$, 336.1115, found, 336.1114; calcd for $C_{16}H_{19}N_3O_3{}^{37}Cl$ $[M + H]^+$, 338.1085, found, 338.1087.

1-(2-Bromobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**9**). Yield, 84%; mp, 142.3−143.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68−7.60 (m, 1H), 7.49−7.39 (m, 2H), 7.30−7.21 (m, 1H), 5.15 (s, 1H), 5.07 (d, J = 2.4 Hz, 1H), 4.89 (d, J = 16.6 Hz, 1H), 4.79 (d, J = 16.6 Hz, 1H), 3.80−3.60 (m, 4H), 1.87−1.67 (m, 4H), 1.61−1.47 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.53, 136.16, 132.39, 129.01, 128.97, 127.79, 121.86, 104.99, 81.31, 68.46, 55.16, 49.50, 45.93, 28.40, 26.74, 14.41 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3{}^{79}Br$ $[M + H]^+$, 380.0610, found, 380.0609; calcd for $C_{16}H_{19}N_3O_3{}^{81}Br$ $[M + H]^+$, 382.0589, found, 382.0588.

1-(3-Bromobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**10**). Yield, 72%; mp, 140.9−142.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.52−7.49 (m, 1H), 7.38−7.30 (m, 2H), 5.13 (s, 1H), 5.06 (d, J = 2.2 Hz, 1H), 5.00 (d, J = 15.4 Hz, 1H), 4.69 (d, J = 15.4 Hz, 1H), 3.74−3.59 (m, 4H), 1.87−1.66 (m, 4H), 1.54 (d, J = 13.8 Hz, 1H), 1.47−1.30 (m, 1H) ppm.^{13}C NMR (100 MHz, DMSO-d_6) δ 156.11, 139.94, 130.54, 130.46, 130.20, 126.78, 121.72, 105.30, 81.20, 68.44, 53.37, 49.35, 45.76, 28.21, 26.74, 14.31 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_3{}^{79}Br$ $[M + H]^+$, 380.0610, found, 380.0609; calcd for $C_{16}H_{19}N_3O_3{}^{81}Br$ $[M + H]^+$, 382.0589, found, 382.0588.

1-(4-Bromobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**11**). Yield, 77%; mp, 149.1−150.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63−7.47 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.11 (s, 1H), 5.06 (d, J = 2.6 Hz, 1H), 4.94 (d, J = 15.2 Hz, 1H), 4.71 (d, J = 15.2 Hz, 1H), 3.78−3.58 (m, 4H), 1.87−1.64 (m, 4H), 1.54 (d, J = 13.8 Hz, 1H), 1.47−1.28 (m, 1H) ppm.^{13}C NMR (100 MHz, DMSO-d_6) δ 156.04, 136.55, 131.27, 129.99, 120.46, 105.30, 81.25, 68.47, 53.25, 49.26, 45.79, 28.28, 26.67, 14.36 ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3{}^{79}BrNa$ $[M + Na]^+$, 402.0429, found, 402.0430; calcd for $C_{16}H_{18}N_3O_3{}^{81}BrNa$ $[M + Na]^+$, 404.0409, found, 404.0408.

1-(2-Methylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**12**). Yield, 80%; mp, 141.3−142.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32−7.15 (m, 4H), 5.14 (s, 1H), 5.08 (d, J = 2.6 Hz, 1H), 4.90 (d, J = 16.0 Hz, 1H), 4.82 (d, J = 16.0 Hz, 1H), 3.77−3.52 (m, 4H), 2.25 (s, 3H), 1.91−1.67 (m, 4H), 1.53−1.48 (m, 2H) ppm.^{13}C NMR (100 MHz, DMSO-d_6) δ 156.38, 135.39, 134.99, 130.08, 127.04, 126.97, 125.92, 105.03, 81.40, 68.62, 51.95, 48.98, 45.85, 28.43, 26.67, 18.55, 14.48 ppm. HRMS (ESI) calcd for $C_{17}H_{21}N_3O_3Na$ $[M + Na]^+$, 338.1481, found, 338.1482.

1-(3-Methylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**13**). Yield, 75%; mp, 111.2−111.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (t, J = 7.4 Hz, 1H), 7.19−7.06 (m, 3H), 5.09 (d, J = 15.2 Hz, 2H), 4.97 (d, J = 15.0 Hz, 1H), 4.70 (d, J = 15.0 Hz, 1H), 3.74−3.53 (m, 4H), 2.30 (s, 3H), 1.87−1.63 (m, 4H), 1.53 (d, J = 13.8 Hz, 1H), 1.46−1.29 (m, 1H) ppm.^{13}C NMR (100 MHz, DMSO-d_6) δ 156.04, 137.55, 136.91, 128.43, 128.35, 128.04, 124.86, 105.34, 81.23, 68.52, 53.55, 49.04, 45.76, 28.17, 26.78, 20.99, 14.28 ppm. HRMS (ESI) calcd for $C_{17}H_{21}N_3O_3Na$ $[M + Na]^+$, 338.1481, found, 338.1482.

1-(4-Methylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**14**). Yield, 89%; mp, 122.9−124.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.17 (m, 4H), 5.37−5.29 (m, 1H), 4.96 (d, J = 14.8 Hz, 1H), 4.83 (d, J = 14.8 Hz, 1H), 3.75−3.64 (m, 1H), 3.63−3.45 (m, 4H), 2.34 (s, 3H), 2.16 (d, J = 13.6 Hz, 1H), 1.94−1.83 (m, 2H), 1.68−1.65 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.53, 137.77, 133.27, 129.53, 128.34, 106.72, 83.02, 69.74, 54.48, 48.37, 46.72, 29.56, 26.48, 21.15, 15.01 ppm. HRMS (ESI) calcd for $C_{17}H_{21}N_3O_3Na$ $[M + Na]^+$, 338.1481, found, 338.1483.

1-(2-Methoxybenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**15**). Yield, 77%; mp, 127.5−128.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32−7.24 (m, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 5.08 (s, 1H), 5.02 (s, 1H), 4.81 (s, 2H), 3.78 (d, J = 8.4 Hz, 3H), 3.76−3.61 (m, 2H), 3.59−3.52 (m, 2H), 1.79−1.60 (m, 4H), 1.49 (d, J = 13.8 Hz, 1H), 1.40−1.22 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.93, 156.15, 128.90, 128.83, 124.44, 120.21, 110.61, 105.33, 81.35, 68.53, 55.18, 49.51, 49.18, 45.96, 28.07, 26.90, 14.12 ppm. HRMS (ESI) calcd for $C_{17}H_{21}N_3O_4Na$ $[M + Na]^+$, 354.1430, found, 354.1431.

1-(3-Methoxybenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**16**). Yield, 81%; mp, 135.3−135.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31−7.25 (m, 1H), 6.92−6.84 (m, 3H), 5.12 (s, 1H), 5.07 (d, J = 2.2 Hz, 1H), 4.93 (d, J = 15.0 Hz, 1H), 4.77 (d, J = 15.0 Hz, 1H), 3.74 (s, 3H), 3.73−3.58 (m, 4H), 1.84−1.65 (m, 4H), 1.53 (d, J = 14.0 Hz, 1H), 1.42−1.32 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.34, 156.02, 138.59, 129.55, 119.89, 113.31, 112.86, 105.42, 81.26, 68.52, 54.94, 53.45, 49.12, 45.83, 28.21, 26.73, 14.32 ppm. HRMS (ESI) calcd for $C_{17}H_{21}N_3O_4Na$ $[M + Na]^+$, 354.1430, found, 354.1431.

1-(4-Methoxybenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**17**). Yield, 86%; mp, 130.7−132.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29−7.24 (m, 2H), 6.94−6.90 (m, 2H), 5.15−5.03 (m, 2H), 4.90 (d, J = 14.6 Hz, 1H), 4.71 (d, J = 14.6 Hz, 1H), 3.78−3.71 (m, 3H), 3.71−3.54 (m, 4H), 1.85−1.44 (m, 7H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.68, 155.87, 129.31, 128.73, 113.84, 105.38, 81.26, 68.55, 55.02, 52.89, 48.83, 45.76, 28.21, 26.71, 14.32 ppm. HRMS (ESI) calcd for $C_{17}H_{21}N_3O_4Na$ $[M + Na]^+$, 354.1430, found, 354.1431.

2-((10-Nitro-2,3,6,7,8,9-hexahydro-5,9-epoxyimidazo[1,2-a]azocin-1(5H)-yl)methyl)benzonitrile (**18**). Yield, 83%; mp, 135.2−136.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dd, J = 8.0, 1.0 Hz, 1H), 7.78−7.73 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 5.21−5.03 (m, 3H), 4.96 (d, J = 16.6 Hz, 1H), 3.84−3.67 (m, 4H), 1.85−1.69 (m, 4H), 1.55−1.50 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.26, 141.26, 133.27, 132.98, 127.93, 127.84, 117.25, 109.84, 105.15, 81.27, 68.39, 53.16, 49.94, 45.85, 28.36, 26.74, 14.32 ppm. HRMS (ESI) calcd for $C_{17}H_{19}N_4O_3$ $[M + H]^+$, 327.1457, found, 327.1458.

3-((10-Nitro-2,3,6,7,8,9-hexahydro-5,9-epoxyimidazo[1,2-a]azocin-1(5H)-yl)methyl)benzonitrile (**19**). Yield, 89%; mp, 144.8−145.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85−7.74 (m, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 5.13 (s, 1H), 5.09−4.99 (m, 2H), 4.73 (d, J = 15.6 Hz, 1H), 3.79−3.61 (m, 4H), 1.84−1.66 (m, 4H), 1.55 (d, J = 13.8

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J. Agric. Food Chem. 2021, 69, 3005−3014

Hz, 1H), 1.46−1.39 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.19, 138.97, 132.50, 131.17, 131.06, 129.55, 118.77, 111.29, 105.23, 81.22, 68.41, 53.55, 49.56, 45.79, 28.28, 26.70, 14.33 ppm. HRMS (ESI) calcd for $C_{17}H_{18}N_4O_3Na$ $[M + Na]^+$, 349.1277, found, 349.1276.

*4-((10-Nitro-2,3,6,7,8,9-hexahydro-5,9-epoxyimidazo[1,2-a]azocin-1(5H)-yl)methyl)benzonitrile (**20**)*. Yield, 72%; mp, 140.9−142.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88−7.81 (m, 2H), 7.54 (d, J = 8.4 Hz, 2H), 5.14 (s, 1H), 5.06−5.03 (m, 2H), 4.81 (d, J = 16.0 Hz, 1H), 3.79−3.60 (m, 4H), 1.84−1.66 (m, 4H), 1.57−1.52 (m, 1H), 1.48−1.37 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.21, 143.24, 132.26, 128.39, 118.80, 109.94, 105.23, 81.25, 68.41, 53.97, 49.62, 45.84, 28.33, 26.65, 14.37 ppm. HRMS (ESI) calcd for $C_{17}H_{19}N_4O_3$ $[M + H]^+$, 327.1457, found, 327.1456.

*10-Nitro-1-(4-nitrobenzyl)-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**21**)*. Yield, 70%; mp, 146.1−146.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 5.17−5.05 (m, 4H), 4.85 (d, J = 16.2 Hz, 1H), 3.79−3.62 (m, 4H), 1.79−1.72 (m, 3H), 1.55 (s, 1H), 1.51−1.41 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.30, 146.69, 145.48, 128.58, 123.43, 105.23, 81.25, 68.41, 53.94, 49.65, 45.87, 28.36, 26.65, 14.39 ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_4O_5Na$ $[M + Na]^+$, 369.1175, found, 369.1176.

*10-Nitro-1-(4-(trifluoromethyl)benzyl)-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**22**)*. Yield, 81%; mp, 128.8−129.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78−7.53 (m, 4H), 5.18−4.96 (m, 3H), 4.82 (d, J = 15.8 Hz, 1H), 3.79−3.61 (m, 4H), 1.85−1.65 (m, 4H), 1.60−1.35 (m, 2H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ-60.78 (s, 3F) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.01, 143.25 (d, J = 249.5 Hz, 1C), 132.20, 128.34 (t, J = 7.4 Hz, 1C), 118.77, 109.96 (d, J = 3.8 Hz, 1C), 105.13, 81.22, 68.45, 53.94, 49.63, 45.85, 28.31, 26.66, 14.29 ppm. HRMS (ESI) calcd for $C_{17}H_{19}N_3O_3F_3$ $[M + H]^+$, 370.1379, found, 370.1376.

*10-Nitro-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**23**)*. Yield, 73%; mp, 147.1−148.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 1.2 Hz, 1H), 8.06 (dd, J = 8.0, 1.2 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 5.15 (s, 1H), 5.08 (d, J = 16.2 Hz, 2H), 4.83 (d, J = 16.2 Hz, 1H), 3.82−3.65 (m, 4H), 1.85−1.68 (m, 4H), 1.55 (d, J = 13.8 Hz, 1H), 1.49−1.35 (m, 1H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ-66.36 (s, 3F) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.91, 156.08, 135.93, 131.36, 130.52, 129.09 (q, J = 22.8 Hz, 1C), 124.83, 105.01, 81.59, 68.79, 48.92, 45.94, 45.31, 28.23, 26.88, 14.35 ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_4O_3F_3$ $[M + H]^+$, 371.1331, found, 371.1332.

*1-([1,1′-Biphenyl]-4-ylmethyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**24**)*. Yield, 84%; mp, 129.6−130.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79−7.56 (m, 4H), 7.55−7.33 (m, 5H), 5.19−4.96 (m, 3H), 4.83 (d, J = 15.2 Hz, 1H), 3.79−3.58 (m, 4H), 1.89−1.65 (m, 4H), 1.63−1.34 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.06, 139.76, 139.25, 136.27, 128.92, 128.38, 127.41, 126.72, 126.59, 105.35, 81.27, 68.53, 53.39, 49.22, 45.82, 28.28, 26.70, 14.37 ppm. HRMS (ESI) calcd for $C_{22}H_{24}N_3O_3$ $[M + H]^+$, 378.1818, found, 378.1816.

*1-(4-(tert-Butyl)benzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**25**)*. Yield, 85%; mp, 137.9−138.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44−7.33 (m, 2H), 7.25−7.21 (m, 2H), 5.13−5.04 (m, 2H), 4.92 (d, J = 15.0 Hz, 1H), 4.77 (d, J = 15.0 Hz, 1H), 3.74−3.55 (m, 4H), 1.83−1.63 (m, 4H), 1.51−1.48 (m, 2H), 1.28 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.03, 149.76, 133.97, 127.44, 125.20, 99.49, 81.24, 68.52, 53.20, 49.14, 45.79, 34.20, 31.11, 28.22, 26.71, 14.31 ppm. HRMS (ESI) calcd for $C_{20}H_{28}N_3O_3$ $[M + H]^+$, 358.2131, found, 358.2132.

*1-(4-Isopropylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**26**)*. Yield, 92%; mp, 140.2−141.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34−7.14 (m, 4H), 5.09−5.06 (m, 2H), 4.92 (d, J = 15.0 Hz, 1H), 4.75 (d, J = 15.0 Hz, 1H), 3.76−3.54 (m, 4H), 2.94−2.80 (m, 1H), 1.83−1.44 (m, 6H), 1.22−1.15 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.01, 147.53, 134.33, 127.75, 126.35, 105.33, 81.24, 68.51, 53.29, 49.11, 45.78, 33.08, 28.21, 26.71, 23.85, 14.31 ppm. HRMS (ESI) calcd for $C_{19}H_{26}N_3O_3$ $[M + H]^+$, 344.1974, found, 344.1976.

*1-(2,6-Dichlorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**27**)*. Yield, 75%; mp, 134.4−134.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71−7.56 (m, 2H), 7.53−7.42 (m, 1H), 5.17−5.01 (m, 3H), 4.95 (d, J = 14.6 Hz, 1H), 3.57−3.33 (m, 4H), 1.90−1.46 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.01, 135.95, 131.37, 130.51, 129.09, 105.04, 81.55, 68.80, 48.95, 45.95, 45.35, 28.22, 26.90, 14.30 ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3{}^{35}Cl_2$ $[M + H]^+$, 370.0725, found, 370.0724; calcd for $C_{16}H_{18}N_3O_3{}^{35}Cl^{37}Cl$ $[M + H]^+$, 372.0696, found, 372.0699; calcd for $C_{16}H_{18}N_3O_3{}^{37}Cl_2$ $[M + H]^+$, 374.0666, found, 374.0671.

*1-(2,6-Difluorobenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**28**)*. Yield, 72%; mp, 143.3−144.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51−7.41 (m, 1H), 7.21−7.11 (m, 2H), 5.15−5.05 (m, 3H), 5.05−4.99 (m, 1H), 3.73−3.59 (m, 2H), 3.58−3.45 (m, 2H), 1.83−1.66 (m, 4H), 1.58−1.48 (m, 1H), 1.42−1.27 (m, 1H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.24 (s, 1F), -114.27 (s, 1F) ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3F_2$ $[M + H]^+$, 338.1316, found, 338.1315.

*1-(2,6-Dimethylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**29**)*. Yield, 84%; mp, 130.7−131.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18−7.12 (m, 3H), 5.13 (d, J = 2.8 Hz, 1H), 5.07 (s, 1H), 4.84 (d, J = 14.4 Hz, 1H), 4.68 (d, J = 14.4 Hz, 1H), 3.59−3.47 (m, 1H), 3.47−3.28 (m, 2H), 3.25−3.13 (m, 1H), 2.31 (s, 6H), 1.91 (d, J = 13.2 Hz, 1H), 1.81−1.67 (m, 3H), 1.63−1.40 (m, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.96, 137.80, 131.66, 128.48, 128.15, 104.97, 81.82, 68.98, 47.67, 46.07, 45.37, 28.54, 26.53, 19.49, 14.54 ppm. HRMS (ESI) calcd for $C_{18}H_{23}N_3O_3Na$ $[M + Na]^+$, 352.1637, found, 352.1636.

*1-(2,5-Dimethylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**30**)*. Yield, 80%; mp, 129.4−130.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 7.6 Hz, 1H), 5.13 (s, 1H), 5.08 (d, J = 2.4 Hz, 1H), 4.90 (d, J = 15.8 Hz, 1H), 4.72 (d, J = 15.8 Hz, 1H), 3.73−3.51 (m, 4H), 2.26 (s, 3H), 2.19 (s, 3H), 1.89−1.66 (m, 4H), 1.55−1.49 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.40, 134.76, 134.67, 132.30, 130.05, 127.92, 127.62, 105.03, 81.37, 68.62, 51.91, 48.81, 45.81, 28.34, 26.79, 20.72, 18.13, 14.43 ppm. HRMS (ESI) calcd for $C_{18}H_{24}N_3O_3$ $[M + H]^+$, 330.1818, found, 330.1819.

*1-(3,4-Dimethylbenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**31**)*. Yield, 88%; mp, 137.1−137.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15−6.99 (m, 3H), 5.16−5.04 (m, 2H), 4.92 (d, J = 14.8 Hz, 1H),

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J. Agric. Food Chem. 2021, 69, 3005−3014

Table 2. Mortality of a Mixture of Imidacloprid (1 mg/L) with the New Compounds 1−33 at Low Concentrations (0.5−4 mg/L) against *A. craccivora*[a]

		mortality (co-applied with imidacloprid) (%)			
compound	R	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L
1	H	nt	35.7 ± 3.9	66.6 ± 2.4	71.8 ± 3.7
2	C_6H_5	nt	41.2 ± 2.3	72.1 ± 2.8	79.8 ± 4.2
3	2-F-C_6H_5	nt	39.2 ± 2.0	69.5 ± 1.7	76.4 ± 1.7
4	3-F-C_6H_5	nt	44.5 ± 3.1	76.5 ± 3.2	77.9 ± 1.7
5	4-F-C_6H_5	nt	53.9 ± 1.2	81.6 ± 1.9	85.3 ± 1.6
6	2-Cl-C_6H_5	nt	34.0 ± 5.5	69.8 ± 1.3	74.6 ± 1.8
7	3-Cl-C_6H_5	nt	38.9 ± 2.4	74.3 ± 2.1	80.1 ± 1.3
8	4-Cl-C_6H_5	nt	55.3 ± 1.8	72.5 ± 1.8	84.4 ± 2.1
9	2-Br-C_6H_5	nt	36.7 ± 2.3	74.8 ± 2.0	80.9 ± 1.7
10	3-Br-C_6H_5	nt	44.4 ± 1.9	76.9 ± 2.5	81.7 ± 1.8
11	4-Br-C_6H_5	nt	45.3 ± 1.5	73.6 ± 2.2	75.4 ± 3.9
12	2-Me-C_6H_5	nt	39.0 ± 1.9	75.6 ± 1.7	76.4 ± 2.4
13	3-Me-C_6H_5	nt	54.1 ± 2.7	75.4 ± 1.2	82.4 ± 2.3
14	4-Me-C_6H_5	59.8 ± 2.4	82.9 ± 2.5	88.5 ± 3.1	91.4 ± 1.9
15	2-OMe-C_6H_5	nt	39.2 ± 1.5	80.7 ± 3.2	81.3 ± 1.5
16	3-OMe-C_6H_5	nt	55.0 ± 2.0	87.6 ± 2.8	88.4 ± 2.3
17	4-OMe-C_6H_5	63.0 ± 1.1	84.8 ± 2.5	90.4 ± 1.8	93.4 ± 1.5
18	2-CN-C_6H_5	nt	39.0 ± 1.5	76.1 ± 1.6	81.2 ± 2.5
19	3-CN-C_6H_5	nt	38.2 ± 1.2	82.9 ± 2.1	85.7 ± 3.0
20	4-CN-C_6H_5	nt	40.4 ± 2.6	85.6 ± 2.9	87.3 ± 1.0
21	4-NO_2-C_6H_5	nt	55.7 ± 1.2	79.7 ± 1.5	82.5 ± 2.2
22	4-CF_3-C_6H_5	nt	58.5 ± 4.0	81.7 ± 2.7	83.0 ± 1.9
23	6-CF_3-pyridyl	nt	49.6 ± 2.4	86.0 ± 1.8	88.7 ± 1.8
24	4-Ph-C_6H_5	34.6 ± 1.2	71.9 ± 1.9	88.2 ± 1.3	92.8 ± 1.3
25	4-*t*-Bu -C_6H_5	77.0 ± 2.0	94.2 ± 0.7	97.0 ± 2.2	98.1 ± 2.7
26	4-*i*-Pr-C_6H_5	56.5 ± 2.0	82.0 ± 4.4	90.1 ± 1.9	92.5 ± 1.6
27	2,6-$(Cl)_2$-C_6H_5	nt	51.6 ± 1.1	69.8 ± 2.4	77.7 ± 6.0
28	2,6-$(F)_2$-C_6H_5	nt	54.7 ± 1.5	76.0 ± 1.8	80.9 ± 2.0
29	2,6-$(Me)_2$-C_6H_5	nt	60.8 ± 2.8	81.7 ± 1.1	87.6 ± 3.9
30	2,5-$(Me)_2$-C_6H_5	nt	64.6 ± 1.7	81.9 ± 3.8	86.2 ± 1.1
31	3,4-$(Me)_2$-C_6H_5	nt	64.7 ± 1.1	82.0 ± 1.4	87.3 ± 1.5
32	3,4-$(OMe)_2$-C_6H_5	nt	60.0 ± 1.9	81.4 ± 1.6	86.3 ± 1.8
33	2-chlorothiazol-5-yl	nt	48.8 ± 2.4	74.5 ± 2.9	84.4 ± 1.6
IPPA08		70.6 ± 2.1	86.6 ± 3.1	90.1 ± 2.5	93.0 ± 0.9

[a]Effects of compounds **1−33** and IPPA08 on imidacloprid (1 mg/L) toxicity against *A. craccivora*. Data are mean of at least six independent experiments ± standard error of the mean (SEM). Imidacloprid alone at a concentration of 1 mg/L gives 29% mortality. nt = not test.

4.66 (d, *J* = 14.8 Hz, 1H), 3.69−3.52 (m, 4H), 2.20 (s, 6H), 1.87−1.62 (m, 4H), 1.53 (d, *J* = 13.8 Hz, 1H), 1.45−1.28 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.97, 136.17, 135.31, 134.24, 129.53, 129.09, 125.33, 105.35, 81.23, 68.54, 53.22, 48.84, 45.74, 28.17, 26.77, 19.39, 19.01, 14.29 ppm. HRMS (ESI) calcd for $C_{18}H_{23}N_3O_3Na$ $[M + Na]^+$, 352.1637, found, 352.1638.

*1-(3,4-Dimethoxybenzyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**32**).* Yield, 70%; mp, 121.9−123.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91−6.87 (m, 3H), 5.14−5.04 (m, 2H), 4.86 (d, *J* = 14.8 Hz, 1H), 4.71 (d, *J* = 14.8 Hz, 1H), 3.73 (d, *J* = 6.4 Hz, 6H), 3.70−3.53 (m, 4H), 1.84−1.64 (m, 4H), 1.51 (d, *J* = 13.8 Hz, 1H), 1.38−1.27 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.95, 148.66, 148.24, 129.15, 120.33, 111.67, 105.54, 81.29, 68.55, 55.46, 55.30, 53.11, 48.85, 45.87, 28.17, 26.77, 14.31 ppm. HRMS calcd for $C_{18}H_{24}N_3O_5$ $[M + H]^+$, 362.1716, found, 362.1717.

*1-((2-Chlorothiazol-5-yl)methyl)-10-nitro-1,2,3,5,6,7,8,9-octahydro-5,9-epoxyimidazo[1,2-a]azocine (**33**).* Yield, 84%; mp, 134.9−135.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 5.31 (s, 1H), 5.24 (d, *J* = 15.4 Hz, 1H), 4.97 (s, 1H), 4.78 (d, *J* = 15.4 Hz, 1H), 3.85−3.74 (m, 1H), 3.73−3.58 (m, 3H), 2.12 (d, *J* = 13.4 Hz, 1H), 1.99−1.78 (m, 2H), 1.77−1.51 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.68, 154.16, 140.49, 135.56, 106.97, 82.71, 69.36, 49.40, 48.31, 46.17, 29.43, 26.47, 14.93 ppm. HRMS (ESI) calcd for $C_{13}H_{15}N_4O_3S^{35}ClNa$ $[M + Na]^+$, 365.0451, found, 365.0452; calcd for $C_{13}H_{15}N_4O_3S^{37}ClNa$ $[M + Na]^+$, 367.0422, found, 367.0422.

BIOLOGICAL RESULTS

Synergistic Effect on Imidacloprid. The mortality caused by the oxabridged compounds and their effects on imidacloprid toxicity against *A. craccivora* were assessed. None of the oxabridged homologues showed any mortality at a low concentration (10 mg/L). When the oxabridged compounds were applied at concentrations of 4 and 2 mg/L together with 1 mg/L imidacloprid, the toxicity against *A. craccivora* strongly increased (Table 2). Moreover, even at a low concentration of 0.5 mg/L, four compounds (**14**, **17**, **25**, and **26**) possessing an electron-donating group (EDG) at position 4 of the phenyl

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J. Agric. Food Chem. 2021, 69, 3005−3014

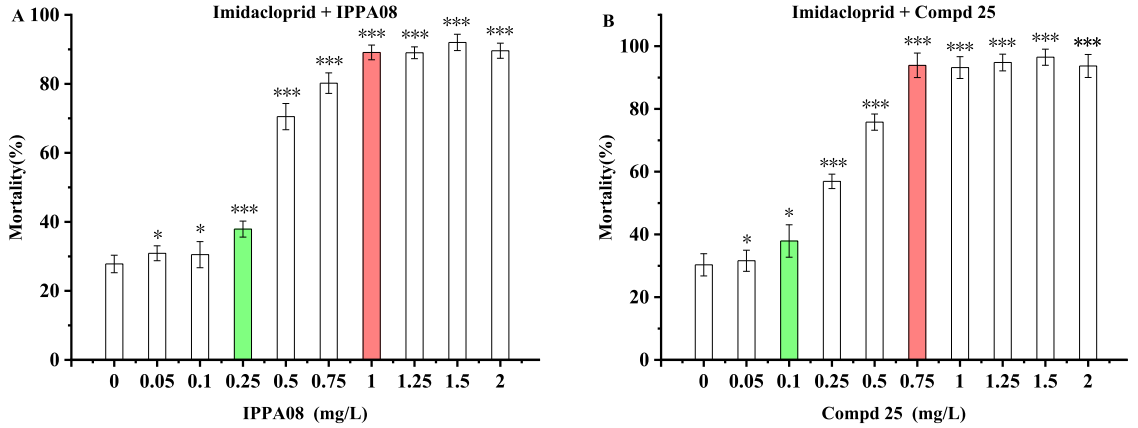
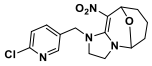
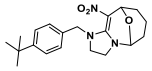


Figure 2. (A) Effects of IPPA08 on imidacloprid (1 mg/L) toxicity against *A. craccivora*. (B) Effects of compound 25 on imidacloprid (1 mg/L) toxicity against *A. craccivora*. Data are means of at least six independent experiments ± SEM. Significant differences from blank control: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

Table 3. Synergistic Effects of IPPA08 and Compound 25 on Imidacloprid Toxicity Against *A. craccivora*[a]

compound	concentration[b]	Imidacloprid LC_{50}	95% CI[c]	slope	SR[d]
	0	1.72	1.19-2.47	2.20	1
	0.25	0.606***	0.446-0.828	1.91	2.84
	0.75	0.492***	0.360-0.665	1.57	3.50
	1	0.382***	0.328-0.443	1.77	4.50
	0	1.72	1.19-2.47	2.20	1
	0.1	0.687***	0.536-0.885	2.02	2.50
	0.25	0.490***	0.369-0.646	1.66	3.51
	0.75	0.263***	0.179-0.363	1.71	6.54

[a]Data are the means of at least six independent experiments. [b]IPPA08 and compound 25 at concentrations in mg/L showed no insecticidal activities against *A. craccivora*. [c]CI = confidence interval (CI can be used to estimate population parameters; the narrower the scope of CI, the better the reliability of population parameters estimated by sample indicators). [d]SR = synergism ratio. Significant differences from blank control: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

ring increased the mortality of *A. craccivora* by imidacloprid and exhibited obvious synergy. In particular, compound **25** showed higher synergistic activity than IPPA08. In addition, compared to compound **24**, compound **25** was more effective, which indicated that electronic factor could be the major factor instead of steric factor.

Further study showed that the mortality of *A. craccivora* by imidacloprid (29% at 1 mg/L) could be increased to 90% with 1.0 mg/L IPPA08, at which IPPA08 alone showed no insecticidal activity (Figure 2A). Similarly, 30% mortality of *A. craccivora* by 1 mg/L imidacloprid was increased to 97% when combined with compound **25** at 0.75 mg/L, a concentration at which compound **25** itself caused no mortality (Figure 2B). Compared to IPPA08, compound **25** presented higher effects to synergize imidacloprid at the same co-applied concentrations (0.25, 0.75 mg/L). For a co-applied concentration at 0.25 mg/L, IPPA08 and compound **25** increased the toxicity of imidacloprid against *A. craccivora* by 2.84- and 3.51-fold, respectively. For a co-applied concentration at 0.75 mg/L, IPPA08 and compound **25** increased the toxicity of imidacloprid against *A. craccivora* by 3.50- and 6.54-fold, respectively. Even though IPPA08 and compound **25** showed optimal co-applied concentrations of 1 and 0.75 mg/L, respectively, compound **25** (6.54-fold) showed a higher synergism ratio than IPPA08 (4.50-fold) (Table 3).

Influence of IPPA08 and Compound 25 on the Toxicities of Other Neonicotinoids. The effects of IPPA08 and compound **25** on the toxicities of other neonicotinoids were also tested, including nitenpyram, dinotefuran, acetamiprid, thiamethoxam, paichongding, and cycloxaprid. For *A. craccivora*, IPPA08 and compound **25** at low concentrations (causing no toxicity by itself) increased the moralities caused by fixed concentrations (1 mg/L) of nitenpyram, acetamiprid, and thiamethoxam, and compound **25** showed higher effectiveness as a synergist (Figure 3A,C,D). However, IPPA08 and compound **25** showed little impact on the toxicities of dinotefuran and paichongding against *A. craccivora* (Figure 3B,E). Interestingly, compound **25** showed weak effects on cycloxaprid toxicity against *A. craccivora* at 4 mg/L (Figure 3F). IPPA08 and compound **25** showed good stability under these conditions, excluding the possibility that the synergistic effects were caused by metabolites (Table 4).

Safety of Compound 25 to Honey Bee. Bee mortalities by the independent use of imidacloprid or by the combined use of imidacloprid and compound **25** (1:1) were tested (Table 5). The mixture of imidacloprid and compound **25** did not exhibit a higher toxicity toward the bee than the imidacloprid alone. However, for *A. craccivora*, the mortality by imidacloprid (30% at 1 mg/L) could be increased to 90% with 1 mg/L compound **25** (Figure 2B). These results

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J. Agric. Food Chem. 2021, 69, 3005−3014

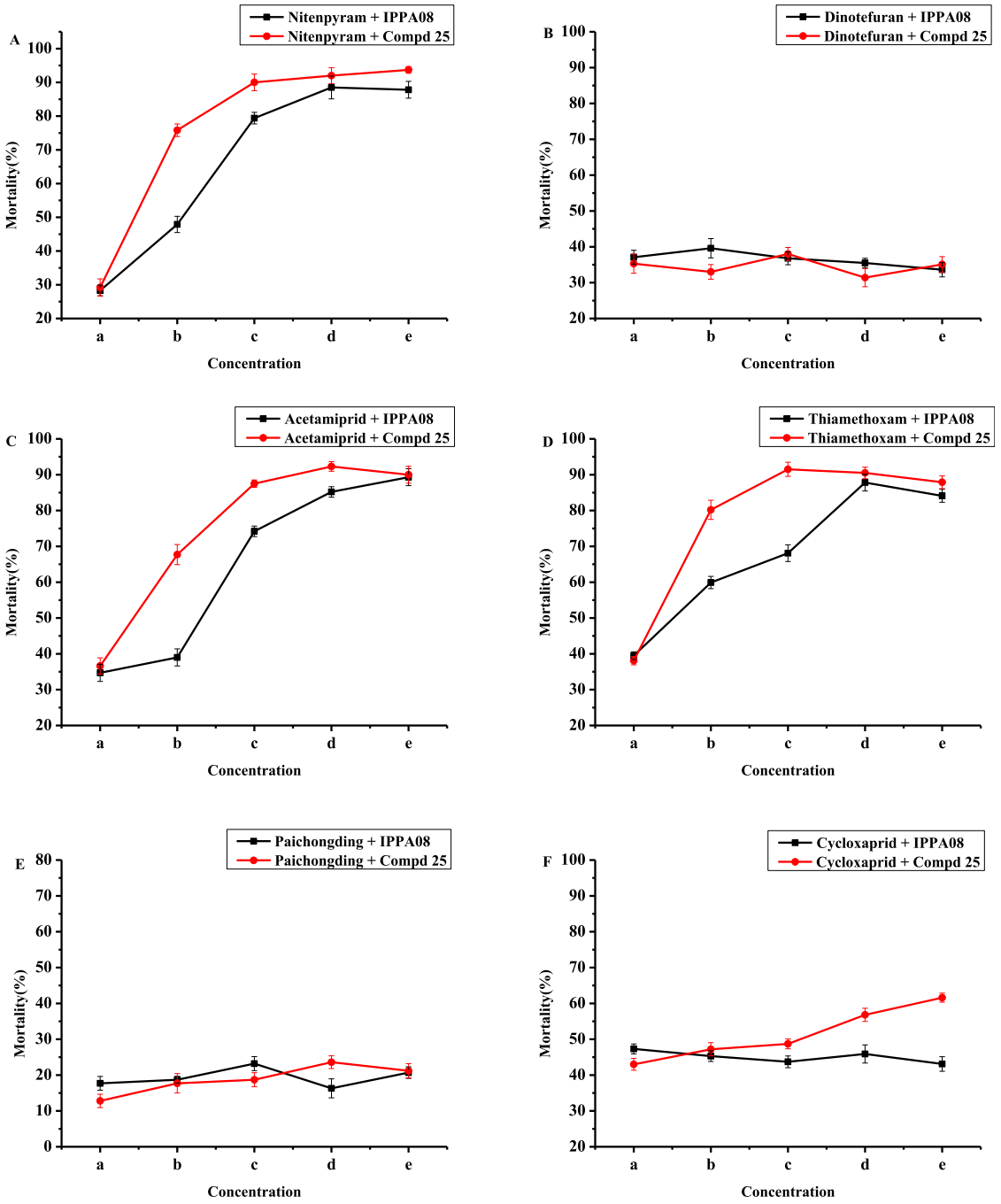

Figure 3. Effects of IPPA08 and compound 25 on the toxicity of neonicotinoid insecticides, including nitenpyram, dinotefuran, acetamiprid, thiamethoxam, paichongding, and cycloxaprid. The concentration for each neonicotinoid insecticide was 1 mg/L, and the concentrations of IPPA08 and compound 25 were (a−e) 0, 0.5, 1, 2, and 4 mg/L, respectively. Data are mean of at least six independent experiments ± SEM.

Table 4. Stability of IPPA08 and Compound 25 in PBS at Different pHs[a]

compound	pH	detection time	degradation rate (%)
IPPA08	4.0	3 days	1.65
	7.0	7 days	0.809
	9.0	5 days	0.501
25 (*t*-Bu)	4.0	3 days	1.49
	7.0	7 days	0.527
	9.0	5 days	0.333

[a]Stability was detected by UPLC.

indicated that compound **25** displayed selectivity in its effects on imidacloprid toxicity against the honey bee (*A. mellifera* L.).

DISCUSSION

Synergists can improve the pesticidal performance of insecticides, such as increasing insecticidal activity, reducing application frequency, and decreasing the rate of resistance development.[20] In our previous study, we found that IPPA08, a novel neonicotinoid with a unique oxabridged substructure, has proven strong synergistic effects on neonicotinoid insecticides, which is currently the most crucial class of insecticides.[15,16] To discover new synergists with higher

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J. Agric. Food Chem. 2021, 69, 3005−3014

Table 5. Bee Toxicity (*A. mellifera* L.) of Imidacloprid and a Mixture of Imidacloprid with Compound 25[a,b]

compound	bee toxicity	times	toxic regression equation	LD_{50} (μg/worker)	95% CI	toxicological grade
25 + IMI (1:1)	contact toxicity	24 h	F	F	F	
		48 h	$y = 1.018x + 2.341$	0.118	0.069−0.228	II
	oral toxicity	24 h	$y = 1.797x + 0.690$	1.93	1.54−2.57	II
		48 h	$y = 1.057x + 2.970$	1.06	0.624−2.60	II
IMI	contact toxicity	24 h	F	F	F	
		48 h	$y = 0.999x + 1.015$	0.096	0.053−0.363	II
	oral toxicity	24 h	F	F	F	
		48 h	$y = 1.383x + 0.234$	0.677	0.555−0.858	II
25	contact toxicity	24 h	F	F	F	
		48 h		>12		IV
	oral toxicity	24 h	F	F	F	
		48 h		>27		IV

[a]F, failed to measure, which means that some of the bee in the test group escaped. [b]The grade of the bee toxicity, very toxicity: I; high toxicity: II; moderate toxicity: III; low toxicity: IV.

effectiveness, a series of eight-membered oxabridged neonicotinoid analogues were synthesized. Biological evaluation revealed that all of these compounds possess significant synergistic effects on imidacloprid toxicity against cowpea aphid (*A. craccivora*) under the concentration of 4 and 2 mg/L. The structure−activity relationships (SARs) showed that compound **25** having an electron-donating group (EDG) *t*-Bu at position 4 of the phenyl ring exhibited excellent synergistic effects for imidacloprid activity. Interestingly, compound **25** presented a higher degree of synergism than IPPA08, along with a notable selectivity in its effects on imidacloprid toxicity against the honey bee (*A. mellifera* L.). These results indicate that replacement of the pyridyl ring by a phenyl ring was a successful strategy to obtain a novel synergist with improved effectiveness. Further studies on field-testing of the title compounds are ongoing.

Our previous investigation found that at low concentrations, IPPA08 can act as a positive allosteric modulator of noncanonical interfaces and likely slow the decay of currents through stabilizing the open-channel state caused by the action of imidacloprid on canonical interfaces.[16] Based on our present results, we propose two hypotheses. First, the origin of the differential synergistic activity of compound **25** and IPPA08 toward *A. craccivora* and *A. mellifera* L. likely resides in the target itself. Second, it is possible that the synergistic mechanism of compound **25** is different from that of IPPA08 considering their structural difference, i.e., phenyl ring and pyridyl ring. We are currently working to gain experimental evidence to further support such hypotheses. In this work, we only provided some implicit cues for such hypotheses. At the same time, our present study provides a unique strategy to alleviate the dilemma from neonicotinoids. When imidacloprid or thiamethoxam are co-applied with compound **25**, at the same insecticidal activity level, the amount of imidacloprid or thiamethoxam was reduced. The reduction in the use of neonicotinoids indirectly improves the safety of honey bees as well as decreases the risk of environmental residue by neonicotinoids. Moreover, compound **25** is expected to be developed as a novel synergist, which is selective and safe for honey bee.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jafc.0c04786.

^{1}H NMR and ^{13}C NMR spectral data of compounds **1**−**33** (PDF)

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Notes

The authors declare no competing financial interest.

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J. Agric. Food Chem. 2021, 69, 3005−3014

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