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Syntheses and Biological Activities of Octahydro-1*H*-cyclopenta[*d*]pyrimidine Derivatives

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Various nitromethylene derivatives were synthesized regioselectively. Compounds **8a**−**f** were obtained by the reaction of 1-((5-chloropyridin-2-yl)methyl)-2-(nitromethylene)-octahydro-1*H*-cyclopenta[*d*]-pyrimidine (**3**) with primary amines and formaldehyde. The synthesized compounds were identified by ^{1}H NMR, HRMS (EI), and IR, and preliminary bioassays indicated that most of them showed moderate insecticidal activities against *Aphis craccivora*. The relationship between hydrophobicity and biological activity was also discussed.

KEYWORDS: Nitromethylene derivatives; synthesis; regioselective; biological activity; hydrophobicity

INTRODUCTION

Since Imidacloprid's (**1a**) introduction in the 1980s as an insecticide for crop protection (*1*), neonicotinoids were used rapidly worldwide for controlling insects because of their potency, low mammalian toxicity, broad insecticidal spectra, and good systemic properties. Neonicotinoids interacting with nicotinic acetylcholine receptors (nAChR) have a higher affinity for the insect receptor than for the mammalian (*2*−*5*) and are relatively safe toward mammals and aquatic life. In recent years, the innovation of neonicotinoid insecticides has been an intense and competitive effort (*6*−*8*).

Compared with Imidacloprid, nitromethylene analogue 6-Cl-PMNI (**1b**) and **1c** (**Figure 1**) exhibit remarkably higher receptor binding activity (*9*−*10*); however, their use was limited owing to its weak hydrophobicity (*11*). When the NH on the 3-position of the imidazolidine ring of 6-Cl-PMNI was replaced by S, the S-analogue **1d** exhibited lower receptor binding activity, but its hydrophobicity was increased and showed similar insecticidal activities against green rice leafhopper as Imidacloprid (*12*), which implied that the hydrophobicity might be the important role to influence their activities. Herein, to improve the hydrophobicity of **1c**, a series of octahydro-1*H*-cyclopenta[*d*] pyrimidines were designed and synthesized by introducing a saturated cyclopentane ring into the lead structure, and also the relationship between hydrophobicity and biological activity is discussed.

MATERIALS AND METHODS

Synthetic Procedures. Melting points (mp) were recorded on Büchi B540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. High-resolution mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Combustion analyses for elemental composition were performed with an Elementar vario EL III. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

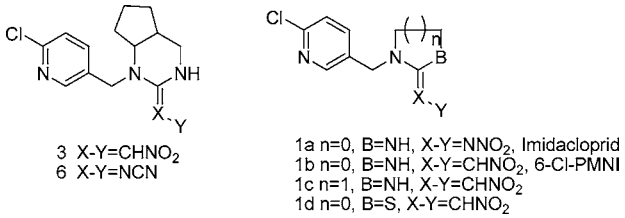

Figure 1. Chemical structures of **3**, **6**, and **1a**–**d**.

2-Iminocyclopentanecarbonitrile (9). 2-Iminocyclopentanecarbonitrile was prepared according to Schroeder's procedure (*13*) in 86% yield. Mp: 145−147 °C (lit. 146−148 °C). GC-MS: *m*/*z* (%) =107 ([M − 1]$^+$, 100), 80 (16), 54 (9).

2-Aminocyclopentanecarbonitrile (10). Sodium borohydride (5.7 g, 150 mmol) was added in one portion to a stirred acetic acid (160 mL) at 10−20 °C. After H_2 evolution ceased (30 min), 2-iminocyclopentanecarbonitrile (5.4 g, 50 mmol) was added. The mixture was allowed to react for 3 h at room temperature, and then the solvent was evaporated under reduced pressure. CH_2Cl_2 (100 mL) was added to the residue, and the organic layer was washed with saturated aqueous sodium carbonate (50 mL × 2). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give **10** (65% yield) as an oil. GC-MS *m*/*z* (%): 110 ([M$^+$], 10), 81 (10), 68 (7), 56 (100).

2-Amino-3-methylcyclopentanecarbonitrile (18). Using the procedure for **10**, 2.3 g (83% yield) of **18** was obtained as a liquid and was used for next reactions without further purification.

2-(Aminomethyl)cyclopentanamine (11). To a suspension of $LiAlH_4$ (0.95 g, 25 mmol) in dry THF (25 mL), 0.55 g (5 mmol) of 2-aminocyclopentanecarbonitrile in dry THF (10 mL) was added at 0

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°C. The mixture was stirred at 0 °C for 15 min, and then at room temperature for 1 h. The reaction was quenched by pouring into water, and the precipitate was filtered off and washed with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **11** as a colorless oil (82% yield). GC-MS *m*/*z* (%): 115 ([MH$^+$], 3), 97 (90), 82 (48), 69 (65), 56 (100).

2-((6-Chloropyridin-3-yl)methylamino)cyclopentanecarbonitrile (13). A mixture of 2-aminocyclopentanecarbonitrile (1.21 g, 11 mmol), Et_3N (1.5 mL), and 2-chloro-5-(chloromethyl)pyridine (1.62 g, 10 mmol) in acetonitrile (30 mL) was stirred at 50−55 °C for 15 h. The reaction mixture was concentrated under reduced pressure and treated with 20 mL of saturated aqueous Na_2CO_3. The solution was then extracted three times with CH_2Cl_2 (15 mL), and the combined extracts were dried over $MgSO_4$. The organic phase was evaporated under reduced pressure, and crude product was purified by flash chromatography. A total of 1.47 g (63% yield) of compound **13** was obtained as a colorless oil. GC-MS: *m*/*z* (%): 235 ([M$^+$], 35), 181 (100), 167 (25), 126 (85), 99 (9), 90 (12).

2-Imino-3-methylcyclopentanecarbonitrile (17). To a THF solution (50 mL) of potassium *tert*-butoxide (22.4 g, 200 mmol) was added hexane dinitrile (10.8 g, 100 mmol).The mixture was cooled to −10 °C, and then CH_3I (14.2 g, 100 mmol) was added within 2 min. The mixture was allowed to react at −10 °C for 30 min then at room temperature for 2 h. The reaction was quenched with 20 mL of saturated aqueous NH_4Cl, and the mixture was extracted three times with ethyl acetate (30 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting residue (11.7 g) was refluxed with NaH (60%, 4.4 g, 110 mmol) in THF (100 mL) for 5 h, then cooled to 20 °C, and quenched by water (40 mL). The mixture was extracted three times with Et_2O (30 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether−ethyl acetate, 3:1) to give 3.2 g (26% yield) of **17** as a colorless oil. GC-MS: *m*/*z* (%): 122 ([M$^+$], 52), 121 (100), 107 (46), 94 (23), 80 (18).

2-((6-Chloropyridin-3-yl)methyleneamino)-3-methylcyclopentanecarbonitrile (19). To the solution of 2-amino-3-methylcyclopentanecarbonitrile **18** (2.3 g, 18.5 mmol) and 6-chloronicotinaldehyde (2.7 g, 19 mmol) in EtOH (20 mL) was added a catalytic amount of concentrated HCl. The mixture was heated under reflux for 8 h and cooled to room temperature. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography (petroleum ether−ethyl acetate, 3:1) to afford 2.1 g (46%) of **19**. GC-MS: *m*/*z* (%): 247 ([M$^+$], 95), 193 (100), 179 (66), 152 (71), 139 (38), 125 (35).

2-(Aminomethyl)-*N*-(pyridin-3-ylmethyl)cyclopentanamine (14). To a solution of compound **13** (0.47 g, 2 mmol) in anhydrous THF (20 mL) at 0−5 °C was added an excess amount of $LiAlH_4$ (0.15 g, 4 mmol), and then the suspension was stirred in room temperature. After 1 h, the reaction was quenched with water (2 mL), and the mixture was extracted three times with Et_2O (5 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. A total of 0.25 g (61% yield) of **14** was obtained as an oil which was used for subsequent reactions without further purification.

2-(Aminomethyl)-*N*-((5-chloropyridin-2-yl)methyl)cyclopentanamine (15). 2-((5-Chloropyridin-2-yl)methylamino)cyclopentanecarbonitrile (*13*) (2.35 g, 10 mmol) in anhydrous THF (20 mL) was added to 1.0 M solution of BH_3·THF (20 mmol) in THF at room temperature over a period of 10 min. The reaction mixture was warmed to 60−65 °C and stirred for 18 h, and then the reaction mixture was cooled to room temperature. Next, 6 N HCl (10 mL) was added dropwise, and the mixture was heated to 65−70 °C for 2 h. After being cooled to room temperature, the mixture was washed with Et_2O (3 × 30 mL) and cooled to 0 °C. Then 10 N NaOH (20 mL) was added to this solution. The amine was extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gives crude **15** (1.62 g, 72% yield). GC-MS: *m*/*z* (%): 239 ([M$^+$], 13), 181 (24), 141 (32), 126 (100), 113 (35), 99 (39), 84 (92).

2-(Aminomethyl)-*N*-((5-chloropyridin-2-yl)methyl)cyclopentanamine (20). Following the above method, the title compound was obtained in 61% yield which was used for following transformations without further purification.

1-((5-Chloropyridin-2-yl)methyl)-2-(nitromethylene)-octahydro-1*H*-cyclopenta[*d*]pyrimidine (3) and 3-((5-Chloropyridin-2-yl)-methyl)-2-(nitromethylene)-octahydro-1*H*-cyclopenta[*d*]pyrimidine (4). To the solution of nitromethylene derivative **12** (0.37 g, 2 mmol) in DMF (10 mL) was added NaH (60%, 0.09 g, 2.2 mmol), and the resulting mixture was stirred at room temperature for 30 min. 2-Chloro-5-(chloromethyl)pyridine in DMF (5 mL) was then added dropwise, and the mixture was stirred at 45−50 °C for 5 h. On completion, to the mixture was added 20 mL of water followed by extraction with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with saturated brine (2 × 20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (dichloromethane−methanol, 20:1) to afford the title compounds **3** (0.05 g, 7.5% yield) and **4** (0.05 g, 7.5% yield), respectively. Mp: 146.6−148.3 °C; ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.24−2.44 (m, 7H), 3.10−3.88 (m, 3H), 4.37−4.59 (m, 2H), 6.54−6.64 (m, 1H), 7.35 (m, 1H), 7.54 (m, 1H), 8.25 (t, 1H), 10.73−10.98 (m, 1H). IR (KBr, cm^{-1}) ν: 3141, 2963, 1589, 1558, 1289, 984. HRMS Anal. Calcd for $C_{14}H_{18}N_4O_2Cl$ (MH$^+$); 309.1118. Found: 309.1136.

Compound (12, 3, 5, 7). General Procedure. A solution of compound **11**, **14**, **15**, **20** (2 mmol), and 1,1-bis(thiomethyl)-2-nitroethylene (2 mmol) in 30 mL of ethanol was refluxed for 8 h and then cooled to room temperature. Evaporation under reduced pressure gave the desired product as an oil after purifiction by flash chromatography.

2-(Nitromethylene)-octahydro-1*H*-cyclopenta[*d*]pyrimidine (12). Yield: 83% (0.305 g). Mp: 172−175 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.25−2.35 (m, 7H), 3.03−3.80 (m, 3H), 6.66 (s, 0.5 H), 6.67 (s, 0.5 H), 8.90 (s, 2H, NH). IR (KBr, cm^{-1}) ν: 3167, 2958, 1614, 1489, 1361, 1206, 58. GC-MS *m*/*z* (%): 149 (100), 120 (71), 106 (24), 94 (26), 67 (68).

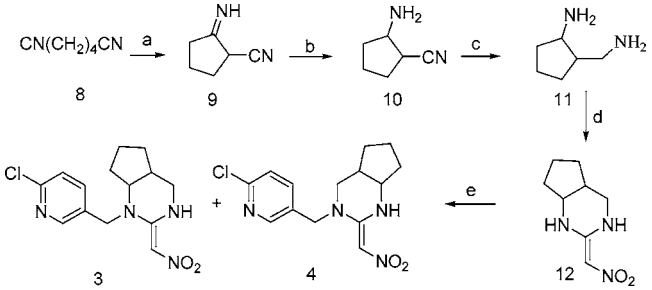
2-(Nitromethylene)-1-(pyridin-3-ylmethyl)-octahydro-1*H*-cyclopenta[*d*]pyrimidine (5). Yield: 45% (0.17 g). Mp: 125.1−126.8 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.25−2.40 (m, 7H), 3.27 (m, 2H), 3.68 (m, 1H), 4.53 (m, 2H, H-5), 6.60 (d, 1H, H-6, J = 10.8 Hz), 7.31 (dd, 1H, H-2, J = 5.7 Hz, J = 13.1 Hz), 7.52 (t, 1H, H-3, J = 6.7 Hz), 8.47 (s, 1H, H-1), 8.57 (t, 1H, H-1, J = 6.1 Hz), 10.95 (d, 1H, NH, J = 7.8 Hz). IR (KBr, cm^{-1}) ν: 3199, 2963, 2871, 1690, 1557, 1426, 1305. HRMS Anal. Calcd for $C_{14}H_{19}N_4O_2$ (MH$^+$): 275.1508. Found: 275.1495.

1-((5-Chloropyridin-2-yl)methyl)-2-(nitromethylene)-octahydro-1*H*-cyclopenta[*d*]pyrimidine (3). Yield: 73% (1.12 g). Mp: 172.2−173.5 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.62 (m, 3H), 1.82 (m, 1H), 1.99 (m, 1H), 2.17 (m, 1H), 2.38 (m, 1H), 3.08 (m, 1H), 3.47 (m, 1H), 3.58 (m, 1H), 4.43 (d, 1H, H-4, J = 17.4 Hz), 4.57 (d, 1H, H-4, J = 17.4 Hz), 6.58 (s, 1H, H-5), 7.34 (d, 1H, H-3, $^3J_{2,3}$ = 8.2 Hz), 7.50 (dd, 1H, H-2, $^4J_{1,2}$ = 2.3 Hz, $^3J_{2,3}$ = 8.2 Hz), 8.24 (d, 1H, H-1, $^4J_{1,2}$ = 2.3 Hz), 10.87 (s, 1H, NH). IR (KBr, cm^{-1}) ν: 3141, 1558, 1589, 1458, 1420, 1289; MS *m*/*z* (%): 308 ([M$^+$], 5), 278 (9), 262 (100), 226 (12), 126 (62), 90 (13). HRMS Anal. Calcd for $C_{14}H_{18}N_4O_2Cl$ (MH$^+$): 309.1118. Found: 309.1136.

1-((6-Chloropyridin-3-yl)methyl)-7-methyl-2-(nitromethylene)-octahydro-1*H*-cyclopenta[*d*]pyrimidine (7). Yield: 65% (1.05 g). Mp: 89.6−92.2 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 0.94 (m, 3H), 1.41 (m, 1H), 1.68 (m, 2H), 1.83 (m, 2H), 2.44 (m, 1H), 3.06 (m, 1H), 3.64 (m, 2H), 4.61 (m, 2H, H-4), 6.59 (s, 1H, H-5), 7.36 (d, 1H, H-3 J = 8.1 Hz), 7.48 (t, 1H, H-2, J = 10.6 Hz), 8.23 (d, 1H, H-1, J = 2.3 Hz), 10.92 (s, 1H, NH). IR (KBr, cm^{-1}) ν: 3145, 1558, 1456, 1367, 1211. MS *m*/*z* (%): 322 (5), 276 (100), 179 (48), 126 (76), 95 (23), 61 (12). HRMS Anal Calcd for $C_{15}H_{19}N_4O_2Cl$ (M$^+$): 322.1197. Found: 322.1177.

1-((2-((6-Chloropyridin-3-yl)methylamino)cyclopentyl)methyl)-3-cyano-2-methylisothiourea (16). A solution of compound **15** (0.12 g, 0.5 mmol) and dimethyl cyanocarbonodithioimidate (0.73 g, 0.5 mmol) in 10 mL of ethanol was refluxed for 8 h and then cooled to room temperature. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (dichloromethane−methanol, 95:5), and 0.14 g (82%) of compound **16** was obtained as a white solid. Mp: 108.4−110.4 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.36−2.28 (m, 7H), 2.42 (s, 3H, H-5), 3.13−3.63 (m, 3H),

Scheme 1[a]



[a] Reagents and conditions: (a) NaH/THF (86%); (b) $NaHB(OAc)_3$/AcOIH (65%); (c) THF/$LiAlH_4$ (82%); (d) 1,1-bis(thiomethyl)-2-nitroethylene/EtOH (83%); (e) NaH/DMF (**3** and **4**, 15%).

3.72−3.87 (m, 2H), 7.34 (d, 1H, H-3, J = 8.2 Hz), 7.57−7.87 (m, 1H, H-2), 8.32 (s, 1H, H-1), 8.43 (s, 1H). IR (KBr, cm^{-1}) ν: 3281, 2811, 2178, 1560, 1519, 1435, 1122. HRMS Anal. Calcd for $C_{15}H_{21}ClN_5S$ (MH^+): 338.1206. Found: 338.1188.

(1-((6-Chloropyridin-3-yl)methyl)-hexahydro-1*H*-cyclopenta[*d*]-pyrimidin-2(3*H*)-ylidene)cyanamide (6). A mixture of compound **16** (0.102 g, 0.3mmol) and AgOAc (0.05 g, 0.3 mmol) in methanol (10 mL) was stirred at 50 °C for 5 h. After filtration, the filtrate was evaporated under vacuum. The residue was purified by flash chromatography to afford compound **6** (0.076 g, yield 87%). Mp: 156.2−156.7 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.51 (m, 3H), 1.78 (m, 1H), 1.91 (m, 1H), 2.10 (m, 1H), 2.31 (m, 1H), 3.03 (m, 1H), 3.30 (m, 1H), 3.47 (m, 1H), 4.29 (d, 1H, H-4, J = 15.4 Hz), 4.99 (d, 1H, H-4, J = 15.4 Hz), 6.19 (s, 1H, NH), 7.31 (d, 1H, H-3, $^3J_{2,3}$ = 8.1 Hz), 7.75 (dd, 1H, H-2, $^4J_{1,2}$ = 2.4 Hz ,$^3J_{2,3}$ = 8.1 Hz), 8.29 (d, 1H, H-1, $^4J_{1,2}$ = 2.4 Hz). IR (KBr, cm^{-1}) ν: 3249, 2170, 1586, 1551, 1457, 1339, 1107. HRMS Anal. Calcd for $C_{14}H_{17}ClN_5$ (MH^+): 290.1172. Found: 290.1152.

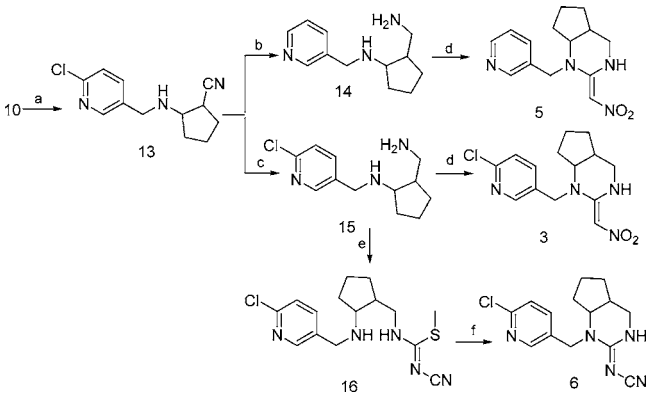
Compound (8a−f). General Procedure. A mixture of compound **3** (0.75 mmol), formaldehyde (1.6 mmol, in the form of 35% aqueous solution), and corresponding amine (0.83 mmol) in ethanol (5 mL) was stirred overnight. The solution thus obtained was concentrated under vacuum and further purified by flash chromatography to give the desired product.

2-[4-(6-Chloropyridin-3-methyl)-7-methyl-5-nitro-1,2,3,3a,4,-6,7,8,9,9a-decahydro-4,7,8a-triazote-cyclopentyl[*b*]naphthalene (8a). Yield: 64% (0.175 g). Mp: 172.5−174.6 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.53 (m, 2H), 1.79 (m, 1H), 1.90 (s, 2H), 2.02 (s, 1H), 2.37 (s, 3H), 2.64 (s, 1H), 3.10 (d, 1H, J = 11.5 Hz), 3.66 (d, 3H, J = 10.0 Hz), 3.81 (s, 2H), 4.26 (s, 1H), 4.48 (s, 1H), 4.58 (d, 1H, J = 15.2 Hz), 7.34 (d, 1H, H-3, J = 8.1 Hz), 7.58 (d, 1H, H-2, J = 7.2 Hz), 8.34 (s, 1H, H-1). IR (KBr, cm^{-1}) ν: 3216, 2957, 1609, 1562, 1461, 1138. MS *m*/*z* (%): 363 ([M^+], 2), 346 (11), 333 (12), 274 (43), 126 (84), 49 (26), 42 (100). HRMS Anal Calcd for $C_{17}H_{22}ClN_5O_2$ (M^+): 363.1462. Found: 363.1432.

2-[4-(6-Chloropyridin-3-methyl)-7-ethyl-5-nitro-1,2,3,3a,4,6,7,8,9,9a-hexahydro-4,7,8a-triazote-cyclopentyl[*b*]naphthalene (8b). Yield: 62% (0.176 g). Mp: 167.2−169.2 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.12 (t, 3H, H-6, $^3J_{5,6}$ = 7.0 Hz), 1.53 (m, 2H), 1.79 (m, 1H), 1.90 (m, 2H), 2.01 (m, 1H), 2.46 (q, 2H, H-5, ^3J = 7.0 Hz), 2.67 (s, 1H), 3.09 (d, 1H, J = 12.2 Hz), 3.58−3.92 (m, 5H), 4.26 (s, 1H), 4.48 (s, 1H), 4.59 (d, 1H, J = 15.3 Hz), 7.34 (d, 1H, H-3, J = 8.2 Hz), 7.58 (d, 1H, H-2, J = 6.9 Hz), 8.32 (d, 1H, H-1, J = 2.2 Hz). IR (KBr, cm^{-1}) ν: 2940, 1557, 1521, 1399, 1374, 1270, 1003. HRMS Anal. Calcd for $C_{18}H_{25}ClN_5O_2$ (MH^+): 378.1697. Found: 378.1679.

2-[4-(6-Chloropyridin-3-methyl)-7-isopropyl-5-nitro-1,2,3,-3a,4,6,7,8,9,9a-hexahydro-4,7,8a-triazote-cyclopentyl[*b*]naphthalene (8c). Yield: 58% (0.17 g). Mp: 158.3−160.6 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.09 (d, 6H, CH_3, $^3J_{5,6}$ = 6.3 Hz), 1.52 (m, 2H), 1.79 (m, 1H), 1.89 (m, 2H), 2.01 (m, 1H), 2.65 (s, 1H), 2.76 (d, 1H, H-5, $^3J_{5,6}$ = 6.0 Hz), 3.08 (s, 1H), 3.62−3.97 (m, 5H), 4.26 (s, 1H), 4.48 (s, 1H), 4.57 (d, 1H, J = 15.3 Hz), 7.33 (d, 1H, H-3, J = 8.2 Hz), 7.58 (d, 1H, H-2, J = 7.5 Hz), 8.32 (d, 1H, H-1, J = 2.0 Hz). IR (KBr, cm^{-1}) ν: 2957, 1550, 1519, 1378, 1265, 1151. MS *m*/*z* (%): 391 ([M^+], 5), 274 (15), 249 (12), 126 (100), 96 (19), 71 (49). HRMS Anal. Calcd for $C_{19}H_{26}ClN_5O_2$ (M^+): 391.1775. Found: 391.1804.

Scheme 2[a]



[a] Reagents and conditions: (a) 2-chloro-5-(chloromethyl)pyridine, Et_3N/CH_3CN (63%); (b) $LiAlH_4$/THF (61%); (c) BH_3/THF (69%); (d) 1,1-bis(thiomethyl)-2-nitroethylene/EtOH) (82%); (f) AgOAc/MeOH (87%).

2-[4-(6-Chloropyridin-3-methyl)-7-propyl-5-nitro-1,2,3,3a,4,6,7,-8,9,9a-hexahydro-4,7,8a-triazote-cyclopentyl[*b*]naphthalene (8d). Yield: 55% (0.16 g). Mp: 155.1−157.3 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 0.92 (t, 3H, $^3J_{4,5}$ = 7.4 Hz), 1.52−2.01 (m, 8H), 2.32 (t, 2H, J = 7.0 Hz), 2.66 (s, 1H), 3.08 (d, 1H, J = 12.1 Hz), 3.57−3.86 (m, 5H), 4.26 (s, 1H), 4.48 (s, 1H), 4.57 (d, 1H, J = 15.3 Hz), 7.33 (d, 1H, H-3, $^3J_{2,3}$ = 8.2 Hz), 7.58 (dd, 1H, H-2, $^4J_{1,2}$ = 1.5 Hz, $^3J_{2,3}$ = 8.2 Hz), 8.32 (d, 1H, H-1, $^4J_{1,2}$ = 1.9 Hz). IR (KBr, cm^{-1}) ν: 2958, 1557, 1518, 1368, 1290. MS *m*/*z* (%): 391 ([M^+], 5), 274 (18), 249 (22), 126 (100), 99 (9), 96 (19), 70 (45). HRMS Anal Calcd for $C_{19}H_{26}ClN_5O_2$ (M^+): 391.1775. Found: 391.1804.

2-[4-(6-Chloropyridin-3-methyl)-7-butyl-5-nitro-1,2,3,3a,4,6,7,-8,9,9a-hexahydro-4,7,8a-triazote-cyclopentyl[*b*]naphthalene (8e). Yield: 63% (0.19 g). Mp: 143.2−144.9 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 0.93 (t, 3H, H-5, $^3J_{4,5}$ = 7.3 Hz), 1.33 (m, 2H), 1.52−2.01 (m, 8H), 2.32 (t, 2H, J = 7.0 Hz), 2.67 (s, 1H, J = 4.8 Hz), 3.08 (d, 1H, J = 12.1 Hz), 3.57−3.86 (m, 5H), 4.26 (s, 1H), 4.48 (s, 1H), 4.57 (d, 1H, J = 15.3 Hz), 7.33 (d, 1H, H-3, $^3J_2$−3 = 8.1 Hz), 7.58 (dd, 1H, H-2, $^4J_1$−2 = 1.5 Hz, $^3J_2$−3 = 8.0 Hz), 8.32 (d, 1H, H-1, $^4J_{1,2}$ = 1.9 Hz). IR (KBr, cm^{-1}) ν: 2956, 1552, 1518, 1367, 1290, 1150. MS *m*/*z* (%): 405 ([M^+], 1), 274 (14), 249 (8), 148 (9), 126 (47), 84 (100). HRMS Anal. Calcd for $C_{20}H_{28}ClN_5O_2$ (M^+): 405.2001. Found: 405.1826.

2-[4-(6-Chloropyridin-3-methyl)-5-nitro-1,2,3,3a,4,6,7,8,9,9a-hexahydro-4,7,8a-triazote-cyclopentyl[*b*]naphthalene-7-yl]ethanol (8f). Yield: 91% (0.18 g). Mp: 184.1−185.6 °C. ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.53 (m, 2H), 1.77−2.01 (m, 5H), 3.13 (d, 1H, J = 11.4 Hz), 3.75 (m, 6H), 4.00 (m, 2H), 4.43 (m, 2H), 4.58 (d, 1H, J = 15.4 Hz), 7.34 (d, 1H, H-3, $^3J_{2,3}$ = 8.1 Hz), 7.58 (dd, 1H, H-2, $^4J_{1,2}$ = 1.7 Hz, $^3J_{3,2}$ = 8.0 Hz), 8.32 (d, 1H, H-1, $^4J_{1,2}$ = 2.0 Hz). IR (KBr, cm^{-1}) ν: 3442, 1558, 1518, 1386, 1342, 1134. HRMS Anal. Calcd for $C_{18}H_{25}ClN_5O_3$ (MH^+): 394.1646. Found: 394.1644.

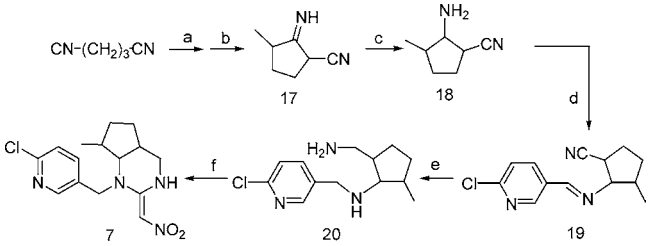
Biology Assay. All compounds were dissolved in acetone and diluted with water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 500.0, 250.0, 125.0 mg L^{-1} and others for bioassays.

Pea Aphids (*Aphis craccivora*) were dipped according to a slightly modified FAO dip test (*14*). Tender shoots of soybean with 40−60 healthy apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mL L^{-1}) for 5 s, the superfluous fluid was removed, and the shoots were placed in the conditioned room (23 ± 1 °C, RH 50%). Water containing Triton X-100 (0.1 mL L^{-1}) was used as control. Mortality was assessed after 24 h, and data were corrected and subjected to probit analysis as before.

RESULTS AND DISCUSSION

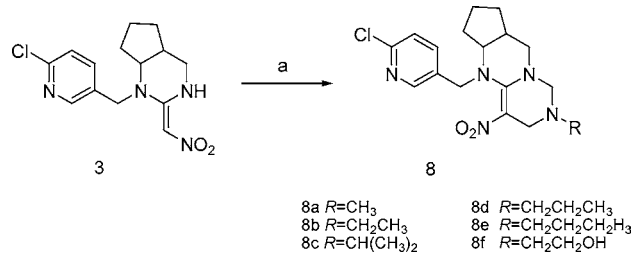
Synthesis. The goal of this research was to develop a synthetic strategy that offers a regioselective access to analogues

Scheme 3[a]



[a] Reagents and conditions: (a) CH_3I, *t*-BuOK/THF; (b) NaH/THF (26%); (c) $NaHB(OAc)_3$/AcOH (71%); (d) 6-chloronicotinaldehye, HCl/EtOH (46%); (e) BH_3/THF (61%); (f) 1,1-bis(thiomethyl)-2-nitroethylene/EtOH (65%).

Scheme 4[a]



[a] Reagents and conditions: (a) RNH_2, CH_2O/EtOH, rt.

3, **6**, and **7** of **1c**. Initially, the route represented in **Scheme 1** was investigated, in which the intermediate **12** was synthesized by reaction of 1,1-bis(thiomethyl)-2-nitroethylene with **11**. Compound **11** could be obtained conveniently via the reduction of **9** with $NaHB(OAc)_3$ in AcOH or $LiAlH_4$ in THF. Compound **12** was treated with sodium hydride and then reacted with 2-chloro-5-(chloromethyl)pyridine to give a mixture of compound **3** and **4**, which could not be separated using silica gel chromatography due to the similar polarity. ^1H NMR spectra indicated that **3** and **4** were formed as a 1:1 mixture, which could be obtained in 15% total yield (**Scheme 1**).

Because this reaction is not regioselective, another procedure (**Scheme 2**) was therefore explored: **10** was reacted directly with 2-chloro-5-chloromethylpridine, and then the formed 2-(aminomethyl)-*N*-((5-chloropyridin-2-yl)methyl)cyclopentanamine **13** was reduced. As has been well-known, stronger reductants such as $LiAlH_4$−THF can reduce cyano and chloro groups. To be a mild reducing agent, BH_3·THF led to the chemoselective reduction of the cyano group, avoiding undesired reduction of the chloro group (**Scheme 2**). Compound **3** was synthesized regioselectively by reaction of **15** with 1,1-bis-(thiomethyl)-2-nitroethylene. Unfortunately, the similar procedure could not give compound **6** from **15**. The reaction stopped at the step of compound **16**. By adding AgOAc, the reaction was promoted forward due to the generation of $AgSCH_3$ (*15*). Synthesis of **7** was performed as indicated in **Scheme 3**. Imine **19** was obtained by reaction **18** with 5-chloropicolinaldehyde, then was reduced using BH_3·THF.

The products **8a**−**8f** in the present study are obtained by stirring compound **3** with the corresponding primary amine and formaldehyde in THF via Mannich reaction (**Scheme 4**).

Structure−**Activity Relationship.** The calculated Log*P* values of **1b**, **1c**, **3**, **7**, and **8** using Cerius[2] (version 4.8) are listed in **Table 1**. The results showed that the hydrophobicity of **3** and **7** were improved significantly compared with **1c**, but most of our designed compounds showed only moderate insecticidal activities at 500 mg/L against *Aphis craccivora*. The results are listed in **Table 2**. Compounds **3**, **5**, **6**, **7**, **8a**, **8d**, **8e**, **8f**, and **16** exhibited 30−80% activities at 500 mg/L; compounds **3**, **5**, **8b**, and **8c** had >80% activities at 500 mg/L. In addition, compound **8c** showed 56% activity at 125 mg/L. The insecticidal activity of mixture of **3** and **4** was 59%, which indicated that activity of compound **4** was <59%. Comparing biological activities of **3** and **6**, it was found that functional group $=CHNO_2$ has more contribution for activities than group =NCN. Though it was reported that the chlorine atom at the 6-position of the 3-pyridyl group plays an important role on increasing insecticidal activity for nitromethylene compounds (*16*), introduction of a chlorine atom to the pyridine ring afforded no such activity enhancement for compound **3** in this paper.

Table 1. Calculated Log*P*s of Compounds **3** and **7** and Parent Compound

1b	**1c**	**3**	**7**	**8a**
1.17	1.70	2.71	3.11	2.20
8b	**8c**	**8d**	**8e**	**8f**
2.75	3.15	3.28	3.81	1.43

Table 2. Insecticidal Screening Results of Nitromethylene Derivatives against *Aphis craccivora*

compd	concn (mg/L)	mortality (%) in vivo at 1 day
3	500	83
3, **4**	500	59
5	500	82
6	500	38
7	500	51
8a	500	54
8b	500	90
8c	450	88
	125	56
8d	500	61
8e	500	32
8f	500	60
16	500	34
1c	62.5	94
	15.625	60

In conclusion, the synthesis of various nitromethene derivatives can be approached successfully by taking advantage of the regioselective cyclization of corresponding diamine. The hydrophobicity of lead nitromethylene compounds was significantly improved via the introduction of the cyclopentane ring, and most of them showed moderate insecticidal activities at 500 mg/L.

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