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Synthesis and Insecticidal Activities and SAR Studies of Novel Benzoheterocyclic Diacylhydrazine Derivatives

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Two series of novel *N*′-*tert*-butyl-*N*′-substituted benzoyl-*N*-2,3-dihydrobenzofuran-5-carbohydrazide derivatives were synthesized, their activities and different insecticidal action modes for different Lepidopteral larvicidal assays were evaluated carefully. The results of larvicidal activities against oriental armyworm and mosquito indicate that different benzoheterocyclic analogues of diacylhydrazide have different structure−activity relationships according to the types and patterns of substitution on the benzene, and 3,5-dimethyl is the most efficient substituent for benzoheterocyclic diacylhydrazine. Among them, *N*′-*tert*-butyl-*N*′-(3,5-dimethylbenzoyl)-*N*-2,4-dimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (**Ii**) stood out as the best compound with high activity. Compound **Ii** and *N*′-*tert*-butyl-*N*′-(3,5-dimethylbenzoyl)-*N*-5-chloro-6-chromanecarbohydrazide (**F**) have higher contact activities against diamond-back moth and stomach toxicities against cotton bollworm than **ANS-118** and **JS-118**. Compound **F** has higher contact toxicity against beet armyworm than **ANS-118** and **JS-118**. These results indicate that different heterocycles and substitutents on the benzene rings of benzoheterocyle moiety not only influence the larvicidal activities strongly but also are very sensitive to the insecticidal action modes for different Lepidopteran larvicidal insects.

KEYWORDS: Benzofuran; diacylhydrazine; ANS-118; JS-118; stomach toxicity; contact toxicity; insecticidal activity; insect growth regulator

INTRODUCTION

N-*tert*-Butyl-*N*,*N*′-diacylhydrazines discovered by Rohm and Haas Co. in the mid-1980s act as a new class of insect growth regulators (IGR) (*1, 2*). Because of their high insecticidal activities, especially in *Lepidoptera*, and low toxicity to nontarget organisms such as mammalians, birds, fishes, and so on, diacylhydrazines have attracted considerable attention in recent years (*3*−*8*). Among these active compounds, *N*-*tert*-butyl-*N*′-4-ethylbenzoyl-*N*-3,5-dimethylbenzoylhydrazide (tebufenozide, **RH-5992**, **A**, **Figure 1**) was the first to be commercialized as a leptidopteran-specific insecticide under the trade names Mimic, Confirm, and Romdan in several countries (*9*). **ANS-118** (**B**, **Figure 1**), a benzoheterocyclic analogue of *N*′-benzoyl-*N*-(*tert*-butyl)benzohydrazide, which was 4 times more active than **RH-5992** against *Spodoptera litura*, was commercialized by Nippon Kayaku Co. Ltd. and Sankyo Co. Ltd. (*10, 11*).

Recently, many benzoheterocyclic analogues of *N*′-benzoyl-*N*-(*tert*-butyl)benzofurancarbohydrazide were reported. Among them compounds **C** and **D** (**Figure 1**) and their analogues show high activity to Lepidopteran insects such as *Spodoptera litura*, *Cnaphalocrocis medinalis* Guenee, and *Adoxophyes orana*

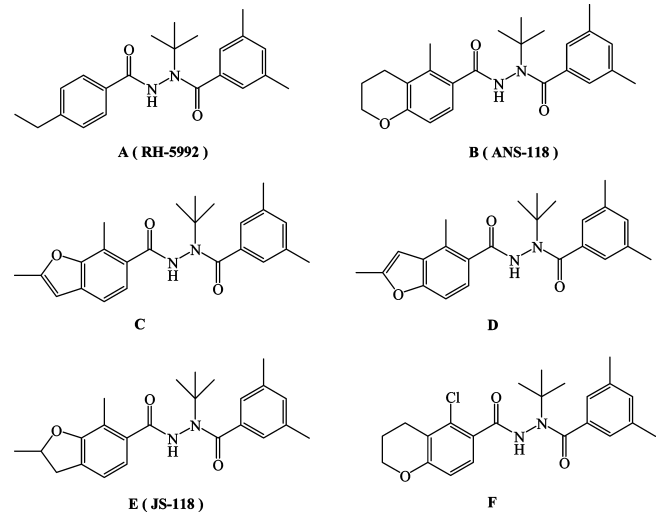

Figure 1. Chemical structures of compounds **A**−**F**.

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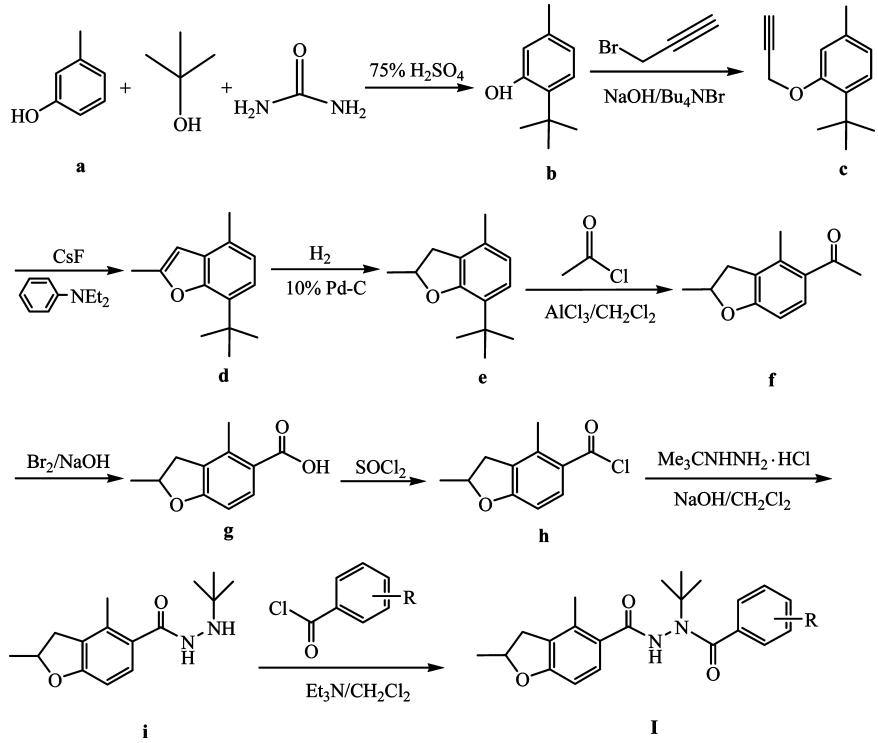
Scheme 1. General Synthetic Route for Compound **I**



Fischer von Roslerstamm (*12*). *N*′-Benzoyl-*N*-(*tert*-butyl)dihydrobenzofurancarbohydrazide analogues such as compound **E** (**Figure 1**), which shows high activity to Lepidopteran insects such as armyworm and diamond-back moth, also have been reported. Compound **E**, named **JS-118**, has been developed by the Jiangsu Institute of Agricultural Chemicals, People's Republic of China (*13*). Recently, we used bioisosterism to design and synthesize a series of novel *N*′-*tert*-butyl-*N*′-substituted benzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives and evaluated their larvicidal activites against oriental armyworm. Among them, compound **F** (**Figure 1**) has the highest activity (*14*).

It is interesting and disappointing that reports about the relationships between the changes of different heterocycles and substitutents on the benzene rings of benzoheterocyle moiety with different Lepidopteran larvicidal insects' activities, especially the insecticidal action modes in depth, are rare. Encouraged by these reports, we designed and synthesized two series of novel *N*′-*tert*-butyl-*N*′-substituted benzoyl-*N*-2,3-dihydrobenzofuran-5-carbohydrazide derivatives **Ia**−**Il** as shown in **Scheme 1** and **IIa**−**IIo** as shown in **Scheme 2**.

MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. HRMS was obtained on FTICR-MS (Ionspec 7.0T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized.

General Synthesis. All anhydrous solvents were dried and purified by standard techniques just before use.

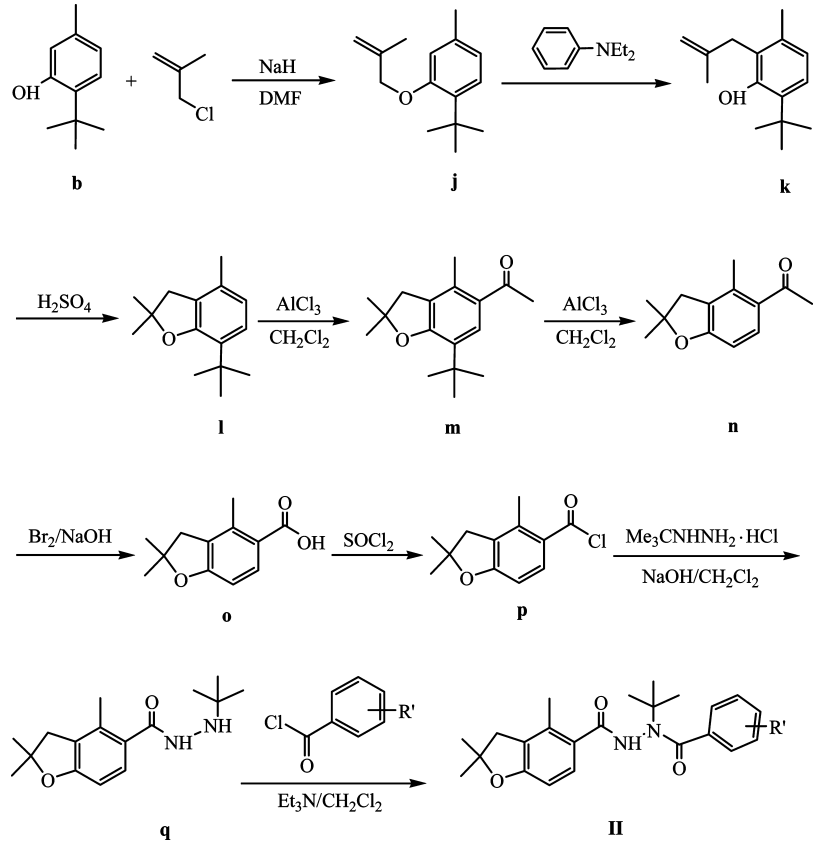
Synthesis of 2-tert-Butyl-5-methylphenol (b). Under stirring, urea (6 g, 0.1 mol) and *tert*-butyl alcohol (7.4 g, 0.1 mol) were added to 75% H_2SO_4 (100 mL) slowly at 10−25 °C. After 2 h, 3-methylphenol (**a**) (10.8 g, 0.1 mol) was added to the reaction mixture at 0−5 °C. After stirring at room temperature for 3 h, the reaction mixture was poured into ice−water. The mixture was extracted with petroleum ether (60−90 °C, 3 × 100 mL). The organic layer was washed successively with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure to give 2-*tert*-butyl-5-methylphenol (**b**) as a yellow liquid (9.88 g, 60%): bp 104−106 °C/2 mmHg [lit. (*15*) bp 224 °C]; ^{1}H NMR ($CDCl_3$) δ 7.17 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.71 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.51 (s, 1H, Ph); 4.71 (s, 1H, PhOH); 2.28 (s, 3H, $PhCH_3$); 1.41 (s, 9H, $C(CH_3)_3$).

Synthesis of 1-tert-Butyl-4-methyl-2-(prop-2-ynyloxy)benzene (c) (*11*). 3-Bromoprop-1-yne (1.74 g, 14.5 mmol) was added to the stirred mixture of compound **b** (2.05 g, 12.5 mmol), toluene (15 mL), 25.3% aqueous sodium hydroxide (2.32 g, 14.7 mmol), and tetrabutylammonium bromide (0.40 g, 1.24 mmol) in an ice bath. After stirring for 4 h at 50−55 °C, the reaction mixture was cooled and diluted with ethyl acetate (20 mL). The organic layer was washed successively with water (2 × 20 mL) and brine (2 × 20 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated to give 1-*tert*-butyl-4-methyl-2-(prop-2-ynyloxy)benzene (**c**) as a yellow oil (1.53 g, 60%): ^{1}H NMR ($CDCl_3$) δ 7.17 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 6.76 (s, 1H, Ph); 6.75 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 4.71 (s, 2H, CH_2); 2.48−2.49 (br, 1H, CH); 2.32 (s, 3H, $PhCH_3$); 1.37 (s, 9H, $C(CH_3)_3$).

Synthesis of 7-tert-Butyl-2,4-dimethylbenzofuran (d). A mixture of compound **c** (0.81 g, 4.0 mmol), cesium fluoride (0.08 g, 0.52 mmol), and *N*,*N*-diethylaniline (7 mL) was refluxed for 3 h. After cooling to room temperature, the reaction mixture was neutralized with hydrochloric acid (2 mol L^{-1}) and then extracted with petroleum ether (60−90 °C, 3 × 10 mL). The organic layer was washed successively with water (3 × 10 mL) and brine (10 mL) and then dried over anhydrous sodium sulfate. After the solvent was removed under vacuum, and the residue was distilled under reduced pressure to give 7-*tert*-butyl-2,4-dimethylbenzofuran (**d**) as a colorless oil (0.67 g, 83%): bp 80−81 °C/1 mmHg; ^{1}H NMR ($CDCl_3$) δ 6.91 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 6.85 (1H, d, $^3J_{HH}$ = 7.6 Hz, Ph); 6.30 (s, 1H, CH); 2.38 (s, 3H, CCH_3); 2.33 (s, 3H, $PhCH_3$); 1.39 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{14}H_{18}O$ (%): C, 83.12; H, 8.97. Found: C, 83.11; H, 8.74.

Synthesis of 7-tert-Butyl-2,4-dimethyl-2,3-dihydrobenzofuran (e). A mixture of compound **d** (10.00 g, 48.95 mmol), acetic acid (100 mL), and 10% palladium on activated carbon (2.00 g, 60% in water) was vigorously stirred under 1 atm of hydrogen at room temperature

Scheme 2. General Synthetic Route for Compound **II**



for 48 h. The reaction mixture was filtered and washed with petroleum ether (60−90 °C, 3 × 50 mL). The filtrate was washed successively with saturated aqueous sodium bicarbonate (2 × 50 mL), water (2 × 50 mL), and brine (50 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give 7-*tert*-butyl-2,4-dimethyl-2,3-dihydrobenzofuran (**e**) as a colorless oil (9.79 g, 97%): ^{1}H NMR ($CDCl_3$) δ 6.99 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.61 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 4.90−4.98 (m, 1H, OCH); 3.20−3.26 (m, 1H, CH_2); 2.67−2.73 (m, 1H, CH_2); 2.21 (s, 3H, $PhCH_3$); 1.46 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3); 1.36 (s, 9H, $C(CH_3)_3$).

Synthesis of 5-Acetyl-2,4-dimethyl-2,3-dihydrobenzofuran (f). Acetyl chloride (3.02 g, 38.44 mmol) was added to a stirred suspension of aluminum chloride (6.46 g, 48.9 mmol) in dichloromethane (140 mL) at −15 °C under N_2. After 1 h of stirring, the solution of compound **e** (7.14 g, 34.95 mmol) in dichloromethane (10 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction mixture was poured into hydrochloric acid (0.5 mol L^{-1}, 80 mL) and extracted with dichloromethane (3 × 40 mL). The organic layer was washed successively with saturated aqueous sodium bicarbonate (100 mL), water (3 × 100 mL), and brine (100 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on a silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 10:1) as the eluent to give 5-acetyl-2,4-dimethyl-2,3-dihydrobenzofuran (**f**) as a colorless crystal (2.77 g, 42%): mp 35−36 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 6.61 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 4.92−4.98 (m, 1H, OCH); 3.21−3.27 (m, 1H, CH_2); 2.70−2.74 (m, 1H, CH_2); 2.43 (s, 3H, O=CCH_3); 2.40 (s, 3H, $PhCH_3$); 1.43 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CCH_3). Anal. Calcd for $C_{12}H_{14}O_2$ (%): C, 75.76; H, 7.42. Found: C, 75.50; H, 7.42.

Synthesis of 2,4-Dimethyl-2,3-dihydrobenzofuran-5-carboxylic Acid (g). Bromine (6.38 g, 39.9 mmol) was added dropwise to a stirred solution of sodium hydroxide (4.99 g, 119.7 mmol) in water (20 mL) in an ice bath. After 30 min, compound **f** (2.53 g, 13.3 mmol) in 1,4-dioxane (25 mL) was added with stirring, and the mixture was stirred overnight at room temperature. Water (100 mL) was added to the reaction mixture and extracted with diethyl ether (2 × 50 mL). The aqueous layer was acidified with hydrochloric acid (1 mol L^{-1}) and extracted with dichloromethane (3 × 100 mL). The combined organic layer was washed successively with water (100 mL) and brine (100 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give 2,4-dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (**g**) as a white amorphous solid (2.33 g, 91%): mp 171−172 °C; ^{1}H NMR ($CDCl_3$) δ 12.81 (br, 1H, COOH); 7.98 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 6.64 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 4.98−5.04 (m, 1H, OCH); 3.29−3.35 (m, 1H, CH_2); 2.76−2.77 (m, 1H, CH_2), 2.53 (s, 3H, Ph); 1.49 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3). Anal. Calcd for $C_{11}H_{12}O_3$ (%): C, 68.74; H, 6.29. Found: C, 68.52; H, 6.09.

Synthesis of N′-tert-Butyl-N-2,4-dimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (i). A mixture of compound **g** (0.20 g, 1.04 mmol) and thionyl chloride (5 mL) was refluxed for 2 h. After excess thionyl chloride was removed under reduced pressure, the residue was dissolved in dichloromethane (2 mL). The resulting solution was added dropwise to a stirred mixture of *tert*-butylhydrazine hydrochloride (0.15 g, 1.25 mmol), sodium hydroxide (0.09 g, 2.29 mmol), dichloromethane (30 mL), and water (2 mL) at −15 °C. After overnight stirring at room temperature, the organic layer was washed successively with water (3 × 15 mL) and brine (15 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give *N′-tert*-butyl-*N*-2,4-dimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (**i**) as a white solid (0.25 g, 93%): mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.58 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.90−5.54 (m, 1H, OCH); 3.24−3.30 (m, 1H, CH_2); 2.71−2.77 (m, 1H, CH_2); 2.34 (s, 3H, $PhCH_3$); 1.47 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3); 1.16 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{15}H_{22}N_2O_2$ (%): C, 68.67; H, 8.45; N, 10.68. Found: C, 68.78; H, 8.47; N, 10.50.

Synthesis of 1-tert-Butyl-4-methyl-2-(2-methylallyloxy)benzene (j). The solution compound **b** (10 g, 60.89 mmol) in *N*,*N*-dimethylformamide (40 mL) was added dropwise to the mixture of sodium hydride (3.46 g, 50% NaH, 72.11 mmol) and *N*,*N*-dimethylformamide (80 mL) at 0 °C. After 1 h of stirring at room temperature, 3-chloro-2-methylprop-1-ene (6.53 g, 72.11 mmol) was added dropwise to the reaction mixture at room temperature. After 4 h of stirring, saturated aqueous ammonium chloride (80 mL) was added to the reaction mixture.

The resulting mixture was extracted with ether (3 × 50 mL). The organic layer was washed with brine (50 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure to give 1-*tert*-butyl-4-methyl-2-(2-methylallyloxy)benzene (**j**) as a colorless oil (11.32 g, 91%): bp 99−100 °C/2 mmHg; ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 6.75 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.73 (s, 1H, Ph); 5.19 (s, 1H, CH_2); 5.03 (s, 1H, CH_2); 4.43 (s, 2H, OCH_2); 2.34 (s, 3H, $PhCH_3$); 1.92 (s, CH_3); 1.43 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{15}H_{22}O$ (%): C, 82.52; H, 10.16. Found: C, 82.59; H, 10.08.

Synthesis of 6-tert-Butyl-3-methyl-2-(2-methylallyl)phenol (k). A mixture of compound **j** (9.04 g, 44.26 mmol) and *N*,*N*-diethylaniline (50 mL) was refluxed for 36 h. After cooling to room temperature, the reaction mixture was neutralized with hydrochloric acid (2 mol L^{-1}) and then extracted with petroleum ether (60−90 °C, 3 × 25 mL). The combined organic layer was washed successively with water (25 mL) and brine (25 mL) and then dried over anhydrous sodium sulfate. After the solvent was removed under vacuum, the residue was purified by column chromatography on a silica gel using petroleum ether (60−90 °C) as the eluent to give 6-*tert*-butyl-3-methyl-2-(2-methylallyl)phenol (**k**) as a colorless oil (6.20 g, 69%): ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 6.80 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 5.35 (s, 1H, PhOH); 4.99 (s, 1H, C=CH_2); 4.84 (s, 1H, C=CH_2); 3.45 (s, 2H, CH_2); 2.33 (s, 3H, $PhCH_3$); 1.86 (s, 3H, CH_3); 1.46 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{15}H_{22}O$ (%): C, 82.52; H, 10.16. Found: C, 82.22; H, 10.24. At the same time, 7-*tert*-butyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (**l**) (0.90 g) was obtained as byproduct.

Synthesis of 7-tert-Butyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (l). A mixture of compound **k** (8.00 g, 39.17 mmol) and sulfuric acid (0.39 g, 3.92 mmol) was heated at 110 °C for 15 min. After the mixture had cooled to room temperature, saturated aqueous sodium bicarbonate (100 mL) was added. The resulting mixture was extracted with petroleum ether (60−90 °C, 3 × 50 mL). The combined organic layer was washed successively with water (2 × 50 mL) and brine (50 mL) and then dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to give 7-*tert*-butyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (**l**) as a yellow solid (6.44 g, 81%): mp 56−58 °C; ^{1}H NMR ($CDCl_3$) δ 7.01 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 6.63 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 2.92 (s, 2H, CH_2); 2.22 (s, 3H, $PhCH_3$); 1.51 (s, 6H, $C(CH_3)_2$); 1.37 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{15}H_{22}O$ (%): C, 82.52; H, 10.16. Found: C, 82.32; H, 10.05.

Synthesis of 5-Acetyl-7-tert-butyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (m). Acetyl chloride (1.85 g, 23.48 mmol) was added dropwise to a stirred suspension of aluminum chloride (3.94 g, 29.88 mmol) in dichloromethane (40 mL) at −15 °C under N_2. After 1 h of stirring, a solution of compound **l** (4.66 g, 21.34 mmol) in dichloromethane (10 mL) was added dropwise. After stirring for 0.5 h, the reaction mixture was poured into ice−water (40 mL). The organic layer was washed with water and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on a silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 30:1) as the eluent to give 5-acetyl-7-*tert*-butyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (**m**) as a colorless crystal (3.09 g, 81%): mp 47−48 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H, Ph); 2.94 (s, 2H, CH_2); 2.55 (s, 3H, CH_3C=O); 2.41 (s, 3H, $PhCH_3$); 1.49 (s, 6H, $C(CH_3)_2$); 1.37 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{17}H_{24}O_2$ (%): C, 78.42; H, 9.29. Found: C, 78.21; H, 9.35.

Synthesis of 5-Acetyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (n). A solution of compound **m** (3.09 g, 11.87 mmol) in dichloromethane (15 mL) was added dropwise to a mixture of aluminum chloride (4.70 g, 35.60 mmol) and dichloromethane (45 mL) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was poured into hydrochloric acid (1 mol L^{-1}, 20 mL). The organic layer was washed successively with water (20 mL) and brine (20 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized from a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 30/1) to give 5-acetyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (**n**) as a white crystal (2.04 g, 84%): mp 49−51 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 6.58 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 2.97 (s, 2H, CH_2); 2.52 (s, 3H, CH_3C=O); 2.43 (s, 3H, $PhCH_3$); 1.49 (s, 6H, $C(CH_3)_2$). Anal. Calcd for $C_{13}H_{16}O_2$ (%): C, 76.44; H, 7.90. Found: C, 76.41; H, 7.89.

Synthesis of 2,2,4-Trimethyl-2,3-dihydrobenzofuran-5-carboxylic Acid (o). The procedure is the same as for preparing 2,4-dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (**g**). 5-Acetyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (**n**) (2.75 g, 13.46 mmol) was reacted with bromine (7.11 g, 44.42 mmol) and sodium hydroxide (7.11 g, 177.67 mmol) in water (10 mL) and 1,4-dioxane (25 mL) to give 2,2,4-trimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (**o**) as a white crystal (2.69 g, 97%): mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 12.45 (s, 1H, COOH); 7.99 (d, 1H, $^3J_{HH}$ = 8.5 Hz, Ph); 6.62 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 3.00 (s, 2H, CH_2); 2.52 (s, 3H, $PhCH_3$); 1.51 (s, 6H, $C(CH_3)_2$). Anal. Calcd for $C_{12}H_{14}O_3$ (%): C, 69.88; H, 6.84. Found: C, 70.00; H, 6.90.

Synthesis of N′-tert-Butyl-N-2,2,4-trimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (q). The procedure is the same as for preparing *N′-tert*-butyl-*N*-2,4-dimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (**i**). First, compound **o** (2.69 g, 13.04 mmol) was reacted with thionyl chloride (10 mL) to give compound **p**. Then compound **p** was reacted with *tert*-butylhydrazine hydrochloride (1.95 g, 15.65 mmol) and sodium hydroxide (1.13 g, 28.69 mmol) in dichloromethane (110 mL) and water (20 mL) at −15 °C to give *N′-tert*-butyl-*N*-2,2,4-trimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (**q**) as a white crystal (2.79 g, 78%): mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.97 (br, 1H, NH); 6.56 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.93 (br, 1H, NH); 2.95 (s, 2H, CH_2); 2.33 (s, 3H, $PhCH_3$); 1.44 (s, 6H, $C(CH_3)_2$); 1.16 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{16}H_{24}N_2O_2$ (%): C, 69.53; H, 8.75; N, 10.14. Found: C, 69.41; H, 8.51; N, 10.03.

General Synthetic Procedure for Target Compounds N′-tert-Butyl-N′-substituted Benzoyl-N-2,3-dihydrobenzofuran-5-carbohydrazide (Ia−Il and IIa−IIo). A solution of substituted benzoyl chloride (1.35 mmol) in dichloromethane (10 mL) was added dropwise to a stirred mixture of *N′-tert*-butyl-*N*-2,3-dihydrobenzofuran-5-carbohydrazide (**i** or **q**, 1.35 mmol), triethylamine (0.16 g, 1.54 mmol), and dichloromethane (10 mL) in an ice bath. After stirring of the reaction mixture at room temperature overnight, dichloromethane (20 mL) was added. The reaction mixture was washed successively with water (3 × 20 mL) and brine (20 mL) and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by recrystallization or column chromatography on silica gel to afford compounds **Ia−Il** and **IIa−IIo** as colorless crystals. The physical properties and elemental analyses of new compounds (**Ia−Il** and **IIa−IIo**) are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula (*16*). Evaluations were based on a percentage scale of 0−100 in which 0 = no activity and 100 = total kill.

Stomach Toxicity against Oriental Armyworm (*Mythimna separate*). The stomach toxicities of the title compounds **Ia−Il** and **IIa−IIo** against oriental armyworm were evaluated by foliar application using the reported procedure (*17−20*). For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed three times. For comparative purposes, **ANS-118** and **JS-118** were tested under the same conditions.

Toxicity against Mosquito (*Culex pipiens pallens*). The toxicities of the title compounds **Ia−Il** and **IIa−IIo** against mosquito were evaluated according to the reported procedure (*21−23*). One milliliter of different concentrated dilutions of each compounds was added to 99 mL of water to obtain different concentrations of tested solution. Then 20 fourth-instar mosquito larvaes were put into the solution. Percentage mortalities were evaluated 7−10 days after treatment. For comparative purposes, **ANS-118** and **JS-118** were tested under the same conditions.

Table 1. Physical Properties and Elemental Analyses of Compounds **Ia**−**Il** and **IIa**−**IIo**

compd	R	mp (°C)	yield (%)	elem anal. (%, calcd)		
				C	H	N
Ia	H	175−177	99	71.95 (72.11)	7.15 (7.15)	7.85 (7.64)
Ib	2-NO_2	108−109	65	64.09 (64.22)	6.07 (6.12)	10.22 (10.21)
Ic	3-NO_2	251−252	13	64.07 (64.22)	5.98 (6.12)	10.48 (10.21)
Id	4-NO_2	262−263	31	64.29 (64.22)	5.99 (6.12)	10.29 (10.21)
Ie	2-Cl	196−197	47	65.72 (65.91)	6.45 (6.29)	6.96 (6.99)
If	3-Cl	202−203	72	65.81 (65.91)	6.33 (6.29)	6.85 (6.99)
Ig	4-Cl	218−219	99	65.75 (65.91)	6.32 (6.29)	7.09 (6.99)
Ih	3-Me	211−212	76	72.40 (72.60)	7.49 (7.42)	7.47 (7.36)
Ii	3,5-Me_2	136−138	98	72.93 (73.07)	7.51 (7.66)	6.97 (7.10)
Ij	3,5-$(NO_2)_2$	134−136	12		479.1541(479.1537)[a]	
Ik	3,5-Cl_2	120−121	59	60.51 (60.70)	5.76 (5.56)	6.21 (6.43)
Il	2,4-Cl_2	164−166	91	60.51 (60.70)	5.51 (5.56)	6.31 (6.43)
IIa	H	194−196	95	72.44 (72.60)	7.20 (7.42)	7.38 (7.36)
IIb	2-NO_2	239−240	73	64.75 (64.93)	6.48 (6.40)	9.86 (9.88)
IIc	3-NO_2	256−258	27	64.65 (64.93)	6.61 (6.40)	9.87 (9.88)
IId	4-NO_2	238−239	80	64.70 (64.93)	6.19 (6.40)	9.71 (9.88)
IIe	2-Cl	184−185	67	66.59 (66.58)	6.43 (6.56)	6.76 (6.75)
IIf	3-Cl	210−211	99	66.64 (66.58)	6.45 (6.56)	6.67 (6.75)
IIg	4-Cl	230−232	80	66.39 (66.58)	6.64 (6.56)	6.74 (6.75)
IIh	2-OMe	235−236	99	70.38 (70.22)	7.11 (7.37)	6.85 (6.82)
IIi	3-OMe	169−170	47	70.38 (70.22)	7.23 (7.37)	6.62 (6.82)
IIj	4-OMe	199−200	87	70.21 (70.22)	7.22 (7.37)	6.80 (6.82)
IIk	3-Me	207−208	64	72.90 (73.07)	7.52 (7.66)	6.95 (7.10)
III	3,5-Me_2	177−179	99	73.41 (73.50)	7.82 (7.90)	6.72 (6.86)
IIm	3,5-$(NO_2)_2$	222−223	18	58.42 (58.72)	5.68 (5.57)	11.98 (11.91)
IIn	3,5-Cl_2	121−123	88	61.65 (61.47)	5.70 (5.83)	6.21 (6.23)
IIo	2,4-Cl_2	181−182	69	61.49 (61.47)	6.00 (5.83)	6.22 (6.23)

[a] The $[M + Na]^+$ value of HRMS.

Stomach Toxicity against Beet Armyworm (*Laphygma exigua* Hübner). The stomach toxicities of the title compounds **Ii** and **F** and the contrast compounds **ANS-118** and **JS-118** against beet armyworm were tested by the leaf-dip method using the reported procedure (*24, 25*). Leaf disks (5 cm × 3 cm) were cut from fresh cabbage leaves and then were dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into boxes (80 cm^3). Each dried treated leaf disk was infested with five third-instar beet armyworm larvae. Percentage mortalities were evaluated 3 days after treatment. Leaves treated with water and acetone were provided as controls. Each treatment was performed three times.

Contact Toxicity against Beet Armyworm (*L. exigua* Hübner). The contact toxicities of the title compounds **Ii** and **F** and the contrast compounds **ANS-118** and **JS-118** against beet armyworm were tested by a topical application method recommended by the FAO (*25, 26*). The compounds were dissolved in acetone to test at various concentrations. For each fourth-instar larva of beet armyworm, 1.0 μL of tested dilution was applied on the thoracic tergite with an automatic microapplicator (Robbins Scientific). After treatment, the insects were then transferred to their standard rearing conditions. Mortalities were calculated 48 and 72 h after treatment, and LC_{50} values were established. Each treatment was performed three times and acetone alone served as a control.

Contact Toxicity against Diamond-back Moth (*Plutella xylostella* L.). The contact toxicities of the title compounds **Ii** and **F** and the contrast compounds **ANS-118** and **JS-118** against diamond-back moth were tested by using an insect-dip method (*27, 28*). The compounds were dissolved in acetone and diluted with water to prepare five concentrations. Each fourth-instar larva of diamond-back moth was immersed in the above solution for 5 min. After treatment, the insects were then transferred to their standard rearing conditions at 25 ± 1 °C. Mortalities were calculated 48 and 72 h after treatment, and LC_{50} values were established. Usually, 30 insects per dose were tested, and each treatment was replicated three times; water alone served as a control.

Stomach Toxicities against Cotton Bollworm (*Helicoverpa armigera* (Hübner)). The stomach toxicities of the title compounds **Ii** and **F** and the contrast compounds **ANS-118** and **JS-118** against cotton bollworm were tested according to the leaf-dip method using the reported procedure (*29*). The compounds were dissolved in acetone to test at 1000 mg L^{-1}. Corn leaves were dipped into the test solution. After air-drying, the treated leaf disks were placed individually into boxes that had 24 holes. Each dried treated leaf disk was infested with 10 third-instar cotton bollworm larvae. Percentage mortalities were evaluated 4 days after treatment.

Contact Toxicity against Cotton Bollworm (*H. armigera* (Hübner)). The contact toxicities of the title compounds **Ii** and **F** and the contrast compounds **ANS-118** and **JS-118** against cotton bollworm were tested by topical application method using the reported procedure (*30, 31*). The compounds were dissolved in acetone to test at 1000 mg L^{-1}. For each third-instar larva of cotton bollworm, 0.5 μL of tested dilution was applied on the thoracic tergite with a microapplicator (PB600-1). After treatment, the insects were then transferred to their standard rearing conditions. Percentage mortalities were evaluated 4 days after treatment.

Stomach Toxicity against Corn Borer (*Ostrinia nubilalis*). The stomach toxicities of the title compounds **Ii** and **F** and the contrast compounds **ANS-118** and **JS-118** against corn borer were tested by the leaf-dip method. Leaf disks (about 5 cm) were cut from fresh corn leaves and then were dipped into the test solution for 3−5 s. After air-drying, the treated leaf disks were placed individually into a glass-surface vessel (7 cm). Each dried treated leaf disk was infested with 10 third-instar corn borer larvae. Percentage mortalities were evaluated 4 days after treatment. Leaves treated with acetone were provided as controls. Each treatment was performed four times. LC_{50} and LC_{95} values were established.

RESULTS AND DISCUSSION

Synthesis. The title compounds **Ia**−**Il** were synthesized as shown in **Scheme 1**. First, 3-methylphenol (**a**) was reacted with urea and *tert*-butyl alcohol in 75% H_2SO_4 to give 2-*tert*-butyl-5-methylphenol (**b**) as a initial intermediate for synthesis of the title compounds **Ia**−**Il** and **IIa**−**IIo** (*32*). 1-*tert*-Butyl-4-methyl-2-(prop-2-ynyloxy)benzene (**c**) was synthesized from compound **b** according to the literature (*11*). Compound **c** was refluxed in *N*,*N*-diethylaniline in the presence of cesium fluoride to give

Table 2. ^{1}H NMR of Compounds **Ia**−**Il** and **IIa**−**IIo**

compd	δ
Ia	7.48 (s, 1H, NH); 7.45−7.46 (m, 2H, Ph); 7.29−7.35 (m, 3H, Ph); 6.47 (d, 1H, $^3J_{HH}$ = 6.4 Hz, Ph); 6.38 (d, 1H, $^3J_{HH}$ = 6.4 Hz, Ph); 4.88−4.95 (m, 1H, CH); 3.12−3.22 (m, 1H, CH_2); 2.59−2.68 (m, 1H, CH_2); 1.96 (s, 3H, $PhCH_3$); 1.60 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ib	8.11 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 7.63 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 7.60 (s, 1H, NH); 7.47−7.53 (m, 2H, Ph); 6.36 (d, 1H,$^3J_{HH}$ = 8.3 Hz, Ph); 6.29 (d, 1H,$^3J_{HH}$ = 8.3 Hz, Ph); 4.88−4.94 (m, 1H, CH); 3.12−3.20 (m, 1H, CH_2); 2.54−2.67 (m, 1H, CH_2); 1.99 (s, 3H, $PhCH_3$); 1.63 (s, 9H, $C(CH_3)_3$); 1.41 (d, 3H, $^3J_{HH}$ = 5.8 Hz, CCH_3)
Ic	8.28 (s, 1H, NH); 8.20 (s, 1H, Ph); 7.92 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.64 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 7.52 (q, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.65 (d, 1H,$^3J_{HH}$ = 8.2 Hz, Ph); 6.40 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.89−4.95 (m, 1H, CH); 3.12−3.20 (m, 1H, CH_2); 2.59−2.66 (m, 1H, CH_2); 1.91 (s, 3H, $PhCH_3$); 1.62 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CCH_3)
Id	8.17 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph); 7.65 (d, 2H,$^3J_{HH}$ = 8.0 Hz, Ph); 7.49 (s, 1H, NH); 6.61 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.41 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.90−4.95 (m, 1H, CH); 3.14−3.20 (m, 1H, CH_2); 2.61−2.67 (m, 1H, CH_2); 1.94 (s, 3H, $PhCH_3$); 1.61 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.1 Hz, CCH_3)
Ie	7.64 (s, 1H, NH); 7.48 (d, 1H, $^3J_{HH}$ = 7.5 Hz, Ph); 7.34 (d, 1H,$^3J_{HH}$ = 7.5 Hz, Ph); 7.22−7.29 (m, 2H, Ph); 6.38 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 6.32 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.89−4.94 (m, 1H, CH); 3.14−3.21 (m, 1H, CH_2); 2.60−2.67 (m, 1H, CH_2); 2.01 (s, 3H, $PhCH_3$); 1.62 (s, 9H, $C(CH_3)_3$); 1.42 (t, 3H,$^3J_{HH}$ = 6.1 Hz, CCH_3)
If	7.50 (s, 1H, NH); 7.46 (s, 1H, Ph); 7.36 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 7.32 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 7.22 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 6.60 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.42 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.90−4.95 (m, 1H, CH); 3.15−3.22 (m, 1H, CH_2); 2.62−2.68 (m, 1H, CH_2); 1.98 (s, 3H, $PhCH_3$); 1.59 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ig	8.04 (s, 1H, NH); 7.45 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph); 7.30 (d, 2H, $^3J_{HH}$ = 8.3 Hz, Ph); 6.62 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 6.45 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.90−4.98 (m, 1H, CH); 3.17−3.23 (m, 1H, CH_2); 2.62−2.67 (m, 1H, CH_2); 1.96 (s, 3H, $PhCH_3$); 1.59 (s, 9H, $C(CH_3)_3$); 1.43 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ih	7.37 (s, NH); 7.31 (s, 1H, Ph); 7.22−7.25 (m, 1H, Ph); 7.15−7.20 (m, 2H, Ph); 6.46 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.39 (d, 1H,$^3J_{HH}$ = 8.2 Hz); 4.89−4.96 (m, 1H, CH); 3.15−3.21 (m, 1H, CH_2); 2.62−2.66 (m, 1H, CH_2); 2.32 (s, 3H, $PhCH_3$); 1.99 (s, 3H, $PhCH_3$); 1.60 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ii	7.38 (s, 1H, NH); 7.06 (s, 2H, Ph); 6.96 (s, 1H, Ph); 6.47 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 6.38 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 4.89−4.95 (m, 1H, CH); 3.14−3.20 (m, 1H, CH_2); 2.61−2.67 (m, 1H, CH_2); 2.26 (s, 6H, $PhCH_3$); 2.01 (s, 3H, $PhCH_3$); 1.59 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ij	9.00 (s, 1H, NH); 8.70 (s, 2H, Ph); 7.72 (s, 1H, Ph); 6.82 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 6.44 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 4.91−4.97 (m, 1H, CH); 3.12−3.21 (m, 1H, CH_2); 2.59−2.67 (m, 1H, CH_2); 1.92 (s, 3H, $PhCH_3$); 1.63 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ik	7.56 (s, 1H, NH); 7.35 (s, 2H, Ph); 7.32 (s, 1H, Ph); 6.75 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.46 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 4.92−4.97 (m, 1H, CH); 3.17−3.24 (m, 1H, CH_2); 2.64−2.70 (m, 1H, CH_2); 2.03 (s, 3H, $PhCH_3$); 1.58 (s, 9H, $C(CH_3)_3$); 1.44 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Il	7.62 (s, NH); 7.45 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 7.36 (s, 1H, Ph); 7.23 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 6.46 (d, 1H, $^3J_{HH}$ = 6.3 Hz, Ph); 6.38 (d, 1H, $^3J_{HH}$ = 6.4 Hz, Ph); 4.91−4.99 (m, 1H, CH); 3.17−3.23 (m, 1H, CH_2); 2.64−2.70 (m, 1H, CH_2); 2.02 (s, 3H, $PhCH_3$); 1.61 (s, 9H, $C(CH_3)_3$); 1.44 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
IIa	7.49 (s, 1H, NH); 7.47 (d, 2H, $^3J_{HH}$ = 6.0 Hz, Ph); 7.31−7.35 (m, 3H, Ph); 6.44 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.35 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.85 (s, 2H, CH_2); 1.95 (s, 3H, $PhCH_3$); 1.60 (s, 9H, $C(CH_3)_3$); 1.43 (s, 3H, CH_3); 1.42 (s, 3H, CH_3)
IIb	8.12 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 7.64 (d, 1H, $^3J_{HH}$ = 4.0 Hz, Ph); 7.62 (s, 1H, NH); 7.54−7.60 (m, 1H, Ph); 7.47−7.51 (m, 1H, Ph); 6.33 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 6.27 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 2.84 (s, 2H, CH_2); 1.99 (s, 3H, $PhCH_3$); 1.64 (s, 9H, $C(CH_3)_3$); 1.43 (s, 3H, CCH_3); 1.42 (s, 3H, CCH_3)
IIc	8.31 (s, 1H, NH); 8.21 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 7.93 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 7.58 (s, 1H, Ph); 7.53 (q, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 6.66 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.39 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 2.84 (s, 2H, CH_2); 1.90 (s, 3H, $PhCH_3$); 1.62 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IId	8.18 (d, 2H, $^3J_{HH}$ = 8.8 Hz, Ph); 7.67 (d, 2H, $^3J_{HH}$ = 6.9 Hz, Ph); 7.48 (s, 1H, NH); 6.62 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.40 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.85 (s, 2H, CH_2); 1.93 (s, 3H, $PhCH_3$); 1.61 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIe	7.64 (s, 1H, NH); 7.48 (d, 1H, $^3J_{HH}$ = 7.5 Hz, Ph); 7.34 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.21−7.29 (m, 2H, Ph); 6.36 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.31 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.85 (s, 2H, CH_2); 2.00 (s, 3H, $PhCH_3$); 1.62 (s, 9H, $C(CH_3)_3$); 1.43 (s, 3H, CCH_3); 1.42 (s, 3H, CCH_3)
IIf	7.70 (s, 1H, NH); 7.43 (s, 1H, Ph); 7.34 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.30 (d, 1H, $^3J_{HH}$ = 7.4 Hz, Ph); 7.22 (q, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 6.59 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.37 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.85 (s, 2H, CH_2); 1.96 (s, 3H, $PhCH_3$); 1.57 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIg	7.50 (s, 1H, NH); 7.45 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph); 7.28 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph); 6.61 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.41 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.87 (s, 2H, CH_2); 1.94 (s, 3H, $PhCH_3$); 1.58 (s, 9H, $C(CH_3)_3$); 1.44 (s, 6H, $C(CH_3)_2$)
IIh	7.87 (s, 1H, NH); 7.44 (d, 1H, $^3J_{HH}$ = 7.4 Hz, Ph); 7.30 (q, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 6.96 (q, 1H, $^3J_{HH}$ = 7.5 Hz); 6.86 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 6.38 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph); 6.34 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 2.84 (s, 2H, CH_2); 1.90 (s, 3H, $PhCH_3$); 1.62 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIi	7.33 (s, 1H, NH); 7.22 (q, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 7.04 (s, 1H, Ph); 7.02 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 6.89 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 6.49 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.37 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 3.77 (s, 3H, OCH_3); 2.85 (s, 2H, CH_2); 1.99 (s, 3H, $PhCH_3$); 1.59 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIj	7.52 (s, 1H, NH); 7.48 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ph); 6.82 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ph); 6.62 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.40 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 3.78 (s, 3H, OCH_3); 2.86 (s, 2H, CH_2); 1.96 (s, 3H, $PhCH_3$); 1.58 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIk	7.36 (s, 1H, NH); 7.31 (s, 1H, Ph); 7.13−7.23 (m, 3H, Ph); 6.46 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.36 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 2.85 (s, 2H, CH_2); 2.31 (s, 3H, $PhCH_3$); 1.97 (s, 3H, $PhCH_3$); 1.60 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIl	8.04 (s, 1H, NH); 7.00 (s, 2H, Ph); 6.92 (s, 1H, Ph); 6.46 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 6.28 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.82 (s, 2H, CH_2); 2.19 (s, 6H, $Ph(CH_3)_2$); 1.95 (s, 3H, $PhCH_3$); 1.53 (s, 9H, $C(CH_3)_3$); 1.41 (s, 6H, $C(CH_3)_2$)
IIm	9.00 (s, 1H, NH); 8.71 (s, 2H, Ph); 7.70 (s, 1H, Ph); 6.82 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 6.42 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.84 (s, 2H, CH_2); 1.91 (s, 3H, $PhCH_3$); 1.63 (s, 9H, $C(CH_3)_3$); 1.43 (s, 6H, $C(CH_3)_2$)
IIn	7.46 (s, 1H, NH); 7.37 (d, 2H, $^3J_{HCl}$ = 1.9 Hz, Ph); 7.33 (d, 1H, $^3J_{HCl}$ = 1.9 Hz, Ph); 6.77 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.45 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.88 (s, 2H, CH_2); 2.02 (s, 3H, $PhCH_3$); 1.58 (s, 9H, $C(CH_3)_3$); 1.45 (s, 3H, CH_3); 1.44 (s, 3H, CH_3)
IIo	7.63 (s, 1H, NH); 7.44 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 7.36 (s, 1H, Ph); 7.23 (d, 1H,$^3J_{HH}$ = 8.2 Hz, Ph); 6.50 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 6.42 (d, 1H, $^3J_{HH}$ = 8.2 Hz, Ph); 2.87 (s, 2H, CH_2); 2.00 (s, 3H, $PhCH_3$); 1.60 (s, 9H, $C(CH_3)_3$); 1.44 (s, 6H, $C(CH_3)_2$)

Table 3. Toxicities (Percent) against Oriental Armyworm and Mosquito of Compounds **Ia**−**Il** and **IIa**−**IIo** and Contrast Compounds **ANS-118** and **JS-118**

	stomach toxicities against oriental armyworm at							toxicities against mosquito at		
compd	200 mg kg^{-1}	100 mg kg^{-1}	50 mg kg^{-1}	25 mg kg^{-1}	10 mg kg^{-1}	5 mg kg^{-1}	2.5 mg kg^{-1}	2 mg kg^{-1}	1 mg kg^{-1}	0.5 mg kg^{-1}
Ia	100	100	90	80	0			0	0	
Ib	100	100	60	20	0			30	20	0
Ic	20	0						20	10	0
Id	60	0						40	0	
Ie	100	100	100	40	0			30	20	10
If	100	100	80	30	10	0		60	20	10
Ig	100	100	100	90	0			0	0	
Ih	100	100	100	100	100	15	0	0	0	
Ii	**100**	**100**	**100**	**100**	**95**	**80**	20	80	10	10
Ij	20	0						30	20	10
Ik	100	100	100	90	90	10	0	80	50	0
Il	100	100	100	90	0			0	0	
IIa	40	10	0					50	30	10
IIb	50	0						40	20	10
IIc	10	0						30	20	10
IId	10	0						20	0	
IIe	60	0						70	20	0
IIf	80	10	0					10	0	
IIg	90	10	0					60	10	0
IIh	0	0						20	10	0
IIi	100	30	20	0				40	30	10
IIj	60	0						10	0	
IIk	100	90	30	0				50	10	10
IIl	100	100	90	20	0			70	0	
IIm	40	0						30	20	10
IIn	60	0						30	20	10
IIo	90	10	0					50	0	
ANS-118	100	100	100	100	100	100	80	100	80	10
JS-118	100	100	100	100	100	100	95	100	100	50

7-*tert*-butyl-2,4-dimethylbenzofuran (**d**) as a new intermediate according to the literature method (*33*); at the same time, 8-*tert*-butyl-5-methyl-2*H*-chromene was obtained as byproduct. We found that acetic acid is a better solvent than other protic solvents such as methanol and ethanol when compound **d** was reduced to 7-*tert*-butyl-2,4-dimethyl-2,3-dihydrobenzofuran (**e**); this is due to the conjugation between furan and benzene to induce greater double-bond stabilization. Compound **e** was reacted with aluminum chloride in dichloromethane to provide 5-acetyl-2,4-dimethyl-2,3-dihydrolbenzofuran (**f**) in one step. This method is easier than the literature method (*11*). Compound **f** was treated with bromine and sodium hydroxide to give the new intermediate 2,4-dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (**g**) in 91% yield. Subsequent chlorination with thionyl chloride and further reaction with *tert*-butylhydrazine hydrochloride provided the new intermediate *N*′-*tert*-butyl-*N*-2,4-dimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (**i**) in 93% yield. Finally, compound **i** was reacted with substituted benzoyl chlorides to give the title compounds **Ia**−**Il**.

The title compounds **IIa**−**IIo** were synthesized as shown in **Scheme 2**. 2-*tert*-Butyl-5-methylphenol (**b**) was reacted with 3-chloro-2-methylprop-1-ene to give the new intermediate, 1-*tert*-butyl-4-methyl-2-(2-methylallyloxy)benzene (**j**) according to the literature method (*34*). At first, we attempted to reflux compound **j** in *N*,*N*-diethylaniline to yield 7-*tert*-butyl-2,2,4-trimethyl-2,3-dihydrobenzofuran (**l**). However, we obtained 6-*tert*-butyl-3-methyl-2-(2-methylallyl)phenol (**k**) as a main product, and compound **l** was obtained only as byproduct. Then, according to the literature method (*35*), we heated **k** at 110 °C for 15 min in the presence of sulfuric acid to give compound **l** in good yield. These new intermediates **m**, **n**, **o**, **q**, and the title compounds **IIa**−**IIo**, were synthesized according to the same procedure as in **Scheme 1**.

The physical properties and elemental analyses of the title compounds **Ia**−**Il** and **IIa**−**IIo** are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

Bioassay. We have reported the larvicidal activity against oriental armyworm of compound **F** (LC_{50} = 2.25 mg L^{-1}) (*14*). To compare insecticidal spectrum and insecticidal level between compound **F** and the commercialized compound **ANS-118** and further study influence of substitutents on the benzene rings of benzoheterocyle moiety on insecticidal activity, we tested their larvicidal activities against other lepidopteral insects as shown below.

Stomach Toxicity against Oriental Armyworm (Mythimna separata Walker). **Table 3** shows the stomach toxicities of the title compounds **Ia**−**Il** and **IIa**−**IIo** and contrast compounds **ANS-118** and **JS-118** against oriental armyworm. The results indicate that compounds **Ia**−**Il** exhibit higher stomach toxicities against oriental armyworm than compounds **IIa**−**IIo**. From **Table 3**, we can also see that the larvicidal activities against oriental armyworm of the compounds **Ia**−**Il** and **IIa**−**IIo** varied drastically, depending upon the types and patterns of substitution on the benzene. Among monosubstitued derivatives, compared to nonsubstituted compound (**Ia** and **IIa**), methoxy (**IIi**) or methyl (**Ih**, **IIk**) at meta is most prominent in increasing activity, and nitro at meta (**Ic**, **IIc**) or para (**Id**, **IId**) can drastically decrease activity. Compared with nonsubstituted compound **IIa**, chloro substitued at meta (**IIf**) or para (**IIg**) can increase the activity, but the activity of 3-chloro (**If**) or 4-chloro (**Ig**) derivatives has no obvious improvement to nonsubstituted compound **Ia**. Among multisubstituted compounds, 3,5-dimethyl (**Ii**) and 3,5-dichloro (**Ik**) derivatives are most prominent in increasing activity, and 3,5-dinitro (**Ij**) derivative has lower activity than nonsubstituted compound (**Ia**). However, compared with

Table 4. Stomach Toxicities (72 h) against Beet Armyworm of Compounds **Ii** and **F** and Contrast Compounds **ANS-118** and **JS-118**

compd	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
Ii	$y = 3.5776 + 1.2906x$	12.7	1
F	$y = 3.5251 + 1.9937x$	5.5	**2.3**
ANS-118	$y = 3.6598 + 1.6786x$	6.3	2.0
JS-118	$y = 3.7029 + 1.8640x$	5.0	2.5

Table 5. Contact Toxicities (48 and 72 h) against Beet Armyworm of Compounds **Ii** and **F** and Contrast Compounds **ANS-118** and **JS-118**

compd	time (h)	$y = a + bx$	LD_{50} (mg/L)	toxic ratio
Ii	48	$y = 2.8008 + 0.9648x$	190.3	1
F		$y = -0.1439 + 4.1538x$	17.3	**11**
ANS-118		$y = 2.8928 + 1.4291x$	29.8	6.4
JS-118		$y = 3.3303 + 0.9406x$	59.6	3.2
Ii	72	$y = 2.6114 + 1.3865x$	52.8	1
F		$y = 2.4583 + 2.3763x$	11.7	**4.5**
ANS-118		$y = 2.7896 + 1.8860x$	14.9	3.5
JS-118		$y = 2.8875 + 1.9192x$	12.6	4.2

nonsubstituted compound (**IIa**), 3,5-dimethyl (**IIl**) and 2,4-dichloro (**IIo**) derivatives are most prominent in increasing activity and 3,5-dinitro (**IIm**) and 3,5-dichloro (**IIn**) derivatives have no obvious effect on the activity. From the above discussion, we conclude that different benzoheterocyclic analogues of diacylhydrazide have different structure−activity relationships according to diversification of substitution on the benzene, and 3,5-dimethyl derivatives **Ii** and **Il** have higher activity than other componds **Ia**−**Il** and **IIa**−**IIo**, respectively. Among them, compound **Ii** (80% mortality at 5 mg L^{-1}) stood out as better than other compounds but is lower than compounds **ANS-118** and **JS-118** against oriental armyworm larvae.

Toxicity against Mosquito (C. pipiens pallens). The title compounds **Ia**−**Il** and **IIa**−**IIo** show moderate activities against mosquito larvae as shown in **Table 3**. They show almost the same disciplines of structure−activity relationship as mentioned above for oriental armyworm larvae.

Stomach Toxicity against Beet Armyworm (L. exigua Hübner). **Table 4** shows the stomach toxicities of compounds **Ii** and **F** and **ANS-118** and **JS-118** against beet armyworm. LC_{50} is the median lethal concentration. The results indicate that the toxicity of compound **Ii** is lower than that of **ANS-118** and **JS-118**, but compound **F** has the same activity as **ANS-118** and **JS-118**.

Contact Toxicity against Beet Armyworm (L. exigua Hübner). **Table 5** shows the contact toxicities of compounds **Ii** and **F** and **ANS-118** and **JS-118** against beet armyworm. LD_{50} is the median lethal dose. The results indicate that the toxicity of compound **Ii** is lower than that of **ANS-118** and **JS-118** at 48 and 72 h after teatment, but compound **F** has a higher contact activity than compound **ANS-118** (1.7 times at 48 h and 1.3 times at 72 h, respectively) and **JS-118** (3.4 times at 48 h and 1.1 times at 72 h, respectively).

Contact Toxicities (48 and 72 h) against Diamond-back Moth (P. xylostella L.). **Table 6** shows the contact toxicities of compounds **Ii** and**F** and **ANS-118** and **JS-118** against diamond-back moth. The results indicate that compounds **Ii** and **F** have higher activity than **ANS-118** and **JS-118**. At 48 h after treatment, the contact activities of compounds **Ii** and **F** were 2 times that of **ANS-118** and 3 times that of **JS-118**, respectively.

Table 6. Contact Toxicities (48 and 72h) against Diamond-back Moth of Compounds **Ii** and **F** and Contrast Compounds **ANS-118** and **JS-118**

compd	time (h)	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
Ii	48	$y = 2.0417 + 1.4133x$	123.9	**3.0**
F		$y = 0.3993 + 2.2393x$	113.4	**3.3**
ANS-118		$y = 1.0496 + 1.6649x$	235.9	1.6
JS-118		$y = 1.9568 + 1.1838x$	372.2	1
Ii	72	$y = 2.2938 + 1.4166x$	81.4	**3.7**
F		$y = 0.7782 + 2.2821x$	70.8	**4.3**
ANS-118		$y = 3.1342 + 0.8929x$	122.9	2.5
JS-118		$y = 2.7788 + 0.8944x$	304.4	1

Table 7. Stomach Toxicities and Contact Toxicities against Cotton Bollworm at 1000 mg L^{-1} of Compounds **Ii** and **F** and Contrast Compounds **ANS-118** and **JS-118**

compd	stomach toxicities (%)	contact toxicities (%)
Ii	**70**	50
F	**80**	40
ANS-118	65	60
JS-118	60	60

Table 8. Stomach Toxicities (4 Days) against Corn Borer of Compounds **Ii** and **F** and Contrast Compounds **ANS-118** and **JS-118**

compd	$y = a + bx$	LC_{50} (mg/L)	LC_{95} (mg/L)
Ii	$y = 1.8041 + 1.9885x$	40.48	271.89
F	$y = 1.6757 + 1.9052x$	55.57	405.65
ANS-118	$y = 2.6107 + 1.8818x$	18.61	139.25
JS-118	$y = 1.9605 + 2.1591x$	25.57	147.78

At 72 h after treatment, the contact activities of compounds **Ii** and **F** were about 1.5 times that of **ANS-118** and about 4 times that of **JS-118**, respectively.

Stomach Toxicities and Contact Toxicities against Cotton Bollworm (H. armigera (Hübner)). **Table 7** shows the stomach toxicities of compounds **Ii** and **F** and **ANS-118** and **JS-118** against cotton bollworm. The results indicate that compounds **Ii** and **F** have a little higher stomach activity than **ANS-118** and **JS-118**. Contact activity of compounds **Ii** and **F** is a little lower than those of **ANS-118** and **JS-118**.

Stomach Toxicity against Corn Borer (O. nubilalis). **Table 8** shows the stomach toxicities of compounds **Ii** and **F** and **ANS-118** and **JS-118** against corn borer. LC_{50} is the median lethal concentration, and LC_{95} is the 95% lethal concentration. The values of LC_{50} and LC_{95} indicate that the toxicity of compound **Ii** is higher than that of compound **F**, but the activities of compounds **Ii** and **F** are lower than those of **ANS-118** and **JS-118**.

From **Table 3**, we know that compound **Ii** (95% mortality at 10 mg L^{-1}) has higher activity against oriental armyworm than compound **Ill** (90% mortality at 50 mg L^{-1}) but has lower activity than **ANS-118** (100% mortality at 5 mg L^{-1}) and **JS-118** (95% mortality at 2.5 mg L^{-1}). The stomach toxicity (72 h) and contact toxicity (48 and 72 h) against beet armyworm of compound **Ii** are obviously lower than that of **ANS-118** and **JS-118** as shown in **Tables 4** and **5**, respectivly. However, compound **Ii** has 2−3 times higer contact toxicity (48 and 72 h) against diamond-back moth than **ANS-118** and **JS-118** as shown in **Table 6**. All of these results indicate that different heterocycles of benzoheterocyclic diacylhydrazide not only influence the larvicidal activities strongly but also are very sensitive to the insecticidal action modes for different Lepidopteran larvicidal insects. The differentiation between compound **F** and **ANS-**

118 is that the methyl of **ANS-118** was substituted by chloride in **F**. However, compound **F** has almost equal stomach toxicity (72 h) against beet armyworm as **ANS-118** (**Table 4**) and obviously higher contact toxicity (48 and 72 h) against beet armyworm and diamond-back moth (48 and 72 h) than **ANS-118** (**Tables 5** and **6**). These results indicate that larvicidal activities are very sensitive to the different types of substituents on the benzene rings of the heterocyclic moieties. Most importantly, they also indicate that different types of substitutents on the benzene rings of benzoheterocycle moiety are also sensitive to the insecticidal action modes for different Lepidopteran larvicidal insects.

In summary, two series of novel *N*′-*tert*-butyl-*N*′-substituted benzoyl-*N*-2,3-dihydrobenzofuran-5-carbohydrazide derivatives were synthesized, and their activities and different insecticidal action modes against larvae of different insect species were studied in depth. Among them, *N*′-*tert*-butyl-*N*′-(3,5-dimethylbenzoyl)-*N*-2,4-dimethyl-2,3-dihydrobenzofuran-5-carbohydrazide (**Ii**) stood out as the best compound with high activity against oriental armyworm; this indicates that types and patterns of substitution on the benzene influence the larvicidal activities strongly and 3,5-dimethyl is the most efficient substituent for benzoheterocyclic diacylhydrazine. The contact activities against diamond-back moth and stomach toxicities against cotton bollworm of compound **Ii** and *N*′-*tert*-butyl-*N*′-(3,5-dimethylbenzoyl)-*N*-5-chloro-6-chromanecarbohydrazide (**F**) are higher than those of **ANS-118** and **JS-118**. Compound **F** has higher contact toxicity against beet armyworm than **ANS-118** and **JS-118**. All of these results indicate that different heterocycles and substitutents on the benzene rings of the benzoheterocyle moiety not only influence the larvicidal activities strongly but also are very sensitive to the insecticidal action modes for different Lepidopteran larvicidal insects.

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