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Synthesis, Crystal Structures, Insecticidal Activities, and Structure−Activity Relationships of Novel *N′-tert*-Butyl-*N′*-substituted-benzoyl-*N*-[di(octa)hydro]benzofuran{(2,3-dihydro)benzo[1,3]([1,4])dioxine}carbohydrazide Derivatives

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Several series of novel *N′-tert*-butyl-*N′*-substituted-benzoyl-*N*-[di(octa)hydro]benzofuran{(2,3-dihydro)benzo[1,3]([1,4])dioxine}carbohydrazide derivatives **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, and **Va**−**Vc** were designed and synthesized. Their structures were confirmed by ^{1}H NMR spectra, HRMS, and X-ray single-crystal structures. The larvicidal activities against oriental armyworm, beet armyworm, diamond-back moth, and corn borer of these compounds were evaluated and contrasted with those of **RH-2485**, **JS-118**, and **ANS-118**. The larvicidal activities against oriental armyworm indicate that monosubstituent or multisubstituents and the substituting group position cannot promote increasing activities and that the cycle region in the general structure of **IIa**−**IIg** is much more sensitive to activity than that in the general structure of **Ia** and **Ib**. The space volume of the A ring in the structure of **Va** cannot be too large; if it is, the activity will be decreased significantly. Stomach toxicities against beet armyworm, diamond-back moth, and corn borer of compounds **Ia**, **Ib** and **IIg** indicate that benzoheterocyclic analogues of *N-tert*-butyl-*N,N′*-diacylhydrazines show significant selectivities to different lepidopterous pests.

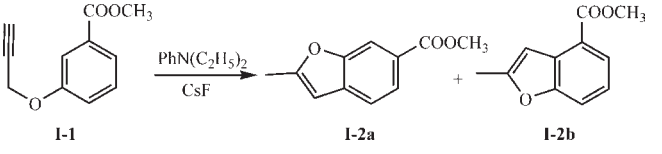
KEYWORDS: Benzofuran; benzoheterocycle; diacylhydrazine; crystal structure; insecticidal activity; SAR; insect growth regulator

INTRODUCTION

N-tert-Butyl-*N*,*N′*-diacylhydrazines as a new class of chemically and mechanistically novel insect growth regulators (IGR) was discovered by Rohm and Haas Co. in the mid-1980s (*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**) was the first to be commercialized as a leptidopteran-specific insecticide under the trade names Mimic, Confirm, and Romdan in several countries (*9*). Methoxyfenozide (**RH-2485**), which was first announced in 1996, is the most efficacious member of the diacylhydrazine class. It shows higher activities against lepidopterous larvae such as *Spodoptera exigua* (Hübner), *Prodenia litura* (Fabricius), *Ostrinia nubilalis* (Hübner) and *Choristoneura fumiferana* than **RH-5992** (*9*−*12*). Recently, it has been reported that benzoheterocyclic, especially (dihydro)benzofuran, (2,3-dihydro)benzo[1,3]([1,4])dioxine, analogues and chroman of *N′*-benzoyl-*N*-(*tert*-butyl)benzohydrazide showed high insecticidal activities against lepidoptera insects (*13*−*19*). Among them, *N′-tert*-butyl-*N′*-(3,5-dimethylbenzoyl)-*N*-(2,3-dihydro-2-methyl)benzofurancarbohydrazide (**JS-118**), which has better activities for *Plutella xylostella* Linnaeus, *O. nubilalis*, and *Mythimna separate* than **RH-5992**, has been developed by Jiangsu Institute of Agricultural Chemicals, People's Republic of China (*20*, *21*), and **ANS-118**, a chroman 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 (*22*).

Encouraged by the above reports, especially the high activities and structures of **RH-2485**, **JS-118**, and **ANS-118**, we designed and synthesized several series of novel *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-[di(octa)hydro]benzofuran{(2,3-dihydro)benzo-[1,3]([1,4])dioxine}carbohydrazide derivatives, **Ia** and **Ib**, **IIa**−**IIg**, **IIIa** and **IIIb**, and **Va**−**Vc** as shown in **Schemes 1**−**8**. In this paper, we report the synthesis, structures, insecticidal activities, and structure−activity relationships (SARs) of compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, and **Va**−**Vc**. For comparative purposes,

Scheme 1. Synthetic Route for the Key Intermediates **I-2a** and **I-2b**



I-1 I-2a I-2b

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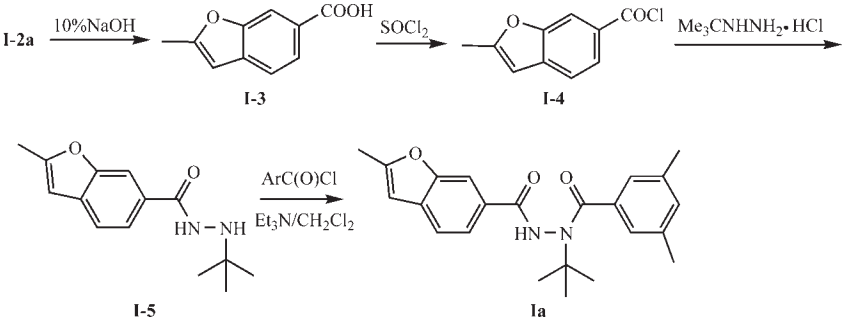
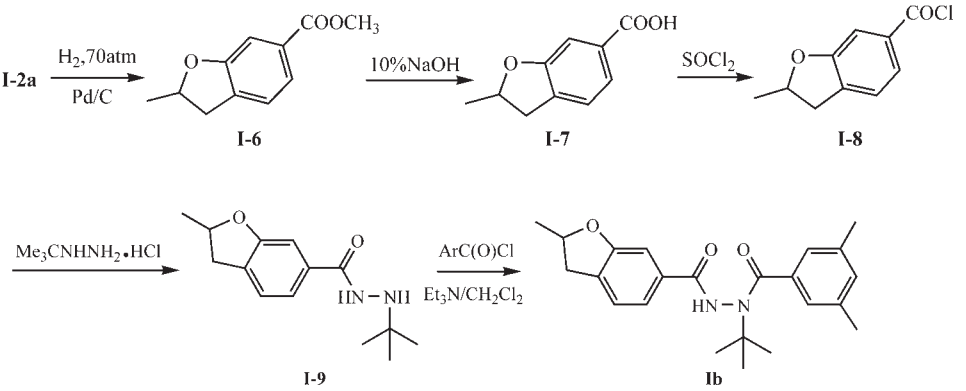
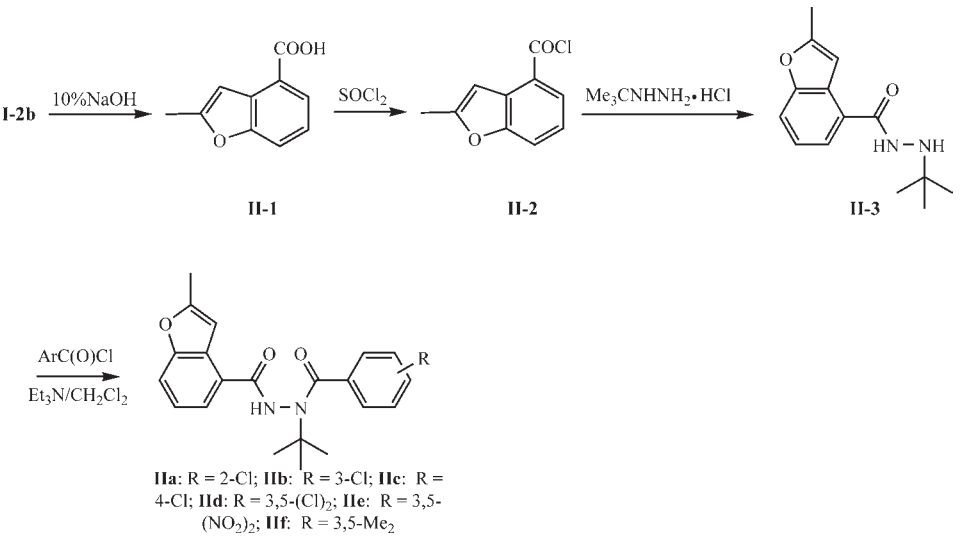
Scheme 2. Synthetic Route for Compound **Ia**



Scheme 3. Synthetic Route for Compound **Ib**



Scheme 4. General Synthetic Route for Compounds **IIa**−**IIf**



IIa: R = 2-Cl; **IIb**: R = 3-Cl; **IIc**: R = 4-Cl; **IId**: R = 3,5-$(Cl)_2$; **IIe**: R = 3,5-$(NO_2)_2$; **IIf**: R = 3,5-Me_2

insecticidal activities and SARs of dihydrochromancarbohydrazide derivatives **IVa**, the synthesis of which has been reported by us recently (*23*), are presented for the first time.

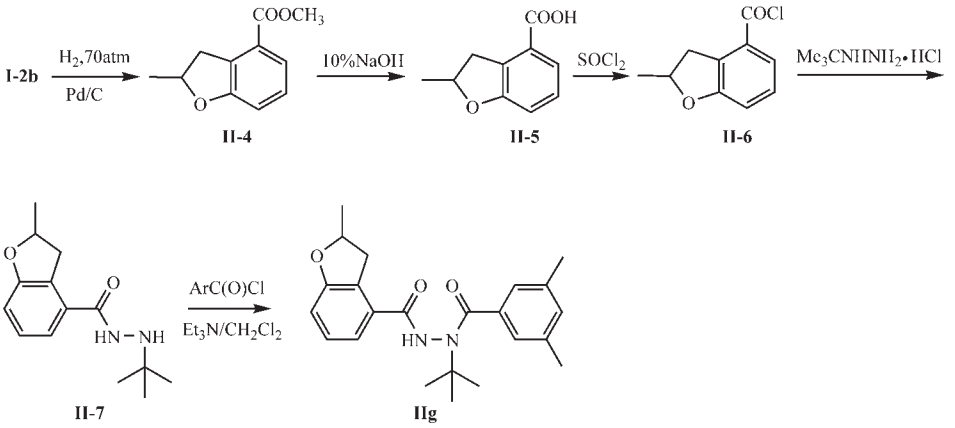
MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Bruker AV400 spectrometer or 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. High-resolution mass spectrometry (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. X-ray single-crystal diffraction was determined on a Bruker SMART 1000 X-ray single-crystal diffraction analyzer. Yields were not optimized.

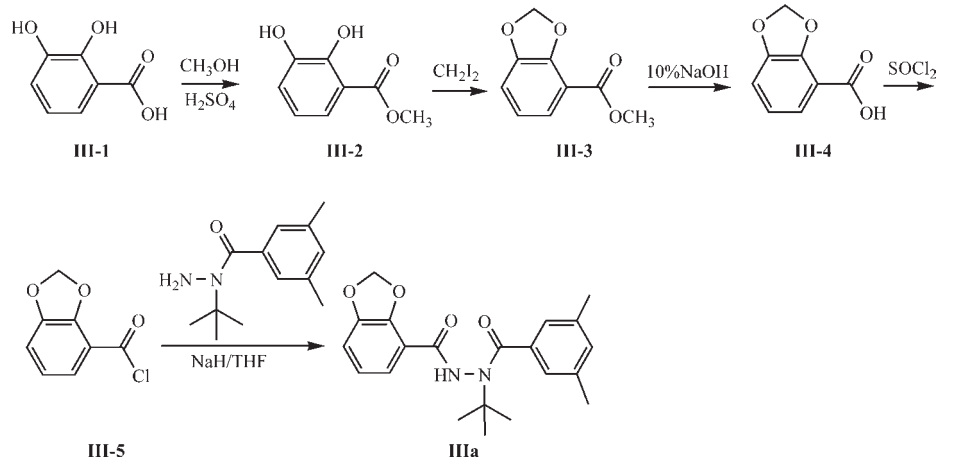
General Synthesis. All anhydrous solvents were dried and purified by standard techniques just before use.

Synthesis of Methyl 2-Methylbenzofuran-6-carboxylate (***I-2a***) *and Methyl 2-Methylbenzofuran-4-carboxylate* (***I-2b***). A mixture of methyl 3-(prop-2-ynyloxy)benzoate (**I-1**) (9.31 g, 48.95 mmol), cesium fluoride (0.99 g, 6.5 mmol), and *N*,*N*-diethylaniline (100 mL) was refluxed for 8 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 × 50 mL). The organic layer was washed successively with water (50 mL) and brine (50 mL) and then dried over anhydrous sodium sulfate. After the solvent had been removed under vacuum, 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 = 50:1) as the eluent to give methyl 2-methylbenzofuran-6-carboxylate (**I-2a**) and methyl 2-methylbenzofuran-4-carboxylate (**I-2b**).

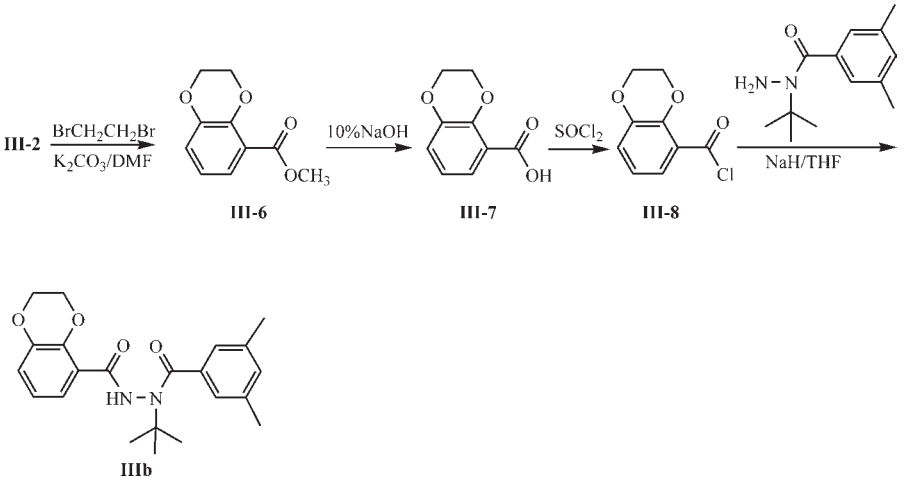
Scheme 5. Synthetic Route for Compound **IIg**



Scheme 6. Synthetic Route for Compound **IIIa**



Scheme 7. Synthetic Route for Compound **IIIb**



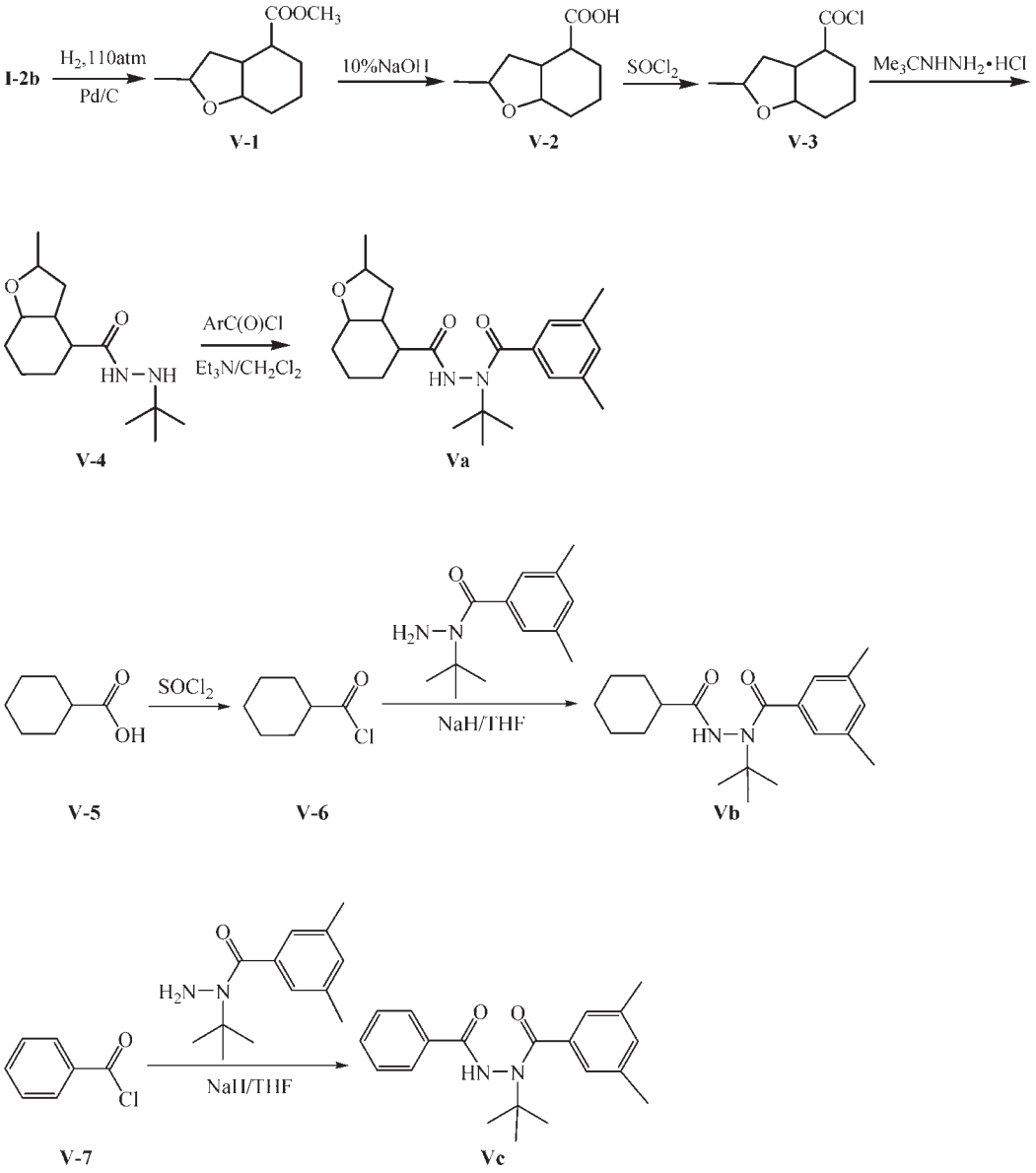
Methyl 2-methylbenzofuran-6-carboxylate (**I-2a**): colorless oil (0.25 g, 3%) [lit. (*24*) bp 110−120 °C/4 mmHg]; ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H, Ph); 7.48 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 7.23 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.42 (s, 1H, CH); 3.93 (s, 3H, CH_3); 2.49 (s, 1H, CH_3).

Methyl 2-methylbenzofuran-4-carboxylate (**I-2b**): light yellow crystal (1.97 g, 21%); mp 21−22 °C [lit. (*24*) bp 120−130 °C/4 mmHg]; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 7.57 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 7.24 (t, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 6.93 (s, 1H, CH); 3.96 (s, 3H, CH_3); 2.50 (t, 1H, $^4J_{HH}$ = 0.92 Hz, CH_3).

Synthesis of 2-Methylbenzofuran-6-carboxylic Acid (***I-3***). A mixture of compound **I-2a** (2.36 g, 12.39 mmol) and sodium hydroxide solution (15 mL, 10%) was refluxed for 3 h. After cooling to room temperature, the reaction mixture was neutralized with hydrochloric acid (1 mol L^{-1}) and then extracted with dichloromethane (3 × 20 mL). The organic layer was washed successively with water (30 mL) and brine (30 mL) and then dried over anhydrous sodium sulfate. After the solvent had been removed under vacuum, the residue was recrystallized from ethyl acetate to give compound **I-3** as a white crystal (2.06 g, 94%): mp 176−177 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H, Ph); 7.98 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 7.52 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 6.46 (s, 1H, CH); 2.53 (s, 3H, CH_3).

Synthesis of N′-tert-Butyl-2-methylbenzofuran-6-carbohydrazide (***I-5***). A mixture of compound **I-3** (1.88 g, 10.67 mmol) and thionyl chloride

Scheme 8. General Synthetic Route for Compounds **Va**−**Vc**



(2 mL) was refluxed for 2 h. After excess thionyl chloride had been removed under reduced pressure, the residue was dissolved in dichloromethane (6 mL). The resulting solution was added dropwise to a stirred mixture of *tert*-butylhydrazine hydrochloride (1.59 g, 12.80 mmol), sodium hydroxide (0.94 g, 23.47 mmol), dichloromethane (75 mL), and water (10 mL) at −15 °C. After stirring overnight at room temperature, the organic layer was washed successively with water (3 × 25 mL) and brine (25 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give compound **I-5** as white solid (1.25 g, 48%): mp 159−160 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H, Ph); 7.57 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.49 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 6.41 (s, 1H, CH); 2.48 (s, 3H, CH_3); 1.70 (s, 9H, $C(CH_3)_3$).

Synthesis of Methyl 2,3-Dihydro-2-methylbenzofuran-6-carboxylate (***I-6***). A mixture of compound **I-2a** (1.03 g, 5.42 mmol), acetic acid (20 mL), and 10% palladium on activated carbon (0.32 g, 54% in water) was vigorously stirred under 70 atm of hydrogen at 70 °C for 2 days. The reaction mixture was filtered and removed under vacuum. Then the residue was purified by column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 50:1) as the eluent to give compound **I-6** as a colorless oil (0.15 g, 14%): ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.36 (s, 1H, Ph); 7.18 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 4.92−5.00 (m, 1H, CH); 3.88 (s, 3H, OCH_3); 3.30−3.37 (m, 1H, CH_2); 2.80−2.86 (m, 1H, CH_2); 1.46 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CH_3).

Synthesis of 2,3-Dihydro-2-methylbenzofuran-6-carboxylic Acid (***I-7***). The procedure is the same as for the preparation of 2-methylbenzofuran-6-carboxylic acid (**I-3**). Compound **I-6** (0.15 g, 0.78 mmol) was reacted with sodium hydroxide solution (5 mL, 10%) to give compound **I-7** as a white crystal (0.11 g, 79%)L mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.45 (s, 1H, Ph); 7.23 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 4.94−5.05 (m, 1H, CH); 3.33−3.41 (m, 1H, CH_2); 2.83−2.91(m, 1H, CH_2); 1.49 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CH_3).

Synthesis of N′-tert-Butyl-2,3-dihydro-2-methylbenzofuran-6-carbohydrazide (***I-9***). The procedure is the same as for the preparation of *N′-tert*-butyl-2-methylbenzofuran-6-carbohydrazide (**I-5**). First, compound **I-7** (0.11 g, 0.62 mmol) was reacted with thionyl chloride (2 mL) to give compound **I-8**. Then compound **I-8** was reacted with *tert*-butylhydrazine hydrochloride (0.09 g, 0.74 mmol) and sodium hydroxide (0.05 g, 1.36 mmol) in dichloromethane (20 mL) and water (3 mL) at −15 °C to give compound **I-9** as a white crystal (0.08 g, 53%): mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.20 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.11 (s, 1H, Ph); 4.92−5.04 (m, 1H, CH); 3.31−3.39 (m, 1H, CH_2); 2.80−2.88 (m, 1H, CH_2); 1.47 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CH_3); 1.15 (s, 9H, $C(CH_3)_3$).

Synthesis of 2-Methylbenzofuran-4-carboxylic Acid (***II-1***). The procedure is the same as for the preparation of 2-methylbenzofuran-6-carboxylic acid (**I-3**). Compound **I-2b** (0.90 g, 4.7 mmol) was reacted with sodium hydroxide solution (10 mL, 10%) to give compound **II-1** as a white crystal (0.63 g, 76%): mp 189−190 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1H,

$^3J_{HH}$ = 7.7 Hz, Ph); 7.64 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.29 (t, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.07 (s, 1H, CH); 2.53 (s, 3H, CH_3).

Synthesis of N′-tert-Butyl-N-2-methylbenzofuran-4-carbohydrazide (***II-3***). The procedure is the same as for the preparation of *N′-tert*-butyl-2-methylbenzofuran-6-carbohydrazide (**I-5**). First, compound **II-1** (0.60 g, 3.4 mmol) was reacted with thionyl chloride (3 mL) to give compound **II-2**. Then compound **II-2** was reacted with *tert*-butylhydrazine hydrochloride (0.52 g, 4.1 mmol) and sodium hydroxide (0.22 g, 7.5 mmol) in dichloromethane (30 mL) and water (4 mL) at −15 °C to give compound **II-3** as a white solid (0.64 g, 72%): mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 7.51 (d, 1H, $^3J_{HH}$ = 7.2 Hz, Ph); 7.24 (t, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.82 (s, 1H, CH); 2.50 (s, 3H, CH_3); 1.19 (s, 9H, $C(CH_3)_3$).

Synthesis of Methyl 2,3-Dihydro-2-methylbenzofuran-4-carboxylate (***II-4***). The procedure is the same as for the preparation of 2,3-dihydro-2-methylbenzofuran-6-carboxylate (**I-6**). Compound **I-4a** (1.53 g, 8.05 mmol) was reacted with 70 atm of hydrogen at room temperature with 10% palladium on activated carbon (0.2 g, 54% in water) as catalyst and acetic acid (20 mL) as solvent for 24 h to give compound **II-4** as a colorless oil (0.38 g, 24%): ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 7.16 (t, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 6.92 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 4.91−5.00 (m, 1H, CH); 3.89 (s, 3H, OCH_3); 3.63−3.70 (m, 1H, CH_2); 3.04−3.15 (m, 1H, CH_2); 1.47 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CH_3).

Synthesis of 2,3-Dihydro-2-methylbenzofuran-4-carboxylic Acid (***II-5***). The procedure is the same as for the preparation of 2-methylbenzofuran-6-carboxylic acid (**I-3**). Methyl 2,3-dihydro-2-methylbenzofuran-4-carboxylate (**II-4**) (0.38 g, 1.97 mmol) was reacted with sodium hydroxide solution (5 mL, 10%) to give compound **II-5** as a white crystal (0.30 g, 86%): mp 165−166 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 7.22 (t, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 6.98 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 4.96−5.02 (m, 1H, CH); 3.69−3.75 (m, 1H, CH_2); 3.14−3.21 (m, 1H, CH_2); 1.49 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CH_3).

Synthesis of N′-tert-Butyl-N-2,3-dihydro-2-methylbenzofuran-4-carbohydrazide (***II-7***). The procedure is the same as for the preparation of *N′*-tert-butyl-2-methylbenzofuran-6-carbohydrazide (**I-5**). First, compound **II-5** (0.30 g, 1.68 mmol) was reacted with thionyl chloride (3 mL) to give compound **II-6**. Then compound **II-6** was reacted with *tert*-butylhydrazine hydrochloride (0.26 g, 2.02 mmol) and sodium hydroxide (0.18 g, 5.42 mmol) in dichloromethane (20 mL) and water (5 mL) at −15 °C to give compound **II-7** as a white crystal (0.35 g, 83%): mp 69−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.17 (t, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 7.04 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 6.88 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 4.99−5.02 (m, 1H, CH); 3.57−3.64 (m, 1H, CH_2); 3.04−3.11 (m, 1H, CH_2); 1.48 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CH_3); 1.16 (s, 9H, $C(CH_3)_3$).

Synthesis of Methyl 2,3-Dihydroxybenzoate (***III-2***). A mixture of 2,3-dihydroxybenzoic acid **III-1** (15.00 g, 97.33 mmol), methanol (150 mL), and sulfuric acid (2.00 g) was refluxed for 10 h. After the solvent had been removed under vacuum, the residue was crystallized by petroleum ether (60−90 °C) and ethyl acetate (v/v = 3:1) to give compound **III-2** as a pink solid (14.50 g, yield = 88%): mp 79−80 °C [lit. (*25*) mp 83−85 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H, OH), 7.38 (d, 1H, $^3J_{HH}$ = 8.1 Hz, ArH), 7.12 (d, 1H, $^3J_{HH}$ = 7.4 Hz, ArH), 6.81 (t, 1H, $^3J_{HH}$ = 8.0 Hz, ArH), 5.65 (s, 1H, OH), 3.97 (s, 3H, OCH_3).

Synthesis of Methyl Benzo[1,3]dioxole-4-carboxylate (***III-3***). After a mixture of 2,3-dihydroxybenzoate **III-2** (2.00 g, 11.89 mmol), potassium carbonate (4.92 g, 35.67 mmol), *N*,*N*-dimethylformamide (15 mL) had been stirred at room temperature for 12 h, a solution of diiodomethane (3.50 g, 13.08 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise. After 5 h of stirring at 60 °C, water (25 mL) was added to the reaction mixture, followed by extraction with ethyl acetate (3 × 25 mL). The organic layer was washed with water (2 × 25 mL) and then dried over anhydrous sodium sulfate. After the solvent had been removed under vacuum, the residue was purified by column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 3:1) as the eluent to give compound **III-3** as a white crystal (0.65 g, 30%): mp 66−68 °C [lit. (*26*) mp 71−73 °C]; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1H, $^3J_{HH}$ = 8.2 Hz, ArH); 6.96 (d, 1H, $^3J_{HH}$ = 7.7 Hz, ArH); 6.85 (t, 1H, $^3J_{HH}$ = 8.0 Hz, ArH); 6.09 (s, 2H, CH_2); 3.91 (s, 3H, CH_3).

Synthesis of Benzo[1,3]dioxole-4-carboxylic Acid (***III-4***). The procedure is the same as for the preparation of 2-methylbenzofuran-6-carboxylic acid (**I-3**). Methyl benzo[1,3]dioxole-4-carboxylate **III-3** (0.50 g, 2.78 mmol) was reacted with sodium hydroxide solution (10 mL, 10%) to give compound **III-4** as a white solid (0.42 g, 91%), distilled at 180 °C [lit. (*27*) mp 227−228 °C]; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1H, $^3J_{HH}$ = 8.2 Hz, ArH); 7.03 (d, 1H, $^3J_{HH}$ = 7.7 Hz, ArH); 6.90 (t, 1H, $^3J_{HH}$ = 8.0 Hz, ArH); 6.14 (s, 2H, CH_2).

Synthesis of Methyl 2,3-Dihydrobenzo[1,4]dioxine-5-carboxylate (***III-6***). After a mixture of 2,3-dihydroxybenzoate **III-2** (2.00 g, 11.89 mmol), potassium carbonate (4.92 g, 35.67 mmol), and *N*,*N*-dimethylformamide (15 mL) had been stirred at room temperature for 2 h, a solution of 1,2-dibromoethane (2.46 g, 13.08 mmol) in *N*,*N*-dimethylformamide (5 mL) was added dropwise. After 5h of refluxing, water (30 mL) was added to the reaction mixture, followed by extraction with ethyl acetate (3 × 50 mL). The organic layer was washed successively with water (50 mL) and brine (50 mL) and then dried over anhydrous sodium sulfate. After the solvent had been removed under vacuum to give compound **III-6** as a white crystal (0.42 g, yield = 18%): mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, 1H, $^3J_{HH}$ = 7.8 Hz, ArH), 7.00 (d, 1H, $^3J_{HH}$ = 7.8 Hz, ArH), 6.84 (t, 1H, $^3J_{HH}$ = 7.8 Hz, ArH), 4.35−4.36 (m, 2H, OCH_2), 4.27−4.29 (m, 2H, OCH_2), 3.87 (s, 3H, OCH_3).

Synthesis of 2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic Acid (***III-7***). The procedure is the same as for the preparation of 2-methylbenzofuran-6-carboxylic acid (**I-3**). Methyl 2,3-dihydrobenzo[1,4]dioxine-5-carboxylate **III-6** (0.42 g, 2.16 mmol) was reacted with sodium hydroxide solution (10 mL, 10%) to give compound **III-7** as a white solid (0.38 g, yield = 97%): mp 202−204 °C [lit. (*28*) mp 195−196 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (br s, 1H, COOH), 7.71 (d, 1H, $^3J_{HH}$ = 7.9 Hz, ArH), 7.11 (d, 1H, $^3J_{HH}$ = 8.0 Hz, ArH), 6.98 (t, 1H, $^3J_{HH}$ = 7.9 Hz, ArH), 4.50−4.52 (m, 2H, OCH_2), 4.36−4.38 (m, 2H, OCH_2).

Synthesis of Methyl Octahydro-2-methylbenzofuran-4-carboxylate (***V-1***). The procedure is the same as for the preparation of 2,3-dihydro-2-methylbenzofuran-6-carboxylate (**I-6**). Compound **I-2b** (7.00 g, 36.80 mmol) was reacted with 110 atm of hydrogen at 70 °C with 10% palladium on activated carbon (4.0 g, 54% in water) as catalyst and acetic acid (100 mL) as solvent for 4 days to give compound **V-1** as a colorless oil (1.48 g, 24%): ^{1}H NMR ($CDCl_3$) δ 4.04−4.13 (m, 1H, CH); 3.66 (s, 3H, OCH_3); 2.66−2.77 (m, 1H, CH); 2.18−2.30 (m, 1H, CH); 1.30−1.97 (m, 9H, CH); 1.21 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CH_3).

Synthesis of Octahydro-2-methylbenzofuran-4-carboxylic Acid (***V-2***). The procedure is the same as for the preparation of 2-methylbenzofuran-6-carboxylic acid (**I-3**). Compound **V-1** (1.48 g, 7.46 mmol) was reacted with sodium hydroxide solution (30 mL, 10%) to give compound **V-2** as a colorless oil (1.18 g, 86%): ^{1}H NMR ($CDCl_3$) δ 10.54 (br, 1H, COOH); 4.02−4.17 (m, 1H, CH); 2.70−2.78 (m, 1H, CH); 2.22−2.33 (m, 1H, CH); 1.30−2.06 (m, 9H, CH); 1.23 (d, 3H, $^3J_{HH}$ = 6.1 Hz, CH_3).

Synthesis of N′-tert-Butyl-N-octahydro-2-methylbenzofuran-4-carbohydrazide (***V-4***). The procedure is the same as for the preparation of *N′-tert*-butyl-2-methylbenzofuran-6-carbohydrazide (**I-5**). First, compound **V-2** (1.18 g, 6.41 mmol) was reacted with thionyl chloride (2 mL) to give compound **V-3**. Then compound **V-3** was reacted with *tert*-butylhydrazine hydrochloride (0.96 g, 7.69 mmol) and sodium hydroxide (0.57 g, 14.1 mmol) in dichloromethane (50 mL) and water (5 mL) at −15 °C to give compound **V-4** as a white crystal (0.70 g, 43%): mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 3.98−4.14 (m, 1H, CH); 3.50 (br, 1H, NH); 2.65−2.73 (m, 1H, CH); 2.30−2.38 (m, 1H, CH); 1.45−1.88 (m, 9H, CH); 1.30 (d, 3H, $^3J_{HH}$ = 6.1 Hz, CH_3); 1.09 (s, 9H, $C(CH_3)_3$).

General Synthetic Procedure for Target Compounds *N′-tert*-Butyl-*N′*-substituted-benzoyl-*N*-[di(octa)hydro]benzofurancarbohydrazide (Ia, Ib, IIa−IIg, and Va). The solution of substituted-benzoyl chloride (0.61 mmol) in dichloromethane (10 mL) was added dropwise to a stirred mixture of *N′-tert*-butyl-*N*-carbohydrazide (**I-5**, **I-9**, **II-3**, **II-7**, and **V-4**, 0.61 mmol), triethylamine (0.07 g, 0.67 mmol), and dichloromethane (10 mL) in an ice bath. After stirring at room temperature overnight, dichloromethane (20 mL) was added. The reaction mixture was washed successively with water (3 × 15 mL) and brine (15 mL) and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by recrystallization or column chromatography on a silica gel to afford the target compounds **Ia**, **Ib**, **IIa**−**IIg**, and **Va** as colorless crystals. The physical properties and HRMS of these compounds (**Ia**, **Ib**, **IIa**−**IIg**, and **Va**) are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

General Synthetic Procedure for Target Compounds *N′*-*tert*-Butyl-*N′*-3,5-dimethylbenzoyl-*N*-(2,3-dihydro)benzo[1,3]([1,4])dioxinecarbohydrazide Derivatives (IIIa and IIIb). A mixture of compound **III-4** or **III-7** (0.60 mmol) and thionyl chloride (2 mL) was refluxed for 2 h. After excess thionyl chloride had been removed under reduced pressure, the residue was dissolved in tetrahydrofuran (5 mL). The resulting solution was added dropwise to a stirred mixture of *N*-*tert*-butyl-3,5-dimethylbenzohydrazide (0.60 mmol), sodium hydride (0.66 mmol), and tetrahydrofuran (20 mL). After 3 h of stirring, the reaction solution was filtered and then was removed under vacuum. The residue was purified by recrystallization or column chromatography on silica gel to afford the target compounds **IIIa** and **IIIb**. The physical properties and HRMS of compounds **IIIa** and **IIIb** are listed in **Table 1**, and their ^{1}H NMR date are listed in **Table 2**.

General Synthetic Procedure for Target Compounds *N′*-*tert*-Butyl-*N′*-3,5-dimethylbenzoyl-*N*-cyclohexane(benzo)carbohydrazide Derivatives (Vb and Vc). The procedure is the same as for the preparation of target compounds **IIIa** and **IIIb**. First, compound **V-5** (0.78 mmol) was reacted with thionyl chloride (2 mL) to give compound **V-6**. Then compound **V-6** or **V-7** was reacted with *N*-*tert*-butyl-3,5-dimethylbenzohydrazide (0.78 mmol) and sodium hydride (0.86 mmol) in tetrahydrofuran (20 mL) to give target compounds **Vb** and **Vc**. The physical properties and HRMS of compounds **Vb** and **Vc** are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

Table 1. Physical Properties and HRMS of Compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, **Va**, and **Vb**

compd	mp (°C)	yield (%)	HRMS (calcd)
Ia	218−220[a]	64	401.1829 (401.1836)[b]
Ib	218−219	92	403.1988 (403.1992)[b]
IIa	180−181	26	407.1125 (407.1133)[b]
IIb	180−181	34	407.1125 (407.1133)[b]
IIc	229−230	56	407.1127 (407.1133)[b]
IId	173−174	34	441.0738 (441.0743)[b]
IIe	201−202	37	463.1217 (463.1224)[b]
IIf	175−176	77	377.1868 (377.1871)[c]
IIg	221−222	50	403.1986 (403.1992)[b]
IIIa	173−174	86	391.1630 (363.1628)[b]
IIIb	222−223[d]	88	405.1781 (405.1785)[b]
Va	277−278	13	373.1520 (373.1523)[b]
Vb	227−228	69	353.2205 (353.2199)[b]
Vc	209−211[e]	77	347.1733 (347.1730)[b]

[a] Literature (*33*), 204−205 °C. [b] The $[M + Na]^+$ value of HRMS. [c] The $[M - H]^-$ value of HRMS. [d] Literature (*19*), 207−209 °C. [e] Literature (*34*), 205−206 °C.

X-ray Crystallographic Study on Compounds IIf and Va. The crystal structures of compounds **IIf** and **Va** were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). All caculations were refined anisotropically. All hydrogen atoms were located from a difference Fourier map and were placed at calculated positions and were included in the refinements in the riding mode with isotropic thermal parameters.

Crystallographic parameters of compound **IIf**: $a = 25.510(5)$ Å, $b = 9.855(2)$ Å, $c = 17.693(4)$ Å, $\alpha = 90°$, $\beta = 109.59(3)°$, $\gamma = 90°$, $V = 4190.8(15)$ Å^3, $Z = 8$, $D_x = 1.200$ mg m^{-3}, $F(000) = 1616$, $T = 113(2)$ K, $2.23° \leq \theta \leq 25.02°$, final R factor, $R_1 = 0.0532$, $\omega R_2 = 0.1432$.

Crystallographic parameters of compound **Va**: $a = 9.974(2)$ Å, $b = 12.166(2)$ Å, $c = 17.499(4)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2123.4(7)$ Å^3, $Z = 4$, $D_x = 1.206$ mg m^{-3}, $F(000) = 836$, $T = 113(2)$ K, $2.04° \leq \theta \leq 25.02°$, final R factor, $R_1 = 0.0738$, $\omega R_2 = 0.1425$.

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. 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*) *and Corn Borer* (*Ostrinia nubilalis*). The stomach toxicities of the title compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, **IVa**, and **Va**−**Vc** and contrast compounds **RH-2485**, **ANS-118**, and **JS-118** against oriental armyworm and corn borer were tested according to the leaf-dip method using the reported procedure (*29*). 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 oriental armyworm or corn borer larvae. Percentage mortalities were evaluated 4 days after treatment. Leaves treated with acetone were provided as controls. Each treatment was performed three times. The insecticidal activity is summarized in **Tables 3** and **5**.

Stomach Toxicity against Beet Armyworm (*Laphygma exigua Hübner*) *and Diamond-back Moth* (*Plutella xylostella L.*). The stomach toxicities of the title compounds **Ia**, **Ib**, **IIf**, **IIg**, and **IIIa** and the contrast compounds **RH-2485**, **ANS-118**, and **JS-118** against beet armyworm and diamond-back moth were tested by the leaf-dip method using the reported procedure (*30*, *31*). Leaf disks (5 cm × 3 cm) were cut from fresh cabbage

Table 2. ^{1}H NMR of Compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, **Va**, and **Vb**

compd	δ
Ia	8.83 (s, 1H, NH); 7.22 (s, 1H, Ph); 7.11 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.04 (s, 2H, Ph); 7.03 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 6.82 (s, 1H, Ph); 6.23 (s, 1H, CH); 2.39 (s, 3H, CH_3); 2.12 (s, 6H $(CH_3)_2$); 1.58 (s, 9H, $C(CH_3)_3$)
Ib	7.68 (s, 1H, NH); 7.08 (s, 1H, Ph); 7.05 (s, 2H, Ph); 6.91 (s, 1H, Ph); 6.82 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 6.71 (d, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 4.89−4.96 (m, 1H, CH); 3.25−3.31 (m, 1H, CH_2); 2.74−2.80 (m, 1H, CH_2); 2.23 (s, 6H, $(CH_3)_2$); 1.57 (s, 9H, $C(CH_3)_3$); 1.42 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3)
IIa	8.01 (s, 1H, NH); 7.47 (d, 1H, $^3J_{HH}$ = 8.7 Hz, Ph); 7.45 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 7.30 (t, 1H, $^3J_{HH}$ = 4.4 Hz, Ph); 7.18 (t, 2H, $^3J_{HH}$ = 4.7 Hz, Ph); 7.08 (t, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 6.90 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 6.50 (s, 1H, CH); 2.43 (s, 3H, CH_3); 1.64 (s, 9H, $C(CH_3)_3$)
IIb	7.75 (s, 1H, NH); 7.51 (s, 1H, Ph); 7.47 (d, 1H, $^3J_{HH}$ = 6.9 Hz, Ph); 7.38 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.07−7.20 (m, 4H, Ph); 6.37 (s, 1H, CH); 2.44 (s, 3H, CH_3); 1.61 (s, 9H, $C(CH_3)_3$)
IIc	7.75 (s, 1H, NH); 7.48 (d, 1H, $^3J_{HH}$ = 8.6 Hz, Ph); 7.46 (d, 2H, $^3J_{HH}$ = 8.5 Hz, Ph); 7.25 (d, 2H, $^3J_{HH}$ = 9.3 Hz, Ph); 7.13 (t, 1H, $^3J_{HH}$ = 7.7 Hz, Ph); 7.05 (d, 1H, $^3J_{HH}$ = 7.5 Hz, Ph); 6.30 (s, 1H, CH); 2.44 (s, 3H, CH_3); 1.61 (s, 9H, $C(CH_3)_3$)
IId	8.19 (s, 1H, NH); 7.45 (d, 1H, $^3J_{HH}$ = 7.5 Hz, Ph); 7.35 (d, 2H, $^4J_{HH}$ = 1.8 Hz, Ph); 7.22 (d, 1H, $^3J_{HH}$ = 1.8 Hz, Ph); 7.10 (d, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.07 (t 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 6.44 (s, 1H, CH); 2.43 (s, 3H, CH_3); 1.60 (s, 9H, $C(CH_3)_3$)
IIe	8.91 (t, 1H, $^4J_{HH}$ = 2.0 Hz, Ph); 8.73 (d, 2H, $^4J_{HH}$ = 2.0 Hz, Ph); 8.03 (s, 1H, NH); 7.49 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.18 (d, 1H, $^3J_{HH}$ = 7.3 Hz, Ph); 7.12 (t, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 6.58 (s, 1H, CH); 2.44 (s, 3H, CH_3); 1.66 (s, 9H, $C(CH_3)_3$)
IIf	8.01 (s, 1H, NH); 7.41 (d, 1H, $^3J_{HH}$ = 7.3 Hz, Ph); 7.06 (s, 2H, Ph); 7.00−7.04 (m, 2H, Ph); 7.11 (s, 1H, Ph); 6.27 (s, 1H, CH); 2.40 (s, 3H, CH_3); 2.18 (s, 6H $(CH_3)_2$); 1.60 (s, 9H, $C(CH_3)_3$)
IIg	7.67 (s, 1H, NH); 7.06 (d, 1H, $^3J_{HH}$ = 8.5 Hz, Ph); 7.05 (s, 2H, Ph); 6.91 (s, 1H, Ph); 6.79 (t, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 6.70 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 4.89−4.96 (m, 1H, CH); 3.25−3.31 (m, 1H, CH_2); 2.74−2.80 (m, 1H, CH_2); 2.23 (s, 6H, $(CH_3)_2$); 1.57 (s, 9H, $C(CH_3)_3$); 1.42 (d, 3H, $^3J_{HH}$ = 6.0 Hz, CH_3)
IIIa	8.50 (s, 1H, NH); 7.37 (d, 1H, $^3J_{HH}$ = 7.8 Hz, ArH); 7.07 (s, 2H, ArH); 6.08 (s, 1H, CH_2); 5.95 (s, 1H, CH_2); 2.20 (s, 6H, $(CH_3)_2$); 1.57 (s, 9H, $C(CH_3)_3$)
IIIb	8.94 (s, 1H, NH); 7.46 (d, $^3J_{HH}$ = 7.8 Hz, 1H, ArH); 7.08 (s, 2H, ArH); 6.96 (d, $^3J_{HH}$ = 7.8 Hz, 1H, ArH); 6.89 (s, 1H, ArH); 6.86 (t, $^3J_{HH}$ = 7.9 Hz, 1H, ArH); 4.20−4.37 (m, 4H, OCH_2); 2.22 (s, 6H, $(CH_3)_2$); 1.59 (s, 9H, $C(CH_3)_3$)
Va	7.59 (s, 1H, NH); 7.27 (s, 2H, Ph); 7.03 (s, 1H, Ph); 3.62−3.74 (m, 1H, CH); 2.26 (s, 6H, $(CH_3)_2$); 2.21−2.23 (m, 1H, CH); 2.05−2.12 (m, 1H, CH); 1.57−1.72 (m, 5H, CH); 1.52 (s, 9H, $C(CH_3)_3$); 1.18−1.41 (m, 4H, CH); 1.16 (d, 3H, $^3J_{HH}$ = 4.1 Hz, CH_3)
Vb	7.27 (s, 1H, ArH); 6.96 (s, 2H, ArH); 2.27 (s, 6H, $(CH_3)_2$); 1.56−1.78 (m, 5H, CH); 1.50 (s, 9H, $C(CH_3)_3$); 1.03−1.32 (m, 6H, CH)
Vc	8.05 (s, 1H, NH); 7.24−7.44 (m, 5H, ArH); 7.05 (s, 2H, ArH); 6.90 (s, 1H, ArH); 2.20 (s, 6H, $(CH_3)_2$); 1.58 (s, 9H, $C(CH_3)_3$)

Table 3. Selected Bond Lengths, Angles, and Torsion Angles of Target Compound **IIf**

selected bond	length (Å)	selected angle	length (deg)	selected torsion angle	torsion angle (deg)
O(1)−C(5)	1.375(2)	C(5)−O(1)−C(2)	106.09(15)	C(10)−N(1)−N(2)−C(15)	81.30(19)
O(1)−C(2)	1.392(3)	C(10)−N(1)−N(2)	119.45(13)	C(10)−N(1)−N(2)−C(11)	−83.32(19)
O(2)−C(10)	1.219(2)	C(15)−N(2)−N(1)	117.07(14)	C(5)−O(1)−C(2)−C(3)	0.0(3)
O(3)−C(15)	1.2357(19)	C(15)−N(2)−C(11)	123.37(13)	C(5)−O(1)−C(2)−C(1)	−179.7(2)
N(1)−C(10)	1.369(2)	N(1)−N(2)−C(11)	117.60(13)	O(1)−C(2)−C(3)−C(4)	−0.4(3)
N(1)−N(2)	1.3937(18)	O(2)−C(10)−N(1)	121.61(15)	N(2)−N(1)−C(10)−O(2)	−12.1(3)
N(1)−H(1)	0.896(9)	N(1)−C(10)−C(9)	115.41(14)	N(2)−N(1)−C(10)−C(9)	166.88(15)
N(2)−C(15)	1.356(2)	O(3)−C(15)−N(2)	121.74(17)	N(1)−N(2)−C(15)−O(3)	−169.64(14)
N(2)−C(11)	1.512(2)	O(3)−C(15)−C(16)	119.02(15)	C(11)−N(2)−C(15)−O(3)	−6.0(2)
C(2)−C(3)	1.345(3)	N(2)−C(15)−C(16)	119.21(14)	N(1)−N(2)−C(15)−C(16)	12.6(2)

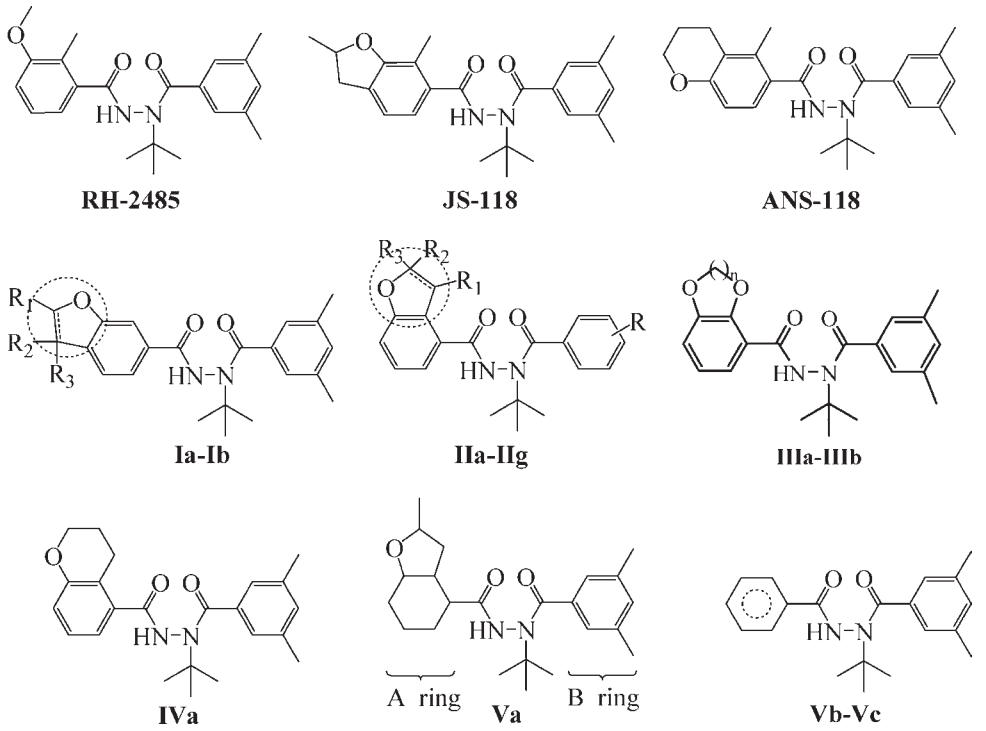


Figure 1. Chemical structures of target compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, **IVa**, and **Va**−**Vc** and contrast compounds **RH-2485**, **JS-118**, and **ANS-118**.

leaves and then dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into boxes (80 cm). Each dried treated leaf disk was infested with 10 third-instar beet armyworm or 10 second-instar diamond-back moth 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. The insecticidal activity is summarized in **Tables 4** and **5**.

RESULTS AND DISCUSSION

Synthesis. The target compounds **Ia**, **Ib**, **IIa**−**IIg**, and **Va** were synthesized as shown in **Schemes 1**−**5** and **8**. They were prepared from the key intermediates **I-2a** and **I-2b**, which were synthesized as shown in **Scheme 1**. Methyl 3-(prop-2-ynyloxy)benzoate (**I-1**) was refluxed in *N*,*N*-diethylaniline with cesium fluoride as catalyst to give the key intermediates **I-2a** and **I-2b** through Claisen rearrangement. Compound **I-3** was obtained by hydrolysis of ester **I-2a** and then reacted with thionyl chloride to successfully produce the corresponding acyl chloride **I-4**, and its subsequent reaction with *tert*-butylhydrazine hydrochloride yielded *N*′-*tert*-butyl-*N*-2-methylbenzofuran-6-carbohydrazide (**I-5**, **Scheme 2**).

Just as shown in **Schemes 3** and **5**, the double bond of the benzofuran in intermediates **I-2a** and **I-2b** can be reduced under 70 atm of hydrogen using Pd/C as catalyst and acetic acid as solvent to give intermediates **I-6** and **II-4**, respectively, whereas the benzofuran derivatives of intermediate **I-2b** can be reduced to octahydrobenzofuran derivatives **V-1** at 110 atm of hydrogen as shown in **Scheme 8**. The intermediates **I-7**, **II-1**, **II-5**, and **V-2** were obtained by hydrolysis of corresponding esters **I-6**, **I-2b**, **II-4**, and **V-1** and then reacted with thionyl chloride to successfully produce the corresponding acyl chlorides **I-8**, **II-2**, **II-6**, and **V-3**, and their subsequent reaction with *tert*-butylhydrazine hydrochloride yielded monocarbohydrazides **I-9**, **II-3**, **II-7**, and **V-4** respectively. Finally, the target compounds **Ia**, **Ib**, **IIa**−**IIg**, and **Va** (**Figure 1**) were synthesized by the reaction of various substituted benzoylchlorides with different intermediates **I-5**, **I-9**, **II-3**, **II-7**, and **V-4** in dichloromethane using triethylamine as proton scavenger.

In **Schemes 6** and **7**, 2,3-dihydroxybenzoic acid **III-1** reacted with methanol to give methyl 2,3-dihydroxybenzoate **III-2** and then reacted with diiodomethane or 1,2-dibromoethane to give methyl benzo[1,3]dioxole-4-carboxylate **III-3** or 2,3-dihydrobenzo[1,4]dioxine-5-carboxylate **III-6**, respectively. Methyl benzo-[1,3]dioxole-4-carboxylic acid **III-4** and 2,3-dihydrobenzo-[1,4]dioxine-5-carboxylic acid **III-7** were obtained by hydrolysis of corresponding esters **III-3** and **III-6** and then reacted with thionyl chloride to successfully produce the corresponding acyl chlorides **III-5** and **III-8**. Finally, the target compounds **IIIa** and

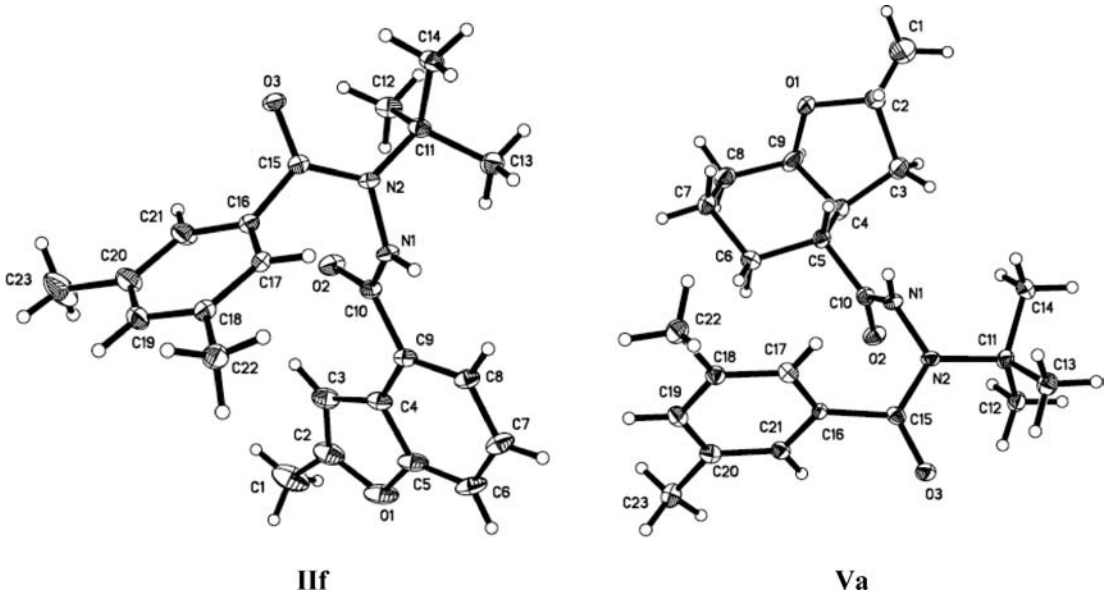


Figure 2. X-ray single-crystal structures of target compounds **IIf** and **Va** with labeling of selected atoms. Hydrogen atoms are drawn as circles with small radii.

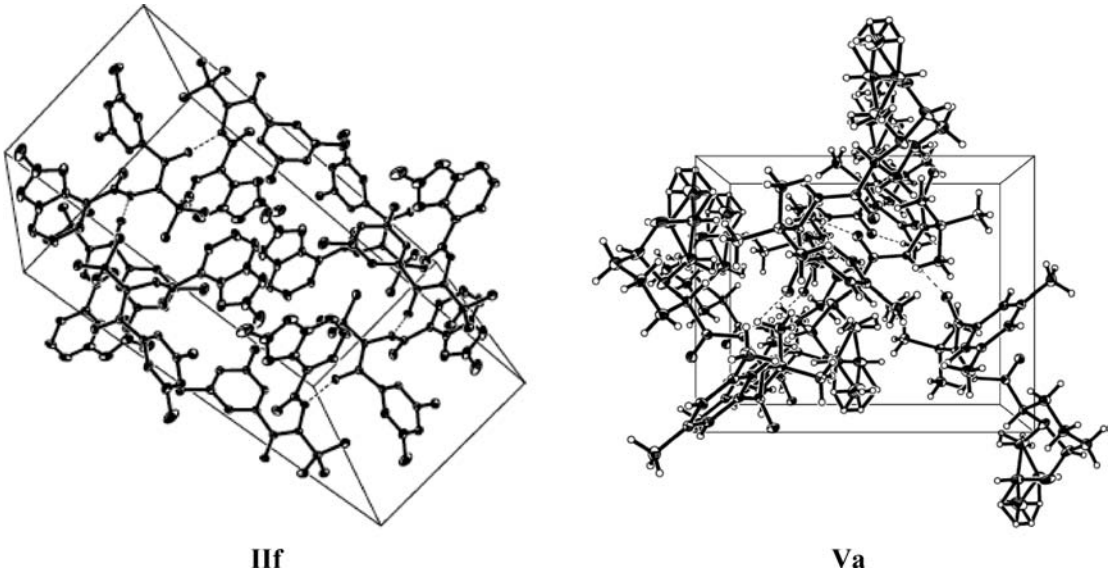


Figure 3. Packing diagrams of target compounds **IIf** and **Va**.

IIIb were synthesized by the reaction of 3,5-dimethylbenzoylchloride with intermediates **III-5** and **III-8** in tetrahydrofuran using sodium hydride as proton scavenger.

Crystal Structure Analysis. Compound **IIf** was recrystallized from isopropyl alcohol, and compound **Va** was recrystallized from isopropyl alcohol and dichloromethane (v/v = 1:1) to give colorless crystals suitable for X-ray single-crystal diffraction. X-ray single-crystal structures of compounds **IIf** and **Va** are shown in **Figure 2**. Packing diagrams of target compounds **IIf** and **Va** are shown in **Figure 3**. Selected bond lengths, angles, and torsion angles of target compounds **IIf** and **Va** are listed in **Tables 3** and **4**, respectively.

It could seen from the X-ray single-crystal analysis of compound **IIf** that it consists of one benzene ring, one benzofuran ring, and one *tert*-butyl, and these structure fragments are connected through the diacylhydrazine bridge. The 2-CH_3 and the benzofuran ring of **IIf** are coplanar, and the bond length of C(2)−C(3) [1.345(3) Å] is shorter than normal C−C (1.54 Å) and is consistent with normal C═C (1.34 Å). It also could be seen from the X-ray single-crystal analysis of compound **Va** that the molecule consists of one benzene ring, one octahydrobenzofuran ring, and one *tert*-butyl. They are connected through the diacylhydrazine bridge. The octahydrobenzofuran ring of **Va** is significantly not coplanar. Among the octahydrobenzofuran ring, the cyclohexane ring is in a chair conformation and the C(4)−C(5) and C(7)−C(8) are coplanar; the tetrahydrofuran ring is in an envelope conformation, and C(9)−O(1)−C(2)−C(3) is coplanar. The torsion angle of C(9)−O(1)−C(2)−C(3) is −1.6(7)°, and the bond length of C(2)−C(3) [1.646(10) Å] is significantly longer than normal C═C (1.34 Å) but is almost consistent with normal C−C (1.54 Å). Comparing the crystal structure of compounds **IIf** and **Va**, we can see that the three-dimensional space volume of the octahydrobenzofuran ring of **Va** is significantly larger than that of the benzofuran ring of **IIf**.

Bioassay. *Stomach Toxicity against Oriental Armyworm* (*M. separata Walker*). **Table 5** shows the stomach toxicities of the target compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, **IVa**, **Va**, and **Vb** and contrast compounds **RH-2485**, **JS-118**, and **ANS-118** against oriental armyworm. Although we have reported that the 3,5-dimethyl substituent is an efficient substituent in diacylhydrazines (*32*),

Table 4. Selected Bond Lengths, Angles, and Torsion Angles of Target Compound **Va**

selected bond	length (Å)	selected angle	length (deg)	selected torsion angle	torsion angle (deg)
O(1)−C(9)	1.412(6)	O(1)−C(9)−C(4)	106.2(4)	C(10)−N(1)−N(2)−C(15)	−78.4(5)
O(1)−C(2)	1.525(10)	O(1)−C(9)−C(8)	110.4(4)	C(10)−N(1)−N(2)−C(11)	89.9(5)
O(2)−C(10)	1.224(5)	C(9)−O(1)−C(2)	115.1(4)	C(6)−C(5)−C(10)−O(2)	73.7(5)
O(3)−C(15)	1.251(5)	C(10)−N(1)−N(2)	120.3(4)	C(4)−C(5)−C(10)−O(2)	−48.0(6)
N(1)−N(2)	1.396(4)	C(15)−N(2)−N(1)	117.4(3)	C(6)−C(5)−C(10)−N(1)	−103.8(5)
N(2)−C(15)	1.352(5)	C(6)−C(5)−C(4)	111.3(4)	C(9)−O(1)−C(2)−C(3)	−1.6(7)
N(2)−C(11)	1.518(5)	C(8)−C(9)−C(4)	115.2(4)	O(1)−C(2)−C(3)−C(4)	−22.2(7)
C(2)−C(3)	1.646(10)	C(9)−C(4)−C(5)	112.0(4)	C(2)−C(3)−C(4)−C(9)	36.2(6)
C(4)−C(9)	1.536(6)	C(16)−C(17)−C(18)	120.8(4)	C(10)−C(5)−C(6)−C(7)	−179.4(4)
C(4)−C(5)	1.538(6)	C(17)−C(16)−C(21)	120.4(4)	C(4)−C(5)−C(6)−C(7)	−59.3(5)

Table 5. Toxicities (Percent) against Oriental Armyworm of Compounds **Ia**, **Ib**, **IIa**−**IIg**, **IIIa**, **IIIb**, **IVa**, **Va**, and **Vb** and Contrast Compounds **RH-2485**, **JS-118**, and **ANS-118**

	oriental armyworm				
compd	200 mg L^{-1}	100 mg L^{-1}	50 mg L^{-1}	25 mg L^{-1}	10 mg L^{-1}
Ia	**100**	**100**	**100**	**100**	**50**
Ib	**100**	**100**	**100**	**100**	**70**
IIa−**IIe**	0				
IIf	80				
IIg	**100**	**100**	**100**	**100**	**60**
IIIa	**100**	**100**	**100**	**30**	
IIIb	0				
IVa	30				
Va	0				
Vb	100	100	20		
Vc	**100**	**100**	**100**	**100**	**80**
RH-2485	100	100	100	100	100
JS-118	100	100	100	100	100
ANS-118	100	100	100	100	100

Table 6. Toxicities (Percent) against Beet Armyworm of Compounds **Ia**, **Ib**, **IIf**, **IIg**, and **IIIa** and Contrast Compounds **RH-2485**, **JS-118**, and **ANS-118**

	beet armyworm			
compd	200 mg L^{-1}	100 mg L^{-1}	50 mg L^{-1}	10 mg L^{-1}
Ia	**100**	**100**	**100**	**90**
Ib	**100**	**100**	**100**	**90**
IIf	70			
IIg	**100**	**100**	**100**	**80**
IIIa	100	80		
IVa	0			
RH-2485	100	100	100	100
JS-118	100	100	100	90
ANS-118	100	100	100	100

the results in **Table 5** indicate that monosubstituent or multisubstituents and the substituting group position cannot promote increasing insecticidal activity by comparing the activities of **IIf** with **IIa**−**IIe**. Compound **Ia** has almost the same activity as compound **Ib**, but compound **IIg** has significantly higher activity than compound **IIf**; these results indicate that the cycle region in the general structure of **IIa**−**IIg** is much more sensitive to their insecticidal activity than the cycle region in the general structure of compounds **Ia** and **Ib**. This SAR is verified by comparing the activities of compound **IIIa** with that of compound **IIIb** or that of compound **IIIg** with that of compound **IVa**. In the crystal structure of compounds **IIf** and **Va**, the three-dimensional space volume of octahydrobenzofuran ring of **Va** is significantly larger than that of benzofuran ring of **IIf**, but the activity of compound **Va** is significantly lower than that of compound **IIf**. This shows that the space volume of the A ring in the structure of **Va** cannot

Table 7. Toxicities (Percent) against Diamond-back Moth and Corn Borer of Compounds **Ia**, **Ib**, **IIf**, **IIg**, and **IIIa** and Contrast Compounds **RH-2485**, **JS-118**, and **ANS-118**

	diamond-back moth			corn borer
compd	200 mg L^{-1}	100 mg L^{-1}	50 mg L^{-1}	200 mg L^{-1}
Ia	**100**	**100**	**70**	40
Ib	80			60
IIf	50			40
IIg	**100**	**100**	**50**	70
IIIa	0			30
IVa	0			0
RH-2485	100	100	100	100
JS-118	100	100	100	100
ANS-118	100	100	100	100

be too large; if it is, the activity will be decreased significantly. The activity of compound **Vc** is higher than that of compounds **Vb** and **Va**, which also indicates that the space volume of the A ring is larger and the corresponding activity is lower.

Stomach Toxicity against Beet Armyworm (*L. exigua Hübner*). The results of insecticidal activities given in **Table 6** indicate that compounds **Ia** and **Ib** exhibit the same excellent activity against beet armyworm, but compound **IIg** shows significantly higher activity than compounds **IIf**, **IIIa**, and **IVa**. These results further verify the above SAR that the cycle region in the general structure of **IIa**−**IIg** is much more sensitive to their activity than the cycle region in the general structure of compounds **Ia** and **Ib**.

Stomach Toxicity against Diamond-back Moth (*P. xylostella L.*) *and Corn Borer* (*O. nubilalis*). Just as shown in **Table 6**, compounds **Ia**, **Ib**, and **IIg** exhibit 80−90% insecticidal activities against beet armyworm at 10 mg L^{-1}. However, in **Table 7**, compounds **Ia** and **IIg** show 50−70% insecticidal activities at 50 mg L^{-1}, and compound **Ib** shows 80% insecticidal activity at 200 mg L^{-1} against diamond-back moth, and these three compounds only show 40−70% insecticidal activities against corn borer at 200 mg L^{-1}. These results indicate that benzoheterocyclic analogues of *N*-*tert*-butyl-*N*,*N*′-diacylhydrazines show significant selectivity to different lepidopterous pests.

In summary, several series of novel *N*′-*tert*-butyl-*N*′-substituted-benzoyl-*N*-[di(octa)hydro]benzofuran-carbohydrazide derivatives (**Ia**−**Ij**, **IIa** and **IIb**, and **IVa**−**IVc**) were designed and synthesized. Larvicidal activities against oriental armyworm, beet armyworm, diamond-back moth, and corn borer of these target compounds were evaluated and contrasted with those of **RH-2485**, **JS-118**, and **ANS-118**. Although the 3,5-dimethyl substituent is an efficient substituent in diacylhydrazines, the bioactivities against oriental armyworm also indicate that monosubstituent or multisubstituents and the substituting group position cannot promote increasing these compounds' activities, and the cycle

region in the general structure of **IIa**−**IIg** is much more sensitive to these compounds' activities than the cycle region in the general structure of compounds **Ia** and **Ib**. Analyzing the properties of the crystal structures of compounds **IIf** and **Va** and comparing the activities of compounds **IIf** and **Va**−**Vc**, we found that the space volume of the A ring in the structure of **Va** cannot be too large; if it is, the activity will be decreased significantly; the space volume of the A ring is larger, and the corresponding activity is lower. Stomach toxicities against beet armyworm, diamond-back moth, and corn borer of target compounds **Ia**, **Ib**, and **IIg** indicate that benzoheterocyclic analogues of *N*-*tert*-butyl-*N*, *N*′-diacylhydrazines show significant selectivities to different lepidopterous pests.

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