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Synthesis and insecticidal evaluation of novel *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives

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Abstract—A series of novel *N′-tert*-butyl- *N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives were synthesized, and their larvicidal activities against Oriental armyworm were evaluated. The results of bioassays indicated that most of these title compounds exhibit higher larvicidal activities than RH-5849, and several of them somewhat lower than the commercial insecticide tebufenozide. The larvicidal activities are strongly associated with the types and patterns of substitution on the benzene, and 3,5-dimethyl, 2-nitro-4-chloro and 3-methyl derivatives are most prominent in increasing activity. Toxicity assays indicated that these derivatives could induce a premature, abnormal, and lethal larval moult.

1. Introduction

A new class of insect growth regulators (IGRs), diacylhydrazines, have been found to act as nonsteroidal ecdysone agonists inducing, especially in *Lepidoptera*, precocious molting, leading to death.[1–5] Among those nonsteroidal ecdysone agonists, *N′-tert*-butyl-*N′*-3,5-dimethylbenzoyl-*N*-4-ethylbenzoylhydrazide (tebufenozide; RH-5992) was first to be commercialized as a *leptidopteran*-specific insecticide under the trade names Mimic, Confirm, and Romdan in several countries.[6,7]

Recently, it has been reported that *N′*-benzoheterocyclecarbonyl-*N*-*tert*-butyl-3,5-dimethylbenzohydrazide analogs showed high insecticidal activities, some of them equal to or superior to that of tebufenozide, and it was believed that the activity strongly depended on the substituents on the benzene ring of the benzoheterocyle moiety.[8–11] Among them, *N′-tert*-butyl-*N′*-3,5-dimethylbenzoyl-*N*-5-methyl-6-chromanecarbohydrazide (Chromafenozide; ANS-118) (**I**) has been commercialized as insecticide under the trade name Matric.[12,13] In the literature,[9] it was also noticed that the insecticidal activity against *Spodoptera litura* of *N′-tert*-butyl-*N′*-3,5-dimethylbenzoyl-*N*-5-methyl-2,3-dihydro-1,4-benzodioxine-6-carbohydrazide (**II**) ($LC_{50} = 1.4\ mg\ L^{-1}$) is equal to that of *N′-tert*-butyl-*N′*-3,5-dimethylbenzoyl-*N*-5-chloro-2,3-dihydro-1,4-benzodioxine-6-carbohydrazide (**III**) ($LC_{50} = 1.4\ mg\ L^{-1}$), which meant that the chloride and the methyl should be bioisosterism. Inspired by these reports, we developed an idea for displacement of the methyl on the benzene ring of 5-methyl-6-chromane of Chromafenozide with the chloride. Therefore, in a search for new insect growth regulators with improved profiles, we designed and synthesized a series of novel *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives (**IV**) as shown in Scheme 1.

Keywords: 5-Chloro-6-chromanecarboxilic acid; Insect growth regulator; Diacylhydrazine; Larvicidal activity; Lethal larval moult.
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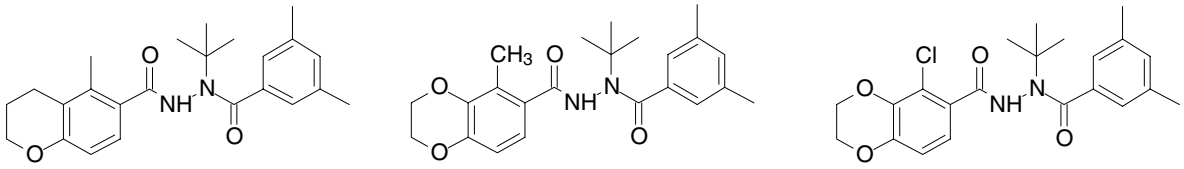

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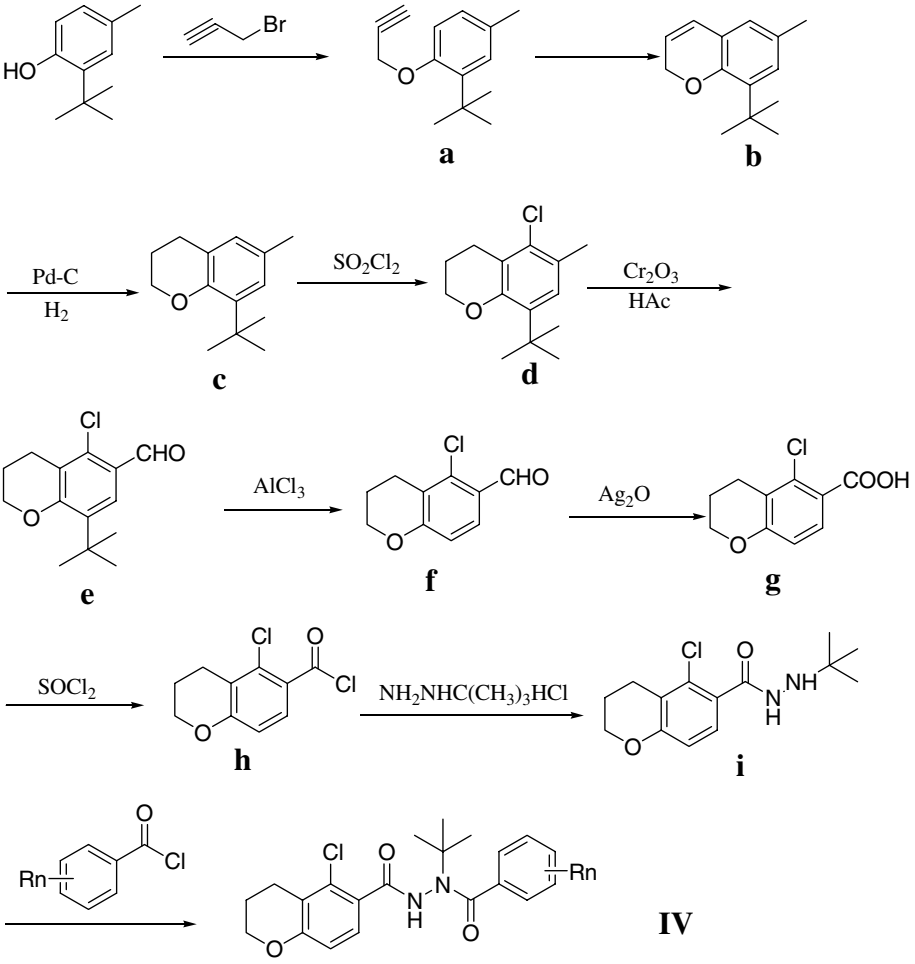
2. Results and discussion

2.1. Synthesis

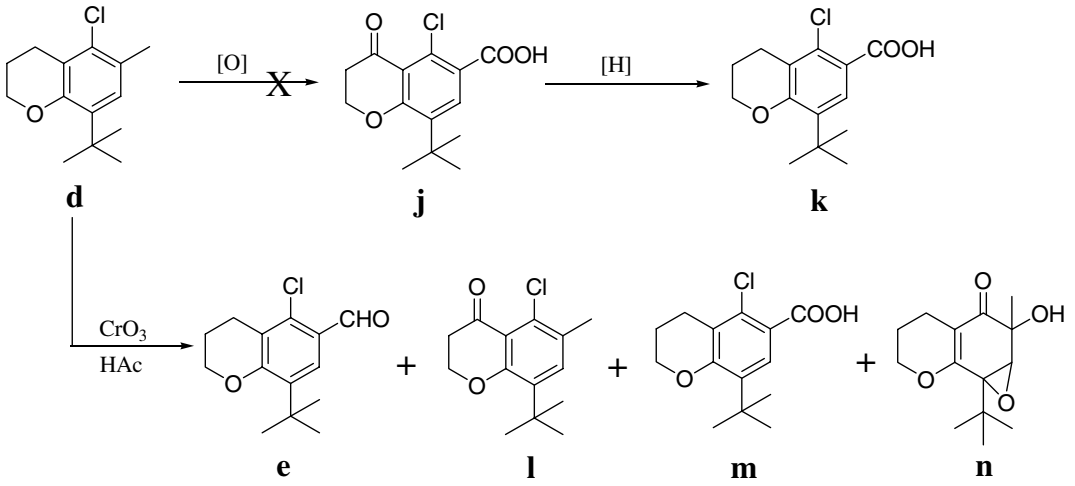
The novel *N*′-*tert*-butyl-*N*′-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives (**IV1–IV29**) were synthesized by the reaction of various substituted-benzoylchloride with *N*′-*tert*-butyl-5-chlorochroman-6-carbohydrazide (**i**) in dichloromethane using triethylamine as acid acceptor. *N*′-*tert*-Butyl-5-chlorochroman-6-carbohydrazide (**i**) were obtained by the reaction of 5-chlorochroman-6-carbonyl chloride (**h**), which was yielded by 5-chlorochromane-6-carboxylic acid (**g**) refluxing in thionyl chloride, with *tert*-butylhydrazine hydrochloride. The synthetic pathway of the key intermediate 5-chlorochromane-6-carboxylic acid (**g**) is outlined in Scheme 1.

2-*tert*-Buty-4-methyl-1-(prop-2-ynyloxy)benzene (**a**) was obtained in excellent yields by the reaction of 2-*tert*-butyl-4-methylphenol with 3-bromoprop-1-yne using tetrabutylammonium bromide as phase-transfer catalyst, and the temperature of the above reaction should be controlled under 60 °C, in order to avoid yielding byproduct, 7-*tert*-butyl-3,5-dimethyl benzofuran. 7-*tert*-Butyl-3,5-dimethyl benzofuran, ^{1}H NMR δ: 1.40 (s, 9H); 2.32 (s, 3H); 2.37 (s, 3H); 6.18 (s 1H); 6.82 (s 1H); 7.03 (s, 1H).

Firstly, we attempted to oxidize 8-*tert*-butyl-5-chloro-6-methylchromane (**d**) to 8-*tert*-butyl-5-chloro-4-oxochromane-6-carboxylic acid (**j**), which further reduced to 8-*tert*-butyl-5-chlorochromane-6-carboxylic acid (**k**), then de-*tert*-butylation provided the key intermediate 5-chlorochromane-6-carboxylic acid (**g**). However, we



Scheme 1. General synthetic route for compounds IV.



Scheme 2.

cannot obtain 8-*tert*-butyl-5-chloro-4-oxochromane-6-carboxylic acid (**j**). 8-*tert*-Butyl-5-chloro-6-methylchromane (**d**) can be subjected to partial oxidation to obtain 8-*tert*-butyl-5-chlorochromane-6-carbaldehyde (**e**) using chromium trioxide as oxidant. At the same time, a little 8-*tert*-butyl-5-chloro-6-methylchroman-4-one (**l**) and 8-*tert*-butyl-5-chlorochromane-6-carboxylic acid (**m**) and 7b-*tert*-butyl-1a,2,5,6-tetrahydro-2-hydroxy-2-methyl-4H-oxireno[2,3-*h*]chromen-3(7bH)-one (**n**) were also obtained (as shown in Scheme 2). And it was unexpected that the compound (**n**) would result from partial oxidation of the aromatic ring, for it has been believed that the aromatic ring is resistant to attack by chromium (VI) that attack the alkyl side chain.[14]

Compound **l**: mp: 93–95 °C, ^{1}H NMR δ: 1.36 (s, 9H); 2.33 (s, 3H); 2.85 (t, 2H,J = 6.0 Hz); 4.49 (t, 2H, J = 6.9 Hz); 7.30 (s, 1H). Anal. Calcd (%) for $C_{14}H_{17}ClO_2$: C: 66.53; H: 6.78. Found (%): C: 66.42; H: 6.68.

Compound **m**: mp: 206–211 °C, ^{1}H NMR δ: 1.38 (s, 9H); 2.04–2.12 (m, 2H); 2.89 (t, 2H, J = 6.6 Hz); 4.24 (t, 2H, J = 5.1 Hz); 7.89 (s, 1H). Anal. Calcd (%) for $C_{14}H_{17}ClO_3$: C: 62.57; H: 6.38. Found (%): C: 62.66; H: 6.38.

Compound **n**: mp: 71–72 °C, ^{1}H NMR δ: 1.13 (s, 9H); 1.33 (s, 3H); 1.77–2.10 (m, 3H); 2.54–2.66 (m, 1H); 3.68 (s, 1H); 3.70 (s, b, 1H); 3.95–4.03 (m, 1H); 4.40–4.47 (m, 1H). Anal. Calcd (%) for $C_{14}H_{20}O_4$: C: 66.65; H: 7.99. Found (%): C: 66.45; H: 7.73.

2.2. Insecticidal activity

Table 1 shows the larvicidal activities against Oriental armyworm of the title compounds, tebufenozide and RH-5849. Most of the title compounds show higher larvicidal activities than RH-5849, and several of them somewhat lower than tebufenozide (LC_{50} = 1.59 mg L^{-1}), for example, **IV6** (LC_{50} = 2.25 mg L^{-1}), **IV20** (LC_{50} = 2.73 mg L^{-1}), **IV3** (LC_{50} = 2.78 mg L^{-1}). Toxicity assays indicated that these derivatives could induce a premature, abnormal, and lethal larval moult.

Table 1. Larvicidal activities against Oriental armyworm of *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives, tebufenozide and RH-5849

Compound	LC_{50} (mg/L)	$Y = a + bx$	R
IV1	5.00	1.191 + 5.449x	1.00
IV2	31.33	1.145 + 2.576x	0.99
IV3	2.78	−3.678 + 2.976x	0.99
IV4	5.57	2.965 + 2.727x	0.99
IV5	6.14	3.272 + 2.174x	0.99
IV6	2.25	3.793 + 3.432x	0.99
IV7	>500		
IV8	10.07	1.426 + 3.564x	0.98
IV9	11.40	0.496 + 4.263x	0.97
IV10	25.06	0.718 + 3.060x	0.99
IV11	19.76	−0.436 + 4.195x	0.99
IV12	42.66	1.358 + 2.234x	0.99
IV13	215.28	−3.491 + 3.639x	0.99
IV14	10.76	1.243 + 3.639x	0.99
IV15	5.98	2.910 + 2.690x	0.99
IV16	4.06	2.858 + 3.522x	0.99
IV17	4.11	−2.470 + 4.120x	0.98
IV18	4.11	−2.470 + 4.120x	0.99
IV19	>500		
IV20	2.73	3.614 + 3.178x	0.97
IV21	8.47	2.526 + 2.663x	0.99
IV22	>500		
IV23	4.75	2.858 + 3.522x	0.99
IV24	5.69	3.103 + 2.513x	0.99
IV25	30.20	1.164 + 2.592x	0.99
IV26	43.55	−2.948 + 4.850x	0.99
IV27	6.54	2.359 + 3.239x	0.99
IV28	399.02	−1.267 + 2.409x	0.97
IV29	29.72	0.618 + 2.974x	0.97
Tebufenozide	1.59	4.397 + 2.990x	0.99
RH-5849	24.38	−4.687 + 6.982x	0.99

The larvicidal activities against Oriental armyworm of the title compounds varied drastically, depending upon the types and patterns of substitution on the benzene. Among mono-substituted derivatives, compared to non-substituent compound (**IV1**), substituents are

unfavorable to activity except for methyl at *meta* or halogen at *para*. And the bulkier substituent, such as C_2H_5O, I, and NO_2 (except for NO_2 at *ortho*), drastically decreased activity, for example, **IV13** ($LC_{50} > 200$ mg L^{-1}) and **IV28** ($LC_{50} > 300$ mg L^{-1}). Among multi-substituted compounds, 3,5-dimethyl and 2-nitro-4-chloro derivatives are most prominent in increasing activity, 2,4-dichloro and 3,5-dichloro derivatives slightly increase activity, while introduction of tri-substituted groups results in rapidly decreasing activity, for example, the activities of compounds **IV7** and **IV19** are too low to be measured.

3. Conclusions

In summary, a series of novel *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives were synthesized, and their larvicidal activities were evaluated. The results of bioassays indicated that most of these title compounds exhibit higher larvicidal activities than RH-5849, and several of them somewhat lower than tebufenozide. The larvicidal activities are strongly associated with types and patterns of substitution on the benzene, 3,5-dimethyl, 2-nitro-4-chloro, and 3-methyl derivatives are most prominent in increasing activity.

4. Experimental

4.1. Analysis and instruments

Proton NMR spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer in $CDCl_3$ solution with TMS as internal standard. Chemical shift values (δ) were given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas–Hoover melting-point apparatus and were uncorrected. Yields were not optimized.

4.2. General synthetic procedure for *N′-tert*-butyl-*N*-5-chlorochroman-6-carbohydrazide (i)

3-Bromoprop-1-yne (42.0 g, 1.20 mol) was added dropwise to a stirred mixture of 2-*tert*-butyl-4-methylphenol (164.0 g, 1.0 mol), toluene (200 ml), sodium hydroxide (150.0 g, 32%, 1.20 mol), and tetrabutylammonium bromide (32.2 g, 0.01 mol) in an ice bath. After stirring at 35–40 °C for 4 h, the reaction mixture was cooled and diluted with ethyl acetate (1000 ml), the separated organic layer was washed successively with water, and brine, then dried over anhydrous sodium sulfate. The solvent was evaporated to give 196.4 g of 2-*tert*-buty-4-methyl-1-(prop-2-ynyloxy)benzene (**a**) as a yellow oil. Yield (%): 97.2. ^{1}H NMR δ: 1.31 (s, 9H); 2.21 (s, 3H); 2.39 (t, 1H, $J = 2.4$ Hz); 4.62 (d, 2H, $J = 2.4$ Hz); 6.78 (d, 1H, $J = 8.1$ Hz); 6.89−7.02 (m, 2H).

2-*tert*-Buty-4-methyl-1-(prop-2-ynyloxy)benzene (**a**) (202.0 g, 1.0 mol) in *N*,*N*-diethylaniline (150 ml) was refluxed for 5 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (500 ml), and washed with hydrochloric acid (2 mol L^{-1}), water and brine, then dried over anhydrous sodium sulfate. After the solvent was evaporated, the residue was vacuum distilled (bp: 98–100 °C/85 Pa) to give 173.5 g of 8-*tert*-butyl-6-methyl-2H-chromene (**b**) as a colorless oil. Yield (%): 85.9. ^{1}H NMR δ: 1.28 (s, 9H); 2.18 (s, 3H); 4.61–4.63 (m, 2H); 5.72–5.77 (m, 1H); 6.31–6.36 (m, 1H); 6.61–6.86 (m, 2H). Anal. Calcd (%) for $C_{14}H_{18}O$: C: 83.12; H: 8.97. Found (%): C: 82.96; H: 8.79.

A mixture of 8-*tert*-butyl-6-methyl-2H-chromene (**b**) (140.0 g, 0.69 mol), wet 10% palladium on activated carbon (12.0 g, 60% in water), and methanol (500 ml) was stirred under 1 atm. of hydrogen at room temperature for 5 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was vacuum distilled (bp: 92–95 °C/100 Pa) to give 126.0 g of 8-*tert*-butyl-6-methylchromane (**c**) as a colorless oil. Yield (%): 89.5. ^{1}H NMR δ: 1.28 (s, 9H); 1.85–1.93 (m, 2H); 2.16 (s, 3H); 2.69 (t, 2H, $J = 6.0$ Hz); 4.07 (t, 2H, $J = 5.1$ Hz); 6.65 (s, 1H); 6.81 (s, 1H). Anal. Calcd (%) for $C_{14}H_{20}O$: C: 82.30; H: 9.87. Found (%): C: 82.19; H: 9.78.

SO_2Cl_2 (89.2 g, 0.66 mol) in dichloromethane (200 ml) was added dropwise to 8-*tert*-butyl-6-methylchromane (**c**) (126.0 g, 0.62 mol) in dichloromethane (200 ml) at 30–35 °C. After stirring at 30–35 °C for 3 h, the reaction mixture was cooled and washed successively with water and brine, then dried over anhydrous sodium sulfate. The solvent was evaporated to give 115.3 g of 8-*tert*-butyl-5-chloro-6-methylchromane (**d**) as colorless crystal. Yield (%): 78.0. mp (°C): 44–46. ^{1}H NMR δ: 1.27 (s, 9H); 1.90–1.99 (m, 2H); 2.22 (s, 3H); 2.72 (t, 2H, $J = 6.9$ Hz); 4.04 (t, 2H, $J = 5.1$ Hz); 6.90 (s, 1H). Anal. Calcd (%) for $C_{14}H_{19}ClO$: C: 70.43; H: 8.02. Found (%): C: 70.32; H:7.95.

A mixture of chromium trioxide (24.0 g, 0.24 mol), acetic acid (80 ml), and water (40 ml) was added dropwise to a stirred solution of 8-*tert*-butyl-5-chloro-6-methylchromane (**d**) (19.2 g, 0.08 mol) in acetic acid (100 ml) under 15 °C. After stirring under 15 °C for 4 h, the reaction mixture was poured into iced water and extracted with ethyl acetate, the organic layer was washed successively with a solution of sodium bicarbonate, water, and brine, then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give 3.66 g of 8-*tert*-butyl-5-chlorochromane-6-carbaldehyde (**e**) as colorless crystal. Yield (%): 18.1. mp (°C): 174–175. ^{1}H NMR δ: 1.37 (s, 9H); 2.05–2.13 (m, 2H); 2.87 (t, 2H, $J = 6.9$ Hz); 4.28 (t, 2H, $J = 4.5$ Hz); 7.77 (s, 1H); 10.39 (s, 1H). Anal. Calcd (%) for $C_{14}H_{17}ClO_2$: C: 66.53; H: 6.78. Found (%): C: 66.48; H: 6.70.

8-*tert*-Butyl-5-chlorochromane-6-carbaldehyde (7.6 g, 0.03 mol) (**e**) in dichloromethane (60 ml) was added dropwise to a stirred suspension of aluminum chloride (8.01 g, 0.06 mol) in dichloromethane (60 ml) in an ice

bath. After stirring at room temperature for 2 h, the reaction mixture was poured into hydrochloric acid (1 mol L^{-1}; 50 ml), the organic layer was washed successively with a solution of sodium bicarbonate, water, and brine, then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give 3.82 g of 5-chlorochromane-6-carbaldehyde (**f**) as colorless crystal. Yield (%): 65.0. mp (°C): 63–65. ^{1}H NMR δ: 2.04–2.12 (m, 2H); 2.84 (t, 2H, J = 6.0 Hz); 4.23 (t, 2H, J = 5.4 Hz); 6.82 (d, 1H, J = 8.4 Hz); 7.73 (d, 1H, J = 8.4 Hz); 10.37 (s, 1H). Anal. Calcd (%) for $C_{10}H_9ClO_2$: C: 61.08; H: 4.61. Found (%): C: 60.96; H: 4.45.

A solution of silver nitrate (6.14 g, 0.036 mol) in water (30 ml) was added to sodium hydroxide (1.6 g, 0.04 mol) in water (15 ml). The mixture was stirred for 5 min, and the silver oxide was collected in a funnel with suction and washed free of nitrates with water. The wet, freshly precipitated silver oxide was transferred to a breaker, covered with water (70 ml), and treated with sodium hydroxide (3.3 g, 0.083 mol) with vigorous stirring. The mixture was warmed to 55–60 °C, 5-chlorochromane-6-carbaldehyde (7.10 g, 0.036 mol) (**f**) was added, stirring was continued for 15 min, the mixture was filtered, and the precipitated silver was washed with hot water, and the resulting solution was poured into hydrochloric acid (40 ml), and the resulting precipitate was collected by filtration. The resulting white solid was recrystallized from 70% ethanol to give 6.96 g of 5-chlorochromane-6-carboxylic acid (**g**) as a white solid. Yield (%): 91.0. mp (°C): 202–205. ^{1}H NMR δ: 1.98–2.14 (m, 2H); 2.85 (t, 2H, J = 6.3 Hz); 4.20 (t, 2H, J = 5.4 Hz); 6.79 (d, 1H, J = 8.4 Hz); 7.85 (d, 1H, J = 8.4 Hz). Anal. Calcd (%) for $C_{10}H_9ClO_3$: C: 56.49; H: 4.27. Found (%): C: 56.47; H: 4.44.

A mixture of 5-chlorochromane-6-carboxylic acid (**g**) (1.1 g, 5 mmol) and thionyl chloride (1 ml) was heated under reflux for 1 h. After excess thionyl chloride was removed under reduced pressure, the residue was dissolved in dichloromethane (5 ml). The solution was added dropwise to a stirred mixture of *tert*-butylhydrazine hydrochloride (1.25 g, 10 mmol), sodium hydroxide (0.70 g, 25 mmol), dichloromethane (15 ml), and water (5 ml) in an ice bath. After stirring for 6 h at room temperature, ethyl acetate (50 ml) was added to the reaction mixture. The organic layer was separated and washed successively with water and brine, and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was washed with cold diethyl ether to give 1.1 g of *N′*-*tert*-butyl-5-chlorochroman-6-carbohydrazide (**i**) as white solid. Yield (%): 78.6. mp (°C): 117–120. ^{1}H NMR δ: 1.18 (s, 9H); 2.01–2.09 (m, 2H); 2.81 (t, 2H, J = 6.6 Hz); 4.17 (t, 2H, J = 5.1 Hz); 6.79 (d, 1H, J = 8.1 Hz); 7.40 (d, 1H, J = 8.1 Hz) Anal. Calcd (%) for $C_{14}H_{19}ClN_2O_2$: C: 59.47; H: 6.77. Found (%): C: 59.22; H: 6.70.

Table 2. Physical properties and elemental analyses of *N′*-*tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives

Compound	Rn	Mp (°C)	Yield (%)	Formula	Analysis calcd (found, %)		
					C	H	N
IV1	H	247–248	76.2	$C_{21}H_{23}ClN_2O_3$	65.20(64.96)	5.99(6.02)	7.24(7.37)
IV2	2-Me	256–257	76.2	$C_{22}H_{25}ClN_2O_3$	65.91(65.88)	6.29(6.18)	6.99(7.03)
IV3	3-Me	235–237	80.9	$C_{22}H_{25}ClN_2O_3$	65.91(65.77)	6.29(6.37)	6.99(6.98)
IV4	4-Me	252–253	85.7	$C_{22}H_{25}ClN_2O_3$	65.91(65.72)	6.29(6.18)	6.99(7.15)
IV5	2,4-di-Me	194–195	77.3	$C_{23}H_{27}ClN_2O_3$	66.58(66.57)	6.56(6.74)	6.75(6.94)
IV6	3,5-di-Me	259–261	55.2	$C_{23}H_{27}ClN_2O_3$	66.58(66.50)	6.56(6.48)	6.75(6.82)
IV7	2,4,6-tri-Me	272–273	56.5	$C_{24}H_{29}ClN_2O_3$	67.20(66.98)	6.81(7.01)	6.53(6.74)
IV8	2-MeO	201–202	72.7	$C_{22}H_{25}ClN_2O_4$	63.38(63.30)	6.04(5.99)	6.72(6.80)
IV9	3-MeO	201–202	77.3	$C_{22}H_{25}ClN_2O_4$	63.38(63.45)	6.04(6.07)	6.72(6.74)
IV10	4-MeO	243–245	72.0	$C_{22}H_{25}ClN_2O_4$	63.38(63.21)	6.04(5.98)	6.72(6.59)
IV11	3,4-di-MeO	221–223	83.3	$C_{23}H_{27}ClN_2O_5$	61.81(61.89)	6.09(6.17)	6.27(6.63)
IV12	3,4,5-tri-MeO	230–231	84.0	$C_{24}H_{29}ClN_2O_6$	60.44(60.33)	6.13(6.16)	5.87(6.06)
IV13	4-C_2H_5O	213–214	78.3	$C_{23}H_{27}ClN_2O_4$	64.11(63.98)	6.32(6.23)	6.50(6.52)
IV14	2-Cl	236–237	81.8	$C_{21}H_{22}Cl_2N_2O_3$	59.87(59.70)	5.26(5.19)	6.65(6.60)
IV15	3-Cl	232–233	68.2	$C_{21}H_{22}Cl_2N_2O_3$	59.87(59.86)	5.26(5.38)	6.65(6.65)
IV16	4-Cl	243–246	80.5	$C_{21}H_{22}Cl_2N_2O_3$	59.87(59.70)	5.26(5.33)	6.65(6.59)
IV17	2,4-di-Cl	142–145	75.0	$C_{21}H_{21}Cl_3N_2O_3$	55.34(55.34)	4.64(4.74)	6.15(6.25)
IV18	3,5-di-Cl	253–255	70.8	$C_{21}H_{21}Cl_3N_2O_3$	55.34(55.30)	4.64(4.74)	6.15(6.15)
IV19	2,4,6-tri-Cl	245–247	58.8	$C_{21}H_{20}Cl_4N_2O_3$	51.45(51.44)	4.11(4.23)	5.71(5.73)
IV20	2-NO_2-4-Cl	215–216	48.0	$C_{21}H_{21}Cl_2N_3O_5$	54.09(53.91)	4.54(4.70)	9.01(9.11)
IV21	2-Cl-4-NO_2	182–185	60.0	$C_{21}H_{21}Cl_2N_3O_5$	54.09(53.92)	4.54(4.62)	9.01(8.87)
IV22	2,6-di-Cl-4-CF_3	233–234	64.3	$C_{22}H_{20}Cl_3F_3N_2O_3$	50.45(50.48)	3.85(3.92)	5.35(5.19)
IV23	2-F	228–230	66.7	$C_{21}H_{22}ClFN_2O_3$	62.30(62.16)	5.48(5.43)	6.92(7.03)
IV24	2,4-di-F	165–166	68.2	$C_{21}H_{21}ClF_2N_2O_3$	59.65(59.67)	5.01(4.96)	6.62(6.90)
IV25	3-I	249–251	74.1	$C_{21}H_{22}ClIN_2O_3$	49.19(49.00)	4.32(4.40)	5.46(5.36)
IV26	4-I	247–249	77.8	$C_{21}H_{22}ClIN_2O_3$	49.19(48.90)	4.32(4.50)	5.46(5.23)
IV27	2-NO_2	261–264	85.0	$C_{21}H_{22}ClIN_3O_5$	58.40(58.31)	5.13(5.16)	9.73(9.90)
IV28	3-NO_2	259–260	75.0	$C_{21}H_{22}ClIN_3O_5$	58.40(58.21)	5.13(5.07)	9.73(9.94)
IV29	4-NO_2	230–232	70.0	$C_{21}H_{22}ClIN_3O_5$	58.40(58.18)	5.13(5.11)	9.73(9.93)

Table 3. ^{1}H NMR Data of *N′-tert*-Butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives

Compound	^{1}H NMR
IV1	1.60 (s, 9H); 1.94–2.04 (m, 2H); 2.70 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.10 (t, 2H, $^3J_{HH}$ = 4.5 Hz); 6.28 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.52 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.28–7.46 (m, 5H); 7.74 (s, 1H, NH)
IV2	1.60 (s, 9H); 1.93–2.01 (m, 2H); 2.35 (s, 3H); 2.69 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.09 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.03 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.48 (d,1H, $^3J_{HH}$ = 8.1 Hz); 7.08–7.27 (m, 4H); 7.67 (s, 1H, NH)
IV3	1.58 (s, 9H); 1.94–2.04 (m, 2H); 2.31 (s, 3H); 2.70 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 4.10 (t, 2H, $^3J_{HH}$ =5.1 Hz); 6.27 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.52 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 7.16–7.26 (m, 4H); 7.84 (s, 1H, NH)
IV4	1.58 (s, 9H); 1.95–2.04 (m, 2H); 2.34 (s, 3H); 2.71 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 4.11 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.34 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.54 (d,1H, $^3J_{HH}$ = 8.4 Hz); 7.23 (m, 4H); 7.77 (s, 1H, NH)
IV5	1.61 (s, 9H); 1.90–2.05 (m, 2H); 2.22–2.40 (m, 6H); 2.64–2.76 (m, 2H); 4.04–4.17 (m, 2H); 6.05–6.15 (m, 1H); 6.46–6.56 (m, 1H); 6.88–7.16 (m, 3H); 7.49 (s, 1H, NH)
IV6	1.60 (s, 9H); 1.95–2.04 (m, 2H); 2.27 (s, 6H); 2.72 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 4.11 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.34 (d, 1H, $^3J_{HH}$ = 9.3 Hz); 6.56 (d, 1H, $^3J_{HH}$ = 9.3 Hz); 6.99 (s, 1H); 7.06 (s, 2H); 7.56 (s, 1H, NH)
IV7	1.64 (s, 9H); 1.94–2.02 (m, 2H); 2.21 (s, 3H); 2.26 (s, 3H); 2.35 (s, 3H); 2.70 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 4.11 (t, 2H, $^3J_{HH}$ = 4.5 Hz); 5.95 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.49 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.9–6.88 (m, 2H); 7.70 (s, 1H, NH)
IV8	1.62 (s, 9H); 1.95–2.05 (m, 2H); 2.71 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 3.82 (s, 3H); 4.11 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.14 (d, 1H, $^3J_{HH}$ = 6.0 Hz); 6.52 (d, 1H, $^3J_{HH}$ = 6.0 Hz); 6.84–7.45 (m, 4H); 8.01 (s, 1H, NH)
IV9	1.58 (s, 9H); 1.94–2.02 (m, 2H); 2.70 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 3.77 (s, 3H); 4.11 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.36 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.54 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.88–7.23 (m, 4H); 7.75 (s, 1H, NH)
IV10	1.58 (s, 9H); 1.95–2.05 (m, 2H); 2.71 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 3.79 (s, 3H); 4.11 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.50 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.58 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.13 (m, 4H); 7.83 (s, 1H, NH)
IV11	1.60 (s, 9H); 1.96–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 3.86 (s, 3H); 3.87 (s, 3H); 4.12 (t, 2H, $^3J_{HH}$ =5.1 Hz); 6.60–7.13 (m, 5H); 7.73 (s, 1H, NH)
IV12	1.60 (s, 9H); 1.96–2.03 (m, 2H); 2.71 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 3.82 (s, 6H); 3.84 (s, 3H); 4.13 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.60–6.76 (m, 4H); 7.67 (s, 1H, NH)
IV13	1.40 (t, 3H, $^3J_{HH}$ = 6.9 Hz); 1.58 (s, 9H); 1.95–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.02 (q, 2H, $^3J_{HH}$ = 6.9 Hz); 4.11 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.50 (d, 1H, $^3J_{HH}$ = 9.3 Hz); 6.58 (d, 1H, $^3J_{HH}$ = 9.3 Hz); 7.12 (m, 4H); 7.79 (s, 1H, NH)
IV14	1.62 (s, 9H); 1.95–2.03 (m, 2H); 2.70 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.11 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.30 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.55 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.28–7.46 (m, 4H); 7.81 (s, 1H, NH)
IV15	1.58 (s, 9H); 1.95–2.04 (m, 2H); 2.71 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.12 (t, 2H, $^3J_{HH}$ = 4.5 Hz); 6.52–6.61 (m, 2H); 7.21–7.43 (m, 4H); 7.86 (s, 1H, NH)
IV16	1.59 (s, 9H); 1.96–2.05 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.57–6.64 (m, 2H); 7.36 (m, 4H); 7.74 (s, 1H, NH)
IV17	1.61 (s, 9H); 1.97–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.59–6.66 (m, 2H); 7.26–7.45 (m, 3H); 7.91 (s, 1H, NH)
IV18	1.59 (s, 9H); 1.97–2.05 (m, 2H); 2.73 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.14 (t, 2H, $^3J_{HH}$ =5.4 Hz); 6.67 (d, 1H, $^3J_{HH}$ =9.0 Hz); 6.81 (d, 1H, $^3J_{HH}$ =9.0 Hz); 7.33–7.36 (m, 3H); 7.78 (s, 1H, NH)
IV19	1.63 (s, 9H); 1.97–2.05 (m, 2H); 2.73 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.14 (t, 2H, $^3J_{HH}$ =5.4 Hz); 6.68 (d, 1H, $^3J_{HH}$ =9.3 Hz); 6.81 (d, 1H, $^3J_{HH}$ =9.3 Hz); 7.26–7.34 (m, 2H); 7.82 (s, 1H, NH)
IV20	1.62 (s, 9H); 1.93–2.03 (m, 2H); 2.68 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.67 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.85 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.57–7.66 (m, 2H); 7.92 (s, 1H, NH); 8.07 (s, 1H)
IV21	1.62 (s, 9H); 1.95–2.03 (m, 2H); 2.68 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.65 (d, 1H, $^3J_{HH}$ = 9.0 Hz); 6.86 (d, 1H, $^3J_{HH}$ = 9.0 Hz); 7.67–8.25 (m, 4H)
IV22	1.65 (s, 9H); 1.96–2.04 (m, 2H); 2.70 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.64 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.75 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 7.51 (s, 1H); 7.58 (s, 1H); 7.80 (s, 1H, NH)
IV23	1.59 (s, 9H); 1.96–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.12 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.56–6.63 (m, 2H); 6.97–7.52 (m, 4H); 7.72 (s, 1H, NH)
IV24	1.60 (s, 9H); 1.99–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.61–6.92 (m, 4H); 7.53–7.61 (m, 1H); 8.01 (s, 1H, NH)
IV25	1.58 (s, 9H); 1.96–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.13 (t, 2H, $^3J_{HH}$ =5.1 Hz); 6.56–6.64 (m, 2H); 7.03–7.08 (m, 1H); 7.45 (d, 1H, $^3J_{HH}$ = 7.5 Hz); 7.69 (d, 1H, $^3J_{HH}$ = 6.9 Hz); 7.76 (s, 1H); 7.78 (s, 1H, NH)
IV26	1.57 (s, 9H); 1.95–2.04 (m, 2H); 2.72 (t, 2H, $^3J_{HH}$ = 6.9 Hz); 4.13 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.47 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 6.61 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.40 (m, 4H); 7.95 (s, 1H, NH)
IV27	1.64 (s, 9H); 1.93–2.01 (m, 2H); 2.65 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 4.10 (t, 2H, $^3J_{HH}$ = 5.4 Hz); 6.58 (s, 2H); 7.47–7.68 (m, 3H); 7.92 (s, 1H, NH); 8.09 (d, 1H, $^3J_{HH}$ = 8.4 Hz)
IV28	1.62 (s, 9H); 1.92–2.05 (m, 2H); 2.68 (t, 2H, $^3J_{HH}$ = 6.0 Hz); 4.11 (t, 2H, $^3J_{HH}$ =5.4 Hz); 6.64 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 6.75 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 7.52 (t, 4H, $^3J_{HH}$ = 7.5 Hz); 7.90–7.95 (m, 2H); 8.17–8.28 (m, 2H)
IV29	1.61 (s, 9H); 1.93–2.05 (m, 2H); 2.69 (t, 2H, $^3J_{HH}$ = 6.6 Hz); 4.12 (t, 2H, $^3J_{HH}$ = 5.1 Hz); 6.63 (d, 1H, $^3J_{HH}$ = 9.0 Hz); 6.78 (d, 1H, $^3J_{HH}$ = 9.0 Hz); 7.83 (s, 1H, NH); 7.91 (m, 4H)

4.3. General synthetic procedure for *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives (IV1–IV29)

The solution of substitutedbenzoylchloride (0.53 mmol) in dichloromethane (1 ml) was added dropwise to a stirred mixture of *N′-tert*-butyl-5-chlorochroman-6-carbohydrazide (**i**) (150 mg, 0.53 mmol), triethylamine (64 mg, 0.64 mmol), and dichloromethane (5 ml) in an ice bath. After stirred at room temperature for 3 h, ethyl acetate (50 ml) was added to the reaction mixture. The organic layer was separated and washed successively

with water and brine, 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 **IV1**–**IV29** as colorless crystals. The physical properties and elemental analyses of new compounds (**IV1**–**IV29**) are listed in Table 2, and their ^{1}H NMR is listed in Table 3.

4.4. Biological assay

The larvicidal activities of the novel *N′-tert*-butyl-*N′*-substitutedbenzoyl-*N*-5-chloro-6-chromanecarbohydrazide derivatives (**IV1**–**IV29**) were evaluated using a previously reported procedure.[2,15–20] The larvicidal activity was tested against Oriental armyworm [*Mythimna(=Pseudaletia) separata*(Walker)] by foliar application. 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 ten fourth-instar armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed in triplicate. The larvicidal activity was expressed in terms of the LC_{50}, and LC_{50} values were obtained by the Probit method. For comparative purposes, RH-5849 (*N-tert*-butyl-*N*,*N′*-dibenzoylhydrazine) and tebufenozide was tested under the same condition. The larvicidal activity is summarized in Table 1.

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