Design and Synthesis of Novel N′-tert-butyl-N′-substitutedbenzoyl-N-[dihydrobenzofuran(chroman)]carbohydrazide Derivatives as Potential Insect Growth Regulators

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Abstract: Six of new N'-tert-butyl-N'-substitutedbenzoyl-N-(2,4-dimethyl-2,3-dihydrobenzofuran)-7-carbohydrazide derivatives and five of new N'-tert-butyl-N'-substitutedbenzoyl-N-(5-methylchroman)-8-carbohydrazide derivatives were designed and synthesized from m-cresol. The synthesis highlighted that some kinds of reactions were ameliorated in methodology. An important feature is that 1-(3-allyl-2-hydroxy-4-methylphenyl)ethanone can easily be transformed into 1-(2,3-dihydro-2,4-dimethylbenzofuran-7-yl)ethanone just with concentrated sulfuric acid as catalyst. In addition, we found that 1-(5-methyl-2H-chromen-8-yl)ethanone could not be reduced to 1-(5-methylchroman-8-yl)ethanone directly by hydrogen with Pd/C as catalyst. It is an effective method for protecting 1-(5-methyl-2H-chromen-8-yl)ethanone with ethylene glycol to obtain 5-methyl-8-(2-methyl-1,3-dioxolan-2-yl)-2H-chromene and then reducing by hydrogen with Pd/C as catalyst to produce 1-(5-methylchroman-8-yl)ethanone in one step. Furthermore, $SOCl_2$ can convert 2,3-dihydro-2,4-dimethylbenzofuran-7-carboxylic acid to 2,3-dihydro-2,4-dimethylbenzofuran-7-carbonyl chloride, but it is inefficient for transforming 5-methylchroman-8-carboxylic acid to the corresponding acyl chloride. Hence, different heterocycles on the benzene ring of benzoheterocyle moiety have influence on the reaction property of the corresponding acid.

Kewords: Dihydrobenzofuran, chroman, benzoheterocycle, diacylhydrazine, synthesis, insect growth regulator.

INTRODUCTION

Diacylhydrazines as a new class of insect growth regulators (IGRs) were discovered by Rohm and Hass company in the mid-1980s [1-3]. Because of its unique action mechanism, low toxicity to vertebrates and high insecticidal selectivity to *Lepidoptera*, diacylhydrazines have attracted considerable attention for decades [1-13]. Recently, it has been reported that N′-benzoheterocyclecarbonyl-N′-tert-butyl-3,5-dimethylbenzohydrazide analogs showed high insecticidal activities [7-13]. Among them, **ANS-118** and **JS-118** are the successful examples. N′-tert-Butyl-N′-3,5-dimethylbenzoyl-N-5-methyl-6-chromancarbohydrazide (**Chromafenozide**, **ANS-118**, **Fig.** (**1**)) has been commercialized as insecticide under the trade name Matric, and N′-tert-butyl-N′-3,5-dimethylbenzoyl-N-2,7-dimethyl-2,3-dihydrobenzofuran-6-

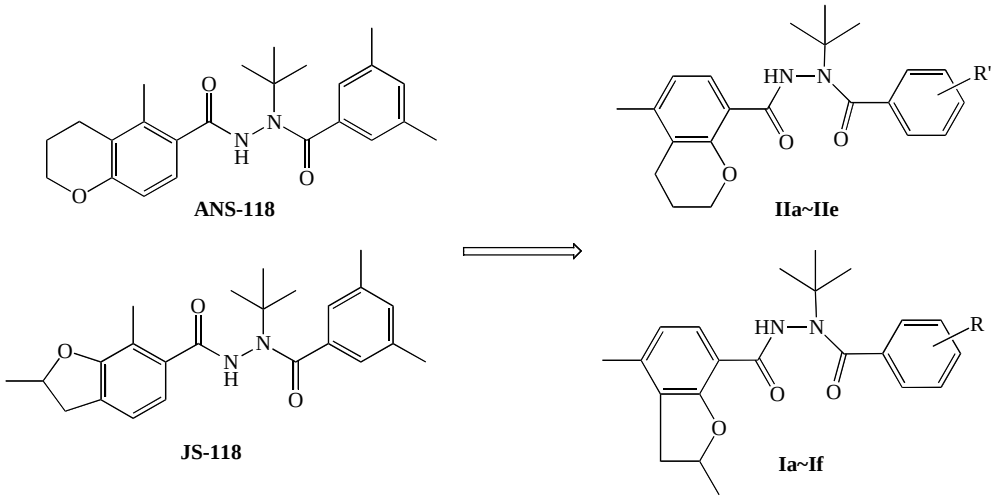

Fig. (1). Design of target molecules **Ia~If** and **IIa~IIe**.

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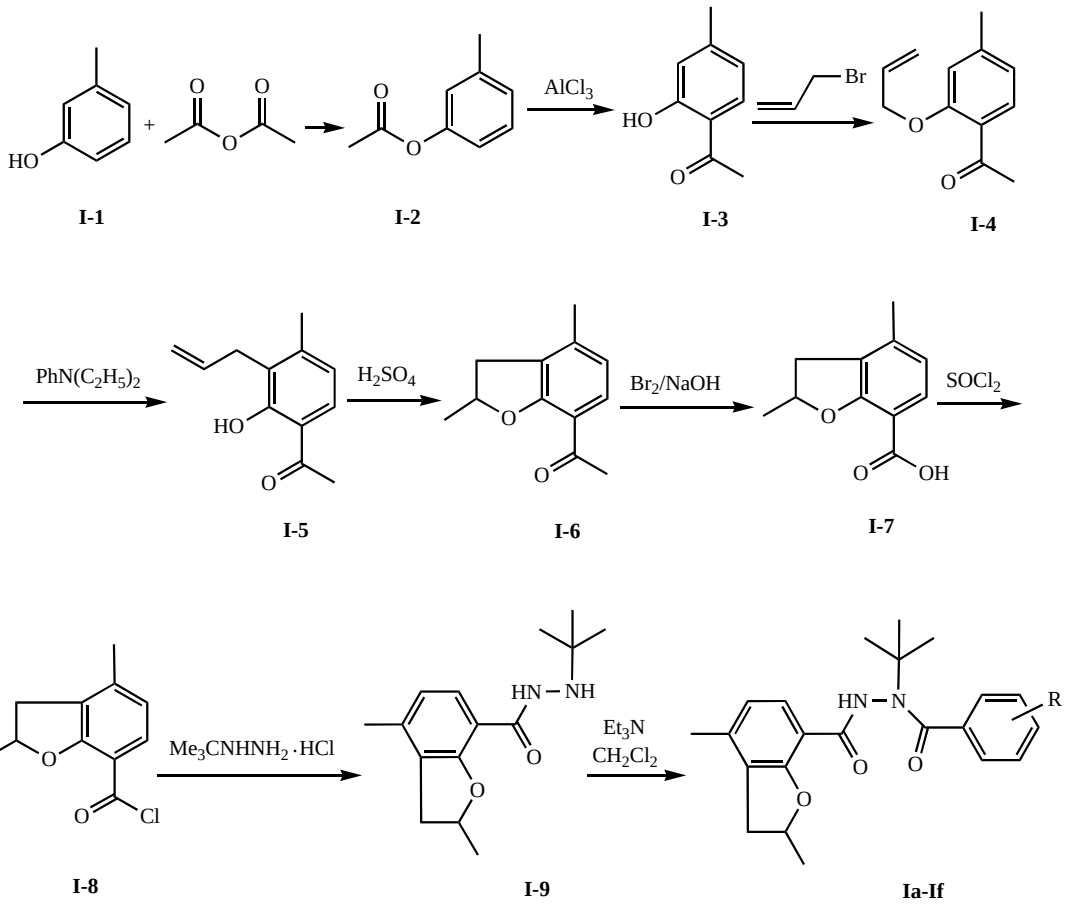


I-1 **I-2** **I-3** **I-4**

I-5 **I-6** **I-7**

I-8 **I-9** **Ia-If**

Scheme 1.

carbohydrazide (**JS-118**, **Fig.** (**1**)) has been developed by the Jiangsu Institute of Agricultural Chemical, P. R. China [9, 11]. In the structures of the two compounds, heterocycles of chroman and dihydrobenzofuran are important parts for their activities. Inspired by these reports, we developed an idea for the synthesis of novel N'-tert-butyl-N'-substitutedbenzoyl-N-(2,3-dihydro-2,4-dimethylbenzofuran)-7-carbohydrazide derivatives (**Ia~If**) and N′-tert-butyl-N′-substitutedbenzoyl-N-(5-methylchroman)-8-carbohydrazide derivatives (**IIa~IIe**) in a research for new insect growth regulators (**Fig.** (**1**)).

RESULTS AND DISCUSSION

The synthetic pathway for N'-tert-butyl-N'-substituted-benzoyl-N-(2,3-dihydro-2,4-dimethylbenzofuran)-7-carbohydrazide (**Ia~If**) is outlined in Scheme **1**. m-Tolyl acetate (**I-2**) and 1-(2-hydroxy-4-methylphenyl)ethanone (**I-3**) were synthesized from m-cresol according to the literature and their ^{1}H NMR spectra were in agreement with those reported in the literature [14]. 1-[2-(Allyloxy)-4-methylphenyl]ethanone (**I-4**) was synthesized from 1-(2-hydroxy-4-methylphenyl) ethanone (**I-3**) and 3-bromoprop-1-ene under phase transfer catalytic condition and then refluxed in N,N-diethylaniline to give 1-(3-allyl-2-hydroxy-4-methylphenyl)ethanone (**I-5**). Then we successfully got 1-(2,3-dihydro-2,4-dimethyl-benzofuran-7-yl)ethanone (**I-6**) from the phenylehanone **I-5** just with concentrated sulfuric acid as catalyst. The reaction was improved with respect to the reported condition using chlorobenzene as solvent and polyphosphoric acid (PPA) as catalyst [15], which is not effective for transforming 1-(3-allyl-2-hydroxy-4-methylphenyl)ethanone (**I-5**) into 1-(2,3-dihydro-2,4-dimethylbenzofuran-7-yl)ethanone (**I-6**). The intermediate **I-6** was oxidized by using bromine and sodium hydroxide to 2,3-dihydro-2,4-dimethylbenzofuran-7-carboxylic acid (**I-7**), subsequent treatment with thionyl chloride provided the corresponding acyl chloride **I-8**, further reaction with tert-butylhydrazine hydrochloride gave N-tert-butyl-N'-2,3-dihydro-2,4-dimethylbenzofuran-7-carbohydrazide (**I-9**). Then the key intermediate **I-9** was condensed with various substituted benzoylchloride in dichloromethane using triethylamine as proton scavenger to obtain the target compounds **Ia~If**. The physical properties and elemental analyses or HRMS of compounds **Ia~If** are listed in Table **1**, and their ^{1}H NMR is listed in Table **2**.

The process of synthesis of N'-tert-butyl-N'-substitute-dbenzoyl-N-(5-methylchroman)-8-carbohydrazide derivatives (**IIa~IIe**) is shown in Scheme **2**.

1-(4-Methyl-2-(prop-2-ynyloxy)phenyl]ethanone (**II-1**) was obtained in excellent yield by the reaction of 1-(2-hydroxy-4-methylphenyl)ethanone (**I-3**) with 3-bromoprop-1-yne using tetrabutylammonium bromide as phase transfer catalytic condition, and then refluxed in N,N-diethylaniline to give 1-(5-methyl-2H-chromen-8-yl)ethanone (**II-2**) through claisen rearrangement. Initially, we expected to reduce 1-(5-methyl-2H-chromen-8-yl)ethanone (**II-2**) to 1-(5-

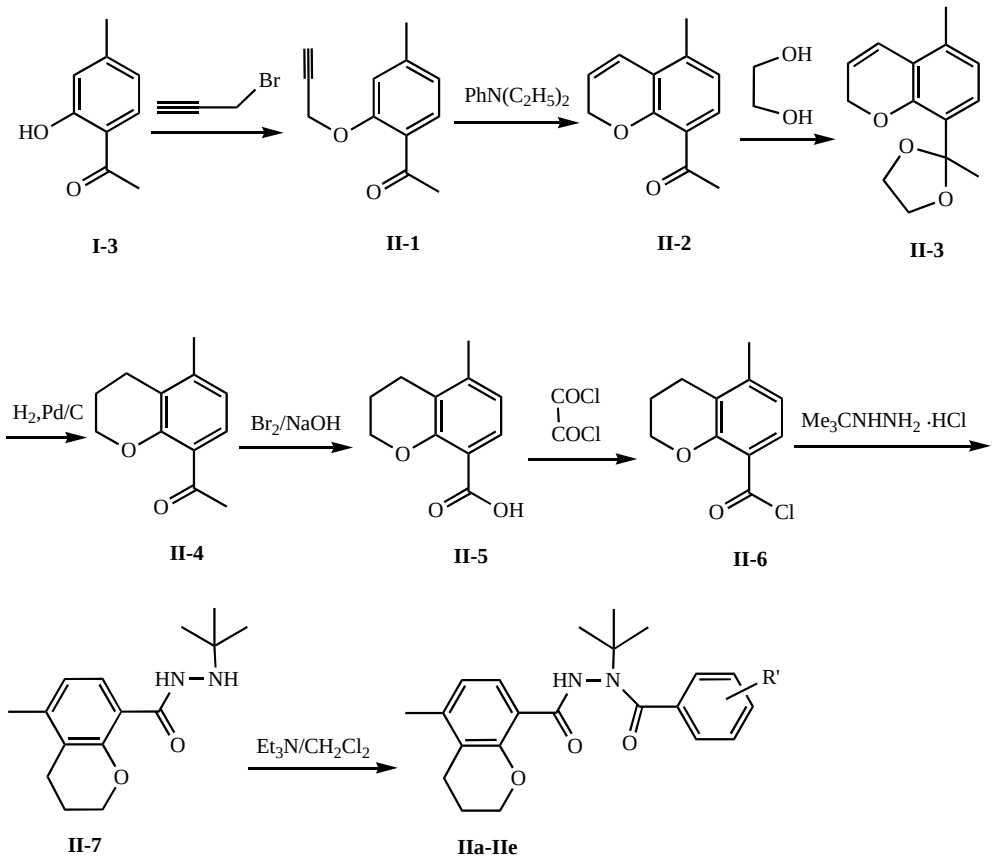
Table 1. Physical Properties and Elemental Analyses (HRMS) of Target Compounds Ia~If and IIa~IIe

Compd.	R (R′)	Yield (%)	mp (˚C)	elem anal. (%, calc)		
				C	H	N
Ia	H	86	207-208	72.27 (72.11)	6.97 (7.15)	7.53 (7.64)
Ib	3-Me	64	112-114	72.65 (72.60)	7.31 (7.42)	7.34 (7.36)
Ic	3-Cl	93	133-134	65.89 (65.91)	6.32 (6.29)	7.05 (7.11)
Id	3,5-Me_2	53	182-183	73.31 (73.07)	7.79 (7.66)	6.91 (7.10)
Ie	3,5-Cl_2	47	176-177	60.79 (60.70)	5.74 (5.56)	6.20 (6.43)
If	3,5-$(NO_2)_2$	41	101-103	457.1713 (457.1718) [a]		
IIa	H	79	240-242	389.1836 (389.1836) [b]		
IIb	2-NO_2	74	jelly	412.1866 (412.1867) [a]		
IIc	3-Cl	38	182-184	457.1050 (457.1056) [b]		
IId	3,5-Me_2	76	190-192	395.2335 (395.2329) [a]		
IIe	2,4-Cl_2	39	149-151	423.1454 (423.1446) [b]		

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

Table 2. ^{1}H NMR Spectral Data of Target Compounds Ia~If and IIa~IIe

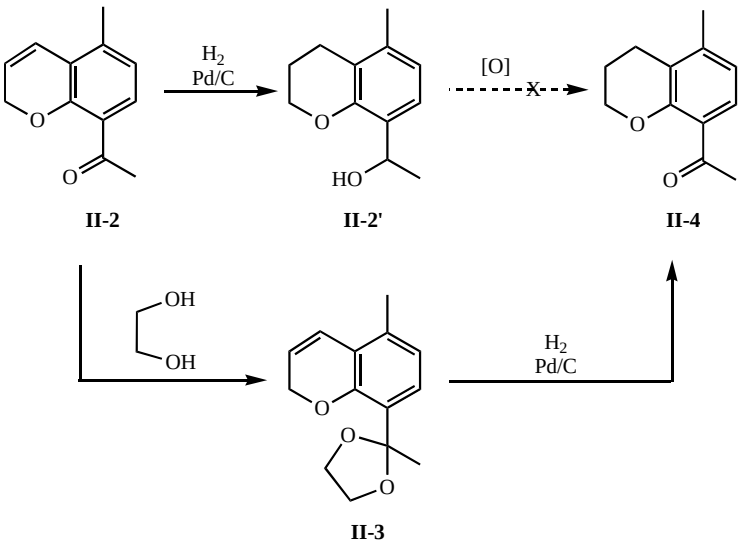
Compd.	^{1}H NMR (δppm)
Ia	(400MHz, $CDCl_3$): 9.16 (brs, 1H, NH); 7.63 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph);7.45-7.52 (m, 2H, Ph) ; 7.21 (brs, 3H, Ph); 6.69 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 4.99-5.14 (m, 1H, CH); 3.19-3.30 (m, 1H, CH_2); 2.64-2.76 (m, 1H, CH_2); 2.20 (s, 3H, $PhCH_3$); 1.58 (s, 9H, $C(CH_3)_3$); 1.48 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ib	(300MHz, $CDCl_3$): 9.14 (brs, 1H, NH); 7.62-7.66 (m, 1H, Ph); 7.23-7.33 (m, 2H, Ph); 7.00-7.11 (m, 2H, Ph); 6.70 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 4.98-5.14 (m, 1H, CH); 3.19-3.30 (m, 1H, CH_2); 2.64-2.76 (m, 1H, CH_2); 2.24 (d, 3H, $^4J_{HH}$ = 3.6 Hz, $PhCH_3$); 2.20 (s, 3H, $PhCH_3$); 1.57 (s, 9H, $C(CH_3)_3$); 1.46 (d, 3H, $^3J_{HH}$ = 6.2 Hz, CCH_3)
Ic	(300MHz, $CDCl_3$): 9.17 (brs, 1H, NH); 7.56-7.65 (m, 1H, Ph); 7.37-7.47 (m, 2H, Ph); 7.12-7.17 (m, 2H, Ph); 6.71 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 5.05-5.15 (m, 1H, CH); 3.22-3.30 (m, 1H, CH_2); 2.66-2.77 (m, 1H, CH_2); 2.21 (s, 3H, $PhCH_3$); 1.56 (s, 9H, $C(CH_3)_3$); 1.46 (d, 3H, $^3J_{HH}$ = 6.1 Hz, CCH_3)
Id	(300MHz, $CDCl_3$): 9.12 (brs, 1H, NH); 7.66 (t, 1H, $^3J_{HH}$ = 7.6 Hz, Ph); 7.09 (d, 2H, $^4J_{HH}$ = 14.0 Hz, Ph); 6.84 (s, 1H, Ph); 6.71 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 4.97-5.13 (m, 1H, CH); 3.19-3.30 (m, 1H, CH_2); 2.65-2.77 (m, 1H, CH_2); 2.21 (s, 6H, $PhCH_3$); 1.57 (s, 9H, $C(CH_3)_3$); 1.41 (d, 3H, $^3J_{HH}$ = 6.1 Hz, CCH_3)
Ie	(300MHz, $CDCl_3$): 9.12 (brs, 1H, NH); 7.64 (t, 1H, $^3J_{HH}$ = 6.7 Hz, Ph); 7.38 (d, 2H, $^3J_{HH}$ = 11.3 Hz, Ph); 7.21 (s, 1H, Ph); 6.73 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 5.08-5.16 (m, 1H, CH); 3.23-3.32 (m, 1H, CH_2); 2.69-2.79 (m, 1H, CH_2); 2.23 (s, 3H, $PhCH_3$); 1.55 (s, 9H, $C(CH_3)_3$); 1.50 (t, 3H, $^3J_{HH}$ = 6.4 Hz, CCH_3)
If	(300MHz, $CDCl_3$): 9.10 (brs, 1H, NH); 9.00 (t, 1H, $^4J_{HH}$ = 2.0 Hz, Ph); 8.79 (d, 2H, $^4J_{HH}$ = 2.0 Hz, Ph); 7.30 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 6.67 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph);4.81-4.93 (m, 1H, CH); 3.11-3.19 (m, 1H, CH_2); 2.58-2.66 (m, 1H, CH_2); 2.17 (s, 3H, $PhCH_3$); 1.29 (s, 3H, CCH_3); 0.95 (s, 9H, $C(CH_3)_3$)
IIa	(400MHz, $CDCl_3$): 9.32 (s, 1H, NH); 7.65 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.46-7.48 (m, 2H, Ph); 7.21-7.24 (m, 3H, Ph); 6.75 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 4.19-4.23 (m, 2H, CH_2); 2.59-2.62 (m, 2H, CH_2); 2.16 (s, 3H, $PhCH_3$); 2.01-2.04 (m, 2H, CH_2); 1.57 (s, 9H, $C(CH_3)_3$)
IIb	(400MHz, $CDCl_3$): 9.60 (s, 1H, NH); 8.04 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 7.82-7.84 (m, 1H, Ph); 7.64 (d, 1H, $^3J_{HH}$ = 7.9 Hz, Ph); 7.55-7.56 (m, 1H, Ph); 7.32-7.37 (m, 1H, Ph); 6.73 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 4.09-4.16 (m, 2H, CH_2); 2.49-2.61 (m, 2H, CH_2); 2.14 (s, 3H, $PhCH_3$); 1.99-2.04 (m, 2H, CH_2); 1.60 (s, 9H, $C(CH_3)_3$)
IIc	(400MHz, $CDCl_3$): 9.35 (s, 1H, NH); 7.67 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.43 (s, 1H, Ph); 7.39 (d, 1H, $^3J_{HH}$ = 7.3 Hz, Ph); 7.13-7.21 (m, 2H, Ph); 6.77 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph); 4.25-4.29 (m, 2H, CH_2); 2.61-2.64 (m, 2H, CH_2); 2.18 (s, 3H, $PhCH_3$); 2.04-2.07 (m, 2H, CH_2); 1.56 (s, 9H, $C(CH_3)_3$)
IId	(400MHz, $CDCl_3$): 9.35 (s, 1H, NH); 7.61 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 7.05 (s, 2H, Ph); 6.81 (s, 1H, Ph); 6.69 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ph); 4.19-4.21 (m, 2H, CH_2); 2.55-2.57 (m, 2H, CH_2); 2.16 (s, 6H, $PhCH_3$); 2.12 (s, 3H, $PhCH_3$); 2.00-2.05 (m, 2H, CH_2); 1.54 (s, 9H, $C(CH_3)_3$)
IIe	(400MHz, $CDCl_3$): 9.66 (s, 1H, NH); 7.67 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 7.35 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 7.24 (s, 1H, Ph); 7.10 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ph); 6.77 (d, 1H, $^3J_{HH}$ = 8.0 Hz, Ph); 4.30-4.35 (m, 2H, CH_2); 2.60-2.64 (m, 2H, CH_2); 2.18 (s, 3H, $PhCH_3$); 2.02-2.08 (m, 2H, CH_2); 1.56 (s, 9H, $C(CH_3)_3$)



Scheme 2.

methylchroman-8-yl)ethanone (**II-4**) by hydrogen with Pd/C as catalyst, but we got unexpected compound, 1-(5-methylchroman-8-yl)ethanol (**II-2'**, Scheme **3**). Physical properties and ^{1}H NMR data of compound **II-2'**, colorless viscous liquid, ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.05 (d, 1H, $^3J_{HH}$ = 7.6, Ph), 6.74 (d, 1H, $^3J_{HH}$ = 7.6, Ph), 4.99-5.04 (m, 1H, CH), 4.20 (t, 2H, $^3J_{HH}$ = 5.1, CH_2O), 2.85 (br, 1H, OH), 2.66 (t, 2H, $^3J_{HH}$ = 6.6, CH_2), 2.22 (s, 3H, $PhCH_3$), 2.04-2.07 (m, 2H, CH_2), 1.50 (d, 3H, $^3J_{HH}$ = 6.5, CH_3).

Because of the influence of heterocycle pyran, 1-(5-methyl-2H-chromen-8-yl)ethanone (**II-2**) can not be oxidized to 1-(5-methylchroman-8-yl)ethanone (**II-4**). At last, compound **II-2'** was protected by ethylene glycol to give 5-methyl-8-(2-methyl-1,3-dioxolan-2-yl)-2H-chromene (**II-3**), and then reduced by hydrogen with Pd/C as catalyst to successfully afford 1-(5-methylchroman-8-yl)ethanone (**II-4**) in one pot (Scheme **3**).



Scheme 3.

Oxidation of 1-(5-methylchroman-8-yl)ethanone (**II-4**) gave 5-methylchroman-8-carboxylic acid (**II-5**) by bromoform reaction. It is interesting that acid **II-5** could not be transformed to 5-methylchroman-8-carbonyl chloride (**II-6**) by thionyl chloride, because acid **II-5** was decomposed to a black solid by $SOCl_2$. As mentioned above, 2,3-dihydro-2,4-dimethylbenzofuran-7-carboxylic acid (**I-7**) could be reacted with $SOCl_2$ to produce the corresponding acyl chloride **I-8**, successfully. This indicated that different heterocycle on the benzene ring of benzoheterocyle moiety can influence the reaction of corresponding acid. 5-Methylchroman-8-carboxylic acid (**II-5**) was reacted with oxalyl chloride to successfully produce the corresponding acyl chloride **II-6**, its subsequent reaction with tert-butylhydrazine hydrochloride yielded N'-tert-butyl-N-5-methylchroman-8-carbohydrazide (**II-7**). Finally, the target compounds **IIa~IIe** were synthesized by the reaction of various substituted benzoylchloride with intermediate **II-7** in dichloromethane using triethylamine as proton scavenger. The physical properties and elemental analyses or HRMS of compounds **IIa~IIe** are listed in Table **1**, and their ^{1}H NMR is listed in Table **2**.

The intermediates **I-4~I-9**, **II-1~II-4**, **II-7** and the target compounds **Ia~If** and **IIa~IIe** are new compounds. The structure of N-tert-butyl-N'-2,3-dihydro-2,4-dimethylbenzofuran-7-carbohydrazide (**I-9**) was also determined by X-ray diffraction (Fig. (**2**)).

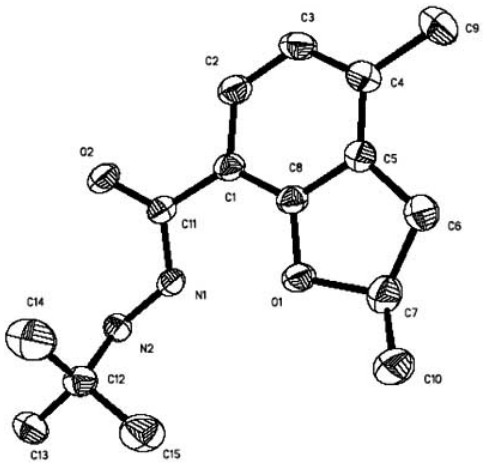


Fig. (2). Crystal structure of compound **I-9**.

In conclusion, six of new N'-tert-butyl-N'-substitutedbenzoyl-N-(2,4-dimethyl-2,3-dihydrobenzofuran)-7-carbohydrazide derivatives (**Ia~If)** and five of new N'-tert-butyl-N'-substitutedbenzoyl-N-(5-methylchroman)-8-carbohydrazide derivatives (**IIa~IIe**) were synthesized and their structures were confirmed by ^{1}H NMR spectra, elemental analysis or high resolution mass spectra (HRMS). The structure of N-tert-butyl-N'-2,3-dihydro-2,4-dimethylbenzofuran-7-carbohydrazide was also determined by X-ray diffraction. An important feature is that 1-(3-allyl-2-hydroxy-4-methylphenyl) ethanone can easily transformed into 1-(2,3-dihydro-2,4-dimethylbenzofuran-7-yl)ethanone just with concentrated sulfuric acid as catalyst. In addition, we found that 1-(5-methyl-2H-chromen-8-yl)ethanone could not be reduced to 1-(5-methylchroman-8-yl)ethanone directly by hydrogen with Pd/C as catalyst. It is an effective method for protecting 1-(5-methyl-2H-chromen-8-yl)ethanone with ethylene glycol to obtain 5-methyl-8-(2-methyl-1,3-dioxolan-2-yl)-2H-chromene and then reducing by hydrogen with Pd/C as catalyst to produce 1-(5-methylchroman-8-yl)ethanone in one step. Furthermore, we noted a new phenomena that $SOCl_2$ can convert 2,3-dihydro-2,4-dimethylbenzofuran-7-carboxylic acid to 2,3-dihydro-2,4-dimethylbenzofuran-7-carbonyl chloride, but it is inefficient for transforming 5-methylchroman-8-carboxylic acid to the corresponding acyl chloride because of its degradation. So it shows that different heterocycle on the benzene ring of benzoheterocyle moiety have influence on the reaction property of the corresponding acid.

EXPERIMENTAL

The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-P300 or Varian Mercury Plus 400 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Chemical shift values (δ) are given in parts per million and J values were given in Hz. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. HRMS was obtained on FTICR-MS (Ionspec 7.0T). X-ray single crystal diffraction was determined on BRUCKER SMART 1000 X-ray single crystal diffraction analyzer. Yields were not optimized.

Synthesis of 1-[2-(allyloxy)-4-methylphenyl]ethanone (I-4)

3-Bromoprop-1-ene (38.6 g, 318.8 mmol) was added to the mixture of compound **I-3** (39.9 g, 265.7 mmol), toluene (200 ml), aqueous solution (30 ml) of sodium hydroxide (12.8 g, 318.8 mmol), tetrabutyl ammonium bromide (8.6 g, 26.6 mmol) at stirring and in ice bath. After stirring for 12 h at 50-55 ˚C, the reaction mixture was cooled and diluted with ethyl acetate (100 ml). The separated organic layer was washed with water (3 × 50 ml) and brine (50 ml) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized from petroleum ether (60-90 ˚C) and ethyl acetate (5/1) to give 1-[2-(allyloxy)-4-methylphenyl]ethanone (**I-4**) as a white crystal (34.2 g, 72%), m.p. 48-49 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.80 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.74 (s, 1H, Ph), 6.04-6.13 (m, 1H, CH_2=CH), 5.43 (d, 1H, $^3J_{HH}$ = 17.3, CH_2=CH), 5.32 (d, 1H, $^3J_{HH}$ = 10.5, CH_2=CH), 4.62 (d, 2H, $^3J_{HH}$ = 5.3, CH_2O), 2.62 (s, 3H, CH_3CO), 2.36 (s, 3H, $PhCH_3$). Anal. Calcd for $C_{12}H_{14}O_2$ (%): C 75.76, H 7.42; found C 75.75, H 7.00.

Synthesis of 1-(3-allyl-2-hydroxy-4-methylphenyl) ethanone (I-5)

A mixture of compound **I-4** (14.7 g, 77.3 mmol), N,N-diethylaniline (150 ml) was refluxed for 7 h. After cooling at room temperature, the reaction mixture was neutralized with hydrochloric acid (2 mol L^{-1}), and then extracted with petroleum ether (60-90 ˚C, 3 × 200 ml). The separated organic layer was washed successively with water (2 × 200 ml) and brine (200 ml), and then dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was vacuum distilled (b.p. 130-132 ˚C/0.5 mmHg) to give 1-(3-allyl-

2-hydroxy-4-methylphenyl)ethanone (**I-5**) as a light yellow oil (14.2 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.69 (s, 1H, PhOH), 7.51 (d, 1H, $^3J_{HH}$ = 8.2, Ph), 6.71 (d, 1H, $^3J_{HH}$ = 8.2, Ph), 5.86-5.99 (m, 1H, CH_2=CH), 4.99 (d, 1H, $^3J_{HH}$ = 11.3, CH_2=CH), 4.93 (d, 1H, $^3J_{HH}$ = 17.1, CH_2=CH), 3.44 (d, 2H, $^3J_{HH}$ = 5.9, CH_2O), 2.59 (s, 3H, CH_3CO), 2.32 (s, 3H, $PhCH_3$).

Synthesis of 1-(2,3-dihydro-2,4-dimethylbenzofuran-7-yl)ethanone (I-6)

A mixture of compound **I-5** (10.0 g, 52.3 mmol), concentrated sulfuric acid (1.1 g, 10.5 mmol) was heated at about 110 ℃ for 0.5 h. The reaction mixture was resolved with CH_2Cl_2 (30 ml) and then was washed successively with water (20 ml) and brine (20 ml), and then dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica-gel column chromatography [petroleum ether (60-90℃)/ ethyl acetate = 30/1] to give 1-(2,3-dihydro-2,4-dimethylbenzofuran-7-yl)ethanone (**I-6**) as a white crystal (4.1 g, 41%), m.p. 73-74℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 6.69 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 5.02-5.10 (m, 1H), 3.22-3.28 (m, 1H), 2.69-2.75 (m, 1H), 2.59 (s, 3H, CH_3CO), 2.24 (s, 3H, $PhCH_3$),1.51(d, 3H, $^3J_{HH}$ = 6.2). Anal. Calcd for $C_{12}H_{14}O_2$ (%): C 75.76, H 7.42; found C 75.66, H 7.40.

Synthesis of 2,3-dihydro-2,4-dimethylbenzofuran-7-carboxylic acid (I-7)

Bromine (2.5 g, 15.6 mmol) was added dropwise to a stirred solution of sodium hydroxide (2.5 g, 15.6 mmol) in water (10 ml) in an ice bath. After 2 h, compound **I-6** (0.9 g, 4.7 mmol) in 1,4-dioxane (10 ml) was added with stirring and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with diethyl ether (2 × 20 ml). The aqueous layer was acidified with hydrochloride (1 mol L^{-1}) and extracted with dichloromethane (3 × 20 ml). The combined organic layer was washed with water (20 ml) and brine (20 ml), and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized with dichloromethane to give 2,3-dihydro-2,4-dimethylbenzofuran-7-carboxylic acid (**I-7**) as a white crystal (0.8 g, 83%), m.p. 203-205 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.39 (brs, 1H, COOH), 7.74 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 6.78 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 5.14-5.26 (m, 1H), 3.27-3.36 (m, 1H), 2.75-2.83 (m, 1H), 2.28 (s, 3H, $PhCH_3$), 1.57(d, 3H, $^3J_{HH}$ = 6.3). Anal. Calcd for $C_{11}H_{12}O_3$ (%): C 68.74, H 6.29; found C 68.50, H 6.45.

Synthesis of 2,3-dihydro-2,4-dimethylbenzofuran-7-carbonyl chloride (I-8) and N'-tert-butyl-N-2,3-dihydro-2,4-dimethylbenzofuran-7-carbohydrazide (I-9)

A mixture of compound **I-7** (0.8 g, 3.9 mmol) and thionyl chloride (3 ml) was refluxed for 2 h. After the excess of thionyl chloride was removed under reduced pressure, the residue was dissolved in dichloromethane (5 ml). The resulting solution was added dropwise to a stirred mixture of tert-butylhydrazine hydrochloride (0.6 g, 4.7 mmol), sodium hydroxide (0.2 g, 4.7 mmol), dichloromethane (40 ml) and water (5 ml) at -15℃. After stirring overnight at room temperature, the organic layer was separated and washed successively with water (2 × 20 ml) and brine (20 ml) then dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica-gel column chromatography [petroleum ether (60-90℃)/ ethyl acetate = 3/1] to give N-tert-butyl-N'-2,3-dihydro-2,4-dimethylbenzofuran-7-carbohydrazide (**I-9**) as a colorless crystal (0.6 g, 55%), m.p. 99-100 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (brs, 1H, NH), 7.81 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.79 (d, 1H, $^3J_{HH}$ =7.9, Ph), 5.07-5.14 (m, 1H), 3.25-3.33 (m, 2H, NH, CH), 2.73-2.81 (m, 1H), 2.26 (s, 3H, $PhCH_3$), 1.52 (d, 3H, $^3J_{HH}$ = 6.2), 1.16 (s, 9H, $C(CH3)_3$). Anal. Calcd for $C_{15}H_{22}N_2O_2$ (%): C 68.67, H 8.45, N 10.68; found C 68.68, H 8.47, N 10.63.

General Synthetic Procedure for N'-tert-butyl-N'-substitutedbenzoyl-N-(2,3-dihydro-2,4-dimethylbenzofuran)-7-carbohydrazide (Ia~If)

The solution of substituted benzoyl chloride (0.4 mmol) in dichloromethane (10 ml) was added dropwise to a stirred mixture of compound **I-9** (0.1 g, 0.4 mmol), triethylamine (0.04 g, 0.42 mmol) and dichloromethane (10 ml) in an ice bath. After stirring the reaction mixture at room temperature overnight. The reaction mixture was washed successively with water (2 × 10 ml) and brine (10 ml) 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~If**. The physical properties and elemental analyses or HRMS of new compounds (**Ia~If**) are listed in Table **1**, and their ^{1}H NMR is listed in Table **2**.

Synthesis of 1-[4-methyl-2-(prop-2-ynyloxy)phenyl]ethanone (II-1)

3-Bromoprop-1-yne (14.3 g, 120.0 mmol) was added to the mixture of compound **I-3** (15.0 g, 100.0 mmol), toluene (600 ml), aqueous solution (10 ml) of sodium hydroxide (9.6 g, 240.0 mmol), tetrabutyl ammonium bromide (3.9 g, 12.0 mmol) at stirring and in ice bath. After stirring for 5 h at room temperature, the reaction mixture was cooled and diluted with ethyl acetate (50 ml). The separated organic layer was washed with water (3 × 50 ml) and brine (50 ml) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized [petroleum ether (60-90 ℃)/ethyl acetate = 10/1] to give 1-[4-methyl-2-(prop-2-ynyloxy)phenyl]ethanone (**II-1**) as a white crystal (15.2 g, 81%), m.p. 69-71 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, 1H, $^3J_{HH}$ = 8.2, Ph), 6.83 (s, 2H, Ph), 4.77 (d, 2H, $^4J_{HH}$ = 2.2, CH_2O), 2.60 (s, 3H, CH_3CO), 2.55 (t, 1H, $^4J_{HH}$ = 2.3, CH),2.37 (s, 3H, $PhCH_3$). Anal. Calcd for $C_{12}H_{12}O_2$ (%): C 76.57, H 6.43; found C 76.57, H 6.40.

Synthesis of 1-(5-methyl-2H-chromen-8-yl)ethanone (II-2)

A mixture of compound **II-1** (17.0 g, 90.1 mmol), N,N-diethylaniline (150 ml) was refluxed for 5 h. After cooling at room temperature, the reaction mixture was neutralized with hydrochloric acid (1 mol L^{-1}), and then extracted with dichloromethane (3 × 100 ml). The separated organic layer was washed successively with water (2 × 70 ml) and brine

(70 ml), and then dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica-gel column chromatography [petroleum ether (60-90℃)/ ethyl acetate = 30/1] to give 1-(5-methyl-2H-chromen-8-yl)ethanone (**II-2**) as a white crystal (10.3 g, 61%), m.p. 51-53 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 6.73 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 6.60 (d, 1H, $^3J_{HH}$ = 10.0, CH=CH), 5.86-5.91 (m, 1H, CH=CH), 4.80-4.81 (m, 2H, CH_2O), 2.56 (s, 3H, CH_3CO), 2.28 (s, 3H, $PhCH_3$). Anal. Calcd for $C_{12}H_{12}O_2$ (%): C 76.57, H 6.43; found C 76.52, H 6.42.

Synthesis of 5-methyl-8-(2-methyl-1,3-dioxolan-2-yl)-2H-chromene (II-3)

The mixture of compound **II-2** (10.3 g, 54.6 mmol), toluene (30 ml), ethylene glycol (4.1g, 65.5 mmol), p-toluenesulfonic acid (0.2 g, 1.1 mmol) was refluxed for about 3 h until there is no water separated from the reaction mixture using water segregator. The reaction mixture was washed successively with saturated sodium bicarbonate solution (20 ml), water (20 ml) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica-gel column chromatography [petroleum ether (60-90℃)/ ethyl acetate = 30/1] to give 5-methyl-8-(2-methyl-1,3-dioxolan-2-yl)-2H-chromene (**II-3**) as a light yellow oil (5.5 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.70 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.62 (d, 1H, $^3J_{HH}$ = 10.0, CH=CH), 5.86-5.91 (m, 1H, CH=CH), 4.76-4.77 (m, 2H, CH_2O), 4.02-4.06 (m, 2H, CH_2O), 3.82-3.877 (m, 2H, CH_2O), 2.28 (s, 3H, CH_3), 1.78 (s, 3H, $PhCH_3$). Anal. Calcd for $C_{14}H_{16}O_3$ (%): C 72.39, H 6.94; found C 72.29, H 6.91.

Synthesis of 1-(5-methylchroman-8-yl)ethanone (II-4)

A mixture of compound **II-3** (5.5 g, 23.6 mmol), ethanol (30 ml) and 10% palladium on activated carbon (0.9 g, 50% in water) was vigorously stirred under 1 atm of hydrogen at room temperature for 5 h. The reaction mixture was filtered. After removal of the solvent, the residue was purified by silica-gel column chromatography [petroleum ether (60-90 ℃)/ ethyl acetate = 30/1] to give1-(5-methylchroman-8-yl)ethanone (**II-4**) as a white crystal (3.2 g, 72%), m.p. 62-63 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.75 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 4.23 (t, 2H, $^3J_{HH}$ = 5.1, CH_2O), 2.67 (t, 2H, $^3J_{HH}$ = 6.6, CH_2), 2.57 (s, 3H, CH_3CO), 2.22 (s, 3H, $PhCH_3$), 2.04-2.10 (m, 2H, CH_2). Anal. Calcd for $C_{12}H_{14}O_2$ (%): C 75.76, H 7.42; found C 76.00, H 7.44.

Synthesis of 5-methylchroman-8-carboxylic Acid (II-5)

Bromine (15.6 g, 97.4 mmol) was added dropwise to a stirred solution of sodium hydroxide (15.6 g, 389.7 mmol) in water (63 ml) in an ice bath. After 2 h, compound **II-4** (5.6 g, 29.5 mmol) in 1,4-dioxane (63 ml) was added with stirring and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with diethyl ether (2 × 40 ml). The aqueous layer was acidified with hydrochloride (1 mol L^{-1}) and extracted with dichloromethane (3 × 40 ml). The combined organic layer was washed with water (20 ml) and brine (20 ml), and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized with dichloromethane to give 5-methylchroman-8-carboxylic acid (**II-5**) as a white crystal (4.0 g, 71%), m.p. 121-122 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.87 (brs, 1H, COOH), 7.91 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 6.90 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 4.40 (t, 2H, $^3J_{HH}$ = 4.8, CH_2O), 2.72 (t, 2H, $^3J_{HH}$ = 6.5, CH_2), 2.27 (s, 3H, $PhCH_3$), 2.12-2.20 (m, 2H, CH_2). Anal. Calcd for $C_{11}H_{12}O_3$ (%): C 68.74, H 6.29; found C 68.55, H 6.35.

Synthesis of 5-methylchroman-8-carbonyl chloride (II-6) and N'-tert-butyl-N-5-methylchroman-8-carbohydrazide (II-7)

A mixture of compound **II-5** (0.5 g, 2.6 mmol) and oxalyl chloride (3 ml) was stirred for 10 h at room temperature. After the excess of oxalyl chloride was removed under reduced pressure, the residue was dissolved in dichloromethane (5 ml). The resulting solution was added dropwise to a stirred mixture of tert-butylhydrazine hydrochloride (0.4 g, 3.12 mmol), sodium hydroxide (0.1 g, 3.1 mmol), dichloromethane (30 ml) and water (5 ml) at -15℃. After stirring overnight at room temperature, the organic layer was separated and washed successively with water (2 × 15 ml) and brine (15 ml) then dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica-gel column chromatography [petroleum ether (60-90℃)/ ethyl acetate = 2/1] to give N'-tert-butyl-N-5-methylchroman-8-carbohydrazide (**II-7**) as a light yellow ropy liquid (0.3 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (brs, 1H, NH), 7.91 (d, 1H, $^3J_{HH}$ = 8.1, Ph), 6.85 (d, 1H, $^3J_{HH}$ = 7.9, Ph), 4.26 (t, 2H, $^3J_{HH}$ = 5.2, CH_2O), 2.74 (t, 2H, $^3J_{HH}$ = 6.4, CH_2), 2.45 (brs, 1H, NH), 2.31 (s, 3H, $PhCH_3$), 2.06-2.12 (m, 2H, CH_2), 1.14 (s, 9H, $C(CH3)_3$).

General Synthetic Procedure for N'-tert-butyl-N'-substitutedbenzoyl-N-(5-methylchroman)-8-carbohydrazide Derivatives (IIa~IIe)

The solution of substituted benzoyl chloride (0.7 mmol) in dichloromethane (10 ml) was added dropwise to a stirred mixture of compound **II-7** (0.2 g, 0.7 mmol), triethylamine (0.07 g, 0.72 mmol) and dichloromethane (10 ml) in an ice bath. After stirring the reaction mixture at room temperature overnight, the reaction mixture was washed successively with water (2 × 10 ml) and brine (10 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 **IIa~IIe**. The physical properties and elemental analyses or HRMS of new compounds (**IIa~IIe**) are listed in Table **1**, and their ^{1}H NMR is listed in Table **2**.

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