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Synthesis and insecticidal activity of chromanone and chromone analogues of diacylhydrazines

Pei-Liang Zhao, Jing Li and Guang-Fu Yang*

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

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Abstract—Diacylhydrazine derivatives have been identified as one of the most important insect growth regulators. A variety of diacylhydrazine derivatives were designed and synthesized in recent years due to their unique action mechanism, simple structure, and environmental benign character. This paper describes the molecular design, synthesis, and insecticidal activities of a series of chromanone and chromone analogues of diacylhydrazine derivatives. The preliminary bioassay showed that some of the chromanone analogues exhibited good insecticidal activity against *Mythima separata* at the dosage of 500 mg L^{-1}. The present work demonstrated that replacement of the chroman ring of ANS-118, a commercial insecticide, with chromanone moiety could result in new compounds with high potent insecticidal activity.

1. Introduction

It is well known that two different types of hormones, juvenile hormones (JHs) and 20-hydroxy-ecdysone (20-HE) as shown in Figure 1, are responsible for regulating molting and metamorphosis in insect development.[1,2] As these hormones play crucial roles in the endocrine systems of insect, it is considered that both agonists and antagonists could be developed as new insect growth regulators. 1-*tert*-Butyl-1,2-dibenzoyl hydrazine (RH-5849, Fig. 1) was reported as the first nonsteroidal ecdysone agonist in 1988.[3,4] Although there exists structural dissimilarity between 20-HE and RH-5849, RH-5849 was thought to mimic the action of 20-HE in activating the ecdysone receptor. Because of the unique action mechanism, simple structure, and environmental benign character of RH-5849, a variety of diacylhydrazine derivatives have been designed and synthesized for the purpose of obtaining new compounds with higher insecticidal activity so far,[5–14] and RH-5992 (Tebufenozide, Fig. 1), RH-2485 (Methoxyfenozide, Fig. 1), RH-0345 (Halofenozide, Fig. 1), and ANS-118 (Chromafenozide, Fig. 1) were developed as high potent ecdysone agonists.[15–17]

The success of ANS-118 indicated that the strategy of *ortho*-substituent cyclization is an effective way to optimize the diacylhydrazine derivatives. In addition, because chromanone derivatives have been found to exhibit broad-spectrum biological activities, such as insecticidal, antifungal, and antibacterial activities, we developed an idea that replacement of the chroman ring of ANS-118 with chromanone moiety might also result in new compounds with high insecticidal activity (Fig. 2). In this paper, we describe the synthesis and insecticidal activity of a series of chromanone analogues **1** of diacylhydrazines. Meanwhile, as a control, we also designed and synthesized a series of chromone analogues **2** of diacylhydrazines.

2. Chemistry

The synthetic route of the designed chromanone analogues **1** of diacylhydrazines is summarized in Scheme 1. The ethyl *p*-hydroxybenzoate **3** was converted to ethyl 3-acetyl-4-hydroxybenzoate **4** by a Friedel–Crafts acylation procedure. Treatment of **4** with acetone in pyridine solution followed by a reaction with 10% NaOH solution afforded compound **6**, 2,2-dimethyl-4-chromanone-6-carboxylic acid. Then, **6** reacted with $SOCl_2$ in anhydrous CH_2Cl_2 solution to afford 2,2-dimethyl-4-chromanone-6-carbonyl chloride **7**, which condensed with *tert*-butylhydrazine hydrochloride to give the key

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* Corresponding author. E-mail: gfyang@mail.ccnu.edu.cn

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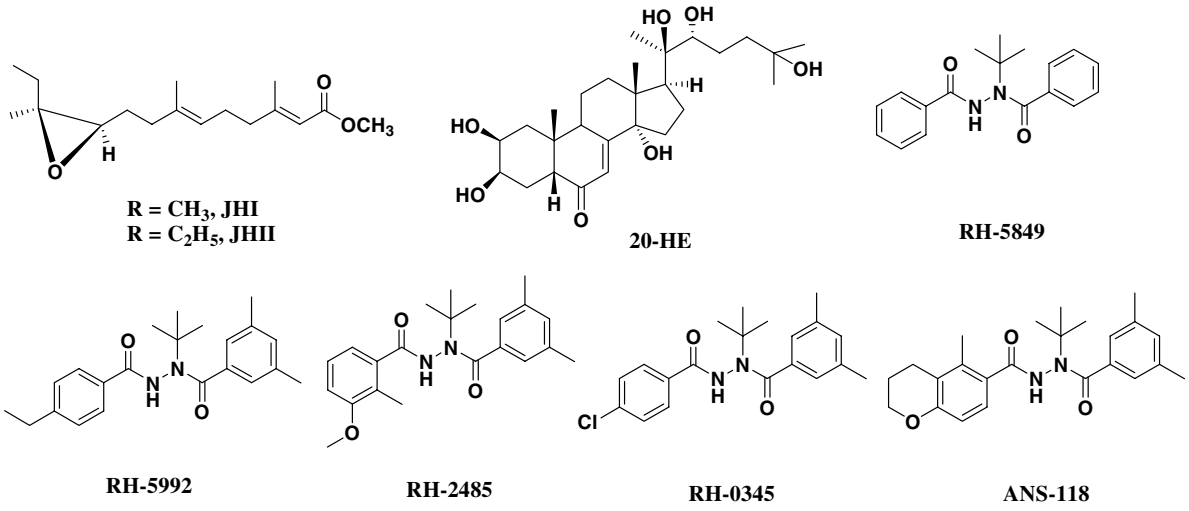


Figure 1. Structures of JHs, 20-HE, RH-5849, RH-5992, RH-2485, RH-0345, and ANS-118.

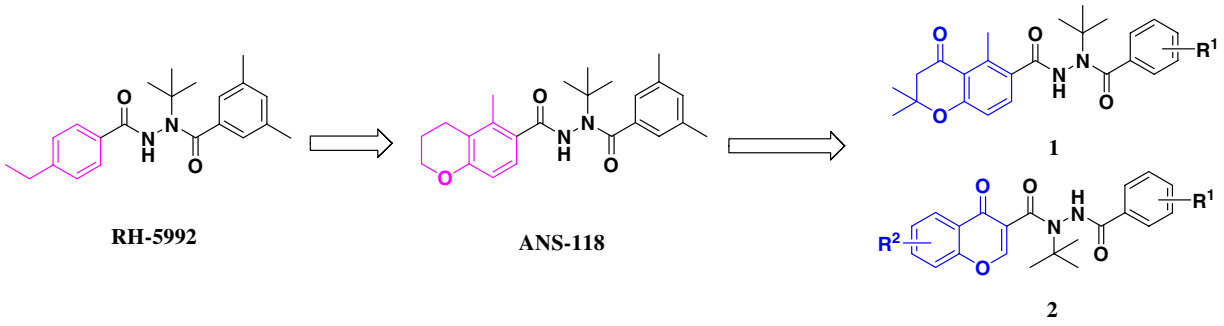
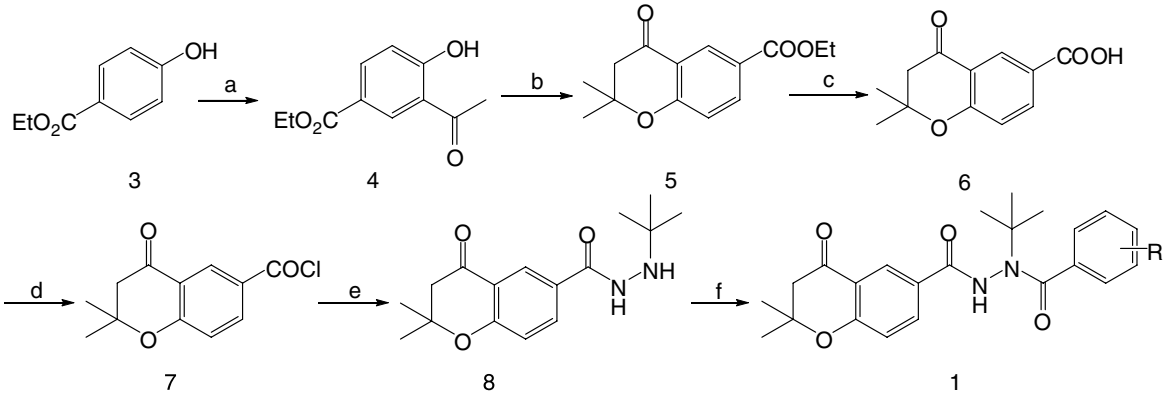


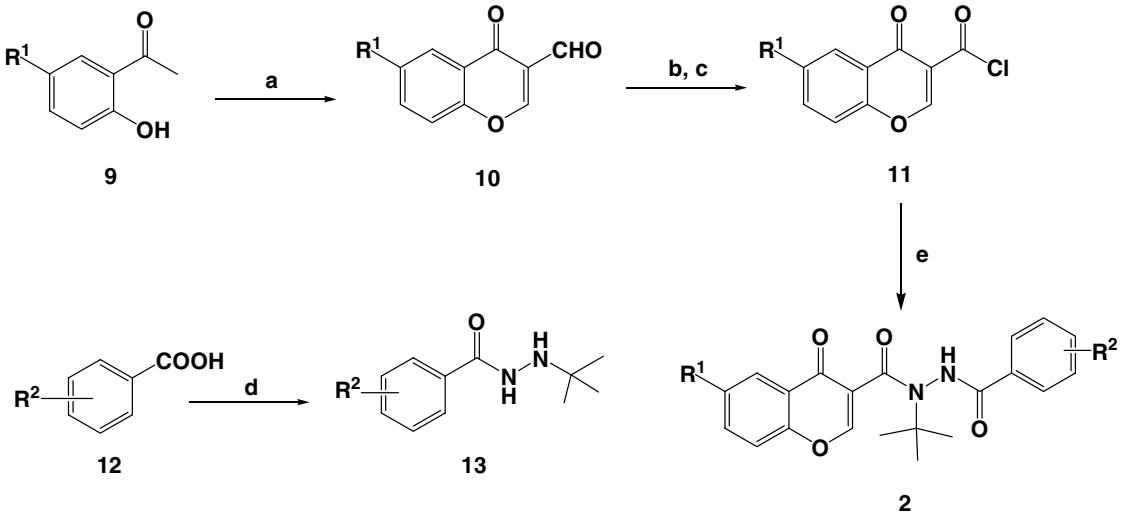
Figure 2. Design strategy of the target compounds.



Scheme 1. Reagents and conditions: (a) $(CH_3CO)_2O$, anhyd $AlCl_3$, 140 °C; (b) acetone, pyridine, reflux for 2 h; (c) 10% NaOH, rt; (d) anhyd CH_2Cl_2, $SOCl_2$, reflux for 5 h; (e) *t*-BuNHNH$_2$·HCl, 10% NaOH, CH_2Cl_2, ice-bath; (f) substituted benzoyl chloride, CH_2Cl_2, Et_3N, rt.

intermediate **8**, *N′-tert*-butyl-2,2-dimethyl-4-chromanone-6-carbohydrazide. Subsequently, compound **8** reacted with various substitutedbenzoyl chlorides to afford the title compounds **1a**–**i** in yields of 58–81%.

The syntheses of the chromone analogues **2** of diacylhydrazines are summarized in Scheme 2. According to the reported method,[18] 6-substituted-4-chromone-3-carbaldehydes **10** were easily prepared by the reaction of 2-hydroxy-5-substituted-acetophenone **9** with DMF in $POCl_3$ solution. Then, **10** was treated with NBS in the presence of catalytic amount of AIBN, followed by reaction with $SOCl_2$, to give the intermediate 6-substituted-4-chromone-3-carbonyl chloride**11**, which reacted with *N′-tert*-butyl-substitutedbenzohydrazide **13** obtained from the reaction of benzoic acids **12** with $SOCl_2$ to give the diacylhydrazine derivatives **2a**–**h** in yields of 66–78%.



Scheme 2. Reagents and conditions: (a) DMF, $POCl_3$, −10 °C; (b) NBS, AIBN, anhyd CCl_4, reflux for 1 h; (c) anhyd CH_2Cl_2, $SOCl_2$, reflux for 5 h; (d) *t*-$BuNHNH_2$·HCl, 10% NaOH, CH_2Cl_2, ice-bath; (e) 13, CH_2Cl_2, Et_3N, rt.

The structures of all the synthesized compounds were characterized by elemental analyses, ^1H NMR, and EI-MS spectrum. Additionally, the crystal structure of **1i** was determined by X-ray diffraction analyses. As shown in Figure 3, compound **1i** has a characteristic T-shaped conformer with the unsubstituted amide bond in *trans* conformation and the *tert*-butyl substituted amide in *cis* conformation, which is very similar to the X-ray crystal structure of RH-5849.[19] The dihedral angle of the two amide planes showed a gauche conformation with an angle of 81.5° that is affected by the bulky *tert*-butyl group.

3. Insecticidal activity

The insecticidal activity results of compounds **1a**–**i** and **2a**–**h** against *Aphis medicagini* (*A. medicagini*), *Nilaparvata legen* (*N. legen*), *Mythima separata* (*M. separata*), and *Tetranychus cinnabarinus* (*T. cinnabarinus*) are shown in Table 1, RH-5849 was used as a control. As shown in Table 1, all compounds had no or very poor activities against *N. legen* and *A. medicagini* at the dosage of 500 mg L^{-1} and 250 mg L^{-1}, respectively. For *T. cinnabarinus*, some compounds, such as **1g**, **1h**, **1i**, and **2b**, exhibited moderate insecticidal activity with the mortalities ranging from 51.7% to 76.7% at the dosage of 250 mg L^{-1}. Interestingly, most of the synthesized compounds **1** and **2** exhibited good to excellent insecticidal activity against *M. separata* at the concentration of 500 mg L^{-1}. For example, the mortalities of compounds **1a**, **1c**, and **1i** are 80%, 84.2%, and 100%, respectively.

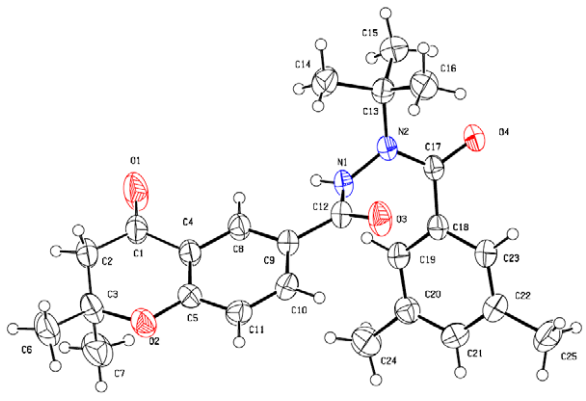


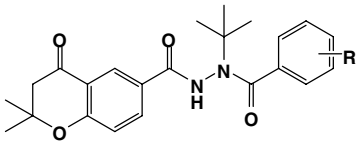
Figure 3. Molecular structure of **1i**.

Additionally, we can find from Table 1 that the insecticidal activities of the target compounds **1** and **2** were influenced by the substituents on the phenyl ring and 3,5-dimethyl substitution gave the highest insecticidal activity. Compared to the chromone analogues **2**, the corresponding chromanone analogues **1** always gave higher activities against *M. separata* and *T. cinnabarinus*, which might be due to the higher structural similarity of the chromanone analogues **1** to ANS-118. To our knowledge, this is the first report about the syntheses and insecticidal activity of diacylhydrazine derivatives bearing chromanone and chromone moieties. Further structural optimization and structure-insecticidal activity relationships about the chromanone analogues well under way.

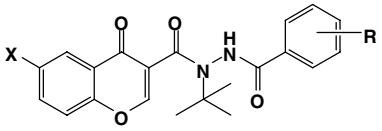
4. Conclusion

In summary, we have described the molecular design, synthesis, and insecticidal activities of a series of chromanone and chromone analogues of diacylhydrazine derivatives. The preliminary bioassay data showed that some of the chromanone analogues exhibited good insecticidal activity against *M. separata* at the dosage of 500 mg L^{-1}. The present work demonstrated that replacement of the chroman ring of ANS-118 with chromanone moiety could result in new compounds with high potent insecticidal activity.

Table 1. Structures and insecticidal activities of compounds **1a–i** and **2a–h**



1a~i



2a~h

Compound	X	R	500 mg L^{-1}		250 mg L^{-1}	
			N. legen	*M. separata*	*T. cinnabarinus*	*A. medicagini*
1a	/	H	0.0	80.0	0.0	8.0
1b	/	2-Me	3.4	40.0	0.0	0.0
1c	/	4-Cl	0.0	84.2	0.0	4.2
1d	/	3-Cl	0.0	13.3	0.0	0.0
1e	/	4-Br	0.0	6.7	0.0	4.0
1f	/	4-F	0.0	0.0	0.0	4.0
1g	/	2-Cl	0.0	66.7	58.3	8.0
1h	/	2-F	3.4	0.0	76.7	4.0
1i	/	3,5-$(Me)_2$	7.1	100.0	66.7	8.0
2a	Cl	H	18.2	58.3	0.0	0.0
2b	Me	H	0.0	60.0	51.7	0.0
2c	H	H	7.1	0.0	0.0	21.1
2d	Cl	2-Cl	0.0	73.3	0.0	16.0
2e	Me	2-Cl	3.4	26.7	0.0	0.0
2f	H	2-Cl	0.0	20.0	0.0	4.0
2g	Cl	2-Me	7.1	26.7	0.0	6.0
2h	H	4-Cl	0.0	66.7	0.0	2.0
RH-5849 (500 mg L^{-1})			/	100	/	/

5. Experimental

5.1. Materials

Ethyl *p*-hydroxybenzoate **3**, 2-hydroxy-5-substituted-acetophenone **9**, substitutedbenzoic acids **12**, and other chemical reagents otherwise noted were commercially available and treated with standard methods before use. Solvents were dried in a routine way and redistilled. *Nilaparvata legen* (*N. legen*), *Tetranychus cinnabarinus* (*T. cinnabarinus*), *Aphis medicagini* (*A. medicagini*), and *Mythima separata* (*M. separata*) were provided through the courtesy of the Center for Bioassay, Zhejiang Chemical Industry Research Institute. The insecticidal activities of compounds **1** and **2** were determined according to our previously reported methods.[20]

5.2. Analysis and instruments

^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ solution on a Varian VNMR 400 MHz spectrometer. MS spectra were determined using a TraceMS 2000 organic mass spectrometry, and the signals are given in *m*/*z*. Melting points were recorded on a Buchi B-545 melting point apparatus. Elemental analysis (EA) was carried out with a Vario EL III CHNSO elemental analyzer.

5.2.1. Preparation of ethyl 3-acetyl-4-hydroxybenzoate (4)[21]. Ethyl *p*-hydroxybenzoate **3** (0.78 mol) was dissolved in acetic anhydride (75 mL). Upon addition of 1 drop of concentrated sulfuric acid, the temperature was raised to 110 °C and maintained at this temperature for 1 h. The mixture was poured into water (300 mL) and extracted with diethyl ether. The organic layer was washed with a saturated $NaHCO_3$ solution, dried over magnesium sulfate, and evaporated under reduced pressure. The resulted oil was heated together with aluminum chloride (1 mol) at 140 °C for 2 h. The mixture was then poured into water (500 mL), filtered, dried, and recrystallized from ethanol to afford ethyl 3-acetyl-4-hydroxybenzoate **4** in a yield of 74%. Mp 90–92 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J = 6.8 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.37 (m, 2H, OCH_2), 6.89 (d, J = 4.2 Hz, 1H, ArH), 7.96 (d, 1H, J = 4.0 Hz, ArH), 8.50 (s, 1H, ArH), 12.71 (s, 1H, OH).

5.2.2. Preparation of 2,2-dimethyl-4-chromanone-6-carboxylic acid (6)[21]. A solution of **4** (0.29 mol) and pyridine (0.45 mol) in acetone (150 mL) was refluxed for 2 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane/ether (6:1, v/v) as eluant to afford ethyl 2,2-dimethyl-4-chromanone-6-carboxylate **5** as a white solid in a yield of 79%. Mp 81–83 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J = 6.8 Hz, 3H, CH_3), 1.48 (s, 6H, 2× CH_3), 2.77 (s, 2H, CH_2), 4.37 (m, 2H, OCH_2), 6.96 (d, J = 9.2 Hz, 1H, Ar-H), 8.14 (m, 1H, Ar-H), 8.56 (d, J = 1.2 Hz, 1H, Ar-H). EI-MS: *m*/*z* (%) 248 (M^+, 61), 232 (100), 203 (27), 192 (13), 164 (11), 118 (7).

A mixture of **5** (20 mmol) and 10% NaOH (35 mL) in ethanol (40 mL) was stirred at room temperature for 24 h. Then the mixture was poured into water (200 mL), and the solution was adjusted to pH ≈ 1–2 with concentrated hydrochloric acid. Then the white

solid was separated by filtration, dried, and recrystallized from methanol to afford 2,2-dimethyl-4-chromanone-6-carboxylic acid **6** in a yield of 69%. Mp 223–225 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 6H, 2× CH_3), 2.78 (s, 2H, CH_2), 7.01 (d, J = 4.4 Hz, 1H, Ar-H), 8.21 (d, J = 0.8 Hz, 1H, Ar-H), 8.66 (d, J = 0.8 Hz, 1H, Ar-H).

5.2.3. Preparation of 2,2-dimethyl-4-chromanone-6-carbonyl chloride (7). Thionyl chloride (40 mmol) was added into a stirring mixture of 2,2-dimethyl-4-chromanone-6-carboxylic acid **6** (20 mmol) and dichloromethane (30 mL). Then, the resulted solution was refluxed for 5 h and the excess of thionyl chloride was removed under reduced pressure to give crude 2,2-dimethyl-4-chromanone-6-carbonyl chloride **7**, which was used for the next reaction without further purification and characterization.

5.2.4. Preparation of *N′*-*tert*-butyl-2,2-dimethyl-4-chromanone-6-carbohydrazide (8). The above-obtained crude 2,2-dimethyl-4-chromanone-6-carbonyl chloride **7** (20 mmol) in dichloromethane (10 mL) was added dropwise into a stirring mixture of *tert*-butylhydrazine hydrochloride (60 mmol), sodium hydroxide solution (1 M, 80 mL), and dichloromethane (80 mL) at 0 °C. The temperature of the reaction mixture was gradually raised to room temperature over a period of 2 h. After stirring the reaction mixture at room temperature overnight, ethyl acetate (100 mL) was added. The organic layer was separated and washed extensively with water and brine, and dried with anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1, v/v) as eluant to give white solid **8** in a yield of 79%. Mp 211–212 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H, *t*-Bu), 1.48 (s, 6H, 2× CH_3), 2.77 (s, 2H, CH_2), 7.02 (d, J = 8.8 Hz, 1H, Ar-H), 8.05 (d, J = 2.0 Hz, 1H, Ar-H), 8.23 (s, 1H, Ar-H). EI-MS: *m*/*z* (%) 290 (M^+, 100), 275 (92), 234 (14), 203 (87), 147 (21), 146 (24).

5.2.5. General Procedure for the synthesis of the target compounds 1a–1i. A mixture of intermediates **8** (1.5 mmol) and triethylamine (1.6 mmol) in anhydrous dichloromethane (10 mL) was stirred in an ice bath and substituted benzoyl chloride (1.5 mmol) was added. After stirring for 3 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was washed extensively with water and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1, v/v) as eluant to afford the target compounds.

5.2.6. Preparation of 6-substituted-4-chromone-3-carbaldehyde (10)[18]. A solution of 2-hydroxy-5-substituted-acetophenone **9** (40 mmol) and anhydrous *N*,*N*-dimethylformamide (80 mL) was stirred at −10 °C for 30 min, and $POCl_3$ (40 mol) was added dropwise below −10 °C during 1 h. The mixture was stirred at room temperature for 15 h and poured into water (200 mL). Then filtered, dried, and recrystallized from ethanol to afford **10** in yields of 44–53%. 4-chromone-3-carbaldehyde, mp 158–160 °C (159–161 °C[22]), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 2H, Ar-H), 7.78 (d, J = 4.4 Hz, 1H, Ar-H), 8.31 (d, J = 4.0 Hz, 1H, Ar-H), 8.57 (s, 1H, 2-H), 10.40 (s, 1H, CHO). EI-MS: *m*/*z* (%) 174 (M^+, 8), 148 (100), 132 (79), 104 (68), 90 (31). 6-methyl-4-chromone-3-carbaldehyde, mp 181–183 °C(181–182 °C[23]), ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 7.44 (d, 1H, J = 4.2 Hz, Ar-H), 7.57 (d, J = 4.2 Hz, 1H, Ar-H). 8.08 (s, 1H, Ar-H), 8.55 (s, 1H, 2-H), 10.39 (s, 1H, CHO). EI-MS: *m*/*z* (%) 188 (M^+, 12), 160 (100), 144 (81), 118 (17), 105 (35), 104 (29). 6-chloro-4-chromone-3-carbaldehyde, mp170–172 °C(173–174 °C[23]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 1H, J = 4.2 Hz, Ar-H), 7.86 (d, J = 4.2 Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.58 (s, 1H, 2-H), 10.41 (s, 1H, CHO). EI-MS: *m*/*z* (%) 208 (M^+, 5), 180 (100), 154 (53), 138 (67), 110 (34), 80 (28).

5.2.7. Preparation of 6-substituted-4-chromone-3-carbonyl chloride (11). A mixture of 6-substituted-4-chromone-3-carbaldehydes **10** (11.4 mmol), *N*-bromosuccinimide (NBS) (14.7 mmol), and 2,2′-azobis-(isobutyronitrile) (AIBN) (10 mg) in anhydrous carbon tetrachloride (100 mL) was refluxed for 1 h. The solvent was removed under reduced pressure and residue was poured into water (100 mL), filtered, dried, and recrystallized from toluene to afford 6-substituted-4-chromone-3-carboxylic acids. Then, thionyl chloride (20 mmol) was added into a stirring mixture of 6-substituted-4-chromone-3-carboxylic acid (10 mmol) and dichloromethane (20 mL). The mixture was refluxed for 5 h and the excess of thionyl chloride was removed under reduced pressure to give crude 6-substituted-4-chromone-3-carbonyl chloride **11**, which was used for the next reaction without further purification.

5.2.8. Preparation of substituted *N′*-*tert*-butyl-substitutedbenzohydrazide (13). Substituted benzoic acid (20 mmol) in thionyl chloride (40 mmol) was refluxed at 80 °C for 5 h, and the excess of thionyl chloride was removed under reduced pressure to give crude substituted benzoyl chloride, which was dissolved in anhydrous dichloromethane (10 mL). The solution was added dropwise into a stirring mixture of *tert*-butylhydrazine hydrochloride (60 mmol), sodium hydroxide solution (1 M, 80 mL), and dichloromethane (80 mL) at 0 °C. The temperature of the reaction mixture was gradually raised to room temperature over a period of 2 h. After stirring the reaction mixture at room temperature overnight, ethyl acetate (100 mL) was added. The combined organic layer was washed extensively with water (100 mL) and brine (100 mL), and dried with anhydrous sodium sulfate. The solvent was evaporated to give the crude compounds **13** as a white solid in yields of 81–88%. *N′*-*tert*-Butylbenzo-hydrazide, mp 69–71 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H, *t*-Bu), 4.74 (br s, 1H, *t*-Bu-NH), 7.37–7.52 (m, 3H, Ar-H), 7.77 (d, 2H, J = 3.4 Hz, Ar-H). *N′*-*tert*-butyl-4-methylbenzohydrazide, mp 108–110 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H, *t*-Bu), 4.72(br s, 1H, *t*-Bu-NH), 7.36–7.40 (m, 3H, Ar-H), 7.61 (d, 2H, J = 3.8 Hz, Ar-H). *N′*-*tert*-butyl-4-chlorobenzohydrazide, mp 74–76 °C,

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H, *t*-Bu), 4.75 (br s, 1H, *t*-Bu-NH), 7.47–7.68 (m, 3H, Ar-H), 7.83 (d, 2H, J = 3.8 Hz, Ar-H).

5.2.9. General procedure for synthesis of the target compounds 2a–2h. A mixture of intermediates **13** (1.5 mmol) and triethylamine (1.6 mmol) in anhydrous dichloromethane (10 mL) was stirred in an ice bath and **11** (1.5 mmol) in 5 mL of anhydrous dichloromethane was added. After stirring for 3 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed extensively 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 column chromatography on silica gel using hexane/ethyl acetate (9:1, v/v) as eluant to afford the target compounds.

Data for ***1a***. Yield, 73%; mp, 219–220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 6H, 2× CH_3), 1.56 (s, 9H, *t*-Bu), 2.70 (s, 2H, CH_2), 6.88 (m, 1H, Ar-H), 7.23–7.27 (m, 3H, Ar-H), 7.44–7.47 (m, 2H, Ar-H), 7.70–7.73 (m, 2H, Ar-H), 8.22 (s, 1H, NH). EI-MS: *m*/*z* (%) 395 ([M+1]$^+$, 7), 339 (100), 337 (83), 321 (16), 304 (10), 203 (88), 147 (12), 146 (11), 104 (40) , 77 (27). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.19; H, 6.57; N, 7.37.

Data for ***1b***. Yield, 81%; mp, 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 6H, 2× CH_3), 1.56 (s, 9H, *t*-Bu), 2.39 (s, 3H, CH_3), 2.69 (s, 2H, CH_2), 6.86 (d, J = 8.4 Hz, 1H, Ar-H), 7.12 (d, J = 4.0 Hz, 3H, Ar-H), 7.23 (d, J = 8.0 Hz, 1H, Ar-H), 7.60 (d, J = 5.6 Hz, 2H, Ar-H), 7.71 (s, 1H, NH). EI-MS: *m*/*z* (%) 409 ([M+1]$^+$, 7), 408 (M$^+$, 6), 352 (100), 335 (12), 203 (94), 147 (28), 119 (42), 91 (19). Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.79; H, 6.93; N, 6.77.

Data for ***1c***. Yield, 65%; mp, 228–230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 6H, 2× CH_3), 1.56 (s, 9H, *t*-Bu), 2.73 (s, 2H, CH_2), 6.84–6.91 (m, 3H, Ar-H), 7.47 (t, J = 5.6 Hz, 2H, Ar-H), 7.80 (d, J = 8.4 Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 8.94 (s, 1H, NH). EI-MS: *m*/*z* (%) 430 ([M+1]$^+$, 7), 429 (M$^+$, 11), 374 (19), 372 (71), 203 (76), 147 (78), 141 (31), 138 (100), 111 (39). Anal. Calcd for $C_{23}H_{25}ClN_2O_4$: C, 64.41; H, 5.88. N, 6.53. Found: C, 64.63; H, 5.93; N, 6.81.

Data for ***1d***. Yield, 68%; mp, 212–214 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45(s, 6H, 2× CH_3), 1.57 (s, 9H, *t*-Bu), 2.73 (s, 2H, CH_2), 6.93 (d, J = 8.8 Hz, 1H, Ar-H), 7.18–7.22 (m, 2H, Ar-H), 7.35 (d, J = 7.2 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.75 (m, 1H, Ar-H), 7.85 (d, J = 2.0 Hz, 1H, Ar-H), 8.12 (s, 1H, NH). EI-MS: *m*/*z* (%) 430 ([M+1]$^+$, 5), 429 (M$^+$, 11), 375 (19), 374 (26), 372 (100), 355 (20), 203 (61), 147 (62), 141 (21), 138 (71), 111 (41). Anal. Calcd for $C_{23}H_{25}ClN_2O_4$: C, 64.41; H, 5.88; N, 6.53. Found: C, 64.29; H, 5.59; N, 6.25.

Data for ***1e***. Yield, 72%; mp, 239–241 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 6H, 2× CH_3), 1.63 (s, 9H, *t*-Bu), 2.74 (s, 2H, CH_2), 6.93 (d, J = 4.4 Hz, 1H, Ar-H), 7.26–7.35 (m, 4H, Ar-H), 7.80–7.83 (m, 1H, Ar-H), 7.90 (d, J = 1.0 Hz, 1H, Ar-H), 8.45 (s, 1H, NH). EI-MS: *m*/*z* (%) 474 ([M+1]$^+$, 12), 473 (M$^+$, 30), 458 (22), 455 (19), 416 (100), 399 (96), 202 (99), 185 (67), 182 (72), 156 (33), 154 (37), 146 (93), 118 (18). Anal. Calcd for $C_{23}H_{25}BrN_2O_4$: C, 58.36; H, 5.32; N, 5.92. Found: C, 58.52; H, 5.42; N, 5.72.

Data for ***1f***. Yield, 74%; mp, 231–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 6H, 2× CH_3), 1.57 (s, 9H, *t*-Bu), 2.73 (s, 2H, CH_2), 6.93 (d, J = 4.4 Hz, 1H, Ar-H), 7.19–7.26 (m, 2H, Ar-H), 7.40 (d, J = 4.2 Hz, 2H, Ar-H), 7.79 (m, 1H, Ar-H), 7.88 (d, J = 1.0 Hz, 1H, Ar-H), 8.38 (s, 1H, NH). EI-MS: *m*/*z* (%) 412 (M$^+$, 3), 374 (27), 372 (100), 354 (19), 203 (59), 146 (48), 138 (65), 110 (29). Anal. Calcd for $C_{23}H_{25}FN_2O_4$: C, 66.98; H, 6.11; N, 6.79. Found: C, 66.69; H, 6.19; N, 6.52.

Data for ***1g***. Yield, 77%; mp, 204–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43(s, 6H, 2× CH_3), 1.60 (s, 9H, *t*-Bu), 2.70 (s, 2H, CH_2), 6.87 (d, J = 4.0 Hz , 1H, Ar-H), 7.16–7.26 (m, 2H, Ar-H), 7.32 (d, J = 2.4 Hz , 1H, Ar-H), 7.40 (s, 1H, Ar-H), 7.56 (d, J = 4.6 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 8.04 (s, 1H, NH). EI-MS: *m*/*z* (%) 430 ([M+1]$^+$, 8), 429 (M$^+$, 10), 374 (19), 372 (75), 203 (75), 147 (78), 141 (31), 138 (100), 111 (37). Anal. Calcd for $C_{23}H_{25}ClN_2O_4$: C, 64.41; H, 5.88; N, 6.53. Found: C, 64.35; H, 6.01; N, 6.27.

Data for ***1h***. Yield, 79%; mp, 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 6H, 2× CH_3), 1.57 (s, 9H, *t*-Bu), 2.74 (s, 2H, CH_2), 6.88–7.10 (m, 3H, Ar-H), 7.23 (m, 1H, Ar-H), 7.49–7.51 (m, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 7.91 (d, J = 17.2 Hz, 1H, Ar-H), 8.42 (s, 1H, NH). EI-MS: *m*/*z* (%) 412 (M$^+$, 3), 355 (30), 203 (21), 147 (28), 123 (100), 95 (29). Anal. Calcd for $C_{23}H_{25}FN_2O_4$: C, 66.98; H, 6.11; N, 6.79. Found: C, 67.17; H, 6.26; N, 6.55.

Data for ***1i***. Yield, 80%; mp, 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 6H, 2× CH_3), 1.57 (s, 9H, *t*-Bu), 2.21 (s, 6H, CH_3), 2.70 (s, 2H, CH_2), 6.79–6.87 (m, 2H, Ar-H), 7.05 (s, 2H, Ar-H), 7.74 (d, J = 8.4 Hz, 2H, Ar-H), 8.06 (s, 1H, NH). EI-MS: *m*/*z* (%) 423 ([M+1]$^+$, 6), 422 (M$^+$, 16), 367 (95), 349 (35), 203 (62), 146 (20), 133 (100), 105 (49), 102 (19). Anal. Calcd for $C_{25}H_{30}FN_2O_4$: C, 71.07; H, 7.16; N, 6.63. Found: C, 70.83; H, 7.10; N, 6.46.

Data for ***2a***. Yield, 66%; mp, 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 9H, *t*-Bu), 7.27–7.46 (m, 5H, Ar-H), 7.60 (d, J = 3.8 Hz, 2H, Ar-H), 8.06 (s, 1H, Ar-H), 8.37 (s, 1H, Ar-H), 9.14 (s, 1H, NH). EI-MS: *m*/*z* (%) 400 ([M+2]$^+$, 14), 399 ([M+1]$^+$, 5), 398 (M$^+$, 42), 344 (11), 341 (37), 293 (12), 209 (17), 208 (22), 206 (100), 154 (18), 153 (31), 104 (71), 103 (64). Anal. Calcd for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80; N, 7.02. Found: C, 63.31; H, 4.82; N, 7.11.

Data for ***2b***. Yield, 74%; mp, 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, *t*-Bu), 2.43 (s, 3H,

CH_3), 7.29–7.35 (m, 3H, Ar-H), 7.40–7.47 (m, 2H, Ar-H), 7.60 (d, J = 3.6 Hz, 2H, Ar-H), 7.94 (s, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 9.23 (s, 1H, NH). EI-MS: *m*/*z* (%) 378 (M^+, 58), 322 (46), 304 (23), 186 (96), 160 (11), 158 (21), 134 (12), 133 (24), 104 (100), 76 (31), 75 (47). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.94; H, 5.89; N, 7.64.

Data for **2c**. Yield, 78%; mp, 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 9H, *t*-Bu), 7.28–7.32 (m, 2H, Ar-H), 7.40–7.46 (m,3H, Ar-H), 7.59 (d, J = 3.6 Hz, 2H, Ar-H), 7.67 (m, 1H, Ar-H), 8.21 (d, J = 3.8 Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 9.14 (s, 1H, NH). EI-MS: *m*/*z* (%) 364 (M^+, 16), 172 (41), 120 (17), 119 (26), 104 (51), 103 (95), 91 (11), 76 (54), 75 (94), 56 (51), 55 (100). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.13; H, 5.75; N, 7.61.

Data for **2d**. Yield, 76%; mp, 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, *t*-Bu), 6.91 (d, J = 4.4 Hz, 1H, Ar-H), 7.14–7.51 (m, 5H, Ar-H), 7.69 (d, J = 4.0 Hz, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 8.44 (s, 1H, Ar-H), 9.57 (s, 1H, NH). EI-MS: *m*/*z* (%) 435 ($[M+2]^+$, 9), 434 ($[M+1]^+$, 15), 433 (M^+, 25), 379 (28), 377 (30), 376 (35), 375 (52), 361 (38), 360 (49), 358 (100), 207 (27), 206 (23), 203 (33), 153 (26), 137 (36). Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_4$: C, 58.21; H, 4.19; N, 6.47. Found: C, 58.34; H, 4.32; N, 6.64.

Data for **2e**. Yield, 76%; mp, 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, *t*-Bu), 2.43 (s, 3H, CH_3), 6.95 (m, 2H, Ar-H), 7.07 (d, J = 3.6 Hz, 1H, Ar-H), 7.19 (m, 1H, Ar-H), 7.42–7.52 (m, 1H, Ar-H), 7.69 (d, J = 4.4 Hz, 1H, Ar-H), 8.10 (d, J = 4.0 Hz, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 9.57 (s, 1H, NH). EI-MS: *m*/*z* (%) 414 ($[M+2]^+$, 39), 413 ($[M+1]^+$, 24), 412 (M^+, 90), 358 (35), 357 (36), 355 (99), 256 (12), 187 (61), 185 (58), 140 (32), 138 (100), 134 (37). Anal. Calcd for $C_{22}H_{21}ClN_2O_4$: C, 64.00; H, 5.13; N, 6.79. Found: C, 64.27; H, 4.98; N, 6.80.

Data for **2f**. Yield, 69%; mp, 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, *t*-Bu), 7.09 (d, J = 3.0 Hz, 2H, Ar-H), 7.22–7.26 (m, 2H, Ar-H), 7.42 (m, 1H, Ar-H), 7.51 (d, J = 4.4 Hz, 1H, Ar-H), 7.73 (m, 1H, Ar-H), 8.10 (d, J = 4.0 Hz, 1H, Ar-H), 8.41 (s, 1H, Ar-H), 9.57 (s, 1H, NH). EI-MS: *m*/*z* (%) 400 ($[M+2]^+$, 23), 399 ($[M+1]^+$, 16), 398 (M^+, 66), 383 (15), 344 (22), 343 (39), 341 (100), 324 (47), 307 (11), 207 (22), 173 (62), 171 (64), 138 (38), 137 (55), 119 (21), 110 (18). Anal. Calcd for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80; N, 7.02. Found: C, 63.50; H, 4.88; N, 6.89.

Data for **2g**. Yield, 76%; mp, 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, *t*-Bu), 2.11 (s, 3H, CH_3), 6.97 (m, 2H, Ar-H), 7.07 (d, J = 3.8 Hz, 1H, Ar-H), 7.21 (m, 1H, Ar-H), 7.42–7.51 (m, 1H, Ar-H), 7.69 (d, J = 4.2 Hz, 1H, Ar-H), 8.08 (d, J = 4.0 Hz, 1H, Ar-H), 8.40 (s, 1H, Ar-H), 9.59 (s, 1H, NH). EI-MS: *m*/*z* (%) 412 (M^+, 19), 315 (21), 260 (12), 205 (45), 204 (22), 203 (39), 130 (36), 128 (59), 118 (100), 117 (97), 116 (60), 113 (67). Anal. Calcd for $C_{22}H_{21}ClN_2O_4$: C, 64.00; H, 5.13; N, 6.79. Found: C, 64.24; H, 5.37; N, 6.81.

Data for **2h**. Yield, 76%; mp, 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H, *t*-Bu), 7.28 (d, J = 4.0 Hz, 1H, Ar-H), 7.41–7.54 (m, 5H, Ar-H), 7.69 (m, 1H, Ar-H), 8.17 (d, J = 4.0 Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 9.23 (s, 1H, NH). EI-MS: *m*/*z* (%) 400 ($[M+2]^+$, 20), 399 ($[M+1]^+$, 28), 398 (M^+, 47), 383 (15), 382 (22), 344 (24), 343 (37), 341 (100), 324 (21), 323 (43), 208 (28), 207 (25), 173 (42), 172 (44), 170 (41), 139 (44), 138 (39), 136 (38), 110 (16), 108 (20). Anal. Calcd for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80; N, 7.02. Found: C, 63.45; H, 5.01; N, 6.77.

5.3. X-ray diffraction

Colorless blocks of **1i** (0.30 mm × 0.20 mm × 0.20 mm) were counted on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 297 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 27.93; 13199 measured reflections; 5043 independent reflections (R_{int} = 0.0196) of which 3983 had $|F_o| > 2|F_o|$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.9758; T_{max} = 0.9838). The structure was solved by direct methods using SHELXS-97;[24] all other calculations were performed with Bruker SAINT System and Bruker SMART programs.[25] Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0739P)^2 + 0.3537P]$ gave final values of R = 0.0481, ωR = 0.1330, and GOF(F) = 1.038 for 338 variables and 5043 contributing reflections. Maximum shift/error = 0.027(3), max/min residual electron density = 0.215/−0.173 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

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