

Synthesis of 2-amide-3-carboxylate-4-aryl-4*H*-chromene derivatives

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Abstract Tetrabutyl ammonium bromide (TBAB) catalyzed one-pot synthesis of 4*H*-chromene via a three-component cyclocondensation of aryl aldehydes, cyanoacetate and dimedone in green media–water. Then, 4*H*-chromene reacted with acyl chloride in acetonitrile at refluxing with catalytic amount of DMAP to yield the title compounds in good yields. The structures of all title compounds were confirmed by ¹H NMR, MS and elementary analyses. The X-ray crystallography of compound **3n** indicated that there were strong intermolecular hydrogen bonds.

Keywords Aromatic aldehydes · Cyanoacetate · Dimedone · One-pot synthesis · 4*H*-chromene · 2-amide-3-carboxylate-4*H*-chromene

Introduction

Heterocyclic compounds, especially pyran and benzopyran derivatives, have played an important role in medicines, pesticides, dyes, and other fine chemical industries. Pyran ring, because of its intrinsic activity, has become a very useful synthon for other heterocyclic compounds [1]. Benzopyran derivatives exhibit excellent physiological and pharmacological activity [2], such as anti-hypoplasia [3], anti-allergic effects [4], treatment of allergic bronchitis [5], and anti-cancer [6].

Furthermore, amides occupy an important place in medicines and pesticides due to their broad-spectrum, high-efficiency active features, for example, bactericidal [7], acaricidal [8], pesticidal [9], herbicidal [10], and other biological activities. In order to find bioactive compounds, we designed and synthesized a series of

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2-amide-4*H*-benzo[*b*]pyran derivatives by assembling benzopyran and amide using particular methodology and obtaining the following results.

Results and discussion

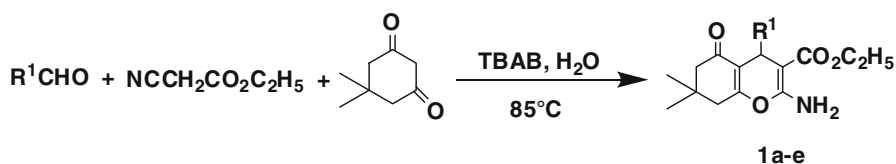
The synthesis of 4*H*-benzo[*b*]pyran derivatives has been reported previously in the literature. Aryl aldehydes, alkyl nitriles, and dimedone have been synthesized in organic solvents (e.g., acetonitrile [1], ethanol [11, 12] and DMF [13]), ionic liquid [14], microwave [15], and so on. The main drawbacks of these methods stem from the requirement for organic solvents, drastic reaction conditions, high temperatures, long reaction times, or the complicated preparation of the catalysts. The methods of solvent-free grinding in the presence of a catalyst (e.g., triethylbenzylammonium chloride, TEBA [16]) and utilizing the reactants in a solid or molten state [17] have also been used for synthesis of these derivatives. Although these reactions were relatively novel, they had some limitations, such as the two-step reaction, very high temperature or requirement for a longer period of time. Recently, organic synthesis in water, such as the Claisen Rearrangement, Aldol Condensation, Diels–Alder Reaction, Michael Addition, and Knoevenagel Condensation, has been reported [18–23]. Three-component one-pot reaction in water could be important for bioactive compounds. Ziarani et al. [24] have reported 2-amine-3-cyano-4*H*-chromenes, which were efficiently synthesized by the one-pot reaction of appropriate aromatic aldehydes, malononitrile and dimedone, in the presence of SiO₂–Pr–SO₃H as a solid acid catalyst. Due to the complicated preparation of the solid acid catalyst, it was difficult to apply this as the industrial process. Moreover, Bandgar et al. [25] have reported catalyst-free synthesis of those very similar products in one-pot reactions in aqueous media. The uncatalyzed reactions have been carried out smoothly at reflux in 3.5 h via three-component reactions of malononitrile, aryl aldehydes, and dimedone. But this method was not suitable for the three-component cyclocondensation involving ethyl cyanoacetate. In our research, the reactions needed a very long time, and during the procedures, clumps were very prone to form. It was difficult to accomplish the three-component reactions to substitute malononitrile with ethyl cyanoacetate under the same conditions. The reason may be that methylene in malononitrile was more active than in ethyl cyanoacetate. Because the electron withdrawing ability of cyano-group was stronger than the ester-group. Here, we have found an efficient, green, and convenient procedure to synthesize 2-amine-3-carboxylate-4*H*-benzo[*b*]pyran derivatives using phase-transfer catalyst in water. We chose tetrabutyl ammonium bromide (TBAB) as a catalyst, and aryl aldehydes, ethyl cyanoacetate, and dimedone reacted to give highly functionalized 4*H*-benzo[*b*]pyrans in water at 85 °C in excellent yields (Table 1). Furthermore, TBAB catalyzed to synthesize 2-amine-3-carboxylate-4*H*-chromenes in one-pot in water has not previously been reported (Scheme 1).

In order to synthesize compounds 3, we have studied the reaction conditions to use compound 1a and benzoyl chloride as a template reaction, and the results were shown in Table 2. It was obvious that the reaction would be accomplished comfortably in acetonitrile at refluxing conditions with a catalytic amount of DMAP. In other conditions, the reaction either did not carry on, or carried on very slowly, and yield

Table 1 Physico-chemical properties of the compounds 1

No.	R ₁	Time (h)	Yields ^a (%)	Mp (°C)	
				Found	Report
1a	C ₆ H ₅	3.5	94	160–162	158–160 [26]
1b	2-NO ₂ C ₆ H ₄	5	89	170–172	169.4–170.8 [27]
1c	3,4-(MeO) ₂ C ₆ H ₃	3	96	156–158	155–157 [28]
1d	2-Furyl	3	95	128–130	128–129 [29]
1e	2,4-Cl ₂ C ₆ H ₃	4	91	177–179	176–178 [30]

^a Isolated yields

**Scheme 1** The synthesis of compounds 1

was trace. At room temperature, no matter in what kind of solvent, no reaction carried on. The reason may be a strong impact from electron-withdrawing groups (e.g., its ortho-ester and benzene ring); the amino group of the pyran ring was not active enough. When the reaction was refluxing, the yields were different from nonpolar solvent to polar solvent, and the yields were very low. Under the condition of catalyst, the yields were higher than with no catalyst. So, it could be speculated that higher temperature, polar solvent, and catalyst were all useful to accomplish the title compounds synthesis. Additionally, an acid-binding agent such as triethylamine should be added, while the reaction system must also be kept dry.

All compounds **3** gave satisfactory elementary analyses and spectroscopic data (¹H NMR and MS) consistent with their assigned structures. For example, in the ¹H NMR spectra, compounds **3** revealed a singlet at δ 11.88–12.26 ppm, which was attributed to amide hydrogen protons. The MS spectra revealed that the molecular ion peaks and fragmentation peaks were in accordance with the synthesized structures of the title compounds **3**, and the molecular ion peaks were observed for all the title compounds (Scheme 2).

The single-crystal structure of **3n** was determined by X-ray crystallography as shown in Fig. 1. The crystal of **3n** revealed an intermolecular hydrogen bond. The distance of N(1)–H(1)…O(5) was 2.64 Å, and the angle of N(1)–H(1)…O(5) was 136.4°.

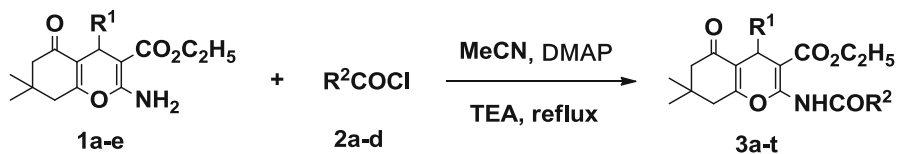
Conclusion

In conclusion, we developed an easy and mild method to synthesize a new series of 2-amide-3-carboxylate-4*H*-benzo[*b*]pyrans in good yields. Further investigations on structural optimization and bioactivities are well under way.

Table 2 Conditions optimization of synthesis of compound 3b

Entry	Solvent	Temp (°C)	Catalyst	Time (h)	Yields
1	Et ₂ O	r.t.	\	96	No reaction
2	Et ₂ O	Reflux	\	96	No reaction
3	Et ₂ O	Reflux	DMAP	96	No reaction
4	CH ₂ Cl ₂	r.t.	\	\	No reaction
5	CH ₂ Cl ₂	Reflux	\	120	Trace
6	CH ₂ Cl ₂	Reflux	DMAP	120	Trace
7	PhCH ₃	r.t.	\	83	No reaction
8	PhCH ₃	Reflux	\	>83	5.2%
9	PhCH ₃	Reflux	DMAP	83	9.3%
10	THF	r.t.	\	96	No reaction
11	THF	Reflux	\	96	6.8%
12	THF	Reflux	DMAP	96	11.5%
13	CH ₃ CN	r.t.	\	24	No reaction
14	CH ₃ CN	Reflux	\	>24	20.6%
15	CH ₃ CN	Reflux	DMAP	11	69.8%

r.t. Room temperature

**Scheme 2** The synthesis of compounds 3

Experimental

Melting points were measured on the $\times 6$ micromelting-point apparatus (China) and are uncorrected. ¹H NMR spectra were recorded on a Bruker AV 400 NMR spectrometer in CDCl₃ with TMS as the internal reference. MS spectra were determined using a Finnigan Trace MS 2000 organic mass spectrometry, and signals were given in *m/z*. Elementary analyses were performed on a Vario EL III elementary analysis instrument. All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried in a routine way and redistilled.

Preparation of the 2-amine-3-carboxylate-4*H*-chromenes (1)

To a stirred solution of cyanoacetate (2.2 mmol) in water (10 mL), a catalytic amount of TBAB, dimedone (5, 5-dimethyl-1, 3-cyclohexanedione, 2.2 mmol) and benzaldehyde (2 mmol) were added. The reaction mixture was stirred at 85 °C for 3–5 h according to thin layer chromatographic (TLC) analysis, and filtered off by

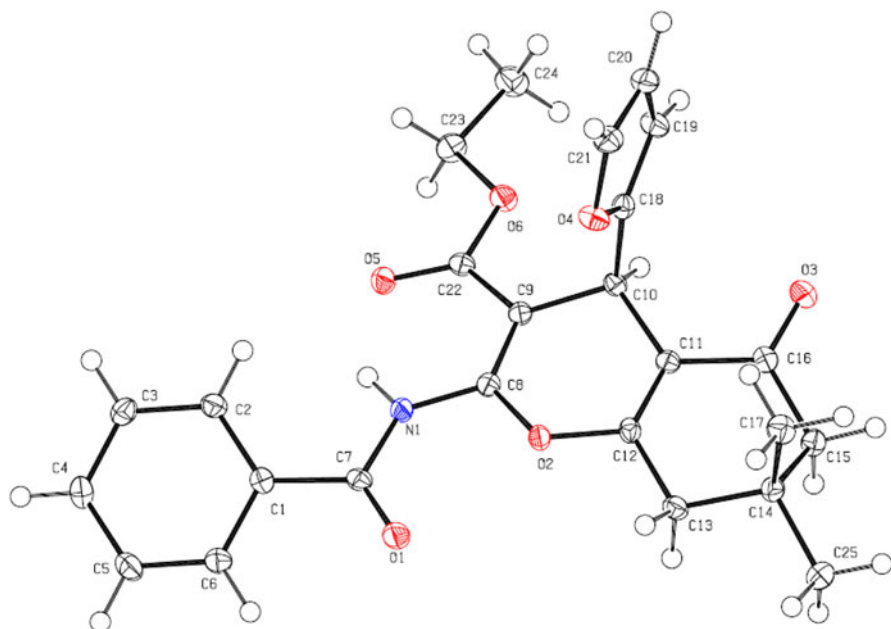


Fig. 1 Crystal structure of compound 3n

suction. For further purification, samples were recrystallized from 95% ethanol to yield the compounds (1).

General procedure for the synthesis of the title compounds (3)

Compounds 1 (2 mmol), triethylamine (2.4 mmol) and catalytic amount of DMAP were added to dry acetonitrile (10 mL) in turn. Then, fresh acyl chlorides 2 (2.2 mmol) was slowly dropped into the mixture by strong stirring on an ice bath. Next, the reaction mixture was refluxed for 10–14 h according to TLC analysis. The mixture was poured into 100 mL of water, extracted with chloroform (30 mL \times 3), the organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated to give the crude product, which was purified by chromatography on silica using petroleum ether/ethyl acetate as the eluent to give the title compounds **3a–t**.

Ethyl 2-acetamido-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3a) white solid; yield, 63.1%; mp 198–200 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.97 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.19 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.18 (s, 3H, CH_3), 2.21 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.60 (s, 2H, CH_2), 4.08–4.13 (m, 2H, CH_2), 4.85 (s, 1H, CH), 7.07–7.26 (m, 5H, ArH), 11.88 (s, 1H, NH); MS (EI): m/z (%) 382 ($[\text{M}-1]^+$, 22), 368 (43), 241 (27), 227 (100), 199 (13), 171 (17), 102 (26), 83 (37). Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.93; H, 6.48; N, 3.66.

Ethyl 2-benzamido-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3b). white solid; yield, 69.8%; mp 214–216 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.98 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.21 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.22 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.64 (s, 2H, CH_2), 4.10–4.16 (m, 2H, CH_2), 4.83 (s, 1H, CH), 7.13–7.99 (m, 10H, ArH), 11.94 (s, 1H, NH); MS (EI): m/z (%) 445 ($[\text{M}]^+$, 8), 368 (38), 322 (6), 294 (6), 105 (100), 77 (24). Anal. Calcd for $\text{C}_{27}\text{H}_{27}\text{NO}_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.68; H, 6.09; N, 3.15.

Ethyl 2-(4-bromobenzamido)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3c). white solid; yield, 60.0%; mp 276–278 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.98 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.22 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.23 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.64 (s, 2H, CH_2), 4.11–4.15 (m, 2H, CH_2), 4.80 (s, 1H, CH), 7.22–8.03 (m, 9H, ArH), 12.16 (s, 1H, NH); MS (EI): m/z (%) 526 ($[\text{M}+2]^+$, 18), 524 ($[\text{M}]^+$, 42), 448 (16), 402 (29), 316 (25), 107 (100), 77 (36). Anal. Calcd for $\text{C}_{27}\text{H}_{26}\text{BrNO}_5$: C, 61.84; H, 5.00; N, 2.67. Found: C, 61.67; H, 5.08; N, 2.68.

Ethyl 2-(4-methoxybenzamido)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3d). white solid; yield, 71.3%; mp 245–247 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.99 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.23 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.25 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.61 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 4.10–4.17 (m, 2H, CH_2), 4.81 (s, 1H, CH), 7.11–7.91 (m, 9H, ArH), 11.98 (s, 1H, NH); MS (EI): m/z (%) 476 ($[\text{M}+1]^+$, 15), 399 (43), 353 (17), 325 (13), 131 (22). Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{NO}_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.74; H, 6.19; N, 2.77.

Ethyl 2-acetamido-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3e). white solid; yield, 57.4%; mp 170–172 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.95 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.10 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.18 (s, 3H, CH_3), 2.20 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.62 (s, 2H, CH_2), 4.03–4.16 (m, 2H, CH_2), 5.80 (s, 1H, CH), 7.25–7.46 (m, 4H, ArH), 11.99 (s, 1H, NH); MS (EI): m/z (%) 428 ($[\text{M}]^+$, 25), 385 (76), 370 (42), 341 (100), 295 (58), 230 (36), 128 (19). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.64; H, 5.59; N, 6.65.

Ethyl 2-benzamido-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3f). white solid; yield, 51.9%; mp 174–176 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.95 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.09 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.20 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.61 (s, 2H, CH_2), 4.02–4.18 (m, 2H, CH_2), 5.84 (s, 1H, CH), 7.26–8.00 (m, 9H, ArH), 12.17 (s, 1H, NH); MS (EI): m/z (%) 490 ($[\text{M}]^+$, 2), 473 (4), 369 (3), 225 (5), 105 (100). Anal. Calcd for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_7$: C, 66.11; H, 5.34; N, 5.71. Found: C, 66.23; H, 5.14; N, 5.76.

Ethyl 2-(4-bromobenzamido)-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3g). white solid; yield, 55.3%; mp 235–236 °C; ^1H NMR (400 MHz, CDCl_3), δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.10 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.23 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.61 (s, 2H, CH_2), 4.02–4.19 (m, 2H, CH_2), 5.88 (s, 1H, CH), 7.30–8.11 (m, 8H, ArH), 12.11 (s, 1H, NH); MS (EI): m/z (%) 571 ($[\text{M}+2]^+$, 10), 569 ($[\text{M}]^+$, 16), 497 (23), 480 (20), 356 (95), 125 (100), 77 (24). Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{BrN}_2\text{O}_7$: C, 56.95; H, 4.43; N, 4.92. Found: C, 56.86; H, 4.46; N, 4.84.

Ethyl 2-(4-methoxybenzamido)-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3h). white solid; yield, 60.2%; mp 220–222 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 0.96 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.09 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.21 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.63 (s, 2H, CH_2), 3.97 (s, 3H, CH_3), 4.01–4.18 (m, 2H, CH_2), 5.82 (s, 1H, CH), 7.27–8.07 (m, 8H, ArH), 12.19 (s, 1H, NH); MS (EI): m/z (%) 520 ($[\text{M}]^+$, 18), 447 (57), 370 (23), 202 (32), 106 (100), 77 (21), 51 (10). Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_8$: C, 64.61; H, 5.42; N, 5.38. Found: C, 64.63; H, 5.37; N, 5.38.

Ethyl 2-acetamido-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3i). white solid; yield, 65.7%; mp 162–164 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 1.00 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.20 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.15 (s, 3H, CH_3), 2.20 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.60 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.10–4.15 (m, 2H, CH_2), 4.85 (s, 1H, CH), 7.11–8.30 (m, 3H, ArH), 12.20 (s, 1H, NH); MS (EI): m/z (%) 443 ($[\text{M}]^+$, 26), 351 (84), 261 (100), 233 (19), 216 (15), 172 (10). Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.87; H, 6.63; N, 3.26.

Ethyl 2-benzamido-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3j). white solid; yield, 61.4%; mp 188–189 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 1.01 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.24 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.25 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.63 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.13–4.16 (m, 2H, CH_2), 4.78 (s, 1H, CH), 7.16–8.12 (m, 8H, ArH), 12.23 (s, 1H, NH); MS (EI): m/z (%) 505 ($[\text{M}]^+$, 18), 459 (5), 400 (13), 368 (23), 354 (15), 105 (100), 77 (24). Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{NO}_7$: C, 68.90; H, 6.18; N, 2.77. Found: C, 68.95; H, 6.19; N, 2.88.

Ethyl 2-(4-bromobenzamido)-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3k). white solid; yield, 59.5%; mp 260–262 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 1.01 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.21 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.20 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.62 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.12–4.14 (m, 2H, CH_2), 4.89 (s, 1H, CH), 7.16–8.12 (m, 7H, ArH), 12.25 (s, 1H, NH); MS (EI): m/z (%) 586 ($[\text{M}+2]^+$, 35), 584 ($[\text{M}]^+$, 22), 512 (27), 354 (100), 292 (42), 262 (20), 166 (32). Anal. Calcd for $\text{C}_{29}\text{H}_{30}\text{BrNO}_7$: C, 59.60; H, 5.17; N, 2.40. Found: C, 59.71; H, 5.09; N, 2.34.

Ethyl 4-(3,4-dimethoxyphenyl)-2-(4-methoxybenzamido)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3l). white solid; yield, 75.3%; mp 244–246 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 1.02 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.21 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.20 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.62 (s, 2H, CH_2), 3.89 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.11–4.13 (m, 2H, CH_2), 4.91 (s, 1H, CH), 7.16–8.19 (m, 7H, ArH), 12.26 (s, 1H, NH); MS (EI): m/z (%) 535 ($[\text{M}]^+$, 43), 462 (23), 353 (99), 291 (100), 261 (31), 177 (25), 77 (36). Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_8$: C, 67.28; H, 6.21; N, 2.62. Found: C, 67.35; H, 6.26; N, 2.74.

Ethyl 2-acetamido-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3m). white solid; yield, 71.6%; mp 145–146 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 1.09 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.27 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.29 (s, 3H, CH_3), 2.71 (s, 2H, CH_2), 4.18–4.23 (m, 2H, CH_2), 5.05 (s, 1H, CH), 6.15–7.63 (m, 3H, ArH), 11.89 (s, 1H, NH); MS (EI): m/z (%) 375

($[M+2]^+$, 15), 329 (33), 270 (45), 228 (32), 182 (35), 103 (100), 77 (22). Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.45; H, 6.03; N, 3.86.

Ethyl 2-benzamido-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3n). white solid; yield, 67.3%; mp 161–163 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.07 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.29 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.31 (s, 2H, CH_2), 2.63 (s, 2H, CH_2), 4.19–4.25 (m, 2H, CH_2), 5.04 (s, 1H, CH), 6.12–7.99 (m, 8H, ArH), 11.91 (s, 1H, NH); MS (EI): m/z (%) 435 ($[M]^+$, 3), 389 (8), 362 (8), 330 (16), 284 (6), 105 (100), 77 (25). Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.98; H, 5.78; N, 3.10.

Ethyl 2-(4-bromobenzamido)-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3o). white solid; yield, 60.5%; mp 230–231 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.08 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.28 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.24 (s, 2H, CH_2), 2.62 (s, 2H, CH_2), 4.21–4.25 (m, 2H, CH_2), 5.08 (s, 1H, CH), 6.11–8.03 (m, 7H, ArH), 11.95 (s, 1H, NH); MS (EI): m/z (%) 516 ($[M+2]^+$, 5), 514 ($[M]^+$, 16), 469 (12), 429 (25), 397 (22), 249 (100), 77 (21). Anal. Calcd for $C_{25}H_{24}BrNO_6$: C, 58.38; H, 4.70; N, 2.72. Found: C, 58.25; H, 4.73; N, 2.75.

Ethyl 4-(furan-2-yl)-2-(4-methoxybenzamido)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3p). white solid; yield, 73.0%; mp 202–204 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.11 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.30 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.35 (s, 2H, CH_2), 2.65 (s, 2H, CH_2), 4.20–4.24 (m, 2H, CH_2), 5.11 (s, 1H, CH), 6.14–8.12 (m, 7H, ArH), 12.02 (s, 1H, NH); MS (EI): m/z (%) 466 ($[M+1]^+$, 16), 420 (25), 318 (19), 286 (100), 240 (36), 77 (24). Anal. Calcd for $C_{26}H_{27}NO_7$: C, 67.09; H, 5.85; N, 3.01. Found: C, 67.13; H, 5.88; N, 2.92.

Ethyl 2-acetamido-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3q). white solid; yield, 59.5%; mp 150–151 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.01 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.21 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.15 (s, 3H, CH_3), 2.21 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.55 (s, 2H, CH_2), 4.08–4.15 (m, 2H, CH_2), 4.81 (s, 1H, CH), 7.11–7.85 (m, 3H, ArH), 12.02 (s, 1H, NH); MS (EI): m/z (%) 453 ($[M+1]^+$, 6), 283 (23), 237 (30), 207 (22), 101 (100), 77 (20). Anal. Calcd for $C_{22}H_{23}Cl_2NO_5$: C, 58.42; H, 5.13; N, 3.10. Found: C, 58.35; H, 5.15; N, 3.15.

Ethyl 2-benzamido-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3r). white solid; yield, 57.1%; mp 231–233 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.01 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.20 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.21 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.63 (s, 2H, CH_2), 4.08–4.16 (m, 2H, CH_2), 4.83 (s, 1H, CH), 7.14–7.99 (m, 8H, ArH), 12.05 (s, 1H, NH); MS (EI): m/z (%) 514 ($[M]^+$, 4), 432 (5), 368 (24), 105 (100), 77 (23). Anal. Calcd for $C_{27}H_{25}Cl_2NO_5$: C, 63.04; H, 4.90; N, 2.72. Found: C, 63.17; H, 4.91; N, 2.74.

Ethyl 2-(4-bromobenzamido)-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3s). white solid; yield, 55.5%; mp 234–236 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.02 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.22 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.21 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.60 (s, 2H, CH_2), 4.10–4.16 (m, 2H, CH_2), 4.83 (s, 1H, CH), 7.20–8.16 (m, 7H, ArH), 12.08 (s, H, NH); MS (EI): m/z (%) 595 ($[M+2]^+$, 10), 593 ($[M]^+$, 8), 513 (15), 467

(21), 334 (12), 185 (100), 77 (22). Anal. Calcd for $C_{27}H_{24}BrC_{12}NO_5$: C, 54.66; H, 4.08; N, 2.36. Found: C, 54.70; H, 4.11; N, 2.41.

Ethyl 4-(2,4-dichlorophenyl)-2-(4-methoxybenzamido)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (3t). white solid; yield, 64.6%; mp 207–209 °C; 1H NMR (400 MHz, $CDCl_3$), δ 1.02 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.23 (t, 3H, CH_3 , $J = 7.12$ Hz), 2.21 (q, 2H, CH_2 , $J = 16.28$ Hz), 2.61 (s, 2H, CH_2), 3.95 (s, 3H, CH_3), 4.10–4.17 (m, 2H, CH_2), 4.83 (s, 1H, CH), 7.21–8.15 (m, 7H, ArH), 12.03 (s, H, NH); MS (EI): m/z (%) 545 ($[M+1]^+$, 7), 463 (13), 361 (29), 212 (18), 140 (100), 77 (24). Anal. Calcd for $C_{28}H_{27}C_{12}NO_6$: C, 61.77; H, 5.00; N, 2.57. Found: C, 61.71; H, 5.02; N, 2.60.

X-ray analysis of compound 3n

The single crystal **3n** was obtained by evaporating the solvent. An Orthorhombic crystal with dimensions of $0.16 \times 0.12 \times 0.10$ mm was mounted on a Bruker SMART APEX CCD single crystal X-ray diffraction at 100(2)K with graphite-monochromated $MoK\alpha$ radiation ($\lambda = 0.71073$ Å). The crystal data for **3n**: $C_{25}H_{25}NO_6$; Triclinic, space group $P-1$, $a = 14.838$ Å, $b = 14.838(2)$ Å, $c = 19.744(3)$ Å, $V = 4347.2(9)$ Å³, $Z = 8$, $D_c = 1.331$ mg/m³. A total of 31,275 reflections were measured in the range of $2.06^\circ \leq \theta \leq 27.00^\circ$, of which 4,739 reflections ($R_{int} = 0.1203$) were independent and 3,650 were observed with $I > 2\sigma(I)$. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedure with Bruker SHELXTL-97 package [31]. All other calculations were performed with Bruker SAINT System and Bruker SMART programs [32]. Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0602P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$ gave final values of $R = 0.0428$, $\omega R = 0.1076$, and $GOF(F) = 1.036$ for 293 variables and 4,739 contributing reflections. Maximum shift/error 0.001, max/min residual electron density = $0.374/-0.281$ e Å⁻³.

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