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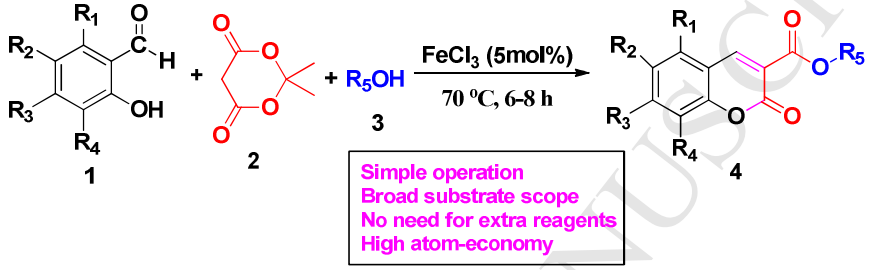
The Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, Institute of Organic Chemistry, College of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China



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The Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, Institute of Organic Chemistry, College of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China

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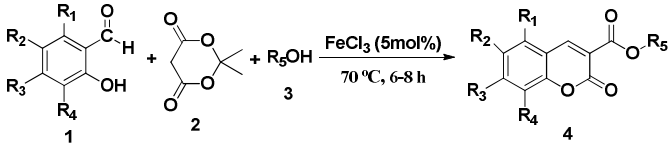
ABSTRACT

A $FeCl_3$-catalyzed multicomponent reaction was developed for the facile synthesis of coumarin-3-carboxylic ester derivatives in a highly atom-economic and environmentally friendly way. Using simple and cheaply available salicylaldehydes, Meldrum's acid and alcohols as the starting materials, the method needs no extra additives and features wide substrate scope, good functional group tolerance and mild reaction conditions.

Introduction

Coumarins are very attractive targets for combinatorial library synthesis due to their wide range of valuable biological activities including anticancer,[1] anti-HIV,[2] anti-acetylcholinesterase,[3] anti-fungal,[4] antioxidant,[5] antihelmintic,[6] antibacterial[7] and antiviral[8] activities. They are also extensively used in fragrances, agrochemicals, insecticides and in food and cosmetics as additives.[9] On the other hand, they have also found applications as photosensitizers, laser dyes, fluorescent indicators, optical brighteners and photosensitizers.[10-13] As a result, the drive to obtain typically functionalized coumarins in one step from readily available starting materials with minimal waste, less time and simple manipulation has been prevalent among the community of organic chemists.[14]

Multicomponent reactions (MCRs) has been one of the best approaches that meet the requirements of green chemistry as well as the library development of medicinal scaffolds.[15] Previously, we have reported $FeCl_3$-catalyzed cascade reaction to efficient approach to functionalized coumarin derivatives.[16] In continuation of our efforts toward the development of novel methodologies for the synthesis of heterocycles,[17] a new synthetic route to coumarin-3-carboxylic esters has been explored. To the best of our knowledge, this work presents the first simple direct route to the important class of coumarin derivatives, which would facilitate relevant studies on the pharmacological properties of these coumarin derivatives. Herein, we report the details of our research on this multicomponent reaction (Scheme 1).



Scheme 1. Synthesis of coumarin-3-carboxylic esters *via* $FeCl_3$-catalyzed multicomponent reaction of salicylaldehydes, Meldrum's acid and alcohols.

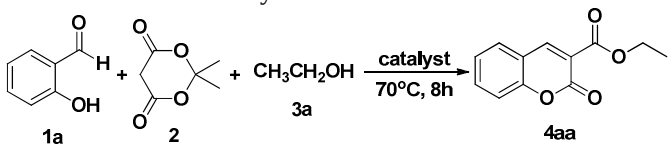
Results and discussion

Initially, salicylaldehyde (**1a**), Meldrum's acid (**2**) and ethanol (**3a**) were chosen as the starting materials in the model reaction. Ethanol played both as the reagent and solvent while different metal salt catalysts were screened (Table 1). Interestingly, when the $FeCl_3$ were used as the catalyst (Table 1, entry 7), the highest yield of the product (92% yield) was obtained, and that $CuBr_2$ (Table 1, entry 2) also had good catalytic ability (86% yield). Here, the yield could not be improved by increasing the amount of catalyst (Table 1, entries 12 and 13), even while decreasing the amount of catalyst to 5 mol% could lead to a slightly higher yield of 93% (Table 1, entry 11). However, the product yield dropped to 72% by further decreasing the catalyst to 2 mol% (Table 1,

* Corresponding author. Tel.: +86-553-5910129; fax: +86-553-5910126; e-mail: shyj@mail.ahnu.edu.cn

entry 9). In the absence of catalyst, the model reaction failed to provide the desired product, while 2-oxo-2*H*-chromene-3-carboxylic acid was isolated as the only product in 72% yield after a prolonged reaction time of 24 h. Therefore, 5 mol% $FeCl_3$ was chosen as catalyst for further optimizing other reaction conditions.

Table 1. Screen of catalysts. [a]

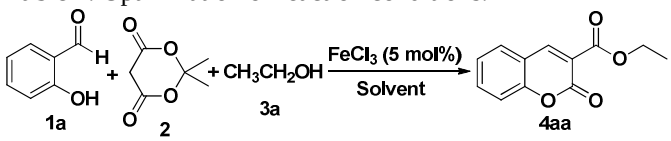


Entry	Catalyst (mol %)	Yield (%) [b]
1	$Cu(OAc)_2$ (10)	10
2	$CuBr_2$ (10)	86
3	$CuSO_4$ (10)	65
4	$NiCl_2 \cdot 6H_2O$ (10)	80
5	$AgNO_3$ (10)	10
6	$K_3Fe(CN)_6$ (10)	trace
7	$FeCl_3$ (10)	92
8 [c]	—	0
9	$FeCl_3$ (2)	72
10	$CuBr_2$ (2)	70
11	$FeCl_3$ (5)	93
12	$FeCl_3$ (15)	92
13	$FeCl_3$ (20)	90

[a] Reaction condition: **1a** (1.0 mmol), **2** (1.2 mmol), **3a** (3 mL), 70 °C, 8 h.
[b] Isolated yields.
[c] 2-oxo-2*H*-chromene-3-carboxylic acid was obtained in 72% yield as the only product after 24 h.

To determine the optimum reaction conditions, the effects of other reaction parameters such as the solvent, temperature, and reaction time were studied. Several other solvents including dimethyl formamide (DMF), tetrahydrofuran (THF), acetonitrile, toluene, dimethylsulfoxide (DMSO), cyclohexane and water were screened but inferior yields were obtained (Table 2, entries 5-11). So in this reaction alcohol was used both as a solvent and as one of the reactants as well. In addition, the effect of temperature and reaction time were also investigated (Table 2, entries 1-4, and 12-14). It was found that neither decreasing nor increasing the reaction temperature/time could improve the yield. Therefore, this reaction could be best performed with 5 mol % of $FeCl_3$ as catalyst in ethanol at 70 °C for 8 h.

Table 2. Optimization of reaction conditions. [a]



Entry	Temp. (°C)	Solvent	Time (h)	Yield (%) [b]
1 [c]	r.t.	EtOH	8	20
2 [c]	50	EtOH	8	60
3 [c]	70	EtOH	8	93
4 [c]	100	EtOH	8	90
5	70	DMF	8	0
6	70	THF	8	60
7	70	CH_3CN	8	60
8	70	Toluene	8	45
9	70	DMSO	8	0
10	70	Cyclohexane	8	50
11	70	H_2O	8	21
12 [c]	70	EtOH	2	40
13 [c]	70	EtOH	5	80
14 [c]	70	EtOH	10	92

[a] Reaction condition: salicylaldehyde **1a** (1.0 mmol), Meldrum's acid **2** (1.2 mmol), ethanol **3a** (1.2 mmol), solvent (3 mL), $FeCl_3$ (0.05 mmol).
[b] Isolated yields.
[c] Ethanol (3 mL) was used as solvent.

Subsequently, various structural diverse salicylaldehydes **1b**-**1j** were subjected to the optimum reaction conditions with Meldrum's acid **2** and ethanol **3a**. The results are summarized in Table 3. A variety of functional groups in the examined substituted salicylaldehydes were well tolerated to give good to excellent yields of ethyl 2-oxo-2*H*-chromene-3-carboxylate (**4aa**-**4ja**), regardless of their electronic nature or steric hindrance. Particularly, when the substituents on salicylaldehydes **1** were strongly electron-donating groups (e.g. $-OCH_3$, $-NEt_2$) at the *para* position of the aldehydes (Table 3, entries 3, 4) or strongly electron-withdrawing groups (e.g. $-NO_2$) at the *para* position of the phenol hydroxyl group (Table 3, entry 8), also gave the desired products in good to excellent yields. Moreover, *tert*-butyl group at the 3,5-position of salicylaldehydes **1e** participated successfully in this reaction (Table 3, entry 5). The structure of the product **4aa** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

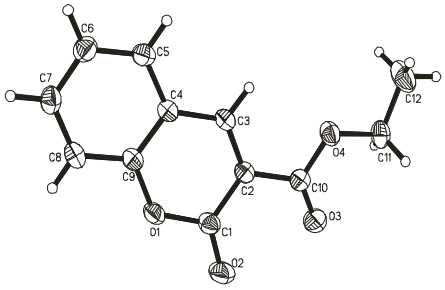
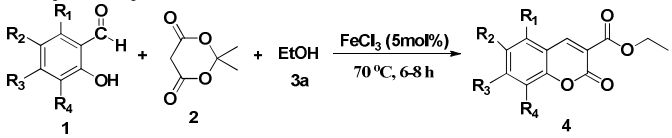


Figure 1. X-ray crystal structure of compound **4aa**.[18]

Table 3. Synthesis of ethyl coumarin-3-carboxylate derivatives *via* $FeCl_3$-catalyzed multicomponent reactions of salicylaldehydes, Meldrum's acid and ethanol.



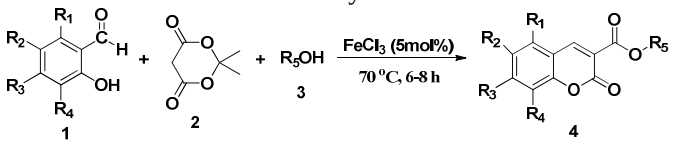
Entry	R_1,R_2,R_3,R_4	Product	Yields (%) [b]
1	**1a** (H, H, H, H)	**4aa**	93
2	**1b** (H, CH_3, H, H)	**4ba**	89
3	**1c** (H, H, CH_3O, H)	**4ca**	89

4	**1d** (H, H, NEt_2, H)	**4da**	83
5	**1e** ($C(CH_3)_3$, H, $C(CH_3)_3$, H)	**4ea**	80
6	**1f** (H, Cl, H, H)	**4fa**	91
7	**1g** (H, Br, H, H)	**4ga**	90
8	**1h** (H, NO_2, H, H)	**4ha**	89
9	**1i** (H, F, H, H)	**4ia**	93
10	**1j** (-CH=CH-CH=CH-, H, H, H)	**4ja**	90

[a] Reaction condition: salicylaldehyde **1** (1.0 mmol), Meldrum's acid **2** (1.2 mmol), ethanol **3a** (3 mL), $FeCl_3$ (0.05 mmol), 70 °C, 6-8 h.
[b] Isolated yields.

Subsequently, a series of alcohols such as methyl alcohol (**3b**), 2-pentanol (**3c**), benzyl alcohol (**3d**) and allyl alcohol (**3e**) were subjected to the reaction with salicylaldehydes **1** and Meldrum's acid **2** (Table 4). We found that both saturated and unsaturated alcohols gave the desired products, and the allyl alcohol gave relatively higher yields of the products. To our delight, good yields of products were also obtained in the case of benzyl alcohol **3d** (Table 4, entries 13-15).

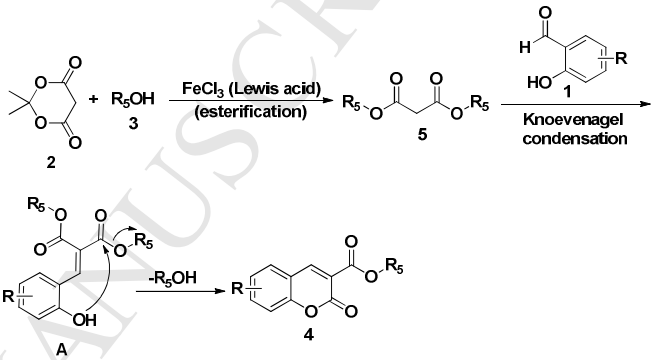
Table 4. $FeCl_3$-catalyzed multicomponent reactions for the formation of coumarin-3-carboxylic esters. [a]



Entry	R_1,R_2,R_3,R_4	R_5	Product	Yields (%) [b]
1	**1a** (H, H, H, H)	CH_3 (**3b**)	**4ab**	91
2	**1b** (H, CH_3, H, H)	**3b**	**4bb**	90
3	**1c** (H, H, CH_3O, H)	**3b**	**4cb**	88
4	**1d** (H, H, NEt_2, H)	**3b**	**4db**	85
5	**1e** ($C(CH_3)_3$, H, $C(CH_3)_3$, H)	**3b**	**4eb**	80
6	**1f** (H, Cl, H, H)	**3b**	**4fb**	89
7	**1g** (H, Br, H, H)	**3b**	**4gb**	88
8	**1h** (H, NO_2, H, H)	**3b**	**4hb**	89
9	**1j** (-CH=CH-CH=CH-, H, H, H)	**3b**	**4jb**	90
10	**1c**	pentan-2-yl (**3c**)	**4cc**	88
11	**1f**	**3c**	**4fc**	90
12	**1g**	**3c**	**4gc**	89
13	**1c**	$C_6H_5CH_2$ (**3d**)	**4cd**	73
14	**1g**	**3d**	**4gd**	81
15	**1h**	**3d**	**4hd**	83
16	**1c**	CH_2=CH-CH_2 (**3e**)	**4ce**	90
17	**1e**	**3e**	**4ee**	85
18	**1f**	**3e**	**4fe**	91
19	**1g**	**3e**	**4ge**	90
20	**1h**	**3e**	**4he**	91
21	**1j**	**3e**	**4je**	91

[a] Reaction condition: salicylaldehyde **1** (1.0 mmol), Meldrum's acid **2** (1.2 mmol), alcohol **3** (3 mL), $FeCl_3$ (0.05 mmol), 70 °C, 6-8 h.
[b] Isolated yields.

In order to understand the reaction mechanism, we examined the reaction of Meldrum's acid **2** with ethanol **3a** catalyzed by $FeCl_3$ in 70 °C. The esterification product of diethyl malonate was obtained in 93% yield after 4 h. On the basis of the above observations and our reported work,[16] a possible reaction mechanism is proposed in Scheme 2. First, Meldrum's acid **2** reacted with alcohol **3** to form the esterification products **5** in the presence of $FeCl_3$ as a Lewis acid catalyst, and then the Knoevenagel condensation between 5 and 2-hydroxy aromatic aldehydes **1** would form the intermediate **A**, which are readily converted to the desired products **4** *via* intramolecular transesterification.



Scheme 2. Proposed mechanism for the formation of coumarin-3-carboxylic esters **4**.

Conclusions

In conclusion, we have developed a highly efficient and environmental friendly method for the synthesis of coumarin-3-carboxylic ester derivatives *via* $FeCl_3$-catalyzed multicomponent reactions in good to excellent yields. The notable advantages of this method are mild reaction conditions, lower amounts of cheap and nontoxic $FeCl_3$ as catalyst, and the reactant of alcohol as solvent. It should be noted that this protocol is an expedient and atom-economic approach to the coumarin-3-carboxylic esters from easy available starting materials. In addition, operational simplicity and no need for extra solvent are the attractive features which make this protocol highly practical for accessing new coumarin scaffolds.

4. Experimental SectionGeneral comments

4.1 General comments

Unless otherwise specified, all reagents and starting materials were purchased from commercial sources and used as received, and the solvents were purified and dried by standard procedures. The chromatography solvents were technical grade and distilled prior to use. Flash chromatography was performed using 200-300 mesh silica gel with the indicated solvent system according to standard techniques. The ^1H and ^{13}C NMR data were recorded on 300 MHz NMR spectrometers, unless otherwise specified. Chemical shifts (δ) in parts per million are reported relative to the residual signals of chloroform (7.26 ppm for ^1H and 76.1 ppm for ^{13}C). Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet), and coupling constants (J) are reported in hertz. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (m/z) ratios in

atomic mass units. IR spectra were measured as dry films (KBr), and peaks are reported in terms of wave number (cm^{-1}).

4.2 General procedure for the synthesis of polysubstituted coumarin-3-carboxylic esters 4.

Anhydrous $FeCl_3$ (0.05 mmol) was added to a stirred solution of salicyladehyde **1a** (1 mmol), Meldrum's acid **2** (1.2 mmol) in ethanol (3 mL). The mixture was heated at 70 °C for 8 h in an oil bath and then cooled down to room temperature. The solvent was removed under vacuum, and the residue was directly purified by flash column chromatography on silica gel with ethyl acetate and petroleum ether (1:6, v/v) as eluting solvent to afford the product **4aa** in 93% yield.

*4.2.1 Ethyl 2-oxo-2H-chromene-3-carboxylate (**4aa**).*[16] White solid, yield 93%, mp 90-91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.60-7.67 (m, 2H), 7.30-7.37 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 156.8, 155.0, 148.6, 134.3, 129.5, 124.8, 118.1, 117.8, 116.6, 61.9, 14.2 ppm. IR (KBr) v: 3062, 1776, 1766, 1606, 1564, 1450, 1375, 1296, 1132, 1033, 962, 775 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{10}O_4$ ($[M+H]^+$) 219.0657, found 219.0657.

*4.2.2 Ethyl 6-methyl-2-oxo-2H-chromene-3-carboxylate (**4ba**).* White solid, yield 89%, mp 108-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.0, 156.9, 153.2, 148.5, 135.4, 134.6, 129.1, 118.0, 117.5, 116.3, 61.8, 20.6, 14.2 ppm. IR (KBr) v: 3053, 1761, 1705, 1620, 1575, 1492, 1375, 1296, 1134, 1039, 979, 798 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{13}O_4$ ($[M+H]^+$) 233.0814, found 233.0814.

*4.2.3 Ethyl 7-methoxy-2-oxo-2H-chromene-3-carboxylate (**4ca**).*[16] Yellow solid, yield 89%, mp 130-132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 7.48 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.77 (s, 1H), 4.39 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.1, 163.7, 157.5, 157.1, 148.9, 130.7, 114.0, 113.6, 111.5, 100.3, 61.6, 56.0, 14.2 ppm. IR (KBr) v: 3053, 1753, 1726, 1714, 1620, 1558, 1506, 1381, 1294, 1172, 1118, 1031, 829, 761 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{12}O_5$ ($[M+H]^+$) 249.0763, found 249.0762.

*4.2.4 Ethyl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate (**4da**).*[16] Pale brown solid, yield 83%; mp 171-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 (s, 1H), 7.34 (d, J = 9.3 Hz, 1H), 6.60 (d, J = 9.0 Hz, 1H), 6.43 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.45 (q, J = 7.2 Hz, 4H), 1.38 (t, J =7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.2, 158.4, 158.3, 152.8, 149.2, 131.0, 109.5, 108.8, 107.6, 96.6, 61.1, 45.0, 14.3, 12.4 ppm. IR (KBr) v: 3354, 1732, 1699, 1622, 1589, 1514, 1477, 1446, 1354, 1222, 1186, 1103, 1028, 819, 792 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{19}NO_4$ ($[M+H]^+$) 290.1392, found 290.1393.

*4.2.5 Ethyl 6,8-di-tert-butyl-2-oxo-2H-chromene-3-carboxylate (**4ea**).* White solid, yield 80%; mp 115-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (s, 1H), 7.66 (s, 1H), 7.39 (s, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.49 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H), 1.34 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.3, 156.6, 152.0, 149.9, 147.1, 137.4, 129.7, 123.9, 117.8, 117.0, 61.7, 35.1, 34.6, 31.2, 29.7, 14.2 ppm. IR (KBr) v: 2981, 1739, 1707, 1618, 1577, 1471, 1396, 1286, 1255, 1211, 1035, 979, 796 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{27}O_4$ ($[M+H]^+$) 331.1909, found 331.1909.

*4.2.6 Ethyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (**4fa**).*[16] White solid, yield 91%, mp 174-175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.60 (s, 1H), 7.26-7.33 (m, 2H), 4.43 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.6, 156.0, 153.4, 147.2, 134.1, 130.1, 128.4, 119.4, 118.8, 118.2, 62.2, 14.2 ppm. IR (KBr) v: 3070, 1755, 1705, 1616, 1560, 1473, 1415, 1367, 1290, 1244, 1211, 1083, 1024, 997, 840, 794, 663, 605 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_9ClO_4$ ($[M+H]^+$) 253.0267, found 253.0267.

*4.2.7 Ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (**4ga**).*[16] White solid, yield 90%, mp 175-177 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.42 (s, 1H), 7.69-7.74 (m, 2H), 7.24 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.6, 155.9, 153.9, 147.0, 136.9, 131.5, 119.4, 119.3, 118.5, 117.3, 62.2, 14.1 ppm. IR (KBr) v: 3070, 1753, 1705, 1616, 1598, 1558, 1477, 1411, 1367, 1290, 1242, 1211, 1024, 794 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_9BrO_4$ ($[M+H]^+$) 296.9762, found 296.9765.

*4.2.8 Ethyl 6-nitro-2-oxo-2H-chromene-3-carboxylate (**4ha**).*[16] White solid, yield 89%, mp 192-193 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.58 (s, 1H), 8.56 (s, 1H), 8.51 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 9.3 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 158.3, 155.0, 146.9, 144.2, 128.6, 125.2, 120.5, 118.0, 117.8, 62.5, 14.1 ppm. IR (KBr) v: 3088, 1780, 1757, 1691, 1618, 1570, 1497, 1348, 1257, 1219, 1095, 1018, 985, 752 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_9NO_6$ ($[M+Na]^+$) 286.0322, found 286.0324.

*4.2.9 Ethyl 6-fluoro-2-oxo-2H-chromene-3-carboxylate (**4ia**).* White solid, yield 93%, mp 104-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48 (s, 1H), 7.59 (s, 2H), 7.32 (d, J = 8.4 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7 (d, $^1J_{CF}$ = 177.4 Hz), 157.1 (d, $^1J_{CF}$ = 62.0 Hz), 151.3, 147.4 (d, $^1J_{CF}$ = 1.8 Hz), 130.5, 122.0 (d, $^1J_{CF}$ = 24.4 Hz), 119.5, 118.5 (d, $^1J_{CF}$ = 8.2 Hz), 114.5 (d, $^1J_{CF}$ = 23.6 Hz), 62.2, 14.2 ppm. IR (KBr) v: 3059, 1751, 1687, 1618, 1571, 1489, 1369, 1294, 1157, 1114, 1026, 993, 796 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{10}FO_4$ ($[M+H]^+$) 237.0563, found 237.0562.

*4.2.10 Ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate (**4ja**).*[16] Yellow solid, yield 90%, mp 118-119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.30 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7, 155.9, 155.0, 143.6, 135.2, 128.3, 128.2, 125.6, 120.5, 115.7, 111.4, 61.1, 13.4 ppm. IR (KBr) v: 3080, 1745, 1697, 1627, 1604, 1568, 1463, 1396, 1296, 1217, 1124, 1095, 742 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{12}O_4$ ($[M+H]^+$) 269.0814, found 269.0813.

*4.2.11 Methyl 2-oxo-2H-chromene-3-carboxylate (**4ab**).* White solid, yield 91%, mp 118-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.53 (s, 1H), 7.56-7.64 (m, 2H), 7.27-7.34 (m, 2H), 3.92 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.8, 156.9, 155.2, 149.1, 134.4, 129.5, 124.9, 117.9, 117.8, 116.7, 52.9 ppm. IR (KBr) v: 3059, 1745, 1701, 1685, 1616, 1560, 1452, 1363, 1311, 1247, 1215, 1155, 997, 756 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_9O_4$ ($[M+H]^+$) 205.0501, found 205.0500.

*4.2.12 Methyl 6-methyl-2-oxo-2H-chromene-3-carboxylate (**4bb**).* White solid, yield 90%; mp 135-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.37 (s, 1H), 7.24 (d, J = 8.7 Hz, 1H), 3.93 (s, 3H), 2.40 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.8, 156.9, 153.3, 149.2, 149.1, 135.6, 134.7, 129.1, 117.7, 117.5, 116.4, 52.8, 20.6 ppm. IR (KBr) v: 3064, 1772, 1755, 1622, 1571, 1492, 1436, 1381, 1294, 1132, 1029, 933, 756 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}O_4$ ($[M+H]^+$) 219.0657, found 219.0655.

4.2.13 Methyl 7-methoxy-2-oxo-2H-chromene-3-carboxylate ***(4cb)***. Yellow solid, yield 88%, mp 226-228 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.00 (d, J = 8.7 Hz, 1H), 6.89 (s, 1H), 3.91 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.1, 151.2, 149.5, 131.7, 130.7, 115.1, 113.7, 100.7, 100.3, 56.3, 52.7 ppm. IR (KBr) v: 3049, 1751, 1681, 1614, 1556, 1473, 1363, 1298, 1205, 1072, 1001, 829, 798 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}O_5$ ($[M+H]^+$) 235.0606, found 235.0605.

4.2.14 Methyl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate ***(4db)***.[16] Yellow solid, yield 85%, mp 173-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 7.34 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 9.0 Hz, 1H), 6.42 (s, 1H), 3.87 (s, 3H), 3.45 (q, J = 7.8 Hz, 4H), 1.22 (t, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9, 158.5, 152.9, 149.6, 131.1, 109.6, 108.3, 107.6, 96.6, 52.2, 45.0, 12.3 ppm. IR (KBr) v: 3502, 1755, 1703, 1618, 1587, 1514, 1446, 1419, 1354, 1224, 1199, 1136, 1078, 796 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}NO_4$ ($M+H^+$) 276.1236, found 276.1235.

4.2.15 Methyl 6,8-di-tert-butyl-2-oxo-2H-chromene-3-carboxylate ***(4eb)***. White solid, yield 80%, mp 157-159 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (s, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 3.90 (s, 3H), 1.46 (s, 9H), 1.31 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.0, 156.5, 152.1, 150.5, 147.2, 137.4, 129.9, 123.9, 117.8, 116.6, 52.7, 35.1, 31.2, 29.7 ppm. IR (KBr) v: 2953, 1739, 1718, 1622, 1581, 1467, 1363, 1288, 1240, 1209, 1018, 956, 767 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{25}O_4$ ($[M+H]^+$) 317.1753, found 317.1754.

4.2.16 Methyl 6-chloro-2-oxo-2H-chromene-3-carboxylate ***(4fb)***. White solid, yield 89%, mp 199-200 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.83 (s, 1H), 8.43 (s, 1H), 7.43 (d, J = 9.6 Hz, 1H), 7.29 (d, J = 9.3 Hz, 1H), 3.92 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.4, 161.9, 153.5, 150.2, 147.7, 135.6, 134.2, 129.3, 128.4, 118.6, 118.3, 53.1 ppm. IR (KBr) v: 3051, 1753, 1680, 1614, 1560, 1475, 1429, 1384, 1300, 1269, 1205, 1087, 1035, 1001, 798 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_8ClO_4$ ($[M+H]^+$) 239.0111, found 239.0111.

4.2.17 Methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate ***(4gb)***. White solid, yield 88%, mp 184-185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.82 (s, 1H), 8.43 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 3.92 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.4, 161.8, 150.0, 147.5, 138.4, 137.1, 132.4, 131.5, 118.8, 118.5, 117.4, 53.0 ppm. IR (KBr) v: 3051, 1750, 1699, 1616, 1564, 1454, 1438, 1365, 1285, 1209, 1092, 1002, 796, 758 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_8BrO_4$ ($[M+H]^+$) 282.9606, found 282.9608.

4.2.18 Methyl 6-nitro-2-oxo-2H-chromene-3-carboxylate ***(4hb)***. White solid, yield 89%, mp 222-224 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.58 (s, 1H), 8.52 (s, 1H), 8.47 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 162.6, 158.3, 147.4, 128.7, 125.2, 120.1, 118.1, 117.7, 53.3 ppm. IR (KBr) v: 3105, 3068, 1780, 1757, 1697, 1618, 1570, 1521, 1477, 1436, 1348, 1305, 1257, 1139, 1095, 1001, 796, 752 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_8NO_6$ ($[M+H]^+$) 250.0351, found 250.0350.

4.2.19 Methyl 3-oxo-3H-benzo[f]chromene-2-carboxylate ***(4jb)***. Yellow solid, yield 90%, mp 162-163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.24 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 3.98 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.0, 156.8, 155.9, 144.9, 136.2, 130.1, 129.3, 129.2, 129.1, 126.6, 121.4, 116.5, 115.8, 112.2, 52.9, 29.6 ppm. IR (KBr) v: 3051, 1745, 1701, 1602, 1570, 1442, 1394, 1296, 1211, 1120, 1103, 1008, 983, 794 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{11}O_4$ ($[M+H]^+$) 255.0657, found 255.0658.

4.2.20 Pentan-2-yl 7-methoxy-2-oxo-2H-chromene-3-carboxylate ***(4cc)***. White solid, yield 88%, mp 125-126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.50 (d, J = 9.0 Hz, 1H), 6.85-6.89 (d, J = 8.7 Hz, 1H), 6.80 (s, 1H), 5.10-5.20 (m, 1H), 3.89 (s, 3H), 1.68-1.75 (m, 1H), 1.51-1.60 (m, 1H), 1.36-1.48 (m, 2H), 1.34 (d, J = 6.3 Hz, 3H), 1.23 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 162.0, 156.6, 147.5, 138.7, 129.7, 113.7, 112.7, 110.7, 99.4, 71.5, 55.1, 37.1, 17.8, 17.5, 13.0 ppm; IR (KBr) v: 2962, 1749, 1697, 1606, 1556, 1506, 1462, 1377, 1263, 1219, 1170, 1022, 794 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}O_5$ ($[M+H]^+$) 291.1232, found 291.1232.

4.2.21 Pentan-2-yl 6-chloro-2-oxo-2H-chromene-3-carboxylate ***(4fc)***. White solid, yield 90%, mp 139-140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 7.54-7.59 (m, 2H), 7.28 (d, J = 8.4 Hz, 1H), 5.12-5.26 (m, 1H), 1.68-1.78 (m, 1H), 1.52-1.61 (m, 1H), 1.39-1.46 (m, 2H), 1.36 (d, J = 6.3 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 156.0, 153.3, 146.5, 133.9, 130.0, 128.4, 119.8, 118.8, 118.2, 73.0, 37.9, 19.8, 18.6, 13.8 ppm. IR (KBr) v: 3097, 1745, 1708, 1625, 1566, 1479, 1363, 1292, 1246, 1118, 1083, 1010, 968, 792 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}ClO_4$ ($[M+H]^+$) 295.0737, found 295.0735.

4.2.22 Pentan-2-yl 6-bromo-2-oxo-2H-chromene-3-carboxylate ***(4gc)***. White solid, yield: 89%, mp 147-148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 7.68-7.74 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 5.14-5.20 (m, 1H), 1.69-1.78 (m, 1H), 1.54-1.61 (m, 1H), 1.39-1.46 (m, 2H), 1.33 (d, J = 6.3 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 155.9, 153.8, 146.4, 136.7, 131.4, 119.9, 119.3, 118.5, 117.2, 73.1, 37.9, 19.9, 18.6, 13.8 ppm. IR (KBr) v: 3091, 1753, 1703, 1624, 1600, 1560, 1475, 1359, 1267, 1209, 1149, 1105, 1010, 968, 792 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}BrO_4$ ($[M+H]^+$) 339.0232, found 339.0232.

4.2.23 Benzyl 7-methoxy-2-oxo-2H-chromene-3-carboxylate ***(4cd)***. Yellow solid, yield 73%, mp 123-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (s, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.33-7.41 (m, 4H), 6.88 (d, J = 9.0 Hz, 1H), 6.81 (s, 1H), 5.37 (s, 2H), 3.89 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 163.1, 157.6, 149.2, 135.7, 130.7, 128.6, 128.3, 113.7, 111.6, 100.3, 67.2, 56.0 ppm; IR (KBr) v: 2951, 1751, 1689, 1614, 1562, 1500, 1463, 1377, 1305, 1276, 1170, 1116, 1026, 1006, 869, 736 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}O_5$ ($[M+H]^+$) 311.0919, found 311.0918.

4.2.24 Benzyl 6-bromo-2-oxo-2H-chromene-3-carboxylate ***(4gd)***. White solid, yield 81%, mp 186-187 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.70-7.73 (m, 2H), 7.45-7.48 (m, 2H), 7.36-7.42 (m, 4H), 7.23 (s, 1H), 5.39 (s, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.3, 155.9, 153.9, 147.4, 137.1, 135.1, 131.5, 128.7, 128.5, 128.3, 119.2, 119.1, 118.5, 117.3, 67.7 ppm. IR (KBr) v: 3091, 3034, 1762, 1693, 1618, 1558, 1473, 1413, 1382, 1288, 1209, 1136, 1072, 985, 792, 744 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{12}BrO_4$ ($[M+H]^+$) 358.9919, found 358.9916.

4.2.25 Benzyl 6-nitro-2-oxo-2H-chromene-3-carboxylate ***(4hd)***. White solid, yield 83%, mp 236-237 °C. ^{1}H NMR (300 MHz, DMSO-d^6) δ: 8.98 (s, 1H), 8.96 (s, 1H), 8.51 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 6.9 Hz, 2H), 7.34-7.42 (m, 3H), 5.34 (s, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d^6) δ: 162.5, 158.5, 155.5, 148.4, 144.1, 136.0, 129.1, 128.9, 128.6, 128.4, 126.6, 119.6, 118.6, 118.2, 107.5, 67.2 ppm. IR (KBr) v: 3086, 3057, 1755, 1703, 1573, 1498, 1452, 1379, 1290, 1217, 1095, 1002, 862, 796 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{12}NO_6$ ($[M+H]^+$) 326.0664, found 326.0664.

*4.2.26 Allyl 7-methoxy-2-oxo-2H-chromene-3-carboxylate (**4ce**).* Yellow solid, yield 90%, mp 108-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.49 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.80 (s, 1H), 595-6.08 (m, 1H), 5.47 (d, J = 17.1 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 4.82 (d, J = 5.7 Hz, 2H), 3.89 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 163.1, 157.6, 157.1, 149.3, 131.6, 130.8, 118.9, 113.7, 113.6, 111.5, 100.3, 66.1, 56.0 ppm. IR (KBr) v: 3047, 3018, 1755, 1732, 1693, 1616, 1560, 1498, 1419, 1379, 1309, 1230, 1172, 1024, 1008, 943, 860, 792 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}O_5$ ([M+H]$^+$) 261.0763, found 261.0762.

*4.2.27 Allyl 6,8-di-tert-butyl-2-oxo-2H-chromene-3-carboxylate (**4ee**).* White solid, yield 85%, mp 122-123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.66 (s, 2H), 7.39 (s, 1H), 5.82-6.01 (m, 1H), 4.81 (d, J = 5.4 Hz, 2H), 4.63 (d, J = 5.7 Hz, 2H), 1.48 (s, 9H), 1.33 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0, 163.0, 156.5, 152.1, 150.3, 147.1, 137.4, 131.6, 131.4, 129.8, 124.0, 118.7, 117.8, 116.5, 66.1, 41.4, 31.2, 29.7 ppm; IR (KBr) v: 2954, 1739, 1710, 1649, 1620, 1579, 1467, 1365, 1282, 1211, 1145, 1010, 993, 796 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{27}O_4$ ([M+H]$^+$) 343.1909, found 343.1906.

*4.2.28 Allyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (**4fe**).* White solid, yield 91%, mp 142-143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 7.59 (s, 2H), 7.32 (d, J = 8.7 Hz, 1H), 5.95-6.08 (m, 1H), 5.49 (d, J = 16.8 Hz, 1H), 5.34 (d, J = 10.2 Hz, 1H), 4.85 (d, J = 5.1 Hz, 2H,) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.3, 155.9, 153.5, 147.4, 134.2, 131.3, 130.1, 128.4, 119.2, 118.7, 118.2, 66.5 ppm. IR (KBr) v: 3053, 1766, 1741, 1701, 1643, 1620, 1562, 1479, 1379, 1301, 1251, 1012, 943, 794 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{10}ClO_4$ ([M+H]$^+$) 265.0267, found 265.0265.

*4.2.29 Allyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (**4ge**).* White solid, Yield 90%, mp 154-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (s, 1H), 7.73 (s, 2H), 7.23 (s, 1H), 5.97-6.04 (m, 1H), 5.48 (d, J = 16.8 Hz, 1H), 5.33 (d, J = 8.7 Hz, 1H), 4.84 (d, J = 6.0 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.2, 155.8, 153.9, 147.3, 137.0, 131.5, 131.3, 119.2, 118.5, 117.3, 66.5 ppm. IR (KBr) v: 3099, 3053, 1766, 1741, 1699, 1643, 1560, 1477, 1415, 1379, 1247, 1207, 1010, 943, 794 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{10}BrO_4$ ([M+H]$^+$) 308.9762, found 308.9760.

*4.2.30 Allyl 6-nitro-2-oxo-2H-chromene-3-carboxylate (**4he**).* Yellow solid, yield 91%, mp 165-166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 8.56 (s, 1H), 8.50 (d, J = 9.3 Hz, 1H), 7.50 (d, J = 9.3 Hz, 1H), 5.95-6.08 (m, 1H), 5.49 (d, J = 17.4 Hz, 1H), 5.35 (d, J = 10.5 Hz, 1H), 4.87 (d, J = 7.2 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.7, 158.3, 154.8, 147.2, 144.2, 131.0, 128.7, 125.2, 120.2, 119.5, 118.1, 117.7, 66.8 ppm. IR (KBr) v: 3074, 3055, 1776, 1755, 1693, 1647, 1622, 1568, 1477, 1346, 1255, 1093, 1006, 939, 752 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{10}NO_6$ ([M+H]$^+$) 276.0508, found 276.0505.

*4.2.31 Allyl 3-oxo-3H-benzo[f]chromene-2-carboxylate (**4je**).* Yellow solid, yield 91%, mp 115-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.30 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 6.00-6.14 (m, 1H), 5.53 (d, J = 17.4 Hz, 1H), 5.35 (d, J = 11.7 Hz, 1H),4.91 (d, J = 6.9 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.2, 156.7, 155.9, 144.7, 136.3, 131.5, 130.1, 129.3, 129.2, 129.1, 126.6, 121.4, 119.1, 116.6, 115.9, 112.1, 66.4 ppm. IR (KBr) v: 3014, 2922, 1745, 1695, 1625, 1600, 1564, 1454, 1392, 1300, 1255, 1134, 1012, 989, 750 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}O_4$ ([M+H]$^+$) 281.0814, found 281.0816.

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References and notes

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18. Crystallographic data for **4aa**: space group *P(2)*1/c, a = 7.933(2) Å, b = 15.745(4) Å, c = 8.748(2) Å, α = 90°, β = 108.157(3)°, γ = 90°, V = 1038.3(4) Å^3, T = 293 K, Z = 4. Crystallographic data for compound **4i** (CCDC-1011994) reported in this paper can be found in the ESI. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.