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L-CYSTEINE CATALYZED ONE-POT SYNTHESIS OF BICYCLIC δ-LACTONES UNDER BALL-MILLING CONDITIONS

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Abstract – A series of bicyclic δ-lactones **4a-4t** were synthesized in moderate to good yields *via* a simple one-pot reaction. The facile method depended on one-pot three-component reaction of aromatic aldehyde, Meldrum's acid and β-diketone in the presence of L-cysteine as a catalyst under ball-milling conditions. The reactions were completed in mere 30 min in 50-87% yields. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS. Environmental acceptability, wide substrate scope, low cost and operational simplicity are the key features of this method.

INTRODUCTION

Bicyclic lactones are highly valuable structural motifs in natural products and bioactive compounds (Figure 1).[1-5] Among them, bicyclic δ-lactones constitute an important class of heterocycles in modern medicinal chemistry due to their versatile biological activities such as antidiabetic,[3] anti-cancer[6] and antimicrobial activity.[7] In view of the importance of bicyclic δ-lactones, tremendous efforts have been made in the past two decades.[8-12] For instance, Shi et al. demonstrated that chiral thiourea−tertiary amine can catalyze [3 + 3] cyclization of 4-arylidene-2-aryloxazol-5(4*H*)-ones with cyclohexane-1,3-diones for the synthesis of bicyclic δ-lactones.[13] In 2018, a bifunctional organocatalyst-catalyzed cascade reaction for the access to bicyclic δ-lactones involving β,γ-unsaturated-α-ketophosphonates and cyclic 1,3-dicarbonyls has been nicely described by Albrecht and co-workers.[14] A further example is reported by the group of Li.[15] They developed a novel methodology for preparing a series of bicyclic δ-lactones using bifunctional squaramide-catalyzed reactions of α,β-unsaturated pyrazolamides with 1,3-dicarbonyl compounds. Although these methods worked nicely in many cases, most of them suffer from limitations

such as narrow substrate scope, harsh reaction conditions, long reaction time and tedious step of catalyst preparation. Therefore, the development of a simple, efficient, versatile, and eco-friendly methodology for the synthesis of bicyclic δ-lactones is still desirable.

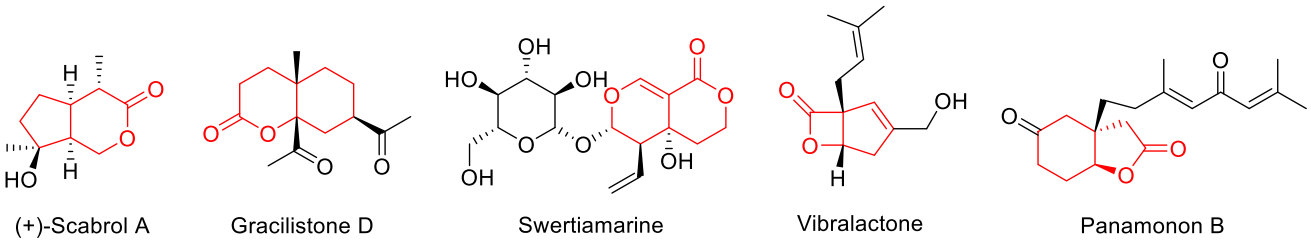
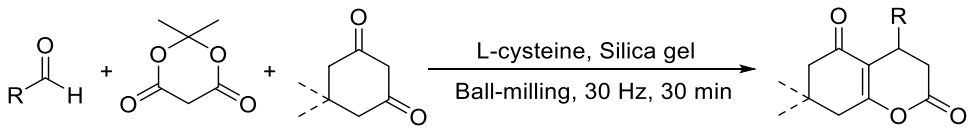


Figure 1. Bioactive compounds containing bicyclic lactone motifs

In the past two decades, great progress has been made in the field of mechanochemical organic synthesis.[16-18] For example, Brahmachari developed a one-pot protocol for the synthesis of coumarin hydrazones using a three-component reaction between 4-hydroxycoumarins, primary aromatic amines and *tert*-butyl nitrite under ball-milling conditions.[19] Xie et al. reported a novel method for the synthesis of sulfonyl quinolines *via* ball-milling promoted coupling of haloquinolines with sulfonic acid.[20] In 2019, Jiang et al. developed a mechanochemical enzymatic method for the synthesis of 1,4-dihydropyridine calcium antagonists.[21] Very recently, we reported a novel mechano-biocatalytic method for the rapid synthesis of 2-amino-3-cyano-4*H*-pyrans.[22] Herein, as part of our ongoing study on the mechanochemical reactions, we report a novel and eco-friendly protocol for the rapid synthesis of bicyclic δ-lactones using L-cysteine as the catalyst under ball-milling conditions (Scheme 1).



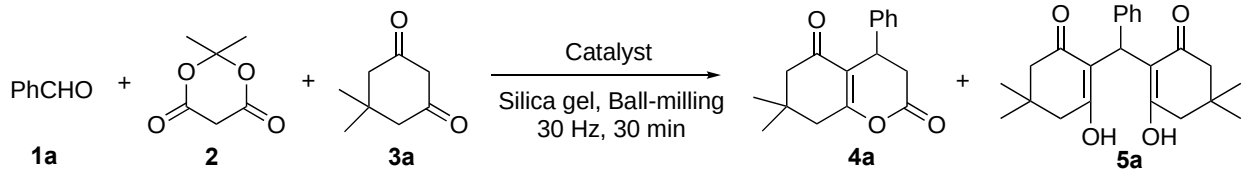
Scheme 1. L-Cysteine catalyzed rapid synthesis of bicyclic δ-lactones under ball-milling conditions

RESULTS AND DISCUSSION

In our initial studies, the reaction of benzaldehyde **1a**, Meldrum's acid **2** and dimedone **3a** were used as a model reaction to optimize the reaction conditions including catalysts, grinding auxiliary and grinding frequency. As shown in Table 1, the target product **4a** was obtained in only 10% yield and the major product **5a** was generated from the Knoevenagel-Michael cascade reactions of benzaldehyde **1a** and dimedone **3a** in the absence of catalyst (Table 1, entry 1). When the reactants were incubated with L-proline, the yield of the desired product **4a** was improved to 46% and the side product **5a** was obtained in 9% yield (Table 1, entry 2). Several amino acids, such as L-tryptophan, L-arginine, L-histidine and L-alanine also showed certain activity to catalyse the model reaction, but side product **5a** was still formed

(Table 1, entries 3-6). To our delight, model reaction under L-cysteine catalysis furnished the title compound **4a** as single product with 80% yield (Table 1, entry 7). Based on the above-mentioned results, L-cysteine was chosen as the catalyst for further investigation. It is well known to all that catalyst loading is an important factor for catalytic reactions. As summarized in Table 1, the yield of the title compound was improved greatly by increasing the catalyst loading from 40 to 120 mg and reached a plateau after 120 mg (Table 1, entries 7-11). Thus, 120 mg L-cysteine was selected as the optimum catalyst loading for the further reactions. Besides, in order to compare the present mechanochemical protocol with its liquid-phase counterpart, a control experiment was conducted and it was found that when the model reaction was performed in DMSO, the target product **4a** was obtained in 60% yield, even after 4 h (Table 1, entry 13). It is noteworthy that the mechanochemical protocol has noticeable advantages including a higher yield and a much shorter reaction time (Table 1, entry 11 vs entry 13).

Table 1. Effect of catalysts on the model reaction[a]



1a 2 3a 4a 5a

Entry	Catalyst	Catalyst loading (mg)	Yield (%)[b]	
			4a	5a
1	-	-	10	86
2	L-proline	100	46	9
3	L-tryptophan	100	51	27
4	L-arginine	100	53	30
5	L-histidine	100	56	13
6	L-alanine	100	59	17
7	L-cysteine	100	80	-
8	L-cysteine	40	63	-
9	L-cysteine	60	71	-
10	L-cysteine	80	72	-
11	L-cysteine	120	87	-
12	L-cysteine	140	87	-
13[c]	L-cysteine	120	60	-

[a] Reaction conditions: benzaldehyde **1a** (1 mmol), Meldrum's acid **2** (1 mmol), dimedone **3a** (1 mmol), catalyst and silica gel (600 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at 30 Hz.

[b] Isolated yields.

[c] Reaction conditions: a mixture of benzaldehyde **1a** (1 mmol), Meldrum's acid **2** (1 mmol), dimedone **3a** (1 mmol), L-cysteine (120 mg), silica gel (600 mg) and DMSO (10 mL) was stirred at room temperature for 4 h.

Subsequently, the effect of grinding auxiliary and grinding frequency were investigated since both of which are known to play important roles in ball-milling reactions. When the reaction was conducted without any grinding auxiliary, the target product **4a** was obtained in 80% yield (Table 2, entry 1). In the cases of γ-Al_2O_3 (neutral) and Na_2SO_4, the corresponding title compound **4a** was obtained in yields of 77 and 81%, respectively (Table 2, entries 2-3). The best results were obtained by using silica gel as the grinding auxiliary, which afforded a yield of 87% (Table 2, entry 4). Then, the influence of grinding frequency was studied. As shown in Table 2, when the grinding frequency increased from 15 Hz to 30 Hz, the yields increased from 42% to 87% (Table 2, entries 4-7). Since the toplimit of ball-milling frequency for Retsch MM 400 Mixer Mill is 30 Hz, the milling frequency of 30 Hz was used in subsequent studies.

Table 2. Influence of grinding auxiliary and grinding frequency on the model reaction[a]

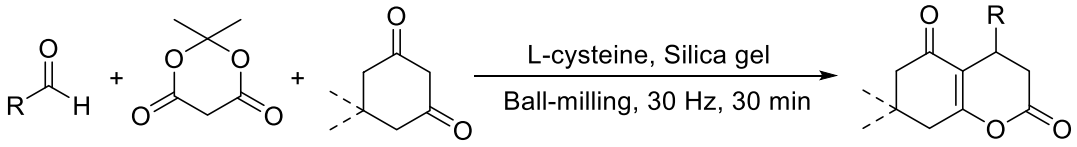
Entry	Grinding auxiliary	Grinding frequency (Hz)	Yield (%)[b]
1	-	30	80
2	γ-Al_2O_3 (neutral)	30	77
3	Na_2SO_4	30	81
4	Silica gel	30	87
5	Silica gel	15	42
6	Silica gel	20	53
7	Silica gel	25	84

[a] Reaction conditions: benzaldehyde **1a** (1 mmol), Meldrum's acid **2** (1 mmol), dimedone **3a** (1 mmol), L-cysteine (120 mg) and grinding auxiliary (600 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at the specified grinding frequency.

[b] Isolated yields.

With the optimal conditions in hand, the reaction scope was investigated (Table 3). It was found that both electron-donating and electron-withdrawing substituents on the benzene ring afforded the corresponding bicyclic δ-lactones in moderate to good yields. When dimedone was used for the reaction, either electron-donating or electron-withdrawing groups at the *para*-position gave higher yields than those with *ortho*- and *meta*-groups (Table 3, entry 4 *vs* entries 2-3, entry 8 *vs* entries 6-7). On the contrary, when 1,3-cyclohexanedione was used for the reaction, the substituent in the *ortho*-position led to higher yields than the same substituent in the *meta*- or *para*-position (Table 3, entry 13 *vs* entries 14-15, entry 17 *vs* entries 18-19). In addition, bis-substituted benzaldehyde also reacted well to give the target products (Table 3, entry 12).

Table 3. Substrate scope of L-cysteine catalyzed synthesis of bicyclic δ-lactones under ball-milling conditions[a]



Entry	R	β-Diketone	Product	Yield (%)[b]
1	C_6H_5	dimedone	**4a**	87
2	2-MeC_6H_4	dimedone	**4b**	52
3	3-MeC_6H_4	dimedone	**4c**	81
4	4-MeC_6H_4	dimedone	**4d**	85
5	4-$MeOC_6H_4$	dimedone	**4e**	87
6	2-ClC_6H_4	dimedone	**4f**	50
7	3-ClC_6H_4	dimedone	**4g**	74
8	4-ClC_6H_4	dimedone	**4h**	79
9	4-FC_6H_4	dimedone	**4i**	81
10	4-BrC_6H_4	dimedone	**4j**	85
11	4-$NO_2C_6H_4$	dimedone	**4k**	77
12	2,3-$Cl_2C_6H_3$	dimedone	**4l**	79
13	2-MeC_6H_4	1,3-cyclohexanedione	**4m**	78
14	3-MeC_6H_4	1,3-cyclohexanedione	**4n**	74
15	4-MeC_6H_4	1,3-cyclohexanedione	**4o**	65
16	4-$MeOC_6H_4$	1,3-cyclohexanedione	**4p**	73
17	2-ClC_6H_4	1,3-cyclohexanedione	**4q**	74
18	3-ClC_6H_4	1,3-cyclohexanedione	**4r**	70
19	4-ClC_6H_4	1,3-cyclohexanedione	**4s**	63
20	4-BrC_6H_4	1,3-cyclohexanedione	**4t**	75

[a] Reaction conditions: aromatic aldehyde **1** (1 mmol), Meldrum's acid **2** (1 mmol), β-diketone **3** (1 mmol), L-cysteine (120 mg) and silica gel (600 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at 30 Hz.

[b] Isolated yields.

To further illustrate the potential of this protocol for bicyclic δ-lactone synthesis, the reutilization of L-cysteine on the model reaction was investigated. After completion of the reaction, the mixture was diluted with CH_2Cl_2, filtered, the mixture of L-cysteine and silica gel was recovered. The filtrate was concentrated in vacuo, and then purified by recrystallization from ethanol to afford the desired product. The recovered mixture of L-cysteine and silica gel was further washed with water, filtered, and silica gel was recovered. Then, the water phase was concentrated in vacuo to recover L-cysteine. After that, L-cysteine and silica gel were dried and reused in the next cycles. As can be seen from Table 4, L-cysteine could be recycled at least four times without significant loss of activity, and product **4a** was obtained in satisfactory yields.

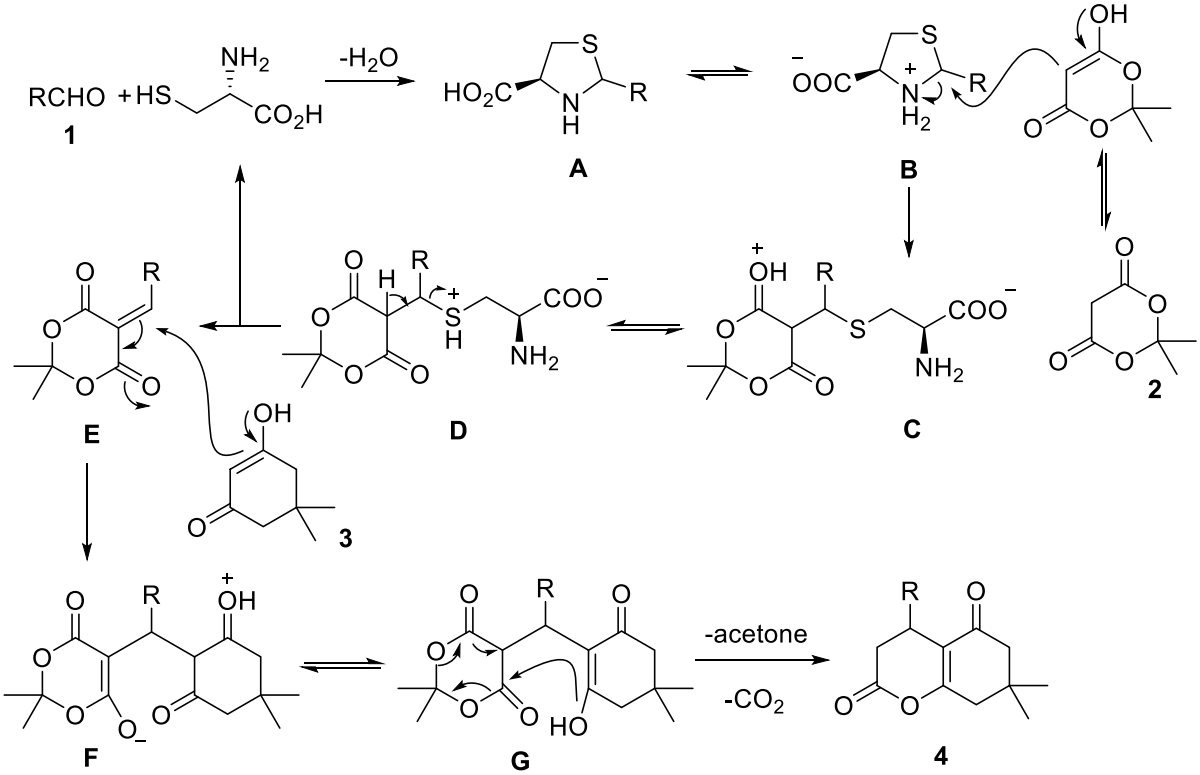
Table 4. Recyclability of L-cysteine

Entry	Cycle	Recovery yield (%)[a]		Yield (%)[b]
		L-cysteine	Silica gel	
1	Fresh	95	94	87
2	First recycle	92	90	83
3	Second recycle	90	87	79
4	Third recycle	86	82	78
5	Fourth recycle	81	76	74

[a] Isolated yields

[b] Isolated yields

On the basis of the above experimental results and some previous reports,[9,23] a plausible mechanism for this L-cysteine catalyzed three-component reaction is depicted in Scheme 2. Firstly, L-cysteine reacted with aromatic aldehyde **1** resulting formation of thioproline derivative **A**. Then a Knoevenagel-type condensation of Meldrum's acid **2** with the intermediate **B** to give intermediate **C**, followed by deprotonation of its tautomeric **D** provided intermediate **E**, accompanied by recovery of the L-cysteine catalyst. Finally, Michael addition of the enol formed β-diketone **3** to the adduct **E**, followed by cyclization of the resulting intermediate **G** via a translactonization reaction liberated a molecular of acetone and CO_2 delivery the final product **4**.



Scheme 2. Plausible mechanism for the L-cysteine-catalyzed synthesis of bicyclic δ-lactones

In conclusion, we have successfully developed a versatile and efficient strategy for the synthesis of bicyclic δ-lactones via one-pot three-component reaction of aromatic aldehyde, Meldrum's acid and β-diketone catalyzed by L-cysteine under solvent-free ball-milling conditions. Environmental friendliness, wide substrate scope, short reaction time, operational simplicity and utilization of inexpensive and reusable catalyst are the key features of this protocol. Studies aimed at enhancing its enantioselectivity by catalyst structural modification are being carried out in our laboratory.

EXPERIMENTAL

General. Melting points were determined with an Optimelt MPA100 melting point apparatus, and uncorrected. NMR spectra were recorded on a Bruker AVANCE III 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) or Bruker AVANCE III 500 spectrometer (500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR) using $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Mass spectra were measured by a Bruker micrOTOF-Q II spectrometer with ESI.

Materials. Unless otherwise noted, all the reagents were obtained from Aladdin Chemicals Reagent Co., Ltd. (Shanghai, China) and used without further purification.

General procedure for the synthesis of bicyclic δ-lactones. A mixture of aromatic aldehyde (1 mmol), Meldrum's acid (1 mmol), dimedone (1 mmol) or 1,3-cyclohexanedione (1 mmol), silica gel (600 mg) and L-cysteine (120 mg) was milled for 30 min at 30 Hz in a Retsch MM 400 Mixer Mill (MM 400, Retsch, Germany) using a 50 mL stainless steel grinding jar with three stainless steel grinding balls (ø = 1 cm). After the milling was stopped, the reaction mixture was diluted with CH_2Cl_2, filtered, the mixture of L-cysteine and silica gel was recovered and reused. The filtrate was concentrated in vacuo, and then purified by recrystallization from EtOH to afford the desired products (**4a**-**4t**). All title compounds were characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS and were compared with those reported in the literatures.[9,10,12,14,24-26]

7,7-Dimethyl-4-phenyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4a**).[24] White solid; mp 102-104 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 5H), 4.33 – 4.29 (m, 1H), 2.96 – 2.92 (m, 2H), 2.55 (s, 2H), 2.33 (s, 2H), 1.16 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.09, 165.94, 165.69, 140.58, 129.07, 127.46, 126.52, 116.11, 50.63, 41.07, 36.32, 33.84, 32.53, 28.56, 28.15. MS (ESI): $[M+H]^+$: 271.24.

7,7-Dimethyl-4-(*o*-tolyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4b**). White solid, mp 101-103 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.05 (m, 3H), 6.89 – 6.82 (m, 1H), 4.51 (d, *J* = 8.0 Hz, 1H), 2.94 (dd, *J* = 15.8, 8.2 Hz, 1H), 2.75 (dd, *J* = 15.8, 1.2 Hz, 1H), 2.60 (d, *J* = 5.3 Hz, 2H), 2.48 (s, 3H), 2.33 (s, 2H), 1.18 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.09, 166.27, 165.81,

138.31, 135.33, 131.26, 127.49, 126.69, 124.79, 116.13, 50.56, 41.04, 35.82, 32.64, 30.14, 28.58, 28.32, 19.50. MS (ESI): $[M+H+MeOH]^+$: 317.02.

7,7-Dimethyl-4-(*m*-tolyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4c**).[12] White solid, mp 122-124 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.99 – 6.91 (m, 2H), 4.30 – 4.24 (m, 1H), 2.96 – 2.91 (m, 2H), 2.57 – 2.53 (m, 2H), 2.34 (s, 2H), 2.32 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.15, 166.05, 165.67, 140.47, 138.74, 128.96, 128.28, 127.36, 123.39, 116.12, 50.64, 41.06, 36.45, 33.80, 32.59, 28.58, 28.19, 21.50. MS (ESI): $[M+H+MeOH]^+$: 317.01.

7,7-Dimethyl-4-(*p*-tolyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4d**).[25] White solid, mp 107-109 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.31 – 4.25 (m, 1H), 2.95 – 2.91 (m, 2H), 2.55 (s, 2H), 2.33 (s, 2H), 2.31 (s, 3H), 1.16 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.15, 166.11, 165.56, 137.56, 137.12, 129.74, 126.39, 116.28, 50.64, 41.06, 36.46, 33.47, 32.56, 28.59, 28.18, 21.01. MS (ESI): $[M+H+MeOH]^+$: 316.97.

4-(4-Methoxyphenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4e**).[24] Yellow solid, mp 134-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.30 – 4.23 (m, 1H), 3.77 (s, 3H), 2.94 – 2.90 (m, 2H), 2.54 (s, 2H), 2.33 (s, 2H), 1.16 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.19, 166.16, 165.47, 158.82, 132.62, 127.60, 116.41, 114.42, 55.26, 50.64, 41.04, 36.55, 33.06, 32.56, 28.59, 28.16. MS (ESI): $[M+Na]^+$: 323.12.

4-(2-Chlorophenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4f**).[9] White solid, mp 135-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.24 – 7.12 (m, 2H), 6.92 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.76 (s, 1H), 2.97 – 2.93 (m, 2H), 2.62 (s, 1H), 2.61 (d, *J* = 1.3 Hz, 1H), 2.36 (s, 2H), 1.20 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.69, 167.06, 165.44, 136.96, 133.42, 130.53, 128.95, 127.36, 126.69, 114.73, 50.54, 41.11, 35.22, 32.56, 31.23, 28.54, 28.45. MS (ESI): $[M+H]^+$: 305.14.

4-(3-Chlorophenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4g**).[24] White solid, mp 122-124 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.01 (m, 4H), 4.29 (d, *J* = 5.9 Hz, 1H), 2.95 (t, *J* = 5.1 Hz, 2H), 2.59 – 2.54 (m, 2H), 2.35 (s, 2H), 1.18 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.01, 166.13, 165.45, 142.51, 134.90, 130.39, 127.81, 126.97, 124.62, 115.44, 50.56, 41.06, 36.13, 33.62, 32.60, 28.56, 28.20. MS (ESI): $[M+H]^+$: 305.19.

4-(4-Chlorophenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4h**).[24] White solid, mp 166-168 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.29 (d, *J* = 6.1 Hz, 1H), 3.00 – 2.90 (m, 2H), 2.54 (s, 2H), 2.33 (s, 2H), 1.16 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.06, 165.91, 165.65, 139.10, 133.32, 129.23, 127.97, 115.77, 50.56, 41.05, 36.10, 33.32, 32.56, 28.60, 28.10. MS (ESI): $[M+H+MeOH]^+$: 337.08.

4-(4-Fluorophenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4i**).[10] White solid, mp 171-173 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 2H), 7.03 – 6.94 (m, 2H), 4.30 (d, *J* = 5.6 Hz, 1H), 3.00 – 2.86 (m, 2H), 2.55 (s, 2H), 2.33 (s, 2H), 1.16 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.11, 165.79, 163.23, 160.78, 136.36, 136.33, 128.22, 128.14, 116.05, 115.84, 50.58, 41.04, 36.35, 33.18, 32.56, 28.58, 28.12. MS (ESI): $[M+H+MeOH]^+$: 321.06.

4-(4-Bromophenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4j**).[26] White solid, mp 157-159 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.27 (d, *J* = 6.4 Hz, 1H), 3.00 – 2.85 (m, 2H), 2.54 (s, 2H), 2.33 (s, 2H), 1.16 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.05, 165.93, 165.62, 139.64, 132.19, 128.33, 121.40, 115.68, 50.56, 41.04, 36.01, 33.39, 32.56, 28.60, 28.10. MS (ESI): $[M+H+MeOH]^+$: 381.00.

7,7-Dimethyl-4-(4-nitrophenyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4k**).[24] Yellow solid, mp 141-143 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 4.42 (d, *J* = 7.3 Hz, 1H), 3.09 – 2.91 (m, 2H), 2.58 (s, 2H), 2.37 (d, *J* = 16.4 Hz, 1H), 2.33 (d, *J* = 16.5 Hz, 1H), 1.18 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.96, 166.48, 165.04, 147.96, 147.28, 127.68, 124.38, 115.02, 50.48, 41.09, 35.56, 33.85, 32.60, 28.60, 28.06. MS (ESI): $[M+H+MeOH]^+$: 348.01.

4-(2,3-Dichlorophenyl)-7,7-dimethyl-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4l**). White solid, mp 190-192 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.84 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.79 (t, *J* = 4.8 Hz, 1H), 2.96 (d, *J* = 5.3 Hz, 2H), 2.65 (d, *J* = 18.1 Hz, 1H), 2.62 (d, *J* = 1.3 Hz, 1H), 2.37 (s, 2H), 1.20 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.57, 167.22, 165.09, 139.31, 134.34, 131.79, 129.87, 127.64, 124.79, 114.56, 50.49, 41.11, 34.97, 32.58, 32.12, 28.52, 28.48. MS (ESI): $[M+H+MeOH]^+$: 370.97.

4-(*o*-Tolyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4m**): White solid, mp 151-153 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.05 (m, 3H), 6.85 (d, *J* = 7.3 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 1H), 2.94 (dd, *J* = 15.8, 8.1 Hz, 1H), 2.84 – 2.64 (m, 3H), 2.48 (s, 3H), 2.46 (d, *J* = 6.9 Hz, 2H), 2.16 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.17, 167.92, 165.63, 138.19, 135.36, 131.22, 127.50, 126.69, 124.74, 117.31, 36.71, 35.73, 30.26, 27.37, 20.73, 19.48. MS (ESI): $[M+H+MeOH]^+$: 288.99.

4-(*m*-Tolyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4n**): White solid, mp 116-118 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.99 – 6.91 (m, 2H), 4.35 – 4.16 (m, 1H), 2.96 – 2.91 (m, 2H), 2.78 – 2.61 (m, 2H), 2.51 – 2.44 (m, 2H), 2.32 (s, 3H), 2.19 – 2.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.39, 167.36, 165.99, 140.44, 138.74, 128.94, 128.31, 127.37, 123.43, 117.27, 36.75, 36.33, 33.75, 27.37, 21.53, 20.62. MS (ESI): $[M+H+MeOH]^+$: 288.99.

4-(*p*-Tolyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4o**).[14] White solid, mp 105-106 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 21.0, 8.1 Hz, 4H), 4.40 – 4.16 (m, 1H), 2.96 – 2.91 (m, 2H), 2.76 – 2.62 (m, 2H), 2.51 – 2.42 (m, 2H), 2.31 (s, 3H), 2.17 – 2.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

196.38, 167.24, 166.04, 137.50, 137.17, 129.73, 126.43, 117.45, 36.75, 36.35, 33.42, 27.36, 21.05, 20.63. MS (ESI): $[M+H+MeOH]^+$: 288.95.

4-(4-Methoxyphenyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione **(4p)**.[14] White solid, mp 134-136 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.34 – 4.23 (m, 1H), 3.78 (s, 3H), 2.95 – 2.90 (m, 2H), 2.74 – 2.63 (m, 2H), 2.52 – 2.42 (m, 2H), 2.19 – 2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.48, 147.56, 143.58, 138.47, 132.05, 131.18, 130.83, 129.64, 128.48, 126.29, 124.71, 123.95, 122.75, 84.22, 26.23, 21.48. MS (ESI): $[M+H+MeOH]^+$: 305.00.

4-(2-Chlorophenyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4q**).[14] White solid, mp 149-151 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 – 7.12 (m, 2H), 6.91 (dd, *J* = 7.3, 2.0 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 3.03 – 2.90 (m, 2H), 2.85 – 2.66 (m, 2H), 2.55 – 2.44 (m, 2H), 2.25 – 2.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.82, 168.79, 165.33, 136.72, 133.47, 130.51, 128.99, 127.38, 126.60, 115.85, 36.68, 35.10, 31.26, 27.43, 20.71. MS (ESI): $[M+H+MeOH]^+$: 308.91.

4-(3-Chlorophenyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4r**).[14] White solid, mp 124-126 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 2H), 7.15 (s, 1H), 7.08 – 7.01 (m, 1H), 4.31 (d, *J* = 6.9 Hz, 1H), 3.05 – 2.87 (m, 2H), 2.81 – 2.60 (m, 2H), 2.56 – 2.40 (m, 2H), 2.21 – 2.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.13, 167.80, 165.31, 142.48, 134.87, 130.36, 127.80, 126.93, 124.69, 116.58, 36.66, 36.05, 33.60, 27.38, 20.57. MS (ESI): $[M+H+MeOH]^+$: 308.94.

4-(4-Chlorophenyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione (**4s**).[14] White solid, mp 135-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.31 (d, *J* = 7.0 Hz, 1H), 3.05 – 2.84 (m, 2H), 2.79 – 2.61 (m, 2H), 2.48 (t, *J* = 6.7 Hz, 2H), 2.21 – 2.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.29, 167.63, 165.56, 139.01, 133.33, 129.22, 128.01, 116.91, 36.68, 36.05, 33.29, 27.37, 20.58. MS (ESI): $[M+H+MeOH]^+$: 308.92.

4-(4-Bromophenyl)-4,6,7,8-tetrahydro-2*H*-chromene-2,5(3*H*)-dione(**4t**).[14] White solid, mp 144-146 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.33 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.29 (d, *J* = 7.0 Hz, 1H), 3.05 – 2.84 (m, 2H), 2.78 – 2.58 (m, 2H), 2.47 (t, *J* = 6.7 Hz, 2H), 2.22 – 2.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.25, 167.64, 165.53, 139.55, 132.16, 128.37, 121.42, 116.83, 36.68, 35.96, 33.37, 27.37, 20.57. MS (ESI): $[M+H+MeOH]^+$: 352.92.

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