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Full Paper

A New Protocol for Total Synthesis of Natural Product Frutinone A and Its Derivatives

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A new protocol for total synthesis of natural product frutinone A was accomplished in three steps by using inexpensive 2′-hydroxyacetophenone as starting material. The key intermediate 3-(2-chlorobenzoyl)-4-hydroxycoumarin was synthesized in one pot through Baker–Venkataraman rearrangement of 2-acetylphenyl 2-chlorobenzoate followed by introduction of methyl chloroformate under basic conditions. Then, base-promoted intramolecular nucleophilic substitution reaction of 3-(2-chlorobenzoyl)-4-hydroxycoumarin provided frutinone A in excellent yield. The synthetic route features good yield, transition metal-free and mild reaction conditions, and high tolerance for functionality, thereby allowing easy substitutions around the frutinone A core.

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Introduction

Frutinones are natural-occurring chromonocoumarins, existing in *Polygala* plants such as *P. dalmaisiana*, *P. gazensis*, and *P. fruticosa*.[1–3] To date, frutinone A, frutinone B, and frutinone C (Fig. 1) have already been isolated. Among these three, frutinone A exhibits strong fungicidal activity against *Cladosporium cucumerinum*[1] and has been reported to strongly inhibit cytochrome P450 1A2 (CYP1A2).[4] Although frutinone A has been synthesized by several methods over the last several decades,[5–7] the reported methods have limited applications because of poor starting material availability and low yields, thereby resulting in limited access to its derivatives. Recently, Doi and coworkers have developed a strategy for the synthesis of frutinone A.[8] More recently, the synthesis of frutinone A and its derivatives using C–H functionalization was also reported by Hong et al.[9] However, their strategy has some disadvantages.

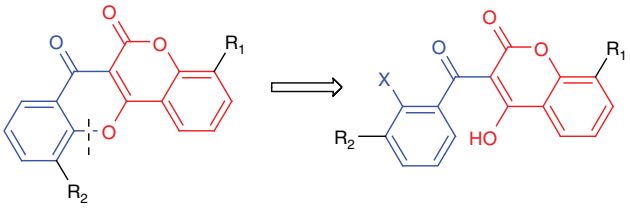


Fig. 1. Design for the synthesis of frutinone A from 4-hydroxylcoumarin scaffold.

For example, the starting material used in their strategy is commercial unavailable, the synthesis route uses an expensive transition metal catalyst, and uses highly toxic carbon monoxide as reactant. Thus, we considered that an alternate strategy, which would provide easy access to frutinone A derivatives and avoid the use of expensive transition metals and toxic reagents, would be necessary.

Because the 4-hydroxycoumarin scaffold is a key component of the frutinones, the introduction of a 2-halogenated benzoyl at the C-3 position in the 4-hydroxycoumarin skeleton is important for achieving the total synthesis of frutinone A (Fig. 1). Several methods for the synthesis of 3-benzyol-4-hydroxycoumarin were reported during the last several decades.[10–13] Traditionally, the method used for the introduction of the benzoyl at the C-3 position in the 4-hydroxycoumarin skeleton is as follows.[10–12] In the first step, 4-hydroxycoumarin is initially *O*-acylated with acyl chloride or carboxylic acid and in the second step, O–C isomerization catalyzed by potassium cyanide (KCN) leads to the synthesis of 3-benzyol-4-hydroxycoumarin. However, the method has limited application because it requires prolonged reaction times and KCN is a highly toxic reagent. Thus, an alternate method for the preparation of 3-benzoyl-4-hydroxycoumarin is justified.

Baker–Venkataraman rearrangement is base-catalyzed acyl transfer reaction that converts α-acyloxyketones to β-diketones.[14] In a typical reaction (**Fig. 2**, Path a), base abstraction of one of the α-hydrogens of the aromatic ketone **1** occurs, which results in the formation of enolate **2**. Intramolecular attack of the enolate occurs onto the ester carbonyl to form the cyclic-charged hemiacetal **3**, the tetrahedral

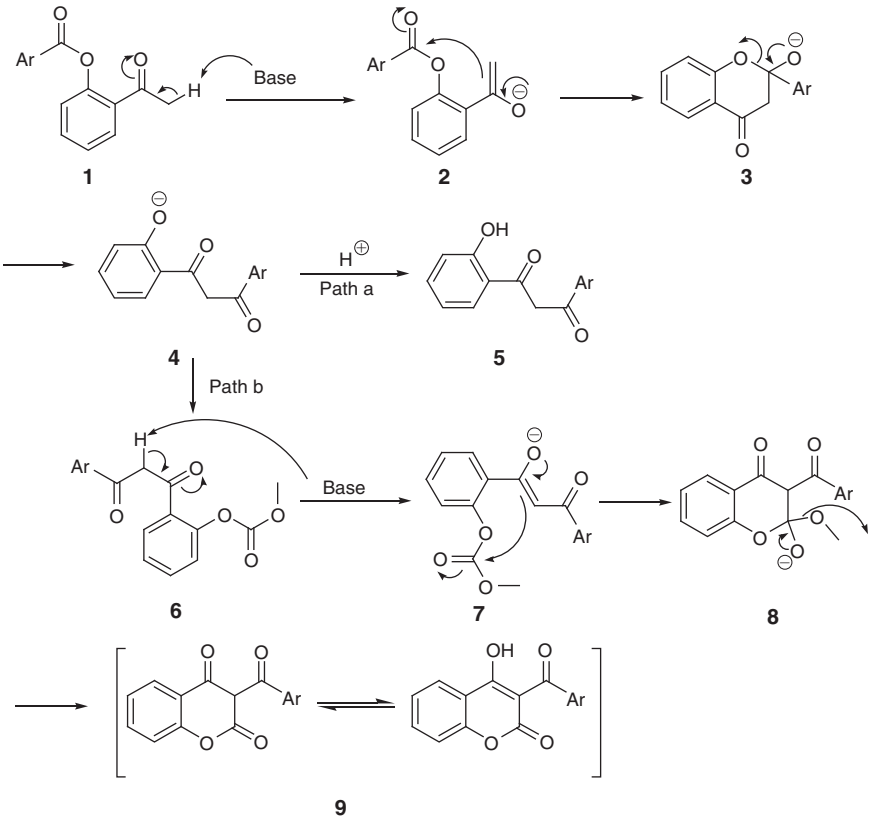
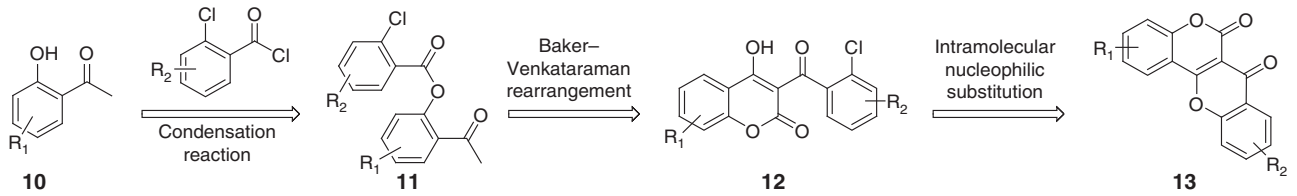


Fig. 2. Proposed mechanism for synthesis of 3-benzoyl-4-hydroxylcoumarin scaffold.



Scheme 1. Synthetic route of frutinone A and its derivatives.

intermediate of which subsequently collapses to form the more stable phenolate **4**, which is protonated during acid workup to give the 1,3-diketone **5**. The modular nature of this mechanism stimulated us to search an alternate route for rapid synthesis of 3-benzoyl-4-hydroxycoumarin (Fig. 2, Path b). We envisaged that the diketone **6** would be formed when methyl chloroformate was added to phenolate **4** before acid workup. Subsequently, intramolecular attack of the enolate **7** occurs onto the ester carbonyl to form the cyclic-charged hemiacetal **8** under basic conditions, which would collapse to give the triketone **9**.

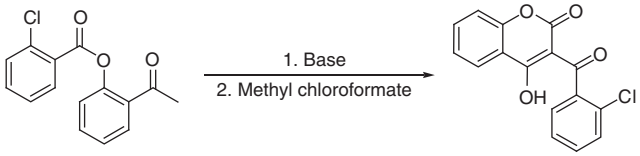
Based on the above consideration, we herein report a new protocol for total synthesis of frutinone A and its derivatives from commercially available 2′-hydroxyacetophenone derivatives as starting materials. Our synthetic strategy for frutinone A and its derivatives is illustrated in Scheme 1. Aromatic ketone **11** could be synthesized via the condensation reaction of 2′-hydroxyacetophenone derivatives **10** with a series of 2-chlorobenzoyl chloride. The desired frutinone derivatives **13** would be obtained by intramolecular nucleophilic substitution reaction of triketones **12**, which would be prepared via Baker–Venkataraman rearrangement of aromatic ketones **11** followed by introduction of methyl chloroformate under basic conditions.

Results and Discussion

The total synthesis of frutinone A and its derivatives was started from commercial available 2′-hydroxyacetophenone derivatives **10**. According to the references,[15–17] the reaction of 2′-hydroxyacetophenone derivatives with a series of 2-chlorobenzoyl chloride in pyridine provided 2-acetylphenyl 2-chlorobenzoate derivatives **11** in good-to-excellent yields.

Subsequently, constructing the skeleton of triketones **12** via the above-mentioned method was investigated and the synthesis of **12-1** was selected as a model to optimize the reaction conditions. The reaction of 2-acetylphenyl 2-chlorobenzoate **11-1** with several cheap and commercially available bases (2.2 equiv.) in tetrahydrofuran (THF) followed by introduction of methyl chloroformate (1.1 equiv.), initially attempted at room temperature (entries 1–4, Table 1). Fortunately, the desired product **12-1** was isolated in a moderate yield with sodium hydride (NaH) or potassium *tert*-butoxide (*t*-KOBu) as base, and

Table 1. Optimization of the reaction for 3-(2-chlorobenzoyl)-4-hydroxycoumarin[A]



11-1 **12-1**

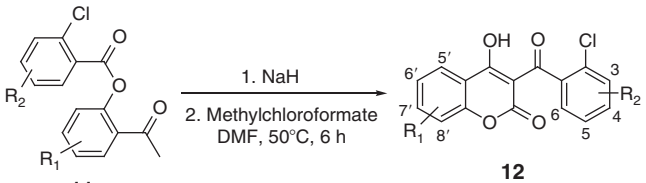
Entry	Solvent	Base	Amount [equiv.]	Temperature [°C]	Time [h]	Yield [%][B]
1	THF	K_2CO_3	2.2	25	6	0
2	THF	Cs_2CO_3	2.2	25	6	0
3	THF	*t*-KOBu	2.2	25	6	37
4	THF	NaH	2.2	25	6	39
5	Dioxane	NaH	2.2	25	6	36
6	Toluene	NaH	2.2	25	6	28
7	DMF	NaH	2.2	25	6	47
8	DMF	NaH	2.2	0	6	38
9	DMF	NaH	2.2	50	6	61
10	DMF	NaH	2.2	75	6	22
11	DMF	NaH	2.2	100	6	0
12	DMF	NaH	2.2	50	9	63
13	DMF	NaH	2.2	50	12	61
14	DMF	NaH	3.0	50	6	60
15	DMF	NaH	4.0	50	6	61

[A]Reaction conditions: compound **11-1** (5 mmol) and solvent (10 mL); [B]Isolated yield.

NaH was found to be the best base. The reaction conditions were further optimized in order to improve the yield of triketone **12-1**. It was found that reaction in *N*,*N*-dimethylformamide (DMF) provided triketone **12-1** in 47 % yield, which is higher than that obtained in THF, 1,4-dioxane, or toluene (entries 4–6, Table 1). The yield increased consistently with increasing temperatures from 0°C to 50°C, and this yield increase was maintained at 50°C (entries 7–9, Table 1). Further increases in the temperature lead to a yield decrease. Moreover, the desired product was not obtained, and 4-hydroxycoumarin was isolated in 59 % yield as the main product at 100°C (entries 10 and 11, Table 1). In addition, the yield increased with time from 61 % (6 h) to a maximum level of 63 % (9 h) (entries 9, 12, 13, Table 1). Thus, extending the reaction time beyond 6 h did not change the yield significantly. Furthermore, increasing the amount of sodium hydride did not result in any changes in the yield (entries 14 and 15, Table 1). The results indicated that the reaction conditions, particularly the solvent and temperature, significantly influence the yield of 3-(2-chlorobenzoyl)-4-hydroxycoumarin.

Under the optimal established conditions, the scope and generality of the reaction was examined subsequently. The results are depicted in Table 2. Twenty 3-(2-chlorobenzoyl)-4-hydroxycoumarin derivatives were obtained under the optimal conditions with yields ranging from 38 % to 72 %. Notably, the electronic properties of substituents on the aromatic rings of 2′-hydroxyacetophenone and 2-chlorobenzoyl acid affected the yield. When the aromatic ring of 2-chlorobenzoyl acid had an electron-donating group, yields were relatively low (such as compounds **12-10** and **12-11**; Table 2). The yields were lower when the aromatic ring of 2′-hydroxyacetophenone bore an electron-donating group when compared with that obtained when the aromatic ring bore an electron-withdrawing group (such as compounds **12-17** to **12-20**; Table 2). Furthermore, the position of substituent on the aromatic rings of 2-chlorobenzoyl

Table 2. Scope of Baker–Venkataraman rearrangement of the aromatic ketone 12[A]

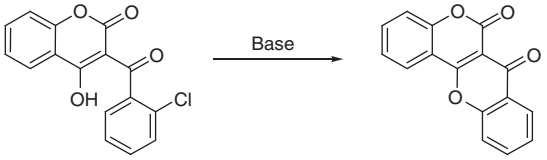


11 **12**

Compound	R_1	R_2	Yield [%][B]
12-1	H	H	61
12-2	H	3-Cl	68
12-3	H	4-Cl	70
12-4	H	5-Cl	64
12-5	H	6-F	38
12-6	H	4-F	71
12-7	H	5-F	69
12-8	H	4-Br	66
12-9	H	4-SO_2Me	72
12-10	H	3-OMe	47
12-11	H	4-OMe	56
12-12	7′-F	H	62
12-13	6′-F	4-Cl	66
12-14	6′-F	H	70
12-15	6′-Br	4-Cl	68
12-16	6′-Br	H	64
12-17	5′-OMe	4-Cl	59
12-18	5′-OMe	H	50
12-19	6′-Me	H	55
12-20	7′-OMe	H	52

[A]Reaction conditions: compound **11** (5 mmol), NaH (2.2 equiv.), DMF (10 mL), 50°C, 2 h, and methyl chloroformate (1.1 equiv.), 50°C, 4 h; [B]Isolated yield.

Table 3. Optimization of the reaction for frutinone A[A]



Entry	Solvent	Base	Temperature [°C]	Time [h]	Yield [%][B]
1	DMF	K_2CO_3	100	2	0
2	DMF	KOH	100	2	0
3	DMF	NaH	100	2	34
4	DMF	K_3PO_4	100	2	48
5	Toluene	K_3PO_4	100	2	0
6	THF	K_3PO_4	70	2	0
7	Dioxane	K_3PO_4	100	2	0
8	DMF	K_3PO_4	120	2	59
9	DMF	K_3PO_4	130	2	63
10	DMF	K_3PO_4	140	2	79
11	DMF	K_3PO_4	150	2	94
12	DMF	K_3PO_4	150	1	72
13	DMF	K_3PO_4	150	3	94
14	DMF	K_3PO_4	150	4	93
15[c]	DMF	K_3PO_4	150	2	93
16[d]	DMF	K_3PO_4	150	2	92

[A]Reaction conditions: compound **12-1** (1 mmol), solvent (10 mL), base (1.0 equiv.); [B]Isolated yield; [C]Base (2.0 equiv.); [D]Base (3.0 equiv.).

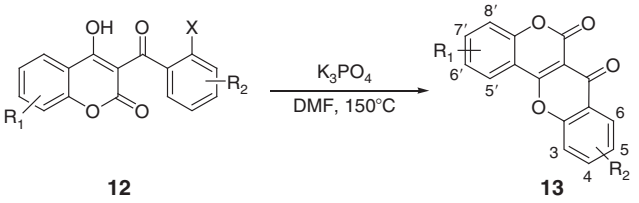
acid affected the yield. Especially, the yield considerably decreased when the aromatic ring of 2-chlorobenzoyl acid bore one substituent at 6-position (such as compound **12-5**; Table 2).

Because we have acquired a new protocol to the triketones **12**, our attention turned to constructing the frutinone A framework. The reaction of **12-1** with a base was performed in DMF to obtain frutinone A, and this reaction was selected as a model to optimize the reaction conditions. The results are summarized in Table 3. A moderate yield of frutinone A could be obtained in the presence of potassium phosphate (K_3PO_4) (entry 4, Table 3), and DMF was found to be the best reaction medium (entry 4, Table 3). Under the conditions of K_3PO_4 and DMF, yields increased consistently with increasing temperatures from 100°C to 150°C, and this yield increase was maintained up to 150°C (entries 4, 8–11, Table 3). In addition, yields increased with time from 72 % (1 h) to a maximum level of 94 % (2 h) (entries 11 and 12, Table 3). Extending the reaction time beyond 2 h did not change the yield significantly. In addition, increasing the amount of K_3PO_4 did not result in a yield change (entries 13 and 14, Table 3). Thus, we conclude that the optimal conditions were as follows: 150°C, 2 h, and K_3PO_4 (1.0 equiv.) in DMF. Subsequently, a series of frutinone A derivatives were synthesized with excellent yields ranging from 80 % to 97 % under the optimal condition. (Table 4)

Conclusions

In conclusion, we have demonstrated a new and concise protocol for the total synthesis of frutinone A. The key intermediate compound 3-benzoyl-4-hydroxycoumarin was synthesized based on Baker–Venkataraman rearrangement of 2-acetylphenyl benzoate. Then, base-promoted intramolecular nucleophilic substitution reaction of 3-(2-chlorobenzoyl)-4-hydroxycoumarin provided frutinone A in excellent yield. Twenty frutinone A

Table 4. Scope of intramolecular nucleophilic substitution reaction of the triketone 12[A]



Compound	X	R_1	R_2	Yield [%][B]
13-1	Cl	H	H	94
13-2	Cl	H	3-Cl	90
13-3	Cl	H	4-Cl	96
13-4	Cl	H	5-Cl	91
13-5	F	H	6-Cl	97
13-6	Cl	H	4-F	94
13-7	Cl	H	5-F	91
13-8	Cl	H	4-Br	94
13-9	Cl	H	4-SO_2Me	92
13-10	Cl	H	3-OMe	80
13-11	Cl	H	4-OMe	81
13-12	Cl	7′-F	H	90
13-13	Cl	6′-F	4-Cl	95
13-14	Cl	6′-F	H	90
13-15	Cl	6′-Br	4-Cl	93
13-16	Cl	6′-Br	H	91
13-17	Cl	5′-OMe	4-Cl	89
13-18	Cl	5′-OMe	H	90
13-19	Cl	6′-Me	H	85
13-20	Cl	7′- OMe	H	89

[A]Reaction conditions: compound **12** (2 mmol), K_3PO_4 (1.0 equiv.), DMF (10 mL), 150°C, 2 h; [B]Isolated yield.

derivatives were obtained with yields ranging from 31 % to 62 % using the protocol.

Experimental

General

Unless otherwise stated, all reactions were carried out under an argon atmosphere, and all commercially available reagents were used without further purification. ^{1}H NMR and ^{13}C NMR were obtained at 400 MHz using Bruker AV400 spectrometer in $CDCl_3$ or d_6-DMSO solution with TMS as the internal standard. Chemical shift values (δ) are given in ppm. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple), dd (doublet of doublet). Coupling constants were reported in Hertz (Hz). High-resolution mass spectroscopy HRMS) was conducted on an Ionspec 7.0T spectrometer by electrospray ionization Fourier transform ion cyclotron resonance (ESI-FTICR) technique. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech. Instruments Co., Beijing, China) and were uncorrected.

*General Synthetic Procedure for Compound **11***

A mixture of 2′-hydroxyacetophenone (10.0 mmol) and 2-chlorobenzoyl chloride (15.0 mmol) were stirred in dry pyridine (10 mL) at room temperature for 2 h. The reaction mixture was then poured into a mixture of crushed ice (15 mL) and concentrated HCl (5 mL), extracted twice with dichloromethane, washed thrice with aqueous K_2CO_3, and then washed thrice with

water. The solvent was removed under reduced pressure. The residue was recrystallized from ethanol to give 2-acetylphenyl 2-chlorobenzoate (**11-1**). The remaining compounds were prepared using a similar procedure to that used for preparing **11-1**.

*2-Acetylphenyl 2-Chlorobenzoate (**11-1**)*

White solid, 92 % yield, mp 53–55°C. δ_H ($CDCl_3$, 400 MHz) 8.20 (1H, d, *J* 7.6), 7.89 (1H, d, *J* 7.7), 7.62 (1H, t, *J* 7.7), 7.59–7.49 (2H, m), 7.47–7.37 (2H, m), 7.30 (1H, d, *J* 8.2,), 2.59 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.57, 163.81, 148.93, 134.45, 133.56, 133.27, 132.18, 131.12, 130.98, 130.37, 129.05, 126.87, 126.36, 123.95, 29.39. HRMS *m*/*z* 275.0467; calcd for $C_{15}H_{11}ClO_3$ 275.0397.

*2-Acetylphenyl 2,3-Dichlorobenzoate (**11-2**)*

White solid, 83 % yield, mp 95–96°C. δ_H ($CDCl_3$, 400 MHz) 8.08 (1H, d, *J* 7.6), 7.90 (1H, d, *J* 7.7), 7.69 (1H, d, *J* 8.0), 7.63 (1H, t, *J* 7.7), 7.46–7.35 (2H, m), 7.30 (1H, d, *J* 8.4), 2.60 (3H, s). δ_C ($CDCl_3$, 100 MHz) 196.44, 162.46, 147.70, 133.67, 132.68, 132.67, 131.13, 130.81, 129.57, 129.48, 128.86, 126.37, 125.51, 122.87, 28.13. HRMS *m*/*z* 309.0084; calcd for $C_{15}H_{10}Cl_2O_3$ 309.0007.

*2-Acetylphenyl 2,4-Dichlorobenzoate (**11-3**)*

White solid, 93 % yield, mp 63–65°C. δ_H ($CDCl_3$, 400 MHz) 8.15 (1H, d, *J* 8.4), 7.87 (1H, d, *J* 7.7), 7.58 (1H, t, *J* 9.2), 7.54 (1H, s), 7.39 (2H, m), 7.25 (1H, d, *J* 7.8), 2.56 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.48, 163.00, 148.77, 139.12, 135.64, 133.68, 133.32, 131.17, 130.61, 130.53, 127.38, 127.31, 126.48, 123.97, 29.19. HRMS *m*/*z* 309.0083; calcd for $C_{15}H_{10}Cl_2O_3$ 309.0007.

*2-Acetylphenyl 2,5-Dichlorobenzoate (**11-4**)*

White solid, 88 % yield, mp 104–106°C. δ_H ($CDCl_3$, 400 MHz) 8.19 (1H, s), 7.91 (1H, d, *J* 7.8), 7.63 (1H, t, *J* 7.8), 7.53–7.45 (2H, m), 7.42 (1H, t, *J* 7.6), 7.28 (1H, d, *J* 7.8), 2.60 (3H, s), δ_C ($CDCl_3$, 100 MHz) 197.37, 162.69, 148.70, 133.74, 133.19, 132.92, 132.78, 132.36, 132.02, 130.58, 130.50, 130.31, 126.58, 123.91, 29.11. HRMS *m*/*z* 309.0084; calcd for $C_{15}H_{10}Cl_2O_3$ 309.0007.

*2-Acetylphenyl 2-Chloro-6-fluorobenzoate (**11-5**)*

White solid, 85 % yield, mp 70–71°C. δ_H ($CDCl_3$, 400 MHz) 7.84 (1H, dd, *J* 7.8, 1.6), 7.60 (1H, td, *J* 8.0, 1.6), 7.50–7.29 (4H, m), 7.15 (1H, t, *J* 8.7), 2.60 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.56, 161.54, 159.01, 148.54, 133.34, 133.14 (d), 132.57 (d), 131.74, 130.12, 126.72, 126.00 (d), 123.45, 121.11 (d), 114.87 (d), 30.01. HRMS *m*/*z* 293.0380; calcd for $C_{15}H_{10}ClFO_3$ 293.0303.

*2-Acetylphenyl 2-Chloro-4-fluorobenzoate (**11-6**)*

White solid, 89 % yield, mp 78–79°C. δ_H ($CDCl_3$, 400 MHz) 8.27 (1H, dd, *J* 8.8, 6.2), 7.90 (1H, d, *J* 7.8), 7.63 (1H, t, *J* 7.7), 7.41 (1H, t, *J* 7.6), 7.32–7.24 (2H, m), 7.15 (1H, td, *J* 8.8, 2.4), 2.59 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.50, 165.86, 163.09 (d), 148.83, 136.62 (d), 134.47 (d), 133.65, 130.70, 130.48, 126.43, 125.14, 123.99, 118.84 (d), 114.39 (d), 29.21. HRMS *m*/*z* 293.0380; calcd for $C_{15}H_{10}ClFO_3$ 293.0303.

*2-Acetylphenyl 2-Chloro-5-fluorobenzoate (**11-7**)*

Light yellow solid, 84 % yield, mp 103–105°C. δ_H ($CDCl_3$, 400 MHz) 7.96–7.89 (2H, m), 7.63 (1H, t, *J* 7.7), 7.51 (2H, dd, *J* 8.8, 4.8), 7.43 (1H, t, *J* 7.6), 7.26 (2H, m), 2.60 (3H, s). δ_C ($CDCl_3$, 100 MHz) 196.36, 161.72, 160.96, 158.49, 147.67, 132.71, 131.61 (d), 131.61 (d), 129.56, 128.49 (d), 125.53, 122.91, 119.49 (d), 118.14 (d), 28.09. HRMS *m*/*z* 293.0380; calcd for $C_{15}H_{10}ClFO_3$ 293.0303.

*2-Acetylphenyl 4-Bromo-2-chlorobenzoate (**11-8**)*

White solid, 88 % yield, mp 75–76°C. δ_H ($CDCl_3$, 400 MHz) 8.09 (1H, d, *J* 8.4), 7.90 (1H, d, *J* 7.8), 7.73 (1H, s), 7.67–7.56 (2H, m), 7.42 (1H, t, *J* 7.6), 7.28 (1H, d, *J* 7.7), 2.58 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.43, 163.13, 148.76, 135.61, 133.98, 133.68, 133.36, 130.60, 130.52, 130.27, 127.86, 127.33, 126.49, 123.96, 29.19. HRMS *m*/*z* 352.9580; calcd for $C_{15}H_{10}BrClO_3$ 352.9502.

*2-Acetylphenyl 2-Chloro-4-(methylsulfonyl)benzoate (**11-9**)*

Light yellow solid, 91 % yield, mp 103–105°C. δ_H ($CDCl_3$, 400 MHz) 8.40 (1H, d, *J* 8.1), 8.12 (1H, d, *J* 1.3), 8.00 (1H, dd, *J* 8.1, 1.5), 7.94 (1H, dd, *J* 7.7, 1.1), 7.70–7.62 (1H, m), 7.45 (1H, t, *J* 7.4), 7.30 (1H, d, *J* 8.3), 3.13 (3H, s), 2.61 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.47, 162.74, 148.52, 144.37, 135.35, 134.43, 134.02, 133.04, 130.86, 129.94, 129.88, 126.83, 125.65, 123.97, 44.39, 28.95. HRMS *m*/*z* 353.0249; calcd for $C_{16}H_{13}ClO_5S$ 353.0172.

*2-Acetylphenyl 2-Chloro-3-methoxybenzoate (**11-10**)*

White solid, 83 % yield, mp 106–108°C. δ_H ($CDCl_3$, 400 MHz) 7.89 (1H, d, *J* 7.7), 7.73 (1H, d, *J* 7.7), 7.62 (1H, t, *J* 7.7), 7.40 (2H, t, *J* 8.0), 7.32 (1H, d, *J* 8.1), 7.17 (1H, d, *J* 8.2), 3.98 (3H, s), 2.59 (3H, s). δ_C ($CDCl_3$, 100 MHz) 196.57, 163.06, 154.81, 147.90, 132.51, 129.98, 129.29, 126.39, 125.33, 122.88, 122.08, 114.29, 55.58, 28.44. HRMS *m*/*z* 305.0579; calcd for $C_{16}H_{13}ClO_4$ 305.0502.

*2-Acetylphenyl 2-Chloro-4-methoxybenzoate (**11-11**)*

White solid, 86 % yield, mp 110–111°C. δ_H ($CDCl_3$, 400 MHz) 8.22 (1H, d, *J* 8.8), 7.88 (1H, dd, *J* 7.8, 1.5), 7.60 (1H, td, *J* 8.0, 1.6), 7.38 (1H, td, *J* 7.7, 0.9), 7.28 (1H, d, *J* 2.7), 7.06 (1H, d, *J* 2.5), 6.94 (1H, dd, *J* 8.8, 2.5), 3.90 (1H, s), 2.57 (1H, s). δ_C ($CDCl_3$, 100 MHz) 197.68, 163.25, 163.21, 149.13, 136.94, 134.81, 134.29, 133.45, 131.19, 130.27, 126.16, 124.04, 120.32, 116.79, 112.85, 55.84, 29.57. HRMS *m*/*z* 305.0579; calcd for $C_{16}H_{13}ClO_4$ 305.0502.

*2-Acetyl-5-Fluorophenyl 2-Chlorobenzoate (**11-12**)*

White solid, 91 % yield, mp 71–72°C. δ_H ($CDCl_3$, 400 MHz) 8.19 (1H, d, *J* 7.6), 7.99–7.90 (1H, m), 7.56 (2H, s), 7.45 (1H, t, *J* 5.6), 7.12 (1H, t, *J* 7.2), 7.05 (1H, d, *J* 8.6), 2.57 (3H, s). δ_C ($CDCl_3$, 100 MHz) 195.96, 166.32, 163.55 (d), 150.76 (d), 134.65, 133.55, 132.43 (d), 132.29, 131.39, 128.51, 127.31, 126.93, 113.56 (d), 111.99 (d), 29.37. HRMS *m*/*z* 293.0381; calcd for $C_{15}H_{10}ClFO_3$ 293.0303.

*2-Acetyl-4-fluorophenyl 2,4-Dichlorobenzoate (**11-13**)*

White solid, 89 % yield, mp 114–115°C. δ_H ($CDCl_3$, 400 MHz) 8.14 (1H, d, *J* 8.5), 7.60–7.55 (2H, m), 7.43 (1H, dd, *J* 8.5, 2.0), 7.33 (1H, m), 7.26 (1H, dd, *J* 8.9, 4.7), 2.57 (3H, s). δ_C ($CDCl_3$, 100 MHz) 196.13, 163.00, 161.28, 158.82, 144.61, 139.39, 135.74, 133.28, 131.89, 131.29, 127.37, 126.99, 125.59 (d), 120.37 (d), 117.02 (d), 29.18. HRMS *m*/*z* 326.9991; calcd for $C_{15}H_9Cl_2FO_3$ 326.9913.

*2-Acetyl-4-fluorophenyl 2-Chlorobenzoate (**11-14**)*

White solid, 86 % yield, mp 68–70°C. δ_H ($CDCl_3$, 400 MHz) 8.17 (1H, d, *J* 8.1), 7.59–7.48 (3H, m), 7.47–7.39 (1H, m), 7.35–7.19 (2H, m), 2.57 (3H, s). δ_C ($CDCl_3$, 100 MHz) 195.16, 162.75, 160.19, 157.73, 143.71, 133.48, 132.45, 131.12, 130.32, 127.60, 125.88, 124.53 (d), 119.23 (d), 115.78 (d), 28.32. HRMS *m/z* 293.0381; calcd for $C_{15}H_{10}ClFO_3$ 293.0303.

*2-Acetyl-4-bromophenyl 2,4-Dichlorobenzoate (**11-15**)*

White solid, 90 % yield, mp 99–101°C. δ_H ($CDCl_3$, 400 MHz) 8.14 (1H, d, *J* 8.5), 7.99 (1H, d, *J* 2.4), 7.72 (1H, dd, *J* 8.6, 2.4), 7.57 (1H, d, *J* 2.0), 7.43 (1H, dd, *J* 8.5, 2.0), 7.17 (1H, d, *J* 8.6), 2.57 (1H, s). δ_C ($CDCl_3$, 100 MHz) 196.09, 162.66, 147.72, 139.46, 136.39, 135.78, 133.32, 133.24, 132.22, 131.31, 127.38, 126.86, 125.73, 119.59, 119.59, 29.22. HRMS *m/z* 386.9189; calcd for $C_{15}H_9BrCl_2O_3$ 386.9112.

*2-Acetyl-4-bromophenyl 2-Chlorobenzoate (**11-16**)*

Light yellow solid, 87 % yield, mp 79–80°C. δ_H ($CDCl_3$, 400 MHz) 8.18–8.13 (1H, m), 7.98 (1H, d, *J* 2.4), 7.72 (1H, dd, *J* 8.6, 2.4), 7.56–7.53 (2H, m), 7.44 (1H, m), 7.19 (1H, d, *J* 8.6), 2.57 (3H, s). δ_C ($CDCl_3$, 100 MHz) 196.19, 163.46, 147.89, 136.28, 134.60, 133.56, 133.09, 132.56, 132.21, 131.39, 128.53, 126.93, 125.72, 119.49, 29.41. HRMS *m/z* 352.9580; calcd for $C_{15}H_{10}BrClO_3$ 352.9502.

*2-Acetyl-3-methoxyphenyl 2,4-Dichlorobenzoate (**11-17**)*

White solid, 83 % yield, mp 84–85°C. δ_H ($CDCl_3$, 400 MHz) 7.98 (1H, d, *J* 8.4), 7.52 (1H, d, *J* 2.0), 7.45–7.31 (1H, m), 6.94–6.79 (2H, m), 3.90 (3H, s), 2.53 (3H, s). δ_C ($CDCl_3$, 100 MHz) 199.47, 161.80, 156.70, 146.47, 138.09, 134.51, 132.07, 130.30, 130.10, 126.20 (d), 123.10, 114.15, 108.12, 55.03, 30.76. HRMS *m/z* 339.0113; calcd for $C_{16}H_{12}Cl_2O_4$ 339.0113.

*2-Acetyl-3-methoxyphenyl 2-Chlorobenzoate (**11-18**)*

White solid, 91 % yield, mp 64–65°C. δ_H ($CDCl_3$, 400 MHz) 8.28–7.82 (1H, m), 7.53–7.47 (2H, m), 7.46–7.37 (2H, m), 6.90 (2H, d, *J* 8.3), 3.91 (3H, s), 2.56 (3H, s). δ_C ($CDCl_3$, 100 MHz) 200.60, 163.66, 157.61, 147.57, 134.30, 133.25, 132.00, 131.22, 131.18, 128.90, 126.85, 124.35, 115.23, 109.04, 56.06, 31.80. HRMS *m/z* 305.0579; calcd for $C_{16}H_{13}ClO_4$ 305.0502.

*2-Acetyl-4-methylphenyl 2-Chlorobenzoate (**11-19**)*

Light yellow solid, 93 % yield, mp 80–81°C. δ_H ($CDCl_3$, 400 MHz) 8.23–8.11 (1H, m), 7.68 (1H, d, *J* 1.5), 7.52 (2H, m), 7.42 (2H, m), 7.17 (1H, d, *J* 8.2), 2.57 (3H, s), 2.45 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.74, 164.03, 146.75, 136.20, 134.37, 134.14, 133.22, 132.13, 131.24, 130.77, 130.57, 129.16, 126.86, 123.63, 29.44, 20.91. HRMS *m/z* 305.0502; calcd for $C_{16}H_{13}ClO_3$ 289.0553.

*2-Acetyl-5-methoxyphenyl 2-Chlorobenzoate (**11-20**)*

White solid, 88 %, mp 74–76°C. δ_H ($CDCl_3$, 400 MHz) 8.21 (1H, dd, *J* 7.8, 1.0, 1H), 7.88 (1H, d, *J* 8.8), 7.49 (1H, m), 7.43–7.35 (2H, m), 6.87 (1H, dd, *J* 8.8, 2.5), 6.75 (1H, d, *J* 2.5), 3.87 (3H, s), 2.52 (3H, s). δ_C ($CDCl_3$, 100 MHz) 195.73, 163.85, 163.68, 151.22, 134.44, 133.24, 132.62, 132.34, 131.23, 129.06, 126.87, 123.12, 111.98, 109.43, 55.81, 29.03. HRMS *m/z* 305.0581; calcd for $C_{16}H_{13}ClO_4$ 305.0502.

*General Synthetic Procedure for Compound **12***

To a solution of 2-acetylphenyl 2-chlorobenzoate (**11-1**) (5.0 mmol) in DMF (10 mL), NaH (12.5 mmol) was added and stirred for 2 h at 50°C. Then, methyl chloroformate (5.5 mmol) was added to the above solution, and the mixture was stirred for 4 h at 50°C. After the reaction was complete (monitored by thin layer chromatography (TLC)), the above mixture was poured into a mixture of crushed ice (15 mL) and concentrated HCl (5 mL). A white solid was precipitated. The formed precipitate was filtered, washed with cold ethanol (3 × 10 mL), and then dried under vacuum to provide 3-(2-chlorobenzoyl)-4-hydroxycoumarin (**12-1**). The remaining compounds were prepared using a similar procedure to that employed to prepare **12-1**.

*3-(2-Chlorobenzoyl)-4-hydroxycoumarin (**12-1**)*

White solid, yield 61 %, mp 126–127°C. δ_H ($CDCl_3$, 400 MHz) 8.13 (1H, dd, *J* 8.0, 1.4), 7.72 (1H, m), 7.45–7.41 (2H, m), 7.40–7.36 (2H, m), 7.33–7.30 (2H, m). δ_C ($CDCl_3$, 100 MHz) 200.02, 177.97, 155.36, 138.70, 136.55, 131.19, 130.14, 129.50, 127.20, 126.89, 125.72, 124.58, 117.30, 114.94, 102.19. HRMS *m/z* 301.0261; calcd for $C_{16}H_9ClO_4$ 301.0189.

*3-(2, 3-Dichlorobenzoyl)-4-hydroxycoumarin (**12-2**)*

Light yellow solid, 68.0 % yield, mp 154–156°C. δ_H ($CDCl_3$, 400 MHz) 8.16 (1H, d, *J* 7.8), 7.77 (1H, t, *J* 7.7), 7.59 (1H, d, *J* 8.0), 7.42 (1H, t, *J* 7.5), 7.36 (2H, t, *J* 7.8), 7.23 (1H, d, *J* 7.4). δ_C ($CDCl_3$, 100 MHz) 199.02, 178.12, 158.57, 155.42, 140.72, 136.80, 133.33, 131.62, 128.43, 127.81, 125.75, 124.97, 124.69, 117.35, 114.77, 101.88. HRMS *m/z* 334.9872; calcd for $C_{16}H_8Cl_2O_4$ 334.9800.

*3-(2, 4-Dichlorobenzoyl)-4-hydroxycoumarin (**12-3**)*

Pale yellow solid, 70 % yield, mp 186–187°C. δ_H ($CDCl_3$, 400 MHz) 8.12 (1H, dd, *J* 8.0, 1.5), 7.77–7.69 (1H, m), 7.44 (1H, d, *J* 1.9), 7.41–7.29 (3H, m), 7.28–7.23 (1H, m). δ_C ($CDCl_3$, 100 MHz) 198.99, 177.97, 158.69, 155.37, 137.20, 136.75, 136.62, 131.21, 129.52, 128.25, 127.34, 125.74, 124.68, 117.32, 114.78, 102.12. HRMS *m/z* 334.9878; calcd for $C_{16}H_8Cl_2O_4$ 334.9800.

*3-(2, 5-Dichlorobenzoyl)-4-hydroxycoumarin (**12-4**)*

Pale yellow solid, 64 % yield, mp 246–249°C. δ_H ($CDCl_3$, 400 MHz) 8.15 (1H, dd, *J* 8.0, 1.5), 7.80–7.73 (1H, m), 7.45–7.37 (3H, m), 7.37–7.30 (2H, m). δ_C ($CDCl_3$, 100 MHz) 198.40, 177.98, 158.58, 155.41, 139.95, 136.83, 132.95, 131.02, 130.66, 128.46, 127.14, 125.76, 124.70, 117.34, 114.71, 102.00. HRMS *m/z* 334.9873; calcd for $C_{16}H_8Cl_2O_4$ 334.9800.

*3-(2-Chloro-6-fluorobenzoyl)-4-hydroxycoumarin (**12-5**)*

Pale yellow solid, 38 % yield, mp 143–144°C. δ_H ($CDCl_3$, 400 MHz) 8.16 (1H, d, *J* 7.9), 7.76 (1H, t, *J* 7.8), 7.40 (2H, dd, *J* 14.4, 7.9), 7.33 (1H, d, *J* 8.4), 7.28 (1H, d, *J* 7.9), 7.11 (1H, t, *J* 8.6). δ_C ($CDCl_3$, 100 MHz) 194.63, 177.06, 158.89, 157.41, 156.40, 154.39, 135.78, 130.24 (d), 129.83 (d), 124.74, 124.30 (d), 123.63, 116.29, 113.72, 113.20 (d), 101.50. HRMS *m/z* 319.0165; calcd for $C_{16}H_8ClFO_4$ 319.0095.

*3-(2-Chloro-4-fluorobenzoyl)-4-hydroxycoumarin (**12-6**)*

Pale yellow solid, 71 % yield, mp 174–176°C. δ_H ($CDCl_3$, 400 MHz) 8.15 (1H, d, *J* 8.0), 7.75 (1H, t, *J* 7.8), 7.42–7.33 (3H, m),

7.21 (1H, dd, *J* 8.5, 2.0), 7.14–7.09 (1H, td, *J* 8.3, 2.1). δ_C ($CDCl_3$, 100 MHz) 199.04, 177.95, 164.53, 162.01, 158.73, 155.35, 136.68, 135.03 (d), 131.79 (d), 129.00 (d), 125.73, 124.64, 117.26 (d), 114.83, 114.37 (d), 102.19. HRMS *m*/*z* 319.0165; calcd for $C_{16}H_8ClFO_4$ 319.0095.

*3-(2-Chloro-5-fluorobenzoyl)-4-hydroxycoumarin (**12-7**)*

Pale yellow solid, 69 % yield, mp 176–178°C. δ_H ($CDCl_3$, 400 MHz) 8.15 (1H, d, *J* 8.0), 7.76 (1H, t, *J* 7.8), 7.41 (2H, m), 7.34 (1H, d, *J* 8.4), 7.14 (1H, td, *J* 8.4, 2.7), 7.06 (1H, dd, *J* 7.9, 2.7). δ_C ($CDCl_3$, 100 MHz) 198.45, 178.00, 162.36, 159.89, 158.56, 155.42, 140.02 (d), 136.79, 131.01 (d), 125.74, 125.11 (d), 124.68, 118.08 (d), 117.34, 114.52 (d), 101.97. HRMS *m*/*z* 319.0165; calcd for $C_{16}H_8ClFO_4$ 319.0095.

*3-(4-Bromo-2-chlorobenzoyl)-4-hydroxycoumarin (**12-8**)*

Pale yellow solid, 66 % yield, mp 183–185°C. δ_H ($CDCl_3$, 400 MHz) 8.12 (1H, dd, *J* 8.0, 1.4), 7.77–7.69 (1H, m), 7.60 (1H, d, *J* 1.7), 7.51 (1H, dd, *J* 8.2, 1.7), 7.38 (1H, dd, *J* 11.3, 4.0), 7.32 (1H, d, *J* 8.4), 7.19 (1H, d, *J* 8.2). δ_C ($CDCl_3$, 100 MHz) 199.03, 177.98, 158.70, 155.36, 137.65, 136.78, 132.26, 131.23, 130.23, 128.38, 125.75, 124.70, 124.52, 117.33, 114.77, 102.09. HRMS *m*/*z* 378.9361; calcd for $C_{16}H_8BrClO_4$ 378.9294.

*3-(2-Chloro-4-(methylsulfonyl)benzoyl)-4-hydroxycoumarin (**12-9**)*

Pale yellow solid, 72 % yield, mp 223–225°C. δ_H ($CDCl_3$, 400 MHz) 16.25 (1H, s), 8.17 (1H, d, *J* 7.4), 8.04 (1H, s), 7.96 (1H, d, *J* 7.2), 7.79 (1H, t, *J* 7.3), 7.51 (1H, d, *J* 7.7), 7.43 (1H, t, *J* 7.5), 7.35 (1H, d, *J* 8.2), 3.15 (3H, s). δ_C ($CDCl_3$, 100 MHz) 198.28, 178.17, 158.75, 155.45, 143.77, 142.60, 137.16, 131.39, 128.53, 127.92, 126.03, 125.85, 124.92, 117.42, 114.58, 101.84, 44.54. HRMS *m*/*z* 379.0041; calcd for $C_{17}H_{11}ClO_6S$ 378.9965.

*3-(2-Chloro-3-methoxybenzoyl)-4-hydroxycoumarin (**12-10**)*

Pale yellow solid, 47 % yield, mp 152–155°C. δ_H ($CDCl_3$, 400 MHz) 8.05 (1H, d, *J* 7.8), 7.64 (1H, t, *J* 7.8), 7.34–7.17 (3H, m), 6.96 (1H, d, *J* 8.2), 6.83 (1H, d, *J* 7.6), 3.86 (3H, s). δ_C ($CDCl_3$, 100 MHz) 199.89, 177.98, 158.48, 155.40, 154.95, 140.14, 136.52, 127.91, 125.70, 124.53, 118.52, 118.46, 117.28, 114.94, 113.24, 102.16, 77.38, 77.07, 76.75, 56.35. HRMS *m*/*z* 331.0370; calcd for $C_{17}H_{11}ClO_5$ 331.0295.

*3-(2-Chloro-4-Methoxybenzoyl)-4-hydroxycoumarin (**12-11**)*

Light yellow solid, 56 % yield, mp 195–197°C. δ_H ($CDCl_3$, 400 MHz) 8.04 (1H, d, *J* 7.4), 7.64 (1H, t, *J* 7.3), 7.35–7.22 (3H, m), 6.89 (1H, d, *J* 2.1), 6.82 (1H, dd, *J* 8.5, 2.1), 3.78 (3H, s). δ_C ($CDCl_3$, 100 MHz) 199.30, 177.70, 161.73, 158.89, 155.27, 136.29, 132.14, 130.92, 129.39, 125.65, 124.46, 117.22, 115.12, 112.79, 102.43, 55.66. HRMS *m*/*z* 331.0372; calcd for $C_{17}H_{11}ClO_5$ 331.0295.

*3-(2-Chlorobenzoyl)-7-fluoro-4-hydroxycoumarin (**12-12**)*

Light yellow solid, 62 % yield, mp 148–150°C. δ_H ($CDCl_3$, 400 MHz) 8.17 (1H, dd, *J* 8.7, 6.1), 7.46 (2H, d, *J* 3.2), 7.44–7.37 (1H, m), 7.34 (1H, d, *J* 7.1), 7.13 (1H, td, *J* 8.6, 2.1), 7.04 (1H, dd, *J* 8.9, 2.0). δ_C ($CDCl_3$, 100 MHz) 199.91, 177.48, 168.90, 166.32, 158.25, 157.00 (d), 138.44, 131.25, 130.18, 129.51, 128.18 (d), 127.04 (d), 113.20 (d), 111.67, 104.72 (d), 101.43. HRMS *m*/*z* 319.0166; calcd for $C_{16}H_8ClFO_4$ 319.0095.

*3-(2,4-Dichlorobenzoyl)-6-fluoro-4-hydroxycoumarin (**12-13**)*

Light yellow solid, 66 % yield, mp 137–139°C. δ_H ($CDCl_3$, 400 MHz) 8.17 (1H, dd, *J* 8.9, 6.0), 7.47 (1H, d, *J* 1.8), 7.38 (1H, dd, *J* 8.2, 1.9), 7.28 (1H, s), 7.14 (1H, td, *J* 8.5, 2.3), 7.05 (1H, dd, *J* 8.9, 2.3). δ_C ($CDCl_3$, 100 MHz) 199.04, 177.09, 160.03, 158.42, 157.58, 151.53, 136.87, 131.26, 129.56, 128.31, 127.40, 124.52 (d), 119.22 (d), 115.69 (d), 110.98 (d), 102.31. HRMS *m*/*z* 352.9786; calcd for $C_{16}H_7Cl_2FO_4$ 352.9705.

*3-(2-Chlorobenzoyl)-6-fluoro-4-hydroxycoumarin (**12-14**)*

Pale yellow solid, 70 % yield, mp 140–142°C. δ_H ($CDCl_3$, 400 MHz) 7.80 (1H, dd, *J* 7.8, 3.0), 7.49–7.43 (3H, m), 7.42–7.38 (1H, m), 7.36–7.31 (2H, m). δ_C ($CDCl_3$, 100 MHz) 200.08, 177.09, 159.98, 158.34, 157.53, 151.55, 138.41, 131.37, 130.19, 129.52, 127.09 (d), 124.28 (d), 119.16 (d), 115.86, 111.06, 110.81, 102.37, 77.36, 77.05, 76.73. HRMS *m*/*z* 319.0167; calcd for $C_{16}H_7ClFO_4$ 319.0095.

*6-Bromo-3-(2,4-dichlorobenzoyl)-4-hydroxycoumarin (**12-15**)*

Pale yellow solid, 68 % yield, mp 221–223°C. δ_H ($CDCl_3$, 400 MHz) 8.23 (1H, d, *J* 2.4), 7.80 (1H, dd, *J* 8.8, 2.4), 7.45 (1H, d, *J* 1.8), 7.37 (1H, dd, *J* 8.2, 1.8), 7.24 (2H, dd, m). δ_C ($CDCl_3$, 100 MHz) 199.00, 176.73, 158.07, 154.14, 139.42, 136.91, 136.82, 131.26, 129.57, 128.32, 128.07, 127.40, 119.11, 117.51, 116.31, 102.34. HRMS *m*/*z* 412.8976; calcd for $C_{16}H_7BrCl_2O_4$ 411.8905.

*6-Bromo-3-(2-chlorobenzoyl)-4-hydroxycoumarin (**12-16**)*

Pale yellow solid, 64 % yield, mp 159–160°C. δ_H ($CDCl_3$, 400 MHz) 8.26 (1H, d, *J* 1.9), 7.82 (1H, dd, *J* 8.8, 2.0), 7.46 (2H, d, *J* 3.7), 7.44–7.37 (1H, m), 7.34 (1H, d, *J* 7.4), 7.23 (1H, d, *J* 8.8). δ_C ($CDCl_3$, 100 MHz) 200.01, 176.74, 158.05, 154.16, 139.21, 138.33, 131.39, 130.21, 129.52, 128.06, 127.28, 126.91, 119.08, 117.38, 116.49, 102.41. HRMS *m*/*z* 378.9358; calcd for $C_{16}H_8BrClO_4$ 378.9294.

*3-(2,4-Dichlorobenzoyl)-5-methoxy-4-hydroxycoumarin (**12-17**)*

Pale yellow solid, 59 % yield, mp 176–179°C. δ_H ($CDCl_3$, 400 MHz) 7.65 (1H, t, *J* 8.4), 7.46 (1H, d, *J* 1.6), 7.37 (1H, dd, *J* 8.2, 1.6), 7.28 (1H, s), 6.92 (1H, d, *J* 8.3), 6.83 (1H, d, *J* 8.5), 4.05 (3H, s). δ_C ($CDCl_3$, 100 MHz) 197.27, 179.43, 159.63, 157.52, 155.93, 136.34, 136.17, 135.32, 130.14, 128.45, 127.19, 126.25, 108.71, 105.66, 104.20, 100.27, 55.64. HRMS *m*/*z* 364.9980; calcd for $C_{17}H_{10}Cl_2O_5$ 364.9905.

*3-(2-Chlorobenzoyl)-5-methoxy-4-hydroxycoumarin (**12-18**)*

Pale yellow solid, 50 % yield, mp 208–211°C. δ_H ($CDCl_3$, 400 MHz) 7.62 (1H, t, *J* 8.4), 7.45–7.34 (3H, m), 7.31 (1H, dd, *J* 6.8, 1.8), 6.90 (1H, dd, *J* 8.4, 0.7), 6.81 (1H, d, *J* 8.4), 4.04 (3H, s). δ_C ($CDCl_3$, 100 MHz) 199.38, 180.51, 160.59, 158.55, 156.97, 138.79, 137.04, 130.97, 130.09, 129.45, 127.19, 126.85, 109.74,

106.59, 105.32, 101.35, 56.67. HRMS *m/z* 331.0368; calcd for $C_{17}H_{10}ClO_5$ 331.0295.

*3-(2-Chlorobenzoyl)-6-methyl-4-hydroxycoumarin (**12-19**)*

Light yellow solid, 55 % yield, mp 177–179°C. δ_H ($CDCl_3$, 400 MHz) 7.92 (1H, d, *J* 1.1), 7.54 (1H, dd, *J* 8.5, 2.1), 7.47–7.43 (2H, m), 7.42–7.37 (1H, m), 7.36 −7.32 (1H, m), 7.22 (1H, d, *J* 8.5), 2.48 (3H, s). δ_C ($CDCl_3$, 100 MHz) 200.01, 178.01, 158.86, 153.62, 138.81, 137.75, 134.47, 131.08, 130.14, 129.47, 127.19, 126.84,S 125.08, 117.06, 114.57, 102.16, 20.83. HRMS *m/z* 315.0421; calcd for $C_{17}H_{11}ClO_4$ 315.0346.

*3-(2-Chlorobenzoyl)-7-methoxy-4-hydroxycoumarin (**12-20**)*

White solid, 52 % yield, mp 204–206°C. δ_H ($CDCl_3$, 400 MHz) 8.04 (1H, d, *J* 8.9), 7.48–7.36 (3H, m), 7.35–7.31 (1H, m), 6.94 (1H, dd, *J* 8.9, 2.4), 6.77 (1H, d, *J* 2.3), 3.94 (3H, s). δ_C ($CDCl_3$, 100 MHz) 199.50, 177.92, 166.80, 159.03, 157.84, 138.92, 130.91, 130.10, 129.45, 127.15, 127.12, 126.82, 113.63, 107.95, 100.50, 100.44, 56.11. HRMS *m/z* 329.0218; calcd for $C_{17}H_{11}ClO_5$ 329.0295.

*General Synthetic Procedure for Compound **13***

To a solution of compound **12-1** (1.0 mmol) in DMF (10 mL), potassium phosphate (1.0 mmol) was added, and the mixture was heated to 150°C for 2 h. After the reaction was complete and cooled down, the mixture was poured into ice water (30 mL), and a yellow solid was precipitated. The formed precipitate was filtered, washed with cold water (3 × 10 mL), and then dried under vacuum to give the natural product frutinone A **13-1**. The remaining target compounds were prepared using a similar procedure to that used to prepare **13-1**.

*Compound **13-1***

White solid 94 % yield, mp 240–242°C. δ_H ($CDCl_3$, 400 MHz) 8.37 (1H, dd, *J* 7.9, 1.6), 8.23 (1H, dd, *J* 8.0, 1.5), 7.83–7.71 (2H, m), 7.64 (1H, d, *J* 8.3), 7.56–7.50 (1H, m), 7.49–7.40 (2H, m). δ_C ($CDCl_3$, 100 MHz) 173.00, 164.97, 156.29, 154.40, 154.30, 135.57, 134.79, 126.96, 126.62, 124.79, 124.52, 124.19, 117.79, 117.44, 113.25, 105.11. HRMS *m/z* 265.0498; calcd for $C_{16}H_8O_4$ 265.0423.

*Compound **13-2***

White solid, 90 % yield, mp 294–296°C. δ_H (DMSO, 400 MHz) 8.18 (1H, d, *J* 7.7), 8.07 (2H, d, *J* 7.9), 7.90 (1H, t, *J* 7.6), 7.58 (2H, t, *J* 7.9), 7.53 (1H, d, *J* 8.4). δ_C (DMSO, 100 MHz) 171.78, 164.44, 155.20, 153.71, 149.49, 136.04, 134.97, 126.92, 125.46, 125.17, 124.58, 123.98, 122.03, 116.97, 112.98, 104.76. HRMS *m/z* 299.0110; calcd for $C_{16}H_7ClO_4$ 299.0033.

*Compound **13-3***

White solid, 96 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.30 (1H, d, *J* 7.8), 8.18–8.07 (2H, m), 7.89 (1H, t, *J* 7.7), 7.65 (1H, d, *J* 8.5), 7.55 (2H, dd, *J* 19.2, 8.0). δ_C (DMSO, 100 MHz) 172.40, 165.52, 155.91, 154.88, 154.26, 139.70, 136.44, 127.94, 127.46, 125.42, 124.95, 123.48, 119.06, 117.40, 113.63, 105.50. HRMS *m/z* 320.9928; calcd for $C_{16}H_7ClO_4$ 321.0033.

*Compound **13-4***

White solid, 91 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.36 (1H, d, *J* 7.6), 8.09 (1H, s), 8.01 (2H, s), 7.91 (1H, t, *J* 7.8), 7.57 (2H, m). HRMS *m/z* 320.9928; calcd for $C_{16}H_7ClO_4$ 321.0033.

*Compound **13-5***

White solid, 97 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.32 (1H, d, *J* 7.7), 8.01–7.77 (3H, m), 7.61 (1H, d, *J* 7.3), 7.55 (2H, dd, *J* 16.4, 8.2). δ_C (DMSO, 100 MHz) 171.73, 164.25, 156.26, 155.87, 154.22, 136.28, 135.09, 132.53, 129.75, 125.39, 124.92, 121.35, 118.58, 117.32, 113.39, 105.92. HRMS *m/z* 299.0110; calcd for $C_{16}H_7ClO_4$ 299.0033.

*Compound **13-6***

White solid, 94 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.29 (1H, d, *J* 7.6), 8.20 (1H, t, *J* 7.2), 7.90 (2H, d, *J* 7.7), 7.62–7.40 (3H, m). δ_C (DMSO, 100 MHz) 171.74, 166.57, 165.15, 164.05, 155.45, 155.19 (d), 153.72, 135.89, 128.52 (d), 124.64 (d), 121.24, 116.91, 114.93 (d), 113.13, 105.63 (d). HRMS *m/z* 283.0407; calcd for $C_{16}H_7FO_4$ 283.0328.

*Compound **13-7***

White solid, 91 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.34 (1H, d, *J* 7.8), 8.03 (1H, d, *J* 6.3), 7.94–7.78 (3H, m), 7.55 (2H, m). HRMS *m/z* 283.0403; calcd for $C_{16}H_7FO_4$ 283.0328.

*Compound **13-8***

White solid, 94 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.33 (1H, d, *J* 8.5), 8.30 (1H, s), 8.05 (1H, d, *J* 8.1), 7.90 (1H, t, *J* 7.4), 7.79 (1H, d, *J* 8.6), 7.56 (2H, m). δ_C (DMSO, 100 MHz) 172.06, 164.97, 155.43, 154.30, 153.78, 135.95, 129.77, 127.96, 127.43, 124.93, 124.49, 123.26, 121.48, 116.90, 113.15, 105.01. HRMS *m/z* 342.9602; calcd for $C_{16}H_7BrO_4$ 342.9528.

*Compound **13-9***

White solid, 92 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.55 (1H, s), 8.39 (2H, dd, *J* 27.0, 7.7), 8.09 (1H, d, *J* 7.3), 7.90 (1H, t, *J* 7.1), 7.56 (2H, m), 3.42 (3H, s). δ_C (DMSO, 100 MHz) 172.39, 165.95, 155.86, 154.33, 154.21, 146.48, 136.67, 127.89, 127.64, 125.52, 125.25, 124.52, 118.65, 117.41, 113.55, 105.80, 43.55. HRMS *m/z* 343.0276; calcd for $C_{17}H_{10}O_6S$ 343.0198.

*Compound **13-10***

White solid, 80.0 % yield, mp 289–291°C. δ_H (DMSO, 400 MHz) 8.14 (1H, d, *J* 7.4), 7.88 (1H, t, *J* 7.3), 7.66 (1H, d, *J* 7.5), 7.61–7.39 (4H, m), 4.06 (3H, s). δ_C (DMSO, 100 MHz) 172.93, 164.80, 156.04, 154.12, 148.99, 144.50, 136.14, 126.92, 125.49, 124.46, 117.40, 117.11, 116.50, 113.90, 105.21, 57.21. HRMS *m/z* 295.0606; calcd for $C_{17}H_{10}O_5$ 295.0528.

*Compound **13-11***

White solid, 81 % yield, mp 231–232°C. δ_H (DMSO, 400 MHz) 8.30 (1H, d, *J* 7.7), 8.03 (1H, d, *J* 8.8), 7.86 (1H, t, *J* 7.6), 7.53 (2H, m), 7.45 (1H, s), 7.15 (1H, d, *J* 8.5), 3.96 (3H, s). δ_C (DMSO, 100 MHz) 171.78, 164.73, 164.44, 155.88, 155.63, 153.63, 135.54, 127.10, 124.78, 124.30, 117.68, 116.84, 115.25, 113.36, 104.67, 101.36, 56.32. HRMS *m/z* 295.0607; calcd for $C_{17}H_{10}O_5$ 295.0528.

*Compound **13-12***

White solid, 90 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.42 (1H, m, *J* 7.6), 8.15 (1H, d, *J* 7.5), 7.93 (2H, q, *J* 8.3), 7.59 (2H, dd, *J* 19.6, 8.6), 7.48 (1H, t, *J* 8.2). δ_C (DMSO, 100 MHz)

172.43, 167.40, 164.86, 164.50, 155.44, 155.22 (d), 154.08, 135.19, 127.18 (d), 126.63, 125.58, 123.95, 118.48, 113.16 (d), 110.41, 104.47 (d). HRMS *m*/*z* 283.0404; calcd for $C_{16}H_7FO_4$ 283.0328.

Compound ***13-13***

White solid, 95 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.20–8.10 (3H, m), 7.79 (1H, td, *J* 8.7, 3.0), 7.63 (2H, m). δ_C (DMSO, 100 MHz) 171.83, 164.34, 159.49, 157.08, 155.26, 154.34, 150.23, 139.27, 127.27 (d), 124.19–121.88 (t), 119.25 (d), 118.63, 114.23 (d), 110.04 (d), 105.32. HRMS *m*/*z* 317.0015; calcd for $C_{16}H_6ClFO_4$ 316.9939.

Compound ***13-14***

White solid, 90 % yield, mp 296–298°C. δ_H (DMSO, 400 MHz) 8.19 (1H, dd, *J* 8.1, 2.2), 8.14 (1H, d, *J* 7.8), 7.94 (2H, bs), 7.77 (1H, td, *J* 8.8, 2.6), 7.60 (2H, dd, *J* 8.8, 4.2). δ_C (DMSO, 100 MHz) 172.96, 164.66, 159.97, 157.56, 155.91, 154.58, 150.66, 135.73, 127.17, 126.07, 124.54, 123.65 (d), 119.65 (d), 119.07, 114.87, 110.57 (d), 105.61. HRMS *m*/*z* 283.0404; calcd for $C_{16}H_7FO_4$ 283.0328.

Compound ***13-15***

White solid, 93 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.54 (1H, d, *J* 2.1), 8.25 (1H, s), 8.13 (1H, d, *J* 8.5), 8.05 (1H, dd, *J* 8.9, 2.2), 7.66 (1H, dd, *J* 8.5, 1.7), 7.52 (1H, d, *J* 8.8). HRMS *m*/*z* 376.9211; calcd for $C_{16}H_6BrClO_4$ 376.9138.

Compound ***13-16***

White solid, 91 % yield, mp >300°C. δ_H (DMSO, 400 MHz) 8.54 (1H, s), 8.15 (1H, d, *J* 7.5), 8.06–7.87 (3H, m), 7.61 (1H, t, *J* 7.1), 7.52 (1H, d, *J* 8.6). δ_C (DMSO, 100 MHz) 172.91, 164.31, 155.66, 154.63, 153.27, 138.50, 135.74, 127.20, 127.07, 126.03, 124.52, 119.70, 119.19, 117.11, 115.82, 105.69. HRMS *m*/*z* 342.9598; calcd for $C_{16}H_7BrO_4$ 342.9528.

Compound ***13-17***

White solid, 89 % yield, mp 282–284°C. δ_H (DMSO, 400 MHz) 8.10 (1H, d, *J* 8.5), 7.99 (1H, d, *J* 1.8), 7.78 (1H, t, *J* 8.4), 7.62 (1H, dd, *J* 8.5, 1.9), 7.09 (1H, d, *J* 8.4), 7.03 (1H, d, *J* 8.2), 4.09 (3H, s). δ_C (DMSO, 100 MHz) 171.72, 166.64, 158.67, 155.23, 155.08, 154.21, 139.17, 136.41, 127.14, 126.95, 122.78, 118.54, 108.78, 107.67, 104.12, 102.98, 56.79. HRMS *m*/*z* 329.0216; calcd for $C_{17}H_9ClO_5$ 329.0139.

Compound ***13-18***

White solid, 90.0 % yield, mp 291–293°C. δ_H (DMSO, 400 MHz) 8.12 (1H, d, *J* 7.7), 7.90 (1H, t, *J* 7.4), 7.77 (2H, t, *J* 7.0), 7.58 (1H, t, *J* 7.3), 7.10 (1H, d, *J* 8.4), 7.03 (1H, d, *J* 8.3), 4.08 (3H, s). δ_C (DMSO, 100 MHz) 172.92, 169.44, 167.00, 159.11, 155.92, 155.58, 154.49, 136.67, 135.41, 127.00, 125.80, 124.38, 119.12, 109.35, 108.19, 103.72, 57.36. HRMS *m*/*z* 295.0606; calcd for $C_{17}H_{10}O_5$ 295.0528.

Compound ***13-19***

White solid, 95 % yield, mp 296–298°C. δ_H (DMSO, 400 MHz) 8.14 (1H, d, *J* 9.5), 8.12 (1H, s), 7.92 (2H, q, *J* 8.3), 7.69 (1H, d, *J* 8.6), 7.60 (1H, t, *J* 6.9), 7.41 (1H, d, *J* 8.5), 2.48 (3H, s). δ_C (DMSO, 100 MHz) 173.09, 165.37, 156.22, 154.62, 152.43, 137.17, 135.61, 134.88, 127.03, 126.08, 124.54, 124.28, 118.93, 117.16, 113.45, 105.22, 20.83. HRMS *m*/*z* 279.0654; calcd for $C_{17}H_{10}O_4$ 279.0579.

Compound ***13-20***

White solid, 89 % yield, mp 290–293°C. δ_H (DMSO, 400 MHz) 8.22 (1H, d, *J* 8.8), 8.13 (1H, d, *J* 7.7), 7.87 (2H, m), 7.57 (1H, t, *J* 7.3), 7.13 (1H, d, *J* 9.1), 7.11 (1H, s), 3.94 (3H, s). δ_C (DMSO, 100 MHz) 172.91, 166.03, 165.59, 156.51, 156.39, 154.58, 135.40, 126.86, 126.38, 126.04, 124.42, 118.80, 114.01, 106.54, 103.13, 101.21, 56.89. HRMS *m*/*z* 295.0607; calcd for $C_{17}H_{10}O_5$ 295.0528.

Supplementary Material

Copies of ^1H and ^{13}C NMR spectra are available on the Journal's website.

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