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Graphical Abstract

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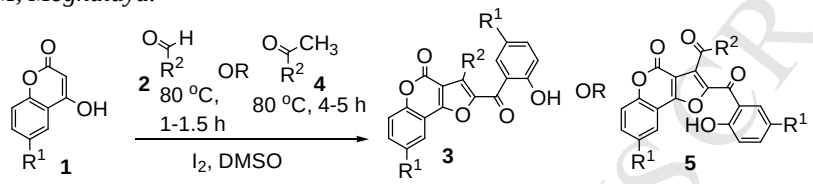

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ABSTRACT

A simple and efficient method for the synthesis of highly functionalized furo[3,2-*c*]coumarins was developed. The reaction occurred *via* initial formation of biscoumarins from the reaction of 4-hydroxycoumarins and aldehydes/aryl methyl ketones in the presence of molecular iodine in DMSO followed by lactone ring opening, cyclization and oxidative aromatization process. The reaction conditions were moderate, work-up procedure was simple and products were obtained in high yield.

1. Introduction

Coumarin and its derivatives are well-recognized naturally occurring compounds with diverse biological activities.[1] Furanocoumarins, particularly furo[3,2-*c*]coumarins are an important class of fused coumarins produced by a variety of plants[2] that possess significant biological, pharmacological and therapeutic activities, such as antifungicidal, insecticidal, insect antifeedant, anti-HIV and anticancer activities.[3] Compounds bearing this molecular motif also exhibit photochemical, photophysical and photobiological activities, and have wide applications as drugs for skin and autoimmune disease as they are photosensitizers of plant origin and increase the sensitivity of biological objects to UVA radiation.[4] Psoralens are example of such type of drugs which are extensively used in the PUVA (psoralen plus UVA radiation) therapy for human skin diseases, including psoriasis, mycosis fungoides, eczema, vitiligo, and graft-versus-host disease.[5] Therefore, development of efficient methods for the synthesis of furo[3,2-*c*]coumarins, and their synthetic manipulation have become an important area of current research. As a result, a number of procedures have been developed for the the synthesis of these compounds which include Pd-catalyzed heteroannulation,[6] cascade addition-cyclization-oxidation reaction,[7] Suzuki cross-coupling reaction strategy,[8] imidazolium ylide activated [4+1] annulations,[9] intramolecular C-O cyclization reactions[10] etc. Very recently, an excellent review on coumarin heterocyclic derivatives has been published.[11]

The reaction of 4-hydroxycoumarins and aldehydes in the presence of acid/Bronsted/Lewis acid catalyst produce biscoumarins.[12] Molecular iodine was also used satisfactorily as catalyst in the reaction to synthesize biscoumarins.[13] But, Shafiee and his co-workers observed that a very small amount of furo[3,2-*c*]coumarins also form along with biscoumarins in the iodine catalyzed reaction process, and subsequently, they have developed a method for the synthesis of furo[3,2-*c*]coumarins first by synthesizing biscoumarins from 4-hydroxycoumarins in presence of I_2 in poly(ethylene glycol) followed by treatment of the biscoumarins with $K_2S_2O_8$ in the presence of Na_2CO_3 as oxidizing agent.[14] However, the method has lot of disadvantages like drastic reaction conditions, long reaction time, expensive reagent, tedious work-up procedure, chromatographic isolation method and low yield of the product. Moreover, their study was limited to aldehydes only. In view of that, very recently, Liu *et al.* reported the synthesis of similar compounds from the reaction of 4-hydroxycoumarins and aldehydes catalyzed by Cu(II) bromide in presence of pyridine.[15] But again, the reaction took long time for completion, required excess use of pyridine, products were separated by chromatographic method and the study was confined to aldehydes only.

Dimethyl sulfoxide (DMSO) is a nontoxic organic solvent which is used in pharmaceutical synthesis, the manufacture of electronics, and drug delivery in body. It is also used as a mild oxidizing agent in various organic transformations, as demonstrated by many fashionable reactions such as Pfitzner-

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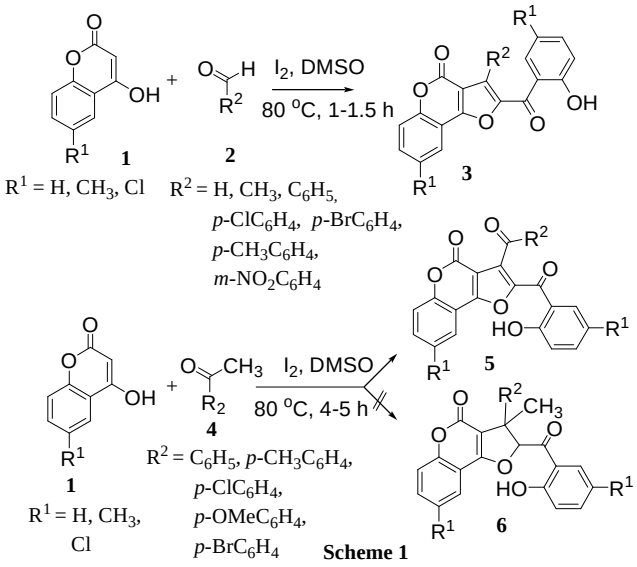
Moffatt oxidation, the Swern oxidation etc.[16] DMSO with iodine (DMSO + I_2) is a very interesting system of reagent with diverse application in organic synthesis.[17]

In continuation to our studies on coumarins,[18] we report here a novel and highly efficient reaction protocol for the synthesis of furo[3,2-*c*]coumarins from the reaction of 4-hydroxycoumarins and aldehydes/aryl methyl ketones in the presence of molecular iodine in DMSO (Scheme 1).

Synthesis of furo[3,2-*c*]coumarins **3** & **5**

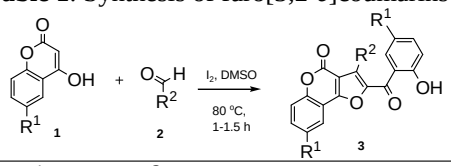


Scheme 1

2. Results and Discussion

The study was initiated with the reaction of 4-hydroxycoumarin **1** (R^1 = H) and formaldehyde **2** (R^2 = H) at 2:1 molar ratio in the presence of iodine (15 mol%) as catalyst in DMSO at room temperature, but no reaction occurred. Then, the reaction temperature was slowly increased and it was observed that the reaction occurred very smoothly at 80 °C to afford the furocoumarin **3a** (R^1 = H; R^2 = H) in excellent yield. Next, the load of the iodine as well as the reaction time was optimized, and established that 7 mol% of iodine is sufficient to provide maximum yield of the product **3a** in just 1h time. Very interestingly, the product was obtained in solid and pure form on pouring the reaction mixture in water followed by removing the iodine by adding sodium thiosulphate, which could be isolated simply by filtration. Increase in the reaction temperature and time did not improve the yield of the product. The structure of the compound was ascertained from the spectroscopic data, elemental analysis and by comparing with the authentic sample.[14] In order to establish the generality of the reaction, a series of furo[3,2-*c*]coumarins **3a-m** were synthesized by utilizing various substituted coumarins **1** with aldehydes **2**, and characterized (Table 1). It was observed that formaldehyde was highly reactive and products were obtained in high yield in crystal form in a short reaction time. The effect of substituent in the benzene ring of 4-hydroxycoumarin as well as in aryl aldehydes was also examined properly and found that electron withdrawing group at the benzene ring of the coumarin molecule and in the aromatic ring of the aryl aldehydes produced better yield of the product in a short reaction time in comparison to the electron donating group (Table 1).

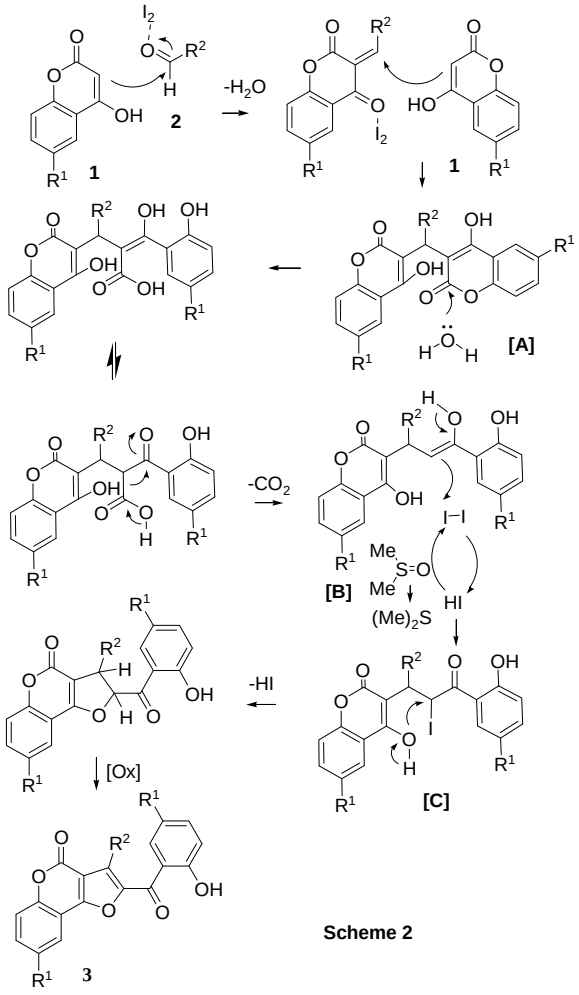
Table 1: Synthesis of furo[3,2-*c*]coumarins **3**



Ent.	R^1	R^2	Prod.	R.T.	Yd. (%)
1	H	H	**3a**	1h	78
2	H	Me	**3b**	1.5h	72
3	H	C_6H_5	**3c**	1.5h	74
4	H	*p*-MeC_6H_4	**3d**	1.5h	73
5	H	*m*-$NO_2C_6H_4$	**3e**	1 h	89
6	H	*p*-BrC_6H_4	**3f**	1h	79
7	H	*p*-ClC_6H_4	**3g**	1h	80
8	Cl	C_6H_5	**3h**	1h	79
9	Cl	*p*-MeC_6H_4	**3i**	1h	77
10	Cl	*p*-BrC_6H_4	**3j**	1h	86
11	Cl	*p*-ClC_6H_4	**3k**	1h	88
12	Me	H	**3l**	1.5h	74
13	Me	C_6H_5	**3m**	1.5h	72

Ent. = Entry, Pd = Product, R.T. = Reaction time, Yd. = Yield

Mechanism for the formation of furo[3,2-*c*]coumarins **3**

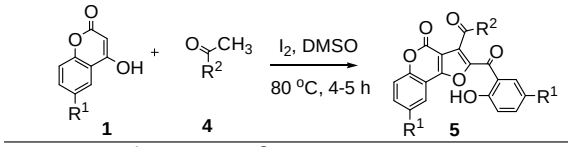


Scheme 2

The mechanism of the reaction is similar to that reported by Shafiee *et. al*, but here DMSO, the solvent, involved as an excellent oxidizing agent in the reaction process to produce the desired product.[14] Hence, first the biscoumarin **[A]** forms from the reaction of 4-hydroxycoumarin **1** and aldehyde **2** in the presence of iodine catalyst which undergoes through a lactone ring opening and decarboxylation process to produce the intermediate **[B]** (Scheme 2). The intermediate **[B]** in the presence of iodine and DMSO produced the iodinated compound **[C]** which after intramolecular cyclization with the elimination of hydrogen iodide followed by oxidation produced the aromatized furo[3,2-*c*]coumarins **3**. DMSO oxidized iodide to iodine and recycles it in the reaction process.

To expand the scope of the reaction, various ketones **4** were utilized with 4-hydroxycoumarins **1** to synthesize more functionnalized furo[3,2-*c*]coumarins. Accordingly, 4-hydroxycoumarin **1** (R^1 = H) was first reacted with acetophenone **4** (R^2 = Ph) under the standard reaction conditions in the presence of iodine as catalyst (7 mol%) in DMSO at 80 ^oC (Scheme 1). A thin layer chromatographic study showed the slow consumption of the reactants and formation of a new compound, but the reaction did not proceed further on increasing the reaction time as well as the temperature. Then we studied the reaction by increasing the load of iodine as well as reaction time and observed that when 50 mol% of iodine was used in the reaction process, the reactants were consumed completely to give exclusively one product in excellent yield in 4 h time. Very interestingly, the product was identified as furo[3,2-*c*]coumarin derivative **5a** (R^1 = H, R^2 = Ph) instead of the expected dihydrofuro[3,2-*c*]coumarins **6** (R^1 = H, R^2 = Ph), from the spectroscopic data and elemental analysis. Subsequently, a large number of furo[3,2-*c*]coumarin derivatives **5a-r** were synthesized by utilizing various coumarins **1** with ketones **4**, which were isolated by simple filtration and characterized (Table 2). As in the earlier case, it was observed that electron withdrawing group at the benzene ring of the coumarin molecule as well as in the aromatic ring of the aryl aldehydes produced better yield of the product in shorter reaction time in comparison to the electron donating group (Table 2). On the other hand, under identical reaction conditions aliphatic ketones did not take part in the reaction process to produce either the furo[3,2-*c*]coumarins or dihydrofuro[3,2-*c*]coumarins of the types **5** or **6** respectively.

Table 2: Synthesis of furo[3,2-*c*]coumarins **5**

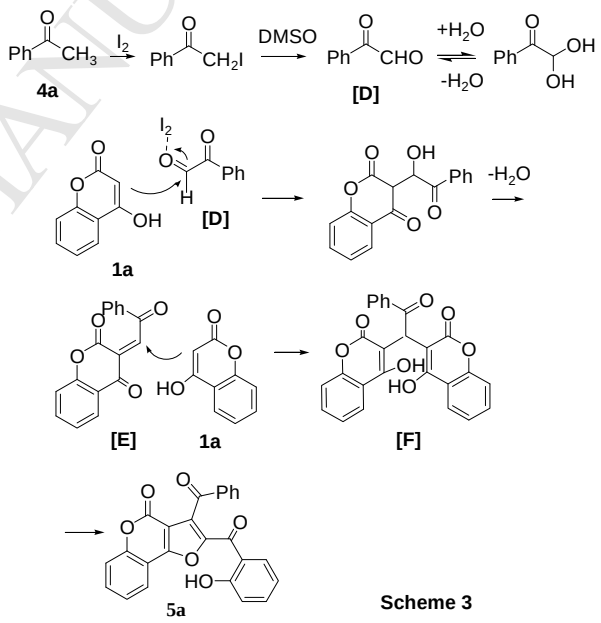


1 4 5

Ent.	R^1	R^2	Pd.	R.T.	Yd. (%)
1	H	C_6H_5	**5a**	5h	78
2	Me	C_6H_5	**5b**	5h	72
3	Cl	C_6H_5	**5c**	4h	81
4	H	*p*-MeC_6H_4	**5d**	5h	73
5	Me	*p*-MeC_6H_4	**5e**	5h	70
6	Cl	*p*-MeC_6H_4	**5f**	4h	79
7	H	*p*-ClC_6H_4	**5g**	4h	78
8	Me	*p*-ClC_6H_4	**5h**	4h	77
9	Cl	*p*-ClC_6H_4	**5i**	4h	89
10	H	*p*-$OMeC_6H_4$	**5j**	5h	71
11	Me	*p*-$OMeC_6H_4$	**5k**	5h	70
12	Cl	*p*-$OMeC_6H_4$	**5l**	4h	77
13	H	*p*-BrC_6H_4	**5m**	4h	80
14	Me	*p*-BrC_6H_4	**5n**	4h	78
15	Cl	*p*-BrC_6H_4	**5o**	5h	86
16	H	C_4H_4S	**5p**	5h	74
17	Me	C_4H_4S	**5q**	5h	71
18	Cl	C_4H_4S	**5r**	5h	79

Ent. = Entry, Pd = Product, R.T. = Reaction time, Yd. = Yield

Mechanism for the formation of furo[3,2-*c*]coumarins **5a**



Scheme 3

A reasonable mechanism of the reaction is depicted in the scheme 3, taking the formation of **5a** as an example. The reaction occurred *via* initial formation of phenylglyoxal **[D]** from phenyl methyl ketone **4a** (Ar = Ph) *via* sp^3-CH activation followed by oxidation[19] which reacts with 4-hydroxycoumarin **1a** (R^1 = H) in the presence of iodine to give the intermediate **[E]** by eliminating water molecule. The intermediate **[E]** then suffers a nucleophilic attack by second molecule of 4-hydroxycoumarin **1a** (R^1 = H) to give the bis-4-hydroxycoumarin **[F]** which finally produced the product **5a** following the reaction path as discussed in the scheme 2. The mechanism of the reaction was established by performing reaction of 4-hydroxycoumarin **1** (R^1 = H) with commercially available phenyl glyoxal **[D]** in the presence of iodine as catalyst in DMSO at 80 °C for 2 h (till completion of reaction checked by TLC) which afforded the product **5a** in high yield.

3. Conclusion

In conclusion, we have developed a very simple and efficient method for the synthesis of highly functionalized furo[3,2-*c*]-coumarin from 4-hydroxycoumarins and aldehydes/aryl methyl ketones mediated by iodine in DMSO. DMSO acts as solvent as well as oxidizing agent and recycles the iodine in the reaction process. The reaction conditions are moderate, work-up procedure is very simple and products were isolated in high yield simply by filtration.

4. Experimental Section

All chemicals were purchased from Merck and Aldrich chemical companies. The reagents and solvents were used without drying. The IR spectra were recorded on Perkin Elmer system 2000 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR Spectra were recorded on Bruker AV500 Avance – III 500 MHz and 125 MHz FT NMR in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ units) are given from TMS (0 ppm). Chemical shifts for DMSO-d_6 were reported at 3.36, 2.50 ppm respectively (δ units). Mass spectra were recorded in Bruker Daltonics ESQUIRE 3000 LC ESI ion trap mass spectrometer. Analytical thin layer chromatography (TLC) was performed using E-Merck aluminium-backed silica gel plates coated with 0.2 mm thickness of silica gel. Melting points (uncorrected) were determined in open capillary tubes on a Buchi B-540 apparatus. Elemental analyses were performed on Perkin-Elmer 2400 spectrometer at the Analytical Chemistry Division, CSIR-NEIST, Jorhat.

General procedure for the synthesis of compound 3:

A mixture of 4-hydroxycoumarin (2 mmol), aldehyde (1 mmol), I_2 (7 mol%) were taken in round bottomed flask containing 5 ml of DMSO. Then the reaction mixture was allowed to heat at 80 °C for 1-1.5 h (till completion of reaction checked by TLC). After completion of the reaction, the mixture was cooled to room temperature and poured into water. Then the iodine was neutralized by adding sodium thiosulphate (5 mL of 5% solution) into the reaction mixture. The crude product **3** was obtained by simple filtration and purified by recrystallization from ethanol.

2-(2-Hydroxybenzoyl)-4H-furo[3,2-c]chromen-4-one ***(3a)***. Yield = 78% (238 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.50; mp = 153-154 ^{o}C (reported 154-156 ^{o}C)[14]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-8.04 (m, 9H), 11.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 110.0, 111.3, 117.1, 118.0, 118.1, 118.5, 121.5, 127.8, 129.9, 131.2, 135.0, 136.1, 151.9, 153.0, 158.1, 161.0, 163.9, 184.4; IR (KBr) ν_{max}: 3436.2, 1765.4, 1628.5 cm^{-1}; MS (ESI): 307.2 $(M + H)^+$.

2-(2-Hydroxybenzoyl)-3-methyl-4H-furo[3,2-c]chromen-4-one ***(3b)***. Yield = 72% (230 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.60; mp = 217-219 ^{o}C (reported 216-218 ^{o}C)[14]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79 (s, 3H), 7.01-8.27 (m, 8H), 12.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 10.8, 111.9, 117.9, 118.6, 119.0, 121.5, 122.0, 122.6, 123.9, 124.2, 130.1, 130.9, 133.1, 148.3, 153.8, 157.3, 157.6, 163.6, 186.7; IR (KBr) ν_{max}: 3382.7, 1762.2, 1626.5 cm^{-1}; MS (ESI): 321.4 $(M + H)^+$.

2-(2-Hydroxybenzoyl)-3-phenyl-4H-furo[3,2-c]chromen-4-one ***(3c)***. Yield = 74% (282 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.50; mp = 203-204 ^{o}C (reported 203-205 ^{o}C)[14]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72-8.16 (m, 13H), 11.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.8, 117.1, 117.7, 119.4, 122.3, 123.3, 126.0, 126.1 (2C), 126.5, 127.8, 130.3 (2C), 131.9, 132.0, 133.0, 135.2, 138.1, 153.4, 157.3, 157.6, 160.0, 163.6, 186.2; IR (KBr) ν_{max}: 3343.3, 1766.1, 1625.8 cm^{-1}; MS (ESI): 383.2 $(M + H)^+$.

2-(2-Hydroxybenzoyl)-3-(p-tolyl)-4H-furo[3,2-c]chromen-4-one ***(3d)***. Yield = 73% (289 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.52; mp = 110-111 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H), 6.68-7.94 (m, 12H), 11.59 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 21.3, 111.8, 112.5, 118.8, 118.9, 120.2, 121.1, 123.8, 124.2, 126.4 (2C), 130.7, 130.8, 131.4 (2C), 131.6, 132.6, 132.8, 136.6, 148.6, 151.8, 155.6, 157.3, 161.2, 185.4; IR (KBr) ν_{max}: 3442.2, 1758.4, 1632.7 cm^{-1}; MS (ESI): 397.1 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{16}O_5$: C, 75.75; H, 4.07%. Found: C, 75.60; H, 4.10%.

2-(2-Hydroxy-benzoyl)-3-(3-nitro-phenyl)-furo[3,2-c]chromen-4-one ***(3e)***. Yield = 89% (380 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.48; mp = 79-81 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): 6.89-8.47 (m, 12H), 11.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 108.9, 110.1, 117.6, 118.4, 118.7, 119.1, 121.7, 123.9, 125.0, 125.4, 127.5, 127.9, 128.9, 131.5, 132.9, 136.1, 137.1, 139.8, 153.2, 157.0, 157.9, 160.1, 163.3, 186.2; IR (KBr) ν_{max}= 3437.1, 1762.7, 1636.2 cm^{-1}; MS (EI): 428.5 $(M+H)^+$; Anal. Calcd. For $C_{24}H_{13}NO_7$: C, 67.45; H, 3.07 %. Found: C, 67.30; H, 2.90 %.

3-(4-Bromophenyl)-2-(2-hydroxybenzoyl)-4H-furo[3,2-c]-chromen-4-one ***(3f)***. Yield = 79% (364 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.50; mp = 114-115 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72-7.98 (m, 12H), 11.49 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.3, 116.6, 118.7, 119.4, 121.9, 123.7, 126.9, 128.0, 130.7, 131.2 (2C), 131.5, 131.7 (2C), 131.8, 133.1, 134.6, 136.9, 146.3, 151.7, 155.0, 155.1, 160.1, 186.7; IR (KBr) ν_{max}: 3446.2, 1769.8, 1634.7 cm^{-1}; MS (ESI): 462.4 $(M + H)^+$; Anal. Calcd. for $C_{24}H_{13}BrO_5$: C, 62.49; H, 2.84%. Found: C, 62.61; H, 2.86%.

3-(4-Chlorophenyl)-2-(2-hydroxybenzoyl)-4H-furo[3,2-c]-chromen-4-one ***(3g)***. Yield = 80% (332 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.49; mp = 212-213 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86-8.03 (m, 12H), 11.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.2, 112.6, 118.6, 118.9, 120.2, 121.1, 123.3, 124.2, 126.3, 130.6 (2C), 130.9, 131.5 (2C), 131.8, 132.6, 132.8, 136.6, 151.6, 155.3, 157.4, 161.2, 163.5, 186.7; IR (KBr) ν_{max}: 3428.5, 1746.3, 1622.8 cm^{-1}; MS (ESI): 417.5 $(M + H)^+$; Anal. Calcd. for $C_{24}H_{13}ClO_5$: C, 69.16; H, 3.14%. Found: C, 69.33; H, 3.17 %.

8-Chloro-2-(3-chloro-2-hydroxybenzoyl)-3-phenyl-4H-furo-[3,2-c]chromen-4-one ***(3h)***. Yield = 79% (356 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.57; mp = 155-157 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96-8.05 (m, 11H), 11.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.2, 112.5, 118.8, 118.9, 120.0, 121.1, 123.8, 124.2, 126.3, 130.7, 130.8 (2C), 131.3, 131.6 (2C), 132.7, 132.9, 136.9, 151.8, 155.6, 157.4, 161.5, 163.5, 184.3; IR (KBr) ν_{max}: 3342.6, 1767.5, 1623.6 cm^{-1}; MS (ESI): 452.6 $(M + H)^+$; Anal. Calcd. for $C_{24}H_{12}Cl_2O_5$: C, 63.88; H, 2.68%. Found: C, 63.76; H, 2.67%.

8-Chloro-2-(3-chloro-2-hydroxybenzoyl)-3-(p-tolyl)-4H-furo-[3,2-c]chromen-4-one ***(3i)***. Yield = 77% (358 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.62; mp = 104-105 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3H), 6.82-8.03 (m,

10H), 11.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 21.5, 111.0, 112.6, 118.6, 118.8, 120.0, 121.2, 123.9, 124.1, 126.3 (2C), 130.7, 130.9, 131.3 (2C), 131.6, 132.5, 132.8, 136.6, 151.8, 155.7, 157.5, 161.5, 164.0, 185.4; IR (KBr) ν_{max}: 3441.8, 1768.2, 1627.7 cm^{-1}; MS (ESI): 466.1 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{14}Cl_2O_5$: C, 64.54; H, 3.03%. Found: C, 64.37; H, 2.99%.

*3-(4-Bromophenyl)-8-chloro-2-(3-chloro-2-hydroxybenzoyl)-4H-furo[3,2-c]chromen-4-one (**3j**)*. Yield = 86% (455 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.55; mp = 200-202 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82-7.99 (m, 10H), 11.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.0, 112.6, 118.8, 118.9, 120.0, 121.1, 123.9, 124.2, 126.3, 130.7, 130.8, 131.4 (2C), 131.6 (2C), 132.6, 132.8, 136.8, 151.9, 155.7, 157.5, 161.6, 164.0, 185.4; IR (KBr) ν_{max}: 3365.7, 1769.0. 1628.5 cm^{-1}; MS (ESI): 531.3 $(M + H)^+$; Anal. Calcd. for $C_{24}H_{11}BrCl_2O_5$: C, 54.37; H, 2.09%. Found: C, 54.21; H, 2.12%.

*8-Chloro-2-(3-chloro-2-hydroxybenzoyl)-3-(4-chlorophenyl)-4H-furo[3,2-c]chromen-4-one (**3k**)*. Yield = 88% (426 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.48; mp = 201-202 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84-8.36 (m, 10H), 11.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.0, 112.5, 118.6, 118.7, 120.0, 121.3, 123.9, 124.1, 126.3, 130.8 (2C), 130.9, 131.3 (2C), 131.6, 132.5, 132.8, 136.6, 148.6, 151.8, 155.6, 157.5, 161.6, 185.3; IR (KBr) ν_{max}: 3443.2, 1766.7, 1624.5 cm^{-1}; MS (ESI): 486.3 $(M + H)^+$; Anal. Calcd. for $C_{24}H_{11}Cl_3O_5$: C, 59.35; H, 2.28%. Found: C, 59.54; H, 2.25%.

*2-(2-Hydroxy-3-methylbenzoyl)-8-methyl-4H-furo[3,2-c]chromen-4-one (**3l**)*. Yield = 74% (247 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.57; mp = 189-190 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.50 (s, 3H), 6.97-7.96 (m, 7H), 11.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 20.6, 20.8, 110.1, 111.4, 117.3, 118.0, 118.1, 118.5, 121.5, 128.6, 130.2, 133.7, 135.0, 138.0, 152.2, 154.1, 157.9, 159.1, 162.0, 184.4; IR (KBr) ν_{max}: 3343.8, 1766.9, 1626.8 cm^{-1}; MS (ESI): 335.4 $(M + H)^+$; Anal. Calcd. for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22%. Found: C, 71.67; H, 4.24%.

*2-(2-Hydroxy-3-methylbenzoyl)-8-methyl-3-phenyl-4H-furo-[3,2-c]chromen-4-one (**3m**)*. Yield = 72% (295 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.58; mp = 194-195 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.58 (s, 3H), 6.72-8.16 (m, 11H), 11.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 20.0, 21.5, 111.9, 117.0, 117.8, 119.2, 122.3, 123.2, 126.0 (2C), 126.1, 126.5, 127.8 (2C), 130.3, 131.9, 132.0, 133.0, 135.2, 138.1, 152.2, 154.1, 157.9, 159.1, 162.1, 185.2; IR (KBr) ν_{max}: 3367.8, 1765.9, 1629.5 cm^{-1}; MS (ESI): 411.7 $(M + H)^+$; Anal. Calcd. for $C_{26}H_{18}O_5$: C, 76.09; H, 4.42%. Found: C, 75.94; H, 4.43%.

General procedure for the synthesis of compound 5:

A mixture of 4-hydroxycoumarin (2 mmol), aryl methyl ketone (1 mmol), I_2 (50 mol%) were taken in round bottomed flask containing 5 ml of DMSO. Then the reaction mixture was allowed to heat at 80 °C for 4-5 h (till completion of reaction checked by TLC). After completion of the reaction, the mixture was cooled to room temperature and poured into water. Then the iodine was neutralized by adding sodium thiosulphate (10 mL of 5% solution) into the reaction mixture. The product **5** was isolated by filtration and recrystallized from ethanol.

*3-Benzoyl-2-(2-hydroxybenzoyl)-4H-furo[3,2-c]chromen-4-one (**5a**)*. Yield = 78% (319 mg); Yellow crystalline solid; Rf (Hexane/EtOAc, 8:2) 0.47; mp = 286-287 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.89-8.03 (m, 13H), 10.51 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 113.2, 118.3, 118.9, 119.8, 121.3, 122.9, 125.4, 128.6, 129.0, 129.1 (2C), 129.3 (2C), 129.4, 129.6, 133.1, 133.8, 134.7, 150.0, 152.3, 155.7, 156.0, 157.3, 181.7, 187.9; IR (KBr) ν_{max}: 3435.6, 2926.3, 1750.5, 1674.7 cm^{-1}; MS (ESI): 411.4 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{14}O_6$: C, 73.17; H, 3.44%. Found: C, 72.99; H, 3.47%.

*3-Benzoyl-2-(2-hydroxy-5-methylbenzoyl)-8-methyl-4H-furo-[3,2-c]chromen-4-one (**5b**)*. Yield = 72% (315 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.49; mp = 268-269 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (s, 3H), 2.43 (s, 3H), 6.86-7.97 (m, 11H), 10.18 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 20.1, 20.7, 110.9, 111.5, 116.9, 117.5, 121.6, 123.5, 128.1, 128.4, 129.3 (2C), 130.1, 131.2 (2C), 134.4, 134.8, 135.3, 135.4, 139.6, 150.1, 152.0, 155.9, 157.7, 158.6, 183.2, 188.3; IR (KBr) ν_{max}: 3521.3, 2922.1, 1751.2, 1681.8 cm^{-1}; MS (ESI): 439.5 $(M + H)^+$; Anal. Calcd. for $C_{27}H_{18}O_6$: C, 73.97; H, 4.14%. Found: C, 73.78; H, 4.12%.

*3-Benzoyl-8-chloro-2-(5-chloro-2-hydroxybenzoyl)-4H-furo-[3,2-c]chromen-4-one (**5c**)*. Yield = 81% (387 mg); Light orange solid; Rf (Hexane/EtOAc, 8:2) 0.46; mp = 257-259 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.91-8.08 (m, 11H), 10.64 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 111.0, 111.7, 117.9, 119.4, 122.2, 125.5, 125.8, 125.9, 129.4 (2C), 130.1, 131.2 (2C), 131.3, 133.9, 134.4, 138.5, 140.0, 148.9, 150.2, 153.8, 156.0, 159.1, 180.9, 186.8; IR (KBr) ν_{max}: 3446.9, 2916.6, 1763.2, 1670.6 cm^{-1}; MS (ESI): 480.3 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{12}Cl_2O_6$: C, 62.65; H, 2.52%. Found: C, 62.80; H, 2.50%.

*2-(2-Hydroxybenzoyl)-3-(4-methylbenzoyl)-4H-furo[3,2-c]-chromen-4-one (**5d**)*. Yield = 73% (309 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.48; mp = 245-246 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.44 (s, 3H), 6.86-8.16 (m, 12H), 10.51 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 21.6, 111.7, 113.2, 118.8, 119.8, 121.3, 123.0, 125.4, 129.2, 129.3 (2C), 129.5 (2C), 129.6, 129.7, 133.1, 133.6, 133.7, 145.5, 149.9, 152.3, 155.7, 155.9, 157.3, 181.7, 187.3; IR (KBr) ν_{max}: 3435.1, 2927.7, 1751.3, 1674.8 cm^{-1}; MS (ESI): 425.6 $(M + H)^+$; Anal. Calcd. for $C_{26}H_{16}O_6$: C, 73.58; H, 3.80%. Found: C, 73.41; H, 3.83%.

*2-(2-Hydroxy-5-methylbenzoyl)-8-methyl-3-(4-methylben-zoyl)-4H-furo[3,2-c]chromen-4-one (**5e**)*. Yield = 70% (316 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.51; mp = 293-295 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.07 (s, 3H), 2.12 (s, 3H), 2.42 (s, 3H), 6.52-7.79 (m, 10H), 10.19 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 20.0, 20.6, 21.0, 110.8, 111.5, 116.9, 117.5, 121.6, 123.5, 128.1, 128.4, 129.3 (2C), 130.1, 131.2 (2C), 134.4, 134.8, 135.3, 135.4, 139.6, 150.3, 151.9, 155.4, 157.2, 161.0, 183.2, 187.1; IR (KBr) ν_{max}: 3435.5, 2927.4, 1745.4, 1669.8 cm^{-1}; MS (ESI): 453.6 $(M + H)^+$; Anal. Calcd. for $C_{28}H_{20}O_6$: C, 74.33; H, 4.46%. Found: C, 74.55; H, 4.43%.

*8-Chloro-2-(5-chloro-2-hydroxybenzoyl)-3-(4-methylbenzo-yl)-4H-furo[3,2-c]chromen-4-one (**5f**)*. Yield = 79% (389 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.49; mp = 275-276 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.40 (s, 3H), 6.90-8.13 (m, 10H), 10.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-

d_6): 21.3, 110.9, 111.8, 117.1, 117.7, 119.4, 122.3, 123.3, 125.7, 129.0, 129.1 (2C), 129.5 (2C), 130.6, 133.5, 134.6, 134.9, 136.0, 150.1, 153.7, 156.1, 158.1, 158.4, 183.3, 188.3; IR (KBr) ν_{max}: 3411.2, 2928.1, 1749.7, 1694.2 cm^{-1}; MS (ESI): 494.4 $(M + H)^+$; Anal. Calcd. for $C_{26}H_{14}Cl_2O_6$: C, 63.31; H, 2.86%. Found: C, 63.16; H, 2.87%.

*3-(4-Chlorobenzoyl)-2-(2-hydroxybenzoyl)-4H-furo[3,2-c]-chromen-4-one (**5g**)*. Yield = 78% (346 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.45; mp = 230-231 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 6.70-8.25 (m, 12H), 10.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 109.2, 111.5, 113.2, 119.8, 121.3, 129.3 (2C), 129.4, 129.7, 129.8, 131.2 (2C), 131.3, 133.0, 134.7, 139.7, 142.3, 145.0, 152.2, 155.7, 158.0, 160.0, 160.4, 181.4, 186.8; IR (KBr) ν_{max}: 3501.4, 2924.3, 1759.2, 1676.3 cm^{-1}; MS (ESI): 445.9 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{13}ClO_6$: C, 67.50; H, 2.95%. Found: C, 67.36; H, 2.93%.

*3-(4-Chlorobenzoyl)-2-(2-hydroxy-5-methylbenzoyl)-8-methyl -4H-furo[3,2-c]chromen-4-one (**5h**)*. Yield = 77% (363 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.46; mp = 282-283 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 2.11 (s, 3H), 2.47 (s, 3H), 6.80-7.87 (m, 10H), 10.14 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 20.0, 20.6, 110.7, 111.5, 116.9, 117.5, 121.5, 123.4, 128.1, 128.4, 129.3, 130.1 (2C), 131.2 (2C), 134.4, 134.8, 135.3, 135.4, 139.6, 151.9, 154.3, 155.2, 158.9, 160.2, 183.3, 188.2; IR (KBr) ν_{max}: 3435.7, 2927.7, 1753.2, 1676.3 cm^{-1}; MS (ESI): 473.9 $(M + H)^+$; Anal. Calcd. for $C_{27}H_{17}ClO_6$: C, 68.58; H, 3.62%. Found: C, 68.79; H, 3.65%.

*8-Chloro-2-(5-chloro-2-hydroxybenzoyl)-3-(4-chlorobenzoyl)-4H-furo[3,2-c]chromen-4-one (**5i**)*. Yield = 89% (456 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.42; mp=225-227 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 6.90-8.13 (m, 10H), 10.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 110.9, 111.8, 114.4, 117.1, 117.7, 119.4 (2C), 122.3, 123.4, 125.7, 129.3 (2C), 130.5, 131.9, 133.3, 134.8, 137.2, 149.8, 153.6, 156.1, 158.1, 158.3, 164.4, 183.2, 186.5; IR (KBr) ν_{max}: 3435.7, 2991.9, 1771.3, 1682.3 cm^{-1}; MS (ESI): 514.6 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{11}Cl_3O_6$: C, 58.45; H, 2.16%. Found: C, 58.28; H, 2.13%.

*2-(2-Hydroxybenzoyl)-3-(4-methoxybenzoyl)-4H-furo[3,2-c]-chromen-4-one (**5j**)*. Yield = 71% (312 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.47; mp = 272-273 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 3.85 (s, 3H), 6.86-8.06 (m, 12H), 10.48 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 56.0, 110.9, 111.9, 114.4, 117.1, 117.7, 119.4, 122.3 (2C), 123.4, 125.7, 129.3, 130.5, 131.9 (2C), 133.4, 134.8, 137.1, 149.9, 153.7, 156.1, 158.1, 158.3, 164.3, 183.3, 186.5; IR (KBr) ν_{max}: 3439.1, 2970.4, 1755.7, 1673.6 cm^{-1}; MS (ESI): 441.2 $(M + H)^+$; Anal. Calcd. for $C_{26}H_{16}O_7$: C, 70.91; H, 3.66%. Found: C, 70.75; H, 3.64%.

*2-(2-Hydroxy-5-methylbenzoyl)-3-(4-methoxybenzoyl)-8-methyl-4H-furo[3,2-c]chromen-4-one (**5k**)*. Yield = 70% (327 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.50; mp = 224-226 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 2.15 (s, 3H), 2.48 (s, 3H) 3.86 (s, 3H), 6.81-7.90 (m, 10H), 10.66 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 20.0, 20.6, 56.0, 110.7, 111.5, 114.2, 117.1, 117.8, 119.2, 122.1, 123.2, 125.6, 129.0 (2C), 130.2, 131.9 (2C), 133.2, 134.9, 137.0, 139.2, 153.8, 156.0, 158.3, 158.9, 164.3, 183.3, 186.8; IR (KBr) ν_{max}: 3441.6, 2967.9, 1743.5, 1682.7 cm^{-1}; MS (ESI): 469.4 $(M + H)^+$; Anal. Calcd. for $C_{28}H_{20}O_7$: C, 71.79; H, 4.30%. Found: C, 71.98; H, 4.34%.

*8-Chloro-2-(5-chloro-2-hydroxybenzoyl)-3-(4-methoxybenzoyl)-4H-furo[3,2-c]chromen-4-one (**5l**)*. Yield = 77% (391 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.47; mp = 215-216 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 3.85 (s, 3H), 6.89-8.06 (m, 10H), 10.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 56.0, 113.2, 114.4, 114.5, 118.7, 119.8, 121.3, 121.5, 122.9 (2C), 125.5, 129.1, 129.2, 129.4, 129.6, 131.9, 133.0 (2C), 133.9, 155.7, 155.9, 157.3, 164.5, 164.6, 181.8, 186.0; IR (KBr) ν_{max}: 3457.2, 2976.4, 1739.8, 1673.3 cm^{-1}; MS (ESI): 510.3 $(M + H)^+$; Anal. Calcd. for $C_{26}H_{14}Cl_2O_7$: C, 61.32; H, 2.77%. Found: C, 61.16; H, 2.75%.

*3-(4-Bromobenzoyl)-2-(2-hydroxybenzoyl)-4H-furo[3,2-c]-chromen-4-one (**5m**)*. Yield = 80% (391 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.44; mp = 233-235 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 6.25-8.17 (m, 12H), 10.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 114.5, 118.7, 119.8, 121.3, 121.5, 122.9 (2C), 125.5 (2C), 129.1, 129.2, 129.4, 129.6, 129.9, 131.9, 133.1, 133.2, 133.6, 155.7, 155.9, 157.3, 164.5, 164.6, 181.7, 186.0; IR (KBr) ν_{max}: 3509.6, 2936.9, 1763.8, 1669.7 cm^{-1}; MS (ESI): 490.4 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{13}BrO_6$: C, 61.37; H, 2.68%. Found: C, 61.23; H, 2.71%.

*3-(4-Bromobenzoyl)-2-(2-hydroxy-5-methylbenzoyl)-8-methyl-4H-furo[3,2-c]chromen-4-one (**5n**)*. Yield = 78% (403 mg); Orange solid; Rf (Hexane/EtOAc, 8:2) 0.45; mp = 245-246 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 2.12 (s, 3H), 2.43 (s, 3H), 6.50-7.79 (m, 10H), 10.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 20.1, 20.9, 114.5, 118.7, 119.8, 121.3, 121.5, 122.9 (2C), 125.5, 129.1, 129.2, 129.4, 129.6, 129.9, 131.9 (2C), 133.1, 133.2, 133.7, 155.7, 155.9, 157.3, 164.5, 164.6, 181.8, 186.0; IR (KBr) ν_{max}: 3516.2, 2924.7, 1773.4, 1662.9 cm^{-1}; MS (ESI): 518.2 $(M + H)^+$; Anal. Calcd. for $C_{27}H_{17}BrO_6$: C, 62.69; H, 3.31%. Found: C, 62.52; H, 3.33%.

*3-(4-Bromobenzoyl)-8-chloro-2-(5-chloro-2-hydroxybenzoyl)-4H-furo[3,2-c]chromen-4-one (**5o**)*. Yield = 86% (479 mg); Light orange solid; Rf (Hexane/EtOAc, 8:2) 0.40; mp = 262-264 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 6.89-8.37 (m, 10H), 10.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 110.7, 111.5, 114.4, 114.5, 116.9, 117.5, 121.5, 121.8, 123.5 (2C), 129.0, 129.1, 129.3, 131.3 (2C), 131.9, 132.0, 135.2, 150.0, 152.0, 155.6, 164.3, 164.4, 186.3, 186.4; IR (KBr) ν_{max}: 3473.8, 2982.6, 1764.5, 1679.7 cm^{-1}; MS (ESI): 559.3 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{11}BrCl_2O_6$: C, 53.80; H, 1.99%. Found: C, 53.65; H, 1.97%.

*2-(2-Hydroxybenzoyl)-3-(thiophene-2-carbonyl)-4H-furo[3,2-c]chromen-4-one (**5p**)*. Yield = 74% (307 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.30; mp = 244-245 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 7.71-8.95 (m, 11H), 11.35 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d_6*): 114.4, 114.5, 118.7, 119.8, 121.3 (2C), 121.5, 122.9, 125.5 (2C), 129.1, 129.2, 129.4, 129.6, 131.9, 133.0, 155.6, 155.9, 157.3, 164.5, 164.6, 181.8, 186.1; IR (KBr) ν_{max}: 3513.7, 2978.5, 1768.3, 1673.1 cm^{-1}; MS (ESI): 417.6 $(M + H)^+$; Anal. Calcd. for $C_{23}H_{12}O_6S$: C, 66.34; H, 2.90%. Found: C, 66.54; H, 2.93%.

*2-(2-Hydroxy-5-methylbenzoyl)-8-methyl-3-(thiophene-2-carbonyl)-4H-furo[3,2-c]chromen-4-one (**5q**)*. Yield = 71% (315 mg); Yellow solid; Rf (Hexane/EtOAc, 8:2) 0.33; mp = 249-250 °C; ^{1}H NMR (500 MHz, DMSO-*d_6*): δ 2.18 (s, 3H) 2.48 (s, 3H) 7.04-8.01 (m, 9H), 10.12 (s, 1H); ^{13}C NMR (125

MHz, DMSO-d_6): 21.6, 21.7, 117.2, 117.7, 119.4, 122.0, 122.3, 123.3, 125.7, 125.8, 129.2, 129.6 (2C), 129.7 (2C), 129.8, 130.6, 131.7, 153.7, 153.8, 156.1, 158.2, 158.4, 183.3, 187.7; IR (KBr) ν_{max}: 3523.8, 2982.6, 1772.9, 1675.8 cm^{-1}; MS (ESI): 445.2 $(M + H)^+$; Anal. Calcd. for $C_{25}H_{16}O_6S$: C, 67.56; H, 3.63%. Found: C, 67.40; H, 3.66%.

*8-Chloro-2-(5-chloro-2-hydroxybenzoyl)-3-(thiophene-2-carbonyl)-4H-furo[3,2-c]chromen-4-one (**5r**)*. Yield = 79% (383 mg); Light yellow solid; Rf (Hexane/EtOAc, 8:2) 0.29; mp = 264-265 ^oC; ^1H NMR (500 MHz, DMSO-d_6): δ 7.33-8.10 (m, 9H), 10.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 118.9, 119.7, 121.3, 122.9, 125.4, 128.6, 129.0, 129.1 (2C), 129.3 (2C), 129.8, 129.9, 133.1, 133.8, 134.7, 150.0, 152.1, 155.8, 156.1, 157.3, 181.7, 188.0; IR (KBr) ν_{max}: 3531.8, 2976.7, 1781.5, 1677.4 cm^{-1}; MS (ESI): 486.2 $(M + H)^+$; Anal. Calcd. for $C_{23}H_{10}Cl_2O_6S$: C, 56.93; H, 2.08%. Found: C, 56.75; H, 2.10%.

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5. References and notes

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