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Diethylamine-catalyzed environmentally benign synthesis of 1-oxo-hexahydroxanthenes and bis-coumarins at ambient temperature

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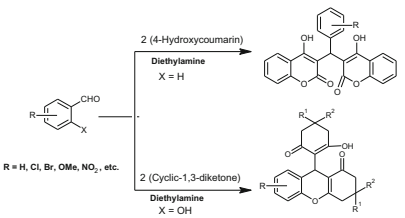
Abstract An extremely simple, economical and environmentally benign protocol has been described for one-pot synthesis of 1-oxo-hexahydroxanthenes by pseudo three-component condensation between salicylaldehydes and dimedone, cyclohexane-1,3-dione or 5-methyl cyclohexane-1,3-dione using diethylamine as the catalyst. Based upon the mechanism of the reaction, the protocol has been extended towards the synthesis of tetraketones and bis-coumarins.

Graphical Abstract



Keywords Domino reactions · 1-Oxo-hexahydroxanthenes · Bis-coumarins · Tetraketones · Diethylamine

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Introduction

The main current issues in the synthesis of complex organic molecules are improvement of efficiency, avoidance of toxic agents, reduction in waste and responsible utilization of natural sources. In this context, use of domino reactions involving the participation of two or more substrates is of relevance both from economic and ecological points of view [1–4]. Amongst domino reactions, Knoevenagel–Michael domino reactions have emerged as a powerful strategy in the synthesis of various oxa- as well as aza-heterocycles [5, 6].

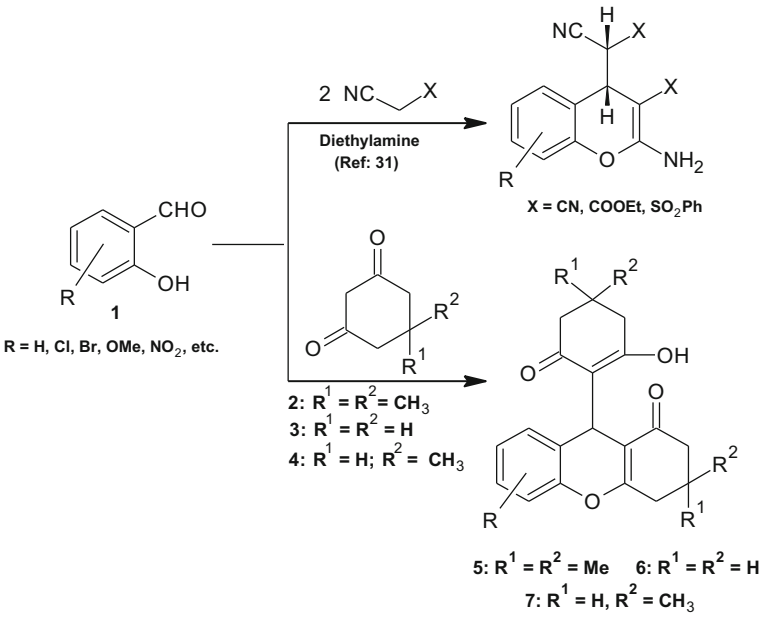
In recent years, construction of xanthene scaffolds has attracted much attention of organic chemists due to their importance in the field of medicine as well as material science [7–11]. Two important classes of compounds containing a xanthene structural motif are 1,8-octahydroxanthenes and 1-oxo-hexahydroxanthenes. Amongst these 1-oxo-hexahydroxanthenes are of particular interest to synthetic organic chemists due to their important pharmacological properties such as, antiestrogenic, antibacterial, antimicrobial as well as hypoglycemic activities [12–15]. They also exhibit thrombin inhibitory activity and serve as a neuropeptide Y Y5 receptor antagonist [16, 17]. Apart from biological activities, Li et al. [18, 19] recently explored the potential of 1-oxo-hexahydroxanthenes in the synthesis of other heterocycles. Synthesis of 1-oxo-hexahydroxanthenes involving one-pot pseudo three-component condensation between salicylaldehyde and two equivalents of dimedone or 1,3-cyclohexanedione was reported earlier using a range of Bronsted [20–23] heteropoly [24] as well as Lewis acid catalysts [25]. On the other hand, a few catalyst-free protocols have also been reported using glycerol [26] as well as water [27, 28] as a solvent. It is noteworthy that most of these reported protocols are operable at the reflux temperature and although their synthesis has been known to follow Knoevenagel–carba–Michael domino pathway, to the best of our knowledge, except for KF-alumina [29], there are no reports on their synthesis using any other basic catalyst. All these observations coupled with our continued interest in the development of environmentally benign protocols for the synthesis of biologically active compounds [30–34] prompted us to develop a base-mediated and easily adaptable protocol for the synthesis of 1-oxo-hexahydroxanthenes.

Diethylamine is a non-toxic, inexpensive and easy to handle organic base available commercially. The first report on the use of diethylamine as a catalyst in Knoevenagel condensation appeared in the 1940s [35]. However, it was interesting to note that it's use in multicomponent reactions had remained unexplored. In fact, we have demonstrated for the first time the use of diethylamine as an efficient organocatalyst in one-pot synthesis of β-phosphonomalononitriles and in diastereoselective synthesis of 2-amino-3-cyano-*4H*-chromenes by pseudo three component condensations between salicylaldehyde and two equivalents of active methylene compounds containing nitrile functionality [30, 31]. These reactions typically involved Knoevenagel–cyclization–carba–Michael domino pathway. Thinking along the same line we envisaged that synthesis of 1-oxo-hexahydroxanthenes could easily be achieved by pseudo three-component condensation between salicylaldehyde and two equivalents of active methylene compounds devoid of

nitrile function viz. dimedone or 1,3-cyclohexanedione using diethylamine as the catalyst (Scheme 1).

Results and discussion

In an initial exploratory reaction, to a well stirred solution of salicylaldehyde (2 mmol) and dimedone (4 mmol) in ethanol (4 mL) was added diethylamine (20 mol%). Stirring was continued at ambient temperature. Upon completion of the reaction [monitored by thin layer chromatography (TLC)], water (10 mL) was added and the resultant solid was filtered, washed with water, dried, washed with hexane–chloroform (9:1, v/v) and dried again. On the basis of comparison of physical and spectroscopic data of the resultant solid with that reported earlier, it was identified to be the desired 1-oxo-hexahydroxanthene, **5a**. During the studies on this model reaction, as targeted 1-oxo-hexahydroxanthene, **5a**, was obtained in excellent yield as well as purity by avoidance of conventional isolation as well as purification procedures and by using diethylamine as a less expensive catalyst, further optimization of the reaction conditions, in particular screening of other basic catalysts for the synthesis of **5a**, was surmised to be unnecessary. However, in pursuance of making this protocol still greener and economical, the model reaction was repeated in water (100 %) as well as a water–ethanol medium (1:2 and 1:1, v/v, respectively), when desired **5a** was obtained in lower yields (63, 58 and 60 %, respectively). Thus, ethanol was selected as the reaction medium for subsequent

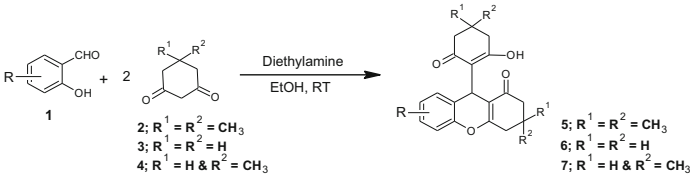


Scheme 1 Diethylamine-catalyzed synthesis of 1-oxo-hexahydroxanthenes

studies. Next, we planned to examine the scope of the developed protocol. Thus, the dimedone component from the aforementioned model reaction was replaced with 1,3-cyclohexanedione, **3**, as well as 5-methylcyclohexane-1,3-dione, **4**. The reactions required slightly longer reaction times; however, upon completion of the reaction, corresponding 1-oxo-hexahydroxanthenes, **6a** and **7a**, were obtained in excellent yields as well as purity. Recently, a model reaction has been performed.

Encouraged with this initial success, we then planned to investigate the generality of the reaction conditions in the synthesis of various 1-oxo-hexahydroxanthene derivatives. Accordingly, under the established reaction conditions, salicylaldehydes bearing electron-withdrawing as well as electron-donating groups were allowed to react with dimedone, cyclohexane-1,3-dione as well as 5-methylcyclohexane-1,3-dione. In all the cases, corresponding 1-oxo-hexahydroxanthene resulted in excellent yields as well as purity (Table 1).

Table 1 Diethylamine catalyzed synthesis of 1-oxo-hexahydroxanthenes[a]

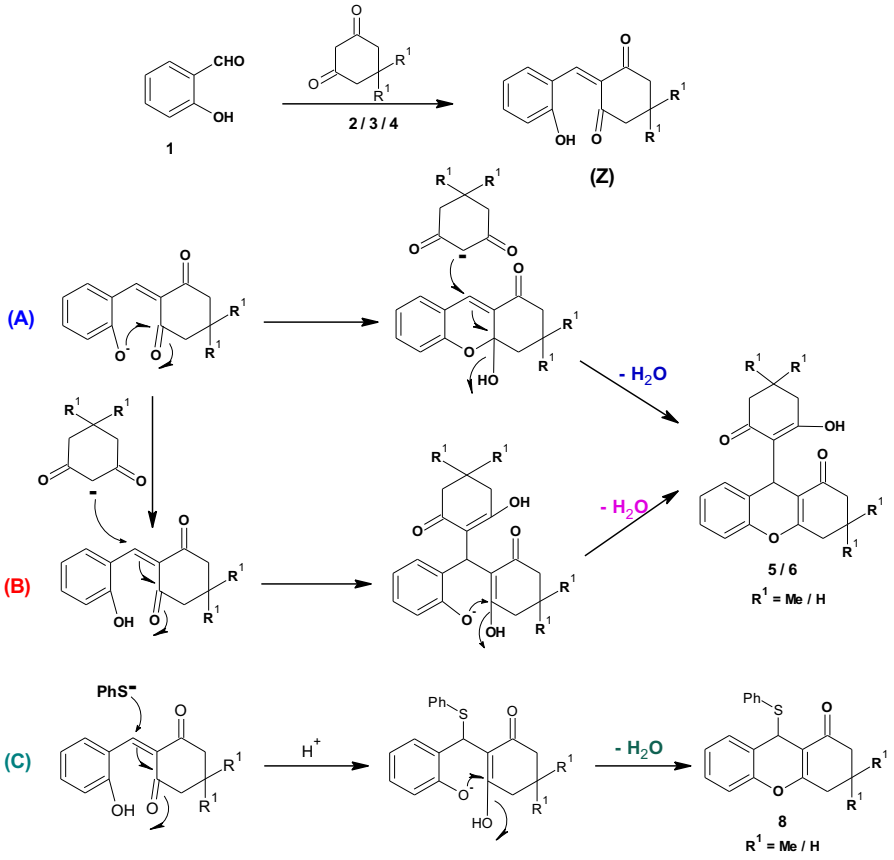


Product	Aldehyde (*R*=)	R^1	R^2	Time (h)	Yield (%)	Melting point (°C)	
						Observed	Lit. References
5a	H	CH_3	CH_3	4.5	92	201–203	204–206 [21]
5b	5-Br	CH_3	CH_3	4.0	90	249–251	251–253 [27]
5c	5-Cl	CH_3	CH_3	4.0	87	232–234	234–236 [25]
5d	3,5-Cl_2	CH_3	CH_3	5.0	85	228–230	227–228 [21]
5e	4-OCH_3	CH_3	CH_3	4.5	87	216–218	215–218 [28]
5f	3-OH	CH_3	CH_3	4.5	85	243–244	245–248 [23]
5g	4-OH	CH_3	CH_3	5.0	87	223–225	225–228 [28]
5h	3-Br-5-NO_2	CH_3	CH_3	6.0	73	228–232	–
5i	5-OCH_3	CH_3	CH_3	4.5	86	181–184	177–181 [20]
5j	4,6-Cl_2	CH_3	CH_3	5.5	78	208–210	–
6a	H	H	H	5.0	84	242–245	242–244 [21]
6b	4-OCH_3	H	H	5.5	81	236–240	–
6c	3-OH	H	H	6.0	80	247–248	–
6d	4-OH	H	H	5.5	79	238–241	242 [23]
6e	4,6-Cl_2	H	H	7.0	65	220–223	–
7a	H	H	CH_3	6.0	82	231–234	–
7b	5-Br	H	CH_3	5.5	81	248–251	–
7c	5-Cl	H	CH_3	5.5	78	241–244	–

[a] Reaction conditions: salicylaldehyde, **1** (2 mmol) and 1, 3-dione (**2/3/4**, 4 mmol), ethanol (4 mL), diethylamine (20 mol%); *RT*

Our primary aim to undertake this work was not limited towards the synthesis of 1-oxo-hexahydroxanthenes but was also to understand the mechanism involved therein for the possible extension of the work towards the synthesis of other biologically active organic compounds. Hence, we turned our attention towards the mechanism of the reaction.

From the mechanistic view point, synthesis of 1-oxo-hexahydroxanthene by pseudo three component condensation between salicylaldehyde and two equivalents of dimedone is believed to proceed by a Knoevenagel–carba–Michael cyclization pathway (Path B, Scheme 2). On the other hand, based upon our earlier success in the synthesis of various 2-amino-*4H*-chromene derivatives [30, 31], we believed that in basic medium the reaction follows a Knoevenagel–cyclization–carba–Michael pathway (Path A, Scheme 2). We surmised that, if the reaction follows Path A, a three-component reaction between salicylaldehyde, dimedone and thiophenol (1 mmol, each) should furnish **8**, as Knoevenagel–cyclization–thia–Michael addition product (Scheme 2c).



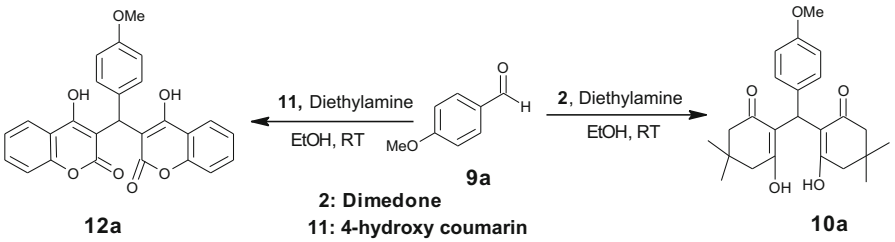
Scheme 2 Plausible pathways for the formation of 1-oxo-hexahydroxanthenes

In an attempt to investigate the correct pathway, a model reaction was carried out between salicylaldehyde, dimedone and thiophenol (1 mmol, each), employing the reaction conditions established for the synthesis of **5a**. Upon completion of the reaction, the resultant product was noticed to be an easily separable mixture of 1-oxo-hexahydroxanthene, **5a**, and **8** (7:3, isolated yields). Thus, it was concluded that in this multicomponent reaction, after the formation of Knoevenagel condensation product, **Z** (Scheme 2), addition of dimedone (carba–Michael) and of thiophenol (thia–Michael) takes place competitively and amongst these, dimedone being more nucleophilic than thiophenol, carba–Michael addition proceeds at a faster rate than thia–Michael addition reaction. To give credence to this supposition, another model reaction was carried out wherein to a stirred solution of salicylaldehyde and thiophenol (1 mmol, each) in ethanol (2 mL) was added dropwise a solution of dimedone (1 mmol) in ethanol (3 mL). The resultant product was once again identified to be the mixture of **5a** and **8** in a 3:2 proportion (isolated yields). Although this success supports the possibility of competitive carba as well as thia–Michael addition in synthesis of **5a** and **8**, respectively, it is not sufficient enough to conclude that the reaction does not follow Path A. Hence, additional experiments were carried out.

Sun and co-workers quite recently reported that in a piperidine-catalyzed reaction between an aldehyde and dimedone, an initial Knoevenagel condensation product, being short-lived, instantaneously undergoes 1,4-conjugate addition with an enolizable ketone like dimedone [36]. With reference to this report, we speculated about similar observation for the reaction between salicylaldehyde and dimedone. Hence, under the established reaction conditions, another model reaction was carried out between salicylaldehyde and dimedone (1 mmol, each). Upon completion of the reaction, as against the Knoevenagel condensation product, we were startled to notice the formation of **5a** as the sole product (43 %, isolated yield). Thus, we concluded that even in the presence of a basic catalyst, formation of 1-oxo-hexahydroxanthene, **5a**, proceeds by Path B and not by Path A. A search of the literature in the context of this reaction mechanism revealed that in ammonium chloride-catalyzed synthesis of **5a** and **8**, Khan and co-workers also proposed Path B [37].

Taking clues from these results, it was surmised that if the reaction follows Path B, the reaction between an aromatic aldehyde devoid of an *ortho* hydroxyl group, e.g. 4-methoxybenzaldehyde, **9a**, with two equivalents of dimedone should furnish 2,2′-(4-phenylmethylene)-bis-(3-hydroxy-3,3-dimethyl-2-cyclohexene-1-one, tetraketone, **10a**, while the similar reaction with the choice of another 1,3-diketone, 4-hydroxycoumarin, **11**, should furnish 3,3′-(4-phenylmethylene)-bis-(4-hydroxycoumarin), **12a**, as Knoevenagel–carba–Michael domino reaction product, respectively (Scheme 3).

In an effort to confirm these speculations, two model reactions were performed employing the reaction conditions established for the synthesis of **5a**, (1) between 4-methoxybenzaldehyde, **9a**, (1 mmol) and dimedone (2 mmol), and (2) between 4-methoxybenzaldehyde, **9a**, (1 mmol) and 4-hydroxycoumarin, **11** (2 mmol). Upon completion of the reactions (monitored via TLC), it was truly gratifying to notice the formation of anticipated tetraketone, **10a**, as well as bis-coumarin, **12a**, in excellent yields. In each case, the resultant solid was simply filtered, washed with



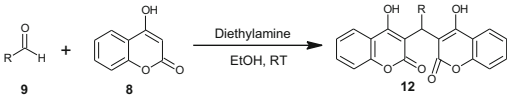
Scheme 3 Diethylamine-catalyzed synthesis of bis-coumarins and tetraketones

water, dried and washed again with hexane–chloroform (9:1, v/v) to obtain pure **10a** and **12a**.

As far as earlier protocols reported for the synthesis of tetraketones and bis-coumarins are concerned, a few interesting reports are noteworthy. For instance, synthesis of tetraketones employing the same reactants has been reported earlier in aqueous medium under catalyst-free conditions at ambient temperature [38]. Logically, we did not pursue to establish generality of the reaction conditions for the synthesis of other tetraketones. On the other hand, synthesis of bis-coumarins has been reported earlier using a variety of catalysts under a range of experimental conditions [39–50]. Interestingly, most of the reported protocols require elevated temperature [39–45] or microwave (MW) irradiation [46–48], while a few of them require the use of an expensive catalyst [49]. Furthermore, their synthesis has although been known to follow a Knoevenagel–carba–Michael domino pathway, to the best of our knowledge, except for piperidine [50], there are no reports on their synthesis using any other basic catalyst. In light of these observations, it was quite evident that development of a protocol that would circumvent the drawbacks associated with most of the earlier reported protocols is essential. The other reason to undertake the synthesis of bis-coumarins was concerned with their well-established biological activities [51–54]. For instance, bis-coumarins are known to exhibit urease inhibitor, anticoagulant as well as snake venom NPP1 inhibitory activity [53]. A few naturally occurring bis-coumarins are known to serve as DNA polymerase beta lyase inhibitor [54]. Hence, we planned to extend the scope of the established reaction conditions towards the synthesis of various bis-coumarins. Accordingly, aromatic aldehydes tethered with electron-withdrawing as well as electron-donating groups and a few heterocyclic aldehydes were allowed to react with 4-hydroxy coumarin. In all the cases, desired bis-coumarin, **12b–k**, was obtained in excellent yields following very simple work-ups as well as purification methods. The results are summarized in Table 2.

Finally, a comparison was made between the protocol developed by us and those reported earlier for the synthesis of **5a** as a model compound. The results summarized in Table 3 clearly reveal the superiority of the protocol developed by us over all other protocols in terms of yield, cost, operational simplicity, etc. On the other hand, to the best of our knowledge, piperidine is the only basic catalyst reported for the synthesis of bis-coumarins, and compared to piperidine, use of diethylamine is certainly advantageous in terms of cost, ease of handling and the toxicity of the catalyst.

Table 2 Diethylamine-catalyzed synthesis of bis-coumarins, **12**



Product	Aldehyde (9)	Time (h)	Yield (%)	Melting point (°C)	
				Obs.	Lit. References
12a	4-Methoxybenzaldehyde	3.0	83	138–140	140–141 [45]
12b	2,5-Dimethylbenzaldehyde	4.0	84	198–200	–
12c	4-Bromobenzaldehyde	3.5	87	260–262	265–267 [40]
12d	6-Nitropiperonal	3.0	83	153–156	–
12e	4-Hydroxybenzaldehyde	4.0	86	205–207	202–204 [51]
12f	4-Nitrobenzaldehyde	5.0	81	228–231	232–234 [45]
12g	Thiophene-2-carbaldehyde	4.0	78	150–152	156–158 [49]
12h	5-Methylfurfural	5.0	80	185–187	–
12i	3-Methyl thiophen-2-carbadehyde	4.0	81	134–136	–
12j	4-Allyloxybenzaldehyde	4.0	79	222–225	–
12k	4-Cyanobenzaldehyde	4.0	89	238–241	240–242 [40]

Reaction conditions: aldehyde (2 mmol), 4-hydroxycoumarin (4 mmol), diethylamine (20 mol%), ethanol (6 mL), RT

Table 3 Comparison between the present protocol and the protocols reported earlier for the synthesis of **5a** as a model compound

No.	Catalyst	Reaction conditions	Time (h)	Yield (%)	References
1	L-Proline	Ethanol, 60 °C	1	98	[23]
2	$[(CH_2)_4\ SO_3H\ HMIM]\ [HSO_4]$	Water, 85 °C	3	95	[22]
3	Cellulose sulfuric acid	SF, RT, grinding	30	96	[20]
4	$CeCl_3$-$7H_2O$	Water, reflux	3	92	[25]
5	2,4,6-Trichloro-1,3,5-triazine	SF,120 °C	3	93	[21]
6	Catalyst-free	Water, reflux	3	90	[27]
7	Catalyst-free	Glycerol, 90 °C	3	84	[26]
9	CH_3COOH	Water, 100 °C	3	89	[17]
10	Heteropolyacid	SF, 120 °C	30	95	[24]
11	Benzyltriethylammonium chloride	Water, 90 °C	3	86	[28]
12	$KF–Al_2O_3$	EtOH, 80 °C	3	83	[29]
13	Diethylamine (20 mol%)	EtOH, RT	4.5	92	This work

Conclusion

In summary, we have developed an operationally simple and environmentally benign protocol for the synthesis of 1-oxo-hexahydroxanthenes as well as bis-coumarins using diethylamine as the catalyst. Excellent yields, easy commercial

availability of the catalyst at an extremely low cost, ambient reaction conditions and avoidance of conventional work-ups as well as purification procedures are the noteworthy advantages of this energy-efficient protocol.

Experimental

General experimental procedure for 5/6/7

To a well stirred solution of salicylaldehyde, **1** (2 mmol) and appropriate 1,3-dione (**2/3/4**, 4 mmol) in ethanol (4 mL) was added diethylamine (20 mol%) and stirring continued. Upon completion of the reaction (TLC), the resultant solid was filtered, washed with water, dried, again washed with a hexane–chloroform mixture (9:1, v/v) and dried. The resultant product, **5/6/7**, was found to be pure for all practical purposes.

General experimental procedure for 12

To a well stirred solution of an aldehyde **9** (2 mmol) and 4-hydroxycoumarin (**11**, 4 mmol) in ethanol (4 mL) was added diethylamine (20 mol%) and stirring was continued at ambient temperature. Upon completion of the reaction (TLC), the resultant solid was filtered, washed with water, dried, washed again with a hexane–chloroform mixture (9:1, v/v) and dried. The resultant bis-coumarins, **12**, were found to be pure for all practical purposes.

Spectral data of new compounds

5-Bromo-3,4-dihydro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-7-nitro-2H-xanthen-1(9H)-one, **5h**: pale yellow solid; M.P.: 228–232 °C; IR (KBr): 3499, 2991, 1720, 1655, 1544, 1487, 1340, 1167, 845 cm^{-1}; [^{1}H-NMR, 300 MHz, deuterated chloroform ($CDCl_3$)]: δ 1.08 (s, 4H), 1.16 (s, 8H), 2.27–2.33 (m, 3H), 2.41 (s, 2H), 2.32–2.39 (m, 3H), 4.83 (s, 1H), 7.78 (s, 1H), 8.29 (s, 1H), 10.38 (brs, 1H); (^{13}C-NMR, 75 MHz, $CDCl_3$): δ 26.19, 27.27, 29.29, 30.00, 32.04, 32.26, 40.91, 46.33, 30.19, 113.23, 114.13, 113.10, 122.86, 124.00, 124.43, 126.13, 127.78, 141.23, 133.13, 137.47, 163.33, 189.90, 198.23 ppm.

6,8-Dichloro-3,4-dihydro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2H-xanthen-1(9H)-one, **5j**: White solid; M. P.: 208–210 °C; IR (KBr): 3455, 2990, 1724, 1644, 1523, 1475, 1323, 1140, 877 cm^{-1}; ^{1}H-NMR : (300 MHz, $CDCl_3$) : δ 0.87 (s, 6H), 1.03 (m, 4H), 1.13 (m, 2H), 2.03–2.06 (m, 3H), 2.14–2.41 (m, 3H), 2.81 (brs, 1H), 4.97 (s, 1H), 6.83 (s, 1H), 6.96–7.01 (m, 1H); ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 23.31, 26.63, 28.37, 29.32, 31.37, 31.98, 48.31, 48.71, 30.94, 31.23, 111.47, 114.41, 124.29, 131.31, 134.04, 143.10, 132.39, 197.13, 198.20 ppm.

3,4-Dihydro-9-(2-hydroxy-6-oxocyclohex-1-enyl)-6-methoxy-2H-xanthen-1(9H)-one, **6b**: White solid; M. P.: 236–240 °C; IR (KBr): 3455, 2990, 1724, 1644, 1523, 1475, 1323, 1140, 877 cm^{-1}; ^{1}H-NMR : (300 MHz, $CDCl_3$) : δ 1.84–1.96 (m, 2H), 2.03–2.14 (m, 4H), 2.41–2.63 (m, 3H), 2.72–2.78 (m, 1H), 3.78 (s, 3H), 4.39 (s, 1H),

6.38–6.92 (m, 2H), 6.91 (d, 1H, $J = 9.1$ Hz), 10.80 (brs, 1H); ^{13}C-NMR: (75 MHz $CDCl_3$) : δ 19.63, 19.94, 27.47, 27.96, 36.02, 33.32, 110.92, 111.03, 112.63, 116.49, 119.79, 128.43, 131.42, 138.92, 170.94, 201.31 ppm.

3,4-Dihydro-5-hydroxy-9-(2-hydroxy-6-oxocyclohex-1-enyl)-2H-xanthen-1(9H)-one, **6c**: White solid; M. P.: 247–248 °C; IR (KBr): 3502, 2996, 1712, 1640, 1568, 1498, 1333, 1145, 878 cm^{-1} ^{1}H-NMR : (300 MHz, $CDCl_3$) : δ 1.71–1.73 (t, 2H, $J = 6.5$ Hz), 1.92–1.96 (t, 2H, $J = 3.5$ Hz), 2.02 (s, 4H), 2.29–2.31 (m, 2H), 2.30–2.61 (m, 1H), 4.83 (s, 1H), 6.41 (d, 1H, $J = 7.4$ Hz), 6.61 (d, 1H, $J = 8$ Hz), 6.67 (t, 1H, $J = 7.8$ Hz); ^{13}C-NMR : (75 MHz, $CDCl_3$) : δ 20.23, 20.40, 26.76, 27.88, 36.89, 112.31, 114.18, 116.39, 118.79, 119.77, 124.00, 126.26, 129.89, 139.06, 144.37, 148.32, 168.43, 198.67 ppm.

6,8-Dichloro-3,4-dihydro-9-(2-hydroxy-6-oxocyclohex-1-enyl)-2H-xanthen-1(9H)-one, **6e**: Solid; M. P.: 220–223 °C; IR (KBr): 3487, 2956, 1630, 1599, 1560, 1341, 1145, 898 cm^{-1}; ^{1}H-NMR : (300 MHz, $CDCl_3$) : δ 1.92–1.98 (m, 3H), 2.00–2.09 (m, 1H), 2.23–2.48 (m, 6H), 2.80 (m, 2H), 4.33 (s, 1H), 7.11(d, 1H, $J = 2.4$ Hz), 7.34 (d, 1H, $J = 2.4$ Hz); ^{13}C-NMR : (75 MHz, $CDCl_3$) : δ 20.07, 20.31, 24.36, 27.46, 34.33, 36.33, 40.17, 49.13, 110.91, 113.98, 121.06, 126.74, 127.13, 127.61, 127.72, 144.94, 168.34, 193.28, 202.67 ppm.

9-(2-Hydroxy-4-methyl-6-oxo-cyclohex-1-enyl)-3-methyl-2,3,4,9-tetrahydro-xanthen-1-one,**7a**: Solid; M. P.: 231–234 °C; IR (KBr): 3499, 2991, 1720, 1655, 1544, 1487, 1340, 1167, 845 cm$^{-1;}$ ^{1}H-NMR: [300 MHz, deuterated dimethyl sulfoxide (DMSO-d_6)]: δ 0.85 (d, 3H, $J = 4.1$ Hz), 0.95(d, 3H, $J = 6.1$ Hz), 1.87 (s, 4H), 2.03–2.26 (m, 6H), 5.04 (s, 1H), 6.75–6.81(m, 2H), 6.90–6.99 (m, 2H); ^{13}C-NMR : (75 MHz, $CDCl_3$) : δ 20.87, 21.38, 26.10, 27.77, 28.41, 36.00, 45.42, 113.05, 115.00, 117.77, 123.81, 126.03, 127.78, 128.96, 150.25, 197.89 ppm.

7-Bromo-9-(2-hydroxy-4-methyl-6-oxo-cyclohex-1-enyl)-3-methyl-2,3,4,9-tetrahydro-xanthen-1-one, **7b**: Solid; M. P.: 248–251 °C; IR (KBr): 3445, 2915, 1714, 1601, 1561, 1544, 1333, 1112, 840 cm^{-1}; ^{1}H-NMR : (300 MHz, DMSO-d_6) : δ 0.90 (d, 3H, $J = 3.1$ Hz), 1.02 (d, 3H, $J = 3.9$ Hz), 1.89–2.02 (m, 4H), 2.13–2.30 (m, 4H), 2.50–2.64 (m, 2H), 4.96 (s, 1H), 6.39 (d, 1H, $J = 7.1$ Hz), 6.57 (d, 1H, $J = 6.8$ Hz), 6.66 (t, 1H, $J = 7.7$ Hz); ^{13}C-NMR : (75 MHz, DMSO-d_6) : δ 20.84, 20.95, 26.13, 27.92, 28.06, 35.93, 45.31, 111.85, 113.98, 118.70, 119.30, 123.94, 126.68, 138.94, 144.61, 166.87, 197.07 ppm.

7-Chloro-9-(2-hydroxy-4-methyl-6-oxo-cyclohex-1-enyl)-3-methyl-2,3,4,9-tetrahydro-xanthen-1-one, **7c**: Solid; M. P.: 241–244 °C; IR (KBr): 3488, 2992, 1712, 1610, 1567, 1515, 1340, 11,122, 878 cm^{-1}; ^{1}H-NMR : (300 MHz, DMSO-d_6) : δ 0.90 (s, 3H), 1.01 (s, 3H), 2.04 (s, 4H), 2.27 (s, 4H), 2.51 (s, 2H), 5.04 (s, 1H), 6.92 (s, 1H), 7.01 (s, 1H), 7.16 (s, 1H), 10.71 (s, 1H); ^{13}C-NMR : (75 MHz, DMSO-d_6) : δ 20.74, 20.86, 25.94, 28.11, 28.28, 35.47, 45.22, 111.53, 117.78, 127.32, 128.07, 128.37, 148.91, 166.44, 196.27 ppm.

2-Hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(2,5-dimethylphenyl)methyl)-4H-chromen-4-one, **12c**, Solid; M. P.: 198–200 °C; IR (KBr): 3434, 2972, 1645, 1614, 1565, 1510, 1321, 1132, 876 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.03 (s, 3H), 2.18 (s, 3H), 5.60 (s, 1H), 6.09 (s, 1H), 6.88 (d, 1H, $J = 7.5$ Hz), 6.96 (d, 1H, $J = 7.3$ Hz), 7.03 (s, 1H), 7.30 (d, 1H, $J = 7.3$ Hz), 7.34 (s, 1H), 7.37 (s, 1H),

7.58 (t, 2H, $J = 7.7$ Hz), 7.62 (d, 1H, $J = 8.0$ Hz), 7.82 (d, 1H, $J = 7.7$ Hz), 7.91 (d, 2H, $J = 7.8$ Hz), 12.56 (brs, 1H); ^{13}C-NMR : (75 MHz, DMSO-d_6): δ 19.56, 21.44, 36.19, 91.48, 104.84, 116.26, 116.47, 116.81, 117.88, 123.66, 124.19, 124.23, 124.36, 127.12, 128.72, 130.82, 132.29, 133.13, 133.36, 134.49, 152.56, 153.98, 162.35, 164.39, 164.62, 166.10 ppm.

2-Hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(6-nitrobenzo[d] [1, 3] dioxol-6-yl)methyl)-4H-chromen-4-one, **12d**, solid; M. P.: 203–205 °C; IR (KBr): 3465, 2948, 1651, 1610, 1555, 1532, 1505, 1367, 1155, 865 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 5.59 (s, 1H), 6.10 (s, 2H), 6.71 (d, 1H, $J = 4.0$ Hz), 6.88 (d, 1H, $J = 2.1$ Hz), 7.20 (d, 1H, $J = 2.5$ Hz), 7.23 (s, 2H), 7.25 (d, 2H, $J = 3.4$ Hz), 7.28 (d, 1H, $J = 2.6$ Hz), 7.32 (d, 1H, $J = 2.2$ Hz), 7.52 (t, 2H, $J = 8.3$ Hz), 7.92 (d, 2H, $J = 8.0$ Hz); ^{13}C-NMR: (300 MHz, DMSO-d_6) (75 MHz, DMSO-d_6): δ 39.78, 96.27, 107.99, 109.51, 110.51, 114.30, 121.09, 121.15, 121.68, 128.28, 128.57, 137.05, 137.24, 147.99, 151.20, 156.01, 157.27, 158.70, 168.59, 169.11, 170.82 ppm.

2-Hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(5-methylfuran-2-yl)methyl)-4H-chromen-4-one, **12h**, solid, M. P.:185–187 °C; IR (KBr): 3445, 2943, 1654, 1621, 1532, 1499, 1353, 823 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.13 (s, 3H), 5.85 (s, 1H), 5.96 (s, 1H), 6.10 (d, 1H, $J = 3.1$ Hz), 7.27 (s, 1H), 7.29 (s, 2H), 7.31 (s, 1H), 7.54 (t, 2H, $J = 7.6$ Hz), 7.93 (d, 2H, $J = 7.6$ Hz), 11.50 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 13.63, 32.00, 103.51, 106.32, 107.98, 116.46, 116.62, 124.17, 124.62, 132.71, 151.28, 152.31, 164.31, 166.54 ppm.

2-Hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(3-methylthiophene-2-yl)methyl)-4H-chromen-4-one, **12i**, Solid, M. P.: 134–136 °C; IR (KBr): 3455, 2988, 1674, 1612, 1514, 1491, 1377, 888 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 2.13 (s, 3H), 5.85 (s, 1H), 5.96 (s, 1H), 6.10 (d, 1H, $J = 3.1$ Hz), 7.27 (s, 1H), 7.29 (s, 2H), 7.31 (s, 1H), 7.54 (t, 2H, $J = 7.6$ Hz), 7.93 (d, 2H, $J = 7.6$ Hz), 11.50 (brs, 2H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 13.58, 32.95, 104.46, 107.27, 108.93, 117.41, 117.57, 125.12, 125.57, 133.66, 148.78, 152.53, 153.26, 165.26, 167.49 ppm.

3-((4-(Allyloxy)phenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-4-hydroxy-2H-chromen-2-one, **12j:** Solid; M. P.: 230–232 °C; IR (KBr): 3435, 2917, 1640, 1612, 1545, 1490, 1342, 808 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.53 (d, 2H, $J = 5.4$ Hz),5.28 (dd, 1H, $J = 9.2$ & 10.5 Hz), 5.41 (dd, 1H, $J = 17.1$ & 15.4 Hz), 5.99–6.12 (m, 1H), 6.87 (d, 2H, $J = 8.8$ Hz), 7.12 (d, 2H, $J = 8.2$ Hz), 7.41 (s, 2H), 7.44 (s, 2H), 7.61–7.67 (m, 2H), 8.02 (d, 1H, $J = 8.0$ Hz), 8.09 (d, 1H, $J = 7.7$ Hz), 11.31 (s, 1H), 11.50 (s, 1H); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 35.53, 68.74, 104.20, 105.81, 114.80, 116.57, 117.59, 124.41, 124.74, 127.04, 127.57, 132.65, 133.31, 152.28, 157.46, 164.39, 165.51, 166.63 ppm.

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