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Synthesis of xanthene and coumarin derivatives in water by using β-Cyclodextrin

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Abstract

Simple and green procedure was developed for the synthesis of various xanthene and coumarin derivatives using beta-cyclodextrin (*β*-CD) as reusable catalyst at 70 °C in water. Condensation of salicylaldehyde (1 mmol) and dimedone (2 mmol) or 1,3 cyclohexadione (2 mmol) gave corresponding xanthene derivatives, while condensation of salicylaldehyde (1 mmol) with Meldrum's acid (1 mmol) or 4-Hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) gave respective coumarin derivatives in impressive yields. Involvement of *β*-CD as catalyst was ascertained by inclusion complex evaluation of *β*-CD-salicylaldehyde with ^{1}H NMR analysis at 70 °C.

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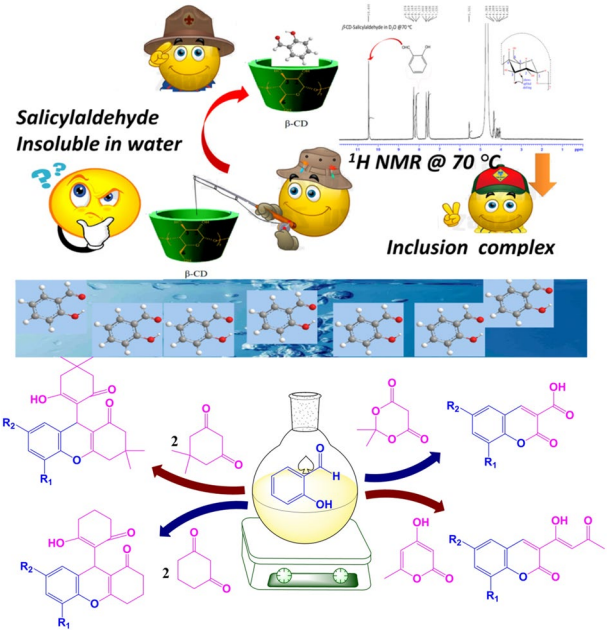
Graphic abstract



Keywords β-CD · Inclusion complex · ^{1}H NMR analysis · Xanthenes · Coumarins

Introduction

Xanthene derivatives have engrossed enormous interest in the field of medical and material chemistry in last few decades [1]. Novel methodologies and number of catalysts have been reported for the synthesis of xanthene derivatives [2]. The catalyst like CsF [3], L-proline [4], PTSA [5], nanoparticles [6–8], ionic liquid [9–11], tetra-n-butylammonium fluoride [12], cellulose sulfuric acid [13], $CeCl_3$-$7H_2O$

Table 1 Literature review on cyclodextrin used in organic synthesis as catalyst

Sr. no	Organic synthesis	Catalyst	Refs
1	Synthesis of xanthenes	Cyclodextrin nanosponges	S. Sadjadi, et al. [39]
2	Enantioselective reduction of ketones	Fe_3O_4@SiO_2/Pr-β-CD	M. J. Nasab et al. [40]
3	Synthesis of spirooxindoles	β-cyclodextrin (Fe_3O_4/COS@β-CD-SO*3*H NPs)	B. Akhlaghinia et al. [41]
4	Synthesis of chromeno[4,3-b]quinolin-isonicotinamides	β-cyclodextrin	M. R. Bhosle et al. [42]
5	Synthesis of kojic acid-based heterocyclic compounds	β-cyclodextrin nanosponge	R. Kardooni et al. [43]

[14], 2,4,6-Trichloro-1,3,5-Triazine [15], TEBA [16] have been used. The catalyst-free synthesis of these derivatives has been described in water [17] and DMF [18]. Coumarin-based organic molecules [19] are known to have biological activity such as antianaphylactic, anticoagulant, diuretic [20], anticonvulsant [21], antimicrobial [22] and insecticidal properties [23]. Coumarin derivatives are extensively used as laser dye and optical brighteners [24]. Reported syntheses of coumarins include the use of biosurfactant [25], L-prolin [26], ionic liquid [27, 28], K_3PO_4 [29], $FeCl_3$ [30], ZnS nanoparticles immobilized on graphitic carbon nitride [31], poly(4-styrenesulfonic acid) mesoporous graphene oxide [32] and $Fe_3O_4@SiO_2@(CH_2)_3$-urea-benzimidazole with sulfonic acid [33]. Cyclodextrins are cyclic oligosaccharides, history of the cyclodextrins (CD's) as supramolecule is very fascinating [34]. Hydrophobic cavities of β-CD hold the organic compounds selectively and assess the organic reactions with good selectivity [35–38]. Among the α, β and γ cyclodextrins (CD's), β-CD has been extensively used in organic synthesis as catalyst. Some reported methodologies are summarized below (Table 1).

Experimental

β-CD was purchased from Himedia, and all remaining chemicals from Sigma Aldrich, Spectrochem, s. d. Fine chemical Limited (India). These chemicals were used as such exclusive of extra purification. Melting points were determined in an open capillary and are uncorrected. Infrared spectra were recorded on PerkinElmer FT-IR spectrometer (KBr discs ~ 5% *w/w*). NMR spectra were recorded on Bruker Avon 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference. ^{1}HNMR spectra of β-CD and β-CD-salicylaldehyde inclusion complex were recorded on Bruker Avon 400 MHz spectrometer using D_2O as solvent and tetramethylsilane as internal reference.

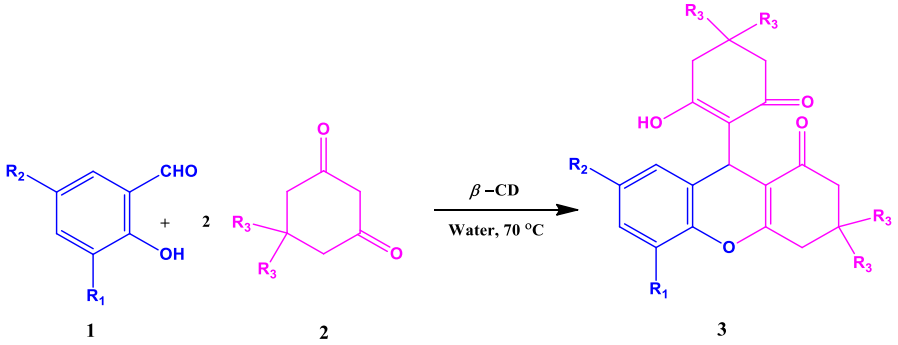
General procedure for synthesis of xanthene derivatives

β-CD (1.135 gm, 1 mmol) was dissolved in water (15 mL) at 70 °C, and to this solution, salicylaldehyde (0.122 g, 1 mmol) and dimedone (0.280 g, 2 mmol) were added in 50-mL-round bottom flask. The reaction mixture was stirred at 70 °C till the reaction was completed (monitored by TLC, ethyl acetate: petroleum ether: 2:8). The reaction mixture was extracted with chloroform (3 × 15 mL), and the organic layer was dried over anhydrous Na_2SO_4. After removal of solvent, crude product was obtained and recrystallized with 95% EtOH.

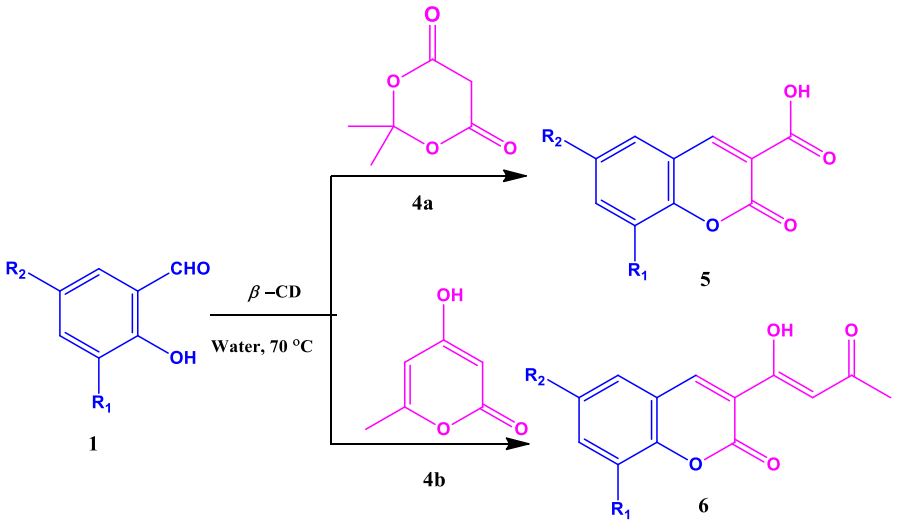
The reusability of β-CD as reaction medium was found to be suitable for five times with no noteworthy loss in yield of product.

General procedure for synthesis of coumarin derivatives

β-CD (1.135 g, 1 mmol) was dissolved in water (15 mL) at 70 °C and to this solution salicylaldehyde (0.122 g, 1 mmol), and Meldrum's acid (0.144 g, 1 mmol) or



Scheme 1 Synthesis of xanthenes derivatives



Scheme 2 Synthesis coumarin derivatives

4-Hydroxy-6-methyl-2H-pyran-2-one (0.126 g, 1 mmol) were added in 50-mL-round bottom flask. The reaction mixture was stirred till the reaction was completed (monitored by TLC, ethyl acetate: petroleum ether: 2:8). Further steps are similar as mentioned above for synthesis of xanthene derivatives.

Table 2 Optimization of the reaction temperature for the synthesis of 1-oxo-hexahydroxanthene derivatives[a]

Entry	β-CD (mmol)	Time (Min)	Temp. (°C)	Yield[b] (%)
1	–	120	rt	Nil
2	1	90	rt	40
3	1	75	40	52
4	1	70	50	69
5	1	65	60	88
6	1	50	70	95
7	1	50	80	94
8	1	50	90	93

rt: room temperature = 25–28 °C

[a]Reaction condition: Salicylaldehyde (1 mmol), dimedone (2 mmol), β-CD (1 mmol), 15 mL water

[b]Isolated yield of product

Table 3 Synthesis of xanthene derivatives by using β-CD at 70 °C temperature in water[a]

Entry	R_1	R_2	R_3	Product	Time (min.)	Yield [b](%)	Mp (°C)		Refs
							Found	Lit	
1	H	H	CH_3	3a	50	95	208–210	210–212	[15]
2	H	NO_2	CH_3	3b	15	95	204–206	203–205	[15]
3	OMe	H	CH_3	3c	30	94	230–232	229–231	[15]
4	OMe	NO_2	CH_3	3d	60	84	212–214	–	–
5	OEt	H	CH_3	3e	30	92	188–190	–	–
6	H	Br	CH_3	3f	15	93	250–252	251–253	[15]
7	H	Cl	CH_3	3 g	15	94	234–236	236–268	[15]
8	Cl	Cl	CH_3	3 h	60	85	250–252	236–237	[15]
9	H	H	H	3i	50	92	246–248	245–246	[16]
10	H	NO_2	H	3j	25	93	244–246	244–246	[15]
11	OMe	H	H	3 k	30	92	195–197	–	–
12	OMe	NO_2	H	3 l	90	82	210–212	–	–
13	OEt	H	H	3 m	30	92	220–222	–	–
14	H	Br	H	3n	20	90	240–242	238–239	[15]
15	H	Cl	H	3o	20	92	215–217	217–219	[15]
16	Cl	Cl	H	3p	90	82	252–254	255–256	[15]
17	2OH-naphthalene-1-carbaldehyde		CH_3	3q	60	82	242–246	240–242	[15]

[a]Reaction conditions: salicylaldehyde (1 mmol), dimedone (2 mmol) or 1,3-cyclohexadione, β-CD (1 mmol), solvent water (15 mL) at 70 °C temperature

[b]Isolated yield of product

Results and discussion

Condensation of various salicylaldehyde (1 mmol) with dimedone (2 mmol) or 1,3-cyclohexadione (2 mmol) gave xanthene derivatives (scheme 1), whereas condensation of salicylaldehydes (1 mmol) with Meldrum's acid (1 mmol) or 4-Hydroxy-6-methyl-2H-pyran-2-one (1 mmol) gave respective coumarin derivatives (scheme 2).

To assure the catalytic activity of β-CD, some series of experiments were performed (Table 2). Initially, the reaction in between salicylaldehyde (1 mmol) and dimedone (2 mmol) was carried out as model reaction without using any catalyst in water at room temperature; no product formation was observed. Subsequently with β-CD (1 mmol) as catalyst the model reaction formed the corresponding product very less amount (40%). The yield of the product was observed to be improved with the increase in reaction temperature and was maximum at 70 °C. This might be due to complete solubilization of β-CD at 70 °C forming homogeneous solution of β-CD in water which lead to form the inclusion complex with substrate molecules via host–guest infarctions. There was negligible change in yield of the product above the 70 °C. The instability of inclusion complex of β-CD with substrate (dimedone) in model reaction at higher temperature leads to decrease in the yield of product above the 70 °C.

The scope and applicability of present protocol was examined for various salicylaldehydes such as salicylaldehyde, 5-Nitro-salicylaldehyde, 3-Methoxy salicylaldehyde, 3-Ethoxy-salicylaldehyde, 5-Bromo-salicylaldehyde, 5-Chloro-salicylaldehyde, 3,5-Dichloro-salicylaldehyde, 3-Methoxy-5-Nitro salicylaldehyde

Table 4 Synthesis of coumarin derivatives by using β-CD at 70 °C temperature in water[a]

Entry	1		4	Product	Time (min.)	Yield[b] (%)	Mp (°C)		Ref
	R_1	R_2					Found	Lit	
1	H	H	4a	5a	20	98	190–192	180–190	[24]
2	OMe	H	4a	5b	15	97	218–220	216–217	[24]
3	OEt	H	4a	5c	15	95	176–178	–	–
4	H	Br	4a	5d	30	96	194–196	196–194	[24]
5	H	Cl	4a	5e	20	98	118–120	120–122	[24]
6	H	H	4b	6a	30	97	144–146	144–145	[28]
7	H	NO_2	4b	6b	40	96	210–212	–	–
8	OMe	H	4b	6c	15	97	172–174	170–172	[28]
9	OEt	H	4b	6d	15	98	202–204	–	–
10	Cl	Cl	4b	6e	50	85	200–202	198–200	[28]
11	2OH- naphthalene-1-carbaldehyde		4b	6f	30	94	222–224	–	–

[a]Reaction conditions: salicylaldehyde (1 mmol), Meldrum's acid or 4-Hydroxy-6-methyl-2H-pyran-2-one (1 mmol), β-CD (1 mmol), solvent water (15 mL) at 70 °C temperature

[b]Isolated yield of product

and 2-Hydroxy-1-naphthyladehyde. The observations and results are presented in Table 3. The monosubstituted salicylaldehydes such as 5-Nitro-salicylaldehyde, 3-Methoxy salicylaldehyde, 3-Ethoxy-salicylaldehyde, 5-Bromo-salicylaldehyde, 5-Chloro-salicylaldehyde reacts very efficiently and yield the corresponding crude products more than 90% (Table 3).

However, 3-Methoxy-5-Nitro salicylaldehyde, 3,5-Dichloro salicylaldehyde, and 2-Hydroxy-1-naphthyladehyde reacts slowly to yield the corresponding xanthene derivatives in poor yield (Table 3, entry 4, 12, 16, 17).

The unfortunate results showed that the disubstituted salicylaldehyde and polynuclear aldehydes are not that much suitable for above optimized reaction conditions. This is due to larger size of substrate (disubstituted salicylaldehyde and polynuclear aldehydes) which could not fit themselves in the hydrophobic cavity of *β*-CD and hence forms unstable inclusion complex via host–guest interaction. The unstable inclusion complex of *β*-CD with substrate leads to increase the duration of reaction, poor yield of product. Those substrates remain outside the hydrophobic cavity of *β*-CD due to unstable inclusion complex formation not converted in to the product hence leads to poor yield of product.

Inspired by previous results obtained for the synthesis of 1-oxo-hexahydroxanthene derivatives (scheme 1), we extended the use of *β*-CD as green and sustainable catalyst for the synthesis 3-carboxycoumarins and 3-acetoacetylcoumarin derivatives. Substituted salicylaldehydes such as 5-Nitro-salicylaldehyde, 3-Methoxy salicylaldehyde, 3-Ethoxy-salicylaldehyde, 5-Bromo-salicylaldehyde, 5-Chloro-salicylaldehyde, 3,5-Dichloro-salicylaldehyde and 2-Hydroxy-1-naphthyladehyde generates corresponding coumarin derivatives.

3,5-Dichloro salicylaldehyde and 2-Hydroxy-1-naphthyladehyde react slowly to yield the corresponding coumarin derivatives in poor yield (Table 4, entry 10–11). The reactivity of salicylaldehyde is not affected by the nature of functional group attached. The all active methylene substrates dimedone,1,3-cyclohexadione, Meldrum's acid or 4-Hydroxy-6-methyl-2*H*-pyran-2-one are found to be very comfortable with electron donating as well as electron withdrawing functional groups. As discussed earlier in some reactions, yield is poor due to larger size of salicylaldehyde. These observations support the importance of stable inclusion complex of *β*-CD during completion of reaction.

The isolated crude product of xanthene as well as coumarin derivatives were recrystallized with 95% EtOH and further analyzed with IR, ^{1}H NMR, ^{13}C NMR spectra to confirm the proposed structures of the synthesized compounds. Spectral analyses of some representative compounds are summarized below.

Spectral analysis

5-Methoxy-7-nitro-9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**3d**); IR (KBr, cm^{-1}): υ_{max} 3420, 2962, 1668, 1637, 1615, 1518, 1489, 1450, 1370,1334, 1301, 1269, 1198, 1163, 1100, 1065, 1019, 889, 743, 576; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (1H, brs), 759–7.67 (2H, m), 4.91 (1H, s), 3.94 (3H, s), 2.55 (3H, s), 2.42 (2H, s), 2.28–2.30 (3H, m), 1.05

(6H, s), 1.14 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 189.6, 164.4, 150.1, 148.6, 140.9, 130.6, 118.4, 117.2, 115.2, 114.0, 105.3, 104.3, 56.3, 50.4, 40.9, 32.1, 31.3, 29.6, 29.2, 27.2, 26.1.

5-Ethoxy-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**3e**); IR (KBr, cm^{-1}): υ_{max} 3270, 2965, 1635, 1580, 1377, 1271, 1229, 1089, 1072; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (1H, bs), 6.93 (1H, t, J = 7.8 Hz, J = 7.8 Hz), 6.77 (1H, d, J = 8.1 Hz), 6.59 (1H, d, J = 7.5 Hz), 4.64 (1H, s), 4.10–4.17 (2H, m), 2.54–2.72 (2H, m),. 2.34–2.39 (4H, m), 1.99 (2H, s), 1.65 (1H, s), 1.47 (3H, t, J = 6.0 Hz, J = 6.0 Hz), 1.14 (3H, s), 1.01–1.14 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9, 196.5, 170.5, 169.0, 146.5, 141.1, 125.2, 124.1, 119.8, 118.2, 112.2, 110.8, 64.9, 50.6, 49.6, 43.2, 41.5, 32.2, 30.9, 29.8, 29.1, 27.8, 27.1, 26.4, 14.8.

9,10-dihydro-12-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-9,9-dimethyl-8H-benzo[a]xanthen-11(12H)-one (**3q**); IR (KBr, cm^{-1}): υ_{max} 3174, 2932, 1642, 1591, 1372, 1314, 1260, 1234, 1011, 1025, 812, 746, 609; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.65 (1H, s), 7.71–7.79 (3H, m), 7.45–7.50 (1H, m), 7.36–7.41 (1H, m), 7.26–7.28 (1H, m), 5.28 (1H, s), 2.40–2.72 (2H, m), 2.34 (2H, s), 1.80–2.06 (2H, m), 1.57 (2H, s), 1.28 (3H, s), 1.08–1.17 (3H, s), 0.87–0.95 (3H, m), 0.733 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.29, 196.97, 170.44, 149.00, 131.41, 131.12, 128.49, 126.70, 124.59, 122.85, 117.72, 116.54, 116.17, 111.23, 50.91, 50.17, 43.22, 41.50, 32.32, 30.59, 29.85, 29.27, 27.03, 26.46, 25.48.

5-Methoxy-9-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**3 k**); IR (KBr, cm^{-1}): υ_{max} 3120, 2952, 2833, 1644, 1614, 1597, 1582, 1479, 1458, 1437, 1422, 1372, 1330, 1275, 1190, 1133, 1096, 980, 934, 854, 830, 758, 747, 643, 587, 529; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.86 (1H, bs), 6.96 (1H, t, J = 9 Hz, J = 9 Hz), 6.78 (1H, d, J = 7.8 Hz), 6.18 (1H, d, J = 7.8 Hz), 4.65 (1H, s), 3.91 (3H, s), 2.39–2.89 (6H, m), 2.02–2.10 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.03, 201.46, 197.09, 170.83, 146.93, 125.57, 124.29, 119.82, 119.66, 112.15, 110.36, 100.34, 56.10, 36.03, 28.02, 19.99, 19.69.

5-Methoxy-7-nitro-9-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**3 l**); IR (KBr, cm^{-1}): υ_{max} 3463, 2950, 1671, 1655, 1588, 1523, 1490, 1359, 1335, 1269, 1176, 1095, 953, 865, 744; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.30 (1H, brs), 7.57 (2H, d, J = 11.4 Hz), 4.92 (1H, s,), 3.94 (3H, s), 2.66–2.79 (4H, m), 2.44 (4H, bs), 2.0 (4H, bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 166.1, 150.3, 148.8, 140.9, 130.7, 116.9. 115.3, 105.4, 56.8, 36.5, 27.2, 25.9, 20.0.

5-Ethoxy-9-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**3 m**); IR (KBr, cm^{-1}): υ_{max} 2953, 1640, 1580, 1371, 1288, 1220, 1187, 1080, 752; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.81 (1H, bs), 6.93 (1H, t, J = 7.8, J = 7.8 Hz), 6.771 (1H, d, J = 8.1 Hz), 6.60 (1H, d, J = 7.5 Hz), 4.64, (1H, s), 4.10–4.17 (2H, m), 2.43–2.83 (7H, m), 2.0–4-2.14 (4H, m), 1.45–1.85 (5H, m); ^{13} CNMR (75 MHz, $CDCl_3$): δ 201.40, 196.90, 172.60, 171.00, 146.30, 140.90, 125.60, 124.20, 119.90, 119.70, 112.20, 112.10, 64., 37.00, 36.00, 29.70, 28.00, 19.60, 14.80.

8-Methoxy-2-oxo-2H-chromene-3-carboxylic acid (**5b**); IR (KBr, cm^{-1}): υ_{max} 3464, 2916, 1748, 1673, 1603, 1507, 1470, 1418, 1368, 1282, 1099, 1028, 960, 815; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.31 (1H, bs), 8.94 (1H, s, CH), 7.39–7.45 (1H,

m), 7.30–7.34 (2H, m), 4.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.72, 162.46, 151.73, 147.41, 144.16, 126.18, 121.34, 119.11, 117.08, 115.04, 56.49.

8-Ethoxy-2-oxo-2H-chromene-3-carboxylic acid (**5c**); IR (KBr, cm^{-1}): υ_{max} 3445, 2923, 1747, 1600, 1419, 1373, 1287, 1208, 1108, 1004, 817; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.36 (1H, s), 8.94 (1H, s), 7.28–7.42 (3H, m), 4.21–4.28 (2H, m), 1.55 (3H, t, J = 6.9 Hz, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.90, 162.52, 151.78, 146.82, 144.34, 129.84, 127.55, 126.14, 121.23, 119.20, 118.17, 114.93, 65.32, 14.64.

8-Nitro-3-acetoacetylcoumarin (**6b**); IR (KBr, cm^{-1}): υ_{max} 1741, 1610, 1576, 1529, 1479, 1425, 1344, 1280, 1187, 1107, 999, 925, 822; ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.75 (1H, s), 8.73 (1H, s), 8.48–8.61 (2H, m), 7.52 (1H, d, J = 9.3), 7.02 (1H, s), 2.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.67, 169.81, 157.43, 156.48, 144.37, 143.69, 129.86, 128.14, 127.58, 125.16, 122.83, 118.50, 117.85, 102.22, 27.89.

8-Methoxy-3-acetoacetylcoumarin (**6c**); IR (KBr, cm^{-1}): υ_{max} 1748, 1608, 1558, 1507, 1363, 1183, 1116, 1034, 816; ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.92 (1H, s), 8.65 (1H, s), 7.29–7.32 (1H, m), 7.17–7.22 (2H, m), 7.07 (1H, s), 4.01 (3H, s), 2.29 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.95, 171.82, 157.53, 146.95, 145.69, 144.03, 124.81, 120.75, 119.13, 115.37, 101.78, 56.35, 27.65.

8-Ethoxy-3-acetoacetylcoumarin (**6d**); IR (KBr, cm^{-1}): υ_{max} 1748, 1601, 1507, 1472, 1419, 1364, 1183, 1110, 1034, 1003, 815; ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.89 (1H, s), 8.64 (1H, s), 7.18–7.28 (3H, m), 7.06 (1H, s), 4.19–4.26 (2H, m), 2.29 (3H, s), 1.53 (3H, t, J = 7.2, J = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.86, 171.99, 157.70, 146.30, 145.76, 144.23, 124.79, 120.68, 119.22, 116.61, 101.72, 65.08, 27.62, 14.73.

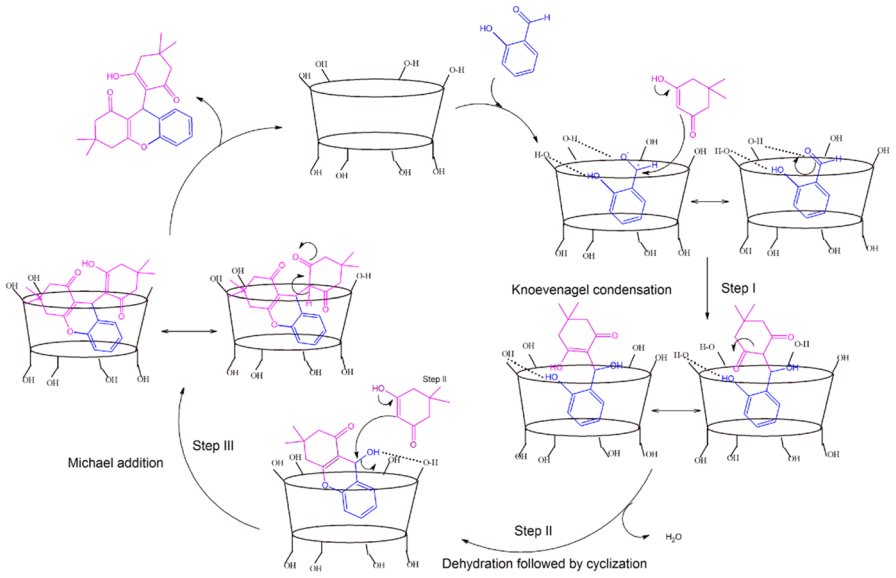


Fig. 1 Plausible reaction mechanism of synthesis of xanthene derivatives

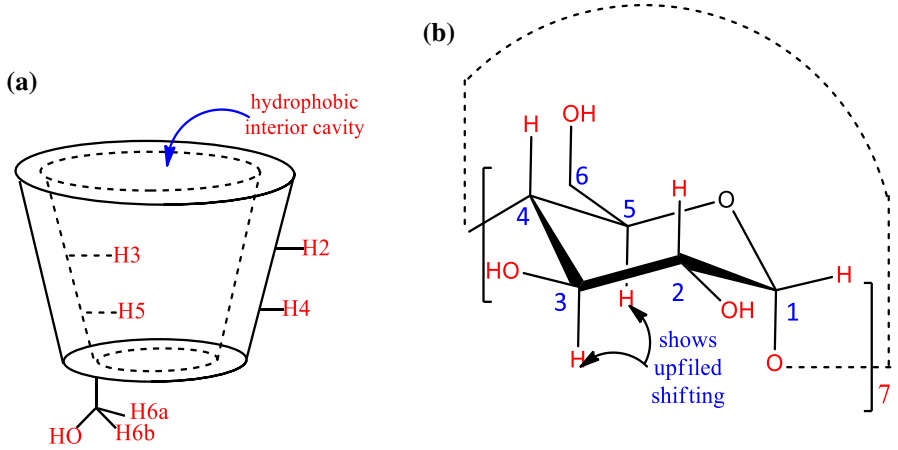


Fig. 2 **a** Schematic side view of cyclodextrin, **b** α-D-glucopyranose unit in cyclodextrin

6,8-Dichloro-3-acetoacetylcoumarin (**6e**); IR (KBr, cm^{-1}): υ_{max} 1748, 1608, 1574, 1416, 1365, 1273, 1183, 1096, 1011, 829; ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.76 (1H, s), 8.56 (1H, s), 7.68 (1H, d J = 3.0 Hz), 7.55 (1H, d J = 3.0 Hz), 7.02 (1H, s), 2.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.49, 170.24, 156.31, 148.59, 143.49, 133.50, 130.07, 127.00, 122.57, 122.50, 120.27, 102.17, 27.80.

2-(1-hydroxy-3-oxobut-1-en-1-yl)-3H-benzo[f]chromen-3-one (**6f**); IR (KBr, cm^{-1}): υ_{max} 1736, 1601, 1567, 1471, 1434, 1350, 1271, 1177, 1092, 966, 820; ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.08 (1H, bs), 9.45 (1H, s), 8.40 (1H, d, J = 9.0), 8.10 (1H, d, J = 9.0), 7.95 (1H, d, J = 6), 7.77 (1H, t, J = 7.8 Hz, J = 7.8 Hz), 7.63 (1H, t,, J = 7.5 Hz, J = 7.5 Hz), 7.49 (1H, d, J = 9 Hz), 2.31 (3H, s), 7.12 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.40, 172.64, 158.16, 154.91, 140.96, 135.79, 130.26, 129.42, 129.19, 129.08, 126.60, 121.74, 118.97, 116.48, 113.04, 101.49, 27.47.

Reaction mechanism

β-CD speed up the enolization of active methylene compounds (dimedone/ 1,3 cyclohexadione) (**2**) and facilitate domino Knoevenagel condensation (step–I) reaction forming the intermediate, which further cyclize after dehydration (step-II). In step-III, Michael addition reaction of the second molecule of active methylene compound (**2**) and cyclized product gives corresponding 1-oxo-hexahydroxanthene derivative (**3**) (Fig. 1).

β-CD-salicylaldehyde inclusion complex forms via host–guest interaction which leads to solubilize the salicylaldehyde in water and accelerate product formation. The host–guest interactions in between β-CD and salicylaldehyde were confirmed by ^{1}H NMR analysis.

The **H3** and **H5** protons of α-D-glucopyranose unit in cyclodextrin show more upfield shift compared to **H2** and **H4** protons (Fig. 2a,b). The **H2** and **H4** protons

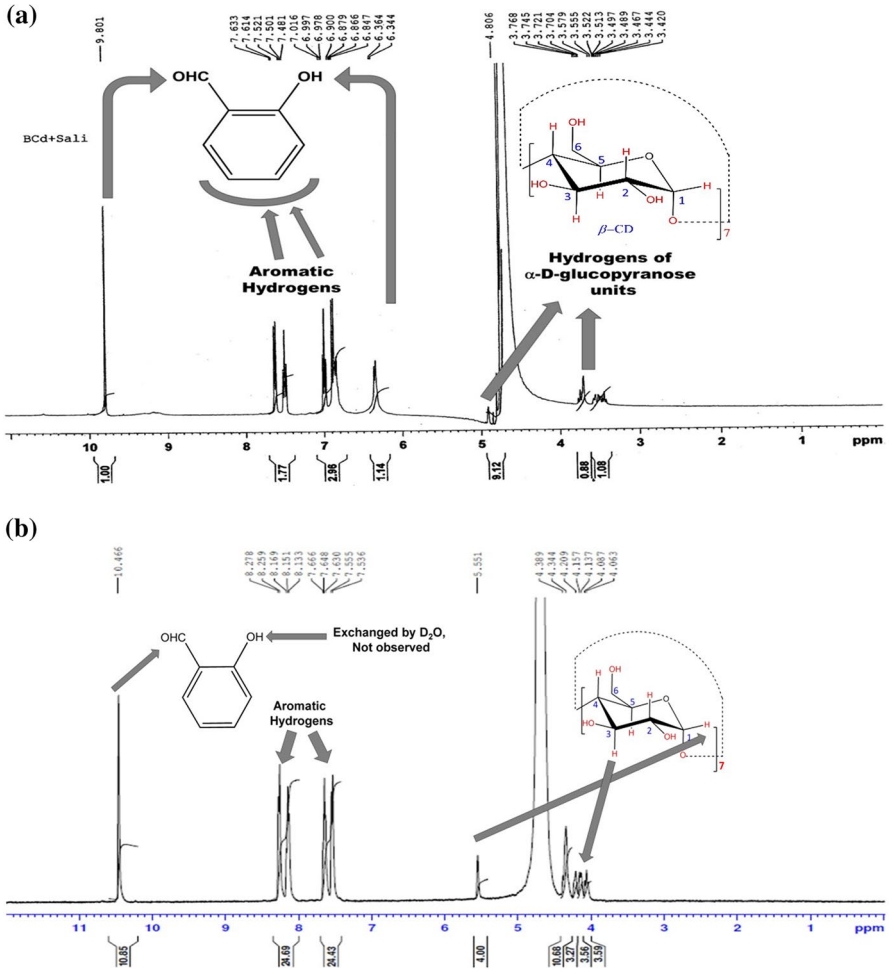


Fig. 3 **a** ^{1}H NMR spectrum of β-CD-salicylaldehyde inclusion complex at 25 °C temperature. **b** ^{1}H NMR spectrum of β-CD-salicylaldehyde inclusion complex at 70 °C temperature

are located outside the cavity of cyclodextrin; hence, they show negligible or zero upfield shifting in ^{1}HNMR spectrum.

The ^{1}HNMR spectrum of β-CD-salicylaldehyde inclusion complex 25 °C (Fig. 3a) showed three indistinguishable multiplates of protons of α-D-glucopyranose unit in at δ 3.49, δ 3.70 and δ 4.80 ppm. The hydroxyl protons (OH) of β-CD not appeared in ^{1}H NMR spectrum due to D_2O exchange however hydroxyl proton (OH) of salicylaldehyde appeared at δ 6.35 ppm. The four protons of salicylaldehyde ring were resonated as two sets multiplates in the range of δ 6.84–7.83

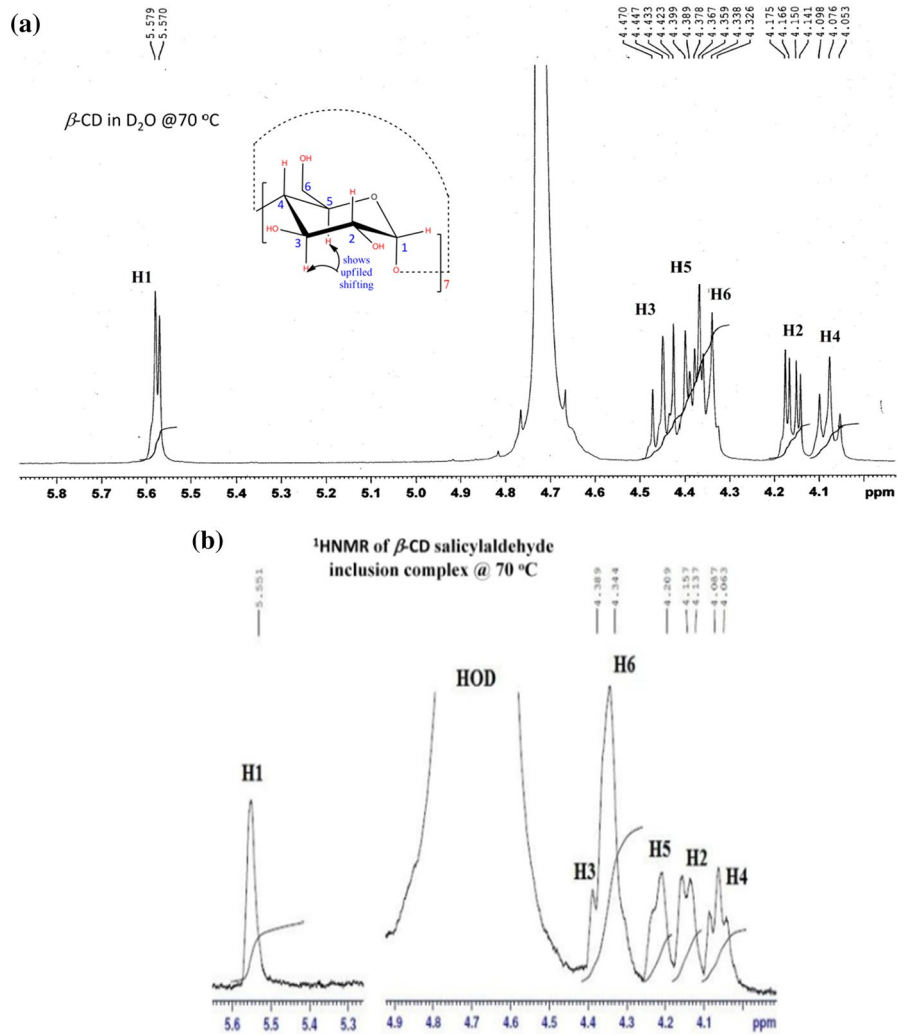


Fig. 4 **a** ^{1}H NMR spectrum of β-CD in D_2O at 70 °C temperature. **b** Magnified view of ^{1}H NMR spectrum of β-CD-salicylaldehyde inclusion complex at 70 °C

Table 5 ^{1}H NMR chemical shifts (δ ppm) of C-H protons of β-CD and β-CD salicylaldehyde inclusion complex[a]

β-CD (δ ppm)	H1 5.574	H2 4.158	H3 4.443	H4 4.075	H5 4.378	H6 4.332
β-CD + Salicylaldehyde inclusion complex (δ ppm)	5.551	4.147	4.389	4.075	4.209	4.344
upfield shifting ($\Delta\delta$ ppm)	+0.023	+0.011	+0.054	0.00	+0.169	−0.012

[a] ^{1}H NMR spectra were recorded with 400 MHz frequency using D_2O as solvent at 70 °C temperature

ppm while sharp singlet at δ 9.80 ppm corresponds to proton of aldehyde group. ^{1}HNMR spectrum of β–CD-salicylaldehyde inclusion complex at 70 °C (Fig. 3b) temperature showed sharp singlet at δ 10.46 ppm corresponding to proton of aldehyde group. The aromatic proton *ortho* to aldehyde group was observed as doublet at δ 7.54 ppm, J = 6.3 Hz. The proton at *meta* position to aldehyde showed triplet at δ 7.64 ppm, J = 5.4 Hz while the proton at *meta* position to hydroxyl group showed triplet at δ 8.15 ppm, J = 5.4 Hz. The proton *ortho* to hydroxy group was observed as doublet at δ 8.26 ppm, J = 5.7 Hz. In this ^{1}HNMR spectrum, the hydroxyl protons (OH) of β-CD and salicylaldehyde not appeared, which vanishes due to D_2O exchange. This observation supports the formation β-CD-salicylaldehyde inclusion complex.

Comparison of NMR spectra of β-CD and β-CD-salicylaldehyde inclusion complex at 70 °C

The ^{1}HNMR spectrum of β-CD at 70 °C (Fig. 4a) showed the four distinctive chemical shifts of protons attached to carbon atom of glucose unit in β-CD. The doublet at δ 5.57 ppm, J = 2.7 Hz, was due to the proton attached to carbon number one; however, the protons attached with C-2, C-3, C-4, C-5 and C-6 were resonated as three indistinguishable multiplates. The hydroxyl protons (OH) of β-CD not appeared in ^{1}HNMR spectrum due to D_2O exchange.

The magnified view of ^{1}HNMR spectrum of β-CD-salicylaldehyde inclusion complex (Fig. 4b) at 70 °C showed upfield shift of **H3** and **H5** protons by δ **0.054** ppm and δ **0.169** ppm respectively (Table 5), which confirms the β-CD-salicylaldehyde inclusion complex formation by host–guest interaction.

Conclusion

The present protocol of synthesis of xanthene and coumarin derivatives is eco-friendly as reactions proceed in water which fulfill prime requirement of chemical industries now a day. The NMR study of β-CD-salicylaldehyde inclusion complex at elevated temperature is faster method of analysis than lyophilization or cryodesiccation method.

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