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ARTICLE

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Green synthesis of bis-coumarin derivatives using $Fe(SD)_3$ as a catalyst and investigation of their biological activities

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Abstract

A convenient, practical, green, and environmentally friendly method was developed for the synthesis of biscoumarins and corresponding tetrakis products from the reaction of 4-hydroxycoumarin and various aldehydes. The bis-coumarins were synthesized in high yield under mild reaction conditions. Products were obtained in the presence of in situ prepared $Fe(SD)_3$ [Iron(III) dodecyl sulfate] as a combined Lewis acid–surfactant catalyst (LASC) in water in short reaction times. Also, the antibacterial activity of compounds was screened against *Pseudomonas aeruginosa* and *Escherichia coli* as Gram-negative bacteria and *Micrococcus luteus* and *Staphylococcus aureus* as Gram-positive bacterial strains. Products **3g**, **3k–l** were most active than cefotaxime against *E. coli* and also compounds **3c** and **3g** were most active than cefotaxime against *S. aureus.*

KEYWORDS

4-Hydroxycoumarin, bis-coumarins, green synthesis, terephthaldehyde, tetrakis-coumarins

1 | INTRODUCTION

Coumarin derivatives are an important class of heterocyclic compounds and their biological activities make them interesting targets for multicomponent reactions (MCRs). Moreover, their biological activities involve HIV inhibitory,[1] antibacterial,[2] anticancer,[3] anticoagulant,[4] antihepatitis C virus,[5] vasorelaxants,[6] enzymatic inhibitors,[7] antitumor,[8] and spasmolytic[9] activities. Also, coumarins are used as food and cosmetic additives and as brightening agents.[10,11] Synthetic routes to coumarins include Pechmann condensation, Perkin, Knoevenagel, and Reformatsky reactions as well as flash vacuum pyrolysis.[12] Among these, the Knoevenagel reaction is the most commonly applied one, in which different types of acid catalysts such as H_2SO_4, P_2O_5, $AlCl_3$, I_2, and F_3CCO_2H are employed.[13,14] Many of the reactions are undesirable for industrial purposes due to difficult conditions, longer reaction times and corrosive reagents. Therefore, finding mild and economical synthetic methods is necessary to overcome the previous procedures. In 2009, Sangshetti et al. reported the use of $MnCl_2.4H_2O$ for condensation of 4-hydroxycoumarin and aldehydes in H_2O at 100°C in moderate to good yields (99%).[15] Other procedures that used microwaves[16] and ultrasound irradiation[17] have been carried out using catalysts such as molecular I_2,[18] [bmim][BF4],[19] $(Bu)_4NBr$ (TBAB),[20] sodium dodecyl sulfate ($NaOSO_2OC_{12}H_{25}$) (SDS),[21] P_4VPy–CuO-NPs,[22] $RuCl_3.nH_2O$,[23] sulfated titania [TiO_2/SO_4^{2-}],[24] Melamine trisulfonic acid (MTSA),[25] tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$,[26] Ni-NPs,[27] $POCl_3$ in dry dimethylformamide (DMF),[28] TiO_2@KSF,[29] ZnO nanocomposite,[30] diethyl aluminum chloride (Et_2AlCl),[31] $LiClO_4$,[32] Piperidine,[33] nano-Fe_3O_4,[34] kit-6-mesoporous silica-coated magnetic nanoparticles,[35] amino glucose-functionalized silica-coated $NiFe_2O_4$ nanoparticles,[36] Fe_3O_4@SiO_2@KIT-6,[37] [BDBDMIm]Br-CAN,[38] citric acid,[39] and SBPDSA.[40] More catalysts and different

conditions for the synthesis of biscoumarins are gathered in our recent review.[41]

With the increasing public concern over environmental degradation, the use of environmentally benign solvents like H_2O represents very powerful green chemical technology procedures from both the economical and synthetic points of view. They have many advantages, such as reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment.[21] Recently, we used H_2O as a green solvent for the synthesis of thiazoles and benzothiazoles.[42,43]

2 | EXPERIMENTAL

All reactions were followed by Thin-layer chromatography (TLC) with detection by UV light. FT-IR spectra were obtained in KBr disks on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-400 Avance spectrometer in DMSO-d_6. Melting points were determined using a Mettler Fp5 apparatus and are uncorrected. 4-Hydroxycoumarin, aldehydes, $Fe(SD)_3$, and solvents were purchased from Merck and used without further purification.

2.1 | General procedure for the synthesis of bis-coumarins 3a–l

4-hydroxycoumarin **1** (2 mmol) and different aldehydes **2a–l** (1 mmol) were added to a mixture of SDS (0.2 mmol) and $FeCl_3$-$6H_2O$ (0.066 mmol) in H_2O (5 mL) and heated to 100°C. The progress of the reaction was monitored with TLC (*n*-hexane:EtOAc 6:3). After completion of the reaction, H_2O (10 mL) was added, and the mixture was filtered off and washed with cold EtOH. The products were dried at room temperature and were recrystallized from EtOH.

2.2 | General procedure for the synthesis of benzothiazoles 3m–o

4-hydroxycoumarin **1** (4 mmol) and aldehydes **2m–o** (1 mmol) were added to a mixture of SDS (0.2 mmol) and $FeCl_3.6H_2O$ (0.066 mmol) in H_2O (26 mL) and heated to 100°C. The progress of the reaction was monitored using TLC (*n*-hexane:EtOAc 6:3). After completion of the reaction, H_2O (10 mL) was added, and the mixture was filtered off and washed with cold EtOH. The products were dried at room temperature and were recrystallized from EtOH.

2.3 | 3,3′-(Phenylmethylene)bis(4-hydroxy-2*H*-chromen-2-one) 3a

White powder, yield: 79%, m.p 217–225°C [m.p 227–228°C].[29] IR (KBr, ν cm^{-1}): 3,440 (OH), 1,624 (C=C, olefin), 1,555 (C=C, olefin), 1,342 (stretch, C–O–C lacton), 1,199 (C–O ether), and 759 (OOP, C–H).

2.4 | 3,3′-([3-Nitrophenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3b

Pink powder, yield: 60%, m.p 209–216°C [m.p 214–216°C].[25] IR (KBr, ν cm^{-1}): 3,436 (OH), 1,614 (stretch, C=C), 1,557 (stretch, NO_2), 1,344 (stretch, NO_2), 1,199 (C–O ether), and 760 (OOP, C–H).

2.5 | 3,3′-([2-Chlorophenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3c

White powder, yield: 60%, m.p 200–204°C [m.p 202–205°C].[29] IR (KBr, ν cm^{-1}): 3,417 (OH), 1,657 (stretch, C=O), 1,612 (C=C, olefin), 1,561 (C=C-stretch, Ar), 1,089 (C–O ether), and 767 (OOP, C–H).

2.6 | 3,3′-((4-[Dimethylamino]phenyl) methylene)bis(4-hydroxy-2*H*-chromen-2-one) 3d

Brown powder, yield: 73%, m.p 210–216°C [m.p 210–215°C]. [44] IR (KBr, ν cm^{-1}): 3,415 (OH), 1,674, 1,645 (stretch, C=O), 1,611 (C=C, olefin), 1,536 (C=C-stretch, Ar), 1,384 (C–O–C lacton), and 754 (OOP, C–H).

2.7 | 3,3′-([4-Methoxyphenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3e

Cream powder, yield: 68%, m.p 249–253°C [m.p 245–246°C].[21] IR (KBr, ν cm^{-1}): 3,450 (OH), 1,667 (stretch, C=O), 1,611 (C=C, olefin), 1,562, 1,507, 1,449 (C=C-stretch, Ar), 1,350 (C–O–C lacton), 1,092 (C–O ether), and 765 (OOP, C–H).

2.8 | 3,3′-([3-Hydroxyphenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3f

Pink color solid, yield: 60%, m.p 204–219°C [m.p 210–213°C].[25] IR (KBr, ν cm^{-1}): 3,443 (OH), 1,662 (stretch, C=O), 1,612 (C=C, olefin), 1,562, 1,507, 1,444 (C=C-stretch, Ar), 1,348 (C–O–C lacton), 1,098 (C–O ether), and 762 (OOP, C–H).

2.9 | 3,3′-([2,4Dichlorophenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3g

Gray powder, yield: 64%, m.p 198–199°C [m.p 190–195°C].[44] IR (KBr, ν cm^{-1}): 3,421 (OH), 1,658 (stretch, C=O), 1,612 (C=C, olefin), 1,561 (C=C-stretch, Ar), 1,102 (C–O ether), and 761 (OOP, C–H).

2.10 | 3,3′-([3-Methoxyphenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3h

Cream powder, yield: 86%, m.p 243–248°C [m.p 235–236°C].[29] IR (KBr, ν cm^{-1}): 3,448 (OH), 1,662 (stretch, C=O), 1,613 (C=C, olefin), 1,567 (C=C-stretch, Ar), 1,349 (C–O–C lacton), 1,097 (C–O ether), and 763 (OOP, C–H).

2.11 | 3,3′-([2-Methoxyphenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3i

Cream powder, yield: 68%, m.p 201–206°C [m.p 213–215°C].[44] IR (KBr, ν cm^{-1}): 3,443 (OH), 1,652 (stretch, C=O), 1,611 (C=C, olefin), 1,560 (C=C-stretch, Ar), and 758 (OOP, C–H).

2.12 | 3,3′-([4-Nitrophenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3j

Pink powder, yield: 82%, m.p 231–239°C [m.p 232–234°C].[21] IR (KBr, ν cm^{-1}): 3,444 (OH), 1,655 (stretch, C=O), 1,611 (C=C, olefin), 1,560, 1,516, 1,447, 1,344 (stretch, NO_2), 1,101 (C–O ether), and 769 (OOP, C–H).

2.13 | 3,3′-([2,6Dichlorophenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3k

Pink powder, yield: 91%, m.p 193–198°C [m.p 178–180°C].[45] IR (KBr, ν cm^{-1}): 3,447 (OH), 1,698 (stretch, C=O), 1,609 (C=C, olefin), 1,556, 1,508, (C=C-stretch, Ar), 1,308, 1,279 (C–O–C lacton), and 743 (OOP, C–H).

2.14 | 3,3′-([3-Bromophenyl]methylene)bis (4-hydroxy-2*H*-chromen-2-one) 3l

Pink powder, yield: 66%, m.p 213–218°C [m.p 225–228°C].[44] IR (KBr, ν cm^{-1}): 3,412 (OH), 1,658 (stretch, C=O), 1,609 (C=C, olefin), 1,558 (C=C-stretch, Ar), 1,345 (C–O–C lacton), 1,099 (Br-Ar), and 761 (OOP, C–H).

2.15 | 3,3′,3″,3‴-(1,4-Phenylenebis [methanetriyl])tetrakis(4-hydroxy-2*H*-chromen-2-one) 3m

White powder, yield: 55%, m.p 288–296°C. IR (KBr, cm^{-1}): 3,450 (OH), 1,658 (stretch, C=O), 1,621 (C=C, olefin), 1,564 (C=C-stretch, Ar), 1,349 (C–O–C lacton), and 761 (OOP, C–H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.89 (s, 4H, H_e), 7.58 (s, 4H, H_c), 7.33–731 (8H, H_b, H_d), 7.01 (s, 4H, H_a), 6.31(s, 2H, H_j), 5.24 (s, 4H, OH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 165.3, 165.1 (C_h, C_a), 152.5 (C_b), 137.1 (C_k), 132.59, 127.14 (C_l, C_d), 124.4, 124.3 (C_e, C_f), 117.6 (C_g), 116.5 (C_c), 104.7 (C_i), and 36.0 (C_j) ppm.

2.16 | 3,3′,3″,3‴-(((Hexane-1,6-diylbis[oxy])bis (4,1-phenylene))bis(methanetriyl))tetrakis (4-hydroxy-2*H*-chromen-2-one) 3n

Pink solid, yield: 60%, m.p 185–191°C. IR (KBr, cm^{-1}): 3,416 (OH), 1,665 (stretch, C=O), 1,612 (C=C, olefin), 1,565, 1,507 (C=C- stretch, Ar), 1,250 (C-O-C lacton), and 761 (OOP, C-H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.91 (s, 4H, H_o), 7.61 (s, 4H, H_m), 7.37 (s, 4H, H_n), 7.06 (s, 4H, H_f), 6.81 (s, 4H, H_e), 6.30 (s, 2H, H_h), 5.20 (s, 4H, OH), 3.95 (s, 4H, H_c), 1.73 (s, 4H, H_b), and 1.48 (s, 4H, H_a) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 165.29 (C_j), 164.16 (C_q), 157.22 (C_d), 152.67 (C_k), 131.8 (C_g), 129.94 (C_f), 128.22 (C_m), 124.38, 124.21 (C_n, C_l), 116.42 (C_p), 115.37 (C_o), 114.48 (C_e), 104 (C_l), 67.69 (C_c), 35.72 (C_h), 29.24 (C_b), and 25.87 (C_a) ppm.

2.17 | 3,3′,3″,3‴-(((Pentane-1,5-diylbis[oxy]) bis(4,1-phenylene))bis(methanetriyl))tetrakis (4-hydroxy-2*H*-chromen-2-one) 3o

Pink powder, yield, yield: 65%, m.p 177–189°C. IR (KBr, cm^{-1}): 3,416 (OH), 1,664 (stretch, C=O), 1,607 (C=C, olefin), 1,565, 1,532, 1,508 (C=C-stretch, Ar), 1,248 (C–O–C lacton), and 762 (OOP, C–H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.88 (s, 4H, OH), 7.87 (s, 4H, H_o), 7.57 (s, 4H, H_m), 7.31 (s, 4H, H_n), 7.15 (s, 4H, H_f), 6.78 (s, 4H, H_e), 6.27 (s, 2H, H_h), 4.13 (s, 4H, H_c), 1.79 (s, 4H, H_b), and 1.58 (s, 2H, H_a) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 165.21,165.21 (C_j, C_q), 157.04 (C_d),152.78 (C_k), 131.96 (C_g), 129.95 (C_f), 128.18 (C_m),124.46 (C_n),123.88 (C_l), 116.25 (C_p),115.40 (C_o), 114.36 (C_e), 104.56 (C_i),68.47 (C_c), 35.76 (C_h), 28.71 (C_b), and 22.68 (C_a) ppm.

2.18 | 3,3′-(Phenylmethylene)bis(4-hydroxy-2*H*-chromen-2-one) and 3,3′-(phenylmethylene) bis(1*H*-indole) (3a and 6)

IR (KBr, cm^{-1}): 3,413 (NH), 1,658 (stretch, C=O), 1,610 (C=C, olefin), 1,562 (C=C-stretch, Ar), and 746 cm^{-1}

(OOP, C–H).^{1}H NMR (DMSO-d_6, 400 MHz) δ (6): 10.83 (s, 2H, H_c), 7.42–7.26 (m, 5H, 2H_e, 2H_m,1H_n), 7.263–7.203 (m, 4H, 2H_h, 2H_l), 7.04 (t, J = 7.6 Hz, 2H, H_f), 6.87 (t, J = 7.6 Hz, 2H, H_g), 6.84 (s, 2H, H_b), and 5.63 (s, 1H, H_a) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ (6): 133.2 (C_k), 131.7 (C_d), 128.7, 128.3 (C_L–C_m), 127.1 (C_i), 123.6 (C_b), 121.3 (C_f), 119.5 (C_g), 118.5.5 (C_h), 116.1 (C_j), 111.9 (C_e), and 56.5 (C_a) ppm. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (3a): 7.86 (t, J = 8.6 Hz, 2H, $H_{e'}$), 7.71 (t, J = 6.8 Hz, 2H, $H_{g'}$), 7.42–7.26 (m, 9H, 2H_d', 2$H_{f'}$, 2H_m', 2H_n', 1H_o'), and 5.84 (s, 1H, H_a') ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ (3a): 165.1 (C_i'), 162.3 ($C_{b'}$), 152.9 ($C_{c'}$),145.4 (C_L'), 128.3–128.1 ($C_{e'}$, $C_{n'}$), 127.1 ($C_{m'}$), 125.5 ($C_{o'}$), 114.8 ($C_{d'}$),116.2 ($C_{h'}$),104.1 ($C_{K'}$), and 36.5 ($C_{a'}$) ppm.

2.19 | Antibacterial assay

The antibacterial activity of products was evaluated biologically using well-diffusion method[46] against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Micrococcus luteus.* Culture media including nutrient agar and nutrient broth cultures were prepared according to manufacturers' instructions. Then, a suspension of each bacterium (30 μL) was added to the nutrient agar plates spread over the agar. Final concentration of each compound in each well was 12 μg/0.1 mL in DMSO. Then, plates were incubated at 37°C for 24 hr, after this time the zone of inhibition was measured and values are expressed in millimeters (mm). Cefetoxim and DMSO were used as positive and negative controls, respectively.

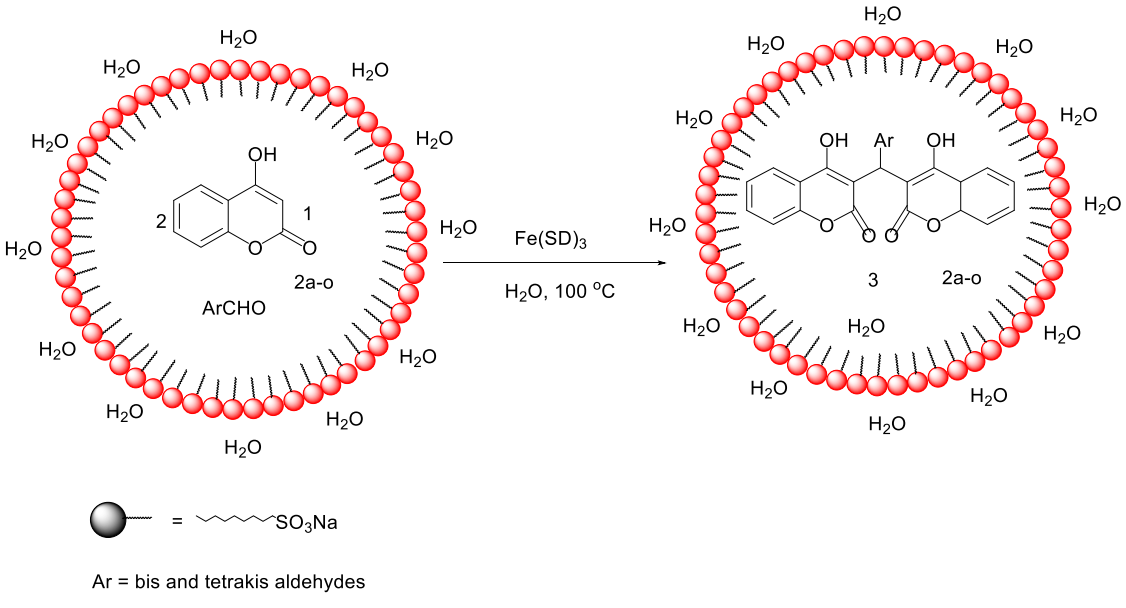
3 | RESULTS AND DISCUSSION

3.1 | Chemistry

In continuation of our recent studies to introduce and development of catalytic properties of $Fe(SD)_3$ and new applications of sodium dodecylsulfate,[42,43] we report herein an efficient, green, and environmentally benign method for the synthesis of biscoumarin derivatives from the reaction of aromatic aldehydes with 4-hydroxycoumarin in the presence of catalytic amounts of $Fe(SD)_3$ in H_2O as a solvent (Scheme 1).

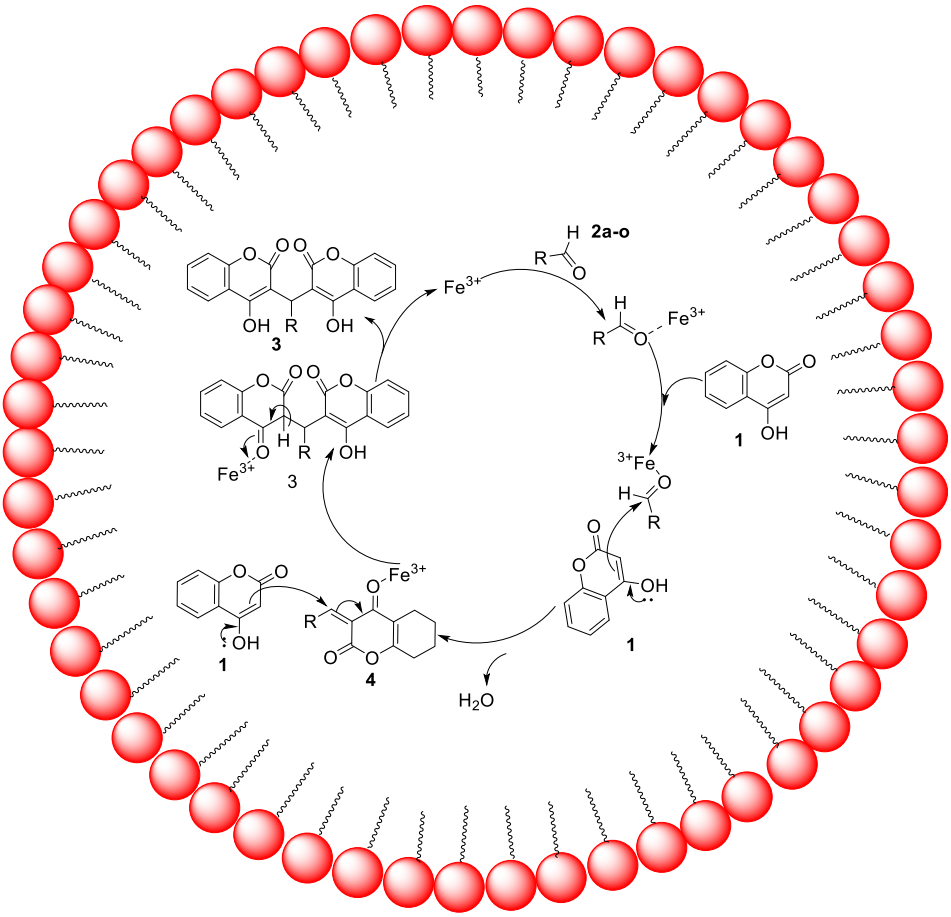
As is shown, nucleophilic attack of 4-hydroxycoumarin **1** on the activated aldehyde (by Fe^{3+} coordination), followed by H_2O elimination, provides intermediate **4** that is further activated by Fe^{3+}, which in turn, undergoes a second nucleophilic attack by another 4-hydroxycoumarin to provide the final product **3**. Also, the hydrophobic chain of SDS forms micelles in water, which can capsulate reactants in a tight place with a diameter of 10–28 Å[47] for the reaction to occur (Scheme 2). Moreover, these micelles in water increase the solubility of organic compounds in water.[48,49]

Product 3a was considered as a typical example, accordingly. The effects of different solvents, catalysts, temperature, and amounts of catalyst were investigated and the reaction conditions were optimized. The reaction using H_2O as a solvent at room temperature and in the presence of a 10% molar amount of $Fe(SD)_3$ catalyst led to the formation of the product in a long reaction time and low yield (Table 1, entry 1). Performing the reaction at higher temperatures resulted in an increase in the reaction efficiency (Table 1, entries 2 and 3). Ultrasound irradiation at temperatures 60°C and 50°C led to higher yields in comparison to



SCHEME 1 The entire reaction occurring in or on the micelles

SCHEME 2 Proposed mechanism for the $Fe(SD)_3$-catalyzed synthesis of biscoumarins



entry 3 and entries 1–2, respectively. However, the decreasing temperature in ultrasound irradiation led to a longer reaction time and lower yields (entries 4–7). Increasing the amount of catalyst from 10 to 20% resulted in a shorter reaction time and higher yield (Table 1, entries 3 and 8). However, increasing the amount of catalyst to 40 and 80% did not improve the reaction yield. Therefore, the optimal reaction condition is 100°C in the presence of 20 mol% of catalyst.

With these encouraging results, the generality of this reaction was examined using various aromatic aldehydes containing electron-donating as well as electron-withdrawing groups. In all cases, the reactions gave the corresponding products in good yields and short reaction times (Table 2).

In the total review of the benefits of synthesized products, the products **3e**, **3h**, and **3i** with metasubstituted methoxy have higher yields than ortho-substituted and para-

TABLE 1 Optimization of the reaction conditions for the synthesis of 3[a]

Entry	Catalyst	Mol (%)	Time (min)	Temperature (°C)	Yield (%)
1	$Fe(SD)_3$	10	90	r.t.	48
2	$Fe(SD)_3$	10	20	70	58
3	$Fe(SD)_3$	10	10	100	61
4	$Fe(SD)_3$	10	10	Ultrasound/60	63
5	$Fe(SD)_3$	10	25	Ultrasound/50	52
6	$Fe(SD)_3$	10	35	Ultrasound/40	46
7	$Fe(SD)_3$	10	55	Ultrasound/30	44
8	$Fe(SD)_3$	20	10	100	79
9	$Fe(SD)_3$	40	20	100	69
10	$Fe(SD)_3$	80	15	100	70

[a]Reaction of 4-hydroxycoumarin **1** (2 mmol) with benzaldehyde **2a** (0.5 mmol).

TABLE 2 Synthesis of bis-coumarins and tetrakis-coumarins in the presence of $Fe(SD)_3$ in H_2O under optimized reaction conditions[a]

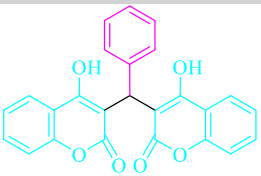
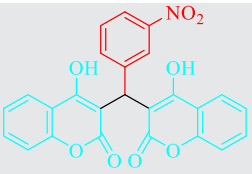
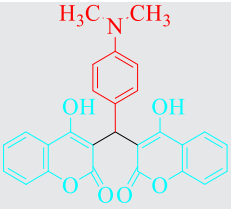
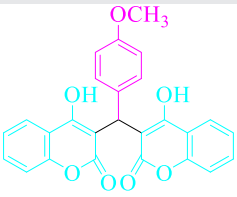
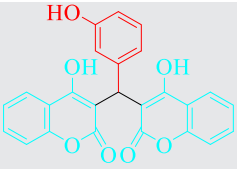
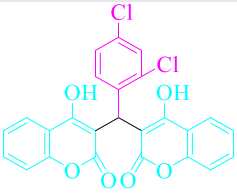
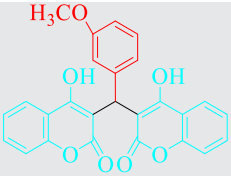
Product	Melting point (°C)		Yield (%)	Time (min)	Product	Product powder
	Reported	Found				
3a	227–228[29]	217–225	79	10		
3b	214–216[25]	209–216	60	10		
3c	202–205[29]	200–204	60	15		
3d	210–215[44]	210–216	73	37		
3e	245–246[21]	249–253	68	30		
3f	210–213[25]	204–219	60	70		
3g	190–195[44]	198–199	64	20		
3h	235–236[29]	243–248	86	30		

TABLE 2 (Continued)

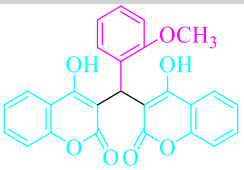
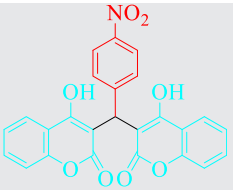
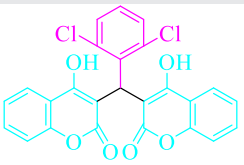
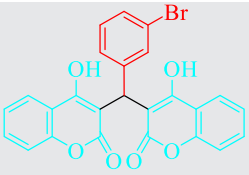
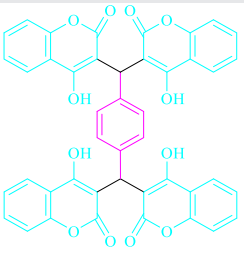
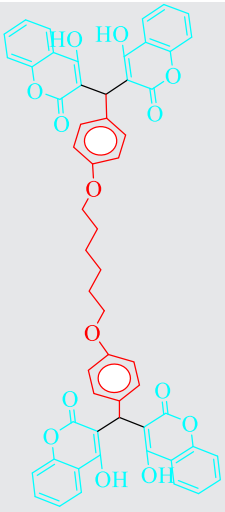
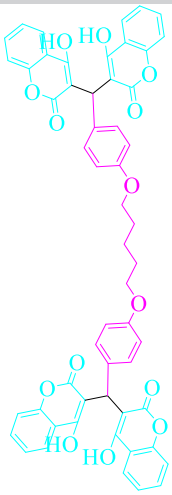
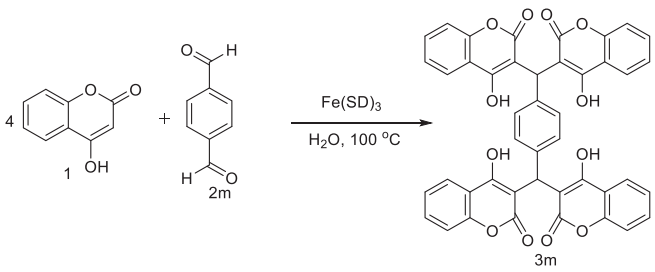
Product	Melting point (°C)		Yield (%)	Time (min)	Product	Product powder
	Reported	Found				
3i	213–215[44]	201–206	68	20		
3j	232–234[21]	231–239	82	20		
3k	178–180[45]	193–198	91	10		
3l	225–228[44]	213–218	66	20		
3m	—	288–296	55	30		
3n	—	185–191	60	35		

TABLE 2 (Continued)

Product	Melting point (°C) Reported	Found	Yield (%)	Time (min)	Product	Product powder
3o	—	177–189	65	30		

[a]*Reaction conditions*: aldehyde (**2a–l**) (1 mmol), 4-hydroxycoumarin (2 mmol), $Fe(SD)_3$ (20 mol%), H_2O (5 mL), and 100°C, aldehyde (**2m**) (1 mmol) (**2n–o**) (0.25 mmol), 4-hydroxycoumarin (4 mmol), $Fe(SD)_3$ (20 mol%), H_2O (26 mL), and 100°C.



SCHEME 3 Synthesis of tetrakis-coumarins in the presence of $Fe(SD)_3$ at 100°C

substituted biscoumarin products. Dichloro-substituted biscoumarins produced a higher yield than monochloro-substituted biscoumarins. *p*-Nitro benzaldehyde gave a higher yield of biscoumarin than a metasubstituted product.

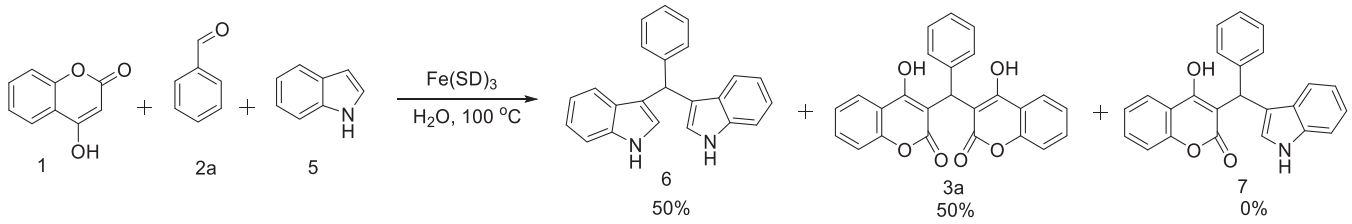
Tetrakis-coumarin product **3m** was synthesized from the reaction of four equivalents of 4-hydroxycoumarin **1** and 1 equivalent of terephthaldehyde **2m** (Scheme 2). In other efforts, two new semitetrakis products **3n** and **3o** with phenyl alkyl ether linkage were prepared (Scheme 3).

To investigate the efficiency of $Fe(SD)_3$ and optimize the reaction conditions, we compared our conditions with some other reported catalysts for the model reaction of 4-hydroxycoumarin **1** (1 mmol) with benzaldehyde **2a** (2 mmol) (Table 3). As is shown, our conditions have the advantages of a shorter reaction time, comparable yield, low amounts of catalyst and use of a green solvent in comparison to other reported procedures.

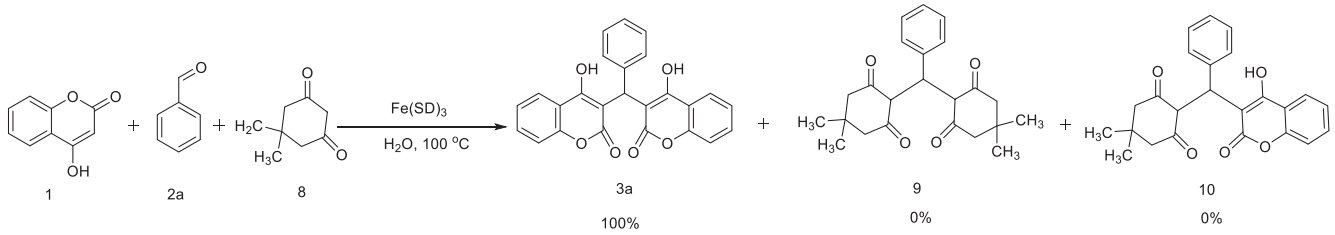
In another effort, the selectivity of the reaction condition was examined according to Schemes 4 and 5. The reaction of a mixture of benzaldehyde **2a**, 4-hydroxycoumarin **1** and indole **5** in the presence of $Fe(SD)_3$ led to biscoumarin **3a** and bis-indole **6**, however, compound 3-((1*H*-indol-3-yl)(phenyl)methyl)-4-hydroxy-2*H*-chromen-2-one **7** was not detected according to the ^{1}H NMR and ^{13}C NMR spectra (Scheme 4). The ratio of compounds **3a** and **6** is equal according to integral of protons in the ^{1}H NMR spectrum. Similarly, the reaction of benzaldehyde **2a**,

TABLE 3 Comparison of our results with some previously reported data for the synthesis of **3a**

Entry	Catalyst	Mol (%)	Solvent	Temperature (°C)	Time	Yield (%)	Ref.
1	DBSA	25 Mol%	H_2O:EtOH	80°C	40–50 min	60–90	42
2	SDS	20 Mol%	H_2O	60°C	2.30–3 hr	84–98	21
3	OBS	50 Mol%	H_2O	Reflux	20–50 min	74–88	46
4	—	—	[bmim]BF_4	60–70°C	2–3 hr	77–91	19
5	$Fe(SD)_3$	20 Mol%	H_2O	100°C	7 min	79	This work



SCHEME 4 $Fe(SD)_3$-catalyzed synthesis of biscoumarin **3a** and bis-indole **6**



SCHEME 5 Selective synthesis of biscoumarin **3a** catalyzed by $Fe(SD)_3$

4-hydroxycoumarin **1**, and 5,5-dimethylcyclohexane-1,3-dione **8** in the presence of $Fe(SD)_3$ only led to biscoumarin derivatives **3a**, compounds 2,2′-(phenylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione) **9** and 2-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(phenyl)methyl)-5,-5-dimethylcyclohexane-1,3-dione **10** were not detected (Scheme 5).

3.2 | Antibacterial activity

Given that the biological activities of bis-coumarin compounds and their derivatives, such as antibacterial, antifungal, and etc., have been proven, we have also investigated the antibacterial activity of our newly synthesized compounds. The biological activity of the synthesized

TABLE 4 Antimicrobial activity of compounds **3a–o**

			Antimicrobial activity (zone of inhibition in mm)			
			Gram-negative		Gram-positive	
Entry	Compound	Conc. Of compound in DMSO (μg/0.1 mL)	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Micrococcus luteus*
1	**3a**	12	—	—	13	10
2	**3b**	12	11	—	9	—
3	**3c**	12	—	—	26	—
4	**3d**	12	10	—	18	—
5	**3e**	12	—	—	14	—
6	**3f**	12	—	—	11	—
7	**3g**	12	18	—	25	—
8	**3h**	12	—	—	15	—
9	**3i**	12	10	9	20	—
10	**3j**	12	11	—	15	—
11	**3k**	12	15	10	8	20
12	**3l**	12	12	—	19	—
13	**3m**	12	—	—	18	17
14	**3n**	12	—	—	—	—
15	**3o**	12	10	—	19	—
16	DMSO	—	—	—	—	—
17	Cefotaxime	30	11	20	26	46

compounds against Gram-negative bacteria (*P. aeruginosa* and *E. coli*) and Gram-positive bacteria (*M. luteus* and *S. aureus*) was investigated. Compounds were dissolved in dimethyl sulfoxide (DMSO) and DMSO was used as a negative control. Also, cefotaxime was used as a positive standard. The diameter of the nongrowth zone of the bacteria around the cavity indicates the effectiveness of the antibacterial activity of the compounds. The results of this study are indicated in Table 4. According to the results, compounds were active against *S. aureus* and *E. coli*, in general, these compounds were more effective on Gram-positive bacteria and had less effect on gram-negative bacteria. Moreover, *E. coli* was most sensitive to compounds **3g**, **3k** and **3l** with halogen substitutions in comparison to cefotaxime. Also, *S. aureus* was most sensitive to compounds **3c** and **3g** in comparison to cefotaxime. Overall, these results are in accordance with our recent study [50] and Lobo et al. [51], in which it was reported that halogenated compounds possessed high antibacterial activity. Furthermore, 2,6-didchloro-substituted compound **3k** showed antibacterial activity against all four tested bacterial strains. According to the results, *M. luteus* as gram-positive bacterial strain was most sensitive to all products except **3n**. The most important difference is that gram-negative bacterial strains have a lipopolysaccharide layer as an outer layer, which excludes antibiotics from penetrating their cell and so are more resistant to antibiotics than are gram-positive bacteria. However, in this study most products especially **3c**, **3g**, and **3k–l** (higher antibacterial activity than cefetoxim) were active against *E. coli* as a resistant gram-negative bacterial strain.

4 | CONCLUSIONS

In summary, we have developed a convenient methodology for the synthesis of biscoumarin derivatives in high yields using in situ "combined Lewis acid-surfactant catalyst (LASC)," derived from the reaction of $FeCl_3.6H_2O$ and SDS with the dual role of catalysts and micelles. Also, dihalogenated substituted compounds showed good antibacterial activity against gram-positive and gram-negative bacterial strains.

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