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Research article

Efficient one-pot synthesis of bis-(4-hydroxycoumarin-3yl) methane derivatives using DMAP as a catalyst studies their antibacterial activity and molecular docking

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ABSTRACT

In the present study, we successfully synthesized a series of 4-hydroxycoumarin with a variety of aromatic aldehydes *via a* one-pot route. The excellent results of this-(4-hydroxycoumarin-3yl) methane derivatives were obtained in the presence of 5.0 mol % DMAP as a catalyst in Ethanol at room temperature using conventional and ultrasonication methodologies. All the synthesized compounds were bioactive. The synthesized bis-coumarin derivatives were evaluated for the antibacterial activity (*in-vitro*) against the *Staphylococcus aureus*, and the results were compared with the standard Kanamycin. Molecular docking analysis was revealed that compound 3,3'-((2-chlorophenyl)methylene) bis (4-hydroxy-2H-chromen-2-one **(3c) s**howed good interaction with bacterial cystathionine gamma-lyase MccB of Staphylococcus aureus protein (-6.8 kcal/mol binding free energy). The results confirmed that majority of the as-synthesized compounds revealed splendid antibacterial activity. The compound **3c** (Minimum inhibitory concentration, 40 µg/mL) shows comparable activity in standard with Kanamycin at the same concentrations against *Staphylococcus aureus*.

Keywords: Antibacterial activity, Bis-(4-hydroxycoumarin-3yl), DMAP Catalyst, Kanamycin, Staphylococcus *aureus* (MTCC 1144).

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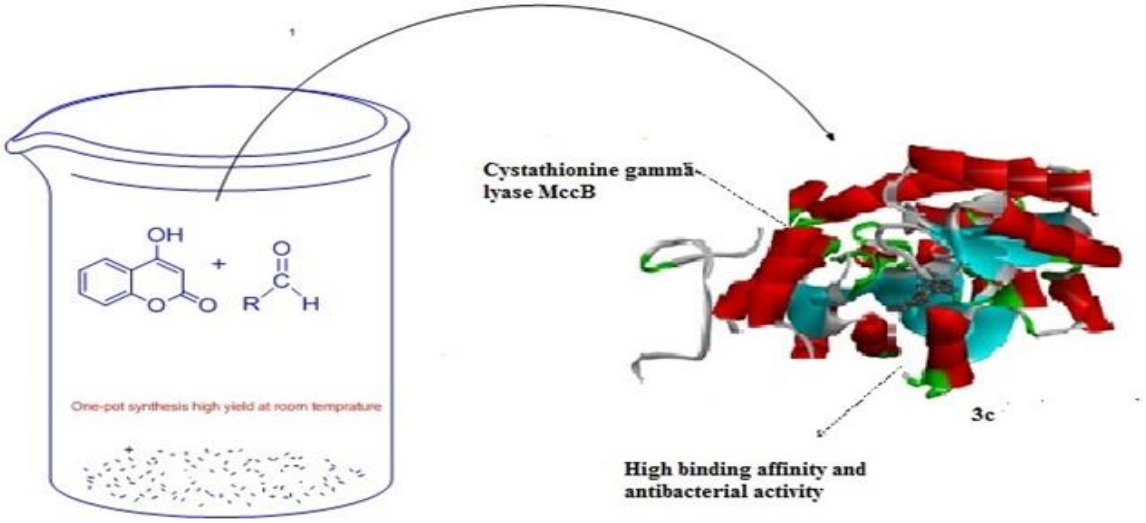
INTRODUCTION

Heterocyclic compounds with oxygen-containing moieties are industrially very important as they serve as precursors. 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 enzyme inhibitors,[1,2] anticoagulants,[3,4] antioxidants,[5,6] antitumor drugs,[7] anti-diabetic (α-glucosidase inhibitors) [8]urease inhibitors,[9,10] anti,[11] anti-bacterials,[12] inhibit c-Met phosphorylation in BaF_3/TPR-Met and EBC-1 NSCLC cell lines,[13] antimicrobial,[14] antiviral,[15] proliferation inhibition of K-562,[16] inhibit HIV-1.[17,] anti-hepatitis C virus,[18] spasmolytic, [19] vasorelaxants, [20] and antitumor, [21]activities. Also, coumarins are used as food and cosmetic additives and as brightening agents [22,23]. Synthetic routes to coumarins include Pechmann condensation, Perkin, Knoevenagel, and Reformatsky reactions as well as flash vacuum pyrolysis [24]. 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 [25,26]. 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. Bis-coumarins are generally prepared by condensing aldehydes with 4-hydroxy coumarin organic solvents [27, 28], which applied a large number of hazardous and toxic solvents related to catalysts.

Several methods have been recently reported for such synthesis which includes use of different catalysts such as molecular iodine [29], $MnCl_2$[30], strong tertiary amine base (DBU) [31], $POCl_3$[32], diethyl aluminum chloride (Et_2AlCl_3) [33], $LiClO_4$[34], SO_3H functionalized, ionic liquids [35], SDS [36], TBAB [37], Zn(Proline)2 [38], [bmim] [BF4] [39],Sulfamic acid [40], $RuCl_3{\cdot}nH_2O$ [41], SiO_2Cl [42], SiO_2-OSO_3H [43], nano-Fe_3O_4[44], Piperidine,[45] Sulfated titania [46]refluxing in ethanol or acetic acid [47],Synthesis of organic compounds led to shorter reaction time, higher yields and benign conditions under ultrasound irradiation and thermal solvent-free microwave[48-50]. More catalysts and different conditions for the synthesis of bis-coumarins are gathered in our recent review [51]. In the present work, we studied the use of 4-Dimethylaminopyridine (DMAP) as a catalyst for the synthesis of bis-(4-hydroxycoumarin-3yl)methane derivatives under conventional and ultrasonic irradiation processes (Figure 3) and

studied their antibacterial activity. Additionally, we have performed a molecular docking study of the highest biological active compound (3c) with protein (protein name) to understand the binding type and their strength. Docking results were in great relevance with in-vitro results.

Figure 1: Graphical Abstract



MATERIALS AND METHODS

Chemicals

All the chemicals were purchased from Sigma-Aldrich and Merck India and used without purification to carry out this work.

Melting Point determination and Purity

Melting points were measured by an open capillary tube. This is the most prominent method which is used for determination of melting point. The purity of the compounds was examined through thin-layer chromatography (silica gel 60 F254), using hexane/ ethyl acetate in the ratio of 6:3, on F254 silica-gel pre-coated sheets (Merck).

Instruments

The infrared (IR) spectra were recorded on an FTIR Bruker Alpha II ECO-ATR spectrometer. The 1H-NMR spectra were studied on a JEOL 500 MHz spectrum DMSO-d_6 using Tetramethylsilane (TMS) as the internal standard.

General procedure for the synthesis of bis-(4-hydroxycoumarin-3-yl) methane derivatives conventional method (3a-j)

To a mixture of 4-hydroxycoumarin (1) (2 mmol) and variety aromatic aldehydes 2(a–j) (1.1 mmol) in ethanol 5ml, (5.0 mol %) 4-Dimethylaminopyridine (DMAP) as catalyst was added and stirred the reaction mixture for 1- 3 hours at room temperature. The progress of the reaction was monitored by TLC. After the reaction completion, the product was extracted using ethyl acetate (10 ml), washed with small quantity of water, dried over sodium sulfate, and evaporated under vacuum to get crude product. The crude product was further purified by column chromatography (silica gel, 100-200 mesh) using n-hexane and ethyl acetate (6:3) as an eluent.

Synthesis of bis-(4-hydroxycoumarin-3-yl) methane derivatives under ultrasound irradiation method (3a-j)

To a solution 4-hydroxycoumarin (1) (2.0 mmol) and variety of aromatic aldehydes 2(a-j) (1.1 mmol) in ethanol (3 mL), (5.0 mol %) 4-dimethylaminopyridine (DMAP) as catalyst was added and subjected to ultrasound irradiation (Model No. KS-750F) at a frequency of 20 kHz at room temperature for 10-35 minutes the reaction was examined by TLC. After the reaction completion, the product was extracted using ethyl acetate (10 ml), washed with a small quantity of water, dried over sodium sulfate, and evaporated under a vacuum to get crude product. The crude product was further purified by column chromatography (silica gel, 100-200 mesh) using n-hexane-ethyl acetate (6:3) as an eluent.

In vitro biological evaluation assay

Antibacterial activity

Well diffusion method was used to evaluate the antibacterial activity of Bis-coumarin on bacterial species [52]. Antibacterial activity of the prepared compound or desired compounds were assessed against the microbial strain *Staphylococcus aureus* (MTCC 1144), purchased from the microbial type culture collection institute in Chandigarh, (India). Broth medium of Luria bertani was inoculated with strain MTCC 1144 and cultivate till logarithmic phase (A600 nm=1) & spread 100 µL of 24 h old culture on the solid surface of Mueller Hinton medium with the help of *L*-shaped spreader. Subsequently wells of 8mm diameter were punched into the agar medium and filled with100 µL (50,100, 150, 200 µg/mL) of desired compounds and allowed to diffuse at room temperature for an hour. The plates were then incubated in the upright position at 37 °C for 24h. Same amount (100 µL) of DMSO was used as a negative control while as standard antibiotic discs of Kanamycin (30 mcg) were used as positive control. Following this bacterial zone inhibition diameters were observed and measured carefully.

Molecular docking study

Molecular docking study was performed with AutoDock Vina to identify the orientation and interaction pattern of compound 3c with bacterial cystathionine gamma-lyase MccB of Staphylococcus aureus(PDB ID: 6KGZ).Cystathionine proteins of the Staphylococcus

aureus were proved to be responsible for transcriptional and posttranscriptional regulation for their activities. Therefore, we chose the reported high resolution (2.0 Å) X-RAY diffraction crystal structure of the target protein and docked it with optimized ligand (3c). Further, Geistenger method was applied for generating partial charge for PIA. Remaining expulsion and inclusion steps as removing of water molecules, co-factors and addition of Kollman charges, polar hydrogen on protein had been done. By the help of literature and blind docking method, active sites had been identified and fitted in the grid box, dimension: center_x = 40.508 Å, y = 39.349 Å and z = 47.405 Å; size_x = 28.62 Å y = 28.62Å z = 28.62 Å; grid spacing of 0.375 Å. [53, 54]

RESULTS AND DISCUSSION

The efficient utilization 4-Dimethylaminopyridineas a catalyst for different organic reactions is due to its cost effectiveness and easy availability. Initially, the reaction between 4-hydroxycoumarin (1) (2 mmol) with benzaldehyde (2) (1.1 mmol) utilizing water as solvent was carried out in presence of 4-Dimethylaminopyridineas a catalyst for 4 hours, at room temperature, and the yield of 70% was obtained. In accordance to the result obtained, different Lewis's acids and Boosted acid catalyst have been utilized using ethanol as a solvent for the former reaction between compound 1 &2, in order to know their catalytic efficiency. Ethanol, thanks to allow solubilizing of both polar-hydrophilic and nonpolar-hydrophobic compounds, was optimized to be good solvent for this reaction.

It produced the products (3a-j) in short reaction time with higher yield than other polar and non-polar solvents. Among the reactions observed with different catalyst, 4-Dimethylaminopyridine (Table 1, entry 1), indicated its highest catalytic activity with the completion of reaction within 2 hour. In order to optimize the reaction conditions, the effect of different solvents was also observed (Table 2), and the ethanol was found to be an effective solvent. Systematic optimization of the solvent was done for the reaction between benzaldehyde and 4-hydroxy coumarin in presence of DMAP using different solvent at room temperature. The optimized solvent (Ethanol) was found to be good to produce higher yield of the product (3a-j) in short time. However, other polar solvents like MeOH and water reduce the solubility of the reactant and therefore low reactivity.

Table 1: The reaction of 4-hydroxycoumarin (1) with benzaldehyde (2) in the presence of various catalysts using ethanol as solvent via the conventional method.

Catalyst[a]	Time (h)	Yield (%)[b]
DMAP	2	88
H_3BO_3	5	72
$CH_3C_6H_4SO_3H$	4	72
Sulfamic acid,	10	68
$LiClO_4$	12	55

[a]5mol% of the catalyst was used.[b] Yields referred to the isolated yield

Acetonitrile was also considerably suitable for the reaction. It was also observed from the results (Table 2, entry 4) that optimum concentration of 5.0 mol % of 4-Dimethylaminopyridinewas required to achieve high yield in shorter reaction times.

Table 2: Optimization of solvents in the Reaction of 4-hydroxycoumarin (1) with benzaldehyde (2) using DMAP as a catalyst by the conventional method

Entry	Solvent	Time (h)	Yield (%)[a]
1	Water	4	70
2	Methanol	3	79
3	Ethanol	2	88
4	Acetonitrile	4	82
5	THF	7	60
6	DCM	10	65
7	Toluene	12	55

[a] Yields referred to the isolated yield

Thus, the reaction of 4-hydroxycoumarin (1) with aromatic aldehyde compounds (2) led to the formation of new bis-(4-hydroxycoumarin-3-yl) methanes derivatives 3(a-j) (Scheme 1) under the optimized reaction conditions in both conventional method and ultrasound irradiation method (Table 3).

Figure 2: Synthesis of bis (4-hydroxycoumarin-3-yl) methanes

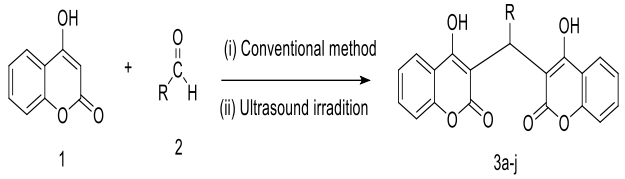


Figure 3: 3(a-j) catalyzed by *DMAP* in Ethanol under conventional and ultrasound irradiation methods

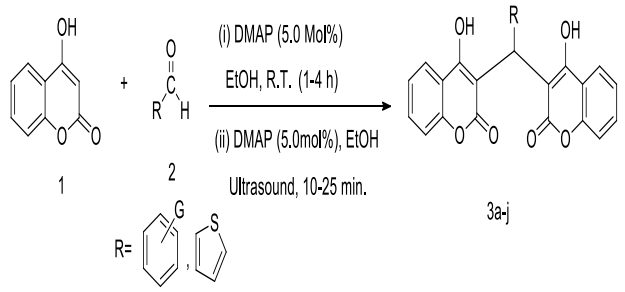


Table 3: Preparation of bis (4-hydroxycoumarin-3-yl)

R-CHO	R	Reflux Condition		Ultrasonic Irradiation	
		Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
PhCHO	C_6H_5(**3a**)	120	88	15	90
4-FC_6H_4CHO	4-FC_6H_5 (**3b**)	120	86	22	89
2-ClC_6H_4CHO	2-ClC_6H_4(**3c**)	90	89	18	91
4-BrC_6H_4CHO	4-BrC_6H_4(**3d**)	120	87	25	90
4-$NO_2C_6H_4CHO$	4-$NO_2C_6H_4$ (**3e**)	60	90	15	93
3-$NO_2C_6H_4CHO$	3-$NO_2C_6H_4$ (**3f**)	70	89	16	91
4-$OCH_3C_6H_4CHO$	4-$OCH_3C_6H_4$ (**3g**)	120	85	22	89
3-$OCH_3C_6H_4CHO$	3-$OCH_3C_6H_4$ (**3h**)	120	87	20	90
2-OH,4-$CH_3C_6H_3CHO$	2-OH,4-$OCH_3C_6H_4$ (**3i**)	160	84	30	88
C_4H_3SCHO	C_4H_3S(**3j**)	210	86	35	89

In vitro antibacterial activity

The obtained results have shown that the newly synthesized derivatives possess antibacterial activities, tested on bacteria species *(S. aureus*) 2-Cholro bis(4-hydroxycoumarin) compound has shown the best activity against *S. aureus*, with the inhibition zone of 24.82±1.23. As seen in Table 4, compounds **3a**, **3b**, **3g**, **3h**, **3i,** and **3j** demonstrated moderate growth-inhibitory activities compared to Kanamycin as a standard against the *Staphylococcus aureus while* as **3c**has exhibited the highest antibacterial activity with MIC value of 40

µg/mL.

Table 4: Antibacterial activity of the synthesized bis (4-hydroxycoumarin-3-yl) methane derivative compounds (**3a-j**)

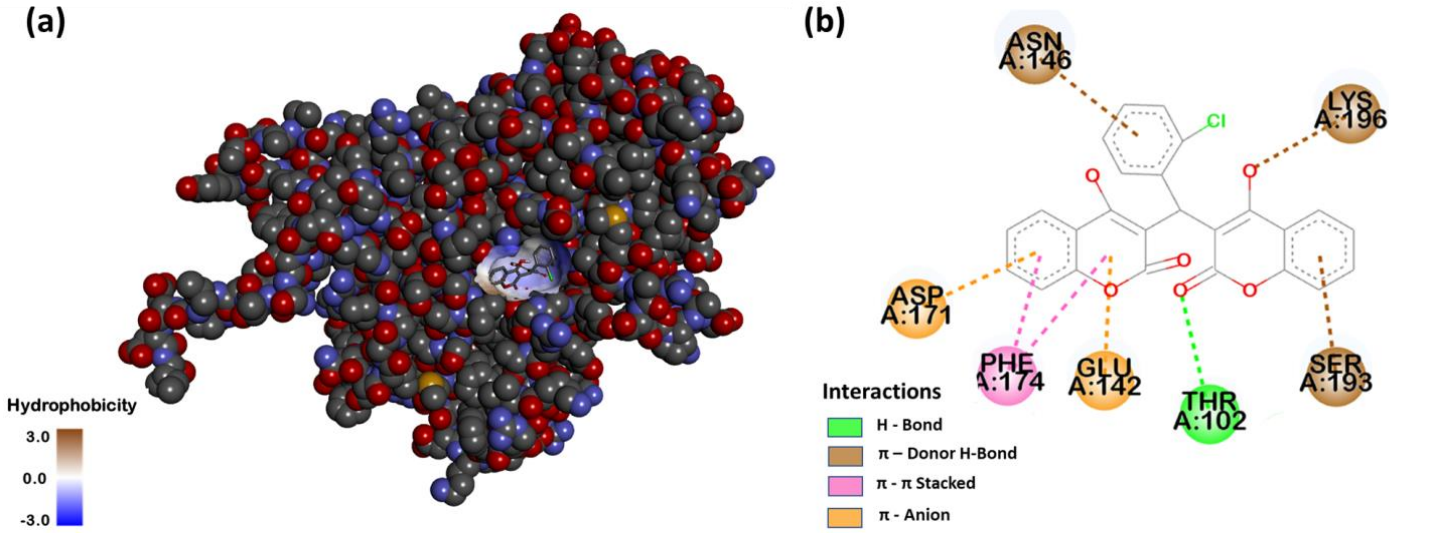
Compound code	Molecular Weight	Zone of inhibition (mm)*	Minimum inhibitory concentration (µg/ml)
3a	412.39	20.84±0.35	120
3b	430.38	22.72±1.16	>60
3c	446.84	24.82±1.23	40
3d	491.29	19.10±0.89	>120
3e	457.39	18.18±0. 32	140
3f	457.39	16.26±0.11	160
3g	442.42	20.10±0.18	>100
3h	442.42	21.02±0.14	100
3i	458.42	22.12±1.18	80
3j	418.42	22.92±0.24	60
Kanamycin standard	484.49	25.60±0.24	40

*Values are given as mean standard deviation (n=3)

Molecular docking

The molecular docking analysis was initiated to understand the binding modes of the synthesized compound 3c and Protein 6KGH. Molecular docking analysis was conducted using AutoDock Vina. From the analysis, the best ligand conforms pose has -6.8 kcal/mol binding free energy (ΔG). The graphical representation of the native docked com-plex figure is shown in Figure1Classical and non-classical bonding between synthesized compound (3c) and protein (6KGH) leads to higher biological activity. This work provides a useful experimental strategy for studying the interaction of 3c with 6KGH and helping to understand the activity and mechanism of drug binding.

Figure 4: Docked molecular structure of protein (6KGH) and synthesized compound (3c). a) Hydrophobic docked molecular presentation of compound 3c in protein pocket. b) 2-D interaction



Spectral and physical data for compounds

3'-(phenyl methylene) bis (4-hydroxy-2H-chromen-2-one) (3a, $C_{25}H_{16}O_6$)

White solid, m.p. 210-212ºC, FTIR (cm^{-1}): 3,445 (OH), 1,624 (C=C), 2,920 (C-H), 1,150 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 5.70 (s, 1H, Ar-CH), 16.40 (s 1H, OH), 7.10 -7.65 (m, 13H, Ar-H).

3'-((4-fluorophenyl) methylene) bis(4-hydroxy-2H-chromen-2-one) (3b, $C_{25}H_{15}FO_6$)

White solid, m.p. 212-214ºC, FTIR (cm^{-1}): 3,445 (OH), 1,628, (C=C), 2,940 (C-H), 1,150 (C–O ether) and 1,250 (C-F),^{1}H NMR (500 MHz, DMSO-d6): δ 6.09 (s, 1H, Ar-CH),16.35 (s 1H, OH), 7.10 -7.74 (m,12H, Ar-H) .

3'-((2-chlorophenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3c, $C_{25}H_{15}ClO_6$)

White solid, m.p. 202-204ºC, FTIR (cm^{-1}) 3,420 (OH), 1,615 (C=C) 2,952(C-H), 1,658 (C=O) and 1,090 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 6.19 (s, 1H, Ar-CH), 16.36 (s 1H, OH), 7.21 -7.79 (m, 12H, Ar-H)

3'-((4-bromophenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3d, $C_{25}H_{15}BrO_6$)

Light yellow solid, m.p. 217-219ºC, FTIR (cm^{-1}) :3,415 (OH), 1,658 (C=O), 2,950 (C-H), 1,612 (C=C), 1,100 (C–O ether) and 1,080 (Br-Ar), ^{1}H NMR (500 MHz, DMSO-d6): δ 6.10 (s, 1H, Ar-CH),16.39 (s 1H, OH), 7.20 -7.78 (m, 12H, Ar-H)

3'-((4-nitrophenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3e, $C_{25}H_{15}NO_8$)

Pink solid, m.p. 234-236ºC, FTIR (cm^{-1}):3,445 (OH), 2,960 (C-H), 1,660 (C=O), 1,616 (C=C) and 1,100 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 6.05 (s, 1H, Ar-CH), 16.42 (s 1H, OH), 7.32 -7.92 (m, 12H, Ar-H

3'-((3-nitrophenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3f, $C_{25}H_{15}NO_8$)

Pink solid, m.p. 210–214ºC, FTIR (cm^{-1}):3,440 (OH), 2,958 (C-H), 1,655 (C=O), 1,614 (C=C) and 1,190 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 5.99 (s, 1H, Ar-CH), 16.40 (s 1H, OH), 7.20 -7.82 (m, 12H, Ar-H.

3'-((4-methoxyphenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3g, $C_{26}H_{18}O_7$)

White solid, m.p. 248-250ºC, FTIR (cm^{-1}): 3,448 (OH), 2,940 (C-H), 1,665 (C=O), 1,614 (C=C) and 1,190 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 5.95(s, 1H, Ar-CH),16.38 (s 1H, OH) 6.65 -7.24 (m, 12H, Ar-H) and.3.29 (s, 3H, OCH_3)

3'-((3-methoxyphenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3h, $C_{26}H_{18}O_7$)

White solid, m.p. 246-248ºC, FTIR (cm^{-1}):3,445 (OH), 2943 (C-H), 1,661 (C=O), 1,616 (C=C, olefin) and 1,094 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 5.90(s, 1H, Ar-CH),16.40 (s 1H, OH) 6.65 -7.24 (m, 12H, Ar-H) and.3.24 (s, 3H, OCH_3)

3'-((2-hydroxy-4-methoxyphenyl) methylene) bis (4-hydroxy-2H-chromen-2-one) (3i, $C_{26}H_{18}O_8$)

White solid, m.p. 244-246ºC, FTIR (cm^{-1}):3,450 (OH), 2,944(C-H), 1,667 (C=O), 1,616 (C=C) and 1199 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 5.90(s, 1H, Ar-CH),16.40 (s, 1H, OH) 5.85 -7.54 (m, 11H, Ar-H),3.62 (s, 3H, OCH_3) and 5.28 (s,1H, aromatic OH)

3'-(thiophen-2-ylmethylene) bis (4-hydroxy-2H-chromen-2-one) (3j, $C_{23}H_{14}O_6S$)

White solid, m.p. 216-218 ºC, FTIR (cm^{-1}):3,440 (OH), 1,628 (C=C), 2,930 (C-H), 1,160 (C–O ether), ^{1}H NMR (500 MHz, DMSO-d6): δ 3.60 (s, 1H, Ar-CH), 16.44 (s 1H, OH), 5.90 -7.12 (m, 11H, Ar-H).

CONCLUSIONS

The reaction of 4-hydroxycoumarin (1) with different aromatic aldehydes compound (2) in the presence of DMAP (5 mol %) as a catalyst in ethanol was carried out to obtain bis (4-hydroxycoumarin-3-yl) derivatives 3(a-j) adopting conventional and ultrasonication methodologies. It was observed that the reaction was completed in shorter reaction times, higher yields, in ultrasonication methodology, as compared to the conventional method. All the as-synthesized compounds were assessed for the antibacterial activity against *Staphylococcus aureus*, interestingly; compound**3a**, **3b**, **3g**, **3h, 3i, and 3j** exhibited acceptable antibacterial activity while as **3c** exhibited excellent antibacterial activity against *Staphylococcus aureus*. The obtained result was supported by molecular docking analysis. Where compound **3c** showed good interaction (-6.8 kcal/mol binding free energy) with bacterial cystathionine gamma-lyase MccB of Staphylococcus aureus protein.

Conflicts of interest

The authors declare no conflict of interest

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