Averrhoa bilimbi in organic transformation: a highly efficient and green biosurfactant for the synthesis of multi-functional chromenes and xanthenes

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A simple, clean and efficient one-pot three-component synthesis of multi-functional chromene and xanthene derivatives has been developed in this study in the presence of a catalytic amount of Brønsted acidic-type biosurfactant bilimbi fruit extract (BFE) under elevated temperature condition. BFE is an unprocessed micellar catalyst that works well in an ethanolic aqueous medium. Employment of ethanol as a co-surfactant enhances catalytic performance of BFE as a biosurfactant. The presence of micelles in the reaction medium was detected using light microscopy and their critical micelle concentration was measured by electrical conductivity method. Some new derivatives of chromene and xanthene are reported here. This novel catalytic medium obtained from an environmentally renewable resource is highly advantageous because of its non-toxicity, higher efficiency, operational simplicity, bio-compatibility as well as absence of any tedious work-up or column chromatography and thus no waste generation. Here, we also signify the 'greenness and sustainability' of the present protocol on the basis of EcoScale metric which validates the practical application of the synthetic procedure.

Keywords: Bilimbi fruit extract, biosurfactant, green chemistry, natural catalyst.

THE development of a proactive protocol for chemical transformations with high efficacy and reduced environmental impact is an important goal in green chemistry and in future sciences. With reduced environmental impact, young discipline of chemistry, green chemistry, promotes the use of highly efficient and environmental benign synthetic procedures to deliver life-saving medicines, and accelerating the guide optimization processes in drug discovery. In the synthetic organic reactions, solvents handle 80% of the total mass and also in 70% of the cases they are just incinerated to recover heat[1,2]. Therefore, their substitution with more environment-friendly options can directly have a positive effect on both emission and hazardous issues[3]. Hence, it is desirable to use environmentally benign water as a safe, abundant, inexpensive and non-toxic solvent instead of organic solvents[4]. Due to the same features, accomplishing organic reactions in water has been explored over the past few decades[5–8].

Methods

Nowadays, a viable alternative for the development of green protocols are biosynthetic processes utilizing bio-based solvents or catalysts for organic tranformations[9]. The advanced and/or newer organic promoters which perform well in the aqueous medium will be beneficial in reaction handling, product selection and purification, improving the reaction rate, and reducing toxic solvent consumption and disposal problems, etc. These are found to be important from the industrial point of view. Henceforth, there is demand for the use of catalyst/media which works avoiding the hydrophobicity of organic precursors and reagents, which is satisfied by the use of surfactant assembled aqueous micelles. Typically, the micellar environment has a pronounced effect in enhancing the reaction rate with good efficiency exhibiting environmentally benign character, which act as 'nanoreactors' characterized by exclusive features[10]. Hitherto, organic transformations involving surfactants in aqueous media have received considerable attention from researchers[11,12].

All these findings validate the case of a naturally occurring medium/phase acting as surfactant, known as a biosurfactant. The surfactants that are directly obtained from natural sources, viz. plants, animals, or microbial cells, or by separation procedures such as extraction, precipitation or distillation are known as biosurfactants. They have potential industrial applications such as use in improved oil recovery, lubricants, food processing

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industry, health care and crude oil recovery[13]. Furthermore, well-known evaluations of the properties of these natural dispersants in dermal and transdermal drug delivery systems, food, and cosmetics and soap preparations are evolving at a rapid rate[14].

Emphasizing the significance of biosurfactants and extending our continuous enduring efforts to develop newer and efficient protocols for the synthesis of bioactive heterocycles from readily available raw materials employing green tools[15], herein we have explored the synthetic utility of extract of fruits of *Averrhoa bilimbi* Linn. in an organic transformation as a catalyst.

According to the literature, tree *A. bilimbi* Linn., family oxalidaceae, is commonly known as bilimbi tree, cucumber tree, tree sorrel, pickle tree. It is widely cultivated throughout the tropical regions for its fruits, which are commonly known as bilimbi[16]. The fruits possess antibacterial, antiscorbutic, astringent and postpartum protective properties[17,18]. They can be eaten raw, used in the preparation of pickles or as a substitute for tamarind. They are also effective in removing iron rust in metals and are used for cleaning utensils. Bilimbi fruits are also utilized in the preparation soft drinks[19] and fruits jam[20].

The bilimbi fruit extract (BFE) has high acidity (pH range 0.9–1.5), which is mainly because of vitamin C and oxalic acid; oxalic acid has a concentration range 0.86%–1.032% (w/w)[21]. Furthermore, the fruit extract consists of volatile compounds like aliphatic acids (47.8%) other than oxalic acid, and significant amount of carbonyl compounds (20.3%), as well as non-terpenoid alcohols (7.8%), phenols (3.5%), terpenoids (2.4%) and miscellaneous compounds (6.5%), according to GC–MS analysis[22]. In this context, bilimbi fruit juice works as a Brønsted acidic-type biosurfactant in organic reaction medium. Hence, we have a better catalytic option compared to traditional harmful corrosive acids and also chemical surfactants for organic transformations.

To the best of our knowledge, there is no report or study on BFE as a biocatalyst for organic transformations. Here, we have used BFE for the synthesis of 10,11-dihydrochromeno[4,3-b]chromene-6,8(7*H*, 9*H*)-diones and 1,8-dioxo-octahydroxanthenes.

Results and discussion

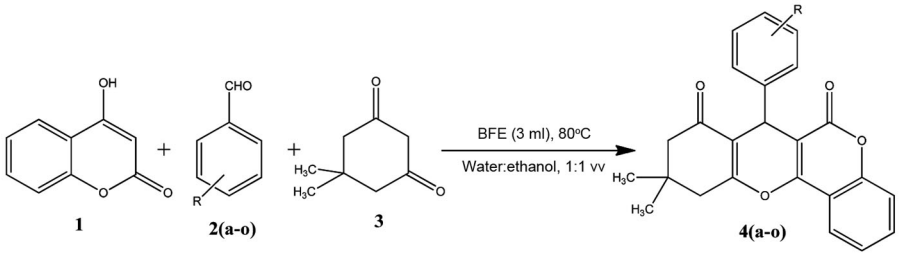
We have selected fruits of genus *Averrhoa* because of their acidic pH, so as to use their extract as a catalytic medium. In this regard, fresh, mature and green bilimbi fruits were collected from the botanical garden of Shivaji University, Kolhapur, Maharashtra, India. The fruits were washed with distilled water, cut into small pieces and then crushed using a mixer-grinder to obtain the extract. This extract was filtered through cotton/muslin cloth so as to remove solid material. This clear extract was stored at 0°–5°C in a refrigerator and used as a catalyst, unless otherwise mentioned. The pH of BFE was measured using a pH-meter (Equip-Tronics digital Model EQ 610) and found to be 1.38, which may change according to the geographical coordinates, seasons, stages in the maturity of the fruits, etc.

We have chosen the pharmaceutically important chromeno[4,3-*b*]chromene nucleus for synthesis, which basically has a coumarin core. It is well known that coumarin-core derivatives are prominent heterocyclic molecules with a diverse range of biological properties[23]. The significant applications of the coumarin-fused heterocycles include antitumor[24], antibacterial[25], antifungal[26], anticoagulant[27], anti-inflammatory[28] and antiviral[29]. The literature survey shows that different catalysts have been reported in the synthesis of chromeno[4,3-b]chromene derivatives, viz. [DMDBSI]·2HSO_4 (ref 30), I_2 in acetic acid[31], $Fe(DS)_3$ (ref. 32), H_3BO_3-SDS/H_2O (ref. 33), *p*-TSA (ref. 34), CuO nanoparticles[35], etc. These reported methods have various drawbacks such as expensive and toxic catalysts, long reaction time, commercial unavailability of reagents, low yield, tedious work-up or chromatographic separation, etc. However, there are no reports on the use of environment-friendly biocatalyst for the preparation of chromeno[4,3-*b*]chromenes.

Herein, we report a green protocol for the synthesis of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione through a one-pot three-component reaction between 4-hydroxycoumarin (**1**), aromatic aldehydes (**2**) and dimedone (**3**) in a non-toxic ethanolic aqueous medium at 80°C using a novel BFE as a micellar biocatalyst (Scheme 1).

To obtain the optimized reaction conditions, a 25 ml round-bottom flask was loaded with 4-hydroxycoumarin (**1**; 1.0 mmol), 4-methoxy-benzaldehyde (**2**; 1.0 mmol), dimedone (**3**; 1.0 mmol) at room temperature and then BFE (1 mL) was added. This model reaction mixture was stirred, which forms the target product in 6.0 h with trace yield. Here, by stirring the substrates, with successive increase in the amount of catalyst from 1.0 mL to 5.0 mL gives the target product **4c** in low yield consecutively, even after prolonged reaction time (Table 1, entries 1–5).

To improve the results, the model reactants were heated at an elevated temperature of 70°C, adding 2 mL of BFE to this, produced a sticky reaction mixture and furnished the product **4c** (25% yield; Table 1, entry 6), which was confirmed by TLC. Following this, increasing the temperature, with more amount of catalyst, was not found to be effective in increasing the amount of the product (Table 1, entries 7–10). So, we focused on testifying the solvent effect on the model reaction, hence reaction treated with 2 mL of water as a solvent, which found to make the reaction mixture turbid immediately on addition of BFE, furnished 68% of product yield at the reflux condition of temperature. While with the ethanol as a common laboratory solvent, reaction gave 71% product yield, indicating less increase but within less time compared with water (Table 1, entries 11 and 12).



Scheme 1. Biosurfactant bilimbi fruit extract (BFE)-catalysed synthesis of 10,11-dihydrochromeno [4,3-*b*]chromene-6,8(7*H*,9*H*)-diones.

Table 1. Optimization of cyclo-condensation reactions between 4-hydroxycoumarin (**1**), 4-methoxy benzaldehyde (**2c**), dimedone (**3**)[a]

Entry	BFE (mL)	Solvent[b]	Temperature (°C)	Time (h)	Yield[c] (%)
1	1.0	–	RT	6.0	Trace
2	2.0	–	RT	4.5	23
3	3.0	–	RT	4.5	23
4	4.0	–	RT	4.5	26
5	5.0	–	RT	4.5	31
6	2.0	–	70	4.0	25
8	2.0	–	80	3.0	37
9	3.0	–	100	2.0	55
10	4.0	–	100	2.0	61
11	2.0	Water	Reflux	3.5	68
12	2.0	Ethanol	Reflux	3.0	71
13	1.0	Water : ethanol	80	3.5	82
14	2.0	Water : ethanol	80	3.5	85
15	3.0	Water : ethanol[d]	80	3.0	87, 96, 91
16	4.0	Water : ethanol	80	3.0	96
17	5.0	Water : ethanol	80	3.0	91
18	–	Water : ethanol	80	4.0	38

[a]Reactions were performed using 4-hydroxycoumarin (**1**; 1.0 mmol), 4-methoxybenzaldehyde (**2**; 1.0 mmol), dimedone (**3**; 1.0 mmol) and BFE. [b]Amount of solvent is 2 ml and water : ethanol composition is 1 : 1 v/v. [c]Isolated yield of pure product. [d]Water : ethanol composition is 2 : 1, 1 : 1, 1 : 2 v/v.

Interestingly, using water : ethanol as a solvent mixture at 80°C, gave 96% of the product yield using 3 ml of BFE in 3.0 h (Table 1, entry 15). On further addition of catalyst, the reaction showed no significant effect with respect to yield and time in product formation (Table 1, entries 16 and 17). Hence 3 ml of BFE was considered as sufficient to successfully catalyse the reaction.

In order to determine the best water : ethanol solvent proportion, we optimized the model reaction at different solvent proportions. The results showed that water : ethanol with 1 : 1 v/v was the best option (Table 1, entry 15). We also optimized the reaction to verify the best catalyst : solvent ratio. The results indicated that the catalyst : solvent ratios 3 : 2 and 4 : 2, which are above the critical micelle concentration (CMC) (63% v/v) of BFE, are best regarding time as well as yield of the product (Table 1, entries 15 and 16). Moreover, reaction at 80°C with no catalyst and using water : ethanol as a solvent gave is low product yield within 4.0 h, emphasizing the importance of catalytic medium to increase the reaction rate so as to give the final target product (Table 1, entry 18).

Thus, on completion of the reaction scrutinized by TLC with *n*-hexane : ethyl acetate (6 : 4) solvent system, the product obtained 10,11-dimethyl-7-(4-methoxyphenyl)-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*, 9*H*)-dione was separated by filtration. After washing with cold distilled water and 96% ethanol several times, it is purified by 96% ethanol. In this way, all other obtained derivatives were characterized by their physical constants and confirmed using spectral techniques, viz., FTIR, ^{1}H-NMR, ^{13}C-NMR and EI-MS.

Initially, it was found that immediately after adding BFE to the reaction mixture with water as the reaction medium, we obtained a turbid emulsion forming a stable colloidal dispersion with entities known as micelles, which were observed using an optical microscope (Figure 1 *b*). When we added BFE, the water-insoluble components from the solution moved into the hydrophobic core of the micelles, where with effective collisions the dehydrative reaction occurred to form the product. The added ethanol enhanced the solubility of organic components and also worked as a co-surfactant in the micellar medium[36]. It is known that ethanol molecules reduce the emulsion size,

lowering the surface tension of the micelles, which increases surface area by providing bonus steric repulsion[37] (Figure 1 *a*). This, in due course ultimately assist to propel the reaction in a proper direction to form the desired product.

For surfactant solutions, a certain minimum concentration at which aggregates are formed in solution by monomers in the surfactant, is known as the critical micelle concentration, at which there is a drastic variation in physico-chemical properties such as turbidity, surface tension, conductivity, etc.[38]. Hence, CMC of BFE in ethanolic aqueous medium (water : ethanol = 1 : 1 v/v) was determined in this study by electrical conductivity method and was found to be 63% (Figure 2). And this is also the optimum concentration of BFE as a catalytic media, which transformed the reactants to the target product effectively and efficiently (Table 1, entry 15 and 16). The reason for this efficient catalysis is not only the acidic media provided by BFE but the unique micellar media, too. The micellar media are proved to be effective in dehydration reactions[39].

To determine the strength of BFE catalyst as an acidic medium providing synergistic effect to micellar media, different natural surfactants obtained from some acidic fruits and commercially available chemical surfactant sodium dodecyl sulphate (SDS) in the presence of oxalic acid as catalyst were explored for their catalytic activity in the present protocol. The obtained results are given in Table 2 and compared with BFE. On comparing with various natural and commercial surfactants, the biosurfactant obtained from BFE was the best considering time and yield of the product (Table 2, entry 1), which emphasizes the role of BFE as a catalyst providing, viz. strong Brønsted acidity also acting as a surfactant in a given reaction medium to promote the given protocol. As pH of the biosurfactants used increases (Table 2, entries 1–7), there is marked decrease in the yield of the product, which confirms that the reaction is in competence to the acidity of the catalytic promoter, among which BFE works best under the said conditions.

Table 2 (entries 8–12) also shows results of the control study of commercial chemical surfactant SDS with oxalic acid as a catalytic medium, mimicking the BFE environment. At first, by adding only aqueous surfactant SDS solution to the model reaction, it proceeded sluggishly to give a low product yield (Table 2, entry 8). However, with the addition of oxalic acid to the micellar SDS–H_2O reaction medium, it prominently yielded 41% of product within 4.5 h (Table 2, entry 9). This indicates that it is necessary to have a medium with acidic pH to successively carry out the reaction. So, the amount of SDS–H_2O and oxalic acid was increased, which resulted in a marginal increase in the product yield (Table 2, entry 10). Thus, by changing the ratio of surfactant : acid (Table 2, entries 11 and 12), there was noticeable increase in the product yield in comparatively less time. These test results predict that the product formation is not only affected by the presence of acid in the micellar medium but also by the ratio of surfactant : acid. Thus, we conclude that the presence of acidic medium provides synergistic effect to the micellar medium of reaction for the present protocol.

Extending the scope and verifying the limitations of BFE as a catalytic medium, from the results of the optimized reaction conditions (using water : ethanol as a solvent system and 3 ml catalyst loading of BFE at 80°C), 10,10-dimethyl-7-(4-aryl)-10,11-dihydrochromeno[4,3-*b*]-chromene-6,8(7*H*, 9*H*)-dione derivatives were synthesized (Table 3, **4a**–**4o**). This multi-component method can be used for electron-donating and electron-withdrawing groups possessing aromatic aldehydes. The heterocyclic aldehydes work well under the given optimized conditions. Here, all the three-component reactions were completed within 2.0–3.5 h to obtain good to excellent yields of the products. The work-up procedure for most of the reactions was only to filter and wash the obtained

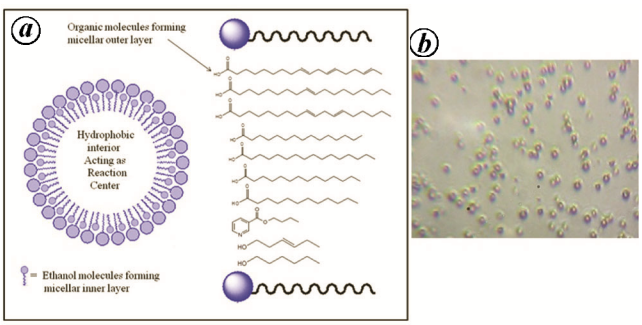


Figure 1. ***a***, Pictorial representation displaying formation of micelles in ethanolic aqueous solution. ***b***, Optical photomicrograph of model reaction mixture in magnified view.

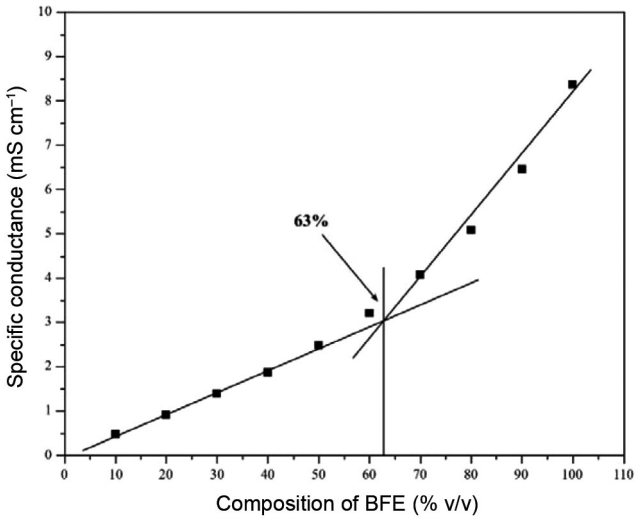
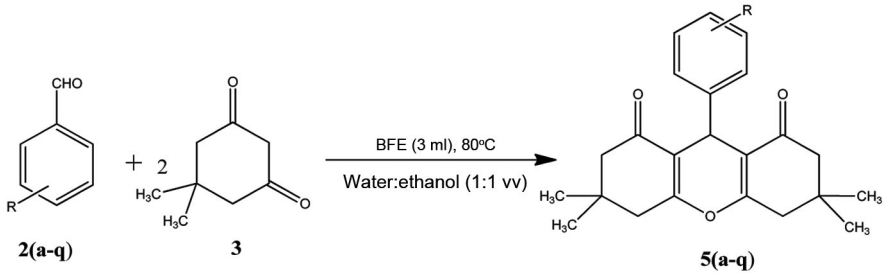


Figure 2. Plot showing critical micelle concentration (CMC) of bilimbi fruit extract (BFE) extract in water : ethanol media using electrical conductivity method.

Table 2. Comparison of efficiency of different biosurfactants[a] and commercial surfactant[b] sodium dodecyl sulphate (SDS) for 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione synthesis

Entry	Surfactant	pH	Time (h)	Yield[c] (%)
1	Bilimbi extract	1.38	3.0	96
2	Starfruit extract	2.76	3.25	75
3	Lime extract	2.40	3.0	76
4	Lemon extract	2.30	3.0	78
5	Pineapple extract	3.71	4.0	61
6	Orange extract	3.51	3.5	65
7	Grapefruit extract	3.38	3.5	65
8	SDS–H_2O (2 ml)	7.08	7.0	33
9	SDS–H_2O (1 ml) + oxalic acid (1 ml)	2.01	4.5	41
10	SDS–H_2O (2 ml) + oxalic acid (2 ml)	2.01	4.5	47
11	SDS–H_2O (3 ml) + oxalic acid (2 ml)	2.01	3.0	71
12	SDS–H_2O (4 ml) + oxalic acid (3 ml)	2.01	2.5	78

[a]Reaction conditions: 4-hydroxycoumarin (**1**; 0 mmol), 4-methoxybenzaldehyde (**2**; 1.0 mmol), dimedone (**3**; 1.0 mmol), biosurfactant (3 ml), water : ethanol (1 : 1 v/v, 2 ml), 80°C temperature. [b]Reaction conditions: 4-hydroxycoumarin (**1**; 1.0 mmol), 4-methoxybenzaldehyde (**2**; 1.0 mmol), dimedone (**3**; 1.0 mmol), aqueous SDS solution (0.1 g/ml of H_2O), oxalic acid (1 N), 80°C temperature. [c]Isolated yield of pure product.



Scheme 2. BEF-catalysed 1,8-dioxo-octahydroxanthene synthesis.

derivative with cold distilled water and 96% ethanol to get the isolated product. The purification of obtained products was done by recrystallization using 96% ethanol.

The synthesis of 1,8-dioxo-octahydroxanthenes is possible by replacing 4-hydroxycoumarin by dimedone (Scheme 2). We found that, this reaction also worked efficiently with the biosurfactant in the Brønsted acidic-type catalytic system (Table 4).

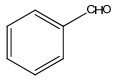
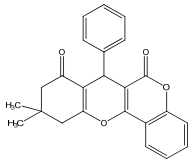
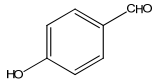
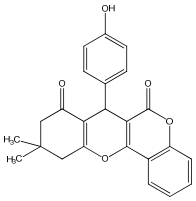
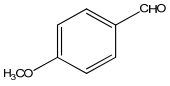
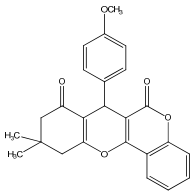
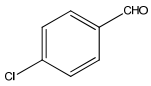
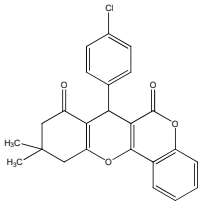
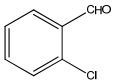
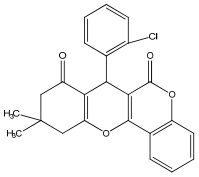
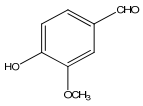
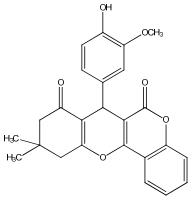
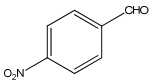
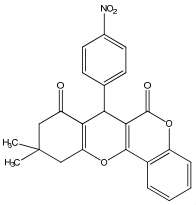
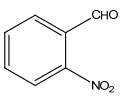
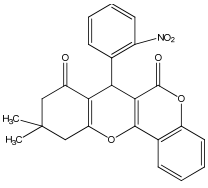
Xanthenes are another class of fused heterocycles having considerable interest due to their widespread and important biological properties[40–45], e.g. anti-cancer[46]. A number of catalysts have been reported for the synthesis of xanthene compounds employing various methodologies[46–49]. However, these methods have certain disadvantages, specifically use of higher catalyst loading, long reaction time, hazardous acidic or basic environment and a narrow range of xanthene derivatives.

Scheme 3 shows the plausible reaction mechanism. Under ambient reaction conditions, in an ethanolic aqueous solution, surfactant molecules from BFE may get aggregated with the hydrophobic tail and hydrophilic head to form micelles. The hydrophobic reactants, i.e. aldehyde (**1**) and enolic form of dimedone (**2′**) in the acidic medium of BFE, repelled by polar water molecules, move inside the lipophilic centre of the micellar structure where effective collisions takes place, releasing water molecules by Knoevenagel condensation, which are repelled out to the hydrophilic surroundings, so as to form the corresponding product (**II**). This Knoevenagel product (**II**) was further reacted with 4-hydroxycoumarin (**3**) in the Michael addition manner forming the desired product (**4**) after cyclo-dehydration.

Post-experimental analysis

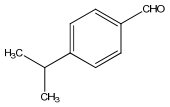
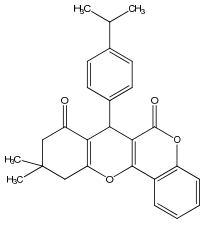
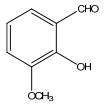
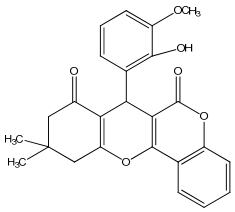
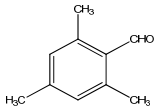
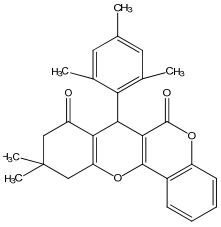
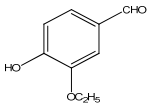
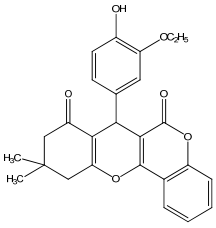
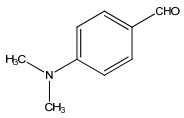
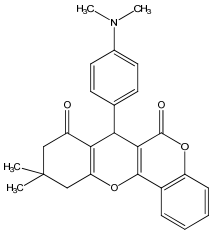
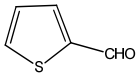
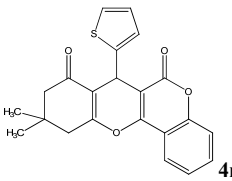
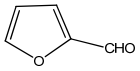
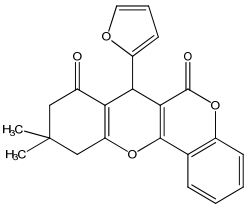
If we design and execute a process as green, then we need metrics to measure greenness. In order to determine the greenest procedure used in a given synthesis, we analysed green factors like EcoScale, e-factor and reaction mass efficiency (RME) for the synthesis of chromeno[4,3-*b*]chromene and 1,8-dioxo-octahydroxanthene derivatives (**4c**) and (**5a**). The EcoScale score for the present protocol, by any valid penalty points, is assessed to maximum value of 100. The penalty points considered for this

Table 3. Biosurfactant BFE-catalysed 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-diones synthesis[a]

Sr. no.	Aromatic aldehyde	Product	Time (h)	Yield[b] (%)
1		 **4a**	3.0	88
2		 **4b**	2.5	89
3		 **4c**	3.0	95
4		 **4d**	2.5	92
5		 **4e**	2.5	90
6		 **4f**	2.25	89
7		 **4g**	3.0	92
8		 **4h**	3.25	91

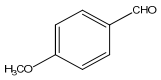
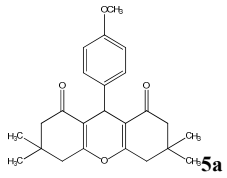
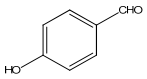
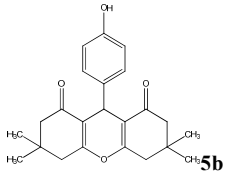
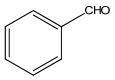
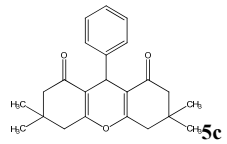
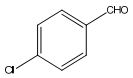
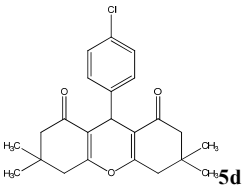
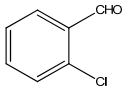
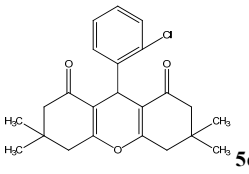
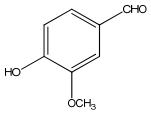
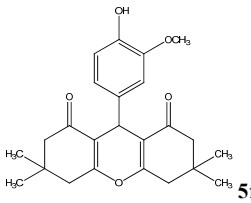
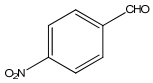
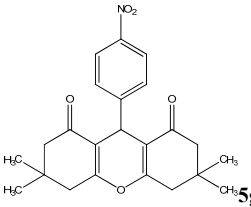
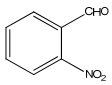
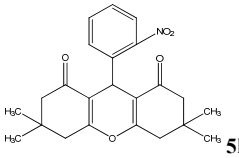
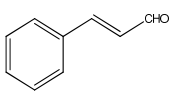
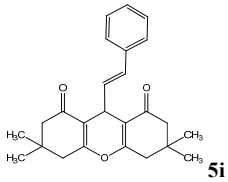
(*Contd*)

Table 3. (*Contd*)

Sr. no.	Aromatic aldehyde	Product	Time (h)	Yield[b] (%)
9		 **4i**	3.0	90
10		 **4j**	2.25	90
11		 **4k**	2.5	88
12		 **4l**	2.5	89
13		 **4m**	2.0	90
14		 **4n**	2.0	88
15		 **4o**	2.5	87

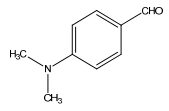
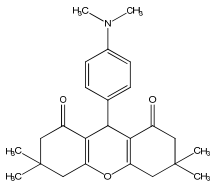
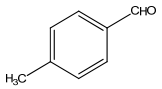
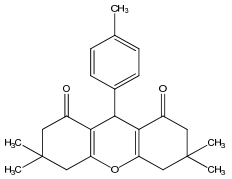
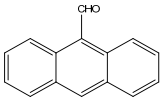
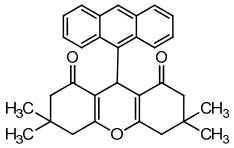
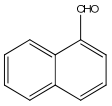
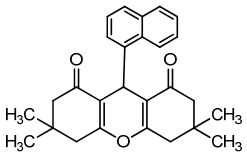
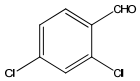
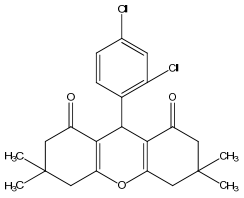
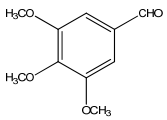
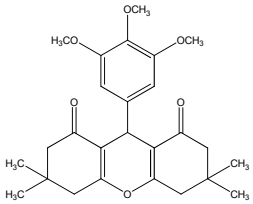
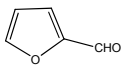
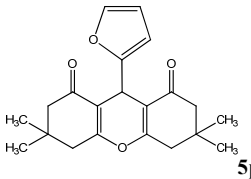
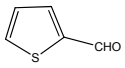
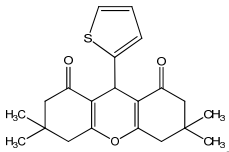
[a]Reaction conditions: 4-hydroxycoumarin (**1**; 1.0 mmol), aromatic aldehydes (**2**; 1.0 mmol), dimedone (**3**; 1.0 mmol), BFE (3.0 ml) in water : ethanol (1 : 1 v/v, 2 ml) medium at 80°C. [b]Isolated yield of pure product.

Table 4. Biosurfactant BFE-catalysed cyclo-condensation of dimedone and aromatic aldehydes[a]

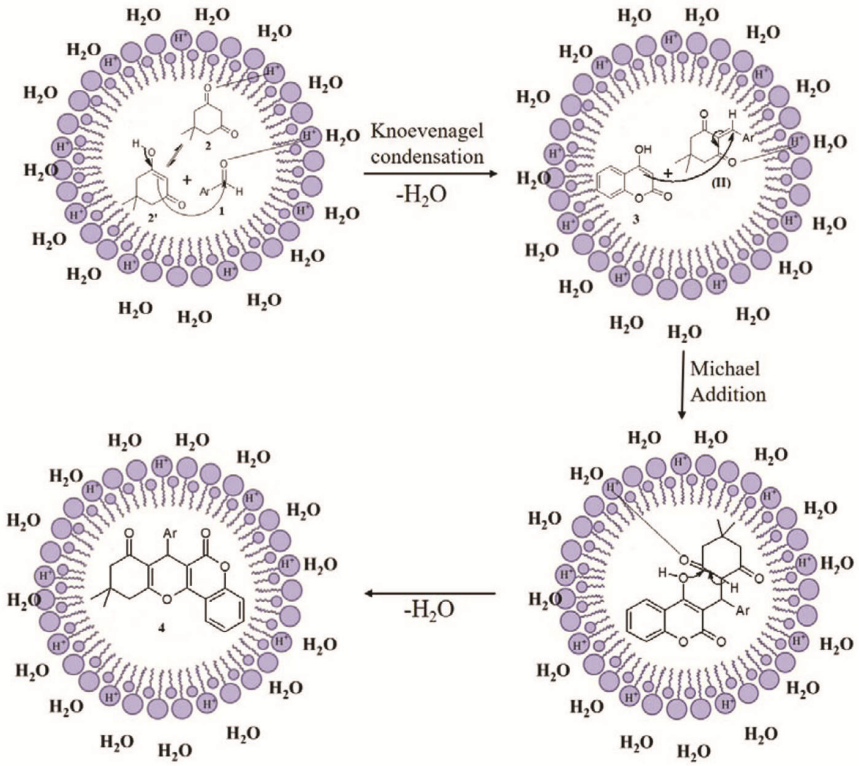
Sr. no.	Aldehyde	Product	Time (h)	Yield[b] (%)
1		 **5a**	3.5	96
2		 **5b**	3.0	94
3		 **5c**	4.0	94
4		 **5d**	3.5	95
5		 **5e**	4.0	97
6		 **5f**	3.0	92
7		 **5g**	3.5	98
8		 **5h**	4.0	95
9		 **5i**	3.0	90

(*Contd*)

Table 4. (*Contd*)

Sr. no.	Aldehyde	Product	Time (h)	Yield[b] (%)
10		 **5j**	3.0	91
11		 **5k**	3.5	91
12		 **5l**	4.0	88
13		 **5m**	4.0	89
14		 **5n**	3.5	92
15		 **5o**	3.5	85
16		 **5p**	4.0	91
17		 **5q**	3.0	92

[a]Reaction conditions: All reactions were performed by stirring aromatic aldehyde (**1**; 1.0 mmol), dimedone (**3**; 2.0 mmol) and BFE (3 ml) in water : ethanol (1 : 1 v/v, 2 ml) at 80°C. [b]Isolated yield of a pure product based on aldehyde.



Scheme 3. Proposed reaction mechanism between dimedone (**1**), aldehyde (**2**) and 4-hydroxycoumarin (**3**) catalysed by Brønsted acidic-type biosurfactant BFE.

Table 5. Calculation of EcoScale green parameter for the synthesis of compounds **4c** and **5a**

Entry	Parameters		Penalty points
1	Yield	100–95 (yield of **4c**)/2	2.5
2	Price of reaction components	<US$ 10	00
3	Safety	Safety	00
4	Technical set-up	Common set-up	00
5	Temperature/time	Heating >1 h	03
6	Workup and purification	Crystallization and filtration	01
	Total		6.5

EcoScale=100 – sum of individual penalties = 100–6.5 = 93.5.

protocol are given in Table 5 and work-up involves no manipulations in the order given by reported methods[50,51].

As demonstrated in Table 6, the present protocol is the greenest among the methods reported in the literature in reference to green environmental parameters in the preparation of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*, 9*H*)-dione (**4c**) and 1,8-dioxo-octahydroxanthene (**5a**) derivatives. The results show that this method is with good combination between RME, e-factor and EcoScale, provides a cleaner and greener synthetic procedure than other reported methods.

Experiments

The HPLC-Q-TOF-MS/MS was carried out using an Agilent 1290 LC system coupled to column Q-TOF-MS with dual ESI source. The specific conductivity was measured (EQUIP-TRONICS conductivity meter model NO EQ-660A). IR spectra were measured (Bruker ALPHAFT-IR spectrophotometer) using KBr pellets in ν_{max} (cm^{-1}). TLC was performed (Merck silicagel60 F_{254} plates) and all melting points, mentioned uncorrected, were measured on DBK programmable melting point apparatus. The ^{1}H-NMR and ^{13}C-NMR spectra were measured (Bruker AVANCE spectrometer) using $CDCl_3$ and DMSO-d_6 as solvents. The chemical shifts were noted in δ parts per million (ppm) with tetramethylsilane (TMS) as a internal reference. The elemental analyses of C, H, and N was also performed (Carl Erba EA 1108).

Optical microscopy measurements: On an ordinary compound microscope, a drop of turbid reaction mixture was scrutinized under 100 × magnification.

Table 6. Comparison of various parameters of green chemistry for the present method[a] and other reported methods

Product	Catalyst	Reaction conditions			Yield (%)	RME[A]	e-factor[B]	EcoScale[C]	Reference
		Solvent (ml)	Temperature (°C)	Time (min/h)					
4c	H_3BO_3, SDS	H_2O	70–80	6.0 h	85	78.71	0.168	89.5	33
4c	$Fe(DS)_3$	H_2O	70	2.5 h	80	74.20	0.237	86.0	32
4c	$[DMDBSI]\cdot 2HSO_4$	H_2O	Reflux	3.0 h	89	82.15	0.119	81.5	30
4c	BFE[a]	EtOH + H_2O	80	3.0 h	95	87.32	0.050	93.5	–
5a	$MgSO_4$	MeOH	Reflux	1–2 h	80	73.32	0.246	81.0	50
5a	$NaHSO_4\cdot SiO_2$ Silica chloride	MeCN	Reflux	6.5 h 6.0 h	95	87.14	0.048	79.5	49
5a	$[TMPSA]HSO_4$ (TSILs)	H_2O	Reflux	2.0 h	93	85.33	0.070	92.5	51
5a	Iodine	i-Propanol	70-80	17 min	90	82.57	0.135	92.0	48
5a	BFE[a]	EtOH + H_2O	80	3.5 h	96	87.14	0.048	94.0	–

Mathematical equations of green parameters used for calculation: [A]RME = Mass of product/sum of mass of reactants × 100; [B]e-factor = Mass of total waste/mass of product; [C]EcoScale = 100 – sum of individual penalties.

Figure 3. ***a***, Bilimbi fruits; ***b***, bilimbi slices; ***c***, BFE.

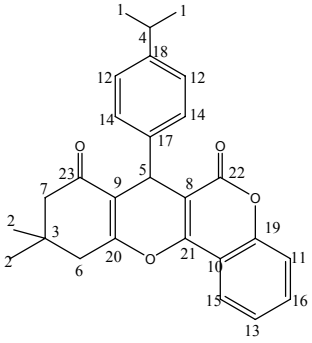
Preparation of fruit extract: Fresh and mature bilimbi fruits were obtained from the botanical garden, at Shivaji University, Kolhapur. They were cut into small pieces by a knife and pressed with the help of domestic pressure to get a turbid extract. This was filtered using a muslin cloth to obtain a clean, white turbid extract (Figure 3). This extract was stored at 0°–5°C and found to be stable for several days.

General procedure for the synthesis of 10,11-dihydrochromeno[4,3-b]chromene-6,8(7H, 9H)-dione (Scheme 1): To a 25 ml round-bottom flask was added 4-hydroxycoumarin (**1**; 1.0 mmol, 0.162 g) aldehyde (**2a**–**2o**; 1.0 mmol), dimedone (**3**; 1.0 mmol, 0.140 g) and BFE catalyst (3 ml) in water : ethanol (1 : 1 v/v, 2 ml). This reaction mixture was kept in a pre-heated oil bath maintained at 80°C and stirred. The formation of the product was examined using TLC with solvent system of *n*-hexane : ethyl acetate (6 : 4). After completion of the reaction, to remove the catalyst, solid product was washed with distilled water (5 ml). Further purification of the products was carried out by recrystallization with ethanol (96%). The identification of synthesized compounds was confirmed by FTIR, ^{1}H-NMR, ^{13}C-NMR and EI-MS spectral analyses.

General procedure for the synthesis of 1,8-dioxo-octahydroxanthenes (Scheme 2): The reaction mixture of an aldehyde (**2a**–**2q**; 1.0 mmol), dimedone (**3**; 2.0 mmol) and BFE catalyst (3 ml) in water : ethanol (1 : 1 v/v, 2 ml) was taken in a 25 ml round-bottom flask and heated in an oil bath maintained at 80°C till completion of the reaction. This was monitored by TLC, which showed a single spot for the product for most of the synthesized derivatives, with the solvent system of *n*-hexane : ethyl acetate (7 : 3). Then the reaction mixture was cooled to room temperature, the obtained product was filtered and washed with distilled water. The product was recrystallized with 96% ethanol, if necessary.

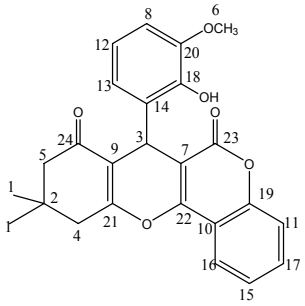
The analytical details of the newly synthesized compounds are provided below.

7-(4-isopropylphenyl)-10,10-dimethyl-10,11-dihyrochromeno[4,3-*b*]chromene-6,8(7*H*, 9*H*)-dione (**4i**): m.p. 248°–250°C (EtOH); IR(KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 2991, 1709, 1657, 1602, 1488, 1353, 1187, 1095, 1017, 894, 765. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.07 (s, 3H, –CH3), 1.12 (s, 3H, –CH3), 2.18 (d, 1H, –CH), 2.34 (d, 1H, –CH), 2.71–2.81 (m, 2H, –CH), 4.63 (s, 1H, –CH), 7.03 (d, 2H, Ar-H), 7.15 (d, 2H, Ar-H), 7.47 (m, 2H, Ar-H), 7.68 (t, 1H, Ar-H), 7.93 (d, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6, 300 MHz):



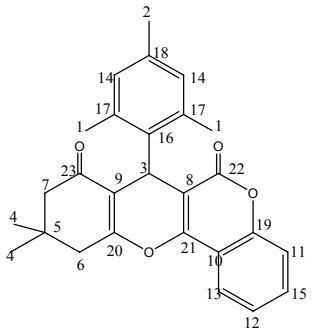
δ 26.8 (C-1), 27.5 (C-2), 29.3 (C-3), 30.4 (C-4), 34.8 (C-5), 33.5 (C-6), 49.5 (C-7), 104.9 (C-8), 113.8 (C-9), 117.7 (C-10), 121.0 (C-11), 123.4 (C-12), 125.1 (C-13), 125.9 (C-14), 126.5 (C-15), 128.8 (C-16), 139.0 (C-17), 145.8 (C-18), 151.2 (C-19), 154.9 (C-20), 160.2 (C-21), 162.8 (C-22), 197.0 (C-23); MS (EI) *m/z*: 415.0834 $[M+1]^+$; Anal calculated for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32. Found: C, 78.37; H, 6.41.

7-(2-hydroxy,3-methoxyphenyl)-10,10-dimethyl-10,11-dihyrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione (**4j**): m.p. 264°–266°C (EtOH); IR(KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 3446, 2987, 1718, 1667, 1610, 1518, 1358, 1270, 1184, 1037, 868, 786. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.07 (s, 3 H, –CH3), 1.11 (s, 3H, –CH3), 2.19 (d, 1H, –CH), 2.36 (d, 1H, –CH), 2.78 (s, 2H, –CH2), 3.71 (s, 3H, –OCH3), 4.68 (s, 1H, –CH), 6.61 (d, 1H, Ar-H), 6.67 (d, 1H, Ar–H), 6.83 (d, 1H, Ar–H), 7.45–7.49 (m, 2H), 7.71 (t, 1H, Ar-H), 7.91 (d, 1H, Ar–H), 8.97 (s, 1H, –OH); ^{13}C-NMR



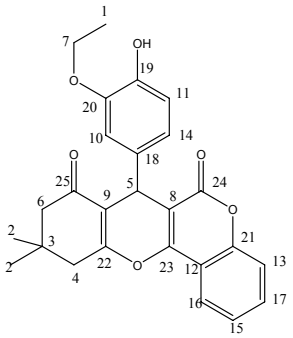
(DMSO-d_6, 300 MHz): δ 26.3 (C-1), 28.4 (C-2), 31.7 (C-3), 32.6 (C-4), 49.7 (C-5), 56.0 (C-6), 105.9 (C-7), 114.5 (C-8), 116.9 (C-9), 117.4 (C-10), 121.3 (C-11), 121.9 (C-12), 123.8 (C-13), 124.7 (C-14), 125.6 (C-15), 126.5 (C-16), 128.4 (C-17), 145.3 (C-18), 150.9 (C-19), 151.8 (C-20), 155.8 (C-21), 160.4 (C-22), 162.5 (C-23), 196.6 (C-24); MS (EI) *m/z*: 403.1763$[M+1]^+$; Anal. calculated for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30, Found: C, 71.63; H, 5.36.

7-(2,4,6-trimethylphenyl)-10,10-dimethyl-10,11-dihyrochromeno[4,3-*b*]chromene-6,8(7*H*, 9*H*)-dione (**4k**): m.p. 264°–266°C (EtOH); IR(KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 2993, 1713, 1662, 1608, 1514, 1361, 1272, 1181, 1033, 863, 779. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.02 (s, 3 H, –CH3), 1.10 (s, 3 H, –CH3), 2.20 (d, 1H, –CH), 2.34 (d, 1H, –CH), 2.76 (s, 2H, –CH2), 3.70 (s, 3H, –CH3), 4.61 (s, 1H, –CH), 6.61 (d, 1H, Ar–H), 6.64 (d, 1H, Ar–H), 6.81 (d, 1H, Ar–H), 7.43–7.48 (m, 2H, Ar–H), 7.69 (t, 1H, Ar–H), 7.92 (d, 1H, Ar–H); ^{13}C-NMR (DMSO-d_6, 300 MHz):



δ 19.5 (C-1), 21.6 (C-2), 31.4 (C-3), 26.9 (C-4), 28.0 (C-5), 43.2 (C-6), 50.6 (C-7), 105 (C-8), 116.2 (C-9), 117.0 (C-10), 121.1 (C-11), 125.5 (C-12), 126.1 (C-13), 127.5 (C-14), 128.2 (C-15), 130.6 (C-16), 135.8 (C-17), 136.5 (C-18), 150.0 (C-19), 155.5 (C-20), 160.8 (C-21), 163.3 (C-22), 196.0 (C-23); MS (EI) *m/z*: 415.1225 $[M+1]^+$; Anal. calculated for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32. Found: C, 78.29; H, 6.19.

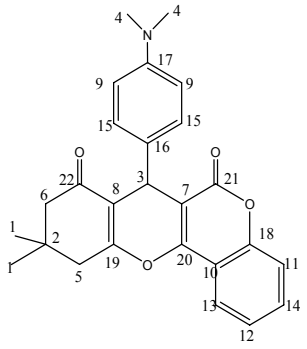
7-(3-ethoxy, 4-hydroxyphenyl)-10,10-dimethyl-10,11-dihyrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione (**4l**): m.p. 235–237°C (EtOH); IR(KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 3434, 2993, 1713, 1662, 1608, 1514, 1361, 1272, 1181, 1033, 863,



779. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.02 (s, 3 H, –CH3), 1.11 (s, 3 H, –CH3), 1.19 (s, 3 H, –CH3), 2.20 (d, 1H, –CH), 2.34 (d,1H, –CH), 2.76 (s, 2H, –CH2), 3.70 (s, 3H, –CH3), 4.61 (s, 1H, –CH3), 6.61 (d, 1H, Ar–H), 6.64 (d, 1H, Ar–H), 6.81 (d, 1H, Ar–H), 7.43–7.48 (m, 2H, Ar–H), 7.69 (t, 1H, Ar–H), 7.92 (d, 1H, Ar–H), 8.88 (s, 1 H); ^{13}C-NMR (DMSO-d_6, 300 MHz): δ 14.6 (C-1), 26.5 (C-2), 28.5 (C-3), 31.9 (C-4), 32.2 (C-5), 50.0 (C-6), 63.9 (C-7), 106.1 (C-8), 113.1 (C-9), 113.9 (C-10), 114.4 (C-11), 115.2 (C-12), 116.4 (C-13), 120.5 (C-14), 122.5 (C-15), 124.6 (C-16), 132.6 (C-17), 133.7 (C-18), 145.8 (C-19), 146.0 (C-20), 151.8 (C-21), 153.2 (C-22), 159.9

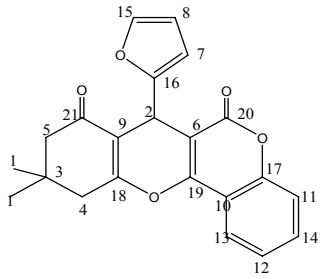
(C-23), 162.3 (C-24), 195.9 (C-25); MS (EI) *m/z*: 432.3481[M^+]; Anal. calculated for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59, Found: C, 72.10; H, 5.47.

7-(4-(dimethylamino)phenyl)-10,10-dimethyl-10,11-dihyrochromeno[4,3-*b*]chromene-6,8(7*H*, 9*H*)-dione (**4m**): m.p. 216°–218°C (EtOH); IR(KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 2951, 1726,



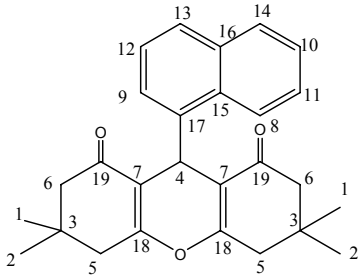
1663, 1606, 1497, 1468, 1363, 1312, 1250, 1183, 1167, 1140, 1033, 893, 764. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.14 (s, 3H, –CH3), 1.17 (s, 3 H, –CH3), 2.21 (m, 2 H, –CH2), 2.39 (m, 2 H, –CH2), 4.85 (s, 1 H, –CH), 7.43 (d, 2H, Ar–H), 7.55 (m, 2H, Ar–H), 7.79 (t, 1H, Ar–H); 7.98 (d, 1H, Ar–H); ^{13}C-NMR (DMSO-d_6, 300 MHz): δ 26.2 (C-1), 28.2 (C-2), 29.1 (C-3), 31.0 (C-4), 32.3 (C-5), 49.5 (C-6), 105.0 (C-7), 114.1 (C-8), 115.2 (C-9), 117.4 (C-10), 121.8 (C-11), 125.3 (C-12), 125.9 (C-13), 128.2 (C-14), 131.9 (C-15), 132.2 (C-16), 136.8 (C-17), 150.1 (C-18), 155.8 (C-19), 159.1 (C-20), 162.0 (C-21), 195.9 (C-22); MS (EI) *m/z*: 415.4322[M^+]; Anal. calculated for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37, Found: C, 75.09; H, 5.84; N, 3.26.

7-(furan-2-yl)-10,10-dimethyl-10,11-dihyrochromeno[4,3-*b*]chromene-6,8(7*H*, 9*H*)-dione (**4o**): m.p. 193°–195°C (EtOH); IR (KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 3023, 1758, 1668, 1608, 1554, 1458, 1352, 1168, 1105, 1036, 871, 769. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.18 (s, 3H, –CH_3), 1.61 (s, 3H,



–CH_3), 2.14 (d, J = 16.4 Hz, 1H, –CH_2), 2.22 (d, 1H, –CH_2), 2.69 (d, 1H, =CH), 2.74 (d, 1H, =CH), 4.93 (s, 1H, –CH), 6.95 (d, 2H, Ar–H), 7.13 (d, 2H, Ar–H), 7.55 (m, 2H, Ar–H), 7.63 (dd, 1H, Ar–H), 7.92 (dd, 1H, Ar–H); ^{13}C-NMR (DMSO-d_6, 300 MHz): δ 26.8 (C-1), 27.1 (C-2), 31.6 (C-3), 32.3 (C-4), 49.8 (C-5), 105.6 (C-6), 113.4 (C-7), 114.5 (C-8), 115.0 (C-9), 115.3 (C-10), 116.3 (C-11), 125.4 (C-12), 126.5 (C-13), 128.8 (C-14), 145.5 (C-15), 152.1 (C-16), 153.2 (C-17), 154.1 (C-18), 160.5 (C-19), 163.8 (C-20), 196.3 (C-21); MS (EI) *m/z*: 362.1239[M^+]; Anal. calculated for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01, Found: C, 72.71; H, 4.90.

9-(naphthalen-1-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**5m**): m.p. 194°–197°C (EtOH); IR (KBr) $\bar{\upsilon}_{max}$ cm^{-1}: 3165, 2880, 1632, 1609, 1415, 1398, 1112, 769, 740; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 6H, 2×–CH3), 1.12 (s, 6H, 2× –CH3), 1.75 (dd, 2H, –CH2), 1.78 (dd, 2H, –CH2), 2.86



(dd, 2H, –CH2), 2.89 (dd, 2H, –CH2), 4.42 (s, 1H, –CH), 7.10 (m, 1H, Ar–H), 7.19 (m, 1H, Ar–H), 7.29 (m, 1H, Ar–H), 7.31 (m, 1H, Ar–H), 7.51 (m, 1H, Ar–H), 7.64 (m, 1H, Ar–H), 7.77 (m, 1H, Ar–H); ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 27.5 (C-1), 29.4 (C-2), 31.6 (C-3), 32.9 (C-4), 41.6 (C-5), 51.6 (C-6), 113.9 (C-7), 124.2 (C-8), 124.3 (C-9), 125.6 (C-10), 125.8 (C-11), 126.5 (C-12), 126.9 (C-13), 128.6 (C-14), 132.6 (C-15), 133.5 (C-16), 134.0 (C-17), 155.1 (C-18), 194.6 (C-19); MS (EI) *m/z*: 400.1263[M^+]; Anal. calculated for $C_{27}H_{28}O_3$: C, 80.97; H, 7.05, Found: C, 80.78; H, 6.94.

Conclusion

We have developed a simple, efficient and green procedure for the synthesis of chromeno[4,3-*b*]chromenes and 1,8-dioxo-octahydroxanthenes using a bio-based natural biosurfactant, BFE. Use of the cost-effective, micellar catalyst obtained from renewable resource utilized in organic synthesis, which shows the formation of the products with better yield with no tedious chromatographic separation within reasonable time having operational simplicity is the main scope of this protocol. The present procedure customs ethanolic aqueous media to run the reaction which works as a better alternative to other volatile, toxic organic solvents and is the obvious advantage of this method. The sustainability of the present green protocol has also been reviewed by the EcoScale method.

Conflict of interest: The authors declare that there is no conflict of interest.

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