

Diisopropyl Ethyl Ammonium Acetate (DIPEAc) promoted facile and green synthesis of Xanthene derivatives under microwave irradiation

Vishal U. Mane^{1*}, Pritam A. Shete²

¹Department of Chemistry, Arts, Commerce and Science College, Shreevardhan, Maharashtra, India; e-mail: vishalum87@gmail.com

²Department of Chemistry, H.P.T. Arts and R.Y.K. Science College, Nashik, Maharashtra, India; e-mail: pritam.shete10@gmail.com

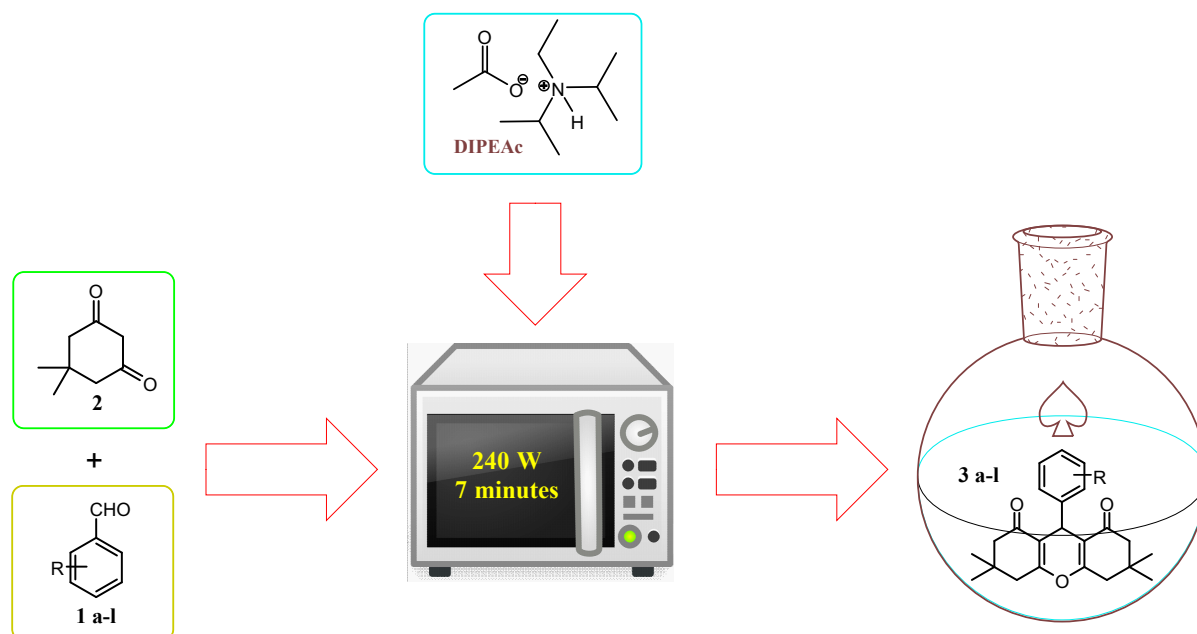
*Corresponding Author E-mail: vishalum87@gmail.com

Abstract

Diisopropyl ethyl ammonium Acetate (DIPEAc)-promoted Knoevenagel condensation followed by cyclization protocol has been developed for the first time by a successive reaction of aldehydes and dimedone to afford xanthene derivatives in high to excellent yields under microwave irradiation (MW = 240 W) to accelerate the chemical transformation. The ionic liquid provided the capability to allow a variability of functional groups, short reaction times, easy workup, high yields, recyclability of the catalyst and solvent-free conditions. This methodology avoids toxic, volatile organic solvents, minimizes reaction times through microwave assistance, and provides economic and environmental advantages, representing a sustainable approach to synthesizing biologically important xanthene scaffolds.

Keywords

How to cite this article: Vishal U. Mane^{1*} Pritam A. Shete². Diisopropyl Ethyl Ammonium Acetate (DIPEAc) promoted facile and green synthesis of Xanthene derivatives under microwave irradiation. Int J Drug Deliv Technol. 2026;16(83s):1623-1631. DOI: 10.25258/ijddt.16.83s.177.



Graphical Abstract

1. INTRODUCTION

Xanthene's derivatives have been investigated for a wide range of pharmacologic indications such as potent antimicrobial,¹ analgesic,² antimalarial,³ antiinflammatory,⁴ antiviral,⁵ antioxidant,⁶ antiproliferative activity,⁷ anticancer,⁸ urease activity,⁹ trypanothione reductase (TryR) inhibition,³ BMP-2 targeted osteogenic agents,¹⁰ selective positive allosteric modulators of the δ -opioid receptor¹¹ and selective estrogen receptor modulators.¹² Additionally, some of the xanthene derivatives are used as antagonists for paralyzing the action of oxalamine,¹³ dyes,¹⁴ in laser technology,¹⁵

as bactericides in agriculture,¹⁶ and number of natural products accommodate the xanthenes nucleus.¹⁷ The structures of representative compounds are shown in Fig. 1.

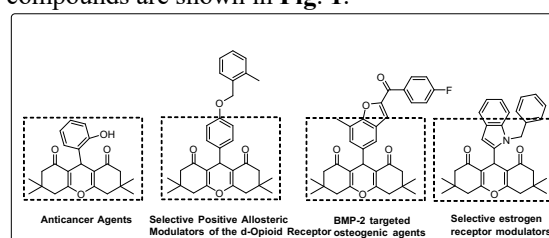
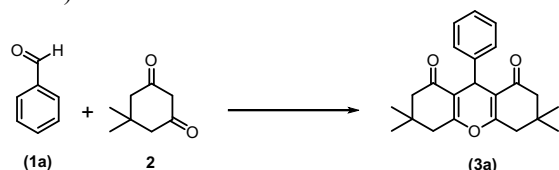


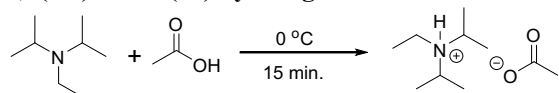
Fig. 1. Xanthenes incorporated bioactive molecules

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Ionic liquids (ILs) have taken the attention of the chemical community all over the globe as a green alternative option to traditional ecofriendly media for catalysis, synthesis, separation, and other several chemical tasks.¹⁸⁻²³ ILs include numerous exclusive properties, such as extensive liquid range, nonvolatility, low toxicity, high thermal stability, noncombustible, excellent solubility, and recyclability.²⁴ ILs act as “neoteric solvents” for a wide range of industrial and chemical processes. In recent times, ILs have been originating to be valuable as environmentally friendly media for countless organic revolutions.²⁵⁻²⁶ Thus, the introduction of a dynamic, inexpensive, mild, and environmentally friendly catalyst for significant cyclization reaction superior to analogues of pharmaceutical and biological prominence is in demand. In this paper, we have validated DIPEAc as ionic liquid catalyzed the efficient synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives under ecofriendly reaction conditions (**Schemes 1 and 2**).



Scheme 1. Synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**3a**) by using DIPEAc as ILs.



Scheme 2. Synthesis of Diisopropylethylammonium Acetate (DIPEAc)

The use of microwave irradiation in combination with ILs, which has very high heat capacity, high polarity and no vapor pressure, and their high potentiality to absorb microwaves and convert them into heat energy, may accelerate the reaction very quickly. The synergy of microwave and ionic liquid in catalyst-free methodologies for the synthesis of heterocyclic compounds has attracted much interest because of the shorter reaction time, milder conditions, reduced energy consumption and higher product selectivity and yields.²⁷

Thus, the extension of synthetic strategies for the construction of this molecule using an economical, reusable, mild, and nontoxic catalyst is of massive importance from the industrial and academic points of view. Even though various modes have been reported in the literature, these reactions can be accomplished under a variability of tentative conditions, and several improvements have been reported in recent years, such as sulfuric acid or hydrochloric acid,²⁸ silica sulfuric acid,²⁹ sulfamic acid,³⁰ *p*-dodecylbenzenesulfonic acid,³¹ boric acid,³² *p*TSA,³³ NaHSO₄-SiO₂,³⁴ TiO₂-SO₄²⁻,³⁵ molecular

iodine,³⁶ amberlyst-15,³⁷ cyanuric chloride,³⁸ core/shell Fe₃O₄@GA@isinglass,³⁶ Fe₃ montmorillonite,³⁹ FeCl₃/[bmim][BF₄],⁴⁰ [Hmim]Tfa,⁴¹ SmCl₃,⁴² trimethylsilyl chloride (TMSCl),⁴³ acyclic acidic ionic liquids⁴⁴ and InCl₃/ionic liquid.⁴⁵

However, numerous of these testified methods become infected with several disadvantages such as strong acidic conditions, use of hazardous or costly reagents, long reaction times, low yields of products, and sophisticated treatment. Moreover, many of these schemes utilize organic solvents as the reaction medium. Hence, the further innovation toward contemporary reaction with easy isolation of product, reusability of catalyst, perhaps with minimal or no waste is highly attractive. As per our investigation, the objective of this work is to begin a rapid and efficient synthetic protocol for obtaining xanthene derivatives under eco-friendly conditions. As an extension of emerging economic and efficient strategy to develop pharmaceutically and biologically significant molecules, herein, we reported synthesis of library of xanthene derivatives promoted by synergistic effect of ionic liquid and microwave irradiation without any added catalyst in good to excellent yields.

1.1. Rationale of Design

Due to the broader significance of xanthene derivatives and scope for the development of new methods, we have introduced a diisopropyl ethyl ammonium acetate (DIPEAc)-promoted Knoevenagel condensation followed by cyclization protocol, developed for the first time, for the successive reaction of aldehydes and dimedone to afford xanthene derivatives in high to excellent yields under microwave irradiation. The synergic couple of microwave and ionic liquid provided the capability to allow a variability of functional groups, short reaction times, easy workup, high yields, recyclability of the catalyst, and solvent-free conditions, thus providing economic and environmental advantages.

2. RESULT AND DISCUSSION

2.1. Chemistry

To achieve optimised conditions, we developed a protocol using benzaldehyde (**1a**, 1 mmol) and dimedone (**2**, 2 mmol) as model substrates. We evaluated different catalysts, temperatures, and solvents, and the results of this study are summarised in Table 1. It was found that when the reaction was carried out in ethanol in the absence of the catalyst, a lower yield of product was obtained after 30 min (Table 1, entry 1). To obtain the preferred product (**3a**), we tested the reaction using different catalysts such as *p*-TSA, SDS, ChCl:2urea, ChCl:2ZnCl₂, PEG-400 and DIPEAc (Table 1, entries 2-7). Thus, room-temperature DIPEAc as the pre-eminent catalyst was tested for this reaction. In the presence of DIPEAc, compound **3a** was isolated in 93% yield after only 7 min under microwave irradiation. The model reaction in water using phase

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transfer catalysts is found to be sluggish and forms the desired 3a in lower yields. Therefore, it can be thought that DIPEAc is green and a superior solvent and catalyst compared to the others shown in Table 1.

Table 1. Efficiency Comparison of Various Catalysts for the Synthesis of Xanthene derivatives (3a).^a

entry	catalyst	medium	Time (min)	Yield ^b (%) / time (h)
1	-	EtOH	30	42
2	<i>p</i> -TSA	H ₂ O	30	71
3	SDS	H ₂ O	20	62
4	ChCl:2urea	ChCl:2urea	20	80
5	ChCl:2ZnCl ₂	ChCl:2ZnCl ₂	20	79
6	PEG-400	PEG-400	20	82
7	DIPEAc	DIPEAc	7	93

^aReaction conditions: aldehyde **1a** (1 mmol), dimedone **2** (2 mmol), DIPEAc (20 mol%) stirred under microwave irradiation (MW = 240 W). ^bIsolated yields. Bold values are for highlighting the good result.

In the next step we examine the efficiency of ionic liquid DIPEAc for the synthesis of xanthene derivatives. A change in the concentration of DIPEAc in the model reaction suggests a much greater effect on the yield of the final product. The catalyst loading study suggest that 20 mol% of DIPEAc catalyst is best for the synthesis of final product in 93% yields (Table 2, entry 4).

Table 2. Effect of catalyst concentration^a

Entry	Catalyst (mol %)	Time (min)	Yield ^b (%)
1	5	20	62
2	10	15	72
3	15	12	82
4	20	7	93
5	25	7	93

^aReaction conditions: **1a** (1 mmol), **2** (2 mmol) and DIPEAc (20 mol%) under microwave irradiation. ^bIsolated yield.

Furthermore, we studied the power level of the microwave effect on the model reaction; according to this study, the desired product showed better results when the reaction was carried out at 240 W (Table 3, entry 3). Detailed reaction conditions are shown in Table 3.

Table 3. Optimization of reaction condition for the synthesis of 3a under microwave set up^a

Entry	Power levels in Watt	Time ^b (min)	Yield ^c
1	140	12	68
2	210	10	85
3	240	7	93
4	280	7	93

^aReaction conditions: **1a** (1 mmol) and **2** (2 mmol) in the presence of DIPEAc (20 mol%) under microwave irradiation. ^bReaction progress monitored by TLC. ^cIsolated yield.

An extremely superlative method to economic and greener preparation is recovery and recyclability of an ionic liquid. Therefore, we have to check the efficiency of the catalyst after recovering it from the reaction media during the work-up procedure. When the reaction is completed, the reaction mass was poured into ice-cold water to obtain fine crystals of the final xanthene derivatives. In the last step, removal H₂O from filtrate using reduced pressure gave viscous liquid, which on cooling gave a pure ionic liquid. Recovered catalysts were reused for the next four repeated cycles without considerable loss in catalytic efficiency (Table 4).

Table 4. Reusability of DIPEAc ionic liquid for model reaction

Entry	Run	Time ^a (min)	Yield ^b
1	fresh	7	93
2	2	7	93
3	3	7	85
4	4	7	82
5	5	7	80

^aReaction progress monitored by TLC. ^bIsolated yield.

2.2 Comparison of DIPEAc (IL) catalyst with the previously reported protocol

We have conducted a comparative study of DIPEAc with other reported catalysts for the preparation of a xanthene derivative. The comparison results proved that DIPEAc is better catalyst in terms of excellent yield and reusability with less reaction time (Table 5, entry 10). In conclusion DIPEAc is found to be a facile and environmentally benign protocol for the synthesis of xanthene derivatives.

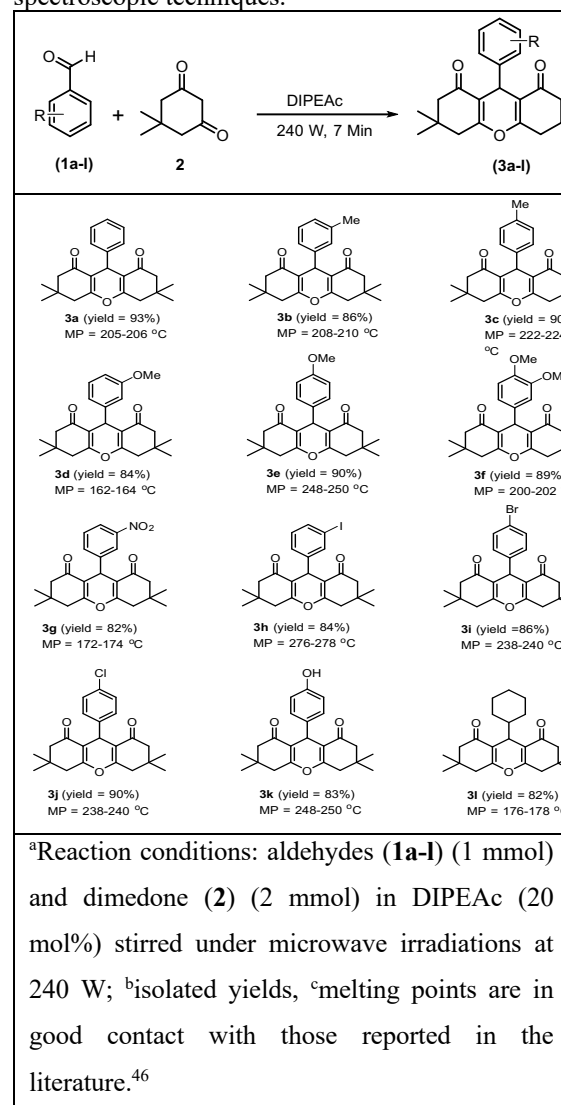
Table 5. Comparative catalytic performance of the DIPEAc (IL) with other previously reported catalysts

Entry	Catalyst	Amount of catalyst	Time (min)	Yield (%)	solvent/condition	Ref.
1	β -CD (1 mmol)	1 mmol	10 h	96	EtOH/60 °C	46
2	SBSSA	30 mg	10 h	98	EtOH/reflux	47
3	FeCl ₃ .6H ₂ O (10 mol%)	10 mol %	6 h	92	[bmim][BF ₄] 80 °C	48
4	Amberlyst-15	200 mg	5 h	92	CH ₃ CN /Reflux	49
5	Cellulosic sulfonic acid	50 mg	5 h	94	Solvent free/110 °C	50
6	[bmim][HSO ₄] (42 mol%)	42 mol %	3 h	85	Solvent free 100 °C	36
7	Fe ³⁺ montmorillonite	85 mg	6 h	94	EtOH/reflux	51
8	Zr(DP) ₂	10 mol %	24 h	98	EtOH/80 °C	52
9	ZnO-CH ₃ COCl	30 mol %	5 h	86	CH ₃ CN /reflux	53
10	DIPEAc	20 mol %	7 min	93	DIPEAc acts as an ionic solvent	Present work

The structure of the titled product **3a** was confirmed by ¹H NMR and ¹³C NMR. The ¹H NMR spectra of compound **3a** exhibit two singlet bands for two methyl groups at δ 1.24 and 1.11 ppm. The -CH₂-C=O protons observed at δ 2.49 ppm, and the CH₂ proton observed at δ 2.30 ppm suggest the presence of dimedone ring in the final compound. The aliphatic CH proton was shown at δ 5.56 ppm, and a multiplet at δ 7.11-7.29 ppm suggests that a phenyl ring is present in the compound.

In the ¹³C NMR spectrum of compound **3a**, distinct -C=O carbonyl group observed at δ 196.65 ppm. The CH, CH₂ and CH₃ peaks observed at δ 50.45, 42.23, 32.45, 31.34, 29.56 and 29.33 ppm confirmed the formation of compound **3a**. In conclusion, the model reaction was most effective and exhibited shorter reaction time at 240 W, using 20 mol% DIPEAc as a catalyst under microwave conditions. With excellent

reaction conditions in hand, the adaptableness of this approach was employing the synthesis xanthene analogues (**3a-l**). Various substituents on aryl aldehyde, including methoxy, methyl, nitro, halogen (-Cl, -Br, -I), and hydroxyl groups were used. Synthesis of compounds (**3a-l**) using optimised reaction conditions and results are shown in **Scheme 3**. The result clearly suggests that the condensation reactions using DIPEAc catalyst shows excellent and remarkable performance irrespective to the electron withdrawing/donating groups present on the aryl aldehydes and hence this method is facile, efficient and general for the synthesis of xanthene analogues. All the synthesized final compounds **3a-l** was well characterized by ¹H NMR and ¹³C NMR spectroscopic techniques.

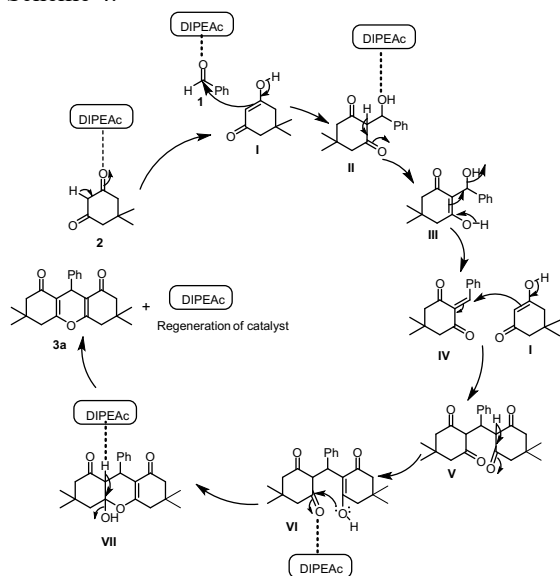


Scheme 3. Synthesis of Xanthene derivatives (3a-l)

2.3 Plausible Reaction Mechanism

We have proposed a reaction-mechanism cycle for the preparation of xanthene analogues using DIPEAc as a catalyst. In the first step, benzaldehyde is activated by DIPEAc and further reacted with enol form of dimedone **I** to give intermediate **II**. The DIPEAc-assisted enolization and subsequent

dehydration of **II** afford intermediate **III** and **IV**, respectively. Next, **I** nucleophilically attacks **IV** to yield intermediate **V**, which upon enolization produces **VI**. The DIPEAc-catalyzed intramolecular cyclization of **VI** gives intermediate **VII**. In the last step, elimination of H₂O from **VII** using DIPEAc results in the formation of the titled xanthene analogue **3a** along with regeneration of the catalyst. The detailed reaction mechanism is presented in Scheme 4.



Scheme 4. Reaction mechanism cycle for the preparation of compound **3a**.

3. EXPERIMENTAL SECTION

3.1 Materials and Methods

All of the reagents used were of laboratory grade. Melting points of all of the synthesized analogues were resolute in an open capillary tube and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography on Merck's silica plates, and imagining was accomplished by iodine/ultraviolet light. NMR spectra were recorded with a Bruker AvIII HD-400 MHz spectrometer operating at 400 MHz for ¹H-NMR and 100 MHz for ¹³C-NMR for 1 using CDCl₃. Chemical shifts (δ) are reported in parts per million using TMS as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); bs (broad singlet), triplet (t); quartet (q); and multiplets (m).

3.2 General Procedure for the Synthesis of Diisopropylethylammonium Acetate (DIPEAc):

A mixture of anhydrous N, N-diisopropylethylamine (1 mmol) and acetic acid (1 mmol) was stirred at 0 °C for 20 min. The viscous liquid, Diisopropylethylammonium acetate, was obtained.

3.3 General Procedure for Synthesis of 2-Amino-4H-pyrans Derivatives

A mixture of aldehyde (**1a**, 1 mmol) and dimedone (**2**, 2 mmol) in DIPEAc (20 mol%) was stirred under microwave irradiation at 240 W. The progress of the reaction was monitored by thin-layer chromatography [ethyl acetate/n-hexane (3:7)] as

the mobile phase. Then the reaction mixture was cooled for 15 min and poured onto crushed ice. Thus, acquired solid was filtered, dried, and purified by crystallization using ethanol as a solvent. The synthesis compound is confirmed by MP, ¹H NMR and ¹³C NMR spectra.

3.4 Spectral Data

3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3a**)

The compound **3a** was synthesized from condensation reaction **1a** and **2** as white solid; Mp: 205-206 °C; Yield: 93%; ¹H NMR (400 MHz, CDCl₃) δ 7.11-7.29 (m, 5H), 7.21-7.09 (m, 3H), 5.56 (s, 1H), 2.30-2.49 (m, 8H), 1.24 (s, 6H), 1.11 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 195.65, 164.07, 143.16, 135.05, 129.49, 127.51, 119.84, 50.45, 42.23, 32.45, 31.34, 29.56 and 29.33.

3,3,6,6-tetramethyl-9-(*m*-tolyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3b**)

The compound **3b** was synthesized from condensation reaction **1b** and **2** as white solid; Mp: 208-210 °C; Yield: 86%; ¹H NMR (400 MHz, CDCl₃) δ 7.13-6.95 (m, 3H), 6.86 (d, *J* = 6.8 Hz, 1H), 4.68 (s, 1H), 2.44 (s, 4H), 2.24 (s, 3H), 2.13 (d, *J* = 13.8 Hz, 4H), 1.05 (s, 6H), 0.95 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 196.31, 162.23, 144.01, 137.26, 129.38, 127.84, 127.13, 125.21, 115.67, 50.76, 40.84, 32.17, 31.68, 29.24, 27.30 and 21.48.

3,3,6,6-tetramethyl-9-(*p*-tolyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3c**)

The compound **3c** was synthesized from condensation reaction **1c** and **2** as yellow solid; Mp: 222-224 °C; Yield: 90%; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.5 Hz, 2H), 4.68 (s, 1H), 2.43 (s, 4H), 2.20 (s, 3H), 2.17-2.07 (m, 4H), 1.06 (s, 6H), 0.95 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 196.36, 162.17, 141.21, 135.61, 128.71, 128.20, 115.67, 77.33, 76.85, 50.75, 40.81, 32.13, 31.40, 29.23, 27.31 and 21.02.

9-(3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3d**)

The compound **3d** was synthesized from condensation reaction **1d** and **2** as yellow solid; Mp: 162-164 °C; Yield: 84%; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (t, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 6.9 Hz, 2H), 6.56 (d, *J* = 7.0 Hz, 1H), 4.66 (s, 1H), 3.66 (s, 3H), 2.40 (s, 4H), 2.11 (d, *J* = 16.2 Hz, 4H), 1.01 (s, 6H), 0.91 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 196.26, 162.35, 159.26, 145.68, 128.77, 120.72, 115.42, 114.26, 111.78, 55.01, 50.70, 40.75, 32.09, 31.73, 29.18, 27.29.

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3e**)

The compound **3e** was synthesized from condensation reaction **1e** and **2** as yellow solid; Mp: 248-250 °C; Yield: 90%; ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 7.8 Hz, 2H), 6.70 (d, *J* = 7.8 Hz, 2H), 4.65 (s, 1H), 3.68 (d, *J* = 4.9 Hz, 3H), 2.42 (s, 4H), 2.23 – 2.08 (m, 4H), 1.05 (s, 6H), 0.94 (s,

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6H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.40, 162.05, 157.90, 136.47, 129.25, 115.72, 113.41, 55.05, 50.74, 40.81, 32.14, 30.92, 29.23 and 27.29.

9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3f)

The compound **3f** was synthesized from condensation reaction **1f** and **2** as yellow solid; Mp: 200-202 °C; Yield: 89%; ^1H NMR (400 MHz, CDCl_3) δ 6.88 (d, J = 8.2 Hz, 1H), 6.84 (dd, J = 8.2, 2.3 Hz, 1H), 6.79 (dd, J = 2.3 Hz, 1H), 4.68 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 2.44 (s, 4H), 2.27 – 2.09 (m, 4H), 1.08 (s, 6H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.85, 168.53, 154.64, 152.87, 141.68, 132.62, 127.24, 126.61, 120.80, 55.48, 54.61, 50.16, 42.13, 32.87, 30.96, 29.29 and 27.13.

3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3g)

The compound **3g** was synthesized from condensation reaction **1g** and **2** as red solid; Mp: 172-174 °C; Yield: 82%; ^1H NMR (400 MHz, CDCl_3) δ 8.06 – 7.90 (m, 2H), 7.78 (m, 1H), 7.39 (t, J = 7.8 Hz, 1H), 4.81 (s, 1H), 2.49 (s, 4H), 2.18 (d, J = 16.3 Hz, 4H), 1.09 (s, 6H), 0.97 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.42, 167.96, 147.56, 141.40, 131.53, 128.54, 127.28, 125.82, 120.68, 51.94, 41.60, 32.97, 31.25, 29.51 and 27.14.

9-(3-iodophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3h)

The compound **3h** was synthesized from condensation reaction **1h** and **2** as pale yellow solid; Mp: 276-278 °C; Yield: 84%; ^1H NMR (400 MHz, CDCl_3) δ 7.53 (m, 1H), 7.41 (m, 1H), 7.31 (m, 1H), 6.94 (t, J = 2.3 Hz, 1H), 4.65 (s, 1H), 2.45 (s, 4H), 2.29-2.09 (m, 4H), 1.08 (s, 6H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.01, 165.83, 140.46, 132.57, 129.02, 127.61, 127.36, 123.87, 112.49, 50.45, 41.59, 33.01, 30.96, 29.20 and 27.42.

9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3i)

The compound **3i** was synthesized from condensation reaction **1i** and **2** as red solid; Mp: 238-240 °C; Yield: 86%; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, J = 6.9 Hz, 2H), 7.17 (d, J = 6.9 Hz, 2H), 4.69 (s, 1H), 2.46 (s, 4H), 2.20 (d, J = 16.4 Hz, 4H), 1.10 (s, 6H), 0.98 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 196.26, 162.41, 143.18, 131.09, 130.13, 120.18, 115.14, 77.32, 77.00, 76.68, 50.65, 40.81, 32.15, 31.52, 29.21 and 27.26.

9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3j)

The compound **3j** was synthesized from condensation reaction **1** and **2j** as yellow solid; Mp: 238-240 °C; Yield: 90%; ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 4.71 (s, 1H), 2.47 (s, 4H), 2.19 (d, J = 16.3 Hz, 4H), 1.10 (s, 6H), 0.98 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 196.28, 162.44, 142.70, 131.93, 129.74, 128.13, 115.18, 77.37, 77.05, 76.73, 50.66, 40.79, 32.14, 31.43, 29.21 and 27.24.

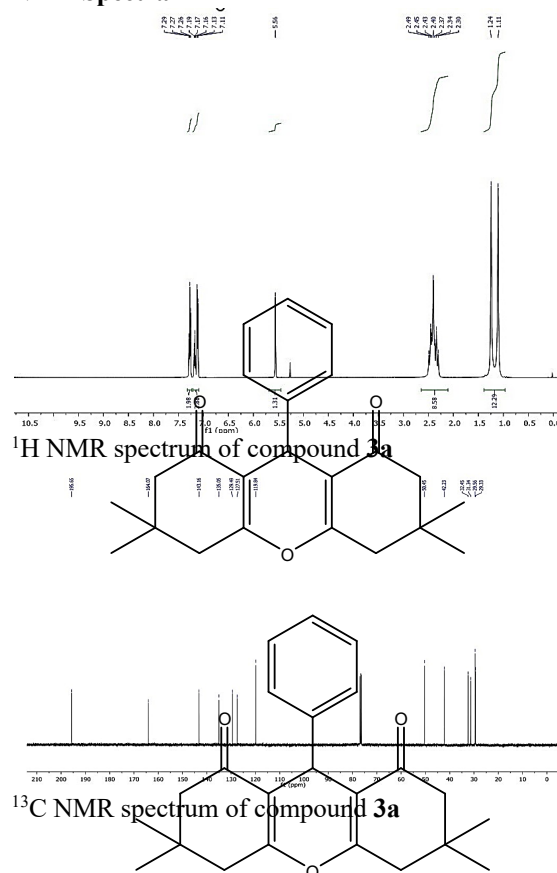
9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3k)

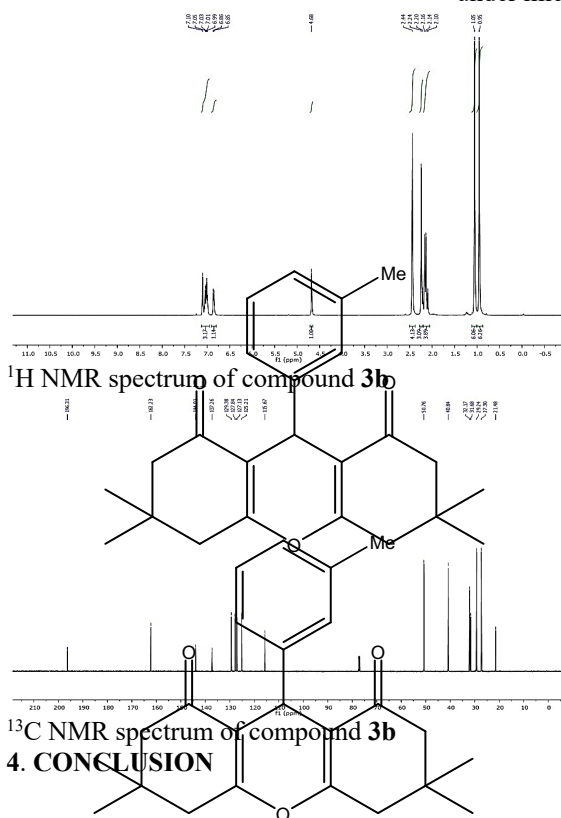
The compound **3k** was synthesized from condensation reaction **1k** and **2** as red solid; Mp: 248-250 °C; Yield: 83%; ^1H NMR (400 MHz, CDCl_3) δ 7.06 (d, J = 7.8 Hz, 2H), 6.54 (d, J = 7.8 Hz, 2H), 4.66 (s, 1H), 2.46 (s, 4H), 2.21 (d, J = 16.4 Hz, 4H), 1.08 (s, 6H), 0.99 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 197.30, 162.45, 154.70, 135.47, 129.29, 115.85, 115.23, 50.72, 40.81, 32.23, 30.93, 29.11 and 27.35.

9-cyclohexyl-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3l)

The compound **3l** was synthesized from condensation reaction **1l** and **2** as white solid; Mp: 176-178 °C; Yield: 82%; ^1H NMR (400 MHz, CDCl_3) δ 2.71 (s, 1H), 2.50 (s, 4H), 2.23 (s, 4H), 1.61 (m, 2 H), 1.53 (m, 2H), 1.46 (m, 1H), 1.49 (m, 1H), 1.43 (m, 2H), 1.42 (m, 1H), 1.35 (m, 2 H), 1.22 (s, 6H), 1.03 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.30, 165.54, 111.77, 50.43, 40.71, 34.51, 33.01, 31.25, 29.20, 27.42, 25.93, 24.52, 23.21, 23.15 and 23.07.

NMR Spectra





4. CONCLUSION

In conclusion, an environmentally and highly efficient green methodology has been established for the synthesis of functionalized xanthene derivatives using an inexpensive and recoverable DIPEAc catalytic solvent-free under microwave irradiation. This reaction scheme offers several advantages, including uniqueness, high atom economy, mild reaction conditions, clean reaction profiles, easy workup, and eco-friendliness. Furthermore, the prevention of hazardous organic solvents during the entire procedure (synthesis, ionic liquid preparation, and workup procedure) makes it a convenient and attractive method for the synthesis of these biologically significant xanthene compounds.

DISCLOSURE AND DECLARATION

This work is an original work and has not been previously published in any other form.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Supporting information for a few representative compounds is provided along with the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

ACKNOWLEDGEMENTS

Not applicable.

REFERENCES

1. Kaya, M.; Demir, E.; Bekci, H. Synthesis, characterization and antimicrobial activity of novel xanthene sulfonamide and carboxamide

derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2013**, 28, 885-893.

2. Kumar, A.; Rout, L.; Achary, L. S. K.; Dhaka, R. S.; Dash, P. Greener Route for Synthesis of aryl and alkyl-14H-dibenzo [a,j] xanthenes using Graphene Oxide-Copper Ferrite Nanocomposite as a Recyclable Heterogeneous Catalyst. *Sci. Rep.* **2017**, 7, 42975.
3. Chibale, K.; Visser, M.; van Schalkwyk, D.; Smith, P. J.; Saravanamuthu, A.; Fairlamb, A. H. Exploring the potential of xanthene derivatives as trypanothione reductase inhibitors and chloroquine potentiating agents. *Tetrahedron*, **2003**, 59, 2289-2296.
4. Jin, T.S.; Liu, L.B.; Zhao, Y.; Li, T.S. Clean Synthesis of Compounds Containing Two 4H-Pyrans or Two Tetraketones in Aqueous Media. *Synth. Commun.* **2005**, 35, 2379-2385.
5. Hafez, H.N.; Hegab, M.I.; Ahmed-Farag, I. S.; El-Gazzar, A.B.A. A facile regioselective synthesis of novel *spiro*-thioxanthene and *spiro*-xanthene-9',2-[1,3,4]thiadiazole derivatives as potential analgesic and anti-inflammatory. *Bioorg. Med. Chem. Lett.* **2008**, 18, 4538-4543.
6. Ilangovan, A.; Anandhan, K.; Prasad, K.M.; Vijayakumar, P.; Renganathan, R.; Ananth, D. A.; Sivasudha, T. Synthesis, DNA-binding study, and antioxidant activity of 14-aryl-14 H-dibenzo [a, j] xanthene derivatives. *Med. Chem. Res.*, **2015**, 24, 344-355.
7. Spatafora, C.; Barresi, V.; Bhusainahalli, V.M.; Di Micco, S.; Musso, N.; Riccio, R.; Bifulco, G.; Condorelli, D.; Tringali, C. Bio-inspired benzo[k,l]xanthene lignans: synthesis, DNA-interaction and antiproliferative properties. *Org. Biomol. Chem.*, **2014**, 12, 2686-2701.
8. Sashidhara, K.V.; Kumar, A.; Dodda, R.P.; Kumar, B.A. A new iodine catalyzed regioselective synthesis of xanthene synthons. *Tetrahedron Lett.* **2012**, 53, 3281-3283.
9. Khurana, J.M.; Magoo, D.; Aggarwal, K.; Aggarwal, N.; Kumar, R.; Srivastava, C. Synthesis of novel 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-thiones and evaluation of their biocidal effects. *Eur. J. Med. Chem.* **2012**, 58, 470-477.
10. Kushwaha, P.; Tripathi, A. K.; Gupta, S.; Kothari, P.; Upadhyay, A.; Ahmad, N.; Sharma, T.; Siddiqi, M. I.; Trivedi, R.; Sashidhara, K. V. Synthesis and study of benzofuran-pyran analogs as BMP-2 targeted osteogenic agents. *Eur. J. Med. Chem.* **2018**, 156, 103-117.
11. Burford, N. T.; Livingston, K. E.; Canals, M.; Ryan, M. R.; Budenholzer, L. M. L.; Han, Y.; Shang, Y.; Herbst, J. J.; O'Connell, J.; Banks, M.; Zhang, L.; Filizola, M.; Bassoni, D. L.; Wehrman, T. S.; Christopoulos, A.; Traynor, J. R.; Gerritz, S. W.; Alt, A. Discovery,

- Synthesis, and Molecular Pharmacology of Selective Positive Allosteric Modulators of the δ -Opioid Receptor. *J. Med. Chem.* **2015**, *58*, 4220-4229.
12. Ramit, S.; Gupta, K. B.; Upadhyay, S.; Dhiman, M., Jaitak, V. Design, synthesis and biological evaluation of novel indole-xanthendione hybrids as selective estrogen receptor modulators. *Bioorg. & Med. Chem.* **2018**, *26*, 266-277.
13. Bhowmik, B. B.; Ganguly, P. Photophysics of xanthene dyes in surfactant solution. *Spectrochim. Acta, Part A*, **2005**, *61*, 1997-2003.
14. Hilderbrand, S. A.; Weissleder, R. One-pot synthesis of new symmetric and asymmetric xanthene dyes. *Tetrahedron Lett.*, **2007**, *48*, 4383-4385.
15. Hideu, T. JP 56005480, Jpn, Tokyo, Nano Nickel-Cobalt Ferrite Catalysed One-Pot Multi-Component Synthesis of Xanthenediones and Acridinediones. *KohoChem. Abstr.*, **1981**, *95*, 80922b.
16. Ojida, A.; Takashima, I.; Kohira, T.; Nonaka, H.; Hamachi, I. Turn-On Fluorescence Sensing of Nucleoside Polyphosphates Using a Xanthene-Based Zn(II) Complex Chemosensor. *J. Am. Chem. Soc.*, **2008**, *130*, 12095-12101.
17. Barmak, A.; Niknam, K.; Mohebbi, G.; Pournabi, H. Antibacterial studies of hydroxyspiro[indoline-3,9-xanthene]trione against spiro[indoline3,9-xanthene]trione and their use as acetyl and butyrylcholinesterase inhibitors. *Microbial Pathogenesis* **2019**, *130*, 95-99.
18. Welton, T. Ionic Liquids in Green Chemistry. *Green Chem.* **2011**, *13*, 225-225.
19. Wang, C.; Guo, L.; Li, H.; Wang, Y.; Weng, J.; Wu, L. Preparation of simple ammonium ionic liquids and their application in the cracking of dialkoxypromanes. *Green Chem.* **2006**, *8*, 603-607.
20. Wang, C.; Zhao, W.; Li, H.; Guo, L. Solvent-free synthesis of unsaturated ketones by the Saucy–Marbet reaction using simple ammonium ionic liquid as a catalyst. *Green Chem.* **2009**, *11*, 843-847.
21. Weng, J.; Wang, C.; Li, H.; Wang, Y. Novel quaternary ammonium ionic liquids and their use as dual solvent-catalysts in the hydrolytic reaction. *Green Chem.* **2006**, *8*, 96-99.
22. Dupont, J.; de Souza, R.F.; Suarez, P.A.Z. Ionic Liquid (Molten Salt) Phase Organometallic Catalysis. *Chem. Rev.* **2002**, *102*, 3667-3692.
23. Sheldon, R. Catalytic reactions in ionic liquids. *Chem. Commun.* **2001**, *23*, 2399-2407.
24. Dolzhenko, A. V.; Dolzhenko, A. V. Green Solvents for Eco-Friendly Synthesis of Bioactive Heterocyclic Compounds. *Green Synthetic Approaches for Biologically Relevant Heterocycles*. Elsevier: Perth, WA, Australia, **2015**, 101-139.
25. Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. Ionic liquid catalyzed Henry reactions. *Tetrahedron Lett.* **2004**, *45*, 2699-2701.
26. Wilkes, J.S. A short history of ionic liquids—from molten salts to neoteric solvents. *Green Chem.* **2002**, *4*, 73-80.
27. Shi, H.; Zhu, W.; Li, H.; Liu, H.; Zhang, M.; Yan, Y.; Wang, Z. Microwave-accelerated esterification of salicylic acid using Bronsted acidic ionic liquids as catalysts. *Catal. Commun.* **2010**, *11*, 588-591.
28. Kantevari, S.; Bantu, R.; Nagarapu, L. HClO₄-SiO₂ and PPA-SiO₂ catalyzed efficient one-pot Knoevenagel condensation, Michael addition and cyclo-dehydration of dimedone and aldehydes in acetonitrile, aqueous and solvent free conditions: Scope and limitations. *J. Mol. Catal. A: Chem.* **2007**, *269*, 53-57.
29. Rajitha, B.; Sunil Kumar, B.; Thirupathi Reddy, Y.; Narsimha Reddy, P.; Sreenivasulu, N. Sulfamic acid: A novel and efficient catalyst for the synthesis of aryl-14H-dibenzo[a,j]xanthenes under conventional heating and microwave irradiation. *Tetrahedron Lett.* **2005**, *46*, 8691-8693.
30. Prasad, D.; Preetam, A.; Nath, M. Microwave-assisted green synthesis of dibenzo[a,j]xanthenes using p-dodecylbenzenesulfonic acid as an efficient Bronsted acid catalyst under solvent-free conditions. *C. R. Chim.* **2012**, *15*, 675-678.
31. Karimi-Jaberi, Z.; Keshavarzi, M. Efficient one-pot synthesis of 14-substituted-14H-dibenzo [a, j] xanthenes using boric acid under solvent-free conditions. *Chin. Chem. Lett.* **2010**, *21*, 547-549.
32. Khosropour, A.R.; Khodaei, M.M.; Moghannian, H. A facile, simple and convenient method for the synthesis of 14-alkyl or aryl-14-H-dibenzo [a, j] xanthenes catalyzed by pTSA in solution and solvent-free conditions. *Synlett* **2005**, *06*, 0955-0958.
33. Das, B.; Thirupathi, P.; Reddy, K.R.; Ravikanth, B.; Nagarapu, L. An efficient synthesis of 1,8-dioxo-octahydroxanthenes using heterogeneous catalysts. *Catal. Commun.* **2007**, *8*, 535-538.
34. Jin, T.S.; Zhang, J.S.; Wang, A.Q.; Li, T.S. Solid-State Condensation Reactions Between Aldehydes and 5,5-Dimethyl-1,3-cyclohexanedione by Grinding at Room Temperature. *Synth. Commun.* **2005**, *35*, 2339-2345.
35. Pasha, M.A.; Jayashankara, V.P. Molecular iodine catalyzed synthesis of aryl-14H-dibenzo[a, j]xanthenes under solvent-free

- condition. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 621-623.
36. Song, G.; Wang, B.; Luo, H.; Yang, L. Fe³⁺-montmorillonite as a cost-effective and recyclable solid acidic catalyst for the synthesis of xanthenediones. *Catal. Commun.* **2007**, *8*, 673-676.
37. Zhang, Z.H.; Tao, X.Y. 2,4,6-Trichloro-1,3,5-Triazine Promoted Synthesis of 1,8-Dioxo-Octahydroxanthenes under Solvent-Free Conditions. *Aust. J. Chem.* **2008**, *61*, 77-79.
38. Pourian, E.; Javanshir, S.; Dolatkhan, Z.; Molaei, S.; Maleki, A. Ultrasonic-Assisted Preparation, Characterization, and Use of Novel Biocompatible Core/Shell Fe₃O₄@GA@Isinglass in the Synthesis of 1,4-Dihydropyridine and 4H-Pyran Derivatives. *ACS Omega* **2018**, *3*, 5012-5020.
39. Fan, X.S.; Li, Y.Z.; Zhang, X.Y.; Hu, X.Y.; Wang, J.J. FeCl₃·6H₂O catalyzed reaction of aromatic aldehydes with 5,5-dimethyl-1, 3-cyclohexandione in ionic liquids. *Chin. Chem. Lett.* **2005**, *16*, 897-899.
40. Avalani, J.; Patel, D.; Raval, D. 1-Methylimidazolium trifluoroacetate [Hmim]Tfa: Mild and efficient Brønsted acidic ionic liquid for Hantzsch reaction under microwave irradiation. *J. Chem. Sci.* **2012**, *124*, 1091-1096.
41. Ilangovan, A.; Malayappasamy, S.; Muralidharan, S.; Maruthamuthu, S. A highly efficient green synthesis of 1, 8-dioxo-octahydroxanthenes. *Chem. Cent. J.* **2011**, *5*, 81.
42. Kantevari, S.; Bantu, R.; Nagarapu, L. TMSCl mediated highly efficient one-pot synthesis of octahydroquinazolinone and 1,8-dioxo-octahydroxanthene derivatives. *Arkivoc* **2006**, 136-148.
43. Venkatesan, K.; Pujari, S. S.; Lahoti, R. J.; Srinivasan, K. V. An Efficient Synthesis of 1,8-Dioxo-Octahydro-Xanthene Derivatives Promoted by a Room Temperature Ionic Liquid at Ambient Conditions under Ultrasound Irradiation. *Ultrason. Sonochem.* **2008**, *15*, 548-553.
44. Fan, X.; Hu, X.; Zhang, X.; Wang, J. InCl₃·4H₂O-promoted green preparation of xanthenedione derivatives in ionic liquids. *Can. J. Chem.* **2005**, *83*, 16.
45. Xia, Y.; Yang, H.; Campbell, C.T. Nanoparticles for Catalysis. *Acc. Chem. Res.* **2013**, *46*, 1671-1672.
46. Kokkiralala, S.; Sabbavarapu, N.M.; Yadavalli, V.D.N. β-Cyclodextrin mediated synthesis of 1,8-dioxooctahydroxanthenes in water. *Eur. J. Chem.*, **2011**, *2*, 272-275.
47. Niknam, K.; Panahi, F.; Saberi, D.; Mohagheghnejad, M. Silica-bonded S-sulfonic acid as recyclable catalyst for the synthesis of 1,8-dioxo-decahydroacridines and 1,8-dioxo-octahydroxanthenes. *J. Heterocycl. Chem.*, **2010**, *47*, 292-300.
48. Das, B.; Thirupathi, P.; Mahender, I.; Reddy, V.S.; Rao, Y.K. Amberlyst-15: An efficient reusable heterogeneous catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes and 1,8-dioxo-decahydroacridines. *J. Mol. Catal. A: Chem.*, **2006**, *247*, 233-239.
49. Oskooie, H.A.; Tahershamsi, L.; Heravi, M.M.; Baghernejad, B. Cellulose Sulfonic Acid: An Efficient Heterogeneous Catalyst for the Synthesis of 1, 8-Dioxo-octahydroxanthenes. *Eur. J. Chem.*, **2010**, *7*, 717.
50. Niknam, K.; Damya, M. 1-Butyl-3-methylimidazolium Hydrogen Sulfate [Bmim]HSO₄: An Efficient Reusable Acidic Ionic Liquid for the Synthesis of 1,8-Dioxo-Octahydroxanthenes. *J. Chin. Chem. Soc.*, **2009**, *56*, 659-665.
51. Ghassamipour, S.; Ghashghaei, R. Zirconium dodecylphosphonate promoted synthesis of xanthene derivatives by condensation reaction of aldehydes and β-naphthol or dimedone in green media. *Monatsh. Chem.* **2015**, *146*, 159-163.
52. Maghsoodlou, M.T.; Habibi-Khorassani, S.M.; Shahkarami, Z.; Maleki, N.; Rostamizadeh, M. An efficient synthesis of 2,2'- arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxooctahydroxanthenes using ZnO and ZnO-acetyl chloride. *Chin. Chem. Lett.* **2010**, *21*, 686-689.
53. Bhosle, M.R.; Khillare, L.D.; Mali, J.R.; Sarkate, A.P.; Lokwani, D.K.; Tiwari, S.V. DIPEAc promoted one-pot synthesis of dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidinetetraone and pyrimido[4,5-*d*]pyrimidine derivatives as potent tyrosinase inhibitors and anticancer agents: *in vitro* screening, molecular docking and ADMET predictions. *New J. Chem.* **2018**, *42*, 18621-18632.