Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Brønsted Acidic Ionic Liquid: An Efficient and Reusable Catalyst for the Synthesis of Xanthenes Derivatives as Antimicrobial and Antioxidant Agents

K.A. Shaikh[1,✉], U.N. Chaudhar[2] and P.J. Doshi[3]

Asian Journal of Organic & Medicinal Chemistry

Volume: 5 Year: 2020
Issue: 1 Month: January–March
pp: 11–19
DOI: https://doi.org/10.14233/ajomc.2020.AJOMC-P218

Received: 19 July 2019
Accepted: 9 January 2020
Published: 5 May 2020

ABSTRACT

In the present investigation, a mild, efficient and simple procedure has been developed for the synthesis of xanthene derivatives is described *via* three component condensation of aromatic aldehydes with β-naphthol or dimedone or mixture of β-naphthol and dimedone using Brønsted acidic ionic liquid, triphenyl(propyl-3-sulphonyl)phosphonium toluene-sulfonate under solvent-free conditions. The synthesized compounds were screened for antimicrobial activities against Gram-positive (*Bacillus subtilis*), Gram-negative (*Pseudomonas aeruginosa*) bacteria and fungus (*Candida albicans*). The antioxidant activities of these compounds were determined by DPPH scavenging free radical method. Present methodology has a number of advantages such as mild reaction condition, inexpensive catalyst, stable at room temperature and it was also found that this catalyst might be recovered quantitatively and reused without much loss of catalytic activity.

KEYWORDS

Ionic liquid, Xanthenes derivatives, Dimedone, β-naphthol, Recyclable catalyst.

INTRODUCTION

In the past few decades, heterocyclic chemistry has been played vital role in organic synthesis and pharmaceutical chemistry [1]. Xanthenes and benzoxanthenes are an important constituent in the area of natural and synthetic organic chemistry. The synthesis of xanthenes and its derivatives has received considerable interest due to their wide range of biological and pharmacological activities, such as antiviral [2], antibacterial [3], anti-inflammatory [4], anti-hypertensive [5], anti-tumor [6], anti-HIV infections [7], anti-hyperlipidemic [8], anti-plasmodial [9], activities. Moreover, because of their useful spectroscopic properties these heterocyclic molecules have been widely used as dyes [10] and found applications in laser technologies [11], as sensitizers in photodynamic therapy [12] and in pH-sensitive fluorescent materials [13]. Thus, the synthesis of xanthenes has enormous significance in organic transformation.

Multi-component reactions (MCRs) have emerged as an efficient and powerful tools to build the products in organic and medicinal chemistry, in which more than two reactant molecules react to form a product for their high degree of atom economy, eco-friendly, minimize cost, saving time and appli-

Author affiliations:

[1]P.G. Department of Chemistry, Sir Sayyed College of Art's, Commerce & Science, Aurangabad-431001, India
[2]Department of Chemistry, Kalikadevi Art's, Commerce & Science College, Shirur-413249, India
[3]Biochemistry Division, Department of Chemistry, Savitribai Phule Pune University, Pune-411007, India

✉To whom correspondence to be addressed:

Fax: + 91 240 2311188
Tel: + 91 240 2313876
E-mail: shaikh_kabeerahmed@rediffmail.com

Available online at: http://ajomc.asianpubs.org

cation in the several of convergent synthesis of complex organic molecules from simple and readily available substrates in a single synthetic operation [14,15]. Furthermore, MCRs offer the benefits of simplicity and synthetic efficiency over conventional chemical reactions [16]. Additionally, solvent-free conditions construct simpler synthesis, save energy and avoid solvent waste hazards and toxicity [17-19]. Hence, it remains a challenge to develop multi-component reactions with suitable various catalysts.

In recent literature, various methods have been developed for the synthesis of xanthenes derivatives such as acetic acid [20], sulfamic acid [21], succinamide-N-sulphonic acid [22], silica sulfuric acid [23], citric acid [24], lactic acid [25], tartaric acid [26], niobium pentachloride [27], *p*-TSA [28], Ln(III) chloride/chloroacetic acid [29], phosphosulfonic acid [30], $InCl_3$ and $(HPO_3)_n$ [31], SiO_2-Pr-SO_3H [32], montmorillonite K10 [33], poly(4-vinylpyridinium)perchlorate [34], iodine [35], *etc*.

However, some of these above mentioned catalysts have significant advantages but yet it has certain limitation such as drastic reaction conditions, longer reaction time, high temperature, expensive and toxic catalyst and low yields. Therefore, the need of development of new procedure to accomplish a simple, efficient, inexpensive, non-toxic and greener approach is desirable. In current literature, researchers are more interest to use of ionic liquids for the organic transformation because of their a number of properties like easy recoverability, reusability, high thermal stability and non-inflammability, negligible vapour pressure and solvating ability [36,37]. Because of such noteworthy advantages of ionic liquid here, we report the use of efficient and reusable Brønsted acidic ionic liquid triphenyl-(propyl-3-sulphonyl)phosphonium toluenesulfonate to perform a dual role as solvent and catalyst for the synthesis of xanthenes derivatives. In literature, reusable Brønsted acidic ionic liquid has been used for different organic transformations such as β-amino carbonyl compounds [38], synthesis of ethyl acetate [39], substituted imidazoles [40], coumarin derivatives [41] and synthesis of 2,3-dihydroquinazolin-4(1H)-ones [42].

EXPERIMENTAL

The reagents and solvents were purchased from Merck, S.D. fine and Aldrich chemical companies. Melting points of all compounds were recorded by open tube capillary method and are uncorrected. The development of reaction and the purity of synthesized compounds were monitored by thin-layer chromatography (TLC), using analytical silica gel plates (Merck 60 F_{254}). ^1H & ^{13}C NMR spectra were recorded on Bruker spectrometer 500 and 125 MHz, respectively in $CDCl_3$ solvent with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a macro mass spectrometer, applying electro spray ionization (ESI) method.

Synthesis of ionic liquid triphenyl(propyl-3-sulphonyl)-phosphonium toluenesulfonate: Triphenyl(propyl-3-sulphonyl)-phosphonium toluenesulfonate as a stable reagent was easily synthesized by the reaction of triphenylphosphine and 1,3-propane sultone [39] (**Scheme-I**).

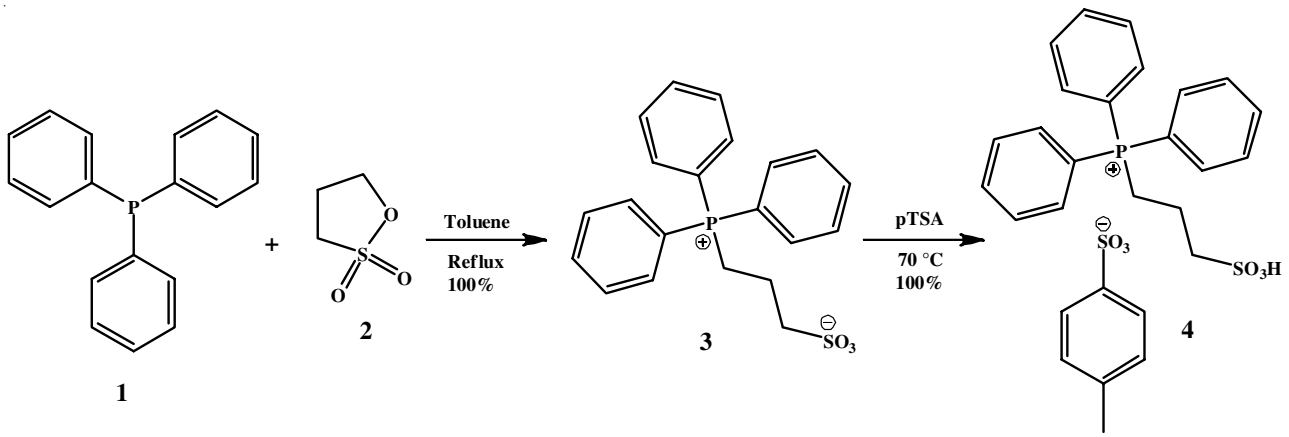
General procedure for the synthesis of xanthene derivatives: A mixture of triphenyl(propyl-3-sulfonyl)phosphonium toluenesulfonate (0.04 g), aromatic aldehyde (1.0 mmol) and the desired substrate (1.0 mmol) was heated at 80 ºC under solvent-free conditions. The development of the reaction was monitored by TLC (**Scheme-II**). After the completion of reaction, ice cold water (10 mL) was poured into the reaction mixture and stirred for 10 min. The catalyst was decanted and the crude product was recrystallized from ethanol.

Spectral data

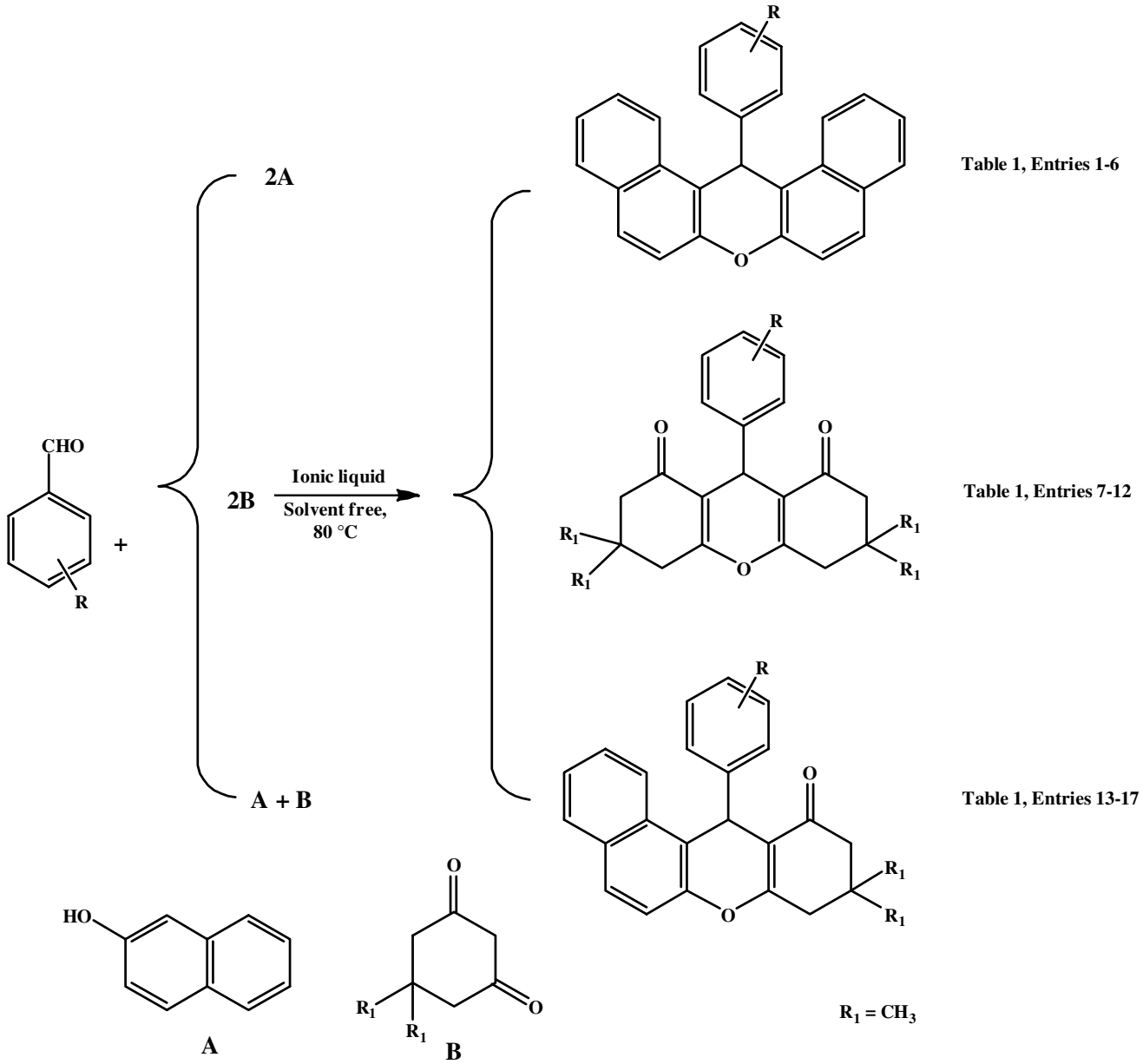
14-(4-Chlorophenyl)-14*H*-dibenzo[*a,j*]xanthenes (Table-1, entry 2): ^1H NMR (500 MHz, $CDCl_3$): δ = 6.45 (s, 1H, CH), 7.07-7.09 (d, *J* = 9.3 Hz, 2H, ArH), 7.39–7.83 (m, 14H, ArH), 8.29-8.31 (d, *J* = 9.5 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.3, 116.7, 118.0, 122.4, 124.3, 126.9, 128.6, 128.9, 129.0, 129.4, 131.0, 131.2, 132.0, 143.4, 148.7; MS: *m/z* = 393 (M + H).

14-(4-Hydroxyphenyl)-14*H*-dibenzo[*a,j*]xanthenes (Table-1, entry 3): ^1H NMR: (500 MHz, $CDCl_3$): δ = 4.73 (1H, br s, OH), 6.42 (s, 1H, CH), 6.56-6.58 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.35-7.58 (m, 8H, Ar-H), 7.76-7.82 (m, 4H, Ar-H), 8.34-8.36 (d, *J* = 8.4 Hz, 2H, Ar-H), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.0, 115.2, 117.4, 118.0, 122.6, 124.2, 126.7, 128.8, 129.3, 131.0, 131.3, 137.4, 148.6, 153.8 ppm MS: *m/z* = 375 (M + H).

14-(3,4-Dimethoxy phenyl)-14*H*-dibenzo[*a,j*]xanthenes (Table-1, entry 4): ^1H NMR (500 MHz, $CDCl_3$): δ = 3.68 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 6.44 (s, 1H, CH), 6.65 (d, *J* =



Scheme-I: Synthesis of ionic liquid triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate



Scheme-II: Synthesis of xanthenes derivatives

8.3 Hz, 1H, ArH), 6.91 (d, *J* = 1.7 Hz, 1H, ArH), 7.11-7.13 (dd, *J* = 8.3 Hz, *J* = 1.8 Hz, 1H, ArH), 7.39-7.58 (m, 6H, ArH), 7.77-7.83 (m, 4H, ArH), 8.40 (d, *J* = 8.4 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.4, 55.7, 110.7, 111.6, 117.4, 117.9, 120.3, 122.7, 124.2, 126.7, 128.7, 128.8, 131.1, 131.4, 137.6, 147.5, 148.7, 149.0 ppm; MS: *m/z* = 419 (M + H).

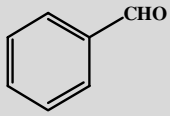
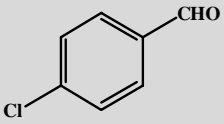
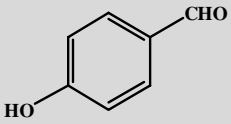
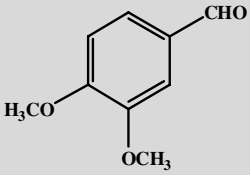
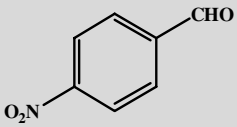
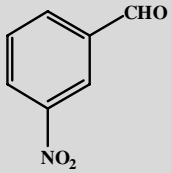
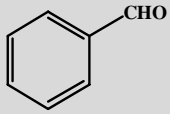
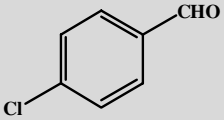
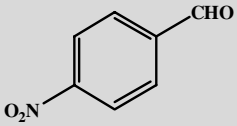
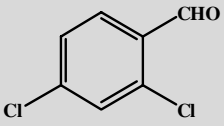
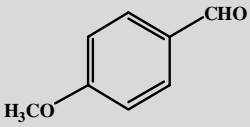
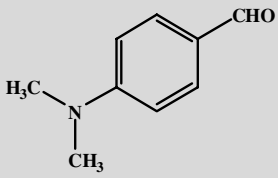
14-(3-Nitrophenyl)-14*H*-dibenzo[*a,j*]xanthenes (Table-1, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.58 (s, 1H, CH), 7.25–7.85 (m, 13H, ArH), 8.28-8.29 (d, *J* = 7.5 Hz, 2H, ArH), 8.40 (s, 1H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8, 148.2, 146.9, 134.2, 131.0, 129.5, 129.0, 127.2, 124.5, 122.7, 122.0, 121.7, 118.1, 115.8, 37.7 ppm; MS: *m/z* = 404 (M + H).

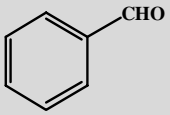
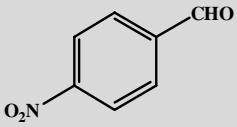
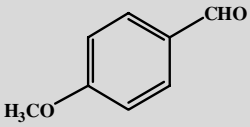
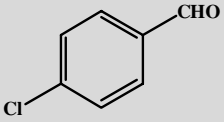
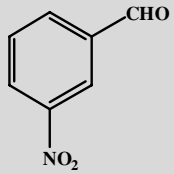
9-(4-Nitrophenyl)-1,8-dioxo-octahydroxanthene (Table-1, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.99 (s, 6H, $2CH_3$), 1.12 (s, 6H, $2CH_3$), 2.15-2.27 (m, 4H, CH_2), 2.49 (s, 4H, CH_2), 4.82 (s, 1H, CH), 7.46-7.48 (d, *J* = 8.6 Hz, 2H, ArH), 8.08-8.10 (d, *J* = 8.8 Hz, 2H, Ar-H), ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 27.2, 29.2, 32.2, 32.3, 40.8, 50.6, 114.5, 123.4, 129.3, 146.4, 151.5, 162.9, 196.2; MS: *m/z* = 396 (M + H).

9-(2, 4-Dichlorophenyl)-1,8-dioxo-octahydroxanthene (Table-1, entry 10): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.01 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$), 2.17 (d, 2H, CH_2), 2.24 (d, 2H, CH_2), 2.44 (d, 2H, CH_2), 2.48 (d, 2H, CH_2), 4.94 (s, 1H, CH), 7.13-7.15 (dd, *J* = 8.3 Hz, *J* = 1.8 Hz, 1H, ArH), 7.24 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.38 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 27.3, 29.2, 32.0, 40.7, 50.6, 113.3, 126.7, 129.8, 132.7, 133.7, 134.0, 138.6, 163.2, 196.5; MS: *m/z* = 419 (M + H).

9-(4-Methoxyphenyl)-1,8-dioxo-octahydroxanthene (Table-1, entry 11): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (S, 6H, $2CH_3$), 1.09 (S, 6H, $2CH_3$), 2.18-2.24 (d, *J* =16.4 Hz, 4H, $2CH_2$), 2.45 (S, 4H, $2CH_2$), 3.73 (S, 3H, OCH_3), 4.69 (S,

TABLE-1
BRØNSTED ACIDIC IONIC LIQUID, TRIPHENYL(PROPYL-3-SULPHONYL) PHOSPHONIUM TOLUENESULFONATE CATALYZED SYNTHESIS OF XANTHENES DERIVATIVES[a]

Entry	Aryl aldehyde	Time (min)	Yield[b] (%)	m.p. (°C)		Ref.
				Found	Reported	
1		12	94	180-182	182-183	[19]
2		10	96	286-288	288-289	[19]
3		15	88	138-140	139-141	[19]
4		12	90	170-172	–	–
5		10	96	311-313	311-312	[19]
6		11	92	210-211	210-212	[19]
7		12	90	203-205	204-206	[12]
8		10	94	232-234	230-231	[9]
9		10	94	226-227	226-228	[12]
10		12	92	178-180	177-179	[12]
11		12	90	247-249	248-249	[12]
12		15	85	218-220	219-221	[11]

13		15	90	150-151	149-151	[13]
14		10	92	173-175	174-176	[13]
15		12	89	202-204	202-204	[13]
16		10	94	178-180	178-180	[13]
17		11	92	164-166	166-168	[13]

[a]Reaction conditions: A mixture of triphenyl(propyl-3-sulfonyl)phosphonium toluenesulfonate (0.04 g), aromatic aldehyde (1 mmol), and the desired substrate (1, mmol, according to **Scheme-II**) was heated at 80 °C under solvent-free conditions. [b]Isolated yield.

1H, CH), 6.76 (d, *J* =8.8 Hz, 2H, Ar-H), 7.20 (d, *J* =8.8 Hz, 2H, Ar-H), ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.3, 29.2, 30.9, 32.2, 40.8, 50.7, 55.1, 113.4, 115.8, 129.3, 136.5, 157.9, 162.0, 196.5 ppm; MS: *m/z* = 381 (M + H).

12-(4-Chlorophenyl)-9,9-dimethyl-8,9,10,12-octahydrobenzo[*a*]xanthenes-11-one (Table-1, entry 16): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.25 (d, *J* = 16.3 Hz, 1H, CH_2), 2.32 (d, *J* = 16.3 Hz, 1H, CH_2), 2.56 (s, 2H, CH_2), 5.68 (s, 1H, CH), 7.08-7.14 (d, *J* = 8.4 Hz, 2H, ArH), 7.25-7.59 (m, 5H, ArH), 7.76-7.90 (m, 2H, ArH), 8.31 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): 27.1, 29.3, 32.2, 34.1, 37.3, 41.4, 50.8, 113.8, 116.7, 117.0, 118.0, 122.4, 123.4, 124.3, 125.0, 126.9, 127.1, 128.4, 128.9, 129.4, 129.8, 131.2, 131.9, 132.0, 143.4, 148.7, 164.0, 196.9 ppm; MS (*m/z*): 389 (M + H).

Antimicrobial activity: The antimicrobial activity of synthesized compound was determined by turbidometric method [43-45]. A sample was prepared in DMSO solvent as per the required concentration of solvent for microbial culture (Luria Bertani broth and potato dextrose Luria Bertani). Incubated microbial cultures were growed in media for 24 h. Before use of microbial culture for antimicrobial activity count of microorganism was carried out. Microbial culture for activity taken as 10^5 in freshly prepared Luria Bertani broth (bacteria) and potato dextrose Luria Bertani (*Candida albicans*) to active final volume 200 µL in 96 well plate and concentration of newly synthesized compound added in seeded culture of 96 well plate. Control was taken as culture and respective media. For this assay, penicillin is used as standard in same plate with culture and media. Microbial plate was incubated for 24 h at 37 ºC and OD was measured at 600 nm by using 96 well plate reader. Assay was conducted in triplicates for same concentration and experimental conditions. From obtained OD antimicrobial activity of compound was calculated as follows:

$$\text{Inhibition (\%)} = \frac{OD_{control} - OD_{sample}}{OD_{control}} \times 100$$

Antioxidant activity: The antioxidant activity of synthesized compounds was determined by using DPPH stable free radical method [46-48] and ascorbic acid was used as a standard. Stock solution of the DPPH radicals was prepared by dissolving in methanol to obtain 0.1 mM concentration. The assay was carried out in a 96 well plate. A 500 µg of compound was added in 200 µL of methanolic 0.1 mM of DPPH. The mixture was shaken and kept in the dark at 37 ºC for 10 min. After 10 min, the absorbance values were measured at 517 nm and converted into the percentage antioxidant activity (%) using the following equation [45]. All the experiments were performed in triplicate.

RESULTS AND DISCUSSION

In the present investigation, a condensation of β-naphthol and variety of aromatic aldehydes in the presence of Brønsted acidic ionic liquid, triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate as a catalyst for the synthesis of 14*H*-dibenzo-[*a*,*j*]xanthenes was carried out.

Further, to study the effect of Brønsted acidic ionic liquid, triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate as catalyst, we have used as a model reaction 4-chlorobenzaldehyde and β-naphthol which leads to formation of 14*H*-dibenzo-[*a*,*j*]xanthenes derivatives (Table-1, entry 2). During this study, the optimized temperature, time and amount of Brønsted acidic ionic liquid, triphenyl(propyl-3-sulphonyl)-phosphonium toluenesulfonate for the reaction was found to be 80 ºC, 10 min and (0.04 g, 8 mol %, 0.08 mmol) of catalyst to carry out the reaction smoothly (Table-2, entry 6). Encouraged by this, experiment was extended to a variety of aromatic aldehydes possessing both electron donating and electron with-

TABLE-2
OPTIMIZATION OF REACTION CONDITION BETWEEN 4-CHLOROBENZALDEHYDE (1.0 mmol) AND β-NAPHTHOL (2.0 mmol) IN THE PRESENCE OF TRIPHENYL (PROPYL-3-SULFONYL) PHOSPHONIUM TOLUENESULFONATE UNDER SOLVENT-FREE CONDITIONS

Entry	Ionic liquid (g)	Temp. (°C)	Time (min)	Yield[a] (%)
1	–	120	360	Trace
2	0.04	50	60	45
3	0.04	60	50	65
4	0.04	65	40	75
5	0.04	70	25	89
6	0.04	80	10	94
7	0.01	80	60	45
8	0.02	80	40	68
9	0.03	80	30	82
10	0.05	80	10	94

[a]Isolated yield.

drawing substituent, which were converted into their corresponding xanthenes derivatives yielding excellent yields (Table-1).

Effect of catalyst: A mixture of 4-chlorobenzaldehyde and β-naphthol was stirred at 120 ºC for 6 h in absence of catalyst (Table-2, entry 1). It was found that the reaction did not give any desired product, indicating that catalyst to be must for this transformation. With this successful synthesis of 14*H*-dibenzo[*a*,*j*]xanthene derivatives from the reactions of 4-chlorobenzaldehyde and β-naphthol react with greater ease under these reaction conditions. Furthermore, one pot efficient synthesis of 1,8-dioxooctahydroxanthene derivatives with excellent yields by replacing β--naphthol with dimedone under same reaction conditions (Table-1, entries 7-12).

It is well documented both above conversion, we finally turned our attention towards the one pot efficient synthesis of 12-aryl-tetrahdrobenzo[*a*]xanthenes-11-ones by condensation of aryl aldehydes with β-naphthol and dimedone under solvent free condition (Table-1, Entries 13-17). In order to understand efficiency and non-toxicity of the catalyst, a comparison to other reported catalyst is shown in Table-3, revealing that more prominent catalytic activity of Brønsted acidic ionic liquid, triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate than the other reported method.

We also studied, recycling of the catalyst under solvent free condition in the reaction of 4-chlorobenzaldehyde and β-naphthol. After completion of the reaction, ice cold water poured into the reaction mixture and the solid precipitate was filtered off for separation of crude product. After complete washing of solid products with water, water soluble ionic liquid had evaporated under reduced pressure and the ionic liquid was recovered and reused. The recoverable catalyst reused for further four times without loss of its significant activity Table-4.

TABLE-4
RECYCLING OF THE CATALYST UNDER SOLVENT FREE CONDITION IN THE REACTION OF 4-CHLOROBENZALDEHYDE AND β-NAPHTHOL

Entry	Time (min)	Isolated yield (%)
1	10	94
2	10	93
3	11	92
4	12	90
5	13	89

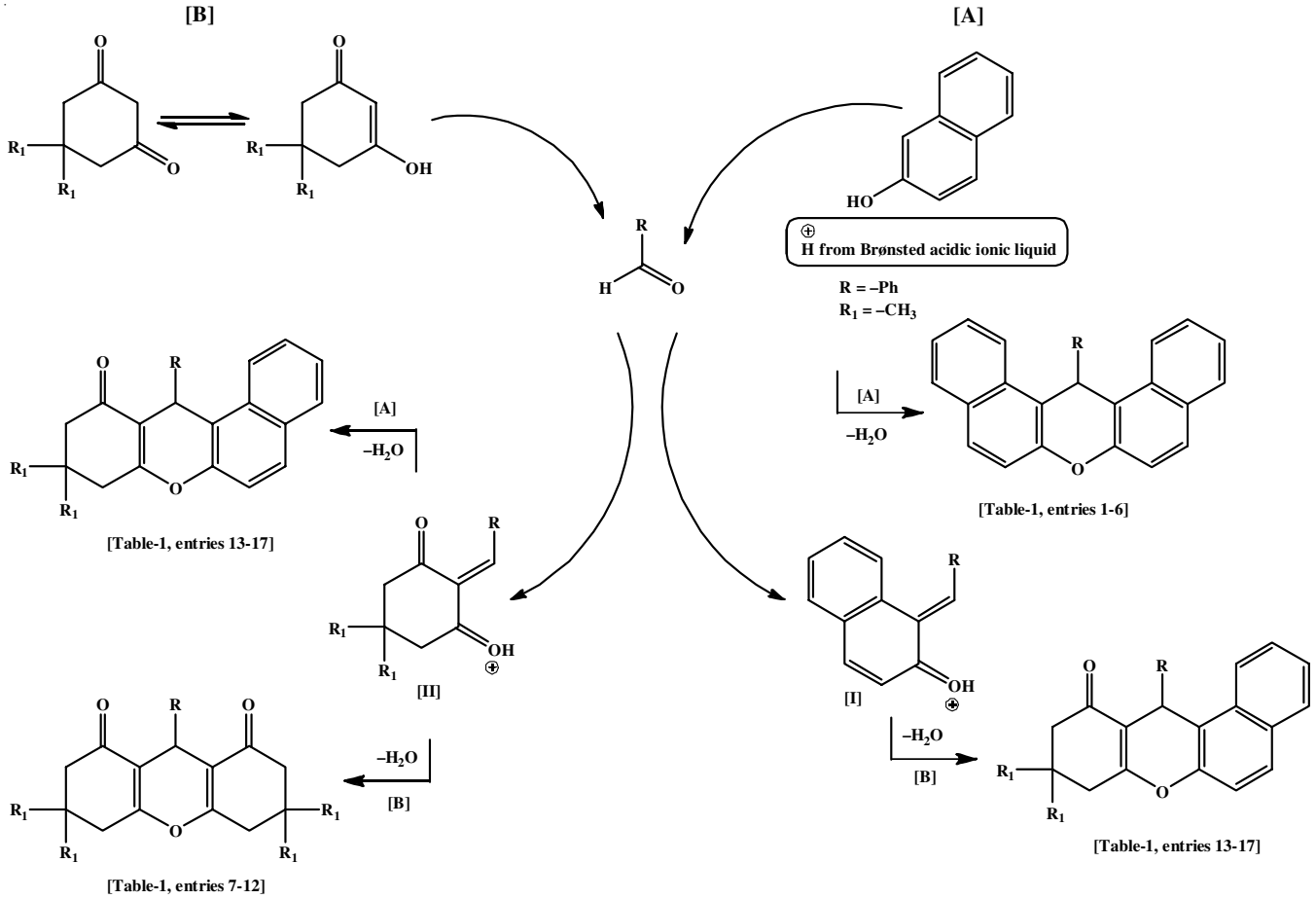
The mechanism pathway for the synthesis of xanthenes derivatives is proposed in **Scheme-III**. Initially, activation of carbonyl group of aromatic aldehydes by triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate (acidic proton), facilitates to nucleophilic attack of 2-naphthol [A] or dimedone [B] to form the Knoevenagel products [I or II]. Then subsequent addition of [I or II] to [A] or [B] gives the acyclic adduct intermediates, followed by intramolecular cyclisation with the participation of two hydroxyl groups to gives xanthenes derivatives (**Scheme-III**).

Microbial activity: The antimicrobial activity of heterocyclic compound studied by turbidometric methods results demonstrate that most of the compounds exhibited promising activity. Standard microbial culture antimicrobial activity profile was studied with respect to standard antibiotic penicillin. The synthesized scaffolds were evaluated for their *in vitro* antibacterial activity. Among the synthesized compounds, only compounds **6**, **10** and **16** shows moderate to less active against Gram-negative bacteria (*Pseudomonas aeruginosa*) at 100 µg sample remaining were less or no active against Gram-negative bacteria and compound **16** showed less to moderate activity against Gram-positive bacteria (*Bacillus subtilis*) at 100 µg sample remaining were less or no active against Gram-positive bacteria compared to standard penicillin (Table-5).

The maximum antifungal activity was observed for compound **9**, while compound **11** shows a moderate activity and remaining compounds showed less or no activity at 100 µg sample against *Candida albicans* compared to standard penicillin (Table-5). These results showed that the nature of substituent groups plays a significant role in the activity of substrate. Electron withdrawing substituent shows a moderate to maximum and electron donating substituent shows less to moderate activity.

TABLE-3
COMPARISON OF EFFICIENCY OF VARIOUS CATALYSTS IN SYNTHESIS OF 14-ARYL-14*H*-DIBENZO [*a*,*j*]XANTHENES

Entry	Catalyst	Conditions	Time	Yield (%)	Ref.
1	Molecular iodine	Solvent-free/90-95 °C	20 min	90	[22]
2	Sulfamic acid	Solvent-free/125 °C	8 h	93	[8]
3	SiO_2-Pr-SO_3H	Solvent-free/125 °C	20 min	98	[19]
4	Phosphosulfonic acid	Solvent-free/110 °C	35 min	93	[17]
5	Succinimide-N-sulfonic acid	Solvent-free/80 °C	35 min	92	[9]
6	Niobium pentachloride	CH_2Cl_2/RT	48 h	90	[14]
7	Montmorillonite K10	Solvent-free/120 °C	3 h	75	[20]
8	Poly(4-vinylpyridinium)perchlorate	Solvent-free, grinding/60 °C	30 min	92	[21]
9	Triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate	Solvent-free/80 °C	12 min	94	Present work



Scheme-III: A plausible mechanism for the synthesis of xanthenes derivatives in the presence of Brønsted acidic ionic liquid under solvent free conditions

TABLE-5
INHIBITION OF ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SYNTHESIZED SCAFFOLDS

Compound	Inhibition (%)		
	Pseudomonas aeruginosa	*Bacillus subtilis*	*Candida albicans*
2	26.69	Nil kare	28.22
3	24.22	23.12	18.55
4	Nil kare	2.27	0.024
6	48.39	22.20	4.30
9	30.17	9.22	70.18
10	40.53	1.07	26.74
11	28.86	Nil kare	33.30
16	47.99	33.58	Nil kare
Penicillin	91.78	93.71	97.74

Antioxidant activity: The newly synthesized xanthenes derivatives was examined for their antioxidant activity against standard free radical like DPPH. Table-6 indicates that most of the xanthenes derivatives show free radical scavenging activity. Maximum free radical scavenging capacity was found for compounds **4** and **11**. Variation in activity might be observed because of the functional groups and electron donating capacity of compound for scavenging free radicals.

Conclusion

In summary, an efficient and environmentally benign method for the synthesis of xanthene derivatives *via* condensation of aromatic aldehydes with β-naphthol or dimedone and/or a mixture of β-naphthol and dimedone in the presence of Brønsted acidic ionic liquid, triphenyl(propyl-3-sulphonyl)phosphonium toluene-sulfonate under solvent-free conditions. Compared with the reported methodologies, present protocol features operational simplicity, inexpensive catalyst, high reaction rates and excellent yields, environmentally benign and no side reactions. In addition, determination of antimicrobial and antioxidant activities of synthesized xanthene derivatives and catalyst can be reused in four successive runs without loss of catalytic activity.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support received from Department of Science and Technology (SERB/F/4992/2013-14; dated 30/01/2013), New Delhi, India.

TABLE 6
SCREENING OF ANTIOXIDANT ACTIVITY OF SYNTHESIZED COMPOUNDS BY DPPH METHOD

Compound		**2**	**3**	**4**	**6**	**9**	**10**	**11**	**16**	Ascorbic acid
Inhibition (%)	DPPH assay	12.17	17.98	30.88	13.76	2.99	9.72	53.70	3.11	95.22

REFERENCES

1. M. Sayyafi, M. Seyyedhamzeh, H.R. Khavasi and A. Bazgir, One-Pot, Three-Component Route to 2*H*-Indazolo[2,1-*b*]phthalazine-triones, *Tetrahedron*, **64**, 2375 (2008); https://doi.org/10.1016/j.tet.2008.01.006
2. J.M. Jamison, K. Krabill, A. Hatwalkar, E. Jamison and C.C. Tsai, Potentiation of the Antiviral Activity of Poly r(A-U) by Xanthene Dyes, *Cell Biol. Int. Rep.*, **14**, 1075 (1990); https://doi.org/10.1016/0309-1651(90)90015-Q
3. A.M. El-Brashy, M.E. Metwally and F.A. El-Sepai, Spectrophotometric Determination of Some Fluoroquinolone Antibacterials by Binary Complex Formation with Xanthene Dyes, *Il Farmaco*, **59**, 809 (2004); https://doi.org/10.1016/j.farmac.2004.07.001
4. K. Chibale, M. Visser, D. van Schalkwyk, P.J. Smith, A. Saravanamuthu and A.H. Fairlamb, Exploring the Potential of Xanthene Derivatives as Trypanothione Reductase Inhibitors and Chloroquine Potentiating Agents, *Tetrahedron*, **59**, 2289 (2003); https://doi.org/10.1016/S0040-4020(03)00240-0
5. Y. Tsurumi, H. Ueda, K. Hayashi, S. Takase, M. Nishikawa, S. Kiyoto and M. Okuhara, WS75624 A and B, New Endothelin Converting Enzyme Inhibitors Isolated from *Saccharothrix* sp. No. 75624, *J. Antibiot.*, **48**, 1066 (1995); https://doi.org/10.7164/antibiotics.48.1066
6. Y. Kumar, R. Green, K.Z. Borysko, D.S. Wise, L.L. Wotring and L.B. Townsend, Synthesis of 2,4-Disubstituted Thiazoles and Selenazoles as Potential Antitumor and Antifilarial Agents. 1. Methyl 4-(isothiocyanatomethyl)thiazole-2-carbamates, -selenazole-2-carbamates and Related Derivatives, *J. Med. Chem.*, **36**, 3843 (1993); https://doi.org/10.1021/jm00076a012
7. F.W. Bell, A.S. Cantrell, M. Hoegberg, S.R. Jaskunas, N.G. Johansson, C.L. Jordan, M.D. Kinnick, P. Lind and J.M. Morin Jr., Phenethylthiazolethiourea (PETT) Compounds, A New Class of HIV-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies of PETT Analogs, *J. Med. Chem.*, **38**, 4929 (1995); https://doi.org/10.1021/jm00025a010
8. R. Pereira, C. Gaudon, B. Iglesias, P. Germain, H. Gronemeyer and A.R. De Lera, Synthesis of the PPARβ/δ-Selective Agonist GW501516 and C4-Thiazole-substituted Analogs, *Bioorg. Med. Chem. Lett.*, **16**, 49 (2006); https://doi.org/10.1016/j.bmcl.2005.09.060
9. F. Zelefack, D. Guilet, N. Fabre, C. Bayet, S. Chevalley, S. Ngouela, B.N. Lenta, A. Valentin, E. Tsamo and M.G. Dijoux-Franca, Cytotoxic and Antiplasmodial Xanthones from *Pentadesma butyracea*, *J. Nat. Prod.*, **72**, 954 (2009); https://doi.org/10.1021/np8005953
10. A.T. Peters and M. Bide, Amino Derivatives of 1,8-Naphthalic Anhydride and Derived Dyes for Synthetic-Polymer Fibres, *Dyes Pigments*, **6**, 349 (1985); https://doi.org/10.1016/0143-7208(85)85005-1
11. M. Ahmad, T.A. King, D.K. Ko, B.H. Cha and J. Lee, Performance and Photostability of Xanthene and Pyrromethene Laser Dyes in Sol-Gel Phases, *J. Phys. D Appl. Phys.*, **35**, 1473 (2002); https://doi.org/10.1088/0022-3727/35/13/303
12. R.M. Ion, A. Planner, K. Wiktorowicz and D. Frackowiak, The Incorporation of Various Porphyrins into Blood Cells Measured *via* Flow Cytometry, Absorption and Emission Spectroscopy, *Acta Biochim. Pol.*, **45**, 833 (1998); https://doi.org/10.18388/abp.1998_4279
13. J. Liu, Z. Diwu and W.-Y. Leung, Synthesis and Photophysical Properties of New Fluorinated Benzo[*c*]xanthene Dyes as Intracellular pH Indicators, *Bioorg. Med. Chem. Lett.*, **11**, 2903 (2001); https://doi.org/10.1016/S0960-894X(01)00595-9
14. A. Domling and I. Ugi, Multicomponent Reactions with Isocyanides, *Angew. Chem. Int. Ed.*, **39**, 3168 (2000); https://doi.org/10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U
15. J. Zhu and H. Bienayme, Multicomponent Reactions, Wily-VCH: France (2005).
16. H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way, *Chem. Eur. J.*, **6**, 3321 (2000); https://doi.org/10.1002/1521-3765(20000915)6:18<3321::AID-CHEM3321>3.0.CO;2-A
17. Y.M. Ren and C. Cai, Three-Components Condensation Catalyzed by Molecular Iodine for the Synthesis of 2,4,6-triarylpyridines and 5-Unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones under Solvent-Free Conditions, *Monatsh. Chem.*, **140**, 49 (2009); https://doi.org/10.1007/s00706-008-0011-8
18. S. Bondock, H. El-Azap, E.E.M. Kandeel and M.A. Metwally, Eco-Friendly Solvent-Free Synthesis of Thiazolylpyrazole Derivatives, *Monatsh. Chem.*, **139**, 1329 (2008); https://doi.org/10.1007/s00706-008-0930-4
19. L. Liu, L.Y. Ji and Y.Y. Wei, Aerobic Selective Oxidation of Alcohols to Aldehydes or Ketones Catalyzed by Ionic Liquid Immobilized TEMPO under Solvent-Free Conditions, *Monatsh. Chem.*, **139**, 901 (2008); https://doi.org/10.1007/s00706-008-0861-0
20. R.J. Sarma and J.B. Baruah, One Step Synthesis of Dibenzoxanthenes, *Dyes Pigments*, **64**, 91 (2005); https://doi.org/10.1016/j.dyepig.2004.03.010
21. A.G. Banerjee, L.P. Kothapalli, P.A. Sharma, A.B. Thomas, R.K. Nanda, S.K. Shrivastava and V.V. Khatanglekar, A Facile Microwave Assisted One Pot Synthesis of Novel Xanthene Derivatives as Potential Anti-Inflammatory and Analgesic Agents, *Arab. J. Chem.*, **9**, S480 (2016); https://doi.org/10.1016/j.arabjc.2011.06.001
22. F. Shirini and N.G. Khaligh, Succinimide-*N*-sulfonic Acid: An Efficient Catalyst for the Synthesis of Xanthene Derivatives under Solvent-Free Conditions, *Dyes Pigments*, **95**, 789 (2012); https://doi.org/10.1016/j.dyepig.2012.06.022
23. M. Seyyedhamzeh, P. Mirzaei and A. Bazgir, Solvent-Free Synthesis of Aryl-14*H*-dibenzo[*a,j*]xanthenes and 1,8-Dioxooctahydroxanthenes using Silica Sulfuric Acid as Catalyst, *Dyes Pigments*, **76**, 836 (2008); https://doi.org/10.1016/j.dyepig.2007.02.001
24. C.A. Navarro, C.A. Sierra and C. Ochoa-Puentes, Aqueous Citric Acid as "Green" Reaction Media for the Synthesis of Octahydroxanthenes, *Rev. Colomb. Quim.*, **42**, 5 (2013).
25. F.N. Sadeh, M. Fatahpour, N. Hazeri, M.T. Maghsoodlou and M. Lashkari, One-Pot Condensation Approach for the Synthesis of Some 1,8-Dioxo-octahydroxanthenes and 14-Aryl-14*H*-dibenzo[*a,j*]Xanthenes using Lactic Acid as an Efficient and Eco-Friendly Catalyst, *Acta Chem. Iasi*, **25**, 24 (2017); https://doi.org/10.1515/achi-2017-0004
26. F. Mohamadpour, M.T. Maghsoodlou, M. Lashkari, R. Heydari and N. Hazeri, Green Synthesis of Polysubstituted Quinolines and Xanthene Derivatives Promoted by Tartaric Acid as a Naturally Green Catalyst under Solvent-free Conditions, *Chem. J. Mold.*, **13**, 74 (2018); https://doi.org/10.19261/cjm.2017.449
27. A. de Andrade Bartolomeu, M.L. de Menezes and L.C. da Silva Filho, Efficient One-pot Synthesis of 14-Aryl-14*H*-dibenzo[*a,j*]xanthene Derivatives Promoted by Niobium Pentachloride, *Chem. Pap.*, **68**, 1593 (2014); https://doi.org/10.2478/s11696-014-0597-8
28. J.M. Khurana and D. Magoo, pTSA-Catalyzed One-pot Synthesis of 12-Aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones in Ionic Liquid and Neat Conditions, *Tetrahedron Lett.*, **50**, 4777 (2009); https://doi.org/10.1016/j.tetlet.2009.06.029
29. B. Pouramiri, M. Shirvani and K. TavakolinejadFacile and Rapid Synthesis of Divers Xanthene Derivatives using Lanthanum(III) Chloride/Chloroacetic Acid as an Efficient and Reusable Catalytic System under Solvent-Free Conditions, *J. Serb. Chem. Soc.*, **82**, 483 (2017); https://doi.org/10.2298/JSC160803034P
30. A.R. Kiasat, A. Mouradzadegun and S.J. Saghanezhad, Phosphosulfonic Acid, An Efficient Solid Acid Catalyst for the One-pot Preparation of 14-Aryl-14*H*-dibenzo[*a,j*]xanthenes and 1,8-Dioxooctahydroxanthenes under Solvent-Free Conditions, *J. Serb. Chem. Soc.*, **78**, 1291 (2013); https://doi.org/10.2298/JSC121108008K
31. B. Karami, S. Nejati and K. Eskandari, An Adapted Route to Efficient Synthesis of 1,8-Dioxooctahydroxanthene Derivatives using $InCl_3$ and $(HPO_3)_n$ as Recyclable Catalysts, *Curr. Chem. Lett.*, **4**, 169 (2015); https://doi.org/10.5267/j.ccl.2015.5.001
32. G.M. Ziarani, A.R. Badiei and M. Azizi, The One-Pot Synthesis of 14-Aryl-14*H*-dibenzo[*a,j*]xanthene Derivatives using Sulfonic Acid Functionalized Silica (-Pr-) under Solvent Free Conditions, *Sci. Iran.*, **18**, 453 (2011); https://doi.org/10.1016/j.scient.2011.05.008
33. C.D. Minoo, A. Seyyedeh and B. Ayoob, One-Pot Synthesis of Xanthene Derivatives Under Solvent-Free Conditions, *Chem. Pap.*, **62**, 522 (2008); https://doi.org/10.2478/s11696-008-0050-y

34. N.G. Khaligh, Synthesis of Xanthene Derivatives in Presence of Poly(4-vinylpyridinium) Perchlorate as a Solid Acid under Grinding and Solvent-Free Conditions, *Polycycl. Aromat. Compd.*, **34**, 493 (2014); https://doi.org/10.1080/10406638.2014.895950
35. M.A. Pasha and V.P. Jayashankara, Molecular Iodine Catalyzed Synthesis of Aryl-14*H*-dibenzo[*a,j*]xanthenes under Solvent-Free Condition, *Bioorg. Med. Chem. Lett.*, **17**, 621 (2007); https://doi.org/10.1016/j.bmcl.2006.11.009
36. T. Welton, Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis, *Chem. Rev.*, **99**, 2071 (1999); https://doi.org/10.1021/cr980032t
37. P. Wasserscheid and W. Keim, Ionic Liquids-New "Solutions" for Transition Metal Catalysis, *Angew. Chem. Int. Ed.*, **39**, 3772 (2000); https://doi.org/10.1002/1521-3773(20001103)39:21<3772::AID-ANIE3772>3.0.CO;2-5
38. S. Sahoo, T. Joseph and S.B. Halligudi, Mannich Reaction in Brönsted Acidic Ionic Liquid: A Facile Synthesis of β-Amino Carbonyl Compounds, *J. Mol. Catal. Chem.*, **244**, 179 (2006); https://doi.org/10.1016/j.molcata.2005.09.012
39. A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes and J.H. Davis, Novel Brønsted Acidic Ionic Liquids and Their Use as Dual Solvent-Catalysts, *J. Am. Chem. Soc.*, **124**, 5962 (2002); https://doi.org/10.1021/ja026290w
40. H.R. Shaterian, M. Ranjbar and K. Azizi, Synthesis of Highly Substituted Imidazoles using Brønsted Acidic Ionic Liquid, Triphenyl(propyl-3-sulphonylphosphonium Toluenesulfonate, As Reusable Catalyst, *J. Iran. Chem. Soc.*, **8**, 1120 (2011); https://doi.org/10.1007/BF03246570
41. H.R. Shaterian and M. Aghakhanizadeh, Ionic-Liquid-Catalyzed Green Synthesis of Coumarin Derivatives onder Solvent-free Conditions, *Chin. J. Catal.*, **34**, 1690 (2013); https://doi.org/10.1016/S1872-2067(12)60654-8
42. F.S. Toosi and M. Khakzadi, A New and Facile Synthesis 2,3-Dihydroquinazolin-4(1*H*)-ones, *Res. Chem. Intermed.*, **41**, 311 (2015); https://doi.org/10.1007/s11164-013-1193-1
43. J. Kukic, V. Popovic, S. Petrovic, P. Mucaji, A. Ciric, D. Stojkovic and M. Sokovic, Antioxidant and Antimicrobial Activity of *Cynara cardunculus* Extracts, *Food Chem.*, **107**, 861 (2008); https://doi.org/10.1016/j.foodchem.2007.09.005
44. J.R. Nguemeving, A.G.B. Azebaze, V. Kuete, N.N. Eric Carly, V.P. Beng, M. Meyer, A. Blond, B. Bodo and A.E. Nkengfack, Laurentixanthones A and B, Antimicrobial Xanthones from *Vismia laurentii*, *Phytochemistry*, **67**, 1341 (2006); https://doi.org/10.1016/j.phytochem.2006.03.018
45. S.G. Funde, Phytochemicals Evaluation, Anticancer, Antioxidant and Antimicrobial Activity of *Acorus calamus* Different Solvent Extracts, *J. Chem. Pharm. Res.*, **7**, 495 (2015).
46. S.F. Barbuceanu, D.C. Ilies, G. Saramet, V. Uivarosi, C. Draghici and V. Radulescu, Synthesis and Antioxidant Activity Evaluation of New Compounds from Hydrazinecarbothioamide and 1,2,4-Triazole Class Containing Diarylsulfone and 2,4-Difluorophenyl Moieties, *Int. J. Mol. Sci.*, **15**, 10908 (2014); https://doi.org/10.3390/ijms150610908
47. A.R. Srividya, S.P. Dhanabal, V.K. Misra and G. Suja, Antioxidant and Antimicrobial Activity of *Alpinia officinarum*, *Indian J. Pharm. Sci.*, **72**, 145 (2010); https://doi.org/10.4103/0250-474X.62233
48. B. Bozin, N. Mimica-Dukic, I. Samojlik, A. Goran and R. Igic, Phenolics as Antioxidants in Garlic (*Allium sativum* L., Alliaceae), *Food Chem.*, **111**, 925 (2008); https://doi.org/10.1016/j.foodchem.2008.04.071