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A REVIEW ON XANTHENE-1,8(2H)-DIONE BASED COMPOUNDS

[1]Dr. Reetu sangwan, [2]Dr. Mithilesh Kumar Singh
[1]Assistant Professor, [2]Assistant Professor (Guest Faculty)
[1,2]Department of Chemistry, R B College, Dalsing Sarai, Samastipur
L.N.M. University, Darbhanga, Bihar, India

Abstract- Xanthenes, the oxygen containing heterocycles present as the basic scaffolds of various pharmacological active molecules like benzoxanthenes and xanthene-1,8(2H)-dione, exhibited a wide array of biological properties The structural features and important biological activities associated with these xanthene-1,8(2H)-dione have attracted chemists to discover various synthetic routes, therefore, a number of strategies are reported for the synthesis of compounds based on xanthene-1,8(2H)-dione. In this review article we have summarized various methods for the synthesis and biological activities of xanthene-1,8(2H)-dione based compounds.

Keywords- Xanthene, dimedone, benzaldehyde, xanthene-1,8(2H)-dione.

I. Introduction

Heterocyclic chemistry is the largest branch of organic chemistry which deals with the different molecules of various biological importances, which are not limited only to the development of new synthetic molecules but also help in the betterment and improvement oflife processes.

Many natural drugs [1-3]such as vinblastine, vincristine, colchicine, papaverine, quinine, emetine, atropine, procaine, codeine, reserpine and morphine etc. belong to the heterocyclic group. Synthetic heterocycles show many types of biological activities such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, antiinflammatory, muscle relaxants, anticonvulsant, anticancer, lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents. [4-10]

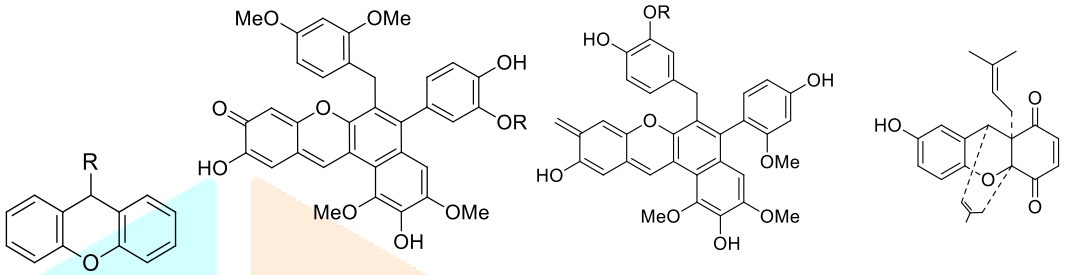
Heterocyclic compounds which containoxygen and nitrogen in ring system are considered as the most desired molecules for designing and synthesis of new molecules of biological interestbecause the introduction of heteroatoms like nitrogen and oxygen in cyclization display enhanced physicochemical properties and reactivity quite different from the parent hydrocarbon system.

Literature survey revealed that pharmacologically active agents havingbasic skeleton of xanthene (**1**) are of great importance in the field of heterocyclic as well as medicinal chemistry.

Xanthenes, the oxygen containing heterocycles present as the basic scaffolds of various pharmacological active molecules, exhibited a wide array of biological properties. Some xanthenes are available from natural sources[11]e.g. santarubins A **(2a)**, santarubins B**(2b)**,santalin A (**3**) and santalin

B (**4**) pigments have been isolated from a number of plant species eg. sandalwood, barwood and camwood.[11] Ehretianone (**5**), a quinonoid xanthene was isolated from *Ehretia buxifolia*, showedantisnake venom activity against *E. carinatus* envenomation in mice.[12]

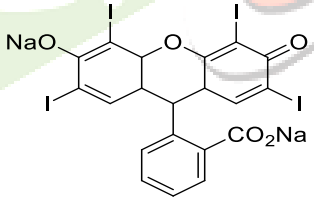
Xanthenes are found as the basicmoiety for many heterocyclic organic compounds like benzoxanthenes and xanthene-1,8(2H)-dione. These xanthene derivatives are biologically and medicinally important precursors for the synthesis of lead molecules due to pharmacological properties like antiviral [13,14], antibacterial [15], anti-inflammatory [16], antimalarial [17], antimicrobial [18], anticancer [19-21], antileukemic [22], insecticidal [23], free radical scavenging activity [24],antimycobacterial [25],antiplasmodial [26–28], antitumor [26],apoptotic effects [29], antiproliferative [30],antioxidant [31],also act as antagonists of the paralyzing action



(1) **2a R=Me 2b R=H** **(3) R=H (4) R=Me** **(5)**

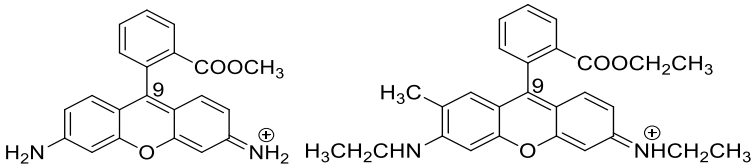
of zoxazolamine [32], photodynamic therapy [33], analgesic [34], novel CCR1 receptor antagonists [35] and potent nonpeptidic inhibitors of recombinant human calpain I36. Compounds based on xanthenes are also used asstarting materials for the synthesis of many target molecules which shows various useful spectroscopic properties therefore used as dyes [37, 38] and in laser technology [39]. For visualization of biomolecules, xanthenes are also used as pH sensitive fluorescent materials [40].

Along with so many biological properties, xanthenes based molecules also have some different properties such as these molecules are also used as food color which is permitted for use within the EU. Erythrosine (**6**) is the xanthene dye used as food color permitted in the EU or USA as Erythrosine (E127). [41]

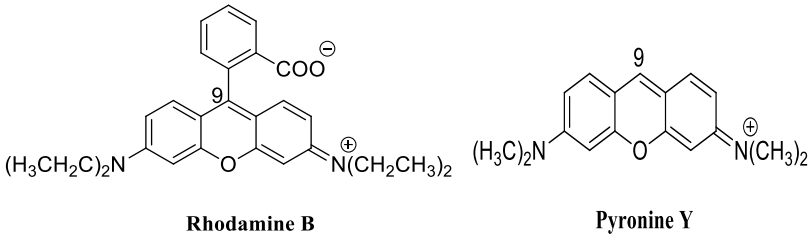


(6)

In the past decade, it was noted that several xanthenes based dyes which were related to methylene blue *viz.* rhodamines 123, 6g and B showed antimalarial properties. All these three rhodamine dyes with substitution at 9-position (**Fig 1**) were three times more potent than the unsubstituted pyronine Y [42]**,**xanthene based fluorophores including rhodamines and fluoresceins have significant photophysical properties, such as high extinction coefficients, excellent quantum yields, great photostability and relatively long emission wavelengths [43]. Some novel chemosensors also developed on the basis of spiroring-opening properties of xanthene derivatives (**Fig 2**).[43].



Rhodamine 123 **Rhodamine 6G**



Rhodamine B **Pyronine Y**

Fig 1: Structures of xanthene dyes

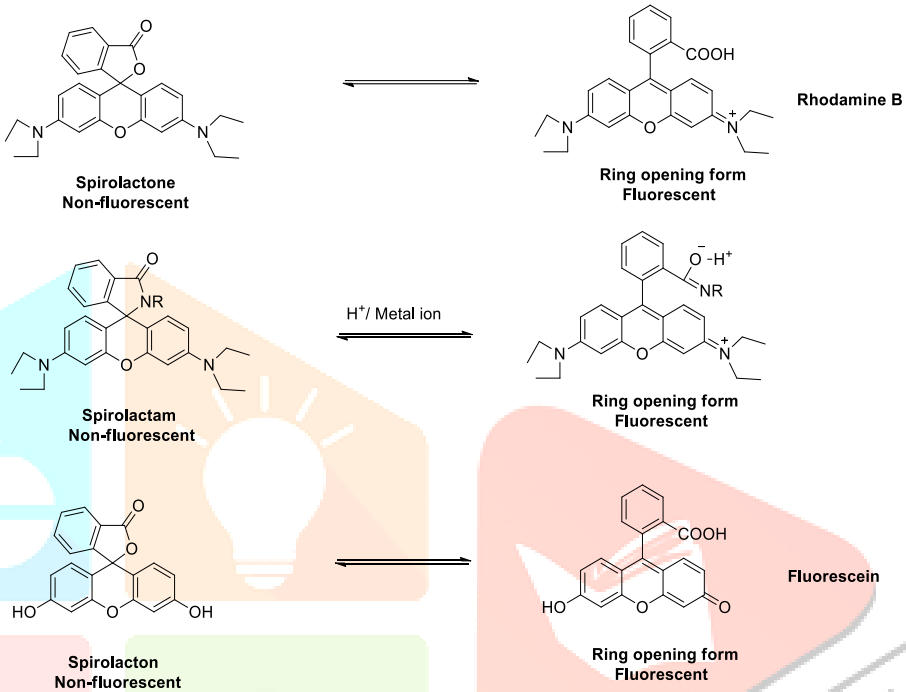
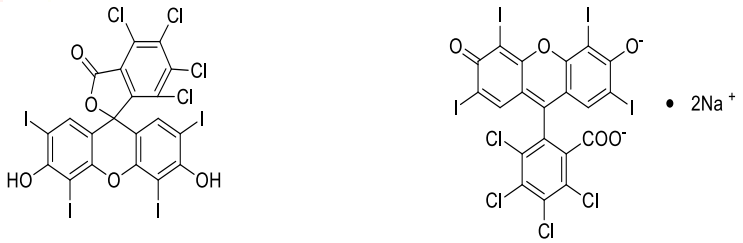


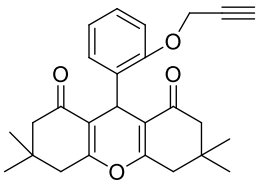
Fig 2: Ring- opening of spirocyclic xanthenes and related derivatives

Rose bengal **(7)** is a xanthene based stain and anticancer agent [44] and its sodium salt (**8**) is commonly used in eyedrops to stain damaged conjunctival and corneal cells and thereby identify damage to the eyes. Rosebengal derivatives of xanthene dyes have also have shown the dye aggregation phenomena [45].



(7) **(8)**

The xanthene group containing drugs (**9-14**) (**Fig 3**) are well known which are used in the cure of different diseases e.g. anticancer **(9, 12** and **13) [**46]and inhibitors of sirtuins **(10, 11** and **14)**[47].Other examples of the drug candidates having xanthene scaffold are Tmr (tetramethylrodamine-5-maleimide) (**15**), Fluorescite (**16**), Propantheline (**17**), Methantheline (**18**), Chlorprothixene (**19**) and Calcein AM (**20**) **(Fig 3)**[48].



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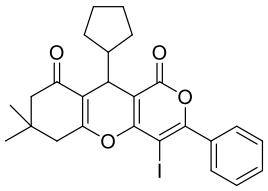

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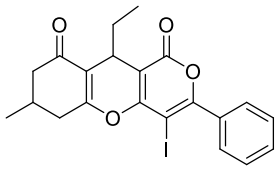
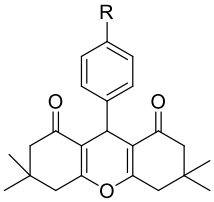
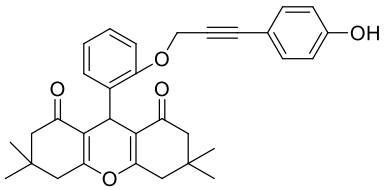


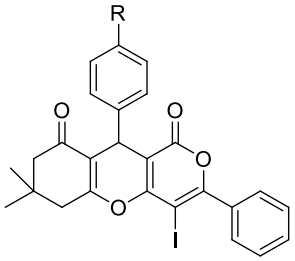
(11)



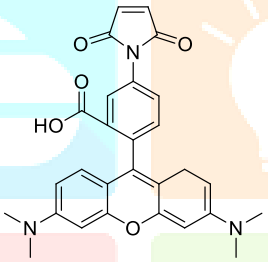
(12)
R = Cl/ F/ NO_2/OCH_3



(13)



(14)
R = F/ OCH_3



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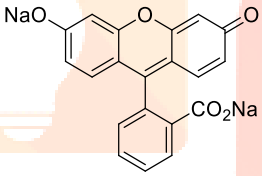

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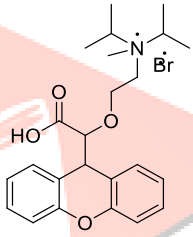

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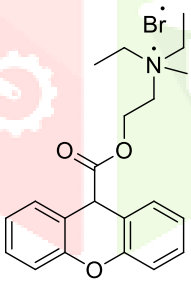
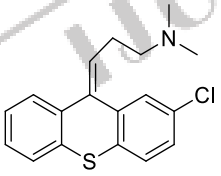


(18)



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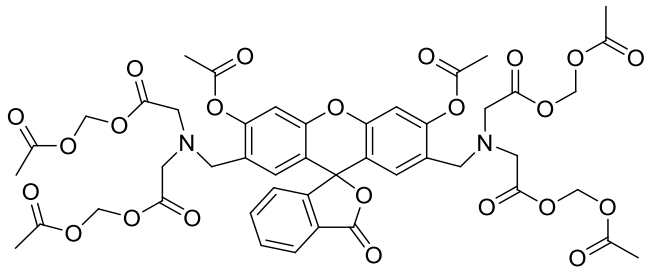


(20)

Fig 3: Pharmacologically active xanthene based drugs

Many methods are reported in literature for the synthesis of xanthenes and benzoxanthenes such as cyclodehydrations [49], phenol assisted trapping of benzynes [50], hetero atoms alkylations[51]. Xanthene based molecules are also formed by the condensation reaction between 2-tetralone and 2-hydroxy aromatic aldehydes [52]. Another reported method involved the intramolecular coupling reactions of phenyl-carbonyls by the use of aromatic aldehydes and acetophenones in the presence of samarium diiodide and hexamethylphosphoramide [53]. In addition xanthenes and related derivatives were reported to be prepared by the reaction of β-naphthol with formamide [54], 1-hydroxy methyl-naphthalen-2-ol [55] and carbon monoxide [56]. Apart from these methods some other methods have been reported for the synthesis of different substituted benzoxanthenes using different catalysts such as Dowex-50 W [57], Molecular iodine [58], Heteropolyacid [59], Fe_3O_4@SiO_2-Imid- PMAn [60], Montmorillonite K-10 [61], $Et_3N–SO_3H$]Cl [62], [H-NMP] [HSO_4] [63], $SiO_2–Pr–SO_3H$ [64], HBF_4-SiO_2 [65], NSPV PHS [66],[CMIm] [BF_4] [67a], [BMIm] [BF_4] [67b] etc.

II. Reported synthesis of xanthene-1,8(2H)-dione based compounds

The structural features and important biological activities associated with these xanthene-1,8(2H)-dione have attracted chemists to discover various synthetic routes, therefore, a number of strategies are reported for the synthesis of compounds based on xanthene-1,8(2H)-dione.

In a recent finding Srinivas *et. al.*[68] (**Scheme 1**) have synthesized xanthenedione derivatives by cyclocondensation of dimedone (**21**) with aromatic aldehydes (**22**) in the presence of trimethylsilyl chloride (TMSCl) in MeCN/DMF. Karthikeyan *et. al*. [69](**Scheme 2**) reported the synthesis of xanthenedione derivatives by the condensation of (**21**) with different benzaldehydes(**22**) using HPWA/MCM-41 mesoporous molecular sieves. Fei He*et. al*. [70](**Scheme 3**) used glycerol as solvent for electrophilic activation of aldehydes for the synthesis of xanthenedione derivatives with (**21**).

Bubun Banerjee*et. al.*[71](**Scheme 4**) reported one-pot multicomponent synthesis of 1,8-dioxooctahydroxanthenes (**23**) from the reaction of (**22**) with(**21**), using ammonium chloride as catalyst. Bahador Karami*et. al.*[72] **(Scheme 5)**reported synthesis of xanthene derivatives by condensation of aryl aldehydes**(22)**with(**21)** in water using Fe_3O_4 nanoparticles as catalyst. Minoo Dabiri*et. al.*[73]**(Scheme 6)** reported one-pot synthesis of xanthene derivatives using montmorillonite K10 as catalyst under solvent-free conditions.

Andivelu Ilangovan*et. al.*[74]**(Scheme 7)** used $SmCl_3$ (20mol%) as catalyst for synthesis of xanthene derivatives. Bahador Karami*et. al.*[75] **(Scheme 8)** synthesized molybdate sulfonic acid (MSA) as a catalyst for the synthesis of octahydroxanthene-1,8-dione**(23)** derivatives by the condensation of different aldehydes with(**21**).Hong-Yan Lu*et. al.*[76**] (Scheme 9)**used $ZrOCl_2 \cdot 8H_2O$ as catalyst for the synthesis of (**23)** from aldehydes and (**21**) under solvent-free conditions.

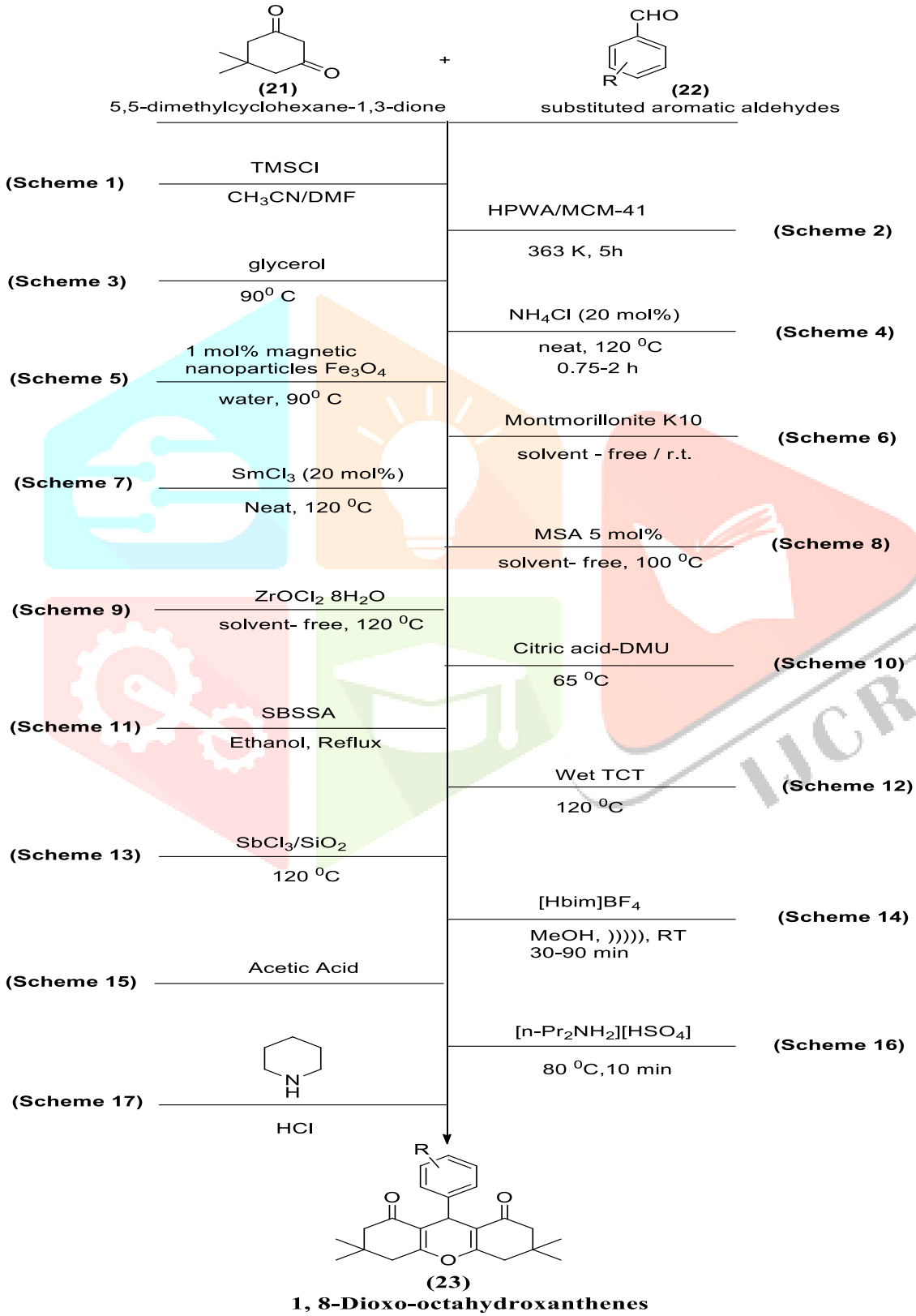
Peihe Li*et. al.*[77**] (Scheme 10)** found a low melting citric acid-urea mixture for the synthesis of xanthenedione derivatives by condensation of (**22**) and cyclic 1,3-dicarbobonyl compounds.Khodabakhsh Nikna*et. al.*[78] **(Scheme 11)** used Silica-bonded S-sulfonic acid (SBSSA) as for the synthesis of 1,8-dioxo-octahydroxanthenes.Zhan-Hui Zhang*et. al.*[79**] (Scheme 12)** synthesized1,8-dioxo-octahydroxanthenes by the reaction of(**22**) with(**21**) under solvent-free conditions in the presence of wet 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride). Zhan-Hui Zhang*et. al.*[80**](Scheme 13)** proposed the synthesis of xanthene derivatives using $SmCl_3/SiO_2$ as catalyst.

K. Venkatesan*et. al.*[81]**(Scheme 14)** proposed the condensation reaction of aldehyde and diketone by the ionic liquid, [Hbim]BF_4 (IL) as a reaction medium with methanol as co-solvent at ambient temperature under ultrasonic irradiation to afford xanthene derivatives.Meryl Maria George*et. al.*[82**] (Scheme 15)** synthesized multi-functionalized xanthenes using arylaldehydes and 1,3-dicarbonyl compounds with acetic acid as the catalyst. Pranab J. Das*et.al.*[83]**(Scheme 16)** prepared ionic liquids (IL) from dialkylamines and concentrated sulphuric acid for the benign synthesis of xanthenes and benzoxanthenes. Anne M. Reeve*et. al.*[84] **(Scheme 17)** reported synthesis of 9-phenylxanthene-1,8-dione by the reaction of (**21)**with(**22)** using piperidine in acidic medium.

Ali Akbari *et. al.*[85]synthesized thetetrahydrobenzo[a]xanthenes-11-one derivatives**24a** and **24b**inthe presence of $BF_3.SiO_2$, and assayed them for their antibacterial activity against *Pseudomonas syringae*, *Xanthomonas citi* and *Pectobacterium carotovorum*.

Zahed karimi-jaberi *et. al.*[86]synthesized the 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives **25a** and **25b** by one-pot, three-component reaction of aryl aldehydes, 2-naphthol and dimedone in the presence of trichloroacetic acid under solvent-free conditions.

Angela *et. al.*[87]reported the synthesis of compounds**26–29,** lignans belonging to a family of synthetic anti proliferative benzoxanthenes, known as DNA binders and also performed the molecular docking with *in vitro* and *in cell* fluorescence assays on the molecular mechanism of the interaction, showing the tendency of these lignans to inhibit the proteasome.

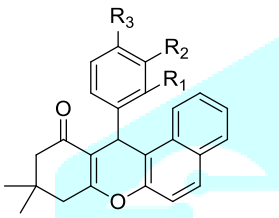


Ahmad *et. al.*[88]synthesized thederivatives of 9-aroyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione **(30)**by the condensation reaction of arylglyoxals with 1,3-diketones and TPAB as catalyst in the presence of ethanol/water under reflux conditions.

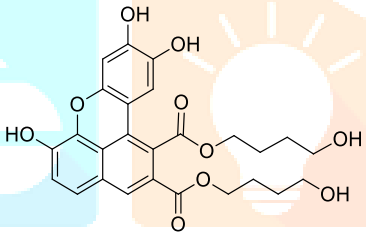
Ana*et. al.*[89]synthesized a series of xanthenedione derivative and assayed them for DPPH scavenging and AChEIactivity. Among all the synthesized compounds, compound **31**bearing a catechol unit, showed higher DPPH scavenging activity than BHT and similar activity to quercetin (EC_{50} = 3.79 ± 0.06 μM) and a potent AChEI (IC_{50} = 31.0 ± 0.09 μM) compared to galantamine (IC_{50} = 211.8 ± 9.5 μM).

T. Okazaki *et. al*[90]synthesized the benzo[kl]xanthenes **(32)** by the annulation of arenediazonium salts in FSO_3H-SbF_5 (4:1)/SO_2ClF and studied by experimental NMR and density function theory (DFT) calculations.

Rodolfo *et. al* [91]reported the photosensitizing properties of dibenzo[b,h]xanthene-5,6,8,13-tetrone derivatives **33a-33c** and dibenzo[b,h]xanthene-5,6,8,13-tetrol acetates **34a-34c**.The results demonstrated that compounds **33a-33c**were characterized as both type I and type II photosensitizers and the derivatives **34a-34c** exhibited fluorescence emission in the ultraviolet region, with short lifetimes and moderate quantum yields for fluorescence emission.



(24, 25)
(24a) R_1, R_2=OH; R_3=H
(24b) R_1, R_2=H; R_3=OH
(25a) R_1, R_2=H; R_3=Cl
(25b) R_1, R_2=H; R_3=OCH_3



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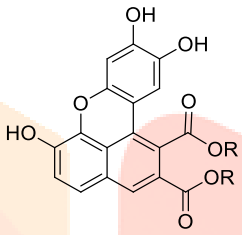
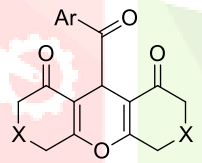
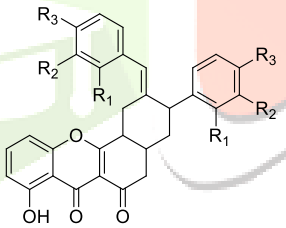


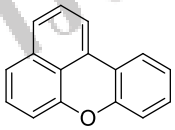
(27, 28, 29)
27 R= -CH_2CH_2Ph
28 R= -CH_2CH_3
29 R= -$CH_2CH_2CH_2CH_3$



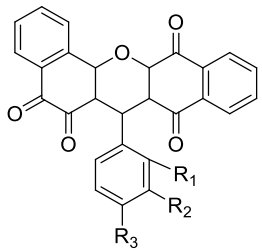
(30)
X= CH_2, $C(CH_3)_2$
Ar= C_6H_5, 4-ClC_6H_4, 4-FC_6H_4



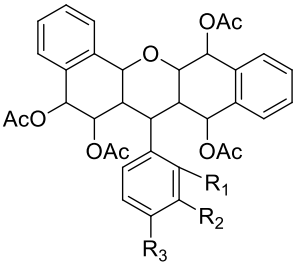
(31)
R_1=H; R_2, R_3=OH



(32)

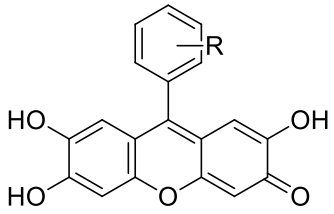


(33)
33a: R_1=R_2=R_3=H
33b: R_1=R_3=H;R_3=Cl
33c: R_1=R_2=H;R_3=Cl



(34)
34a: R_1=R_2=R_3=H
34b: R_1=R_3=H;R_3=Cl
34c: R_1=R_2=H;R_3=Cl

Zukić*et. al*[92, 93] reported the synthesis and antiproliferative activity on HeLa cervical cell lines on a series of9-aryl substituted 2,6,7-trihydroxyxanthen-3-one **(35)** and 3,3,6,6,-tetramethyl-9-aryl-substituted-xanthen-1,8(2H)-dione derivatives **(23)**. Further IC_{50} values together with calculated molecular descriptors were subjected to Quantitative Structure-Activity Relationship (QSAR) study.



(35)

Kasabe *et.al*[94] synthesized a series of hexahydro-1H-xanthene-1,8(2H)-dione **(23)** derivatives via the condensation reaction of dimedone**(21)** and aromatic aldehydes **(22)**using ZSM-5 zeolite as a catalyst and screened for their anti-virulence properties viz., the inhibition of biofilm formation, morphogenesis, and adhesion against Candida albicans and demonstrated potential activity of biofilm and morphogenesis inhibition at concentrations of 47.34–107.10 μM and showed adhesion inhibition at 25 μM concentration. The active derivatives were further evaluated for their cytotoxicity against the epithelial cell line derived from the human kidney embryo (HEK 293) and were found to be non-toxic. (**Scheme 18)**

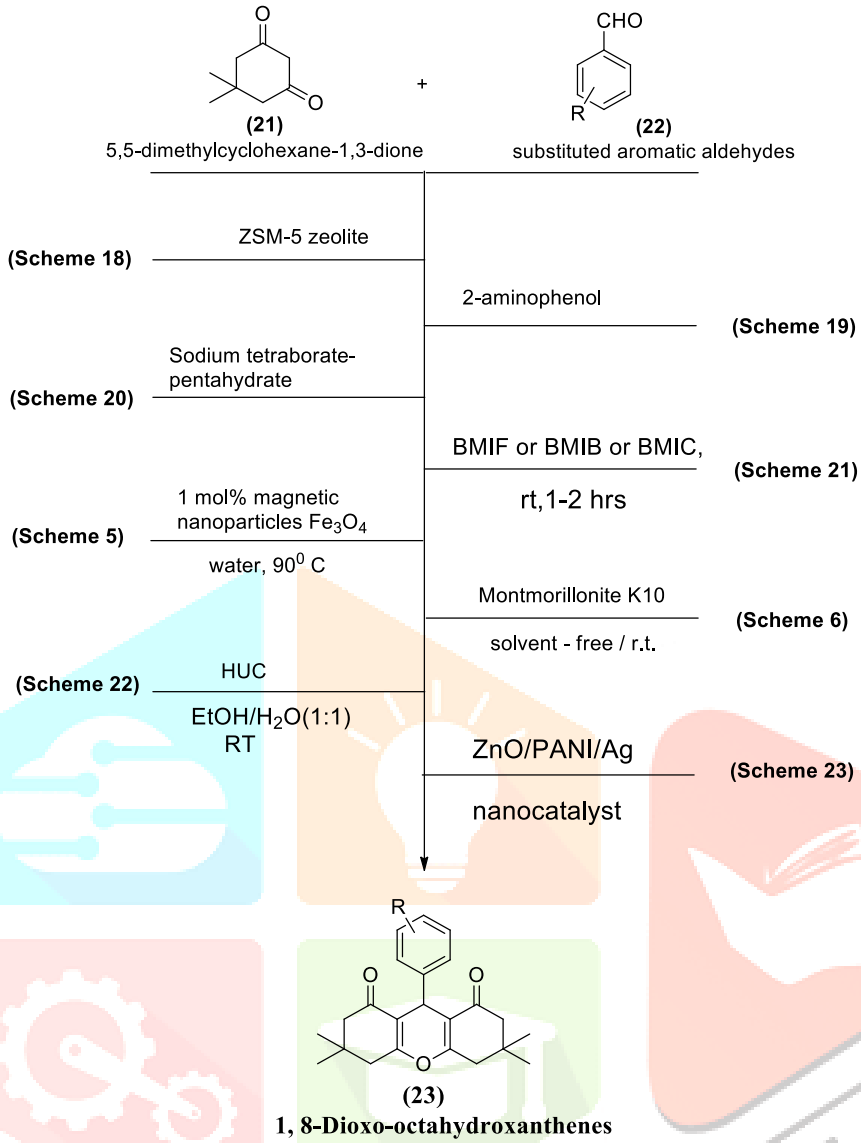
Imon *et. al* [95] synthesized some biologically active 3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione derivatives **(23)**via three-component one-pot condensation of aldehydes, 2-naphthol, and dimedone mediated by 2-aminophenol with good yields,short reaction time, easy product isolation and metal-free process. (**Scheme 19)**

Amiri*et. al* [96] introduced the green preparation of xanthene-1,8-dione derivatives **(23)**in the presence of sodium tetraborate pentahydrate as a nontoxic or minimally toxic, readily available, cheap, and ecologically favorable agent catalyst having some advantages such as high efficiency, avoidance of organic solvents, and simple work-up. (**Scheme 20)**

Sangwan*et. al* [97] developed an eco friendly and efficient method for the synthesis of 1,8-dioxooctahydroxanthene derivatives in excellent yield (~90%) using ionic liquids 1-butyl-3-methylimidazoliumtetrafluoroborate (BMIF), 1-butyl-3-methylimidazoliumbromide (BMIB) and 1-butyl-3-methylimidazoliumchloride (BMIC) under solvent free condition for the first time. All the synthesized compounds were fully characterized by analysis of spectral data along with quantum chemical studies one of the synthesized compound, 3,3,6,6-tetramethyl-9-(2,3,4-trimethoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione. All the synthesized compounds were further assayed for in vitro antitumor activities against human lung cancer cell line (A549) and found that 9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione was found to be most potent agent and significantly inhibited the tested cancer cell line A549 (IC50 3.88) with 88.77% inhibiton at 10 mM concentration. (**Scheme 21)**

Siddiqui *et. al* [98] presented an novel route to synthesize mesoporous human urine carbon (HUC)-containing heteroatoms, i.e., C, Na, Cl, N, S, and P, using a human urine waste.. The HUC catalyst had a moderately crystalline nature due to the graphitic phase of carbon with a particle size of 20–50 nm, which was successfully used to synthesizing chromenes, 1,8-di-oxo-octahydroxanthenes through a one-pot multicomponent reaction with 20 mg of catalyst in EtOH/H_2O solvent. (**Scheme 22)**

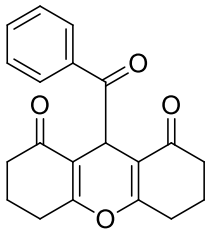
Nisha *et. al* [99] have developed an effective and novel heterogeneous ZnO/polyaniline (PANI)/Ag nanocomposite, which was characterized by X-ray diffraction, Fourier-transform infrared spectroscopy, energy-dispersive X-ray spectroscopy, X-ray photoelectron spectroscopy, transmission electron microscopy, dynamic light scattering and field emission scanning electron microscopy. Further, the high catalytic activity of ZnO/PANI/Ag nanocatalyst was investigated for the one-pot synthesis of xanthene derivatives via condensation of 5,5-dimethylcyclohexane-1,3-dione and different aromatic aldehydes with short reaction time, easy work-up, solvent free, high product yield, good chemistry metrices values, easily recoverable and reusable catalyst up to six cycles. (**Scheme 23)**



(23)

1, 8-Dioxo-octahydroxanthenes

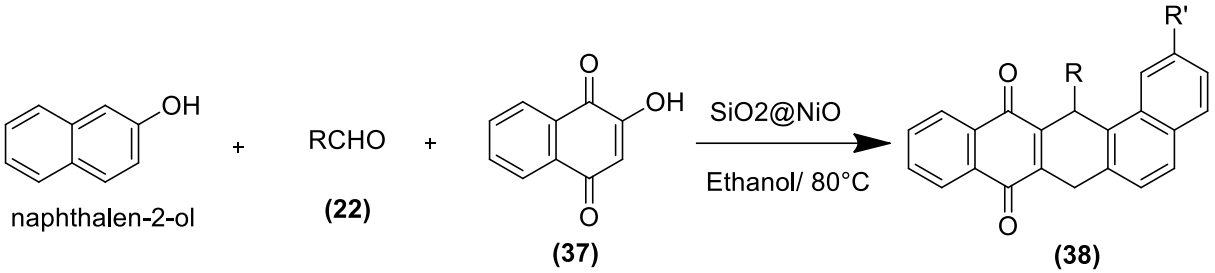
Sima Abdollahi *et. al* [100] were synthesized a 9-benzoyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione **(36)** and studied using FT-IR, NMR and UV/Vis spectra both experimentally and using density functional theory (DFT) methods. The absoulte average deviation (AAD) between experimental NMR chemical shifts and DFT results calculated at B3LYP/6-311+g(d,p) level was 3.9 % and 4.8 % for ^{1}H and ^{13}C-NMR, respectively. UV/Vis spectra in water, ethanol, acetonitrile and n-hexane solvents measured experimentally and calculated using time-dependent CAM-B3LYP/6-311+g(d,p) method.



(36)

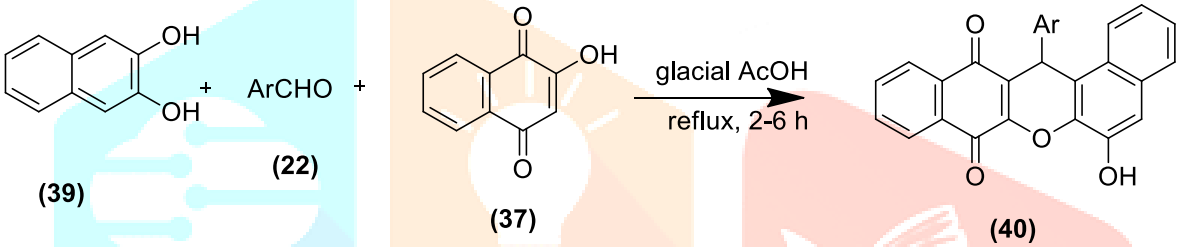
Thanaraj *et. a.* [101] reported the multicomponent condensation reaction of substituted aromatic aldehydes **(22)**with 2-naphthol/2,7-dihydroxynaphthalene and 2-hydroxynaphthalene-1,4-dione **(37)**was catalyzed by nickel oxide supported on silica core-shell nanoparticles (SiO_2@NiO) as Lewis acid catalyst in the ethanolic medium at 80 °C to synthesize diverse 14-Aryl-14H-dibenzo[a,i]xanthene-8,13-diones**(38)** in good yields with a high turnover number within a short reaction time leading to good

reusability with almost unchanged catalytic activity. The synthesized compounds were screened for in vitro antimicrobial activity and found to exhibit promising antibacterial and antifungal activities. (**Scheme 24)**



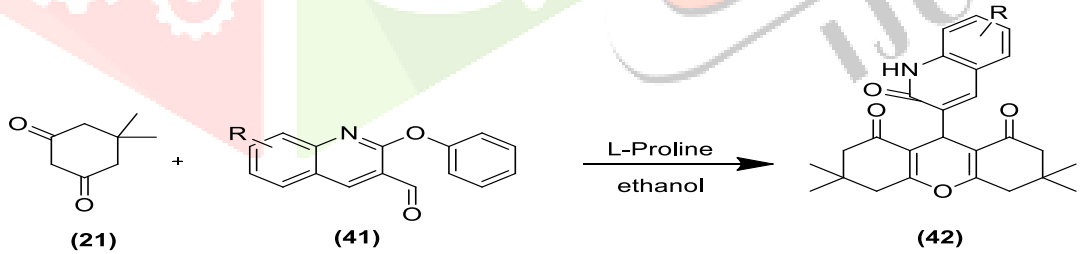
(Scheme 24)

Olyaei *et.al*[102] developed an efficient and convenient procedure for the synthesis of novel 6-hydroxy-14-aryl-8H-dibenzo[a,i]xanthene-8,13(14H)-dione derivatives **(40)** by one-pot, three-component condensation reaction between 2-hydroxynaphthalene-1,4-dione**(37)**, aromatic aldehydes and 2,3-naphthalenediol**(39)** in glacial acetic acid under reflux conditions. (**Scheme 25)**



(Scheme 25)

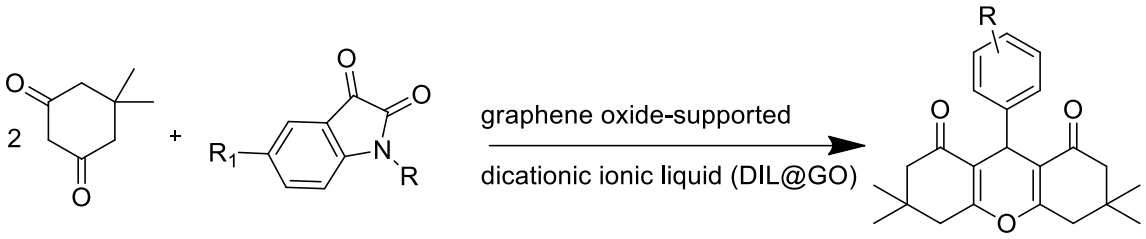
Reddy *et. al* [103] reported a L-proline catalyzed highly efficient, three-component one-pot Knoevenagel condensation reaction of substituted-2-phenoxyquinoline-3-carbal9dehyde**(41)**, 1,3-cyclohexanedione/dimedone or ammonium acetate. These reactions afford unexpected products of xanthene**(42)** based quinolones in ethanol with good yields. (**Scheme 26)**



(Scheme 26)

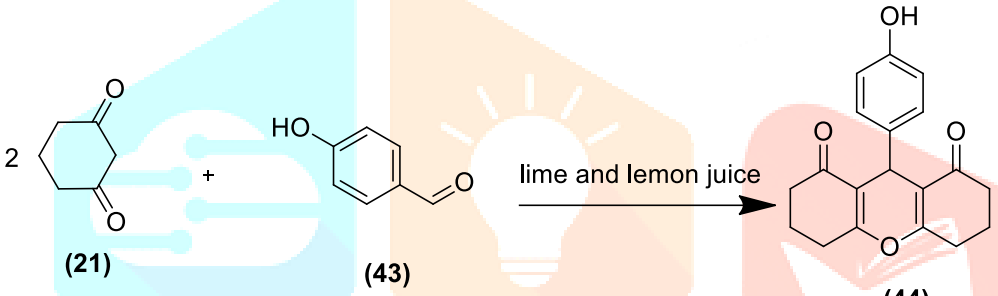
Lambat *et. al* [104] has been introduced ZnO-β zeolite nanoparticle as, an inexpensive and efficient heterogeneous catalyst for the one-pot multicomponent synthesis of 7-benzodioxolo[4,5-b]xanthenedione under microwave (MW) irradiations with excellent yields of the products (>90%), simple work-up procedures, faster reactions, use of MW as source of energy and recyclability of the catalyst.

Amiri-Zirtol *et.al* [105] has been developed synthetic route for the synthesis of spiro[indoline-3,9′-xanthene]trione derivatives using graphene oxide-supported dicationic ionic liquid (DIL@GO) as a heterogeneous catalyst in aqueous media. (**Scheme 27)**



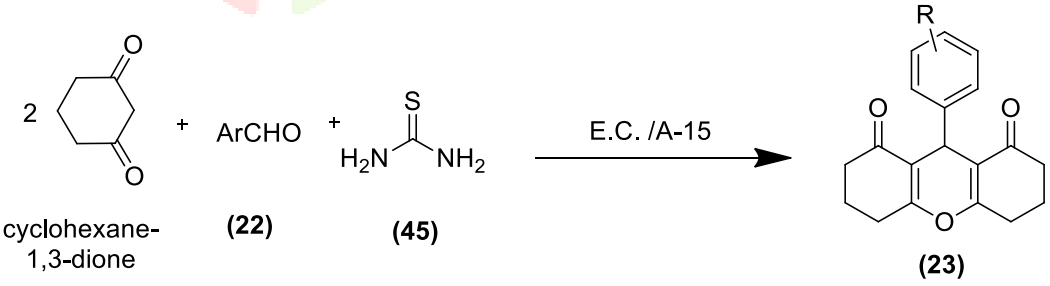
(Scheme 27)

Retnosari *et.al* [106] synthesized 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione**(44)** from 4-hydroxybenzaldehyde**(43)**and 1,3-cyclohexanedione**(21)**. This reaction has been catalyzed by lime and lemon juice under the free solvent condition. The advantages of using them as catalysts are biodegradable, environmentally safe, and cheap. Besides that, the synthesis of this compound only required one reaction stage, and the product was easily purified. The structure of the pure product was determined by FT-IR, H-NMR, and GC-MS. The antioxidant activity of this compound was investigated by the DPPH method. This compound had an antioxidant activity with inhibition percentage over 53.42%. (**Scheme 28)**



(Scheme 28)

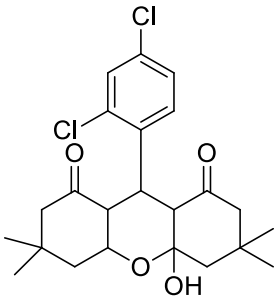
El-Nassan*et. al*[107] reported the unexpected formation of xanthene-1,8-diones upon attempt to perform Biginelli reaction by reacting cyclohexanedione, thiourea **(45)**and different aldehydes under electrochemical conditions in either ethanol or deep eutectic solvents and utilizing Amberlyst-15® as a heterogeneous acidic catalyst. The mechanism of formation of xanthene-1,8-dione was followed up by cyclic voltammetry. (**Scheme 29)**



(Scheme 29)

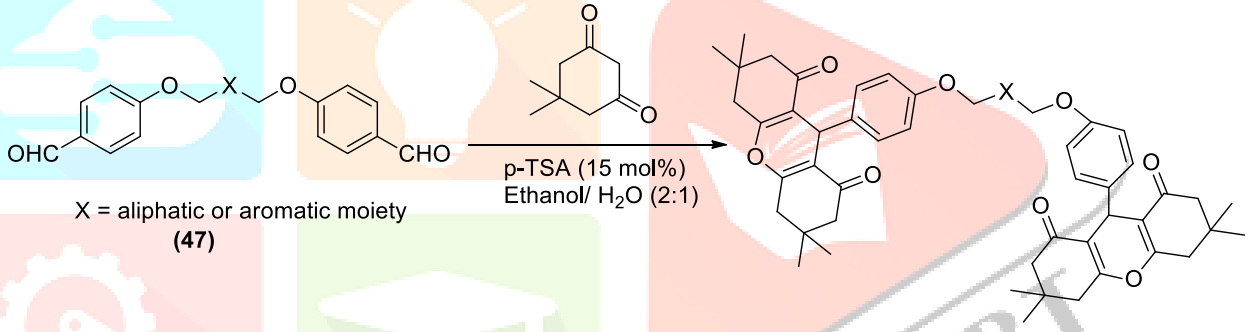
Fatima*et. al* [108 a, b] reportedthe single crystal X-ray diffraction of 9-(2,4-dichlorophenyl)-4a-hydroxy-tetramethyl-octahydro-1H-xanthene-1,8(2H)-dione **(46)**to investigate the crystal, and the most stable optimised structure was identified using the B3LYP/6-311++G(d,p) basis set, followed by FTIR and NMR analysis. The Density Functional Theory (DFT) approach was used to accomplish the theoretical computations by TD-DFT/6-311++G(d,p) approach. For various solvents, chemical reactivity assessments, Molecular Electrostatic Potential (MEP) maps with surface area maps, and electron excitation investigations were performed. The docking studies were used to look into the interactions of

the ligand (DCX) with appropriate protein targets, indicating that DCX could be used as an anticancer and anti-inflammmetry drug.



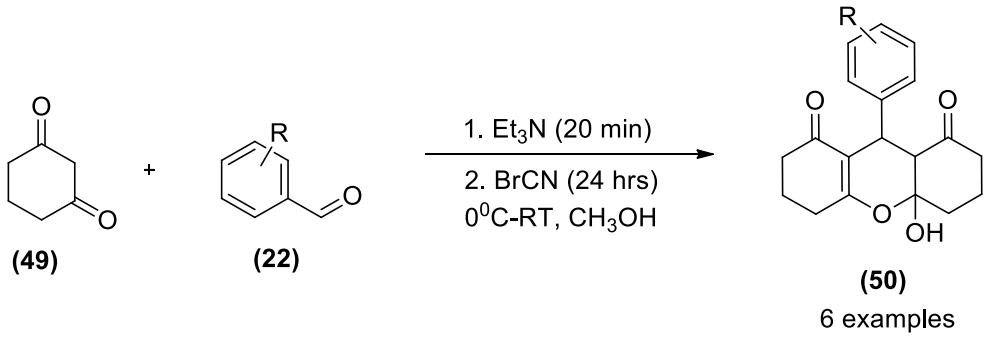
(46)

Darweesh *et. al* [109] reported the green synthesis of novel bis(hexahydro-1H-xanthene-1,8(2H)-diones)**(48)**which are linked to aliphatic or aromatic spacers**(47)** via ether or ester linkages were performed in good to excellent yields by the reaction of 5,5-dimethyl-1,3-cyclohexanedione **(22)**with the appropriate bis-aldehydes using p-TSA as an organic acid solid catalyst. The reaction of the bis-aldehydes with barbituric acid or 1,3-dimethylbarbituric acid instead of 5,5-dimethyl-1,3-cyclohexanedione afforded the corresponding Knoevenagel condensation adducts in good yield. (**Scheme 30)**



(Scheme 30)

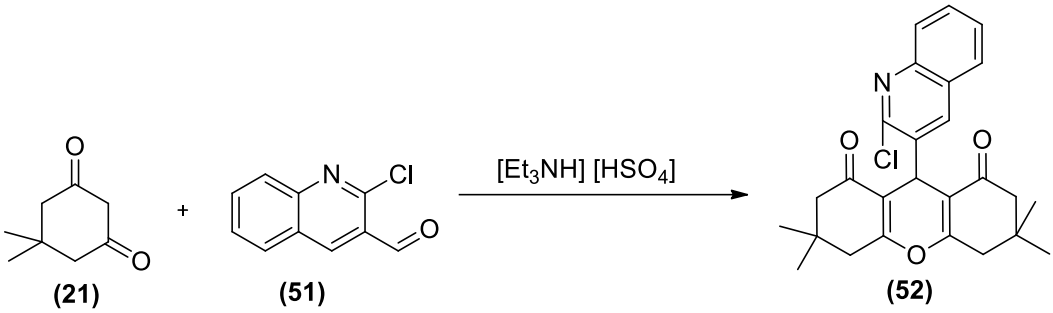
Pesyan *et. al* [110] designed an easy and convenient technique for the one-pot synthesis of compounds of octahydro-1H-xanthenes with cyclohexane-1,3-dione and aromatic aldehydes in triethylamine and cyanic bromideunder mild reaction conditions. IR, ^{1}H NMR, ^{13}C NMR spectrometry, and X-ray diffraction analysis were used to identify the structures of these compounds. (**Scheme 31)**



(Scheme 31)

Bhat *et. al*[111] reported a series of novel 2-chloro quinoline incorporated xanthene derivatives **(52)**by using various 2-chloro-3-formyl quinolone **(51)**, dimedone **(21)**and triethylammonium hydrogen

sulfate [Et_3NH][HSO_4] as a catalyst as well solvent to give good to excellent yields. All the xanthene compounds were investigated for their in vitro antimycobacterial activity against M. tuberculosis H37Ra (MTB) and M. bovis BCG strains. Most of the active compounds were non-cytotoxic against THP-1, HCT-116, A549 and MCF-7 cell lines. (**Scheme 32)**



(Scheme 32)

III. CONCLUSION

This review report presents various types of reactions used for the synthesis of xanthenes based compounds. The reactions were carried out under diverse conditions, including solvent-free systems, aqueous media, and with the use of various green solvents. A wide range of catalysts and nanocatalysts were employed. Some reactions proceeded efficiently at room temperature, while others required heating or microwave irradiation.

IV. ACKNOWLEGMENT

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