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Exploring the Potential of Xanthene Derivatives in Medicinal Chemistry: A Review

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Abstract: *Xanthenes are a special class of oxygen incorporating tricyclic compounds, structurally related to xanthones. The presence of different substituents on position 9 strongly influences on their physical and chemical properties as well as their various biological applications. Novel methodologies and number of catalysts have been reported for the synthesis of xanthene derivatives. They have also received significant interest from many pharmaceutical and synthetic chemist. Although Xanthenes are rare natural products and have been isolated from two different plant families, Compositae and Fabaceae [1-3]. The compounds based on these core templates exhibit a broad spectrum of biological pharmaceutical antimicrobial properties.*

Keywords: Xanthenes.

I. INTRODUCTION

Xanthene **1** has chemical formula $C_{13}H_{10}O$ and its melting point is 101-102^0 C and boiling point is 310-312^{0}C. Xanthene is yellow organic heterocyclic compound. Recently, a brief review considering the biological activities of xanthene derivatives was published [4]. Most of the xanthene derivatives obtained artificially through cyclization process of suitable building blocks or modification of related compounds namely xanthones. Several interesting derivatives have been reported regarding synthetic strategies and bioactivities in scientific literature and patent applications. The present work highlights the importance of xanthene in medicinal chemistry, its various biological activities. Several synthetic strategies also discussed here. Xanthene derivatives also generating considerable interest as a hole indicator or transporting injected holes for organic devices due to low cost.[26]

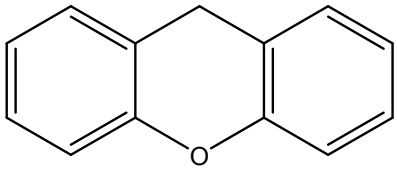

Fig. 1

II. SYNTHESIS OF XANTHENE DERIVATIVES

2.1 BFE catalysed 1,8- dioxo-octahydroxanthene Synthesis

The reaction mixture of aldehyde (1mmol), dimedone (2mmol) and BFE (Bilimbi Fruit Extract) catalyst 3 ml in water: ethanol is taken in 25 ml of round bottom flask and heated in oil bath at 80^0 C till completion of reaction. The reaction was monitored by TLC, which shows single spot for all derivatives in n-hexane and ethyl acetate (7:3).[5]

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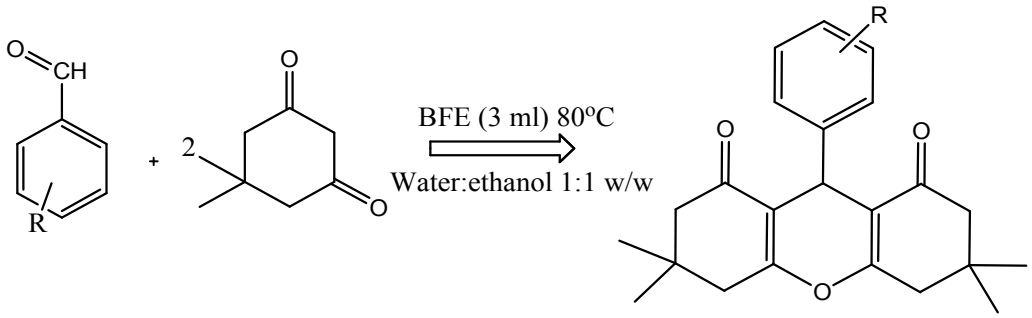
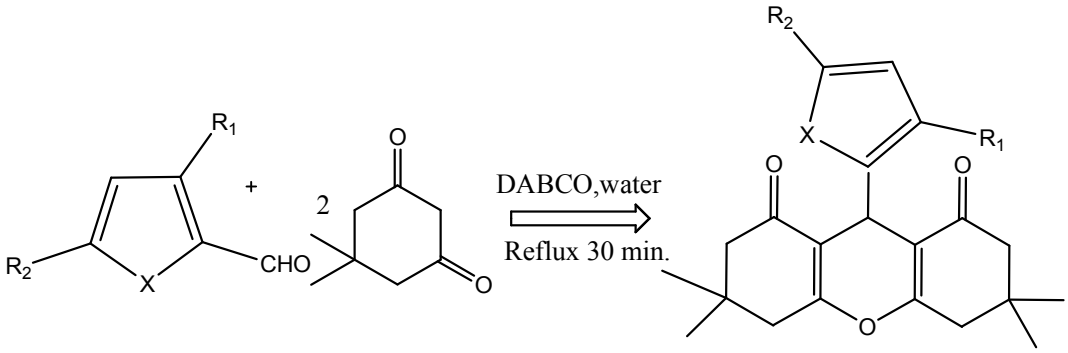


Scheme 1. BEF-catalysed 1,8-dioxo-octahydroxanthene synthesis.

2.2. DABCO catalysed Synthesis of heteroaryl substituted Xanthenes

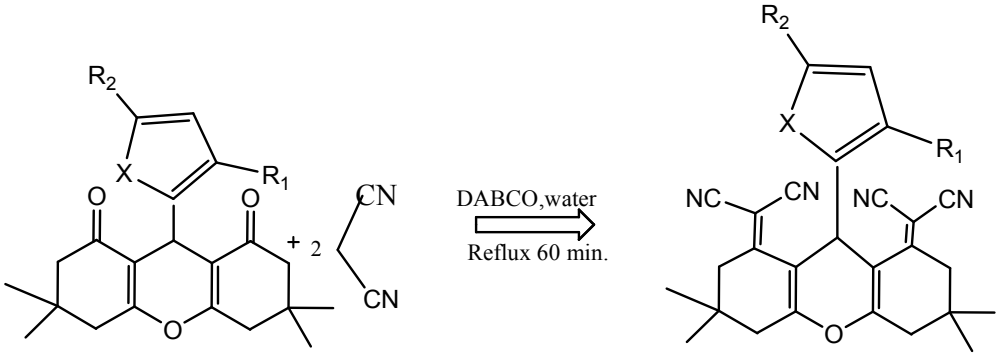
Reflux a mixture of 5 membered heteroaryl aldehyde (1 mmol), dimedone (2 mmol) and DABCO (1,4 diazabicyclo [2.2.2] octane) (10 mmol %) in water (20 ml) for 30 min. the reaction progress by TLC. After completion the mixture cooled to room temperature, the solid was filtered off and washed with water.[6]



Scheme 2. Synthesis of heteroaryl substituted Xanthenes

2.3. DABCO catalysed Synthesis of Alkylidenes

Mixture of heteroaryl substituted xanthene (1 mmol), malonitrile (2mmol) and DABCO (10 mmol %) in water (20 ml) for 60 min. the reaction progress was monitered by TLC. After cooling product was filtered and washed with water. The product purified by column chromatography.



Scheme. 3 Synthesis of alkylidenes using heteroaryl substituted xanthene

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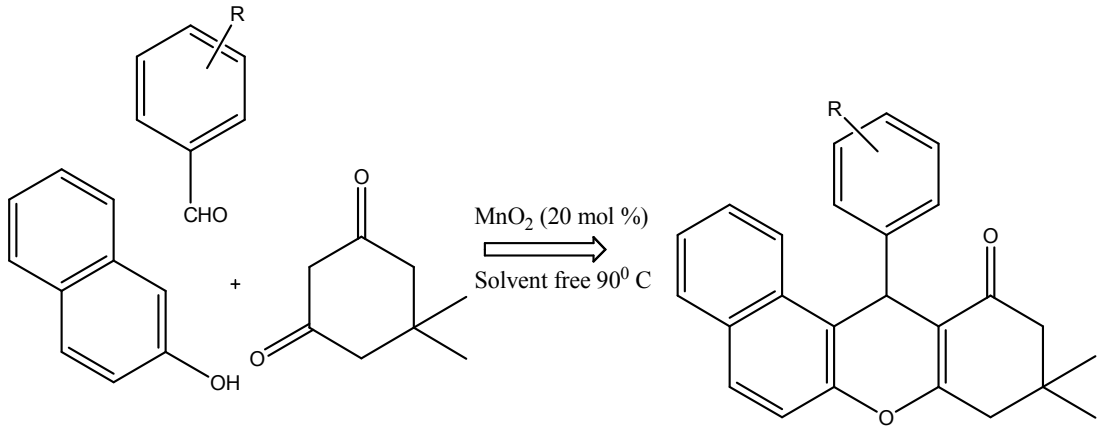
2.4. General Procedure for the Preparation of 12-aryltetrahydrobenzo[α] Xanthene-11- Derivatives.

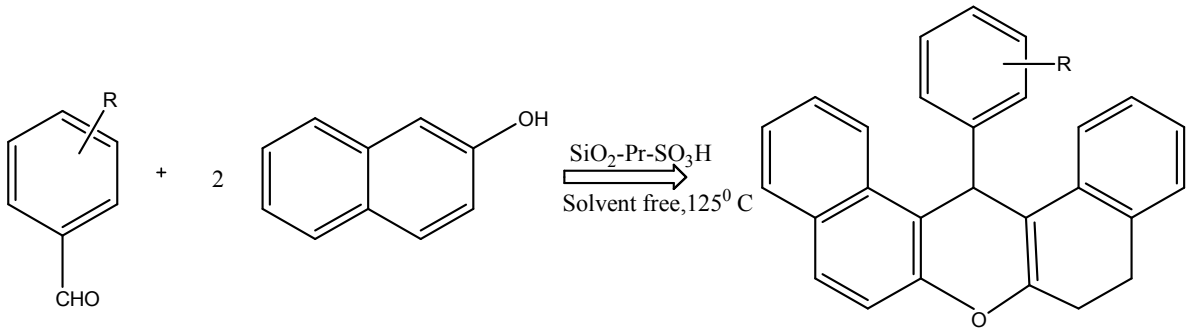
Solvent free multicomponent synthesis of xanthene can be carried out by a mixture of β-naphthol (1 mmol), aromatic aldehyde derivative (1 mmol) and dimedone MnO_2 at 90^0 as a catalyst. The reaction is monitored by TLC. The reaction mixture is then cooled at room temperature, the product is then purified by recrystalized with alcohol.[7]



Scheme. 4 Synthesis of 12-aryltetrahydrobenzo[α] xanthene-11- derivatives.

2.5. Synthesis of 14-aryl-14Hdibenzo Xanthene Derivatives by Silica Based Sulphonic Acid Catalyst

The silicon based sulphonic acid catalyst was activated (0.02 gm) in vacuum in 100^0 C, then allow to cool to room temperature. Then added a mixture of 2-napthol (1 mmol) and aldehyde (2 mmol) in round bottom flask and heat the reaction mixture at 125^0 C for specific time period. The progress of reaction monitored by TLC.The catalyst was removed by heating the crude product in ethyl acetate followed by filtration.[8]



Scheme. 5 Synthesis of 14-aryl-14Hdibenzo xanthene derivatives

2.6. Ce-ZSM-11 Zeolite Catalysed 1,8- Dioxo-Octahydroxanthene Synthesis

Mixture of aromatic aldehyde (1mmol), 5,5, dimethyl-cyclohexane 1-3-dione (2 mmol) and Ce-ZSM-11 catalyst (0.1 g) in water (10 ml) as a solvent were added and refluxed up to two hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered, the catalyst was separated and crude product recrystalized.[10]

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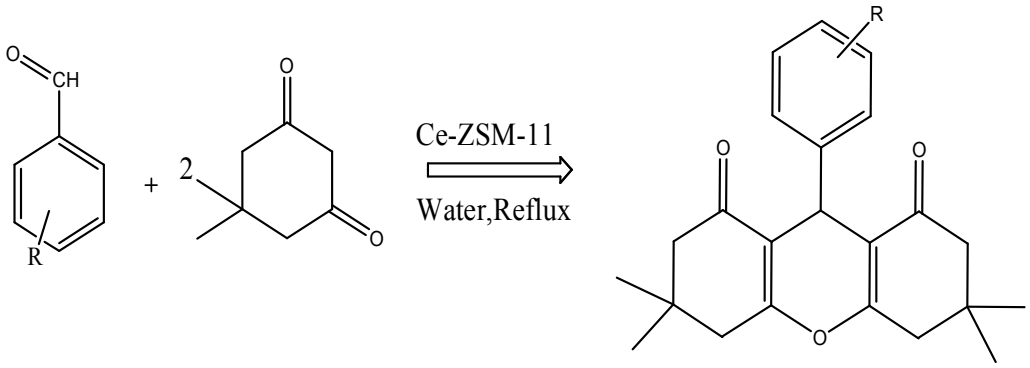
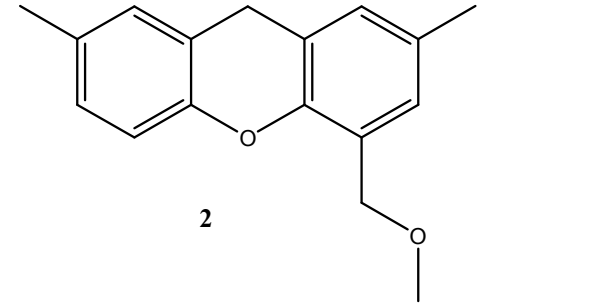


Scheme 6: Synthesis of 1,8- dioxo-octahydroxanthene

III. Biological Application of Xanthene

3.1. Antifungal and antibacterial activities.

Two derivatives of xanthene **2 & 3** were isolated from foliar fungal endophytes of *Pinus Strobus* and tested for the antimicrobial activity.[11] In addition, they exhibited significant activity against gram positive bacterium *bacillus subtilis* with a MIC of 24.5 µg/ml and 36.1 µg/ml respectively.



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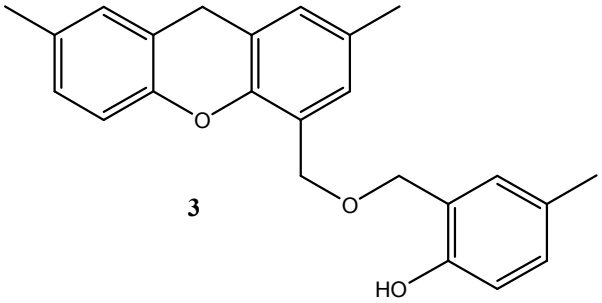

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Enhancement of antifungal activity is carrying out by preparing nanofiber fabric by electrospinning technology. Those nano fabrics had higher colour strength of photosensitiser was found to be having good antifungal activity as the drug remain in contact with surface for longer duration.[12]

3.2. Anti-Inflammatory and Analgesics Activities

Agonist of glucocorticoids receptor are widely used as anti-inflammatory drugs in autoimmune disease, but they have several side effects. The introduction of pyridine nitrogen in the xanthene core makes a useful derivative act as anti-inflammatory agent.[13]

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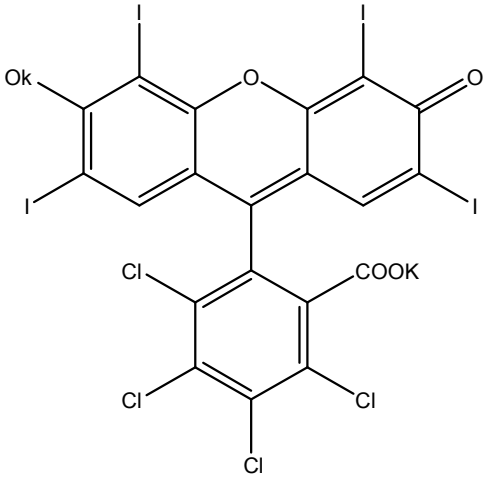
3.3. Antipsychotic Activity

Antipsychotic activity can be associated with aza-xanthenes which are structurally related with phenothiazines and act by supressing the effect of dopamine in the brain. Other structurally related Xanthenes also been assessed for antipsychotic activity.[14]

3.4 Antiviral Activity

Rose Bengal **4** containing xanthene moity has some antiviral activity. It has also been used for the negative staining of bacteria and for spirochaetes in blood.[15] Tobaco mosaic virus is a pathogen able to reproduce and multiply in the host cell of the plant. It also known to affect the other plant families and some ornamental plant flowers.[16]



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3.5. Antidiabetic Activity

Xanthene compounds were chosen as an antidiabetic agent due to the similarity with Magniferin, a xanthene secondary metabolite used as a supplement to treat diabetes mellitus.[17]

3.6. Antitubercular Activity

Tuberculosis (TB) caused by *mycobacterium tuberculosis* global health problem. Currently available antituberculosis drugs has some side effects and get some resistance from mycobacterium species. Certain xanthene scaffold shows antimycobacterial and immunomodulatory properties.[18]

3.7. Anticancer Activity

A series of substituted xanthene's shows anticancer properties, particularly ([N,N-diethyl]-9 hydroxy-9-(3-methoxyphenyl)-9H-xanthene-3-carboxamide) shows more potency to inhibit cancer cell growth with IC50 values from 36 to 50 µM.[19]

3.8. Antioxidant Activity

Certain xanthone derivatives shows strong antioxidant activity. In order to see the effect of some xanthene derivatives as a bio-antioxidant their capacity to scavenge free radical and inhibit lipid oxidation process assessed by different methods like radical scavenging, chain breaking antioxidant activity and quantum chemical calculations.[20] Radical scavenging activity gives the information H-atom donating capacity of xanthene derivative **5**. An antioxidant activity of 14-aryl-14H-dibenzo xanthene derivatives shows free radical antioxidant activity.[21]

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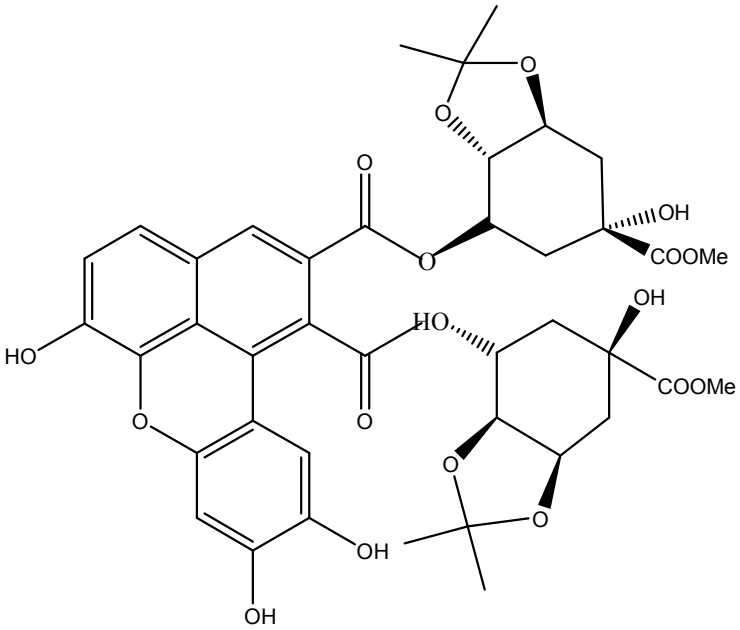

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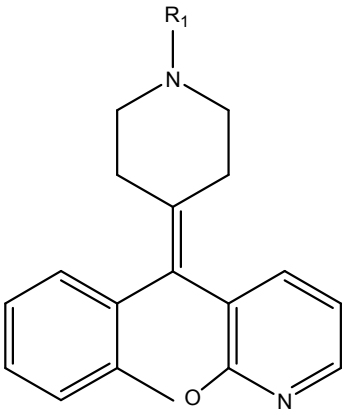
3.9. Antihistaminic Activity



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One of the synthesized compounds **6** shows strong bronchodilator effect and some moderate antihistaminic activity. It also used to inhibit the release of histamine from peritoneal mast cells.

3.10. Anticonvulsant Activity

3-azaxanthene used as anticonvulsant in rats but shows lack of potency and short duration of action.[22]

3.11. Antiparasitic Activity

9,9 dimethylxanthene derivatives are evaluated against Trypanothione reductase.[23] Wu et al. prepared a small series of 9H-xanthene derivatives and evaluated their intrinsic activity against some strains of plasmodium falciparum, along with their cytotoxicity. Study on the antimalarial activity of xanthene derivatives with dispiro-β-lactam moiety good to excellent activities were obtained against falciparum K14 strain.

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IV. CONCLUSION

The main objective for this review is focused on the different strategies for the synthesis of various xanthene derivatives as an important class of pentacyclic heterocycles using different catalyst under different conditions. It is clear from the content that xanthene derivatives are very important chemical materials with tremendous biological applications. These have moderate to excellent activities against number of biological targets. With changing the substituents on the xanthene nucleus, the biological targets vary from microbial disease to viral problems and variety of cancerous cells. The presence of different substituents at position 9 has a large impact on their physical and chemical properties as well as their biological applications. It is also cleared from the contents of this review that the synthesis of these compounds remained very active field of research.

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