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Review Article

REVIEW ON MEDICINAL IMPORTANCE OF XANTHENE DERIVATIVES

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ABSTRACT

Now a day's Xanthene is found to most multifaceted heterocyclic ring having as it is having variety of activity and utilization. Xanthene dyes is used as a fungicide and it is also a use as intermediate in organic synthesis. Xanthenes dyes shows antiviral activity, anti-tubercular, anti-microbial, anticancer, malonate derivatives was having antispasmodic activity. Sulphonamide and carboxamide derivatives of xanthenes found to be having anti-microbial activity. Apart from that xanthene derivatives also increases glucose utilization & xanthene dyes or derivatives are found to be inducing an ultrasonic action of lowering the threshold of acoustic strength causing acoustic cavitation's.

1. INTRODUCTION

2. Historical Background of xanthenes

Xanthene (9*H*-xanthene, 10*H*-9-oxaanthracene) having chemical formula is $C_{13}H_{10}O$ & melting point is 101-102 °C , boiling point is 310-312 °C. Xanthene is a yellow organic heterocyclic compound. Derivatives of xanthene are commonly referred as xanthenes and among other uses are the basis of a class of dyes which includes fluorescein, eosins, and rhodamines. Xanthene dyes tend to be fluorescent, yellow to pink to bluish red, brilliant dyes. Many xanthene dyes can be prepared by condensation of derivates of phthalic anhydride with derivates of resorcinol or 3-aminophenol.

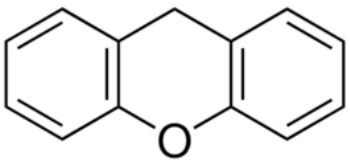
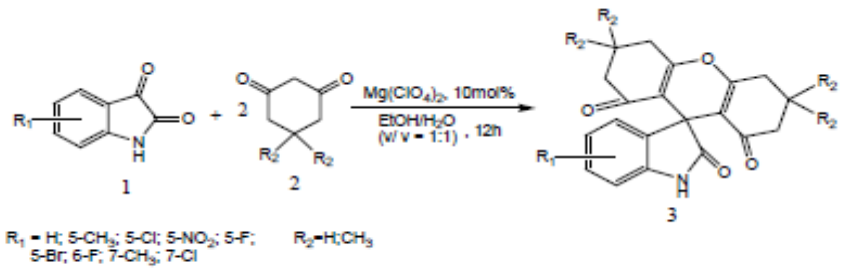


Fig. 1: Xanthene

3. Synthesis of Xanthenes derivative

3.1General Procedure for the Synthesis of Spiro [indoline-3, 90 -xanthenes]trione

Mg(ClO4)2 (0.1 g) was mix to a mixture of isatin (2 mmol), and dimedone (4 mmol) in aqueous ethanol solution (50%, v/v, 5 mL), and stirred the mixture at 80°C for 10–12 h. Cool the mixture to room temperature and resulting solid was filtered and washed successively with water 60 ml (and cold aqueous ethanol (2 × 1 mL) to obtained a crude product, and recrystallized from EtOH to obtained the pure product 3. Possibility of insolubility could be observed in the refluxing ethanol during the recrystallization process, which should be filtered when hot.[1]



Scheme.1: Synthesis of spiro[indoline-3,9'-xanthene] trione

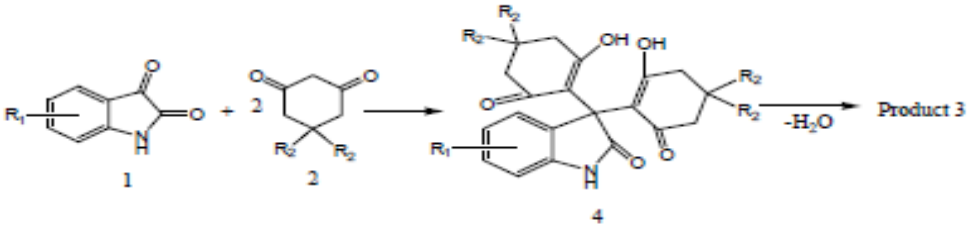
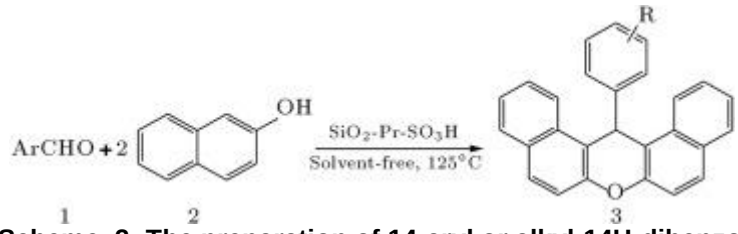


Fig. 2: Proposed mechanism for the synthesis of spiro[indolone-3,9'-xanthene] trione

3.2 General procedure for the preparation of 14-aryl-14H-dibenzo [a,j] xanthene derivates

The Silica based sulphonic acid catalyst was activated (0.02 g) in a vacuum at 100 °C and then allow to cool to room temperature, Then added a mixture of 2-naphtol (1 mmol), and aldehyde (2 mmol) in flask and stirred. Heat the reaction mixture at 125 °C for an specific time period, checking of reaction completion carried out by TLC, and cool the reaction mixture to room temperature. Catalyst was removed by heating the crude product in ethyl acetate followed by filtration. The pure product was obtained by cooling of the filtrate. Characterization of new compounds was carried out by IR and NMR spectroscopy.[2]



Scheme. 2: The preparation of 14-aryl or alkyl-14H-dibenzo [a,j]xanthenes using SiO_2-Pr-SO_3H

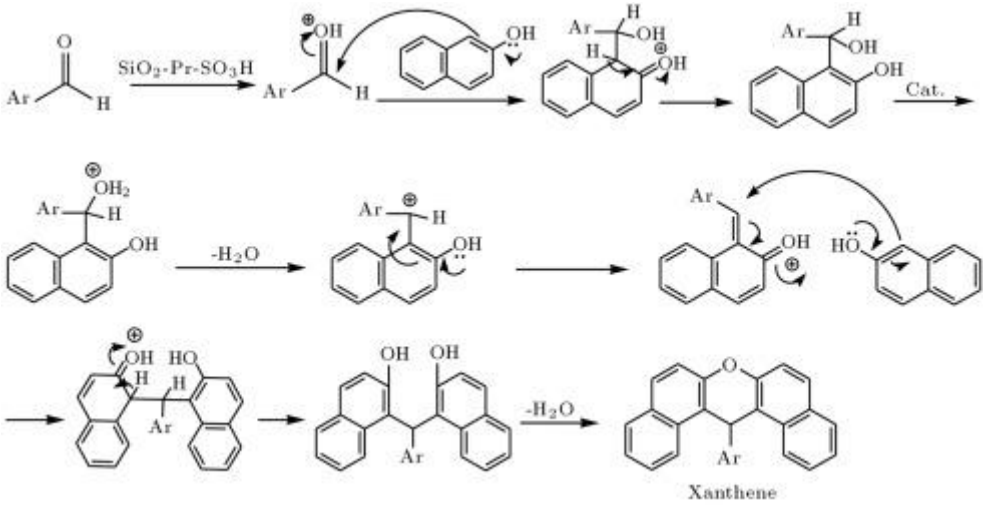


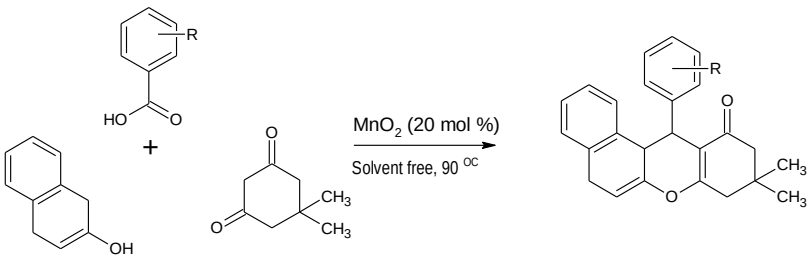
Fig. 3: Mechanism for the SiO_2-Pr-SO_3H catalyzed transformation

Table 1: SiO_2-Pr-SO_3H catalyzed the synthesis of 14-substituted-14H-dibenzo [a,j]xanthenes under solvent-free condition

Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p. (°C)
1	Ph	3a	20	98	182-183
2	4-ClC_6H_4	3b	25	97	288–289
3	2,4-$Cl_2C_6H_4$	3c	30	98	254–255
4	2,6-$Cl_2C_6H_4$	3d	30	98	269–270
5	4-$NO_2C_6H_4$	3e	40	98	311–312
6	3-$NO_2C_6H_4$	3f	40	99	210–212
7	4-FC_6H_4	3g	20	99	239
8	3-$CH_3C_6H_4$	3h	35	97	198
9	4-$CH_3C_6H_4$	3i	35	97	227
10	3-$OCH_3C_6H_4$	3j	30	98	174–176
11	4-$OCH_3C_6H_4$	3k	30	98	204–205
12	4-OHC_6H_4	3l	35	97	139–141

3.3 General procedure for preparation of 12-aryltetrahydrobenzo[α]xanthene-11-one derivatives

Solvent free one pot Facile synthesis of xanthene was carried out by heating a mixture of β-naphthol (1, 1.0 mmol), aromatic aldehyde derivatives (2, 1.0 mmol), dimedone (3, 1.0 mmol) and MnO2 at 90^{o}C in which by Manganese (IV) oxide act as an efficient, mild and inexpensive catalyst under solvent-free conditions. Competition of reaction is observed by TLC. The mixture is then allowed to cool to room temperature. after that ethanol was added and the precipitated was separated with filtration and then recrystallized from ethanol to obtained pure product. This is Green chemistry approach for synthesis of xanthene derivative.[3]



Scheme. 3: Synthesis of 12-aryltetrahydrobenzo[α]xanthene-11-one derivatives

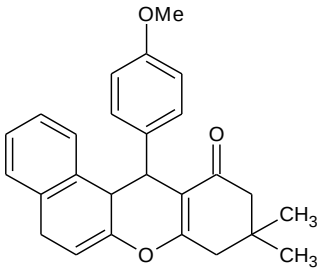
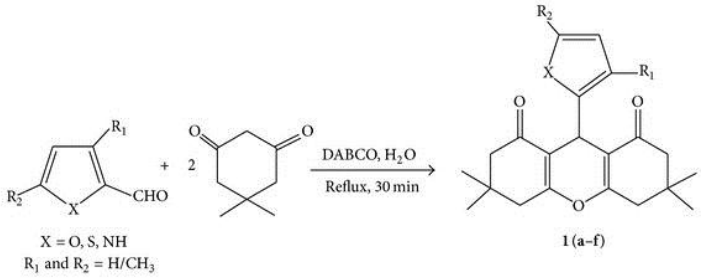


Fig. 4: 9,9-dimethyl-12-(4-methoxyphenyl)-8,9,10, 12-tetrahydrobenzo[a] xanthen-11-one

3.4 Dabco catalyzed synthesis of Heteroaryl Substituted Xanthenes

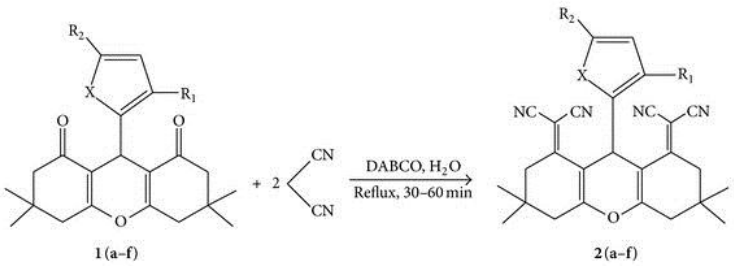
Reflux a mixture of 5-membered, Heteroaryl aldehyde (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (2 mmol), and DABCO (10 mmol%) in H_2O (20 mL) for 30 min. The reaction progress was monitored by TLC. After completion, the mixture was cooled to room temperature, and the solid was filtered off and washed with H_2O. and the crude product was recrystallized from 95% ethanol.[4]



Scheme. 4: Synthesis of Heteroaryl Substituted Xanthenes

3.4.1 General Procedure for the Synthesis of Alkylidenes 2(a–f)

A mixture of *heteroaryl substituted xanthenes* (1 mmol), malononitrile (2 mmol), and DABCO (10 mmol %) in H_2O (20 mL) was stirred for 60 min. The reaction progress was monitored by TLC. After completion cool the reaction, the mixture to room temperature and filtered off and washed with H_2O. The crude product was purified by column chromatographic technique using hexane: ethyl acetate.



Scheme. 5: Synthesis of alkyidenes using heteroaryl Substituted Xanthenes

Table 2: Synthesis of Heteroaryl substituted xanthenes and its alkylidene derivatives

Entry	X	R_1	R_2	Product	M.P (°C)
1	O	H	H	**1a**	168-169
2	O	H	CH_3	**1b**	158–160
3	S	H	H	**1c**	142–144
4	S	CH_3	H	**1d**	156-157
5	S	H	CH_3	**1e**	145–147
6	NH	H	H	**1f**	88–90
7	O	H	H	**2a**	212-213
8	O	H	CH_3	**2b**	183–185
9	S	H	H	**2c**	197-198
10	S	CH_3	H	**2d**	170–172
11	S	H	CH_3	**2e**	177–179
12	NH	H	H	**2f**	112–114

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4. Biological Application of Xanthene

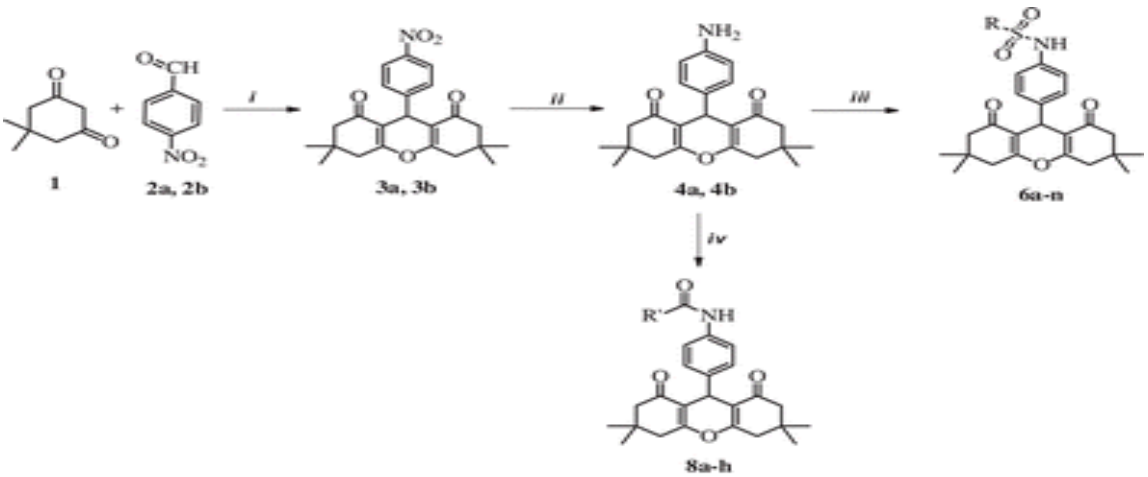
4.1 Antifungal Activity

Enhancement of antiungal activity is carried out by preparing nanofiber fabric by elctrospinning technology. By using this we can obtained fibers in the range from 200 nm to 5 micro m in diameter. A high voltage (20 kV) was applied between needle tip and roller collector. This can obtained by dissolving 18% w/v nylon 6 ,6 pellets into formic acid and agitating at 70^0C for 8 hrs. Then the solution was put into a 10-mL syringe and placed on the pump. To obtained water soluble photosnsitizers using Xanthene dyes has to be incorporated into poly (acrylic acid) (PAA) via polymerization. The precipitate of benzyl-xanthene dye (VBXD where XD refers to the xanthene dye RB or PB were prepared by stirring 3 g of RB or 2.5 g of PB in a 70-mL solution of 50:50 v/v distilled water/acetone and 0.51 mL of 4-vinyl-benzyl chloride at 65^0C for 3 h. Followed by filtration and washing of the dye. Then dissolved the VBXD in water and acetone at the volume ratio of 1:1 and polymerized with 4-styrene sulfonic acid (SAA) and acrylic acid (AC) at1:40:140 molar ratio of VBXD: SSA:AC to increase water solubility to the polymers. After copolymerization, poly (acrylic acid-co-styrene sulfonic acid-co-vinyl benzyl rose bengal or phloxine B) were obtained. Chemical reaction is enhance by using condensing agent, 4-(4, 6-dimethoxy-1, 3, 5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), between –COOH groups of PAA of polymerized dye solution to NH2 end-groups of nylon 6,6 fabrics to produce amide linkages.

Those nano fabrics had higher color strength of photosensitizes was found to be having good antifungal activity as the drug will remain in contact with surface for longer duration.[5]

4.2 Antimicrobial Activity

Antimicrobial activity can be obtained by preparing amino xanthenes, sulphonamide xanthenes and xanthene amide derivative by following way



i: DBSA/H_2O; ii: Sn/HCl, EtOH; iii:RSO_2Cl; iv: R'COCL/THF

Scheme. 6: Synthesis of Amino, sulphonamide and amide xanthene

Table 3: Substitutions of Amino, sulphonamide and amide xanthene

	R	R'
6a	C_6H_5	-
6b	p-$CH_3C_6H_5$	-
6c	p-CH_3O C_6H_5	-
6d	p-CH_3OC C_6H_5	-
6e	2,4,6-$(CH3)_2C_2H_5$	-
6f	3,5-Cl_2-2-OH C_6H_5	-
6g	$C_{10}H_7$	-
6h	C_6H_5	-
6i	P-CH_3 C_6H_5	-
6j	p-CH_3O C_6H_5	-
6k	p-CH_3OC C_6H_5	-
6l	2,4,6-$(CH3)_2C_2H_5$	-
6m	3,5-Cl_2-2-OH C_6H_5	-
6n	$C_{10}H_7$	-
8a	-	C_6H_5
8b	-	p-NO_2 C_6H_5
8c	-	3,5-$(NO_2)_2$ C_6H_5
8d	-	CH_3
8e	-	C_6H_5
8f	-	p-NO2 C_6H_5
8g	-	3,5-$(NO_2)_2$ C_6H_5
8h	-	CH_3

4.2.1 General procedure for preparation of amino xanthenes

For the preparation of amino xanthenes add Sn (3.0 g) and conc. HCL (37%) in a solution of appropriate xanthenes compound weighing 1g, 2.53 mmol in 10 ml ethanol. Then reflux the solution by heating for 1 hr. Then adjust the pH 7-8 by addition of 15% NaOH solution. Precipitate obtained was separated. Washed the crude product 3 times with 50 ml of distilled H2O. Dried over MgSO4. Then, the obtained solid was recrystallized from ethanol.

4.2.2General procedure for preparation of xanthene sulfonamides

To obtained xanthenes sulphonamide stirred and refuluxed a mixture of the amino xanthene derivative **(**0.5mmol**)** and the sulphonyl chlorides **(**0.5 mmol) in dry THF (15 mL). them remove the solvent by vacuum and recrystallised from ethanol.

4.2.3 General procedure for preparation of xanthene amides

The xanthene amines obtained by above mention method **(**0.5 mmol**)** were dissolved in 10 mL THF and added to a solution of 0.5mmol acyl chlorides in THF (5 mL). The mixture was reflux by heating for 24 h. After that the solvent was removed and , the crude products was purified by recrystallization from ethanol.[6]

4.3 Antispasmodic Action

Xanthenatom-9-ol undergoes condensation with many compounds possessing an active hydrogen atom but not with diethyl malonate under ordinary conditions. Diethyl xanthene-9-malonate was obtained by the reaction of silver xanthene-9-malonate and ethyl iodide. But it can also be obtained by facile condensation with ethyl malonate to form monoethyl xanthene-9-malonate.which was derived to 2-diethylaminoethyl ethyl xanthene-9-malonate hydro chloride and ethyl xanthene-9-malonamate. In a same way, diethyl thioxan thene-9-malonate, monoethyl thioxanthene-9-malonate, 2-diethylaminoethyl ethyl thioxanthene-9-malonate hydrochloride, and ethyl thioxanthene-9-malonamate can be synthesized from thioxanthen-9-ol. Oxidation of monoethyl thioxanthene-9-malonate with hydrogen peroxide gave monoethyl thioxanthene-9-malonate 10, 10-dioxide which was derived to 2-diethylaminoethyl ethyl thioxanthene-9-malonate 10, 10-dioxide hydrochloride. Oxidation of ethyl thioxanthene-9-malonamate gave ethyl thioxanthene-9-malonamate 10, 10-dioxide. Antiacetylcholine action of 2-diethylaminoethyl ethyl thioxanthene-9-malonate 10, 10-dioxide hydrochloride is stronger than that of 2-diethylaminoethyl thioxanthene-9-acetate 10, 10-dioxide hydrochloride, but both 2-diethylaminoethyl ethyl xanthene-9-malonate hydro chloride and 2-diethylaminoethyl ethyl thioxanthene-9-malonate hydrochloride have weaker antiacetylcholine, anti-barium chloride, and antihistamine activities than the corresponding acetate derivatives.[7]

4.3 Antidiabetic activity

Therefore AMPK activators are considered to be effective drug targets for treatment of metabolic diseases like diabetes mellitus. Xanthenes derivatives were screened to identify AMPK activators. It was found that the AMPK activators 9H-xanthene-9-carboxylic acid {2,2,2-trichloro-1-[3-(3-nitro-phenyl)-thioureido]-ethyl}-amide (a) and 9H-xanthene-9-carboxylic acid {2,2,2-trichloro-1-[3-(3-cyano-phenyl)-thioureido]-ethyl}-amide (b) elevated glucose uptake in L6 myotubes by stimulating translocation of glucose transporter type 4 (GLUT4). Treatment with the chemical AMPK inhibitor compound C and infection with dominant-negative AMPKa2-virus inhibited AMPK phosphorylation and glucose uptake in myotubes induced by either (a) or (b) of the two major upstream kinases of AMPK, it was found that 9H-xanthene-9-carboxylic acid {2,2,2-trichloro-1-[3-(3-nitro-phenyl)-thioureido]-ethyl}-amide and 9H-xanthene-9-carboxylic acid {2,2,2-trichloro-1-[3-(3-cyano-phenyl)-thioureido]-ethyl}-amide showed LKB1 dependency by knockdown of STK11, an ortholog of human LKB1. Single intravenous administration of above mention compound to high-fat diet-induced diabetic mice stimulated AMPK phosphorylation of skeletal muscle and found to improved glucose tolerance. By considering together these results, suggest that the nitro and cyno group containing xanthene derivatives regulate glucose homeostasis through LKB1-dependent AMPK activation and that the compounds are useful drugs for the treatment of type 2 diabetes mellitus.Xanthene Derivatives Increase Glucose Utilization through Activation of LKB1-Dependent AMP-Activated Protein Kinase[8].

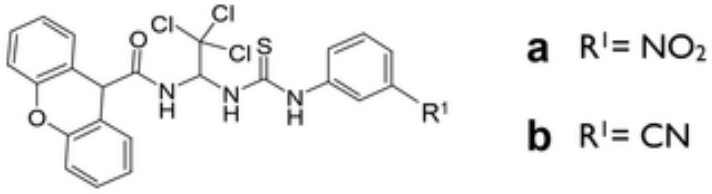
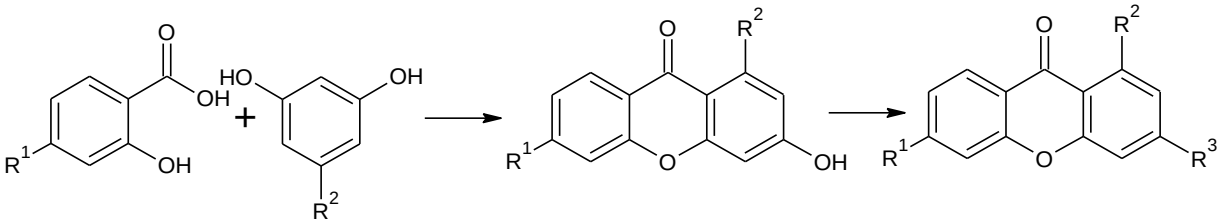


Fig. 5: Potent AMPK synthesized Activators

4.3.1 General procedure for synthesis of hydroxy xanthones

Hydroxy xanthones intermediate was synthesized by using Salicylic acid derivative and polyhydroxy phenols and further alkylation done by various alkyl bromides in the presence of acetone (Scheme 1). For the synthesis of hydroxyxanthones Eaton's reagent (Eaton and Carlson,
1973) was added in the mixture of salicylic acid derivative (60 mmol) and polyhydroxy phenol (60 mmol), followed by stirring at 70°C for 30 min. The mixture cooled, stirred with cold water, keeping temperature 0-4°C for 2.5 hours. The resulting product was collected by filtration, washed with water until pH 6 and dried at 60°C . Potassium carbonate (2.5 mmol) was added to the intermediate (2 mmol) and alkyl bromide (3 mmol) in acetone (55-60 mL). Mixture was refluxed under stirring for 2-4 hours and cooled, filtered followed by recrystallization and the product collected as yellow solid.[9]



Scheme. 7: Synthesis of hydroxy xanthones

Wherein,

P2; R1 = H, R2 = OH, R3 = OCH3

P4; R1 = H, R2 = OH, R3 = OC3H7

P5; R1 = H, R2 = OH, R3 = OC4H9

P10; R1 and R2 = H, R3 = OC4H9

4.4 Anticancer activity

A series of substituted xanthenes was synthesized and screened for anticancer activity using DU-145, MCF-7, and HeLa cancer cell growth inhibition assays. Out of which ([N,N-diethyl]-9-hydroxy-9-(3-methoxyphenyl)-9H-xanthene-3-carboxamide) found to be most potent compound, which inhibit cancer cell growth with IC_{50} values ranging from 36 to 50 µM across all three cancer cell lines. Structure-activity relationship (SAR) data is presented that indicates that potency may be further enhance by derivatization of the compounds by incorporation of 7-fluoro substituent to ([N, N-diethyl]-9-hydroxy-9-(3-methoxyphenyl)-9H-xanthene-3-carboxamide).From the result it was also observed

that the compounds function through a unique mechanism of action as compared to that of related acridine and xanthones anticancer agents (which intercalate into DNA and inhibit topoisomerase II activity).[10]

4.4.1 Bhattacharya *et al.* synthesized xanthenes from the one-pot condensation of β-naphthol and aryl aldehydes catalysed by $TaCl_5$ under solvent-free conventional heating. The synthesized xanthenes Fig. were evaluated against a group of six human tumor lines such as SW-620, 502713 and Colo-205 (colon), SKNSH (CNS), A-549 (lung) and PC-3 (prostate), using sulforhodamine B. following compounds were found to having potent anticancer activity.[11]

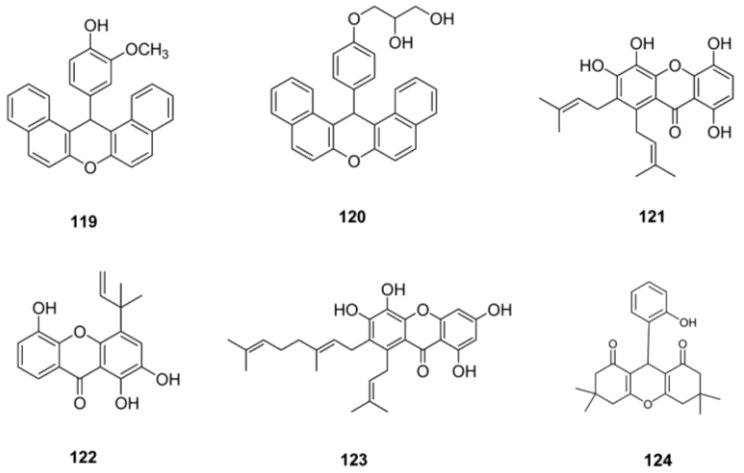


Fig. 6: Potent anticancer synthesized compounds

4.5 Antitubercular Activity

Xanthene derivatives were evaluated for their antitubercular activity against aerobic as well as dormant form of *Mycobacterium tuberculosis* H37Ra (ATCC 25177). Antitubercular screening was performed using (XTT) and menadione assay. Chlorophenyl xanthene derivative found to inhibit aerobic *M.tuberculosis* H37Ra (ATCC 25177) with MIC of 0.30 mg/ml (IC_{50}=0.118 mg/ml) and showed higher percentage inhibition in anaerobic assay as compared to Rifampin. It was also explored for its immunomodulatory potential using *in vitro* and *in vivo* techniques.[12]

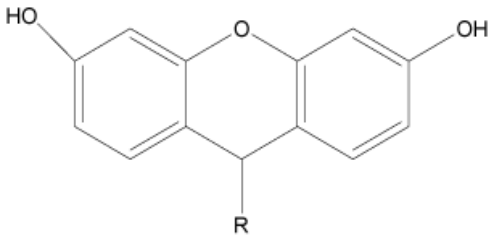


Fig. 7: General structure of previously synthesized xanthenes derivatives

Table 4: Xanthenes derivatives

Compound No.	R
1	4-Chlorophenyl
2	2-Nitrophenyl
3	4-Nitrophenyl
4	4-Hydroxyphenyl
5	4-Methoxyphenyl
6	-styryl

4.6 Antiviral Activity

Rose bengal, 4,5,6,7-Tetrachloro-3',6'-dihydroxy-2',4',5',7'-tetraiodospiro[isobenzofuran-1(3H), 9'-[9H]xanthen]-3-one dipotassium or disodium salt, $C_{20}H_2Cl_4I_4K_2O_5$, has the following chemical structure and used as marker for Herpes keratitis.

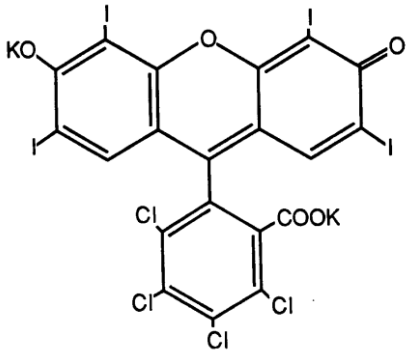


Fig. 8: Xanthene derivative having potent Antiviral Activity

It has also been used for the negative staining of bacteria, and for spirochaetes in blood. Also, used in Delprat and Stowe's test for liver function, in combination with Iodine 131 for photoscanning the liver, and as a useful fluorochrome in the study of fats under ultraviolet illumination. Smith and Dawson (1944) used the dye as a bacteriostatic agent.

Eosin Y, 2',4',5',7'-tetrabromofluorescein, disodium salt, $C_{20}H_6O_5Br_4Na_2$, has the following structure used for staining the oxyphil granules of cells, Also, it has been employed as a counterstain for hematoxylin and the green or blue basic dyes. Eosin Y, in combination with methylene blue, used as a blood stain in the technique of Romanovsky and in Mann's stain to stain nerve cells, Negri bodies, anterior hypophysis, collagen, and erythrocytes.[13]

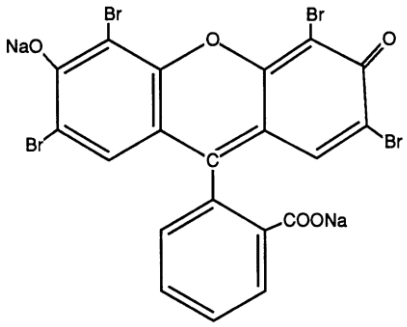


Fig. 9: Xanthene derivatives having potent Antiviral Activity

5. CONCLUSION

Xanthene derivatives are very important chemicals with tremendous biological application. In medicinal applications these compounds share an important part. Xanthene derivatives have moderate to excellent activities against number of biological targets. With changing substituent's on the Xanthene nucleus the biological targets vary from microbial diseased to viral problems and variety of cancerous cells. Xanthene derivatives target different biological problems by interacting with enzymes and proteins.

6. REFERENCES

1. Chunfeng C, Chunlei L, Jianfeng L, Jianqing J, Lijun W, Chunlei W and Runpu S. An Efficient Synthesis of Spiro[indoline-3,90 - xanthene]trione Derivatives Catalyzed by Magnesium Perchlorate. (MDPI) Molecules. 2017;22:1295.
2. Mohammadi GZ and Azizi M. The one-pot synthesis of 14-aryl-14H-dibenzo [a,j]xanthene derivatives using sulfonic acid functionalized silica (SiO2-Pr-SO3H) under solvent free conditions. Scientia Iranica. 2011;18(3): 453-457.
3. Farzaneh M. Solvent-free and One-pot Facile Synthesis of 12-aryl-tetrahydrobenzo[α]xanthene-11-one Derivatives Promoted by Manganese (IV) oxide as Efficient Catalyst. Trends in Green Chemistry. 2017; 3(17):1-5.
4. Pradeep P, Srinivasa R, Jetti A, Bhatewara TK and Shubha J. DABCO Catalyzed Synthesis of Xanthene Derivatives in Aqueous Media. ISRN Org Chem. 2013;526173.
5. Joo RK and Stephen M. Synthesis of antigungal agents from Xanthenes and Thiazine dyes and Analysis of their Effect. Nanomaterials (Basel). 2016; 6(12):243.
6. Muharrem K, Ersin D and Hatice B. Synthesis, characterization and antimicrobial activity of novel xanthene sulfonamide and carboxamide derivatives. J Enzyme Inhib Med Chem. 2013; 28(5):885-93.
7. Ichizo O and Kayoko O. Synthesis of Xanthene Derivatives having Antispasmodic Action. Derivatives of Xanthene and Thioxanthene-9-malonic Acids. Article in Japanese. 1966;86 (9):828-32.
8. Yonghoon K, Parkyong S, Jong H, Yoon J, Ghim DK, Byungjun K, Taehoon GL, Jin-A, Joong-KC, In Kwon Y, Hyeon-KL and Sung HR. Xanthene Derivatives Increase Glucose Utilization through Activation of LKB1-Dependent AMP-Activated Protein Kinase. Journal pone. 2014;10.1371.
9. Partha SB, Aparoop D, Nainwal LM, Mohanta TK, Kumawat MK, Mohapatra PK and Parida P. Design, Synthesis and Antidiabetic Activity Evaluation of Some Novel Xanthones Derivatives Targeting α-Glucosidase. Bangladesh J Pharmacol. 2016;11:308-318
10. Rajan GJ, Goodell CX, Adam B, Harmeet K, Hiroshi H and David M. Ferguson. Synthesis and cancer cell cytotoxicity of substituted xanthene. Bioorganic and Medicinal Journal. 2010;18(4): 1456-1463.
11. Dinesh K , Pooja S, Harmanpreet S, Kunal N, Girish KG, Subheet KJ and Fidele NK. The value of pyrans as anticancer scaffolds in medicinal chemistry. RSC Adv. 2017;7:36977-36999.
12. Chitre TS, Khedkar VM, Asgaonkar KD, Dube AS, Shurpali K, Sarkar D and Kathiravan M. Exploring the potential of xanthene derivatives for antitubercular activity. Open Access Text. 2017; DOI: 10.15761/GDT.1000129.
13. Antiviral therapy using thiazine and xanthene dyes. EP.0471794 B1.