Heterocyclic Letters
Vol. 15| No.2|431-441|Feb-April|2025
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

REVIEW ON SYNTHESIS OF OXOCHROMENYL XANTHENONE AND INDOLYL XANTHENONE DERIVATIVES

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Abstract: Xanthones are one of the biggest classes of O-heteroaromatic tricyclic compounds exhibiting a wide range of biological and pharmaceutical activities. A number of xanthones moieties have been extracted from natural sources of elevated plants. Xanthenone derivatives find usages in photodynamic therapy, laser technology and dyes. This review gives an impending of the recent literature disclosed to obtain the xanthone nucleus, by exploiting the optimization of well-known procedures as well as disruptive developed methodologies.

Introduction:

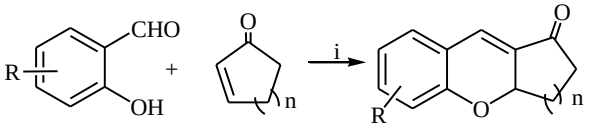
Xanthenone derivatives are the significant class of heterocycles being the principal components of many natural products of high plants. Chromenes has the general applications as food additives, cosmetic agents and potential biodegradable agrochemicals.[i-iii] Now a day, chromene derivatives has more attention due to their biological and pharmacological properties. The Xanthenone derivatives shows the various pharmacological properties such as anti-coagulant, anti-cancer,[iv]diuretic,[v] anti-HIV,[vi] antitumor,[vii] anti-malarial activities,[viii] antileukemic,[ix] antibacterial,[x] anti-malarial[xi] and anti-anaphylactic activities.[xii] Moreover several natural products like calanolides, calanone, calophyllolides contains chromene derivatives as the main components.[xiii] In addition, xanthenones can be used for the treatment of neurodegenerative disease as a cognitive enhancers, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's diseases, Parkinson's disease, AIDS-associated dementia and Down syndrome as well as for the treatment of schizophrenia and myoclonus.[xiv] A number of chromene derivatives acts as photoactive materials.[xv]

In previous literature, observed that a chromene derivative has high potency against wild-type HIV-1 replication.[xvi-xvii] It has been speculated that adding an indole and coumarin ring onto the xanthenone ring of xanthenone nucleus could produce a more rigid planar system, and the extended conjugation might sustain or even increase the vigorous interaction between the ligand and target protein.

Various methods are found in literature for the synthesis of xanthene derivatives, due to the special attention of xanthenes as diverse array of biological activities.[xviii-xxv] Knoevenagel reaction between 1,3-dicarbonyl compounds and formaldehyde, aromatic aldehyde with malononitrile or cyanoacetic ester; and isatin with malononitrile using was carried out using boric acid, *L*-proline, $HClO_4$-SiO_2.[xxvi] $Fe(OTf)_3$ was also applicable for the synthesis of

xanthenones.[xxvii] Quite recently, Yanlong Gu reported an elegant Brønsted acid-mediated nucleophilic alkylation to carbonyl compounds.[xxviii,xxix] Due to the importance of xanthenone in medical as well as pharmaceutical field, this review gives the various methods for the synthesis of xanthenone.

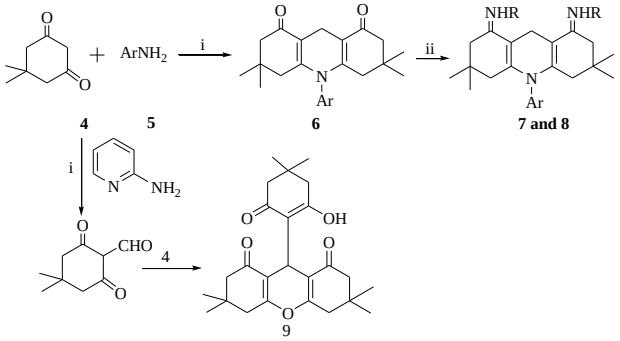
K. Y. Lee *et al.* developed method for one-pot condensation of salicylaldehyde**1,** 2-cyclohexen-1-one or 2-cycloenten-1-one **2**using DMAP in aqueous THF as a catalyst and variety of 2,3,4,4a-tetrahydroxanthen-1-ones or 3, 3a-dihydro-2*H*cyclopenta[b]chromen-1-ones derivatives **3** were prepared in good yields (**Scheme1**). [xxx]



1 **2** **3**

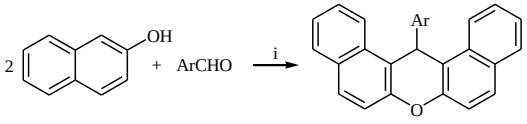
Scheme 1*: Reagent and conditions*: i) THF /H_2O, DMAP, rt, 6-7 hr, 39-58%.

E. H. El Ashry *et al.* describes microwave (MW) irradiation activated reaction of dimedone**4** with aniline or p-chloroaniline**5** in formic acid in to give the acridine derivatives **6**, which can be derivatized as the bisoximes**7** and bisphenylhydrazone**8**. However, under the same reaction conditions 2-aminopyridine gave the xanthene derivative **9** and not the expected acridine derivative **6 (Scheme 2).** [xxxi]



Scheme 2: *Reagent and conditions*: i) HCO_2H, 150^oC, MW, 12 min. ii) $NH_2OH.HCl$ or $PhNHNH_2$.

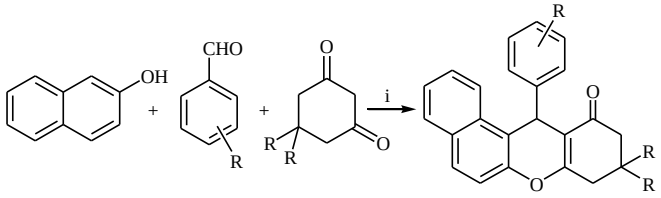
M. M. Amini *et al* used polytungstozincate acid as an efficient catalyst for the synthesis of xanthene derivatives **12** under solvent free conditions. A mixture of 2-naphthol **10**, substituted aldehydes **11** and polytungstozincateacid was heated at 80^oC for an appropriate time to get xanthene derivatives **(Scheme 3).**[xxxii]



10 **11** **12**

Scheme 3: *Reagent and conditions*: i) Polytungstozincate acid, solvent free, 1-2hr, 81-91%.

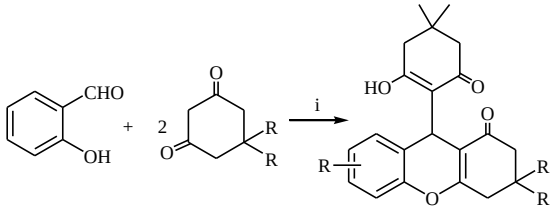
Z. H. Zhang *et* al developed an efficient and direct protocol for the preparation of 12-aryl-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one **16** derivatives employing a three-component one-pot reaction of aryl aldehydes **13,** 2-naphthol **14** and cyclic 1,3-dicarbonyl compounds **15** in the presence of a catalytic amount of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) under solvent-free conditions (**Scheme 4).**[xxxiii]



14 **15** **16** **17**

Scheme 4: *Reagent and conditions***:** i) TCT, solvent free, 80^{o}C, 30-70 min, 83-93 %.

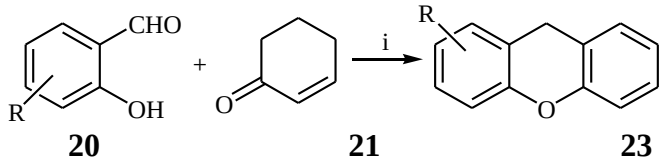
D. M. Pore *et al* synthesized 1-oxo-hexahydroxanthenes **19** by a reaction of salicylaldehyde**17** with cyclohexane-1,3-dione or dimedone**18** in water as universal solvent at reflux condition without a catalyst using an efficient and ecofriendly protocol **(Scheme 5).**[xxxiv]



17 **18** **19**

Scheme 5: *Reagent and conditions*: i) H_2O, Reflux, 3.5-5 hr, 84-91%.

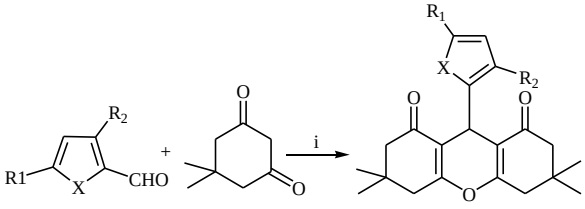
E. Bob *et al* reported a two method for the synthesis of substituted xanthenes derivatives **23**. He developed one-pot condensation of substituted salicylaldehyde**20**, cyclohexenone**21**or tetralones**22,** is catalyzed by Lewis acids like scandium triflate and furnishes substituted xanthenes in good to excellent yields using either microwave or thermal heating. Microwave heating results in significantly shortened reaction times of 30 min and generally higher yields **(Scheme 6)**.[xxxv]



20 **21** **23**

Scheme 6: *Reagent& conditions*: i) a) M.W. at 180^{o}C, 30 min. b) $Sc(OTf)_3$, reflux, 18-44hr.

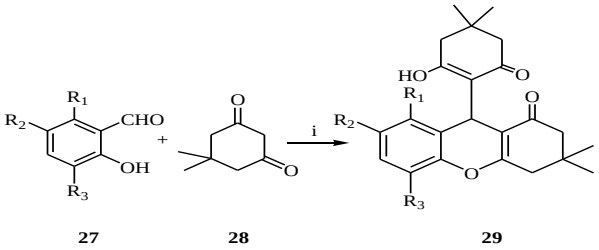
P. Pradeep *et al* proceeds reaction via initial Knoevenagel, subsequent Micheal and final heterocyclization reactions using 1,4- diazabicyclo (2.2.2)octane (DABCO) as catalyst for the synthesis of a variety of 1,8-dioxo-octahydroxanthenes derivatives **26** via facile condensation of heteroaryl aldehyde **24** and 5,5'-dimethyl-1,3-cyclohexanedione (dimedone,**25**) **(Scheme 7).**[xxxvi]



24 **25** **26**

Scheme 7: *Reagent and conditions*: i) DABCO, reflux, 30min, 87-94%

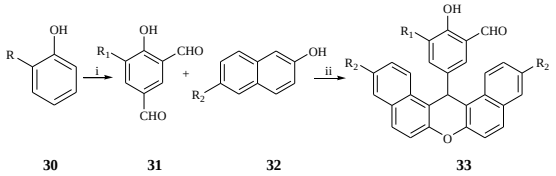
Synthesis of 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-onederivatives **29** was reported by N. N. Pesyan and coworkers using acetic acid. They developed method using one-pot condensation of substituted salicylaldehyde**27**, and dimedone **28 (Scheme 8)**.[xxxvii]



27 **28** **29**

Scheme 8: *Reagent and conditions*: i) ACOH, reflux.

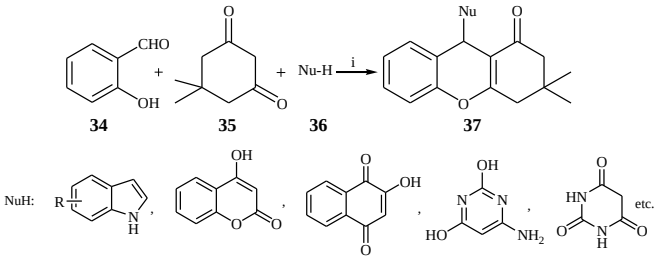
The Duff reaction on 2-*sec*-butylphenol **30**gave compound 5-*sec*-butyl-4-hydroxyiso phthalaldehyde 31which on condensation with β-naphthol**32** in presence of catalytic amounts of iodine furnished para-selective dibenzoxanthenes**33** derivatives in good to excellent yields was described by K. V. Sashidhara *et al.* (**Scheme 9)**.[xxxviii]



30 **31** **32** **33**

Scheme 9: *Reagent and conditions*: i) Hexamethylenetetramine / TFA, 120 ºC, 3hr; ii) I_2,90-100 ºC, 15 min,
80-90 %.

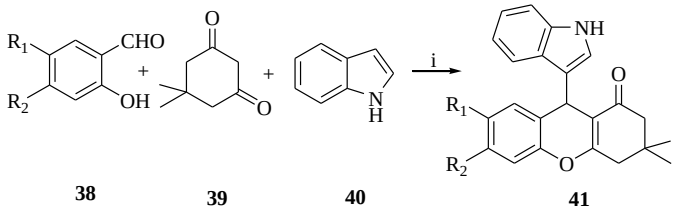
M. Li *et al* developed one pot and three-component reactions of salicylaldehydes **34**, 1,3-cyclohexanediones **35** and a sulfur, carbon, or nitrogen based carbon nucleophile (Nu-H) **36**, by using *L*-proline as a catalyst, which generated various substituted 4H-chromene **37** derivatives in good to excellent yields. The reactions were performed in ethanol under mild and metal-free conditions (**Scheme 10**).[xxxix]



34 **35** **36** **37**

Scheme 10: *Reagent and Conditions*: i) EtOH, 80ºC, 3-11hr, 85-99%.

N. C. Ganguly*et al* developed a facile*L*-proline-catalyzed three-component coupling of substituted 2-hydroxybenzaldehyde **38**, 5,5- dimethyl-1,3-cyclohexanedione (dimedone) **39**, and indole **40** has been accomplished under mild aqueous micellar conditions to deliver a derivative of 9-(1H-indol-3- yl)-xanthen-4-(9H)-ones **41(Scheme 11)**.[xxxx]

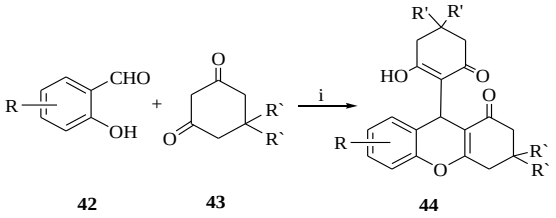


38 **39** **40** **41**

Scheme 11: *Reagent and conditions*: i) *L*-proline, SDS, water, rt, 2 hr, 86-96%.

D. Prasad coworkers using *L*-proline as catalyst reported synthesis of 9-substituted-2, 3, 4, 9-tetrahydro-1Hxanthen-1-one derivatives **44**. They developed method using one-pot condensation of dimedone or 1,3-cyclohexanedione **43** with substituted salicylaldehydes**42** in ethanol under mild reaction conditions in presence of catalytic amount of *L*-proline **(Scheme**

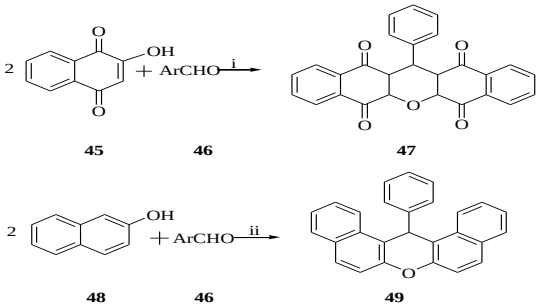
12).[xxxxi]



42 **43** **44**

Scheme 12: *Reagent and conditions:*i) *L*-proline, EtOH, 60ºC, 0.5-5hr, 80-99%.

A simple and convenient procedure for the synthesis of 5H-dibenzo [*b,i*]xanthene-tetraones**47** and aryl-14H-dibenzo[*a,j*]xanthenes**49** is described by D. Liu *et al* through the condensation of aldehydes **46** with 2-naphthol **48** or 2-hydroxy-1, 4-naphthoquinone **45** under solvent-free conditions in the presence of ferric chloride hexahydrate**(Scheme 13).**[xxxxii]

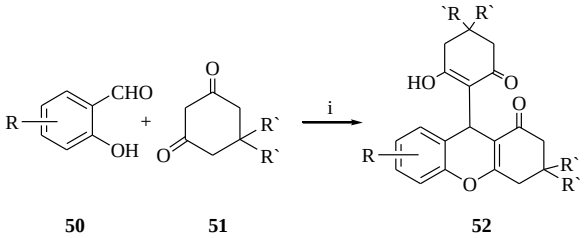


45 **46** **47**

48 **46** **49**

Scheme 13: *Reagent and conditions*: i) $FeCl_3 \cdot 6H_2O$, Solvent-free, 90°C, 2-3hr, 87-95%.
ii) $FeCl_3 \cdot 6H_2O$, Solvent-free, 90°C, 2-3hr, 83-94%.

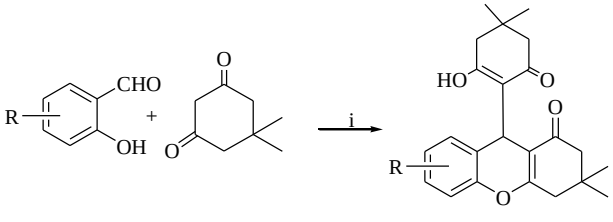
T. R. Mandlimathand co-researcher developed method for synthesis of 1-Oxo-hexahydroxanthene derivatives **52** using nano-$ZnAl_2O_4$ catalyst. They carried out synthesis by one-pot condensation of aromatic aldehyde **50**, 1, 3-diketone**51** and calculated amount of nano-$ZnAl_2O_4$ along with ethanol solvent at 80ºC **(Scheme 14)**.[xxxxiii]



50 **51** **52**

Scheme 14: *Reagent and conditions*: i) $ZnAl_2O_4$, Ethanol, reflux, 10-15min, 88-99%.

K. M. Khan *et al* developed the protocol for the synthesis of a series of functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one **55** by reacting dimedone **54** with substituted salicylaldehydes**53** using CsF catalyzed tandem Knoevenagel–Michael reaction **(Scheme 15).**[xxxxiv]

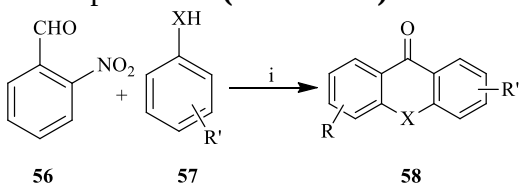


53 **54** **55**

Scheme 15: *Reagent and Conditions*: i) Csf, DCM, stirred at rt, 30-40min, 70-86%.

A.Venkannna and coworkers described the method for the synthesis of xanthones **58** and thio-xanthones using $CuFe_2O_4$ as a nano catalyst and K_3PO_4as a base in DMF solvent at

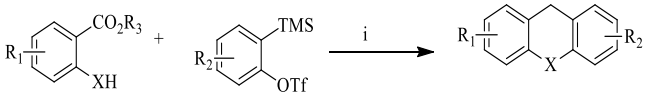
80^0C under ligand free conditions, through an intermolecular catalytic coupling of 2-substituted benzaldehydes**56** and substituted phenols**57(Scheme 16)**.[xxxxv]



56 **57** **58**

Scheme 16: *Reagent and conditions*: i) Nano-$CuFe_2O_4$, K_3PO_4, DMF, 80ºC, air.

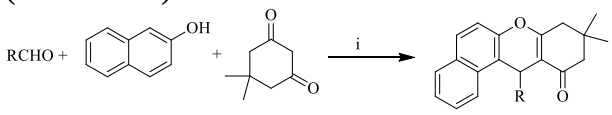
Jian Zhao et.al. developed the reaction for the synthesis of xanthones and thioxanthones**61**fromsilylaryltriflates**60**, CsF and salicylates **59(Scheme 17)**.[xxxxvi]



59 **60** **61**

Scheme 17: *Reagent and Conditions*: i) CsF, Silylaryl triflate, THF at 65 °C for 24 h.

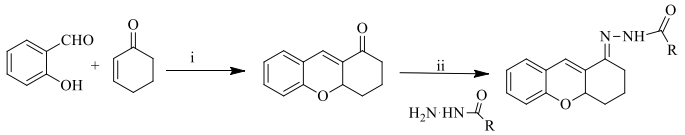
Bruna S. Terra and his co-workers were synthesized xanthenones via one-pot tricomponent reaction, under solvent-freeconditions, using aldehydes, phenolic and cyclic 1,3-dicarbonyl compounds (**Scheme 18**).[xxxxvii]



62 **63** **64** **65**

Scheme 18: *Reagent and Conditions***:** i) Oxalic acid, MW, 130ºC, Solvent free reaction.

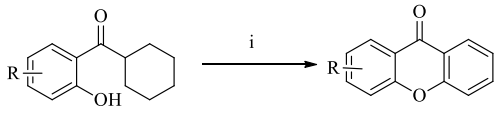
Xanthenone based hydrazone derivatives (5a–n) have been synthesized as potential α-glucosidase inhibitors. Series of substituted hydrazide (4a–n) were taken to react with 2,3,4,4a-tetrahydroxanthen-1-one (3) prepared by previously reported methodology **(Scheme 19)**.[xxxxviii]



66 **67** **68** **69** **70**

Scheme 19: *Reagent and Conditions***:** i) Me_3N, MeOH, rt, 24hrs; ii) AcOH, EtOH, reflux.

An extraordinary approach to the xanthone**72** scaffold from cyclohexyl(2-hydroxyphenyl)methanone **71** was reported by Yoon Hu Jang and et al via dehydrogenative cyclization and a successive aromatization (**Scheme 20**).[xxxxix]

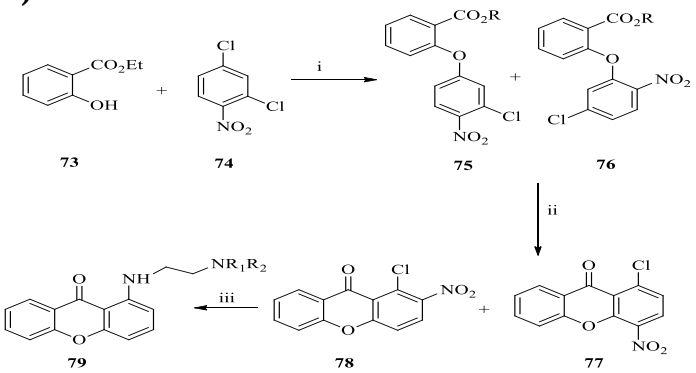


71 **72**

Scheme 20: *Reagent and Conditions***:** i) $Cu(AcO)_2$, 1,10-Phen, TEMPO, KOAc, t-Amyl-OH,130ºC.

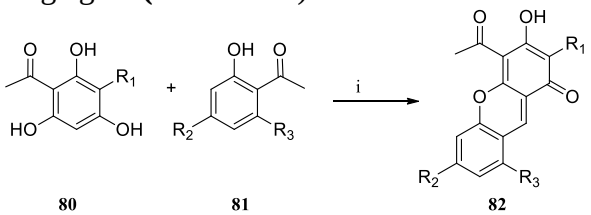
Kamila Rzad and coworkers synthesized xanthone derivatives by the reaction of ethyl salicylate 73 with 2,4-dichloronitrobenzene 74 afforded a mixture of the isomeric diarylethers 75, 76 respectively. Trituration of both mixtures with methanol resulted in pure 76, while we obtained a 1/1 mixture of 75, 76, which could not be further purified. For the synthesis of the ortho-substituted amines 79, each of the above mixtures was saponified under mild conditions. Without further purification, the resulting mixture of acids 75, 76, was ring closed upon

treatment with polyphosphoric acid (PPA) to afford nitro compounds 77, 78 inseparable mixtures **(Scheme 21).**[xxxxx]



Scheme 21: *Reagent and conditions*: (a) K_2CO_3, Cu_2O, DMF dry, 110°C; (b) NaOH 40%, EtOH, rt; (c) PPA, 110 °C; (d) suitable amine, pyridine, reflux.

Raaginie Tamil Segram reported the synthesis of xanthenones using strong non-nucleophilic base catalyst, and the described synthesis of prenylated or geranylated acylphloroglucinol-based xanthenones was synthesized via aldol condensation of 2,4,6-trihydroxy-3-prenylacetophenone (tHPA) or 2,4,6-trihydroxy-3-geranylacetophenone (tHGA) and 2-hydroxybenzaldehyde derivatives in the presence of lithium bis(trimethylsilyl) amide (LiHMDS) as deprotonating agent **(Scheme 22**).[xxxxxi]



Scheme 22: *Reagent and conditions***:** i) LiHMDS, HCl, N_2 Room temperature.

Conclusion: The importance of Oxochromenyl Xanthenone and Indolyl Xanthenone derivatives in medicinal chemistry world led to the development of advanced synthetic methodologies in the heterocyclic chemistry. Various ways are employed for the synthesis of Xanthenone derivatives. The cyclisation can be achieved by a wide range of methodologies, being also a multistep approach. On the other hand, the chromone route is typically a one-step strategy. These reactions are being transversal to the synthesis of many heterocycles, such as flavones, coumarins, acridines. This review summarizes not only various synthetic routes for the synthesis of Oxochromenyl Xanthenone and Indolyl Xanthenone but also the pharmaceutical and biological significance. We expect that in a near future, particularly the environment-benign approach; can become a useful tool in reporting the more examples of complex xanthenones. This may further enlarge the importance of this scaffold as a fortunate structure in search of new bioactive molecules.

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Received on November 12, 2024.