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Review Article

SYNTHESIS AND BIOLOGICAL PROPERTIES OF PHARMACEUTICALLY IMPORTANT XANTHONES AND BENZOXANTHONE ANALOGS: A BRIEF REVIEW

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ABSTRACT

Xanthones are one of the biggest classes of compounds in natural product chemistry. A number of xanthones have been isolated from natural sources of higher plants such as fungi, ferns, and lichens. Synthetic analogs of xanthones have shown a large number of pharmacological properties such as antioxidant, anti-inflammatory, antidiabetics, antihistamine, antitumoral, antiulcer, and algicidal. Moreover, they also find usages in photodynamic therapy, laser technology, and dyes. This review lays stress on various solvents, catalyst and synthetic route for synthesis of xanthones, benzoxanthones analogs. The review has also focused on the classifications of xanthone as well as extensively studied biological properties of the xanthones and benzoxanthones analogs.

Keywords: Multicomponent reactions, Xanthones, Benzoxanthones, Biological properties.

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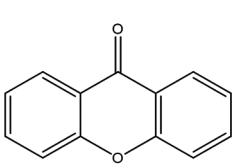
INTRODUCTION

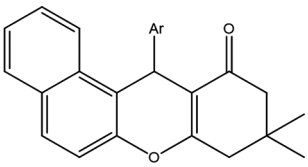
During the past few decades, there has been widespread interest in multicomponent reactions (MCRs) due to their increasing importance in organic and medicinal chemistry [1-3]. MCRs are the processes in which three or more reactants are combined in a single step to yield products by combining suitable portions of all the reactants. These reactions are very effective in synthesizing highly functionalized small organic molecules from easily available starting materials in a single step and in short duration of time period. MCR also provides a higher overall percentage of yield. Thus these reactions reduces labor by reducing a number of synthetic operations such as extraction, purification, and generates lesser amount of waste as compare to conventional multistep reactions of a complex molecule [4-6]. A large number of MCRs are already known, and the searches for new MCRs are still on. One such reaction which belongs to MCR category is a synthesis of xanthones and its derivatives with extended conjugation, i.e., Benzoxanthones.

Xanthones are naturally occurring polyphenolic compounds. Xanthone nucleus is the main framework of large number of natural and synthetic materials. These are parent of several natural yellow pigments. These comprise an important class of oxygenated heterocycles. Xanthone Skelton possesses good thermal oxidative and hydrolytic stability, that's why these are considered as structural motif in high performance and engineering polymers [7]. Numerous derivatives of xanthones are isolated from higher plants, fungi, and lichens [8]. However, the naturally occurring xanthones are limited to a fewer number of substituent, so efforts are made to synthesize them from their constituent fragments.

Xanthones and benzoxanthones constitute an important class of biologically active heterocycles. Due to their remarkable pharmacological and biological applications, their synthesis has drawn great attention in the field of medicinal and pharmaceutical chemistry. They possess antiviral [9], anti-inflammatory [10], antibacterial [11], antimalarial [12], anti-HIV [13], antimicrobial, antioxidant, and anticarcinogenic [14,15] activities. These are also used as an antagonist for paralyzing action of zoxazolamine [16]. Furthermore, these compounds can be used in photodynamic therapy [17], as dyes [18] in laser technology [19] and in fluorescent materials which are sensitive to pH for visualization of biomolecules [20].



1. Xanthone



2. Benzoxanthone

Classification of xanthone

Naturally occurring xanthones are broadly classified into six categories:

1. Simple oxygenated xanthone.
2. Xanthone glycosides.
3. Prenylated xanthone.
4. Bisxanthones.
5. Xantholignoids.
6. Miscellaneous xanthones.

Simple oxygenated xanthone

These xanthones carry simple hydroxyl, methoxy, and methyl groups. These are further subdivided into various categories such as mono, di, tri, tetra, penta, and hexa oxygenated depending on the level of oxygenation [21-23]. For example, 2-hydroxyxanthone (3), 2-hydroxy-1-methoxyxanthone (4).

Xanthone glycosides

The xanthone in which sugar moiety is attached to xanthone nucleus is called xanthone glycosides. These are further of two types, i.e., C-glycosides and O-glycosides. In C-glycosides sugar moiety is attached to xanthone nucleus by C-C bond whereas in O-glycosides glycosidic linkage, i.e. C-O-C joins sugar moiety to xanthone. C-glycosides are fewer in number as compare to O-glycosides. For example, mangiferin (22) and isomangiferin are most common C-glycosides, and Swertia japonica (24) and gentioside are few O-glycosides.

Prenylated xanthone

These are the xanthones in which 5-carbon unit such as isoprenyl and 1,1-dimethylprop-2-enyl,3-hydroxy-3-methylbutyl [24-26] is attached as a substituent to xanthone nucleus, for example,

Allanxanthone-A (25).

Bisxanthones

These are dimeric xanthones. First bisxanthone C-glycoside was swertipunicoside (26). It was isolated from Swertia punicea Hemsl plant. A few more examples are dimeric xanthone (27), globulixanthone E (28) [27], and ploiarixanthone. A total of 12 bisxanthones are known.

Xantholignoids

One of the most important category xanthone is xantholignoids. These were thought to be formed by coupling of cinnamoyl alcohol with an o-hydroxyxanthone. Some of the Xantholignoids are Kielcorin (29a) [28], 6-methylkielcorin (29b), Cadensin C (29c) [29], and Hypericorin (29d).

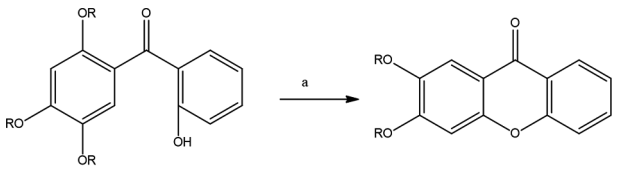
Miscellaneous xanthone

Xanthone with substituents other than those discussed above are included in this category. Few examples are xanthopterin [30], xantholiptin [31], and xanthofulvin (30) and vinaxanthone (31) [32].

Synthesis of xanthone and benzoxanthone

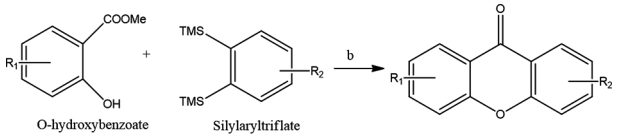
Synthesis of xanthone and its benzo-fused analogs, i.e., Benzoxanthone is extremely important due to its broad range of applications as mentioned above. Scientists have already invented an easy, efficient, and economic method to synthesize xanthone and benzoxanthone through one-pot multicomponent condensation reaction. Various schemes used by researchers to synthesize xanthone and benzoxanthone are mentioned here:

Scheme 1 [33]



Scheme-1: a- CAN, water,chloroform,acetonitrile

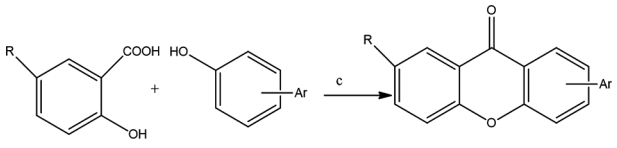
Scheme 2 [34]



O-hydroxybenzoate Silylaryltriflate

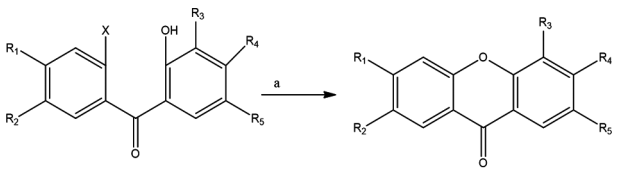
Scheme-2: b= CsF

Scheme 3 [35]



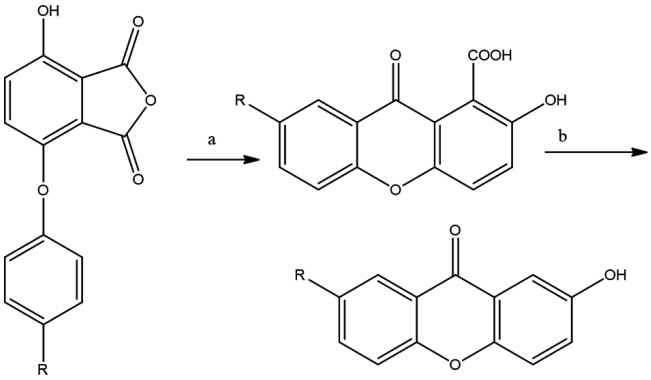
Scheme 3: c= POCl3,b=Heat(80 degree C)

Scheme 4 [36]



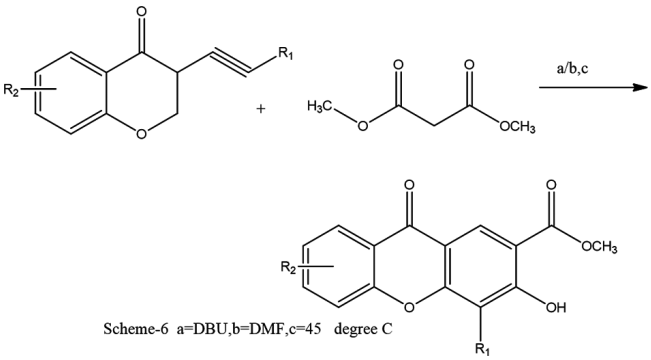
Scheme-1:a=Cu, TMEDA, water,Heat

Scheme 5 [37]



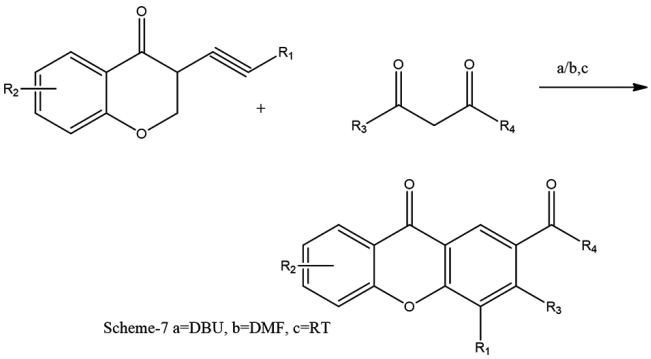
Scheme-5: a= AlCl3 b=Heat, Cu

Scheme 6 [38]



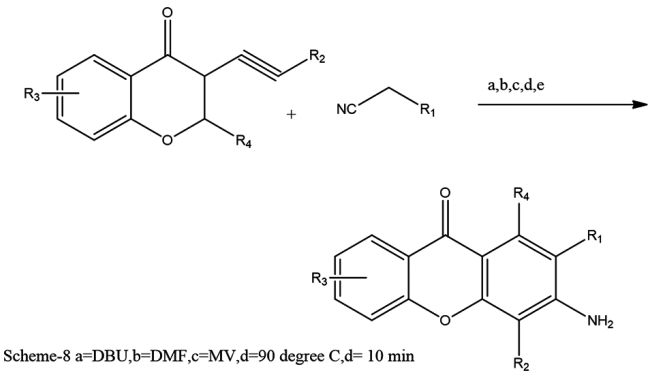
Scheme-6 a=DBU,b=DMF,c=45 degree C

Scheme 7 [38]



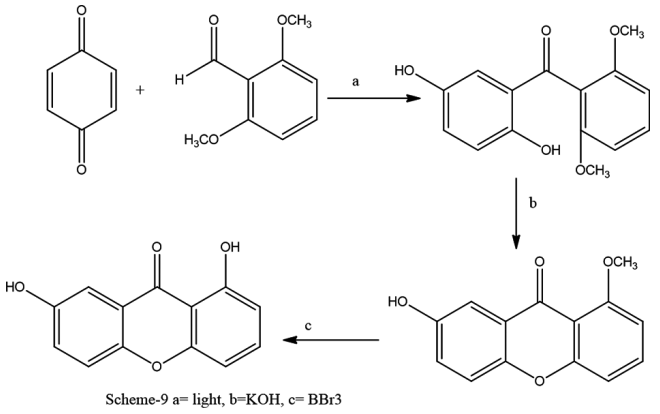
Scheme-7 a=DBU, b=DMF, c=RT

Scheme 8 [39]



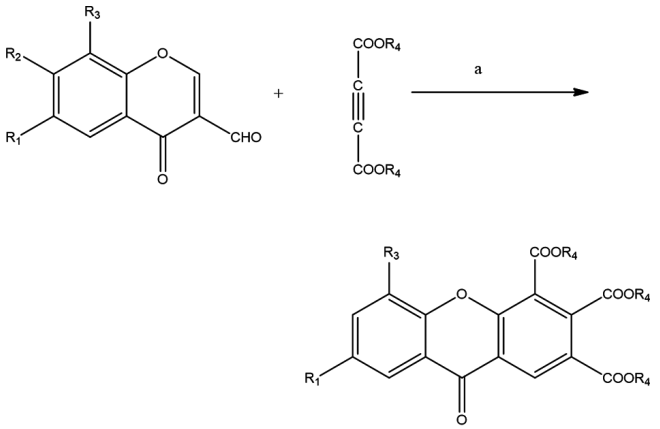
Scheme-8 a=DBU,b=DMF,c=MV,d=90 degree C,d= 10 min

Scheme 9 [40]



Scheme-9 a= light, b=KOH, c= BBr3

Scheme 10 [41]

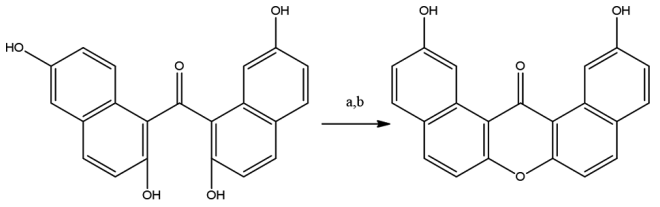


Scheme-10 : a=DME, DMAP, 4-Picoline,-18 degree C-RT

Synthesis of benzoxanthone

Scheme 1: [42] a = K_2CO_3/H_2O

b = 150°C, 6 h

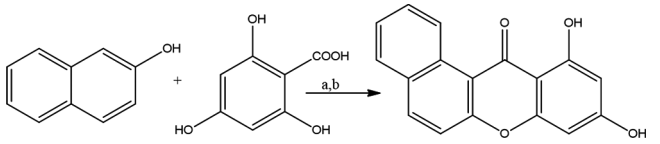


Dihydroxybenzopenone

Dibenzoxanthone

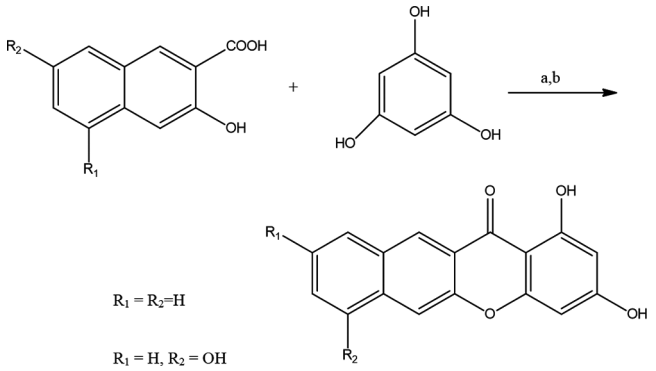
Scheme 2: [43] a = $ZnCl_2$, b = $POCl_3$

70–80°C, 1–5 h



Scheme 3: [43] a = $ZnCl_2$,b = $POCl_3$

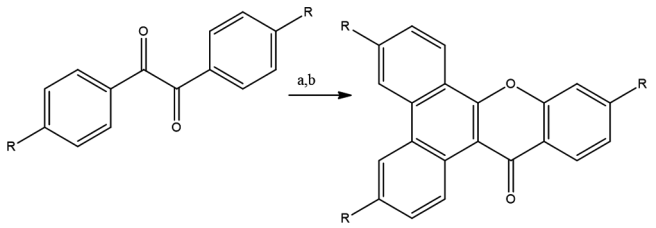
70–80°C, 1–5 h



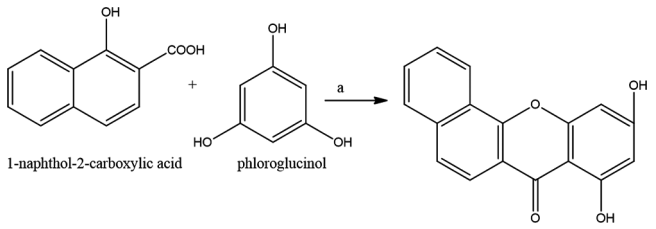
$R_1 = R_2$=H Scheme-2

R_1 = H, R_2 = OH

Scheme 4: [44] a = 350 nm, b = MeOH



Scheme 5: [45] a = $POCl_3$, 70°C, heating (6 h)



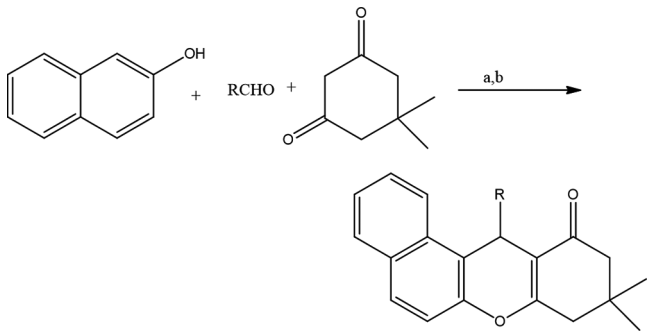
1-naphthol-2-carboxylic acid

phloroglucinol

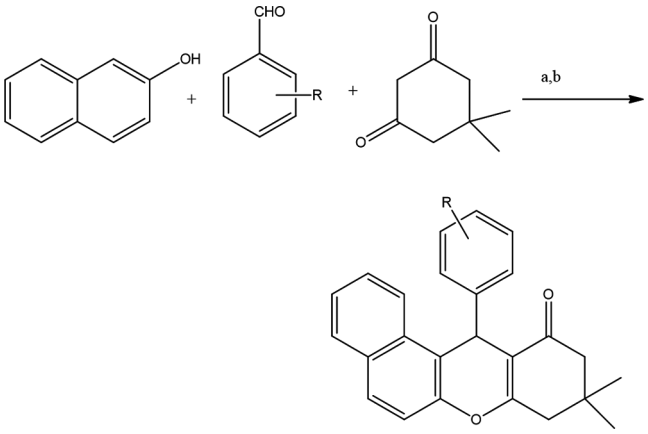
Scheme 6: [46] a = HBF_4/SiO_2, b = 80°C

or

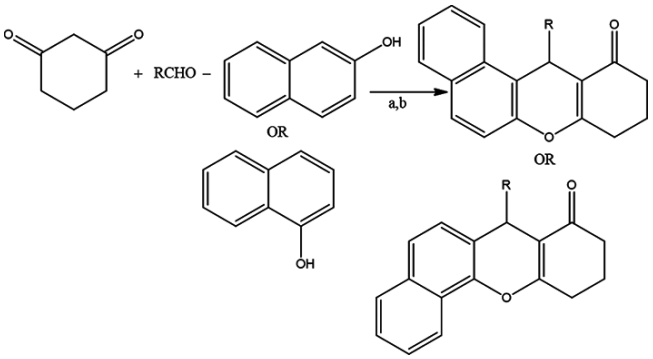
$InCl_3$ or P_2O_5, 120°C, solvent free [47]

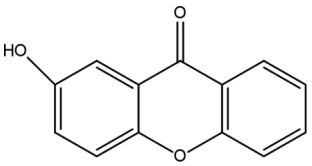


Scheme 7A: [48] a = $HClO_4/SiO_2$, b=80°C or 7B: [49] a = SSA, b = 80°C, 15–210 min, solvent free or 7C: [50] a = H_2SO_4, b = H_2O, reflux or 7D: [50] a = PTS b = MW, neat or 7E: [51] $HClO_4$, MW, solvent free 7F: [52] a = $NaHSO_4.SiO_2$, b = CH_2Cl_2, reflux 5 h or 7G: [53] a = $Sr(OTf)_2$, b = 1,2-dichloroethane, 80°C or 7H: [54] PEG-400 or 7I: [55] a = $ClSO_3H$, b = ultrasound irradiations or 7J: [56] a = TBAF, b = H_2O or CH_2Cl_2 or CH_3CN or DMF or DMSO or MeOH,100°C 7K: [57] CAN, 120°C, Solvent. free



Scheme 8: [58] a = proline triflate, b = H_2O





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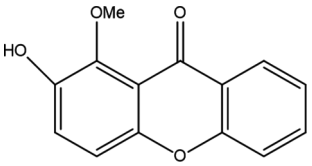

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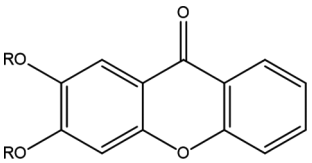
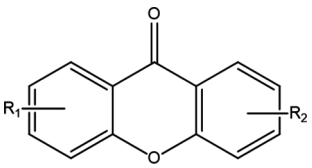


5 (R=CH_3)



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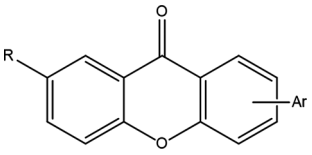
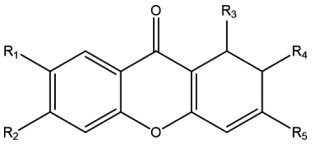


7 (R=H or OH)



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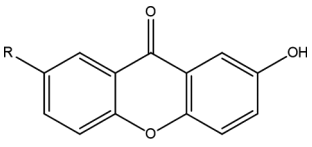

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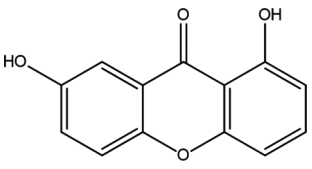

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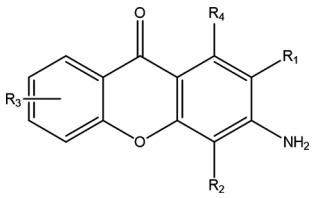

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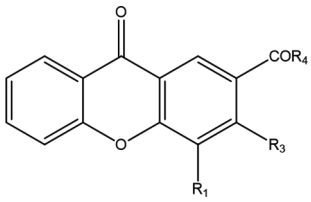

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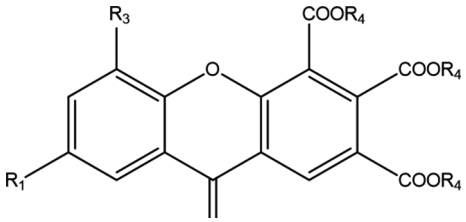

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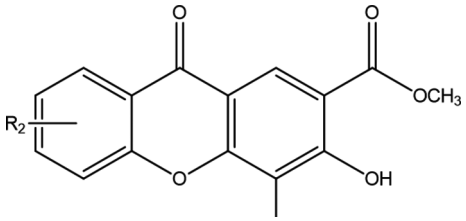

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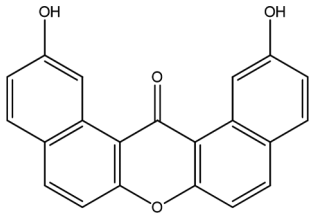

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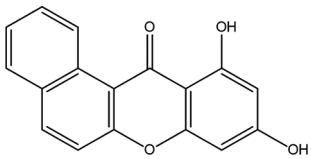

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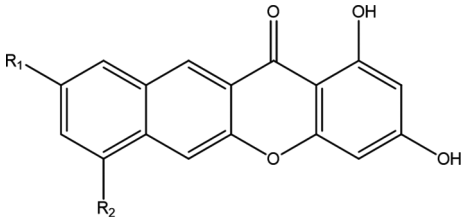

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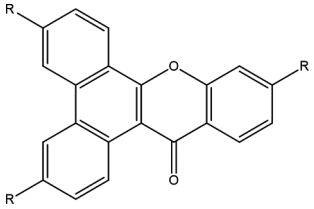

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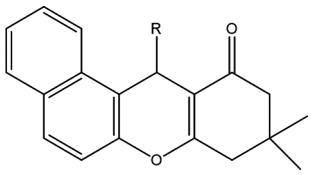

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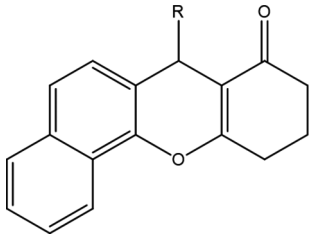

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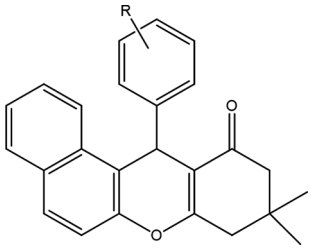

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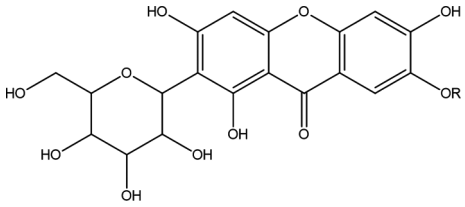
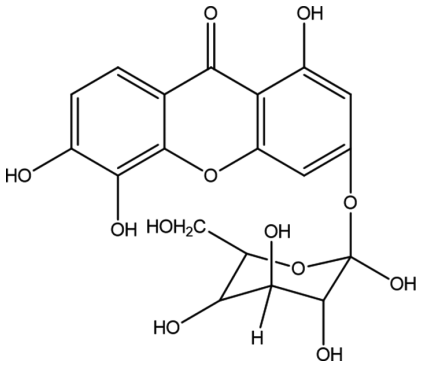


22 R=H

23 R=beta-D-glucopyranosyl



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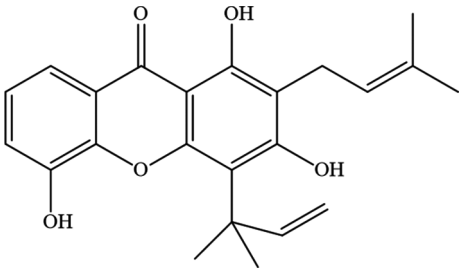

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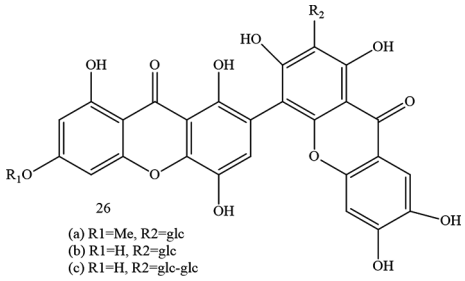
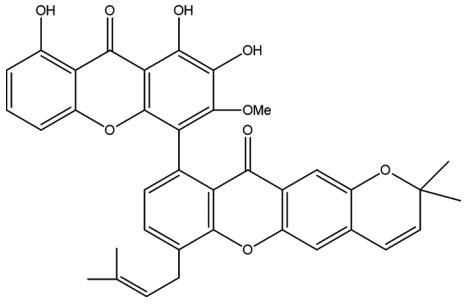


26

(a) R1=Me, R2=glc
(b) R1=H, R2=glc
(c) R1=H, R2=glc-glc



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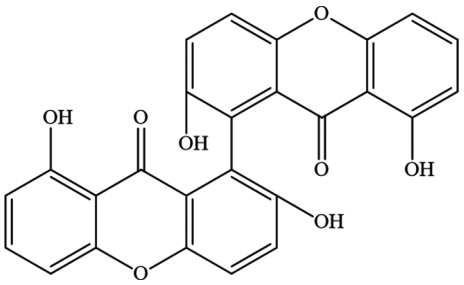

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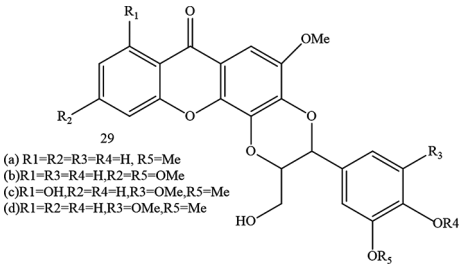
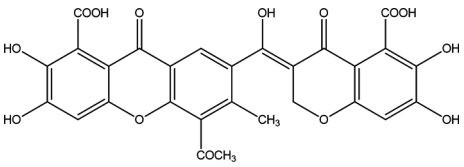


29

(a) R1=R2=R3=R4=H, R5=Me
(b)R1=R3=R4=H,R2=R5=OMe
(c)R1=OH,R2=R4=H,R3=OMe,R5=Me
(d)R1=R2=R4=H,R3=OMe,R5=Me



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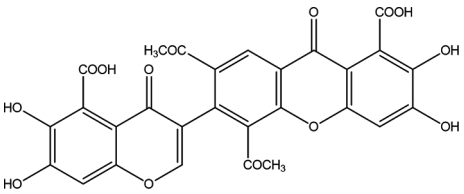

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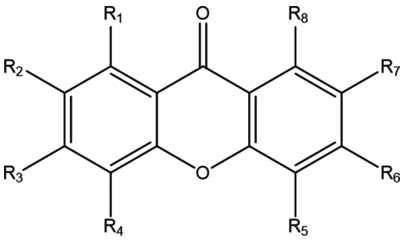

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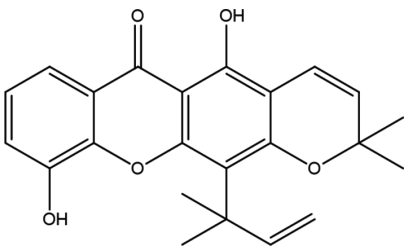

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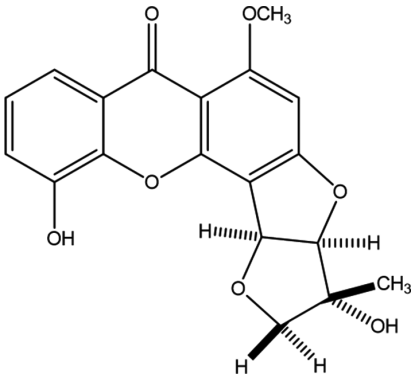

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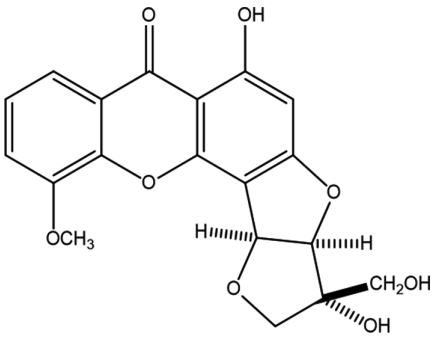

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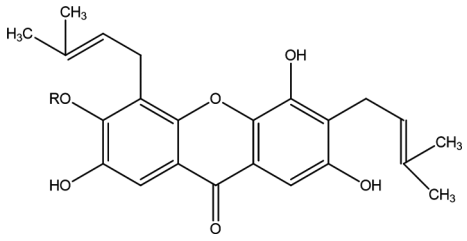

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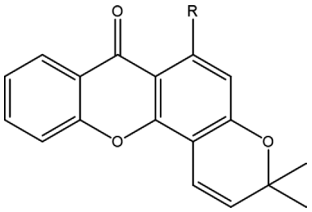

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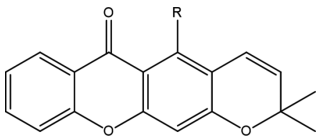

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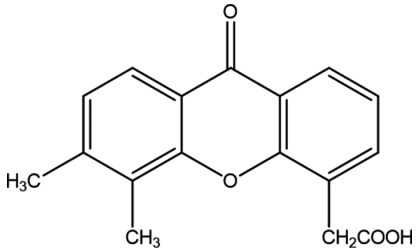

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Table 1: Various reaction condition, catalysts and solvents for synthesis of xanthones

S. No.	Compound	Solvent	Catalyst	Reaction conditions	Reference
1	5	H2O or CHCl3 or MeCN	CAN	-	[33]
2	6	Various solvents like CH3COCH3, CH3CN, C6H5CH3 THF, DME, CH_3 NO2, CH2Cl2	CsF	RT-100°C	[34]
3	7	-	POCl3	Heat (80°C)	[35]
4	8	H2O	Cu, TMEDA	Heat	[36]
5	9	-	AlCl3	Heat	[37]
6	10	Boiling CH3OH	KOH	Light	[40]
7	11	-	-	DBU/DMF, MV, 90°C, 10 min	[39]
8	12	-	-	DBU/DMF, RT	[38]
9	13	DME	4-Picoline, MAP	Heat (−18°C-RT)	[41]
10	14	-	-	DBU/DMF, 45°C	[38]

Table 2: Various reaction condition, catalysts, and solvents for synthesis of benzoxanthones

S. No.	Compound	Solvent	Catalyst	Reaction conditions	Reference
1	15	H_2O	K_2CO_3	Heat (150°C), 6 h	[42]
2	16	-	$ZnCl_2$, $POCl_3$	Heat (70–80°C), 1–5 h	[43]
		-	$POCl_3$	Heat (70°C), 6 h	[45]
3	17	-	$ZnCl_2$, $POCl_3$	Heat (70–80°C), 1–5 h	[43]
4	18	CH_3OH	-	Light radiations (350 nm)	[44]
5	19	-	HBF_4-SiO_2	Heat (80°C)	[46]
		-	$InCl_3$ or P_2O_5	Heat (120°C)	[47]
		H_2O	Proline triflate	-	[58]
6	20	H_2O	Proline triflate	-	[58]
7	21	-	$HClO_4$-SiO_2	Heat (80°C)	[48]
		-	SSA	Heat (80 C), 15–210 min	[49]
		H_2O	H_2SO_4	Reflux (3 h)	[50]
		-	PTS	MW	[50]
		-	$HClO_4$	MW	[51]
		DCM	$NaHSO_4$-SiO_2	Reflux (5 h)	[52]
		1,2-DCE	Sr $(OTf)_2$	Heat (80°C)	[53]
		PEG-400		Heat 120°C (5–8 h)	[54]
		-	$ClSO_3H$	Ultrasound	[55]
		H_2O or DCM or MeCN or MeOH or THF or DMSO or DMF	TBAF	Heat (100°C)	[56]
		-	CAN	Heat 120°C	[57]

Table 3: Biological properties of xanthones and their analogs

S. No.	Biological property	Compound	Compound name	Reference
1	Antimalarial	32	2,3,4,5,6-pentahydroxyxanthone (X5) $R^2=R^3=R^4=R^5=R^6$=OH, $R^1=R^7=R^8$=H	[12]
2	Antimicrobial	51	Inoxanthone	[59]
		52	Psorofebrin	[60]
		53	5/-Hydroxyisopsorofebrin	
3	Antidiabetic	22	Mangiferin (xanthone glucoside)	[61]
		23	Mangiferin-7-O-beta-gluoside	
4	Antiplatelet aggregation	33,34	2,3,6,7 ($R^2=R^3=R^6=R^7$=OAc, $R^1=R^4=R^5=R^8$=H) and 3,4,6,7 ($R^3=R^4=R^6=R^7$=OAc, $R^1=R^2=R^5=R^8$=H) tetrahydroxyxanthone tetraacetate	[62]
		35	1,3,5,6-tetrahydroxyxanthone $R^1=R^3=R^5=R^6$=OH, $R^2=R^4=R^7=R^8$=H	
5	Antiviral	22	Mangiferin (xanthone glucoside)	[63]
		54	Mangostin (R=CH3) Gamma mangostin (R=H)	[64]
6	Antioxidant		Garcinia indica extract G. Mangostana extract G. Kola extract G. Atroviridis crude extract	[65-68]
		36,37	2,3,6,8-tetrahydroxy-1-methylxanthone $R^2=R^3=R^6=R^8$=OH, $R^4=R^5=R^7$=H, R^1=Me and 3,6,8-trihydroxy-1-methylxanthone $R^3=R^6=R^8$=OH, $R^2=R^4=R^5=R^7$=H R^1=Me	[69]
7	Antifungal		Garcinia indica extract or G. atroviridis crude extract	[65,68]
		38	1,7-dihydroxy-4-methoxyxanthone ($R^1=R^7$=OH, $R^2=R^3=R^5=R^6=R^8$=H, R^4=OMe)	[70]
		39	1,7-dihydroxy-3,5,6-trimethoxyxanthone ($R^1=R^7$=OH, $R^3=R^5=R^6$=OMe, $R^2=R^4=R^8$=H	
8	Antiasthmatic	40	7-methylsulfinylxanthone-2-carboxylic Acid (R^7=SOMe R^2=COOX (X=H or Na), $R^1=R^3=R^4=R^5=R^6=R^8$=H)	[71]
		41	7-(methylthio) xanthone-2-carboxylic acid (R^7=SMe, R^2=COOX (X=H or Na), $R^1=R^3=R^4=R^5=R^6=R^8$=H)	
9	Analgesic		Mangifera extract	[74]
10	Antitumoral		Garcinia atroviridis extract	[68]
11	Anticancer	42	(a) Oxygenated xanthones ($R^2=R^4=R^5=R^6=R^7=R^8$=OH/Me/OMe/CHO)	[75]
		55,56	Pyranoxanthenone (R=$CONHCH_2CH_2NR'R'$ or $CH_2NHCH_2CH_2NR'R'$	[76]
		57	DMXXA (Dimethylxanthone-4- acetic acid)	[77]
12	Anti-inflammatory		(a) Garcinia mangostana extract (b) G. Kola extract (c) Vimang (aqueous extract of Mangifera indica)	[66,67,72,74]
		43-50	(a)1,3-dihydroxyxanthone($R_1=R_3$=OH) (b)3,5-dihydroxyxanthone($R_3=R_5$=OH) (c)1,6-dihydroxyxanthone($R_1=R_6$=OH) (d)1,3,7-trihydroxyanthone($R_1=R_3=R_7$=OH) (e)1,3,8-trihydroxyanthone($R_1=R_3=R_8$=OH) (f)1,3,5,6-terahydroxyxanthone($R_1=R_3=R_5=R_6$=OH) (g)2,3,6,7-terahydroxyxanthone($R_2=R_3=R_6=R_7$=OH) (h) 3,4,5,6-terahydroxyxanthone ($R_3=R_3=R_5=R_6$=OH)	[73]

From Table 1, it is evident that xanthones can be synthesized using various solvents under harsh reaction conditions. Most of the solvents employed for the preparation of xanthone are not environmentally, and the catalysts used for xanthones synthesis are not ecofriendly. Most effective method is the one which is carried out under solvent-free and catalyst-free conditions at room temperature or in microwave (for compounds 11, 12, and 14).

Table 3, for synthesis of benzoxanthone, shows that they can be prepared by employing a number of solvents and also under neat conditions by making use of variety of acidic catalysts under different reaction conditions such as heat, microwave, ultrasound, and visible radiations. However, use of microwave, ultrasound and visible radiations is preferred to carry out reaction they are considered as green methodology.

Table 3 summarizes a list of almost all the literature reported biological properties of xanthones and their derivatives. These compounds are used for the treatment of a number of diseases such as diabetes, cancer, malaria and also the diseases caused by herpes virus, bacteria, and fungi. Extracts of plants containing xanthone and their analogs are also employed for curing allergic, inflammatory, cardiotonic, convulsant, mutagenic, analgesic, ulcergenic, etc., activities. Due to their remarkable pharmacological and biological activities, it has now become an essential part of chemistry to study their synthesis.

CONCLUSION

This review summarizes not only various synthetic routes for the synthesis of xanthones and benzoxanthones but also the pharmaceutical and biological significance of these compounds in different area have been highlighted in this review.

AUTHORS CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

Declared none.

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