· Reviews ·

Advances in Isolation and Synthesis of Xanthone Derivatives

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Abstract: Xanthone and its derivatives occupy a large part of the family of natural polyphenolic compounds with various biological and pharmacological activities. In recent years (from 2006 to 2011), it was reported that 127 xanthones were discovered from plants and fungi using various modern separation methods including silica gel/polyamide column chromatography, HPLC, high-speed counter-current chromatography, high-performance centrifugal partition chromatography, etc. Since total synthesis and structure modification for xanthone and its derivatives have been given attention worldwide, we introduced the synthetic methods of xanthone skeletons as well. Unfortunately, to date, there are still weaknesses in current methods of separation and synthesis, which need to be improved. This review, to a certain extent, provides necessary foundation for the further research and development of medicines containing xanthone and its derivatives.

Key words: derivative; HPLC; isolation; synthesis; xanthones
DOI: 10.3969/j.issn.1674-6384.2012.02.003

Introduction

Xanthones are natural polyphenolic compounds with a simple three-ring skeleton, which mainly exist in the plants of Gentianaceae, Moraceae, Guttiferae, Polygalaceae, and Leguminosae, or fungi as well as lichen. It is well known that xanthones have thousands of derivatives, mainly substituted by hydroxyl, methoxyl, and prenyl, etc. They have remarkable biological and medicinal activities, including anti-bacterial, antiviral, anti-oxidative, anti-inflammatory, antihypertensive, antithrombotic, anticancer, cytotoxic, coagulant, and monoamine oxidase (MAO) inhibitor activities (Wang, Liu, and Zhang, 2010). Due to the unique chemical structures and good pharmacological activities, researchers inclined to isolate or synthesize xanthone derivatives as novel drug candidates. After Vieira (2005) reviewed xanthones discovered from 2000 to 2004, we focused on them in isolation and synthesis during 2006—2011.

New xanthones and their derivatives

Over the past five years, more than 100 xanthones were isolated from plants or fungi. Xanthone derivatives mainly include simple oxygenated xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, and miscellaneousness. Most of them were hydroxylated xanthones with prenyl or geranyl. The new xanthones and their corresponding sources are presented in Table 1 and only structures elucidated are shown in Fig. 1.

Isolation of xanthones

Xanthone and its derivatives were isolated from plants mainly through solvent extraction and various column chromatographies. The main chromatographic separation methods are reviewed as follows.

Column chromatography (CC)

The methanol or ethanol extracts of the dry plants were concentrated in reduced pressure and low temperature. Extracted by medium polar solvents (e.g. ethyl acetate and *n*-butanol, etc), the extract was subjected to polyamide or silica gel column chromatography directly, gradually eluted with polar solvents

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Received: June 7, 2011; Revised: June 12, 2011; Accepted: Janurary 19, 2012

Table 1 New xanthones isolated from plants or fungi during 2006－2011

No.	Compounds	Sources	References
1	artomandin	*Artocarpus kemando* (Moraceae)	Ee *et al*, 2011
2	pyranocycloartobiloxanthone A	*Artocarpus obtusus*	Hashim *et al*, 2010
3	dihydroartoindonesianin C		
4	pyranocycloartobiloxanthone B	*A. obtusus*	Hashim *et al*, 2012
5	calopolyanic acid	*Calophyllum polyanthum*	Wang *et al*, 2010
6	isocalopolyanic acid		
7	isorecedensic acid		
8	caloxanthone O	*C. inophyllum*	Dai *et al*, 2010
9	caloxanthone P		
10	1,3,5-trihydroxy-2-(1,1-dimethylallyl)xanthone		Li *et al*, 2009
11	inophinone		Mah *et al*, 2011
12	caloxanthone Q		Wei *et al*, 2011
13	nodusuxanthone	*C. nodusum* (Guttiferae)	Nasir *et al*, 2011
14	trapezifolixanthone A		
15	soulattrin	*C. soulattri*	Mah *et al*, 2011
16	1,8-dihydroxy-3,5-dimethoxyxanthone	*Comastoma pedunlulatum*	Tang *et al*, 2011
17	1-*O*-[2-(4′-hydroxy-3′,5′-dimethoxy-*E*-cinnamoyl)]-β-*D*-xylopyranosyl-(1-6)-β-*D*-glucopyranoside		
18	1,5,8-trihydroxy-3,6,7-trimethoxyxanthone	*Centaurium spicatum*	El-Shanawany *et al*, 2011
19	1,3,8-trihydroxy-2,4-dimethoxyxanthone	*Cratoxylum arborescen*	Reutrakul *et al*, 2006
20	1,7-dihydroxy-2,8-dimethoxyxanthone		
21	6-hydroxy-3,7-dimethoxy-8-(3-methylbut-2-enyl)-6′,6′-dimethyl-5′-hydroxy-4′,5′-dihydropyrano(2′,3′:1,2) xanthone	*C. cochinchinense*	Jin *et al*, 2009
22	6-hydroxy-3,7-dimethoxy-8-(2-oxo-3-methylbut-3-enyl)-6′,6′-dimethyl-5′-hydroxy-4′,5′-dihydropyrano(2′,3′:1,2) xanthone		
23	1,3,7-trihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-4-(3-methylbut-2-enyl)- xanthone		Nguyen *et al*, 2011
24	8-hydroxy-1,2,3-trimethoxyxanthone		
25	3-*O*-methylmangostenone D		
26	pruniflorosides A	*C. formosum* ssp *pruniflorum*	Duan *et al*, 2011
27	pruniflorosides B		
28	pruniflorone S		
29-31	neriifolone A－C	*C. Sumatranum* ssp. *neriifolium*	Nuangnaowarat, Phupong, and Isaka, 2010
32-34	cochinxanthone A－C	*C. cochinchinense*	Laphookhieo *et al*, 2008
35-36	pruniflorone K, L	*C. formosum* ssp. *pruniflorum*	Boonnak *et al*, 2009
37-39	pruniflorone M－O		
40	3-methoxy-5′-demethoxycadensin G		
41	1,6,7-trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone	*Cudrania fruticosa*	Liang *et al*, 2007
42	3,6,7-trihydroxy-1-methoxyxanthone		
43-46	cudratricusxanthones J－M	*C. tricuspidata*	Hwang *et al*, 2007
47	costatin	*Garcinia costata* (Guttiferae)	Nuangnaowarat *et al*, 2010
48-52	cowaxanthones A－E	*G. cowa*	Kanda *et al*, 2006
53	cowaxanthones F		Kanda, Nongporn, and Ampai, 2009
54-55	afzeliixanthones A, B	*G. afzelii*	Kamdem *et al*, 2006
56	oxy-guttiferones K	*G. cambogia*	Masullo *et al*, 2008
57-59	oxy-guttiferones M, K2, and I,		Masullo *et al*, 2010
60	1,5,6-trihydroxy-3-methoxy-4-(3-hydroxyl-3-methylbutyl)xanthone	*G. cowa*	Shen and Yang, 2006
61	1,5-dihydroxy-3-methoxy-6′,6′-dimethyl-2*H*-pyrano(2′,3′:6,7)-4-(3-methylbut-2-enyl)xanthone		

(To be continued)

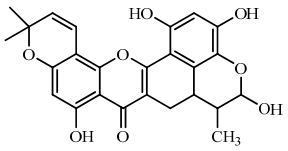
(Continued Table 1)

No.	Compounds	Sources	References
62	gamboketanol	*G. hanburyi*	Tao *et al*, 2010
63	gambogefic acid A		
64	gambogellic acid A		
65	7-methoxydesoxymorellin		Reutrakul *et al*, 2007
66	2-isoprenylforbesione		
67	8,8a-epoxymorellic acid		
68	1,5,6-trihydroxy-6′,6′-dimethyl-2*H*-pyrano(2′,3′:3,4)-2-(3-methylbut-2-enyl)xanthone	*G. lancilimba*	Yang *et al*, 2007
69	1,6,7-trihydroxy-6′,6″-dimethyl-2*H*-pyrano(2′,3′:3,2)-4-(3-methylbut-2-enyl)xanthone		
70	1,3,6-trihydroxy-2,5-bis(3-methylbut-2-enyl)-6′,6′-dimethyl-4′,5′-dihydropyrano[2′,3′:7,8]xanthone	*G. mangostana*	Zhao *et al*, 2010
71	3-hydroxy-6-methoxy-5′-isopropyl-4′,5′-dihydrofuro[2′,3′:7,8]-6,6-dimethyl-4,5-dihydropyrano[2,3:1,2]xanthone		Zhao *et al*, 2012
72	1,6-dihydroxy-7-methoxy-8-(3-methylbut-3-enyl)-6′,6′-dimethyl-4′,5′-dihydropyrano[2′3′:3,2]xanthone		
73-75	garcimangosxanthone A－C		Yang *et al*, 2010
76-77	garcimangosxanthones D, E		Zhou *et al*, 2011
78-80	mangostenones C－E		Suksamrarn *et al*, 2006
81	1,6-dihydroxy-5-methoxy-6,6-dimethylpyrano[2′,3′:2,3]-xanthone	*G. nitida*	Ee *et al*, 2011
82-83	oblongixanthones A, C	*G. oblongifolia*	Huang *et al*, 2009
84	6-*O*-methylcowanin	*G. oliveri*	Ha *et al*, 2009
85	oliverixanthone		
86	4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone	*G. penangiana*	Jabit *et al*, 2007
87	penangianaxanthone		
88-91	staudtiixanthones A－D	*G. staudtii*	Ngoupayo, Tabopda, and Ali, 2009
92	1,4,6-trihydroxy-5-methoxyxanthone	*G. xanthochymus*	Zhong *et al*, 2008
93	1,2,5-trihydroxy-6-methoxyxanthone		
94	1,2,7-trihydroxy-4-(1,1-dimethylallyl) xanthone		
95-99	garcinexanthones A－E		Chen *et al*, 2008
100	garcinexanthone F		Chen *et al*, 2011
101	bigarcinenone B		
102	corymbiferin 3-*O*-β-*D*-glucopyranoside,	*Gentianella amarella* ssp. a*cuta*	Urbain *et al*, 2008
103	swertiabisxanthone-I-8′-*O*-β-*D*-glucopyranoside		
104	1,5-dihydroxy-2,3,4-trimethoxyxanthone	*Halenia elliptica*	Sun, Sun, and Yu, 2011
105	1,3,5-trihydroxy-6,7-[2′-(1-methylethenyl)-dihydrofurano]-xanthone	*Hypericum ascyron*	Hashida, Tanaka, and Takaishi, 2007
106	1,3,5-trihydroxy-6,7-[2′-(1-hydroxy-1-methylethyl)-dihydrofurano]-xanthone		
107	1,3,5-trihydroxy-6-*O*-prenyl-xanthone		
108	4,6-dihydroxy-2,3-dimethoxyxanthone	*H. chinense*	Tanak and Takaishi, 2007
109	2,6-dihydroxy-3,4-dimethoxyxanthone		
110	6-hydroxy-2,3,4-trimethoxyxanthone		
111	3,6-dihydroxy-1,2-dimethoxyxanthone		
112	4,7-dihydroxy-2,3-dimethoxyxanthone		
113	3,7-dihydroxy-2,4-dimethoxyxanthone		
114-117	biyouxanthones A－D		Tanaka *et al*, 2010
118	hyperielliptone HF	*H. geminiflorum*	Lin *et al*, 2011
119-120	hypericorin A, B	*H. oblongifolium*	Ali *et al*, 2011
121-122	hypericumxanthone A, B	*H. sampsonii*	Xin *et al*, 2010

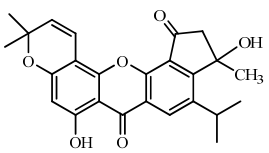
(To be continued)

(Continued Table 1)

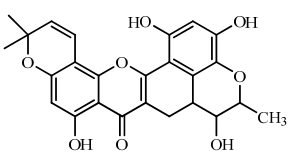
No.	Compounds	Sources	References
123	sampsone C	*H. sampsonii*	Xin *et al*, 2011
124-127	butyraxanthones A—D	*Pentadesma butyracea*	Zelefack *et al*, 2009
128	pentadexanthone		Lenta *et al*, 2011
129	3,6-dihydroxy-1,2,7-trimethoxyxanthone	*Polygala crotalarioides.*	Hua *et al,* 2006
130	1,3,6-trihydroxy-2,7,8-trimethoxyxanthone		
131	3,6-dihydroxy-1,2,7,8-tetramethoxyxanthone		
132-133	polyhongkongenoxanthones A, B	*P. hongkongensis*	Wu *et al*, 2011
134	1,3-dihydroxy-5,6,7-trimethoxyxanthone	*P. sibirica* var. *megalopha*	Wan *et al*, 2008
135	3,7-dihydroxy-1,2-dimethoxyxanthone	*P. japonica*	Fu, Zhang, and Chen, 2006
136	1,2,7-trihydroxy-3-methoxyxanthone		
137	1,3-dihydroxy-2,5,6,7-tetramethoxyxanthone		Xue *et al*, 2009
138	3-hydroxy-1,2,5,6,7-pentamethoxyxanthone		
139	3,8-dihydroxy-1,2,6-trimethoxyxanthone		
140	1,5,6-trihydroxy-3-methoxy-7-geranylxanthone	*Rheedia acuminata*	Marti *et al*, 2010
141	2,3-dihydroxy-7-methylxanthone	*Rhus coriaria*	Singh, Ali, and Akhtar, 2011
142	2,3,6-trihydroxy-7-hydroxymethylene xanthone-1-carboxylic acid		
143	2-methoxy-4-hydroxy-7-methyl-3-*O*-β-*D*-glucopyranosyl xanthone-1,8-dicarboxylic acid		
144	2-hydroxy-7-hydroxymethylene xanthone-1,8-dicarboxylic acid 3-*O*-β-*D*-glucopyranosyl -(2′→3″)-3″-*O*-stigmast-5-ene		
145	1,7-dihydroxy-2-methoxyxanthone	*Securidaca inappendiculata*	Kang, and Xu, 2008
146	1,2, 5-trihydroxy-6,8-dimethoxy-9H-xanthen-9-one		Kang, Li, and Song, 2008
147	1,5-dihydroxy-2,6,8-trimethoxy-9H-xanthen-9-one		
148	globulixanthone F	*Symphonia globulifera*	Mkounga *et al,* 2009
149-150	angustins A, B	*Swertia angustifolia*	Zhu et al, 2012
151	1-*O*-β-*D*-glucopyranosyl-3,5,6-trimethoxy-xanthone	*S. mussotii*	Gao *et al*, 2011
152	1-*O*-[β-*D*-xylopyranosyl-(1→6)-β-*D*-glucopyranosyl]-3,5,6-trimethoxy-xanthone		
153	1,7-dihydroxy-2,3,8-trimethoxyxanthone		Zhang *et al*, 2011
154-155	puniceasides A, B	*S. punicea*	Du *et al*, 2010
156-157	termicalcicolanone A, B	*Madagascar rain forest*	Cao *et al*, 2007
158-159	aspergillusones A, B	*Aspergillus sydowii*	Trisuwan *et al*, 2011
160	15-chlorotajixanthone hydrate	*Emericella sp.*	Fiqueroa *et al*, 2009
161	14-methoxytajixanthone		
162-163	acremoxanthone C, D	*Hypocreales* (MSX 17022)	Ayers *et al*, 2012
164	8-hydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylic acid methyl ether	*mangrove fungi* (strain No. K38 and E33)	Li *et al*, 2011
165	8-(methoxycarbonyl)-1-hydroxy-9-oxo-9H-xanthene-3-carboxylic acid	*Penicillium*	Shao *et al*, 2008
166	dimethyl 8-methoxy-9-oxo-9H-xanthene-1,6-dicarboxylate	sp. (ZZF 32#)	
167	1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methyl-9H-xanthen-9-one	*Phoma* sp. SK_3RW_1M	Pan *et al*, 2010
168	1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-methyl-9H-xanthen-9-one		
169	7-hydroxy-3-(hydroxymethyl)-1-methoxy-9H-xanthen-9-one	*Xylaria* sp. FRR 5657	Davis and Pierens, 2006
170	2,5-dihydroxy-8-methoxy-6-methyl-9-oxo-9H-xanthene-1-carboxylic acid		
171	1,3,6,8-tetrahydroxy-2,5-dimethoxyxanthone	*Securidaca longepedunculata*	Marion, Rakuambo, and Hussein, 2008
172	1,6,8-trihydroxy-2,3,4,7-tetramethoxyxanthone		
173	crotalarioides xanthone F	*Polygala crotalarioides*	Zhou, Zhou, and Hua, 2011



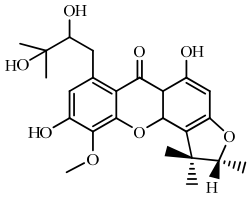
pyranocycloartobiloxanthone A (**2**)



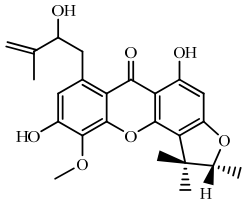
dihydroartoindonesianin C (**3**)



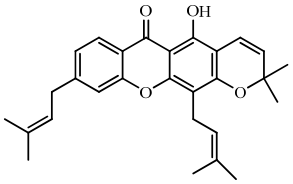
pyranocycloartobiloxanthone B (**4**)



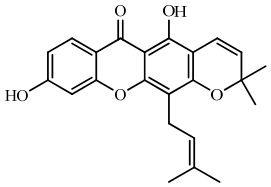
caloxanthone O (**8**)



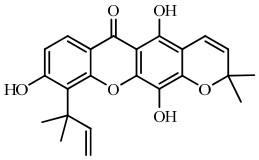
caloxanthone P (**9**)



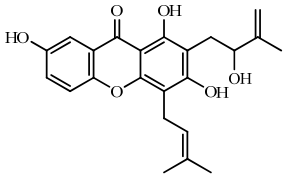
nodusuxanthone C (**13**)



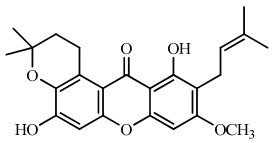
trapezifolixanthone A (**14**)



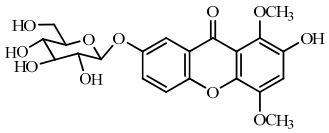
soulattrin O (**15**)



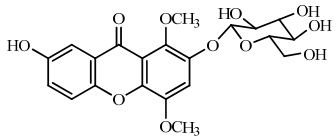
1,3,7-trihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-4-(3-methylbut-2-enyl)-xanthone (**23**)



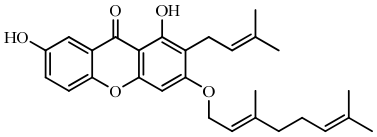
3-*O*-methylmangostenone D (**25**)



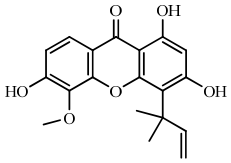
pruniflorosides A (**26**)



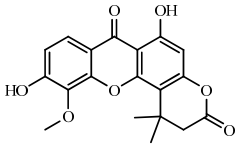
pruniflorosides B (**27**)



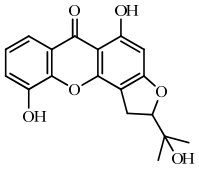
pruniflorone S (**28**)



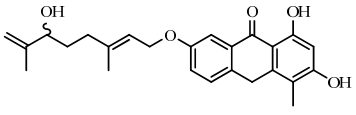
pneriifolone A (**29**)



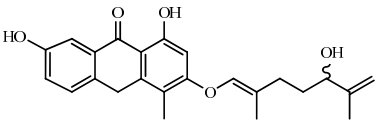
neriifolone B (**30**)



neriifolone C (**31**)



cochinxanthone A (**32**)



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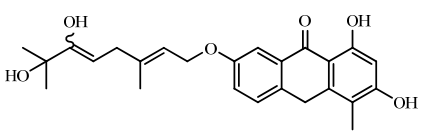
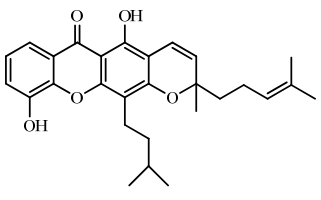
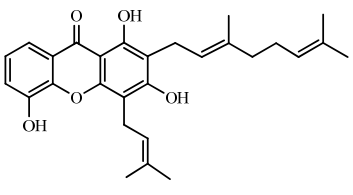


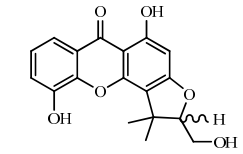
cochinxanthone C (**34**)



pruniflorone K (**35**)



pruniflorone L (**36**)



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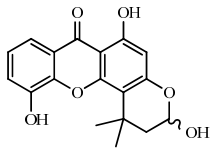

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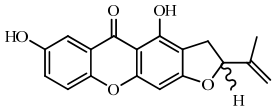

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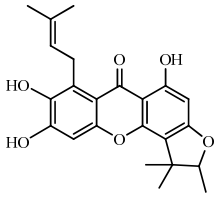

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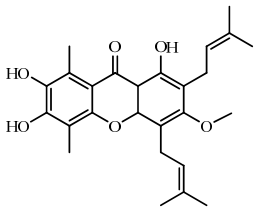

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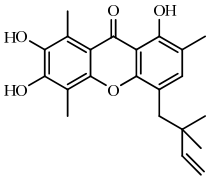

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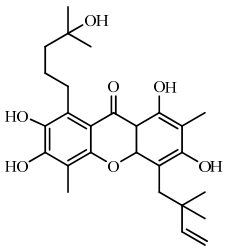

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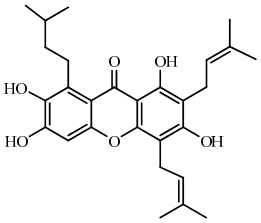

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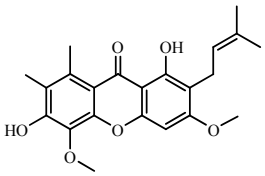

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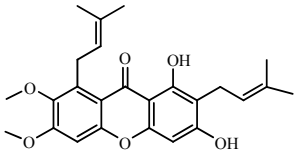

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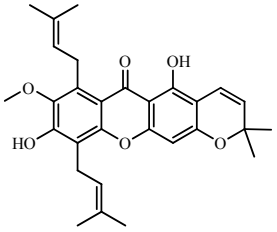

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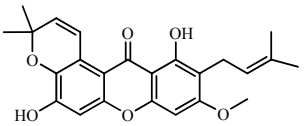

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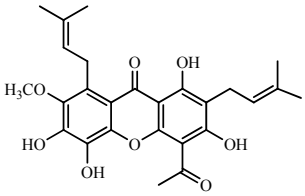

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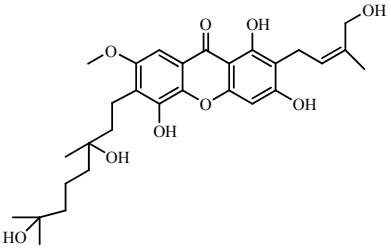

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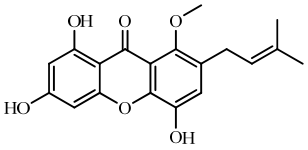

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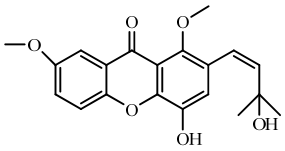

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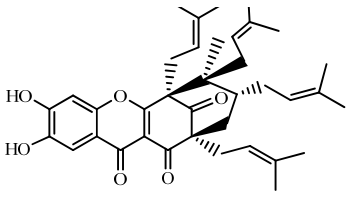
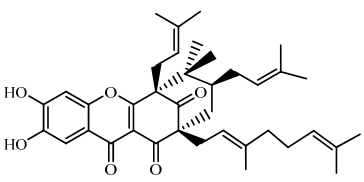


oxy-guttiferones K (**56**)



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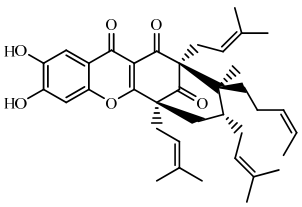

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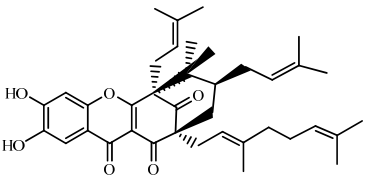

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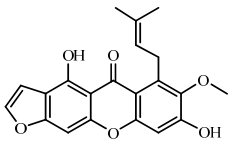

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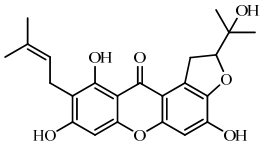

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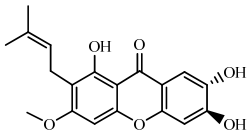

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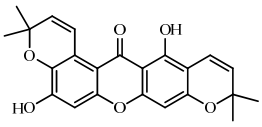

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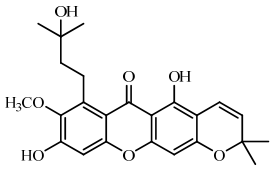

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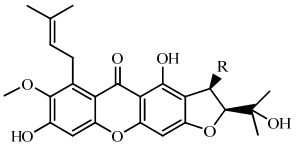
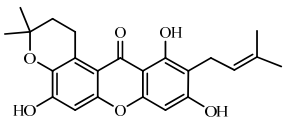


mangostenones C (**78**)



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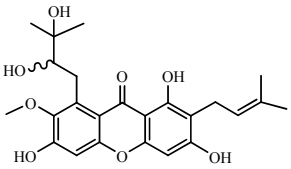

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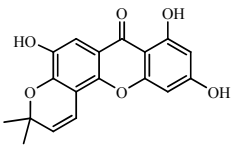

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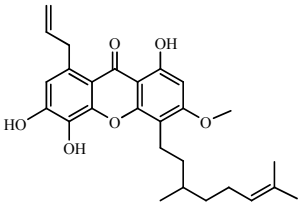

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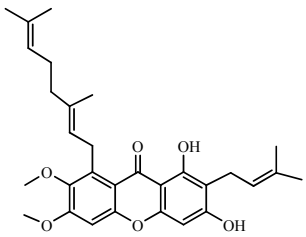
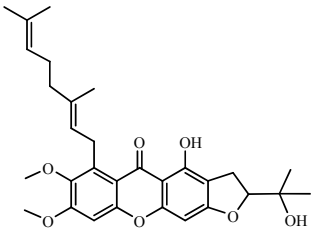


6-*O*-methylcowanin (**84**)



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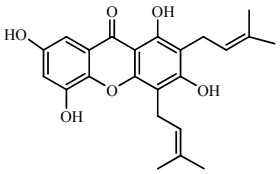

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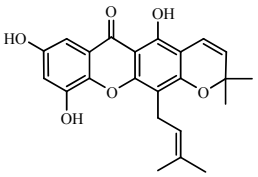

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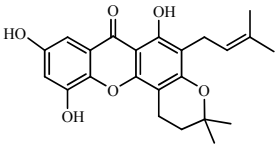

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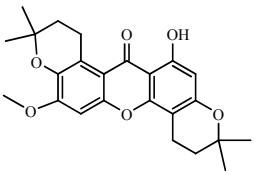

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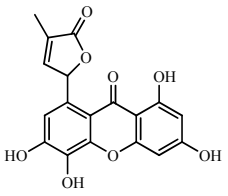
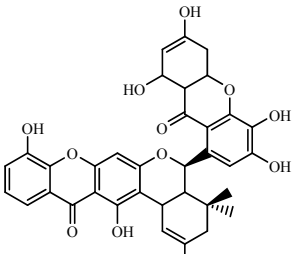
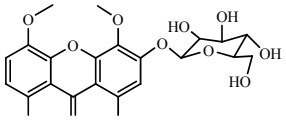


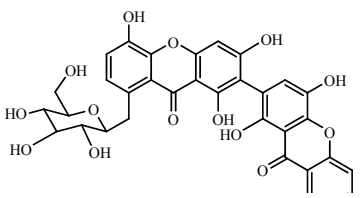
garcinexanthone F (**100**)



bigarcinenone B (**101**)



corymbiferin 3-*O*-β-*D*-glucopyranoside (**102**)



swertiabisxanthone-I-8′-*O*-β-*D*-glucopyranoside (**103**)

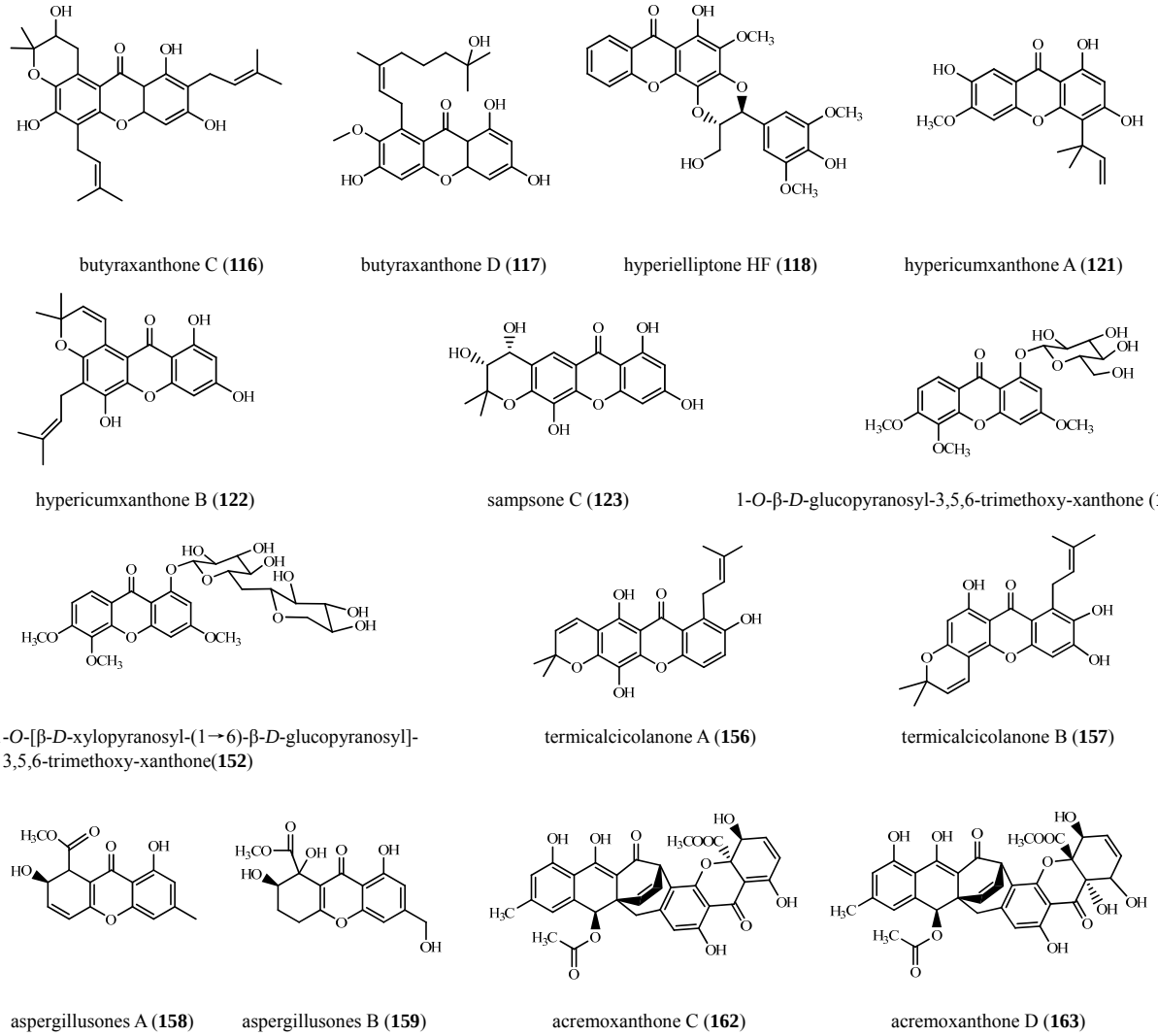


Fig. 1 Structures of xanthone derivatives

such as water-methanol, water-ethanol, and chloroform-methanol gradient elution. Based on TLC detection, the similar eluents were combined and concentrated, then purified by column chromatography on repeated polyamide silica gel, or Sephadex LH-20, until the pure substance was obtained.

High performance liquid chromatography (HPLC)

HPLC is used in the separation and analysis of xanthone and its derivatives. Most of xanthone glycosides could be isolated mainly using cyanosilane-bonded silica gel column with methanol-water or water-acetonitrile gradient eluants, while xanthone aglycones are isolated on an RP C_{18} column, using aqueous phosphoric acid and acetonitrile as mobile phase. For example, Ahmed *et al* (2003) isolated xanthone derivatives from the marine fungus by HPLC. Mycelia and medium were diluted with water and homogenized using a blender. The resulted mixture was exhaustively extracted with ethyl ether to yield a great amount of viscous brownish black oil. The extract was fractionated by columns, gradiently eluted from water to methanol, and different fractions have different compounds. A part of fractions were subjected to HPLC, eluted with water-methanol.

High-speed counter current chromatography (HSCCC)

The coil column of HSCCC was entirely filled with the upper phase of the solvent system at a high speed, while the lower phase was pumped into the column at a low speed. After the mobile phase front emerged and hydrodynamic equilibrium was established in the

column, sample solution containing crude extract was injected through the injector. The effluent from the outlet of the column was continuously monitored by detector and collected (Han, Yu, and Lai, 2010). This method was used to isolate mangiferin and neomangiferin from the extract of *Anemarrhena asphodeloides* Bunge (Zhou *et al*, 2007).

High performance centrifugal partition chromatography (HPCPC)

Xanthones could be isolated with high purity in one step using HPCPC with solvent system composed of petroleum ether, ethyl acetate, methanol, and water. Shan and Zhang (2010) have isolated α-mangostins and γ-mangostins from mangosteen pericarp in one run.

Synthesis of xanthones

The Grover, Shah, and Shah reaction, the cyclodehydration of 2,2′-dihydroxybenzophenones, and electrophilic cycloacylation of 2-aryloxybenzonic acids are the most popular methods to synthesize xanthones. Since Sousa and Pinto (2005) have reviewed synthetic methods of xanthones, here we just introduce the new reactions to synthesize xanthones from 2006 to 2010. Different strategies of molecular modification resulted in diversity of xanthone derivatives. The following sections were presented according to variant catalysts.

Heterogeneous catalyzing

The present approach offered several advantages, such as shortening reaction time, high yields, low cost, and mild reaction conditions. Furthermore, the catalyst could be recovered easily and reused without the loss of catalytic activity.

Multi-component reactions

HBF_4/SiO_2 was used as an efficient, green, and inexpensive catalytic system for synthesizing 12-aryl or 12-alkyl-8,9,10,12-tetrahydro-11H-benzo [a] xanthen-11-one derivatives via an one-pot three-component reaction of aldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds. The reactions proceeded rapidly at 80 ℃ under solvent-free conditions (Fig. 2) (Zhang, Wang, and Ren, 2009).

Using perchloric acid adsorbed on silica gel ($HClO_4$-SiO_2) as heterogeneous catalyst, a procedure for the one-pot multicomponent coupling of arylaldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds under solvent-free conditions has been developed (Fig. 3) (Mo and Chen, 2010).

Multi-component reactions give rise to production

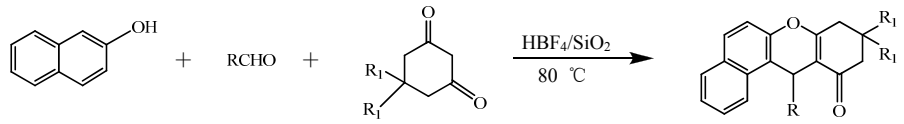


Fig. 2 Heterogeneous catalyst reaction

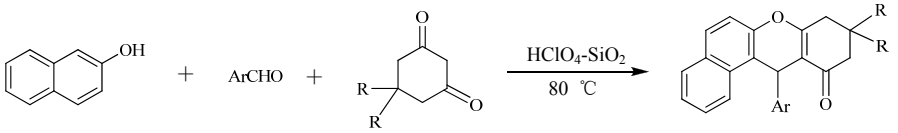


Fig. 3 One-pot multicomponent heterogeneous catalyst reaction

of complicated molecules in only one process. It is a very fast, efficient, and time-saving manner. In addition, solvent-free conditions mean a simpler synthesis, energy and solvent-saving process with low hazards and toxicity.

Montmorillonite K10 clay heterogeneous catalysis

Microwave-assisted organic synthesis has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yields and selectivity. Prenylation of the xanthone building blocks with prenyl bromide was set in alkaline medium, using microwave irradiation, and then the oxyprenylated xanthones and diprenylated by-products were produced. Microwave irradiation of oxyprenylated xanthones will produce three new Claisen rearranged products and dihydrofuranoxanthones described previously. Furthermore, dihydropyranoxanthones could also be prepared by a one-pot synthesis, using montmorillonite K10 clay as a heterogeneous catalyst combined with microwave irradiation (Fig. 4) (Raquel *et al*, 2009).

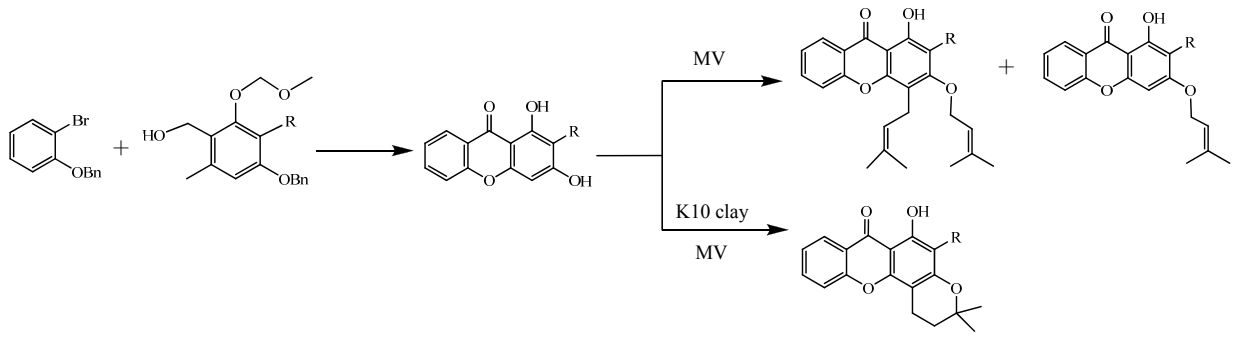


Fig. 4 Montmorillonite K10 clay heterogeneous catalyzing

Much attention has been paid to clays, which could act as solid catalysts for a wide range of organic reactions and a subgroup of clays. Montmorillonite is particularly useful in the reaction, for it proceeds not only under mild conditions but also with selectivity, high yields, and short reaction time. Since this catalyst could be easily separated from the reaction mixture and be regenerated, the purification procedures are usually simple.

Organic catalyzed synthesis

Organic matters were used as catalyst in these reactions. Different catalysts produced different outcomes.

Organocatalyzed reactions

Organocatalysts, called small organic molecules, play a great role in the rapidly growing areas of organic synthesis, e.g. 4-dimethylaminopyridine (DMAP) and 4-picoline. Organocatalyzed reactions, most typically happened between chromones and acetylenedicarboxylates, give the birth of xanthone derivatives. The product of the reactions depends on the nature of both the chromone substituents and the basicity of the organocatalyst (Terzidis *et al*, 2011). DMAP, hetero Diels-Alder reactions, and Friedel-Crafts reactions were all used in this method in one pot (Fig. 5).

Friedländer synthesis

Friedländer synthesis was mainly used for the synthesis of xanthone glycoside derivatives. Xanthone glycoside derivatives were obtained at higher temperature and prolonged in the reaction time, which may be attributed to the less reactive nature of 2-amino-3-chromonecarboxaldehyde with β-*C*-glycosylic ketones (Fig. 6). Antimicrobial studies of sugar-heterocyclic xanthone derivatives show excellent activity against different microbes (Subbiah *et al*, 2010).

Proline triflate catalyzation

Ammonium triflate has been used as a mild and efficient catalyst in organic synthesis. To optimize the formation of xanthone derivatives, further optimization of the reaction using different catalysts was undertaken.

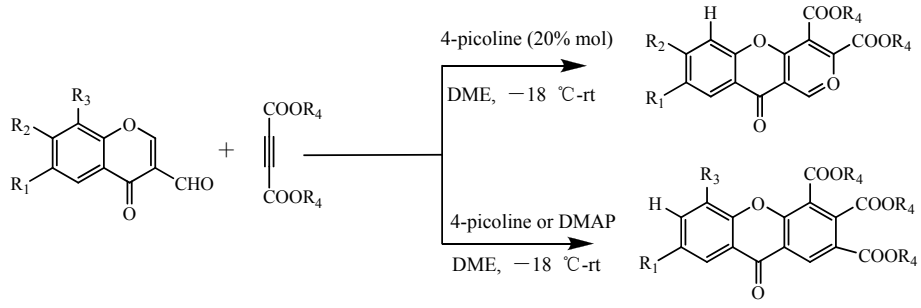


Fig. 5 Organocatalyzed reactions

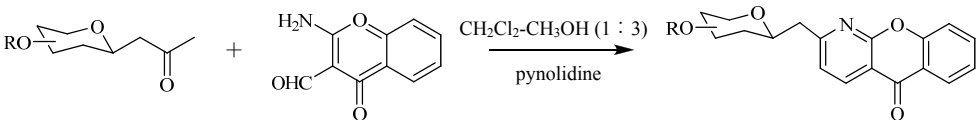


Fig. 6 Friedländer synthesis

The proline triflate has higher activity and selectivity in this reaction. Catalyzed by proline triflate, benzoxanthenes were obtained in high yields from the condensation of naphthols, aldehydes, and 1,3-dicarbonyl compounds in water. A possible mechanism of this reaction is proposed in Fig. 7 (Li, Lu, and Suo, 2010).

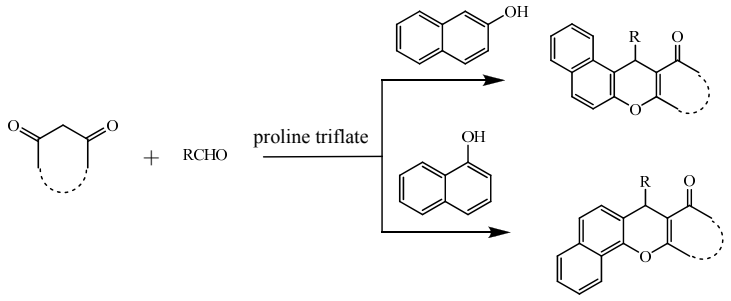


Fig. 7 Proline triflate catalyze

Metal catalyzation

The metal catalysts employed in synthesizing xanthone derivatives are usually expensive metals, such as Ru, Rh, Pt, Pd, and Au, etc. In recent years, the development of sustainable, environmentally friendly, and low-cost C−C bond-forming methods attracted much attention in synthesizing xanthones. And the effective and economical catalysts were carried out such as ceric ammonium nitrate (CAN), $FeCl_3$, $AlCl_3$, Cu, $TiCl_4$, and so on. In these catalyzing reactions, most of the metal catalysts could be recovered and reutilized.

CAN-mediated oxidations

Many xanthone derivatives were synthesized by CAN-mediated oxidations (Myron *et al*, 2010), for example, the reaction of (2,4,5-trimethoxyphenyl) (2-hydroxyphenyl) methanone with CAN furnishing the xanthone, 2,3-dimethoxy-9H-xanthen-9-one.

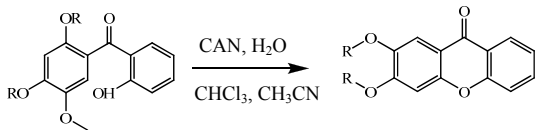


Fig. 8 CAN-mediated oxidation reaction

Cascade benzylation-cyclization

Using $FeCl_3$ as the catalyst under microwave irradiation conditions, benzyl acetates, benzyl bromides, and benzyl carbonates as suitable benzylating reagents, the reactions benzylation-cyclization of phenols proceed to prepare both 9-aryl and 9-alkyl xanthone derivatives in high yield (Fig. 9) (Xu *et al*, 2010).

Copper-catalyzed reaction

Using copper as catalyst, intramolecular *O*-arylation of 2-halobenzophenones will produce valuable xanthone framework under the aqueous environment (Fig. 10) (Barbero *et al*, 2009).

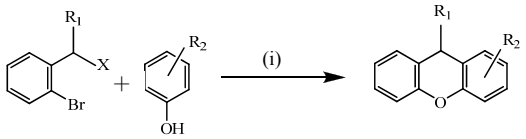


Fig. 9 Cascade benzylation-cyclization

(i) Cat, $FeCl_3$, MV, 50 ℃, 10 min or base, MV, 130 ℃, 10 min

R_1, R_2=Alkyl, Aryl, X=OAc, Br, OCO_2Et

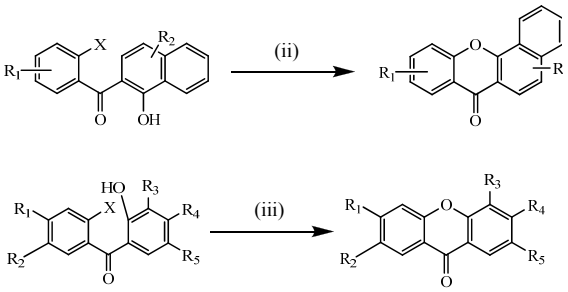


Fig. 10 Copper-catalyzed reaction

(ii) Aqueous layer of Cu extracted from organic layer three times

(iii) 3.5 equiv, TMEDA, Cu (Cat.), H_2O, 120 ℃

This is a safe and efficient protocol for the copper-catalyzed intramolecular *O*-arylation of 2-halobenzophenones on water. The aqueous solution containing copper catalyst could be recovered and reutilized.

Cyclocondensations

Functionalized 2-aryloxybenzoates were prepared by formal [3+3] cyclocondensations of 3-aryloxy-1-silyloxy-1,3-butadienes with 3-silyloxy-2-en-1-ones. The reaction of 2-aryloxybenzoates with concentrated sulfuric acid resulted in the formation of xanthones (Fig. 11) (Mross *et al*, 2009).

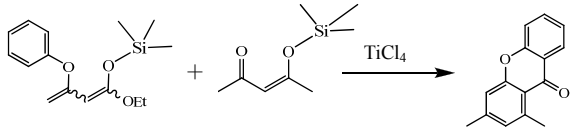


Fig. 11 Cyclocondensations

Diels-Alder reaction

The compounds underwent cyclization with the aluminum chloride and formed 2-hydroxyxanthone carboxylic acids, and the yield was about 80%—86% (Fig. 12). The structure of the xanthonecarboxylic acids was confirmed by converting them upon decarboxylation into the known hydroxyxanthones (Oleinik *et al*, 2007).

Uncatalyzed reaction

Still some other synthesis methods were conducted without catalysts. The methods mentioned below provide an efficient approach for synthesizing xanthone skeleton.

One-pot tandem reaction

Tandem reactions provide an efficient way to generate molecular complexity from readily accessible intermediates. This tandem process involved multiple reactions, such as Michael addition-elimination, cyclization, 1,2-addition, and elimination reactions (Fig. 13). This process requires no transition metal catalyst (Zhao *et al*, 2009).

Liu *et al* (2009) developed the base-promoted one-pot tandem reaction from 3-(1-alkynyl)chromones with various acetonitriles to prepare functionalized amino-substituted xanthones under microwave irradiation for 10 min (Fig. 14).

The sequence involved multiple reactions, including Michael addition, cyclization, and 1,2-addition, and without a transition metal catalyst. The methods mentioned above provide an efficient approach for the diversified amino-substituted xanthone skeleton.

Photoacylation

The key step in synthetic route involved a photoacylation using 2,6-dimethoxybenzaldehyde and benzoquinone. Reacting with potassium hydroxide in boiling methanol for 12 h, compound **1** will produce xanthone **2**. Xanthone **2** was demethylated by boron tribromide, and then euxanthone **3** was prepared. The yield was about 56% (Fig. 15) (Kraus *et al*, 2009).

Discussion

Xanthones showed some important pharmacological activities, such as potent cytotoxic activity against several tumor cell lines and antibiotic activities. It is extremely necessary to study the synthetic methodology of xanthones. Our aim is to provide a comprehensive

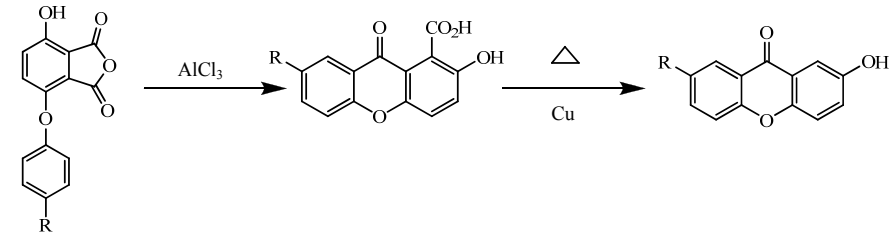


Fig. 12 Diels-Alder reaction

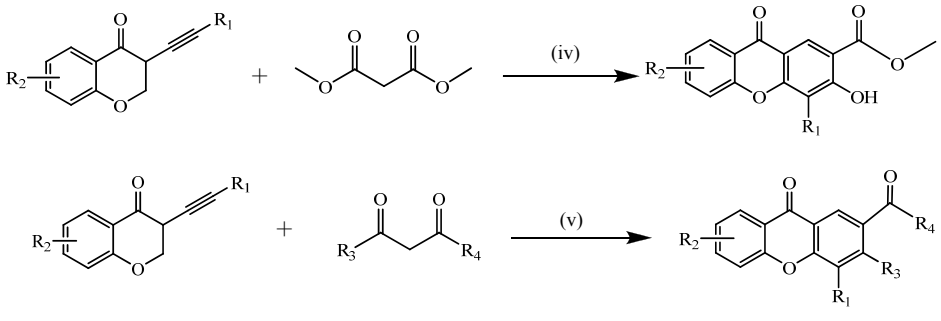


Fig. 13 One-pot tandem reaction

(iv): DBU/DMF, 45 ℃, R^3=alkoxyl; (v): DBU/DMF, RT, R^3=alkyl or aryl

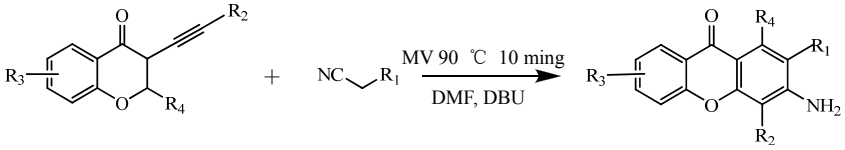
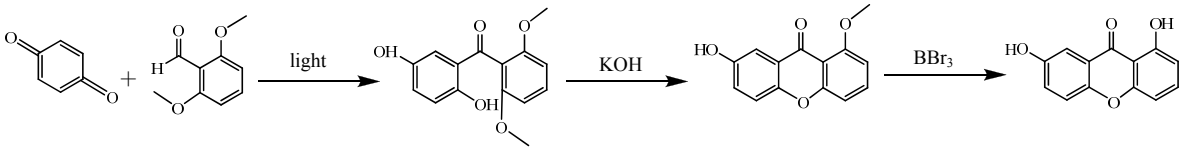


Fig. 14 One-pot tandem reaction



1 **2** **3**

Fig. 15 Photoacylation

overview of xanthones and their derivatives to date, and to display the current studies. So far, the researchers mainly focused on the extraction and synthesis of xanthones, as well as their pharmacological activities. To meet the needs of medical science and life, more and more attention is paid to xanthones with distinctive function. The activities of xanthones are also dramatically altered by the substituents and their positions. Many researchers have done systematic and deep researches on xanthones. Heterogeneous and organic catalyzed reactions are the novel synthetic methods, which are attracting widespread interests. In these methods we have seen the appearance of xanthone derivatives with high yield. On the other hand, to find the recoverable and cost-efficient metal catalysts, synthesizing is a hot area currently in metal catalyzing reactions.

Many progresses in isolation and synthesis of xanthone derivatives had been made, however in which there were some defects. Xanthone derivatives could be obtained from plants and fungus, but the source was still limited. And the methods to isolate and synthesize xanthones were not convenient. Although the synthetic methods with better yield have emerged at present, such as building blocks, Diels-Alder reaction, and heterogeneous catalysts, etc the yield of some xanthone derivatives synthesized were still not high enough. Using xanthones and their derivatives as the materials, more diversified xanthones could be synthesized on the base of core ring, and the activities of xanthones could be altered by the substituents and their positions. But, researches still failed to synthesize xanthones precursor in high yield. Therefore, more researches on the isolation and synthesis of xanthones as well as their derivatives are still needed with a promising potential in the future.

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