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REVIEW ARTICLE NUMBER 43

XANTHONES FROM GUTTIFERAE

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Key Word Index—Guttiferae, xanthones; benzophenones, chemotaxonomy; biosynthesis.

Abstract—Since the last review in 1980, over eighty new xanthones have been isolated from the Guttiferae. These are listed with reference to structure elucidation and synthesis. The distribution of xanthones is examined in relation to the taxonomic divisions of the Guttiferae Xanthone biosynthesis is discussed in the light of new biosynthetic results and the various pharmacological properties of xanthones are summarized

INTRODUCTION

As the quest for new natural products continues, it becomes increasingly clear that xanthones are very restricted in occurrence. The majority of natural xanthones have been found in just two families of higher plants—Guttiferae and Gentianaceae [1] Simple, oxygenated xanthones occur in both families and are generally more highly oxygenated in the Gentianaceae. Prenylated xanthones are widely distributed in the Guttiferae but not known in the Gentianaceae, and whereas *O*-glycosylxanthones are common in the Gentianaceae [2], only two have been reported from the Guttiferae

Xanthones occur sporadically throughout the remainder of the plant kingdom. The Moraceae contain several Guttiferae-type prenylated xanthones and the Polygalacae, simple hydroxy- and alkoxyxanthones [1]. *C*-Glucosylxanthones have been found in certain ferns, and in over one hundred species of higher plants [3], and fungi produce xanthones with substitution patterns characteristic of their acetate derivation [4].

Several earlier reviews have summarized the literature on xanthones [5–10], with emphasis on biosynthesis [7, 8], synthesis [6, 9] or phylogeny [10]. In the last review in 1980, Sultanbawa listed 95 xanthones from the Guttiferae [1]. Since then there has been a steady stream of reports in which more than 80 new xanthones have been characterized and many known xanthones re-isolated from *ca* 60 species of Guttiferae.

The aim of this review is to summarize the recent work on xanthones from the Guttiferae as a supplement to the 1980 review. The combined data will then be studied from a chemotaxonomic point of view to determine if any patterns of xanthone distribution exist within the family, and the implications of new biosynthetic results will be discussed. Structure elucidation, synthesis, and pharmacology will also be covered.

DISTRIBUTION

The family Guttiferae numbers over 1000 species, mainly confined to the tropics—the major exception being the genus *Hypericum*, which occurs widely in temperate regions. According to Engler's Syllabus [11] the family comprises six subfamilies (Table 1). The subfamily Hypericoideae has been treated by some taxonomists (notably Hutchinson [12]) as a separate family, but the recent surge of interest in the chemistry of this group has led to the isolation of several prenylated xanthones, supporting its inclusion in the Guttiferae. The only related family in which xanthones have been found is the Bonnetiaceae, which, in keeping with Thorn's recent classification [13], is included in the Kielmeyeroideae subfamily in Table 1.

Xanthones or the related benzophenones have been found in all the major and several minor genera of the Guttiferae. The approximate number of species [14], and the number that have been found to contain xanthones is given for each genus (Table 1). It appears from the number of chemically investigated species (for three of the larger genera), that a large proportion of the species contains xanthones. A species–xanthone index is included as an appendix

Simple oxygenated xanthones

The symmetrical nature of the xanthone nucleus, coupled with its mixed biogenetic origin in higher plants, necessitates that the carbons be numbered according to a biosynthetic convention. Carbons 1–4 are assigned to the acetate-derived ring A, (often characterized by 1,3-dioxygenation) and carbons 5–8 to the shikimate-derived ring B (e.g. 1,3,7,8-tetrahydroxy rather than 1,2,6,8). All higher plant xanthones appear to have 5- and/or 7-oxygenation [8] and with this assumption, only xanthones with 2,5(or 4,7)-oxygenation have alternative names. In cases where only ring B is oxygenated the lowest numbers are used except in the biosynthetic discussion [e.g. 2- rather than 7-hydroxyxanthone (**1**)].

Structural assignments are based mainly on ^{1}H NMR and UV spectroscopy. Shifts of ring or side-chain protons due to acetylation or alkylation of adjacent hydroxyls and changes in the UV spectrum on addition of the usual shift reagents, are especially useful in determining substitution patterns. Confirmation of assignment may be

Table 1 The family Guttiferae

SUB-FAMILY	TRIBE	GENUS	NO. OF SPECIES*
Kielmeyeroideae	Kielmeyereae	*Kielmeyera*	20/9(10)
		Mahurea	8/1
	Caraipeae	*Caraipa*	20/4
		Haploclathra	4/3
	(Bonnetiaceae)	*Bonnetia*	18/1
		Archytaea	2/1
Calophylloideae	Calophylleae	*Calophyllum*	110/21(32)
		Mesua(inc.Kayea)	40/5
		Mammea(inc. Ochrocarpus)	50/5
Clusioideae	Clusieae	*Clusia*	145/4
		Tovomita	60/6
	Garcinieae	*Allanblackia*	8/1
		Garcinia	400/29(38)
		Pentaphalangium	7/1
		Rheedia	45/4
Moronoboideae		*Moronobea*	7/1
		Pentadesma	4/1
		Platonia	1-2/1
		Symphonia	20/1
Lorostemonoideae		*Lorostemon*	3/2
Hypericoideae	Cratoxyleae	*Cratoxylum*	6/2
	Hypericeae	*Hypericum*	400/18
	Vismieae	*Harungana*	1/1
		Psorospermum	40/1
		Vismia	35/3

*Approx no. of species [14]/no of species in which xanthones and closely related compounds have been found Numbers in parentheses refer to number of species chemically investigated

obtained by derivatization (sometimes not possible due to the scarcity of material), although often synthesis is necessary

The synthesis of xanthones has been reviewed [15, 9]. The standard method is the Grover, Shah and Shah condensation between an *ortho*-oxygenated benzoic acid and a reactive phenol in the presence of phosphorous oxychloride and zinc chloride [16] A recent variation of this method uses methylsulphonic acid and phosphorous pentoxide in place of the above reagents [17]. Alternatively, benzophenones, prepared by Friedel–Crafts acylation [18], may be converted to xanthones by dehydrative or oxidative cyclization. Two other methods have appeared recently. The nucleophilic addition of salicylic acid derivatives to *p*-benzoquinones has been used to prepare a series of 1,4(or 5,8)-dihydroxyxanthones [19], and 3-hydroxyxanthone has been prepared in 50% yield by a cycloaddition reaction between a diene and a benzopyranone [20]

Mono-oxygenated xanthones. Two mono-oxygenated xanthones (**1** and **2**, Table 2) have recently been isolated from seven species 4-Hydroxyxanthone also occurs in Guttiferae. These compounds are now known to occur in eight genera from three subfamilies. Notable is their absence from Clusioideae (> 50 species investigated).

Dioxygenated xanthones The majority of the recently isolated dioxygenated xanthones (Table 3) are from species of the Hypericoideae, reflecting the recent interest in this subfamily Dioxygenated xanthones are however, also common in species of *Calophyllum*, *Mammea* and *Mesua* and found in all subfamilies 1,7-Dihydroxyxanthone (**4**), has now been isolated from 40 species of Guttiferae The 2,5-dioxygenation pattern of xanthones **5** and **10** is new from nature

Table 2 Mono-oxygenated xanthones

2-Hydroxyxanthone(1)	2-Methoxyxanthone(2)
Calophyllum zeylanicum Kosterm.[21]	Caraipa psidifolia Ducke [29]
Hypericum balearicum L. [22]	Hypericum mysorense [27]
Hypericum canariensis L. [24]	Vismia guaramirangae Huber [28]
Hypericum ericoides L. [25]	
Hypericum mysorense [26,27]	
Vismia guaramirangae Huber [28]	

*First reported occurrence in nature
†First reported occurrence in Guttiferae.

Table 3 Dioxygenated xanthones

1,5-Dihydroxyxanthone(3)	1-Hydroxy-7-methoxyxanthone(7)
Calophyllum zeylanicum Kosterm.[21]	Bonnetia stricta (Nees) Ness Mart. [31]
Garcinia xanthochymus Hook. f. [30]	Haploclathra paniculata (Mart.) Benth. [33]
1,7-Dihydroxyxanthone(4)(Euxanthone)	Haploclathra verticillata Ducke[29]
Bonnetia stricta (Nees) Ness & Mart.[31]	Hypericum mysorense [26]
Calophyllum zeylanicum Kosterm.[21]	Mahurea tomentosa Ducke [29]
Garcinia indica Choisy [50]	Vismia guaramirangae Huber [28]
Garcinia xanthochymus Hook. f.[30]	**2-Hydroxy-1-methoxyxanthone(8)**
Haploclathra verticillata Ducke[29]	Vismia guaramirangae Huber [28]
Hypericum balearicum L. [22]	**2-Hydroxy-3-methoxyxanthone(9)**
Hypericum canariensis L. [24]	*Hypericum mysorense [26]
Hypericum ericoides L. [25]	**2-Hydroxy-5-methoxyxanthone(10)**
Hypericum mysorense [26,27]]	*Hypericum androsaemum L. [34]
Mahurea tomentosa Ducke [29]	Hypericum canariensis L. [24]
Vismia guaramirangae Huber [28]	**3-Hydroxy-2-methoxyxanthone(11)**
2,5-Dihydroxyxanthone(5)	Hypericum androsaemum L. [34]
*Hypericum canariensis L. [24]	Hypericum balearicum L. [22]
2,3-Dimethoxyxanthone(6)	Psorospermum febrifugum Sprach [35]
*Hypericum mysorense [27,32]	Vismia guaramirangae Huber [28]

Trioxygenated xanthones. Twenty trioxygenated xanthones, of which nine are new natural products, are shown in Table 4. Novel oxygenation patterns are 1,5,8- (**17**), 1,4,7- (**19**) and 2,3,5- (**27**), and xanthones **33** and **34** are the first trimethoxyxanthones from the Guttiferae. Two 1,2,5-trioxygenated xanthones (**12** and **14**) have been

Table 4 Trioxygenated xanthones

1,2-Dihydroxy-5-methoxyxanthone(12)

*Garcina xanthochymus Hook f [30]

1,3-Dihydroxy-2-methoxyxanthone(13)

*Vismia guaramirangae Huber [28]

1,5-Dihydroxy-2-methoxyxanthone(14)

*Garcinia xanthochymus Hook. f [30]

1,5-Dihydroxy-3-methoxyxanthone(15)

Garcinia xanthochymus Hook f.[30]

Haploclathra lieantha (Benth) Benth [36]

Haploclathra paniculata (Mart) Benth [33]

Vismia guaramirangae Huber [28]

1,5-Dihydroxy-6-methoxyxanthone(16)

*Tovomita excelsa Andrade-Lima et G Mariz [37]

1,5-Dihydroxy-8-methoxyxanthone(17)

*Vismia guaramirangae Huber [28]

1,6-Dihydroxy-5-methoxyxanthone(18) (Buchanoxanthone)

Calophyllum zeylanicum Kosterm [21]

Tovomita excelsa Andrade-Lima et G Mariz [37]

1,7-Dihydroxy-4-methoxyxanthone(19)

*Vismia guaramirangae Huber [28]

1,7-Dihydroxy-6-methoxyxanthone(20)

*Tovomita excelsa Andrade-Lima et G Mariz [37]

1,7-Dihydroxy-8-methoxyxanthone(21)

Bonnetia stricta (Nees) Ness & Mart [31]

Haploclathra lieantha (Benth) Benth. [36]

Haploclathra paniculata (Mart) Benth. [33]

5,6-Dihydroxy-1-methoxyxanthone(22)

*Tovomita excelsa Andrade-Lima et G.Mariz [37]

1-Hydroxy-3,5-dimethoxyxanthone(23)

Haploclathra paniculata (Mart) Benth [33]

1-Hydroxy-6,7-dimethoxyxanthone(24)

Hypericum mysorense [26]

1-Hydroxy-7,8-dimethoxyxanthone(25)

Haploclathra paniculata (Mart) Benth [33]

2-Hydroxy-3,4-dimethoxyxanthone(26)

Hypericum canariensis L [24]

Hypericum sampsonii Hance [39]

Kielmeyera rubiflora Camb [40]

*Kielmeyera speciosa St.Hill [40]

3-Hydroxy-2,5-dimethoxyxanthone(27)

*Hypericum androsaemum L [34]

4-Hydroxy-2,3-dimethoxyxanthone(28)

Caraipa grandiflora Mart. [29]

5-Hydroxy-1,3-dimethoxyxanthone(29)

Haploclathra paniculata (Mart.) Benth. [33]

1,3,5-Trihydroxyxanthone(30)

Garcinia xanthochymus Hook. f [30]

1,3,7-Trihydroxyxanthone(31) (Gentisein)

Haploclathra paniculata (Mart.) Benth [33]

Hypericum degenii Bornm. [41]

1,6,7-Trihydroxyxanthone(32)

Platonia insignis Mart [29]

1,3,5-Trimethoxyxanthone(33)

†Haploclathra paniculata (Mart.) Benth [33]

2,3,4-Trimethoxyxanthone(34)

*Hypericum ericoides L [25]

reported from *Garcinia xanthochymus*, but their physical data have not been published.

Three of the four xanthones isolated from the trunk wood of *Tovomita excelsa*, were assigned a 1,5,6-dihydroxymethoxy structure [37]. Two of these (**16**, **18**) were known compounds, whereas the 1-methoxy structure (**22**)

Table 5. Tetra- and pentaoxygenated xanthones

1,3-Dihydroxy-5,6-dimethoxyxanthone (Leiaxanthone) (35)

†*Haploclathra lieantha* (Benth) Benth [36]

1,5-Dihydroxy-6,7-dimethoxyxanthone (36)

Caraipa grandiflora Mart [29]

Caraipa psidifolia Ducke [29]

Caraipa valioi Paula [29]

Tovomita brasiliensis Walp [42]

1,6-Dihydroxy-5,7-dimethoxyxanthone (37)

Hypericum canariensis L [24]

1,7-Dihydroxy-3,8-dimethoxyxanthone (Gentiaculein) (38)

†*Haploclathra lieantha* (Benth) Benth [36]

Haploclathra paniculata (Mart) Benth. [33]

2,5-Dihydroxy-1,6-dimethoxyxanthone (39)

**Garcinia thwaitesii* Pierre [43]

3,7-Dihydroxy-1,8-dimethoxyxanthone (40)

**Haploclathra paniculata* (Mart.) Benth [33]

3,8-Dihydroxy-1,7-dimethoxyxanthone (Isogentiaculein) (41)

†*Haploclathra paniculata* (Mart.) Benth [33]

5,6-Dihydroxy-1,3-dimethoxyxanthone (Ferrxanthone) (42)

Haploclathra lieantha (Benth) Benth. [36]

**Mesua ferrea* L. [23]

2-Hydroxy-5,6,7-trimethoxyxanthone (43)

**Hypericum ericoides* L [25]

3-Hydroxy-1,2,4-trimethoxyxanthone (44)

**Psorospermum febrifugum* Sprach [35]

3-Hydroxy-1,5,6-trimethoxyxanthone (45)

Haploclathra lieantha (Benth) Benth [36]

7-Hydroxy-1,3,8-trimethoxyxanthone (Anthaxanthone) (46)

**Haploclathra lieantha* (Benth) Benth [36]

1,3,5,6-Tetrahydroxyxanthone (47)

Hypericum androsaemum L [34]

1,3,6,7-Tetrahydroxyxanthone (48) (Norathyriol)

Cratoxylum pruniflorum Kurz [130]

Garcinia mangostana L. [16]

Hypericum androsaemum L. [34]

Hypericum aucheri Jaub et Sprach. [47]

1,3,5-Trihydroxy-6-methoxyxanthone (49)

Haploclathra lieantha (Benth) Benth. [36]

1,5,6-Trihydroxy-3-methoxyxanthone (50)

†*Hypericum androsaemum* L. [34]

1,7,8-Trihydroxy-6-methoxyxanthone (51)

**Archytaea multiflora* Benth. [31]

2,4,5-Trihydroxy-1-methoxyxanthone (BR-xanthone-B) (52)

**Garcinia mangostana* L. [83]

3,8-Dihydroxy-1,2,4-trimethoxyxanthone (53)

**Psorospermum febrifugum* Sprach [35]

was new. An unambiguous synthesis of **22** has been completed by the methylation of 1-hydroxy-5,6-dibenzyloxyxanthone followed by debenzylation, and the product shown to be different from the natural compound [38]. 4,5-Dihydroxy-3-methoxyxanthone is suggested as a likely alternative structure

The sodium acetate induced shifts in the UV spectrum of a 2,3,4-hydroxydimethoxyxanthone from *Kielmeyera* species, led to the assignment of the more acidic 3-hydroxy structure. However, the ^{13}C NMR spectrum has indicated that both methoxy groups are di-*ortho*-substituted and that therefore the structure should be 2-Hydroxy-3,4-dimethoxyxanthone (**26**) [40]. Consequently, the structure of a xanthone from *Hypericum canariensis* should also be revised to **26**, as in Table 4.

Ten xanthones have been isolated from the roots of *Vismia quaramirangae* [28] Based mainly on ^1H NMR spectroscopy, one of the three new xanthones was as-

signed the structure of 1,7-dihydroxy-4-methoxyxanthone (**19**), rather than the 2-methoxy alternative that was indicated by a positive Gibbs test. Two *para*-dioxygenated analogues also gave positive Gibbs tests, suggesting that this test is unreliable in certain cases

Tetraoxygenated xanthones The newly isolated tetraoxygenated xanthones are shown in Table 5. In the first investigations of the genus *Haploclathra*, three species have yielded 17 different xanthones [29, 33, 36]. These include four 1,3,5,6- and four 1,3,7,8-tetraoxygenated xanthones, the latter being common in the Gentianaceae Xanthone 35 has been synthesized [44] and shown to be identical to a compound from *Centaurium linarifolium*, but to differ somewhat from the *Haploclathra* xanthone.

Several unusual oxygenation patterns have been found. The stem bark and timber of *Garcinia thwaitesi* yielded 2,5-dihydroxy-1,6-dimethoxyxanthone (**39**), and the structure of 2-hydroxy-5,6,7-trimethoxyxanthone (**43**), isolated from *Hypericum ericoides* [24], has been confirmed by synthesis (Scheme 1) [45] A 1,2,4,5-tetraoxygenated xanthone, BR-xanthone-B (**52**), has been isolated from the fruit of *Garcinia mangostana*.

The inclusion of *Archytaea* (Bonnetiaceae) in the subfamily Kielmeyeroideae is supported by the isolation of a 1,6,7,8-tetraoxygenated xanthone (**51**) from *Archytaea multiflora* [31] This oxygenation pattern is only known in other three species, two of which belong to this subfamily

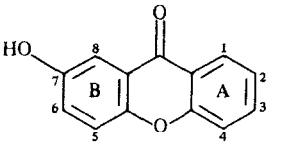
Pentaoxygenated xanthones. These compounds are rare in the Guttiferae but common in the Gentianaceae The new compound, 3,8-dihydroxy-1,2,4-trimethoxyxanthone (**53**, Table 5) is related to **44** from the same plant, and brings the total number known to five

Alkylated xanthones

Alkylated xanthones in Guttiferae are usually mono- or di-C_5-substituted The C_5 group may be 3-methylbut-2-enyl (as in **54**), or less often 1,1-dimethylprop-2-enyl (as in **89**), and these are frequently cyclized with *ortho* hydroxyls giving 2,2-dimethylpyrano (or dihydropyrano), 2,2,3-trimethylfurano (possible artefacts), or rarely 2-isopropenyldihydrofurano compounds Occasionally, hydroxylation or hydration of the side chain occurs C_{10} substituents, in which two prenyl groups are joined together, include geranyl (as in **112**) and lavandulyl (as in **115**)

The oxygenation patterns of alkylated xanthones are less diverse than in the unalkylated compounds Four patterns predominate: 1,3,5-, 1,3,7-, 1,3,5,6-, and 1,3,6,7-Di- and pentaoxygenated compounds are rare.

Mono-C_5-trioxygenated xanthones Fractionation of the cytotoxic ethanol extract of the roots of *Psorospermum febrifugum* led to the isolation of the anti-leukaemic xanthones, psorospermin (**57**, Table 6) and its chlorohydrin (**58**) [51, 52]. Their ready interconversion suggested a possible artefact Tandem mass spectrometry has confirmed that psorospermin is a natural product, while the possibility that **58** is an artefact has not been rigorously excluded [53] The other derivatives (**59–61**), show no anti-leukaemic properties The absolute stereochemistry of psorospermin has been determined as



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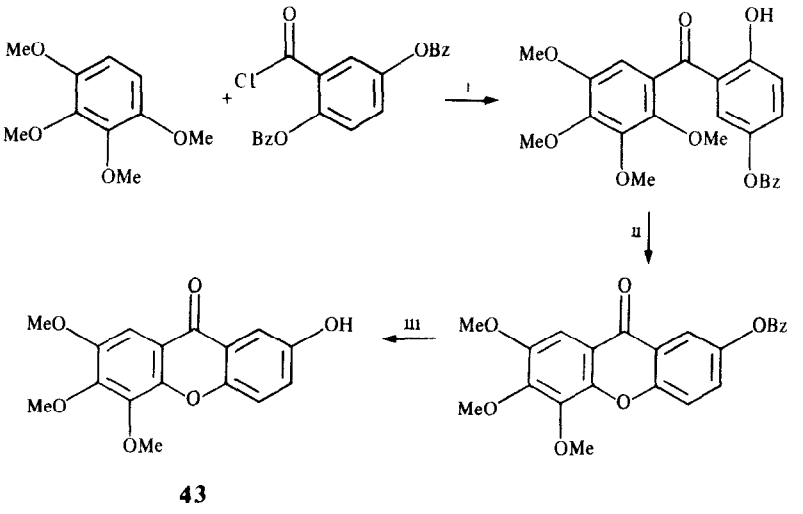
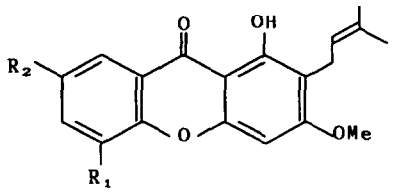


43

Reagents (i) $AlCl_3$ / ether, (ii) Me_4NOH / reflux, (iii) H_2, Pd / C

Scheme 1

Table 6 Mono-C_5-trioxygenated xanthones

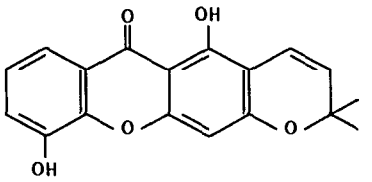


(54) R_1 = OH, R_2 = H

Garcinia mangostana L. [48,49]

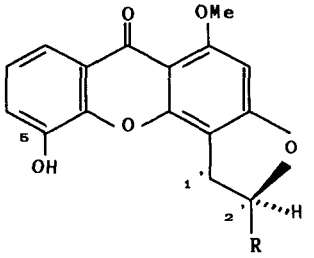
(55) R_1 = H, R_2 = OH

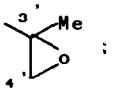
Garcinia mangostana L. [48]

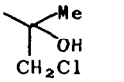


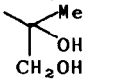
(56) **6-Deoxyjacareubin**

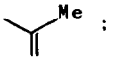
Calophyllum zeylanicum Kosterm.[21]

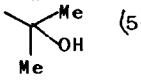


(57) R =  ; **Psorospermin** (2'R,3'R)

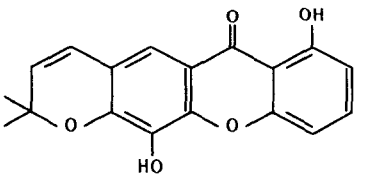
(58) R =  (2'R,3'S)

(59) R =  (2'R,3'R)

(60) R =  ; **3',4'-Deoxypsorospermin**

(61) R =  (5-O-Methyl)

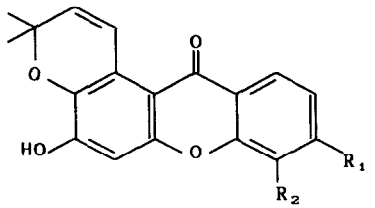
Psorospermum febrifugum Sprach. [51,52,54]



(62) **Rheediachromenoxanthone**

Rheedia brasiliensis (Mart.) Pl. and Tr.[58]

Rheedia gardneriana Pl. and Tr.[59]



(63) R_1 = H, R_2 = OH; **Hypericanarin**

Hypericum canariensis L. [24]

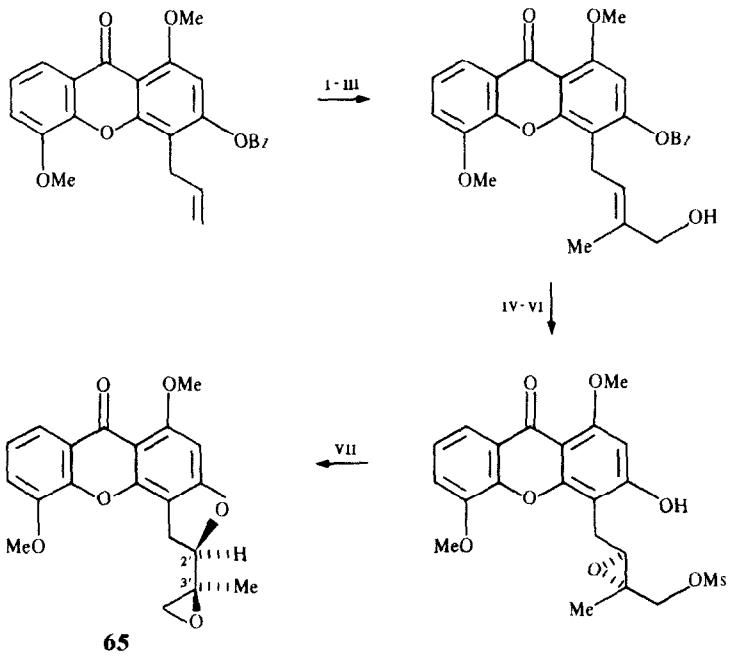
(64) R_1 = OH, R_2 = H; **Hyperxanthone**

Hypericum sampsonii Hance [39]

2'*R*,3'*R* by an ORD, ^{1}H NMR and TLC comparison with analogous epoxides derived from rotenone [54].

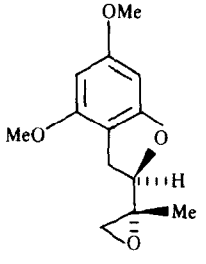
A stereoselective synthesis of 5-methyl-(±)-2'*R*,3'*S*-psorospermin (**65**) has been completed and is shown in part in Scheme 2 [55]. The final step in the synthesis involves two consecutive displacements, producing a racemic mixture of the 2*R*',3'*S* and 2'*S*,3'*R* epoxides (**65**). Progress towards a total synthesis of psorospermin has been made by the enantioselective preparation of the 2'*R*,3'*R*-dihydrobenzofuran (**66**) [56] A synthesis of the 5-methyl-1',2'-dehydro derivative of 3',4'-deoxypsorospermin (**60**) has also been reported [57].

Rheediachromenoxanthone (**62**) and hyperxanthone (**64**) appear to be derived from tetraoxygenated xan-



65

Reagents (I) $OsO_4/NaIO_4$, dioxane / H_2O (II) $Ph_3P{=}C(Me)CO_2Et$, benzene (III) $LiAlH_4$ / THF (IV) MCPBA, CH_2Cl_2 (V) MsCl/py (VI) H_2, Pd/C (VII) KO^tBu



66

Scheme 2

thones by nuclear reduction at the 3- and 1-positions respectively In fact, **64** occurs with the expected precursor, toxyloxanthone B (**82**) in *Hypericum sampsonii* The unusual 4,6,7- (or 2,3,5-?) oxygenation pattern of hypericanarin (**63**) is otherwise only known in **27** from *Hypericum androsaemum*. The structures of **63** and **64** are supported by significantly different physical data

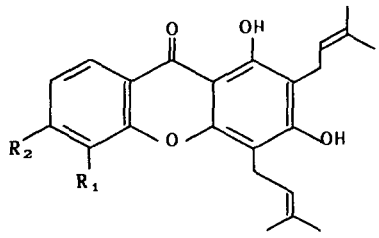
Di-C_5-trioxygenated xanthones Garcinone A from *Garcinia mangostana* was assigned a novel 1,3,6-trihydroxy structure (**68**, Table 7), an oxygenation pattern unknown in the Guttiferae However, the synthetic substance, prepared by the prenylation of 1,3,6-trihydroxyxanthone, showed little similarity with the natural compound [66].

The stem bark of *Garcinia quadrifaria* produces xanthone **69**, which shows a rare prenylation, *para*, rather than *ortho* to a hydroxyl group. 6-Deoxy-γ-mangostin (**70**) has been isolated from the seed arils of *Garcinia mangostana* fruit and is a possible biosynthetic precursor to mangostin (**70**; $R_1 = Me$, $R_2 = OH$), the major metabolite from the same plant (see Biosynthesis).

The stem bark of *Calophyllum walkeri* contains xanthones **74** and **76**–**78** The hydroxymethyl group in thwaitesixanthanol (**77**) was located by mild acetylation Shielding of H-3″ was observed, while H-3′ was unaffected [65]. The 2-isopropenyldihydrofuran group of **78** is otherwise only known (without the hydroxy) in 3′,4′-deoxypsorospermin (**60**) The *cis* configuration of **78** was assigned from the 6 Hz coupling between the 2″ and 3″ protons The 3″ proton was also coupled to H-6 and strongly deshielded, suggesting that it is almost in the same plane as the xanthone nucleus

Mono-C_5-tetrahydroxyxanthones Xanthone **79** (Table 8) is the second 1,3,5,8-tetra-oxygenated xanthone from *G. mangostana*, the other being gartanin (**79**; $R_1 = H$, R_2 = prenyl). This oxidation pattern is otherwise unknown in the Guttiferae but common in the Gentianaceae Three 2-prenyl-3-methoxyxanthones (**54**, **55**, and **79**) have been

Table 7 Di-C_5-trioxygenated xanthones

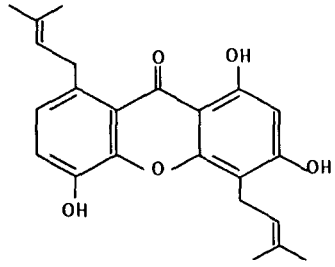


(67) R_1 = OH, R_2 = H, **8-Desoxygartanin**

Rheedia brasiliensis (Mart.) Pl. and Tr [58]
Rheedia gardneriana Pl and Tr [60]

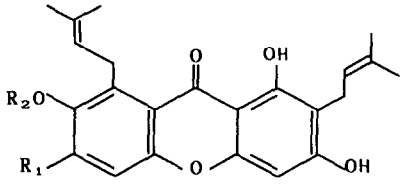
(68) R_1 = H, R_2 = OH; **Garcinone A**

**Garcinia mangostana* L. [61]



(69) **4,8-Di(3-methylbut-2-enyl)-1,3,5-trihydroxyxanthone**

**Garcinia quadrifaria* Baill ex Pierre [62]

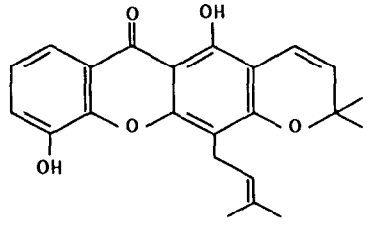


(70) R_1=R_2=H; **6-Deoxy-γ-mangostin**

**Calophyllum thwaitesi* Pl. and Tr [63]
Garcinia mangostana L [49]

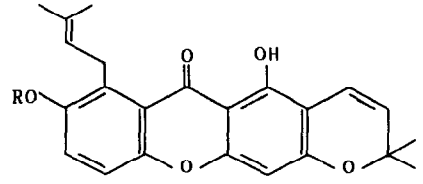
(71) R_1=H, R_2=Me; **Calcocalabaxanthone (6-Deoxymangostin)**

Calophyllum bracteatum Thw. [63]
**Calophyllum calaba* var. *calaba* L [63,64]



(72) **Trapezifolixanthone**

Calophyllum calaba var. *calaba* L [63]

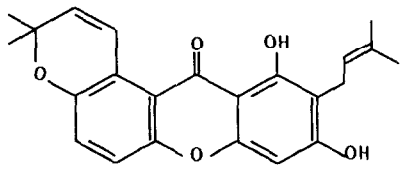


(73) R = Me; **Calabaxanthone**

Calophyllum calaba var. *calaba* L.[64]
Calophyllum zeylanicum Kosterm.[21]
Garcinia mangostana L. [49]

(74) R = H ; **Demethylcalabaxanthone**

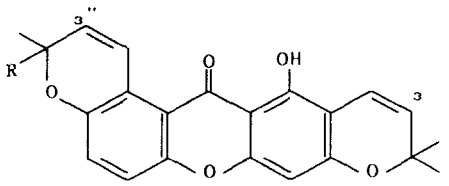
**Calophyllum walkeri* Wight [65]
Garcinia mangostana L. [49]



(75) **Calothwaitesixanthone**

**Calophyllum thwaitesi* Pl.and Tr.[63]

Table 7 *Continued*

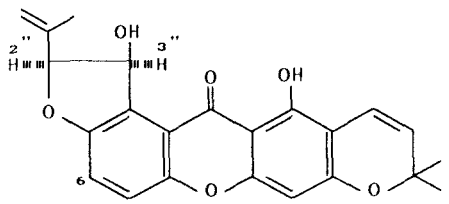


(76) R = Me; **Thwaitesixanthone**

Calophyllum walkeri Wight [65]

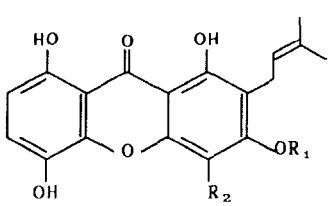
(77) R = CH_2OH, **Thwaitesixanthonol**

Calophyllum walkeri Wight [65]



(78) *Calophyllum walkeri* Wight [65]

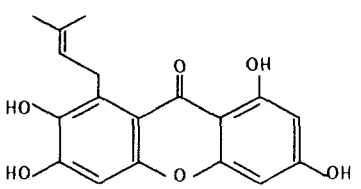
Table 8 Mono-C_5-tetraoxygenated xanthones



(79) R_1 = Me, R_2 = H

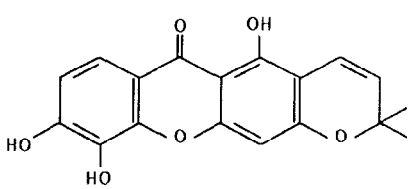
1,5,8-Trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthone

Garcinia mangostana L [67]



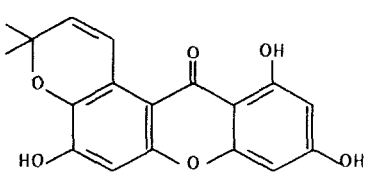
(80) **1,3,6,7-Tetrahydroxy-8-(3-methylbut-2-enyl)xanthone**

Hypericum androsaemum L [34]



(81) **Jacareubin**

Calophyllum zeylanicum Kosterm [21]



(82) **Toxyloxanthone B**

†*Hypericum androsaemum* L [34]

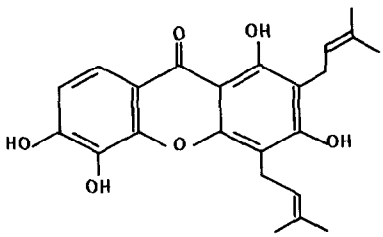
Hypericum sampsonii Hance [39]

found in *Garcinia mangostana* The 3-methoxy group prevents further prenylation in the 4-position, however the presence of a methylating enzyme does not preclude 4-prenylation as is shown by the presence of **67** in the same plant

Toxyloxanthone B (**82**), first found from the Moraceae, has been isolated from *Hypericum androsaemum* together with its probable biogenetic precursor (**80**)

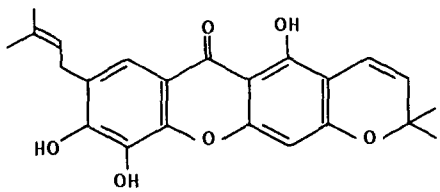
Di-C_5-tetraoxygenated xanthones While the xanthones in this category (Table 9) are more numerous than

Table 9 Di-C_5-tetraoxygenated xanthones



(83) **Xanthone V_{1a}**

*Vismia guineensis (L.) Choisy [68]



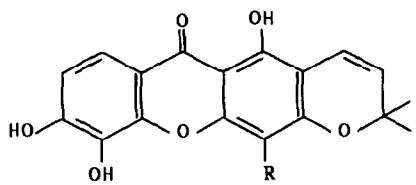
(84) **7-Prenyljacereubin**

*Rheedia gardneriana Pl.and Tr.[60]

(85) R = 3-Methylbut-2-enyl; **Xanthone V_1**

*Vismia guineensis (L.) Choisy [68]

(86) R = 1,1-Dimethylprop-2-enyl;



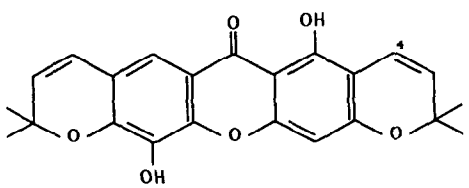
Macluraxanthone

Garcinia ovalifolia Oliv. [69]

†Rheedia benthamiana Pl. and Tr.[70]

Rheedia brasiliensis (Mart.) Pl.and Tr.[58]

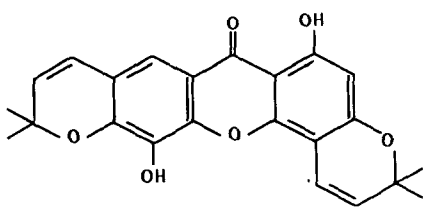
Rheedia gardneriana Pl. and Tr.[59]



(87) **Pyranojacereubin**

Rheedia brasiliensis (Mart.) Pl.and Tr.[58]

*Rheedia gardneriana Pl.and Tr.[60]



(88) **Rheediaxanthone A**

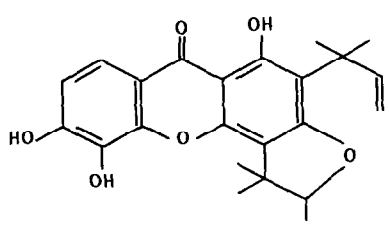
*Garcinia densivenia Engl. [71]

Garcinia staudtii Engl. [62]

Rheedia benthamiana Pl. and Tr. [70]

Rheedia brasiliensis (Mart) Pl. and Tr. [58]

Rheedia gardneriana Pl. and Tr. [59]



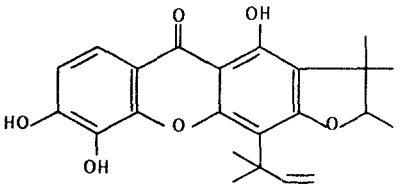
(89) **Rheediaxanthone B**

*Rheedia benthamiana Pl. and Tr. [70]

Rheedia brasiliensis (Mart.) Pl. and Tr. [58]

Rheedia gardneriana Pl and Tr. [59]

Table 9 *Continued*

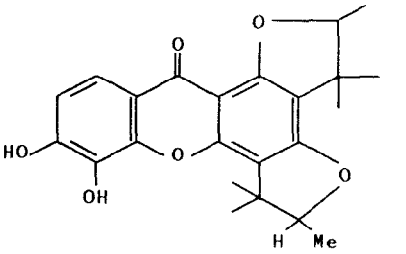


(90) **Isorheediaxanthone B**

Garcinia polyantha Oliv. [72]

Rheedia brasiliensis (Mart.) Pl and Tr.[58]

**Rheedia gardneriana* Pl and Tr. [59]

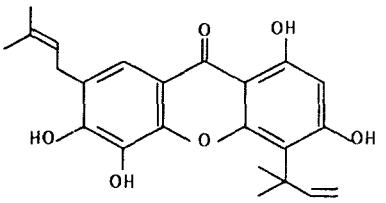


(91) **Rheediaxanthone C**

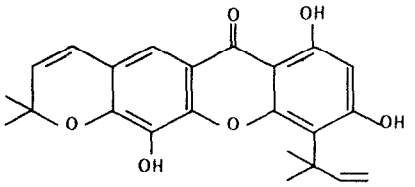
**Rheedia benthamiana* Pl. and Tr [70]

Rheedia brasiliensis (Mart) Pl and Tr. [58]

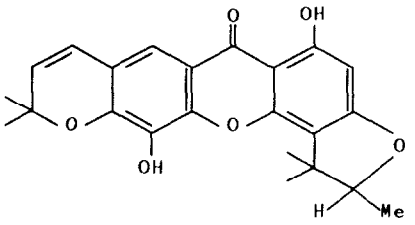
Rheedia gardneriana Pl. and Tr [59]



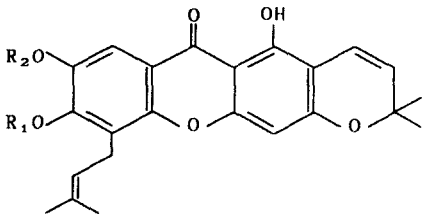
(92) **Rheedia brasiliensis* (Mart.) Pl.and Tr [58]



(93) **Rheedia brasiliensis* (Mart.) Pl.and Tr [58]

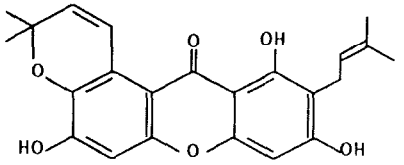


(94) **Rheedia brasiliensis* (Mart) Pl and Tr.[58]



(95) R_1= Me, R_2 = H; **Manglexanthone**

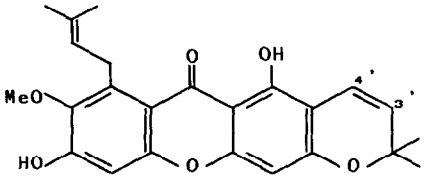
**Tovomita mangle* G Maritz [73]



(96) **Garcinone B**

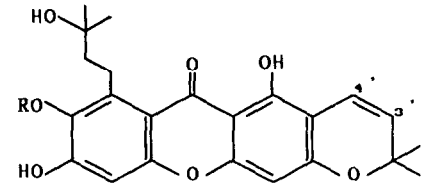
**Garcinia mangostana* L [61,147]

Table 9 *Continued*



(97) *Garcinia mangostana L. [74]

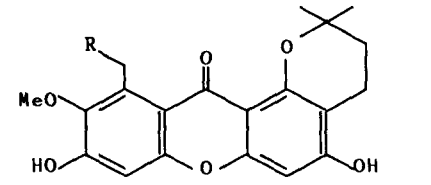
(98) 3',4'-Dihydro 93; **3-Isomangostin**
*Garcinia mangostana L.[49]



(99) R = H; **Garcinone C**
*Garcinia mangostana L. [61]

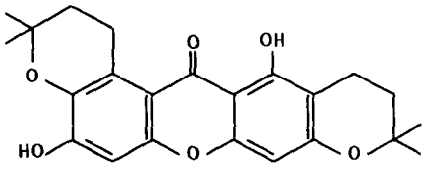
(100) R = Me; **Garcinone D**
*Garcinia mangostana L. [75]

(101) 3',4'-Dihydro 96; **3-Isomangostin Hydrate**
*Garcinia mangostana L. [49]



(102) R = $-C{=}CHMe_2$; **1-Isomangostin**

(103) R = $-CH_2C(OH)Me_2$; **1-Isomangostin Hydrate**
*Garcinia mangostana L. [49]



(104) **BR-xanthone-A**
*Garcinia mangostana L. [83]

the monoprenylated compounds, there is little structural variation This is due in part to the fact that most of these xanthones have been isolated from only a few species of the closely allied genera *Garcinia* and *Rheedia*. Dialkylated xanthones, especially dipyrano compounds, give rise to doubly-charged ions in their mass spectra due to the simultaneous loss of two alkyl fragments [58]. Apart from macluraxanthone (**86**), which is known from a Moraceae species, all the xanthones in Table 9 are new natural products.

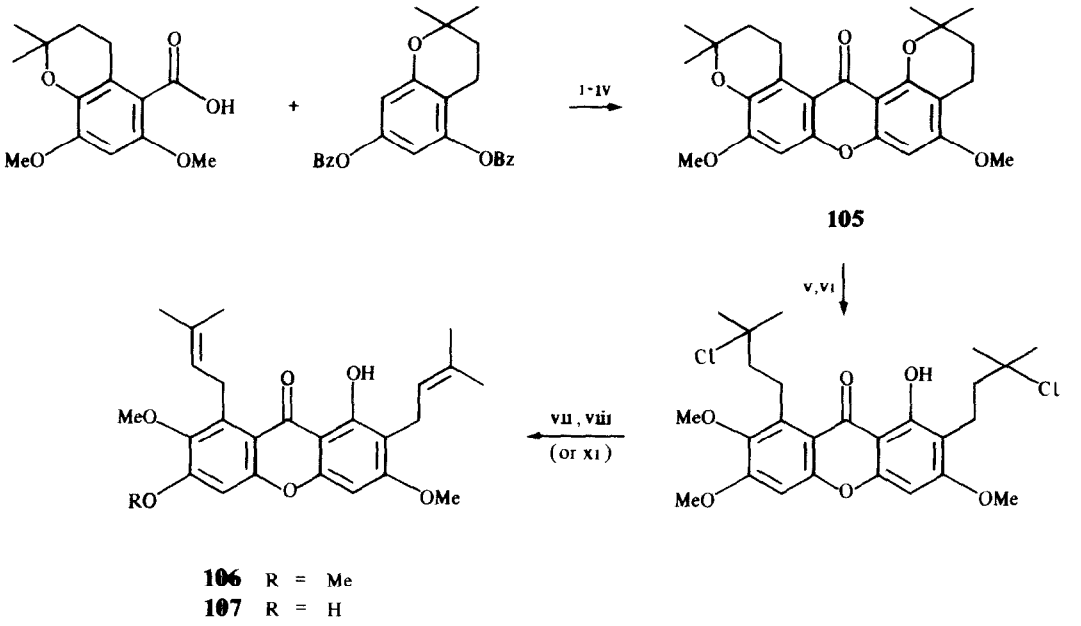
A dipyranoxanthone from *Garcinia densivenia* was originally assigned the linear structure of pyranojacereubin (**87**) on the basis of the size of the diamagnetic shift of H-4' upon *O*-acetylation [71]. Subsequently, when a similar compound was isolated from *Rheedia gardneriana* and the two compounds compared, the structure of the *G. densivenia* xanthone was revised to that of rheediaxanthone A (**88**), and the new compound assigned the structure of pyranojacereubin (**87**) [60]. This example serves to highlight the problem of differentiating between substituents at the 2- and 4-positions. Upon acetylation, H-4' of **87** was deshielded by $\delta 0.26$ (expected $\sim\delta 0.30$), compared to $\delta 0.19$ for H-4' of **88** [60].

Compounds which contain a 1,1,2-trimethyldihydrofuran ring are possible artefacts due to the ease with which the parent 1,1-dimethylallyl group cyclizes with an *ortho*-hydroxyl. Rheediaxanthone B (**89**) and xanthones **90** and **94** are optically active and should therefore be true natural products; however rheediaxanthone C (91), although also optically active, is thought to be an artefact of **89** [70].

Nine of the xanthones in Table 9 were isolated from *Rheedia brasiliensis* and are biogenetically closely related (eg. **92–94**). The location of the methoxyl in manglexanthone (**95**) was confirmed by its ^{13}C NMR chemical shift ($>\delta 60$), indicating di-*ortho*-substitution [70]. Therefore **95** is apparently different from tovopyrifolin A (**95**; $R_1 = H$, $R_2 = Me$) which is found in the same genus [76].

During the last eight years an equal number of papers have described new xanthones from *Garcinia mangostana*. Those shown in Table 9 all contain the 1,3,6,7-tetraoxygenation pattern and are cyclized or hydrated derivatives of the major metabolite, mangostin (**70**; $R_1 = Me$, $R_2 = OH$) or γ-mangostin (**70**) $R_1 = H$, $R_2 = OH$). The chromanoxanthones (**98** and **101–104**) had been synthesised previously by the *p*-toluenesulphonic acid catalysed cyclization of mangostin [77]. Whereas this reagent gave both linear and angular chroman rings, methanolic HCl gives only the linear product [78].

Dimethylmangostin (**106**), which may be selectively demethylated to give the natural mangostins, has been synthesized by Lee (Scheme 3) [79]. The problem of



105

106 R = Me
107 R = H

Reagents (i) TFAA/CH_2Cl_2 (ii) H_2,Pd/C (iii) CH_2N_2 (iv) Me_4NOH/py (v) BCl_3/CH_2Cl_2 (vi) MeI/K_2CO_3 (vii) MeCOCl/K_2CO_3 (viii) LiCl/DMF (xi) KO^{t}Bu/DMSO

Scheme 3

selective prenylation in the 2- and 8-positions was overcome by the preparation of the dichromanoxanthone (**105**). Ring opening was accomplished with boron trichloride to give a dichloride which underwent dehydrochlorination with lithium chloride in DMF, producing **106** Alternatively, treatment of the dichloride with potassium-*t*-butoxide in DMSO gave *β*-mangostin (**107**)

Tri-C_5-tetraoxygenated xanthones. Five xanthones of this type are now known, and the two new ones are shown in Table 10. The structure of garcinone E (**108**) is tentative, and based mainly on the formation of a trichromano compound with methanolic HCl [78]

The novel ring B substitution pattern of nervosaxanthone (**109**) was suggested by the deshielded methylene of one of the prenyl groups, placing it *peri* to the carbonyl, and the ^{1}H NMR resonance of the single aromatic proton [72] The arrangement of the 2- and 4-substituents was determined by an ^{1}H NMR study of the tri- and tetra-acetates

Di-C_5-pentaoxygenated xanthones The first natural examples of this type are xanthones V_2 (**110**) and V_{2a} (**111**) (Table 10) from *Vismia quineensis* They are the 7-methoxy derivatives of xanthones V_1 (**83**) and V_{1a} (**85**) (Table 9) Together these constitute the only occurrences of prenylated xanthones in the genus *Vismia*

More complex xanthones. Garcinia pyrifera shows a link with *G. cowa* and *G. rubra* by producing 8-geranyl-1,3,6,7-tetraoxygenated xanthones (**112–114**; Table 11) [72] The optically active maculatoxanthone (**115**) is the first xanthone with a lavandulyl side chain, although this arrangement is found in three benzophenones—tovophenones A and B (**141, 142**) and xanthochymol (**144**). Calozeyloxanthone (**116**) contains a novel C_{10} arrangement, presumably a cyclized geranyl group

Calophyllum wightianum produces a palmitic acid clathrate which yielded a xanthone named wightianone [81]. A 5,5-diprenyl structure was proposed. However, on comparison [21], it was found to be identical with a sample of zeyloxanthanone (117) isolated from *Calophyllum zeylanicum* Gambogic acid (**118**) has been reisolated from *Garcinia hanburyi* together with a new derivative, neo-gambogic acid (**119**) [82]

Xanthone glycosides

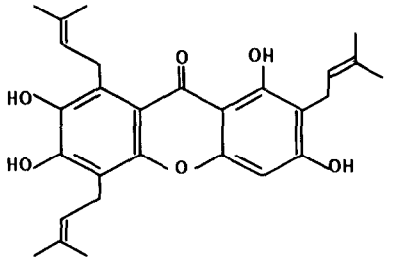
The *C*-glucosylxanthones, mangiferin (**120**; Table 12) and isomangiferin (**121**) have been found in several species of *Hypericum* and *Cratoxylum pruniflorum* but are not known in the rest of the family. The taxonomic significance of this will be discussed later There are only two examples of *O*-glycosides in Guttiferae (**122, 123**), although neither has been properly characterized Both *O*- and *C*-glycosylxanthones are common in the Gentianaceae [2]

Xanthonolignoids

Kielcorin was first isolated from *Kielmeyera* species, and its structure has been defined as a racemate of the two 5,6-*trans* isomers (**124**) [88] It has recently been isolated from several *Hypericum* species and *Vismia guaramirangae*. The other xanthonolignoids in Table 13 also have the *trans* configuration and are optically inactive.

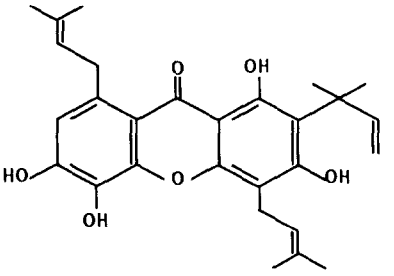
Biogenetically, xanthonolignoids are thought to be formed by the coupling of a cinnamyl alcohol with an *ortho*-dihydroxyxanthone Kielcorin and 2,3,4-(or 5,6,7)-trioxygenated xanthones co-occur in *Hypericum calycinum* and *H. ericoides* as well as in three *Kielmeyera*

Table 10 Tri-C_5-tetraoxygenated and Di-C_5-pentaoxygenated xanthones



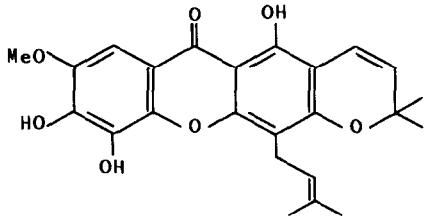
(108) **Garcinone E**

*Garcinia mangostana L. [78]



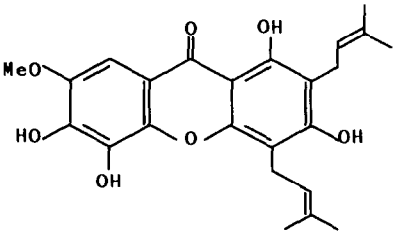
(109) **Nervosaxanthone**

*Garcinia nervosa Miq. [72]



(110) **Xanthone V_2**

*Vismia guineensis (L.) Choisy [68]



(111) **Xanthone V_{2a}**

*Vismia guineensis (L.) Choisy [68]

species. The 1,5,6,7-tetraoxygenated candensins A and C (**125**, **126**) are found alongside similarly substituted xanthones in the two *Caraipa* species and *H. canariensis* Furthermore, syringaresinol (**129**), a likely precursor to the C_6C_3 moiety of candensins A and C, has been isolated as the diacetate from *Vismia quaramirangae*.

Kielcorin (**124**) has been synthesized by two different routes [91, 92] One involves the biomimetic coupling of 2-methoxy-3,4-dihydroxyxanthone (**130**, Scheme 4) and coniferyl alcohol (**131**) [91] *cis*-Kielcorin (**124**, 5,6-*cis*) was a minor product.

Candensin D and hypericorin from *Hypericum canariensis* and *H. mysorense* respectively, have been assigned the same structure (**127**) and their physical data compare reasonably well. An isomer of kielcorin, named kielcorin B has been identified in *Kielmeyera coriacea* and tentatively assigned structure **128**.

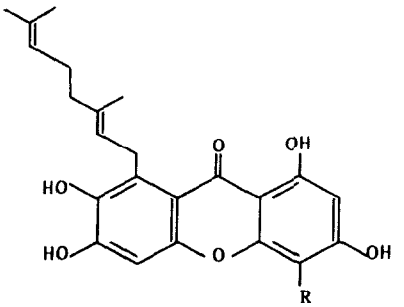
Benzophenones

Benzophenones are of interest as they have been implicated in xanthone biosynthesis. Simple benzophenones are rare in the Guttiferae. They have been found in the heartwood of five species (Table 14)—usually with analogous xanthones. For example, maclurin (134) occurs with 1,3,6,7-tetrahydroxyxanthone (**48**) in *Garcinia mangostana*, with **48** and 1,3,5,6-tetrahydroxyxanthone in *Symphonia globulifera* and with xanthochymol (**144**) in *Garcinia xanthochymus*.

Prenylated benzophenones

These compounds shown in Table 15, may be divided into two groups, true benzophenones (**136–142**) and those with reduced A rings, the so-called polyisoprenylated

Table 11 More complex xanthones

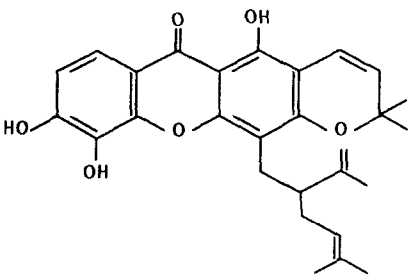


(112) R = H, **Rubraxanthone**

(113) R = 3-Methyl-2-butenyl; *__Iscowanin__

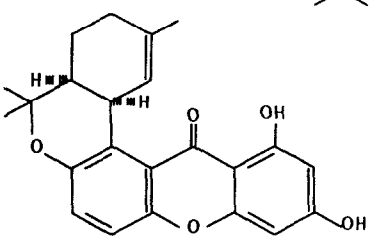
(114) R = 3-Methyl-4-hydroxy-2-butenyl; *__Isocowanol__

Garcinia pyrifera Ridl. [72]



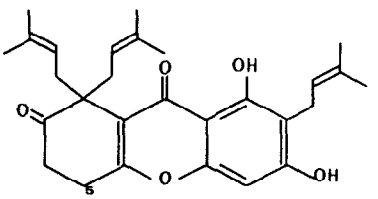
(115) **Maculatoxanthone**

**Hypericum maculatum* Crtz. [80]



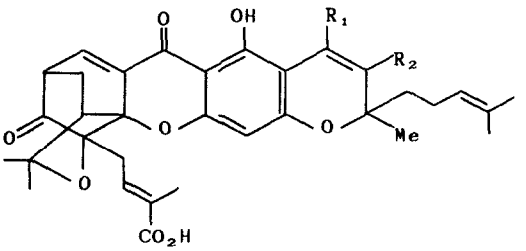
(116) **Calozeyloxanthone**

**Calophyllum zeylanicum* Kosterm. [21]



(117) **Zeyloxanthonone (Wightianone)**

Calophyllum wightiagnum T Anders [81]



(118) $R_1=R_2=H$, **Gambogic acid**

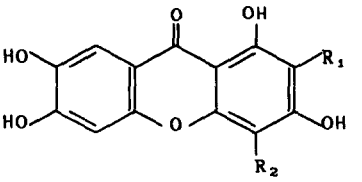
(119) $R_1=H$, OH, $R_2=H_2$ (no d b); **Neogambogic acid**

**Garcinia hanburyi* Hook f [82]

benzophenones (**143–148**) Of the former group, five contain unsubstituted B rings, and therefore have no known xanthone analogues. The vismiaphenones (**136–139**) have been synthesized by the prenylation of suitably substituted benzophenones [98–100]. Tovophenones A and B (**141, 142**) contain the rare lavandulyl side chain, and kolanone (**143**) from the edible fruit of *Garcinia kola*, shows broad antimicrobial activity [102]

There has been some controversy regarding the structures of the four closely related compounds containing a bicyclononene moiety (**144–147**). The X-ray determined structures of xanthochymol (**144**) and isoxanthochymol (**146**) are shown in Table 15 Cambogin (**147**) was shown to be the antipode of the latter and camboginol (**145**),

Table 12. Xanthone glycosides

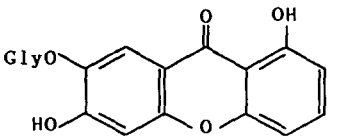


(120) R_1=β-D-Glucopyranosyl, R_2=H; **Mangiferin**

Cratoxylum pruniflorum Kurz. [130]
Hypericum aucheri Jaub et Sprach [47]
Hypericum barbatum Jack [84]
Hypericum boissieri Petrovic [85]
†*Hypericum humifusum* L. [86]
Hypericum maculatum Crantz [84]
Hypericum rocheli Griseb. and Schenk. [85]
Hypericum rumeliacum Boiss [84]
Hypericum sampsonii Hance [39]

(121) R_1=H, R_2=β-D-Glucopyranosyl; **Isomangiferin**

Cratoxylum pruniflorum Kurz. [130]
Hypericum boissieri Petrovic [85]
Hypericum hirsutum [87]
Hypericum rocheli Griseb and Schenk [85]
†*Hypericum sampsonii* Hance [39]

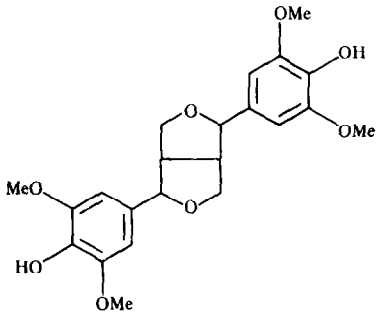


(122) R_1=R_2=H; **1,3,6,7-Tetrahydroxy-O-glucosylxanthone**

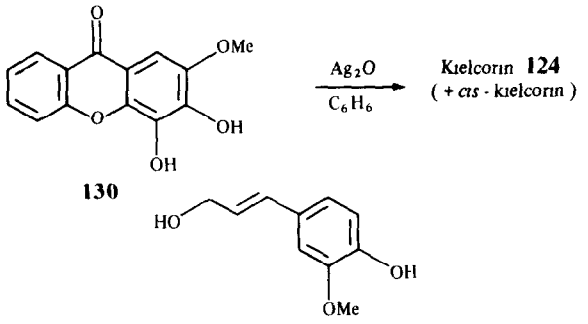
Garcinia mangostana L. [46]

(123) 1,6,7-Trihydroxyxanthone-7-O-glycoside

Platonia insignis Mart. [29]
(Gly: unidentified sugar)



129



130 **131**

Scheme 4

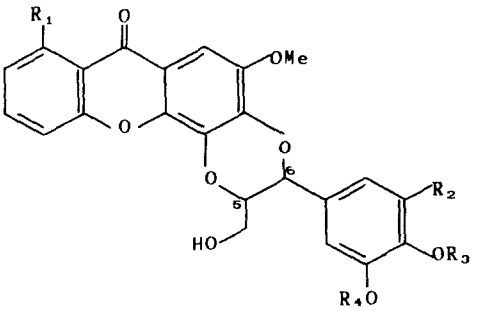
which can be prepared from cambogin, was assigned the structure of the enantiomer of xanthochymol with a shifted double bond [106].

Two related pigments, namely garcinol and isogarcinol were isolated from *Garcinia indica* [107] Garcinol was assigned the structure of camboginol (**145**), however, their UV spectra in ethanol differed significantly, and it was suggested that camboginol lacked the extended conjugation in the cyclohexane ring. The UV spectrum of camboginol was repeated in cyclohexane and shown to be compatible with the originally proposed structure. A solvent-dependent UV spectrum had already been noted for xanthochymol [108] Ultimately, the X-ray crystal structure of isogarcinol indicated its identity with cambogin (147), and the formation of isogarcinol from garcinol, as well as physical data, suggest that the latter is identical to camboginol (**145**) [111]

A related compound, nemorosonol, isolated from the fruits of *Clusia nemorosa* has been assigned the tricyclodecane structure (**148**). It is suggested that the various polyisoprenylated benzophenones may originate from a common precursor (**150**, R = prenyl or 2-isopropenylhex-4-enyl) by cyclization between C-1 and C-6 to form the bicyclic compounds and C-10–C-1 and C-6–C-7 to form **148**.

Sarothralin (**149**) from *Hypericum japonicum* has antimicrobial properties, and is closely related to other filicinic acid derivatives (which lack a benzoyl group) found in this and other *Hypericum* species. Three other

Table 13 Xanthonolignoids



(124) R_1=H, R_2=H, R_3=H, R_4=Me,

Kielcorin

Hypericum androsaemum L [34,88]

Hypericum calycinum L [88]

Hypericum canariensis L [24]

Hypericum ericoides L [89]

Hypericum maculatum Crantz [88]

Hypericum perforatum L. [88]

Vismia guaramirangae Huber [28]

(125) R_1=OH, R_2=H, R_3=OMe, R_4=H

Candensin A

Cariapa grandiflora Mart [29]

Caraipa valoi Paula [29]

Vismia guaramirangae Huber [28]

(126) R_1=OH, R_2=OMe, R_3=H, R_4=Me,

Candensin C

Hypericum canariensis L [24]

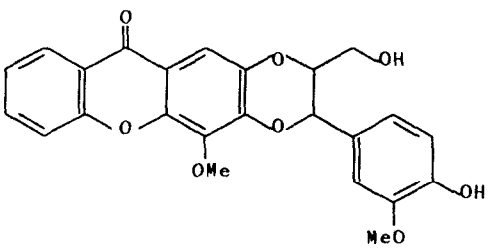
**Vismia guaramirangae* Huber [28]

(127) R_1=H, R_2=OMe, R_3=H, R_4=Me,

Candensin D (Hypericorin)

**Hypericum canariensis* L [24]

Hypericum mysorense [90]



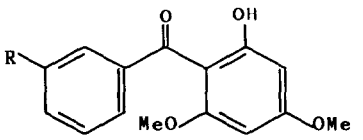
(128) Kielcorin B

**Kielmeyera coriacea* Mart. [91]

prenylated benzophenones (bronianone, clusianone, and marupone) were mentioned in the earlier review [1].

Finally, one other compound of interest is hermionic acid. Originally isolated from *Garcinia hermonii*, and assigned a diphenyl structure [1], it has now been re-isolated from *G. quaesita*, and on the basis of its conversion to a xanthone and ^{13}C NMR evidence, its structure has been revised to the diphenylether (**149**) [113]. Decarboxylated hermionic acid (**150**) and its demethyl derivative (**151**), named quaesitol were also isolated [114].

Table 14 Benzophenones



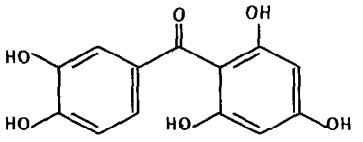
(132) R = H; **(Hydrocotoin)**

2-Hydroxy-4,6-dimethoxybenzophenone

(133) R = OH

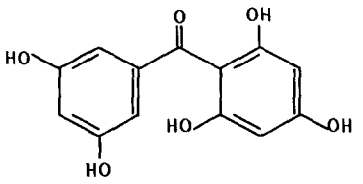
2,3'-Dihydroxy-4,6-dimethoxybenzophenone

Allanblackia floribunda Oliv. [93]



(134) **2,3',4,4',6-Pentahydroxybenzophenone (Maclurin)**

Garcinia mangostana L. [46]
Garcinia xanthochymus Hook. f [30]
Symphonia globulifera L. [94]



(135) **2,3',4,5',6-Pentahydroxybenzophenone**

Garcinia pedunculata Roxb. [95]

Biogenetically, these compounds appear to be very closely related to xanthones.

CHEMOTAXONOMY

Recent reviews have outlined the principles of chemotaxonomy and the taxonomic importance of various classes of secondary metabolites [115–117]. As xanthones occur widely in only a few, unrelated families of higher plants, their potential taxonomic value is restricted to within these few families. This section will examine the distribution of xanthones within the Guttiferae.

The oxygenation pattern is the most variable structural feature of Guttiferae xanthones, and almost forty different patterns are known. The major oxygenation patterns are shown at the top of Table 16, grouped mainly according to B-ring oxygenation. The number of species in which xanthones with each oxygenation pattern occur is given for various sub-divisions of the family (cf. Table 1).

It can be seen from Table 16 that the variation of xanthone oxygenation pattern is of some systematic significance. Some oxygenation patterns appear throughout the family, while others are restricted to certain plant groups. Clearly, the first three of the six subfamilies each produce xanthones with a different range of oxygenation patterns, suggesting that there are different biogenetic constraints on the species of each group. A similar or somewhat narrower range of oxygenation patterns is shown by the tribes or genera of each of these subfamilies. This overall picture may become clearer as more plants are studied.

A species from a particular genus generally does not contain the whole range of oxygenated xanthones found in the genus. Some species appear not to synthesize xanthones, e.g. *Calophyllum macrocarpum*. This plant accumulates a C_6C_1 compound, 3,4-dihydroxybenzaldehyde, perhaps, it is suggested, due to the absence of a key enzyme [65]. Similarly, some species appear to produce only benzophenones, or only simple rather than prenylated xanthones

At first sight, such wide variations within a genus may appear to suggest that xanthones are of little taxonomic value at this level; however, when considered with other taxonomic characters, xanthones may be useful in aiding infra-generic classifications. For example, closely related species of *Calophyllum* have many xanthones in common.

The xanthone distribution within each subfamily will now be examined in more detail. Besides xanthones, the Guttiferae contain a wide variety of other metabolites many of which are also of taxonomic value and these will be mentioned briefly.

Kielmeyeroideae

The species of this South American subfamily are characterized by an abundance of simple oxygenated xanthones The two tribes, Kielmeyereae and Caraipeae, show nine oxygenation patterns in common (Table 16). Several rather unique patterns containing 7,8-oxygenation are evident, and interestingly, xanthones with 6,7-dioxygenated B-rings have not been found. Simple 1,3,5-trioxygenated xanthones are common only in this subfamily, and perhaps related to this is the rare occurrence of prenylated xanthones. Prenylation is absent in the Caraipeae tribe, but three prenylated xanthones have been found in species of the Kielmeyereae tribe. Two of

these xanthones are very common in *Calophyllum* species.

A further difference between the two tribes is that xanthones without 1-oxygenation are common only in the Kielmeyereae tribe Similarly, xanthonolignoids, which otherwise only occur in the Hypericoideae subfamily, are 5,6,7-trioxygenated in *Kielmeyera* species but 1,5,6,7-tetraoxgenated in *Caraipa* species.

Remarkably. the two genera of the Caraipeae tribe, so far have no oxygenation patterns in common (*Caraipa*: 7-, 1,3,7-, 1,5,6,7-, 5,6,7- and 1,6,7,8-oxygenation, and *Haploclathra*: 1,7-, 1,3,5-, 1,3,5,6-, 1,3,7,8- and 1,7,8-oxygenation).

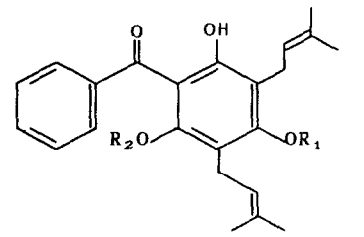
For a long time a morphological link has been recognised between the Kielmeyeroideae and the family Bonnetiaceae (*Bonnetia* and *Archytaea* genera), and Hutchinson has even grouped the two together as a single family [118]. However, the Bonnetiaceae have also been classified as a tribe in Theaceae [119], a related family in which xanthones have not been found The xanthones that have recently been isolated from two Bonnetiaceae species show the characteristic oxidation patterns of the Kielmeyeroideae [31], and have led one taxonomist to submerge the Bonnetiaceae into this subfamily [13].

Calophylloideae

In Table 16 this subfamily has been divided into two groups; *Calophyllum* and *Mesua/Mammea*. Both groups contain a similar range of simple xanthones, and show the same common oxygenation patterns (1,5-, 1,7- and 1,5,6-), but there is a clear distinction, in that the latter group shows an almost total absence of prenylated xanthones. Only two are known from a species of *Kayea* (= *Mesua*) [1]

The 180 species of *Calophyllum* are found mainly from India to New Guinea [120] The genus appears to be the most homogeneous in the family as far as xanthone distribution is concerned. Almost all the 21 xanthone-containing species show both simple and prenylated xanthones Jacareubin (**81**) occurs in 17 of these species (and with 6-deoxyjacareubin (56) in 11), and is therefore classed as a taxonomic marker for the genus [121] This

Table 15 Prenylated benzophenones



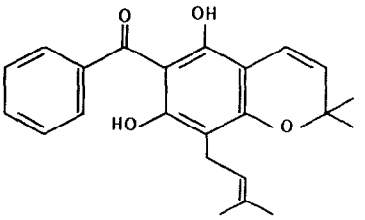
(136) R_1 = H, R_2 = Me, **Vismiaphenone A**

*Vismia decipiens Schlecht-Cham [96]

Vismia guaramirangae Huber [28]

(137) R_1 = Me, R_2 = H; **Vismiaphenone C**

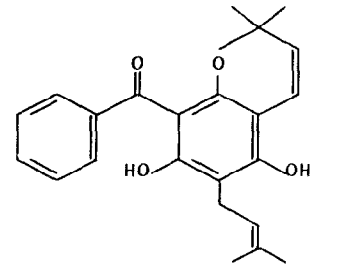
*Vismia guaramirangae Huber [28]



(138) **Vismiaphenone B**

Clusia ellipticifolia Cuatr. [97]

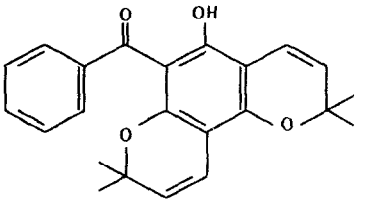
*Vismia decipiens Schlecht-Cham [96]



(139) **Isovismiaphenone B**

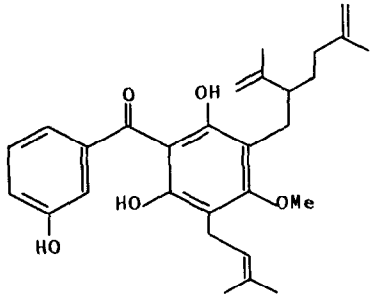
Clusia ellipticifolia Cuatr. [97]

*Vismia decipiens Schlecht-Cham [96]



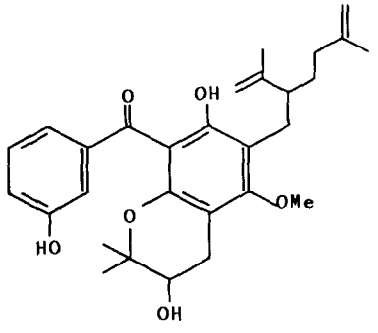
(140) *Clusia ellipticifolia Cuatr. [97]

Table 15 *Continued*



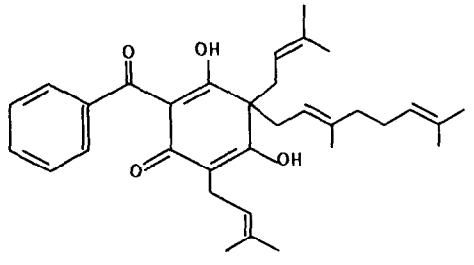
(141) **Tovophenone A**

*Tovomita mangle G.Maritz [101]



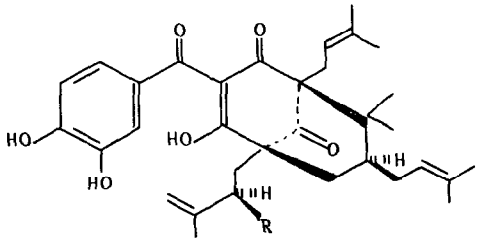
(142) **Tovophenone B**

*Tovomita mangle G.Maritz [101]



(143) **Kolanone**

*Garcinia kola Heckel [102]



(144) R = 3-Methylbut-3-enyl

Xanthochymol

Garcinia mannii Oliv. [103]

Garcinia ovalifolia Oliv [69]

Garcinia polyantha Oliv. [72]

Garcinia staudii Engl. [62]

Garcinia xishuanbannanensis Y H.Li [104]

Rheedia madrunno (HBK) Pl and Tr [105]

(145) R = 3-Methylbut-2-enyl

"enantiomer" of **144**

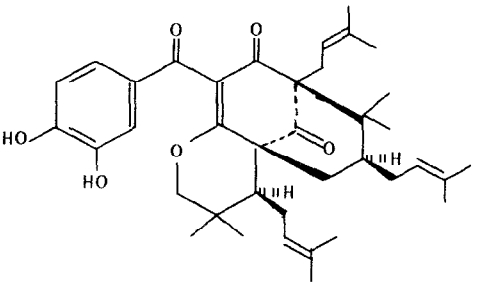
Camboginol(Garcinol)

*Garcinia cambogia Desr.[106,108]

Garcinia huillensis [109]

Garcinia indica Choisy [107,111]

Table 15 *Continued*



(146) Isoxanthochymol

Garcinia ovalifolia Oliv [69]

Garcinia polyantha Oliv [72]

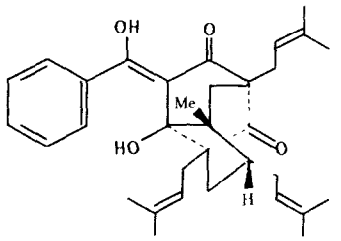
Garcinia xishuanbannanensis Y H Li [104]

(147) Enantiomer of **146**

Cambogin(Isogarcinol)

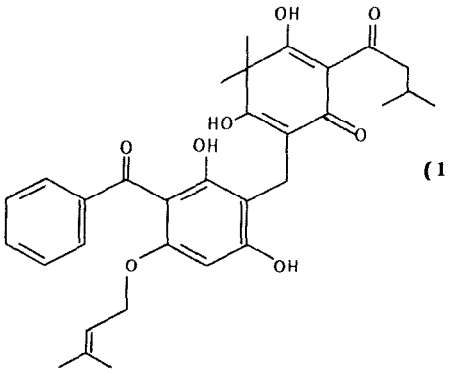
**Garcinia cambogia* Desr [106]

Garcinia indica Choisy [107, 111]



(148) Nemorosonol

Clusia nemorosa G F.W Meyer [110]



(149) Sarothralin

Hypericum japonicum Thunb [112]

uniformity may be a reflection of the rather narrow geographic range, and close relationship of many of the species investigated

Interestingly, the xanthone content of *Calophyllum* species often varies greatly with the part of the plant. For example, the three xanthones found in the bark of *C zeylanicum*, were not found in the timber, which contained seven other xanthones [21] This phenomenon, as well as the structural similarities of many of the xanthones, makes the chemical comparison of *Calophyllum* species difficult

In a recent review of the genus [120], Stevens equated *C. zeylanicum* (now *C lankaensis*? [21]) with *C. trapezifolium*. They do in fact have seven xanthones in common, and only differ in that they each produce two xanthones not found in the other [21, 122] A possible geographical variation is suggested in *C. walkeri* [65] A plant from India yielded four xanthones that were not found in the Sri Lankan plant of the same name, however, the bark of the latter was not thoroughly investigated [123] Significant differences have also been found in two varieties of *C calaba* [63, 64, 124]

Table 16. The distribution* of simple and alkylated xanthones and related metabolites in the Guttiferae

	Oxygenation patterns																											
	Simple xanthones																				Alkylated xanthones							
Subfamily/Tribe† (No of species)	5	7	15	17	135	1235	137	1356	156	56	1367	167	67	1567	567	1378	178	78	1678	*Others*‡	135	137	1356	1367	*Others*§	*XG*‖	*XL*‖	*BZ*‖
Kielmeyereae (9)		5		4	6		1	1							6	1	3	3	1	12378	3	3	1				3	
Caraipeae (7)		1		2	2		1	1						4	1	2	2		1								3	
{Bonnetiaceae (2)				1													1		1}									
Calophyllum (21)	2	3	8	14		2	1	1	11	1	1	1					2		1	12378	14	14	18		24, 15			
Mesua, Mammea (10)	3	4	7	6	2	1	1	3	5	1	2	1	2		1					37, 13567			1		1235			
Clusieae (10)						1			1			1		1						1345, 345? [38]				4	156			4
Garcinia (29)			5	5	1		1		3		5	1								125, 1245, 1256, 1347, 1357	2	2	8¶	5	1358	1		12
Rheedia etc (6)			3	2	1				1		2										3	2	3	1	167			2
Moronoboideae (4)				2		1		1	1		1	1										2	2	1	125, 1256	1		2
Lorostemoideae (2)																								2				
Cratoxyleae (2)											1														1567	1		
Hypericeae (18)		4		4			1	1			2	1	3	1	3					25, 235, 2567			1	3	235, 367	9	7	1
Vismieae (5)		1		2	1								2					1		147, 158, 5678, 15678	1		1		13567		1	2

*Numbers in Table refer to number of species in which xanthones with the particular oxygenation have been found.
†Genera in which several plants have been examined are separated from the rest of the subfamily or tribe (cf Table 1)
‡These minor oxygenation patterns, apart from one, have been found in one species; 2,5-dioxygenation found in two species
§1,5-Dioxygenation and 1,6,7-trioxygenation found in eight and two species respectively, remainder found in one species
‖XG, xanthone glycosides, XL, xantholignoids, BZ, simple and prenylated benzophenones
¶Includes three species which contain xanthones with reduced B-ring

Neoflavonoids (and other 4-substituted coumarins) and chromones occur in many *Calophyllum* species [125, 126].

Clusiodeae

Generally xanthones occur less frequently in the Clusiodeae than in the preceding subfamilies, and the range of major oxygenation patterns is rather restricted. Xanthones in which 1-oxygenation is absent are not known, but several unique oxygenation patterns containing 2- and 4-oxygenation occur Species of both tribes produce prenylated benzophenones, often as the major metabolites, but otherwise the tribes show little in common.

In the Clusieae tribe, xanthones and benzophenones occur in *Tovomita* species, but the large, poorly-studied *Clusia* genus has so far not yielded any xanthones. Recently, Delle Monache and co-workers have begun to study a number of *Clusia* species [110]

The Garcineae tribe is divided into two groups in Table 16 *Garcinia* and *Rheedia/Pentaphalangium/Allanblackia*. The tribe appears fairly homogeneous, with each group showing a similar range of simple and prenylated xanthones

Xanthones have been found in about half the *Garcinia* species studied Biflavonoids occur in almost all species and benzophenones in 11 Waterman and co-workers have systematically examined several *Garcinia* species from tropical Africa The subsequent chemotaxonomic review of the genus shows that in certain cases xanthone structure correlates well with the infra-generic classification [127]

Three species from the section Rheediopsis of the genus have been investigated, and each contains prenylated xanthones with 1,3,5,6-tetraoxygenation as well as xanthochymol (**144**) The benzophenones cambogin (**147**) and camboginol (**145**) occur in two species from the Gamogin section, and the two species which produce gambogic acid (**118**) and other xanthones with reduced B-rings are from the section Hebradendron 8-Geranylated xanthones are only known in three *Garcinia* species, two of which belong to section Oxycarpus It has been suggested that the third species, which has so far not been assigned to a section, may also go here [72] Such correlations were not found in many other sections, but as only 10% of *Garcinia* species have been studied it is perhaps too early to tell

Also of interest is the apparent geographical variation of tetraoxygenation patterns [127] African *Garcinia* species contain 1,3,5,6- (and no 1,3,6,7-) tetraoxygenated xanthones, whereas Asian species, apart from one, show only 1,3,6,7-tetraoxygenation. Some xanthones from African *Garcinia* also occur in species of the related South American genus, *Rheedia*, which so far has also yielded only 1,3,5,6-tetraoxygenated xanthones

The Moronboideae subfamily is rather small, and the four investigations so far have produced xanthones similar to those in the Clusiodeae The Lorostemoideae subfamily contains only two species from which one prenylated xanthone has been isolated

Hypericoideae

This subfamily of three tribes is closely related to the rest of the Guttiferae [128, 129], although it is sometimes classed as a separate family, the Hypericaceae [12] The following evidence supports such a relationship Prenylated xanthones, have been found in all three tribes of the Hypericoideae, and although they have unique structures, they are similar to those found in other subfamilies (e g **63**, **80**) The presence of xanthones with 7,8- and 5,6,7-oxygenation and xanthonolignoids shows a link with the Kielmeyeroideae subfamily, and two benzophenones (**138**, **139**) from *Vismia decipiens* also occur in a species of *Clusia*

Unlike the rest of the family, the Hypericoideae contain *C*-glucosylxanthones. They have been found in several species of *Hypericum* [84, 85] and *Cratoxylum prunifolium* [130], and occur with both simple and prenylated xanthones, as well as flavonoids As it appears that these glycosides may be biogenetically different from the xanthones in the rest of the family (see Biosynthesis), their presence should not be regarded as evidence of 'xanthones' to support the inclusion of the subfamily in the Guttiferae Interestingly, simple xanthones with 6,7-oxygenated B-rings are unusually common in *Hypericum* species They occur with the similarly substituted glycosides and may be biogenetically related

A chemotaxonomic survey of the *Hypericum* genus has recently appeared [131] In addition to xanthones, many flavonoids and other phloroglucinol derivatives have been found *Vismia* species produce prenylated anthranoids and other anthracene derivatives (vismiones) [132] Similar metabolites also occur in *Psorospermum* species [133]

BIOSYNTHESIS

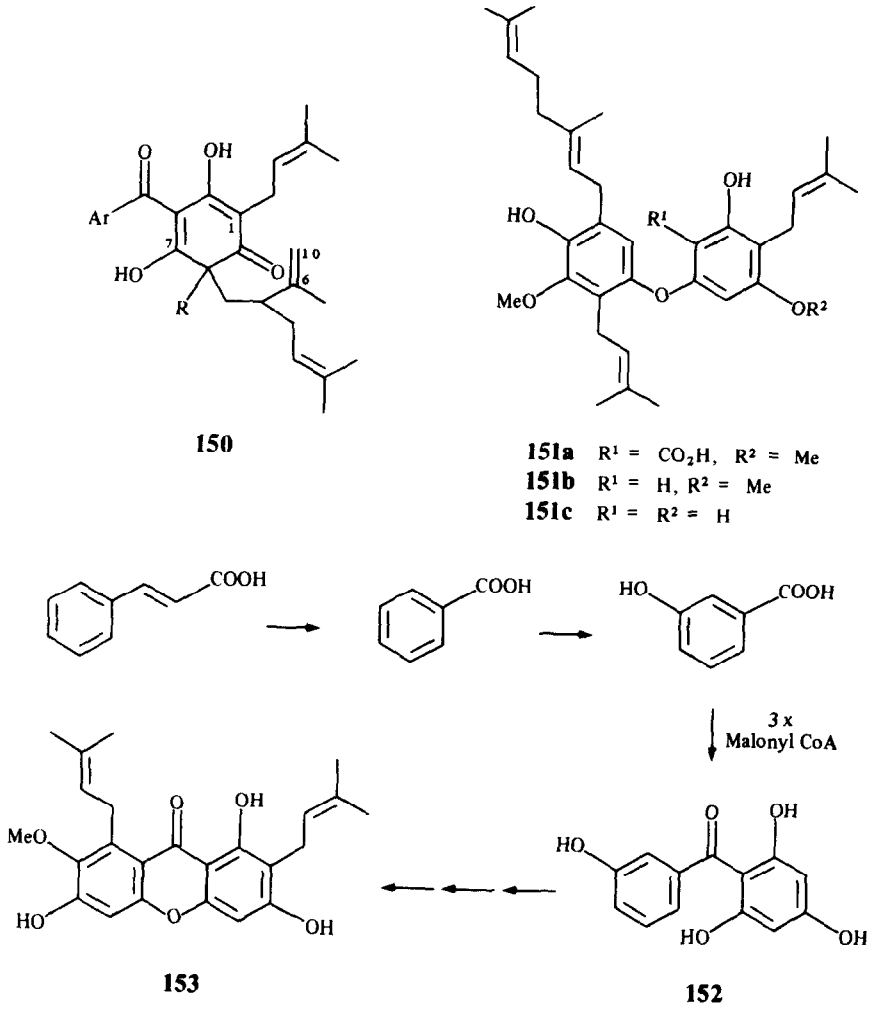
The characteristic oxygenation patterns of xanthones from higher plants were recognised early on as being due to a mixed shikimate-acetate biogenesis [5] Along these lines various biosynthetic pathways were proposed [7, 8, 10] and these have been reviewed [1]

Early biosynthetic studies were limited to the 1,3,7-trioxygenated xanthones of *Gentiana lutea* (Gentianaceae) [134, 135] The results indicated that the xanthone nucleus was formed from acetate (ring A) and a C_6C_1 unit derived from phenylalanine The participation of an intermediate benzophenone (**152**) was demonstrated by the incorporation of tritiated **152** [135]

The first study on the biosynthesis of xanthones in the Guttiferae has recently been reported [136] Cinnamic acid, benzoic acid, *m*-hydroxybenzoic acid and the benzophenone (**152**) as well as malonic acid were efficient precursors to mangostin (**153**) in *Garcinia mangostana*, implying the pathway depicted in Scheme 5

Furthermore, the labelled benzophenone (**152**) was significantly incorporated into 8-desoxygartanin (67) and gartanin (**79**, R_1 = H, R_2 = prenyl) in the same plant These findings, coupled with the earlier studies on *Gentiana lutea*, indicate the involvement of benzophenone **152** in the biosynthesis of xanthones with four different oxygenation patterns (1,3,5-, 1,3,7-, 1,3,6,7- and 1,3,5,8-), and suggest that it may be an intermediate in the biosynthesis of most higher plant xanthones

The proposed direct *m*-hydroxylation of benzoate (Scheme 5) was suggested, in part, by the poor incorporation of *p*-substituted precursors Earlier biosynthetic proposals, such as the choice of maclurin (**134**) as a universal xanthone precursor [10] and the idea of spirodieneone intermediates [7], were formulated with the assumption that shikimate derivatives were necessarily



Scheme 5.

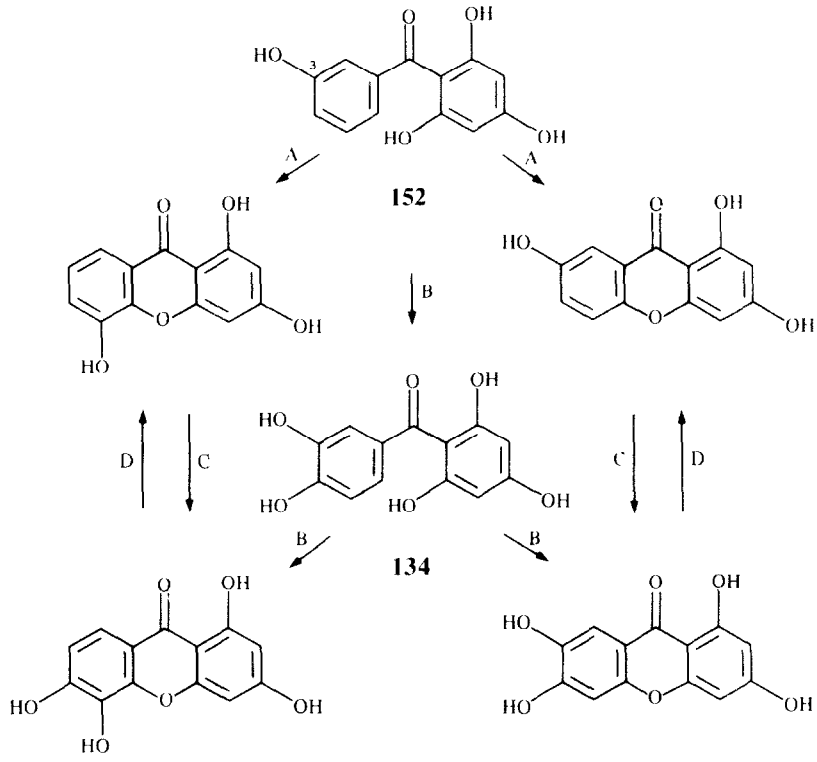
oxygenated in the *p*-position. As it now appears that xanthone biosynthesis may not involve such shikimate derivatives, the earlier proposals require re-evaluation.

Of the various modes of xanthone formation proposed to date, phenol oxidative coupling [137, 138] can most neatly account for the large variety and co-occurrence of oxgenated xanthones [8] Carpenter *et al*, postulated the oxidative coupling of a series of suitably hydroxylated benzophenones to account for the major xanthone oxygenation patterns [8]. This suggestion is compatible with the new biosynthetic results, as the benzophenones all require the *meta*- or 3'-oxygenation for oxidative coupling, and may be derived from benzophenone **152**. For example, the oxidative coupling of **152** can give 1,3,5- and 1,3,7-trihydroxyxanthones (Scheme 6, Route A) and maclurin (134), which may be formed by the 4'-hydroxylation of **152**, can produce 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthones (Route B)

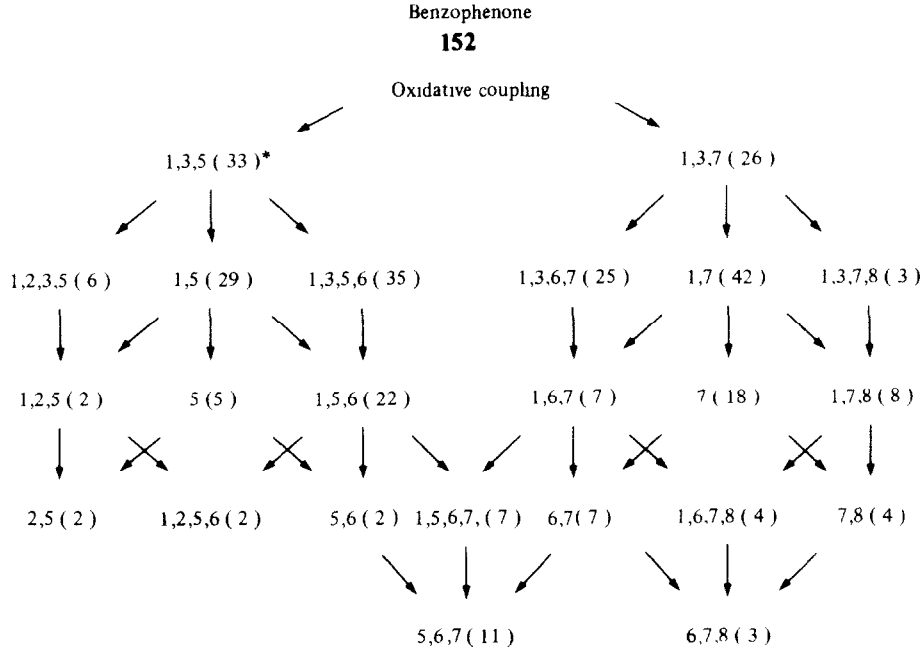
An alternative to the view that xanthones are formed from a series of benzophenones, is the proposal of Rezende and Gottlieb that the xanthone oxygenation pattern is modified after initial xanthone formation from a single benzophenone—maclurin (**134**) [10]. The 'primitive', maclurin-derived 1,3,5,6- and 1,3,6,7-tetraoxygenated xanthones could lead to all other oxygenation patterns by successive nuclear oxidations and/or reductions. For example, the reduction of the 6-position of these xanthones would give 1,3,5- and 1,3,7-trioxygenated xanthones (Scheme 6, Route C).

In view of the recent biosynthetic studies, the 1,3,5- and 1,3,7-trioxygenated xanthones appear more suited to occupy the positions of 'primitive' xanthones, as they are clearly more likely to be formed by the direct oxidative coupling of benzophenone 152 (Scheme 6, Route A), than by a three-step route via maclurin (**134**) (Route B + Route C). The 1,3,5,6- and 1,3,6,7-tetraoxygenated xanthones may alternatively be formed by the 6-oxygenation of the 1,3,5- and 1,3,7-trioxygenated xanthones (Scheme 6, Route D)

Similar nuclear oxidations/reductions of the trioxygenated xanthones, can lead to the major oxygenation patterns of Guttiferae xanthones, as illustrated in Scheme 7 It can be seen that the most common oxygenation patterns (particularly 1,3,5-, 1,3,7-, 1,7-, 1,5-, and 7-) are more directly accessible from **152** than from maclurin (**134**) in the earlier proposal.



Scheme 6



*No of species that produce xanthones with each oxygenation pattern

Scheme 7

The discussion so far has centred on the four predominant oxygenation patterns of prenylated xanthones, but avoided the issue of prenylation Prenylation is almost always found *ortho* to an oxygen function 2-Prenylation is the most common, but is only found in the presence of 1,3-dioxygenation, suggesting perhaps that the prenyl

group inhibits reduction of the 3-hydroxyl, which is very often absent in simple xanthones

Monoprenylation occurs less often in the 4-, 8-, or 7-positions. A second prenyl group frequently occurs in the 4- or 8-positions 2,4-Diprenylation is associated with 1,3,5-, 1,3,5,6,- or 1,3,5,8-oxygenation, but interestingly, not known with 1,3,7- or 1,3,6,7-oxygenation, and 2,8-diprenylation is limited to 1,3,7- and 1,3,6,7-oxygenation patterns

As with oxygenation, there is little evidence to suggest whether prenylation occurs at the benzophenone or xanthone stage, although the latter is preferred, e.g. ref [139] 2-Prenyl-1,3,5-trihydroxyxanthone has been postulated as a precursor to 6-deoxyjacareubin (**56**) and jacareubin (**81**) [140], a route involving 6-oxygenation at the xanthone stage, and in keeping with Scheme 7 These three xanthones are found together in four *Calophyllum* species. Similarly, 2-prenyl-1,3,7-trihydroxyxanthone could lead to mangostin (**153**) via 6-deoxy-γ-mangostin (**70**). The alternative, that **153** and **70** derive from two benzophenones, is less attractive, as it does not indicate such a close relationship between these co-occurring xanthones It can be seen that a series of modifications (oxygenation, further prenylation, cyclization etc) to the two basic 2-prenylxanthones can produce over 40, or about half of the known prenylated xanthones.

It had been suggested that mangiferin (**120**) was biogenetically related to flavonoids [5, 141], due to its occurrence in some plants in the presence, or apparently in place of C-glucosylflavones [142], rather than with other xanthones Fujita and Inoue have conducted a thorough study on the biosynthesis of mangiferin (**120**) and isomangiferin (**121**) in *Anemarrhena asphodeloides* (Liliaceae) [143, 144]. The results indicate that the xanthone nucleus is indeed formed from a flavonoid-type C_6C_3 precursor (*p*-hydroxycinnamate) coupled with two malonates (Scheme 8) The labelled benzophenones, iriflophenone (**154**) and maclurin (**134**) were significantly incorporated into **120**, whereas labelled 1,3,6,7-tetrahydroxyxanthone was not, suggesting that the glucosylation occurs at the maclurin stage, and that both **120** and **121** are formed by the oxidative coupling of 3-glucosylmaclurin (**156**)

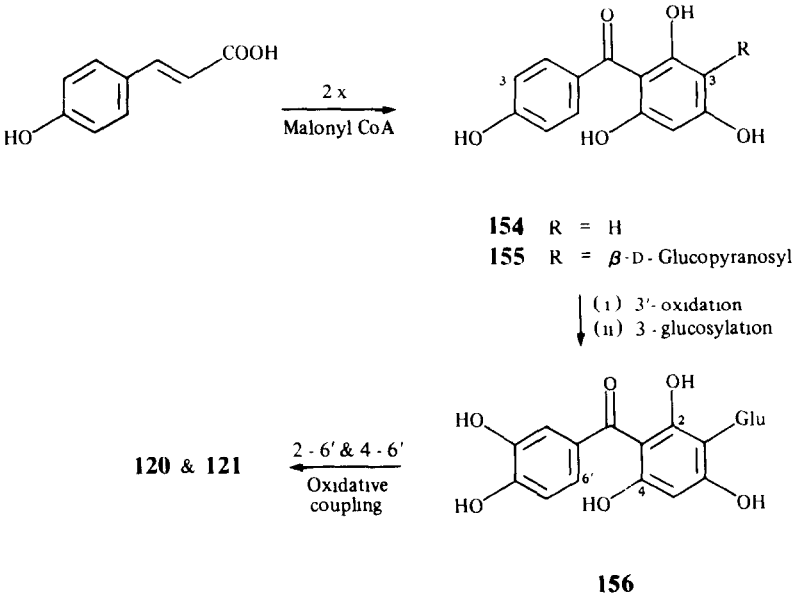
Interestingly, mangiferin (**120**) has recently been found together with 3-*C*-glucosyliriflophenone (**155**) in two ferns (*Hypodematium*) [145], and with the 1,3,7-xanthone analogue of **155** in *Gentiana lactea* [146].

PHARMACOLOGY

Probably the most important development in this area has been the identification of the cytotoxic xanthone psorospermin (**57**) [51, 52, 54] It shows significant *in vivo* activity in P338 leukaemia, colon (C6) and mammary (CD) tumour systems [148]. Synthetic studies on psorospermin are in progress [55–57] (see earlier), and analogues are being prepared and tested for similar activity [149].

Mangiferin (**120**) has been the subject of several studies. Anti-inflammatory [150], antihepatoxic [151] and antiviral (herpes) [152] properties have been reported. Mangiferin has also been shown to cause the *in vitro* activation of the lymphocytes of tumour-bearing rats [153].

In contrast to mangiferin (**120**), which is reported to be a CNS stimulant [154], mangostin (153) and several of its derivatives [155] as well as xanthones from *Calophyllum inophyllum* and *Mesua ferrea* [156] produce CNS depression in rats and mice. Many of these xanthones, especially mangostin, exhibit significant anti-inflammatory properties at doses of 50 mg/kg [155, 156]. They have no analgesic or antipyretic effect, but mangostin shows antiulcer activity The interference of mangostin with inflammatory and immunopathological responses has been further studied [157]. The synthetic 3,6-di-*O*-glucosylmangostin produces myocardial stimulation and a rise in blood pressure in dogs [155, 158].



Scheme 8

More xanthones have been tested for *in vitro* inhibition of monoamine oxidases (MAO's) [159] Two compounds, 1-hydroxy-3,8-dimethoxyxanthone and 1,3-dihydroxy-7,8-dimethoxyxanthone (swertinin) were identified as the most effective inhibitors of type A MAO, but were weak type B MAO inhibitors In another study 1,5,8-trihydroxy-3-methoxyxanthone also showed selective type A inhibition [146] A number of xanthones also inhibit xanthine oxidase [160] 1,3,6,7-Tetrahydroxyxanthone was the most potent of the compounds tested

Several prenylated xanthones possess significant antimicrobial properties Mangostin shows broad spectrum antibacterial activity, including the inhibition of penicillin-resistant strains of *Staphylococcus aureus*, as well as antifungal properties [161, 162] Xanthones from *Calophyllum inophyllum*, particularly 6-deoxyjacareubin (**56**) and jacareubin (**81**) [163], and the benzophenones kolanone (**143**) [102] and garcinol (**145**) [109] also exhibit antimicrobial properties

A tuberculostatic effect has been noted in many natural and synthetic xanthones [164]. A quantitative structure-activity relationship (QSAR) study has found a correlation between ^{13}C NMR chemical shifts of C-4b and C-7 of various 1,3-oxygenated xanthones and tuberculosis inhibition [165]. Three potent xanthones were identified, of which gentisein (**31**) was the most active

CONCLUSION

In conclusion, the Guttiferae produce a wide variety of both simple and prenylated xanthones The growing interest in these compounds is shown by the large number isolated during the last eight years An attempt has been made in this review to correlate xanthone structure with the classical taxonomic divisions of the Guttiferae. The new results on xanthone biosynthesis support the idea of a common benzophenone precursor, although further studies are still required Lastly, the pharmacology of xanthones has been summarized, indicating their potential as medicinal agents

Acknowledgements—The authors are grateful to Dr G M Kitanov for his communications, and one of us (GJB) thanks the National University of Singapore for the award of a scholarship

APPENDIX

Species–compound index

Xanthones except (*ital*)-xantholignoid, { }-glycoside ( )-benzophenone

Allanblackia floribunda Oliv	(**132**), (**133**)
Archytea multiflora Benth	**51**
Bonnetia stricta (Nees) Nees & Mart	**4**, **7** **21**
Calophyllum bracteatum Thw	**71**
C calaba var calaba L	**71**–**73**
C thwaitesii Pl and Tr	**70**, **75**
C walkeri Wight	**74**, **76**–**78**
C wightianum T Anders	**117**
C zeylanicum Kosterm (=*C lankaensis* Kosterm)	**1**, **3** **4**, **18**, **56**, **73**, **81**, **116**
Caraipa grandiflora Mart	**28**, **36**, (**125**)
C psidifolia Ducke	**2**, **36**
C valioi Paula	**36**, (**125**)
Clusia elliptucifolia Cuatr	(**138**–**140**)
Clusia nemorosa G F W Meyer	(**148**)
Cratoxylum pruniflorum Kurz	**48**, {**120**}, {**121**}
Garcinia cambogia Desr	(**145**) (**147**)
G densivenia Engl	**88**
G hanburyi Hook f	**118**, **119**
G huillensis	(**145**)
G indica Choisy	**4**, (**145**), (**147**)
G kola Heckel	(**143**)
G mangostana L	**48**, **52**, **54**, **55**, **68**, **70**, **73**, **74**, **79**, **96**–**104** **108**, {**122**}, (**134**)
G mannii Oliv	(**144**)
G nervosa Miq	**109**
G ovalifolia Oliv	**86**, (**144**), (**146**)
G pedunculata Roxb	(**135**)
G polyantha Oliv	**90**, (**144**), (**146**)
G pyrifera Ridl	**112**–**114**
G quadrifaria Baill ex Pierre	**69**
G quaesita Kosterm	[**151 a**–**c**]
G staudtii Engl	**88**, (**144**)
G thwaitesii Pierre	**39**
G xanthochymus Hook f	**3**, **4**, **12**, **14**, **15**, **30**, (**134**)
G xishuanbannanensis Y H Li	(**144**), (**146**)

APPENDIX *Continued*

Haploclathra leantha (Benth.) Benth	**15**, **21**, **35**, **38**, **42**, **45**, **46**, **49**
H paniculata (Mart) Benth	**7**, **15**, **21**, **23**, **25**, **29**, **31**, **33**, **38**, **40**, **41**
H verticillata Ducke	**4**, **7**
Hypericum androsaemum L	**10**, **11**, **27**, **47**, **48**, **50**, **80**, **82**, (**124**)
H aucheri Jaub et Sprach	**48**, {**120**}
H balearicum L	**1**, **4**, **11**
H barbatum Jack	{**120**}
H boissieri Petrovic	{**120**}, {**121**}
H calycinum L	(**124**)
H canariensis L	**1**, **4**, **5**, **10**, **26**, **37**, **63**, (**124**), (**126**), (**127**)
H. degenii Bornm	**31**
H ericoides L	**1**, **4**, **34**, **43**, (**124**)
H hirsutum	{**121**}
H humifusum L	{**120**}
H. japonicum Thunb	{**149**}
H maculatum Crantz	**115**, {**120**}, (**124**)
H mysorense	**1**, **2**, **4**, **6**, **7**, **9**, **24**, (**127**)
H perforatum L	(**124**)
H rocheli Griseb and Schenk	{**120**}, {**121**}
H rumeliacum Boiss	{**120**}
H sampsonii Hance	**26**, **64**, **82**, {**120**}, {**121**}
Kielmeyera coriacea Mart.	(**128**)
K rubiflora Camb	**26**
K speciosa St Hill	**26**
Mahurea tomentosa Ducke	**4**, **7**
Mesua ferrea L	**42**
Platonia insignis Mart.	**32**, {**123**}
Psorospermum febrifugum Sprach	**11**, **44**, **53**, **57–61**
Rheedia benthamiana Pl and Tr	**86**, **88**, **89**, **91**
R. brasiliensis (Mart) Pl and Tr	**62**, **67**, **86–94**
R gardneriana Pl and Tr	**62**, **67**, **84**, **86–91**
R madrunno (HBK) Pl	(**144**)
Symphonia globulifera L	(**134**)
Tovomita brasiliensis Walp	**36**
T excelsa Andrade-Lima & G Maritz	**16**, **18**, **20**, **22**
T mangle G Maritz	**95**, (**141**), (**142**)
Vismia decipiens Schlect-Cham	(**136**), (**138**), (**139**)
V guaramirangae Huber	**1**, **2**, **4**, **7**, **8**, **11**, **13**, **15**, **17**, **19**, (**124–126**), (**136**), (**137**)
V guineensis (L) Choisy	**83**, **85**, **110**, **111**

REFERENCES

1 Sultanbawa, M U S (1980) *Tetrahedron* **36**, 1465
2 Hostettmann, K and Wagner, H (1977) *Phytochemistry* **16**, 821
3 Richardson, P M (1983) *Biochem. Syst Ecol.* **11**, 371, (1984) *ibid* **12**, 1
4 Birch, A J, Baldas, J, Hlubeck, J R, Simpson, T J and Westerman, P W (1976) *J Chem Soc, Perkin Trans I* 898
5 Roberts, J C (1961) *Chem Rev* **61**, 591
6 Dean, F M (1963) in *Naturally Occurring Oxygen Ring Compounds*, p 266 Butterworths, London
7 Gottlieb, O R (1968) *Phytochemistry* **7**, 411
8 Carpenter, I, Locksley, H D and Scheinmann, F (1969) *Phytochemistry* **8**, 2013
9 Afzal, M and Al-Hassan, J M (1980) *Heterocycles* **14**, 1173
10 Rezende, C M A Da M. and Gottlieb, O R (1973) *Biochem Syst. Ecol* **1**, 111
11 Melchoir, H (ed) (1964) *A. Engler's Syllabus Der Pflanzenfamilien* 12th edn. band 2 p 170 Gebruder Borntrager, Berlin.
12 Hutchinson, J (1973) *The Families of Flowering Plants* 3rd Edn, p 336 Oxford University Press, London
13 Thorne, R F (1983) *Nord J Botany* **3**, 85
14 Willis, J C (1973) *A Dictionary of Flowering Plants and Ferns* 8th Edn (revised by Shaw, H K A) Cambridge University Press, Cambridge
15 Dean, F M (1977) in *The Total Synthesis of Natural Products* (Apsimon, J, ed) Vol 1, p 534 Wiley, New York
16 Grover, P K, Shah, G D and Shah, R C (1955) *J Chem. Soc* 3982
17 Pillai, R K M, Naiksatam, P, Johnson, F, Rajagopalan, R, Watts, P C, and Cricchio, R and Borras, S. (1986) *J Org Chem* **51**, 717
18 Quillinan, A J and Scheinmann, F (1973) *J Chem. Soc., Perkin Trans I* 1329
19 Simoneau, B and Brassard, P (1984) *J Chem Soc, Perkin Trans I* 1507.
20 Cremins, P J, Saengchantara, S T and Wallace, T W (1987) *Tetrahedron* **43**, 3075
21 Gunasekera, S P, Sotheeswaran, S and Sultanbawa, M U S (1981) *J Chem Soc, Perkin Trans I* 1831
22 Marco, J A, Villar, E. and Seoane, E. (1981) *An Quim, Ser*

C **77**, 355 [(1982) *Chem Abst* **96**, 214363b]
23 Walia, S and Mukerjee, S K (1984) *Phytochemistry* **23**, 1816
24 Cardona, M L, Pedro, J R, Seoane, E and Vidal, R (1985) *J Nat Prod* **48**, 467, Cardona, M L, Fernandez, M I, Pedro, J R, Seoane, E and Vidal, R (1986) *ibid* **49**, 95
25 Cardona, M L and Seoane, E (1982) *J Nat Prod* **45**, 134
26 Gunatilaka, A A L, De Silva, A M Y J and Sotheeswaran, S (1982) *Phytochemistry* **21**, 1751
27 Kikuchi, T, Kadota, S, Matsuda, S, Tanaka, K and Namba, T (1985) *Chem Pharm Bull* **33**, 557
28 Delle Monache, F, Marquina Mac-Quhae, M, Delle Monache, G, Marini Bettolo, G B and Alves De Lima, R (1983) *Phytochemistry* **22**, 227
29 Gabriel, S J, Gottlieb, O R, Alves De Lima, R and Mesquita, A A L (1977) *Acta Amazonica* **7**, 289
30 Venkataraan, K (1973) *Proc Indian Nat Acad Sci* **39A**, 365, Baslas, R K and Kumar, P (1979) *Current Sci* **48**, 814
31 Kubitzki, K, Mesquita, A A L and Gottlieb, O R (1978) *Biochem Syst Ecol* **6**, 185
32 Gunatilaka, A A L, Balasubramaniam, S and Kumar, V (1979) *Phytochemistry* **18**, 182
33 Nagem, T J and Da Silveira, J C (1986) *Phytochemistry* **25**, 2681
34 Nielsen, H and Arends, P (1979) *J Nat Prod* **42**, 301
35 Habib, A M, Reddy, K S, McCloud, T G, Chang, C-J and Cassady, J M (1987) *J Nat Prod* **50**, 141
36 Nagem, T J and Da Silveira, J C (1986) *Phytochemistry* **25**, 503, (1988) *ibid* **27**, 646
37 Oliveira, W G de, Mesquita, A A L, Alves De Lima, R, Gottlieb, O R and Gottlieb, H E (1984) *Phytochemistry* **23**, 2390
38 Patnaik, M, Sharma, V K, Parmar, V S and Boll, P M (1987) *Acta Chem Scand*, *B* **41**, 210
39 Chen, M-T and Chen, C-M (1985) *Heterocycles* **23**, 2543
40 Gottlieb, O R and Nagem, T J (1977) *Rev Latinoam Quim* **8**, 137
41 Kitanov, G M and Achtardjev, Chr (1979) *Pharmazie* **34**, 447
42 Braz Filho, R, Miranda, C A S, Gottlieb, O R and Magalhaes, M T (1982) *Acta Amazonica* **12**, 801
43 Gunatilaka, A A L, Sriyani, H T R, Sotheeswaran, S and Waight, E S (1983) *Phytochemistry* **22**, 233
44 Gil, S, Parra, M, Sanz, V and Tortajada, A (1988) *J Nat Prod* **51**, 339
45 Gil, S, Sanz, V and Tortajada, A (1987) *J Nat Prod* **50**, 301
46 Holloway, D M and Scheinmann, F (1975) *Phytochemistry* **14**, 2517
47 Kitanov, G M and Blunova, K F (1980) *Khim Prir Soedin* 256 [(1980) *Chem Abst* **93**, 110568u]
48 Sen, A K, Sarkar, K K, Majumder, P C and Banerji, N (1981) *Phytochemistry* **20**, 183
49 Mahabusarakam, W, Wiriyachitra, P and Taylor, W C (1987) *J Nat. Prod* **50**, 474
50 Cotterill, P I, and Scheinmann, F and Puranik, G S (1977) *Phytochemistry* **16**, 148
51 Kupchan, S M, Streelman, D R and Sneden, A T (1980) *J Nat Prod* **43**, 296
52 Cassady, J M, Chang, C-J, Habib, A M, Ho, D, Amonkar, A and Masuda, S (1984) in *Natural Products and Drug Development* (Krogsgaard- Larsen, P, Christensen, S B and Kofod, H, eds), p 228 Munksgaard, Copenhagen
53 Pachuta, R R, Cooks, R G, Cassady, J M, Cong, P, McCloud, T G and Chang, C-J (1986) *J Nat Prod* **49**, 412
54 Habib, A M, Ho, D K, Masuda, S, McCloud, T, Reddy, K S, Aboushoer, M, McKenzie, A, Byrn, S R, Chang, C-J and Cassady, J M (1987) *J Org Chem* **52**, 412
55 Ho, D K, McKenzie, A T, Byrn, S R and Cassady, J M (1987) *J Org Chem* **52**, 342, see also Streelman, D R (1978) *Diss Abstr Int B* **39**, 759
56 Reddy, K S, Ko, O H, Ho, D, Persons, P E and Cassady, J M (1987) *Tetrahedron Letters* **28**, 3075
57 Scannell, R T and Stevenson, R (1986) *J Heterocyclic Chem* **23**, 857
58 Delle Monache, G, Botta, B, De Mello, I F, De Barros Coelho, J S and Menichini, F (1984) *J Nat Prod* **47**, 620
59 Delle Monache, G, Delle Monache, F, Marini Bettolo, G B and Alves De Lima, R (1983) *J Nat Prod* **46**, 655
60 Delle Monache, G, Delle Monache, F, Waterman, P G, Crichton, E G and Alves De Lima, R (1984) *Phytochemistry* **23**, 1757
61 Sen, A K, Sarkar, K K, Majumder, P C, Banerji, N, Uusvuori, R and Hase, T A (1982) *Phytochemistry* **21**, 1747
62 Waterman, P G and Hussain, R A (1982) *Phytochemistry* **21**, 2099
63 Dharmaratne, H R W, Sotheeswaran, S, Balasubramaniam, S and Reisch, J (1986) *Phytochemistry* **25**, 1957
64 Kumar, V, Sotheeswaran, S, Surendrakumar, S and Balasubramaniam, S (1982) *Phytochemistry* **21**, 807
65 Ampofo, S A and Waterman, P G (1986) *Phytochemistry* **25**, 2617
66 Ahluwalia, V K and Tehim, A K (1984) *Tetrahedron* **40**, 3303
67 Perveen, M and Khan, N U-D (1987) *Chem Ind* 418
68 Botta, B, Delle Monache, G, Delle Monache, F, Marini Bettolo, G B and Menichini, F (1986) *Phytochemistry* **25**, 1217
69 Waterman, P G and Crichton, E G (1980) *Planta Med* **40**, 351
70 Delle Monache, F, Botta, B, Nicoletti, M, Barros Coelho, I S de and Andrade Lyra, F D de (1981) *J Chem Soc, Perkin Trans 1* 484
71 Waterman, P G and Crichton, E G (1980) *Phytochemistry* **19**, 2723
72 Ampofo, S A and Waterman, P G (1986) *Phytochemistry* **25**, 2351
73 Marta, M, Delle Monache, F, Marini Bettolo, G B, Andrade Lyra, D, Mello, J F de and Lima, O G de (1976) *Gazz Chim Ital* **106**, 651
74 Sen, A K, Sarkar, K K, Majumder, P C, Banerji, N, Uusvuori, R and Hase, T A (1980) *Phytochemistry* **19**, 2223.
75 Sen, A K, Sarkar, K K, Majumder, P C and Banerji, N (1986) *Ind J Chem, Sect B* **25B**, 1157
76 Mesquita, A A L, Oliveira, W G de, Neiva, R M T and Gottlieb, O R (1975) *Phytochemistry* **14**, 803
77 Yates, P and Bhat, H B (1970) *Can J Chem* **48**, 680
78 Dutta, P K, Sen, A K, Sarkar, K K and Banerji, N (1987) *Ind J Chem, Sect B* **26B**, 281
79 Lee, H H (1981) *J Chem Soc, Perkin Trans 1* 3205
80 Arends, P (1969) *Tetrahedron Letters* 4893
81 Dean, F M, Khan, H, Minhaj, N, Prakash, S and Zaman, A (1980) *J Chem Soc, Chem Commun* 283
82 Lu, G, Yang, X and Huang, Q (1984) *Yaoxue Xuebao* **19**, 636 [(1985) *Chem Abst* **102**, 21181z]
83 Balasubramanian, K and Rajagopalan, K (1988) *Phytochemistry* **27**, 1552
84 Kitanov, G M and Blunova, K F (1978) *Khim Prir Soedin* 524 [(1978) *Chem Abstr* **89**, 176377e]
85 Kitanov G M (1987) Chemotaxonomic Investigation of

two closely related species of *Hypericum*, in *Proceedings of Fourth National Conference—Botany* Vol 1, p 91–96, Sofia
86 Lebreton, P and Bouchez, M -P (1967) *Plant Med Phytother* **1**, 188
87 Kitanov, G (1988) *Khim Prir Soedin* 132 [(1988) *Chem Abstr* **108**, 201791f]
88 Nielsen, H and Arends, P (1978) *Phytochemistry* **17**, 2040
89. Cardona, M L and Seoane, E. (1982) *Phytochemistry* **21**, 2759
90 Vishwakarma, R A, Kapil, R S and Popli, S P (1986) *Indian J Chem, Sect B* **25B**, 1155
91 Pinto, M M De M, Mesquita, A A L and Gottlieb, O R (1987) *Phytochemistry* **26**, 2045
92 Vishwakarma, R A, Kapil, R S and Popli, S P (1986) *Indian J Chem, Sect B* **25B**, 1021
93 Locksley, H D and Murray, I G (1971) *J Chem Soc, (C)* 1332
94. Locksley, H D, Moore, I and Scheinmann, F (1967) *Tetrahedron* **23**, 2229
95 Rama Rao, A V, Sarma, M R, Venkataraman, K and Yemul, S S (1974) *Phytochemistry* **13**, 1241
96 Delle Monache, G, Gonzalez Gonzalez, J, Delle Monache, F and Marini Bettolo, G B (1980) *Phytochemistry* **19**, 2025
97 Gonzalez Gonzalez, J, Cuellar, V, Betancourt, A and Pinzon, M I (1983) *Phytochemistry* **22**, 2088
98. Ahluwalia, V K, Khanna, M. and Singh, R P (1981) *Indian J Chem, Sect B* **20B**, 990
99. Pathak, V P and Khanna, R N (1982) *Bull Chem Soc Jpn* **55**, 2264
100 Pathak, V P, Saini, T R and Khanna, R N (1984) *Indian J. Chem, Sect B* **23B**, 571
101 Delle Monache, F, Delle Monache, G, Marini Bettolo, G B., Andrade Lyra, D and Lwande, W (1984) *Gazz Chim Ital* **114**, 55
102. Hussain, R A, Owegby, A G, Parimoo, P and Waterman, P G (1982) *Planta Med* **44**, 78
103 Hussain, R A and Waterman, P G (1982) *Phytochemistry* **21**, 1393
104. Zhong, J, Wang, W, Tao, G and Li, K (1986) *Acta Bot Sin* **28**, 533 [(1987) *Chem Abst* **106**, 15766k].
105 Botta, B, Marquina Mac-Quhae, M, Delle Monache, G, Delle Monache, F and Mello, J F de (1984) *J Nat Prod.* **47**, 1053
106 Rama Rao, A V and Venkatswamy, G (1981) *Indian J Chem Sect B* **20B**, 983
107 Rama Rao, A V., Venkatswamy, G and Pendse, A D (1980) *Tetrahedron Letters* **21**, 1975
108 Krishnamurthy, N, Lewis, Y S and Ravindranath, B (1981) *Tetrahedron Letters* **22**, 793, Rama Rao, A V, Venkatswamy, G and Yemul, S S (1980) *Indian J Chem, Sect B* **19B**, 627
109. Bakana, P, Claeys, M, Totte, J., Pieters, L. A. C., Van Hoof, L, Tamba, V, Van der Berghe, D A and Vlietinck, A. J (1987) *J Ethnopharmacol* **21**, 75
110 Delle Monache, F., Delle Monache, G., Pinheiro, R M and Radics, L (1988) *Phytochemistry* **27**, 2305
111 Krishnamurthy, N, Ravindranath, B, Row, T N G. and Venkatesan, K (1982) *Tetrahedron Letters* **23**, 2233
112 Ishiguro, K, Yamaki, M., Takagi, S., Yamagata, Y and Tomita, K (1985) *J Chem Soc, Chem Commun* 26
113 Gunatilaka, A A L., Sotheeswaran, S and Sriyani, H. T B (1982) *Tetrahedron Letters* **23**, 2987
114. Gunatilaka, A A. L, Sriyana, H T B and Sotheeswaran, S (1984) *Phytochemistry* **23**, 2679
115 Hegnauer, R (1986) *Phytochemistry* **25**, 1519
116. Waterman, P G and Gray, A I (1987) *Nat. Prod Rep.* **4**, 175
117 Gershenzon, J and Mabry, T J (1983) *Nord J Botany* **3**, 5
118 Hutchinson, J (1973) *The Families of Flowering Plants* 3rd Edn, p 332 Oxford University Press, London
119 Cronquist, A (1981) in *An Integrated System of Classification of Flowering Plants*, p. 320 Columbia University Press, New York
120 Stevens, P F (1980) *J Arn Abor.* **61**, 117
121 Kumar, V Ramachandran, S, and Sultanbawa, M. U S (1976) *Phytochemistry* **15**, 2016
122. Somanathan, R and Sultanbawa, M U S (1974) *J Chem Soc, Perkin Trans 1* 2515
123 Dahanayake, M, Kitagawa, I, Somanathan, R. and Sultanbawa, M U S (1974) *J Chem Soc, Perkin Trans 1* 2510.
124 Somanathan, R and Sultanbawa, M U S (1972) *J Chem Soc., Perkin Trans 1* 1935
125 Bandara, B M R, Dharmaratne, H W R, Sotheeswaran, S and Balasubramaniam, S (1986) *Phytochemistry* **25**, 425
126 Samaraweera, U, Sotheeswaran, S, Sultanbawa, M. U S. and Balasubramaniam, S (1983) *J Chem Soc., Perkin Trans 1* 703
127 Waterman, P G. and Hussain, R A (1983) *Biochem Syst Ecol* **11**, 21
128. Robson, N. K (1973) *Bull. Br. Mus Nat Hist (Bot.)* 293
129 Cronquist, A (1981) in *An Integrated System of Classification of Flowering Plants*, p 337 Columbia University Press, New York
130 Kitanov, G, Assenov, I and Dam The Van (1988) *Die Pharmazie* **43**, (in press); see also Dam, T V, Kitanov, G and Asenov, I (1987) *Farmatsiya*, **37**, 30 [(1988) *Chem. Abst.* **107**, 194972q]
131 Kitanov, G M. and Blinova, K F. (1987) *Khim. Prir Soedin* 185.
132 Cassinelli, G, Geroni, C, Botta, B., Delle Monache, G. and Delle Monache, F (1986) *J Nat Prod* **49**, 929.
133 Delle Monache, G, Delle Monache, F, Benedelto, R. D and Oguakwa, J U (1987) *Phytochemistry* **26**, 2611
134 Floss, H G and Rettigg, A (1964) *Z Naturforsch B* **19**, 1103
135 Gupta, P and Lewis, I R (1971) *J Chem Soc (C)* 629
136 Bennett, G I and Lee, H H (1988) *J Chem Soc., Chem Commun* 619
137 Lewis, J R (1963) *Pro Chem Soc.* 373
138 Atkinson, I E and Lewis, I R (1969) *J. Chem Soc. (C)* 282.
139 Ollis, W D, Ramsay, M. V. J, Sutherland, I O. and Mongolsuk, S (1965) *Tetrahedron* **21**, 1453
140 Karunanayake, S, Sotheeswaran, S, Sultanbawa, M U S. and Balasubramaniam, S (1981) *Phytochemistry* **20**, 1303.
141 Swain, T (1975) in *The Flavonoids* (Harborne, J B., Mabry, T. J and Mabry, H, eds) p. 1116 Chapman & Hall, London
142 Bate-Smith, E. C. and Harborne, J B (1963) *Nature* **198**, 1307
143. Fujita, M and Inoue, T (1980) *Chem. Pharm Bull* **28**, 2476 and 2482
144 Fujita, M and Inoue, T. (1981) *Phytochemistry* **20**, 2183
145. Murakami, T, Tanaka, N, Hiroaki, W, Saiki, Y and Chen, C M (1986) *Yakugaku Zasshi* **106**, 378 [(1986) *Chem Abst.* **105**, 168852q]
146 Schlaufelberger, D and Hostettmann, K. (1988) *Planta Med* **49**, 221
147 Ravikumar, K and Rajan, S. S (1987) *Acta Cryst.* **C43**, 1927
148 Douros, J. and Suffness, M. (1981) *Cancer Treatment Revs* **8**, 63

149 Cassady, J M, Chang, C-J, and McLaughlin, J L (1981) in *Natural Products as Medicinal Agents* (Beal, J L, and Reinhard, E eds), p 93 Hippocrates, Stuttgart
150 Shankaranarayanan, D, Gopalakrishnan, C, and Kameswaran, L (1979) *Indian J Pharmaceut Sci* **42**, 78
151. Shankaranarayanan, D, Gopalakrishnan, C, Kameswaran, L and Arumugam, S (1979) *Mediscope* **22**, 65
152 All-Union Scientific-Research Institute of Medicinal and Aromatic Plants (1983) Japanese Patent 72, 517 [(1983) *Chem Abstr* **99**, 76864z]
153 Chattopadhyay, U, Das, S, Guha, S and Ghosal, S (1987) *Cancer Letters* **37**, 293
154 Bhattacharya, S K, Ghosal, S, Chaudhuri, R K and Sanyal, A K (1972) *J Pharm Sci* **61**, 1838
155 Shankaranarayanan, D, Gopalakrishnan, C and Kameswaran, L (1979) *Arch Int Pharmacodyn* **239**, 257
156 Gopalakrishnan, C, Shankaranarayanan, D, Nazimudeen, S. K and Kameswaran, L (1980) *Indian J Pharmacol* **12**, 181.
157 Gopalakrishnan, C, Shankaranarayanan, D, Kameswaran, L and Nazimudeen, S K (1980) *Indian J Exp Biol* **18**, 843
158 Pai, B R, Natarajan, S, Suguna, H, Kameswaran, L, Shankaranarayanan, D and Gopalakrishnan, C (1979) *J Nat Prod* **42**, 361
159 Suzuki, O, Katsumata, Y, Oya, M, Chari, V M, Vermes, B, Wagner, H and Hostettmann, K (1981) *Planta Med* **42**, 17
160 Noro, T, Ueno, A, Mizutami, M, Hashimoto, T, Miyase, T, Kuroyanagi, M and Fukushima, S (1984) *Chem Pharm Bull* **32**, 4455
161 Sundaram, B M, Gopalakrishnan, C, Subramanian, S, Shankaranarayanan, D and Kameswaran, L (1983) *Planta Med* **49**, 60
162 Mahabusarakam, W, Wiriyachitra, P and Phongpaichit, S (1986) *J Sci Soc Thailand* **12**, 239
163 Sundaram, B M, Gopalakrishnan, C and Subramanian, S (1986) *Arogya* **12**, 48, (1986) [*Chem Abst* **105**, 57798y]
164 Goshsal, S, Biswas, K and Chaudhuri, R K (1978) *J Pharm Sci* **67**, 721
165 Hambloch, H, Frahm, A W and Wiedemann, B (1985) *Eur J Med Chem* **20**, 71