Xanthone Dimers: A Rare Case of Being Common and Privileged

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ARTICLE

Xanthone Dimers: A Compound Family which is both Common and Privileged

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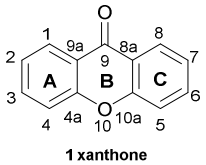
Xanthone dimers are a widespread, structurally-diverse family of natural products frequently found in plants, fungi and lichens. They feature an intriguing variety of linkages between the component xanthones (benzannulated chromanones). These synthetically elusive secondary metabolites are of great interest due to their broad array of bioactivities, which has led to the xanthones being designated as 'privileged structures'. We seek herein to give an overview of all reliably-described xanthone dimers, their structures, occurrence, and the bioactivities established to date. The possible biosynthetic pathways leading to members of this family are also discussed in light of our current knowledge.

Introduction

Xanthones comprise a group of structurally diverse, biosynthetically intriguing, biologically active and synthetically challenging natural products. Many and many xanthones have been found to exhibit pronounced biological activities, for example anti-tumour effects.[1-5] Xanthone chemistry is satisfyingly rich, with the conjugated donor-acceptor motif of the central *B*-ring ensuring that these compounds display a degree of personality greater than their apparently simple core structure might suggest.



1 xanthone

Figure 1: Xanthone monomer core with numbering

The xanthone family has been studied for over a century since the early 1900's[6, 7] and has since been investigated and reviewed, particularly for the monomeric species and plant-derived species.[8-14] Several reviews on xanthones have been published in recent years, covering xanthones from fungi,[15] lichens and bacteria,[16] structure-activity relationships,[2] antimalarial properties of xanthones,[17] biological activity,[18] chemical synthesis of xanthone cores,[19-21] and their biosynthesis.[22-27] Nonetheless, the field of xanthone chemistry is growing rapidly; every few years see the publication of an update on novel naturally-occurring xanthones.[8, 21, 28-30] Analytical techniques have been optimised specific for xanthones, including crystallography[31] and chromatographic methods.[32] The structure, activity and synthesis of polycyclic yet monomeric xanthones has recently been reviewed,[33] as well as the specific class of the caged xanthones.[34, 35] Most of these articles focus mainly on monomeric xanthones, and to date no has focused on dimeric and trimeric xanthones.

For the sake of simplicity and easy comparison between structural features, structural numbering will follow the monomeric parent xanthone core (**1**, Figure 1) throughout this Review.

Biosynthesis

The biosynthesis of dimeric xanthones is a topic which stands in need of further research progress, especially the identification and description of the key dimerisation processes (see also references[15, 16]). As the biosynthesis of the dimeric structures is a point of considerable interest, remains largely unknown, we will give a necessarily brief outline of the achievements so far - the full elucidation of the biosynthesis no doubt awaits us close by over the horizon.

Monomer Xanthones

It has been for some time that the biosynthesis of the monomeric xanthone core proceeds differently in fungi[25, 36] and higher plants.[37, 38] The synthesis of the xanthones in fungi has been studied in detail since the radiolabelled acetate feeding experiments of Birch in the 1950's, showing that polyketides are the biosynthetic precursors of the xanthone core for fungi. More recently, Simpson has reported findings resulting from the sequencing of the *Aspergillus nidulans* genome.[39] The sequencing revealed the presence of 32 clusters containing

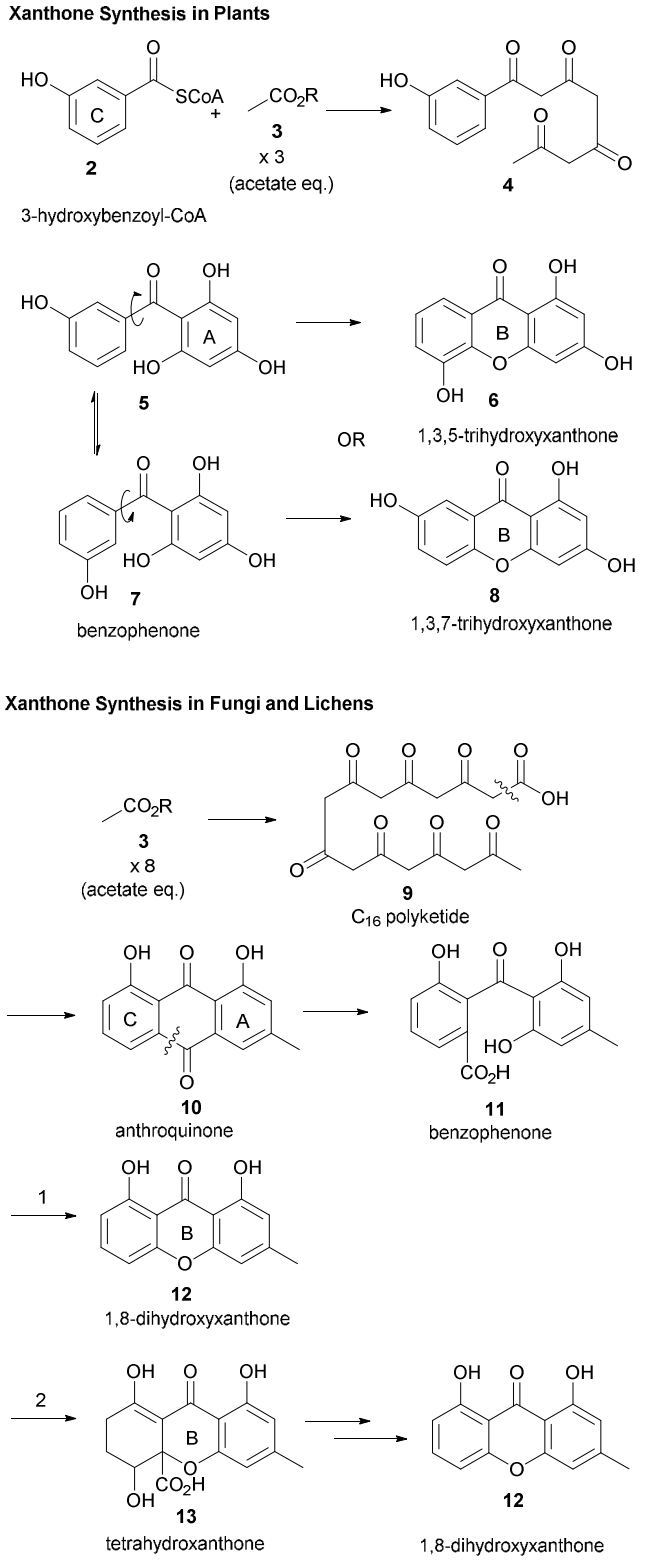
polyketide synthase (PKS) genes, which were studied by gene deletion to reveal information about the biosynthetic pathway which converts emodin *via* key steps of oxidative ring-scission and decarboxylative cyclisation to xanthones and eventually prenylated and cyclised products such as shamixanthone, tajixanthone and sterigmatocystin. As part of a comprehensive study on the formation of aflatoxin in *Aspergillus* species, Townsend and co-workers described the generation of xanthone monomers through a complex sequence of epoxidation, rearrangement, deoxygenation, Baeyer−Villiger oxidation, and further deoxygenation leading to the tricyclic xanthone core of sterigmatocystin.[40] Interpretation of the sequences may differ markedly[41] in terms of the sequences of events, and the structural homology of biomolecules involved in the pathway in differing species may not, in fact, be a reliable method for determining correlations between pathways.

Müller and co-workers have recently discussed the importance of reductive steps in the synthesis of xanthones commencing from the (polyketide-derived) anthraquinone, emodin, and passing through chrysophanol.[42] Contrastingly, the biosynthesis of xanthones in plants results from a convergent synthesis of polyketide and shikimic acid pathways, whereby 3-hydroxybenzoyl-CoA (obtained from an early shikimate pathway intermediate) is condensed with a polyketide, which may be then cyclised to form the *C*-ring and then *B*-ring.[26] A consequence of these two distinct pathways, both of which pass through a freely-rotatable benzophenone intermediate, is that the pattern of oxidation between xanthones from plant and fungi frequently differs. Fungal xanthones (or their biosynthetic precursors) almost ubiquitously display *C*-1 and -8-hydroxylation, whilst plants frequently display *C*-1, -3 and -5 or -7-hydroxylation.

In terms of further diversification of the xanthone core, some processes have now understood better than others. The investigations of Elix and co-workers have led to a fuller understanding of some of the pathways of further structural elaboration of the xanthone nucleus in lichens. Particularly, cladistical/phylogenetic analysis of related species was studied to develop a fuller understanding of the relationship between enzymes responsible for methylation and chlorination.[43,44] Prenylation of the dimers is frequently found in plant-derived xanthones.[45] Pendant sugars are also found as a structural feature of dimers, see for example puniceaside C (**72**, plant derived) and Hirtusneanoside (**120**, lichenoid). It is also known that some substituents are removed from the xanthone core, such as the reduction of hydroxyl functions and reductive dearomatisation.

Xanthone Dimerisation

There are a variety of ways in which a dimeric and trimeric xanthones can be linked: (i) a rotatable or atropisomeric biaryl *C*–*C* bond or (ii) a biaryl ether *C*–*O*–*C* linkage. Also, because xanthones, particularly from plants, can be decorated with prenyl groups, the linkages are also often in the form of (iii) aryl–*O*–alkyl linkages, or (iv) prenyl derivative-prenyl derivative linkages. The incorporation of nitrogeneous bases to form polyaromatic antibiotic xanthones is also frequently observed, and readers are directed to the recent review by Porco and co-workers on this subject.[33]

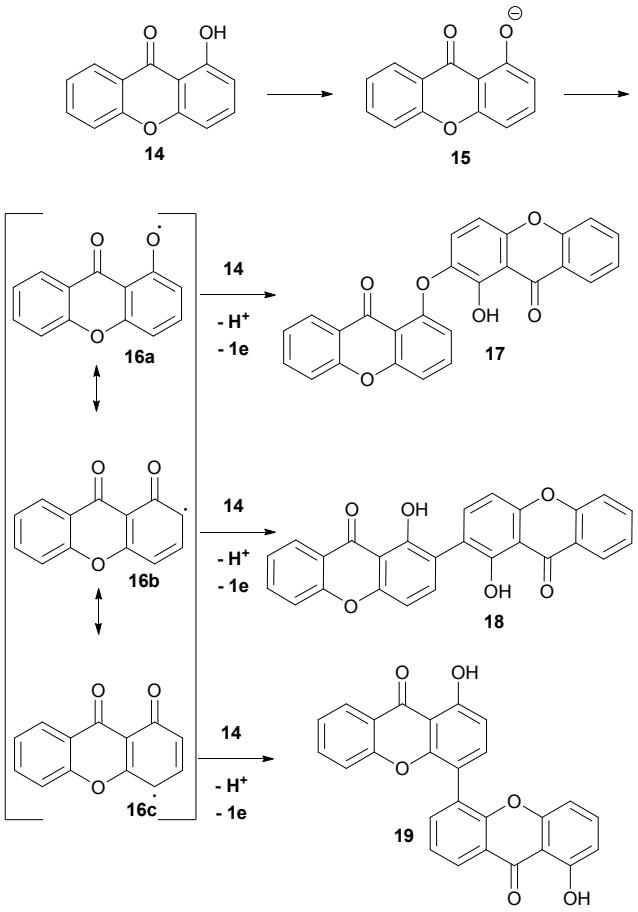


Scheme 1: Xanthone biosynthesis differs in plants and fungi.

One of the more common ways in which dimerisation is found

in the xanthones is through the biaryl linkage. Regio- and stereo-selective biaryl linkage of phenolic compounds is common in plants, bacteria, lichen, and fungi –as Bringmann and co-workers noted in their seminal work on natural biaryl linkages, "wherever in Nature phenolic aromatics can be found… the corresponding homo- or hetero-dimeric biaryls have to be expected".[46] Certainly, the discovery of the blennolides (hemisecalonic acids)[47] in 2008 supported the putative dimerisation of discrete monomers as the likely method of dimer formation, rather than a more complex and difficult to imagine tandem biosynthesis pathway –the side-by-side cyclisation of a double-length polyketide to form *e.g.* a secalonic acid seems unlikely. Despite efforts in detailed study biosynthesis of dimeric xanthones, particularly the secalonic acids by Frank and co-workers,[23, 40, 48-50] the dimerisation of xanthones remains a tricky subject for both the synthetic and biosynthetic chemist –the extent of involvement of enzymes, and their nature, is at present unclear. There has been, at the time of writing, no direct observation of enzymatic dimerisation of the monomer units.

Enzymatically-mediated or not, the oxidative pathway which is most commonly invoked is shown here (Scheme 2), whereby single electron transfer deprotonation of a hydroxyxanthone, 2, leads to an intermediate which can be readily oxidised by single-electron-transfer to xanthonyl radical **16**. Resonance contributors of the delocalised aryl radical, **16a**–**c**, can then couple to electron-donors, notably the *ortho* and *para*-*C* positions.



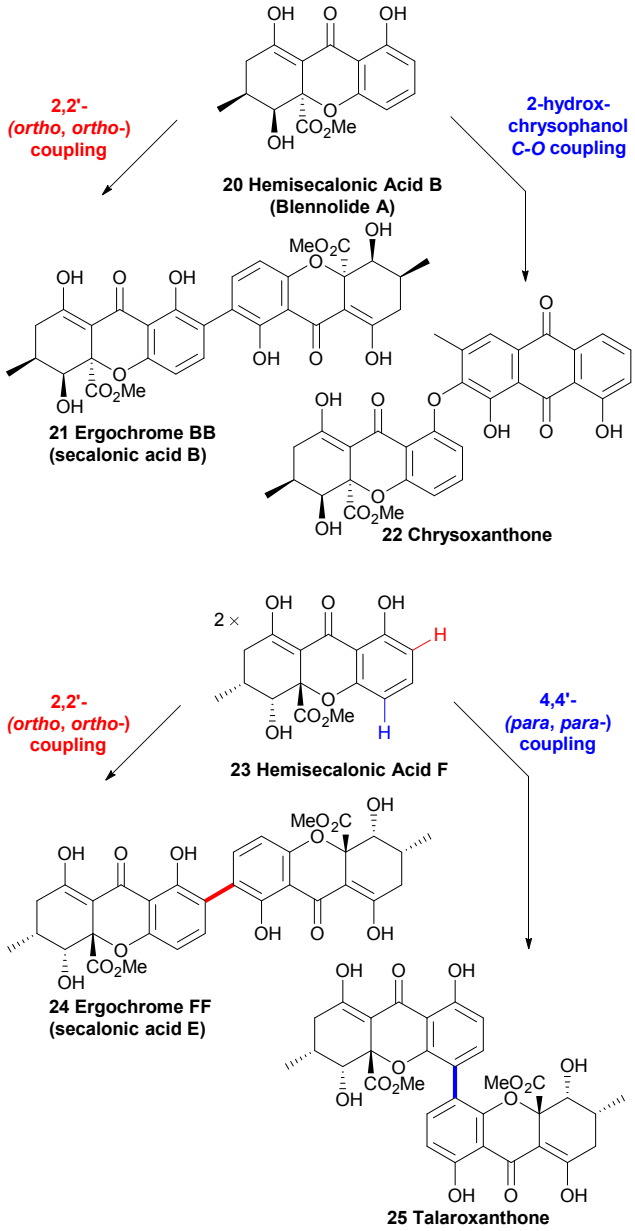
Scheme 2: Phenolic dimerisation reactions adapted for xanthones. For clarity, coupling of **16a–c** at the *ortho*-position of **14** is shown.

Regiochemical Evidence for Enzyme Dimerisation

The resulting biaryl bond linkages are formed which, in the absence of an enzyme or other structurally-influencing substrate, is determined largely by the spin-density distribution of the radical generated, and presumably in some cases other inherent stereoelectronic characteristics of the substrate molecule. As Kozlowski has put it, in the absence of external factors, "the substrate typically dictates the available coupling products".[51] This leads us as chemists to an interesting corollary –if there are differing regio- and atropo-isomeric biaryl-linked dimers of the same substrate to be found in Nature, then it must be the case that there are external forces at play in their biosynthesis to lead to this divergence, rather than 'spontaneous' oxidative dimerisation with oxidants such as intracellular O_2. Prominent examples supporting this line of thinking can be seen in Scheme 3, where both secalonic acid B/chrysoxanthone and secalonic acid E/Talaroxanthone are presumably generated with alternative (chemo- and regio-) selectivity from the monomer units, hemisecalonic acids B and F, respectively. The oxidative dimerisation of the xanthones is thus most likely mediated by enzymes, as shown for a number of model compounds.[52-54] It can be mimicked by chemical oxidases.[55] In some cases, the dimerisation led to the formation

of diaryl ethers (*e.g.* chrysoxanthone **22**, Scheme 3) instead of to a *C*—*C* bond formation.

Hemisecalonic acid A[47] are dimerised at the *ortho*-positions to form secalonic acid B **21** (Scheme 2; see under for more information) in a variety of fungal species.[49,148-150,153,185-187] From the same substrate in the case of the xanthone-anthraquinone chrysoxanthone, the coupling of the hemisecalonic acid A with a 2-hydroxy variant of chrysophanol, a widespread polyketide natural product, dimerisation leads to the *C*—*O* bond formation of diaryl ethers *i.e.* chrysoxanthone.[56] Another example of biosynthetic divergence is likely involved in the regioisomeric selectivity which leads to the formation of talaroxanthone **25**, a 4,4′-linked xanthone dimer (from the endophytic fungi *Talaromyces sp.*)[57] and secalonic acid E **24**, a 2,2′-linked xanthone dimer (from *e.g. Phoma terrestris*).[58, 59] That a statistical mixture of the three regioisomers is produced by each of the organisms in question and the two differing regioisomers have been selectively isolated by the researcher groups in each case is highly unlikely (see Scheme 2). The selective discovery of these regioisomers can therefore be considered indirect evidence for the active role of yet-to-be discovered enzymes.

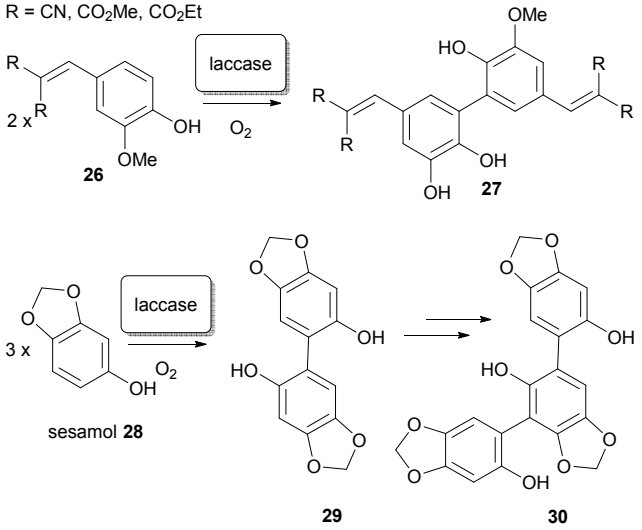


Scheme 3: Multiple pathways from the same monomer units strongly suggest the involvement of enzymatic processes in xanthone dimerisation.

In the laboratory, regioisomeric control over the biaryl bond formation[60-62] is often difficult to impose, and frequently requires innovative solutions.[63-66] In natural biosynthesis, it has been demonstrated that selectivity between 2,2′- 2,4′- and 4,4′-coupling can presumably be imposed by enzymes, although little direct evidence exists for this –no enzyme has yet been identified which fulfils the role of regioselective differentiation in dimerisation of xanthones in nature. Nonetheless, high selectivity for such processes has been demonstrated with enzymes in the laboratory, oxidative dimerisation at a specific *ortho*-position to form ferulic acid derivatives has been reported by Beifuss and co-workers has been achieved by application of the (single electron) oxidase enzyme[67, 68] laccase,[69] from

Trametes versicolor in the presence of O_2.[70] Additionally, selective coupling at the *C*-6 position of sesamol led to dimer intermediates and then trimers in good yield.[71] The outcome was markedly different than in the application of laccase from *Agaricus bisporus*, and also from electrochemical non-enzymatic oxidative coupling of this substrate by the method of Waldvogel and co-workers.[72, 73] Aside from their potential relevance to xanthone dimerisation, the synthetic application of enzyme-catalyzed transformations has significant additional benefits: they can be performed in aqueous solvent systems and under mild reaction conditions, a remarkably broad substrate spectrum that can be expanded even more by using mediators.[74]

It is therefore logical to support the assertion of Bringmann and co-workers that the dimerisation of phenolic aromatics (both *C*-*C* and *C*-*O* coupling) is through "- mostly – enzymatically-assisted biogenetic pathways".[41] Based on related processes in the chemical literature on both natural products[75-79] and synthesis,[80-82] one possibility is that a laccase is responsible. Another possibility is a monooxygenase, such as cytochrome P450; evidence for a likely mechanism for stereoselectivity is also found in this case.

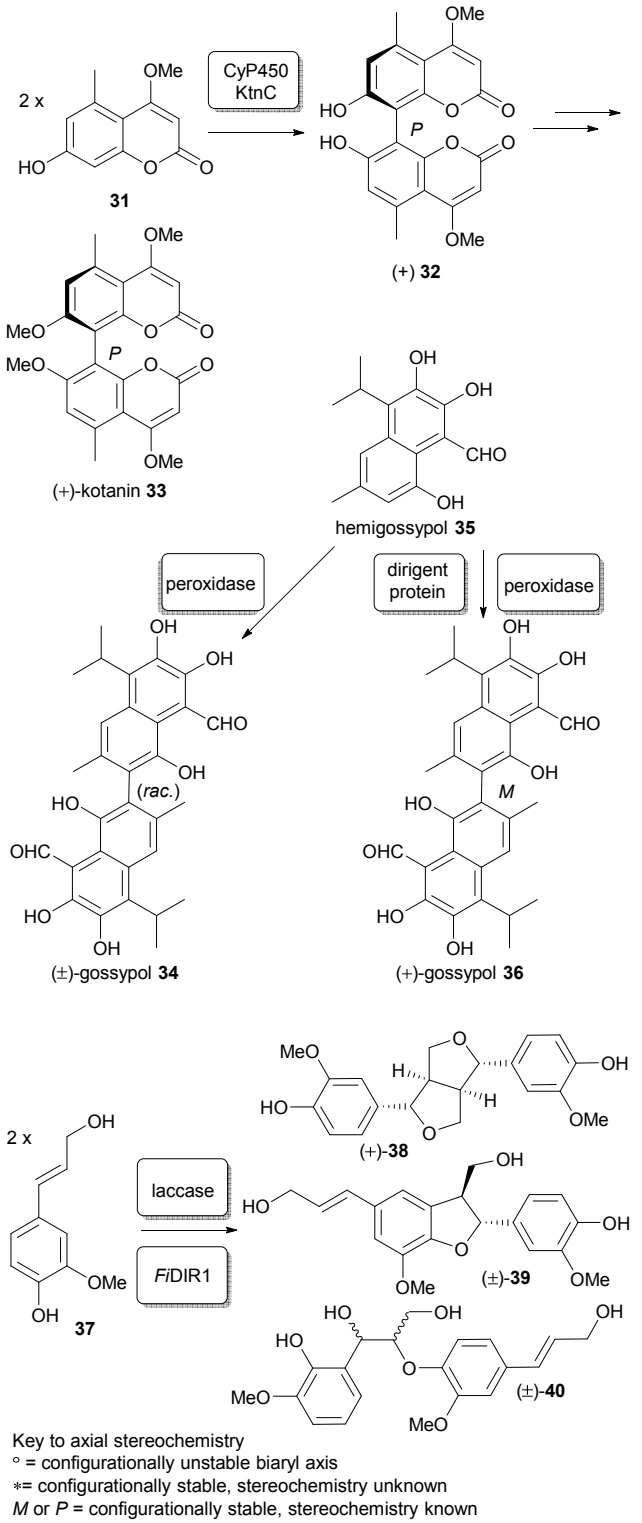


Scheme 4: The synthetic usage of laccase enzymes in biphenolic coupling to biaryl-linked dimers

Stereochemical Features of the Biaryl Xanthone Dimer

Substituted biaryls exhibit varying degrees of barrier to rotation, ranging from freely rotating (microsecond time-frame) through slow room-temperature interconversion up to atropisomers which may be isolable and thereafter stable, dimeric xanthones show this feature also. Stereochemical biaryl bond formation is displayed in the secondary metabolism each of bacteria, fungi, lichens and plants, and has herein been denoted alongside the structures of biaryl-linked dimers utilising the notation of Bringmann and co-workers (see Scheme 5).[44] As both chiral and *meso*-dimers have been found in the secalonic acid series, various mechanisms for the origin of the dimers can be invoked. The reasons for this could certainly be due to different biosynthesis routes employed between the classes of species. In fungi, all xanthone dimers display a biaryl xanthan-xanthone bond between one or more di- or tetra-hydro xanthones. It could possibly be argued that the dimerisation process could be influenced by the asymmetrically-substituted C-ring, a possible explanation for non-enzymatic axial chirality generation. However, the fully aromatic xanthone dimer ploiarixanthone **68**, which is optically active ($[\alpha]_D^{25} = +23°$),[83] must involve axial-chirality influencing biomolecules in the stereospecific dimerisation step.

The involvement of stereoselectivity-mediating proteins may prove to be the origin of stereospecific pathways in the formation of dimeric xanthones. One case where the explanation for the regio- and stereo-chemical control observed in a biphenolic coupling has been uncovered is the mechanism of selective phenol coupling in *Aspergillus niger* by Müller and co-workers.[54] They showed that an oxidative phenol coupling is also the key stereo-divergent step in the formation of *P*-(+)-kotanin (**33**, Scheme 5) from two equivalents of coumarin **31** catalyzed by cytochrome P450 monooxygenase KtnC, which was identified by targeted gene deletion in the *A. niger* strain. The facially-selective interaction of the two monomer subunits with the heme-containing active site of the CyP450 was modelled *in silico* by homology studies and docking of both the substrates and product. Stipanovic and co-workers showed enzymatic coupling of hemigossypol (**35**, Scheme 5) this compound by *in vitro* application of a pure peroxidase only led to a racemic product (±)-gossypol, whereas the addition of a cotton-plant dirigent protein gave predominantly (+)-(*S*)-gossypol.[84a] Naturally-occurring gossypol is found as a mixture of (+) and (—) isomers, which have found to exist in a continuum of ratios between 68 and 2% (—)-(*R*)-gossypol, depending on the strain of the cotton plant *G. barbadense*,[84b] possibly indicating a variation in the type or extent of dirigent protein control in the coupling. Stereoselective phenol coupling of **37** resulting in *C*– and *O*–alkylation products (+)-**38** or racemic **39** and **40**, reminiscent of the kind of transformations of some linked and/or cyclized dimeric xanthones, has also been achieved with a combination of laccase and dirigent protein *Fi*DIR1.[85] It may be the case that for xanthones there are also mediator proteins associated with oxidase enzymes involved in the stereoselective generation of the biaryl bonds.



Scheme 5: Examples of stereoselective phenolic coupling with enzymes *in vitro*

The absolute stereochemical assignation of regioisomerically identical xanthone dimers isolated from different biological sources is, unfortunately, in many cases incomplete. X-ray structures have been used to determine the relative and absolute stereochemistry of the stereochemical centres and axes (*e.g.* for Phomoxanthone A **106** and phomalevones A **103**).[86] In some cases, however, modern DFT calculations have allowed to compute CD spectra which were used for comparison with experimental data (blennolides).[47] In particular, the quantitative consideration of vibronic effects, conformer equilibria and solvents effect were included in most of the models.[87] As biological activity and their biology targets are different for different diastereomers (e.g. compare secalonic acid A and E), it is very important to address stereochemical issues of dimeric xanthones. Unfortunately, many data are not available (due to the lack of instrumentation and/or authentic material).

The True Biological Sources of Xanthone Dimers?

In some cases researchers have reported dimeric xanthones as being isolated from endophytes.[57, 86,88-90] Certainly culture broth production of dimeric xanthones has demonstrated that this class of molecules can be produced by fungi alone. This raises the question for 'plant-derived' compounds: Are the plants really the true producers, or fungi? Is there a mixed origin, or is it really only the (undetected) fungi which produce the xanthone dimers?

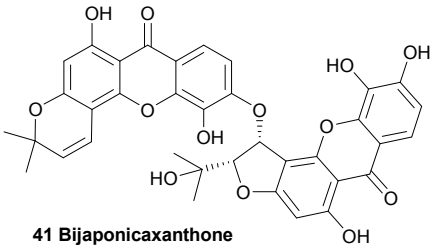
For monomeric xanthones, the plant-fungus contributions have been at least partially unveiled on at least two occasions. In the biosynthesis of the monomeric xanthone 2,7-dichlorolichexanthone (not shown) was isolated from samples of the lichen *Lecanora dispersa*. Cultures of the fungal species in the absence of the alga, the xanthone biosynthesis was halted.[91] In an example for xanthone dimers, the eumitrins (see below**)** are produced by the lichen (algae-fungal symbiotic organism), and not by only the fungus in isolation.[92] It is conceivable that in some situations that involve plant-microbe combinations, the biosynthesis may even involve a to-and-thro sequence of enzymatic transformations carried out by each organism. Such a scenario, if it does exist, is likely to be complex and case-specific.

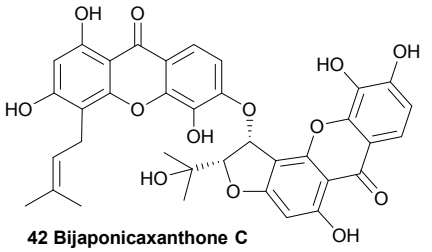
Xanthone Dimers from Plants

Xanthone dimers from plants, like the monomers themselves, commonly feature prenylated and multi-prenylated cores. The presence of these many prenylated monomeric xanthones shows that prenylation occurs readily prior to dimerisation, although there is no evidence to suggest that it does not also occur post-dimerisation.

Bijaponicaxanthones

Several interesting xanthones where isolated from the ethanol extracts of the dried aerial parts of the *Hypericum japonicum*, a Chinese medicinal plant, including one dimeric xanthone named bijaponicaxanthone (**41**). By comparing the NMR spectra with known compounds such as the monomeric xanthone isojacareubin (not shown) and by analysing additional 2D NMR spectra, its structure could be assigned. The relative configuration between the two chiral centres was determined to be *cis* for the two protons, based on their coupling constant.[93-95]

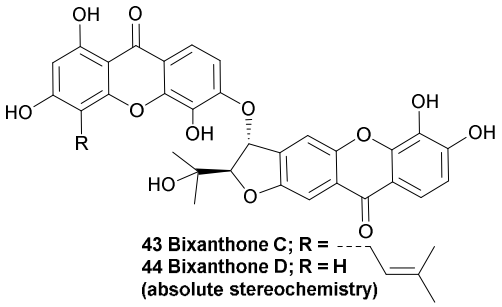

41 Bijaponicaxanthone


42 Bijaponicaxanthone C

In 2005 a similar dimeric xanthone was isolated from the *Hypericum japonicum*. After detailed structural analysis the xanthone was found to be prenylated instead of having a fourth ring and the natural product was named bijaponicaxanthone C (**42**).[96] Bijaponicaxanthone C was also reported to have been isolated from the roots of the *Hypericum riparium* plant.[97]

Bixanthones

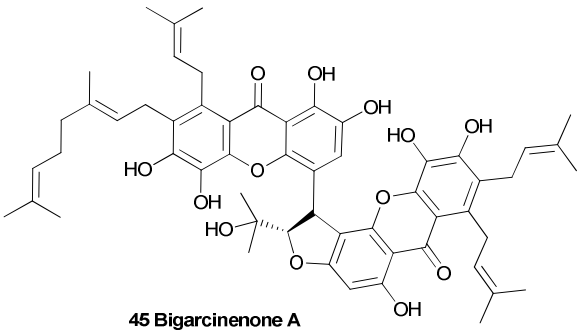
The structurally very similar Bixanthones C and D (**43**, **44**), as reported in a Chinese patent, were also isolated from the *Hypericum japonicum.* The patent claims these compounds as active ingredients in a traditional Chinese medicine, which is used to treat a variety of liver diseases and describes the use of the flavone component of that plant species medicament for treating hepatic fibrosis.[98] These compounds are missing OH groups on the furannulated xanthone component, presumably due to enzymatic reduction.

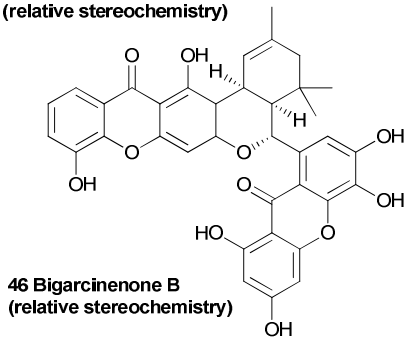

43 Bixanthone C; R =
44 Bixanthone D; R = H
(absolute stereochemistry)

Bigarcinenones

Since the plant *Garcinia xanthochymus* is widely used as traditional Chinese medicine, Yang *et al.* investigated the extracts from the bark of the plant. They observed a strong antioxidant activity (IC_{50}: 4.6 μg/mL, as determined by a 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging bioassay) in the ethyl acetate soluble fraction from the ethanol extracts, and proceeded with a more detailed study on the contents of these extracts. Along with seven known xanthones, they found a novel bisxanthone being named bigarcinenone A (**45**).

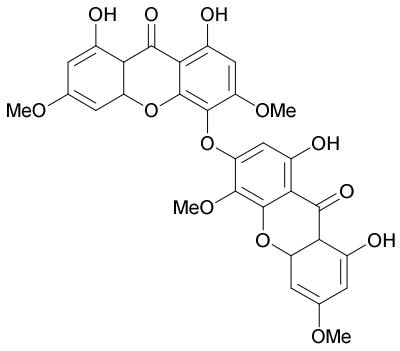
Using mainly 2D-NMR techniques, the authors identified the dimeric xanthone to be coupled through a side-chain of one of the two subunits. Bigarcinenone A performed relatively good in a DPPH radical scavenging activity assay (IC_{50}: 9.2 μg/mL), outperforming all other isolated xanthones from this extract (IC_{50}: 16.3-250 μg/mL) as well as BHT (IC_{50}: 20.0 μg/mL), a well-known synthetic antioxidant.[99] In 2011, bigarcinenone B was isolated from the bark of the same plant and its structure and relative stereochemistry was also elucidated using mainly 2D NMR techniques such as HMBC, HSQC, ROESY. A possible biosynthetic pathway was proposed by the authors that would lead to the unique connection through the two six membered rings. A Diels Alder reaction between the two prenyl groups of the monomers would lead to the cyclohexene derivative, which would undergo a second cyclisation to form the final ring. The antioxidant activity of bigarcinenone B (**7**) was tested with a DPPH assay (IC_{50}: 20.14 μM versus 13.16 μM for ascorbic acid) and a H_2O_2 assay (IC_{50}: 2.85 μM versus 0.76 μM for ascorbic acid).[100]


45 Bigarcinenone A
(relative stereochemistry)


46 Bigarcinenone B
(relative stereochemistry)

Chiratanin

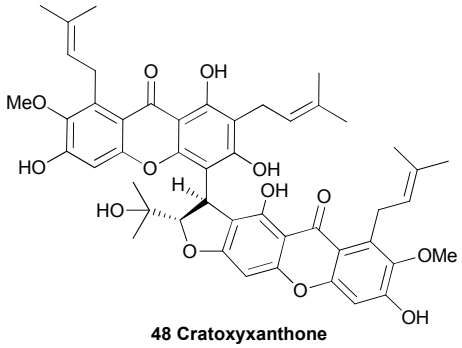
An interesting biaryl-ether linked dimeric xanthone named chiratanin (**47**) was isolated together with several monomeric xanthones and other secondary metabolites from the benzene extracts of the plant *Swertia chirata*.[101] At the time, this was the first report of the occurrence of a dimeric xanthone in a higher plant. After detailed analysis of the NMR spectra the authors identified the positions of the oxygen atoms in the molecule, and with D_2O exchange experiments all the phenolic hydroxyl groups were identified. However, the actual connection of the two xanthones remained difficult to determine, and three possible structures were identified. The molecular asymmetry was instructive in determining the final structure, which they named chiratanin.



47 Chiratanin

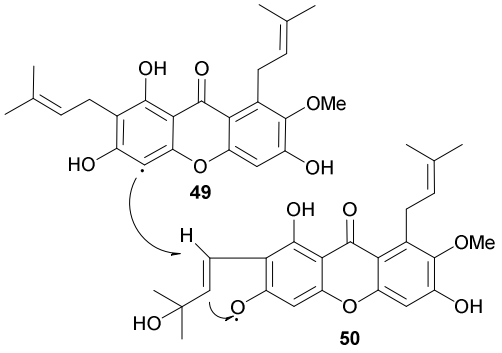
Cratoxyxanthone

Several natural products were isolated from the bark of *Cratoxylum cochinchinense* in 1995 by Sim *et al.*[102] After extensive HPLC purification of the isolated compounds, detailed high field NMR spectroscopy was used to identify a novel dimeric xanthone, named cratoxyxanthone (**48**).



48 Cratoxyxanthone

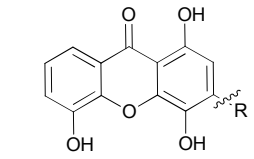
The authors speculated on a biosynthetic pathway involving the coupling of two mangostin-derived radicals, as depicted in Scheme 6. Cratoxyxanthone was also isolated from the chloroform soluble extracts of the stem bark of *Garcinia mangostana* in 2009.[103] In this study it was found that cratoxyxanthone had a very poor *in vitro* activity in cytotoxicity (HT-29 cell line) and ELISA NF-κB (p65 and p50) assays.



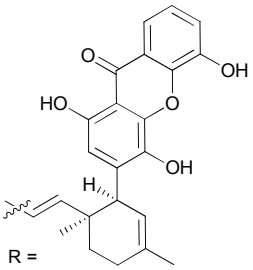
Scheme 6: Proposed biosynthetic coupling of two mangostin-derived radicals to form cratoxyxanthone

Garcilivins A-C

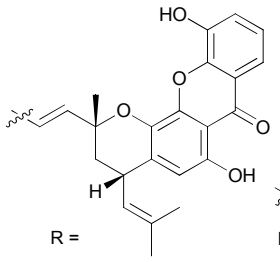
Bark from the roots of the South African plant *Garcinia livingstonei* was phytochemically investigated in a larger study aiming to find reversible monoamine-oxidases inhibitors for antidepressant drugs. This study resulted in the discovery of several prenylated xanthones, including three dimeric xanthones named the garcilivins (**51**-**53**).[104] The structures were elucidated using extensive mass and NMR spectroscopy and by comparing with monomeric xanthone spectra.[105] In 1992 it was reported that these xanthones were currently being assayed for their biological activities, but as far as the authors know, no follow-up paper was published until Pieters *et al.* in 2006.[106] They report the isolation of several xanthones and flavonoids from a Tanzanian *G. livingstonei* and tested the isolated compounds on their antiparasitic activity and cytotoxicity. Garcilivin A and C showed a very interesting difference in their toxicity tests, considering they are diastereoisomers. Both compounds were tested against four parasites and garcilivin A showed a very strong non-selective activity in all the assays, whereas garcilivin C only showed significant activity against *Trypanosoma brucei*. Especially noteworthy is the score for cytotoxicity against MRC-5 cells of 2.0 μM for garcilivin A and 52.3 μM for garcilivin C.



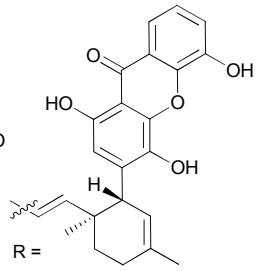
Garcilivin A-C
(relative configuration)



51 Garcilivin A



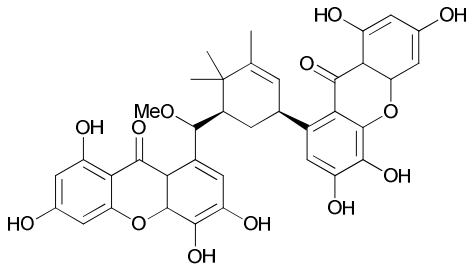
52 Garcilivin B



53 Garcilivin C

Garciobioxanthone

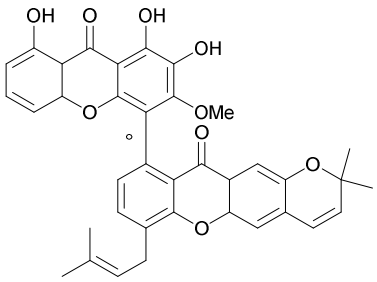
Recently, the novel garciobioxanthone (**54**) was isolated from the ethanol extracts from the bark of *Garcina oblongifolia*, along with several known compounds. Using 2D NMR techniques the relative configuration and structure was determined.[107]



54 Garciobioxanthone
(relative configuration)

Globulixanthone E

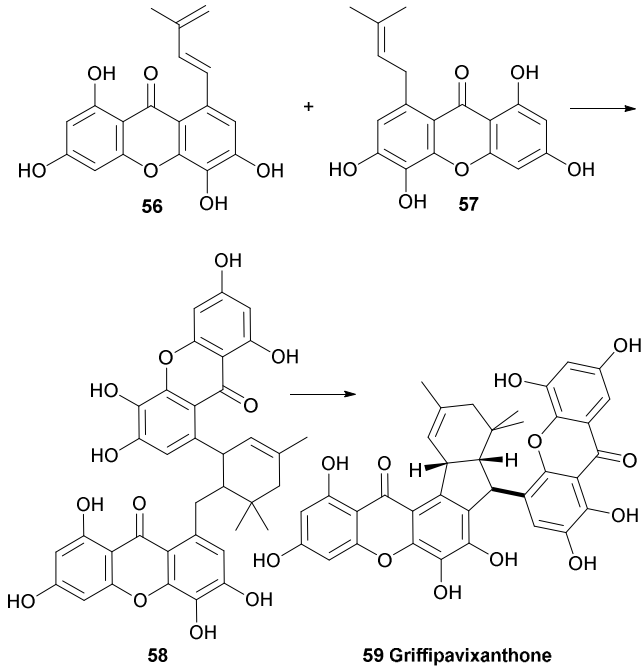
Three prenylated xanthones were isolated from the root bark of the large forest tree *Symphonia globulifera* and named globulixanthone C-E. The tree is widely used in Cameroon as a medicinal plant and laxative for pregnant women. Globulixanthone C and D were found to be monomeric xanthones, but globulixanthone E was found to be a bisxanthone and its structure (**55**) was elucidated using ESI-TOF MS, IR and NMR spectroscopic methods. Using NOESY spectra and by comparing the obtained spectra with the other isolated xanthones, the structure was determined. The three xanthones were tested for their *in vitro* antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Vibrio anguillarium* and *Escherichia coli* in an agar well diffusion assay. The monomeric xanthones showed a moderate activity to *S. aureus* (MIC: 8.05–14.05 μg/mL) and *B. subtilis* (MIC: 8.24–12.5 μg/mL), but globulixanthone E showed a remarkably high activity against all tested organisms (MIC: 5.56–3.12 μg/mL) except *E. coli* and outperformed the positive control in the case of *S. aureus* (MIC: 4.51 μg/mL versus 6.25 μg/mL for streptomycin sulfate).[108]



55 Globulixanthone E

Griffipavixanthone

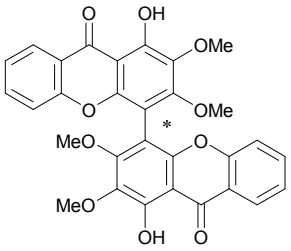
An investigation into the secondary metabolites of the Malaysian plants *Garcinia pavifolia* and *G. griffithi* lead to the discovery of a new bisxanthone named griffipavixanthone.[109] Using advanced spectroscopic methods, including NOESY, HMBC and INEPT NMR studies, the relative structure was elucidated. In a later study the bisxanthone was also found in *G. maingayii*.[110] Griffipavixanthone was the first example of a dimeric xanthone that is connected via a 5 and a 6 membered ring.[109] The authors suggest a possible biosynthetic pathway involving an initial Diels Alder reaction of two prenyl groups on the two xanthones (Scheme 7). The resulting cyclohexene is then followed by another cyclisation, either ionic or radical to yield the 5-membered ring. The bisxanthone was also isolated from *Garcina oblongifolia*[107] (along several other xanthones, such as garciobioxanthone) and G. virgate[111] (along with two new monomeric xanthones named virgataxanthone A and B, not shown). The isolated compounds in the latter study were tested on antioxidant capacity and it was noted that griffipavixanthone showed a notably high radical scavenging ability, with an EC_{50} lower than the references used in the study (EC_{50}: Griffipavixanthone: 11.5 μg/100 mL, 2,6-di-tert-butyl-4-hydroxy-anisol: 13.6 μg/100 mL, α-tocopherol: 13.8 μg/100 mL) In *in vitro* cell line cytotoxicity tests griffipavixanthone showed high activity against P388, LL/2 and Wehil64 cell lines with very promising ED_{50} between 3.40 and 6.80 μg/mL.[109] A Chinese patent reports promising anti-cancer properties for griffipavixanthone. They claim a strong inhibition effect of the bisxanthone or its salts on human lung, breast, prostatic and intestinal cancer cells, while showing no cytotoxicity to normal kidney epidermal cells. For lung cancer cells H520 specifically they found that the cell cycle was blocked in the S stage, thereby preventing the cancers to propagate.[112]



Scheme 7: Proposed biosynthetic pathway

Hyperidixanthone

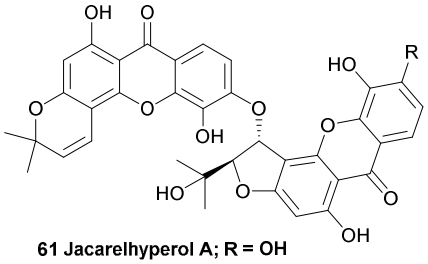
Hyperidixanthone (**60**) is a symmetrical dimeric being isolated from the plant *Hypericum chinense*.[113] The compound was identified by a barrage of NMR techniques, including HMBC, and mass spectral data. Although hyperidixanthone is almost certainly axially chiral, the authors reported no details of optical activity.



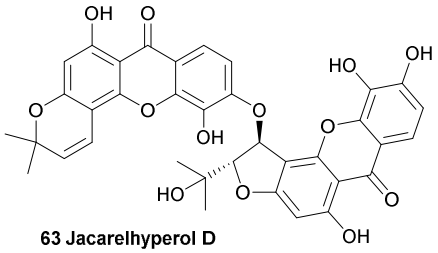
60 Hyperidixanthone

Jacarelhyperols A, B and D

Jacarelhyperols A and B (**61**, **62**) were isolated from *Hypericum japonicum* only a few years later than the bijaponicaxanthones and the measured NMR spectra were found to be very similar to the spectra obtained from the bijaponicaxanthones. The relative structure of jacarelhyperol A was elucidated to be an epimer of bijapoincaxanthone with a *trans*-configuration of the two protons at the chiral centres. Jacarelhyperol B was subsequently identified as a 6′-dehydroxy variant of jacarelhyperol A. Both jacarelhyperols A and B were found to significantly inhibit the platelet-activating factor (PAF) induced hypertension at 10 mg/kg in mice without causing their blood pressure to rise. Therefore PAF inhibitors are considered to be potential drugs against allergic diseases.[114] The isolation and structure elucidation of jacarelhyperol D from the same plant species was reported in 2007 in a short communication paper by Chen *et al.*[115]



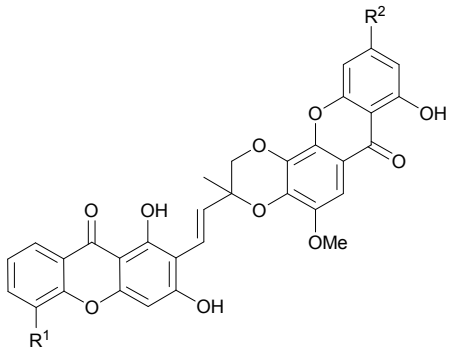
61 Jacarelhyperol A; R = OH
62 Jacarelhyperol B; R = H



63 Jacarelhyperol D

Mesuabixanthones A and B

The bark of the south-east Asian tree *Mesua ferrea* has been widely used in traditional local medicine and is reported to exhibit antimicrobial and antiasthmatic activity. Therefore the stem bark was investigated in an attempt to isolate the active compounds. Interestingly, the two novel bisxanthones mesuabixanthones A and B (**64**, **65**) were isolated from an extracted fraction that showed little biological activity in their initial bioassays. Using conventional mass spectrometric and NMR spectroscopic methods they identified the two novel bisxanthones. Mesuabixanthone B differed from mesuabixanthone A only by the methylation of the hydroxyl group at *C*-8, as determined by a NOESY experiment. No biological testing on the isolated compounds was reported.[116]



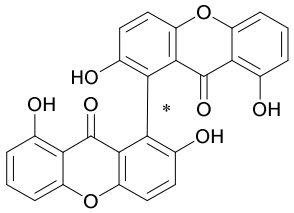
64 Mesuabixanthone A; R^1 = OH, R^2 = OMe
65 Mesuabixanthone B; R^1 = OMe, R^2 = OMe
66 Mesuferrol A; R^1 = OH, R^2 = OH
67 Mesuferrol B; R^1 = OMe, R^2 = OH

Mesuferrols A and B

The very similar mesuferrol A and B (**66**, **67**) have been isolated from an acetone extract of the bark of the same tree and were purified using chromatography.[117] Mesuferrol A and B were identified by means of NMR spectroscopy and HR FAB-MS.

Ploiarixanthone

In 1990 a novel dimeric xanthone metabolite was isolated from branches of the shrub *Ploiarium alternifolium*. By synthesising of a tetracetylated derivative and detailed comparison of the obtained NMR spectra with the data from the natural product, they identified ploiarixanthone (**68**) to be 8,8′-linked.[83] Ploiarixanthone is optically active ($[\alpha]_D^{25}$ = +23°), providing strong evidence for enzymatic dimerisation process in its formation.



68 Ploiarixanthone

Puniceasides

In 1991 the first isolation and structure elucidation of a bisxanthone *C*-glucoside named swertipunicoside (**77a**, Figure 2) was reported. It was isolated from extracts from the whole plant *Swertia punicea* and the structure was confirmed by NMR experiments and particularly the selective INEPT technique (Insensitive Nuclei Enhanced by Polarisation Transfer).[118] Only one year later the same group was able to also isolate and characterise 3-*O*-demethylswertipunicoside (**77b**) using several

NMR techniques including APT, HETCOR and selective INEPT.[119] Puniceasides B and C and Isopuniceaside B have all been partially reduced to feature one tetrahydroxanthone core.

Recently, investigations showed that 3-*O*-demethyl-swertipunicoside has potent neuroprotective capabilities. Several oxidative toxicity tests were performed on xanthone treated and untreated PC12 cells. Increased cell viability was found in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell death assay where the cells were exposed to 1-methyl-4-phenylpyridiniumion (MPP+), rotenone or hydrogen peroxide. These neuroprotective effects were found to be caused by the elevation of TH and DJ-1 protein levels.[120]

Hostettmann *et al.* isolated several xanthones from *Gentianella amarella* ssp. acuta, including one new dimeric xanthone. After structure elucidation with the use of 2D-NMR experiments and mass spectrometric they named the compound swertiabisxanthone I 8′-*O*-β-D-glucopyranoside (**73b**).[121]

Remarkably, its aglycone, swertiabisxanthone I (**73a**), was first isolated and identified already more than twenty years earlier from *Swertia macrosperm* plants.[122] Recently both the glycone and the aglycone of swertiabisxanthone I have also been isolated from *Swertia punicea*.[123] In 2010, Guo *et al.* isolated two new dimeric *O*-glycoside xanthones, one new trimeric *O*-glycoside xanthone, two new trimeric *C*-glycoside xanthones and 12 known xanthones from the plant *Swertia punicea*.[123] The five new xanthones were identified using extensive HRESIMS and NMR spectroscopic experiments and were named puniceasides A-E (**69a, 70a, 72a, 75a, 76a**). For puniceaside B the *cis* configuration between H-5 and H-8 was confirmed using NOESY experiments. Also, it was found that the H-6′ resonance pattern indicated that two different rotameric forms of puniceaside B exist. By heating to 120 °C in a ^{1}HNMR experiment, the two singlets of H-6′ merged into one singlet. Puniceaside C was confirmed to be a trimeric xanthone glycoside by close examination of the results from mass spectrometric methods and HMBC NMR experiments. As far as known, this was the first trimeric xanthone reported in literature. By subjecting the compound to acid hydrolysis, the glycosidic moiety was found to be D-glucose. Two more trimeric xanthones were identified as puniceasides D and E. HMBC correlations showed the presence of the OMe group in puniceaside E. The absolute configurations of **75a** and **76a** could not be determined due to insufficient quantities of compounds. The presence of different rotameric configurations is likely, since heating the ^{1}H NMR samples to 120 °C resulted in the merging of the two singlets of H-6′ into one singlet, similar as was observed for puniceaside B. Puniceasides A-E, swertiabisxanthone I 8′-*O*-β-D-glucopyranoside, 3-*O*-demethyl-swertipunicoside and swertipunicoside were tested for their neuroprotective activity against hydrogen peroxide-induced PC12 cell damage. Especially puniceaside B, was found to be very potent with a cell viability of 98.1±6.8% at a concentration of 25 µg/mL compared to hydrogen peroxide treated cells. Interestingly, swertiabisxanthone I 8′-*O*-β-D-glucopyranoside and 3-*O*-demethylswertipunicoside were found to potently stimulate the damaged PC12 cells to grow, resulting in cell viability scores of 123% and 158%. In 2012, Guo *et al*. reported the characterisation of 16 new xanthone compounds from extracts of *Swertia punicea*. After studying the ESI-MS fragmentation behaviours of 17 known xanthones very closely they could apply this knowledge to high-performance liquid chromatography diode-array detection/tandem mass spectrometric results and thus identify 11 new dimeric and 4 new trimeric xanthones (**69b-d, 70b-c, 71a-b, 72b, 75b, 76b, 74, 73c-e, 77c**).[124]

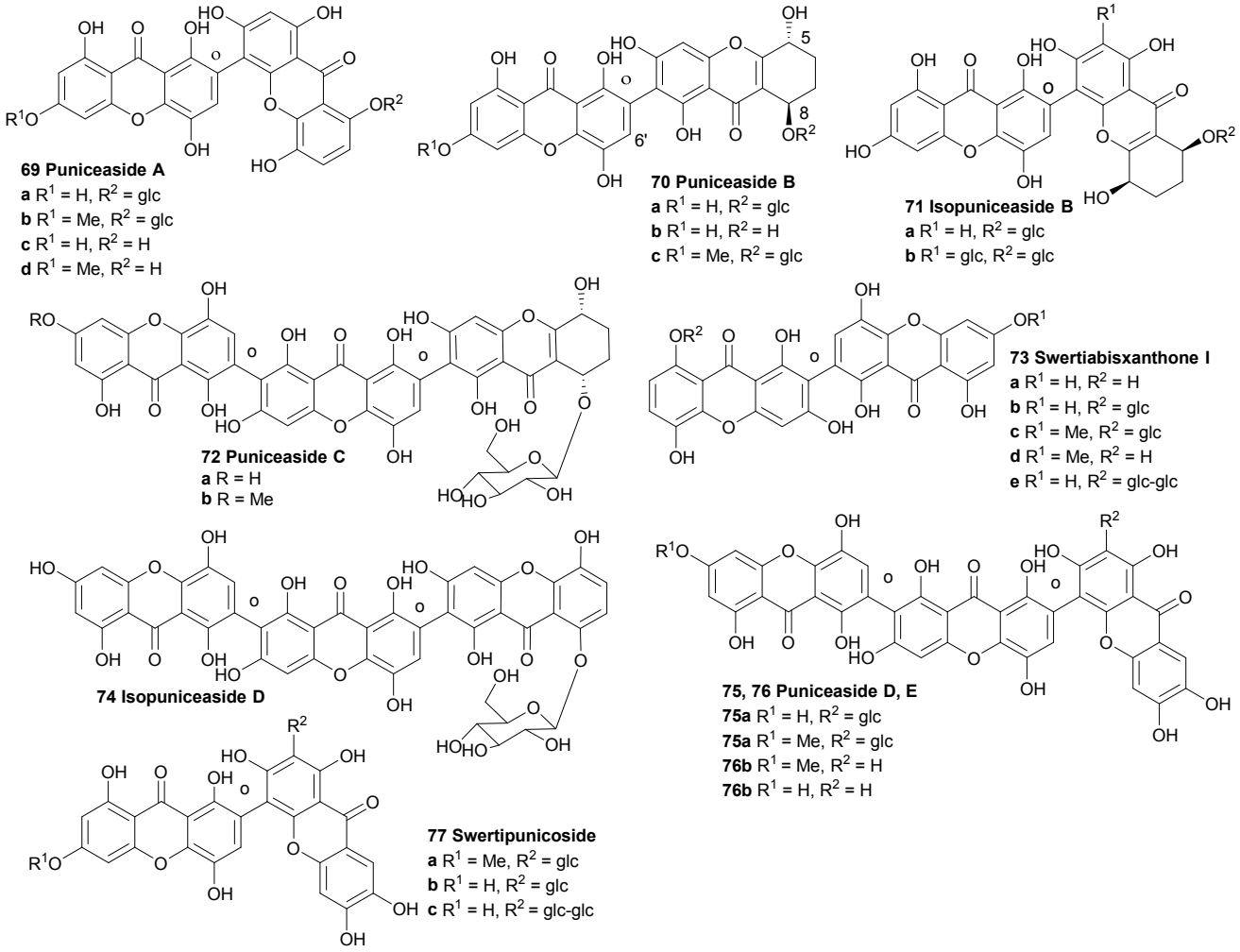


Figure 2: Puniceaside and swertiabisxanthone derivatives (absolute stereochemistries shown)

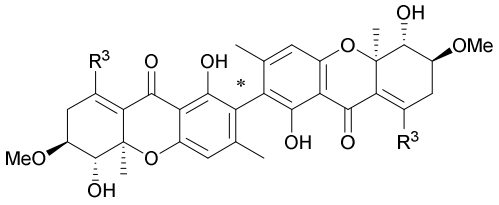
Xanthone Dimers from Fungi

Fungi have yielded some beautiful xanthone dimers, the majority of which possess a common a biaryl bond as the method of their linkage. The biaryl bond is most often arranged in a 2,2′-manner with respect the common xanthone hydroxyl moiety; in a couple of cases, natural products with 2,4′-biaryl bonds have been described, as has the somewhat rarer 4,4′-biaryl linkage. Additionally, the position of methylation of the xanthone core is found at the *C*3, *C*6 or sometimes *C*10a positions, which can provide insight to the biosynthetic origin of the compounds (see Table S-1 for structural details).

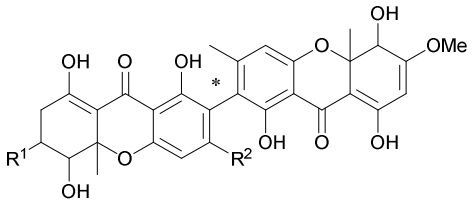
Ascherxanthones

Ascherxanthone A (**78**) was isolated from the methanol extract of the mycelia of *Aschersonia* sp. BCC 8401, after significant antimalarial activity in *Aschersonia* cultures was observed.[125] Evidence for the symmetric homodimeric structure of ascherxanthone A was provided by mass spectrometry and the presence of only 16 carbon signals in the ^{13}C NMR spectrum. The tetrahydroxanthone structure was established on the basis of the HMBC correlations and using COSY and HMQC NMR spectroscopic methods the entire structure was elucidated. Intense correlation from the phenolic proton to the quaternary carbon placed this carbon at *C*2, confirming a 2,2′-biaryl-linked dimer. Interestingly, the structure of ascherxanthone A is very close to TMC 315A$_1$, TMC 315A$_2$, TMC 315B$_1$ and TMC 315B$_2$ (**80-83**);

four dimeric xanthones that were isolated from *Ceuthospora* sp. TMC1678 and reported in a Japanese patent to be RANKL (Receptor activator of NF-κB ligand) antagonists that can prevent or control osteoporosis.[126] It should be noted the Japanese patent does not provide any stereochemical information for TMC 315A$_2$ (**81**), which may therefore be in fact identical to ascherxanthone B (**79**). Note that ascherxanthone A bears one less hydroxyl than the other compounds in this family, and one component of each TMC 315B$_1$ and B$_2$ has been reduced to the relatively rare dihydroxanthone tricycle.



78 Ascherxanthone A; R_1 = OMe, R_2 = Me, R_3 = H (relative stereochem.)
79 Ascherxanthone B; R_1 = OMe, R_2 = Me, R_3 = OH (relative stereochem.)
80 TMC 315A; R_1 = Me, R_2 = OMe, R_3 = OH (no stereochemistry known)
81 TMC 315A$_2$; R_1 = OMe, R_2 = Me, R_3 = OH (no stereochemistry known)

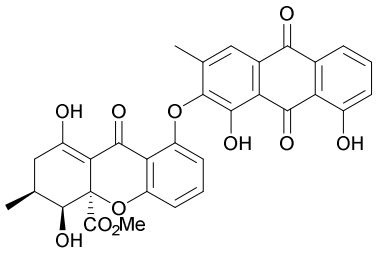


82 TMC 315B$_1$; R_1 = Me, R_2 = OMe
83 TMC 315B$_2$; R_1 = OMe, R_2 = Me

In a search for new agents against the rice blast fungus *Magnaporthe grisea,* that has developed a fungicide resistance, culture broth extracts from approximately 800 fungal strains were investigated in an *in vitro* screening assay. A culture of *Aschersonia luteola* BCC 8774 was found to produce ascherxanthone B, a compound active against *M. grisea* with an IC_{90} value of 0.58 μg/mL The structure of ascherxanthone B (**79**) was elucidated using COSY, HMBC and HMQC NMR experiments and found to be almost identical to ascherxanthone A, with the only difference the replacement of the olefinic proton at δ_H 6.87 (*H*-8) in ascherxanthone A with a chelated hydroxy resonating at δ_H 13.43 (*C*-8 hydroxyl, broad singlet). Interestingly, it was found that ascherxanthone A was nearly inactive in the same biological assay against *M. grisea* with an IC_{90} value of over 50 μg/mL.[127] However, ascherxanthone A did show significant activity against *Plasmodium falciparum* K1 (IC_{50} = 0.20 μg/mL). Furthermore, it also showed cytotoxicity to Vero cells (IC_{50} 0.80 μg/mL) and three cancer cell lines (IC_{50} values between 1.7 and 0.16 μg/mL).[125]

Chrysoxanthone

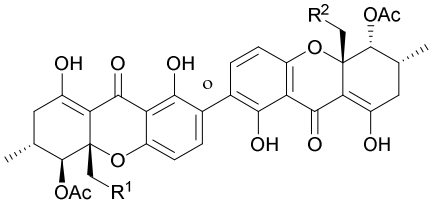
Chrysoxanthone, although not a xanthone dimer, is included here as an unusual example of the mixed-biological derivative 'xanthraquinones', which also include the beticolins[128-131] and the xanthoquinodins.[132-135] Chrysoxanthone, as reported by Anke and co-workers,[56] features a form in which 2-hydroxychrysophanol is coupled to blennolide A (hemisecalonic acid B) through a biaryl ether linkage. The authors determined the novel structure with 2D NMR and mass spectral techniques, and was found to possess antimicrobial and antifungal properties. These most likely result directly from the discrete bioactivities of each the xanthone and anthraquinone components. This compound, alongside the xanthoquinodins and beticolins, represents a biosynthetic junction of a xanthone and one of its likely biosynthetic precursors (anthraquinone). The synthesis of an ether linkage between two xanthenes has been recently reported by Sahin, Nieger and Bräse.[136]



22 Chrysoxanthone

Dicerandrols A-C

Dicerandrols A-C (**84-86**) were isolated from the culture broth of the *Phomopsis longicolla* an endogenous fungi from the mint species *Dicerandra frutescens*. Extensive NMR experiments were complemented by a positive $FeCl_3$ experiment, indicating the 2,2′-linkage mode of the dimer (the test is positive for a *para*-unsubstituted phenol). The ^{1}H NMR spectrum of dicerandrol C was found to be simple, suggesting a plane of symmetry. 2D NMR experiments were used to determine the relative stereochemistry for this compound, and by inference, those of dicerandrol B and C.[137] In 2013 the absolute configurations of dicerandrols B and C was determined by TDDFT electronic circular dichroism (ECD) calculations.[138] It is likely that dicerandrol A has the same absolute stereochemical configuration, but to date only the relative configuration has been reported.



84 Dicerandrol A (relative configuration); R^1 = OH, R^2 = OH
85 Dicerandrol B (absolute configuration); R^1 = OAc, R^2 = OH
86 Dicerandrol C (absolute configuration); R^1 = OAc, R^2 = OAc

The dicerandrols have antimicrobial activities (*Bacillus subtilis* and *Staphylococcus aureus*) with increased activities related to the decreased degree of acetylation of the molecules (i.e., A > B > C). The dicerandrols were also active against two cancer cell lines, HCT-116 and A549 (colon and lung tumour, respectively).[137] In 2008, dicerandrol A was also isolated from *Phomopsis* sp. PSU-D15 and used in comparison studies to help identify a new member of the phomoxanthones (deacetylphomoxanthone B **101**).[90] Dicerandrol C was isolated from a *P. longicolla* obtained from red seaweed *Bostrychia radicans* and identified with use of 1D and 2D NMR spectroscopic methods as well as by mass spectrometry.[89] Another study performed several biological tests on dicerandrols A, B, and C that were also isolated from *P. longicolla*. Using disk diffusion assays they found that dicerandrols A and B possess antibacterial activity against

Xanthomonas oryzae KACC 10331, a cause for bacterial blight in rice. Subsequently, dicerandrol A was also tested for antimicrobial activity against seven other *X. oryzae* strains, several Gram-positive and Gram-negative bacteria, a fungus and a yeast. It was found that dicerandrol A showed a relatively high activity in this broad spectrum of species, although it was often bested by commercial antibiotics. By performing growth and time-dependent production of secondary metabolites studies, it was found that the dicerandrols were produced mainly after 4 days of fermentation and that the maximal production was at day 10. This lead to a maximal antibacterial activity after day 14.[139] These results are useful in the production of a natural preventive medicine against bacterial blight of rice, which is very relevant since it was found that *X. oryzae* has developed a resistance to the available antibiotics. A more detailed continuation study on the time-dependent production of dicerandrols and other antibacterial compounds in *P. longicolla* confirmed that the optimum fermentation time for maximal antibacterial activity of the fungus is indeed 14 days.[140] Dicerandrols A–C were also isolated in 2013 from the mycelium of a culture broth of *Phomopsis longicolla* S1B4 and were tested against a strain of *X. oryzae.* In this antimicrobial activity test the dicerandrols A-C showed a MIC of 8, 16 and 16 μg/mL respectively.[140]

The dicerandrols and the structurally similar penexanthone A were submitted in several biological activity tests versus a broad range of tumour cell lines.[141] The majority of the *in vitro* screening tests were performed in the presence of non-malignant accessory cells, such as bone marrow stromal cells, since they were found that the activities of potential drug can be affected by microenvironment-dependent drug resistance or sensitisation of the tumour cells.[142] Among the tested compounds, dicerandrol B was found to be the most promising candidate for further investigations. It showed moderate activity against Dox40, Farage, H929, HT, OPM2 and RPMI8226 cell lines in the presence of stromal cells with IC_{50} values of 2.3, 1.3, 3.4, 1.3, 1.5, and 1.2 μM, respectively. More importantly, it was found that dicerandrol B showed a relatively low toxicity against human immortalised non-malignant cells, such as HS-5 bone marrow stromal cells, HOBIT osteoblast-like cells, THLE-3 hepatocytes, and SVGp12 astrocytes compared to the values found for cancer cell lines RPMI8226 and H929. This relative selectivity is cause for further investigations into the biological activity of this compound.[141] Dicerandrols A-C were also isolated from *Phomopsis* sp. HNY29-2B and tested for their cytotoxicity against human breast cancer, colon cancer, lung cancer, liver cancer and breast epithelial cell lines. Dicerandrol A showed a broad anti-tumour activity, but was also cytotoxic to the breast epithelial cells. Dicerandrol B and penexanthone A (**101**) showed also some cytotoxicity to the cancer cells, but were found to be more selective and less strongly damage the breast epithelial cells. In this assay dicerandrol C was found to be not very cytotoxic, suggesting that the free hydroxy groups important as key pharmacophore.[143] In a study that mainly focusses on the biological activity of phomoxanthone A (**106**) also dicerandrols B and C are investigated. It was found that the dicerandrols were both cytotoxic to murine lymphoma cancer cell lines (IC_{50} values of 10 and 1.1 μM, respectively) and that dicerandrol C is slightly pro-apoptotic.[138]

Ergochromes

Ergochrome dimers comprise a colourful group of xanthones first reported by Kraft in 1906 as a single compound of the formula $C_{14}H_{14}O_6$ after separation from *Claviceps purpurea*.[144] The contamination of rye with ergochrome-containing *C. purpurea* led to epidemics known as ergotism or 'St. Anthony's Fire' in middle-ages Europe. The mixture of toxins produced by this fungus was responsible for the toxicity and debilitating effects on the affected population. The ergochrome dimers (**21**, **23**, **87** to **99**, Figure 3) include the wide-spread secalonic acids, ergochrysins, ergoflavins and chrysergonic acid, many of which possess a huge variety of potent bioactivities. The ergochrome dimers are composed of several monomeric units (hemisecalonic acids A-F, aka 'blennolides'),[47] which are arranged in a variety of dimers and heterodimers. In all known secalonic acids, the methyl and methoxycarbonyl substituents are found to be *trans*-configured. Whilst secalonic acids are ester homodimers, other heterodimer ergochromes are known. For example, ergochrysins are lactone/ester heterodimers, ergoflavin is a homodimer,[145] whilst ergoxanthin has undergone structural rearrangement to form a pendant butyrolactone ring on one half of the molecule.[146]

Due to the early time at which they were first studied, modern spectral methods were not applicable to facilitate the structural elucidation of the ergochromes, and early structural assignations on these compounds were frequently revised in later years. For example, the initial misidentification of ergochrysin and ergoflavin as secalonic acids was later revised by Bergmann in 1932 as dimers with the formula $C_{28}H_{28}O_{12}$.[147] A number of papers followed in the 1950's to 70's, over which time more secalonic acids were isolated and identified. One major point of contention in the early days of exploration of this compound class was as to whether the natural products were 2,2′-, 4,4′- or even 2,4′-linked.[148, 149] The biaryl linkages was finally definitively assigned as 2,2′-linked when Mayo and Aberhart reported on the isolation in crystalline form of six compounds from a Portuguese ergot drug in 1965.[150] In contrast to earlier reports,[151] these authors showed that ergochrome dimers ubiquitously gave positive results in the Gibbs test, indicating the presence of an unsubstituted aryl methine in a position *para*- to the phenolic moiety, and thus a 2,2′-linkage.

A comprehensive analysis of the ergochrome constituents of *C. purpurea* by Franck and co-workers led to the reporting of a total of ten component compounds, including a new homodimer named ergochrome DD (**94**, Figure 3), as well as the remaining six heterodimers possible with combination of one subunit of each of those four species A, B, C and D, the majority of which they identified as The ergochromes are diastereomeric at positions 6,6′, 5,5′, 10 and 10′. The authors also identified the absolute stereochemistry at these centres.[152]

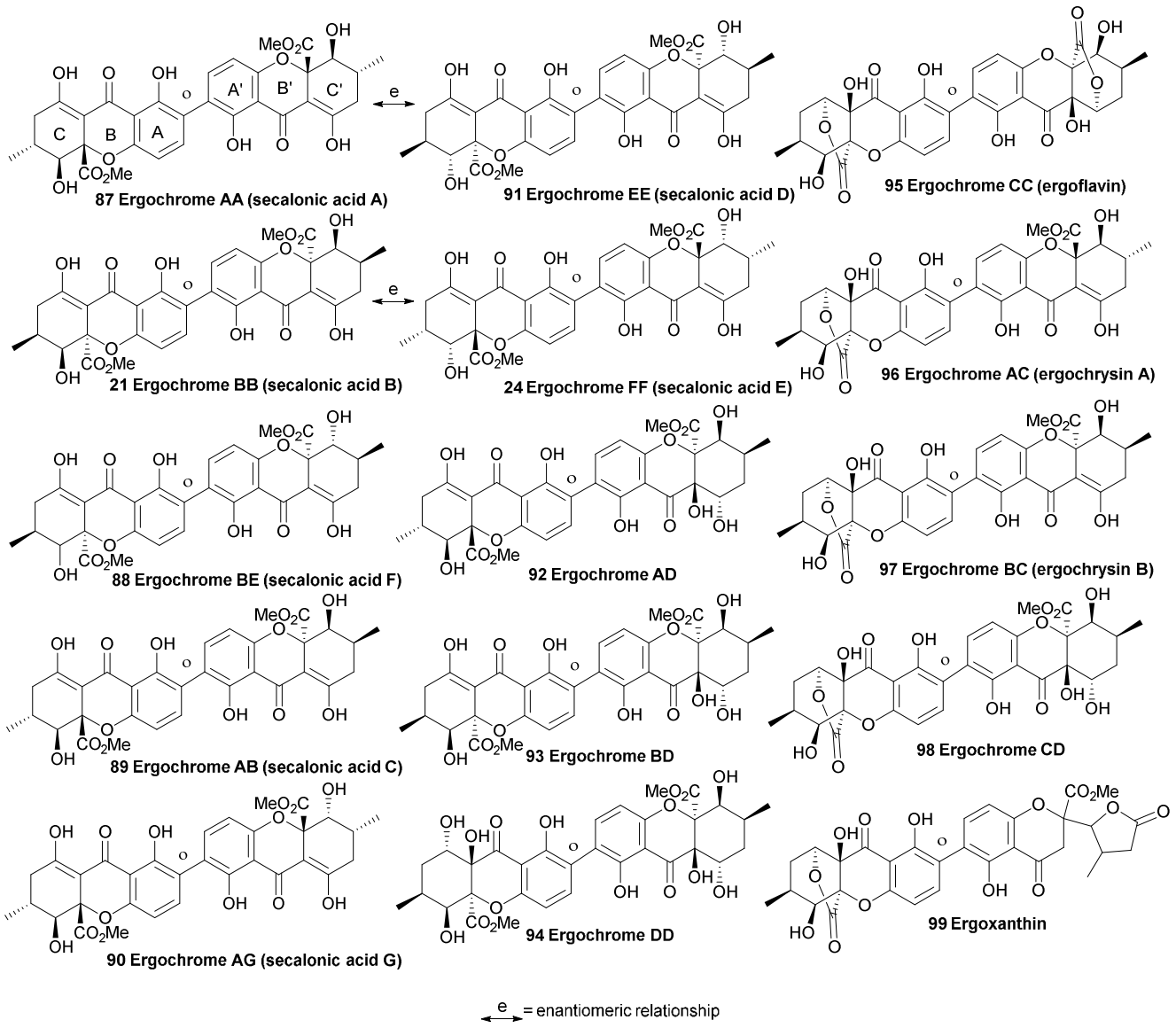


Figure 3: Ergochromes showing heterodimer structures, stereochemistry and enantiomeric relationship

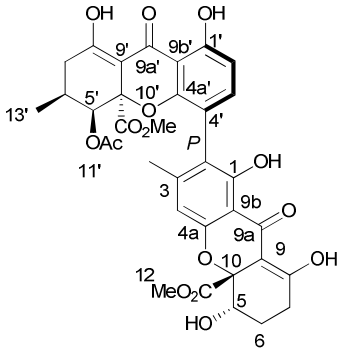
Büchi and co-workers reported novel secalonic acid F (**88**, ergochrome BE) and secalonic acid D (**91**, ergochrome EE) in 1977, following isolation from the fungus *Aspergillus aculeatus*.[153] The following year, then-novel secalonic acid G (**90**) was isolated alongside secalonic acids A and E from *Pyrenochaeta terrestris* and the structure elucidated by CD and NMR spectroscopy.[23]

Secalonic acid D (SAD) is a major environmental toxin, being isolated from *Penicillium oxalicum*, a major microbial contaminant of freshly-harvested corn (in one study present on 44% of pre-harvest corn crops).[154] Teratogenic effects were observed in the development of rats that were exposed to SAD injected during fetal development. SAD was lethal to mice when injected intraperitoneally in the 25-50 mg/kg range.[155] The teratogenic and toxic nature of these compounds is alarming in light of their propensity to contaminate foodstuffs.[156] The rate of birth-defects and teratogenicity-initiated spontaneous abortions in humans is also alarmingly frequent.

Despite the widespread occurrence of the ergochromes, none had been synthesised until the end of 2013, and neither had any other xanthone dimers or trimers. In early 2014, Porco and co-workers at long last described the synthesis of secalonic acids A and D, utilising a Cu(I) catalysed di-destannylative coupling.[157, 158] This reaction represents a significant breakthrough for the study of the xanthone dimers,[62] and may open up the field to the synthesis of interesting analogues for medicinal chemistry studies. Recent advances in Ullmann coupling may make the strategy of Whalley and co-workers towards ergoflavin a more feasible route to the natural products than was originally the case in 1971.[159] Bräse and co-workers have described a novel one-pot methodology for the synthesis of symmetrical biaryls[160] as a part of their ongoing investigations in the synthesis of the secalonic acids. Sahin, Nieger and Bräse have also published on the oxidative coupling of various hexahydroxanthenols. The application of an iron complex as oxidant converted 2-hydroxy substituted xanthenes to the 3,3′-bis-coupled bixanthenes.[136] It appears that these two papers represent until the end of 2013 the only successful chemistry published on the topic of xanthone or xanthene biaryl-coupling.

Neosartorin

Neosartorin (**100**) was isolated in 1998 from the cultured mycelium of the soil mould *Neosartorya fischeri*. A combination of 2D NMR experiments determined that neosartorin was an isomer of eumitrin A_1. However, close examination of long range coupling constants of nuclei around the two arene units revealed a 2,4′-biaryl linkage instead of the 4,2-linkage found in eumitrin A_1.[161] A closer investigation of the low-intensity long-range NOEs by a 1D double-pulsed field gradient spin-echo NOESY NMR experiment resulted in confirmation of the relative configuration of the two xanthone subunits. The absolute stereochemistry of neosartorin was axially *P* and found to be (a*R*,5*S*,10*R*,5′*S*,6′*S*,10′*R*), this was determined on the basis of its electronic circular dichroism (ECD) spectra in conjunction[162] with TDDFT-ECD calculations. They found that the nonplanar configuration of the aromatic rings connecting the two subunits was stabilised by long-range nonbonding interactions between the substituents of different xanthone units.[163]



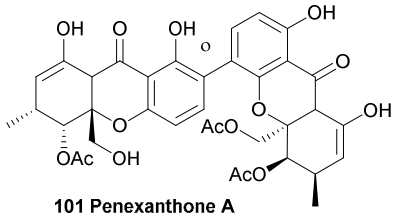
100 Neosartorin (absolute configuration)

A taxonomical study of *Aspergillus* species conducted in 2005 report the production of neosartorin in the new species *A. lentulus*, *A. fumigatiaffinis* and *A. novofumigatus*, but not in *A. fumigatus*. The presence of neosartorin was based on evaluation of UV spectrum evidence. Based on these findings and other similarities they conclude that the taxa of *Neosartorya fischeri* and the *Aspergillus* species are chemically related.[164] Neosartorin was found to show a strong activity against Gram-positive bacteria such as *Staphylococcus aureus* (MIC: 8 μg/mL) and *Bacillus subtilis* (MIC: 4 μg/mL), while it did not affect the tested Gram-negative bacteria. In cytotoxicity tests against several cancer cell lines it scored very badly, showing almost no notable cytotoxicity.[162]

Penexanthone A

Recently, Clardy *et al.*[141] isolated dicerandrols A-C and a novel dimeric xanthone named penexanthone A (**101**) from CR1642D, a *Penicillium* sp. obtained from the Costa Rican rainforest. The structure, including relative configuration, of penexanthone A was elucidated using mainly 2D NMR techniques (HSQC, HMBC, NOESY and ROESY) and molecular modelling with Chem3D Ultra (9.0). The two monomers were found to be connected through a 2,4′-linkage. The dicerandrols were identified by comparison of several physical and spectroscopic data sets (UV, IR, ^{1}H NMR, $[\alpha]_D$ and MS) with the literature values. The authors note that the structure of penexanthone A was already reported in a Korean patent, although the ^{1}H NMR spectra was unclean, suggesting an impure sample.[165] Penexanthone A is identical with a monodeacetylated phomoxanthone B (*vide infra*). Penexanthone A was submitted in several biological activity tests versus a broad range of tumour cell lines, however the observed IC_{50} values indicate that penexanthone A is only weakly active in the presence of stromal cells.[141] Penexanthone A was also isolated from *Phomopsis* sp. HNY29-2B and tested for its cytotoxicity against human breast cancer, colon cancer, lung cancer, liver cancer and breast epithelial cell lines. The

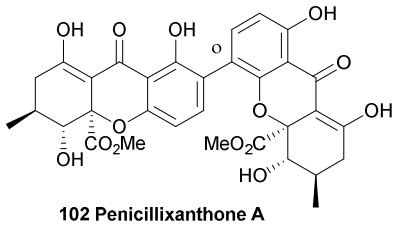
dimeric xanthone showed relatively high cytotoxicity to the cancer cells and a reduced cytotoxicity towards the immortalised breast epithelial cells, which is a very useful feature when developing new anti-cancer drugs.[143]



101 Penexanthone A

Penicillixanthone

The 2,4′-biaryl-linked dimer penicillixanthone was reported around ten years ago[88, 166] by Chinese groups, who described the absolute stereochemistry. This compound has been re-isolated in 2013.[167]

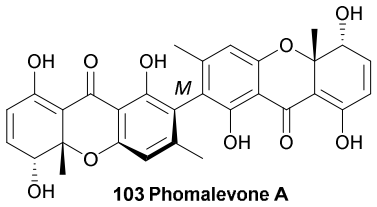


102 Penicillixanthone A (absolute stereochemistry)

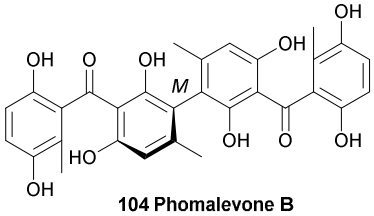
Phomalevones

In 2011 phomalevones A-C (**103-105**) were isolated from a Hawaiian isolate of *Phoma* sp. (MYC-1734 = NRRL 39060; *Cucurbitariaceae*). The structures of phomalevones A-C were determined by detailed analysis of NMR and MS data.[168] The absolute configuration of the sp^3 stereogenic centres of phomalevone A were revealed by analysis of NMR spectra of Mosher type derivatives.

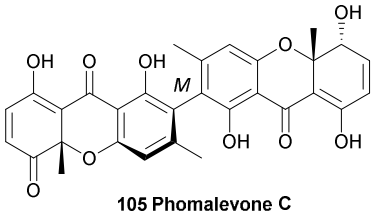
Phomalevone A was found to resemble ascherxanthone B. The ^{13}C NMR spectrum of phomalevone B showed only 15 carbon signals, thus indicating a symmetrical, homodimeric structure. Via HR-ESI-MS data it was determined that phomalevone B is an isomer of phomalevone A. However, the NMR spectra showed a significant downfield shift of the only carbonyl signal relative to its location in the spectrum of phomalevone A and the presence of two sp^2 carbon signals instead of sp^3 signals as in spectrum of phomalevone A. By comparing the NMR spectroscopic data with that of acremonidin D,[169] a symmetrical dimer with two benzophenone monomer units connected via a methylene linkage, a structural assignment could be made.[168] The occurrence of phomalevone A together with the benzophenone analogue, phomalevone B, is consistent with several reports that hydroxylated benzophenones are very likely to be key intermediates in xanthone biosynthesis.[25, 170, 171] HMBC spectra of phomalevone C revealed its heterodimeric nature, with one subunit the same as the monomer unit in phomalevone A, while the other has one secondary alcohol group oxidised to a carbonyl group. Phomalevone A-C showed antibacterial activity in agar disk diffusion assays at 100 μg/disk against *Bacillus subtilis* and *Staphylococcus aureus*. Additionally phomalevone B was also active against *Candida albicans* and *Escherichia coli* and phomalevone C showed activity against *Fusarium verticillioides* and *Aspergillus flavus* (IC_{50} value of 4 μg/mL, compared to an IC_{50} value of 5 μg/mL for the antifungal standard Nystatin).[168]



103 Phomalevone A



104 Phomalevone B



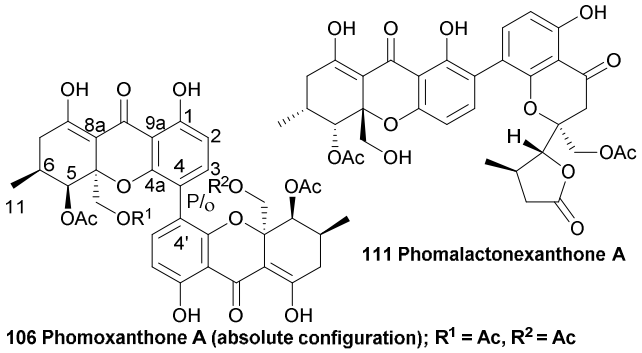
105 Phomalevone C

Phomoxanthones

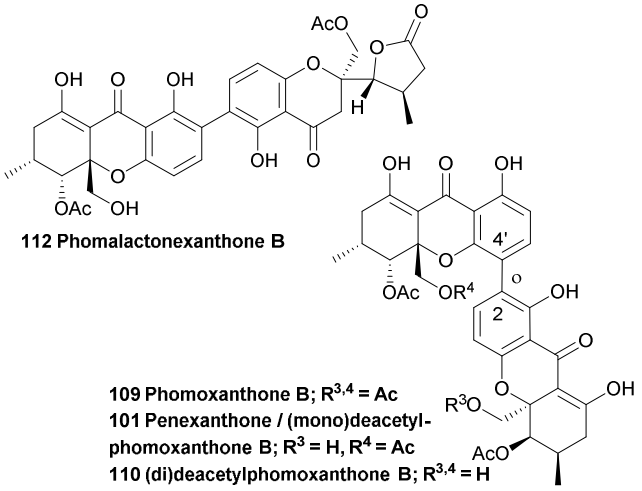
The antimalarial activity of methanolic extracts of mycelia of the endophytic fungus *Phomopsis* sp. BCC 1323 led to researchers isolating and identifying phomoxanthones A and B (**106**, **109**). The relative stereochemistry could be determined by synthesising a deacetyl derivative of phomoxanthone A and comparing the change in coupling signals. Phomoxanthones A and B were the first reported examples of naturally occurring xanthone dimers with 4,4′ or 2,4 linkages.[172] In 2008, the deacetyl derivative of phomoxanthone B (**110**) was isolated from the same fungus species by Kirtikara *et al*.[90] Phomolactonexanthone A and B are both derived either from coupling of a lactone-analogue of a xanthone (as the blennolides)[47] and a xanthone itself, or from the further derivatisation from a dimeric xanthone.

Biological tests with deacetylphomoxanthone B showed a higher antibacterial effect against the pathogen *Xanthomonas oryzae* KACC 10331, a cause for bacterial blight in rice, than a positive control with 2,4-diacetyphloroglucinol.[139] Deacetylphomoxanthone B and C (**108**) and phomolactonexanthones A and B (**111**, **112**), that were isolated from *Phomopsis* sp. HNY29-2B, were tested for their cytotoxicity against a series of human cancer lines and it was found that while deacetylphomoxanthone B has a reasonable cytotoxicity against all tested cancer cell lines, deactylphomoxanthone C and the phomolactonexanthones were virtually inactive against all cell lines.[143] Phomoxanthones A

and B showed antimalarial (*Plasmodium falciparum* K1, multi drug resistant strain, IC_{50} of 0.11 and 0.33 μg/mL, compared to IC_{50} of 0.16 and 0.0011 μg/mL for chloroquine diphosphate and artemisinin respectively) and antitubercular activity (*Mycobacterium tuberculosis* H37Ra strain IC_{50} of 0.5 and 6.25 μg/mL, compared to IC_{50} of 0.05 and 2.5 μg/mL for isoniazid and kanamycin sulfate, respectively). Biological tests on cancer cell lines (KB cells, BC-1 cells and Vero cells) showed that the natural products are cytotoxic (IC_{50} μg/mL; 0.51-1.4 for phomoxanthone A and IC_{50} μg/mL 0.7-4.1 for phomoxanthone B), although it was noted that standard drugs are more potent in both bacterial and the cancer cells tests. The deacetyl derivative was also investigated in these assays and was found to be mostly inactive in all the tests -it is speculated that this might be due to its lower lipophilicity.[172]



106 Phomoxanthone A (absolute configuration); R^1 = Ac, R^2 = Ac
107 12-deacetylphomoxanthone A; R^1 = H, R^2 = Ac
108 Deacetylphomoxanthone C (relative configuration); R^1 = H, R^2 = H



109 Phomoxanthone B; $R^{3,4}$ = Ac
101 Penexanthone / (mono)deacetyl-phomoxanthone B; R^3 = H, R^4 = Ac
110 (di)deacetylphomoxanthone B; $R^{3,4}$ = H

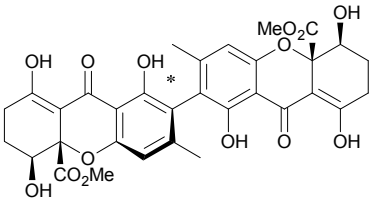
The absolute configuration (a*S*,5*R*,6*R*,10a*R*,5´*R*,6´*R*,10a´*R*) of phomoxanthone A was determined by a combination of single crystal X-ray analysis with measured and calculated CD spectra in 2005.[86] However, in 2013 the absolute configuration was revised to be (a*R*,5*S*,6-S,10a*S*,5′*S*,6′*S*,10a′*S*), when a team of researchers performed a detailed X-ray analysis study and TDDFT ECD calculations after they suspected that the configuration might have been wrongfully assigned.[138] The suspicion arose when they isolated phomoxanthone A together with dicerandrols B and C from *Phomopsis longicolla* and found that all their stereocenters had the *S* absolute configuration. In this same study they also found a new natural product from the same endophyte, which was identified by NMR studies as 12-deactylphomoxanthone A (**107**).

Biological tests showed that phomoxanthone A has promising activity against Gram-positive bacteria and fungi.[86] In 2013 Lee *et al*. isolated several secondary metabolites from the mycelium of a culture broth of *Phomopsis longicolla* S1B4, including dicerandrols A-C (**84-86**) and a compound they named deacetylphomoxanthone B, **101** (which is in fact a monodeacetylphomoxanthone and is identical to penexanthone A). This compound exhibits a strong antimicrobial activity against the gammaproteobacteria *Xanthomonas oryzae* with a MIC of 32 μg/mL, compared to dicerandrols A-C which showed 8, 16 and 16 μg/mL respectively.[140] Phomoxanthone A has also been found to strongly inhibit the proliferation of the murine lymphoma cell line L5178Y, as well as other cell lines including some cisplatin resistant cancer cell lines.[138] Remarkably the cytotoxicity of phomoxanthone A towards the lymphoma cells was found to be over 100-fold increased with respect to healthy blood cells. A semisynthetic fully deacetylated phomoxanthone A showed no activity in this assay. Proksch *et al.* also analysed the apoptosis inducing potential of phomoxanthone A by flow cytometric analyses of hypodiploid nuclei in Jurkat T cells.[138] The presence of these hypodiploid nuclei is indicative of aspartate-directed cysteine proteases (caspase) induced DNA fragmentation, which is an indicator for apoptosis. They found that among all tested substances the 4,4′-linked phomoxanthone A and deacetylphomoxanthone A scored highest on these tests and actively induce apoptosis. On top of that they also found that they activate immune effector functions in murine immune cells, such as primary T lymphocytes, NK cells and macrophages, as was observed by the upregulation of cell-type specific activation markers. During a preliminary structure-activity assessment the authors conclude that the presence of the acetyl groups and the 4,4′-linked system in xanthone dimers **106** and **107** are important to maintain the interesting biological properties, possibly because of an underlying mechanism where there is a necessity to pass the cellular membrane. The deacetylated xanthones are less lipophilic and therefore often score very low on biological tests.

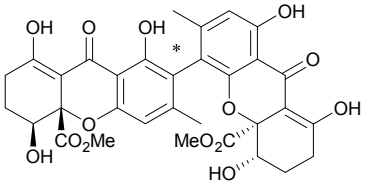
When comparing the overall activity of the phomoxanthones with other similar xanthones, it must indeed be noted that the acetylated species, such as the dicerandrols and neosartorin often show quite interesting biological properties, whereas more often the non-acetylated compound either were not tested, or did not show promising activities. One could speculate that this is possibly may be due to enhanced cell penetration, however, in the case of the dicerandrols, the more acetylated dicerandrol C was found to be much less cytotoxic to cancer cells than the dicerandrols A and B, that have free hydroxyl groups.

Rugulotrosins

Rugulotrosins A and B (**113**, **114**) were isolated from cultures of *Penicillium* sp. Derived from Australian soil samples. Rugulotrosin A is symmetrically 2,2′-linked while rugulotrosin B is a 2,4′-linked dimer. The structures of these compounds were determined by NMR and MS techniques, and supported by single crystal X-ray analysis of rugulotrosin A. The compounds were of considerable activity against several microbial species (*Bacillus subtilis*, *Enterococcus faecalis* and *Bacillus cereus*.[173]



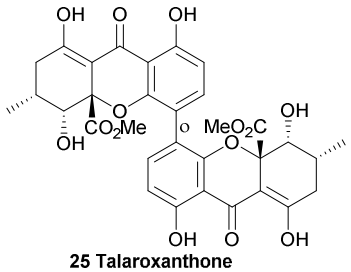
113 Rugulotrosin A
(relative configuration)



114 Rugulotrosin B
(relative configuration)

Talaroxanthone

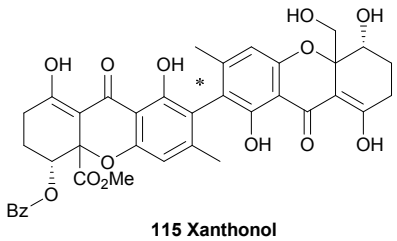
The identity of talaroxanthone (**25**) was reported by Koolen and co-workers in 2013. This compound, featuring a 4,4′-linked biaryl motif, was isolated from the culture broth of DgCr22.1b, an endophytic *Talaromyces sp.* fungi isolated from the healthy tissue of the medicinal plant *Duguetia stelechantha* in the Amazonian rainforest. The yellow powder that was subsequently isolated by chromatographic techniques was determined to be the structure shown by HRMS and several 2D NMR techniques. Whether the medicinal qualities of the plant material are due to the presence of this fungal-derived compound is as yet unclear.[57]



25 Talaroxanthone

Xanthonol

The unsymmetrical 2,2′-biaryl-linked dimeric xanthone, xanthonol (**115**), was isolated from the fermentation broth of a non-sporulating fungi found in the leaf litter of the plant *Manikara bidentata*. Xanthonol bears the methyl-substituents upon the aryl positions, rather than the 6,6′- methylation of the ergochromes etc.. Also interesting is the benzoylated alcohol at the *C5′* position. Xanthonol is an anthelmintic, as revealed by tests upon the larvae of *Lucilia sericata*, *Aedes aegypti*, and *Haemonchus contortus*.[174]

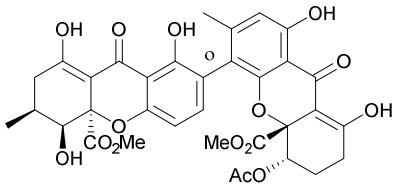


115 Xanthonol

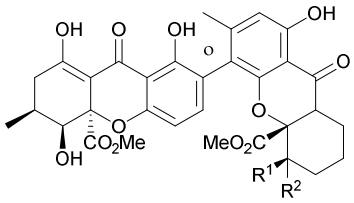
Xanthone Dimers from Lichens

Eumitrins

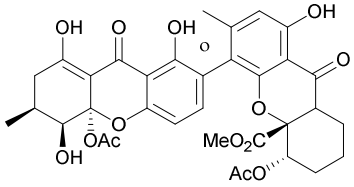
In 1967 Asahina first reported the occurrence of yellow pigments named eumitrins A_1, A_2, B and T (**116-119**) isolated from the lichen *Usnea baileyi*.[175] Eumitrins A and B were later isolated from benzene extracts of the dried lichen thalli.[176] Shibata *et al.* found that the fraction of eumitrin A could be separated into A_1 and A_2 by recrystallisation and elucidated the chemical structured of eumitrins A_1, A_2 and B by spectroscopic methods.[177] By measuring differences in chemical shifts in NMR experiments after acetylation of the compounds they were able to assign that the biphenyl junction in these dimers is a 4,2′-linkage. Using single-crystal X-ray analysis of a tribromo derivative of eumitrin B they confirmed the structures of eumitrins A_1, A_2 and B. Interestingly, these xanthones have been reduced down from their normal oxidation states to bear a non-oxygenated/non-aromatic cyclohexenyl *C*–ring.



116 Eumitrin A_1



117 Eumitrin A_2; R^1 = OAc, R^2 = H
118 Eumitrin B; R^1 = H, R^2 = OAc

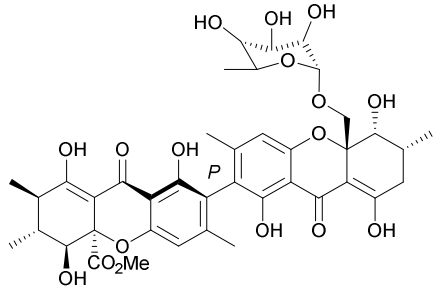


119 Eumitrin T

In 2002 a Japanese patent was filed, claiming that eumitrins A_1 and A_2 could be used as inhibitors for nitric oxide formation by macrophages and thus be useful for a wide range of illnesses.[178] Elix *et al.* report the extraction of secalonic acid A and eumitrin T from the lichen-forming fungus *Physconia distort.* Interestingly, they found that these dimeric xanthones were only found when intact lichen thalli were investigated and not in axenic cultures of the fungus, indicating a clear difference in metabolic pathways between the lichen and the axenic fungus.[92] Recently the same group investigated the contents of 18 lichen obtained from the mountainous areas of Malaysia using TLC and HPLC analyses. Amongst the secondary metabolites found in the lichen *Usnea baileyi* they found eumitrins A_1, A_3, B_1 and B_2. However, the structures of eumitrins A_3 and B_2 are not yet elucidated.[179]

Hirtusneanoside

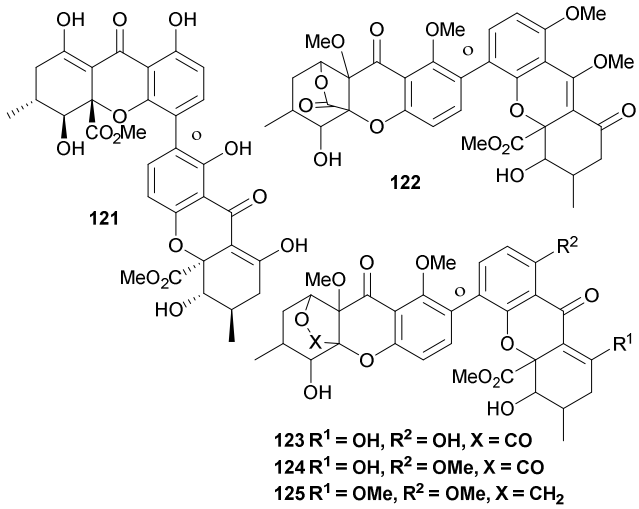
Hirtusneanoside (**120**), was first isolated from the lichen *Usnea hirta* in 2007 by Řezanaka and Sigler, and found to be a L-rhamnose-*O*-deoxyglycoside of an unsymmetrical dimeric tetrahydroxanthone.[180] Fascinatingly, hirtusneanoside features an additional methyl in relation to the secalonic acids; the biosynthetic origin of this methyl group is as yet unknown. Hirtusneanoside is effective against *Staphylococcus aureus* and *Bacillus subtilis*.



120 Hirtusneanoside A
(absolute stereochemistry)

Unnamed dimeric xanthones

A number of unnamed xanthones have been reported, some due to the lack of full proof of their structure, some as parts of patent applications (Figure 4). In compound **125**, the lactone bridge appears to have been reductively transformed to a furan.



121
122
123 R^1 = OH, R^2 = OH, X = CO
124 R^1 = OH, R^2 = OMe, X = CO
125 R^1 = OMe, R^2 = OMe, X = CH_2

Figure 4: Miscellaneous unnamed dimeric xanthones

Supplementary information

In order to provide a clear overview of the structural features, natural sources and biological activities of the discussed xanthones, three tables detailing these topics have been added as supplementary information (available online).

Table S-1 lists the contrasting structural features of the biaryl linked xanthones that are discussed in this Review.

Table S-2 shows a comprehensive list of all known dimeric and trimeric xanthones from nature, alongside their compound numbers in this Review, their CAS numbers for ease of cross-referencing with the scientific literature, associated references detailing their natural occurrence, and the name of the species in nature from which they have been isolated.

Dimeric xanthones have been found to be active in an extremely varied array of disease states and at a wide variety of structurally despondent biotargets. These include antibiotic, antifungal, antitumour and as antihypertensives and antioxidants. Several factors make it extremely difficult to link

the bioactivities observed for these dimeric xanthones and the structural features that enable these bioactivities. First and foremost, no systematic study of the biological activity of xanthones, let alone their dimeric derivatives, has been conducted –for understandable practical reasons, as these compounds are not centrally stored in a chemical repository. The logistics of such an assay would furthermore be complicated by the variety of potential screens, many of which are non-standardised and specific to particular research Institutions and even groups. Furthermore, broadly ascribing bioactivities to structural features, (*e.g.* the antibacterial activity of chrysoxanthone to the presence of a biaryl ether linkage) is overly simplistic. When considering xanthones as leads for medicinal chemistry campaigns, it should be noted that the xanthone core commonly features polyhydroxylated and carbonyl-substituted arene core, a structural motif which may result in indiscriminate binding to a variety of target biomolecules. Nonetheless, **Table S-3** details the known bioactivities of dimeric xanthones in a variety of disease states, their associated activity and also details related to concentration and or dosage at which these effects were observed.

Conclusions

Dimeric xanthones are a structurally highly diverse group of compounds from various Kingdoms of organisms, including plants, fungi and lichens. We have reviewed their origins, structural features, and, where applicable, bioactivities. Within the last five years, a number of monomeric xanthones have been prepared[16] and the first synthesis of ergochromes has been achieved. We assume that in the next decade or so -with the further advent of arylation methods suitable for the unique requirements of these species- the synthesis of dimeric xanthones will be tackled with success.

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Notes and references

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