Flavonoids and their glycosides, including anthocyanins

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This review describes more than 600 new examples of naturally occurring flavonoids found either as aglycones or glycosides, comprising flavones, flavonols, chalcones, dihydrochalcones, aurones, flavanones, dihydroflavonols, anthocyanidins and anthocyanins. The main topics addressed are source, identification, biological activity, biosynthesis, synthesis, and ecological or chemosystematic significance, and 514 references are cited.

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1 Introduction

This is the fifth in a series of triennial reviews of the flavonoid literature, the first three of which were published by Harborne and Williams.[1–3] The most recent, by Williams and Grayer, described more than 450 new flavonoids reported between 2001 and 2003.[4] The present review is similar to its predecessors in terms of coverage, although some changes have been introduced, the most important of which is the inclusion of *C*-glycosylflavonoids as a natural extension to the discussion of *O*-glycosides. The sequence in which the different classes of flavonoids is described has also been modified slightly to reflect the distribution of new compounds published in the 2004–2006 period, with anthocyanins now appearing at the end. As before, much of the text is concerned with flavones, flavonols and the so-called 'minor' flavonoids (chalcones, dihydrochalcones, aurones, flavanones and dihydroflavonols), together with their glycosides. Flavans and proanthocyanidins are not included, but a recent book chapter by Ferreira and colleagues surveys the 1992–2003 literature on these compounds.[5] Contemporary reviews of the literature on isoflavonoids describe those found in the Leguminosae (1997–2004)[6] and non-leguminous plant families (to 2005).[7,8] It seems remarkable that even without these groups, the number of new flavonoids reported between 2004 and 2006 exceeds 600, a clear reflection of continuing interest in the field.

Two important books on flavonoids were published in 2006. *Flavonoids: Chemistry, Biochemistry and Applications* is one of the most comprehensive works available to date on this group of natural products.[9] Edited by Andersen and Markham, it comprises reviews both of topical subjects and the main flavonoid classes. Seen as a successor to the series, *The Flavonoids: Advances in Research*,[10] it is concerned mainly with the literature from 1992 to 2003. *The Science of Flavonoids*, edited by Grotewold, focuses on trends in flavonoid research since 1990, overviews of which appear in nine chapters.[11] Several specialised reviews also deserve mention. Some are concerned with particular classes of compound, such as furanoflavonoids (literature to 2004)[12] or the complex pigments comprising anthocyanins, flavone glycosides and metal ions that give rise to blue flower colours.[13] Others focus on the flavonoid chemistry of particular genera or species, such as *Erythrina* (Leguminosae),[14] *Artocarpus* (Moraceae)[15] or the hop, *Humulus lupulus* (Cannabinaceae).[16] De Rijke *et al.* have reviewed current separation and detection methods for flavonoids, with particular emphasis on hyphenated analytical techniques (note that the many papers which appear in the literature on the flavonoid analysis of particular plant species and plant products are outside the scope of the present review, since few of these are concerned with new compounds).[17] A retrospective account of four decades of research by Emeritus Professor Ragai Ibrahim (Concordia University, Canada) offers a fascinating insight into the development of several areas of flavonoid biochemistry, with an emphasis on enzymatic *O*-methylation, sulfonation and prenylation.[18] Koes *et al.* have reviewed the biosynthesis of flavonoid pigments, and the regulation of the biochemical pathways concerned,[19] whereas Schijlen *et al.* focus on the regulation and modification of flavonoid biosynthesis in crops.[20]

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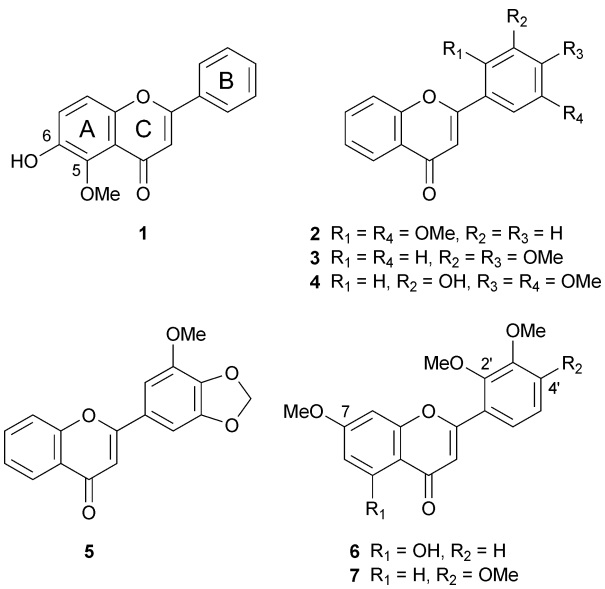
New flavonoids reported in the current review period are presented in the following nine sections, which follow a standard pattern so far as is practicable. For aglycones, those considered to have simple patterns of *O*-substitution (*i.e.* OH, OMe and $–OCH_2O–$) are treated first, followed by their *C*-methyl derivatives. Broadly speaking, these are placed in order of increasing *O*-substitution. Prenylated flavonoids, which follow next, are presented in groups arranged alphabetically by plant family and species, as this allows structural trends of chemosystematic interest to be seen more clearly. The sections continue with miscellaneous structures, which in the case of the minor flavonoids (Sections 5–9) are preceded by glycosides. The large number of glycosides of flavones and flavonols calls for their treatment in a separate section, in which the compounds are tabulated for convenience. Anthocyanins are described in Section 10. Points of interest mentioned in connection with all new flavonoids include those relating to source, structural elucidation, biological activity, biosynthesis, synthesis, chemosystematics and ecology. To avoid presenting the material purely as a checklist of flavonoids published as new in each category, some disputed or doubtful structures appearing in the review period are also discussed. Although these are referred to in the text, they do not form part of the numbered sequence of compounds. Species names abstracted from the flavonoid literature have been cross-checked with several databases, including the International Plant Names Index (IPNI),[21] the World Checklist of Selected Plant Families,[22] and the International Legume Database and Information Service (ILDIS).[23] Where possible, the currently accepted name and family are given, and publication under names that are synonyms is noted together with the relevant botanical authorities (at their first citation in the text only). Semi-systematic or trivial names are used to describe flavonoid structures.

2 Flavones

More than 60 new flavones were published as natural products between 2004 and 2006. Predominant among these are examples characterised by simple patterns of *O*-substitution (OH, OMe) (**1–13**) and prenylation (**16–54**). Reports of *C*-alkylflavones (**14,15**), flavone esters (**55,56**) and flavonolignans (**61,62**) remain infrequent. Valant-Vetschera and Wollenweber have reviewed the literature on flavones from 1992 to 2003, and provide invaluable checklists containing new structures and additional sources of known compounds.[24] An overview of flavones and their biosynthesis has been given by Martens and Mithöfer.[25]

Ethanolic extracts of the leaves of *Casimiroa edulis* (Rutaceae) contain 6-hydroxy-5-methoxyflavone (**1**) and its 6-*O*-β-glucopyranoside (**95**).[26] The uncommon 5,6-di-*O*-substitution pattern of the A-ring is common to a number of Rutaceae flavones, including the well-known derivative, zapotin (5,6,2′,6′-tetramethoxyflavone),[27] and both **8** and **12**.[28] Four lipophilic flavones substituted only in the B-ring (**2–5**) have been isolated from leaf material (both field-collected and in vitro cultures) of *Primula veris* (Primulaceae),[29] and are presumed to be exudate compounds. The physical properties of the di-*O*-substituted derivatives **2** and **3** were comparable to synthetic material.[29] Only one other example of the 3′,4′,5′-tri-*O*-substitution pattern of **4** and **5** has been recorded (3′,4′,5′-trimethoxyflavone from the flowers of *Primula veris*).[30] MeOH extracts of the whole plant of *Andrographis paniculata*



1

2 $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
3 $R_1 = R_4 = H$, $R_2 = R_3 = OMe$
4 $R_1 = H$, $R_2 = OH$, $R_3 = R_4 = OMe$

5

6 $R_1 = OH$, $R_2 = H$
7 $R_1 = H$, $R_2 = OMe$

Nigel Veitch

Nigel Veitch studied chemistry at the University of Oxford, and obtained a DPhil there with Professor R. J. P. Williams. In 1992 he moved to the Royal Botanic Gardens, Kew, where his interests include flavonoids (especially of the Leguminosae), and the NMR spectroscopy of natural products and proteins. He was, with Renée Grayer, a contributor to Flavonoids: Chemistry, Biochemistry and Applications (CRC Press, 2006).

Renée Grayer

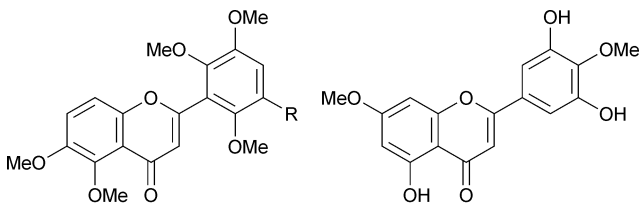
Renée Grayer studied biology with chemistry at the University of Leiden, The Netherlands, and obtained her PhD there under the supervision of Professor R. Hegnauer. From 1975 to 1994 she worked on flavonoids with Prof. J. B. Harborne at the University of Reading, before moving to the Royal Botanic Gardens, Kew, where she specialises in flavonoids and terpenoids of the family Lamiaceae.

(Acanthaceae) yielded 5-hydroxy-7-2′,3′-trimethoxyflavone (**6**) and a related flavanone (**458**).[31] This is only the second example of this substitution pattern in flavones, following the publication of 5,7,2′,3′-tetramethoxyflavone from *Andrographis viscosula* in 2003.[32] However, 2′-oxygenation is relatively common in the genus[24,33] (see also **13**), and may be of chemotaxonomic significance. Maheswara *et al.* isolated 7,2′,3′,4′-tetramethoxyflavone (**7**) from the whole plant of *Calliandra inermis* (Leguminosae), together with the corresponding flavanone (**459**).[34] This substitution pattern has not been found previously. The positions of the methoxy groups were determined using connectivities detected in NOE and HMBC experiments.

Studies of plants used by the Yucatec Maya of Mexico in traditional medicine resulted in the discovery of two highly methylated derivatives, 5,6,2′,3′,6′-pentamethoxyflavone (**8**) and 5,6,2′,3′,5′,6′-hexamethoxyflavone (**12**). Both were obtained from ethanolic extracts of the leaves of *Casimiroa tetrameria* (Rutaceae), the former being characterised in a mixture with zapotin.[28] The substitution patterns of these new flavones have not been reported previously. Extracts of the powdered leaves and twigs of *Gardenia tubifera* (Rubiaceae) yielded 5,3′,5′-trihydroxy-7,4′-dimethoxyflavone (**9**), a dimethyl ether of tricetin that showed anti-HIV-1 activity in the syncytium assay using the ΔTat/RevMC99 virus and 1A2 cell line system.[35] The same compound was inactive in an HIV-1 reverse transcriptase assay.[35] Two 8-hydroxyflavones (**10**, **11**) isolated from the stem bark of *Muntingia calabura* (Tiliaceae) showed cytotoxicity in the P-388 cell line.[36] Flavones characterised by the 7,8,3′,4′,5′-*O*-substitution pattern are known only from this species.[37] The hexa-substituted 5,4′-dihydroxy-7,8,2′,3′-tetramethoxyflavone (**13**)[38] from aerial parts of *Andrographis paniculata* (Acanthaceae) was reported previously from the roots of this species, but as the 5-*O*-β-glucopyranoside (andrographidin F).[39] A *C*-methylflavone characterised as 5-hydroxy-7,5′-dimethoxy-3′,4′-methylenedioxy-6,8-dimethylflavone (**14**) occurs in *Elsholtzia stauntonii* (Lamiaceae), although the plant tissue from which this compound was isolated was not specified.[40] This species also contains a *C*-methylflavone with B-ring prenylation (**19**).[40] Anadanthoflavone (**15**) is one of a small number of flavones substituted by acrylic acid at C-6, in this case as the methyl ester. Obtained by bioassay-guided fractionation of extracts of the aerial parts of *Anadenanthera colubrina* var. *cebel* (Leguminosae), it showed inhibition of human platelet 12-lipoxygenase and human reticulocyte 15-lipoxygenase.[41]

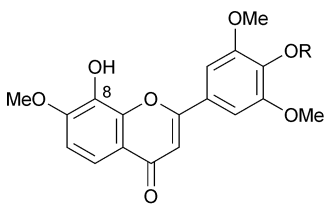
Although the 5,6,7,8,4′-penta-*O*-substitution pattern is relatively common for flavones, the corresponding derivatives tend to occur as di- to penta-methyl ethers.[24] In this respect, a mono-methyl ether, 5,6,7,8-tetrahydroxy-4′-methoxyflavone, published as a constituent of the roots of *Trifolium repens* L. (Leguminosae) is atypical.[42] However, there are several anomalies in the NMR data presented in support of this compound (limited to 1D ^{1}H and ^{13}C spectra acquired in DMSO-d_6) which merit further investigation, notably the assignment of a resonance in the ^{13}C NMR spectrum at δ 97.9 to C-10 and the lack of downfield shift to H-3′,5′ of the B-ring (δ 6.92 in the ^{1}H NMR spectrum) expected for methylation at 4′-OH. The same study also describes 5,6,7,8,4′-pentahydroxyflavone as a known compound (source; shoots of *T. repens* colonised by the arbuscular mycorrhizal fungus *Glomus intraradices*), referring to it incorrectly as ponkanetin (one of the trivial names used for 5,6,7,8,4′-pentamethoxyflavone).[42] No record of 5,6,7,8,4′-pentahydroxyflavone as a natural product has been traced in the literature. The reported isolation of 5,8-dihydroxy-6,7,4′-trimethoxyflavone from *Limnophila indica* (Scrophulariaceae) is erroneous,[43] as the ^{1}H NMR spectrum of this constituent acquired in $CDCl_3$ is the same as that of 5,7-dihydroxy-6,8,4′-trimethoxyflavone (nevadensin),[44] which is already known to occur in this genus.[45,46]

New prenylated flavones have been found mainly in the Leguminosae (23%) and Moraceae (62%), the remaining family representation comprising only the Berberidaceae, Convolvulaceae,

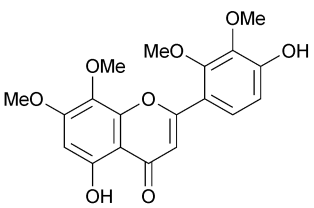


8 R = H
12 R = OMe

9



10 R = H
11 R = Me



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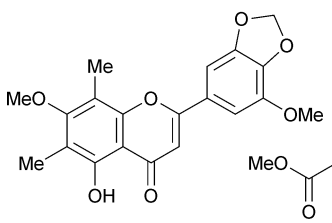

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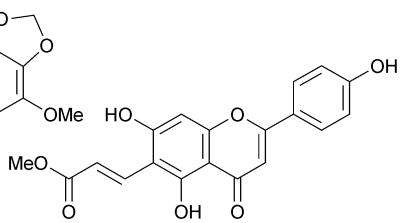
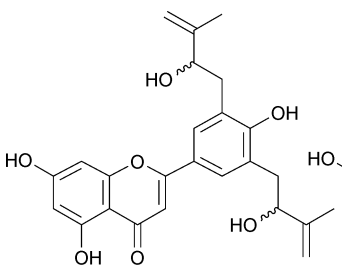
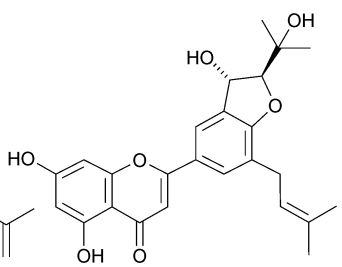


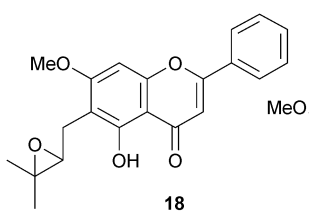
15 Anadanthoflavone



16 Breviflavone A



17 Breviflavone B



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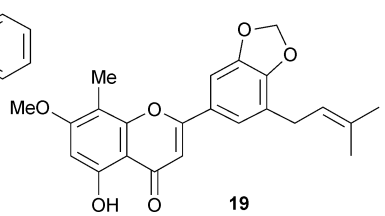
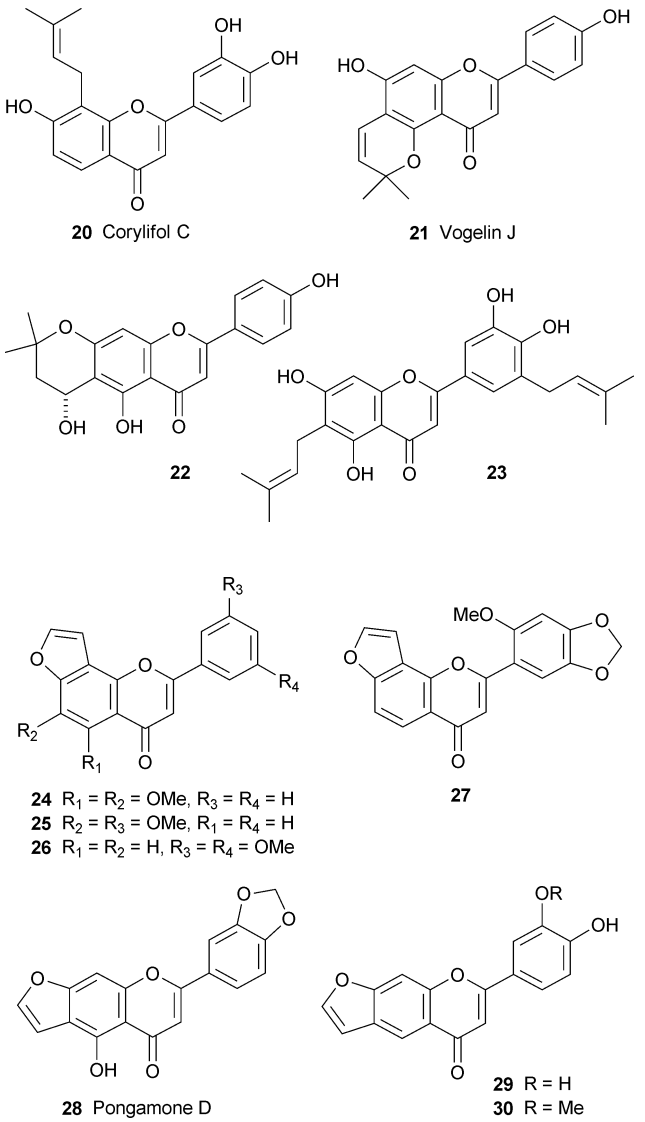


19

Lamiaceae and Ochnaceae. Breviflavones A (**16**) and B (**17**) were obtained by bioassay-guided fractionation of extracts of the aerial parts of *Epimedium brevicornum* (Berberidaceae), a species used in Chinese traditional medicine.[47] Breviflavone B (**17**) reproduced the profile of estrogenic activity shown by crude ethanolic extracts, with biphasic stimulation and inhibition of breast cancer cell proliferation at low and high doses, respectively. A 6-(2,3-epoxy-3-methylbutyl) derivative (**18**) of tectochrysin (5-hydroxy-7-methoxyflavone) isolated from the stems of *Cuscuta reflexa* (Convolvulaceae) has been given the trivial name 'reflexin', which is already in use for different compound (note also that **18** was incorrectly described as a flavanone in the title and abstract of the paper concerned).[48]

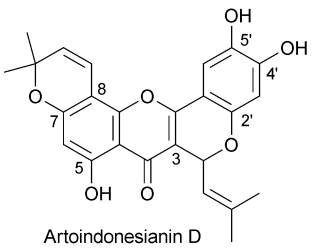
The seeds of *Cullen corylifolium* (L.) Medik. (published under the synonym *Psoralea corylifolia* L.) (Leguminosae) are the source of corylifol C (**20**), an 8-prenyl derivative of 7,3′,4′-trihydroxyflavone which co-occurs with its precursor chalcone, corylifol B (**348**).[49] The west African species, *Erythrina vogelii* (Leguminosae), is best known as a source of prenylated isoflavonoids (vogelins A–G).[50,51] However, a study of material collected in Nigeria revealed the presence of the pyranoflavone vogelin J (**21**), in stem bark extracts.[52] The linear dihydropyranoflavone **22** is a constituent of MeOH extracts prepared from the branches of *Eysenhardtia platycarpa* (Leguminosae), a small tree of southern Mexico (see also **478**).[53] The absolute configuration of the secondary hydroxyl group at C-4″ of the dihydropyran ring was determined using Mosher's method.[53] Bai *et al.* have reported 6,5′-diprenylluteolin (**23**) from the leaves of *Glycyrrhiza uralensis* (Leguminosae).[54] The isomeric 8,5′-diprenylluteolin (epimedokoreanin B) is already known from *Epimedium koreanum* (Berberidaceae).[55] A series of angular and linear furanoflavones (**24–28**) completes the remaining entries for Leguminosae. Magalhães *et al.* isolated 5,6-dimethoxyfurano[2″,3″:7,8]flavone (**24**) from the roots of *Lonchocarpus muehlbergianus* as one of several flavonoids with no B-ring substituents.[56] The isomeric 6,3′-dimethoxyfurano[2″,3″:7,8]flavone (**25**) from pods of *Millettia erythrocalyx* is remarkable on account of its unusual B-ring substitution pattern.[57] Similar derivatives with the B-ring oxygenated solely at C-3′ have been reported from *Millettia pinnata* (L.) Panigrahi, but under the widely used synonym, *Pongamia pinnata* (L.) Pierre.[12] This species is also the source of **26** (isolated from stem bark),[58] **27** (stems and roots; published using the synonym *Derris indica* (Lam.) Benn.)[59] and **28** (stems).[60] The structures of two linear furanoflavones (**29**, **30**) obtained from root bark of *Ochna squarrosa* (Ochnaceae) were confirmed by synthesis.[61]

Prenylated flavones of the genus *Artocarpus* (Moraceae) are noted for their structural diversity, which derives in part from their tendency to undergo prenylation at C-3. The flavone skeleton can be further elaborated by cyclisation between C-3 prenyl groups and the B-ring, which typically bears a 2′,4′,5′-tri-*O*-substitution pattern.[24] In a recent review of the flavonoids of Indonesian species of *Artocarpus*, Hakim and colleagues also discuss their biogenesis, biological activity and chemotaxonomic significance.[15] In terms of the present survey, the new derivatives artochamins B–E (**31–34**)[62] serve as an example of the variety of structures obtained, although artochamin C (**32**), which showed cytotoxicity in a number of human tumour cell lines, is a simple pyranoflavone derived from an 8-prenylluteolin precursor.

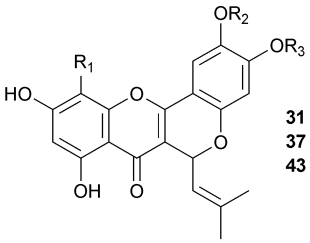


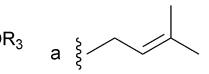
Artochamin D (**33**) is a typical 3-prenylflavone, and the 4′-methyl ether of the known compound, artonin V. The latter is a constituent of the root bark of the domesticated breadfruit, *Artocarpus altilis*,[63] whereas artochamins B–E occur in the roots of *Artocarpus chama* (isolated from EtOH extracts).[62] Artochamins B (**31**) and E (**34**) represent two different modes of cyclisation involving the 3-prenyl side chain and either 2′-OH or C-6′, resulting in flavones with an additional oxygenated 6-membered ring, or a xanthonoid structure, respectively. Although artochamin A was published as new in the same study,[62] it was first reported as artoindonesianin D in 2000, from root bark of *Artocarpus maingayi*.[15] Artoindonesianin V (**36**) has a xanthonoid structure and was isolated together with its precursor, artoindonesianin U (**35**), from $CHCl_3$ extracts of the heartwood of *Artocarpus champeden* Spreng. (a synonym of *Artocarpus polyphema* Pers.).[64] Both compounds showed significant cytotoxicity towards P-388 tumour cells, as was also the case for artoindonesianins A-2 (**37**) and A-3 (**38**), two further derivatives from the same source.[65]

MeOH extracts of the heartwood of *Artocarpus communis* yielded the new stereoisomers, (–)-cycloartocarpin (**39**) and

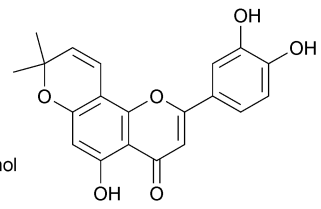


Artoindonesianin D
(Artochamin A)

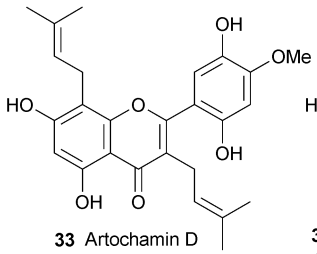




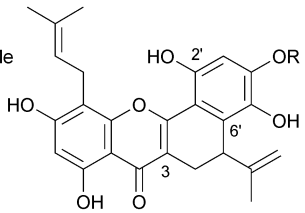
31 R_1 = a, R_2 = R_3 = H; Artochamin B
37 R_1 = R_2 = H, R_3 = Me; Artoindonesianin A-2
43 R_1 = R_3 = H, R_2 = Me; Cyclocomunomethonol



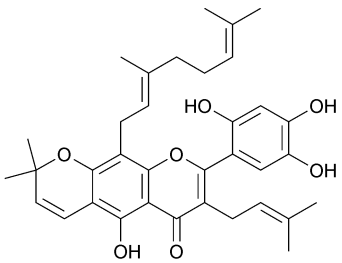
32 Artochamin C



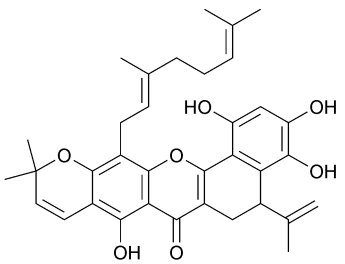
33 Artochamin D



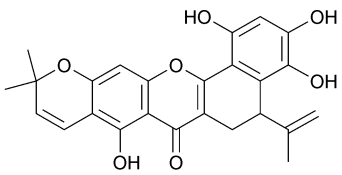
34 R = H; Artochamin E
41 R = Me; Dihydroartomunoxanthone



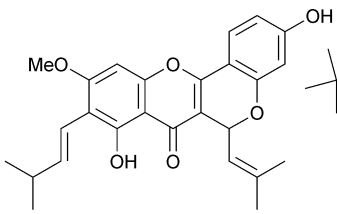
35 Artoindonesianin U



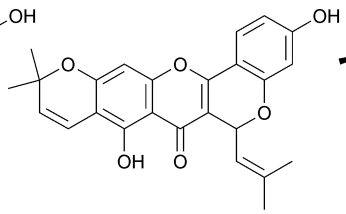
36 Artoindonesianin V



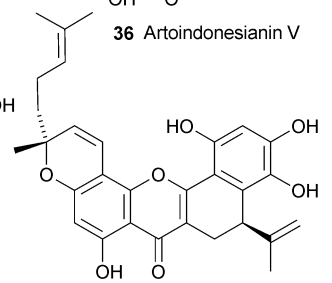
38 Artoindonesianin A-3



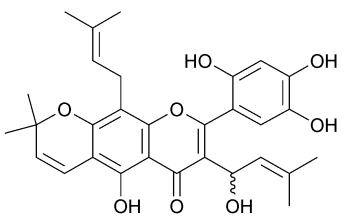
39 (–)-Cycloartocarpin



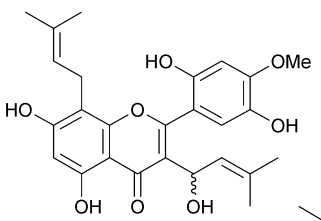
40 (–)-Cudraflavone A



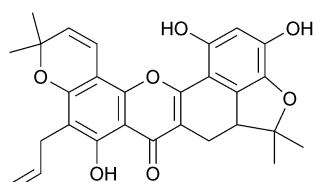
42 Artomunoisoxanthone



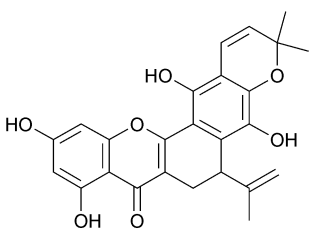
44 Artelastoheterol



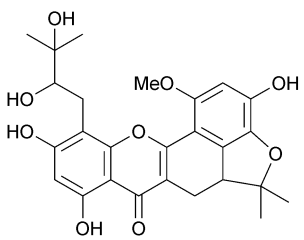
45 Artelasticinol



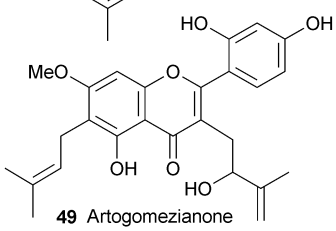
46 Cycloartelastoxanthone



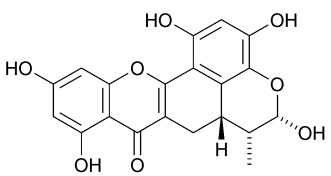
47 Artelastoxanthone



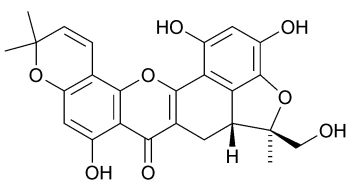
48 Cycloartelastoxanthendiol



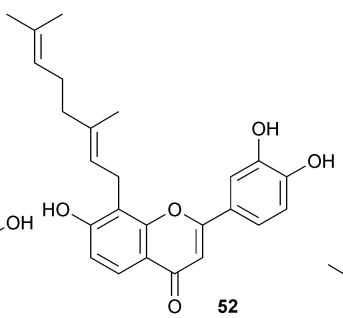
49 Artogomezianone



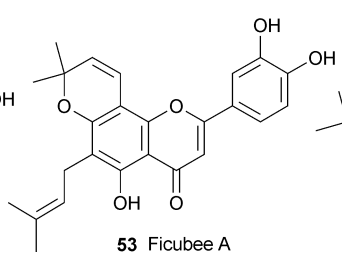
50 Artoindonesianin Z-1



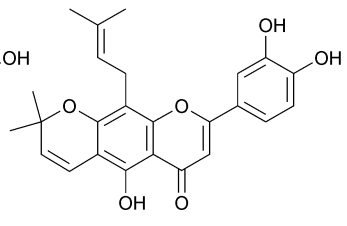
51 Artoindonesianin Z-2



52



53 Ficubee A



54 Ficubee B

(–)-cudraflavone A (**40**), both of which showed inhibitory activity towards NO production in lipopolysaccharide-activated murine macrophage RAW264.7 cells.[66] The cytotoxicity of **39** is relatively low, giving it a favourable selectivity index compared to the positive control, N^{ω}-monomethyl-L-arginine. Investigation of root cortex constituents of the same species afforded dihydroartomunoxanthone (**41**), which is the 4′-methyl ether of artochamin E (**34**), artomunoisoxanthone (**42**) and cyclocomunomethonol (**43**).[67] In assays for antiplatelet activity, only **41** showed significant inhibition of platelet aggregation induced by adrenalin in human platelet-rich plasma.[67] The pyranoflavone artelastoheterol (**44**) is characterised by 3-(1-hydroxy-3-methylbut-2-enyl) substitution, in common with artelasticinol (**45**). These compounds were isolated from the root bark of *Artocarpus elasticus* together with cycloartelastoxanthone (**46**), artelastoxanthone (**47**), and cycloartelastoxanthendiol (**48**), which have xanthonoid structures.[68] An additional level of complexity is suggested by the structures of **46** and **48**, in which the prenyl side chain at C-3 is coupled to both C-6′ and 5′-OH of the flavone B-ring. Artelastoxanthone (**47**) was later found in the root bark of *Artocarpus rigidus* subsp. *rigidus*, and published as new with the trivial name, 7-demethylartonol E.[69] Artogomezianone (**49**) is a constituent of MeOH extracts of the heartwood of *Artocarpus gomezianus*.[70] Two further examples of prenylated flavones from *Artocarpus lanceifolius* were reported by Syah *et al.* as artoindonesianins Z-1 (**50**) and Z-2 (**51**).[71] Both have extensively modified xanthonoid structures. The fruits of *Artocarpus nobilis* are rich in geranylated flavonoids, including the previously unrecorded derivative, 8-geranyl-7,3′,4′-trihydroxyflavone (**52**).[72] The structural complexity of *Artocarpus* flavones is not reproduced elsewhere in the Moraceae, as two examples (**53**, **54**) isolated from the roots of *Ficus beecheyana* illustrate.[73] These pyranoflavones are the 3′-hydroxy derivatives of laxifolin and isolaxifolin, respectively, compounds which occur in *Derris laxiflora* (Leguminosae).[74]

Only three flavone esters have been recorded in the literature to 2003.[24] To these can be added apigenin 7-*O*-*p*-hydroxybenzoate (**55**) from the aerial parts of the fern *Pteris vittata* (Pteridaceae),[75] and 8,2′,5′-trihydroxyflavone 5′-*O*-benzoate (**56**), which Iinuma *et al.* obtained from the farinose exudate of *Primula palinuri* (Primulaceae) together with the known 2′,5′-dihydroxyflavone 5′-*O*-acetate (see also **324**).[76] Niruriflavone (**57**) is the first example of a flavone sulfonic acid, in this case of acacetin (5,7-dihydroxy-4′-methoxyflavone), and was isolated from ethanolic extracts of the whole plant of *Phyllanthus niruri* (Euphorbiaceae).[77] Flavonol 8-sulfonic acids have been reported previously from *Phyllanthus virgatus*.[78]

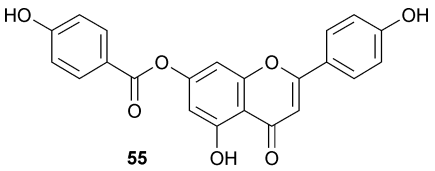
A survey of cytotoxic constituents of ferns (pteridophytes) from the Taiwanese flora led to the discovery of the 'protoflavones' **58–60**, which occur in MeOH extracts of the whole plant of *Thelypteris torresiana* (Thelypteridaceae).[79] A panel of 5 cell lines was used to assess their cytotoxicity, revealing protoapigenone (**59**) to be the most active. The compounds have non-aromatic B-rings, in common with the protoflavanones **529–532**, which also occur in ferns.[80] Lycopodone (**61**) is a flavonolignan isolated from the fern *Lycopodium japonicum* (Lycopodiaceae).[81] As with similar compounds, the parent flavone is tricin (5,7,4′-trihydroxy-3′,5′-dimethoxyflavone).[82] This is also the case with a new flavonolignan (**62**) isolated from extracts of *Avena sativa* (Poaceae).[83] Although its structure resembles that of neohydnocarpin, it is based on tricin and coniferyl alcohol, rather than luteolin and caffeyl alcohol. The absolute configuration of **62** was determined from CD spectra.[83]

3 Flavonols

A review of the flavonol literature from 1992 to 2003 was published by Valant-Vetschera and Wollenweber in 2006.[24] For the subsequent three-year period, 32 flavonols can be considered as new compounds, most of which are characterised by simple patterns of *O*-substitution (OH, OMe) (**63–70**) or prenylation (**74–88**). A small number of flavonols with unusual *C*-linked groups (**89–94**) have also been described in addition to the more commonly found *C*-methylflavonols (**71–73**).

Evaluation of extracts of *Iris germanica* (Iridaceae) for molluscidal activity against the snail *Biomphalaria alexandrina* led to the isolation of 5,2′-dihydroxy-3-methoxy-6,7-methylenedioxyflavone (**63**), irilins A and B, and the flavanone, **454**.[84] Although obtained from an active fraction, the compounds were not tested individually. Two novel flavonol salts (**64,65**) were reported by Zhang *et al.* in a study of the flavonoid constituents of root extracts of *Cudrania cochinchinensis* (Moraceae), which also afforded a new dimethyl ether (**66**) of morin (3,5,7,2′,4′-pentahydroxyflavone) and the corresponding dihydroflavonol (**534**).[85] Cochinchinols A (**64**) and B (**65**) are the Mg^{2+} and Ca^{2+} salts of morin 5-methyl ether and morin, respectively. Cation analysis was by inductively coupled plasma mass spectrometry. The NMR spectra of **64** show several interesting features when compared with those of morin 5-methyl ether, not least the shifted ^{13}C resonances of C-3 (+4.9 ppm), C-2′ (+2.9 ppm) and C-6′ (−3.7 ppm), and the downfield-shifted exchangeable ^{1}H resonance at 13.73 ppm assigned to 2′-OH from its HMBC connectivities with C-1′, C-2′ and C-3′. These offer support for a model of complex formation involving both 3-OH (in a deprotonated state) and 2′-OH. Similar trends can be seen in the NMR spectra of **65**.[85]

Melanoxetin (3,7,8,3′,4′-pentahydroxyflavone) and its methyl ethers have been reported from several species of *Acacia* (Leguminosae).[24] In a new study of *Acacia confusa*, the 4′-methyl ether (**67**) was found as a minor component of extracts of the heartwood together with melanoxetin and its 3-methyl ether.[86] The latter, which are major components, were more effective than quercetin (3,5,7,3′,4′-pentahydroxyflavone) as scavengers of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. The 3,8,3′-trimethyl ether (**68**) of melanoxetin has been isolated from aerial parts of *Prosopis farcta* (Banks & Sol.) J.F.Macbr. (published under the synonym of *Lagonychium farctum* (Banks & Sol.) Bobrov) (Leguminosae), together with **69**, a 5,6,3′-trimethyl ether of quercetagetin (6-hydroxyquercetin).[87] An octa-*O*-substituted flavonol identified as 3,5-dihydroxy-6,7,8,3′,4′,5′-hexamethoxyflavone (**70**) has been isolated from acetone extracts of the leaves of bush tea, *Athrixia phylicoides* (Asteraceae).[88] Tupichinols E (**71**) and F (**72**) are the 8-*C*-methyl derivatives of rhamnocitrin (kaempferol 7-methyl ether) and isokaempferide (kaempferol 3-methyl ether), respectively, and occur in the rhizomes of *Tupistra chinensis* (Ruscaceae).[89] The structure of a 6,8-dimethyl ether (**73**) of ermanin (kaempferol 3,4′-dimethyl ether) sourced from the aerial parts of *Eucalyptus*



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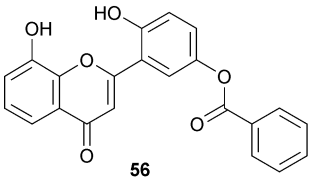

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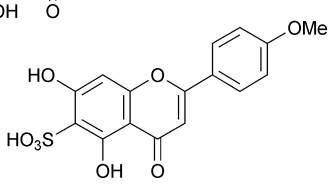
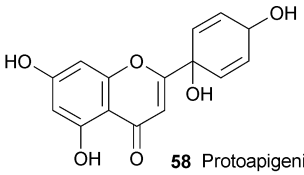
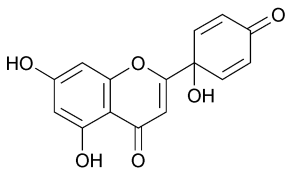


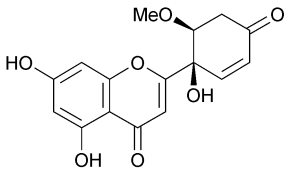
57 Niruriflavone



58 Protoapigenin



59 Protoapigenone



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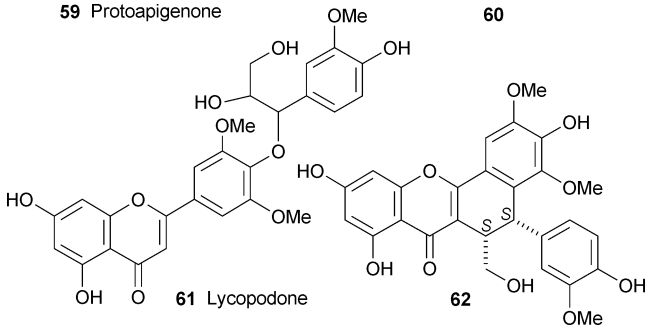
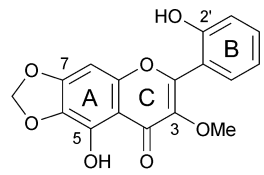


61 Lycopodone

62



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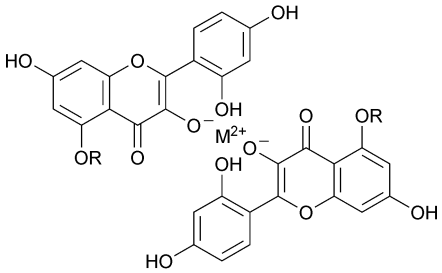
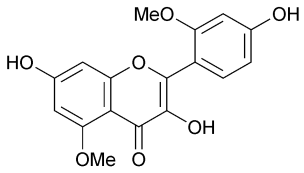


64 M = Mg, R = Me; Cochinchinol A
65 M = Ca, R = H; Cochinchinol B



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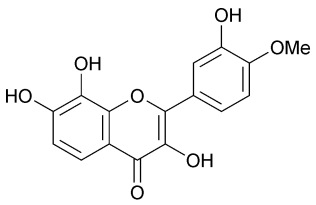

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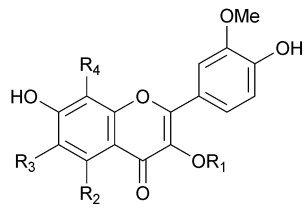
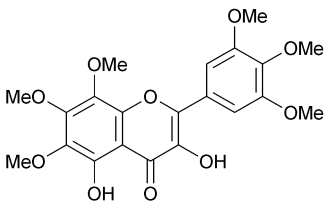


68 R_1 = Me, R_2 = R_3 = H, R_4 = OMe
69 R_1 = R_4 = H, R_2 = R_3 = OMe



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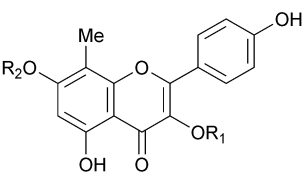
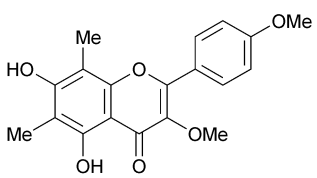


71 R_1 = H, R_2 = Me; Tupichinol E
72 R_1 = Me, R_2 = H; Tupichinol F



73

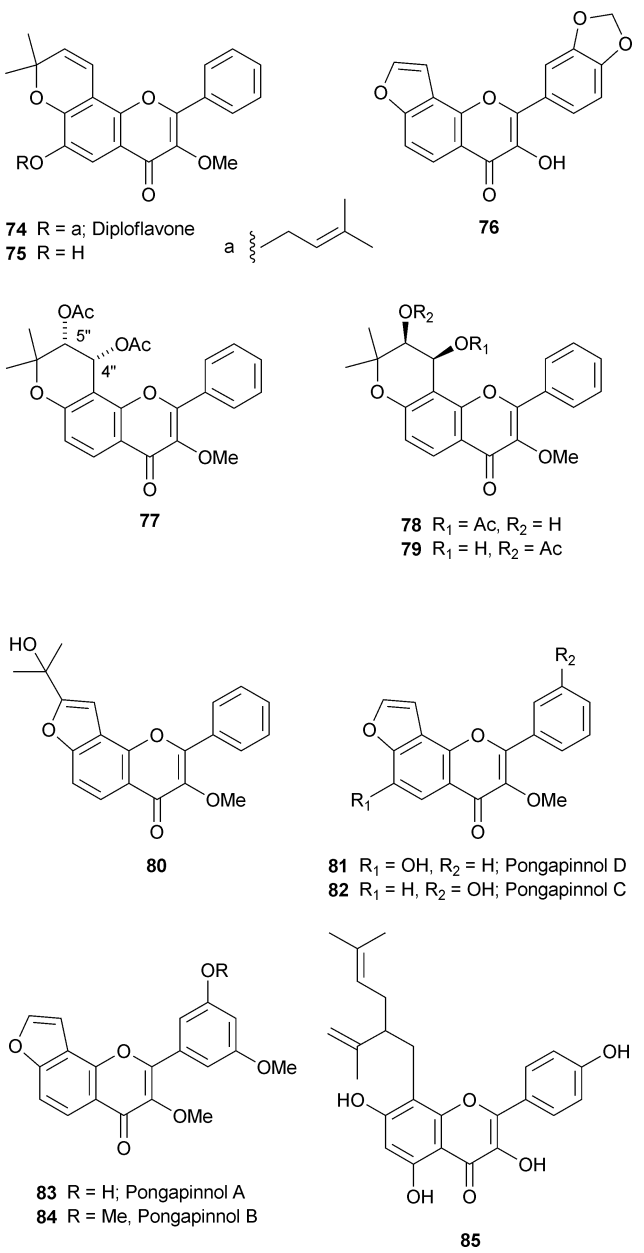
occidentalis (Myrtaceae) was confirmed by X-ray crystallography.[90] A related derivative, the 6,8-dimethyl ether of isokaempferide, was also obtained. Both compounds were shown to induce apoptosis in human myeloid leukemia cells by a mechanism involving caspase activation and cytochrome *c* release.[90]

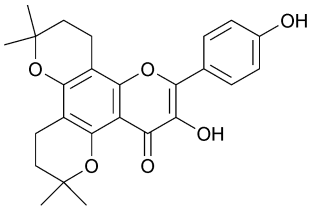
Some flavonols described as new during the 2004–2006 period deserve further comment because of conflict between the structures proposed for them and supporting data. Apicin, a compound isolated from MeOH extracts of the whole plant of *Artemisia apiacea* (Asteraceae), was published as a new derivative with the structure 3,5,3′-trihydroxy-6,7,5′-trimethoxyflavone.[91] Not only is a 3′,5′-di-*O*-substituted B-ring unlikely from a biogenetic point of view, but this pattern of oxygenation is unknown for *Artemisia* flavonoids, many examples of which have been characterised to date.[92] It is also clear that the assignment of a resonance at 154.1 ppm in the ^{13}C NMR spectrum (DMSO-d_6) of apicin to C-3 cannot be reconciled with its identification as a flavonol. The ^{1}H NMR spectrum, which comprises only singlets (1H at 7.44, 7.09, 6.95 and 6.55; 3H at 3.92, 3.80

and 3.71 ppm), corresponds to that of a known flavone, arcapillin.[93,94] Thus the structure proposed for apicin should be revised to 5,2′,4′-trihydroxy-6,7,5′-trimethoxyflavone. The latter has been found previously in *Artemisia annua*[93] and *Artemisia capillaris*,[94] and is one of a small number of *O*-methylated *Artemisia* flavonoids with 2′,4′,5′-oxygenation in the B-ring.[92] A previously unrecorded derivative, 3,7,8-trihydroxyflavone, has been reported as new from the roots of *Momordica dioica* (Cucurbitaceae).[95] However, this is not supported by the corresponding ^{1}H NMR data, which suggest that the structure is probably that of 3,5,7-trihydroxyflavone (galangin). A 4′-methyl ether of resokaempferol (3,7,4′-trihydroxyflavone) is one of several flavonoids reported as constituents of *Trifolium repens* (Leguminosae) when grown in the presence or absence of the arbuscular mycorrhizal fungus *Glomus intraradices*.[42] However, no ^{1}H NMR data were given for this compound, which has not been recorded as a natural product. The shoots of untreated and treated material were said to contain 5,6,7,8,4′-pentahydroxy-3-methoxyflavone and 5,6,7,8-tetrahydroxy-3-methoxyflavone, respectively, both cited as new. In a parallel study on *Brassica alba* (Brassicaceae), a species showing resistance to mycorrhizal colonisation, flavonoid constituents reported as new included 3,5,6,7,8-pentahydroxyflavone (from roots and root exudates) and 3,5,6,7,8-pentahydroxy-4′-methoxyflavone (from shoots).[96] However, anomalies in the NMR spectral assignments (which were not supported by 2D data) of all these (3,5,6,7,8)-penta-*O*- and (3,5,6,7,8,4′)-hexa-*O*-substituted flavones indicate that further investigation is necessary for full proof of structure. In particular, the upfield-shifted δ values assigned to C-10 in the range 95.3–97.1 ppm are unprecedented.[97,98] It is also curious that all the compounds were isolated as colourless solids when flavonols with free 6- and 8-OH groups are invariably yellow in colour. The relative instability of highly hydroxylated flavonoids with a free 8-OH group has been noted previously,[99] and should be considered in the context of the isolation procedure used for the above compounds (exhaustive extraction of plant material with EtOH for 4 days).

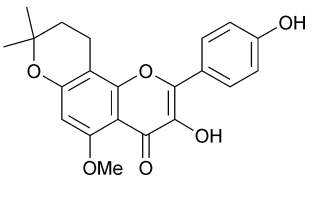
Fifteen new prenylated flavonols (**74–88**) have been described, all of which are from species in the Leguminosae. The structure of diploflavone (**74**) is interesting from a chemotaxonomic point of view, as almost all *O*-prenylated flavonols described to date occur in the Rutaceae.[24] First discovered in the stem bark of *Diplotropis ferruginea*,[100] this compound was later reported from the stems of *Fordia cauliflora* together with **75**.[101] MeOH extracts of the pods of *Millettia erythrocalyx* contain the furanoflavonol **76**,[57] which is the 3-demethyl ether of pongapin. The latter is a constituent of *Millettia pinnata*,[27] although most phytochemical studies on this species use the names *Derris indica*, *Pongamia glabra* or *Pongamia pinnata*, which are all synonyms. For example, two groups reported the dihydropyranoflavonol **77** from *Millettia pinnata*, but under two different names (*Derris indica* and *Pongamia pinnata*).[59,102] The *cis*-relationship between the acetoxy groups was deduced from $^3J_{4'',5''}$ values (4.8 or 5.0 Hz) in the corresponding ^{1}H NMR spectra, but the absolute configuration of **77** is unknown. The monoacetoxy derivatives **78** and **79** also occur in extracts of the stem bark of *Millettia pinnata*.[103] Although the relative configurations at C-4″ and C-5″ are *cis* ($^3J_{4'',5''} = 4.8$ Hz), positive optical rotations were recorded, in contrast to the negative values obtained for **77**.

Five furanoflavonols have been obtained from *Millettia pinnata*, one from stem bark extracts (**80**)[102] and the remainder, pongapinnols A–D (**81–84**), from fruits.[104] The chemical constituents of the roots of *Sophora flavescens* continue to be studied because of their extensive use in Chinese traditional medicine (Radix Sophorae Flavescentis, Kushen).[105] Jung *et al.* obtained 8-lavandulylkaempferol (**85**) from MeOH extracts of this material,[106] and demonstrated its ability to scavenge DPPH radicals and peroxynitrite (the same compound was later reported by Shen *et al.*).[107] Flavenochromane B (**86**)[108] and sophoranodichromane C (**88**)[109] are bis(dihydropyrano)-derivatives of kaempferol, whereas flavenochromane C (**87**)[108] is a dihydropyrano-derivative of kaempferol 5-methyl ether. The latter (**87**) showed cytotoxicity against a panel of 5 human tumour cell lines with IC_{50} values of 1.0–3.6 μM, whereas flavenochromane B (**86**) was less active (IC_{50} values of 3.2–6.9 μM).[108]

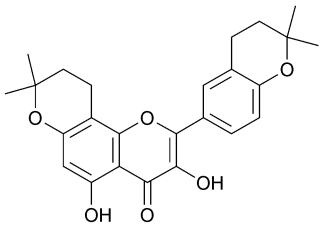




86 Flavenochromane B

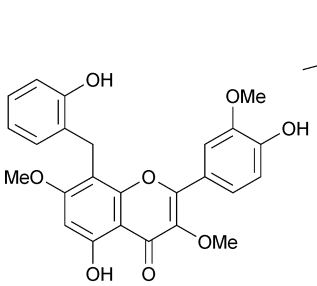


87 Flavenochromane C

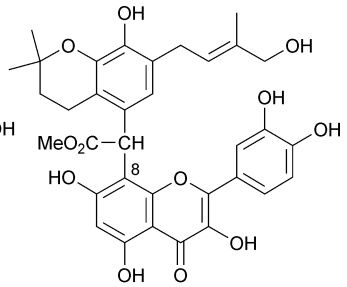


88 Sophoranodichromane C

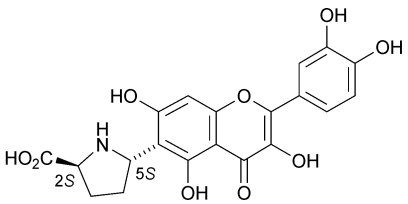
One further example (**89**) of a so-called 'cycloflavonol' has been reported from the legume *Millettia pinnata* (using the synomym *Derris indica*).[59] These compounds are the result of cyclisation between 3-OH of the C-ring and C-2′ of the B-ring such that an additional carbon is incorporated (possibly from 3-OMe). Literature records indicate that these peltogynoid structures have been found in all three sub-families of the Leguminosae, but not elsewhere.[24] An alkylated derivative (**90**) of 6-hydroxykaempferol 5,6-dimethyl ether isolated from MeOH extracts of the whole plant of *Duranta repens* (Verbenaceae) showed α-glucosidase inhibitory activity (see also **275, 276**).[110] Miliufavol (**91**) is an 8-*C*-(2-hydroxybenzyl) derivative of pachypodol (quercetin 3,7,3′-trimethylether) and a constituent of the aerial parts of *Miliusa balansae* (Annonaceae).[111] Similar compounds have been reported from the Asteraceae and Lamiaceae.[24] The structure of sabian (**92**) was determined after extensive NMR analysis (HMQC, HMBC, NOESY).[112] This 8-*C*-derivatised flavonol with a novel carbon framework was isolated from MeOH–H_2O (90 : 10) extracts of the aerial parts of *Sabia yunnanensis* (Sabiaceae). Perhaps the most unusual of the 'hybrid' flavonol structures to appear in the recent literature are two *C*-prolinylquercetin derivatives (**93,94**) isolated from the cocoon shells of the silkworm, *Bombyx mori*.[113] According to Hirayama *et al.*, these are insect metabolites, as neither compound was detected in the leaves of the host plant, the mulberry tree, *Morus alba* (Moraceae). Feeding experiments indicate that the quercetin is of dietary origin.[113] No previous examples of flavonoids conjugated to amino acids have been reported, and although a few alkaloidal flavonoids are known,[114] they are considered to be rare natural products.



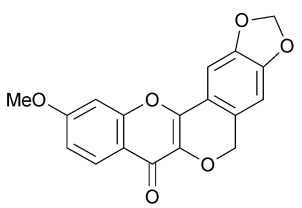
91 Miliufavol



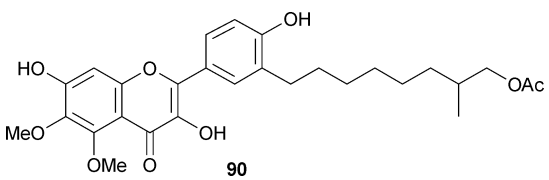
92 Sabian



93 (2*S*,5*S*); Prolinalin A
94 (2*S*,5*R*); Prolinalin B



89



90

4 Flavone and flavonol glycosides

This section covers both *O*- and *C*-glycosylflavonoids, although the *O*-glycosides of chalcones, dihydrochalcones, aurones, flavanones and dihydroflavonols appear under separate headings, as they are relatively few in number compared to those of flavones and flavonols. Two checklists of known flavone and flavonol *O*-glycosides published by Williams in 2006 comprise 680 and 1384 entries, respectively, and cover the literature to the end of 2003.[115] This continues to be a very active area of flavonoid research, with many additional examples reported in the subsequent three-year period. Most of the compounds that qualify for inclusion do so on the basis of previously unrecorded patterns of glycosylation in combination with known aglycones. Acylation of the sugars is frequently observed. The importance of full characterisation of the glycosidic component during the structure elucidation of these glycosides cannot be too highly emphasised. However, a minority of studies exist where this is inadequate or incomplete, with the result that some doubtful or incorrect structures have been introduced into the literature in the 2004–2006 period. These are discussed separately at the end of the appropriate sections. The numbered entries in Tables 1 and 2 represent flavone and flavonol *O*-glycosides whose structures are well supported by experimental data. A review on *C*-glycosylflavonoids published recently by Jay *et al.* includes literature references to 2004.[116] Among the topics covered are separation and identification, synthesis, localisation, biological activity and chemosystematics. New flavone *C*-glycosides published in the period 2004–2006 are discussed in Sections 4.3–4.5.

Table 1 New flavone glycosides reported in the period 2004–2006

No.	Compound [a]	Sub.[b]	Source [c]	Family	Tissue [d]	Ref.
	6-Hydroxy-5-methoxyflavone	5,6				
95	6-*O*-β-Glc*p*		*Casimiroa edulis*	Rutaceae	Leaf	26
	3′-Hydroxyfurano[2″,3″:7,8]flavone	7,3′				
96	3′-*O*-β-Glc*p* (pongamoside A)		*Millettia pinnata*	Leguminosae	Fruit	117
	5,7,4′-Trihydroxyflavone (apigenin)	5,7,4′				
97	7-*O*-(6-*O*-protocatechuoyl-β-Glc*p*) (chrozophorin)		*Chrozophora tinctoria*	Euphorbiaceae	Aerial parts	118
98	7-*O*-(4-*O*-acetyl-6-*O*-malonyl-β-Glc*p*)		*Chamomilla recutita*	Asteraceae	Floret	119
99	7-*O*-(4,6-di-*O*-acetyl-β-Glc*p*)		*Chamomilla recutita*	Asteraceae	Floret	119
100	4′-*O*-(2-*O*-*E*-*p*-coumaroyl-β-D-Glc*p*)		*Palhinhaea cernua* (club moss)	Lycopodiaceae	Whole plant	120
101	7-*O*-[3-*O*-acetyl-α-Rha*p*-(1→6)]-β-Glc*p*		*Scoparia dulcis*	Scrophulariaceae	Aerial parts	121
102	7-*O*-[2,3-di-*O*-acetyl-α-Rha*p*-(1→6)]-β-Glc*p*		*Scoparia dulcis*	Scrophulariaceae	Aerial parts	121
103	7-*O*-[6-*O*-*E*-*p*-coumaroyl-β-Glc*p*-(1→2)]-α-Rha*p*-(1→3)-α-Rha*p* (brauhenefloroside C)		*Stocksia brahuica*	Sapindaceae	Fruit	122
	5,7-Dihydroxy-4′-methoxyflavone (acacetin)					
104	7-*O*-(3-*O*-acetyl-β-Glc*p*)		*Chrysanthemum morifolium*	Asteraceae	Flower	123
			Chrysanthemum sinense		Flower	124
105	7-*O*-(6-*O*-*E*-*p*-coumaroyl-β-D-Glc*p*)		*Chrozophora senegalensis*	Euphorbiaceae		125
	4′-Hydroxy-5,7-dimethoxyflavone (apigenin 5,7-dimethyl ether)					
106	4′-*O*-β-Glc*p*-(1→5)-β-Api*f*		*Strobilanthes formosanus*	Acanthaceae	Stem & root	126
	3′-Hydroxy-6-methoxyfurano[2″,3″:7,8]flavone	6,7,3′				
107	3′-*O*-β-Glc*p* (pongamoside B)		*Millettia pinnata*	Leguminosae	Fruit	117
	5,6,7,4′-Tetrahydroxyflavone (scutellarein)	5,6,7,4′				
108	7-*O*-[2,3-di-*O*-acetyl-α-Rha*p*-(1→6)]-β-Glc*p*		*Scoparia dulcis*	Scrophulariaceae	Aerial parts	121
	5,7,4′-Trihydroxy-6-methoxyflavone (scutellarein 6-methyl ether)					
109	7-*O*-β-All*p*		*Eriocaulon ligulatum*	Eriocaulaceae	Cap. & scapes	127
	5,7,2′-Trihydroxy-8-methoxyflavone	5,7,8,2′				
110	7-*O*-β-D-Glc*p*		*Scutellaria amabilis*	Lamiaceae	Root	128
111	2′-*O*-β-D-Glc*p*		*Scutellaria amabilis*	Lamiaceae	Root	128
	5,7-Dihydroxy-8,2′-dimethoxyflavone					
112	7-*O*-β-D-Glc*p*		*Scutellaria amabilis*	Lamiaceae	Root	128
	5,7,2′,5′-Tetrahydroxyflavone	5,7,2′,5′				
113	7-*O*-β-D-GlcA*p*		*Scutellaria amabilis*	Lamiaceae	Root	128
	5,2′,6′-Trihydroxy-7-methoxyflavone	5,7,2′,6′				
114	5-*O*-(6-*O*-acetyl-β-Glc*p*)		*Andrographis alata*	Acanthaceae	Whole plant	129
115	2′-*O*-(2-*O*-acetyl-β-Glc*p*)		*Andrographis alata*	Acanthaceae	Whole plant	129
116	2′-*O*-(6-*O*-*E*-crotonyl-β-Glc*p*)		*Andrographis alata*	Acanthaceae	Whole plant	129
117	2′-*O*-(2,6-di-*O*-acetyl-β-Glc*p*)		*Andrographis alata*	Acanthaceae	Whole plant	129
118	2′-*O*-(3,6-di-*O*-acetyl-β-Glc*p*)		*Andrographis alata*	Acanthaceae	Whole plant	129
	5,7,3′,4′-Tetrahydroxyflavone (luteolin)	5,7,3′,4′				
119	7-*O*-β-Api*f*-(1→2)-β-Xyl*p*		*Schlerochiton vogelii*	Acanthaceae	Not stated	130
120	7-*O*-β-Glc*p*-(1→2)[α-Rha*p*-(1→6)]-β-Glc*p*		*Schlerochiton vogelii*	Acanthaceae	Not stated	130
121	7-*O*-(4-*O*-sulfato-β-Glc*p*)		*Washingtonia filifera*	Arecaceae	Aerial parts	131
122	7-*O*-[4-*O*-acetyl-α-Rha*p*-(1→2)]-β-GlcA*p*		*Phlomis lunariifolia*	Lamiaceae	Aerial parts	132
	5,7,4′-Trihydroxy-3′-methoxyflavone (chrysoeriol)					
123	7-*O*-(6-*O*-*E*-*p*-coumaroyl-β-Glc*p*)		*Marrubium velutinum*	Lamiaceae	Aerial parts	133
124	4′-*O*-(2,6-di-*O*-*E,E*-*p*-coumaroyl-β-Glc*p*)		*Lycopodium clavatum*	Lycopodiaceae	Aerial parts	134
125	4′-*O*-(2,6-di-*O*-*E,Z*-*p*-coumaroyl-β-Glc*p*)		*Lycopodium clavatum*	Lycopodiaceae	Aerial parts	134
126	7-*O*-[6-*O*-acetyl-β-All*p*-(1→2)]-β-Glc*p*		*Stachys bombycina*	Lamiaceae	Aerial parts	135
127	7-*O*-[6-*O*-acetyl-β-Glc*p*-(1→2)]-β-Glc*p*		*Carduus crispus*	Asteraceae	Whole plant	136
128	7-*O*-[2-*O*-*E*-caffeoyl-β-Glc*p*-(1→2)]-β-Glc*p* (ozturkoside B)		*Sideritis ozturkii*	Lamiaceae	Aerial parts	137
129	7-*O*-[2-*O*-*E*-caffeoyl-6-*O*-acetyl-β-Glc*p*-(1→2)]-β-Glc*p* (ozturkoside A)		*Sideritis ozturkii*	Lamiaceae	Aerial parts	137
130	7-*O*-[2-*O*-*E*-*p*-coumaroyl-6-*O*-acetyl-β-Glc*p*-(1→2)]-β-Glc*p* (ozturkoside C)		*Sideritis ozturkii*	Lamiaceae	Aerial parts	137

Table 1 *(Contd.)*

No.	Compound [a]	Sub.[b]	Source [c]	Family	Tissue [d]	Ref.
	5,7,3′-Trihydroxy-4′-methoxyflavone (diosmetin)					
131	7-*O*-(6-*O*-acetyl-β-Glc*p*)		*Chrysanthemum morifolium*	Asteraceae	Flower	123
	3′,4′-Dihydroxy-5,7-dimethoxyflavone (luteolin 5,7-dimethyl ether)					
132	4′-*O*-β-Api*f*		*Strobilanthes formosanus*	Acanthaceae	Stem & root	126
	5,7,4′-Trihydroxy-6,8-dimethoxyflavone (desmethoxysudachitin)	5,6,7,8,4′				
133	7-*O*-[6-*O*-(3-hydroxy-3-methylglutaryl)-β-Glc*p*] (3′-desmethoxysudachiin C)		*Citrus sudachi*	Rutaceae	Peel	138
	5,6,7,3′,4′-Pentahydroxyflavone (6-hydroxyluteolin)	5,6,7,3′,4′				
134	7-*O*-β-Glc*p*-(1→3)-β-Glc*p*		*Globularia alypum*	Globulariaceae	Aerial parts	139
135	7-*O*-(6-*O*-protocatechuoyl-β-Glc*p*)		*Veronica thymoides* subsp. *pseudocinerea*	Scrophulariaceae	Aerial parts	140
	5,7,3′,4′-Tetrahydroxy-6-methoxyflavone					
136	7-*O*-β-All*p*		*Eriocaulon ligulatum*	Eriocaulaceae	Cap. & scapes	127
	5,6,7,3′-Tetrahydroxy-4′-methoxyflavone					
137	7-*O*-α-Rha*p*-(1→2)[6-*O*-acetyl-β-Glc*p*-(1→3)]-β-Glc*p* (sarachoside)		*Veronica pectinata* var. *glandulosa*	Scrophulariaceae	Aerial parts	141
	5,7,4′-Trihydroxy-6,3′-dimethoxyflavone					
138	7-*O*-α-Ara*p*-(1→6)-β-Gal*p*		*Melilotus indicus*	Leguminosae	Seed	142
	5,4′-Dihydroxy-7,3′,5′-trimethoxyflavone (tricin 7-methyl ether)	5,7,3′,4′,5′				
139	5-*O*-β-Glc*p* (pleioside B)		*Pleioblastus amarus*	Poaceae	Leaf	143
140	4′-*O*-β-Glc*p* (pleioside A)		*Pleioblastus amarus*	Poaceae	Leaf	143
	5,7-Dihydroxy-3′,4′,5′-trimethoxyflavone (tricin 4′-methyl ether)					
141	7-*O*-β-Glc*p*		*Stachys officinalis*	Lamiaceae	Leaf	144
			Stachys scardica	Lamiaceae	Aerial parts	144
			Vittaria anguste-elongata	Vittariaceae	Whole plant	145
	Modified luteolin derivative					
142	4′-*O*-β-Glc*p* (pleioside C)		*Pleioblastus amarus*	Poaceae	Leaf	143

[a] Standard three letter codes for monosaccharides are used; *p* = pyranoside, *f* = furanoside. Absolute configurations are given only where determined experimentally. For di- and trisaccharides *O*-linked to flavones, the last listed sugar (primary) is that attached to the aglycone. Entries are presented in order of increasing glycosylation, with non-acylated before acylated derivatives. [b] The *O*-substitution pattern of the parent flavone is indicated. Compounds are listed in order of increasing *O*-substitution, with the A-ring substituents taking precedence over those of the B-ring (primed numbers). [c] Accepted names are quoted. Entries published under synonyms (shown in parentheses): *Millettia pinnata* (= *Pongamia pinnata*). [d] Cap. = capitulae.

Table 2 New flavonol glycosides reported in the period 2004–2006

	Compound [a]	Sub.[b]	Source [c]	Family	Tissue	Ref.
	3,5,7,4′-Tetrahydroxyflavone (kaempferol)	3,5,7,4′				
143	3-*O*-α-Ara*p*-(1→2)-α-Rha*p* (kapinnatoside)		*Kalanchoe pinnata*	Crassulaceae	Leaf	159
144	3-*O*-α-L-Ara*p*-7-*O*-β-D-Glc*p*		*Datura suaveolens*	Solanaceae	Leaf	160
145	3-*O*-β-Glc*p*-7-*O*-α-Ara*f*		*Pyrrosia petiolosa*	Polypodiaceae	Whole plant	161
146	7-*O*-β-Glc*p*-(1→4)-β-Glc*p*		*Opuntia dillenii*	Cactaceae	Stem	162
147	3-*O*-α-Rha*p*-(1→2)[β-Glc*p*-(1→3)]-β-GlcA*p*		*Diospyros rhombifolia*	Ebenaceae	Leaf	163
148	3-*O*-α-Ara*p*-(1→6)-β-Glc*p*-7-*O*-β-Glc*p*		*Corydalis bungeana*	Papaveraceae	Whole plant	164
149	3-*O*-α-Rha*p*-(1→6)-β-Glc*p*-(1→3)[α-Rha*p*-(1→2)]-β-Glc*p*		*Diospyros rhombifolia*	Ebenaceae	Leaf	163
150	3-*O*-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→2)[α-L-Rha*p*-(1→6)]-β-D-Gal*p* (mildbraedin)		*Mildbraediodendron excelsum*	Leguminosae	Leaf	165
151	3-*O*-(3-*O*-acetyl-α-L-Ara*f*)		*Rodgersia podophylla*	Saxifragaceae	Aerial parts	166
152	3-*O*-(5-*O*-acetyl-α-L-Ara*f*)		*Rodgersia podophylla*	Saxifragaceae	Aerial parts	166
153	3-*O*-(5-*O*-galloyl-α-Ara*f*)		*Triplaris cumingiana*	Polygonaceae	Leaf	167
154	3-*O*-(3-*O*-*E*-feruloyl-β-Glc*p*)		*Picea abies*	Pinaceae	Needle	168
155	3-*O*-[4-*O*-(3-hydroxy-3-methylglutaroyl)-α-Rha*p*]		*Vaccinium vitis-idaea*	Ericaceae	Berry	169
156	3-*O*-(2,3-di-*O*-acetyl-α-Rha*p*)		*Zingiber aromaticum*	Zingiberaceae	Rhizome	170
157	3-*O*-(2-*O*-*Z*-*p*-coumaroyl-4-*O*-*E*-*p*-coumaroyl-α-Rha*p*)		*Cinnamomum kotoense*	Lauraceae	Leaf	171
158	3-*O*-(2,3-di-*O*-galloyl-β-Glc*p*)		*Geranium pyrenaicum*	Geraniaceae	Aerial parts	172
159	3-*O*-(2,3,4-tri-*O*-acetyl-α-Rha*p*)		*Zingiber aromaticum*	Zingiberaceae	Rhizome	170
160	7-*O*-(2-*O*-*E*-*p*-coumaroyl-α-Rha*p*)		*Tetrapanax papyriferus*	Araliaceae	Flower	173
161	7-*O*-(2,3-di-*O*-*E*-*p*-coumaroyl-α-Rha*p*)		*Tetrapanax papyriferus*	Araliaceae	Flower	173
162	3-*O*-[6-*O*-acetyl-β-Glc*p*-(1→2)]-β-Glc*p*		*Vernonia travancorica*	Asteraceae	Inflorescence	174
163	3-*O*-[6-*O*-*E*-caffeoyl-β-Glc*p*-(1→2)]-β-Glc*p* (camsibriside A)		*Camptosorus sibiricus*	Aspleniaceae	Aerial parts	175
164	3-*O*-α-L-Rha*p*-(1→6)-[4-*O*-*E*-*p*-coumaroyl-α-L-Rha*p*-(1→2)]-(4-*O*-*E*-*p*-coumaroyl-β-D-Gal*p*)		*Adina racemosa*	Rubiaceae	Leaf, flower, twig	176
165	3-*O*-α-Rha*p*-(1→6)-[6-*O*-*E*-feruloyl-β-Glc*p*-(1→3)]-β-Glc*p*		*Derris trifoliata*	Leguminosae	Aerial parts	177
166	3-*O*-[6-*O*-*E*-caffeoyl-β-Glc*p*-(1→2)]-β-Glc*p*-7-*O*-β-Glc*p* (camsibriside B)		*Camptosorus sibiricus*	Aspleniaceae	Aerial parts	175
167	3-*O*-[6-*O*-*E*-*p*-coumaroyl-β-Glc*p*-(1→2)]-β-Glc*p*-7-*O*-β-Glc*p* (camsibriside C)		*Camptosorus sibiricus*	Aspleniaceae	Aerial parts	175
168	3-*O*-β-Glc*p*-(1→2)-(6-*O*-malonyl-β-Glc*p*)-7-*O*-β-Glc*p*		*Papaver nudicaule*	Papaveraceae	Petal	178[d]
169	3-*O*-β-Glc*p*-(1→2)-(6-*O*-malonyl-β-Glc*p*)-7-*O*-(6-*O*-malonyl-β-Glc*p*)		*Papaver nudicaule*	Papaveraceae	Petal	178[d]
170	3-*O*-[6-*O*-*E*-*p*-coumaroyl-β-Glc*p*-(1→2)]-β-Xyl*p*-7-*O*-α-Rha*p* (myriophylloside D)		*Oxytropis myriophylla*	Leguminosae	Not stated	179
171	3-*O*-β-Glc*p*-7-*O*-[2-*O*-*E*-sinapoyl-β-Glc*p*-(1→6)]-β-Glc*p*		*Descurainia sophia*	Brassicaceae	Seed	180
172	3-*O*-α-Rha*p*-(1→6)[α-Rha*p*-(1→2)]-(4-*O*-*E*-*p*-coumaroyl-β-Glc*p*)-7-*O*-α-Rha*p*		*Exostema mexicanum*	Rubiaceae	Leaf	181
173	3-*O*-α-Rha*p*-(1→6)[2,4-di-*O*-acetyl-α-Rha*p*-(1→2)]-(4-*O*-*E*-*p*-coumaroyl-β-Glc*p*)-7-*O*-α-Rha*p*		*Exostema mexicanum*	Rubiaceae	Leaf	181
174	3-*O*-β-Glc*p*-(1→3)-(4-*O*-*E*-*p*-coumaroyl-α-Rha*p*)-(1→6)-β-Glc*p*-7-*O*-β-Glc*p*-(1→3)-α-Rha*p*		*Aconitum naviculare*	Ranunculaceae	Aerial parts	182
	5,7,4′-Trihydroxy-3-methoxyflavone (isokaempferide)					
175	7-*O*-(6-*O*-methyl-β-GlcA*p*)		*Cirsium rivulare*	Asteraceae	Flower	183
	3,5,4′-Trihydroxy-7-methoxyflavone (rhamnocitrin)					
176	3-*O*-α-Rha*p*-(1→3)-α-Rha*p*-(1→6)-β-Glc*p*		*Ribes fasciculatum* var. *chinense*	Saxifragaceae	Stem, twig	184
177	3-*O*-(6-*O*-*E*-feruloyl-β-Gal*p*)-4′-*O*-β-Glc*p* (kansuensisoside A)		*Oxytropis kansuensis*	Leguminosae	Whole plant	185
	3,5-Dihydroxy-7,4′-dimethoxyflavone (kaempferol 7,4′-dimethyl ether)					
178	3-*O*-β-D-Gal*p* (polygalin A)		*Polygala japonica*	Polygalaceae	Aerial parts	186
179	3-*O*-β-D-Api*f*-(1→2)-β-D-Gal*p* (polygalin B)		*Polygala japonica*	Polygalaceae	Aerial parts	186
	7-Hydroxy-3-methoxy-3′,4′-methylenedioxyflavone	3,7,3′,4′				
180	7-*O*-β-Glc*p* (pongamoside D)		*Millettia pinnata*	Leguminosae	Fruit	117
	3,5,6,7,4′-Pentahydroxyflavone (6-hydroxykaempferol)	3,5,6,7,4′				
181	7-*O*-(6-*O*-acetyl-β-Glc*p*)		*Rhaponticum carthamoides*	Asteraceae	Aerial parts	187
	5,4′-Dimethoxy-3-hydroxy-6,7-methylenedioxyflavone					
182	3-*O*-β-Api*f*-(1→6)-β-Glc*p* (periginatorine I)		*Polygonum peregrinatoris*	Polygalaceae	Root	188
	3,5,7,4′-Tetrahydroxy-8-methoxyflavone (sexangularetin)	3,5,7,8,4′				
183	3-*O*-(6-*O*-malonyl-β-Glc*p*)		'Crataegi folium cum flore' (*Crataegus*)[e]	Rosaceae	Leaf & flower	189
	5,7,4′-Trihydroxy-3,8-dimethoxyflavone (herbacetin 3,8-dimethyl ether)					
184	5-*O*-β-D-Glc*p*		*Amberboa ramosa*	Asteraceae	Whole plant	190

Table 2 *(Contd.)*

	Compound [a]	Sub.[b]	Source [c]	Family	Tissue	Ref.
	3,5,7,3′,4′-Pentahydroxyflavone (quercetin)	3,5,7,3′,4′				
185	4′-*O*-α-Ara*f*		*Triplaris cumingiana*	Polygonaceae	Leaf	167
186	3-*O*-α-Ara*p*-(1→2)-α-Rha*p*		*Alphitonia philippinensis*	Rhamnaceae	Stem	191
			Kalanchoe blossfeldiana	Crassulaceae	Flower	192
187	3-*O*-β-Glc*p*-(1→2)-α-Ara*p*		*Ilex cornuta*	Aquifoliaceae	Leaf	193[f]
188	3-*O*-β-Glc*p*-(1→2)-β-Ara*p*		*Carrichtera annua*	Brassicaceae	Aerial parts	194
189	7-*O*-α-Ara*p*-(1→6)-β-Glc*p* (gigantoside)		*Cephalaria gigantea*	Dipsacaceae	Flower	195
190	7-*O*-β-Glc*p*-(1→3)-α-Rha*p*		*Aconitum naviculare*	Ranunculaceae	Aerial parts	182
191	3-*O*-α-Rha*p*-(1→2)-α-Ara*p*-(1→2)-α-Rha*p*		*Alphitonia philippinensis*	Rhamnaceae	Stem	191
192	3-*O*-β-Xyl*p*-(1→3)-α-Rha*p*-(1→6)-β-Gal*p* (flagaloside C)		*Astragalus galegiformis*	Leguminosae	Leaf	196
193	3-*O*-β-D-Xyl*p*-(1→3)-α-L-Rha*p*-(1→6)-β-D-Glc*p* (camellianoside)		*Camellia japonica*	Theaceae	Leaf	197
194	3-*O*-α-Ara*p*-(1→6)-β-Glc*p*-7-*O*-β-Glc*p*		*Corydalis bungeana*	Papaveraceae	Whole plant	164
195	3-*O*-α-Rha*p*-(1→6)-β-Gal*p*-7-*O*-β-Api*f*		*Silphium albiflorum*	Asteraceae	Leaf	198
196	3,4′-di-*O*-β-D-Glc*p*-7-*O*-α-L-Rha*p* (moricandin)		*Moricandia arvensis*	Brassicaceae	Flower	199
197	3-*O*-β-Xyl*p*-(1→2)[α-Rha*p*-(1→6)]-β-Glc*p*-3′-*O*-β-Glc*p* (aescuflavoside)		*Aesculus chinensis*	Hippocastanaceae	Seed	200
198	3-*O*-(2-*O*-acetyl-α-Ara*f*)		*Berchemia floribunda*	Rhamnaceae	Bark	201
199	3-*O*-(5-*O*-acetyl-α-L-Ara*f*)		*Rodgersia podophylla*	Saxifragaceae	Aerial parts	202
200	3-*O*-(6-*O*-dihydrooleuropeoyl-β-D-Gal*p*) (cypellogin C)		*Eucalyptus cypellocarpa*	Myrtaceae	Leaf	203
201	3-*O*-(6-*O*-oleuropeoyl-β-D-Gal*p*) (cypellogin B)		*Eucalyptus cypellocarpa*	Myrtaceae	Leaf	203
202	3-*O*-(6-*O*-oleuropeoyl-β-D-Glc*p*) (cypellogin A)		*Eucalyptus cypellocarpa*	Myrtaceae	Leaf	203
203	3-*O*-(6-*O*-*p*-hydroxybenzoyl-β-Glc*p*)		*Schinus molle*	Anacardiaceae	Leaf	204
204	3-*O*-(2-*O*-*Z*-caffeoyl-α-Rha*p*)		*Calliandra haematocephala*	Leguminosae	Leaf & stem	205
205	3-*O*-(3-*O*-galloyl-α-Rha*p*)		*Calliandra haematocephala*	Leguminosae	Leaf & stem	205
206	3-*O*-[4-*O*-(3-hydroxy-3-methylglutaroyl)-α-Rha*p*]		*Vaccinium vitis-idaea*	Ericaceae	Berry	169
207	7-*O*-(6-*O*-*E*-feruloyl-β-Glc*p*)		*Anoectochilus roxburghii*	Orchidaceae	Whole plant	206
208	3-*O*-(3,5-di-*O*-acetyl-α-L-Ara*f*)		*Rodgersia podophylla*	Saxifragaceae	Aerial parts	166
209	3-*O*-(2,3-di-*O*-galloyl-β-D-Gal*p*)		*Euphorbia lunulata*	Euphorbiaceae	Whole plant	207
210	3-*O*-(4,6-di-*O*-galloyl-β-Glc*p*)		*Triplaris cumingiana*	Polygonaceae	Leaf	167
211	3-*O*-(2,3-di-*O*-galloyl-α-Rha*p*)		*Calliandra haematocephala*	Leguminosae	Leaf & stem	205
212	3-*O*-[2-*O*-*E*-caffeoyl-α-Ara*p*-(1→2)]-β-Glc*p*		*Helleborus foetidus*	Ranunculaceae	Leaf	208
213	3-*O*-[2-*O*-acetyl-α-Ara*p*-(1→6)]-β-Glc*p*[g]		*Meconopsis quintuplinervia*	Papaveraceae	Aerial parts	209
214	3-*O*-[2-*O*-acetyl-β-Glc*p*-(1→6)]-β-Glc*p*		*Meconopsis quintuplinervia*	Papaveraceae	Aerial parts	209
215	3-*O*-[2,6-di-*O*-acetyl-β-Glc*p*-(1→6)]-β-Glc*p*		*Meconopsis quintuplinervia*	Papaveraceae	Aerial parts	209
216	3-*O*-[6-*O*-*E*-sinapoyl-β-Glc*p*-(1→2)]-β-Ara*p*[h]		*Carrichtera annua*	Brassicaceae	Seed	210
217	3-*O*-α-Rha*p*-(1→2)[6-*O*-galloyl-β-Gal*p*]		*Schinus molle*	Anacardiaceae	Leaf	204
218	3-*O*-α-L-Rha*p*-(1→6)-(3-*O*-*E*-*p*-coumaroyl-β-D-Gal*p*)		*Adina racemosa*	Rubiaceae	Leaf, flower, twig	176
219	3-*O*-[3-*O*-syringoyl-α-Rha*p*-(1→6)]-β-Gal*p* (heteronoside)		*Leonurus heterophyllus*	Lamiaceae	Whole plant	211
220	3-*O*-(6-*O*-acetyl-β-Glc*p*)-7-*O*-α-Ara*p*		*Knoxia corymbosa*	Rubiaceae	Whole plant	212
221	3-*O*-(6-*O*-*E*-caffeoyl-β-D-Glc*p*)-3′-*O*-β-D-Glc*p*		*Chrozophora senegalensis*	Euphorbiaceae	Leaf	125
222	3-*O*-α-Rha*p*-(1→6)-[4-*O*-*E*-caffeoyl-α-Rha*p*-(1→2)]-β-Gal*p*		*Bougainvillea glabra*	Nyctaginaceae	Aerial parts	213[i]
223	3-*O*-α-L-Rha*p*-(1→6)-[4-*O*-*E*-caffeoyl-α-L-Rha*p*-(1→2)]-(3-*O*-*E*-*p*-coumaroyl-β-D-Gal*p*)		*Adina racemosa*	Rubiaceae	Leaf, flower, twig	176
224	3-*O*-α-L-Rha*p*-(1→6)-[4-*O*-*E*-*p*-coumaroyl-α-L-Rha*p*-(1→2)]-(3-*O*-*E*-*p*-coumaroyl-β-D-Gal*p*)		*Adina racemosa*	Rubiaceae	Leaf, flower, twig	176
225	3-*O*-α-L-Rha*p*-(1→6)-[4-*O*-*E*-*p*-coumaroyl-α-L-Rha*p*-(1→2)]-(4-*O*-*E*-*p*-coumaroyl-β-D-Gal*p*)		*Adina racemosa*	Rubiaceae	Leaf, flower, twig	176
226	3-*O*-[2-*O*-*E*-*p*-coumaroyl-β-Glc*p*-(1→2)]-β-Glc*p*-7-*O*-β-Glc*p*		*Ranunculus lanuginosus*	Ranunculaceae	Leaf	214[j]
227	3-*O*-[6-*O*-*E*-*p*-coumaroyl-β-Glc*p*-(1→2)]-β-Glc*p*-7-*O*-α-Rha*p* (myriophylloside F)		*Oxytropis myriophylla*	Leguminosae	Not stated	179
228	3-*O*-[6-*O*-*E*-caffeoyl-β-Glc*p*-(1→2)]-β-Xyl*p*-7-*O*-α-Rha*p* (myriophylloside C)		*Oxytropis myriophylla*	Leguminosae	Not stated	179
229	3-*O*-[6-*O*-*E*-*p*-coumaroyl-β-Glc*p*-(1→2)]-β-Xyl*p*-7-*O*-α-Rha*p* (myriophylloside B)		*Oxytropis myriophylla*	Leguminosae	Not stated	179
230	3-*O*-[6-*O*-*E*-feruloyl-β-Glc*p*-(1→2)]-β-Xyl*p*-7-*O*-α-Rha*p* (myriophylloside E)		*Oxytropis myriophylla*	Leguminosae	Not stated	179
231	3-*O*-β-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→6)[α-L-Ara*p*-(1→3)]-(2-*O*-*E*-*p*-coumaroyl-β-D-Glc*p*)		*Camellia sinensis*	Theaceae	Leaf (oolong tea)	215
232	3-*O*-β-Glc*p*-(1→3)-(4-*O*-*E*-*p*-coumaroyl-α-Rha*p*)-(1→6)-β-Glc*p*-7-*O*-β-Glc*p*-(1→3)-α-Rha*p*		*Aconitum naviculare*	Ranunculaceae	Aerial parts	182
	5,7,3′,4′-Tetrahydroxy-3-methoxyflavone (quercetin 3-methyl ether)					
233	7-*O*-α-L-Rha*p*-(1→6)-(2-*O*-*E*-coumaroyl-β-D-Glc*p*)		*Chrozophora senegalensis*	Euphorbiaceae	Leaf	125

Table 2 *(Contd.)*

	Compound [a]	Sub.[b]	Source [c]	Family	Tissue	Ref.
	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone (isorhamnetin)					
234	3-*O*-β-Xyl*p*-(1→2)-β-Xyl*p* (flagaloside D)		*Astragalus galegiformis*	Leguminosae	Leaf	196
235	7-*O*-β-Glc*p*-(1→6)-β-Glc*p*		*Descurainia sophia*	Brassicaceae	Seed	180
236	3-*O*-α-Rha*p*-(1→6)-β-Gal*p*-7-*O*-β-Api*f*		*Silphium albiflorum*	Asteraceae	Leaf	198
237	3-*O*-(6-*O*-*Z*-*p*-coumaroyl-β-Glc*p*)		*Alphitonia philippinensis*	Rhamnaceae	Stem	191
238	3-*O*-(6-*O*-(3-hydroxy-3-methylglutaroyl)-β-Glc*p*)		*Sphaerophysa salsula*	Leguminosae	Root & stem	216
239	3-*O*-[2-*O*-acetyl-β-Glc*p*-(1→6)]-β-Glc*p*		*Meconopsis quintuplinervia*	Papaveraceae	Aerial parts	209
240	3-*O*-[5-*O*-*E*-feruloyl-β-Api*f*-(1→2)]-β-Glc*p* (sphaerophyside SA)		*Sphaerophysa salsula*	Leguminosae	Seed	217
241	3-*O*-α-Rha*p*-(1→2)-(6-*O*-*E*-feruloyl-β-Glc*p*)		*Opuntia ficus-indica* var. *saboten*	Cactaceae	Leaf	218
	3,5,7,3′-Tetrahydroxy-4′-methoxyflavone (tamarixetin)					
242	3-*O*-β-Glc*p*-7-*O*-α-Rha*p*		*Tephrosia purpurea*	Leguminosae	Aerial parts	219
243	3-*O*-β-Xyl*p*-(1→2)-β-Glc*p*-3′-*O*-β-Glc*p* (aescuflavoside A)		*Aesculus chinensis*	Hippocastanaceae	Seed	200
	3,5,3′-Tetrahydroxy-7,4′-dimethoxyflavone (ombuin)					
244	3-*O*-β-D-Api*f*-(1→2)-β-D-Gal*p* (polygalin C)		*Polygala japonica*	Polygalaceae	Aerial parts	186
	3,7,3′,4′-Tetrahydroxy-5-galloyloxyflavone (quercetin 5-gallate)					
245	3-*O*-α-L-Ara*f*		*Calycolpus warszewiczianus*	Myrtaceae	Leaf	220
	3,5-Dihydroxy-6,7,2′,5′-tetramethoxyflavone	3,5,6,7,2′,5′				
246	3-*O*-β-D-Glc*p* (hetranthin B)		*Indigofera heterantha*	Leguminosae	Stem	221
	3,5,6,7,3′,4′-Hexahydroxyflavone (quercetagetin)	3,5,6,7,3′,4′				
247	7-*O*-(6-*O*-*E*-caffeoyl-β-Glc*p*)		*Tagetes maxima*	Asteraceae	Aerial parts	222
248	7-*O*-(6-*O*-*E*-*p*-coumaroyl-β-Glc*p*)		*Tagetes maxima*	Asteraceae	Aerial parts	222
249	7-*O*-(6-*O*-galloyl-β-Glc*p*)		*Tagetes maxima*	Asteraceae	Aerial parts	222
	3,5,7,3′,4′-Pentahydroxy-6-methoxyflavone (patuletin)					
250	7-*O*-(6-*O*-*E*-caffeoyl-β-Glc*p*) (tinctoside)		*Anthemis tinctoria*	Asteraceae	Flower	223
251	3-*O*-[5-*O*-*E*-feruloyl-β-Api*f*-(1→2)]-β-Glc*p*		*Atriplex littoralis*	Chenopodiaceae	Aerial parts	224
	3,5,7,8,3′,4′-Hexahydroxyflavone (gossypetin)	3,5,7,8,3′,4′				
252	3′-*O*-β-Glc*p*		*Abelmoschus manihot*	Malvaceae	Flower	225
	5,7,8,3′,4′-Pentahydroxy-3-methoxyflavone (gossypetin 3-methyl ether)					
253	8-*O*-β-Glc*p*		*Fagopyrum dibotrys*	Polygonaceae	Rhizome	226
	3,5,7,3′,4′,5′-Hexahydroxyflavone (myricetin)	3,5,7,3′,4′,5′				
254	3-*O*-β-Glc*p*-(1→2)-β-Glc*p*-4′-*O*-β-Glc*p*		*Ajuga remota*	Lamiaceae	Aerial parts	227[k]
255	3-*O*-α-Rha*p*-(1→2)-α-Rha*p*-3′-*O*-α-Rha*p*		*Ajuga remota*	Lamiaceae	Aerial parts	227
256	3-*O*-α-Rha*p*-(1→6)-β-Glc*p*-3′-*O*-α-Rha*p*		*Ajuga remota*	Lamiaceae	Aerial parts	227
257	3-*O*-(3-*O*-acetyl-α-L-Ara*f*)		*Calycolpus warszewiczianus*	Myrtaceae	Leaf	220
258	3-*O*-(5-*O*-acetyl-α-L-Ara*f*)		*Polygonum bellardii*	Polygonaceae	Aerial parts	228
259	3-*O*-(3-*O*-acetyl-α-L-Ara*p*)		*Pteleopsis suberosa*	Combretaceae	Leaf	229
260	3-*O*-(4-*O*-acetyl-α-L-Ara*p*)		*Pteleopsis suberosa*	Combretaceae	Leaf	229
261	3-*O*-(2-*O*-galloyl-α-L-Ara*p*)		*Limonium gmelinii*	Plumbaginaceae	Whole plant	230
262	3-*O*-(3,5-di-*O*-acetyl-α-L-Ara*f*)		*Calycolpus warszewiczianus*	Myrtaceae	Leaf	220
	3,5,7,4′,5′-Pentahydroxy-3′-methoxyflavone (larycitrin)					
263	3-*O*-α-Rha*p*-(1→2)-α-Rha*p*-5′-*O*-β-Gal*p*		*Ajuga remota*	Lamiaceae	Aerial parts	227
264	3-*O*-α-Rha*p*-(1→2)[α-Rha*p*-(1→4)]-β-Glc*p*-5′-*O*-β-Glc*p*		*Ajuga remota*	Lamiaceae	Aerial parts	227
	3,5,3′,5′-Tetrahydroxy-7,4′-dimethoxyflavone (myricetin 7,4′-dimethyl ether)					
265	3-*O*-α-Rha*p*		*Sageretia theezans*	Rhamnaceae	Leaf	231
	3,5,7,4′-Tetrahydroxy-3′,5′-dimethoxyflavone (syringetin)					
266	3-*O*-α-Rha*p*-7-*O*-β-Glc*p*		*Embelia keniensis*	Myrsinaceae	Leaf	232[l]
267	3-*O*-α-Rha*p*-7,4′-di-*O*-β-Glc*p*		*Embelia keniensis*	Myrsinaceae	Leaf	232
	PRENYLATED FLAVONOL GLYCOSIDES					
	6-Hydroxy-3-methoxyfurano[2″,3″:7,8]flavone	3,6,7				
268	6-*O*-β-Glc*p* (pongamoside C)		*Millettia pinnata*	Leguminosae	Fruit	117

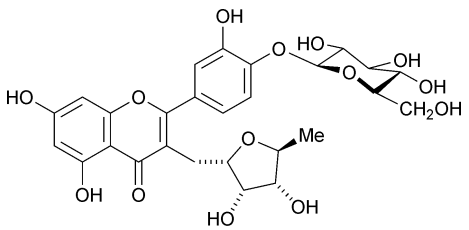
Table 2 *(Contd.)*

	Compound [a]	Sub.[b]	Source [c]	Family	Tissue	Ref.
	8-Prenylkaempferol (noranhydroicaritin)	3,5,7,4′				
269	7-*O*-(6-*O*-acetyl-β-Glc*p*)[m]		*Phellodendron japonicum*	Rutaceae	Leaf	233
	8-Prenylkaempferol 4′-methyl ether (anhydroicaritin)					
270	3-*O*-[6-deoxy-β-*ribo*-hexopyranos-3-ulosyl-(1→2)]-α-Rha*p*		*Epimedium koreanum*	Berberidaceae	Aerial parts	234
271	3-*O*-α-Rha*p*-7-*O*-(2-*O*-acetyl-β-Glc*p*) (acetylicariin)		*Epimedium koreanum*	Berberidaceae	Aerial parts	235
	8-(2,3-Epoxy-3-methylbutyl)-kaempferol 4′-methyl ether					
272	3-*O*-α-Rha*p* (neoicariin)		*Epimedium sagittatum*	Berberidaceae	Aerial parts	236
	3,5-Dihydroxy-4′-methoxy-5″-(2-methoxyisopropyl)furano[2″,3″:7,8]flavone					
273	3-*O*-α-Rha*p*-(1→2)-α-Rha*p*		*Ziziphus jujuba* var. *spinosa*	Rhamnaceae	Seed	237
	5,7,3′-Trihydroxy-3-methoxy-6,8-dimethyl-6″,6″-dimethylpyrano[2″,3″:4′,5′]flavone	3,5,7,3′,4′				
274	7-*O*-β-Api*f*-(1→6)-β-Glc*p*		*Pteris multifida*	Pteridaceae	Root	238
	ALKYLATED FLAVONOL GLYCOSIDES					
	3′-(4-Acetoxy-3-methylbutyl)-6-hydroxykaempferol 5,6-dimethylether	3,5,6,7,4′				
275	7-*O*-α-D-Glc*p*		*Duranta repens*	Verbenaceae	Whole plant	110
	3′-(4-Acetoxy-3-methylbutyl)-6-hydroxykaempferol 6,4′-dimethylether					
276	7-*O*-α-D-Glc*p*		*Duranta repens*	Verbenaceae	Whole plant	110

[a] Standard three letter codes for monosaccharides are used; *p* = pyranoside, *f* = furanoside. Absolute configurations are given only where determined experimentally. For di- and higher saccharides *O*-linked to flavonols, the last listed sugar (primary) is that attached to the aglycone (see Fig. 1 for a guide to the notation). Entries are presented in order of increasing glycosylation, with non-acylated before acylated derivatives. New saccharides not listed by Williams[115] for flavonol glycosides appear in **147**, **149**, **150**, **165**, **186**, **187**, **191**, **193**, **212**, **231** and **270**. New acyl groups not listed by Williams[115] for flavonol glycosides occur in **200–202** (dihydrooleuropeic and oleuropeic acids). [b] The *O*-substitution pattern of the parent flavonol is indicated. Compounds are listed in order of increasing *O*-substitution, with the A-ring substituents taking precedence over those of the B-ring (primed numbers). [c] Accepted names are quoted. Entries published under synonyms (shown in parentheses): *Millettia pinnata* (= *Pongamia pinnata*). [d] Similarly glycosylated co-pigments termed nudicaulins were also characterised, which may have their origin in Diels–Alder or ionic (4 + 2)-cycloadditions between chalcone precursors and indole. [e] Dried hawthorn leaves and flowers purchased as a herbal drug in Norway. [f] NMR spectral assignments for the anomeric centres appear to be interchanged. [g] $J_{3,4}$ for Ara*p* (9.3 Hz) should be revised to 4.7 Hz (J.-G. Shi, personal communication). [h] Further derivatives detected by LC-MS await full structural characterisation. [i] Incorrectly named in abstract. The caffeoyl group resides on the 2- not the 6-linked Rha*p*. [j] Quercetin 3-*O*-*p*-coumaroylsophoroside-7-*O*-glucoside was previously reported from *Ranunculus*, but the site of acylation was not determined.[27] [k] A report of kaempferol 3-*O*-α-Rha*p*-(1→6)-β-Glc*p*-7-*O*-α-Rha*p*-(1→6)-β-Glc*p* could not be substantiated from the NMR data. [l] Reports of two further flavonol glycosides described as new could not be substantiated from NMR data. [m] Incorrect trivial name cited; should be 6″-*O*-acetylepimedoside C instead of 6″-*O*-acetylamurensin.

4.1 Flavone *O*-glycosides

The sources and structures of more than 45 new flavone *O*-glycosides reported from 2004–2006 are listed in Table 1.[26,117–145] Many are based on commonly occurring flavones such as apigenin (5,7,4′-trihydroxyflavone) and luteolin (5,7,3′,4′-tetrahydroxyflavone). In contrast, the aglycone 6-hydroxy-5-methoxyflavone (**1**) was unrecorded until described together with its 6-*O*-β-glucopyranoside (**95**) from the leaves of *Casimiroa edulis* (Rutaceae).[26] Neither 3′-hydroxy-6-methoxyfurano[2″,3″:7,8]flavone nor luteolin 5,7-dimethyl ether, the aglycones of **107** and **132**, respectively, are known in the literature. The structure of pleioside C (**142**) is particularly unusual. Based on luteolin 4′-*O*-β-glucopyranoside, it also incorporates 2,5-anhydro-1,6-dideoxyaltritol *C*-linked through a methylene bridge at C-3. Co-occurring compounds include pleiosides A (**140**) and B (**139**), tricin 7-*O*-β-glucopyranoside and tricin (5,7,4′-trihydroxy-3′,5′-dimethoxyflavone).[143]



142 Pleioside C

Three saccharides appear in Table 1 that are new combinations for flavone and flavonol *O*-glycosides, the disaccharides β-Glc*p*-(1→5)-β-Api*f* and α-Rha*p*-(1→2)-β-GlcA*p* (corresponding to **106** and **122**, respectively),[126,132] and the linear trisaccharide, β-Glc*p*-(1→2)-α-Rha*p*-(1→3)-α-Rha*p* (in **103**).[122] More than 60% of the entries in Table 1 are for acylated glycosides, the majority of which are characterised by acetic, malonic, *p*-coumaric or caffeic acid, sometimes in combination. Less common is protocatechuic acid (3,4-dihydroxybenzoic acid), found for the first time as an acylating group of flavone glycosides **97** and **135**.[118,140]

Several of the sources for new flavone *O*-glycosides listed in Table 1 are plant species with a history of medicinal use. Using LC-MS techniques, Švehlíková *et al.* analysed the flavone content of the flowers of chamomile, *Chamomilla recutita* (Asteraceae), which are rich in apigenin glycosides.[119] Two acylated derivatives (**98**, **99**) were isolated and the structures confirmed by NMR. A second example of an apigenin 7-*O*-β-glucopyranoside bearing both acetyl and malonyl groups (similar to **98**) was detected, but the sites of acylation remain to be confirmed. Other tentative identifications were made to monoacetylated derivatives of apigenin 7-*O*-β-glucopyranoside at 3-OH and 4-OH of the sugar. The same study demonstrates that acylated apigenin glycosides rapidly undergo decarboxylation and hydrolysis; thus, fresh petals extracted at low temperature (−20 °C) are richer in malonylated compounds.[119] The choice of extracting solvent and pH also affect the profile of apigenin glycosides obtained from the plant material. The flowers of *Chrysanthemum morifolium* (Asteraceae), which are also used as a tea (notably in traditional Chinese medicine), contain acetylated derivatives of acacetin (**104**; also reported from *Chrysanthemum sinense*)[124] and diosmetin (**131**).[123] The malonyl equivalent of **131** has been reported previously.[146] The isolation of 3′-desmethoxysudachiin C (**133**) from the peel of the citrus fruit *Citrus sudachi* (Rutaceae) deserves comment, as this source is a waste product of food processing (the annual fruit production from this species is approximately 8000 tons in Japan).[138]

The results of bioassays carried out with the flavone glycosides in Table 1 comprise data on antioxidant (**95**, **97**, **105**, **126**, **134**, **135**, **137**), immunomodulatory (**139**, **140**, **142**), nerve growth factor potentiating (**101**, **102**) and xanthine oxidase inhibition (**100**, **104**) activity. Most compounds tested had antioxidant activity (typically expressed as scavenging ability for the 1,1-diphenyl-2-picrylhydrazyl radical) comparable to or less than that of quercetin. Among the 6-hydroxyluteolin glycosides, **134** showed superior radical scavenging ability to butylhydroxytoluene,[139] while that of **135** and **137** was better than or comparable to the controls α-tocopherol and butylhydroxyanisole, respectively.[140,141] The nerve growth factor potentiating activity of MeOH extracts of aerial parts of *Scoparia dulcis* (Scrophulariaceae) was uncovered during a screening programme with Paraguayan plants.[121] The acylated apigenin glycosides **101** and **102** (obtained from this source by bioassay-guided fractionation) increased the neural growth factor-induced proportion of neurite-bearing PC12D cells by 16.1 and 14.9%, respectively.[121] Inhibition of xanthine oxidase by **100**, a constituent of the club moss *Palhinhaea cernua* (used in traditional Chinese medicine to treat various conditions, including joint pain and rheumatism), was comparable to that of allopurinol, which is prescribed clinically for the alleviation of gout.[120]

A few points of chemosystematic interest arise from the data in Table 1. Sulfated flavonoids such as **121** (isolated from the California fan palm *Washingtonia filifera*)[131] occur quite widely in the Palm family (Arecaceae), although are generally scarce elsewhere.[147] In other work, Marin *et al.* noted that glycosides of tricetin methyl ethers, such as **141**, occur in *Stachys* subgenus *Betonica* but not subgenus *Stachys*.[144] The same compound was later republished as new from the fern *Vittaria anguste-elongata*, using the trivial name vittariflavone.[145]

Apigenin 7,4′-di-*O*-β-glucopyranoside, one of the components of protodelphin, the blue flower pigment of *Salvia patens*, has been synthesised for the first time by Oyama and Kondo using naringenin (5,7,4′-trihydroxyflavanone) as starting material.[148] Different approaches were adopted to glycosylate the two sites (7-OH and 4′-OH). The Koenigs–Knorr method was effective for 7-OH but not 4′-OH, for which the use of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylfluoride with a Lewis acid–base promotion system was required. These procedures can be adapted to prepare both 7-*O*- and 4′-*O*-monoglucosides of apigenin and naringenin, and may be generally applicable to syntheses of similar flavonoid glycosides. Non-natural variants in which L-glucose is incorporated are accessible by the same routes.[148]

Stachyfloroside E, published in 2005 as a new acylated flavone glycoside from the whole plant of *Stachys parviflora* (Lamiaceae), was assigned the structure 6,7,8,3′,4′-pentahydroxyflavone 7-*O*-[6-*O*-acetyl-β-Gal*p*-(1→2)]-β-Glc*p*.[149] In this study, both the aglycone and acetylated disaccharide were misidentified. The lack of a 5-OH group in stachyfloroside E was inferred

from the absence of the characteristic singlet which appears between 12–14 ppm in the ^{1}H NMR spectrum. However, this exchangeable proton resonance is not observed in CD_3OD, the solvent in which the NMR data were acquired. Furthermore, the NMR spectral assignments given for H-5 (δ_H 6.76 s, δ_C 101.7) are typical of those of H-6 in a 5,7,8-tri-*O*-substituted flavone A-ring.[150] The NMR data for the disaccharide indicate that the acetylated terminal sugar is β-allopyranose rather than β-galactopyranose. Although allose is generally rare in flavonoid glycosides, it occurs quite frequently in flavone *O*-glycosides from *Stachys* and *Veronica*.[151,152] The excellent agreement between the published NMR data (CD_3OD) for hypolaetin (5,7,8,3′,4′-pentahydroxyflavone) 7-*O*-[6-*O*-acetyl-β-All*p*-(1→2)]-β-Glc*p*[150] and that given for stachyfloroside E,[149] confirms that this is the true identity of the latter. MeOH extracts of the roots of *Amaranthus spinosus* (Amaranthaceae) yielded spinoside, described as the new flavone glycoside 7-*O*-*p*-coumaroylapigenin-4′-*O*-β-Glc*p*.[153] Two features of the NMR data point to a different structure for this compound. The downfield-shifted ^{1}H resonances of CH_2-6 of Glc*p* (δ_H 4.25 and 4.40, both dd, DMSO-d_6) indicate that the *p*-coumaroyl group must be located at C-6 of the sugar. Similarly, the lack of downfield shifts corresponding to H-2′/6′ and H-3′/5′ of the B-ring cannot be reconciled with glycosylation at 4′-OH. Spinoside appears instead to be the well known compound apigenin 7-*O*-[6-*O*-*p*-coumaroyl-β-Glc*p*]. Several additional reports of new flavone *O*-glycosides have been noted in which either serious inconsistencies between spectroscopic data and proposed structures exist, or crucial data are lacking to confirm interglycosidic linkages.[154–157] The identity of a constituent from aerial parts of *Schouwia thebaica* (Brassicaceae) described as chrysoeriol 7-*O*-Xyl*p*-(1→2)-Api*f* is difficult to confirm in the absence of ^{1}H NMR data for the sugar residues.[158]

4.2 Flavonol *O*-glycosides

More new flavonoids have been reported in this category than any other covered in this review, bringing the total number of known examples to approximately 1500. Information on their structures and sources is presented in Table 2,[110,117,125,159–238] which also indicates those saccharides and acyl groups not previously found in flavonol *O*-glycosides.[115] Although few such compounds are known with four or more sugars, the increasing use of hyphenated analytical techniques to study flavonoids in plant extracts is improving their detection rate. In a detailed survey of the flavonoids of broccoli inflorescences (*Brassica oleracea* var. *italica*; Brassicaceae), Vallejo *et al.* identified the 3-*O*-sophorotrioside-7-*O*-sophorosides, 3-*O*-sophorotrioside-7-*O*-glucosides and 3-*O*-glucoside-7-*O*-sophorosides of both quercetin and isorhamnetin, using LC–UV–ESI-MS.[239] These glycosides, comprising five, four and three glucoses, respectively, were previously unknown, although their isolation and full structural analysis has yet to be achieved. More than twenty unrecorded acylated derivatives of the 3-*O*-sophorotrioside-7-*O*-glucosides and 3-*O*-sophoroside-7-*O*-glucosides of both kaempferol and quercetin were also present in extracts of this species. In terms of structural characterisation, use of MS^n analyses allowed the authors to distinguish glycosylation at C-3 or C-7, the 1→2 linkages of sophorotriose (Glc*p*-(1→2)-Glc*p*-(1→2)-Glc*p*) and sophorose (Glc*p*-(1→2)-Glc*p*), and the existence of acylation at 3-*O*-linked sugars. MS^n protocols for distinguishing the 1→2 and 1→6 interglycosidic linkages in flavonol sophorosides and gentobiosides, respectively, have also been published.[240] In a related study of leaf extracts of tronchuda cabbage (*Brassica oleracea* var. *costata*; Brassicaceae), Ferreres *et al.* used LC–UV–ESI-MS^n to detect and partially characterise several previously unreported kaempferol glucosides, including one novel example with four glucoses at C-3 and two at C-7.[241] Although these are important advances, analysis by NMR is still required for confirmation of aglycone substitution sites and interglycosidic linkages, as well as identification of specific sites of acylation and anomeric configuration.[98]

Among the entries in Table 2 are three unusual compounds (**149**, **150**, **231**) characterised by new branched tetrasaccharides *O*-linked at C-3 of either kaempferol or quercetin (Fig. 1). MeOH extracts of dried leaves of *Diospyros rhombifolia* (Ebenaceae) yielded **149** together with **147**, which bears a new branched trisaccharide with β-glucuronopyranose as the primary sugar.[163] Mildbraedin (**150**) is the major phenolic component of the leaves of the tropical forest legume, *Mildbraediodendron excelsum*. Analytical HPLC showed similar flavonoid profiles for leaf material of this species obtained from living specimens and

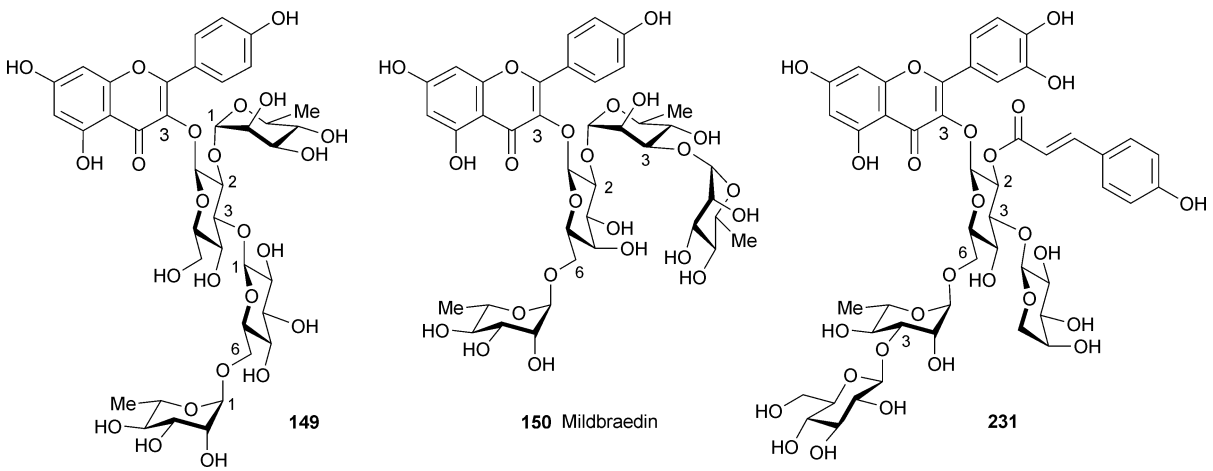
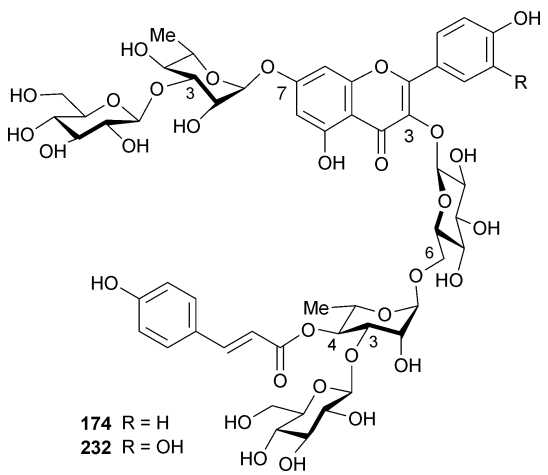


Fig. 1 New flavonol glycosides published between 2004 and 2006 with tetrasaccharides *O*-linked at C-3.

herbarium material collected in the field in 1928, a clear indication of the long-term stability of this kaempferol tetraglycoside.[165] Hot water extracts of oolong tea (a product of *Camellia sinensis*; Theaceae), which are rich in phenolics, yielded the acylated quercetin tetraglycoside, **231**.[215] The *p*-coumaroyl group is at 2-OH of the primary sugar (β-Glc*p*), which is *O*-linked at C-3 (Fig. 1). Coupling constant data extracted from the ^{1}H NMR spectrum indicates that the anomeric configuration of the L-Ara*p* moiety at 3-OH of the primary sugar is α and not β as stated ($^3J_{1,2}$ = 7.0 Hz). Two remarkable pentaglycosides of kaempferol (**174**) and quercetin (**232**) isolated from aerial parts of *Aconitum naviculare* (Ranunculaceae) have identical patterns of glycosylation, comprising an acylated linear trisaccharide at 3-OH and a disaccharide at 7-OH (see also **190**).[182]



Bioassay data are available for some of the glycosides listed in Table 2, with a bias towards measurements of antioxidant activity. In an important study using hyphenated techniques, Miliauskas *et al.* identified an antioxidant acetylglucoside of 6-hydroxykaempferol (**181**) by LC–UV–SPE-NMR with on-line radical scavenging detection.[187] Full structural elucidation required the acquisition of 2D NMR spectra off-line after compound trapping by SPE (solid phase extraction). The antioxidant activity (DPPH assay) of **181** was less than that of the controls, rosmarinic acid and Trolox.[187] When comparing the activities of a flavonol glycoside and its aglycone, that of camellianoside (**193**), a quercetin glycoside with a linear trisaccharide *O*-linked at C-3, was only slightly greater than quercetin itself, suggesting that the contribution of the sugar is relatively insignificant.[197] In contrast, two acylated derivatives (**247**, **248**) of quercetagetin 7-*O*-β-glucopyranoside had greater activity than quercetin and four other antioxidant standards in both DPPH and hydroxyl radical scavenging assays. Levels of inhibition of the superoxide anion radical were similar to those shown by quercetin. Parejo *et al.* ascribed the improved activity of **247** and **248** relative to quercetin to a combination of the additional 6-OH group in the A-ring of quercetagetin (3,5,6,7,3′,4′-hexahydroxyflavone), and the presence of acyl groups.[222] Again, the contribution of the sugar itself appeared to be minimal.

In other studies (see Table 2), the results of assays for antileishmanial (**143**, **158**), anti-plasmodial (**245**), cytotoxic (**153**, **160**, **161**, **185**, **210**), hepatoprotective (**199**) and protein synthesis inhibition (**164**) activity have been documented. Kuo *et al.* reported that **157**, a 3-*O*-[2(*Z*),4(*E*)-di-*p*-coumaroyl-α-rhamnopyranoside] of kaempferol, suppressed proliferation of human peripheral blood mononuclear cells stimulated by phytohemagglutinin.[171] Similar activity was displayed by the known 2(*E*),4(*E*)-isomer. Both compounds were isolated from leaves of the endemic species *Cinnamomum kotoense* (Lauraceae), an evergreen tree of Lanyu Island, Taiwan.[171] Nishimura *et al.* carried out cell proliferation-based screening assays based on human ligand-dependent cell lines to fractionate acetone extracts of the whole plant of *Euphorbia lunulata* (Euphorbiaceae), a species used in traditional Chinese medicine for the treatment of bronchial asthma and chronic bronchitis. These yielded **209**, a new digalloylated derivative of hyperin (quercetin 3-*O*-β-D-galactopyranoside) with proliferative activity in an insulin-dependent cell line, and quercetin 3-*O*-(2-*O*-galloyl-β-D-galactopyranoside), a known analogue showing similar levels of activity. Compounds with these properties are of interest for the development of non-peptidyl insulin substitutes.[207] Several bioactive flavonol glycosides have been identified through the work of the International Cooperative Biodiversity Group in Panama, whose aims are twofold; the discovery of new natural products with activity against cancer, HIV and tropical diseases, and biodiversity conservation. Bioassay-guided fractionation (human cancer cell lines) of EtOAc extracts of leaves of *Triplaris cumingiana* (Polygonaceae), a species widespread in Panama, yielded **153**, **185** and **210**, of which **153** showed cytotoxicity in the H-460 (lung) cell line.[167] A galloylated arabinofuranoside of quercetin (**245**) showed weak activity towards a chloroquine-resistant strain of *Plasmodium falciparum*. This is one of three new flavonol arabinofuranosides (see also **257** and **262**) obtained by bioassay-guided fractionation (anti-plasmodial) of extracts of young leaves of *Calycolpus warszewiczianus* (Myrtaceae).[220]

Several authors have investigated the biological properties of acetylated derivatives of afzelin (kaempferol 3-*O*-α-rhamnopyranoside). Usia *et al.* found that kaempferol 3-*O*-(2,3,4-tri-*O*-acetyl-α-rhamnopyranoside) (**159**) inhibited the activity of CYP3A4, a cytochrome P-450 enzyme of human liver microsomes (IC_{50} = 14.4 μM with [*N*-methyl-^{14}C]erythromycin as substrate). In contrast, kaempferol 3-*O*-(2,3-di-*O*-acetyl-α-rhamnopyranoside) (**156**), showed only moderate inhibitory activity.[170] Kaempferol 3-*O*-(3,4-di-*O*-acetyl-α-rhamnopyranoside) is a known derivative of afzelin, newly isolated from *Forsteronia refracta* (Apocynaceae),[242] and a specific inhibitor of p90 ribosomal S6 kinase (K_i = 1 μM, *in vitro* kinase assay).[243] However, its inhibitory activity in intact cells is weaker (EC_{50} ~ 50 μM; measured as inhibition of the proliferation of the human breast cancer cell line, MCF-7), possibly due to limited cellular uptake.[243] To test this hypothesis, Smith *et al.* synthesised two analogues with greater hydrophobicity, the unnatural kaempferol 3-*O*-(3,4-di-*O*-butyryl-α-rhamnopyranoside), and **159**.[244] These were no more effective in the *in vitro* kinase assay than kaempferol 3-*O*-(3,4-di-*O*-acetyl-α-rhamnopyranoside). In intact cells, the triacetylated derivative **159** showed a twofold improvement in inhibitory activity towards MCF-7 cell proliferation. The kinase inhibitory activity of the dibutyrylated analogue was less specific than that of **159**, which preferentially limits cell growth of MCF-7 over the normal human breast cell line MCF-10A.[244]

According to Williams' checklist, glycosides of prenylated flavonols represent only about 3% of all flavonol glycosides described to 2003.[115] Of the 7 examples (**268–274**) listed in Table 2, two are the first recorded furanoflavonol glycosides (**268**, **273**).[117,237] Glycosides of 8-prenylkaempferol and its methyl ethers are most commonly reported from *Epimedium*, although a few examples from other Berberidaceae genera (*Berberis*, *Vancouveria*) are known.[115,245] This trend is reflected in three new derivatives isolated from aerial parts of *Epimedium koreanum* (**270, 271**) and *Epimedium sagittatum* (**272**).[234–236] Note that the unusual hexulose sugar of **270** is without precedent in flavonol glycosides. The structure of acetylicariin (**271**) was proposed only on the basis of (ESI)-MS^n experiments, but derives support from comparable MS analyses on known glycosides of 8-prenylkaempferol 4′-methyl ether.[235] Fractionation of extracts of *Duranta repens* (Verbenaceae) showing α-glucosidase inhibitory activity yielded the 7-*O*-α-D-glucopyranosides of two *C*-alkylated 6-hydroxykaempferol dimethyl ethers (**275**, **276**). Analysis of coupling constant data from the corresponding ^{1}H NMR spectra confirms that the uncommon α-anomeric configuration is present ($^3J_{1,2}$ = 3.7 Hz for the doublet resonance of Glc H-1; for *O*-linked β-glucopyranosides, $^3J_{1,2}$ ~7–8 Hz). In assays with the purified compounds, **275** showed greater inhibition of α-glucosidase than the control, deoxynojirimycin, whereas **276** was inactive.[110]

Several new syntheses of flavonol *O*-glycosides have been published during the review period. Du *et al.* obtained quercetin 3-*O*-sophorotrioside in 8 linear steps and 39% overall yield from 7,4′-di-*O*-benzylquercetin.[246] The most effective strategy employed phase-transfer-catalyzed glycosylation at 3-OH followed by silver triflate-promoted carbohydrate chain elongation with both sugar bromide and trichloroacetimidate donors. The same starting material was used by Needs and Kroon to prepare several quercetin glucuronides and sulfates, including the first synthesis of the 3′-*O*-glucuronide.[247] These compounds are of interest as the main human plasma metabolites of quercetin, and are produced by biotransformation of quercetin *O*-glycosides (and to a lesser extent, the aglycone) present in the diet, *e.g.* in fruit and vegetables. In synthesising the 3-*O*-α-rhamnopyranosyl(1→2)-β-glucopyranosides (neohesperidosides) of the isomeric quercetin methyl ethers, tamarixetin (quercetin 4′-methyl ether) and isorhamnetin (quercetin 3′-methyl ether), Peng *et al.* demonstrated that an earlier report of tamarixetin 3-*O*-neohesperidoside as a natural product from *Costus spicatus* (Costaceae)[248] was in error.[249] Comparison of NMR data indicates that the structure given for the latter should be revised to isorhamnetin 3-*O*-neohesperidoside, which is known from several sources. Doubt has also been cast on the structure proposed for aescuflavoside A (**243**),[200] following its total synthesis.[250] A revised structure for the naturally occurring compound is still awaited.

A number of flavonol *O*-glycosides published as new in the 2004–2006 period have been omitted from Table 2 either because their characterisation appears incomplete, or difficulties exist in reconciling the structures proposed for them with the accompanying spectroscopic data.[251–269] In terms of incomplete characterisation, a common problem is that interglycosidic linkages and points of attachment between aglycone and glycosyl moieties are not always fully defined. This is particularly important where unusual linkages are suggested. These should be supported by full assignment of the ^{1}H and ^{13}C NMR spectral resonances of the participating glycosyl units based on data from 2D experiments (typically COSY, HSQC or HMQC and HMBC) rather than by chemical shift comparison with existing compilations. HMBC and/or ROE/NOE data can be used to define the linkages themselves. Care must also be taken to distinguish the isomeric sugar pairs, β-Gal*p*/β-Glc*p* and α-Ara*p*/β-Xyl*p*, which are sometimes misidentified. If NMR is the primary means of identification then a full set of multiplicities and coupling constants for the sugar proton resonances in the ^{1}H spectrum is desirable. TLC analysis of monosaccharides after acid hydrolysis of flavonol *O*-glycosides may not be sufficient to correctly discriminate between these sugar pairs; ideally derivatisation followed by GC–MS analysis should be carried out, a method that can be adapted (by use of chiral reagents) to give the absolute configurations of the saccharides. Although a full discussion of every case is beyond the scope of this review, some specific examples are given to highlight recurring problems. Misidentification of the site of substitution of the glycosidic component is one of these, as illustrated by two doubtful reports of quercetin 7-*O*-glycosides, a neohesperidoside from *Zea mays*,[261] and a robinobioside from *Ebenus haussknechtii*.[259] In both cases the UV spectra are typical of quercetin 3-*O*-glycosides,[270] and in the corresponding ^{1}H NMR spectra, the characteristic downfield shifts expected for H-6 and H-8 of the A-ring when 7-OH is glycosylated are absent.[98,271] Further scrutiny reveals a lack of evidence both for the (1→2)-linkage of the neohesperidoside, and for β-Gal*p* as the primary sugar of the robinobioside (as opposed to β-Glc*p*). Both compounds appear therefore to be quercetin 3-*O*-rutinoside (rutin), the most commonly found flavonol *O*-glycoside in flowering plants. In a second case, MeOH extracts of the leaves of *Ternstroemia japonica* (Theaceae) yielded a compound described as a new flavonol *O*-glycoside, kaempferol 3-*O*-β-xylopyranosyl-(1→2)-β-glucopyranoside-4′-*O*-β-glucopyranoside.[253] There are several indications from the NMR data that this structure is incorrect; the absence of the downfield shift corresponding to H-3′/5′ of the B-ring expected for a 4′-*O*-glycoside, the resonance assigned to C-6 of the 4′-*O*-glucoside with a marked downfield shift where none would be expected (δ_C 66.6 in CD_3OD, ~ +4 ppm), and the anomalous combination of an upfield-shifted resonance for C-5 of the primary Glc (δ_C 75.7, ~ –2 ppm, suggesting that 6-OH is glycosylated) with a value for C-6 of δ_C 62.6 (suggesting that 6-OH is not glycosylated). Taken together, these observations suggest that there is no B-ring glycosylation, that the ^{13}C NMR assignments for C-6 of the two Glc residues should be interchanged, and that 6-OH of the primary Glc must be glycosylated. On these grounds a revised structure of kaempferol 3-*O*-β-xylopyranosyl(1→2)[β-glucopyranosyl(1→6)]-β-glucopyranoside can be proposed. Less commonly the aglycone is wrongly identified, as is the case for a compound described as an acylated glycoside of morin 7,4′-dimethyl ether (3,5,2′-trihydroxy-7,4′-dimethoxyflavone), also from *Ebenus haussknechtii*.[259] Here the NMR spectral assignments for one of the methoxy resonances (δ_H 3.33, δ_C 48.6) are clearly those of the solvent in which the data were acquired (CD_3OD). There are also examples where an acyl group has been placed on the aglycone instead of the glycosyl moiety of a flavonol

O-glycoside. An interesting case is that of a compound obtained from leaves of *Moldenhawera nutans* (Leguminosae) which was identified as 5-galloyllarycitrin 3-*O*-β-xylopyranoside.[269] However, in the ^{1}H NMR spectrum the chemical shift value for H-6 of the aglycone A-ring is essentially identical to that found in larycitrin itself, whereas H-2 of the sugar moiety shows a substantial downfield shift. This is a clear indication that the galloyl group should be placed at 2-OH of the sugar and not 5-OH of the aglycone. It must also be noted that the value quoted as $^3J_{1,2} = 6.4$ Hz for the anomeric proton is more typical of a 3-*O*-α-arabinopyranoside than a 3-*O*-β-xylopyranoside. However, these sugars are not easily distinguished by NMR alone unless $^3J_{3,4}$ is recorded,[98] which is not the case here.

Several reported structures in which sugars rarely found in flavonol *O*-glycosides are incorporated deserve closer scrutiny. EtOH extracts of the flowers of *Castanea mollissima* (Fagaceae) yielded two compounds (castanosides A and B) described as coumaroylated derivatives of kaempferol 3-*O*-α-mannopyranoside.[254] Evidence for α-Man*p* was limited to TLC of the acid-hydrolysed sugar and comparison of ^{13}C NMR datasets with an existing literature compilation. The ^{1}H NMR datasets lacked multiplicities and coupling constants for H-2 to CH_2-6; however, the 4.0 Hz coupling constant cited for the doublet resonance of the anomeric proton in each compound is in conflict with literature data for α-Man*p* ($^3J_{1,2} \sim 1.8$ Hz).[272] It is also interesting to note that for kaempferol 3-*O*-(6-*O*-*E*-*p*-coumaroyl-α-Man*p*) (castanoside A), the ^{13}C NMR data for the sugar are similar to those of kaempferol 3-*O*-(6-*O*-acetyl-β-Gal*p*) (both datasets in DMSO-d_6).[273] Clearly further work is desirable to confirm the identity of these compounds. Nelumborosides A and B are two isorhamnetin *O*-glycosides from the stamens of *Nelumbo nucifera* (Nymphaeaceae) that are said to contain α-lyxopyranose.[266] Again, evidence for the presence of this sugar rests mainly with TLC analysis of monosaccharides released by acid hydrolysis. A full set of multiplicity and coupling constant data for the ^{1}H NMR resonances assigned to the α-lyxopyranosyl moiety are required to substantiate this claim. In a study of EtOH extracts of leaves of *Bridelia tomentosa* (Euphorbiaceae), evidence was presented for the presence of the 3-*O*-α-ribopyranoside and 3-*O*-β-xylopyranosyl(1→2)-α-ribopyranoside of tamarixetin (quercetin 4′-methyl ether).[267] However, there was no independent determination of the sugar components. One further area of difficulty is that the $^3J_{1,2}$ values for the resonances assigned to H-1 of α-Rib*p* in the ^{1}H NMR spectra of the two derivatives were different (3.2 and 5.2 Hz), similarly for $^3J_{2,3}$.[267]

4.3 Mono *C*-glycosylflavones

Information relating to new flavone *C*-glycosides published between 2004 and 2006 appears in Table 3,[131,274–297] in which the mono *C*-glycosylflavones are listed first. LC–ESI-MS (HPLC coupled to MS detection with electrospray ionisation) analysis of the fruits of *Cyclanthera pedata* (Cucurbitaceae) revealed the presence of three malonylated derivatives of 6-*C*-fucopyranosylchrysin, two of which (**277**, **278**) were subsequently isolated from MeOH extracts of the leaves. The sites of malonylation of these compounds were identified using NMR as 3″-OH (**277**) and 4″-OH (**278**) of the β-fucopyranosyl moiety.[274] Drymariatin B (**279**) is the 6-*C*-(2-deoxy-β-fucopyranoside) of apigenin (5,7,4′-trihydroxyflavone), and one of several new flavone *C*-glycosides obtained from EtOH extracts of the whole plant of *Drymaria cordata* Willd. ex Schult. subsp. *diandra* (Blume) J.A.Duke (published under the synonym *Drymaria diandra* Blume) (Caryophyllaceae).[275] Another 6-deoxy sugar, β-quinovopyranose (6-deoxy-β-glucopyranose), has been found as 8-*C*-β-quinovopyranosylapigenin (**280**) in tubers of the orchid *Prosthechea michuacana* (Lex.) W.E.Higgins (published under the synonym *Encyclia michuacana* (Lex.) Schltr.).[276] Comparison of calculated values for the ^3J coupling constants of the α- and β-anomers of apigenin 8-*C*-quinovopyranoside (**280**) with experimental data (extracted from the ^{1}H NMR spectrum) supported the assignment of the β-configuration.[276] The flowers of *Trollius ledebourii* (Ranunculaceae) are a rich source of flavone *C*-glycosides, yielding new acylated derivatives of vitexin (apigenin 8-*C*-β-glucopyranoside) (**281–283**),[277,278] isoswertisin (apigenin 7-methyl ether 8-*C*-β-glucopyranoside) (**284**, **285**),[277] orientin (luteolin 8-*C*-β-glucopyranoside) (**290–293**)[277,278] and isoswertiajaponin (luteolin 7-methyl ether 8-*C*-β-glucopyranoside) (**294**).[284] Cai *et al.* also reported the latter compound (using the trivial name, trollisin I) as a constituent of the flowers of *Trollius chinensis* (Ranunculaceae), together with trollisin II (**295**).[283] Other plant families from which acylated derivatives of either isoorientin (luteolin 6-*C*-β-glucopyranoside) or orientin have been obtained are the Liliaceae (**287**, **288**),[280] Gentianaceae (**289**)[281] and Verbenaceae (**293**).[282]

Aqueous extracts of the heartwood of *Pterocarpus marsupium* (Leguminosae) yielded 7,3′,4′-trihydroxyflavone 8-*C*-β-glucopyranoside (**286**), a rare 5-deoxyflavone *C*-glycoside.[279] Only a handful of similar examples are known, including bayin, the 8-*C*-β-glucopyranoside of 7,4′-dihydroxyflavone, which occurs in species of *Castanospermum*, *Cladrastis* and *Sophora* (Leguminosae).[27] A new derivative of isoscoparin (luteolin 3′-methyl ether 6-*C*-β-glucopyranoside) characterised by 8-hydroxy substitution in the A-ring (**296**) has been reported from the aerial parts of the California fan palm, *Washingtonia filifera* (Arecaceae).[131]

Two total syntheses of a novel fused 6-*C*-β-mannopyranosyl derivative of apigenin have been reported.[298,299] This compound (**297**), which possesses potent anti-inflammatory activity, was first mentioned in the patent literature in 2002 as a minor constituent of extracts of oolong tea.[300] Later studies indicate that it may have chemopreventive activity for colon cancer.[301] Nakatsuka *et al.* obtained it in 14 steps from 3,4,6-tri-*O*-benzyl-D-glucal, with an overall yield of 0.2%. They also prepared the chrysin equivalent (*i.e.* lacking 4′-OH), which showed greater anti-inflammatory activity than **297**.[298] The route adopted by Furuta *et al.* led to the synthesis of **297** from a monobenzyl protected acetophenone derivative in 6 steps with 3% overall yield.[299] Both schemes employ an intramolecular Mitsunobu reaction to form the fused ring system comprising the flavone A-ring and sugar moieties.

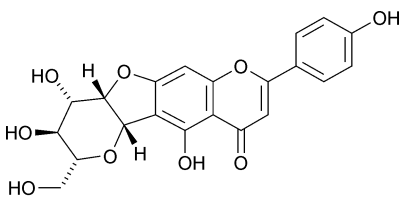


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Table 3 New flavone *C*-glycosides reported in the period 2004–2006

No.	Compound [a]	Sub.[b]	Source [c]	Family	Tissue	Ref.
	MONO *C*-GLYCOSYL FLAVONES					
	5,7-Dihydroxyflavone (chrysin)	5,7				
277	6-*C*-(3″-*O*-malonyl-β-Fuc*p*)		*Cyclanthera pedata*	Cucurbitaceae	Fruit	274
278	6-*C*-(4″-*O*-malonyl-β-Fuc*p*)		*Cyclanthera pedata*	Cucurbitaceae	Fruit	274
	5,7,4′-Trihydroxyflavone (apigenin)	5,7,4′				
279	6-*C*-(2-deoxy-β-Fuc*p*) (drymariatin B)		*Drymaria cordata* subsp. *diandra*	Caryophyllaceae	Whole plant	275
280	8-*C*-β-Qui*p* (β-Qui = 6-deoxy-β-Glc*p*)		*Prosthechea michuacana*	Orchidaceae	Tubercles	276
281	8-*C*-[2″-*O*-(3,4-dimethoxybenzoyl)-β-Glc*p*]		*Trollius ledebourii*	Ranunculaceae	Flower	277
282	8-*C*-[2″-*O*-(2-methylbutanoyl)-β-Glc*p*]		*Trollius ledebourii*	Ranunculaceae	Flower	277
283	8-*C*-(2″-*O*-vanilloyl-β-Glc*p*)		*Trollius ledebourii*	Ranunculaceae	Flower	278
	5,4′-Dihydroxy-7-methoxyflavone (apigenin 7-methyl ether, genkwanin)					
284	8-*C*-[2″-*O*-(2-methylbutanoyl)-β-Glc*p*]		*Trollius ledebourii*	Ranunculaceae	Flower	277
285	8-*C*-[3″-*O*-(2-methylbutanoyl)-β-Glc*p*]		*Trollius ledebourii*	Ranunculaceae	Flower	277
	7,3′,4′-Trihydroxyflavone	7,3′,4′				
286	8-*C*-β-Glc*p*		*Pterocarpus marsupium*	Leguminosae	Heartwood	279
	5,7,3′,4′-Tetrahydroxyflavone (luteolin)	5,7,3′,4′				
287	6-*C*-(6″-*O*-malonyl-β-Glc*p*)		*Asphodelus aestivus*	Liliaceae	Flower	280
288	6-*C*-[6″-*O*-(3-hydroxy-3-methylglutaroyl)-β-Glc*p*]		*Asphodelus aestivus*	Liliaceae	Flower	280
289	7-*O*-*E*-feruloyl-8-*C*-β-Glc*p* (7-*O*-feruloylorientin)		*Gentiana piasezkii*	Gentianaceae	Whole plant	281
290	8-*C*-[2″-*O*-(3,4-dimethoxybenzoyl)-β-Glc*p*]		*Trollius ledebourii*	Ranunculaceae	Flower	277
291	8-*C*-(2″-*O*-*E*-feruloyl-β-Glc*p*)		*Trollius ledebourii*	Ranunculaceae	Flower	278
292	8-*C*-[2″-*O*-(2-methylbutanoyl)-β-Glc*p*]		*Trollius ledebourii*	Ranunculaceae	Flower	277
293	8-*C*-[2″-*O*-(4-hydroxybenzoyl)-β-Glc*p*]		*Vitex altissima*	Verbenaceae	Leaf	282
	5,3′,4′-Trihydroxy-7-methoxyflavone (luteolin 7-methyl ether)					
294	8-*C*-[2″-*O*-(2-methylbutanoyl)-β-Glc*p*] (trollisin I)		*Trollius chinensis*, *Trollius ledebourii*	Ranunculaceae	Flower	283,284
295	8-*C*-[2″-*O*-(3,4-dimethoxybenzoyl)-β-Glc*p*] (trollisin II)		*Trollius chinensis*	Ranunculaceae	Flower	283
	5,7,8,4′-Tetrahydroxy-3′-methoxyflavone	5,7,8,3′,4′				
296	6-*C*-β-Glc*p* (8-hydroxyisoscoparin)		*Washingtonia filifera*	Arecaceae	Aerial parts	131
	DI *C*-GLYCOSYL FLAVONES					
	5,7-Dihydroxyflavone (chrysin)	5,7				
298	6-*C*-β-Glc*p*-8-*C*-β-Glc*p*		*Lychnophora ericoides*	Asteraceae	Leaf	285
	5-Hydroxy-7-methoxyflavone (chrysin 7-methyl ether)					
299	6-*C*-β-Oli*p*-4′-*C*-β-Glc*p* (diandraflavone)		*Drymaria cordata* subsp. *diandra*	Caryophyllaceae	Leaf	286
	5,7,4′-Trihydroxyflavone (apigenin)	5,7,4′				
300	6-*C*-[2″-*O*-feruloyl-β-Glc*p*]-8-*C*-β-Glc*p*		*Dregea volubilis*	Asclepiadaceae	Flower	287
	O-GLYCOSYL-*C*-GLYCOSYL FLAVONES					
	6-*C*-β-Boivinopyranosylapigenin	5,7,4′				
301	4′-*O*-β-Glc*p* (rhamnellaflavoside B)		*Rhamnella inaequilatera*	Rhamnaceae	Leaf	288
	6-*C*-2-Deoxy-β-fucopyranosylapigenin					
302	7-*O*-β-Glc*p* (drymariatin C)		*Drymaria cordata* subsp. *diandra*	Caryophyllaceae	Whole plant	275
	6-*C*-β-4-Epioliopyranosylapigenin					
303	4′-*O*-β-Glc*p* (rhamnellaflavoside C)		*Rhamnella inaequilatera*	Rhamnaceae	Leaf	288
	6-*C*-β-Fucopyranosylapigenin					
304	2″-*O*-α-Rha*p* (carambolaflavone)		*Averrhoa carambola*	Oxalidaceae	Leaf	289
	6-*C*-β-Galactopyranosylapigenin					
305	2″-*O*-β-Xyl*p* 7-*O*-β-Glc*p*		*Syzygium aromaticum*	Myrtaceae	Seed	290
306	2″-*O*-β-Xyl*p* 7-*O*-(6-*O*-*E*-*p*-coumaroyl-β-Glc*p*)		*Syzygium aromaticum*	Myrtaceae	Seed	290
	6-*C*-β-Glucopyranosylapigenin (isovitexin)					
307	3″-*O*-β-Glc*p*		*Isatis tinctoria*	Brassicaceae	Leaf	291
308	6″-*O*-β-Xyl*p* 4′-O-Glc*p*		*Gentiana lutea*	Gentianaceae	Rhizome & root	292
309	7-*O*-*E*-sinapoyl		*Wasabia japonica*	Brassicaceae	Leaf	293
310	7-*O*-*E*-sinapoyl 4′-*O*-β-Glc*p*		*Wasabia japonica*	Brassicaceae	Leaf	293
311	7-*O*-*E*-sinapoyl 4′-*O*-(6-*O*-*E*-sinapoyl-β-Glc*p*)		*Wasabia japonica*	Brassicaceae	Leaf	293
312	6″-*O*-(2-*O*-*E*-sinapoyl-β-Glc*p*) 7-*O*-*E*-sinapoyl		*Wasabia japonica*	Brassicaceae	Leaf	293
313	6″-*O*-(2-*O*-*E*-sinapoyl-β-Glc*p*) 7-*O*-*E*-sinapoyl-4′-*O*-β-Glc*p*		*Wasabia japonica*	Brassicaceae	Leaf	293
314	2″-*O*-(6-*O*-*E*-caffeoyl-β-Glc*p*)		*Oxalis triangularis*	Oxalidaceae	Leaf	294
315	6″-*O*-Ac 7-*O*-β-Glc*p*		*Stellaria media*	Caryophyllaceae	Aerial parts	295
	6-*C*-3-Keto-β-digitoxopyranosylapigenin					
316	7-*O*-β-Glc*p* (drymariatin D)		*Drymaria cordata* subsp. *diandra*	Caryophyllaceae	Whole plant	275

Table 3 *(Contd.)*

No.	Compound [a]	Sub.[b]	Source [c]	Family	Tissue	Ref.
	6-*C*-β-Oliopyranosylapigenin					
317	4′-*O*-β-Glc*p* (rhamnellaflavoside A)		*Rhamnella inaequilatera*	Rhamnaceae	Leaf	288
	8-*C*-β-Glucopyranosylapigenin (vitexin)					
318	2″-*O*-β-Gal*p*		*Trollius ledebourii*	Ranunculaceae	Flower	278
319	7-*O*-α-Rha*p*		*Pteris vittata*	Pteridaceae	Aerial parts	296
	8-*C*-β-Glucopyranosylcirsimaritin (abrusin)	5,6,7,4′				
320	2″-*O*-β-Xyl*p*		*Corallodiscus flabellatus*	Gesneriaceae	Whole plant	297
	8-*C*-β-glucopyranosylluteolin (orientin)	5,7,3′,4′				
321	2″-*O*-β-Gal*p*		*Trollius ledebourii*	Ranunculaceae	Flower	278
	6-*C*-β-glucopyranosylchrysoeriol (isoscoparin)					
322	3″-*O*-β-Glc*p*		*Isatis tinctoria*	Brassicaceae	Leaf	291
	8-*C*-β-glucopyranosylcirsiliol	5,6,7,3′,4′				
323	2″-*O*-β-Xyl*p*		*Corallodiscus flabellatus*	Gesneriaceae	Whole plant	297

[a] Standard three-letter codes for monosaccharides are used; *p* = pyranoside, *f* = furanoside. Entries are presented in order of increasing glycosylation, with non-acylated before acylated derivatives. [b] The *O*-substitution pattern of the parent flavone is indicated. Compounds are listed in order of increasing *O*-substitution, with the A-ring substituents taking precedence over those of the B-ring (primed numbers). [c] Accepted names are quoted. Entries published under synonyms (shown in parentheses): *Drymaria cordata* subsp. *diandra* (= *Drymaria diandra*), *Prosthechea michuacana* (= *Encyclia michuacana*).

4.4 Di *C*-glycosylflavones

Only three new di-*C*-glycosylflavones were reported from 2004 to 2006 (Table 3). Of these, 6,8-di-*C*-β-glucopyranosylchrysin (**298**) was obtained together with a known compound, vicenin-2 (6,8-di-*C*-β-glucopyranosylapigenin), from the leaves of *Lychnophora ericoides* (Asteraceae).[285] This species is used as a traditional medicine in Brazil, where products derived from it are available commercially as analgesics and anti-inflammatory agents. Bioassays indicate that of the two di-*C*-glycosylflavones found in *Lychnophora ericoides*, only vicenin-2 has significant anti-inflammatory activity.[285] Diandraflavone (**299**) is a di-*C*-glycoside of chrysin 7-methyl ether (5-hydroxy-7-methoxyflavone) obtained from the whole plant of *Drymaria cordata* subsp. *diandra* (published under the synonym *Drymaria diandra*) (Caryophyllaceae). An unusual feature is the *C*-linked sugar at C-4′ of the B-ring. The 2,6-dideoxyhexose, β-oliopyranose, is *C*-linked at C-6 of the A-ring. This compound showed selective inhibition of superoxide generated from human neutrophils induced with formyl-L-methionyl-L-leucyl-L-phenylalanine (IC_{50} = 10.0 μg ml^{-1}).[286] Dregeanin (**300**), a previously unrecorded feruloyl derivative of vicenin-2, occurs in the flowers of the woody climbing plant *Dregea volubilis* (Asclepiadaceae).[287]

The total synthesis of vicenin-2 has been achieved in eight steps and 35.2% yield using di-*C*-β-D-glucopyranosylphloroacetophenone as starting material.[302] The latter is available through direct *C*-glycosylation of phloroacetophenone with unprotected D-glucopyranose in aqueous solution using scandium(III) trifluoromethanesulfonate as catalyst.[303]

4.5 *O*-Glycosides of *C*-glycosylflavones

This group comprises *C*-glycosylflavones which are *O*-glycosylated either at the *C*-linked sugar or the aglycone, or both. Rhamnellaflavosides A–C are the 4′-*O*-β-glucopyranosides of three rare 6-*C*-glycosylapigenin derivatives, in which the *C*-linked sugars are β-oliopyranose (**317**), β-boivinopyranose (**301**) and β-4-epioliopyranose (**303**), respectively. These compounds were isolated from the *n*-BuOH-soluble portion of MeOH extracts of the leaves of *Rhamnella inaequilatera* (Rhamnaceae).[288] The whole plant of *Drymaria cordata* subsp. *diandra* (published under the synonym *Drymaria diandra*) (Caryophyllaceae) yielded the 7-*O*-β-glucopyranosides of two 6-*C*-glycosylapigenin derivatives published as drymariatins C (**302**) and D (**316**) (see also **279** and **299**).[275] Araho *et al.* described a 2″-*O*-α-rhamnopyranosyl derivative of 6-*C*-β-fucopyranosylapigenin from leaves of the starfruit tree, *Averrhoa carambola* (Oxalidaceae), assigning it the trivial name of carambolaflavone (**304**).[289] An earlier record of the same compound noted in HPLC analyses of corn silk extracts (as 4″-hydroxyapimaysin)[304] could not be verified, as no physical data were located for it in the literature. Two *O*-glycosyl-*C*-glycosylflavones (**305**, **306**) isolated from the seeds of *Syzygium aromaticum* (Myrtaceae) were identified as derivatives of 6-*C*-β-galactopyranosylapigenin, an uncommon analogue of isovitexin (6-*C*-β-glucopyranosylapigenin). However, the evidence for β-Gal is limited, being based largely on correlations of ^{13}C NMR spectral data with the literature and only a partial set of ^{1}H NMR spectral assignments (lacking those for H-3 to CH_2-6).[290]

Two rarely found (1→3)-linked *O*-glycosides of isovitexin (**307**) and isoscoparin (**322**) have been identified in MeOH extracts of fresh leaves of the woad plant *Isatis tinctoria* (Brassicaceae), a species best known for its use as an indigo dye. The isovitexin derivative was a minor component of the extract (only 70 μg isolated), but the sample was analysed successfully using a 500 MHz NMR spectrometer equipped with a cryoprobe. The interglycosidic linkages of both **307** and **322** were confirmed from long-range connectivities observed in HMBC experiments.[291] Extracts of the roots and rhizomes of *Gentiana lutea* (Gentianaceae) yielded an *O*-β-xylopyranosyl derivative (**308**) of isosaponarin (isovitexin 4′-*O*-β-glucopyranoside).[292] Analysis of MeOH extracts of fresh leaves of the Japanese horseradish, *Wasabia japonica* (Brassicaceae), revealed five *O*-glycosides of isovitexin acylated with (*E*)-sinapic acid (**309–313**). Each of these

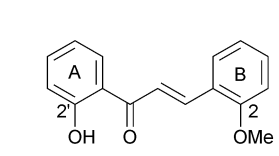
compounds has 7-OH of the aglycone as an acylation site, although **311–313** have additional sites on *O*-linked sugars.[293] Analysis of NMR spectra of a new caffeoyl derivative (**314**) of isovitexin 2″-*O*-β-glucopyranoside found in the leaves of *Oxalis triangularis* (Oxalidaceae) indicated that solution conformers were present. These are thought to arise from rotational hindrance about the glycoside–flavone bond.[294] An acetyl derivative (**315**) of saponarin (isovitexin 7-*O*-β-glucopyranoside) has been reported from the aerial parts of *Stellaria media* (Caryophyllaceae), which are rich in *C*-glycosylflavones.[295]

Zou *et al.* obtained the 2″-*O*-β-galactopyranosides of vitexin (**318**) and orientin (**321**) as constituents of the flowers of *Trollius ledebourii* (Ranunculaceae), together with **283** and **291**.[278] The absolute configurations of the *O*-linked sugars were given without appropriate experimental verification as β-L-Gal*p*; however, β-D-Gal*p* is expected for a flavonoid galactoside. The 7-*O*-α-rhamnopyranoside of vitexin (**319**) has been found in EtOH extracts of aerial parts of the fern *Pteris vittata* (Pteridaceae).[296] Water extracts of the whole plant of *Corallodiscus flabellatus* (Gesneriaceae) yielded 2″-*O*-β-xylopyranosyl derivatives of two flavone methyl ether 8-*C*-β-glucopyranosides based on cirsimaritin (**320**) and cirsiliol (**323**).[297] The first synthesis of an *O*-glycosylated *C*-glycosylflavone has been published by Oyama and Kondo for flavocommelin (apigenin 7-methyl ether 6-*C*-β-glucopyranoside-4′-*O*-β-glucopyranoside = swertisin 4′-*O*-β-glucopyranoside),[305] best known as a component of the blue flower pigment from *Commelina communis* (Commelinaceae).[306]

A compound described as new in a paper on the *C*-glycosylflavones of *Mimosa pudica* (Leguminosae)[307] was characterised as the 2″-*O*-α-rhamnopyranoside of 6-*C*-β-glucopyranosyl-7,8,3′,4′-tetrahydroxyflavone. This proposal is not fully supported by the NMR data (assignments in CD_3OD for H-5 and C-5 of 6.48 and 94.7 ppm are those of H-8 and C-8, respectively, similarly C-8 of the latter compound would not appear as far downfield as 158.8 ppm, which is typical of C-5). On this basis the structure should be revised to the 2″-*O*-α-rhamnopyranoside of 6-*C*-β-glucopyranosyl-5,7,3′,4′-tetrahydroxyflavone (isoorientin). The latter was also identified as a known constituent, but the corresponding NMR data appear to be those of the 2″-*O*-α-rhamnopyranoside of 8-*C*-β-glucopyranosyl-5,7,3′,4′-tetrahydroxyflavone (orientin).

5 Chalcones

Six new chalcones with simple patterns of *O*-substitution have been described in the review period. One of the most interesting reports is of 2′-hydroxy-2-methoxychalcone (**324**), which was found together with 2′,2-dihydroxychalcone and 2′,β-dihydroxychalcone in the farinose exudate of inflorescences of *Primula palinuri* (Primulaceae).[76] Di-*O*-substituted chalcones are characteristic components of the farinose exudates of several species of *Primula*.[308] Typically they co-occur with flavones that are also distinguished by unusual or unique patterns of *O*-substitution (see also **2–5**). Methanol extracts of the fruits of *Alpinia rafflesiana* (Zingiberaceae) afforded 2′,3′,4′,6′-tetrahydroxychalcone (**325**), a compound with DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity superior to that of both ascorbic acid (vitamin C) and α-tocopherol (vitamin E).[309] An unusually substituted derivative, 2′-hydroxy-4′,2,3-trimethoxychalcone (**326**), was isolated from extracts of the whole plant of *Andrographis macrobotrys* (Acanthaceae), although it is not, as claimed, the first example of a naturally occurring chalcone with 2,3-dioxygenation in the B-ring.[310] This distinction belongs instead to the related 2′-hydroxy-4′,6′,2,3-tetramethoxychalcone, reported in 2003 as a constituent of the leaves of *Caesalpinia pulcherrima* (Leguminosae).[311] The unsubstituted B-ring of 2′,4′,5′,6′-tetrahydroxy-3′-methoxychalcone (**327**) is a characteristic feature of Lauraceae chalcones.[308] This compound was obtained from the bark of *Lindera erythrocarpa* (Lauraceae), together with the related derivatives, 2′,4′-dihydroxy-3′,6′-dimethoxychalcone and 2′-hydroxy-3′,4′,5′,6′-tetramethoxychalcone.[312] Extracts of the fruits of *Brahea armata* (Arecaceae) showing inhibition of steroid 5-α reductase II yielded 2′,4,β-trihydroxy-4′,6′-dimethoxychalcone (**328**), together with other phenolics.[313] However, the activity of the purified chalcone was not reported. A hepta-*O*-substituted chalcone identified as 3′,5′,β-trihydroxy-4′,3,4,α-tetramethoxychalcone (**329**) was purified by Chou and Wang from EtOAc extracts of Herba Siegesbeckiae.[314] According to the Chinese Pharmacopoeia, the latter comprises the dried aerial parts of *Siegesbeckia glabrescens*, *S. orientalis* or *S. pubescens* (Asteraceae).[315]



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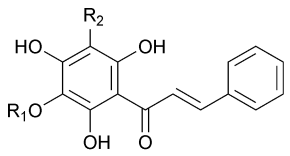
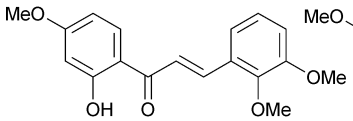


325 $R_1 = R_2 = H$
327 $R_1 = Me$, $R_2 = OH$



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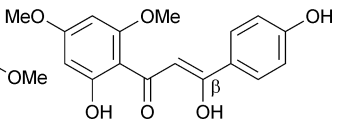

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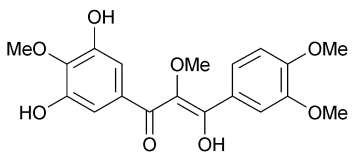
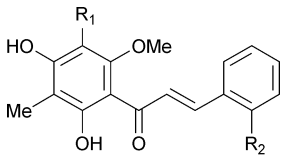


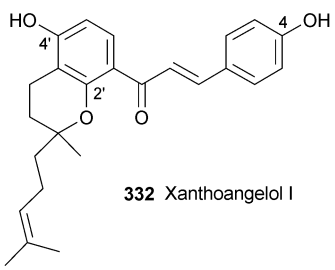
329

Ye *et al.* obtained 2′,4′-dihydroxy-6′-methoxy-3′-methyl-5′-formylchalcone (**330**) from the air-dried buds of *Cleistocalyx operculatus* (Myrtaceae), together with the flavanone **464**.[316] Bioassay-guided fractionation of ethanol extracts of the aerial parts of *Psorothamnus polydenius* (Leguminosae) yielded 2′,4′,2-trihydroxy-6′-methoxy-3′,5′-dimethylchalcone (**331**), which displayed leishmanicidal and trypanicidal activity.[317] This perennial shrub, known also as the 'smoke bush', is a desert species of California, Nevada and Utah, and valued as a traditional medicinal plant. Salem and Werbovetz consider it to be potentially useful as a low-cost herbal remedy for leishmaniasis, based on the antiprotozoal activities of **331** and the known constituents, 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone and dalrubone.[317]

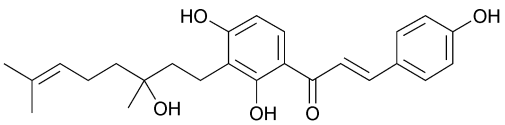


330 R_1 = CHO, R_2 = H
331 R_1 = Me, R_2 = OH

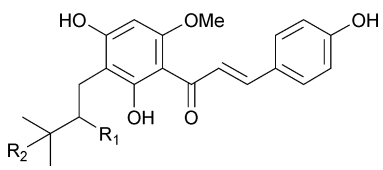
New prenylated chalcones have been reported from only seven plant families, with examples from the Leguminosae and Moraceae predominating. Xanthoangelols I (**332**) and J (**333**) were obtained by Akihisa *et al.* from EtOAc-soluble fractions of the stem exudates of *Angelica keiskei* (Apiaceae).[318] Both feature modified geranyl substituents. The compounds inhibited induction of Epstein–Barr virus early antigen by 12-*O*-tetradecanoylphorbol-13-acetate in Raji cells (human Burkitt's lymphoma cell line), and activation of the NO donor (±)-(*E*)-methyl-2[(*E*)-hydroxyimino]-5-nitro-6-methoxy-3-hexemide (NOR 1). In each case the degree of inhibition was equivalent or better than that of the reference compounds, retinoic acid and glycyrrhizin, respectively.[318] The hop plant, *Humulus lupulus* (Cannabinaceae) continues to be an important source of new prenylated chalcones and other flavonoids. A topical review on important developments in this area was published by Stevens and Page in 2004.[16] Estrogenic constituents of 'spent hops' (hop cones after extraction with supercritical CO_2) are the focus of a comprehensive study by Chadwick *et al.*, in which three new prenylated chalcones (**334**, **339** and **340**) and four related derivatives (**336–338**, **341**) were reported.[319] The latter were known previously only as either metabolites (**336–338**),[320] or a microbial transformation product (**341**),[321] of xanthohumol (2′,4′,4-trihydroxy-6′-methoxy-3′-prenylchalcone). A full spin system analysis for the resonances of the ^{1}H NMR spectrum of xanthohumol H (**336**) was achieved using spectral simulation and prediction software.[319] Xanthohumol I (**341**) was also obtained by Wang *et al.* from an 80% EtOH extract of hops, and shown to inhibit human stomach carcinoma cells.[322] The EtOAc-soluble fraction of a hops CAS pellet analysed by Zhao *et al.* yielded an additional example of a xanthohumol derivative with an oxidised prenyl side chain at C-3′ of the A-ring (**335**).[323] At concentrations less than 10 μM, this compound inhibited NO production in a murine macrophage cell line (RAW 264.7) without cytotoxicity. The authors refer to an earlier paper in which they reported the inhibitory effect of **335** and other hop constituents on NO production and the expression of an inducible NO synthase (iNOS).[324] However, the compound shown in the latter report is an isomer of **335**, with a 3′-(2-methoxy-3-methyl-3-hydroxybutyl) side chain rather than the 3′-(2-hydroxy-3-methyl-3-methoxybutyl) equivalent of the latter. This discrepancy requires clarification. Mallotophilippens C–E (**342–344**), three chalcones isolated from fruits of *Mallotus philippinensis* (Euphorbiaceae), also inhibited NO production and iNOS mRNA expression in the same cell line (RAW 264.7).[325] Cellular viability was unaffected up to concentrations of 30 μg ml^{-1}. The compounds also downregulated gene



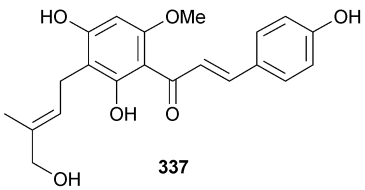
332 Xanthoangelol I



333 Xanthoangelol J



334 R_1 = R_2 = OH; Xanthohumol G
335 R_1 = OH, R_2 = OMe
336 R_1 = H, R_2 = OH; Xanthohumol H



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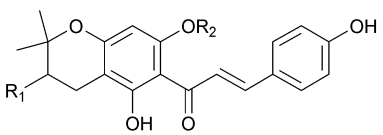
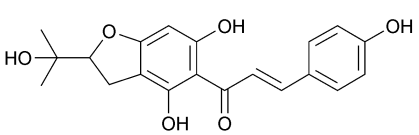
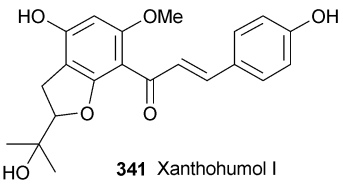


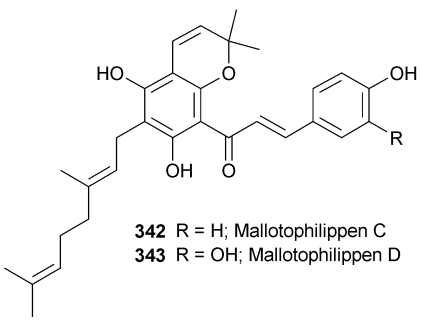
338 R_1 = H, R_2 = Me; 4'',5''-Dihydroxanthohumol C
339 R_1 = OH, R_2 = H; Desmethylxanthohumol B



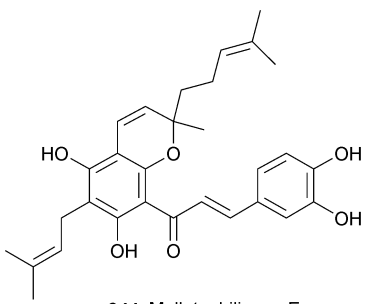
340 Desmethylxanthohumol J



341 Xanthohumol I



342 R = H; Mallotophilippen C
343 R = OH; Mallotophilippen D

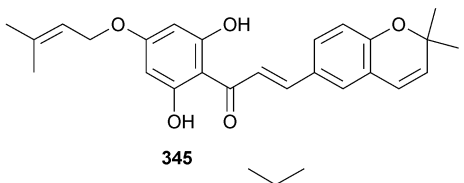


344 Mallotophilippen E

expression of cyclooxygenase-2, interleukin-6 and interleukin-1β, by inhibiting mRNA production. The underlying mechanism of inhibition is thought to involve inactivation of the transcription factor, NF-κB.[325] Li *et al.* achieved the first total synthesis of mallotophilippen C (**342**) in 11 linear steps from phloroacetophenone, with a yield of 28%.[326]

Extracts of the heartwood of the neotropical tree *Beilschmiedia tovarensis* (Lauraceae), a species found from Central America to the Andean region, yielded **345**, with an uncommon *O*-prenyl group, and 2′,6′,4-trihydroxy-3′,4′-methylenedioxy-3-prenylchalcone (**346**).[327] Thirteen new prenylated chalcones have been characterised from the Leguminosae. Crotaorixin (**347**), the 3′-prenyl derivative of homobutein (2′,4′,4-trihydroxy-3-methoxychalcone), is a constituent of the aerial parts of *Crotalaria orixensis* (Leguminosae), an annual species found mainly in northern Ethiopia and western peninsular India. At 10 μg ml^{-1}, it completely inhibited maturation of the malaria parasite, *Plasmodium falciparum*, from ring to schizont stage.[328] Vitali *et al.* obtained the same compound by transformation of homobutein and γ,γ-dimethylallyldiphosphate with prenyltransferase present in microsomal fractions prepared from cell cultures of *Morus nigra* (Moraceae).[329] The enzyme, which was not purified to homogeneity, requires a divalent cation (preferably Mg^{2+}) as cofactor and has a pH-optimum of 7.5 in Tris-HCl buffer. It showed no activity towards flavones and flavanones, but genistein (5,7,4′-trihydroxyisoflavone) was converted to its 6-prenyl analogue.[329] Corylifol B (**348**), a 3′-prenyl derivative of butein (2′,4′,3,4-tetrahydroxychalcone), showed antibacterial activity towards *Staphylococcus aureus* and *S. epidermidis*. This compound occurs in the seeds of *Cullen corylifolium* (published under the synonym *Psoralea corylifolia*) together with the prenylated flavone, corylifol C (**20**).[49] Heyneanachalcone (**349**) is a 3′-prenyl derivative of isoliquiritigenin 4-methyl ether (2′,4′-dihydroxy-4-methoxychalcone) and a constituent of the leaves of *Derris heyneana* (Leguminosae).[330] 5-Prenylbutein (**350**), isolated from EtOAc extracts of the stem bark of *Erythrina abyssinica* (Leguminosae), showed moderate antiplasmodial activity against chloroquine-sensitive and resistant strains of *Plasmodium falciparum*.[331] Abyssinone VI 4-methyl ether (**351**) was isolated together with other prenylated flavonoids by bioassay-guided fractionation of EtOAc extracts of the root bark of *Erythrina mildbraedii* (Leguminosae). This used an *in vitro* assay for protein tyrosine phosphatase-1B inhibition (associated with treatment of type 2 diabetes and obesity), in which **351** shows promising activity.[332] Licochalcone E (**352**) is an interesting example of a prenylated retrochalcone, in which the typical patterns of substitution of the A- and B-rings appear to be interchanged. Obtained by cytotoxicity-guided fractionation of H_2O extracts of the roots of *Glycyrrhiza inflata* (Leguminosae), this compound gave an IC_{50} value of 45.2 μM in the HT1080 cell line.[333] Hedysarumine B (**353**), isolated by Liu *et al.* from EtOH extracts of the roots of *Hedysarum gmelinii* (Leguminosae),[334] co-occurs with hedysarumine A, a prenylated chalcone found previously in two species of *Dorstenia* (Moraceae) and published under the name, angusticornin A (see **374**).[335] MeOH extracts of the pods of *Millettia erythrocalyx* (Leguminosae) yielded the 4′-*O*-prenyl derivative of homobutein, **354**, together with 2′-hydroxy-3,4-dimethoxyfurano[2″,3″:4′,3′]chalcone (**355**).[57] Yin *et al.* reported the 5′-prenyl derivative (**356**) of glabrachromene II from the stem bark of *Millettia pinnata* (using the synonym *Pongamia pinnata*).[58] Cyclokuraridin (**357**), obtained from MeOH extracts of the roots of *Sophora flavescens* (Leguminosae), showed moderate cytotoxicity in the KB tumour cell line.[107] The roots and rhizomes of *Sophora tonkinensis*, used widely as 'Shan Dou Gen' in traditional Chinese medicine,[336] afforded tonkinochromane C (**358**) as a minor component.[337] A study of root material of *Tephrosia spinosa* yielded spinochalcone D (**359**), the 2′-methyl ether of lonchocarpin.[338]

MeOH extracts of the heartwood of the breadfruit tree, *Artocarpus communis* (Moraceae), yielded the new pyranochalcone **360**, which showed potent inhibition of NO production in lipopolysaccharide-activated murine macrophage cells (RAW 264.7), with low cytotoxicity.[66] The 2′,4′,2,4-tetra-*O*-substitution pattern observed here is typical of Moraceae chalcones, a further example of which is given by artonin ZB (**362**), isolated together with its isoliquiritigenin (2′,4′,4-trihydroxychalcone) analogue (artonin ZA, **361**) from the leaves of *Artocarpus heterophyllus* (Moraceae).[339] Four chalcones characterised by modified geranyl side chains at C-3′ of the A-ring were obtained from either leaves (**363**, **364**)[340] or fruits (**365**, **366**)[72] of the Sri Lankan endemic, *Artocarpus nobilis* (Moraceae). These are derivatives of either butein (2′,4′,3,4-tetrahydroxychalcone) or isoliquiritigenin. In preliminary bioassays, **363** and **364** showed antifungal (*Cladosporium cladosporioides*) and antioxidant activity (DPPH radical scavenging).[340] Brosimacutin M (**367**) is a derivative of isoliquiritigenin characterised by 2,3-dihydroxy-3-methylbutyl



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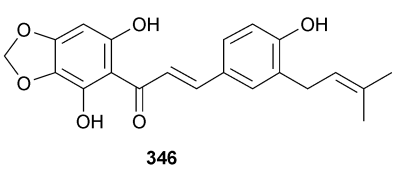

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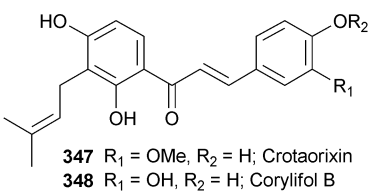
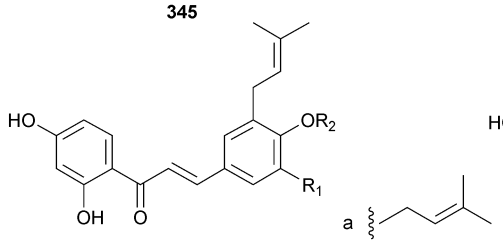
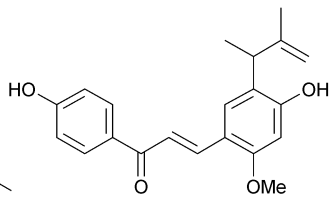


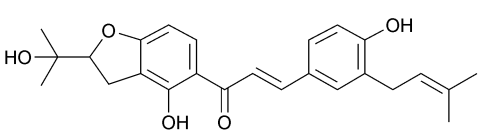
347 R_1 = OMe, R_2 = H; Crotaorixin
348 R_1 = OH, R_2 = H; Corylifol B
349 R_1 = H, R_2 = Me; Heyneanachalcone



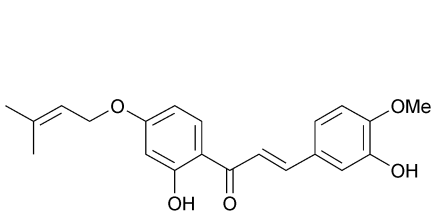
350 R_1 = OH, R_2 = H; 5-Prenylbutein
351 R_1 = a, R_2 = Me; Abyssinone VI 4-methyl ether



352 Licochalcone E



353 Hedysarumine B



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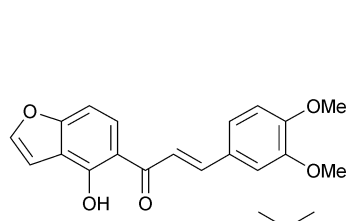

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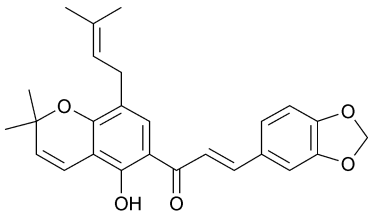

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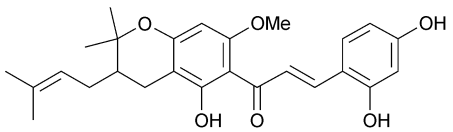
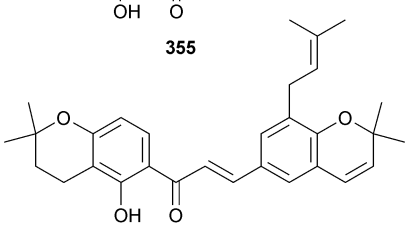
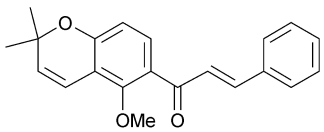


357 Cyclokuraridin



358 Tonkinochromane C

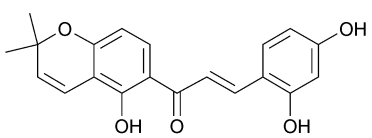


359 Spinochalcone D

substitution at C-3′ of the A-ring. It is one of many prenylated flavonoids (notably flavans and flavanones) obtained from the bark of *Brosimum acutifolium* (Moraceae), some of which also feature a 2,3-dihydroxy-3-methylbutyl group.[341] The dihydrofuranochalcone brosimacutin G (**368**), published in 2002, was also obtained from this source, but not cited in previous reviews.[342] It has now been synthesised by Zou and colleagues.[343] Brosimacutin M (**367**) showed cytotoxicity towards vincristine-resistant murine leukemia P388 cells.[341] No fewer than six new prenylated chalcones have been isolated from extracts of the twigs of *Dorstenia barteri* var. *subtriangularis* (**369–374**), two of which (**371**, **374**) also occur in *Dorstenia angusticornis* (Moraceae).[335,344] All feature prenyl groups at C-5′ and C-3 of the A- and B-rings, respectively, in some cases in cyclised forms. Acid hydrolysis of bartericin B (**372**), an isomer of hedysarumine B (**353**), yielded bartericin C (**373**) as the major product.[344] The biogenetic precursor of the *Dorstenia* chalcones **369–374** is likely to be stipulin (2′,4′,4-trihydroxy-5′,3-diprenylchalcone), which occurs in both of the species studied.[335,344]

Three new glycosides of the well-known chalcones, butein (2′,4′,3,4-tetrahydroxychalcone), chalconaringenin (2′,4′,6′,4-tetrahydroxychalcone) and okanin (2′,3′,4′,3,4-pentahydroxychalcone) have been reported. Bidenoside G (**375**) is the 6-*O*-acetyl derivative of coreopsin (butein 4′-*O*-β-glucopyranoside) and a constituent of the aerial parts of *Bidens bipinnata* (Asteraceae).[345] A malonyl derivative of coreopsin is known from two species of *Dahlia* (Asteraceae), however, in this case the site of acylation was not determined.[346] The unusual chalconaringenin 2′,4′,4-tri-*O*-β-glucopyranoside (**376**) is a major constituent of the leaves of many species of *Asarum* sensu lato (Aristolochiaceae).[347] In a survey of 75 taxa it was detected in species belonging to the *Asiasarum*, *Geotaenium* and *Heterotropa* groups, but not in *Asarum* sensu stricto. As a chemical character, its distribution supports Maekawa's classification of the genus *Asarum*.[347] Extracts of the flowers of *Coreopsis tinctoria* (Asteraceae) yielded okanin 4′-*O*-(6-*O*-malonyl-β-glucopyranoside) (**377**), together with okanin 4′-*O*-β-glucopyranoside.[348] The corresponding acetyl analogue was previously described from the flowers of *Bidens pilosa* (Asteraceae),[349] but probably arises by decarboxylation of the malonyl derivative.

Luxenchalcone (**378**) is an *O*-linked dimer of isoliquiritigenin and butein isolated from extracts of the leaves and branches of *Luxembergia octandra* (Ochnaceae), a small tree of southeastern Brazil.[350] The constituent chalcones are linked by a C–O–C bond from C-3 of butein to C-4 of isoliquiritigenin. More unusual in structural terms is a C–C linked dimer of 2′-hydroxy-4-



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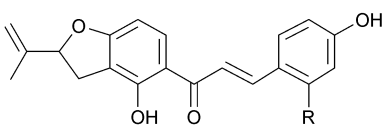
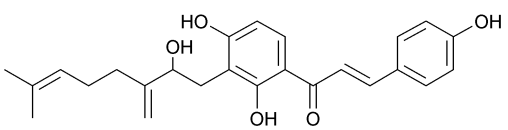


361 R = H; Artonin ZA
362 R = OH, Artonin ZB



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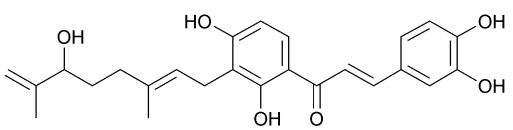

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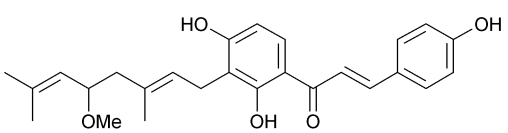

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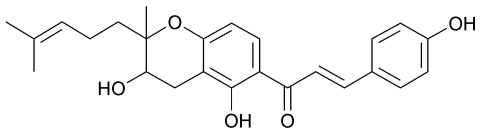

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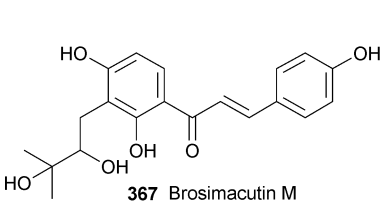
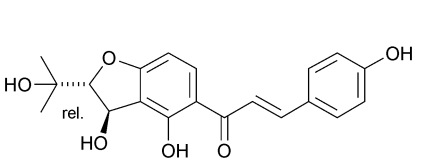
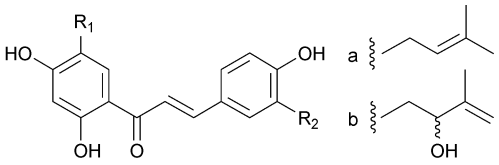


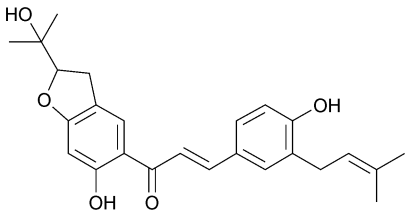
367 Brosimacutin M



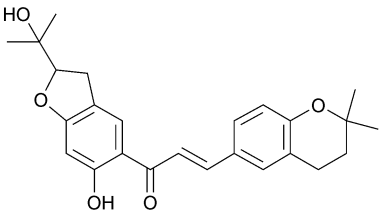
368 Brosimacutin G



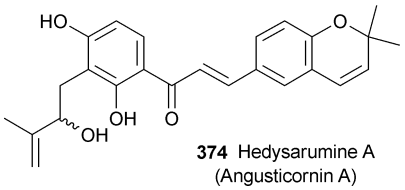
369 R_1 = b, R_2 = a; Bartericin A
370 R_1 = a, R_2 = b; Bartericin D
371 R_1 = R_2 = b; Angusticornin B



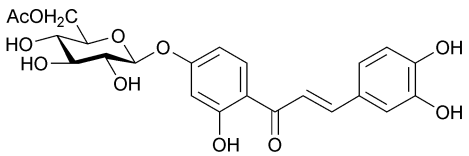
372 Bartericin B



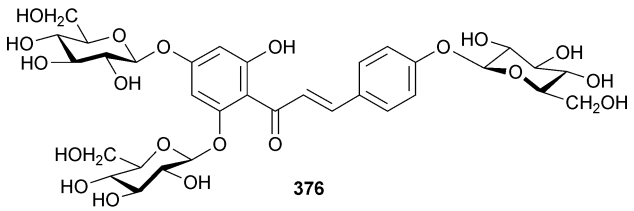
373 Bartericin C



374 Hedysarumine A
(Angusticornin A)



375 Bidenoside G



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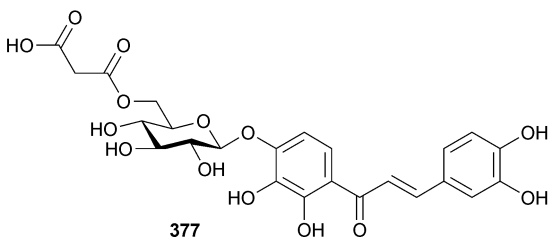
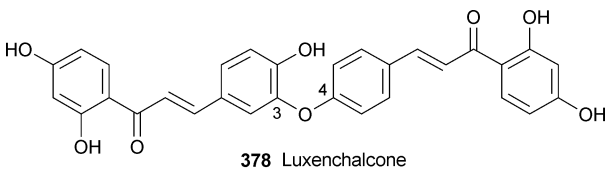
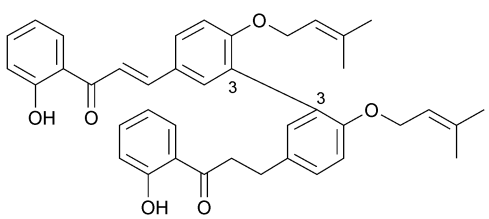


377

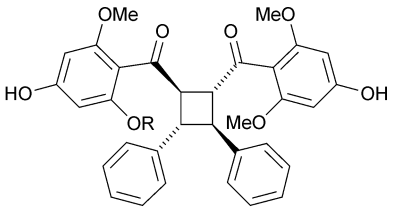
prenyloxychalcone and its dihydrochalcone analogue (**379**), isolated from bark material of *Gentiana lutea* (Gentianaceae).[351] These components, neither of which is known as a natural product, are linked through C-3 of their B-rings. Acid hydrolysis of **379** afforded the equivalent dimer of 2′,4-dihydroxychalcone and its dihydrochalcone analogue. This product was more effective as a monoamine oxidase (MAO) inhibitor than **379**; however both dimers showed greater inhibition of the B-isoenzyme (MAO-B) than the A (MAO-A).[351] Three new cyclobutane derivatives formed from chalcones have been reported (**380**–**382**),[352,353] all of which are examples of so-called 'head-to-head' (truxinic-type) dimers. Compounds **380** and **381** were obtained from dichloromethane extracts of the aerial parts of *Combretum albopunctatum* (Combretaceae), together with cardamonin (2′,4′-dihydroxy-6′-methoxychalcone), one of the monomeric constituents of **380**. The lack of a dimer originating from two molecules of cardamonin led Katerere *et al.* to suggest that **380** might be formed from 2′,6′-dimethoxy-4′-hydroxychalcone followed by demethylation of one chalcone unit.[352] An X-ray crystal structure solved for **381** confirmed the identity and relative configuration of this dimer of 2′,6′-dimethoxy-4′-hydroxychalcone.[352] The isoliquiritigenin dimer, **382**, was isolated from acetone extracts of the roots of *Agapanthus africanus* (Alliaceae).[353] Debate continues as to whether these dimers are of biogenetic origin (suggested by their optical rotation values), or artefacts produced by photochemical cycloaddition reactions. Dimerisation of chalcone monomers may also proceed with inclusion of an oxygen atom to give substituted tetrahydrofurans such as lophirone L (**383**), a constituent of the root bark of *Ochna squarrosa* (Ochnaceae).[61] Derived from isoliquiritigenin, this dimer is isomeric with lophirones F and G, found previously in the stem bark of *Lophira lanceolata* (Ochnaceae).[354] An unusual symmetrical tetramer (ridiculuflavonylchalcone A, **384**) comprising two *O*-linked chalcone–flavone dimers has been isolated from the leaves of *Aristolochia ridicula* (Aristolochiaceae),[355] a species from which similar compounds have been reported.[356] The constituents of each dimeric unit are 2′,4′-dihydroxy-6′,4-dimethoxychalcone (chalconaringenin 6′,4-dimethyl ether) and 5,7,4′-trihydroxy-3′-methoxyflavone (chrysoeriol).



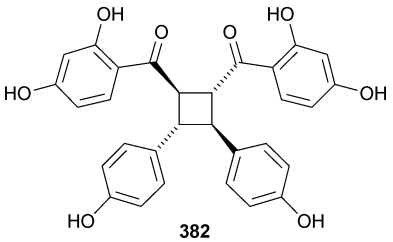
378 Luxenchalcone



379



380 R = H
381 R = Me



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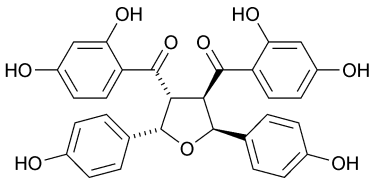
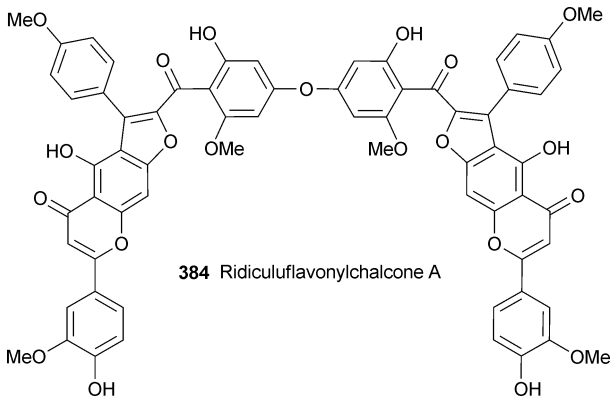


383 Lophirone L



384 Ridiculuflavonylchalcone A

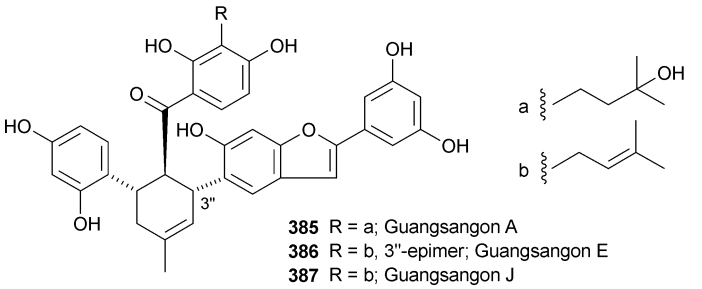
Diels–Alder adducts in which chalcones are the dienophile component, and less commonly the diene (as dehydroprenylated chalcones), are found in several plant families, notably the Moraceae. Twenty-one new examples (**385–404**, **406**)[357–362] have been reported from two species in the genus *Morus* (mulberry trees), *M. macroura* (guangsangon series) and *M. mongolica* (mongolicin series). These are listed in Table 4, which illustrates the range of flavonoids and other phenolics that constitute the

Table 4 New Diels–Alder adducts of chalcones reported in the period 2004–2006

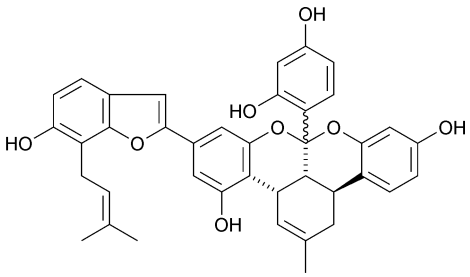
No.	Compound [a]	Diene [b]	Dienophile (chalcone) [c]
		2-Arylbenzofuran	
385	Guangsangon A	6,3′,5′-triOH, 5-MBD	2′,4′,2,4-tetraOH, 3′-(3-hydroxy-3-methylbutyl)
386	Guangsangon E	6,3′,5′-triOH, 5-MBD	2′,4′,2,4-tetraOH, 3′-prenyl
387	Guangsangon J	6,3′,5′-triOH, 5-MBD	2′,4′,2,4-tetraOH, 3′-prenyl
388	Mongolicin A	6,3′,5′-triOH, 7-prenyl, 4′-MBD	2′,4′,2,4-tetraOH
389	Mongolicin B	6,3′,5′-triOH, 4′-MBD	2′,4′,2,4-tetraOH
390	Mongolicin C	6,3′,5′-triOH, 4′-MBD	2′,4′,2,4-tetraOH
391	Mongolicin F	6,3′,5′-triOH, 4′-MBD	2′,4′,2,4-tetraOH, 3′-prenyl (chalcomoracin epimer)
		Benzaldehyde	
392	Guangsangon L	2,4-diOH, 5-MBD	2′,4′,2,4-tetraOH
		Chalcone	
393	Guangsangon C	2′,4′,2,4-tetraOH, 5-MBD	2′,4′,2,4-tetraOH
		Dihydrochalcone	
394	Mongolicin G	2′,4′,2,4-tetraOH, 3′-MBD	2′,4′,2,4-tetraOH, 3′-prenyl
		Dihydroflavonol	
395	Guangsangon D	(2*R*,3*R*)-3,7,2′-triOH, 5′-MBD	2′,4′,2,4-tetraOH
396	Guangsangon F	(2*R*,3*R*)-3,7,2′-triOH, 5′-MBD	2′,2,4-triOH, 6″,6″-dimethylpyrano[2″,3″:4′,3′]
397	Guangsangon H	(2*R*,3*R*)-3,7,2′-triOH, 5′-MBD	2′,4′,2,4-tetraOH, 3′-prenyl
398	Guangsangon K	(2*R*,3*R*)-3,7,2′,4′-tetraOH, 3′-MBD	2′,4′,2,4-tetraOH
		Flavanone	
399	Guangsangon M	(2*R*)-7,2′,4′-triOH, 5′-MBD	2′,4′,2,4-tetraOH
400	Guangsangon N	(2*S*)-7,2′,4′-triOH, 5′-MBD	2′,4′,2,4-tetraOH
		Flavone	
401	Mongolicin D	5,7,2′,4′-tetraOH, 3-prenyl, 8-MBD	2′,4′,4-triOH, 3′-prenyl
		Flavonol	
402	Guangsangon G	3,7,4′-triOH, 3′-MBD	2′,4′,2,4-tetraOH
403	Guangsangon I	3,7,2′,4′-tetraOH, 3′-MBD	2′,4′,2,4-tetraOH
404	Guangsangon O	3,7,2′,4′-tetraOH, 3′-MBD	2′,4′,2,4-tetraOH (epimer of I)
		Monoterpene	
405	Panduratin C	β-ocimene	2′,4′,4-triOH, 6′-OMe
		Stilbene	
406	Guangsangon B	4,3′,5′-triOH, 3-MBD	2′,4′,2,4-tetraOH

[a] Sources: Guangsangons A–E,[357] F–J,[358] K–N[359] and O,[360] stem bark of *Morus macroura* (Moraceae); mongolicins A–D and F,[361] and G,[362] stem and root bark of *Morus mongolica* (Moraceae); panduratin C, rhizome of *Boesenbergia pandurata* (Zingiberaceae).[364] [b] MBD = 3-methylbut-1,3-dienyl, prenyl = 3-methylbut-2-enyl. [c] The parent chalcone (dienophile component of the Diels–Alder reaction) is indicated. Note that the chalcone components of mongolicins A–C are further modified after Diels–Alder adduct formation.

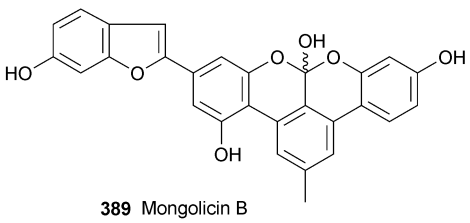
diene component of the adducts. With only one exception (**401**), the dienophile components feature the typical 2′,4′,2,4-*O*-substitution pattern of Moraceae chalcones. Where prenylation occurs, this is invariably at C-3′ of the A-ring. The 2-arylbenzofuran dienes of the guangsangon (**385–387**) and mongolicin series (**388–391**) are characterised by A- and B-ring dehydroprenylation (3-methylbut-1,3-dienyl substitution), respectively. Among flavonoid dienes, 5-deoxy compounds predominate, the only exception being the flavone component of mongolicin D (**401**).[361] Within the guangsangon series, most compounds showed better antioxidant activity than vitamin E in assays to measure the inhibition of malondialdehyde production.[358–360] Guangsangons A, B, D and H–J also exhibited moderate anti-inflammatory activity.[357,358] The ^{1}H NMR spectra of guangsangons A–N in acetone-d_6 at 25 °C are subject to exchange broadening of the resonances corresponding to the methylcyclohexene ring, a phenomenon interpreted in terms of conformational isomerism.[357–359] Dai *et al.* used variable temperature studies with DMSO-d_6 as solvent to extract the required coupling constants from the spectra.[357–359] These data, together with chiroptical measurements (optical rotation and CD), allowed assignment of absolute configuration based on correlations with similar compounds in the literature.



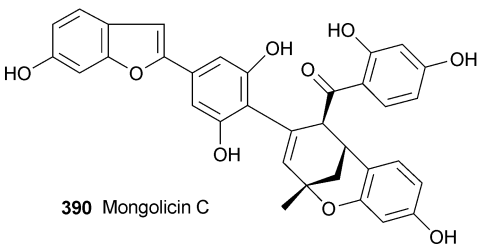
385 R = a; Guangsangon A
386 R = b, 3″-epimer; Guangsangon E
387 R = b; Guangsangon J



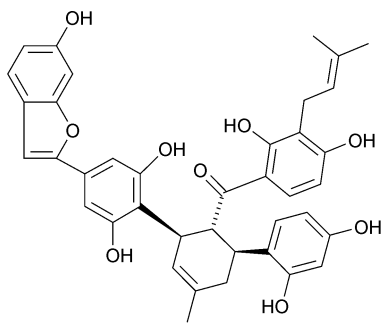
388 Mongolicin A



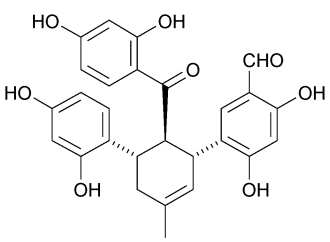
389 Mongolicin B



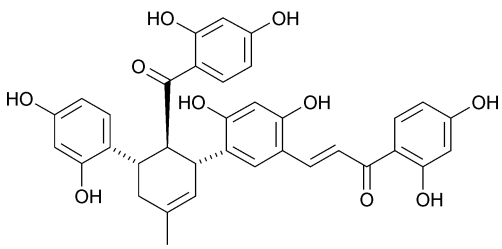
390 Mongolicin C



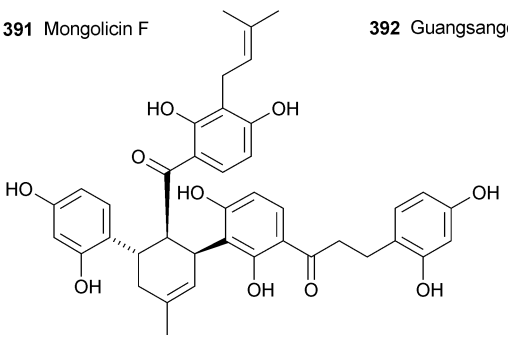
391 Mongolicin F



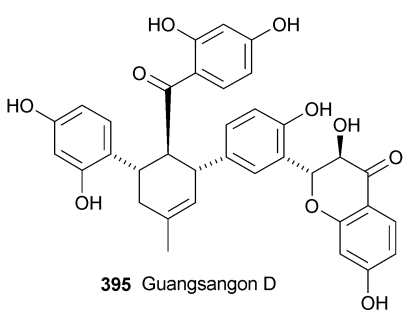
392 Guangsangon L



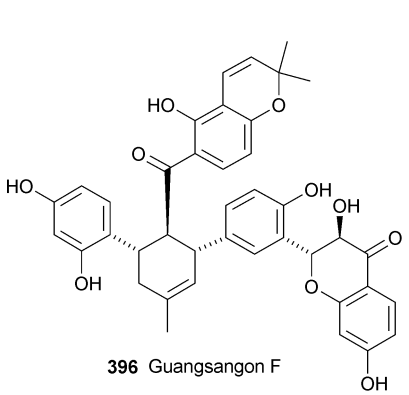
393 Guangsangon C



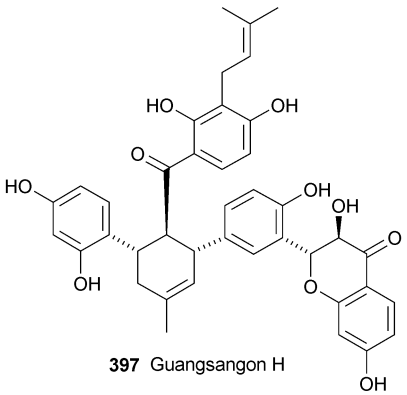
394 Mongolicin G



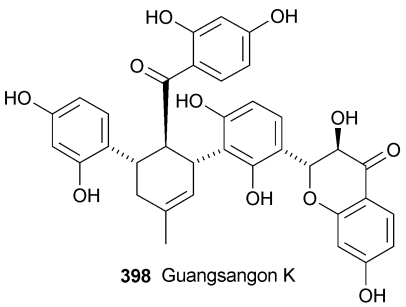
395 Guangsangon D



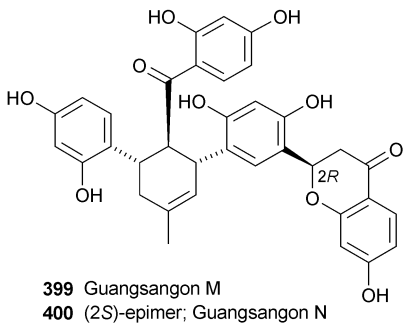
396 Guangsangon F



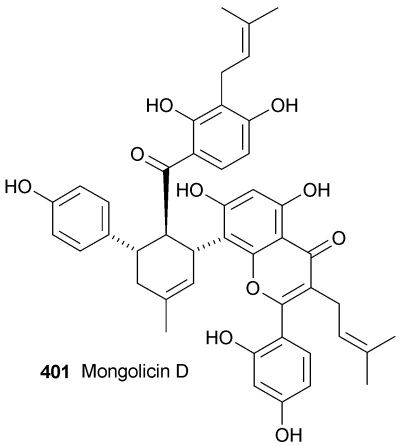
397 Guangsangon H



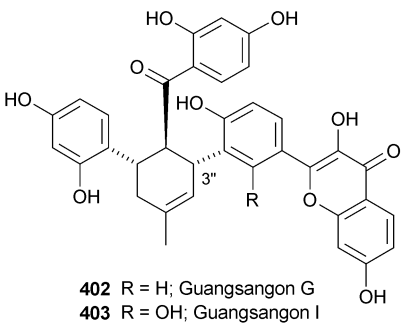
398 Guangsangon K



399 Guangsangon M
400 (2*S*)-epimer; Guangsangon N



401 Mongolicin D

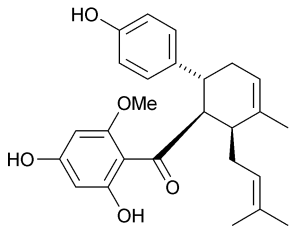


402 R = H; Guangsangon G
403 R = OH; Guangsangon I
404 R = OH, 3"-epimer; Guangsangon O

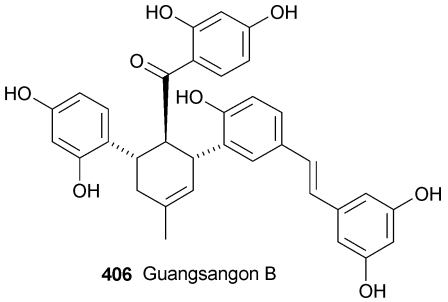
The modification of chalcone-derived Diels–Alder adducts, for example by additional cyclisation reactions, leads to structurally more complex derivatives, as illustrated by mongolicins A–C (**388–390**).[361] In the case of mongolicin B (**389**), the A-ring of the original chalcone dienophile component has been lost, and the methylcyclohexene ring aromatised. Taken out of context, the chalcone origins of this compound are not immediately obvious. Mongolicin F (**391**) co-occurs with chalcomoracin, an epimeric form known from *Morus alba* (Moraceae).[363] Kang *et al.* reported that mongolicins A (**388**) and F (**391**) show antioxidant activity, and C (**390**) shows potent anti-inflammatory activity.[361]

Panduratin C (**405**) represents the only entry in Table 4 from a plant family other than the Moraceae. It is an adduct of helichrysetin (2′,4′,4-trihydroxy-6′-methoxychalcone) and β-ocimene, and was obtained from MeOH extracts of the rhizomes of *Boesenbergia pandurata* (Zingiberaceae).[364]

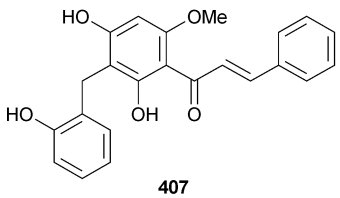
A derivative of cardamonin (2′,4′-dihydroxy-6′-methoxychalcone) characterised by 2-hydroxybenzyl substitution at C-3′ (**407**) has been described by Wirasathien *et al.* from the aerial parts of *Ellipeiopsis cherrevensis* (Annonaceae).[365] This showed cytotoxicity in several cancer cell lines, antiplasmodial activity (*Plasmodium falciparum*) and antibacterial activity (*Mycobacterium tuberculosis*). Although *C*-benzylation is more commonly associated with dihydrochalcones, the related 3′-(2,6-dihydroxybenzyl) derivative of cardamonin is present in *Desmos chinensis*, another species in the Annonaceae.[366] Until recently, diarylheptanoid conjugates of chalcones were known only from *Alpinia blepharocalyx* (Zingiberaceae).[308] However, three examples (**408–410**) have now been isolated from MeOH extracts of the rhizomes of *Alpinia pinnanensis*.[367] According to the classification of Kadota *et al.*,[368] alpinnanins A (**408**) and B (**409**) belong to type (i), *i.e.*, acyclic diarylheptanoids with a chalcone at C-7. In this respect they are similar structurally to calyxins B and H, and their epimeric forms (epicalyxins B and H), although the chalcone component of alpinnanins A (**408**) and B (**409**) is cardamonin rather than helichrysetin (2′,4′,4-trihydroxy-6′-



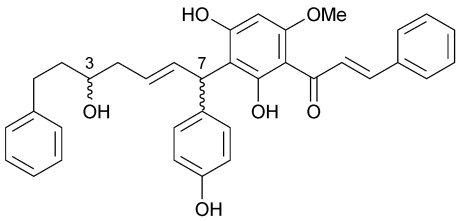
405 Panduratin C



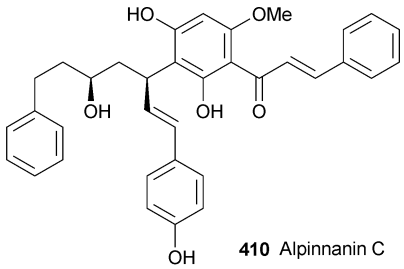
406 Guangsangon B



407



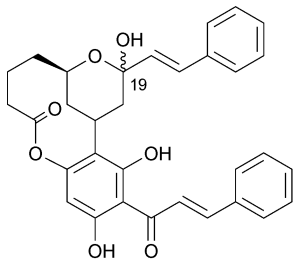
408 (3*R*,7*S*); Alpinnanin A
409 (3*S*,7*S*); Alpinnanin B



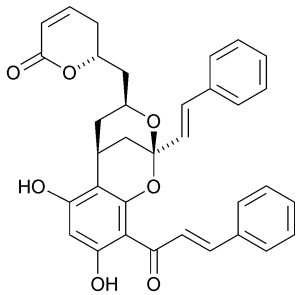
410 Alpinnanin C

methoxychalcone). Alpinnanin C (**410**) is a diarylheptanoid with a chalcone at C-5, and thus belongs with type (ii) compounds such as calyxin A and deoxycalyxin A. Again the chalcone component is cardamonin, which was also found in free form in *A. pinnanensis*.[367]

Unusual chalcone conjugates continue to be found in the Lauraceae, as illustrated by kurzichalcolactone B (**411**) (an epimer of kurzichalcolactone A) and obochalcolactone (**412**), two new constituents from the trunk bark of *Cryptocarya obovata*, a tropical tree known as the pepperberry.[369] Obochalcolactone (**412**) showed cytotoxicity ($IC_{50} = 5$ μM) in the KB cell line. Biosynthetic pathways have been proposed for the formation of kurzichalcolactone B (**411**) and obochalcolactone (**412**). In both cases, the participating chalcone is 2′,4′,6′-trihydroxychalcone, which was also isolated from *C. obovata*.[369] Acetone extracts of kamala, a red-coloured exudate found on the granular hairs of fruits of the kamala tree, *Mallotus philippensis* (Euphorbiaceae), yielded kamalachalcones C (**413**) and D (**414**), two chalcone conjugates characterised by fused benzopyran rings. Furusawa *et al.* suggest that kamalachalcone D (**414**) may arise by condensation of rottlerin (a known constituent of the kamala exudate), an acetylated benzopyran and a pyranochalcone; however, the actual biosynthetic pathway is unknown at present.[370]



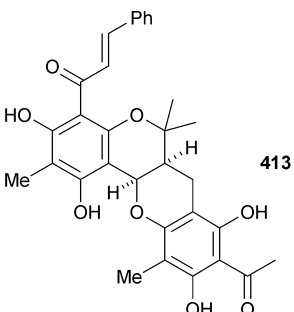
411 Kurzichalcolactone B



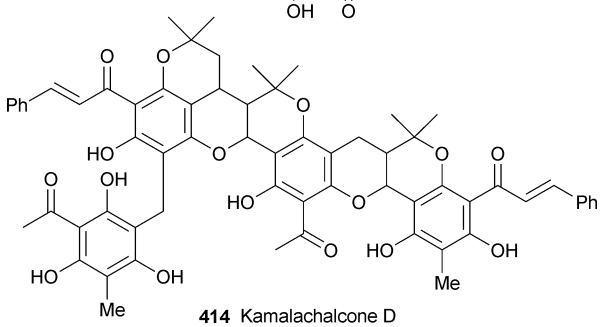
412 Obochalcolactone

6 Dihydrochalcones

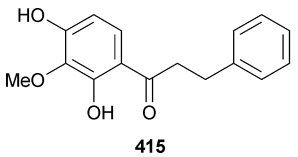
Two new dihydrochalcones with a previously undescribed 2′,3′,4′-tri-*O*-substitution pattern in the A-ring have been isolated from MeOH extracts of the leaves of *Muntingia calabura* (Tiliaceae).[371] Although 2′,4′-dihydroxy-3′-methoxydihydrochalcone (**415**) showed cytotoxicity in a P-388 cell line ($IC_{50} = 16.7 \pm 1.8$ μg ml^{-1}), it was more than 50 times less active than its chalcone equivalent, larrein ($IC_{50} = 0.30 \pm 0.03$ μg ml^{-1}). In contrast, β-hydroxylation had little effect on the cytotoxicity, with 2′,4′, β-trihydroxy-3′-methoxydihydrochalcone (**416**) returning an IC_{50} value of 11.1 ± 1.0 μg ml^{-1} in the same assay.[371] EtOH extracts of the aerial parts of *Artemisia dracunculus* (Asteraceae) with aldose reductase (ALR2) inhibitory activity yielded 2′,4′-dihydroxy-4-methoxydihydrochalcone (**417**) on bioassay guided fractionation.[372] Levels of inhibition were comparable to those of the positive control, quercitrin (quercetin 3-*O*-rhamnoside). Inhibitors of ALR2 are sought for the management of diabetes-associated conditions such as sorbitol accumulation in eye and nerve cells, a consequence of excess glucose production (the enzyme converts blood sugar to sorbitol with NADPH as cofactor).[372] An unusual α-hydroxymethyl substituted dihydrochalcone **418** has been reported by López *et al.* from the leaves of *Polygonum ferrugineum* (Polygonaceae). The corresponding homoisoflavanone (ring-closed form) was also obtained.[373]



413 Kamalachalcone C



414 Kamalachalcone D



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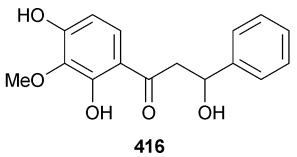

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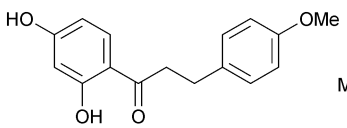

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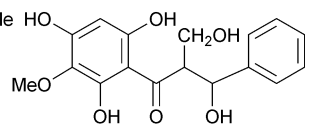
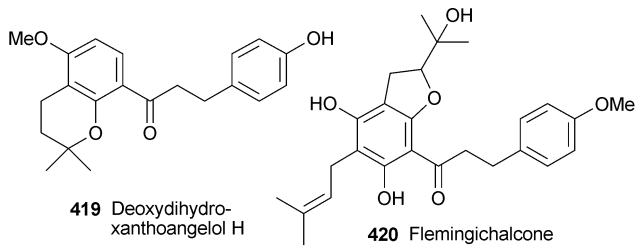


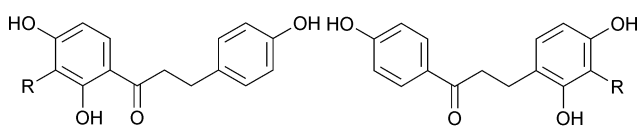
418

Deoxydihydroxanthoangelol H (**419**) is a new prenylated dihydrochalcone obtained from stem exudates of the perennial herb *Angelica keiskei* (Apiaceae), a native species of eastern Asia and Japan used in traditional medicine. The main constituents of this plant are chalcones and coumarins.[318] EtOH extracts of the aerial parts of *Flemingia macrophylla* (Leguminosae) afforded flemingichalcone (**420**), which is characterised by diprenylation in the A-ring.[374] The isomeric brosimacutins H (**421**) and I (**422**) represent a 3′-(2,3-dihydroxy-3-methylbutyl)-substituted dihydrochalcone and its retrodihydrochalcone equivalent, respectively.[342] Although reported in 2002, these compounds were not recorded in previous reviews.[4,308] Both are constituents of the bark of *Brosimum acutifolium* (Moraceae), which also yielded the prenylated chalcones, brosimacutins G (**368**) and M (**367**). New dihydrochalcones continue to be found in the Rutaceae, including two geranyl-substituted derivatives (**423**, **424**) from the leaves of *Esenbeckia grandiflora* subsp. *brevipetiolata*.[375] Earlier work on subsp. *grandiflora* yielded dihydrochalcones with 2′,4′,6′,3,4- rather than 2′,4′,6′,4-*O*-substitution patterns.[376] Dihydroglychalcone A (**425**), obtained from the leaves of *Glycosmis chlorosperma* (Rutaceae), is characterised by dimethylpyrano substitution of the A-ring.[377]



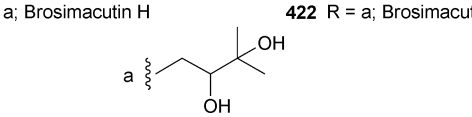
419 Deoxydihydroxanthoangelol H

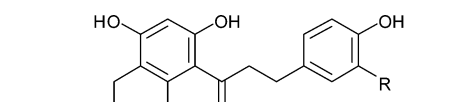
420 Flemingichalcone



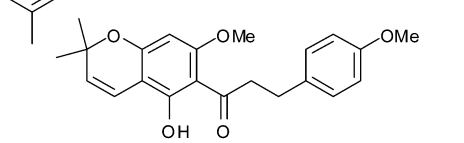
421 R = a; Brosimacutin H

422 R = a; Brosimacutin I



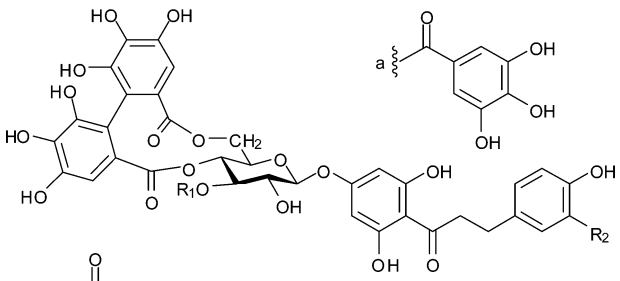


423 R = a
424 R = H

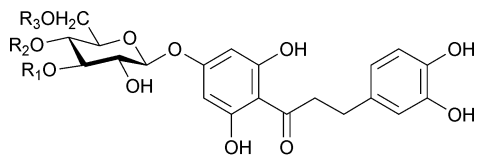


425 Dihydroglychalcone A

The number of dihydrochalcone glycosides reported in the literature has increased significantly, with 13 new examples in 2004–2006 compared to only 12 for 1992–2003.[308] MeOH extracts of fresh aerial parts of the parasitic plant *Balanophora tobiracola* (Balanophoraceae), yielded 7 dihydrochalcone glucosides acylated with caffeic, gallic and (*S*)-hexahydroxydiphenolic acids in various combinations (**426–432**).[378] Of these, **426–429** and **432** showed greater activity than the control, epigallocatechin 3-gallate, in assays for α-glucosidase inhibition. Prior to the discovery of **426–429**, only two (4,6-*O*,*O*-(*S*)-hexahydroxydiphenoyl)-β-glucopyranosides of dihydrochalcones had been reported (thonningianins A and B), both as 4′-*O*-glycosides of 2′,4′,6′-trihydroxydihydrochalcone. These occur in the roots of *Thonningia sanguinea*, which also belongs to the Balanophoraceae.[379] In contrast, neither dihydrochalcone glycosides nor their acylated analogues were found in *Balonophora japonica* Makino, a species more closely related to *B. tobiracola*.[378]



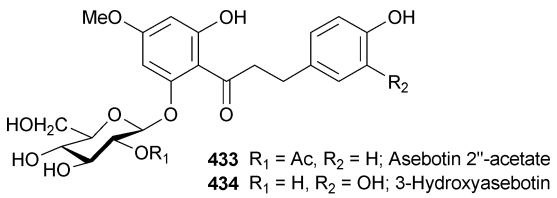
426 R_1 = a, R_2 = H
427 R_1 = H, R_2 = OH
428 R_1 = a, R_2 = OH
429 R_1 = b, R_2 = OH



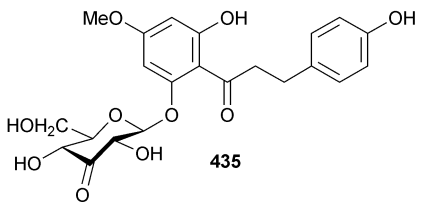
430 R_1 = R_2 = H, R_3 = a
431 R_1 = R_2 = a, R_3 = H
432 R_1 = H, R_2 = R_3 = a

The leaves of *Pieris japonica* (Ericaceae) are a recently identified source of dihydrochalcones, with aglycones, glycosides and dimers characterised to date.[380] The glycosides comprise 4 new examples (**433–436**) together with phloridzin and asebotin (the 2′-*O*-β-glucopyranosides of 2′,4′,6′,4-tetrahydroxy- and 2′,6′,4-trihydroxy-4′-methoxydihydrochalcone, respectively). X-Ray crystallography was used to confirm the structure of 3-hydroxyasebotin (**434**), a compound which significantly inhibited the proliferation of murine T cells.[380] The keto-glycoside **435** is a 2′-*O*-β-ribohexo-3-ulopyranoside of asebogenin (2′,6′,4-trihydroxy-4′-methoxydihydrochalcone), and the first chalcone or dihydrochalcone glycoside reported to contain this sugar. The most remarkable feature of the diglucoside **436** is its unusual 3′,4′,5′-*O*-substitution pattern in the A-ring. At present, the corresponding aglycone is unknown. The leaves of a recently discovered species, *Symplocos vacciniifolia* (Symplocaceae), are used as a sweetener in the northern Guangdong province of China, a property attributed to the presence of a dihydrochalcone glycoside, trilobatin.[381] MeOH extracts of the leaves also yielded vacciniifolin (**437**), the 4′-*O*-β-glucopyranoside of

2′,4′,3,4-tetrahydroxydihydrochalcone, and the known dihydrochalcone glycosides, confusoside and sieboldin.[381] The leaves of the South African shrub *Aspalathus linearis* (Leguminosae), which are used to make rooibos tea, also contain dihydrochalcones, notably the *C*-glycosides, nothofagin and aspalathin. The structure of aspalalinin (**438**), a novel cyclised analogue of aspalathin, was confirmed by X-ray crystallography.[382] This compound was isolated from MeOH extracts of dried leaves of *A. linearis* obtained under refluxing conditions, and may therefore be artefactual in origin.



433 R_1 = Ac, R_2 = H; Asebotin 2''-acetate
434 R_1 = H, R_2 = OH; 3-Hydroxyasebotin



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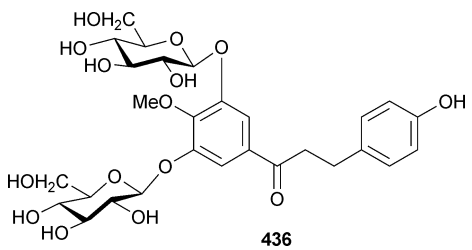

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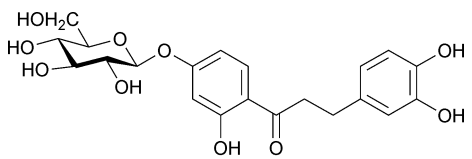
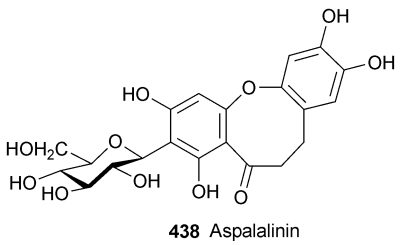
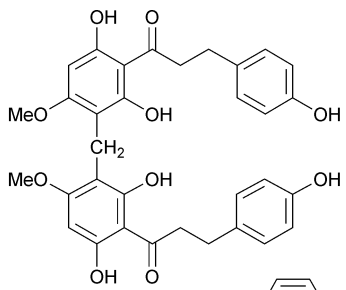


437 Vacciniifolin

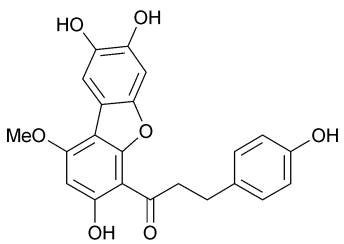


438 Aspalalinin

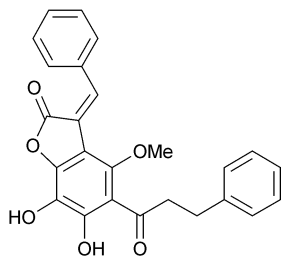
In addition to dihydrochalcone glycosides (**433–436**), the leaves of *Pieris japonica* (Ericaceae) contain pierotins A (**439**) and B (**440**), the former of which comprises two molecules of 2′,6′,4-trihydroxy-4′-methoxydihydrochalcone (asebogenin) linked by a methylene bridge between C-3′ of their A-rings.[380] A similar dimer, but of 2′,6′-dihydroxy-4′-methoxydihydrochalcone, was reported previously from *Piper aduncum* (Piperaceae) as piperaduncin C.[383] Pierotin B (**440**) is one of a number of compounds loosely classified as dihydrochalcone conjugates, which are often of uncertain biogenetic origin. In the case of pierotin B (**440**) there is a clear structural connection to asebogenin, in common with the *Pieris japonica* dihydrochalcones, **433**, **435** and **439**.[380] MeOH extracts of the stems of the climbing shrub *Fissistigma bracteolatum* (Annonaceae) yielded bractelactone (**441**), which Lan *et al.* considered to be either a dihydrochalcone–cinnamic acid conjugate, or the degradation product of a dimer.[384] This compound inhibited NO generation by macrophage cells (RAW 264.7) stimulated by lipopolysaccharide. The IC_{50} value was 1.55 ± 0.42 μg ml^{-1}, and no cytotoxicity was reported.[384] Two new *C*-benzylated dihydrochalcones, isochamuvaritin (**442**) and acumitin (**443**), have been described by Ichimaru *et al.* as constituents of the roots of *Uvaria acuminata* (Annonaceae).[385] Both compounds were cytotoxic towards human promyelocytic leukemia HL-60 cells. The occurrence of a *C*-benzylated derivative (**444**) of 2′,4′-dihydroxy-6′-methoxydihydrochalcone (uvangoletin) in *Sarcandra glabra* (Chloranthaceae) is of interest,[386] as previous reports of *C*-benzylated dihydrochalcones are restricted to the Annonaceae.[308,387]



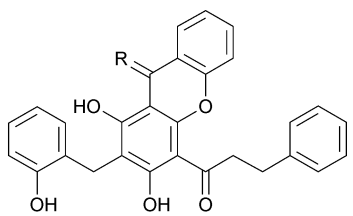
439 Pierotin A



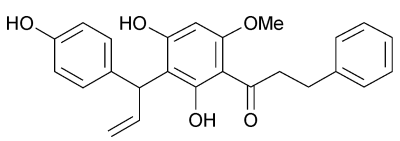
440 Pierotin B



441 Bractelactone



442 R = H_2; Isochamuvaritin
443 R = O; Acumitin



444

7 Aurones

Only a few new examples of this uncommon class of flavonoids were reported in the 2004–2006 period; however, progress has been made in understanding their biosynthesis,[388–390] which is crucial to the production of yellow and orange flower colour in some species of the Asteraceae and other plant families.[308] The key enzyme is aureusidin synthase (AmAS1), which was first characterised in 2000 following work on the yellow flower colour of the snapdragon, *Antirrhinum majus* (Scrophulariaceae).[391] The precursors of aurones are chalcones, as demonstrated by *in vitro* studies with AmAS1 in which the conversion of chalconaringenin (2′,4′,6′,4-tetrahydroxychalcone) to aureusidin (4,6,3′,4′-tetrahydroxyaurone) and bracteatin (4,6,3′,4′,5′-pentahydroxyaurone) was observed. Similarly, 2′,4′,6′,3,4-pentahydroxychalcone can be converted to bracteatin, and the 4′-*O*-glucosides of the two chalcones give the 6-*O*-glucosides of the corresponding aurones. However, it has now been shown that transgenic flowers in which the *AmAS1* gene is expressed do not produce aurones.[388] In fact, chalcone 4′-*O*-glucosides are the true substrates of AmAS1 *in vivo*, rather than the corresponding chalcone aglycones. Thus on coexpression of *AmAS1* with *Am4′CGT*, the gene encoding chalcone 4′-*O*-glucosyltransferase, aureusidin 6-*O*-glucoside accumulates in transgenic flowers. This glucosyltransferase enzyme is the first to be found for chalcones.[388] The chalcones undergo 4′-*O*-glycosylation in the cytoplasm, and are then transported to the vacuole,[389] where they are transformed to aurone 6-*O*-glycosides by AmAS1 (Fig. 2). In an experiment that should attract the interest of plant breeders and horticulturalists, Ono *et al.* demonstrated the introduction of yellow flower colour to *Torenia hybrida* cv. 'Summer Wave Blue', which normally has blue flowers.[388] This required anthocyanin biosynthesis to be down-regulated as well as coexpression of the *AmAS1* and *Am4′CGT* genes.

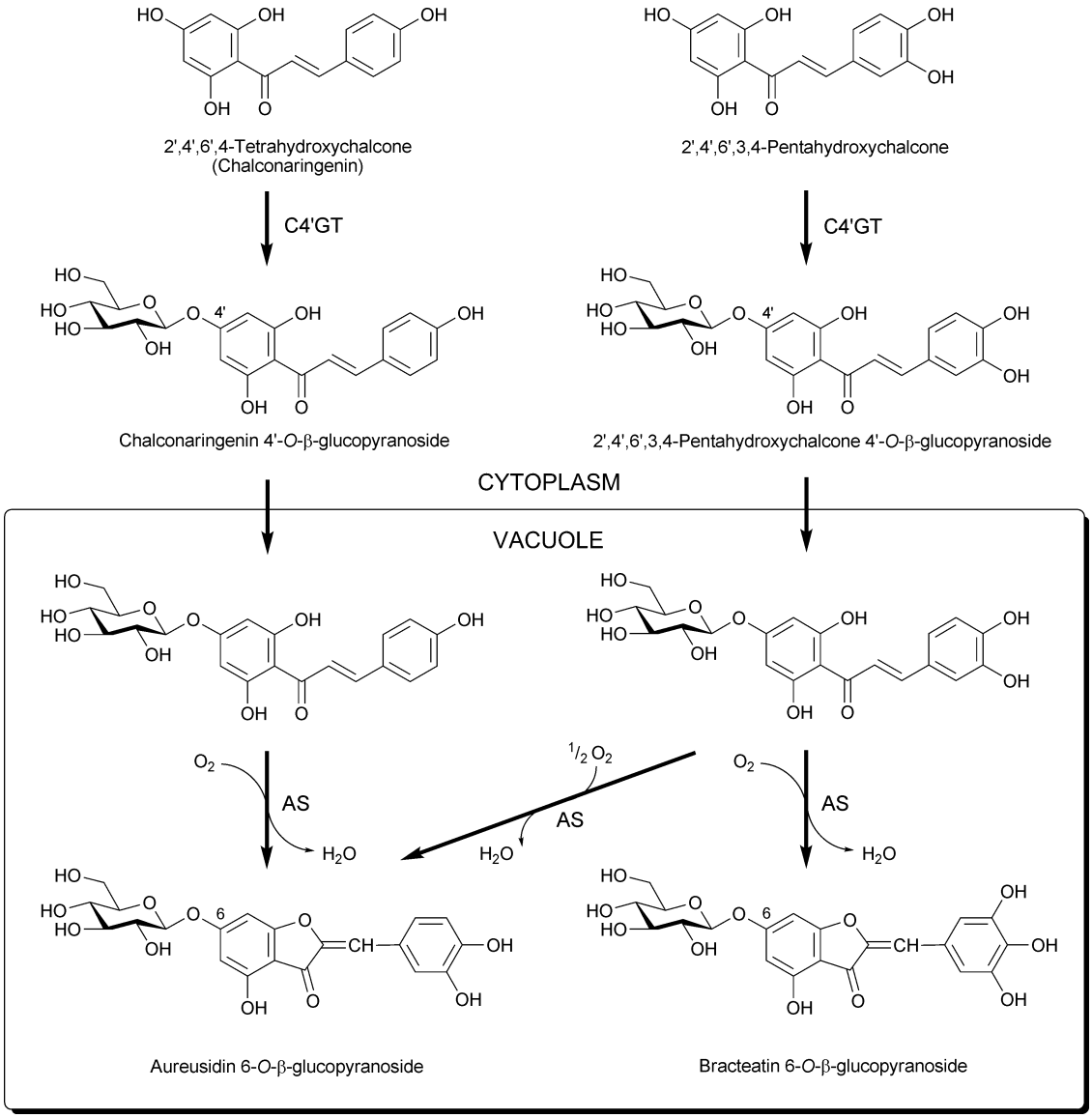
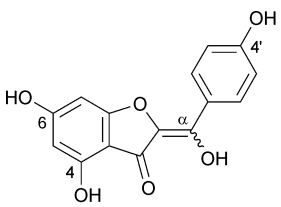


Fig. 2 Biosynthesis of aurone glycosides based on studies of the snapdragon, *Antirrhinum majus* (Scrophulariaceae). AS, aureusidin synthase (AmAS1); C4′GT, chalcone 4′-glucosyltransferase (note that C-4′ of chalcones is equivalent to C-6 of aurones).

An α-hydroxyaurone isolated from MeOH extracts of the leaves of *Diospyros melanoxylon* (Ebenaceae) has been identified as 4,6,4′,α-tetrahydroxyaurone (**445**), which was found as a 15 : 85 mixture of *E*- and *Z*-isomers.[392] Aerial parts of *Caragana sinica* (Leguminosae) yielded carasinaurone (**446**), an auronol (2-hydroxy-2-benzylcoumaranone) derivative whose structure was confirmed by X-ray crystallography.[393] The first heptasubstituted aurone has been reported by Ferreira *et al.*, who obtained it in glycosidic form (**447**) from EtOH extracts of the whole plant of *Gomphrena agrestis* (Amaranthaceae).[394] This derivative showed antibacterial activity towards strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. A rare example (**448**) of an auronol glycoside has been isolated by bioassay-guided fractionation of *n*-BuOH extracts of the leaves of *Artocarpus tonkinensis* (Moraceae).[395] Identified as a 4-*O*-β-glucopyranoside of alphitonin (2,4,6,3′,4′-pentahydroxy-2-benzylcoumaranone), this compound exhibited immunosuppressive activity in a lymphocyte stimulation assay. A similar pattern of activity was recorded for the 4-*O*-β-glucopyranoside of maesopsin (2,4,6,4′-tetrahydroxy-2-benzylcoumaranone), which also occurs in this species.[395] Marsuposide (**449**) is the first auronol *C*-glycoside to be reported, and a constituent of the heartwood of *Pterocarpus marsupium* (Leguminosae).[279] In solution it exists as a pair of interconverting C-2 epimers, evidence for which was provided by the exchange cross-peak observed between the H-2 resonances of the two forms in NOESY spectra.[396] Deuterium labelling was used to investigate the exchange mechanism, which proceeds by ring opening to a diketone followed by keto–enol tautomerism.[396] Two *C*-glycosides that are related structurally to marsuposide (**449**) were obtained from the same source, pteroside (**450**) and pteroisoauroside (**451**).[279] These are not aurones (the latter being described as an isoaurone), but their biogenetic relationship to marsuposide (**449**) is clearly of interest.

In 2003, two aurone glycosides described as the 4-*O*-rhamnoside of 4,6-dihydroxy-3′,4′,5′-trimethoxy-7-methylaurone and



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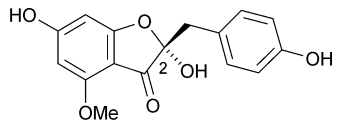
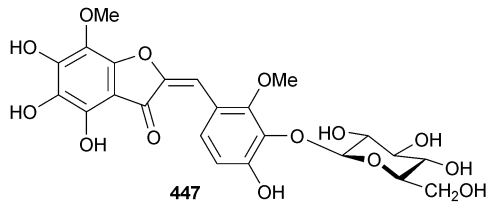


446 Carasinaurone



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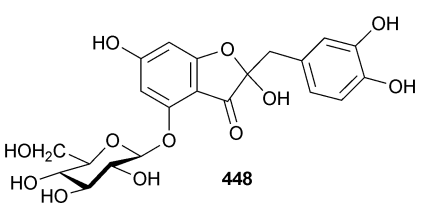

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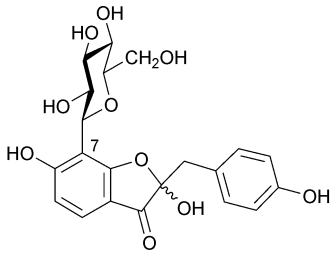
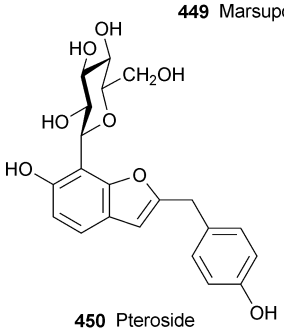
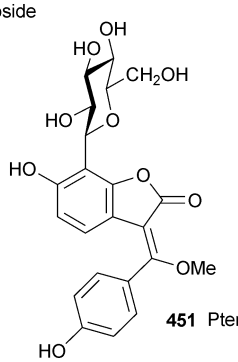


449 Marsuposide



450 Pteroside



451 Pteroisoauroside

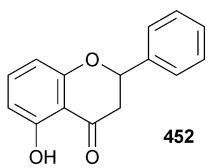
the 4-*O*-neohesperidoside (4-*O*-α-rhamnopyranosyl-(1→2)-β-glucopyranoside) of 4,6,4′-trihydroxyaurone were obtained from EtOH extracts of the heartwood of *Pterocarpus santalinus* (Leguminosae).[397] These identifications have been regarded as preliminary due to the incomplete nature of the NMR data presented for the sugar residues.[308] However, in the following year, a second paper published by different authors described two aurone glycosides from the heartwood of the same species, which, although reproducing the method of the earlier paper in almost every detail, gave the determinations as the 4-*O*-rhamnoside of the isomeric 4,6-dihydroxy-3′,4′,5′-trimethoxy-5-methylaurone, and the 4-*O*-rutinoside (4-*O*-α-rhamnopyranosyl-(1→6)-β-glucopyranoside) of 4,6,4′-trihydroxyaurone, respectively.[398] Comparison of the physical and spectroscopic data for the latter compounds with those published in 2003 reveals a high degree of similarity,[397,398] despite some anomalies, suggesting that the two sets of aurone glycosides may be the same. With respect to the aurone 4-*O*-rhamnoglucosides, the chemical shift values quoted for the anomeric protons of the sugars in ^{1}H NMR spectra ($CDCl_3$) were 4.9–5.1 and 4.9 ppm (Rha H-1), and 5.27 ppm (Glc H-1, both papers), indicating that in each case, the disaccharide was the same, although paradoxically, the values given for Rha CH_3-6 were different (1.3 and 0.92 ppm). Although the weight of evidence from the anomeric proton data favours the neohesperidoside as the correct identification, further investigation is clearly warranted to resolve these discrepancies.

8 Flavanones

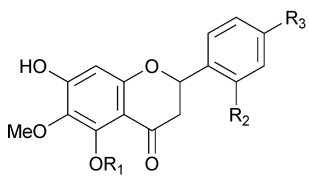
New flavanones published in the 2004–2006 period comprise derivatives characterised by simple patterns of *O*-substitution (OH and OMe) (**452–463**), *C*-methylation (**464–466**), prenylation (**467–501**) and glycosylation (**502–524**). A few examples of what can loosely be described as flavanone conjugates (**525–528**) and protoflavanones (**529–532**) have also been recorded. Methods for the determination of the absolute configuration at C-2 of flavanones were reviewed by Slade and colleagues.[399] In CD

spectra, observation of negative and positive Cotton effects at approximately 270–290 and 320–330 nm allows the 2*S* configuration to be assigned, which is that most commonly found for naturally occurring flavanones.[400] The reverse situation applies to (2*R*)-flavanones. In both cases, ^{1}H NMR spectra reveal that ^3J(H-2,H-3$_{ax}$) is large, indicating that the B-ring at C-2 is equatorial *i.e.* the conformation most favoured on thermodynamic grounds is adopted.[399] It has been assumed therefore, that laevorotatory flavanones will have the 2*S* configuration. As a cautionary note, however, of 34 compounds in the present survey for which absolute configurations were determined by CD, 3 examples of (2*S*)-flavanones with positive $[\alpha]_D$ values (**461**, **462**, **489**) and one (2*R*)-flavanone with a negative $[\alpha]_D$ value (**509**) were recorded.

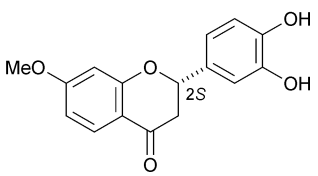
MeOH extracts of the bark of *Gentiana lutea* (Gentianaceae) yielded 5-hydroxyflavanone (**452**),[351] which is only the third mono-*O*-substituted flavanone to be found as a natural product.[400] In assays for monoamine oxidase (MAO) activity, **452** showed greater inhibition of MAO-B (the B-form of the enzyme) than MAO-A.[351] No new di-*O*-substituted flavanones have been reported, but Usman *et al.* obtained the tri-*O*-substituted derivative, 7-hydroxy-5,6-dimethoxyflavanone (**453**), from the tree bark of *Cryptocarya costata* (Lauraceae).[401] Other flavanones with 6-oxygenation in the A-ring include the tetra-*O*-substituted derivatives **454** and **455**, which occur in rhizomes of *Iris germanica* (Iridaceae)[84] and the aerial parts of *Chromolaena odorata* (Asteraceae),[402] respectively (see also **460** and **463**). Hetranthin A (**456**) is a 5-deoxyflavanone with lipoxygenase inhibitory activity isolated from EtOAc extracts of the stems of *Indigofera heterantha* (Leguminosae).[221] Flavonoids lacking *O*-substituents at C-5 are a characteristic feature of the Leguminosae, as is also illustrated by 7,2′,3′,4′-tetramethoxyflavanone (**459**), which was obtained from the whole plant of *Calliandra inermis* (Leguminosae) together with the corresponding 5-deoxyflavone (**7**).[34] A report on 7,3′,5′-trihydroxyflavanone as a new compound from the wood of *Amorpha fruticosa* (Leguminosae)[403] is in error, as its ^{1}H and ^{13}C NMR spectra are identical to those of the well known derivative 7,3′,4′-trihydroxyflavanone (butin).[404]



452

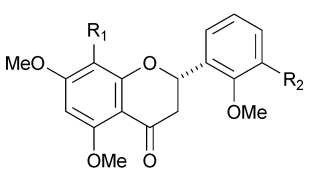


453 R_1 = Me, R_2 = R_3 = H
454 R_1 = R_3 = H, R_2 = OH
455 R_1 = R_2 = H, R_3 = OMe

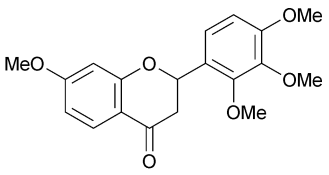


456 Hetranthin A

Flavanones characterised by 2′-oxygenation in the B-ring have a relatively limited distribution, and are particularly associated with the genus *Andrographis* (Acanthaceae), although other sources include the Asteraceae, Iridaceae, Leguminosae and Moraceae.[400] This trend is corroborated by the present survey, with 5,7,8,2′-tetramethoxyflavanone (**457**) isolated from hexane extracts of the whole plant of *Andrographis macrobotrys*,[310] and 5,7,2′,3′-tetramethoxyflavanone (**458**) from *Andrographis paniculata* (whole plant; MeOH extract).[31] Other new 2′-oxygenated flavanones include **454** (Iridaceae), **459** (Leguminosae) and artomunoflavanone (**461**), the latter being isolated from root material of the breadfruit, *Artocarpus communis* (Moraceae).[67] Nubatin (**460**)[405] and persinol (**462**)[406] are penta-*O*-substituted flavanones from the whole plant of *Salvia nubicola* (Lamiaceae) and *Aerva persica* (Amaranthaceae), respectively. Hexa-*O*-substituted flavanones are relatively uncommon, with only 4 entries appearing in a checklist covering the literature to 2003.[400] To these can be added 5,3′-dihydroxy-6,7,8,4′-tetramethoxyflavanone (**463**), a constituent of $CHCl_3$ extracts of the whole plant of *Tillandsia recurvata* (Bromeliaceae).[407]



457 R_1 = OMe, R_2 = H
458 R_1 = H, R_2 = OMe



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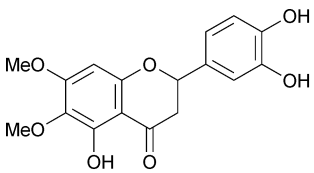
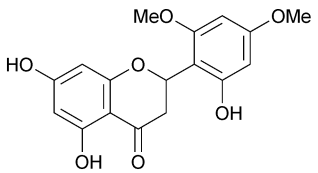
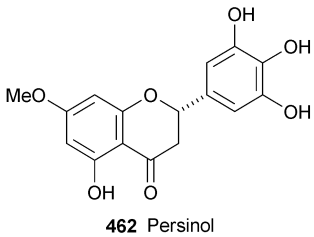


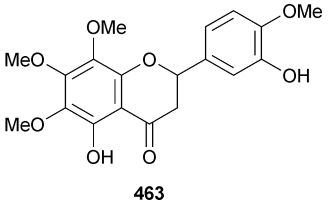
460 Nubatin



461 Artomunoflavanone



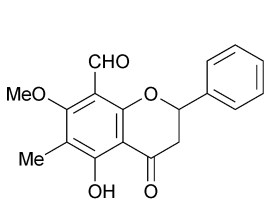
462 Persinol



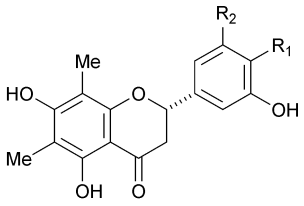
463

The buds of *Cleistocalyx operculatus* (Myrtaceae), a medicinal plant of southern China, yielded 8-formyl-5-hydroxy-7-methoxy-6-methylflavanone (**464**) together with two known derivatives, 8-formyl-5,7-dihydroxy-6-methylflavanone and 7-hydroxy-5-methoxy-6,8-dimethylflavanone (see also **330**).[316] Two di-*C*-methylflavanones (**465**, **466**) isolated from rhizomes of the fern *Dryopteris sublaeta* (Dryopteridaceae) are positional isomers at C-4′ and C-5′ of the B-ring.[408,409] However, the rarely encountered 3′,5′-di-*O*-substitution pattern proposed for the B-ring of **466** merits further investigation. The presence of *C*-methylflavanones in the Myrtaceae and Pteridophyta (ferns) is consistent with previous work on the distribution of these compounds.[400]

Prenylated flavanones continue to represent a significant proportion of the compounds described in this Section, with 35 additional entries (**467–501**) for 2004–2006. More than half of these come from the Leguminosae alone (**472–489**). The potential for structural diversity lies not only in new combinations and substitution patterns for the commonly found C_5 (prenyl)



464

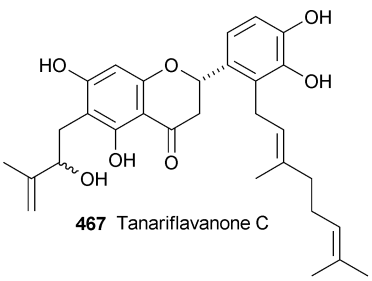


465 R_1 = OMe, R_2 = H
466 R_1 = H, R_2 = OMe

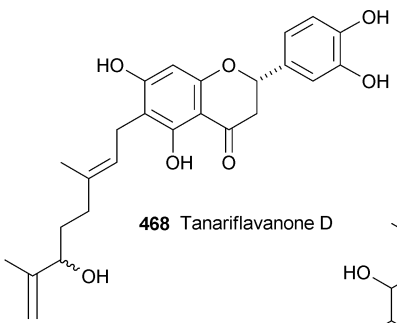
and C_{10} (geranyl, lavandulyl) units, but also in their oxidised and cyclised forms, as the following examples illustrate. $CHCl_3$ extracts of the leaves of *Macaranga tanarius* (Euphorbiaceae), a Thai medicinal plant, are the source of tanariflavanones C (**467**) and D (**468**).[410] From the same genus, leaves of *Macaranga triloba* (Euphorbiaceae) afforded a 3′-geranyl derivative (**469**) of steppogenin (5,7,2′,4′-tetrahydroxyflavanone).[411] Note that in previous work, the related macarangaflavanone A, a 3′-geranyl derivative of naringenin (5,7,4′-trihydroxyflavanone), was obtained from leaves of *Macaranga pleiostemona* (Euphorbiaceae).[412] Analysis of the leaf constituents of *Mallotus apelta* (Euphorbiaceae) revealed the presence of **470** (mallotusin), an unrecorded 6-prenyl derivative of isosakuranetin (5,7-dihydroxy-4′-methoxyflavanone).[413] In addition to new chalcones (**413**, **414**), extracts of kamala (the red-coloured exudate from granular hairs of fruits of the kamala tree, *Mallotus philippensis*), yielded the flavanone, 4′-hydroxyisorottlerin (**471**).[370]

The shrub *Dendrolobium lanceolatum* (Leguminosae) is a species of tropical Asia, the roots of which are used medicinally in Thailand. Two 8,2′-diprenylated flavanones (**472**, **473**) isolated from this source showed moderate activity against a panel of antimalarial, antimycobacterial and cytotoxicity assays.[414] EtOAc extracts with anti-plasmodial activity prepared from stem bark of *Erythrina abyssinica* (Leguminosae) yielded 5-deoxyabyssinin II (**474**), the chalcone **350**, and several known flavonoids.[331] According to bioassay data, these contribute to the activity of the crude extract (the species concerned is used in traditional medicine to treat malaria).[331] Chacha *et al.* later reported erylatissin C (**475**), an isomer of **474**, from the stem wood of *Erythrina latissima* (Leguminosae).[415] Screening for protein tyrosine phosphatase-1B inhibitory activity during bioassay-guided fractionation of EtOAc extracts of root bark from *Erythrina mildbraedii* (Leguminosae) resulted in the isolation of **476**, **477**, and the structurally related chalcone, **351**.[332] A 6-*C*-methyl derivative (**478**) of 8-prenylisosakuranetin has been found in leaves of *Eysenhardtia platycarpa* (Leguminosae).[53] The corresponding 4′-demethyl derivative was previously published from *Eysenhardtia texana*.[416] Hexane extracts of root material from the Mexican endemic *Lonchocarpus yucatanensis* (Leguminosae) afforded the pyranoflavanone **479**.[417] A furanoflavanone (**480**) from the pods of *Millettia erythrocalyx* (Leguminosae) is one of several new furanoflavonoids isolated from this species, a known source of compounds of this type.[57] Many furano- and pyranoflavonoids have been characterised from *Millettia pinnata*, which is more commonly known by its synonym, *Pongamia pinnata* (Leguminosae).[12] Pongamones B (**481**) and C (**482**) are two further derivatives obtained from the stems of this species.[60] The bis(pyrano)flavanone 3-deoxy-MS-II (**483**), occurs in MeOH extracts of the leaves and flowers of the Madagascan endemic *Mundulea chapelieri* (Leguminosae), together with MS-II, the corresponding dihydroflavonol.[418] The latter was first obtained from *Mundulea sericea* (Willd.) A.Chev. (published under the synonym *Mundulea suberosa* (DC.) Benth.).[419] Sophoranodichromane B (**484**) is one of several bis(dihydropyrano)flavonoids found in the roots of *Sophora flavescens* (Leguminosae), a species used in traditional Chinese medicine.[109] Further compounds from the same source are the 8-*C*-lavandulyl derivative, sophoraflavanone K (**485**), and sophoraflavanone L (**486**).[107] A bis(dihydropyrano)flavanone, tonkinochromane A (**487**), is present in roots and rhizomes of *Sophora tonkinensis* (Leguminosae) together with tonkinochromane B (**488**), a likely precursor.[337] Hisham *et al.* reported a rare example of a flavanone substituted by two fused furan rings as (+)-apollineanin (**489**), a constituent of the leaves of *Tephrosia apollinea* (Leguminosae).[420] Similarly modified flavones and chalcones have been found in several species of *Tephrosia*.[24,308] The absolute configuration of **489** was determined using Mosher's method and CD spectroscopy.[420]

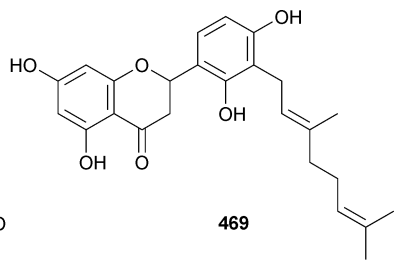
MeOH extracts of the flowers of the neem tree, *Azadirachta indica* (Meliaceae), yielded azharone (**490**), a flavanone



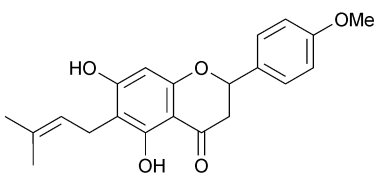
467 Tanariflavanone C



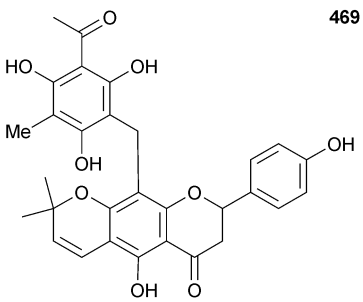
468 Tanariflavanone D



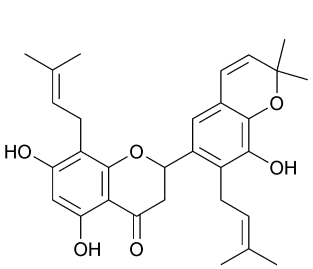
469



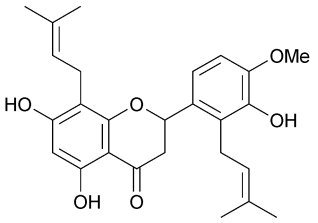
470 Mallotusin



471 4′-Hydroxyisorottlerin



472



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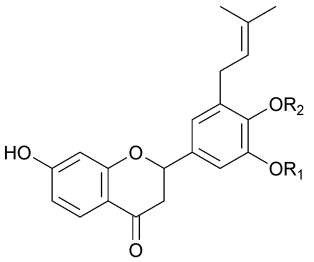
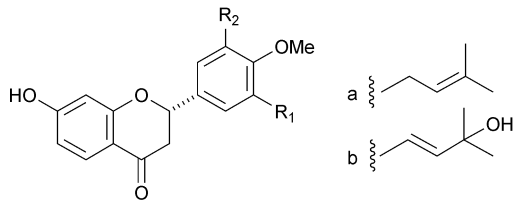
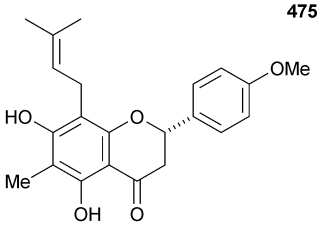


474 R_1 = Me, R_2 = H
475 R_1 = H, R_2 = Me; Erylatissin C



476 R_1 = R_2 = a; Abyssinone IV 4'-methyl ether
477 R_1 = b, R_2 = a



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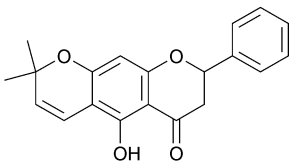

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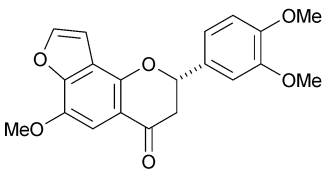

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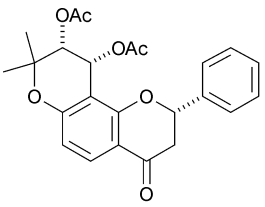
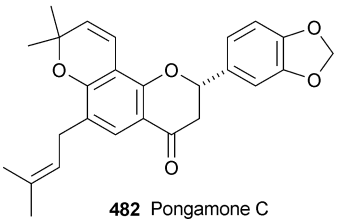
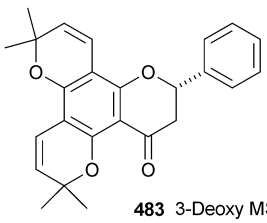


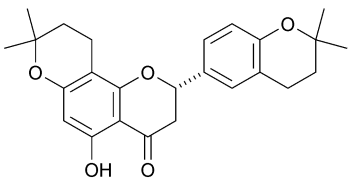
481 Pongamone B



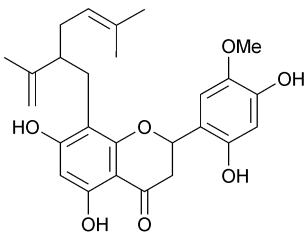
482 Pongamone C



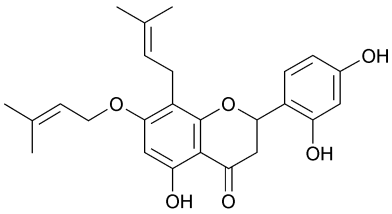
483 3-Deoxy MS-II



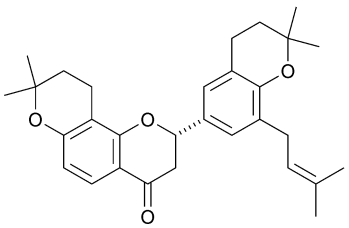
484 Sophoranodichromane B



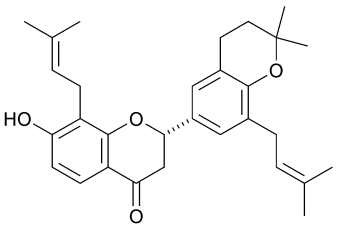
485 Sophoraflavanone K



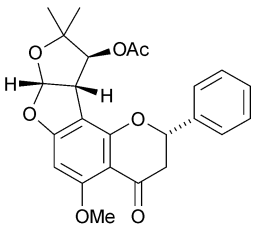
486 Sophoraflavanone L



487 Tonkinochromane A

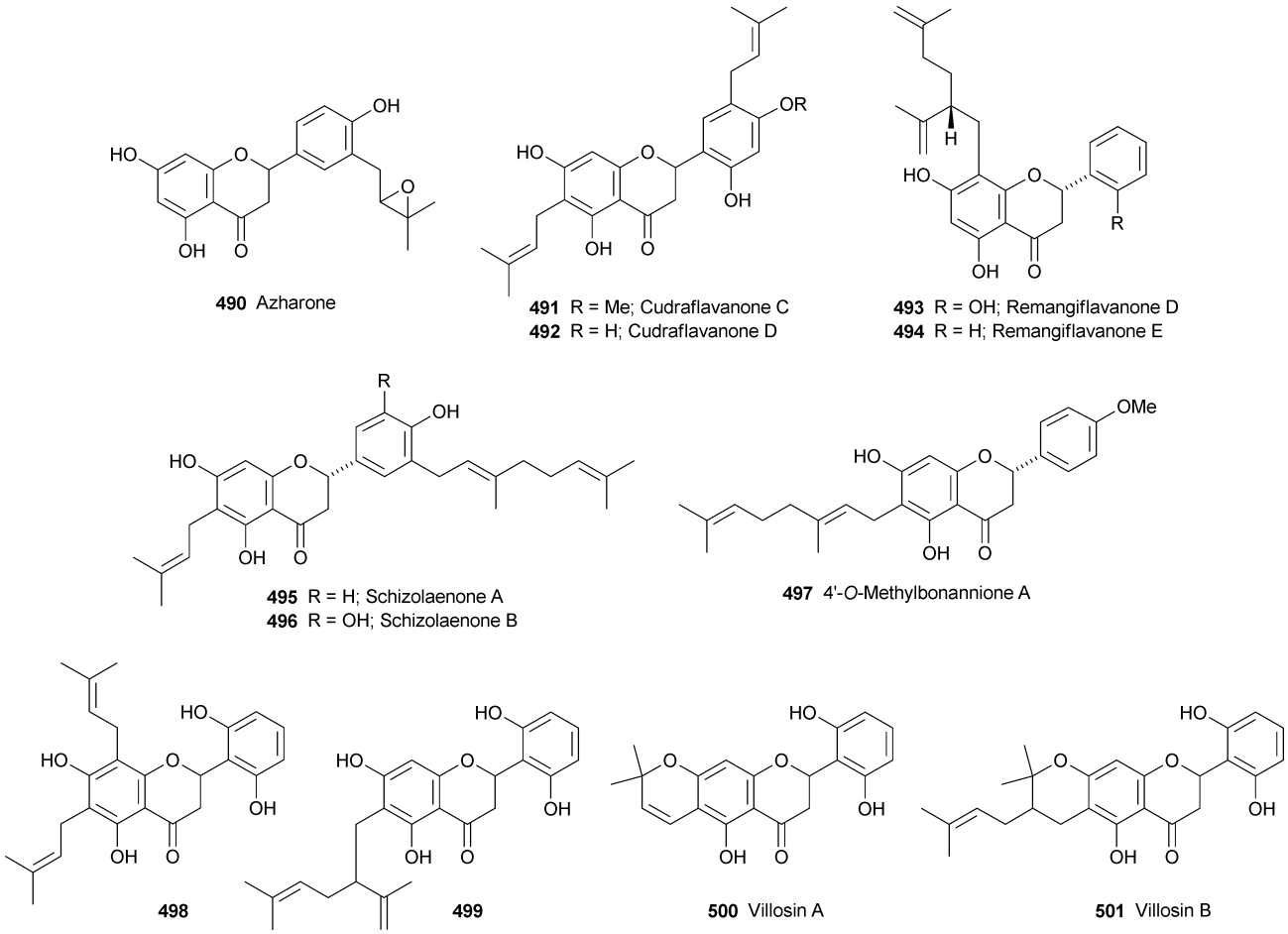


488 Tonkinochromane B



489 (+)-Apollineanin

characterised by 3′-(3-methyl-2,3-epoxybutyl) substitution of the B-ring.[421] Two 8,3′-diprenylated flavanones have been reported previously from this species.[422,423] The 2′,4′-di-*O*-substitution pattern of the B-ring of cudraflavanones C (**491**) and D (**492**) is typical of Moraceae flavonoids, these new examples being isolated from the roots of *Cudrania tricuspidata*.[424] Remangiflavanones D (**493**) and E (**494**) are constituents of the Madagascan endemic *Physena madagascariensis* (Physenaceae), and were obtained by bioassay-guided fractionation (A2780 ovarian cancer cell line cytotoxicity assay) of EtOH extracts of aerial parts of the plant.[425] Note that the lavandulyl substituent at C-8 of the A-rings is in the rare limonene form. This is also a feature of remangiflavanones A–C obtained previously from the same species.[426] Remangiflavanone C was the most cytotoxic of this series of 5 derivatives (remangiflavanones A–E) tested in the A2780 assay, with an IC_{50} value of 2.5 μg ml^{-1}.[425] In a study of another Madagascan endemic, Murphy *et al.* described the geranyl-substituted flavanones schizolaenone A (**495**), schizolaenone B (**496**), and 4′-*O*-methylbonannione A (**497**). These were isolated from EtOH extracts of the fruits of *Schizolaena hystrix* (Sarcolaenaceae), but showed only weak cytotoxicity in the A2780 cell line.[427] Four prenylated flavanones (**498–501**) isolated



from the whole plant of *Patrinia villosa* (Valerianaceae) have been described by Peng *et al.* in a series of papers (although with some duplication).[428–430] All are based on 5,7,2′,6′-tetrahydroxyflavanone, which features an unusual B-ring substitution pattern most commonly associated with the genus *Scutellaria* (Lamiaceae).[400] In biogenetic terms, the 6-lavandulyl derivative **499** is a likely precursor of the linear dihydropyranoflavanone, villosin B (**501**).[428,429] The isomeric angular dihydropyranoflavanone, exiguaflavanone L (precursor 8-lavandulyl-5,7,2′,6′-tetrahydroxyflavanone), is known as a constituent of the roots of *Sophora exigua* (Leguminosae).[431]

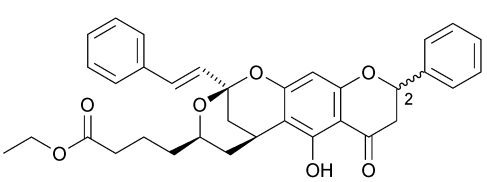
New flavanone glycosides are listed in Table 5, which contains information on 23 compounds (**502–524**).[128,138,139,233,406,432–440] The majority are mono- or disaccharides *O*-linked at C-7, C-4′ or both, these being typical patterns of flavanone glycosylation. Less common is glycosylation at 6-OH, as illustrated by the 6-*O*-β-glucopyranoside of carthamidin (**511**) isolated from EtOH extracts of the flowers of *Carthamus tinctorius* (Asteraceae) using high-speed counter-current chromatography.[438] A 6,7-di-*O*-β-glucopyranoside of carthamidin was reported previously from the same species,[441] but no other flavanone 6-*O*-glycosides are known. Glycosylation at 2′-OH is also unusual, and thus 6 acetylated 2′-*O*-β-glucopyranosyl-(1→3)-α-rhamnopyranosides of 5,7,2′,5′-tetrahydroxyflavanone (**513–518**) described by Fang *et al.* are of particular interest.[439] These occur in the rhizomes of the fern *Cyclosorus acuminatus* (Thelypteridaceae), and are moderately antibacterial towards *Streptococcus pneumoniae* and *Haemophilus influenzae*. Recorded uses of this species in traditional Chinese medicine include the treatment of diarrhoea, rheumatism and wounds.[439] Other acylated derivatives (which comprise just over 40% of the entries in Table 5) include a rare example of an *O*-linked 4,6-*O*,*O*-hexahydroxydiphenoyl-β-glucopyranoside (**504**),[433] previously found only at C-7 of matteucinol (5,7-dihydroxy-4′-methoxy-6,8-dimethylflavanone).[442] Dihydrochalcone glycosides acylated by hexahydroxydiphenolic acids have also been reported (see **426–429**).[378] The first record of 2-hydroxypropanoic acid as an acylating group for flavanone glycosides is represented by the liquiritigenin derivative **505**.[434] Two reports describing naringenin 4′-*O*-glycosides from species of *Impatiens* require clarification due to discrepancies in supporting data.[443,444] Further work is also needed to confirm the structure of a compound from stem bark of *Terminalia chebula* (Combretaceae) described as a 4′-*O*-diglycoside of 5,7,2′-trimethoxy-4′-hydroxyflavanone.[445]

Oboflavanones A (**525**) and B (**526**) are stereoisomers of pinocembrin (5,7-dihydroxyflavanone) modified by a C_{17}-unit (the ethyl ester side chain may be an artefact of extraction). Isolated from EtOH extracts of the trunk bark of *Cryptocarya obovata* (Lauraceae), they co-occur with the chalcone conjugates **411** and **412**.[369] Some related derivatives of pinocembrin have been reported from *Cryptocarya kurzii* (Lauraceae).[446] Ito *et al.* described two stereoisomeric conjugates of an alkylphloroglucinol and 5,7-dihydroxy-8-methylflavanone from the leaves of *Kunzea ambigua* (Myrtaceae), assigning them the trivial names

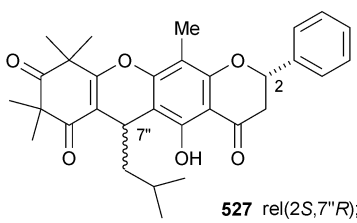
Table 5 New flavanone glycosides reported in the period 2004–2006

No.	Compound [a]	Conf.[b]	Sub.[c]	Source	Family	Tissue	Ref.
	5,7-Dihydroxyflavanone (pinocembrin)		5,7				
502	7-*O*-β-D-Api*f*-(1→2)-β-D-Glc*p*	2*S*		*Viscum articulactum*	Loranthaceae	Whole plant	432
503	7-*O*-[5-*O*-cinnamoyl-β-D-Api*f*-(1→2)]-β-D-Glc*p*	2*S*		*Viscum articulactum*	Loranthaceae	Whole plant	432
504	7-*O*-[3-*O*-galloyl-4,6-HHDP]-β-Glc*p*			*Penthorum chinense*	Saxifragaceae	Whole plant	433
	7,4′-Dihydroxyflavanone (liquiritigenin)		7,4′				
505	4′-*O*-[6-*O*-(2-hydroxypropanoyl)-β-Glc*p*]			*Glycyrrhiza uralensis*	Leguminosae	Root & rhizome	434
	7,2′-Dihydroxy-5-methoxyflavanone		5,7,2′				
506	7-*O*-β-D-GlcA*p*	2*S*		*Scutellaria amabilis*	Lamiaceae	Root	128
	5,4′-Dihydroxy-7-methoxyflavanone (sakuranetin)		5,7,4′				
507	5,4′-di-*O*-β-Glc*p*			*Populus davidiana*	Salicaceae	Stem bark	435
508	4′-*O*-α-Rha*p*-(1→6)-β-Glc*p*			*Vitex negundo*	Verbenaceae	Root	436
	5,7,4′-Trihydroxy-8-prenylflavanone						
509	7-*O*-β-Glc*p* ((2*R*)-phellodensin F)	2*R*		*Phellodendron japonicum*	Rutaceae	Leaf	233
	7,3′,4′-Trihydroxyflavanone (butin)		7,3′,4′				
510	4′-*O*-β-Api*f*-(1→2)-β-Glc*p*			*Rosa damascena*	Rosaceae	Flower	437
	5,6,7,4′-Tetrahydroxyflavanone (carthamidin)						
511	6-*O*-β-Glc*p*	2*S*		*Carthamus tinctorius*	Asteraceae	Flower	438
	5,7,2′,5′-Tetrahydroxyflavanone		5,7,2′,5′				
512	7-*O*-β-D-GlcA*p*	2*S*		*Scutellaria amabilis*	Lamiaceae	Root	128
513	2′-*O*-β-Glc*p*-(1→3)-[2-*O*-acetyl-α-Rha*p*]	2*S*		*Cyclosorus acuminatus*	Thelypteridaceae	Rhizome	439
514	2′-*O*-[6-*O*-acetyl-β-Glc*p*]-(1→3)-[2-*O*-acetyl-α-Rha*p*]	2*S*		*Cyclosorus acuminatus*	Thelypteridaceae	Rhizome	439
515	2′-*O*-[2,6-di-*O*-acetyl-β-Glc*p*]-(1→3)-[2-*O*-acetyl-α-Rha*p*]	2*S*		*Cyclosorus acuminatus*	Thelypteridaceae	Rhizome	439
516	2′-*O*-[3,6-di-*O*-acetyl-β-Glc*p*]-(1→3)-[2-*O*-acetyl-α-Rha*p*]	2*S*		*Cyclosorus acuminatus*	Thelypteridaceae	Rhizome	439
517	2′-*O*-[4,6-di-*O*-acetyl-β-Glc*p*]-(1→3)-[2-*O*-acetyl-α-Rha*p*]	2*S*		*Cyclosorus acuminatus*	Thelypteridaceae	Rhizome	439
518	2′-*O*-[2,3,6-tri-*O*-acetyl-β-Glc*p*]-(1→3)-[2-*O*-acetyl-α-Rha*p*]	2*S*		*Cyclosorus acuminatus*	Thelypteridaceae	Rhizome	439
	5,7,3′,4′-Tetrahydroxyflavanone (eriodictyol)		5,7,3′,4′				
519	7-*O*-β-Glc*p*-(1→2)-β-Glc*p*			*Globularia alypum*	Globulariaceae	Aerial parts	139
520	7,4′-di-*O*-β-D-Glc*p*	2*R*		*Viscum coloratum*	Loranthaceae	Leaf & branch	440
	5,7,4′-Trihydroxy-3′-methoxyflavanone (homoeriodictyol)						
521	7,4′-di-*O*-β-D-Glc*p*	2*S*		*Viscum coloratum*	Loranthaceae	Leaf & branch	440
522	4′-*O*-[6-*O*-(3-hydroxy-3-methylglutaryl)-β-Glc*p*]	2*S*		*Citrus sudachi*	Rutaceae	Peel	138
	5,3′,4′-Trihydroxy-7-methoxyflavanone (sternbin)						
523	4′-*O*-β-D-Glc*p* (persinoside A)			*Aerva persica*	Amaranthaceae	Whole plant	406
	5,7,3′,4′,5′-Pentahydroxyflavanone		5,7,3′,4′,5′				
524	7-*O*-β-D-Glc*p* (persinoside B)			*Aerva persica*	Amaranthaceae	Whole plant	406

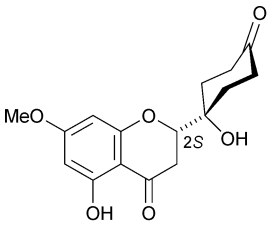
[a] Standard three-letter codes for monosaccharides are used; *p* = pyranoside, *f* = furanoside. Absolute configurations are given only where determined experimentally. For disaccharides *O*-linked to flavanones, the last listed sugar (primary) is that attached to the aglycone. Entries are presented in order of increasing glycosylation, with non-acylated before acylated derivatives (HHDP = hexahydroxydiphenoyl). [b] Absolute configurations at C-2 are given where determined by CD spectroscopy. [c] The *O*-substitution pattern of the parent flavanone is indicated. Compounds are listed in order of increasing *O*-substitution, with the A-ring substituents taking precedence over those of the B-ring (primed numbers).



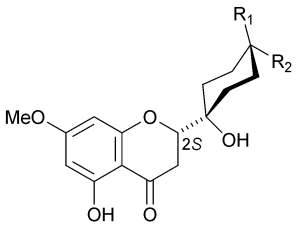
525 (2*S*); Oboflavanone A
526 (2*R*); Oboflavanone B



527 rel(2*S*,7″*R*); Kunzeanone A
528 rel(2*S*,7″*S*); Kunzeanone B



529 (2*S*)-Ongokein-4'-one



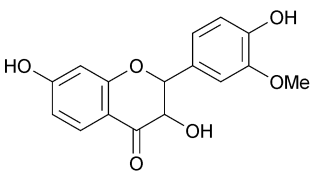
530 $R_1 = R_2 = OMe$; (2*S*)-4',4'-Dimethoxyongokein
531 $R_1 = H$, $R_2 = OH$; (2*S*)-*cis*-4'-Hydroxyongokein
532 $R_1 = OH$, $R_2 = H$; (2*S*)-*trans*-4'-Hydroxyongokein

kunzeanone A (**527**) and B (**528**). Their relative configurations were determined from X-ray crystallographic analyses of both **527** and cocrystallised **527** and **528**.[447] The protoflavanones **529–532**, which are characterised by non-aromatic B-rings, were obtained from both stem bark and root material of *Ongokea gore* (Olacaceae), a tropical tree of west and central Africa.[80] Previous reports of these compounds are limited to protofarrerol and its 7-*O*-β-glucopyranoside, which occur in ferns.[448,449]

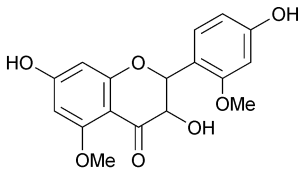
9 Dihydroflavonols

This is a relatively scarce group of flavonoids, with only 16 additional examples published between 2004 and 2006. In structural terms they are 3-hydroxyflavanones, and as such have asymmetric carbon atoms at both C-2 and C-3. Their relative configuration can be determined from the magnitude of the $^3J_{2,3}$ coupling constant in ^{1}H NMR spectra. For the new dihydroflavonols described here, this parameter was 11.1–12.8 Hz for *trans*-isomers, and 2.1 Hz for a *cis*-isomer. The absolute configuration at C-2 is obtained by CD spectroscopy, from which that at C-3 follows, having identified whether a *trans*- or *cis*-isomer is present. For a detailed discussion, the recent review by Slade *et al.* is recommended.[399] Absolute configurations are only shown in the accompanying structure drawings if supported by both NMR and CD measurements.

Erycibenin D (**533**) is the 3′-methyl ether of fustin (3,7,3′,4′-tetrahydroxyflavanone) and a constituent of the stems of *Erycibe expansa* (Convolvulaceae), which contain many flavonoids and isoflavonoids.[450] Root extracts of *Cudrania cochinchinensis* (Moraceae) yielded **534**, a dimethyl ether of dihydromorin (3,5,7,2′,4′-pentahydroxyflavanone).[85] The B-ring of this compound has the 2′,4′-di-*O*-substitution pattern typical of Moraceae flavonoids. Nakagawa *et al.* obtained **535**, a stereoisomer of pallisiin (3,5,7,3′,5′-pentahydroxy-4′-methoxyflavanone), in work on the Columbian medicinal plant *Maytenus laevis* (Celastraceae).[451] The $^3J_{2,3}$ coupling constants for **535** and pallisiin are 2.1 Hz (*cis*-isomer)[451] and 11.0 Hz (*trans*-isomer),[452] respectively. A *C*-methyldihydroflavonol present in aqueous acetone extracts of bark from the pine tree, *Pinus sylvestris* (Pinaceae), has been identified as 3,5,4′-trihydroxy-7-methoxy-6-methylflavanone (**536**), and its NMR spectra analysed in detail.[453] Smith *et al.* have reported silychristin B (**537**) as a new diastereoisomer of a flavonolignan, silychristin, which they suggest renaming as silychristin A. These compounds, which result from the coupling of taxifolin (3,5,7,3′,4′-pentahydroxyflavanone) and coniferyl alcohol, occur in extracts of the fruits of the milk thistle *Silybum marianum* (Asteraceae).[454]



533 Erycibenin D



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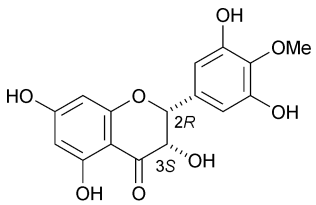

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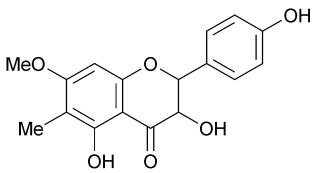

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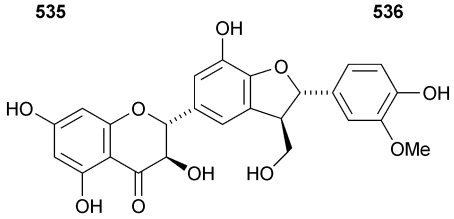
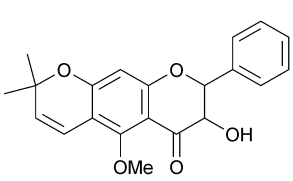


537 Silychristin B

New prenylated dihydroflavonols (**538–541**) have only been reported from the Leguminosae. MeOH extracts of the roots of *Lonchocarpus guatemalensis* Benth. (published under the synonym *Lonchocarpus xuul* Lundell), an endemic species of the Yucatan peninsula, yielded the pyranodihydroflavonol, **538**.[417] Isomundulinol (**539**) co-occurs with the flavanone 3-deoxy MS-II (**483**) in extracts of the leaves and flowers of *Mundulea chapelieri*.[418] Sophoranodichromane A (**541**)[109] and its 2′-hydroxy analogue, flavenochromane A (**540**),[108] are bis(dihydropyrano) dihydroflavonols from the roots of *Sophora flavescens*.

Heliciosides A (**542**) and B (**547**) are the 5-*O*-β-glucopyranosides of aromadendrin (3,5,7,4′-tetrahydroxyflavanone) and taxifolin (3,5,7,3′,4′-pentahydroxyflavanone), respectively. They occur in the leaves of *Helicia cochinchinensis* (Proteaceae), a species selected for study as part of a survey of the plants of Okinawa Island, Japan.[455] Neomicranthoside (**543**) is a further example of a 5-*O*-β-glucopyranoside, but of aromadendrin 7-methyl ether. A constituent of the leaves of *Eupatorium micranthum* (Asteraceae), it co-occurs with its enantiomer, micranthoside, which has the (2*R*,3*R*)-configuration.[456] Two new glycosides of 8-prenylaromadendrin have been described from species of *Phellodendron* in the Rutaceae. Phellodensin G (**544**) is a 7,4′-di-*O*-β-glucopyranoside from the leaves of *P. chinense*,[457]



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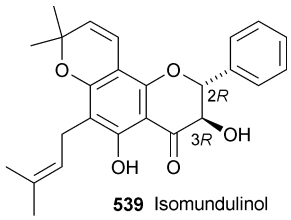
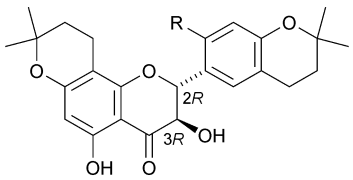


539 Isomundulinol



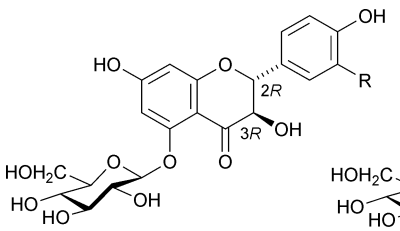
540 R = OH; Flavenochromane A
541 R = H; Sophoranodichromane A

whereas **545** was obtained from leaves of *P. japonicum* (Japanese corktree).[233] As an acetyl derivative of phellamurin (8-prenylaromadendrin 7-*O*-β-glucopyranoside), it is a rare example of an acylated dihydroflavonol glycoside. The parent compound phellamurin has been shown to mediate DNA strand scission (Cu^{2+}-dependent relaxation of supercoiled plasmid DNA).[458] Hosoi *et al.* obtained (2*S*,3*S*)-taxifolin 3-*O*-arabinoside (**546**) from the leaves of *Trachelospermum jasminoides* var. *pubescens* (Apocynaceae), although the arabinosyl moiety was not fully characterised (^{1}H NMR assignments lacking).[459] Previous reports on the corresponding (2*R*,3*R*)- and (2*R*,3*S*)-stereoisomers are of the α-arabinopyranosides.[460] It is interesting to note that **546** was not effective as a zoospore attractant of *Aphanomyces cochlioides* (a pathogenic fungus of sugar beet and spinach), in contrast to its (2*R*,3*R*)-stereoisomer and (2*R*,3*R*)-taxifolin 3-*O*-glucoside.[459] Tricusposide (**548**) is the 7-*O*-β-glucopyranoside of gericudranin C, a benzylated derivative of (2*R*,3*R*)-taxifolin. Both compounds are found in bark extracts of *Cudrania tricuspidata* (Moraceae).[461] A glycoside of 3,5,7,4′-tetrahydroxy-6-methoxyflavanone described as being a constituent of *Pulicaria undulata* (Asteraceae) has been characterised as a 3-*O*-β-glucopyranoside with the trivial name of undulatoside.[257] However, the ^{1}H NMR assignments for 6-CH_2 of the glucosyl moiety are not in agreement with this determination (at δ 4.43 and 4.43 in CD_3OD they show a significant downfield shift consistent with substitution at 6-OH of the sugar), which deserves further investigation.

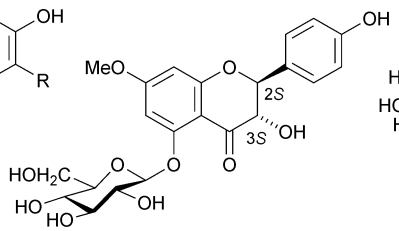
10 Anthocyanins

An extensive review of anthocyanins and anthocyanidins describing new structures reported between 1993 and 2004 was published by Andersen and Jordheim in 2006. Other areas covered include colour stability, anthocyanin production in cell cultures, synthesis, localisation in plant cells, and chemotaxonomy.[462] The subject of anthocyanins (and other flavonoids) in wine has been treated by Cheynier.[463] Many papers on anthocyanins from the period under review deal with their analysis in fruit and vegetable extracts or wines, principally by HPLC (usually in combination with electrospray ionisation mass spectrometry, ESI-MS), and often with a focus on health-promoting properties such as antioxidant activity. However, these subjects are largely outside the scope of the present review, which is concerned mainly with new compounds from flowers and other plant tissues. Nevertheless, useful articles that deserve to be highlighted are a review on anthocyanins, flavonoids and other phenolics in food by Manach *et al.*,[464] who also discuss the bioavailability of these compounds, and a short review on the bioactivity of anthocyanins by Wrolstad.[465]

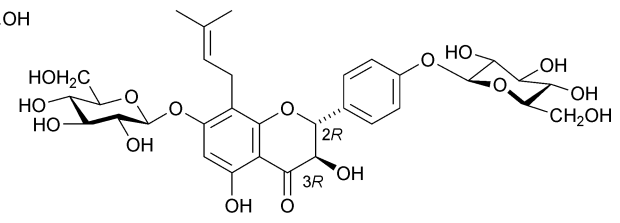
The structures of two novel anthocyanidins and more than 50 new anthocyanins from plants have been determined in full in the period 2004–2006, details of which are shown in Table 6.[466–488] Many of these were isolated from flower petals, but other sources include fruits, roots, leaves and seed coats. In addition, a number of new anthocyanin adducts were obtained by adding organic acids or phenolics to anthocyanin solutions. Other potentially new compounds have been detected by HPLC–ESI-MS, but await full characterisation. Although some artefacts and partially identified compounds are mentioned in the text below, they have not been entered in the numbered series. Several of the fully characterised compounds have 4-substituted flavylium moieties, including the two interesting blue anthocyanidin-type pigments, rosacyanins A1 (**549**) and A2 (**550**), from the mauve



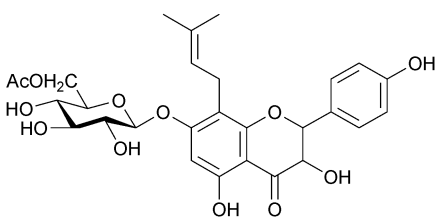
542 R = H; Helicioside A
547 R = OH; Helicioside B



543 Neomicranthoside



544 Phellodensin G



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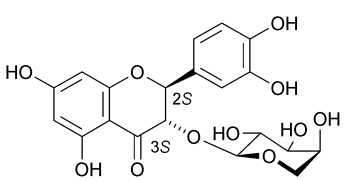

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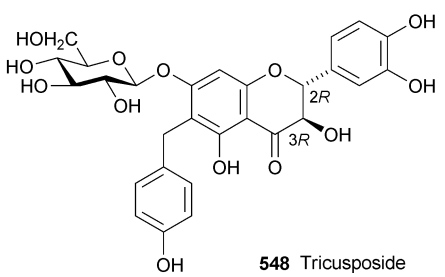


548 Tricusposide

Table 6 New anthocyanidins and anthocyanins reported in the period 2004–2006

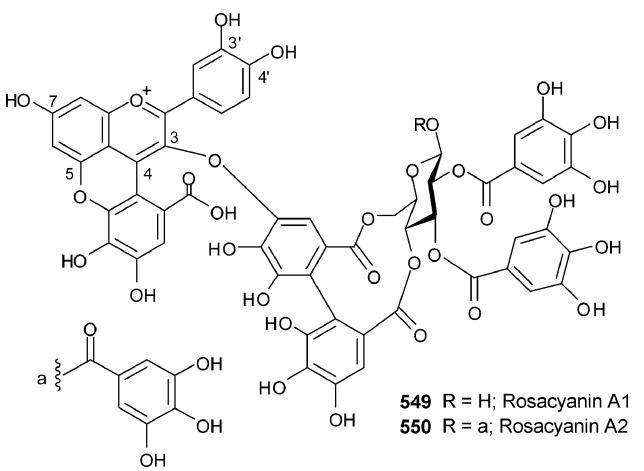
No.	Compound [a]	Source	Family	Tissue	Ref.
	ANTHOCYANIDINS				
549	Rosacyanin A1	*Rosa hybrida* cv. 'M'me Violet'	Rosaceae	Flower	466
550	Rosacyanin A2	*Rosa hybrida* cv. 'M'me Violet'	Rosaceae	Flower	466
	ANTHOCYANINS				
	4-Substituted anthocyanins				
551	5-CarboxypyranoPg 3-glucoside	*Fragaria ananassa*	Rosaceae	Fruit	467
552	Vinylphenol adduct of Cy 3-(2-xylosylgalactoside)	*Daucus carota*	Apiaceae	Juice	468
553	Vinylcatechol adduct of Cy 3-(2-xylosylgalactoside)	*Daucus carota*	Apiaceae	Juice	468
554	Vinylguaiacol adduct of Cy 3-(2-xylosylgalactoside)	*Daucus carota*	Apiaceae	Juice	468
555	Vinylcatechol adduct of Cy 3-[2-xylosyl-6-(6-feruloylglucosyl)galactoside]	*Daucus carota*	Apiaceae	Juice	468
556	Vinylcatechol adduct of Cy 3-[2-xylosyl-6-(6-sinapoylglucosyl)galactoside]	*Daucus carota*	Apiaceae	Juice	468
557	Vinylguaiacol adduct of Cy 3-[2-xylosyl-6-(6-feruloylglucosyl)galactoside]	*Daucus carota*	Apiaceae	Juice	468
	***C*-Glycosyl anthocyanins**				
558	8-*C*-(6-Sinapoylglucosyl)-Cy 3-(6-malonylglucoside)	*Tricyrtis formosana*	Liliaceae	Flower	469
	Pelargonidin, cyanidin and delphinidin glycosides				
559	Pg 3-(6-feruloyl-2-glucosylglucoside)-5-(4-glucosyl-6-malonylglucoside)	*Raphanus sativus*	Brassicaceae	Rhizome	470
560	Pg 3-[6-feruloyl-2-(6-feruloylglucosyl)-glucoside]-5-(4-glucosylglucoside)	*Raphanus sativus*	Brassicaceae	Rhizome	470
561	Pg 3-[6-feruloyl-2-(6-feruloylglucosyl)-glucoside]-5-(4-glucosyl-6-malonylglucoside)	*Raphanus sativus*	Brassicaceae	Rhizome	470
562	Pg 3-[6-feruloyl-2-(6-feruloylglucosyl)-glucoside]-5-(6-malonylglucoside)	*Raphanus sativus*	Brassicaceae	Rhizome	470
563	Pg 3-[2-(6-(3-glucosylcaffeoyl)-glucosyl)-glucoside]	*Ipomoea nil*	Convolvulaceae	Flower	471
564	Cy 3-(6-feruloylglucoside)	*Prunus mume* 'Nanjing Hong'	Rosaceae	Flower	472
565	Cy 3-(6-galloylglucoside)	*Prunus mume* 'Nanjing Hong'	Rosaceae	Flower	472
566	Cy 3-[2-(2-(4-(6-(4-glucosylcaffeoyl)-glucosyl)-caffeoyl)-xylosyl)-6-(4-glucosyl-*p*-coumaroyl)-glucoside]-5-(6-malonylglucoside)	*Orychophragonus violaceus*	Brassicaceae	Flower	473
567	Cy 3-[2-(2-(4-(6-(4-glucosylcaffeoyl)-glucosyl)-caffeoyl)-xylosyl)-6-(4-glucosylferuloyl)-glucoside]-5-glucoside	*Orychophragonus violaceus*	Brassicaceae	Flower	473
568	Cy 3-[2-(2-(4-(6-(4-glucosylcaffeoyl)-glucosyl)-caffeoyl)-xylosyl)-6-(4-glucosylsinapoyl)-glucoside]-5-(6-malonylglucoside)	*Orychophragonus violaceus*	Brassicaceae	Flower	473
569	Cy 3-(2-xylosyl-6-rhamnosylglucoside)-7-glucoside	*Corydalis elata*, *Corydalis flexuosa*	Fumariaceae	Flower	474
570	Cy 3-(6-malonylglucoside)-7-(6-*p*-hydroxybenzoylglucoside)-3′-[6-(4-glucosyl-*p*-hydroxybenzoyl)-glucoside]	*Dendrobium* × *superbiens*	Orchidaceae	Flower	475
571	Purprocampanin (Cy 3,7-diglycoside acylated with 3 molecules of *p*-hydroxybenzoic acid)	*Campanula medium*	Campanulaceae	Flower	476
572	Cy 3-(2-xylosyl-6-*p*-coumaroylglucoside)-5-(6-malonylglucoside)	*Lunaria annua*	Brassicaceae	Flower	477
573	Cy 3-(2-xylosyl-6-(*Z*)-*p*-coumaroylglucoside)-5-(6-malonylglucoside)	*Lunaria annua*	Brassicaceae	Flower	477
574	Cy 3-(2-xylosyl-6-feruloylglucoside]-5-(6-malonylglucoside)	*Lunaria annua*	Brassicaceae	Flower	477
575	Cy 3-(2-xylosyl-6-(4-glucosyl-*p*-coumaroyl)-glucoside]-5-glucoside	*Lobularia maritima*	Brassicaceae	Flower	477
576	Cy 3-[2-(2-caffeoylxylosyl)-6-(4-glucosyl-*p*-coumaroyl)-glucoside]-5-glucoside	*Lobularia maritima*	Brassicaceae	Flower	477
577	Cy 3-[2-(2-caffeoylxylosyl)-6-*p*-coumaroylglucoside]-5-glucoside	*Lobularia maritima*	Brassicaceae	Flower	477
578	Cy 3-[2-(2-feruloylxylosyl)-6-*p*-coumaroylglucoside]-5-glucoside	*Lobularia maritima*	Brassicaceae	Flower	477
579	Cy 3-(2-xylosylglucoside)-7-glucoside	*Meconopsis grandis*	Papaveraceae	Petal	478
580	Dp 3-(2-glucosylarabinoside)	*Lens culinaris*	Leguminosae	Seed	479
581	Dp 3-(6-malonylglucoside)-3′-glucoside	*Clitoria ternatea*	Leguminosae	Flower	480
582	Dp 3-[6-(4-(6-(4-glucosylcaffeoyl)-glucosyl)-caffeoyl)-glucoside]-5-(6-malonylglucoside) (phacelianin)	*Phacelia campanularia*	Hydrophyllaceae	Flower	481
583	Dp 3-(6-malonylglucoside)-7,3′-di-(6-sinapoylglucoside)	*Vanda* cultivars	Orchidaceae	Flower	482
584	Dp 3-glucoside-7,3′-di-(6-sinapoylglucoside)	*Vanda* cultivars	Orchidaceae	Flower	482
	Malvidin and peonidin glycosides				
585	Mv 3-[6-(4-malonylrhamnosyl)glucoside]-5-glucoside	*Oxalis triangularis*	Oxalidaceae	Leaf	483
586	Mv 3-(6-rhamnosylglucoside)-5-(6-malonylglucoside)	*Oxalis triangularis*	Oxalidaceae	Leaf	483
587	Mv 3-(6-(4-malonylrhamnosyl)-glucoside)-5-(6-malonylglucoside)	*Oxalis triangularis*	Oxalidaceae	Leaf	483

Table 6 *(Contd.)*

No.	Compound [a]	Source	Family	Tissue	Ref.
588	Mv 3-[6-(4-malonylrhamnosyl)-glucoside]	*Oxalis triangularis*	Oxalidaceae	Leaf	483
589	Mv 3-(6-(*Z*)-*p*-coumaroylglucoside)-5-glucoside	*Oxalis triangularis*	Oxalidaceae	Leaf	483
590	Pn 3-[2-(6-caffeoylglucosyl)-glucoside]	*Ipomoea nil*	Convolvulaceae	Flower	484
591	Pn 3-[2-(6-caffeoylglucosyl)-glucoside]-5-glucoside	*Ipomoea nil*	Convolvulaceae	Flower	484
592	Pn 3-[2-(6-(3-glucosylcaffeoyl)-glucosyl)-6-(4-(6-(3-glucosylcaffeoyl)-glucosyl)-caffeoyl)-glucoside	*Ipomoea nil*	Convolvulaceae	Flower	484
593	Pn 3-[2-(6-caffeoylglucosyl)-6-(4-(6-(3-glucosylcaffeoyl)-glucosyl)-caffeoyl)-glucoside]	*Ipomoea nil*	Convolvulaceae	Flower	484
594	Pn 3-[2-(6-caffeoylglucosyl)-6-(4-(6-(3-glucosylcaffeoyl)-glucosyl)-caffeoyl)-glucoside]-5-glucoside	*Ipomoea nil*	Convolvulaceae	Flower	484
595	Pn 3-[6-(4-(4-(6-caffeoylglucosyl)-*p*-coumaroyl)-rhamnosyl)-glucoside]-5-glucoside	*Petunia* cultivars	Solanaceae	Flower	485
596	Pn 3-[6-(4-(4-glucosyl-*p*-coumaroyl)-rhamnosyl)-glucoside]-5-glucoside	*Petunia* cultivars	Solanaceae	Flower	485
	7-*O*-Methylanthocyanidin glycosides				
597	7-*O*-MethylCy 3-galactoside	*Mangifera indica* cv. 'Tommy Atkins'	Anacardiaceae	Fruit peel	486
	Anthocyanin-flavone conjugate				
598	(6-(Dp -3-[6-(glucosyl)glucoside])) (6-(luteolin 7-glucosyl))malonate (*Eichhornia* anthocyanin B)	*Eichhornia crassipes*	Pontederiaceae	Flower	487
	Anthocyanin-flavanol dimers				
599	Catechin(4α→8)Pg 3-glucoside	*Fragaria ananassa*	Rosaceae	Fruit	488
600	Epicatechin(4α→8)Pg 3-glucoside	*Fragaria ananassa*	Rosaceae	Fruit	488
601	Afzelechin(4α→8)Pg 3-glucoside	*Fragaria ananassa*	Rosaceae	Fruit	488
602	Epiafzelechin(4α→8)Pg 3-glucoside	*Fragaria ananassa*	Rosaceae	Fruit	488

[a] Abbreviations: Pg, pelargonidin; Cy, cyanidin; Dp, delphinidin; Mv, malvidin; Pn, peonidin. The linkages between anthocyanidins or anthocyanins and sugars, and between sugars and other sugars or acyl groups, are all -*O*-, unless specified as -*C*-. Anomeric configurations are β for glucose, galactose and xylose and α for rhamnose and arabinose. Sugars are all in the pyranose form. In those entries where the acyl groups are hydroxycinnamic acids (caffeic acid, ferulic acid, sinapic acid, *p*-coumaric acid), the *E*-configuration can be assumed unless otherwise indicated.

petals of *Rosa hybrida* cv. 'M'me Violet' (Rosaceae).[466] Their structures comprise a chromophore containing cyanidin with a galloyl group linked at C-4 and C-5 of the flavylium nucleus, and the ellagitannins tellimagrandin 1 or tellimagrandin 2, respectively, linked to the flavylium 3-OH. This is the first natural pigment in which a flavylium nucleus is linked to an ellagitannin through an ether bond and not *via* a sugar. It is conceivable that blue roses might be developed by selective breeding of varieties which produce large amounts of rosacyanins A1 and A2, or the previously reported rosacyanin B.[489] The latter pigment contains the galloyl group at C-4 and C-5 of the anthocyanidin, but lacks the ellagitannin moiety.

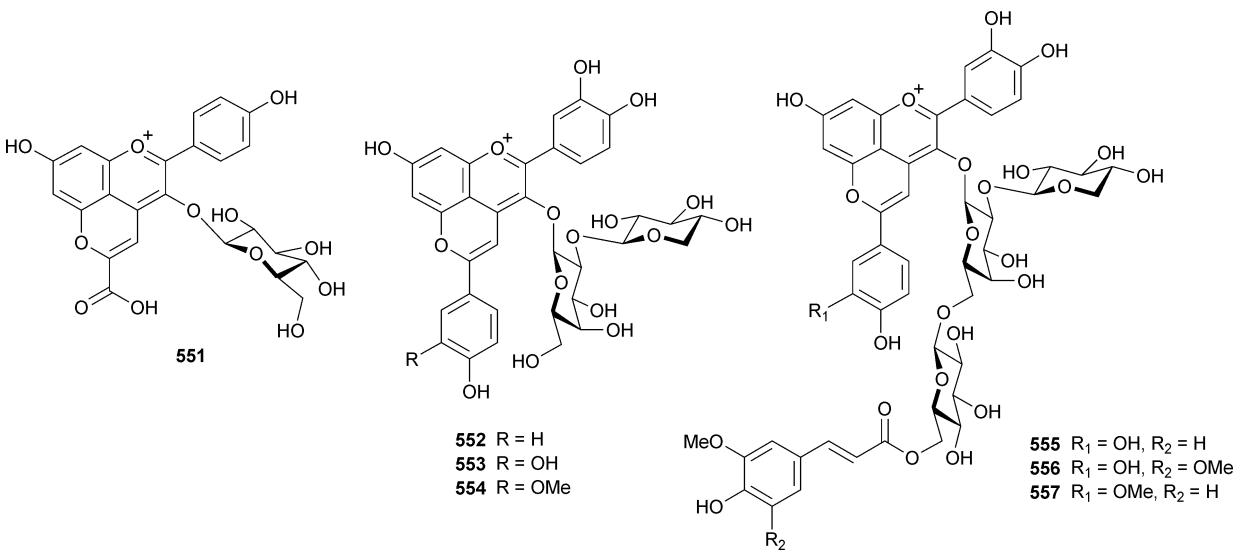


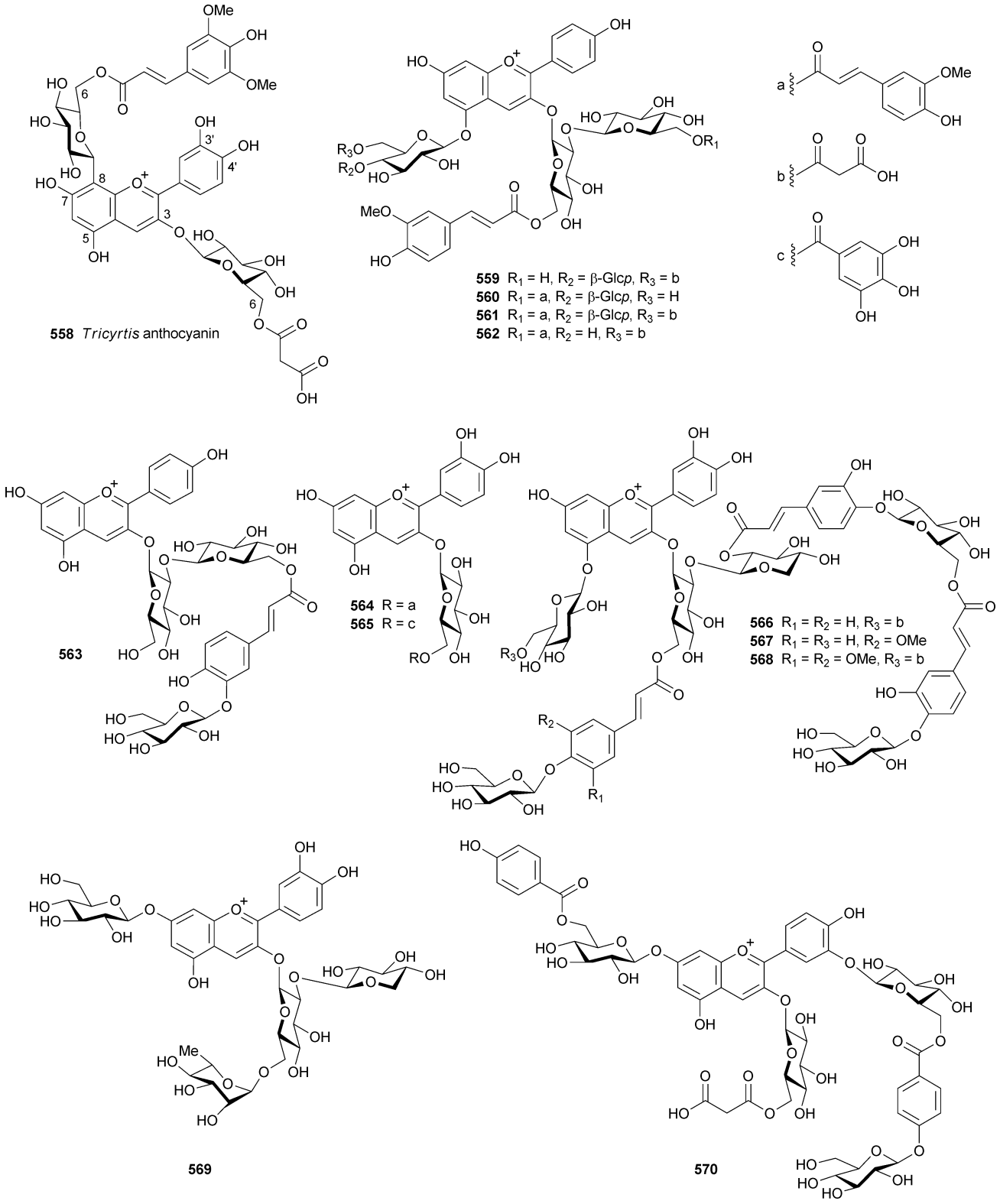
Acidified methanolic extracts of strawberry fruits (*Fragaria ananassa*, Rosaceae) yielded a novel 4-substituted anthocyanin identified as 5-carboxypyranopelargonidin 3-*O*-β-glucopyranoside (**551**). At pH 5.1, **551** had a molar absorptivity (ε) nearly four times greater than the corresponding pelargonidin glycoside, which may indicate that 5-carboxypelargonidin derivatives have potential as colourants in solutions at this pH.[467] Six further 4-substituted anthocyanins (**552–557**) were detected by HPLC-ESI-MS^n in the juice of black carrots (*Daucus carota*, Apiaceae). These appeared to be formed during storage of the juice, presumably through the direct reaction of *p*-coumaric, caffeic and ferulic acids with the natural anthocyanins present in the carrots.[468] This process is similar to reactions between anthocyanins and organic acids that take place in wine and redcurrant juice (see below). The two major compounds of carrot juice are the vinylcatechol adducts, **553** and **555**. Also present are the vinylphenol (**552**) and vinylguaiacol adducts (**554**) of cyanidin 3-[2-(xylosyl)-galactoside], and vinylguaiacol (**557**) and vinylcatechol adducts (**556**) of acylated cyanidin glycosides with a branched trisaccharide at 3-OH.[468] Several studies describe experiments in which organic acids or phenolics known to be present in wine are added to anthocyanin solutions and the resulting adducts analysed. Mateus *et al.* used this procedure to synthesise a new pigment, the structure of which corresponded to a pyruvic acid adduct of malvidin 3-glucoside linked to a vinyl phenol group.[490] This was also detected in a red wine sample by HPLC-UV-MS. In other work, ferulic acid, sinapic acid or 4-vinylsyringol were added to strawberry and raspberry juices.[491] New anthocyanin derivatives detected by HPLC coupled to nano-ESI-MS were tentatively identified as the 4-vinylguaiacol and 4-vinylsyringol adducts of pelargonidin and cyanidin 3-glycosides.[491] These had more stable colours than the parent anthocyanins. The

antioxidant potential of related pigments in wine formed through the chemical interaction of anthocyanins with pyruvic acid (the so-called vitisins A) has been compared to that of the original anthocyanins. However, the latter showed higher iron-reducing capacity and 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) and peroxyl radical scavenging activities than the adducts. In terms of the anthocyanin structures, glycosides of delphinidin showed the highest antioxidant activity.[492]

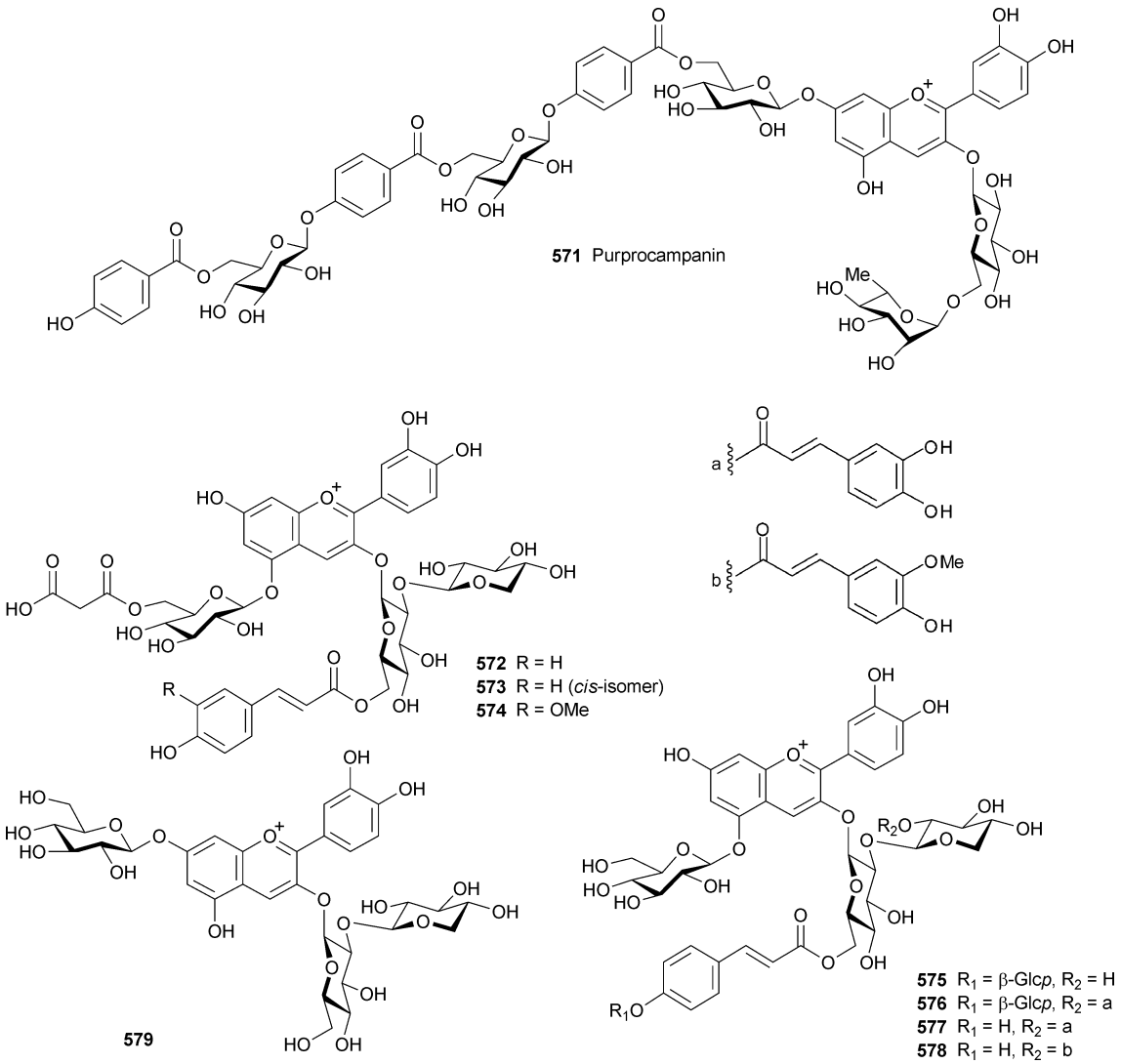
An unusual *C*-glycosylanthocyanin (**558**) has been described by Tatsuzawa *et al.* from the flowers of the toad lily, *Tricyrtis formosana* (Liliaceae).[469] This species remains the only recorded source of *C*-glycosylanthocyanins, the first example of which was published in 2003.[493] The majority of the remaining anthocyanins reported from plants from 2004 to 2006 are *O*-glycosides, usually highly acylated, of the common anthocyanidins pelargonidin, cyanidin and delphinidin, or their methylated derivatives, malvidin, peonidin and 7-*O*-methylcyanidin. No new glycosides based on petunidin or 6-hydroxyanthocyanidins were recorded in this period. Four pelargonidin glycosides (**559–562**) sourced from red radish (*Raphanus sativus*, Brassicaceae) were isolated from extracts of the Chinese cultivar 'Beijing hong xin'.[470] These are based on pelargonidin 3-sophoroside-5-glucoside, with each anthocyanin acylated by one or two feruloyl residues. In addition, **559**, **561** and **562** contain a malonyl residue. This species may yield further new anthocyanins, as analysis by HPLC–ESI-MS revealed the presence of 32 pelargonidin and two cyanidin glycosides, many of which were acylated with malonic acid on the sugar attached to 5-OH and with ferulic, caffeic, *p*-coumaric and/or *p*-hydroxybenzoic acids on the sugar(s) attached to 3-OH. However, these compounds were only tentatively identified.[494] The pelargonidin derivative **563** was reported from the pale brownish-red flowers of a *duskish-2* mutant of *Ipomoea nil* (Convolvulaceae).[471] Two new acylated cyanidin glycosides isolated from the pink flowers of *Prunus mume* 'Nanjing Hong' (Nanjing red) (Rosaceae) were identified as cyanidin 3-*O*-(6-*O*-*E*-feruloyl-β-glucopyranoside) (**564**) and cyanidin 3-*O*-(6-*O*-galloyl-β-glucopyranoside) (**565**).[472] In contrast, three structurally complex acylated cyanidin 3-sambubioside-5-glucosides (**566–568**) were obtained from the violet–blue flowers of the cruciferous plant *Orychophragonus violaceus*.[473] Cyanidin 3-*O*-[2-*O*-β-xylopyranosyl-6-*O*-α-rhamnopyranosylglucopyranoside]-7-*O*-β-glucopyranoside (**569**) occurs in the flowers of *Corydalis elata* and *C. flexuosa* (Fumariaceae).[474] Although malonic and hydroxycinnamic acids are most commonly found as acylating groups of anthocyanins, *p*-hydroxybenzoic acid is present in a cyanidin derivative (**570**) from the flowers of *Dendrobium* × *superbiens* (Orchidaceae).[475] The flowers of this orchid hybrid also contain a cyanidin 3-malonylglucoside-7-glucosyl-*p*-hydroxybenzoylglucoside-3′-*p*-hydroxybenzoylglucoside, but this was only provisionally identified. Three molecules of *p*-hydroxybenzoic acid are present as acylating groups in a new cyanidin glycoside from a red–purple-flowered cultivar of *Campanula medium* (Campanulaceae), which was assigned the trivial name of purprocampanin (**571**).[476] The corresponding pelargonidin glycoside, rubrocampanin, previously isolated from pink cultivars of the same species,[495] was also present in the red–purple flowers.[476] Nine complex acylated cyanidin 3-sambubioside-5-glucosides, including seven new examples (**572–578**), were isolated from the flowers of three garden plants belonging to the family Brassicaceae (Cruciferae). Of these, **572–574** were obtained from *Lunaria annua* (red–purple flowers) and **575–578** from *Lobularia maritima* (purple–violet flowers).[477] Extracts of the sky-blue petals of the Himalayan poppy, *Meconopsis grandis* (Papaveraceae), yielded cyanidin 3-*O*-(2-*O*-β-xylopyranosyl)-β-glucopyranoside-7-*O*-β-glucopyranoside (**579**), which is thought to be a component of the blue metal-containing pigment of the flowers.[478]

Five delphinidin glycosides have been fully characterised as new anthocyanins in the review period, including 3-*O*-[(2-*O*-β-glucopyranosyl)-α-arabinopyranoside] (**580**) from Beluga black lentils (*Lens culinaris*, Leguminosae).[479] Since this non-acylated pigment was extracted using 3% HCl in methanol, a procedure which tends to remove dicarboxylic acids such as malonic acid from glycosides during extraction,[496] it is possible that the anthocyanin present in lentils contains a malonyl group. Delphinidin 3-*O*-(6-*O*-malonyl)-β-glucopyranoside-3′-*O*-β-glucopyranoside (**581**), which was isolated from the blue petals of *Clitoria ternatea* (Leguminosae) is a postulated intermediate in the biosynthesis of ternatins, a group of blue acylated 3,3′,5′-triglucosylated



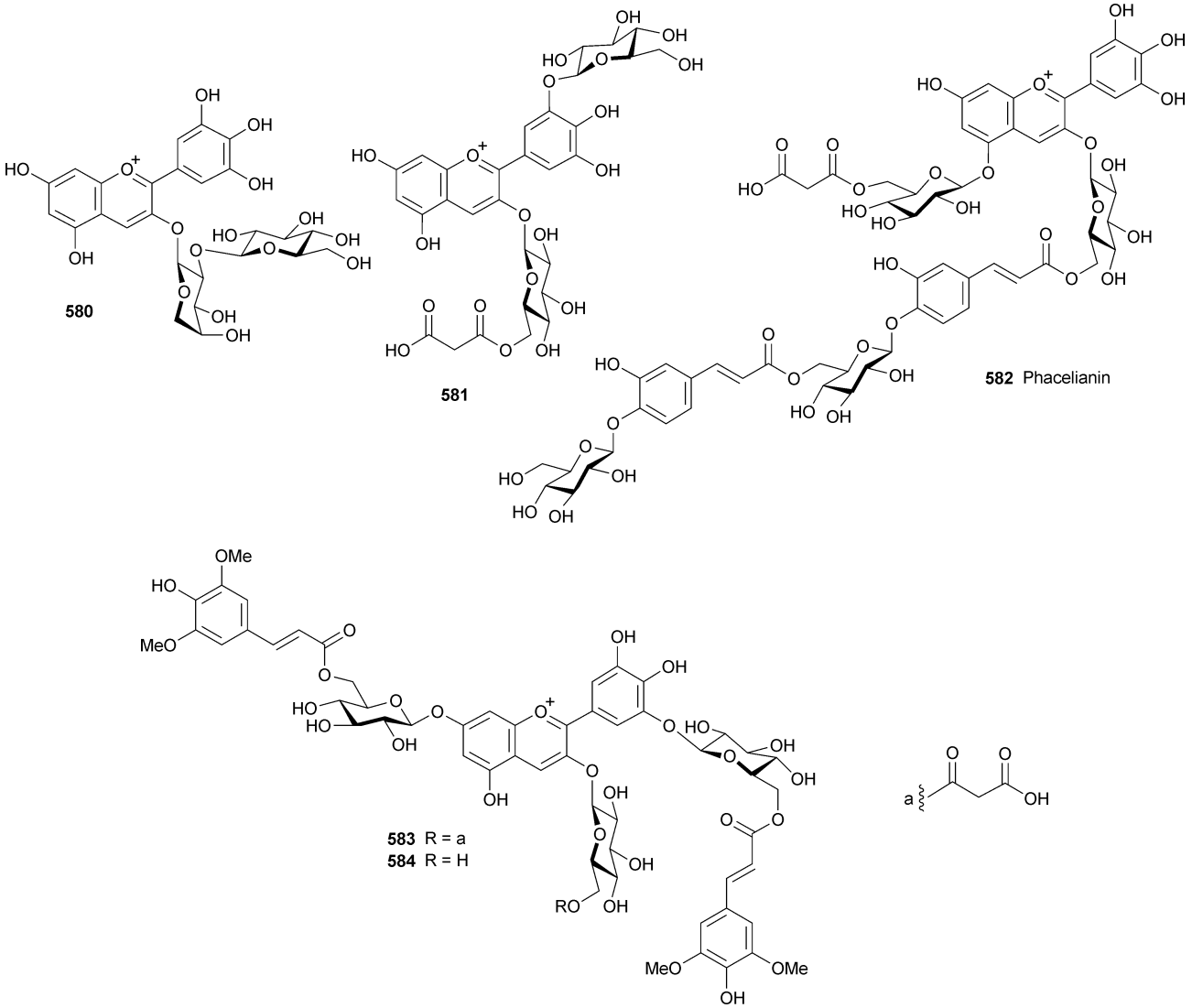


delphinidins found in *C. ternatea* petals.[480] Mori *et al.* obtained the complex dicaffeoyl delphinidin glycoside, phacelianin (**582**), from the blue flowers of *Phacelia campanularia* (Hydrophyllaceae).[481] According to the authors, this pigment is the first fully characterised polyacylated anthocyanin to exhibit two modes of molecular association, self-association and intramolecular stacking. In weakly acidic aqueous solutions, phacelianin (**582**) displayed the same blue colour as in the petals, but gradually precipitated, suggesting that a small amount of Al^{3+} or Fe^{3+} may be required to stabilise the blue colour. Re-examination of the major anthocyanin from the blue petals of *Evolvulus pilosus* (Convolvulaceae) revealed that this compound was identical



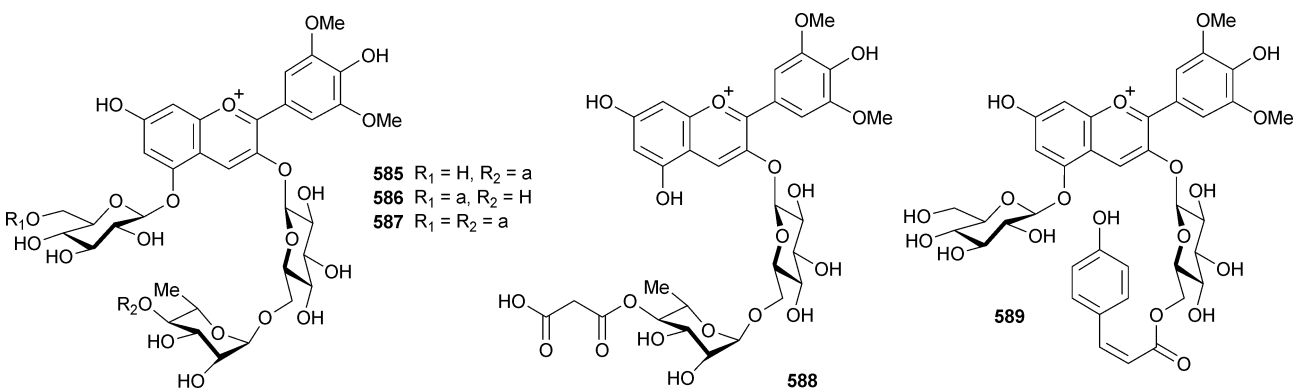
to phacelianin.[481] Of four new acylated delphinidin 3,7,3′-triglucosides found in the violet–blue flowers of *Vanda* cultivars (Orchidaceae), only two were fully characterised, delphinidin 3-*O*-[6-*O*-(malonyl)-β-glucopyranoside]-7,3′-di-[6-*O*-(sinapoyl)-β-glucopyranoside] (**583**) and its demalonyl analogue (**584**). A third glycoside was determined to be delphinidin 3-*O*-malonylglucoside-7,3′-diferuloylglucoside by chromatographic methods, and a fourth tentatively identified as a delphinidin 3-malonylglucoside-7,3′-diglucoside acylated by feruloyl and sinapoyl residues.[482]

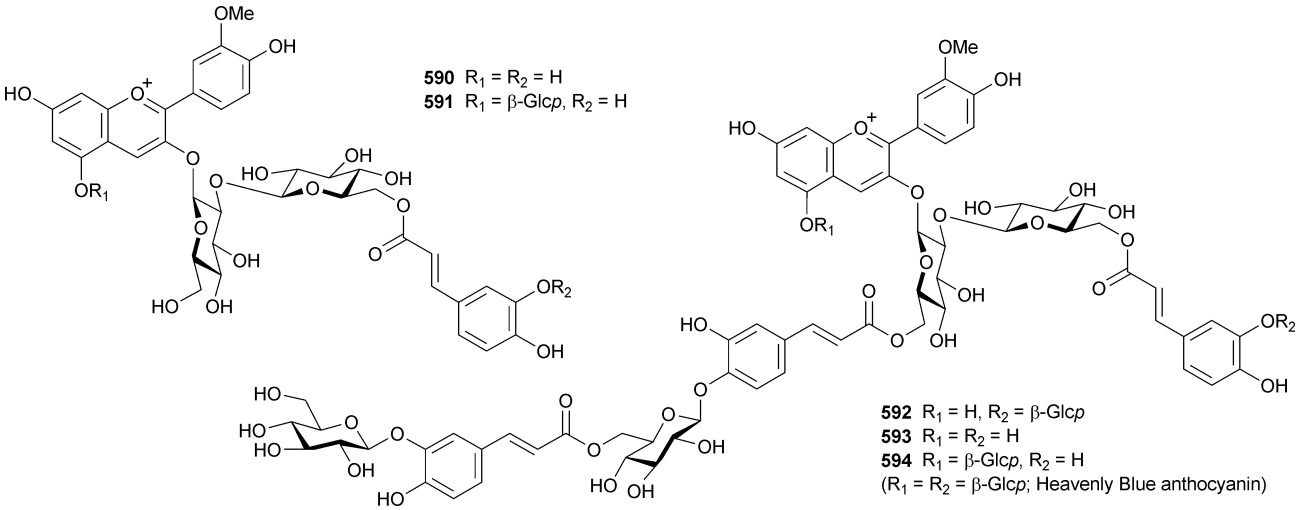
Thirteen examples of anthocyanins with methylated aglycones (**585–597**) appear in Table 6, five of which (**585–589**) are based on malvidin (3,5,7,4′-tetrahydroxy-3′,5′-dimethoxyflavylium). The latter were isolated from the purple leaves of the purple shamrock, *Oxalis triangularis* (Oxalidaceae). Three of these (**585–587**) are acylated derivatives of malvidin 3-rutinoside-5-glucoside. The remainder comprise malvidin 3-*O*-(6-*O*-(4-*O*-malonyl-α-rhamnopyranosyl)-β-glucopyranoside) (**588**) and malvidin 3-*O*-(6-*O*-(*Z*)-*p*-coumaroyl-β-glucopyranoside)-5-*O*-β-glucopyranoside) (**589**).[483] Saito *et al.* observed 17 different anthocyanins on HPLC analysis of the grey–purple flowers of a *duskish* mutant of the Japanese morning glory, *Ipomoea nil* (Convolvulaceae), including 'heavenly blue anthocyanin', a well-known pigment from the blue-flowered wild type and normal cultivars of *I. nil*, and five new acylated peonidin glycosides (**590–594**). These are caffeoylated derivatives of peonidin 3-sophoroside (**590**, **592**, **593**) or peonidin 3-sophoroside-5-glucoside (**591**, **594**), but less complex structurally than 'heavenly blue anthocyanin' itself.[484] The authors discuss the effects of mutations on glycosylation and acylation with respect to anthocyanin biosynthesis in *I. nil* flowers. Two acylated peonidin glycosides (**595**, **596**) have also been identified in commercial cultivars of *Petunia* with pink flowers.[485] Few 7-*O*-methylated anthocyanins have been recorded to date,[462] such that the isolation of 7-*O*-methylcyanidin 3-*O*-β-D-galactopyranoside (**597**) from the peel of the mango, *Mangifera indica* cv. 'Tommy Atkins' (Anacardiaceae), is of particular interest. Full spectroscopic characterisation of the aglycone (7-*O*-methylcyanidin) was given for the first time.[486] More than a decade ago, the first anthocyanin covalently linked to a flavone co-pigment by a disubstituted dicarboxylic acid was described as *Eichhornia* anthocyanin A from the flowers of the water hyacinth, *Eichhornia crassipes* (Pontederiaceae).[497] In the meantime, further representatives of this type of anthocyanin have been discovered,[462]

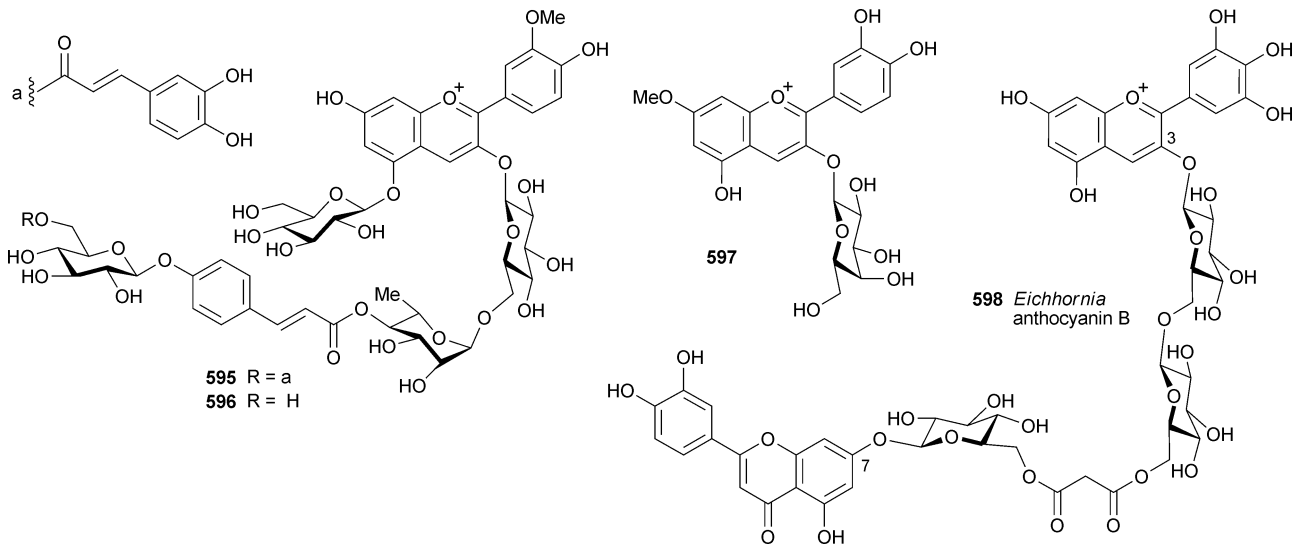


the most recent example of which is *Eichhornia* anthocyanin B (**598**). This was also isolated from the blue–purple flowers of *Eichhornia crassipes*, and is the luteolin analogue of *Eichhornia* anthocyanin A.[487]

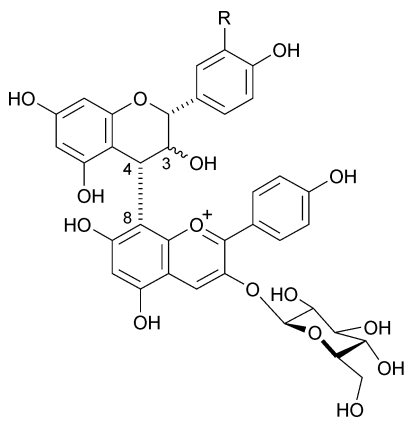
Flavanol–anthocyanin dimers have attracted particular attention during the review period. Although dimers of this kind have been known since the 1960s from wine, and later from beverages and fruit juices, they were thought to be artefacts resulting from direct condensation of anthocyanins and flavanols during processing and storage. Recently, however, this type of pigment has been shown to occur in fresh extracts of fruits and seeds on the basis of HPLC-ESI-MS analysis. In 2004, four purple-coloured dimers, catechin(4α→8)pelargonidin 3-*O*-β-glucopyranoside (**599**), epicatechin(4α→8)pelargonidin 3-*O*-β-glucopyranoside (**600**), afzelechin(4α→8)pelargonidin 3-*O*-β-glucopyranoside (**601**) and epiafzelechin(4α→8)pelargonidin 3-*O*-β-glucopyranoside (**602**),







were isolated from extracts of strawberry fruits (*Fragaria ananassa*, Rosaceae). These comprise anthocyanin and flavan-3-ol units connected by a C–C bond.[488] Although observed on HPLC of crude extracts, the authors suggest that there is a possibility that the compounds do not actually occur in the plant but are formed *in vitro* between anthocyanins and organic acids, giving rise to adducts with a more stable colour. A year later, similar anthocyanin–flavanol condensation products were observed in fresh extracts and juices of 10 varieties of blackcurrant (*Ribes nigrum*, Grossulariaceae).[498] For two of the compounds, MS and MS^2 spectra were consistent with delphinidin and cyanidin rutinosides covalently linked to epigallocatechin or gallocatechin. As these were present in fresh extracts, it seems likely that they are genuine constituents of the fruits and not artefacts.[498] Studies of other fruit and seed extracts gave similar results.[499] For example, the presence of catechin(4→8)pelargonidin 3-glucoside and afzelechin(4→8)pelargonidin 3-glucoside was confirmed in fresh extracts of strawberries (cv. 'Camarose'), and the new dimer, afzelechin(4→8)pelargonidin 3-rutinoside tentatively identified. In purple corn (*Zea mays* cv. 'Morado', Poaceae) (epi)catechin–cyanidin 3-glucoside-5-glucoside was detected; in red grape skin (*Vitis vinifera* cv. 'Tempranille', Vitaceae) (epi)catechin–peonidin 3-glucoside and (epi)catechin–malvidin 3-glucoside; and in extracts of the seed coat of the scarlet runner bean, *Phaseolus coccineus* (Leguminosae), (epi)catechin–cyanidin 3-glucoside and (epi)gallocatechin–delphinidin.[499] The latter is a dimer of a flavanol and an anthocyanidin, rather than an anthocyanin. Subsequently, two further examples were tentatively identified in extracts of the seed coat of *P. coccineus* as (epi)catechin–petunidin and (epi)catechin–peonidin.[500] (Epi)gallocatechin–delphinidin and (epi)catechin–peonidin were also present in the extracts of



a *P. vulgaris* cultivar from Guatemala together with (epi)catechin–cyanidin.[500] The seed coats of these *Phaseolus* species also contained mono- and diglycosides of cyanidin and pelargonidin, and in addition the free anthocyanin aglycones (anthocyanidins) delphinidin, cyanidin, pelargonidin and malvidin.[499–501] These are the first reports of the presence of free anthocyanidins in plant samples. Previously it was thought that these pigments only occurred as conjugates, notably as glycosides.[501] Several flavanol–anthocyanin pigments have been produced in model solution systems. To test whether flavanol–anthocyanin adducts could be the result of a mechanism involving acid-catalysed cleavage of flavanol oligomers followed by nucleophilic addition of an anthocyanin moiety to the flavanol carbocation, the procyanidin dimer epicatechin(4→8)epicatechin 3-*O*-gallate was added to a solution of malvidin 3-glucoside at pH 2. A new pigment was detected with the UV-vis and MS properties of epicatechin–malvidin 3-glucoside.[502] Another method for synthesising flavanol–anthocyanin dimers employed the dihydroflavonol taxifolin as a source of the catechin carbocation after reduction to a flavan-3,4-diol followed by protonation and dehydration.[503] Reaction with malvidin 3-*O*-glucoside gave two flavanol–anthocyanin dimers. According to NMR analysis, the C–C linkages between catechin and anthocyanin in the dimers were 4→8 and 4→6.[504] A pyranomalvidin 3-glucoside linked to a (+)-catechin unit through a vinyl linkage was obtained in aqueous alcoholic solution by reaction of a malvidin 3-glucoside–pyruvic acid derivative with (+)-catechin in the presence of acetaldehyde.[504] Ethyl-linked anthocyanin–flavanol pigments have been identified in wine. The mechanism of their formation was studied in model solutions containing catechin or epicatechin and malvidin 3-glucoside together with acetaldehyde. The same pigments were produced in model fermentations containing added malvidin 3-glucoside and (epi)catechin when inoculated with the acetaldehyde-producing wine yeast, *Saccharomyces cerevisiae*. These observations suggest that the formation of ethyl-linked anthocyanin–flavanol pigments may contribute significantly to the purple colouration of young wines.[505]

Kondo *et al.* have developed a novel and efficient method for the synthesis of cyanidin 3-*O*-β-D-glucopyranoside from (+)-catechin by biomimetic oxidation.[506] The 3-hydroxyl of (+)-catechin was glucosylated, and the 4-position subsequently oxidised and hydrated to give the 5,7,3′,4′-tetra-*O*-(*tert*-butyldimethylsilyl)-flav-3-en-3-ol 3-*O*-β-D-glucopyranoside as a key intermediate. This compound was deprotected and oxidised under air in HCl–methanol to give cyanidin 3-*O*-β-D-glucopyranoside.[506]

The structure of the stable blue metallic pigment, protocyanin, from the cornflower, *Centaurea cyanus* (Asteraceae), has been fully elucidated after almost a century of research by many investigators.[13] It was in 1913 that Willstätter isolated an anthocyanin from the blue petals of *C. cyanus* which he called cyanin.[507] Later he isolated the same anthocyanin from red roses,[508] an apparently paradoxical result since the petals of these two plant species do not have the same colour. Initial explanations based on pH effects[508] were questioned by Shibata, who advocated a metal complex theory in 1919.[509] Research during the last three decades indicates that various factors contribute towards the blueing of anthocyanins, including the presence of acyl groups, co-pigments (usually flavonoids) and metal ions.[13] The components involved in the formation of protocyanin were found to be the anthocyanin, cyanidin 3-*O*-(6-*O*-succinylglucoside)-5-*O*-glucoside, the flavone glycoside co-pigment, apigenin 7-*O*-glucuronide-4′-*O*-(6-*O*-malonylglucoside), and the metal ions Fe^{3+}, Mg^{2+} and Ca^{2+}. Using these components (Fe^{2+} was used in the reconstruction experiments, but is present as Fe^{3+} in the complex), a pigment identical to protocyanin from cornflower was obtained and crystallised successfully for the first time.[510] According to X-ray crystallographic analysis, the blue protocyanin pigment consists of a complex of six molecules each of anthocyanin and flavone glycoside, with one ferric ion, one magnesium ion and two calcium ions.[511] For further insight into the history of the discovery of the complex structures of protocyanin and other blue metallic anthocyanin pigments such as commelinin from the flowers of *Commelina communis*, protodelphin from the blue flowers of *Salvia patens* and the pigment from blue hydrangea petals (*Hydrangea macrophylla*), the review by Takeda is recommended.[13] The latter pigment consists of delphinidin 3-*O*-glucoside-Al^{3+}-3-caffeoylquinic acid or 3-*p*-coumaroylquinic acid, in which the aluminium ion complexes with the *ortho*-dihydroxy group of the anthocyanin B-ring and the carboxyl and α-hydroxyl groups of the quinic acid moiety.[512] In order to clarify the mechanism of blue sepal colour development in hydrangea, attempts to reproduce the blue colour *in vitro* by mixing the anthocyanin part with designed synthetic co-pigments in the presence of Al^{3+} at pH 4.0 were carried out, and essential structural characteristics of the co-pigment determined.[513] Although the Himalayan blue poppy, *Meconopsis grandis* (Papaveraceae), contains cyanidin glycosides (**579** and a malonylated derivative) as the anthocyanin components (as in the case of the blue cornflower), the co-pigments are flavonol glycosides based on kaempferol.[478,514] The development of the blue colour of the petals was studied by mixing the different anthocyanin and flavonol components and adding small amounts of metal ions in different concentrations.[478] These experiments indicated that the malonyl group of the anthocyanin was not needed for blue colour development, but that flavonol glycosides (2 equivalents), Fe^{3+} (1/6 equivalent) and an excess of Mg^{2+} ions were required. The full structure of the supramolecular complex has not yet been solved, but may represent a new type of metal pigment complex similar to that responsible for the blue flower colour of hydrangea.[478]

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