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Sesquiterpene coumarins

Anna Gliszczyńska · Peter E. Brodelius

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Abstract Plants have a long history as therapeutic tools in the treatment of human diseases and have been used as a source of medicines for ages. In search of new biologically active natural products, many plants and herbs used in traditional medicine are screened for natural products with pharmacological activity. In this paper, we present a group of natural products, the sesquiterpene coumarins isolated from plants, and describe their wide range of biological activity. Sesquiterpene coumarins are found in some plants of the families Apiaceae (Umbelliferae), Asteraceae (Compositae) and Rutaceae. The coumarin moiety is often umbelliferone (7-hydroxycoumarin) but scopoletin (7-hydroxy-6-methoxycoumarin) and isofraxidin (7-hydroxy-6,8-dimethoxycoumarin) are also found. These coumarins are linked to a C_{15} terpene moiety through an ether linkage. Another group of sesquiterpene coumarins is the prenylated 4-hydroxycoumarins where the link between the coumarin and the C_{15} terpene moiety is a C–C-bond at carbon 3 of the coumarin moiety. Finally, the prenyl-furocoumarin-type sesquiterpenoids are a separate group of sesquiterpene coumarins based on the suggested biosynthetic pathway. Our relatively limited knowledge on the biosynthesis of sesquiterpene coumarins is reviewed.

Keywords Farnesyldiphosphate · 4-Hydroxycoumarin · Isofraxidin · Prenylated coumarins · Prenyl-furocoumarin sesquiterpenenes · Scopoletin · Sesquiterpene coumarins · Umbelliferone

Abbreviations

AChE	Acetylcholinesterase
BIS	Bisphenyl synthase
CPE	Cytopathic effect
F6′H1	Fe(II)- and 2-oxoglutarate-dependent dioxygenase
FDP	Farnesyl diphosphate
FDU7T	Farnesyl diphosphate umbelliferone transferase
HRV	Human rhinoviruses
INH	Isonicotinic acid hydrazide
M4Beu	Human metastatic pigmented malignant melanoma cells
MDR	Multidrug resistance
MIC	Minimum inhibitory concentration
NDP	Nerolidyl diphosphate
SHC	Squalene-hopene cyclase
SQE	Squalene epoxidase
VEGF	Vascular endothelial growth factor
UPE	Umbelliprenin epoxidase

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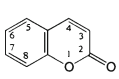
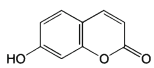
Introduction

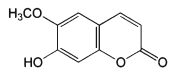
Sesquiterpene coumarins constitute an interesting family of natural products. They are a group of molecules whose structures are based on a C_{15} terpene moiety linked through either an ether linkage with the 7-hydroxy group of umbelliferone (7-hydroxycoumarin) (**2**), scopoletin (7-hydroxy-6-methoxycoumarin) (**3**) or isofraxidin (7-hydroxy-6,8-dimethoxycoumarin) (**4**) or through a C–C bond with carbon 3 of 4-hydroxycoumarin (**5**). The prenyl-furocoumarin-type sesquiterpenoids constitute a separate group of sesquiterpene coumarins. Numbering of the coumarin ring system is given in coumarin (**1**).



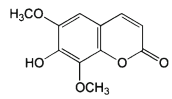
1 coumarin



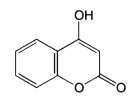
2 umbelliferone



3 scopoletin



4 isofraxidin



5 4-hydroxycoumarin

Sesquiterpene coumarins are found in some plants of the families Apiaceae (Umbelliferae), Asteraceae (Compositae) and Rutaceae. They occur in the genera *Ferula, Heptaptera, Heraclum, Peucedanum, Angelica* (Apiaceae), *Artemisia* (Asteraceae) and *Haplophyllum* (Rutaceae). The *Ferula* genus is a very rich source of sesquiterpene coumarins. It comprises more than 150 species widespread in central Asia, Middle East and around the Mediterranean area. The systematics of *Ferula* is still quite a controversial matter. Chemical varieties of different type of plants from different regions are still the major aim of studies of many research groups. Sesquiterpene coumarins have been used as chemosystematic markers. Studies on the chemical constituents of this genus have developed rapidly over the last 20 years and around 130 different sesquiterpene coumarins have been reported from this genus (Lee et al. 2009). Thus, there is a considerable interest in the chemistry and pharmacology of plants belonging to the *Ferula* genus. For instance, investigations of populations of *Ferula communis* growing in Sardinia established that two chemotypes of this plant occur in this region (Marchi et al. 2003). One chemotype contained toxic prenylated 4-hydroxycoumarins while the second chemotype contained sesquiterpene coumarin ethers and exhibited therapeutic activity. Several species of the *Ferula* genus are used as spices and are well known as medicinal plants with documented wide range of biological activities. Sesquiterpene coumarins isolated mainly from the *Ferula* genus exhibit antiviral, antibacterial, antileishmanial, anti-inflammatory and antitumor activity. At present, our knowledge about how sesquiterpene coumarins are biosynthesized is very limited.

Sesquiterpene umbelliferyl (7-hydroxycoumarin) ethers

Umbelliprenin (**6**) is a secondary metabolite that is found in some plants. This compound occurs in the genera *Ferula, Heptaptera, Heracleum, Peucedanum* and *Angelica* from the family Apiaceae and also in the genus *Haplophyllum* belonging to the Rutaceae family (Ahmed 1999; Appendino et al. 1997; Filippini et al. 1998; Murphy et al. 2004; Murray 2002). Umbelliprenin (**6**) isolated from the flowers of *Magydaris tomentosa* was reported to inhibit growth of pathogenic bacterial strains (Rosselli et al. 2007).

Shahverdi et al. (2005) established an antibacterial effect of the chloroform extract of *Ferula persica* var. *persica* against 13 species of microorganisms and identified that umbelliprenin (**6**) was the biologically active compound in this fraction. The inhibitory effect of this compound isolated from the roots of *F. persica* on pigmentation in *Serratia marcescens* has also been described (Iranshahi et al. 2004). The process of depigmentation was concentration depended. Umbelliprenin (**6**) started to cause bleaching of the bacteria at 0.6 μM but the best results were observed at 1.5 μM.

Furthermore, it was shown that umbelliprenin (**6**) inhibits high matrix metalloproteinases. The

cytotoxicity of umbelliprenin (**6**) towards the fibrosarcoma cell line Wehi 164 was dose-dependent and showed good activity at 50 μg/mL (Shahverdi et al. 2006). Khorramizadeh et al. (2010) reported that the combination of Fe_3O_4 magnetite nanoparticles with umbelliprenin (**6**) was much more cytotoxic against human fibrosarcoma cell line (HT-1080) (IC_{50} = 9 μg/mL) than umbelliprenin (**6**) alone (IC_{50} = 50 μg/mL). This 7-prenyloxycoumarin exhibited also anticoagulant activity (Rosselli et al. 2007) as well as antileishmanial activities against promastigotes of *Leishmania major* (Iranshahi et al. 2007). After 48 h of incubation, umbelliprenin (**6**) significantly inhibited promastigote growth (IC_{50} = 4.9 μg/mL).

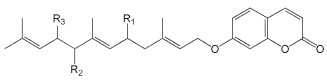
The cytotoxic effect of umbelliprenin (**6**) from *Ferula szowitsiana* on five human solid cancer cell lines and human primary fibroblasts were also the subject of a recent study (Barthomeuf et al. 2008). The best antiproliferative effect was observed for human metastatic pigmented malignant melanoma cells (M4Beu). These cells were more susceptible than normal fibroblasts and umbelliprenin (**6**) (IC_{50} = 12.4 μM) was almost two times more active than cisplatin (IC_{50} = 23.1 μM) a chemotherapy drug used to treat various types of cancers. At lower concentrations, the M4Beu cells were inhibited through cell-cycle arrest in the G1 stage while at higher concentrations (above 25 μM) cell death was the results of the apoptosis process.

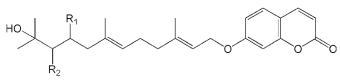
Barthomeuf et al. (2008) showed that the ether-linked sesquiterpene moiety is important for high biological activity. Iranshahi et al. (2009b) described umbelliprenin (**6**) as a potent inhibitor of soybean 5-lipoxygenase. In this study, umbelliprenin (**6**) showed significant higher inhibition (IC_{50} = 0.07 μM) than caffeic acid used as a standard inhibitor (IC_{50} = 600 μM). Based on these results and many other studies, umbelliprenin (**6**) has been described as an agent for cancer chemoprevention along with other 7-prenyloxycoumarins (Iranshahi et al. 2008; Iranshahi et al. 2009a; Sahebkar and Iranshahi 2010).

Among the compounds isolated from the roots of *Ferulago campestris* three sesquiterpene coumarins: umbelliprenin (**6**), coladonin (**34**) and coladin (**33**) were found and used as new acetylcholinesterase (AChE) inhibitors. All three showed moderate activity with IC_{50} ranging from 380 to 1.171 μM (Dall'Acqua et al. 2010). Umbelliprenin (**6**) was also a potent inhibitor of squalene-hopene cyclase (SHC) (IC_{50} = 70 μM) (Cravotto et al. 2004). It should be pointed out that Cravotto et al. (2004) synthesized a number of farnesyloxycoumarins derivatives starting from 4- and 7-hydroxy coumarin and investigated the structure-activity relationship. They proved that the 7-hydroxycoumarin-moiety was a good starting structure for the design of SHC inhibitors. Using human peripheral lymphocytes exposed to oxidative stress, Soltani et al. (2009) evaluated the antigenotoxicity effects of umbelliprenin (**6**). At higher concentrations (>100 μM), **6** showed similar protective effect compared to ascorbic acid.

The oxygenated farnesol derivatives (**7–9**) were the major fraction obtained from *Ferula assafoetida* by Appendino et al. (1994). The 5′,8′-dihydroxylated derivative of umbelliprenin (**6**), asacoumarin (**10**), was for the first time reported by Kajimoto et al. (1989). The absolute configuration at C5′ of compound (**10**) was determined to be *S* using the Mosher method (Lee et al. 2009). A new sesquiterpene coumarin ether, 5′-acetoxy-8′-hydroxy-umbelliprenin (**11**), was found in the extract of *F. assafoetida* along with its analogue 8′-acetoxy-5′-hydroxyumbelliprenin (**12**) (Lee et al. 2009; Appendino et al. 1994; Abd El-Razek et al. 2007). 8′-Acetoxy-5′-hydroxyumbelliprenin (**12**) was an anti-inflammatory agent inhibiting NF-κB (Appendino et al. 2006). It also exhibited antiviral activity against influenza A virus (H_1N_1) (IC_{50} = 0.81 μg/mL) (Lee et al. 2009).

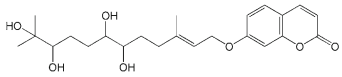
10′*R*-Karatavicinol (**13**) was isolated from various *Ferula* species: *Ferula foetida* (Abd El-Razek et al. 2007), *Ferula arrigonii* (Appendino et al. 1997) and *F. assafoetida* (Lee et al. 2009). Karatavicinol (**13**) and 6′,7′-dihydroxykaratavicinol (**17**) were isolated from *Ferula sinaica* (Ahmed 1999). Karatavicinol (**13**) showed a strong inhibitory effect (IC_{50} = 65 μM) on SHC from *Alicyclobacillus acidocaldarius* (Cravotto et al. 2004). Compounds (**13**), (**17**) and 10′*R*-acetoxy-11′-hydroxyumbelliprenin (**14**) were observed in an extract from *F. assafoetida* by Lee et al. (2009). The source of (9*S*,10*R*)-9′,10′,11′-trihydroxyumbelliprenin (**15**) was the fruits of *Heptaptera anisoptera* and *Heptaptera anatolica* (Appendino et al. 1992). The structure of (**15**) was confirmed by acetylation of (**15**) in acetic anhydride/pyridine to (**16**).





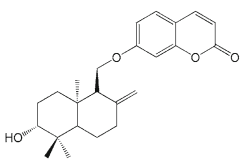
	R_1	R_2	R_3
6 umbelliprenin	H	H	H
7 5'-hydroxyumbelliprenin	OH	H	H
8 8'-hydroxyumbelliprenin	H	OH	H
9 9'-hydroxyumbelliprenin	H	H	OH
10 asacoumarin	OH	OH	H
11 5'-acetoxy-8' hydroxyumbelliprenin	OAc	OH	H
12 8'-acetoxy-5'-hydroxyumbelliprenin	OH	OAc	H

	R_1	R_2
13 10'*R*- Karatavicinol	H	OH
14 10'-acetoxy-11'-hydroxyumbelliprenin	H	OAc
15 9',10',11'-trihydroxyumbelliprenin	OH	OH
16 9',10'-diacetoxy-11-hydroxy-umbelliferone	OAc	OAc

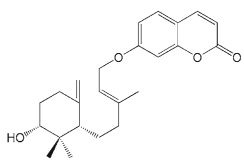


17 6',7'-dihydroxykaratavicinol

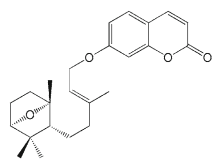
Oughlissi-Dehak et al. (2008), interested in the chemistry and pharmacology of *Ferula* species, investigated the extract of the aerial parts of *Ferula vesceritensis*. They isolated 11 sesquiterpene derivatives and among them were two sesquiterpene coumarins: farnesiferol A (**18**) and feselol (**22**). Based on previous reports on the potential role of sesquiterpene coumarins as reversal agents of multidrug resistance (MDR) in cancer cells (Barthomeuf et al. 2006), the authors studied the interactions of the isolated compounds with efflux pumps. Using the parasitic model of the P-glycoprotein nucleotide-binding domain of MDR-like efflux pump in *Cryptosporidium parvum,* they confirmed the chemotherapeutic potential role of farnesiferol A (**18**) (IC_{50} = 24.9 μM) and feselol (**22**) (IC_{50} = 32.5 μM) as reversing agents of MDR (Oughlissi-Dehak et al. 2008).



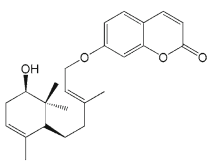
18 farnesiferol A



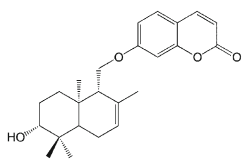
19 farnesiferol B



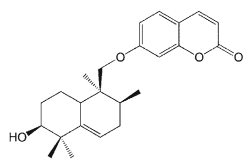
20 farnesiferol C



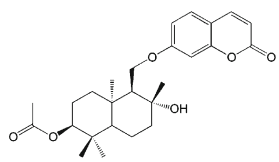
21 farnesiferol D



22 feselol



23 microlobidene



24 kellerin

Farnesiferol B (**19**), farnesiferol C (**20**) and two other sesquiterpene coumarins, microlobidene (**23**) and kellerin (**24**)**,** were isolated from the *F. assafoetida* gum resin and tested as antiviral agents (Rollinger et al. 2008). In the studies on biological activity, the molecular modeling data of the compounds were used. Antiviral activities were assessed by determination of the inhibition of the cytopathic effect (CPE) induced by human rhinoviruses (HRV). In the CPE-inhibitory effect assays, farnesiferol B (**19**) and C (**20**) showed dose-dependent antiviral activities against HRV. The

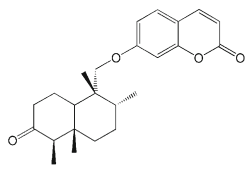
authors indicated that farnesiferol B (**19**) and C (**20**) may find an application in the treatment of upper respiratory diseases.

Recent work demonstrated that farnesiferol C (**20**) isolated from *F. assafoetida* exhibited antiangiogenic activity (Lee et al. 2010). Farnesiferol C (**20**) inhibited vascular endothelial growth factor (VEGF) and the expression of matrix metalloproteinase-2 at concentrations ranging from 10 to 40 μM. Moreover, the authors pointed out that farnesiferol C (**20**) inhibited the angiogenic sprouting of VEGF-treated rat aorta in an *ex vivo* model. Furthermore, in vivo growth of mouse Lewis lung cancer allograft was inhibited to 60% at a daily dosage of 1 mg/kg body weight of fanesiferol C (**20**) without negative effects on the weight of the host mice.

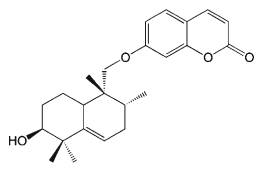
Mashinchian et al. (2010) described the synthesis of polymer based smart thermosensitive nanocarriers for delivery of natural active products. In this study, farnesiferol C (**20**) was used as a potent anticancer agent. Farnesiferol C (**20**) was dissolved into the hydrophobic core of the polymeric micelles and the effect of temperature on drug release was investigated.

Farnesiferol D (**21**) was isolated from *Ferula assafoetida* and was found to exhibit antimutagenic activity on *Salmonella typhimurium* strain TA 100 (45% protection) utilizing a modified Ames test (Pillai et al. 1999) at a concentration of 32 μg benzo(a)pyrene/plate.

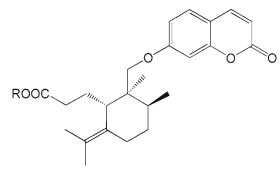
Several cyclic sesquiterpene coumarins (**19–21**) and (**25–32**) were obtained from *F. szowitsiana* and *Ferula gumosa* (Iranshahi et al. 2007; Iranshahi et al. 2010). Szowitsiacoumarin A (**25**), szowitsiacoumarin B (**26**), gumosin (**29**) and the glycosides gumoside A (**30**) and B (**31**) had not been reported previously. The isolated compounds were tested for antiproliferative activity towards many cancer cell lines: M14 (human melanoma), MCF-7 (breast carcinoma), T98G (glioblastoma), A549 (lung carcinoma), Saos-2 (osteosarcoma), FRO (thyroid carcinoma) and U937 (leukemic monocyte lymphoma) (Iranshahi et al. 2010). Feselol (**22**) was the most active compound and efficiently inhibited proliferation of leukemic cells (IC_{50} = 8 μM).



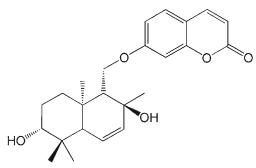
25 szowitsiacoumarin A



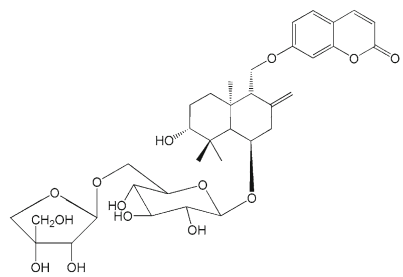
26 szowitsiacoumarin B



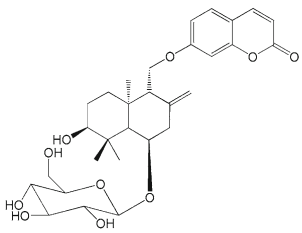
	R
27 galbanic acid	H
28 methyl galbanate	Me



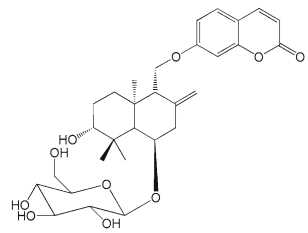
29 gumosin



30 gumoside A



31 gumoside B

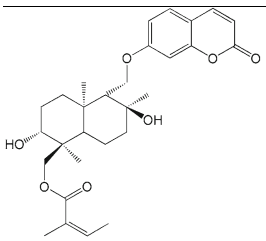


32 cauferoside

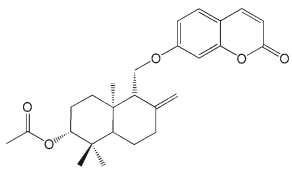
Galbanic acid (**27**) was isolated from *F. szowitsiana* by Shahverdi et al. (2007) and used in antibacterial tests against *Staphylococcus aureus.* At concentrations lower than 120 μg/ml, no inhibitory effect of galbanic acid (**27**) on the tested strain was observed but its combination (100 μg/ml) with penicillin G or cephalexin significantly reduced the minimal inhibitory concentrations (MIC) for both of these antibiotics (64- and 128-times, respectively). Fazly Bazzaz et al. (2009) reported that galbanic acid (**27**) is a modulator of antibiotic resistance in clinical isolates of *S. aureus,* since this metabolite from acetone extract of *F. szowitsiana* roots reduced the MIC values of ciprofloxacin, methicillin and tetracycline. Recently it was shown that galbanic acid (**27**) is a potent inhibitor of protein farnesyltransferase (IC_{50} = 2.5 μM) (Cha et al. 2011)

Jabrane et al. (2010) isolated the new sesquiterpene coumarin, tunetacoumarin A (**33**) from the roots of *Ferula tunetana* along with well-known coladin (**34**), coladonin (**35**), isosamarcandin (**36**) and 13-hydroxyfeselol (**37**). The cytotoxic activity of the isolated compounds (**33–37**) was tested towards the human colorectal cancer cell lines HCT 116 and HT-29. Three of them, i.e. coladin (**34**), coladonin (**35**) and 13-hydroxyfeselol (**36**), showed weak cytotoxicity. Coladonin (**35**) was also isolated from the resin of *F. foetida* (Abd El-Razek et al. 2007) and from roots of *F. campestris* (Dall'Acqua et al. 2010) along with coladin (**34**) and umbelliprenin (**6**). The constituents of the extract from *F. campestris* were investigated as new potential AChE inhibitors. Measured IC_{50}-values for coladin (**34**) and coladonin (**35**) were lower than those reported by Rollinger et al. (2004) for scopoletin (**3**). The authors also concluded that the presence of a free hydroxy group in coladonin (**35**) determined the interaction with enzymes and reduced the inhibitory activity to around half of that of coladin (**34**).

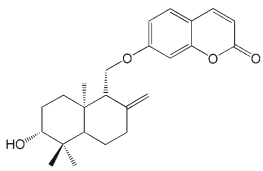
The structure of conferol (**38**) was fully established for the first time for the compound isolated from *Ferula conocaula* and *Ferula moschata* (Vandyshev et al. 1972). Conferol (**38**) and its oxidation product—conferone (**39**) were extracted from dried roots of *Ferula sumbul* and studied as anti-HIV agents and inhibitors of cytokine release (Zhou et al. 2000). Conferone (**39**) obtained from another species, *Ferula schtschurowskiana,* was determined to be a biologically active modulator of P-glycoprotein (an ABC transporter) transport (Zhong et al. 2001).



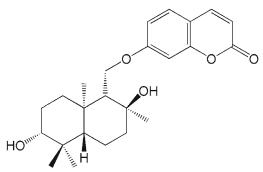
33 tunetacoumarin A

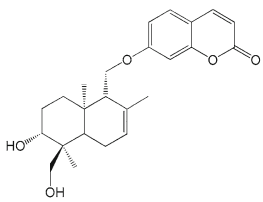


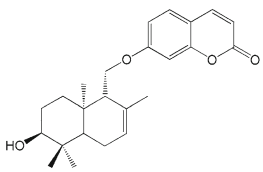
34 coladin



35 coladonin



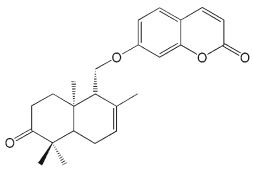




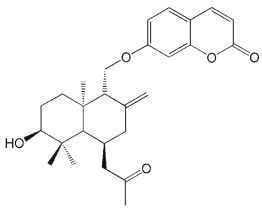
A number of sesquiterpene coumarins, including compounds **7**, **12**, **18**, **20**, **27**, **28** and **38**, isolated from an extract *F. assafoetida* showed powerful effects against influenza A (H_1N_1) virus (IC_{50} = 0.26–0.86 μg/ml) and were more active than adamantine (IC_{50} = 0.92 μg/ml), a prescription antiviral drug (Lee et al. 2009). The strongest activity was observed for methyl galbanate (**28**) (IC_{50} = 0.26 μg/ml). These findings were in line with the fact that *F. assafoetida* was used as a remedy during the 1918 Spanish Flu pandemic in China. Consequently, one or more of these sesquiterpene coumarins may be developed into new antiviral drugs.

Two new sesquiterpene coumarins: isofeterin (**40**) and sinkianone (**42**) were obtained from the roots of

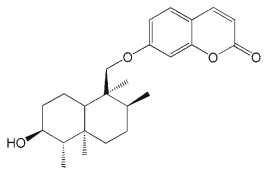
36 isosamarcandin



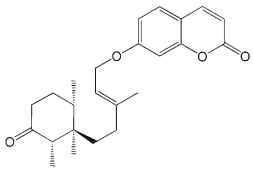
37 13-hydroxyfeselol



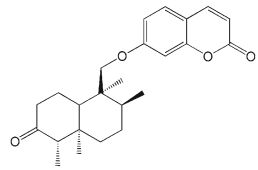
38 conferol



39 conferone



40 isofeterin



41 lehmannolol

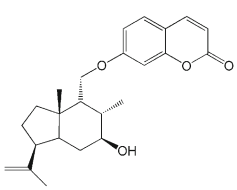
42 sinkianone

43 lehmanolone

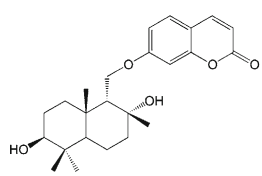
Ferula sinkiangensis besides the known compounds lehmannolone (**43**) and lehmannolol (**41**) (Yang et al. 2006). The derivative of isosamarcandin (**36**), isosamarcandin angelate (**46**)**,** was isolated from the roots of *Ferula tingitana* (Miski and Ulubelen 1985).

A study of the constituents of the Egyptian medicinal plant *Ferula sinaica* afforded two new sesquiterpene coumarins: the cyclopentanesesquiterpene coumarin ferusinol (**44**) and samarcandin diastereomer (**45**) (El-Bassuony et al. 2007). Their structures were established on the basis of spectral data and a biosynthetic route for ferusinol (**44**) was proposed as outlined below in the context of sesquiterpene coumarins biosynthesis. Both compounds were tested in vitro against gram-positive *Bacillus cereus* and *S. aureus* as well as gram-negative *Serratia* sp.*, Pseudomonas* sp. and *Escherichia coli.* Ampicilin and amoxillin were used as positive control and the MIC-values were evaluated. Ferusinol (**44**) showed high activity against both gram-positive and gram-negative strains while samarcandin diastereomer (**45**) was active only towards gram-negative strains.

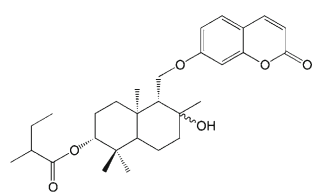
44 ferusinol



45 samarcandin diastereomer



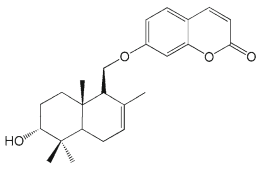
46 isosamarcandin angelate



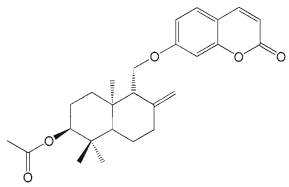
The extract of dried *Ferula badrakema* roots contained several 7-*O*-prenylated sesquiterpene coumarins: mogoltacin (**47**), feselol (**22**), badrakemin acetate (**48**), ferocaulidin (**49**), conferone (**39**) and conferol acetate (**50**) (Iranshahi et al. 2009c). Mogoltacin (**47**) was described to significantly enhanced the cytotoxicity of vincristine (by 32.8%) towards human transitional cell carcinoma without causing any toxic effects on the cells (Rassouli et al. 2009). The resins of *F. vesceritensis* and *F. sinaica* afforded many sesquiterpene coumarins including a compound with rare carbon skeleton—ferulsinaic acid (**51**) (Ahmed et al. 2007). Ferulsinaic acid (**51**) extended the life span of *Caenorhabditis elegans* in a dose dependent manner (Sayed 2011), i.e. from 18.6 days to 20.8 or 22.3 days at concentrations of 10 and 100 μM, respectively. It was concluded that ferulsinaic acid (**51**) had therapeutic efficacy as an antioxidant with the possibility of its use as an antioxidant drug. Assafoetidnol A (**52**) and assafoetidnol B (**53**) (not previously reported) were isolated along with six other sesquiterpene coumarins: gummosin (**54**), polyanthin (**55**), badrakemin (**56**), neveskone (**57**), samarcandin diastereomer (**45**) and galbanic acid (**27**) from roots of *Ferula assafoetida* (Abd El-Razek et al. 2001). Bandyopadhyay et al. (2006) fractioned the gum of *F. assafoetida* with hexane and ethyl acetate and

isolated a new ether derivative of umbelliferone—saradaferin (**58**).

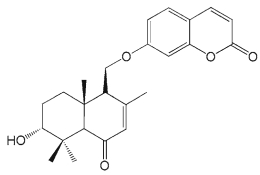
A new scopoletin-based sesquiterpene ether, driportlandin (**61**) was isolated from *Euphorbia portlandica* and tested as a potential modulators of MDR in tumour cells (Madureira et al. 2004). The MDR-reversing activity of driportlandin (**61**) was evaluated on multidrug resistant L5178 mouse lymphoma cells using a rhodamine 123 exclusion test. Driportlandin (**61**) showed significant P-glycoprotein inhibitory activity (9 μM) in comparison with the verapamil (20 μM), which was used as a positive control (Madureira et al. 2004).



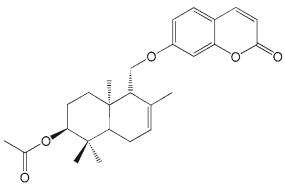
47 mogoltacin



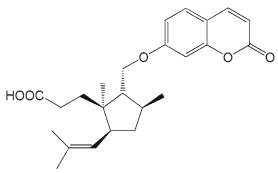
48 badrakemin acetate



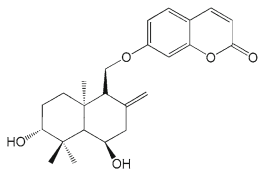
49 ferocaulidin



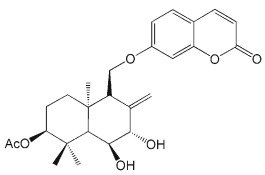
50 conferol acetate



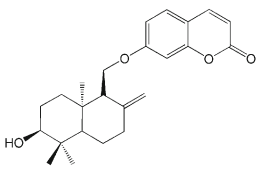
51 ferulsinaic acid



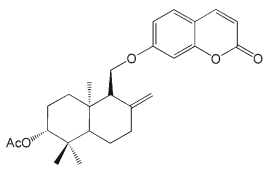
52 assafoetidnol A



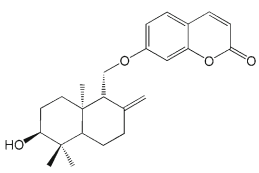
53 assafoetidnol B



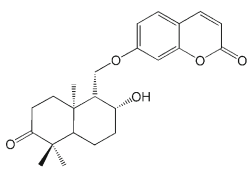
54 gummosin



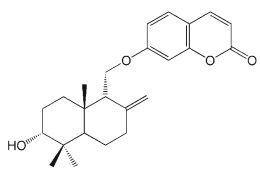
55 polyanthin



56 badrakemin



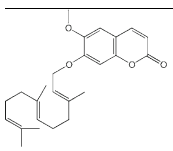
57 neveskone



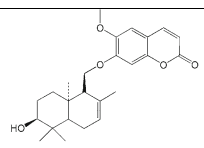
58 saradaferin

Scopoletin-derived sesquiterpene ethers

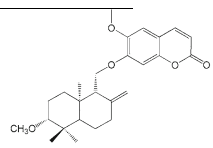
Sesquiterpene derivatives of 7-hydroxy-6-methoxy-coumarin (scopoletin (**3**)) are not so common. The roots of *Artemisia persica* afforded in addition to isofraxidin-derived sesquiterpene ethers, the scopoletin farnesyl ether—scopofarnol (**59**) and the scopoletin drimenyl ether—scopodrimol (**60**) (Hofer and Greger 1984b). Scopodrimol (**60**) was also isolated from *Achillea* and *Artemisia* species (Hofer et al. 1983).



59 scopofarnol



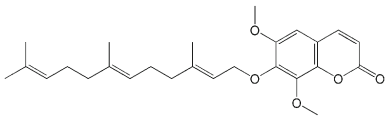
60 scopodrimol



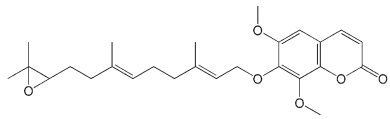
61 driportlandin

Isofraxidin-derived sesquiterpene ethers

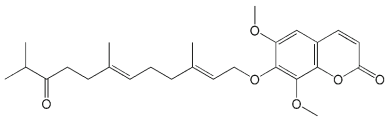
Sesquiterpene coumarin ethers with an isofraxidin moiety (7-hydroxy-6,8-dimetoxycoumarin) (**4**) are found in the genera *Artemisia*, *Achillea* and *Ferula*. Farnochrol (**62**) dominated in roots of several *Artemisia* species (*A. pontica*, *A. persica*, *A. abrotanum*, *A. gmelinii*, *A. vestita*) and *Achillea* species (*A. ochroleuca*, *A. pseudopectinata*, *A. depressa*). Farnochrol (**62**) is the biogenetic precursor of all derivatives belonging to this class of compounds (Greger et al. 1982b; Hofer and Greger 1984a) as discussed below in the context of biosynthesis. The extensive studies of secondary metabolites in the genera *Artemisia* (section *Abrotanum)* and *Achillea* have shown that the accumulation of sesquiterpene-isofraxidin ethers can be used as a parameter for systematics. A number of papers describing the isolation and structural characterization of isofraxidin-derived sesquiterpene coumarins have been published (Greger et al. 1982a, b, 1983; Hofer et al. 1983; Hofer and Greger 1984a). The open chain sesquiterpene-coumarin ethers (**62–64**) and a new compound ochroketolate (**65**) were isolated from *Achillea ochroleuca* (Jandl et al. 1997). Epoxyfarnochrol (**63**) and drimartol B (**68**) were isolated from the roots of *Ferula jaeskeana* (Razdan et al. 1989).



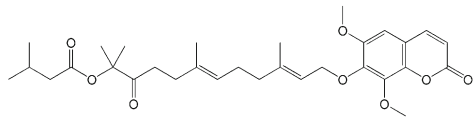
62 farnochrol



63 epoxyfarnochrol

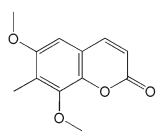


64 oxofarnochrol

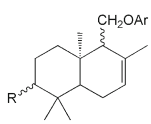


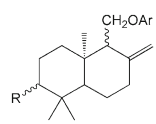
65 ochroketolate

A new isofraxidin drimenyl ether was obtained from roots of *Tanacetum parthenium* transformed with *Agrobacterium rhizogenes.* The structure of this compound was established by spectroscopic methods and elucidated to be 9-epipectachol B (**80**) (Kisiel and Stojakowska 1997). Similarily drimartol A (**66**) was isolated from hairy root cultures of *Artemisia annua* (Zhai and Zhong 2010). Jatrophadioxan (**81**) was isolated as a new compound from *Jatropha integrrima* (Euphorbiaceae) (Sutthivaiyakit et al. 2009).

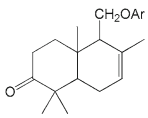


Ar





	R			R	
66 drimartol A	OH ax	CH_2OAr ax	**71** pectachol	OH ax	CH_2OAr ax
67 iso-drimartol B	OH ax	CH_2OAr eq	**72** albartol	OH ax	CH_2OAr eq
68 drimartol B	OH eq	CH_2OAr ax	**73** acetylpectachol	OAc ax	CH_2OAr ax
69 acetyldrimartol A	OAc ax	CH_2OAr ax	**74** albatrin	OAc ax	CH_2OAr eq
70 acetyldrimartol B	OAc eq	CH_2OAr ax			



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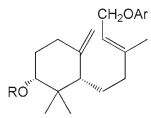
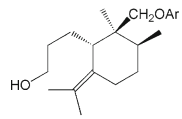
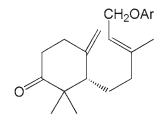


R

76 acetyldeparnol Ac
77 deparnol H



78 secodriol



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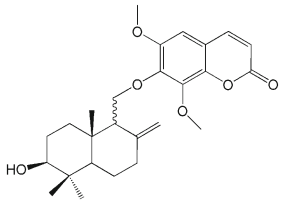
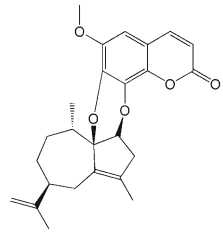


80a 9αH-epipectachol B
80b 9βH-epipectachol B



81 jatrophadioxan

Prenylated 4-hydroxycoumarins

Ferulenol (**82**) is a major constituent of the poisonous chemotype of *F. communis* (Valle et al. 1987, Appendino et al. 1988, Al-Yahya et al. 1998) and the universal precursor of farnesylated 4-hydroxycoumarins. In the extract isolated from *F. communis,* two *ω*-hydroxylated derivatives of ferulenol were found, i.e. *E*-*ω*-hydroxyferulenol (**84a**) and *Z*-*ω*-hydroxyferulenol (**84b**). *E*-*ω*-Acetoxyferulenol (**86a**) and *Z*-*ω*-acetoxyferulenol (**86b**) were also identified as well as *E*-*ω*-oxoferulenol (**85**). Another sesquiterpene coumarin—ammoresinol (**83**) was isolated from ammoniacum, an oleo gum resin from *Dorema ammoniacum* (Appendino et al. 1991).

Ahmed et al. (2005) reported ferulenol (**82**) as a constituent in extracts of roots of the wild carrot (*Daucus carota* ssp. *carota*). They estimated MIC value of less than 2.5 μg/mL on the growth of *S. aureus, Streptomyces scabies, Bacillus subtilis, B. cereus* or *Pseudomonas aeroginosa* were estimated for ferulenol (**82**) and 4.5–5.0 μg/mL with *E. coli, Fusarium oxysporum and Aspergillus niger.* These results confirmed earlier findings that ferulenol (**82**) and its acetate (**88**) exhibited antibacterial activity towards *Mycobacterium intracellulare*, *M. xenopei, M. chelonei* or *M. smegmatis* (Al-Yahya et al. 1998; Mossa et al. 2004) with MIC values much lower (1.25–5.0 μg/mL) than those of the positive controls (streptomycin sulfate, isonicotinic acid hydrazide (INH) and amikacin sulfate). Moreover their synergistic action with INH towards the same strains of *Mycobacterium* increased the biological effect more than 50%.

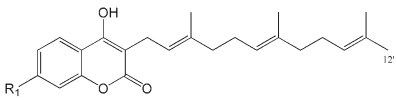
Appendino et al. (2004) reported on the toxicity of ferulenol (**82**) and other natural and synthetic farnesylated 4-hydroxycoumarins (**84a**), (**88**), (**89**) against fast-growing mycobacterial strains *M. fortuitum, M. phlei, M. aurum,* and *M. smegmatis.* The structural modification of ferulenol (**82**) showed that the introduction of a hydroxyl- (**84**) or an acetoxyl- (**86**) group at position C-12′ caused a reduction of potency, whereas a benzoyloxy substituent at C-12′ (**89**) resulted in higher activity against the tested *Mycobacterium* strains.

Parameters beyond the antibacterial activity were also investigated. Tligui et al. (1994) demonstrated the influence of ferulenol (**82**) on coagulation factors in animals. Bocca et al. (2002) reported that ferulenol (**82**) displays microtubule-interacting properties as indicated by its cytotoxic effects towards cancer cell line MCF-7 (human breast), Caco-2 (colon), HL-60 (leukemic), SKOV-3 (ovarian). Monti et al. (2007) studied antiproliferative activity of ferulenol (**82**) and its *ω*-hydroxy- (**84**) and *ω*-acetoxyderivatives (**86**) isolated from *F. communis* on the hepatoma cell line HepG2 and two kidney cell lines, i.e. Human Embryonic Kidney 293 and Baby Hamster Kidney. In this test, ferulenol (**82**) showed cytotoxic activity. The authors suggested

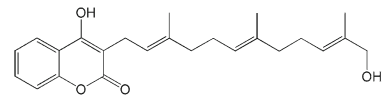
that the cytotoxic effect of ferulenol (**82**) may be related to the impairment of microtubule dynamic and mitochondrial function. Finally, Lahouel et al. (2007) speculated that mitochondria may be involved in ferulenol (**82**) cytotoxicity. They studied the effects of ferulenol (**82**) isolated from *F. vesceritensis* on the oxidative phosphorylation process in mitochondria isolated from rat liver. The authors pointed out that the inhibition effect of ferulenol (**82**) is connected with interactions with adenine nucleotide translocase and the mitochondrial complex II of the respiratory chain (succinate ubiquinone reductase).

Prenyl-furocoumarin-type sesquiterpenes

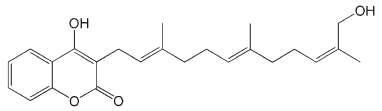
These furocoumarin derivatives formally derive from 4-hydroxycoumarin and were assumed to arise from alpha-farnesylation of a 3-phenyl-3-ketopropionyl-CoA (benzoylacetyl-CoA) substrate (Kojima et al. 2000; Isaka et al. 2001). In light of the new findings on the biosynthesis of 4-hydroxycoumarins (see below), however, it is more likely that the prenylation occurs at the stage of 4-hydroxycoumarin and the conjugate is further modified by hydroxylation and cyclization to yield the dihydrofuran ring. Numbering of carbons in the final products requires the distinction of straight



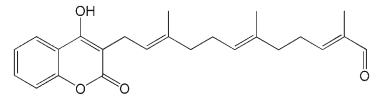
	R_1
82 ferulenol	H
83 ammoresinol	OH



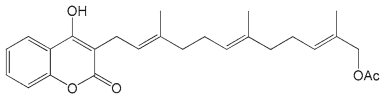
84a *E*-ω-hydroxyferulenol



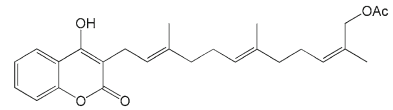
84b *Z*-ω-hydroxyferulenol



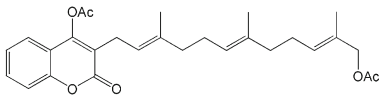
85 *E*-ω-oxoferulenol



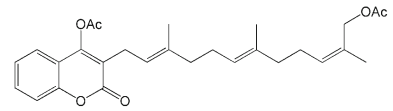
86a *E*-ω-acetoxyferulenol



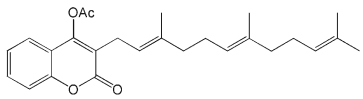
86b *Z*-ω-acetoxyferulenol



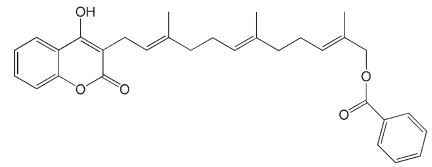
87a



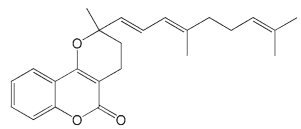
87b



88 4-acetylferulenol



89



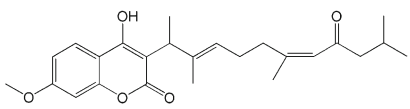
90 isoferprenin

chain prenyl- or dihydrofurano-components from the coumarin nucleus by single and double quotes, respectively, and the kind of dihydrofurano-cyclization determines whether the prenylchain is attached at carbon 2″ or 3″.

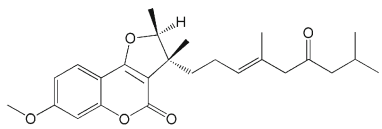
The new prenylated 7-methoxycoumarines—pallidones A (**91**) and B (**92**) were obtained from *Ferula pallida* (Su et al. 2000).

A phytochemical study of roots of *Ferula ferulioides* afforded thirteen novel 2″- and 3″-prenylfurocoumarin-type sesquiterpenoid derivatives (**93–105**) in which the prenyl side chain is attached to the C-2 or C-3 position of the furocoumarin moiety (Kojima et al. 2000; Isaka et al. 2001). The authors proposed biosynthetic pathways for all these products as discussed below.

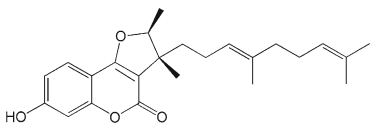
Another series of compounds of this type (**106–109**) were isolated from roots of *Ferula fukanensis* (Motai and Kitanaka 2004, 2006) along with compounds **98** and **103**. The structures of the new sesquiterpene coumarins (**106–109**) were determined spectroscopically (Motai and Kitanaka 2004), while the structures of compounds (**100**), (**103**) and (**105**) were assigned by comparison with literature data (Isaka et al. 2001). Motai and Kitanaka (2004) tested the inhibitory effects of the isolated compounds (**100**, **105–109**) on the nitric oxide (NO) production in murine macrophage-like cells (RAW 264.7). Activation of NO synthase (iNOS) by lipopolysaccharide and recombinant mouse interferon-γ was inhibited by these coumarins. IC_{50}-values were 87.5 and 27.8 μM for (**100**) and (**105**), respectively, which indicates that a methoxy group is



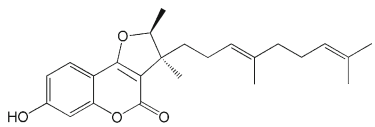
91 pallidones A



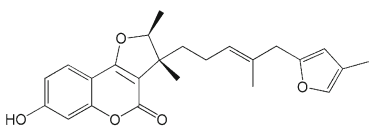
92 pallidone B



93



94



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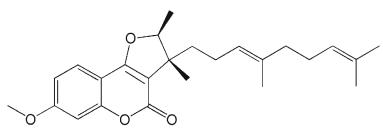

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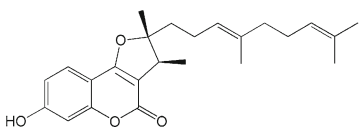

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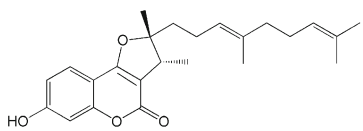

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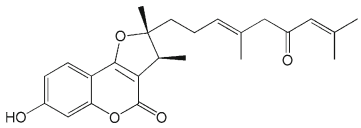

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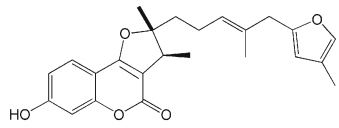

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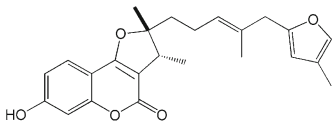

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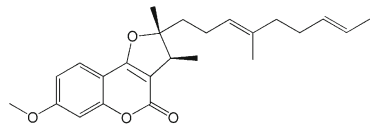

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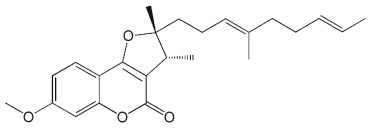

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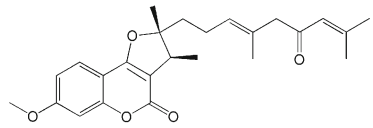

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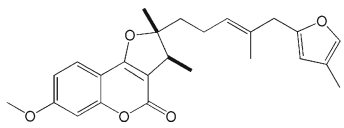
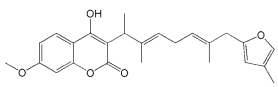
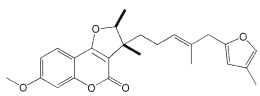


105

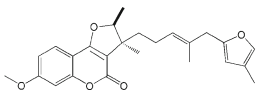
responsible for the enhanced biological activity. It has also been shown that compounds **105, 106** and **107** inhibited iNOS mRNA expression in RAW264.7 cells in a dose-dependent manner.



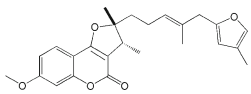
106 fukanemarin B



107 fukanefuromarin E

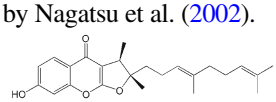


108 fukanefuromarin F



109 fukanefuromarin G

The isolation and identification of three novel 2″-prenyl-dihydrofurochrome-type sesquiterpenoids (**108–110**) from dried root of *Ferula ferulaeoides* was reported by Nagatsu et al. (2002).



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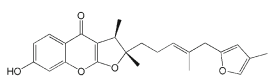

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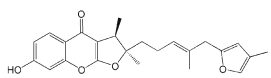
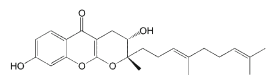
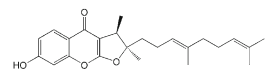


112

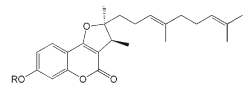
A significant inhibitory activity of sesquiterpene coumarins against α-glucosidase was described by Choudhary et al. (2001). In a methanol extract of the roots of *Ferula mongolica,* four new coumarin derivatives (**111–114**) where found along with two known compounds **91** and **108**.



113 baigene A



114 baigene B

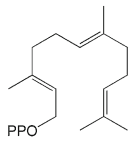


115 baigene C R=H
116 *O*-methylbaigene C R=CH_3

Biosynthesis of sesquiterpene coumarins

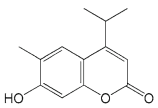
At present, our knowledge about how sesquiterpene coumarins are biosynthesized from the putative precursors farnesyl diphosphate (FDP) (**117**) and a coumarin is very limited. The biosynthesis of FDP (**117**) through the mevalonate pathway in plants is well

characterized (Bouvier et al. 2005). The intermediates isopentenyl diphosphate and dimethylallyl diphosphate are also synthesized in plastids through the MEP pathway. There is a cross-talk between the two pathways and therefore, sesquiterpenoids may contain a C_5 unit from the MEP pathway.

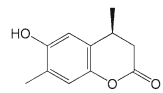


117 farnesyl diphosphate

The biosynthesis of coumarins from phenylpropanoids has long been assumed to involve cytochrome P450 dependent enzymes. While this applies to *para*- or *meta*-hydroxylation of the cinnamoyl moiety to 4-coumaric acid and caffeoylshikimate (references), respectively, the *ortho*-hydroxylation of hydroxycinnamic acids is a crucial step in the biosynthesis of coumarins (Bourgaud et al. 2006). It is not until recently that this particular hydroxylation was shown to require a CoA-ester as substrate and to be catalyzed by a soluble Fe(II)- and 2-oxoglutarate-dependent dioxygenase (F6′H1), i. e. converting feruloyl-CoA (**118**) to scopoletin (**3**) in *Arabidopsis thaliana* (Fig. 1a) (Kai et al. 2008). Analogous *ortho*-hydroxylations of coumaroyl- and sinapoyl-CoA by orthologous enzymes may be involved in the biosynthesis of umbelliferone (**2**) and isofraxidin (**4**), respectively, in plants. A slighty different path leads to 4-hydroxycoumarin, which was known to be formed from coumarin in mold-infested plants (Murray et al. 1982), involving a fungal P450 monooxygenase. Recently, however, the biosynthesis of 4-hydroxycoumarin (**5**) by a bisphenyl synthase (BIS), a Type III polyketide synthase, from *Sorbus aucuparia* (Liu et al. 2010). This enzyme used salicoyl-CoA (**119**) as a substrate and catalyzed a single decarboxylative condensation with malonyl-CoA (**120**) to give 4-hydroxycoumarin (**5**) (Fig. 1b). Yet another route was proposed for a few substituted coumarins, which are in fact norsesquiterpenes, such as the bisnorsesquiterpenoid 7-hydroxy-4-isopropyl-6-methoxycoumarin (**121**) (Paknikar and Fondekar 2001) and the tetranorsesquiterpenoid 6-hydroxy-4,7-dimethyl-3,4-dihydrocoumarin (**122**) (Nadkarni et al. 1994) isolated from *Macrothelypteris torresiana* and *Heritiera ornithocephala*, respectively.



121 7-hydroxy-4-isopropyl-6-methoxycoumarin



122 6-hydroxy-4,7-dimethyl-3,4-dihydrocoumarin

The prenylation of aromatic compounds is a reaction widely found in plant secondary metabolism. A number of recent reviews may be consulted for further information regarding aromatic prenyltransferases (Brandt et al. 2009; Saleh et al. 2009; Yazaki et al. 2009).

The prenylation of coumarin moieties has been studied in a few cases. For instance, the 7-*O*-

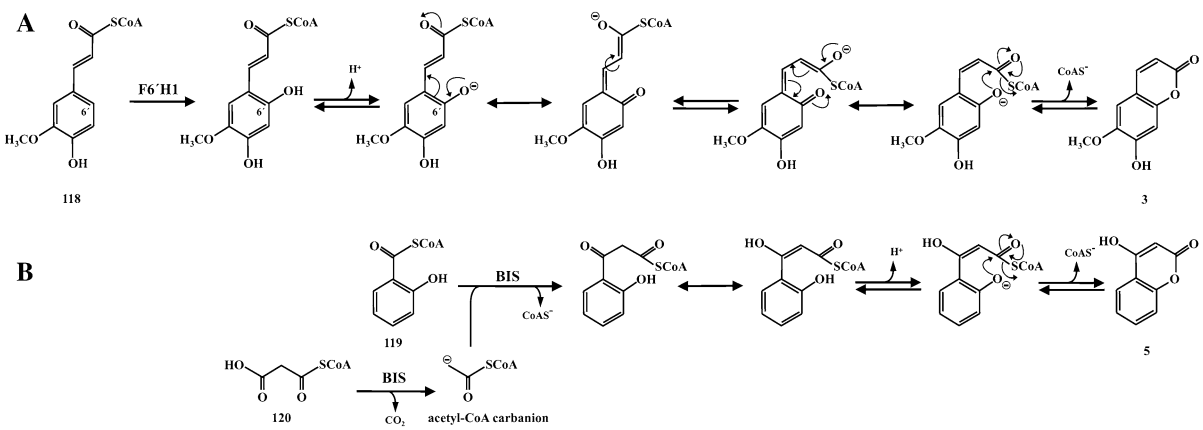


Fig. 1 Biosynthesis of coumarins. **a** scopoletin (adapted from Kai et al. 2008), **b** 4-hydroxycoumarin (adapted from Liu et al. 2010). F6′H1: Fe(II)- and 2-oxoglutarate-dependent dioxygenase; BIS: bisphenyl synthase

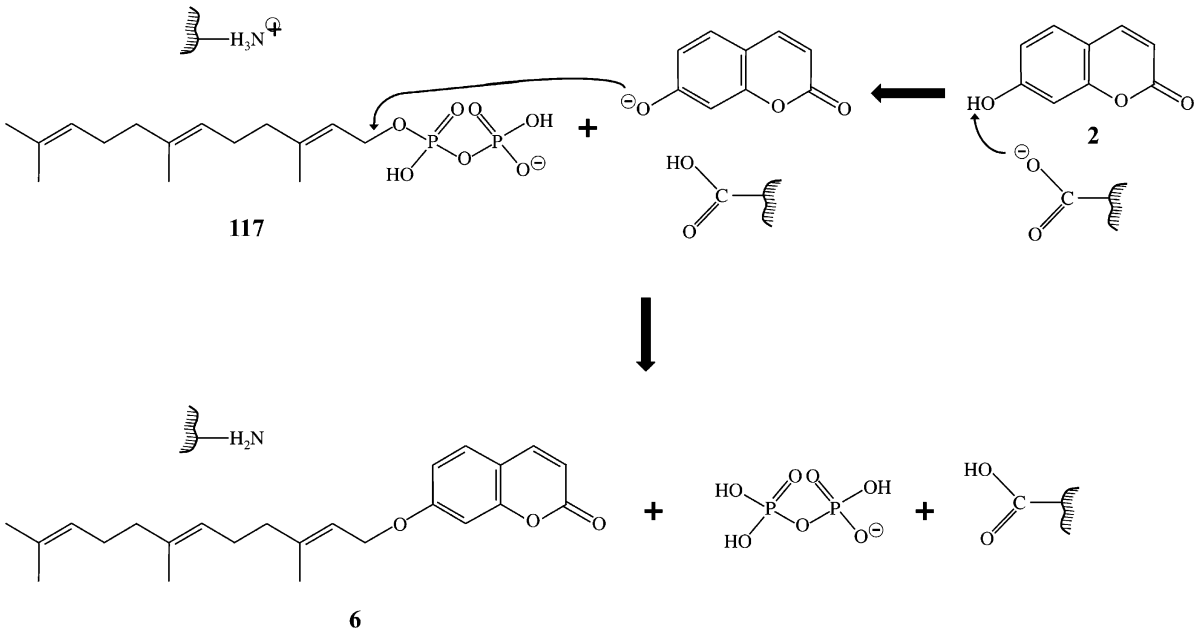


Fig. 2 7-O-Farnesylation of umbelliferone (**2**) to yield umbelliprenin (**6**). Initially, a negatively charge residue (e.g. aspartate) in the active site extract a proton to create a phenolate anion, which will direct the farnesyl cation to attack at this position. Hydrolysis of the FDP (**11**) will generate a farnesyl cation and a pyrophosphate ion that is protonated by a lysine (or arginine) residue. (Adapted from Brandt et al. 2009)

prenylation of umbelliferone (**2**) with the C_5-compound dimethylallyl diphosphate in the biosynthesis of phytoalexins via 7-isopentenylumbelliferone in cell cultures of *Ammi majus* has been characterized (Hamerski et al. 1990). The coupling step is catalyzed by the enzyme dimethylallyl diphosphate umbelliferone dimethylallyltransferase (DDU-7 transferase, E.C. 2.5.1). This enzyme is located in the membrane of the endoplasmic reticulum as a number of prenyltransferases involved in secondary metabolism (Yazaki et al. 2002; Zhao et al. 2003; Sasaki et al. 2008). It may be assumed that similar membrane-bound farnesyl transferases are present in plants producing *O*-farnesylated coumarins. A likely reaction sequence for the 7-*O*-prenylation is outlined in Fig. 2. The 7-*O*-prenylation of umbelliferone (**2**), scopoletin (**3**) or isofraxidin (**4**) with FDP (**117**) affords umbelliprenin (**6**), scopofarnol (**59**) and farnochrol (**62**), respectively.

C-Prenylation of aromatic compounds is also widely used in plant secondary metabolism. The prenylation of 4-hydroxycoumarin results in the formation of ferulenol (**82**) as outlined in Fig. 3.

Cyclic sesquiterpene structures might be formed before linkage to the coumarin entity or arise from linear sesquiterpene coumarins. For all isofraxidin-derived sesquiterpene coumarin ethers, at least, circumstantial evidence suggested farnochrol as the biogenetic precursor (Caglioti et al. 1959; Hofer and Greger 1984a). In line with this, we suggest that all the farnesylated coumarins, i.e. umbelliprenin (**6**), scopofarnol (**59**), farnochrol (**62**) and ferulenol (**82**), produced by the aromatic prenyltransferases are the biogenetic precursors of all sesquiterpene coumarins belonging to the umbelliferone-, scopoletin-, isofraxidin- and 4-hydroxycoumarin-based sesquiterpene coumarins, respectively.

Sesquiterpenes are normally synthesized from FDP (**117**) by the action of sesquiterpene synthases (cyclases) through variations of a common mechanism involving: ionization and electrophilic attack of the resultant allylic cation on one of the remaining *p*-bonds of the substrate; subsequent cationic transformations (additional electrophilic cyclizations, hydride transfers and Wagner-Meerwein rearrangements) and quenching of the positive charge by deprotonation or capture of an exogenous nucleophile such as water. However, we suggest that the cyclization of the farnesyl-moiety of sesquiterpene coumarins is carried out by another type of enzyme. The fact that all 7-*O* sesquiterpene coumarins carry an oxygene

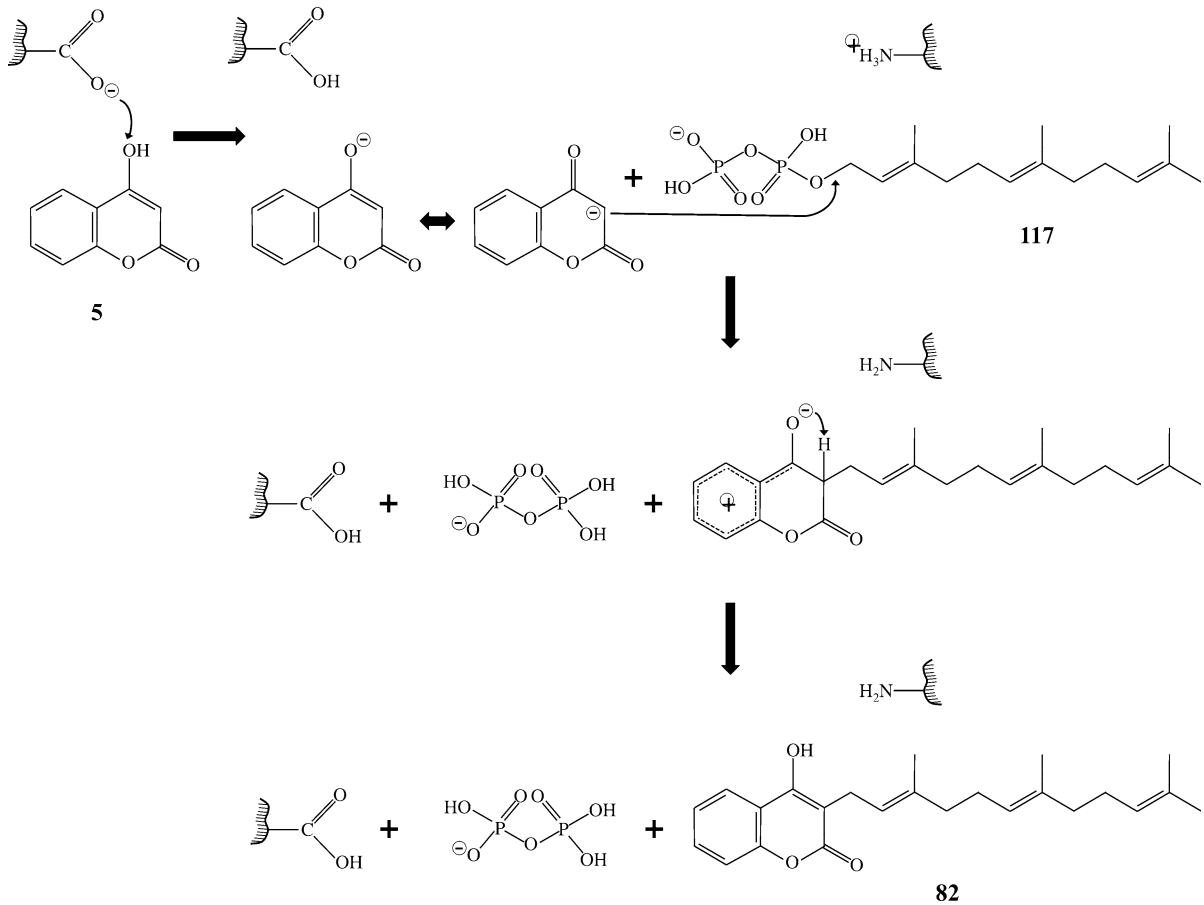
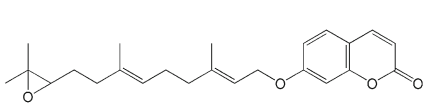
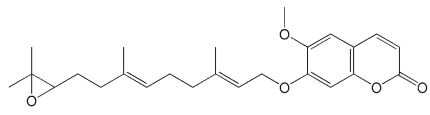


Fig. 3 Farnesylation of 4-hydroxycoumarin to yield ferulenol (**82**). Initially, a negatively charge residue (e.g. aspartate) in the active site extract a proton to create a phenolate anion, which creates a negative charge at the *ortho*-position. This will direct the farnesyl cation to attack at this position. Hydrolysis of the FDP (**117**) will generate a farnesyl cation and a pyrophosphate ion that is protonated by a lysine (or arginine) residue. (Adapted from Brandt et al. 2009)

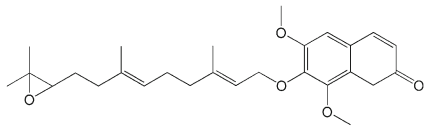
function on the 3′-carbon indicates an enzymatic mechanism similar to that of triterpene cyclases using oxidosqualene as substrate. We suggest that the umbelliprenin (**6**), scopofarnol (**59**) or farnochrol (**62**) is converted to the corresponding 2′,3′-oxido-compounds (**123**, **124**, **63**) in a reaction similar to the conversion of squalene to 2,3-oxido-squalene catalyzed by squalene epoxidase. Squalene epoxidase-like enzymes may have functions other than the epoxidation of squalene. For exmple, six *Arabidopsis*



123 2′,3′-oxidoumbelliprenin



124 2′,3′-oxidoscopofarnol



63 2′,3′-oxidofarnochrol

thaliana squalene epoxidase genes (*SQE1–SQE6*) were identified and cloned (Rasbery et al. 2007). Functional expression in yeast of these genes showed that *SQE1–SQE3* are true squalene epoxidases. However, the substrates and products for the proteins encoded by genes *SQE4–SQE6* could not be established (Rasbery et al. 2007). Obviously, there are squalene epoxidase like enzymes expressed in *A. thaliana* with other functions than the epoxidation of squalene. Accordingly, plants producing sesquiterpene coumarins may express such squalene epoxidase-like enzymes for the epoxidation of 7-*O* farnesylated coumarins and the generation of a carbocation analogous to the protosteryl or dammarenyl cation in triterpene biosynthesis (Phillips et al. 2006). Following this assumption, biogenetic patterns have been outlined for several natural sesquiterpene coumarins (Appendino et al. 1994; Gohar and El-Bassuony 2007; Ahmed et al. 2007; Kojima et al. 2000; Isaka et al. 2001, Nagatsu et al. 2002; Motai and Kitanaka 2004). Nevertheless, the evidence for these biosynthetic steps was primarily inferred from related terpene pathways and needs further experimental support in case of the sesquiterpene coumarins.

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