Minor Flavonoids (Chalcones, Flavanones, Dihydrochalcones, and Aurones)

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Abstract

Chalcones, flavanones, dihydrochalcones, and aurones are categorized into minor flavonoids. However, these compounds take the significant roles in plant kingdom. These minor flavonoids are unique to plants and are an essential part of their success in adapting to life as sedentary organisms in diverse and inconstant surrounding. Furthermore, these compounds are subclasses of the interesting naturally occurring flavonoids in view of their structural pattern as well as biochemical and pharmacological relevance. It seems that they are important not only for plants but also for animals including human beings. This chapter deals with these minor flavonoids.

Keywords

Aurone • chalcone • dihydrochalcone • flavanone

Abbreviations

AmAS1	Aureusidin synthase
CHI	Chalcone isomerase
CHS	Chalcone synthase
CoA	Coenzyme A
COX	Cyclooxygenase
LPS	Lipopolysaccharide
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NF	Nuclear factor
NO	Nitric oxide
ROS	Reactive oxygen species
TNF	Tumor necrosis factor

1 Chalcone

1.1 Introduction

Chalcones, 1,3-diaryl-2-propen-1-ones, belong to the plant flavonoid family. The name "chalcone" comes from a Greek word *chalcos* (bronze). Chemically, they consist of open-chain flavonoids in which the two aromatic rings (A and B) are joined by

a three-carbon α,β-unsaturated carbonyl system. Chalcones possess the conjugated double bond and a completely delocalized π-electron system on both aromatic rings. Although chalcone skeleton is the initial intermediate structure used in biosynthesis of all flavonoids, chalcones are one of the minor subclasses of flavonoids.

1.2 Occurrence of Chalcones

Chalcones were originally discovered in plants as the yellow flower pigments of *Coreopsis* and other yellow-rayed Compositae. After that, they have subsequently been found in other plant families including Solanaceae, Anacardiaceae, Caesalpiniaceae, Piperaceae, and Apiaceae. 6′-Deoxychalcones were known to be chemical constituents of leguminous plants, but it is scarcely reported that they were found in other plant species. A lot of chalcones were isolated from either Compositae (Asteraceae) or Leguminosae (Fabaceae), two families well known to accumulate these. Besides, various prenylchalcones can be found in hop plants (Cannabaceae).

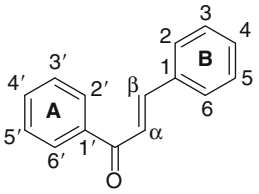
1.3 Phytochemistry of Chalcones

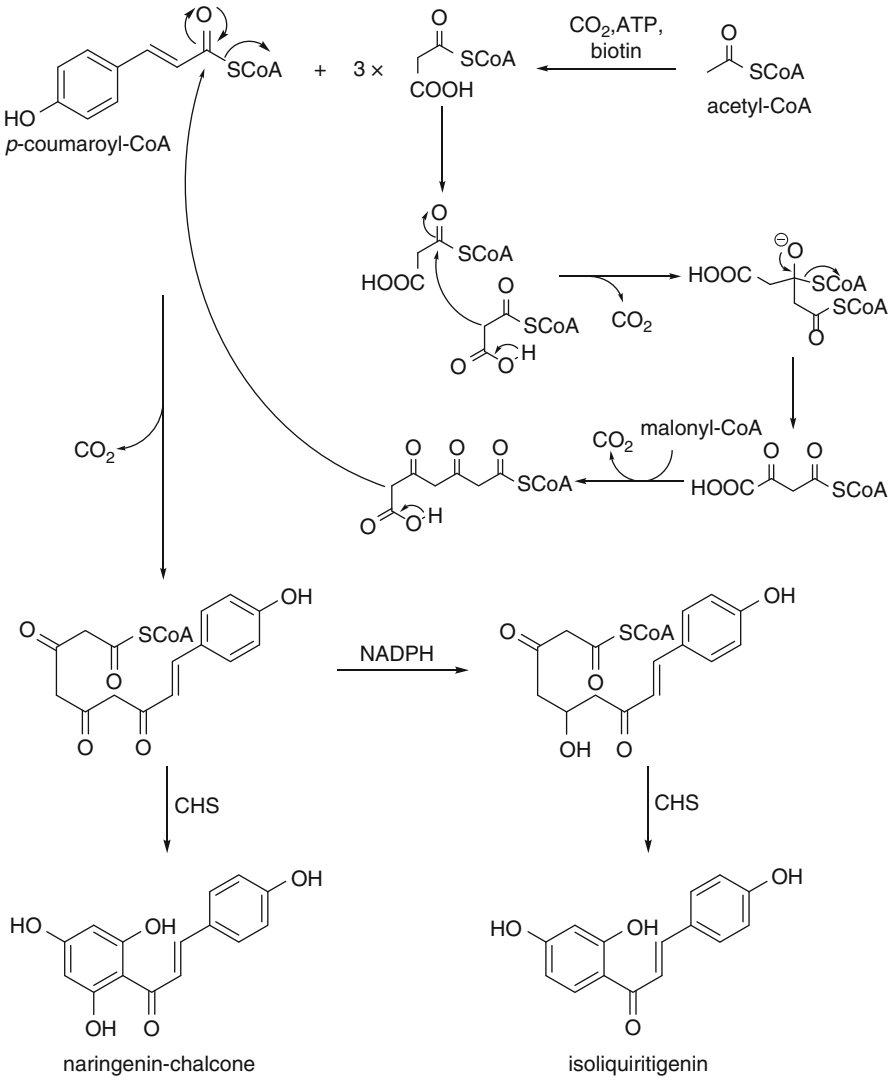
Chalcone numbering is shown in Fig. 61.1. A vast number of naturally occurring chalcones are polyhydroxylated in the aromatic rings. Usually, chalcones have hydroxyl group at C2′-, C4′-, and/or C6′-positions in A-ring because the A-ring is biosynthesized via the acetate-malonate pathway. Prenylchalcones have prenyl group(s) between the hydroxyl groups. Cyclization of the prenyl group and the adjoining hydroxyl group produces pyrano ring on the aromatic ring. Chalcones, which do not have an oxygen function at the 2′-position, are called retrochalcones. The B-ring generally has a hydroxyl group at C4-position. They are both intermediates and end products in flavonoid biosynthesis, act as defensive compounds, participate in plant-insect interactions, and contribute to the medicinal value of herbs.

1.4 Biosynthesis of Chalcones

Chalcones are biosynthesized through the combination pathway of acetate-malonate and shikimate pathways [1–3]. Malonyl-CoA is synthesized from acetyl-CoA, whereas *p*-coumaroyl-CoA originates from phenylalanine, which is produced via the shikimate pathway. Chalcone synthase (CHS) catalyzes the significant step of chalcone biosynthesis. It first condenses a phenylpropanoid-CoA (e.g., *p*-coumaroyl-CoA) with three units of malonyl-CoA and cyclizes the resulting tetraketide intermediate to afford a chalcone (e.g., naringenin-chalcone). 6′-Deoxychalcones (e.g., isoliquiritigenin) having a resorcinol-type A-ring are biosynthesized by coactions of NADPH-dependent chalcone reductase and CHS (Scheme 61.1).

Fig. 61.1 Basic skeleton of chalcones





Scheme 61.1 Biosynthesis of chalcones

1.5 Biological Activities of Chalcones

Considerable attention has been devoted to research of chalcones [4–6], which are distributed in fruits, spices, tea, and soy-based foodstuff, because of their interesting and potential pharmacological activities. Naringenin-chalcone is found in Compositae, Lamiaceae, and Solanaceae [7]. Naringenin-chalcone is one of the predominant flavonoids found in tomatoes (*Solanum lycopersicum*) and accumulates almost exclusively in the tomato peel [8]. This compound inhibited histamine release with an IC_{50} value of 68 μg/ml and was found to be the most promising antiallergic polyphenol of this extract [9]. The effect on the production of naringenin-chalcone proinflammatory mediators in lipopolysaccharide (LPS)-stimulated macrophages has been examined. This compound inhibited the production of tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, and nitric oxide (NO) by LPS-stimulated RAW 264.7 macrophages in a dose-dependent manner [10]. Naringenin-chalcone exhibited anti-inflammatory properties by inhibiting the production of proinflammatory cytokines in the interaction between adipocytes and macrophages. In addition, the oral administration of naringenin-chalcone was shown to suppress Th2 cytokine production from CD4 T cells in the spleen and to attenuate allergic airway inflammation and airway hyperreactivity [11]. The eating naringenin-chalcone could contribute to the prevention and improvement of insulin resistance and related metabolic syndrome [12]. Isosalipurposide, the glucoside derivative of naringenin-chalcone isolated from *Nymphaea caerulea* or *Helichrysum maracandicum*, exhibited the inhibition of ROS (reactive oxygen species) generation in HL60 cells [13] and strong antiproliferative activity against cultured cells of SENCAR mouse in vitro [14]. Isoliquiritigenin is found in *Glycyrrhiza* species (Leguminosae) such as *G. uralensis*, *G. glabra*, *G. inflata*, Lardizabalaceae, and Amaryllidaceae [15–19]. Isoliquiritigenin is known as a natural aldose reductase inhibitor [20]. It was reported to possess antioxidative and super oxide scavenging activities [16], antiplatelet aggregation effect [21], estrogenic property [22], and inhibitory on xanthine oxidase activity in vitro [23]. And it demonstrates its anti-inflammatory effect by inhibiting LPS-induced iNOS and COX-2 expression via the attenuation of NF-κB in RAW 264.7 macrophages [24]. Interestingly, isoliquiritigenin was also found to inhibit cocaine-induced dopamine release by modulating $GABA_B$ receptor [25]. Besides, it was found that isoliquiritigenin had good effects on inhibition proliferation, including apoptosis and locking cell cycle progression in the G1 phase against human lung cancer A549 cells [26]. It induced cell cycle arrest and p21 expression in these cells [27], apoptosis and p53-expression in human liver carcinoma Hep G2 cells [28], and also induces apoptosis by depolarizing mitochondrial membranes in human prostate cancer DU145 cells [29]. Moreover, isoliquiritigenin induced monocytic differentiation of human leukemia HL60 cells [30]. It was reported that isoliquiritigenin has the ability to protect cells from AA (arachidonic acid) and iron-induced ROS production and mitochondrial dysfunction; the cytoprotective effect mediated via AMPK (AMP-activated protein kinase)-dependent GSK3β (glycogen synthase kinase-3β) inactivation.

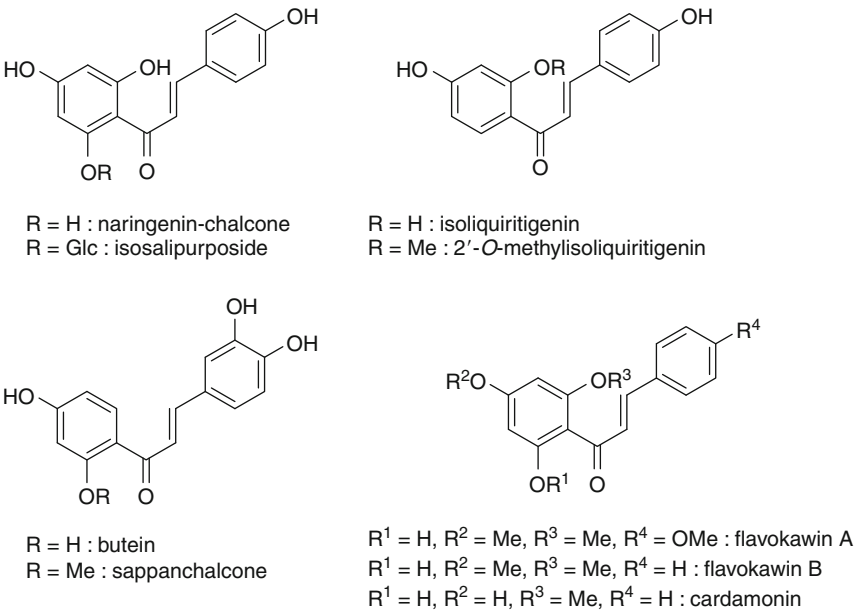


Fig. 61.2 Structures of bioactive chalcones

Isoliquiritigenin is useful to protect mitochondria from an iron catalyzed burst of oxidative stress [31]. 2′-*O*-Methyl isoliquiritigenin isolated from the root of *Dalbergia odorifera T. Chen* had the obvious antioxidative effect and the inhibitory effect of decrease of glutathione (GSH) level of rat lens induced by UV irradiation [32] (Fig. 61.2).

Butein (2′,3,4,4′-tetrahydroxychalcone) can be isolated from stembark of cashews and *Rhus verniciflua* Stokes. Past investigations suggested that butein exhibits anticarcinogenic effects. The organic extract purified from *R. verniciflua* Stokes inhibited the growth of transformed hepatic cells but not the untransformed parent cells [33], whereas butein alone could induce G(2)/M phase arrest in Hep G2 cells [34]. Its antiproliferative or pro-apoptotic effects can be brought about through downregulating STAT3-related gene expressions [35] and inhibiting telomerase activity [36]. This compound can also resensitize the TRAIL-resistant leukemia cells undergoing apoptosis upon TRAIL treatment [37] and reduce clonogenic growth of human breast cancer UACC-812 cells [38]. In addition, butein can suppress the proliferation of many human cancers including colon carcinoma, osteosarcoma, and hepatic stellate cells in vitro [39–43]. Sappanchalcone isolated from sappan lignum (the dried heartwood of *Caesalpinia sappan*) showed rapid vasorelaxant activity on the mesenteric artery [44]. This chalcone exhibited the anti-inflammatory effect in LPS-induced human periodontal ligament HPDL cells by protecting from H_2O_2 [45]. Sappanchalcone suppressed human oral cancer cell

(HN4 and HN12) growth and induces apoptosis through the activation of p53-dependent mitochondrial, p38, ERK, JNK, and NF-κB signaling [46]. Additionally, other biological effects of this compound involve the inhibition of β-hexosaminidase release [47] and anti-influenza virus activity [48]. Flavokawin A and B were isolated from kava (*Piper methysticum*) with anti-inflammatory activity. They inhibited TNF-α-induced degradation and translocation of p50 and p65 NF-κB subunits from the cytoplasm to the nucleus [49]. Flavokawin B produced pronounced antinociception effect against both chemical and thermal models of pain in mice that exhibited both peripheral and central analgesic activity [50]. Cardamonin isolated from *Alpinia rafflesiana*, *Artemisia absinthium*, or *Syzygium samarangense* inhibited NO and prostaglandin E_2 (PGE_2) production from LPS- and IFN-γ-activated RAW 264.7 macrophages by the inhibition of p65NF-κB nuclear translocation due to prevention of I-κBα phosphorylation, which subsequently caused the accumulation of I-κBα [51, 52]. This chalcone also inhibited the generation of the stable thromboxan metabolite, thromboxan B2 (TxB_2), via both COX-1 and COX-2 pathways; generation of intracellular ROS; and secretion of TNF-α from RAW 264.7. Cardamonin demonstrated its cytotoxic activity against human colon cancer SW-480 cells [53].

Xanthohumol, desmethylxanthohumol, 4′-methylxanthohumol, and 2′-*O*-methyl-3′-prenylchalconaringenin can be found in hop plants (*Humulus lupulus*). Xanthohumol is the most abundant prenylchalcone present in hops (concentrations up to 1 %, w/w). It is accompanied by its homologue, desmethylxanthohumol, albeit in lower concentrations [54]. Xanthohumol, desmethylxanthohumol, and 4′-methylxanthohumol were reported to exhibit strong antioxidative effects in ORAC assay [55]. Xanthohumol has been suggested to have potential cancer chemopreventive activities by inhibiting human breast MCF-7, colon HT-29, ovarian cancer A-2780 [56], and B-chronic lymphocytic leukemia cell proliferation in vitro [57]. This also showed antiangiogenic properties in vitro and in vivo where it inhibited proliferation of endothelial and Kaposi's sarcoma-derived tumor cells in vitro, prevented angiogenesis in the Matrigel sponge model, and reduced Kaposi's sarcoma xenograft growth in vivo. The antiangiogenic effects of xanthohumol correlated with a block of NF-κB activation and decreased phosphorylation of Akt [58, 59]. Isobavachalcone, which is a prenylchalcone found in *Angelica keiskei*, *Dorstenia barteri*, or *Psoralea corylifolia*, has been demonstrated to exhibit cancer antipromotive and antiproliferative activity [60]. Previous studies have shown that isobavachalcone exerts inhibitory effect against skin tumor promotion in vivo mouse skin carcinogenesis [61], and the ability of this chalcone to induce apoptosis in neuroblastoma IMR-32 and NB-39 cells has been reported [62]. Isobavachalcone significantly reduced pro-caspase-3 and pro-caspase-9 and subsequently increased the level of cleaved caspase-3 and cleaved caspase-9 in both cell lines. In addition, isobavachalcone demonstrated strong antifungal activity against various fungi, *Candida albicans*, *C. glabrata*, *Microsporum audorium*, and *Trichophyton rubrum* [63]. Crotaorixin isolated from the aerial parts of *Crotalaria orixensis* and medicagenin, which is a diprenylchalcone, isolated from the roots of *Crotalaria medicagenia* exhibited

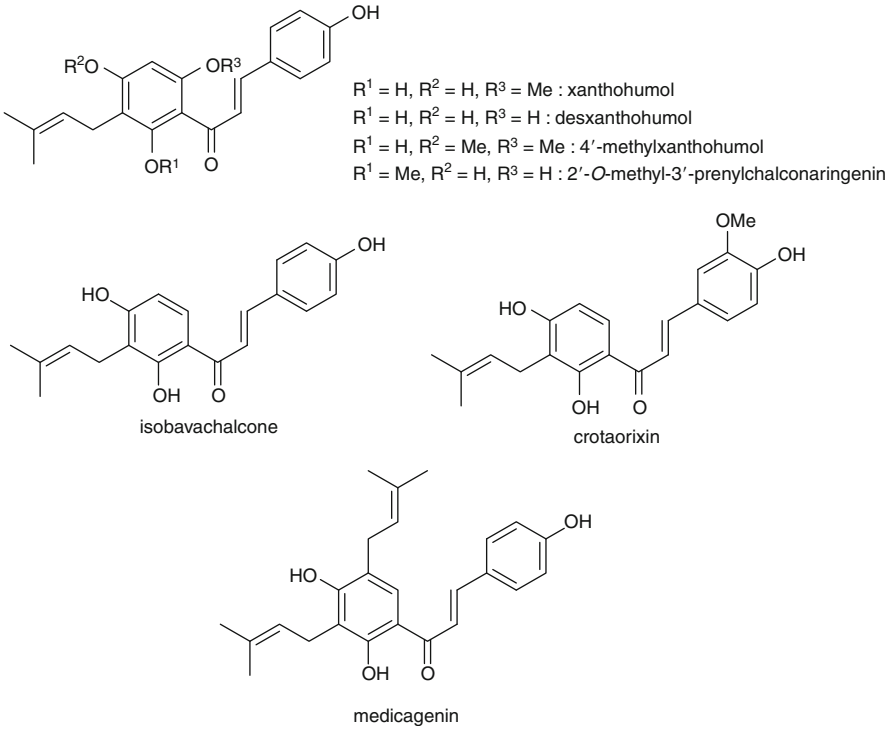


Fig. 61.3 Structures of bioactive prenylchalcones

the high antimalarial activity. They showed 100 % inhibition of maturation of *Plasmodium falciparum* parasites from ring stage to schizont stage at low concentrations [64] (Fig. 61.3).

Licochalcones such as licochalcone A, B, and C isolated from licorice (the root and rhizome of *Glycyrrhiza* spp. *G. uralensis*, *G. glabra*, and *G. inflate*) are classified into the retrochalcones (chalcones which do not have an oxygen function at the 2′-position). The content of licochalcone A in licorice was found to be very high [65]. Previous studies showed that licochalcone A possessed radical scavenging [65], antileishmanial [66], and antispasmodic effects [67]. This chalcone has been used to treat various abdominal spasmodic symptoms in Japan [68]. Licochalcone A is well known to be a natural antiparasitic agent. Licochalcone A is a potent membrane-active compound that transforms normal erythrocytes into echinocytes in parallel with the inhibition of growth of *P. falciparum* cultures. The erythrocyte membrane-modifying effect was also transiently observed in vivo in mice after intravenous administration [69]. This compound exhibited the antimicrobial activity by inhibiting the growth of *Staphylococcus aureus*, *Bacillus subtilis*, and the activity of *Helicobacter pylori* [70, 71]. Furthermore, licochalcone A significantly inhibited LPS-induced NF-κB activation. This chalcone specifically inhibited the phosphorylation of p65 NF-κB at serine 276, leading to the inhibition of NF-κB transactivation [72]. Licochalcone A also has

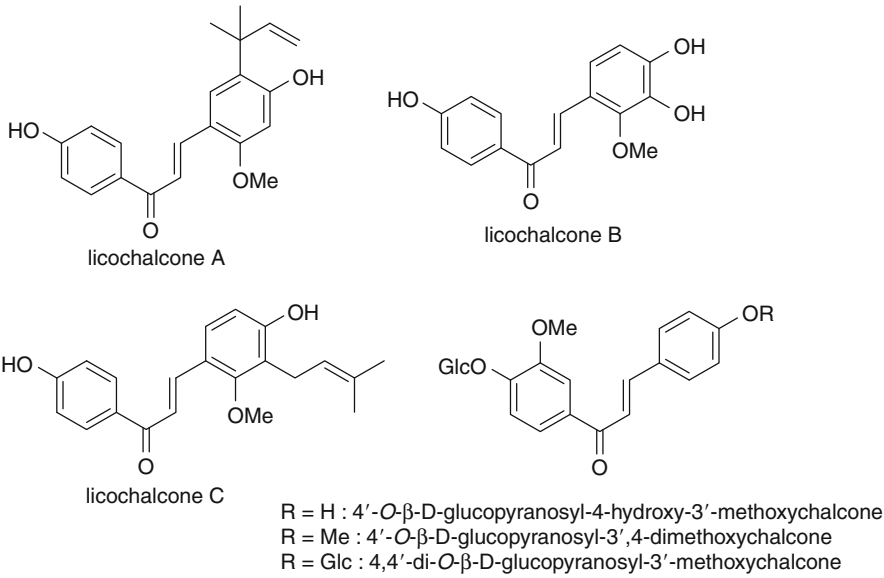


Fig. 61.4 Structures of retrochalcones

anticancer effects, induced apoptosis in MCF-7, HL60, and human prostate cancer LNCaP cells, and arrested G2 and late-G1 in human prostate cancer PC-3 cells [73–75]. Licochalcone B showed the high antioxidative effect stronger than that of licochalcone A on the 5-lipoxygenase-dependent peroxidation in arachidonate metabolism [76]. Licochalcone C also exhibited the anti-inflammatory activity by inhibiting NF-κB signaling [77]. Recently, chalcone glycosides, which do not have an oxygen function at the 2′-position, were isolated from the aerial parts of *Brassica rapa* L. "hidabeni" [78]. These 4′-*O*-β-D-glucopyranosyl-4-hydroxy-3′-methoxychalcone and 4′-*O*-β-D-glucopyranosyl-3′,4-dimethoxychalcone markedly inhibited antigen-stimulated degranulation in rat basophilic leukemia RBL-2H3 cells. The inhibitory effects were mainly due to suppression of intracellular Ca^{2+} elevation by suppression of intracellular ROS production through NOX inactivation [79]. Moreover, 4′-*O*-β-D-glucopyranosyl-3′,4-dimethoxychalcone inhibited LPS-induced iNOS expression and NO production in rat immortalized microglia HAPI cells. The inhibitory effect is due to the prevention of phosphorylation of signal transduction and activator of translocation 1 (STAT1) [80] (Fig. 61.4).

Lonchocarpin, which is a pyranochalcone, isolated from *Lonchocarpus sericeus* showed significant antiplatelet effect. The effect was suggested to be mediated by phosphodiesterase activity by inhibition or elevation of intracellular levels of adenosine 3′:5′-cyclic monophosphate and guanosine 3′:5′-cyclic monophosphate [81]. Crotaramosmin isolated from *Crotalaria ramosissima* showed weak antimalarial activity and strong antileishmanial effect [64].

Carthamin, which is a bichalcone, occurs in the tubular flowers at a late phase of the flowering stage in safflower *Carthamus tinctorius* [82]. This compound is known to be

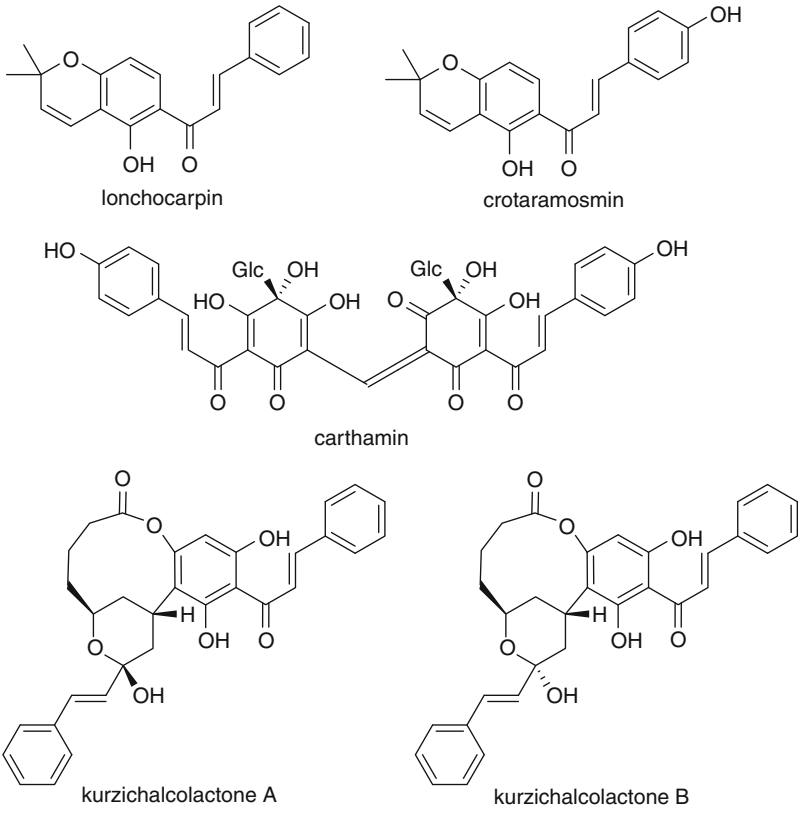


Fig. 61.5 Structures of rare chalcones

called Natural Red 26. Carthamin has been extensively used as a natural food color additive and created to cosmetics for geisha and kabuki artists for a long time in Japan. Carthamin administration could improve the blood fluidity by decreasing whole blood viscosity [83]. Kurzichalcolactones A and B, which have an unprecedented carbon side chain on the chalcone A-ring, were isolated from *Cryptocarya kurzii* with cytotoxic activity against human epidermoid carcinoma KB cells [84] (Fig. 61.5).

2 Flavanone

2.1 Introduction

Within the plant secondary metabolites of flavonoids, flavanones define one of the minor subclasses. They may be called dihydroflavones. The basic chemical structure of flavanones involves two benzene rings (A and B), which are linked by a heterocyclic ring (C). The most characteristic point of flavanone structures is that the C-ring is saturated. Flavanones have an asymmetric carbon at C2-position.

They are also interesting compounds because they are the obligate intermediates in flavonoid biosynthesis. Although flavanones are minor chemical constituents of plants, they have attracted a lot of attention in chemistry and biological sciences.

2.2 Occurrence of Flavanones

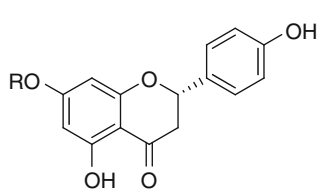
Flavanones occur in several plant families including Libiatae, Annonaceae, Acanthaceae, Compositae, Leguminosae, and also Rutaceae [85]. Flavanones having a hydroxyl group at 5-position in A-ring constitute the majority of flavonoids in Rutaceae fruits such as sweet (*Citrus sinensis*), sour oranges (*C. aurantium*), and their relatives. All orange-type citrus fruits contain the flavanone aglycones naringenin and hesperetin, but they rarely occur as free aglycones in the fruit itself. The dominant flavanone glycosides in sweet oranges (*C. sinensis*) are hesperidin and narirutin, whereas in sour oranges (*C. aurantium*), the two predominant flavanone glycosides are neohesperidin and naringin. The major difference between the flavanone glycosides of sweet and sour oranges is in their sugar moieties, which influence taste. The sugar rutinose (6-*O*-α-L-rhamnosyl-β-D-glucose) causes the flavanones hesperidin and narirutin to have a neutral taste and is relatively high in sweet oranges, tangerines, and tangors. The sugar neohesperidose (2-*O*-α-L-rhamnosyl-β-D-glucose) is high in tangelos and sour oranges and imparts a tangy or bitter taste to the glycosides neohesperidin and naringin [86]. The representative citrus flavanones and their glycosides are shown in Fig. 61.6. On the other hand, various flavanones, which do not have a hydroxyl group at 5-position, can be found in Leguminosae (Fabaceae) family.

2.3 Phytochemistry of Flavanones

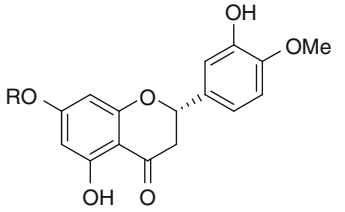
Flavanone numbering is shown in Fig. 61.7. As a rule, flavanones have hydroxyl groups at 5- and 7-positions in A-ring and 4′-position in B-ring. And flavanones exist as glycosides in nature. Naturally occurring flavanones usually have the 2*S*-configuration, but racemization can occur during extraction. Flavanones can be easily converted to isomeric chalcones in alkaline media (or vice versa in acidic media) provided that there is a hydroxyl substituent at 2′- or 6′-position of the chalcone. In general, the physical properties of flavanones are greatly different from that of flavones. The content of flavanones may control the sweetness or bitterness of fruits. The flavanones are less soluble than the chalcones, tend to separate first in fractional crystallization, and are easily precipitated at low pH, especially if solutions are chilled or frozen.

2.4 Biosynthesis of Flavanones

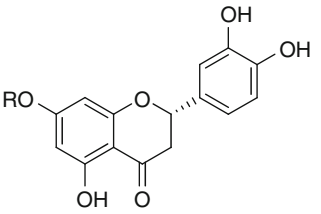
The enzyme chalcone isomerase (CHI) is the second key enzyme of flavonoid biosynthesis in higher plants and catalyzes the conversion of chalcones to their



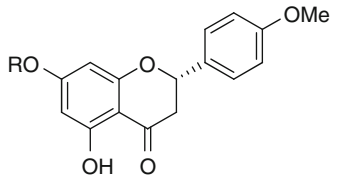
R = H : naringenin
R = rutinose : narirutin
R = neohesperidose : naringin



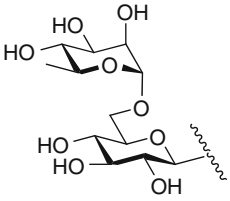
R = H : hesperetin
R = rutinose : hesperidin
R = neohesperidose : neohesperidin



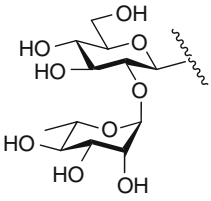
R = H : eriodictyol
R = rutinose : eriocitrin
R = neohesperidose : neoeriocitrin



R = H : isosakuranetin
R = rutinose : neoponcirin
R = neohesperidose : isosakuranetin
-7-*O*-neohesperidoside



rutinose



neohesperidose

Fig. 61.6 Structures of citrus flavanones

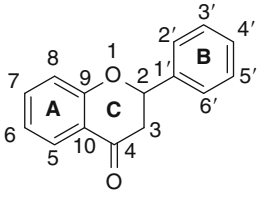
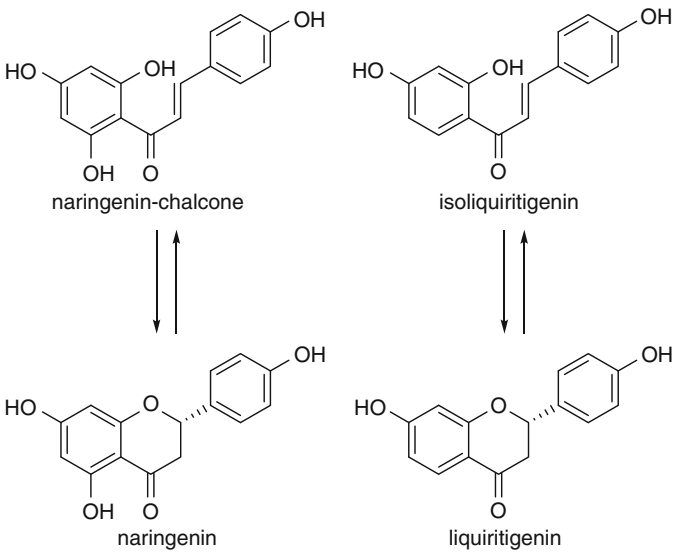


Fig. 61.7 Basic skeleton of flavanone

corresponding flavanones. Chalcones having a hydroxyl group at C2′-position, especially those further possessing a 6′-hydroxy substitution, are spontaneously converted into a racemic mixture of the respective 2 *S*- and 2*R*-flavanones. However, they are stereospecifically isomerized into 2*S*-flavanones more rapidly by CHI



Scheme 61.2 Biosynthesis of flavanones

than spontaneous conversion in plants (Scheme 61.2). Flavanones have a chiral center at C-2 position so that naturally occurring members are often optically active.

2.5 Biological Activities of Flavanones

Naringenin, which is abundant in grapefruits (*Citrus* × *Paradisi*) and other citrus fruits, has been shown to inhibit microsomal lipid peroxidation [87], nonenzymatic lipid peroxidation [88], and ascorbic acid-induced malondialdehyde (MDA) formation. Hesperetin showed a similar level of inhibition. Naringenin, however, had no effect on ferrous sulfate-induced MDA production [88]. This flavanone was found to inhibit TxB_2 production in platelets stimulated with either thrombin or AA (arachidonic acid), whereas the glycoside form naringin was inactive [89]. Naringenin also inhibited the formation of oxygenated metabolites in platelets stimulated with thrombin and inhibited AA-induced platelet aggregation. Although eriodictyol offered protection against TNF-α-induced cytotoxicity in murine fibroblast L-929 cells, naringenin was not protective [90]. Naringenin and hesperetin have beneficial effects on cardiovascular diseases involving vasodilation. They displayed a concentration-dependent inhibition of the agonist-induced contractile responses [91]. It was known that naringenin was able to traverse the blood-brain barrier [92] and exert a diverse array of neuronal effects through their ability to interact with the protein kinase C (PKC) signaling pathways [93]. Naringenin can bind to both estrogen receptors, ER-α and ER- β [94]. Importantly, naringenin competed more effectively with 17-β-estradiol for binding to ER-β than for ER-α.

Interaction of naringenin with ER-β may be relevant for cardiovascular effects as this receptor is present in significant amount in arterial tissue [95]. Furthermore, results of anticarcinogenesis experiments indicated that naringenin, but not naringin, inhibited aflatoxin B1-induced carcinogenesis [96] and that naringenin caused cytotoxicity and apoptosis via a transient induction of caspase-3 activity in HL60 cells [97]. Additionally, it exhibited strong antiproliferative activity in various cancer cells, and its treatment dose showed no toxic effect on normal cells [98–101]. Narirutin, which is found in immature oranges, was reported to inhibit airway inflammation in the allergic mouse model [102]. The anti-inflammatory effect is likely to be associated with the reduction in the ovalbumin (OVA)-induced increases of interleukin (IL)-4 and immunoglobulin E (IgE). Naringin, which is found in the peels of citrus fruits such as grapefruit, *C. hassaku*, and others, is hydrolyzed to a major metabolite, naringenin which readily crosses the blood-brain barrier. It has been reported to possess antiviral, antihypertensive, and neuroprotective effects [103–105]. Naringin has potent antioxidative activity which has been observed in various in vitro and in vivo animal models [106, 107]. This compound also has metal chelating, free radical scavenging properties and offers some protection against mutagenesis and lipid peroxidation [108]. The antioxidative effects have been shown to be similar to GSH (glutathione). Naringin plays the important role in regulating antioxidative capacity by increasing superoxide dismutase (SOD) and catalase (CAT) activities and by upregulating the gene expression of SOD, CAT, and glutathione peroxidase (GPx) [109]. In cholesterol metabolism, naringin is known to act as an inhibitor for a hydromethylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway [110]. In addition, naringin enhanced the proliferation of cells including rat osteosarcoma UMR106, mouse osteoblastic MC3T3-E1, and mouse leukemia P388 cells [99, 111, 112]. Hesperetin is reported to be a powerful radical scavenger and a promoter of cellular antioxidant defense-related enzyme activities [113]. This compound exhibited anti-inflammatory activity by inhibiting of LPS-induced expression of the COX-2 gene in RAW 264.7 macrophages [114]. Hesperetin is a potent chemopreventive agent; its supplementation during the initiation, post-initiation, and entire period stages of colon carcinogenesis in the male rat model in vivo significantly reversed these activities [115]. Administration of hesperetin to 1,2-dimethylhydrazine (DMH)-treated rats decreased the tumor incidence and the number of aberrant crypt foci with simultaneous enhancement of tissue lipid peroxidation, glutathione S-transferase (GST), GPx, SOD, and CAT activities [116]. Hesperetin induced Notch homolog 1 (NOTCH1) expression in human gastrointestinal carcinoid (BON) cells, subsequently suppressing tumor cell proliferation and bioactive hormone production [117]. Therapeutically useful properties of hesperidin, which is found in the peels of citrus fruits (*C. aurantium* var. *daidai*, *C. natsudaidai*, and *C. unshiu*), have also been described. Hesperidin can prevent microvascular leakage by virtue of its vasoprotective action through the inhibition of the enzyme hyaluronidase which is reported to regulate the permeability of capillary walls and supporting tissues [118]. Additionally, it has been demonstrated that hesperidin can decrease blood cell and platelet aggregation, believed to be

beneficial in cases of capillary permeability and fragility [119]. Besides, their effect on vascular permeability and ocular blood flow, both hesperidin and hesperetin, demonstrate strong antioxidative properties [120]. The antioxidative activity is through their ability to quench oxidative radical chain reactions and can thus help preserve neuronal health. Hesperidin also exhibited significant anti-inflammatory activity by modulating the prostaglandin synthesis and COX-2 gene expression pathways [114]. Hesperidin has been reported to possess analgesic, hypolipidemic, antihypertensive, and diuretic activity [121–123]. Another potential therapeutic application of hesperidin is its anticancer activity mediated through the suppression of cell proliferation [124, 125]. Neohesperidin also showed antiproliferative activity in Hep G2 cells [126] and the antiallergic effect on dermatitis in mice [127]. Eriodictyol, which is abundant in lemon, was found to reduce NO production from LPS-stimulated RAW 264.7 macrophages [128]. The inhibitory effect was found to be caused by blockage of NF-κB activation and phosphorylation of p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and c-Jun N-terminal kinase (JNK). It has been reported that eriocitrin, which is a lemon (*C. limon*) flavanone, is effective in the prevention of oxidative damages caused by acute exercise-induced oxidative stress in the rat liver [129]. Neoeriocitrin showed free radical scavenging activity, the inhibition of superoxide formation [130], and the better effect than naringin on proliferation and osteogenic differentiation in mouse preosteoblast MC3T3-E1 cells [131]. Isosakuranetin, which is found in blood oranges (*C. sinensis*), grapefruits, and others, exhibited the neuroprotective effect. This compound increased cell viability and catalase activity (CA) and decreased membrane damage, ROS generation, intracellular calcium level ($[Ca2^{+}]_i$), and caspase-3 activity in H_2O_2-treated PC12 cells [132]. Interestingly, isosakuranetin is known to be an allelopathic molecule and acts by affecting K^+ uptake and K^+-dependent acid extrusion [133].

Liquiritigenin is extracted from *Glycyrrhizae radix*, a herbal that is frequently used to treat injury or swelling or for detoxification in traditional medicine. Liquiritigenin is also one of the major active compounds of menopausal formula 101 (MF101), a herbal extract used in clinical trials for the treatment of hot flushes and night sweats in postmenopausal women [134]. Liquiritigenin is shown to be a selective agonist of ER-β [135] and that targeting this receptor may be associated with anti-inflammatory effects. Liquiritigenin inhibited NO and TNF-α production induced by LPS in RAW 264.7 macrophages [136]. Studies have already proven that liquiritigenin exerts cytoprotective effects against heavy metal-induced toxicity in cultured hepatocytes [137] and has protective effects against liver injuries induced by acetaminophen and buthione sulfoximine (BSO) in rats [138]. Besides, liquiritigenin has been reported to have the choleretic effect and the ability to induce hepatic transporters and phase II enzymes [139] and inhibit amyloid β-peptide-induced neurotoxicity, not only in hippocampal neurons [140], but also in rats [141]. In addition, liquiritigenin inhibited the growth of human gastric carcinoma SGC-7901, human hepatocellular carcinoma SMMC-7721, and human colorectal cancer Lovo cells [142]. Liquiritin, an active component of *Glycyrrhiza uralensis*, might be a good candidate for treating various neurodegenerative diseases including Alzheimer's disease or Parkinson's disease [143]. This compound showed neuroprotection and neurotrophism on primary cultured hippocampal cells

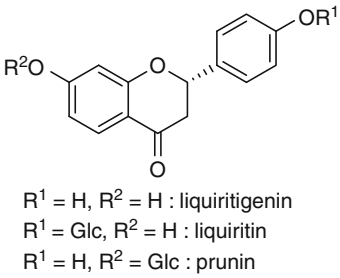


Fig. 61.8 Structures of bioactive 5-deoxyflavanones

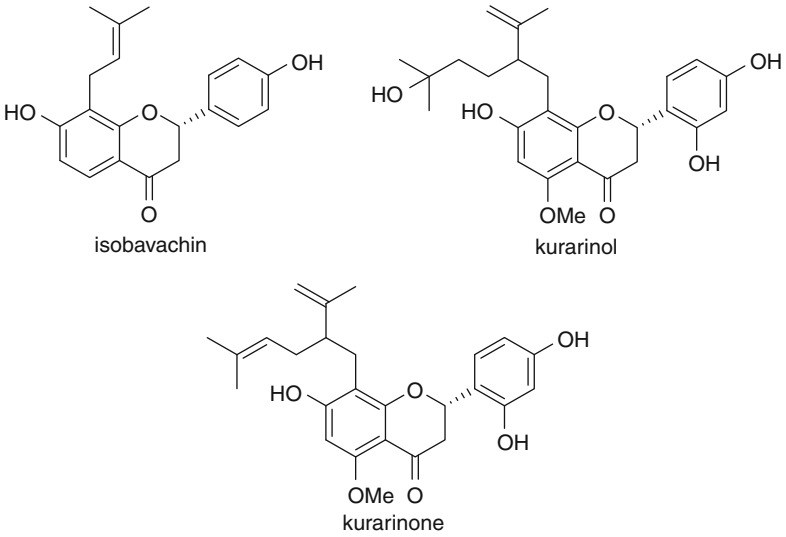


Fig. 61.9 Structures of prenyl and lavandulyl flavanones

[144]. Liquiritin provided obviously neuroprotective effect on middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia/reperfusion (I/R), the effect attributable to its antioxidative and antiapoptosis activities [145]. It has been reported that liquiritin produced significant antidepressant effects in the forced swimming test and tail-suspension test in mice [146]. Prunin showed the inhibitory effect on caffeine N3-demethylation, a marker activity of CYP1A2, in human liver microsomes [147]. Additionally, prunin was tested against Gram-positive and Gram-negative bacteria, yeasts, and molds. Prunin showed no inhibitory effect against the microorganisms assayed but stimulated growth of *Pseudomonas aeruginosa* and different *Bacillus* sp. [148] (Fig. 61.8).

Isobavachin, which is a prenylated flavanone, isolated from *Psoralea corylifolia* showed cytotoxicity against rat hepatoma H4IIE and rat glioma C6 cells [149],

promoting effect on neurogenesis of mouse embryonic stem cells by prenylation of protein [150]. Lavandulylated flavanones such as kurarinol and kurarinone were isolated from the root of *Sophora flavescens*. Kurarinol is known to be a natural tyrosinase inhibitor; this compound markedly inhibited melanin synthesis [151, 152]. And kurarinol is a potent inhibitor of sortase A, an enzyme that plays a key role in cell wall protein anchoring and virulence in *Staphylococcus aureus* [153]. Kurarinol and kurarinone were reported to exhibit hypolipidemin effects in cholesterol-fed rats [154]. In addition, these flavanones also showed significant inhibitory activities against intracellular ROS levels as well as NF-κB activation [155] (Fig. 61.9).

3 Dihydrochalcone

3.1 Introduction

Dihydrochalcones, 1,3-diphenylpropan-1-ones, are natural phenolics related to chalcones. They consist of the C_6–C_3–C_6 skeleton structure, two aromatic rings connected by a C_3 chain. The difference with chalcones is that dihydrochalcones lack a double bond at C_2–C_3 position.

3.2 Occurrence of Dihydrochalcones

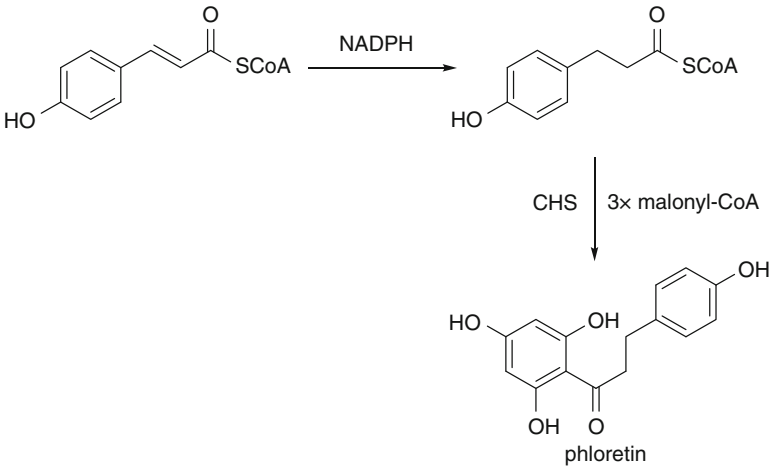
In contrast to the ubiquitously present flavonoids, occurrence of dihydrochalcones is limited. In apple trees, the major subclass of flavonoids is represented by dihydrochalcones, which are found in large amounts (up to 5% of dry weight) in leaves and immature fruits. Although they were thought for a long time to be exclusive of *Malus* sp., dihydrochalcones have been reported in several other genera like *Balanophora*, *Fragaria*, and *Symplocos*. Nowadays, dihydrochalcones seem to be restricted to approximately 30 plant families, especially Rosaceae, Rutaceae, Lauraceae, and Leguminosae.

3.3 Phytochemistry of Dihydrochalcones

Dihydrochalcone numbering is the same as the chalcone ones. The substituted pattern of hydroxyl group of dihydrochalcones resembles that of chalcones, too. Their function *in planta* remains unresolved. They have been hypothesized to act as UV filters in leaves, and a role in resistance to pathogens has been suggested.

3.4 Biosynthesis of Dihydrochalcones

Whereas *p*-coumaroyl-CoA is the precursor for the naringenin-chalcone and further flavonoid formation, *p*-dihydrocoumaroyl-CoA is required for the biosynthesis of

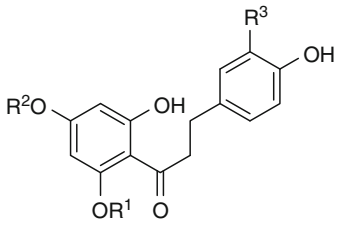


Scheme 61.3 Biosynthesis of dihydrochalcones

dihydrochalcones such as phloretin. It is assumed that *p*-dihydrocoumaroyl-CoA is formed from *p*-coumaroyl-CoA by a NADPH-dependent dehydrogenase. Dihydrochalcones are produced by the common CHS with equal chalcone biosynthesis [156, 157] (Scheme 61.3). However, in past radiolabeled biosynthetic experiments, *p*-dihydrocoumaric acid was not detected as the intermediate.

3.5 Biological Activities of Dihydrochalcones

Phloretin and its glycoside phloridzin are abundantly present in apples (*Malus* × *domestica*), especially in the peel, and strawberries. Phloretin has been reported to display antioxidative properties [158] and to prevent cytokine-induced expression of endothelial adhesion molecules and to reduce activation of human platelet activation [159]. In addition, phloretin may be beneficial for reducing insulin resistance through its potency to regulate adipocyte differentiation and function [160, 161]. Phloretin is a penetration enhancer in the delivery of lidocaine, which is a common local anesthetic and antiarrhythmic drug, through skin [162, 163]. Phloretin has been reported to inhibit the growth of human acute lymphoblastic leukemia MOLT4 cells in vitro [164] and Fisher bladder carcinoma and rat mammary adenocarcinoma cells in vivo [165]. And phloretin induced apoptosis B16 melanoma 4A5 cells by inhibition of glucose transmembrane transport [166]. Phloridzin, which is mainly distributed in plants of *Malus*, is known to be an antidiabetic agent. This compound inhibited intestinal glucose uptake via the sodium D-glucose cotransporter and similarly inhibited renal glucose reabsorption



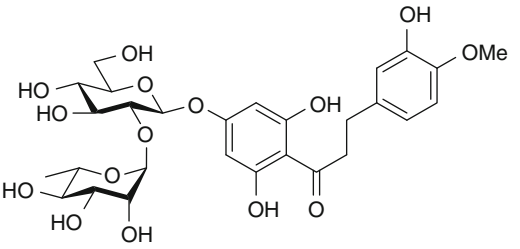
R^1 = H, R^2 = H, R^3 = H : phloretin
R^1 = Glc, R^2 = H, R^3 = H : phloridzin
R^1 = H, R^2 = Glc, R^3 = OH : sieboldin
R^1 = H, R^2 = Glc, R^3 = H : trilobatin

Fig. 61.10 Structures of bioactive dihydrochalcones

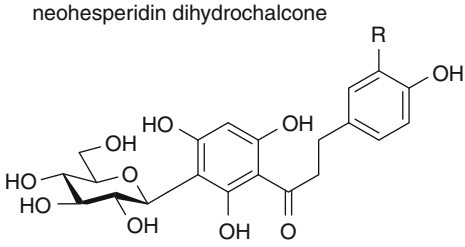
[167, 168]. Correction of hyperglycemia with phloridzin has been shown to normalize the effects of insulin on glucose metabolism in the liver and other peripheral tissues such as muscle and adipose tissue in diabetic rat models [169]. In addition, phloridzin improved hyperglycemia but not hepatic insulin resistance in a transgenic mouse model of type 2 diabetes [170]. Other biological functions of phloridzin involve estrogenic and antiaging activity and the inhibitory effect against the three human concentrative nucleoside transporters hCNT1, hCNT2, and hCNT3 [171–173]. Sieboldin and trilobatin, which can be found in apple leaves, were reported to contribute to the antioxidative activity and blocking effects of bacterial spread of apples [174]. Trilobatin inhibited against α-glucosidase and α-amylase linked to type 2 diabetes [175] (Fig. 61.10).

Neohesperidin dihydrochalcone, which is a non-nutritive sweetening agent of oranges, inhibited DPPH radical, lipid peroxidation, inflammation-related ROS, and xanthine oxidase activity [176–178]. Aspalathin, a dihydrochalcone *C*-glycoside, is the most abundant flavonoid in rooibos (*Aspalathus linearis*), which is well known as a herbal tea in many countries. Unfermented rooibos plant material contains between 4% and 12% aspalathin. Aspalathin also has beneficial effects on glucose homeostasis in type 2 diabetes through stimulating glucose uptake in muscle tissues and insulin secretion from pancreatic β-cells [179]. Aspalathin appeared to have in vitro antioxidative and antimutagenic effects [180–182]. Nothofagin, which is found in *Aspalathus linearis*, has been reported to exhibit the antioxidative and antimutagenic effects as same as aspalathin [182, 183] (Fig. 61.11).

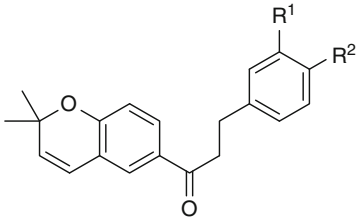
Crotaramin and crotin, which are pyranodihydrochalcones isolated from *Crotalaria ramosissima*, exhibited weak inhibition of maturation of *Plasmodium falciparum* (NF-54) parasites [64]. Dimeric dihydrochalcones verbenachalcone and littorachalcone were isolated from the aerial parts of *Verbena littoralis*. These compounds were reported to act as enhancers of nerve growth factor (NGF)-mediated neurite outgrowth and axonal branching in rat pheochromocytoma PC12D cells [184, 185] (Fig. 61.12).



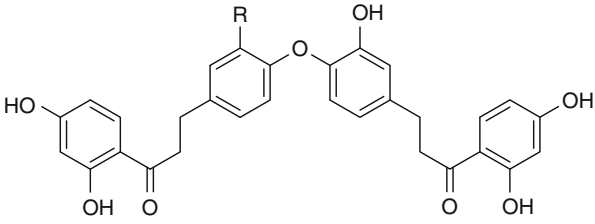
neohesperidin dihydrochalcone



R = OH : aspalathin
R = H : nothofagin



R^1 = H, R^2 = OMe : crotaramin
R^1, R^2 = OH : crotin



R = OMe : verbenachalcone
R = H : littorachalcone

Fig. 61.11 Structures of bioactive dihydrochalcone glycosides

Fig. 61.12 Structures of rare dihydrochalcones

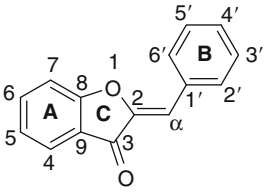


Fig. 61.13 Basic skeleton of aurone

4 Aurone

4.1 Introduction

Aurones, 2-benzylidene-coumaran-3-ones, belong to the subclass of plant flavonoids that provides the bright yellow color of some important ornamental flowers. The name "aurone" comes from a Latin word *aurum* (= gold) because of the golden yellow color of the pigments. They consist the three-ring C_6—C_3—C_6 system, and the heterocyclic C-ring is the five-membered ring [186]. Aurones are structurally the isomeric of flavones.

4.2 Occurrence of Aurones

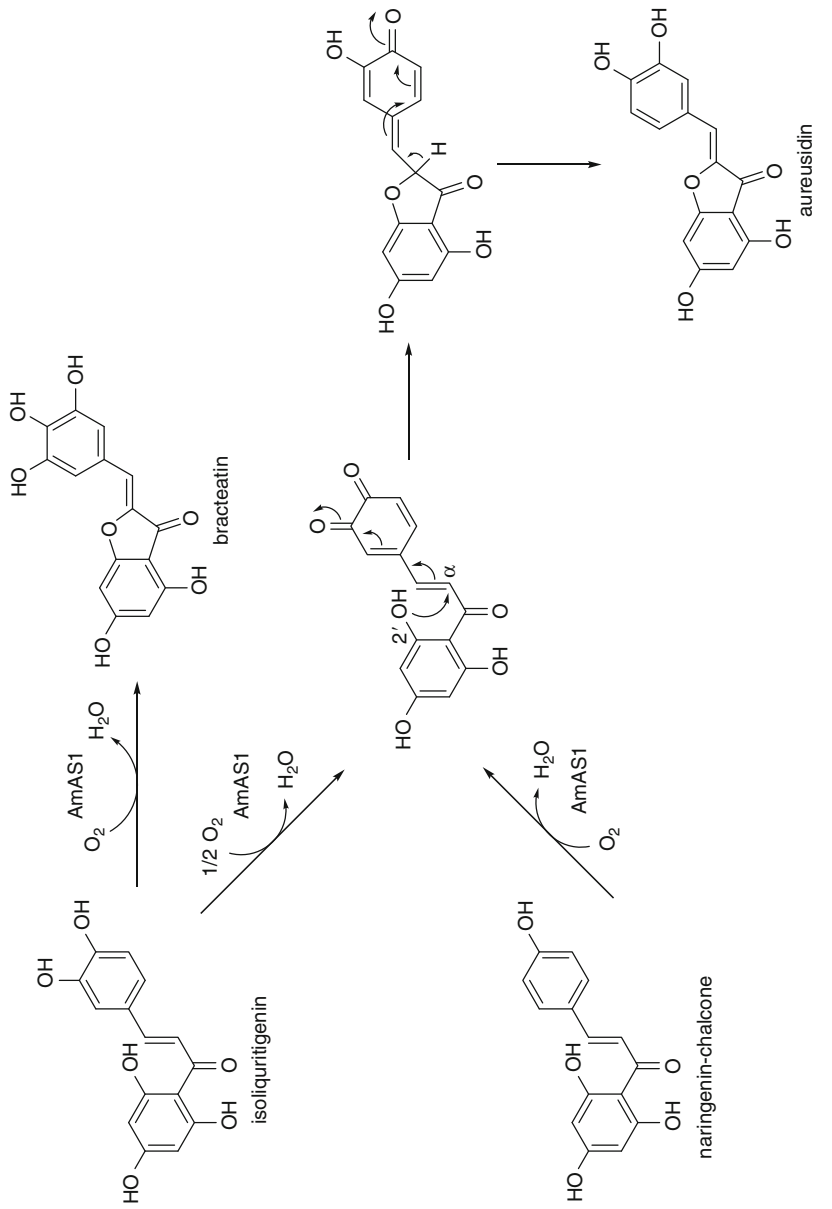
Aurones are found in a number of flowers of some Scrophulariaceae (e.g., snapdragon [*Antirrhinum majus*]) and Compositae (e.g., *Coreopsis*, *Cosmos*, and *Dahlia*). The yellow snapdragon flower is probably one of the best sources of aurones in the vacuoles of the epidermal cells of the flowers. In some other plant species, however, aurones are also found in the bark, wood, leaves, seedlings, and nectar. In 2001, the occurrence of aurone (4′-chloroaurone) in marine organisms has been reported [187]. However, its structure was revised to 3-(4′-chloroisocoumarin) later [188].

4.3 Phytochemistry of Aurones

Aurone numbering is shown in Fig. 61.13. Naturally occurring aurones are polyhydroxylated in the aromatic rings. On the whole, aurones have hydroxyl groups at 4- and 6-positions in A-ring and 4′-position in B-ring. Aurones have been described as phytoalexins, used by the plant as defense agents against various infections.

4.4 Biosynthesis of Aurones

Biosynthesis of aurones from chalcones involves dual chemical transformation of chalcones such as hydroxylation of the B-ring moiety and oxidative cyclization (2′,α-dehydrogenation) to give the aurone structure [2]. Several lines of evidence



Scheme 61.4 Biosynthesis of aurones

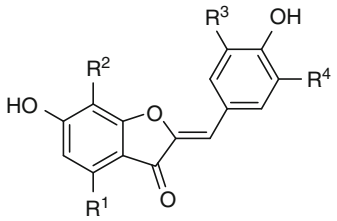


Fig. 61.14 Structures of bioactive aurones

R^1 = OH, R^2 = H, R^3 = OH, R^4 = H : aureusidin
R^1 = OH, R^2 = H, R^3 = OH, R^4 = OH : bracteatin
R^1 = H, R^2 = OH, R^3 = OH, R^4 = H : maritimetin
R^1 = OH, R^2 = H, R^3 = H, R^4 = H : 4,4′,6-trihydroxyaurone
R^1 = H, R^2 = H, R^3 = H, R^4 = H : hispidol
R^1 = H, R^2 = H, R^3 = OH, R^4 = H : sulfuretin

suggest that a single enzyme, which is called aureusidin synthase (AmAS1), catalyzes both these transformations. Aureusidin can be produced from either naringenin-chalcone or isoliquiritigenin, whereas bracteatin arises solely from isoliquiritigenin. The mechanistic investigations showed that AmAS1 acts as an oxygenase. It was established that AmAS1 is responsible for the transformation of a variety of chalcones to aurones [189]. According to the screening of a panel of hydroxylated and glycosylated chalcones, it is found that only chalcones, which are hydroxylated at C2′ and C4′ positions, are transformed to aurones (Scheme 61.4). Furthermore, the AmAS1 is definitely specific to chalcones because flavanones are inert for the enzyme action.

4.5 Biological Activities of Aurones

Aureusidin which is found in snapdragon, maritimetin which is an anthochlor pigment of *Coreopsis tinctoria* and *Baeria chrysostoma*, and bracteatin which is isolated from *Helichrysum bracteatum* have been studied with regards to their radical scavenging potential using density functional theory (DFT) [190–192]. 4,4′,6-Trihydroxyaurone isolated from *Pterocarpus santalinus* and *Smilax bracteata* and hispidol which can be found in *Trichilia hispida* were able to induce significant tyrosinase inhibition. In particular, 4,4′,6-trihydroxyaurone was highly active when compared to kojic acid [193]. Sulfuretin isolated from the heartwood of *Rhus verniciflua* is an active antirheumatoid arthritis agent. This compound showed significant inhibitory effects on hind paw edema and trypsin inhibitor activity induced by Freund's complete adjuvant reagent (FCS reagent) and on vascular permeability caused by acetic acid [194]. In addition, sulfuretin exhibited the anti-inflammatory effect by the suppression of NF-κB transcription activity via the inhibitory regulation of IκB kinase β-phosphorylation in LPS-induced RAW 264.7 macrophages [195]. Also, sulfuretin demonstrated the antidiabetogenic effect by the suppression of NF-κB activation [196] (Fig. 61.14).

5 Conclusions

The minor flavonoids are important subclasses of plant polyphenols. Especially, chalcones and flavanones are the obligate intermediates in flavonoid biosynthesis. These naturally occurring compounds also play significant roles as pigments, phytoalexins, and signaling molecules in pathogenesis and symbiosis. Additionally, considerable attention has been devoted to these compounds because of their potential pharmaceutical applications in recent years. For this reason, they are an object of continuously growing interest among the scientists. The attention is mainly drawn to the common skeleton and possibilities for its modifications guided by mechanistic and structure-activity relationship studies.

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